ABSTRACT

THE REACTIONS OF ORGANOLITHIUM COMPOUNDS:

I. A NEW SYNTHETIC ROUTE TO THE THIOPHENECARBOXALDEHYDES AND ACYLTHIOPHENES

II. THE SYNTHESIS OF FLUORINATED HETEROCYCLICS WITH PERCHLORYL FLUORIDE

by David D. Taft

I.

In connection with an investigation of thiophenecarboxaldehydes and acylthiophenes under Baeyer-Villiger reaction conditions, it was necessary to prepare 2- and 3-thiophenecarboxaldehydes and numerous 2- and 3-acylthiophenes. 2-Thiophenecarboxaldehyde can be synthesized in 45-88% yield by the formanilide reaction with thiophene and phosphorus oxychloride followed by hydrolysis (1). However, the experimental procedure uses expensive reagents and involves a time-consuming steam distillation. The corresponding 3-aldehyde is obtainable in only 32% yield by the Sommelet reaction from 3-bromomethylthiophene (2). The 2-acylated derivatives are readily obtainable through normal Friedal-Crafts reactions (3). However, the 3-acylated thiophenes are prepared with difficulty through the interaction of 3-thenoyl chloride and the corresponding organocadmium derivatives (4).

A general method of synthesis for these thiophene derivatives has now been developed. The reaction involves a nucleophilic displacement by an organolithium compound on a N, N-disubstituted amide. Thus, when N, N-dimethylformamide is reacted with 2-thienyllithium,

obtained by the direct metallation of thiophene with n-butyllithium, a 61% yield of 2-thiophenecarboxaldehyde is obtained following hydrolysis. Similarly, 3-thienyllithium from the halogen-metal interconversion of 3-bromothiophene yielded 73% of 3-thiophenecarboxaldehyde.

With the reaction between 2-thienyllithium and the corresponding homologs of N, N-dimethylformamide, the following 2-acetylated derivatives were prepared: 2-acetylthiophene 54%, 2-propanoylthiophene 52%, 2-(phenylacetyl)-thiophene 43%, 2-benzoylthiophene 73%, and 2-thenoylthiophene 63%. Analogously, 3-thienyllithium and the N, N-dimethylacylamides gave the following 3-acylated derivatives: 3-acetylthiophene 61%, 3-propanoylthiophene 38%, 3-isobutyrylthiophene 29%, 3-(phenylacetyl)-thiophene 60%, 3-benzoylthiophene 61%, and 3-thenoylthiophene 64%.

In addition 2, 5-thienyldilithium with N, N-dimethylformamide gave 32% of 2, 5-thiophenedicarboxaldehyde and with N, N-dimethylacetamide 59% of 2, 5-diacetylthiophene.

II.

In connection with investigations of biologically important heterocyclic compounds, it was of interest to obtain fluorinated derivatives of thiophenes and thianaphthenes. One of the simplest fluoro heterocyclics, 2-fluorothiophene, has previously been reported as obtainable in less than 10% yields, by the reaction of thiophene with antimony pentafluoride in nitromethane as a reaction media (5). However, simple fluorothianaphthalenes such as the 2- or 3-fluoro derivatives have, as yet, to be reported. A convenient laboratory method has now been developed for the synthesis of 2-fluoro-5-methylthiophene, 2-fluorothiophene, and 2-fluorothianaphthene by the exothermic reaction of gaseous perchloryl fluoride with the corresponding organolithium heterocyclic compounds in anhydrous ether as a reaction solvent. This simple procedure gave 44, 49 and 70% yields of these fluoro heterocyclics, respectively. Vapor phase chromatography, infrared spectra, nuclear magnetic resonance, and elemental analysis of these products supports the assigned structures of these fluoro compounds.

The application of the fluorination procedure with perchloryl fluoride to the lithium derivatives of arene hydrocarbons, such as phenyllithium and 1-naphthyllithium, and to the sodium salts of ethyl cyanoacetate and benzonitrile yielded negligible amounts of the corresponding fluoro derivatives.

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TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

Page

LIST OF TABLES

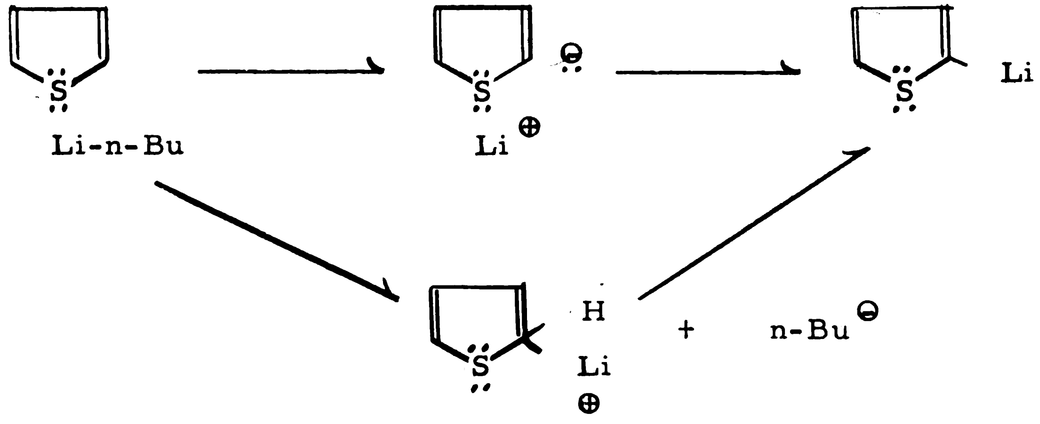
LIST OF FIGURES

INTRODUCTION AND HISTORICAL

I.

The study of the thienyllithiums and their subsequent reactions is a relatively new field with respect to other investigations in the chemistry of organolithium compounds. Gilman first prepared 2-thienyllithium (1) by the direct metallation of thiophene with an n-butyllithium-ether solution. The organolithium compound was then converted to 2-thiophenecarboxylic acid in an 87% yield by carbonation and hydrolysis. Gilman also observed that upon treatment with an n-butyllithium-ether solution at 0° the 2-halogenated thiophenes produced essentially quantitative yields of 2-thienyllithium (2). However, the advantage of a quantitative yield in this method was offset by the inavailability of the halogenated thiophenes, all of which are prepared from the parent heterocyclic. The mechanism of the metal-halogen conversion is well understood, whereas that of the direct metallation is still open to question. One theory (3) asserts that an organometallic ion-pair is formed from a coordinate bond between the metal cation and a pair of electrons on the sulfur atom. The carban ion portion of the organometallic ion-pair attacks an adjacent hydrogen atom, removing it as a proton. This proton removal is facilitated by the coordinate bond between the metal cation and the hetero atom which in turn weakens the ionic bond between the metal and the carban ion and at the same time polarizes the adjacent carbon-hydrogen bond. In this way the mechanism is similar to a halogen-metal interconversion (4).

The other mechanism involves the initial coordination of the cation with the heteroatom. The coordination is followed by an electrophilic attack of the metal cation on the carbon atom from which the hydrogen is to be removed (5).



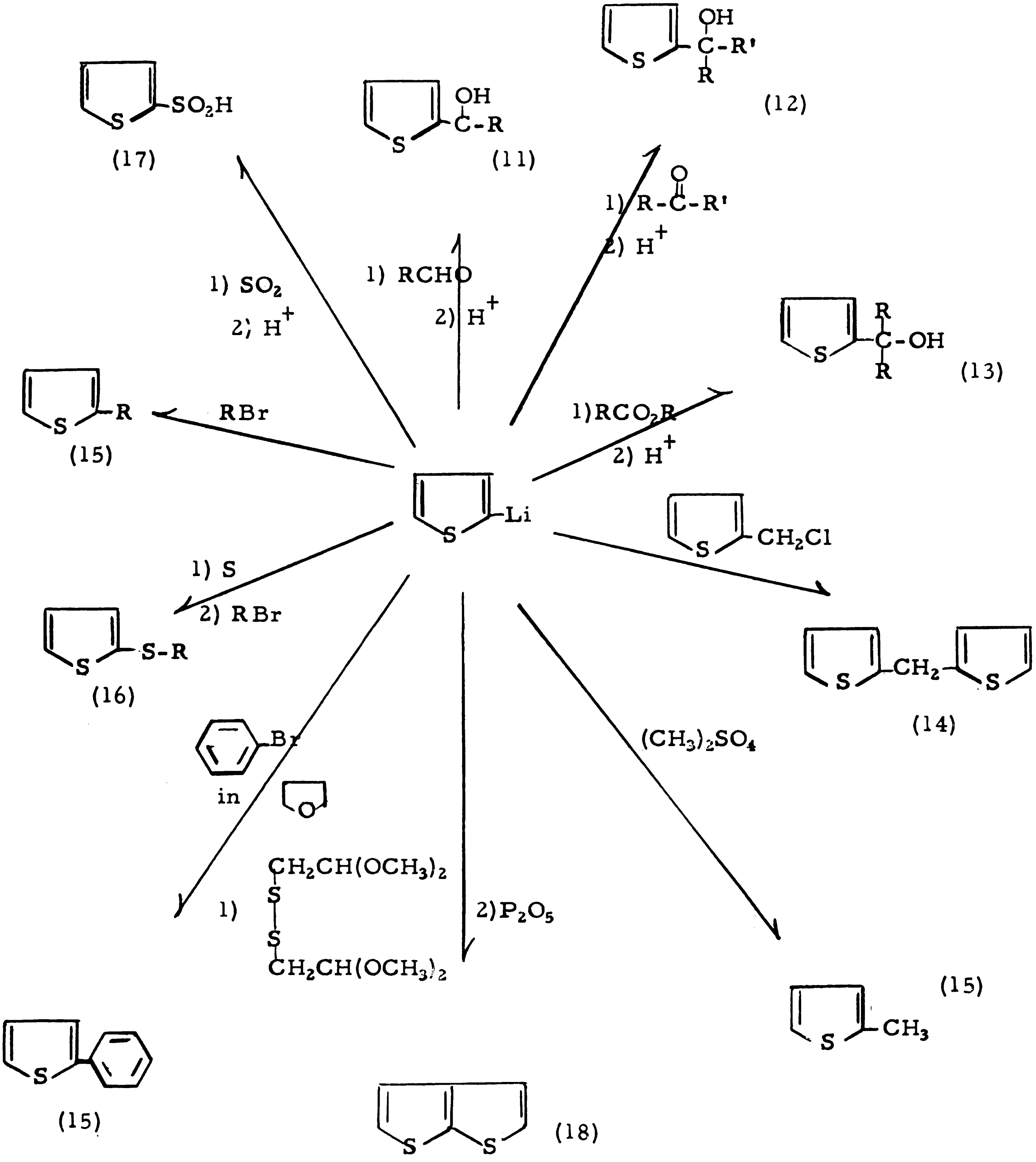
The preparation of 3-thienyllithium can only be achieved by the halogen-metal interconversion at extremely low temperatures (6). For example, 3-bromothiophene on treatment with n-butyllithium at -70° yielded 79% of 3-thienyllithium as shown by carbonation and hydrolysis to 3-thiophenecarboxylic acid. The reaction must be conducted below -65° to prevent the normal direct metallation at the 2 position, for if 3-bromothiophene is treated at room temperature with n-butyllithium, 3-bromo-2-thienyllithium and 2-thienyllithium are formed (7). The latter product is formed by equilibration of 3-thienyllithium with the more favored 2-isomer. In a similar manner, 3,4-dibromothiophene on treatment at -70° with n-butyllithium gave 4-bromo-3-thienyllithium. When the reaction is conducted at room temperature a mixture of 3-bromo-2-thienyl and 3,4-dibromo-2-thienyllithium is formed. Also, 2,3,4,5-tetrabromothiophene treated at 0° with excess n-butyllithium gave 74% of the 3,4-dibromo-2,5-dicarboxylic acid upon carbonation (8). Thus, the direct metallation proceeds at a much faster rate at the 2-position than the halogen-metal interconversion at the 3-position. A similar dimetallation has been conducted on 2,5-diiodothiophene with phenyllithium followed by carbonation to give 52% of 2,5-thiophenedicarboxylic acid (9). This simple conversion is in marked contrast to the difficult preparation of o-phenyldilithium obtained through the dimercuric chloride derivative (10).

Many of the reactions of the thienyllithium derivatives are similar to those of the corresponding Grignard reagents. For example, 2-thienyllithium with an aldehyde gave a secondary alcohol (11), with a ketone a tertiary alcohol (12), an ester a tertiary alcohol (13). Since the organolithium compounds are stronger as carban ion sources than the corresponding Grignard reagents, coupling can be readily effected: 2-thienyllithium and 2-chloromethylthiophene gave di-2-thienyl-methane (14). When treated with dimethyl sulfate, 2-thienyllithium yielded 65% of 2-methylthiophene, a convenient synthetic procedure for this homolog. Alkylation is conducted on 2-thienyllithium with the various bromides to give 61% of 2-ethylthiophene, 47% of 2-n-butylthiophene, 46% of 2-n-octylthiophene and 62% of 2-benzylthiophene. When tetrahydrofuran is used as a solvent, 2-phenylthiophene can be obtained in 31% yield by the alkylation with bromobenzene (15).

Another synthetically important reaction is the treatment of the 2- and 3-thienyllithium with sulfur followed by hydrolysis or reaction with various alkyl halides to give excellent yields of the mercaptans or thioethers (16).

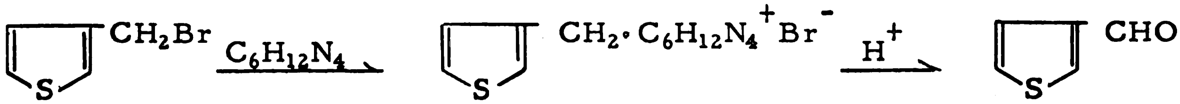
When the organolithium derivative is reacted with sulfur dioxide with subsequent hydrolysis, a low yield of 2-thiophenesulfinic acid is obtained (17). Similarly the reaction between 2-thienyllithium and

FIGURE I

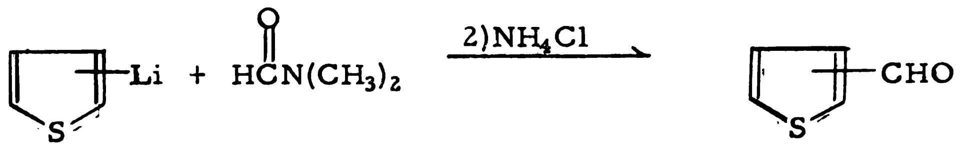

SO₂H
(17)
1) SO₂
2) H⁺
OH
C-R
(11)
1) RCHO
2) H⁺
OH
C-R'
R
(12)
1) R-C(=O)-R'
2) H⁺
R
C-OH
R
(13)
1)RCO₂R
2) H⁺
R
(15)
RBr
Li
CH₂Cl
CH₂
(14)
1) S
2) RBr
S-R
(16)
Br
in
(CH₃)₂SO₄
1) CH₂CH(OCH₃)₂ S S CH₂CH(OCH₃)₂
2)P₂O₅
CH₃
(15)
(15)
(18)
S

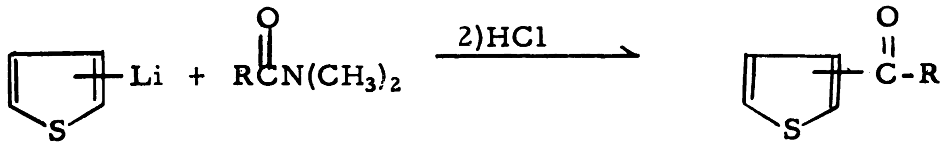
2,2,2',2'-tetramethoxydiethyldisulfide yielded thienyldimethoxyethylsulfide which on treatment with phosphoric acid gave bithiophene (18).

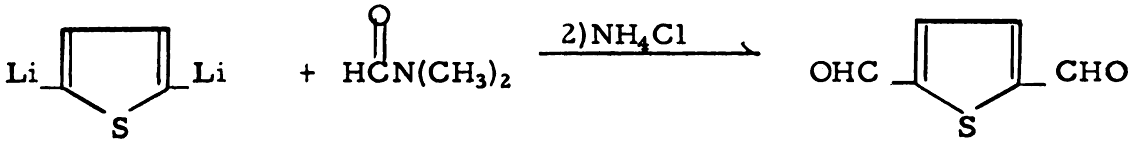
However, a simple conversion which has not been extensively studied is the reaction of 2- and 3-thienyllithium with N, N-dimethylformamide to give the corresponding aldehydes (19). Generally, 2-thiophenecarboxaldehyde is prepared in 45-88% yields by the N-methylformanilide procedure (20). However, the procedure utilizes expensive starting materials and requires a time consuming steam distillation to effect complete hydrolysis of the intermediate complex. The corresponding 3-aldehyde, 3-thiophenecarboxaldehyde, is most easily obtained through the Sommelet reaction (21). However, starting with 3-bromomethylthiophene the overall yield is only 32%.

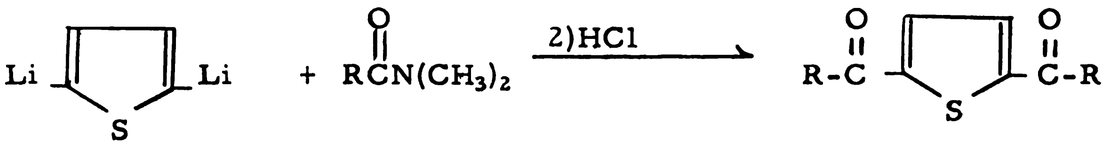


The reaction between the organolithium compounds and N, N-dimethylformamide should provide a better route to both of these aldehydes. In addition, if instead of N, N-dimethylformamide, other N, N-dimethyl substituted amides were utilized in the reaction with the thienyllithiums, another possible route to the 2- and 3-acyl derivatives would be opened. If the 2,5-thienyldilithium were utilized, a convenient route to the 2,5-dialdehyde and diacyl derivatives would be developed.

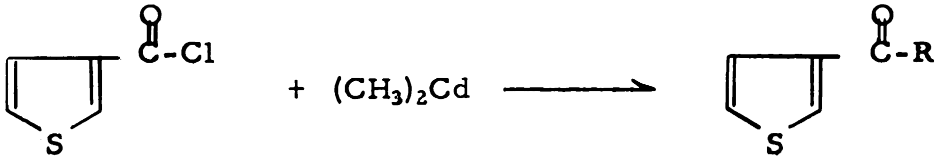








Previous methods for the preparation of the 2-acyl derivatives have relied on Friedel-Crafts procedures. Thiophene is reacted with acylhalides in the presence of various metal catalysts (23), with acid anhydrides and phosphoric acid (24), or with carboxylic acids and phosphorus pentoxide (25). Thus, the proposed procedure would not provide a better method of synthesis. However, with the 3-acyl derivative, the previous method of preparation has involved the use of the unstable organocadmium derivatives which are obtained from the corresponding Grignard reagents. By this method Campaigne and LeSuer were able to prepare 3-acetylthiophene in an 81% yield (22).



In addition other 3-acylated derivatives--3-benzoylthiophene, 3-propionylthiophene, 3-n-butyrylthiophene, 3(2-thenoyl)-thiophene, n-butyl-2-thienylketone--have been prepared from the organocadmium derivative (26). The proposed method would provide, therefore, a more efficient and economical preparation of these compounds.

II.

In connection with investigations of biologically important heterocyclic compounds, it was of interest to obtain fluorinated derivatives of thiophenes and thianaphthenes. One of the simplest fluoro heterocyclics, 2-fluorothiophene, has previously been reported as obtainable in less than 10% yields, by the reaction of thiophene with antimony pentafluoride in nitromethane as a reaction media (27). However, the simple fluorothioanaphthenes such as the 2- or 3-fluoro derivatives have, as yet, to be reported.

With respect to the rather extensive work conducted with thienyllithium derivatives, a possible synthesis using this versatile and reactive intermediate is proposed. The procedure would involve the reaction between 2-thienyllithium and perchloryl fluoride, a colorless, sweet smelling gas, (b.p. -46-48°) (28) to accomplish the direct fluorination of the thiophene nucleus. Since perchloryl fluoride has been commercially available for only a few years, and the published research on the reactions of this reagent with organic compounds has been very limited, it was felt a review of the reactions of perchloryl fluoride with organic molecules is desirable.

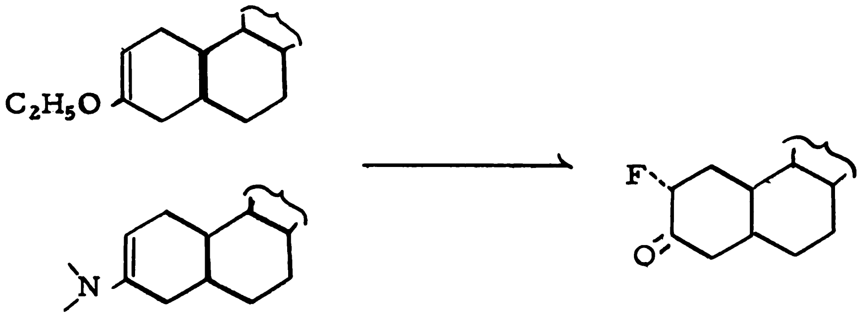
Inman and Oesterling, the initial investigators in this area (29), observed that perchloryl fluoride could be used in a Friedel-Crafts reaction in the presence of aluminum chloride or bromide with benzene to give perchlorylbenzene. The following mechanism, analogous to a Friedel-Crafts acylation, was proposed in which the benzene ring is attacked by the electrophilic $ClO_3^{\oplus}$ ion, available from the aluminum chloride assisted heterolytic cleavage of the fluorine-chlorine bond.

$$ClO_3F + AlCl_3 \longrightarrow [ClO_3F \cdot AlCl_3] \longrightarrow ClO_3^+ \, AlCl_3F^-$$

$$H^+ + FAlCl_3^- \longrightarrow AlCl_2F + HCl$$

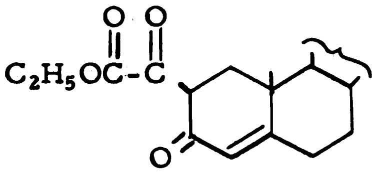
Since perchloryl fluoride and aluminum chloride did not react by themselves to form the complex, it was felt that the benzene must be present as an acceptor for the $ClO_3^{\oplus}$ ion. In its structure the ClO_3 group has retained the original symmetry of the perchloryl fluoride since in strong alkaline solutions perchloryl aromatics are hydrolyzed rapidly to phenol and chlorate ion by the nucleophilic replacement of the perchloryl group by hydroxide ion. The perchloryl aromatics are stable at room temperature, but may be detonated by vigorous shock or high temperatures. The compounds exhibit strong Cl-O infrared absorption between 8.2 and 8.4 μ and are meta-orienting. Additional work by Oesterling (30) has shown the extremely high leaving ability of the perchloryl group in a number of reactions.

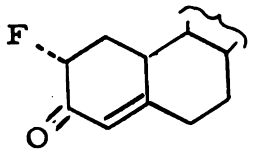
The reaction between enol ethers and perchloryl fluoride to produce fluorinated ketones was first described by Nakanishi et al. (31). In the absence of acids the fluorine atom of perchloryl fluoride appeared to be electrophilic and reacted with the negative center established at the β-carbon atom by the unshared electrons of the alkoxy group. For example, treatment of 1-ethoxycyclohexene in pyridine with perchloryl fluoride at 0° gave 2-fluorocyclohexanone. Similarly, in the steroid series the respective 3-ethoxy-Δ^2 compounds treated with perchloryl fluoride in pyridine produced 2-α-fluorocholestan-3-one, 2-α-fluoroandrostane-3, 17-dione, and 2-α-fluorodihydrotestosterone acetate in yield of 75-90% as shown by optical rotatory dispersion and n.m.r. Analogously, these fluorinated steroids can be obtained by perchloryl fluoride treatment of the corresponding steroid enamines (32).



Cholestane-3-one pyrrolidyl enamine was treated with perchloryl fluoride in benzene and after the usual isolation procedure gave 2-α-fluorocholestan-3-one in 72% yield. However, in contrast to enamines which yielded 4,4-difluoro-3-keto-Δ^5-steroids, enol ethers of Δ^4-3-keto-steroids are fluorinated at position 6 (31). Thus, 3-ethoxy-3,5-cholestadiene with perchloryl fluoride gave the 6-β-derivative.

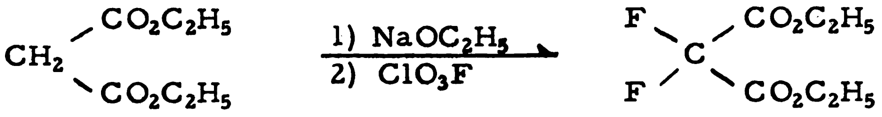
In a similar manner 2-alkoxalyl-Δ^4-3-ketones with perchloryl fluoride followed by dealkoxalylation afforded 2-α-fluoro-Δ^4-3-ketones (32).



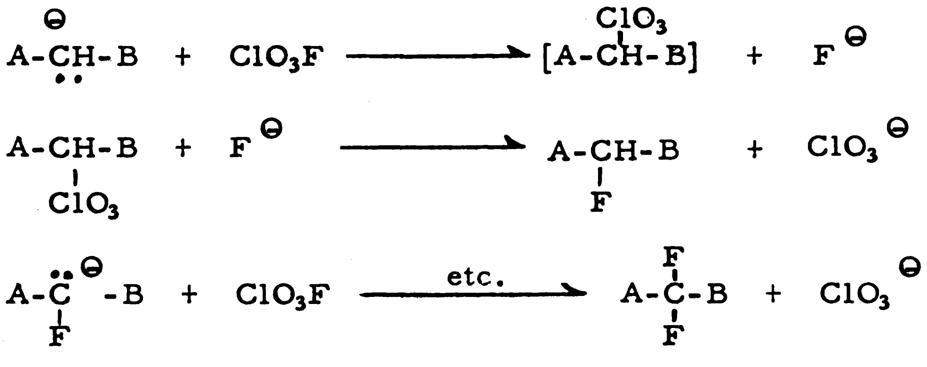


The same reaction has been utilized by Kende (34) and Allinger (35) in the preparation of 2-fluorocyclohexanone by treatment in pyridine at 0° of 2-hydroxymethylenecyclohexanone with perchloryl fluoride.

The most fruitful area of investigation has been the reaction of perchloryl fluoride with strong organic bases. This reaction initiated the present investigation of the treatment of 2-thienyllithium with perchloryl fluoride. In the case of the sodium salts of active methylene compounds, the reaction was found to introduce fluorine into the molecule. For example, when perchloryl fluoride is reacted with the sodium salt of diethyl malonate, diethyl difluoromalonate is produced in an almost quantitative yield.



Only the difluorinated material is obtained, even though the reaction obviously passes through the monofluoroderivative. The monofluoro compound is a stronger acid than diethyl malonate and, thus, competes effectively for the available ethoxide ion, undergoing reaction with perchloryl fluoride a second time to form the difluorinated compound before additional monofluorocompound can be formed. In a similar manner ethyl 2, 2-difluoroacetoacetate, 3, 3-difluoro-2, 4-pentandione, and diethyl 2-fluoro-2-phenylmalonate can be obtained from the unsubstituted parent compounds by treatment with ethoxide ion and perchloryl fluoride in yields of 59%, 77% and 93% respectively (36). The mechanism for the reaction can be explained by two paths. If a direct heterolytic cleavage of the perchloryl fluoride is assumed, the following sequence can be postulated:

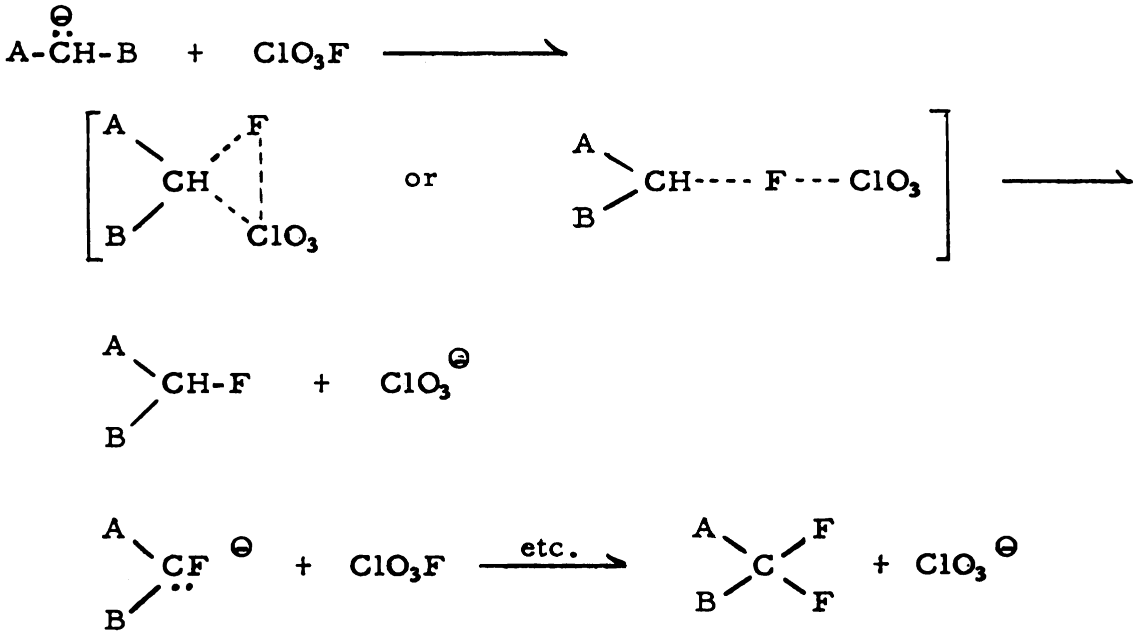


$$\text{A-}\overset{\ominus}{\underset{\bullet\bullet}{\text{CH}}}\text{-B} + ClO_3F \longrightarrow [\text{A-}\overset{ClO_3}{\text{CH}}\text{-B}] + F^{\ominus}$$

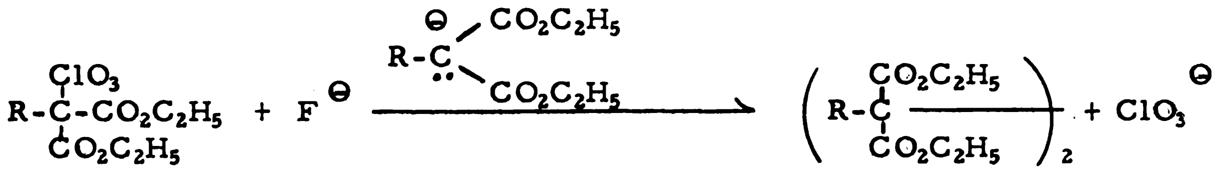
$$\text{A-}\underset{ClO_3}{\text{CH}}\text{-B} + F^{\ominus} \longrightarrow \text{A-}\underset{F}{\text{CH}}\text{-B} + ClO_3^{\ominus}$$

$$\text{A-}\underset{F}{\overset{\bullet\bullet\ominus}{\text{C}}}\text{-B} + ClO_3F \xrightarrow{\text{etc.}} \text{A-}\overset{F}{\underset{F}{\text{C}}}\text{-B} + ClO_3^{\ominus}$$

This series of steps would seem unlikely since the reaction is carried out in the presence of a stronger base (ethoxide) than fluoride, and consequently, a competitive reaction should occur. A more plausible mechanism involves a single step concerted displacement passing through one, or both of, two intermediates, the exact nature of which has not as yet been established.



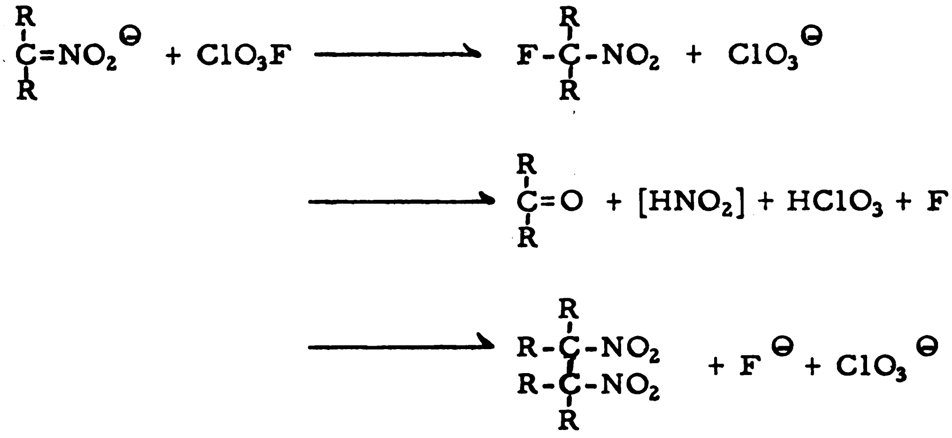
In the light of Inman's work, it was thought that the perchloryl fluoride treatment of ethyl formamido- and ethyl acetamidomalonate followed by hydrolysis should yield the fluorinated amino acids. Instead these compounds in the presence of ethoxide when treated with perchloryl fluoride were oxidatively dimerized in 40 and 50% yields respectively. The course of the reaction was shown by hydrolysis to diamino- and diacetamidosuccinic acid (37). The dimerization is thought to proceed by initial perchloryl fluoride attack on the sodium salt of diethyl malonate to give the perchloryl intermediate. The perchloryl group is then displaced by another malonate anion to give the dimer.



$$\text{R-}\overset{\text{ClO}_3}{\underset{\text{CO}_2\text{C}_2\text{H}_5}{\text{C}}}\text{-CO}_2\text{C}_2\text{H}_5 + \text{F}^{\ominus} \xrightarrow{\text{R-}\overset{\ominus}{\underset{\bullet\bullet}{\text{C}}}(\text{CO}_2\text{C}_2\text{H}_5)_2} \left(\text{R-}\overset{\text{CO}_2\text{C}_2\text{H}_5}{\underset{\text{CO}_2\text{C}_2\text{H}_5}{\text{C}}}\right)_2 + \text{ClO}_3^{\ominus}$$

R = HCONH-, CH$_3$CONH-

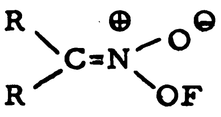
Schechter(38) has investigated the reaction between the sodium salts of secondary nitro compounds with perchloryl fluoride in methanol at 0-10°. The reaction gave the fluoronitro compounds (36-42%) and by-products of ketones (32-55%) and vicinal dinitro compounds (1-7%) obtained by oxidative coupling of the mononitronate ions:

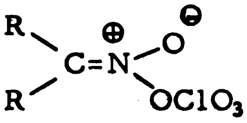


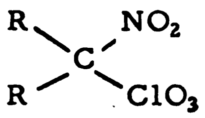
$$\begin{aligned}\overset{\text{R}}{\underset{\text{R}}{\text{C}}}\text{=NO}_2^{\ominus} + \text{ClO}_3\text{F} &\longrightarrow \text{F-}\overset{\text{R}}{\underset{\text{R}}{\text{C}}}\text{-NO}_2 + \text{ClO}_3^{\ominus}\\ &\longrightarrow \overset{\text{R}}{\underset{\text{R}}{\text{C}}}\text{=O} + [\text{HNO}_2] + \text{HClO}_3 + \text{F}^{\ominus}\\ &\longrightarrow \begin{matrix}\text{R}\\ \text{R-C-NO}_2\\ \text{R-C-NO}_2\\ \text{R}\end{matrix} + \text{F}^{\ominus} + \text{ClO}_3^{\ominus}\end{aligned}$$

Hence, sodium 2-propanenitronate plus excess perchloryl fluoride in methanol yielded 2-fluoro-2-nitropropane (36%), acetone (54%) and 2,3-dimethyl-2,3-dinitrobutane (6%). Also, sodium 2-butanenitronate gave 2-fluoro-2-nitrobutane (38%), 2-butanone (45%), and 3,4-dimethyl-3,4-dinitrohexane (7%).

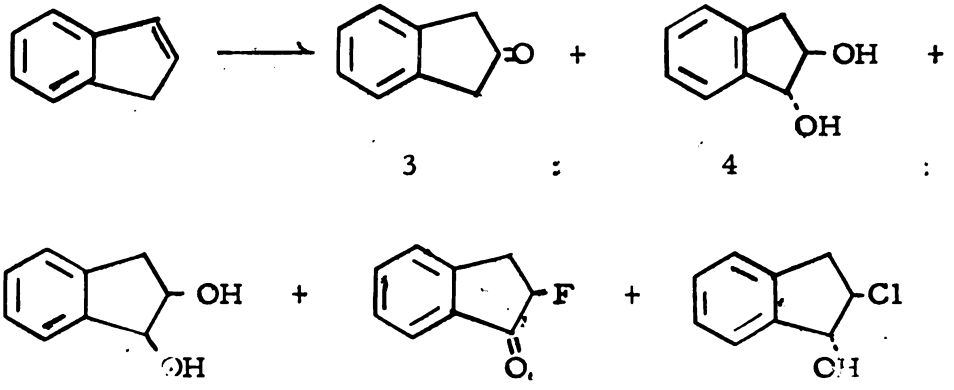
When perchloryl fluoride was reacted with the sodium salts of primary nitro compounds in methanol at 0° or dimethylformamide at 20°, aldehydes were the main products. Sodium 1-propane nitronate with excess perchloryl fluoride yielded propionaldehyde (64%), 3,4-dinitrohexane (0.5%), 1-nitropropane (38% recovered), and 1-fluoro-1-nitropropane and 1,1-difluoro-1-nitropropane (3-5%). The mechanism in these conversions is unknown, although it is suspected that the fluoronitro compounds are obtained by nucleophilic attack of the nitronate ion on perchloryl fluoride with concurrent displacement of the chlorate ion. The aldehydes or ketones and the vicinal dinitro compounds may be formed from the following intermediates by thermal decomposition, hydrolysis, or displacement by the nitronate ion respectively.







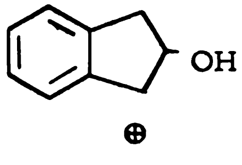
Neeman and Osawa (39) have reacted perchloryl fluoride with a carbon carbon double bond which is devoid of any activating species. Thus, the 2, 3 double bond of indene undergoes bident attack by the fluorine and oxygen of the perchloryl fluoride. In this way treatment of indene in a dioxane-water solution with perchloryl fluoride gave five products: 2-indanone, cis- and trans-1, 2-dihydroxyindan, 2-fluoroindanone, and trans-2-chloroindanol.



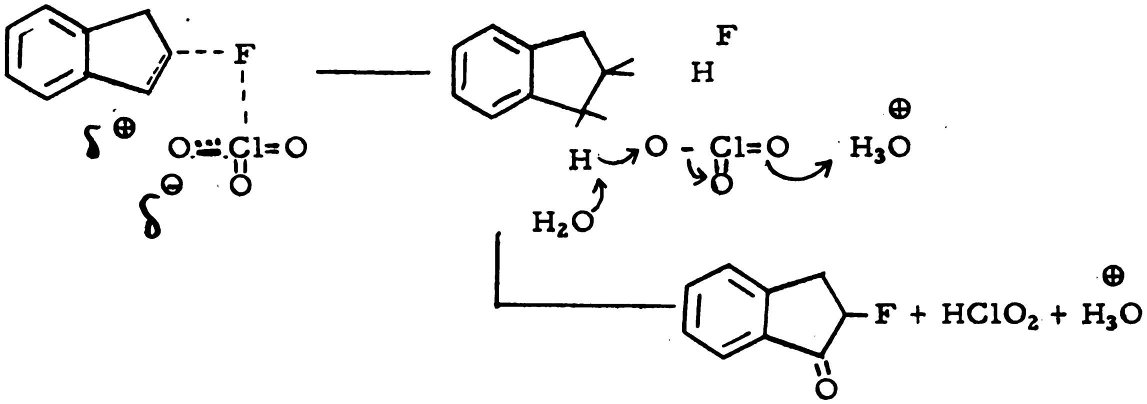
3 : 4 :

5 : 18 : 9

Also, 1, 2-epoxyindan with perchloryl fluoride gave the first three products, indicating a common intermediate carbonium ion for both reactions:



The fluoro compound, the major component, is formed by perchloryl fluoride attack on the double bond to give an intermediate fluoro chlorate which undergoes a concerted elimination of chlorous acid in an oxidation step. The chlorous acid in turn can disproportionate and add across the indene double bond to produce the chlorohydrin product.



RESULTS AND DISCUSSION

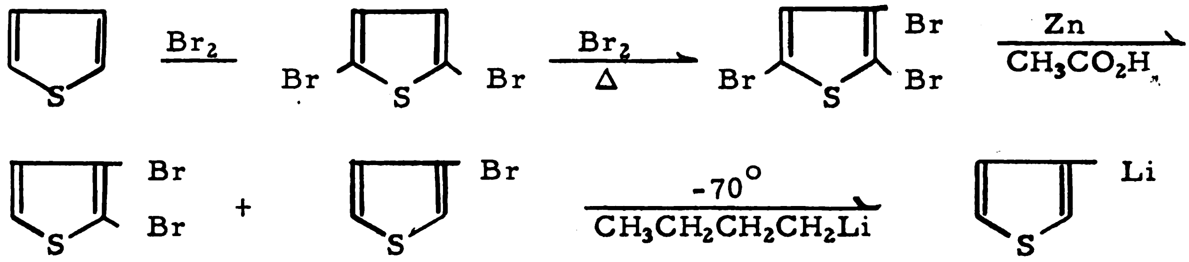
I.

The reaction between N, N-disubstituted amides and organolithium compounds was investigated as a possible synthetic route to the various acylated and formylated derivatives in the thiophene series (19). In order to include a thorough study it was decided to observe the reactions of 2-thienyllithium, 3-thienyllithium, and 2, 5-thienyldilithium with numerous N, N-disubstituted amides. The amides chosen for the study were N, N-dimethylformamide, N, N-dimethylacetamide, N, N-dimethylpropionamide, N, N-dimethylisobutyramide, N, N-dimethylbenzamide, N, N-dimethyl-2-thiophenecarboxamide, and N, N-dimethylphenylacetamide. From an examination of the reactions between these materials, it was further hoped to obtain some qualitative data concerning the mechanism.

The starting amides were readily available through simple conversions. Two of the amides--N, N-dimethylformamide and N, N-dimethylacetamide--were obtained from Eastman Kodak (White label) and were purified just prior to use. The other amides were prepared by the reaction of the corresponding acid chlorides with gaseous dimethyl amine in ether under rapid stirring and cooling. In this manner N, N-dimethylpropionamide, N, N-dimethylisobutyramide, N, N-dimethylbenzamide, N, N-dimethyl-2-thiophenecarboxamide and N, N-dimethylphenylacetamide were synthesized in yields of 61%, 57%, 67%, 63%, and 58%, respectively, after purification by distillation under reduced pressure.

A modified procedure was utilized for the preparation of one of the reactive intermediates, 2-thienyllithium. An n-butyllithium-ether solution (0.1 mole) was obtained by the slow addition of n-butyl bromide into a suspension of lithium slivers suspended in anhydrous ethyl ether at -10° to 0° (40). To the deep purple solution was added an equimolar amount of redistilled thiophene. Gilman (1) stirred the solution at an undesignated temperature for fifteen minutes and poured the reaction mixture over a dry ice-ether slurry. Hydrolysis gave 2-thiophenecarboxylic acid in an 87% yield. However, when this procedure was repeated low yields of the carboxylic acid were obtained. It was evident that the metallation reaction between the n-butyllithium and thiophene was not occurring to any appreciable extent. Two methods were developed to force the reaction to completion. The thiophene-ether solution was added to the n-butyllithium at 0°, and the mixture was allowed to warm to its reflux temperature to force the evolution of the butane formed in the hydrogen-metal exchange. In the alternate method the thiophene-ether solution was added at room temperature, and the flask was evacuated to purge off the butane and shift the equilibrium to favor metallation of the thiophene. In the latter procedure the exclusion of moisture was accomplished, with some difficulty, by using a nitrogen atmosphere in equalizing the pressure in the reaction system. The former method proved to be more convenient, since little, if any, n-butyllithium decomposition occurred before its reaction with the thiophene. Both methods gave better than 90% yields of 2-thiophenecarboxylic acid.

The 3-thienyllithium was prepared by the halogen-metal interaction between 3-bromothiophene and n-butyllithium dissolved in anhydrous ether solution at -70 to -80° (6). The 3-bromothiophene was synthesized in a three step conversion beginning with the bromination of thiophene with a two molar quantity of bromine. The 2, 5-dibromothiophene was isolated from the other possible monobrominated materials and treated with an equimolar amount of bromine. The crude 2, 3, 5-tribromothiophene was refluxed with a suspension of zinc dust in acetic acid (41). After an exhaustive steam distillation a 42% yield of 3-bromothiophene was obtained. The other major component (31%) was 2, 3-dibromothiophene.



Campaigne (9) has prepared 2, 5-thienyldilithium by the metallation with phenyllithium of 2, 5-diiodothiophene. A better yield was realized by the slow addition of 2, 5-diiodothiophene, dissolved in anhydrous ether, to a n-butyllithium-ether solution at room temperature. After carbonation and hydrolysis a 72% yield of 2, 5-thiophenedicarboxylic acid was obtained. The starting material was prepared by a modification of Minnis's procedure (42) by the treatment of thiophene dissolved in benzene with a two molar excess of a mixture of orange mercuric oxide and iodine.

The formylation of thiophene was conducted under a nitrogen atmosphere. An equimolar amount of N, N-dimethylformamide was added at -25° to the rapidly stirred green 2-thienyllithium-ether solution, forming a light yellow solid. The slurry, on warming to room temperature, was hydrolyzed with a saturated ammonium chloride solution. The ammonium chloride solution was used instead of dilute acid as a precautionary measure against decomposition of the 2-thiophenecarboxaldehyde. After a reduced pressure distillation a 61% yield of the desired product was obtained. The entire procedure from n-butyl bromide and thiophene to the purified, formylated product required, on a 0.2 mole scale, just six hours. The time factor compared favorably to the 15 hour period required for the equivalent formylation with N-methylformanilide and phosphorus oxychloride (20). Thus, this metallation method presented a more economical route to this synthetically important aldehyde. The formylation of 3-thienyllithium was performed below -65° by the slow addition of pre-cooled N, N-dimethylformamide to the brown 3-thienyllithium-ether solution. Product isolation in the usual manner afforded 73% of 3-thiophenecarboxaldehyde, again, providing an elegant method for obtaining this compound. When this procedure was extended to the diformylation of thiophene by the addition of N, N-dimethylformamide to 2, 5-thienyldilithium, only a 32% yield of the previously unknown 2, 5-thiophenedicarboxaldehyde was realized. The structure was assigned on the basis of its elemental analysis and n.m.r. spectrum.

Acetylation of the thiophene ring was carried out by this procedure using the homolog of N, N-dimethylformamide. Accordingly, N, N-dimethylacetamide was added to an equimolar quantity of 2-thienyllithium dissolved in anhydrous ether. Acidification of the intermediate lithium salt with dilute hydrochloric acid and distillation gave a 54% yield of 2-acetylthiophene. Similarly, when the substituted acetamide was added to an ether solution of 3-thienyllithium maintained below -65° and was followed by dilute hydrochloric acid hydrolysis, 3-acetylthiophene was obtained in a 61% yield. Diacetylation of the 2, 5-dilithio derivative produced 59% of 2, 5-diacetylthiophene, as shown in Table I.

Obviously, this acetylation procedure provides a more efficient method of synthesis of the 3-acetylthiophene which was prepared previously by the reaction between dimethyl cadmium and the acid chloride of 3-thiophenecarboxylic acid (22). Also, the diacetyl derivative was obtained previously in only trace amounts by the Friedel-Crafts diacetylation of thiophene in the presence of zinc chloride (23). Of course, 2-acetylthiophene is readily obtained through numerous Friedel-Crafts procedures (23, 24). Thus, the metallation reaction provides an additional path to this common derivative.

Table I. Formylation and Acetylation

Moles	Moles	G. prod.	Yield	B.p.	Mm.	M.p.	n_D
0.25 thiophene	0.25 N, N-dimethylformamide	15.9	61%	78-80°	13		$n_D^{20}=1.5919$
0.12 3-bromothiophene	0.10 N, N-dimethylformamide	9.7	73%	79-80°	14		$n_D^{18}=1.5873$
0.05 2, 5-diiodothiophene	0.10 N, N-dimethylformamide	2.2	32%			116-116.5°	
0.12 thiophene	0.12 N, N-dimethylacetamide	8.1	54%	76-77°	4		$n_D^{20}=1.5665$
0.12 3-bromothiophene	0.12 N, N-dimethylacetamide	9.2	61%	78-79°	3	57°	
0.05 2, 5-diiodothiophene	0.10 N, N-dimethylacetamide	4.92	59%			169-170°	

Other N, N-disubstituted amides were reacted with 2- and 3-thienyllithium to obtain the corresponding acylthiophenes. The results are summarized in Table II.

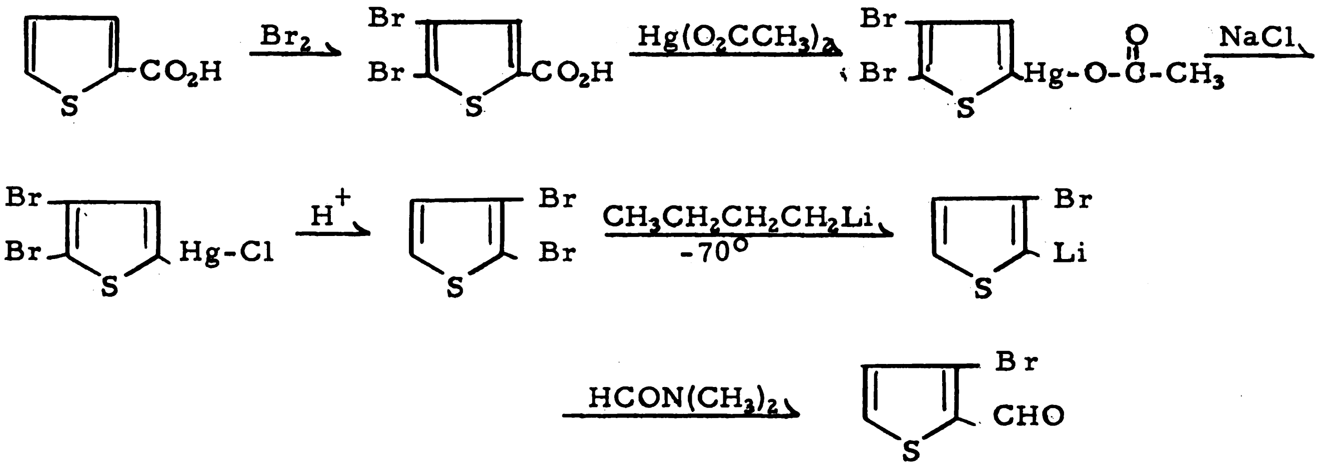
From Table II it can be observed that this experimental procedure for the preparation of 3-acetylated derivatives provides a better route to these derivatives than the method described by Campaigne (26).

The structure assignment for many of these compounds was based on a comparison to the physical properties of the previously prepared materials. For the 2-acylated thiophenes, the infrared spectra were taken and compared to published spectra or to spectra obtained from the independent synthesis of the 2-acyl derivatives by Friedel-Crafts methods (23, 24). With the 3-acylthiophenes the infrared spectra showed the expected carbonyl absorption. The n.m.r. spectra and integration identified the position of attack in both series as well as the ratio of aromatic to aliphatic hydrogens (see Appendix). On the basis of these instrumental techniques, the need to prepare known and unknown derivatives, e.g., 2,4-dinitrophenylhydrazones, of these compounds was considered unnecessary.

In addition, the preparation of the 2, 3-dilithio derivative of thiophene was attempted. The starting material, 2, 3-dibromothiophene, was prepared by the zinc debromination of 2, 3, 5-tribromothiophene in acetic acid as previously described (41). The dibromo compound was also prepared by the method of Steinkopf (43, 44) involving a three step reaction: bromination of 2-thiophenecarboxylic acid to 2, 3-dibromo-5-thiophenecarboxylic acid, conversion to the mercuric chloride derivative, and subsequent acid-steam hydrolysis to yield 68% of 2, 3-dibromothiophene.

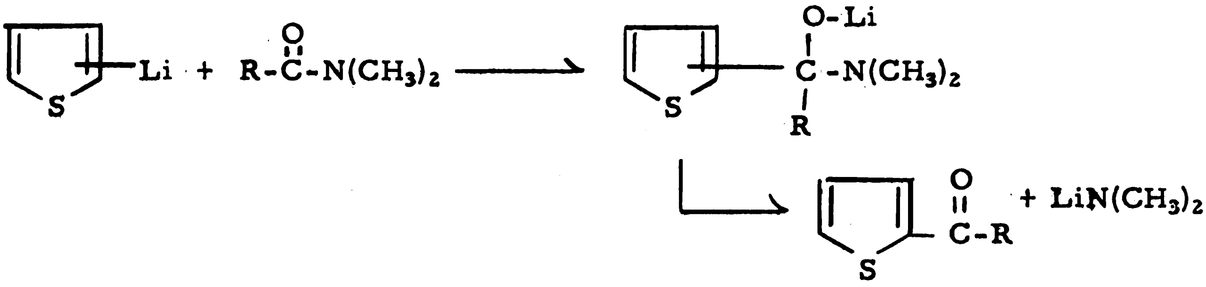
Table II. Acylation Reactions

Moles	Moles	G. prod.	Yield	B.p.	Mm.	M.p.	n_D
0.10 thiophene	0.10 N, N-dimethylpropionamide	7.3	52%	73-78°	2.5		$n_D^{20}=1.5469$
0.12 thiophene	0.12 N, N-dimethylbenzamide	16.3	73%	122-126°	1-2	56°	
0.10 thiophene	0.05 N, N-dimethylphenylacetamide	4.3	43%	150-155°	2-3	48-49°	
0.10 thiophene	0.08 N, N-dimethylthiophene-2-carboxamide	9.8	63%	187-191°	10-11	87-88°	
0.10 3-bromothiophene	0.10 N, N-dimethylpropionamide	5.3	38%	83-86°	5		$n_D^{24}=1.5378$
0.10 3-bromothiophene	0.10 N, N-dimethylisobutyramide	4.4	29%	85-89°	5		$n_D^{25}=1.5283$
0.10 3-bromothiophene	0.10 N, N-dimethylbenzamide	11.5	61%	112-120°	0.3	60.5-62.5°	
0.10 3-bromothiophene	0.10 N, N-dimethylphenylacetamide	12.1	60%			93.5-94.5°	
0.10 3-bromothiophene	0.09 N, N-dimethylthiophene-2-carboxamide	11.2	64%	116-118°	0.35	62°	



The reaction between this compound and an n-butyllithium-ether solution at -65°, followed by N, N-dimethylformamide treatment, hydrolysis, and distillation afforded a white solid which was tentatively assigned the structure, 2, 3-thiophenedicarboxaldehyde. This assignment agreed with Ried's study (45) on the dilithio derivative of thianaphthene readily obtained from 2, 3-dibromothianaphthene. However, the analysis and n.m.r. spectra proved conclusively that the solid was instead 3-bromo-2-thiophenecarboxaldehyde. (The n.m.r. spectra were integrated showing the ratio of ring to aldehydic protons to be 2:1). The conversion of the dibromo compound to 3-bromo-2-thienyllithium either sufficiently deactivated the 3-bromo position from further reaction, or the energy barrier to produce two neighboring anionic carbon atoms was too great to allow reaction at this low temperature. The latter explanation is suspected since in thianaphthene this concentration of anionic charge can be distributed into the benzene ring, whereas the thiophene ring in this case must accommodate the total charge. In contrast, the facile conversion of 2, 5-diiodothiophene to 2, 5-thienyldilithium (9) is explained by the easier cleavage of the carbon-iodine bond on the more reactive 2 and 5 positions.

A mechanism for the reaction of the thienyllithiums, on the basis of this study, is straightforward. Initially the organolithium component attacks the carbonyl group of the substituted amide to give the intermediate lithium salt:



Upon hydrolysis with hydrochloric acid elimination of lithio dimethylamine occurs to yield the desired ketone, lithium chloride, and dimethyl amine hydrochloride. If it is assumed that the thienyllithium reacts with a minimal amount of steric inteference with the amide, then, the more electron withdrawing the R group is, the higher the yield of ketone and vice-versa so long as the reaction times are equivalent. Thus, in the 3-acyl series an increase in yield from R = iso-propyl (29%), ethyl (38%), methyl (61%), benzyl (60%), phenyl (60%), 2-thienyl (64%) corresponds to the electronic effects of these groups on the carbonyl carbon atom. Similarly, with the 2-acyl series an increase in yield from R = ethyl (52%), methyl (51%), 2-thienyl (63%), phenyl (73%) corresponds to the expected electronic effects on the proposed mechanism.

No correlation between the 2- and the 3-acyl thiophene yields can be made since the initial formation of the organolithium components in the one case involved a direct metallation (3) and in the other a metal-halogen exchange (4) at positions quite different in reactivity.

It is observed that the formylation reaction with the 2- and the 3-thienyllithium gave 64 and 73% of the corresponding aldehydes. However, the reaction of the 2- and the 3-thienyllithium with N, N-dimethylbenzamide produced only a 73 and a 61% yield of the corresponding benzoylthiophenes. The same was true for the 2-thenoylthiophenes

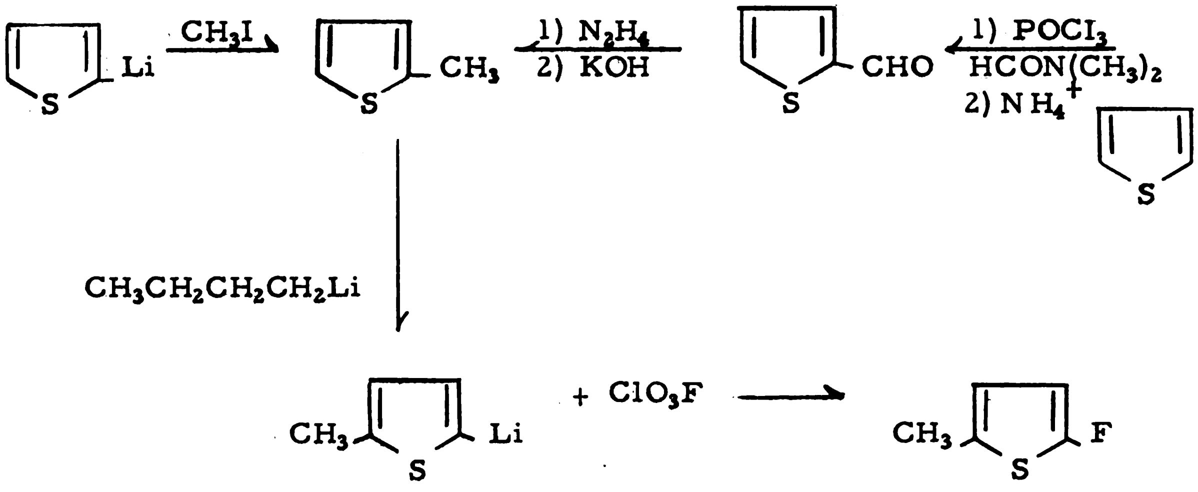
(63 and 64% respectively). If the proposed mechanism is assumed, then a slight steric factor is present, for larger yields of ketones should be obtained since the aromatic groups exhibit a withdrawing effect on the carbonyl carbon atom. The formyl group with the proton on the carbonyl carbon has little, if any, electronic or steric effect.

The low yield of the diformyl derivative, 2,5-thiophenedicarboxaldehyde is rationalized on the basis of the withdrawing effect of the formyl group. Once, one formyl group is attached to the ring, it sufficiently deactivates the anionic species so that attack on the substituted amide occurs only to a slight extent.

II.

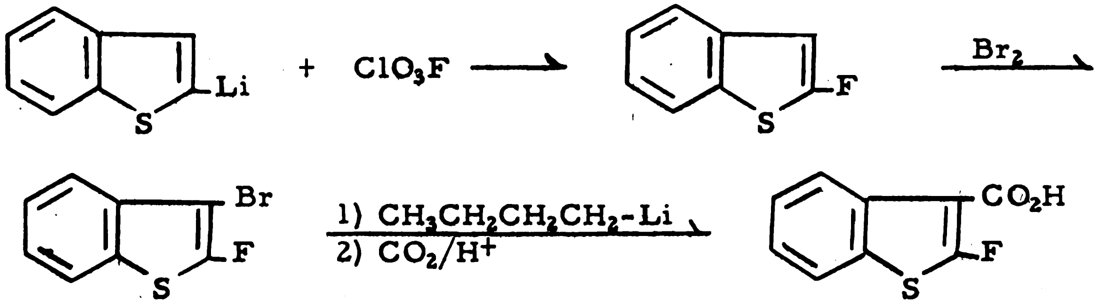
The treatment of 2-thienyllithium with perchloryl fluoride was investigated as a possible method of ring fluorination to yield biologically important percursors. A 2-thienyllithium-ether solution prepared as previously described was treated under various temperature conditions with gaseous perchloryl fluoride. At a low temperature (below -50°) the desired reaction was sluggish, and the yields of fluorinated product were low, whereas at refluxing temperatures severe oxidation of the organic material occurred. The optimum condition for the exothermic reaction was between 0 and 30°. Once the 2-thienyllithium solution was no longer alkaline, and the blue fluorescence characteristic of the reaction had disappeared, the addition of fluorination reagent was stopped. The reaction mixture was hydrolyzed with a saturated sodium carbonate solution to destroy traces of acid formed from any excess perchloryl fluoride. Hydrolysis with hydrochloric acid caused a severe darkening and subsequent tarring of the reaction mixture. Distillation afforded a mixture of thiophene (12.3%) and 2-fluorothiophene (87.4%), thus giving an overall yield of 48.8% of the fluorinated product. A sample of the major product was isolated for infrared and elemental analysis by preparative gas chromatography through a 30% silicone on Chromosorb column. Since the two components of the mixture differed only slightly in their physical properties, it was necessary to utilize a freshly packed column, as any contaminants caused a coalescing of the peaks. Even under optimum conditions, the collected portion was rechromatographed at least twice to obtain a pure sample. The use of other percentages of silicon oil or fluorosil on Chromosorb failed to improve the separations.

The fluorination reaction was applied to 5-methyl-2-thienyllithium under the same reaction conditions to gain additional information on the reaction so that mechanistic interpretations could be made. The starting material, 2-methylthiophene, was prepared either by the alkylation of 2-thienyllithium with methyl iodide or by the Wolff-Kischner reduction of 2-thiophenecarboxaldehyde (20). Metallation with n-butyllithium gave the green 5-methyl-2-thienyllithium-ether solution. Upon treatment in a similar manner of this intermediate with perchloryl fluoride, followed by the normal isolation procedure, a mixture of 2-methylthiophene (9.9%), 2-fluoro-5-methylthiophene (61.9%), (overall, 44%), and unidentified side products was obtained.



A sample of the major product was isolated for analysis, infrared, and n.m.r. spectra by preparative gas chromatography as previously described. A comparison of the infrared spectra of 2-methyl and 2-fluoro-5-methylthiophene showed a sharp C-F peak at 7.6 μ. The n.m.r. conclusively showed ring fluorination. Integration gave the correct ratio of methyl to ring hydrogens (3:2) for the assigned structure. Further, the spectra exhibited additional splitting from the fluorine atom (see Appendix).

The reaction was extended to the thianaphthene system. Under similar conditions 2-thianaphthenyllithium produced a 70% yield of 2-fluorothianaphthene. No unreacted thianaphthene was present in the final distillate, as it either reacted immediately with the perchloryl fluoride or was oxidized to unidentifiable side products. Elemental analysis, n.m.r., and infrared spectra substantiated the structural assignment. Integration of the n.m.r. showed the correct ratio of thiophene to benzene hydrogens (1:4). Derivatives of the fluorinated thianaphthene were prepared. Bromination gave 3-bromo-2-fluorothianaphthene which was metallated with n-butyllithium followed by carbonation to produce 55% of 2-fluoro-3-thianaphthenecarboxylic acid.



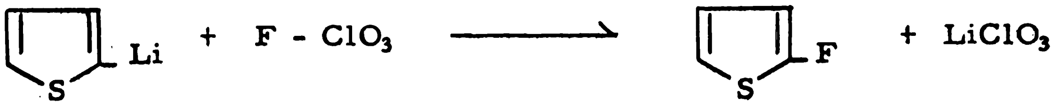
In order to gain insight into the nature of the reaction, 2-thienylsodium prepared from thiophene and sodium amalgam (46) and 2-thienylmagnesium iodide obtained by the interaction of 2-iodothiophene and magnesium (47) were treated with perchloryl fluoride. In the former case 9% of 2-fluorothiophene and unreacted thiophene were detected. With the Grignard reagent no fluorinated product was observed, and only decomposition occurred.

In addition, 1-naphthyllithium, prepared from 1-bromonaphthalene and lithium slivers in ether (48), was treated with perchloryl fluoride under the normal reaction conditions. No reaction occurred as shown by vapor phase chromatography of the final distillate. Only naphthalene was obtained from the hydrolysis of the organolithium derivative. However, when phenyllithium was treated with the fluorination reagent, an 11% yield of perchlorylbenzene was obtained. The compound was identified by comparison of its infrared spectrum to the known spectrum of this material (29).

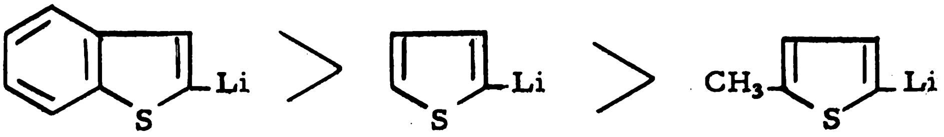
Inman's procedure (36) for the fluorination of diethyl malonate in the presence of sodium ethoxide was repeated, to obtain 60% of diethyl α, α-difluoromalonate and 6% of diethyl α-fluoromalonate. The lower yield was in contrast to the quantitative yield previously reported. Inman reported no monofluoro product in the reaction. However, the n.m.r. showed an impurity substantially different from the α-hydrogens of diethyl malonate, which was assigned to the monofluoro derivative.

In reference to Inman's work, the attempted fluorination of the sodium salt of ethyl cyanoacetate with perchloryl fluoride gave after the normal isolation procedure a mixture of six components. The major component (66%) was unreacted ethyl cyanoacetate. Attempts were made to isolate two of the other components (11.2%, 12.1%), but vapor phase chromatography utilizing 30% or 5% silicone on Chromosorb preparative columns did not separate effectively these components from the mixture. Similarly the treatment of the sodium salt of phenylacetonitrile, obtained from the acid-base equilibrium of sodamide on the parent compound, with perchloryl fluoride and the subsequent product isolation yielded the starting material and an unidentified side product in the ratio 8:1.

Some indication as to the mechanism of this fluorination reaction can be attempted on the basis of these results. With the lithium derivatives of thiophene and thianaphthene, the electronegativity of the sulfur atom delocalizes the carban ion charge yielding a stable anionic system, which may react effectively with the slightly polar chlorine-fluorine bond in the perchloryl fluoride, displacing the chlorate ion.



The more this charge is delocalized the higher the yield of fluorinated material under similar conditions of reaction. Thus, the increase in yield of fluorinated material from the lithio derivatives of 2-methylthiophene to thiophene to thianaphthene is explained on the basis of the delocalization of the intermediate anion.



The more stable the anion is, the more it should yield a fluorinated product. This statement is substantiated in Inman's work on the fluorination of diethyl malonate with perchloryl fluoride in the presence of excess ethoxide (36) ion.

Phenyl and 1-naphthyllithium-carbon bonds are more covalent with less delocalization of the anionic charge, and apparently these less stable anionic species are unable to activate the chlorine-fluorine bond of perchloryl fluoride in the displacement reaction. To the limited extent that reaction occurs, less discrimination, in favor of the fluorine, is achieved in the displacement step. Experimental evidence for this was found in this study by the observation that some perchlorylbenzene

(11%) results from the reaction of phenyllithium and perchloryl fluoride.

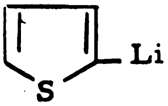
EXPERIMENTAL

I.

n-Butyllithium: $CH_3CH_2CH_2CH_2Li$

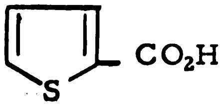
The method of Gilman (49) was modified in this preparation. A suspension of 1.76 g. (0.24 g.-atom) of lithium metal, cut into fine slivers, and 50 ml. of anhydrous ethyl ether (previously stored over sodium wire) was placed in a 500 ml. three-necked flask which had been flushed with a rapid flow of dry nitrogen for 20 minutes. The flask was fitted with a mechanical stirrer, a dropping funnel, and an Allihn condenser through which was suspended a -35 to +50° thermometer. The system was protected from moisture by a long rubber tube to which was attached a six inch calcium chloride or drierite drying tube. In other preparations, the reflux condenser, thermometer and drying tube apparatus were replaced by a two-hole rubber stopper fitted with the thermometer and a 6 mm. tubing which was connected with Tygon tubing to a cold-trap immersed in a dry-ice methyl cellosolve bath. To the cold trap was attached a six foot length of rubber tubing fitted with a calcium chloride drying tube. The latter system was flushed with nitrogen before immersing the cold trap and proved superior to the former system in excluding moisture when the laboratory humidity exceeded 50%. To the slowly stirred suspension, cooled to -10° to -5° in a dry-ice methyl cellosolve bath, was added dropwise a solution of 17.5 g. (0.12 mole) n-butyl bromide (Matheson, Coleman, and Bell) dissolved in 25 ml. of anhydrous ether. In five to 10 minutes the reaction mixture became cloudy and bright spots appeared on the lithium. After initiation of the reaction, the reaction temperature was held below -10° by immersion of the reaction flask in the dry ice-methyl cellosolve bath during the addition of the remaining alkyl halide solution (20 minutes). The mixture was stirred for an additional hour, maintaining its temperature below -10°, or until only traces of unreacted lithium remained. The purple butyllithium-ether complex was cooled to -30° and filtered through a tygon tube, fitted with a wool plug in one end, directly into a nitrogen-flushed flask and used immediately in the next reaction. This method of separation of the butyllithium from the unreacted lithium chips could also be effected by suspending a gauze net on a wire loop into the solution under rapid stirring. This latter method is preferred when the laboratory humidity exceeded 50%.

2-Thienyllithium



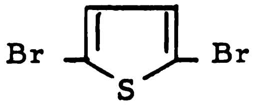
A solution of n-butyllithium, prepared as described above from 9 g. (1.3 g.-atom) of lithium, 82.2 g. (0.6 mole) of n-butylbromide, and 400 ml. of anhydrous ethyl ether, was transferred to a one l. three-necked flask, fitted with a stirrer, a -50 to +35° thermometer (below liquid level) suspended in an Allihn condenser protected from moisture. The reaction flask was then precooled to -10° by immersion in a dry ice-methyl cellosolve bath, and a solution containing 42 g. (0.5 mole) thiophene dissolved in 130 ml. anhydrous ethyl ether was added during a half hour to the stirred alkyllithium solution. Two methods of forcing the equilibrium metallation reaction to completion were utilized. One involved evacuating the flask at 0° with a water aspirator to purge off the butane. Upon equalizing the pressure with dry nitrogen, traces of moisture entered the system so that the second method was preferred. In the latter procedure the reaction flask was heated to 20° in a water bath whereupon the evolution of butane became vigorous. The bath temperature was allowed to rise to 30° until butane evolution had ceased. The green 2-thienyllithium solution was cooled to -10°, stirred for an hour and used immediately in subsequent reactions.

2-Thiophenecarboxylic Acid

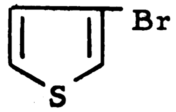


A 2-thienyllithium-ether solution, one mole of aryllithium dissolved in one l. of anhydrous ethyl ether was prepared as previously described. The 2-thienyllithium was cautiously added to a rapidly stirred slurry of dry ice suspended in anhydrous ether. A vigorous reaction ensued, after which the mixture was allowed to warm to room temperature. The yellow slurry was poured into a beaker containing 40 ml. of concentrated hydrochloric acid, 200 g. ice and 300 ml. water. The ether layer was separated, the aqueous residue was extracted several times with ether, and the combined ethereal portions were washed with a 20% sodium hydroxide solution. The alkaline extract was boiled in the presence of activated charcoal, allowed to stand overnight, and filtered. The filtrate was acidified with concentrated hydrochloric acid to pH = 1 (Hydrion). The white solid was recovered by filtration on a Buchner funnel, washed with 50 ml. of cold water, and dried to obtain 121 g. (0.94 mole, 94%) of crude 2-thiophenecarboxylic acid. The crude acid was recrystallized from hot water, with activated charcoal added, to obtain 106 g. (0.83 mole, 83%) of a white crystalline material (needles) melting at 129-130°. Literature value, m.p. 130° (50).

2,5-Dibromothiophene

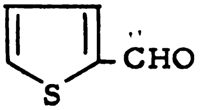


A 252 g. (3 moles) quantity of thiophene was placed in a two l. three-necked flask fitted with an addition funnel, a mechanical stirrer, and an Allihn condenser. The flask was cooled to 0° by immersion in an ice bath, and bromine (960 g., 6 moles) was added to the stirred solution at such a rate that hydrogen bromide evolution was not too vigorous. After addition of the halogen the solution was stirred for 24 hours at room temperature as hydrogen bromide was evolved. The heavy oil was washed first with 500 ml. of water, then with two 500 ml. portions of a 20% sodium hydroxide solution, and dried over calcium chloride. The yellow oil was distilled in vacuo to yield 523 g. (2.15 moles, 72%) of a colorless oil, b.p. 89-90° at 13 mm., $n_D^{25} = 1.6265$. Literature value, b.p. 210.3° at 1 atm., $n_D^{25} = 1.6288$ (51).

3-Bromothiophene 

A 485 g. (2.0 moles) quantity of 2,5-dibromothiophene was placed in a one l. three-necked flask fitted with a reflux condenser, an addition funnel, and a mechanical stirrer. Bromine (332 g., 2.08 moles) was added during an hour to the well-stirred 2,5-dibromothiophene, while chilling the reaction flask in an ice bath. After the addition of the halogen the mixture was stirred at room temperature for 18 hours as the hydrogen bromide was evolved. A solution containing 120 g. of potassium hydroxide dissolved in 250 ml. of methanol was added, and the mixture was heated at its reflux temperature for three hours. The heating was followed by exhaustive steam distillation which required fifteen hours. A yellow oil (615 g.) was separated from the distillate and transferred to a three liter three-necked flask fitted with a reflux condensor and a mechanical stirrer. To the oil were added 320 ml. of glacial acetic acid, 1200 ml. of water, and 185 g. of zinc dust. The addition of the zinc dust initiated an exothermic reaction which held the reaction mixture at its reflux temperature for 30 minutes. It was maintained at this temperature for an additional 18 hours and then steam distilled until all of the organic material had been removed. The organic layer was separated, dried over calcium chloride, and distilled under reduced pressure to give two major fractions: identified as 3-bromothiophene, (135 g., 0.83 mole, 41.5%), b.p. 68.5-69.5° at 33 mm., n_D^{22} = 1.5901, and 2,3-dibromothiophene, (147 g., 0.61 mole, 31%), b.p. 93-95° at 15 mm., n_D^{23} = 1.6303. Literature value for 3-bromothiophene, b.p. 157-158°, n_D^{20} = 1.5860 (50). Literature value for 2,3-dibromothiophene, b.p. 212°, n_D^{20} = 1.6309 (50).

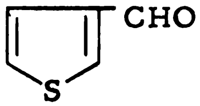
2-Thiophenealdehyde



A. n-butyllithium solution was prepared by the slow addition of 35 g. (0.25 mole) of n-butyl bromide dissolved in 25 ml. of anhydrous ethyl ether into a suspension of 3.5 g. (0.5 g.-atom) lithium chips in 75 ml. of anhydrous ether at -10 to -5° to a 500 ml. flask, previously flushed with nitrogen, fitted with a mechanical stirrer, a reflux condenser, an addition funnel, a -35 to +50° thermometer, and a Drierite tube. Into the n-butyllithium solution at -10° was added a 21 g. (0.25 mole) amount of thiophene dissolved in 25 ml. of anhydrous ether. The reaction mixture was allowed to warm to 30° in order to purge off the butane. The rapidly stirred reaction solution was then cooled to -25° by immersion of the flask in a dry ice-methyl cellosolve solution, and an 18.25 (0.25 mole) quantity of N, N-dimethylformamide dissolved in 25 ml. of anhydrous ether was added during a 15 minute period.
A yellow-white solid formed immediately. The slurry was allowed to warm to room temperature under stirring and was poured into a saturated ammonium chloride solution. The ether layer was separated the aqueous layer was extracted with 200 ml. of ether, and the combined extracts were dried over anhydrous magnesium sulfate. The ether was removed over a steam bath. The residue was distilled <u>in vacuo</u> to obtain 15.9 g. (0.153 mole, 61%) of 2-thiophenecarboxaldehyde, b.p. 78-80° at

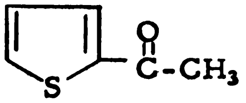
13 mm. Literature value, b.p. 66-67° at 4 mm. (20). The infrared spectrum agreed with the reported spectrum with a carbonyl absorption at 6.05 μ (52).

3-Thiophenecarboxaldehyde



To 50 ml. of a n-butyllithium-ether solution, cooled to -70° by immersion of the reaction flask in a dry ice-methyl cellosolve bath, was added during 15 minutes a 19.6 g. (0.12 mole) quantity of 3-bromothiophene dissolved in 25 ml. of anhydrous ether. The aryllithium solution was stirred for 15 minutes, and N, N-dimethylformamide (8.75 g., 0.12 mole) dissolved in 25 ml. of anhydrous ether was added while the reaction temperature was held below -70° by cooling in a dry ice-methyl cellosolve bath. Distillation, after ammonium chloride hydrolysis and the usual product isolation from the reaction mixture, gave 9.7 g. (0.081 mole, 73%) of 3-thiophenecarboxaldehyde, a colorless liquid, b.p. 79-80° at 14 mm., $n_D^{20} = 1.5865$. Literature value, b.p. 72-78° at 12 mm., $n_D^{20} = 1.5860$ (53). (Infrared carbonyl absorption at 6.06 μ.)

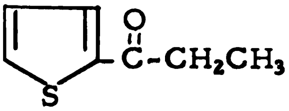
2-Acetylthiophene



An 11 g. (0.12 mole) quantity of thiophene dissolved in 25 ml. of anhydrous ether was added as previously described to 75 ml. of a n-butyllithium-ether solution (0.12 mole of alkyllithium). N, N-dimethylacetamide (10.5 g., 0.12 mole) dissolved in 25 ml. of anhydrous ether was added slowly during rapid stirring to the precooled (-10°) 2-thienyllithium solution. The white slurry was allowed to warm to room temperature and poured into a 10% hydrochloric acid solution. The ether layer was separated, the aqueous layer was extracted with ether, and the combined extracts were dried over anhydrous magnesium sulfate.

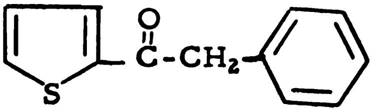
The ether was removed over a steam bath, and the residue distilled *in vacuo* to give 8.1 g. (0.065 mole, 54%) of 2-acetylthiophene, b.p. 76-77° at 4 mm., n_D^{20} = 1.5665. Literature value, b.p. 77° at 4 mm., n_D^{20} = 1.5666 (24). The infrared spectrum exhibited intense carbonyl absorption at 6.05 μ.

2-Propionylthiophene



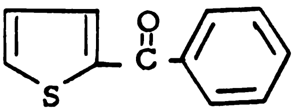
A 10 g. (0.10 mole) quantity of N, N-dimethylpropionamide dissolved in 25 ml. of anhydrous ether was added to a solution of 2-thienyllithium (0.10 mole) dissolved in 100 ml. of anhydrous ether. Distillation after the usual hydrolysis and product isolation gave 7.3 g. of 2-propionylthiophene (0.052 mole, 52%), b.p. 73-78° at 2.5 mm., n_D^{20} = 1.5469. Literature value, b.p. 88° at 7 mm., n_D^{20} = 1.5531 (24). (Infrared carbonyl absorption at 6.04 μ.)

2-(Phenylacetyl)-thiophene



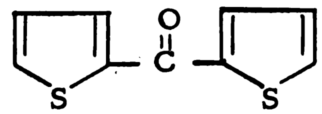
An 8.2 g. (0.05 mole) quantity of N, N-dimethyl phenylacetamide dissolved in 25 ml. of anhydrous ether was added to a solution of 2-thienyllithium (0.10 mole) dissolved in 100 ml. of anhydrous ether. Distillation after hydrolysis and product isolation gave 4.3 g. (0.021 mole, 43%) of a light yellow oil, b.p. 150-155° at 2-3 mm., which crystallized upon standing, m.p. 48-49°. Literature value, b.p. 165° at 5 mm., m.p. 51° (54).

2-Benzoylthiophene



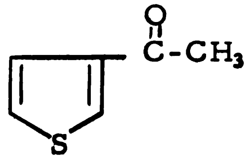
A 17.9 g. (0.12 mole) quantity of N, N-dimethylbenzamide dissolved in 25 ml. of anhydrous ether was added to a solution of 2-thienyllithium (0.12 mole) dissolved in 100 ml. of anhydrous ether. Distillation after hydrolysis and product isolation gave 16.3 g. (0.086 mole, 73%) of a colorless oil, b.p. 122-126° at 1-2 mm., which crystallized upon standing. The solid on recrystallization from an ethanol-water mixture gave 12.4 g. of white crystalline needles, m.p. 56°. Literature values, b.p. 120-121° at 2 mm., m.p. 56.5-57° (25).

Di-2-thienyl Ketone



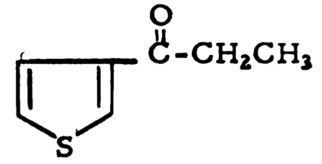
The above procedure was modified using 12 g. of N, N-dimethyl-2-thiophenecarboxamide (0.08 mole). Distillation of the hydrolyzed product gave 9.8 g. (0.051 mole, 63%) of a light yellow oil, b.p. 187-191° at 10-11 mm., which immediately crystallized on cooling. The solid was recrystallized from ethanol to give light yellow needles, m.p. 87-88°. Literature value, b.p. 189-190° at 10 mm., m.p. 88-89° (25). The infrared spectrum exhibited strong carbonyl absorption at 6.17 μ.

3-Acetylthiophene



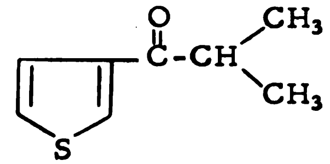
A 3-thienyllithium-ether solution, 0.12 mole of aryllithium dissolved in 100 ml. of anhydrous ether, was prepared from the addition of 19.6 g. (0.12 mole) of 3-bromothiophene dissolved in 25 ml. of anhydrous ether to 0.12 mole of n-butyllithium dissolved in 75 ml. of anhydrous ether at -70°. To the rapidly stirred solution held below -65° by immersion of the reaction flask in a dry ice-methyl cellosolve bath was added a 10.5 g. (0.12 mole) quantity of N, N-dimethylacetamide dissolved in 25 ml. of anhydrous ether. After the addition, the slurry was stirred for 30 minutes and poured into a 10% solution of hydrochloric acid. Product isolation from the reaction mixture and distillation _in vacuo_, b.p. 78-79° at 3 mm., gave 9.2 g. (0.073 mole, 61%) of 3-acetylthiophene, which solidified on cooling. The solid was recrystallized from an ethanol-water mixture to give long, white, prismatic needles, m.p. 56-57°. Literature values, b.p. 208-210° at 748 mm., m.p. 57° (22).

3-Propionylthiophene



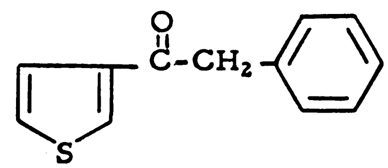
A 10 g. (0.10 mole) quantity of N, N-dimethylpropionamide dissolved in 25 ml. of anhydrous ether was added to a solution of 3-thienyllithium (0.10 mole) dissolved in 100 ml. of anhydrous ether. Throughout the addition of the amide the reaction temperature was held below -65°. After the normal hydrolysis and product isolation, distillation *in vacuo* yielded 5.3 g. (0.038 mole, 38%) of a colorless oil, b.p. 83-86° at 5 mm., $n_D^{24} = 1.5378$. Literature value, b.p. 72-74° at 4 mm., $n_D^{18} = 1.5471$ (26).

3-Isobutyrylthiophene



An 11.5 g. quantity of N, N-dimethylisobutyramide dissolved in 25 ml. of anhydrous ether was combined with a solution of 3-thienyllithium (0.10 mole) dissolved in 100 ml. of anhydrous ether in the manner previously described. Distillation after the normal product isolation gave 4.4 g. (0.029 mole, 29%) of a colorless oil, b.p. 85-89° at 5 mm., $n_D^{25} = 1.5283$. Anal. calc'd. for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.47; H, 6.67; S, 20.90. (Intense carbonyl absorption at 6.02 μ.)

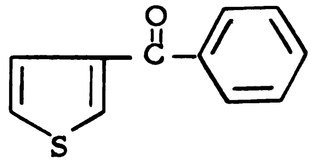
3-(Phenylacetyl)-thiophene



A 16.39 g. quantity of N, N-dimethylphenylacetamide (0.10 mole) was added to 0.10 mole of 3-thienyllithium in the usual manner.

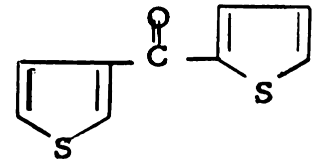
Hydrolysis, product isolation and distillation yielded 12.1 g. (0.06 mole, 60%) of a light yellow oil which solidified on being set aside at room temperature. The solid was recrystallized from an ethanol-water mixture to give fine, white needles, m.p. 93.5-94.5°. Anal. calcd. for $C_{12}H_{10}OS$: C, 71.25; H, 4.98; S, 15.85. Found: C, 71.28; H, 5.17; S, 15.72. Strong carbonyl absorption in the infrared occurred at 6.08 μ.

3-Benzoylthiophene



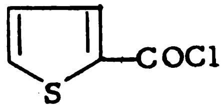
N, N-dimethylbenzamide (14.9 g., 0.10 mole) was combined with 0.10 mole of 3-thienyllithium in the prescribed manner. Distillation after product isolation gave 11.5 g. (0.06 mole, 61%) of a heavy, colorless oil, b.p. 112-120° at 0.3 mm., which solidified on being set aside at room temperature. Its recrystallization from an ethanol-water mixture yielded white plates (7.5 g.), m.p. 60.5-62.5°. Literature values, b.p. 129-130° at 3 mm., m.p. 63-64° (55).

3-(2-Thenoyl)-thiophene (2-Thienyl-3-thienyl Ketone)



A 15.5 g. (0.09 mole) quantity of N, N-dimethyl-2-thiophenecarboxamide was added to 0.10 mole of 3-thienyllithium, and the product was isolated in the usual manner. Distillation in vacuo gave 11.2 g. (0.058 mole, 64%) of a light yellow oil, b.p. 116-118° at 0.35 mm. The oil solidified on cooling and was recrystallized from an ethanol-water mixture to yield 7.8 g. of fine, pale yellow needles. Literature values, b.p. 133-136° at 2 mm., m.p. 63° (26). It showed intense carbonyl absorption in the infrared at 6.19 μ.

2-Thenoyl Chloride



During 30 minutes, 260 g. (2.2 moles) of thionyl chloride were added to 56 g. (0.44 mole) of 2-thiophenecarboxylic acid contained in a 500 ml. round bottom flask fitted with a reflux condenser. The reaction solution was held at its reflux temperature for an hour by heating on a steam bath. The excess thionyl chloride was removed by distillation at atmospheric pressure, and the residue was distilled in vacuo through a 10 cm. Vigreux column to obtain 51 g. (0.35 mole, 79%) of a colorless liquid boiling at 72° (56). Literature value, b.p. 72° at 5 mm.

N, N-Dimethylamides

N, N-dimethylformamide and N, N-dimethylacetamide were obtained from Eastman Kodak and used after distillation. The additional N, N-dimethylamides used in this study were prepared from the corresponding acid chlorides by reaction with dimethyl amine. A typical procedure is described:

N, N-Dimethylphenylacetamide

A 36 g. quantity (0.225 mole) of phenylacetyl chloride was mixed with 200 ml. of anhydrous ethyl ether in a 500 ml. three-necked flask fitted with a stirrer, a reflux condenser, a thermometer, and a gas inlet tube. The mixture was cooled to 0° by immersion of the flask in an ice bath, and gaseous dimethyl amine was bubbled in at a moderate rate. Cooling was necessary to maintain the temperature of the reaction mixture at its reflux temperature. After addition of the dimethyl amine the solution was washed with water and then with a dilute hydrochloric acid solution. The ether layer was dried with anhydrous magnesium sulfate, and the ether was removed over a steam bath.

The residue was distilled to obtain 21 g. (0.13 mole, 58%) of a colorless oil which boiled at 118-121° at 1-2 mm. The oil solidified on cooling to a waxy solid, m.p. 41°. Literature values, b.p. 155° at 10 mm., m.p. 43.5° (57).

The N, N-dimethylamides used in this investigation are listed together with their boiling points, melting points, yields and literature references:

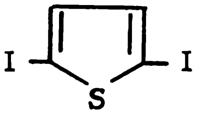
N, N-Dimethylpropionamide: b.p. 174-176° at 1 atm.; 61%; Literature value, b.p. 81.5-82° at 26 mm. (58).

N, N-Dimethylisobutyramide: b.p. 74-75° at 13 mm.; 57%; Literature value, b.p. 175-176° at 745 mm. (59).

N, N-Dimethylbenzamide: b.p. 115° at 4-5 mm.; m.p. 44-46°; 67%; Literature value, m.p. 45-46° (60).

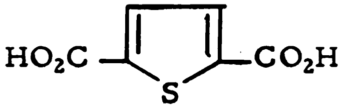
N, N-Dimethyl-2-thiophenecarboxamide: b.p. 105-106° at 0.6 mm.; 63%.

2, 5-Diiodothiophene



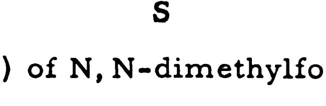
The procedure of Minnis (42) was modified for this preparation. To a vigorously stirred solution of thiophene (71 g., 0.84 mole) and benzene (100 ml.) contained in a one l. flask immersed in an ice bath were added 300 g. of mercuric oxide (1.40 moles) and 436 g. of iodine (1.76 g.-at.), alternately, in small amounts during a period of 45 minutes. The mixture was allowed to warm to room temperature and then vacuum filtered to remove the mercuric iodide. This was washed with three 25 ml. portions of ether. The filtrate was shaken with a 5% solution of sodium thiosulfate to remove any excess iodine, and then it was dried over anhydrous sodium sulfate. The ether and benzene were removed by distillation over a steam bath. The residue was fractionally distilled in vacuo to yield 80 g. of 2-iodothiophene (0.38 mole, 46%), b.p. 61° at 5-6 mm. and 85 g. of 2,5-diiodothiophene (0.26 mole, 32%), b.p. 77-78° at 0.15 mm., m.p. 39-40.5°. Literature values (see preceding reference), 2-iodothiophene, b.p. 65.5-66.5° at 9 mm. (42); 2,5-diiodothiophene, m.p. 40-41° (61).

2,5-Thiophenedicarboxylic Acid



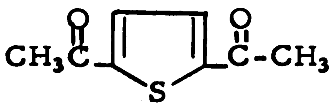
A 0.1 mole quantity of n-butyllithium-ether solution (60 ml.) was prepared as previously described. 2,5-Diiodothiophene, 7 g. (0.021 mole), dissolved in 25 ml. of anhydrous ether was added dropwise to the organolithium solution with rapid stirring at -10°. A precipitate of lithium iodide formed immediately. After addition of the dihalothiophene the reaction solution was stirred for 20 minutes. The 2,5-thienyldilithium was poured into a dry ice-ether slurry. After carbonation the mixture was allowed to warm to room temperature, and a solution of 4 ml. of concentrated hydrochloric acid, 20 g. of ice and 30 ml. of water was added. The ether layer was separated, the aqueous layer was extracted twice with ether, and the combined extracts were washed three times with a 15% sodium hydroxide solution. The alkaline solution was boiled in the presence of activated charcoal, filtered, and acidified with concentrated hydrochloric acid. The quantity of crude acid obtained was 2.56 g. (0.015 mole, 72%). The white solid was recrystallized from boiling water to yield 2.2 g. (61%) of 2,5-thiophenedicarboxylic acid, m.p. 355-357°. Literature value, m.p. 358-359° (62).

2,5-Thiophenedicarboxaldehyde



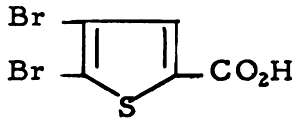
A 10.5 g. quantity (0.15 mole) of N,N-dimethylformamide dissolved in 25 ml. of anhydrous ether was added, with stirring at 0°, to 0.05 mole of 2,5-thienyldilithium dissolved in 100 ml. of anhydrous ether. After addition of the amide the solution was stirred for 30 minutes and poured into a saturated ammonium chloride solution. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ethereal extracts were dried over anhydrous magnesium sulfate. The ether was removed over a steam bath leaving a brown oil which solidified on cooling. The solid mass was recrystallized from 95% ethanol to give 2.2 g. (0.016 mole, 32%) of light yellow plates, m.p. 114-116°. A portion of the crystals was sublimed at 100° at 1 atm. to give long white needles, m.p. 116-116.5°. The infrared spectrum of this material agreed with the assigned structure, and the n.m.r. spectrum gave the correct ratio of aldehydic to ring protons (1:1). Anal. calcd. for $C_6H_4O_2S$: C, 51.41; H, 2.88; S, 22.87. Found: C, 51.40; H, 2.85; S, 22.71. (Infrared carbonyl absorption at 6.07 μ.)

2, 5-Diacetylthiophene



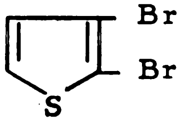
A 0.15 mole quantity of n-butyllithium dissolved in 75 ml. of anhydrous ether was prepared. A solution of 16.85 g. (0.05 mole) of 2,5-diiodothiophene dissolved in 25 ml. of anhydrous ether was added as previously described. To the slurry at -15° was added a 10.5 g. (0.12 mole) quantity of N,N-dimethylacetamide dissolved in 25 ml. of anhydrous ether. The product was hydrolyzed by pouring it into a dilute (10%) hydrochloric acid solution. The aqueous layer was extracted with ether, and the combined extracts were dried over anhydrous magnesium sulfate. The ether was removed by evaporation over a steam bath. Recrystallization of the yellow residue from a mixture of ethyl acetate and petroleum ether (30-60°) gave 4.92 g. (0.029 mole, 59%) of pale yellow plates, m.p. 169-170°. Literature value, m.p. 172-173° (23). Its infrared spectra agreed with the proposed structure.

2, 3-Dibromo-5-thiophenecarboxylic Acid



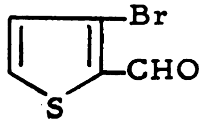
A 70 g. quantity of 2-thiophenecarboxylic acid (0.55 mole) was added slowly to 525 g. (3.29 moles) of bromine contained in a 500 ml. three-necked flask fitted with a stirrer and a reflux condenser. Cooling was required to prevent evaporation of bromine during the vigorous evolution of the hydrogen bromide. The addition of the acid required two hours. The reaction mixture was then stirred overnight after which it was heated on a steam bath to remove excess bromine. Cautiously, the solid mass was poured into a saturated ammonium carbonate solution which destroyed all traces of bromine. Concentrated hydrochloric acid was added to precipitate the crude acid. The solid product was recovered by filtration and recrystallized from ethanol in the presence of activated charcoal to obtain a light brown crystalline material (146 g., 0.51 mole, 93%), m.p. 225-227°. Literature value, m.p. 227-228° (63).

2, 3-Dibromothiophene



This compound was prepared according to the procedure of Steinkopf (42). 2, 3-Dibromo-5-thiophenecarboxylic acid (115 g., 0.4 mole), mercuric acetate (286 g., 1.1 moles), and 1000 ml. of acetic acid were mixed and heated with stirring for four hours in a 2 l. three-necked flask fitted with a reflux condenser. The mixture was cooled and filtered. The white mercuric acetate derivative was suspended in a liter of 20% sodium chloride, contained in a two l. flask fitted with a reflux condenser and heated at the suspension's reflux temperature for an hour. The reaction solution was then treated with 100 ml. of concentrated hydrochloric acid and exhaustively steam distilled at 100°. The oily layer in the steam distillate was extracted with several portions of ether and dried over anhydrous magnesium sulfate. The ether was removed over a steam bath. Distillation of the residue through a 10 cm. Vigreux column gave 65.7 g. (0.27 mole, 68%) of 2,3-dibromothiophene, b.p. 93-95° at 15 mm. Literature value, b.p. 212-213° at 1 atm. (50).

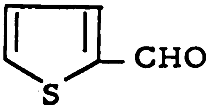
3-Bromo-2-thiophenecarboxaldehyde



A n-butyllithium-ether solution, 0.1 mole of alkyl lithium dissolved in 60 ml. of anhydrous ethyl ether, was prepared as previously described. A 12.57 g. (0.05 mole) quantity of 2,3-dibromothiophene dissolved in an equal volume of anhydrous ether was added dropwise during a 30 minute period to the n-butyllithium solution held below -65° by immersion of the reaction flask in a dry ice-methyl cellosolve bath. After addition of the dibromothiophene the gray solution was stirred for 30 minutes. A 7.3 g. (0.1 mole) quantity of N,N-dimethylformamide dissolved in an equal volume of anhydrous ether then was added dropwise to the 3-bromo-2-thienyllithium solution maintained below -65°. The white slurry, after stirring for 30 minutes, was poured into a saturated ammonium chloride solution. The ether layer was separated, and dried over anhydrous magnesium sulfate. The ether was evaporated over a steam bath. The residue was distilled to obtain 4.42 g. (0.023 mole, 46%) of a yellow oil, b.p. 80-84° at 1 mm., $n_D^{20} = 1.6243$. Its infrared spectrum showed only a single carbonyl peak at 6.03 μ. The n.m.r. indicated only two aromatic hydrogens in an AB system and only one aldehydic proton. Anal. calc. for C_5H_3BrOS: C, 31.44; H, 1.59; S, 16.73; Br, 42.27. Found: C, 31.60; H, 1.62; S, 16.46; Br, 41.97.

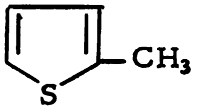
II.

2-Thiophenecarboxaldehyde



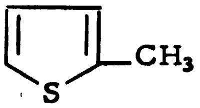
Basically, the method of Campaigne and Archer (64) was employed in the preparation of this material. A 252 g. (3.0 moles) quantity of thiophene and 276 g. (1.92 moles) of N, N-dimethylformamide were placed in a liter three-necked flask fitted with an Allihn condenser (protected by a calcium chloride tube), a mechanical stirrer, and a dropping funnel. The well-stirred solution was cooled to 0° in an ice bath, and 576 g. of (3.72 moles) phosphorus oxychloride were added during a 30 minute period. The reaction was initiated, as evidenced by a vigorous refluxing action, by heating it on a steam bath. After the initial reaction had subsided the mixture was heated for an additional hour on a steam bath, during which a color change from yellow to brown was observed in the reaction mixture. The solution was cooled and slowly poured onto 3.0 kg. of well-stirred cracked ice contained in a four liter beaker. The cold brown solution was neutralized to a pH of 5 (Hydrion paper) with a saturated solution of sodium acetate (using approximately 1500 g. of salt), followed by exhaustive steam distillation for eight hours. The organic layer was separated from the distillate, and the aqueous layer was extracted with three 300 ml. portions of ethyl ether. The combined organic extracts were washed with 100 ml. of 10% sodium bicarbonate to a pH of 7 (Hydrion paper), dried over anhydrous sodium sulfate. After removal of the sulfate salt by filtration, the ether was removed at atmospheric pressure over a steam bath. The organic residue was distilled *in vacuo* using a 100 mm. Vigreux column to obtain 276 g. (2.46 moles, 81%) of a colorless liquid boiling at 65° (4 mm). The liquid was stored in a brown bottle under refrigeration to prevent decomposition. Literature values, b.p. 66-67° at 4 mm. (65).

2-Methylthiophene



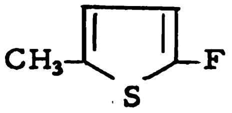
The experimental procedure of King and Nord (20) was followed to obtain this compound. In a three liter three-necked flask fitted with a thermometer (below liquid level), a 150 mm. Vigreux column, and a simple distillation head were placed 276 g. (2.46 moles) of 2-thiophenealdehyde, 490 ml. (10 moles) of 85% hydrazine hydrate and 1775 ml. of ethylene glycol. The reaction solution was heated at 130-165° until hydrazine and water ceased to distill (column temperature range 100-140°). Approximately 80 ml. of oil were separated from the distillate and returned to the flask. The solution was cooled to 40°, the Vigreux column was replaced by an Allihn condenser, and 490 g. of potassium hydroxide pellets were added, which caused the evolution of a small amount of nitrogen. The mixture was cautiously heated to 100° where the evolution of nitrogen became vigorous. Heating was discontinued and the evolution of nitrogen continued noticeably for two hours (temperature 100-145°). The mixture was set aside overnight (12 hours) after which it was heated to its reflux temperature for two hours. The reflux condenser was replaced by a 100 mm. Vigreux column and simple distillation head, and the solution distilled until the still head temperature reached 145° at atmospheric pressure. The distillate was extracted with several portions of ethyl ether; these were combined, washed twice with a 1:1 hydrochloric acid solution, and twice with water. After drying with anhydrous sodium sulfate, the solution was heated on a steam bath to remove the ether. The residue was distilled using a 10 inch glass-helices packed column to obtain 177 g. (1.81 moles, 73%) of colorless 2-methylthiophene boiling at 111-112° (1 atm.). Literature value (20), b.p. 112-113° at 1 atm.

2-Methylthiophene



A. n-butyllithium-ether solution, 0.6 mole of alkyllithium dissolved in 350 ml. of anhydrous ethyl ether, was prepared as previously described. A 0.5 mole quantity of 2-thienyllithium was prepared in the prescribed manner by the addition of 42 g. (0.5 mole) of redistilled thiophene. The aryllithium-ether solution was stirred under nitrogen for an hour at -10°, and then a solution of 32 ml. (0.71 g., 0.5 mole) of methyl iodide dissolved in 100 ml. of anhydrous ethyl ether was added dropwise to it during a 30 minute period, maintaining the reaction temperature at -10° by immersion of the reaction flask in a cooling bath. The solution was allowed to warm to room temperature and after heating at its reflux temperature for one hour was poured into 700 ml. of a crushed ice-ammonium chloride solution (20%). The ether layer was separated, and the aqueous layer was extracted three times with 50 ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, and the ether was removed over a steam bath at atmospheric pressure. The residue was distilled through a 10 cm. Vigreux column to obtain 21.5 g. (0.22 mole, 44%) of a colorless product boiling at 110-111° (1 atm.). The product was shown to be pure by vapor phase chromatography. Literature value, b.p. 111° at 747 mm. (15).

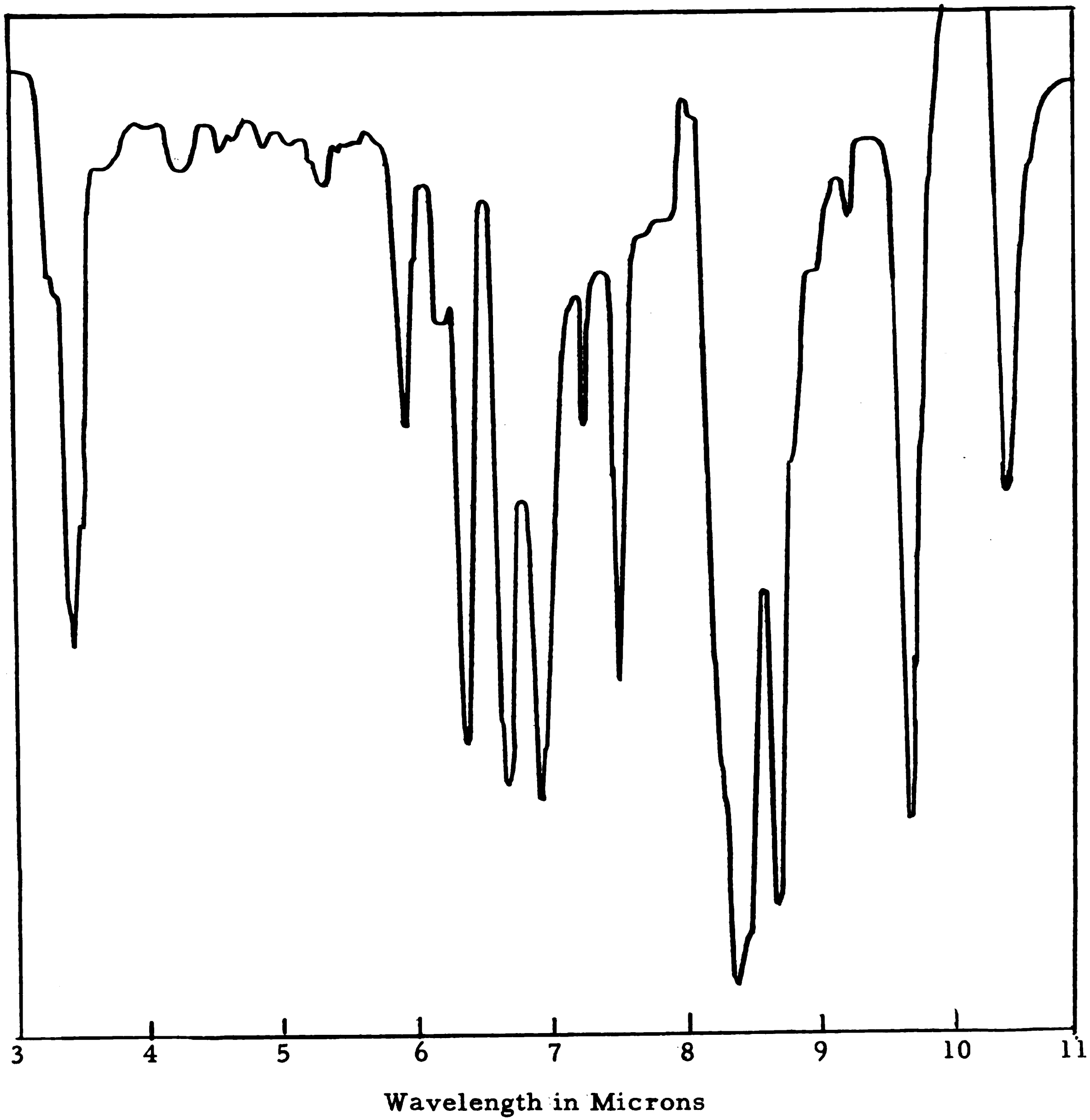
2-Fluoro-5-methylthiophene



A n-butyllithium-ether solution, 1.5 moles of alkyllithium dissolved in 500 ml. of anhydrous ethyl ether, was prepared as previously described in a liter three-necked flask fitted with a stirrer, addition funnel, Allihn condenser, and a -35 to +50° thermometer suspended by a wire through the condenser. The apparatus was protected from moisture by a calcium chloride tube. A 98 g. (1.0 mole) quantity of 2-methylthiophene dissolved in an equal volume of anhydrous ethyl ether was added dropwise during an hour to the alkyllithium-ether solution kept at 0-5° by immersion of the reaction flask in a dry ice-methyl cellosolve bath. If a gradual color change from purple to green, indicating the formation of 5-methyl-2-thienyllithium, did not appear in the reaction mixture, the flask was evacuated to remove butane forcing the metallation equilibrium reaction to completion. The resultant organolithium-ether solution was stirred under nitrogen for an hour at 0-5°. Gaseous perchloryl fluoride was then bubbled, at a moderate rate, through a back-up trap and Tygon tubing connected to a 6 mm. tube immersed below the liquid level of the reaction solution. The addition was extremely exothermic, the reaction temperature rising to the reflux temperature of the solution (30-35°) within 30 seconds. When the fluorination reaction had increased the temperature as noted, the addition of fluorination reagent was stopped, the reaction solution was cooled, and further addition of perchloryl fluoride was continued. During the time of reaction the solution changed from a green to a yellow solution, and a precipitate of lithium chlorate formed. In the absence of light an intense blue fluorescence could be observed throughout the solution. The reaction was completed in two hours, as evidenced by the disappearance of the blue fluorescence, a constant reaction temperature, the acidity of the solution to litmus, and a severe darkening caused by oxidation with the excess perchloryl fluoride. Nitrogen was passed through the mixture under rapid stirring for an hour to remove excess perchloryl fluoride. The mixture was then poured into 500 ml. of a saturated sodium carbonate solution (sodium hydroxide caused a severe darkening of the reaction phase). The precipitated inorganic salts caused emulsion formation between the aqueous and organic phases which could not be dispersed. Consequently, the ether layer was decanted, the remaining emulsion filtered with a water aspirator through a Celite filter pad, and the filtrate extracted with several portions of ether. The combined extracts were washed with additional sodium carbonate solution and again filtered. The filtrate was washed twice with water, dried over anhydrous magnesium sulfate, and heated on a steam bath to remove the ether. The residue was distilled through a 28 inch spiraled glass fractionating column, the fraction boiling uniformly from 102-112° at 1 atm. being collected (74 g.). Vapor phase chromatography analysis using a 30% silicone on 40 mesh Chromosorb column (6 ft. by 1/8 inch) in a Beckman Model GC-2 system, with 30 lb. carrier gas pressure (helium) showed the distillate contained 69.1% of 2-fluoro-5-methylthiophene, 9.9% of 2-methylthiophene (identified by retention time of a pure sample), and unidentifiable side products, accounting for an over-all yield of 51.9 g. (0.45 mole, 44%) of 2-fluoro-5-methylthiophene. A sample of the major product, assigned the structure 2-fluoro-5-methylthiophene, was isolated for analysis, infrared, and n.m.r. spectra by preparative gas chromatography utilizing a 30% silicone on 40 mesh Chromosorb column (108 x 0.75 in.) in a Perkin-Elmer Model 154 vapor fractometer. Infrared analysis by comparison of 2-fluoro-5-methyl and 2-methylthiophene gave a C-F peak at 7.6 μ, and n.m.r. gave the correct ratio of methyl to ring hydrogens (3:2) and showed additional splitting from the fluorine atom. Anal. calcd. for C_5H_5SF: C, 51.70; H, 4.34; F, 16.36; S, 27.60. Found: C, 51.99; H, 4.58; F, 16.34; S, 27.55. Strong infrared peaks at 3.5, 4.7, 6.5, 6.6, 6.9, 7.6, 8.2, 8.3, 8.4, 9.8 and 11.9 μ.

Perchloryl fluoride is a stable compound quite safe to handle. It is, however, a powerful oxidizing agent, and all mixtures with oxidizable substances should be considered potentially dangerous. No difficulties were encountered in handling perchloryl fluoride under the conditions of the present experiments. The details of handling and safety of perchloryl fluoride have been fully described in Booklet DC-1819, "Perchloryl Fluoride," Commercial Development Department, Pennsalt Chemical Corp., 3 Penn Center, Philadelphia 2, Penn.

Figure II. Infrared Spectrum of 2-Fluoro-5-methylthiophene taken in Carbon Tetrachloride



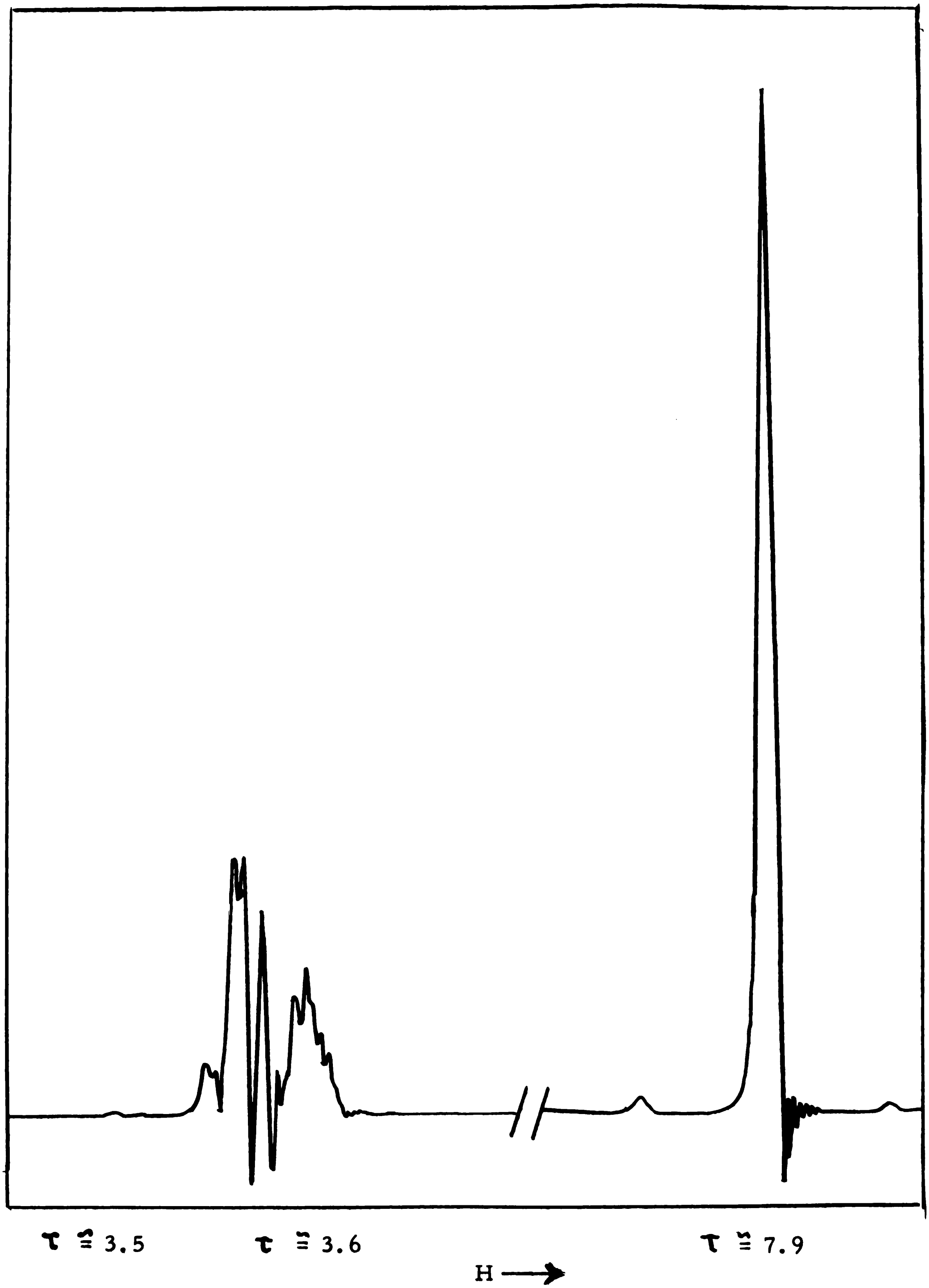


Figure III. N.m.r. Spectrum of 2-Methylthiophene in Carbon Tetrachloride at a Sweep Width of 500 c.p.s.

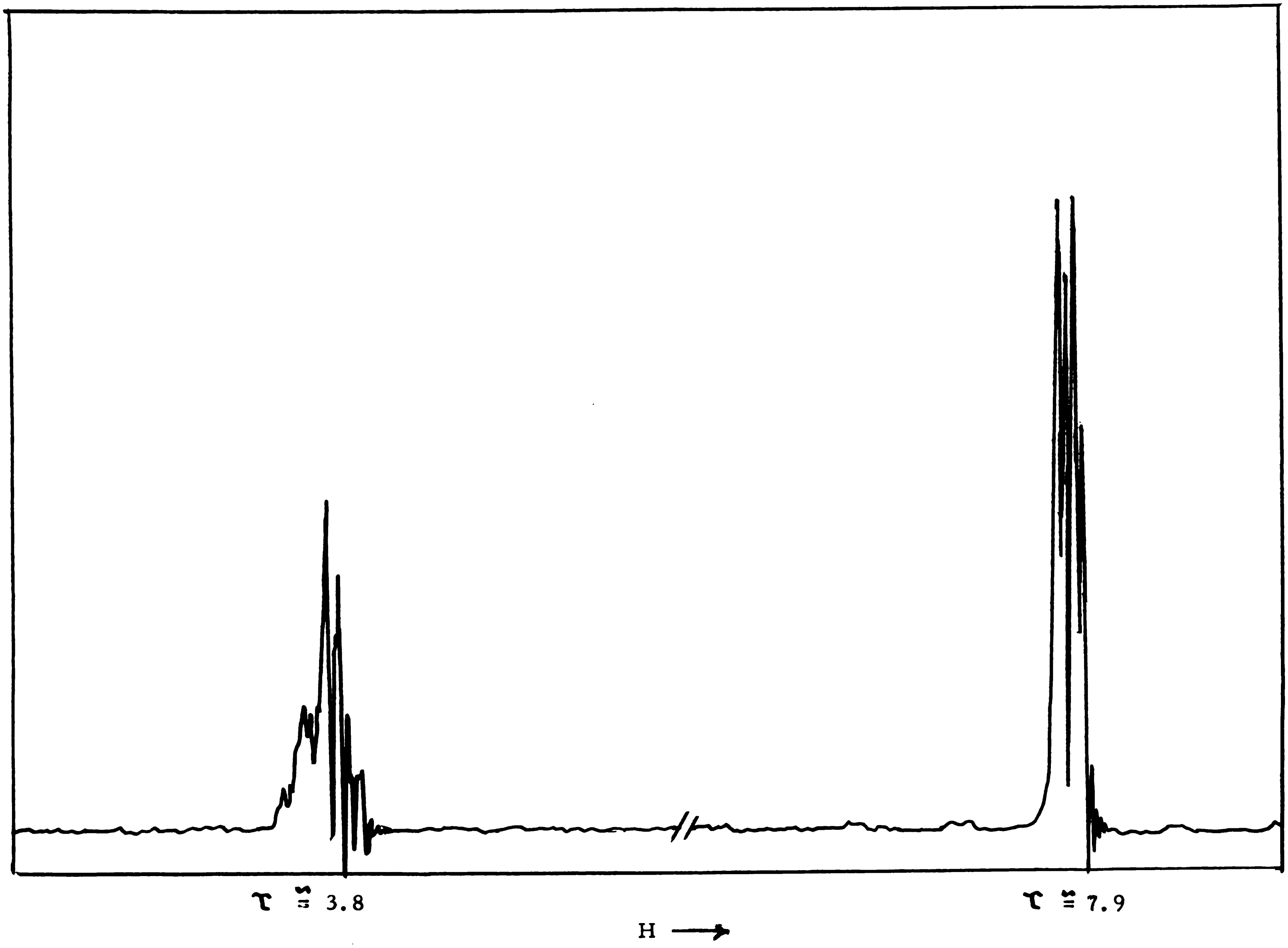
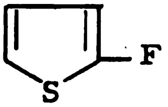
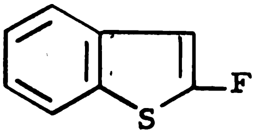


Figure IV. N.m.r. Spectrum of 2-Fluoro-5-methylthiophene in Carbon Tetrachloride at a Sweep Width of 500 c.p.s.

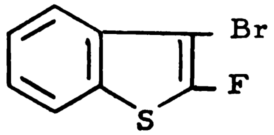
2-Fluorothiophene 

An 84 g. (1 mole) quantity of thiophene was added to 500 ml. of a n-butyllithium-ether solution (1.5 moles). Into the 2-thienyllithium-ether solution precooled to 0° by immersion of the reaction flask in a dry ice-methyl cellosolve bath was cautiously bubbled perchloryl fluoride. The addition of fluorination reagent was stopped when the temperature reached 30°, the solution was cooled, and subsequent addition of perchloryl fluoride was continued. When the intense blue fluorescence had disappeared, and the reaction was acid to litmus, the reaction was stopped. The product isolation was carried out in the manner previously described in the preparation of 2-fluoro-5-methylthiophene. Distillation through a 28 inch spiraled glass fractionating column gave 56.9 g. of a colorless liquid boiling in the range of 80-90° (760 mm.). Vapor phase chromatography through a 20% silicone on 40 mesh Chromosorb column using a Beckman Model GC-2 vapor fractometer showed two major peaks, the smaller of which was shown to be thiophene (12.3%) by comparison to the retention time of a pure sample. The larger peak was tentatively assigned as that of 2-fluorothiophene (87.4%), thus giving an over-all yield of 49.6 g. (0.53 mole, 48.8%) of fluorinated product. A sample for analysis and infrared was isolated by preparative gas chromatography in the manner previously described for 2-fluoro-5-methylthiophene. Anal. calcd. for C_4H_3SF: C, 47.04; H, 2.96; F, 18.60. Found: C, 47.23; H, 3.16; F, 18.23. $n_D^{20} = 1.4896$.

2-Fluorothianaphthene 

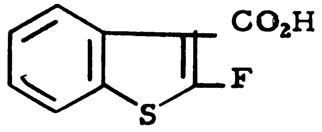
To a solution cooled in an ice bath and containing 0.3 mole of n-butyllithium dissolved in 100 ml. of anhydrous ether was added 26.8 g. (0.2 mole) of thianaphthene dissolved in 50 ml. of ether. In order to remove butane and force the metallation reaction to completion, the system was evacuated while heating the reaction solution over a steam bath. Upon removal of the ether the system was treated with dry nitrogen to equalize the pressure, and additional anhydrous ether was added. This procedure was repeated until the evolution of butane was completed. The 2-thianaphthenyllithium-ether solution was cooled to 0°, and perchloryl fluoride was bubbled slowly into the solution. When the blue fluorescence had subsided, the addition of fluorination agent was stopped. The reaction slurry was treated with a saturated sodium carbonate solution, and the ether layer was washed twice with water. The ether layer was separated, dried over anhydrous magnesium sulfate, and the ether removed over a steam bath. Distillation of the residue through a 20 cm. Vigreux column gave a liquid product (21.3 g., 70%) boiling at 93-94° (25 mm.), $n_D^{27} = 1.5910$, m.p. 20-20.5°. A sample for analysis, n.m.r. and infrared spectra was isolated by preparative gas chromatography. Nuclear magnetic resonance spectrum showed the correct ratio of thiophene to benzene hydrogens (1:4). Anal. calcd. for C_8H_5SF: C, 63.16; H, 3.29; S, 21.05; F, 12.50. Found: C, 63.19; H, 3.51; S, 21.20; F, 12.67.

2-Fluoro-3-bromothianaphthene



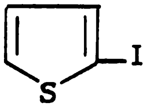
A solution of 14.9 g. (0.093 mole) of bromine dissolved in 14.0 ml. of anhydrous chloroform was added dropwise, at 25°, during 30 minutes to a second solution prepared from 14.3 g. (0.093 mole) of 2-fluorothianaphthene and 14.5 g. (0.17 mole) of anhydrous sodium acetate dissolved in 65 ml. of anhydrous chloroform and contained in a 300 ml. three-necked flask fitted with a stirrer, an additional funnel, and a reflux condenser. The orange-colored reaction solution was stirred an additional hour, and 50 ml. of water was added to dissolve the inorganic material. The organic layer was separated, washed successively with 100 ml. of water, 50 ml. of 5% aqueous sodium hydroxide, 100 ml. of water, 100 ml. of a saturated sodium chloride solution, and finally with 100 ml. of water. The organic extract was dried over anhydrous magnesium sulfate, and the ether was removed over a steam bath. The residue was distilled using a 10 cm. Vigreux column to obtain 11.0 g. (0.0475 mole, 51.5%) of a pale yellow oil boiling at 76-78° (1 mm.), m.p. 21-21.5°. Anal. calcd. for C_8H_4SFBr: C, 41.56; H, 1.73; S, 13.85; F, 8.23; Br, 34.63. Found: C, 41.65; H, 1.86; S, 13.78; F, 8.23, 8.26; Br, 34.27, 34.35.

2-Fluoro-3-thianaphthenecarboxylic Acid



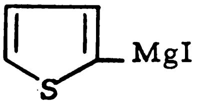
A 1.47 g. (0.023 mole) quantity of n-butyllithium dissolved in 3 ml. of anhydrous ether was prepared in a 50 ml. three-necked flask fitted with an addition funnel, a reflux condenser, and a magnetic stirrer. A solution of 5.34 g. (0.023 mole) of 3-bromo-2-fluorothianaphthene dissolved in 5.0 ml. of anhydrous ether was added during five minutes while the temperature was maintained below -70°. The reaction mixture was then poured rapidly over a dry ice-ether slurry which was then allowed to warm to room temperature. The ether solution was extracted with 25 ml. of water followed by two 50 ml. portions of a 5% aqueous sodium hydroxide solution. The aqueous extracts were combined, boiled in the presence of activated charcoal, cooled, and acidified with concentrated hydrochloric acid. The white precipitate which formed on acidification was recovered by filtration and washed with water. It was crystallized three times from a minimum of 95% ethanol to afford 2.5 g. (0.0127 mole, 55%) of fine white needles, m.p. 188-188.5°. Anal. calcd. for $C_9H_5O_2SF$: C, 55.10; H, 2.55; S, 16.33; F, 9.69. Found: C, 54.94; H, 2.60; S, 16.49; F, 9.48, 9.46.

2-Iodothiophene



This compound was prepared according to the method of Minnis (42). To a vigorously stirred solution of 140 g. (1.67moles) of thiophene and 200 ml. of benzene contained in a two liter two-necked flask cooled to 0° by immersion in an ice-salt bath were added in small amounts during a period of an hour 300 g. (1.4 moles) of orange mercuric oxide and 436 g. (1.72 g.-at.) of iodine. The orange mercuric oxide changed to crimson mercuric iodide. (The orange mercuric oxide was used instead of the yellow oxide, but it caused a spontaneous, uncontrolled reaction if added too quickly. Nevertheless, the orange oxide gave a better yield in all preparations). The reaction mixture was allowed to warm to room temperature. The mercuric iodide was removed by vacuum filtration and the precipitate was washed three times with 50 ml. portions of ether. The ether-benzene filtrate was shaken with a 5% sodium thiosulfate solution to remove excess iodine and then dried over 25 g. of calcium chloride. The ether and benzene were removed by distillation on a steam bath, and the residue was fractionally distilled <u>in vacuo</u> through a 10 cm. Vigreux column. The fraction boiling from 72-77° at 13 mm. was collected as pure 2-iodothiophene 268 g. (1.28 moles,77%). Literature value, b.p. 73° at 15 mm. (60).

2-Thienylmagnesium Iodide

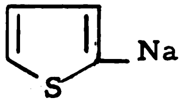


The general procedure of Steinkopf (47) was used in this preparation. To a suspension of 7 g. (0.25 g.-atom) of magnesium shavings (activated by washing with an iodine-ether solution and then adding four to five drops of ethyl bromide) in 50 ml. of anhydrous ethyl ether contained in a 500 ml. three-necked flask equipped with a stirrer, a dropping funnel, and an Allihn condenser, was added at a rate sufficient to maintain the reaction mixture at its reflux temperature, a solution containing 53 g. (0.25 mole) of 2-iodothiophene dissolved in 150 ml. of anhydrous ether. The reaction mixture was heated at its reflux temperature for an additional hour and cooled to 0°. Perchloryl fluoride was then added at a rate which maintained the reaction temperature below 20°. No blue fluorescence was observed. The only noticeable change was a severe darkening of the mixture to a black intractable mass. Upon removal of the ether, the mixture solidified to an ether insoluble mass. Water and organic solvents had no effect upon the solid, and it was assumed that the Grignard reagent had not reacted with the perchloryl fluoride in the desired manner. Oxidation with subsequent decomposition had probably occurred.

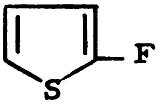
Sodium Amalgam

A suspension of 25 g. sodium (1.1 g.-atom) in 60 ml. of toluene was placed in a 500 ml. Erlenmeyer flask. The sodium was melted over a hot plate and 10 g. of mercury was added cautiously causing a vigorous reaction. The toluene was decanted, and the amalgam was stored in a wax-sealed bottle in a desiccator. The amalgam was pulverized with mortar and pestle in a dry box before using.

2-Thienylsodium

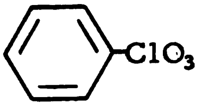


The organosodium derivative was prepared according to the method of Schick and Hartough (66). A cold mixture of 78 g. (0.5 mole) of bromobenzene dissolved in 300 ml. of anhydrous ethyl ether was added dropwise during an hour to a cooled mixture ($5-10^{\circ}$) of 42 g. (0.5 mole) of thiophene and 25 g. of sodium amalgam sand, (1.09 g.-atom sodium with 10 g. (0.05 g.-atom) mercury), in 200 ml. of anhydrous ethyl ether in a liter three-necked flask fitted with a reflux condenser, a mechanical stirrer, and an addition funnel. A change in coloration from cloudy to brown and finally to blue occurred. After the addition of the arene bromide was complete, the mixture was stirred for 30 minutes before removing the ice bath. The mixture was allowed to warm gradually to room temperature and then heated at its reflux temperature over a steam bath for two hours. The 2-thienylsodium solution was cooled to 0° by immersion of the reaction flask in an ice bath, and gaseous perchloryl fluoride was cautiously bubbled into it maintaining the reaction temperature below 30°. Upon completion (one hour) the reaction had a dark brown coloration, and no blue fluorescence had been observed during the addition of the fluorination reagent. The excess perchloryl fluoride was removed by bubbling nitrogen into the mixture for 30 minutes, after which 200 ml. of ether saturated with water was added to destroy any unreacted sodium. The reaction mixture was poured into 500 ml. of a saturated sodium carbonate solution, and the ether layer was separated and dried over anhydrous magnesium sulfate. The ether was removed over a steam bath. The liquid residue was distilled through a 10 cm. Vigreux column, the fraction (33 g.) boiling from 80-86° (1 atm.) being collected. Vapor phase chromatography analysis, utilizing a 30% silicone on 40 mesh Chromosorb column (6 ft. x 1/8 in.) in a Beckman Model GC-2 instrument showed 87% of unreacted thiophene and 9% 2-fluorothiophene assigned by comparison to the retention time of pure samples. Thus, 3 g. (0.03 mole, 5.8%) of 2-fluorothiophene was present. The non-stoichiometry of the final distillate is due probably to oxidation by perchloryl fluoride as a black solid residue remained in the distillation flask.

2-Fluorothiophene 

A n-butyllithium-ether solution, prepared from 54.8 g. (0.4 mole) of n-butyl bromide and 5.6 g. (0.8 g.-atom) of lithium suspended in 120 ml. of anhydrous ether, was prepared as previously described. To this stirred solution 63 g. (0.3 mole) of 2-iodothiophene dissolved in 30 ml. of anhydrous ether was added during 30 minutes, maintaining the reaction temperature below 20° by immersion of the reaction flask in an ice bath. An immediate reaction was evident by the precipitation of white lithium iodide and the change of coloration from purple to dark green. The 2-thienyllithium solution was stirred for three quarters of an hour. Perchloryl fluoride was cautiously bubbled into the solution maintaining the temperature below 20°. When the solution was no longer alkaline (litmus paper), and the blue fluorescence had disappeared, the addition was stopped. The dark brown solution was flushed with a rapid stream of nitrogen for 30 minutes to remove excess perchloryl fluoride. The reaction mixture was then poured into a saturated sodium carbonate solution, forming an emulsion, which was treated as described previously. The ethereal extract was washed with water, dried over anhydrous magnesium sulfate, and the ether was removed over a steam bath. The residue was distilled using a 28 inch spiral glass column giving 20.8 g. of a clear liquid, b.p. 60-87°. A sample of this liquid was subjected to vapor phase chromatography using a 20% silicone on Chromosorb column (6 ft x 1/8 in.) on a Beckman GC-2 instrument at 70° with a carrier gas pressure of 30 lb. (helium). Three peaks in the ratio of 3/8: 2 3/8: 7 2/8 were resolved and assigned by comparison to the retention times of pure samples. The small peak was shown to be due to excess solvent, the second peak due to (23.8%) pure thiophene, and the large peak due to (72.7%) 2-fluorothiophene. Thus, 15.2 g. (0.15 mole, 49.6%) of 2-fluorothiophene were present in the distillate.

Perchlorylbenzene



Into a 300 ml. three-necked flask fitted with a stirrer, an addition tube, an Allihn condenser, and a calcium chloride drying tube was placed a suspension of 1.4 g. (0.2 g.-atom) of lithium slivers suspended in 50 ml. of anhydrous ethyl ether. The suspension was cooled to -10° by immersion of the flask in a dry ice-methyl cellosolve bath, and 17.9 g. (0.1 mole) of bromobenzene dissolved in 50 ml. of anhydrous ether were added dropwise during 30 minutes. The solution turned cloudy and eventually a dark gray with the formation of phenyllithium. Perchloryl fluoride was bubbled at a moderate rate into the reaction solution at 0° causing a highly exothermic reaction to occur. When the reaction temperature reached 20°, the addition of perchloryl fluoride was stopped, and after the solution had cooled, subsequent gas addition continued. When the mixture was no longer alkaline, and the crackling sound had stopped, perchloryl fluoride addition was stopped. The flask was flushed with nitrogen (0.5 hour) and the reaction mixture was poured into a saturated sodium carbonate solution. The ether layer was separated, washed with water, and dried over anhydrous magnesium sulfate. After removal of the ether, vacuum distillation of the crude product gave 1.8 g. (0.011 mole, 11%) of perchlorylbenzene, b.p. 78-79° (2 mm.) as identified by its infrared spectrum (29).

The Attempted Synthesis of 1-Fluoronaphthalene or 1-Perchlorylnaphthalene

The method of Gilman (47) was utilized to prepare 1-naphthyllithium. Into a 300 ml. three-necked flask fitted with a stirrer, an addition funnel and an Allihn condenser with a calcium chloride drying tube was placed a suspension of 1.52 g. (0.2 g.-atom) of lithium slivers suspended in 60 ml. of anhydrous ethyl ether. To this suspension was added, during an hour, a solution of 20.7 g. (0.1 mole) of 1-bromonaphthalene dissolved in 60 ml. of anhydrous ether. A change of coloration from gray to purple occurred. After the addition of the arylbromide the solution was stirred for three quarters of an hour. Perchloryl fluoride then was bubbled into the reaction mixture at a moderate rate at 0°, the reaction temperature not being allowed to rise above 30°. When the solution had become dark brown and was no longer alkaline, the fluorination reagent addition was stopped. The system was flushed with a rapid stream of nitrogen and poured into a saturated sodium carbonate solution. The ether layer was separated, the aqueous layer extracted with two 100 ml. portions of ether, and the combined ethereal extracts were dried over anhydrous magnesium sulfate. The ether was removed over a steam bath, and the residue vacuum distilled, collecting the fraction boiling from 85-100° at 12 mm. Vapor phase chromatography as described in the previous procedure showed unreacted naphthalene as the major product and trace amounts (less than 1%) of tentatively assigned fluorinated and perchlorylated naphthalenes.

The Attempted Synthesis of 2-Perchlorylthiophene

The attempted synthesis was carried out by a modification of Inman's procedure (29). Perchloryl fluoride was bubbled through a well stirred solution of 33 g. of anhydrous stannic chloride suspended in 250 g. (3.0 moles) of thiophene maintained at 10-20°. The reaction mixture immediately turned orange, then brown and finally black. Heat of reaction was apparent, and some cooling was required. Upon completion of the addition of the perchloryl fluoride the solution was flushed of excess perchloryl fluoride by a rapid stream of nitrogen and then heated on a steam bath for 30 minutes. The black tarry residue was extracted several times with ether; the ether layer was washed with water and dried over anhydrous magnesium sulfate, and the ether was removed.

Vapor phase chromatography showed only unreacted thiophene, and infrared analysis showed none of the peaks characteristic to the perchloryl group in perchlorylbenzene.

The Attempted Fluorination of Ethyl Cyanoacetate

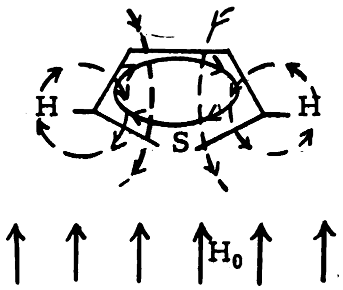
To a stirred solution of sodium ethoxide (1.0 mole) dissolved in 500 ml. of absolute alcohol (previously distilled from sodium and ethyl phthalate) was added a 56.5 g. (0.5 mole) quantity of ethyl cyanoacetate. A white precipitate of the sodium salt of ethyl cyanoacetate appeared immediately. The solution was cooled to 0° and stirred for an hour. Perchloryl fluoride was bubbled into the reaction mixture at a moderate rate sufficient to maintain the reaction temperature below 20°. The reaction was not highly exothermic, and the addition of perchloryl fluoride was stopped when the solution was no longer alkaline. Nitrogen was passed through the solution to remove any excess perchloryl fluoride. The yellow solution was poured into three times its volume of water and stirred to dissolve inorganic salts. The ether layer was separated, and the aqueous solution was extracted with several portions of ether. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and the ether was removed over a steam bath. The residue was distilled <u>in vacuo</u> to obtain 12.6 g. of a colorless liquid, b.p. 87-102° at 10 mm. A large amount of black residue remained in the distilling flask. Vapor phase chromatography with a 30% silicone on Chromosorb column (4 ft. x 1/8 in.) using a Perkin-Elmer vapor fractometer showed five components to be present in the percentages of 6.2%, 2.6%, 66.2%, 12.1%, 2.7% and 11.2%, from the fastest to slowest retention time. The largest peak in 66.2% yield was shown to be unreacted ethyl cyanoacetate by comparison to the retention time of a pure sample. The other components could not be resolved into their pure forms.

The Reaction of Phenylacetonitrile with Perchloryl Fluoride

A 300 ml. three-necked flask, fitted with a stirrer, a reflux condenser, and an addition funnel was charged with 11 g. (0.26 mole) of sodium amide suspended in 50 ml. of anhydrous ethyl ether. A 15 g. amount (0.13 mole) of phenylacetonitrile dissolved in 50 ml. of anhydrous ether was added to the rapidly stirred amide suspension. The reaction solution was refluxed on a steam bath for one hour, causing an evolution of ammonia and a change of coloration to a red-brown. Perchloryl fluoride was then cautiously bubbled into the reaction vessel at 0-20°. The exothermic reaction was stopped when the temperature remained constant (one hour). The brown mixture was slowly poured into 250 ml. of water to destroy any unreacted sodium amide. The ether layer was separated, the aqueous layer was extracted twice with ether, and the combined extracts were dried over anhydrous magnesium sulfate. The ether was removed over a steam bath, and the residue was distilled to obtain 12.2 g. of a colorless distillate. Vapor phase chromatography through a 30 inch 20% silicone on Chromosorb column under 10 lb. carrier gas (helium) pressure showed two components in the ratio of 8:1. The major component was shown to be unreacted phenylacetonitrile by comparison to the retention time of a pure sample. The minor component was assigned the structure of the difluorinated material, although it could not be successfully isolated.

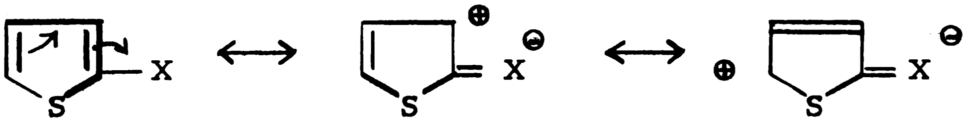
APPENDIX

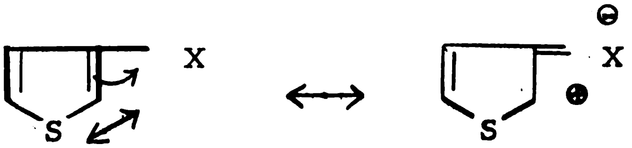
The nuclear magnetic resonance spectra of the 2- and 3-substituted thiophenes provided an unequivocal method of structure determination. In the majority of the compounds considered, both aliphatic and aromatic protons were present. Because of the diamagnetic currents associated with a closed loop of atomic centers, as in the π-electron system of thiophene, the protons attached to the ring are deshielded with respect to the applied field. Thus, they appear at lower field strengths in the spectra (67):



As a result the aliphatic hydrogens appearing at a higher field do not interfer with the aromatic protons. Structural assignments and integration are, therefore, straightforward.

In a series of monosubstituted thiophenes, Gronowitz (68) has shown the aromatic proton frequencies to reside in the range of τ = 1.66 to τ = 3.89, depending upon the electronic effects of the substituent. If an electron withdrawing group is present on the 2-position, the 3- and 5-protons will be deshielded by the substituents resonance effect and will appear at lower fields (τ = 2.2-2.4) than the 4-proton (τ= 2.8-2.9). The converse is also true. If an electron withdrawing substituent is present at the 3-position, the 2-proton will experience a twofold effect: the electronegative attraction of the sulfur atom and the resonance effect of the substituent.





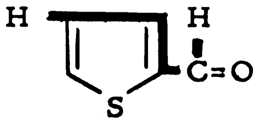
As a result the proton will resonate at a much lower field (τ = 1.6-1.9). The 4- and 5-protons will experience equally the resonance and electronegative effect, respectively, and appear at a slightly lower field (τ=2.2-2.6). With an electron donating substituent at the 3-position, the resonance effect together with the electronegativity of the sulfur atom will initiate a "push-pull" flow of electrons through the 2-position. Consequently, the 2-protons will require a high field to resonate (τ=3.3-4.0). The 4-proton (τ =2.3-3.4) being "ortho" to the substituent will appear usually between the 2- and 5-protons (τ =2.0-3.1) on the spectrum.

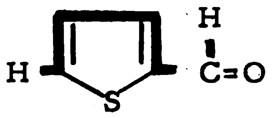
These generalizations provide an elegant method of determining the position of attack on the thiophene ring without having to expand the spectra to calculate the known coupling constants (this latter process can be complicated with an ABX system but extremely difficult with an ABC system--e.g.--an electron donating group substituted at the 3-position). The spectra of the 2- and 3-acetyl and propionylthiophenes and 3-isobutyrylthiophene are presented to illustrate the preceding discussion. It is noticed how the 2- and 3-substituted derivatives are easily distinguished from one another.

With a disubstituted thiophene the structure determination is much easier since an A^2 or AB system are usually present. Therefore, the coupling constants and resonance frequencies are readily determined.

Two of the compounds investigated exhibited unusual spectra which deserve mention. With 3-bromo-2-thiophenecarboxaldehyde a simple

AB spectra system was found with $J_{45} = 5.2 \pm 0.1$ cps. The 5-proton is assigned at a lower field $\tau_5 \cong 0.7$ than the 4-proton $\tau_4 \cong 1.6$, while the aldehydic proton appeared at $\tau\,CH \cong -1.7$. The interesting feature is the splitting of the aldehydic proton by the 4- and 5-protons:

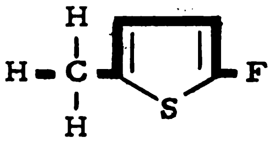


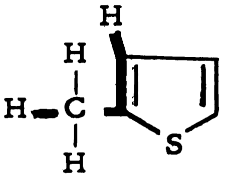


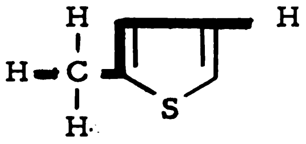
$J_{4\text{-}CH} = 0.0 \pm 0.1$ cps

$J_{5\text{-}CH} = 1.3 \pm 0.1$ cps

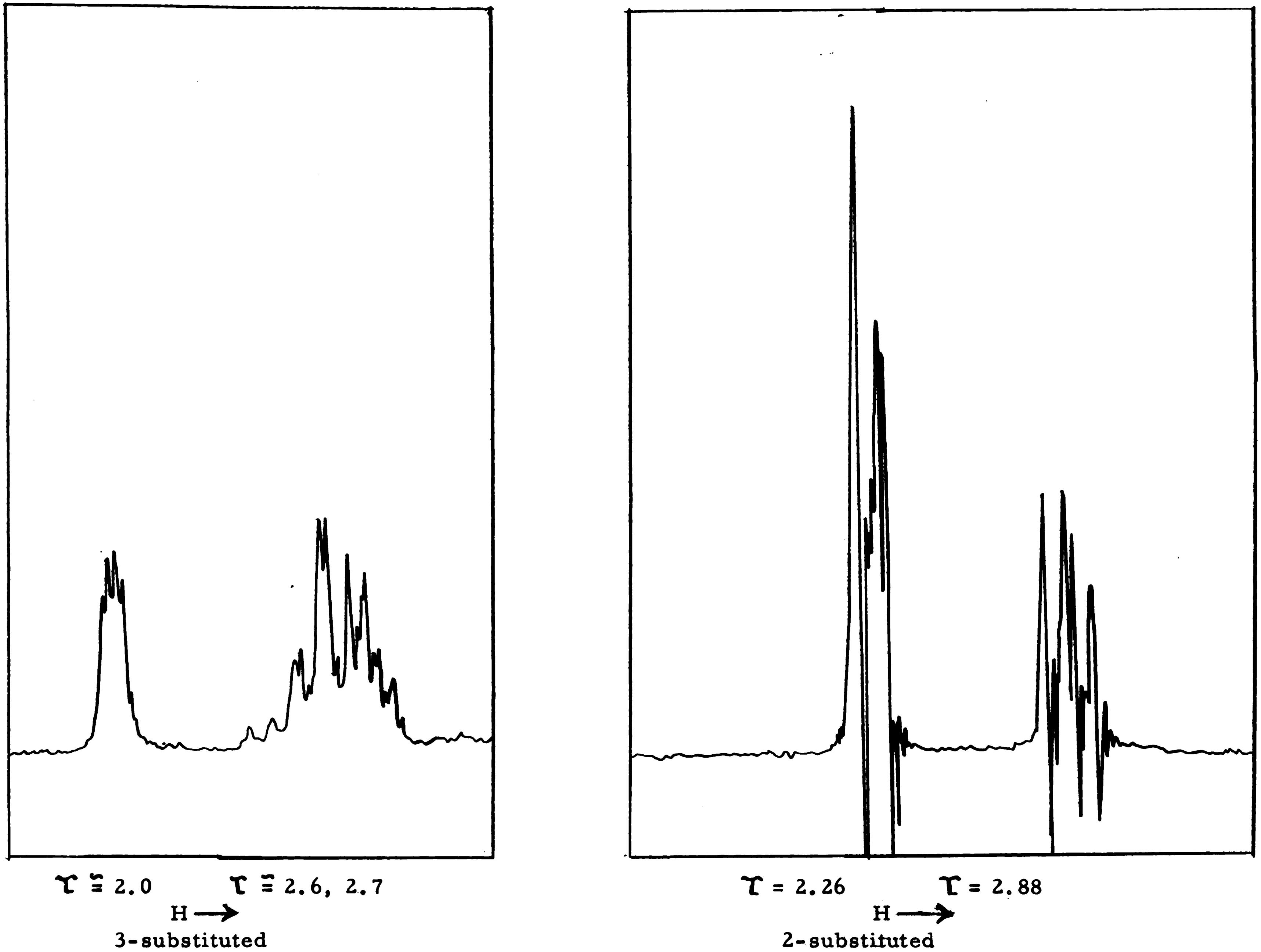
The n.m.r. of 2-methylthiophene consists of two areas of resonance: a complex ABC spectrum in the aromatic region from $\tau \cong 3.4\text{-}3.7$ and a singlet attributed to the aliphatic protons at $\tau \cong 7.9$. However, when the 5-proton is replaced by a fluorine atom to give 2-methyl-5-fluorothiophene, some interesting splitting occurs. First, the aromatic protons appear upfield ($\tau \cong 3.8$) in a more compact AB system. Obviously, the aromatic protons are shielded to a greater extent by the fluorine atom activating the inductive hyperconjugative effect of the methyl group. The aliphatic proton region has shifted downfield ($\tau \cong 7.6$) because of the increased hyperconjugation which deshields the methyl protons. More interesting is the severe splitting of the aliphatic protons into two doublets by the fluorine and one of the protons on carbon 3 or 4, or by the protons on carbon 3 and 4. Two coupling constants for this long range splitting can be found:





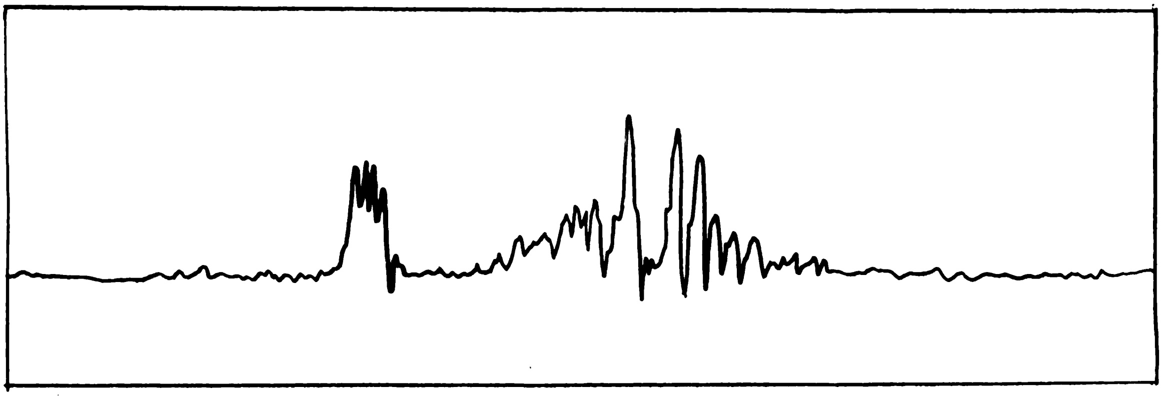


$J_{HF} = 2.6 \pm 0.2,\ 2.9 \pm 0.2$

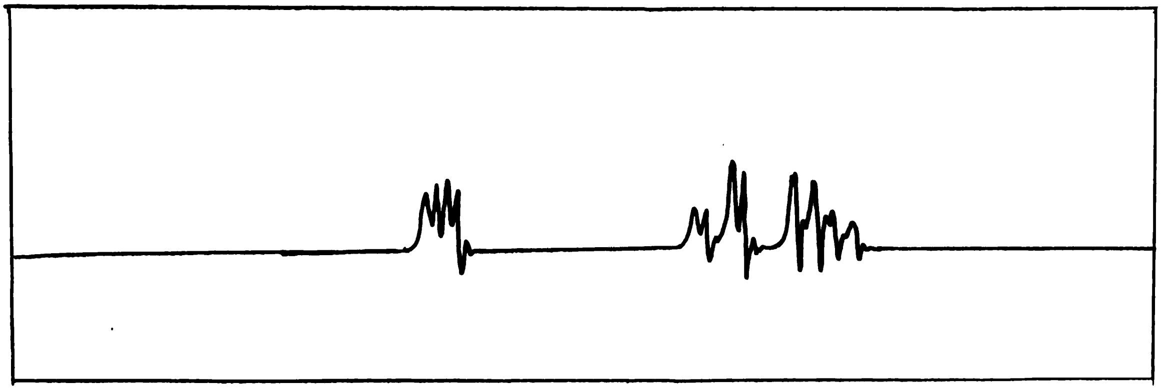


igure V. N.m.r. Spectra of the Aromatic Regions of 2- and 3-Propionylthiophenes in Carbon Tetrachloride at a Sweep Width of 500 c.p.s.

2-acetylthiophene H ⟶



3-acetylthiophene H ⟶



3-isobutyrylthiophene H ⟶

Figure VI. N.m.r. Spectra of the Aromatic Regions of 2- and 3-Acetylthiophenes and 3-Isobutyrylthiophene taken at a Sweep Width of 500 c.p.s.

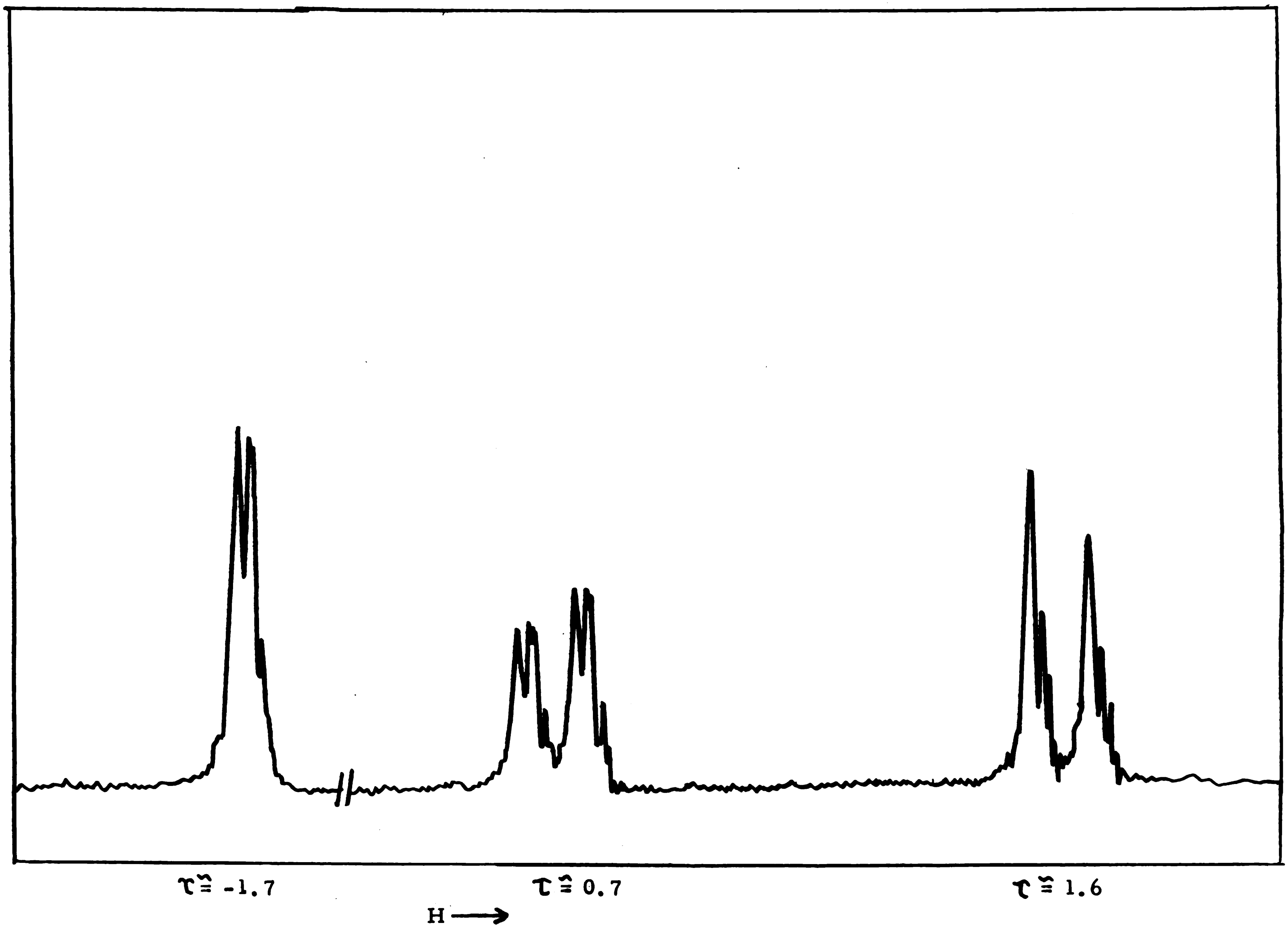


Figure VII. N.m.r. Spectrum of 3-Bromo-2-thiophenecarboxaldehyde taken Carbon Tetrachloride at a Sweep Width of 250 c.p.s.

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