

The University of Manitoba

A STUDY OF ISOTHIAZOLIUM SALTS

presented by

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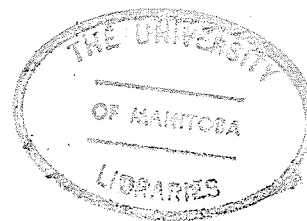
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ABSTRACT

A general method for the preparation of isothiazolium salts has involved the reaction of various 1,2-dithiolium salts with primary amines followed by ring closure by iodine oxidation of the 1-amino prop-1-ene-3-thiones formed in the reaction. This produced isothiazolium triiodides which were then converted to isothiazolium perchlorates.

In the process of devising a general method for the synthesis of isothiazolium salts, two 1,2-dithiolium salts, one aminopropene-thione and seven isothiazolium salts (two of them as the methiodides of isothiazole thiones) that have not appeared in the literature before had been prepared.

All attempts to place an acylidene side-chain at the 3-position of isothiazolium salts unsubstituted in that position in an effort to prepare the aza analogue of the thiothiophthene system had failed.

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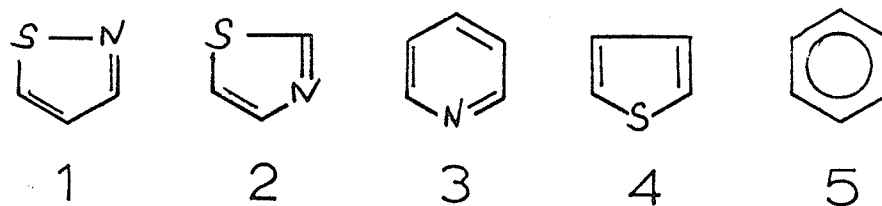
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INTRODUCTION

INTRODUCTION

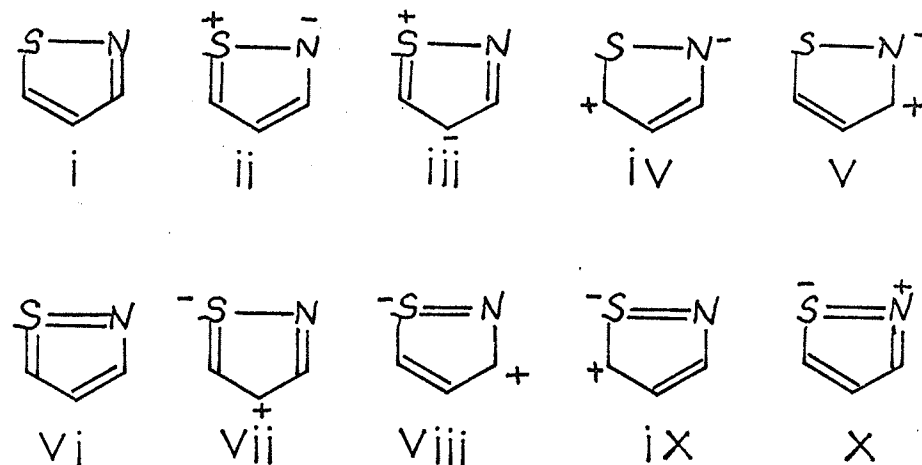
General

Isothiazole (1) is a five-membered heterocyclic system containing two heteroatoms, namely sulfur and nitrogen, which are adjacent. According to Longuet-Higgins' theory of isosterism,¹ a $-\text{CH}=\text{CH}-$ group of an aromatic system is electronically similar to the formally bivalent $-\text{S}-$ if participation of the sulfur 3d orbitals is taken into account. Isothiazole and thiazole (2) should then be related to pyridine as thiophen (4) is to benzene.



This is shown to be so by the similarity of their chemical and physical properties as well as their odor. In Figure 1 the resonance forms i--v are the contributing structures of isothiazole not utilizing sulfur 3d orbitals while structures vi--x are significant contributing structures using d orbitals.

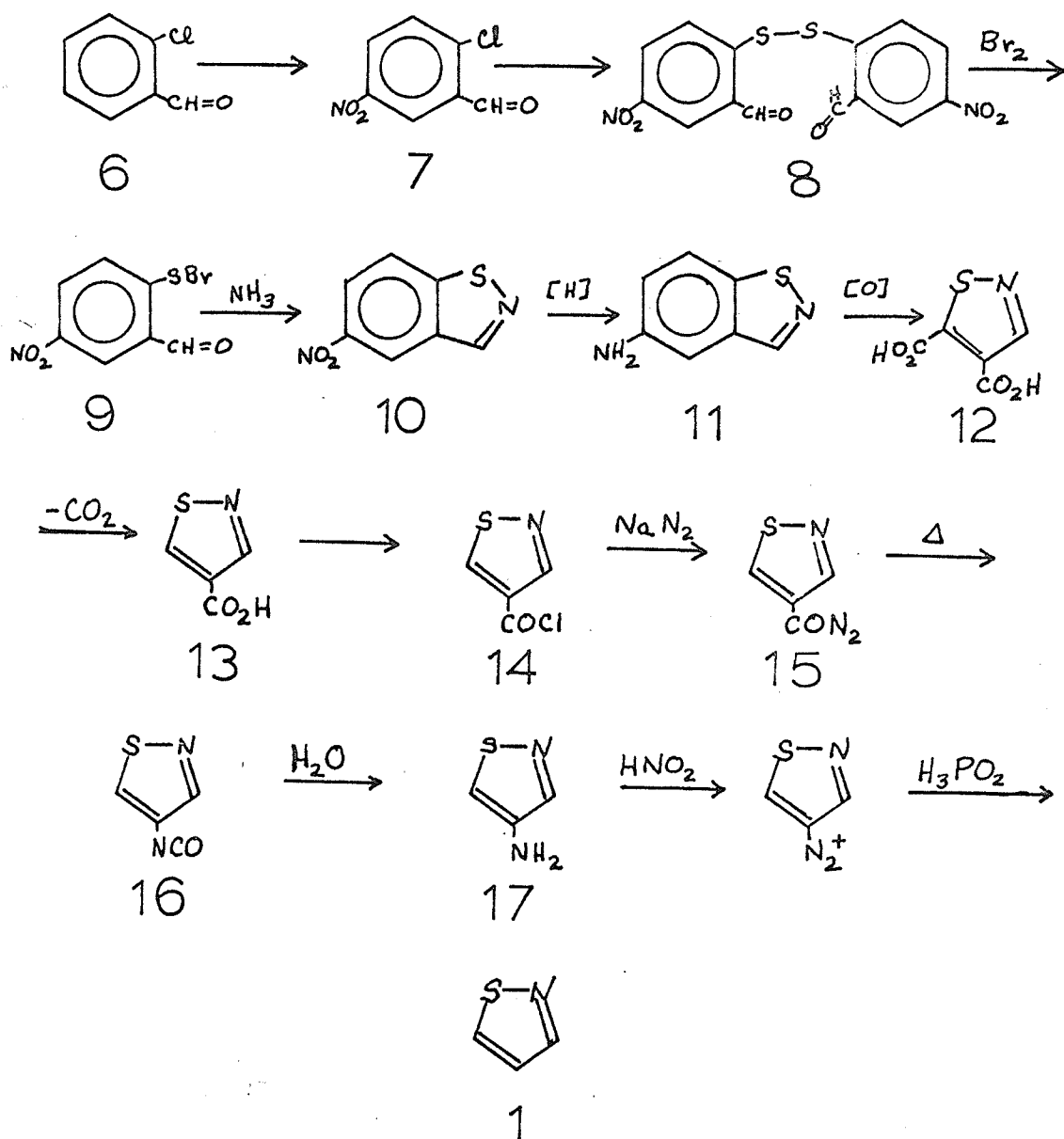
FIGURE 1



PREPARATIONS OF ISOTHIAZOLES

The thiazole system² has been known since 1925. Isothiazole was first prepared³ in 1956 by the degradative oxidation of 5-amino-benz-d-isothiazole (11); benzisothiazoles were known as early as 1895⁴ Figure 2 illustrates the procedures involved in the classical preparation of isothiazole.

FIGURE 2



The first step was the nitration of o-chlorobenzaldehyde (6) followed by sulfurization to produce the dimeric compound (8). Treatment with bromine cleaved the dimer to yield 2-thiobromo-4-nitrobenzaldehyde (9). Ring closure was effected by passing ammonia gas into a solution of compound 9, producing 5-nitrobenz-d-isothiazole (10) which was then reduced to the corresponding aminobenzisothiazole (11). Oxidation with alkaline permanganate solution yielded isothiazole-4,5-dicarboxylic acid (12), evidence of the considerable stability of the isothiazole ring. The ease of decarboxylation of compound 12 to form isothiazole-4-carboxylic acid (13) recalls the ease of decarboxylation of pyridine-3,4-dicarboxylic acid to form the 3-carboxylic acid.⁵ In both cases it is the carboxyl group "para" to the ring nitrogen atom which is lost. Further decarboxylation was possible only via the Curtius sequence of reactions (13 → 17) to produce 4-amino isothiazole (17). Isothiazole was prepared by diazotization of the aminoisothiazole and treatment of the diazonium salt with hypophosphorous acid.

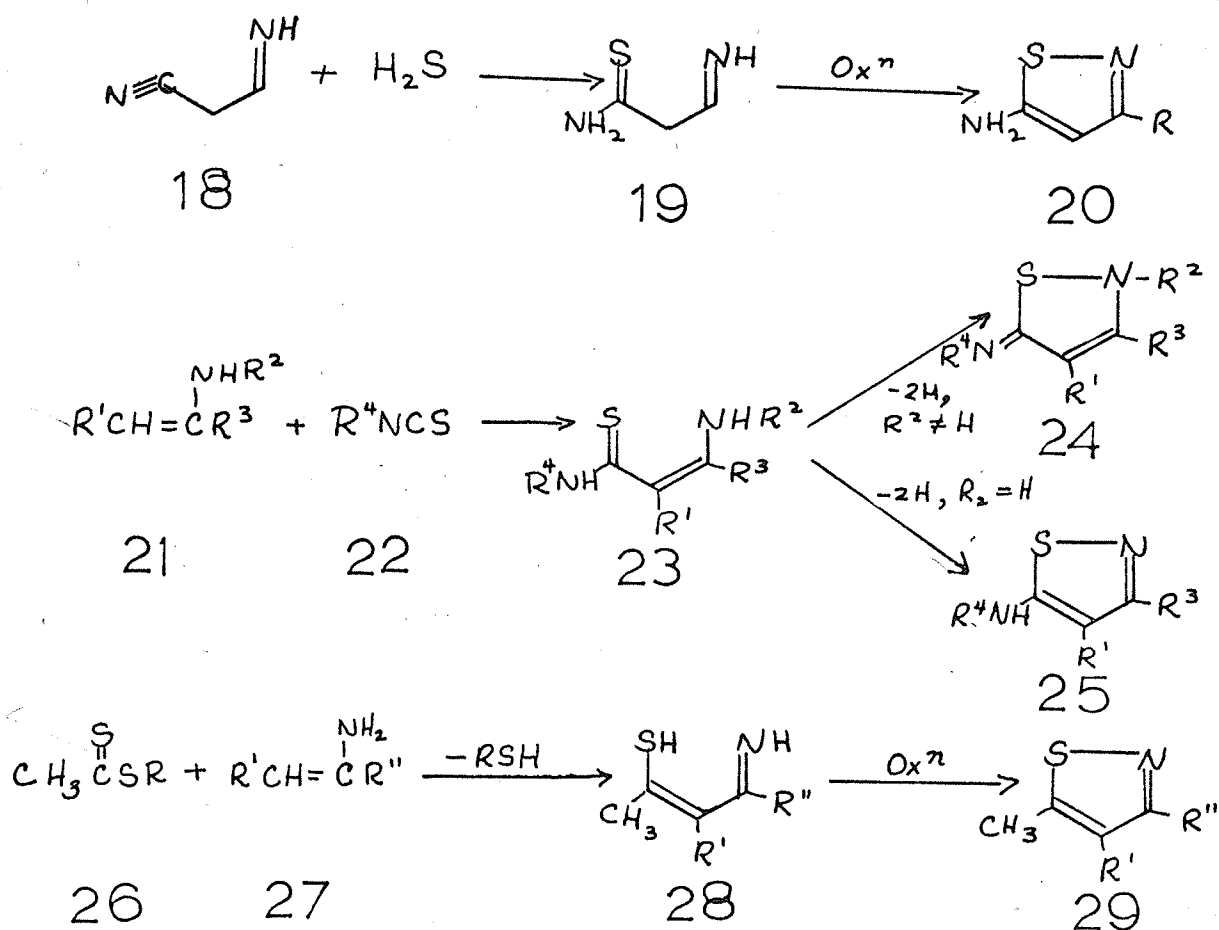
Simpler syntheses have been developed. One general method involved the oxidation of acyclic intermediates formed in addition or condensation reactions. (See Figure 3, page 4.)

An example of such a procedure was the synthesis of substituted 5-amino isothiazoles⁶ (20) by oxidation with hydrogen peroxide, chloramine or persulfates of the compounds formed by the addition of hydrogen sulfide to β -imino propionitriles (18).

Goerdeler and coworkers⁷⁻¹¹ independently developed a similar method for the preparation of 5-amino isothiazoles (25) and 5-imino isothiazolines (24) by the addition of isothiocyanates (22) to

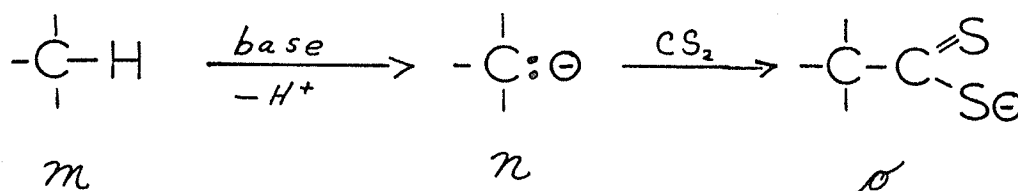
primary ($R^2 = H$) and secondary enamines (21) followed by cyclization with hydrogen peroxide, chloramine, bromine or iodine in pyridine or with bromine in acetic acid. They extended their reactions to prepare 3-hydroxy, -alkoxy and -amino isothiazoles by the oxidative cyclization of suitable intermediates.

FIGURE 3



Low yields of substituted isothiazoles have been obtained by thioacylation of primary enamines¹² followed by oxidation with hydrogen peroxide or iodine/benzene solution in the presence of potassium carbonate (26 \rightarrow 29).

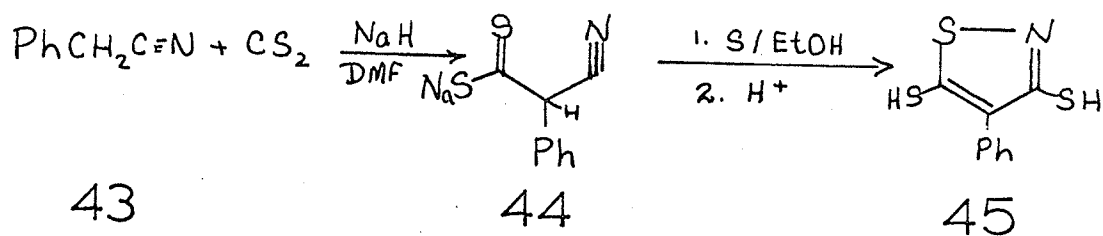
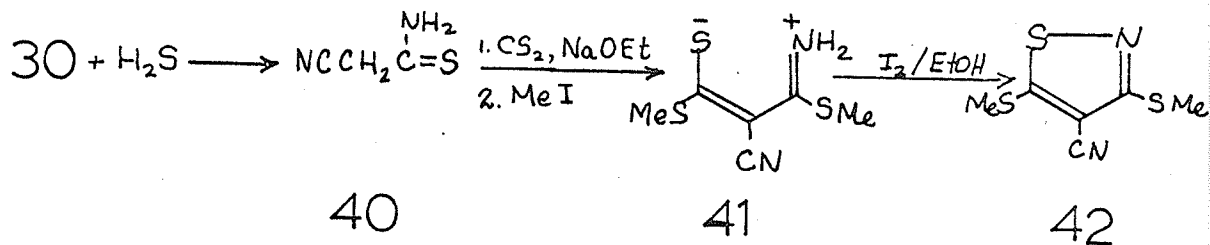
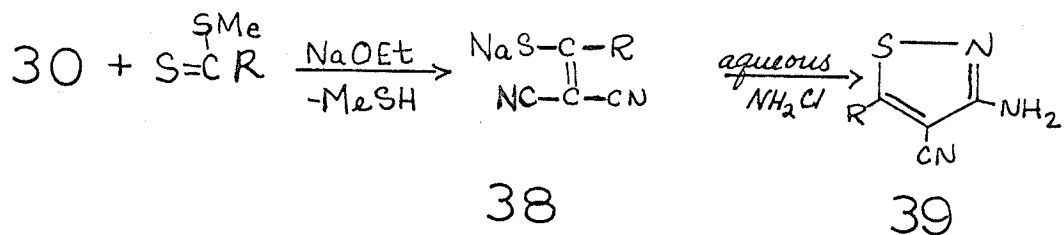
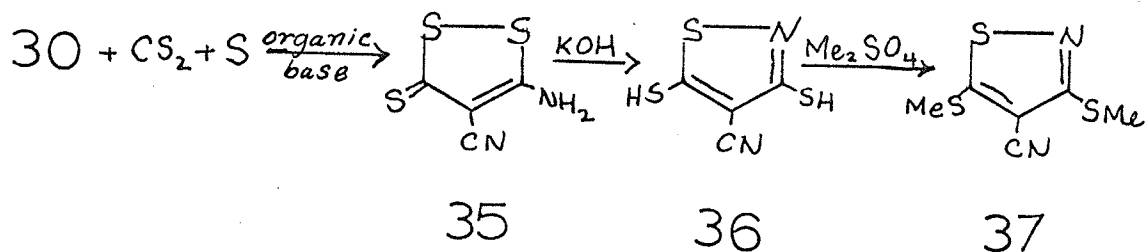
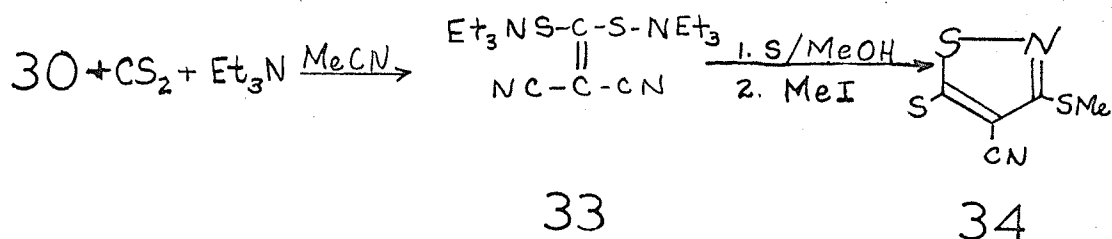
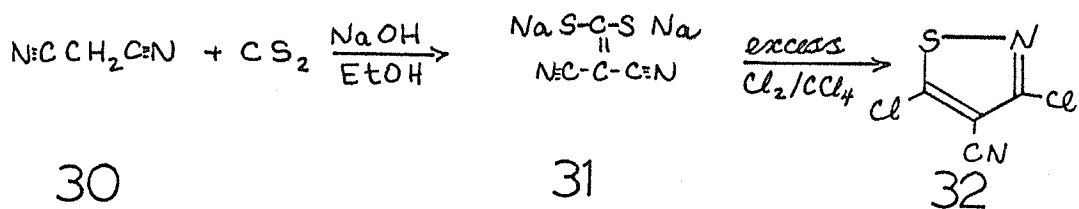
Active nucleophilic methylene groups such as those found in malononitrile (30) and phenylacetone nitrile (43) have been utilized in the presence of a base to form intermediate compounds which were treated with sulfur to yield isothiazoles. The base may serve as an activator of elementary sulfur S_8 . The base may be an amine or any other base of comparable nucleophilic strength including any sulfide, polysulfide or sulfite which may be formed during sulfurization. The base may also be present to act as the proton acceptor in the formation of the actual nucleophile (n). Carbon disulfide can add to nucleophiles when such an auxiliary base is present.



Problems arose when carbon disulfide reacted with the auxiliary base which is also a nucleophile. Hence it was convenient to use systems which were nucleophilic enough themselves to react with carbon disulfide without the aid of an auxiliary base. Such nucleophilic compounds are enamines, dienamines, Schiff bases, alkynes and CH-acid nitriles¹³ e.g. malononitrile. Sulfur, carbon disulfide and dithioesters are all capable of reacting with them. Figure 4 on the following page presents the reactions that the methylene groups have been shown to undergo in the preparation of various isothiazoles.

Malononitrile reacted with carbon disulfide with sodium hydroxide as the auxiliary base to produce di(sodiomer-capto)methylenemalononitrile (31).¹⁴ Treatment of compound 31 with excess chlorine in carbon tetrachloride gave 3,5-dichloro-4-cyano isothiazole (32).

FIGURE 4



Addition of acetonitrile in triethylamine to a solution of malononitrile in carbon disulfide¹⁵ afforded di(triethylammonio)-methylenemalononitrile (33), analogous to compound 31. Oxidation was performed under mild conditions by refluxing with sulfur in methanol. 3,5-Di(methylthio)-4-cyano isothiazole (34) was produced when methyl iodide was added to the solution.

Gewald and Mayer¹⁶ treated malononitrile with sulfur and carbon disulfide in the presence of a base such as diethylamine or triethylamine (to act as activator and proton acceptor) to prepare 4-cyano-5-amino-1,2-dithiol-3-thione (35). Potassium hydroxide effected ring opening by the scission of the -S-S- bond. Isomerization about the carbon-carbon double bond of compound 35 and ring closure afforded di-potassium-3,4-dithio-4-cyano isothiazole (36). Methylation of the rearranged product produced 3,5-dimercapto-4-cyano isothiazole (37).

Malononitrile was thioacylated¹⁷ with esters of dithiocarboxylic, thionocarboxylic, trithiocarbonic and xanthic acids in anhydrous ethanol with a base such as sodium ethoxide as a catalyst to form sodium vinyl sulfides (38). These sulfides afforded 3-amino-4-cyano isothiazoles (39) when treated with chloramine.

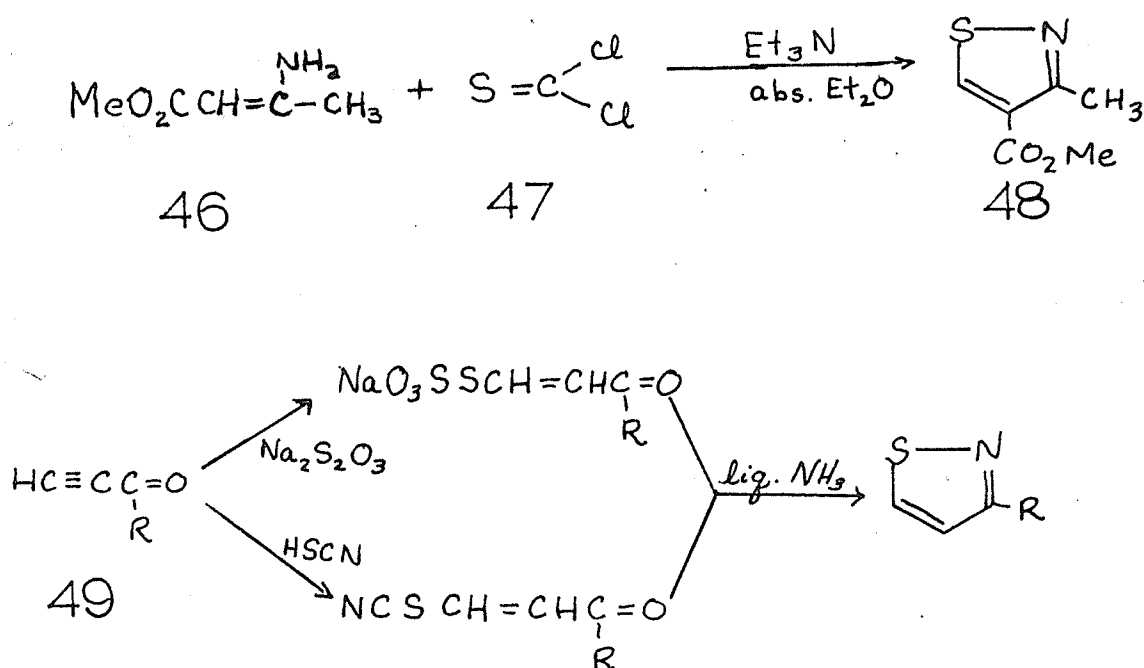
The reaction of one mole each of hydrogen sulfide and malononitrile produced cyanothioacetamide (40) which reacted with carbon disulfide in the presence of a base such as sodium alkoxide.¹⁸ Methylation of the addition product yielded the intermediate (41) which on oxidation with ethanolic iodine gave 3,5-dimethylthio-4-cyano isothiazole (42).

Phenylacetonitrile (43) treated with carbon disulfide with sodium hydride as the base and dimethylformamide as a catalyst produced

a dithioic acid salt (44) as an intermediate which was cyclized by refluxing with sulfur in ethanol. Acidification afforded 4-phenyl-3,5-dithio isothiazole (45).¹⁹

There are two examples of where acidic methyne groups have been utilized to prepare isothiazoles. (See Figure 5.)

FIGURE 5



Addition of thiophosgene (47) to methyl β -aminocrotonate (46)²⁰ in absolute ether in the presence of triethylamine as a basic catalyst afforded methyl 3-methyl-4-isothiazole carboxylate (48).

Propynal (49, $\text{R}=\text{H}$) treated with sodium thiosulfate or with thiocyanic acid yielded an intermediate which on cyclization with liquid ammonia produced isothiazole or a 3-alkyl isothiazole (if a propyne ketone were used instead of propynal).²¹

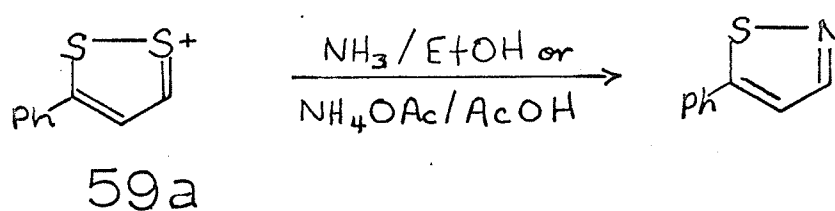
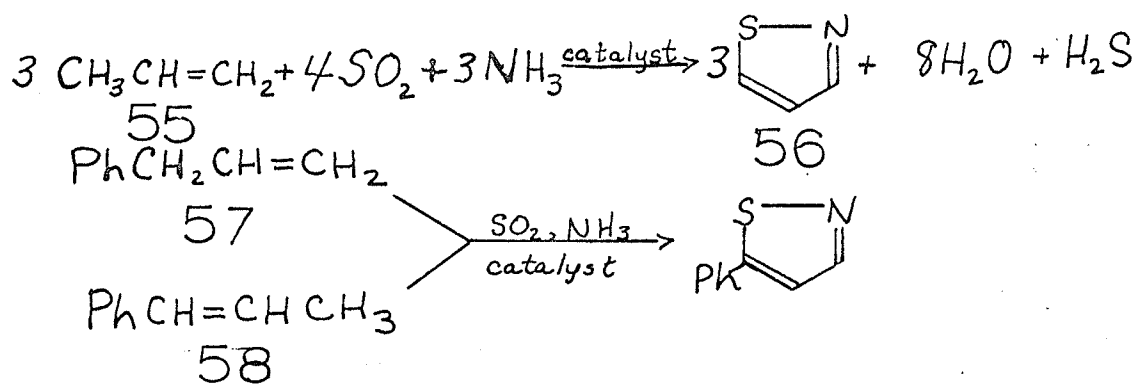
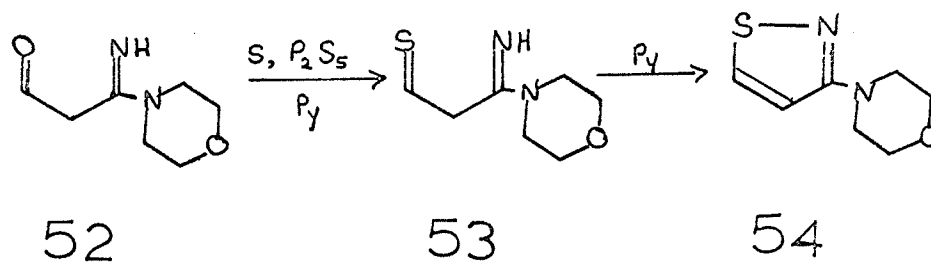
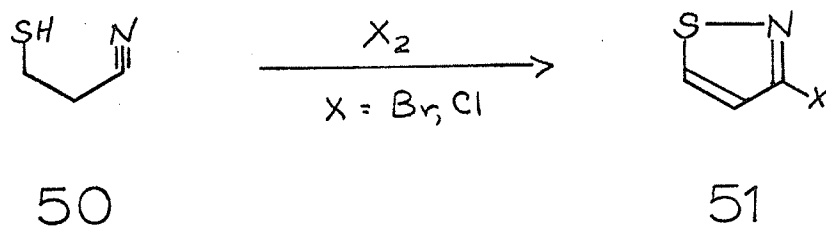
There are several other preparations of isothiazoles, the equations of which appear in Figure 6, page 10. The first reaction is unique in that similar reactions have not appeared in the literature; the second reaction may be general but it has not yet been shown to be so; the third reaction is a general preparation of alkyl and aryl isothiazoles; the fourth has also been shown to be quite general.

One method has involved the oxidative cyclization of β -mercapto-propionitrile (50)²² with chlorine or bromine in an inert solvent to yield 3-halo isothiazoles (51). Three protons are lost in the conversion but the details of the route are not known.

Another preparation was the sulfurization of a suitable β -imino ketone such as β -imino- β -morpholinoethyl phenyl ketone (52) with sulfur and phosphorus pentasulfide with pyridine as the solvent.²³ Pyridine, which is a base, would behave as an activator of the sulfur and of the thione that is formed. Thus activated, the thione may then undergo ring closure to produce 3-morpholino-5-phenyl isothiazole (54).

A fairly efficient and simple preparation of alkyl and aryl isothiazoles was introduced by Hubenett, Flock and Hoffman.²⁴ It involved the reaction of olefins with three or more carbon atoms with sulfur dioxide and ammonia at temperatures of 300-350°C. over suitable catalysts, for example, activated alumina or silica gel containing oxides of aluminum, titanium or other multivalent metals.²⁵ (55 \rightarrow 56) The authors found that n-butenes invariably gave mixtures of 3-methyl and 5-methyl isothiazoles while both allyl benzene (57) and α -methylstyrene (58) yielded only 5-phenyl isothiazole. It appeared

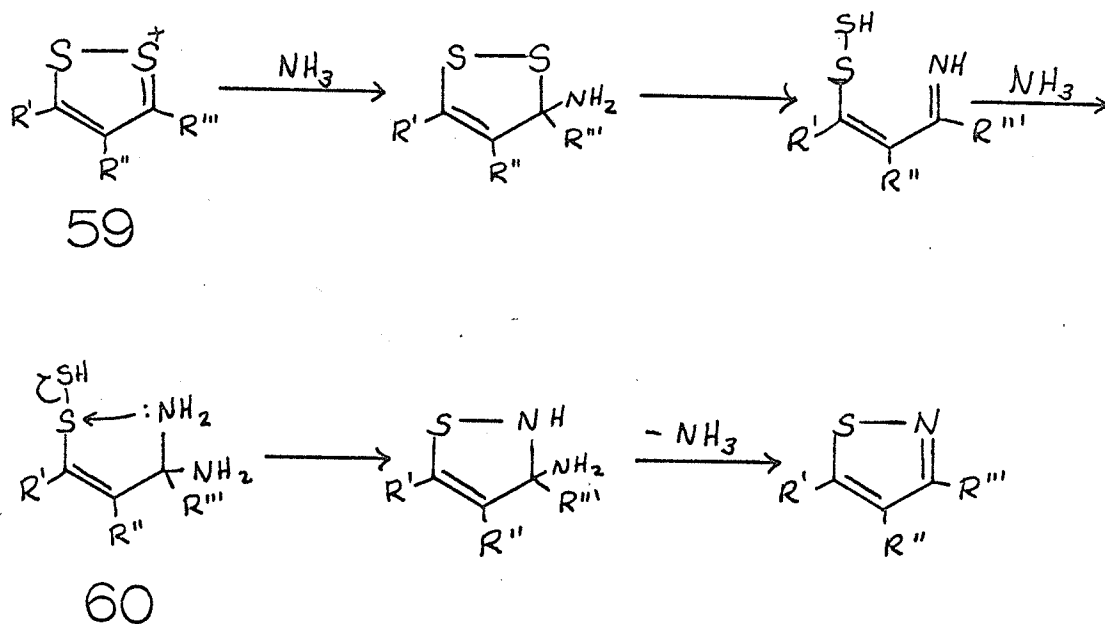
FIGURE 6



that the n-butenes reacted as an equilibrium mixture of the 1- and 2-butene while the aryl butenes had their equilibrium displaced largely toward the α -methylstyrene form²⁵ which is the more stable form due to conjugation. It was then assumed that the nitrogen entered the position γ to the benzene ring and the sulfur added at the double bond to form a reactive sulfur-nitrogen compound which cyclized to form isothiazole.

Isothiazoles have been prepared by the reaction of certain 1,2-dithiolium salts (59) with ammonia in ethanol or with ammonium acetate in acetic acid.^{26,27} Unsymmetrical dithiolium salts reacted preferentially in one direction. It was determined that the operative mechanism was one of addition-elimination followed by ring closure via displacement of the sulfhydryle ion by the nucleophilic nitrogen of the NH_2 group of the intermediate non-isolated open chain compound (60). The mechanism is shown in Figure 7.

FIGURE 7

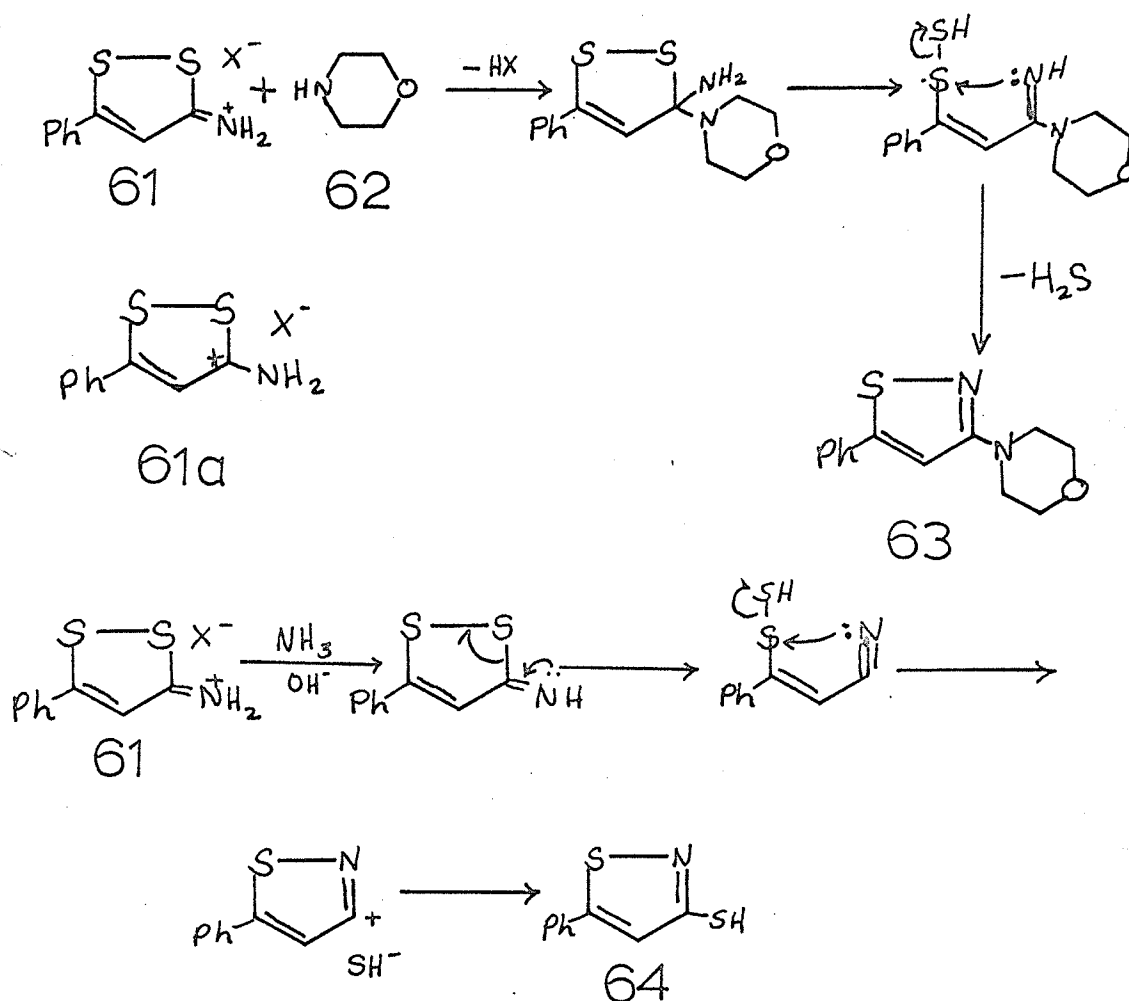


It is possible that in the reaction of olefins with sulfur

dioxide and ammonia just mentioned analogous sulfur heterocycles were formed which then reacted with ammonia to produce isothiazoles.

Isothiazole was obtained as a minor product on the treatment of 1,2-dithiolium salts with aqueous ammonia in the presence of ammonium chloride.²⁸

FIGURE 8

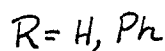
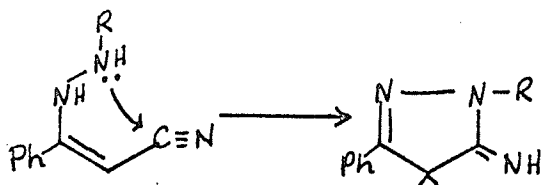
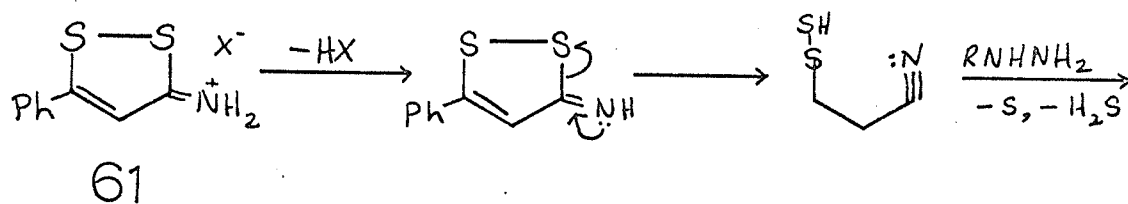


Tornetta²⁹ had assigned the structure of 5-phenyl-3-amino-1,2-dithiolium cation to the product obtained by the reaction of phosphorus pentasulfide with cyanoacetophenone. However, the behaviour of the compound led the author to believe that the correct

structure was that of the 5-phenyl-3-imino-1,2-dithiolium cation (61) which can also be represented as a carbonium ion (61a). In a manner somewhat similar to the addition of ammonia to the 1,2-dithiolium salts to produce isothiazoles compound 61 has been shown to undergo nucleophilic attack at the 3-position by morpholine³⁰ with subsequent elimination of HX, ring cleavage, then ring closure via the displacement of the sulfhydryde ion by the nucleophilic nitrogen of the imino group to yield 3-morpholino-5-phenyl isothiazole (63) with the evolution of hydrogen sulfide.

Treatment of the 5-phenyl-3-imino-1,2-dithiolium salt with ammonia and alcoholic potassium hydroxide promoted isomerization to 3-mercapto-5-phenyl isothiazole.³⁰ The proposed mechanism involved the cleavage of the dithiol ring with formation of a nitrile intermediate. Condorelli, Pappalardo and Tornetta³⁰ found further evidence for the nitrile intermediate in the interpretation of the formation of imino-pyrazolones obtained by the action of hydrazine and phenylhydrazine on compound 61. (See Figure 9) In Figure 9 it

FIGURE 9



observed that the hydrazine displaces the -S-S-H chain before the nitrogen of the nitrile had an opportunity to displace the sulfhydryde ion by nucleophilic attack as was shown in Figure 8.

Isothiazoles have also been obtained by the reaction of isothiazolium salts with ammonia.³¹ The mechanism is similar to that observed in the reaction of 1,2-dithiolium salts with ammonia and will be discussed with the other reactions of isothiazolium salts.

ISOTHIAZOLIUM SALTS

Theory

Isothiazolium salts (65) are isothiazoles with the ring nitrogen atom quaternized. They are isoelectronic with thiazolium salts (66), pyridinium salts (67) and with benzene (5).

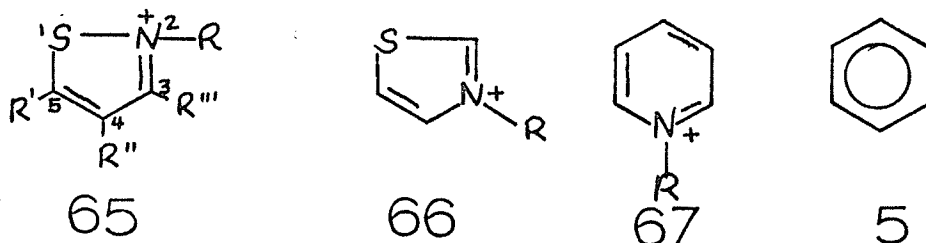
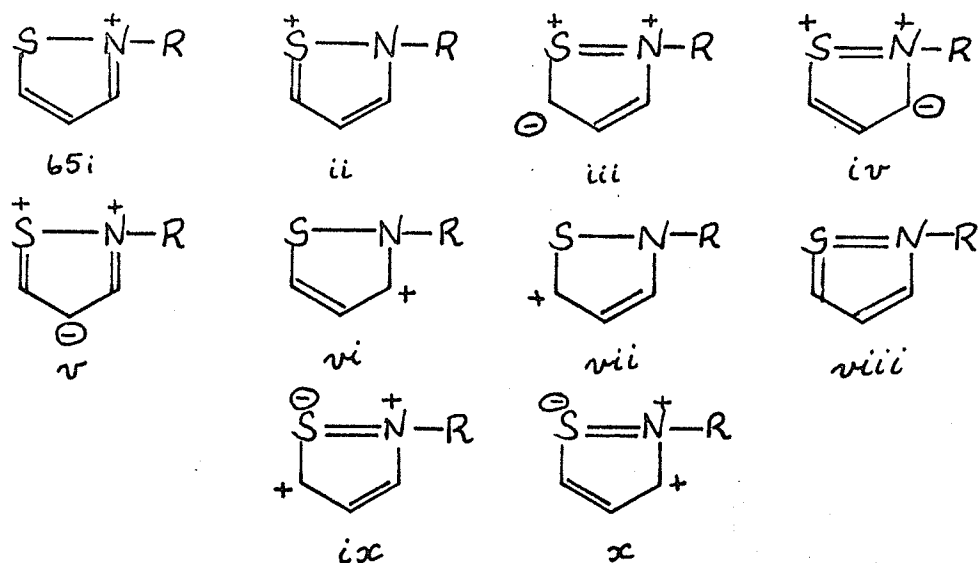


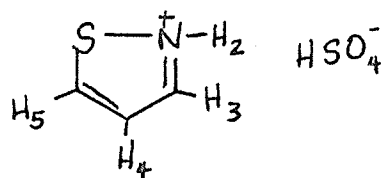
Figure 10 represents the possible contributing structures of isothiazolium salts; structures 65(viii-x) utilize sulfur d-orbitals while 65(i-vii) do not.

FIGURE 10



The contribution of structures 65(iii, iv, v, and x) would be

expected to be negligible because of the high energy requirement for two adjacent positive centres. Experiments on rates of deprotonation³² have shown proton loss to occur in positions 3 and 5, with exchange rates higher for the 5-position than for the 3-position. This is indeed surprising since it is contrary to L.C.A.O. molecular orbital calculations or even simple consideration of inductive or coulombic effects. Most of the positive charge should be on the nitrogen atom. This strange behaviour was explained by the fact that d-orbital overlap of the sulfur atom would stabilize the deprotonated species.³² Additional evidence for the lower electron density at the 5-position than at the 3-position is the nuclear magnetic resonance spectrum of isothiazole in sulfuric acid (i.e. of isothiazolium hydrogen sulfate),



which showed peaks at τ for $H_5 = 0.4$, τ for $H_3 = 0.9$ and τ for $H_4 = 2.1$.³³

In agreement with these observations, it would seem that of the structures not utilizing sulfur d-orbitals, 65(vi and vii) present a significant contribution, and of the structures using d-orbitals, 65(ix) would be the most significant.

ISOTHIAZOLIUM SALTS

Reactions

The reactions of isothiazolium salts have yet to be extensively studied. The salts would be expected to be reactive to nucleophilic reagents and unreactive to electrophilic reagents. Their reactions would be expected to parallel those of 1,2-dithiolium salts (59), thiazolium salts (66) and N-substituted pyridinium salts (67)

From the discussion on deprotonation rates and n.m.r. spectra of isothiazolium salts (page 15), it is fairly obvious that nucleophilic attack on the isothiazolium nucleus would occur in either of positions 3 or 5, but preferentially in position 5 if both positions are unoccupied. In fact nucleophilic attack has been shown to occur with two isothiazolium salts (65 a, b), with sulfur attacking the unoccupied 3-position to produce isothiazole-3-thiones which were treated with methyl iodide and isolated as the corresponding 3-methylthio isothiazolium iodides. Klingsberg³⁴ has shown that 1,2-dithiolium salts with either position 3 or 5 unsubstituted undergo a similar oxidation by sulfur in boiling pyridine to provide the corresponding 1,2-dithiol-3-thiones. Thiazolium salts also readily form thiazole-2-thiones under similar conditions.³⁵

Another example of nucleophilic attack on the isothiazolium system was shown by Landesberg and Olofson.³¹ The formation of isothiazole by the nucleophilic attack of ammonia on 2-ethyl-4-phenylisothiazolium fluoroborate has been shown to proceed via an addition-elimination pathway Figure 11, p. 26. Addition of ammonia at the 3-position results in ring cleavage to produce the intermediate 68ii.

This intermediate then undergoes ring closure when the electrons of the imino nitrogen atom displace the ethylamino group to give 4-phenyl isothiazole. Other nucleophiles have reacted with isothiazolium cations to yield additional heterocycles in analogous reactions. 3-phenyl isothiazolium perchlorate reacted with hydrazine to give 3-phenyl pyrazole and with phenyl hydrazine to give a mixture of 1,3-diphenyl and 1,5-diphenyl pyrazole.

1,2-dithiolium salts in general have been shown to react with ammonia to produce isothiazoles. The 3-phenyl-1,2-dithiolium cation reacts with phenylhydrazine to give a mixture of 1,5-diphenyl and 1,3-diphenyl pyrazole in a manner similar to that of the 3-phenyl isothiazolium cation.²⁷

Isothiazolium salts³² as well as 1,2-dithiolium salts,³⁶ thiazolium salts³⁷ and pyridinium salts³⁸ all decompose on treatment with base. Pyridinium salts require heat for decomposition to take place.

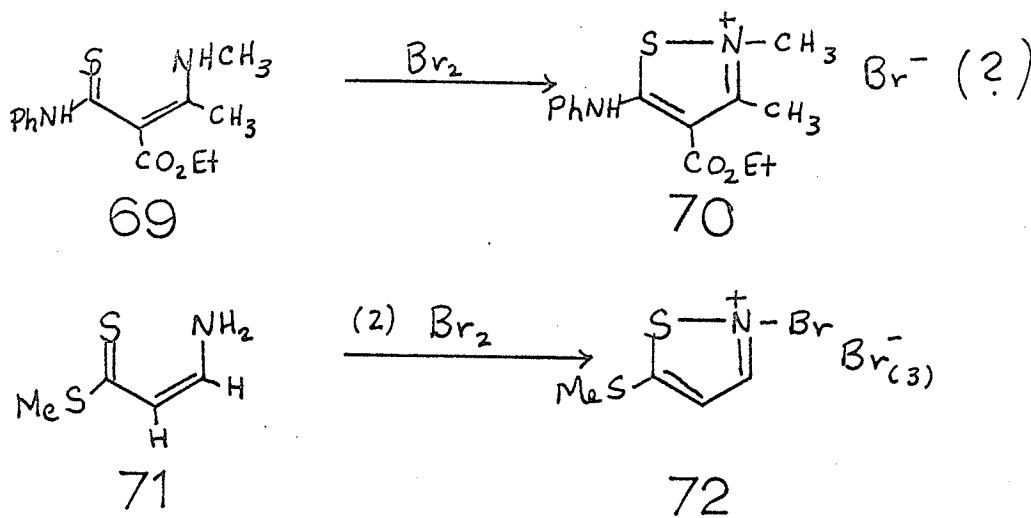
ISOTHIAZOLIUM SALTS

Preparations

There are generally two methods of obtaining isothiazolium salts and that is by i) alkylation of isothiazoles and ii) ring closure of suitable compounds..

Isothiazoles have been alkylated by being allowed to stand for prolonged periods of time with methyl or ethyl iodide,³⁹ by refluxing with benzylbromide,³⁹ or by addition of triethyloxonium fluoroborate.³¹ The obvious limitation to this approach is that N-aryl isothiazolium salts cannot be prepared in an analogous manner.

Goerdeler⁸ had suggested that treatment of 2-ethoxycarbonyl-3-methylamino-N-phenyl-thiobut-2-ene-amide⁴⁰ (69) with bromine might produce an isothiazolium salt. Using this approach, Faust⁴¹ synthesized 5-(methylthio)-isothiazolium bromide and tribromide (72) by dehydrogenation of 3-aminodithioacrylates (71) with one or two moles of bromine respectively.



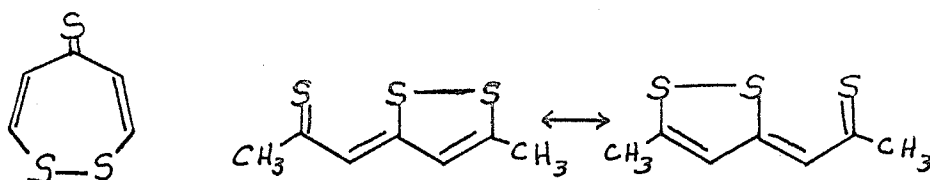
N-aryl isothiazolium salts can be prepared only by ring synthesis, or more specifically, the oxidation of suitable intermediate compounds. This paper shall deal with the preparation of N-aryl and N-alkyl isothiazolium salts by these means.

DISCUSSION

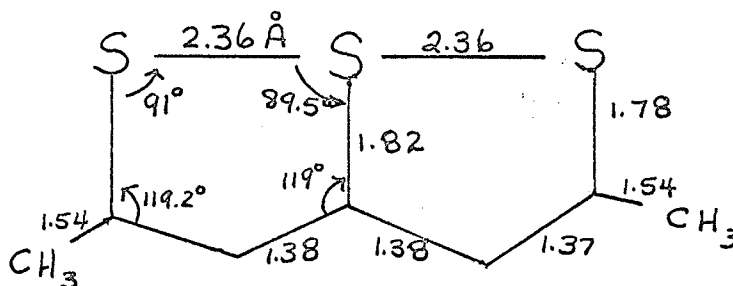
DISCUSSION

Object of Research

The compound obtained by the treatment of diacetyl acetone with phosphorus pentasulfide in benzene was erroneously given the structure of a seven-membered ring disulfide by Arndt.⁴² However, Bezzi, Mammi & Garbuglio⁴³ gave the compound so obtained the thiothiophthene structure (73), correctly named as {1,2}-dithiolo(1,5b)-{1,2} dithiol-7-S.^{IV} These authors also reported that the molecule was characterized by single bond-no bond resonance which conferred an aromatic character on the two rings.

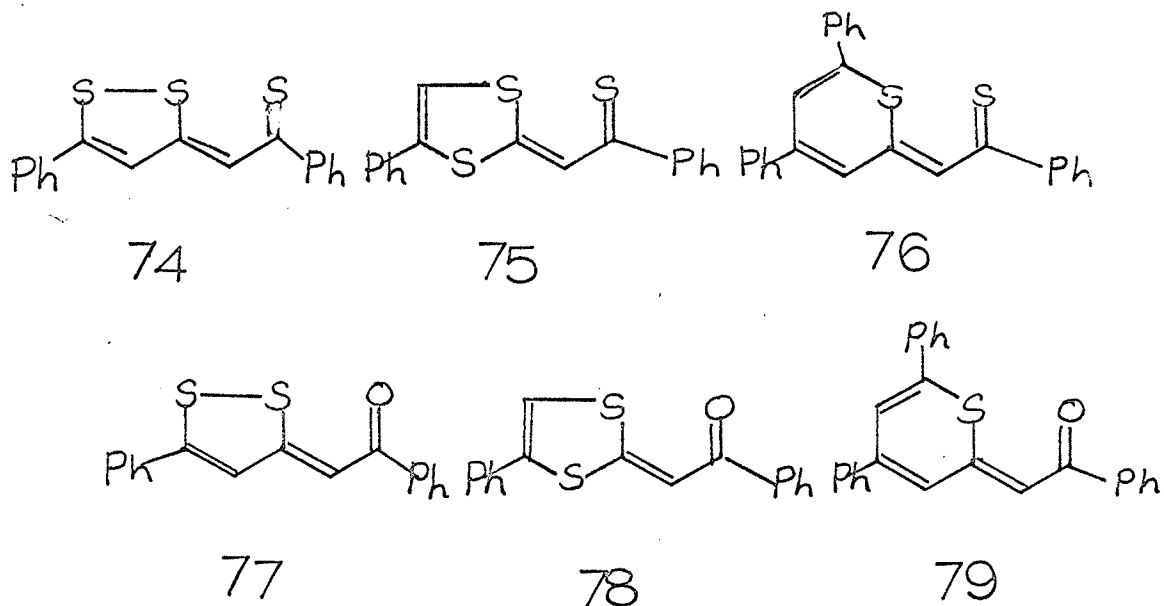


73



From the diagram of the bond lengths and bond angles of the thiothiophthene system, one observes that the bond lengths of 1.37-1.38 Å between the ring carbon atoms indicate that the nucleus is aromatic. The fact that the sulfur to sulfur bond is 2.36 Å whereas in dithio compounds R-S-S-R it is 2.04 Å indicates that the sulfur-

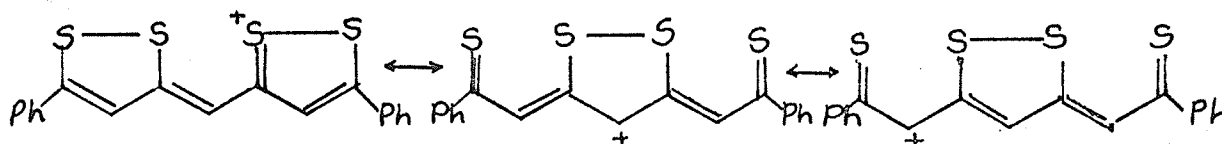
sulfur bond order is less than unity. Leaver and McKinnon⁴⁴ argued that although proton magnetic resonance indicated a symmetrical structure for compound 73, this may be caused by rapid tautomerism rather than by single bond-no bond resonance. In support of this view they showed that the ultraviolet spectra and visible spectra of the thiothiophthene system (74) were similar to those of compounds 75 and 76 in neither of which resonance of the type described for compound 74 is possible. Wavelengths of visible maxima of compounds 74, 75, and 76 differed from those of the corresponding ketones (77, 78, 79) by roughly the same increment (67, 69 and 60 mμ respectively).



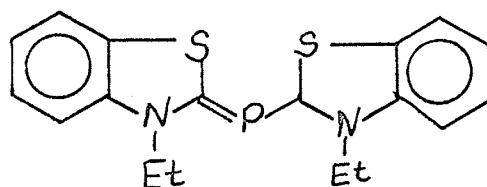
Maeda⁴⁵ has investigated the participation of the sulfur d-orbitals in the hybridization of the sulfur atoms forming the linear S-S-S bonds of thiothiophthenes. The calculations, involving simple L.C.A.O. approximations showed that participation of the $3p_z$ orbital of the sulfur atoms was more likely than that of $3d_{xy}$ orbitals.

Single bond-no bond resonance was also considered to make minor contributions to the structure of dithiolocyanine perchlorates⁴⁶ (80)

due to the existence of an unusually short distance between the two internal sulfur atoms ($3.0 - 3.1 \text{ \AA.}$)



80



81

Easton, Leaver and McKinnon⁴⁷ however argued that i) no evidence had yet been presented to indicate that the S-S bonds in the dithiol nucleus are unusually long and that ii) the central S-S distance is longer than the value of 2.95 \AA found for the phosphacyanine (81),⁴⁸ in which single bond-no bond resonance is highly improbable. They regarded the partial interannular bonding of the dithiolocyanines as a result of the expansion of the valence shells of the two internal sulfur atoms, i.e. as a result of the utilization of sulfur 3d orbitals which have a greater extension in space than do $3p_z$ orbitals and whose probability to overlap is thus greater.

It has been suggested that the long S-S bond found in thiothiophenes can be better explained by the delocalization of all π -electrons to form an 8-centred system (5 carbon atoms and 3 sulfur atoms), the S-S bonds being purely π -bonds without any δ -bonding,⁴⁸ similar to the structure of the N-N bond in N_2O_2 .⁴⁹

Hence we are presented with three possible explanations for the symmetry of thiothiophthenes: i) single bond-no bond resonance, i.e. delocalization of all π -electrons to form an 8-centred system ii) rapid tautomerism iii) utilization of sulfur d-orbitals.

Replacing the central sulfur atom of S-S-S in the thiothiophthene system by a tertiary nitrogen to form S-N-S would leave a molecule which may or may not be symmetrical, depending on which of the three aforementioned factors plays a leading role. Unlike the sulfur atom, the nitrogen atom has no d-orbitals available to allow for expansion of its valence shell. Hence if the molecule were found to be symmetrical, it could not be due to iii. The preparation of these aza analogues of thiothiophthenes required the availability of isothiazolium salts. The object of this research was to devise a general preparation of isothiazolium salts and to attempt synthesis of this aza analogue of the thiothiophthene system. A paper, "Synthesis of some isothiazolium salts" by D.M. McKinnon and E.A. Robak has been published in the Canadian Journal of Chemistry, 46, 1855 (1968), dealing with the general preparation of isothiazolium salts devised in our laboratory.

Materials

It was decided to start from 1,2-dithiolium salts since these are readily available and it has been observed⁵⁰ that treatment of these salts with primary amines gave substituted 1-aminopropene thiones. Since these are structurally related to earlier precursors (71) of isothiazolium salts, it seemed reasonable that they too would oxidize to form isothiazolium salts.

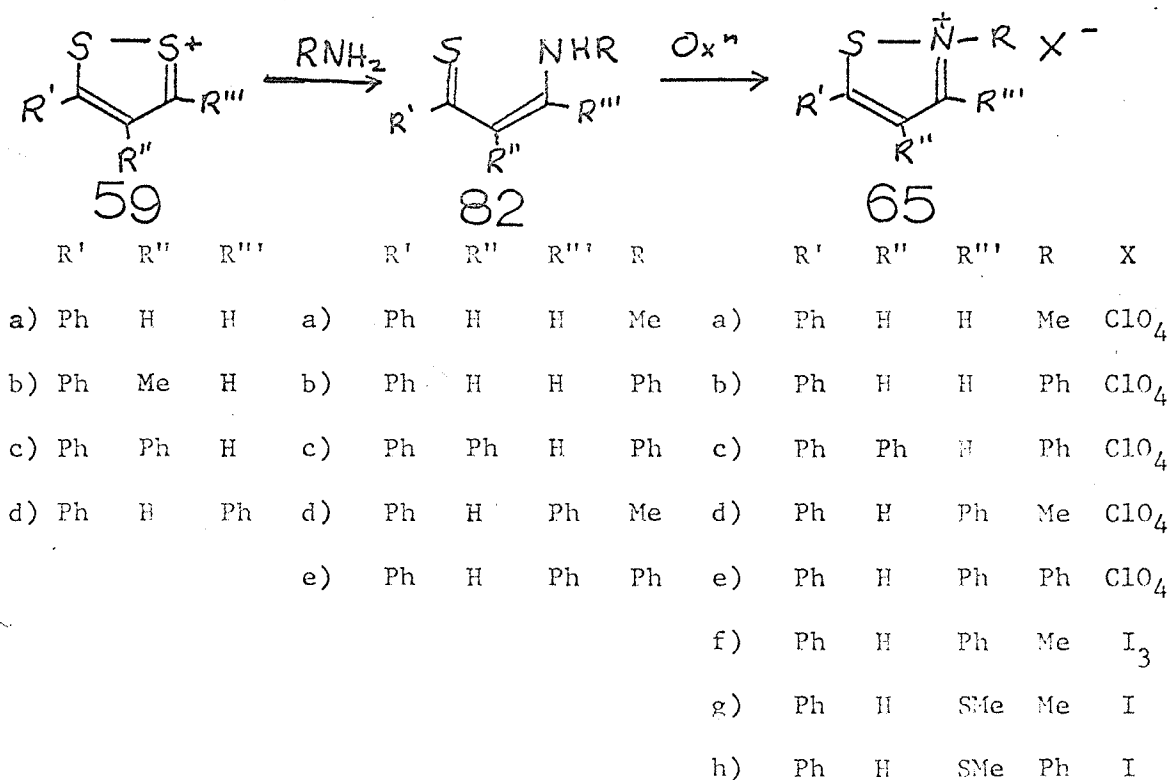
Two of the dithiolium salts (59a,d) had been prepared before^{36,51} but two new ones (59b,c) were synthesized by an adaptation of known methods. An attempt was made to prepare a known 1,2-dithiole-3-thione by a method different from that found in the literature. This thione could then be oxidized to produce a new dithiolium salt. An unexpected product was obtained.

The 1,2-dithiolium salts were treated with primary amines to produce 1-arylamino and 1-alkylamino prop-1-ene-3-thiones (82). One of these thiones was new (82d), two had been made before (82b,c),⁵⁰ and two others (82a,c) were not isolated but were oxidized in the solution in which they had been formed. Six different isothiazolium salts were prepared by oxidation of the propenethiones. Of these six, five had not been prepared before and one (65a) had been previously prepared by N-methylation of 5-phenyl isothiazole. One cation was identified as the perchlorate (65d) and as the triiodide (65f) salt.

Since the production of isothiazolium salts involves the loss of a hydride ion from the aminopropene thione precursors, it would be expected that 2,3,5-triphenyl isothiazolium perchlorate (65e) could be synthesized directly from 1-anilino-1,3-diphenyl prop-1-ene-3-thione (82e) using triphenylmethyl perchlorate (92), a reagent

known to abstract hydride ions.⁵² Ring closure, however, was not effected; N-tritylation occurred instead.

FIGURE 11



Isothiazolium salts have been shown to undergo oxidation with sulfur in pyridine⁵³ to provide the corresponding isothiazole-3-thiones. This is exactly analogous to the reaction of 1,2-dithiolium salts with sulfur in pyridine³⁴ to produce 1,2-dithiol-3-thiones.

Certain 1,2-dithiolium salts were shown to react with methyl and methylene carbonyls which on sulfurization with phosphorus pentasulfide produced various thiothiophthenes.⁵⁴ Similar reactions were attempted with isothiazolium salts.

2,5-diphenyl isothiazolium perchlorate was treated with dimethyl formamide in an attempt to prepare a carbene in a manner analogous

to the preparation of carbenes from thiazolium salts.³⁵

An attempt was made to determine whether the aminopropene thiones behaved as dienes by refluxing one of the thiones (82e) with a dienophile such as dimethyl acetylene dicarboxylate (100).

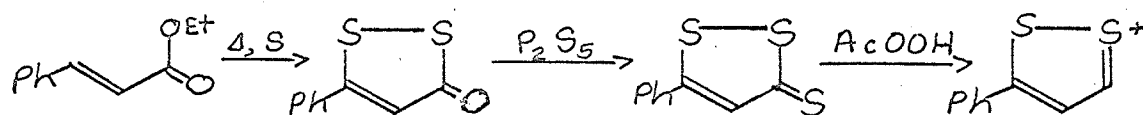
Preparations of 1,2-dithiolium salts

The 1,2-dithiolium salts 59a, 59b, and 59c were prepared by the peracetic acid oxidation of the corresponding 1,2-dithiol-3-thiones, viz. 5-phenyl-1,2-dithiol-3-thione,³⁶ 4-methyl-5-phenyl-1,2-dithiol-3-thione,⁵⁵ and 4,5-diphenyl-1,2-dithiol-3-thione^{56,57} respectively. 3,5-Diphenyl-1,2-dithiolium perchlorate was prepared by the method of Behringer and Grimm.⁵¹

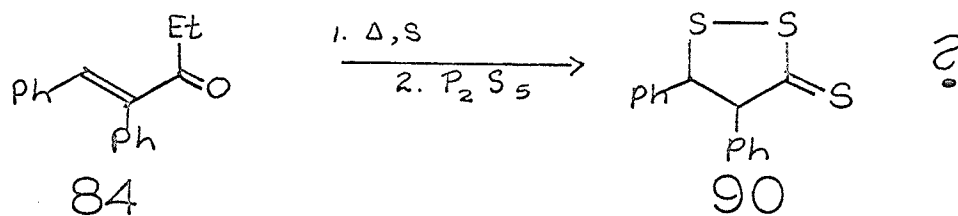
The preparation of 5-phenyl-1,2-dithiol-3-thione involved refluxing ethyl cinnamate with sulfur³⁶ and sulfurization of the 5-phenyl-1,2-dithiol-3-one with phosphorus pentasulfide. It was believed that 4,5-diphenyl-1,2-dithiol-3-thione could be prepared by refluxing ethyl α -phenyl cinnamate with sulfur followed by treatment with phosphorus pentasulfide. However it was found that after an hour and a half of refluxing sulfur and α -phenyl cinnamic ester, tetraphenyl thiophen was obtained instead. (See Figure 12, page 29)

A possible sequence of reactions would be the condensation of two ester molecules to form the tetraphenyl quinone intermediate (85) which may then react with sulfur to form first the 1,4-thiopyranone intermediate which could extrude sulfur to produce tetraphenylcyclopentadieneone (87), which has been reported by Dilthey⁵⁸ to react with sulfur at reflux temperatures to produce tetraphenylthiophen (89). The tetraphenyl quinone may also react with two gram atoms of sulfur to produce the 1,4-dithiin which may lose sulfur at high temperatures to produce the tetraphenylthiophen. It is possible that the increased acidity of the CH-proton due to conjugation between the two phenyl groups through the double bond or the presence of impurities in the starting material may have been responsible for the reaction to have

FIGURE 12

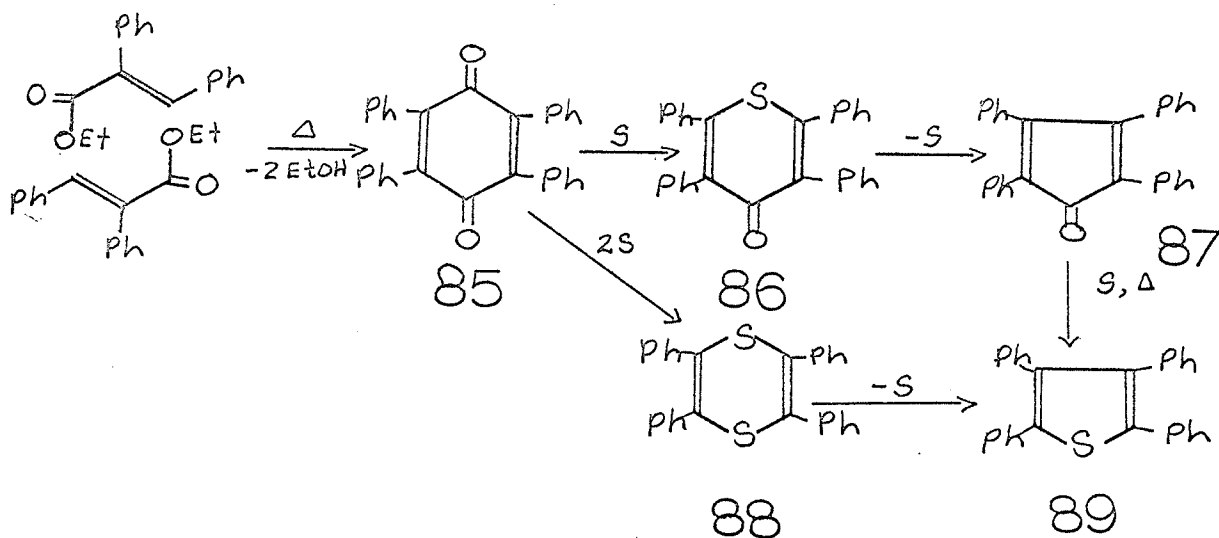


83



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90



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86

87

88

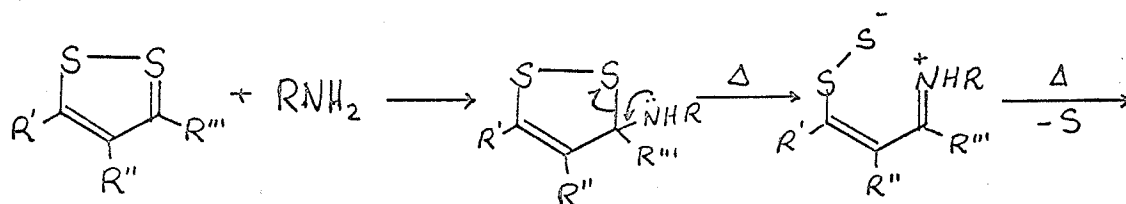
89

proceeded in this unexpected manner. However, a good yield of the desired thione (90) was obtained by the treatment of α -methyl stilbene with sulfur.^{56,57}

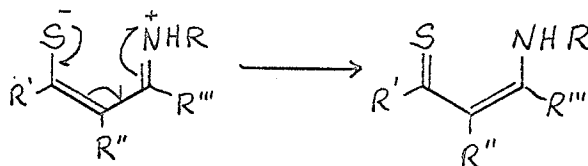
Preparations of 1-arylamino- and 1-alkylamino-prop-1-ene-3-thiones

Aniline and methylamine (the commercial 40% aqueous solution) reacted with 1,2-dithiolium salts (59a, c & d) suspended in ethanol immediately producing a red colored solution with an addition product suspended in it. This involved simple addition of the amine to the 3-position of the 1,2-dithiolium perchlorate with elimination of perchloric acid to produce the intermediate addition product (91, Figure 13). Heating the mixture gently produced a homogeneous red sol-

FIGURE 13



59



82

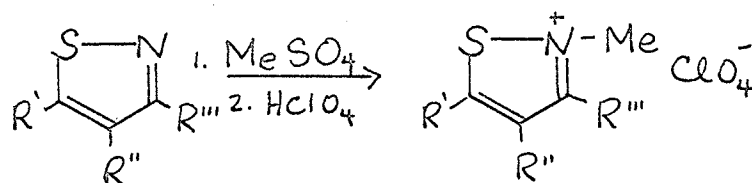
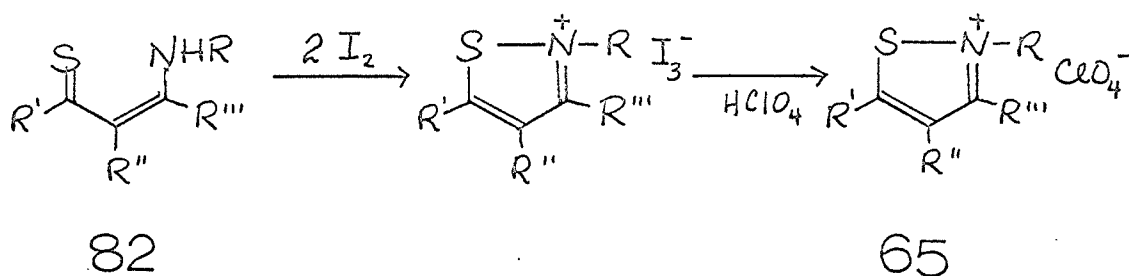
ution which on cooling produced the aminopropene thiones as orange to deep red precipitates as well as a small amount of sulfur which had been extruded during the course of the reaction. Heating the addition product resulted in the opening of the dithiol ring with a non-bonding electron of the nitrogen forming a double bond. Heating the disulfide so produced resulted in the loss of a sulfur atom. Electron rearrangement produced the 1-amino-prop-1-ene-3-thione which was isolated

when the solution was cooled. 4-Methyl-5-phenyl-1,2-dithiolium perchlorate could not be successfully treated with an amine because it decomposed on heating in ethanol. An attempt to perform the reaction in benzene was unsuccessful. Treatment of 3-phenyl-1,2-dithiolium perchlorate with methylamine produced 1-methylamino-3-phenyl-prop-1-ene-3-thione which, because it was unstable, was not analysed but used immediately in the oxidation step to produce 2-methyl-5-phenyl isothiazolium perchlorate (65a). The aminopropenethione from 4,5-diphenyl-1,2-dithiolium perchlorate and aniline could not be obtained when the reaction was done in ethanol and could be obtained as an amorphous red solid in low yield when the reaction was performed in benzene.

Preparations of isothiazolium salts

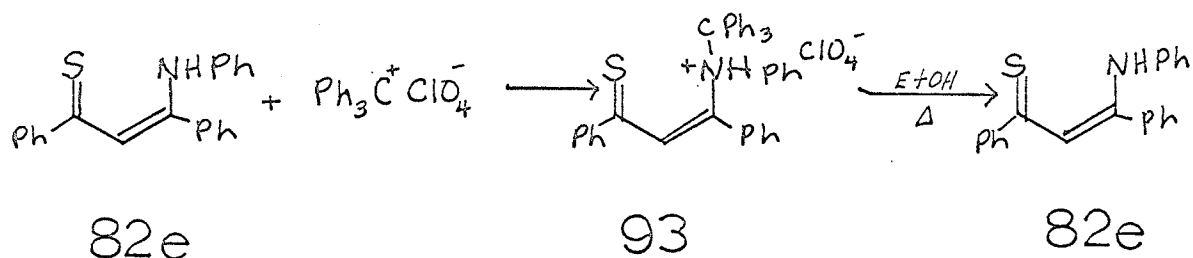
When aminopropenethiones were treated with iodine in hot ethanol, methanol or benzene solution, immediate brown precipitates were formed which analysis showed to be isothiazolium triiodides. Since the propenethione from 4,5-diphenyl-1,2-dithiolium perchlorate was difficult to isolate, the iodine solution was added directly to the solution containing the thione. The conversion of the triiodides to perchlorates was effected by treatment with a nitromethane-perchloric acid solution and dilution with ether to produce isothiazolium perchlorates.

Methylation of 5-phenyl isothiazole by heating with dimethylsulfate gave 2-methyl-5-phenyl isothiazolium methylsulfate which was converted to the perchlorate. This perchlorate had the melting point and infra red spectrum identical with that of the compound produced by oxidation of 1-methylamino-3-phenyl-prop-1-ene-3-thione. This evidence confirmed that the original synthesis had proceeded as had been expected.



Reaction of triphenylmethyl perchlorate with
1-anilino-1,3-diphenyl prop-1-ene-3-thione

Since formally all that is required in the conversion of an aminopropenethione to the isothiazolium salt is the removal of a hydride ion, triphenylmethyl perchlorate (92), a reagent known to abstract hydride ions⁵² would be expected to be a suitable reagent for converting aminopropenethiones directly into the corresponding isothiazolium perchlorates. Mixing 1-anilino-1,3-diphenyl-prop-1-ene-3-thione with trityl perchlorate (92) in acetone gave a color change from red to yellow. Addition of ether produced a cloudiness and eventually a yellow precipitate, the mass spectrum and n.m.r. spectrum of which indicated the presence of ether molecules incorporated in the crystal lattice or in the molecule itself to produce an etherate. Elemental analysis indicated that the compound was not a 1:1 adduct of ether and starting materials. Recrystallization of this compound obtained in acetic acid with some perchloric acid present removed the ether, as shown by the n.m.r. spectrum. Analysis of this recrystallized substance showed it to be the N-tritylated product (93). Boiling compound 93 in ethanol regenerated the 1-anilino-1,3-diphenyl-prop-1-ene-3-thione. This regeneration of the aminopropenethione may be facilitated by the ready loss of the bulky triphenylmethyl cation.

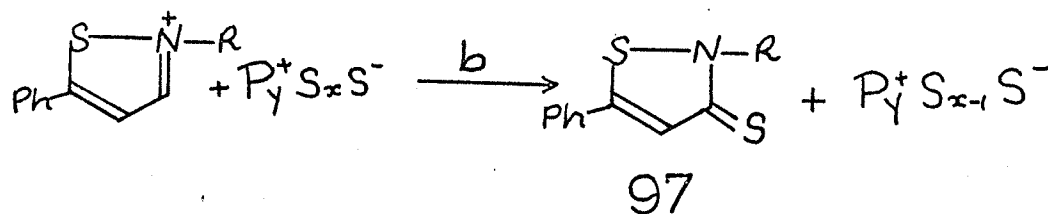
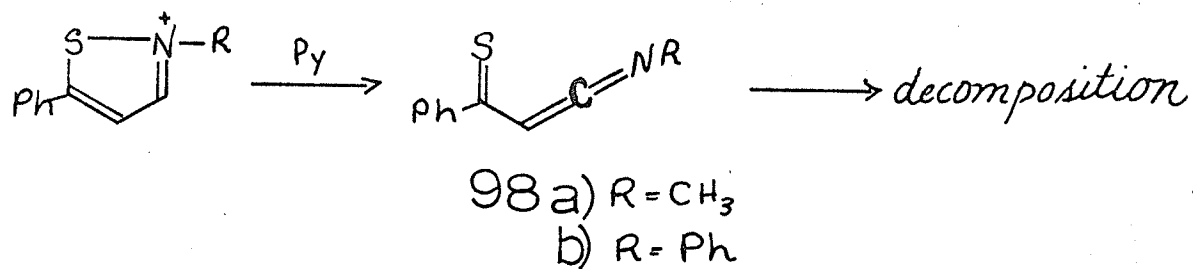
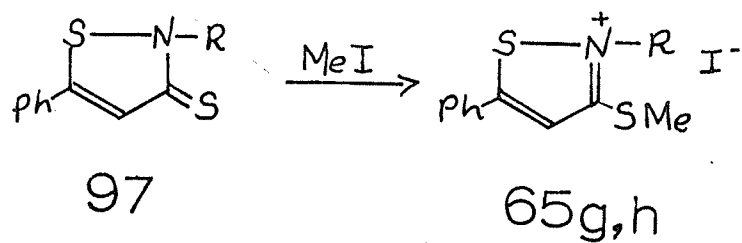
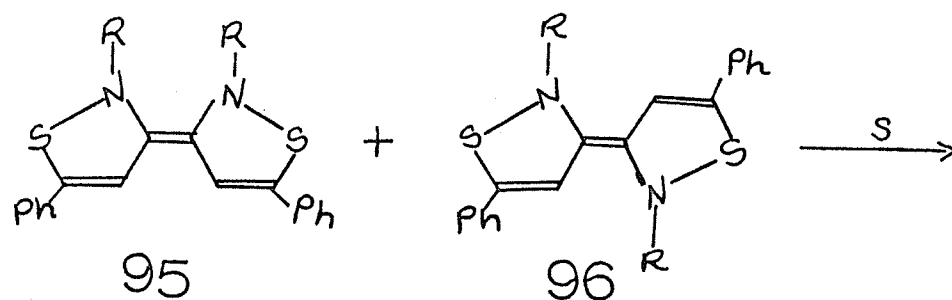
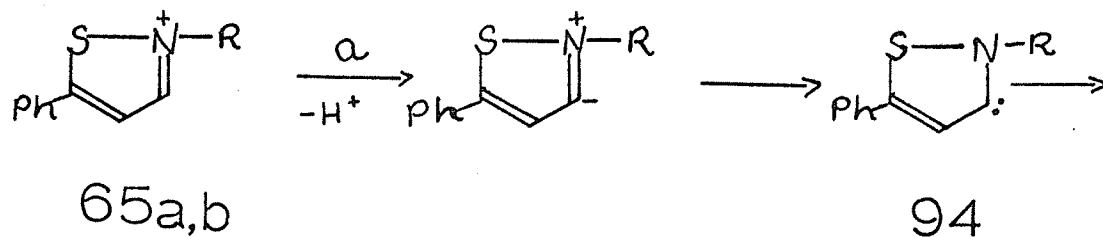


Reaction of isothiazolium salts with sulfur

1,2-dithiolium salts³² unsubstituted in positions adjacent to the sulfur atom and thiazolium salts³⁵ unsubstituted in the 2-position undergo oxidation by sulfur in boiling pyridine to produce the corresponding thiones. Hence it seemed probable that isothiazolium salts unsubstituted in the 3-position would form isothiazole-3-thione under similar conditions. In fact two of the isothiazolium salts studied (65a,b) have produced the corresponding isothiazole-3-thiones (96) which were isolated as their methiodides, formulated as 3-methylthio isothiazolium iodides. Dithiole thiones³² and thiazole thiones³⁵ react similarly with methyl iodide. Alkylation of the sulfur is more likely than alkylation of the nitrogen for several reasons: i) The phenyl or methyl group at the ring nitrogen will provide some steric hindrance for the incoming methyl group ii) The C=S bond is a highly polar bond which would tend to withdraw electrons from the nitrogen, making it less reactive towards methyl iodide. It might be noted that the -N-C=S system is very similar to that of a thioamide. iii) Formation of the methylthio compound restores the aromaticity of the isothiazolium ring.

There are two possible schemes whereby these isothiazole thiones may be evolved. One such scheme (a) would involve the loss of a proton from the 3-position (the 5-position is substituted) to form a carbene (see Figure 14, page 35) which is oxidized by sulfur, possibly after dimerization, to form the thione. Wanzlick³⁵ has shown that certain thiazolium salts lose a proton on treatment with a base to produce a carbene which, following dimerization, was converted to the thiazole-2-thiones.

FIGURE 14



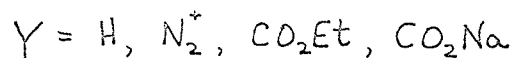
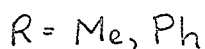
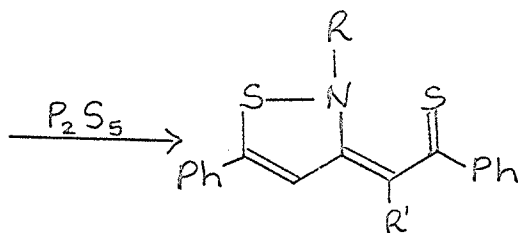
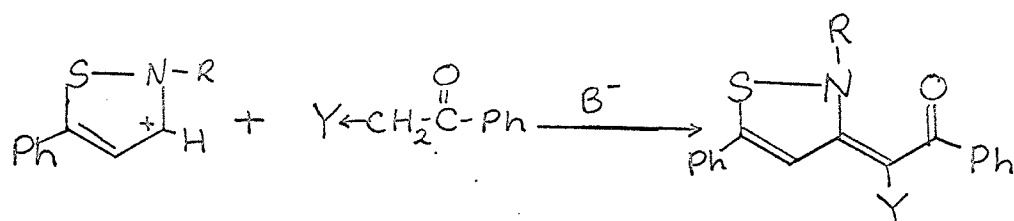
The lower yields of isothiazole-3-thiones as compared with the yields of dithiole-3-thiones and thiazole-2-thiones may be accounted for by the presence of a competing reaction leading to the formation of a thioketimine (98) with ensuing decomposition. It has been shown that isoxazolium salts produce ketoketimines when treated with tertiary amines.⁵⁹ Hence a similar reaction of isothiazolium salts in the presence of pyridine cannot be dismissed.

The other possible mechanism (b, Figure 14) may involve direct nucleophilic attack on the 3-position of the isothiazolium salt by the activated polysulfide anion to produce the isothiazole-3-thione.

Which mechanism is operative (a or b) cannot be decided at this stage because, experimentally, these two mechanisms cannot be distinguished with any certainty. It might be noted here, however, that when isothiazolium salts are placed in pyridine alone, a red to blue solution results immediately. This may be evidence for the formation of a carbene or the highly conjugated dimer, or it may be the manifestation of the formation of the thioketimine.

Reaction of isothiazolium salts with methyl and methylene carbonyls

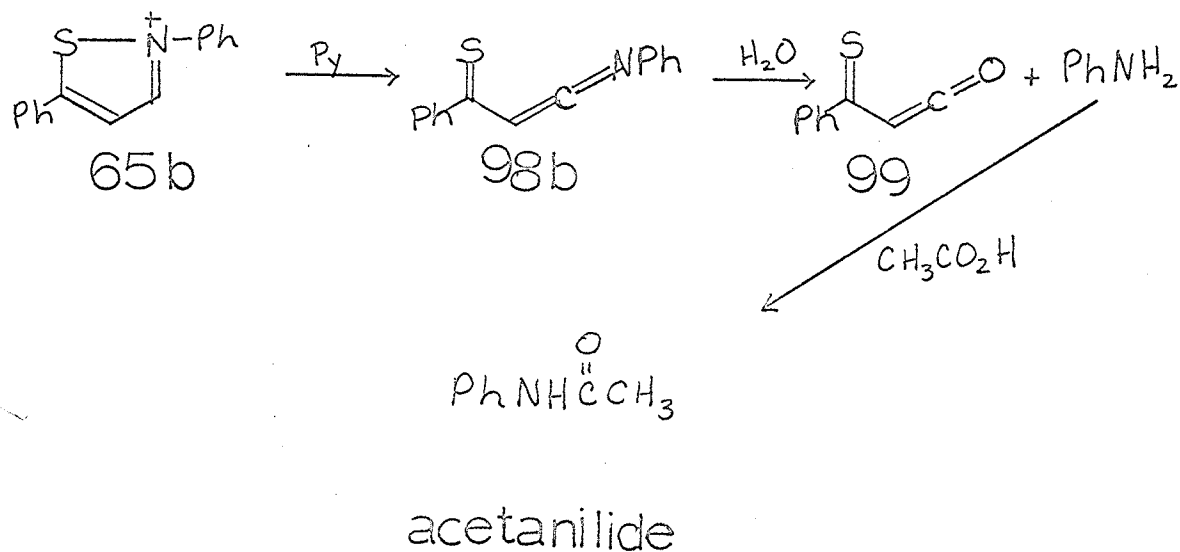
Thiothiophthene derivatives were prepared by the condensation of 4-phenyl- and 3-phenyl-1,2-dithiolium salts with methyl and methylene carbonyls followed by treatment with phosphorus pentasulfide. The latter salt gave poor yields.⁵⁴ It was believed that similar treatment of isothiazolium salts would produce the aza analogues of thiothiophthenes:



Certain isothiazolium salts were treated with acetophenone in refluxing ethanol but only starting materials were obtained. The salts were also treated with diazoacetophenone⁶⁰ in various media - pyridine, triethylamine, quinoline and methylene chloride - but no product was identified.

2,5-diphenyl isothiazolium perchlorate was refluxed with ethyl benzoylacetate in the presence of pyridine with acetic acid as the solvent. One product was isolated by column chromatography. The melting point (113-115° C) and elemental analysis verified that the com-

pound that had been isolated was acetanilide (C_8H_9NO , mp. $114^\circ C.$) This series of reactions could explain its formation - the formation of the thioketimine (98b) by the action of pyridine on the isothiazolium salt (65b), hydrolysis of the thioketimine to form aniline and a ketene (99), and the reaction of aniline so formed with acetic acid which was the solvent.



In a reaction analogous to one done with 1,2-dithiolium salts⁶¹ 2,5-diphenyl isothiazolium perchlorate was heated with sodium benzoyleacetate. No product was obtained.

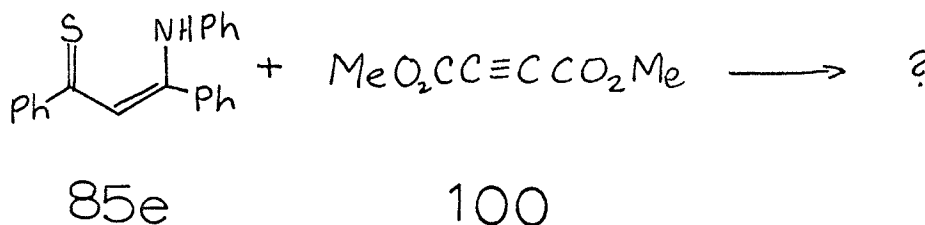
Reaction of 2,5-diphenyl isothiazolium perchlorate
in dimethylformamide with a base

In an attempt to isolate a carbene or dimer from the isothiazolium salt, the salt and dimethylformamide were mixed, producing an immediate red colour. To this mixture triethylamine was added. The solution was not heated but rather kept in the freezer. Particles of non-isolable semi-solid were observed in the oily red mass. An extraction with ether was done after leaving the liquid exposed to the vacuum line for two days. The infra red spectrum of the ether soluble portion indicated a strong peak at 1660 cm^{-1} , indicative of the carbonyl of dimethylformamide or of a C=C stretch of the dimer (which would not be expected to be a strong absorption since the dimer would be symmetrical) and another strong peak indicative of the perchlorate anion (which is not understandable since perchlorates are generally insoluble in ether).

Reaction of an aminopropenethione with a dienophile

An attempt was made to determine whether aminopropenethiones would behave as dienes when subjected to prolonged reflux with a typical dienophile such as acetylene dicarboxylic ester (100). Thus 1-anilino-1,3-diphenyl prop-1-ene-3-thione and dimethyl acetylene dicarboxylate were refluxed for twenty-four hours. A large amount of the thione starting material was obtained. Thin layer chromatography of the solution left after removal of the propenethione revealed the presence of several substances, the major component being isolated. The n.m.r. spectrum of this substance was fairly simple (see Experimental section); the mass spectrum gave m/e 396 as the parent peak and m/e 395 as the base peak (see Experimental section). Even with this information and the infra red spectrum, the substance has yet to be identified.

Refluxing the two starting materials for fifty-six hours gave a smaller amount of the thione starting material. Thin layer chromatography once more showed the presence of several substances, the most abundant one being isolated. The substance obtained was a yellow semi-solid, the n.m.r. and infra red spectrum of which were more complex than those of the substance isolated after twenty-four hours of reflux. This substance was not identified either. (See Experimental section.)



CONCLUSIONS

A general method for the preparation of isothiazolium salts has involved the reaction of various 1,2-dithiolium salts with primary amines followed by ring closure by iodine oxidation of the 1-amino prop-1-ene-3-thiones formed in the reaction. This produced isothiazolium triiodides which were then converted to isothiazolium perchlorates in satisfactory yields.

In the process of devising a general method for the synthesis of isothiazolium salts, two 1,2-dithiolium salts, one aminopropene-thione and seven isothiazolium salts (two of them as the methiodides of isothiazole thiones) that have not appeared in the literature before had been prepared.

All attempts to place an acylidene side-chain at the 3-position of isothiazolium salts unsubstituted in that position in an effort to prepare the aza analogue of the thiothiophthene system have failed.

Because of the low yields of methylthio isothiazolium iodides obtained from the reaction of isothiazolium perchlorates with sulfur in pyridine, it seems that the approach to the preparation of the aza analogue of the thiothiophthene system utilizing the reaction of the methylthio isothiazolium iodide with a methyl or methylene carbonyl should be used only if no other method can be found.



EXPERIMENTAL

CONCLUSIONS

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All melting points given were determined on the Fischer-Johns melting point apparatus and are uncorrected.

Solutions were dried over calcium chloride.

Column chromatography was performed on aluminum oxide made by Camag, 504-C acidic Brockmann No. 808123, obtained from Mondray Ltd., 4180 de Courtrai, Montreal, P.O., Canada

Thin layer chromatography was performed on silica gel DSF-5, made by Camag, obtained from Mondray Ltd., 4180 de Courtrai, Montreal.

Infrared spectra were obtained on a Perkin-Elmer Model 137 Infrared Spectrometer.

The n.m.r. spectra were performed by Mr. Robert Fitch on a Varian A-56/60A spectrometer, using deuterated chloroform (99.8% D) containing tetramethylsilane as the internal standard.

The mass spectra were performed by Mr. Charles Reichert and Mr. Denis Lin on a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

The elemental analyses were done by Alfred Bernhardt, Microanalytical Laboratory, Max Planck Institute, 433 Mülheim (Ruhr), West Germany.

EXPERIMENTAL

EXPERIMENTAL

5-phenyl-1,2-dithiolium perchlorate (59a) was prepared from 5-phenyl-1,2-dithiole-3-thione by oxidation in acetic acid solution with three equivalents of 30% hydrogen peroxide.³⁶

3,5-diphenyl-1,2-dithiolium perchlorate (59d) was prepared by the method of Behringer and Grimm.⁵¹

4-methyl-5-phenyl-1,2-dithiolium perchlorate (59b) was prepared by dissolving 4-methyl-5-phenyl-1,2-dithiole-3-thione (4.4 g.)⁵⁵ in a solution of acetic acid (100 ml.) and 30% hydrogen peroxide (6 ml.). the solution was kept below 30°C. for twenty minutes. Perchloric acid (70%, 1 ml.) was added and the solution then diluted with ether to produce pale yellow crystals of m.p. 159-160°C. (61% yield). Analysis found C, 40.90; H, 2.91; S, 22.04; Cl, 12.91; $C_{10}H_9S_2ClO_4$ requires C, 41.03; H, 3.08; S, 21.88; Cl, 12.12.

4,5-diphenyl-1,2-dithiolium perchlorate (59c) was prepared by the oxidation of 4,5-diphenyl-1,2-dithiole-3-thione^{56,57} using peracetic acid according to the method described in the above preparation. Lemon yellow needles of m.p. 230-231.5°C. were formed in 67% yield. Analysis found C, 50.90; H, 3.51; S, 17.69; Cl, 9.70; $C_{15}H_{11}S_2ClO_4$ requires C, 50.78; H, 3.10; S, 18.06; Cl, 10.00.

Tetraphenyl thiophen

Ethyl α -phenyl cinnamate (50 g) and sulfur (9 g.) were heated to 280°C. then allowed to remain at 210°C. for a total heating time of thirty minutes. Starting materials were obtained. The unreacted ester was further heated with sulfur (7g.) for an

hour and a half. Ethanol was added to the dark solution and the mixture heated: a dark oil was formed at the bottom of the flask. The ethanol was decanted and cooled, producing white crystals, m.p. 186-188°C. (ethanol). The dark oil was dissolved in benzene and left to cool overnight. Crystals were obtained and were found to be a mixture of sulfur (soluble in boiling ethanol) and some white crystals (only sparingly soluble in boiling ethanol). These white crystals were dissolved by heating in benzene. Addition of ethanol to the hot benzene solution produced white crystals m.p. 183-184°C. Recrystallization from benzene alone gave crystals of m.p. 190°C., from nitromethane, 187.5-188.5°C., and from an ethanol/benzene solution m.p. 183-184°C. Elemental analysis by fusion with sodium metal was positive for sulfur. According to the literature,⁶² tetraphenyl thiophen melts at 184-185°C. Warming the white crystals in acetic acid solution with hydrogen peroxide⁶³ gave a yellow compound of m.p. 265-270°C. Tetraphenyl thiophen-S,S-dioxide melts at 265°C.⁶³

1-alkylamino and 1-arylamino prop-1-ene-3-thiones (82)

General Method:

The 1,2-dithiolium salts (0.5 g.) suspended in a small quantity of ethanol (7 ml.) were treated with a slight excess of the primary amines (0.5 ml. aniline or 1.0 ml. commercial 40% aqueous methylamine solution were used). The mixture was heated gently until homogeneous and allowed to cool. The thione precipitated was crystallized from ethanol.

1-methylamino-3-phenyl prop-1-ene-3-thione (82a) was obtained from

3-phenyl-1,2-dithiolium perchlorate and methylamine. However,

this compound was quite unstable and in most cases was used immediately in the next step for the preparation of the isothiazolium salt, viz. oxidation with iodine solution. In one case the thione was collected to give a yield of 0.22g., 64% . Due to the rather rapid decomposition of the propenethione the melting point was not taken, nor was the elemental analysis performed.

1-anilino-3-phenyl prop-1-ene-3-thione (82b) was obtained from the reaction of 3-phenyl-1,2-dithiolium perchlorate with aniline.

The yield was 0.33 g., 77%; m.p. 105°C.: literature m.p. 105.5°C.⁵⁰

1-anilino-2,3-diphenyl prop-1-ene-3-thione (82c)

The treatment of 4,5-diphenyl-1,2-dithiolium perchlorate in hot ethanol with aniline produced no crystals on cooling. The dithiolium salt (0.25 g.) was heated in a mixture of aniline (1½ ml.) and benzene (1½ ml.) for 5 minutes. Cooling overnight produced no crystals. Petroleum ether was added to the thick red solution, stirred in, then decanted. This was repeated several times until a red amorphous solid was formed. This solid was not analyzed but rather used in the next step immediately to produce the isothiazolium triiodide. In most cases, however, the thione was not isolated but oxidized as it was formed in the benzene/aniline solution.

1-methylamino-1,3-diphenyl prop-1-ene-3-thione (82d) was prepared

from 3,5-diphenyl-1,2-dithiolium perchlorate and methylamine.

The yield was 0.2 g., 56%; melting point was 83-84°C. Analysis found C, 75.81; H, 5.96; N, 12.73; S, 5.53: $C_{16}H_{15}NS$ requires C, 75.85; H, 5.97; N, 12.62; S, 5.52.

1-anilino-1,3-diphenyl prop-1-ene-3-thione (82e) was prepared from 3,5-diphenyl-1,2-dithiolium perchlorate and aniline. The yield was 0.32 grams, 72%; m.p. 156-158°C.; literature m.p. was given as 158°C.⁵⁰

1-anilino-2-methyl-3-phenyl prop-1-ene-3-thione could not be obtained by the reaction of 4,5-diphenyl-1,2-dithiolium perchlorate with aniline in ethanol because simply heating the salt in ethanol led to its decomposition. Replacing ethanol with benzene did not lead to the formation of the thione either on addition of aniline.

Isothiazolium salts

A. By oxidation of 1-aminoprop-1-ene-3-thiones

The thione was dissolved in the minimum quantity of hot ethanol. The solution was heated and to it was added a saturated ethanolic iodine solution (methanolic and benzene-iodine solutions were also used) until precipitation was complete. The brown precipitate was recrystallised from nitromethane. One of the isothiazolium salts obtained in this manner was identified as the stable isothiazolium triiodide (65f). The triiodides were generally converted to the perchlorates by heating with a minimum amount of nitromethane/perchloric acid solution (20/1) in a steam bath or over a gentle flame. Pouring the warm solution into ether afforded the required isothiazolium salts.

The percent yields quoted were calculated as the overall percentage yield from the 1,2-dithiolium salts, which were the starting materials.

2-methyl-5-phenyl isothiazolium perchlorate (65a)

Yield - 19%; m.p. 144-145°C.; color - tan

Analysis found C, 43.73; H, 3.70; N, 4.92; S, 11.55; Cl, 12.75:

$C_{10}H_{10}NSClO_4$ requires C, 43.65; H, 3.63; N, 5.08; S, 11.99;
Cl, 12.87.

2.5-diphenyl isothiazolium perchlorate (65b)

Yield - 59%; m.p. 194-196°C.; color - orangish-brown

Analysis found C, 54.63; H, 3.70; N, 3.69; S, 9.25; Cl, 9.88:

$C_{15}H_{12}NSClO_4$ requires C, 53.40; H, 3.56; N 4.15; S, 9.48; Cl, 10.50.

2,4,5-triphenyl isothiazolium perchlorate (65c)

Yield - 51% ; m.p. 208°C.; color - yellow

Analysis found C, 60.84; H, 3.98; N, 3.38; S, 7.82; Cl, 8.48:

$C_{21}H_{16}NSClO_4$ requires C, 60.94; H, 3.90; N, 3.38; S, 7.74; Cl, 8.67.

2-methyl-3,5-diphenyl isothiazolium perchlorate (65d)

Yield - 40%; m.p. 162-163°C.; color - tan

Analysis found C, 54.95; H, 4.05; N, 3.76; S, 11.28; Cl, 9.37:

$C_{16}H_{14}NSClO_4$ requires C, 54.70; H, 4.02; N, 3.98; S, 9.18; Cl, 10.11.

2,3,5-triphenyl isothiazolium perchlorate (65e)

Yield - 53%; m.p. 250-253; color- yellow

Analysis found C, 61.03; H, 3.94; N, 3.25; S, 7.88; Cl, 8.49:

$C_{21}H_{16}NSClO_4$ requires C, 60.94; H, 3.90; N, 3.38; S, 7.74; Cl, 8.67.

2-methyl-3,5-diphenyl isothiazolium triiodide

Yield - 45%; m.p. 150-151 color - brown

Analysis found C, 30.22; H, 2.18; N, 2.09; S, 5.09; I, 60.24:

$C_{16}H_{14}NSI_3$ requires C, 30.44; H, 2.23; N, 2.21; S, 5.07; I, 60.05.

B. By methylation of 5-phenyl isothiazole

5-phenyl isothiazole (0.5 g.) and dimethyl sulfate (1 ml.) were heated at 100°C. for two hours. Dilution of the solution with ether afforded an oily precipitate which was crystallized from acetic acid containing a few drops of 70% perchloric acid. Dilution with ether gave 2-methyl-5-phenyl isothiazolium perchlorate as light tan plates, mp.p. 144-145°C., in 40% yield. The infrared spectrum and melting point were identical with those of the compound prepared by method A.

Reaction of isothiazolium salts and sulfur in pyridine

The isothiazolium salt (65a or 65b) (1.0 g.) was slowly added to a saturated solution of sulfur in boiling pyridine (10 ml.). The mixture became deep red in color and was refluxed half an hour. Dilution with water gave precipitates which on ether extraction and evaporation produced a brown pasty solid. The crude isothiazole-3-thione was dissolved in methyl iodide and after twenty-four hours a yellow solid was filtered off and recrystallized from nitromethane.

2-methyl-3-methylthio-5-phenyl isothiazolium iodide (65g)

Yield - 42%; m.p. 162-163 with decomposition

Analysis found C, 37.72; H, 3.58; N, 4.04; S, 18.50; I, 36.15:

$C_{11}H_{12}NS_2I$ requires C, 37.65; H, 3.44; N, 4.02; S, 18.38; I, 36.15.

2,5-diphenyl-3-methylthio isothiazolium iodide (65h)

Yield - 23% m.p. 211-214 with decomposition

Analysis found C, 45.47; H, 3.42; N, 3.34; S, 16.20; I, 32.11:

$C_{16}H_{14}NS_2I$ requires C, 46.50; H, 3.39; N, 3.39; S, 15.64; I, 30.08.

Reaction of 2-methyl-5-phenyl isothiazolium perchlorate (65a) with acetophenone

2-methyl-5-phenyl isothiazolium perchlorate (0.9 g.) and acetophenone (0.4 ml.) were refluxed in ethanol (12.5 ml.) for two hours then cooled. The crystals formed were found to be starting material.

Reaction of 2,5-diphenyl isothiazolium perchlorate (65b) with diazoacetophenone⁶⁰ in pyridine.

2,5-diphenyl isothiazolium perchlorate (0.2 g.) and diazoacetophenone (0.1 g) were mixed, pyridine (5 ml.) was added and the mixture was heated over a flame until the solution turned reddish. Water was added and the aqueous solution was extracted with benzene which was dried and then removed under reduced pressure to leave a deep reddish brown oil. Chromatography produced four bands - yellow, orange, colorless and brown. The yellow band produced a yellow oil with a smell reminiscent of a cinnamate which disappeared on standing for a week. The infrared spectrum of the oil in methylene chloride had peaks at 2900, 2840, 1730, 1650, 1610, 1590, 1580, 1540, 1500, 1315, 1205, 1175, 1095, 1020 and 867 cm^{-1} . After standing for a week, the same peaks were still present except that the peaks 1730-1175 cm^{-1} and 867 cm^{-1} had greatly diminished relative to the peaks at 2900, 2840, 1095, and 1020 cm^{-1} .

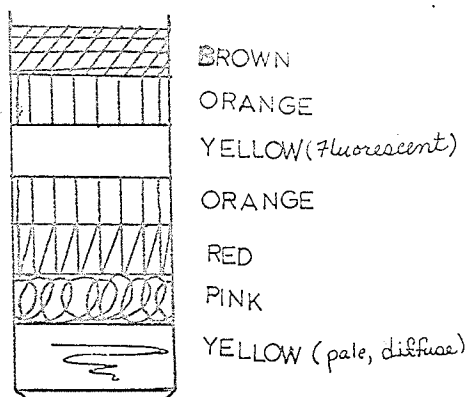
in triethylamine

The salt (0.5 g.) and diazoacetophenone (0.2 g.) were heated with triethylamine (10 ml.) to produce a red oil. An infrared spectrum of this oil showed peaks at 3080, 3000, 2140, 1630 ,

1605, 1585, 1500, 1475, 1400, 1380, 1370, 1110, 938, 840, 812, 794, 769, and 705 cm^{-1} . The peak at 2140 cm^{-1} indicated the presence of unreacted diazoacetophenone. Addition of water followed by extraction with benzene resulted in the collection of a precipitate at the interface of the two layers. This precipitate was found to be unreacted 2,5-diphenyl isothiazolium perchlorate.

in quinoline

The salt (0.4 g), diazoacetophenone (0.2 g.) and quinoline (10 ml.) were heated to boiling. The solution had turned red immediately. Cooling produced no crystals, just a brown solution. An infrared spectrum of this red solution showed that diazoacetophenone was no longer present. Dilute hydrochloric acid was added to the solution which was then extracted with benzene. After drying, the benzene was removed under reduced pressure, leaving a brown oil. An infrared spectrum of this brown oil showed these peaks: 3300, 3010, 2900, 1690, 1640, 1610, 1575, 1550, 1535, 1500, 1480, 1450, 1360, 1350, 1320, 1270, 1180, 1155, 1105, 1075, 1030, 1005, 960, 934, 910, 762 and 690 cm^{-1} . The red oil was then chromatographed on an alumina column. The bands appeared as in the diagram below.



The infrared spectrum of the fluorescent yellow band had peaks at 3660, 2910, 2860, 1730, 1635, 1610, 1580, 1500, 1420, 1350, 1310, 1300, 1245, 1180, 1140, 1080, 1070, 1030, 895, 868 and 822 cm^{-1} (methylene chloride.)

The infrared spectrum of the red layer showed peaks at 3650, 3590, 2890, 1730, 1640, 1610, 1580, 1525, 1500, 1280, 1240, 1060, 1030 and 868 cm^{-1} (done in methylene chloride).

in methylene chloride with pyridine

The salt (0.5 g.), diazoacetophenone (0.15 g.) sodium carbonate (0.20 g.) methylene chloride (20 ml.) and pyridine (1 ml.) were refluxed for twenty-four hours after which time the solution had become a brown color, The solid remaining was filtered off and found to be 2,5-diphenyl isothiazolium perchlorate, starting material. The solution was washed with water then dried. The methylene chloride was removed under reduced pressure, leaving a liquid (pyridine) with yellow crystals in it (diazoacetophenone). No other product could be obtained pure.

Reaction of 2,5-diphenyl isothiazolium perchlorate with ethyl benzovlacetate

The salt (0.85 g.), ethyl benzovlacetate (1.0 g.) and pyridine (0.4 ml.) were refluxed in glacial acetic acid (19 ml.) for fifteen hours. A vacuum of 4-5 mm. was used in removal of the liquid, leaving a solid residue. Benzene dissolved some of the material, leaving an insoluble red solid. Recrystallized in ethanol, the solid was light brown in colour with a melting point range of 264-280°C. The infrared spectrum of this solid in nujol indicated peaks at 3200, 3100, 3040, 1635, 1610, 1530, 1480, 1335, 1255, 1175, 1100, 1050, 1030, 1000, 750 and 678 cm^{-1} in additioon to those of nujol. The strong peak at 1100 cm^{-1} indicated the presence of a perchlorate salt. It was not starting material, which has a melting point of 194-196°C.

The benzene solution was chromatographed on alumina to produce three bands. The first had no visible color, the second was yellow and the third was brown. The first portion produced a solid m.p. 113-115°C. with a pleasant odour. Chemical and elemental analysis showed this compound to be C_8H_9NO , acetanilide, m.p. 114°C.

Reaction of 2,5-diphenyl isothiazolium perchlorate and sodium benzoylacetate

Benzoylacetic acid (0.04 g.) with sodium (0.006 g.) in ethanol (4 ml.) was heated with the salt (0.09 g.) until the solution was homogeneous. No product was isolated.

Reaction of 2,5-diphenyl isothiazolium perchlorate with dimethylformamide.

An immediate red color was formed when the salt (0.06 g.) and absolute dimethylformamide (1 ml.) were mixed. To this solution triethylamine (0.4 ml.) was added. The solution was kept overnight at a temperature of -20°C. Semi-solid particles had formed in the thick red liquid. The solution was then left connected loosely to the vacuum line for two days to produce a dark red mass. Some of the material dissolved in ether, the remainder was found to be triethylamine perchlorate. The ether was removed under reduced pressure, leaving a red paste whose infrared spectrum in methylene chloride showed peaks at 2810, 2590, 1660, 1580, 1475, 1400, 1100, 1075, 1030 cm^{-1} . The peak at 1100 cm^{-1} (strong) indicated the presence of a perchlorate anion. A perchlorate salt is not usually soluble in ether.

Reaction of triphenylmethyl perchlorate and 1-anilino-1,3-diphenyl prop-1-ene-3-thione (82e)

The propenethione (0.2 g.) in acetone (10 ml.) was stirred with a slight excess of triphenylmethyl perchlorate. The red solution became yellow in a few minutes. Dilution with ether produced yellow crystals m.p. 189°C . whose n.m.r. spectrum and mass spectrum indicated the presence of several ether molecules incorporated into the crystals. Recrystallization from acetic acid containing a drop of perchloric acid gave the N-tritylated 1-anilino-1,3-diphenyl prop-1-ene-3-thione, m.p. $188-190^{\circ}\text{C}$. (79%) Analysis found C, 71.30; H, 4.91; N, 2.21; S, 4.76; Cl, 5.04: $\text{C}_{40}\text{H}_{32}\text{NSClO}_4$ requires C, 72.4; H, 4.96; N, 2.16; S, 4.98; Cl, 5.49.

Reaction of N-triphenylmethyl perchlorate of 1-anilino-1,3-diphenyl prop-1-ene-3-thione with ethanol

The yellow perchlorate salt (0.4 g.) dissolved in ethanol (2 ml.) was heated gently for two minutes. The solution had gradually become a deep red color. On cooling, 1-anilino-1,3-diphenyl prop-1-ene-3-thione m.p. 158°C . was precipitated.

Reaction of 1-anilino-1,3-diphenyl prop-1-ene-3-thione and dimethyl acetylene dicarboxylate

The thione (1 g.) and acetylene dicarboxylate (1 ml.) were refluxed for twenty-four hours. A portion of the solution was then removed and chromatographed on alumina in benzene. The red thione was present in relatively large quantity. A yellow and an orange band were collected together. Removal of the solvent by reduced pressure followed by thin layer chromatography revealed several different substances. The substance in the

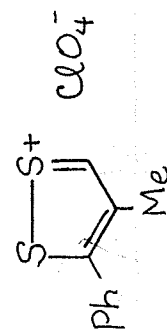
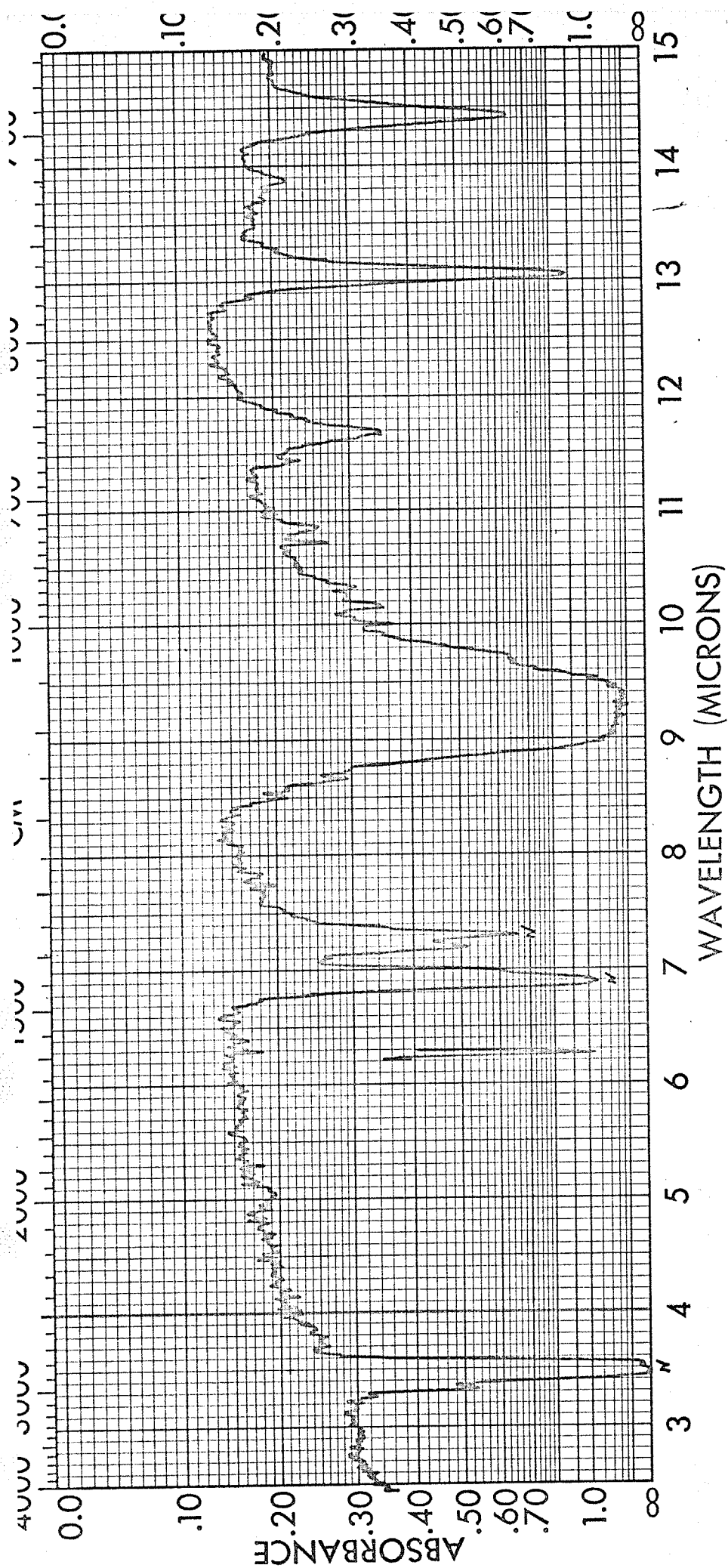
major band was isolated. Peaks in the infrared spectrum occurred at 3690, 3610, 2940, 1740, 1620, 1600, 1580, 1535, 1500, 1380, 1300, 1230, 1130, 1075, 1060, 865 and 860 cm^{-1} (in methylene chloride). The mass spectrum of this yellow solid, m.p. around $85^{\circ}\text{C}.$, showed the following m/e peaks (followed by per cent of peak height relative to base peak height.) Peaks under 10% have been omitted, except for the first one.

398(9.0), 397(28.2), 396(91.7), 395(100) 366(11.1), 339(12.5), 191(16.0), 164(11.1), 163(75.0), 161(17.4), 149(25.7), 121(15.3), 111(10.0), 109(10.0), 105(25.0), 97(14.6), 95(14.6), 91(24.3), 85(15.3), 83(21.5), 82(10.0), 81(11.4), 77(36.8), 71(19.4), 69(22.2), 57(29.2), 55(22.9), 45(16.7), 44(11.1), 43(31.3), 41(15.3), 29(13.2), 28(16.0)

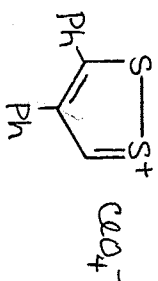
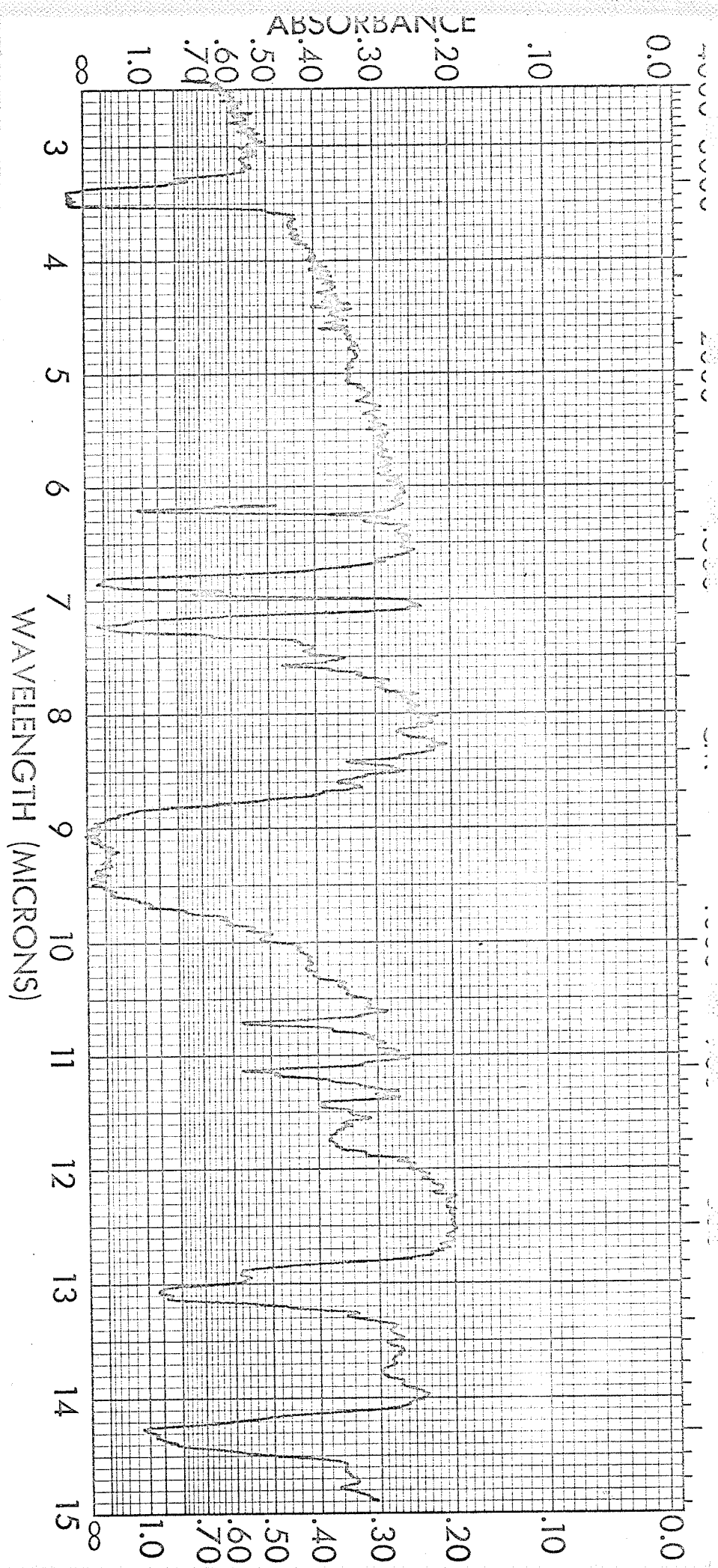
The remaining portion of the solution was allowed to reflux a further twenty-four hours. The solution was treated in a manner similar to the first, the major component being isolated from the TLC plate. The substance was a very thick yellow liquid. The infrared spectrum of this substance in methylene chloride revealed the following peaks: 3020, 2960, 2925, 2860, 1970, 1760, 1748, 1735, 1725, 1705, 1675, 1665, 1610, 1590, 1550, 1545, 1530, 1515, 1500, 1460, 1390, 1355, 1330, 1310, 1225, 1205, 1170, 1120, 1100, 1090, 1075, 1035, 1020, 1015, 1010, 963 and 962 cm^{-1}

The n.m.r. spectrum of the first compound obtained -the yellow solid-consisted of two singlets, one at $\tau=2.78$ and the other at $\tau=6.27$. The n.m.r. spectrum of the second substance was too complicated to be interpreted satisfactorily.

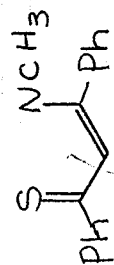
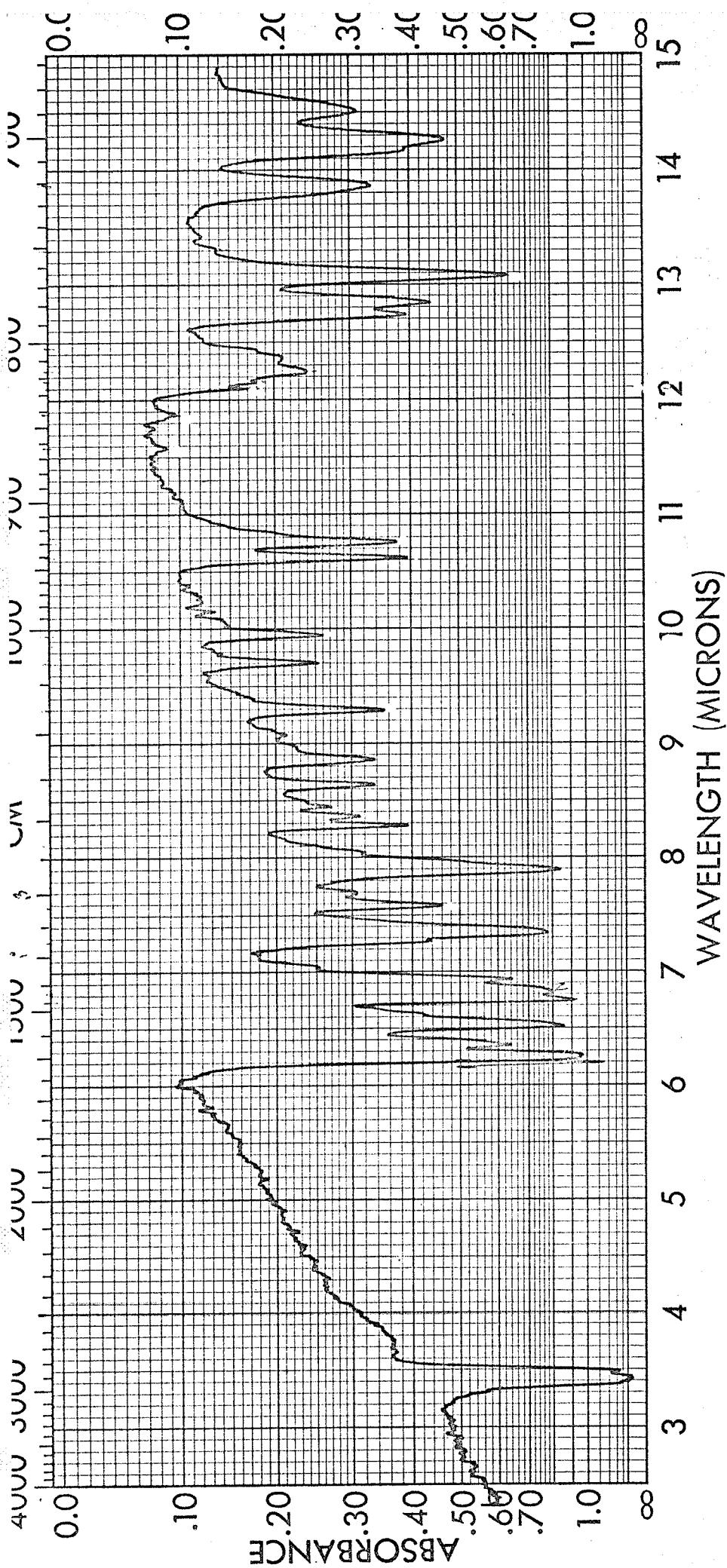
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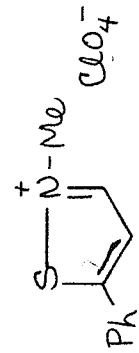
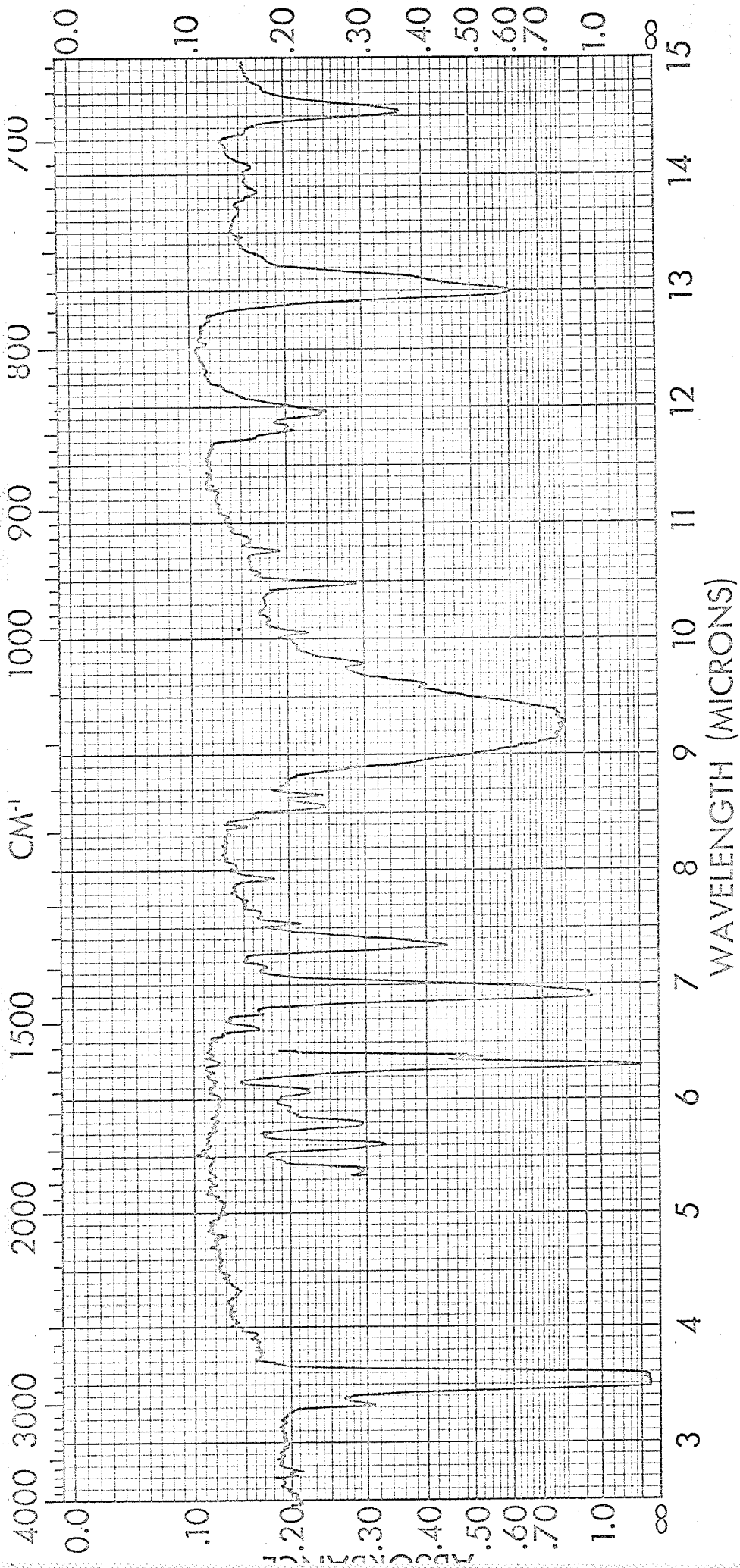
59b



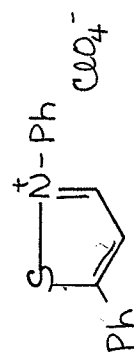
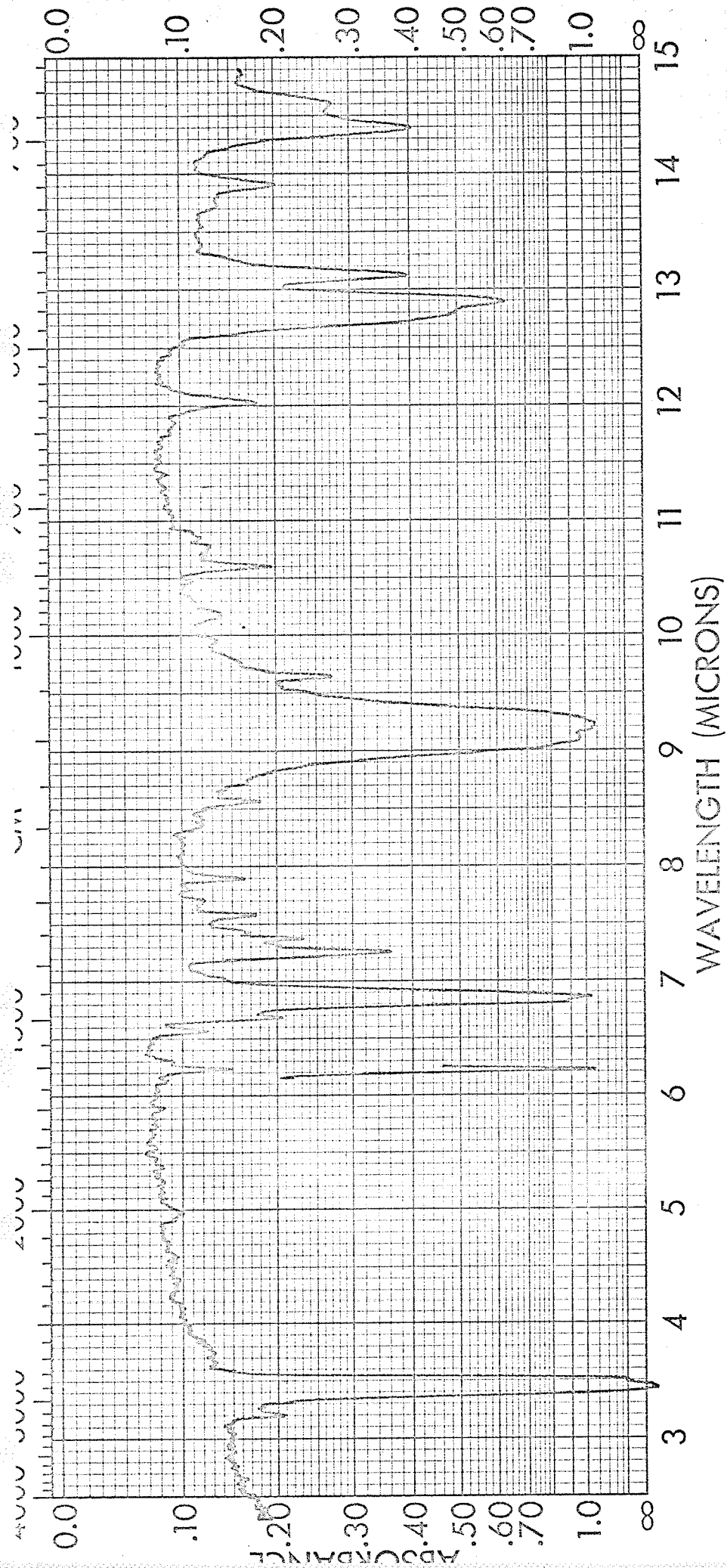
59c



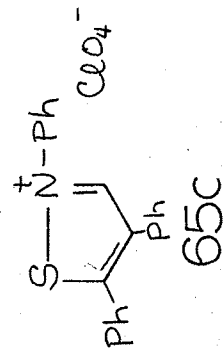
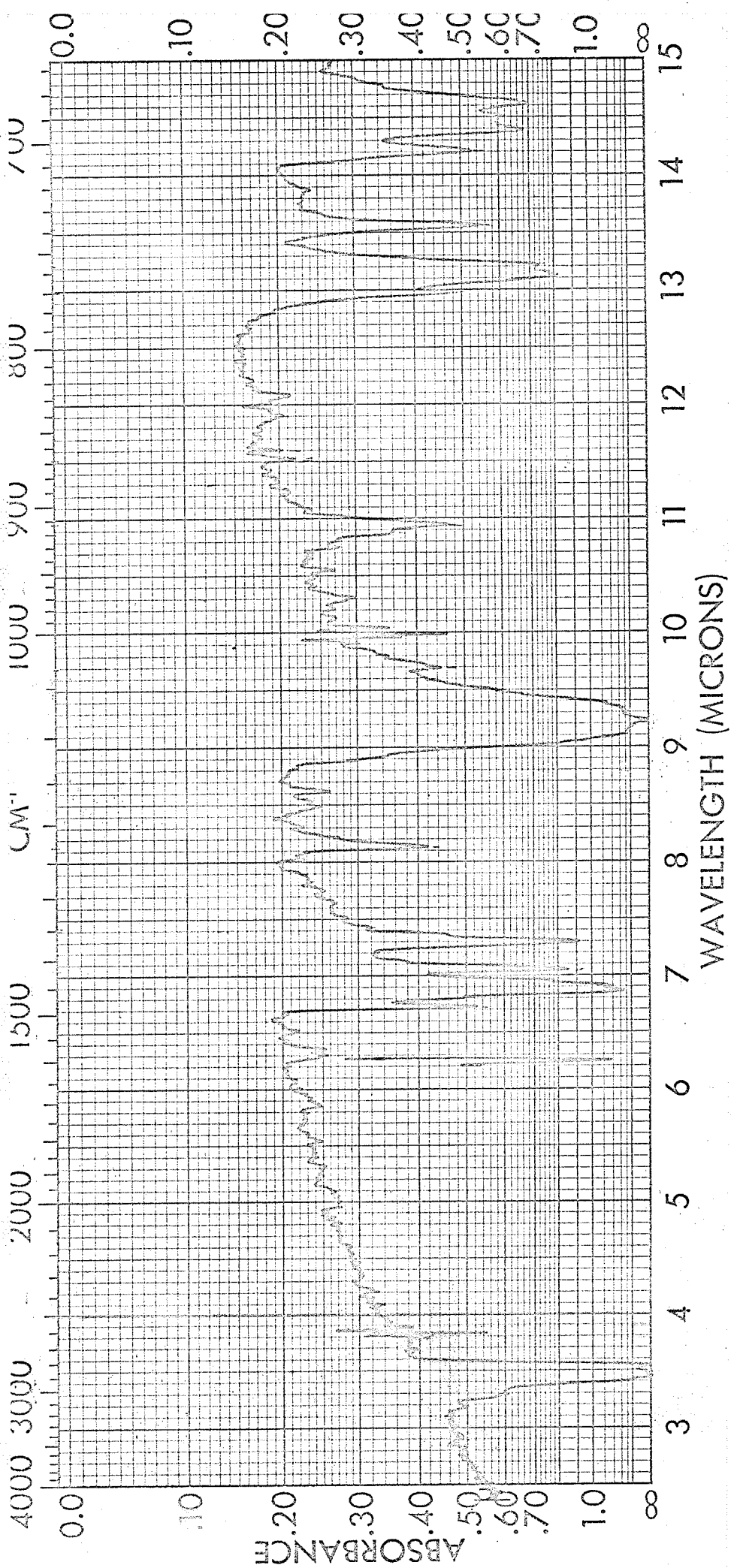
82d

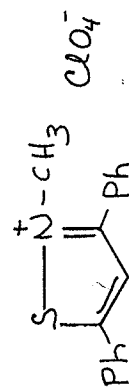
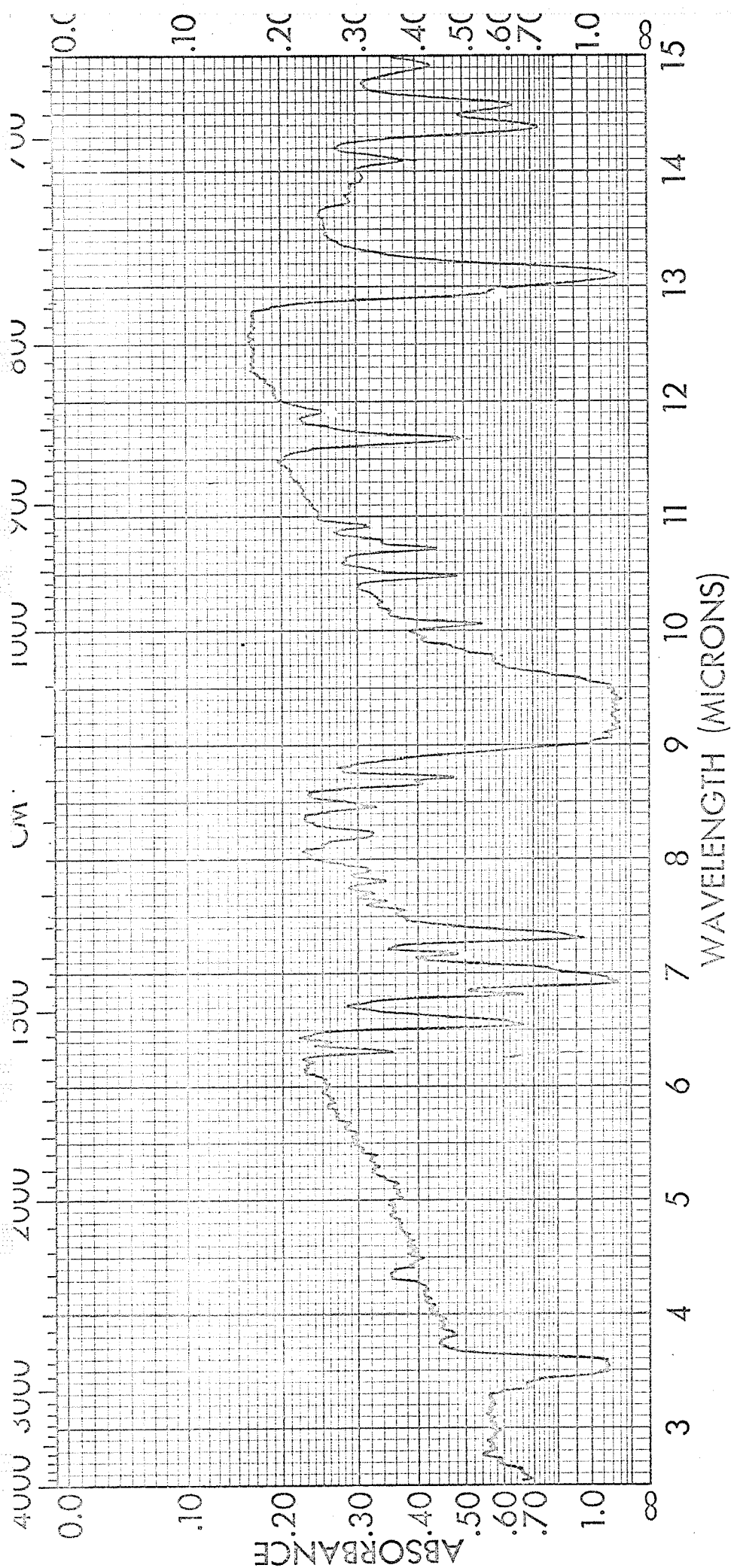


65a

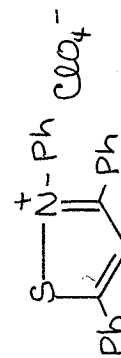
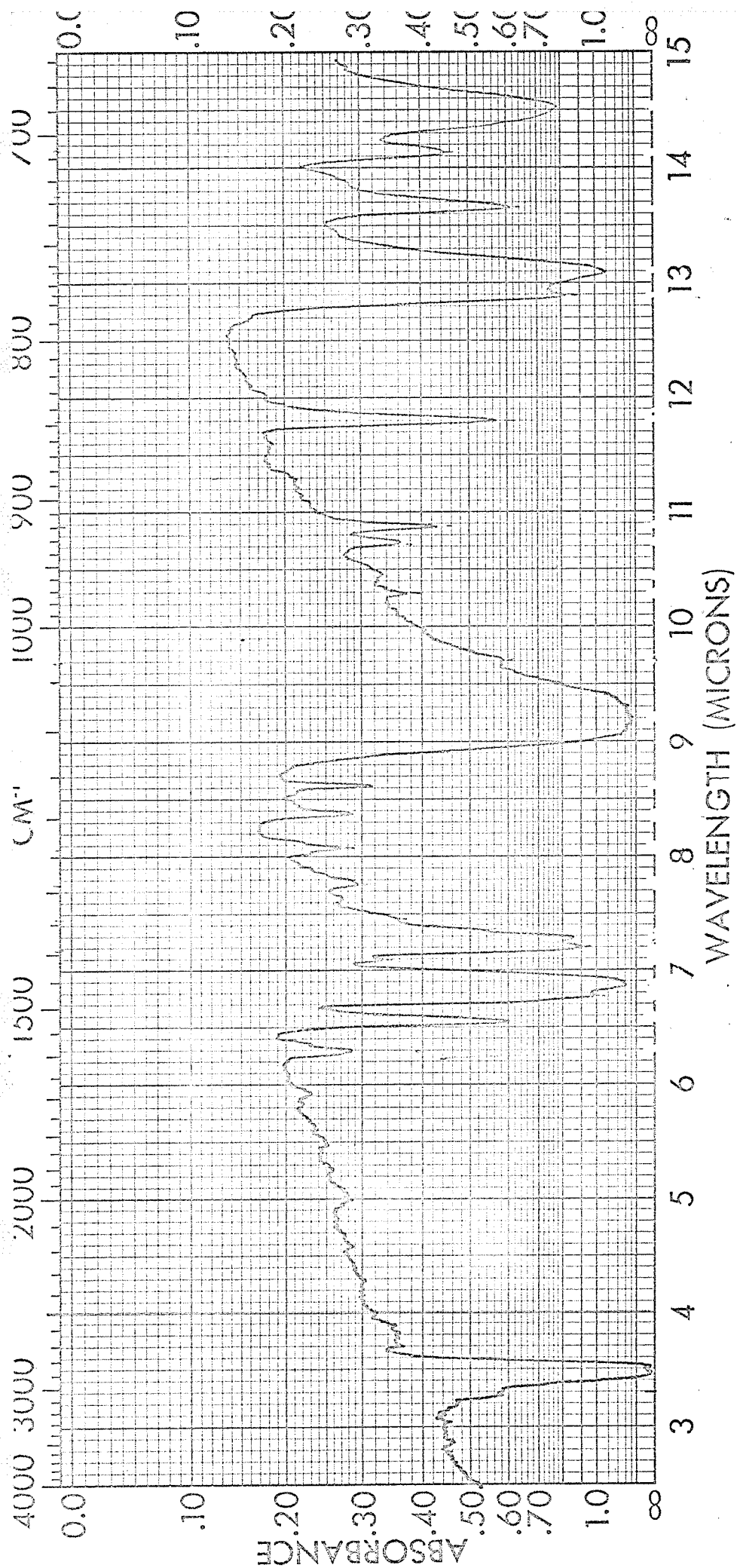


65b

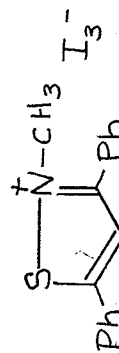
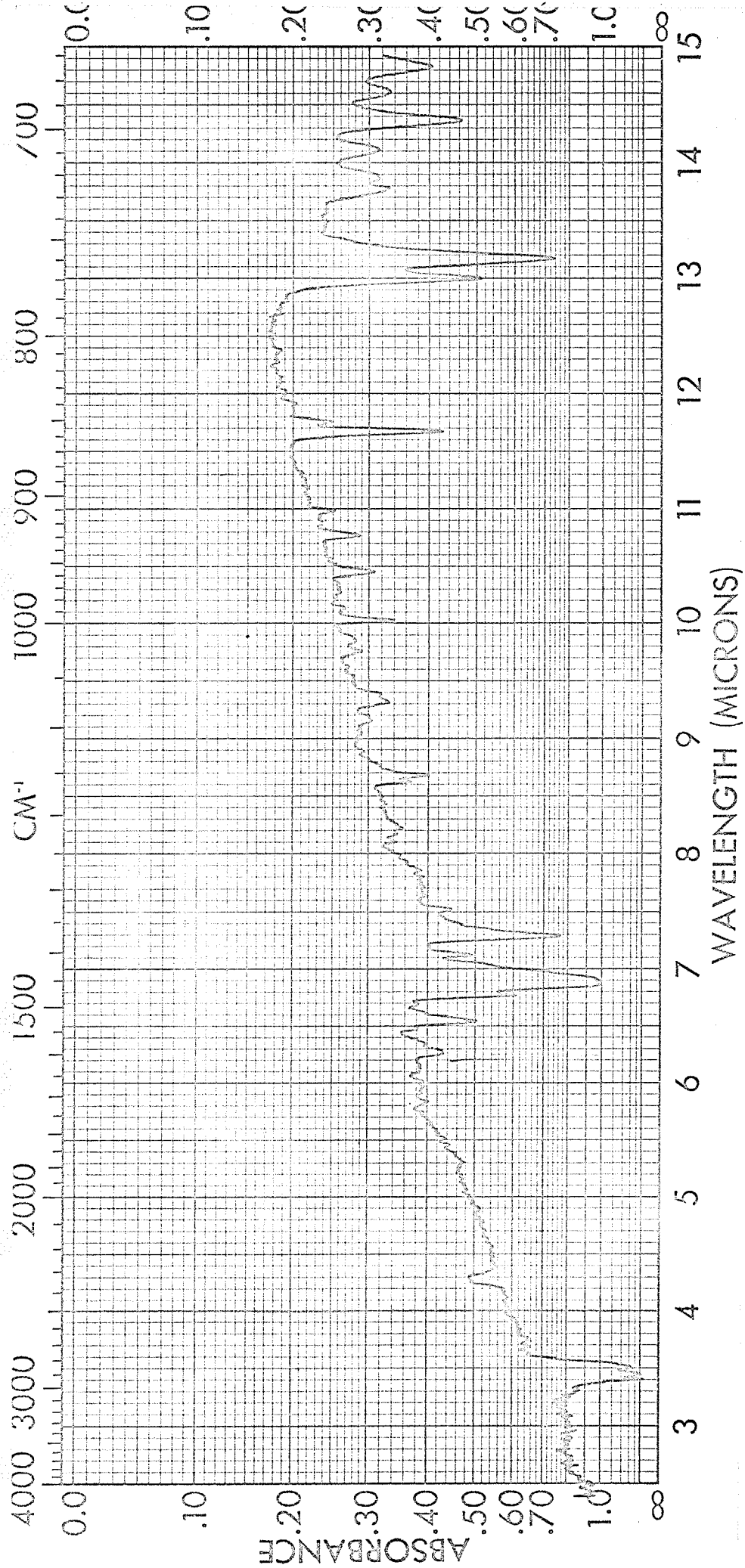




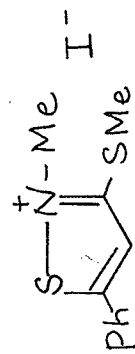
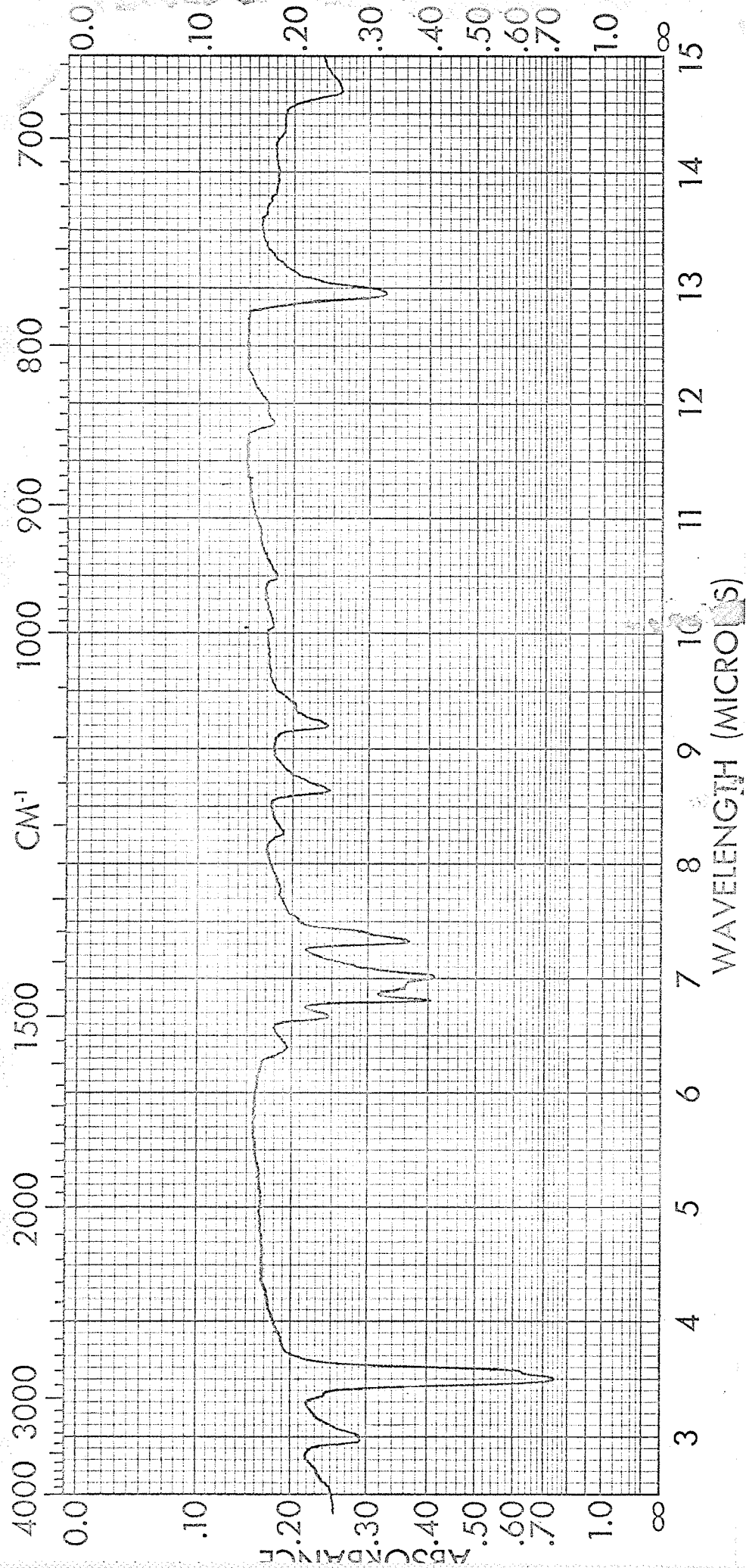
65d



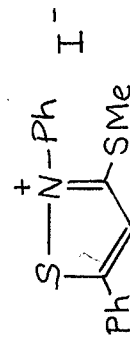
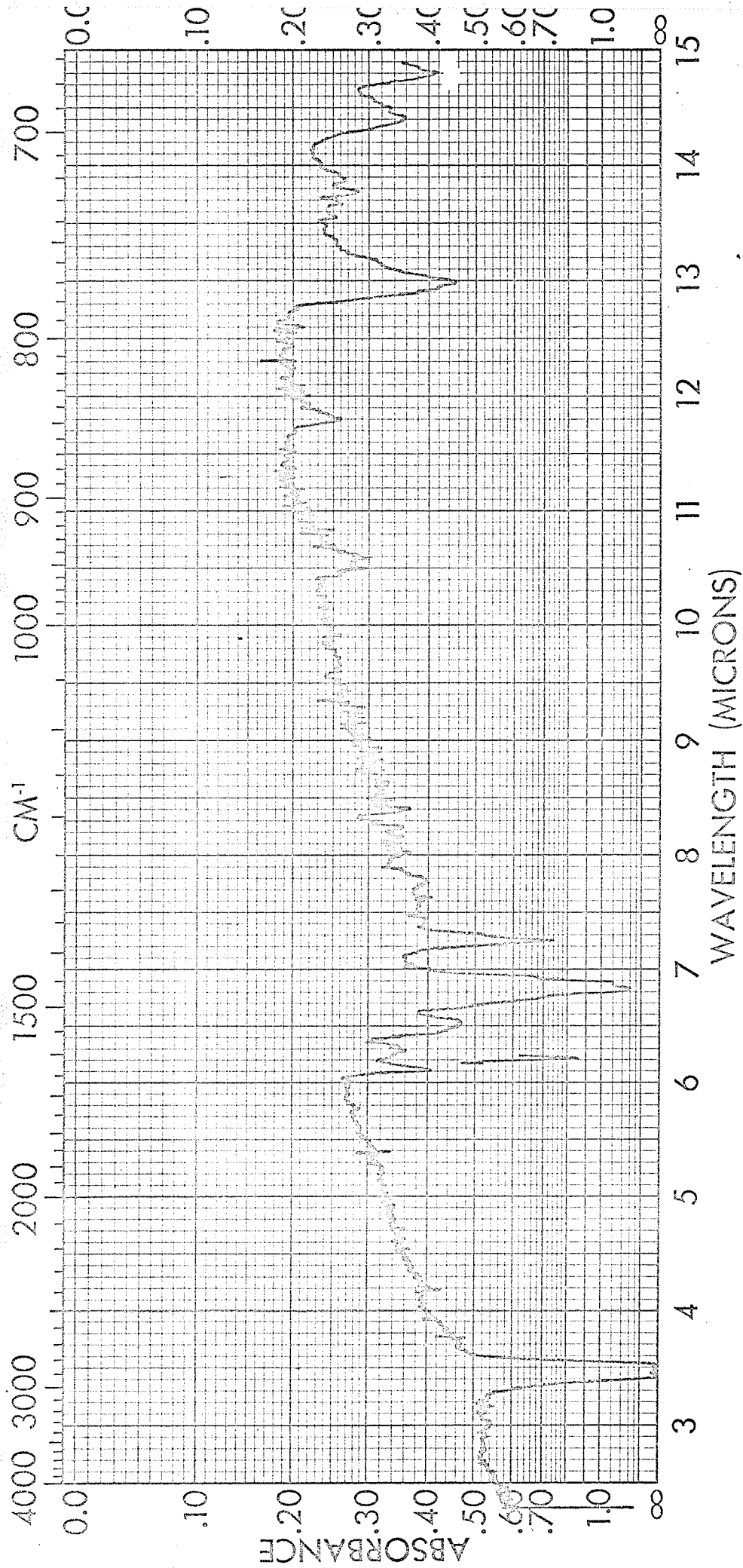
65e



65f



65g



65h

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