

THE SYNTHESIS OF SUBSTITUTED
THIOPHENETHIOLS AND SOME
 ω -(N, N-DIALKYLAMINOALKYL) THIENYL
SULFIDE HYDROCHLORIDE DERIVATIVES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY

Robert James Fawcett

1957

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THE SYNTHESIS OF SUBSTITUTED THIOPH METHIOLS AND
SOME ω -(N,N-DIALKYLAMINOALKYL)THIOMYL SULFIDES
HYDROCHLORIDE DERIVATIVES

By

Robert James Fawcett

A THESIS

Submitted to the School for Advanced Graduate Studies of Michigan
State University of Agriculture and Applied Science
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1957

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VITA

Robert James Fawcett

Date and Place of Birth: June 9, 1926, in Walbridge, Ohio.

Education: Public School of Walbridge, Ohio. Graduated from Walbridge High School, 1944.
Bowling Green State University, Bowling Green, Ohio, 1946-1950. Bachelor of Science, Cum Laude, 1950.
Michigan State University, East Lansing, Michigan 1950-1955.

Professional Positions: Student Assistant, Bowling Green State University, 1949.
Research Assistantship, Bowling Green State University, 1950.
Graduate Assistant Michigan State University, 1950-1955.
Chemist, Research and Development Department, Wyeth Inc., Mason, Michigan, summer 1952.
Research Assistant, Engineering Experimental Station, Michigan State University, summer 1954.
Research Chemist, The B. F. Goodrich Co., Brockville, Ohio, 1955-

Professional and Honor Societies: American Chemical Society.
The Society of the Sigma Xi.
Kappa Klu Epsilon.
Book and Motor Scholastic Honorary Society.
Chemical Journal Club of Bowling Green State University.
Chemical Fellow, Bowling Green State University.

THE SYNTHESIS OF SUBSTITUTED TRITHIOMETHANES AND
SOME ω -(N,X-DIALKYLAMINOALKYL)TRITHIOMETHYL SULFIDE
HYDROLYZING DERIVATIVES

27

Robert James Lawcett

AN ABSTRACT

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Department of Chemistry

Year 1957

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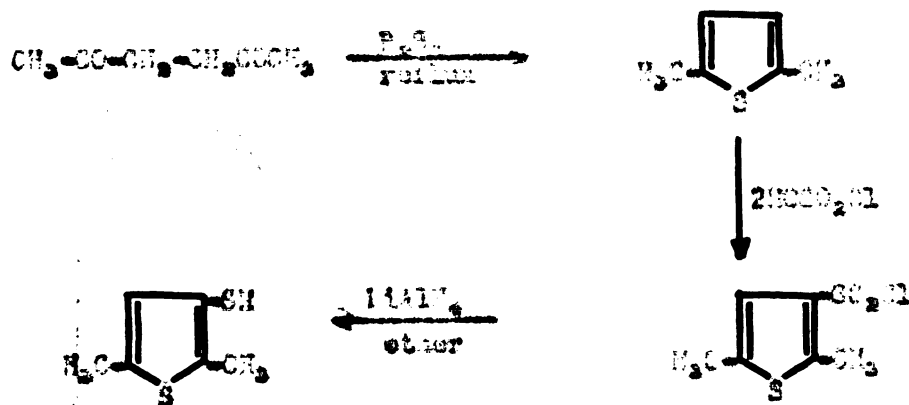
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ABSTRACT

The present investigation was initiated with two main objectives; namely, the study of methods for synthesizing new substituted thiophenethiols and the preparation of *W*-(*N,N*-disubstitylaminoalkyl)thienyl sulfide hydrochloride derivatives from such thiophenethiols. The first aim is of general interest because of the chemistry involved and the other is of pharmacological interest as a possible discovery of new local anesthetics in the latter type of materials.

Three substituted thiophenethiols were synthesized which have never been reported previously. The first was 2,5-dimethyl-3-thiophenethiol and its method of preparation is represented by the following equations.



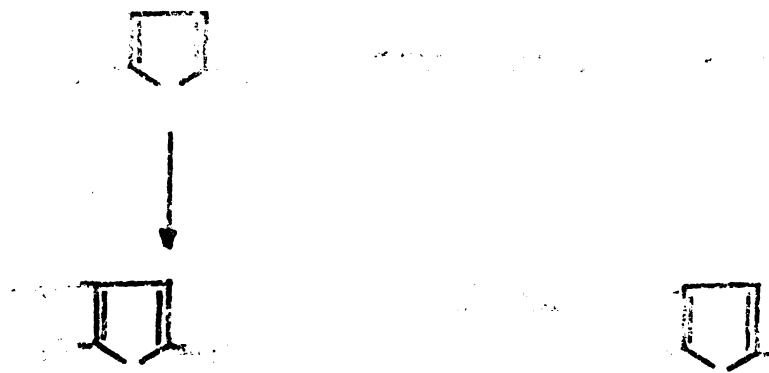
The second new substituted thiophenethiol prepared was 2,5-dichloro-3-thiophenethiol, and it was obtained by the following sequence of reactions.

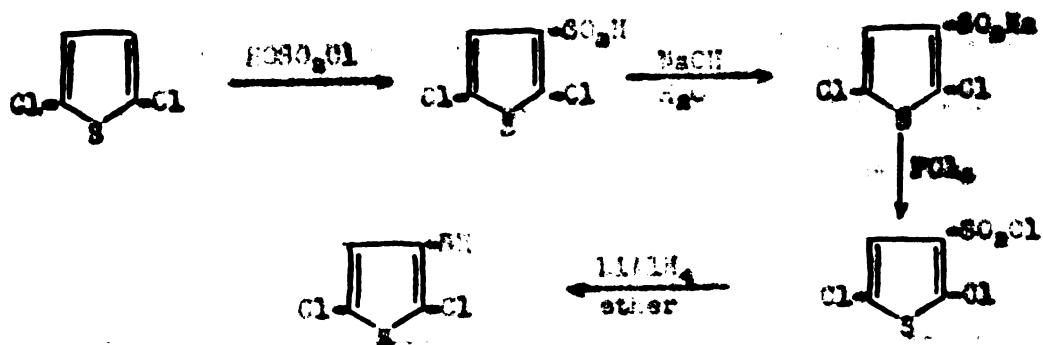
1. The first step is to identify the problem. This involves understanding the situation and the goals that need to be achieved. It is important to gather all relevant information and to consider the perspectives of all stakeholders involved.

2. The second step is to develop a plan. This involves identifying the resources that are available and determining the best way to use them. It is important to set clear objectives and to establish a timeline for the project.

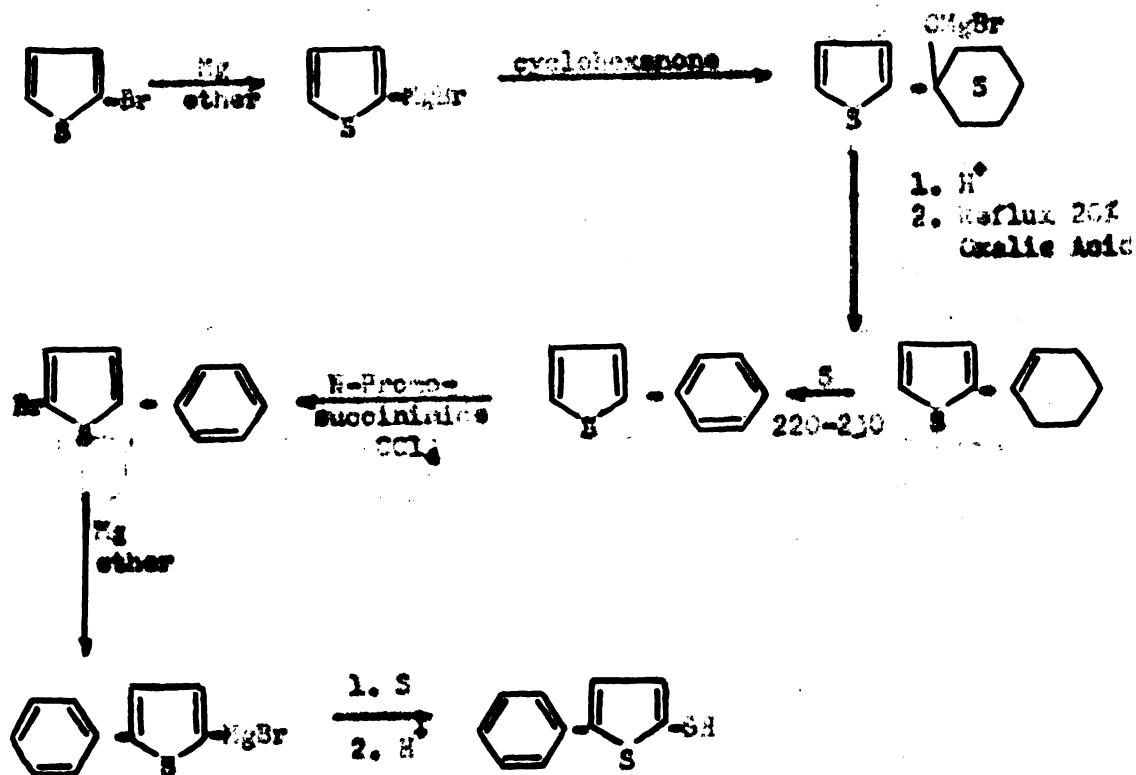
3. The third step is to implement the plan. This involves putting the plan into action and monitoring progress. It is important to communicate regularly with all stakeholders and to be flexible in the face of change.

4. The fourth step is to evaluate the results. This involves assessing the outcomes of the project and determining whether the goals have been achieved. It is important to gather feedback from all stakeholders and to use this information to improve future projects.

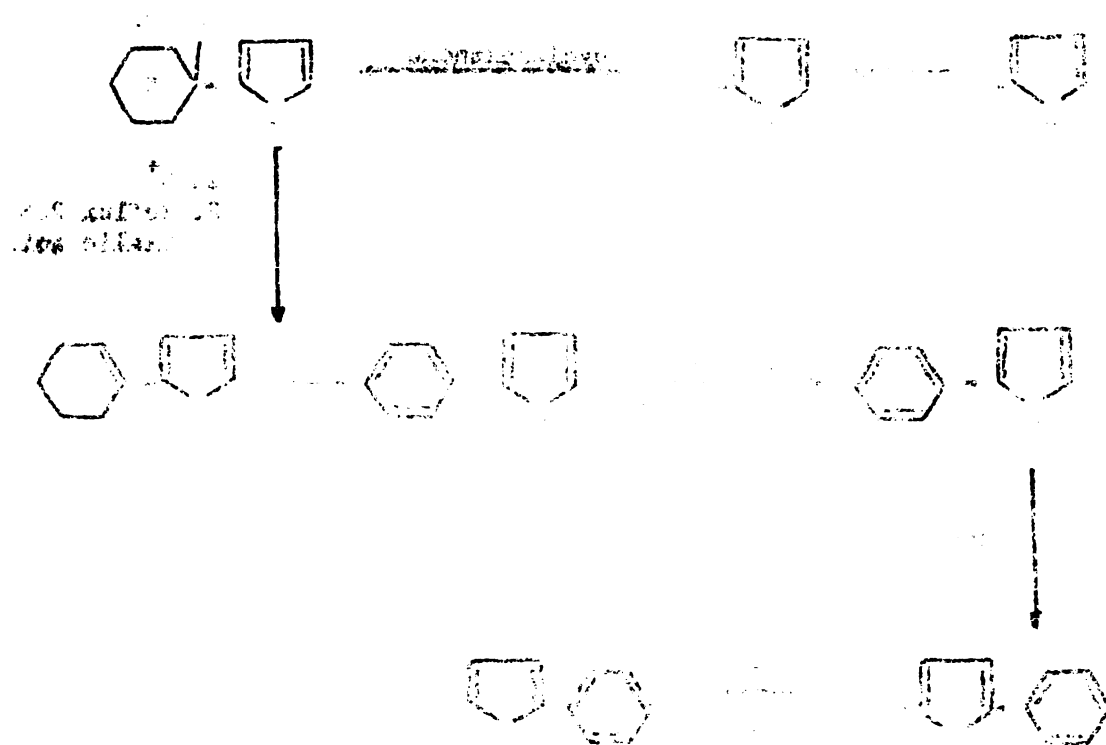
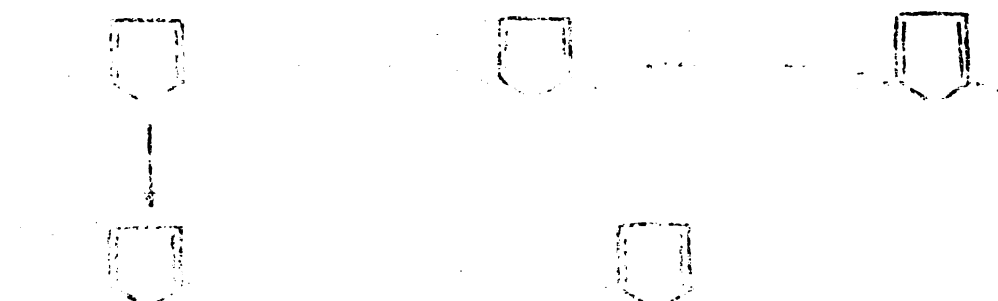




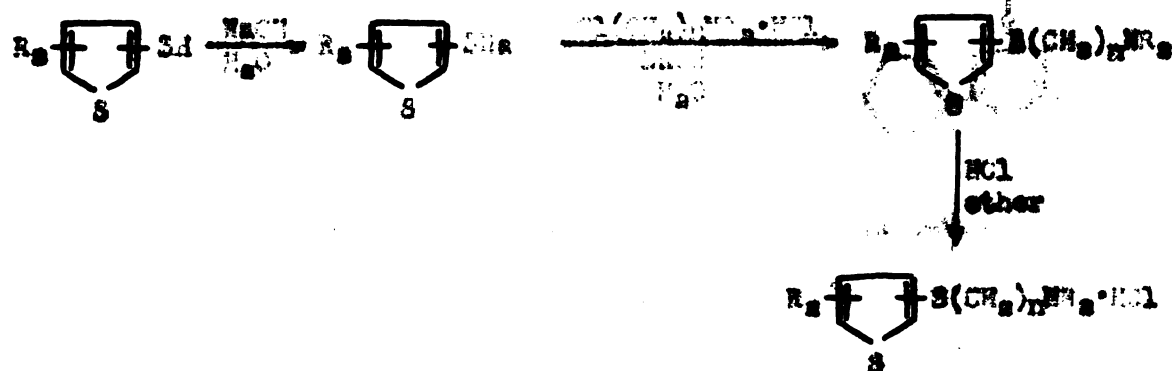
The third thiophenethiol synthesized for the first time was 5-phenyl-2-thiophenethiol. The following sequence of reactions show the method by which it was secured.



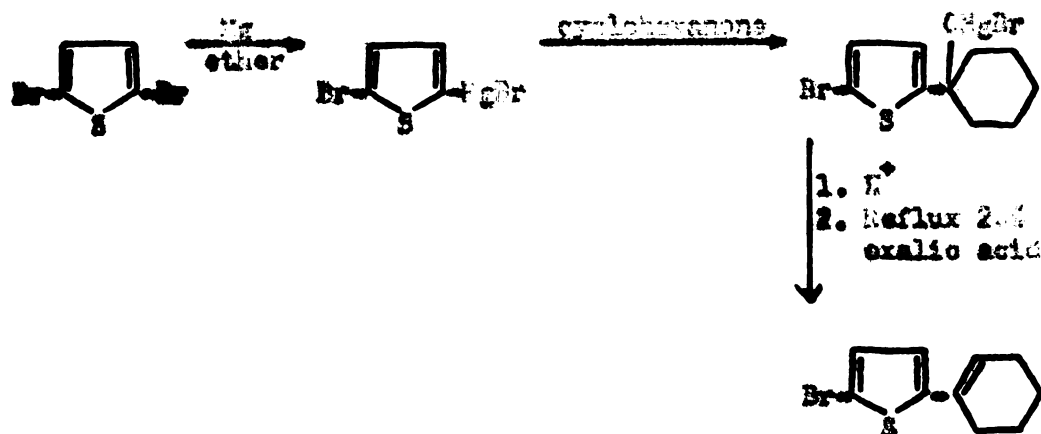
The infra-red spectra of the substituted thiophenethiols were determined and recorded.



Nine ω -(N,N-dialkylamino) allyl-2,5-dichloro-3-thienyl sulfide hydrochlorides, six ω -(N,N-dialkylamino) allyl-2,5-dichloro-3-thienyl sulfide hydrochlorides and two ω -(N,N-dialkylamino) allyl-5-phenyl-2-thienyl sulfide hydrochlorides were synthesized for the first time by the following general scheme of reactions.



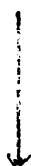
The compound, 5-bromo-2-(1'-cyclohexenyl) thiophene was synthesized for the first time by the following sequence of reactions, which is a much superior method than any previously reported in the literature.



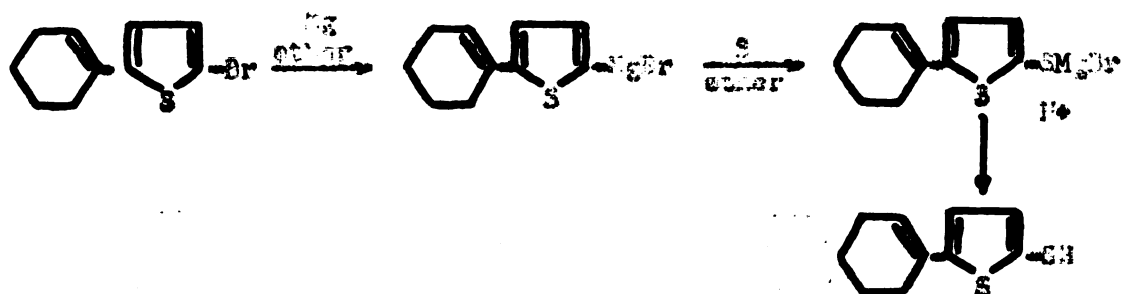
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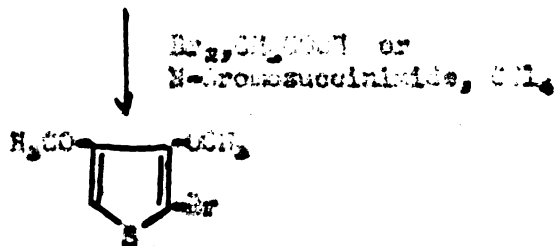
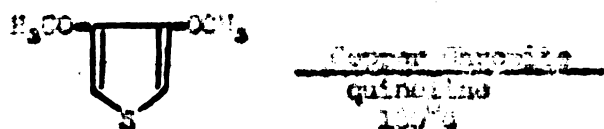
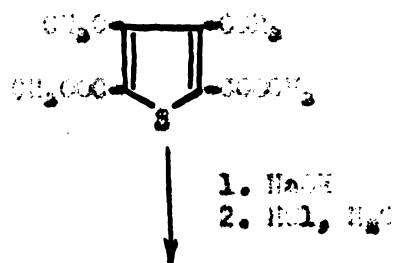
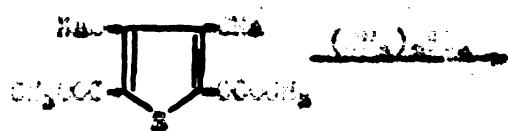
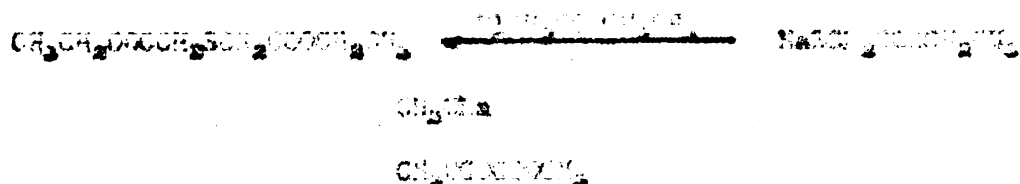
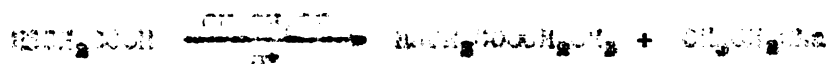


The synthesis of 5-(1'-cyclohexenyl)-2-thiophenethiol was attempted by the following sequence of reactions.



The infra-red spectra of what has been reasonably well established to be 5-(1'-cyclohexenyl)-2-thiophenethiol was determined despite the fact that all attempts to prepare a solid derivative of this compound failed.

The compound 3,4-diethoxy-2-bromothiophene was prepared for the first time by the following sequence of reactions and some of its physical properties were determined.



Other possible methods for the synthesis of substituted thiophenethiols were investigated.

Information concerning the pharmacological properties of these compounds has not been given since this investigation was concerned only with a study of the methods of synthesis of the compounds reported here for the first time.

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INTRODUCTION

Since the discovery and isolation of thiophene in 1882 by Victor Meyer, the history of thiophene chemistry shows periods of rapid and moderate growth. The discovery and isolation of thiophene was not the actual beginning of thiophene chemistry. Laurent (1), in 1844, isolated a compound formed when polymeric thiobenzaldehyde was destructively distilled. It was not until 1891, however, that this compound was shown to be 2,3,4,5-tetraphenylthiophene by Baumann and Fromm (2) who synthesized it from stilbene and sulfur. Following the period of discovery and study of thiophene by Victor Meyer (3), highlighted by the publication of his book "Die Thiophengruppe," interest was generated in thiophene chemistry as shown by the fifty articles which appeared in the literature during the following two years. The next period of development in thiophene chemistry was initiated in 1910 when Wilhelm Steinkopf began a lifetime study of thiophene and its derivatives. This period reached its peak of interest in 1941 with the publication by Steinkopf of his book "Die Chemie des Thiophens" (4). The current enhanced interest in thiophene began in 1945 following the discovery and development by Socony-Vacuum Oil Co., Inc. of a commercial method for producing thiophene from sulfur and butane. This has made available, in semi commercial quantities, thiophene and a number of its derivatives. By 1950 the chief commercial use for thiophene and its derivatives was as intermediates in the drug industry. This period in the development of thiophene chemistry was

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highlighted by Hartough's book, "Thiophene and Its Derivatives" (5), which gave real impetus to the interest in thiophene chemistry and has continued until the present time.

The present investigation deals with a rather specific branch of thiophene chemistry; namely, the synthesis of new thiophenethiols and their derivatives as well as thiophene derivatives which could serve as intermediates for the synthesis of new thiophenethiols. Until the present investigation was undertaken only three thiophenethiols were known; namely, 2-thiophenethiol, 3-thiophenethiol and 2-ethyl-3-thiophenethiol. The 3-thiophenethiol is obtained as a by-product in the commercial thiophene synthesis. As a result of the availability of 3-thiophenethiol in the late 1940's and early 1950's from the thiophene process, a good deal of interest was created in this compound and some of its derivatives. However, very little had been done in the way of developing procedures for synthesizing other thiophenethiols. The methods for introducing a thiol group into the thiophene ring were very limited. The lithium aluminum hydride reduction of a sulfonyl chloride group to yield a sulfhydryl group was found applicable, for the first time, in this investigation for synthesizing a thiol group attached to the thiophene ring. New thiophenethiols were synthesized for the first time with other substituents present in the thiophene nucleus such as dichloro, dimethyl and phenyl groups. In addition to obtaining new thiophenethiols some new thiophene derivatives were synthesized which have potential use for preparing additional new thiophenethiols.

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The second phase of the present investigation involved the synthesis of some ω -(N,N-dialkylamino)alkyl-2 and 3 thieryl sulfide hydrochlorides from the heretofore unknown thiophenethiols prepared for the first time in this study. The interest in this class of sulfur heterocyclic compounds resulted from the discovery by Schuetz and Houff (6,7) that some ω -(N,N-dialkylamino)alkyl-3-thieryl sulfide hydrochlorides had local anesthetic activity equal to or greater than procaine in the guinea pig wheel test. On the other hand, these same investigators demonstrated that some ω -(N,N-dialkylamino)alkyl-2-thieryl sulfide hydrochlorides did not possess local anesthetic activity. In view of this fact, greater emphasis was placed on the preparation of nuclearly substituted 3-thiophenethiols.

The alkyl side chains as well as the terminal tertiary amino group in the ω -(N,N-dialkylamino)alkyl-2 and 3-thieryl sulfide hydrochlorides were systematically varied to ascertain their influence on the pharmaceutical activity of the tertiary amine sulfide.

This investigation deals only with the study of methods for preparing thiophenethiol compounds, as well as preparing several series of the derivatives to be tested for their potential pharmacological value. The actual testing and evaluation of these compounds as drugs is not included in the work herein reported. Their usefulness as new pharmacological agents must await the laboratory and clinical testing which will be done by an independent laboratory and reported elsewhere.

HISTORICAL

The undertaking of this investigation had two main purposes. The first, and considered the more important, was a study of the chemistry leading to the synthesis of new ring substituted thiophenethiols. The second was to utilize the new thiophenethiols to prepare derivatives of potential pharmacological value.

Schmets and Houff (6,7) discovered that some *W*-(*N,N*-dialkylamino)allyl-3-thienyl sulfide hydrochlorides had local anesthetic activity that equaled or exceeded procaine in the guinea pig visceral test. In contrast to this they also found that the *W*-(*N,N*-dialkylamino)allyl-2-thienyl sulfide hydrochlorides had none or very little local anesthetic activity in the same test. From these results it was anticipated that any ring substituted *W*-(*N,N*-dialkylamino)allyl-3-thienyl sulfide hydrochlorides would be of particular interest because of the pharmacological activity of the unsubstituted 3-thienyl sulfide derivatives. Further, there was no assurance that because the *W*-(*N,N*-dialkylamino)allyl-2-thienyl sulfide hydrochlorides previously described (7) had no local anesthetic activity that other ring substituted *W*-(*N,N*-dialkylamino)allyl-2-thienyl sulfide hydrochlorides would not have such activity. Therefore, it was of interest to prepare some of the tertiary amine derivatives of thiophene ring substituted 2-thienyl allyl sulfides for pharmacological evaluation.

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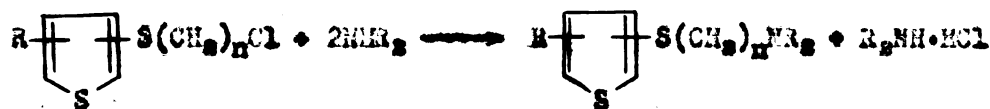
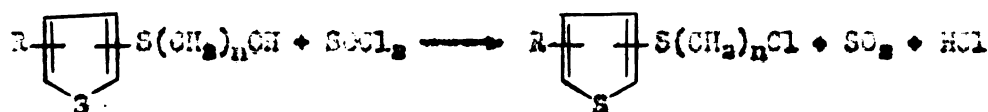
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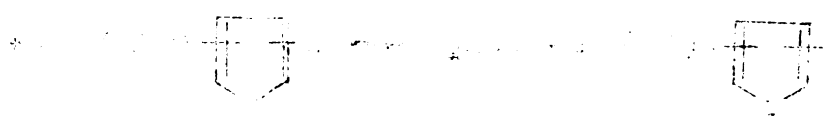
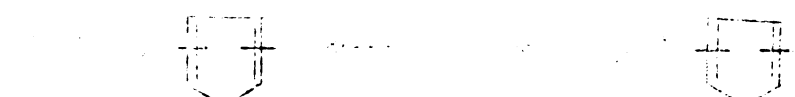
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There were available two methods, or variations of these, by which the tertiary amine derivatives of, thiophene ring substituted, 2 and 3-thienylalkyl sulfides could be prepared. They can be represented by the following two sequences of reactions,



The first method involves the condensation of the sodium salt of the substituted thiophenethiol with a chloroaliphin to form the ω -hydroxyalkyl-3-thienyl sulfide. This was then allowed to react with thionyl chloride to obtain the ω -chloroalkyl-3-thienyl derivative. In the final step of

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the sequence the tertiary derivative can be prepared by allowing the secondary amine to react with the ω -chloroalkyl-3-thienyl sulfide. The second method involves first preparing the ω -dialkylaminoalkyl chloride and then reacting it directly with the sodium salt of the substituted thiophenethiol.

In the present investigation, the latter sequence of reaction steps was employed entirely since the over-all yield of the desired product with respect to the substituted thiophenethiol was greater than in the first method. This was a consideration of primary importance because of the difficulties involved in synthesizing the necessary quantities of the substituted thiophenethiols.

Several methods were available for the synthesis of the intermediate tertiary amino alcohols and their chloroderivatives. Braun (8) and his collaborators reported a method for the synthesis of dialkylamino alcohols by the reaction of piperidine with ethylene chlorohydrin in acetone as a solvent.



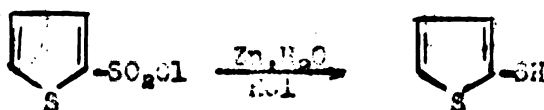
Clinton (9) and his co-workers used a similar method, obtaining ninety-five percent yields, using ethyl alcohol as a solvent and a small quantity of sodium iodide. The sodium iodide shortened the reaction time by exchange of iodine for the chlorine atom in the chlorohydrin.

Mason and Block (10) prepared β -chloroethyl morpholine by reacting β -hydroxyethyl morpholine with thionyl chloride.



Adams and Whitmore (11) synthesized γ -chloropropyl morpholine by the interaction of morpholine and trimethylene chlorobromide in absolute benzene, to obtain the desired product and the hydrobromide of morpholine in stoichiometric quantities.

Until the present work, only three different thiophenethiols have been reported in the literature. Listed in the order of their discovery, they are, 2-thiophenethiol, 2-ethyl-2-thiophenethiol and 3-thiophenethiol. Biedermann (12) prepared 2-thiophenethiol in less than a three percent yield by reducing 2-thiophenesulfonyl chloride with zinc dust and hydrochloric acid



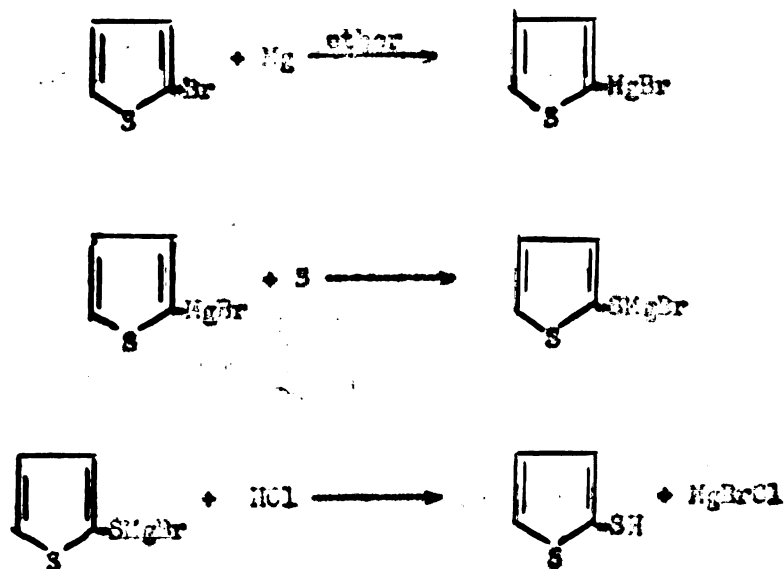
V. Moyer and Maure (13) discovered 2-thiophenethiol in the alkali-soluble portion resulting from the preparation of thiophene from succinic acid and phosphorus pentasulfide. Caesar and Branton (14) prepared 2-thiophenethiol in a 20-30% yield by the addition of sulfur to 2-thienylmagnesium iodide. Schuets and Houff (7) prepared 2-thiophenethiol from 2-bromothiophene by a Grignard reaction with sulfur and from 2-thiophenesulfonyl chloride by a zinc dust sulfuric acid reduction. They obtained a 67% yield by the Grignard route and a 59% yield by the metal acid reduction of 2-thiophenesulfonyl chloride.



trans-1,2-dimethylcyclohexane is the thermodynamically more stable isomer. The energy difference between the two isomers is 1.7 kcal/mol. The energy difference is due to the difference in the steric strain between the two isomers. In the cis isomer, the two methyl groups are on the same side of the ring, which causes steric strain. In the trans isomer, the two methyl groups are on opposite sides of the ring, which reduces steric strain. The energy difference is also due to the difference in the torsional strain between the two isomers. In the cis isomer, the two methyl groups are in a gauche conformation, which causes torsional strain. In the trans isomer, the two methyl groups are in an anti conformation, which reduces torsional strain.



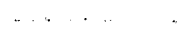
trans-1,2-dimethylcyclopentane is the thermodynamically more stable isomer. The energy difference between the two isomers is 1.7 kcal/mol. The energy difference is due to the difference in the steric strain between the two isomers. In the cis isomer, the two methyl groups are on the same side of the ring, which causes steric strain. In the trans isomer, the two methyl groups are on opposite sides of the ring, which reduces steric strain. The energy difference is also due to the difference in the torsional strain between the two isomers. In the cis isomer, the two methyl groups are in a gauche conformation, which causes torsional strain. In the trans isomer, the two methyl groups are in an anti conformation, which reduces torsional strain.



Challenger and Harrison (15) prepared 2-ethyl-3-thiophenethiol by reducing thieno[3,2-b]-thiophene with sodium in alcohol.



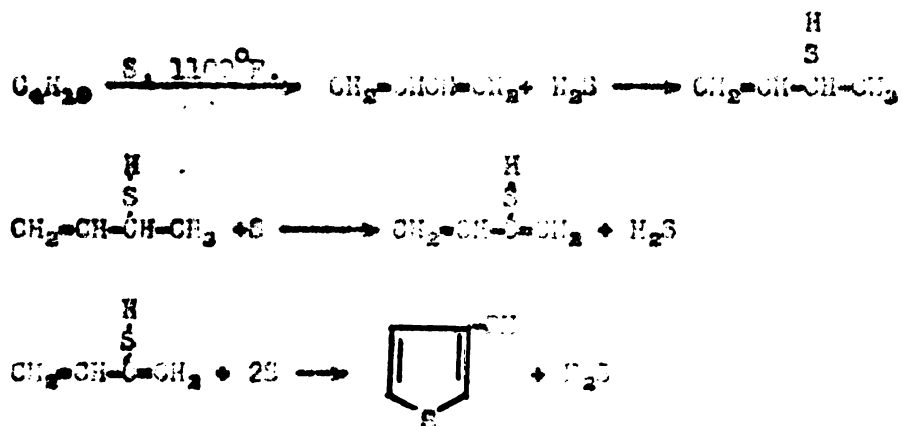
The mercaptan, 3-thiophenethiol was obtained from the tars formed in the commercial production of thiophene. Thiophene is obtained by allowing butane and sulfur to react at 1100° F. (16). The process produces approximately a 40% yield of thiophene and an equal amount of tar (14). Destructive distillation of the tar in vacuo gives a 30-40% yield of 3-thiophenethiol. The following reaction scheme has been proposed to account for the 3-thiophenethiol produced in this process:



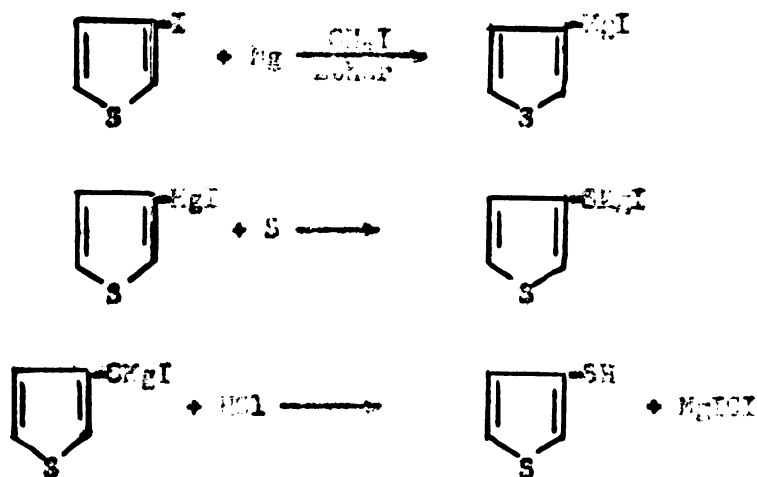
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 A. 乙炔与氯化氢反应 B. 乙炔与溴水反应 C. 乙炔与高锰酸钾反应 D. 乙炔与银氨溶液反应



2. 下列各反应中，哪一个反应是亲电加成反应？
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This reaction sequence was proposed after the observation was made that sulfur and hydrogen sulfide failed to react with thiophene under the same conditions as in the high temperature thiophene process. Caspar and Branton (14) prepared an authentic sample of 3-thiophenethiol by adding sulfur to 3-thienylmagnesium iodide.



The same authors reported the infrared spectra of 2-thiophenethiol and 3-thiophenethiol.

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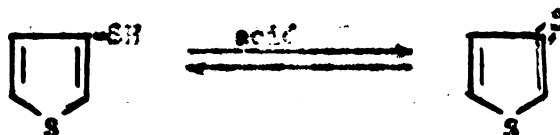
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Brooks (17) and his collaborators reported a large number of derivatives of 3-thiophenethiol. All of the derivatives were thioethers and did not have any substituents on the thiophene ring except the thioether linkage.

The thiophenethiols polymerize on storage to dimeric substances. The dimer of 3-thiophenethiol can be pyrolyzed in part to give the original mercaptan. The 3-thiophenethiol has been shown to exist in both the thione and thiol forms. In neutral and basic solutions the thiol form predominates, but in acid the thione form is present in large amounts (18).



Marvel and Caesar (19) prepared p-thiocresol and n-butyl-mercaptan by the lithium aluminum hydride reduction of p-toluenesulfonyl chloride and n-butylsulfonyl chloride respectively. The procedure developed for these preparations was used in the present investigation as a model to reduce 2,5-diethyl-3-thiophenesulfonyl chloride and 2,5-dichloro-3-thiophenesulfonyl chloride with lithium aluminum hydride to the corresponding substituted thiophenethiols.

Since the number of thiophenethiols known was very limited it was decided to prepare a number of thiophenethiols having different substituents in the thiophene ring. The structure of the thiophenethiols had to be known unequivocally. The sulfhydryl group was of greatest interest

1. The first step in the synthesis of the compound is the reaction of the starting material with the reagent. This step is crucial for the formation of the intermediate product. The reaction conditions, such as temperature and time, must be carefully controlled to ensure the desired outcome.

2. The second step involves the purification of the intermediate product. This is typically achieved through a series of extraction and washing steps, followed by a final purification step. The purity of the intermediate is essential for the subsequent steps in the synthesis.

3. The third step is the final conversion of the intermediate into the target compound. This step often involves a specific reagent and conditions that facilitate the final transformation. The resulting compound is then characterized using various analytical techniques to confirm its identity and purity.



The reaction scheme shows the conversion of a cyclopentadiene derivative to a cyclopentadiene derivative. The starting material is a cyclopentadiene ring with a substituent group. The reagent used is a specific chemical compound, which is shown in a box. The reaction arrow indicates the transformation of the starting material into the product. The product is a cyclopentadiene ring with a different substituent group, indicating a transformation of the starting material.

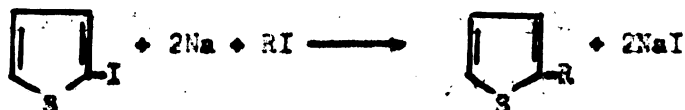
The reaction conditions are specified as follows: the reaction is carried out in a specific solvent at a certain temperature for a defined period of time. The reagent is added in a specific amount to the reaction mixture. The resulting product is then purified and characterized using various analytical techniques.

The final product is a cyclopentadiene derivative, which is characterized by its specific chemical structure and properties. The synthesis of this compound is a multi-step process, and the reaction scheme provides a clear overview of the steps involved.

when in the three position of the thiophene ring as previous work (5,7) indicated that derivatives of such compounds would have pharmacological value. However, the thiol group in the two position of the thiophene ring was of interest also since only one previous thiophene-thiol of this type had previously been prepared.

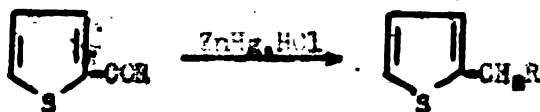
A thiophenethiol with alkyl groups and the thiol group in the three position was first sought. A literature search for the methods of introducing an alkyl group into the thiophene ring was made. The important methods of historical interest will be briefly discussed and the reasons for selecting the procedure employed to obtain the alkyl-3-thiophenethiol will be indicated.

V. Meyer and Kreis (20) were the first investigators to prepare an alkyl thiophene by applying a Wurtz-Fittig type reaction to thiophene.



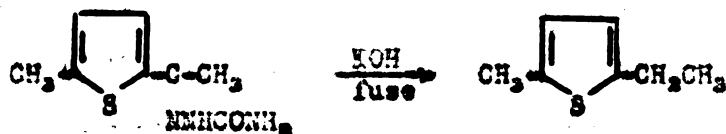
They found that the two position of thiophene was more active than the three position and that the iodo derivative was best suited to this reaction but that the bromo derivative would undergo the alkylation reaction but gave lower yields.

Steinkopf and Schubart (21) have shown that acylthiophenes can be converted to alkylthiophenes by a Clemmensen reduction of the acyl derivative.



Since their original work a large number of alkylthiophenes have been prepared in this manner.

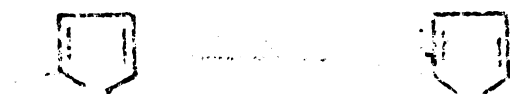
Shepard (22) prepared 2-ethyl-5-methylthiophene by the action of moist caustic on the semicarbazone of 2-acetyl-5-methylthiophene.



Other alkyl thiophenes have been prepared in this manner.

A large number of alkyl thiophenes have been prepared by a Friedel and Crafts type reaction. This has been accomplished with alkylhalides as well as with olefins. Schleicher (23) was the first to investigate this reaction in its application to thiophene.

The most common method for synthesizing alkyl thiophenes is by the ring closure of an appropriate intermediate. A very excellent review of these procedures has been written by Wolf and Folkers (24) and includes many references to experimental details. These methods can be divided into two general groups. The first group consists of the reactions of alkanes or alkenes with sulfur or compounds containing sulfur, such as hydrogen sulfide and sulfur dioxide. Such syntheses are usually only of commercial importance. The other general method used to obtain



The reaction is a [1,3]-sigmatropic shift. The substituent 'R' moves from the top-right carbon to the top-left carbon. This is a concerted process involving the movement of three electron pairs. The reaction is reversible, as indicated by the double-headed arrow.



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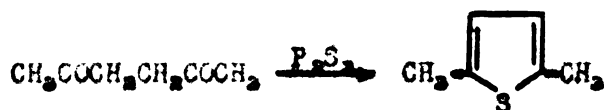
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alkylthiophenes is to effect a ring closure of a γ -dicarbonyl compounds with phosphorus sulfides. The γ -dicarbonyl compounds may be in the form of a γ -diketone, γ -dialdehyde, succinic acid and some of its derivatives, or a γ -keto acid.

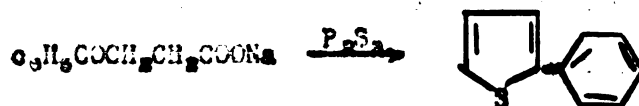
An alkylated thiophene was required from which an alkyl-3-thiophenethiol of known structure could be prepared in sufficient quantity to permit the synthesis of a series of compounds, each in a moderate amount, for biological testing. The thiophene derivative, 2,5-dimethylthiophene, possessed the necessary requirements. This compound is symmetrical and thus, the 2 positions of the thiophene nucleus are equivalent. A possible starting material for its preparation was acetylacetone which was easily available in sufficient quantities to obtain the necessary amounts of the desired final product. Bun-Hoi, Nguyen-Hoan (25) and Paal (26) synthesized 2,5-dimethylthiophene in an average yield of 60%, from two preparations, by the ring closure of acetylacetone.



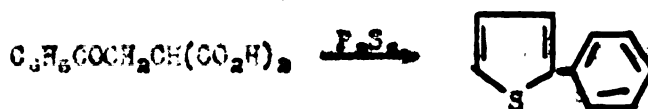
In the present work the experimental procedures were modified to obtain better yields, than any previously reported, of 2,5-dimethylthiophene from acetylacetone and phosphorus pentasulfide.

The aryl thiophene, 2-phenylthiophene, was required for the preparation of 5-phenyl-2-thiophenethiol. The former compound has been prepared by several methods. Kues and Paal (27) and Chrzasczewska (28)

prepared 2-phenylthiophene from β -benzoylpropionic acid and also from its sodium salt, by cyclization reactions with sulfides of phosphorus.

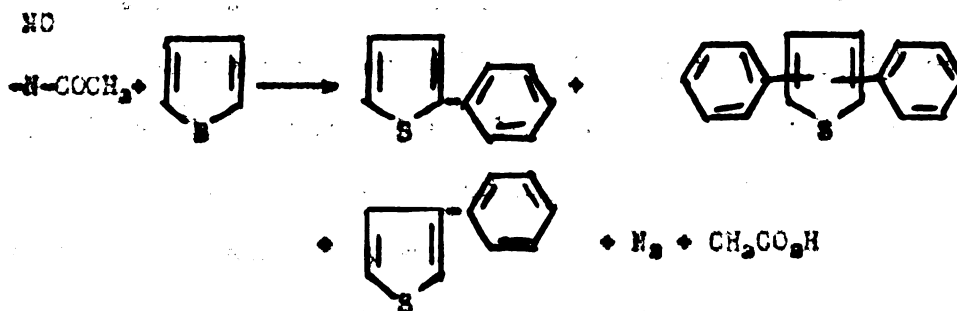


Chrastasczewski (23) used sand as a diluent to moderate the reaction during the pyrolysis phase. Kues and Paal (27) also prepared 2-phenylthiophene from a substituted malonic acid and phosphorus pentasulfide in less than ten percent yield.



Mohlau and Berger (29) prepared what they described as a mixture of 2- and 3-phenylthiophenes by the interaction of benzenediazonium chloride with thiophene in the presence of aluminum chloride.

Bamberger (30) reacted N-nitrosoacetanilide with thiophene to obtain a mixture of mono and diphenylthiophenes.



Chemical reactions

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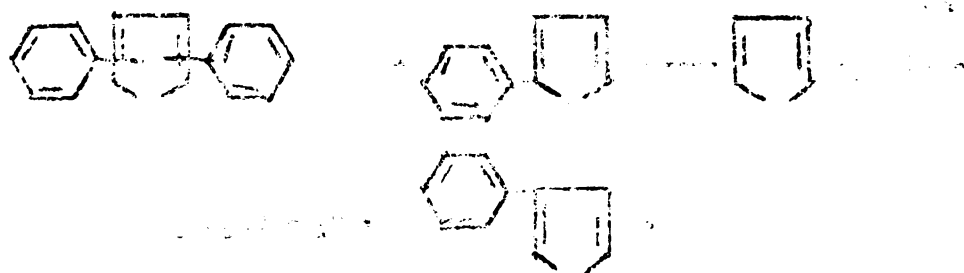
The reaction of benzene with maleic anhydride to form a Diels-Alder adduct is shown below. The reaction is reversible and the equilibrium constant is 1.0.



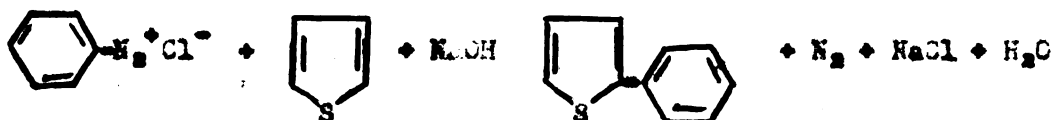
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Gomberg and Bachmann (31) prepared 2-phenylthiophene in an eleven percent yield from benzenediazonium chloride and thiophene in the presence of sodium hydroxide. The active intermediate was benzenediazonium hydroxide formed from the benzenediazonium chloride.



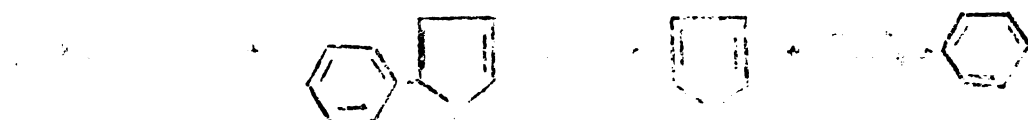
Broun and Veronkov (32) have done considerable work on the synthesis of 2-phenylthiophene from 1-phenylbutane, 1-phenylbutenes, and 1-phenylbutadiene by allowing the latter three compounds to react with sulfur for ten to fifteen hours at temperatures of 200-245°C. in sealed tubes. The yields were, with phenylbutane 5%, with 1-phenylbutadiene 5%, and with 1-phenylbutenes from 25 to 35%.

The 2,5-dimethyl-3-thiophenesulfonyl chloride was synthesized as an intermediate needed to prepare 2,5-dimethyl-3-thiophenethiol. This could be done by first forming the 2,5-dimethyl-3-thiophenesulfonic acid and converting this to its sulfonyl chloride with phosphorus pentachloride or the sulfonic acid chloride could be obtained by the direct interaction of the 2,5-dimethylthiophene with a molar excess of chlorosulfonic acid. In general the methods used in sulfonating or chlorosulfonating thiophene can be also used for alkylthiophenes.

Victor Meyer (33) first prepared thiophenesulfonic acid by treating coal tar benzene with ninety-six percent sulfuric acid. Weitz (34)

the β -phenyl group of the monomer is not involved in the reaction.

It is interesting to note that the polymerization of β -phenylstyrene in the presence of TiCl_4 and AlR_3 is inhibited by the addition of TiCl_4 alone, but is not inhibited by the addition of AlR_3 alone. This is probably due to the fact that TiCl_4 alone is not a strong enough Lewis acid to initiate the polymerization of β -phenylstyrene, while AlR_3 alone is not a strong enough Lewis base to initiate the polymerization of β -phenylstyrene.

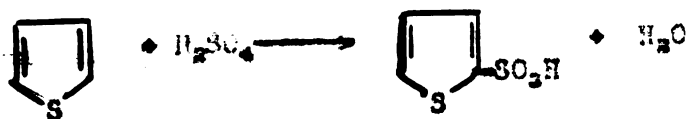


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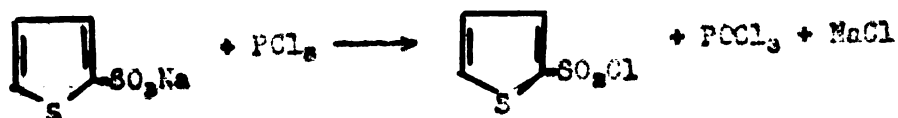
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prepared 2-thiophenesulfonic acid by the method of Meyer and characterized its various metal salts.



Meyer and Kreis (35) obtained 2-thiophenesulfonyl chloride from sodium-2-thiophenesulfonate and phosphorus pentachloride.



The acid chlorides 2-thiophenesulfonyl chloride was synthesized by Steinkopf and Hopner (36) and also by Burton and Levy (37) by allowing chlorosulfonic acid to react with thiophene at a temperature of -15°C .



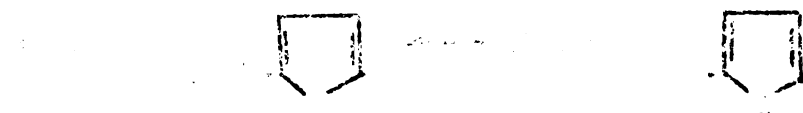
Langer (38) first prepared 3-thiophenesulfonic by the sulfonation of 2,5-dibromothiophene with pyrosulfuric acid to obtain 2,5-dibromo-3-thiophenesulfonic acid. The bromo groups were subsequently removed by a five percent sodium amalgam reduction.

Steinkopf, Jacob and Pens (39) and then Keiser (40) sulfonated both 2,4 and 2,5-dimethylthiophenes with sulfuric acid to obtain mono and disulfonic acid derivatives of these dialkylthiophenes.

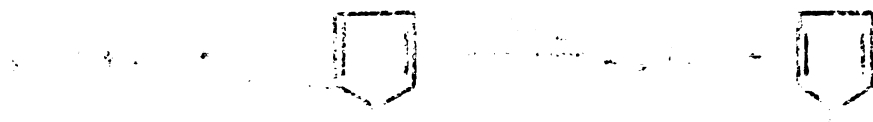
the following reaction scheme, which is a simplified representation of the actual process, showing the conversion of a reactant into a product.



The reaction is carried out under conditions of high temperature and pressure, and the catalyst used is a mixture of various metal salts.



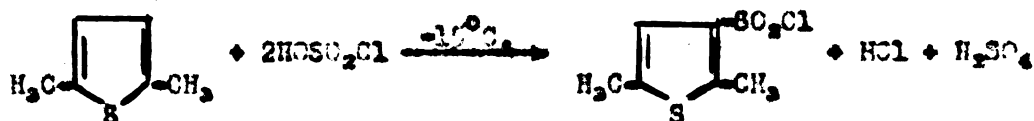
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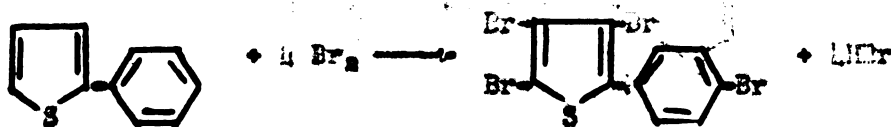
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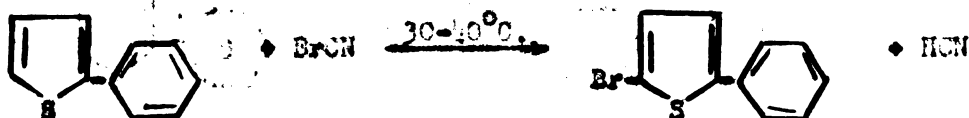
In the present work 2,5-dimethylthiophene was chlorosulfonated directly with an excess of chlorosulfonic acid using a modification of the experimental procedures developed by Steinkopf and Hopner (36) and also by Barton and Davy (37) to obtain 2,5-dimethyl-3-thiophenesulfonyl chloride.



The compound, 5-phenyl-2-bromothiophene was prepared as an intermediate in the synthesis of 5-phenyl-2-thiophenethiol. Thiophene brominates much more readily than benzene but the bromination of 2-phenylthiophene with bromine could not be directed exclusively to the thiophene nucleus (27). The para position of the phenyl group had a tendency to be brominated. Exhaustive bromination of 2-phenylthiophene yielded a tetrabromothiophene. This has been reported to be 2-(4'-bromophenyl)-3,4,5-tribromothiophene.

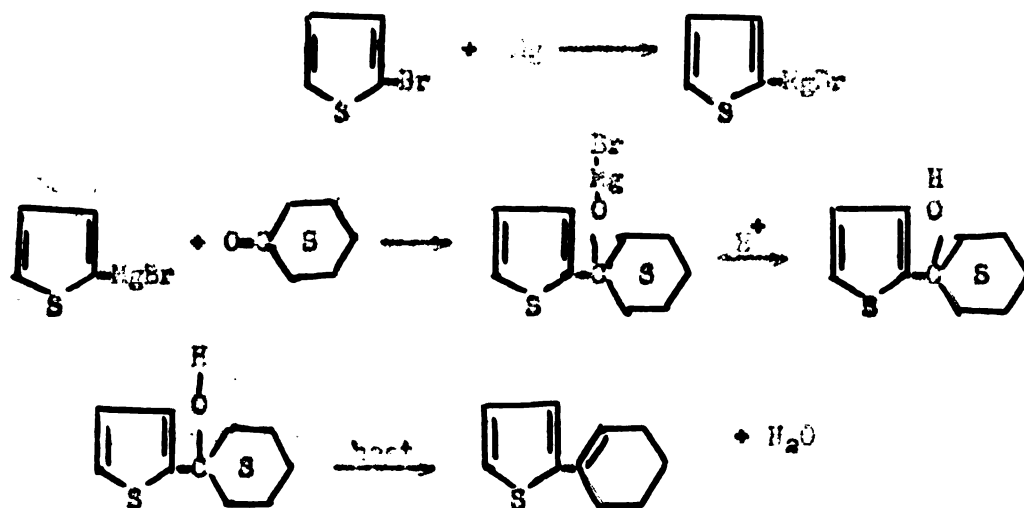


Steinkopf, Petersdorff, and Gording (31) reported they brominated 2-phenylthiophene with cyanogen bromide as the brominating agent to obtain 5-phenyl-2-bromothiophene in a ninety percent yield.



This work could not be repeated even when extremely pure 2-phenylthiophene was used. In the present work, N-bromosuccinimide in chloroform as a solvent was found to brominate 2-phenylthiophene, in the 5- position, in excellent yields. A melting point of $85-86^{\circ}$ C. for the product was obtained, which was the same as that reported for 5-phenyl-2-bromothiophene by the cyanogen bromide method of bromination. Elemental analysis verified that the product obtained with N-bromosuccinimide was the monobromo derivative of 2-phenylthiophene.

A new method was developed in the present work for preparing 2-phenylthiophene by the aromatization of 2-(1-cyclohexenyl)thiophene. The starting material for this synthesis, 2-(1'-cyclohexenyl)thiophene, was first prepared by Fieser and Samuszovics (42) and then later by Tilford and his co-workers (43). These investigators treated 2-thienylmagnesium bromide with cyclohexanone to obtain 2-(1'-cyclohexenyl) thiophene which was dehydrated to 2-(1'-cyclohexenyl)thiophene during its purification by distillation,



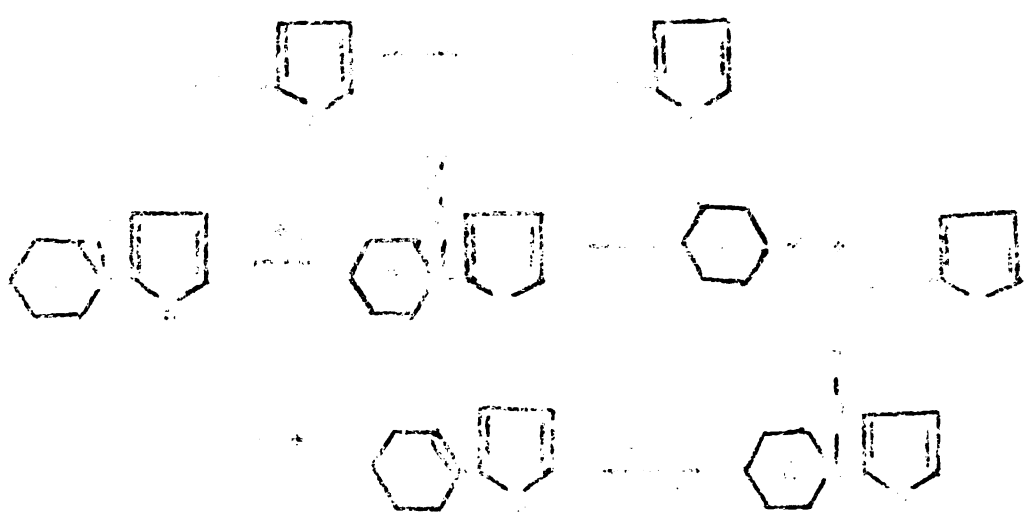
The first step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene, at a temperature of 60-80°C. The initiator is added to the solution, and the reaction mixture is stirred for a period of time. The reaction is then stopped by the addition of a suitable reagent, such as methanol. The resulting polymer is then purified by precipitation into a large volume of methanol. The purified polymer is then dried under vacuum at 60°C for 24 hours. The final product is a white, crystalline solid.

The second step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene, at a temperature of 60-80°C. The initiator is added to the solution, and the reaction mixture is stirred for a period of time. The reaction is then stopped by the addition of a suitable reagent, such as methanol. The resulting polymer is then purified by precipitation into a large volume of methanol. The purified polymer is then dried under vacuum at 60°C for 24 hours. The final product is a white, crystalline solid.

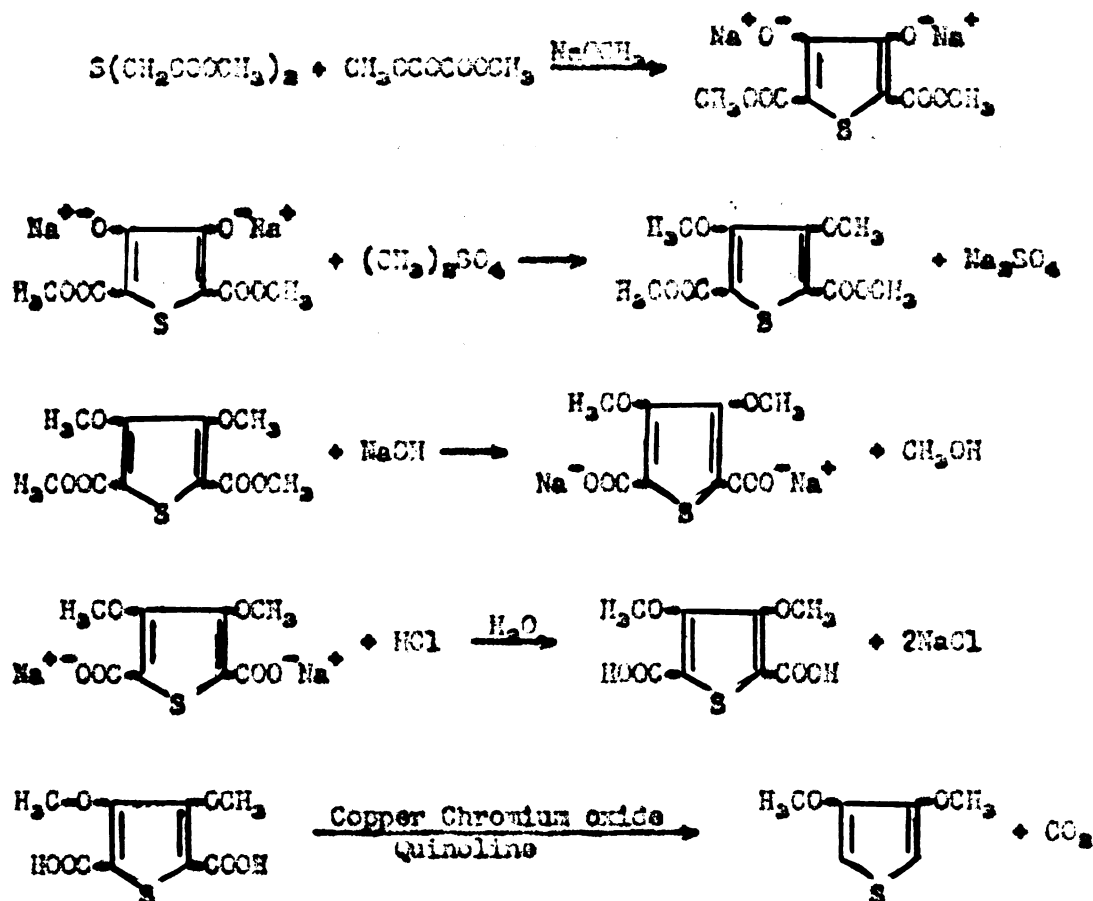
The third step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene, at a temperature of 60-80°C. The initiator is added to the solution, and the reaction mixture is stirred for a period of time. The reaction is then stopped by the addition of a suitable reagent, such as methanol. The resulting polymer is then purified by precipitation into a large volume of methanol. The purified polymer is then dried under vacuum at 60°C for 24 hours. The final product is a white, crystalline solid.

The fourth step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene, at a temperature of 60-80°C. The initiator is added to the solution, and the reaction mixture is stirred for a period of time. The reaction is then stopped by the addition of a suitable reagent, such as methanol. The resulting polymer is then purified by precipitation into a large volume of methanol. The purified polymer is then dried under vacuum at 60°C for 24 hours. The final product is a white, crystalline solid.

The fifth step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene, at a temperature of 60-80°C. The initiator is added to the solution, and the reaction mixture is stirred for a period of time. The reaction is then stopped by the addition of a suitable reagent, such as methanol. The resulting polymer is then purified by precipitation into a large volume of methanol. The purified polymer is then dried under vacuum at 60°C for 24 hours. The final product is a white, crystalline solid.



The material, 3,4-dimethoxythiophene has been prepared by Hinsburg (44) using a ring closure method. Fager (45) prepared 3,4-dimethoxythiophene by the following sequence of reactions, involving a ring closure reaction employing the Hinsberg method, a methylation with dimethylsulfate, followed by hydrolysis and finally a decarboxylation step.



Turnbull (46) prepared 3,4-dimethoxythiophene by the decarboxylation of 3,4-dihydroxy-2,5-dicarboxythiophene in refluxing pyridine followed by a methylation of the 3,4-dihydroxythiophene with diazomethane.

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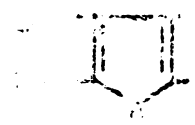
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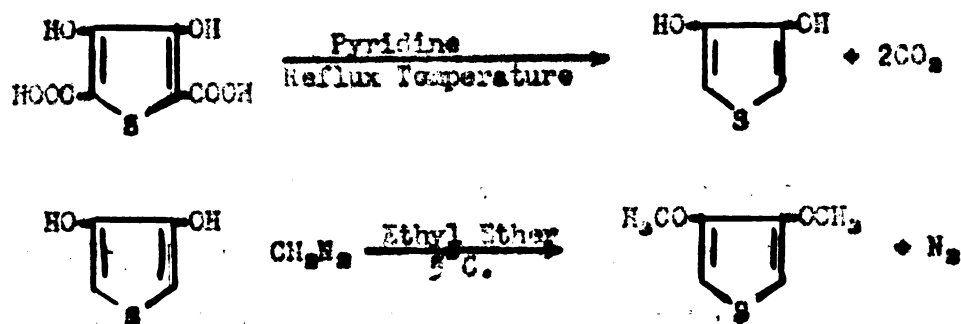


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Overberger and Lal (47), prepared 3,4-dimethoxythiophene by a method similar to Fager's with a slight modification of the procedure. They used copper powder as the catalyst in the decarboxylation of 3,4-dimethoxy-2,5-dicarboxythiophene without the aid of an organic base such as pyridine or quinoline.



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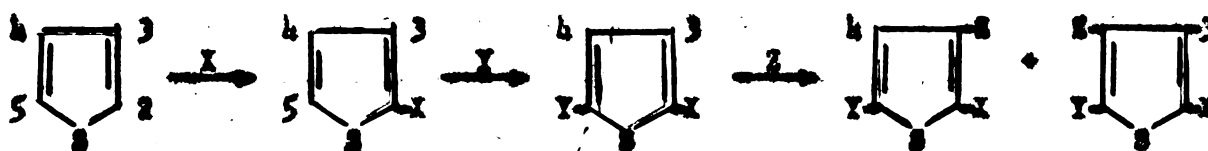


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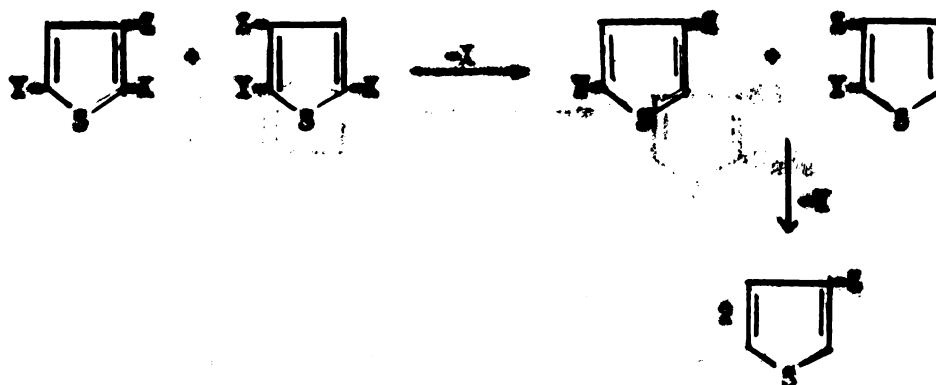
DISCUSSION

After careful consideration of the two main objects of this investigation; namely, the synthesis of previously unknown thiophenethiols and the preparation of new tertiary aminoalkyl thienyl sulfide hydrochlorides from the thiophenethiols, it was decided to attempt first to prepare substituted 3-thiophenethiols in view of the previous work of Schuets and Rouff (5,7). These investigators found that the 3-thienyl sulfide derivatives have local anesthesia activity while the isomeric 2-thienyl sulfide derivatives failed to show such activity. The problem of preparing 3-thiophenethiols is complicated by the fact that the three and four positions of thiophene are considerably less reactive than the two and five positions. To surmount this difficulty several methods were attempted. The two and five positions of thiophene could be blocked by first introducing groups in these positions. These groups could be of two types, those which could later be removed or others which could be left intact in the final 3-thienyl sulfide derivative. The groups introduced in the two and five positions had to be stable toward experimental conditions later used to introduce the thiol group into the three or four positions. If the blocking groups were later removed after adding the thiol group then one or more other groups would have to be placed on the thiophene ring after the thiol or sulfide linkage was in place. This presented an additional problem since the thiol group is

relatively unstable toward many reagents. If the two and five positions of thiophene are blocked with two different substituents then the problem arises that the three and four positions of thiophene are not equivalent and consequently if the blocking substituents are left intact then a structure proof is necessary to determine which isomer or whether both isomers were prepared.



If the two and five substituents are removed then the structure problem no longer exists since the resulting compounds become equivalent.

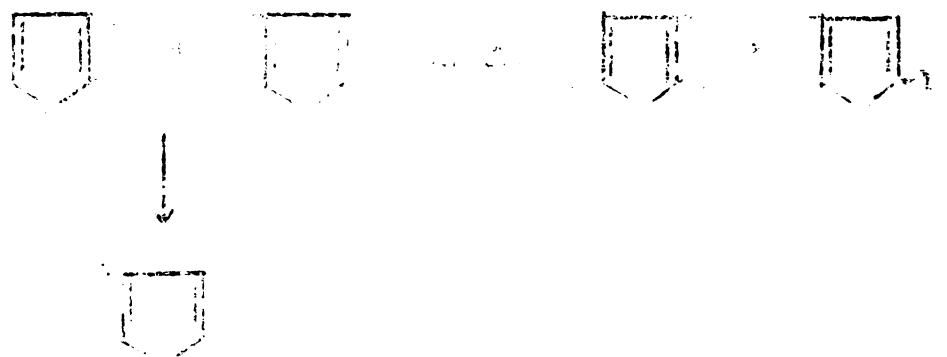


However, the problem becomes even more complex when one or more substituents are introduced into a nonsubstituted thiophene ring. Here, the number of possible isomers increases as can be easily envisioned and with still another substituent the possible number of isomers would very rapidly increase.

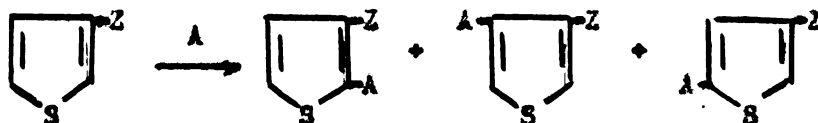
The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \sum_{n=0}^{\infty} a_n x^n$, where a_n are the coefficients of the power series. It is shown that $f(x)$ is a continuous function of x and that it satisfies the functional equation $f(x) = f(x^2) + x f(x)$. This equation is solved by the method of successive approximations, and it is shown that the solution is unique. The second part of the paper is devoted to the study of the properties of the function $g(x)$ defined by the equation $g(x) = \sum_{n=0}^{\infty} b_n x^n$, where b_n are the coefficients of the power series. It is shown that $g(x)$ is a continuous function of x and that it satisfies the functional equation $g(x) = g(x^2) + x g(x)$. This equation is solved by the method of successive approximations, and it is shown that the solution is unique.



The third part of the paper is devoted to the study of the properties of the function $h(x)$ defined by the equation $h(x) = \sum_{n=0}^{\infty} c_n x^n$, where c_n are the coefficients of the power series. It is shown that $h(x)$ is a continuous function of x and that it satisfies the functional equation $h(x) = h(x^2) + x h(x)$. This equation is solved by the method of successive approximations, and it is shown that the solution is unique.



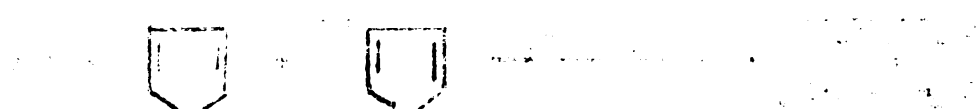
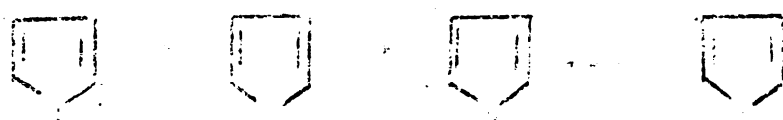
The fourth part of the paper is devoted to the study of the properties of the function $k(x)$ defined by the equation $k(x) = \sum_{n=0}^{\infty} d_n x^n$, where d_n are the coefficients of the power series. It is shown that $k(x)$ is a continuous function of x and that it satisfies the functional equation $k(x) = k(x^2) + x k(x)$. This equation is solved by the method of successive approximations, and it is shown that the solution is unique. The fifth part of the paper is devoted to the study of the properties of the function $l(x)$ defined by the equation $l(x) = \sum_{n=0}^{\infty} e_n x^n$, where e_n are the coefficients of the power series. It is shown that $l(x)$ is a continuous function of x and that it satisfies the functional equation $l(x) = l(x^2) + x l(x)$. This equation is solved by the method of successive approximations, and it is shown that the solution is unique.

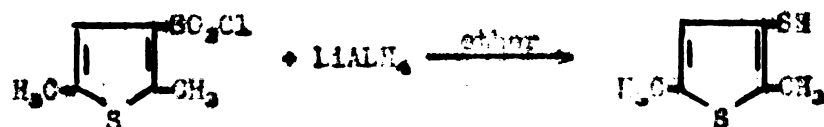
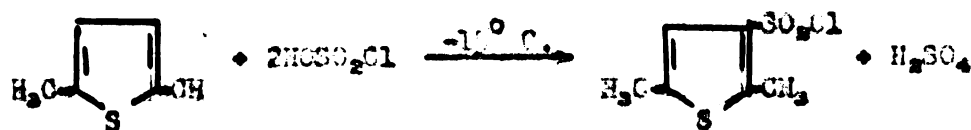
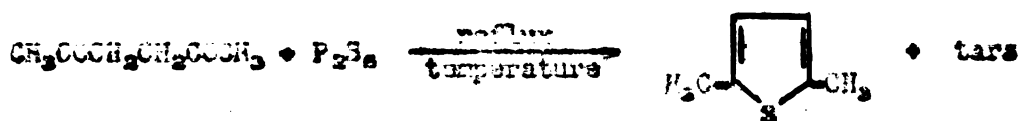


One other method is available for obtaining 3-thiophenethiols with other substituents on the ring. This method involves a ring closure of a 1,4-dicarbonyl compound which will form thiophene derivatives with the thiol group as well as other substituents in place on the thiophene ring. The only two 3-thiophenethiols reported in the literature were first prepared by this method (15,16).



The first successful synthesis, in the present study, of a new substituted thiophene thiol was accomplished by substituting the two and five positions of the thiophene ring with identical groups and then introducing the thiol group in the three position which is equivalent to the four position thereby eliminating the isomer problem and the structure of the resulting compound was unequivocal. The first compound prepared by this method was 2,5-dimethyl-3-thiophenethiol. The following sequence of reactions was employed.





The ring closure of acetonyl acetone with phosphorus pentasulfide was a modification of several methods reported in the literature where phosphorus trisulfide had been used as the cyclizing agent (25,25). There are claims in the literature that phosphorus pentasulfide is not as effective in the ring closure reactions to produce thiophene derivatives as phosphorus trisulfide, however, it has been shown that phosphorus trisulfide is really a mixture of phosphorus pentasulfide and sulfur (24). In the present investigation the use of phosphorus pentasulfide gave yields which were better than those reported for the phosphorus trisulfide after a satisfactory experimental procedure had been developed. A yield of 2,5-dimethylthiophene of over eighty percent was obtained. The phosphorus pentasulfide was a commercial grade and was used without further purification. It was found that the best yields were obtained by adding a small amount of acetonyl acetone to the finely powdered phosphorus pentasulfide and while the nearly dry powdery mixture was stirred it was cautiously heated until the reaction had initiated.

Figure 1



Figure 2



Figure 3



Figure 4



The first of these is the effect of the shape of the cross-section. The second is the effect of the material properties. The third is the effect of the loading. The fourth is the effect of the boundary conditions. The fifth is the effect of the time of exposure. The sixth is the effect of the environment. The seventh is the effect of the maintenance. The eighth is the effect of the inspection. The ninth is the effect of the repair. The tenth is the effect of the replacement. The eleventh is the effect of the demolition. The twelfth is the effect of the reconstruction. The thirteenth is the effect of the renovation. The fourteenth is the effect of the restoration. The fifteenth is the effect of the preservation. The sixteenth is the effect of the conservation. The seventeenth is the effect of the protection. The eighteenth is the effect of the prevention. The nineteenth is the effect of the mitigation. The twentieth is the effect of the adaptation. The twenty-first is the effect of the resilience. The twenty-second is the effect of the sustainability. The twenty-third is the effect of the equity. The twenty-fourth is the effect of the justice. The twenty-fifth is the effect of the inclusion. The twenty-sixth is the effect of the participation. The twenty-seventh is the effect of the consultation. The twenty-eighth is the effect of the collaboration. The twenty-ninth is the effect of the partnership. The thirtieth is the effect of the alliance. The thirty-first is the effect of the coalition. The thirty-second is the effect of the network. The thirty-third is the effect of the community. The thirty-fourth is the effect of the society. The thirty-fifth is the effect of the culture. The thirty-sixth is the effect of the values. The thirty-seventh is the effect of the beliefs. The thirty-eighth is the effect of the attitudes. The thirty-ninth is the effect of the behaviors. The fortieth is the effect of the outcomes. The forty-first is the effect of the impacts. The forty-second is the effect of the consequences. The forty-third is the effect of the results. The forty-fourth is the effect of the achievements. The forty-fifth is the effect of the successes. The forty-sixth is the effect of the failures. The forty-seventh is the effect of the challenges. The forty-eighth is the effect of the opportunities. The forty-ninth is the effect of the risks. The fiftieth is the effect of the rewards. The fifty-first is the effect of the costs. The fifty-second is the effect of the benefits. The fifty-third is the effect of the losses. The fifty-fourth is the effect of the gains. The fifty-fifth is the effect of the profits. The fifty-sixth is the effect of the losses. The fifty-seventh is the effect of the gains. The fifty-eighth is the effect of the profits. The fifty-ninth is the effect of the losses. The sixtieth is the effect of the gains. The sixty-first is the effect of the profits. The sixty-second is the effect of the losses. The sixty-third is the effect of the gains. The sixty-fourth is the effect of the profits. The sixty-fifth is the effect of the losses. The sixty-sixth is the effect of the gains. The sixty-seventh is the effect of the profits. The sixty-eighth is the effect of the losses. The sixty-ninth is the effect of the gains. The seventieth is the effect of the profits. The seventy-first is the effect of the losses. The seventy-second is the effect of the gains. The seventy-third is the effect of the profits. The seventy-fourth is the effect of the losses. The seventy-fifth is the effect of the gains. The seventy-sixth is the effect of the profits. The seventy-seventh is the effect of the losses. The seventy-eighth is the effect of the gains. The seventy-ninth is the effect of the profits. The eightieth is the effect of the losses. The eighty-first is the effect of the gains. The eighty-second is the effect of the profits. The eighty-third is the effect of the losses. The eighty-fourth is the effect of the gains. The eighty-fifth is the effect of the profits. The eighty-sixth is the effect of the losses. The eighty-seventh is the effect of the gains. The eighty-eighth is the effect of the profits. The eighty-ninth is the effect of the losses. The ninetieth is the effect of the gains. The ninety-first is the effect of the profits. The ninety-second is the effect of the losses. The ninety-third is the effect of the gains. The ninety-fourth is the effect of the profits. The ninety-fifth is the effect of the losses. The ninety-sixth is the effect of the gains. The ninety-seventh is the effect of the profits. The ninety-eighth is the effect of the losses. The ninety-ninth is the effect of the gains. The hundredth is the effect of the profits.

The acetyl acetone was then added dropwise to the stirred mixture at a rate sufficient to maintain the reaction mixture at its reflux temperature. When all of the acetyl acetone had been added the reaction mixture was heated at its reflux temperature for a period of thirty minutes and finally the crude product was isolated by distillation. The product was further purified by washing with a sodium hydroxide solution, drying and fractionating the product. The rate of reaction became very violent if too large a quantity of acetylacetone was added prior to the initiation of the reaction.

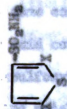
The chlorosulfonation of 2,5-dimethylthiophene to obtain 2,5-dimethyl-3-thiophenesulfonyl chloride was accomplished by adding 2,5-dimethylthiophene to chlorosulfonic acid at temperatures below zero degree Centigrade. This procedure was a modification of the method of Steinkopf and Hopner (18). If the temperature of the reaction mixture was allowed to rise much above zero degree Centigrade there was considerable charring and tars would form. The crude reaction mixture always had a deep red color. The product was isolated by pouring the reaction mixture onto ice, extracting with carbon tetrachloride, washing with water, drying, and fractionating the crude product. The 2,5-dimethylthiophene-3-sulfonyl chloride was characterized by forming the sulfonamide derivative and also by its saponification equivalent. Some properties of the sulfonamide derivative are recorded in Table I.

The reduction of 2,5-dimethyl-3-thiophenesulfonyl chloride caused considerable difficulty. Many attempts were made to reduce this acid chloride with zinc dust and sulfuric acid. This method of reduction was

the first of these is the fact that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The second is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The third is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The fourth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The fifth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion. The sixth is that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The seventh is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The eighth is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The ninth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The tenth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion.

TABLE I

2,5-DISUBSTITUTED-3-THIOPHENENE SULFONAMIDES

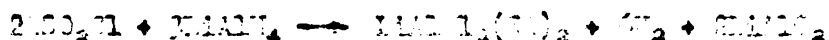


Compound	Formula	M.p., °C.	Percent Carbon Calcd. Found	Percent Hydrogen Calcd. Found	Percent Sulfur Calcd. Found	Percent Chlorine Calcd. Found
-3-Thiophene sulfonamide						
2,5-Dimethyl	$C_7H_8NO_2S$	111.5-112	37.68 37.62	4.74 4.51	33.53 33.37	---
2,5-Dichloro	$C_6H_4Cl_2NO_2S$	130-130.5	20.70 20.85	1.30 1.47	27.63 27.45	30.55 30.75

successfully used by Schuette and Hault (7) for the preparation of 2-thiophenethiol from 2-thiophenesulfonyl chloride without isolating the intermediate sulfonyl chloride. The method is an adaptation of the reduction of benzenesulfonyl chloride described by Gilman (15).

Biederman (12) was successful in preparing 2-thiophenethiol in poor yield by a zinc dust reduction of 2-thiophenesulfonic acid. After many attempts to reduce 2,5-diethyl-3-thiophenesulfonyl chloride by varying the reaction time, concentrations, and mesh size of zinc the acid metal method of reduction was abandoned. The products from these unsuccessful reactions appeared to be 2,5-diethyl-3-thiophenesulfonic acid and possibly some corresponding sulfinic acid. The 2,5-diethyl-3-thiophenesulfonic acid could have been formed by hydrolysis of the 2,5-diethyl-3-thiophenesulfonyl chloride during the attempted reduction. To determine if the zinc metal was the cause for the failure of this reduction, 2-thiophenesulfonyl chloride was prepared and reduced by this same method. Yields corresponding to that found in the literature were obtained for the 2-thiophenethiol. Therefore, it was concluded that neither the technique nor reagents were at fault, but that the method was not applicable to prepare 2,5-diethyl-3-thiophenethiol.

The method which was successful for the reduction of the sulfonyl chloride to the thiol group was an adaptation of the method of Marvel and Caesar (19) for the reduction of p-toluenesulfonyl chloride and 1-butanethiol to p-thiocresol and n-butyl mercaptan respectively. The above authors proposed the following equation for this reduction. However, the stoichiometry of this equation has not been verified.



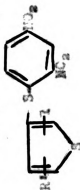
The product was then isolated by acidification. The procedure used for the preparation of 2,5-dimethyl-3-thiophenesulfonyl chloride was to dissolve a large excess of powdered lithium aluminum hydride in dry ether and then add an ethereal solution of 2,5-dimethyl-3-thiophenesulfonyl chloride to the lithium aluminum hydride solution kept at its reflux temperature. The 2,5-dimethyl-3-thiophenethiol was isolated by destroying the excess lithium aluminum hydride with water, separating the ether layer, extracting the product from the ether with a sodium hydroxide solution, acidifying the basic salt, extracting it from the aqueous mixture with ether, drying, and vacuum fractionating the crude thiol. The yields obtained were as high as eighty-eight percent based on the 2,5-dimethyl-3-thiophenesulfonyl chloride used in the reduction.

The 2,5-dimethyl-3-thiophenethiol was characterized by the formation of the 2,4-dinitrophenylsulfide derivative and elemental analysis. The results of this analysis are to be found in Table II. The 2,5-dimethyl-3-thiophenethiol was found to be relatively unstable at room temperature especially in contact with air. It appeared to have a tendency to either oxidize or dimerize. After standing in an atmosphere of nitrogen for several weeks in a refrigerator, some of the material would no longer dissolve in 6N sodium hydroxide, whereas it completely dissolved when initially prepared.

The infra red spectra was determined on a freshly prepared sample of 2,5-dimethyl-3-thiophenethiol. An absorption band at 3.22μ indicated

TABLE II

2,4-DINITROPHENYLSULFIDE DERIVATIVES OF RING-SUBSTITUTED THIOPHENETHIOLS



Compound	Formula	M.P. °C.	Percent Carbon Calcd. Found	Percent Hydrogen Calcd. Found	Percent Sulfur Calcd. Found	Percent Chlorine Calcd. Found
2,4-Dinitrophenyl sulfide Derivative of						
2,5-Dimethyl-3-thiophenethiol	$C_{12}H_{10}N_2O_4S_2$	101.5-105	46.44 45.46	3.25 3.29	20.66 20.62	— —
2,5-Dichloro-3-thiophenethiol	$C_{10}H_6Cl_2N_2O_4S_2$	136.5-137	54.20 54.44	1.15 1.32	16.26 16.13	20.13 20.21
5-Phenyl-2-thiophenethiol	$C_{10}H_{10}N_2O_4S_2$	158-158.2	53.62 53.80	2.61 2.97	17.59 17.71	— —



the sulhydryl group present. The infra red spectra of 2,5-dimethyl-3-thiophenethiol is shown in Figure 1.

The synthesis of 2,5-dimethyl-3-thiophenethiol was attempted without success by two alternative methods. One method involved the preparation of 2,5-dimethyl-3-iodothiophene and 2,5-dimethyl-3-bromothiophene. An attempt was made to react the halo derivative with magnesium and finally with sulfur to give the thiol group on hydrolysis.

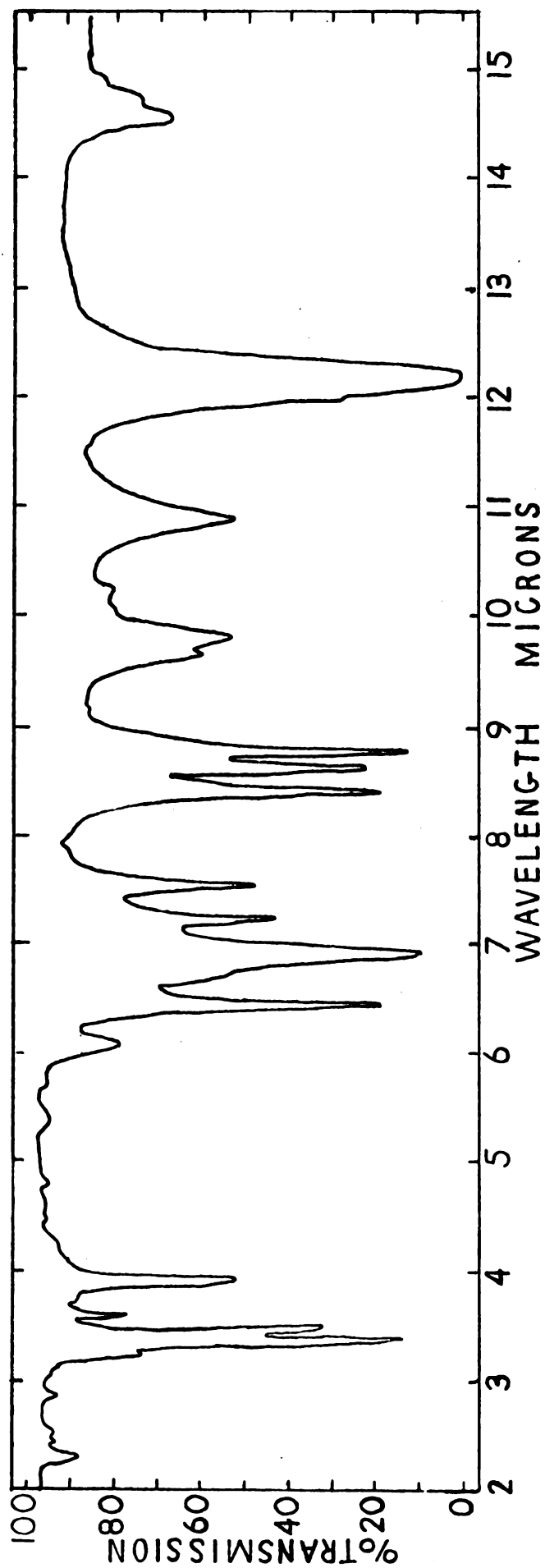
The 2,5-dimethyl-3-bromothiophene was prepared by brominating 2,5-dimethylthiophene in carbon disulfide as a solvent. Even though the product was washed with aqueous sodium carbonate to remove the side product that resulted from bromination of the methyl groups rather than the three position of the thiophene ring, the final product readily darkened on standing and fused when exposed to the air. Because of this difficulty, as well as the desire to take advantage of the greater reactivity of the iodo group, the experimental work with the bromo derivative was discontinued and the remainder of the work was done with 2,5-dimethyl-3-iodothiophene. The 2,5-dimethyl-3-iodothiophene was synthesized by a procedure adapted from a method reported by Minnis (50) for the synthesis of 2-iodothiophene.



The iodine and freshly prepared yellow mercuric iodide were added alternately, in small quantities, to the 2,5-dimethylthiophene dissolved in



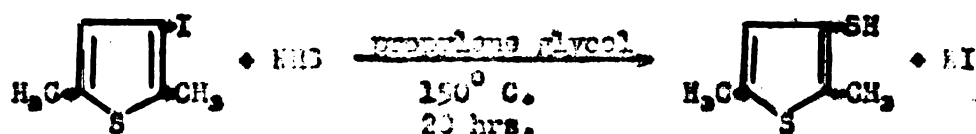
INFRARED ABSORPTION SPECTRA OF 2,5-DIMETHYL-3-THIOPHENETHIOL

FIGURE 1.

benzene. The reaction was easily followed by the disappearance of the yellow mercuric oxide color and the appearance of the crimson mercuric iodide color. The yellow mercuric oxide's function was to remove the hydrogen iodide immediately as it was formed, to prevent reduction of the product. An attempt was made to obtain the 2,5-dimethyl-3-thiophenethiol from the iodo derivative by forming a Grignard reagent and then reacting the latter with sulfur. The method of Hurd and Krous (51) was employed to prepare the Grignard reagent. A mole quantity of 2-iodopropane was used in conjunction with the 2,5-dimethyl-3-iodothiophene. Addition of sulfur to the resulting Grignard reagent, followed by hydrolysis of the reaction mixture, failed to yield any 2,5-dimethyl-3-thiophenethiol. A second attempt was made using only a trace of 2-iodopropane to initiate the Grignard reaction; however, the results were again negative when sulfur was added to the Grignard reaction mixture. In order to determine whether the 2,5-dimethyl-3-thienylmagnesium iodide formed under the conditions employed, the Grignard reaction with 2,5-dimethyl-3-iodothiophene was repeated and the resulting Grignard complex was carbonated, following the method of Massey (52), by pouring the Grignard reagent over powdered dry ice suspended in ether. A very small amount of 2,5-dimethyl-3-thiophene carboxylic acid was isolated and identified by its melting point. Further, active Grignard reagent was probably formed during the reaction of 2,5-dimethyl-3-iodothiophene with magnesium as was shown by the very exothermic reaction as well as the reactivity of the resulting solution when a small portion was allowed to

react with water. Because of the low yield previously reported by Cassar and Branton (14), for the preparation of 3-thiophenethiol through the Grignard reaction as well as the fact that a better method was developed by the lithium aluminum hydride reduction of the 2,5-dimethyl-3-thiophenesulfonyl chloride the Grignard method was not investigated further.

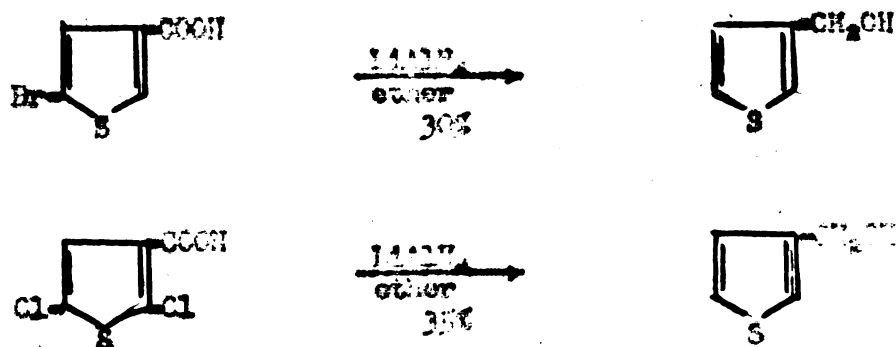
A single attempt was made to synthesize 2,5-dimethyl-3-thiophenethiol by allowing 2,5-dimethyl-3-iodothiophene to react with potassium hydrogen sulfide in propylene glycol as a solvent.



The potassium hydrogen sulfide was freshly prepared by the method of Thirtle (53), which involved saturating a potassium hydroxide solution with hydrogen sulfide and evaporating it to dryness. The dry potassium hydrogen sulfide was dissolved in propylene glycol. The expected reaction, as indicated in the equation, failed to occur and the 2,5-dimethyl-3-iodothiophene was isolated unchanged. No further attempts were made to develop this method for introducing the mercapto group into the thiophene nucleus.

The second new thiophenethiol synthesized was 2,5-dichloro-3-thiophenethiol. There were two reasons which prompted the investigation into the synthesis of this particular thiophenethiol. A variety of different substituents on the parent thiophenethiol compound was sought. The first synthesis involved allyl groups, therefore, the investigation

of additional thiophenethiols involving other substituents than allyl groups was made. A halo thiophenethiol was the choice for the second attempted synthesis of a new thiophenethiol. The 2,5-dihalo thiophene was chosen because of its symmetry as in the case of the 2,5-dimethylthiophene. The dichloro was chosen in preference to the dibromo or diiodo derivatives because of the relative reactivities of the chloro, bromo, and iodo substituents on the thiophene ring, the chloro group being the least reactive of the three. This was an important consideration because it was planned to use the same sequence of reactions as was employed with the 2,5-dimethylthiophene and the possibility of removal of the chloro groups by the lithium aluminum hydride reduction existed. A previously reported example of a chloro group being removed from the two position of thiophene was made by Campaigne and Bourgeois (24). They reported that the chloro group was reduced from the thiophene ring when a carbonyl group in the three position was being reduced to a hydroxymethyl substituent as is illustrated in the following equations.



There was no assurance that the same thing would not happen with 2,5-dichloro-3-thiophenesulfonyl chloride. The reactivities of the two

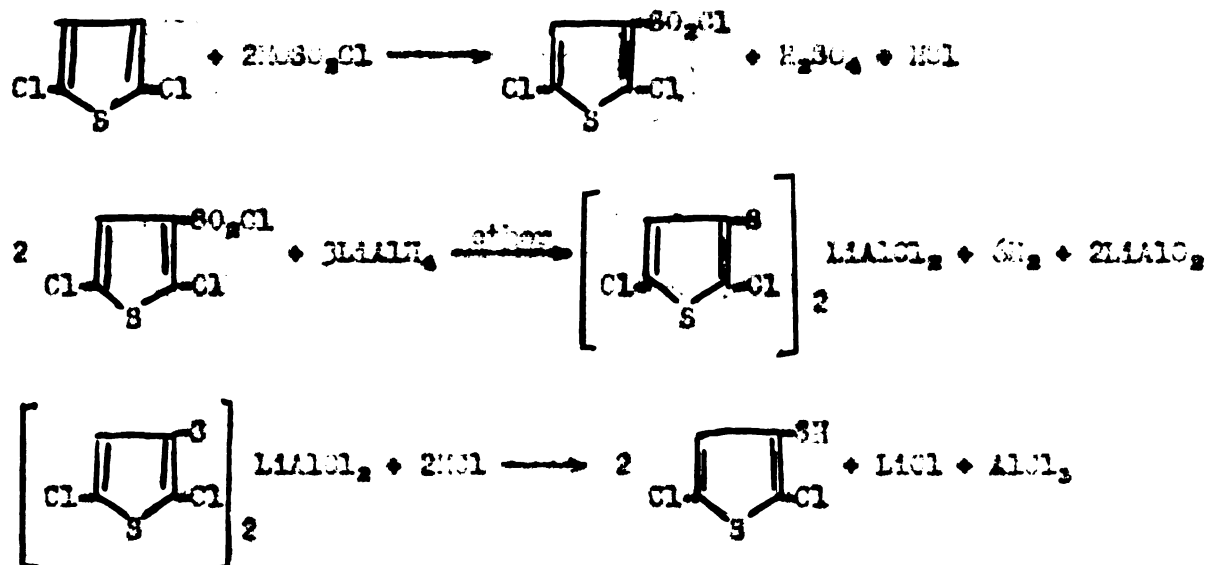
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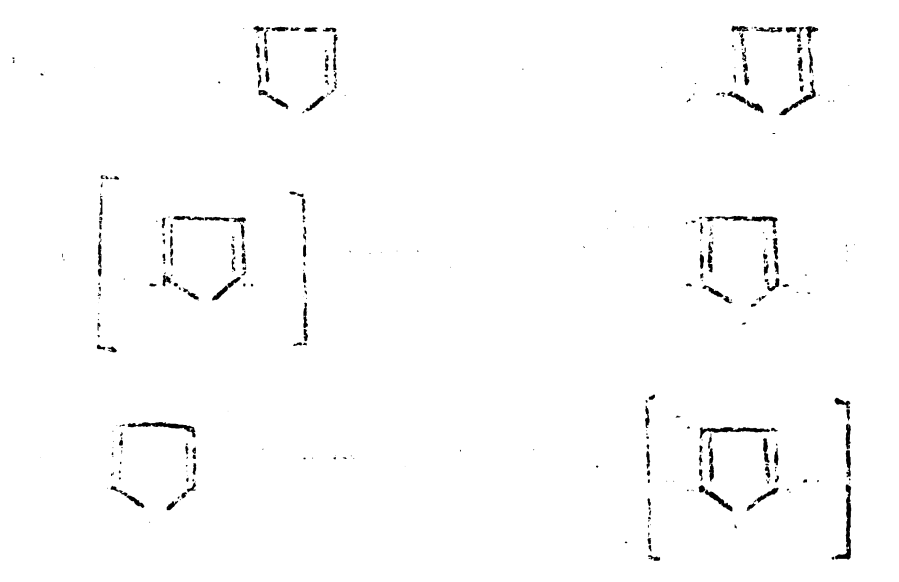
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chlorine atoms toward lithium aluminum hydride should not be identical with a different substituent in the three position on the thiophene ring. The following sequence of reactions was therefore chosen for the preparation of 2,5-dichloro-3-thiophenethiol.



The 2,5-dichlorothiophene was commercially available from The Michigan Chemical Corporation and was purified by fractional distillation. The chlorosulfonation of 2,5-dichlorothiophene did not proceed as easily as with 2,5-diethylthiophene. The yields of 2,5-dichloro-3-thiophenesulfonyl chloride were considerably lower than in the corresponding case with 2,5-diethylthiophene. A cursory study was made of this reaction. The mole ratio of 2,5-dichlorothiophene to chlorosulfonic acid was varied and the yields of 2,5-dichloro-3-thiophenesulfonyl chloride was determined by isolation of the product. The isolation of the product was carried out in the same manner as with 2,5-diethyl-3-thiophenesulfonyl chloride.

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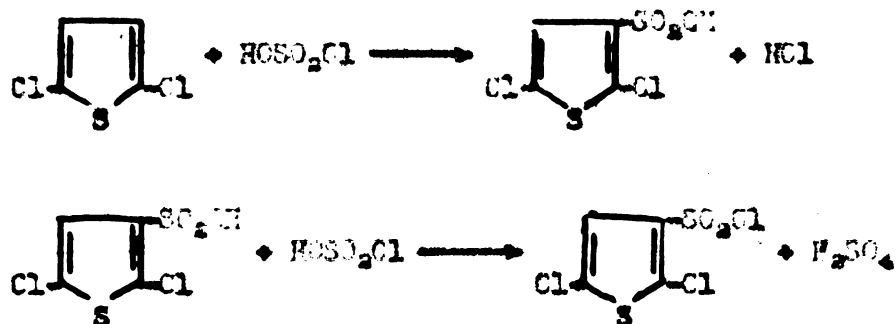
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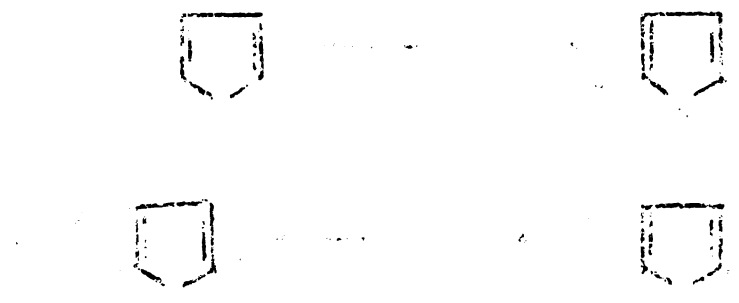
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It was found that the greater the mole ratio of chlorosulfonic acid to 2,5-dichlorothiophene the greater the yield of 2,5-dichloro-3-thiophenesulfonyl chloride obtained. For purposes of discussion this reaction can be considered to proceed in two steps; as follows:



Under the conditions of the reaction, the first step is probably irreversible. The second step of the reaction could be reversible. The equilibrium would be shifted in favor of the 2,5-dichloro-3-thiophenesulfonyl chloride with increasing concentration of chlorosulfonic acid. This would explain the increase in yield with higher concentration of chlorosulfonic acid. Some evidence favors this explanation rather than an explanation which indicates the initial step is the cause of lower yields. The 2,5-dichlorothiophene reacts with chlorosulfonic acid very vigorously to give a reddish black colored reaction mixture. Tar formation is greatly accelerated when the reaction temperature is allowed to rise much above 0°C . This indicates that chlorosulfonic acid and 2,5-dichlorothiophene readily react, but does not indicate that the reaction product is the desired one. In all cases a considerable quantity of 2,5-dichloro-3-thiophenesulfonic acid was formed, and this



was isolated as either its sodium or potassium salt. Unfortunately, the individual yields of the 2,5-dichloro-3-thiophenesulfonic acid were not determined and thus there is no indication of whether the yield of this material is markedly effected by chlorosulfonic acid concentration. In all of the reactions studied large quantities of hydrogen chloride were liberated which is also an indication that the first step in the chlorosulfonation proceeded as written. The results of the chlorosulfonation experiments are summarized in Table III, and yields against the mole ratio of chlorosulfonic acid to 2,5-dichlorothiophene are plotted in Figure 2.

Since the quantity of 2,5-dichloro-3-thiophenesulfonyl chloride needed was large and the yields of this material obtained by the direct chlorosulfonation of 2,5-dichlorothiophene were rather low and the 2,5-dichloro-3-thiophenesulfonic acid was employed as an intermediate in the synthesis of 2,5-dichlorothiophenethiol. The 2,5-dichloro-3-thiophenesulfonic acid, obtained as a by-product of the chlorosulfonation reaction, was isolated by forming its sodium salt by neutralizing the acid solution with sodium hydroxide, drying this salt, and then extracting the sodium 2,5-dichloro-3-thiophenesulfonate from the sodium sulfate with anhydrous methanol. It was found that the sodium salt was more easily extracted from sodium sulfate than the corresponding potassium salt was from potassium sulfate.

A single attempt was made to prepare 2,5-dichloro-3-thiophenesulfonic acid directly by the interaction of equimolar quantities of

TABLE III

CHLOROSULFATION OF 2,5-DICHLOROTHIOPHENE WITH CHLOROSULFONIC ACID

Moles Chlorosulfonic Acid	Moles 2,5-Dichlorothiophene	Mole Ratio HOSO ₂ Cl:2,5-Dichlorothiophene	Moles 2,5-Dichlorothiophene- 3-sulfonyl chloride	Percent Yield 2,5-Dichlorothiophene- 3-sulfonyl chloride
2	1	2	0.0190	5.86
3	1	3	0.0931	9.81
5	1	5	0.192	19.2

CHLOROSULFONATION OF
2,5-DICHLOROTHIOPHENE

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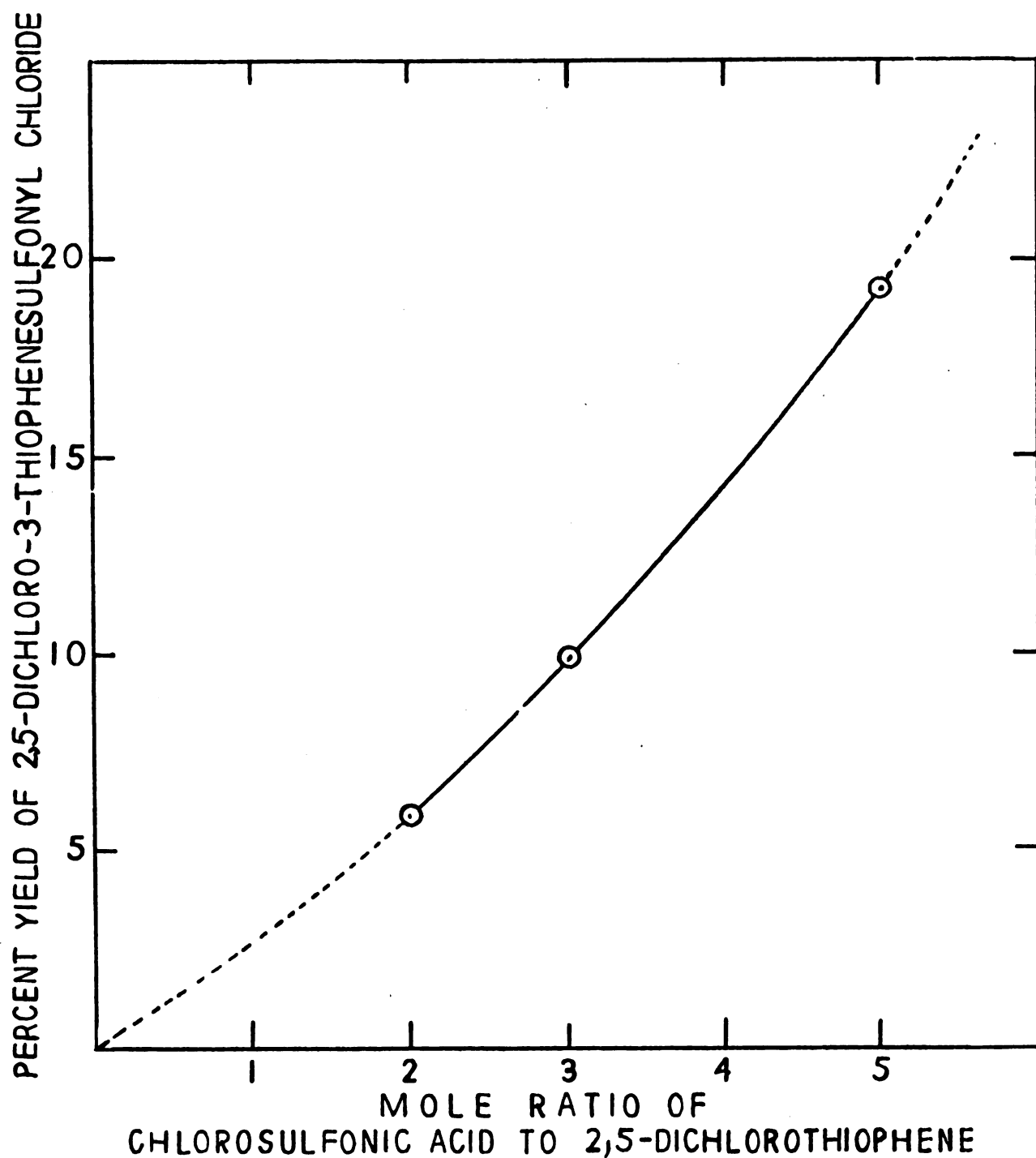


FIGURE 2.

chlorosulfonic acid and 2,5-dichlorothiophene. Control of the temperature of the reaction mixture was not efficient enough for the quantities of reagents employed and a sudden vigorous reaction set in yielding mainly tarry materials and a very low yield of the desired product was obtained.

The sodium and potassium salts of 2,5-dichloro-3-thiophenesulfonic acid were converted to 2,5-dichloro-3-thiophenesulfonyl chloride by means of phosphorus pentachloride by a modification of Adams and Marvel (55) procedure. The 2,5-dichloro-3-thiophenesulfonyl chloride was isolated by hydrolysis of the excess phosphorus pentachloride, extraction of the product with carbon tetrachloride, drying, and fractional distillation to obtain the pure product. The 2,5-dichloro-3-thiophenesulfonyl chloride was characterized by the formation of its sulfonamide and elemental analysis of the latter. These results are shown in Table II.

The lithium aluminum hydride reduction of 2,5-dichloro-3-thiophenesulfonyl chloride to 2,5-dichloro-3-thiophenethiol was accomplished by the same method as was employed for the reduction of 2,5-dimethyl-3-thiophenesulfonyl chloride. The reduction was more vigorous for the dichlorothiophene derivative than for the dimethyl derivative. When the ethereal solution of 2,5-dichlorothiophene-3-sulfonyl chloride came into contact with the ethereal solution of lithium aluminum hydride the resulting localized precipitate glowed a fiery red color. When this material adhered to the inside of the flask the glowing was observable for several seconds. The reduction of the chlorosulfonyl group was accomplished without the reductive removal of the chlorine atoms from

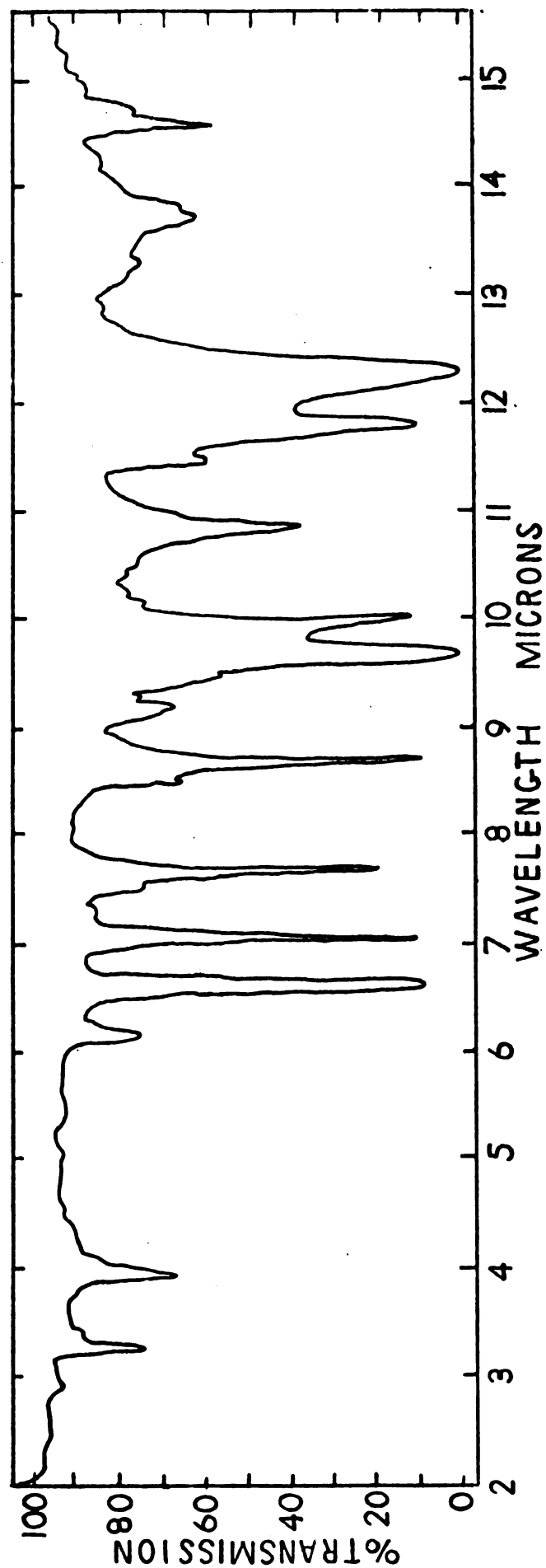
the first of these is the fact that the majority of the population of the United States is of European descent. This is a fact which has been recognized by the government and the people alike. It is a fact which has been recognized by the government and the people alike. It is a fact which has been recognized by the government and the people alike.

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the thiophene ring. The resulting 2,5-dichloro-3-thiophenethiol was characterized by forming its 2,4-dinitrophenyl sulfide derivative and making an elemental analysis of this derivative. The results of this analysis are to be found in Table II. The infra-red spectra of 2,5-dichloro-3-thiophenethiol was determined on a fresh sample which is shown in Figure 3. The infra-red spectra indicated a sulfhydryl group present by the absorption band at 3.9μ . The 2,5-dichloro-3-thiophenethiol was unstable even when stored in a freezing chest under an atmosphere of nitrogen over a long period of time. As the material aged it became partially insoluble in a sodium hydroxide solution. This instability could be due to either dimerization or to oxidation of the thiol to the corresponding disulfide from residual oxygen left in the container after sweeping it with nitrogen. However, oxygen could have entered the container since it was opened frequently for removal of material to prepare derivatives.

After two previously undescribed 3-thiophenethiols were successfully synthesized an attempt was made to synthesize some heretofore unknown 2-thiophenethiols. These were of interest for the same reasons as the 3-thiophenethiols; namely, to study a method for preparing them as well as to investigate some of their derivatives for possible pharmacological activity. Even though the work of Schuetz and Houff (6,7) indicated that the 2-thiophenethiol derivatives showed no local anesthetic activity whereas the 3-thiophenethiol derivatives did, there was no assurance that substituted 2-thiophenethiols would follow this same pattern.



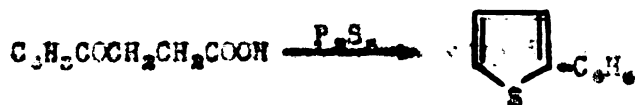
INFRARED ABSORPTION SPECTRA OF 2,5-DICHLORO-3-THIOPHENETHIOL

FIGURE 3

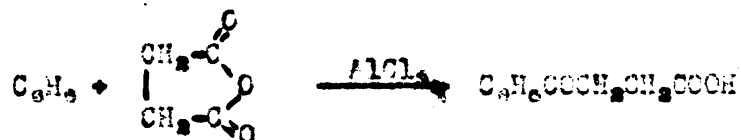
In order to obtain thiols with a different substituent than an alkyl or halo group, a phenyl group was chosen as the next group to have present in the thiophene ring with the thiol group. After a careful search of the literature it was decided to synthesize 5-phenyl-2-thiophenethiol. This compound could be obtained by way of the previously reported 5-phenyl-2-bromothiophene (41). Although the structure of 5-phenyl-2-bromothiophene had not been vigorously proven previously, the present investigation supports the earlier work of Steinkopf and his co-workers (41). They brominated 2-phenylthiophene by cyanogen bromide to obtain the monobromo 2-phenylthiophene. The point of attack of the bromine would be expected to be at the most active position remaining, which is the five position. When elemental bromine was used, Kues and Paul (27) reported difficulty in exclusively brominating the thiophene nucleus. Presumably the para position of the phenyl group was also easily brominated. In the present investigation several attempts were made to brominate 2-phenylthiophene with cyanogen bromide, but all attempts failed. This was even true when analytically pure 2-phenylthiophene was employed. Whatever was inhibiting the bromination could only be present in trace amounts in the 2-phenylthiophene or was present in the freshly purchased white label Eastman Chemical Company cyanogen bromide. The bromination was tried with two different samples of cyanogen bromide. The other possibility exists that an impurity was present in the previous work of Steinkopf (41), which catalyzed the reaction to give exclusive attack in the five position of the thiophene ring. The 5-phenyl-2-bromothiophene was prepared by brominating

2-phenylthiophene with N-bromosuccinimide in carbon tetrachloride as the solvent. The product obtained had the same melting point as that reported by the cyanogen bromide method and analyzed correctly for mono-bromo 2-phenylthiophene. A further attempt was made to prove the structure of 5-phenyl-2-bromothiophene and will be elaborated upon following the discussion of the synthesis of 2-phenylthiophene.

The synthesis of 2-phenylthiophene has been accomplished by several different methods. None of the methods already reported in the literature gave very high yields of 2-phenylthiophene. After the various methods available were tried, a method was developed for the synthesis of 2-phenylthiophene which gave better yields and also was applicable to large quantities of material. The first method used was a ring closure of β -benzoylpropionic acid with phosphorus pentasulfide (27).



The β -benzoylpropionic acid was prepared by a procedure reported by Somerville and Allen (66) which involved a Friedel Crafts acylation of benzene with succinic anhydride in the presence of anhydrous aluminum chloride.



The ring closure reaction of this material to yield 2-phenylthiophene gave very poor yields. The β -benzoylpropionic acid and phosphorus

pentasulfide were intimately mixed and then heated in a Wurts flask. After the reaction had been initiated by carefully heating the mixture it became very vigorous and considerable charring of the reagents ensued. Only small quantities of 2-phenylthiophene could be distilled from the reaction mixture. To moderate the reaction, the β -benzoylpropionic acid was converted to its sodium salt by neutralizing the acid with a sodium hydroxide solution and evaporating the resulting sodium β -benzoylpropionate solution to dryness. The dry sodium β -benzoylpropionate after mixing with phosphorus pentasulfide was an improvement over the use of the free acid, but even with this modification the yields were only slightly improved. Chruszczewski (28) reported the same reaction with improved yields by using sand as diluent in the reaction mixture. This method was employed using sodium β -benzoylpropionate, sand, and phosphorus heptasulfide. This modification moderated the reaction but the product obtained was very impure and the yields were still very poor. The procedure was slightly improved by conducting the ring closure reaction in an evacuated Wurts flask so that as the 2-phenylthiophene formed it was immediately distilled from the reaction mixture to prevent its thermal decomposition. This procedure gave a crude product that was more easily purified. After preparing 2-phenylthiophene by the ring closure procedures using β -benzoylpropionic acid or its sodium salt, it was concluded that a better method was needed to conveniently prepare the larger quantities of 2-phenylthiophene needed in the present work.

• The first step in the process of creating a business plan is to conduct a market research. This involves identifying the target market, understanding the needs and preferences of the customers, and analyzing the competitive landscape. Market research can be conducted through various methods, including surveys, interviews, focus groups, and secondary research. The information gathered from market research is used to develop a clear understanding of the market and to identify opportunities for the business.

• The second step in the process of creating a business plan is to develop a marketing strategy. This involves determining the marketing objectives, identifying the target market, and selecting the marketing mix. The marketing mix consists of the product, price, place, and promotion. The marketing strategy should be designed to achieve the marketing objectives and to reach the target market effectively.

• The third step in the process of creating a business plan is to develop a financial plan. This involves determining the financial objectives, identifying the sources of capital, and projecting the financial performance of the business. The financial plan should be designed to achieve the financial objectives and to provide a clear picture of the financial health of the business.

• The fourth step in the process of creating a business plan is to develop an operational plan. This involves determining the operational objectives, identifying the resources, and developing the operational procedures. The operational plan should be designed to achieve the operational objectives and to provide a clear picture of the operational health of the business.

• The fifth step in the process of creating a business plan is to develop a management plan. This involves determining the management objectives, identifying the management team, and developing the management procedures. The management plan should be designed to achieve the management objectives and to provide a clear picture of the management health of the business.

• The sixth step in the process of creating a business plan is to develop a risk management plan. This involves identifying the risks, assessing the risk, and developing the risk management strategies. The risk management plan should be designed to identify the risks, assess the risk, and develop the risk management strategies.

• The seventh step in the process of creating a business plan is to develop a legal plan. This involves identifying the legal requirements, assessing the legal risk, and developing the legal strategies. The legal plan should be designed to identify the legal requirements, assess the legal risk, and develop the legal strategies.

• The eighth step in the process of creating a business plan is to develop a human resources plan. This involves identifying the human resources requirements, assessing the human resources risk, and developing the human resources strategies. The human resources plan should be designed to identify the human resources requirements, assess the human resources risk, and develop the human resources strategies.

• The ninth step in the process of creating a business plan is to develop a technology plan. This involves identifying the technology requirements, assessing the technology risk, and developing the technology strategies. The technology plan should be designed to identify the technology requirements, assess the technology risk, and develop the technology strategies.

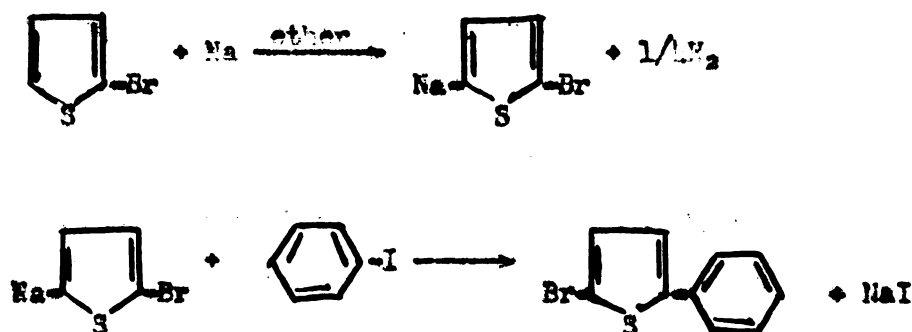
• The tenth step in the process of creating a business plan is to develop a sustainability plan. This involves identifying the sustainability requirements, assessing the sustainability risk, and developing the sustainability strategies. The sustainability plan should be designed to identify the sustainability requirements, assess the sustainability risk, and develop the sustainability strategies.

Gomberg and Bachmann (31) prepared 2-phenylthiophene in an eleven percent yield by reacting benzenediazonium chloride with thiophene in the presence of a two percent excess of caustic. When this reaction was attempted on a one mole scale the yield of 2-phenylthiophene was less than six percent. The success of the method depends on using a large enough excess of thiophene so that when the heterogeneous aqueous mixture of benzenediazonium chloride and thiophene is vigorously stirred, the suspension of thiophene will extract the unstable benzenediazo oxide from the mixture as rapidly as it is formed from the benzenediazonium chloride when the sodium hydroxide is slowly added to the reaction mixture. The yellow solid formed when the base is added has been postulated (36) to be the diazo anhydride, $\text{HN}_2\text{-O-N}_2\text{H}$, which undergoes hydrolysis to give the active species. These compounds are exceedingly unstable and explosive in the dry or moist state; therefore, it is imperative that the active intermediate be extracted immediately into the thiophene phase where it forms the arylthiophene compound. The reaction mixture is hazardous if a large excess of the benzenediazo oxide is allowed to accumulate in the reaction mixture. The product was isolated by flash steam distillation with the distillation flask immersed in an oil bath kept at 130°C . to prevent foaming. The product was very slowly steam distilled, necessitating large quantities of distillate having to be collected. The Gomberg and Bachmann method is an elegant synthesis of arylthiophenes, especially the arylthiophenes that are substituted with other groups such as halo, nitro and cyano.

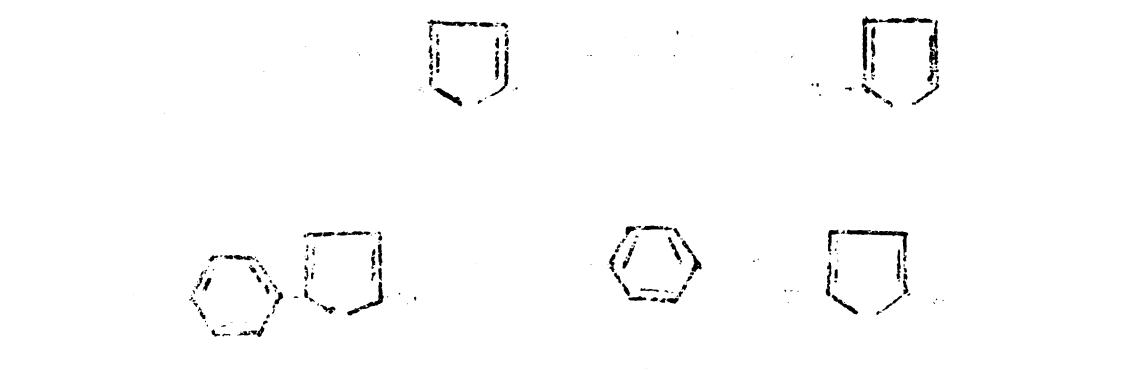
Starting with substituted aniline, Gomberg and Zachmann (31) obtained approximately twenty-five percent yields of the corresponding substituted arylthiophenes.

The difficulty in applying this reaction to a large scale preparation lies in the fact that very efficient stirring is needed to rapidly extract the benzenediazo oxide into the thiophene phase before it undergoes decomposition. This was probably the main factor responsible for the low yield obtained in the one attempt to apply this method in the present investigation.

A single attempt was made to synthesize 5-phenyl-2-bromothiophene directly from 5-bromo-2-thienyl sodium as illustrated in the following equations.



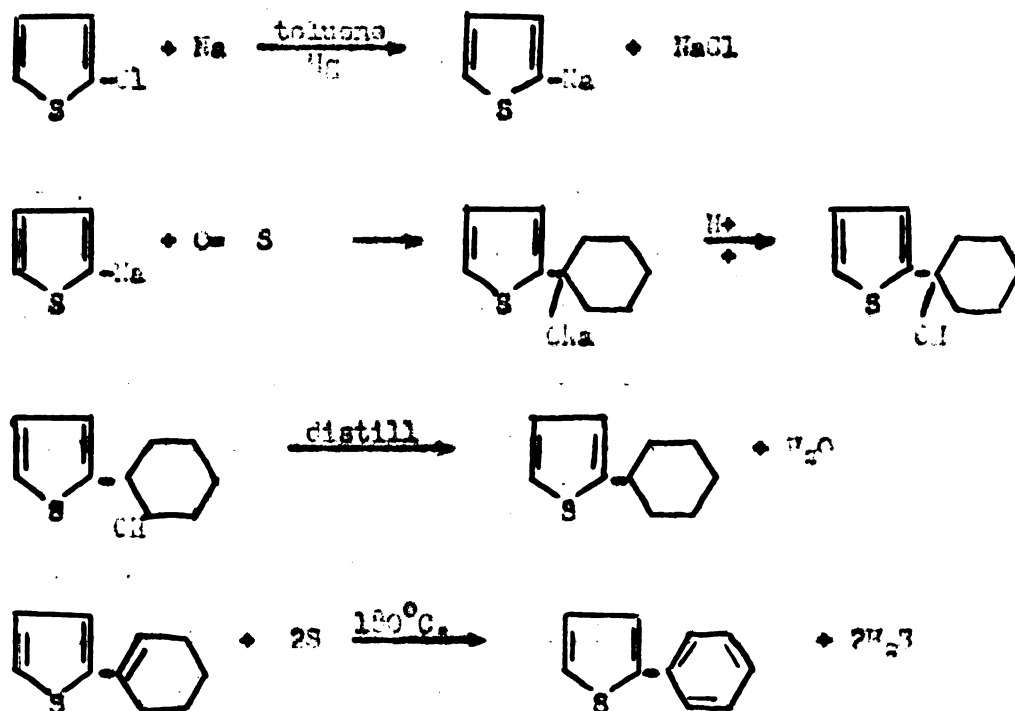
Hartough and Schick (57) discovered that when 2-halothiophenes are treated with amalgamated sodium sand at the reflux temperature of diethyl ether 5-halo-2-thienylsodium is formed. If the reaction is carried out in toluene or benzene as a solvent at the reflux temperatures of the reaction mixture, then the halogen is replaced by the sodium atom to yield 2-thienylsodium. Apparently at the lower temperature and with



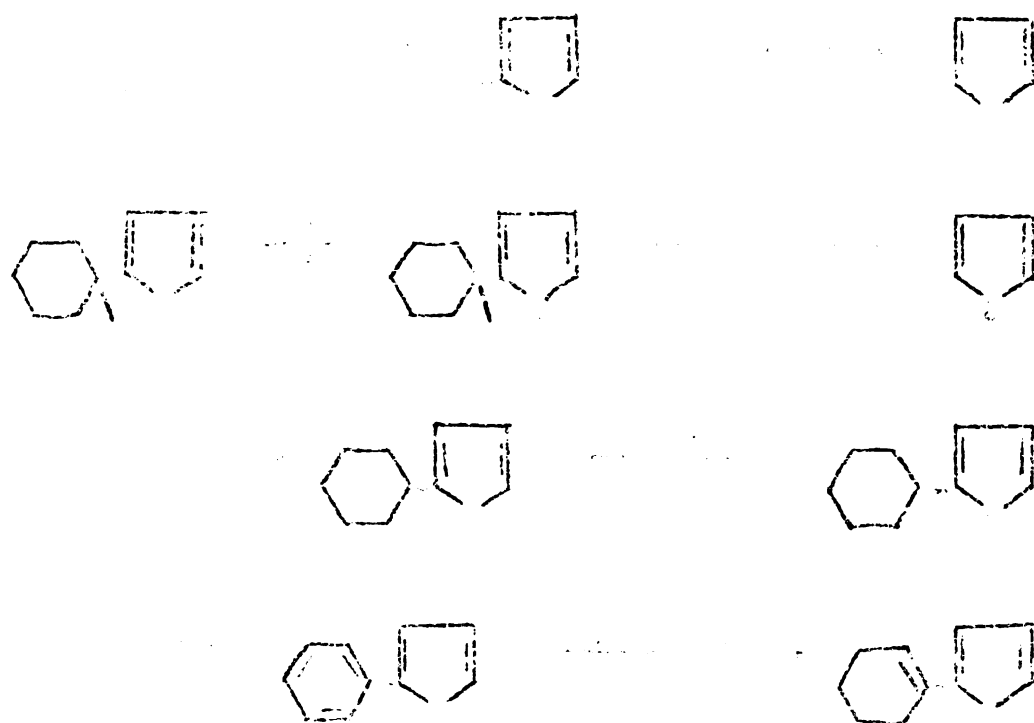
diethyl ether as the solvent the hydrogen in the five position of 2-halothiophenes is acidic enough to be replaced by the sodium metal. Hartough and Schick attempted the same reaction with other solvents such as, butyl ether, diisopropyl ether, diphenyl ether, anisole, hexane, benzene and toluene, but were unsuccessful in metalating the thiophene nucleus using these solvents.

The amalgamated sodium sand was prepared by a method described by Hartough (22). The mercury and sodium were placed in dry toluene and heated to 100° C. at which temperature an exothermic reaction occurred causing the reaction mixture to reflux spontaneously for approximately a minute. The reaction mixture was vigorously stirred until the temperature fell to 35° C. The toluene was siphoned from the amalgamated sodium sand through a fritted tube and then the amalgamated sodium was covered with dry diethyl ether. The 2-bromothiophene was added to this ethereal mixture at the reflux temperature of the ether. The 5-bromo-2-thienyl sodium was not isolated but was used directly in the next reaction. A three and a half molar excess of iodobenzene was added to the 5-bromo-2-thienylsodium mixture and the mixture was kept at its reflux temperature for five hours. When the reaction mixture was worked up by, destroying any sodium present with alcohol and water, steam distillation, and fractional distillation of the organic portion of the steam distillate which had been combined with the residual material in the steam distillation pot, the iodobenzene and most of the 2-bromo-thiophene was recovered unchanged. No further attempts were made to prepare 5-phenyl-2-bromothiophene by this method.

The 2-thienylsodium was prepared by the following method for the first time, as illustrated by the following equations.



The 2-thienylsodium was prepared from amalgamated sodium sand, as described previously, and 2-chlorothiophene in refluxing benzene as a reaction medium. The amalgamated sodium sand was prepared in toluene and then the toluene was replaced with dry benzene. The 2-chlorothiophene was added to the amalgamated sodium sand suspension in the benzene. The reaction was exothermic which caused the benzene to reflux spontaneously after the reaction had been initiated by external heating. The freshly prepared 2-thienylsodium was used directly in the reaction with cyclohexanone without prior isolation. The cyclohexanone was added to the 2-thienylsodium suspension in benzene while the mixture was



cooled in an ice bath maintained between 4° and 12° C. After the reaction mixture had warmed to room temperature and it had been allowed to react an additional forty-five minutes the excess sodium or sodium derivatives which might have been present was destroyed with ethanol and water. The reaction mixture was then acidified with hydrochloric acid. The organic portion was washed, dried, and finally fractionated using a one foot Vigreux column. Two fractions were collected which appeared to be the desired product along with some impurities. One fraction boiling at $113-115^{\circ}$ C./1.5 mm. Hg readily decolorized a bromine carbon tetrachloride solution with no visible signs of hydrogen bromide evolution. Another fraction boiling at $153-157^{\circ}$ C./2.5 mm. Hg only decolorized small amounts of bromine solution. The infra red spectra of the first fraction indicated unsaturation while that of the second showed only a relatively weak absorption band for unsaturation. Whereas the first fraction had only a weak absorption for the hydroxyl band the second fraction had a stronger absorption for the hydroxyl band. It was concluded that the first fraction was mainly 2(1'-cyclohexenyl)thiophene and the second was mainly 2(1'-cyclohexenyl)thiophene. Each was contaminated with some of the other because of the poor efficiency of the fractionating column.

The lower boiling fraction was further treated with sulfur to dehydrogenate the 2(1'-cyclohexenyl)thiophene to yield 2-phenylthiophene by a method reported by Sherwood and his collaborators (59). The theoretical amount of sulfur needed to split out two molecules of hydrogen was heated at $180-220^{\circ}$ C. with some of the lower boiling fraction.

1. The first step in the process of the scientific method is to make an observation or ask a question. For example, a scientist might observe that a plant grows better in one type of soil than another.

2. Next, the scientist forms a hypothesis, which is a prediction or an educated guess about the outcome of an experiment. For instance, the scientist might hypothesize that the plant will grow taller in soil A than in soil B.

3. The third step is to design an experiment to test the hypothesis. This involves setting up a controlled experiment where only one variable is changed at a time. In this case, the scientist would plant the same type of plant in two different soils and measure their growth over time.

4. After conducting the experiment, the scientist collects data and analyzes it. This step involves looking for patterns and trends in the data to see if they support the hypothesis.

5. Finally, the scientist draws a conclusion based on the results of the experiment. If the data supports the hypothesis, the scientist may accept it. If not, the scientist may reject it and form a new hypothesis.

6. The scientific method is a systematic approach to investigating a question or solving a problem. It involves making observations, forming hypotheses, designing experiments, collecting data, and drawing conclusions.

7. One of the key features of the scientific method is that it is self-correcting. If a hypothesis is proven wrong, the scientist can reject it and start over with a new hypothesis.

8. The scientific method is used in many fields of study, including biology, chemistry, physics, and earth science. It is a fundamental part of the scientific process.

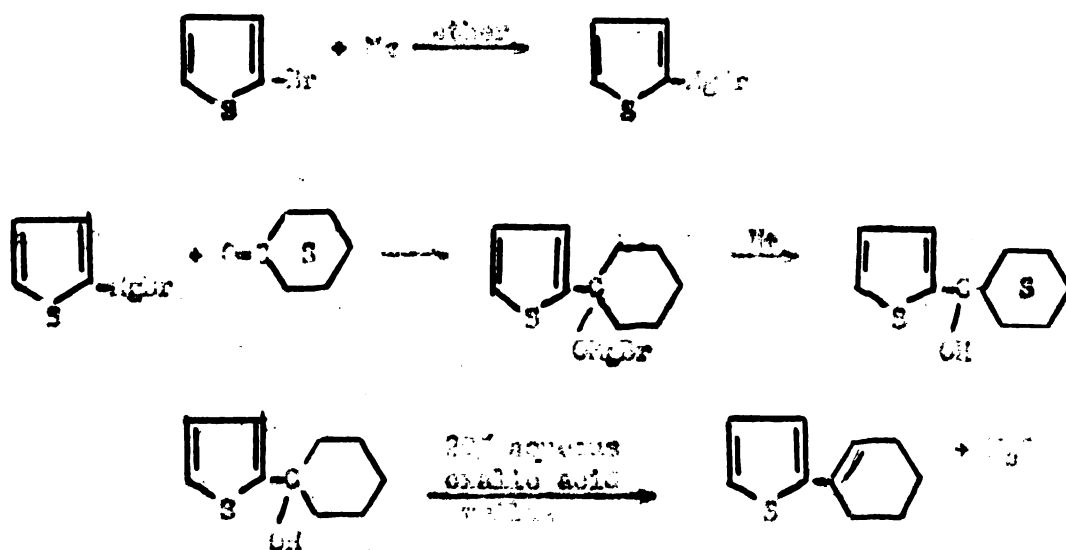
9. The scientific method is a way of thinking that helps scientists to understand the natural world. It is a process that involves making observations, asking questions, and testing ideas.

10. The scientific method is a way of thinking that helps scientists to understand the natural world. It is a process that involves making observations, asking questions, and testing ideas.

lower temperatures, namely 173°C ., was found to give only partial dehydrogenation. The product, isolated by distillation, solidified when allowed to cool. After recrystallizing the material several times from ethanol it melted at $12-13^{\circ}\text{C}$. which is the reported (27,28,31) melting point for 2-phenylthiophene. This was further evidence that the low boiling fraction contained 2-(1'-cyclohexenyl)thiophene as the main component.

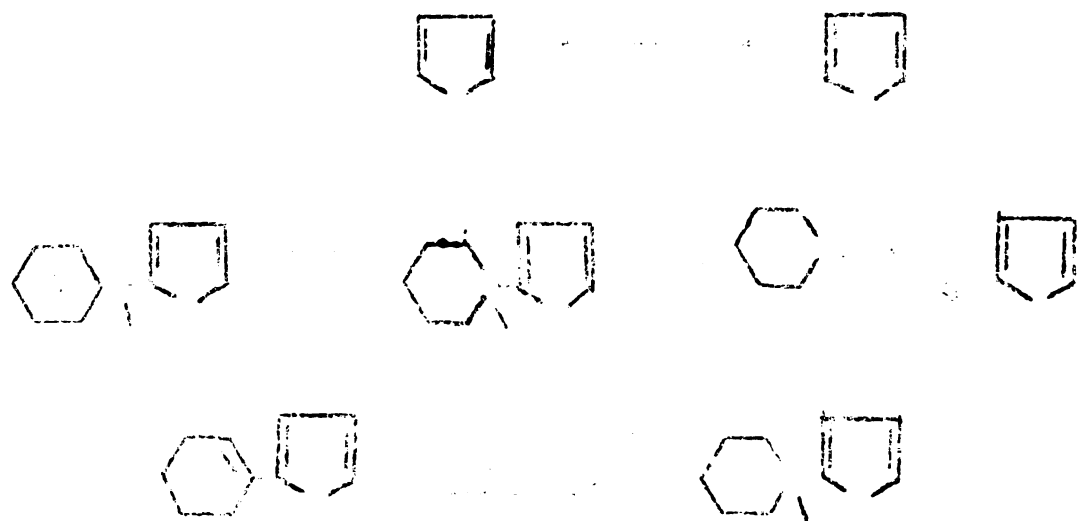
The higher boiling fraction which was assumed to be 2-(1'-cyclohexanolyl)thiophene was treated with formic acid to dehydrate it to 2-(1'-cyclohexenyl)thiophene. When this was carried out a very exothermic reaction ensued and a material was isolated which boiled in the proper range for 2-(1'-cyclohexenyl)thiophene, along with other materials. The product readily decolorized bromine in carbon tetrachloride without visible signs of hydrogen bromide being evolved. This lends support that the higher boiling fraction could be partly 2-(1'-cyclohexanolyl)thiophene. The material was not investigated further, because a better method was used to prepare the same products in pure form with good yields. This was the first time that 2-phenylthiophene was synthesized by the above route.

After it was demonstrated that 2-phenylthiophene could be synthesized from 2-(1'-cyclohexenyl)thiophene by dehydrogenation with sulfur a better method for obtaining 2-(1'-cyclohexenyl)thiophene was sought. This was accomplished through a Grignard reaction of 2-thionyl magnesium bromide with cyclohexanone followed by a dehydration reaction, as represented by the following equations.



This series of reactions proceeded very smoothly with an over-all yield of better than eighty percent in the first attempt. At the time 2-(1'-cyclohexenyl)thiophene was prepared it was thought that this was an original synthesis, because of an omission of a reference to it in Hartough's monograph. However, a later very careful search of the literature disclosed that Fieser and Szmanski (42) had synthesized 2-(1'-cyclohexenyl)thiophene by a similar method. The Grignard reaction procedure was essentially the same; however, they dehydrated the intermediate tertiary alcohol by heating it in a vacuum. The boiling point and elemental analysis of the compound obtained by the oxalic acid dehydration method was in agreement with the previously reported method of synthesis.

The 2-phenylthiophene was synthesized by dehydrogenation of 2-(1'-cyclohexenyl)thiophene with sulfur. The sulfur and 2-(1'-cyclohexenyl)thiophene were thoroughly mixed in a flask and then immersed in



Diels-Alder reaction is a type of cycloaddition reaction between a diene and a dienophile. It is a concerted process, meaning it occurs in a single step without the formation of intermediates. The reaction is stereospecific, meaning the stereochemistry of the reactants is preserved in the product. For example, if the diene is in a cis configuration, the product will also be in a cis configuration. The reaction is also regioselective, meaning the substituents on the diene and dienophile end up in specific positions in the product. The Diels-Alder reaction is a very important reaction in organic chemistry, and it is used to synthesize a wide variety of cyclic compounds. It is also a key reaction in the synthesis of natural products and polymers.

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an oil bath. The dehydrogenation started when the temperature reached approximately 200° C. as evidenced by the evolution of hydrogen sulfide. The reaction was continued at 205° C. for two hours and finally the temperature of the bath was raised to 220° C. for five hours. Employing 200.0 g., 1.22 moles, of 2-(1'-cyclohexenyl)thiophene the yield of 2-phenylthiophene was fifty percent with recovery of, 8.34 g., 0.051 mole, of starting material. In a second preparation of 2-phenylthiophene where the temperature was held at 220° C. for four and three-quarter hours, the yield was essentially the same. In all cases the 2-phenylthiophene was isolated by fractional distillation. The product was further purified for some of the experiments with cyanogen bromide by crystallizing it from absolute ethanol.

The next step in the synthesis of 5-phenyl-2-thiophenethiol was the preparation of 5-phenyl-2-bromothiophene. The method of Steinkopf (11) which involves reacting 2-phenylthiophene with cyanogen bromide was attempted.



When this reaction was carried out at 40° C., bromination did not occur and the 2-phenylthiophene was isolated unchanged. To eliminate the possibility of failure of the reaction due to impure 2-phenylthiophene, the material isolated was further purified by recrystallizing it from ethanol and analyzing the product. The analysis, reported in Table IV, indicated that the 2-phenylthiophene was very pure. The analyzed pure



TABLE IV
ANALYTICAL RESULTS ON SUBSTITUTED THIOPHENE

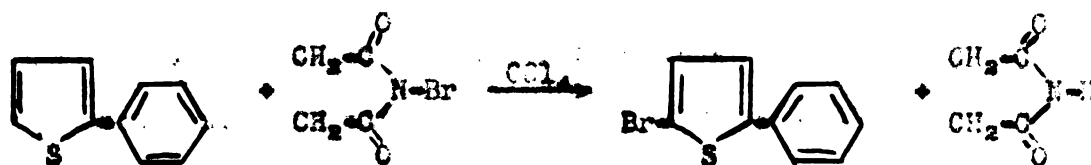
Compound	M.P., °C.	Formula	Percent Carbon Calcd. Found	Percent Hydrogen Calcd. Found	Percent Sulfur Calcd. Found
2-(1'-cyclohexenyl)thiophene	119-120°C./3.0mm.Hg.	$C_{10}H_{12}S$	73.12 72.92	7.37 7.42	19.52 19.39
2-phenylthiophene	42.5-43.0	$C_{10}H_8S$	74.96 74.86	5.03 5.18	20.01 20.14
2-phenyl-5-bromothiophene	85.5-86°	$C_{10}H_7BrS$	50.22 50.27	2.95 3.13	13.41 13.22
5-phenyl-2-thienyl disulfide	143-144°	$C_{20}H_{14}S_2$	62.79 62.97	3.69 3.90	33.52 33.47
5-(1'-cyclohexenyl)-2-thienyl disulfide	133-134°C.	$C_{20}H_{16}S_2$	61.49 61.20	5.68 6.07	32.83 32.66

^a Bromine analysis calcd. 33.42; found 33.26.

^b The compound may be the dimer of the parent substituted thiophenethiol rather than the disulfide.

2-phenylthiophene was then employed in the reaction, using a recently obtained sample of Eastman Chemical Company White Label cyanogen bromide. The mixture was heated at 60° C. and again bromination failed to occur and the 2-phenylthiophene was isolated unchanged. Following the second failure to obtain bromination of 2-phenylthiophene with cyanogen bromide this method was abandoned.

The 2-phenylthiophene was brominated in excellent yields with N-bromosuccinimide in dry carbon tetrachloride as a solvent.



The 2-phenylthiophene and N-bromosuccinimide, in equal molar quantities, were dissolved in carbon tetrachloride at room temperature and vigorously stirred for approximately an hour, and then heated at the reflux temperature of the reaction mixture for a period of five to ten hours. During the course of the reaction the succinimide crystallized from the reaction mixture. After cooling the reaction mixture the succinimide was removed by filtration. The 5-phenyl-2-bromothiophene was isolated by evaporating the carbon tetrachloride and recrystallizing the solid obtained in this manner from absolute ethanol. The melting point agreed with that reported and product analyzed correctly as is shown in Table IV.

The yields of 5-phenyl-2-bromothiophene were approximately eighty-eight percent without recovery of material from the mother liquor from

1. 在反应过程中，反应物与产物的化学式应正确书写，并配平。
 2. 反应条件应注明，如加热、光照、催化剂等。
 3. 反应物和产物的状态应注明，如气态（g）、液态（l）、固态（s）、水溶液（aq）等。
 4. 反应物和产物的名称应正确书写，并符合化学命名规则。
 5. 反应物和产物的分子式应正确书写，并符合化学式书写规则。
 6. 反应物和产物的结构式应正确书写，并符合化学结构式书写规则。
 7. 反应物和产物的物理性质应正确书写，如颜色、状态、气味等。
 8. 反应物和产物的化学性质应正确书写，如酸性、碱性、氧化性、还原性等。
 9. 反应物和产物的用途应正确书写，如工业用途、实验室用途等。
 10. 反应物和产物的制备方法应正确书写，如合成法、分离法、提纯法等。

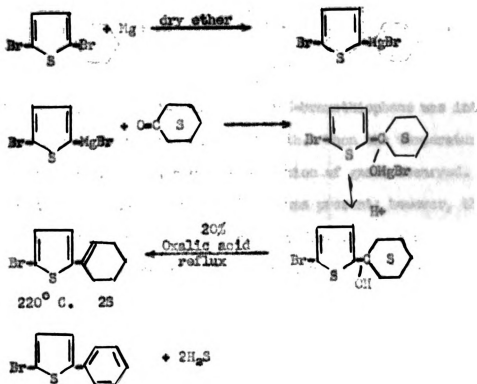


1. 在反应过程中，反应物与产物的化学式应正确书写，并配平。
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 10. 反应物和产物的制备方法应正确书写，如合成法、分离法、提纯法等。

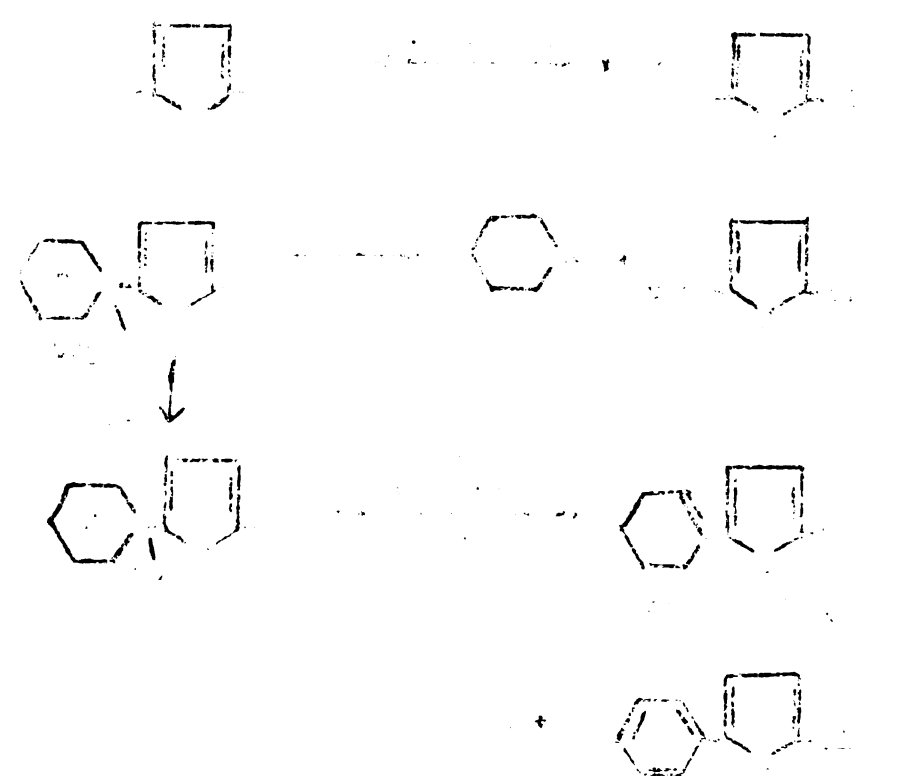
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 10. 反应物和产物的制备方法应正确书写，如合成法、分离法、提纯法等。

the crystallizations. During the course of the reaction some hydrogen bromide was evolved, which was probably due to the free bromine present in the N-bromosuccinimide. The small amount of bromine present did not cause difficulty in obtaining pure 5-phenyl-2-bromothiophene. Elemental bromine cannot be used to synthesize 5-phenyl-2-bromothiophene from 2-phenylthiophene because the phenyl group also brominates. In addition, difficulty is experienced in obtaining only monobromination. The present investigation is the first instance where N-bromosuccinimide was used to synthesize 5-phenyl-2-bromothiophene. From the yields obtained, it is apparent that the bromination is almost exclusive in the two position of the thiophene nucleus with little if any bromination occurring in the phenyl nucleus.

A further attempt was made to establish the structure of 5-phenyl-2-bromothiophene by preparing it by an alternative method as outlined in the following equations.

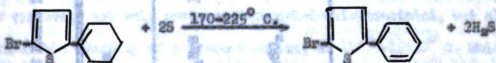


The first reaction is the polymerization of isoprene to form polyisoprene. This reaction is catalyzed by a variety of catalysts, including organotin compounds. The second reaction is the polymerization of isoprene to form polyisoprene. This reaction is catalyzed by a variety of catalysts, including organotin compounds. The third reaction is the polymerization of isoprene to form polyisoprene. This reaction is catalyzed by a variety of catalysts, including organotin compounds. The fourth reaction is the polymerization of isoprene to form polyisoprene. This reaction is catalyzed by a variety of catalysts, including organotin compounds. The fifth reaction is the polymerization of isoprene to form polyisoprene. This reaction is catalyzed by a variety of catalysts, including organotin compounds.



The formation of the 5-bromo-2-thienylmagnesium bromide was accomplished without difficulty. The reaction of this Grignard reagent with cyclohexanone followed by acidification and then removal of ether was also very easy. The 2-(1'-cyclohexenyl)-2-bromothiophene was not isolated in its pure form, but dehydrated directly with twenty percent oxalic acid to obtain 2-(1'-cyclohexenyl)-5-bromothiophene in a forty-eight percent yield based on the 2,5-dibromothiophene used. The product was isolated by fractional distillation. The synthesis of 2-(1'-cyclohexenyl)-5-bromothiophene has not been reported previously in the literature. The analytical results and some of its physical properties are reported in Table V.

An attempt was made to dehydrogenate the 2-(1'-cyclohexenyl)-5-bromothiophene with sulfur to 2-phenyl-5-bromothiophene in the same manner that 2-(1'-cyclohexenyl)thiophene was dehydrogenated to 2-phenylthiophene.



The sulfur and 2-(1'-cyclohexenyl)-5-bromothiophene was intimately mixed and heated in a flask in an oil bath. When the temperature of the bath had reached 170°C. , a sudden evolution of gases occurred. A lead acetate test indicated hydrogen sulfide was present; however, the fumes appeared also to have hydrohalide present from the odor and the strong acid test with litmus paper. In any case, no 5-phenyl-2-bromothiophene

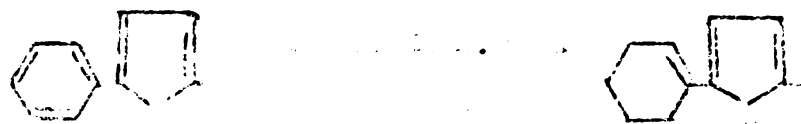
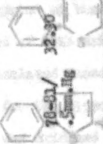
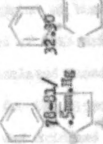


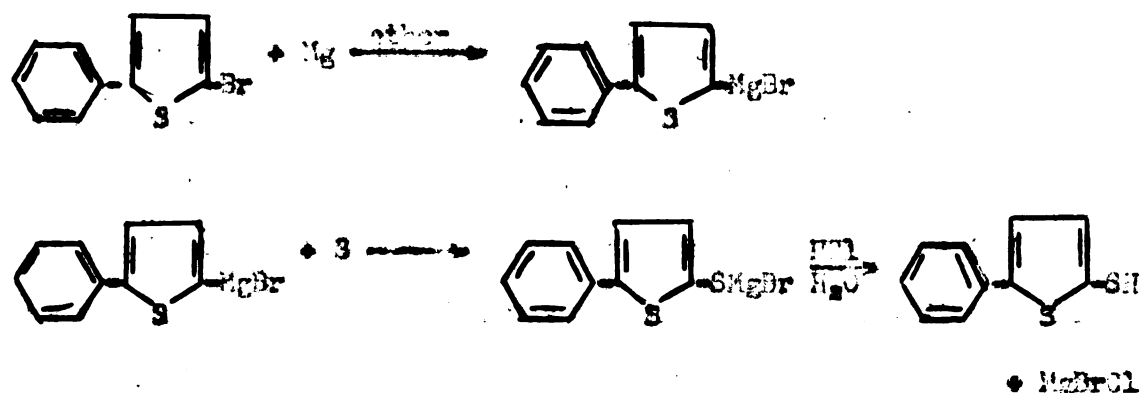
TABLE V

NEW BOND DERIVATIVES OF SUBSTITUTED THIOPHENES

Compound	Formula	M.p. °C.	B.p. °C.			Percent Carbon Calc'd. Found	Percent Hydrogen Calc'd. Found	Percent Sulfur Calc'd. Found	Percent Chlorine Calc'd. Found
5-Bromo-2-(1-cyclohexenyl)- thiophene	$C_{10}H_{11}BrS$	33.5-35.1	155-156/ 3.5mm.Hg			49.39	4.77	13.18	32.87
3,4-Dimethoxy-2-bromothiophene	$C_6H_4BrO_2S$	70-71/ 0.5mm.Hg				32.51	3.19	11.20	35.61

could be isolated and a considerable amount of tarry material was left in the steam distillation flask. It appeared as though hydrogen bromide split out from the 2-(1'-cyclohexenyl)-5-bromothiophene in a manner that formed a polymeric material resulting in the tarry residue. No further attempt was made to dehydrogenate the 2-(1'-cyclohexenyl)-5-bromothiophene.

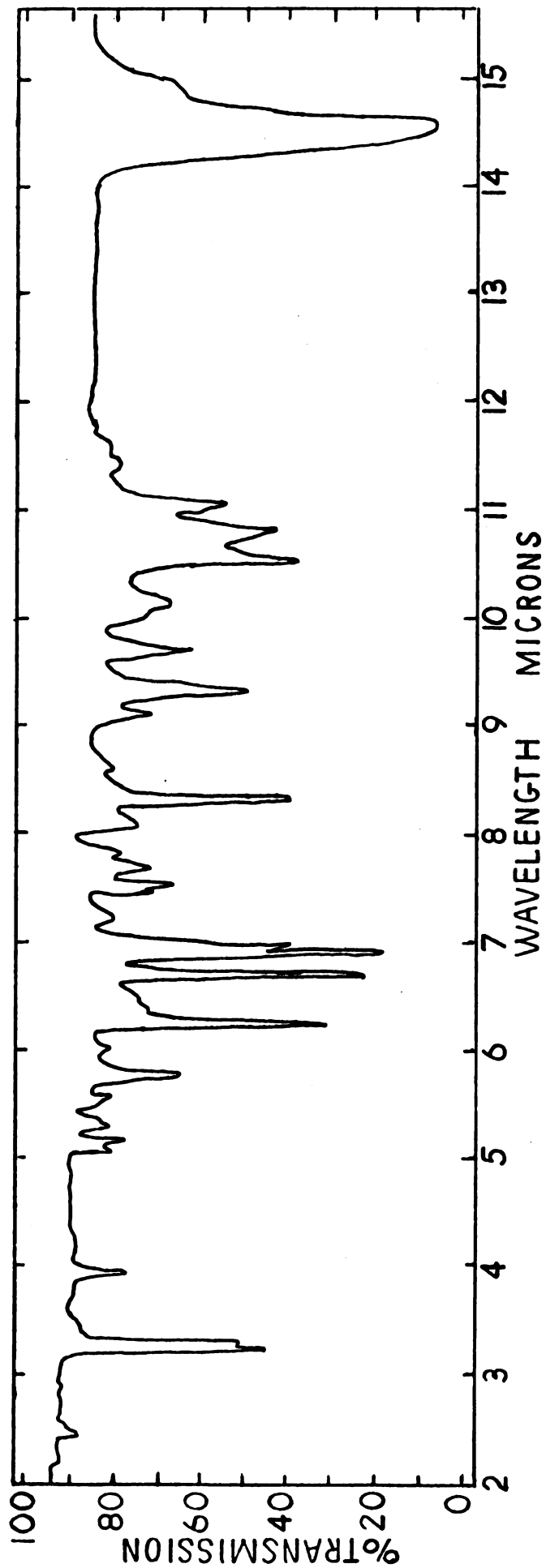
The compound, 5-phenyl-2-thiophenethiol was synthesized from 5-phenyl-2-bromothiophene through a Grignard reaction followed by interaction of the Grignard reagent with sulfur.



This synthesis not only produced 5-phenyl-2-thiophenethiol, but also a considerable quantity of a product melting at 146.5-147.0° C. which analyzed for the disulfide, 2,2'-diphenyldithienyl disulfide, as is shown in Table IV. This compound could possibly be a dimer of 5-phenyl-2-thiophenethiol, however, the analytical results agreed better with the disulfide than with the dimer. However, both could be considered within experimental error. Disulfide formation began immediately upon the addition of sulfur to the 5-phenyl-2-thienylmagnesium bromide. The disulfide was removed by filtration after acidification of the Grignard

complex. The 5-phenyl-2-thiophenethiol was isolated by extracting it from the ether layer with a sodium hydroxide solution followed by acidification, whereupon it crystallized from the aqueous solution and was easily recovered by filtration. The disulfide could have formed as a result of oxidation by the sulfur present during the addition of the sulfur to the 5-phenyl-2-thienylmagnesium bromide. As air was excluded from the reaction vessel at all times it could not have been the cause for the oxidation. The crude 5-phenyl-2-thiophenethiol melted at $72-73^{\circ}\text{C}$. and when an attempt was made to recrystallize it from a methyl alcohol-cyclohexane mixture the melting point of the material isolated was $113-114^{\circ}\text{C}$. A mixed melting point of this material with the 2,2'-diphenyl-dithienyl disulfide previously isolated showed no depression in melting point and it analyzed correctly for the disulfide. Apparently during the recrystallization the thiol was oxidized to the disulfide or it dimerized. An infra-red spectrum was determined for the 5-phenyl-2-thiophenethiol and is shown in Figure 4. An absorption band is indicated at $3.94\ \mu$ which is characteristic for the sulfhydryl group. A 2,4-dinitrophenyl sulfide derivative was prepared and it analyzed correctly for 2,4'-dinitrophenyl-5-phenyl-2-thienyl sulfide. Some of the physical properties and derivatives of 5-phenyl-2-thiophenethiol are summarized in Table II. The mercaptan 5-phenyl-2-thiophenethiol has not been reported previously in the literature. Two, previously unknown amine, -piperidinoalkyl-5-phenyl-2-thienylsulfide hydrochloride derivatives were prepared from this mercaptan and some of their physical properties are summarized in Table VIII.

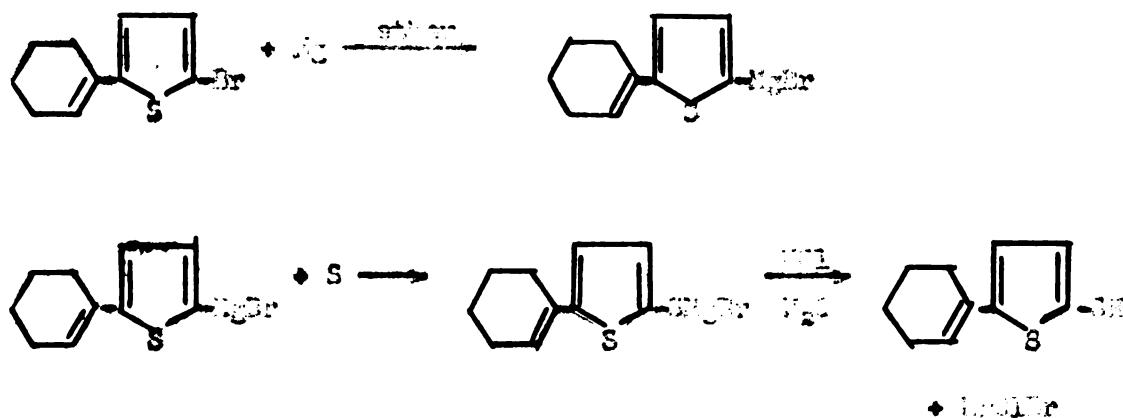
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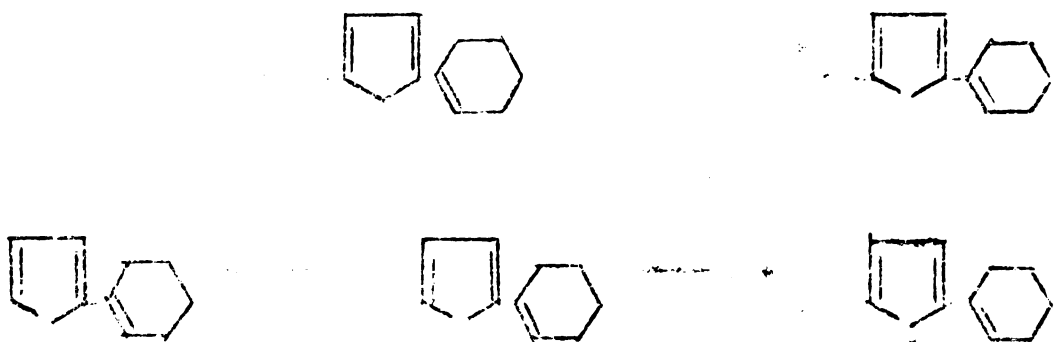
INFRARED ABSORPTION SPECTRA OF 5-PHENYL-2-THIOPHENETHIOL

FIGURE 4

An attempt was made to synthesize 5-(1'-cyclohexenyl)-2-thiophenethiol from 5-(1'-cyclohexenyl)-2-thiophenemagnesium bromide through the Grignard reaction.

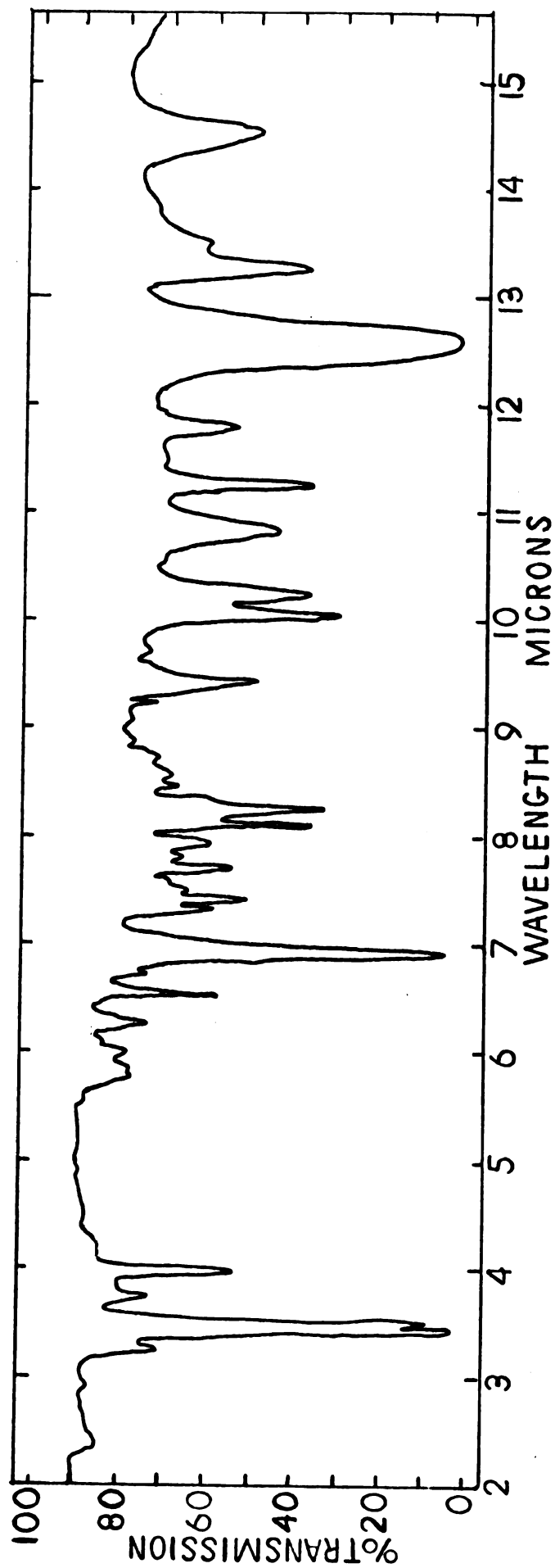


When the powdered sulfur was added to the 5-(1'-cyclohexenyl)-2-thiophenemagnesium bromide an exothermic reaction occurred. On acidification of the reaction mixture to free the 5-(1'-cyclohexenyl)-2-thiophenethiol from the magnesium salt a yellow precipitate immediately formed. The yellow precipitate was insoluble in ten percent aqueous sodium hydroxide solution which indicated it was probably not 5-(1'-cyclohexenyl)-2-thiophenethiol. The yellow precipitate was purified by recrystallization from isopropyl alcohol and then from acetone. Analysis of this material indicated it could be a dimer of 5-(1'-cyclohexenyl)-2-thiophenethiol. The analysis also was in good agreement with the disulfide of 5-(1'-cyclohexenyl)-2-thiophenethiol. In an attempt to prove that this compound was the disulfide a sample was reduced with lithium aluminum hydride by the method of Arnold *et al.* (10). The reaction mixture was first acidified, and the aqueous layer extracted with ether. The combined ether layer



and ether extract was then extracted with sodium hydroxide. The alkaline extract was acidified and extracted with ether. After drying the ether extract the ether was removed by distillation. The residue was not fractionally distilled to prevent thermal decomposition but an infra-red spectra was obtained immediately on the material. All attempts to prepare a 2,4,- dinitrophenyl sulfine derivative resulted only in oils which could not be induced to crystallize. The infra red spectrum indicated a sulfinyl group present by an absorption band at 3.76μ as is shown in Figure 5. The infra red absorption spectrum of the lithium aluminum hydride reduction product was similar to the infra red absorption spectrum of the material obtained in the original synthesis of 5-(1'-cyclohexenyl)-2-thiophenethiol by the Grignard reaction. There were some absorption bands present in the material obtained from the lithium aluminum hydride reduction which were not present originally and these would be expected in view of the fact that the material from the lithium aluminum hydride reduction was not fractionally distilled. There were absorption bands at 3.95μ and 6.50μ which are in the region for the sulfate ion. These bands were probably present due to the use of magnesium sulfate in drying the material. The evidence still is inconclusive as to whether the solid material is the dimer of the thiol or whether it is the disulfide.

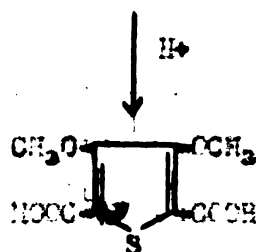
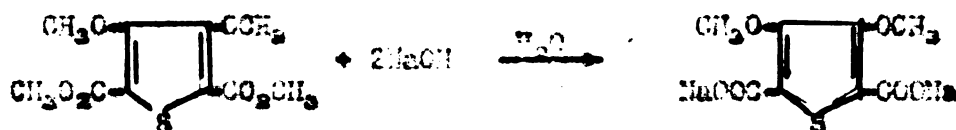
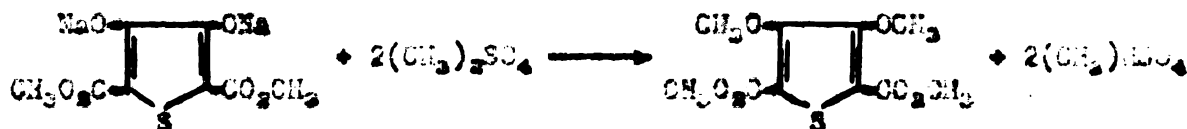
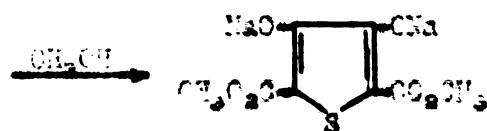
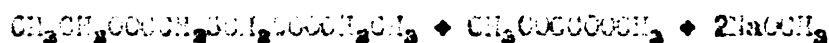
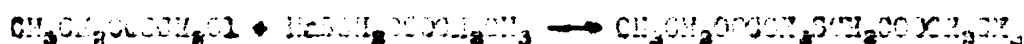
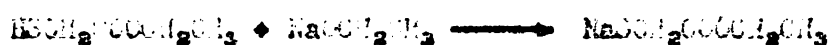
As no thiophenethiols with a methoxy group has previously been reported in the literature, an attempt was made to prepare a thiophenethiol of this type. After a careful review of the methods for obtaining



INFRARED ABSORPTION SPECTRA OF 5-(1'-CYCLOHEXENYL)-2-THIOPENETHIOL

FIGURE 5.

a methoxy substituted thiophene the 3,4-dimethoxythiophene was chosen as the parent compound. The method employed for the preparation of 3,4-dimethoxythiophene was a modification of those described by Fager (45), Overberger and Lai (47) and is represented by the following equations.



1. 在平面内，以点O为圆心，以r为半径画圆，则圆上任意一点到点O的距离都等于r。
 2. 在平面内，以点O为圆心，以r为半径画圆，则圆内任意一点到点O的距离都小于r。
 3. 在平面内，以点O为圆心，以r为半径画圆，则圆外任意一点到点O的距离都大于r。

4. 在平面内，以点O为圆心，以r为半径画圆，则圆上任意一点到点O的距离都等于r。

5. 在平面内，以点O为圆心，以r为半径画圆，则圆内任意一点到点O的距离都小于r。

6. 在平面内，以点O为圆心，以r为半径画圆，则圆外任意一点到点O的距离都大于r。

7. 在平面内，以点O为圆心，以r为半径画圆，则圆上任意一点到点O的距离都等于r。



8. 在平面内，以点O为圆心，以r为半径画圆，则圆内任意一点到点O的距离都小于r。

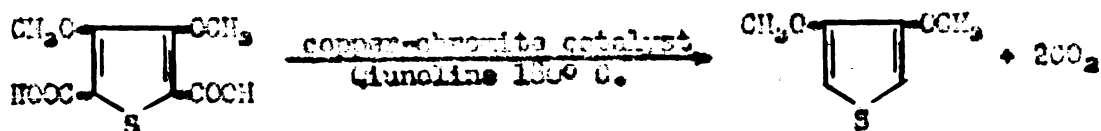


9. 在平面内，以点O为圆心，以r为半径画圆，则圆外任意一点到点O的距离都大于r。



10. 在平面内，以点O为圆心，以r为半径画圆，则圆内任意一点到点O的距离都小于r。





The esterification of thioglycolic acid was accomplished by a method first employed by Fieser (51). This involves heating a mixture of thioglycolic acid and ethanol at its reflux temperature for eight hours in the presence of sulfuric acid as a catalyst. The ethyl thioglycolate was isolated by adding excess anhydrous sodium carbonate to neutralize the sulfuric acid and glycolic acid as well as absorb water. Ether was added to precipitate the inorganic salts and the ethyl thioglycolate was finally isolated and purified by fractional distillation. The yield of ethyl thioglycolate depends largely on the ratio of thioglycolic acid to ethanol employed in the esterification. When the mole ratio was 1:3.19 the yield was 54.9% and when the mole ratio was 1:9.58 the yield was 65.6%.

Diethyl thioglycolate was synthesized by forming the sodium salt of ethyl thioglycolate by interchange with sodium ethoxide in ethanol as a solvent. The resulting sodium derivative was coupled with ethyl chloroacetate in ethanol as a solvent. The reagents were mixed at 50° C. and the mixture was heated to its reflux temperature for a half hour. Sodium chloride precipitated immediately upon mixing the reagents. Ether was finally added to the reaction mixture to precipitate the partially soluble sodium chloride and after filtering the mixture the diethyl thioglycolate was isolated in good yields by fractional

distillation. The yields were approximately eighty percent and higher yields could have been obtained by refractionating the forerun from the distillation.

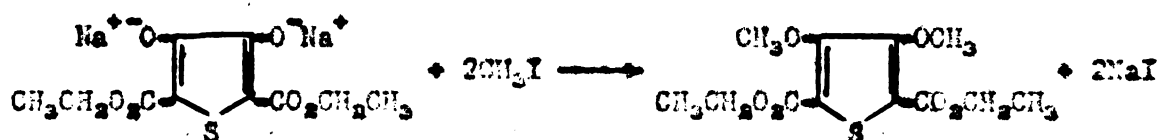
The disodium salt of 3,4-dihydroxy-2,5-dicarbomethoxythiophene was prepared by mixing the diethyl thiocdiglycolate with an excess of dimethyl oxalate and adding this mixture to a methanol solution containing twice the molar quantity of sodium methoxide compared to dimethyl oxalate, at a temperature below 10° C. The yellow disodium salt of 3,4-dihydroxy-2,5-dicarbomethoxythiophene began precipitating shortly after the reagents were initially mixed. The mixture was finally heated at its reflux temperature for a period of from one and a half to two and a half hours. After cooling the reaction mixture the product was filtered from the methanol mixture and washed with methanol. Over one hundred percent yields were obtained because of the contamination of coprecipitated sodium methoxide and possible incomplete removal of methanol. The sodium salt was not purified further, but used directly in the next step of the synthesis.

The methylation of the sodium salt of 3,4-dihydroxy-2,5-dicarbomethoxythiophene was accomplished by using an excess of dimethylsulfate. The method of Overberger and Lal (47) proved unsuccessful in the present investigation. They heated a mixture of dimethylsulfate and the sodium salt of 3,4-dihydroxy-2,5-dicarbomethoxythiophene at its reflux temperature for thirty minutes. When this was attempted in the present study, the reaction mixture charred and considerable difficulty was

experienced in attempting to isolate the 3,4-dimethoxy-2,5-dicarboxythiophene. After hydrolysis with aqueous sodium hydroxide solution, only a 14.6% yield of the acid was obtained. It was found that the quantity of sodium salt of 3,4-dimethoxy-2,5-dicarboxymethoxythiophene taken to be methylated could not be much larger than three quarters of a mole if high yields of the 3,4-dimethoxy-2,5-dicarboxythiophene were to be obtained. This was true because of the large heat of the reaction. When the reaction was initiated the interior of the reaction mixture tended to quickly overheat and char. Whereas with small quantities the heat could easily be dissipated to the outer walls of the reaction vessel by vigorous stirring. The best yields were obtained by mixing the salt and dimethylsulfate at room temperature and then while stirring the mixture, an oil bath, at approximately 100° C., was raised around the reaction flask. When the inside temperature of the reaction mixture began to quickly rise the oil bath was rapidly lowered. A very exothermic reaction ensued causing some refluxing of the reaction mixture. The reaction mixture temperature usually rose to 125-135° C. After the temperature had fallen to 110° C. the oil bath was replaced and the reaction mixture was heated for thirty minutes at 110° C. The reaction mixture's color changed from yellow to white when the exothermic reaction occurred. If sufficient cooling was not effected it rapidly turned to a black color. If the interior temperature of the mixture didn't rise above 125° C. the mixture stayed a light color. The excess dimethylsulfate was removed by vacuum distillation. The 3,4-dimethoxy-2,5-dicarboxymethoxythiophene was

not isolated but hydrolyzed directly with excess 6N sodium solution. The 3,4-dimethoxy-2,5-dicarboxythiophene was isolated by acidification of the reaction mixture with hydrochloric acid. The product was further purified by redissolving it in base, decolorizing with charcoal and then reacidification with acid. The highest purity was obtained by recrystallizing the acid from a water-methanol mixture with a charcoal purification. Yields of eighty percent or better were obtained by this method of methylation. If the 3,4-dimethoxy-2,5-dicarboxythiophene was not pure it had a tendency to become gray on standing, otherwise it remained white.

A single attempt was made to methylate the sodium salt of 3,4-dihydroxy-2,5-dicarbomethoxythiophene with methyl iodide.



The sodium salt and methyl iodide mixture was heated in absolute methanol at the reflux temperature of the reaction mixture for eighteen hours. The yellow sodium salt was very insoluble. The reaction mixture was filtered and from the filtrate a small amount of a white crystalline material was isolated which melted in the temperature range 153-168° C. The 3,4-dimethoxy-2,5-dicarbomethoxythiophene has not been previously reported in the literature. The 3,4-dimethoxy-2,5-dicarbethoxythiophene is reported to melt at 52-53° C. (47). Due to the extremely low yield and wide difference in melting points, as well as the availability of a better method of methylating involving dimethylsulfate, the reaction

employing methyl iodide was not investigated further in the present work.

The 3,4-dimethoxythiophene was synthesized by the decarboxylation of 3,4-dimethoxy-2,5-dicarboxythiophene using copper chromite as a catalyst suspended in quinoline. The copper chromite catalyst was freshly prepared by the method of Conner and his collaborators (42). The decarboxylation was carried out by two different procedures. The first method involved heating the 2,5-dicarboxy-3,4-dimethoxythiophene with copper chromite catalyst in quinoline as a reaction medium under an atmosphere of nitrogen for approximately thirty minutes. The reaction mixture was diluted with ether and the catalyst was removed by filtration. The quinoline was extracted from the product with hydrochloric acid and the unreacted starting material was removed by a sodium hydroxide extraction. The 3,4-dimethoxythiophene was finally isolated by fractional distillation. The filtration step in the above experimental procedure was sometimes difficult because of the tars which formed during the reaction. An earlier method of carrying out the decarboxylation reaction and isolation of the product was to mix the reagents as described previously and then after the reaction had been completed to distill the product and a considerable amount of quinoline from the reaction mixture under reduced pressures. This gave a very clean mixture of quinoline and 3,4-dimethoxythiophene from which it was easier to extract the quinoline and isolate the product as discussed above. The two methods gave comparable yields. The method and yields are summarized in Table VI.

control of the situation.

1990

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2009

2010

2011

2012

TABLE VI

SUMMARY OF THE DECARBOXYLATION OF 3,4-DIMETHOXY-2,5-DICARBETHYTHIOPHENE

Moles 3,4-dimethoxy- 2,5-dicarbethythiophene	Grams Copper Chromium catalyst	ML. Quinoline	Reaction Time Minutes	Procedure	Moles 3,4-dimethoxy- thiophene	Percent Yield 3,4-dimethoxy- thiophene
0.071	2	50	34	A	0.0334	47.1
0.072	2	50	19	A	0.0399	55.3
0.071	2	65	30	B	0.0313	44.1
0.284	8	200	30	A	0.00756	2.66
0.142	6	100	35	A	0.0502	42.4
0.142	4	100	12	A	0.0517	36.4
0.142	10	100	31	B*	0.1724	50.0
0.159	10	100	30	B*	0.1724	50.0
0.0442	5	75	20	B*	0.1724	50.0

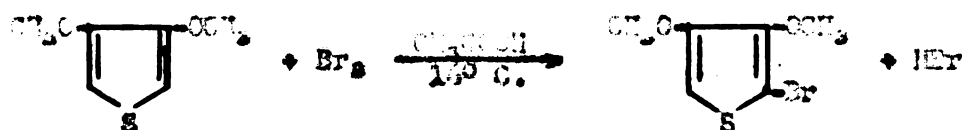
A = Reaction period followed by a vacuum distillation of product and some quinoline from the crude reaction mixture followed by extraction of quinoline and a final distillation.

B = Reaction period followed by extraction of quinoline from the crude reaction mixture followed by distillation.

* = Crude reaction mixtures were combined and then worked up.

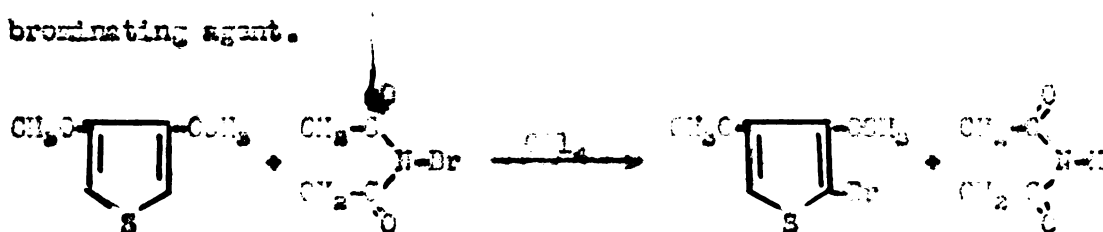
The yields were lowest when larger quantities of reactants were employed. A considerable amount of tar formed during the decarboxylation reaction. There was always an increase in weight of the catalyst during the reaction. In one case where 2 grams of copper chromium oxide was used, the spent catalyst was isolated by filtration, followed by a thorough washing with ether and a final drying in oven. The final weight of spent catalyst was 5.35 grams. The increase in weight was probably the result of the absorption of impurities during the reaction which were not quinoline or ether soluble.

The 3,4-dimethoxythiophene was brominated by two different experimental methods. The first procedure is illustrated by the following equation.



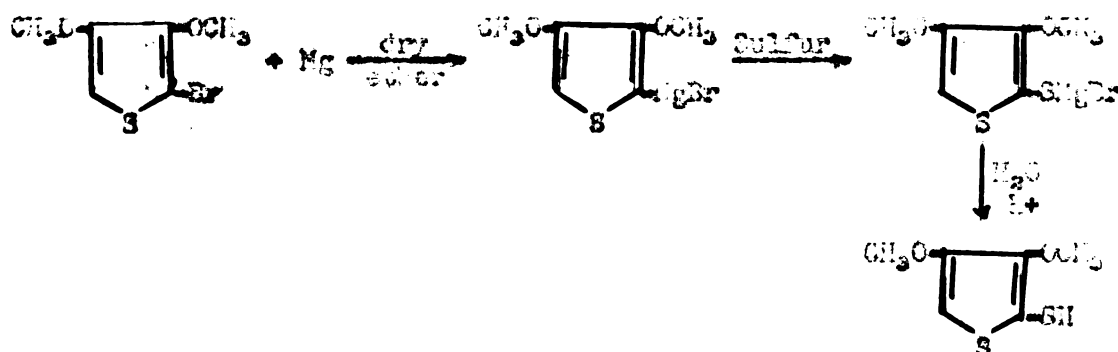
The bromine, dissolved in glacial acetic acid, was slowly added to the vigorously stirred 3,4-dimethoxythiophene dissolved in glacial acetic acid at a temperature of approximately 14° C. Even under these conditions a considerable amount of the 2,5-dibromo-3,4-dimethoxythiophene formed as was indicated by the wide range in boiling points of the products. Some unreacted 3,4-dimethoxythiophene was isolated and some higher boiling residues remained after the distillation which very probably was the dibromo derivative. The maximum yield of 3,4-dimethoxy-2-bromothiophene obtained was 70.2%.

The second method of bromination employed N-bromosuccinimide as a brominating agent.



The N-bromosuccinimide was added to the 3,4-dimethoxythiophene in dry carbon tetrachloride. This method had the advantage that hydrogen bromide was not formed. However, traces of hydrogen bromide were detected, probably occurring from the elemental bromine present in the N-bromosuccinimide. The succinimide crystallized from the reaction mixture as the 2-bromo-3,4-dimethoxythiophene formed. The yield of 2-bromo-3,4-dimethoxythiophene obtained by this method was 37.6%. The results of the analysis of this material is to be found in Table V. The N-bromosuccinimide method proved to be the better of the two methods. In both cases the crude product was thoroughly washed with a sodium hydroxide solution to remove any product formed from the bromination of the methyl groups of the methoxy moiety of the molecule. The 3,4-dimethoxy-2-bromothiophene has not been previously reported in the literature.

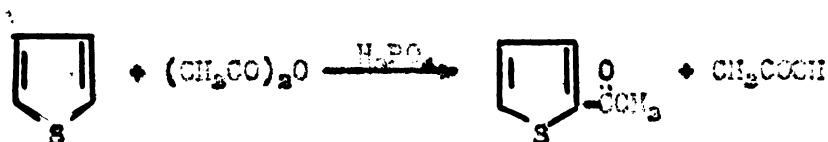
A single attempt was made to synthesize 3,4-dimethoxy-2-thiophenethiol. The method employed is indicated by the following equations.



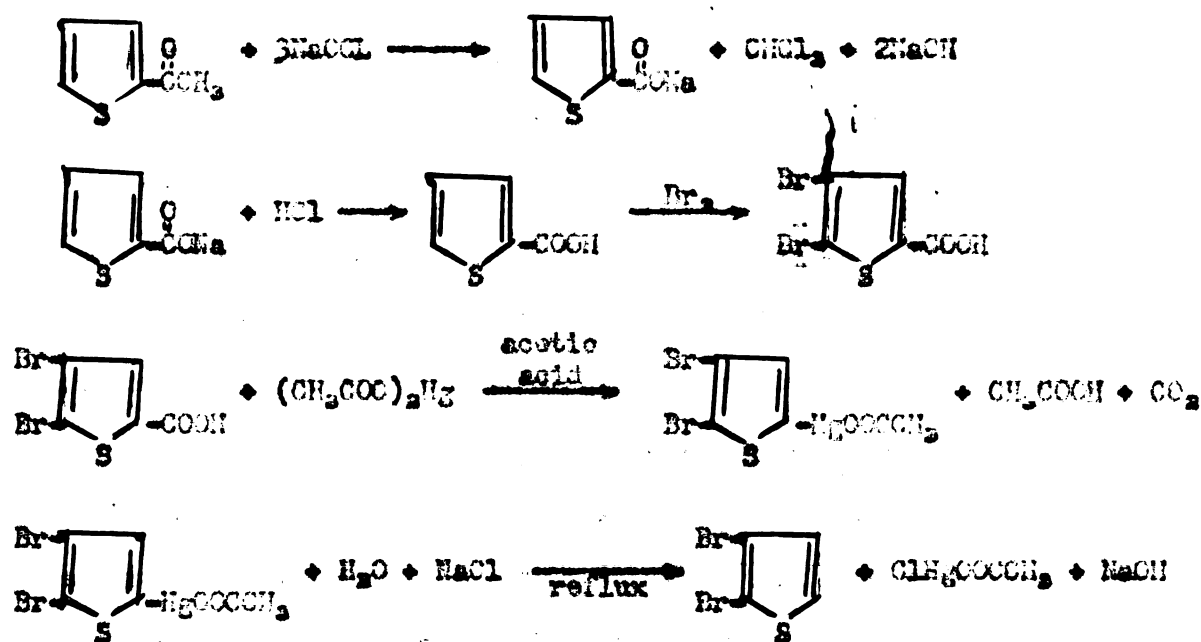


The procedure used was the same as that employed in the preparation of 5-phenyl-2-thiophenethiol. The Grignard reagent appeared to form as evidenced by the spontaneous refluxing of the mixture as the 3,4-di-methoxy-2-bromothiophene was added to the magnesium turnings in the ether. However, the usual vigorous reaction, when sulfur is added to a Grignard reagent, did not appear to occur in this case. When the isolation of product was attempted by alkaline extraction, acidification, ether extraction, and a final distillation, only a tarry residue was obtained which was undistillable. The procedure was not repeated. Possibly the 3,4-dimethoxy-2-thiophenethiol is extremely active and dimerized or decomposed on heating to give polymeric materials. The other possibility is that the thiol derivative did not form. However, if this were the case the starting material would have been lost during the alkaline extraction procedure. No attempt to obtain a material balance on the reaction mixture was made in this case.

Since substituted 3-thiophenethiol derivatives were desired during the initial stages of this investigation the various synthetic routes to 3-thiophenethiols were considered. One such route was investigated but finally abandoned for the reasons indicated. The following series of reactions was used to obtain a 3-bromothiophene derivative.



1.  



The acetylation of thiophene was accomplished by the method of Hartough and Kosak (53) in a little more than a sixty percent yield. The oxidation of the 2-acetylthiophene was carried out by the method of Hartough and Conley (54), which employs the halo-form reaction, to give an almost quantitative yield of 2-thiophenecarboxylic acid. The bromination of 2-thiophenecarboxylic acid was done by the method of Steinkopf (39,65). The procedure was not a very desirable one as a large excess of bromine and 2-thiophenecarboxylic acid had to be mixed, which caused a sticky thick mass to form. The reaction mixture was allowed to remain in the open to permit hydrogen bromide and excess bromine to escape. The last traces of bromine were destroyed with an ammonium carbonate solution. A yield of almost seventy percent of 4,5-dibromo-2-thiophenecarboxylic acid was obtained. Further complications in this procedure are that the hydrogen bromide and excess bromine are difficultly removed and a thorough mixing of the reagents was rather difficult.

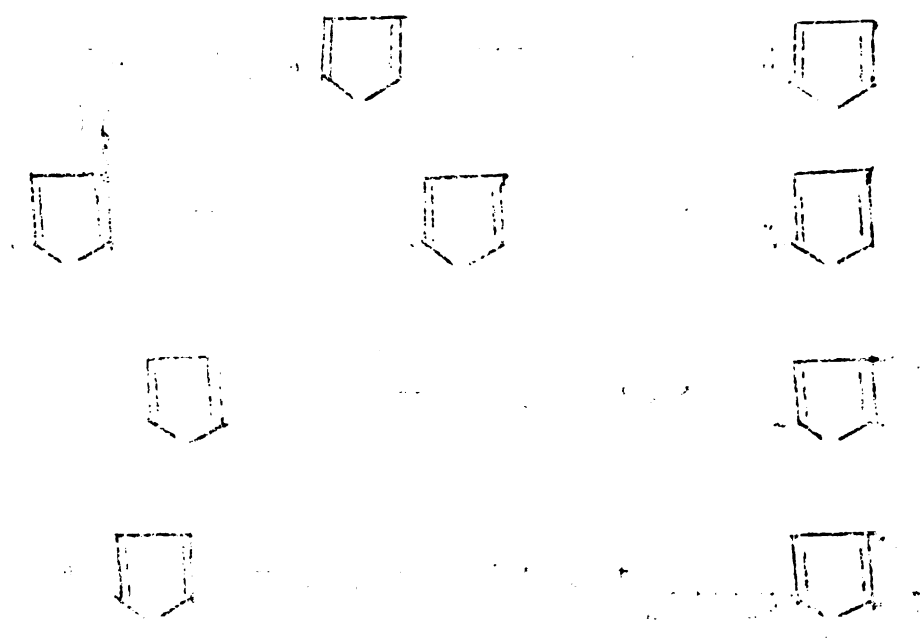


Figure 1.10: Drawing a cube

Figure 1.10 shows a sequence of 10 steps for drawing a cube. The first step is a simple square. The second step adds a vertical line to the right side. The third step adds a horizontal line to the top. The fourth step adds a vertical line to the left side. The fifth step adds a horizontal line to the bottom. The sixth step adds a vertical line to the right side. The seventh step adds a horizontal line to the top. The eighth step adds a vertical line to the left side. The ninth step adds a horizontal line to the bottom. The tenth step adds a vertical line to the right side. The final result is a 3D cube.

The brominated acid was decarboxylated by replacing the carboxyl group with a mercuriacetate group and then removal of the latter group by heating it in a 20% aqueous sodium chloride solution at the reflux temperature of such a solution. This was followed by acidification and steam distillation of the reaction mixture to obtain the product. This method failed when the mercuriacetate derivative was not isolated before its final decomposition. When the mercuriacetate derivative was isolated from the mercuric acetate solution and then subjected to decomposition in a sodium chloride solution, followed by a steam distillation, and finally a fractional distillation of the product, a better than fifty percent yield of 2,3-dibromothiophene was obtained.

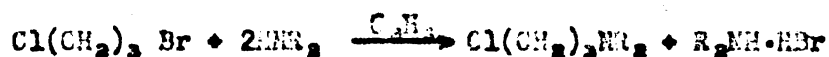
The original intention was to remove or replace the bromine in the two position through a selective Grignard formation by taking advantage of the relative differences in the reactivities of the bromine atoms in the two and three position.



This was to be followed by the conversion of the 3-bromothiophene derivative to its corresponding Grignard reagent and interaction of the latter with sulfur to give 3-thiophenethiol. When it was found that very low yields resulted from the formation of the thiol group in the three position through the Grignard reaction the method was

abandoned as a useful synthesis in reasonable quantities of substituted 3-thiophenethiols. The quantity of thiols that were needed in the initial investigation to make the necessary quantity of final derivatives for biological assay would have made this method a rather laborious procedure. For the study of new substituted 3-thiophenethiols, the method has utility and can surely be used. No further investigations on this method were made in the present work.

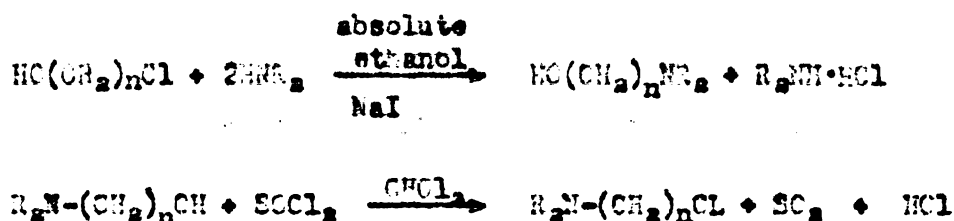
The ω (N,N-dialkylamino)alkyl chlorides were prepared by two general methods. The three carbon chain length alkyl groups were prepared by a very direct method indicated in the following equation.



Two moles of the secondary amine were allowed to interact with one mole of trimethylene chlorobromide in anhydrous benzene. The reaction was exothermic and refluxed spontaneously for a moderate period of time. The secondary amine hydrobromide crystallized from the reaction mixture and was removed by filtration. The secondary amine was recovered from the amine hydrobromide. The ω (N,N-dialkylamino)alkyl chloride was isolated by extraction of the benzene solution with hydrochloric acid, reprecipitated with base, extraction with ether, drying, and fractional distillation. The free amines were not stable during long periods of storage in the refrigerator. Intermolecular quaternary salts formed which resulted in high molecular weight polymers. To avoid this the free amines were converted to their hydrochlorides by treatment with

anhydrous hydrogen chloride in anhydrous ether solutions. The hydrochloride salts were very stable and the amines were regenerated with base when used in the synthesis of the ω (N,N-dialkylamino)alkylthienyl sulfides hydrochlorides. The piperidino, diethylamino, and morpholino analogs were prepared by the method just described. The method was successful because the bromo group is sufficiently more reactive toward the amines than the chloro group that mixtures of the halo compounds were not formed.

The second general method, used to prepare the ω (N,N-dialkylamino)-alkyl chloride compounds, employed chlorohydrins as the starting materials. The two and four carbon homologues were prepared by this method, and it can be represented by the following equations.



The chlorohydrin was allowed to react with the secondary amine using a ratio of one mole of chlorohydrin to two moles of secondary amine; one mole of amine being consumed in forming the amine hydrochloride. This reaction was very exothermic when piperidine was employed as the amine. After the initial reaction subsided the reaction mixture was stirred and heated at its reflux temperature for twenty-four hours. When morpholine was used as the amine component no initial exothermic reaction occurred, which indicates the relative basic strength of

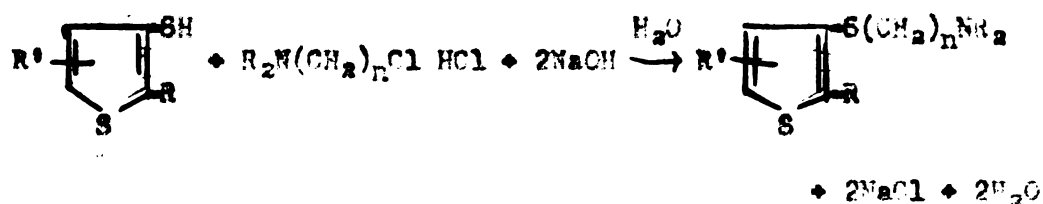
The following table shows the number of persons in the population of the United States, by race and sex, in 1900, 1910, 1920, 1930, 1940, 1950, 1960, 1970, 1980, 1990, and 2000. The population of the United States has increased steadily over the years, with a significant increase in the number of persons of color.

• *Chlorophyll a* and *Chlorophyll b* are the primary photosynthetic pigments in most plants.

morpholine and piperidine. The product was isolated by neutralizing the reaction mixture with sodium ethoxide, adding ether to precipitate the sodium chloride which had formed, removing the latter salt by filtration and finally fractionally distilling the product. Yields of seventy-five percent or higher were obtained by this procedure. The compounds prepared by this method were 2-piperidino-1-ethanol, 2-morpholino-1-ethanol, 4-piperidino-*n*-butanol and 4-morpholino-*n*-butanol.

The ω (N,N-dialkylamino)alkanols were converted to the corresponding ω (N,N-dialkylamino)alkylchlorides by the Darzen reaction employing thionyl chloride in anhydrous chloroform as the reaction medium. The hydrochlorides of the ω (N,N-dialkylamino)alkyl chlorides crystallized from the reaction medium and they were isolated by filtration and purified by repeated recrystallizations from absolute alcohol.

The tertiary amino derivatives of the substituted 2 and 3-thiaryl alkyl sulfides were obtained from the ω (N,N-dialkylamino)alkyl chlorides by treating the later with the substituted thiophanethiol in an aqueous solution containing an excess of sodium hydroxide. This synthesis can be represented by the following equation,



The most convenient method for accomplishing this synthesis is to use an excess of the thiophanethiol with respect to the ω (N,N-dialkylamino)

alkyl chloride hydrochloride. In this manner there is no excess of the tertiary amine left in the reaction mixture to cause difficulties in the isolation procedure, due to its precipitation as a hydrochloride with the hydrochloride of the product. From the mixture of hydrochlorides it is sometimes difficult to obtain the pure hydrochloride of the product. Even though this was a potential difficulty, equal molar quantities of the thiophenethiols and ω (N,N-dialkylamino) alkyl chlorides or their amine hydrochlorides were employed in most instances, since it was preferred not to sacrifice any of the substituted thiophenethiol. The reaction was carried out at the reflux temperature of the reaction medium. The sodium salt of the substituted thiophenethiol was first prepared by dissolving the thiol in the sodium hydroxide solution. Enough sodium hydroxide was employed to form the sodium salt of the substituted thiophenethiol as well as to liberate the ω (N,N-dialkylamino)alkyl chloride from its hydrochloride and to have left a small excess of sodium hydroxide. Where the free amine was used instead of the hydrochloride the sodium hydroxide concentration was adjusted accordingly. The ω (N,N-dialkylamino)alkyl chloride solution was added dropwise to the stirred, refluxing, alkaline mercaptan solution. The reaction mixtures were stirred at their reflux temperatures for an additional three to eight hours, at the end of which time a yellow oil had separated from the reaction solution. The oil was extracted with ether, washed with an alkaline solution, dried and finally the product was precipitated from an ether solution as the hydrochloride by adding anhydrous hydrogen chloride. Difficulties were

experienced if hydrogen chloride was added to the ethereal solution in excess of the amount necessary for the hydrochloride salt formation. When this occurred oily products formed which were difficult or impossible to crystallize. To avoid this the hydrochloride formation was accomplished in several steps, by adding small amounts of dry hydrogen chloride, filtering the product formed, and then adding another quantity of dry hydrogen chloride. This procedure was repeated until no additional ω (N,N-dialkylamino)alkyl disubstituted thienyl sulfide hydrochloride formed on further addition of gaseous hydrogen chloride. The crystalline nature of the product was greatly improved by setting aside the freshly precipitated hydrochloride in the ethereal mixture for several hours at 0° C. before filtering. The ω (N,N-dialkylamino-alkyl)disubstituted thienyl sulfides hydrochlorides were purified by recrystallizing in most instances from anhydrous isopropyl alcohol. It was absolutely essential to maintain anhydrous conditions during the handling of the hydrochlorides. Many of the crude products were very hygroscopic and on very humid days, they had a tendency to liquify. In such cases the filtrations were carried out using a glass fritted funnel with a calcium chloride tube fitted in the top of the funnel. The calcium chloride tube was quickly put in place after the material had been placed in the funnel and dry air was drawn over the crystalline product. The purified hydrochlorides had none or only a slight tendency to be hygroscopic. In general the yields in these reactions were eighty percent or above. Altogether, six new ω (N,N-dialkylaminoalkyl) 2,5-dichloro-2-thienyl sulfide hydrochlorides, nine new

ω -(N,N-dialkylaminoalkyl)-2,5-dimethyl-3-thienyl sulfide hydrochlorides and two ω -(N,N-dialkylaminoalkyl)-5-phenyl-2-thienyl sulfide hydrochlorides were synthesized for the first time. A summary of some of their physical properties and analytical results are given in Tables VII, VIII, and IX.

TABLE VII

ω-(N,N-DIALKYLAMINO)ALLYL-2,5-DIMETHYL-3-THIENYL SULFIDE HYDROCHLORIDES



Compound	Formula	M. p. °C.	Percent Carbon		Percent Hydrogen		Percent Sulfur	
			Calc'd.	Found	Calc'd.	Found	Calc'd.	Found
β-Piperidinoethyl	C ₁₃ H ₂₃ ClNS ₂	173-174	53.19	53.55	7.60	7.55	21.97	21.72
β-Morpholinoethyl	C ₁₂ H ₂₀ ClNS ₂	201.5-212	49.04	49.17	6.86	6.84	21.82	21.51
β-Diethylaminoethyl	C ₁₂ H ₂₂ ClNS ₂	142.0-142.5	51.19	51.62	7.92	7.79	22.91	22.66
β-Dimethylaminoethyl	C ₁₀ H ₁₈ ClNS ₂	161.5-162.5	47.69	47.79	7.20	7.27	25.46	25.76
γ-Piperidino-n-propyl	C ₁₄ H ₂₄ ClNS ₂	171.5-172	54.96	55.01	7.91	8.20	20.96	20.73
γ-Morpholino-n-propyl	C ₁₃ H ₂₃ ClNS ₂	140-140.5	50.71	50.53	7.20	7.30	20.82	20.60
γ-Diethylamino-n-propyl	C ₁₃ H ₂₄ ClNS ₂	109-110	53.12	52.90	8.23	8.20	21.82	21.70
β-Dimethylamino-α-methyl-ethyl	C ₁₁ H ₂₀ ClNS ₂	170-171	49.69	49.74	7.58	7.56	24.12	23.91
β-Morpholino-α-butyl	C ₁₄ H ₂₄ ClNS ₂	140-140.5	52.23	52.03	7.51	7.42	19.92	19.71



TABLE VIII

ω-(N,N-DIALKYLAMINO)ALKYL-2,5-DICHLORO-3-THIENYL SULFIDE HYDROCHLORIDES



Compound	Formula	M.p. °C.	Percent Carbon		Percent Hydrogen		Percent Sulfur		Percent Chlorine	
			Calc'd.	Found	Calc'd.	Found	Calc'd.	Found	Calc'd.	Found
p-Piperidinoethyl	$C_{11}H_{16}Cl_2NS_2$	170-170.8	39.70	39.84	4.85	4.91	19.27	19.02	31.97	31.78
p-Diethylaminoethyl	$C_{10}H_{14}Cl_2NS_2$	150-151	37.45	37.69	5.03	4.85	19.99	20.18	33.17	33.01
p-Dimethylamino-n-methylsethyl	$C_9H_{14}Cl_2NS_2$	149.5-150	35.24	35.48	4.60	4.59	20.91	20.86	34.68	34.61
p-Piperidino-n-propyl	$C_{13}H_{20}Cl_2NS_2$	155-156	41.56	41.65	5.23	5.29	18.49	18.81	30.68	30.60
p-Morpholino-n-propyl	$C_{11}H_{16}Cl_2NOS_2$	114-115.5	37.88	38.01	4.63	4.85	18.39	18.19	30.50	30.27
p-Diethylamino-n-propyl	$C_{11}H_{18}Cl_2NS_2$	117.5-118.5	39.47	39.62	5.42	5.48	19.15	19.01	31.78	32.02

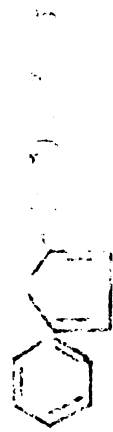


TABLE IX

ω-(PIPERIDINO) ALKYL-5-PHENYL-2-THIENYL SULFIDE HYDROCHLORIDES

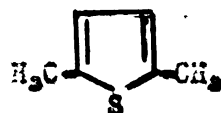


Compound	Formula	M.P. °C.	Percent Carbon		Percent Hydrogen		Percent Sulfur	
			Calc'd.	Found	Calc'd.	Found	Calc'd.	Found
5-Phenyl-2-thienyl hydrochloride	$C_{17}H_{15}S_2$	161.2-161.5	60.06	60.21	6.52	6.53	18.86	18.66
ω-(Piperidino)ethyl	$C_{19}H_{21}S_2$	115-116	61.08	61.00	6.83	6.88	18.12	17.91
ω-(Piperidino)-n-propyl	$C_{20}H_{23}S_2$							



EXPERIMENTAL

2,5-Dimethylthiophene



The preparation of 2,5-dimethylthiophene was carried out four times with only slight modifications in the experimental procedure and these resulted in some variations in the yields. Into a three liter, three neck round bottom flask fitted with a reflux condenser, stirrer and dropping funnel was placed 200 g., 0.90 mole, of phosphorus pentasulfide. A 300 g., 2.63 moles, quantity of 2,5-hexanedione was placed in the dropping funnel. Stirring was started and approximately 50 to 60 ml. of the 2,5-hexanedione was added gradually to the stirred phosphorus pentasulfide. At this point there was no indication of any reaction taking place, and the addition of the 2,5-hexanedione was discontinued. Stirring was continued and the reaction flask was gently heated by means of an electric mantle. This procedure initiated a vigorous reaction necessitating removal of the heating mantle and immersion of the reaction flask into a water bath to control the reaction. Even with this precaution some of the product was unreacted 2,5-hexanedione escaped through the condenser. When the initial reaction had subsided the ice bath was removed and the remainder of the 2,5-hexanedione was added dropwise at a rate sufficient to maintain a gentle reflux of the stirred reaction mixture. Following the complete addition



of the 2,5-hexanedione the reaction mixture was kept at its reflux temperature for an additional fifteen minutes. At this point external heating of the reaction mixture was stopped and the reflux condenser was replaced with a distillation take off tube containing a thermometer and a condenser. The crude dark brown thick product was distilled with stirring using a mantle as the source of heat. Distillation was discontinued when decomposition set in as indicated by the appearance of dense white fumes, charring of solid material, and a very rapid darkening in color of the residue in the distillation flask. The weight of the crude clear water white product of 2,5-dimethylthiophene was 153.8 g. and it had a boiling point range of 90° to 125° C. The crude 2,5-dimethylthiophene was placed in a separatory funnel, washed with 80 ml. of 3 N sodium hydroxide solution followed by 50 ml. of distilled water. The crude product was dried by being set aside over night in contact with anhydrous magnesium sulfate after which it was redistilled. The fraction boiling at 135.0° C. sharp, with a refractive index, $n_D^{20} = 1.5084$, was collected. It weighed 122.8 g., 1.1 moles, and represented a 41.6% yield.

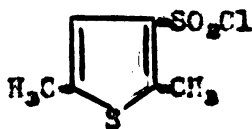
The second preparation of 2,5-dimethylthiophene was accomplished with better yields by varying the ratio of phosphorus pentasulfide to 2,5-hexanedione. The same apparatus as previously described was employed except for the use of a more efficient bulb type condenser. In this preparation the reaction was initiated with a mild flame from a Bunsen burner, which gave better control of the initial vigorous reaction. The interaction of 250 g., 1.12 moles, of phosphorus

pentasulfide and 300 g., 2.63 moles, of 2,5-hexanedione followed by isolation of the product as previously described gave 186.5 g., 1.66 moles, a 63.3% yield of pure 2,5-dimethylthiophene which boiled at 134-138° C. and had a refractive index, $n_D^{20.1} = 1.5094$.

A third preparation of 2,5-dimethylthiophene carried out as just previously described and starting with the same quantities of reactants gave, 239.5 g., 2.13 moles, an 81.1% yield of the desired thiophene derivative with a refractive index, $n_D^{25} = 1.5100$.

The final preparation of 2,5-dimethylthiophene was carried out employing twice the quantities of reagents as in the two previous preparations, namely, 500 g., 2.24 moles, of phosphorus pentasulfide and 600 g., 5.26 moles, of 2,5-hexanedione. The yield obtained in this case was, 437.6 g., 3.90 moles, 74.3% of the theoretical and the product boiled at 134-135° C. The reported boiling range for 2,5-dimethylthiophene is 134-135° C. (26).

Preparation of 2,5-Dimethyl-3-thiophenesulfonyl Chloride



A 500 ml., three neck round bottom flask was equipped with a stirrer, thermometer, and a 125 ml. dropping funnel. The quantity 121.1 g., 1.04 moles, of chlorosulfonic acid was placed in the flask and the latter was then placed in an ice salt mixture bath and cooled

to 0° C. A 33.3 g., 0.277 mole, quantity of 2,5-diethylthiophene was placed in the dropping funnel. The 2,5-diethylthiophene was added dropwise to the vigorously stirred cold chlorosulfonic acid. This required thirteen minutes during which time the temperature of the reaction mixture rose to 2° C. After the addition of the dialkylthiophene was complete the reaction mixture was stirred for an additional hour to insure completeness of reaction after which it was poured onto 500 g. of crushed ice. This caused a pink precipitate to form and an attempt was made to isolate this material. It was collected on a filter but as soon as the material warmed up to room temperature it liquified. The pink material was taken up in carbon tetrachloride and the aqueous filtrate was extracted with three 100 ml. portions of carbon tetrachloride. The combined carbon tetrachloride extracts were dried in contact with anhydrous magnesium sulfate. The carbon tetrachloride was removed using a water aspirator and the 2,5-diethyl-3-thiophenesulfonyl chloride was fractionated employing a one foot heat jacketed Vigreux column. The fraction boiling at 103.5-107.0° C./3mm. Hg. was collected. The weight of this fraction was 26.05 g., which is 11.8% of the theoretical yield. The 2,5-diethyl-3-thiophenesulfonyl chloride was converted to 2,5-diethyl-3-thiophenesulfonamide and analyzed. The neutralization equivalent of 2,5-diethylthiophene-3-sulfonyl chloride was determined. The results of these determinations are given in later experiments.

Determination of the Neutralization Equivalent of
2,5-dimethyl-3-thiophenesulfonyl chloride

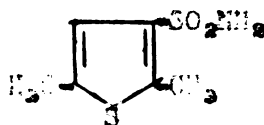
A 50 ml. volume of 0.1238 N sodium hydroxide solution was pipetted into a 250 ml. round bottom flask fitted with a reflux condenser. A 0.4510 g. sample of the 2,5-dimethyl-3-thiophenesulfonyl chloride was weighed in a small vial and stoppered. The stopper of the vial was removed and after removing the reflux condenser the vial and its contents were dropped into the standard sodium hydroxide contained in the flask. The reflux condenser was set in place and the reaction mixture was kept at its reflux temperature by means of a microburner for two and a quarter hours. The oily material in the vial soon dissolved in the standard base. The flask and contents were cooled and a few drops of phenolphthalein were added. The alkaline mixture was titrated with 0.1412 N hydrochloric acid to a colorless end point which required 12.39 ml. volume of acid. A 40.94 ml. volume of the same acid was required to titrate a 50 ml. volume of the sodium hydroxide solution used in the above hydrolysis. From this data and the fact that one equivalent of 2,5-dimethyl-3-thiophenesulfonyl chloride requires two equivalents of sodium hydroxide it was found that the experimental molecular weight of the product isolated was 212. The theoretical value is 211 which is an error of 1 unit or approximately 0.47 percent.

THE HISTORY OF THE UNITED STATES

The history of the United States is a story of growth, struggle, and achievement. From the first European settlers to the present day, the nation has evolved through a series of challenges and triumphs. The early years were marked by the search for a stable government and the expansion of territory. The American Revolution was a pivotal moment, leading to the birth of a new nation. The 19th century was a period of rapid growth and change, with the Civil War being a defining event. The 20th century brought new challenges, including the Great Depression and the rise of the atomic age. Today, the United States continues to shape the world through its leadership in science, technology, and international relations.

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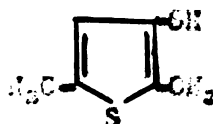
2,5-Dimethyl-3-thiophenesulfonamide (57)



A 500 mg. quantity of 2,5-dimethyl-3-thiophenesulfonyl chloride, 10 ml. of concentrated aqueous ammonium hydroxide and 2 g. of powdered ammonium carbonate were placed in an eight inch test tube. The mixture was stirred with a glass stirring rod which caused a vigorous evolution of gas. When the gas evolution had ceased the mixture was heated in a water bath at 60° C. for fifteen minutes and then at 80-90° C. for an additional ten minutes. A white crystalline solid formed and it was removed from the hot reaction mixture by filtration. The clear filtrate was cooled in an ice bath and the 2,5-dimethyl-3-thiophenesulfonamide crystallized from the filtrate as a white crystalline solid. The crystals were filtered and dried. The crystalline material obtained from the hot reaction mixture melted at the same temperature as the material obtained from the cold filtrate. Therefore, they were combined and recrystallized once from water. The melting point of this product was 111.5-112.0° C. The reported melting point for 2,5-dimethyl-3-thiophenesulfonamide is 135° C. (50). Elemental analysis of the compound for carbon, hydrogen and sulfur gave the following results: Calc'd for $C_8H_9NO_2S$: C, 37.6%; H, 4.7%; S, 33.5. Found C, 37.62; H, 4.51; S, 33.37.



Preparation of 2,5-Dimethyl-3-thiophenethiol



A one liter, three neck flask was fitted with a reflux condenser having a calcium chloride tube attached to the top end, a stirrer, and a dropping funnel. The apparatus was dried in an oven at 110° C. prior to its being assembled. A 10.5 g., 0.284 mole, quantity of lithium aluminum hydride was pulverized in a dry mortar under an inverted funnel which had a stream of dry nitrogen flowing through it. The pulverized lithium aluminum hydride and 10 ml. of dry ether were added to the reaction flask. The stirred mixture was heated at its reflux temperature for three hours to dissolve the lithium aluminum hydride. A 20.0 g., 0.0949 mole, quantity of 2,5-dimethyl-3-thiophenesulfonyl chloride dissolved in 100 ml. of dry ether was placed in the dropping funnel. This solution was added dropwise to the lithium aluminum hydride solution at a rate sufficient to keep the stirred reaction mixture at its reflux temperature. Fifty minutes were required to add the 2,5-dimethyl-3-thiophenesulfonyl chloride solution. The mixture was stirred and heated at its reflux temperature an additional half hour and then set aside overnight. The following day 100 ml. of water were slowly added to the stirred reaction mixture from the dropping funnel while the reaction flask was immersed in an ice bath. A 51 ml. quantity of 98% sulfuric acid was diluted with 370 ml. of water, placed in a beaker



100

1. *Chlorophyll a* (Chl *a*)

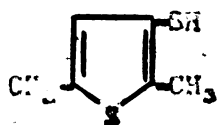
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and chilled in an ice bath. The hydrolyzed reaction mixture was slowly poured into the well stirred sulfuric acid solution. The ether layer was separated in a separatory funnel and the aqueous phase was extracted with two, 100 ml. portions of ether. The ether extracts and original ether layer were combined and extracted with two, 25 ml. portions of a 15% aqueous sodium hydroxide solution. An oily layer separated from the combined alkaline extracts on acidification of the latter with a 6 molar sulfuric acid solution. After separating the oily layer the aqueous portion was extracted with two, 15 ml. portions of ether. The combined oily layer and ether extracts were dried in contact with anhydrous magnesium sulfate. After removing the magnesium sulfate by filtration the ether was removed by distillation on a steam bath. The residue was distilled using a modified semi-micro Claisen distillation flask. A fraction boiling at $70-75^{\circ}$ C./mm. Hg. weighing 10.69 g., 0.0712 mole, was collected which represents a 78.2% yield of 2,5-dimethyl-3-thiophenethiol based on the initial amount of 2,5-dimethyl-3-thiophenesulfonyl chloride.

The same general experimental procedure was used in a second preparation of 2,5-dimethyl-3-thiophenethiol as in the lithium aluminum hydride reductions of 2,5-dimethyl-3-thiophenesulfonyl chloride just described. The quantities of materials used were 87.6 g., 0.416 mole, of 2,5-dimethyl-3-thiophenesulfonyl chloride and 47.4 g., 1.28 moles, of lithium aluminum hydride contained in a total of 250 ml. of dry ether. The lithium aluminum hydride solution was prepared by refluxing

the lithium aluminum hydride in the dry ether for two hours, then setting it aside overnight. A three and a half hour period was required to add all of the 2,5-dimethyl-3-thiophenesulfonyl chloride to the lithium aluminum hydride solution. The 2,5-dimethyl-3-thiophenethiol was isolated as previously described. The fraction boiling between 61-66° C./1.5-1.8 mm. Hg. weighed 44.2 g., 0.396 mole, which is 73.9% of the theoretical yield. The yield was lower than in the first preparation of this material since even though the crude 2,5-dimethyl-3-thiophenethiol was stored in ether under an atmosphere of nitrogen for three days, there were indications of some oxidation and decomposition. The reduction of 2,5-dimethyl-3-thiophenesulfonyl chloride was repeated a third and fourth time; on a 0.329 mole scale an 83.7% yield of the mercaptan was obtained and on a 0.16 mole scale an 88.5% yield of 2,5-dimethyl-3-thiophenethiol was obtained. The ratio of lithium aluminum hydride to 2,5-dimethyl-3-thiophenesulfonyl chloride was the same as in the previously described reductions. The refractive index of 2,5-dimethyl-3-thiophenethiol was determined, $n_D^{25.5^\circ \text{C.}} = 1.5771$.

Attempted Synthesis of 2,5-Dimethyl-3-thiophenethiol by Zinc
Sulfuric Acid Reduction of 2,5-Dimethyl-
3-thiophenesulfonyl Chloride



A 175 g., 1.5 moles, quantity of chlorosulfonic acid was placed in a one liter beaker supported in an ice salt bath and cooled to +15° C. A stirrer was immersed in the cold acid and 85.2 g., 0.5 mole, of

The first part of the document discusses the importance of maintaining accurate records of all transactions and activities. It emphasizes that proper record-keeping is essential for transparency and accountability, particularly in financial matters. The text outlines various methods for collecting and organizing data, including the use of spreadsheets and databases. It also mentions the need for regular audits to ensure the integrity of the information.

The second part of the document focuses on the legal aspects of record-keeping. It references relevant laws and regulations that govern the retention and disposal of records. The text highlights the consequences of non-compliance, such as fines and legal action. It also provides guidance on how to properly document and store records to meet legal requirements.

The third part of the document discusses the role of record-keeping in decision-making. It explains how having accurate and up-to-date information allows managers to make informed decisions based on facts rather than assumptions. The text also mentions that records can be used to track progress and identify areas for improvement.

The fourth part of the document addresses the challenges of record-keeping. It acknowledges that maintaining large volumes of data can be time-consuming and costly. However, it argues that the benefits of having reliable records outweigh the costs. The text suggests several strategies to overcome these challenges, such as automating data collection and using secure storage solutions.

The fifth part of the document concludes by reiterating the importance of record-keeping. It states that records are a valuable asset that can provide a clear history of an organization's activities. The text encourages organizations to invest in proper record-keeping practices to ensure long-term success.

In conclusion, record-keeping is a critical component of any organization's operations. It provides a foundation for transparency, legal compliance, and informed decision-making. By following the guidelines outlined in this document, organizations can ensure that their records are accurate, secure, and useful.



The following table provides a summary of the key points discussed in the document. It is intended to serve as a quick reference for readers.

Topic	Key Points
Importance of Record-Keeping	Transparency, Accountability, Informed Decision-Making
Legal Requirements	Retention Periods, Disposal Procedures, Consequences of Non-Compliance
Challenges	Time, Cost, Volume of Data
Solutions	Automation, Secure Storage, Regular Audits

2,5-diethylthiophene were added dropwise, from a dropping funnel supported above the beaker, to the vigorously stirred acid, at a rate sufficient to keep the reaction temperature below -10° C. During the addition of the thiophene derivative to the acid the reaction mixture turned a bright red color. A 343 g., 3.5 moles, quantity of cold concentrated sulfuric acid was poured onto 900 g. of ice contained in a three liter three neck flask equipped with a stirrer and reflux condenser, and supported in an ice-salt bath. The reaction mixture of chlorosulfonic acid and 2,5-diethylthiophene was poured into the vigorously stirred ice and sulfuric acid. Following this, 163.5 g., 2.5 moles, of a mixture of zinc dust and 30 mesh zinc powder were added to the stirred mixture during a one hour period. After the addition of the zinc had been completed the reaction mixture was stirred an additional three hours at approximately -10° C. to complete the reduction. The reaction mixture was then cautiously allowed to warm to room temperature at which point the evolution of hydrogen was quite vigorous. When the gas evolution had subsided the stirred reaction mixture was heated by means of an electric mantle at its reflux temperature for two hours, allowed to cool to room temperature, loosely stoppered, and set aside overnight. The gray reaction mixture was next refluxed until all of the zinc had dissolved at which point the mixture had turned red in color. The condenser was arranged for steam distillation, and after an additional quantity of water had been added to the stirred reaction mixture it was steam distilled. The oily

layer in the distillate was taken up in ether and the aqueous layer was extracted with several 100 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and then distilled using a Vigreux column after removal of the ether. Following a small forerun of 0.51 g. boiling below 130° C., a fraction which amounted to 24.28 g. was collected which boiled at $130-137^{\circ}$ C. and had a refractive index of $n_D^{25} = 1.5034$. This material was identified as impure 2,5-dimethylthiophene and therefore no appreciable yield of 2,5-dimethyl-3-thiophenethiol was obtained. Apparently a very small amount of the desired 2,5-dimethyl-3-thiophenethiol was formed as indicated by the strong typical odor of a thiophenethiol which was noted immediately following the wine reduction. The recovered 2,5-dimethylthiophene amounted to 28.5% of that initially used.

Attempted Monobromination of 2,5-Dimethylthiophene

A solution containing 37.6 g., 0.33 mole, of 2,5-dimethylthiophene dissolved in 200 ml. of carbon disulfide was placed in a one liter three neck round bottom flask equipped with a reflux condenser, stirrer, and dropping funnel. To this vigorously stirred solution was added, during a two and a half hour period, 53.5 g., 0.33 mole, of bromine dissolved in 100 ml. of carbon disulfide. The reaction flask was cooled in an ice bath at intervals to prevent loss of carbon disulfide and bromine through the condenser. Following the complete addition of the bromine solution the reaction mixture was stirred an additional hour

and a quarter to insure completeness of reaction. After being set aside for five hours the reaction mixture was washed, in a separatory funnel, with two, 150 ml. portions of twenty percent aqueous sodium carbonate solution and one, 100 ml. portion of distilled water. The carbon disulfide layer was separated and dried by being set aside overnight in contact with anhydrous magnesium sulfate. During the washing procedure there were vivid color changes observed in the carbon disulfide solution. The reaction mixture before washing was green and copious quantities of hydrogen bromide were emitted. The carbon disulfide solution changed colors during washing from green to purple, then to pink and finally to a light yellow color. While the solution was being dried the magnesium sulfate turned pink then purple and the solution turned to a purple color again. After being set aside overnight the solution again gave off fumes. The reaction solution was fractionated using a one foot heated Vigreux column to give, the solvent carbon disulfide, 14.5 g. of unreacted 2,5-dimethylthiophene boiling at $136-137^{\circ}$ C., a 4.7 g. intermediate fraction which was discarded and finally 36.4 g., 0.19 mole, a 57% yield of 2,5-dimethyl-3-bromothiophene was collected boiling in the range $194-200^{\circ}$ C. at atmospheric pressure. The reported boiling point of this material is $195-198^{\circ}$ C. (69).

Preparation of Yellow Mercuric Oxide

The quantity, 159.4 g., 0.5 mole, of mercuric acetate were dissolved in 150 ml. of distilled water. A 42 g., 1.05 moles, quantity of sodium hydroxide, a 5% excess of the theoretical amount needed, was

dissolved in 200 ml. of distilled water and the resulting basic solution was chilled in an ice bath. The mercuric acetate solution was poured into the vigorously stirred cold sodium hydroxide solution resulting in the immediate precipitation of the yellow mercuric oxide. After allowing the insoluble mercuric oxide to remain in an ice bath for one-half hour it was recovered on a Buchner funnel, transferred to a beaker, washed with 400 ml. of water and then again filtered on a Buchner funnel. While the precipitate was on the funnel it was washed first with 95% ethanol to remove water and then with ethyl ether. The precipitate was air dried and stored in a vacuum desiccator. The product was a very fine yellow powder and the yield was quantitative.

In a second preparation of mercuric oxide it was found expedient to employ a coarse fritted glass filter in place of the Buchner funnel in all filtration operations, which greatly facilitated the filtration and washing of the yellow mercuric oxide.

Preparation of 2,5-Dimethyl-3-iodothiophene



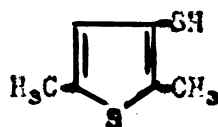
The quantities, 50 ml. of benzene and 47.1 g., 0.42 mole, of 2,5-dimethylthiophene were placed in a 300 ml. wide mouthed bottle. The bottle was stoppered and cooled in an ice water bath. A 75 g., 0.35 mole, quantity, of freshly prepared yellow mercuric oxide and 109 g., 0.43 mole, of iodine were weighed into two separate beakers.

The bottle containing the benzene solution of 2,5-dimethylthiophene was shaken continuously and small portions of the iodine and mercuric oxide were alternately added to the reaction bottle. The bottle and its contents were occasionally cooled in an ice water bath to keep the temperature on the reaction bottle warm to the feel of the hand. The progress of the reaction was followed by the color changes of the reaction mixture. After all of the iodine and mercuric oxide had been added the crimson colored reaction mixture was shaken an additional fifteen minutes to insure completeness of reaction. The mercuric iodide was collected on a Buchner funnel and washed with three, 25 ml. portions of ether. The ether washings and filtrate were combined and shaken with 90 ml. of a ten percent solution of sodium thiosulfate. The organic layer was separated from the aqueous layer, dried over calcium chloride, the ether and benzene were removed by distillation, and the product was vacuum distilled employing a Claisen type head. The initial fraction boiling in the temperature range 28-62° C. at 2.5 mm. Hg. weighed 9.2 g. and was discarded. The next fraction distilling at 62-68° C./2.0 mm. Hg. weighed 74.0 g., 0.311 mole, 73.3%, was collected as product. A 3.04 g. quantity of residue remained in the flask. The product had a slight iodine color and required further purification. A small amount of freshly prepared yellow mercuric oxide and calcium chloride were added to the product and it was set aside for a day. The mercuric oxide and calcium chloride were removed by filtration and the product was again distilled using a Claisen type flask. The material boiling between 68-70° C./2.0 mm. Hg. was collected. The purified 2,5-dimethyl-3-

iodothiophene weighed 69.7 g., 0.233 mole, which is 69.7% of the theoretical yield. Its refractive index was 1.6076 at 25° C.

This preparation was repeated again, exactly as described above except that the product was distilled using a heated one foot Vigreux column. The fraction boiling between 67-69° C./5 mm. Hg. was collected. It weighed 74.4 g., 0.312 mole, which is 74.4% of the theoretical yield. The refractive index of the product was 1.6087 at 24.5° C. The reported boiling range for 2,5-dimethyl-3-iodothiophene is 99-100/11.5 mm. Hg. (70).

Attempted Synthesis of 2,5-dimethyl-3-thiophenethiol by the Grignard Reaction on 2,5-dimethyl-3-iodothiophene



A one liter, three neck flask was equipped with an efficient reflux condenser, stirrer, and a "Y" tube containing a gas inlet tube and 125 ml. dropping funnel. The unassembled apparatus was dried overnight in an oven at 110° C. A 7.0 g., 0.29 mole, quantity of dried magnesium turnings were placed in the flask and while dry nitrogen was swept through the apparatus it was cautiously flame dried as an extra precaution to remove any traces of moisture from the apparatus that may have accumulated while it was being assembled. Dry nitrogen was swept through the apparatus during the remainder of the experiment. A 25.6 g., 0.15 mole, quantity of freshly distilled 2-iodopropane, dissolved in 100 ml. of anhydrous ether, was placed in the dropping

funnel. Approximately five milliliters of the 2-iodopropane ether solution was added to the magnesium turnings. The reaction flask was heated gently on a steam bath while the magnesium turnings and the 2-iodopropane ether solution were vigorously stirred to initiate the reaction. As soon as the reaction had started 100 ml. of anhydrous ether was added to the reaction flask and the remainder of the 2-iodopropane ether solution was added dropwise to the vigorously stirred contents of the reaction flask over a half hour period. The quantity, 23.8 g., 0.1 mole, of 2,5-dimethyl-3-iodothiophene, dissolved in 100 ml. of anhydrous ether, was placed in the dropping funnel. This solution was added dropwise to the vigorously stirred reaction mixture over a period of a half hour. The reaction was sufficiently exothermic to keep the reaction mixture at its reflux temperature during the addition of the 2,5-dimethyl-3-iodothiophene solution. The reaction mixture was stirred an additional half hour, while being kept at its reflux temperature, by applying external heat with an electric mantle. At this point the reaction mixture was allowed to cool to room temperature, stoppered under an atmosphere of nitrogen and set aside overnight. A 8.35 g., 0.26 mole, quantity of sulfur, which is a 0.01 mole excess of the theoretical amount needed, was added in small quantities to the stirred Grignard reagent by means of a dry addition tube. The addition of the sulfur caused the reaction to reflux mildly. The reaction mixture was stirred and kept at its reflux temperature for an additional four hours. Dry nitrogen was slowly swept through the reaction apparatus during all the above operations. The reaction mixture was cooled in an ice bath and a cold sulfuric acid solution,

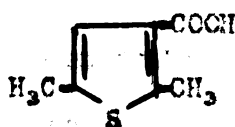
prepared from 18 ml. of concentrated sulfuric and 200 ml. of water, which corresponds to a 11.2% by weight solution of sulfuric acid, was slowly added from the dropping funnel into the cold, stirred, Grignard reaction mixture. After all of the sulfuric acid solution had been added the ether layer was separated from the aqueous layer. The aqueous layer was extracted with two, 50 ml. portions of ether and combined with the original ether layer. The combined ether solution was extracted with three, 20 ml. portions of 20 percent sodium hydroxide. The combined aqueous basic extracts, while being kept cool in an ice bath, were acidified with 12 N sulfuric acid. There was only a slight cloudiness when the basic extracts were acidified; indicating there was little if any 2,5-dimethyl-3-thiophenethiol being released. The cloudy mixture was extracted with three, 25 ml. portions of ether. The combined ether extracts were dried in contact with anhydrous magnesium sulfate and then distilled through a semi micro modified Claisen flask. After all of the ether had been removed there was only a very small amount of residue remaining in the distillation flask. Apparently the procedure was inadequate for the preparation of 2,5-dimethyl-3-thiophenethiol.

The experiment was repeated with several modifications. The same apparatus as in the previous experiment was dried thoroughly and used in this experiment. A 4.27 g., 0.176 mole, quantity of dried magnesium turnings was placed in the flask and while sweeping dry nitrogen through the apparatus the magnesium and apparatus were carefully heated with a small flame from a Bunsen burner to insure complete removal of moisture.

A 33 g., 0.126 mole, quantity of 2,5-dimethyl-3-iodothiophene was dissolved in 100 ml. of dry ether and placed in the dropping funnel. A few milliliters of this later solution were added to the stirred magnesium turnings in the reaction flask. When the reaction failed to start even after heating it was initiated by adding to it a reacting mixture, from a six inch test tube, which consisted of a few milliliters of dry ether, a few magnesium turnings and several drops of 2-iodopropane. A 100 ml. volume of ether was added to the reaction mixture and then the 2,5-dimethyl-3-iodothiophene was added dropwise at a rate sufficient to maintain the reaction mixture at its reflux temperature. An atmosphere of dry nitrogen was kept in the apparatus throughout the experiment. After all of the 2,5-dimethyl-3-iodothiophene had been added, the mixture was stirred and kept at its reflux temperature for an hour and was then set aside for several hours. A 5.0 g., 0.156 mole, quantity of sulfur was carefully spooned into the reaction vessel. An exothermic reaction set in which caused the reaction mixture to reflux. Slightly more than 5.0 g., 0.156 mole, of sulfur were added before any visible sign of a reaction occurred. The reaction mixture was stirred and heated at its reflux temperature for an additional hour. After the flask and contents had been cooled in an ice bath, 150 ml. of 3 N hydrochloric acid were slowly added to the reaction mixture to hydrolyze any Grignard sulfur addition product that might have formed. The aqueous layer was separated from the ether layer and extracted with two, 50 ml. portions of ether. The ether extracts and original ether layer were combined and extracted with four, 20 ml. portions of 3 N sodium hydroxide solution. The combined

basic extracts were cooled in an ice bath and acidified with 6 N hydrochloric acid. The acidified solution which contained only a small amount of oil was extracted with three, 25 ml. portions of ether. The combined ether extracts were dried in contact with anhydrous magnesium sulfate and distilled using a semi-micro Claisen flask, modified with a Vigreux type side arm. After the ether had been removed by distillation only a trace of residue remained in the flask which indicated that no 2,5-dimethyl-3-thiophenethiol had been produced. Apparently the product of the reaction was not soluble in base and was lost in the original ether solution that was extracted with base. In later experimental work it was discovered that thiophenethiols readily form disulfides in the presence of sulfur in an ether medium. This could explain the lack of yield of 2,5-dimethyl-3-thiophenethiol.

2,5-Dimethyl-3-thiophenecarboxylic Acid



A three neck, 500 ml. round bottom flask was equipped with a stirrer, reflux condenser, and a "Y" tube containing a dropping funnel and gas inlet tube. The apparatus was dried in the oven before assembling. A 4.86 g., 0.2 mols, quantity of magnesium was dried in an oven and then placed in the reaction flask. Nitrogen which was first dried by bubbling it through a drying tower containing concentrated sulfuric acid, was swept through the apparatus while a small gas flame was used to gently

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heat the apparatus and magnesium. After the apparatus had cooled, 23.6 g., 0.10 mole, of 2,5-dimethyl-3-iodothiophene dissolved in 100 ml. of dry ether was placed in the dropping funnel. Part of the 2,5-dimethyl-3-iodothiophene solution was added to the vigorously stirred magnesium turnings. Dry nitrogen was slowly swept through the apparatus during the entire remainder of the experiment. When the reaction failed to start, even on heating, it was initiated by adding to it, from a six inch test tube, a reacting mixture of several drops of 2-iodopropane, ether and a few magnesium turnings. When the reaction of the 2,5-dimethyl-3-iodothiophene with magnesium had started, 100 ml. of ether was added to the reaction flask and the remainder of the 2,5-dimethyl-3-iodothiophene solution was added to the vigorously stirred contents of the reaction flask at a rate sufficient to keep the reaction mixture at its reflux temperature. A period of twenty-two minutes were required to add all of the 2,5-dimethyl-3-iodothiophene solution. The mixture was stirred an additional three hours while a very gentle stream of dry nitrogen was passed through the apparatus. At the end of this time there was some white insoluble material adhering to the sides of the reaction flask, and a large amount of the ether had evaporated. That there was still active Grignard reagent present was shown by adding some of the ether solution to water which caused a vigorous reaction to take place. A 100 ml. volume of ether was added to the reaction flask and after stirring two distinct layers formed which could possibly have been due to the insolubility of the 2,5-dimethyl-3-thiophenemagnesium iodide.

The addition of 30 ml. of benzene followed by stirring made the mixture completely miscible. The Grignard reagent was carbonated by employing the method of Russey (52). A 250 g. quantity of dry ice was pulverized in a mortar and placed in a one liter, three neck round bottom flask equipped with a high speed stirrer. A 200 ml. volume of dry ether was added to the dry ice and the mixture was stirred vigorously to form a slurry. The 2,5-dimethyl-3-thiophenemagnesium iodide solution was transferred to a dropping funnel and added to the vigorously stirred dry ice ether slurry over a five minute period. There was a vigorous evolution of carbon dioxide during the addition of the Grignard reagent. The reaction mixture was stirred until all of the dry ice had disappeared which required fifty minutes. The reaction flask and its contents was placed in an ice bath and while the latter was being stirred 100 ml. of 6 N hydrochloric acid was added slowly to hydrolyze the Grignard addition product. The ether benzene layer was separated from the aqueous layer. The latter was extracted with two 50 ml. portions of ether and the combined ether extracts were added to the original ether benzene solution containing any possible 2,5-dimethyl-3-thiophene carboxylic acid. The solution was extracted first with a 40 ml. and then with a 30 ml. portion of 3 N sodium hydroxide solution. The combined alkaline extracts were acidified with 6 N hydrochloric acid which resulted in the immediate formation of a brown precipitate. The crystalline material was set aside in contact with the aqueous medium for nine days, then filtered and recrystallized from hot water. Some of the solid would not

dissolve in the hot water and was removed as an impurity by filtration. After the solution had cooled a slightly yellow colored crystalline solid separated from solution. Decolorizing charcoal was added to the mixture and it was again heated to its boiling temperature and filtered. Crystalline material failed to separate after the solution had been set aside overnight in a refrigerator. Two drops of concentrated hydrochloric acid were added to the cold solution and immediately a white crystalline solid formed. After cooling in an ice bath for a half hour the white crystalline solid was filtered and dried. Only approximately 0.1 g. of material was obtained. The melting point as carefully taken on a melting point block was $117-118^{\circ}\text{C}$. The reported (71) melting point of 2,5-dimethyl-3-thiophenecarboxylic acid is $119-120^{\circ}\text{C}$.

Preparation of Potassium Hydrogen Sulfide (53)

A 500 g., 7.85 moles, quantity of reagent grade, 85% potassium hydroxide were dissolved in 325 ml. of water. A cylinder of hydrogen sulfide was connected to a trap which was then connected to a gas dispersion tube. The potassium hydroxide solution was cooled in an ice bath. The hydrogen sulfide was bubbled into the potassium hydroxide solution until there appeared to be no further adsorption of hydrogen sulfide gas as indicated by the rapid evolution of the hydrogen sulfide gas. This required approximately three hours. The potassium hydrogen sulfide solution was transferred to a reactor vessel equipped with a

ground glass lid containing standard tapered ground glass openings. The reactor was equipped with a condenser for distillation and the vessel was placed in a mineral oil bath thermostated between the limits of 150-160° C. and heated by two knife electric blade heaters. The condenser was equipped with a vacuum take off and a receiver, the vacuum in the apparatus being obtained by a water aspirator. Boiling stones were added to the vessel and the water was removed from the potassium hydrogen sulfide by vacuum distillation. The product, solid potassium hydrogen sulfide was heated under vacuum at 150° C. for four hours to remove the last traces of water. The dried potassium hydrogen sulfide adhered tenaciously to the inside of the vessel after the lid was removed and considerable difficulty was experienced in trying to scrape the product from the vessel. To circumvent this, 1500 ml. of propylene glycol was added, a calcium chloride tube was placed on the reactor vessel to protect the contents from moisture and the vessel was placed on a steam bath overnight after which the potassium hydrogen sulfide was easily removed. Though additional propylene glycol was added to completely dissolve the potassium hydrogen sulfide. The resulting solution had a concentration of approximately 3.5 molar with respect to potassium hydrogen sulfide.

1. The first part of the paper is devoted to the study of the asymptotic behavior of the solutions of the system of equations (1) as $t \rightarrow \infty$. It is shown that the solutions of this system tend to zero as $t \rightarrow \infty$ if and only if the matrix A is stable. This result is obtained by using the method of the variation of constants.

2. In the second part of the paper, the problem of the asymptotic stability of the solutions of the system (1) is considered. It is shown that the system (1) is asymptotically stable if and only if the matrix A is stable and the matrix B is positive definite. This result is obtained by using the method of the variation of constants.

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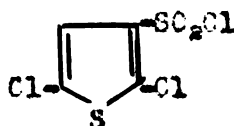
Attempted Synthesis of 2,5-dimethyl-3-thiophenethiol by the
Reaction of Potassium Hydrogen Sulfide with
2,5-dimethyl-3-iodothiophene



A 500 ml., three neck flask was equipped with a stirrer, reflux condenser and a "Y" tube fitted with a dropping funnel and gas inlet tube. A 200 ml. volume of propylene glycol containing 0.7 mole of potassium hydrogen sulfide, was placed in the flask. A 40 g., 0.17 mole, quantity of 2,5-dimethyl-3-iodothiophene was placed in the dropping funnel. The stirred potassium hydrogen sulfide solution was heated to 150° C. by means of an electric mantle and the 2,5-dimethyl-3-iodothiophene was added dropwise to it over a thirty minute period. A slight positive pressure of nitrogen was maintained in the apparatus during the experiment to prevent air from entering the apparatus and oxidizing any 2,5-dimethyl-3-thiophenethiol formed as a result of the reaction. The stirred reaction mixture was kept at a temperature of 150° C. for a total of twenty hours by heating in a series of four hour intervals over a three day period. A vacuum distillation apparatus was assembled consisting of a Claisen flask and an oil bath heated by means of a hot plate. All of the propylene glycol solvent and unreacted 2,5-dimethyl-3-iodothiophene was removed at a pressure of five millimeters of mercury. The head temperature in the Claisen flask rose to 101° C./5 mm. Hg. A considerable amount of unreacted

2,5-dimethyl-3-iodothiophene was noticed as evidenced by the double phase of the distillate resulting from the immiscibility of propylene glycol and the 2,5-dimethyl-3-iodothiophene. A thick brown syrupy residue remained in the distillation flask. A 300 ml. volume of water was added to the residue, and while keeping this mixture cool it was acidified with 6 N hydrochloric acid which resulted in the liberation of hydrogen sulfide and the formation of a brown precipitate. This material was filtered and extracted first with a 200 ml. portion and then with three, 100 ml. portions of ether. The combined ether extracts were in turn extracted with two, 50 ml. portions of 3 N sodium hydroxide. The combined basic extracts were acidified with 6 N hydrochloric acid and extracted first with a 50 ml. portion and then with two 25 ml. portions of ether. During the acidification with hydrochloric acid very little insoluble material separated from solution. The combined ether extracts were dried in contact with anhydrous magnesium sulfate, and ether was then removed on a steam bath. Only a slight trace of residue remained in the distilling flask, indicating that none of the desired product had formed. The unreacted 2,5-dimethyl-3-iodothiophene collected during the initial distillation of this material and propylene-glycol was recovered.

**Preparation of 2,5-Dichloro-3-thiophenesulfonyl Chloride by
Direct Chlorosulfonation**



1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0) = 1$.

2. In the second part, we consider the function $g(x)$ defined by the equation $g(x) = \int_0^x g(t) dt$. It is shown that $g(x)$ is a constant function, and its value is determined by the initial condition $g(0) = 1$.

3. The third part of the paper is devoted to the study of the properties of the function $h(x)$ defined by the equation $h(x) = \int_0^x h(t) dt$. It is shown that $h(x)$ is a constant function, and its value is determined by the initial condition $h(0) = 1$.

4. In the fourth part, we consider the function $k(x)$ defined by the equation $k(x) = \int_0^x k(t) dt$. It is shown that $k(x)$ is a constant function, and its value is determined by the initial condition $k(0) = 1$.

5. The fifth part of the paper is devoted to the study of the properties of the function $l(x)$ defined by the equation $l(x) = \int_0^x l(t) dt$. It is shown that $l(x)$ is a constant function, and its value is determined by the initial condition $l(0) = 1$.

6. In the sixth part, we consider the function $m(x)$ defined by the equation $m(x) = \int_0^x m(t) dt$. It is shown that $m(x)$ is a constant function, and its value is determined by the initial condition $m(0) = 1$.

7. The seventh part of the paper is devoted to the study of the properties of the function $n(x)$ defined by the equation $n(x) = \int_0^x n(t) dt$. It is shown that $n(x)$ is a constant function, and its value is determined by the initial condition $n(0) = 1$.

8. In the eighth part, we consider the function $o(x)$ defined by the equation $o(x) = \int_0^x o(t) dt$. It is shown that $o(x)$ is a constant function, and its value is determined by the initial condition $o(0) = 1$.

9. The ninth part of the paper is devoted to the study of the properties of the function $p(x)$ defined by the equation $p(x) = \int_0^x p(t) dt$. It is shown that $p(x)$ is a constant function, and its value is determined by the initial condition $p(0) = 1$.

10. In the tenth part, we consider the function $q(x)$ defined by the equation $q(x) = \int_0^x q(t) dt$. It is shown that $q(x)$ is a constant function, and its value is determined by the initial condition $q(0) = 1$.

The author is grateful to the referee for his valuable remarks and suggestions.



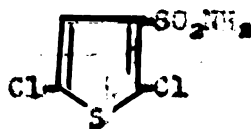
A one liter, three neck round bottom flask was fitted with a stirrer, dropping funnel and a "T" tube containing a thermometer which reached to the bottom of the flask and an outlet tube to conduct gas away from the apparatus. The flask was charged with 319.6 g., 3.0 moles of freshly distilled chlorosulfonic acid and then immersed in an ice salt bath and allowed to cool to -2.0° C. A 153.0 g., 1.0 mole quantity of 2,5-dichlorothiophene was placed in the dropping funnel and added dropwise to the stirred cold chlorosulfonic acid over a sixty-five minute period. After all of the 2,5-dichlorothiophene had been added the red colored reaction mixture was stirred an additional twenty minutes. The reaction mixture was poured onto two liters of crushed ice causing a green colored precipitate and oil to form. The precipitate and oil were extracted into several portions of carbon tetrachloride which were combined and washed with 100 ml. of water and then dried in contact with anhydrous magnesium sulfate. The carbon tetrachloride was removed on a steam bath using a Claisen type flask and the residue was fractionated employing a one foot heat jacketed Vigreux column. A liquid forerun boiling at $68-111^{\circ}/4$ mm. Hg. which amounted to 4.17 g. was discarded. The colorless fraction boiling in the range $111-119^{\circ}/5$ mm. Hg. was collected and on cooling solidified. The yield was 24.45 g., 0.0921 moles which is 9.81% of the theoretical yield. A 4.00 g. residue remained in the flask after the distillation.

The chlorosulfonation of 2,5-dichlorothiophene was repeated using the same apparatus as described above. A different ratio of reactant and reaction times were used. A 233.1 g., 2.0 moles quantity of

freshly distilled chlorosulfonic acid was placed in the flask and cooled to -5°C . in an ice salt bath. A 153.0 g., 1.0 mole quantity of 2,5-dichlorothiophene was placed in the dropping funnel and added dropwise to the stirred cold chlorosulfonic acid over a one hour period. The reaction mixture was stirred an additional thirty-five minutes, then poured onto crushed ice, and extracted with three 100 ml. portions of carbon tetrachloride. The combined carbon tetrachloride extracts were washed with 50 ml. of water and then dried in contact with anhydrous magnesium sulfate. The carbon tetrachloride was distilled from the product on a steam bath and the residue was fractionated using a one foot heat jacketed Vigreux column. The forerun fraction, weighing 5.30 g., boiling at $22-219^{\circ}\text{C}/4.5\text{ mm. Hg.}$ was collected which weighed 14.74 g., 0.099 mole and corresponds to a 5.86% yield. A 5.35 g. residue remained in the distillation flask.

To determine the effect of ratio of reagents on yield the exact procedure was repeated as described above using 502.6 g., 5.0 moles of freshly distilled chlorosulfonic acid and 153.0 g., 1.0 mole of 2,5-dichlorothiophene. The fraction boiling at $26-217^{\circ}\text{C}/4.1\text{ mm. Hg.}$ weighing 9.57 g. was discarded, and the fraction boiling at $215-220^{\circ}\text{C}/4.1\text{ mm. Hg.}$ weighing 46.19 g., 0.192 mole a 19.2% was collected. A 5.53 g. residue remained in the distillation flask.

Preparation of 2,5-dichloro-3-thiophenesulfonamide (27)



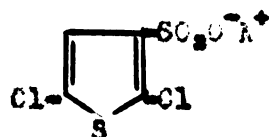
A 125 ml. Erlenmeyer flask was fitted with a reflux condenser. A mixture of 8 g. of ammonium carbonate and 40 ml. of concentrated ammonium hydroxide was placed in the flask and 2 g. of 2,5-dichloro-3-thiophenesulfonyl chloride was added. The mixture was stirred and set aside for fifteen minutes at room temperature, with occasional shaking. The reaction flask was immersed in a water bath at 60° C. for five minutes, the bath was then heated to 80° C. and held between 70-80° C. for an additional ten minutes. The flask and its contents were shaken occasionally during the heating period. The hot solution was filtered to remove the excess ammonium carbonate and on cooling the filtrate, white crystalline needles of 2,5-dichloro-3-thiophenesulfonamide crystallized from the solution. The product was recrystallized three times from 75 ml. of hot water to yield 2,5-dichloro-3-thiophenesulfonamide melting at 130-130.5° C., after each recrystallization.

Analysis of the compound for carbon, hydrogen, sulfur, and chlorine gave the following results: Calc'd. for $C_4H_2S_2Cl_2NO_2$: C, 20.70; H, 1.30; Cl, 27.63; S, 30.55. Found: C, 20.85; H, 1.47; Cl, 30.75; S, 30.75.

filtered from the hot solution. The clear filtrate was evaporated to dryness in a beaker on a steam bath while a stream of air was blown into the beaker to accelerate the evaporation. The solid residue was transferred to a crystallizing dish and dried in an oven at $110^{\circ}\text{C}.$, overnight. The yield of sodium 2,5-dichloro-3-thiophenesulfonate was 109.5 g., 0.43 mole. The dried material burned readily leaving only a small amount of residue, indicating the removal of the major part of the sodium sulfate.

The aqueous solutions from all previous chlorosulfonation reactions were combined and neutralized with forty percent sodium hydroxide and the salts were filtered. The filtrate was evaporated to dryness on a steam bath with occasional removal of the salts by filtration as they crystallized from the concentrated solution. The salts were dried and extracted with methanol as described above.

Preparation of Potassium 2,5-dichloro-3-thiophenesulfonate



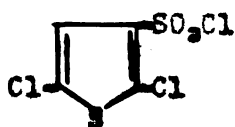
A one liter, three neck flask immersed in an ice salt bath, was fitted with a mechanical stirrer, an outlet tube connected to a hydrogen chloride trap, and a "1" tube which contained a thermometer and dropping funnel. A 292 g., 2.5 moles, quantity of freshly distilled chlorosulfonic acid was added to the flask and cooled to $-3.5^{\circ}\text{C}.$ A 366.1 g., 2.0 moles, quantity of 2,5-dichlorothiophene was added dropwise to the

cold stirred chlorosulfonic acid from the dropping funnel. After adding the 2,5-dichlorothiophene for a half hour the reaction temperature had risen to 6.0°C . and further addition of the halothiophene was stopped until the temperature had dropped to 1.0°C . After again adding halothiophene for a third of an hour the reaction mixture became very thick and when the stirring rate was increased it solidified and the temperature rose rapidly. It was difficult to determine the temperature since the thermometer could not be immersed into the reaction medium. An additional seven minutes were required to finish adding the 2,5-dichlorothiophene. As much of the contents of the flask as possible were poured onto crushed ice. After cooling the flask in an ice bath, ice and water were added cautiously to the reaction flask. A vigorous reaction ensued and then the remainder of the material in the flask was emptied onto the ice with the original material. The aqueous mixture was neutralized with potassium hydroxide and the neutral solution of crude potassium 2,5-dichlorothiophenesulfonate and inorganic salts was evaporated to dryness, assisted by an air stream blowing over it, on a steam bath. The solid material was pulverized in a mortar and dried in an oven at 110°C . for two days. The dry potassium salt mixture was extracted with five, one liter portions of absolute methanol. During each extraction, the salts were stirred in the refluxing methanol for six to eight hours, then filtered and the filtrate was evaporated on a steam bath, assisted by a stream of air blowing over the surface of the methanol to hasten the evaporation. The white solid obtained in this manner from the five extractions weighed 125.1 g. after drying overnight in an oven at 110°C .

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If the solid was pure potassium 2,5-dichloro-3-thiophenesulfonate, the yield was 0.462 mole or 23.1% which shows that the solubility of the potassium salt of 2,5-dichlorothiophenesulfonate was not nearly as effective in its isolation by methanol extraction as the sodium salt. Additional amounts of the product could have been obtained by further methanol extraction as was shown by the fact that the crude salt mixture after extraction was still quite combustible when ignited over a Bunsen burner flame, which indicated organic material present in the mixture.

Preparation of 2,5-Dichloro-3-thiophenesulfonyl Chloride from
Sodium 2,5-Dichloro-3-thiophenesulfonate

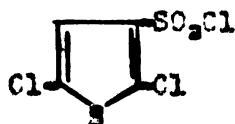


The method employed for the preparation of 2,5-dichloro-3-thiophenesulfonyl chloride was a modification of that developed by Adams and Marvel (55) for the preparation of benzenesulfonyl chloride. A 109.47 g., 0.428 mole quantity of sodium 2,5-dichloro-3-thiophenesulfonate, which contained a little sodium sulfate as impurity, was pulverized in a mortar. A 52.1 g., 0.257 mole quantity of phosphorus pentachloride was also pulverized in a mortar. The pulverized sodium 2,5-dichloro-3-thiophenesulfonate and phosphorus pentachloride were mixed intimately in a one liter round bottom flask. The flask was fitted with a reflux condenser containing a calcium chloride drying tube to protect the contents of the flask from atmospheric moisture. The flask was then lowered into a mineral oil constant temperature bath set at 175° C.

The first of these is the fact that the United States is a young nation. It is only about 150 years old, and its history is therefore a very recent one. This is in contrast to the history of the European countries, which have been for centuries. The second fact is that the United States is a large country. It covers a vast area of land, and its population is very large. This is in contrast to the European countries, which are much smaller. The third fact is that the United States is a free country. It has a long history of freedom, and its people are very proud of their liberties. This is in contrast to the European countries, which have often been ruled by tyrants. The fourth fact is that the United States is a democratic country. Its people have the right to elect their representatives, and they are free to express their opinions. This is in contrast to the European countries, which have often been ruled by kings. The fifth fact is that the United States is a peaceful country. It has never been at war with any other country, and its people are very fond of peace. This is in contrast to the European countries, which have often been at war with each other. The sixth fact is that the United States is a progressive country. Its people are always looking for new ways to improve their lives, and they are not afraid to try new things. This is in contrast to the European countries, which are often very conservative. The seventh fact is that the United States is a powerful country. It has a very strong army and navy, and it is one of the most powerful countries in the world. This is in contrast to the European countries, which are often much weaker. The eighth fact is that the United States is a rich country. It has a very large economy, and its people are very wealthy. This is in contrast to the European countries, which are often much poorer. The ninth fact is that the United States is a happy country. Its people are very content with their lives, and they are very friendly to each other. This is in contrast to the European countries, which are often very unhappy. The tenth fact is that the United States is a beautiful country. It has a very large area of land, and it is very beautiful. This is in contrast to the European countries, which are often very small and ugly.

If the solid was pure potassium 2,5-dichloro-3-thiophenesulfonate, the yield was 0.462 mole or 23.1% which shows that the solubility of the potassium salt of 2,5-dichlorothiophenesulfonate was not nearly as effective in its isolation by methanol extraction as the sodium salt. Additional amounts of the product could have been obtained by further methanol extraction as was shown by the fact that the crude salt mixture after extraction was still quite combustible when ignited over a Bunsen burner flame, which indicated organic material present in the mixture.

Preparation of 2,5-dichloro-3-thiophenesulfonyl Chloride from
Sodium 2,5-dichloro-3-thiophenesulfonate



The method employed for the preparation of 2,5-dichloro-3-thiophenesulfonyl chloride was a modification of that developed by Adams and Marvel (55) for the preparation of benzenesulfonyl chloride. A 109.47 g., 0.428 mole quantity of sodium 2,5-dichloro-3-thiophenesulfonate, which contained a little sodium sulfate as impurity, was pulverized in a mortar. A 52.1 g., 0.251 mole quantity of phosphorus pentachloride was also pulverized in a mortar. The pulverized sodium 2,5-dichloro-3-thiophenesulfonate and phosphorus pentachloride were mixed intimately in a one liter round bottom flask. The flask was fitted with a reflux condenser containing a calcium chloride drying tube to protect the contents of the flask from atmospheric moisture. The flask was then lowered into a mineral oil constant temperature bath set at 175° C.

The first part of the report deals with the general situation of the country and the position of the various groups. It is found that the country is in a state of general confusion and that the various groups are in a state of mutual hostility. The second part of the report deals with the specific details of the situation and the measures that have been taken to deal with it. It is found that the measures taken have been inadequate and that further action is required.



The third part of the report deals with the future of the country and the measures that should be taken to bring about a state of general peace and order. It is found that the measures taken should be more comprehensive and that the various groups should be brought into a state of mutual cooperation. The fourth part of the report deals with the conclusion of the report and the measures that should be taken to bring about a state of general peace and order. It is found that the measures taken should be more comprehensive and that the various groups should be brought into a state of mutual cooperation.

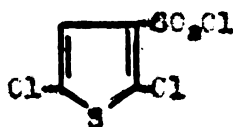
After four hours the mixture was a thick white paste, but when the flask was stoppered and shaken the paste became a liquid slurry. After shaking another fifteen minutes while occasionally releasing the pressure in the flask the liquid cooled and again became a thick paste. The flask was returned to the constant temperature bath and was heated an additional fifteen hours, being removed from the oil bath at four hour intervals and shaken in the manner just described. After the first eight hours 20 g., 0.096 mole of additional phosphorus pentachloride were added to the flask. At the end of fifteen hours the reaction mixture was poured onto crushed ice and an oily layer formed on the bottom of the beaker. The mixture was extracted with three, 100 ml. portions of carbon tetrachloride. The combined extracts were washed with 50 ml. of water and dried in contact with anhydrous magnesium sulfate. The carbon tetrachloride was removed on a steam bath. The residue was fractionally distilled using a one foot heat jacketed Vigreux column. The fraction distilling between $112-122^{\circ}\text{C.}/3.7-4.0\text{ mm. Hg.}$ was collected. The yield was 80.86 g., 0.3222 mole, 75.1% of the theoretical. The starting material was impure because of the extraction method of obtaining it, therefore the yield of 2,5-dichloro-3-thiophenesulfonyl chloride would be higher if a correction were made for the sodium sulfate present as an impurity in the starting material.

The reaction was repeated on a larger scale using 320.0 g., 1.253 mole, quantity of sodium 2,5-dichloro-3-thiophenesulfonate and 146.0 g., 0.7 mole, of phosphorus pentachloride. The reaction time was twenty hours at 175°C. The product was isolated as before. The fraction

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boiling at 110-120° C./3.6 mm. Hg. was collected which amounted to 212.57 g., 0.846 mole, a 67.5% yield of 2,5-dichloro-3-thiophenesulfonyl chloride. The sulfonamide derivative of this product was prepared for elemental analysis. The analytical data are reported under the preparation of the 2,5-dichloro-3-thiophenesulfonamide.

Preparation of 2,5-dichloro-3-thiophenesulfonyl Chloride from
Potassium 2,5-dichloro-3-thiophenesulfonate (55)



The apparatus used in this preparation was the same as that described in the previous experiment. A 125.1 g., 0.462 mole, quantity of potassium 2,5-dichloro-3-thiophenesulfonate was finely ground in a mortar and mixed thoroughly by shaking in a 500 ml. stoppered round bottom flask with 43.2 g., 0.231 mole, of previously ground phosphorus pentachloride. A pressure was continually developed and had to be released every few minutes to prevent the stopper from being forced out of the flask. The flask containing the intimate mixture of powdered reagents was fitted with a condenser and placed in an oil bath at 175° C. for twenty hours. The flask was removed from the oil bath every four hours and after cooling it was stoppered and shaken for a quarter of an hour. During the shaking the pressure in the flask had to very frequently be released. At the end of twenty hours the syrupy mixture was poured onto 500 g. of ice contained in a two liter beaker. A dark oily layer formed on the

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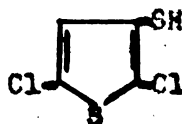
THE UNIVERSITY OF CHICAGO



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bottom of the beaker and was separated. The aqueous layer was extracted with three, 100 ml. portions of carbon tetrachloride. The combined carbon tetrachloride extracts were added to the original oily portion, then washed with 50 ml. of water and dried in contact with anhydrous magnesium sulfate. The magnesium sulfate was filtered from the carbon tetrachloride solution and the carbon tetrachloride was removed from the crude product by distillation on a steam bath. The residue was fractionated employing a semi-micro modified Claisen distilling flask. The forerun boiling between $65-122^{\circ}\text{C./4.0 mm. Hg.}$ was discarded and the fraction boiling at $127-130^{\circ}\text{C./5.8 mm. Hg.}$ was collected. A 3.90 g. residue remained in the distillation flask. A 36.21 g., 0.144 mole, 31.2% yield of 2,5-dichloro-3-thiophenesulfonyl chloride was obtained based on the potassium 2,5-dichloro-3-thiophenesulfonate used in the reaction. The low yield indicates the possibility that potassium sulfate was present in the methanol extracted potassium 2,5-dichloro-3-thiophenesulfonate.

Preparation of 2,5-dichloro-3-thiophenethiol



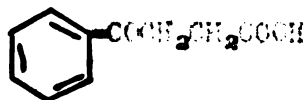
A two liter three neck flask was fitted with a bulb type reflux condenser, containing a calcium chloride drying tube, stirrer and a "Y" tube containing a dropping funnel in one side of the "Y" and the other side was stoppered. The entire glass apparatus was dried in an oven at 110°C. prior to assembling. An 18.1 g., 0.477 mole quantity of

lithium aluminum hydride was pulverized in a mortar and added to the flask through the arm of the "Y" tube after removing the stopper. A 575 ml. quantity of sodium dried, ether was added to the flask and the lithium aluminum hydride was stirred in the refluxing ether until it had dissolved. A 40 g., 0.157 mole, quantity of 2,5-dichloro-3-thiophenesulfonyl chloride dissolved in 100 ml. of dry ether, was added dropwise to the vigorously stirred lithium aluminum hydride solution at a rate sufficient to maintain a gentle reflux of the ether. During the addition of the 2,5-dichloro-3-thiophenesulfonyl chloride occasionally lumps of reacting material would adhere to the flask and took on a glowing red color. After the addition of the 2,5-dichloro-3-thiophenesulfonyl chloride was complete the reaction mixture was stirred at its reflux temperature for an additional two hours. It was then cooled and 200 ml. of water was cautiously added dropwise to the stirred contents of the flask while the latter was immersed in an ice bath. A gray precipitate formed which was redissolved by adding 6 N hydrochloric acid and stirring. The ether layer was separated from the aqueous layer and the latter was extracted with three 100 ml. portions of ether. The ether extracts were combined with the original ether layer. The resulting ether solution was extracted with two, 100 ml. portions and one, 50 ml. portion of 15% sodium hydroxide. The combined sodium hydroxide extracts were acidified with 16 N sulfuric acid which caused some oily material to separate from solution. This was extracted from the aqueous solution with three 50 ml. portions of ether. The combined ether extracts were washed with 50 ml. of water and dried in

contact with anhydrous magnesium sulfate. The ether was removed by distillation using a modified Claisen flask. The residue was fractionated using a small Vigreux modified Claisen flask. The fraction boiling between 85-90°C./5.0 mm. Hg. was collected. The weight of 2,5-dichloro-3-thiophenethiol was 11.35 g., 0.0613 mole, which is a 38.5% yield. The product was stored under a nitrogen atmosphere in a refrigerator.

The above reaction was repeated twice using different scales of reactants and in each case a different yield was obtained. The general procedure and apparatus were the same as in the previous experiment with the exception that a 6 N sulfuric acid solution was used to acidify the reaction mixture in place of 6 N hydrochloric acid. A 56.9 g., 1.5 moles, quantity of lithium aluminum hydride and 125.8 g., 0.5 mole, quantity of 2,5-dichloro-3-thiophenesulfonyl chloride were employed. Four hours were required to mix the reagents and the reaction mixture was set aside overnight. Following this it was heated at its reflux temperature for one hour. A fraction boiling at 73-75°C./1.4 mm. Hg. weighing 22.53 g., 0.1217 mole, was isolated which is a 24.4% yield of 2,5-dichloro-3-thiophenethiol. The refractive index of the product was $n_D^{24} = 1.6251$.

In the other preparation using 50.9 g., 1.341 moles, of lithium aluminum hydride and 112.3 g., 0.447 mole, of 2,5-dichloro-3-thiophenesulfonyl chloride with a 4.5 hour mixing time, three hour period of being set aside and a two hour heating period at the reflux temperature of the reaction mixture, a 22.0 g., 0.119 mole, 26.6% yield of 2,5-dichloro-3-thiophenethiol boiling at 85-88°C./5.5 mm. Hg. with $n_D^{20} = 1.6260$ was obtained.

Preparation of β -Benzoylpropionic Acid (65)

A five liter, three neck, round bottom flask was fitted with a Hirschberger mechanical stirrer, reflux condenser and a powder addition flask made by connecting together two 2.-40 standard taper joints with about eight inches of rubber tubing of the same diameter as the standard joints. One taper joint was fitted to the five liter flask and the other to a 500 ml. round bottom flask which contained the powder to be added to the reaction flask. The rubber tubing was folded to seal off the smaller flask from the five liter reaction flask. A 200 g., 2.00 moles, quantity of powdered succinic anhydride and 1200 ml., 1050 g., 13.5 moles, of benzene were placed in the five liter flask. A 600 g., 4.5 moles, quantity of anhydrous aluminum chloride was quickly powdered in a mortar to prevent moisture in the air from hydrating the anhydrous aluminum chloride. The mortarizing was done in 100 g. portions which were immediately added to the 500 ml. powder addition flask from which it was in turn added to the stirred benzene and succinic anhydride mixture. Hydrogen chloride was rapidly evolved from the stirred reaction mixture. During the addition of the last 100 g. portion of anhydrous aluminum chloride, the reaction mixture became so viscous that stirring was very difficult. After all of the anhydrous aluminum chloride had been added to the reaction flask the stirrer stalled because of the very viscous layer on the bottom of the flask. The stirrer was raised



to the upper portion of the reaction medium. The powder addition flask was removed and replaced with a bulb type reflux condenser. The reaction mixture finally became so viscous that it was impossible to stir any portion of it. One of the reflux condensers was stoppered and the other was fitted with a calcium chloride drying tube to prevent moisture from entering the reaction mixture while it was set aside overnight under a hood. The following day the reaction flask was gently heated on a steam bath, which caused copious quantities of hydrogen chloride to be evolved. After heating on the steam bath for an hour the viscous mass became quite fluid so that it was easily stirred. The steam bath was replaced with a heating mantle and the stirred mixture was kept at its reflux temperature for a half hour. The mantle was replaced by an ice bath and one of the reflux condensers was replaced with a dropping funnel. A 300 ml. quantity of water was slowly added to the cold stirred reaction mixture from the dropping funnel. After the water had been added, 300 ml. of concentrated hydrochloric acid were slowly added to the mixture. The dropping funnel was replaced with a condenser fitted to the flask by means of a 45 degree elbow and the apparatus was arranged for steam distillation. The reflux condenser was removed and a steam inlet tube was fitted to the reaction flask. The reaction mixture became very dark as the excess benzene was rapidly steam distilled from the reaction mixture. The hot non steam volatile residue was transferred to a three liter beaker and on cooling the β -benzoylpropionic acid crystallized from solution. The contents of the beaker was cooled to 0° C. and the solid β -benzoylpropionic acid was recovered by filtration. The crude

acid was washed with a cold solution of 100 ml. of concentrated hydrochloric acid diluted with 300 ml. of water, after which it was mixed thoroughly with 400 ml. of cold water in a beaker and again filtered. The product was a very dark brown color. The crude β -benzoylpropionic acid was dissolved in a boiling solution prepared from 263 g., 2.12 moles, of sodium carbonate monohydrate and 1500 ml. of water. The small amount of aluminum hydroxide which formed was filtered from the dissolved acid and washed with four, 50 ml. portions of hot water. The filtrate was decolorized with charcoal and again filtered. The decolorized filtrate was transferred to a four liter beaker, cooled to 50-60° C., and carefully acidified with 390 ml. of concentrated hydrochloric acid. The precipitated β -benzoylpropionic acid was cooled to 0° C. in an ice salt bath, filtered and washed with four moderate quantities of cold water. The β -benzoylpropionic acid was dried overnight at room temperature and finally for a day in an oven at 50° C. to give 290.62 g., 1.63 moles, an 80.0% yield of β -benzoylpropionic acid melting at 114-115° C. The reported melting point (56) is 116° C.

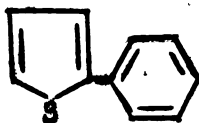
Preparation of Sodium β -Benzoylpropionate



A solution of 40 g., 1.0 mole, of sodium hydroxide dissolved in 100 ml. of water was prepared. A 170.3 g., 1.0 mole, quantity of β -benzoylpropionic acid was dissolved in the hot alkaline solution. The solution was transferred to a two liter reaction vessel, fitted

with a condenser and vacuum adaptor for distilling under reduced pressure. The apparatus was evacuated by means of a water aspirator. The reaction vessel was immersed in an oil bath heated to a temperature sufficient to cause gentle distillation. After the mixture had evaporated to dryness, the ground glass lid of the reaction vessel was removed and the solid material was transferred to an evaporating dish and placed in an oven at 55°C . for two days. The solid was finally pulverized in a mortar. The yield of sodium β -benzoylpropionate obtained was quantitative.

Preparation of 2-Phenylthiophene from
 β -Benzoylpropionic Acid (27)



A 50 ml. Wurts flask was fitted with an air cooled condenser and a 50 ml. Erlenmeyer flask served as a receiver in the apparatus used to carry out the cyclization reaction. A 9.00 g., 0.0505 mole, quantity of β -benzoylpropionic acid and a 11.2 g., 0.0503 mole, quantity of phosphorus pentasulfide were intimately mixed by grinding them together in a mortar. The finely ground mixture was placed in the Wurts flask and the apparatus was assembled. A Bunsen burner was regulated to obtain a small blue flame. The flame was cautiously passed back and forth under the bottom of the Wurts flask. The reaction mixture first started to melt and then suddenly a vigorous reaction occurred and the contents of the flask began to char and foam. The foam had a tendency

to climb up the side arm of the Wurtz flask. The reaction mixture was heated gently to distill material from the flask, but due to excess foaming, heating the reaction mixture had to be discontinued. At this point only a small amount, less than a gram, of a reddish colored material had distilled from the reaction mixture. This material was covered with 10 ml. of water and shaken vigorously. A 10 ml. quantity of ether was added to the aqueous mixture and after shaking, the mixture was transferred to a small separatory funnel, and the ether extract was separated from the aqueous phase. The ether solution was transferred to a 50 ml. beaker and the ether was evaporated on a steam bath. The small amount of residue obtained in this manner was dissolved in a milliliter of hot ethanol, filtered through a Hirsch filter, and then evaporated to nearly half its volume. After cooling in an ice bath a few crystals of material were obtained which melted between 38 and 42° C. The reported melting point of 2-phenylthiophene is $42-43^{\circ}$ C. (27). The experiment was repeated using a 150 ml. Wurtz flask so that the foam produced during the reaction could be more easily retained in the flask. The quantity of β -benzoylpropionic acid used was the same, but the amount of phosphorous pentasulfide was reduced to 5.60 g., 0.0251 mole, with the aim of reducing the amount of charring during the reaction. However, the reaction mixture charred when the reaction was initiated with heat as in the previous experiment. The yield of crude 2-phenylthiophene was 0.30 g. and it was not purified further. This method of preparing 2-phenylthiophene was abandoned and sodium β -benzoylpropionate was employed in place of the free acid.

Preparation of 2-Phenylthiophene from
Sodium *p*-Benzoylpropionate (26)

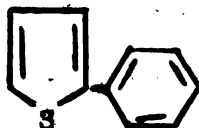
A 150 ml. Wurts distillation flask fitted with an air cooled condensor and a 50 ml. Erlenmeyer flask used as a receiver constituted the apparatus employed in this synthesis. A 30.0 g., 0.15 mole, quantity of dry sodium *p*-benzoylpropionate and a 45.0 g., 0.129 mole, quantity of phosphorus heptasulfide, P_4S_7 , was thoroughly mixed in a mortar and placed in the Wurts flask. The flask was heated gently with a Bunsen burner. Again charring occurred when the reaction started, but not as much as with the free acid as was just described in the previous experiments. The material was collected in three fractions weighing 0.20 g., 0.33 g., and 0.35 g. in the order in which they were collected. Fractions two and three solidified on cooling to a reddish brown colored solid. After combining fractions two and three and recrystallizing and decolorizing with charcoal in ethanol as a solvent, approximately 0.4 g., of a material was obtained which melted at 42-43° C., in agreement with the reported melting point for 2-phenylthiophene.

The experiment was repeated, using the same apparatus and quantities of materials as above, except that 20.0 g. of sand was added as a diluent. The dry materials were intimately mixed in a mortar and placed in the Wurts flask. The experimental procedure used for the remainder of the experiment was the same as that described in the previous experiment. There was not as much charring of the reaction mixture at the initial phases of the pyrolysis as in the previous experiments. A 2.61 g., 0.0165 mole, 11.0% yield of crude 2-phenylthiophene was obtained.

After several recrystallizations from ethanol a small quantity of material was obtained which melted at $42-43^{\circ}$ C.

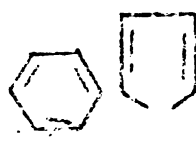
Several other attempts to obtain higher yields were made. The quantity of sand as a diluent was increased but this failed to give higher yields. The ratios of phosphorus heptasulfide to sodium *p*-benzoylpropionate were varied, but this likewise failed to increase the yields. The experiment was repeated exactly as in the previous case except that a vacuum was applied to the system, using a side arm six inch test tube as a receiver. The test tube side arm was connected to a water aspirator through a trap. The crude product in this case was not as colored and was easier to purify, consequently a slightly higher yield of pure 2-phenylthiophene was obtained as less was lost in its purification. Care had to be taken at the end of the pyrolysis since the Wurtz flask had a tendency to collapse when heated under reduced pressure.

Preparation of 2-Phenylthiophene by
the Diazo Reaction (56,73,74)



A mechanical stirrer was arranged above a two liter beaker so that efficient mixing of the contents of the beaker could be accomplished. A 93.12 g., 1.00 mole, quantity of freshly distilled aniline and 80 ml. of water were mixed in the beaker and 200 ml. of concentrated hydrochloric acid was added to the stirred mixture. The beaker was set in

The first step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer and the initiator, and the reaction is initiated by the addition of a small amount of a catalyst. The reaction is carried out at a temperature of 60°C for 24 hours. The reaction is monitored by the change in the color of the solution, which changes from colorless to a deep red color. The reaction is then stopped by the addition of a small amount of a quenching agent. The reaction is then carried out in a solution of the monomer and the initiator, and the reaction is initiated by the addition of a small amount of a catalyst. The reaction is carried out at a temperature of 60°C for 24 hours. The reaction is monitored by the change in the color of the solution, which changes from colorless to a deep red color. The reaction is then stopped by the addition of a small amount of a quenching agent.



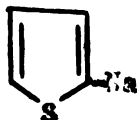
The reaction is then carried out in a solution of the monomer and the initiator, and the reaction is initiated by the addition of a small amount of a catalyst. The reaction is carried out at a temperature of 60°C for 24 hours. The reaction is monitored by the change in the color of the solution, which changes from colorless to a deep red color. The reaction is then stopped by the addition of a small amount of a quenching agent. The reaction is then carried out in a solution of the monomer and the initiator, and the reaction is initiated by the addition of a small amount of a catalyst. The reaction is carried out at a temperature of 60°C for 24 hours. The reaction is monitored by the change in the color of the solution, which changes from colorless to a deep red color. The reaction is then stopped by the addition of a small amount of a quenching agent.

a pan of ice water and the solution was mechanically stirred as it cooled in order to precipitate the aniline hydrochloride in a fine crystalline form. A solution of 72.0 g., 1.04 mole, of sodium nitrite dissolved in 144 ml. of water was placed in a 250 ml. dropping funnel supported above the beaker containing the aniline hydrochloride. Some ice was added to the reaction mixture and when its temperature had fallen to 2.5° C. the sodium nitrite solution was added to the contents of the beaker over a 75 minute period, at the end of which time a starch iodide paper end point was obtained with a few drops of the reaction mixture. The diazotized aniline was transferred to a one gallon wide mouth jar and ice was packed around the jar and an efficient mechanical stirrer was arranged over the jar so that thorough mixing of the contents of the jar could be obtained. A 500 g., 5.94 moles, quantity of thiophene, which had been previously cooled in an ice bath, was added to the jar. A 242 ml. quantity of 5 N. sodium hydroxide solution was added from a dropping funnel to the vigorously stirred reaction mixture, kept at 2° C., during a period of two and a half hours in which time the reaction mixture had turned red in color. The stirred reaction mixture was allowed to warm to room temperature which caused it to change to a deep reddish brown in color. It was transferred to a three liter separatory funnel and after acidifying with hydrochloric acid the emulsion broke and the organic layer was separated from the aqueous layer. A three liter three neck, round bottom flask was equipped and arranged for steam distillation. After the reaction mixture was transferred to the three liter flask, it was immersed almost completely in

an oil bath, set at 170° C. to prevent excessive foaming during the steam distillation and to hasten the distillation. The excess thiophene was steam distilled from the reaction mixture very rapidly. It was collected and fractionated for further use. The 2-phenylthiophene steam distilled very slowly. It had a tendency to crystallize in the condenser. A total of approximately 15 liters of distillate were collected. After chilling portions of it in an ice bath, the solid crude 2-phenylthiophene was filtered from the aqueous distillate on a Buchner funnel and immediately transferred to an Erlenmeyer flask, as the product melted at room temperature. The entire distillate was extracted with two liters of ether in portions large enough to handle easily in a three liter separatory funnel. The ether extracts were combined with the original crude solid which had been filtered from the aqueous portion, and the resulting ether solution was dried in contact with anhydrous magnesium sulfate. The magnesium sulfate was filtered from the ethereal solution of crude 2-phenylthiophene and the ether was removed on a steam bath. The residue weighed 25.96 g. and would solidify if cooled in an ice bath. It had a light reddish brown color. There was a tendency for two phases to form in the ether solution which indicated all of the water had not been removed by drying the ether solution in contact with magnesium sulfate. The residue was dissolved in hot ethanol and decolorized with charcoal. The 2-phenylthiophene crystallized on cooling the ethanol solution. The 2-phenylthiophene was recrystallized again from ethanol to give 6.62 g., 0.0598 mole, a 5.38% yield of 2-phenylthiophene, melting at $42-43^{\circ}$ C. No effort was made to recover additional product from the mother liquors.

[illegible]

Preparation of 2-Thienylsodium (56)



A three liter, three neck flask, supported in a heating mantle, was fitted with a mechanical stirrer, reflux condenser, and a "Y" tube containing a thermometer and dropping funnel. A 750 ml. quantity of toluene, previously dried with sodium, was added to the flask. To the toluene, 27 g., 0.14 mole, of mercury and 50 g., 2.17 moles, of sodium were added and the mixture was warmed rapidly to 95° C. and then slowly to 133° C. at which temperature the toluene refluxed spontaneously for approximately a minute and a half after the heating mantle had been removed. Heat was again applied and the reaction mixture was kept at its reflux temperature for an additional two minutes. The reaction mixture was stirred vigorously and allowed to cool to 44° C. The toluene was removed from the amalgamated sodium by drawing it through a fritted glass tube into a trap by means of a water aspirator. After removing the toluene one liter of sodium dried benzene, was added to the amalgamated sodium. A 113 g., 1.0 mole, quantity of 2-chlorothiophene was added to the amalgamated sodium suspended in benzene. This mixture refluxed spontaneously for a quarter of an hour, without applying external heat, after it had been initially heated at its reflux temperature for about five minutes. When the reaction mixture had stopped refluxing spontaneously it had a black powdery appearance.



External heating was again applied to the reaction flask and the stirred mixture was kept at its reflux temperature for an additional four hours. The 2-thienylsodium was used immediately and allowed to react with cyclohexanone without isolating the organo sodium compound from the reaction medium.

The Reaction of 2-Thienylsodium with Cyclohexanone (75)

The apparatus containing the freshly prepared 2-thienylsodium, whose preparation was just described, was used in the present synthesis to avoid transferring the oxygen sensitive organo sodium compound. The "Y" tube was fitted with a thermometer which extended into the reaction mixture, a side arm adapter for nitrogen inlet, and a dropping funnel. The apparatus was kept under a slight positive pressure of dry nitrogen to prevent air from getting into contact with the reaction mixture. The apparatus was supported in an ice bath and the 2-thienylsodium benzene mixture was cooled to 4°C . A 137.35 g., 1.1 moles, quantity of cyclohexanone, which had been dried over anhydrous magnesium sulfate and distilled, was dissolved in 150 ml. of dry benzene and placed in the dropping funnel. The cyclohexanone solution was slowly added to the stirred solution of 2-thienylsodium over a forty minute interval. At the end of this time, the reaction mixture was black in color and its temperature had risen to 12.0°C . The ice bath was removed and the reaction mixture was stirred an additional forty-five minutes and then set aside for three quarters of an hour. The flask was again supported in an ice bath and 50 ml. of ethanol were slowly

the first of these is the fact that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The second is that the system is not a static one, but a dynamic one, in which the various parts are constantly changing and evolving. The third is that the system is not a closed one, but an open one, in which the various parts are constantly interacting with the environment. The fourth is that the system is not a linear one, but a non-linear one, in which the various parts are constantly interacting with each other in a non-linear fashion. The fifth is that the system is not a deterministic one, but a probabilistic one, in which the various parts are constantly interacting with each other in a probabilistic fashion.

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The twenty-fifth is that the system is not a homogeneous one, but a heterogeneous one, in which the various parts are constantly interacting with each other in a heterogeneous fashion.

added to the reaction mixture, to destroy any excess sodium present, followed by 100 ml. of water. After an hour and a quarter, 400 ml. of 6 N hydrochloric acid were added to the stirred reaction mixture. It was then transferred to a separatory funnel and the organic layer was separated, and washed first with 100 ml. of water, then with 100 ml. of 3 N sodium hydroxide solution and finally with 100 ml. of water after which it was dried in contact with anhydrous magnesium sulfate for twelve hours. The magnesium sulfate was removed from the benzene solution by filtration and the filtrate was fractionated using a one foot heat jacketed Vigreux column. The distillate was collected in six fractions. The first four fractions contained benzene and unreacted 2-chlorothiophene. The two fractions collected at 103-115° C./1.8 mm. Hg., 27.21 g. (I), and 153-157° C./2.3 mm. Hg., 16.72 g. (II), were investigated for the presence of 2-(1'-cyclohexanyl)thiophene and 2-(1'-cyclohexanyloxy)thiophene. Both fractions decolorized a carbon tetrachloride solution of bromine. However, (I) rapidly decolorized large amounts while (II) only slowly decolorized small amounts, and in neither case was there any sign of hydrogen bromide evolution. This indicated (I) probably contained a large percentage of an unsaturated compound where as in (II) there were only traces of the unsaturated compound present. Infra-red analysis verified this, as (I) showed a strong absorption band and (II) weak absorption for unsaturation, and further (I) had a very weak absorption and (II) a strong absorption for the hydroxyl group. The refractive indexes were: (I) $n_D^{20} \text{ } ^\circ \text{C.} = 1.5753$ and (II) $n_D^{20} \text{ } ^\circ \text{C.} = 1.5267$.

The dehydration of the higher boiling fraction, II, was attempted in the following manner. A 90 ml. round bottom flask was fitted with a reflux condenser and supported in a heating mantle. A 5 g. quantity of (II) and 25 ml. of concentrated formic acid were placed in the flask and heated gently. The mixture refluxed very vigorously for approximately a minute. After the initial reaction subsided, the mixture was kept at its reflux temperature for fifteen minutes, then cooled and diluted with 200 ml. of water, and extracted with three, 100 ml. portions of ether. The combined ether extracts were washed with two, 100 ml. portions of 6 N sodium hydroxide solution and dried in contact with anhydrous magnesium sulfate. After the magnesium sulfate was removed from the ethereal solution by filtration, the ether was removed on a steam bath. The residue was fractionated using a semi micro modified Claisen flask. Two fractions boiling at 100-120° C./1.3 mm. Hg., 0.89 g. and 120-135° C./1.3 mm. Hg., 0.65 g., were collected. Both fractions readily decolorized bromine carbon tetrachloride solution without any visible evidence of hydrogen bromide being evolved.

Apparently the dehydration was not complete. The reaction was not studied further by this method of dehydration. Subsequent dehydrations were accomplished with 20% acetic acid.

To establish that (I) was 2-(1-cyclohexenyl) thiophene its dehydrogenation to 2-pyrylthiophene was attempted (59) in the following manner. A 250 ml. round bottom flask was fitted with a reflux condenser and the flask was immersed in a hydrogenated vegetable oil bath equipped with two blade heaters and an electric stirrer. One blade

heater with a 500 watt capacity, was controlled by a powerstat and the other with a 125 watt capacity was controlled by a thermostat. A 10 g., 0.061 mole, quantity of (I), later proven to be 2-(cyclohexenyl) thiophene, and 3.2 g., 0.12 mole, of sulfur were mixed in the flask and heated to 173° C., at which point gas began to be evolved from the molten reaction mass. It had the odor of hydrogen sulfide and when moistened lead acetate paper was placed over the end of the reflux condenser, it immediately turned black, indicating the presence of sulfide ion. The temperature of the oil bath was raised from 173° to 193° C. during two and a quarter hours. At the end of this period a positive lead acetate test was still given, but the reaction was discontinued. The crude reaction mixture was distilled from a 25 ml. Wurts flask under diminished pressure. Two fractions were collected, one boiling at 76-100° C./2 mm. Hg., 4.02 g. and the other at 106-157° C./5.3 mm. Hg., 3.05 g. The first fraction gave a very positive test for unsaturation with bromine in carbon tetrachloride. The second fraction gave a very weak positive test with bromine, indicating only a small amount of unsaturated material was present and this fraction partially crystallized on cooling it in an ice bath. The first fraction appeared to be mainly unchanged starting material and the second mainly 2-phenylthiophene, contaminated with starting material and side reaction products. The small amount of crystalline material in the second fraction was isolated by rapid filtration on a small Hirsch funnel and after recrystallization from ethanol it melted at 41-42° C. The literature reports two melting points for 2-phenylthiophene, 42-43° C. (27,28,31) and 31-34.5° C. (32).

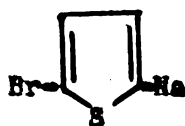
The dehydrogenation of (I) was repeated using the same apparatus and quantities of reagents as in the previous experiment, but at a higher temperature and a longer reaction time. The oil bath temperature reached 180°C . before a positive lead acetate test for sulfides was obtained in the open end of the reflux condenser. The temperature of the bath was raised to 200°C . and maintained at that temperature for three hours and then it was finally increased to 220°C . for an hour and three quarters. The reaction mixture was cooled and transferred to a semi micro modified Cleisen flask for distillation. A fraction boiling at $108-110^{\circ}\text{C}/1.4\text{ mm. Hg.}$, 3.04 g., solidified in the condenser and after several recrystallizations from ethanol its melting point was $42-43^{\circ}\text{C}$. which indicated the product was 2-phenylthiophene. A large scale preparation of 2-phenylthiophene with its physical constants and chemical analyses are given later.

Preparation of Sodium Amalgam in Ether (58)

The preparation of the sodium amalgam was carried out using a modification of Hartough's (30) method. A three liter, three neck flask was fitted with a reflux condenser, mechanical stirrer, and thermometer. To the flask were added, 400 ml. of toluene, 17.2 g., 0.75 mole, of sodium, and 12.5 g., 0.0625 mole, of mercury. The vigorously stirred contents of the flask were heated rapidly, with an electric mantle, to 95°C ., then slowly from 95° to 100°C . at which point the toluene refluxed vigorously for approximately a minute. After the toluene stopped refluxing due to the heat of amalgamation of the sodium,

the mixture was vigorously stirred and kept at its reflux temperature by external heating for three minutes. The heating mantle was removed and the mixture was vigorously stirred until the temperature had fallen to 35° C. A fritted glass filter stick, connected to a water aspirator through a trap, was placed in the reaction mixture. The toluene was removed from the sodium amalgam by drawing it through the filter stick into the trap. A 300 ml. quantity of anhydrous ether was added to the flask to cover the sodium amalgam, protecting it from attack by moisture and air.

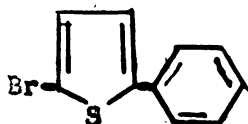
Preparation of 5-Bromo-2-thienylsodium (57)



The sodium amalgam obtained in the previous preparation was used in the present synthesis, utilizing the same apparatus employed in the sodium amalgam preparation, except that the thermometer was replaced with a "Y" tube containing a dropping funnel and nitrogen gas inlet tube. A solution of 81.52 g., 0.5 mole, of freshly distilled 2-bromothiophene dissolved in 500 ml. of anhydrous ether was placed in the dropping funnel. A continuous stream of dry nitrogen was swept slowly through the apparatus. The ether sodium amalgam mixture was heated to its reflux temperature and the 2-bromothiophene was added dropwise to the stirred refluxing ethereal mixture over a period of two hours. The reaction mixture was kept at its reflux temperature for an

additional two hours, under an atmosphere of nitrogen, to complete the reaction. The resulting product 5-bromo-2-thienylsodium, was a suspension of brown colored powder in the ether medium.

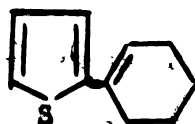
Attempted Preparation of 5-Phenyl-2-bromothiophene



The apparatus already containing the 5-bromo-2-thienylsodium, whose preparation has just previously been described, was used in the present preparation of 5-phenyl-2-bromothiophene. A 458 g., 2.25 moles, quantity of freshly distilled iodobenzene, which boiled at 186° C., was placed in the dropping funnel. The phenyliodide was added dropwise to the stirred refluxing ethereal mixture of 5-bromo-2-thienylsodium, over a one hour period. The stirred reaction mixture was kept at its reflux temperature an additional four hours and after cooling, it was stoppered, and set aside overnight. The excess sodium was destroyed by adding 100 ml. of ethanol followed by 50 ml. of water and stirring the mixture for an hour. A 500 ml. quantity of water was then added to the flask and the apparatus was arranged for vacuum steam distillation by replacing the reflux condenser with a 45 degree elbow, condenser, side arm adaptor and receiver. The steam distillate boiled at 51° C./101 mm. Hg. The non-steam volatile residue was transferred to a separatory funnel and the aqueous layer separated. The organic layer

was washed with 200 ml. of water and then 1400 ml. of ethanol was added to the organic layer. Due to the black dirty appearance of the solution, at this point, it was decolorized with charcoal. The alcoholic solution was fractionated using a one foot heat jacketed Vigreux column, but no 5-phenyl-2-bromothiophene was obtained. A 225.7 g., 1.10 moles, quantity of iodobenzene was recovered from the fractionation, leaving a black tarry residue in the distillation flask. The distillate from the steam distillation was transferred to a separatory funnel and the aqueous phase was removed from the organic material and the latter was dried in contact with anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration. The organic material was fractionated using a one foot heat jacketed column. A 223.23 g., 1.09 moles, quantity of iodobenzene and a 55.45 g., 0.34 mole, quantity of 2-bromothiophene were recovered. The total recovery of unreacted iodobenzene amounted to 97%. The 25.06 g. of unrecovered 2-bromothiophene probably decomposed during the reaction which accounted for the black tarry residues obtained.

Preparation of 2-(1'-Cyclohexenyl) thiophene



A three liter, three neck flask was fitted with a reflux condenser, mechanical stirrer, and a "Y" tube containing a gas inlet tube and dropping funnel. All of the glassware was dried at 110° C. for approximately twelve hours prior to assembling. Nitrogen gas which had been

dried by bubbling it through a concentrated sulfuric acid tower, was slowly swept through the apparatus during the entire experiment. A 53.50 g., 2.20 moles, quantity of magnesium, previously dried in an oven at 110° C. for twelve hours, was placed in the three liter flask and the entire apparatus was further dried by heating with a small Bunsen burner flame while sweeping dry nitrogen through it. After the apparatus had cooled to room temperature, 100 ml. of dry ether and 2 ml. of freshly distilled ethyl bromide were added. After the reaction between the ethyl bromide and magnesium had started it was diluted with 750 ml. of ether. To this vigorously stirred reacting mixture was added, from a dropping funnel, a solution of 325.1 g., 2.0 moles, of 2-bromothiophene dissolved in 300 ml. of dry ether over a three hour period. The 2-bromothiophene was added at a rate sufficient to maintain a gentle reflux of the ether in the reaction flask. After the addition of the halothiophene was complete the reaction mixture was kept at its reflux temperature for an additional hour and forty minutes, and then cooled to room temperature. A solution of 215.91 g., 2.20 moles, of freshly distilled cyclohexanone, dissolved in 200 ml. of dry ether was slowly added from the dropping funnel to the stirred reaction mixture over a forty-five minute period. The stirred reaction mixture was kept at its reflux temperature an additional thirty minutes. During the addition of the cyclohexanone, the reaction mixture changed from a black to a brown color and finally a tan precipitate formed as the last of the cyclohexanone was being added. The reaction mixture was cooled in an ice bath and hydrolyzed with 6 N hydrochloric acid by

adding the acid slowly from the dropping funnel. The reaction mixture was transferred to a separatory funnel and the aqueous phase was separated from the organic phase. The aqueous layer was washed with three, 100 ml. portions of ether and the ether washings were combined with the original organic portion. The ethereal solution was dried in contact with anhydrous magnesium sulfate. The drying agent was filtered from the ethereal solution and the filtrate was transferred to a distillation apparatus where the ether was distilled from the product on a steam bath. The dark viscous residue of crude 2-(1'-cyclohexanolyl) thiophene was transferred to a one liter, three neck flask fitted with a reflux condenser and stirrer. A 500 ml. quantity of a 20% by weight aqueous oxalic acid solution was added to the flask and the stirred mixture was heated at its reflux temperature for an hour. The reaction mixture was cooled, transferred to a separatory funnel, and the aqueous phase was separated and extracted with two, 300 ml. portions of ether which were added to the original organic phase. The ether solution was washed with 100 ml. of a 3 N sodium hydroxide solution, then with 50 ml. of water and dried in contact with anhydrous magnesium sulfate. The drying agent was filtered from the solution, and the ether was removed from the crude product by distillation on a steam bath. The liquid residue was fractionated using a one foot heat jacketed Vigreux column. The fraction boiling at 117-120° C./3.0 mm. Hg., with a refractive index of $n_D^{20} = 1.5366$, was collected. It weighed 265.98 g., 1.62 moles, which was an 81.0% yield,

1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0)$.

2. In the second part, we consider the problem of finding the maximum value of the function $f(x)$ on the interval $[0, 1]$. It is shown that the maximum value is attained at $x = 0$ and is equal to $f(0)$.

3. The third part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0)$.

4. In the fourth part, we consider the problem of finding the maximum value of the function $f(x)$ on the interval $[0, 1]$. It is shown that the maximum value is attained at $x = 0$ and is equal to $f(0)$.

5. The fifth part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0)$.

6. In the sixth part, we consider the problem of finding the maximum value of the function $f(x)$ on the interval $[0, 1]$. It is shown that the maximum value is attained at $x = 0$ and is equal to $f(0)$.

7. The seventh part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0)$.

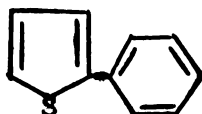
8. In the eighth part, we consider the problem of finding the maximum value of the function $f(x)$ on the interval $[0, 1]$. It is shown that the maximum value is attained at $x = 0$ and is equal to $f(0)$.

9. The ninth part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0)$.

10. In the tenth part, we consider the problem of finding the maximum value of the function $f(x)$ on the interval $[0, 1]$. It is shown that the maximum value is attained at $x = 0$ and is equal to $f(0)$.

based on 2-bromothiophene, or 2-(1'-cyclohexenyl)thiophene. The reported boiling point for 2-(1'-cyclohexenyl) thiophene is 89-91° C./C.1 mm. Hg. (42). Elemental analyses of the product for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{10}H_{12}S$: C, 73.12; H, 7.37; S, 19.52. Found: C, 72.92; H, 7.42; S, 19.39.

Preparation of 2-Phenylthiophene



A 500 ml. round bottom flask was fitted with a reflux condenser and supported in an oil bath equipped with a thermostat, a 500 watt and a 125 watt heating blades, and a stirrer. A 100.0 g., 0.609 mole, quantity of 2-(1'-cyclohexenyl) thiophene and a 39.1 g., 1.22 moles, quantity of sulfur were added to the flask and thoroughly mixed by stirring with a glass rod. When the temperature of the bath reached 200° C. an evolution of gas was evident and a positive test for sulfide was obtained by holding moistened lead acetate paper over the top of the condenser. The bath was maintained at 205° C. for two hours, then raised to 220° C. for four hours, and then the flask was removed from the oil bath, stoppered, and set aside overnight. The following day the oil bath was heated to 220° C. and the flask with the condenser was again placed in it for an hour. No gases could be seen rising from the surface of the reaction mixture, but a positive test for sulfide at the top of the condenser was still obtainable. The reaction mixture



was transferred to a distillation apparatus and fractionated using a one foot heat jacketed Vigreux column. A forerun of 8.45 g., 0.0514 mole, of 2-(1'-cyclohexenyl) thiophene was recovered. A fraction boiling in the range 103-105° C./2.8 mm. Hg. was collected which solidified in the receiver. This represented a, 44.75 g., 0.279 mole, 50.3% yield based on 2-(1'-cyclohexenyl) thiophene. The product, 2-phenylthiophene, had a melting point of 42-43° C. after recrystallization from ethanol. The reported melting points of this compound was 42-43° C. (27,23,31) and 34-34.5° C. (32). Its boiling point is reported (32) to be 256.1° C.

Due to the large amount of residue remaining in the distillation flask, an attempt was made to isolate additional quantities of 2-phenylthiophene by heating the residue an additional five and a third hours in an oil bath at 230° C. A very weak positive sulfide test was still obtained from the vapors being evolved from the residue. However, when the mixture was distilled only a small amount of material distilling at 159-161° C./2.2 mm. Hg. was obtained and this remained liquid at room temperature. Following the experimental procedure just described the preparation of 2-phenylthiophene was repeated. A 160.4 g., 0.982 mole, quantity of 2-(1'-cyclohexenyl) thiophene and a 63.0 g., 1.964 mole, quantity of sulfur were used. The reaction mixture was heated in an oil bath for four and three-quarter hours at 220° C. When the reaction mixture was fractionated, a fraction boiling at 106-107° C./2.9 mm. Hg. was collected. This represented a 77.97 g., 0.486 mole, 49.6% yield, of 2-phenylthiophene based on the amount of

2-(1'-cyclohexenyl) thiophene used. The product melted at the same temperature as in the previous preparation.

Attempted Bromination of 2-Phenylthiophene
with Cyanogen Bromide (41)

A 250 ml. one neck flask was fitted with a reflux condenser and supported in an oil bath. The latter was heated with a blade heater regulated by a thermostat. The top of the condenser was connected by means of glass tubing to a trap containing an aqueous sodium hydroxide solution. A 10 g., 0.0625 mole, quantity of 2-phenylthiophene and a 6.62 g., 0.0625 mole, quantity of cyanogen bromide were placed in the flask and the apparatus was assembled. The oil bath was placed under the reaction flask and heated to 40° C. There were no visible indications of gas being liberated. According to work reported by Steinkopf (41) a green color should have developed in the reaction mixture, but instead it became a reddish brown. The reaction mixture was heated for three and two-thirds hours at 40° C. and then 100 ml. of a 3 N sodium hydroxide solution was added to the flask. The reaction mixture was heated at its reflux temperature for an additional two hours and then transferred to a 500 ml. three neck flask arranged for steam distillation. The distillate from the steam distillation was cooled in an ice bath and the solid material was filtered from the aqueous suspension. The solid material was crystallized from ethanol to yield 8.65 g. of unchanged 2-phenylthiophene melting sharply at 42.5-43.0° C. Elemental analyses for $C_{10}H_8S$ gave the following results.

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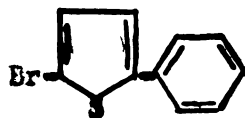
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Calc'd: C, 74.96; H, 5.03; S, 20.01. Found: C, 74.88; H, 5.13; S, 20.14.

The reaction was repeated using the same apparatus and experimental procedure. A 5.68 g., 0.0536 mole, quantity of newly purchased Eastman Chemical Company white label cyanogen bromide and 8.60 g., 0.0536 mole, of recovered and repurified 2-phenylthiophene were added to the flask and the mixture was heated at 80° C., but since at this temperature the cyanogen bromide vaporized and collected in the reflux condenser the temperature of the bath was lowered to 60° C. The circulation of water in the reflux condenser was discontinued until the crystallized cyanogen-bromide melted and ran back into the reaction flask. The reaction mixture was heated at 60° C. for four and a quarter hours and then 70 ml. of a 3 N solution of sodium hydroxide was added to the flask. The reaction mixture was heated at its reflux temperature for an additional two hours. After isolating the product in the same manner as described in the previous experiment and crystallizing it from ethanol a 6.80 g., of unchanged 2-phenylthiophene was obtained which melted at 42-43° C.

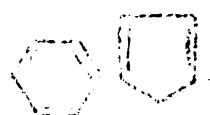
Preparation of 2-phenyl-5-bromothiophene



A two neck, 200 ml. round bottom flask was fitted with a mechanical stirrer and reflux condenser, containing a calcium chloride tube attached to the upper end of the condenser. A 10.0 g., 0.0625 mole, quantity of

100

100



2-phenylthiophene was dissolved in 50 ml. of dry carbon tetrachloride and placed in the flask. A 11.12 g., 0.0625 mole, quantity of N-bromosuccinimide was added to the 2-phenylthiophene carbon tetrachloride solution. The solution was vigorously stirred for a half hour at room temperature and then it was heated with a heating mantle at its reflux temperature for ten hours. The reaction mixture changed from a light yellow to red and finally to a brownish red color. Succinimide crystallized from the reaction mixture on the sides of the reaction flask. Hydrogen bromide gas was evolved from the reaction mixture during the course of the reaction. The reaction mixture was cooled in an ice bath and the crystalline succinimide was filtered from the carbon tetrachloride by collecting it on a Buchner funnel. The succinimide was washed with 35 ml. of cold carbon tetrachloride and this was combined with the original filtrate. The carbon tetrachloride solution was dried in contact with anhydrous magnesium sulfate. A 50 ml. modified Claisen distillation flask was supported on a steam bath and a 50 ml. dropping funnel was fitted in the top of the Claisen flask. The dried carbon tetrachloride solution was transferred to the dropping funnel and then it was slowly added to the Claisen flask as the carbon tetrachloride was distilled. The mixture had a tendency to foam during the distillation. After all of the carbon tetrachloride solution had been added and most of the carbon tetrachloride had been distilled from the Claisen flask, the apparatus was evacuated to 2.0 mm. Hg. pressure and while the distilling flask was being heated in a warm water bath the last traces of carbon tetrachloride were removed. The residue in the

flask solidified to a brownish gray colored solid which had a melting range of 79-83° C., and weighed 17.45 g., which represented a 116.8% yield of crude 2-phenyl-5-bromothiophene. The crude 2-phenyl-5-bromothiophene after three recrystallizations from ethanol gave 13.1 g., 0.0515 mole, an 87.5% yield of 2-phenyl-5-bromothiophene, melting at 85.5-86.0° C. The reported melting point for 2-phenyl-5-bromothiophene is 85-86° C. (11), prepared by brominating 2-phenylthiophene with cyanogen bromide. Analyses for $C_{10}H_7BrS$ gave the following results. Calc'd: C, 50.22; H, 2.95; S, 13.41; Br, 33.42. Found: C, 50.27; H, 3.13; S, 13.22; Br, 33.26.

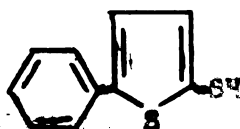
The bromination of 2-phenylthiophene with N-bromosuccinimide was repeated twice with the following variations in quantities of reagents and time of reaction. The apparatus was identical to the apparatus used in the initial preparation.

A solution of 20.52 g., 0.128 mole, of 2-phenylthiophene dissolved in 100 ml. of dry carbon tetrachloride was placed in the reaction flask and to this, 22.8 g., 0.128 mole, of N-bromosuccinimide was added. The mixture was stirred for an hour and ten minutes at room temperature and then at its reflux temperature for five hours. The isolation of the product, as described previously, yielded 25.6 g., 0.111 mole, an 87.0% yield of 2-phenyl-5-bromothiophene, melting at 85.5-86.0° C.

The largest scale preparation of 2-phenyl-5-bromothiophene was made using 57.0 g., 0.32 mole, of 2-phenylthiophene dissolved in 300 ml. of dry carbon tetrachloride. A 500 ml. round bottom reaction flask was substituted for the 200 ml. flask. The 2-phenylthiophene solution

was placed in the 500 ml. flask, and 51.37 g., 0.32 mole, of N-bromo-succinimide was added to it. The reaction mixture was stirred for an hour and a quarter at room temperature and then at its reflux temperature for five hours. This reaction mixture behaved differently than the previous one in that after the reaction mixture was heated to its reflux temperature, the rate of reflux became so vigorous that the heating mantle had to be removed. The reaction mixture continued to reflux spontaneously for several minutes. The product was isolated in the usual manner to yield 88.19 g., 0.369 mole, a 115.2% yield of a yellowish gray colored crude material. After two recrystallizations from ethanol, decolorizing with charcoal during the first crystallization, a 62.18 g., 0.260 mole, 81.3% yield of colorless 2-phenyl-5-bromothiophene was obtained which melted at 85.5-86.0° C.

Preparation of 5-Phenyl-2-thiophenethiol



A one liter, three neck round bottom flask was fitted with a reflux condenser which had a calcium chloride tube fitted to the upper end, a mechanical stirrer, and a "Y" tube containing a gas inlet tube and dropping funnel. The unassembled glass apparatus was dried for three hours in an oven at 115° C. After the apparatus was assembled, a stream of nitrogen, dried by bubbling it through a concentrated sulfuric acid tower, was slowly swept through the apparatus. A 4.62 g., 0.193 mole,

quantity of magnesium, which had been dried for a day in an oven at 110°C ., was placed in the one liter reaction flask. While the apparatus was being swept with dry nitrogen, it was cautiously heated with a Bunsen burner flame to remove any moisture that might have accumulated. During the entire experiment dry nitrogen was slowly passed through the apparatus. After the apparatus was cooled, 10 ml. of sodium dried ether was added to the flask through the dropping funnel. A 42.93 g., 0.166 mole, quantity of 5-phenyl-2-bromothiophene was dissolved in 200 ml. of dry ether and placed in the dropping funnel. Several milliliters of this solution were added to the flask and gently heated on a steam bath. When the reaction had started, as indicated by a continuous reflux of the ether after the steam bath had been removed, 250 ml. of dry ether were added to the reaction flask and stirred vigorously. The ether solution of 5-phenyl-2-bromothiophene was added slowly to the stirred reaction mixture at a rate sufficient to maintain a gentle reflux of the ether. An hour was required to add the ether solution of 5-phenyl-2-bromothiophene. The reaction mixture was heated at its reflux temperature for an additional hour. When the mechanical stirrer was stopped an oily phase settled to the bottom of the reaction flask, from the light yellow colored reaction mixture. The dropping funnel was replaced by a powder addition device, made by connecting two standard tapered inter joints by a rubber tubing of the same diameter and attaching a 50 ml. standard tapered neck round bottom flask on one standard joint. The other standard joint was placed in the neck of the reaction flask. A 5.73 g., 0.13 mole, quantity of dry powdered

sulfur was placed in the 50 ml. flask. The sulfur was slowly added to the stirred reaction mixture at a rate which produced a gentle reflux of the ether. The addition of the sulfur required fifteen minutes. The last remaining sulfur in the powder addition flask was washed into the reaction mixture with 40 ml. of ether. A bright yellow precipitate, which did not appear to be free sulfur, formed when the sulfur was added to the reaction mixture. The stirred reaction mixture was heated at its reflux temperature for twenty minutes and then cooled. The apparatus was stoppered and set aside for an hour. The reaction flask was then packed in ice and 100 ml. of 6 N hydrochloric acid was added to the stirred reaction mixture through the dropping funnel. The yellow precipitate which had formed during the reaction was removed from the reaction mixture on a fluted filter. The yellow precipitate was recrystallized from a cyclohexane ethanol mixture to yield 10.44 g. of material. After three recrystallizations from cyclohexane this material melted at 143-144° C. This was later shown to be 5-phenyl-2-thienyl-disulfide or the dimer of 5-phenyl-2-thiophenethiol. The material was dried in a drying pistol at 15 mm. Hg. at the temperature of refluxing ethanol. Elemental analysis for carbon, hydrogen and sulfur gave the following results. Analysis for $C_{22}H_{14}S_4$. Calc'd.: C, 62.79; H, 3.69; S, 33.52. Found: C, 62.97; H, 3.90; S, 33.47. The filtrate, from which the yellow precipitate had been obtained, was transferred to a separatory funnel and the aqueous phase was separated from the ethereal phase. The aqueous phase was extracted with three, 50 ml. portions of ether and then combined with the original ether portion and extracted

with three, 30 ml. portions of 6 N sodium hydroxide solution. The combined alkaline extracts were acidified with 110 ml. of 6 N hydrochloric acid solution. During the acidification of the combined sodium hydroxide extracts a yellow precipitate formed. The yellow precipitate was filtered from the acid solution and washed with several portions of cold water. The crude dry precipitate melted at $73-85^{\circ}$ C. as determined on a melting point block. The yellow precipitate was initially soluble in methyl alcohol but on continued heating a yellow precipitate crystallized from solution. After this material was crystallized from a methyl alcohol cyclohexane solution three times and dried in a vacuum pistol at the reflux temperature of ethanol a material was obtained that melted at $113.5-114^{\circ}$ C. A mixed melting point of this substance with the original yellow solid obtained from the initial reaction described above gave no depression in melting point. Apparently the 5-phenyl-2-thiophenethiol oxidized to the disulfide or dimerized during the recrystallization procedure. A 19.72 g., 0.102 mole, 82.0% yield of 5-phenyl-2-thiophenethiol was obtained when a correction is made for the previously isolated 5-phenyl-2-thienyl disulfide. Elemental analysis for the recrystallized material gave the following results: Calc'd. for $C_{20}H_{14}S_4$: C, 62.79; H, 3.69; S, 33.52. Found: C, 62.49; H, 3.61; S, 33.29.

Preparation of 5-Bromo-2-thienylmagnesium Bromide



A three liter, three neck flask was fitted with a reflux condenser containing a calcium chloride tube at the top, a mechanical stirrer, and a "T" tube containing a gas inlet tube and a 500 ml. dropping funnel. All glass parts of the apparatus were dried for twelve hours in an oven at 115° C. and then assembled while hot. Nitrogen gas, dried by bubbling it through a concentrated sulfuric acid tower, was slowly swept through the apparatus. A 25.75 g., 1.10 moles, quantity of magnesium, which had previously been dried for 12 hours in an oven at 110° C., was placed in the flask. As a further precaution against moisture, the apparatus and magnesium turnings were cautiously heated with a Bunsen burner while dry nitrogen was being swept through the apparatus. A slow stream of dry nitrogen was passed through the apparatus during the entire course of the experiment. After the apparatus had cooled to room temperature, several milliliters of dry ether and 10 g. of freshly distilled ethyl bromide were added to the flask by means of the dropping funnel. A reaction immediately started as was indicated by the refluxing ether and the appearance of a grayish powder cast in the ether solvent. A 1100 ml. quantity of sodium dried ether, was added to the flask. A 211.95 g., 1.00 mole, quantity of freshly distilled 2,5-dibromothiophene dissolved in 400 ml. of ether was added slowly to the vigorously



The first part of the report discusses the importance of maintaining accurate records of all transactions. It is essential for the company to have a clear and concise system in place to ensure that all data is properly documented and accessible. This will help in the identification of trends and anomalies, which can be used to make informed decisions about the future of the business.

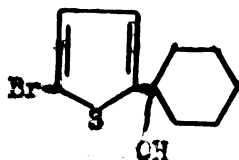
In the second part, we analyze the current state of the market and the competitive landscape. We find that there is a significant opportunity for growth in the current market conditions, particularly in the areas of digital marketing and customer service. However, it is also important to recognize the challenges that the company may face, such as increased competition and fluctuating demand.

The third part of the report provides a detailed financial analysis of the company's performance over the past year. This includes a breakdown of revenue, expenses, and profit, as well as a comparison to industry benchmarks. The analysis shows that the company has made significant progress in reducing costs and increasing revenue, but there is still room for improvement in certain areas.

Finally, we offer our recommendations for the future. We suggest that the company focus on expanding its digital marketing efforts and improving its customer service. Additionally, we recommend that the company continue to monitor the market and adjust its strategy as needed to stay competitive.

stirred reaction mixture from the dropping funnel. The 2,5-dibromo-thiophene was added at a rate sufficient to produce a gentle reflux of the ether, which required an hour and ten minutes. The reaction mixture, which at this point was a light brown in color, was stirred for an additional half hour at its reflux temperature. When the mechanical stirrer was stopped a brown oily layer settled to the bottom of the reaction vessel. This material was considered to be 5-bromo-2-thienylmagnesium bromide and was immediately reacted with cyclohexanone without further isolation.

The Preparation of 5-bromo-2-(1'-cyclohexanonyl) thiophene



The apparatus just described in the previous preparation was employed in the present synthesis.: The 5-bromo-2-thienylmagnesium bromide, prepared previously and stored in a nitrogen atmosphere was cooled to 0° C. by immersing the reaction flask in an ice bath. A 107.95 g., 1.10 moles, quantity of cyclohexanone, which had been dried in contact with anhydrous magnesium sulfate and distilled, was dissolved in 100 ml. of dry ether and placed in the dropping funnel. The cyclohexanone solution was added slowly to the stirred Grignard reagent over a thirty minute period during which time the reaction mixture turned yellow and a large amount of a yellow precipitate formed. After the ketone had been added the stirred

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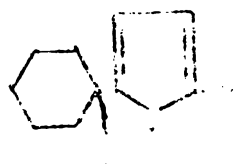
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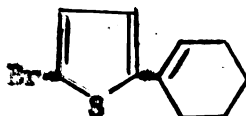
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reaction mixture was heated at its reflux temperature for an additional half hour. After cooling the reaction mixture 500 ml. of 6 N hydrochloric acid were slowly added to it followed by 400 ml. of water. The reaction mixture was transferred to a separatory funnel and the ether layer was separated, washed with 100 ml. water, and dried in contact with anhydrous magnesium sulfate. The magnesium sulfate was filtered from the ethereal solution and the filtrate was transferred to a distillation apparatus. The ether was distilled from the solution on a steam bath. The resulting oily residue, considered to be crude 5-bromo-2-(1'-cyclohexenyl) thiophene, was not purified further but was used directly in the next preparation.

Preparation of 5-bromo-2-(1'-cyclohexenyl) thiophene



A two liter, three neck flask was fitted with a reflux condenser and mechanical stirrer and supported in a heating mantle. The crude 5-bromo-2-(1'-cyclohexenyl) thiophene, whose preparation is described in the previous experiment, was transferred to the two liter reaction flask. A 100 g. quantity of oxalic acid was dissolved in 400 ml. of hot water and the acid solution was poured into the reaction flask. The vigorously stirred reaction mixture was heated at its reflux temperature for an hour. The reaction mixture was cooled, transferred

to a separatory funnel, and the organic phase was separated. It was washed with two, 100 ml. portions of water and then dried in contact with anhydrous magnesium sulfate. The magnesium sulfate was filtered from the solution and the filtrate was fractionated using a one foot heat jacketed Vigreux column. An 18.49 g., forerun, boiling between $97-155^{\circ}\text{C.}/3.7-4.5\text{ mm. Hg.}$, was discarded. The fraction boiling at $155-156^{\circ}\text{C.}/3.5\text{ mm. Hg.}$ which solidified on cooling was collected. It amounted to 117.35 g., 0.403 mole, which was a 48.3% yield of 5-bromo-2-(1'-cyclohexenyl)thiophene based on the amount of 2,5-dibromothiophene used. The 5-bromo-2-(1'-cyclohexenyl)thiophene melted over the range $33.5-35.1^{\circ}\text{C.}$ Elemental analysis for $\text{C}_{12}\text{H}_{11}\text{BrS}$ gave the following results. Calc'd.: C, 49.39; H, 4.56; S, 13.18; Br, 32.87. Found: C, 49.32; H, 4.77; S, 13.08; Br, 33.08.

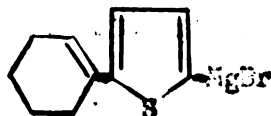
Attempted Dehydrogenation of 5-Bromo-2-(1'-cyclohexenyl)
thiophene to form 2-Bromo-5-phenylthiophene

A 250 ml. flask was fitted with a reflux condenser and immersed in an oil bath whose temperature was controlled by two blade heaters. A 500 watt blade heater was controlled by a "Powerstat" and a 125 watt heater was controlled by a thermostat. The "Powerstat" control was used to raise the bath temperature to within 5°C. of the desired temperature and the thermostat was set to obtain the desired temperature by furnishing the additional heat needed. A 10 g., 0.0412 mole, quantity of 5-bromo-2-(1'-cyclohexenyl)thiophene and a 3.02 g., 0.0248 mole, quantity of sulfur were placed in the flask and thoroughly mixed. When the bath temperature reached 170°C. there was a rapid

evolution of fumes. The fumes gave a positive test for sulfide with moistened lead acetate paper. This positive lead acetate test appeared to be much slower than in the previous dehydrogenation experiments, however, the evolution of gases was much more rapid. The fumes had an irritating odor similar to a hydrohalide, therefore, they were tested for acid, and it was found that blue litmus readily turned red when held above the condenser. The temperature of the bath was raised to 200° C. and kept there for two and a quarter hours. The temperature was then raised to 215° C. for an additional two and a quarter hours. At the end of this time, even though the lead acetate test was still positive, the reaction mixture was cooled to room temperature. A 60 ml. quantity of benzene was added and the mixture was filtered through a Buchner filter to remove a small amount of solid material from the solution. The filtrate was steam distilled which removed the benzene and only a small amount, less than 0.5 g., of a material which solidified on cooling to approximately 10° C. A large amount of tarry residue remained in the flask and could not be steam distilled. The reported melting point of 2-bromo-5-phenylthiophene is 85-86° C. (41) and it is steam distillable. If any 2-bromo-5-phenylthiophene was formed in the sulfur dehydrogenation reaction it was much less than 0.5 g. The material in the dehydrogenation reaction was not investigated further.

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**Preparation of 5-(1'-Cyclohexenyl)-2-thienylmagnesium
Bromide and Its Reaction with Sulfur**



A three liter, three neck round bottom flask was fitted with a mechanical stirrer, a condenser containing a calcium chloride drying tube and a "T" side arm tube carrying a gas inlet tube and dropping funnel. The unassembled glass apparatus was dried overnight in an oven at 110° C. A 9.44 g., 0.358 mole, quantity of magnesium turnings, which had been dried for a day in an oven at 110° C., was placed in the reaction flask. While nitrogen, dried by bubbling it through a concentrated sulfuric acid drying tower, was slowly swept through the apparatus, the latter was cautiously flamed with a Bunsen burner to drive out any moisture that may have collected in the apparatus after it had been assembled. After the apparatus had cooled 350 ml. of dry ether was added to the reaction flask by means of the dropping funnel. Dry nitrogen was slowly swept through the apparatus continuously to prevent air from entering the apparatus. A 10 g., 0.091 mole quantity of ethylbromide, was added to the ether and magnesium turnings and stirred vigorously until the Grignard reaction was initiated. An 85.82 g., 0.353 mole, quantity of 5-(1'-cyclohexenyl)-2-bromothiophene was dissolved in 500 ml. of dry ether and added during an hour, to the vigorously stirred reaction mixture through the dropping funnel. The reaction mixture turned a brownish yellow color. The reaction mixture was stirred and heated at its reflux temperature for an hour

and forty minutes. When the stirrer was stopped a yellow brown oil formed on the bottom of the reaction flask. The dropping funnel was replaced with a powder addition tube prepared from two 24-40 inner standard taper joints connected by a six inch length of rubber tubing. One standard taper joint was connected to the reaction flask and the other was fitted to a 50 ml. round bottom flask. A 13.0 g., 0.406 mole, quantity of sulfur, dried by desiccating with phosphorus pentoxide in a vacuum desiccator for two days, was placed in the 50 ml. flask. The sulfur was added, during a fifteen minute period, to the stirred reaction mixture in small portions at a rate sufficient to maintain the ether at its reflux temperature. The last traces of sulfur were washed into the reaction mixture with 50 ml. of dry ether. The reaction mixture was stirred and heated at its reflux temperature for an additional hour at which time it was a bright yellow in color. The reaction flask was placed in an ice bath and 200 ml. of 6 N hydrochloric acid solution was placed in a dropping funnel and the latter was fitted in the apparatus in place of the powder addition tube. The acid solution was added dropwise to the stirred reaction mixture. A bright yellow precipitate formed immediately. A 100 ml. quantity of water was added to the reaction mixture and the yellow precipitate was filtered from the ethereal and aqueous solutions with a fluted filter. The yellow precipitate was slightly soluble in ether and insoluble in 10% sodium hydroxide. The ether phase of the reaction mixture was a bright yellow color, indicating it was saturated with the yellow precipitate. The aqueous acid phase was separated from the ether phase in a separatory funnel.

1. The first step in the process of the scientific method is to make an observation or ask a question. For example, a scientist might observe that a plant grows better in one type of soil than another.

2. Next, the scientist forms a hypothesis, which is a prediction or an educated guess about the outcome of an experiment. For example, the scientist might hypothesize that the plant will grow taller in soil A than in soil B.

3. The third step is to design and conduct an experiment to test the hypothesis. This involves setting up a controlled experiment where the only variable that changes is the type of soil.

4. After the experiment is completed, the scientist collects data and analyzes the results. If the plant in soil A is indeed taller, the hypothesis is supported.

5. Finally, the scientist draws a conclusion based on the results of the experiment. If the hypothesis is supported, the scientist might conclude that soil A is better for growing this type of plant.

6. The scientific method is a systematic approach to investigating a question or solving a problem. It involves making observations, forming hypotheses, conducting experiments, and drawing conclusions based on the results.

7. The scientific method is a process that scientists use to investigate natural phenomena. It involves making observations, asking questions, forming hypotheses, conducting experiments, and drawing conclusions based on the results.

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The aqueous phase was extracted with three, 50 ml. portions of ether and the ether extracts were combined with the original ether phase. The ether phase was extracted with three, 100 ml. portions of 10% potassium hydroxide solution. The combined potassium hydroxide solutions were acidified with 6 N hydrochloric acid. A dark brown oil formed. The oil was extracted from the aqueous mixture with three, 100 ml. portions of ether and the combined ether extracts were dried overnight in contact with anhydrous magnesium sulfate under a nitrogen atmosphere to prevent air oxidation. The ether was distilled from the crude product using a modified Claisen semi micro distillation flask. The residue was fractionated using the same distillation apparatus. A fraction boiling at $133.0^{\circ}\text{C./2.2 mm. Hg.}$ was collected. A 25.56 g., 0.13 mols, 36.8% yield of 5-(1'-cyclohexenyl)-2-thiophenethiol was obtained. An analysis was not made on this product because of its instability. An infra-red spectra was determined, showing that a sulphydryl group was present indicated by an absorption band at 3.96μ . All attempts to prepare a 2,4-dinitrophenyl sulfide derivative of the product failed to yield a crystalline derivative.

The yellow precipitate which had formed when the Grignard reaction mixture was hydrolyzed was purified. The crude yellow precipitate melted in the range $123-130^{\circ}\text{C.}$ on a melting point block. After recrystallizing the material twice from isopropyl alcohol and once from methanol a material melting at $133-134^{\circ}\text{C.}$ was obtained. The elemental analysis for $\text{C}_{20}\text{H}_{22}\text{S}_2$ gave: Calc'd.: C, 61.43; H, 5.65; S, 32.83. Found: C, 61.23; H, 5.67; S, 32.66. The other portion of the Grignard

reaction mixture was evaporated to dryness on a steam bath to yield 12.30 g. of crude 5-(1'-cyclohexenyl)-2-thienyl disulfide. A portion of this material was recrystallized from isopropyl alcohol and it gave the same melting point as the original precipitate. A mixed melting point of this material with the original precipitate showed no depression. The 5-(1'-cyclohexenyl)-2-thienyl disulfide was reduced with lithium aluminum hydride, as shown in the subsequent preparation, for further proof of its structure.

Lithium Aluminum Hydride Reduction of 5-(1'-Cyclohexenyl)-
2-thienyl Disulfide

A one liter, three neck flask was fitted with a reflux condenser, mechanical stirrer and dropping funnel. The unassembled glass apparatus was dried overnight in an oven at 110° C. before assembling. A 0.70 g., 0.0135 mole, quantity of lithium aluminum hydride was finely ground in a carefully dried mortar under a stream of dry nitrogen, by placing the mortar under an inverted funnel, which was connected to a dry nitrogen source. The finely ground lithium aluminum hydride was placed in a liter reaction flask and 200 ml. of dry ether was added to the reaction flask. The lithium aluminum hydride ether mixture was stirred at its reflux temperature for fifteen minutes to dissolve the lithium aluminum hydride. A 6.00 g., 0.0153 mole, quantity of 5-(1'-cyclohexenyl)-2-thienyl disulfide was dissolved in 200 ml. of dry ether and placed in the dropping funnel. The ether solution of 5-(1'-cyclohexenyl)-2-thienyl disulfide was added dropwise to the vigorously stirred lithium

aluminum hydride at a rate sufficient to maintain the reaction mixture at its reflux temperature without external heating. When all the 5-(1'-cyclohexenyl)-2-thienyl disulfide had been added, the reaction mixture was stirred and heated at its reflux temperature for an additional hour and a quarter. The reaction mixture was cooled in an ice bath and 50 ml. of water were slowly added to destroy any excess lithium aluminum hydride. The reaction mixture was then poured into 100 ml. of vigorously stirred 6 N hydrochloric acid. The reaction mixture was transferred to a separatory funnel and the aqueous phase was separated from the ether phase. The aqueous phase was extracted with three, 50 ml. portions of ether and the ether extracts were combined with the original ether phase and extracted with three, 25 ml. portions of 10% potassium hydroxide solution. The combined aqueous potassium hydroxide extracts were acidified with 6 N hydrochloric acid, whereupon a brown oil formed in the acidified aqueous medium. The oil was extracted from the aqueous solution with three, 50 ml. portions of ether and the combined ether extracts were dried in contact with anhydrous magnesium sulfate under an atmosphere of nitrogen. The ether was distilled from the ethereal solution using a semi micro modified Claisen distillation apparatus and a sample was taken from the remaining residue for an infra-red analysis. The infra-red spectrum contained an absorption band at 3.96μ indicating a sulfhydryl group was present. The residue was not fractionally distilled in order to prevent either thermal decomposition or air oxidation. All attempts to prepare a 2,4-dinitro-phenyl sulfide derivative from the residue failed to give a crystalline material.

Preparation of Ethyl Thioglycolate (21)



A two liter, one neck round bottom flask was fitted with a reflux condenser carrying an attached calcium chloride drying tube. A 491.2 g., 5.36 moles, quantity of thioglycolic acid was dissolved in one liter, 787 g., 17.1 moles, of absolute ethanol contained in the flask. A 40 g., quantity of concentrated sulfuric acid was carefully added to the thioglycolic acid solution. The reaction mixture was kept at its reflux temperature for eight hours and then set aside at room temperature for two days. The mixture was poured into a three liter beaker and while it was stirred, anhydrous sodium carbonate was added in portions until carbon dioxide evolution had ceased. After the addition of sodium carbonate had been completed, a liter of anhydrous ether was added to the mixture to precipitate the excess sodium carbonate, and sodium sulfate from the ethyl thioglycolate which was soluble in the alcoholic solution. The precipitate was collected on a Buchner funnel and washed with ether which was combined with the original filtrate. The filtrate was transferred to a distillation apparatus equipped with a one foot heat jacketed Vigreux column. The major part of the ether was removed by distillation on a steam bath at atmospheric pressure and the remainder at 60 mm. Hg. and a temperature of 45° C. The residue was subjected to vacuum distillation and the fraction boiling at 61-63° C./12.0 mm. Hg. was collected. This represented a 242.59 g., 2.94 moles, 54.96 yield

of ethyl thioglycolate. The refractive index of the product was, $n_D^{20} = 1.4571$. The reported boiling point of ethyl thioglycolate is $155-5^\circ \text{C./atmospheric pressure (76)}$.

The preparation of ethyl thioglycolate was repeated using a larger excess of ethanol. The same experimental procedure was followed. A 125.01 g., 5.36 moles, quantity of thiodiglycolic acid, 2270 g., 51.5 moles, 3 liters, of absolute ethanol and 113.5 g., 1.13 moles, of concentrated sulfuric acid were used in the synthesis. The reaction mixture was kept at its reflux temperature for eight hours and after cooling it was neutralized with a 130 g., 1.13 moles, quantity of anhydrous sodium carbonate. A two liter quantity of anhydrous ether was used to precipitate the salts. The remainder of the isolation of the product was carried out as described above. The fraction boiling at $45-60^\circ \text{C./19 mm. Hg.}$ was collected as product and represented a, 123.77 g., 3.53 moles, 65.6% yield of ethyl thioglycolate. Its refractive index was $n_D^{20} = 1.4571$.

Preparation of Diethyl Thiodiglycolate



A three neck, three liter flask was fitted with a stirrer, a reflux condenser with calcium chloride tube, and "Y" tube, containing a thermometer and a 500 ml. dropping funnel. A 57.5 g., 2.5 moles, quantity of sodium was added to a liter of absolute ethanol contained in the reaction flask at a rate sufficient to keep the alcohol at its reflux temperature. After preparing and cooling the sodium ethoxide solution,

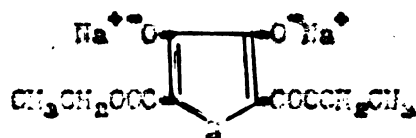
a 510 g., 2.5 moles, quantity of ethyl thioglycolate was rapidly added to it while it was vigorously stirred. A 507 g., 2.5 moles, quantity of ethyl chloroacetate was added, over a one hour period, from the dropping funnel to the stirred sodium ethyl thioglycolate solution at a rate which kept the reaction temperature below 31°C . A white precipitate of sodium chloride appeared after the initial addition of ethyl chloroacetate. After the addition of the ethyl chloroacetate had been completed the stirred reaction mixture was kept at its reflux temperature for a half hour, then it was cooled in an ice bath, and a liter of ether was added to it to decrease the solubility of sodium chloride. The sodium chloride was filtered from the reaction mixture on a Buchner funnel and washed on the funnel with three, 200 ml. portions of ether. A one foot asbestos covered Vigreux column, was used to fractionate the distillate. The ether was removed by distillation on a steam bath at atmospheric pressure and then at reduced pressure, obtained with a water aspirator. The residue was fractionated and the fraction boiling at $111-115^{\circ}\text{C}/1.9\text{ mm. Hg.}$ was collected. A 370.09 g., 1.955 moles, 77.5% yield of diethyl thiodiglycolate was obtained which had a refractive index of $n_{\text{D}}^{20.0} = 1.4614$. The reported boiling point of diethyl thiodiglycolate is $267-8^{\circ}\text{C. (77)}$.

The synthesis of diethyl thiodiglycolate was repeated on a larger scale. An 81.2 g., 3.53 moles, quantity of sodium, 1500 ml. of absolute ethanol, 423.8 g., 3.53 moles, of ethyl thioglycolate, and 432.0 g., 3.53 moles, of ethyl chloroacetate were used in the second preparation. Two thirds of an hour was required to add the ethyl chloroacetate and

the first of these is the fact that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The second is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The third is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The fourth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The fifth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion. The sixth is that the system is not a simple one, but a complex one, in which the parts are interrelated and interdependent. The seventh is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The eighth is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The ninth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The tenth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion.

the reaction mixture was heated at its reflux temperature for an hour and ten minutes. The crude product was fractionated and the fraction boiling at 117-119° C./2.0 mm. Hg. was collected which amounted to 496.7 g., 2.41 moles, a 68.6% yield of diethyl thioldiglycolate. It had a refractive index of $n_D^{20} = 1.4644$.

Preparation of the Disodium Salt of 2,5-Bis(carbomethoxy-3,4-dihydroxythiophene (45,47)



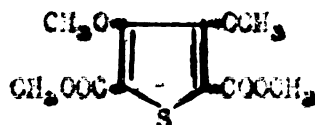
A five liter, three neck round bottom flask was fitted with a mechanical stirrer, a reflux condenser containing a calcium chloride tube, and a "Y" tube containing a dropping funnel and a thermometer which extended into the five liter reaction flask. A solution of sodium methoxide was prepared by allowing 115 g., 5.0 moles, of sodium to react with 1,000 ml. of absolute methanol in the five liter flask. The sodium was added to the methanol at a rate sufficient to keep the methanol at its reflux temperature. After all of the sodium had reacted with the methanol, the solution was cooled to 5° C. in an ice bath. A solution containing 295.0 g., 2.5 moles, of dimethyl oxalate and 396.5 g., 1.92 moles, of diethyl thioldiglycolate in 1.5 liters of absolute methanol was prepared. This solution was added dropwise from the dropping funnel to the stirred sodium methoxide solution during a period of two hours. The reaction temperature was kept below 10° C.

During the first quarter hour of the reaction, the reaction mixture became bright yellow in color and the yellow insoluble disodium salt of 2,5-dicarbomethoxy-3,4-dihydroxythiophene began to precipitate. After all of the reactants had been added to the flask the stirred reaction mixture was kept at its reflux temperature for an hour and a half and then it was set aside overnight. The reaction mixture was cooled to 0° C. in an ice bath and the yellow colored sodium salt was filtered from the methanol solution on a fritted glass filter by a vacuum created with a water aspirator. The yellow salt was removed from the filter and washed with 500 ml. of cold absolute methanol and then filtered again. The crude material was air dried for a day and then ground to a fine powder. It amounted to 624.3 g., 2.26 moles, a 113% yield of the crude disodium salt of 2,5-dicarbomethoxy-3,4-dihydroxythiophene.

The preparation of this product was repeated using different quantities of reactants and a different reaction time. The apparatus and procedure followed were the same as described above. A 167.0 g., 7.25 moles, quantity of sodium was allowed to react in 1600 ml. of absolute methanol. A 490 g., 2.38 moles, quantity of diethyl thioldiglycolate and 424 g., 3.59 moles, of diethyl oxalate were dissolved in 1590 ml. of absolute methanol. The resulting solution was added dropwise, over a two and a half hour period, to the sodium methoxide solution kept at a temperature below 15° C. The yellow precipitate, as before, was stirred and refluxed for an hour after all the reactants had been added to the reaction flask. The reaction solution and

precipitate were cooled to 0° C. and filtered through a coarse glass sintered filter. The yellow colored solid product was washed with cold methanol. After the yellow solid had been air dried for three days with occasional stirring from day to day to aid evaporation, the yellow crude material was ground to a fine powder in a mortar. This weighed 757.8 g., 2.74 moles, a 11% yield of the crude disodium salt of 2,5-dicarbomethoxy-3,4-dihydroxythiophene was obtained. Again this yield is high and compares to the previous preparation, even though the ratio and quantity of reactants employed were different. The impurity could be adsorbed methanol in the precipitate as well as diethylmalate. The material was not oven dried because of the odor produced during the drying process. No physical constants are reported for the disodium salt of 2,5-dicarbomethoxy-3,4-dihydroxythiophene.

3,4-Dimethoxy-2,5-dicarbomethoxythiophene (45,47)



This synthesis was carried out six times and the yields of product ranged from poor to good. Due to the sensitivity of the synthesis to the quantity of reagents employed, the preparation will be described several times to give an indication of the difficulties involved in this synthesis.

A three liter, three neck round bottom flask was fitted with a stirrer and reflux condenser and the apparatus was supported on a

heating mantle. A 624 g., 2.25 moles, quantity of previously prepared and slightly impure disodium salt of 2,5-dicarbomethoxy-3,4-dihydroxy-thiophene was placed in the reaction flask. A 1460 g., 11.6 moles, 1050 ml., quantity of freshly distilled dimethylsulfate was quickly added to the sodium salt through the side neck of the reaction flask. The side neck of the reaction flask was stoppered and a calcium chloride drying tube was fitted in the top of the condenser to prevent moisture from entering the reaction flask. The reaction mixture was stirred and heated gently with a heating mantle. The yellow salt suddenly started to become black in localized areas next to the walls of the flask. The heating mantle was quickly removed. The black color soon spread throughout the reaction mixture. The mixture became very difficult to stir. The heating mantle was replaced and the reaction mixture was heated to its reflux temperature and maintained at that temperature for 40 minutes. The reaction vessel was cooled, stoppered, and set aside overnight. The apparatus was arranged for vacuum distillation by placing a 45 degree elbow in the side arm of the reaction flask and fitting a condenser with a side arm adaptor and receiver to the 45 degree elbow. A water aspirator was connected to the side arm of the adaptor through a trap. The reaction flask was heated and 464.1 g., 3.68 moles, of dimethylsulfate was vacuum distilled from the reaction mixture. The residue in the reaction flask was a black solid mass. The reaction mixture was hydrolyzed by adding one liter of a 6 N sodium hydroxide solution to it in the reaction flask. The reaction mixture was heated at its reflux temperature for an hour and a half. It had a black color

and considerable tar was present. The black tar material was removed by collecting it on a Buchner funnel. The filtrate was acidified with a 6 N hydrochloric acid solution, which caused a black precipitate to form. The latter was very difficult to remove by filtration on a Buchner funnel. The original tarry material obtained in the initial filtration was again heated at its reflux temperature with 500 ml. of a 6 N sodium hydroxide solution. The mixture was filtered and the filtrate was acidified as in the previous case but no solid product could be isolated. The black precipitate isolated above from the acidification was difficultly soluble in water. The precipitate was best purified by dissolving it in hot methanol, treating it with charcoal, filtering and adding water to the hot filtrate to crystallize the product. The mixture was cooled to 0° C. in an ice bath and then filtered. The crystals were grayish black colored needles. The methanol charcoal treatment was repeated twice to yield gray colored needles. When the crystalline needles had been dried and were exposed to the air and light they darkened considerably. A 75.26 g., 0.328 mole, 14.6% yield of 3,4-dimethoxy-2,5-dicarboxythiophene was obtained which decomposed at approximately 294° C. with some sublimation above 200° C. The reported decomposition of this material is above 250° C. (45). When a small amount of the material was dissolved in a rather large quantity of hot water, treated with charcoal, and cooled, it yielded a very white product which decomposed with darkening at approximately the same temperature it did before it was recrystallized from water.

the first of these is the fact that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The second is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The third is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The fourth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The fifth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion. The sixth is that the system is not a simple one, but a complex one, in which the various parts are interrelated and interdependent. The seventh is that the system is not a static one, but a dynamic one, in which the parts are constantly changing and evolving. The eighth is that the system is not a closed one, but an open one, in which the parts are constantly interacting with the environment. The ninth is that the system is not a linear one, but a non-linear one, in which the parts are constantly interacting with each other in a non-linear fashion. The tenth is that the system is not a deterministic one, but a probabilistic one, in which the parts are constantly interacting with each other in a probabilistic fashion.

The above synthesis was repeated on a smaller scale and the apparatus was slightly modified, being the same except that a 500 ml. round bottom flask was used for the reaction vessel and a thermometer was fitted in one of the side necks in such a manner that the thermometer bulb extended well into the reaction mixture. The reaction flask was charged with 45.0 g., 0.163 mole, of the finely ground disodium salt of 2,5-dicarboethoxy-3,4-dihydrothiophene and 120 g., 0.952 mole, of freshly distilled diethylsulfate. The stirred reaction mixture was heated with a heating mantle, until its temperature reached 100° C. at which point it rose suddenly to 125° C. due to a vigorous exothermic reaction occurring which caused the reaction mixture to reflux. The heating mantle was quickly removed when the temperature began to rise. The reaction mixture was stirred until its temperature had fallen to 110° C. and then the mantle was replaced under the reaction flask and heat was supplied to maintain the reaction temperature at 110° C. for a total of thirty minutes, timed from the point the reaction mixture had reached a maximum of 125° C. During the half hour interval the reaction changed from its original yellow color to white, and then to black. The reaction mixture was cooled and the apparatus was arranged for vacuum distillation as was done in the previous preparation except that a mechanical pump was used instead of a water aspirator. A 36.11 g., 0.286 mole, quantity of diethylsulfate was distilled from the reaction mixture at 50° C./2 mm. Hg. The mixture was cooled and 150 ml. of a 6 N sodium hydroxide solution was added and the reaction mixture was heated and stirred at its reflux temperature for a half hour. A small

amount of a tan colored precipitate was present in the flask and this was removed by collecting it on a fritted glass funnel. The dark colored filtrate was treated with charcoal and then filtered. The filtrate was acidified with 90 ml. of concentrated hydrochloric acid which precipitated a creamy white material. This material was collected with difficulty by vacuum filtration on a fritted glass filter after which it was washed thoroughly with cold water. The white precipitate darkened while air drying, until it was nearly black in color when dry. The black material was redissolved in 6 N sodium hydroxide solution and treated three times with charcoal by adding the charcoal, heating for ten to fifteen minutes and then filtering. The final filtrate was cooled and acidified with concentrated hydrochloric acid to yield a nearly white precipitate. The precipitate was collected on a Buchner funnel, washed several times thoroughly with cold water and air dried. The dry material was a very light gray in color. The quantity of 2,5-dicarboxy-3,4-dimethoxythiophene obtained was 15.74 g., 0.0679 mole, 11.6% yield, which decomposed at approximately the same temperature as the material obtained in the previous preparation.

Since the yield was increased threefold on the second attempt, compared to the original synthesis of 2,5-dicarboxy-3,4-dimethoxythiophene, the preparation was repeated with a further modification of the apparatus to obtain better temperature control. The apparatus was identical in this preparation except that the heating mantle was replaced by an oil bath supported on a mechanical laboratory jack so it could be quickly raised and lowered. The quantities of reagents and the experimental

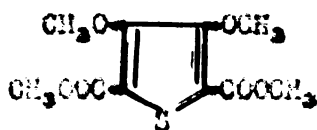
procedure used were the same as in the preparation just described. The oil bath was heated with a blade heater to 103°C . before raising it around the reaction flask. Three minutes after the oil bath was raised there were visible signs of a reaction shown by the yellow color fading to white. Five minutes after the oil bath had been raised the reaction mixture temperature suddenly rose to 135°C . and the oil bath was quickly lowered. When the temperature of the reaction mixture had dropped to 110°C . the bath was raised and the temperature was maintained at 110°C . for a half hour, timed from the point when the initial reaction had occurred. The excess diethylsulfate was removed by distillation at $57^{\circ}\text{C}/3\text{ mm. Hg}$. After cooling the residue in the flask, 200 ml. of 6 N sodium hydroxide was added and the mixture was kept at its reflux temperature for a half hour. The product was isolated by acidifying the mixture after it had been cooled in an ice bath with 125 ml. of concentrated hydrochloric acid. A creamy white precipitate formed, but it turned black on air drying and it possessed a pungent odor. The product was further purified by dissolving it in a sodium hydroxide solution, decolorizing with charcoal, and then reprecipitating by acidification. After washing and drying a, 29.55 g., 0.127 mole, 78.0% yield of 2,5-dicarbony-3,4-dihydroxythiophene was obtained which had the same decomposition temperature as the previously prepared samples.

The preparation was repeated again, using the technique just described but on a much larger scale. A 210.74 g., 0.763 mole, quantity of the disodium salt of 2,5-dicarbony-3,4-dihydroxythiophene and 562 g.,

4.45 moles, of freshly distilled dimethylsulfate were used. The reaction mixture turned black in this experiment because heat could not be conducted away from the interior of the reaction mixture rapidly enough. A 144.52 g., 0.623 mole, 81.6% yield of product was obtained. This material became dark on being set aside in the laboratory for several days. It was recrystallized from a water-methanol mixture being treated with charcoal in each recrystallization. A very white product was obtained. The final weight of this material was 49.12 g., 0.211 mole, a 27.7% yield.

Two additional preparations of 2,5-dicarboxy-3,4-dimethoxythiophene were carried out using approximately 200 g. quantities of the disodium salt of 2,5-dicarboxymethoxy-3,4-dihydroxythiophene, obtaining essentially the same results as those described above.

Attempted Synthesis of 2,5-dicarboxymethoxy-3,4-dimethoxythiophene with Methyl Iodide



A one liter, three neck flask, supported in a heating mantle, was fitted with a stirrer and reflux condenser. A 30.0 g., 0.0109 mole, quantity of the finely ground disodium salt of 2,5-dicarboxymethoxy-3,4-dihydroxythiophene, 42.6 g., 0.03 mole, of freshly distilled methyl iodide and 500 ml. of absolute methanol were placed in the flask. The stirred yellow suspension of salt in the methanol and methyl iodide was

heated at its reflux temperature for eighteen hours. The yellow appearance of the reaction mixture became slightly lighter in color during the eighteen hour period. The yellow solid was filtered from the hot solution. The methanol was vacuum distilled from the solution using a water aspirator. Water was added to the hot residue until a cloudy appearance developed, then the mixture was chilled in an ice bath. A white crystalline material separated from the solution. The crystalline material was collected on a small Buchner funnel and recrystallized from a water-methanol mixture. A 2.8 g., yield of a white crystalline material was obtained, which melted over a $158-166^{\circ}\text{C}$. temperature range as determined on a melting point block. No physical constants for 2,5-dicarbomethoxy-3,4-dimethoxythiophene are given in the literature. This material was not studied further since a better method was developed to obtain the same product. The homologue, 3,4-dimethoxy-2,5-dicarbomethoxythiophene, melts at $52-53^{\circ}\text{C}$. (47) which indicated that the crystalline material may not have been the desired product.

Preparation of Copper Chromite Catalyst

The experimental procedure reported by R. Connor (62) and his co-workers describing the preparation of catalyst 3721², was followed. A 900 ml. quantity of an aqueous solution, containing 261 g., 1.00 moles, of cupric nitrate trihydrate and 31.1 g., 0.119 mole, of barium nitrate, was heated to 80°C . and poured into 900 ml. of a second aqueous solution containing 151.2 g., 0.60 mole, of ammonium dichromate and 225 ml. of a 23% ammonium hydroxide solution.

1. The first part of the document discusses the importance of maintaining accurate records of all transactions and activities. It emphasizes that proper record-keeping is essential for transparency and accountability, particularly in financial matters. The text suggests that organizations should implement robust systems to track every aspect of their operations, from procurement to sales.

2. The second section focuses on the role of technology in modern business management. It highlights how digital tools can streamline processes, reduce errors, and improve overall efficiency. The author argues that embracing technology is not just a luxury but a necessity for staying competitive in today's market. Examples of various software solutions are provided to illustrate their practical applications.

3. The third part of the document addresses the challenges of human resource management. It discusses the importance of recruiting the right talent and providing ongoing training and development. The text notes that a skilled and motivated workforce is the backbone of any successful organization. Strategies for employee engagement and retention are also explored, emphasizing the need for a supportive work environment.

4. The fourth section delves into the complexities of financial management. It covers topics such as budgeting, cost control, and financial reporting. The author stresses that sound financial practices are crucial for the long-term sustainability of a business. It provides insights into how to effectively allocate resources and manage cash flow to ensure the organization remains financially healthy.

5. The final part of the document discusses the importance of strategic planning and vision. It encourages leaders to set clear goals and develop a roadmap for the future. The text argues that without a strategic vision, an organization is likely to lose direction and fail to achieve its long-term objectives. It concludes by emphasizing the need for flexibility and adaptability in the face of changing market conditions.

An orange precipitate formed which was collected on a Buchner filter and partially dried by drawing air through it with a water aspirator. The precipitate was subsequently dried overnight in an oven at 60° C. and then finely ground in a mortar. The precipitate was divided into approximately four equal portions and each was decomposed separately by placing it in a porcelain casserole and heating the latter over a Bunsen burner. The decomposition was accomplished by stirring the precipitate with a spatula while it was being heated. After the decomposition was well started the flame was removed and the precipitate was continuously stirred, until there was a sudden evolution of gases accompanied by the material turning black. The powder was removed from the casserole and allowed to cool. After the four portions were separately decomposed in this manner they were recombined and leached, for thirty minutes, with 600 ml. of a 10% acid solution prepared by dissolving 60 g. of glacial acetic acid in 540 g. of water. The black material was filtered from the solution, and washed with six, 100 ml. portions of water. After drying the black copper chromite in an oven overnight at 125° C., it was finely ground in a mortar. Following the above procedure, 134.90 g. of copper chromite catalyst were obtained.

Preparation of 3,4-diethoxythiophene (45,47)



A 250 ml., two neck flask was fitted with a standard taper tube having a 45° side arm. A mechanical stirrer was fitted through the

straight part of the standard taper and extended to the bottom of the 250 ml. flask. The side neck of the flask was fitted with a gas inlet tube to permit nitrogen to be swept through the apparatus. A water cooled condenser was fitted in the 45° side arm of the standard taper and the condenser was fitted with a side arm adaptor and receiver. The side arm of the adaptor was connected to a dry ice trap, manometer, and a water aspirator. The reaction flask was supported above an oil bath which could be easily raised around the reaction flask. The oil bath was heated to 180° C. with two heating blades, of 500 and 125 watt capacity. A 50 ml. quantity of freshly distilled quinoline was added to the reaction flask through the side neck. A 16.5 g., 0.071 mole, quantity of 3,4-dimethoxy-2,5-dicarboxythiophene and 2 g. of copper chromium oxide were added to the stirred quinoline. The gas inlet tube was put in place and the apparatus was thoroughly swept with nitrogen. The oil bath, preheated to 180° C., was raised around the reaction flask. The stirred reaction mixture was heated for a half hour period. At the end of this period the nitrogen inlet tube was clamped shut and the water aspirator was started and while the stirred reaction mixture was heated the quinoline and 3,4-dimethoxythiophene mixture distilled between 66 and 22 mm. Hg. pressure. A 16 ml. quantity of distillate was collected. The distillate was dissolved in 200 ml. of ether and the resulting solution was extracted first with a 100 ml. portion of a 6 N hydrochloric acid solution and then with two, 50 ml. portions of a 3 N hydrochloric acid solution to remove the quinoline. The ether solution was then washed with a 50 ml. portion of a 3 N sodium hydroxide's

solution followed by a 25 ml. portion of water. The ether solution was dried in contact with anhydrous magnesium sulfate and after removal of the latter by filtration the ether was removed by distillation on a steam bath. The residue was fractionated using a semi micro modified Claisen distillation head. After a small forerun was discarded a fraction was collected boiling at 108-115° C./11 mm. Hg. It weighed 4.82 g., 0.0334 mole, and represented a 47.1% yield of 3,4-dimethoxythiophene. The reported boiling points for 3,4-dimethoxythiophene are, 110° C./17 mm. Hg. (47), 108-115° C./12 mm. Hg. (45) and 100-101.5° C./10-11 mm. (47).

The preparation of 3,4-dimethoxythiophene was repeated employing the apparatus described above. In this case 2 g. of copper chromium oxide catalyst, 50 ml. of quinoline and 13.74 g., 0.0721 mole, of 3,4-dimethoxy-2,5-dicarboxythiophene were allowed to interact for a period of 20 minutes at 180° C. A 5.75 g., 0.0399 mole, 55.3% yield of 3,4-dimethoxythiophene boiling at 110-115° C./12 mm. Hg. was obtained. The residue in the reaction flask was diluted with ether, filtered using a small Buchner funnel to recover the catalyst and insoluble material. After washing this with several 50 ml. portions of ether, and finally drying it overnight in an oven at 110-115° C. it weighed 5.35 g. Apparently the catalyst gains weight by absorbing impurities during the reaction.

In a third preparation of 3,4-dimethoxythiophene the experimental procedure was modified to determine the effect on the yield of product. A 250 ml., two neck flask was equipped with a mechanical stirrer in

one neck and the other was fitted with a standard taper having a side arm for a gas inlet and a reflux condenser. A 65 ml. quantity of freshly distilled quinoline, 16.5 g., 0.071 mole, of 3,4-dimethoxy-2,5-dicarboxythiophene and 2 g. of copper chromium oxide catalyst were placed in the reaction flask. The stirred reaction mixture was kept in an atmosphere of nitrogen while an oil bath at 180-185° C. was used to heat the reaction mixture for 30 minutes. After cooling the reaction mixture, 200 ml. of ether was added to it and the very dark colored solution was filtered through a fluted filter to remove the catalyst and residue. The filtrate was extracted first with a 100 ml. portion of 6 N hydrochloric acid solution, then with two, 100 ml. portions of 3 N hydrochloric acid solution, next with two 100 ml. portions of 3 N sodium hydroxide solution and finally with a 50 ml. portion of water. The ether solution was dried in contact with anhydrous magnesium sulfate and filtered. The ether was removed by distillation on a steam bath. The residue from the ether distillation was fractionated using a semi micro Claisen flask to give a fraction boiling at 109-115° C./11 mm. Hg., which weighed 4.51 g., 0.0313 mole, and represented a 44.1% yield of 3,4-dimethoxythiophene.

It is noteworthy that when a larger quantity of 3,4-dimethoxy-2,5-dicarboxythiophene was decarboxylated the yield was very poor. The procedure for vacuum distillation of the crude reaction mixture, described in the previous preparations, was used. In a fourth preparation of this compound a 65 g., 0.284 mole, quantity of 3,4-dimethoxy-2,5-dicarboxythiophene, 8 g. of copper chromium oxide catalyst, and 200 ml.

of quinoline were used. The reaction time was a half hour and the isolation procedure was the same as described above. A fraction boiling at 85-95° C./1.5 mm. Hg., weighing 1.09 g., 0.00756 mole, which is a 2.66% yield of 3,4-dimethoxythiophene was obtained.

Five additional preparations of 3,4-dimethoxythiophene were made. The vacuum distillation procedure of the crude reaction mixture was followed in all these syntheses because of the ease of purification of the final product. For the purpose of easy comparison, the quantities of reagents together with the yields obtained are tabulated in Table VI along with the previously described preparations of 3,4-dimethoxythiophene.

Synthesis of 3,4-dimethoxy-2-bromothiophene



A 500 ml., three neck round bottom flask was equipped with a stirrer and dropping funnel. A 5.0 g., 0.0347 mole, quantity of 3,4-dimethoxythiophene was dissolved in 200 ml. of glacial acetic acid contained in the reaction flask. A 5.51 g., 0.0347 mole, quantity of bromine was dissolved in 100 ml. of glacial acetic acid and the solution was cooled to 16.0° C., the temperature at which it started to crystallize due to freezing. The reaction flask and its contents were cooled to 16.0° C. in an ice bath and the reaction mixture was maintained at this temperature by raising and lowering the ice bath as



necessary. The cold bromine solution was added to the dropping funnel in small portions in order to keep the solution cold until it was used. The bromine solution was added dropwise to the vigorously stirred cold 3,4-dimethoxythiophene solution over a 42 minute period. The reaction mixture was a light brown color when all the bromine solution had been added. The ice bath was removed from the reaction flask and while the reaction mixture was stirred for 23 minutes it was allowed to warm up to 22° C. The reaction mixture was poured into 900 ml. of water and the aqueous mixture was extracted first with a 200 ml. and then with two, 150 ml. portions of ether. The combined ether extracts were washed with a 100 ml. portion and then with a 200 ml. portion of a 6 N sodium hydroxide solution. The ethereal solution was dried in contact with anhydrous magnesium sulfate. The ether was removed by distillation on a steam bath and the residue was fractionated using a semi micro modified Claisen flask. Two fractions were collected; one at 85-98° C./0.5 mm. Hg., 2.11 g., and the other at 98-114° C./0.7 mm. Hg., 3.67 g. This combined very impure material amounted to 5.78 g., 0.0259, a 74.8% yield of 3,4-dimethoxy-2-bromothiophene. Due to the large range in the boiling points of the fractions, the experiment was repeated by adding the bromine solution at a slower rate. Actually the above fractions distilled mainly at 98° C./0.5-0.7 mm. Hg.

The repeated bromination of 3,4-dimethoxythiophene was done on a larger scale. The apparatus used was the same with the exception that a one liter reaction vessel was employed. A 15.0 g., 0.104 mole quantity of 3,4-dimethoxythiophene dissolved in 300 ml. of glacial

acetic acid and a 16.6 g., 0.104 mole quantity of bromine dissolved in 200 ml. of glacial acetic acid were employed in this experiment. The procedure was the same as in the previous experiment. The bromine solution was added slower, over an hour and a half period and then the mixture was stirred for an additional 30 minutes at which time the reaction mixture was dark brown in color. The reaction mixture was poured into three times its volume of water and then extracted first with a 500 ml. portion and then with two, 200 ml. portions of ether. The combined ether extracts were washed with three 100 ml. portions of a 6 N sodium hydroxide solution and finally with a 100 ml. portion of a 3 N sodium hydroxide solution before the washings tested basic to litmus. The ethereal solution was then washed with three, 100 ml. portions of water which removed most of the black color that had developed. The ethereal solution was dried in contact with magnesium sulfate and distilled as described above. A small forerun was discarded and the remainder of the product boiled in a relatively narrow range, 79-82° C./0.8 mm. Hg. An 18.16 g., 0.0213 mole, 70.2% yield of product was obtained. Analytical data on this product is recorded at the end of the following experiment.

Preparation of 3,4-Dimethoxy-2-bromothiophene Using
m-Bromosuccinimide as the Brominating Agent

A 500 ml. three neck flask was fitted with a condenser and mechanical stirrer. The remaining side neck opening was used to add the reagents. An 18.19 g., 0.126 mole, quantity of 3,4-dimethoxythiophene was dissolved in 200 ml. of dry carbon tetrachloride and the

resulting solution was placed in the reaction flask. A 22.4 g., 0.126 mole quantity of N-bromosuccinimide was slowly added to the stirred solution of 3,4-dimethoxythiophene. The reaction mixture was stirred for an hour with no external heating, and then it was heated at its reflux temperature for five hours. A considerable quantity of solid succinimide formed during the reflux period. The reacting mixture was cooled in an ice bath to 0° C. and the insoluble succinimide was filtered from the carbon tetrachloride solution of 3,4-dimethoxy-2-bromothiophene by means of a Buchner funnel. The filtrate was washed in a separatory funnel with three, 100 ml. portions of a 5 N sodium hydroxide solution, and finally with 50 ml. of water. The carbon tetrachloride solution was dried in contact with anhydrous magnesium sulfate. After the magnesium sulfate was removed by filtration, the carbon tetrachloride was removed by distillation on a steam bath. The residue was fractionally distilled using a semi micro modified Claisen distillation apparatus. The fraction boiling at 78-81° C./0.4-0.5 mm. Hg. was collected. A 25.07 g., 0.112 mole, 89.0% yield of 3,4-dimethoxy-2-bromothiophene was obtained. Elemental analysis of the product gave the following results. Calcd. for $C_6H_7O_2SBr$: C, 32.30; H, 3.16; S, 14.37; Br, 35.22. Found: C, 32.51; H, 3.19; S, 14.20; Br, 35.61.

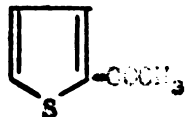
Attempted Synthesis of 3,4-Dimethoxy-2-thiophenethiol



A 500 ml., three neck flask was fitted with a condenser in one of the side necks, a mechanical stirrer in the center neck, and a "Y" tube containing a dropping funnel and a gas inlet tube. The glass portion of the apparatus was dried in an oven overnight at 110° C. prior to its assembling. The open end of the condenser was fitted with a calcium chloride drying tube. A 1.17 g., 0.048 mole, quantity of dry magnesium metal chips was added to the reaction flask through one arm of the "Y" tube after removing the dropping funnel. While dry nitrogen was slowly swept through the apparatus, the entire apparatus was cautiously heated with a small bunsen burner flame. The dry nitrogen was swept slowly through the apparatus during the entire course of the experiment. After the apparatus had cooled to room temperature a 100 ml. portion of anhydrous ether was added to the reaction flask through the dropping funnel. A 10.0 g., 0.045 mole, quantity of 3,4-dimethoxy-2-bromothiophene was dissolved in 30 ml. of anhydrous ether and was placed in the dropping funnel. The 3,4-dimethoxy-2-bromothiophene solution was added dropwise to the rapidly stirred suspension of magnesium in ether. The reaction was initiated by gently heating it on a steam bath. The 3,4-dimethoxy-2-bromothiophene was added at a rate sufficient to maintain a gentle reflux of the reaction mixture, which required

approximately 15 minutes to add the thiophene derivative. After the 3,4-dimethoxy-2-bromothiophene solution had been added the stirred reaction mixture was heated at its reflux temperature for 30 minutes. A 1.11 g., 0.015 mole, quantity of dry sulfur was added to the stirred reaction mixture in small portions through a powder addition tube. The stirred reaction mixture was heated at its reflux temperature for 30 minutes and then it was cooled in an ice bath. A 100 ml. portion of a 6 N hydrochloric acid solution was added to the reaction mixture. A yellow solid formed and this was removed by filtration. It melted between 112-113° C. and appeared to be sulfur. The aqueous phase was separated from the ether phase. The aqueous layer was extracted with three 60 ml. portions of ether. The ether extracts and original ether layer were combined and extracted with three 50 ml. portions of 3 N sodium hydroxide solution. The combined alkaline extracts were acidified with 140 ml. of a 6 N hydrochloric acid solution. Only a slightly cloudy appearance formed in the solution. The aqueous material was extracted with several 100 ml. portions of ether. The ether extracts were combined and dried in contact with anhydrous magnesium sulfate. After the latter had been removed by filtration the ether was removed by distillation on a steam bath. Only a slight amount of a colored residue remained in the distilling flask, which was tarry and could not be identified.

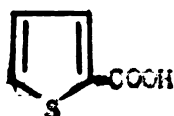
2-Acetylthiophene



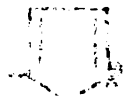
A one liter, three neck flask was fitted with a stirrer, reflux condenser, electric heating mantle, and a "Y" tube. The latter was equipped with a thermometer and a 125 ml. dropping funnel. The quantities, 336.5 g., 4.0 moles, of thiophene and 510.5 g., 5.0 moles, of acetic anhydride were placed in the flask and brought initially to a temperature of 60° C. by means of the heating mantle. A 50 g., 0.51 mole, quantity of ortho phosphoric acid was placed in the dropping funnel, and added dropwise to the stirred thiophene acetic anhydride mixture, with the external heat source disconnected, at a rate sufficient to maintain the reaction mixture temperature below 90° C. Following the acid addition the stirred reaction mixture was maintained at a temperature of 100°-110° C. for three hours. After allowing the reaction mixture to cool to room temperature it was transferred to a three liter beaker and one liter of water was added after which the contents was stirred for an hour. The oily organic layer was separated from the aqueous layer and washed three times with 200 ml. portions and once with a 100 ml. portion of 10% sodium carbonate solution, followed by drying in contact with anhydrous magnesium sulfate. The crude product was fractionally distilled under vacuum using a one foot heat jacketed Vigreux column. The fraction boiling at 72-73° C./3 mm. Hg. was

collected, and amounted to 232.5 g., 2.47 moles, of 2-acetylthiophene, a 61.7% yield. The reported boiling point for 2-acetylthiophene is $213.9^{\circ}\text{C.}/750\text{ mm. (75)}$ and $77^{\circ}\text{C.}/4\text{ mm. Hg. (63)}$.

2-Thiophene carboxylic Acid

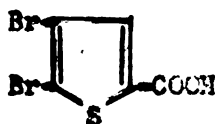


The 2-acetylthiophene was oxidized to 2-thiophenecarboxylic acid with a freshly prepared alkaline sodium hypochlorite solution. In a three liter, three neck flask, a 218 g., 5.5 moles, quantity of sodium hydroxide was dissolved in 300 ml. of water. The reaction flask and its contents were then cooled to 0°C. in an ice bath and 1250 g. of ice were added to the reaction flask after which the flask and its contents were tared on a trip balance. Chlorine gas was rapidly bubbled into the cold sodium hydroxide solution, by means of a glass tube connected to a trap which in turn was connected to a chlorine cylinder, until the reaction solution had absorbed 161 g., 4.5 moles, of chlorine. No external cooling of the reaction flask was necessary during the chlorine addition. The flask was then fitted with a reflux condenser, stirrer, and a "Y" tube containing a thermometer and a 125 ml. dropping funnel. A 63.0 g., 0.5 mole, quantity of 2-acetylthiophene was placed in the addition funnel. The stirred contents of the flask was heated initially to 55°C. by means of a mantle and then the 2-acetylthiophene was added dropwise, over a half hour period, at a rate adjusted to



maintain a reaction temperature of 55° C. Following the addition of the 2-acetylthiophene the reaction mixture was stirred an additional 45 minutes while keeping its temperature below 55° C. The excess sodium hypochlorite was destroyed by adding aqueous 20% by weight sodium bisulfite until several drops of the reaction mixture gave a negative test when added to an acidified potassium iodide solution. Acidification of the reaction mixture with 200 ml. of concentrated hydrochloric acid resulted in the immediate precipitation of 2-thiophene carboxylic acid. The precipitate was chilled in an ice bath and collected by filtration on a Buchner funnel. After recrystallization from 600 ml. of water, and drying it weighed 62.4 g., 0.486 mole, which is a 97.4% yield. It melted at $129-130^{\circ}$ C. The previously reported melting point for this material is $127-130^{\circ}$ C. (61) and 129° C. (72).

4,5-Dibromo-2-thiophenecarboxylic Acid (39,65)



In a three neck half liter round bottom flask equipped with a stirrer and reflux condenser was placed 438 g., 2.74 moles, of bromine. The stirrer was started and 58.5 g., 0.46 mole, of 2-thiophenecarboxylic acid were added in small portions through a side neck of the flask. When all the acid had been added to the reaction mixture it was set aside overnight, in the hood, in an open flask to permit the excess bromine to evaporate. The resulting sticky material was then transferred

to an open beaker and a stream of air was blown across it to further remove free bromine. The last traces of free bromine were removed from the crude brominated 2-thiophenecarboxylic acid by stirring it into a half liter of 0.5 molar ammonium carbonate. The aqueous solution on acidification with 6 N hydrochloric acid yielded a white product which was collected by filtration on a Buchner funnel and dried. The crude product after a single recrystallization from ethanol amounted to a 67.7% yield, 88.2 g., 0.30 mole. The reported melting point of 4,5-dibromo-2-thiophenecarboxylic acid (39) is 225-227° C. and that observed for the above material was 225-227° C. with some sublimation occurring above 210° C.

2,3-Dibromothiophene



A solution containing 88.2 g., 0.31 mole, of 4,5-dibromo-2-thiophenecarboxylic acid dissolved in 766 ml. of glacial acetic acid was placed in a three liter, three neck flask equipped with a stirrer and reflux condenser. To this stirred solution 219 g., 0.69 mole, of mercuric acetate was added after which the reaction mixture was heated at its reflux temperature for four hours during which time there was evidence of carbon dioxide being liberated as indicated by the formation of gas bubbles. The mixture was allowed to cool to room temperature where upon a white insoluble salt separated which was recovered by filtration on a Buchner funnel and pressed as dry as possible.

the first of these is the fact that the *Journal of the Royal Society of Medicine* has been published since 1847, and has since that time been one of the most important and influential of medical journals. It has been the source of much of the information which has been used in the preparation of this book, and it is to be hoped that it will continue to be so for many years to come. The second of the reasons mentioned above is the fact that the *Journal of the Royal Society of Medicine* has been one of the most important and influential of medical journals. It has been the source of much of the information which has been used in the preparation of this book, and it is to be hoped that it will continue to be so for many years to come.

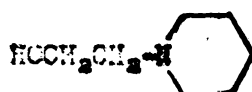


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The mercuric salt derivative was placed in one liter of an aqueous 20% sodium chloride solution contained in the original apparatus and heated with stirring at its reflux temperature for an hour. At this point 100 ml. of concentrated hydrochloric acid was added to the reaction mixture and it was steam distilled. Some difficulty was encountered during this operation due to a tendency of the mixture to foam. Only a very small amount of an oily product was obtained by the steam distillation leaving a large amount of precipitate in the distillation flask. This was filtered, washed with water, and after drying amounted to 97.69 g., a weight which was greater than that of the starting material. This material had a tendency to sublime at 224°C . and melted in the range $225\text{--}229^{\circ}\text{C}$. with the majority of it melting at 227°C ., which was very near the melting point of the starting compound. However, when a mixed melting point of the original 4,5-dibromo-2-thiophenecarboxylic acid and the decarboxylated product was made there resulted a vigorous evolution of gas to 200°C . with decomposition, indicating that the two materials were not identical. A 5.7 g. quantity of the product was set aside for future reference while the remainder of the material was subjected to decarboxylation and again placed in the original apparatus. One liter of glacial acetic acid and 286 g., 0.877 mole, of mercuric acetate were added and the stirred mixture was refluxed for five hours. After allowing the mixture to cool to room temperature the white precipitate was collected, washed with water and dried. This white crystalline material did not melt or decompose at temperatures up to 300°C . but did turn slightly brown.

This material was again stirred and refluxed in one liter of a 20% by weight aqueous solution of sodium chloride for three hours, after which 100 ml. of concentrated hydrochloric acid was added, and the mixture was subjected to steam distillation. The oily product was separated from the aqueous distillate and an additional quantity of product was recovered by saturating the aqueous distillate layer with sodium chloride. The combined oils were dried in contact with calcium chloride and distilled from a Claisen flask collecting the material boiling at 202-203° C. which weighed 40.7 g., 0.159 mole, a 54.6% yield, discounting the small amount of the initially decarboxylated material set aside for reference. The reported boiling point (80) of 2,3-dibromothiophene is 212-213° C. Apparently the decarboxylation failed the first time, but did take place the second time when the mercuric salt was thoroughly dried prior to decomposition with 20% by weight aqueous sodium chloride solution.

Preparation of 2-Piperidino-1-ethanol



A two liter, three neck flask was equipped with a stirrer, reflux condenser and supported in a heating mantle. The quantity, 241.6 g., 3.0 moles, of 2-chloroethanol was dissolved in 700 ml. of absolute alcohol contained in the flask. A 30 g. quantity of sodium iodide was next dissolved in the 2-chloroethanol solution and finally to this

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that every entry, no matter how small, should be recorded to ensure the integrity of the financial data. This includes not only sales and purchases but also expenses and income. The document further states that regular audits are essential to identify any discrepancies or errors in the accounting process. It also mentions the need for transparency and accountability in all financial dealings.

The second part of the document focuses on the role of the accounting department in providing accurate and timely financial information to management. It highlights the importance of maintaining up-to-date financial statements and reports. The document also discusses the need for effective communication between the accounting department and other departments within the organization. It stresses that clear and concise reporting is crucial for informed decision-making.

The third part of the document addresses the challenges faced by the accounting department in managing complex financial transactions. It mentions the need for strong internal controls and procedures to minimize the risk of fraud and error. The document also discusses the importance of staying up-to-date with the latest accounting standards and regulations. It emphasizes the need for continuous learning and professional development for all accounting staff.

The fourth part of the document discusses the role of the accounting department in supporting the overall business strategy. It mentions the need for the accounting department to provide valuable insights and analysis to management. The document also discusses the importance of maintaining accurate and reliable financial data to support strategic planning and decision-making. It emphasizes the need for the accounting department to be proactive in identifying potential risks and opportunities.



The fifth part of the document discusses the role of the accounting department in ensuring compliance with applicable laws and regulations. It mentions the need for the accounting department to stay up-to-date with the latest tax laws and accounting standards. The document also discusses the importance of maintaining accurate and reliable financial data to support compliance reporting. It emphasizes the need for the accounting department to be proactive in identifying potential compliance risks.

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solution was added 430.9 g., 5.05 moles, of piperidine. The reaction mixture was stirred and an exothermic reaction set in which caused the ethanol to reflux for approximately five minutes. After the initial spontaneous reaction subsided the stirred reaction mixture was heated at its reflux temperature for a twenty-four hour period. Piperidine hydrochloride crystallized from the reaction mixture as the reaction proceeded. A two liter, three neck flask was equipped with a reflux condenser and the other openings in the flask were stoppered. The quantity, 69 g., 3.0 moles, of sodium were dissolved in small portions in 1150 ml. of ethanol in the flask at a rate sufficient to cause a gentle reflux of the ethanol. The sodium ethoxide solution was allowed to cool to room temperature and the 2-piperidino-1-ethanol, piperidine hydrochloride reaction mixture was poured into a 3 liter beaker and cooled to room temperature in a cold water bath. The freshly prepared sodium ethoxide solution was poured with stirring into the reaction mixture in the beaker. The resulting mixture was stirred for several minutes during which time solid sodium chloride crystallized from the alcoholic solution. The reaction slurry was chilled in an ice bath and filtered on a Buchner funnel to remove the insoluble sodium chloride which was then washed with three 50 ml. portions of ethyl ether. The combined filtrate and other washings after drying in contact with anhydrous magnesium sulfate were distilled using a one foot Vigreux column and the material distilling below 117° C. was collected for recovery of unreacted piperidine. The material remaining in the distillation flask was diluted with three times its volume

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2. The second part of the document addresses the challenges of data management in a rapidly changing environment. It highlights the need for flexible and scalable solutions that can adapt to new technologies and evolving business requirements. The author argues that organizations must invest in training and development to ensure their staff are equipped with the skills necessary to manage complex data sets effectively. Additionally, the text stresses the importance of regular audits and reviews to identify and address any potential issues or vulnerabilities in the data management process.

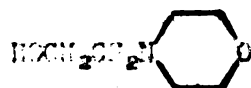
3. The third part of the document focuses on the role of technology in enhancing data management practices. It explores various tools and platforms that can streamline data collection, storage, and analysis. The author notes that while technology offers significant advantages, it also presents new challenges, such as ensuring data privacy and security. Organizations are encouraged to adopt a balanced approach, leveraging technology to improve efficiency while maintaining strict controls to protect sensitive information. The text also mentions the importance of staying up-to-date with the latest industry trends and innovations to remain competitive.

4. The fourth part of the document discusses the importance of collaboration and communication in successful data management. It argues that data is often siloed within different departments, which can lead to inefficiencies and errors. The author advocates for a culture of open communication and shared information, where all team members are encouraged to contribute their expertise and insights. Regular meetings and reports are suggested as ways to facilitate this collaboration and ensure that everyone is on the same page. The text also emphasizes the need for clear roles and responsibilities to avoid confusion and overlap.

5. The fifth part of the document concludes by summarizing the key points discussed and offering final thoughts on the future of data management. The author reiterates that while the challenges are significant, the benefits of effective data management are immense. Organizations that prioritize data management will be better positioned to make informed decisions, improve their operations, and achieve their long-term goals. The text ends with a call to action, urging organizations to take immediate steps to enhance their data management practices and embrace the opportunities that technology offers.

with diethyl ether, causing the precipitation of inorganic salts which were removed from the solution by filtration. The ether was removed by distillation on a steam bath and the residue was then fractionated under reduced pressure using a one foot Vigreux column. The material boiling in the temperature range 89-90° C. at 20 mm. of mercury was collected. The yield was 271.0 g., 2.25 moles, 75.0% of the theoretical. The reported boiling point of the product is 89-91° C./mm. Hg. (61).

Preparation of 2-Morpholino-1-ethanol



A two liter, three neck flask was equipped with a stirrer and reflux condenser. The quantities, 241.6 g., 3.0 moles, of 2-chloro-ethanol and 30 g., 0.20 mole, of sodium iodide were dissolved in 700 ml. of ethanol contained in the reaction flask. A 522.7 g., 6.0 moles, quantity of morpholine was added to the reaction mixture and it was then kept at its reflux temperature for a period of twenty-four hours and then cooled to room temperature. The quantity 67.0 g., 3.0 moles, of sodium were carefully dissolved in 1150 ml. of absolute ethanol contained in a two liter flask equipped with a reflux condenser. The cooled sodium ethoxide solution was poured into the 2-morpholino-1-ethanol, morpholine hydrochloride reaction mixture which had been transferred to a three liter beaker. The resulting mixture was stirred for several minutes to allow the sodium chloride to crystallize from

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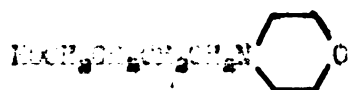
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the solution. After cooling in an ice bath the mixture was filtered on a Buchner funnel to remove the sodium chloride precipitate and the latter was washed with three, 50 ml. portions of ether. The filtrate was distilled using a one foot Vigreux column. Distillate was collected to a head temperature of 130° which removed the ether and excess morpholine, at which point crystals began to form in the distillation flask. The material in the flask was filtered and the filtrate was diluted to three times its volume with ether to insure complete precipitation of any additional salt. After chilling in an ice bath the salt was again removed by filtration and the filtrate was dried in contact with anhydrous magnesium sulfate for several hours before the final distillation of the filtrate. The magnesium sulfate was filtered from the ethereal solution and the ether was removed by distillation at atmospheric pressure. A one foot Vigreux column was arranged for a vacuum distillation. The initial fraction of material boiling below 115° C./25.0 mm. was discarded. The 2-morpholino-1-ethanol distilling at $118-124^{\circ}$ C. at 19.5 mm. pressure was collected and weighed 304.2 g., 2.32 moles, which is 77.4% of the theoretical yield. The reported boiling range for 2-morpholino-1-ethanol is $118-120^{\circ}$ C./24 mm. Hg. (32).

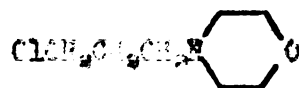
Preparation of 4-morpholino-1-butanol



In a one liter three neck flask fitted with a reflux condenser, stirrer and a heating mantle, 20 g., 0.12 mole, of potassium iodide was

dissolved in 300 ml. of dry ethanol. To this solution, 113.57 g., 1 mole of 4-chlorobutanol and 37.12 g., 2 moles, of morpholine were added. The reaction mixture was stirred at its reflux temperature for one day. A solution of sodium ethoxide in ethanol was prepared by allowing 23 g., 1.0 mole, of sodium to react with 300 ml. of dry ethanol. After the stirred reaction mixture containing the crude 4-morpholino-1-butanol was chilled in an ice bath, the precooled sodium ethoxide solution was slowly added to it. After about five minutes the precipitated sodium chloride was collected on a Buchner filter and washed with ether. The filtrate and ether washings were combined and distilled to a head temperature of 135°C . to remove the ethanol and most of the unreacted morpholine. The residue from the distillation was diluted with three times its volume of ether to precipitate additional sodium chloride which again was collected on a Buchner filter and washed with ether. The filtrate and ether washings were combined and distilled on a steam bath to remove the ether, and the residue was distilled using a one foot Vigreux column. The fraction boiling at $117\text{--}125^{\circ}\text{C}/2.8$ to 3.2 mm. Hg. was collected. The reported boiling points of 4-morpholino-1-butanol are $131\text{--}133^{\circ}\text{C}/7$ mm. (33) and $116\text{--}117^{\circ}\text{C}/5$ mm. (34). The refractive index of the fraction collected was, $n_{\text{D}}^{25.7} = 1.4752$, and it weighed 79.27 g., which is 49.8% of the theoretical yield.

3-Morpholino-1-chloropropane

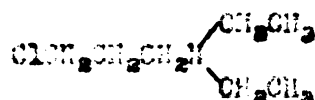


A two liter round bottom flask was equipped with a reflux condenser. A 346.5 g., 4.0 moles, quantity of morpholine was dissolved in 500 ml. of benzene contained in the reaction flask. A 314.9 g., 2.0 moles, quantity of trimethylene chlorobromide was added to the morpholine solution. The resulting solution was allowed to stand at room temperature, with occasional shaking of the flask and its contents, for an hour during which time solid separated from solution. The contents of the flask were protected from moisture by means of a calcium chloride tube and set aside at room temperature for a weekend. The reaction mixture was then heated at its reflux temperature for three hours, cooled in an ice bath, and the insoluble morpholine hydrobromide was removed by filtration and washed with anhydrous ether. The ether washings and filtrate were combined and extracted with three, 300 ml. portions of 3 N hydrochloric acid. A fair quantity of heat was evolved in the initial part of the extraction. The combined acid extracts were made strongly basic with 10 N sodium hydroxide solution which resulted in the formation of an insoluble oily layer which was separated from the aqueous layer. The aqueous layer was extracted first with three 100 ml. and then with one, 50 ml. portion of ether. The original oily material and ether extracts were combined, dried in contact with anhydrous potassium carbonate, and the ether was removed by distillation on a steam bath.



The crude product was fractionated, using a one foot Vigreux column, under vacuum. The fraction boiling at 105-108° C./11 mm. Hg. was collected. The reported boiling point is 113-115° C./25 mm. Hg. (11). The refractive index was $n_D^{25.3} = 1.4730$. The yield was 160.9 g., 1.11 moles, which was 55.5% of the theoretical yield.

3(N,N-Diethylamino)-1-chloropropane



A two liter flask was equipped with a reflux condenser and 292.6 g., 4.0 moles, of diethylamine dissolved in 900 ml. of benzene were added to the flask. A 324.9 g., 2.3 moles, quantity of trimethylene chlorobromide was added to the solution in the flask. The mixture was shaken frequently during a one hour period then protected from moisture with a calcium chloride tube, and set aside for two days at room temperature. The reaction mixture was then kept at its reflux temperature for a period of three hours, cooled in an ice bath, and the crystalline diethylamine hydrobromide was removed from the solution by filtration and washed with ether. The ether washings and filtrates were extracted first with three, 250 ml. portions, then with two 150 ml. portions, and finally with a 100 ml. portion of 3 N hydrochloric acid. The combined acid extracts were made basic with 10 N sodium hydroxide solution resulting in the formation of an oily layer. The latter was separated and the aqueous layer was extracted with three, 150 ml. portions of ether.

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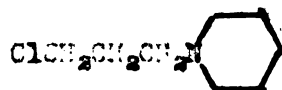
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The oily material and other extracts were combined, dried in contact with anhydrous potassium carbonate, and the ether was removed on a steam bath. The crude product was fractionated using a one foot Vigreux column and the fraction boiling between $60-68^{\circ}$ C./10 mm. Hg. was collected. A 55.2 g., quantity of material boiling between $68-88^{\circ}$ C. was discarded. The yield was 117.7 g., 1.01 moles, which is 50.7% of the theoretical yield. The refractive index of the product is $n_D^{25} = 1.4389$. The reported boiling range for 3(N,N-diethylamino-1-chloropropane is $70-75^{\circ}$ C./25 mm. Hg. (85).

3-Piperidino-1-chloropropane



A two liter round bottom flask was equipped with a reflux condenser and 310.6 g., 4.0 moles, of piperidine dissolved in 900 ml. of benzene was placed in the flask. A 311.9 g., 2.0 moles, quantity of trimethylene chlorobromide was added rapidly to the solution in the reaction flask and shaken well to thoroughly mix the solution. The reaction was left unattended for twenty minutes and instead of slowly reacting as in the cases of the previously described morpholine and diethylamino derivatives it became rather vigorous and a large amount of the benzene was driven out of the condenser. Some of the reactants very probably were lost at the same time. A 500 ml. quantity of additional anhydrous benzene was added to the reaction mixture and after it had subsided it was kept at its reflux temperature for three hours. After cooling the

reaction mixture in an ice bath the crystalline piperidine hydrobromide was removed by filtration and washed with ether. The combined washings and filtrates were extracted with 3 N hydrochloric acid. The combined acid extracts were made basic with 10 N sodium hydroxide which caused an oily layer to separate. The basic aqueous layer was extracted with ether and the ether extract and oily portion were combined and dried in contact with anhydrous potassium carbonate. The ether was removed on a steam bath and the oily residue was fractionated using a one foot Vigreux column. The fraction boiling at $85-87^{\circ}$ C./6 mm. Hg. was collected. A 12.1 g. forerun and a 15 g. quantity of residue were discarded. The latter appeared to be a quaternary salt polymer of 3-piperidino-1-chloropropane. The yield was 150.07 g., 0.923 mole, of 3-piperidino-1-chloropropane which is 16.1% of the theoretical yield. The reported boiling range for 3-piperidino-1-chloropropane is $95-103^{\circ}$ C./25 mm. Hg. (85).

Preparation of 4-morpholino-1-chlorobutane Hydrochloride



A one liter, three neck flask was fitted with a reflux condenser, mechanical stirrer and a "Y" tube containing a thermometer extending into the reaction flask and a dropping funnel. A 79.0 g., 0.193 mole, quantity of 4-morpholinobutanol was dissolved in 100 ml. of dry chloroform and placed in the reaction flask. A solution of 81.5 g., 0.635

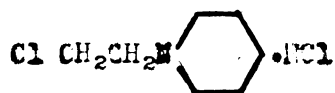
mole, of freshly distilled thionyl chloride contained in 50 ml. of dry chloroform was prepared in the dropping funnel. The contents of the flask were heated to 40° C. on a steam bath and then the thionyl chloride chloroform solution was added dropwise to the stirred reaction mixture at a rate sufficient to maintain the reaction mixture at $50-55^{\circ}$ C. without the aid of a steam bath. One hour and fifteen minutes were required to add all of the solution. A calcium chloride tube was fitted in place of the dropping funnel and a tube leading to a water aspirator was connected to the top of the condenser. While a slow stream of air was drawn through the apparatus to remove sulfur dioxide fumes, the reaction mixture was stirred and heated at its reflux temperature for two hours. The apparatus was arranged for distillation and approximately 75 ml. of chloroform was distilled from the reaction mixture. The reaction mixture was cooled, whereupon crystals formed. The crystalline solid was collected on a Buchner funnel. The product was very crude and four recrystallizations from isopropyl alcohol, with charcoal treatment in each recrystallization, were required to obtain a product melting at $120-121^{\circ}$ C. The reported literature value of the melting point is $120-121^{\circ}$ C. (36). A 61.0 g., 0.285 mole, 57.5% yield was obtained.

Preparation of 2-Morpholino-1-chloroethane Hydrochloride



The same general procedure and apparatus as previously described were employed, using 75.0 g., 0.572 mole, of 2-morpholinoethanol dissolved in 100 ml. of dry chloroform and 82.4 g., 0.693 mole, of thionyl chloride dissolved in 50 ml. of dry chloroform. Two hours were required to mix the reagents and the reaction mixture was heated at its reflux temperature for thirty minutes. After isolating the product in the usual manner and recrystallizing it from isopropyl alcohol a 95.17 g., 0.512 mole, 89.5% yield of a product melting at 182-183° C. was obtained. The melting point given in the literature for this substance is 182-182.5° C. (10).

Preparation of 2-Piperidino-1-chloroethane Hydrochloride



The same general procedure and apparatus as previously described were employed except that a two liter reaction flask was used instead of a one liter flask. A 129.2 g., 1.0 mole, quantity of 2-piperidinoethanol dissolved in 200 ml. of dry chloroform and 142.8 g., 1.2 moles, of freshly distilled thionyl chloride required one hour and fifty-five minutes to combine followed by a thirty minute reflux period. A 156.5 g.,



The cyclohexane ring is a common structural motif in organic chemistry. It is a saturated six-membered carbon ring, which can adopt various conformations, most notably the chair and boat forms. The cyclohexane ring is often used as a model for studying the properties of saturated hydrocarbons. It is also a key component in many natural and synthetic compounds, including cyclohexane derivatives and cyclohexane-based polymers. The cyclohexane ring is a fundamental building block in the study of organic chemistry, and its properties and reactions are well understood.



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0.555 mole, 85.5% yield of material melting at 224-225° C., after recrystallizing from ethanol, was obtained. The reported melting point of this material is 203° C. (37).

Preparation of Tetraethylene Chlorohydrin (38)



A one liter, three neck flask was equipped with a reflux condenser, gas dispersion tube, and a thermometer. The open end of the reflux condenser was connected to a dry ice isopropyl alcohol trap by a seven millimeter glass tube. A hydrogen chloride generator was constructed by fitting a rubber stopper containing a separatory funnel in a one liter suction flask. The side arm of the suction flask was connected to the gas dispersion tube in the reaction flask. Sodium chloride was placed in the suction flask and covered with concentrated hydrochloric acid. Concentrated sulfuric acid was placed in the separatory funnel. The quantity, 432.6 g., 6.0 moles, of tetrahydrofuran was placed in the reaction flask and heated to its reflux temperature, 64° C., by means of an electric mantle. The concentrated sulfuric acid was slowly added to the hydrochloric acid sodium chloride mixture, liberating gaseous hydrochloric acid which was slowly bubbled into the refluxing tetrahydrofuran. The hydrogen chloride generator was shaken occasionally to give an even flow of gas. This procedure was continued until the temperature of the reaction mixture reached 106° C. which required approximately fourteen hours. Fractionation of the reaction mixture

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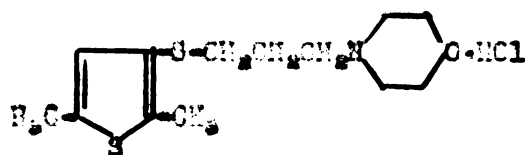
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under reduced pressure yielded, as the main fraction, a crude product boiling at $80-93^{\circ}$ C./15 mm. Hg. The reported boiling point for the fraction collected was $80-90^{\circ}$ C./14 mm. Hg. This material was re-distilled to give a 354.5 g., 3.26 moles, 54.5% yield, of pure tetramethylene chlorohydrin boiling $81-82^{\circ}$ C./14 mm. Hg. The reported boiling point for tetramethylene chlorohydrin is $81-82^{\circ}$ C./14 mm. Hg. or $70-71^{\circ}$ C./7 mm. Hg. (10).

Preparation of γ -Morpholino-n-propyl-2,5-dimethyl-3-thienyl Sulfide Hydrochloride

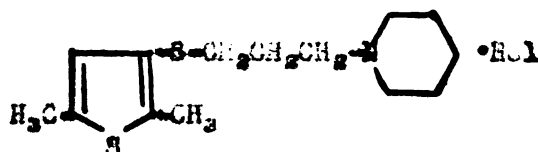


A 500 ml. three neck flask was fitted with a stirrer, reflux condenser, and dropping funnel. A 6.65 g., 0.166 mole quantity of sodium hydroxide dissolved in 100 ml. of water was added to the flask. A 9.06 g., 0.055 mole quantity of 3-morpholino-1-chloropropane was placed in the dropping funnel. An 8 g., 0.055 mole quantity of 2,5-dimethyl-3-thiophenethiol was dissolved in the sodium hydroxide solution and heated to its reflux temperature. The 3-morpholino-1-chloropropane was added dropwise to the vigorously stirred alkaline solution over a period of fifteen minutes after which the reaction mixture was refluxed an additional two and a half hours with vigorous stirring. On cooling an oil layer separated from the reaction mixture and this was separated from the aqueous layer. The aqueous portion

was extracted with three 25 ml. portions of ether and combined with the original oily material. The ethereal solution was washed with 25 ml. of five percent sodium hydroxide then with 50 ml. of water, and dried in contact with anhydrous magnesium chloride. A three neck 500 ml. flask was fitted with a stirrer, calcium chloride drying tube and a 6 mm. inlet tube constricted to approximately one millimeter at the end. Dry hydrogen chloride was generated by dropping concentrated sulfuric acid onto a sodium chloride concentrated hydrochloric acid mixture contained in a one liter suction flask. The stream of hydrogen chloride from the outlet of the suction flask was passed through a concentrated sulfuric acid drying tower and then slowly bubbled into the vigorously stirred ethereal solution of γ -morpholino-n-propyl-2,5-dimethyl-3-thienyl sulfide. After the initial white precipitate had formed the hydrogen chloride was bubbled into the ether solution an additional two minutes after which the flask was stoppered and set aside in an ice bath for six hours to facilitate crystallization of the precipitate. The white precipitate was then filtered on a Buchner funnel and washed with ether. The crude product which melted at 137-140° C. was recrystallized twice from isopropyl alcohol. The yield of recrystallized γ -morpholino-n-propyl-2,5-dimethyl-3-thienyl sulfide hydrochloride was 12.77 g., 75.0% of the theoretical yield. The melting point of the product after drying overnight at 65° C. in an evacuated drying pistol filled with calcium chloride and paraffin was 140.0-140.5° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the

following results: Calc'd. for $C_{15}H_{21}S_2 \cdot HCl$; C, 59.71; H, 7.34; S, 29.62. Found: C, 59.50; H, 7.30; S, 29.60.

Preparation of γ -piperidino-n-propyl-2,5-dimethylthiaryl Sulfide Hydrochloride

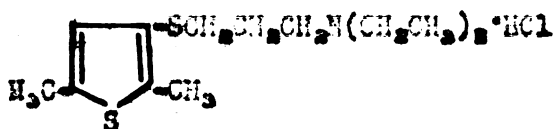


A 500 ml. three neck flask was fitted with a stirrer, reflux condenser and dropping funnel. A solution containing 6.65 g., 0.186 mole of sodium hydroxide dissolved in 100 ml. of water was prepared and placed in the flask. To this solution 8 g., 0.055 mole of 2,5-dimethyl-3-thiophenethiol was added and dissolved by stirring. An 8.95 g., 0.055 mole quantity of 3-piperidino-1-chloropropane was placed in the dropping funnel and added dropwise during a twelve minute period to the vigorously stirred refluxing solution contained in the reaction flask. After all of the 3-piperidino-1-chloropropane had been added the reaction mixture was stirred at its reflux temperature an additional three hours. On cooling the reaction mixture an oil layer formed which was separated and the aqueous portion was extracted with three portions of 25 ml. of ether. The combined ether extracts were added to the original crude oily γ -piperidino-n-propyl-2,5-dimethylthiaryl sulfide. The resulting ethereal solution was washed with 25 ml. of 5% sodium hydroxide solution followed by 50 ml. of water and then dried in contact with anhydrous magnesium sulfate. The dried ethereal solution was then transferred to a three neck, 500 ml. round bottom flask,



fitted with a calcium chloride drying tube, hydrogen chloride gas inlet tube and a stirrer. Dry hydrogen chloride was bubbled into the stirred ethereal solution while the flask was immersed in an ice bath. After the initial white precipitate formed, the hydrogen chloride was bubbled into the solution an additional two minutes after which the flask was stoppered and set aside in ice for six hours to obtain a more crystalline product. The crude *N*-piperidino-*n*-propyl-2,5-dimethyl-3-thienyl sulfide hydrochloride was filtered and washed with ether. Dry hydrogen chloride was again bubbled into the filtrate to obtain an additional yield of crude product. The total weight of crude *N*-piperidino-*n*-propyl-2,5-dimethyl-3-thienyl sulfide hydrochloride was 15.42 g. After two recrystallizations from dry isopropyl alcohol 13.22 g., 0.433 mole, a 78.1% yield of a product melting at 171.5-172.1° C. was obtained. Elemental analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{16}H_{24}S_2HCl$: C, 58.96; H, 7.91; S, 29.96. Found: C, 55.01; H, 8.26; S, 29.73.

Preparation of *N*-(*N,N*-diethylamino)-*n*-propyl-2,5-dimethyl-3-thienyl Sulfide Hydrochloride



A 6.65 g., 0.166 mole, quantity of sodium hydroxide was dissolved in 100 ml. of water contained in a three neck, 500 ml. flask fitted with a stirrer, reflux condenser, and dropping funnel. In the alkaline

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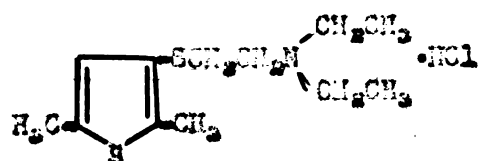


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solution 8.00 g., 0.055 mole, of 2,5-dimethyl-3-thiophenethiol was dissolved. An 8.29 g., 0.055 mole, quantity of 3-diethylamino-1-chloropropane was placed in the dropping funnel and added dropwise to the vigorously stirred refluxing mercaptan solution over a period of fifteen minutes. The reaction mixture was stirred at its reflux temperature for three and a quarter hours at which point an oily layer had formed. This was separated after cooling the reaction mixture in an ice bath and the aqueous portion was extracted with three, 50 ml. portions of ether. The combined ether extracts were added to the original oily material. The resulting ethereal solution of crude γ -(N,N-diethylamino)- α -propyl-2,5-dimethyl-3-thienyl sulfide was washed with 25 ml. of 5% sodium hydroxide solution, followed by 50 ml. of water and then dried in contact with anhydrous magnesium sulfate. Dry hydrogen chloride was bubbled through the stirred ethereal solution contained in a 500 ml. three neck flask immersed in an ice bath and fitted with a stirrer, calcium chloride tube, and gas inlet tube. A gray crude γ -(N,N-diethylamino)- α -propyl-2,5-dimethyl-3-thienyl sulfide hydrochloride precipitate formed which after being set aside in the ethereal solution at 0° C. for six hours was filtered and washed with ether. Dry hydrogen chloride was again bubbled through the original filtrate to obtain a second quantity of gray crude product, which when combined with the initial crude product gave a total weight of material amounting to 13.41 g. The crude product was recrystallized twice from dry isopropyl alcohol. The yield of recrystallized γ -(N,N-diethylamino)- α -propyl-2,5-dimethyl-3-thienyl sulfide hydrochloride was 10.46 g., 0.040 mole,

a 72.2% of the theoretical yield, melting at 109-110° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{13}H_{24}S_2NCl$: C, 53.12; H, 8.23; S, 21.82. Found: C, 52.90; H, 8.23; S, 21.70.

Preparation of β -(N,N-diethylamino)ethyl-2,5-diethyl-3-thienyl Sulfide Hydrochloride



The same apparatus was used as in the previous preparations of hydrochloride salts of amine sulfides. A solution of 8.2 g., 0.205 mole of sodium hydroxide in 50 ml. of water was prepared and placed in the reaction flask. A 8.00 g., 0.0554 mole quantity of freshly prepared 2,5-diethyl-3-thiophenethiol was dissolved in the sodium hydroxide solution. A 9.55 g., 0.0554 mole quantity of 2-(diethylamino)ethyl chloride hydrochloride was dissolved in 50 ml. of water and placed in the dropping funnel. While the contents of the flask was vigorously stirred at its reflux temperature, the 2-(diethylamino)ethyl chloride hydrochloride solution was added dropwise over a one hour period. The reaction mixture was stirred at its reflux temperature an additional eight hours, then cooled and the oily material was extracted with three 100 ml. portions of ether. The combined ether extracts were washed with 20 ml. of 5% sodium hydroxide and then with 20 ml. of water. The ethereal solution of the crude β -(N,N-diethylamino)ethyl-2,5-diethyl-3-thienyl

the same time, the *Journal of the American Medical Association* (JAMA) published a similar article, but with a different title, "The Problem of the Medical Student." The article was written by a group of medical students and faculty members from the University of Chicago. It discussed the challenges of medical education and the need for reform.

The article was published in the *Journal of the American Medical Association* (JAMA) in 1910. It was a significant contribution to the discussion of medical education at the time. The article was written by a group of medical students and faculty members from the University of Chicago. It discussed the challenges of medical education and the need for reform.

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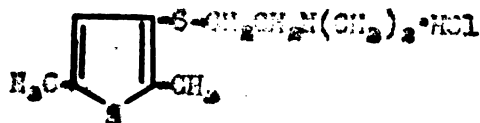
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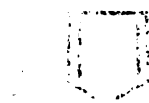
sulfide was dried overnight in contact with anhydrous magnesium sulfate. The magnesium sulfate was filtered from the dry ethereal solution and dry hydrogen chloride was added from the apparatus described in the previous preparations. The crude 8 (N,N-diethylamino)ethyl-3-thienyl sulfide hydrochloride was precipitated in two portions, removing each by filtration to prevent the addition of excess hydrogen chloride. The combined dry crude material weighed 13.65 g. After two recrystallizations from dry isopropyl alcohol the yield was 13.12 g., 0.0469 mole, 84.7% of the theoretical yield. The pure product had a melting point of 112.0-112.5° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{13}H_{22}S_2 \cdot HCl$: C, 51.19; H, 7.92; S, 22.51. Found: C, 51.62; H, 7.79; S, 22.66.

Preparation of 9 (N,N-dimethylamino)ethyl-2,5-dimethyl-3-thienyl Sulfide Hydrochloride



The same apparatus was employed as in the previous preparations of the amine hydrochloride sulfides. An 8.2 g., 0.205 mole quantity of sodium hydroxide was dissolved in 50 ml. of water contained in a 500 ml. flask. To this stirred solution, 3.0 g., 0.0554 mole of 2,5-dimethyl-3-thiophenethiol was added and the mixture was heated to its reflux temperature. A solution containing 9.55 g., 0.0664 mole of N,N-diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of

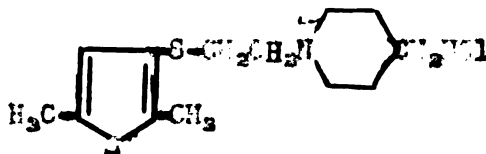
10. The following are the first four terms of a sequence: 1, 2, 3, 4. The sequence is defined by the recurrence relation $a_n = a_{n-1} + a_{n-2}$ for $n \geq 5$. Find the 10th term of the sequence.
11. A sequence of numbers is defined by $a_1 = 1$ and $a_n = 2a_{n-1} + 1$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
12. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
13. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
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27. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
28. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
29. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.
30. A sequence of numbers is defined by $a_1 = 1$ and $a_n = a_{n-1} + 2^{n-1}$ for $n \geq 2$. Find the sum of the first 10 terms of the sequence.

water was placed in the dropping funnel and added to the refluxing sodium salt solution of 2,5-diethyl-3-thiophenethiol over a period of an hour. After the mixture had refluxed an additional hour and a half it was discovered that an excess of 2-diethylaminoethyl chlorides hydrochloride had been added originally, therefore, a 1.52 g., 0.011 mole additional quantity of 2,5-diethyl-3-thiophenethiol was added and the stirred reaction mixture was heated at its reflux temperature for an additional eight hours. After allowing it to cool, the reaction mixture was extracted three times with 100 ml. portions of ether. The combined ether extracts were washed with 20 ml. of a 5% sodium hydroxide solution and 15 ml. of water, then dried in contact with anhydrous magnesium sulfate, overnight. Dry hydrogen chloride was bubbled into the filtered ethereal solution as previously described. The initial precipitate of crude product was filtered from the ether solution and washed with ether after which a second precipitate was formed by additional treatment with hydrogen chloride. The combined dried crude precipitates weighed 12.93 g. The crude product was recrystallized twice from dry isopropyl alcohol to obtain a 12.37 g., 0.0092 mole, 74.2%, yield of β -(N,N-diethylamino)ethyl-2,5-diethyl-2-thienyl sulfide hydrochloride melting at 161.5-162.5° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{18}H_{24}S_2 \cdot HCl$: C, 47.59; H, 7.26; S, 25.46. Found: C, 47.79; H, 7.27; S, 25.76.

Preparation of *N*-(2-piperidinoethyl)-2,5-dimethyl-3-thienyl
Sulfide Hydrochloride



Employing the apparatus used in the previous preparations of the amine hydrochloride sulfides a solution containing 8.2 g., 0.285 mole of sodium hydroxide dissolved in 50 ml. of water was prepared in the 500 ml. reaction flask. An 8.00 g., 0.0554 mole quantity of 2,5-dimethyl-3-thiophenethiol was dissolved in the sodium hydroxide solution and the latter was heated to its reflux temperature. A solution containing 10.20 g., 0.0554 mole of 2-piperidinoethyl chloride hydrochloride dissolved in 50 ml. of water was placed in the dropping funnel and added dropwise to the stirred refluxing alkaline solution of the sodium salt of 2,5-dimethyl-3-thiophenethiol over a one hour period. The stirred reaction mixture was kept at its reflux temperature an additional six hours, and then cooled in an ice bath. The oily material which had separated was extracted with three, 100 ml. portions of ether. The combined ether extracts were washed first with 20 ml. of a 5% sodium hydroxide solution, then with 20 ml. of water, and dried in contact with anhydrous magnesium sulfate, overnight. The ethereal solution was filtered to remove the drying agent then transferred to the previously described apparatus for adding dry hydrogen chloride to the ethereal solution of the crude *N*-(piperidino)ethyl-2,5-dimethyl-3-thienyl sulfide.

Figure 1. Schematic representation of the proposed model.

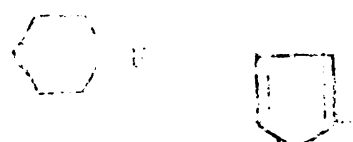


Figure 1 shows the schematic representation of the proposed model. The model is based on the assumption that the reaction of the monomer with the initiator is the rate-determining step. The reaction of the monomer with the initiator is assumed to be a second-order reaction, and the reaction of the monomer with the initiator is assumed to be a first-order reaction. The reaction of the monomer with the initiator is assumed to be a second-order reaction, and the reaction of the monomer with the initiator is assumed to be a first-order reaction. The reaction of the monomer with the initiator is assumed to be a second-order reaction, and the reaction of the monomer with the initiator is assumed to be a first-order reaction.

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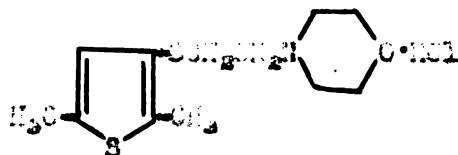
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The β -piperidinoethyl-2,5-diethyl-3-thienyl sulfide hydrochloride was precipitated by two separate hydrogen chloride additions. The crude product was filtered from the solution after each precipitation to prevent excess hydrogen chloride from being added to the ethereal solution. The fresh precipitates, each time, were stored in an ice bath for three hours to facilitate crystallization prior to filtering. The dry crude β -piperidinoethyl-2,5-diethyl-3-thienyl sulfide hydrochloride weighed 14.80 g. After two recrystallizations from dry isopropyl alcohol the weight of pure dry β -piperidinoethyl-2,5-diethyl-3-thienyl sulfide hydrochloride was 14.11 g., 0.0434 mole an 87.5% yield. It melted at 173-174° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{15}H_{22}S_2 \cdot HCl$: C, 53.49; H, 7.60; S, 21.97. Found: C, 53.55; H, 7.45; S, 21.72.

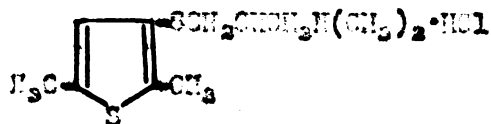
Preparation of β -morpholinoethyl-2,5-diethyl-3-thienyl
Sulfide Hydrochloride



The apparatus used in this preparation was the same as that described in the previous preparations of the amine hydrochloride sulfides. An 8.2 g., 0.0265 mole quantity of sodium hydroxide was dissolved in 50 ml. of water initially added to the 500 ml. reaction flask of the apparatus. An 8.00 g., 0.0554 mole quantity of 2,5-diethyl-3-thiophenethiol was dissolved in the sodium hydroxide solution. A solution containing 12.3 g., 0.0554 mole of β -morpholinoethyl chloride was dissolved in 50 ml. of

water and placed in the dropping funnel. The etheral solution of the sodium salt of 2,5-dimethyl-3-thiophenethiol was kept at its reflux temperature while the solution of 2-morpholinomethyl chloride was added dropwise over a period of a half hour. The reaction mixture was stirred and heated at its reflux temperature for an additional seven hours, then allowed to cool after which it was extracted with three, 100 ml. portions of ether. The combined ether extracts were washed with 25 ml. of 1% sodium hydroxide solution, then with 25 ml. of water and dried in contact with anhydrous magnesium sulfate, overnight. The filtered dry ethereal solution was transferred to the previously described apparatus for adding dry hydrogen chloride. The crude 2-morpholinomethyl-2,5-dimethyl-3-thiophenyl sulfide hydrochloride was isolated as described above. A 12.17 g. quantity of crude product was obtained which was recrystallized twice from 25 ml. of dry isopropyl alcohol to yield 11.81 g., 0.237 mole, a 77.3% yield of pure 2-morpholinomethyl-2,5-dimethyl-3-thiophenyl sulfide hydrochloride. The product melted at 211.5-212° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{12}H_{15}N_2S_2Cl$: C, 49.0%; H, 6.34; S, 21.82. Found: C, 49.17; H, 6.31; S, 21.51.

Preparation of β -(N,N-dimethylamino- α -ethylethyl-2,5-dimethyl-3-thienyl Sulfide Hydrochloride

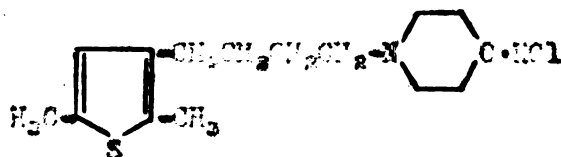


The apparatus used in the present preparation was the same as that used in the previous similar preparations. A solution of 0.2 g., 0.005 mole of sodium hydroxide in 50 ml. of water was prepared in the 500 ml. flask of the apparatus. An 8.00 g., 0.0354 mole quantity of 2,5-dimethyl-3-thiophenethiol was dissolved in the sodium hydroxide solution and heated to its reflux temperature. A solution of 8.76 g., 0.0354 mole of dimethylaminoisopropyl chloride hydrochloride dissolved in 50 ml. of water was placed in the dropping funnel and added to the stirred refluxing alkaline mercaptan solution over a half hour period. The reaction mixture was stirred at its reflux temperature for an additional half hour, then cooled and extracted with three, 100 ml. portions of ether. The combined ether extracts were washed with 25 ml. of a 5% sodium hydroxide solution and then with 25 ml. of water. The washed ethereal solution was dried in contact with anhydrous magnesium sulfate. The ethereal solution was filtered to remove the drying agent and the crude β -(N,N-dimethylamino- α -ethylethyl-2,5-dimethyl-3-thienyl sulfide hydrochloride was isolated as in previous preparations by two separate precipitations with anhydrous hydrogen chloride each precipitation being followed by storing the material in an ice bath prior to filtering.



A 12.93 g. yield of a very crude hygroscopic material melting at 112-125° C. was isolated. After three recrystallizations from dry isopropyl alcohol a 6.67 g., 0.027 mole, 46.5%, yield of pure 6-(4-morpholino-n-butyloxy)-2,5-dimethyl-3-thienyl sulfide hydrochloride melting at 170-171° C. was isolated. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{18}H_{25}NO_2S$: C, 67.6; H, 7.55; S, 2.22. Found: C, 67.75; H, 7.56; S, 2.21.

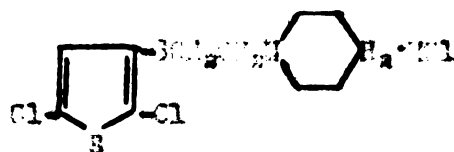
Preparation of 6-(4-morpholino-n-butyloxy)-2,5-dimethyl-3-thienyl sulfide hydrochloride



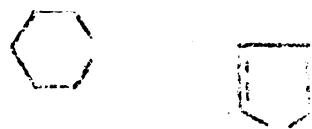
The same apparatus and general procedure were used as that described in the previous experiments using 6.0 g., 0.0554 mole, of 2,5-dimethyl-3-thiophenethiol dissolved in 100 ml. of water containing 8.2 g., 0.055 mole, of sodium hydroxide and 11.9 g., 0.0554 mole, of 4-morpholino-1-chlorobutane hydrochloride dissolved in 50 ml. of water. Fifty minutes were required to add the aqueous 4-morpholino-1-chlorobutane solution to the 2,5-dimethyl-3-thiophenethiol solution. This was followed by an eight hour reflux period. After isolating the material in the usual manner a, 6.74 g., 0.0023 mole, 4.1% yield of a product melting at 150-150.5° C., after two recrystallizations from isopropyl alcohol was obtained. Analysis of the compound for carbon, hydrogen, and sulfur

gave the following results: Calc'd. for $C_{14}H_{14}S_2NCl$: C, 52.11; H, 7.51; S, 19.92. Found: C, 52.02; H, 7.43; and S, 19.71.

Preparation of *N*-(piperidinomethyl)-2,5-dichloro-3-thienyl
Sulfide Hydrochloride

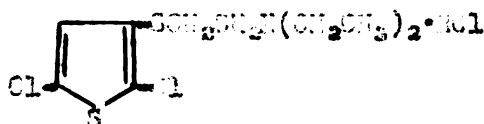


The same apparatus as described in the previous preparations of amine hydrochloride sulfides was used. A solution of 5.6 g., 0.11 mole, of sodium hydroxide in 100 ml. of water was prepared in the 500 ml. reaction flask of the apparatus. A 7.00 g., 0.0273 mole, quantity of 2,5-dichloro-3-thiophenethiol was dissolved in the sodium hydroxide solution and the latter was heated to its reflux temperature. A solution of 6.96 g., 0.0278 mole, of 2-(piperidino)ethyl chloride hydrochloride dissolved in 50 ml. of water was added dropwise from the dropping funnel into the vigorously stirred refluxing solution during a thirty minute period. The reaction mixture was stirred at its reflux temperature for an additional six hours, then cooled and extracted with four, 100 ml. portions of ether. The combined ether extracts were washed first with 20 ml. of a 5% solution of sodium hydroxide, and then with 20 ml. of water. The ethereal solution was dried in contact with anhydrous magnesium sulfate. The crude *N*-(piperidinomethyl)-2,5-dichloro-3-thienyl sulfide hydrochloride was isolated in the manner already described from the filtered ethereal solution by passing dry hydrogen chloride into



the cold ethereal solution. The product was very hygroscopic and all manipulations and filtrations of the product were done in a dry atmosphere by placing a tight fitting drying tube in a rubber stopper over the funnels used in the filtrations. A 11.30 g. yield of a white crude product was obtained. After three recrystallizations from dry isopropyl alcohol a 9.26 g., 0.0387 mole, 71.6%, yield of a white crystalline β -piperidinomethyl-2,5-dichloro-3-thienyl sulfide hydrochloride, melting at $178.0-178.5^\circ \text{C}$., was obtained. Analysis of the compound for carbon, hydrogen, chlorine and sulfur gave the following results: Calc'd. for $\text{C}_{11}\text{H}_{11}\text{S}_2\text{NCl}_3$: C, 39.73; H, 4.35; Cl, 31.67; S, 19.27. Found: C, 39.84; H, 4.21; Cl, 31.78; S, 19.02.

Preparation of β -(N,N-diethylamino)ethyl-2,5-dichloro-3-thienyl
Sulfide hydrochloride

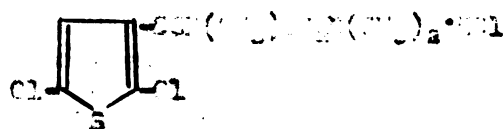


A solution of 5.6 g., 0.11 mole of sodium hydroxide in 50 ml. of water was prepared in the reaction flask of the apparatus previously described. A 7.00 g., 0.0378 mole quantity of 2,5-dichloro-3-thiophenethiol was dissolved in the sodium hydroxide solution and the latter was heated to its reflux temperature. A solution of 6.51 g., 0.0373 mole of 2-diethylaminoethane hydrochloride dissolved in 50 ml. of water was added dropwise to the stirred, refluxing alkaline mercaptan solution over a thirty minute period. The reaction mixture was kept at its reflux temperature an additional six hours, then cooled and extracted



with three, 100 ml. portions of ether. The combined ether extracts were washed first with 25 ml. of water, and dried in contact with anhydrous magnesium sulfate. The ethereal solution was filtered and the crude β -(diethylamino)ethyl-2,5-dichloro-3-thienyl sulfide hydrochloride was isolated in the usual manner by precipitating in two separate additions of dry hydrogen chloride to obtain 10.65 g., of a crude product. After three recrystallizations from dry isopropyl alcohol a, 8.35 g., 0.026 moles, 69.0% yield, of β -(diethylamino)ethyl-2,5-dichloro-3-thienyl sulfide hydrochloride was obtained which had a melting point of $150-151^{\circ}$ C. Analysis of the compound for carbon, hydrogen, chlorine, and sulfur gave the following results: Calcd. for $C_{15}H_{21}S_2Cl_2$: C, 37.45; H, 5.04; Cl, 33.17; S, 19.99. Found: C, 37.69; H, 4.85; Cl, 33.01; S, 20.12.

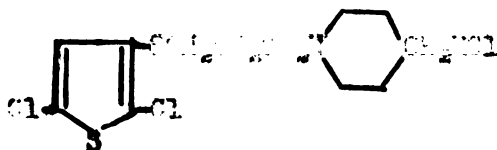
Preparation of β -(N,N-diethylamino)- α -methyl-2,5-dichloro-3-thienyl sulfide hydrochloride



The apparatus used in the present preparation was identical to that described in the previous preparations of alkyl hydrogen levulic sulfides. A 7.80 g., 0.0273 mole, quantity of 2,5-dichloro-3-thienylthiol was dissolved in a solution, prepared from 5.6 g., 0.11 mole, of sodium hydroxide and 100 ml. of water, contained in the reaction flask of the apparatus. A solution of 5.25 g., 0.0273 mole, of diethylamine-isopropylchloride hydrochloride dissolved in 50 ml. of water was added

to the stirred refluxing alkaline mercaptan solution over a thirty minute period. The stirred reaction mixture was kept at its reflux temperature for an additional six hours, then cooled and extracted with three, 100 ml. portions of ether. The combined ether extracts were washed initially with 20 ml. of a 5% sodium hydroxide solution and then with 20 ml. of water. The ethereal solution was dried in contact with anhydrous magnesium sulfate, filtered, and dry hydrogen chloride was bubbled through the ethereal filtrate. Difficulty was experienced in isolating the crude β -(N,N-diethylamino)- α -methyl-ethyl-2,5-dichloro-3-thienyl sulfide hydrochloride. The first material which precipitated, during the addition of dry hydrogen chloride, very quickly changed to an oil. The flask was stoppered and placed in an ice bath, whereupon the oil solidified. The ethereal suspension of the crude material was set aside, overnight, in a refrigerator to allow it to crystallize. The material adhered strongly to the flask, therefore, the ether was decanted from it and the crude material after drying was weighed in the flask by difference and found to be 10.07 g. After three recrystallizations from dry isopropyl alcohol a, 6.21 g., 0.0225 mole, 59.6%, yield of β -(N,N-diethylamino)- α -methyl-ethyl-2,5-dichloro-3-thienyl sulfide hydrochloride, melting at 147.6-150° C. was obtained. Analysis of the compound for carbon, hydrogen, chlorine, and sulfur, gave the following results: Calc'd. for $C_{19}H_{24}Cl_2NS$: C, 35.2%; H, 4.60; Cl, 34.60; S, 20.91. Found: C, 35.4%; H, 4.50; Cl, 34.61; S, 20.85.

Preparation of γ -piperidino-n-propyl-2,5-dichloro-3-thiaryl
sulfide hydrochloride

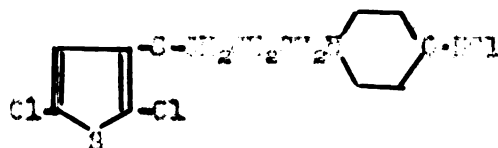


The same apparatus as that employed in previous preparations of antischistosomal sulfides was used. A solution of 5.6 g., 0.21 mole of sodium hydroxide dissolved in 50 ml. of water was prepared in the half liter reaction flask of the apparatus. A 7 g., 0.0373 mole quantity of 2,5-dichloro-3-thiophenethiol was dissolved in the sodium hydroxide solution. A solution of 7.49 g., 0.0373 mole of 3-piperidino-1-chloro-propene hydrochloride contained in 50 ml. of water was placed in the dropping funnel and added dropwise to the stirred refluxing basic mercapten solution over a half hour period. The stirred reaction mixture was kept at its reflux temperature for an additional six hours, then cooled and extracted with three, 100 ml. portions of ether. The combined ether extracts were washed with 10 ml. of 5% sodium hydroxide followed by 20 ml. of water. The ethereal solution was dried in contact with anhydrous magnesium sulfate, filtered, and then dry hydrogen chloride was passed into the solution in a manner already described to precipitate the crude γ -piperidino-n-propyl-2,5-dichloro-3-thiaryl sulfide hydrochloride, in two partial precipitations, filtering between each precipitation. The crude product was washed with ether and dried to yield 11.71 g. of a crude product. After three recrystallizations from isopropyl alcohol a, 8.17 g., 0.0241 mole, 64.8% yield of pure



γ -morpholino- α -propyl-2,5-dichloro-3-thienyl sulfide hydrochloride melting at 155-156° C. was obtained. Analysis of the compound for carbon, hydrogen, chlorine, and sulfur gave the following results: Calc'd. for $C_{12}H_{13}S_2Cl_2$: C, 41.56; H, 5.23; Cl, 30.60; S, 18.19. Found: C, 41.61; H, 5.25; Cl, 30.64; S, 18.81.

Preparation of γ -morpholino- α -propyl-2,5-dichloro-3-thienyl sulfide hydrochloride



The apparatus used in the present synthesis was the same as was employed in the previous preparations of the amine hydrochloride sulfides. A 7.00 g., 0.0373 mole, quantity of 2,5-dichloro-3-thiophenethiol was dissolved in a solution prepared from 5.6 g., 0.14 mole, of sodium hydroxide and 100 ml. of water and the alkaline mercaptan solution was heated to its reflux temperature in the reaction flask of the apparatus. A solution of 6.18 g., 0.0373 mole, of 3-morpholino-1-chloropropane dissolved in 50 ml. of water was added dropwise to the refluxing alkaline mercaptan solution during a thirty-five minute period. The reaction mixture was stirred at its reflux temperature for an additional six hours. After the reaction solution had cooled, the oily material was extracted with three 100 ml. portions of ether. The combined ether extracts were washed first with 20 ml. of a 5% sodium hydroxide solution, then with 20 ml. of water, and the ethereal solution was dried in contact with

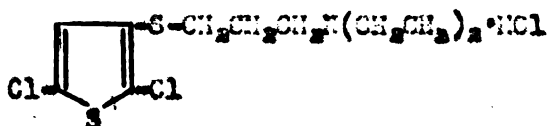
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anhydrous magnesium sulfate. The crude γ -morpholino-*n*-propyl-2,5-dichloro-3-thienyl sulfide hydrochloride was isolated in the manner described above by bubbling dry hydrogen chloride through the dry ethereal solution. After three recrystallizations from isopropyl alcohol a yield of 9.97 g., 0.0266 mole, 75.7% of γ -morpholino-*n*-propyl-2,5-dichloro-3-thienyl sulfide hydrochloride melting at 114-115.5° C. was obtained. Analysis of the compound for carbon, hydrogen, chlorine, and sulfur gave the following results: Calc'd. for $C_{11}H_{14}S_2HCl_2$: C, 37.30; H, 4.60; Cl, 30.50; S, 13.39. Found: C, 38.01; H, 4.85; Cl, 30.27; S, 13.19.

Preparation of γ -(*N,N*-Diethylamino)-*n*-propyl-2,5-dichloro-3-thienyl Sulfide Hydrochloride



The same apparatus was employed as that used in the previous syntheses of the hydrochlorides of amine sulfides. A solution of 5.6 g., 0.14 mole of sodium hydroxide was dissolved in 50 ml. of water in the reaction flask of the apparatus. A 7.00 g., 0.0378 mole quantity of 2,5-dichloro-3-thiophenethiol was dissolved in the sodium hydroxide solution and heated to its reflux temperature. A solution of 7.04 g., 0.0378 mole of 3-diethylamino-1-chloropropane hydrochloride in 50 ml. of water was added from the dropping funnel to the vigorously stirred refluxing alkaline mercaptan solution over a period of forty minutes.

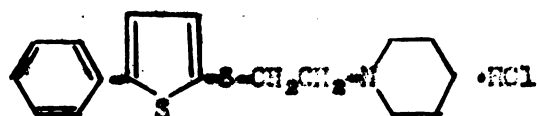
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The reaction mixture was stirred at its reflux temperature for an additional six hours, cooled and extracted with three, 100 ml. portions of ether. The combined ether extracts were washed first with 10 ml. of a 5% sodium hydroxide solution, then with 20 ml. of water, and dried in contact with anhydrous magnesium sulfate. The ethereal solution was filtered and the crude γ -(N,N-diethylamino)-n-propyl-2,5-dichloro-3-thienyl sulfide hydrochloride was isolated in the previously described manner using two separate additions of dry gaseous hydrogen chloride. The crude product was washed with ether. After three recrystallizations from dry isopropyl alcohol a 7.45 g., 0.0223 mole, 59.0% yield of pure γ -(diethylamino)-n-propyl-2,5-dichloro-3-thienyl sulfide hydrochloride melting at 117-118.5° C. was obtained. Analysis of the compound for carbon, hydrogen, chlorine, and sulfur gave the following results: Calcd. for $C_{11}H_{16}S_2HCl_2$: C, 39.47; H, 5.42; Cl, 31.70; S, 19.15. Found: C, 39.62; H, 5.48; Cl, 32.02; S, 19.01.

Preparation of β -[4-(peridininoethyl)-5-phenyl-2-thienyl
Sulfide Hydrochloride



A three neck, 500 ml. round bottom flask, supported in a heating mantle, was fitted with a reflux condenser, mechanical stirrer, and dropping funnel. A 6.20 g., 0.154 mole, quantity of sodium hydroxide dissolved in 100 ml. of water was placed in the reaction flask. An 8.00 g., 0.0416 mole, quantity of 5-phenyl-2-thiophenethiol was dissolved in

The first step in the synthesis of the polymer is the reaction of the monomer with the initiator. This reaction is carried out in a solution of the monomer in a suitable solvent, such as benzene or toluene. The initiator is added to the solution, and the reaction is allowed to proceed for a certain period of time. The reaction is then stopped by adding a suitable reagent, such as a radical scavenger. The resulting polymer is then purified by precipitation into a suitable solvent, such as methanol. The purified polymer is then dried under vacuum to remove any residual solvent. The final product is a solid polymer, which can be used for a variety of applications.

The second step in the synthesis of the polymer is the reaction of the polymer with a suitable reagent, such as a cross-linking agent. This reaction is carried out in a solution of the polymer in a suitable solvent, such as benzene or toluene. The reagent is added to the solution, and the reaction is allowed to proceed for a certain period of time. The reaction is then stopped by adding a suitable reagent, such as a radical scavenger. The resulting polymer is then purified by precipitation into a suitable solvent, such as methanol. The purified polymer is then dried under vacuum to remove any residual solvent. The final product is a solid polymer, which can be used for a variety of applications.

The third step in the synthesis of the polymer is the reaction of the polymer with a suitable reagent, such as a cross-linking agent. This reaction is carried out in a solution of the polymer in a suitable solvent, such as benzene or toluene. The reagent is added to the solution, and the reaction is allowed to proceed for a certain period of time. The reaction is then stopped by adding a suitable reagent, such as a radical scavenger. The resulting polymer is then purified by precipitation into a suitable solvent, such as methanol. The purified polymer is then dried under vacuum to remove any residual solvent. The final product is a solid polymer, which can be used for a variety of applications.



The fourth step in the synthesis of the polymer is the reaction of the polymer with a suitable reagent, such as a cross-linking agent. This reaction is carried out in a solution of the polymer in a suitable solvent, such as benzene or toluene. The reagent is added to the solution, and the reaction is allowed to proceed for a certain period of time. The reaction is then stopped by adding a suitable reagent, such as a radical scavenger. The resulting polymer is then purified by precipitation into a suitable solvent, such as methanol. The purified polymer is then dried under vacuum to remove any residual solvent. The final product is a solid polymer, which can be used for a variety of applications.

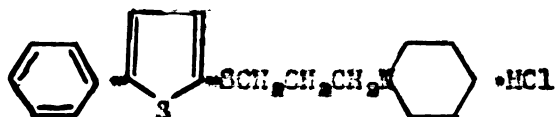
The fifth step in the synthesis of the polymer is the reaction of the polymer with a suitable reagent, such as a cross-linking agent. This reaction is carried out in a solution of the polymer in a suitable solvent, such as benzene or toluene. The reagent is added to the solution, and the reaction is allowed to proceed for a certain period of time. The reaction is then stopped by adding a suitable reagent, such as a radical scavenger. The resulting polymer is then purified by precipitation into a suitable solvent, such as methanol. The purified polymer is then dried under vacuum to remove any residual solvent. The final product is a solid polymer, which can be used for a variety of applications.

the sodium hydroxide solution. The quantity, 7.36 g., 0.040 mole, of 2-piperidino-1-chloroethane hydrochloride, was dissolved in 100 ml. of water and placed in the dropping funnel. The stirred alkaline solution of 5-phenyl-2-thiophenethiol was heated to its reflux temperature and the 2-piperidino-1-chloroethane hydrochloride solution was added to it dropwise over a fifteen minute period. The reaction mixture was stirred at its reflux temperature for an additional five and a half hours. At the end of this period stirring was stopped, and an oil phase formed on the bottom of the reaction flask. After cooling the reaction mixture, it was transferred to a separatory funnel and the oil phase was separated from the aqueous phase. The aqueous phase was extracted with three, 30 ml. portions of ether and combined with the oil phase. The ethereal solution was washed first with 10 ml. of 6 N sodium hydroxide then with 20 ml. of water and dried in contact with anhydrous magnesium sulfate. After the magnesium sulfate had been filtered from the ethereal solution the 2-piperidinoethyl-5-phenyl-2-thienyl sulfide hydrochloride was precipitated from the ether by bubbling into the ether solution anhydrous hydrogen chloride in the same manner as in the previously described experiments. The product was isolated in two precipitations to prevent excess hydrogen chloride from being added to the ethereal solution. After the 2-piperidinoethyl-5-phenyl-2-thienyl sulfide hydrochloride was recrystallized twice from isopropyl alcohol a, 10.52 g., 0.031 mole, 77.5% yield of product was obtained which melted at 161.2-161.5° C. Analysis of the compound for carbon, hydrogen, and sulfur gave the

• The first step in the process of creating a new product is to identify a market need. This can be done through market research, which involves gathering information about the target market and its needs. Once a market need has been identified, the next step is to develop a concept for a new product that meets this need. This concept should be based on the market research and should take into account the needs and preferences of the target market. The concept should also be feasible, meaning that it can be developed and produced within the available resources and budget. Once a concept has been developed, the next step is to create a prototype of the product. This can be done using a variety of methods, including 3D printing, computer-aided design (CAD), and traditional manufacturing techniques. The prototype should be used to test the product and to gather feedback from potential customers. This feedback can be used to refine the product and to make any necessary changes. Once the product has been refined, the next step is to develop a business plan for the new product. This plan should outline the marketing strategy, the production process, and the financial projections for the product. Once a business plan has been developed, the next step is to secure funding for the product. This can be done through a variety of methods, including venture capital, angel investors, and crowdfunding. Once funding has been secured, the next step is to develop a marketing plan for the product. This plan should outline the strategies for promoting the product and for reaching the target market. Once a marketing plan has been developed, the next step is to launch the product. This can be done through a variety of methods, including direct sales, retail partners, and online sales. Once the product has been launched, the next step is to monitor its performance and to make any necessary adjustments. This can be done through a variety of methods, including market research, customer feedback, and sales data. Once the product's performance has been monitored, the next step is to evaluate the success of the product. This can be done by comparing the product's performance to the goals set out in the business plan. If the product is successful, the next step is to consider expanding the product line or developing new products. If the product is not successful, the next step is to consider discontinuing the product and to focus on other areas of the business.

following results: Calc'd. for $C_{17}H_{21}S_2ClN$: C, 60.36; H, 6.52; S, 15.95. Found: C, 60.21; H, 6.89; S, 17.91.

Preparation of γ -Piperidino-n-propyl-5-phenyl-2-thienyl Sulfide Hydrochloride

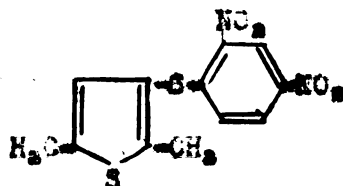


A 500 ml., three neck round bottom flask, supported in a heating mantle, was fitted with a reflux condenser, mechanical stirrer, and dropping funnel. A solution containing 6.20 g., 0.154 mole, of sodium hydroxide dissolved in 100 ml. of water was placed in the reaction flask. An 8.00 g., 0.0415 mole, quantity of 5-phenyl-2-thiophenethiol was added to the alkaline solution in the reaction flask. A 7.94 g., 0.040 mole, quantity of 3-piperidino-1-chloropropane hydrochloride was dissolved in 100 ml. of water and placed in the dropping funnel. While the alkaline mercaptan mixture was vigorously stirred and heated at its reflux temperature, the 3-piperidino-1-chloropropane hydrochloride solution was added dropwise to it over an eight minute period. The reaction mixture was stirred and heated at its reflux temperature an additional five hours to complete the reaction. After the reaction mixture had cooled, it was transferred to a separatory funnel and the lower organic phase was separated from the aqueous phase. The aqueous phase was extracted with two, 50 ml. portions of ether and the extracts were combined with the original organic phase. The ethereal solution was washed first with 20 ml. of 6 N sodium hydroxide solution, then with

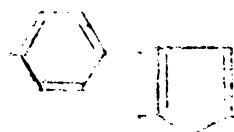


20 ml. of water and dried in contact with anhydrous magnesium sulfate. After the magnesium sulfate had been filtered from the ethereal solution the product was isolated by bubbling dry hydrogen chloride into the solution in the manner already described. The γ -piperidino-n-propyl-5-phenyl-2-thienyl sulfide hydrochloride was isolated by two separated additions of hydrogen chloride to prevent excess hydrogen chloride from being added to the ethereal solution. After two recrystallizations from dry isopropyl alcohol a, 12.13 g., 0.0352 mole, 87.8% yield, of γ -piperidino-n-propyl-5-phenyl-2-thienyl sulfide hydrochloride was obtained which melted at 145-146° C. Elemental analysis of the product for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{14}H_{24}S_2 \cdot 2HCl$: C, 61.08; H, 6.93; S, 18.12. Found: C, 61.00; H, 6.86; S, 17.91.

Preparation of 2',4'-Dinitrophenyl-2,5-dimethyl-3-thienyl Sulfide

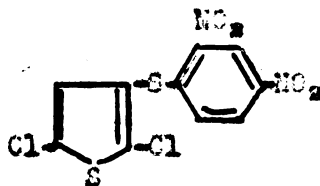


A 0.60 g., 0.0030 mole, quantity of 2,4-dinitrochlorobenzene was dissolved in 4 ml. of absolute methanol in an eight inch test tube. A 0.43 g., 0.0030 mole quantity of 2,5-dimethyl-3-thiophenethiol was dissolved in 8 ml. of methanol and ten drops of a 6 N sodium hydroxide solution were added. The alkaline 2,5-dimethyl-3-thiophenethiol solution was poured into the 2,4-dinitrochlorobenzene solution, a boiling

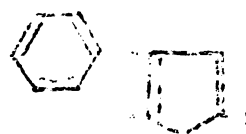


chip was added, and the mixture was heated at its reflux temperature for five minutes using a micro Bunsen burner. A yellow precipitate formed rapidly upon mixing the two solutions. The hot solution was filtered using a Hirsch funnel and the filtrate was allowed to cool whereupon a yellow crystalline solid formed. After recrystallization of the solid twice from methanol it was dried at the reflux temperature of methanol in a drying pistol at 17 mm. Hg. The melting point of the product was 104.5-105.0° C. Elemental analysis of this material gave the following results: Calc'd. for $C_{12}H_{11}S_2N_2O_4$: C, 46.44; H, 3.25; S, 20.62. Found: C, 46.46; H, 3.29; S, 20.62.

Preparation of 2',4'-dinitrophenyl-2,5-dichloro-3-thienyl Sulfide



An eight inch test tube was fitted with a six inch reflux condenser and 1.8 g., 0.008 mole of 2,4-dinitrochlorobenzene was dissolved in 12 ml. of absolute methanol, added initially to the test tube. In a second eight inch test tube, 1.67 g., 0.0070 mole of 2,5-dichloro-3-thiophenethiol was dissolved in 24 ml. of absolute methanol containing 22 drops of 6 N sodium hydroxide solution. The alkaline solution of 2,5-dichloro-3-thiophenethiol was poured into the 2,4-dinitrochlorobenzene solution, a boiling stone was added, and the reaction mixture was heated at its reflux temperature for ten minutes using a semi micro burner. The solution was filtered while hot and upon cooling the yellow



2',4'-dinitrophenyl-5-chlorothiophenyl sulfide crystallized. The crude derivative was recrystallized three times from absolute methanol to give a product melting at 136.5-137° C. Analysis of the compound for carbon, hydrogen, chlorine and sulfur gave the following results. Calc'd. for $C_{10}H_4S_2ClN_2O_4$: C, 34.2%; H, 1.15; Cl, 20.19; S, 13.26. Found: C, 34.44; H, 1.32; Cl, 20.21; S, 13.13.

Preparation of 2',4'-dinitrophenyl-5-phenyl-2-thienyl Sulfide



A 50 ml. Erlenmeyer flask was fitted with a semi micro reflux condenser and supported on a ring stand above a semi micro Bunsen burner. A 6.9 g., 4.5 milliequivalent, quantity of 2,4-dinitrochlorobenzene was dissolved in 5 ml. of absolute methanol contained in the 50 ml. Erlenmeyer flask. In a second 50 ml. Erlenmeyer flask a 1.15 g., 6.0 milliequivalent, quantity of 5-phenyl-2-thiophenethiol was dissolved in 15 ml. of absolute methanol by adding 24 drops of 6 N sodium hydroxide solution to the methanol to form the sodium salt of 5-phenyl-2-thiophenethiol. The 2,4-dinitrochlorobenzene solution was heated to its reflux temperature and the alkaline 5-phenyl-2-thiophenethiol solution was quickly poured into the hot 2,4-dinitrochlorobenzene solution. The mixture was thoroughly shaken and then heated at its reflux temperature for three minutes. A yellow precipitate formed immediately while the reaction solution was hot.



The precipitate was filtered from the black colored solution on a Hirsch funnel. The yellow precipitate was crystallized once from a cyclohexane isopropyl alcohol mixture and then twice from cyclohexane. After the material was dried in a drying pistol at 1 mm. Hg. pressure at the reflux temperature of ethanol it melted at 158-158.2° C.

Elemental analysis of the compound for carbon, hydrogen, and sulfur gave the following results: Calc'd. for $C_{15}H_{10}S_2H_2O_4$: C, 53.62; H, 2.81; S, 17.89. Found: C, 53.80; H, 2.97; S, 17.61.

SUMMARY

1. The compounds 2,5-dimethyl-3-thiophenethiol and 2,5-dichloro-3-thiophenethiol were synthesized for the first time by the lithium aluminum hydride reduction of 2,5-dimethyl-3-thiophenesulfonyl chloride and 2,5-dichloro-3-thiophenesulfonyl chloride respectively.
2. The compound 2-phenylthiophene was synthesized by a method never previously used for this compound which permits larger quantities of this compound to be synthesized conveniently. This was accomplished through the addition of thiophyl magnesium bromide to cyclohexanone, followed by dehydration and aromatization with sulfur.
3. The compound 5-phenyl-2-thiophenethiol was prepared for the first time and characterized.
4. The compounds 5-bromo-2-(1'-cyclohexenyl)thiophene and 3,4-dimethoxy-2-bromothiophene were synthesized for the first time.
5. A series of W-(N,N-dialkylamino)alkyl substituted thiophyl sulfide hydrochlorides were prepared from the newly synthesized substituted 2 and 3 thiophenethiols.

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