AN INVESTIGATION OF THE SYNTHESIS AND BASE INDUCED REARRANGEMENT OF SOME DITHIENYL DIKETONES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
GEORGE PETER NILLES
1970

This is to certify that the

thesis entitled

AN INVESTIGATION OF THE SYNTHESIS
AND BASE INDUCED REARRANGEMENT
OF SOME DITHIENYL DIKETONES

presented by

George Peter Nilles

has been accepted towards fulfillment
of the requirements for

Ph. D. degree in Chemistry

Major professor

Date 8/26/70

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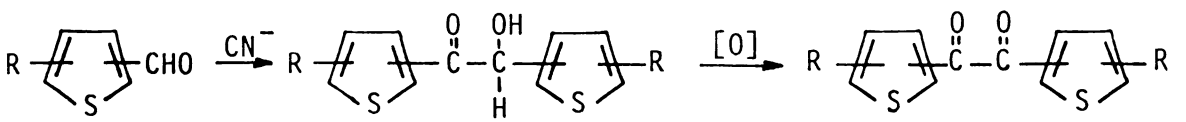
ABSTRACT

AN INVESTIGATION OF THE SYNTHESIS
AND BASE INDUCED REARRANGEMENT
OF SOME DITHIENYL DIKETONES

By

George Peter Nilles

An investigation of the synthesis and reactivity of various dithienyl diketones (thenils, III) has been carried out.



I II III

These compounds, listed below, were prepared, for the most part, by Vilsmeier-Haack formylation of various substituted thiophenes, followed by cyanide catalyzed condensation of the resulting aldehydes (I) to give the thenoins (II). Oxidation of the thenoins, usually by Cu^{II}, gave the thenils.

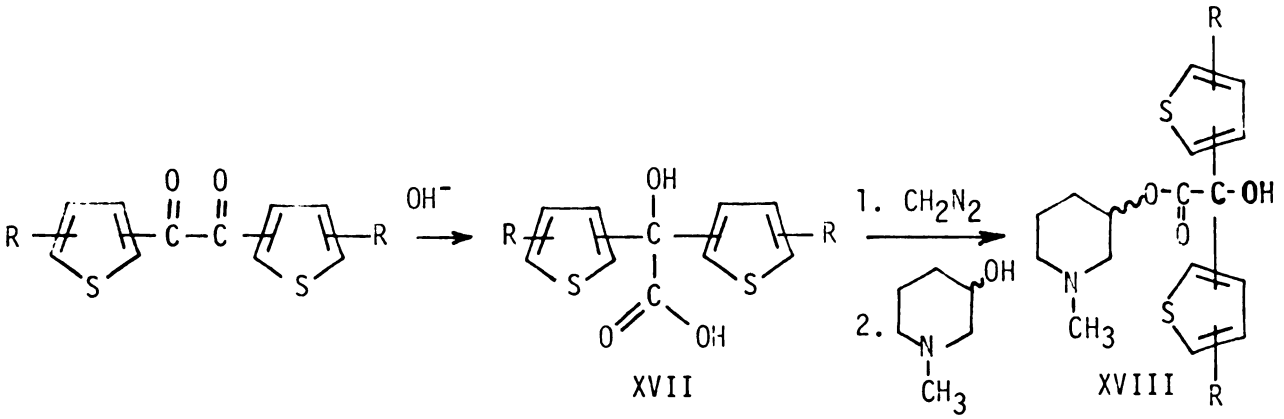
Two of the diketones (VII) and (XV) were prepared by reacting the corresponding thienyllithiums with dimethyl oxalate. One of them (IX) was formed by oxidation of the thenoin prepared by reacting 5-methyl-2-thienylmagnesium iodide with 2-thienylglyoxal. This new reaction appears to have general synthetic utility. The structures of the thenils were confirmed by nmr, infrared and ultraviolet spectroscopy.

Various Thenils Prepared In This Investigation

2,2'-thenil	(IV)	3,3'-thenil	(XI)
5,5'-dimethyl-2,2'-thenil	(V)	2-thienylphenyl diketone	(XII)
5,5'-dichloro-2,2'-thenil	(VI)	5,5'-methoxy-2,2'-thenil	(XIII)
5,5'-difluoro-2,2'-thenil	(VII)	5,5'-isopropoxy-2,2'-thenil	(XIV)
5,5'-di-(2"-thienyl)-2,2'-thenil	(VIII)	5,5'-di-(1"-adamantyl)-2,2'-thenil	(XV)
5-methyl-2,2'-thenil	(IX)	3,3'-benzo[b]thenil	(XVI)
2,2'-benzo[b]thenil	(X)		

Upon treatment with potassium hydroxide, the thenils were rearranged to the thenilic acids (XVII). These acids, which are unstable at room temperature in the solid state, were converted to their methyl esters with diazomethane for characterization and further reaction studies.

Four of the esters, prepared from thenils (IV), (VI), (X) and (XI) were transesterified with N-methyl-3-piperidinol to give dithienyl isosteres of JB 336 (XVIII). These amino esters may have significant anti-cholenergic and psychotomimetic properties (1).



Thenils (XIII) and (XVI) gave anomalous products when rearrangement was attempted. Thenil (XV) proved to be much to insoluble in organic solvents for any further investigations.

The kinetics of the thenil-thenilic acid rearrangement were studied in a 2:1 dioxane:water solution at temperatures of 15-80°.

Rate data are given for compounds (IV) through (XII). The rearrangement of 2,2'-thenil, as determined by the loss in base as a function of time, was second order overall, analogous to the previously established benzilic acid rearrangement (2). The rate of rearrangement of 2,2'-thenil was found to be 12.2 times faster than benzil under the same conditions. This may be attributed to the strong -I effect of the 2-thienyl group (3).

Thermochemical parameters, evaluated from the Arrhenius and Eyring equations were in accord with the Ingold mechanism for the rearrangement (4).

Determinations of the dissociation constants of nine substituted and unsubstituted thenoic acids were made at 49.5° with a glass electrode. A new series of σ values, σ_θ, based on these pK's are suggested for use in correlating reactivities and other physical parameters in Hammett type relationships for thiophene. Improved correlations in the thenil-thenilic acid rearrangement, r=0.994 using σ_θ, vs r=0.923 using σ were noted.

The strong deviations noted in the Hammett plot and the isokinetic plot for the halothenils (VI) and (VII) indicate the existence of an equilibrium step involving the thenil and hydroxide in the rearrangement mechanism. This is in accord with the Ingold mechanism and at variance with the Ott-Clark mechanism (5).

In addition, many new fluorothiophenes were synthesized and long range ring fluorine to side chain nmr couplings were determined.

The previously reported colorations of thienylgylcolic acids in sulfuric acid were shown to be due to the formation of α-carboxy carbonium ions. In particular, the ion generated from 2,2'-thenilic acid and methyl 2,2'-thenilate was studied by nmr and visible spectroscopy (6).

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AN INVESTIGATION OF THE SYNTHESIS AND BASE INDUCED REARRANGEMENT OF SOME DITHIENYL DIKETONES

By

George Peter Nilles

A THESIS

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1970

DEDICATION

To: My Mother and Father who
dont always understand but
who never lose their faith.

ACKNOWLEDGMENTS

The author has on occasions refered to himself, and has been refered to as "The Great Nilles" with tongue-in-cheek agreement. Such a sobriquet implies a status like unto a self sufficient being. In demonstrable refutation, he wishes to list at random those persons who have performed invaluable service to his development. He humbly extends acknowledgment to:

Professor Robert D. Schuetz, major professor, for his constant encouragement, scientific inspiration, and timeless philosophy; and to Professor Edward Leete for two fascinating and instructive years as an undergraduate research assistant; other members of the faculty, and in particular; Professor Andrew Timnick for his friendship and for serving on both of the author's examining committees; Professor Harry Eick for numerous intercessions on the author's behalf both financial and administrative and for serving as a member of the author's guidance committee; Professor William Reusch, also a guidance committee member, for many services and recommendations; Professor Donald Farnum for many kind words when the author was deeply in need of them; and to Professor Matt Zabik, former fellow grad student and future employer, for the loan of various instruments.

Many of the friendships formed here at MSU were probably instrumental in keeping the author from going "over the edge" as it were. He hesitates to name names for fear of overlooking anyone.

Turning the other cheek, the author extends a thank you to those individuals who, by happenstance or whatever, became the sharp shards in the author's path. A callous or two will serve to make future encounters of a like nature more bearable.

He also extends deep appreciation to accounts 11-3653 for financing his research and to 11-3651 for the financing of his existence in the form of teaching assistantships from Sept., 1964 to March, 1970---and of course

to the people who administered them.

In everyone's existence, there are those "deities" who guide the development of what the person is and will be. In the author's case, Henry Miller, Salvador Dali, Robert Burns Woodward, and Bob Dylan, and many others have meant much to him in terms of his *atman*, his own breath of being, and they are rightfully acknowledged.

I didn't know half of you half as well as I should like;
and I like less than half of you half as well as you deserve.

J. R. R. Tolkien

The Lord of the Rings

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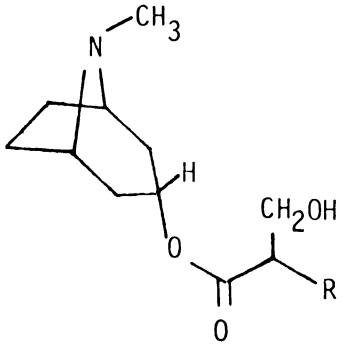
INTRODUCTION AND HISTORICAL

One could justifiably describe Atropa Belladonna L. as quite an eye opener. Courtesans of Louis XIV were wont to apply an effusion of the berries to their conjunctival sacs, thereby relaxing the mydriatic muscles, dilating the pupils, and making the eyes appear more attractive, albeit at the expense of blurred vision (1).

This property of mydriasis is shared by Atropa Belladonna L. (Deadly Nightshade), Hyocyamus Niger L. (Black Henbane), Datura Stramonium L. (Jimson Weed), and many other members of the Solanaceae family. The active principle atropine (I) and atropines levo isomer, hyoscyamine, form about 0.25% of the roots and leaves of the plants.



(I) R= phenyl

(II) R= 2-thienyl

Its striking physiological properties attracted early attention, and as a result, the active principles have been known for some 140 years (2).

Pharmacologically, atropine is classed as an anticholenergic and is most useful clinically as an antispasmodic, affecting all smooth muscle tissue.

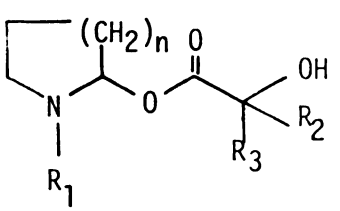
Usually it is given in 0.5 to 2 mg doses to counter the discomfort of peptic ulcer, arterial spasm, postoperative nausea and motion sickness as well as being used extensively as a preanesthetic.

It is, unfortunately, a rather general antispasmodic and its non-specificity in regard to its properties and concomitant side effects, such as mydriasis, bradycardia, urinary retention, and occular hyperbaricity,have led to the medicinal chemist to search for analogs which will retain the desired qualities and reduce or eliminate the side effects.

One of the most obvious variations in structure is isosteric replacement of various noncritical functional groups. Steinkopf (3) succeeded in synthesizing the thienyl atropine (II), although not in sufficient quantity to permit physiological evaluation.

As the study in this area progressed, it was determined that quite extensive changes in the gross structure of the parent atropine molecule could be made while retaining considerable spasmolytic activity.

Biel and Abood (4) have reviewed the structural modifications necessary to elicit anticholenergic and spasmolytic activity from the atropine-like molecules whose basic structure is shown below.



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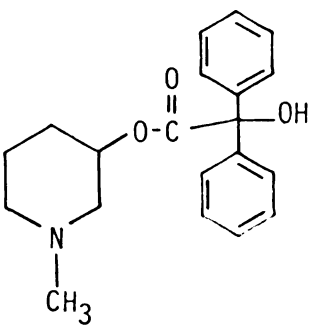


(IV)

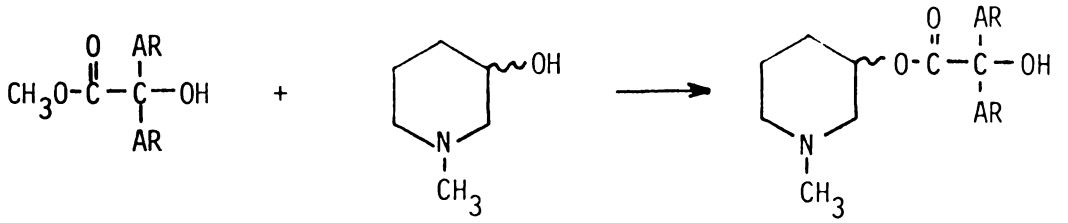
Maximum desired response is obtained when n=1 or 2, R_1=methyl or ethyl, R_2=phenyl, and R_3 is cycloalkyl, phenyl, or 2-thienyl.

Many of these compounds had reached the clinical evaluation stage when it was noted that one of them, designated JB 336 (IV), exhibited potent psychotomimetic activity in humans (5). Hallucinatory manifestations ranged from aberrant interpretation of all sensory stimuli to the illusion of space time regression. While this aspect of the compound limited its usefulness as a spasmolytic, it was quickly recognized that it had the potential to serve as a valuable adjunct in psychotherapy (1,6) analogous to LSD-25.

It was also discovered, by Biel (7) that JB 336 had 0.6 times the activity of atropine against acetylcholine induced spasms in the isolated guinea pig ileum. Isosteric replacement of one of the phenyls by 2-thienyl gave a compound which registered approxiametly three times the activity of JB 336.

Consequently, this property became of interest in these laboratories, and work was directed toward the synthesis of compounds in which both phenyls are replaced by thienyls and substituted thienyls.

The piperidyl esters (VII) are readily prepared (7) by transesterification of 2-hydroxy-2,2-bis(aryl)-acetates (v) with N-methyl-3-piperidinol (VI).



(V) (VI) (VII)

Prior to the initiation of this study only 2-hydroxy-2,2-bis(2'-thienyl)-acetic acid, i.e. 2,2'-thenilic acid and the 3,3'-isomer had been described (8,9).

The acids were reported to be unstable, resinifying in a few hours at room temperature. Esters of these acids were unknown. It was anticipated they should be accessible via the "thenil-thenilic acid" rearrangement, followed by treatment with diazomethane. Thus the problem resolved itself into the preparation of the here-to-fore unknown thenils.

There is certainly no dearth of methods for the preparation of 1,2-diaryl-1,2-diketones. The methods listed below are intended to be illustrative and not exhaustive.

One of the most efficient methods is the direct introduction of the 1,2-diketone function on an appropriately substituted substrate.

1) $R\text{-}I + Ni(CO)_4 \xrightarrow{THF} R\text{-}\underset{\underset{O}{\|}}{C}\text{-}\underset{\underset{O}{\|}}{C}\text{-}R$ ref (10)

2) $RH + Cl\text{-}\underset{\underset{O}{\|}}{C}\text{-}\underset{\underset{O}{\|}}{C}\text{-}Cl \xrightarrow{AlCl_3}$ " ref (11)

3) $R\text{-}Li + CH_3O\underset{\underset{O}{\|}}{C}\underset{\underset{O}{\|}}{C}OCH_3 \longrightarrow$ " ref (12)

Desoxybenzoins may be oxidized to benzils by selenium dioxide in nearly quantitative yield (13). Since desoxybenzoins may be readily prepared by the following routes

4) $R\text{-}\overset{\overset{O}{\|}}{C}H + RCHN_2 \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2R$ ref (14)

5) $R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 + RMgX \longrightarrow$ " ref (15)

6) $R\text{-}C\equiv C\text{-}R \xrightarrow{H_2SO_4/H^+}$ " ref (16)

7) $R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}Cl + RH \xrightarrow{AlCl_3}$ " ref (17)

they could serve as a useful basis for the synthesis of the desired thenils.

Far more general is the simple and efficient oxidation of benzoins to benzils using nitric acid (18), sulfuryl chloride (19), cupric-sulfate-pyridine (20), ammonium nitrate in the presence of Cu^{II} (21), or a stream of oxygen in dimethylsulfoxide (22).

Various procedures have been evolved for the synthesis of benzoins (23).

8) $R\text{-}CCl \xrightarrow[2.\ H_2O]{1.\ Be} R\text{-}C(=O)\text{-}C(OH)(H)\text{-}R$ ref (24)

9) $R\text{-}COH \xrightarrow{\text{"MgI"}}$ " ref (25)

10) $R\text{-}C(OH)(H)\text{-}CONH_2 \xrightarrow{RMgX}$ " ref (23)

11) $R\text{-}C(=O)\text{-}CH(=O) + RH \xrightarrow{AlCl_3}$ " ref (23)

12) $RMgX \xrightarrow[CoCl_2]{CO}$ " ref (26)

13) $R\text{-}CHO \xrightarrow{CN^-}$ " ref (23)

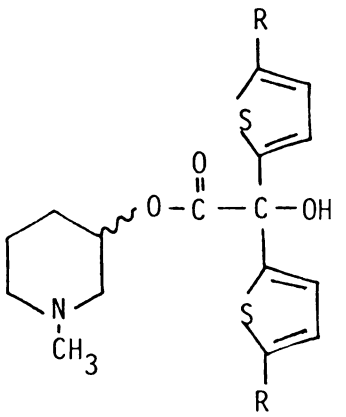
Of these, the most generally applicable is method (13) known as the benzoin condensation. Recently, a somewhat more complex reaction (14) involving the condensation of anils with cyanide has been reported. Mechanistically, it is reminiscent of the benzoin condensation, and furnishes diketanils which may be hydrolyzed to diketones in quite good yield.

14) $AR\text{-}CH(H)\text{=}N\text{-}AR \xrightarrow{CN^-} AR\text{-}C(=N\text{-}AR)\text{-}C(=N\text{-}AR)\text{-}AR \xrightarrow{H^+} AR\text{-}C(=O)\text{-}C(=O)\text{-}AR$ ref (27)

In terms of the thienyl aldehydes, this was largely an unknown area, indeed only 2-thienylcarbaldehyde, 3-thienylcarbaldehyde, and the 2 and 3-thianapthylcarbaldehydes had been shown to undergo the benzoin condensation.

Method (3) for the synthesis of thenils had not been reported at the inception of this work. Method (2) is limited to reactions involving substrates with strongly electron donating substituents. Method (1) was found to be inapplicable to the synthesis of thenils. Therefore, the most direct approach seemed to be to synthesize the thenils via oxidation of the thenoins, and the thenoins via the "thenoin condensation" of the aldehydes with cyanide.

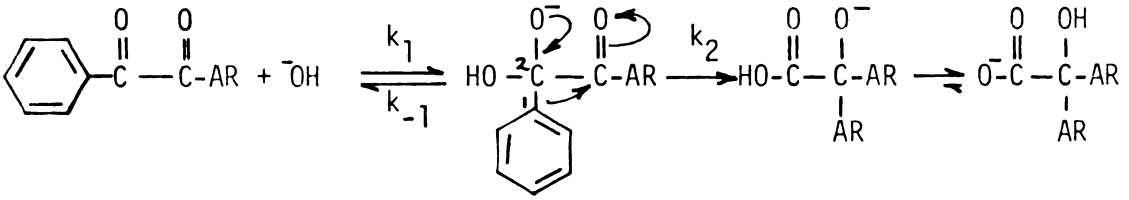
Considerable work has been previously reported in correlating Hammett and Taft sigma parameters in semi empirical equations with structure activity relationships in biological systems (28). An objective of this investigation was to synthesize as many 5,5'-disubstituted piperidyl thenilates (VIII) as possible in order to determine the physiologic response of the substituent.



(VIII)

In addition to being motivated by the possibility of developing some highly useful pharmaceuticals, we were intrigued by the observation that rather scant attention had been paid to substituent effects in the benzilic acid rearrangement.

The discovery of the benzilic acid rearrangement postdated that of the isolation of atropine by five years. Ninety years later, Ingold (29) proposed a mechanism, shown on the next page, which is well supported by more recent mechanistic investigations.



The first step is the rapid and reversible addition of hydroxide ion to one of the carbonyls. This is supported by Urey's findings (30) that benzil exchanges O^{18} from O^{18} enriched water containing sodium hydroxide much faster than it rearranges to benzilate anion. The exchange occurs, although at a slower rate, even in the absence of hydroxide ion. Water is unnecessary for the reaction to occur, as shown by Evans and Dehn (31) who obtained potassium benzilate from potassium hydroxide and benzil in anhydrous ether.

That proton transfer is most likely not involved in the rate determining step was shown by Hine (32) who failed to obtain an isotope effect using sodium deuteroxide in D_2O-dioxane. Indeed, the reaction was 85% faster in D_2O-dioxane than in H_2O-dioxane.

In accordance with Ingold's mechanism, the rate of the reaction should be represented by

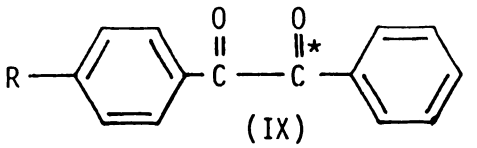
$$\frac{d[OH]}{dt} = \frac{k_1 k_2 [OH][benzil]}{k_{-1}}$$

with the observed rate constant, $k_r = k_1 k_2 / k_{-1}$. Westheimer (33) has shown that the reaction is second order overall, first order in both benzil and hydroxide.

Pfeil et al. (34) have reported half lives for the reaction of benzil, 4,4'-dichlorobenzil, and 4,4'-dimethylbenzil with various bases. They found that dichlorobenzil rearranges faster than benzil, which in turn rearranges faster than dimethylbenzil. This is in accord with the postulate that electron withdrawing groups should increase k_1, by making C-2 more positive, and k_2 by stabilizing the developing negative character at C-1, increasing the electrophilicity of the migration terminus, and weakening the C-1 to C-2 bond.

If these statements are valid, they may gain support by observing the rate of rearrangement of bis substituted compounds and determining if a Hammett correlation holds according to the following equation: $\log k/k_o = 2\sigma\rho$ where k is the observed rate constant of the rearrangement of the substituted compound, k_o is the rate constant for the rearrangement of the unsubstituted compound, σ is the log of the ratio of some other physical parameter of the substituted vs the unsubstitited compound of similar structure, e.g. ionization constants of the corresponding acids, and ρ is the slope of the linear relationship indicative of the electron demand of the transition state. If both substituents affect the rate of the rearrangement, σ would be doubled to obtain the required relationship. That both substituents have an effect on the activation energy may be determined from the observation of the rate of rearrangement of a mono substituted compound.

An alternate hypothesis to the Ingold mechanism has been postulated by two laboratories (35, 36). These authors propose that hydroxide attack and rearrangement occur as a concerted process. That is to say, the established (30) equilibrium between hydroxide and benzil plays no role in the mechanism, but occurs only as a side reaction, although at a rate greater than the rearrangement. They base their view on the fact that in singley labeled benzils such as (IX) in which one carbonyl is C^{14}, the relative migratory



(IX)

aptitude of the substituted vs nonsubstituted ring gave, after correction for a small isotope effect, a linear $\sigma\rho$ plot.

Thus one goal of the present study was to search for evidence that the equilibrium between the diketone and hydroxide is a discrete step in the rearrangement mechanism.

One additional factor must be reckoned with, namely the nature of the ortho effect of the heterocyclic sulfur. One may take three approaches to the effects of an ortho substituent. Most experimenters have simply ignored any errors that result in using Hammett σ constants in substituted thienyl (or other heterocyclic) systems. There is a tendency to do this in view of the fact that thiophene is a rigid aromatic system, thereby eliminating steric perturbations and field effects on σ. However, resonance and inductive effects would not be expected to be linearly correlated in both thiophene and benzene. This can lead to scatter in some Hammett plots that use sigma based on the ionization constants of benzoic acid.

A second approach is to make use of a modified Hammett equation (37-39) of the type

$$\log \frac{k}{k_o} = c_i + \rho \sum_i a_i \sigma_i$$

where a_i and c_i may be constants used to best fit the plot to a linear relationship and may usually be ascribed to steric effects (Taft equation) and Σ is the summation of the σ values of the individual contributing substituents.

A third alternative ignores all previous computed values and instead returns to the original definition of the Hammett equation: $\log \frac{k}{k_o} = \sigma\rho$ but uses a different base for computing sigma. Thus, an appropriate base for the thienyl system might be the log of the ratio of the ionization constants of the thenoic acids rather than the benzoic acids. Automatically, this would be expected to take in all effects on the substituents arising from the substrate whether from inductive, resonance, steric or field effects. The possibility existed that a simple relationship between these σ_θ values and σ might be found. This would extend the usefulness of the large compilation of constants already evaluated for benzene and increase the accuracy

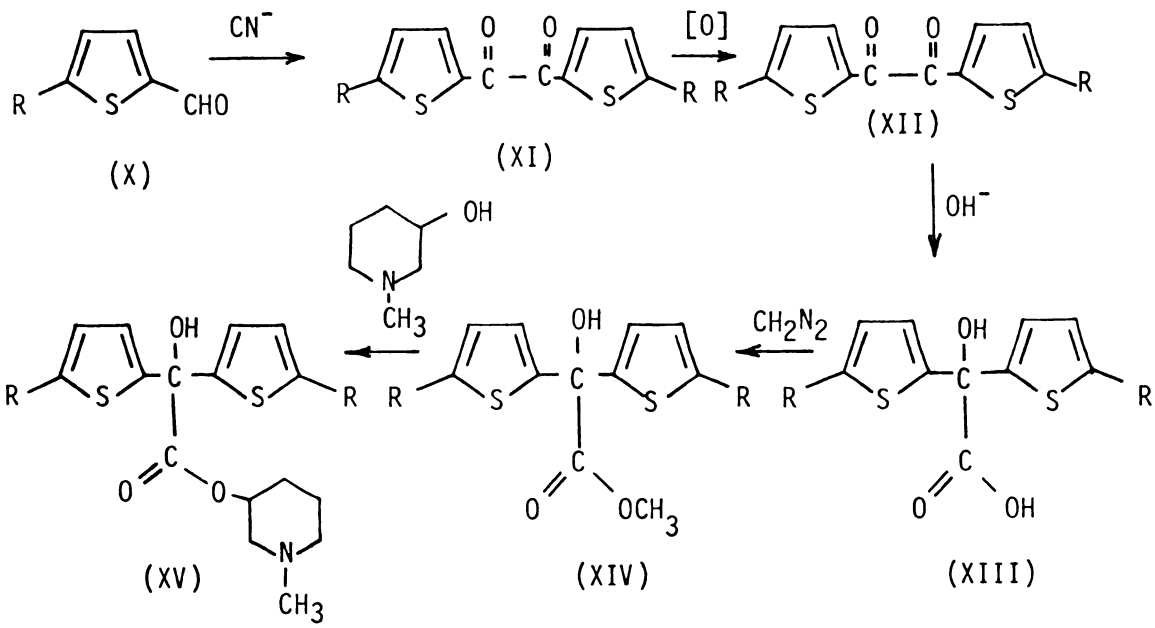
of predicting physical parameters for the thiophene ring.

It was a purpose of the present work to investigate such a possibility in regard to the thenil-thenilic acid rearrangement, dispite the complexity of the reaction and the uncertainty in the mechanism.

In summary, the purpose of the present investigation was: to synthesize and describe the properties of a number of thienyl isosteres of JB 336 as gastrointestinal antispasmodics and potential psychopharmaceuticals; to investigate qualitatively the substituent effect in regard to the application of the benzoin condensation to some thienyl aldehydes; to explore the substituent effect in synthetic, kinetic, and thermodynamic aspects of the benzilic acid rearrangement as applied to bis(thienyl)-1,2-diketones (thenils); to determine quantitative differences, if any, in substituent effects in thiophene vs benzene; and to attempt a quantitative evaluation of the nature of the 2-thienyl group as a substituent. In addition, several serendipitous observations were uncovered and will be fully described in the discussion section of this work.

DISCUSSION, PART I: SYNTHETIC EXPLORATIONS

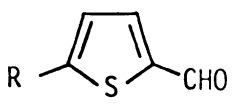
It was the choice of the most suitable substituents that guided the overall design of this phase of the research. There were two points in the total synthesis scheme where consideration of the substituents was of paramount importance. The first was the thenil-thenilic acid rearrangement, i.e. (XII) to (XIII) in which a major share of the total endeavor was concerned with the substituent effect. The second point of concern was the very last product in the synthetic sequence, namely the piperidyl thenilates (XV). Substituents had to be chosen which could possibly enhance the desired physiologic properties of the parent molecule.



It was envisioned that all of the desired thenils could be prepared by the synthetic sequence outlined above.

The unsymmetrical thenoins (XI) should be accessible by cocondensation of an equimolar mixture of the two appropriate aldehydes, since it has been shown that this process usually results in the formation of only one of the four possible products (23, 40).

Since the first objective in the thenoin condensation study was the synthesis of the aldehydes, the substituent problem had to be resolved at this point. For a monosubstituted thiophene aldehyde, there are six positional isomers possible.



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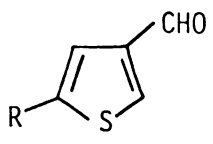

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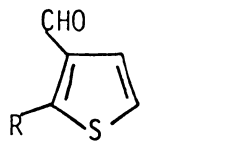

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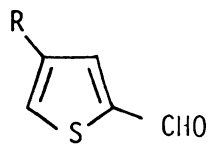
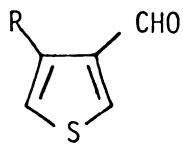
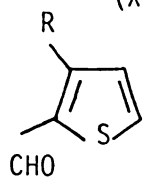


(XIX)

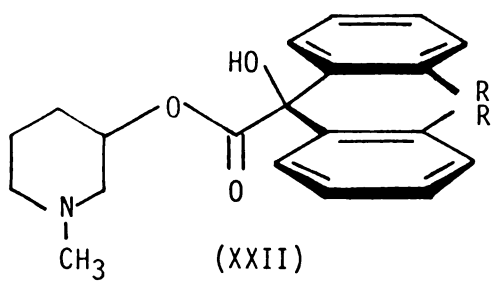


(XX)



(XXI)

From a pharmacologic viewpoint, aldehydes (XVIII), (XX), and (XXI) are undesireable, since it has been shown that in the piperidyl benzilates, activity decreases when the benzene rings are substituted in such a manner that reduces their freedom to achieve a coplaner conformation (41), as in (XXII).



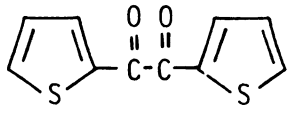
(XXII)

In addition, the proximity of the ring substituent to the aldehyde function would later introduce an obfuscating steric effect in the Hammett studies.

Furthermore all of the aldehydes except (XVI) are inordinately difficult to synthesize, indeed most of them are unknown. Thus, only 5-substituted-2-thenaldehydes were deemed best suited to the present investigation.

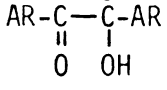
The choice of substituents was further restricted to those which would survive the strongly basic conditions of the thenilic acid rearrangement. A more meaningful comparison of substituent effects in thiophene vs benzene would only be arrived at by evaluations on both the positive and negative side of the sigma scale using groups having accurately established primary sigma values. For these reasons, the final choices for substituents were reduced to methyl, methoxy, chloro, fluoro, benzo[b], phenoxy, and nitro in order to achieve as wide a range of electromeric effects as possible. In addition, three other functions were selected; the 1-adamantyl group since its substituent constant had not been previously determined and because of its desirable pharmacologic properties; the 2-thienyl group which would give an experimental measure of the electron density at the 2-position of the thiophene ring; and the trifluoromethyl group, of interest since its substituent effect is probably purely inductive.

The most convenient and efficient method for the preparation of most of the thiophene aldehydes was found to be by Vilsmeier formylation. Fortunately, electrophilic attack on 2-substituted thiophenes normally gives rise to considerable 2,5-disubstitution regardless of the nature of the directing group. Indeed, for all but -I-M substituents, the 2,5-product is the only one obtained (42). Based on this rather general procedure, the synthesis of each aldehyde, thenoin, and thenil was undertaken.

Synthesis of 2,2'-thenil  (XXIII)

Thiophene was reacted with phosphorus oxychloride and dimethylformamide to obtain a good yield of 2-thenaldehyde. The aldehyde was condensed with itself in the presence of potassium cyanide to give the known thenoin (8). Since it is known (23) that traces of impurities inhibit the benzoin condensation, an excess of cyanide was used rather than the usual catalytic amount. It was also observed that the reflux time of the reaction is rather critical, being about 15 minutes. Shorter reflux time results in considerable unreacted starting material, while longer reaction times result in much tar formation.

The typical intense color formation observed during the benzoin condensation was noted for the thenoin condensation as well. The reaction of 2-thenaldehyde and potassium cyanide in ethanol-water produces a deep emerald green color. Such behavior has been ascribed (43) to radical formation of the type shown in (XXIV).



(XXIV)

The green color of 2,2'-thenoin in ethanolic sodium hydroxide is rapidly discharged upon shaking in air or acidification. The color persists just long enough for the visible spectrum of the solution to be determined. Absorption maxima were recorded at 558, 604, and 655 nm as well as a broad band beginning at 720 nm to beyond the limits of the instrument as shown in Figure 1, on page 15. It must also be considered that the color of the solution may be due to the presence of ion (XXV) or to a hypothetical complex between the thenoin and the thenil.

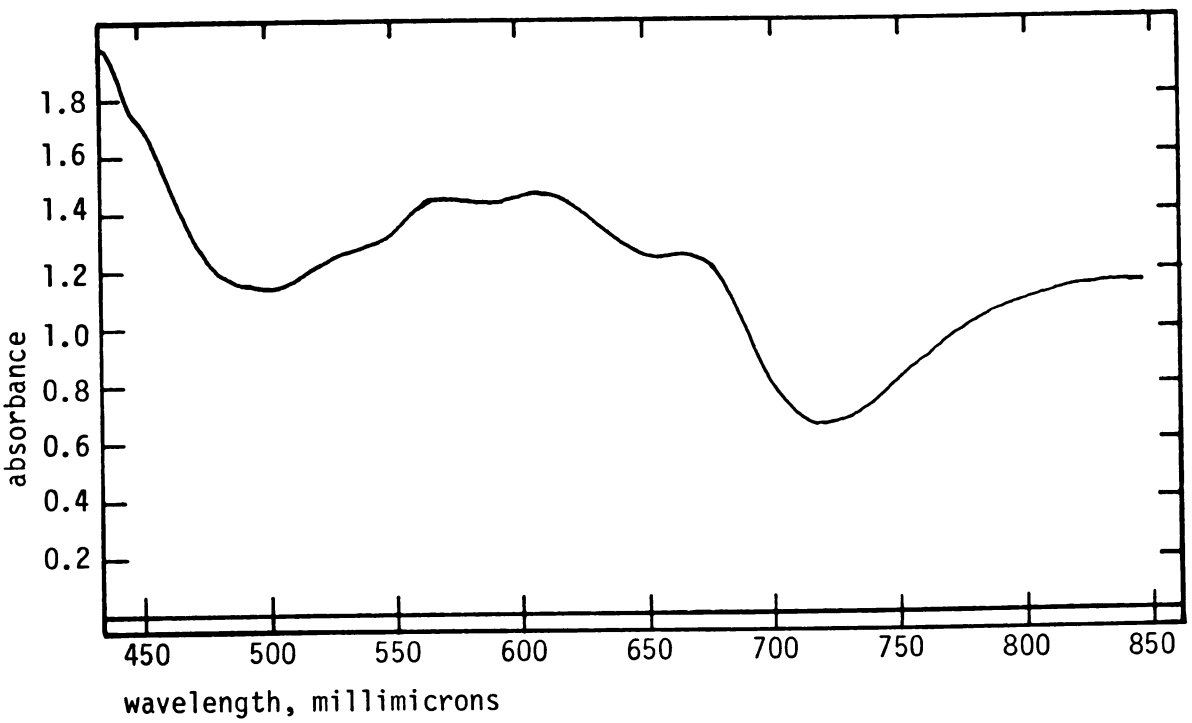
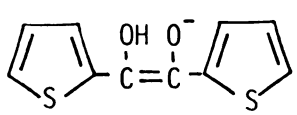


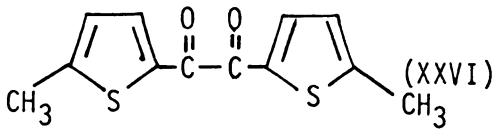
Figure 1. Visible spectrum of an ethanolic solution of sodium hydroxide and 2,2'-thenoin.



(XXV)

These colors were noted for the other thienyl aldehydes upon reaction with cyanide in nonaqueous media as well. Indeed, formation of color was used as a convenient sign indicating whether or not the desired condensation was occuring.

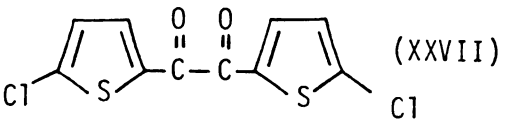
The best reagent for the oxidation of 2,2'-thenoin to 2,2'-thenil was iodine and sodium methoxide in methanol. The success of the method depends on the skill of the experimenter since the iodine must be added and the reaction mixture quenched as rapidly as possible. Delay causes considerable tar to form, presumably by reaction of the thenil with sodium methoxide (44). In this manner, 2,2'-thenil was obtained in 20% yield from thiophene.

Synthesis of 5,5'-dimethyl-2,2'-thenil  (XXVI)

The starting material, 2-methylthiophene,was prepared by Huang-Minlon reduction of 2-thenaldehyde. Vilsmeier formylation of 2-methylthiophene gave the known 5-methyl-2-thenaldehyde (45). All attempts to prepare 5,5'-dimethyl-2,2'-thenoin by conventional thenoin condensation conditions in ethanol-water failed.

It should be pointed out that only sodium and potassium cyanide are readily effective in catalyzing the benzoin condensation (23), therefore recourse to other cyanides was not attempted.

However, the characteristic deep green coloration of the condensation developed at room temperature using dimethyl sulfoxide as the reaction medium. Unfortunately, only intractable tar resulted when this mixture was quenched with water. The tar apparently contains some amounts of the thenoin, since oxidation of it with the cupric sulfate-pyridine complex gave 5,5'-dimethyl-2,2'-thenil in a 29% yield based on the starting aldehyde. This represents a 20% overall yield from thiophene.

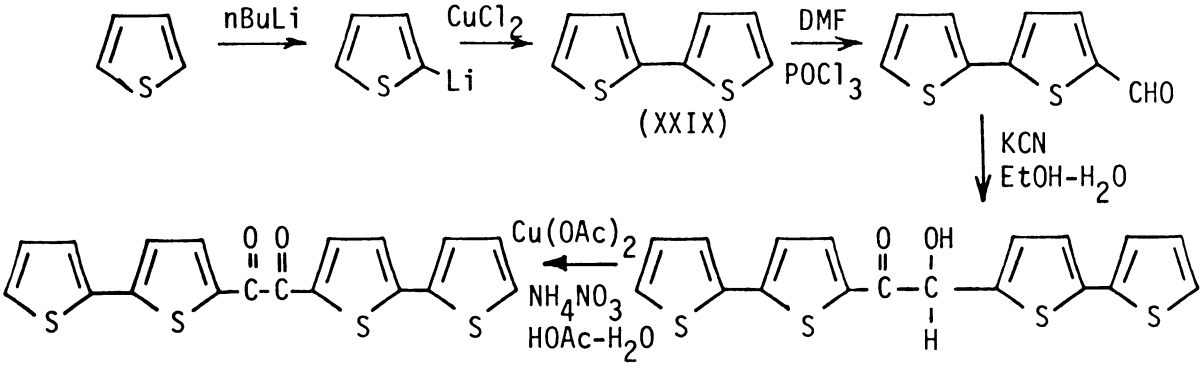
Synthesis of 5,5'-dichloro-2,2'-thenil  (XXVII)

Fortunately, 2-chlorothiophene is one of the more reasonably priced commercially available thiophenes. It was formylated smoothly by reaction with phosphorus oxychloride and dimethylformamide. Like 5-methyl-2-thenaldehyde, however, 5-chloro-2-thenaldehyde fails to give an isolable thenoin upon treatment with cyanide. When the condensation was carried out in tetrahydrofuran containing 2% dimethyl sulfoxide, an intense prussian blue color was produced.

Neutralization of this solution with acetic acid, followed by oxidation with cupric sulfate-pyridine gave the desired thenil in 26% yield based on 2-chlorothiophene.

Synthesis of 5,5'-di-(2"-thienyl)-2,2'-thenil (XXVIII)

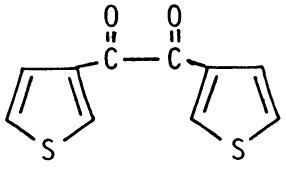
This compound has been described previously (46). The starting aldehyde is readily prepared by the Vilsmeier formylation of 2,2'-bithienyl(47) (XXIX). The later is prepared by the cupric chloride catalyzed coupling of 2-lithiothiophene (48).



(XVIII)

The aldehyde undergoes the thenoin condensation and may be easily isolated. Weiss (49) discovered the facile oxidation of α-hydroxyketones to 1,2-diketones using Cu^{II} in the presence of ammonium nitrate as the secondary oxidant. Aqueous acetic acid is the usual solvent and yields range from 80% to quantitative. Employing this method in the synthesis of 5,5'-di-(2"-thienyl)-2,2'-thenil gave the desired product in a 35% overall yield based on thiophene.

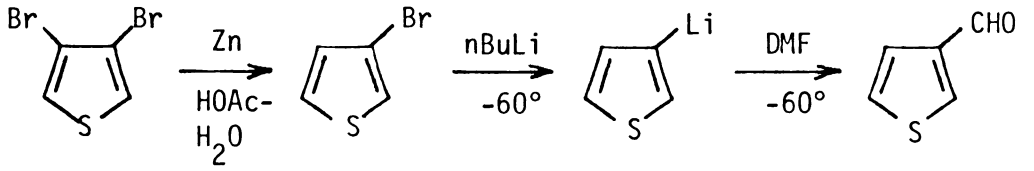
Synthesis of 3,3'-thenil



(XXX)

The strong preference for electrophilic attack at the 2-position vs the 3-position in thiophene has been long established experimentally and recently supported by SCF calculations (50).

The cumbersome Sommelet synthesis via 3-methylthiophene to 3-thenylbromide to the hexamethylenetetramine salt to 3-thenaldehyde (51) has been superseded by the general method shown below.



Normally, 3-bromothiophene is prepared by tetrabrominating thiophene with elemental bromine followed by reduction with zinc dust in acetic acid (52). This results in a 3:2 mole ratio mixture of 3-bromothiophene and 3,4-dibromothiophene. In the present work, a good yield of 3-bromothiophene was obtained from 3,4-dibromothiophene, available from previous thiophene studies in these laboratories, by prolonged reflux in aqueous acetic acid with intermittent addition of zinc dust.

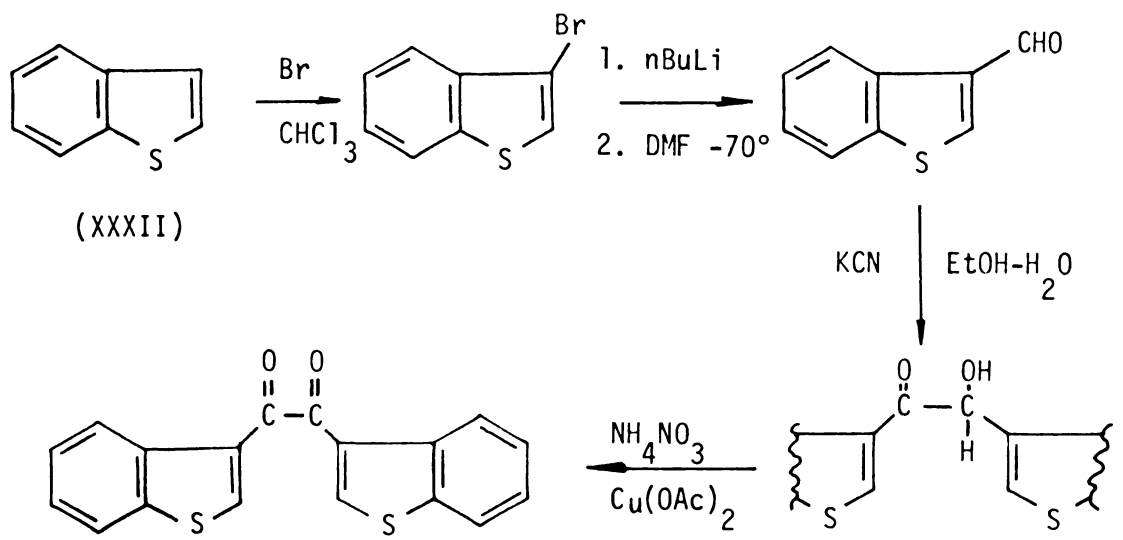
It was known that 3-lithiothiophene must be prepared at -60° or lower. At higher temperatures, rapid transmetalation occurs to give 2-lithiothiophene. The bromothiophenes do not metalate directly, but they may be formed by transmetalation with n-butyllithium. Gronowitz' procedure (53) gave the aldehyde as shown above. The aldehyde was reacted with potassium cyanide as before to give the known thenoin (54). It was easily oxidized to the reported (9) 3,3'-thenil in 18% overall yield based on 3,4-dibromothiophene.

Synthesis of 3,3'-benzo[b]thenil (XXXI)

Electrophilic attack on thianapthene (XXXII) occurs at the 3-position.

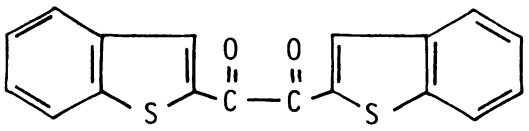
This is in accord with a large body of experimental evidence and recent SCF calculations which show that the highest π-electron density is at the 3-position (50). While Vilsmeier formylation does give 3-thianapthaldehyde (55), the low yield, 9%, prompted the use of a new synthesis. Campaigne prepared the aldehyde in 48% yield via the Sommelet reaction sequence (56). The method illustrated below gave the aldehyde in 55% yield from thianapthene. While this work was in progress, this synthesis was reported (57).

Despite numerous attempts, the condensation of 3-thianapthaldehyde with cyanide gave yields that were 15-20% of theory compared to the 73% yield reported by Campaigne (56). The oxidation of the 3,3'-benzo[b]thenoin to 3,3'-benzo[b]thenil went smoothly, however, using the cupric acetate-ammonium nitrate method. The melting point of the product did not agree with that reported.

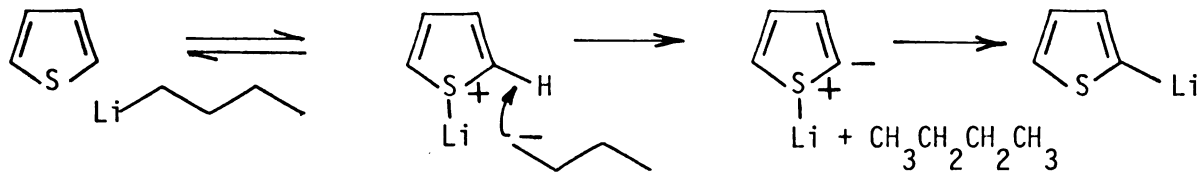


Infrared evidence showed the carbonyl absorbance at 1640 cm^{-1}, typical of 1,2-diaryl-1,2-diketones. The mass spectrum gave a parent peak at m/e 322 (22%), calculated for 3,3'-benzo[b]thenil, 322. As expected, the molecule underwent cleavage through the two acyl groups to give a peak at m/e 161 (100%) which in turn gave the decarbonylated signal at m/e 133 (29%).

Thus the structure was confirmed and the thenil was realized in a 7.7% overall yield from thianapthene (XXXII).

Synthesis of 2,2'-benzo[b]thenil  (XXXIII)

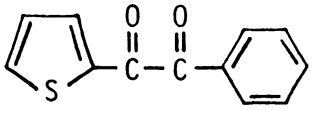
The direct metalation of thianapthene with alkyl lithiums gives 2-substitution. This is expected since the C-2 hydrogen is more acidic than the C-3 hydrogen. However, this quick rational is somewhat too naive, since it does not explain the lithiation of thiophene in the 2-position, in which the C-3 hydrogen is more acidic than the C-2. A deeper look at the metalation process (58) is shown schematically below.



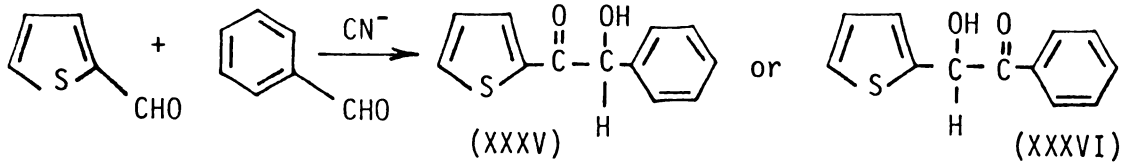
The first step is the coordination of the lithium with the thiophene sulfur. Secondly, the C-2 hydrogen is removed by attack of the alkyl carbanion, a process whose equilibrium lies far to the right since the estimated difference in pK values between butane and thiophene is about 10. Lastly, tautomeric shift of the lithium to the 2-position occurs.

Accordingly, thianapthene was lithiated and treated with dimethylformamide to give 2-thianapthaldehyde. The difference in ease with which 2-thianapthaldehyde undergoes the thenoin condensation is remarkable compared to 3-thianapthaldehyde. An 85% yield of the known (59) 2,2'-benzo[b]thenoin was realized after 20 minutes of reflux in ethanol-water-cyanide. It will be recalled that 3-thianapthaldehyde gave only about 20% yield of the thenoin in the same length of time. Yields of about 50% were obtained from 2-thenaldehyde and 3-thenaldehyde in the thenoin condensation.

Once again, the ammonium nitrate-cupric acetate oxidation was used to give an excellent yield of the previously unknown 2,2'-benzo[b]thenil. The overall yield of the diketone was 57% based on thianapthene.

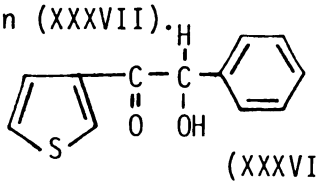
Synthesis of 2-thienylphenyl diketone  (XXXIV)

The mixed benzoin condensation between 2-thenaldehyde and benzaldehyde could result in two possible products.



(XXXV) (XXXVI)

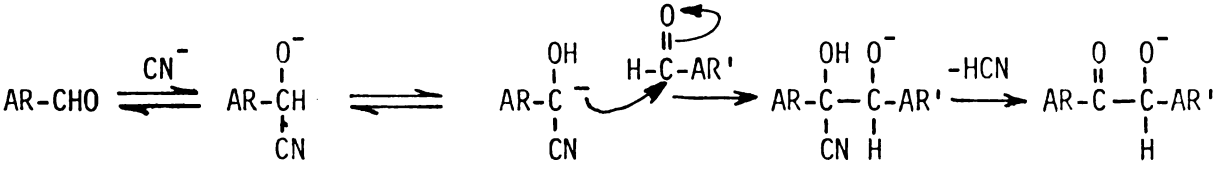
In practice only one product is isolated, although in the earlier report of this compound (7) the structure was not determined. Campaigne and Bourgeois have shown (9) that the condensation of 3-thenaldehyde with benzaldehyde gives the mixed benzoin (XXXVII).



(XXXVII)

This was shown by the conversion of the benzoin to its oxime, followed by Beckmann rearrangement to give benzaldehyde and 3-cyanothiophene.

Naively,it might be assumed that 2-thenaldehyde and benzaldehyde should give the benzoin (XXXV). It is difficult to rationalize this conclusion from the proposed mechanism for the condensation (23).



(XXXVIII)

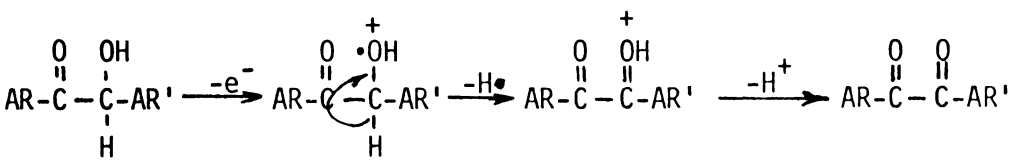
The cyanide ion should initially attack the most highly unsaturated carbonyl.

Both 2-thenaldehyde and 3-thenaldehyde have carbonyl absorptions in the infrared about 40 cm^{-1} lower energy than benzaldehyde, 1670 cm^{-1} for the former thiophene compounds and 1710 cm^{-1} for benzaldehyde. Therefore, the cyanide ion would be expected to attack the benzaldehyde carbonyl preferentially and benzoin (XXXVI) should be formed.

However, since the benzoin condensation takes place in a slightly basic milieu, it is reasonable to assume that ion (XXXVIII) can tautomerize to the structure in which the carbonyl is adjacent to the more electron donating aromatic center thus increasing the conjugation path of any electron donating substituent. Since thienyl appears to be a better electron donor than phenyl (60) (more saturated carbonyl) it is likely that the initially formed ion tautomerizes to give benzoin (XXXV).

A firmer basis for the structure of the benzoin was sought. Ideally, the mass spectrum might reveal the difference in the two proposed structures if cleavage occurred as shown.

The mass spectrum of the mixed benzoin failed to show a parent peak at m/e 218, but did give rise to a very weak P-2 signal at m/e 216 (5%), shown in Figure 2, page 23. The signals at m/e 111 (55%), m/e 105 (100%) and the absence of a parent peak indicate that the molecule probably oxidizes as shown upon electron impact.



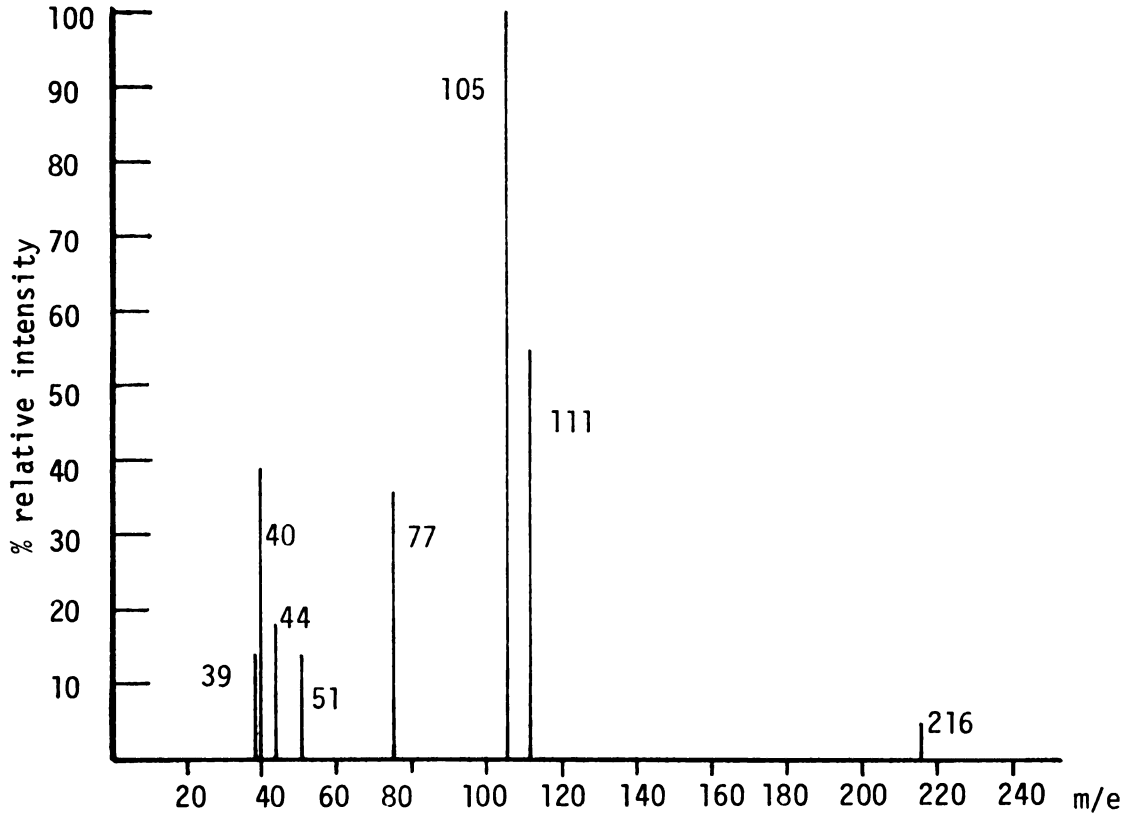


Figure 2. Mass spectrum of compound (XXXV)

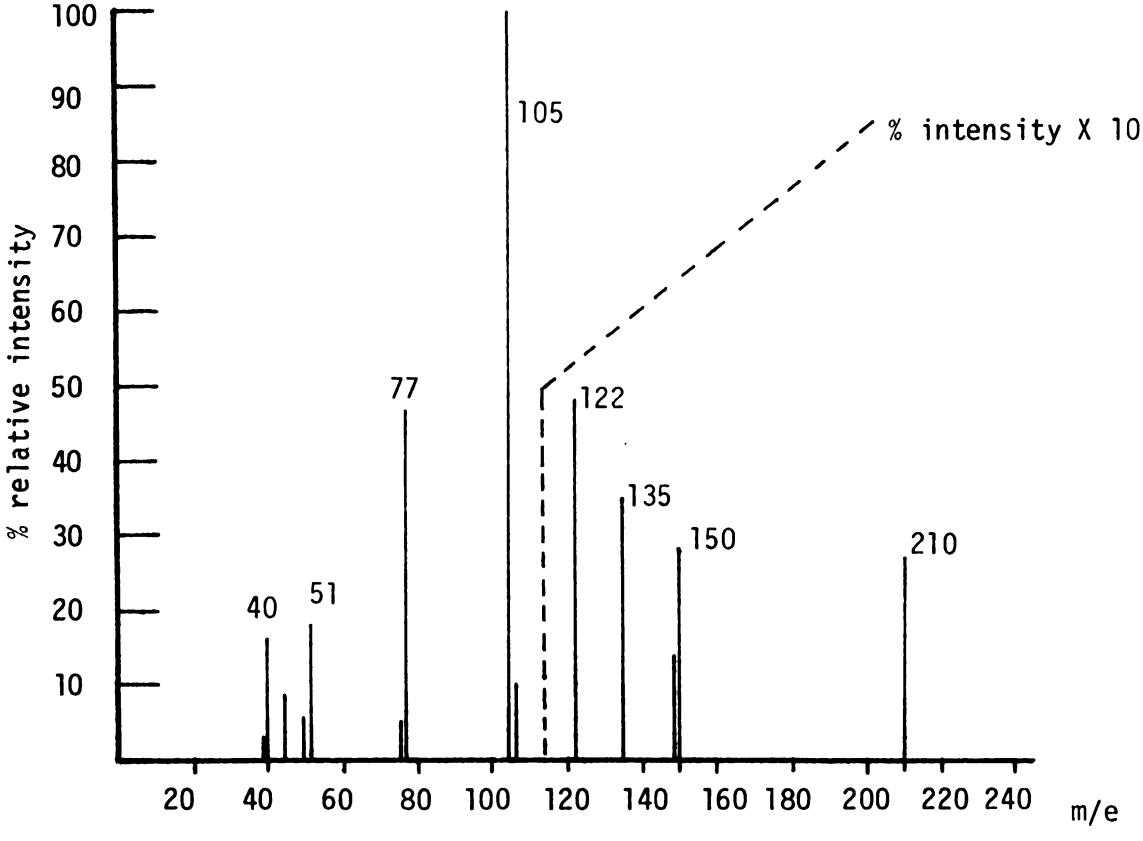


Figure 3. Mass spectrum of benzoin

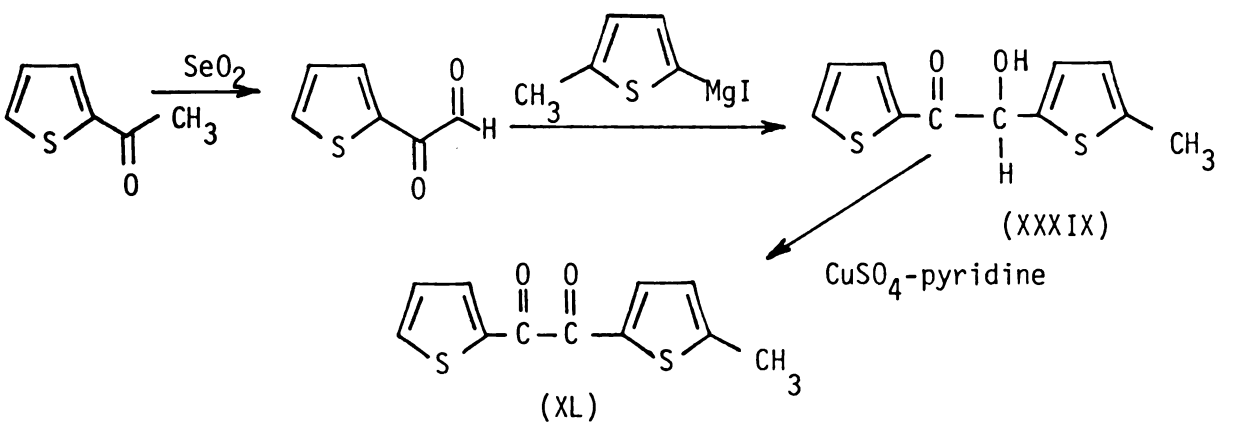
No precedent exists for this in the literature since the mass spectra of benzoins have apparently been neglected. A determination of the mass spectrum of benzoin in these laboratories reveals the same behavior as the mixed benzoin (XXXV); it showed no parent and only a very weak P-2 peak at m/e 210 .

The structure of the mixed benzoin was finally elucidated by its unambiguous synthesis. The reaction of 2-thienylglyoxal with phenylmagnesium iodide gave compound (XXXV). Compound (XXXV) proved to be identical with the benzoin resulting from the condensation of 2-thenaldehyde with benzaldehyde by melting point, mixed melting point, and infrared spectrum. In terms of the of synthesis of the thenil, it didn't matter, of course, which benzoin had been obtained.

Oxidation with ammonium nitrate-cupric acetate gave the known (7) 2-thienylphenyl diketone in 51% overall yield from 2-thenaldehyde.

Synthesis of 5-methyl-2,2'-thenil (XL)

Several attempts were made to condense 2-thenaldehyde with 5-methyl-2-thenaldehyde. The procedure used in the synthesis of 5,5'-dimethyl-2,2'-thenil and 5,5'-dichloro-2,2'-thenil also failed to give the desired product. It was obtained by the application of the new procedure illustrated.

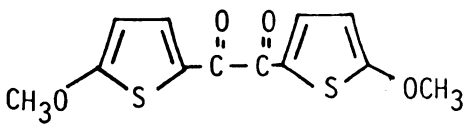


Selenium dioxide oxidation of 2-acetylthiophene gave 2-thienylglyoxal (61). Although 5-methyl-2-iodothiophene had been previously prepared by Steinkopf (62), by treating 2-thienylmercuric chloride with potassium triiodide, it was far more convenient to prepare it by treating 2-methylthiophene with mercuric oxide and iodine analogous to the method described for 2-iodothiophene (63).

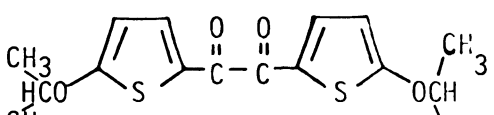
A thorough search of the literature failed to reveal the reaction of arylglyoxals with Grignard reagents, although the reaction of arylglyoxilic acids with Grignards to give arylglycolic acids has received considerable attention (9). It appeared reasonable to assume that the more sterically accessible and more highly unsaturated aldehyde carbonyl might react selectively with a Grignard to give the desired thenoin. Indeed, addition of 5-methylmagnesium iodide to a solution of 2-thienylglyoxal at -50° gave an immediate reaction with formation of a brick red adduct. Workup with ammonium chloride gave a rather poor but practical yield of 37% of the needed thenoin (XXXIX). The structure proof rested on the subsequent oxidation of this material to 5-methyl-2,2'-thenil (XL) in 75% yield by the cupric sulfate-pyridine method.

This Grignard reaction with arylglyoxals should be quite general in scope although no attempt was made to test it further or to find optimum conditions. It has been previously mentioned that phenylmagnesium iodide reacts with 2-thienylglyoxal to give benzoin (XXXV) in 21% yield.

Synthesis of 5,5'-dimethoxy-2,2'-thenil and 5,5'-diisopropoxy-2,2'-thenil



(XLI)



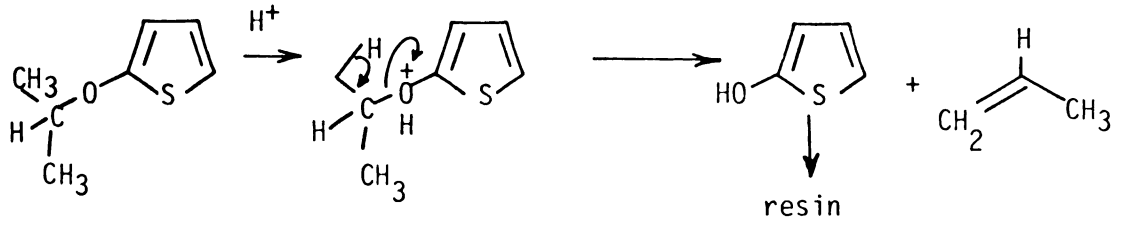
(XLII)

The alkoxythiophenes are readily obtained by displacement of a thienyl halide with alkoxide ion (64, 65). The prefered method for the preparation of 2-iodothiophene is by oxidative iodination using iodic acid and iodine. In this manner, a quantitative yield of 2-iodothiophene may be realized (66).

The synthesis of 5-methoxy-2-thenaldehyde has been reported (64). The heretofore unknown 2-isopropoxythiophene was prepared in poor yield by Sice's method (64). A solution of sodium isopropoxide in isopropanol was refluxed 30 hours with 2-iodothiophene and cupric oxide to obtain an 11% yield of the ether. The ether forms a azeotrope with unreacted 2-iodothiophene and the mixture had to be grignardized to remove the halide.

Previous studies (11) have shown that oxalyl chloride can be utilized to give benzils via a double Friedel-Crafts acylation. The method is restricted to aryl rings bearing strongly electron donating substituents such as alkoxy or tert-amino. Less reactive aromatic systems require more vigorous conditions under which oxalyl chloride decarbonylates to phosgene, especially in the presence of lewis acids. This results in the formation of diarylmonoketones.

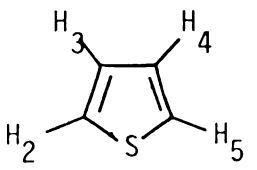
In the present investigation, the alkoxythenils were formed by reaction of the appropriate alkoxythiophene with oxalyl chloride in carbon disulfide at 0° using stannic chloride at the catalyst. While the yield is not good, 33% for the 5,5'-dimethoxy compound, it was particularly bad, 17%, for the 5,5'-diisopropoxy thenil.The latter molecule suffers from severe degradation during the acylation probably of the type shown.



Indeed, 2-tertbutoxythiophene and a trace of acid give an excellant yield of the highly unstable 2-hydroxythiophene (67).

It was necessary to exclude the very slight chance that oxalylation had occurred at the 3-position rather than at position 5 in either or both rings.

Gronowitz has shown (68) that the nmr coupling constants for some 65 di-substituted thiophenes fall in the range shown below.



J_{2-3} = 4.90-5.80 Hz

J_{2-4} = 1.25-1.70 Hz

J_{2-5} = 3.20-3.65 Hz

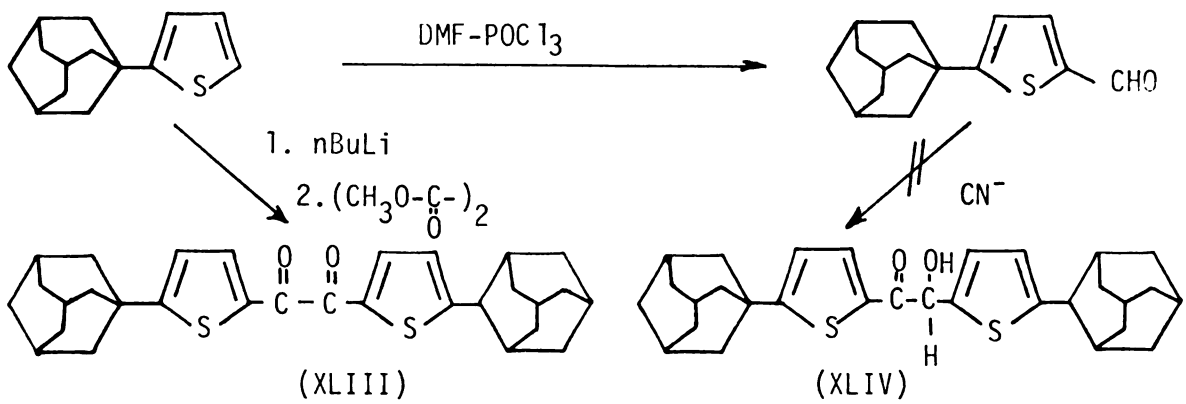
J_{3-4} = 3.45- 4.35 Hz

The coupling constant in 5,5'-dimethoxy-2,2'-thenil was determined to be 4.4 ± 0.2 Hz. This indicates 2,5-substitution but does not firmly exclude 2,3-substitution.

Oxidation of the molecule should give the known 5-methoxy-2-thenoic acid. The thenil turned out to be surprisingly resistant to all common oxidizing agents. It was recovered unchanged after treatment with refluxing potassium permanganate, or aqueous periodic acid at 90° for two hours. Likewise chromium trioxide in acetic acid at room temperature for 30 minutes had no effect. It was completely destroyed (no aromatic protons in the nmr) by 90% hydrogen peroxide for 30 minutes. Finally upon reaction with sodium cyanide and ammonium chloride (21, 70) followed by reflux with aqueous sodium hydroxide and acidification, 5-methoxy-2-thenoic acid was obtained. The identity of the cleavage product was confirmed by comparison of the melting point and infrared spectra to that of an authentic sample of the acid. Thus the thenil prepared was the desired one. Further characterization of 5,5'-diisopropoxy-2,2'-thenil was not attempted.

Synthesis of 5,5'-di-(1"-adamantyl)-2,2'-thenil (XLIII) and 5,5'-difluoro-2,2'-thenil (L)

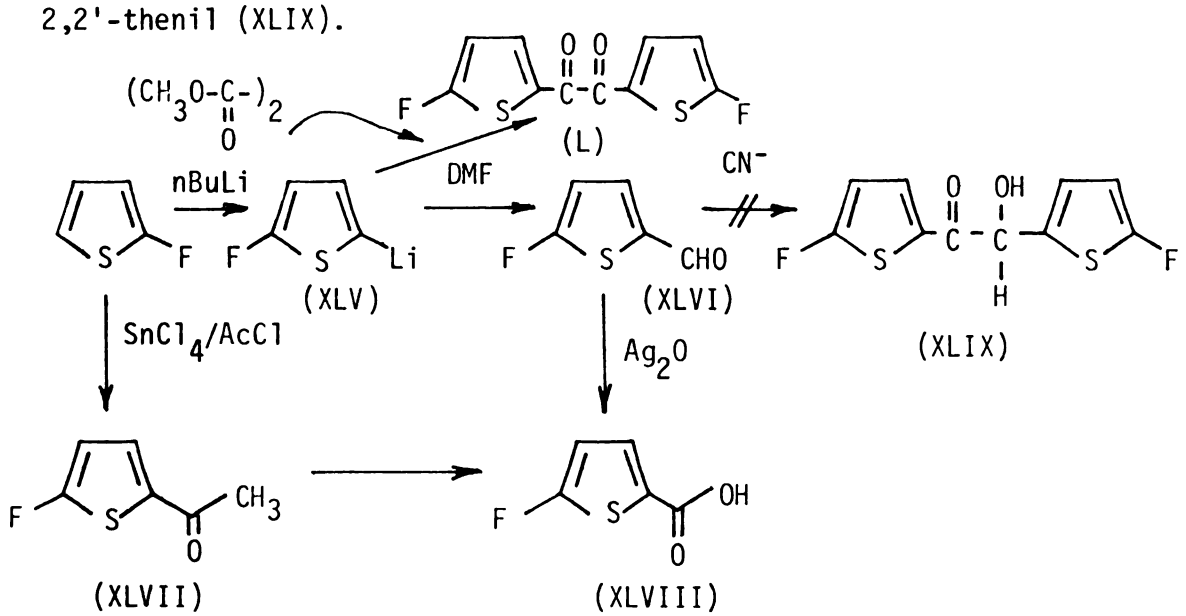
The adamantylation of thiophene by 1-bromoadamantane and stannic chloride produces both 2- and 3-(1'-adamantyl)-thiophene in a 2:1 mole ratio respectively. Selective chloromercuration serves to separate the two isomers and the chloromercuri function is readily removed by refluxing hydrochloric acid.



(XLIII) (XLIV)

Vilsmeier formylation gave the aldehyde shown (71) for which no set of reaction conditions could be found that would give the desired thenoin (XLIV).

A similar situation occurred in the attempted synthesis of 5,5'-difluoro-2,2'-thenil (XLIX).



(XLV) (XLVI) (XLIX)

(XLVII) (XLVIII)

The previously unknown 5-fluoro-2-thenaldehyde was prepared as illustrated on the previous page. An attempted thenoin condensation of the aldehyde gave only intractable tar under all of the earlier sucessful reaction conditions for the other thenoins.

A brief digression at this point will be made to consider some new fluorothiophene chemistry. Despite the ready availability of 2-fluorothiophene (72, 73), its chemical reactivity has not been reported. It was found that fluorine is more electron withdrawing in thiophene than in benzene, cf p 55.Consequently, it became of interest to determine the position of electrophilic substitution in this molecule.

The lithiation of 2-fluorothiophene proceeded with facility. The lithium salt was reacted with dimethylformamide to give an aldehyde which was demonstrated to be the 5-aldehyde (XLVI) on the basis of the nmr spectrum, Figures 4 and 5, pp 30 and 31. Remarkably, J_{F-CHO} was 4.2 Hz. The magnitude of this coupling prompted an attempt to synthesize the 5-acetyl compound in the expectation of being able to observe a side chain ring fluorine coupling.

Treatment of 2-fluorothiophene with acetyl chloride and stannic chloride in carbon disulfide gave 5-acetyl-2-fluorothiophene. Both the pmr and F^{19} nmr revealed a coupling constant of 0.45 Hz between the fluorine and the acetyl protons, Figures 6 and 7, pp 32 and 33. A haloform reaction of the acetyl compound (XLVII) gave 5-fluoro-2-thenoic acid (XLVIII) which was identical by melting point and nmr spectrum to the acid prepared by silver oxide oxidation of 5-fluoro-2-thenaldehyde (XLVI).

Further confirmation of the substituents' positions was based on studies by Gronowitz (73) who determined the coupling constants in 2-fluorothiophene. He found J_{F-H_3} = 1.62 Hz, J_{F-H_4} = 3.07 Hz, J_{F-H_5} = 3.10 Hz and $J_{H_3-H_4}$ = 3.89 Hz.

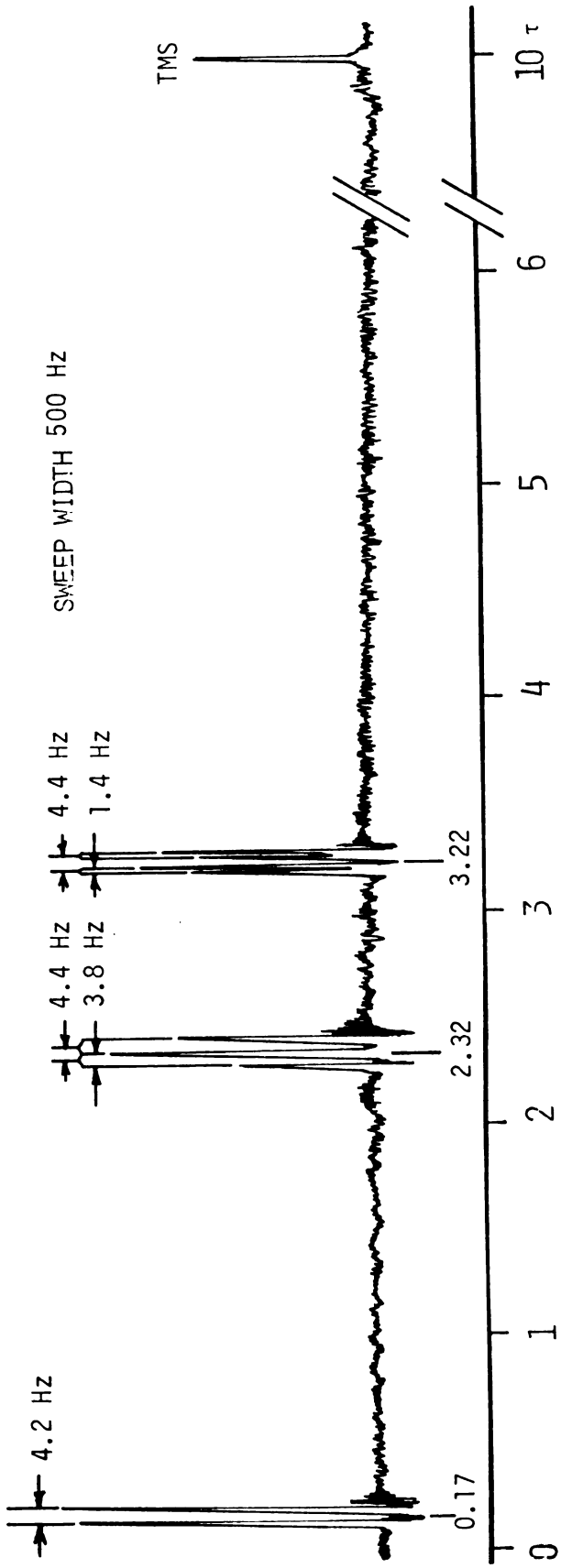


Figure 4. PMR spectrum of 5-fluoro-2-thenaldehyde.

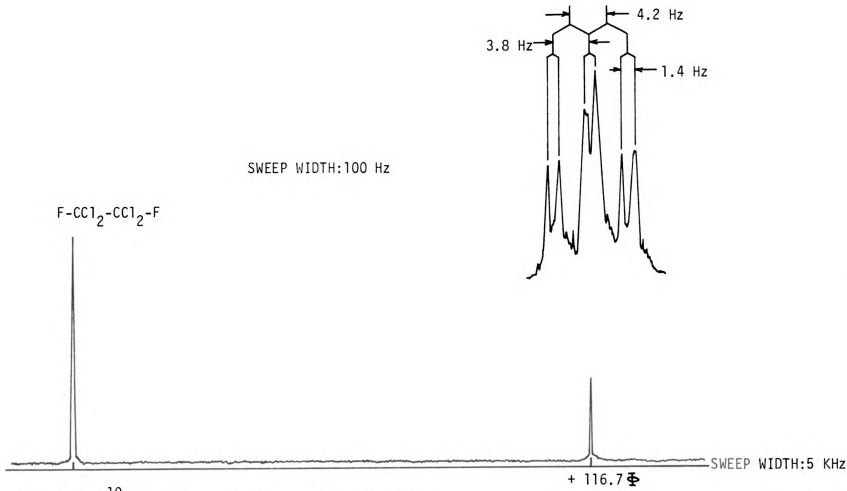


Figure 5. F^{19} nmr spectrum of 5-fluoro-2-thenaldehyde.

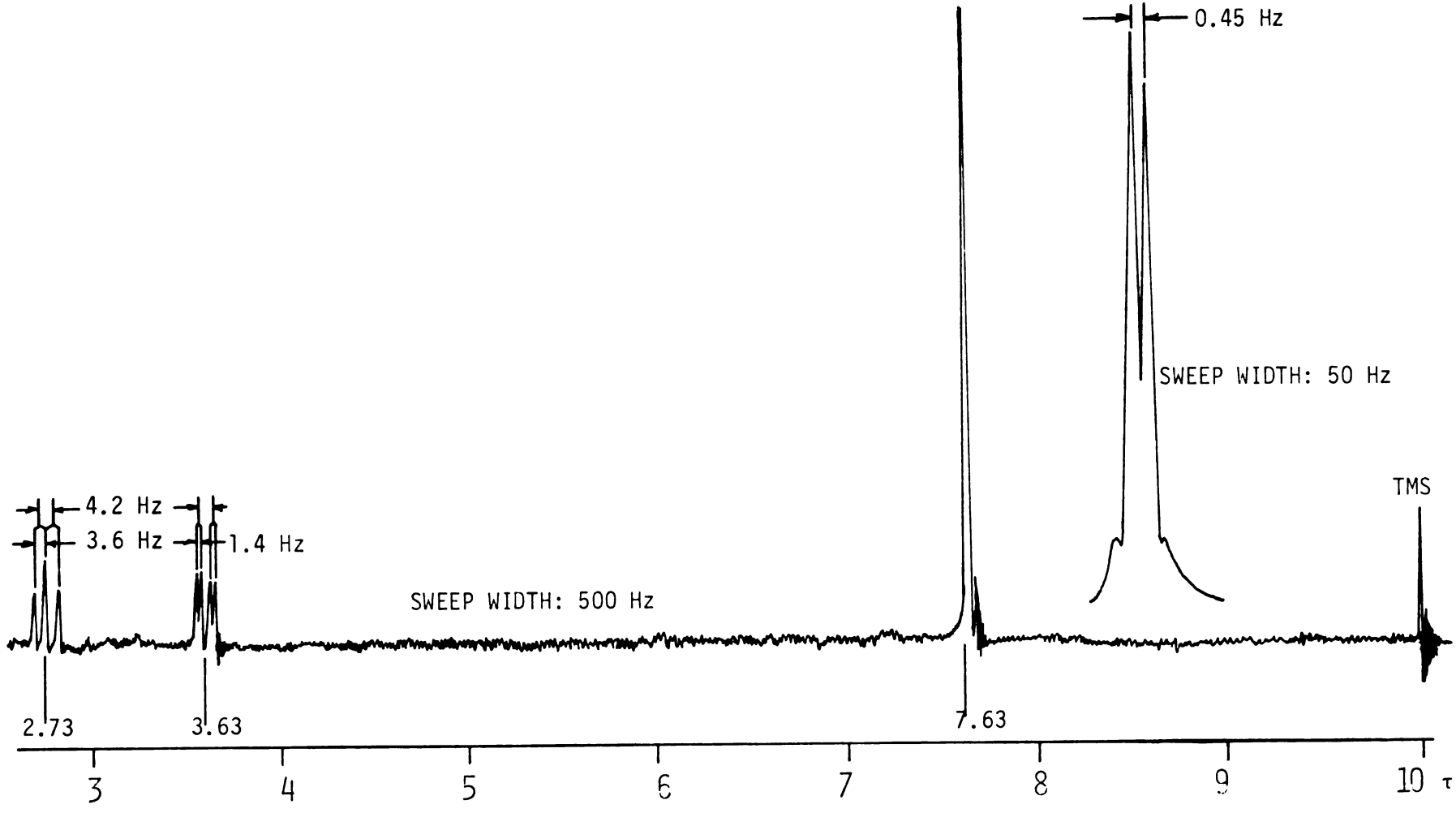


Figure 6. PMR Spectrum of 5-acetyl-2-fluorothiophene

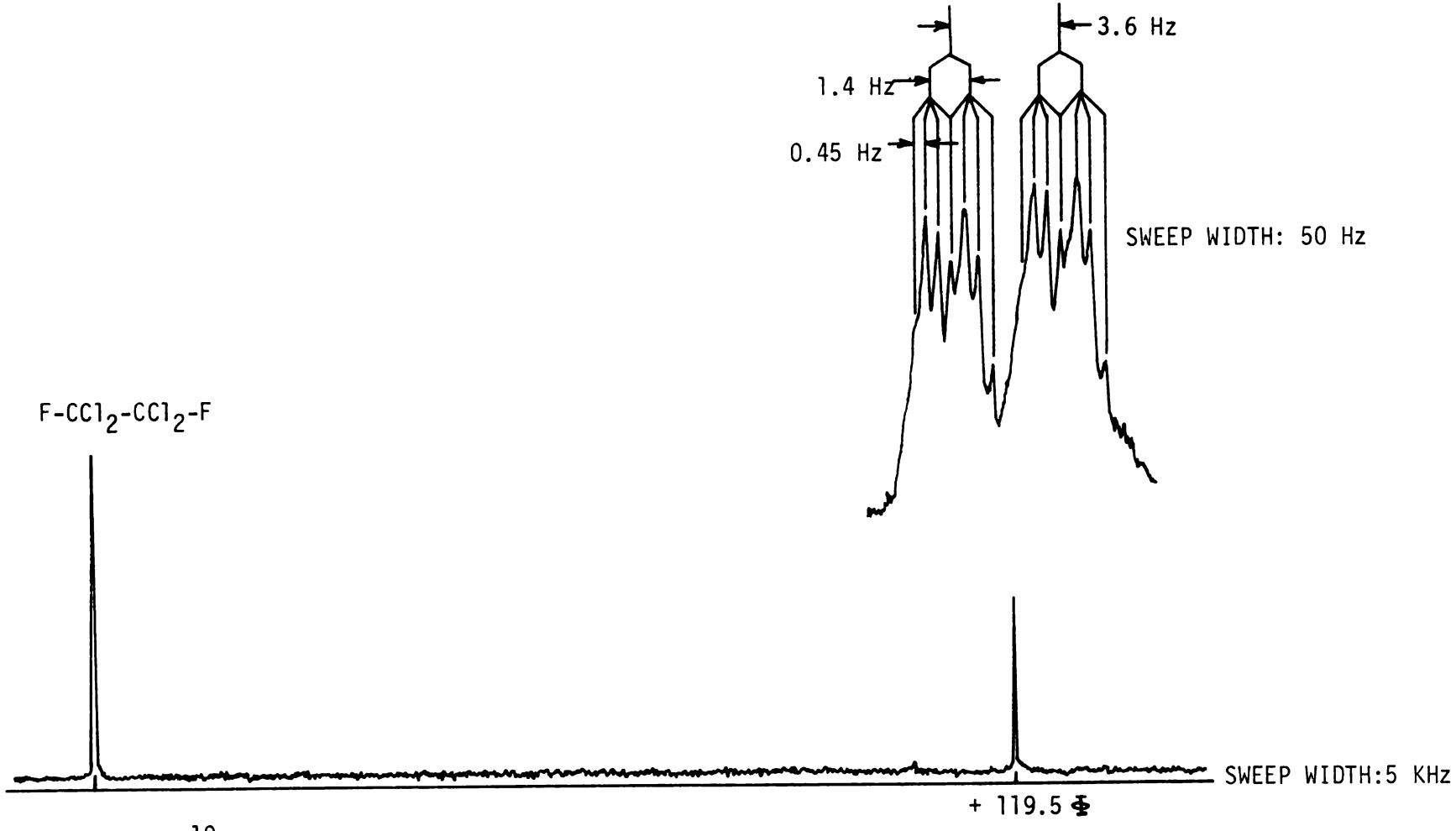


Figure 7. F^{19} nmr spectrum of 5-acetyl-2-fluorothiophene

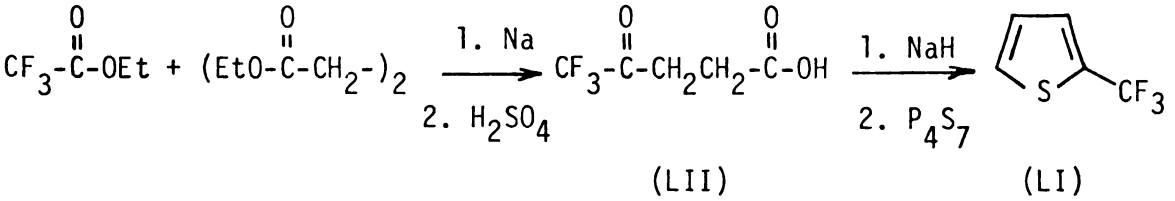
As may be seen in Figures 4 and 5, the very small "ortho" J_{F-H_3} is observed thereby confiming 2,5-substitution. Furthermore, $J_{H_3-H_4}$ = 4.2 Hz is in the range found for other 2,5-substituted compounds (68) of this type.

Since Wynberg had shown (71) that lithiation of 2-(1'-adamantyl)-thiophene occurs in the 5-position, the stage was set for the facile application of a newly reported thenil synthesis. The addition of 2- and 3-thienyllithium to dimethyl oxalate at -70° gave 2,2'-thenil and 3,3'-thenil respectively, (12). Application of this method to 2-fluorothiophene gave the desired 5,5'-difluoro-2,2'-thenil in 7% yield from thiophene. The adamantylthenil (XLIII) was prepared from 2-(1'-adamantyl)-thiophene in the same manner in 9% yield based on 1-bromoadamantane.

Three unsucessful attempts to prepare some thenils

Not all of these attempts to prepare the thenils met with sucess. The nitrothenil could not be prepared due to failure of 5-nitro-2-thenaldehyde to undergo the thenoin condensation. The other methods, such as the double Friedel-Crafts and the reaction of thienyl lithiums with dimethyl oxalate were clearly not applicable. An attempt was made to nitrate 2,2'-thenil. This should have resulted in a presumably separable mixture of nitro products. A solution of 2,2'-thenil could be recovered unchanged after heating for 30 hours at 60° in a mixture of 90% nitric acid and acetic acid. Further attempts to prepare this compound were abandoned.

Kabbe (74) in these laboratories had made an earlier futile attempt to synthesize 2-trifluoromethylthiophene (LI) by the reaction of phenylsulfur-trifluoride with 2-thenoic acid. In the present study, an effort to prepare this compound by treatment of the sodium salt of 5,5,5-trifluorolevulinic acid (LII) with phosphorus heptasulfide met with similar success.



(LII) (LI)

The Ullmann reaction is a well established method for the synthesis of diaryl ethers (75). Since thiophenes readily undergo nucleophilic attack to give alkyl aryl ethers (64, 65) and dithienylsulfides (76, 77), there was ample precedent for the synthesis of 2-phenoxythiophene by the Ullmann reaction.

The reaction failed under all reasonable reaction conditions; either starting material was recovered in most cases or the reaction mixture was totally degraded. Reaction times ranged from one hour to one week; temperatures up to the boiling point of phenol were employed. The usually efficacious copper salts failed to have the desirable result.

It is known that the usual mechanism for nucleophilic displacement of an aryl halide from a nondeactivated aromatic center involves a benzyne intermediate (78). No really firm evidence for thiophyne (dehydrothiophene) as an intermediate in any reaction has ever been presented (78, 79). From this one might infer that nucleophilic displacement of a thienyl halide occurs exclusively through an addition-elimination mechanism rather than elimination-addition. A thiophyne intermediate would be expected to result in the formation of some 3- as well as 2-substituted product (cine substitution). Such an occurrence has not been reported.

Neglecting steric factors, the addition-elimination reaction should be favored as the polarity of the carbon-halogen bond increases. In the reaction of 2-halogeno-5-nitrothiophenes with piperidine, which because of the nitro substituent almost certainly proceed by the addition-elimination mechanism the relative rates were: Cl, 1.00; Br, 0.64; I, 0.076, (80).

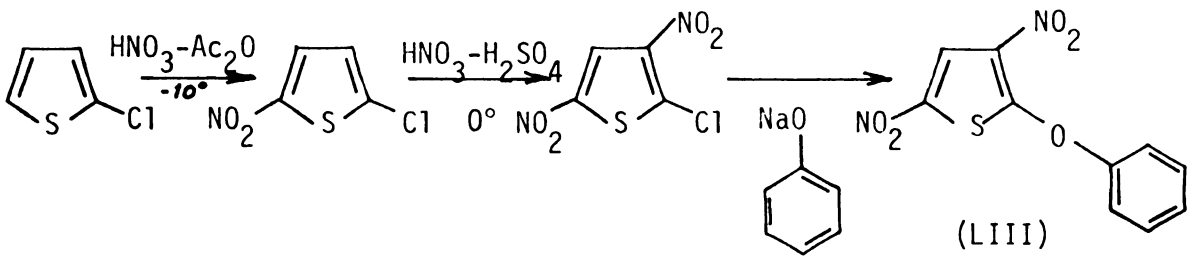
However, 2-bromo, 2-chloro, and 2-fluorothiophene gave the same results as 2-iodothiophene when treated with phenolate.

The use of a more labile leaving group might aid the displacement process, especially with weak nucleophiles such as the phenolate ion. Behringer (81) in some rather elegant work on phenylating agents, has prepared diaryl ethers by the reaction of diaryliodonium salts with various phenolates, under quite mild conditions.

$$AR\text{-}\overset{+}{I}\text{-}AR\ X^- \xrightarrow{M^{+-}O\text{-}AR'} AR\text{-}O\text{-}AR' + M^+X^- + AR\text{-}I$$

This appeared to be quite attractive in the present study since the displacement should be well favored by the adjacent positive charge on the iodine. Depending on the relative nucleophilicity, there can be competition from the iodonium salt anion. Only the halothiophenes, resulting from this internal attack could be isolated when bis(2-thienyl)-iodonium iodide or bromide were treated with either sodium or potassium phenolate in solvents or neat.

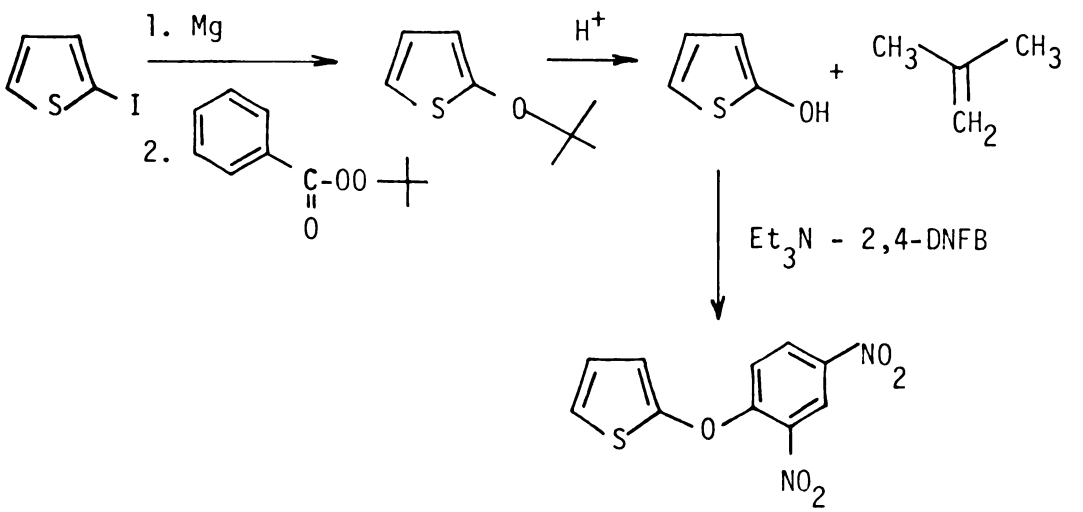
Hurd and Kreuz (82) have prepared 2-phenoxy-3,5-dinitrothiophene (LIII) in the following manner.



It should be fairly straightfoward to remove the nitro groups by reduction to the amino function, double diazotization, and reduction of the diazonium groups to hydrogen using formaldehyde. While the aminothiophenes are notoriously unstable compounds, 2-aminothiophene only recently was adequately characterized (83), they are quite stable as their chlorostannate salts (84).

All attempts at reduction of (LIII) with tin and hydrochloric acid gave a vigorous evolution of hydrogen sulfide and resinification of the entire reaction mixture.

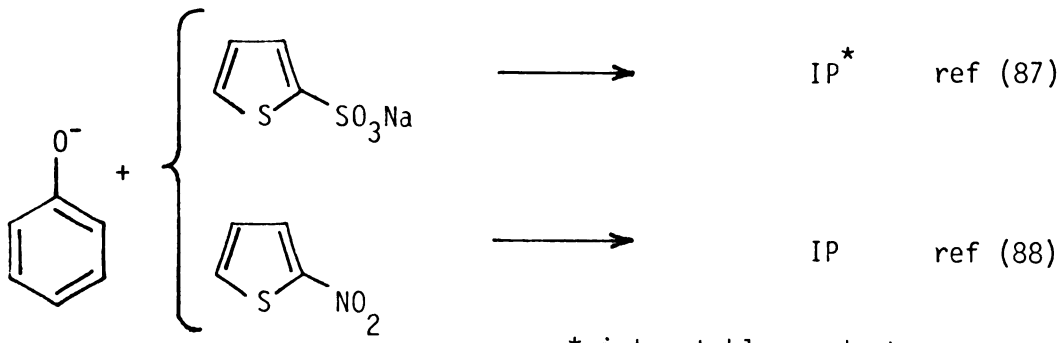
Next this process was examined from the reverse direction. An attempt was made to synthesize 2-(2',4'-dinitrophenoxy)thiophene as illustrated, since it is known that the 2,4-dinitrophenyl moity can survive reduction to the 2,4-diamino radical (85).



Excellent yields of 2,4-dinitroaryl ethers have been obtained from the reaction of 2,4-dinitrofluorobenzene with various phenols in the presence of triethylamine (86). The reaction of 2-hydroxythiophene, triethylamine, and 2,4-dinitrofluorobenzene was totally anomalous, producing almost instantly a dark brown tar which was partially soluble in water. Careful examination of the reaction products failed to reveal any of the expected dinitrophenoxythiophene.

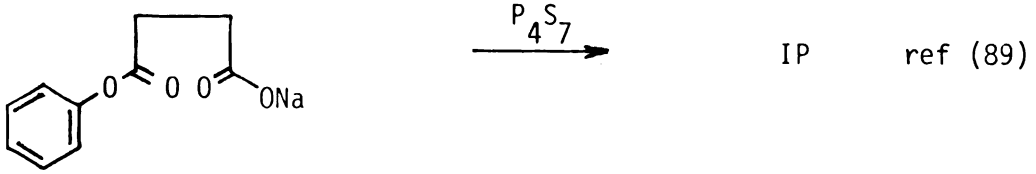
Other procedures which were cursorily examined were also in vain. Reference numbers are given for analogously sucessful reactions with benzene derivatives.

These reactions were: The reaction of sodium phenolate with 2-nitrothiophene and sodium 2-thienylsulfonate, both neat and in dimethylformamide;

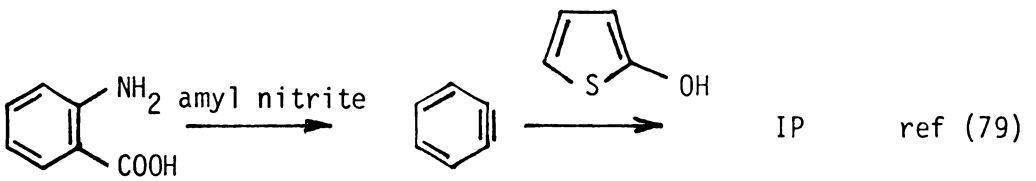


* intractable products

The ring closure of sodium phenylsuccinate with phosphorus heptasulfide;



The trapping of aprotically generated benzyne by 2-hydroxythiophene.



At this point, it was concluded that the synthesis of 2-phenoxythiophene was definitely not a trivial exercise in well known chemistry.

The H_3-H_4 coupling constants of the 5,5'-disubtituted-2,2'-thenils were 4.3 $\pm$ 0.2 Hz. The infrared spectra of the thenils all showed a characteristic carbonyl absorption at 1630 $\pm$ 30 cm^{-1} as given in Table 1. p 39. The constant appearance of this absorption, together with the corroborative nmr evidence and satisfactory elemental analysis, not to mention their bright yellow to rust orange color, was taken as sufficient justification for the proposed structures for the thenils.

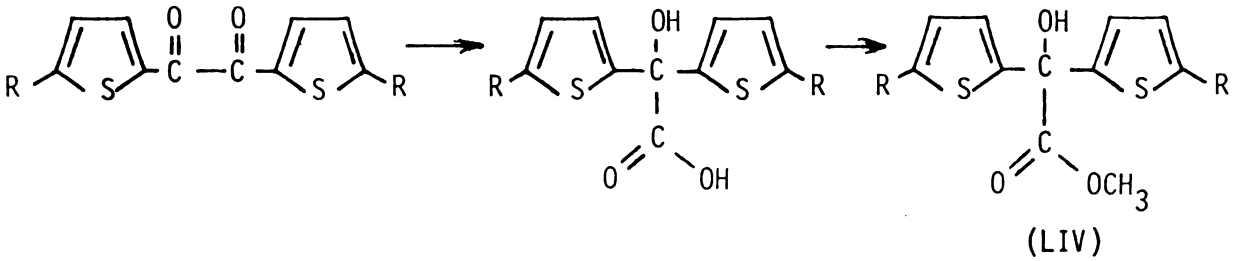
Table 1. Spectral Properties of Various Thenils

Compound	J (H_3-H_4) Hz	$\nu_{C=O}$ cm^{-1}	$\pi_2 \rightarrow \pi_2^*$ $\lambda(\log\varepsilon)$
2,2'-thenil	-	1650	310(4.236)
3,3'-thenil	-	1655	273(4.261)
5,5'-dimethoxy-2,2'-thenil	4.5	1620	350(4.335)
5,5'-diisopropoxy-2,2'-thenil	4.5	1610	354(4.631)
5,5'-dichloro-2,2'-thenil	4.2	1633	335(4.278)
5,5'-difluoro-2,2'-thenil	4.4	1625	314(4.482)
5,5'-dimethyl-2,2'-thenil	4.4	1633	324(4.282)
5-methyl-2,2'-thenil	-	1635	317(4.236)
5,5'-di-(2"-thienyl)-2,2'-thenil	-	1620	397(4.775)
5,5'-di-(1"-adamantyl)-2,2'-thenil	4.5	1630	324(4.557)
2,2'-benzo[b]thenil	-	1640	336(4.723)
3,3'-benzo[b]thenil	-	1655	316(4.459)
2-thienylphenyl diketone	-	1620	290(4.014)

Before any kinetic work or further synthetic investigations could be carried out, it was necessary to show the nature of the product(s) obtained by the interaction of the thenils with hydroxide.

Three different laboratories had shown earlier (8, 9, 7) that 2,2'-thenil, 3,3'-thenil, and 2-thienylphenyl diketone respectively rearranged to give the corresponding thenilic acids when treated with hydroxide (the thenil-thenilic acid rearrangement).

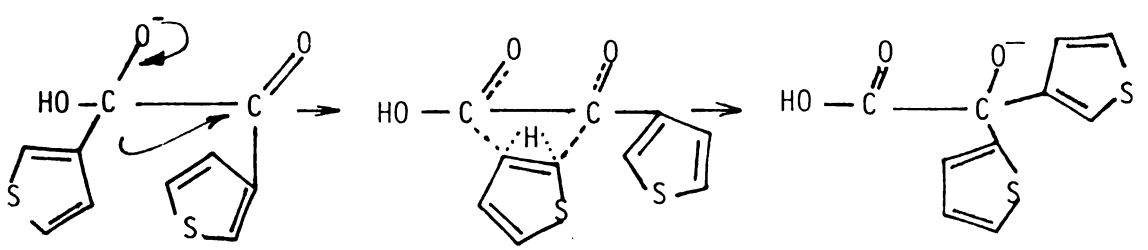
Of these, 2,2'-thenilic acid and 3,3'-thenilic acid were found to be singularly unstable in the solid state, resinifying in a desiccator in a few hours at room temperature. This was found to be the case in the present studies as well, however, the acids are perfectly stable, for at least two years at -20° or in solution. Fortunately, their isolation is not necessary. The ethereal extract obtained from the product isolation of the rearrangement reaction mixture may be treated with diazomethane to give good to excellent yields of the methyl esters.



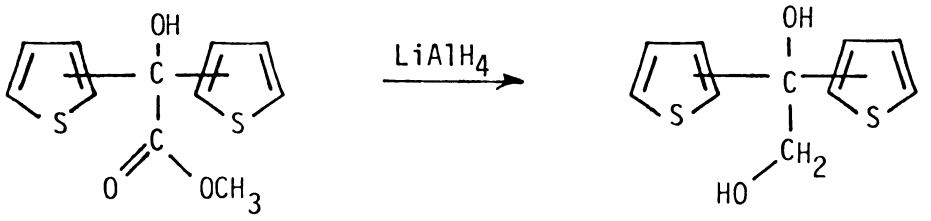
(LIV)

The structures of all of the thenilic esters (LIV) were checked by nmr and showed proper field positions and integral ratios for aromatic to methyl protons. All esters showed a shift in the carbonyl absorptions from 1630 ± 30 cm^{-1} for the thenils to typical aliphatic ester absorptions at 1725 ± 10 cm^{-1}. All new esters were submitted for elemental analysis and all of them checked satisfactorily.

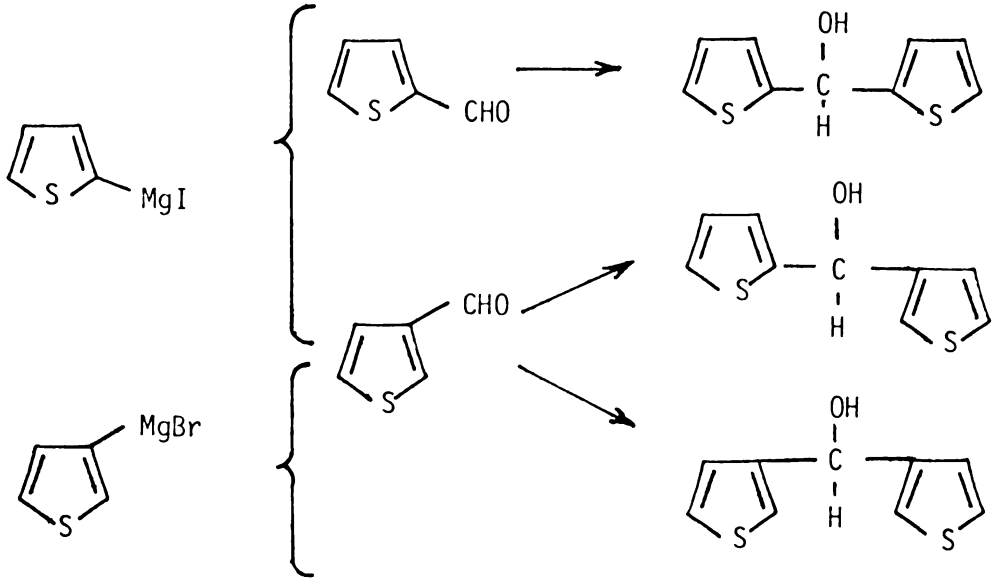
One slight doubt remained, however, and that was the possibility that a 1,2 proton shift on the migrating thienyl ring might occur during the thenilic acid rearrangement.



This would appear to depend on the extent of anionic character of the migrating carbon, the relative acidities of the hydrogens at the 2 or 3 positions, and the relative rate of proton vs thienyl migration. The problem was amenable to nmr investigation. However, a further complication arose at this point in that the thiophene rings are not magnetically equivalent and one or both of them suffers from anisotropic perturbation by the ester carbonyl. To obviate this problem, the methyl thenilates were reduced by lithium aluminum hydride to the 1,1-bis(thienyl)-ethyleneglycols.



The aromatic region of their nmr spectra was then compared to the same region of all three dithienylcarbinols which were unambiguously synthesized from the 2- and 3-thenaldehydes by reaction with 2- and 3-thienylmagnesium halides.



The comparison of these spectra are shown in Figure 8, p 42. It is clearly evident that neither 3,3'-thenil or 2,2'-thenil undergoes prototropic rearrangement during the thienyl migration.

With but three exceptions, 5,5'-diisopropoxy-2,2'-thenil, 5,5'-dimethoxy-2,2'-thenil, and 3,3'-benzo[b]thenil which gave anomalous products, the rearrangement was especially clean and no evidence for the formation of any other compound or degradation product could be found. This was particularly important since the kinetic determinations were to be made only by following the rate of disappearance of the hydroxide.

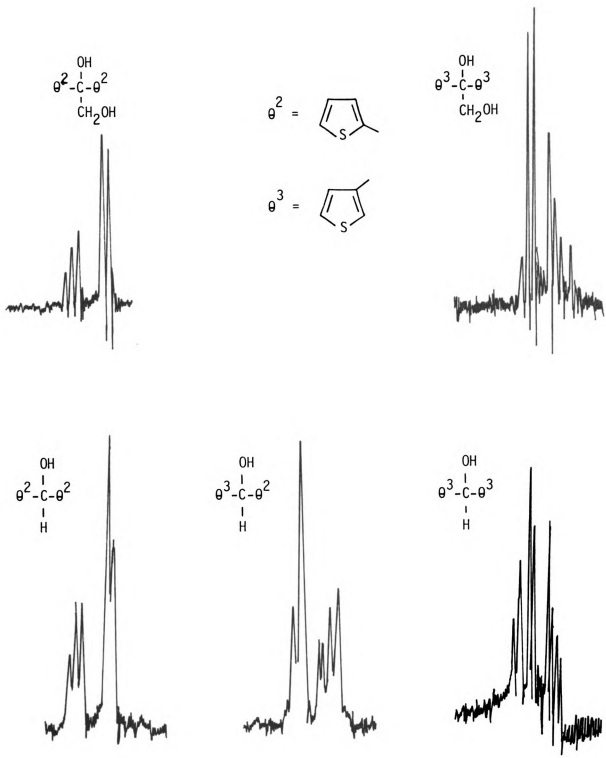
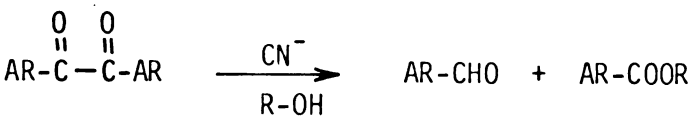


Figure 8. Nmr spectra of the aromatic region of various dithienylcarbinols.

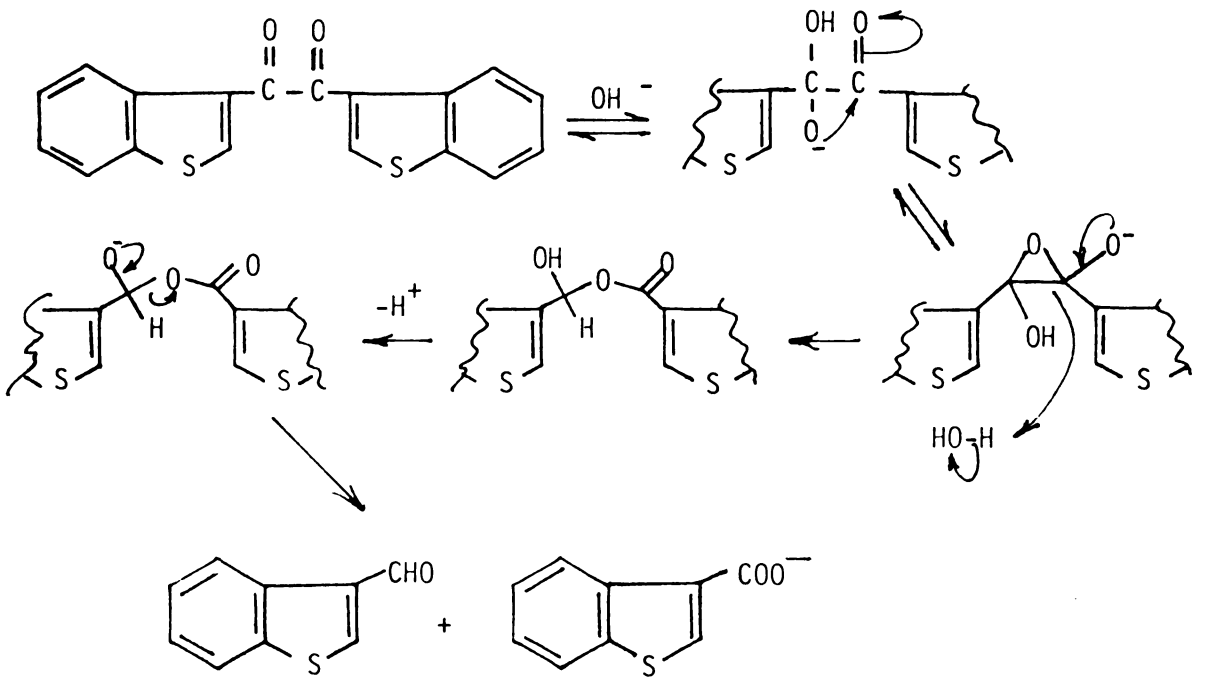
Neither kinetic nor synthetic observations concerning the rearrangement of 5,5'-di-(1"-adamantyl)-2,2'-thenil were possible owing to the low solubility of the compound in virtually all solvents. In the synthetic study of the rearrangement, the solvent used in all cases was water with the addition of sufficient dioxane to effect solution at the reaction temperature. The use of ethanol or other alcohols occasionally lead to cleavage of the thenil and the formation of methyl thenoates after workup.

The reaction of 3,3'-benzo[b]thenil with potassium hydroxide gave only 3-benzo[b]thenoic acid, isolated as the methyl ester after the usual reaction workup with diazomethane. The ester was identified on the basis of its mass spectrum. Signals were found at m/e 192 (parent, 35%), at m/e 161 (P-31, loss of CH_3O-, 65%), and m/e 133 (loss of CO from m/e 161, 17%).

The cleavage of benzils by hydroxide in the absence of alcohols appears to be without precedent in the literature. It did not occur with any other thenil studied. The mechanism of this reaction could well be analogous to Dakin and Harrington's reaction (21) which was used earlier to degrade 5,5'-dimethoxy-2,2'-thenil to 5-methoxy-2-thenoic acid. That procedure involved the cyanide catalyzed cleavage of the diketone in the presence of alcohol to give an aldehyde and ester derived from the two halves of the benzil.

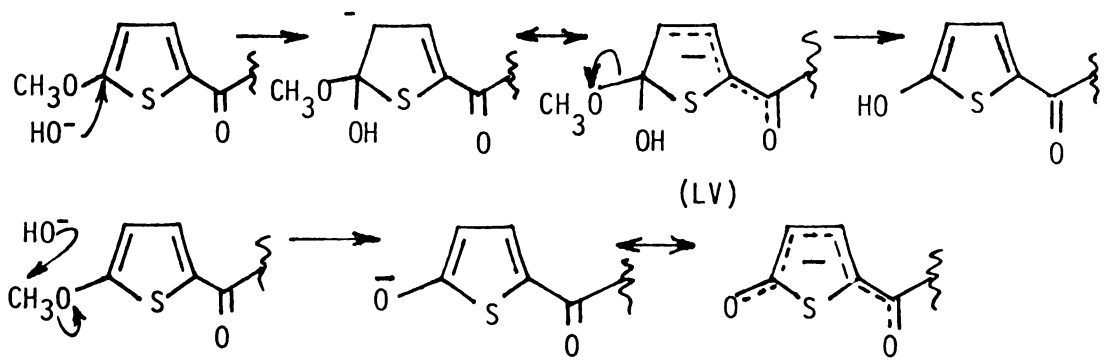


A mechanism is proposed for the hydroxide cleavage reaction which is similar to the one proposed by Kwart (70) for the aforementioned cyanide cleavage. Presumably, the 3-thianapthaldehyde formed is converted to 3-benzo[b]thenoic acid and 3-hydroxymethylthianapthene by the Cannizzaro reaction. This would result in a 75% theoretical yield of 3-benzo[b]thenoic acid from the thenil.



It is uncertain why this one thenil of all the thenils studied should undergo this anomalous reaction.

When the rearrangement of 5,5'-dimethoxy-2,2'-thenil was attempted, the thenil was degraded into unidentifiable products. Repeated efforts at isolating the ester after the usual workup from the rearrangement reaction mixture failed. Purely on the basis of olfactory and visual evidence, the failure to obtain the expected thenilic acid may be rationalized by the formation of a 2-hydroxythiophene via a transient Meisenheimer type complex (LV). It is known that such complexes can be formed with hydroxide (90) and from thiophenes (91).



(LV)

Alternatively, one may visualize an S_N2 attack on the methoxy carbon. In either case, the resulting hydroxythenil or hydroxythenilic acid, would most likely be as unstable as 2-hydroxythiophene itself (92).

It would have been quite tedious to prepare a sufficient quantity of 5,5'-diisopropoxy-2,2'-thenil for synthetic investigations. However, one kinetic run of this compound indicated the same abnormal type of behavior as the methoxythenil. The decrease in the apparent second order rate constant for the disappearance of hydroxide compared to the methoxythenil indicates that either of the two decomposition mechanisms may be valid on the basis of steric arguments.

Two more synthetic endeavors remained to be accomplished; the synthesis of a series of substituted thenoic acids corresponding for the most part, to the substituted thenils; and the synthesis of the piperidyl thenilates, the original prime objective for this research.

Synthesis of the thenoic acids

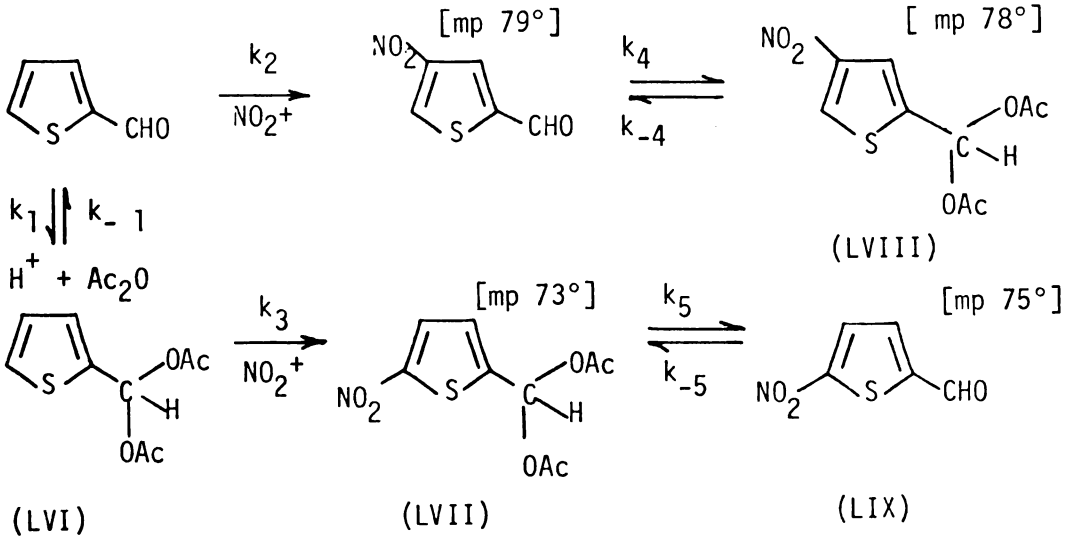
A series of substituted thenoic acids was prepared so that primary sigma values for substituents on thiophene might be determined. From this data, a measure of the deviation of σ values in benzene vs σ values in thiophene was evaluated. The results are treated in detail in Part II of the discussion section of this tnesis. The same criteria used in selecting substituents for the thenils guided the selection of substituted thenoic acids which were prepared. Accordingly, 5-methyl, 5-methoxy, 5-nitro, 5-chloro, 5-fluoro-2-thenoic acids as well as 2-thenoic, 3-thenoic, 2-benzo[b]thenoic, and 3-benzo[b]thenoic acids were prepared. All of these were readily available, with the exception of 5-nitro-2-thenoic acid by oxidation of the previously described aldehydes with silver oxide in aqueous sodium hydroxide.

Of these, only 5-fluoro-2-thenoic acid had not been previously reported.

As a consequence of the strong -I-M character of the aldehyde function, the nitration of 2-thenaldehyde gives a mixture of 4- and 5-nitro-2-thenaldehydes depending on quite critical reaction conditions.

Buu-Hoi (93) nitrated 2-thenaldehyde with fuming nitric acid in acetic anhydride and obtained the 5-nitroaldehyde (LIX) together with a "small amount" of the 4-isomer. Foye (94) found only 4-nitro-2-thenaldehyde using nitric acid in sulfuric acid as the nitrating medium. A eutectic mixture of the 4- and 5-aldehydes was reported by Giver (95) who nitrated 2-thenaldehyde diacetate (LVI) with nitric acid in acetic anhydride. Fournari and Chane (96) repeated both the nitration in acetic anhydride and the nitration in sulfuric acid. They found that neither aldehyde was formed, in acetic anhydride, but rather a mixture of the 5- and 4-nitro-2-thenaldehyde diacetates (LVII) and (LVIII) in an 87:1 mole ratio respectively. Nitration of 2-thenaldehyde in sulfuric acid gave the 4-nitroaldehyde exclusively.

From the simplified scheme illustrated, it is evident that the extent of 4-nitro products depends on the position of the k_1/k_{-1} equilibrium and whether or not equilibrium has been reached before introduction of the nitrating agent.



It depends on the relative values of k_2 and k_3 (competitive nitration). Thus, the products which are isolated depend on the temperature of the reaction, the order of addition of the reagents, and the position of the k_4/k_{-4} and k_5/k_{-5} equilibria. The identification of the products is complicated by the fact that all four possible products melt within six degrees of each other.

In the present study, 90% nitric acid was added to a 40% solution of 2-thenaldehyde in acetic anhydride at 10°, and the reaction mixture was allowed to stand at least 12 hours at 0°. The only product in evidence was 2-diacetoxymethyl-5-nitrothiophene. The nmr spectrum of the purified material revealed an H_3-H_4 coupling constant of 4.2 Hz, Figure 9, p 48, thereby confirming 2,5-substitution. No other proton signals were detected in the aromatic region. A coupling constant of 0.6 Hz of the diacetoxymethyl proton with the ring H_3 proton was noted.

The diacetate was smoothly oxidized to 5-nitro-2-thenoic acid by potassium dichromate in aqueous sulfuric acid.

Synthesis of the piperidyl thenilates

The final synthetic effort was directed toward a brief exploration of the scope of the transesterification of the methyl thenilates with N-methyl-3-piperidinol. The objective, of course, was the preparation of certain thiophene isosteres of JB 336 or N-methyl-3-piperidyl benzilate.

The primary interest in these compounds was their potential physiologic properties, both anticholenergic and psychotomimetic. Thus a sufficient amount of each amino ester was to be prepared to permit preliminary evaluation of these properties. Four of the esters were prepared as shown on p 49.

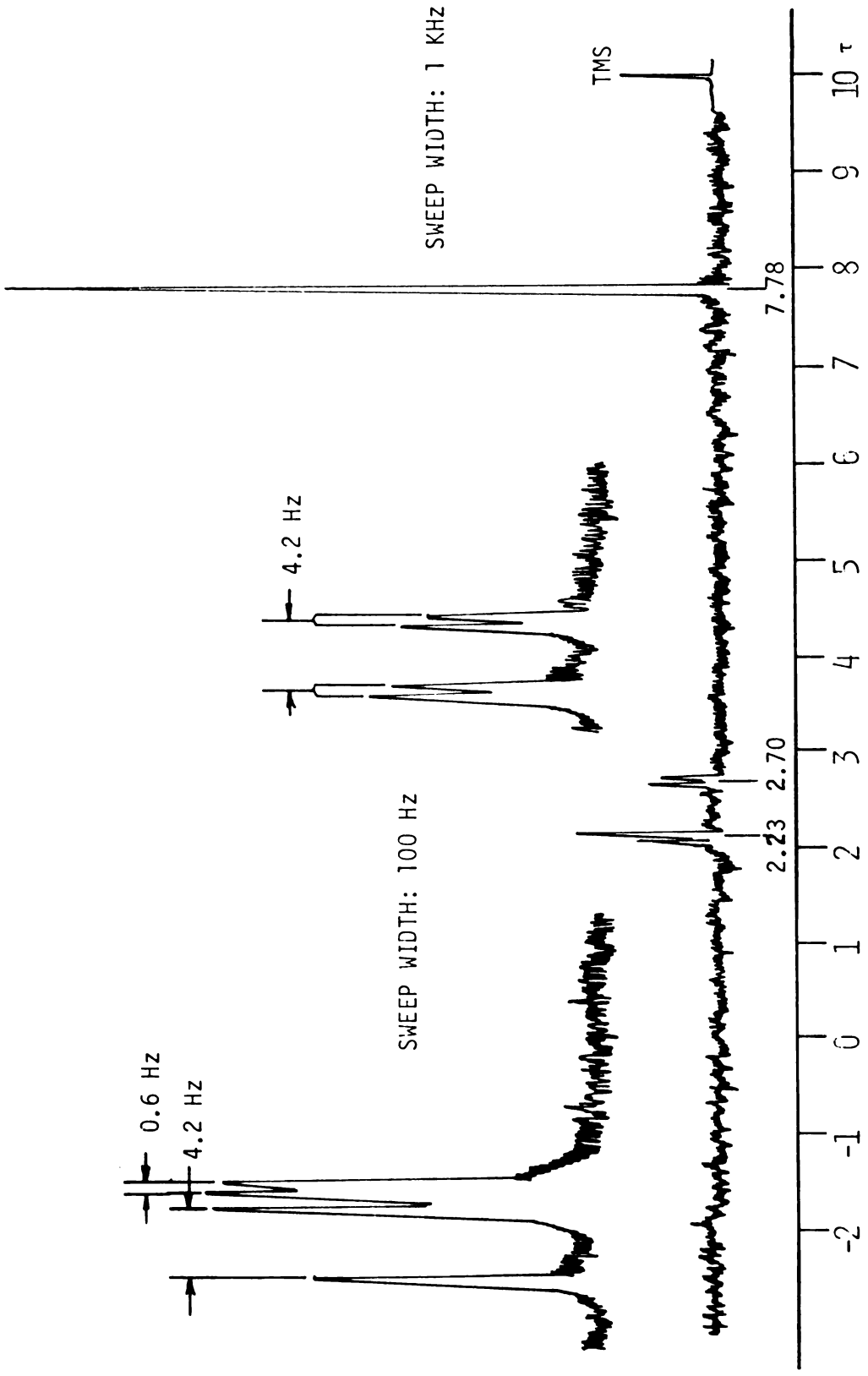
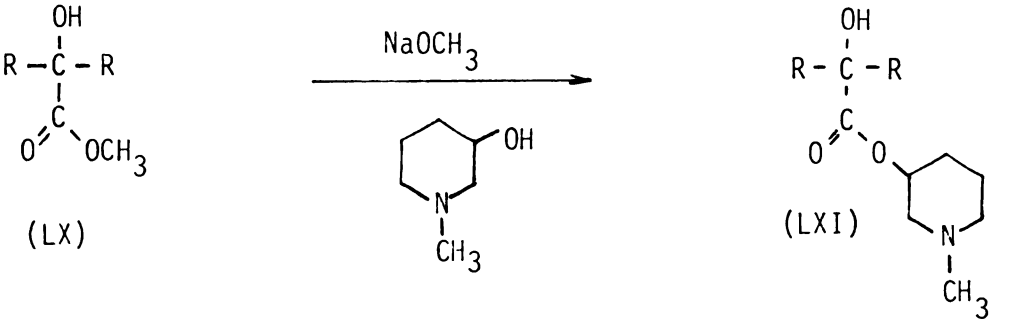


Figure 9. Nmr spectrum of 2-diacetoxymethyl-5-nitrothiophene



(LX) (LXI)

R = 2-thienyl R = 2-thienyl

R = 3-thienyl R = 3-thienyl

R = 5-chloro-2-thienyl R= 5-chloro-2-thienyl

R = 2-benzo[b]thienyl R = 2-benzo[b]thienyl

The sharp decrease in research funding from various agencies of the federal government and other sources made the initiation of the pharmacologic work impossible. For this reason, it was decided to show only the general nature of the transesterification reaction and not prepare all possible piperidyl thenilates.

DISCUSSION, PART II, KINETIC INVESTIGATIONS

Certainly, one of the main expedients of the chemist, or any scientist for that matter, is the reduction of qualitative observations to quantitative data. An extremely useful tool to the chemist is the ability to predict the extent of change in physical properties for a molecule as a result of structural modifications of the molecule.

Some 33 years ago, Louis Hammett elucidated the phenomenological correlation in equation 1.

$$\log \frac{k}{k_o} = \sigma\rho \qquad 1$$

The universal nature and countless experimental and theoretical justifications for its validity render any background discussion here redundant. Suffice it to say, the original definition predicated on the reactivities of substituted benzenes has been extended, with more or less success, to correlate data involving many other rate and equilibria measurements in all types of molecules and in addition such physical properties as nmr data, infrared absorbances, half-wave potentials, and biological activity (97).

The chemist as statistician must be concerned, however, not merely with whether or not correlations exist between his data and some other body of factors, but rather with how <u>well</u> do they correlate.

Considering the Hammett equation in particular, the logs of the ratio of the rate constants for a reaction of a series of substituted vs nonsubstituted compounds are plotted as a function of σ as defined in equation 2.

$$\sigma = \log \frac{k}{k}_{ref} \qquad 2$$

The slope of the line is defined as ρ ,usually calculated by the least squares method. The certainty that all the points fall on the line is indicated by r, the correlation coefficient, as defined in equation 3 (98), in which x and y are the coordinates of a given point.

$$r = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\left[\sum_{i=1}^{n}(x_i - \bar{x})^2 \sum_{i=1}^{n}(y_i - \bar{y})^2\right]^{1/2}} \qquad 3$$

The values of r will range from +1, perfect positive correlation between rates and σ, to 0, no correlation whatsoever, to -1, perfect negative correlation between rates and σ. Whether or not a "good" correlation has been obtained is obviously a matter of rather arbitrary definition. Jaffe (99) defines correlations for $r>0.99$ as excellent, $r>0.95$ as good, and $r>0.90$ as fair. In terms of equation 1, $r<0.90$ is unacceptable and may indicate serious secondary perturbation in the reaction. In addition, nonreliability of the Hammett equation is indicated when the standard deviation,s, from the regression line, as given by equation 4 exceeds certain values dependant on the value of ρ. Jaffe's maximum allowable limits for s are 0.4 for $\rho>4$, 0.3 for $\rho>3$, 0.25 for $\rho>2$, and 0.2 for $\rho>1$.

$$s = \left\{\left[\sum_{i=1}^{n}(y_i - \bar{y})^2 - \frac{\left[\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})\right]^2}{\sum_{i=1}^{n}(x_i - \bar{x})^2}\right](n-2)^{-1}\right\}^{1/2} \qquad 4$$

These definitions shall be employed in the following discussion.

By way of definition of the problem, we will look at three previous investigators efforts in the light of these criteria.

Imoto and his co-workers have performed several investigations into the possibility of extension of the Hammett equation to thiophenes (100). Some of this work, shown in Table 2, indicates that a reasonable fit to the Hammett equation has been obtained in most cases, providing that the number of compounds, n, entering into the plot is small or carefully selected.

Table 2. Some Statistical Parameters For Imoto's Thiophene Studies

Reaction	ρ	s	r	n
pK of 5-R-2-thenoic acids	1.10	0.10	0.988	5
Base hydrolysis of ethyl 5-R-2-thienyl carboxylates	1.86	0.30	0.975	4
Acid catalyzed methanolysis of 5-R-2-thenoic acids	-0.34	0.10	0.884	5
$E_{1/2}$ of 2-nitro-5-R-thiophenes	0.20	0.06	0.718	12
Base hydrolysis of ethyl 5-R-3-thienyl carboxylates	1.63	0.07	0.998	4

His σ values were the classical one based on the ionization of substituted benzoic acids (101). As the number of entries is increased, e.g. the plot of $E_{1/2}$ of 2-nitro-5-R-thiophenes, the correlation coefficient drops to totally unacceptable levels.

The same order of correlation; r=0.972, ρ=0.44, s=0.053, was obtained by Schuetz and Teller (102) for the thermal decomposition of some bis(thenoyl) peroxides. It must be noted that this reaction displays a rather low order of dependence on the substituent and as a consequence would not be expected to show large standard deviations.

Gronowitz has pointed out that large deviations from linearity should be expected for strong +M substituents in thiophene (103).

He has also stated that an alternate set of σ values should be used for correlations in thiophene systems (42).

To this end, Janssen (104) in 1965 reported an investigation of the hydrolysis of five 5-substituted-2-thienyl ethyl esters. He defined σ_{th} as in equations 5 and 6

$$\sigma_{th} = \sigma^* - \sigma_H^* \qquad 5$$

$$\sigma^* = \log k_b/k_a - \log k_o b/k_o a \qquad 6$$

where k_b and k_a are the rate constants for the basic and acidic hydrolysis respectively and $k_o b$ and $k_o a$ are the rate constants for the basic and acidic hydrolysis of ethyl acetate at 25°. His rate constants at 25° were extrapolated from data taken at 100° and 50°. Since only two temperatures entered into his Arrhenius plot, we have no means of estimating errors for the first term in equation 6. A plot of log k/k_o vs σ_{th} gives r=0.608, indicating far too much scatter of the data to have any real significance.

The concept of a "σ_{th}" is an attractive one, however. By basing values on some intrinsic property of the thiophene ring, perturbations associated with it, such as steric, resonance, inductive and field effects would presumably be minimized.

Barlin and Perrin (112) have tabulated the pK_a's of a number of thenoic acids. A fair prediction of the values of the acids is given by equation 7

$$pK_a = 4.20 - (0.72 + \sigma) \qquad 7$$

where 4.20 is the pK_a of benzoic acid, 0.72 is the difference in pK_a between benzoic acid and 2-thenoic acid and σ has its usual meaning. The pK_a's, however, all come from one laboratory (Imoto's). Furthermore nothing was reported of the method of measurement of these values or their accuracy.

Therefore work was initiated in these laboratories to determine the ionization constants of a series of thenoic acids. We planned for reasons outlined in the introduction to this thesis, to limit the study mainly to the 5-substituted-2-thenoic acids.

The pK_a's of the acids were determined potentiometrically with a glass electrode in water at 49.5° using the method described by Albert and Serjeant (105). Potassium hydroxide was employed as the titrant to eliminate the sodium ion error inherent in the glass electrode. The concentrations of the acids were typically in the range of 10^{-3} molar in order to minimize the need for activity corrections*. A complete description of the procedure is given in the experimental section. The results are collected in Table 3, p 55.

The difference between the pK_a of a substituted acid and the pK_a of 2-thenoic acid is defined as σ_θ for that substituent. A plot of σ_θ vs Hammett's σ gives ρ=1.18, s=0.12, and r=0.943 as seen in Figure 10, p 56.

Several points are immediately evident. The value for ρ is in agreement with that found by Imoto, Table 3. The correlation coefficient has decreased relative to Imoto's r, indicating greater scattering of the data and the non-linear relationship between σ and σ_θ. The halogens, especially fluorine, appear to be much more electron withdrawing in thiophene than in benzene as reflected in the ionization constants of the corresponding acids.

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* Corrections to true thermodynamic pK_a values may be made. For a uni-univalent electrolyte, the extended Debye-Huckel equation reduces to:

$$-\log f_{\pm} = \frac{0.5\sqrt{\mu}}{1 + 2\sqrt{\mu}}$$

where μ the ionic strength is approxiametly constant at 0.001. This gives a value for the mean activity coefficient of 0.966 and raises the values given for the ionization constants in Table 3 by 0.015 pK units (106). This value cancels, of course in calculating σ_θ.

Table 3. Ionization Constants and Sigma Values for Nine Thenoic Acids

Compound	pK_a	σ_θ	σ (d)
2-thenoic acid	3.617 ± 0.016	0.000[b]	----
5-methyl-2-thenoic acid	3.784 ± 0.019	-0.167 ± 0.035	-0.170 ± 0.02
5-chloro-2-thenoic acid	3.341 ± 0.014	0.276 ± 0.030	0.227 ± 0.02
5-nitro-2-thenoic acid	2.620 ± 0.018	0.997 ± 0.034	0.778 ± 0.02
5-fluoro-2-thenoic acid	3.430 ± 0.014	0.187 ± 0.030	0.062 ± 0.02
5-methoxy-2-thenoic acid	3.842 ± 0.014	-0.225 ± 0.030	-0.268 ± 0.02
3-thenoic acid	4.157 ± 0.014	----	----
3-benzo[b]thenoic acid	4.032 ± 0.036	0.125 ± 0.050[c]	0.042 ± 0.02
2-benzo[b]thenoic acid	3.336 ± 0.012	0.251 ± 0.028	0.042 ± 0.02

[a]at 49.5°; ranges are the average of the standard deviations of 3 runs of 9 determinations each.

[b]by definition

[c]based on the pK_a of 3-thenoic acid

[d]reference 101

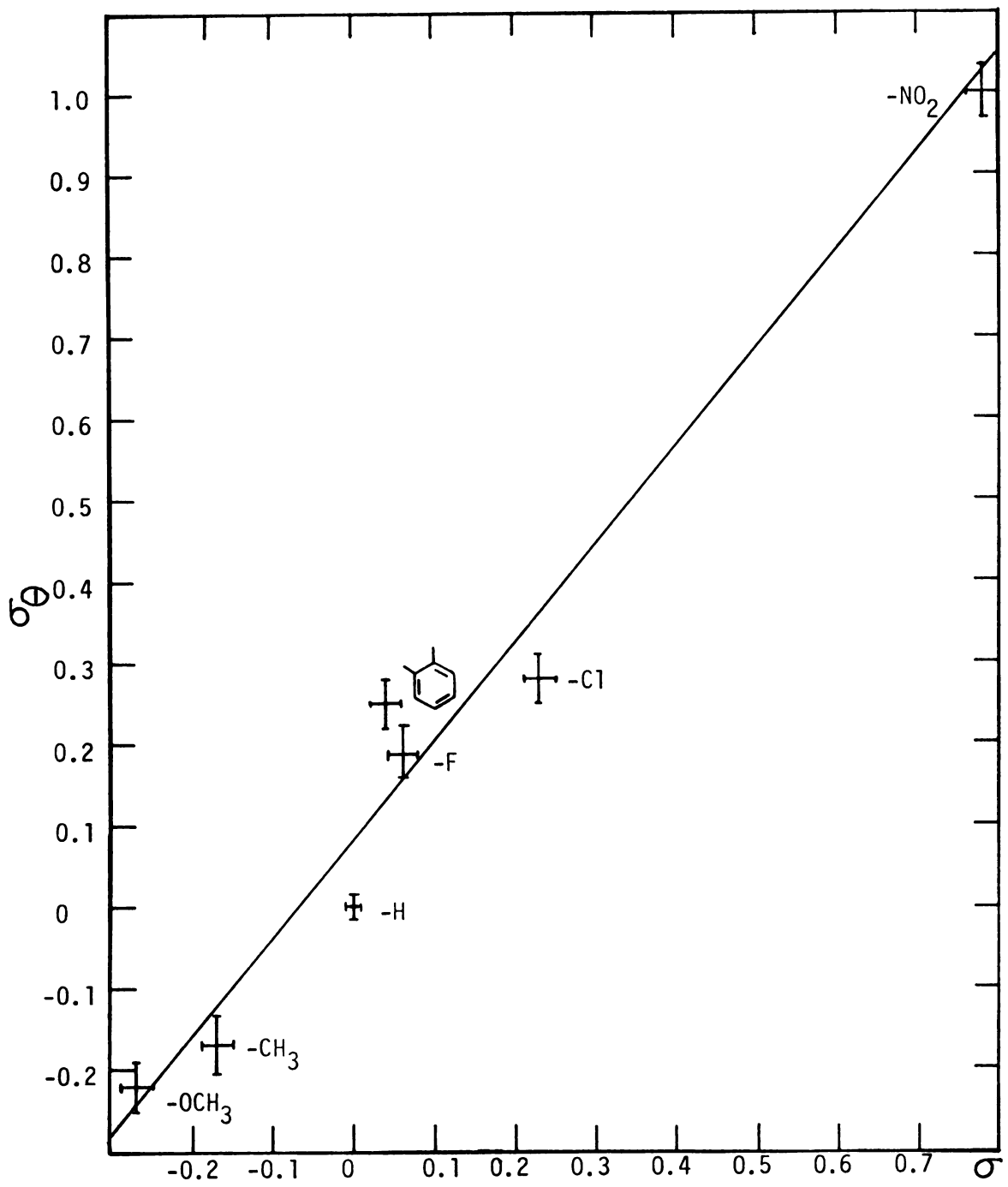


Figure 10. Plot of σ vs σ_θ.

The same holds true for the 3,4-benzo group and the nitro function. The pK_a of 3-thenoic acid is quite comparable to benzoic acid and the difference in pK between 3-thenoic acid and 3-benzo[b]thenoic acid gives a σ value more in agreement with Hammett's sigma for the 3,4-benzo group.

The increases noted for σ_θ for the electron withdrawing groups are probably not due to a steric effect but rather to inductive effects via polarization of the σ and π framework of the molecule or to through space (field) effects. For comparison, the same phenomenon is observed in the ionization of methylthioacetic acid, pK_a=3.72 and n-butyric acid, pK_a=4.81 (107).

It may also be pointed out that Imoto obtained much better correlations between Hammett's σ values and the rate of hydrolysis of ethyl 5-R-3-thienyl carboxylates compared to ethyl 5-R-2-thienyl carboxylates. Presumably, 3-thienyl,in which the effects of the sulfur atom are shielded by the extra intervening carbon atom, is much more like benzene in its reactivity.

It will be demonstrated that better correlations are obtained by the use of σ_θ instead of σ for a reaction involving considerable negative charge in the transition state, namely the thenil-thenilic acid rearrangement.

In Part I of this discussion, the rearrangement of thenils to thenilic acids was described. With the exceptions noted of 3,3'-benzo[b]thenil, 5,5'-dimethoxy-2,2'-thenil and 5,5'-diisopropoxy-2,2'-thenil, the rearrangement gave the thenilic acids, isolated as their methyl esters, in yields of 62-94%. No evidence was found of any reaction that might interfere with a quantitative study of this reaction.

The reaction of the thenils with potassium hydroxide was followed by titrimetric determination of the loss in base as a function of time. All determinations of the rate constants were carried out in a 2:1 mixture by volume of dioxane and water. The temperature of the reaction mixture was held

to ± 0.04° or better. Reaction times were measured by three different timing devices initially triggered simultaneously. Further details are described in the experimental section.

Westheimer had already shown that the benzilic acid rearrangement is first order in benzil and hydroxide, second order overall (33). For a reaction of this type in which the stoichiometry is 1:1 and the initial concentrations of the reagents are deliberately set such that $[OH^-]_i > [DK]_i$, the rate constant is given by equation 8 (108).

$$k = \frac{\ln\left[\frac{DK}{OH}\right]_i + \ln\left[\frac{OH}{DK}\right]}{t[OH - DK]_i} \qquad 8$$

where t is time, i refers to initial concentrations, and DK and OH refer to thenil and hydroxide concentrations respectively. This equation is conveniently rearranged to give

$$\ln\left[\frac{OH}{DK}\right] = kt[OH - DK]_i - \ln\left[\frac{DK}{OH}\right]_i \qquad 9$$

Thus, a plot of the instantaneous ln of the ratio of hydroxide to thenil concentration vs time should give a straight line. A representative example of equation 9 is shown in Figure 11, p 59 for the reaction of 2,2'-thenil at 60° with hydroxide. Although rate constants can be calculated from the slope of this line, it was simpler to obtain them directly from equation 8.

A good estimate of the accuracy of the rate constants can be made in the following manner. The temperature of the various kinetic determinations was known to ±0.013%. Time could easily be measured to 1 second in 10,000 or 0.01%.

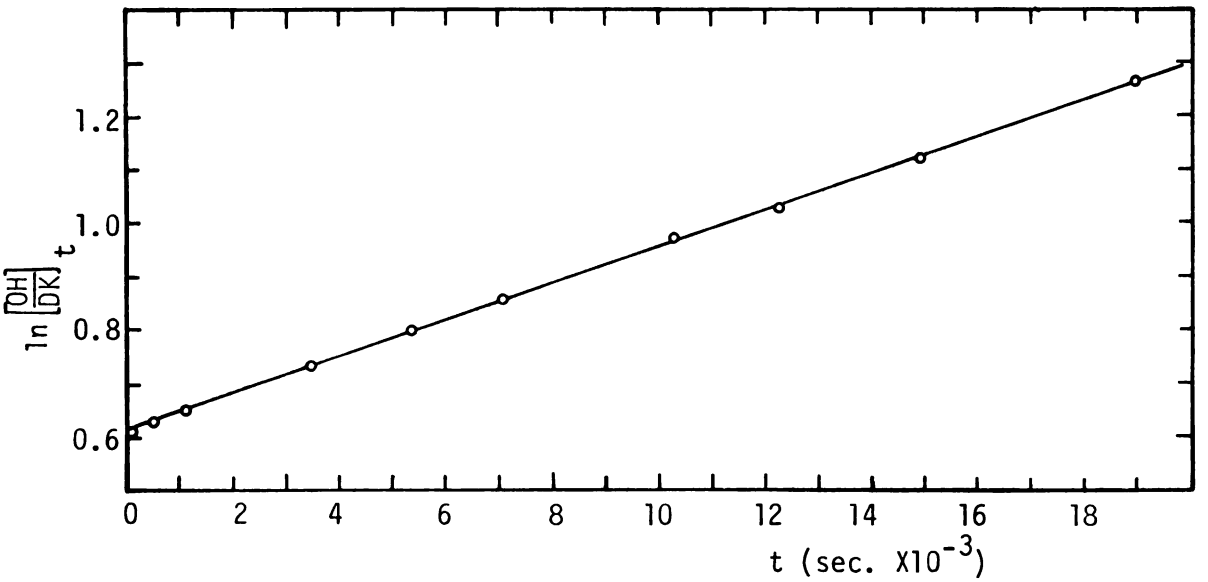


Figure 11. Second Order Kinetic Plot by Equation 9 for 2,2'-thenil at 60°

All glassware was calibrated to 0.01 ml and all weighings were made to 0.1 mg. Total systematic errors were therefore, estimated at not greater than 0.2%. Thus, the uncertainty in the rate constants must arise principally from random errors. These random errors are expressed as the standard deviation, i.e. the 68.3% confidence level of the individual rate determinations. The usual practice was to make only one run at a given temperature and to reject any determination that fell outside the limits of experimental error in the Arrhenius plot. Occasionally, random runs were redetermined to insure the reproducibility of the rate determinations. This was especially necessary in the determination of the rate constant for 2,2'-thenil at 50°, since much of the data used in the Hammett plots would depend on this rate constant. With the exception of the three compounds mentioned earlier, all of the thenils gave consistent rate constants in accordance with equation 8 and equation 9. A complete summary of the rate data is presented in Table 4, p 60.

Table 4. Second Order Rate Constants for the Thenil-Thenilic Acid Rearrangement at Various Temperatures

Compound [a,b]	15°	30°	40°	50°
2,2'-thenil	6.07×10^{-5}	2.35×10^{-4}	$5.35\pm0.14\times10^{-4}$	$1.22\pm0.04\times10^{-3}$
5,5'-dimethyl-2,2'-thenil	1.22×10^{-5}	4.50×10^{-5}	$9.85\pm0.73\times10^{-5}$	$1.96\pm0.30\times10^{-4}$
5-methyl-2,2'-thenil	3.84×10^{-5}	1.28×10^{-4}	$2.74\pm0.13\times10^{-4}$	$5.20\pm0.31\times10^{-4}$
5,5'-dichloro-2,2'-thenil	$1.29\pm0.04\times10^{-2}$	$4.50\pm0.33\times10^{-2}$	$9.18\pm0.14\times10^{-2}$	1.86×10^{-1}
5,5'-difluoro-2,2'-thenil	$5.11\pm0.14\times10^{-3}$	$1.81\pm0.07\times10^{-2}$	3.90×10^{-2}	$8.07\pm0.35\times10^{-2}$
5,5'-di-(2"-thienyl)-2,2'-thenil	1.24×10^{-4}	4.88×10^{-4}	1.12×10^{-3}	$2.57\pm0.12\times10^{-3}$
2,2'-benzo[b]thenil	8.53×10^{-4}	3.84×10^{-3}	$9.77\pm1.23\times10^{-3}$	$2.36\pm0.07\times10^{-2}$
2-thienylphenyl diketone	1.99×10^{-5}	3.11×10^{-5}	$1.82\pm0.14\times10^{-4}$	$3.68\pm0.12\times10^{-4}$
3,3'-thenil	3.61×10^{-5}	7.92×10^{-5}	$1.31\pm0.07\times10^{-4}$	$1.87\pm0.15\times10^{-4}$

	60°	70°	80°
2,2'-thenil	$2.46\pm0.08\times10^{-3}$	$4.96\pm0.11\times10^{-3}$	$9.36\pm0.11\times10^{-3}$
5,5'-dimethyl-2,2'-thenil	$3.84\pm0.31\times10^{-4}$	$7.54\pm0.45\times10^{-4}$	$1.57\pm0.15\times10^{-3}$
5-methyl-2,2'-thenil	$1.00\pm0.02\times10^{-3}$	$1.93\pm0.07\times10^{-3}$	$3.40\pm0.07\times10^{-3}$
5,5'-dichloro-2,2'-thenil	3.60×10^{-1}	6.70×10^{-1}	1.20
5,5'-difluoro-2,2'-thenil	1.60×10^{-1}	3.03×10^{-1}	5.55×10^{-1}
5,5'-di-(2"-thienyl)-2,2'-thenil	$5.11\pm0.38\times10^{-3}$	$1.14\pm0.07\times10^{-2}$	$2.01\pm0.34\times10^{-2}$
2,2'-benzo[b]thenil	$5.46\pm0.23\times10^{-2}$	$1.12\pm0.08\times10^{-1}$	2.33×10^{-1}
2-thienylphenyl diketone	$8.79\pm0.62\times10^{-4}$	$1.48\pm0.07\times10^{-3}$	$3.65\pm0.25\times10^{-3}$
3,3'-thenil	$3.07\pm0.11\times10^{-4}$	$4.60\pm0.24\times10^{-4}$	6.85×10^{-4}

[a]Rate constants shown without standard deviations are those extrapolated from the Arrhenius plot.

[b]The unit for all rate constants is liter/mole-second.

In order to obtain accurate rate constants, a few minor corrections were occasionally necessary. As might be expected, the strongly alkaline solutions employed in the reaction necessitated something other than glass for a reaction vessel. Polyethylene containers were tried but it was noted that values for the rate constants tended to decrease slightly with time, and correspondingly, the vessels were stained a bright yellow. This problem was corrected by employing teflon bottles in all rate constant determinations.

Despite this, determinations of k (run in teflon) now trended upward slightly on long runs at high temperatures. This effect must be ascribed to consumption of base by the solvent, since a blank run, that is a typical kinetic run under the same conditions but omitting the thenil, still showed a small consumption of base with time. By determining a blank run simultaneously with each kinetic run, an appropriate correction could be made for base which was not being consumed by the rearrangement. This was found to be necessary only at temperatures of 70° or 80° and for reaction times longer than 10^5 seconds. This correction was never more than 3% of the total base consumed.

A small temperature dependent correction in initial concentration of the reatants arose from the departure from ideality of the mixture of dioxane and water. That is to say, the 150 ml of 2:1 dioxane-water employed in a given kinetic run was slightly less than 150 ml at various temperatures. The correction is easily made by comparing the determined density of the mixture as a function of the temperature of the mixture (109) with the weighted sums of the densities of the individual components as a function of temperature (110).

This correction amounts to about 2% in the temperature range of 50-80°. A table showing the correction employed at each temperature is given in the experimental section, p 144.

It was difficult to obtain accurate and precise rate constants for reactions with half lives <150 seconds. At the other end of the time scale, tedium and the aforementioned reaction of the solvent with hydroxide made accurate work difficult for reactions with half lives greater than 200,000 seconds. While direct measurements of the rate constants were not made at all temperatures for a given thenil, they were readily calculated from equation 10, the Arrhenius equation.

$$k = Ae^{-E_a/RT} \qquad \text{or} \qquad \ln k = \ln A - \frac{E_a}{RT} \qquad 10$$

Such calculated rate constants are indicated in Table 4 by omission of the standard deviation.

The slope of equation 10 is equal to the activation energy, E_a times the gas constant R. Arrhenius plots with slopes calculated by least squares analysis are given in Figures 12-20, pp 63-65. The intercept of the Arrhenius plot gives the ln of the pre-exponential factor A. For a reaction in solution, the activation energy can be converted to the thermodynamically more useful enthalpy of activation $\Delta H^{\ddagger}$ by equation 11.

$$E_a = \Delta H^{\ddagger} + RT \qquad 11$$

The Eyring equation, 12 may be used to calculate $\Delta S^{\ddagger}$, the entropy of activation with κ, the transmission coefficient being assumed equal to unity (111a).

$$k = \frac{\kappa k' T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R} \qquad 12$$

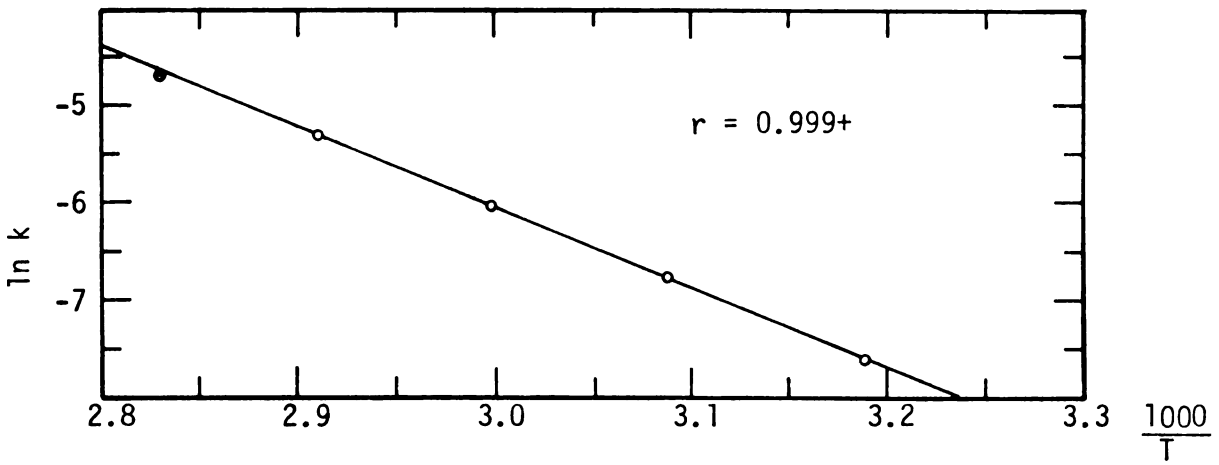


Figure 12. Arrhenius plot of 2,2'-thenil

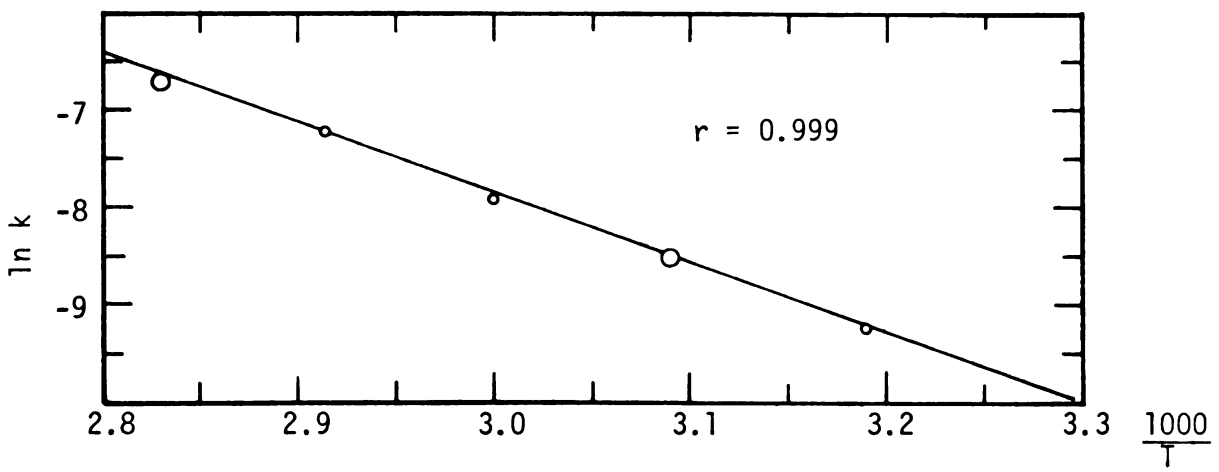


Figure 13. Arrhenius plot of 5,5'-dimethyl-2,2'-thenil

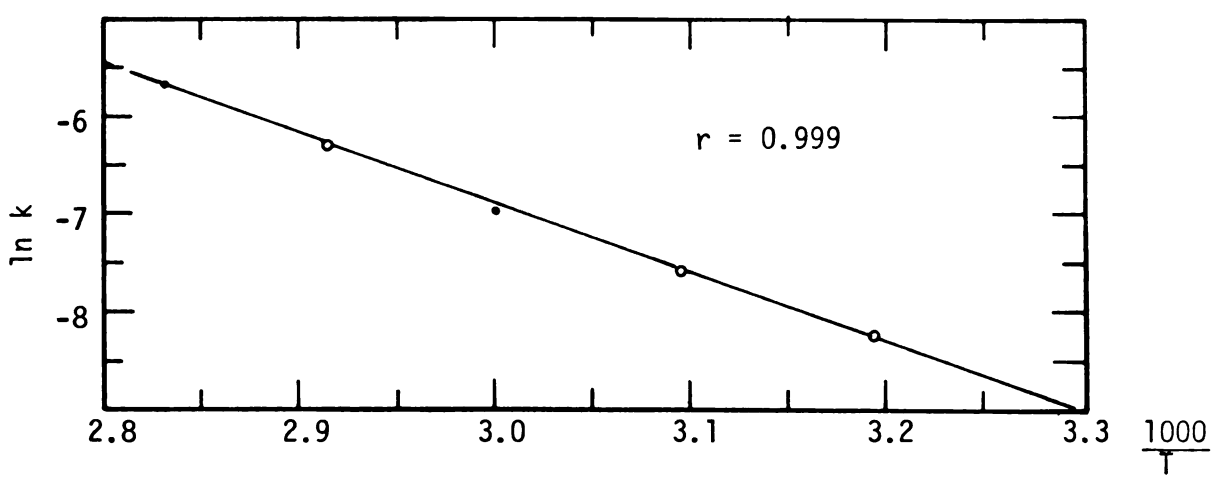


Figure 14. Arrhenius plot of 5-methyl-2,2'-thenil

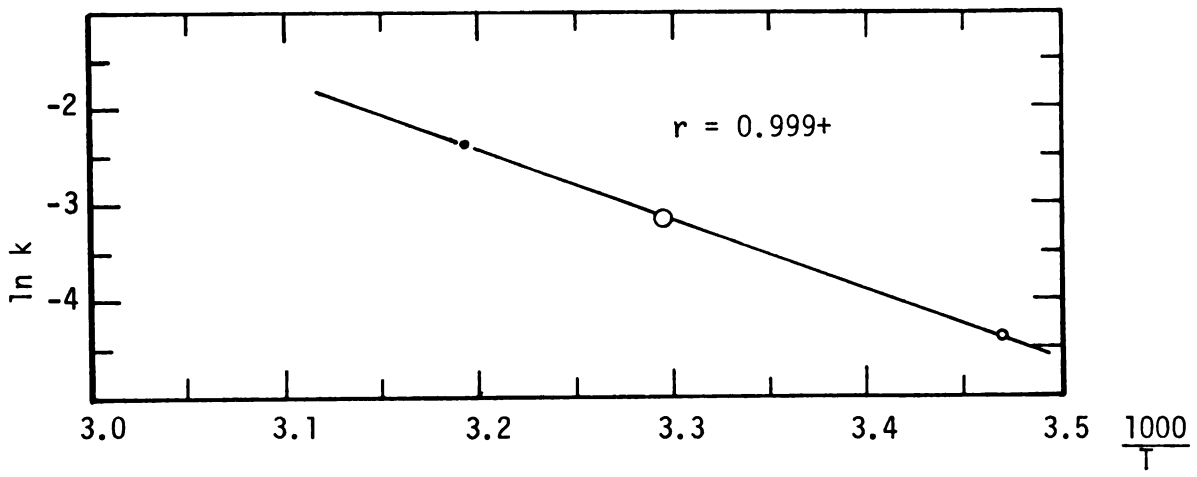


Figure 15. Arrhenius plot of 5,5'-dichloro-2,2'-thenil

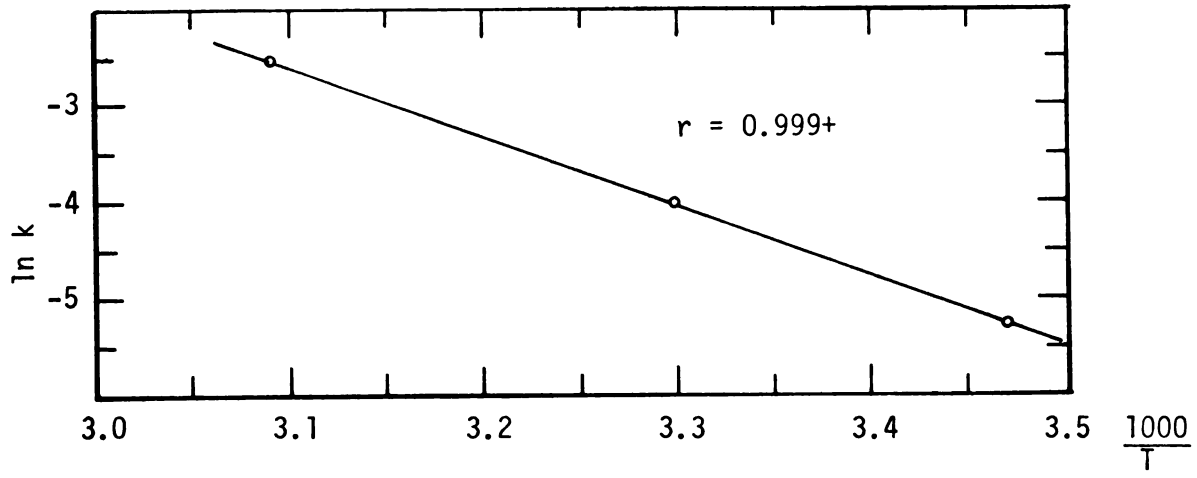


Figure 16. Arrhenius plot of 5,5'-difluoro-2,2'-thenil

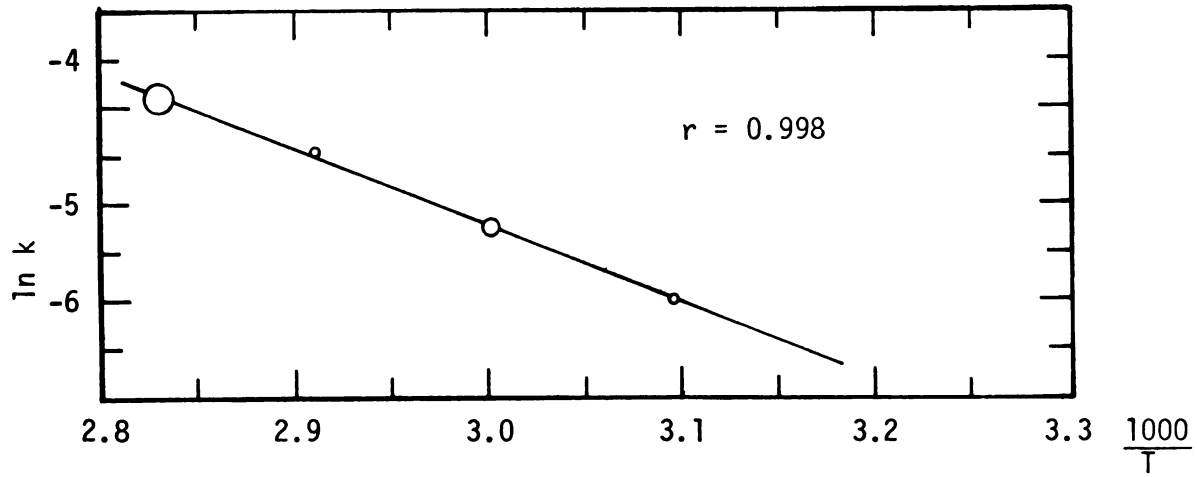


Figure 17. Arrhenius plot of 5,5'-di-(2"-thienyl)-2,2'-thenil

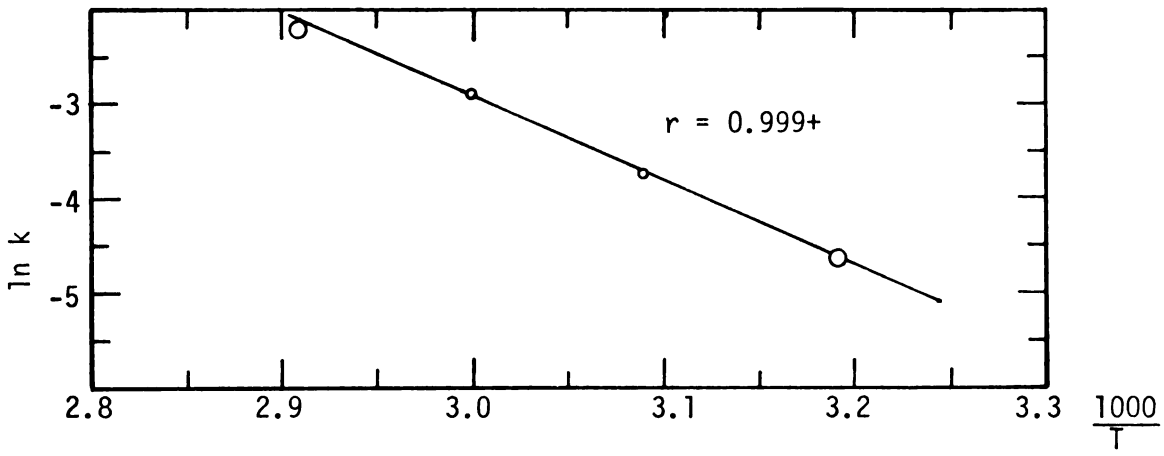


Figure 18. Arrhenius plot of 2,2'-benzo[b]thenil

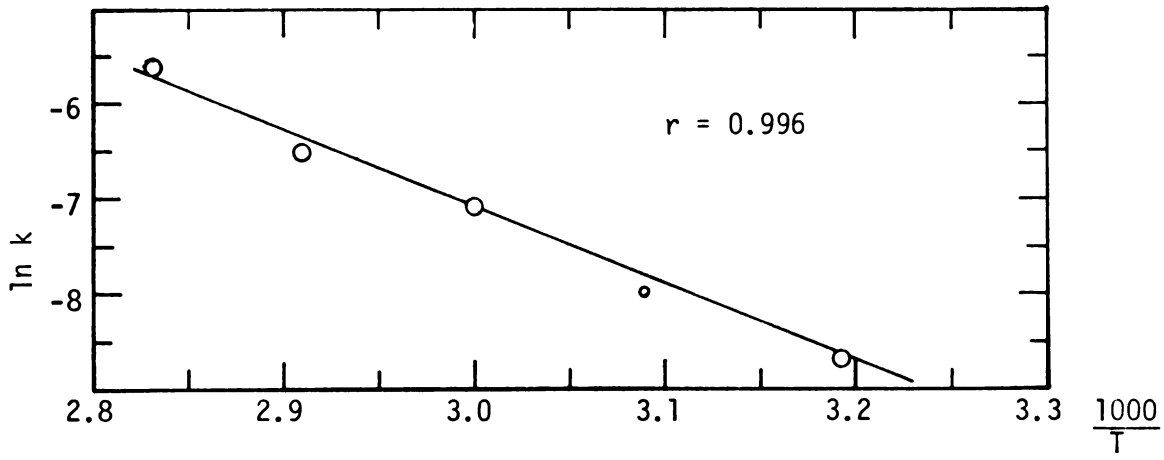


Figure 19. Arrhenius plot of 2-thienylphenyl diketone

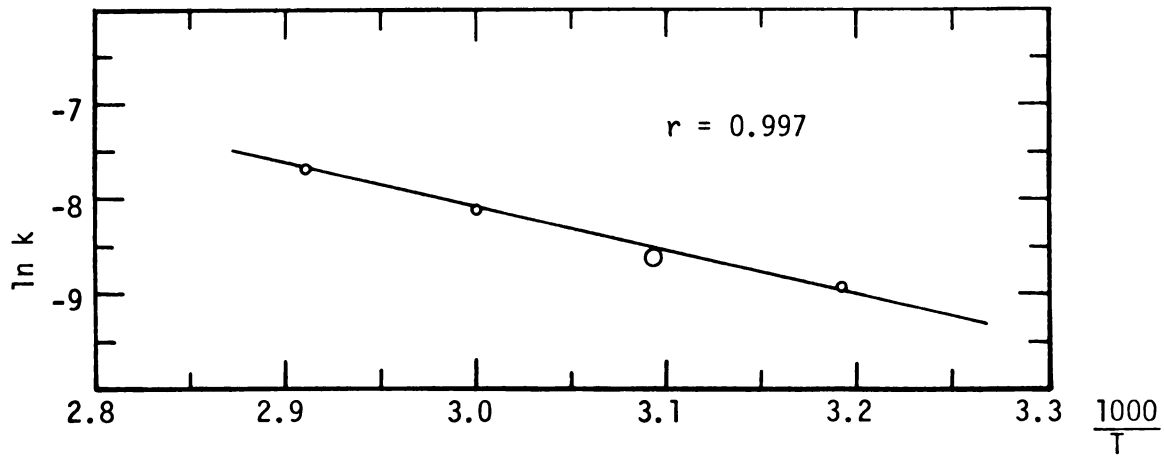


Figure 20. Arrhenius plot of 3,3'-thenil

Equation 13, readily derived from equations 10, 11, and 12 gives $\Delta S^{\ddagger}$ directly in terms of A, the pre-exponential factor, when time is expressed in seconds and the temperature is approximetely 323°K. Within a range of $\pm$ 30° , the maximum error arising from the use of equation 13 to calculate $\Delta S^{\ddagger}$ at other temperatures is only 0.4%.

$$\Delta S^{\ddagger} = 4.576 \log A - 60.689 \qquad 13$$

According to Benson (113) the errors in $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ are easily calculated. Use of the Arrhenius equation to determine E_a leads to the fractional error in E_a to be

$$\left(\frac{\Delta \bar{E}}{\bar{E}}\right)^2 = \left(\frac{T_2}{T_1-T_2}\right)^2 \left(\frac{T_1}{T_1}\right)^2 + \left(\frac{T_1}{T_1-T_2}\right)^2 \left(\frac{T_2}{T_2}\right)^2 + \left[\frac{1}{\ln(k_2/k_1)}\right]^2 \left[\left(\frac{k_1}{k_1}\right)^2 + \left(\frac{k_2}{k_2}\right)^2\right] \qquad 14$$

We have already seen that errors in the temperature are negligible, therefore the first two terms in equation 14 may be dropped, leaving the error dependant only on the standard deviations in the rate constants. In the error equation 14, k_2 and k_1 are the experimentally measured rate constants at the extremes of the Arrhenius plot.

Wiberg has shown that the error in $\Delta S^{\ddagger}$ is linerally related to the error in $\Delta H^{\ddagger}$ (114). He derived equation 15 which expresses the fractional error in $\Delta S^{\ddagger}$ as a function of δ, the error in $\Delta H^{\ddagger}$ and α, the error in the rate constants. In the present study α was taken to equal the average of the standard deviations in all the rate constants for a given compound.

$$\frac{\Delta \Delta S^{\ddagger}}{\Delta S^{\ddagger}} = \delta(1/T) + R\ln(1 + \alpha) \qquad 15$$

The thermodynamic properties of the thenil-thenilic acid rearrangement are summarized in Table 5.

Table 5. Thermodynamic Constants for the Thenilic Acid Rearrangement

Compound [a]	$\Delta H^{\ddagger}_{323°K}$	$\Delta S^{\ddagger}_{323°K}$	$\Delta F^{\ddagger}_{323°K}$	logA
2,2'-thenil	15.0±0.3	-25.6±1.3	23.3±0.7	7.676
5,5'-dimethyl-2,2'-thenil	14.5±1.0	-30.8±5.5	24.4±2.8	6.522
5-methyl-2,2'-thenil	13.3±0.4	-32.5±2.4	23.8±1.2	6.162
5,5'-dichloro-2,2'-thenil	13.5±0.6	-20.3±1.6	20.0±1.1	8.820
5,5'-difluoro-2,2'-thenil	14.6±0.4	-20.5±1.5	20.6±0.9	8.773
2,2'-benzo[b]thenil	16.8±1.0	-14.2±1.8	21.4±1.6	10.155
5,5'-di-(2"-thienyl)-2,2'-thenil	15.2±1.3	-23.6±4.0	22.8±2.6	8.104
2-thienylphenyl diketone	15.6±0.6	-26.1±3.0	24.0±1.6	7.569
3,3'-thenil	8.40±0.8	-49.5±5.4	24.4±2.5	2.447

[a] $\Delta H^{\ddagger}$ and $\Delta F^{\ddagger}$ are in units of kcal/mole $\Delta S^{\ddagger}$ is in cal/°K-mole

The determination of ρ, the reaction constant, was of importance from a mechanistic interpretation and as a test of the validity of using σ_θ instead of σ, in the Hammett plot. Only the first six compounds in Table 5 are suitable for a $\sigma_\theta\rho$ plot. The plot of log k/k_o for these six thenils at the seven temperatures employed in the kinetic studies are shown in Figures 21-27, pp 68-71.

At 50° a plot of log k/k_o vs σ given in Table 3 shows a rather poor correlation coefficient of 0.923, Figure 24, in contrast to the"excellent" values given in Table 6, p 71. Table 6 represents a complete summary of ρ values, standard deviations, and correlation coefficients as a function of temperature. The σ_θ values used in these plots were those of Table 3, p 55.

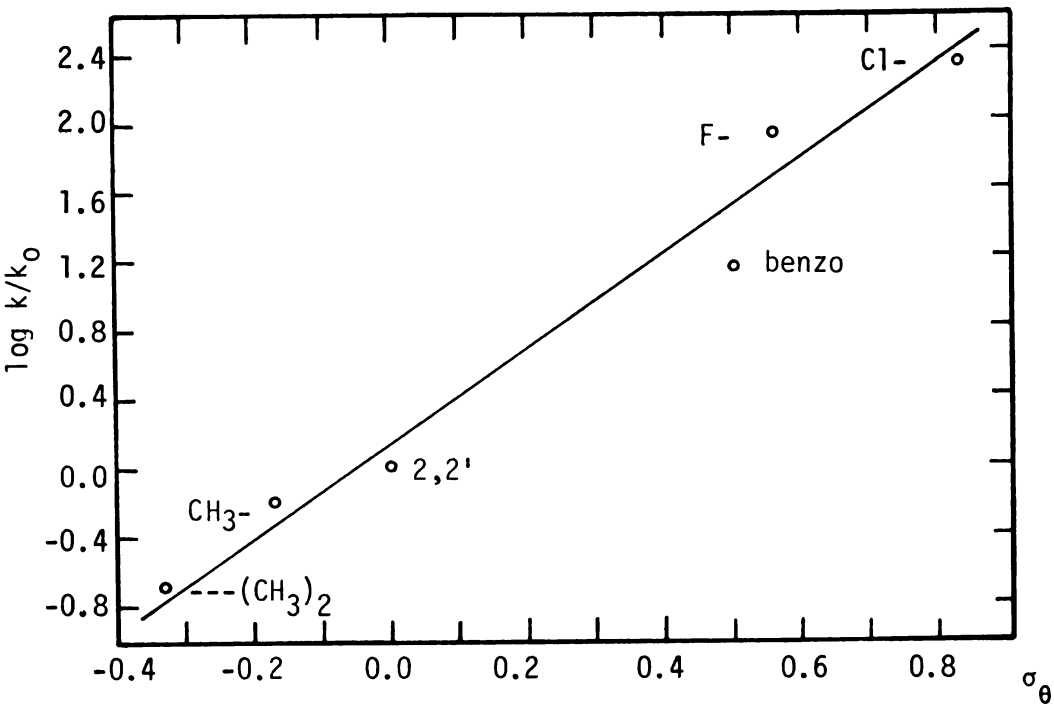


Figure 21. Hammett plot for the thenilic acid rearrangement at 15°

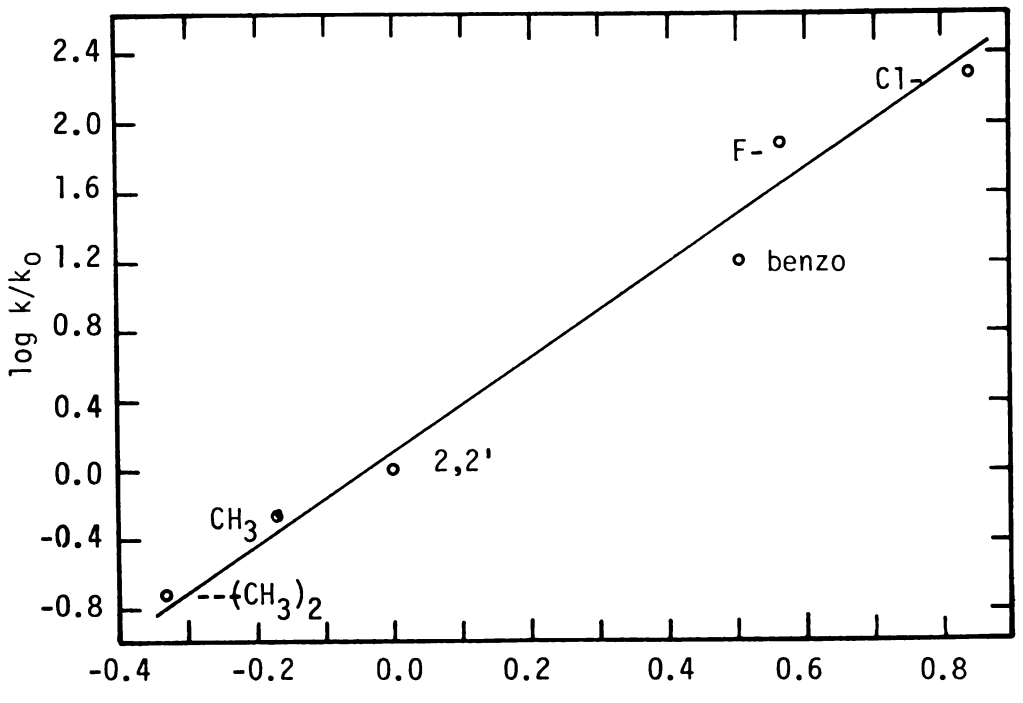


Figure 22. Hammett plot for the thenilic acid rearrangement at 30°

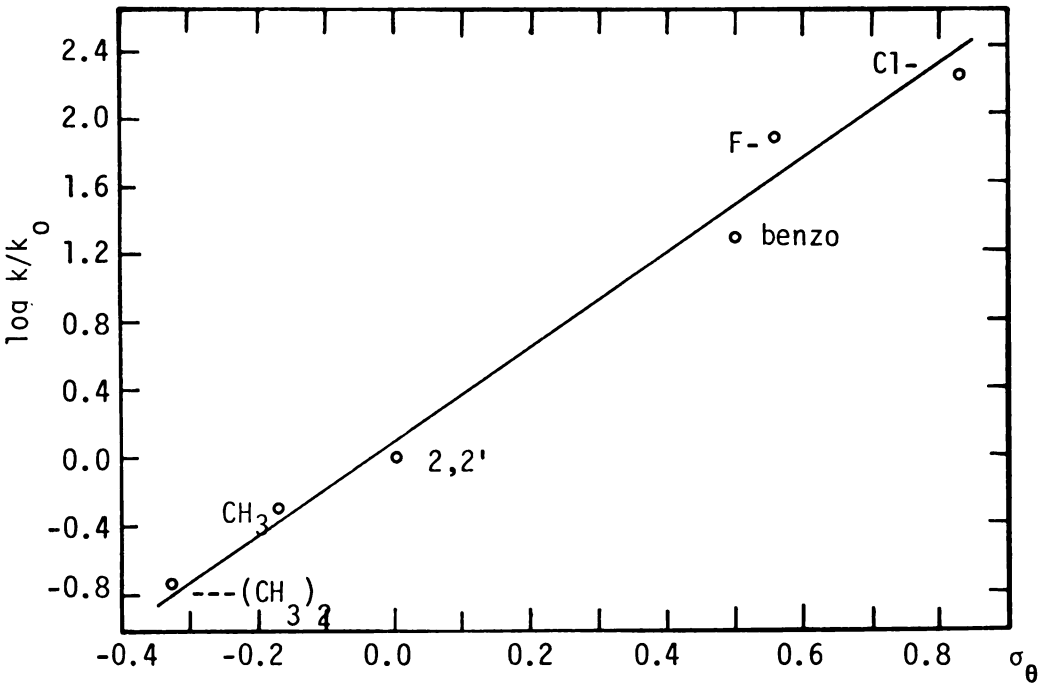


Figure 23. Hammett plot for the thenilic acid rearrangement at 40°

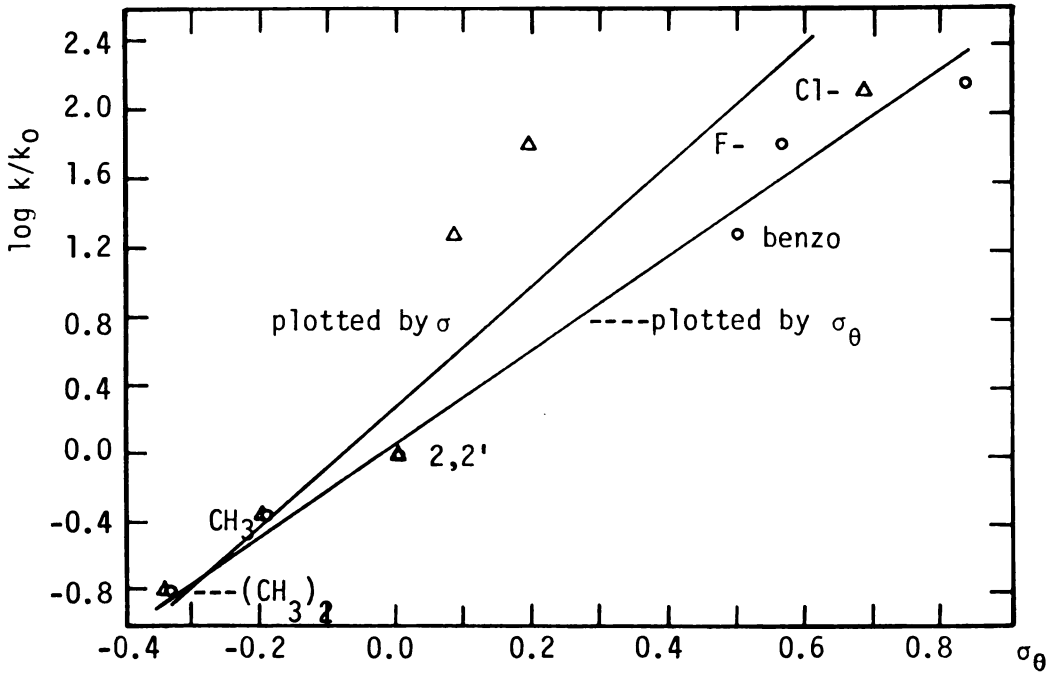


Figure 24.Hammett plot for the thenilic acid rearrangement at 50°

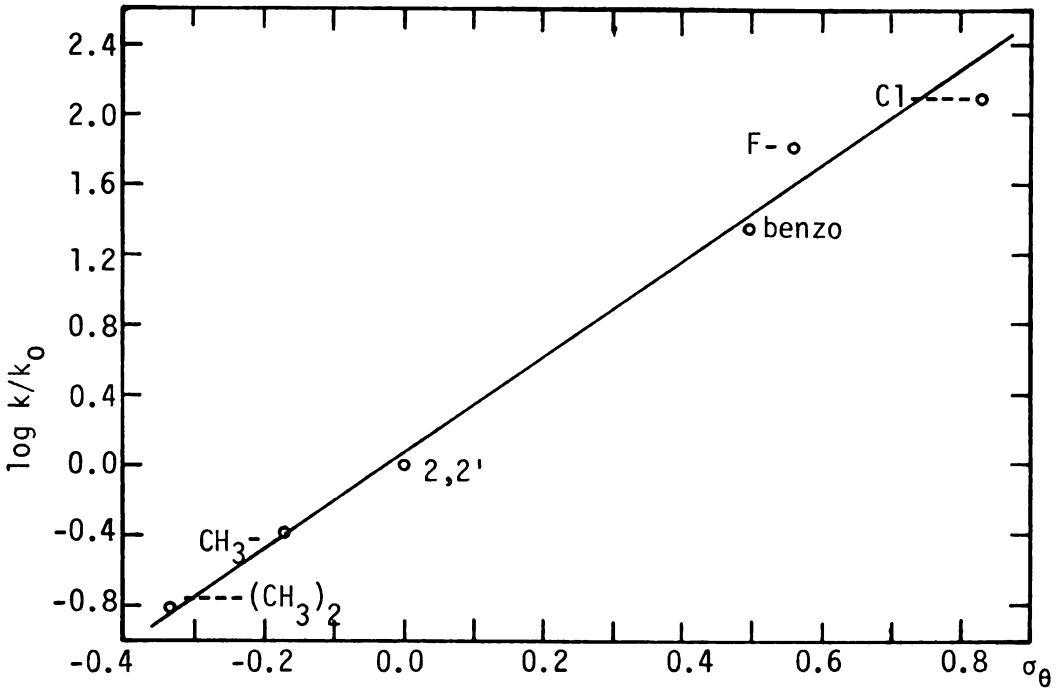


Figure 25. Hammett plot for the thenilic acid rearrangement at 60°

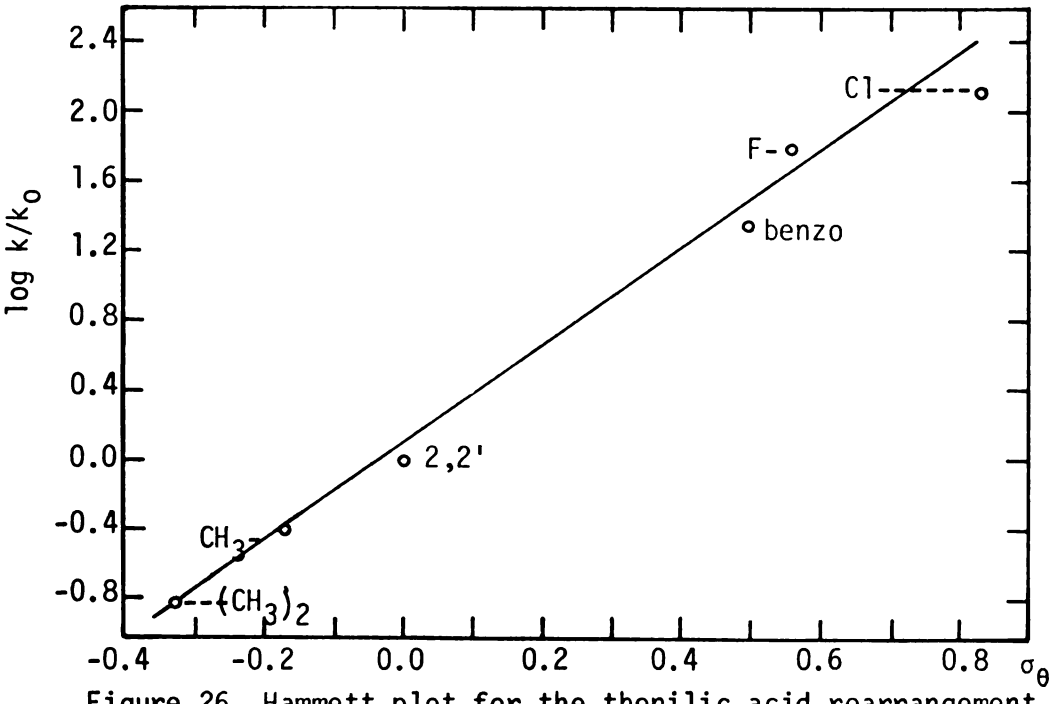


Figure 26. Hammett plot for the thenilic acid rearrangement at 70°

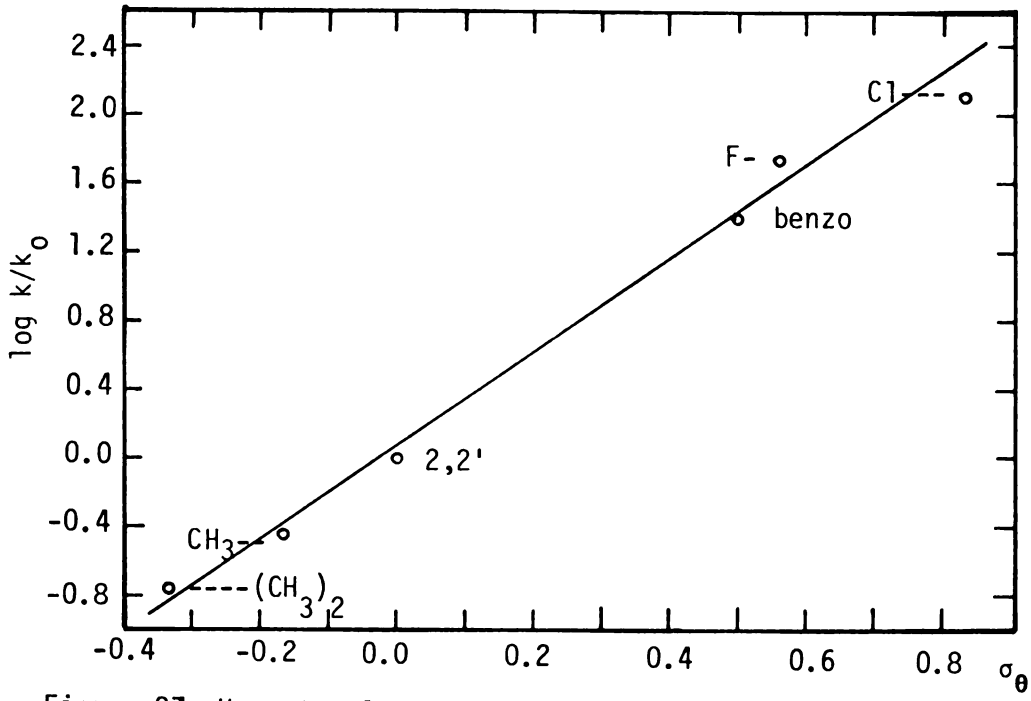


Figure 27. Hammett plot for the thenilic acid rearrangement at 80°

In Figures 21-27, the thenils were represented by the symbols $(CH_3)_2$ for 5,5'-dimethyl-2,2'-thenil; CH_3 for 5-methyl-2,2'-thenil; 2,2' for 2,2'-thenil; benzo for 2,2'-benzo[b]thenil; F- for 5,5'-difluoro-2,2'-thenil; and Cl- for 5,5'-dichloro-2,2'-thenil.

Table 6. Rho Values, Standard Deviations, and Correlation Coefficients for the Thenilic Acid Rearrangement in the Temperature Range of 15-80°.

	15°	30°	40°	50°	60°	70°	80°
ρ	2.624	2.640	2.636	2.662	2.662	2.667	2.649
s	0.238	0.194	0.173	0.147	0.215	0.138	0.151
r	0.985	0.990	0.992	0.994	0.988	0.995	0.994

[a] calculated by the least squares method

Leffler has derived a quantity β, called the isokinetic temperature,(111b) defined as the slope of a plot of $\Delta H^{\ddagger}$ as a function of $\Delta S^{\ddagger}$. Theory predicts that ρ will undergo a sign inversion, that the σρ plot will exhibit maximum scatter and the effect of substituents on the reaction rate will be a minimum at the isokinetic temperature. Therefore, it is essential that rate studies have been made at temperatures remote from β before any mechanistic interpretation of either the magnitude or the sign of ρ can be assessed. The isokinetic plot of all nine thenils given in Table 5 is shown in Figure 28.

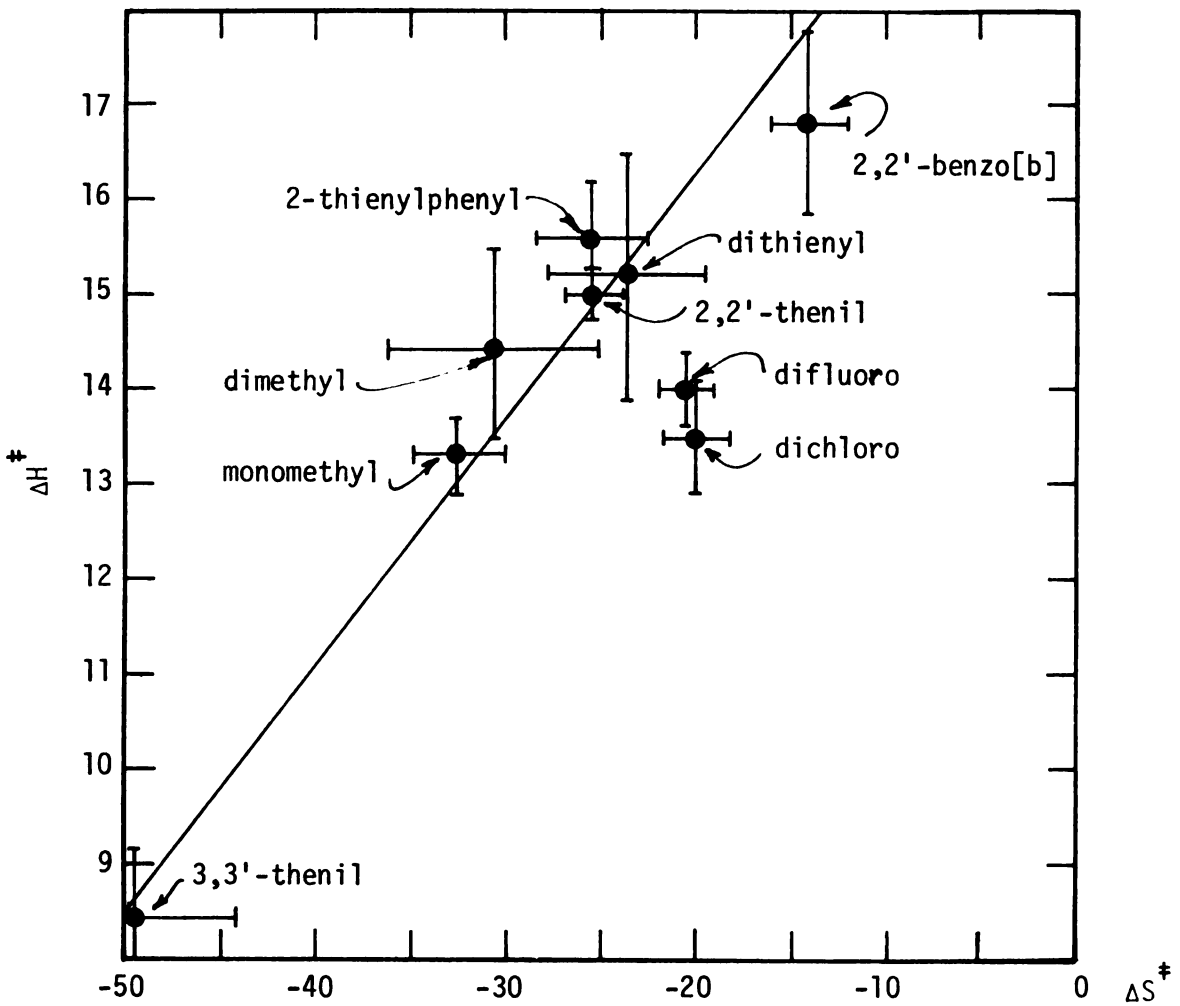


Figure 28. Isokinetic plot for the thenilic acid rearrangement.

The halothenils were omitted in the calculation of the isokinetic temperature. A postulate will be presented later that indicates the non-concerted nature of the thenilic acid rearrangement, which causes a strong deviation by the halothenils from the isokinetic line. Indeed, deviation from the isokinetic line often indicates the occurance of an additional perturbation on the mechanism.

The correlation coefficient, based on seven points, for the isokinetic plot was 0.971 and the isokinetic temperature was 242±24°K. It must be pointed out that the isokinetic temperature is arrived at in an ex post facto manner, that is after the rate constants have been determined in some arbitrarily chosen temperature range. In the present case, it can be seen that the kinetic determinations were fortuitously carried out in a valid temperature range.

Many observations and a great deal of postulation can now be presented.

The entropies of activation are in agreement with those expected for a reaction involving considerable restricted geometry in the transition state. The entropy of activation of -14.2 eu for the rearrangement of 2,2'-benzo[b]thenil indicates that a lesser degree of ordering may be necessary in going from the ground state to the transition state for the reaction. This may be due to steric interactions in the ground state which invoke a specific conformation of the benzo[b]thienyl rings. Coincidentally, this geometry may be similar to that required by the transition state and hence shows up as a more positive entropy of activation, relative to the other thenils.

In a similar manner, the high value of $\Delta S^{\ddagger}$ of -49.5 eu for the 3,3'-thenil rearrangement could indicate that the geometry of the transition state bears little resemblence to the ground state. It must be kept in

mind, however, that according to the Ingold mechanism for the rearrangement the observed thermodynamic data would be a function both of the equilibrium reaction between the thenil and hydroxide and the rearrangement of that intermediate to the thenilate anion.

Other factors, such as differences is solvation between the ground state and the transition state will also affect the entropy of activation, but such effects should be small relative to steric effects.

The rearrangement of 2,2'-thenil is faster ($k=1.22X10^{-3}$ l/mole-sec) than benzil ($k=1.00X10^{-4}$ l/mole-sec, ref 32) at 50° in 2:1 dioxane-water. This is a rather clear manifestation of the electron withdrawing nature of the 2-thienyl group which parallels the acidity of benzoic acid ($pK_a=4.229$ at 49.5°) vs 2-thenoic acid ($pK_a=3.617$ at 49.5°). One is tempted to postulate stabilization of the incipient negative charge at the migration origin via d-orbital interaction, although at this point there is nothing to substantiate this. It can be noted, though, that 3,3'-thenil in which the sulfur is one more carbon removed from the active site of the diketone rearranges at a rate almost the same as benzil.

Gronowitz has stated (116) that the -I effect of the thiophene ring is greater than benzene. If this is true, substitution of the 5- and 5'-hydrogens in 2,2'-thenil by 2-thienyl groups should increase the rate of rearrangement. This was found to be the case, cf Table 4, although the effect is not very dramatic. Using the value of 2.66,ρ,in the Hammett plot yields a secondary value for σ_θ of +0.04 for 2-thienyl.

In the interpretation of the rate data, a valid point may be raised that the rates of two of the diketones, 5,5'-di-(2"-thienyl)-2,2'-thenil and 2,2'-benzo[b]thenil were not determined at the same concentrations as the other thenils, and a correspondingly smaller amount of hydroxide

was used in the kinetic determinations. As a consequence of this, the rate constants would not be comparable if the rearrangement were subject to large salt effects. More than likely, this is a negligible factor as Westheimer has shown (33) that the salt effect in the benzilic acid rearrangement is very small. He found that an increase in the sodium ion concentration by a factor of 15 (compared with 3 for potassium ion in the present study) caused only a 14% increase in the rate constant for the rearrangement of benzil.

It is simple to calculate the rate constants for the rearrangement (k) of a hybrid compound like 2-thienylphenyl diketone from equation 16, where k_o and k' are the rate constants for the rearrangement of benzil and 2,2'-thenil.

$$k = (k'k_o)^{1/2} \qquad \underline{16}$$

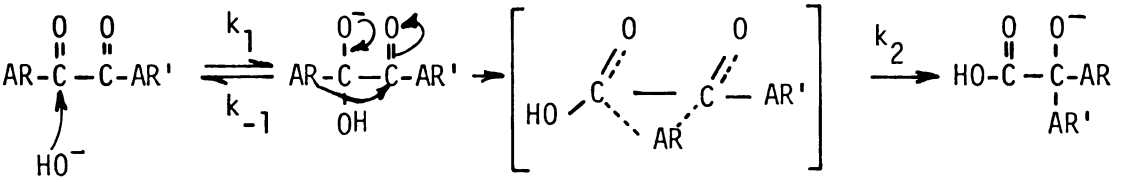
Thus the rate constant for the rearrangement of 2-thienylphenyl diketone by equation 16 is $3.49X10^{-4}$ at 50°, while the experimental value was found to be $3.68X10^{-4}$. In a similar manner, the calculated rate constant for the rearrangement of 5-methyl-2,2'-thenil is $4.89X10^{-4}$ based on the rate constants for 2,2'-thenil and 5,5'-dimethyl-2,2'-thenil. The experimentally measured value was $5.20X10^{-4}$. These calculated values are within the limits of experimental error.This simple relationship should allow one to predict the rate constants for any substituted thenils provided the values of the other two k's related to it in this manner are known.

The fairly large positive and constant value for ρ at all temperatures indicates that the reaction is facilitated by electron withdrawing substituents in accord with both the Ott-Clark (35, 36) and Ingold (117) mechanisms. The developing negative character at the migration origin as well

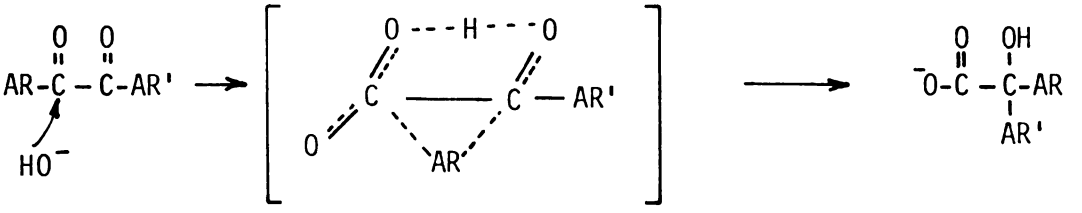
as the facilitating unsaturation of the carbonyl migration terminus should both be favored by electron withdrawing groups. For this reason, the σ_θ values used in the Hammett plot were taken as the sum of the two substituents.

Shown below are the two mechanisms proposed for the benzilic acid rearrangement.

THE INGOLD MECHANISM



THE OTT-CLARK MECHANISM



The essential difference between the two is the existence of an initial rapid equilibrium of the hydroxide and the diketone in the Ingold mechanism. If the Ingold mechanism is the correct one, then the observed rate constant will be given by equation 17, where K is the equilibrium constant.

$$k_{obs} = \frac{k_1}{k_{-1}} k_2 = Kk_2 \qquad \underline{17}$$

For substituents of the same type, alkyl, aryl for example, K should be nearly constant. For strongly electron withdrawing groups, e.g. halo or nitro, the equilibrium constant may be quite different. This naturally will have an effect on k_{obs} which cannot be accounted for purely on the basis of the substituent effect, unless one knows the value of the equilibrium constant.

In the thenilic acid rearrangement, the two methyl compounds and the benzo[b] compound did correlate well with $2\sigma_\theta$, at all temperatures. It must be noted here that σ_θ gives a much better fit than σ for the benzo[b] function. The halo σ's even using the larger values of σ_θ do not correlate well unless σ_θ is multiplied by three.

Several points now need to be borne in mind. If the Ott-Clark mechanism is valid, one would expect to observe a deuterium isotope effect on the experimental rate constant since their mechanism proposes that proton migration occurs as a concerted process with the rearrangement. Hine (32) failed to find an isotope effect, but instead found rate enhancement when the rearrangement was conducted using NaOD in D_2O. Since we do not know a priori, the enhancement of rate due to the greater basicity of NaOD in D_2O relative to NaOH in H_2O, it is possible that an isotope effect may exist which does not completely compensate for the isotopic rate enhancement. Therefore, Hine's study does not rule out the Ott-Clark mechanism.

In addition, Ott and Clark contend that the observed rapid uptake of O^{18} from O^{18}-enriched water (30) occurs through an equilibration process that is only incidental to the rearrangement.

Ott and Clark have measured the relative migratory aptitude of one aryl group vs the other in various unsymmetrically substituted carbonyl C^{14} monolabeled benzils. Since the ratios of the migrating aryls correlated with σ they argued that the reaction had to be concerted. However, it is difficult to explain why the equilibration step should affect the subsequent relative migration of one group with respect to the other.

In the present study, it was found that the halothenils did not correlate with σ_θ or σ. Indeed, the σ_θ values for both chloro and fluoro had to be multiplied by 3 to fit the $\sigma_\theta\rho$ plot. This coefficient of 3 may

be purely fortuitous. If we consider a more generalized Hammett equation 18

$$\log \frac{k}{k_o} = \rho n \sum \sigma_i \qquad 18$$

it is seen that we have assumed that n=1, i.e. the proper value of the substituent constant in the $\sigma_\theta\rho$ plot is obtained from the simple sum of the two sigmas. Considering Ingold's mechanism, we must include the equilibrium step in the value for k_{obs} , but we do not have any estimate of the proportion of contribution by each step in the mechanism to the magnitude of ρ.

In other words, n may have any value other than unity making it impossible to determine ρ unless the equilibrium constant K is known. However, the existence of the equilibrium step is verified by the nonconsistent values for n, or for what is actually observed, deviations from the linear relationship in the Hammett plot. Phrasing it still another way, the large rate enhancement due to the halo substituents, above that predicted on the basis of their σ_θ values, strongly suggests that the equilibrium step is part of the nonconcerted rearrangement in accord with the Ingold mechanism.

It was mentioned earlier that the reaction of hydroxide with 5,5'-dimethoxy-2,2'-thenil does not yield identifiable products. It was, however, somewhat surprising that the disappearance of hydroxide with time fits the rate law shown in equation 19, that is second order in hydroxide only.

$$\frac{d\,[OH]}{dt} = k[OH]^2 \qquad 19$$

A plot of ln[OH/DK] vs time gave a sharply rising plot, while the plot of of [1/OH] vs time was linear to over two half lives of the hydroxide as may be seen in Figure 29.

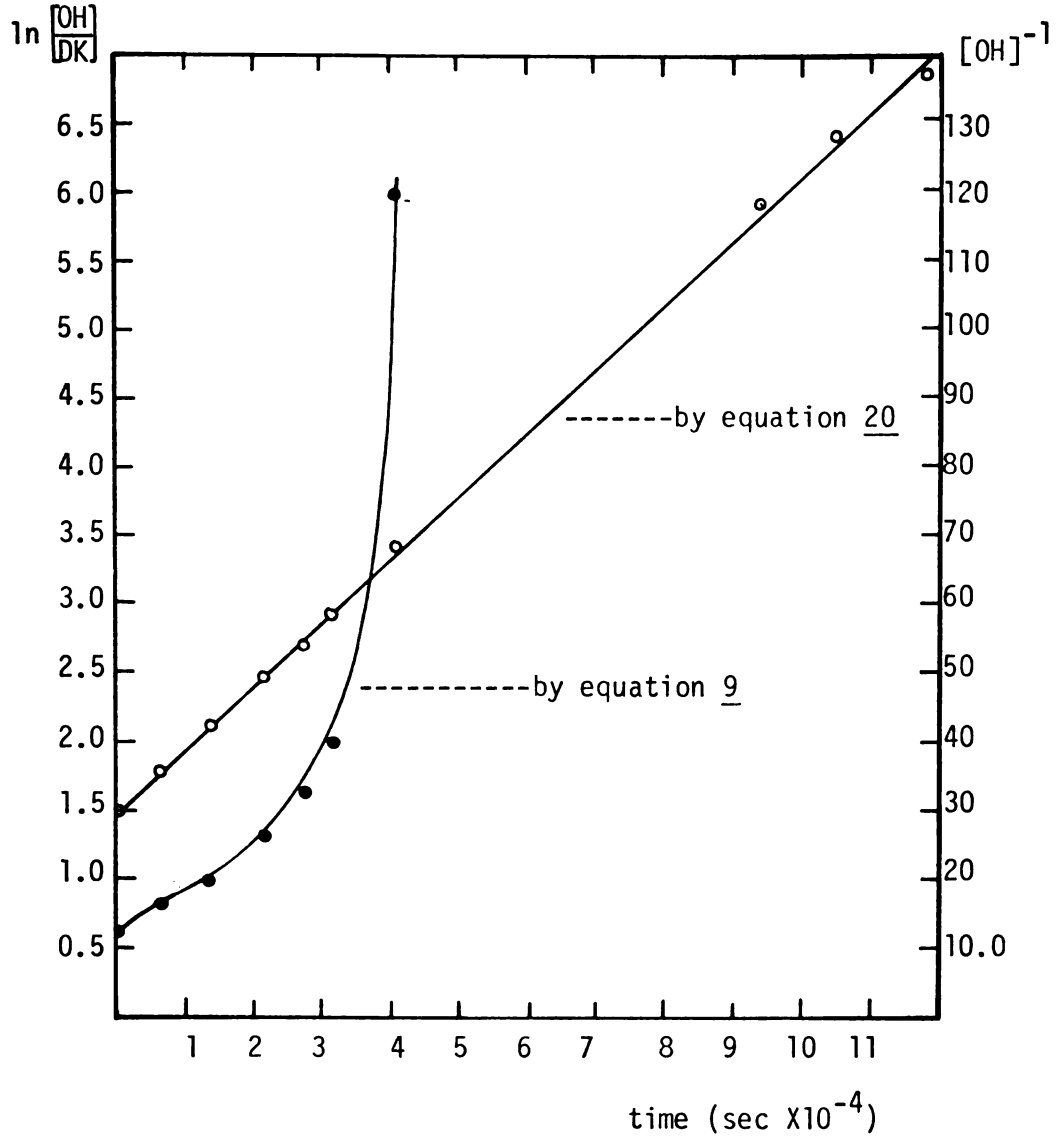


Figure 29. Second order kinetic plots for 5,5'-dimethoxy-2,2'-thenil by equations 9 and 20 at 80°.

Equation 19 is easily integrated to give equation 20.

$$k = 1/t(1/OH_t - 1/OH_i) \qquad 20$$

This rate expression holds reasonably well in the temperature range 40-80° as seen by the linearity of the Arrhenius plot in Figure 30.

It is easily hypothecated that the reaction depends in some manner on the attack of hydroxide at the alkoxy group. The more sterically hindered 5,5'-diisopropoxy-2,2'-thenil gave what appears to be mixed order kinetics

for the reaction with hydroxide although a roughly linear correlation was obtained by equation 20, Figure 31.

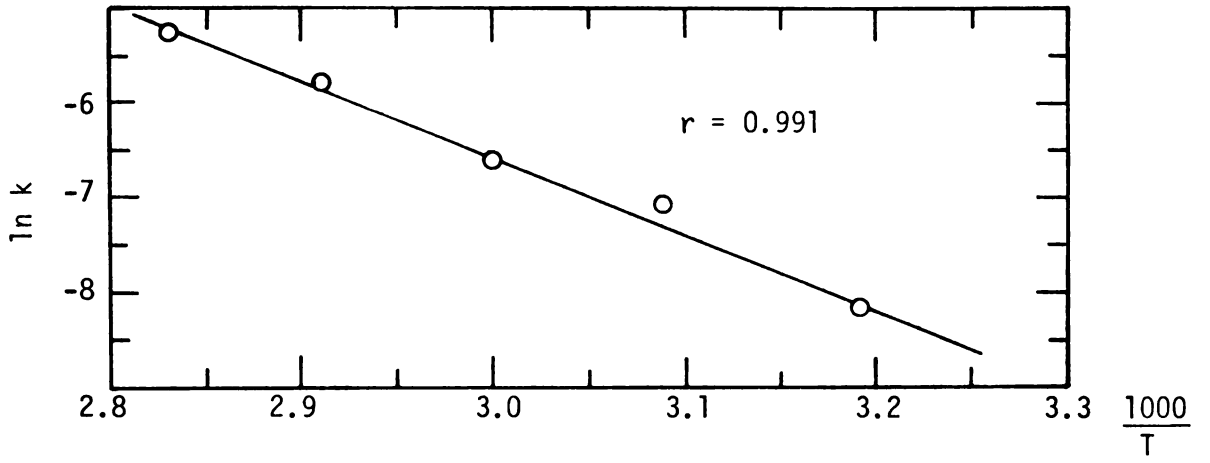


Figure 30. Arrhenius plot of 5,5'-dimethoxy-2,2'-thenil

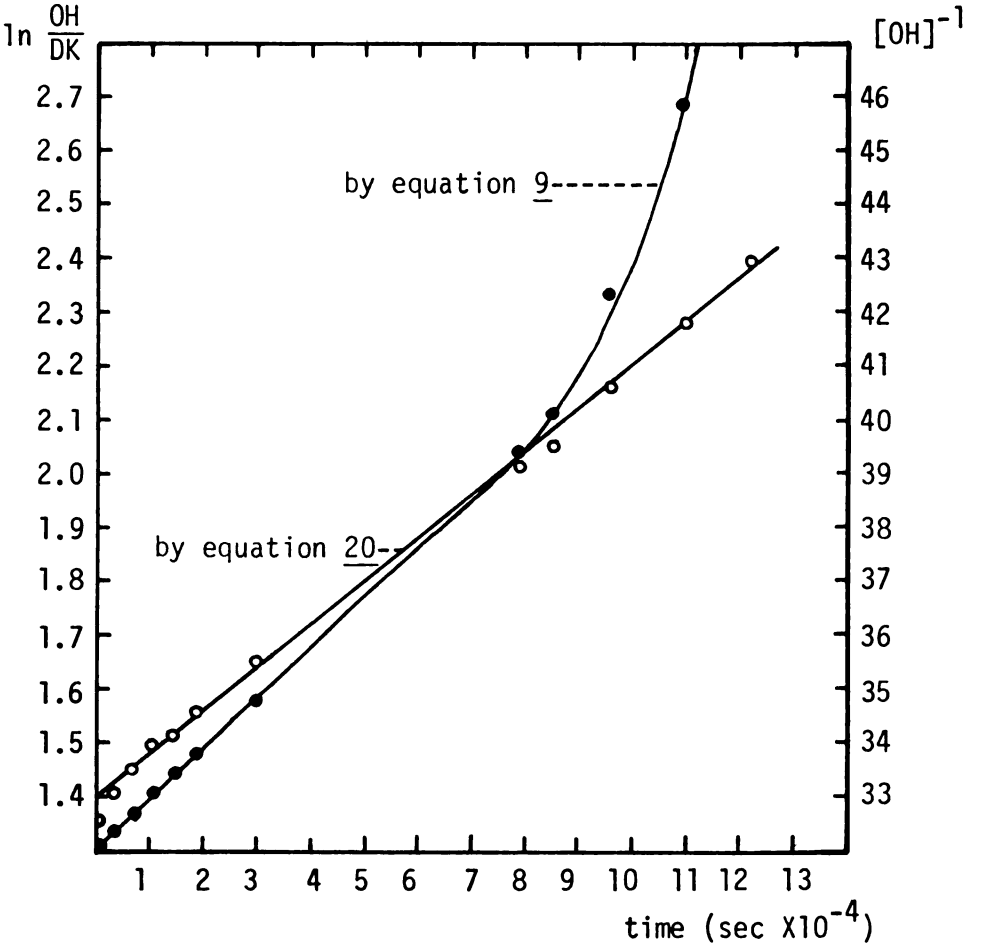


Figure 31. Second order kinetic plots for 5,5'-diisopropoxy-2,2'-thenil by equations 9 and 20 at 50°.

Approxiametly 5 times as great a reaction period was required to reduce the concentration of the isopropoxy compound by one half compared to the methoxythenil. This slow rate of disappearance strengthens the argument that the alkoxy group is involved directly with the reaction site. Two reasonable theories, one involving the intermediacy of a Meisenheimer type complex to give a labile hydroxythiophene and the other, an S_N2 attack on the alkoxy carbon were discussed on p 44.

On p 43, the anomalous reaction of 3,3'-benzo[b]thenil with hydroxide was mentioned. The thenil was cleaved and at least one of the products was identified as 3-benzo[b]thenoic acid. A nearly unvarying apparent rate constant was given by equation 21.

$$k = \frac{\ln[DK/OH]_i + \ln[OH/DK]}{t \cdot \ln[OH/DK][OH - DK]_i} \qquad 21$$

A plot of ln[OH/DK] as a function of time gives the steadily rising curve shown in Figure 32, p 82, while a plot of ln[OH/DK] vs k from equation 9 shows a linear relationship. This behavior could indicate a second consecutive reaction which according to the hypothetical scheme on p 44 would be the Cannizzaro reaction of the intermediate 3-thianapthaldehyde.

The 2-thienyl group appears to be a -I+M substituent in which either the inductive effect or the resonance effect can predominate depending on the reaction requirements. We have seen that the -I effect is dominant in the thenilic acid rearrangement. However, a serendipitous example of the +M effect was uncovered during the course of this investigation.

In a report of the synthesis of diarylglycolic acids by Blicke (118) he noted that they displayed characteristic colors of red to blue when dissolved in concentrated sulfuric acid. During the present synthetic

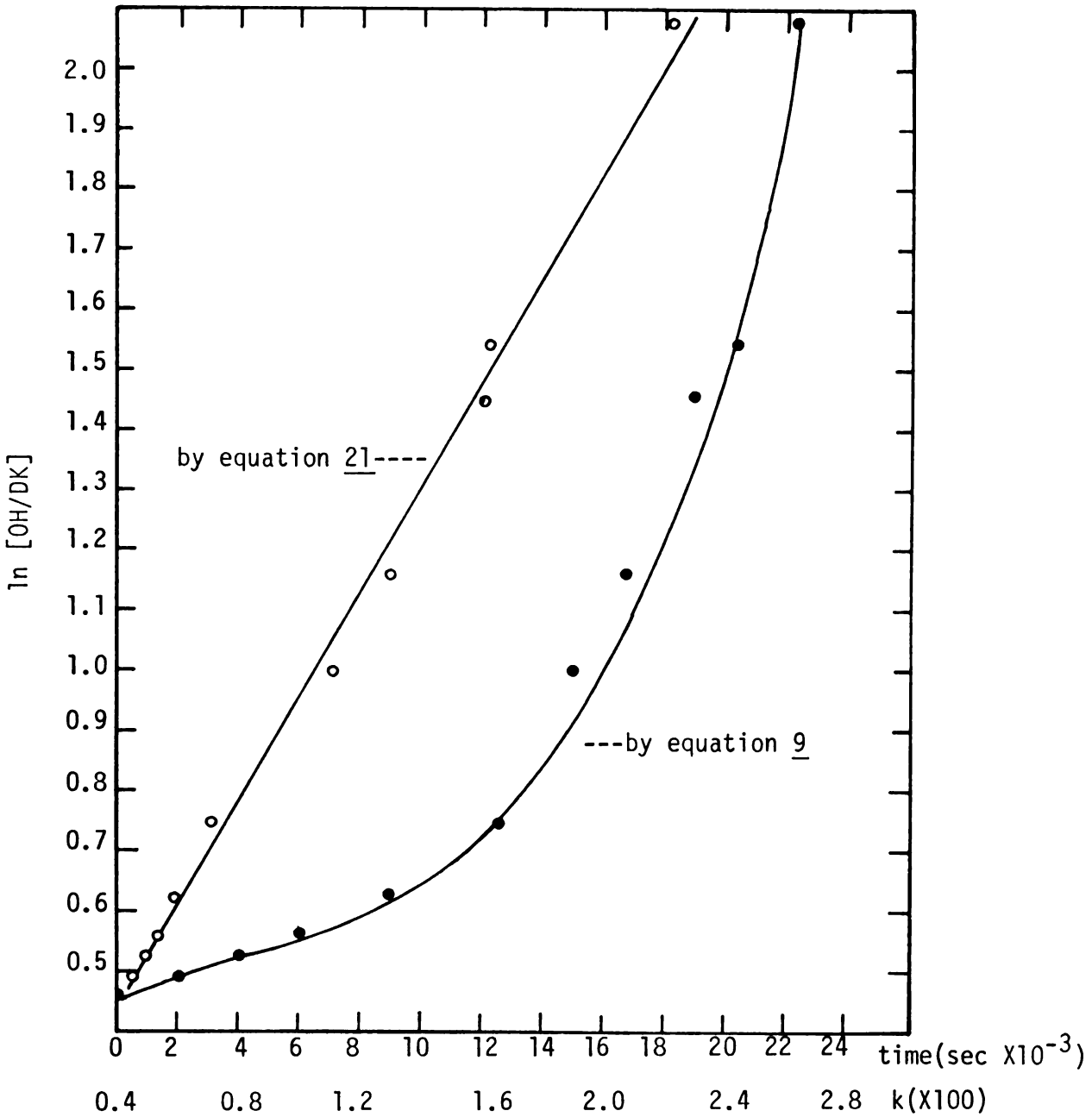


Figure 32. Kinetic plots for 3,3'-benzo[b]thenil by equations 9 and 21.

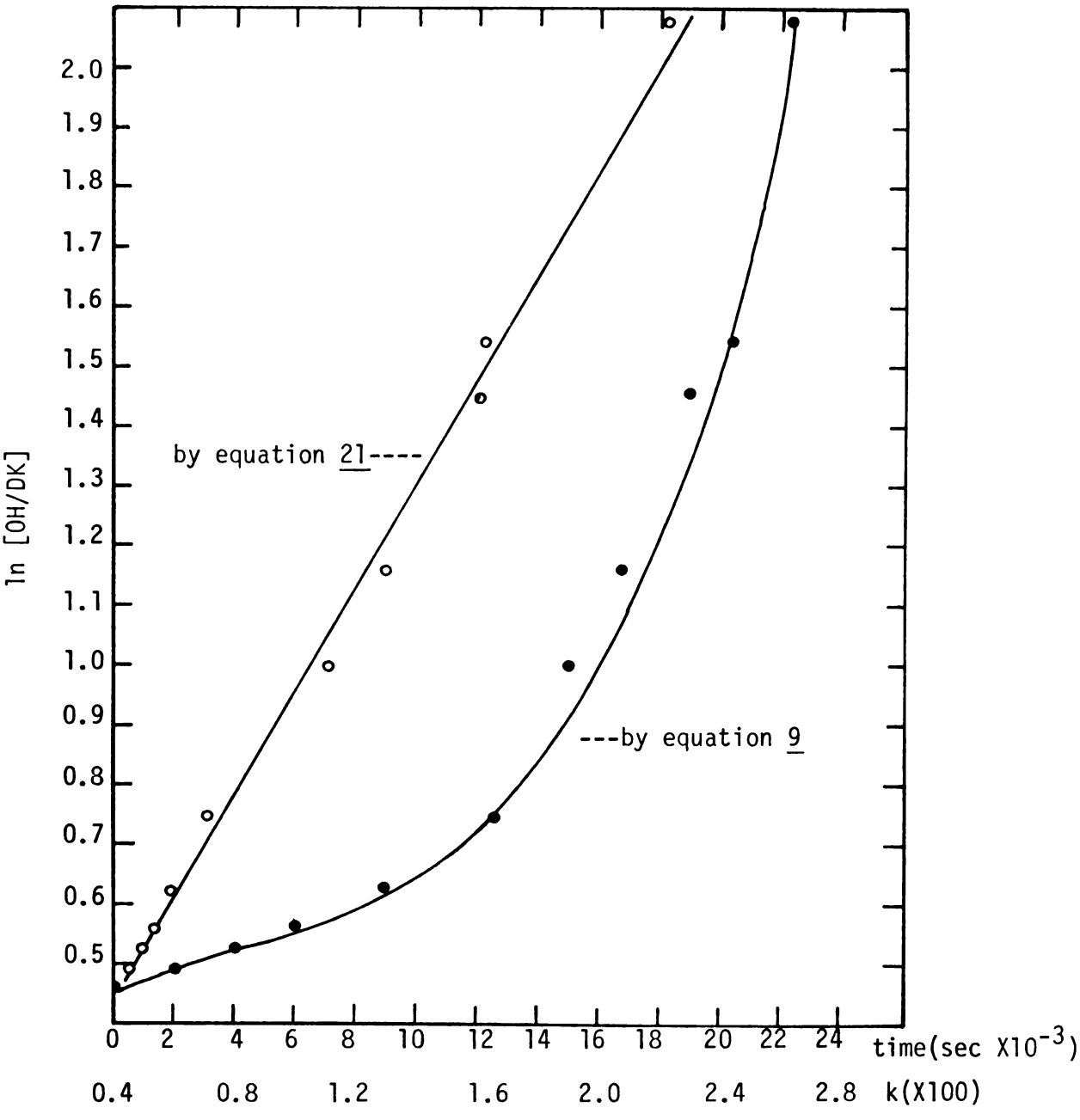
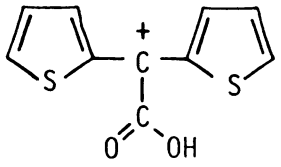


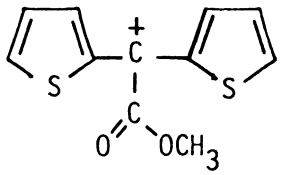
Figure 32. Kinetic plots for 3,3'-benzo[b]thenil by equations 9 and 21.

work, overacidification of the alkaline reaction mixture from the rearrangement of 2,2'-thenil gave a transient pink coloration. Sensing that this might be due to a "stable" carbonium ion (119) solutions of 2,2'-thenilic acid and its methyl ester in strong acids were examined by visible and nmr spectroscopy.

The visible spectrum, Figure 33, p 84 was determined in 50% (w/w) chlorosulfonic acid-methylene chloride, and shows λ_{max} at 518 nm (log ε = 4.52) indicative of an aryl stabilized carbonium ion.



(LXII)



(LXIII)

The decomposition of (LXII) could be monitored by observing the absorbance at 518 nm. Increasing the concentration of chlorosulfonic acid above 50% or decreasing it below 1% hastened the decomposition. At 10% $ClSO_3H$, the absorbance at 518 nm fell to half its initial value in 21 hours at 25±2°, with a starting concentration of $2X10^{-5}$ molar. Stable solutions of (LXII), i.e. no change in λ_{max} or initial log ε, could be formed in sulfuric acid-water mixtures down to 80% (w/w) sulfuric acid. The rate of decompsition increased as the percent of water was increased.

If the ruby red solutions of (LXII) in $ClSO_3H$-CH_2Cl_2 were quenched at -50° with anhydrous methanol or ethanol, and treated with diazomethane after workup, the methoxy (LXIV) or ethoxy (LXV) dithienyl acetic esters could be isolated in better than 95% yield. The nmr spectra of these compounds clearly indicate that no quenching of an acylcarbonium ion occurred.

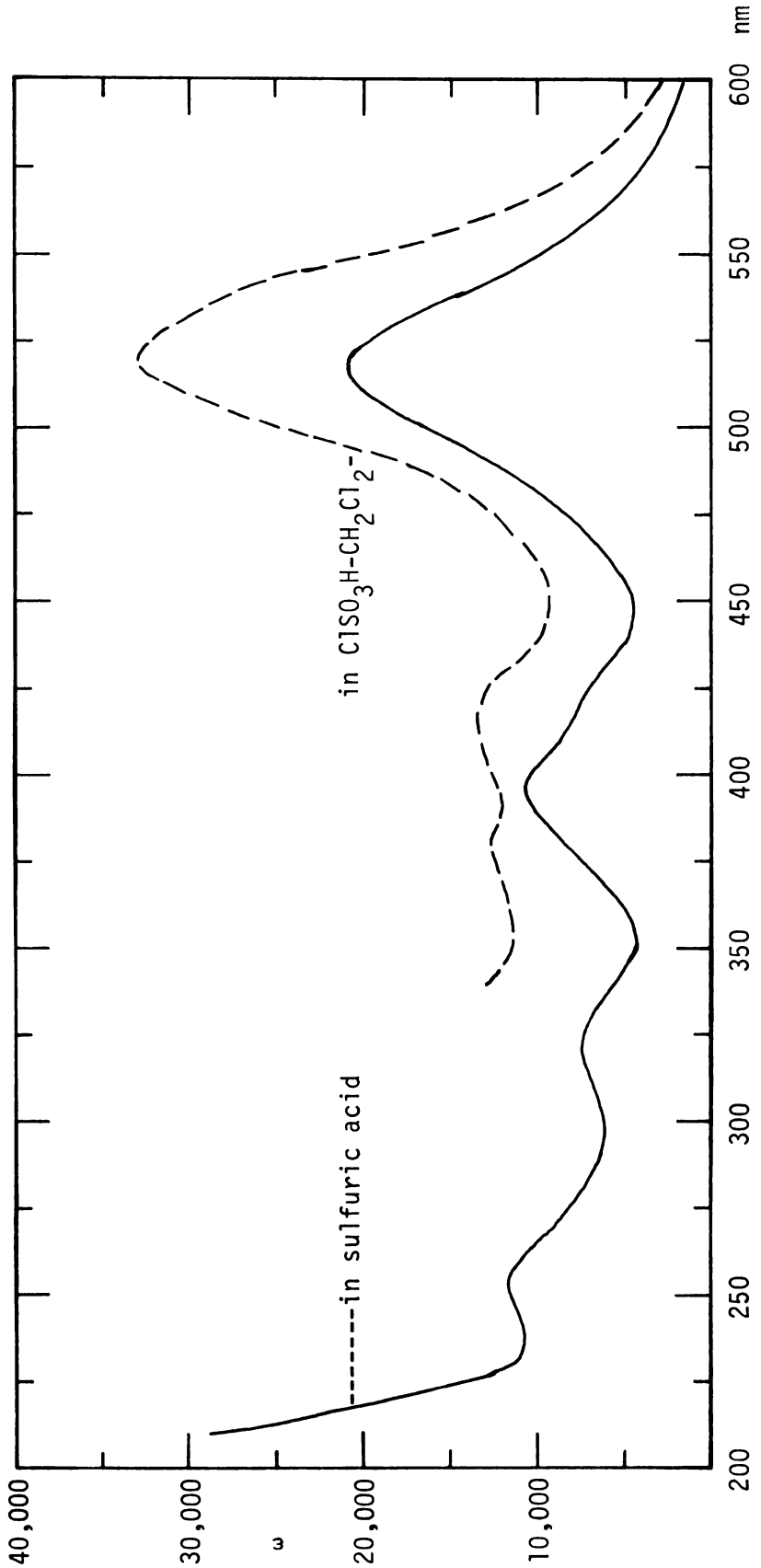
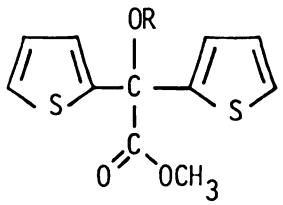


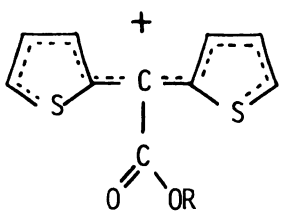
Figure 33. Visible spectrum of ion (LXII) in strong acid at 25°



(LXIV) $R=CH_3$

(LXV) $R=C_2H_5$

Olah and Pittman (120) have reported on the effect of an adjacent carbonium ion on the chemical shift of thienyl protons. The nmr spectrum appeared to be considerably complicated by coupling to adjacent protons. In contrast, the nmr spectrum of (LXII) as an 8% solution in 25% (w/w) $ClSO_3H$-CH_2Cl_2 at -55° with tetramethylammonium tetrafluoroborate (τ=6.90, ref 121) as a second internal standard gave the simple spectrum shown in Figure 34, p 86. This spectrum together with large downfield shift of the thienyl protons may be taken as evidence for considerable and symmetrical participation by the thiophene rings in stabilizing the carbonium ion as in (LXVI).



(LXVI)

Although ion (LXII) was rapidly decomposed at room temperature, the nmr spectrum of ion (LXIII) could be determined at +30°. It was unchanged from the spectrum at -55° and strikingly similar to the spectrum of ion (LXII) under the same conditions. The spectrum of ion (LXIII) is shown in Figure 35, p 87. The downfield chemical shift of the methoxy protons of (LXIII) compared with methyl 2,2'-thenilate (τ=6.20) is probably due to the inductive effect of the adjacent carbonium ion. Of course, there is the possibility that some of this difference may be due to solvent effects. Use of external tetramethylsilane as a standard, in general gave chemical shifts 0.2 ppm lower field than internal tetramethylammonium tetrafluoroborate.

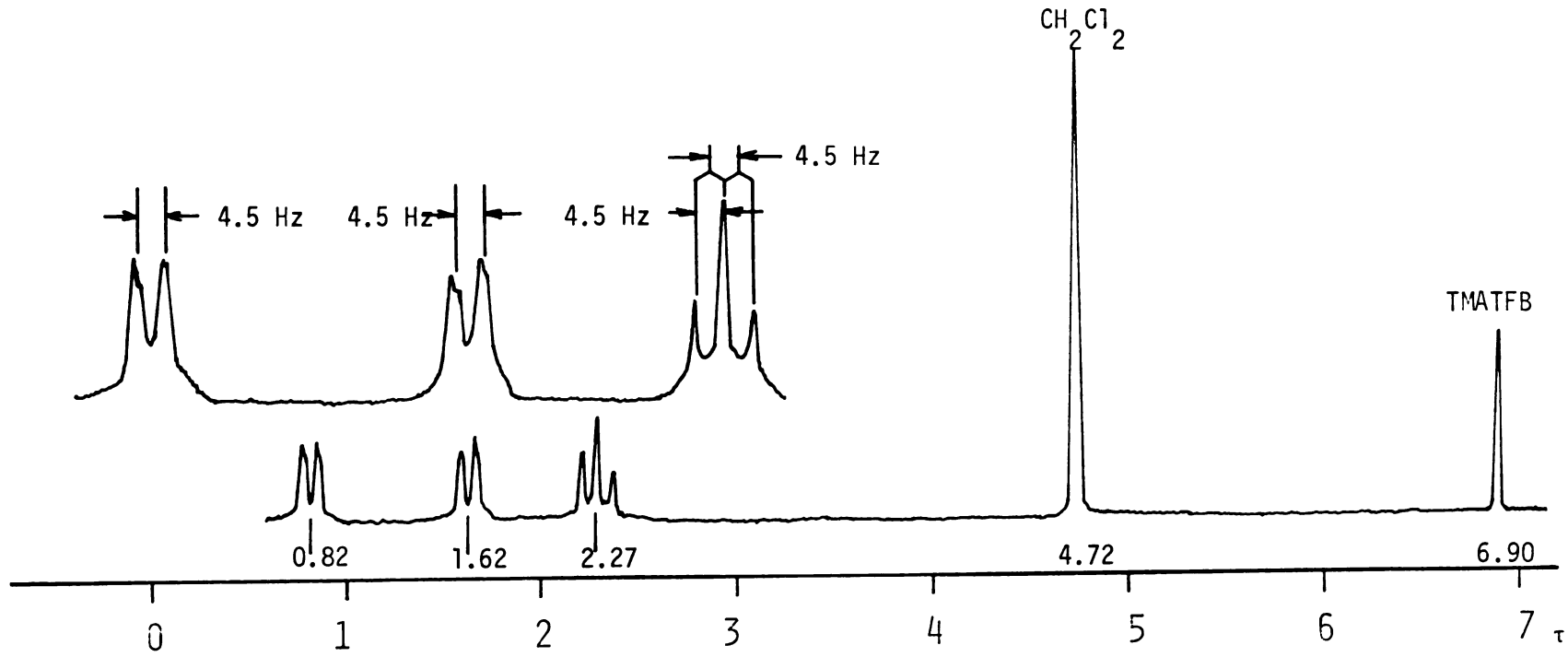


Figure 34. Nmr spectrum of ion (LXII) in $ClSO_3H$-CH_2Cl_2 at -55°.

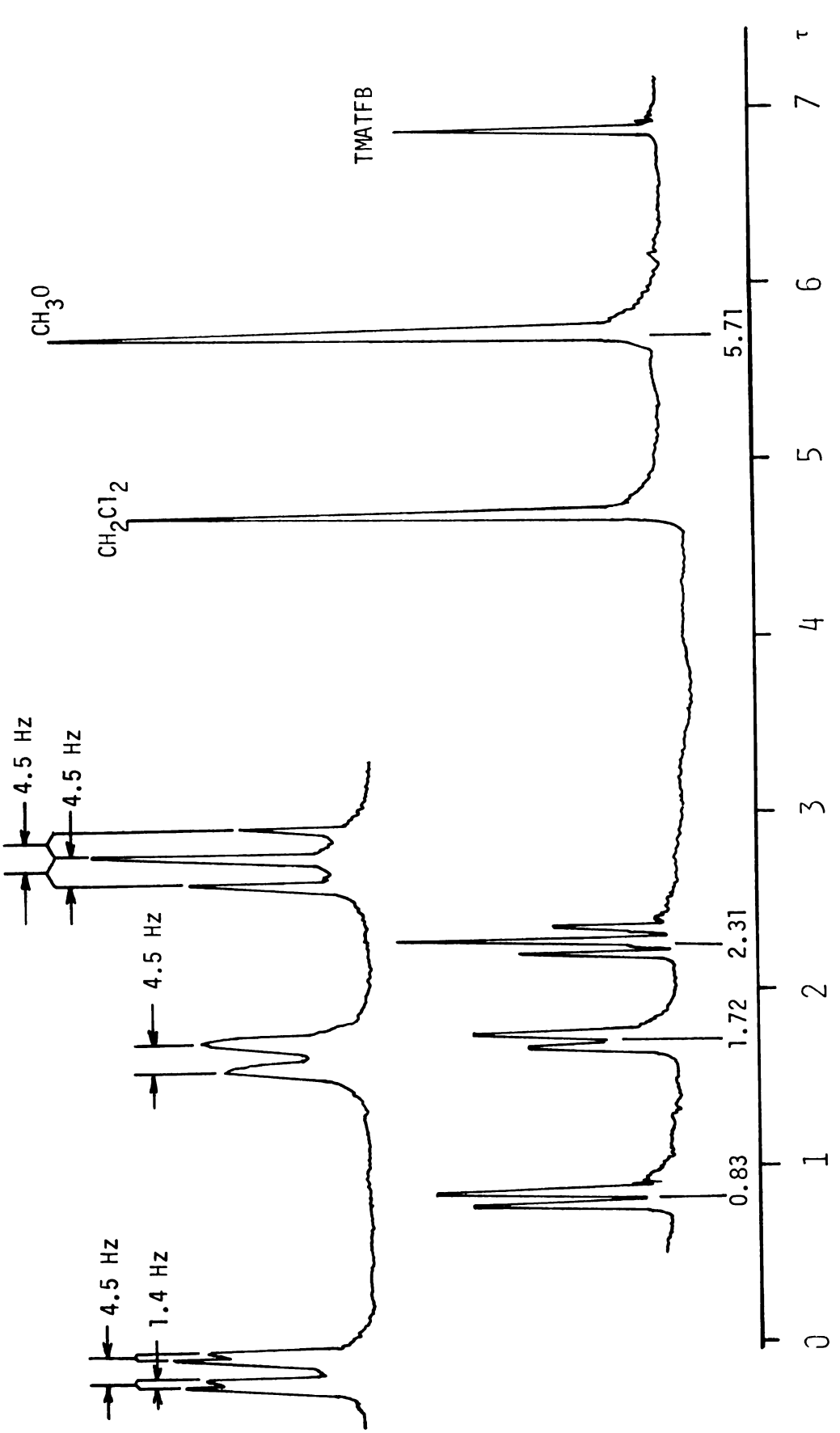
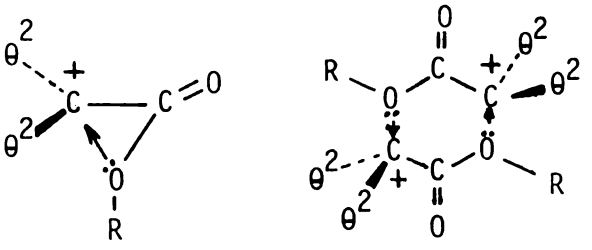


Figure 35. Nmr spectrum of ion (LXIII) in $ClSO_3H$-CH_2Cl_2at +30°.

While small rapid reversible protonation of the ester function cannot be ruled out, it may be noted that no quenching of any such protonated form by ethanol occurred, i.e. no ethyl esters could be isolated from either (LXII) or (LXIII) when quenched with ethanol.

There is the possibility that the carbonium ion may be stabilized by some participation of the type shown below. In either the monomeric or the dimeric form, the methyl group should be more effective in stabilizing the positive charge than hydrogen and this may explain the observed greater thermodynamic stability of (LXIII) vs (LXII).

R=H or CH_3



Indeed, ion (LXIII) is so stable that it is readily formed at room temperature simply by adding the solid ester to a mixture of chlorosulfonic acid and methylene chloride. An attempt was made to perform the same experiment with methyl benzilate. The initially orange-red solution decomposed before its nmr spectrum could be examined, that is within 3 or 4 minutes. This is in strong contrast to the solution of (LXIII) which gave a virtually unchanged nmr spectrum after 20 hours at room temperature in a sealed nmr tube.

This greater stability of the thiophene carbonium ion is a qualitative demonstration of the +M effect of the 2-thienyl group.

It would seem that the +M effect will dominate in those reactions involving positive character at the reaction site and likewise, the -I effect will dominate for reactions that involve negative character in the transition state. For this reason, the value of σ_θ will be reaction dependent and no one value for it can be properly assigned that will hold for all reactions.

SUMMARY

Thus we have come in a quasi-anfractuous manner through a rather mixed aggregate of thiophene chemistry. Many supposedly unique observations owed more to the author's naivete than to originality. However, listed below are the major and some minor conclusions unearthed for the first time.

The cyanide catalyzed condensation of various thiophene aldehydes, the thenoin condensation, was studied. It was found to be as unpredictable as the normal benzoin condensation, in regard to sucess or failure to yield the desired products.

The synthesis of ten new thenils, dithienyl diketones, was accomplished by various methods including the oxidation of the corresponding thenoins and the reaction of thienyl lithiums with dimethyl oxalate.

The thenils were subjected to base induced rearrangement to give, after treatment with diazomethane, the methyl esters of many heretofore unreported thenilic acids in good to excellent yields.

Four of these esters were transesterified with N-methyl-3-piperidinol to give dithienyl isosteres of JB 336. They may have significantly useful pharmacologic properties.

A new synthesis of benzoins, which is applicable to both symmetrical and unsymmetrical benzoins was formulated. It consists of the reaction of aryl glyoxals with aryl grignard reagents.

The mass spectrum of benzoins was found to be characterized by the absence of a parent peak as well as the presence of a P-2 peak, indicating that the

initial fragmentation process is the loss of hydrogen to give a benzil.

The abnormal cleavage 3,3'-benzo[b]thenil by hydroxide was noted, as well as the anomalous reaction of two alkoxythenils with potassium hydroxide.

The kinetics of the thenil-thenilic acid rearrangement were studied for the parent compound and for many substituted thenils. The parent 2,2'-thenil rearranges faster than benzil in accord with the prediction based on the -I character of the 2-thienyl group relative to the phenyl group.

The ionization constants for a series of nine thenoic acids were determined potentiometrically with the glass electrode in water at 49.5°. From these a new series of substituent constants, σ_θ, was calculated.

A plot of the log of the relative rate constants for rearrangement for some susbtituted thenils vs 2,2'-thenil was found to give better correlation with σ_θ than σ.

A demonstration of the existence of the equilibrium step in the Ingold mechanism of the benzilic acid rearrangement was infered from the abnormal rate enhancement due to halo substituents.

Long range ring fluorine to side chain couplings in 5-fluoro-2-thenaldehyde and 5-fluoro-2-acetylthiophene were recorded. Several other fluorothienyl compounds were synthesized for the first time.

An α-carboxyl carbonium ion was generated and examined. Solutions of it were examined by nmr and visible spectroscopy in order to confirm the structure. The stability of the ion emphasizes the +M character of the 2-thienyl group.

EXPERIMENTAL

Melting points were taken on an Electrothermal Melting Point Apparatus calibrated with furnished standards. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer as KBr pellets for solids or as films between NaCl plates for liquids. All spectra were calibrated at 1601.4 cm^{-1} with polystyrene film. Nuclear magnetic resonance spectra were recorded on a Varian A60, a Varian A56/60, or a Jeolco C60H instrument at ambient probe temperature using tetramethylsilane as internal standard for proton spectra, and Freon 112 as internal standard for F^{19} spectra. Ultraviolet and visible spectra were determined on a Unicam SP800 or a Cary 14 spectrophotometer in 95% ethanol. Mass spectra were determined by Mrs. Lorraine Guile of this department on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer at 70 eV ionization potential. Vapor phase chromatograms were run on a Varian A90-P3 gas chromatograph equipped with a 5 ft X 1/4 in 20% SE-30 on Chromosorb W column. Refractive indices were determined with a Bausch and Lomb Abbe-3L refractometer at the temperature indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thiophene, technical grade, was purchased from Pennsalt Chemicals Corp., Philadelphia, Pa. All thienyl aldehydes were stored at -10° in a refrigerator until needed. Unless otherwise noted, anhydrous sodium sulfate was used to dry extracts in all product isolation procedures.

Preparation of 2-thenaldehyde

The procedure of Campaigne and Archer (122) was used in this synthesis. A 500 ml three-neck flask fitted with a reflux condenser and a thermometer to extend below the level of the flask contents, was charged with 126 g (1.50 moles) of freshly distilled thiophene and 138 g (1.89 moles) of recently distilled dimethylformamide. The mixture was cooled in an ice bath and stirred during the rapid but cautious addition of 288 g (1.87 moles) of phosphorus oxychloride. The ice bath was removed and the reaction mixture temperature was allowed to rise to 90-100° with occasional cooling to hold its temperature in this range. After spontaneous heating had ceased, the reaction mixture was heated on a steam bath for one hour and poured into 1 kg of crushed ice. The solution was neutralized to pH 6 (Hydrion B) with 5 M sodium hydroxide. The oily aqueous suspension was extracted continuously with ether for 16 hours. The extract was dried,and the ether evaporated on a steam bath. The residue was distilled under vacuum to obtain 144 g (1.28 moles, 86.4%) of 2-thenaldehyde: bp 49-50°(1.4 torr); n_D^{24} 1.5870; reported values (123) bp 44-45° (1.1 torr); n_D^{20} 1.5920.

Preparation of 2,2'-thenoin

The reported procedure (8) was modified in this synthesis. A solution of 28.0 g (0.250 mole) of 2-thenaldehyde in 250 ml of 95% ethanol was heated to reflux and 19.5 g (0.300 mole) of potassium cyanide in 100 ml of water was added in one portion through the condenser. The mixture was refluxed for 15 minutes. Longer or shorter reflux time resulted in the formation of a very tarry product. The dark green reaction mixture was cooled to 20° and acidified with 2N hydrochloric acid to pH 4. A total of 250 ml of water was continuously added during this process with stirring. The pale orange precipitate was

collected and air dried to yield 11.2 g (0.050 mole, 40.0%) of product. This material was used without further purification for the preparation of 2,2'-thenil.

Preparation of 2,2'-thenil

The literature procedure (124) was somewhat modified in this synthesis. The previously prepared crude 2,2'-thenoin, 7.36 g (0.0331 mole) was dissolved in 200 ml of boiling methanol (purified by Fieser's method, ref 125). To this, a solution of sodium methoxide prepared by dissolving 1.61 g (0.070 mole) of sodium metal in 60 ml of purified methanol was added. Heating of the dark green solution was discontinued and 10.2 g (0.040 mole) of solid iodine was added as rapidly as possible. Immediately upon completion of the iodine addition, the entire reaction mixture was rapidly quenched in a mixture of 300 g of ice and 10 ml of acetic acid. The resulting yellow-brown product was collected to obtain 6.09 g (0.0274 mole) of crude thenil. The crude material was extracted continuously with 30-50° petroleum ether in a Soxhlet apparatus for 24 hours. The petroleum ether was removed with a stream of air and the residue was recrystallized from methanol to obtain 4.20 g (0.0189 mole, 57.1%); mp 82-84°; reported (124) 81-82°. The infrared spectrum is shown on p 147. The ultraviolet spectrum is shown on p 154.

Preparation of 2,2'-thenilic acid

A suspension of 2.00 g (0.00900 mole) of 2,2'-thenil in an alkaline solution prepared from 6.00 g (0.107 mole) of potassium hydroxide in 40 ml of water was heated with stirring at 80° in an oil bath for 1.5 hours. After cooling in an ice bath to 20°, the reaction mixture was rapidly acidified to congo red with concentrated hydrochloric acid and extracted with ether (3X25 ml).

The combined ether extracts were dried, and the ether was removed under reduced pressure to yield 1.86 g (0.00726 mole, 86.0%) of 2,2'-thenilic acid: mp 98-100° dec; reported (8) 80° dec; neutralization equivalent: calc'd for $C_{10}H_8O_3S_2$, 240.2; found, 241. This material decomposes in a few hours at room temperature, but is stable for at least 2 years at -20°.

Preparation of diazomethane

Diazomethane was prepared from N-methyl,N-nitrosourea (126) as described (127) in the literature. Typical analyses gave 61-65% yield of diazomethane.

Preparation of methyl 2,2'-thenilate

This compound is most conveniently prepared directly from the combined dried ethereal extracts of the 2,2'-thenilic acid preparation described previously. Alternatively, it may be prepared from the isolated acid which is dissolved in ether and then treated with diazomethane. Thus, the ethereal thenilic acid solution from the rearrangement of 2.22 g (0.0100 mole) of 2,2'-thenil was stirred and treated with 50 ml of distilled ethereal diazomethane. The diazomethane was prepared from 2.38 g (0.0231 mole, 56% excess) of N-methyl,N-nitrosourea.

The stirring was continued for 15 minutes and the ether was then removed under reduced pressure in a bell jar with stirring but with no external heat. The dried ester was recrystallized from 60-90° petroleum ether to obtain 1.70 g (0.00693 mole, 69.3%) of pure product. For analysis, the ester was recrystallized three times from 60-90° petroleum ether: mp 93°.

Analysis, Calc'd for $C_{11}H_{10}O_3S_2$: C, 51.95; H, 3.96; S, 25.22.

Found: C, 51.86; H, 3.80; S, 25.02.

Preparation of 2-methylthiophene

This material was prepared essentially by the method of King and Nord (45). A three liter, three-neck flask equipped with an overhead stirrer, a thermometer extending below the level of the reaction mixture, and a reflux condenser with a distillation takeoff, was charged with 140 g (1.25 mole) of 2-thenaldehyde, 250 ml (4.42 moles) of 85% hydrazine hydrate and 1000 ml of ethylene glycol. The solution was stirred and heated until 280 ml of water and hydrazine hydrate had been removed by distillation. The distillate was extracted with ether (2X50 ml) and the ether extract was added to the cooled reaction mixture which was then heated to remove the ether by distillation. When the thermometer indicated 60°, 250 g of potassium hydroxide was added to the reaction mixture in one portion causing a rapid temperature rise to 90°, along with a strong evolution of gas. After the gas evolution had subsided, the mixture was refluxed 15 minutes, and the 2-methylthiophene was removed azeotropically. It was separated from the water, dried, and heated to 70° to remove a small amount of low boiling material. The remaining 2-methylthiophene was colorless and sufficiently pure to be used directly in the preparation of 5-methyl-2-thenaldehyde. The yield was 95.2 g (0.971 mole, 77.7%): n_D^{24} 1.5151; reported (45) n_D^{20} 1.5203.

Preparation of 5-methyl-2-thenaldehyde

A 300 ml three-neck flask equipped with a condenser and magnetic stirrer was charged with 23.2 g (0.236 mole) of 2-methylthiophene and 21.9 g (0.300 mole) of dimethylformamide. To this mixture, 44.4 g (0.290 mole) of phosphorus oxychloride was added in one portion with stirring. After the highly exothermic reaction had susbsided, the reaction mixture was heated on a steam bath for two hours, cooled and poured onto 100 g of crushed ice. An ice bath

was used to maintain the solution temperature below 40° while the pH was adjusted to 8 by the addition of 5M sodium hydroxide. The oily aqueous suspension was extracted with ether (3X70 ml). The combined, dried extracts were flash distilled, and the residue was vacuum distilled to obtain 25.6 g (0.203 mole, 86.0%) of the desired aldehyde: bp 62-64° (1.3 torr), n_D^{24} 1.5791; reported (128) bp 81-82° (6 torr) n_D^{20} 1.5742.

Preparation of 5,5'-dimethyl-2,2'-thenil

A mixture of 2.5 g (0.0510 mole) of sodium cyanide, 12.6 g (0.100 mole) of 5-methyl-2-thenaldehyde, and 50 ml of dimethyl sulfoxide in a 100 ml round bottom flask under a nitrogen atmosphere was sealed and shaken occasionally during two days. The reaction mixture gradually changed from green to brown. At the end of this period, the reaction mixture was poured into 500 ml of water and the aqueous suspension was extracted with ether (3X100 ml). The ether extracts were combined and the ether was removed by evaporation. The oily residue was treated with 20 g of cupric sulfate pentahydrate in 200 ml of pyridine. The deep blue solution was then heated on a steam bath for 2 hours and poured into 1.5 l. of cold water. After being set aside overnight in the refrigerator, the solution was filtered and the collected precipitate air dried. This solid material was extracted continuously in a Soxhlet apparatus with 30-50° petroleum ether for 30 hours. Upon evaporation of the petroleum ether, the bright yellow-orange thenil was obtained. It weighed 3.35 g (0.0148 mole, 29.6%). For analysis it was sublimed twice at 70° (0.05 torr): mp 85-86°. The infrared spectrum is shown on p150. The ultraviolet spectrum is shown on p 156.

Analysis, Calc'd for $C_{12}H_{10}O_2S_2$: C, 57.57; H, 4.03; S, 25.62.

Found: C, 57.44; H, 4.01; S, 25.60.

Preparation of methyl 5,5'-dimethyl-2,2'-thenilate

A 0.50 g (2.0 mmoles) quantity of 5,5'-dimethyl-2,2'-thenil was added to 1.0 g (18 mmoles) of potassium hydroxide in a mixture of 15 ml of water and 3 ml of dioxane previously heated to 80° in an oil bath. After solution was effected, in about 4 hours, the dark violet solution was cooled in an ice bath to 10°, and acidified to pH 3 with concentrated hydrochloric acid. The precipitated thenilic acid was immediately extracted with 25 ml of ether, and the aqueous soltuion was extracted with another 25 ml portion of ether. The combined ether extracts were shaken with a mixture of anhydrous sodium sulfate and Norit-A and filtered. The stirred filtrate was treated with an ethereal solution of diazomethane, prepared from 0.5 g of N-methyl,N-nitrosourea. The ether was removed at reduced pressure at room temperature. The yield of ester was 0.46 g (1.6 mmoles, 80%). The crude product was crystallized twice from 60-90° petroleum ether for analysis: mp 57-58°.

Analysis, Calc'd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.00; S, 22.71.

Found: C, 55.60; H, 4.95; S, 21.47.

Preparation of 5-chloro-2-thenaldehyde

A mixture of 119 g (1.00 mole) of 2-chlorothiophene (Columbia Chemical Co., Columbia, S.C.) and 80.4 g (1.10 moles) of dimethylformamide was stirred while 176 g (1.15 moles) of phosphorus oxychloride was added dropwise to the mixture. Heat was applied with a steam bath until the strongly exothermic reaction was initiated. The reaction temperature was held below 130° by occasional cooling in an ice bath. After the reaction had subsided, heating was continued for an additional 2 hours. The reaction mixture was cooled in an ice bath and hydrolyzed by the cautious addition of 500 g of crushed ice. The pH was adjusted to 8 with solid sodium hydroxide, keeping the temperature below 50°.

The oily product was extracted with ether (4X300 ml). The combined ether extracts were dried and the ether removed by flash distillation. The residue was vacuum distilled to yield 91.9 g (0.627 mole, 62.7%) of the desired aldehyde: bp 50-52° (0.5 torr); reported (122) bp 52-53° (0.5 torr).

Preparation of 5,5'-dichloro-2,2'-thenil

A suspension of 7.05 g (0.144 mole) of sodium cyanide in 300 ml of anhydrous tetrahydrofuran containing 2% dimethyl sulfoxide was prepared under a nitrogen atmosphere. To this, 41.4 g (0.282 mole) of 5-chloro-2-thenaldehyde was added in one portion. The flask was sealed and the contents magnetically stirred for 30 hours. The flask was opened momentarily to add 7 ml of glacial acetic acid. The flask was reclosed and the contents stirred an additional 30 minutes. Following this neutralization, 300 ml of anhydrous pyridine, and 70.5 g (0.282 mole) of cupric sulfate pentahydrate was added and the reaction mixture was stirred vigorously for 3 hours. At the end of this period, the entire contents of the flask were poured into 2 l. of cold water and refrigerated overnight. The ice cold suspension was filtered and the dark brown filter cake was washed well with water and air dried. The solid was continuously extracted with 30-50° petroleum ether in a Soxhlet apparatus until the bright orange color was exhausted. The petroleum ether was removed with a stream of air and the residue was crystallized from 300 ml of methanol to obtain 14.8 g (0.0508 mole, 41.2%) of the thenil. For analysis the thenil was crystallized three times from methanol: mp 121-122°. The infrared spectrum is shown on p 149. The ultraviolet spectrum is shown on p 156.

Analysis: Calc'd for $C_{10}H_4Cl_2O_2S_2$: C, 41.25; H, 1.38; S, 22.02.

Found: C, 41.36; H, 1.49; S, 22.00.

Preparation of methyl 5,5'-dichloro-2,2'-thenilate

A solution of 0.80 g (0.014 mole) of potassium hydroxide in 15 ml of water was heated to 90° in an oil bath. To this alkaline solution, 1.00 g (0.00345 mole) of 5,5'-dichloro-2,2'-thenil was added and the suspension was stirred under nitrogen until solution was effected in about 45 minutes. The reaction mixture was cooled to 15° in an ice bath and acidified to pH 3 with concentrated hydrochloric acid. The acid solution was quickly extracted with ether (2X50 ml). The combined, dried ether extracts were stirred with an ethereal solution of diazomethane, prepared from 1.5 g of N-methyl,N-nitrosourea. Removal of the ether under reduced pressure gave an oil, weighing 1.02 g (0.00316 mole, 91.6%). For analysis, the oil was subjected to distillation by micro molecular still at 130° (0.01 torr).

Analysis, Calc'd for $C_{11}H_8Cl_2O_3S_2$: C, 40.87; H, 2.49; S, 19.84.

Found: C, 41.05; H, 2.63; S, 19.47.

Preparation of 2,2-bithienyl

This compound was prepared using a minor modification of the procedure described by Gronowitz (48). A solution of 30.0 g (0.360 mole) of thiophene in 100 ml of dry ether was added dropwise with overhead stirring to 250 ml of 1.6N n-butyllithium in hexane (Foote Chemical Co., Exton, Penn.), at such a rate that the temperature could be maintained below 10° by an ice bath. After stirring an additional 2 hours in the ice bath, the thienyllithium solution was refluxed for 15 minutes and then cooled to 5°. By means of a Gooch tube attached to one neck of the reaction flask, 50.0 g (0.37 mole) of anhydrous cupric chloride was added cautiously in one portion. The reaction mixture became quite exothermic despite immersion in the ice bath. Following the addition of the cupric chloride, the suspension was refluxed 3 hours,

cooled, and 300 ml of 2N hydrochloric acid was cautiously added. The organic layer was separated and the aqueous layer was extracted with ether (2X100 ml). The ether solutions were combined and the ether was removed on a steam bath. The residue was steam distilled. After one liter of distillate was collected, it was extracted with ether (3X150 ml) and the combined ether extracts were dried and evaporated to obtain 20.0 g (0.12 mole, 67%) of 2,2'-bithienyl.

Preparation of 5-(2'-thienyl)-2-thenaldehyde

A vigorously stirred mixture of 16.9 g (0.110 mole) of phosphorus oxychloride and 9.04 g (0.110 mole) of dimethylformamide was cooled in an ice bath and 16.6 g (0.100 mole) of 2,2'-bithienyl was added in one portion. After 15 minutes of stirring, the reaction temperature rose rapidly to 80-90° and the mixture solidified. Following heating on a steam bath an additional 30 minutes, the semisolid was cooled and added to 60 g of sodium acetate in 100 ml of water. This suspension was stirred for one hour and basified to pH 10 with solid sodium hydroxide. The basic solution was extracted with ether (4X100 ml). The ether extracts were combined and washed successively with 200 ml of 2N hydrochloric acid, 200 ml of saturated sodium bicarbonate, and 200 ml of water. Evaporation of the solvent gave 16.1 g (0.0830 mole, 83.0%) of the aldehyde. It was recrystallized from methanol-water: mp 55-56°; reported (47) mp 56°.

Preparation of 5,5'-di-(2"-thienyl)-2,2'-thenoin

A solution of 0.59 g (0.010 mole) of potassium cyanide in 4 ml of water was added in one portion to 1.94 g (0.0100 mole) of 5-(2'-thienyl)-2-thenaldehyde in 10 ml of refluxing ethanol. After 15 minutes of refluxing, the reaction flask was plunged into an ice bath. The pH was adjusted to 3 with

concentrated hydrochloric acid. The acid solution was heated to boiling and water was added to incipient cloudiness. After further cooling in the ice box, the thenoin crystallized and yielded 1.46 g (0.00396 mole, 75.2%) of product: mp 117-121°. It was recrystallized from carbon tetrachloride: mp 126-128°; reported (46) 125-130°.

Preparation of 5,5'-di-(2"-thienyl)-2,2'-thenil

This compound was prepared by oxidizing the thenoin in the manner described by Weiss (49). A mixture of 1.46 g (3.76 mmoles) of 5,5'-di-(2"-thienyl)-2,2'-thenoin, 0.40 g (5.0 mmoles) of ammonium nitrate, approxiametly 0.1 g of cupric acetate and 20 ml of 80% acetic acid-water was stirred and refluxed for one hour. The reaction mixture was then cooled in the ice box and the thenil was collected by filtration. The yield of the dark brown thenil was 1.22 g (3.16 mmoles, 84.7%). It was recrystallized from dioxane-water: mp 188-189°; reported (46) 189-191°. The infrared spectrum is shown on p 151. The ultraviolet spectrum is shown on p 155.

Preparation of methyl 5,5'-di-(2"-thienyl)-2,2'-thenilate

A 1.00 g (0.259 mmole) quantity of 5,5'-di-(2"-thienyl)-2,2'-thenil was suspended in a mixture of 10 ml of dioxane and 5 ml of water. To this, 1.5 g (27 mmoles) of potassium hydroxide was added and the mixture was refluxed under nitrogen for 4 hours, during which time most of the thenil dissolved. The solution was cooled and acidified with 6N hydrochloric acid to congo red. After extraction of the aqueous layer with ether (3X25 ml), the extracts were combined and dried. This ethereal solution was immediately treated with a solution of diazomethane in ether prepared from 0.51 g of N-methyl,N-nitrosourea. Removal of the solvent under reduced pressure gave an oil which was

crystallized from 60-90° petroleum ether to obtain 0.98 g (0.23 mmoles, 94%) of the ester: mp 112-113°. For analysis, it was recrystallized from 60-90° petroleum ether.

Analysis, Calc'd for $C_{19}H_{14}O_3S_4$: C, 54.52; H, 3.37; S, 30.64.
Found: C, 54.62; H, 3.37; S, 30.70.

Preparation of 3-bromothiophene

A three liter, three-neck flask fitted with an overhead stirrer and reflux condenser was charged with 900 ml of water, 400 g (6.12 moles) of zinc dust and 750 ml of glacial acetic acid. The suspension was heated to reflux with vigorous stirring and 1290 g (5.33 moles) of 3,4-dibromothiophene was added in one portion. After an hour of refluxing, 100 g of fresh zinc dust was added. A second portion of 100 g of zinc dust was added an hour later, and a final portion of 100 g of zinc dust was added after another two hours. The reaction mixture was then refluxed an additional 9 hours with vigorous stirring. After cooling the reaction flask, a Dean-Stark trap was interposed between the condenser and the reaction vessel. The reaction mixture was then heated until only one phase distilled over. The distillate was washed with water (100 ml) and saturated sodium bicarbonate (100 ml). The oily product was dried and distilled through an 8 inch Vigreaux column under vacuum to obtain 614 g (3.76 mole, 68.0%): bp 83-86° (58 torr), n_D^{24} 1.5892; reported (129) bp 149-151° (760 torr), n_D^{20} 1.5861. The yield based on recovery of 232 g of 3,4-dibromothiophene was 86.1%.

Preparation of 3-thenaldehyde

This material was prepared as described by Vincent (130). A three liter, three-neck flask was equipped with a nitrogen inlet tube, a dropping funnel,

a thermometer extending below the level of the reaction mixture, a condenser, and an overhead stirrer. Lithium metal, 17.5 g (2.52 moles), previously hammered and scissored (131) was added to 400 ml of anhydrous ether in the flask. The ether suspension of lithium metal was cooled to -5° by immersion in a dry ice-isopropanol bath and 157 g (1.15 moles) of n-butylbromide was added with stirring during two hours. After one hour, the n-butyllithium solution was cooled to -60° and 163 g (1.00 mole) of 3-bromothiophene in 100 ml of dry ether was added dropwise during 1.5 hours maintaining the temperature below -60°. The 3-thienyllithium solution was then treated dropwise during one hour at -60° with a solution of 100 g (1.26 moles) of freshly distilled dimethylformamide in 100 ml of dry ether. The reaction temperature was maintained below -60° with constant stirring for an additional 6 hours, and then poured into 200 ml of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether (3X200 ml). The combined ether extracts were dried and the ether was removed by flash distillation. The residue was vacuum distilled to obtain 71.2 g (0.635 mole, 63.5%): bp 50-53° (1.3 torr) n_D^{24} 1.5806; reported (132) bp 78° (14 torr) n_D^{20} 1.5860.

Preparation of 3,3'-thenoin

This compound was prepared by the method of Campaigne and LeSuer (54). A refluxing solution of 28.0 g (0.250 mole) of 3-thenaldehyde in 250 ml of 95% ethanol was treated in one portion with 19.5 g (0.300 mole) of potassium cyanide in 100 ml of water. The bright red-orange solution was refluxed 2 hours, cooled, and acidified to pH 3 with 2N hydrochloric acid. After further dilution with 600 ml of cold water and cooling in the refrigerator, the precipitate of crude thenoin was collected. It amounted to 12.0 g (0.0536 mole, 42.8%): mp 111-113°. Upon concentration of the mother liquor to one

third its volume, an additional 2.2 g of product were obtained. The total yield of product was 14.2 g (0.0633 mole, 50.7%).

Preparation of 3,3'-thenil

The procedure described by Campaigne and Bourgeois (9) was employed with some modifications in this synthesis. A solution of 32.6 g (0.130 mole) of cupric sulfate pentahydrate in 45 ml of pyridine and 25 ml of water was heated on a steam bath and 11.8 g (0.0527 mole) of 3,3'-thenoin was added. After heating and stirring for two hours, the reaction mixture was poured into 600 ml of cold water. The dark brown precipitate was collected by filtration after refrigerating the reaction mixture overnight. It was air dried and continuously extracted with 30-50° petroleum ether for 24 hours. The petroleum ether was evaporated with an air stream and the bright yellow thenil weighing 9.88 g (0.0445 mole, 84.4%) was obtained. It was sublimed for further purification: mp 75-76°; reported (9) mp 75-76°. The infrared spectrum is shown on p147. The ultraviolet spectrum is shown on p154 .

Preparation of 3,3'-thenilic acid

This compound was prepared from 3,3'-thenil under exactly the same conditions as described for the synthesis of 2,2'-thenilic acid from 2,2'-thenil. The crude acid is apparently less stable than its 2,2'-isomer, precluding a meaningful % yield determination. The crude acid, a pale tan powder, chars at 85-90° and melts at 101-103°. It is reported (9) to char below 90°. Neutralization equivalent, calc'd for $C_{10}H_8O_3S_2$: 240; found: 257 and 259.

Preparation of methyl 3,3'-thenilate

A solution of 15.0 g (0.268 mole) of potassium hydroxide in 100 ml of water

under a nitrogen atmosphere was heated to 80° in an oil bath with vigorous stirring, and 5.55 g (0.0250 mole) of 3,3'-thenil was added. Heating and stirring were continued until solution was effected in about 4 hours. The reaction mixture was cooled below room temperature in an ice bath and neutralized to congo red with concentrated hydrochloric acid. The acidified solution was extracted with ether (3X50 ml) and the combined extracts were dried. This stirred solution was immediately treated with an ethereal solution of diazomethane prepared from 5.0 g of N-methyl,N-nitrosourea. After stirring for 30 minutes, the ether was removed under reduced pressure. The residue was recrystallized from 60-90° petroleum ether to obtain 4.48 g (0.0176 mole, 70.3%) of the ester: mp 80-81°. For analysis, the ester was recrystallized twice from 60-90° petroleum ether.

Analysis, Calc'd for $C_{11}H_{10}O_3S_2$: C, 51.95; H, 3.96; S, 25.18.
Found: C, 52.06; H, 3.97; S, 25.18.

Preparation of 3-bromothianapthene

The procedure described by Szmuszkovicz (133) was used without modification in this synthesis. A two liter, three-neck flask was charged with 71.9 g (0.535 mole) of thianapthene, 73 g (0.89) of sodium acetate and 380 ml of chloroform. With vigorous overhead stirring, 28 ml (86.8 g, 0.543 mole) of bromine in 70 ml of chloroform was added dropwise during 30 minutes to the thianapthene solution. The reaction mixture was cooled by occasional immersion in an ice bath to keep the temperature near 25°. After stirring an additional hour following the bromine addition, 100 ml of water was added, and the chlorform solution was separated, washed with 200 ml of water, 100 ml of 5% sodium hydroxide, 200 ml of water, and finally, 200 ml of saturated sodium chloride. The chloroform solution was dried, and the solvent removed by

rotary evaporator. The residue was vacuum distilled to yield 93.8 g (0.440 mole, 82.3%) of 3-bromothianapthene: bp 83-84° (0.4 torr) n_D^{25} 1.6592; reported (133) bp 90-105° (1.5 torr).

Preparation of 3-thianapthaldehyde

This compound was prepared by the reaction of 3-thianapthyllithium and dimethylformamide, and has since been reported (57). A solution of 75 ml of 1.6N n-butyl lithium in hexane (Foote Chemical Co., Exton Penn.) was cooled to -70° in a dry ice-isopropanol bath. A solution of 21.3 g (0.100 mole) of 3-bromothianapthene in 50 ml of dry ether was added during a period of 20 minutes with constant stirring. The reaction temperature was allowed to warm to -20° and stirred an additional 30 minutes. The thianapthyllithium solution was treated with 8.78 g (0.120 mole) of freshly distilled dimethylformamide in 50 ml of dry ether during 30 minutes with stirring. After one hour of further stirring, the reaction mixture was hydrolyzed by pouring it into 60 ml of 3N hydrochloric acid and 100 g of ice. The ether layer was separated and the aqueous layer was extracted with ether (3X100 ml). The combined dried ether solutions were flash distilled to remove the solvent. The crude aldehyde was dissolved in 50 ml of ethanol and treated with 30 g of sodium bisulfite in 100 ml of water. After being set aside for several minutes, the bisulfite adduct crystallized and was collected by vacuum filtration, washed with ether, and air dried. It was dissolved in 100 ml of warm water, and 100 ml of saturated sodium carbonate was added. The oily aldehyde crystallized on being set aside in the ice box. The yield of product was 10.8 g (0.0666 mole, 66.6%): mp 53-55°; reported (57) mp 56-57°.

Preparation of 3,3'-benzo[b]thenoin

This compound was prepared exactly as described by Campaigne and Neiss (56). The procedure was repeated at least 20 times, however, no increase in yield could be realized. The melting points in the original article for both 3,3'-benzo[b]thenoin and 3,3'-benzo[b]thenil are in error (134). A mixture of 6.0 g (0.037 mole) of 3-thianapthaldehyde, 20 ml of 95% ethanol and 1.0 g (0.015 mole) of potassium cyanide was refluxed for 3 hours. The reaction mixture was set aside overnight in the ice box, and then neutralized with glacial acetic acid. After one week, the product precipitated and was collected by filtration. After recrystallization from ethanol, the thenoin melted at 128-130° and amounted to 1.00 g (0.00309 mole, 16.7%).

Preparation of 3,3'-benzo[b]thenil

This compound was prepared by oxidation of the thenoin using Weiss' method (49). A mixture of 1.00 g (0.00309 mole) of 3,3'-benzo[b]thenoin, 0.36 g (0.0045 mole) of ammonium nitrate, approxiametly 0.1 g of cupric acetate, and 10 ml of 80% acetic acid-water was refluxed for 90 minutes with stirring. After cooling the reaction mixture in an ice bath, the thenil crystallized. It was collected by vacuum filtration, and washed with ethanol, then ether and air dried to obtain 0.82 g (0.00255 mole, 82.5%) of product: mp 188-189°, mol wt (by mass spectrum) calc'd for $C_{18}H_{10}O_2S_2$: 322; found: 322. The infrared spectrum is shown on p 152. The ultraviolet spectrum is shown on p 154.

Attempted preparation of methyl 3,3'-benzo[b]thenilate

Various quantities of 3,3'-benzo[b]thenil were subjected to reaction conditions that had previously been shown to sucessfully result in rearrangement of a thenil to a thenilic acid. With 3,3'-benzo[b]thenil, however, they were

uniformly unfruitful. Following exactly the procedure described for the preparation of 2,2'-thenilic acid, but using 3,3'-benzo[b]thenil, gave, after treatment of the reaction mixture workup with diazomethane, a residue which resisted crystallization attempts. An infrared spectrum showed a typical ester carbonyl absorption at 1720 cm^{-1} but no -OH absorption. The mass spectrum showed a strong parent peak at m/e 192 (72%) and no peaks beyond this ratio. Since methyl 3-thianapthylcarboxylate has a mass of 192, and is a liquid, the evidence suggests this compound as the product.

Attempted preparation of 3,3'-benzo[b]thenil

An alternate synthesis of diaryl diketones described by Bauld (10) was tried in the synthesis of 3,3'-benzo[b]thenil. A solution of 3.23 ml (4.25 g, 0.025 mole) nickel tetracarbonyl (K&K Laboratories, Plainview, N.Y.) was added in one portion* to 6.50 g (0.025 mole) of 3-iodothianapthene in 50 ml of dry tetrahydrofuran. The reaction apparatus had been previously swept clear of air with a stream of purified nitrogen. The reaction mixture was heated slowly until a thermometer an inch above the level of the reaction mixture registered 65°. After cooling, the reaction mixture was set aside for 6 hours, and 150 ml of water was then added. Another 12 hours were allowed to elapse before further product isolation. The solid material was removed by filtration, air dried, and extracted continuously with 30-50° petroleum ether. Evaporation of the petroleum ether gave 4.2 g of pale yellow product in the form of needles, mp 172-174°. The infrared spectrum showed no absorptions in

* The nickel tetracarbonyl was most conveniently removed from the steel shipping cylinder by a short piece of tygon tubing attached to a glass inlet on the top of the addition funnel. Gentle suction applied to the apparatus then effected removal. Caution is emphasized; antidotes for nickel tetracarbonyl poisoning are only partially effective.

the 1620-1660 cm^{-1} range, typical of thenils prepared in this study. The product did show a strong carbonyl absorption at 1685 cm^{-1}. Since 3,3-dithianapthylketone melts at 174° (135) this compound may have been formed instead of the desired product.

Preparation of 2-thenoylphenylmethanol

The procedure described by Biel (7) was slightly modified for the synthesis of this material. A solution of 11.2 g (0.100 mole) of freshly distilled 2-thenaldehyde, 10.6 g (0.100 mole) of benzaldehyde and 10 g of potassium cyanide in 50 ml of 95% ethanol and 20 ml of water was refluxed for 30 minutes. The hydroxyketone spontaneously crystallized when the reaction mixture was cooled in an ice bath. The product was collected by vacuum filtration and triturated with 300 ml of 5% aqueous sodium bicarbonate for 30 minutes. The suspension was filtered and the filter cake washed well with water and dried: mp 123-124°; reported (7) 132-134°. This compound was further purified by washing it with several portions of 50/50 (v/v) ether-30-50° petroleum ether to obtain 16.6 g (0.0732 mole, 73.2%) of product. This material is pure enough to be used directly in the preparation of 2-thienylphenyl diketone.

Preparation of 2-thienylphenyl diketone

The procedure described by Biel (7) was followed exactly in this preparation. A suspension of 10.9 g (0.050 mole) of 2-thenoylphenylmethanol, 0.5 g of cupric acetate and 5.6 g (0.070 mole) of ammonium nitrate in 100 ml of 80% acetic acid-water was refluxed and stirred for 90 minutes. After cooling the reaction mixture to room temperature, 100 ml of water was added and the product was allowed to crystallize in the refrigerator. The diketone

was collected by vacuum filtration and air dried to obtain 7.54 g (0.0349 mole, 69.8%). It was further purified by crystallization from 50/50 methanol-water: mp 67-68°; reported (7) 59-60°. The infrared spectrum is shown on p 153. The ultraviolet spectrum is shown on p 155.

Preparation of 2-thienylglyoxal

The procedure described by Kipnis and Ornfelt (61) was used to prepare this compound. A mixture of 160 ml of dioxane, 5.5 ml of water, and 27.8 g (0.250 mole) of selenium dioxide was stirred and heated at 60° until the solid dissolved. To this selenous acid solution, 31.5 g (0.250 mole) of 2-acetylthiophene was added, and the mixture was heated at reflux for 4 hours. Gray selenium metal was deposited as a lump which caused some interference with the stirrer. The solution was filtered hot through a sintered glass funnel to remove the selenium metal, and the dioxane was removed under reduced pressure with gentle heat. The residue of 2-thienylglyoxal and 2-acetylthiophene was vacuum distilled and the fraction boiling at 62-72° (0.5 torr) was collected. The yield was 21.6 g (0.154 mole, 61.6%). This material was 88% pure by nmr, the only impurity being 12% 2-acetylthiophene. No further purification was attempted.

Preparation of 5-iodo-2-methylthiophene

The procedure described here has not been previously reported in the synthesis of this compound. A solution of 23.8 g (0.243 mole) of 2-methylthiophene in 30 ml of benzene in a 500 ml Morton flask was cooled in an ice bath and small alternate portions of 43.3 g (0.200 mole) of yellow mercuric oxide and 63.0 g (0.248 mole) of iodine were added during a period of 30 minutes, with vigorous stirring. The suspension of mercuric iodide was

removed by filtration and the filter cake was washed with ether. The combined organic solvents were washed with 50 ml of saturated sodium thiosulfate solution, dried, and the solvents were removed on a steam bath. The residue was vacuum distilled to obtain 46.8 g (0.209 mole, 83.6%) of product: bp 61-64° (0.5 torr); reported (136) bp 88-89° (14 torr).

Preparation of 5'-methyl-2,2'-thenoin

A Grignard reagent was prepared from 17.9 g (0.0800 mole) of 5-methyl,2-iodothiophene and 1.94 g (0.0800 mole) of magnesium in 200 ml of dry ether, under nitrogen in a dropping funnel. With constant overhead stirring, the Grignard reagent was added dropwise to 10.4 g (0.0732 mole) of 2-thienylglyoxal in 200 ml of dry ether at -50°. The addition required about 60 minutes. After stirring an additional 60 minutes, during which time the brick red precipiate of the adduct changed to beige, the reaction temperature was allowed to rise to 0°, and 50 ml of saturated aqueous ammonium chloride was added in one portion. The suspension was allowed to stir until solution was effected. The ether layer was separated, and the aqueous layer was extracted with ether (3X100 ml). The combined ether solutions were dried, and the ether was removed in a rotary evaporator. The residue of thenoin weighing 6.43 g (0.0270 mole, 36.9%) mp 118-120°, was sufficiently pure to be used for the synthesis of 5-methyl-2,2'-thenil.

Preparation of 5-methyl-2,2'-thenil

A 3.75 g (0.0158 mole) quantity of the crude 5'-methyl-2,2'-thenoin was dissolved in a mixture of 15 ml of pyridine and 8 ml of water. To this, 10.0 g (0.0400 mole) of cupric sulfate pentahydrate was added, and the mixture was stirred and heated in an oil bath at 80° for 90 minutes. The solution was poured into 300 ml of cold water and refrigerated for 4 hours. After

neutralizing the reaction mixture with concentrated hydrochloric acid, the cold solution was extracted with methylene chloride (4X50 ml). The combined extracts were dried and the solvent was removed with a stream of air. The residue was continuously extracted with 30-50° petroleum ether in a Soxhlet apparatus until the bright yellow color was exhausted. After evaporation of the petroleum ether with a stream of air, the yellow thenil was collected and amounted to 2.81 g (0.0119 mole, 75.3%): mp 42-45°. For analysis it was sublimed twice at 70° (0.01 torr) mp 44-46°. The infrared spectrum is shown on p 150. The ultraviolet spectrum is shown on p 155.

Analysis, Calc'd for $C_{11}H_8O_2S_2$: C, 55.91; H, 3.41; S, 27.14.

Found: C, 55.74; H, 3.41; S, 26.97.

Preparation of methyl 5-methyl-2,2'-thenilate

A suspension of 472 mg (2.00 mmoles) of 5-methyl-2,2'-thenil in 15 ml of water and 1.0 g (18 mmoles) of potassium hydroxide was heated at 80° under nitrogen until solution was effected, about 3 hours being required. The reaction mixture was cooled to 10° and acidified to pH 2 with concentrated hydrochloric acid. The precipitated thenilic acid was immediately extracted with ether (2X30 ml). The combined ether solutions were shaken with a mixture sodium sulfate and Norit-A and filtered. The ether solution was immediately treated with an ether solution of diazomethane prepared from 0.5 g of N-methyl,N-nitrosourea and set aside for one hour at room temperature. The solvent was removed under reduced pressure at room temperature, and the residue of ester crystallized from 60-90° petroleum ether. The yield of product was 326 mg (1.12 mmole, 56.1%): mp 93-96°. For analysis, it was recrystallized twice from 60-90° petroleum ether: mp 95-96°.

Analysis, Calc'd for $C_{11}H_{12}O_3S_2$: C, 53.91; H, 4.15; S, 23.99.
Found: C, 53.71; H, 4.22; S, 24.10.

Preparation of 2-iodothiophene

This compound was prepared by the method described by Wirth et al. (66). The process is more convenient than the more usual method using iodine and mercuric oxide. A 500 ml Morton flask was charged with the following reagents in the order listed: 120 ml of water, 5.6 ml of concentrated sulfuric acid, 320 ml of glacial acetic acid, 80 ml of carbon tetrachloride, 32.8 g (0.186 mole) of iodic acid, and 84.0 g (1.00 mole) of thiophene. This mixture was stirred vigorously with an overhead stirrer while 81.6 g (0.321 mole) of iodine was added in small portions during a 30 minute period. The reaction mixture was poured into a seperatory funnel and 100 ml of carbon tetrachloride was added. The aqueous layer was separated, and the organic layer was washed with 100 ml of water, followed by 100 ml of 10% sodium thiosulfate. The organic phase was dried and the solvent was removed by distillation through an 8 inch Vigreaux column at atmospheric pressure. The residue was vacuum distilled to obtain 132 g (0.629 mole, 62.9%) of 2-iodothiophene based on thiophene. The yield was 98.0% based on iodine: bp 62-72° (12 torr); reported (66) 73-78° (18 torr).

Preparation of 2-methoxythiophene

The method reported by Sice (64) was employed in the preparation of this compound. A solution of 59.1 g (2.57 mole) of sodium metal in 700 ml of anhydrous methanol (freshly distilled from magnesium) was prepared. To this sodium methoxide solution, 177 g (0.843 mole) of 2-iodothiophene and 33.6 g of powdered cupric oxide were added. The mixture was refluxed with moderate

stirring for 30 hours. The cooled reaction mixture was poured into 1.5 l. of cold water and extracted with ether (4X400 ml). The ether extracts were combined and washed with water (2X200 ml). The ether solution was dried and the solvent removed by flash distillation. The residue was vacuum distilled to obtain 74.4 g (0.652 mole, 77.3%) of 2-methoxythiophene: bp 71-74° (50 torr) n_D^{24} 1.5258; reported (64) bp 74-75° (50 torr) n_D^{24} 1.5261.

Preparation of 5-methoxy-2-thenaldehyde

With constant stirring, 16.9 g (0.110 mole) of phosphorus oxychloride was added dropwise to 8.76 g (0.120 mole) of dimethylformamide during a period of 15 minutes, maintaining the reaction temperature below 50°. To this mixture 11.4 g (0.100 mole) of 2-methoxythiophene was added dropwise, maintaining the temperature below 30°. The reaction mixture formed a thick paste, which was heated to 50° for a few minutes on a steam bath. After being set aside for 30 minutes, the semisolid material was hydrolyzed with 50 ml of ice and water. The pH of the mixture was adjusted to 6 with 5M sodium hydroxide and the aqueous oily suspension was extracted with ether (3X50 ml). The combined dried ether extracts were flash distilled to remove the ether. The residue was vacuum distilled to obtain 5.65 g (0.0398 mole, 39.8%) of the aldehyde: bp 71-72° (0.1 torr); reported (64) 79-81° (0.9 torr).

Preparation of 5,5'-dimethoxy-2,2'-thenil

A solution of 11.4 g (0.100 mole) of 2-methoxythiophene in 150 ml of carbon disulfide was cooled to 5° and 26.1 g (0.100 mole) of stannic chloride in 30 ml of carbon disulfide was added dropwise with stirring. This was followed by the addition of 6.35 g (0.0500 mole) of oxalyl chloride in 30 ml of carbon disulfide. Both additions were made a rate to maintain the

reaction temperature below 5°. The mixture was stirred an additional 2 hours at 0-5°, and then poured into 100 ml of ice water. The reaction mixture was filtered to remove the bulk of the crude product.

The filtrate was poured into a separatory funnel and the carbon disulfide was separated. The aqueous layer was extracted with ether (4X100 ml). The combined organic phases were washed with saturated sodium bicarbonate until the aqueous layer was basic to litmus. The organic phase was dried, and evaporated to obtain a tar residue. The residue was dissolved in a minimum amount of methylene chloride and chromatographed on alumina (Merck Act. II, column prepared in 30-50° petroleum ether). The column was eluted with acetone, and all bright yellow fractions were collected and combined. Evaporation of the acetone with a stream of air gave a bright orange solid which was crystallized from methanol and combined with the material isolated from the original reaction mixture following hydrolysis. The total yield was 4.64 g (0.0165 mole, 33.0%): mp 136-138°. For analysis the thenil was recrystallized three times from methanol. The infrared spectrum is shown on p 148. The ultraviolet spectrum is shown on p 156.

Analysis, Calc'd for $C_{12}H_{10}O_4S_2$: C, 51.05; H, 3.57; S, 22.72.
Found: C, 51.08; H, 3.56; S, 22.79.

Preparation of 2-isopropoxythiophene

To a solution of 23.0 g (1.00 mole) of sodium metal in 500 ml of dry isopropanol (freshly distilled from sodium) 105 g (0.500 mole) of 2-iodothiophene and 20 g of cupric oxide were added. The mixture was stirred well and refluxed for 30 hours. The reaction mixture was then cooled until it became quite viscous, and 300 ml of water was added with constant stirring. This mixture was poured into 2 l. of water in a separatory funnel and the

lower layer was separated. The upper layer was extracted with methylene chloride (4X100 ml). The lower layer was combined with the methylene chloride extracts and filtered through a bed of celite, and then through anhydrous magnesium sulfate. The solvent was removed in a rotary evaporator at water pump pressure. The residue was distilled to obtain 8.02 g (0.0564 mole, 11.3%): bp 50-65° (13 torr), of material slightly contaminated with 2-iodothiophene. The 2-iodothiophene can be removed only by reacting the mixture with magnesium under grignard conditions, and hydrolyzing with water. A final distillation serves to remove the thiophene.

Preparation of 5,5'-diisopropoxy-2,2-thenil

A mixture of 1.42 g (10.0 mmoles) of 2-isopropoxythiophene and 2.61 g (10.0 mmoles) of stannic chloride in 50 ml of carbon disulfide was cooled to 0° and 0.64 g (5.0 mmoles) of oxalyl chloride in 10 ml of carbon disulfide was added with constant stirring during 30 minutes. After an additional 15 minutes of stirring, the reaction mixture was poured into 50 g of ice and the reaction flask was washed with 50 ml of ether. The carbon disulfide-ether-water solutions were combined and the aqueous layer was separated and extracted with ether (2X50 ml). The combined organic phases were washed with water and saturated sodium bicarbonate until the washings were basic to litmus. The solvents were removed with a stream of air, and the tarry residue was dissolved in 50 ml of methanol, treated with Norit, filtered, and set aside. The solid material which separated from the solution was sublimed at 140° (0.1 torr) to yield 0.28 g (0.828 mmole, 16.6%) of the bright yellow thenil: mp 101-103°. For analysis, it was resublimed. The infrared spectrum is shown on p 148. The ultraviolet spectrum is shown on p 156.

Analysis, Calc'd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36; S, 18.95.

Found: C, 56.80; H, 5.49; S, 19.07.

Preparation of 2-thianapthaldehyde

The procedure described by Shirley and Danzig (59) was followed with minor modifications for the synthesis of this compound. A two liter, three-neck flask, equipped with an overhead stirrer was charged with 400 ml of 1.6N n-butyllithium in hexane (Foote Chemical Co., Exton, Penn.) . With constant stirring, 67.0 g (0.500 mole) of thianapthene in 200 ml of dry ether was added to the butyllithium solution dropwise over a period of 1.5 hours in an atmosphere of nitrogen at -10°. After all the thianapthene had been added, the reaction temperature was raised briefly to 20° to allow the evolution of butane and then recooled to 0°. The lithiothianapthene was then treated dropwise with 36.6 g (0.500 mole) of freshly distilled dimethylformamide in 200 ml of dry ether during 30 minutes. The reaction mixture was then refluxed for 1.5 hours and poured into 400 ml of 3N hydrochloric acid and 500 g of crushed ice. After separation of the ether layer, the aqueous layer was extracted with ether (3X300 ml). The organic phases were combined, dried, and the ether was removed in a rotary evaporator. The residue of aldehyde was dissolved in 300 ml of 95% ethanol and 200 g of sodium bisulfite in 700 ml of water was added. The resulting bisulfite adduct was collected by vacuum filtration, washed copiously with ether until white, and air dried. The adduct was dissolved in 500 ml of water with gentle heat, and 500 ml of saturated sodium carbonate was added to decompose it. The resulting aldehyde separated from solution as an oil which solidified on being set aside in the ice box. The yield was 54.9 g (0.339 mole, 67.8%): mp 33-35°; reported (59) mp 34-34.5°.

Preparation of 2,2'-benzo[b]thenoin

This compound was prepared according to the method described by Shirley and Danzig (59). Thus, 32.4 g (0.200 mole) of 2-thianapthaldehyde in 400 ml of 50% ethanol-water and 2.0 g of potassium cyanide was refluxed for 20 minutes. The thenoin separated from solution spontaneously during the reflux period. After cooling to room temperature, the thenoin was collected, washed well with water and air dried. The yield was 27.4 g (0.0846 mole, 84.6%): mp 152-154°; reported (59) 154-156°.

Preparation of 2,2'-benzo[b]thenil

Weiss' oxidation method was used to prepare this thenil (49). A mixture of 30.3 g (0.0942 mole) of 2,2'-benzo[b]thenoin, 12.0 g (0.15 mole) of ammonium nitrate, 1 g of cupric acetate, and 200 ml of 80% acetic acid-water was heated at reflux for 90 minutes. The thenil crystallized spontaneously from the violet solution on cooling. It was collected by vacuum filtration, washed with cold methanol and ether, and dried. The yield of product was 29.9 g (0.0928 mole, 98.7%) mp 236-238°. For analysis, it was recrystallized twice from benzene: mp 239-240°. The infrared spectrum is shown on p 152. The ultraviolet spectrum is shown on p 154.

Analysis, Calc'd for $C_{18}H_{10}O_2S_2$: C, 67.06; H, 3.12; S, 19.89.
Found: C, 67.08; H, 3.08; S, 19.96.

Preparation of methyl 2,2'-benzo[b]thenilate

This compound was prepared under the typical thenilic rearrangement conditions described previously. Thus, 1.61 g (5.00 mmoles) of 2,2'-benzo[b]thenil and 1.12 g (20 mmoles) of potassium hydroxide in 20 ml of water was heated

to 80° in an oil bath with stirring under a nitrogen atmosphere. Complete solution of the thenil was effected in about one hour. After cooling to room temperature in an ice bath, the reaction mixture was acidified to congo red with concentrated hydrochloric acid, and then immediately extracted with ether (3X50 ml). The dried extracts were immediately treated with an ether solution of diazomethane prepared from 1.03 g of N-methyl, N-nitrosourea. Evaporation of the solvent gave a solid which was recrystallized from 60-90° petroleum ether to obtain 1.10 g (3.10 mmoles, 62.0%) of the ester: mp 103-104°. For analysis it was recrystallized from 60-90° petroleum ether.

Analysis, Calc'd for $C_{19}H_{10}O_3S_2$: C, 64.38; H, 3.98; S, 18.09.
Found: C, 64.15 H, 3.95; S, 17.98.

Preparation of 2-(1'-adamantyl)thiophene

This compound was prepared by following Wynberg's procedure exactly (71). A vigorously stirred, refluxing solution of 64.5 g (0.300 mole) of 1-bromoadamantane (Aldrich Chemical Co., Milwaukee, Wisc.) in 500 ml of freshly distilled thiophene was treated dropwise with 83.0 g (0.320 mole) of stannic chloride during 30 minutes. The reaction was allowed to continue an additional 15 minutes after the evolution of hydrogen bromide ceased. A mixture of 200 ml of concentrated hydrochloric acid and 200 g of ice was added to the cooled reaction mixture. The organic phase was separated and washed with 100 ml of 4N sodium hydroxide and 200 ml of water. After drying the solution with magnesium sulfate, the thiophene was removed by distillation. The residue was distilled and all material boiling between 120-150 (1 torr) was collected. This distillate, amounting to 50.8 g (0.243 mole) of a mixture of 2- and 3-(1'-adamantyl)thiophenes was dissolved in 230 ml of ethanol. To this

well stirred refluxing solution, a mixture of 93 ml of saturated aqueous sodium acetate and 62.5 g (0.226 mole) of mercuric chloride in 230 ml of ethanol was added dropwise during two hours. After refluxing an additional 15 minutes, the suspension of 2-chloromercuri-5-(1'-adamantyl)thiophene was cooled to 50° and filtered. The solid was air dried and then refluxed in 500 ml of 6N hydrochloric acid containing a few mls of benzene until the solid had all dissolved. The acid solution was cooled and extracted with benzene (3X100 ml). The benzene was removed in a rotary evaporator at reduced pressure and the residue of 2-(1'-adamantyl)thiophene was crystallized from ethanol. The yield was 26.8 g (0.123 mole, 41.0%).

Preparation of 5,5'-di-(1"-adamantyl)-2,2'-thenil

A 15 ml quantity of 1.6N n-butyllithium in hexane (Foote Chemical Co., Exton, Penn.) was added in one portion with stirring to 4.36 g (0.020 mole) of 2-(1'-adamantyl)thiophene in 30 ml of dry ether under a nitrogen atmosphere. This reaction was carried out in a jacketed addition funnel. After 10 minutes of stirring, the jacket of the addition funnel was filled with a mixture of dry ice and isopropanol. The thoroughly chilled solution of adamantylthienyllithium was added dropwise over a period of 20 minutes to 1.18 g (0.0100 mole) of dimethyl oxalate in 50 ml of dry ether with stirring at -60° or lower. After one hour of stirring at -60°, the reaction temperature was allowed to rise to -10° and 50 ml of 5% sulfuric acid was added. The organic phase was separated and the aqueous phase was extracted with 50 ml ether. The combined dried extracts were evaporated to yield an orange residue. This was triturated with 2:1 benzene:methanol to give a bright yellow solid: mp 244-247°. It was recrystallized from cyclohexane to obtain 1.07 g (0.00218 mole, 21.8%): mp 257-258°, of the thenil. For analysis it was

recrystallized twice from cyclohexane. The infrared spectrum is shown on p 151. The ultraviolet spectrum is shown on p 156.

Analysis, Calc'd for $C_{30}H_{34}S_2O_2$: C, 73.42; H, 6.98: S, 13.07.

Found: C, 73.17; H, 6.83; S, 12.91

Preparation of 2-fluorothiophene

This compound was prepared using a combination of the procedures developed by Schuetz (72) and Gronowitz (73). Lithium metal, 7.29 g (1.05 moles) was hammered and scissored (131) and the pieces added to 150 ml of dry ether in a one liter, three-neck flask. After cooling the lithium suspension to -10° by means of a dry ice-isopropanol bath, 54.5 g (0.500 mole) of ethyl bromide was added with stirring while holding the temperature between 0° and -10°. The ethyllithium solution was stirred an additional hour after the lithium metal had dissolved, and then was treated dropwise with 33.6 g (0.400 mole) of freshly distilled thiophene in 100 ml of dry ether during 20 minutes. The ethane was driven off by heating the reaction mixture to 30° for a few minutes. The thienyllithium solution was recooled to -10° and a strong stream of perchloryl fluoride (Columbia Chemical Co., Columbia, S.C.) was added. The addition was accompanied by a strong blue luminescence. The addition of the perchloryl fluoride was stopped when the luminescence was no longer noted and the reaction mixture began to turn dark brown. The solution was purged with nitrogen for 45 minutes and then poured into 200 ml of 5M sodium carbonate solution. After filtering the reaction mixture, the aqueous suspension was extracted with ether (3X200 ml). The ether extracts were combined, dried and distilled from a water bath heated to 40° to remove the ether. The residue was examined by nmr and was found to be 50% 2-fluorothiophene, 30% thiophene, and 20% ether. The yield of

2-fluorothiophene was, therefore, 8.4 g (0.0823 mole, 21%). This material was distilled through a 24 inch spinning band column at atmospheric pressure to give an azeotrope boiling at 77°. Examination of this material by nmr showed it to consist of 88% 2-fluorothiophene and 12% thiophene. This material was used in all subsequent experiments calling for 2-fluorothiophene.

Preparation of 5-fluoro-2-thenaldehyde

A solution of 1.6N n-butyllithium in hexane, 70 ml (Foote Chemical Co., Exton, Penn.) was cooled in an ice bath to 3° and 10.2 g (0.100 mole) of 2-fluorothiophene in 50 ml of dry ether was added dropwise during one hour. After stirring 15 minutes following the 2-fluorothiophene addition, a solution of 8.0 g (0.11 mole) of freshly distilled dimethylformamide in 40 ml of dry ether was added dropwise during 30 minutes while maintaining the reaction temperature below 10°. The reaction mixture was allowed to stir 15 minutes longer, and then poured onto 100 g of ice. After acidifying with 50 ml of 6N hydrochloric acid, the organic phase was separated, and the aqueous phase was extracted with ether (4X100 ml). The organic layers were combined, dried and the ether was removed by flash distillation. The residue was vacuum distilled to obtain 8.2 g (0.063 mole, 63%): bp 60-61° (63 torr) n_D^{23} 1.5482, of aldehyde. A 2,4-dinitrophenylhydrazone was prepared of the aldehyde in the usual manner and recrystallized twice from ethanol for analysis: mp 257-258° dec.

Analysis, Calc'd for $C_{11}H_6FN_4O_4S$: C, 42.72; H, 1.96; N, 18.12; S, 10.37.
Found: C, 42.64; H, 2.01; N, 17.96; S, 10.44.

Preparation of 5,5'-difluoro-2,2'-thenil

This compound was synthesized in a manner analogous to the preparation

of 5,5'-di-(1"-adamantyl)-2,2'-thenil. A solution of 3.69 g (0.0362 mole) of 2-fluorothiophene in 30 ml of anhydrous ether was stirred and treated under a nitrogen atmosphere, with 25 ml of 1.6N n-butyllithium in hexane (Foote Chemical Co., Exton Penn.). The mixture was stirred 15 minutes at room temperature, then cooled to -60° and added dropwise to 2.18 g (0.0181 mole) of dimethyl oxalate in 100 ml of dry ether also cooled to -60°. The addition was performed at such a rate that the reaction temperature was maintained below -50°. After one hour of additional stirring, the reaction mixture was allowed to warm to room temperature and 50 ml of water was added, followed by 20 ml of 10% hydrochloric acid. The layers were separated and the aqueous layer was extracted with ether (2X50 ml) and combined with the original ether layer. The ether solution of the thenil was dried and the solvent was evaporated with an air stream to leave a black iridescent residue. The residue was continuously extracted with 30-50° petroleum ether in a Soxhlet apparatus. Evaporation of the petroleum ether gave 1.60 g (0.00620 mole, 34.3%) of the thenil: mp 89-95°. The product was purified by sublimation at 70° (0.5 torr) to give the analytically pure thenil: mp 126-128°. The infrared spectrum is shown on p 149. The ultraviolet spectrum is shown on p 155.

Analysis, Calc'd for $C_{10}H_4F_2O_2S_2$: C, 46.50; H, 1.56; S, 24.83.
Found: H, 46.70; H, 1.65; S, 24.62.

Preparation of methyl 5,5'-difluoro-2,2'-thenilate

A solution of 0.6 g (11 mmoles) of potassium hydroxide in 10 ml of water was heated to 80° in an oil bath with stirring under nitrogen and 0.190 g (0.737 mmole) of 5,5'-difluoro-2,2'-thenil was added in one portion. The suspension was heated and stirred until solution was complete, about 45 minutes being required. The reaction mixture was cooled in an ice

bath below room temperature and acidified to congo red with 6N hydrochloric acid. The acid solution was quickly extracted with ether (3X25 ml). The combined ether extracts were dried and treated with an ethereal solution of diazomethane prepared from 0.2 g of N-methyl,N-nitrosourea. Evaporation of the ether gave a pale yellow oil, which solidified on being set aside. The thenilic ester, 0.166 g (0.572 mmole, 77.7%) was sublimed twice for analysis: mp 55-57°.

Analysis, Calc'd for $C_{11}H_8F_2O_3S_2$: C, 45.51; H, 2.78; S, 22.09.
Found: C, 45.74, H, 2.63; S, 22.18.

Preparation of 5-acetyl-2-fluorothiophene

A solution of 1.02 g (0.010 mole) of 2-fluorothiophene and 0.87 g (0.011 mole) of acetyl chloride in 15 ml of carbon disulfide was cooled to 5° in an ice bath. The cold solution was then treated dropwise with 2.87 g (0.011 mole) of stannic chloride with stirring during a one hour period. Stirring was continued for an additional hour, and the purple solution was then hydrolyzed by cautiously adding 10 ml of water. After separation of the carbon disulfide layer, the aqueous layer was extracted with carbon disulfide (2X20 ml). The combined extracts were washed with 20 ml of water and dried. The dried organic solution was filtered and flash distilled to remove the solvent. The residue, 1.15 g (0.0072 mole, 72%) was distilled in a micro molecular still at 80° (15 torr) to obtain the pure product. A 2,4-dinitrophenylhydrazone of the ketone prepared in the usual manner, was twice crystallized from ethanol for analysis: mp 246-248°.

Analysis, Calc'd for $C_{12}H_8FN_4O_4S$: C, 44.58; H, 2.49; N, 17.33; S, 9.92.
Found: C, 44.46; H, 2.54; N, 17.21; S, 9.84.

Preparations Directed Toward the Synthesis of 2-Trifluoromethylthiophene

Preparation of 5,5,5-trifluorolevulinic acid

The procedure described by Brown et. al. (137) was used with some modification in this synthesis. A well stirred mixture of 39.2 g (0.276 mole) of ethyl trifluoroacetate, 48.2 g (0.276 mole) of dimethyl succinate, and 6.35 g (0.276 mole) of sodium metal pellets (K&K Chemical Co., Plainview, N.Y.) was heated cautiously to initiate the reaction. After the exothermic reaction had cooled to room temperature, 50 ml of dry ether was added and the reaction mixture was refluxed for 18 hours. The ether was removed by distillation and 100 ml of 10N sulfuric acid was added cautiously. The acidic solution was extracted with ether (6X50 ml). The extracts were combined and dried by filtration through magnesium sulfate. After removal of the ether by evaporation on a steam bath, the residue was distilled to give 56.8 g (0.208 mole, 74.8%) of diethyl trifluoroacetosuccinate: bp 100-135° (0.5 torr) n_D^{19} 1.4000; reported (137) n_D^{20} 1.4104. The distillate was hydrolyzed by refluxing it in 350 ml of 43% aqueous sulfuric acid for 7 hours. After cooling, the acid solution was extracted with ether (6X50 ml). The ether extracts were combined and dried, and the ether was removed in a rotary evaporator. The crude acid was distilled to obtain 17.4 g (0.102 mole) of trifluorolevulinic acid: bp 66-68° (0.1 torr). The acid was recrystallized from benzene to obtain 12.3 g (0.0723 mole, 26.2%) of pure product based on ethyl trifluoroacetate: mp 53-56°; reported (137) 54-56°.

Attempted preparation of 2-trifluoromethylthiophene

An attempt was made to synthesize the title compound using as a guide the procedure described by Hartough (138) for the synthesis of 2-methylthiophene.

A 12.3 g (0.0723 mole) quantity of 5,5,5-trifluorolevulinic acid was dissolved in 50 ml of dry ether, and 1.73 g (0.0720 mole) of sodium hydride was added in small portions with stirring. The ether was then removed in a rotary evporator, and the residue of sodium 5,5,5-trifluorolevulinate, 13.8 g (0.0719 mole, 99.4%) was mixed with 35 g of phosphorous pentasulfide and 50 g of sand. This mixture was cautiously heated to 190° during 90 minutes. A continuous stream of nitrogen was passed through the apparatus during the heating period. Provision was made to trap any volatile material in a cold trap at 0°. At 130-135°, a strong evolution of white fumes began but no material could be trapped. The pot residue consisted of a totally intractable tar. None of the desired product was in evidence.

Preparations Directed Toward the Synthesis of 2-Phenoxythiophene

Via the Ullmann reaction

Various 2-halothiophenes were treated under typical Ullmann reaction conditions with sodium or potassium phenolate. The method reported by Bacon (139) and the one described by Jones and Moodie (76) were used as guides in these attempted syntheses of 2-phenoxythiophene.

A quantity of the halothiophene ranging from 10 to 100 mmoles was dissolved in 10 times its volume of solvent. To this solution, an equivalent of cupric oxide, or cuprous oxide, or finely divided copper metal was added along with a 5% excess of sodium or potassium phenolate. This mixture was heated at reflux usually 24 hours, with stirring under nitrogen. In one experiment, using 2-iodothiophene with dimethylformamide as the solvent and cuprous oxide as the catalyst, the reaction time was one week. The solvents were either removed by evaporation at reduced pressure or extracted with water.

The residue was examined by nmr after distillation unless vpc had indicated that no reaction had occurred. The following reaction systems were examined: 2-iodothiophene in water, dimethylformamide, methanol, ethanol, dimethyl sulfoxide, dimethylacetamide, molton phenol, and pyridine; 2-bromothiophene was tried in all these solvents except water; 2-chlorothiophene was tried in dimethylformamide and dimethyl sulfoxide; 2-fluorothiophene was tried in dimethylformamide, dimethylacetamide and dimethyl sulfoxide. In no case could even a trace of material be isolated as to indicate that the desired reaction had occurred. In almost all cases, the halothiophene was recovered in better than 95% yield.

Preparation of bis(2-thienyl)iodonium salts

The procedure described by Behringer (140) was utilized for this synthesis. A well stirred mixture of 130 ml of acetic acid, 40 ml of acetic anhydride, 20 g (0.094 mole) of potassium iodate and 58 g (0.69 mole) of thiophene was cooled below 10° by immersion in an ice bath. A cold mixture of 30 ml of acetic acid and 24 ml of sulfuric acid was added to the above mixture, while taking extreme care not to allow the reaction temperature to rise above 10°. After stirring overnight at room temperature, the reaction mixture was diluted with 200 ml of water and extracted with ether (3X100 ml). The ether extracts were discarded and the aqueous layer was treated with Norit-A and filtered. The colorless filtrate was treated with a solution of 15 g of potassium iodide in 100 ml of water. The precipitated bis(2-thienyl)iodonium iodide was collected by filtration and air dried to obtain 8.50 g (0.0202 mole, 21.6%) mp 127-128°; reported (140) 128-129°. The substitution of 15 g of sodium bromide in 100 ml of water in place of the potassium iodide gave 8.15 g (0.0218 mole, 23.4%) of bis(2-thienyl)iodonium bromide: mp 185-186°. The crude iodonium bromide was recrystallized from dimethyl sulfoxide: mp

210-212°; reported (140) 215-219°. These compounds were not purified further.

Reaction of sodium phenolate with bis(2-thienyl)iodonium salts

Behringer's method (81) for the synthesis of diaryl ethers was used as a guide in this reaction attempt, as well as a modification described by Crowder et al. (141). A stirred suspension of 4.20 g (0.0100 mole) of bis(2-thienyl)iodonium iodide and 5.80 g (0.0500 mole) of sodium phenolate (City Chemical Corp., New York, N.Y.) was heated in 50 ml anhydrous methanol at reflux for 24 hours. The methanol was then removed in a rotary evaporator and 100 ml of water and 100 ml of ether was added to the residue. After shaking the mixture, the ether was removed and dried. Evaporation of the ether gave only phenol and 2-iodothiophene, identified by vpc. The same procedure was tried using water as the reaction solvent. Again only phenol and 2-iodothiophene could be isolated. The use of bis(2-thienyl)iodonium bromide in the procedure described above yielded only phenol and presumably a mixture of 2-bromothiophene and 2-iodothiophene.

Preparation of 2-hydroxythiophene

The method reported in Organic Synthesis was modified for use in this preparation. A Grignard reagent prepared from 84.0 g (0.400 mole) of 2-iodothiophene, and 10.0 g (0.412 mole) of magnesium turnings in 400 ml of dry ether was cooled to 0-5° by immersion in an ice bath. A solution of 62 g (0.32 mole) of tert-butyl perbenzoate in 100 ml of dry ether was added during 45 minutes to the cold, well stirred Grignard solution. After stirring an additional 3 hours, the solution was hydrolyzed by pouring it into 500 g of ice and 5 ml of concentrated hydrochloric acid. The ether layer was quickly

separated and the aqueous layer extracted with ether (2X100 ml). The combined ether solutions were extracted with 2N sodium hydroxide (3X60 ml), washed with water until neutral, and dried. After establishing the absence of peroxides, the ether was removed by distillation in a water bath held at 50°. The residue was distilled at water pump pressure to obtain 37.6 g (0.240 mole, 75.0%), of 2-tert-butoxythiophene.

A 7.81 g (0.0500 mole) quantity of 2-tert-butoxythiophene was transfered to a round bottom flask fitted with a distillation head. The apparatus was purged with nitrogen, and 0.1 g of p-toluenesulfonic acid was added. The distillation apparatus was again purged with nitrogen by several flush-evacuate cycles. The distillation flask was immersed in an oil bath previously heated to 125° and kept there until a brisk evolution of isobutane ensued, which was drawn off by a water aspirator. The water aspirator was replaced by an oil pump when the gas evolution had ceased and the 2-hydroxythiophene was distilled. The yellow product, 4.82 g (0.00482 mole, 96.4%) bp 51° (1 torr); reported (67) 91-93° (13 torr) was stored in the freezer at -20° until needed.

Attempted preparation of 2-(2',4'-dinitrophenoxy)thiophene

A stirred solution of 2.00 g (0.0200 mole) of 2-hydroxythiophene in 20 ml of anhydrous ether was treated in small portions with 0.48 g (0.0200 mole) of sodium hydride. After the evolution of hydrogen had ceased, a solution of 3.72 g (0.0200 mole) of 2,4-dinitrofluorobenzene in 10 ml of ether was added. An immediate dark blue color formed. After stirring for 30 minutes, a brown-violet precipitate formed and was collected. This material,weighing 4.2 g, was water soluble and was discarded without further characterization. Further workup failed to reveal any of the desired phenoxythiophene.

The reaction was repeated under conditions described by Reinheimer et al. (86) for the preparation of 2,4-dinitrophenyl ethers of various phenols. The main difference in this procedure is that triethylamine is substituted for sodium hydride, and the reaction is carried out in acetone. In the present study, the same brown-violet solid was formed when Reinheimer's method was used as was noted previously. The product was apparently a condensation product with the 2,4-dinitrofluorobenzene, since without this material being present, no reaction occurred. Further characterization of the product was not attempted.

Preparation of 2-chloro-3,5-dinitrothiophene

The procedure described by Hurd and Kreuz (82) was followed to prepare this compound. A well stirred solution of 37 g (0.31 mole) of 2-chlorothiophene, and 100 ml of acetic anhydride was cooled to -10° in an isopropanol-dry ice bath. To this solution, a mixture of 50 g of 90% nitric acid (0.72 mole) and 100 ml of acetic anhydride was added dropwise at such a rate that the reaction temperature remained below 0°. After 8 hours at this temperature the reaction mixture was poured into 400 g of crushed ice. The cold solution was extracted with 30-50° petroleum ether (3X250 ml). The organic phase was filtered and the ether was removed by evaporation to give a yellow oil. The oil was vacuum distilled and yielded 27 g (0.16 mole, 52%) of product: bp 57° (0.3 torr).

The oily 5-nitro-2-chlorothiophene was added with stirring during a 30 minute period to a mixture of 150 g of 90% nitric acid and 150 g of concentrated sulfuric acid cooled by immersion in an ice bath. The temperature was maintained at 0-5° during the addition of the thiophene compound. The dinitro compound spontaneously crystallized from the nitrating mixture as it

formed. The reaction mixture was quenched by pouring it into 300 g of crushed ice. The dinitro compound was collected by filtration and air dried to obtain 22.5 g (0.11 mole, 69%). It was used without further purification.

Preparation of 2-phenoxy-3,5-dinitrothiophene

The method used by Hurd and Kreuz (82) was employed on a larger scale in this synthesis. A 4.17 g (0.0200 mole) quantity of 2-chloro-3,5-dinitrothiophene was placed in a large porcelain mortar and just covered with 30 ml of 30-50° petroleum ether. In small portions, and with constant grinding, 2.32 g (0.0200 mole) of sodium phenolate was added. The grinding was continued until all of the ether evaporated. The resulting salmon colored solid was recrystallized from 2:1 methanol-benzene to obtain 2.98 g (0.0114 mole, 57.0%) of the ether: mp 153-154°; reported (82) 151.5-152.5°.

Attempted reduction of 2-phenoxy-3,5-dinitrothiophene

An attempt was made to reduce the nitro functions of 2-phenoxy-3,5-dinitrothiophene, using a procedure developed for the reduction of 2-nitrothiophene to 2-aminothiophene (84). A mixture of 5.32 g (0.0200 mole) of 2-phenoxy-3,5-dinitrothiophene and 20 ml of concentrated hydrochloric acid was warmed to 40°. In small portions, 7.08 g (0.0600 mole) of 30 mesh tin was added during a 15 minute period. The reaction temperature was held to 40° or lower during the addition of the metal by means of an ice bath. After about one fourth of the tin had been added, a strong evolution of hydrogen sulfide ensued. The tin addition was continued until all had been added, during which time an intractable tar separated from the reaction mixture. All attempts to separate the expected stannic chloride salt of the diaminothiophene failed.

Attempted preparation of 5,5'-dinitro-2,2'-thenil

A 0.50 g (0.0023 mole) quantity of 2,2'-thenil was dissolved in 20 ml of acetic acid and 2 ml of 90% nitric acid was added in one portion. The temperature was held at 60° in an oil bath for 30 hours. The yellow solution was poured into 50 ml of ice water and stirred until the oil crystallized. This solid proved to be starting material, identified by mixed melting point, and recovered in 97% yield.

Preparation of 1,1-di-(2'-and 3'-thienyl)ethylene glycol

A 0.254 g (1.00 mmole) quantity of methyl 2,2'-thenilate or methyl 3,3'-thenilate in 15 ml of dry ether was allowed to stir for 18 hours with 50 mg (1.32 mmoles) of lithium aluminum hydride. The reaction mixture was then refluxed 30 minutes, and cooled. The solution was cautiously hydrolyzed with 1% hydrochloric acid. The ethereal layer was separated and the aqueous layer extracted with 15 ml of ether. The combined ether solutions were dried and the ether was removed in a rotary evaporator. The residue was recrystallized from 60-90° petroleum ether in the case of the 2,2'-compound. The 3,3'-compound was an oil and was not further purified. The yield of 1,1-di-(2'-thienyl) ethylene glycol was 0.190 g (0.852 mmole, 85.2%): mp 62-63°. The yield of 1,1-di-(3'-thienyl)ethylene glycol was 0.170 g (0.752 mmole, 75.2%). Examination of the aromatic portion of the nmr spectrum of each compound was made. These spectra are shown on p 42. They clearly confirm that prototropic rearrangement does not occur during the thenilic acid rearrangement.

Degradation of 5,5'-dimethoxy-2,2'-thenil

The method described by Dakin and Harington (21) was used to degrade

5,5'-dimethoxy-2,2'-thenil to 5-methoxy-2-thenoic acid. A mixture of 0.20 g (0.71 mmole) of 5,5'-dimethoxy-2,2'-thenil, 15 ml of water, 10 ml of methanol, 0.3 g of sodium cyanide, and 0.3 g of ammonium chloride was refluxed on the steam bath for 12 hours. The mixture was taken to dryness on a rotary evaporator, and 20 ml of 50/50 (v/v) ethanol-water and 2.0 g of sodium hydroxide was added to the residue. This mixture was refluxed for 3 hours, treated while hot with Norit-A and filtered. The filtrate was cooled in the ice box and then acidified with concentrated hydrochloric acid. The crude acid was collected and air dried. It was sublimed at 110° (0.05 torr) and weighed 0.11 g (0.69 mmole,97%). The pure material was shown to be identical to 5-methoxy-2-thenoic acid by mp and mixed mp: mp 162-163°; reported (64) 162-163°, and by infrared spectrum.

General preparation of thenoic acids

The thenoic acids used in the pK_a determinations were usually prepared by silver oxide oxidation of the corresponding aldehydes. A general description of the procedure used in the preparation of 2-thenoic, 3-thenoic, 5-chloro-2-thenoic, 5-methyl-2-thenoic, 5-methoxy-2-thenoic, 5-fluoro-2-thenoic, and 2-benzo[b]thenoic acid follows.

An alkaline silver oxide suspension was prepared from 3.0 g (18 mmoles) of silver nitrate and 2.0 g (50 mmoles) of sodium hydroxide in 30 ml of water. A 10 mmole quantity of the aldehyde was added in one portion to the silver oxide suspension, and the mixture was allowed to stir for one hour or at least 30 minutes after a silver mirror had formed on the surface of the reaction vessel. The solution was filtered, shaken with a small amount of Norit-A and refiltered. The solution of the acid salt was acidified to pH 3 with 2N hydrochloric acid. The precipitated acid was collected and dried. The acid

was recrystallized from water using a small amount of Norit-A for decoloration. For the pK_a determinations, the acids were recrystallized three times from water, or until their melting points were constant. They were then dried at 56° in a drying pistol at 0.1 torr, and stored in a desiccator over phosphorous pentoxide for one week. The acids prepared by this method are shown in Table 7.

Table 7. Thenoic Acids Prepared by Oxidation of the Corresponding Aldehydes

Acid	% yield	melting point	lit. melting point
2-thenoic acid	84	129-130°	129-130° (142)
3-thenoic acid	91	135-137°	138.4° (142)
5-chloro-2-thenoic acid	72	151-151.5°	146-147° (142)
5-methyl-2-thenoic acid	88	138-139°	138-138.5° (142)
5-methoxy-2-thenoic acid	75	162-163°	162-163° (64)
5-fluoro-2-thenoic acid	48	145-146°	---
2-benzo[b]thenoic acid	47	243-244°	240-241.5° (143)

Preparation of 2-diacetoxymethyl-5-nitrothiophene

A solution of 22.4 g (0.200 mole) of 2-thenaldehyde in 50 ml of acetic anhydride was cooled to 10° and maintained there or below during the addition of 12.1 ml (18.2 g, 0.260 mole) of 90% nitric acid. After the addition of the nitric acid was completed, the reaction mixture was set aside in the ice box overnight, and then poured into 400 ml of water. The solid product was immediately collected, air dried, and recrystallized from 90% methanol. The yield was 29.5 g (0.114 mole, 57.0%): 71-73°; reported (96) mp 73°.

Preparation of 5-nitro-2-thenoic acid

A suspension of 5.18 g (0.0200 mole) of 2-diacetoxymethyl-5-nitrothiophene and 8.82 g (0.0300 mole) of potassium dichromate in 30 ml of water was treated dropwise with 20 ml of concentrated sulfuric acid at such a rate that

the reaction temperature did not exceed 60°. The solution was refluxed 30 minutes, cooled and 20 ml of water was added. The precipitated acid was collected, washed copiously with water and air dried. The yield of 5-nitro-2-thenoic acid was 1.73 g (0.0100 mole, 50.0%): mp 159-161°. For the pK_a determination, it was dried in the same manner as described previously for the other 2-thenoic acids. The melting point of the purified acid was 159-160°; reported (142) 158°.

Purification of 3-benzo[b]thenoic acid

A sample of 3-benzo[b]thenoic acid previously prepared in these laboratories by Dunigan (144) was purified as described previously for the thenoic acids. The melting point was 162-164°; reported (143) 174-175°.

Preparation of methyl 2,2-di-(2'-thienyl),2-ethoxyacetate

Method A

A solution of 2,2'-thenilic acid, prepared from 1.00 g (4.52 mmoles) of 2,2'-thenil,in 15 ml of methylene chloride was cooled to -70° in a dry ice-isopropanol bath. To this solution, 6 ml (10.6 g, 91.5 mmoles) of chlorosulfonic acid was added in one portion with vigorous stirring. After 5 minutes, the dark red solution was quenched by pouring it into 25 ml of anhydrous ethanol, freshly distilled from sodium metal and previously cooled to -70°. After adding 20 ml of water, the acid solution was neutralized to congo red by adding, in small portions, solid sodium carbonate while maintaining the temperature below 0°. The solution was filtered, and the filtrate was extracted with methylene chloride (2X20 ml). The combined methylene chloride solutions were dried and immediately treated with an ether solution of diazomethane, prepared from 3.0 g of N-methyl,N-nitrosourea. After stirring

the solution for one hour at room temperature, the solution was treated with Norit-A and filtered and the ether was removed at water pump pressure and finally with an oil pump. The yield of crude ethoxyester was 1.19 g (4.21 mmoles, 93.3%). For analysis, the ester was distilled twice in a micro molecular still at 110° (0.3 torr). The nmr spectrum showed τ 2.7-3.3 (6H's, m); τ 6.30 (3H's, s); τ 6.65 (2H's, q); τ 8.80 (3H's, t).

Analysis, Calc'd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.00; S, 22.71.

Found: C, 55.13; H, 4.94; S, 22.95.

Method B

Following the same procedure as outlined in Method A, 1.00 g (3.94 mmoles) of methyl 2,2'-thenilate was treated with the same amount of chlorosulfonic acid as used before. The treatment with diazomethane was omitted. The combined dried methylene chloride extracts of the ethoxyester were taken to dryness in a rotary evaporator at reduced pressure. The residue of product, 1.07 g (3.79 mmoles, 96.3%) was examined by nmr and found to be identical with the material from Method A. In particular, no transfer of the methyl group from the alcohol portion of the ester to the acid portion had occured in the carbonium ion.

Preparation of N-methyl-3-piperidyl-2',2"-thenilate hydrochloride

The synthesis of this compound was based on a procedure reported by Biel et al. (7). To 30 ml of n-heptane (dried over sodium) was added 1.00 g(3.94 mmoles) of methyl 2,2'-thenilate and 0.459 g (3.98 mmoles) of N-methyl-3-piperidinol (Aldrich Chemical Co., Milwaukee, Wisc.). The mixture was stirred and heated to reflux. When all the reactants had dissolved, approxiametely 0.02 g of sodium methoxide was added in one portion, and the reaction was allowed to continue for an additional 6 hours. At the end of this reaction

time, 15 ml of solvent was removed by distillation, the reaction mixture was cooled, and 15 ml of water was added. The ether-heptane solution was extracted with water (2X20 ml) and the organic phase was dried. The solvents were removed in a rotary evaporator at reduced pressure to obtain an orange oil. The oil was dissolved in 20 ml of isopropanol and 30 ml of ether, previously saturated with hydrogen chloride, was added. After being set aside for a few minutes, the product crystallized, and was collected to obtain 0.35 g (0.946 mmole, 24%): mp 201-204° of the ester. For analysis, the amino-ester hydrochloride was recrystallized three times from 90% ethanol; mp 201-204°.

Analysis, Calc'd for $C_{16}H_{20}ClNO_3S_2$: C, 51.39; H, 5.39; N, 3.75; S, 17.15.
Found: C, 51.22; H, 5.43; N, 3.86; S, 17.18.

In the same manner as described for the synthesis of N-methyl-3-piperidyl-2',2"-thenilate hydrochloride, the N-methyl-3-piperidyl ester hydrochlorides of three other thenilic acids were prepared.

From methyl 3,3'-thenilate, the yield of N-methyl-3-piperidyl-3',3"-thenilate hydrochloride was 0.71 g (1.90 mmoles, 47.7%): mp 228-231°.

Analysis, Calc'd for $C_{16}H_{20}ClNO_3S_2$: C, 51.39; H, 5.39; N, 3.75; S, 17.15
Found: C, 51.44; H, 5.45; N, 3.66; S, 17.10.

From methyl 5,5'-dichloro-2,2'-thenilate, the yield of N-methyl-3-piperidyl-5',5"-dichloro-2',2"-thenilate hydrochloride was 0.65 g (1.47 mmoles, 37.4%): mp 203-205° dec.

Analysis, Calc'd for $C_{16}H_{18}Cl_3NO_3S_2$: C, 43.40; H, 4.10; N, 3.16; S, 14.48.
Found: C, 43.54; H, 4.07; N, 3.02; S, 14.20.

From methyl 2,2'-benzo[b]thenilate, the yield of N-methyl-3-piperidyl-2',2"-benzo[b]thenilate hydrochloride was 0.80 g (1.66 mmoles, 42%) mp 233-234°.

Analysis, Calc'd for $C_{24}H_{24}ClNO_3S_2$: C, 60.81; H, 5.10; N, 2.96; S, 15.53.
Found: C, 61.05; H, 5.17; N, 2.84; S, 13.32.

Nonsynthetic Experimental Procedures

Reagents

Reagent grade acetone, "Spectroquality" methylene chloride, and "Iron Free" chlorosulfonic acid were purchased from Matheson, Coleman and Bell, East Rutherford, N.J., and were used as received. Tetramethylammonium tetrafluoroborate (TMATFB) was purchased from Aldrich Chemical Co., Milwaukee, Wisc., and was dried in a vacuum desiccator over phosphorus pentoxide before use. Reagent grade dioxane was further purified by stirring it with lithium aluminum hydride for 24 hours, then refluxing it for 6 hours, and finally distillation. It was stored over 5A molecular seive. After three days, any unused dioxane was repurified. Potassium hydroxide solution was prepared from 0.1 N "Accolutes" standard solution ampules (Anachemia Chemical Co., Champlain, N. Y.) and stored in a polyethylene container. It was standardized against potassium hydrogen phthalate (145). Addition of a sample of the potassium hydroxide solution to 2N barium hydroxide solution produced no observable turbidity. Hydrochloric acid was prepared as a 0.1 N stock solution and standardized in the manner described by Laitinen (146). The acid used in the kinetic studies was diluted to 0.01 N. Sulfuric acid was standardized against standard potassium hydroxide. Distilled water, used for all dilutions, was boiled 15 minutes to remove carbon dioxide and stored in a container protected from the atmosphere by an Ascarite tube. For the kinetic studies, the thenils were sublimed (3X) at 120° (0.1 torr), except for 5,5'-dimethoxy-2,2'-thenil and 5,5'-di-(2"-thienyl)-2,2'-thenil which were recrystallized (3X) from methanol and dioxane, respectively.

Determination of the carbonium ion spectra

A. The ultraviolet spectra

Aliquots (100 ul) of a 0.01013 M solution of 2,2'-thenilic acid in glacial acetic acid were added to 50.0 ml samples of various weight percentage solutions of aqueous sulfuric acid as shown in Table 8 below. The spectra of the resulting red carbonium ion solutions were scanned in the region of 650 nm to 340 nm on a Cary 14 spectrophotometer at 25±2°. Similarly, 100 ul aliquots of the thenilic acid solution were added to 50.0 ml samples of various weight percentage solutions of chlorosulfonic acid in methylene chloride as shown in Table 8. Since some of the solutions were somewhat unstable, the time of mixing was noted and refered to t_o. The spectra were scanned three times in the region of λ_{max} and ε for λ_{max} was extrapolated back to t_o. The loss in absorbance was linear as a function of time.

Table 8. Extinction Coefficients for the Di-(2-thienyl),carboxycarbonium Ion as a Function of Acid Concentration.

wgt % H_2SO_4	ε_{t_o} (λ=516 nm)	wgt % $ClSO_3H$	ε_{t_o} (λ=518 nm)
98.86	21,200	100	30,000
89.87	22,000	50.0	33,050
85.02	24,300	10.0	33,050
80.29	20,300	5.00	33,100
69.91	*	1.00	33,800
		0.50	31,200
		0.10	24,900
		0.0024	*

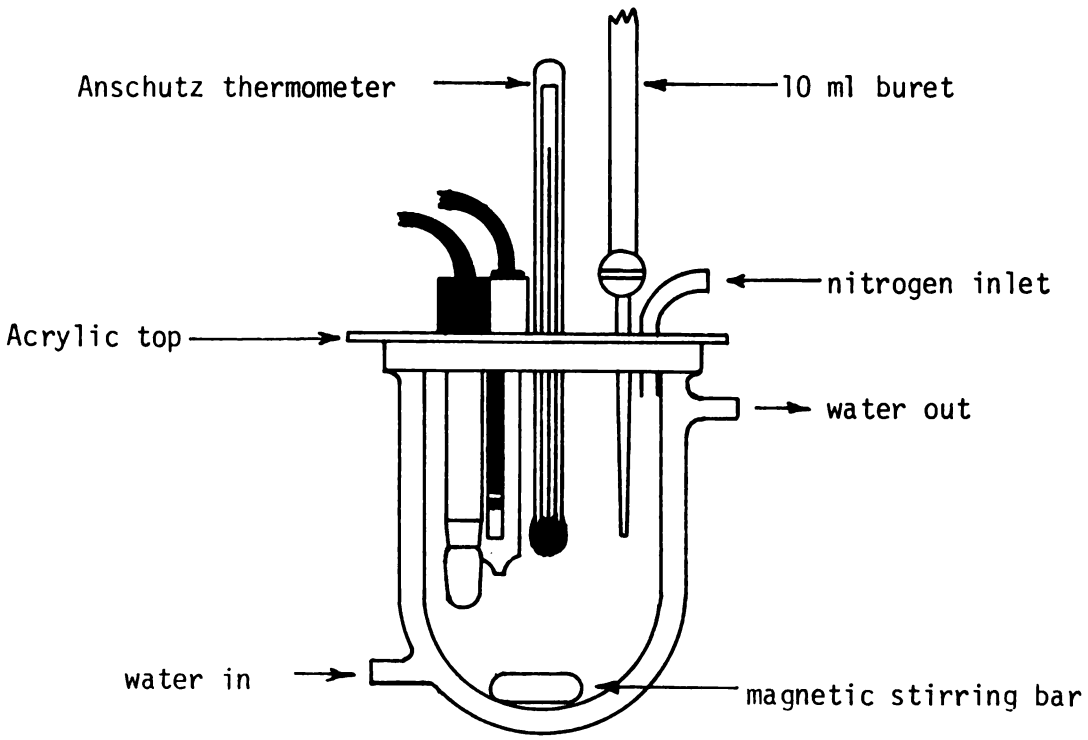
* unmeasurable

B. The nuclear magnetic resonance spectra

The nmr spectra of the di-(2-thienyl)carboxycarbonium ion were determined on a Jeolco C60H high resolution spectrometer at -55° (measured by an internal thermocouple) and at +30° (measured by a thermometer inserted in the probe). In practice, a magnetically stirred solution of 0.30 g of 2,2'-thenilic acid and 0.1 g of TMATFB in 2.0 ml of methylene chloride was cooled to -70° in a dry ice-isopropanol bath. To this solution, 0.5 ml of chlorosulfonic acid was added in one portion and allowed to stir for 15 seconds. A portion of this solution was transfered to an nmr tube precooled to -70°, and after the sample had equilibrated in the spectrometer, the spectrum was scanned from -7 to +10 τ. The carbonium ion solution derived from 2,2'-thenilic acid was not sufficiently stable to allow its spectrum to be determined at +30°. However, the ion derived from methyl 2,2'-thenilate could be observed at this temperature. The same procedure was used as in the acid derived spectra.

Determinations of the ionization constants of the thenoic acids

The ionization constants of the thenoic acids were determined following the potentiometric method described by Albert and Serjeant (105). A titration cell was constructed from a 125 ml glass jacketed resin kettle as illustrated on p 141. In practice, a continuous flow of water at 49.5° supplied by the same constant temperature bath as was used in the kinetic studies, was maintained through the jacket during all pH measurements. A Beckmann Model 1019 research pH meter was standardized with Matheson pH 4 buffer solution (pH=4.06 at 50°) and the meter was checked with Beckmann pH 7 buffer solution (pH=6.975 at 50°). The buffer solutions and the electrodes (Corning # 476002 SCE reference electrode, Beckmann # 40498 glass electrode) were previously equilibrated in the titration cell and continually checked until no



no drift was noted on the pH meter.

After standardization, the cell was emptied, dried, and 100.0 ml of CO_2-free water was pipetted into the cell. A quantity of the purified thenoic acid, never less than 0.10 mmole or more than 0.12 mmole,was weighed to 0.1 mg, and dissolved in the cell by stirring. The cell was flushed with nitrogen, and a slow stream of nitrogen, which had been previously passed through a wash bottle containing CO_2-free water, was maintained in the cell during the entire pK_a determination.

After the entire apparatus, including the electrodes had equilibrated, 1.000$\pm$0.002 ml of 0.1002$\pm$0.0001 N potassium hydroxide was added to the solution of the thenoic acid by means of a certified class A 10 ml buret protected from the atmosphere by an Ascarite tube. The pH meter reading was recorded after the meter had stabilized at the new value. Nine sucessive 1.000 ml amounts of potassium hydroxide were added to the thenoic acid solution, taking the pH meter reading after each addition. These readings were used to

compute the pK_a of the thenoic acids as described on p 144. The pK_a of each acid was determined three times in succession.At the end of a series of measurements on one acid, the cell was recharged with fresh pH 4 buffer and the meter was rechecked. The pH 4 reading consistently checked within 0.004 pH units of the correct value.

Procedure for the kinetic determinations

A constant temperature bath of eight gallons capacity (the large volume helped to minimize temperature variations during the heating cycle) was regulated to $\pm$0.04°. Temperatures were measured by a Will Scientific Inc. (New York, N.Y.) #26846, -5° to +101° thermometer graduated to 0.1° and stated to comply with the National Bureau of Standards Circular #8. The temperature was further checked by a calibrated Hewlett-Packard (Palo Alto, Cal.) #2801A quartz digital thermometer. It was not possible to detect any variation in temperature at different points in the bath. Temperatures below room temperature were achieved by using a pump driven heat exchanger immersed in a dry ice-isopropanol bath at -70°. The pump was activated by the thermostat.

Kinetic measurements for all of the thenils, with the exception of 3,3'-benzo[b]thenil, 2,2'-benzo[b]thenil, and 5,5'-di-(2"-thienyl)-2,2'-thenil, were carried out in the same manner. A sample of the thenil, in the range of 2.5 to 3.0 mmoles, was weighed to 0.1 mg and placed in a 250 ml teflon screw cap bottle, along with a magnetic stirring bar. The thenil was dissolved in 100.0 ml of equilibrated dioxane with stirring. The solution was continuously stirred during the kinetic run by means of a G. Frederick Smith submersible magnetic stirrer mounted directly beneath the reaction vessel. A 50.00 ml quantity of 0.1 N temperature equilibrated potassium hydroxide solution was pipetted into the thenil solution with vigorous stirring. The vessel

was sealed with a screw cap arrangement that permitted the insertion and withdrawal of a pipette. A 10.00 ml aliquot of the thenil solution was immediately withdrawn. The aliquot was quenched in a 10 ml sample of ice cold acetone and the clock was started. Time was measured by three different timers which could be triggered simultaneously. They consisted of a common wall clock and two rotary timers, one measuring in tenths of a minute and the other in hundredths of a minute. No differences could be detected in time duration with any of the timers in periods up to 300,000 seconds. The sample was titrated to either a phenolphthalein (pH=8.3) or thymol blue (pH=8.0) end point with 0.01 N hydrochloric acid. The initial aliquot determination was designated as $[OH]_i$ in equation 9, p 58. At various intervals, depending on the rate of potassium hydroxide disappearance, 10 ml aliquots were withdrawn and titrated as described.

Simultaneously with the kinetic runs, a blank sample was determined under the same conditions described above, except that the thenil was omitted. In this manner it was possible to correct for any acidic impurity present in the thenil and also for any reaction of the base with the solvent. During the 80° runs and to a lesser extent at 70°, a small correction (by never more than 3%) was found to be necessary. At other temperatures, the correction was too small to be measured.

Samples of 3,3'-benzo[b]thenil, 2,2'-benzo[b]thenil, and 5,5'-di-(2"-thienyl)-2,2'-thenil were too insoluble to be determined at the concentrations used above for the other thenils. Accordingly, samples in the range 0.3 to 0.8 mmole, but never less than 0.1000 g were used in the kinetic determinations. The amount of dioxane used was 100 ml, but the 50 ml of potassium hydroxide was replaced by 15 ml of potassium hydroxide and 35 ml of water. All other conditions were the same. The solubility of 5,5'-di-(1"-adamantyl)-2,2'-thenil did not permit kinetic determinations to be made at any concentration.

Since a mixture of dioxane and water does not constitute an ideal solution in the thermodynamic sense, an additional correction was employed in calculating the initial concentrations of the reactants. The following equation was used to calculate the actual volume of the reaction mixture at the start of a given kinetic run

$$V_{mix} = \frac{v_1(\rho_1) + v_2(\rho_2)}{\rho_{mix}} \qquad \underline{22}$$

where v_1 and v_2 are the volumes of dioxane and water measured out, ρ_1 and ρ_2 are the densities of dioxane and water at a given temperature (110) and ρ_{mix} is the density of the mixture at the same temperature (109). In these calculations, the thenils and potassium hydroxide are assumed to behave ideally. Thus, by equation 22, 150 ml of the mixture of dioxane and water actually has the volumes indicated in Table 9 as a function of temperature.

Table 9. Actual Volume of a Mixture of 100 ml of Dioxane and 50 ml of Water as a Function of Temperature.

Temperature	15°	30°	40°	50°	60°	70°	80°
Volume (ml)	147.8	147.3	147.1	147.0	147.0	147.0	147.0

Ionization constant calculations

By definition:

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

then

$$pK_a = pH + -\log\left[\frac{A^-}{HA}\right] = pH + \log\left[\frac{HA}{A^-}\right]$$

where "pH" is read from the pH meter.

However, $[HA] = [HA]_{st} - [HA]_{dis} = [HA]_{st} - [H^+]$

that is, [HA] = the stoichiometric amount of the acid less that which has dissociated,

and $[A^-] = [A^-]_{st} + [HA]_{dis} = [A^-]_{st} + [H^+]$

that is, $[A^-]$ = the stoichiometric amount of the anion plus that which arises from the dissociation of the acid. This gives the pK_a as in equation 23.

$$pK_a = pH + \log \frac{[HA] - [H^+]}{[A^-] + [H^+]} \qquad 23$$

Naturally, each stoichiometric concentration must be corrected with the appropriate dilution factor as the titrant is added.

Calculations

All calculations in this study were performed on a Wang 320 electronic calculator. This device was used in preference to a larger computing system, which is actually more time consuming since it requires the transposition of data to punch cards, running the data and program decks, and waiting for the print out. Even this assumes that an error free program is available and there is no waiting to get on line.

The introduction of the directly addressable computing system such as the Wang 700 series or the Hewlett-Packard 9100 series obviates the need for a computor language such as FORTRAN, ALGOL or even the much simpler BASIC. Furthermore, the capacity of these systems, 8K bit core memory in

the Wang 700B and up to twenty 960-step programs, provides any organic chemist certainly, and most scientists in general, with the capacity to perform virtually any desired mathamatical manipualtion, but with the highly desired advantage of instant output, as visual or hard copy.

The author believes that the next generation or two of such "desk top computors" with greater capacity and reduced access time will render obsolete present computing systems except, perhaps, for the most complex calculations, or as large information storage systems.

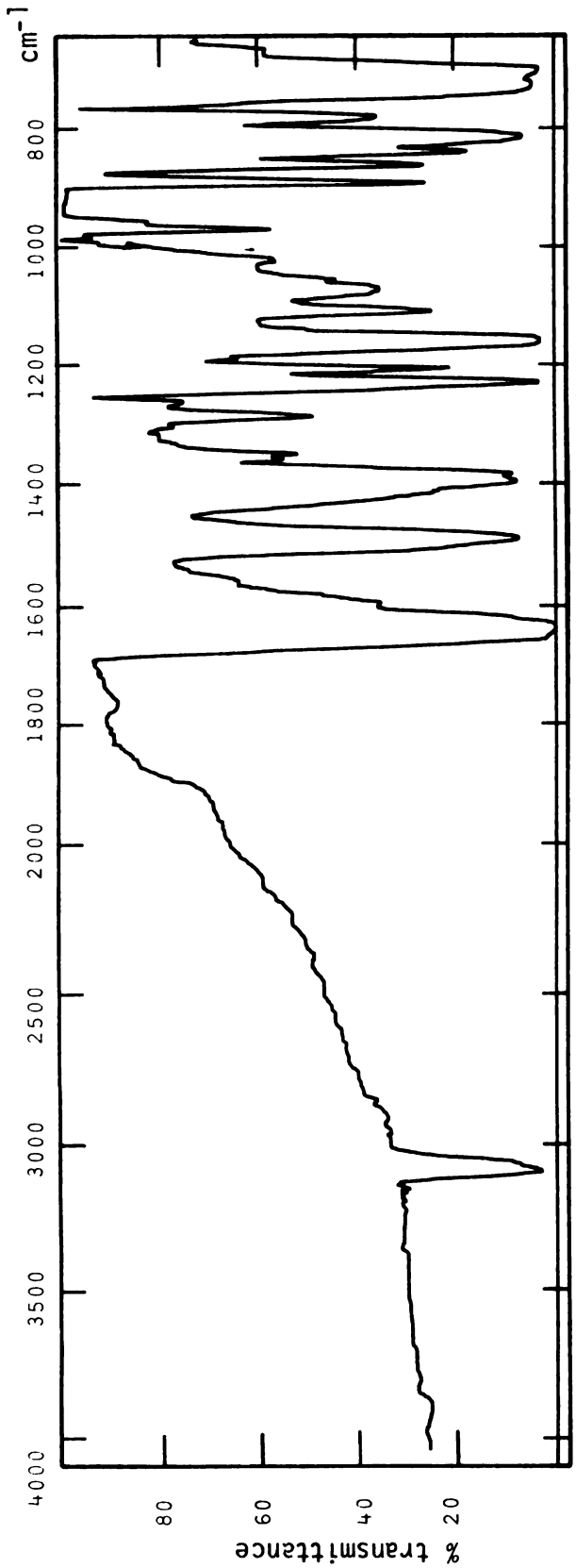


Figure 36. Infrared spectrum of 3,3'-thenil

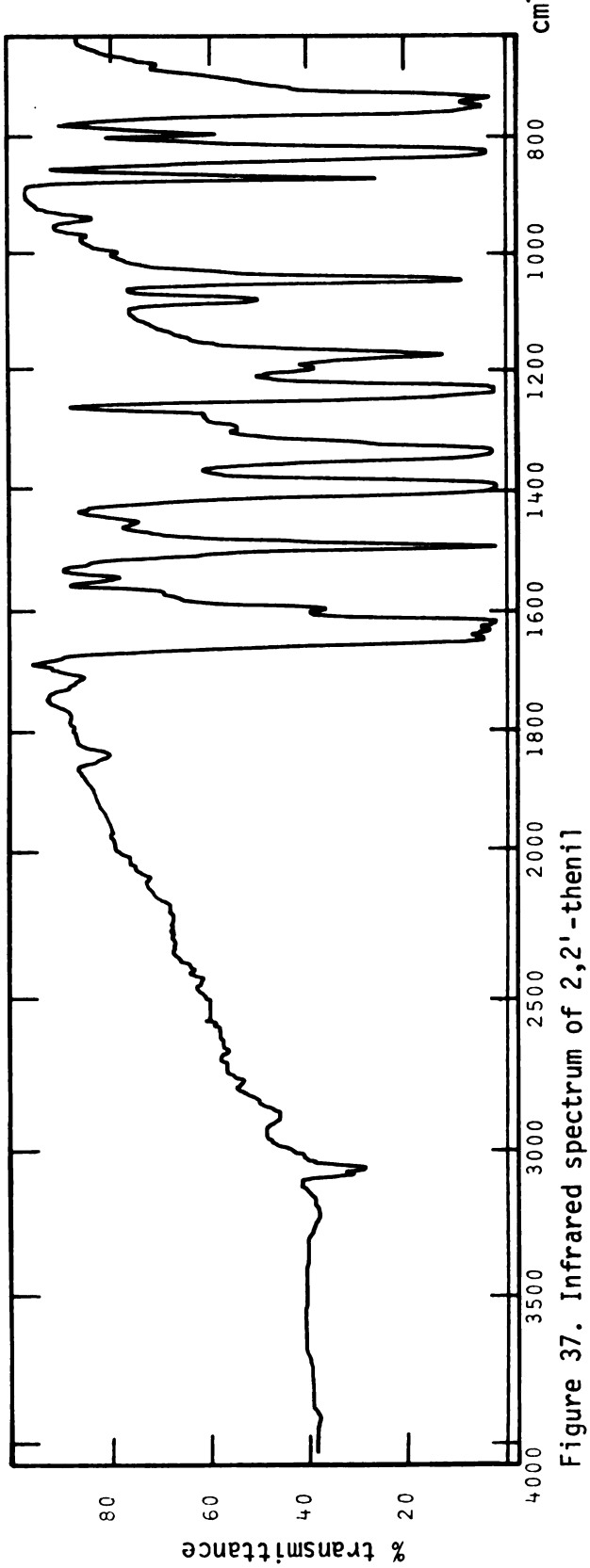


Figure 37. Infrared spectrum of 2,2'-thenil

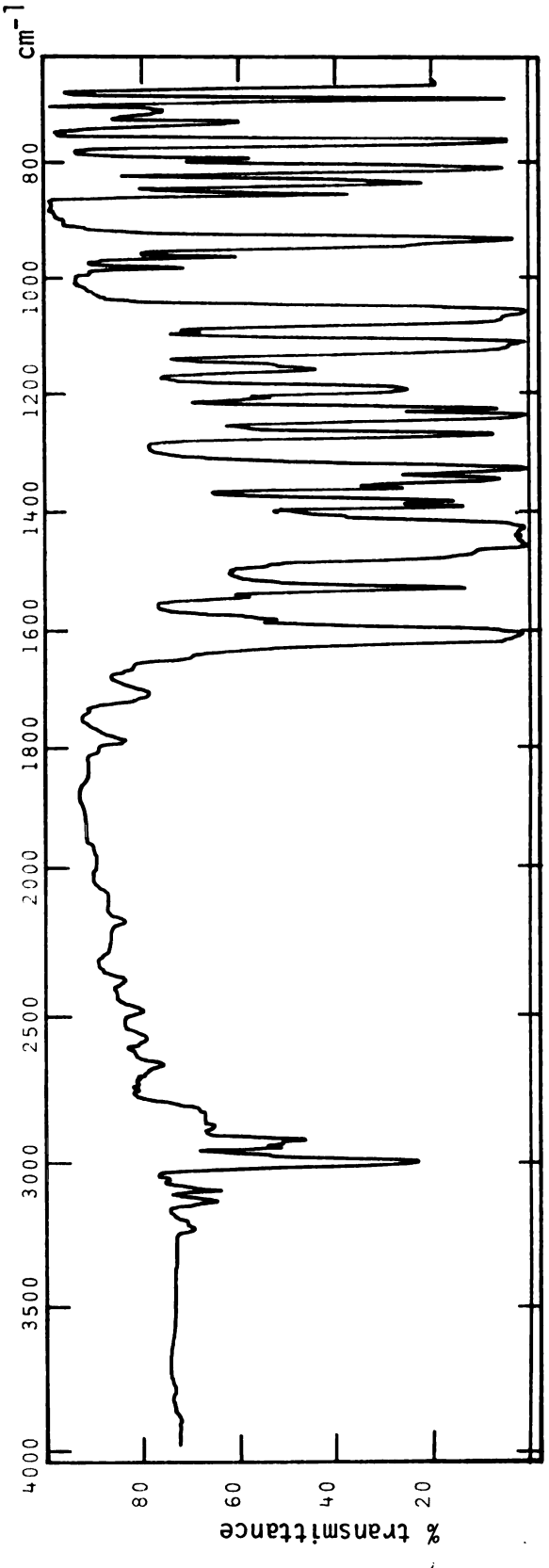


Figure 38. Infrared spectrum of 5,5'-diisopropoxy-2,2'-thenil

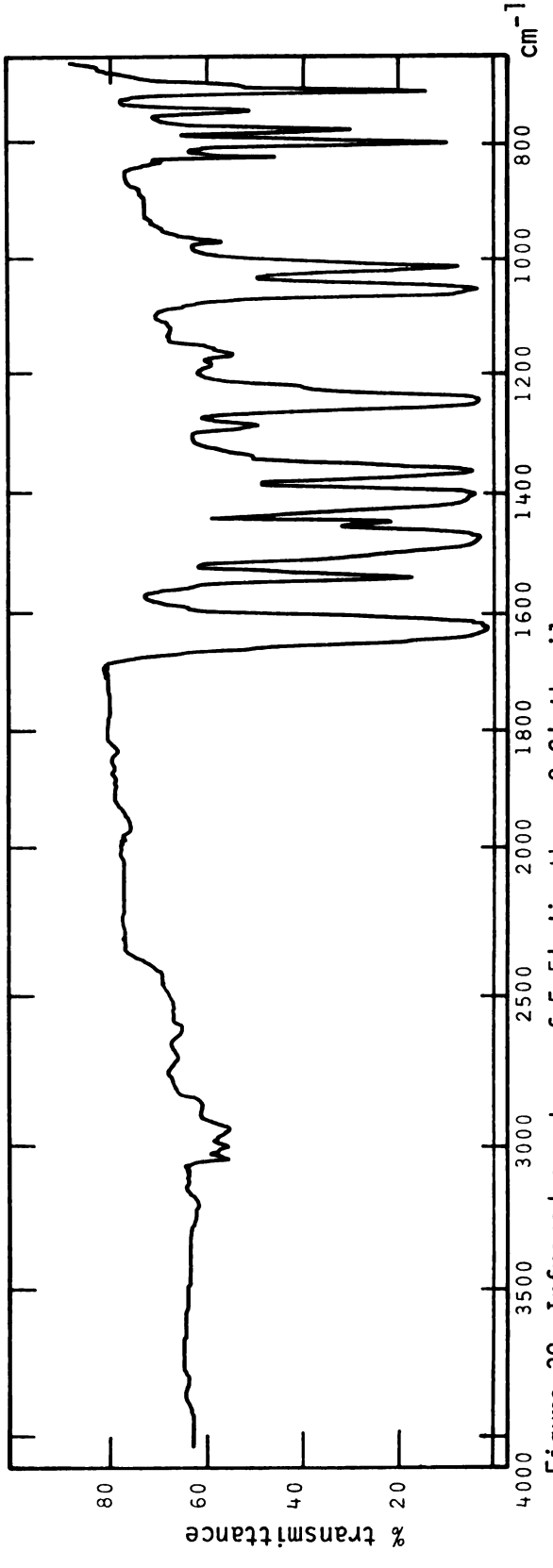


Figure 39. Infrared spectrum of 5,5'-dimethoxy-2,2'-thenil

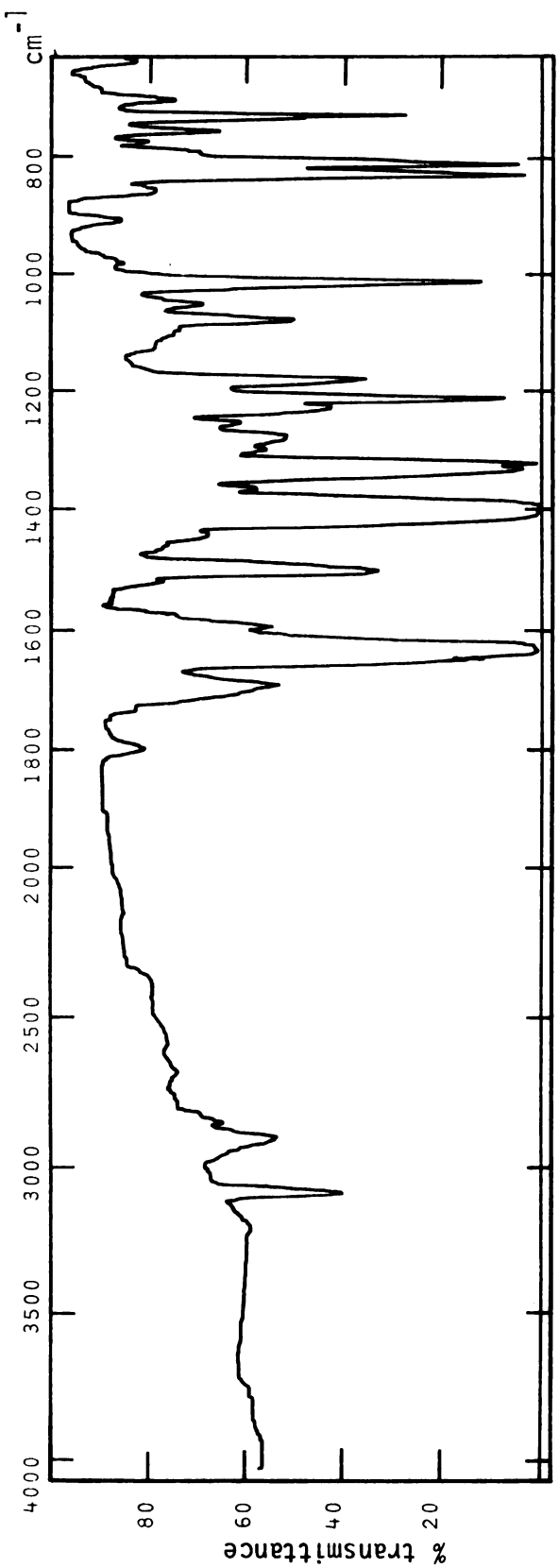


Figure 40. Infrared spectrum of 5,5'-dichloro-2,2'-thenil

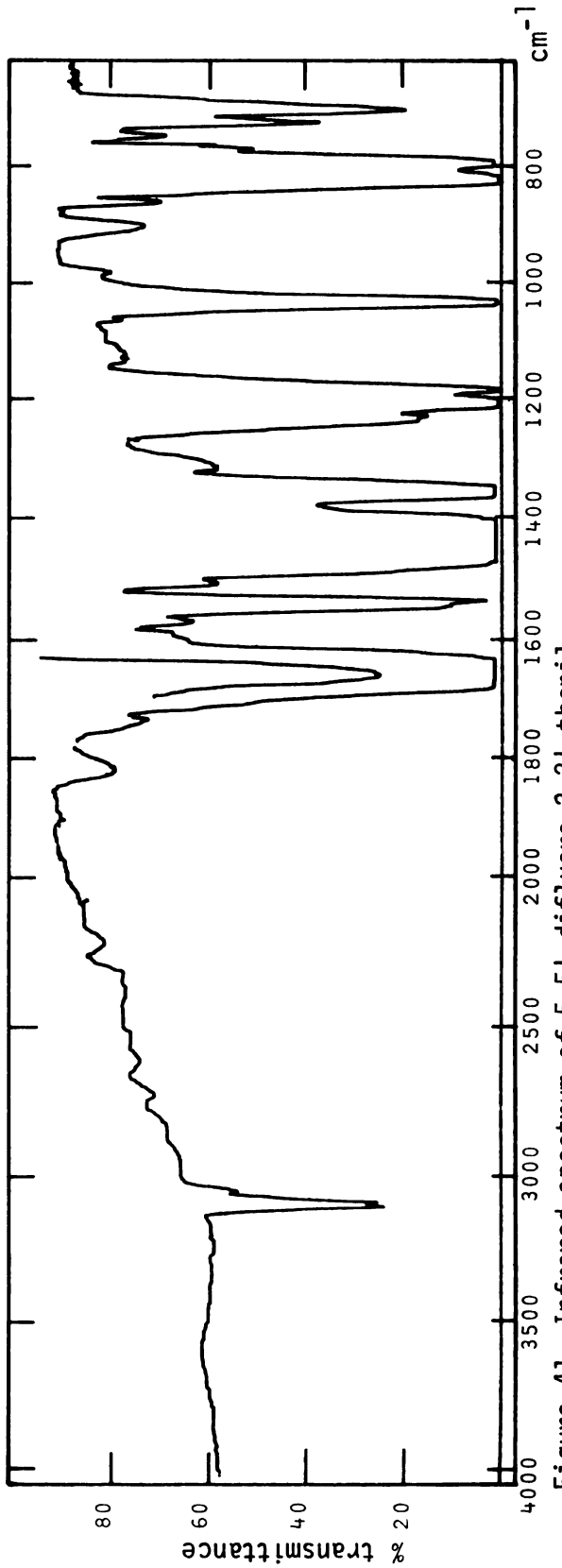


Figure 41. Infrared spectrum of 5,5'-difluoro-2,2'-thenil

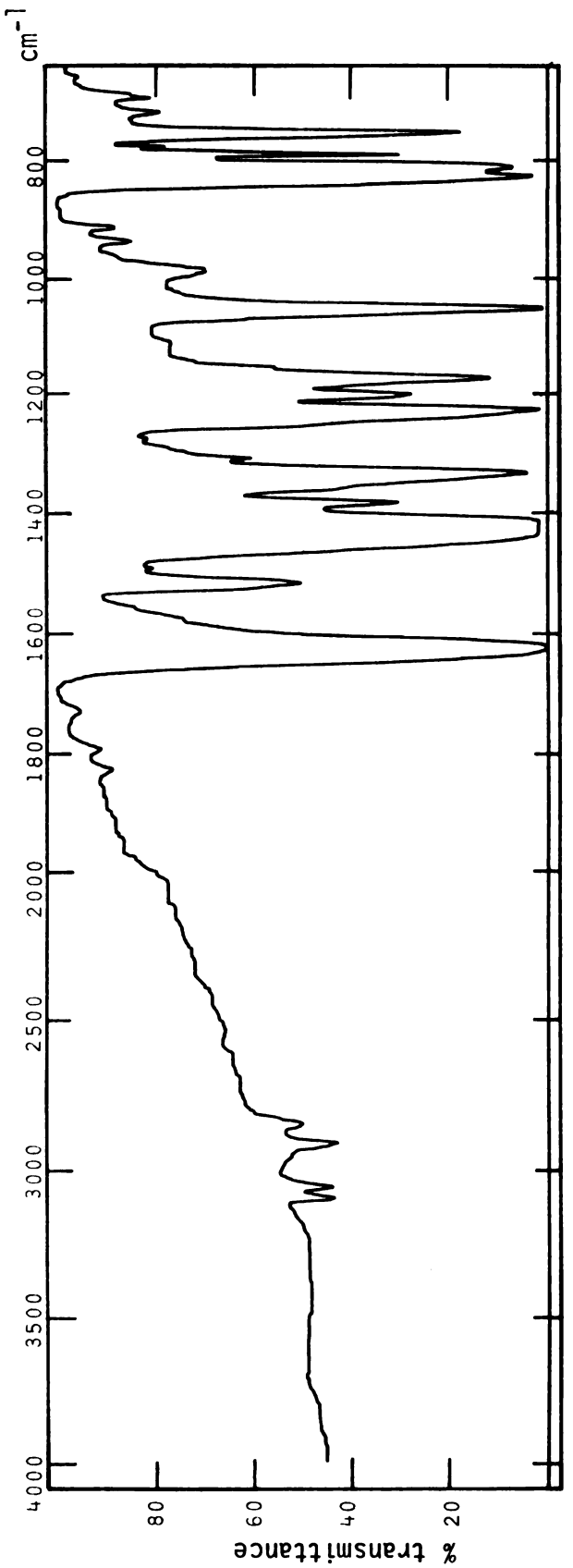


Figure 42. Infrared spectrum of 5,5'-dimethyl-2,2'-thenil

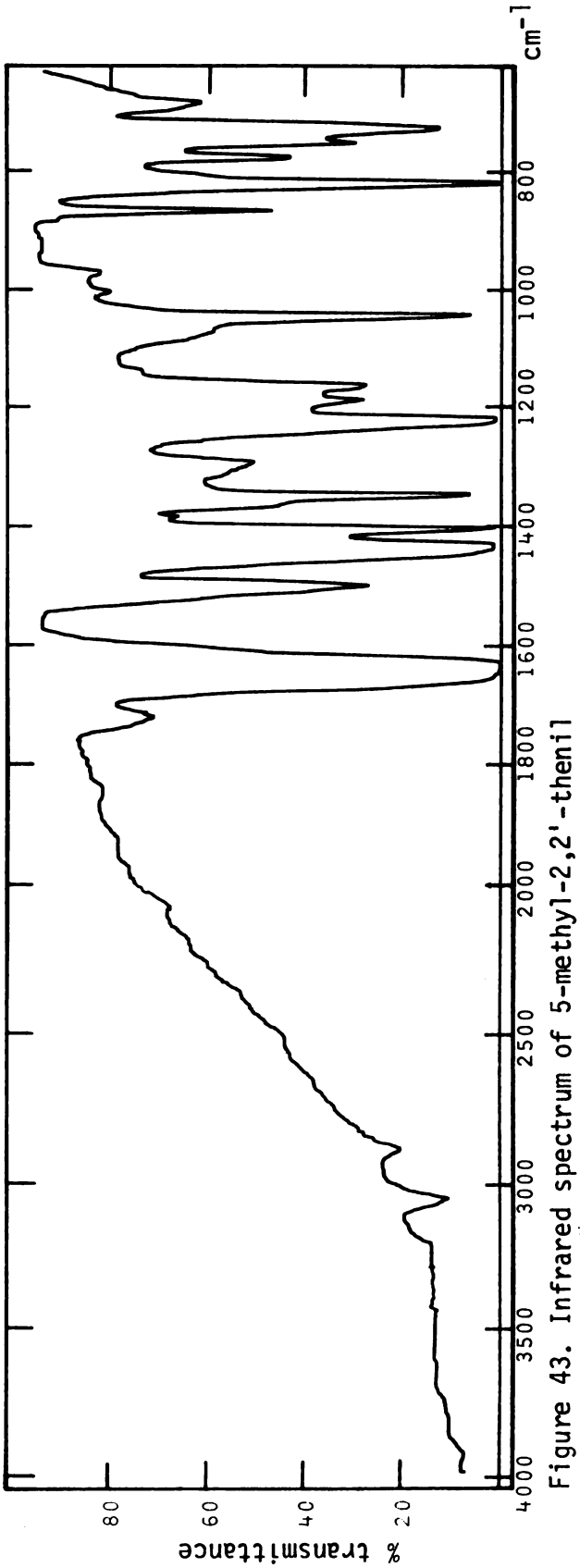


Figure 43. Infrared spectrum of 5-methyl-2,2'-thenil

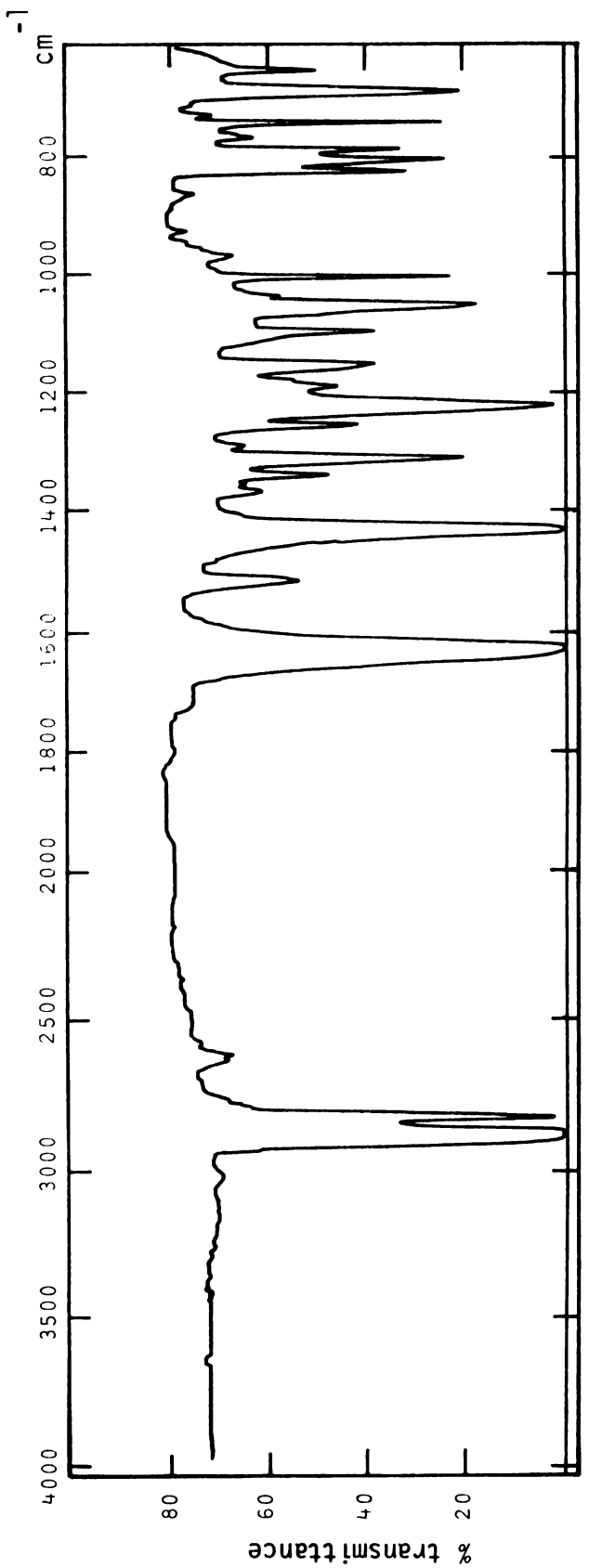


Figure 44. Infrared spectrum of 5,5'-di-(1''-adamantyl)-2,2'-thenil

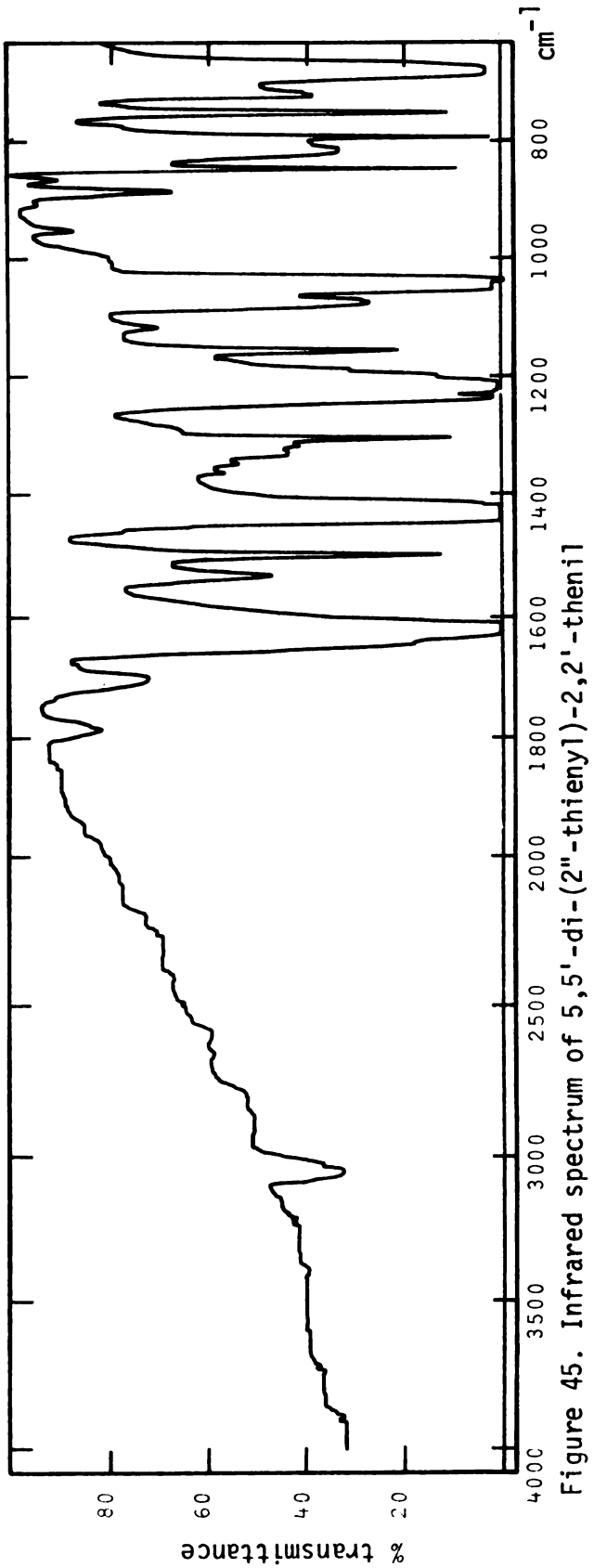


Figure 45. Infrared spectrum of 5,5'-di-(2''-thienyl)-2,2'-thenil

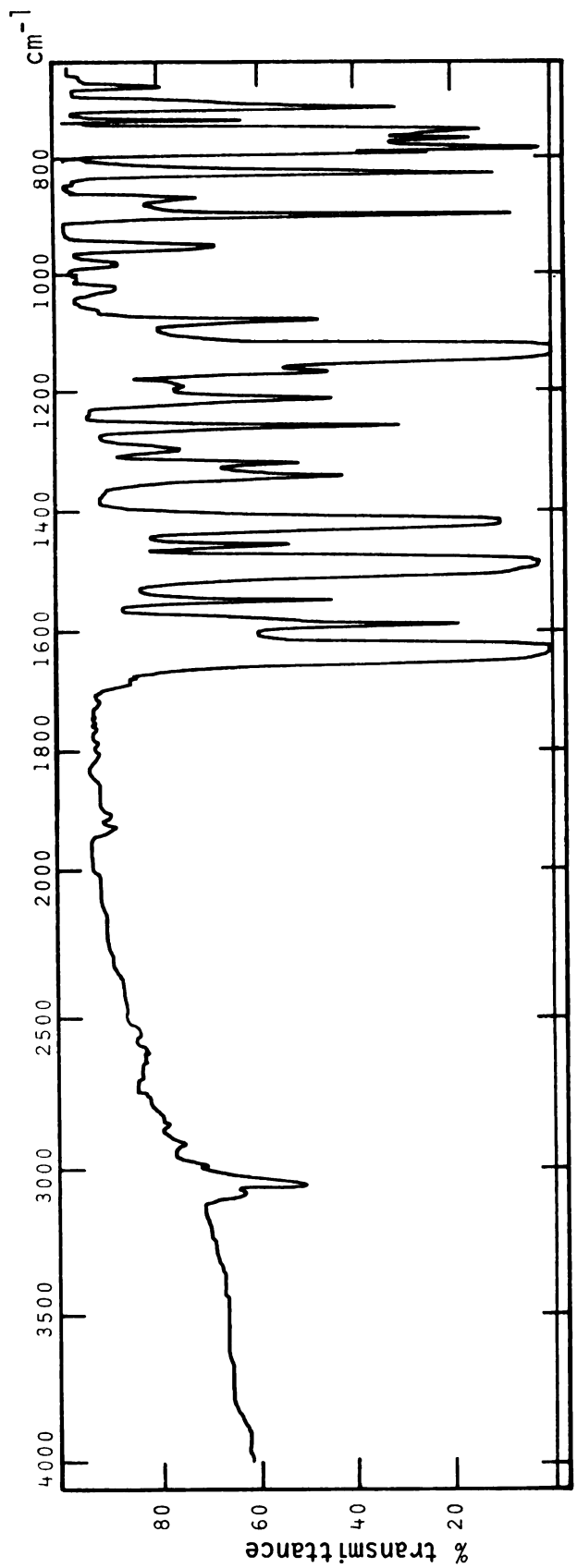


Figure 46. Infrared spectrum of 2,2'-benzo[b]thenil

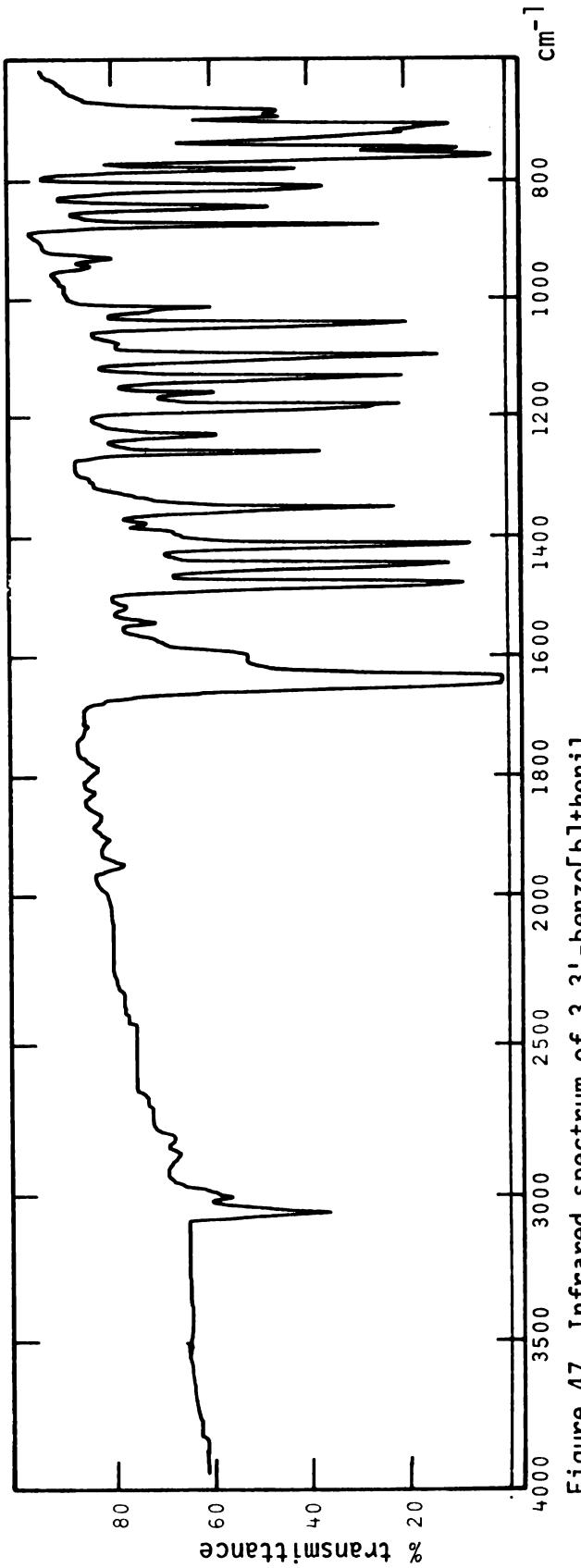


Figure 47. Infrared spectrum of 3,3'-benzo[b]thenil

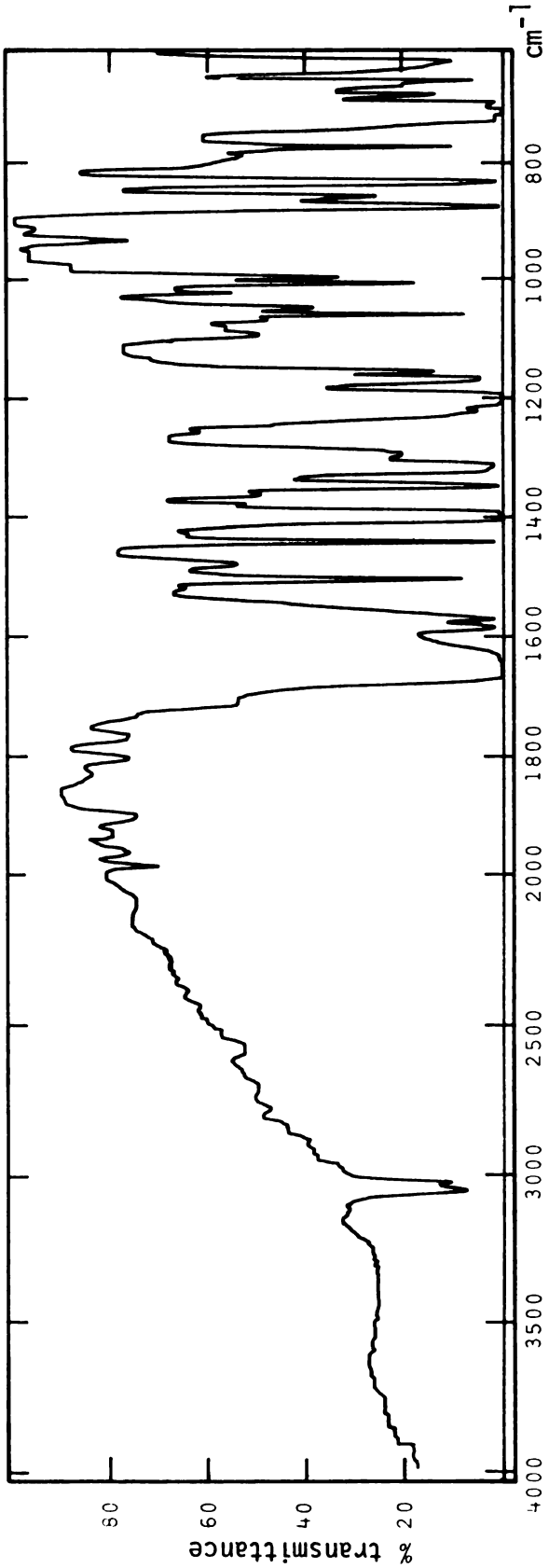


Figure 48. Infrared spectrum of 2-thienylphenyl diketone

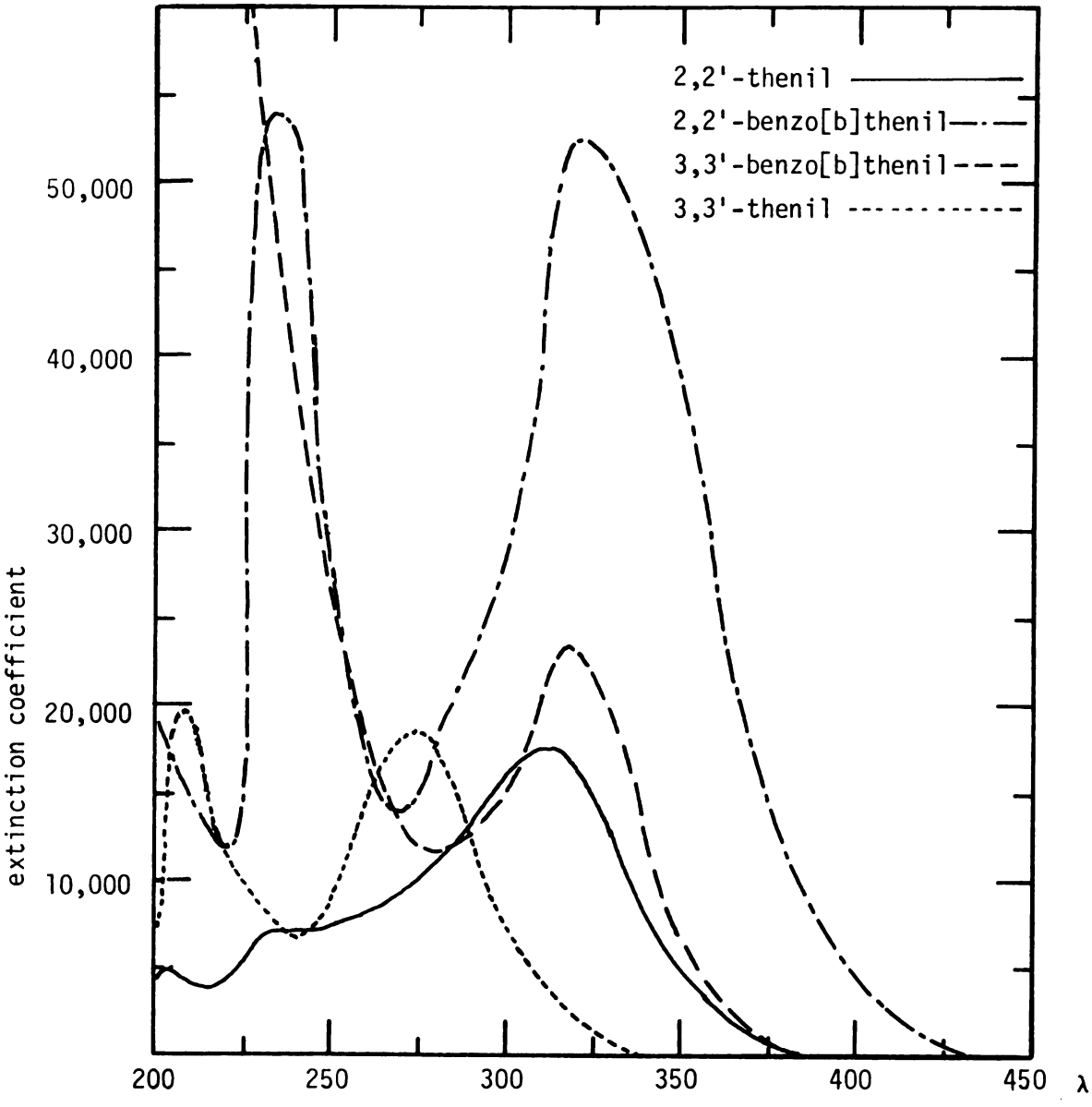


Figure 49. Ultraviolet spectra of various thenils

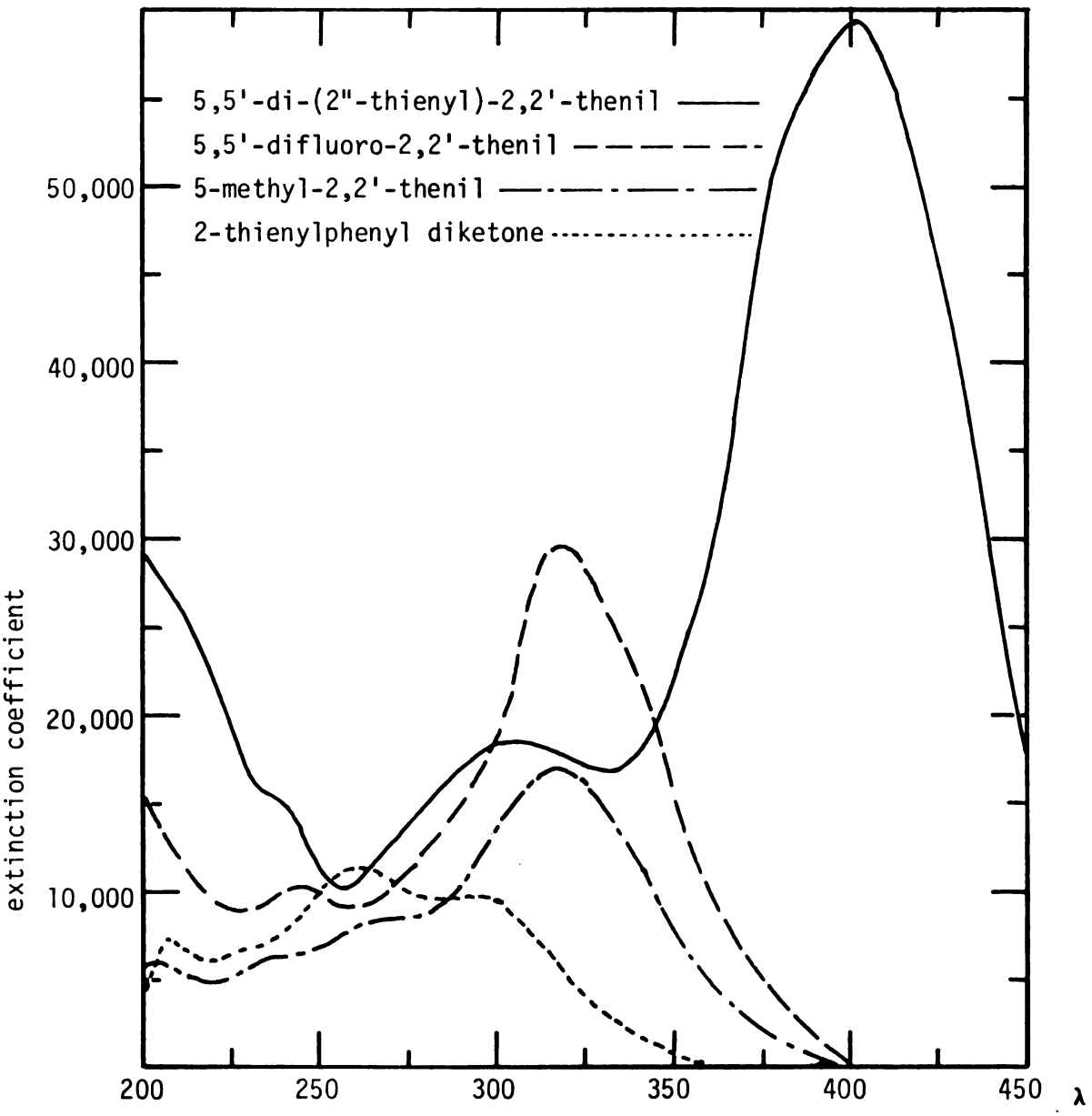


Figure 50. Ultraviolet spectra of various thenils

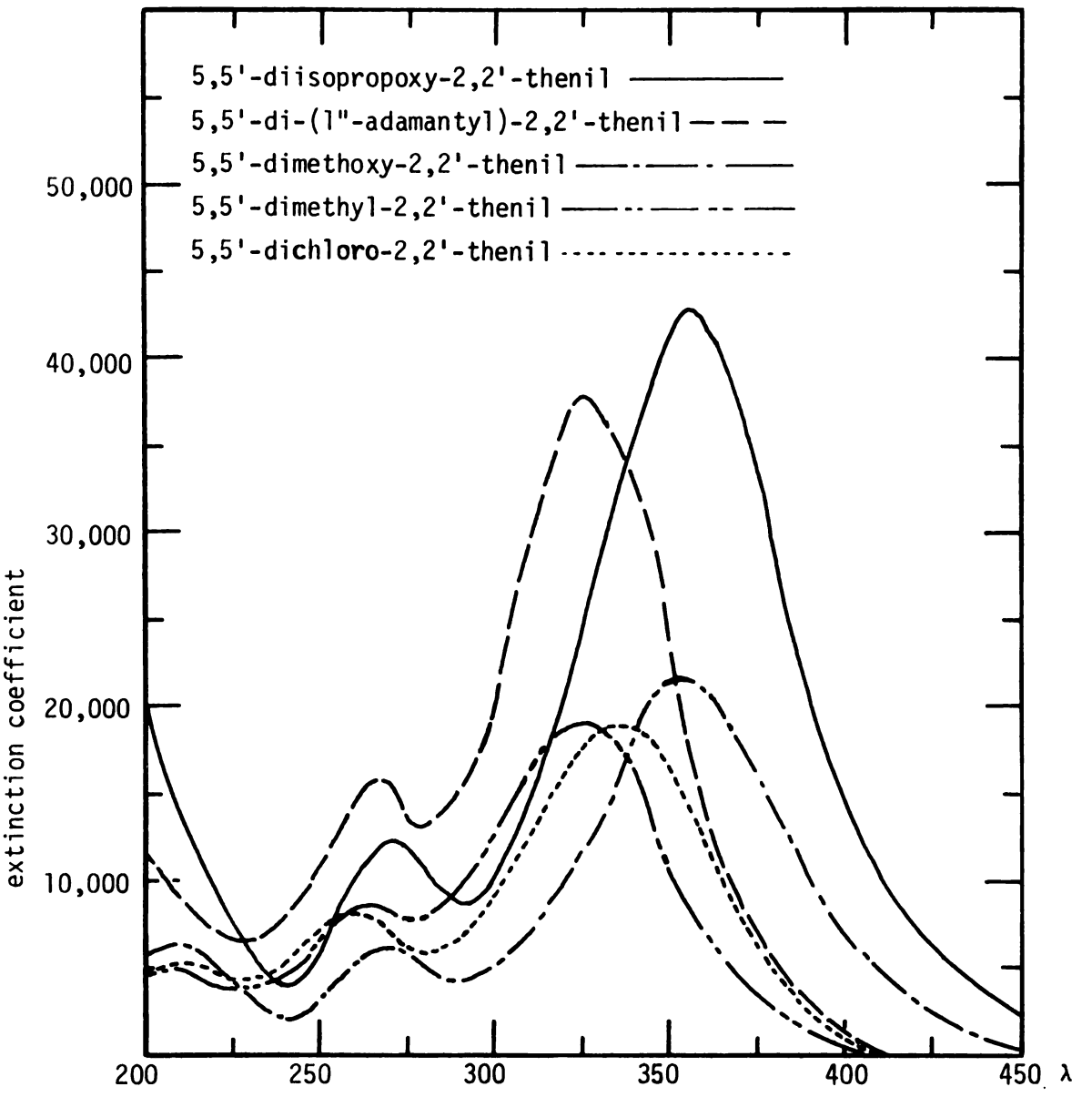


Figure 51. Ultraviolet spectra of various thenils

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