THE SYNTHESES OF SOME β-(N, N-DIALKYLAMINO) ETHYL THIOTHENOATES

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Matthew John Zabik

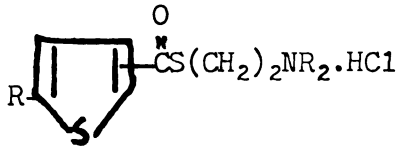
1962

ABSTRACT

THE SYNTHESES OF SOME
β-(N,N-DIALKYLAMINO) ETHYL THIOTHENOATES

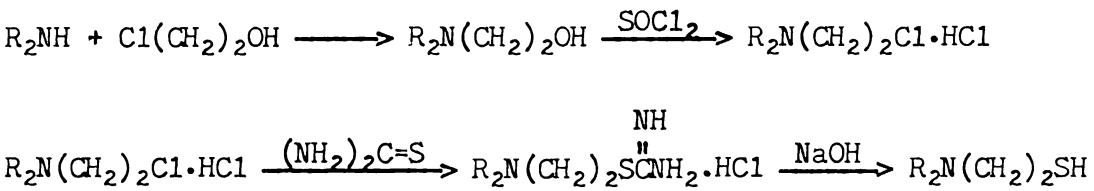
by Matthew John Zabik

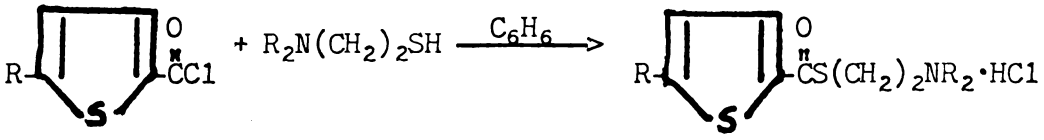
This investigation was undertaken to develop a general method for the preparation of a series of thiophene derivatives having the general structure,



Such compounds, it was anticipated, should possess high physiological activity, since excellent activity has been reported[1,2,3] for the corresponding phenyl isosters. Further, low toxicity was anticipated for these substances due to the lower toxicity of the thiophene ring as compared to the phenyl ring in similar compounds[4].

The general method for the synthesis of these thiothenoates involved the following sequency of reactions,





The intermediate β-(N,N-dialkylamino) ethanols were prepared by refluxing a secondary amine and chlorohydrin in absolute ethanol as a reaction media. The synthesis of the β-(N,N-dialkylamino) ethyl chlorides hydrochlorides involved the careful addition of thionyl chloride to a solution of the β-(N,N-dialkylamino) ethanols in chloroform as a solvent. The β-(N,N-dialkylamino) ethyl isothiouronium chloride hydrochlorides were prepared by the interaction of the β-(N,N-dialkylamino) ethyl chlorides hydrochlorides with thiourea in absolute ethanol. Treatment of the β-(N,N-dialkylamino) ethyl isothiouronium chloride hydrochlorides with a base, sodium hydroxide, yielded the free β-(N,N-dialkylamino) ethyl thiols.

The thenoic and substituted thenoic acids were prepared using accepted procedures previously reported in the literature. The acids were converted to the corresponding thenoyl chlorides by their treatment with a five-fold excess of thionyl chloride.

The β-(N,N-dialkylamino) ethyl thiothenoates were synthesized by the interaction of a β-(N,N-dialkylamino) ethyl thiol with a thenoyl chloride in a benzene-sodium bicarbonate reaction media. The thioesters were isolated and characterized as their hydrochloride salts . Altogether nineteen previously undescribed β-(N,N-dialkylamino) ethyl thiothenoates were prepared and some of their physical properties were determined.

The research described here is concerned with the preparation and chemistry of β-(N,N-dialkylamino) ethyl thiothenoates and does not include the physiological studies of these materials which will be reported elsewhere.

REFERENCES

(1) A. Einhorn and E. Uhlfelder, Ann., 371, 131 (1909).

(2) F. L. Pyman, J. Chem. Soc., 93, 1793 (1908).

(3) H. Erdtman and H. Lofgren, Svensk. Kem. Tid., 49, 163 (1937); Chem. Abst., 31, 7854[8] (1937).

(4) Y. K. Nolle, Farm. i. Farmakol. (USSR), (1937); Chem. Abst., 34, 3820 (1940).

(5) E. Campaign and W. M. Le Seur, J. Am. Chem. Soc., 71, 333 (1949).

(6) E. Campaign and W. M. Le Seur, J. Am. Chem. Soc., 70, 3498 (1948).

(7) W. H. Houff and R. D. Schuetz, J. Org. Chem., 18, 916 (1953).

THE SYNTHESES OF SOME

β-(N,N-DIALKYLAMINO) ETHYL THIOTHENOATES

By

Matthew John Zabik

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

1962

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Robert D. Schuetz for his friendly counsel throughout the course of this work.

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

Extensive chemical research has been conducted on the elucidation of the structural relationship of organic compounds to their physiological and pharmacological properties. The discovery of a new biologically active compound usually gives rise to an extended search for closely related compounds of similar, more effective, or more specific activity. Such a search is aided very often by the concept of isosteric replacement. This requires the substitution of one atom or group of atoms in the parent compound for another with similar electronic and steric configuration. In a surprising number of cases, there result compounds of similar or even greater activity. An excellent example is the synthesis of "Novocain" by Einhorn[1] which has superior physiological action to that of its naturally occurring isoster "Cocaine".

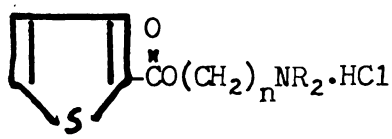
First, Pyman[2] and then later, and in more specific terms, Lofgren[3] defined the structural characteristics of compounds which should possess local anesthetic or antispasmodic action as,

$$A - M - (C)_n - N =$$

where A represents an aryl group, and M is a heteroatom or heterogroup.

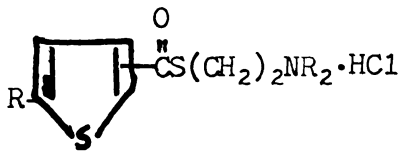
Due to their similarity in chemical structure, compounds having thio esters in place of the typical oxygen esters have been prepared and examined for local anesthetic activity. Thiocaine, the isoster thiol ester of "Novocain", has excellent local anesthetic value; however, it is more toxic than "Novocain". Because of the lower toxicity of the thiophene nucleus compared to the benzene nucleus[4,5,6,7], a

series of isosters of "Novocain" of the general structure have been prepared[6,7]:



These compounds, as it had been expected, showed lower toxicity while retaining an activity comparable to "Novocain"[7].

The present investigation was undertaken to prepare a series of compounds which embodied both the thiol ester group and the thiophene nucleus as indicated by the general structure,



It is possible that the relatively low toxicity of the thiophene nucleus will overcome the somewhat high toxicity of the thiol ester group. Thus, a compound containing both of these groups might possess excellent local anesthetic value with low toxicity. However, only laboratory and clinical tests can establish the real value of their physiological usefulness.

HISTORICAL

The use of local anesthetics in medicine originated with Karl Koller's[8] use of cocaine in 1884. Since then, a large number of compounds have been prepared with local practical anesthetic value. The majority of these compounds conform with the anesthesiophoric principle of Lofgren[3] which relates chemical structure to such activity. According to this concept a compound should contain three basic units, a lipophillic center, an intermediate chain, and a hydrophillic center. The lipophillic center should be an aromatic ring, while the intermediate chain should consist of a hydrocarbon chain joined to the aromatic position through an ester, amide, ether oxygen, aminonitrogen, or ketonic carbonyl linkage, and finally the hydrophillic center should be a tertiary or secondary amino group.

In accordance with this principle, β-(N,N-dialkylamino) ethyl thiothenoates can be classified as possible local anesthetics since they contain the necessary units.

A number of phenyl compounds containing thioester linkages have been prepared which show local anesthetic value[9,10,11]. An excellent example is thiocaine which has good local anesthetic value but unfortunately has a seven-fold irritating value compared to "Novocain". This has prevented its extensive use medicinally.

Several investigators[6,7] have prepared β-(N,N-dialkylamino) alkyl thenoates, compounds in which the benzene ring has been replaced by a thiophene ring, and some of these compounds have good local anesthetic value with lower toxicity than the corresponding benzene isoster.

Compounds containing both the thiophene ring and thioester group have not yet been prepared. The preparation of a series of such compounds should be of value since the lower toxicity reported when the thiophene ring is a constituent of the compound may offset the somewhat higher toxicity found when the thioester is a constituent of the compound, and result in a useful anesthetic.

The research reported here is concerned with the preparation and chemistry of β-(N,N-dialkylamino) ethyl thiothenoates and does not include the physiological studies of these materials, which will be reported elsewhere.

An historical review of feasible methods available for the synthesis of β-(N,N-dialkylamino) ethyl thiothenoates as well as the intermediates necessary for their preparation will be discussed first to indicate the basis for the selection of the methods used in this investigation.

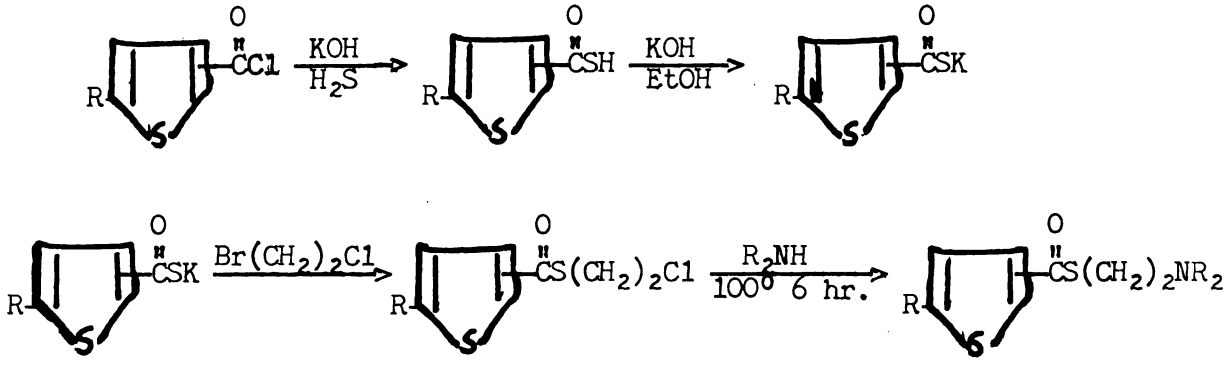
In the main, there were available two methods by which the β-(N,N-dialkylamino) ethyl thiothenoates could be synthesized. These are summarized in the two sequences of reactions,

a.[7,11,12] $R_2NH + Cl(CH_2)_2OH \longrightarrow R_2N(CH_2)_2OH$

$$R_2N(CH_2)_2OH \xrightarrow{SOCl_2} R_2N(CH_2)_2Cl\cdot HCl \xrightarrow{(NH_2)_2C=S} R_2N(CH_2)_2S\overset{\overset{NH}{\|}}{C}NH_2\cdot 2HCl$$

$$R_2N(CH_2)_2S\overset{\overset{NH}{\|}}{C}NH_2\cdot 2HCl \xrightarrow{OH^-} R_2N(CH_2)_2SH + R\text{-}\underset{S}{\langle\rangle}\text{-}\overset{\overset{O}{\|}}{C}Cl \longrightarrow R\text{-}\underset{S}{\langle\rangle}\text{-}\overset{\overset{O}{\|}}{C}S(CH_2)_2NR_2$$

and b.(1,3,13)



In the first procedure Burnett et al.(14) reported a satisfactory method for the synthesis of dialkylamine alcohols involving the reaction of two moles of a secondary amine with one of a chlorohydrin.

$$C_5H_{10}NH + Cl(CH_2)_2OH \xrightarrow{120^0} C_5H_{10}N(CH_2)_2OH\cdot HCl$$

Clinton et al.(9) employed a similar method, to obtain 95% yields of the dialkylamine alcohols, using ethyl alcohol as a solvent and a small quantity of sodium iodide. The latter reagent decreased the reaction time by the exchange of iodine for chlorine in the chlorohydrin. Clinton and his group(9) also prepared the β-dialkylamino ethanols by the interaction of a secondary amine with ethylene oxide.

$$R_2NH + H_2C\overset{O}{\diagup\diagdown}CH_2 \xrightarrow[\text{reflux}]{CH_3OH} R_2N(CH_2)_2OH$$

Satisfactory conversions of the β-dialkylamino alcohols into the corresponding chloro compound was accomplished by Mason and Block(15) by treatment of the alcohols with thionyl chloride in anhydrous chloroform as a solvent. Good reaction temperature control was necessary to obtain acceptable yields.

$$C_5H_{10}N(CH_2)_2OH + SOCl_2 \xrightarrow[50^0]{CHCl_3} C_5H_{10}N(CH_2)_2Cl\cdot HCl + SO_2$$

Adams and Whitmore(16) reported the synthesis of a β-dialkylamino alkyl chloride involving the interaction of a secondary amine with trimethylene chlorobromide in dry benzene, to obtain the desired product and the hydrobromide of the secondary amine.

$$2\ C_5H_{10}N + Br(CH_2)_3Cl \xrightarrow{C_6H_6} C_5H_{10}N(CH_2)_3Cl + C_5H_{10}NH\cdot HBr$$

The presence of the latter by-product does not complicate the purification of the desired product.

β-Dialkylamine thiols have been prepared by Albertson and Clinton(11) using isothiouronium salts as intermediates.

$$C_5H_{10}N(CH_2)_2Cl + (NH_2)_2C{=}S \longrightarrow C_5H_{10}N(CH_2)_2S\overset{NH}{\overset{\|}{C}}NH_2\cdot 2HCl \xrightarrow{OH^-} C_5H_{10}N(CH_2)_2SH$$

The isothiouronium salt intermediates are obtained in almost quantitative yields. Treatment of these salts with base gave the corresponding thiols in overall yields (from the chloride) of 50-75%. Staudinger and Freudenberger(17) reported the preparation of thiols by the interaction of sodium hydrosulfide with alkyl chlorides or bromides.

$$RCl + NaSH \longrightarrow RSH + NaCl$$

Bennett(18) using approximately the same procedure obtained thiols in yields of 50-55%.

Thiol esters have been prepared by the interaction of a thiol with the free acid. However, this is an equilibrium reaction and must be forced to completion and thus is not often used.

The reaction of an acid chloride with a thiol is the common procedure used for the preparation of thiol esters. Many investigators

(9,12,19) have reported the interaction of benzoyl chlorides with amine thiols yielding the thioesters quantitatively.

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}Cl + HS(CH_2)_2NR_2 \longrightarrow C_6H_5\text{-}\overset{O}{\overset{\|}{C}}S(CH_2)_2NR_2\cdot HCl$$

In the second procedure Hansen and Fosdick(20) reported the preparation of aryl thiol acids, in very high yields through the interaction of an aryl acid chloride with hydrogen sulfide in the presence of potassium hydroxide.

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}Cl \xrightarrow[H_2S,\ 0^0]{KOH} C_6H_5\text{-}\overset{O}{\overset{\|}{C}}SH$$

This is essentially the method used by other researchers(1, 13).

The corresponding β-chloroethyl thiobenzoates are prepared by the interaction of ethylene chlorobromide with the potassium salt of the thioesters.

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}SH \xrightarrow[EtOH]{KOH} C_6H_5\text{-}\overset{O}{\overset{\|}{C}}SK \xrightarrow[100^0\ (70\%)]{Br(CH_2)_2Cl} C_6H_5\text{-}\overset{O}{\overset{\|}{C}}S(CH_2)_2Cl$$

An alternate method for the preparation of these compounds in 75% yields was reported by Karjala and McElvain(19) and involved the reaction of an acid chloride with β-bromoethanethiol. However, this method involves the additional step of preparing the β-bromoethanethiol.

The final product can then be prepared by the reaction of the appropriate secondary amine with the bromo or chloro alkyl thiobenzoate. Yields of 80-85% are usually obtained.(1,13)

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}S(CH_2)_2Br + R_2NH \longrightarrow C_6H_5\text{-}\overset{O}{\overset{\|}{C}}S(CH_2)_2NR_2$$

DISCUSSION

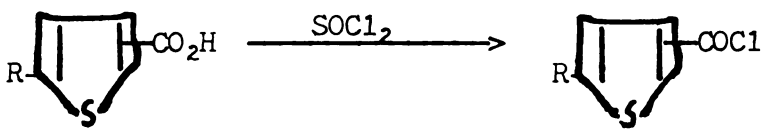
After consideration of the several methods available for the preparation of β-(N,N-dialkylamino) ethyl-2(or 3)-thiothenoate hydrochlorides, the following procedure was selected,

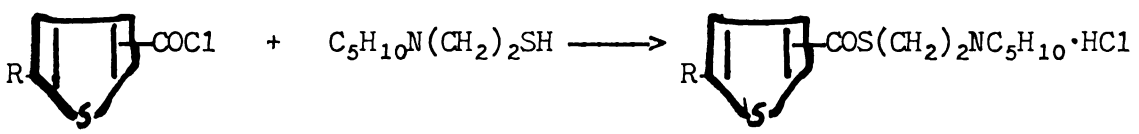
$$C_5H_{10}NH + Cl(CH_2)_2OH \xrightarrow{NaI} C_5H_{10}N(CH_2)_2OH$$

$$C_5H_{10}N(CH_2)_2OH \xrightarrow{SOCl_2} C_5H_{10}N(CH_2)_2Cl\cdot HCl$$

$$C_5H_{10}N(CH_2)_2Cl\cdot HCl \xrightarrow{(NH_2)_2C=S} C_5H_{10}N(CH_2)_2SC(=NH)NH_2\cdot 2HCl$$

$$C_5H_{10}N(CH_2)_2SC(=NH)NH_2\cdot 2HCl \xrightarrow{NaOH} C_5H_{10}N(CH_2)_2SH$$





This general sequence of reactions had the advantage of excellent yields, few side-reactions, and simple methods for purification of the products. Further an important consideration was that the difficult-to-prepare substituted thiophenes are used in the final reaction step thereby reducing the quantities of these intermediates needed, compared to procedures using them earlier in the reaction sequence.

The β-dialkylamino ethanols, in which the β-dialkylamino group was either β-diethylamino, β-dimethylamino, or β-piperidino, were prepared by the interaction of the corresponding secondary amine with ethylene chlorohydrin in absolute ethanol as the solvent, catalyzed by sodium iodide. The latter accelerated the reaction by replacing the organic chlorine with iodine. The molarratio of reactants employed was two of the amine to one of ethylene chlorohydrin, and the reaction time was approximately a day. The precipitate of secondary amine hydrochloride separated, in 80-90% yields, during the reaction. The free β-hydroxy compounds were obtained as colorless liquids by vacuum distillation.

The β-dialkylamino ethyl chloride hydrochlorides were obtained from the corresponding β-dialkylamino ethyl alcohols by means of the Darzens reaction using dry chloroform as the reaction solvent. Yields ranging from 90-95 percent were obtained by treating the β-dialkylamino ethyl alochols with a 25% excess of thionyl chloride with a reaction temperature maintained at 50-55°. The reaction was completed by holding the reaction mixture at its reflux temperature for an additional hour, during which the hydrochloride salt crystallized from the reaction medium. Less amorphous intractable material was formed if a current of dry nitrogen gas was swept across the reaction surface to remove the sulfur dioxide formed during the reaction.

The β-dialkylamino ethyl isothiouronium chlorides hydrochlorides were easily obtained from the corresponding β-dialkylamino ethyl chloride hydrochloride and thiourea by using the reagents in stoichiometric quantities. The reaction was completed in a day at the reflux temperature of the reaction mixture. Toward the end of the reaction period,

initial crystallization of the salt product from the reaction solution had started. Filtration of the cold reaction mixture gave the product in yields of 80 to 95 percent.

Treatment of an aqueous solution of the β-dialkylamino-ethyl isothiouronium chloride hydrochlorides with sodium hydroxide yielded the corresponding β-dialkylamino ethyl thiols. Yields of the thiols were improved by the addition of benzene to the salt solution prior to their treatment with base. The amine thiols were then purified either by distillation in vacuo of the free amine thiol or by the formation of its hydrochloride salt followed by recrystallization. In general, yields of 50 to 70 percent were obtainable.

The 2-bromo and 2,5-dibromo thiophenes were prepared by the reaction of thiophene with a half mole excess of bromine in glacial acetic acid as a solvent. The intermediate addition products formed in these reactions were dehydrohalogenated to the desired products by adding water to the reaction mixture and refluxing it with solid potassium hydroxide. The products were fractionally distilled at atmospheric pressure to obtain 70 to 75 percent yields based on the thiophene. The 3-bromo thiophene was obtained by adding directly to pure 2,5-dibromothiophene one mole of bromine to obtain the intermediate 2,3,5-tribromothiophene which was not isolated. The bromine atoms in the 2,5-positions were removed by spontaneous debromination with zinc dust. The product was steam distilled from the excess zinc and fractionally distilled to give 80 to 85 percent yields of a colorless product.

The 2-thenal was prepared by the interaction of a quarter mole excess of dimethylformamide with thiophene using phosphorous oxychloride

as a catalyst. The reaction was spontaneous and was complete in approximately an hour. The product was separated from the reaction mixture by steam distillation and distilled in vacuo to give an 81 percent yield of the aldehyde.

The acetylthiophene was prepared by the acylation of thiophene with acetic anhydride using orthophosphoric acid as a catalyst. A four-fold excess of thiophene was employed to act as the reaction solvent as well as a reactant. The product was distilled in vacuo giving excellent yields of a colorless product.

The alkylthiophenes, 2-methyl and 2-ethyl, were prepared by the Wolf Kishner reduction of 2-thenal and 2-acetylthiophene, respectively. In each case, a four-fold excess of 85% hydrazine hydrate was allowed to react with the carbonyl group in ethylene glycol as a reaction media. Excess water and hydrazine hydrate were removed by distillation. Potassium hydroxide pellets were added and the reaction mixture was heated to 90-100° at which temperature the reaction became spontaneous with the evolution of nitrogen. The product formed an immiscible liquid in the reaction flask. It was distilled at atomspheric pressure to give 70 to 80 percent yields of alkyl thiophenes.

The 2-t-butylthiophene was prepared by the alkylation of thiophene with t-butyl chloride using carbon disulfide as the reaction solvent and anhydrous stannic chloride as the catalyst. A 45% yield of this alkyl thiophene, free from isomers as shown by vapor phase chromatography, was obtained.

The preparation of 5-nitro-2-thenal was accomplished by the direct nitration of the aldehyde using fuming nitric acid dissolved in glacial acetic acid at 0°. The nitration mixture was diluted with water to

precipitate the product which after recrystallization gave a 90% yield of a light yellow colored solid product.

The thiophene derivative 5-chloro-2-acetylthiophene was prepared by the acetylation of 2-chloro thiophene with acetic anhydride using orthophosphoric acid as the catalyst. The product was prevented from crystallizing during purification by the addition of benzene to the reaction mixture. The product was distilled in vacuo to obtain a colorless liquid which solidified on cooling. Yields of approximately 70% of a colorless crystalline product were obtained.

The intermediate acids used in the investigation were prepared by four different methods depending on the availability of starting materials.

The acids, 2-thenoic and 5-bromo-2-thenoic, were obtained by the formation of Grignard reagents of the corresponding 2-bromo and 2,5-dibromothiophenes and subsequent carbonation of these with a dry ice-ether slurry. Employing normal isolation procedures the acids, in yields of 95-97%, were obtained as colorless crystalline solids.

The acids, 3-thenoic acid, and three additional derivatives of 2-thenoic, 5-methyl, 5-ethyl, and 5-t-butyl, were prepared by the formation of the lithium salt, by reaction of the alkyl thiophene with n-butyl lithium, and then carbonation of the salt with a dry ice-ether slurry. These acids were obtained as white crystalline solids in 85 to 90% yields, employing the usual isolation procedures.

The Haloform oxidation of 5-chloro-2-acetyl thiophene was employed to obtain 5-chloro-2-thenoic acid. A four-mole excess of sodium hypochloride was used. Excess oxidizing agent was destroyed with sodium bisulfite following completion of the reaction. The product was

recrystallized from hot water to give 98.5% yield of colorless product.

One additional acid, 5-nitro-2-thenoic acid, was prepared by the silver oxide oxidation of 5-nitro-2-thenal. The product was recrystallized from hot water to give a 51.9% yield of a light yellow colored crystalline product.

The thenoyl chlorides were prepared by the addition of a five-fold excess of thionyl chloride directly to the corresponding acid in the absence of a solvent. The pure acid chlorides were obtained in yields of 70 to 93 percent by distillation in vacuo.

The β-(N,N-dialkylamino) ethyl-5-substituted-2-thiothenoate hydrochlorides and the β-(N,N-dialkylamino) ethyl-2(or 3)-thiothenoate hydrochlorides were prepared by the same experimental procedure. An equal mole mixture of the amine thiol and the thenoyl chloride was heated in a sodium bicarbonate-benzene solution at 50° for a half hour. The hydrochloride salts were formed by the addition of anhydrous hydrogen chloride gas. The salts were purified by recrystallization from a chloroform-ether solution to obtain white crystalline products in yields of about 90%.

EXPERIMENTAL

2-Bromo Thiophene, C_4H_4SBr and 2,5-Dibromo Thiophene, BrC_4H_3SBr

Hartough's(21) experimental procedure was used to obtain these compounds. A solution containing 1007 g. (6.3 moles) of bromine dissolved in 1600 ml. of glacial acetic acid and precooled to 10° was added to a stirred solution of 336 g. (4.0 moles) of thiophene dissolved in 1600 ml. of glacial acetic acid and cooled to 10° in a five-liter three-necked flask fitted with a reflux condenser, stirrer, and a liter dropping funnel. The reaction mixture was allowed to warm to toom temperature and was stirred for an additional seven hours during which it took on a dark brown coloration. Bromine addition products were destroyed by adding 5 l. of water to the mixture. The organic layer was extracted with ether, washed with 10% sodium hydroxide until the wash solution showed a pH of 7, dried with anhydrous sodium sulfate, and the ether removed by distillation at atmospheric pressure. To the well-stirred residue, heated to 80°, in a three-liter three-necked flask fitted with a reflux condenser and stirrer, was added 200 g. of potassium hydroxide pellets during an hour. The reaction mixture was kept at its reflux temperature for nine hours, filtered, and dried over anhydrous sodium sulfate. The products were distilled using a 12" helices packed column to obtain 254 g. (1.56 moles) of colorless 2-bromo thiophene boiling at 149-152° (1 atm.) or 41° (12 mm.) and 333 g. (1.38 moles) of colorless 2,5-dibromo thiophene boiling at 209-213° (1 atm.) or 88° (12 mm.), a combined yield of 75% of the halothiophenes. Literature values(21), b.p. 149-152° (1 atm.) for 2-bromo thiophene; 210-212° (1 atm.) for 2,5-dibromo thiophene.

3-Bromo Thiophene, C_4H_3SBr

A 485.0 g. (2.0 moles) quantity of 2,5-dibromothiophene was placed in a liter three-necked flask fitted with a reflux condenser, dropping funnel, and stirrer. Bromine, 332.0 g. (2.08 moles), was added during an hour to the well-stirred 2,5-dibromothiophene, while chilling the reaction flask in an ice bath. Following the addition of the halogen the reaction mixture was stirred for two hours at room temperature and set aside overnight (16 hours). A basic solution containing 120.0 g. of potassium hydroxide dissolved in 250 ml. of methanol was added and the mixture was heated at its reflux temperature for three hours followed by exhaustive steam distillation. A yellow oil (approximately 615 g.) was separated from the distillate and transferred to a three-liter three-necked flask fitted with a reflux condenser and stirrer. To the oil was added 320 ml. of glacial acetic acid, 1200 ml. of water, and 185 g. of zinc dust. The addition of the zinc dust initiated a spontaneous reaction which held the reaction mixture at its reflux for 40 minutes. It was maintained at this temperature for an additional 18 hours and steam distilled using a 6-inch Vigreux column until the distillate temperature reached 102°. The organic layer was separated from the distillate, dried over anhydrous calcium chloride, and distilled at atmospheric pressure to obtain 284.6 g. (1.74 moles, 82.0%) of a product boiling at 155-160°, $n_D^{20} = 1.5915$. Literature values(22), b.p. 157-158°, $n_D^{20} = 1.5860$.

2-Thenal, C_4H_3SCH (O)

Basically, the method of Campaigne and Archer(23) was employed in the preparation of this material. A solution containing 252 g. (3.0

moles) of thiophene dissolved in 276 g. (3.84 moles) of dimethyl formamide and contained in a liter three-necked flask fitted with an Allihn condenser (protected by a calcium chloride tube), stirrer, and dropping funnel was cooled to 0°. To this well-stirred solution, 576 g. (3.72 moles) of phosphorous oxychloride were added, at 0°, during a half hour. The reaction was initiated, as evidenced by vigorous refluxing action, by heating it on a steam bath. When the initial reaction had subsided, the mixture was heated on a steam bath for an additional hour, during which time it took on a dark brown coloration. The stirred solution was cooled and poured onto 2.5 kg. of well-stirred ice contained in a beaker. It was neutralized with a saturated solution of sodium acetate to a pH of 5, (Hydrion paper) and exhaustively steam distilled. The organic layer was separated from the distillate, washed with 100 ml. of 10% sodium bicarbonate to a pH of 7, (Hydrion paper) dried over anhydrous sodium sulfate, and distilled <u>in vacuo</u> using a 12" helices packed column to obtain 273 g. (1.25 moles, 81%) of a colorless liquid boiling at 54° (3 mm.) or 65° (4 mm.). Literature values(23), b.p. 44-45° (1.1 mm.).

2-Acetyl Thiophene, $C_4H_3S\overset{\overset{O}{\|}}{C}CH_3$

The method of Hartough and Kosak(24) was used in the synthesis of this compound. A solution containing 1008 g. (12.0 moles) of thiophene dissolved in 468 g. (4.4 moles) of 95% acetic anhydride was heated to 70° in a three-necked three-liter flask fitted with reflux condenser, dropping funnel, stirrer, and thermometer. To this vigorously stirred solution, 40 g. of 85% orthophosphoric acid was added during a quarter of an hour. A modest temperature rise occurred at the start of the

addition of the orthophosphoric acid and external cooling of the reaction mixture was necessary towards the end of the addition of the catalyst to maintain the reaction temperature below 90°. The reaction solution was held at its reflux temperature, 96-97°, for two hours and then cooled to 50°. A volume of 800 ml. of water was added and the solution was stirred for another quarter of an hour. The organic layer was separated and washed with a 10% sodium carbonate solution until the wash water showed a pH of 10 to Hydrion paper, followed by washing with 800 ml. of water. The thiophene-water azeotrope was removed by distillation at 68°, followed by excess thiophene distilling at 84°. Vacuum distillation of the residue using a 12" helices packed column gave 480 g. (3.80 moles, 95%) of colorless 2-acetylthiophene boiling at 78° (2 mm.), $n_D^{20} = 1.5658$. Literature values(24), b.p. 77° (4 mm.), $n_D^{20} = 1.5666$.

5-Nitro-2-Thenal, $HCC_4H_3SNO_2$

The procedure developed by Buu-Hoi(25) was used to obtain this compound. During a half hour period a solution containing 59.4 g. of fuming nitric acid dissolved in 150 g. of glacial acetic acid was added drop-wise to a solution prepared by dissolving 78.0 g. (0.696 moles) of 2-thenal in 150 g. of acetic anhydride contained in a liter three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. The externally cooled mixture was stirred for two hours at 0°, after which 600 ml. of water was added, causing the immediate precipitation of a yellow solid. The precipitate was removed by filtering, washed thoroughly with water, air dried, and recrystallized from 95% ethanol to obtain 105.0 g. (0.63 moles, 90.2%) of light yellow colored crystalline product melting at 73-75°. Literature value(25), m.p. 77°.

5-Chloro-2-Acetylthiophene, $ClC_4H_2SC(=O)CH_3$

The procedure of Hartough and Conley(26) was used in the preparation of this compound. A mixture prepared from 355.5 g. (3.0 moles) of 2-chlorothiophene, 377 g. (3.5 moles) of 95% acetic anhydride, and 35 g. of orthophosphoric acid was placed in a three-liter three-necked flask equipped with a stirrer and two Allihn condensers. It was heated at its reflux temperature (130°) for three hours, during which the reaction solution initially darkened and finally turned black in color. After cooling to 50°, 500 ml. of water was added and the mixture was steam distilled to recover 72 g. of 2-chlorothiophene. A 100 ml. volume of benzene was added to the residue to prevent crystallization of the product while it was being further purified. The organic layer was separated and washed with 10% sodium carbonate solution until the wash water had a pH of 10 to Hydrion paper. It was then washed with 500 ml. of water, dried over anhydrous sodium sulfate, and the benzene was removed by distillation at atmospheric pressure. The residue was distilled <u>in vacuo</u> to obtain 351 g. (2.19 moles, 72.9%) of a colorless liquid boiling at 89-91° (4 mm.). This solidified on cooling, yielding a white crystalline material melting at 46-47°. Literature values (26), b.p. 88° (4 mm.), m.p. 46.5-47°.

2-Methyl Thiophene, $C_4H_3SCH_3$

The experimental procedure of King and Nord(27) was followed to obtain this compound. A solution containing 112 g. (1.0 mole) of 2-thenal, 200 ml. (4.0 moles) of 85% hydrazine hydrate and 800 ml. of ethylene glycol was stirred in a two-liter three-necked flask fitted

with a stirrer, thermometer (below liquid level), and a Vigreux column fitted with a distillation head. The reaction solution was heated to 185° to remove excess hydrazine and water. The residue was cooled to 40°, the Vigreux column was replaced by an Allihn condenser, 200 g. of potassium hydroxide pellets were added, and the strong alkaline mixture was heated until a vigorous evolution of nitrogen had been initiated (about 90°). The mixture was allowed to cool and set aside for 12 hours, after which it was heated at its reflux temperature for an hour. The reflux condenser was replaced by a Vigreux column and distilling head, and the distillate boiling up to 145° at atmospheric pressure was collected. This was extracted with several portions of ethyl ether, which were combined, washed with a 1:1 hydrochloric acid solution, and finally with water. The ether solution of the product was dried over anhydrous sodium sulfate and the ether was removed by distillation on a steam bath. The residue was distilled using a 12" helices packed column to obtain 69.7 g. (0.71 mole, 71%) of colorless 2-methyl thiophene boiling at 111° (1 atm.). Literature value(27), b.p. 112-113° (1 atm.).

2-Ethyl Thiophene, $C_4H_3SCH_2CH_3$

The experimental procedure of King and Nord(27) was employed to prepare this compound. A solution containing 126 g. (1.0 mole) of 2-acetyl thiophene, 200 ml. (4.0 moles) of 85% hydrazine hydrate and 800 ml. of ethylene glycol was stirred in a three-liter three-necked flask fitted with a stirrer, thermometer (below liquid level), and Vigreux column fitted with a distillation head. The reaction solution was heated at 130-160° to remove excess hydrazine and water. The

residue was cooled to 40°, the Vigreux column was replaced by an Allihn condenser, 200 g. of potassium hydroxide pellets were added, and the basic reaction mixture was heated until the evolution of nitrogen initiated (about 100°). The mixture was cooled and set aside for 12 hours, after which it was heated at its reflux temperature for two hours. The reflux condenser was replaced by a Vigreux column and distilling head, and the distillate boiling up to 160° at atmospheric pressure was collected. This was extracted with several portions of ethyl ether; these were combined, washed with a 1:1 hydrochloric acid solution and finally with water. After drying the ether solution over anhydrous sodium sulfate, the solvent was removed by distillation on a steam bath. The residue was distilled using a 12" helices packed column to obtain 91.5 g. (0.82 mole, 82%) of colorless 2-ethyl thiophene boiling at 132-135° (1 atm.). Literature value(28), b.p. 132-134° (1 atm.).

2-t-Butyl Thiophene, $C_4H_3SC(CH_3)_3$

The general procedure described by Sy, Buu-Hoi, and Xuong(29) was used for the preparation of this material. To an ice-cooled, well-stirred solution prepared by dissolving 112.0 g. (1.33 moles) of thiophene and 148 g. (1.6 moles) of t-butyl chloride in 2000 ml. of anhydrous carbon disulfide (dried over phosphorus pentoxide), and contained in a five-liter three-necked flask fitted with a calcium chloride drying tube, was added 418.0 g. (1.6 moles) of anhydrous stannic chloride during an hour. The orange-colored reaction mixture was maintained at room temperature for five hours, and then poured into 500 ml. of cold dilute hydrochloric acid. The organic layer was separated, washed first

with dilute aqueous sodium hydroxide, then with water, and dried over anhydrous calcium chloride. The carbon disulfide was removed by distillation on a warm water bath at atmospheric pressure. The residue was fractionated using a 12" helices packed column to obtain 84.2 g. (0.60 mole, 45.0%) of a colorless product boiling at 164.5-165.0° (1 atm.), refractive index n_D^{23} = 1.5020. The product was shown to be isomer free by vapor phase chromotography. Literature values(30), b.p. 165° (1 atm.) and n_D^{23} = 1.5024.

2-Thenoic Acid, $C_4H_3SCO_2H$

The general procedure of Gronowitz(31) was used for the preparation of this acid. To a suspension of 29.2 g. (1.2 moles) of magnesium shavings (activated by washing with an iodine-ether solution and then adding four or five drops of ethyl bromide) in 200 ml. of anhydrous ethyl ether contained in a two-liter three-necked flask equipped with a stirrer, a dropping funnel and a bulb condenser was added, at a rate sufficient to maintain the reaction mixture at its reflux temperature, a solution containing 194.4 g. (1.2 moles) of 2-bromo thiophene dissolved in 500 ml. of anhydrous ethyl ether. The reaction mixture was heated at its reflux temperature for an additional 2.5 hours, cooled to 0°, and then carbonated by pouring it, with stirring, into a slurry of 1.7 kg. of powdered dry ice and 900 ml. of anhydrous ethyl ether (31). The carbonation reaction yielded a substance, taffy-like in appearance, which turned to a hard brittle mass on standing. The excess dry ice was allowed to evaporate (approximately two hours) after which the reaction mass was carefully acidified with a 10% hydrochloric acid solution. The ether layer was separated and extracted with a 10%

potassium hydroxide solution. The basic extracts were combined, cooled to 0°, and acidified with a 1:1 hydrochloric acid solution to precipitate the crude product. This was recrystallized from hot water to obtain 149.3 g. (1.16 moles, 97.3%) of a white crystalline material melting at 129-130°. Literature value(26), m.p. 130°.

5-Bromo-2-Thenoic Acid, $BrC_4H_2SCO_2H$

The basic procedure of Gronowitz(31) was used to obtain this acid. To a suspension of 24.32 g. (1 mole) of magnesium shavings (activated by washing with an iodine-ether solution and then adding three drops of ethyl bromide) and 100 ml. of anhydrous ethyl ether contained in a liter three-necked flask fitted with a reflux condenser and drying tube, stirrer, and dropping funnel was added a solution prepared from 242.0 g. (1 mole) of 2,5-dibromothiophene and 100 ml. of anhydrous ethyl ether at a rate sufficient to maintain the reaction mixture at its reflux temperature. Following the addition of the dihalothiophene the reaction mixture was held at its reflux temperature for an additional two hours, cooled to 0°, and then carbonated by pouring it, with vigorous stirring, into a slurry of 1.5 kg. of powdered dry ice and 800 ml. of anhydrous ethyl ether contained in a three-liter beaker. When the excess dry ice had evaporated (approximately 1.5 hours) the reaction mixture was carefully acidified with 10% sulfuric acid. The product was isolated by extraction of the ether layer with 10% potassium hydroxide solution, followed by acidification of the basic extracts with dilute hydrochloric acid to precipitate the crude acid. After recrystallization of the crude acid from methanol, it gave 195.3 g. (0.94 moles, 94.3%) of a white crystalline product melting at 140-141°. Literature value(33), m.p. 142°.

n-Butyl Lithium, $CH_3(CH_2)_3Li$

Basically, the procedure of Mork(34) was used for the preparation of the lithium alkyl. A suspension of 6.8 g. (0.975 mole) of lithium metal (cut into fine slivers) and 100 ml. of anhydrous ethyl ether was placed in a 500 ml. three-necked flask equipped with a stirrer, a -100 to +30° thermometer (below liquid level), and a dropping funnel. A solution containing 61.6 g. (0.45 mole) of n-butyl bromide dissolved in 60 ml. of anhydrous ethyl ether was placed in the dropping funnel and about 10 ml. of this solution was added to the reaction flask. Stirring was initiated and in about 5 to 10 minutes the reaction mixture in the flask became cloudy and bright spots appeared on the lithium. The reaction temperature was lowered to -20° by immersion of the reaction flask in a dry ice-acetone bath and the remainder of the alkyl halide was added at a steady rate during approximately an hour, after which the mixture was stirred for an additional hour while the reaction temperature was allowed to gradually rise to +10°. The solution was cooled to -30° and filtered through a tygon tube fitted with a glass wool plug in one end directly into a flask and used immediately in the next reaction.

3-Thenoic Acid, $C_4H_3SCO_2H$

A solution of n-butyl lithium, prepared as previously described from 27.2 g. (3.92 moles) of lithium, 246.4 g. (1.80 moles) of n-butyl bromide, and 1050 ml. of anhydrous ethyl ether and contained in a two-liter three-necked flask fitted with a stirrer, a -100 to +30° thermometer (below liquid level) and a dropping funnel, was cooled to -70° by immersion of the reaction flask in a dry ice-acetone bath. A solution

containing 208.8 g. (1.28 moles) of 3-bromothiophene dissolved in 100 ml. of anhydrous ethyl ether was added to the lithium alkyl solution during 0.75 hr. while maintaining the reaction temperature at -70°. The solution was stirred for an additional 1.5 hrs. at -70° and then carbonated by pouring it, with vigorous stirring, into a slurry of 3.0 kg. of dry ice suspended in a liter of anhydrous ethyl ether contained in a four-liter beaker. The excess dry ice was allowed to evaporate (approximately 2 hrs.), after which the reaction mixture was carefully acidified with a 1:1 hydrochloric acid solution. The ether layer was separated and the product was isolated by extracting it with 10% potassium hydroxide, followed by acidification of the combined basic extracts with cold dilute hydrochloric acid to precipitate the acid. After recrystallization from hot water, it gave 160.0 g. (1.25 moles, 97.4%) of a very pale yellow crystalline product melting at 136-138°. Literature value(35) m.p. 138°.

5-Methyl-2-Thenoic Acid, $CH_3C_4H_2SCO_2H$

A solution of n-butyl lithium, prepared as described previously from 13.6 g. (1.96 moles) of lithium, 820 ml. of anhydrous ethyl ether, and 123.2 g. (0.90 mole) of n-butyl bromide, was placed in a liter three-necked flask fitted with a stirrer, a -100 to +30° thermometer (below liquid level) and a dropping funnel and cooled to -20° by immersion of the reaction flask in a dry ice-acetone bath. A solution containing 62.7 g. (0.64 mole) of 2-methyl thiophene dissolved in 100 ml. of anhydrous ethyl ether was added to the n-butyl lithium solution during a half hour, while keeping the reaction temperature below -20°. The solution was stirred for an additional hour while its temperature

was allowed to rise to 0° and then it was poured, with stirring, into a slurry of 750 g. of powdered dry ice and 400 ml. of anhydrous ethyl ether contained in a three-liter beaker. The excess dry ice was allowed to evaporate (approximately an hour) after which the reaction mixture was carefully acidified with a 1:1 hydrochloric acid solution. The ether layer was separated and the product was isolated by extraction of the latter with 10% potassium hydroxide, followed by acidification of the combined basic extracts with cold dilute hydrochloric acid. This precipitated the crude product which after recrystallization from hot water, gave 87.0 g. (0.61 mole, 95.5%) of a white crystalline product melting at 136-138°. Literature value(36) m.p. 138-138.5°.

5-Ethyl-2-Thenoic Acid, $CH_3CH_2C_4H_2SCO_2H$

The general procedure previously described for the preparation of 5-methyl-2-thenoic acid was employed to obtain this acid. The quantities of reactants used were: 13.6 g. (1.96 moles) of lithium, 123.2 g. (0.90 mole) of n-butyl bromide, 71.7g. (0.64 mole) of 2-ethyl thiophene, 1320 ml. of anhydrous ethyl ether, and 750 g. of powdered dry ice. Recrystallization of the crude product from hot water yielded 94.8 g. (0.61 mole, 95.0%) of a white crystalline product melting at 70-71°. Literature value(37), m.p. 71°.

5-t-Butyl-2-Thenoic Acid, $(CH_3)_3CC_4H_2SCO_2H$

The general procedure previously described for the preparation of 5-methyl-2-thenoic acid was employed to synthesize this acid. The quantities of reactants used were: 13.6 g. (1.96 moles) of lithium, 123.2 g. (0.90 mole) of n-butyl bromide, 93.4 g. (0.64 mole) of 2-t-butyl thiophene, 1320 ml. of anhydrous ethyl ether, and 750 g. of dry

ice. Recrystallization of the crude product from hot water yielded 100.7 g. (0.55 mole, 85.7%) of a white crystalline material melting at 126-128.5°. Literature value(36), m.p. 127-128°.

5-Chloro-2-Thenoic Acid, $ClC_4H_2SCO_2H$

The general procedure of Newman and Holmes(38) was used for the preparation of this heterocyclic. To a solution containing 218.0 g. (5.45 moles) of sodium hydroxide dissolved in 300 ml. of water and contained in a three-liter beaker was added 1250 g. of ice followed by chlorine gas until 161.0 g. (4.5 moles) of chlorine had been absorbed by the solution. The reaction flask was then supported in a clamp and fitted with a thermometer and stirrer. The solution was warmed to 55° and 80.5 g. (0.5 mole) of 5-chloro-2-acetylthiophene was added to the halogen saturated solution. The mixture was stirred vigorously and, when the exothermic reaction had been initiated, the reaction temperature was held between 60-70° for an hour by frequent cooling in an ice bath. Excess hypochlorite was destroyed by the addition of 50 g. of sodium bisulfite dissolved in 200 ml. of water. After cooling to room temperature, the reaction mixture was transferred to a four-liter beaker and carefully acidified with 200 ml. of concentrated hydrochloric acid. The crude colorless product was collected by filtration on a Buchner funnel, washed with cold water, and recrystallized from hot water to obtain 80.0 g. (0.49 mole, 98.5%) of a colorless product melting at 145-146°. Literature value(39), m.p. 146-147°.

5-Nitro-2-Thenoic Acid, $NO_2C_4H_2SCO_2H$

The experimental procedure described by Schuetz and Teller(40) was

used to obtain this acid. A 47.0 g. (0.30 mole) quantity of 5-nitro-2-thenal was suspended in a solution prepared from 102.0 g. (0.60 mole) of silver nitrate dissolved in a mixture of 1000 ml. of water and 500 mol. of 95% ethanol contained in a five-liter three-necked flask fitted with a stirrer, reflux condenser, thermometer and dropping funnel. The vigorously stirred reaction mixture was warmed to 45° and an alkaline solution containing 48.0 g. of sodium hydroxide dissolved in 600 ml. of water was added drop-wise at a rate sufficient to maintain the reaction temperature in the range 45-50°. The addition of base required an hour, after which the reaction mixture was stirred at 50° for a quarter of an hour, cooled to room temperature by immersion of the reaction flask in an ice bath, and filtered to remove metallic silver. After washing the silver with hot water, the combined filtrates and washings were evaporated in a rotary evaporator to remove ethanol and reduce the volume of the filtrate to approximately a liter. A 500 ml. volume of ethyl ether was added and the stirred mixture was carefully acidified with concentrated hydrochloric acid. The ether layer was separated. The aqueous layer was extracted with ethyl ether and the combined ether extracts and initial ether phase were dried over anhydrous magnesium sulfate. Evaporation of the ether gave 28 g. of a yellow solid. Recrystallization of this solid from hot water yielded 27 g. (0.16 mole, 51.9%) of a light yellow crystalline product melting at 157-158°. Literature value(41), m.p. 158°.

Thenoyl Chlorides

The thenoyl chlorides used in this study were prepared from the corresponding acids by reaction with thionyl chloride. A typical procedure is described.

5-Chloro-2-Thenoyl Chloride, $ClC_4H_2S\overset{O}{\overset{\|}{C}}Cl$

During an hour period, 327.0 g. (2.75 moles) of thionyl chloride was added to 80.0 g. (0493 mole) of 5-chloro-2-thenoic acid contained in a 500 ml. round bottom flask fitted with a reflux condenser. The reaction solution was held at its reflux temperature for an hour on a steam bath. Excess thionyl chloride was removed by distillation at atmospheric pressure and the residue was distilled in vacuo using a 12" helices packed column to obtain 75.6 g. (0.42 mole, 84.8%) of a light yellow liquid boiling at 97-98° (11 mm.). Literature value(42), b.p. 103° (15 mm.).

The thenoyl chlorides prepared in this investigation, together with their boiling points, melting points, yields, and literature references, are summarized in Table 1.

β-Piperidinoethyl Alcohol, $C_5H_{10}N(CH_2)_2OH$

The procedure of Clinton et al.(9) was used to obtain this amine alcohol. A mixture containing 302.0 g. (3.55 moles) of piperidine, 143.0 g. (1.78 moles) of ethylene chlorohydrin, 13.7 g. (0.091 mole) of sodium iodide, and 366 ml. of absolute ethanol was placed in a liter three-necked flask fitted with a stirrer and reflux condenser and heated at its reflux temperature for a day. At the end of the initial hour of heating the piperidine hydrochloride began to precipitate. After cooling to room temperature, the reaction mixture was treated with a solution prepared by dissolving 41 g. (1.78 moles) of sodium metal in 685 ml. of absolute ethanol. The precipitate of inorganic salts was removed by filtration and washed with three 50-ml.

Table I. Preparation and Properties of the Thenoyl Chlorides

Thenoyl Chloride	Yield %	b.p. °C	m.p. °C	Reference
2-Thenoyl Chloride	80.4	72 (5 mm.)	--	42
3-Thenoyl Chloride	78.0	111 (36 mm.)	51.5-52	35
5-Bromo-2-Thenoyl Chloride	71.3	127 (14 mm.)	40 -42	33
5-Chloro-2-Thenoyl Chloride	84.8	97 (11 mm.)	--	33
5-Methyl-2-Thenoyl Chloride	91.5	98-99 (8 mm.)	--	33
5-t-Butyl-2-Thenoyl Chloride	85.3	135 (16 mm.)	--	29
5-Ethyl-2-Thenoyl Chloride	93.7	101 (3 mm.)	--	43
5-Nitro-2-Thenoyl Chloride	90.3	107-109 (2 mm.)	52 -53	41

portions of anhydrous ethyl ether. The combined filtrate and washings were distilled until a temperature of 110° was reached in the column head to remove ether, alcohol, and unreacted piperidine. A 300 ml. volume of anhydrous ethyl ether was used to dissolve the residue and the solution was filtered to remove any remaining inorganic salts. The ether was removed on a steam bath and the residue was distilled using a 12" helices packed column to obtain 210.3 g. (1.63 moles, 91.8%) of a colorless product boiling at 90° (18 mm.). Literature value(44), b.p. 89-91° (20 mm.).

β-Diethylaminoethyl Alcohol, $(CH_3CH_2)_2N(CH_2)_2OH$

This alkanolamine was prepared using the procedure described for the synthesis of β-piperidinoethyl alcohol. A stirred mixture containing 134 ml. (2 moles) of ethylene chlorohydrin, 413 ml. (4.0 moles) of diethyl amine, 412 ml. of absolute ethanol, and 15.5 (0.1 mole) of sodium iodide was heated at its reflux temperature for a day in a three-liter, three-necked flask equipped with a reflux condenser and stirrer. The reaction solution was cooled and treated with a basic solution prepared by dissolving 46.0 g. (2.01 moles) of sodium metal in 770 ml. of absolute ethanol. The precipitated inorganic salts were removed by filtration and washed with two 50-ml. portions of dry ether. The combined filtrate and washings were distilled at atmospheric pressure to remove the ether, alcohol, and unreacted diethyl amine. The residue was distilled <u>in vacuo</u> using a 12" helices packed column to give 175.4 g. (1.5 moles, 75.0%) of a colorless product boiling 55-58° (10-11 mm.) or 160° (1 atm.); refractive index $n_D^{25} = 1.4390$. Literature values(9,45), b.p. 160-161° (1 atm.).

β-Dimethylaminoethyl Alcohol, $(CH_3)_2N(CH_2)_2OH$

Following the procedure for preparing alkanol amines described above, a well-stirred mixture containing 134 ml. (2 moles) of ethylene chlorohydrin, 180 g. (4 moles) of dimethyl amine, 412 ml. of absolute ethanol, and 15.5 g. (0.1 mole) of sodium iodide contained in a three-liter three-necked flask fitted with a reflux condenser and stirrer was heated at its reflux temperature for a day. The crude product was isolated as already described and distilled to obtain 160 g. (1.8 moles, 90.0%) of a clear colorless product boiling at 135-136° (1 atm.). Literature value(46), b.p. 135° (1 atm.).

β-Piperidinoethyl Chloride Hydrochloride, $C_5H_{10}NCH_2CH_2Cl \cdot HCl$

The basic procedure of Mason and Block(15) was used for the preparation of this material. In a liter three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 100 g. (0.78 mole) of β-piperidinoethyl alcohol and 200 ml. of dry chloroform. A stream of dry nitrogen was passed through the reaction flask to remove sulfur dioxide formed during the reaction. To the reaction flask was added a solution of 110.9 g. (0.93 mole) of thionyl chloride dissolved in 154 ml. of dry chloroform at a rate sufficient to maintain the reaction temperature in the range 50-55°. The reaction mixture was heated at its reflux temperature for an hour and on cooling to room temperature, a crystalline solid separated from solution. This was collected on a filter and washed with anhydrous ethyl ether. The combined ether washings and filtrate were evaporated to a quarter of its original volume and, on cooling, a second quantity of crystals was obtained. These were combined with the original crystalline material

and recrystallized from absolute ethanol, using Norit A to remove colored material. The light tan crystalline product, after washing with ether and drying, weighed 137.0 g. (0.75 mole, 96.7%) and melted at 206.5-208.5°. Literature value(47), m.p. 208°.

β-Diethylaminoethyl Chloride Hydrochloride, $(CH_3CH_2)_2N(CH_2)_2Cl \cdot HCl$

The procedure described above was used to obtain this hydrochloride salt. A solution prepared from 150 g. (1.28 moles) of β-diethylaminoethyl alcohol and 250 ml. of dry chloroform was placed in a liter three-necked flask equipped with a reflux condenser, stirrer, dropping funnel, and a dry nitrogen tube to permit passing gas over the surface of the solution to remove the sulfur dioxide formed during the reaction. The reaction mixture was heated to 40° and a solution containing 128 ml. (1.76 moles) of thionyl chloride dissolved in 150 ml. of dry chloroform was added at a rate sufficient to maintain the reaction temperature in the range 50 to 55°. Following the addition of the thionyl chloride the mixture was held at its reflux temperature for an hour. On cooling the reaction mixture a precipitate formed which was recovered by filtration and recrystallized from absolute ethanol to obtain 120 g. (0.70 mole, 56.0%) of a white crystalline product melting at 204°. Literature value(11), m.p. 205°.

β-Dimethylaminoethyl Chloride Hydrochloride, $(CH_3)_2N(CH_2)_2Cl \cdot HCl$

The identical procedure and apparatus used for the preparation of β-diethylaminoethyl chloride hydrochloride was employed in the preparation of this amine hydrochloride. The quantities of reactants used were; 113.0 g. (1.28 moles) of β-dimethylaminoethyl alcohol dissolved

in 250 ml. of dry chloroform and 128 ml. (1.76 moles) of thionyl chloride contained in 150 ml. of dry chloroform. Isolation of the product was accomplished as previously described and recrystallization of the crude product from absolute ethanol gave 139.0 g. (0.96 mole, 75.0%) of a white crystalline material melting at 181°. Literature value(48), m.p. 182°.

β-Piperidinoethyl Isothiouronium Chloride Hydrochloride,

$$C_5H_{10}NCH_2CH_2S\overset{\overset{NH}{\|}}{C}NH_2 \cdot 2HCl$$

The general procedure of Albertson and Clinton(11) was used to obtain this compound. A mixture of 90.0 g. (0.49 mole) of β-piperidinoethyl chloride hydrochloride, 37.4 g. (0.49 mole) of thiourea, and 300 ml. of absolute ethanol contained in a liter one-necked flask fitted with a reflux condenser was held at its reflux temperature for a day. The resulting clear solution was cooled to 0°, and a 300 ml. volume of anhydrous ethyl ether was added to precipitate the product. The latter was collected on a filter, washed with anhydrous ethyl ether, and dried to obtain 107.3 g. (0.48 mole, 94.7%) of a white crystalline product melting at 225-226°. Literature value(48), m.p. 225-225.5°.

β-Piperidinoethyl Thiol, $C_5H_{10}NCH_2CH_2SH$

Albertson's and Clinton's(11) general procedure was used to obtain this mercaptan. To a suspension of 90.0 g. (0.40 mole) of β-piperidinoethyl isothiouronium chloride hydrochloride in 100 ml. of water and contained in a liter separatory funnel was added 100 ml. of benzene and a preheated solution of 28.8 g. (0.72 mole) of sodium

hydroxide dissolved in 75 ml. of water. The benzene layer immediately took on a pink coloration. The mixture was saturated with salt and the organic layer was separated. The aqueous layer was extracted with two 50-ml. portions of benzene. The organic layer and the benzene extracts were combined, dried over anhydrous sodium sulfate, and the benzene was removed by distillation through a 12" helices packed column at atmospheric pressure. The residual crude oily product was distilled *in vacuo* to obtain 40.3 g. (0.276 mole, 69%) of a colorless product boiling at 85° (11 mm.) or 95° (14 mm.) and having a refractive index of n_D^{25} = 1.4975. Literature values(48), b.p. 85° (11 mm.) and n_D^{25} = 1.4995.

β-Diethylaminoethylthiol Hydrochloride, $(CH_3CH_2)_2N(CH_2)_2SH \cdot HCl$

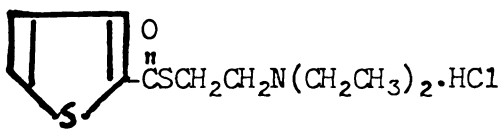
The procedure of Clinton *et al.*(46) was used to synthesize this material. A solution prepared from 39.2 g. (0.52 mole) of thiourea and 125 ml. of absolute ethanol and contained in a liter single necked flask fitted with a reflux condenser was heated to its reflux temperature. To this hot solution was added, during a period of a half hour, a second solution containing 88.1 g. (0.52 mole) of β-diethylaminoethyl chloride hydrochloride dissolved in 250 ml. of absolute ethanol. The reaction mixture was held at its reflux temperature for a day, cooled, and diluted with a mixture of 500 ml. of ethyl acetate and 125 ml. of ligroin, to precipitate the product. This was recovered by filtration and air dried. The crude isothiouronium salt was dissolved in 200 ml. of water, and a warm solution containing 32.5 g. (0.81 mole) of sodium hydroxide dissolved in 120 ml. of water was added to it, causing a pink oily upper layer to separate from the aqueous solution.

The mixture was saturated with salt and extracted with three 75-ml. portions of ether. These were combined, dried over anhydrous sodium sulfate and treated with anhydrous hydrogen chloride gas to precipitate the impure product. The crude precipitate was recovered by filtration and recrystallized from a 1:1 absolute ethanol-ligroin mixture to obtain 56.0 g. (0.33 mole, 63.5%) of a white crystalline product melting at 170-172°. Literature value(48), m.p. 172-173°.

β-Dimethylaminoethylthiol Hydrochloride, $(CH_3)_2N(CH_2)_2SH.HCl$

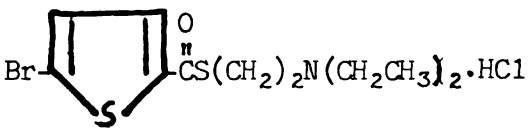
The procedure and apparatus employed for the preparation of β-diethylaminoethylthiol hydrochloride was again used for the synthesis of this amino mercaptan. A solution containing 39.2 g. (0.52 mole)of thiourea, 75.0 g. (0.52 mole) of β-dimethylaminoethyl chloride hydrochloride and 375 ml. of absolute ethanol was heated at its reflux temperature for a day. The isothiouronium salt was precipitated from the reaction media by the addition of a mixture of 500 ml. of ethyl acetate and 125 ml. of ligroin. The crude precipitate was air dried and then dissolved in 200 ml. of water. To this solution was added 32.5 g. (0.81 mole) of sodium hydroxide dissolved in 170 ml. of water. Following ether extraction of the solution by the usual procedure, the organic layer was dried over anhydrous sodium sulfate and treated with anhydrous gaseous hydrogen chloride to precipitate the crude product. The resulting precipitate was recrystallized from absolute ethanol to obtain 42.5 g. (0.30 mole, 58.0%) of a white crystalline product melting at 156°. Literature value(49), m.p. 157°.

β-(N,N-Diethylamino) Ethyl-2-Thiothenoate Hydrochloride,



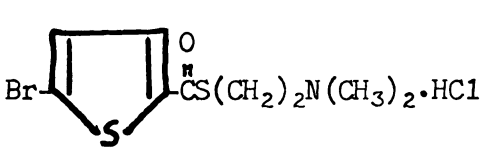
To a mixture prepared from 100 ml. of 10% sodium bicarbonate and 70 ml. of benzene and contained in a 300 ml. round bottom flask fitted with a reflux condenser was added 8.1 g. (0.048 mole) of β-diethylaminoethanethiol hydrochloride and 7.0 g. (0.048 mole) of 2-thenoyl chloride. A white precipitate formed immediately but redissolved on neutralization of the hydrogen chloride with bicarbonate. The reaction mixture was heated at 50° for a half hour and was shaken every five minutes during this period. It was then cooled to room temperature and the organic layer separated. The aqueous layer was extracted with 25-ml. of benzene. The organic layer and the benzene extract were combined, washed with water, and dried thoroughly over anhydrous magnesium sulfate. The dry stirred solution was chilled, diluted with 50 ml. of anhydrous ethyl ether, and treated with a moderate stream of anhydrous hydrogen chloride until no further precipitation of the amine hydrochloride occurred. The bulky hydrochloride precipitate was collected on a sintered glass funnel and washed with anhydrous ethyl ether. The filtrate was treated again with hydrogen chloride gas to complete the precipitation of the amine hydrochloride. The additional salt precipitate was collected and washed with anhydrous ethyl ether. The combined crude hydrochloride precipitates were recrystallized from a dry 1:1 chloroform-anhydrous ethyl ether solution, washed with anhydrous ethyl ether, and dried to obtain 12.90 g. (0.046 mole, 96.6%)

β-(N,N-Diethylamino) Ethyl-5-Bromo-2-Thiothenoate Hydrochloride,

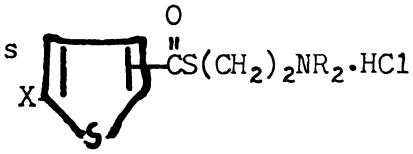


A reaction mixture containing 6.8 g. (0.040 mole) of β-diethylaminoethanethiol hydrochloride, 9.0 g. (0.040 mole) of 5-bromo-2-thenoyl chloride, 100 ml. of 10% sodium bicarbonate, and 70 ml. of benzene was heated at 50° for a half hour and then cooled to room temperature. The benzene layer was separated, dried, diluted with 50 ml. of anhydrous ethyl ether, and treated with anhydrous hydrogen chloride gas to precipitate the product as the hydrochloride salt. The crude product following recrystallization gave 10.7 g. (0.030 mole, 74.9%) of a white crystalline product melting at 200.0°. Analysis of this material for carbon, hydrogen, sulfur, nitrogen, and halogen gave;
Calc'd for $C_{11}H_{17}S_2ONClBr$: C, 36.83; H, 4.78; S, 17.88; N, 3.90; X, 32.16.
Found: C, 37.15; H, 4.86; S, 17.72; N, 4.01; X, 31.81.
The molecular weight determinations of this salt gave,
Calc'd: 358.8 g.. Found: 358.2 g.

β-(N,N-Dimethylamino) Ethyl-5-Bromo-2-Thiothenoate Hydrochloride,



Utilizing the experimental procedure described previously for the preparation of thioester amine salts 8.8 g. (0.062 mole) of β-dimethyl-

Table II. Properties and Analysis of β-(N,N-Dialkylamino) Ethyl Thiothenoate Hydrochlorides 

X	Position	NR_2	Formula	m.p. °C[b]	Analysis[a] %C Calc'd	%C Found	%H Calc'd	%H Found	%S Calc'd	%S Found	%N Calc'd	%N Found	%X Calc'd	%X Found
H	2	DiEt	$C_{11}H_{18}S_2ONCl$	150.5	47.21	47.00	6.48	6.61	22.92	23.00	5.01	4.77	12.67	12.57
H	3	DiEt	$C_{11}H_{18}S_2ONCl$	150.0-150.5	47.21	47.04	6.48	6.38	22.92	22.93	5.01	4.95	12.67	12.74
H	2	DiMe	$C_9H_{14}S_2ONCl$	164.5	42.93	42.76	5.60	5.53	25.47	25.70	5.56	5.39	14.08	14.16
H	3	DiMe	$C_9H_{14}S_2ONCl$	165.0-166.0	42.93	42.83	5.60	5.54	25.47	25.69	5.56	5.43	14.08	14.13
t-Bu	2	DiEt	$C_{15}H_{26}S_2ONCl$	158.0-158.5	53.63	53.45	7.80	7.87	19.09	19.35	4.17	4.13	10.55	10.44
t-Bu	2	DiMe	$C_{13}H_{22}S_2ONCl$	168.0-168.5	50.71	50.92	7.20	7.23	20.83	20.73	4.55	4.40	11.52	11.50
Et	2	DiEt	$C_{13}H_{22}S_2ONCl$	161.0-161.5	50.71	50.78	7.20	7.18	20.83	20.87	4.55	4.44	11.52	11.47
Et	2	DiMe	$C_{11}H_{18}S_2ONCl$	142.0-142.5	47.21	47.27	6.48	6.56	22.92	22.80	5.01	5.01	12.67	12.63
Br	2	DiEt	$C_{11}H_{17}S_2ONClBr$	200.0	36.83	37.15	4.78	4.86	17.88	17.72	3.90	4.01	32.15	31.81
Br	2	DiMe	$C_9H_{13}S_2ONClBr$	219.0-220.0	32.64	32.71	3.96	3.97	19.39	19.30	4.24	4.20	34.88	34.78
Cl	2	DiEt	$C_{11}H_{17}S_2ONCl_2$	179.0	42.04	41.99	5.45	5.40	20.40	20.12	4.46	4.43	22.56	22.44
Cl	2	DiMe	$C_9H_{13}S_2ONCl_2$	197.5-198.0	37.76	37.83	4.58	4.51	22.40	22.36	4.89	4.89	24.77	24.64
Me	2	DiEt	$C_{12}H_{20}S_2ONCl$	150.0	49.04	48.86	6.86	6.98	21.82	21.59	4.77	4.51	12.06	11.87
Me	2	DiMe	$C_{10}H_{16}S_2ONCl$	171.0	45.18	45.40	6.07	6.02	24.12	24.06	5.27	4.99	13.34	13.17
H	2	Pip[c]	$C_{12}H_{18}S_2ONCl$	201.0	49.38	49.37	6.22	6.27	21.97	22.06	4.80	4.79	12.15	12.22
H	3	Pip	$C_{12}H_{18}S_2ONCl$	187.5	49.38	49.10	6.22	6.03	21.97	21.97	4.80	4.84	12.15	12.01
Me	2	Pip	$C_{13}H_{20}S_2ONCl$	220.0	51.04	51.22	6.59	6.53	20.97	20.72	4.58	4.31	11.59	11.50
t-Bu	2	Pip	$C_{16}H_{26}S_2ONCl$	194-195	55.23	55.03	7.53	7.51	18.43	18.71	4.03	4.13	10.19	10.14
Cl	2	Pip	$C_{12}H_{17}S_2ONCl_2$	221.5-222.0	44.17	44.31	5.25	5.26	19.65	19.40	4.29	4.32	21.73	21.51

a. All analysis were done by Micro-Tech Laboratories, Skokie, Illinois.

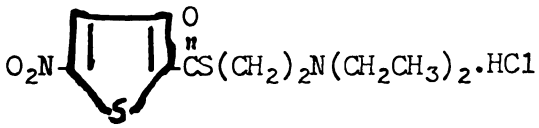
b. All melting points are uncorrected.

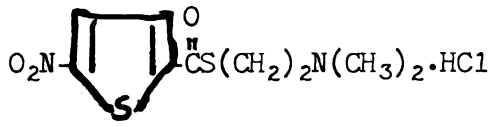
c. Pip = piperidine.

Attempted Preparation of

β-(N,N-Diethylamino) Ethyl-5-Nitro-2-Thiothenoate Hydrochloride and

β-(N,N-Dimethylamino) Ethyl-5-Nitro-2-Thiothenoate Hydrochloride,





Attempts to prepare these thioester amines were made following the general procedure already described in detail for synthesising similar compounds. Stoichiometric quantities of β-dialkylaminoethanethiol hydrochloride and 5-nitro-2-thenoyl chloride were mixed with 50 ml. of benzene and 150 ml. of 10% sodium bicarbonate. Almost immediately black tarry materials formed in the reaction mixture and all attempts at product isolation were without success. This reaction was repeated, using the same quantities of reactants, but at a reaction temperature of 0^{0}, and again the result was the same, only tars being obtainable. The reaction was run a third and fourth time with a higher dilution (500 ml. of benzene) and with anhydrous ethyl ether and dry pentane substituted for the benzene, but again only non-retractable tars resulted. The tarry material, which very probably is polymeric in nature, may be produced due to resonance of the thioester carbonyl oxygen with the nitro group through the thiophene ring. This may form ionic species which could polymerize to yield the high molecular weight polymeric material.

ANALYSIS

Molecular Weight Determinations

The molecular weight determinations of the thioester amine hydrochlorides were carried out by conductiometric titrations. These measurements were performed by determining the resistance of the hydrochloride solution using a 60 cycle Sefrass conductance bridge with the cell compensator set at one. A weighed sample of the salt (150-200 mg.) was dissolved, diluted with 75 ml. of distilled water and titrated with 0.0690 N. sodium hydroxide under vigorous stirring. The resistance was recorded following the addition of each milliliter of base. The results were plotted; milliliters of base added on the abscissa and $1/R\ (\frac{V_a+V_b}{V_a})$ on the ordinate. The term, $(\frac{V_a+V_b}{V_a})$, is the correction factor for the volume change due to the addition of the base. Since equivalent conductance (mobility) of the amine hydrochloride is very low, almost constant resistance is obtained until the equivalence point is reached. Here, excess hydroxyl and sodium ions cause a sharp decrease in resistance due to their greater mobility compared to the amine hydrochloride. Since the resistance curve obtained is round near the equivalence point, the end point was taken as the intersection of the best straight line preceeding the equivalence point with the best straight line following the equivalence point(50). The milliliters of base at the end point is the amount required to neutralize the hydrochloride portion of the amine hydrochloride salt and therefore was used to calculate the equivalent weight of the compound which, in this case, corresponds to its molecular weight.

SUMMARY

1. Three β-(N,N-dialkylamino) ethyl-3-thiothenoates were prepared for the first time and some of their physical properties were determined.
2. Three β-(N,N-dialkylamino) ethyl-2-thiothenoates were synthesized for the first time and some of their physical properties were investigated.
3. Thirteen previously unreported β-(N,N-dialkylamino) ethyl-5-substituted-3-thiothenoates were prepared and some of their physical properties were determined.

REFERENCES

1. A. Einhorn and E. Uhlfelder, Ann., 371, 131 (1909).

2. F. L. Pyman, J. Chem. Soc., 93, 1793 (1908).

3. H. Erdtman and N. Lofgren, Svensk. Kem. Tid., 49, 163 (1937); Chem. Abstr., 31, 7854^{8} (1937).

4. Y. K. Nolle, Farm. i. Farmakol (USSR)., (1937); Chem. Abstr., 34, 3820^{5} (1940).

5. E. Campaign and W. M. LeSeur, J. Am. Chem. Soc., 69, 333 (1947).

6. E. Campaign and W. M. LeSeur, ibid., 70, 3498 (1948).

7. W. H. Houff and R. D. Schuetz, J. Org. Chem., 18, 916 (1953).

8. K. Koller, Wien. Med. Wochenschr., 34, 1271 (1864).

9. R. O. Clinton, U. J. Salvador and S. C. Laskowski, J. Am. Chem. Soc., 71, 3366 (1949).

10. F. P. Luduena, R. O. Clinton and S. C. Laskowski, Science, 118, 138 (1953).

11. N. F. Albertson, and R. O. Clinton, J. Am. Chem. Soc., 67, 1222 (1945).

12. R. O. Clinton, U. J. Salvador and S. C. Laskowski, ibid., 76, 5121 (1954).

13. S. I. Sergievskaya and K. P. Preobrazhenskaya, J. Gen. Chem. (USSR), 10, 950 (1940); Chem. Abstr., 35, 4003 (1941).

14. W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreyer and R. Adams, J. Am. Chem. Soc., 59, 2248 (1937).

15. J. P. Mason and H. W. Block, ibid., 62, 1443 (1940).

16. R. R. Adams and F. C. Whitmore, ibid., 67, 735 (1945).

17. H. Staudinger and H. Freudenberger, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 573.

18. G. M. Bennett, J. Chem. Soc., 119, 418 (1921).

19. S. A. Karjala and S. M. McElvain, J. Am. Chem. Soc., 55, 2966 (1933).

20. H. L. Hansen and L. S. Fosdick, ibid., 55, 2872 (1933).

21. H. D. Hartough, "The Chemistry of Heterocyclic Compounds," Volume III, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N.Y., 1952, p. 498.

22. W. Steinkopf, Ann., 543, 128 (1940).

23. E. Campaigne and W. L. Archer, J. Am. Chem. Soc., 75, 989 (1953).

24. H. D. Hartough and A. I. Kosak, ibid., 69, 3093 (1947).

25. Ng. Ph. Buu-Hoi and O. Lavit, J. Chem. Soc., 1721 (1958).

26. H. D. Hartough and L. G. Conley, J. Am. Chem. Soc., 69, 3096 (1947).

27. W. J. King and F. F. Nord, J. Org. Chem., 13, 635 (1948).

28. W. J. King and F. F. Nord, ibid., 14, 638 (1949).

29. M. Sy, Ng. Ph. Buu-Hoi and N. D. Xuong, J. Chem. Soc., 1975 (1954).

30. C. J. Jacobs and G. S. Parks, J. Am. Chem. Soc., 56, 1513 (1934).

31. S. Gronowitz, Arkiv f. Kemi., 7, 267 (1954).

32. A. S. Hussey, J. Am. Chem. Soc., 73, 1364 (1951).

33. Ng. Ph. Buu-Hoi and N. Hoan, Rec. Trav. Chim., 68, 5 (1949).

34. H. Mork, unpublished papers.

35. E. Campaigne and W. M. LeSuer, J. Am. Chem. Soc., 70, 1555 (1948).

36. J. W. Schick and H. D. Hartough, ibid., 70, 1645 (1948).

37. E. Schleicher, Ber., 18, 3015 (1885).

38. M. S. Newman and H. L. Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 428.

39. J. F. Bunnett, D. M. Bachman, L. P. Snipper and J. H. Maloney, J. Am. Chem. Soc., 71, 1493 (1949).

40. D. M. Teller, Ph. D. Thesis, M.S.U., 21 (1959).

41. O. Dann, Ber., 76, 419 (1943).

42. M. C. Ford and D. Mackay, J. Chem. Soc., 4620 (1957).

43. J. Shea, unpublished papers.

44. O. A. Barnes and R. Adams, J. Am. Chem. Soc., 49, 1307 (1927).

45. F. Fenwich and E. Gilman, J. Biol. Chem., 84, 605 (1929).

46. L. Knorr and H. Matthes, Ber., 34, 3483 (1901).

47. L. Knorr, H. Horlein and P. Roth, Ber., 38, 3136 (1905).

48. R. O. Clinton, U. J. Salvador, S. C. Laskowski and C. M. Suter, J. Am. Chem. Soc., 70, 950 (1948).

49. F. Y. Rachinskii, N. M. Slavachevskaga and D. V. Soffe, Zhur. Obshchei Khim., 28, 2998 (1958); Chem. Abstr., 53, 9045f (1959).

50. G. W. Ewing, "Instrumental Methods of Chemical Analysis," McGraw-Hill Book Company, Inc., New York, N.Y., 1960, p. 248.