CARBONYL DERIVATIVES OF THIOPHENE

PART I - THE REFORMATSKY REACTION

PART II - THE SCHMIDT REACTION

By

William H. Houff

A THESIS

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1955

ACKNOWLEDGMENT

The author wishes to express his appreciation to Doctor Robert D. Schuetz for his friendly counsel throughout the course of this investigation.

He is also indebted to his wife, Donna, for her sympathetic understanding which helped to make possible the completion of this thesis.

VITA

William Harper Houff

Candidate for the degree of

Doctor of Philosophy

Major Subject: Organic Chemistry

Minor Subjects: Analytical and Biological Chemistry

Biographical Data:

Date of Birth: April 27, 1928 in New Hope, Virginia

Education:

B. S. in Chemistry, The College of William and Mary, 1950
M. S. in Organic Chemistry, Michigan State College, 1952
Additional Graduate Study, Michigan State College, 1955

Experience:

Graduate Assistant, Michigan State College, 1950-1952
Research Chemist, Michigan State College, 1952-1953
Research Chemist, Renite Plastics, Inc., 1953-1954
Director of Research, Tylene Plastics, Inc., 1954-Present

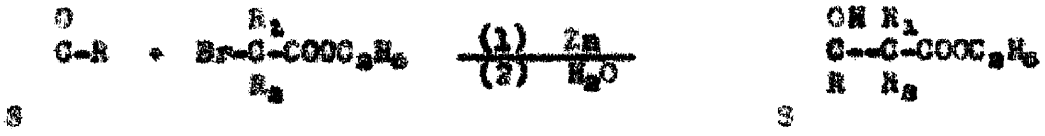
Professional Affiliations:

American Chemical Society
The Society of Sigma Xi

ABSTRACT

PART I

The Reformatsky reaction between 2 and 3-thienyl aldehydes, and the 2 and 3-thienyl alkyl ketones with a variety of active halogen compounds was carried out in an effort to correlate products and yields with steric factors, reaction solvents and conditions, and inductive effects. The first study was of the reaction of several -bromoesters with thienyl carbonyl derivatives in the presence of zinc and an inert solvent according to the equation:



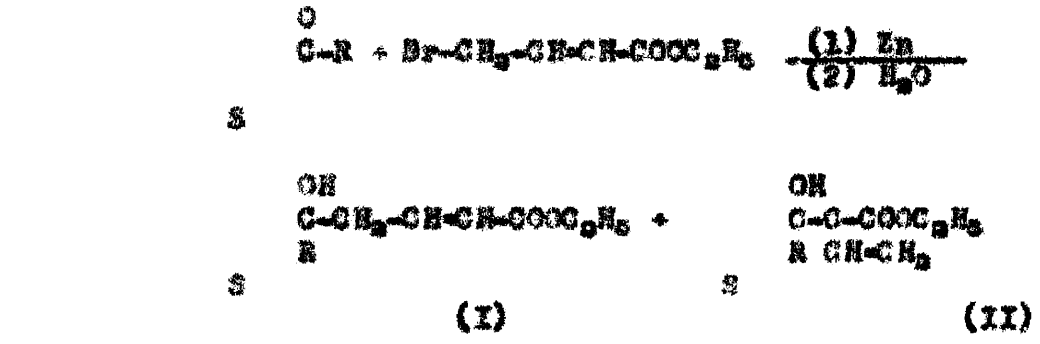
where R is hydrogen, methyl, ethyl or propyl, R_1 is hydrogen or methyl, and R_2 is hydrogen or methyl.

The yields of -hydroxyester obtained from 2 and 3-thenal were uniformly good (56-65%) regardless of the nature of the halogen reagent employed. From the ketones yields varied widely and were found to be dependent upon the amount of steric interaction between the R groups of the ketone and the -bromoester. The yield of product was decreased by 10-20% through increased enolization of the ketone when dioxane was used as the reaction solvent.

The -hydroxyesters obtained as products were dehydrated to the corresponding unsaturated esters by treatment with boiling 6% aqueous oxalic acid.

Altogether, 18 ethyl 3-(thienyl)-3-hydroxyalkanoates were prepared through the Reformatsky reaction and 12 ethyl -(thienyl) acrylates were obtained by dehydration.

The Reformatsky reaction of carbonyl derivatives of thiophene with ethyl -bromocrotonate proceeds according to the following equation:

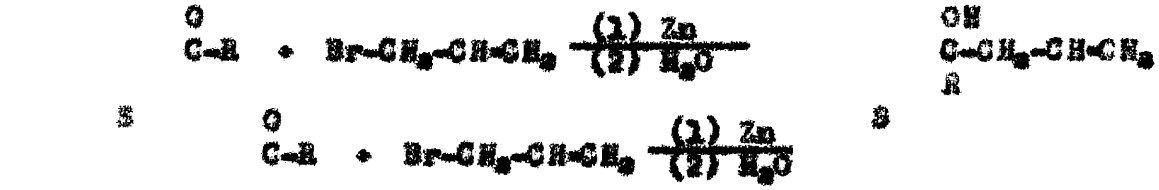


where R is hydrogen, methyl, ethyl or propyl.

From 2 and 3-thenal the product isolated in largest amount was II while from 2-acetylthiophene there was obtained a larger quantity of I. The only product resulting from 2-propionyl-, 2-butyryl-, and 2-acetyl-3-methyl thiophene was that resulting from the dehydration of I.

Altogether, six ethyl 5-(thienyl)-5-alkyl-2,4-pentadienoates three ethyl 2-ethenyl-3-hydroxy-3-(thienyl)alkanoates and three ethyl 5-(thienyl)-5-hydroxy-2-alkenoates were prepared by the Reformatsky reaction.

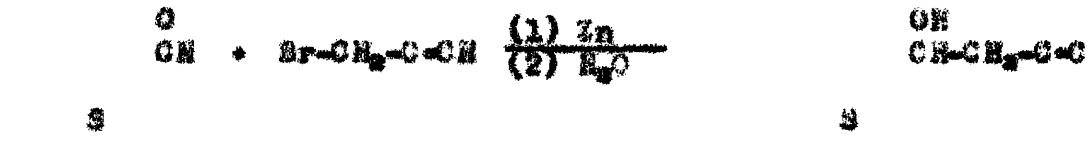
The Reformatsky reaction of allyl bromide with thienyl carbonyl derivatives proceeds readily with resultant high yields:



where R is hydrogen, methyl, ethyl and propyl.

Altogether, seven 4-(thienyl)-4-hydroxy-1-alkenes were prepared by this application of the Reformatsky reaction.

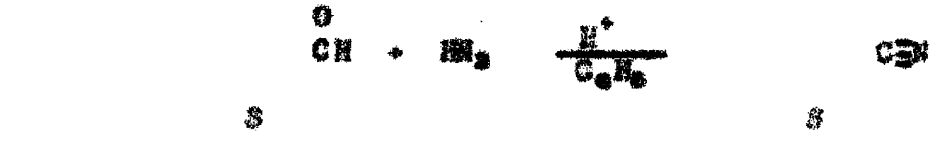
From the Reformatsky reaction of propargyl bromide with 2- and 3-thenal, good yields of the expected product were obtained.



When thienyl alkyl ketones were allowed to undergo reaction with propargyl bromide in the presence of zinc, only large amounts of unchanged ketone were recovered. Apparently the halozinc derivative of propargyl bromide causes extensive enolization of the ketone resulting in its recovery.

PART II

The Schmidt reaction of 2 and 3-thienyl aldehydes and 2 and 3-thienyl alkyl ketones with hydrazoic acid in the presence of strong acid was studied. From the interaction of 2 and 3-thenal with hydrazoic acid dissolved in benzene, good yields of the expected nitriles were obtained when either concentrated sulfuric acid or phosphoric acid was used as the catalyst.



The Schmidt reaction with 2 and 3-acetylthiophene, 2-propionylthiophene and 2-butyrylthiophene gave only low yields of the corresponding acylamidothiophenes and smaller amounts of the thenoalkylamides.

The thenoalkylamides could not be isolated in a pure condition and were converted by basic hydrolysis to the corresponding thenoic acid.

The low yields were largely due to side reactions such as sulfonation of the products, degradation of the thiophene ring by the strong acid catalyst and formation of complexes between the ketone and the catalyst. The use of solutions of hydrazoic acid and suspensions of sodium azide in benzene, acetic acid and chloroform failed to give any notable success in increasing yields and decreasing side reactions.

The use of trichloroacetic acid, phosphoric acid and trifluoroacetic acid as catalyst and reaction solvent was unsuccessful. Benzene, chloroform or acetic acid solutions of these two acids failed to promote the Schmidt reaction.

Through the interaction of excess hydrazoic acid with 2-thenal there was obtained a fair yield of 5-(2-thienyl)tetrazole.

In an effort to determine whether the nitrile was an intermediate in the formation of the tetrazole, 2-thenonitrile was allowed to react with hydrazoic acid under identical conditions. Apparently a different tetrazole was formed indicating that 2-thenonitrile is not an intermediate in the formation of 5-(2-thienyl)tetrazole from 2-thenal.

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued Page

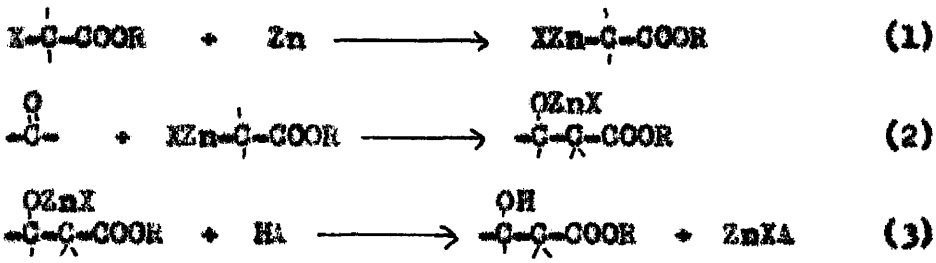
LIST OF TABLES

PART I

THE REFORMATSKY REACTION

INTRODUCTION

The Reformatsky reaction involves the interaction of an -halo-ester with a carbonyl compound such as an aldehyde, ketone, or an ester in the presence of zinc under anhydrous conditions (1). In this reaction a new carbon-carbon bond is created and apparently the following sequence of steps and intermediates are involved (2).

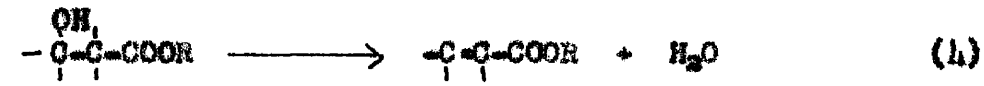


(1)

(2)

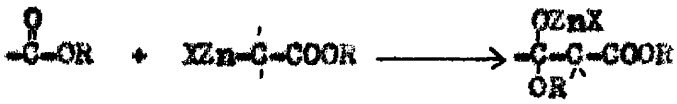
(3)

Thus, from aldehydes and ketones, β-hydroxyesters are obtained as the final product. Under certain experimental conditions or with some types of reactants, dehydration occurs during the reaction and results in an unsaturated ester. Where dehydration does not occur during the reaction, the β-hydroxyester may be converted to the corresponding α, β-unsaturated ester during a subsequent step.

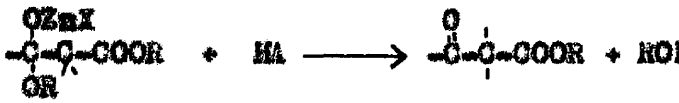


(4)

Where an ester is used instead of an aldehyde or ketone the process appears to involve the following steps (assuming equation 1) and yields a β-ketoester.



(5)



(6)

While the reaction is generally considered to proceed between the reactants indicated, numerous variations in these have been successfully applied. The halogen component may be a β-haloester (3,4), a vinylog of an α-haloester (5-18), an allyl halide (19), a propargyl halide (20-23), a benzyl halide (24), an α,α-dihaloester (16,25,26), or an α-haloamide (27). Likewise, an ethylene oxide (28,29), a Shiff base (16,30), or an amide (31) may be used as the second reactant.

Due to the synthetic utility of the Reformatsky reaction, it was the purpose of the work described here to investigate extensively the reactions of thienyl aldehydes and thienyl alkyl ketones with a variety of halogen components in an effort to determine possible correlations between the yield of product, steric factors in the reactants, reaction solvent effects and substituent effects in the reactants. Previous studies of the Reformatsky reaction with carbonyl derivatives of thiophene have been reported (4,16,23,65,66). However, these are of a superficial nature in that only the two substituted isomers were investigated, the variety of reactants was restricted to the aldehyde and methyl ketone of thiophene and certain other aspects of the investigations such as rearranged products, by-products and solvent effects were in need of further study.

HISTORICAL

The Reformatsky reaction was first reported in a series of papers (1,2,32-36) by Reformatsky and Plesconoff and immediately became the subject of a wide and varied investigation by numerous people (37). It represents an extension of the reactions of organozinc compounds with carbonyl compounds, but has the advantage that isolation of the intermediate organozinc compound is not required. The reaction involves the interaction of a carbonyl compound with an active halogen compound in the presence of zinc under anhydrous conditions. An intermediate organozinc halide is formed which then attacks the carbonyl component to yield an addition complex.

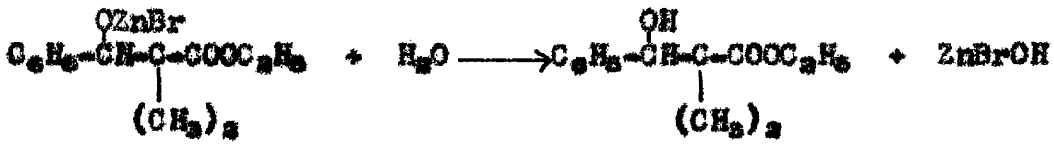
Evidence that an organozinc halide is formed was provided by Dain (38) when he was able to isolate and analyze the product from the reaction:

$$(CH_3)_2\text{-}\underset{\displaystyle Br}{\underset{|}{C}}\text{-}COOC_2H_5 \;+\; Zn \longrightarrow (CH_3)_2\text{-}\underset{\displaystyle ZnBr}{\underset{|}{C}}\text{-}COOC_2H_5$$

Dain further demonstrated that the addition complex results from the interaction of the carbonyl component with the organozinc halide intermediate.

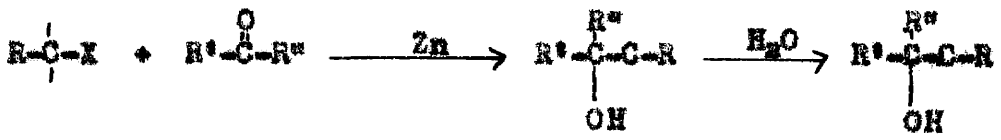
$$C_6H_5\text{-}\overset{\displaystyle O}{\overset{\|}{C}}H \;+\; (CH_3)_2\text{-}\underset{\displaystyle ZnBr}{\underset{|}{C}}\text{-}COOC_2H_5 \longrightarrow C_6H_5\text{-}\overset{\displaystyle OZnBr}{\overset{|}{C}}H\text{-}\underset{\displaystyle (CH_3)_2}{\underset{|}{C}}\text{-}COOC_2H_5$$

Decomposition of the addition complex by hydrolysis yields the corresponding hydroxy compound.



The order of reactivity of the haloesters is, as would be expected iodo > bromo > chloro. Esters with secondary or tertiary α -halogens are considerably more reactive than the corresponding primary derivatives, but in many instances the reactivity of a given halo compound may be modified by steric factors operative in the ester. As the carbonyl component the aldehydes are more reactive than the ketones and the latter compounds in turn, are more reactive than the esters (37).

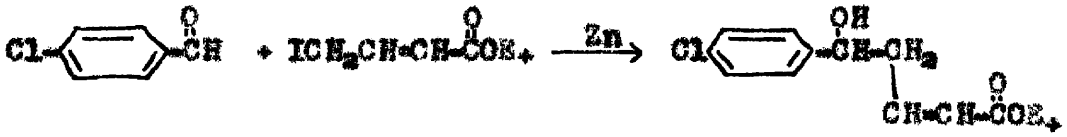
The over-all reaction of either a ketone or aldehyde with an active halogen compound under Reformatsky conditions results in the formation of a β -hydroxyester which may be converted by dehydration to the corresponding unsaturated ester.



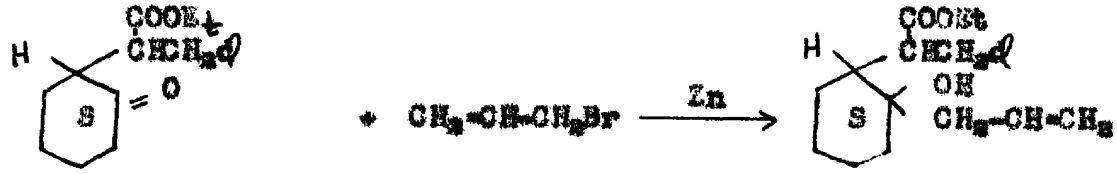
When an ester is used as the carbonyl component the product is generally a β -ketoester.

Miller and Nord (4) succeeded in utilizing -bromoesters for Reformatsky reaction where others (3,8) reported none or only moderate success by substituting magnesium for zinc and carrying out the reaction in tetrahydrofuran.

The vinylogs of the α -haloesters undergo the Reformatsky reaction (5-18). Thus, Fuson reports (8) that ethyl γ -iodocrotonate, p-chlorobenzaldehyde, and zinc react to form the expected condensation in a 42% yield.



Crewe (19) found that cyclic ketones react with allyl bromide and zinc in diethyl ether and anisole to give a typical Reformatsky product.



An active halogen compound analogous to allyl bromide is propargyl bromide. A number of investigators have reported that it functions in the Reformatsky reaction to give good yields (20-23). Henbest and co-workers (20,21) found that a variety of carbonyl compounds could

be employed with propargyl bromide.

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + CH{\equiv}C{-}CH_2{-}Br \xrightarrow[HgCl_2]{Zn} CH_3{-}\overset{OH}{\overset{|}{C}}{-}CH_2{-}C{\equiv}CH \quad (CH_3)$$

Fuson and Cook (24) observed that benzyl halides react with aromatic aldehydes to yield stilbene derivatives. The unsaturated compounds result through the easy dehydration of the carbinols during distillation. Thus, benzaldehyde reacts with benzyl chloride to yield stilbene in a 24% yield.

$$C_6H_5\overset{O}{\overset{\|}{C}}H + C_6H_5CH_2Cl \xrightarrow{Zn} C_6H_5\overset{OH}{\overset{|}{C}}H{-}CH_2C_6H_5$$

$$\xrightarrow{-H_2O} C_6H_5CH{=}CHC_6H_5$$

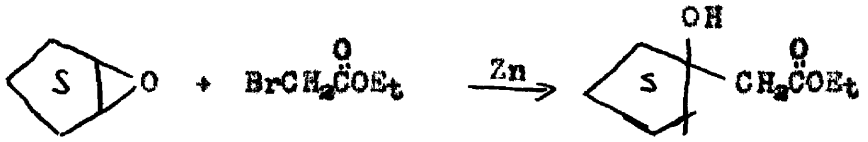
In a process reminiscent of the Darzens glycidic ester condensation (39), hydroxychloresters are obtained when α,α-dihaloesters are allowed to react with carbonyl compounds (16,25,26). For example the interaction of acetophenone with ethyl dichloroacetate gives the Reformatsky type product in a 90% yield (25).

$$C_6H_5\overset{O}{\overset{\|}{C}}CH_3 + Cl_2CHCOOC_2H_5 \longrightarrow C_6H_5\overset{CH_3}{\overset{|}{C}}{-}\underset{OH\ Cl}{\overset{|}{C}}HCOOC_2H_5$$

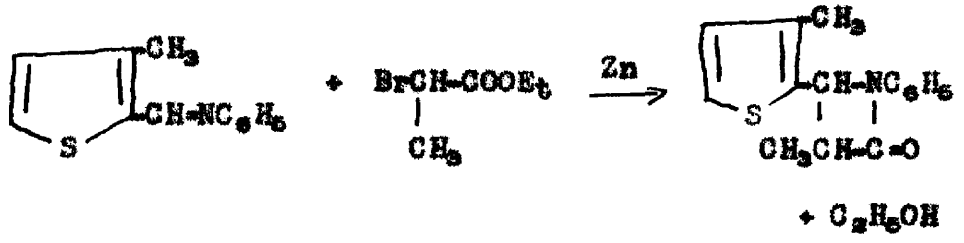
Employing a zinc-copper alloy in place of zinc, Drake (27) prepared N,N-dialkyl- β-hydroxy amides by the treatment of carbonyl compounds with α-bromoamides.

$$BrCH_2\overset{O}{\overset{\|}{C}}NR_2 + R\overset{O}{\overset{\|}{C}}H \xrightarrow{ZnCu} R\overset{OH}{\underset{|}{C}}H\text{-}CH_2\overset{O}{\overset{\|}{C}}NR_2$$

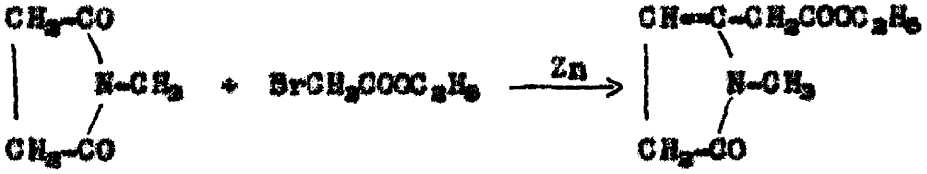
Certain epoxides react with ∝-haloesters in the presence of zinc to produce hydroxyesters analogous to those obtained from carbonyl compounds in the normal Reformatsky reaction (28,29). Ethyl 1-hydroxycyclopentylacetate is formed from cyclopentene oxide by condensation with ethyl bromoacetate (28).



The interaction of Shiff bases with ∝-bromoesters in the presence of zinc proceeds in an expected manner with simultaneous loss of an alcohol to give a 2-azetidinone (16,30). Thus, Miller and Nord (16) prepared 1-phenyl-3-methyl-4-(3-methyl-2-thienyl)-2-azetidinone in 55% yield by reacting 3-methyl-2-thenalaniline with ethyl ∝-bromopropionate under Reformatsky reaction conditions.



Lukes (31) has obtained ethyl 1-methyl-2-pyrrolone-5-acetate in about 20% yield by treating N-methyl succinimide with ethyl bromoacetate and zinc.



Experimental Conditions

In the early work on (1,2,32-36), the Reformatsky reaction, it was carried out by mixing the reactants at room temperature without a solvent followed by external cooling of the system to moderate the vigorous initial reaction. After being allowed to stand at room temperature for varying periods of time, the reaction mixture was briefly heated, 60-80° C., and then decomposed with dilute acid. In the more recent applications of the reaction a solvent has been employed and one of the reactants may be added portionwise with stirring and at the reflux temperature of the solvent. It is essential that the solvent employed be one in which the products are soluble in order to prevent coating of the surface of the zinc which greatly inhibits the reaction. Prolonged reaction times are to be avoided since, even at low temperatures, extended reaction time results in an increase in the amount of high-boiling by-products (40,41).

Strictly anhydrous conditions are required for successful utilization of the Reformatsky reaction. In the presence of minute quantities of moisture the reaction may be initiated only after an induction period or the use of catalysts such as iodine, amalgamated zinc or the copper complex of acetoacetic ester (42).

The quality of zinc used in the reaction is often responsible for differences of opinion concerning reaction time, yield, catalyst and purification procedure. It should be of a high degree of purity and have a fresh clean surface. One of the better procedures for conditioning the zinc is reported by Fieser and Johnson (43), who advise immersion of 30-mesh zinc in hot concentrated sulfuric acid to which a few drops of nitric acid have been added. The zinc is washed with water and acetone and then dried in an oven. In certain investigations amalgamated zinc, mixtures of zinc and copper powder (40) or zinc-copper alloys (27,44,45) have been used. Numerous instances are reported (4,20,21,46,47) in which mercuric chloride was used in conjunction with zinc to improve the yields in the Reformatsky reaction. Other metals or metal combinations which have been investigated are aluminum (48), magnesium (4,49,50), magnesium-iodine (51,52), magnesium-cobaltous chloride (4) and magnesium-copper (53).

The solvents most generally employed in the Reformatsky reaction are diethyl ether, benzene, toluene, xylene, dioxane, dibutyl ether, anisole and tetrahydrofuran. The criteria for determining the solvent to be used in a specific case are solubility of reactants and products, reaction temperature desired, and in certain cases, the effect of the solvent on the course of the reaction. Dioxane, for example, is said to promote enolization of the carbonyl component, thereby decreasing the yield of product (54).

Side Reactions of the Reformatsky Reaction

Various side reactions result whenever the Reformatsky reaction is executed (37). The organozinc halide intermediate may add to the α-haloester forming an acetoacetic ester. Hann and Lapworth (55) observed that zinc and ethyl bromoacetate interact to give ethyl α-bromoacetoacetate.

$$2\ BrCH_2COOC_2H_5 + Zn \longrightarrow BrCH_2\underset{\underset{OC_2H_5}{|}}{\overset{\overset{OZnBr}{|}}{C}}CH_2COOC_2H_5$$

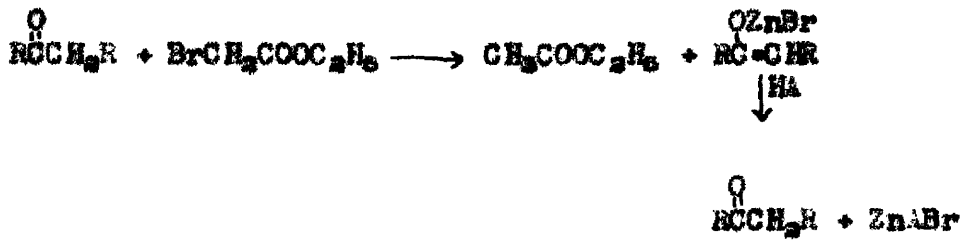
$$\xrightarrow{H_2O} \quad BrCH_2\overset{\overset{O}{\|}}{C}CH_2COOC_2H_5 + C_2H_5OZnBr$$

This reaction would be of minor concern when aldehydes and ketones are used since they possess greater carbonyl reactivity than the ester grouping of the haloester.

Another side reaction which is of importance only where the carbonyl component is an ester is the coupling of the haloester by the zinc.

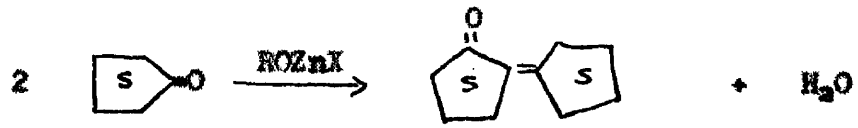
$$2\ BrCH_2COOCH_3 + Zn \longrightarrow \underset{\underset{CH_2COOCH_3}{|}}{CH_2COOCH_3} + ZnBr_2$$

Newman has reported (54) that the organozinc compound may induce enolization of the carbonyl component. This results in recovery of the original carbonyl compound and the reduced ester.



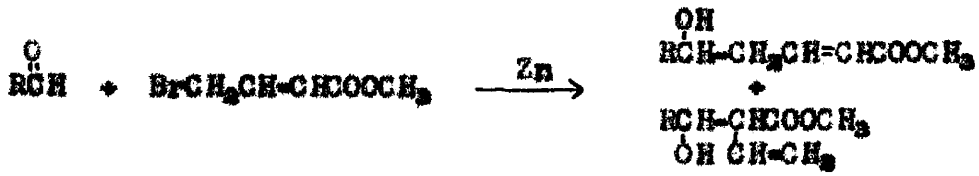
The amount of enolization has been found to be a function of the type of solvent, the halogen derivative employed, and the steric blocking by groups in the ketone (56,57). Dioxane, for instance, is said to promote enolization (54).

When aliphatic aldehydes and ketones are used, these may undergo aldolization through the influence of the zinc salts.

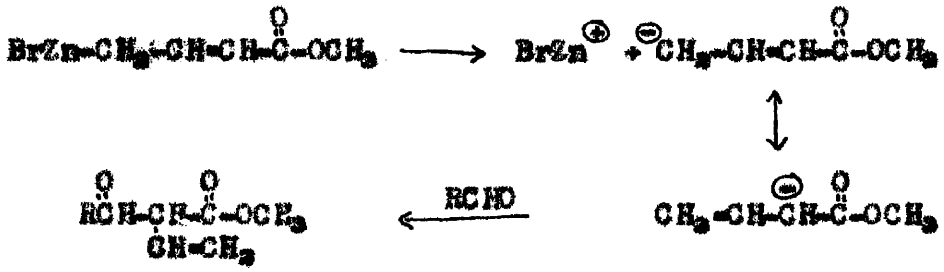


In addition to consuming aldehyde or ketone, this aldolization, followed by dehydration of the aldol produces water, which in turn causes decomposition of the organozinc halide intermediate.

The formation of a rearranged product during the Reformatsky reaction has been reported in two cases. English and Gregory (18) and Jones, O'Sullivan and Whiting (17) isolated two isomeric products from Reformatsky reactions employing methyl γ-bromocrotonate. The products were identified as being the normal product and an isomeric α-vinyl derivative.



Presumably, the α-vinyl derivative results through a charge migration in the negative species of the organozinc halide.



Mechanism of the Reformatsky Reaction

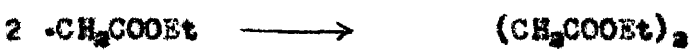
Very little direct investigation has been reported concerning the mechanism of the Reformatsky reaction. Evans and Pearson (58), who made a thorough study of the Grignard reagent, RMgX, also conducted a cursory examination of the Reformatsky reagent, RZnX. Results of transference studies conducted by these investigators indicate that the halo organometallic complex in ether solution may be represented by the following expression:

$$RZnX \rightleftharpoons R:^{\ominus} + {}^{\oplus}ZnX$$

It was found that benzene solutions of the reagent do not conduct, while ether solutions are excellent conductors. This may be attributed to solvation by ether of the organometallic complex.

The reaction of the Reformatsky complex is presumed to proceed by an initial carbanion attack on the carbonyl carbon.

There may be certain reasons to believe that free radicals are involved in the Reformatsky reaction. These are suggested by the isolation of esters of succinic and substituted succinic acids as a result of a coupling reaction between two molecules of α-haloester. However, there is considerable controversy as to whether coupling reactions of this type proceed by a free radical or ionic mechanism (59).



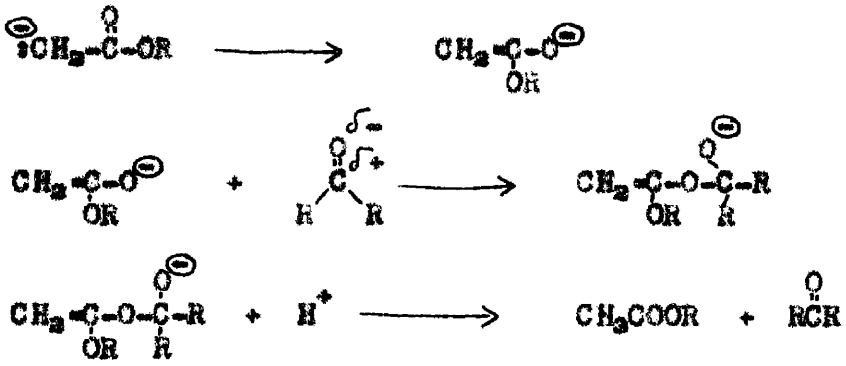
or

then by S_N2 displacement:

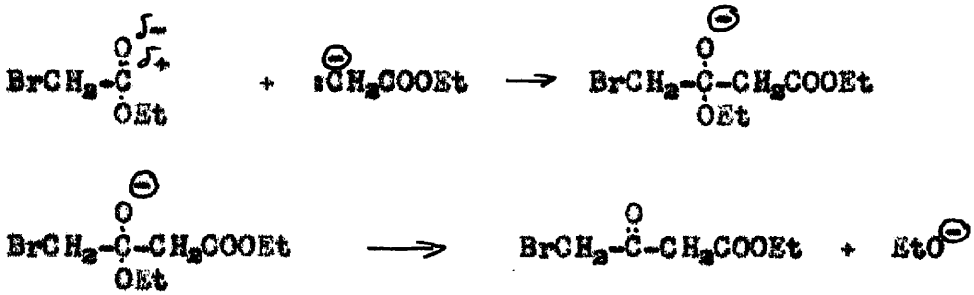
The recent investigations (60) on the Wurtz reaction tend to indicate an ionic mechanism.

Evidence supporting the ionic mechanism of the Reformatsky reaction may be found in a study of the products formed from the vinylogs of the esters of bromoacetic acid. English and Gregory (16) carried out reactions between cyclic aldehydes and ethyl γ-bromocrotonate and reported the isolation of two isomeric products, and a possible mode for the formation of these products through an ionic mechanism (17) has already been discussed.

The isolation of unreacted carbonyl compound and nonhalogenated ester in the Reformatsky reaction has been explained by Newman (54) on the assumption that enolization of the ketone is promoted by the organometallic complex followed by interaction of the latter with the enol to yield nonhalogenated ester and the halometallic complex of the enol which regenerates the ketone when the reaction mixture is hydrolyzed. This mechanism, however, fails to account for the isolation of unreacted carbonyl compound and nonhalogenated ester in the numerous cases where the ketone or aldehyde is incapable of enolization. In such cases it is more plausible that the ionic form is responsible for the isolation of unreacted carbonyl compound (17).

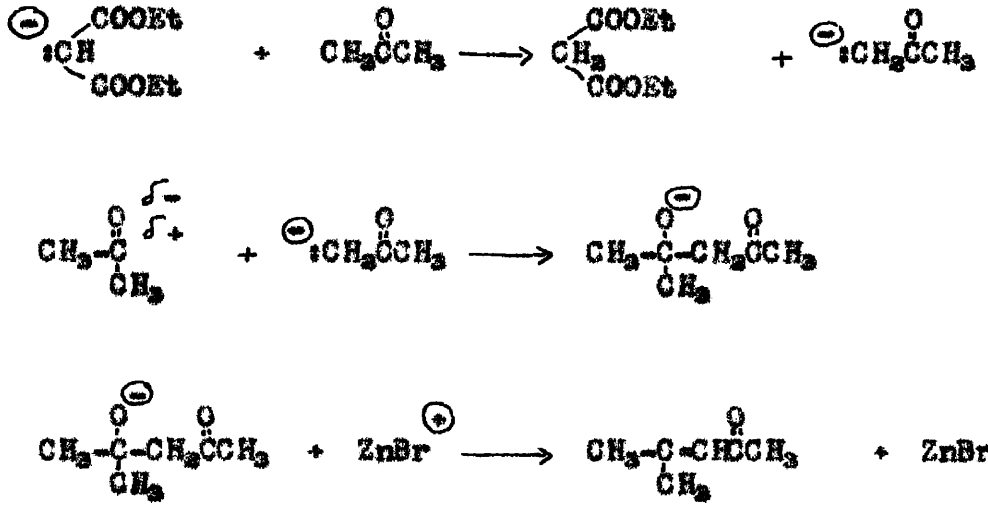


In view of an ionic species of the type $:\overset{\ominus}{C}H_2COOEt$, it is not surprising that the isolation of Claisen type condensation products has been reported (55). This may be represented as proceeding by a typical Claisen mechanism (61).



Since aldehydes and ketones are much more reactive than esters, this side reaction is important only where the carbonyl component is an ester. In fact, the reaction of a Reformatsky reagent with an ester may be represented by the same sort of mechanism as described above.

Most α,β -unsaturated ketones undergo the normal Reformatsky reaction. However, Kohler and co-workers (62) observed that methyl bromozincmalonate adds 1,4 to benzalacetophenone. Iyer (63) found that when acetone is treated with the same Reformatsky reagent the only product isolated is that corresponding to 1,4 addition of the halocster to mesityl oxide. Apparently, the first step of the reaction is the condensation of acetone to give mesityl oxide. The occurrence of this aldol type condensation and dehydration of the aldol may be represented by a mechanism similar to that of a typical aldol condensation (64).



Thus, the various products isolated from the Reformatsky reaction may be explained on the basis of a single ionic species. Only more extensive investigation will confirm or disprove these possibilities.

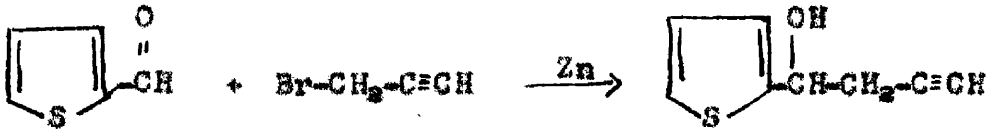
Previous Investigation of the Reformatsky Reaction on Thienyl Carbonyl Compounds

In a series of publications (4,16,23,65,66) Nord and collaborators reported the application of the Reformatsky reaction to a series of 2-thienyl ketones and aldehydes. These investigations were conducted on the more readily available ketones and aldehydes and no attempt was made toward the investigation of the more difficultly prepared 3-thienyl compounds.

The first of these papers (65) discusses the interaction 2-acetylthiophene, 2-thenal, and some methyl and halogen substituted 2-thenals with the ethyl esters of bromoacetic acid, α-bromopropionic acid, α-bromoisovaleric acid, bromomalonic acid and α-bromo-n-butyric acid. Zinc metal and a benzene-toluene mixture were the ether

components of the system. The yields reported were consistent with expectations drawn by analogy from the corresponding benzene derivatives, being 10-63% depending on the nature of the reactants. Where ethyl bromoacetate, ethyl α-bromoisovalerate and ethyl bromomalonate were employed, these investigators were unable to isolate the β-hydroxy esters, but obtained instead the corresponding unsaturated esters. As a further preparation, the products from reactions yielding β-hydroxy esters were refluxed with 6% oxalic solution to yield the dehydration products.

The second paper, by Keskin, Miller and Nord (23), describes the preparation of some acetylenic derivatives of thiophene in which 1-(2-thienyl)-3-butyn-1-ol and 1-(2-thienyl)-1-hexen-5-yn-3-ol were synthesized through the reaction of zinc and propargyl bromide in a benzene-tetrahydrofuran mixture with 2-thenal and β-2-thienylacrolein respectively.

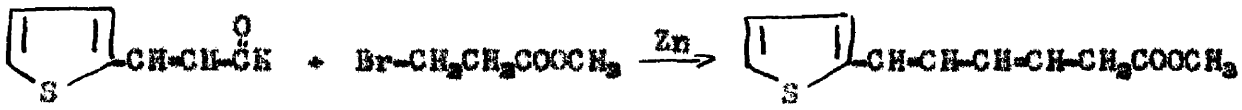


No investigation was conducted on the reaction of thienyl ketones with propargyl bromide.

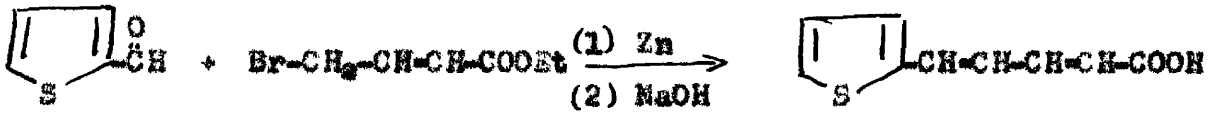
The third publication (4) concerns the selection of a condensing agent for the utilization of α-chloro and β-bromo esters in Reformatsky reactions. The only carbonyl derivative of thiophene investigated was 2-acetylthiophene. It was found that mercuric chloride

serves satisfactorily as a promoter in Reformatsky reactions involving the above mentioned halogen compounds giving expected products in yields as high as 32%. The reaction of 2-acetylthiophene with ethyl dichloroacetate to give a 23% yield of ethyl β-methyl-(2-thienyl) acrylate is reported.

In a study of the synthesis of some thiophene polyenes (66), Miller and Nord employed their previously described procedure (4) of the interaction of β-2-thienylacrolein with methyl β-bromopropionate.



The final paper (16) by Miller and Nord reports the preparation of some 2-thienyl polyene acids by the reaction of 2-thenal and β-2-thienyl-acrolein with ethyl γ-bromocrotonate and methyl ω-bromosorbate.



They were unable to isolate either the corresponding hydroxy or unsaturated esters and so saponified and dehydrated the reaction mixtures with methanolic sodium hydroxide to obtain the unsaturated acids. Despite the findings of Jones, O'Sullivan and Whiting (17) and those of English and Gregory (18) for similar reactions with benzaldehyde, these investigators could not find any evidence that the rearranged α-vinyl acids were formed along with the normal products. They do, however, support the

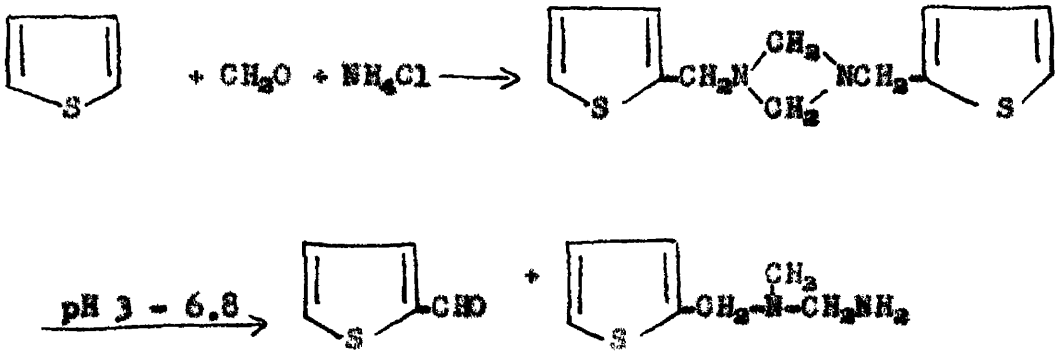
mechanism proposed by Jones and collaborators for the isolation of unreacted aldehydes where enolization cannot occur. No thienyl ketones were studied in this investigation.

DISCUSSION

Preparation of Intermediates

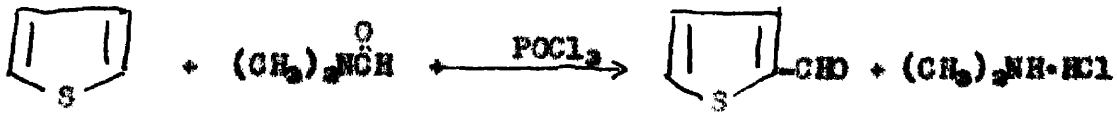
The 2- and 3-thienyl aldehydes and ketones employed in this investigation were synthesized by standard procedures described in the literature.

The preparation of 2-thenal was accomplished by two different methods. Hartough and Dickert (67) prepared 2-thenal through an adaptation of the aminomethylation reaction to thiophene (68). This involves the interaction of thiophene, 37% formaldehyde and ammonium chloride giving the intermediate N,N'-di-(2-thienyl)-1,3-diazacyclobutane, which is not isolated but is hydrolyzed in dilute acid solution (pH = 3.0-6.8) to give a 48% yield of 2-thenal and a 47% yield of N-methyl-2-thenylamine.



The best yield obtained in the present investigation was 46.7%. A better procedure from the standpoint of yields and simplicity of reaction conditions for the preparation of 2-thenal is that described by Champaigne and Archer (69). This synthesis involves the direct

formylation of the thiophene nucleus by dimethylformamide in the presence of phosphorus oxychloride. Champaigne and Archer reported a 72% yield of 2-thenal; the present study confirmed this with a 74% yield of the aldehyde.



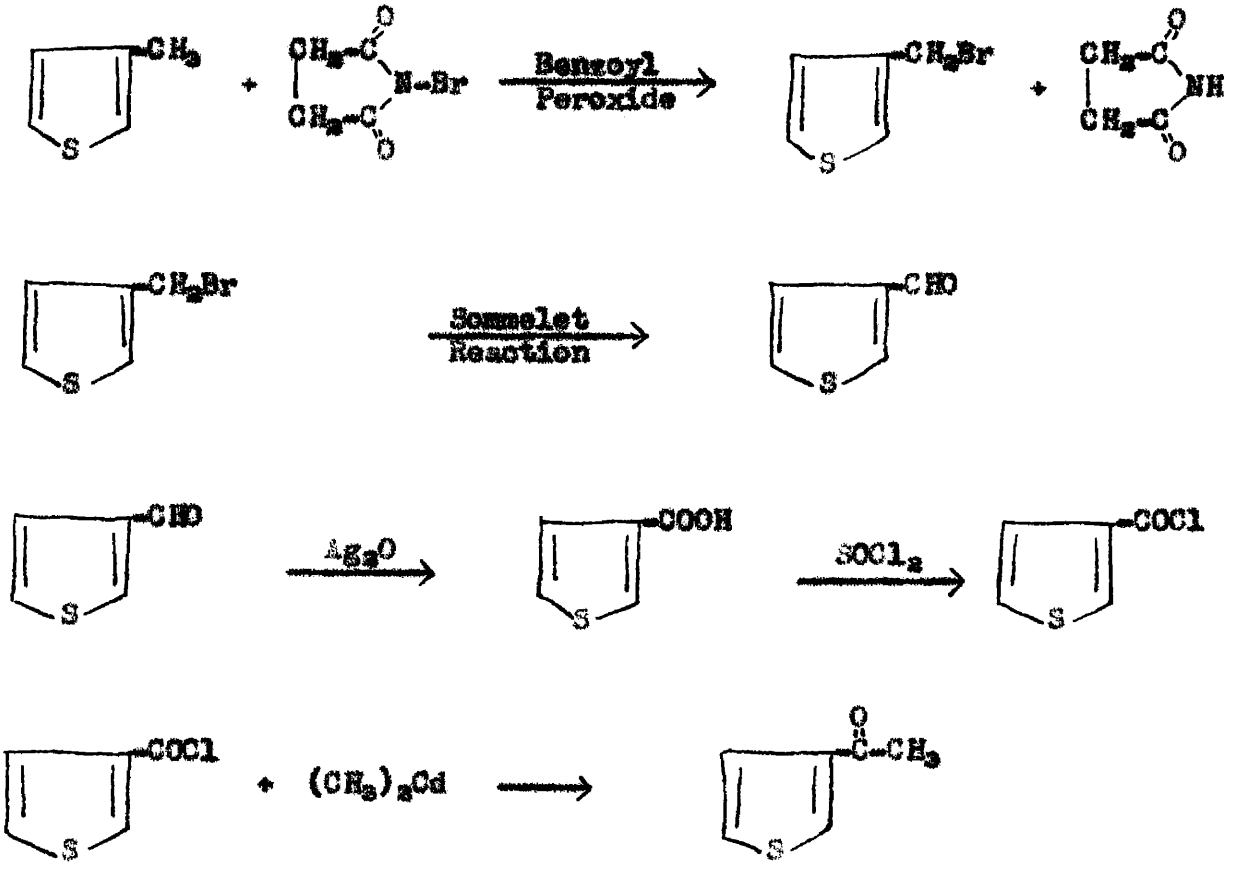
The 2-acylthiophenes were obtained by the acylation of thiophene with acid anhydrides in the presence of catalytic amounts of ortho phosphoric acid according to a method described by Hartough and Kosak (70). After extraction of the phosphoric acid the product is isolated in good yield by vacuum distillation. Employing this procedure, 2-acetylthiophene was prepared in 86% yield; 2-propionylthiophene was obtained in 72.7% yield and the yield of 2-butyrylthiophene was 74.5% when thiophene was acylated with acetic anhydride, propionic anhydride and butyric anhydride respectively. Using the same process, 3-methylthiophene was acylated with acetic anhydride to give a 66% yield of 2-acetyl-3-methylthiophene as well as a 12% yield of the isomeric 2-acetyl-4-methylthiophene.

Since direct substitution at the 3 position in the thiophene ring does not occur lengthy procedures were required for the preparation of 3-thenal and 3-acetylthiophene. By reacting 3-methylthiophene with N-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride as solvent according to the method elucidated by Dittmer and

collaborators (71), a maximum yield of 60.6% of 3-thenyl bromide was obtained. The reaction is quite exothermic and the product isolated is 2-bromo-3-methylthiophene if the benzoyl peroxide is omitted or decomposed. In addition, the normal product, 3-thenyl bromide, is a strong lachrymator and was found to be unstable, decomposing with violence after a storage period of several months. The Sommelet reaction provides a convenient method for the preparation of 3-thenyl from 3-thenyl bromide (72). A solution of 3-thenyl bromide in chloroform was treated with hexamethylenetetramine to form a complex salt which was hydrolyzed by hot water to give a 48% yield of 3-thenal. The aldehyde, 3-thenal was converted to 3-thenoic acid by oxidation with silver oxide following a previously described method (72). Silver oxide was formed by the treatment of a silver nitrate solution with aqueous sodium hydroxide. To the resultant brown suspended silver oxide is added 3-thenal and the precipitated silver is removed by filtration. After acidification of the filtrate a 95% yield of solid 3-thenoic acid is obtained. The 3-thenoic acid was converted to 3-thenoyl chloride by thionyl chloride with the product being isolated in 80% yield by vacuum distillation after removal of excess thionyl chloride (72). Campaigne and LeSeur (72) used a procedure developed by Gilman and Nelson (73) to convert 3-thenoyl chloride into 3-acetylthiophene. A prepared solution of methyl magnesium bromide was treated with finely ground cadmium chloride to give a solution of dimethyl cadmium to which was added slowly and with cooling 3-thenoyl chloride.

After hydrolysis of the reaction mixture with dilute sulfuric acid the liquid product was obtained by vacuum distillation in a yield which was 73% of the theoretical.

The transformations involved in the preparations of 3-thenal and 3-acetylthiophene are represented by the following equations:



Of the active halogen compounds used for the Reformatsky reactions, ethyl bromoacetate, ethyl α-bromopropionate and allyl bromide were commercially available.

Ethyl α-bromoisobutyrate was prepared in good yields by a rather elegant adaptation of the Hell-Volhard-Zelinsky reaction. Bromine was

added slowly to a stirred solution of phosphorus pentachloride in isobutyric acid. After being set aside overnight, the mixture was treated with an excess of thionyl chloride to give α-bromoisobutyryl chloride which was not isolated, but, after removal of excess thionyl chloride, was treated with absolute ethanol. By vacuum distillation, a 77% over-all yield of ethyl α-bromoisobutyrate was obtained.

Using the method described by Schmidt and Karrer (74), ethyl γ-bromocrotonate was prepared from ethyl crotonate through the interaction of N-bromosuccinimide with ethyl crotonate in the presence of benzoyl peroxide employing carbon tetrachloride as a solvent. Ethyl γ-bromocrotonate was isolated by distillation in a 82% yield. Ethyl crotonate was synthesized in 75% yield by the esterification of crotonic acid with 95% ethanol and sulfuric acid.

Kirrman's method (75) for the synthesis of propargyl bromide from propargyl alcohol was used successfully to produce a 72% yield of propargyl bromide. Phosphorus tribromide was added dropwise to propargyl alcohol dissolved in dry pyridine as a solvent and the alkyne halide was isolated by distillation.

Reformatsky Reaction of α-Bromoesters

The α-bromoesters employed as the active halogen constituent were ethyl bromoacetate, ethyl α-bromopropionate and ethyl α-bromoisobutyrate. This selection of bromoesters allowed an examination of the reactivity of a primary halogen, a secondary halogen and a tertiary halogen.

The carbonyl derivatives of thiophene examined were 2-thenal, 3-thenal, 2-acetylthiophene, 3-acetylthiophene, 2-propionylthiophene, 2-butyrylthiophene and 2-acetyl-3-methylthiophene. The variation of thienyl derivatives was in the position of substitution on the thiophene ring, the length of the alkyl chain in the 2-acylthiophenes and the presence of a methyl group adjacent to the acyl group.

The solvent employed was benzene since no reaction was found to occur in ethyl ether and excessive decomposition took place in toluene. The use of a benzene-toluene mixture was found to offer no advantages.

By the Reformatsky reaction of carbonyl derivatives of thiophene with α-bromoesters a variety of branch chained ethyl 3-(2-thienyl) or 3-(3-thienyl)-3-hydroxyalkanoates were produced.

Equimolar quantities of the thienyl carbonyl compound and α-bromoester were dissolved in anhydrous benzene and to this solution, with stirring, was added a similar quantity of dry acid washed zinc dust. The reaction was initiated by a slight application of heat to the bottom of the reaction vessel, and once started the vigorous exothermic reaction had to be moderated by brief immersion of the apparatus in an ice bath. When the initial reaction had subsided the mixture was heated at its reflux temperature for one hour and then hydrolyzed by the addition of an ice cold 10% sulfuric acid solution. The non-aqueous layer was separated and combined with a subsequent ether

extract of the aqueous portion. The combined extracts were given consecutive treatments with water, 10% sodium carbonate and water in order to remove traces of sulfuric acid. After the solution was dried over anhydrous sodium sulfate, the ether and benzene were removed at reduced pressure and the residue was distilled under vacuum. A quantity of recovered ketone or aldehyde was first received followed by the β-hydroxy ester. Distillation pressures of less than one millimeter of mercury were usually required to avoid dehydration of the β-hydroxy-ester to the corresponding unsaturated ester.

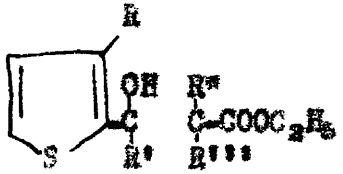
In all cases the β-hydroxyesters were isolated in a pure condition. Apparently the use of a lower boiling solvent and lower distillation temperatures account for the successful isolation of the β-hydroxy-esters as compared to Miller and Nord's (65) failure to isolate these compounds where ethyl bromoacetate was used.

Altogether, ten ethyl 3-(2-thienyl)-3-hydroxyalkanoates and six ethyl 3-(3-thienyl)-3-hydroxyalkanoates which have not previously been reported were prepared and some of their properties are summarized in Tables I and II respectively. The yields and percentage of recovered ketone are reported in Tables III and IV.

The yields where ethyl bromoacetate was interacted with the unsubstituted thienyl derivatives ranged from 58 to 68%. Little change in yield occurs with variations in the length of acyl group attached to the thiophene nucleus. A marked decrease in the amount of product obtained occurred where 2-acetyl-3-methyl thiophene was used as only a 25% yield resulted from the interaction of this compound with ethyl

TABLE I

ETHYL 3-(2-THIENYL)-3-HYDROXYALKANOATES

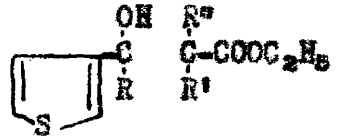


R	R'	R''	R'''	Formula	B.p. °C	(mm. Hg)	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
H	H	H	H	$C_9H_{12}O_3S$	113-114	(0.2)	54.0	54.1	6.0	6.2
H	H	H	CH_3	$C_{10}H_{14}O_3S$	108-110	(0.5)	a			
H	H	CH_3	CH_3	$C_{11}H_{16}O_3S$	113-114	(0.1)	57.9	57.9	7.0	6.4
H	CH_3	H	H	$C_{10}H_{14}O_3S$	93-94	(0.2)	56.1	55.9	6.5	6.6
H	CH_3	H	CH_3	$C_{11}H_{16}O_3S$	102-103	(0.1)	a			
H	CH_3	CH_3	CH_3	$C_{12}H_{18}O_3S$	100-101	(0.1)	59.5	59.8	7.4	7.3
H	C_2H_5	H	H	$C_{11}H_{16}O_3S$	95-96	(0.2)	57.9	58.2	7.0	6.9
H	C_2H_5	H	CH_3	$C_{12}H_{18}O_3S$	103-104	(0.1)	59.5	59.6	7.4	7.4
H	n-C_3H_7	H	H	$C_{12}H_{18}O_3S$	97-98	(0.2)	59.5	59.9	7.4	7.4
H	n-C_3H_7	H	CH_3	$C_{13}H_{20}O_3S$	112-113	(0.1)	60.9	60.7	7.8	8.0
CH_3	CH_3	H	H	$C_{11}H_{16}O_3S$	114-116	(0.5)	57.9	58.0	7.0	7.0
CH_3	CH_3	H	CH_3	$C_{12}H_{18}O_3S$	117-118	(0.2)	59.5	59.4	7.4	7.3

a Previously prepared and reported (65).

TABLE II

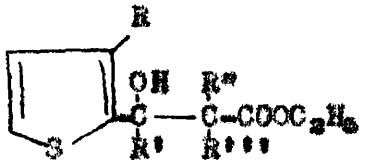
ETHYL 3-(3-THIENYL)-3-HYDROXYALKANOATES



R	R'	R''	Formula	B.p. °C.	(mm. Hg)	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
H	H	H	$C_9H_{12}O_3S$	114-116	(0.5)	54.0	54.2	6.0	5.9
H	H	CH_3	$C_{10}H_{14}O_3S$	114-115	(0.5)	56.1	56.1	6.5	6.8
H	CH_3	CH_3	$C_{11}H_{16}O_3S$	116-118	(0.5)	57.9	58.0	7.0	7.2
CH_3	H	H	$C_{10}H_{14}O_3S$	93-94	(0.1)	56.1	56.4	6.5	6.8
CH_3	CH_3	CH_3	$C_{11}H_{16}O_3S$	104-106	(0.5)	57.9	58.0	7.0	7.0
CH_3	CH_3	CH_3	$C_{12}H_{18}O_3S$	105-107	(0.5)	59.5	59.3	7.4	7.5

TABLE III

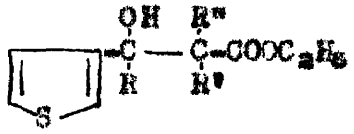
ETHYL 3-(2-THIENYL)-3-HYDROXYALKANOATES



R	R'	R''	R'''	Yield (Benzene)	% Carbonyl Recovered	Yield (Dioxane)	% Carbonyl Recovered
H	H	H	H	62	8		
H	H	H	CH_3	57	6		
H	H	CH_3	CH_3	64	9		
H	CH_3	H	H	66	16	42	40
H	CO_2	H	CH_3	63	17	53	30
H	CH_3	CH_3	CH_3	15	56		
H	C_2H_5	H	H	65	15	43	37
H	C_2H_5	H	CH_3	62	13	55	34
H	n-C_3H_7	H	H	58	16	43	36
H	n-C_3H_7	H	CH_3	54	14	46	34
CH_3	CH_3	H	H	25	48		
CH_3	CH_3	H	CH_3	20	57		

TABLE IV

ETHYL 3-(3-THIENYL)-3-HYDROXYALKANOATES



R	R'	R''	Yield	% Recovered Carbonyl
H	H	H	65	9
H	H	CH_3	58	5
H	CH_3	CH_3	63	7
CH_3	H	H	68	14
CH_3	CH_3	CH_3	56	22
CH_3	CH_3	CH_3	26	56

bromoacetate under Reformatsky conditions. The amount of recovered ketone was high (48%). The low yields and high recovery of starting material are presumably due to the blocking effect of the 3-methyl group on the thiophene ring. A similar result was reported by Newman (56) for the Reformatsky reaction involving acetyl mesitylene. Newman attributed the high recovery of unchanged acetyl mesitylene to enolization of the ketone by the organometallic derivative which then reacted with the enol form of the ketone to produce a reduced ester and the halozinc complex of the enol. On hydrolysis of the reaction mixture the halozinc complex regenerates the ketone.

$$R\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \xrightarrow{XZn\text{-}CH_2\text{-}COOR} R\text{-}CH{=}\overset{OH}{\overset{|}{C}}\text{-}R$$

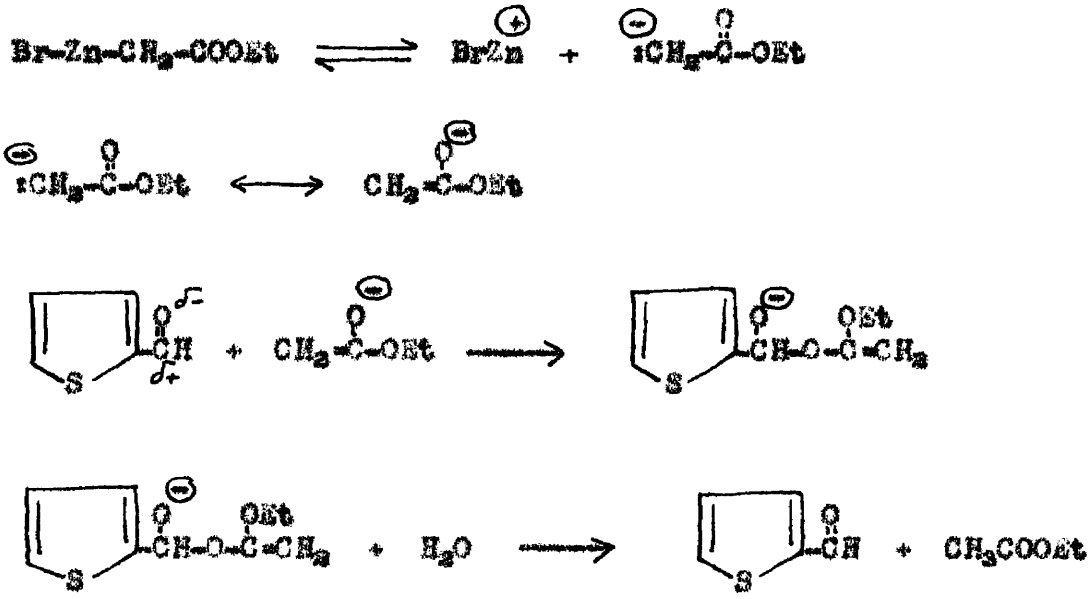
$$R\text{-}CH{=}\overset{OH}{\overset{|}{C}}\text{-}R + XZn\text{-}CH_2\text{-}COOR \longrightarrow R\text{-}CH{=}\overset{OZnX}{\overset{|}{C}}\text{-}R + CH_2\text{-}COOR$$

$$R\text{-}CH{=}\overset{OZnX}{\overset{|}{C}}\text{-}R + HA \longrightarrow R\text{-}CH{=}\overset{OH}{\overset{|}{C}}\text{-}R + ZnXA$$

The amount of enolization has been found to be a function of the type of solvent, the halogen employed, and the steric blocking by groups in the ketone (56,57). Usually the enolization reaction proceeds at a slower rate than the normal reaction except in those cases where steric factors hinder formation of the normal product.

From the reactions involving the aldehydes of thiophene some unreacted aldehyde was recovered. This recovery, 5-10%, was accompanied, as with the ketones by a comparable amount of reduced ester.

As enolization does not occur with aldehydes of thiophene, their recovery in the Reformatsky reaction must be accounted for by some other explanation. The ideas offered by Jones and collaborators (17) for the recovery of benzaldehyde from its reaction with methyl γ-bromocrotonate may be offered as an explanation. The organozinc derivative of the ester dissociates into ionic species. A resonance structure with the negative charge on the carbonyl oxygen then attacks the aldehyde and results in a product which, when hydrolyzed, would yield the aldehyde and reduced ester.



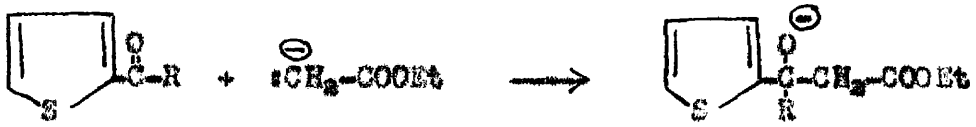
When ethyl α-bromopropionate served as the active halogen component in the Reformatsky reaction, yields were slightly lower, 54-63%, except where 2-acetyl-3-methyl thiophene was used in which case the yield was only 20%. Apparently any increased steric effect of the longer carbon chain in the haloester is overcome by the increased

reactivity of the secondary halogen. The percentages of recovered starting material were not appreciably different from those where ethyl bromoacetate was used. Once again, no important variation in yields was noticed with the variation in the length of the carbon chain in the acyl group of the carbonyl derivative.

The use of ethyl -bromoisobutyrate resulted in considerable fluctuation of yields of products obtained. From 2 and 3-thenal yields of 64 and 63% were obtained, while with 2 and 3-acetyl thiophene yields of only 15 and 26% were obtained. The longer chained 2-acyl thiophenes gave only large amounts of recovered ketone. Similar results were observed where 2-acetyl-3-methyl thiophene was employed. The results with the acyl thiophenes are due to the heavy blocking effect of the two α-methyl groups in the haloester. The enolization reaction is the only one that proceeds at any reasonable rate. Increasing the reaction time and raising the temperature of the reaction resulted in excessive decomposition and no improvement in yields.

As an over-all observation, some slight improvement in yields was noted for those cases where the 3-thienyl derivatives were employed in comparison with the corresponding 2-thienyl compounds. This difference may have been greater in view of the fact that the molar quantities utilized in the reactions of the 3-thienyl derivatives were only one-half of the amounts used for the 2-thienyl carbonyl compounds. The percentage lost through mechanical manipulations was certainly larger in the cases of 3-thienyl compounds which were used in smaller quantities because of the much greater difficulties involved in their preparation.

Any difference in yields between the two groups of isomers may be due to the increased electronegativity of the two position in the thiophene ring as compared to that of the three position resulting in a slightly decreased tendency for the negative species to attack the carbonyl carbon. Thus, according to the possible mechanism,



the more electronegative the carbonyl carbon the less is the likelihood that the anionic attack will occur.

The use of dioxane as a reaction solvent was studied to determine if yields were decreased due to the promotion of enolization as was reported, by Hussey and Newman (57), in the phenyl ketones. These investigators found that yields were reduced by as much as 40% with the recovery of unreacted ketone being proportionately higher. Maintaining other conditions constant, dioxane was used instead of benzene as a solvent in the Reformatsky reaction of the thienyl ketones, and it was observed that yields were reduced by only 10-20% for the thiophene derivatives. Correspondingly greater reductions were observed in those cases where ethyl bromoacetate was used than in those where ethyl α-bromopropionate was the halogen component. No significant variation was noted in the amount of enolization in dioxane with the variation in the size of the acyl chain. The use of dioxane as a solvent for the reactions of the 3-thienyl ketones was not investigated because of

the limited quantity of these compounds available. The results of this study are recorded in Table III.

The dehydration of the Reformatsky products to the corresponding unsaturated esters was carried out according to a procedure described by Miller and Nord (65). Five gram quantities of the β-hydroxyesters were refluxed in 6% oxalic acid solution for six hours. The product was extracted with ethyl ether and after drying and concentration of the solution, the ethyl β-(thienyl) acrylate was distilled under reduced pressure. The use of acetic anhydride, 85% formic acid (76), zinc chloride in acetic acid (77), or benzene solutions of iodine (78) as a dehydrating agent resulted in the formation of tars and highly colored reaction mixtures. The unsaturated products are presumed to be α,β-unsaturated, but there is the possibility that in certain instances β,γ-unsaturated esters may have been produced (79). In no case, however, were two isomeric unsaturated esters isolated. Through the dehydration reaction, eight ethyl β-(thienyl) acrylates which have not been previously reported were prepared. Some of the properties of these compounds are recorded in Table V.

Reformatsky Reaction of Ethyl γ-Bromocrotonate

The reaction of ethyl γ-bromocrotonate with thienyl carbonyl derivatives under Reformatsky conditions yields a variety of products, the origin of which are dependent on the nature of the carbonyl component. The carbonyl compounds investigated were 2-thenal, 3-thenal, 2-acetylthiophene, 2-propionylthiophene, 2-butyrylthiophene and 2-acetyl-3-methyl thiophene.

TABLE V

ETHYL β-(THIENYL) ACRYLATES

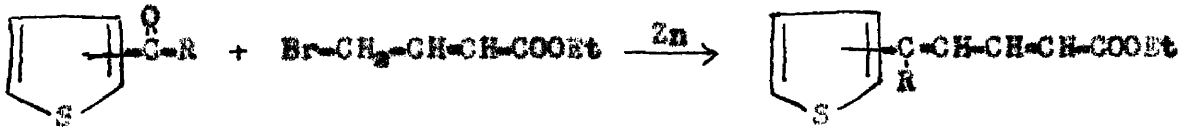
Thienyl Derivative	R	R'	Formula	B.p. °C	(mm. Hg)	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	H	H	$C_9H_{10}O_2S$	115-116	(1)	a			
2	H	CH_3	$C_{10}H_{12}O_2S$	109-110	(0.5)	a			
2	CH_3	H	$C_{10}H_{12}O_2S$	104-106	(1)	a			
2	CH_3	CH_3	$C_{11}H_{14}O_2S$	110-112	(3)	a			
2	C_2H_5	H	$C_{11}H_{14}O_2S$	116-117	(1)	62.8	62.2	6.8	6.7
2	C_2H_5	CH_3	$C_{12}H_{16}O_2S$	111-112	(1)	64.3	64.5	7.1	7.1
2	n-C_3H_7	H	$C_{12}H_{16}O_2S$	117-119	(1)	64.3	64.3	7.1	7.3
2	n-C_3H_7	CH_3	$C_{13}H_{18}O_2S$	114-115	(1)	65.6	65.7	7.6	7.5
3	H	H	$C_9H_{10}O_2S$	114-115	(1)	59.3	59.4	5.5	5.6
3	H	CH_3	$C_{10}H_{12}O_2S$	112-113	(1)	61.2	60.7	6.1	6.3
3	CH_3	H	$C_{10}H_{12}O_2S$	99-100	(1)	61.2	61.0	6.1	6.3
3	CH_3	CH_3	$C_{11}H_{14}O_2S$	103-105	(1.5)	62.8	62.5	6.8	6.8

a Previously prepared and reported (65).

Benzene was found to be the best reaction medium for the Reformatsky reaction of ethyl γ-bromocrotonate with the thienyl carbonyl derivatives. Ethyl ether, toluene or benzene-toluene mixtures offered no advantages.

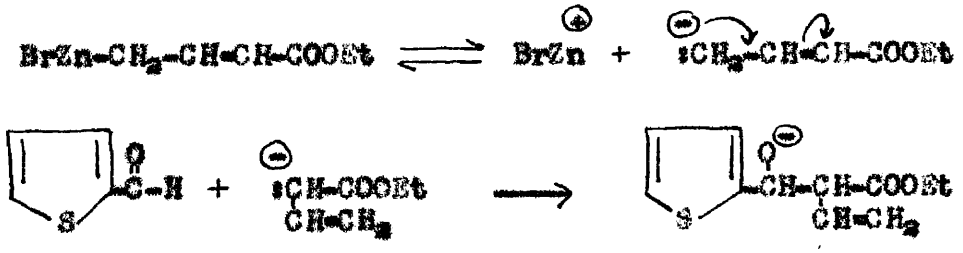
In the case of 2- and 3-thenal, the hydroxyesters were isolated in a pure condition from the reaction mixture by vacuum distillation. The products of 2-acetyl, 2-propionyl, 2-butyryl, and 2-acetyl-3-methyl thiophene were contaminated by the corresponding dehydration products. The dehydration of the hydroxyesters is presumed to have occurred during their distillation, since repeated distillation failed to improve the purity of the products, and only resulted in further dehydration. These products were, therefore, converted to the unsaturated esters by refluxing for eight hours in a 6% oxalic acid solution. Miller and Nord (16) were unable to isolate either the hydroxy or unsaturated esters and so saponified and dehydrated the products with methanolic sodium hydroxide to obtain the corresponding acids.

By the Reformatsky reaction of ethyl γ-bromocrotonate with carbonyl compounds of thiophene a variety of branched ethyl 5-(thienyl)-5-alkyl-2,4-pentadienoates were synthesized.



The interaction of both 2- and 3-thenal with ethyl γ-bromo-crotonate resulted in two isomeric hydroxyesters whose boiling points

differed by approximately 25° C. The lower boiling of the products, which was isolated in the larger amount, rapidly adsorbed one mole of bromine. Further, the treatment of the lower boiling ester with ozone followed by hydrolysis of the ozonide, resulted in the formation of formaldehyde. This latter observation is indicative of a terminal multiple bond linkage, while the rapid reaction with bromine is characteristic of a double bond which is not adjacent to an electronegative group. Consideration of these two reactions strongly suggest that a rearranged product having a terminal vinyl group was formed. The higher boiling isomer reacted with bromine at a much slower rate, a property characteristic of a double bond adjacent to or in conjugation with an electronegative group. Although Miller and Nord (16) were unable to isolate any products corresponding to α -vinyl esters, the isolation of such rearranged products have been effected before in Reformatsky reactions employing methyl γ -bromocrotonate (17,18). These investigators reported that the α -vinyl isomer boils at a considerably lower temperature than does the normal product. The present investigation confirms this observation. Presumably, the α -vinyl derivative results through a charge migration in the negative species of the organozinc halide.



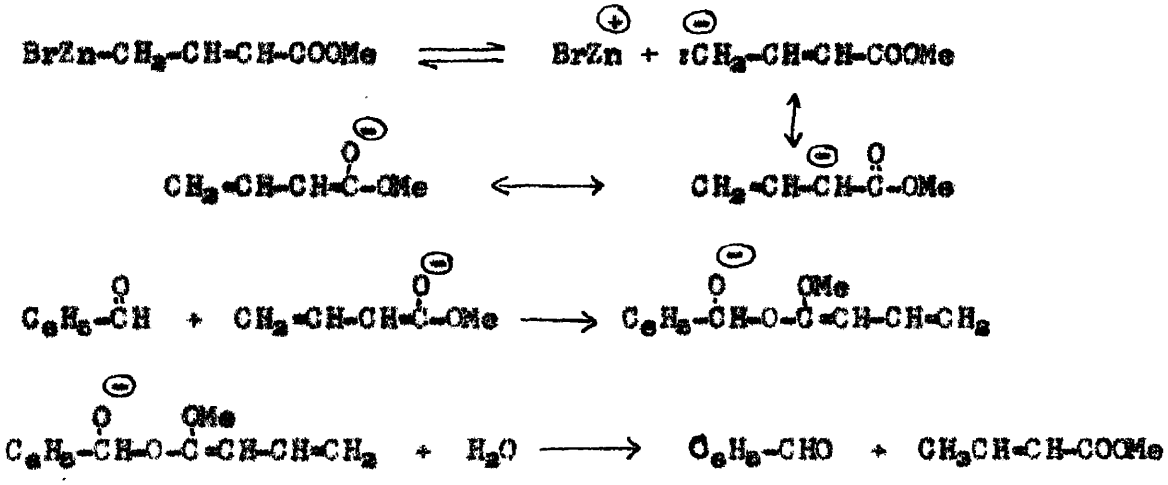
In the case of 2-thenal, the yield of α-vinyl-β-hydroxyester was 28% of the theoretical while that of the normal product was 16% of the theoretical. With 3-thenal the yields of the vinyl isomers were 29% and 17% respectively.

The formation of an α-vinyl isomer was noted to have occurred with 2-acetylthiophene although to a lesser extent than with the aldehyde, 2-thenal. The normal hydroxy ester tended to dehydrate upon distillation while the α-vinyl derivative could be isolated and characterized as the hydroxyester. The normal product was dehydrated and characterized as the alkadienoic ester. The yield of α-vinyl isomer was 7% of the theoretical while that of the normal product was 26% of the theoretical. There were no isomeric products formed in these reactions where 2-propionyl and 2-butyrylthiophene served as the carbonyl compound. Presumably, the increase in size of the ketonic alkyl group tends to inhibit the attack of the more bulky anionic species bearing the charge on the α-carbon.

Large quantities (52-62%) of recovered thienyl ketones resulted from their interaction with ethyl γ-bromocrotonate. A comparable quantity of ethyl crotonate was isolated from each of the reaction mixtures. This may be ascribed to enolization of the ketone by the organozinc halide intermediate resulting in reduction of the halocster and the recovery of unchanged ketone.

A small amount (10-11%) of recovered aldehyde was found in those reaction mixtures in which the thenals were employed. Jones, O'Sullivan

and Whiting (17) observed a similar occurrence when benzaldehyde, which cannot enolize, underwent the Reformatsky reaction with methyl γ-bromocrotonate. The explanation was advanced that the isolation of benzaldehyde was due to the formation from the γ-bromocrotonate of an intermediate which is a resonance hybrid and as such can react to form an anionic species of the organozinc halide which on hydrolysis yields benzaldehyde and reduced ester.



A similar mechanism accounts for the isolation of the thenals from the reaction mixtures in the present investigation.

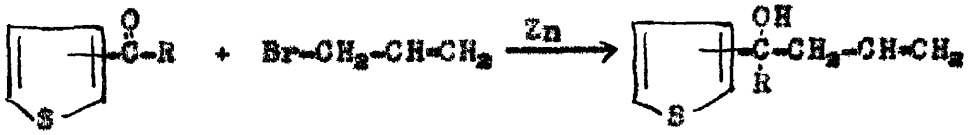
The Reformatsky reactions were carried out by mixing equimolar quantities of carbonyl compound, ethyl γ-bromocrotonate, and zinc dust in dry benzene. A small crystal of iodine was added as a reaction initiator, stirring was commenced and the bottom of the reaction vessel was heated gently to start the reaction. It was necessary to moderate the vigorous exothermic reaction by temporary immersion of the flask in an ice bath. The reaction mixture was heated at its reflux

temperature for one hour after the spontaneous refluxing had subsided to complete the reaction. After hydrolyzing the reaction mixture with an ice cold 10% sulfuric acid solution the non-aqueous layer was separated and extracted successively with water, sodium carbonate solution and water. The organic solution was dried over sodium sulfate and the solvents were removed, after which the residue was subjected to vacuum distillation. The forerun contained ethyl crotonate and unreacted carbonyl compound followed by the product or products.

Altogether, five thienyl substituted hydroxyesters which have not previously been reported were prepared. The properties of these materials are summarized in Table VI. In addition, six ethyl 5-(thienyl)-5-alkyl-2,4-pentadienoates were synthesized. A summarization of the properties of these compounds is shown in Table VII.

Reformatsky Reaction of Allyl Bromide

The condensation of allyl bromide with carbonyl derivatives of thiophene under the conditions of the Reformatsky reaction leads to the formation of 4-(thienyl)-4-hydroxy-1-alkenes.

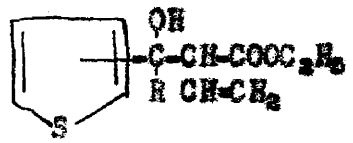


The use of allyl bromide in the Reformatsky reaction has received very little attention (19) previous to this investigation.

This active bromine compound was found to react with the thienyl carbonyl derivatives to give excellent yields of the expected product.

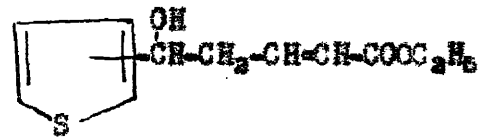
TABLE VI

ETHYL 2-ETHENYL-3-HYDROXY-3-(THIENYL)-ALKANOATES



Thienyl Derivative	R	Formula	B.p. °C	(mm.Hg)	% Yield	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	H	$C_{11}H_{14}O_3S$	132-134	(1)	28	58.3	58.6	6.2	6.3
2	CH_3	$C_{12}H_{16}O_3S$	107-108	(1)	7	59.9	59.7	6.7	6.8
3	H	$C_{11}H_{14}O_3S$	134-135	(1)	29	58.3	57.8	6.2	6.4

ETHYL 5-(THIENYL)-5-HYDROXY-2-PENTENOATES



Thienyl Derivative	Formula	B.p. °C	(mm. Hg)	% Yield	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	$C_{11}H_{14}O_3S$	160-161	(1)	16	58.3	58.6	6.2	6.0
3	$C_{11}H_{14}O_3S$	158-160	(1)	17	58.3	58.3	6.2	6.4

TABLE VII

ETHYL 5-(THIENYL)-2,4-ALKADIENOATES

Thienyl Derivative	R	Formula	B.p. °C	(mm. Hg)	% Yield	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	H	$C_{11}H_{12}O_2S$	148-149	(1)	a	63.5	63.7	5.8	5.9
2	CH_3	$C_{12}H_{14}O_2S$	147-148.5	(1)	26	64.8	64.7	6.3	6.4
2	C_2H_5	$C_{13}H_{16}O_2S$	149-150	(1)	25	66.1	65.9	7.6	7.8
2	n-C_3H_7	$C_{14}H_{18}O_2S$	162-164	(1)	32	67.9	68.0	7.2	7.4
3	H	$C_{11}H_{12}O_2S$	149-151	(1)	a	63.5	63.2	5.8	5.6
2-(3-Me)	CH_3	$C_{12}H_{14}O_2S$	164-165	(1)	20	66.1	65.9	7.6	6.9

a Prepared as derivatives

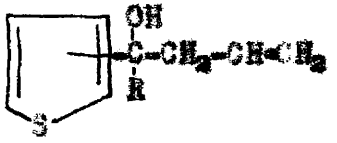
Since only very small quantities of unreacted ketone were recovered, it may be speculated that the enolization reaction is of minor importance when allylic bromides are used. There was no indication that the products obtained underwent any degree of dehydration during distillation at low pressures. The yields obtained were of the order 70-80% and very little variation in yields was noted between the thenals and acylthiophenes nor between the 2-thienyl and 3-thienyl derivatives.

The reaction was carried out by the interaction of equimolar quantities of carbonyl compound, allyl bromide and zinc dust in a mixture of equal volumes of benzene and tetrahydrofuran. The presence of the tetrahydrofuran prevented the precipitation of the allylzinc bromide intermediate which caused early termination of the Reformatsky reaction. After the initial exothermic reaction had subsided the reaction mixture was heated at its reflux temperature for an additional hour. Ice cold 30% acetic acid was used to achieve hydrolysis of the reaction mixture. After the aforementioned washings, drying and removal of the solvents, the residue was distilled in vacuo to yield, first, a very small amount of unreacted carbonyl compound followed by the pure liquid product.

Altogether, seven previously unreported 4-thienyl-4-hydroxy-1-alkenes were prepared by this procedure. Their physical properties are summarized in Table VIII.

TABLE VIII

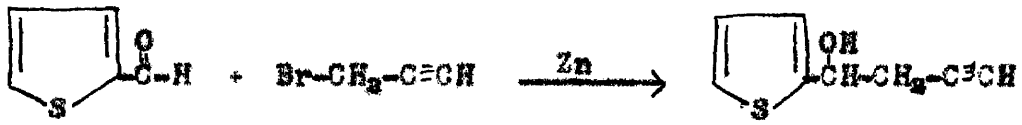
4-(THIENYL)-4-HYDROXY-1-ALKENES



Thienyl Derivative	R	Formula	B.p. °C	(mm. Hg)	% Yield	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	H	$C_8H_{10}OS$	89-90	(1)	78	62.3	62.1	6.5	5.9
2	CH_3	$C_9H_{12}OS$	82-84	(2)	70	64.3	64.5	7.1	6.9
2	C_2H_5	$C_{10}H_{14}OS$	94-96	(1.5)	72.5	65.9	65.7	7.7	7.9
2	n-C_3H_7	$C_{11}H_{16}OS$	94-95	(0.5)	73	67.3	66.8	8.2	8.1
3	H	$C_8H_{10}OS$	90-91	(1)	80	62.3	62.7	6.5	6.3
3	CH_3	$C_9H_{12}OS$	80-81	(1)	72	64.3	64.5	7.1	7.2
2-(3-Me)	CH_3	$C_{10}H_{14}OS$	97-98.5	(0.5)	70	65.9	65.7	7.7	7.8

Reformatsky Reaction of Propargyl Bromide

A previous report (66) describes only the interaction of propargyl bromide with 2-thenal to yield the expected 1-(2-thienyl)-3-butyn-1-ol. This study reports a more extensive investigation of this particular aspect of the Reformatsky reaction to a wide variety of carbonyl derivatives which included 3-thenal, 2-acetylthiophene, 2-propionylthiophene and 2-butyrylthiophene. The reaction was found to proceed as reported with 2-thenal resulting in a 60% yield of the expected product.



Likewise the reaction with 3-thenal took place with a 62% yield of the corresponding 3-thienyl derivative.

With the 2-thienyl ketones, however, even though the reaction appeared to proceed vigorously, with the zinc being completely consumed, it was impossible to obtain any Reformatsky type product. The recovery of unreacted ketone was for 2-acetylthiophene 64%, 2-propionylthiophene 76% and for 2-butyrylthiophene 73%. As small quantities of nondistillable material remained in the distillation flask it is possible that small amounts of the expected products may have been formed, but were destroyed by pyrolysis during the distillation. The use of a higher boiling solvent such as toluene or the increase of reaction time up to four hours gave no thienyl alkynols, but only resulted in more extensive decomposition in the reaction mixture. Based upon the large

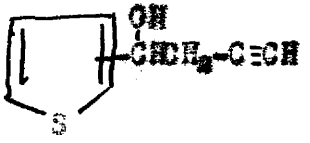
percentages of unreacted ketone recovered, it seems that the intermediate propargyl zinc bromide promotes considerable enolization of the 2-thienyl ketones. This result is in sharp contrast to the small amount of enolization which occurred in the Reformatsky reaction with allyl bromide. No suitable explanation may be offered for this phenomenon.

The Reformatsky reactions of propargyl bromide were carried out in the same manner as were those involving allyl bromide. The reactions proceeded vigorously and without the application of heat. Initially, cooling of the reaction vessel with an ice bath was required to moderate the reaction. Hydrolysis of the reaction mixture was accomplished with an ice cold 30% acetic acid solution. After the usual extractions, washings and drying the concentrated residue was distilled under reduced pressure.

The properties of the two 1-(thienyl)-3-butyn-1-ols which were prepared are reported in Table IX. One of these compounds has not been reported previously.

TABLE IX

1-(THIENYL)-3-BUTYN-1-OLS



Thienyl Derivative	Formula	B.p. °C	(mm. Hg)	% Yield	% Carbon Calc'd.	% Carbon Found	% Hydrogen Calc'd.	% Hydrogen Found
2	C_8H_8OS	84-85	(0.1)	60	a			
3	C_8H_8OS	83-84.5	(0.1)	62	63.2	63.2	5.3	5.5

a Previously prepared and reported (66).

CHEMICAL REAGENTS

Thiophene-Practical grade, Eastman Kodak Co.

Acetic Anhydride-95%, Eastman Kodak Co.

Propionic Anhydride-Practical grade, Eastman Kodak Co.

Butyric Anhydride-95%, Eastman Kodak Co.

Zinc dust-300 mesh, activated by immersion in hot concentrated sulfuric acid to which a few drops of nitric acid has been added. The zinc was washed with distilled water and acetone and dried at 50° C. for twenty minutes.

Benzene-C. P. grade, dried by distillation from sodium.

Tetrahydrofuran-C. P. grade, dried by distillation from sodium.

Dioxane-C. P. grade, dried with magnesium sulfate and stored over sodium.

Toluene-C. P. grade, dried by distillation from sodium.

3-Methyl thiophene-Courtesy of Socony-Vacuum Oil Co., purified by drying over magnesium sulfate and distillation from sodium.

Ethyl bromoacetate-White label, Eastman Kodak Co.

Ethyl α-bromopropionate-White label, Eastman Kodak Co.

Formaldehyde-Practical, 37% solution.

Isobutyric Acid-Practical, Eastman Kodak Co.

Crotonic Acid-Practical, Eastman Kodak Co.

N-Bromosuccinimide-White label, Eastman Kodak Co.

Benzoyl Peroxide-Commercial grade, Lucidol Corp.

Carbon Tetrachloride-C. P. grade, absolute, Merck & Co.

Allyl Bromide-White label, Eastman Kodak Co., purified by drying over magnesium sulfate and distillation through a Claisen column.

Dimethylformamide-White label, Eastman Kodak Co.

Hexamethylenetetramine-White label, Eastman Kodak Co.

Chloroform-C. P. grade, absolute, Merck & Co.

Thionyl chloride-C. P. grade, purified by distillation from quinoline followed by distillation from boiled linseed oil.

Methyl Bromide-White label, Eastman Kodak Co.

Magnesium-C. P. turnings, Eastman Kodak Co.

Cadmium chloride-C. P. anhydrous, Baker Chemical Co.

Propargyl Alcohol-White label, Eastman Kodak Co.

Pyridine-Practical, Eastman Kodak Co., distilled from barium oxide.

Phosphorus Tribromide-Practical, Eastman Kodak Co.

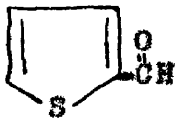
Phosphorus Trichloride-Practical, Eastman Kodak Co.

Phosphorus Oxychloride-Practical, Eastman Kodak Co.

EXPERIMENTAL

Preparation of Intermediates

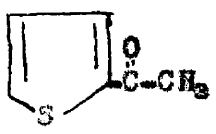
2-Thenal



Method A -- A well stirred mixture of 252 g. (3.0 moles) of thiophene, 1020 g. (12 moles) of 37% formaldehyde and 321 g. (6 moles) of ammonium chloride was heated to 67° and allowed to cool to 55°. At 67° the cloudy reaction mixture cleared and became straw colored. By the careful addition of 10% potassium hydroxide solution with rapid stirring, the reaction mixture was brought to a pH of 6 (Universal Indicator paper). The mixture was steam distilled; the portion boiling above 98° was collected and neutralized with concentrated hydrochloric acid to a pH of 6.5. After separation of the oily layer, the aqueous layer was extracted three times with 300 ml. portions of ethyl ether. The extracts were combined with the oil and dried over anhydrous calcium sulfate. After removal of the ether the residue was distilled in vacuo through a Claisen column to yield 153 g. (1.37 moles; 46%) of clear pleasant smelling product. Its physical properties were: b.p. 51° (1 mm.); n_D^{25} 1.5927. The reported physical properties of the product are: b.p. 72.5° (7 mm.); n_D^{25} 1.5920 (67).

Method B -- In a one liter three-necked flask fitted with a reflux condenser, stirrer and dropping funnel were placed 126 g. (1.5 moles) of thiophene and 138 g. (1.92 moles) of dimethylformamide. From the dropping funnel 288 g. (1.86 moles) of phosphorus oxychloride was added slowly to the rapidly stirred and cooled reaction mixture. After an initial heating on the steam bath the reaction commenced and proceeded vigorously with the evolution of hydrogen chloride. When the initial reaction had subsided the reaction mixture was heated for one hour with stirring on the steam bath and then cooled to room temperature. The dark colored solution was poured over 1500 g. of cracked ice and treated with 300 ml. of saturated sodium acetate. The oily layer which separated was combined with subsequent ether extracts of the aqueous layer and washed thoroughly with 10% sodium bicarbonate solution. After drying over anhydrous sodium sulfate, the ether solution was concentrated on the steam bath and the residue was distilled under reduced pressure. A forerun of unreacted thiophene was followed by 124 g. (1.11 moles; 74%) of clear liquid. Its physical properties were b.p. 47-48° (0.3 mm.); n_D^{25} 1.5906.

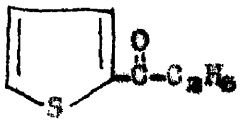
2-Acetylthiophene



To a mixture, heated to 70°, of 378 g. (4.5 moles) of thiophene and 175 g. (1.55 moles) of 95% acetic anhydride contained in a one

liter three-necked flask fitted with a reflux condenser and thermometer was added 15 g. of 85% phosphoric acid. A vigorous reaction set in on shaking the flask and its contents necessitating immersion of the reaction vessel in an ice bath to control the temperature of the solution which rose rapidly to 90°. After being set aside for a half hour the mixture was refluxed at 96° for two hours and allowed to cool to 50°. A volume of 300 ml. of water was added to the reaction flask followed by shaking of the mixture for five minutes. The organic layer was separated and washed with 300 ml. of 10% sodium carbonate followed by washing with 300 ml. of water. The solution was transferred to a Claisen flask where a thiophene-water azeotrope was removed by distillation at 68° followed by the excess thiophene at 84°. The apparatus was arranged for vacuum distillation and a water clear product was obtained. Its physical properties were: b.p. 75° (3 mm.); n_D^{25} 1.5637. A total of 168 g. (1.33 moles; 86%) of 2-acetylthiophene was obtained. The reported (70) physical properties of this compound are: b.p. 77° (4 mm.); n_D^{25} 1.5640.

2-Propionylthiophene



Using the apparatus and procedure described above, 504 g. (6.0 moles) of thiophene, 301 g. (2.2 moles) of propionic anhydride and 20 g. of phosphoric acid were interacted at a reflux temperature of 100°.

After the addition of water and washing the crude product in the manner described in the previous preparation the organic layer was concentrated and distilled at reduced pressure. There was received 224 g. (1.60 moles; 72.7%) of clear liquid whose physical properties were: b.p. 82-83° (1 mm.); n_D^{25} 1.5442. The reported (80) physical properties are: b.p. 88° (7 mm.); n_D^{25} 1.5435.

2-Butyrylthiophene

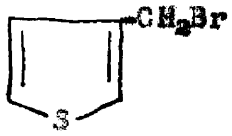
The apparatus and procedure employed here were the same as that used in the two previous preparations. This compound was prepared by the reaction of 504 g. (6.0 moles) of thiophene with 366 g. (2.2 moles) of 95% butyric anhydride in the presence of 20 g. of phosphoric acid. This reaction mixture was heated at its reflux temperature of 106° for two hours. Following the separation procedure used in the former preparations, the crude product was fractionated, yielding 254 g. (1.65 moles; 74.5%) of pure product which had the following physical properties: b.p. 83-85° (1 mm.); n_D^{25} 1.5408. Its reported (80) physical properties are: b.p. 87-92° (3 mm.); n_D^{25} 1.5418.

2-Acetyl-3-methyl thiophene

Using the same general procedure discussed above, 294 g. (3.0 moles) of 3-methyl thiophene, 175 g. (1.55 moles) of 95% acetic anhydride and 15 g. of phosphoric acid were interacted and the crude product was isolated in the usual manner. Fractionation of the crude product through a column 30 cm. in height, 12 mm. in diameter packed with 1/8" glass helices, yielded 143 g. (1.02 moles; 66%) of 2-acetyl-3-methyl thiophene, refractive index n_D^{25} 1.5604, boiling at 74-74.5° (1 mm.), and 26 g. (0.185 moles; 12%) of 2-acetyl-4-methyl thiophene, refractive index n_D^{25} 1.5581, boiling at 77.5-78.5° (1 mm.). The reported (81) physical constants for 2-acetyl-3-methyl thiophene are: b.p. 79° (4 mm.); n_D^{25} 1.5618; and those for 2-acetyl-4-methyl thiophene are: b.p. 86° (3 mm.); n_D^{25} 1.5600.

For further characterization the thiosemicarbazones of 2-acetyl-3-methyl and 2-acetyl-4-methyl thiophene were prepared. The melting points for these derivatives were 206-207° and 219-220° respectively. The reported (81) melting points for the thiosemicarbazones are for 2-acetyl-3-methyl thiophene, 207-207.5° and for 2-acetyl-4-methyl thiophene, 219-220°.

3-Thenyl Bromide

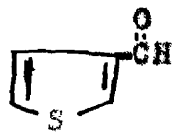


In a two liter three-necked flask fitted with an efficient reflux condenser and stirrer were placed 282 g. (2.88 moles) of 3-methyl

thiophene and 3.5 g. of benzoyl peroxide dissolved in 700 ml. of dry carbon tetrachloride. To this solution was added, with stirring, 500 g. (2.88 moles) of N-bromosuccinimide containing an additional quantity of 4 g. of benzoyl peroxide. The brominating agent was added during a two hour period and at such a rate as to allow a steady refluxing of the reaction mixture. Following the complete addition of the N-bromosuccinimide the reaction mixture was heated at its reflux temperature for five hours and then allowed to cool to room temperature. The insoluble succinimide was removed by filtration and the filtrate was concentrated at reduced pressure. The residue on vacuum distillation yielded 309 g. (1.75 moles; 60.6%) of pungent smelling liquid boiling at 75-82° (1 mm.). The reported (72) boiling point of 2-thenyl bromide is 75-78° (1 mm.).

Of two previous preparations of 2-thenyl bromide one became so violent that the reaction mixture was lost through the condenser, the other gave 178 g. (1.01 moles) only a 35% of the expected product. It should be noted that a stored sample of about 200 g. of 3-thenyl bromide decomposed with considerable violence after several months of standing.

3-Thenal



To 177 g. (1.0 mole) of 3-thenyl bromide in 350 ml. of chloroform contained in a one liter flask fitted with a reflux condenser was

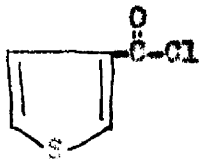
added 138 g. (1.0 mole) of hexamethylenetetramine. The mixture was heated at its reflux temperature for one hour, cooled and filtered. The white crystalline solid was dissolved in 500 ml. of water and steam distilled until one liter of distillate had been collected. After neutralization of the distillate with dilute hydrochloric acid the oily organic layer was separated and combined with three subsequent ether extractions of the aqueous layer. Using calcium sulfate, the ether solution was dried and then concentrated on the steam bath. By distillation at reduced pressure 54 g. (0.48 mole; 48%) of clear liquid product was obtained. Its physical properties were: b.p. 76-77° (12 mm.). The reported (82) physical properties of 3-thenal are: b.p. 78° (14 mm.). This preparation was repeated to yield 55 g. (0.49 mole; 49%) of 3-thenal.

3-Thenoic Acid

The combination of a solution of 150 g. (0.883 mole) of silver nitrate in 300 ml. of water with a solution of 70 g. (1.75 moles) of sodium hydroxide in 300 ml. of water gave a brown suspension of silver oxide. To this suspension was added, with rapid stirring, 47.5 g. (0.424 mole) of 3-thenal over a 25 minute period, during which time it was necessary to cool the reaction mixture to moderate the exothermic reaction. At the completion of the addition of thenal the characteristic

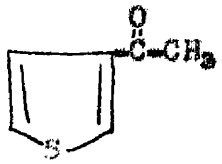
odor of this aldehyde had disappeared and a heavy precipitate of silver had settled to the bottom of the beaker. The metallic silver was removed by filtration and washed with 200 ml. of water which was combined with the basic filtrate. Acidification of the filtrate with concentrated hydrochloric acid caused the precipitation of a white solid. The mixture was set aside in the refrigerator for twelve hours during which time 51 g. (0.40 mole; 95%) of product crystallised from solution. It was filtered and dried. The product had a melting point of 135.5-137°. The reported (72) melting point is 137-138°.

3-Thenoyl chloride



The addition of 59.5 g. (0.50 mole) of thionyl chloride to 51 g. (0.40 mole) of 3-thenoic acid over a two hour period, during which time the reaction mixture was kept at its reflux temperature, gave a clear yellow solution. After removal of the excess thionyl chloride on the steam bath the residue was distilled under reduced pressure. At a temperature of 99-101° (30 mm.) there was obtained 46.7 g. (0.32 mole; 80%) of slightly yellow liquid product which solidified to a solid having a melting point of 49-51°. The reported (72) physical constants for this acid chloride are: b.p. 110-111° (36 mm.); m.p. 51-52°.

3-Acetylthiophene



Methyl magnesium bromide was prepared by the interaction of 43 g. (0.46 mole) of methyl bromide with 11 g. (0.46 mole) of magnesium turnings in 300 ml. of anhydrous ether. To this rapidly stirred and cooled Grignard reagent was added 44.7 g. of finely powdered anhydrous cadmium chloride. The reaction vessel was removed from the cooling bath and the mixture stirred for an additional hour at room temperature. After replacing the reaction vessel in a cooling bath, 46.7 g. (0.32 mole) of 3-thenoyl chloride was added in small portions. When the spontaneous refluxing had subsided the reaction mixture was heated at its reflux temperature for an hour and then allowed to cool to room temperature. The heterogeneous solution was poured, with vigorous stirring, onto a mixture of dilute sulfuric acid and cracked ice. A 300 ml. ether extract of the mixture was washed twice with water and dried over anhydrous sodium sulfate. After removal of the ether the residue was distilled under reduced pressure to yield 29.5 g. (0.234 mole, 73%) of clear product with the physical constants: b.p. 77-78° (4 mm.); n_D^{25} 1.5621. The reported (72) boiling point is 84-85° (6 mm.); n_D^{25} 1.5612.

The 2,4 dinitrophenylhydrazone of the product had a melting point of 265.5-266°. The reported (72) melting point is 265°.

Ethyl α-bromoisobutyrate

$$\begin{array}{c} CH_3 \\ Br-C-COOC_2H_5 \\ CH_3 \end{array}$$

Into a one liter three necked flask fitted with an efficient reflux condenser, thermometer and dropping funnel were added 275 g. (3.13 moles) of isobutyric acid 5 g. of phosphorus pentachloride. To the stirred solution, maintained at a temperature of 78°, was added cautiously 525 g. (3.28 moles) of bromine. The resulting dark colored reaction mixture was heated on the steam bath for seven hours during which time the temperature of the mixture rose to 87° and the red color of bromine practically disappeared. After being set aside overnight the mixture was warmed to remove any unreacted bromine and it was then treated cautiously with 440 g. (3.70 moles) of thionyl chloride followed by heating of the reaction mixture for a two hour period at its reflux temperature. The condenser was then removed and the excess thionyl chloride allowed to boil off. To the solution, after allowing it to cool to room temperature, was slowly added 184 g. (4.0 moles) of ethyl alcohol with an occasional shaking of the reaction vessel. Following the addition of the alcohol the solution was heated at reflux temperature for fifteen minutes and then transferred to a one liter Claisen distillation apparatus. The ethanol and a small quantity of unreacted ethyl butyrate were removed by distillation at atmospheric pressure and the apparatus was then arranged for vacuum distillation. Distillation under these conditions gave 467 g. (2.40 moles; 77%) of

clear liquid product distilling at 50-51° (10 mm.) which had a refractive index of n_D^{25} 1.4407. The reported (83) boiling point is 63-65° (14 mm.).

Ethyl crotonate

$$CH_3CH=CH-COOC_2H_5$$

A mixture of 258 g. (3.0 moles) of crotonic acid, 750 ml. of ethanol and 250 g. of sulfuric acid was placed in a two liter flask fitted with a reflux condenser and heated at its reflux temperature for three hours. The resulting slightly yellow reaction mixture was then poured into a three liter beaker containing 1000 g. of cracked ice and neutralized by the careful addition of 25% sodium hydroxide solution using litmus paper to indicate neutrality. After removal of the excess ethanol by distillation the two layers were separated and the aqueous layer was extracted with 250 ml. of ethyl ether. The ether extract was combined with the nonaqueous layer and dried over anhydrous sodium sulfate. After removing the ether on a steam bath there remained a straw colored oily liquid which on distillation yielded 266 g. (2.26 moles; 75%) of product boiling at 137-139°. The reported (83) boiling point is 136.7°.

Ethyl γ-bromocrotonate

$$Br-CH_2-CH=CH-COOC_2H_5$$

To a one liter flask fitted with a reflux condenser was added

118 g. (1.0 mole) of ethyl crotonate, 174 g. (1.0 mole) of N-bromosuccinimide, 1.17 g. of benzoyl peroxide and 400 ml. of carbon tetrachloride. This mixture was heated at its reflux temperature for an hour and a half and then treated with an additional 200 ml. of carbon tetrachloride followed by immediate filtration to remove the insoluble succinimide. The filter cake was washed thoroughly with carbon tetrachloride and the combined filtrate was concentrated and distilled under reduced pressure. After a forerun of a few milliliters of ethyl crotonate there was obtained 158 g. (0.82 moles; 82%) of a clear product having the physical constants: b.p. 74.5-76° (2 mm.); n_D^{25} 1.4932. The reported (74) physical constants of this compound are: b.p. 92-93° (10 mm.) n_D^{25} 1.4941.

Propargyl bromide

$$Br\text{-}CH_2\text{-}C\equiv CH$$

To a solution of 119 g. (1.0 mole) of propargyl alcohol and 12 g. of pyridine contained in a 500 ml. three necked flask fitted with a dropping funnel and reflux condenser with an attached drying tube was added dropwise, with occasional shaking of the reaction flask, 95 g. (0.35 mole) of phosphorus tribromide. The temperature of the reaction mixture was held at -10° by means of an ice-salt bath during the addition of the prominating agent. After the complete addition of the latter the reaction mixture was immediately distilled to yield 86 g. (0.72 mole; 72%) of a water clear product boiling at 81.5-84°. The reported (75) boiling point of propargyl bromide is 82-85°.

Reformatsky Reactions of ∝ -Bromoesters

Ethyl 3-(2-thienyl)-3-hydroxypropanoate

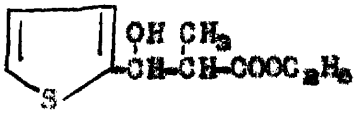
Under anhydrous conditions, 11.2 g. (0.10 mole) of 2-thenal, 16.7 g. (0.10 mole) of ethyl bromoacetate and 50 ml. of dry benzene were placed in a 250 ml. three necked flask equipped with an efficient stirrer and a reflux condenser fitted with a drying tube. To the mixture in the flask was added 6.5 g. (0.10 mole) of dry acid washed zinc dust, and a small crystal of iodine. After starting the stirrer, the reaction flask was heated lightly to initiate the reaction after which it was necessary to moderate the vigorous reaction by a brief immersion of the reaction vessel in an ice bath. When the initial exothermic reaction had subsided, the mixture was heated, with stirring, at its reflux temperature for an hour. The reaction mixture, after being allowed to cool to room temperature, was hydrolyzed by the addition, with rapid stirring, of 75 ml. of an ice cold 10% sulfuric acid solution. The non-aqueous layer was separated and combined with a subsequent ether extract of the aqueous portion. The combined solutions were given consecutive treatments with 100 ml. of water, 100 ml. of 10% sodium carbonate solution and 100 ml. of water followed by drying over anhydrous sodium sulfate. The ether and benzene were removed at reduced pressure and the residue was distilled under vacuum.

At 63-64° (4 mm.) 0.7 g. of 2-thenal was recovered followed by 12.8 g. (0.062 mole; 62%) of a clear colorless product boiling at 113-114° (0.2 mm.) which had a refractive index of n_D^{25} 1.5220. Analysis of the compound for carbon and hydrogen gave the following results:

Calc'd. for $C_9H_{12}O_3S$: C, 54.0; H, 6.0.
Found: C, 54.1; H, 6.2.

A previous preparation of this material following the above procedure resulted in a 51.5% yield of the expected product. When toluene was employed as the solvent with other experimental conditions being held constant the yield dropped to 7.5% of the theoretical amount and the quantity of undistillable residue in this case was 10.0 g.

Ethyl 3-(2-thienyl)-3-hydroxy-2-methylpropanoate



Using the apparatus and procedure described above, 11.2 g. (0.10 mole) of 2-thenal, 18.1 g. (0.10 mole) of ethyl α-bromopropionate and 6.5 g. (0.10 mole) of zinc dust were allowed to interact in 50 ml. of dry benzene as a reaction media. After hydrolysis and several washings the crude product was distilled to yield 0.3 g. of 2-thenal followed by 9.7 g. (0.057 mole; 57%) of slightly yellow product, with a refractive index of n_D^{25} 1.5129, and boiling at 108-110° (0.5 mm.). The reported (65) physical properties of this substance are: b.p. 119-122° (4 mm.); n_D^{25} 1.5151.

Ethyl 3-(2-thienyl)-3-hydroxy-2,2-dimethylpropanoate

The apparatus and procedure employed were the same as in previous preparations. The above compound was prepared by the interaction of 5.6 g. (0.05 mole) of 2-thenal, 9.75 g. (0.05 mole) of ethyl α-bromoisobutyrate and 3.25 g. (0.05 mole) of dry zinc in 25 ml. of anhydrous benzene. Following the separation procedure used in the former experiments, the crude product was fractionated to yield 7.3 g. (0.032 mole; 64%) of straw colored product whose physical constants were: b.p. 113-114° (0.1 mm.); n_D^{25} 1.5112. Analysis of the compound for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{16}O_3S$: C, 57.9; H, 7.0.
Found: C, 57.9; H, 6.4.

Ethyl 3-(2-thienyl)-3-hydroxybutanoate

The interaction of 12.6 g. (0.10 mole) of 2-acetyl thiophene, 16.7 g. (0.10 mole) of ethyl bromoacetate, and 6.5 g. (0.10 mole) of zinc in 50 ml. of dry benzene proceeded vigorously and spontaneously. After the usual separation the residue was subjected to vacuum distillation, and there was obtained at 86-88° (2 mm.) 2.0 g. of 2-acetyl thiophene followed by the clear colorless product with the physical

properties: b.p. 93-94° (0.2 mm.); n_D^{25} 1.5083. The yield of product was 14.2 g. (0.066 mole; 66%). Analysis of the compound for carbon and hydrogen gave the following results:

Calc'd. for $C_{10}H_{14}O_2S$: C, 56.1; H, 6.5.
Found: C, 55.9; H, 6.6.

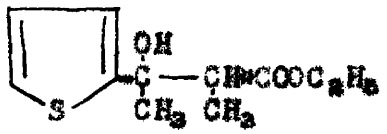
The use of only 25 ml. of benzene as a reaction solvent with the other experimental conditions and amounts of reactants being held constant resulted in a 32% yield of the same product.

A third preparation of this material involving initially the same reagents and amounts as above followed by the addition, after fifteen minutes, of an additional 1.6 g. (0.025 mole) of zinc and 4.2 g. (0.025 mole) of ethyl bromoacetate resulted in 14.0 g. (0.065 mole; 65%) of the expected hydroxy ester and the recovery of 2.3 g. of unreacted 2-acetyl thiophene.

When 50 ml. of anhydrous toluene was used instead of benzene as the reaction solvent the yield of product was reduced to 1.2 g. (0.0065 mole; 6.5%) and 3.8 g. of unchanged ketone was recovered, with the amount of high boiling by-products being 8.4 g.

The interaction of 12.6 g. of 2-acetyl thiophene, 16.7 g. of ethyl bromoacetate and 6.5 g. of zinc in 50 ml. of dry dioxane was vigorous and exothermic. Working up the product in the usual manner yielded 5.1 g. of unreacted 2-acetyl thiophene and 8.9 g. (0.042 mole; 42%) of product boiling at 102-104° (1 mm.) which had a refractive index of n_D^{25} 1.5077.

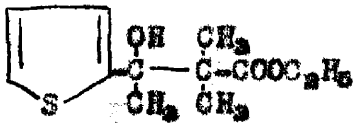
Ethyl 3-(2-thienyl)-3-hydroxy-2-methylbutanoate



The same general procedure as previously described was employed, using 12.6 g. (0.1 mole) of 2-acetylthiophene, 18.1 g. (0.1 mole) of ethyl α-bromopropionate and 6.5 g. (0.1 mole) of zinc dust in 50 ml. of dry benzene. Following the separation procedures discussed above, vacuum distillation of the crude product gave 4.1 g. of 2-acetylthiophene and 12.5 g. (0.055 mole; 55%) of slightly yellow liquid boiling at 102-103° (0.1 mm.). Its refractive index was n_D^{25} 1.5122. The reported (65) physical properties for this compound are: b.p. 113-117° (3 mm.); n_D^{25} 1.5168.

When the same reaction was carried out in 50 ml. of dioxane it gave 3.8 g. of unreacted ketone and 9.8 g. (0.053 mole; 53%) of the expected Reformatsky reaction product.

Ethyl 3-(2-thienyl)-3-hydroxy-2,2-dimethylbutanoate

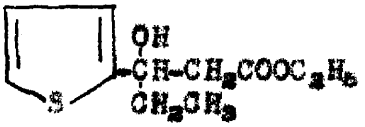


Using the same experimental technique as in the above reactions, 12.6 g. (0.10 mole) of 2-acetylthiophene, 19.5 g. (0.10 mole) of ethyl α-bromoisobutyrate and 6.5 g. (0.10 mole) of zinc were allowed to interact in 50 ml. of anhydrous benzene. After hydrolysis and

separation the residue was distilled under reduced pressure to yield 3.3 g. of ethyl isobutyrate and 3.9 g. of 2-acetylthiophene followed by 3.6 g. (0.015 mole; 15%) of light yellow liquid product boiling at 100-101° (0.1 mm.) with a refractive index of n_D^{25} 1.5534. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{18}O_3S$: C, 59.5; H, 7.4.
Found: C, 59.8; H, 7.3.

Ethyl 3-(2-thienyl)-3-hydroxypentanoate



To a dry three-necked 250 ml. flask fitted with stirrer and reflux condenser was added 14.0 g. (0.10 mole) of 2-propionylthiophene, 16.7 g. (0.10 mole) of ethyl bromoacetate, 6.5 g. (0.10 mole) of dry zinc dust and 50 ml. of dry benzene. The crude product was isolated in the usual manner and subjected to vacuum distillation to yield 2.1 g. of unreacted ketone boiling at 82-83° (1 mm.) and 14.8 g. (0.065 mole; 65%) of clear liquid product boiling at 95-96° (0.2 mm.), which had a refractive index of n_D^{25} 1.5105. Analysis of the compound for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{18}O_3S$: C, 57.9; H, 7.0.
Found: C, 58.2; H, 6.9.

When the above synthesis was repeated using only 25 ml. of benzene as a reaction solvent the amount of unreacted 2-propionylthiophene was 5.9 g. and the yield of product was 8.2 g. (0.036 mole, 36%).

The substitution of dioxane for benzene as a reaction media and maintaining other experimental conditions constant gave 5.2 g. of unreacted ketone and 9.2 g. (0.043 mole; 43%) of the expected product.

Ethyl 3-(2-thienyl)-3-hydroxy-2-methylpentanoate

Following the previously described method, 14.0 g. (0.10 mole) of 2-propionylthiophene, 18.1 g. (0.10 mole) of ethyl α-bromopropionate and 6.5 g. (0.10 mole) of zinc were allowed to interact in 50 ml. of dry benzene. After obtaining the crude product by methods already discussed it was distilled at reduced pressure to yield 1.8 g. of 2-propionyl thiophene and 12.3 g. (0.062 mole; 62%) of yellowish liquid product whose physical properties were: b.p. 103-104° (0.1 mm.); n_D^{25} 1.5018. Analysis of the compound for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{18}O_3S$: C, 59.5; H, 7.4.
Found: C, 59.6; H, 7.4.

Repetition of the above reaction using dioxane as a reaction media instead of benzene gave 4.8 g. of unreacted ketone and 11.1 g. (0.055 mole; 55%) of the expected hydroxy ester.

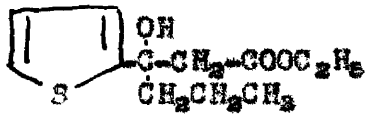
Reaction of 2-propionylthiophene with ethyl α-bromoisobutyrate

Employing the experimental technique described previously, 14.0 g. (0.10 mole) of 2-propionylthiophene, 19.5 g. (0.10 mole) of ethyl α-bromoisobutyrate and 6.5 g. (0.10 mole) of zinc were allowed to

interact in 50 ml. of benzene. The reaction proceeded vigorously, but after working up the reaction mixture in the usual manner and distilling the crude product, only 9.5 g. of unreacted 2-propionylthiophene was obtained boiling at 76-77° (0.5 mm.). There remained in the distillation flask 5.6 g. of an unidentified high boiling residue.

The same reaction was repeated again using 24.4 g. (0.125 mole) of ethyl α-bromoisobutyrate, 14.0 g. (0.10 mole) of 2-propionylthiophene and 8.1 g. (0.125 mole) of dry zinc and heating the reaction mixture at its reflux temperature for three hours. Again there was obtained by distillation 8.7 g. of unreacted ketone with 7.2 g. of non-distillable residue remaining.

Ethyl 3-(2-thienyl)-3-hydroxyhexanoate



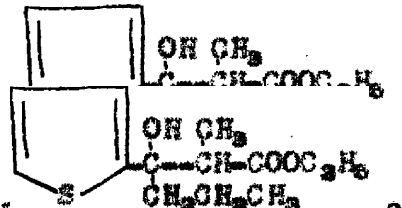
The apparatus and experimental procedure were the same as outlined above. The reaction of 15.4 g. (0.10 mole) of 2-butyrylthiophene, 16.7 g. (0.10 mole) of ethyl bromoacetate and 6.5 g. (0.10 mole) of zinc dust in 50 ml. of benzene gave 2.4 g. of unreacted ketone and 14.0 g. (0.058 mole; 58%) of a straw colored liquid product boiling at 97-98° (0.2 mm.); n_D^{25} 1.5084. The results of analysis for carbon and hydrogen were:

Calc'd. for $C_{12}H_{18}O_3S$: C, 59.5; H, 7.4.
Found: C, 59.9; H, 7.4.

A previous preparation of this substance using the same experimental conditions and quantities of reactants resulted in 3.1 g. of unreacted ketone and 12.7 g. (0.052 mole; 52%) of product.

From a similar synthesis of this compound in which dioxane was used as the reaction solvent there was isolated 5.5 g. of 2-butyrylthiophene and 10.6 g. (0.043 mole; 43%) of product boiling at 115-116° (1 mm.) which had a refractive index n_D^{25} 1.5073.

Ethyl 3-(2-thienyl)-3-hydroxy-2-methylhexanoate



The interaction of 15.4 g. (0.20 mole) of 2-butyrylthiophene, 18.1 g. (0.10 mole) of ethyl α-bromopropionate and 6.5 g. (0.10 mole) of dry zinc dust in 50 ml. of dry benzene proceeded in a manner similar to previously described Reformatsky reactions. After the usual separation and distillation under reduced pressure there was obtained 2.1 g. of unreacted ketone and 13.5 g. (0.064 mole; 64%) of a yellow liquid product boiling at 112-113° (0.1 mm.) which had a refractive index of n_D^{25} 1.4970. Analysis of the compound for carbon and hydrogen gave the following results:

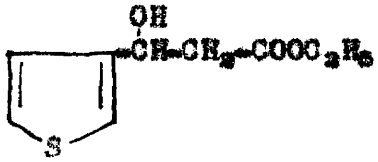
Calc'd. for $C_{12}H_{20}O_3S$: C, 60.9; H, 7.8.
Found: C, 60.7; H, 8.0.

When the above reactants were allowed to interact in 50 ml. of dry dioxane as a reaction media there was obtained 5.3 g. of 2-butyrylthiophene and 9.7 g. (0.046 mole; 46%) of the expected product.

Reaction of 2-butyrylthiophene with ethyl α-bromoisobutyrate

According to the previously described experimental conditions, 15.4 g. (0.10 mole) of 2-butyrylthiophene, 19.5 g. (0.10 mole) of ethyl α-bromoisobutyrate and 6.5 g. (0.10 mole) of zinc dust were allowed to interact in 50 ml. of dry benzene. Although the reaction proceeded vigorously, there was isolated by distillation 10.7 g. of unreacted 2-butyrylthiophene boiling at 79-82° (0.5 mm.). A total of 6.1 g. of unidentified and non-distillable residue remained in the distillation flask.

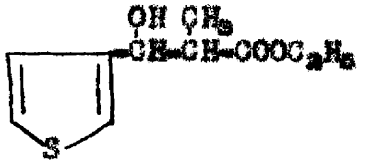
Ethyl 3-(3-thienyl)-3-hydroxypropanoate



Using no change in experimental conditions, the interaction of 5.6 g. (0.05 mole) of 3-thenal with 8.4 g. (0.05 mole) of ethyl bromoacetate and 3.3 g. (0.051 mole) of zinc in 50 ml. of anhydrous benzene took place vigorously. After the same separation procedures as described above, vacuum distillation gave 1.1 g. of 3-thenal distilling at 63-64° (4 mm.) followed by 6.5 g. (0.0325 mole; 65%) of clear colorless product boiling at 114-116° (0.5 mm.) whose refractive index was n_D^{25} 1.5202. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_9H_{12}O_3S$: C, 54.0; H, 6.0.
Found: C, 54.0; H, 5.9.

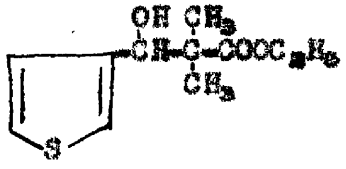
Ethyl 3-(3-thienyl)-3-hydroxy-2-methylpropanoate



Using the apparatus and procedure described above, 5.6 g. (0.05 mole) of 3-thenal, 8.4 g. (0.05 mole) of ethyl α-bromopropionate and 3.3 g. (0.051 mole) of dry zinc powder were allowed to interact in 50 ml. of dry benzene. After hydrolysis, washing, drying and removal of the reaction solvent the crude product was distilled to yield 0.7 g. of unreacted 3-thenal followed by 5.9 g. (0.0275 mole; 55%) of product boiling at 114-115.5° (0.5 mm.) whose refractive index was n_D^{25} 1.5110. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{10}H_{14}O_3S$: C, 56.1; H, 6.5.
Found: C, 56.1; H, 6.8.

Ethyl 3-(3-thienyl)-3-hydroxy-2,2-dimethylpropanoate

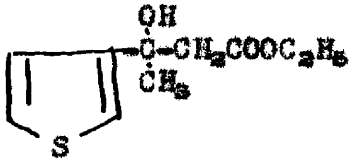


To a 250 ml. three-necked flask was added the quantities, 5.6 g. (0.05 mole) of 3-thenal, 9.8 g. (0.05 mole) of ethyl α-bromoisobutyrate, 3.3 g. (0.051 mole) of zinc dust and 50 ml. of benzene. After the usual vigorous reaction, separation procedures and removal of benzene

the crude product was distilled under reduced pressure to yield 0.5 g. of unreacted 2-thenal and 7.2 g. (0.0316 mole; 63%) of a slightly yellow liquid product boiling at 116-118° (0.5 mm.) which had a refractive index of n_D^{25} 1.5098. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{16}O_3S$: C, 57.9; H, 7.0.
Found: C, 58.0; H, 7.2.

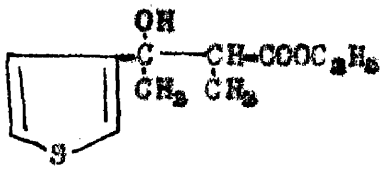
Ethyl 3-(3-thienyl)-3-hydroxybutanoate



The interaction of 6.3 g. (0.05 mole) of 3-acetylthiophene, 8.4 g. (0.05 mole) of ethyl bromoacetate, 3.3 g. (0.051 mole) of zinc in 50 ml. of benzene as a solvent proceeded spontaneously. Separation of the crude product in the usual manner and its vacuum distillation resulted in 0.9 g. of unreacted 3-acetylthiophene and 7.3 g. (0.034 mole; 68%) of clear colorless product distilling at 93-94.5° (0.1 mm.) whose refractive index was n_D^{25} 1.5067. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{10}H_{14}O_3S$: C, 56.1; H, 6.5.
Found: C, 56.4; H, 6.8.

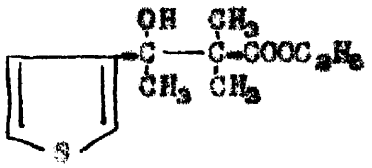
Ethyl 3-(3-thienyl)-3-hydroxy-2-methylbutanoate



The reaction of 6.3 g. (0.05 mole) of 3-acetylthiophene, 9.1 g. (0.05 mole) of ethyl α-bromopropionate and 3.3 g. (0.051 mole) of zinc in 50 ml. of dry benzene took place rapidly. After the usual separation, the crude product was distilled to give 1.8 g. of unreacted 3-acetylthiophene boiling at 70-71° (1 mm.) followed by 5.3 g. (0.028 mole; 56%) of liquid product collected at 104-106° (0.5 mm.) which had a refractive index of n_D^{25} 1.5114. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{16}O_3S$: C, 57.9; H, 7.0.
Found: C, 58.0; H, 7.0.

Ethyl 3-(3-thienyl)-3-hydroxy-2,2-dimethylbutanoate

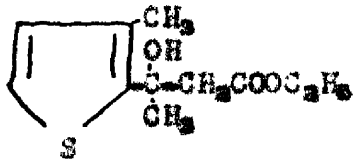


Following previously described experimental conditions, 6.3 g. (0.05 mole) of 3-acetylthiophene, 9.8 g. (0.05 mole) of ethyl α-bromoisobutyrate and 3.3 g. (0.051 mole) of dry zinc were allowed to undergo interaction in 50 ml. of dry benzene. The crude product was isolated from the reaction mixture by the usual method and on vacuum distillation

gave 3.5 g. of unreacted 3-acetylthiophene and 3.1 g. (0.013 mole; 26%) of a straw colored product boiling at 105-107° (0.5 mm.) which had a refractive index of n_D^{25} 1.5521. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{16}O_3S$: C, 59.5; H, 7.4.
Found: C, 59.3; H, 7.5.

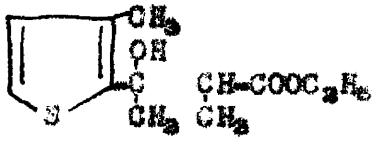
Ethyl 2-(2-(3-methylthienyl)-3-hydroxybutanoate



Employing the previously described apparatus and experimental procedure, 14.0 g. (0.1 mole) of 2-acetyl-3-methyl thiophene were allowed to react with 16.7 g. (0.10 mole) of ethyl bromoacetate and 6.5 g. (0.10 mole) of zinc dust in 100 ml. of dry benzene. There was obtained by distillation, after hydrolysis, washing, and removal of the reaction media, 6.8 g. of unreacted 2-acetyl-3-methyl thiophene distilling at 73-74° (1 mm.) followed by 6.6 g. (0.025 mole; 25%) of a slightly yellow product boiling at 114-116° (0.5 mm.) n_D^{25} 1.5137. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{16}O_3S$: C, 57.9; H, 7.0.
Found: C, 58.0; H, 7.0.

Ethyl 2-(2-(3-methylthienyl)-3-hydroxy-2-methylbutanoate



A mixture of 14.0 g. (0.10 mole) of 2-acetyl-3-methyl thiophene, 18.1 g. (0.10 mole) of ethyl α -bromopropionate and 6.5 g. (0.10 mole) of zinc in 100 ml. of anhydrous benzene reacted vigorously. After the described hydrolysis, washing and solvent removal procedures the mixture was distilled in vacuo yielding 7.1 g. of unreacted ketone and 4.9 g. (0.020 mole; 20%) of liquid product distilling at 117-118° (0.2 mm.) whose refractive index was n_D^{25} 1.5083. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{18}O_3S$: C, 59.5; H, 7.4.
Found: C, 59.4; H, 7.3.

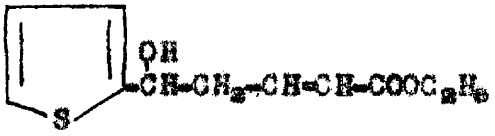
Reaction of 2-acetyl-3-methyl thiophene with ethyl α -bromoisobutyrate

The interaction of 14.0 g. (0.1 mole) of 2-acetyl-3-methyl thiophene with 19.5 g. (0.10 mole) of ethyl α -bromoisobutyrate and 6.5 g. (0.10 mole) of dry zinc powder in 100 ml. of benzene proceeded spontaneously. After the usual manipulations, the crude product was distilled to yield 7.6 g. of 2-acetyl-3-methyl thiophene boiling at 72-74° (1 mm.), and leaving in the distillation vessel 12.2 g. of a non-distillable material.

Reformatsky Reactions of Ethyl γ-bromocrotonate

Ethyl 2((2-thienyl)-hydroxymethyl)-3-butenoate

Ethyl 5-(2-thienyl)-5-hydroxy-2-pentenoate



In a typical reaction, 11.2 g. (0.10 mole) of 2-thenal, 19.3 g. (0.10 mole) of ethyl γ-bromocrotonate and 6.5 g. (0.10 mole) of zinc dust were added to 100 ml. of dry benzene and the resulting mixture was put in a three-necked flask equipped with a stirrer and a reflux condenser with a calcium chloride tube. A small crystal of iodine was added, stirring was commenced and the bottom of the reaction vessel was heated lightly to initiate the reaction, after which it was necessary to moderate the vigorous exothermic reaction by temporary immersion of the flask in an ice bath. After spontaneous refluxing had subsided, the reaction was continued for a half hour at the reflux temperature of the reaction mixture after which the contents of the flask were allowed to cool to room temperature. Hydrolysis of the reaction mixture was accomplished by the addition, with vigorous stirring, of 75 ml. of an ice cold 10% sulfuric acid solution. The non-aqueous layer was separated and combined with a subsequent ether extract of the aqueous

portion. The combined solutions were extracted successively with 100 ml. of water, 100 ml. of 10% sodium carbonate and 100 ml. of water followed by drying over anhydrous sodium sulfate. After removal of the solvents on a steam bath, the residue was distilled in vacuo. The forerun contained 1.3 g. of ethyl crotonate boiling at 30-40° (80 mm.) and 1.2 g. of 2-thenal; b.p. 58-59° (2 mm.). Following these fractions of unreacted material was the first product which amounted to 6.2 g. (0.028 mole; 28%) of ethyl 2-((2-thienyl)-hydroxymethyl)-3-butenoate, boiling at 132-134° (1 mm.) which had a refractive index of n_D^{25} 1.5270. Analysis of this product for carbon and hydrogen gave the following results:

Calc'd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2.
Found: C, 58.6; H, 6.3.

The second product amounted to 3.6 g. (0.016 mole; 16%) of ethyl 5-(2-thienyl)-5-hydroxy-2-pentenoate and distilled at 160-161° (1 mm.). Its refractive index was n_D^{25} 1.5573. Analysis of this product for carbon and hydrogen gave the following results:

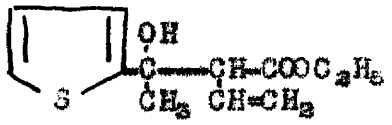
Calc'd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2.
Found: C, 58.6; H, 6.0.

The first of these products reacted rapidly with bromine in carbon tetrachloride while the second did not.

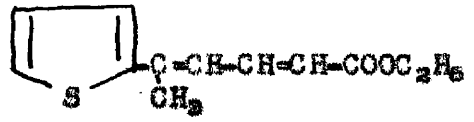
Following a previously reported procedure for ozonalysis (17), 0.2 g. of ethyl 2-((2-thienyl)-hydroxymethyl)-3-butenoate was dissolved in 10 ml. of acetic acid and treated with a stream of ozone for an hour. The ozonide was decomposed with zinc dust and water and then distilled

until 20 ml. of distillate had been collected. The distillate was treated with 0.25 g. of dimedone and set aside for a twelve hour period in the refrigerator during which time an insoluble material crystallized from solution. This was removed by filtration and recrystallized from a methanol-water mixture of equal parts to yield about 0.1 g. of a material which melted sharply at 187-187.5°. There was no depression in the melting point when the latter substance was mixed with the product obtained on interaction of formaldehyde with dimedone.

Ethyl 2-Ethenyl-3-hydroxy-3-(2-thienyl)-butanoate



Ethyl 5-(2-thienyl)-2,4-hexadienoate



Employing the usual procedure, 12.6 g. (0.10 mole) of 2-acetylthiophene, 19.3 g. (0.10 mole) of ethyl γ-bromocrotonate and 6.5 g. (0.10 mole) of zinc dust were allowed to interact in 100 ml. of anhydrous benzene. After carrying out the isolation procedures described above, the products were vacuum distilled. The first fraction obtained was 7.1 g. of ethyl crotonate followed by 7.8 g. of 2-acetylthiophene. Following these fractions of unreacted starting materials there was

obtained 1.5 g. (0.007 mole; 7%) of ethyl 2-ethenyl-3-hydroxy-3-(2-thienyl)-butanoate boiling at 107-108° (1 mm.) which had a refractive index of n_D^{25} 1.4959. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{16}O_3S$: C, 59.9; H, 6.7.
Found: C, 59.7; H, 6.8.

The next fraction boiling at 155-156° (1 mm.) did not give a correct analysis for the isomeric ester and as a result was refluxed for eight hours in a 6% oxalic acid solution from which there was isolated 5.8 g. (0.026 mole; 26%) of ethyl 5-(2-thienyl)-2,4-hexadienoate boiling at 147-148.5° (1 mm.). Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{12}H_{14}O_2S$: C, 64.8; H, 6.3.
Found: C, 64.7; H, 6.5.

The first of the above product took up bromine rapidly while the second reacted only slowly.

Ethyl 5-(2-thienyl)-2,4-heptadienoate

Using the previously described method, 14.0 g. (0.10 mole) of 2-propionylthiophene, 19.3 g. (0.10 mole) of ethyl γ-bromocrotonate and 6.5 g. (0.10 mole of zinc were allowed to undergo reaction in 100 ml. of dry benzene. Distillation of the isolated crude product gave 7.8 g. of ethyl crotonate and 8.7 g. of 2-propionylthiophene, followed

by 5.9 g. (0.025 mole; 25%) of product boiling at 149-150° (1 mm.). Its refractive index was n_D^{25} 1.5777. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{18}H_{18}O_2S$: C, 66.1; H, 7.6.
Found: C, 65.9; H, 7.8.

This later product reacted slowly with bromine in carbon tetrachloride.

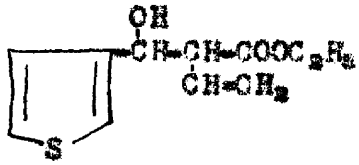
Ethyl 5-(2-thienyl)-2,4-octadienoate

The reaction of 15.4 g. (0.10 mole) of 2-butyrylthiophene with 19.3 g. (0.10 mole) of ethyl γ-bromocrotonate and 6.5 g. (0.10 mole) of zinc powder in 100 ml. of dry benzene occurred spontaneously. After the usual isolation procedure, there was obtained by vacuum distillation 6.8 g. of ethyl crotonate, 8.8 g. of unreacted ketone and 8.3 g. (0.032 mole; 32%) of a product boiling at 162-164° (1 mm.). Analysis of the product for carbon and hydrogen gave the following results:

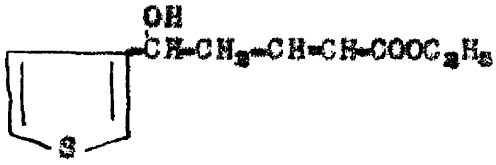
Calc'd. for $C_{14}H_{18}O_2S$: C, 67.9; H, 7.2.
Found: C, 68.0; H, 7.4.

A very slow reaction occurred between the product and bromine in carbon tetrachloride.

Ethyl 2-((3-thienyl)-hydroxymethyl)-3-butenoate



Ethyl 5-(3-thienyl)-5-hydroxy-2-pentenoate



Following the above described procedure, 5.6 g. (0.05 mole) of 3-thenal, 3.25 g. (0.05 mole) of zinc and 9.7 g. (0.05 mole) of ethyl γ-bromocrotonate were allowed to interact in 50 ml. of dry benzene as a solvent to yield two Reformatsky products. The first amounted to 3.3 g. (0.0146 mole; 29%) of ethyl 2-((3-thienyl)-hydroxymethyl)-3-butenoate, and had the following physical properties: b.p. 134-135° (1 mm.); n_D^{25} 1.5255. Analysis of the product for carbon and hydrogen gave the following results:

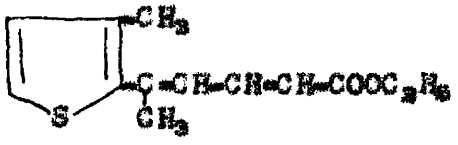
Calc'd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2.
Found: C, 57.8; H, 6.4.

The second product, distilling at 158-160° (1 mm.), amounted to 1.9 g. (0.0084 mole; 17%) of ethyl 5-(3-thienyl)-5-hydroxy-2-pentenoate and had a refractive index of n_D^{25} 1.5555. Carbon and hydrogen analysis of the product gave the following results:

Calc'd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2.
Found: C, 58.3; H, 6.4.

The first of the above products reacted rapidly with a carbon tetrachloride solution of bromine while the second reacted only slowly.

Ethyl 5-[2-(3-methylthienyl)]-2,4-hexadienoate



Using the same procedure as in the above synthesis, 14.0 g. (0.10 mole) of 2-acetyl-3-methyl thiophene, 19.3 g. (0.10 mole) of ethyl γ-bromocrotonate and 6.5 g. (0.10 mole) of dry zinc were allowed to interact in 100 ml. of anhydrous benzene. As the reaction proceeded a small quantity of precipitate formed which dissolved on the addition of 50 ml. of additional benzene. After hydrolysis and washing, the reaction mixture was distilled under reduced pressure to yield 7.3 g. of unreacted 2-acetyl-3-methyl thiophene followed by 5.5 g. of a product which gave rather poor analysis for carbon and hydrogen. The product was subsequently dehydrated by 6% oxalic acid solution to give 5.1 g. (0.020 mole; 20%) of yellowish product distilling at 164-165° (1 mm.). The analysis of the product for carbon and hydrogen gave the following results which were high in carbon and low in hydrogen.

Calc'd. for $C_{13}H_{16}O_2S$: C, 66.1; H, 7.6.
Found: C, 65.9; H, 6.9.

With this material only a very slow reaction occurred with bromine in carbon tetrachloride solution.

Reformatsky Reactions of Allyl Bromide

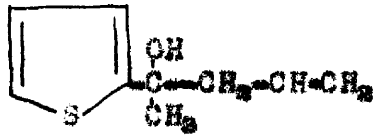
1-(2-Thienyl)-3-buten-1-ol

Under anhydrous conditions, 11.2 g. (0.10 mole) of 2-thenal, 12.1 g. (0.10 mole) of allyl bromide, 6.5 g. (0.10 mole) of zinc dust, 50 ml. of benzene and 50 ml. of anhydrous tetrahydrofuran were placed in a 250 ml. three-necked flask equipped with an efficient stirrer and a reflux condenser having an attached drying tube. A small crystal of iodine was added and the reaction was initiated by lightly heating the bottom of the reaction vessel. After the spontaneous refluxing had subsided, the reaction mixture was heated at its reflux temperature for an hour and then allowed to cool to room temperature. Hydrolysis was carried out by the addition, with rapid stirring, of 100 ml. of an ice cold 30% acetic acid. The resulting two layers were separated and the aqueous layer was extracted with ether which was combined with the non-aqueous portion. This solution was washed with successive 100 ml. portions of water, 10% sodium carbonate, and again in water and then dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the crude product was then distilled under reduced pressure to yield 12.0 g. (0.078 moles; 78%) of clear colorless liquid boiling at 89-90.5° (1 mm.) whose refractive index was n_D^{25} 1.5439.

Carbon and hydrogen analysis of the product gave the following results:

Calc'd. for $C_8H_{10}OS$: C, 62.3; H, 6.5.
Found: C, 62.1; H, 6.9.

4-(2-Thienyl)-1-penten-4-ol



Following the experimental procedure used in the above synthesis, 12.6 g. (0.10 mole) of 2-acetylthiophene, 12.1 g. (0.10 mole) of allyl bromide and 6.5 g. (0.10 mole) of dry zinc were allowed to interact in a mixture of 50 ml. of benzene and 50 ml. of tetrahydrofuran. After hydrolysis washing, the crude product was distilled to yield 11.8 g. (0.070 mole; 70%) of liquid product distilling at 82-84° (2 mm.). Its refractive index was n_D^{25} 1.5512. Carbon and hydrogen analysis gave the following results:

Calc'd. for $C_9H_{12}OS$: C, 64.3; H, 7.1.
Found: C, 64.5; H, 6.7.

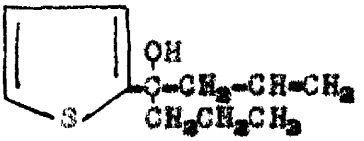
4-(2-Thienyl)-1-hexen-4-ol

The procedure employed was the same as that previously described. The interaction of 14.0 g. (0.10 mole) of 2-propionylthiophene, 12.1 g. (0.10 mole) of allyl bromide and 6.5 g. (0.10 mole) of zinc in a solvent mixture of 50 ml. each of benzene and tetrahydrofuran proceeded

vigorously. After the usual separation method the crude product was distilled under vacuum to yield 13.2 g. (0.0725 mole; 72.5%) of clear liquid product. Its physical properties were: b.p. 94-95° (1.5 mm.); n_D^{25} 1.5260. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{10}H_{14}OS$: C, 65.9; H, 7.7.
Found: C, 65.7; H, 7.9.

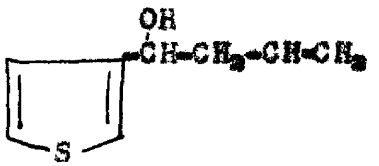
4-(2-Thienyl)-1-hepten-4-ol



The preparation of this compound was accomplished by the interaction of 15.4 g. (0.10 mole) of 2-butyrylthiophene, 12.1 g. (0.10 mole) of allyl bromide and 6.5 g. (0.10 mole) of zinc in 100 ml. of a mixture of equal parts of benzene and tetrahydrofuran. After hydrolysis, washing and removal of the reaction solvents the remainder was distilled to yield 14.3 g. (0.073 mole; 73%) of liquid product. The physical properties of this material were: b.p. 94-95° (0.5 mm.); n_D^{25} 1.5205. Carbon and hydrogen analysis of the product gave the following results:

Calc'd. for $C_{11}H_{16}OS$: C, 67.3; H, 8.2.
Found: C, 66.8; H, 8.1.

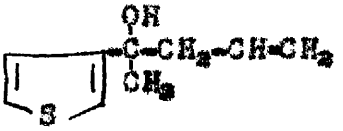
1-(3-Thienyl)-3-buten-1-ol



Using the previously developed experimental method, 5.6 g. (0.05 mole) of 3-thenal, 3.3 g. (0.05 mole) of zinc dust and 6.1 g. (0.05 mole) of allyl bromide were allowed to undergo reaction in 50 ml. of a one to one mixture of anhydrous benzene and tetrahydrofuran. The reaction mixture was worked up according to the previously described procedure. The product was distilled to yield 6.1 g. (0.040 mole; 80%) of a colorless liquid with the following physical properties: b.p. 90-91° (1 mm.); n_D^{25} 1.5422. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_8H_{12}OS$: C, 62.3; H, 6.5.
Found: C, 62.7; H, 6.3.

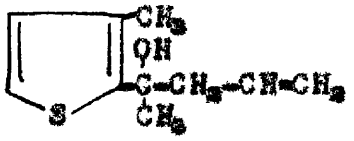
4-(3-Thienyl)-1-penten-4-ol



The interaction of 6.3 g. (0.05 mole) of 3-acetylthiophene, 6.2 g. (0.05 mole) of allyl bromide and 3.3 g. (0.05 mole) of dry zinc dust in 50 ml. of a one to one mixture of benzene and tetrahydrofuran took place vigorously. Employing the same separation procedure as previously described followed by vacuum distillation of the crude product yielded 6.0 g. (0.036 mole; 72%) of clear colorless product. Its physical properties were: b.p. 80-81° (1 mm.); n_D^{25} 1.5498. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_9H_{12}OS$: C, 64.3; H, 7.1.
Found: C, 64.5; H, 7.2.

4-[2-(3-Methylthienyl)]-1-penten-4-ol



According to the already described experimental conditions, 14.0 g. (0.10 mole) of 2-acetyl-3-methyl thiophene, 12.1 g. (0.10 mole) of allyl bromide and 6.5 g. (0.10 mole) of dry zinc were allowed to undergo interaction in 50 ml. each of dry benzene and dry tetrahydrofuran. There was isolated by the usual procedure, from this reaction mixture 12.0 g. (0.070 mole; 70%) of a clear liquid product. Its physical properties were: b.p. 97-98.5° (0.5 mm.); n_D^{25} 1.5340. Analysis of the product for carbon and hydrogen gave the following results:

Calc'd. for $C_{10}H_{14}OS$: C, 65.9; H, 7.7.
Found: C, 65.7; H, 7.8.

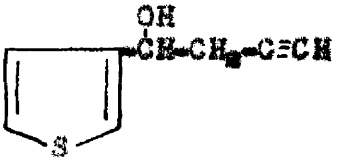
Reformatsky Reactions of Propargyl Bromide

1-(2-Thienyl)-3-butyn-1-ol

The conditions used for the Reformatsky reactions of propargyl bromide were identical to those used for allyl bromide. According to conditions previously described, 11.2 g. (0.10 mole) of 2-thenal,

11.9 g. (0.10 mole) of propargyl bromide and 6.5 g. (0.10 mole) of zinc were interacted in a mixture of 50 ml. of anhydrous benzene and 50 ml. of dry tetrahydrofuran. After separation, the crude product was distilled in vacuo to yield 9.1 g. (0.060 mole; 60%) of liquid product. This compound had the following physical properties: b.p. 84-85° (0.1 mm.); n_D^{25} 1.5220. The reported (66) physical properties for this compound are: b.p. 98-100.5° (3 mm.); n_D^{25} 1.5235.

1-(3-Thienyl)-3-butyn-1-ol



A spontaneous reaction took place when 5.6 g. (0.05 mole) of 3-thenal, 5.95 g. (0.05 mole) of propargyl bromide and 3.3 g. (0.05 mole) of zinc dust were added to a mixture of 25 ml. of benzene and 25 ml. of tetrahydrofuran. After hydrolysis, washing and removal of the reaction solvents the crude product was distilled at reduced pressure giving 4.6 g. (0.031 mole; 62%) of a product which had these physical constants: b.p. 83-84.5° (0.1 mm.); n_D^{25} 1.5207. Carbon and hydrogen analysis of the product gave the following results:

Calc'd. for C_8H_8OS: C, 63.2; H, 5.3.
Found: C, 63.2; H, 5.5.

Reaction of 2-acetylthiophene with propargyl bromide

A vigorous reaction ensued when 12.6 g. (0.10 mole) of 2-acetylthiophene, 11.9 g. (0.10 mole) of propargyl bromide and 6.5 g. of zinc dust were added to 100 ml. of a one to one benzene and tetrahydrofuran mixture. All of the zinc was completely consumed and the reaction appeared to be complete after the usual period of heating. When the reaction mixture was hydrolyzed, washed and reaction solvents removed, distillation yielded 10.4 g. of unreacted 2-acetyl thiophene boiling at 55-56° (0.1 mm.). No further products could be obtained from the 2.2 g. of high boiling residue which remained in the distillation flask.

The reaction was repeated using a longer reaction period of three hours instead of the usual one, but there resulted 9.1 g. of unreacted 2-acetylthiophene and no further distillable material. In this case the residue amounted to 2.9 g.

Repetition of the above reaction using 100 ml. of toluene as the solvent resulted in the formation of a precipitate which dissolved upon the addition of 50 ml. of dry tetrahydrofuran. The reaction was completed and after the usual treatment of the reaction mixture there was obtained 8.6 g. of unreacted 2-acetylthiophene and 4.2 g. of a non-distillable material.

The use of 100 ml. of tetrahydrofuran as a reaction medium gave no better results with the only isolatable material being 10.6 g. of unreacted 2-acetylthiophene. In this instance very little high boiling residue remained.

Reaction of 2-propionylthiophene with propargyl bromide

The results of the interaction of 14.0 g. (0.10 mole) of 2-propionylthiophene with 11.9 g. (0.10 mole) of propargyl bromide and 6.5 g. (0.10 mole) of dry zinc dust were similar to those of the preceding experiment. Distillation yielded 10.6 g. of unreacted 2-propionylthiophene boiling at 64-65° (0.2 mm.). The amount of residue after distillation was 2.6 g.

Reaction of 2-butyrylthiophene and propargyl bromide

The result obtained here was comparable to that of the other ketones, as 15.4 g. (0.10 mole) of 2-butyrylthiophene appeared to react with 11.9 g. (0.10 mole) of propargyl bromide and 6.5 g. of zinc in 50 ml. of benzene and 50 ml. of tetrahydrofuran. However, distillation of the mixture gave 11.3 g. of 2-butyrylthiophene with 3.1 g. of high-boiling residue remaining in the distillation vessel.

Reaction of 2-acetyl-3-methyl thiophene and propargyl bromide

The interaction of 14.0 g. (0.10 mole) of 2-acetyl-3-methyl thiophene, 11.9 g. (0.10 mole) of propargyl bromide and 6.5 g. (0.10 mole) of zinc in 100 ml. of a one to one mixture, by volume, of benzene and tetrahydrofuran resulted in the isolation of 10.3 g. of unreacted ketone and 2.5 g. of residue, which could not be distilled.

Dehydration of β -Hydroxyesters

In a typical preparation, 5 ml. of the β -hydroxyester was placed in a 100 ml. flask fitted with a reflux condenser and 50 ml. of a 6% oxalic acid solution was added. The resulting immiscible liquid mixture was heated at its reflux temperature with occasional agitation for three hours and then allowed to cool to room temperature. A quantity of 25 ml. of ether was added and the mixture was shaken. Following the separation of the two layers, the ether layer was dried over anhydrous sodium sulfate and the ether was removed on the steam bath. The product was distilled under reduced pressure. The yields in these dehydration reactions were almost quantitative.

SUMMARY

1. The Reformatsky reactions of the α-bromoesters; ethyl bromoacetate, ethyl α-bromopropionate and ethyl α-bromo-isobutyrate; with 2- and 3-thenal, 2- and 3-acetylthiophene, 2-propionylthiophene, 2-butyrylthiophene and 2-acetyl-3-methyl thiophene were carried out. Yields of β-hydroxy esters were largely a property of the amount of steric hindrance involved in the formation of the product. The use of dioxane instead of benzene as the reaction media caused only slight reduction in yields through enolization of the ketone employed. The properties of the β-hydroxy esters formed as well as the properties of the corresponding unsaturated esters are reported.

2. The Reformatsky reactions of ethyl γ-bromocrotonate with 2- and 3-thenal, 2-acetylthiophene, 2-propionylthiophene, 2-butyrylthiophene and 2-acetyl-3-methyl thiophene were carried out. Yields were relatively low and in the case of the first three thiophene derivatives mentioned there was received some isomeric rearranged product along with the expected product. The properties of the products are reported.

3. The Reformatsky reactions of allyl bromide with 2- and 3-thenal, 2- and 3-acetylthiophene, 2-propionylthiophene, 2-butyrylthiophene and 2-acetyl-3-methyl thiophene were carried out. The yields of 4-(Thienyl)-4-hydroxy-1-alkenes were uniformly high with very little unreacted ketone being recovered. The properties of the products are reported.

4. The Reformatsky reactions of propargyl bromide with 2- and 3-thenal, 2-acetylthiophene, 2-propionylthiophene and 2-butyrylthiophene were carried out. Only in the case of the thenals was any Reformatsky type product isolated in good yields. From the ketones no product was formed, but large quantities of unreacted ketone were recovered. The properties of the products resulting from the thenals are reported.

5. Wherever feasible, yields are correlated with steric considerations, inductive effects and reaction solvents.

PART II

THE SCHMIDT REACTION

INTRODUCTION

The interaction of equimolar quantities of hydrazoic acid with a carbonyl compound in the presence of a strong acid has become known as the Schmidt reaction. Through it, is available a convenient method for the preparation of a number of organic nitrogen compounds. Thus acids yield amines according to the following equation,

$$R\text{-}COOH + HN_3 \xrightarrow{H^+} R\text{-}NH_2 + CO_2 + N_2$$

from aldehydes, there are obtained nitriles and formamides while ketones yield amides.

$$R\text{-}CHO + HN_3 \xrightarrow{H^+} RCN \quad \text{and} \quad R\text{-}NH\text{-}CHO$$

$$RCOR + HN_3 \xrightarrow{H^+} RCONHR + N_2$$

The reaction was first recorded by Karl Schmidt in 1923 when he observed that benzene had an accelerating effect on the decomposition of hydrazoic acid in the presence of mineral acid (84,85) and that variations in the reaction temperature resulted in different products. He found that the addition of benzophenone to the mixture resulted in a vigorous reaction and an almost quantitative yield of benzanilide. Since that time the scope of the reaction has been broadened considerably to include not only carbonyl compounds but olefins, lactones, anhydrides, esters, acid halides, quinones, nitriles, imido esters, amides, isocyanides, oximes and many other types of compounds (86), although when most of these later compounds are a reactant with hydrazoic acid such interactions are not generally considered as constituting a true Schmidt reaction.

There has been reported very little work on the Schmidt reaction of carbonyl derivatives of heterocyclic compounds and only one of these deals with thiophene derivatives (87). In this study, Hurd and Moffat conducted a rather cursory examination of the Schmidt reaction of 2-acetylthiophene and found that a mixture of the two possible products, 2-acetamidothiophene and 2-thenomethylamide, resulted.

It was the purpose of the presently described investigation to study the Schmidt reaction of the ketones and aldehydes of thiophene under a variety of conditions. Both the two and three substituted thienyl carbonyl derivatives were studied and a large number of acids were employed as the catalyst. Further, several different solvents were investigated and considerable variation in reaction temperatures was examined.

The thiophene derivatives investigated in this study included 2-thenal, 3-thenal, 2-acetylthiophene, 2-propionylthiophene, 2-n-butyryl-thiophene and 3-acetylthiophene. The resultant products were, in all cases, known compounds which had been previously prepared by unequivocal methods. The aldehydes of thiophene gave uniformly high yields, of the expected nitriles, while only rather poor yields of amides were obtained from the ketones.

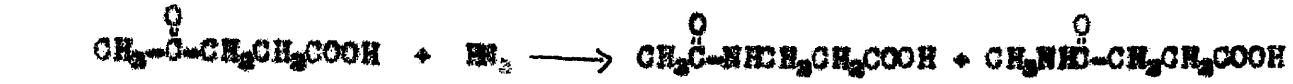
HISTORICAL

The Schmidt reaction has found its most extensive application in the synthesis of amines from acids. With straight chained aliphatic acids the yield of amine generally increases with the length of the alkyl chain (88,89), but no such generalization can be made in the case of the more complicated branch-chained acids. In general, dibasic acids yield the corresponding diamines (90,91) with the exception that malonic acid and substituted malonic acids yield α -amino acids (92,93) which do not undergo further reaction with hydrazoic acid.

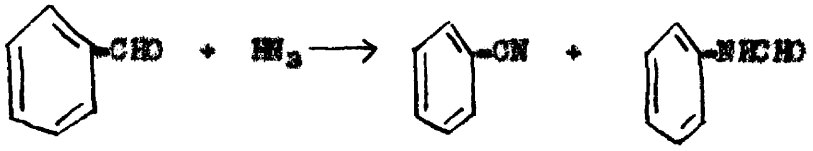
$$R\text{-}CH\begin{matrix}COOH\\COOH\end{matrix} + HN_3 \xrightarrow{H_2SO_4} R\text{-}\underset{NH_2}{CH}\text{-}COOH$$

The reaction proceeds readily even with acids in which the carboxyl group is relatively inert. The numerous departures and exceptions (86) to these generalizations will not be discussed here since this particular study was not concerned with the thenoic acids.

The Schmidt reaction is known to proceed more readily with aldehydes and ketones than with acids. The difference in the reactivity of hydrazoic acid with carbonyl compounds and acids is large enough that a keto acid will react with one mole of hydrazoic acid in the presence of an acid catalyst to give exclusively two amides with no amines resulting (90,94).



The reaction of aldehydes with hydrazoic acid has not been as extensively investigated as the reaction of the later reagent with ketones. The principal product resulting from aldehydes is the corresponding nitrile, but in certain instances a formamide is obtained. Thus, from benzaldehyde two reaction products, benzonitrile and formanilide, are obtained (85,95). The relative yields of these products



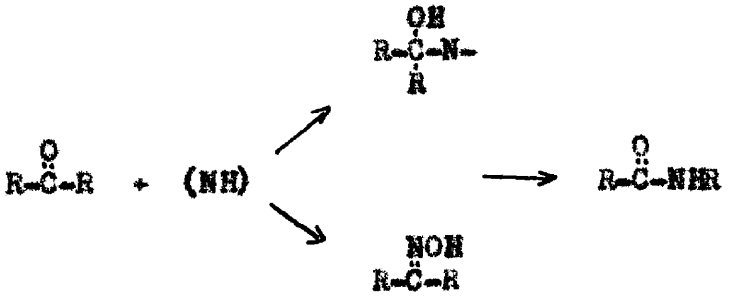
are dependent on the amount of sulfuric acid used as a catalyst. Larger amounts of this catalyst cause the formation of a greater proportion of formanilide.

The corresponding acid amides result when symmetrical ketones undergo the Schmidt reaction. Thus acetone is reported (85) to give a quantitative yield of methylacetamide while cyclohexanone and cyclooctanone give 70% yields of ϵ-caprolactam and 8-aminocaprylic lactam, respectively (96,97).

In those cases where unsymmetrical ketones are employed there is the possibility of one or both of two different products resulting.

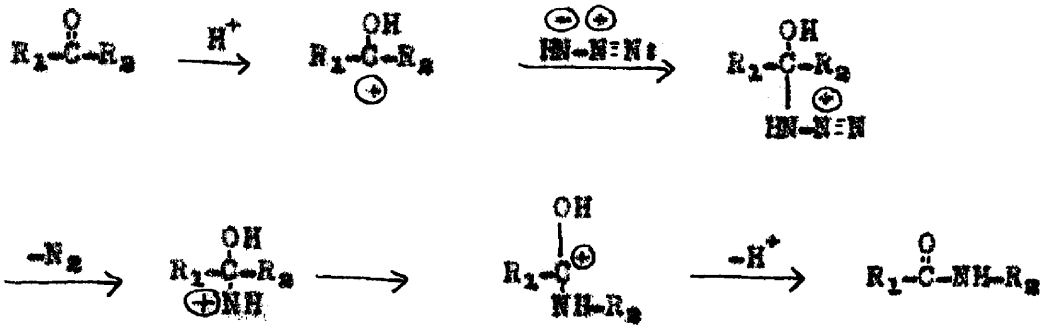
As noted above, levulinic acid reacts to give the two possible amides. However, since the larger proportion of product results through the migration of the propionic acid group, the nature of the main product is in many cases largely dependent on the relative electronegativities of the two groups involved. From acetophenone there is obtained a 77% yield of acetanilide with none of the other isomer being isolated (92). Smith reports (98) that the proportion of isomers produced is dependent upon the acidity of the medium as determined by the acidity of the catalyst, basicity of the solvent, basicity of the carbonyl compound and bulk factors of the groups attached to the carbonyl carbon.

A brief discussion of the presently accepted ideas concerning a mechanistic picture of the Schmidt reaction is in order. Schmidt proposed a mechanism (85) in which he suggested that the hydrazoic acid cleaved the strong acid catalyst to yield nitrogen and the imide radical which then attacked the carbonyl group, followed by a rearrangement similar to the Beckman reaction.



In 1948, Newman and Gildenhorn (99) proposed a carbonium ion mechanism which was more acceptable in light of more recent evidence.

According to their theory, the carbonyl group oxygen is protonated yielding a carbonium ion which is attacked by one of the resonance species of hydrazoic acid, followed by the elimination of nitrogen and the migration of one of the groups attached to the carbonyl carbon.



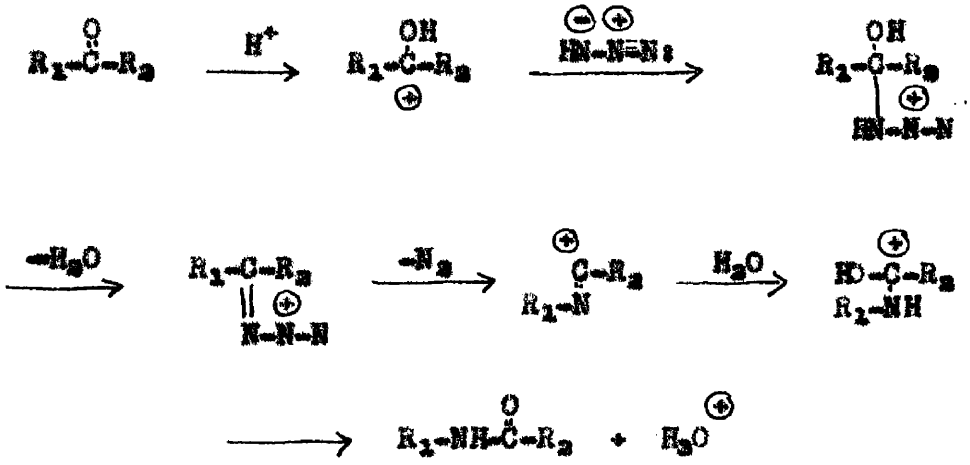
Newman and Gildenhorn postulated that the group which migrated was that which possessed the greater migratory appitude. This theory was apparently strengthened by the results of a study of the reaction of unsymmetrical diarylethylenes with hydrazoic acid in the presence of sulfuric acid conducted by McEwen, Gilland and Sparr (100). From this particular work it seemed rather evident that the group which migrated from carbon to nitrogen was that possessing the greater intrinsic migratory aptitude. They found the order of migratory aptitudes to be according to the following scheme:

p-anisyl> p-tolyl> p-biphenyl> phenyl> p-chlorophenyl> methyl

This order is in qualitative agreement with the migratory aptitudes found in the Pinacol rearrangement.

Almost simultaneously, Smith (98) proposed a similar mechanism in which the emphasis was not upon the migratory aptitudes of the

groups, but rather upon the relative bulkiness of the two groups. This mechanism was postulated to account for a number of instances in which the group migrating was not that which would be expected to have the greater migratory aptitude, but the one having the larger bulk. This concept of a bulky group is also discussed by Schuerch and Huntress (101,102). The distinguishing factor in Smith's mechanism is that it presents an intermediate species exhibiting geometrical isomerism analogous to the oximes.



The dehydration step of the mechanism causes the formation of a single species which may have two geometrical configurations about the double bond. It would be expected that a preponderance of this species would be in a form so that the larger group would be trans to the azo group causing less strain. Consequently, in the succeeding step, proceeding through the loss of nitrogen and shift of an R group to nitrogen, the group which would be expected to migrate would be the one trans to the azo group. It is evident that the larger group does

migrate preferentially from later work by Smith (103-105). It is significant that in the p-substituted benzophenone series, almost equal amounts of each rearrangement product are obtained. This is inexplicable in terms of purely electrical factors, but it is in agreement with the steric considerations which have been described. Since the para substituents do not increase the bulk of a phenyl group as far as the azo group is concerned, an equal mixture of isomeric products would be expected.

There are three general methods for carrying out the Schmidt reaction with a carbonyl compound. The first of these entails the addition of a benzene or chloroform solution of hydrazoic acid to the organic compound dissolved in about twice its volume of concentrated sulfuric acid. This method is most generally applied to the preparation of amines from acids and is not useful where the organic compound is sensitive to high concentrations of strong acid. The speed of the reaction is observed by leading the evolved gases through a wash bottle arranged as a bubble counter. The amount of hydrazoic acid employed is usually 1 to 1.2 moles per carbonyl group and following the complete addition of the hydrazoic acid solution, stirring of the reaction mixture is continued until gas evolution has ceased (89,91-93, 106-113).

The second general method and the one applied most frequently in the case of aldehydes and ketones involves the addition of concentrated sulfuric acid to a stirred solution of the carbonyl compound and hydrazoic acid in chloroform or benzene. Prolonged contact of the

organic compound with sulfuric acid is avoided. This latter procedure is the only one that has been successfully applied to the reaction of aldehydes with hydrazoic acid (85,92,86,111,114,115).

A less commonly employed procedure requires the addition of a solution of the carbonyl compound and hydrazoic acid to a well stirred quantity of concentrated sulfuric acid or to a mixture of sulfuric acid and chloroform (85,97,114).

Frequently, a variation of the first method can be successfully applied. In this procedure, solid sodium azide is added in small portions to the carbonyl compound contained in sulfuric acid or other acid catalysts, or it can be added to the acid catalyst dissolved in solvents such as acetic acid (90,103,104,107,108,116-118).

A variety of solvents have been employed in the Schmidt reaction, the most common being chloroform and benzene. Recently, trichloroacetic acid has attained some prominence, both as a solvent and catalyst (98,103,104). There has been at least one instance in which acetic acid served satisfactorily as a reaction media (119) and the use of trichloroethylene as a solvent has been reported (120). Ethyl ether is not a satisfactory solvent (92), although its use has been claimed in a few patents (114,121).

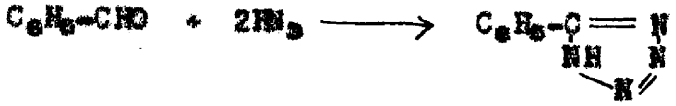
Since the Schmidt reaction is normally quite exothermic some method of temperature control is required. The reaction with aldehydes and ketones is usually carried out with cooling of the reaction mixture in an ice bath, and controlled addition of the hydrazoic acid. Only

when the reaction is sluggish is a higher temperature of any advantage. However, with aldehydes and ketones this is likely to lead to excessive decomposition and there is the further danger of loosing hydrazoic acid (b.p. 37°).

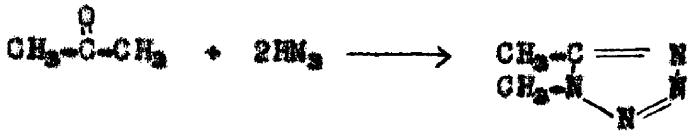
Considerable work has been devoted to ascertaining the type of utilizable catalyst and the concentrations which will give the highest yields. Concentrated sulfuric acid in amounts of about double that of the carbonyl compound has been used most extensively as the catalyst. Decreased yields result from the use of dilute sulfuric acid (85,92), but there is considerable evidence that the use of 95% sulfuric acid is the most satisfactory for ketones (122). Smith and others (98,103, 104,122,123) have shown that trichloroacetic acid is excellent catalyst for the Schmidt reaction. Other catalysts which have been mentioned are hydrogen chloride (97,107); phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride; ferric chloride, stannic chloride, thionyl chloride; sulfonic acids (95); phosphoric acid (114); aluminum chloride (95); and ultraviolet light (124). There is no evidence that any of these catalysts serve as well as sulfuric or trichloroacetic acid.

The most common biproduct resulting from the reaction of a ketone or aldehyde with hydrazoic acid in the presence of a strong mineral acid is a tetrazole. This is of minor importance where the molar ratio of carbonyl compound to hydrazoic acid is one, but in the presence of large excesses of hydrazoic acid tetrazoles may be the major product.

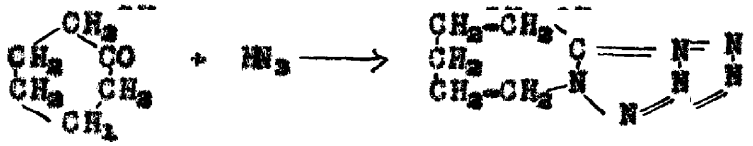
Phenyltetrazole is reported (95) to result from the interaction of benzaldehyde with hydrazoic acid.



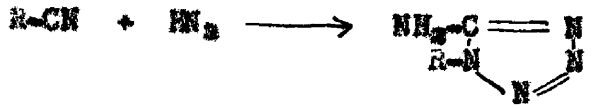
In the presence of excess hydrazoic acid, acetone readily yields 1,5-dimethyltetrazole (85,125). Cyclic ketones are found to react in a



similar manner (95,123,126-128). Accordingly, the heart stimulant Metrazole is prepared from cyclohexanone and hydrazoic acid (85,125).

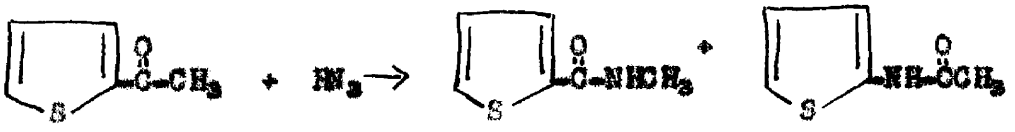


It has been established that the tetrazoles resulting from ketones do not result from the further reaction of excess hydrazoic acid with the amide, which would be the expected product of the Schmidt reaction, since if this amide is subjected to treatment with hydrazoic acid under the same experimental conditions, no tetrazole results (85,115). The origin of tetrazoles resulting from aldehydes is even less well established. There is some indication that a nitrile is not the intermediate since the reaction of a nitrile with hydrazoic acid in the presence of concentrated sulfuric acid yields a 5-amino-1-alkyl-tetrazole (129-132). Phenyltetrazole has been reported (95), as the



product resulting from benzaldehyde.

Hurd and Moffat (87) made the only report of the Schmidt reaction being carried out with a carbonyl derivative of thiophene. These investigators were seeking a simple one step preparation of 2-acetamidothiophene from 2-acetylthiophene and made use of the Schmidt reaction. By their procedure, a cold solution of 2-acetylthiophene dissolved in chloroform was treated with 96% sulfuric acid and a chloroform solution of hydrazoic acid. They were able to recrystallize from benzene and pentane a eutectic mixture of 2-acetamidothiophene and 2-thenomethylamide which was separated by solution of the products in a mercuric acetate-sodium acetate solution and extraction of the 2-thenomethylamide with chloroform. When these investigators carried out the reaction



at elevated temperatures they obtained only a minute amount of 2-thenomethylamide and a considerable amount of material which they presumed to be an acetamidothiophenesulfonic acid. There was considerable decomposition in this latter reaction. Since their interest was strictly in the synthetic nature of the reaction, Hurd and Moffat made no further investigation.

DISCUSSION

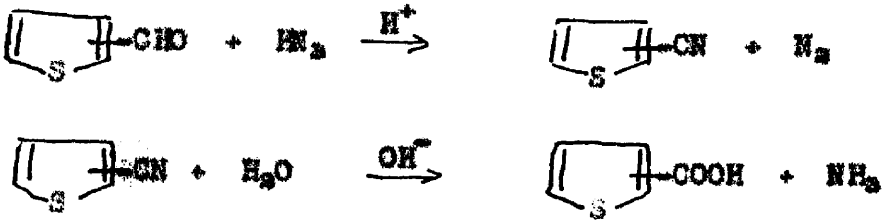
The Schmidt Reaction with Thenals

In carrying out the Schmidt reaction on 2-thenal and 3-thenal, the most readily executed experimental procedure was examined. A benzene solution of 2-thenal having a slight excess of hydrazoic acid and contained in a beaker was treated, while being stirred, with a small amount of concentrated sulfuric acid. A steady stream of gas was evolved and at its completion a mixture of ice and water was added to the reaction mixture and the resulting layers were separated. After washing with dilute sodium hydroxide, the benzene layer was treated with a concentrated sodium bisulfite solution to remove unreacted aldehyde and was then dried over anhydrous sodium sulfate. The benzene was removed by evaporation and the residue was distilled under reduced pressure to give an 84% yield of 2-thenonitrile which was identified by means of its boiling point, refractive index and conversion of a sample by basic hydrolysis to the known 2-thenoic acid.

A second preparation of 2-thenonitrile was carried out except that sirupy phosphoric acid was used as the catalyst. The reaction seemed to proceed somewhat slower as determined by the evolution of nitrogen, but after the above described isolation method there was obtained a 60% yield of 2-thenonitrile.

These same two procedures were applied to 3-thenal and where sulfuric acid was employed as the catalyst a 79% yield of 3-thenonitrile

resulted while from the phosphoric acid catalyzed reaction, there was obtained a 62% yield of the expected product. The identity of the products was determined by boiling point, refractive index and conversion to the solid 3-thenoic acid.



The properties, derivatives, yields and methods of preparation of these products are summarized in Table X.

In all of the above described studies the temperature was held at 20° C. or less. One study was conducted in which 2-thenal and hydrazoic acid were allowed to undergo reaction in the presence of sulfuric acid at 45°. This reaction was carried out in a flask fitted with stirrer and reflux condenser to prevent the loss of hydrazoic acid. As the reaction proceeded considerable decomposition was in evidence. When the evolution of nitrogen had ceased the mixture was worked up in the usual manner to yield a rather large amount of tarry material and only 21% of the theoretical amount of 2-thenonitrile. There was also present a large amount of a base soluble material which yielded a yellow insoluble precipitate with barium chloride solution. This was probably a substituted thiophene sulfonic acid salt, but no further examination of the substance was conducted.

TABLE I

SUMMARY OF PRODUCTS AND METHODS FOR THE THENALS

Aldehyde	Catalyst	Product	Yield	Boiling Point °C/mm Hg	n_D^{25}	M.p. of Thenoic Acid
2-Thenal	H_2SO_4	2-Thenonitrile[a]	84%	90-90.5 (21mm)	1.5653	128.5-129.5
2-Thenal	H_3PO_4	2-Thenonitrile[a]	60%	86-86.5 (19mm)	1.5651	128.5-130
3-Thenal	H_2SO_4	3-Thenonitrile[b]	79%	84.5-86 (18mm)	1.5551	136-137.5
3-Thenal	H_3PO_4	3-Thenonitrile[b]	62%	88-89 (20mm)	1.5538	136.5-138

a Reported (133) B.p. 77.5-78° (12mm); n_D^{25} 1.5641. M.p. 2-Thenoic acid 129-130° (135).
b Reported (134) B.p. 203-205°; n_D^{25} 1.5534. M.p. 3-Thenoic acid 137-138° (72).

The Schmidt Reaction with the Acylthiophenes

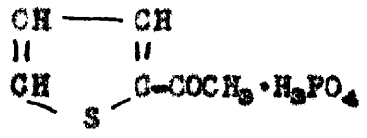
A study of the Schmidt reaction of the acylthiophenes is beset by considerably more difficulty than is that of the thenals. First, the work of Hurd and Moffat (87), which was not completely satisfactory in that they received a mixture of products from which they were able to isolate only 2-thenomethylamide, was repeated. The interaction of 2-acetylthiophene with hydrazoic acid in the presence of sulfuric acid with chloroform as the solvent proceeded readily at 0-10°. Following these author's procedure, the mixture was poured onto ice and the aqueous layer was repeatedly extracted with chloroform which was combined with the original chloroform layer and washed with dilute alkali. After evaporation of the chloroform the product was recrystallized from benzene and a second crop of crystals was obtained by the addition of pentane. The first product melted over a range of 108-139° while the second had a sharp melting point of 101-102°. Repeated recrystallizations of both products from various solvents failed to effect any further separation. These observations followed closely those of Hurd and Moffat. The mixture of the two crops of crystals was subjected to basic hydrolysis to yield a very dark colored solution from which it was possible to isolate a low yield of 2-thenoic acid by acidification. This indicated that the majority of the product was 2-acetamidothiophene with a smaller portion being 2-thenomethylamide.

It was thought that changing the reaction solvent to benzene might result in a preponderance of a single product and thereby avoid

a very difficult separation of the two isomeric amides. The addition of concentrated sulfuric acid to a benzene solution of hydrazoic acid and 2-acetylthiophene, at 0°, resulted in a dark red solution. After the previously described separation the benzene was removed by evaporation to yield a dark red oil which was taken up in absolute ethanol and treated with Norite A. Slow evaporation of the ethanol resulted in the formation of the same red oil which was taken up in hot benzene and cooled slowly. When a few white crystals appeared these were immediately separated and dried. They melted at 159-160° (136). When no further crystals could be isolated from the benzene solution it was concentrated and treated with a barium chloride solution which caused an immediate precipitation of a yellow solid. This was presumably due to the formation of the barium salt of a sulfonic acid. The remaining benzene solution was evaporated to a light red oil which was distilled at reduced pressure to yield some 2-acetyl thiophene, but no further products could be isolated.

Repetition of the above procedure resulted in the formation of a 7% yield of 2-acetamidothiophene, a 23% recovery of 2-acetylthiophene and a large amount of a barium salt. There is a report in the literature (137) of the formation of red complexes between 2-acetylthiophene and sulfuric acid. It was thought that this may account for the isolation of some unreacted thiophene. Accordingly, a benzene solution of 2-acetylthiophene was treated at 0° C. with a small amount of sulfuric acid to yield an immediate dark red solution whose intense color was lightened considerably by dilution with water.

An attempt to employ phosphoric acid as a catalyst for the reaction of 2-acetylthiophene and hydrazoic acid was unsuccessful because of the formation of a crystalline complex between phosphoric acid and 2-acetylthiophene which inhibited the Schmidt reaction. This white solid complex was first reported by Klages and Allendorf (138) who noted that it melts at 92-96°.



In an effort to improve the yield of products obtainable from 2-acetylthiophene in the Schmidt reaction the method of Smant and McIntosh was employed (119). The addition of solid sodium azide to a mixture of 2-acetylthiophene and sulfuric acid in glacial acetic acid resulted in a rapid and vigorous evolution of nitrogen. After a half hour the reaction mixture was poured onto ice, neutralized with ammonium hydroxide, and extracted several times with benzene. The benzene solution was dried and concentrated to a brownish oily liquid which was poured onto crushed ice to yield a tan solid melting at 110-133°. The solid was dissolved in a small volume of benzene and treated slowly with hexane to give a material melting at 152-157°. A further recrystallization of this material from a water and ethanol mixture resulted in a material melting at 158.5-159.5°. This melting point was not depressed when the product was mixed with a sample of pure 2-acetamidothiophene.

Numerous variations of this procedure were examined without any notable success. The use of larger amounts of sulfuric acid caused more extensive decomposition of the reaction mixture as did prolonged reaction time and elevated temperatures. The reaction proceeded rather sluggishly at 5° and yields were not improved.

Using the procedure of Smant and McIntosh (119) on 2-propionyl-thiophene and 2-n-butyrylthiophene resulted in 24 and 22% yields respectively of 2-propionamidothiophene and 2-butyramidothiophene. In both cases there was evidence of extensive decomposition of the reaction mixture. There was obtained during the recrystallization of both of the crude products an oily material which when cooled to low temperatures gave a semisolid of indefinate melting point. Basic hydrolysis of this material resulted in the formation of a small amount of 2-thenoic acid indicating that some thenamide had resulted in the Schmidt reaction of these acylthiophenes.

From 3-acetylthiophene the yield of 3-acetamidothiophene was only 13%. Here, as in the above experiments, a small amount of the corresponding thenoic acid was isolated by basic hydrolysis.

The use of trichloroacetic acid as both catalyst and solvent was examined. When this procedure was attempted on 2-acetylthiophene with the hydrazoic acid being generated in the reaction mixture by the addition of sodium azide, an almost immediate gelation and charring of the system occurred. This was found to be due to the high acidity and relatively high melting point of trichloroacetic acid (59°) since dissolving 2-acetylthiophene in the liquid acid resulted in a similar

occurrence. Accordingly, this possibility was abandoned.

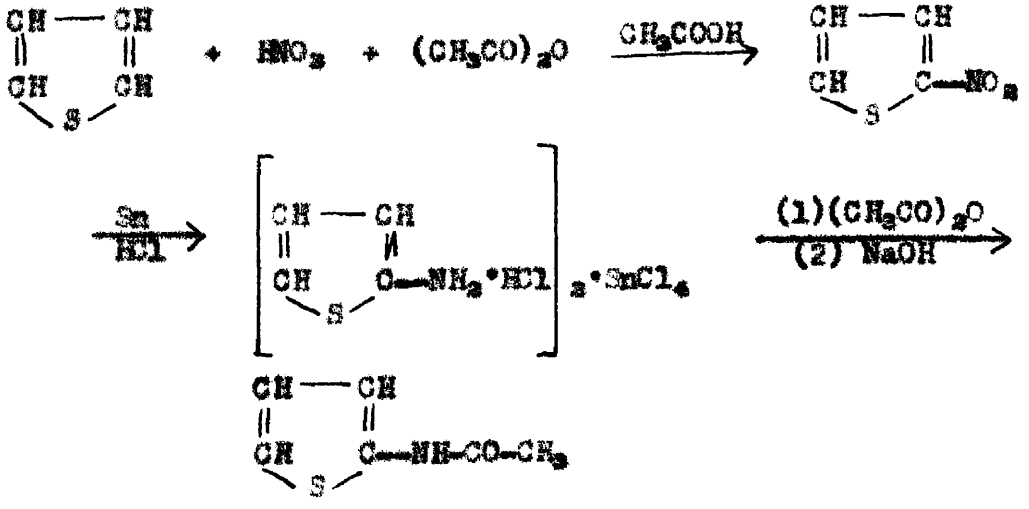
It was thought that trichloroacetic acid might serve satisfactorily as a catalyst if a solvent were employed to allow the mixture to remain liquid at lower temperatures. When benzene was employed as the solvent the reaction failed to occur even at elevated temperatures. The addition of sulfuric acid caused the usual vigorous reaction with decomposition. Apparently the dimerization of trichloroacetic acid in benzene was effective in reducing the acidity of the medium to such a point that the Schmidt reaction did not occur. A similar phenomenon occurred when chloroform served as the reaction medium. In both cases only 2-acetylthiophene and a small amount of decomposed material could be isolated from the reaction mixture.

Acetic acid was examined for its suitability as a solvent where trichloroacetic acid is used as the catalyst in the Schmidt reaction. A mixture of 2-acetylthiophene, trichloroacetic acid and acetic acid was treated with finely powdered sodium azide with no apparent reaction occurring. The temperature was increased from 20°C. to 50° C. without inducing any reaction to occur. When a sample of the reaction mixture was withdrawn and treated with concentrated sulfuric acid an immediate and vigorous evolution of gas took place. The remainder of the solution was neutralized with ammonium hydroxide and extracted repeatedly with benzene. The benzene extract was concentrated and the remaining liquid was distilled to yield a 95% recovery of the starting material, 2-acetylthiophene.

Because of its low melting point and high acidity, trifluoroacetic acid was studied as a reagent to serve both as catalyst and solvent in the Schmidt reaction. The addition of 2-acetylthiophene, in absence of hydrazoic acid or sodium azide, to this acid resulted in a very rapid decomposition and charring indicating the futility of attempting to conduct the Schmidt reaction in this medium. As with trichloroacetic acid, a reaction would not occur between 2-acetylthiophene, sodium azide and trifluoroacetic acid in acetic acid.

A summarization of the products resulting from the interaction of the acylthiophenes with hydrazoic acid and sulfuric acid in acetic acid is to be found in Table XI.

The identity of the amides resulting from the Schmidt reaction with acylthiophenes was ascertained by a comparison of the products with the same amides prepared by the following sequence of reactions:



The nitration procedure was carried out to give an 82% yield of 2-nitrothiophene by treating thiophene with a mixture of acetic

TABLE XI

SUMMARY OF PRODUCTS FROM THE ACYLTHIOPHENES

Acylthiophene	Main Product	Yield	M.p. °C.	Amount Thenoic Acid Isolated
2-Acetylthiophene	2-Acetamidothiophene	20%	158.5-159.5	0.8 g.
2-Propionylthiophene	2-Propionamidothiophene	24%	109-110.5	0.9 g.
2-Butyrylthiophene	2-Butyramidothiophene	22%	128-129	1.2 g.
3-Acetylthiophene	3-Acetamidothiophene	13%	146-147.5	0.7 g.

anhydride and nitric acid in acetic acid at room temperature. The product was isolated by pouring the reaction mixture onto crushed ice and collecting the yellow solid by filtration (139). The 2-nitrothiophene was reduced to the stannic chloride-hydrogen chloride double salt of 2-aminothiophene by reaction with metallic tin in the presence of concentrated hydrochloric acid (136) at 45°. The product, which precipitated as a yellowish solid, was separated by filtration, washed with ether and dried. The desired acylamidothiophene was obtained from the 2-aminothiophene salt by treatment with the appropriate acid anhydride dissolved in an equal volume of ether (136). After the initially exothermic reaction had subsided, the mixture was treated with a concentrated solution of sodium hydroxide and crushed ice. The precipitated product was quickly filtered, washed with water and then with ether. The amide was recrystallized from water and dried.

The preparation of the acylthiophenes and thenals is discussed in Part I of this dissertation.

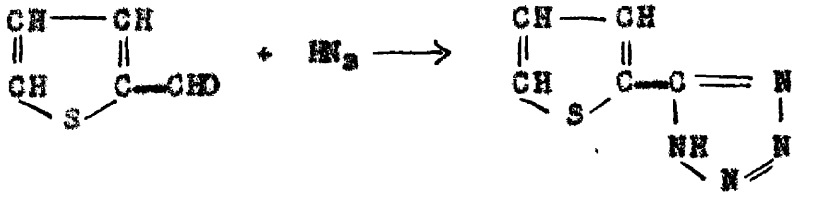
A rather cursory examination of the reaction of 2-thenal with excess hydrazoic acid to yield the tetrazole was conducted. When 2-thenal was treated with a two fold excess of hydrazoic acid in benzene and 95% sulfuric acid a vigorous evolution of nitrogen occurred. The reaction mixture was poured onto ice and treated with a 20% sodium carbonate solution. The volume of the resulting solution was reduced by evaporation and ethanol was added to precipitate sodium sulfate which was removed by filtration. After careful treatment of the

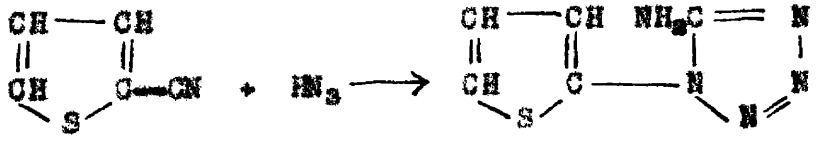
concentrated solution with 6 normal hydrochloric acid, a yellowish solid separated which was filtered off and redissolved in sodium carbonate solution and filtered again to remove a considerable amount of yellow amorphous solid. Careful acidification of the carbonate solution with 6 normal hydrochloric acid, caused the product to separate as a white solid which was collected by filtration. There was received a 44% yield of 5-(2-thienyl)tetrazole which was identified by its melting point and comparison with the reported (134) melting point of the same compound prepared by a different procedure. In a second preparation following the above procedure, a 42% yield of the same tetrazole derivative was obtained.

An attempt was made to determine whether or not the tetrazole resulted from the reaction of an intermediate nitrile with the excess hydrazoic acid. Using the same experimental procedure and conditions as described above, 2-thenonitrile was allowed to interact with hydrazoic acid and sulfuric acid in benzene. Distinctive from the previous reactions was the fact that the sulfuric layer discolored rapidly and appeared to contain considerable decomposed material. The reaction mixture was poured onto ice and slowly neutralized with sodium carbonate solution yielding an amorphous black tar which was slightly soluble in ethanol and completely soluble in dilute sulfuric. This latter property was completely opposed to the base solubility of 5-(2-thienyl)-tetrazole. All efforts to decolorize or crystallize the product were abortive.

Based on the different solubility of the product resulting from the nitrile, it would seem that the nitrile was not an intermediate in the reaction of 2-thenal with excess hydrazoic acid to yield the tetrazole. Under the conditions employed, nitriles usually yield 1-substituted-5-aminotetrazoles which are soluble in strong acid and insoluble in bases. Presumably, the tetrazole resulting from 2-thenonitrile was decomposed through its solubility and reaction with sulfuric acid. It would be expected that the thiophene ring of 1-(2-thienyl)-5-aminotetrazole would be easily attacked by sulfuric acid leading to substitution and probable ring rupture, while 5-(2-thienyl)tetrazole should be considerably more stable in the reaction mixture due to the deactivation of the thiophene ring by the electronegative tetrazole ring and the low solubility of the compound in sulfuric acid.

The probable reactions occurring between 2-thenal and 2-thenonitrile with excess hydrazoic acid are,





However, since this investigational phase is by no means complete, it cannot be said absolutely that these speculations are proven.

CHEMICAL REAGENTS

Hydrazoic acid solutions -- Prepared by the addition of sulfuric acid to a solution of sodium azide covered with a layer of benzene or chloroform. The organic layer was separated and dried over anhydrous sodium sulfate.

Sodium azide -- Practical grade, Eastman Kodak Co.

Acetic Acid -- C. P. grade, Merck & Co.

Trichloroacetic acid -- White label, Eastman Kodak Co.

Chloroform -- C. P. grade, Merck & Co.

Trifluoroacetic acid -- Obtained as student preparation.

Nitric acid (fuming) --Practical grade, Eastman Kodak Co.

Tin (shot) -- Practical grade, Eastman Kodak Co.

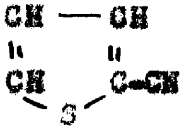
Acetic anhydride -- White label, Eastman Kodak Co.

Propionic anhydride -- Practical grade, Matheson Co.

Butyric anhydride -- White label, Eastman Kodak Co.

EXPERIMENTAL

2-Thenonitrile



A 100 ml. benzene solution of 11.2 g. (0.1 mole) of 2-thenal, and 1.0 molar in hydrazoic acid contained in a 400 ml. beaker was treated slowly, while being stirred, with 4 ml. of concentrated sulfuric acid. A vigorous evolution of gas occurred which subsided in about 20 minutes. After being set aside for an additional 15 minutes 200 g. of ice water was added to the reaction mixture and the resulting two layers were separated with the benzene layer being thoroughly washed with dilute sodium hydroxide solution followed by drying over anhydrous sodium sulfate. The benzene was removed by evaporation and the resulting oil was distilled under reduced pressure to yield 9.2 g. (0.084 mole; 84%) of clear colorless product whose physical constants were: b.p. 90-90.5° (21 mm.); n_D^{25} 1.5653.

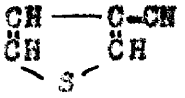
The reported (133) physical constants of 2-thenonitrile are 77.5-78° (12 mm.); n_D^{25} 1.5641.

A quantity of 5.0 g. of the product was refluxed for one-half hour in 50 ml. of a 10% sodium hydroxide solution during which time the oder of ammonia was very apparent. The solution was cooled,

extracted once with ether and then carefully treated with dilute hydrochloric acid which caused a white precipitate to rapidly settle out of solution in the form of needle shaped crystals. The latter were collected and dried, and amounted to 4.8 g. of a product melting at 128.5-129.5° indicating that the nitrile had been converted to 2-thenoic acid. The reported (135) melting point of 2-thenoic acid is 129-130°.

In a repetition of the reaction of 2-thenal with hydrazoic acid the same quantity of reactants were employed with the exception that 10 ml. of sirupy phosphoric acid was used as the catalyst instead of sulfuric acid. The reaction proceeded somewhat more slowly, but after two hours the reaction mixture was subjected to the same separation procedure to yield 6.5 g. (0.060 mole; 60%) of 2-thenonitrile distilling at 86-86.5° (19 mm.), and which had a refractive index of n_D^{25} 1.5651. The product was subjected to the same method of hydrolysis to yield 2-thenoic acid melting at 128.5-130°.

3-Thenonitrile



Following the above described procedure, 5.6 g. (0.05 mole) of 3-thenal, 50 ml. of 1 molar hydrazoic acid in benzene and 2 ml. of concentrated sulfuric acid were allowed to interact. After the usual separation scheme there was isolated, by distillation, 2.15 g.

(0.0395 mole; 79%) of 3-thenonitrile whose physical constants were: b.p. 84.5-86° (18 mm.); n_D^{25} 1.5551. The reported (134) physical constants of 3-thenonitrile are 203-205°; n_D^{25} 1.5534.

A sample of the product was converted to 3-thenoic acid by basic hydrolysis. Its melting point was 136-137.5°. The reported melting point of 3-thenoic acid is 137-138°.

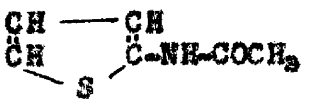
In a second study of the reaction of 3-thenal with hydrazoic acid the same quantities of reagents were used as above except that 5 ml. of phosphoric acid were employed instead of sulfuric acid. After a reaction period lasting two hours the product was separated and isolated according to the previously described procedure. There was obtained by distillation 3.38 g. (0.031 mole; 62%) of a colorless liquid product which had the following physical constants: b.p. 88-89° (20 mm.); n_D^{25} 1.5538. Basic hydrolysis of a quantity of the product yielded 3-thenoic acid which melted at 136.5-138°.

The Schmidt Reaction with 2-Acetylthiophene

Following the procedure elucidated by Hurd and Moffat (4) 5.4 g. (0.043 mole) of 2-acetylthiophene dissolved in 100 ml. of chloroform was treated with 5 ml. of 96% sulfuric acid and 40 ml. of a 1.5 molar solution of hydrazoic acid in chloroform. The reaction solution was kept at 0-10° for 15 minutes, while being stirred, and then poured onto ice. The resulting two layers were separated and the aqueous layer was extracted repeatedly with chloroform. After the combined chloroform solutions had been washed with dilute sodium hydroxide the

chloroform was removed on a steam bath to yield a yellowish brown solid which was taken up in hot benzene. The first crop of slightly yellow crystals amounted to 1.13 g. and melted over a range 108-139°. The addition of pentane to the remaining benzene solution caused the separation of 1.22 g. of yellowish crystals melting sharply at 101-102°. That this second crop was not a product expected from the Schmidt reaction is indicated by the fact that the expected products 2-acetamidothiophene melts at 160-161° while 2-thenomethylamide has a melting point of 113-114°. Following Hurd and Moffat's suggestion that this material was a eutectic mixture of the two possible products, the two crops of crystals obtained were combined and subjected to hydrolysis by refluxing for 2 hours in 50 ml. of a 10% sodium hydroxide solution. The dark colored mixture was cooled and extracted twice with 50 ml. portions of ether. Upon acidification of the aqueous portion and concentration to a volume of 15 ml. there was obtained 0.29 g. of 2-thenoic acid which melted at 129-130°.

2-Acetamidothiophene



To a well stirred mixture of 12.6 g. (0.1 mole) of 2-acetylthiophene in 110 ml. of a 1 molar benzene solution of hydrazoic acid, at 0°, was added 4 ml. of concentrated sulfuric acid. The evolution of gas was so vigorous that a 20 minute period was required to

complete the addition of acid after which the ice cold reaction mixture was allowed to warm to room temperature and it was then poured into a mixture of ice and water. The resulting two layers were separated and the benzene layer was extracted with a 10% sodium bicarbonate solution and then dried over anhydrous sodium sulfate. When the benzene was removed by evaporation a red oil separated and this was taken up in absolute ethanol and treated with Norite A. Slow evaporation of the ethanol caused the red oil to separate again and it was taken up in hot benzene and this solution was allowed to cool slowly. After a few crystals had separated they were immediately removed by filtration and dried. They had a melting point of 159-160°. When a sample of this material was combined with an authenic sample of 2-acetamidothiophene there was no depression in its melting point. The reported (140) melting point of 2-acetamidothiophene is 160-161°. As the benzene solution was cooled further the reddish oil again separated and it was redissolved in a larger volume of benzene and extracted with 5% barium chloride solution which caused a yellow precipitate to form in the aqueous portion. This material was assumed to be the barium salt of a sulfonic acid, but was not examined further. The remaining benzene solution was concentrated to give a light red oil which on distillation yielded 5.4 g. of 2-acetylthiophene boiling at 75-76° (3 mm.). No further material could be isolated.

A second application of the Schmidt reaction to 2-acetylthiophene resulted in a 7% yield of 2-acetamidothiophene and a 23% recovery of unreacted 2-acetylthiophene. There was also obtained a rather large amount of a barium salt.

In an attempt to decrease the amount of sulfonation which was apparently occurring when sulfuric acid was used as a catalyst, a mixture of 12.6 g. (0.1 mole) of 2-acetylthiophene and 110 ml. of a 1 molar benzene solution of hydrazoic acid was treated with 10 ml. of phosphoric acid. The addition of the acid resulted in the instantaneous formation of a white precipitate without any gas evolution. The solid was recovered by filtration and dried under vacuum. It had a melting point of 93-97° which agrees closely with the melting point reported by Klages and Allendorf (64) for the complex formed between 2-acetylthiophene and phosphoric acid.

A different procedure for the reaction of 2-acetylthiophene and hydrazoic acid was tried which involved the addition of 8.4 g. (0.13 mole) of sodium azide to a stirred solution of 12.6 g. (0.1 mole) of 2-acetylthiophene and 10 ml. of sulfuric acid in 100 ml. of acetic acid at 35°. Gas evolution had ceased after approximately two hours and the dark red reaction mixture was poured onto crushed ice and neutralized with ammonium hydroxide. To the neutralized mixture was added 100 ml. of benzene and the layers were separated. The aqueous layer was extracted three times with 100 ml. portions of benzene and these were combined with the original benzene extract and dried over anhydrous sodium sulfate. The benzene was removed and the residual red oil was poured onto crushed ice where upon it solidified to a tan solid. After one recrystallization from benzene the product melted over a range of 110-133°. The melting point increased to 152-157° after a recrystallization from a mixture of equal parts of

benzene and hexane. There was obtained 2.8 g. (0.02 mole; 20%) of white crystalline product after a final recrystallization from a mixture of ethanol and water. The melting point was 158.5-159.5° and it was not depressed when a sample of the product was mixed with an authentic sample of 2-acetamidothiophene. The reported (140) melting point of 2-acetamidothiophene is 160-161°.

A repetition of the above reaction using 20 ml. of sulfuric acid resulted in a red oily plastic appearing product which could not be induced to crystallize. It was completely soluble in sodium hydroxide and gave a yellow precipitate when treated with 5% barium chloride solution.

When the reaction was carried out at 5° the evolution of nitrogen was extremely slow and only by warming the mixture to approximately 35° could it be caused to proceed at a normal rate. Employing the isolation method which was just described there was obtained a 17% yield of 2-acetamidothiophene.

2-Propionamidothiophene

To a stirred mixture of 14.0 g. (0.1 mole) of 2-propionylthiophene, 20 ml. of concentrated sulfuric acid and 100 ml. of acetic acid was added, in small portions, 8.4 g. (0.13 mole) of finely pulverized sodium azide. After approximately two hours at the reaction temperature

of 35° gas evolution had ceased and the red reaction mixture was poured onto crushed ice and neutralized with dilute ammonium hydroxide. Employing the previously described separation procedure there was obtained, after two recrystallizations from a mixture of benzene and hexane, 3.5 g. (0.024 mole; 24%) of a crystalline product which melted at 109.5-110.5°. A sample of the product when mixed with 2-propionamidothiophene had a melting point of 109-110.5°; the reported (140) melting point of 2-propionamidothiophene is 110-111°.

Evaporation of the benzene solution from which the initial crop of crystalline product was isolated yielded a semisolid material which was refluxed for two hours in a 10% sodium hydroxide solution. Upon neutralization of the resulting solution there was obtained 0.9 g. of 2-thenoic acid which melted at 129-130°.

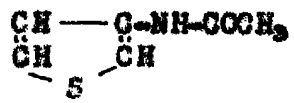
2-Butyramidothiophene

Following the same general method described previously, 15.4 g. (0.1 mole) of 2-butyrylthiophene, 20 ml. of 95% sulfuric acid and 8.4 g. (0.13 mole) of sodium azide were allowed to interact in 100 ml. of glacial acetic acid at 35°. After approximately two hours the reaction mixture was processed to yield 3.7 g. (0.022 mole; 22%) of slightly yellow crystals which melted at 128-129°. A mixed melting point of 128-129° was obtained when the product was intermixed with

an authenic sample of 2-butyramidothiophene. The reported (140) melting point of the product is 128.5-129.5°.

The original benzene mother liquor was evaporated to yield a semisolid mass which was hydrolyzed in a sodium hydroxide solution, to yield 1.2 g. of 2-thenoic acid which melted at 128.5-129°.

3-Acetamidothiophene



The interaction of 12.6 g. (0.1 mole) of 3-acetylthiophene, 20 ml. of 95% sulfuric acid and 8.4 g. (0.13 mole) of sodium azide in 100 ml. of acetic acid proceeded in a manner similar to the reaction of 2-acetylthiophene. After neutralization of the reaction mixture with ammonium hydroxide and extraction with several portions of benzene there was obtained after two recrystallizations from a mixture of benzene and cyclohexane 1.8 g. (0.013 mole; 13%) of a product melting at 146-147.5°. The reported (140) melting point of 3-acetamidothiophene is 145-148°.

Treatment of the original benzene extract residue with boiling sodium hydroxide and neutralization of the mixture with dilute hydrochloric acid resulted in the formation of 0.7 g. of 3-thenoic acid which melted at 136.5-137.5°.

The Schmidt Reaction of 2-Acetylthiophene in Trichloroacetic Acid

A mixture of 3 g. (0.024 mole) of 2-acetylthiophene and 35 g. of trichloroacetic acid was warmed to 60° to effect a homogeneous solution to which was added in small portions 2 g. (0.031 mole) of powdered sodium azide. Within five minutes after the first two components had been brought into solution the reaction mixture charred badly and became semisolid. The resultant mass was infusible and insoluble.

It was found that a mixture of 2-acetylthiophene and trichloroacetic acid at 60° rapidly reached a charred solid state.

To 12.6 g. (0.10 mole) of 2-acetylthiophene dissolved in 110 ml. of a 1 molar benzene solution of hydrazoic acid was added 10 g. of trichloroacetic acid. No gas evolution was observed even at temperatures as high as 45°. Finally 5 ml. of concentrated sulfuric acid were added with the resultant expected evolution of nitrogen.

Employing 12.6 g. (0.10 mole) of 2-acetylthiophene, 8.4 g. (0.13 mole) of sodium azide and 10 g. of trichloroacetic acid in 100 ml. of chloroform gave a result identical to the one just discussed. The addition of 5 ml. of sulfuric caused the reaction to proceed.

In a variation of experimental procedure 12.6 g. (0.10 mole) of 2-acetylthiophene and 40 g. of trichloroacetic acid dissolved in 100 ml. of glacial acetic acid were treated with 8.4 g. (0.13 mole) of sodium azide. The solubility of sodium azide in the reaction medium was relatively low and no reaction seemed to occur. When the temperature was raised to 50° the mixture became homogeneous, but no gas

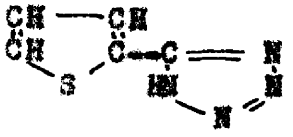
evolution or other evidence of reaction occurred. Finally, after two hours, the solution was neutralized with ammonium hydroxide and extracted twice with 150 ml. volumes of benzene which were combined, washed with water, dried over anhydrous sodium sulfate and evaporated to leave an oily liquid residue. This liquid was subjected to distillation at reduced pressure to yield a single liquid fraction which has the following physical constants: b.p. 92-94° (12 mm.); n_D^{25} 1.5634. These properties agree with those of 2-acetylthiophene of which there was 11.7 g. recovered. No other material could be isolated from the reaction mixture.

The Schmidt Reaction of 2-Acetylthiophene in Trifluoroacetic Acid

To determine the compatibility of 2-acetylthiophene in trifluoroacetic acid, 2 g. of the former were dissolved in 5 ml. of the acid at 0°. An instantaneous charring occurred indicating the futility of carrying out the Schmidt reaction with trifluoroacetic acid as solvent and catalyst.

In a separate experiment, 6.3 g. (0.05 mole) of 2-acetylthiophene and 20 ml. of trifluoroacetic acid dissolved in 50 ml. of acetic acid was treated, at 10°, with 4.2 g. (0.065 mole) of finely powdered sodium azide. No evidence of reaction occurred so the mixture was warmed to 50° resulting in a darkening of the solution, but still no evolution of nitrogen.

Formation of Tetrazoles



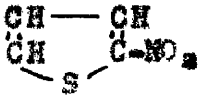
To 5.6 g. (0.05 mole) of 2-thenal dissolved in 150 ml. of a 1 molar benzene solution of hydrazoic acid was added 8 ml. of 95% sulfuric acid with rapid stirring. The evolution of nitrogen was prompt and vigorous and after an hour the mixture was poured onto 100 g. of ice followed by neutralization with a 20% sodium carbonate solution. The neutralized solution was evaporated to a volume of 50 ml. and treated with 30 ml. of ethanol to precipitate sodium sulfate which was removed by filteration. The addition of 6 normal hydrochloric acid to the filtrate caused a white precipitate to form which was separated and redissolved in 50 ml. of 20% sodium carbonate and refiltered to remove a small amount of yellowish amorphous solid. The careful addition of 6 normal hydrochloric to this second filtrate caused the product to reprecipitate. It was recovered by filtration and after drying amounted to 3.29 g. (0.022 mole; 44%) of white crystalline solid melting at 202.5-204.5°. The reported (60) melting point of 5-(2-thienyl)tetrazole is 204.7-205°.

In a second preparation by the same procedure there was isolated 3.21 g. (0.021 mole; 42%) of 5-(2-thienyl)tetrazole which melted at 203-205°.

Reaction of 2-Thenonitrile with Hydrazoic Acid

Employing the same experimental conditions as were just described, a mixture of 2.2 g. (0.020 mole) of 2-thenonitrile and 80 ml. of a 1 molar benzene solution of hydrazoic acid were treated with 8 ml. of 95% sulfuric acid. Vigorous gas evolution continued for about a half hour during which time the sulfuric acid layer became very dark in color. The mixture was poured onto 50 g. of ice and neutralized with a 20% sodium carbonate solution which caused the precipitation of a black tarry material. The latter was slightly soluble in ethanol and completely soluble in 6 normal sulfuric acid. The black tarry material was taken up in hot ethanol and treated with Norite A with little success in decolorization, as the tarry material separated from solution again as the ethanol cooled. It was then dissolved in dilute sulfuric acid and again treated with Norite A. Neutralization of the acid solution with a sodium carbonate solution resulted in the separation of the original tarry material. A repetition of this procedure netted the same result.

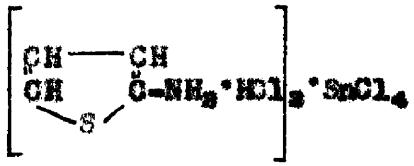
2-Nitrothiophene



Into a flask fitted with a reflux condenser was poured one half of a solution composed of 160 g. (2.4 moles) of fuming nitric acid

and 1200 ml. of acetic acid. To this was added slowly, at 10° and with agitation, one half of a solution containing 168 g. (2 moles) of thiophene and 680 ml. of acetic anhydride. The addition of the latter solution required two and a half hours during which time the temperature of the reaction mixture was not allowed to rise above 25°. At this point in the preparation the reaction mixture was again cooled to 10° and the remainder of the nitric acid and acetic acid solution was added. This was followed by the addition, during an hour and a half, of the remainder of the thiophene acetic anhydride solution under the same conditions as were described above. After the reaction mixture had been set aside for an additional two hours at room temperature the light colored solution was poured onto 2000 g. of cracked ice which caused the formation of a light yellow precipitate of 2-nitrothiophene. This was recovered by filtration and dried.

2-Aminothiophene Hydrochloride Stannic Chloride Salt



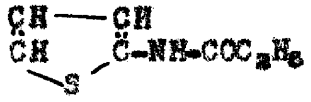
A solution of 140 g. (1.09 moles) of 2-nitrothiophene and 2500 ml. of concentrated hydrochloric acid contained in a 4000 ml. beaker was warmed to 45°. To this solution, while being stirred, was added 270 g. of 30 mesh tin shot during a half hour period. After an additional hour and a half of stirring the reaction mixture was filtered to remove the white insoluble product which was mixed

thoroughly with ethyl ether and refiltered. After drying, this material amounted to 201 g. (0.86 mole; 79%) of a slightly tan colored product which was stored in a brown bottle under refrigeration.

2-Acetamidothiophene

To a rapidly stirred solution of 42 g. (0.079 mole) of 2-aminothiophene hydrochloride stannic chloride salt in 120 ml. of water was added 30 g. (0.268 mole) of acetic anhydride dissolved in 30 ml. of ethyl ether. After 15 minutes, a solution of 52 g. (1.3 mole) of sodium hydroxide in 50 ml. of water was added slowly while cooling of the reaction mixture. The solid which separated was immediately removed by filtration and washed with water followed by ether. After a single recrystallization from hot water there was obtained 9.87 g. (0.(7(mole; 88%) of product which melted at 160.5-161.5°. The reported (140) melting point of 2-acetamidothiophene is 160-161°.

2-Propionamidothiophene



According to the above experimental method, 42 g. (0.079 mole) of 2-aminothiophene hydrochloride stannic chloride salt in 120 ml. of water and 33 g. (0.254 mole) of propionic anhydride in 30 ml. of

ether were allowed to interact. After neutralization of the mixture there was obtained 9.20 g. (0.064 mole; 81%) of a product melting at 110-110.5°. The reported melting point (140) of 2-propionamidothiophene is 110-111°.

2-Butyramidothiophene

The reaction of 42 g. (0.079 mole) of 2-aminothiophene hydrochloride stannic chloride salt with 36 g. (0.23 mole) of butyric anhydride in 120 ml. of water and 30 ml. of ethyl ether resulted in the formation of 9.15 g. (0.054 mole; 67%) of 2-butyramidothiophene which had a melting point of 127.5-129°. The reported (140) melting point of 2-butyramidothiophene is 128.5-129.5°.

SUMMARY

1. The Schmidt reaction with 2- and 3-thenal were carried out using hydrazoic acid in benzene. Good yields of the expected nitriles were obtained when either concentrated sulfuric acid or phosphoric acid was used as the catalyst.

2. The Schmidt reaction with 2- and 3-acetylthiophene, 2-propionylthiophene and 2-butyrylthiophene gave only low yields of the acylamidothiophenes and small amounts of the thenoalkylamides. The low yields were largely due to side reactions such as complex formation with the catalyst, sulfonation of the products and lack of stability of the thiophene derivative toward the reagents employed. The use of solutions of hydrazoic acid and suspensions of sodium azide in benzene, chloroform and acetic acid was investigated. A variety of acids, including sulfuric acid, phosphoric acid, trichloroacetic acid and trifluoroacetic acid, were studied as catalysts for the reaction.

3. The formation of tetrazoles through the interaction of excess hydrazoic acid with 2-thenal and 2-thenonitrile was studied. The same tetrazole was not isolated from the two starting compounds indicating that the nitrile probably is not an intermediate in the formation of a tetrazole from 2-thenal and excess hydrazoic acid.

REFERENCES

1. S. Reformatsky, Ber., 20, 1210 (1887).
2. S. Reformatsky, J. prakt. Chem., 54, 469 (1896).
3. G. Haberland and E. Heinrich, Ber., 72, 1222 (1939).
4. R. E. Miller and F. F. Nord, J. Org. Chem., 16, 728 (1951).
5. J. W. Cook and R. Philip, J. Chem. Soc., 162 (1948).
6. J. W. Cook and R. Schoental, J. Chem. Soc., 288 (1945).
7. J. English, J. Am. Chem. Soc., 73, 615 (1951).
8. R. C. Fuson, J. Am. Chem. Soc., 60, 2272 (1938).
9. R. C. Fuson and P. L. Southwick, J. Am. Chem. Soc., 66, 679 (1944).
10. K. Ziegler, Ann., 557, 80, 120 (1942).
11. W. E. Bachman and A. S. Dreiding, J. Org. Chem., 13, 317 (1948).
12. Brit. Pat., 626,712 (1949).
13. S. I. Heilbron, J. Chem. Soc., 866 (1946).
14. S. H. Harper and J. F. Oughton, Chem. and Ind.,574 (1950).
15. A. E. Linnell and W. C. Shen, J. Pharm. Pharmacol., I, 971 (1949).
16. R. E. Miller and F. F. Nord, J. Org. Chem., 16, 1720 (1951).
17. E. R. Jones, D. G. O'Sullivan and M. C. Whiting, J. Chem. Soc., 1415 (1949).
18. J. English and J. D. Gregory, J. Am. Chem. Soc., 69, 2123 (1947).
19. R. Grewe, Ber., 76B, 1076 (1943).
20. H. B. Henbest, E. R. Jones, and I. M. Walls, J. Chem. Soc., 2696 (1949).

21. H. Henbest, J. Chem. Soc., 3646 (1950).

22. N. I. Huber and B. O. Businger, U. S. Pat., 2,540,116 (1951).

23. H. Koskin, R. E. Miller and F. F. Nord, J. Org. Chem., 16, 199 (1951).

24. R. C. Fuson and H. G. Cook, J. Am. Chem. Soc., 62, 1180 (1940).

25. Darzens, Compt. rend., 203, 1374 (1936).

26. E. R. Blout and R. C. Elderfield, J. Org. Chem., 8, 29 (1943).

27. N. L. Drake, J. Am. Chem. Soc., 70, 677 (1948).

28. G. R. Clemo and J. Ormston, J. Chem. Soc., 362 (1933).

29. V. K. Arbuzov, J. Gen. Chem. (U.S.S.R.), 9, 255 (1939).

30. H. Gilman and M. Spaeter, J. Am. Chem. Soc., 65, 2255 (1943).

31. R. Lukes, Coll. Czech. Chem. Commun., 4, 81 (1932).

32. S. Reformatsky, J. prakt. Chem., 54, 477 (1896).

33. S. Reformatsky, Ber., 28, 3262 (1895).

34. S. Reformatsky and B. Plesconoff, Ber., 28, 2838 (1895).

35. S. Reformatsky, J. Russ. Phys. Chem. Soc., 22, 194 (1890).

36. S. Reformatsky, Ber., 28, 2842 (1895).

37. R. Adams, "Organic Reactions", Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 1-38.

38. I. U. Dain, J. Russ. Phys. Chem. Soc., 28, 593 (1896).

39. R. Adams, "Organic Reactions", Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 413-440.

40. J. A. Nieuwland and S. F. Daly, J. Am. Chem. Soc., 53, 1842 (1931).

41. D. Lipkin and T. D. Stewart, J. Am. Chem. Soc., 61, 3295 (1939).

42. E. P. Kohler, G. L. Heritage and A. L. MacLeod, Am. Chem. J., 46, 221 (1911).

43. L. F. Fieser and W. S. Johnson, J. Am. Chem. Soc., 62, 575 (1940).

44. J. H. Gladstone and A. Tribe, J. Chem. Soc., 567 (1879).

45. F. Krause and A. von Grosse, "Die Chemie der Metallorganischen Verbingungen", Edwards Bros., Inc., Ann Arbor, Mich., 1943, p. 63.

46. W. A. Weehs, Am. Perfumer Essent. Oil Rev., 44, 25 (1942).

47. M. Sommelet and J. F. Hamel, Bull. soc. chim., (4) 29, 545 (1921).

48. A. C. Ray and S. B. Dutt, J. Indian Chem. Soc., 5, 109 (1928).

49. N. Zelinsky and J. Dutt, Ber., 35, 2140 (1902).

50. R. Willstatter and D. Hatt, Ann., 418, 148 (1919).

51. S. Lewinsohn, Perfumery Essent. Oil Record, 15, 44 (1924).

52. A. von Baeyer, Ber., 38, 2759 (1905).

53. H. Gilman, J. M. Petersen, and F. Schultz, Rec. trav. chim., 47, 19 (1928).

54. M. S. Newman, J. Am. Chem. Soc., 62, 870 (1940).

55. A. C. Mann and A. Lapworth, Proc. Chem. Soc., 19, 189 (1903).

56. M. S. Newman, J. Am. Chem. Soc., 64, 2131 (1942).

57. A. S. Hussey and M. S. Newman, J. Am. Chem. Soc., 70, 3024 (1948).

58. W. V. Evans and R. Pearson, J. Am. Chem. Soc., 64, 2865 (1942).

59. E. R. Alexander, "Ionic Organic Reactions", John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 203-206.

60. R. L. Letsinger, J. Am. Chem. Soc., 70, 406 (1948).

61. R. Adams, "Organic Reactions", Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 266-302.

62. E. P. Kohler, G. L. Heritage and A. L. MacLeod, Am. Chem. J., 46, 221 (1911).

63. G. R. Iyer, J. Indian Chem. Soc., 17, 215 (1940).

64. E. R. Alexander, "Ionic Organic Reactions", John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 176-179.

65. R. E. Miller and F. F. Nord, J. Org. Chem., 15, 89 (1950).

66. R. E. Miller and F. F. Nord, J. Org. Chem., 16, 1380 (1951).

67. H. D. Hartough and J. J. Dickert, J. Am. Chem. Soc., 71, 3922 (1949).

68. H. D. Hartough, S. J. Lukasiewicz and E. H. Murray, J. Am. Chem. Soc., 70, 1146 (1948).

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

70. H. D. Hartough and A. I. Kosak, J. Am. Chem. Soc., 69, 3093 (1947).

71. K. Dittmer, J. Am. Chem. Soc., 71, 1201 (1949).

72. E. Campaigne and W. M. LeSeur, J. Am. Chem. Soc., 70, 1557 (1948).

73. H. Gilman and J. F. Nelson, Rec. trav. chim., 55, 518 (1936).

74. H. Schmidt and P. Karrer, Helv. Chim. Acta., 29, 573 (1946).

75. A. Kirrman, Bull. Soc. Chim., 39, 698 (1926).

76. H. Rupe, Ann., 369, 321 (1909).

77. L. Tetry, Bull. Soc. Chim., 27, 600 (1902).

78. H. Hibbert, J. Am. Chem. Soc., 37, 1748 (1915).

79. G. A. Ken and K. S. Nargund, J. Chem. Soc., 2461 (1932).

80. G. W. Steinkopf and S. H. Schubart, Ann., 424, 1 (1920).

81. H. D. Hartough and C. S. Conley, J. Am. Chem. Soc., 69, 309 (1947).

82. G. W. Steinkopf and H. Schmidt, Ann., 533, 264 (1938).

83. N. S. Bruylants, Bull. Soc. Chim. Belg., 38, 138 (1929).

84. K. Schmidt, Z. angew. Chem., 36, 511 (1923).

85. K. Schmidt, Ber., 57, 704 (1924).

86. R. Adams, "Organic Reactions", Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 307.

87. C. D. Hurd and J. Moffat, J. Am. Chem. Soc., 73, 613 (1951).

88. D. W. Adamson and J. Kenner, J. Chem. Soc., 838 (1934).

89. J. v. Braun, Ann., 490, 100 (1931).

90. M. Oesterlin, Z. angew. Chem., 45, 536 (1932).

91. U. S. Patent 1,926,756 (C. A., 27, 5752 (1933).

92. L. H. Briggs, G. C. DeAth and S. R. Ellis, J. Chem. Soc., 61 (1942).

93. Ger. Patent 544,890 (Frdl., 18, 3054 (1933).

94. V. Meyer and W. M. Wolff, Gazz. chim. ital., 71, 189 (1941).

95. U. S. Patent 1,637,661 (C. A., 21, 3057 (1927).

96. J. v. Braun and L. Heymons, Ber., 63, 502 (1930).

97. L. Ruzicka, M. W. Goldberg, M. Hurbin and H. A. Boeckenoogen, Helv. Chim. Acta., 16, 1323 (1933).

98. P. A. S. Smith, J. Am. Chem. Soc., 70, 320 (1948).

99. M. S. Newman and H. L. Gildenhorn, J. Am. Chem. Soc., 70, 317 (1948).

100. W. E. McEwen, M. Gilliland and B. I. Sparr, J. Am. Chem. Soc., 72, 3212 (1950).

101. C. Schuerch and E. H. Huntress, J. Am. Chem. Soc., 71, 2233 (1949).

102. C. Schuerch and E. H. Huntress, J. Am. Chem. Soc., 71, 2238 (1949).

103. P. A. S. Smith and B. Ashby, J. Am. Chem. Soc., 72, 2503 (1950).

104. P. A. S. Smith and J. P. Horowitz, J. Am. Chem. Soc., 72, 3212 (1950).

105. P. A. S. Smith, J. Am. Chem. Soc., 76, 431 (1954).

106. J. v. Braun and E. Anton, Ber., 64, 2865 (1931).

107. D. W. Adamson, J. Chem. Soc., 1564 (1939).

108. J. v. Braun and E. Friehmelt, Ber., 66, 684 (1933).

109. E. H. Buchmann, A. O. Reims, T. Skei and M. J. Schlatter, J. Am. Chem. Soc., 64, 2696 (1942).

110. J. v. Braun and H. Wittmayer, Ber., 67, 1739 (1934).

111. L. H. Briggs and G. C. Death, J. Chem. Soc., 456 (1937).

112. J. v. Braun and W. Pinkernelle, Ber., 67, 1056 (1934).

113. C. Jansen and A. I. Pope, Proc. Roy. Soc. London, A154, 53 (1936).

114. U. S. Patent, 1,564,631 (C. A., 20, 423 (1926).

115. M. A. Spielman and F. L. Austin, J. Am. Chem. Soc., 59, 2658 (1937).

116. V. Prelog, M. Heimbach and R. Rezek, Ann., 545, 231 (1940).

117. E. Cerkovnikov and V. Prelog, Ber., 74, 1648 (1941).

118. E. E. Ceroma, Gazz. chim. ital., 71, 475 (1941).

119. H. N. Samant and J. J. McIntosh, J. Am. Chem. Soc., 72, 4835 (1950).

120. L. H. Briggs and J. W. Lyttleton, J. Chem. Soc., 421 (1943).

121. Ger. Patent, 427,858.

122. J. R. Dice and P. A. S. Smith, J. Org. Chem., 14, 179 (1949).

123. D. V. Nightingale and M. Maienthal, J. Am. Chem. Soc., 72, 4823 (1950).

124. R. N. Keller and P. A. S. Smith, J. Am. Chem. Soc., 66, 1122 (1944).

125. U. S. Patent, 1,599,493 (C. A., 20, 3460 (1926).

126. L. Ruzicka, M. W. Goldberg and M. Hurbin, Helv. Chim. Acta., 16, 1335 (1933).

127. Brit. Patent, 555,140 (C. A., 39, 944 (1945).

128. U. S. Patent, 2,029,799 (C. A., 30, 1950 (1936).

129. J. v. Braun and W. Keller, Ber., 65, 1677 (1932).

130. R. Stolle, Ber., 55, 1289 (1922).

131. C. Oliveri-Mandalà, Gazz. chim. ital., 52, 139 (1922).

132. R. Stolle and S. Henke-Stark, J. prakt. Chem., 124, 261 (1930).

133. M. Putukhin and V. Egorova, J. Gen. Chem., (U.S.S.R.), 19, 1866 (1949); (C. A., 43, 3816 (1949).

134. B. Elpern and F. C. Nachod, J. Am. Chem. Soc., 72, 3379 (1950).

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

136. G. W. Steinkopf, "Die Chemie des Thiophens", Steinkopf, Dresden, 1941, p. 59.

137. H. D. Hartough, "Thiophene and Its Derivatives", Interscience Press, New York, N. Y.

138. A. Klages and P. Allendorf, Ber., 31, 1298 (1898).

139. H. Gilman, "Organic Synthesis", Vol. 14, John Wiley and Sons, Inc., New York, N. Y., 1934, p. 76.

140. G. W. Steinkopf, Ann., 403, 17 (1914).