SYNTHESIS OF THIENYL AND THIANAPHTHENYL DIOXOLANES AND THIENYL DICARBONYLS

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
ALBERT JOSEPH MUELLER
1968

This is to certify that the

thesis entitled

SYNTHESIS OF THIENYL AND THIANAPHTHENYL DIOXOLANES AND THIENYL DICARBONYLS

presented by

Albert Joseph Mueller

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Major professor

Date May, 1968

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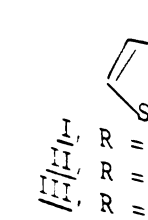

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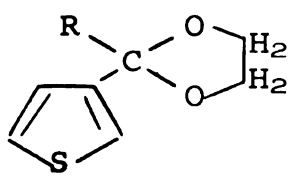
ABSTRACT

SYNTHESIS OF THIENYL AND THIANAPHTHENYL DIOXOLANES AND THIENYL DICARBONYLS

By

Albert Joseph Mueller

Few studies have been reported on the syntheses of thienyl and thianaphthenyl dicarbonyls. An objective of this investigation was to explore and develop new synthetic routes for the preparation of vicinally disubstituted formyl, acetyl and benzoylthiophenes and thianaphthenes. Further, it was anticipated that such dicarbonyl compounds would undergo cyclization reactions to yield thienothiepins, a new heterocyclic system. The hydrogen-metal interchange reaction, using n-butyllithium in hexane-ether, of 2-hydrogen, 2-methyl or 2-phenyl-2-(3'-thienyl)-1,3-diosolanes (I, II and III respectively) and 2-methyl or 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolanes (IV and V respectively) occurred



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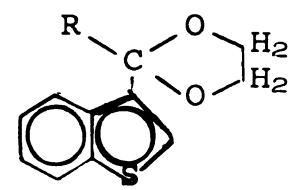
III, R = C_6H_5



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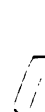

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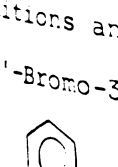

VII

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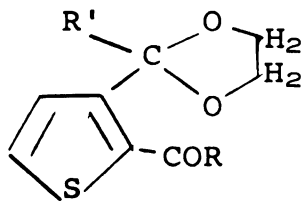
rapidly in nearly quantitative yields at the more hindered 2-position of thiophene and thianaphthene. Nine formyl, acetyl and benzoyl thienyl, VI, and thianaphthenyl, VII,



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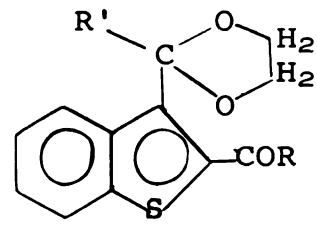
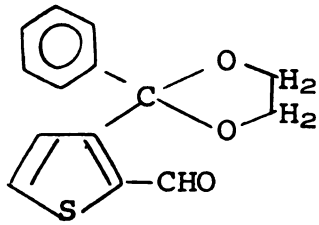


VII

dioxolanes were obtained in isolated yields of 32-81%, upon the interaction of thienyl and thianaphthenyl dioxolane lithiums with N,N-dimethylformamide, N,N-dimethylacetamide and N,N-dimethylbenzamide. Hydrolysis of carbonyl substituted thienyl and thianaphthenyl dioxolanes readily gave the 2,3-dicarbonyl thiophenes and thianaphthenes.

2-Phenyl-2-(2'-formyl-3'-thienyl, VIII, and 3'-thianaphthenyl, IX)-1,3-dioxolanes failed to survive hydrolysis conditions and did not yield stable isolatable products. 2-(4'-Bromo-3'-thienyl)-1,3-dioxolane, X, was subjected to a



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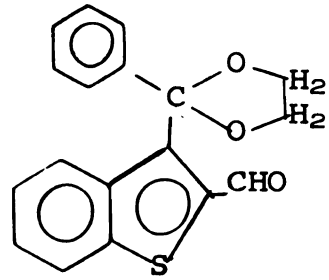

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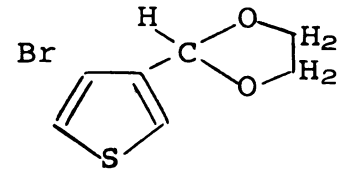

X

bromine-metal interchange reaction with n-butyllithium. The lithium dioxolane on reaction with N,N-dimethylformamide yielded a 3,4-diformylthiophene.

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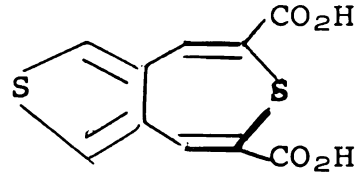
Product structures were assigned from UV, IR and NMR spectral data. Coupling constants of the thiophene ring hydrogens were determined to be (cps): J_{45}=5.0-5.2, J_{25}= 2.9-3.1, J_{24}=1.5-1.7 and $J_{(CHO)_2-5}$ = 0.85-1.4. The introduction of sterically larger groups into the 3-position of 2-thenal and 2-thienyl ketones produced hypsochromic shifts at 8-17 mμ in the carbonyl band of the UV spectra. Corresponding shifts of 10-50 cm^{-1} in the carbonyl band of the IR were also observed for these same compounds.

Thieno[3,4-d]thiepin-2,4-dicarboxylic acid, XI, was



XI

was synthesized in 52% yield from 3,4-diformylthiophene and diethyl thiodiglycolate. Attempts to carry out similar cyclization reactions under Hinsberg reaction conditions, to obtain thieno[3,4-d]oxepin-2,4-dicarboxylic acid and thieno[2,3-d]thiepin-2,4-dicarboxylic acid were unsuccessful with 3,4-diformylthiophene and dimethyl diglycolate and 2,3-diformylthiophene and diethyl thiodiglycolate.

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By

Albert Joseph Mueller

A THESIS

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1968

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ACKNOWLEDGMENTS

Many people have played a part in my doctoral studies. To them my gratitude is boundless.

I owe a great deal to my major professor, Dr. Robert D. Schuetz, for his advice and guidance in both technical and personal problems encountered during my studies. The kindness, patience, and generosity he has shown me during our association at Michigan State University will never be forgotten.

I owe a debt of gratitude to my parents, Mr. and Mrs. Herman J. Mueller, who encouraged me to pursue my college education. Without their hope, confidence, and financial aid my studies might not have reached this peak.

Included along with my parents are my parents-in-law, Mr. and Mrs. Martin N. May, who likewise encouraged me by their faith and kindness to continue my pursuit.

Last, but not least, I owe much to my wife, Bonnie, who has shared innumerable hardships and disappointments. Without her patience and understanding, my studies could not have been completed. By her reading along and typing much of the original manuscript of this thesis, I am convined that she could ultimately become a better chemist than I.

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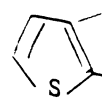

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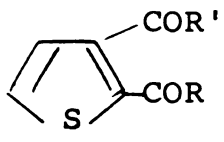
INTRODUCTION

The syntheses and chemical reactivity of the simple thiophene and thianaphthene aldehydes and ketones are well-known and their chemistry has been extensively reviewed [1,2,3]. Recently, interest has been increasing in the syntheses and application of thiophene and thianaphthene dicarbonyl compounds, particularly, their subsequent use as intermediates in further synthetic applications. For example, Janda and Dvorak [4] synthesized 2-formyl-5-propionylthiophene and demonstrated its feasibility as an antibiotic. Vicinally substituted dicarbonyl thiophenes, I or II, and thianaphthenes, III, could be used as substrates for future studies on the intramolecular reduction of the two vicinally substituted carbonyl groups.



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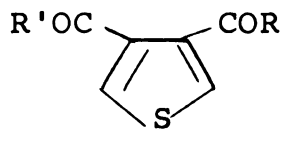

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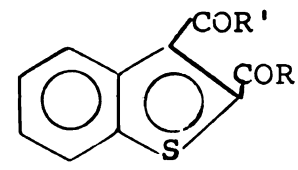

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Intramolecular reduction of dicarbonyl compounds is a well-established subject for research.

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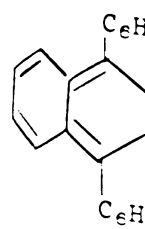

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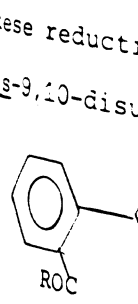

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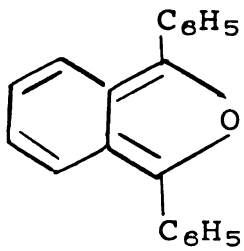
o-Dibenzoylbenzene has been photochemically reduced (sunlight) in the presence of isopropyl alcohol to 1,3-diphenylbenzo[c]furan, IV (5). The same reduction of o-dibenzoylbenzene has also been accomplished using sodium, lithium or potassium in various aprotic solvents (6) yielding 1,3-diphenylbenzo[c]furan, 10-hydroxy-1-phenylanthrone, V, or anthraquinone, VI. A recent review (7) has summarized the cyclization reactions of 2,2'-dicarbonyldiphenyls, VII, via intramolecular reduction (sodium amalgam, zinc-base or magnesium-magnesium iodide) of the two carbonyl groups.



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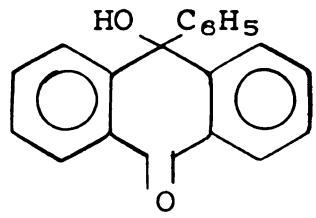

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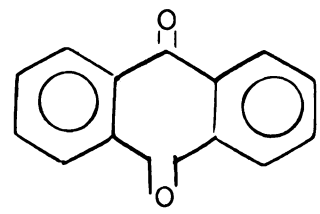
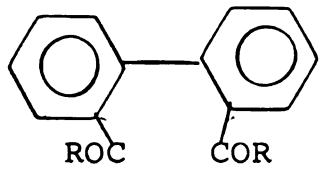


VI

These reductive cyclizations in the majority of cases gave cis-9,10-disubstituted-9,10-dihydroxyphenanthrenes, VIII.



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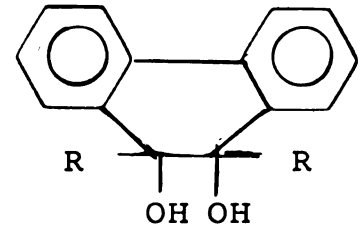

VIII

Vicinally substituted dicarbonyl thiophenes and thianaphthenes could be further annulated by condensation reactions with compounds possessing active hydrogen, e.g., diethyl

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IX, thieno[2,

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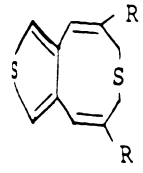

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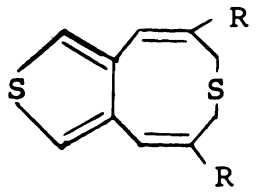
thiodiglycolate or diethyl acetonedicarboxylate, or with compounds such as hydrazine. For example, these condensation reactions could easily give substituted thieno[3,4-d]thiepins, IX, thieno[2,3-d]oxepins, X, thieno[3,4-d]cyclohepadienones, XI, or thieno[2,3-d]pyridazines.



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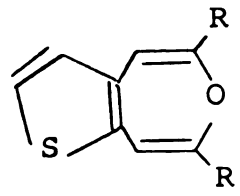

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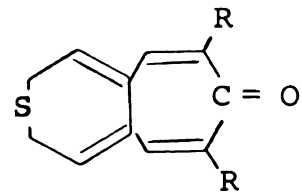

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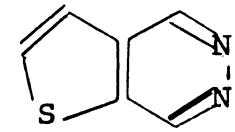

XII

The importance of having vicinally substituted dicarbonyl thiophenes and thianaphthenes for the preparation of theinothiepins and thienoxepins is threefold. Primarily, seven membered unsaturated heterocycles are of interest in connection with the question of aromatic stability of other than (4n + 2) electron-containing ring systems, since planarity, a chief requirement for resonance, appears feasible in these 8-electron ring systems. The parent ring compounds, oxepin, thiepin (8) and azepin are not known, although thiepin-1,1-dioxide (9) and several benzo analogs of these ring systems (see History) have already been described. Secondly, several thienobenzothiepins have been reported within the last year to possess a high level of antihistamine, antiserotonin and antiemetic activity. Typical compounds possessing these properties are 4-(3-dimethylammopropylidene)-4,9-dihydrothieno-[2,3-b]benzo[e]thiepin, XIII, (10) and N-substituted-4-

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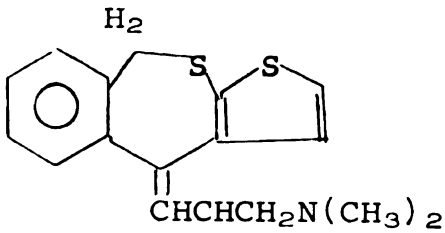
(1-piperazinyl)-4,5-dihydrothieno[2,3-d]benzo[f]thiepin, XIV, (11). Thirdly, the recent synthesis of thieno[3,4-d]-thiepin, XV, (12) by a non-condensation method has shown that



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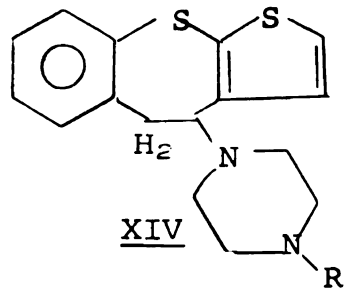

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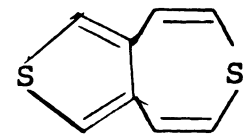
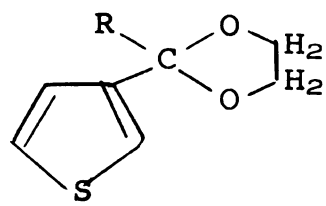


XV

this molecule possesses "extended conjugation" by its unusual UV spectrum (13 maxima from 210 mμ to 390 mμ). Thieno[3,4-d]-thiepin was also shown to have unusual stability toward thermal desulfurization; whereas, benzo[d]thiepin derivatives are easily desulfurized thermally to naphthalene derivatives (13-17).

In view of the potential applicability of vicinally substituted dicarbonyl thiophenes and thianaphthenes, an investigation of a general synthesis scheme to produce these compounds would seem to be of value. For this purpose, the hydrogen-metal interchange reactions of 2-substituted 2-(3'-thienyl, XVI, and 3'-thianaphthenyl, XVII)-1,3-dioxolanes were studied using n-butyllithium.



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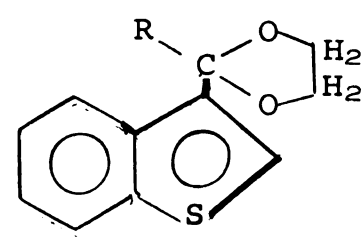

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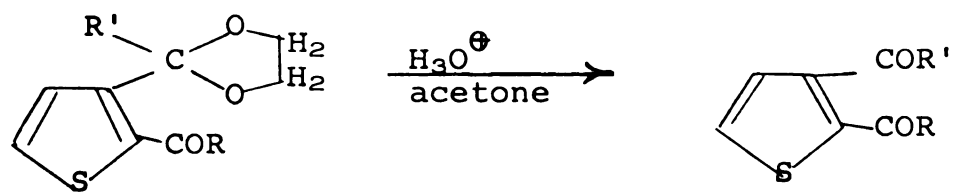
For the thiophene derivatives, one specific purpose was to study the substituent effects of the dioxolane moiety on the hydrogen-metal interchange reaction of the thiophene ring. An additional objective was to study the ability of these intermediate thienyl and thianaphenyl lithiums to react further with several N,N-dimethylacylamides to produce precursors of dicarbonyl thiophenes and thianaphthenes. Spectroscopic evidence will be presented which shows that these precursors are 2-substituted-2-(2'-acyl-3'-thienyl)-1,3-dioxolanes, XVIII, which upon acid hydrolysis in acetone, give 2,3-dicarbonyl thiophenes, I.



XVIII I

A short study was made to determine the feasibility of preparing thienothiepins and thienoöxepins by base catalyzed condensation of 2,3-diformyl and 3,4-diformylthiophenes with ethyl thiodiglycolate and dimethyl diglycolate; the results of this study are described in the Results and Discussion section of this thesis.

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HISTORY

The Metallation of Thiophene

The metallation of thiophene with n-butyllithium, reported by Gilman, yields 2-thienyllithium in nearly quantitative yield (18). Gronowitz (19) has suggested the following mechanism for this metallation reaction. Coordination of the metallating agent to the sulfur of the thiophene ring appears to occur first, followed by attack of the carbanion moiety to the most "acid like" proton alpha to the sulfur on the thiophene ring. Such a mechanism is in accord with exclusive metallation of the alpha position on the thiophene ring and with directive effects of substituents in the beta (or 3) position of thiophene (20). Using the furyl thiophene mixed heterocyclic system, Klinke (21) has shown by the carbonation products that thiophene in furyl thiophenes coordinates a mono equivalent of n-butyllithium exclusively. Metallation of isotope labeled thiophene gave a K_H/K_T of 16 $\pm$ 4 and a K_H/K_D of 6.6 $\pm$ 0.3, in accord with the nucleophilic character of n-butyllithium, indicating that elimination of hydrogen, or alpha carbon-hydrogen bond breaking, is the rate determining step (22).

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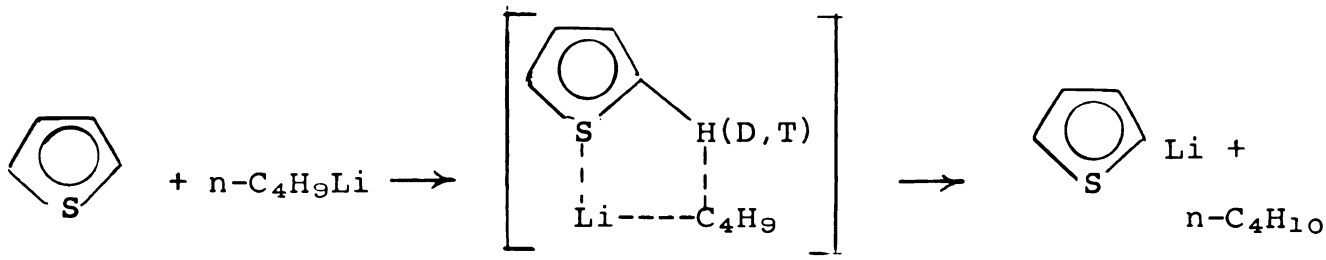

This alpha selectivity was shown by the fact that 2-alkyl (23-26), 2-methoxy (24,27) and 2-alkylthio-thiophenes (26) and alkyl thenyl sulfides (28,29) were all metallated in the 5-position of the thiophene ring. This selectivity was not observed with conventional reagents in electrophilic aromatic substitution. Metallation of a mixture of thiophene and 2-methylthio-thiophene with a half molar equivalence of n-butyllithium gave exclusively 5-methylthio-2-thenoic acid upon carbonation of the intermediate thienyllithium (26), thus showing the activating effect of the methylthio group on competitive metallation. When both alpha positions were blocked, this highly specific reactivity disappeared and metallation with n-butyllithium depended on the nature of substituents present. While 2,5-dimethyl thiophene was not metallated, 2-methoxy-5-methyl thiophene was metallated readily (27) in the 3-position due to the coordination effect of the methoxyl oxygen.

Gronowitz and his associates have studied n-butyllithium metallation of a number of 3-substituted thiophenes to determine the mechanism of the reaction and to study its synthetic utility (3). 3-Methylthiophene was metallated in the 5-position; competitive experiments with thiophene show

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3-methylthiophene to be metallated at a slower rate than thiophene (19,24,30). This is expected as the + I effect (Ingold's terminology (31)) of the methyl group increases preferentially the electron density of the 2-position and decreases the "acidity" of this proton. Both the 2 and 5 protons of 3-methylthiophene are less acidic than the corresponding hydrogens of thiophene (19). 3-Methoxy (28), 3-methylthio (25) and 3-bromothiophenes (19) were metallated in the 2-position, which has been ascribed to -I effects and during the reaction, corresponding inductomeric effects increased this mode of reactivity. This influence is quite strong, as 3-t-butoxythiophene was metallated with n-butyllithium and carbonated exclusively to the considerably more hindered 2-position (29). A secondary coordination of n-butyllithium to these electron rich 3-substituents may also aid in 2-position substitution (29). Gronowitz has used this effect in the metallation of 2-(3'-thienyl)-1,3-dioxolane to prepare 3-formyl-2-thenoic acid exclusively, thus establishing no trace of 5-position metallation (32).

Metal-Halogen Interchange of Halogenated Thiophenes

Halogen-metal interconversion between bromothiophenes and n-butyllithium can be defined as a nucleophilic substitution of halogen. This reaction occurs readily at temperatures as low as -70° (19,33-35). This fact is important as Grignards of bromothiophenes are prepared in small yield

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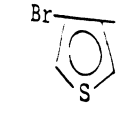

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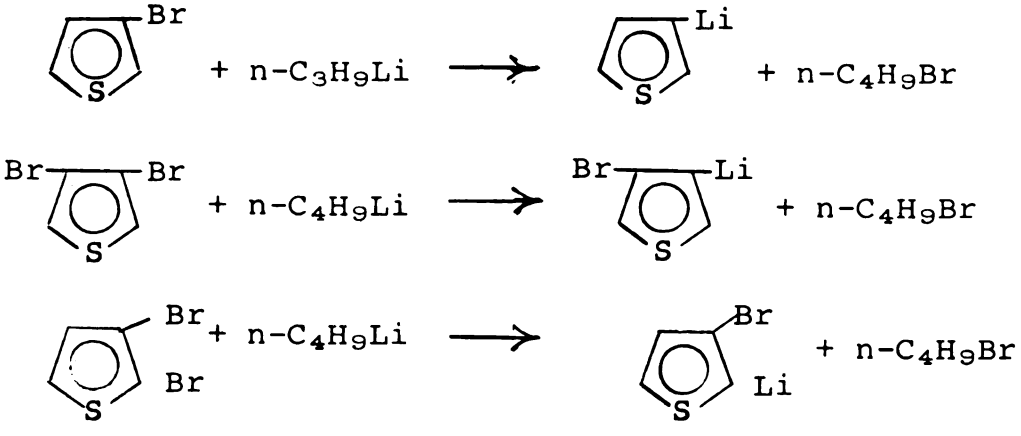
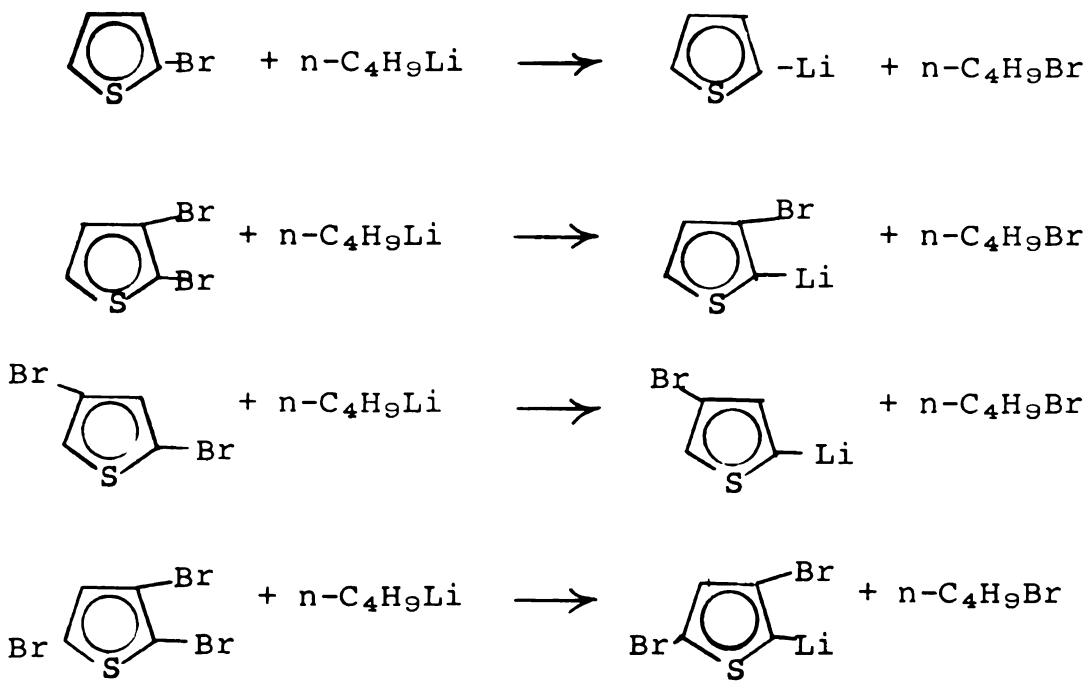
by entrainment with a co-Grignard such as ethyl magnesium bromide (33,34,36-38). By the use of n-butyllithium with 3-bromothiophene, a whole range of typical Grignard products could be prepared in the 3-position.

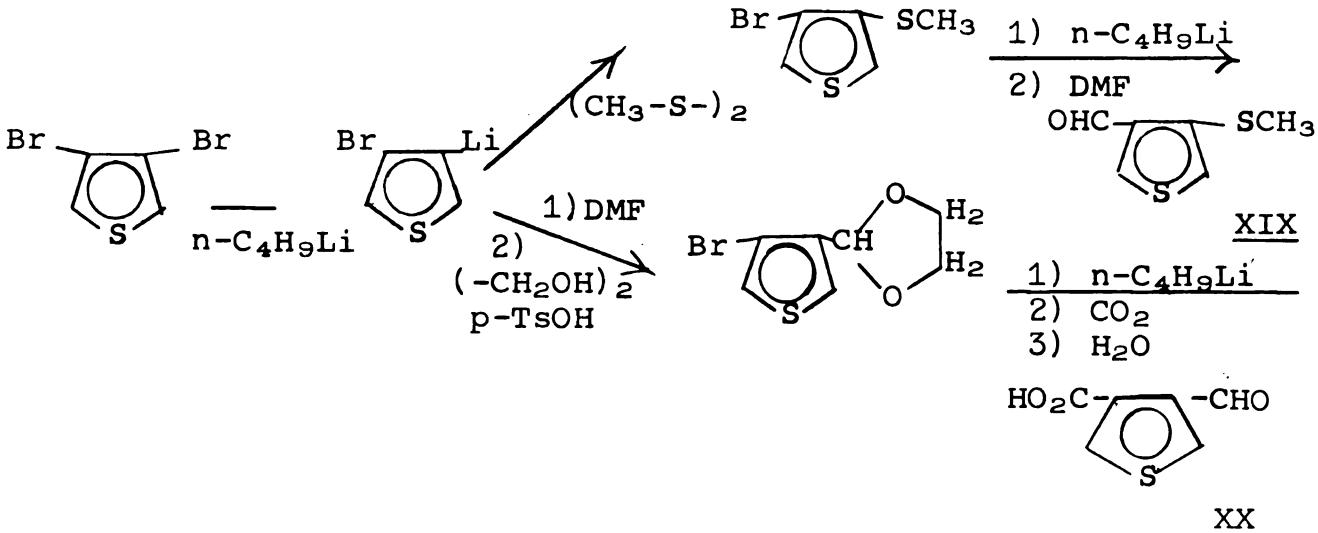
Gronowitz and Moses (35) have studied the stability of thienyllithiums derived from 3-bromothiophene and 3,4- and 2,3-dibromothiophenes. In these reactions, the lithium did not replace the acidic alpha hydrogens of thiophene, which



indicated that these were kinetically controlled reactions. This was further amplified by the fact that the intermediate thienyllithium had been found stable at -70° for ten hours, but did rearrange to complex mixtures as the temperature was raised (38). The ease of halogen-metal exchange over alpha hydrogen abstraction was shown by the observation that 2-bromo, 2,3- and 2,4-dibromo and 2,3,5-tribromo easily and selectively underwent halogen-metal exchange at low temperatures (39). The reaction of tribromothiophene and n-butyllithium showed the added inductive effect of the 3-bromo substituent on the direction of the metallation reaction (35).



The stability of the thienyllithiums derived from 2,3-, 2,4- and 3,4-dibromothiophene at -70° has made them very useful for preparing isomer free difunctional group derivatives, since halogen-metal interchange with n-butyllithium can be done individually with each bromine atom. For example, 4-methylthio-3-thenal, XIX, (24) and 3-formyl-4-thenoic acid, XX, (40) have been prepared from 3,4-dibromothiophene using dimethyl disulfide and N,N-dimethylformamide.



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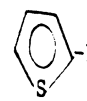

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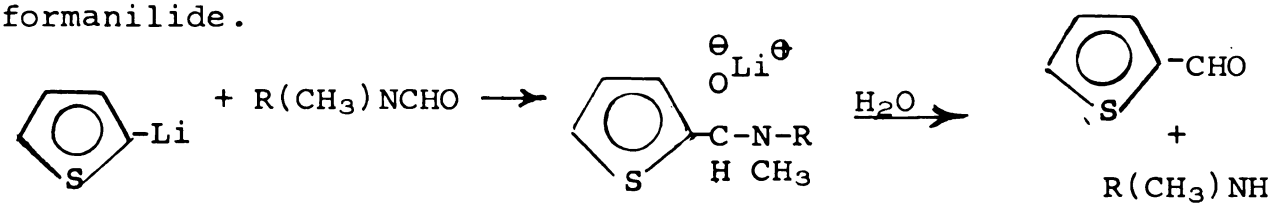
Previous Synthesis of Thiophene Dicarbonyl Compounds

The reaction of thienyllithiums with compounds such as N,N-dimethylformamide and N-methylformanilide is one of several methods to obtain thenals. Before the availability of n-butyllithium, Gatterman (41) first described a variation of this reaction whereby a 70% yield was obtained by attack of nucleophilic 2-thienyl magnesium bromide upon N-methyl-formanilide.



R = CH_3, C_6H_5

Gronowitz used this reaction with n-butyllithium extensively in preparing unsubstituted (42) 3-thenal and the isomeric formyl thenoic acids (32,40); the latter were synthesized by repeated metallations of various dibromothiophenes by n-butyllithium, followed by reaction with N,N-dimethylform-amide and carbon dioxide.

Previous studies of dicarbonyl thiophenes had been limited for the most part to the synthesis of the four known thiophene dicarboxaldehydes. The synthesis of 2,5-thiophene biscarboxaldehyde was initially reported by two groups of investigators using an identical synthetic scheme (43,44). Bis-chloromethylthiophene was allowed to react with pyridine to obtain a bispyridinium hydrochloride, XXI, which in turn

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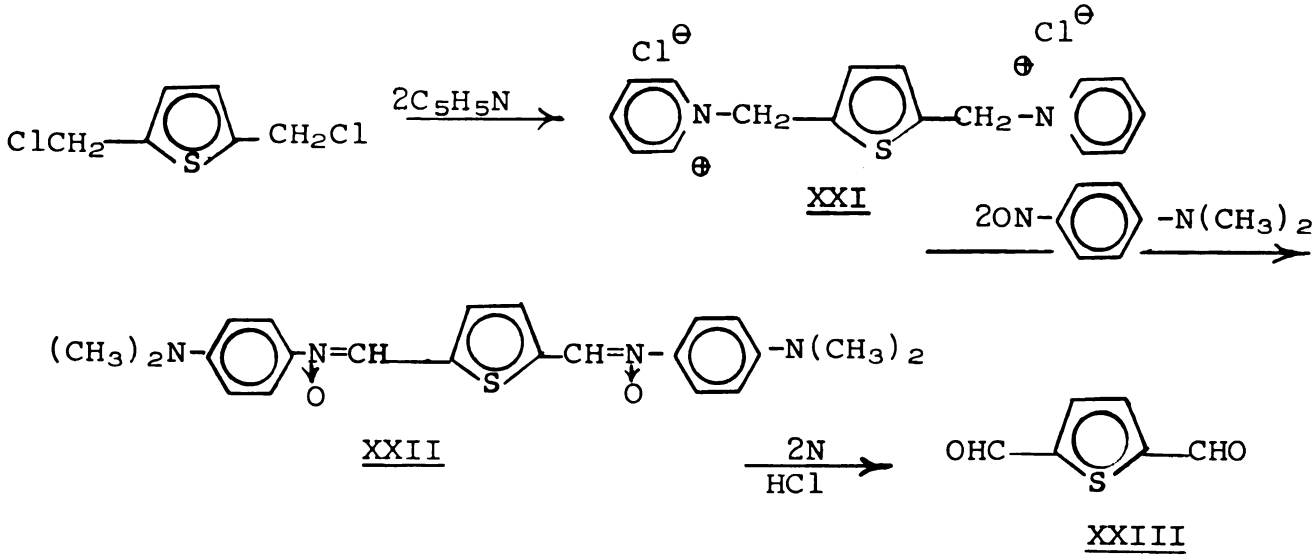
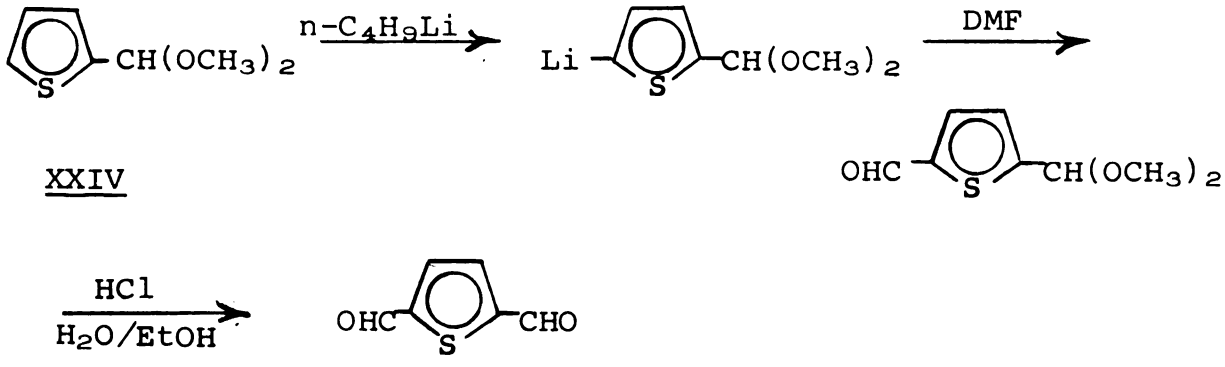
was treated with N,N-dimethyl-p-nitroso aniline to yield an intermediate bisnitrone, XXII. The nitrone was decomposed in aqueous hydrochloric acid to give 2,5-thiophenedicarboxaldehyde, XXIII.



Gol'dfarb and Rogovik (45) have synthesized 2,5-thiophene biscarboxaldehyde using the n-butyllithium metallation of 2-thenal dimethylacetal, XXIV, followed by formylation of the 5-position with N,N-dimethylformamide.



Thames and McCleskey (46) used the same procedure to prepare a variety of 5-substituted -2-thenals and 2-acetothienones.

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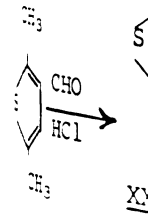

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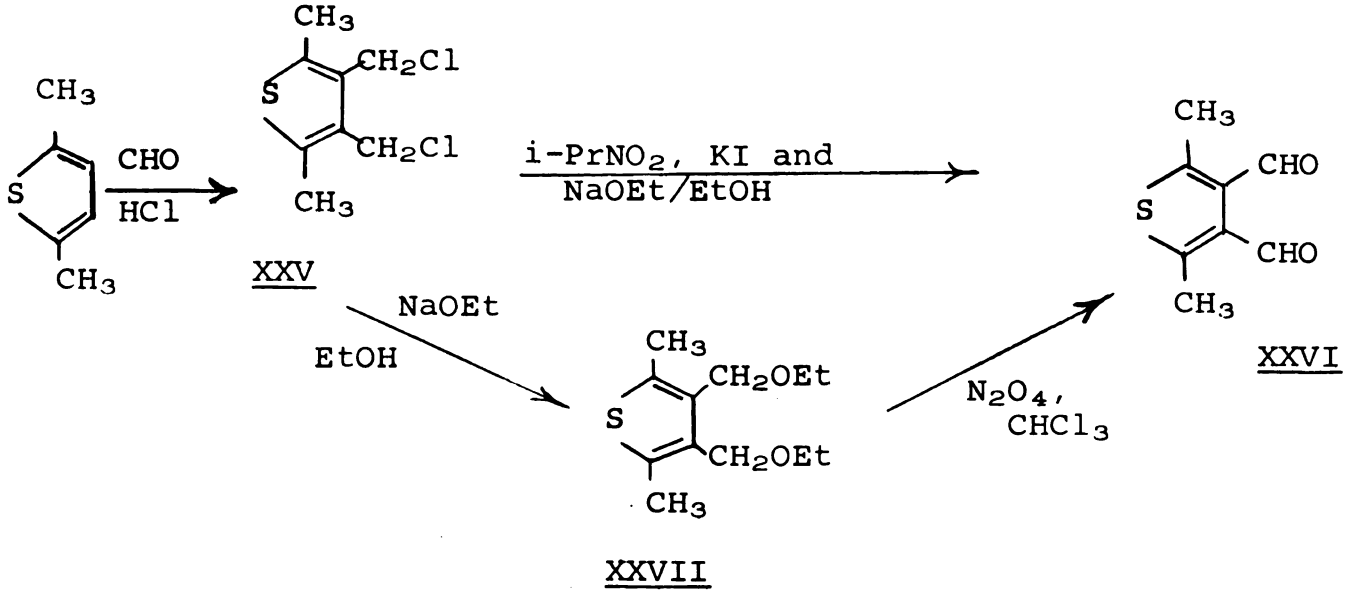
Recently, several researchers have synthesized dicarbonyl thiophenes by oxidation of appropriate chloromethylthiophenes. El'tsov and Ginesina (47) prepared 3,4-diformyl-2,5-dimethylthiophene, XXVI, by oxidation of 3,4-bischloromethyl-2,3-dimethylthiophene, XXV, using 2-nitropropane, potassium iodide and sodium ethoxide. Dimroth et al., (48) previously synthesized 3,4-diformyl-2,5-dimethylthiophene by oxidation of 3,4-bisethoxymethyl-2,5-dimethylthiophene, XXVII, using dinitrogen tetraxide in chloroform. Janda and Dvorak (4) chloromethylated 2-propionylthiophene to obtain 5-chloromethyl-2-propionylthiophene. Subsequent oxidation of this compound with $Pb(NO_3)_2$ gave 5-formyl-2-propionylthiophene. This latter compound was reported to possess antibiotic properties.



Gronowitz (40) in his studies on the synthesis of the isomers of formyl thenoic acid has shown that the ethylene glycol acetal of 3-thenal is metallated and subsequently carbonated in the 2-position. Pastour (49) et al. have been

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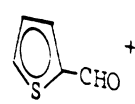
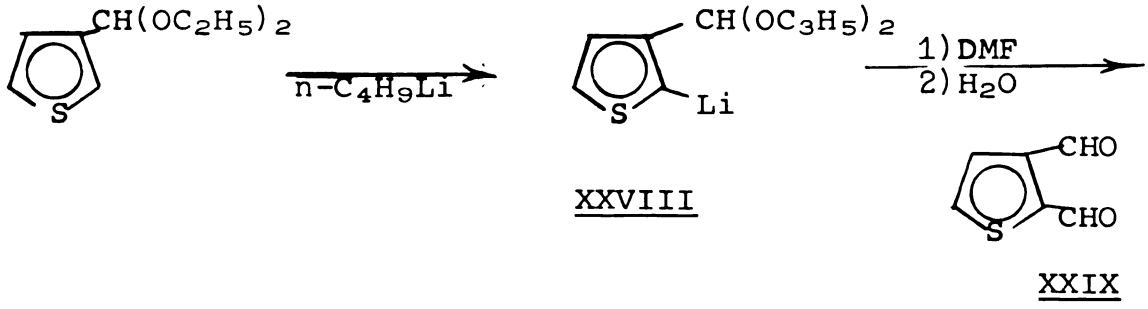


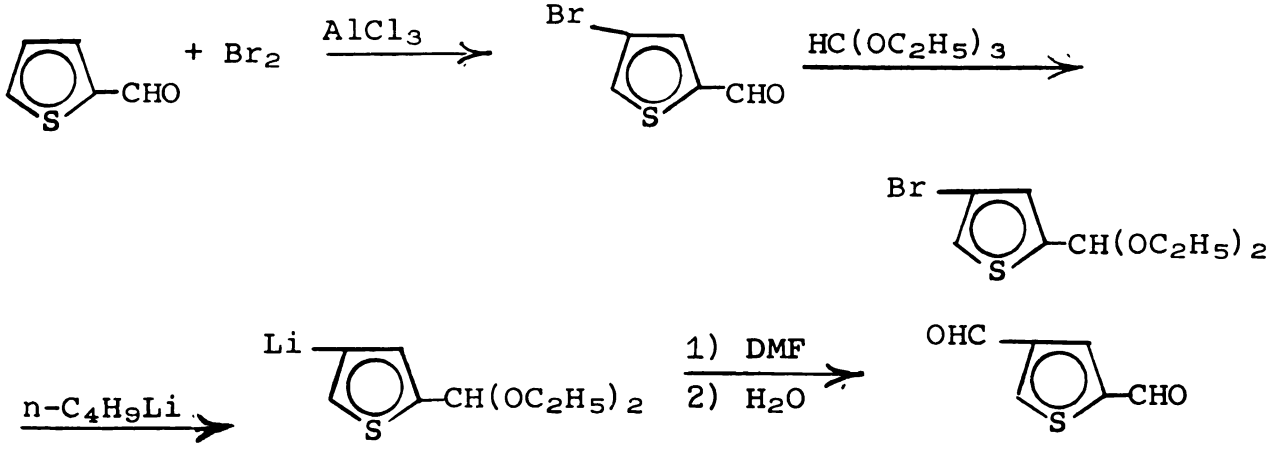
able to prepare 2,3-thiophene biscarboxaldehyde, XXIX, via the diethyl acetal of 3-thenal-2-lithium, XXVIII, using N,N-dimethylformamide.



XXVIII

XXIX

Gol'dfarb et al. (50) have synthesized thiophene-2,4-biscarboxaldehyde in a rather unusual manner. 2-Thenal was monobrominated using $AlCl_3$ as a catalyst, to obtain 4-bromo-2-thenal. The diethyl acetal of 4-bromo-2-thenal was subjected to a bromine-metal interchange reaction using n-butyllithium followed by treatment of the resulting lithium derivative, XXX, with N,N-dimethylformamide. Thiophene-2,4-biscarboxaldehyde was obtained by hydrolysis of the resulting aldehyde acetal.



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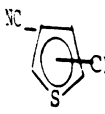

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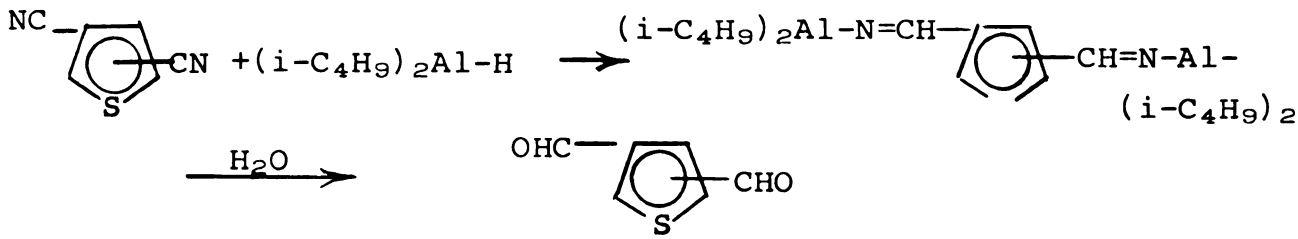
The reduction of thiophene bisnitriles using diisobutyl aluminum hydride has been reported in two cases to yield thiophene biscarboxaldehydes. Trofimenko (51) has prepared thiophene-3,4-biscarboxaldehyde in a 23% yield by reduction of the corresponding dinitrile. Pastour (49) et al. have reported the synthesis of thiophene-2,4-biscarboxaldehyde by reduction of thiophene-2,4-bisnitrile using diisobutyl aluminum hydride.



Synthesis of Thiophene Biscarboxaldehydes from Dilithiated Thiophenes

When thiophene or dihalogenated thiophenes are treated with two equivalents of n-butyllithium, thiophene dilithiums have been reported. Taft (52) has reported that thiophene 2,5-dilithium gave a 32% yield of thiophene-2,5-biscarboxaldehyde on reaction of two equivalents of n-butyllithium with 2,5-diiodothiophene followed by treatment with N,N-dimethylformamide. Iodine-metal conversion of 2,5-diiodothiophene using phenyllithium to the dilithium derivative was reported by Campaigne and Foye (53) as shown by a 53% yield of thiophene 2,5-biscarboxylic acid upon carbonation. Ostman (54) has

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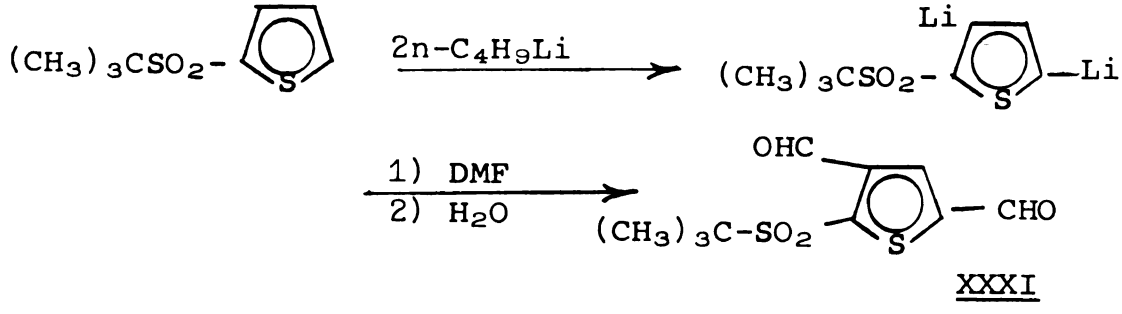
shown that 3-bromothiophene gives rise to thiophene-2,3-dicarboxylic acid upon addition of an excess of n-butyllithium followed by carbonation. Recently, Robba et al. (55), have successfully synthesized 2,3-diformylthiophene by treatment of thiophene-2,3-dilithium (prepared from two equivalents of n-butyllithium and 3-bromothiophene) with N,N-dimethylformamide. Fedorov and Stoyanovich (56) have produced 5-t-butylsulfonylthiophene-2,4-biscarboxaldehyde, XXXI, by the direct treatment of t-butyl 2-thienyl sulfone, first with two equivalents of n-butyllithium followed by reaction with two equivalents of N,N-dimethylformamide.



XXXI

The use of a double iodine-metal interconversion of diiodothiophenes with two equivalents of n-butyllithium followed by addition of the organo metallic complex to N,N-dimethylformamide has been successfully applied by Robba et al. (57) to the synthesis of each of the four thiophene biscarboxaldehydes. Winn and Bordwell (58) recently have prepared 3,4-diformyl-3,5-dimethylthiophene by the double iodine-metal interchange reaction with n-butyllithium upon 3,4-diiodo-2,5-dimethylthiophene, followed by reaction of the thiophene-3,4-dilithium with N,N-dimethylformamide.

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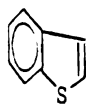

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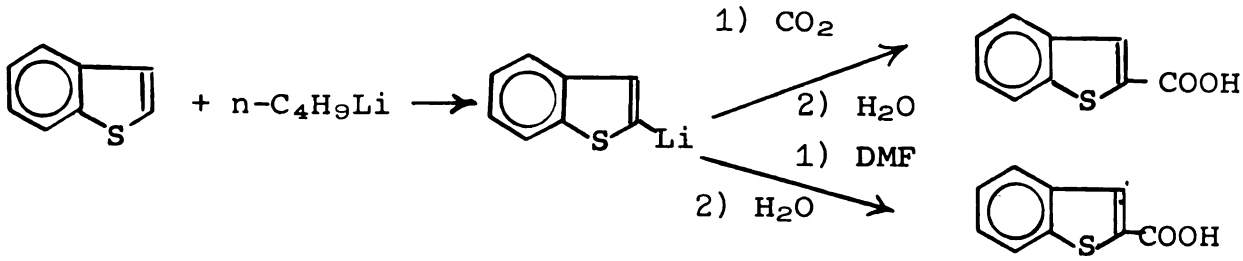
Although the yields were not reported in these studies, it is expected that these procedures for producing thiophene dialdehydes probably give low yield and do not have the added feature of allowing variation of the carbonyl groups introduced.

Thianaphthene Metallation and Thianaphthene-2,3-biscarboxaldehydes

The metallation of thianaphthene was first reported by Shirley and Cameron (59) using n-butyllithium. Carbonation of the lithium complex gave 2-thianaphthene carboxylic acid. Shirley and Danzig (60) later applied this reaction procedure to the synthesis of 2-thianaphthene carboxaldehyde using the intermediate 2-thianaphthene lithium and N-methylformanilide.



Reid and Bender (61) prepared thianaphthenyl-2,3-dilithium by two different methods and carbonated the organo lithium salt to the known thianaphthene-2,3-dicarboxylic acid. This was accomplished experimentally by treatment of 2,3-dibromo-thianaphthene with a single equivalent of n-butyllithium followed by addition of finely divided lithium metal to exchange the second halogen atom. The alternate procedure

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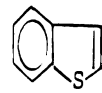

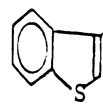

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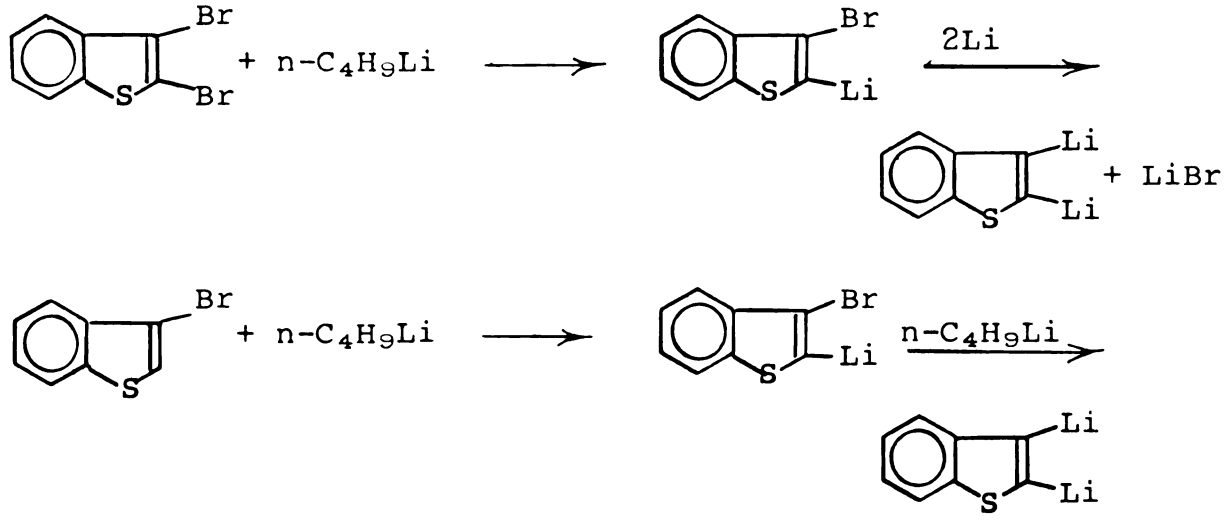
utilized 3-bromothianaphthene and two equivalents of n-butyllithium to obtain thianaphthenyl-2,3-dilithium in a single step.



It was also observed that no dialdehyde was produced when thianaphthenyl-2,3-dilithium was added to two equivalents of N-methylformanilide. Reid and Bender have reported the only synthesis of a thianaphthenyl biscarboxaldehyde, 2,3-diformylthianaphthene, XXXV, (61). Bischloromethylation of thianaphthene gave 2,3-bischloromethylthianaphthene, XXXII. This was converted to the corresponding bispyridinum hydrochloride, XXXIII. The hydrochloride intermediate was then converted to its bisnitrone, XXXIV, by interaction with N,N-dimethyl-p-nitrosoaniline. Acid hydrolysis of the bisnitrone gave the biscarboxaldehyde derivative.

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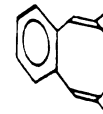
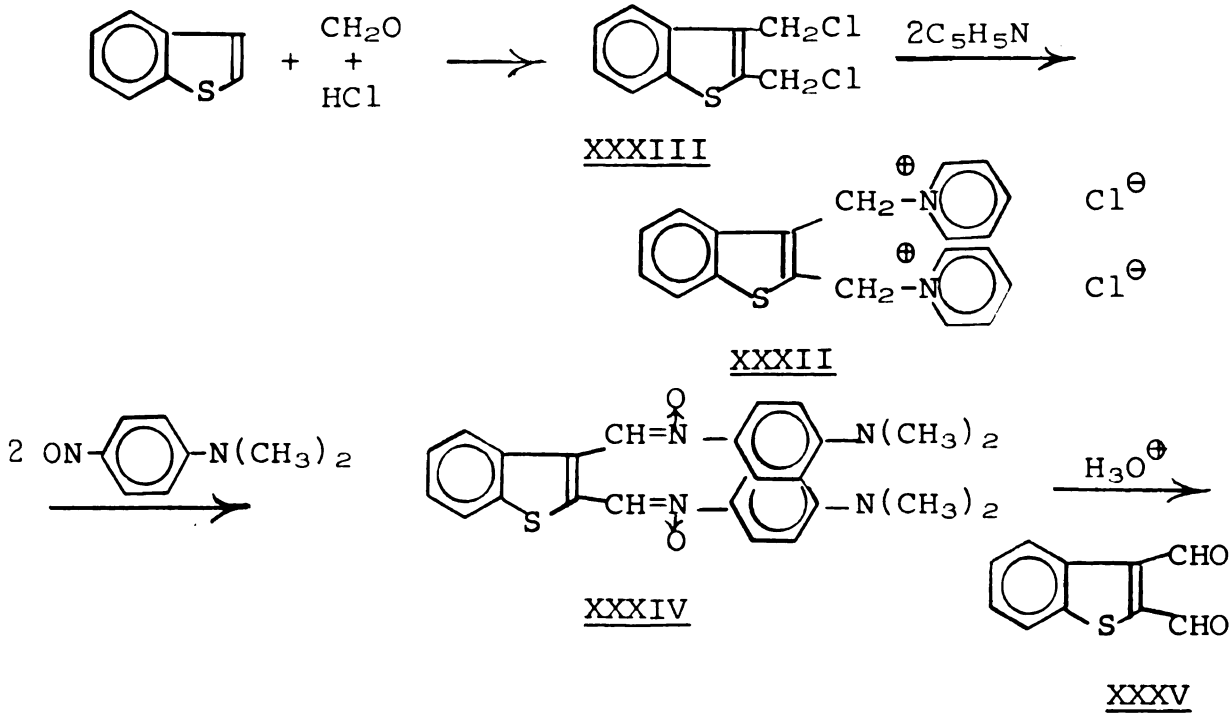




XXXIII

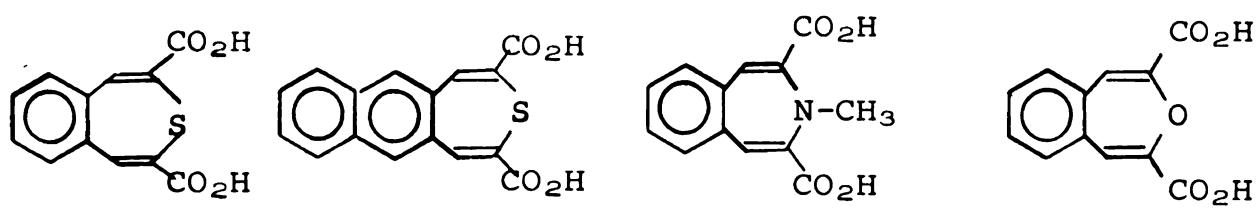
XXXII

XXXIV

XXXV

Cyclic Condensations of Some Vicinal Dialdehydes

The base catalyzed condensations of o-diformylbenzene with compounds possessing active hydrogens are well-known. Benzo[d]thiepin-2,4-dicarboxylic, XXXVI, (15,17) has been prepared using diethyl thiodiglycolate and o-diformylbenzene. Loudon and Sloan (16) have prepared in a similar manner 2,4-dibenzoylnaphtheno[2,3-d]thiepin, XXXVII, from 2,3-diformylnaphthalene and diphenacyl sulfide. Dimroth and



XXXVI XXXVII XXXVIII XXXIX

Freyschlag

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Benzo[

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condensed w

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ether. Dim

$2(C_6H_5)_3P$

+

$(BrCH_2)_2O$

XLI +

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2,5-dimethyl

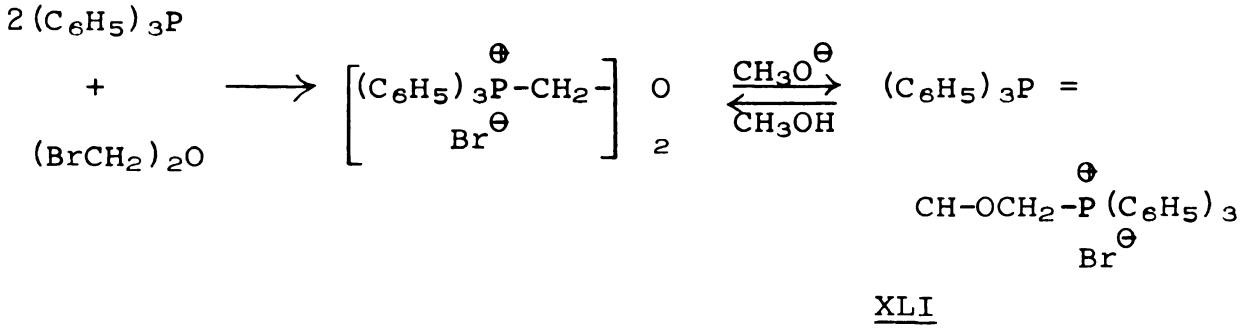
Several

2,3- and 3,4

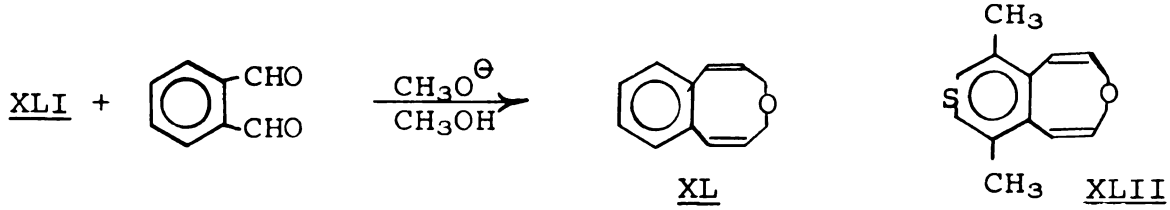
Winn and Bor

Freyschlag (63) have prepared N-methyl benzo[d]azepin-2,4-dicarboxylic acid, XXXVIII, from diethyl N-methyl iminodiacetate and o-diformylbenzene.

Benzo[d]oxepin-2,4-dicarboxylic acid, XXXIX, (63,64) has also been prepared by several researchers by the base catalyzed condensation of o-diformylbenzene and diethyl diglycolate. A unique synthesis of benzo[d]oxepin, XL, has been reported by Dimroth et al. (48). o-Diformylbenzene was condensed with the Wittig salt, XLI, prepared from two moles of triphenylphosphine and one mole of α,α'-dibromodimethyl ether. Dimroth et al., (48) also prepared



XLI



XL XLII

6,8-dimethylthieno[3,4-d]oxepin, XLII, using 3,4-diformyl-2,5-dimethylthiophene (see above) and the Wittig salt, XLI.

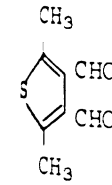
Several condensations of unsubstituted and substituted 2,3- and 3,4-diformylthiophenes have been reported. Both Winn and Bordwell (58) and El'tsov and Ginesina (47) have

prepared

XLIII, h

and 3-pe

(55,57)



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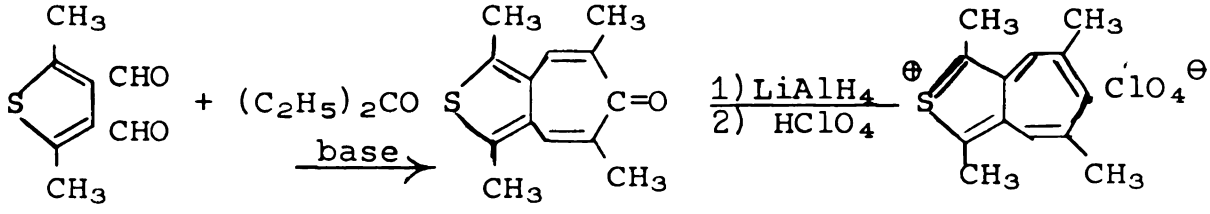
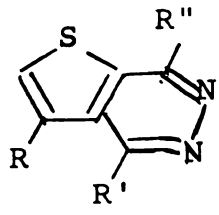
prepared the 1,3,5,7-tetramethyl 2-thiaazulenium salts, XLIII, by condensation of 2,5-dimethyl-3,4-diformylthiophene and 3-pentanone in the presence of base. Robba et al., (55,57) and El'tsov and Ginesino (47) have prepared several

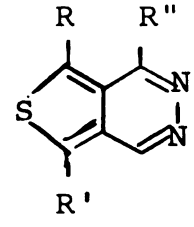


XLIII

differently substituted thieno[2,3-d]pyridazines, XLIV, and thieno[3,4-d]pyridazines, XLV, by condensation of vicinally substituted dicarbonyl thiophenes with hydrazines; these compounds were synthesized for pharmaceutical study.



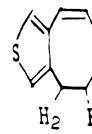
XLIV



XLV

Recently, Schlessinger and Ponticello (12) have synthesized thieno[3,4-d]thiepin, XV, by treating 4,5-dihydro thieno[3,4-d]thiepin-3-oxide, XLVII, with acetic anhydride. The sulfoxide, XLVII, was prepared readily from the previously known 4,5-dihydrothieno[3,4-d]thiepin, XLVI, (65).

Eglinton



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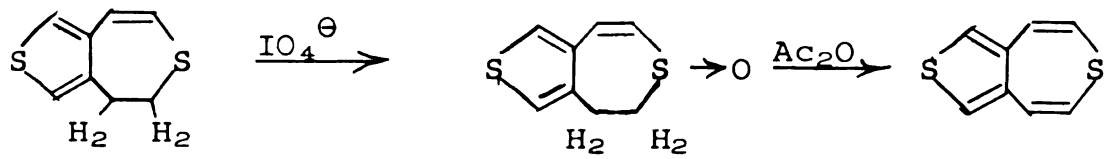
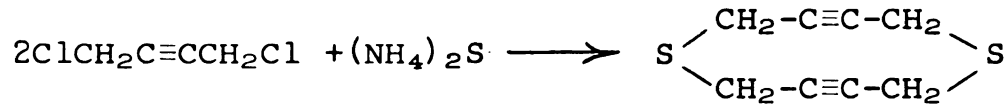
Gave tw

Eglinton et al. (65) have synthesized this precurser, i.e.,



XLVI XLVI XVI

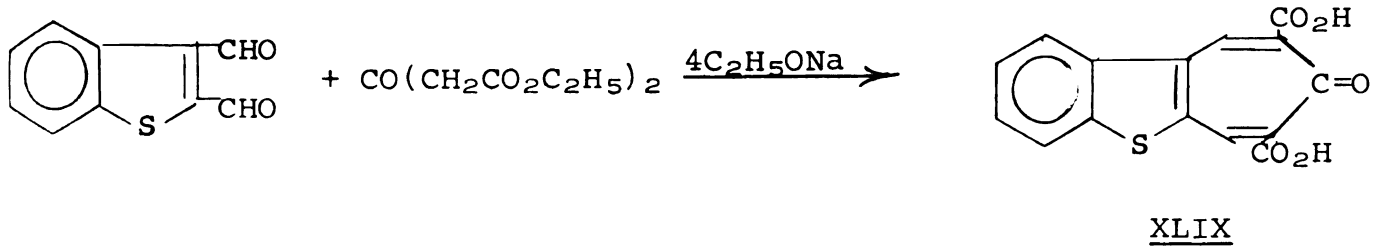
4,5-dihydro thieno[3,4-d]thiepin, by a base catalyzed ($(CH_3)_3COK$) isomerization of 1,6-dithiacyclodeca-3,8-diyne, XLVIII, which in turn was prepared by the reaction of 1,4-dichloro-2-butyne and ammonium sulfide.



XLVIII

XLVI

The condensation of thianaphthene-2,3-biscarboxaldehyde with acetone dicarboxylic acid diethyl ester has been reported by Reid and Bender (61) to give thianaphtheno-2',3':-4,5-2,6-cycloheptadienone-2,7-dicarboxylic acid, XLIX, with 1,4-cyclohexadione, thianaphthene-2,3-biscarboxaldehydes gave two isomeric bisthianaphtheno anthraquinones, L and LI.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+ CO(CH2CO2C2H5)2
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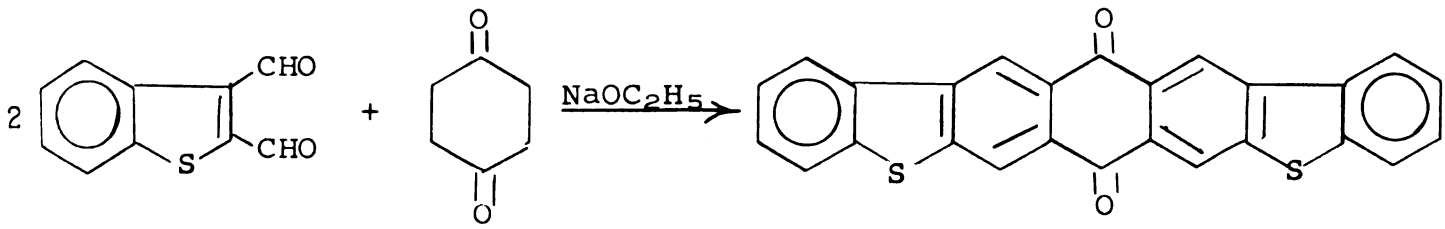
C=O
CO2H
S

XLIX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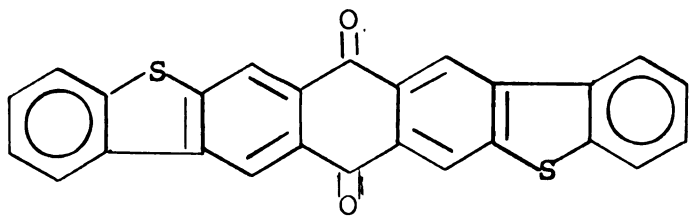
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RESULTS AND DISCUSSION

The syntheses of 2,3-thienyl and 2,3-thianaphthenyl dicarbonyls was accomplished through hydrogen-metal interchange of the "activated" 2' position of 2-substituted 2-(3'-thienyl, XV, and 3'-thianaphthenyl, XVI)-1,3-dioxolanes using n-butyllithium. Treatment of these intermediate organo lithiums with N,N-dimethylacylamides yielded carbonyl substituted thienyl and thianaphthanyl dioxolanes, which on hydrolysis gave the corresponding dicarbonyl compounds. The initial 3-thienyl aldehydes or ketones were prepared from 3-bromothiophene, using the method described by Taft (52), via a halogen-metal interchange reaction using n-butyllithium. The 3-thienyllithium was then converted to an aldehyde or ketone using N,N-dimethylformamide and N,N-dimethylacylamides. 3-Bromothiophene was prepared by the procedure described by Gronowitz (66,67) from 2,3,5-tribromothiophene. The 3-thianaphthenyl ketones were prepared by direct acylation by the method of Farrar and Levine (68), which occurred predominately in the 3-position of thianaphthene.

2-Thienyl and 3-Thianaphthenyl Monocarbonyls and Dioxolanes

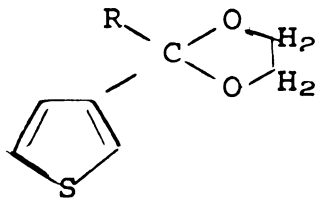
The preparation of 3-bromothiophene was synthesized using a method developed by Gronowitz (67). Tribromination of

thiophene with elemental bromine occurred readily without a catalyst. 2,3,5-Tribromothiophene, isolated by steam distillation, was debrominated(zinc-acetic acid) in the 2,5-positions to obtain 43% of pure 3-bromothiophene based on the initial amount of thiophene used in the reaction.

The preparations of 3-thenal, 3-acetothienone and 3-benzoylthiophene were accomplished by using methods described initially by Taft (52); 3-thenal and 3-acetothienone were obtained on treatment of 3-thienyllithium with N,N-dimethylformamide and N,N-dimethylacetamide. The use of 3-thienyllithium and N,N-dimethybenzamide to prepare 3-benzoylthiophene represented an extension of Taft's work.

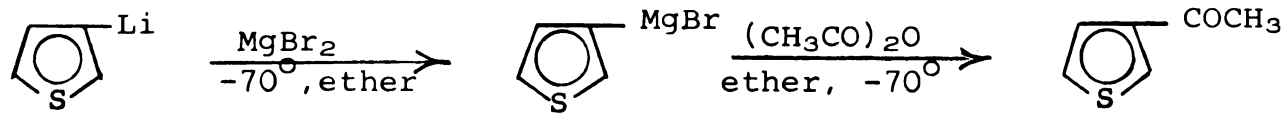
These procedures resulted in the formation of 3-thenal, 3-acetothienone and 3-benzoylthiophene respectively in isolated yields of 76, 68 and 94 percent. The reported physical properties and infrared spectra of 3-thenal (42,69), 3-acetothienone (70) and 3-benzoylthiophene (66) agreed with the physical properties of the compounds prepared in this study. The use of these distinctly different N,N-dimethylacylamides in this experimental procedure, demonstrates the general applicability of this synthetic method for the preparation of ketones. The aldehyde and both ketones were then converted to dioxolane derivatives by the procedure of Bergmann et al. (71) using ethylene glycol, p-toluenesulfonic acid in a benzene reaction solvent in yields of 65-81 percent. Both 2-(3'-thienyl)-1,3-dioxolane, LIII, (32) and

2-methyl-2-(3'-thienyl)-1,3-dioxolanes, LIV, (55) have been synthesized and their physical properties agreed with those reported. 2-Phenyl-2-(3'-thienyl)-1,3-dioxolane, LV, is a new compound synthesized for this present study.



LIII, R = H
LIV, R = CH_3
LV, R = C_6H_5

The use of 3-thienyllithium and N,N-dimethylacylamides represented a significant departure from past practice in the synthesis of sulfur heterocyclic ketones. Gronowitz (70) prepared 3-acetothienone by converting 3-thienyllithium first to the corresponding Grignard reagent using magnesium bromide etherate followed by treatment of the Grignard with acetic anhydride.

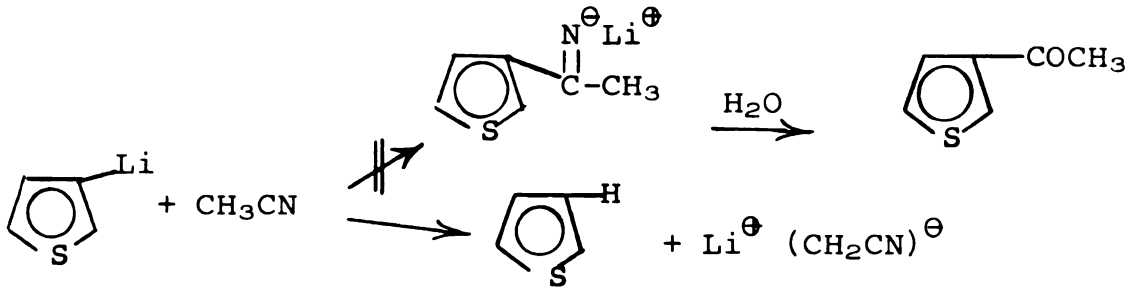


+ $[CH_3CO_2MgBr]$

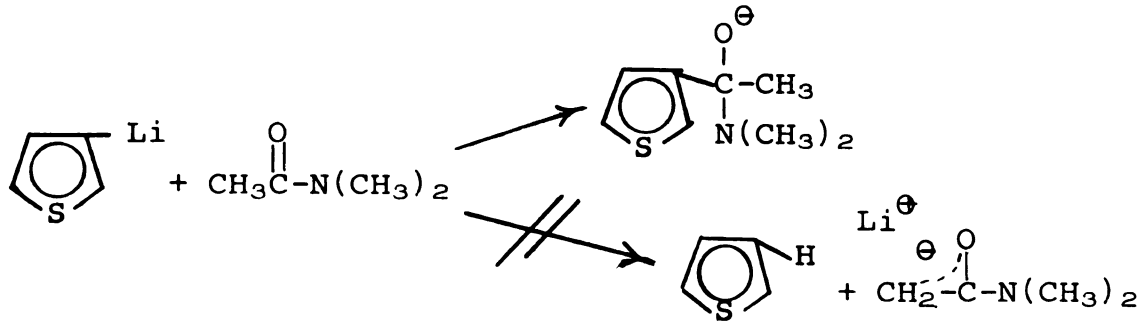
Gronowitz (66) also treated 3-thienyllithium with acetaldehyde to obtain the intermediate 3-thienyl methyl carbinol, which on oxidation with chromic oxide in acetic acid gave

3-acetothienone. 3-Benzoylthiophene had been previously prepared (70) in a 75 percent yield by the interaction of benzonitrile with 3-thienyllithium.

It is interesting to note that the reaction of 3-thienyllithium with acetonitrile gave very small amounts of 3-acetothienone at -70° (70). A strong base, viz. 3-thienyllithium, could be expected to readily abstract an alpha hydrogen from acetonitrile. However, 3-thienyllithium added readily to the carbonyl carbon of N,N-dimethylacetamide



yielding 3-acetothienone, rather than reacting to abstract hydrogen from the alpha carbon of N,N-dimethylacetamide to give thiophene and the lithium salt of N,N-dimethylacetamide. This is surprising, since Hauser et al. (72) have reported

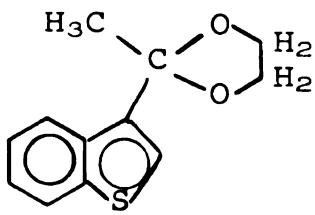


that two equivalents of n-butyllithium and one equivalent of acetanilide react rapidly and quantitatively below 0° to

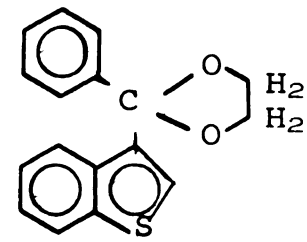
give a dicarbanion. Since the addition of 3-thienyllithium to (rather than hydrogen abstraction from) N,N-dimethylacetamide appears complete within minutes at -70°, it appears that addition is a kinetically favored process over that of hydrogen abstraction.

The preparation of 3-acetyl and 3-benzoylthianaphthene was accomplished by the method of Badger and Christie (73), using the appropriate acyl chlorides and stannic tetrachloride as the catalyst with benzene as the reaction solvent. 3-Acetylthianaphthene was separated from the 2-isomer by fractional crystallization of the reaction product from 95% aqueous ethanol following the procedure of Farrar and Levine (68). In the case of 2-benzoylthianaphthene, it could not be separated from minor amounts of the 2-isomer formed by fractional crystallization, since 2-benzoylthianaphthene is reported to be a liquid (74), solidifying to a glass at room temperatures. Following the usual ketalization reaction using ethylene glycol, etc., the distilled reaction mixture on being set aside for three months, eventually crystallized to a mass of crystals in the oily distillate. Recrystallization of this crystalline material from 95% aqueous ethanol, gave 33% of pure 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane, LVII, based on initial thianaphthene used in its synthesis. The isomer was shown to be pure by thin-plate, silica-gel chromatography (benzene eluent). This dioxolane represents the first crystalline derivative obtained using the carbonyl group of 3-benzoylthianaphthene. Attempts to prepare oximes

and phenylhydrazone derivatives have reportedly failed (74). 2-Methyl-2-(3'-thianaphthenyl)-1,3-dioxolane, LVI, was readily prepared in an 86 percent yield based on the amount of 3-acetylthianaphthene used in the synthesis. Both 2-methyl and 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolanes were new compounds which were synthesized for this present study.



LVI



LVII

Spectral Properties of 2-Substituted-2-(3'-Thienyl and 3-thianaphthenyl)-1,3-dioxolanes

The infrared and ultraviolet spectra and physical properties of 2-(3'-thienyl)-1,3-dioxolane were identical to those previously reported (30). The NMR resonance spectrum of 2-(3'-thienyl)-1,3-dioxolane (20 w./v. percent in CCl_4), which was not reported, showed complex absorption, typical of an ABX pattern, with H_2 at 2.75 τ; H_4, 2.98 τ; H_5, 2.90 τ. The acetal hydrogen appeared at 4.22 τ as a barely resolved doublet (J=0.7 cps) coupled to hydrogen 2 of thiophene. The hydrogens of the dioxolane ring appeared centered at 6.16 τ as a symmetrical A_2B_2 multiplet, showing hydrogens both cis

and trans to the thiophene ring. Figure 1 shows the aromatic portion of this NMR spectrum. The coupling constants are J_{45}=5.2 cps, J_{25}=3.1 cps, J_{24}=1.4 cps and J_{CH-2} = 0.7 cps. The infrared spectra indicated the absence of carbonyl absorption at 1691 cm^{-1} and strong C-O-C stretching absorption at 1100 cm^{-1}.

The preparation of 2-methyl and 2-phenyl-2-(3'-thienyl)-1,3-dioxolanes was easily accomplished as already described. Following distillation of the reaction products at reduced pressures, the two dioxolanes were crystallized from aqueous ethanol. They had melting points respectively of 33-4^{o} and 79.5-80^{o}. The infrared spectra of 2-methyl and 2-phenyl-2-(3'-thienyl)-1,3-dioxolanes are reproduced as Figures 2 and 3. While the physical properties of 2-methyl-2-(3'-thienyl)-1,3-dioxolane prepared in this study agreed with those reported by Robba et al., (55), it is interesting to note that no spectral evidence was reported. The description of these spectral properties, together with those for 2-phenyl-2-(3')thienyl)-1,3-dioxolane follows. For 2-methyl-2-(3'-thienyl)-1,3-dioxolane, the carbonyl stretching frequency at 1688 cm^{-1} has disappeared and been replaced by the C-O-C stretching and methylenic carbon-hydrogen stretching frequencies at 1053 cm^{-1} and 2875 cm^{-1} respectively. Likewise with 2-phenyl-2-(3'-thienyl)-1,3-dioxolane, the carbonyl stretching frequency at 1656 cm^{-1} has been replaced by C-O-C stretching and methylenic carbon-hydrogen stretching

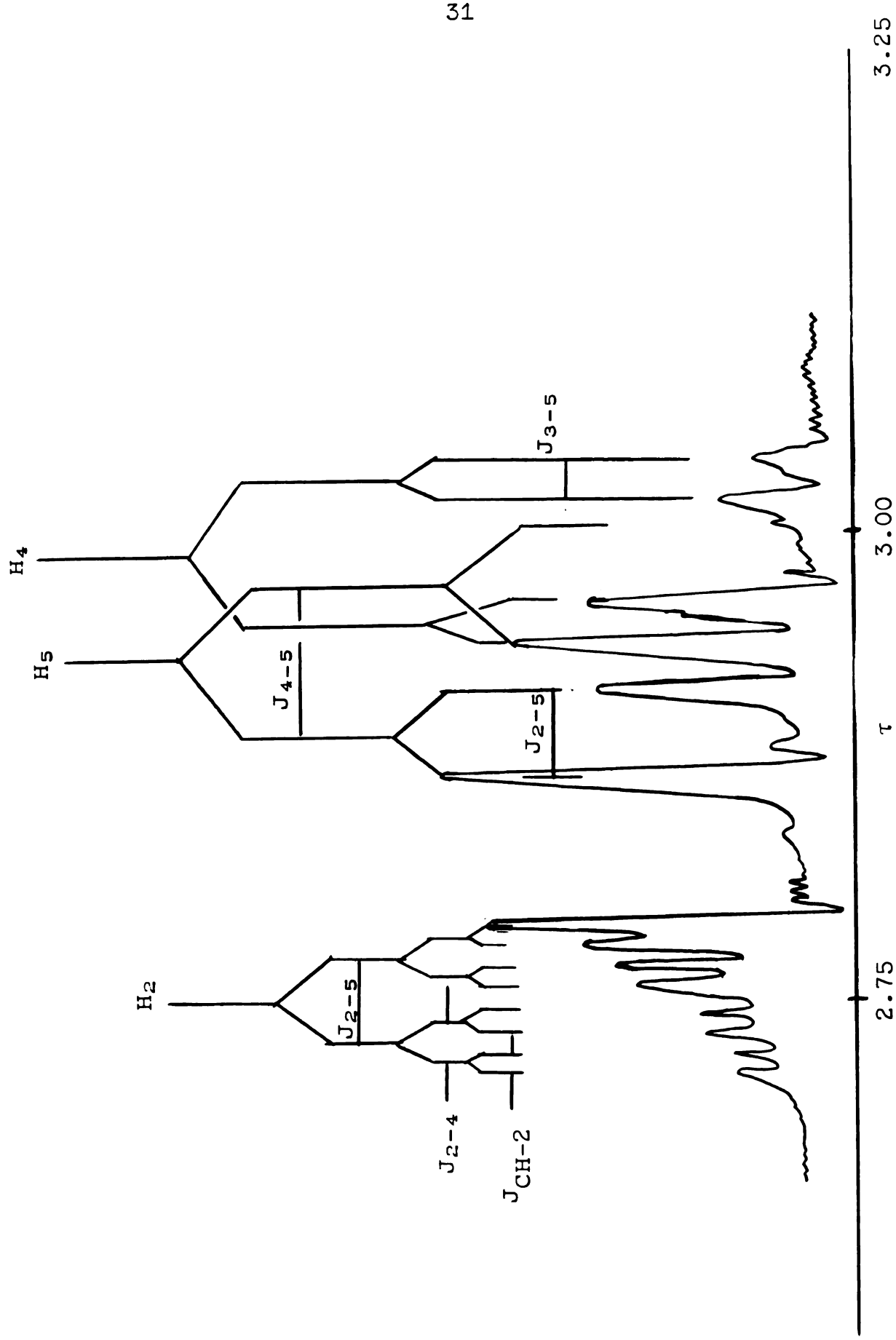


Figure 1. NMR spectrum of aromatic hydrogens of 2-(3'-thienyl)-1,3-dioxolane taken in CCl_4 (20 vol. %).

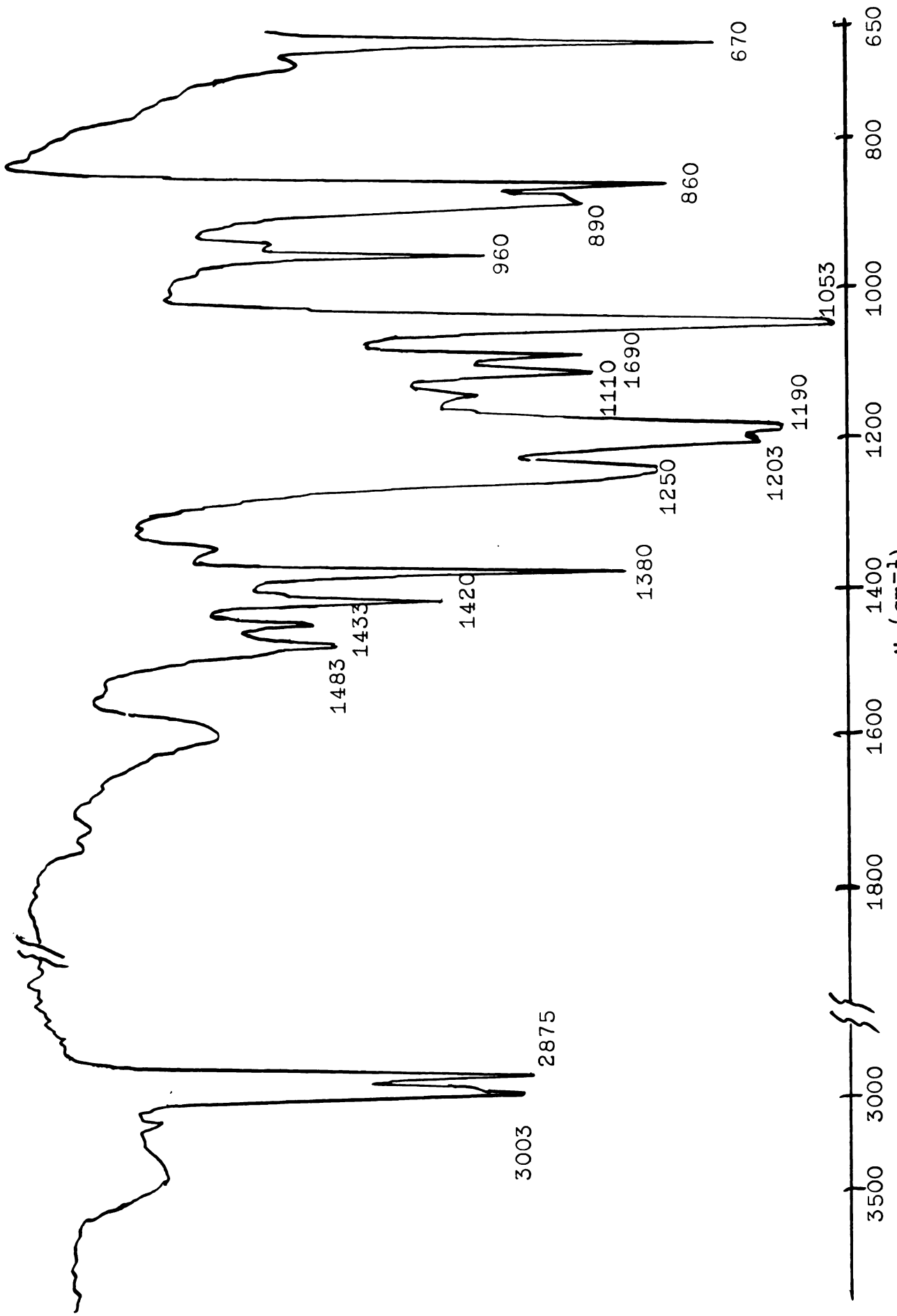


Figure 2. Infrared spectrum of 2-methyl-2-(3'-thienyl)-1,3-dioxolane in CCl_4.

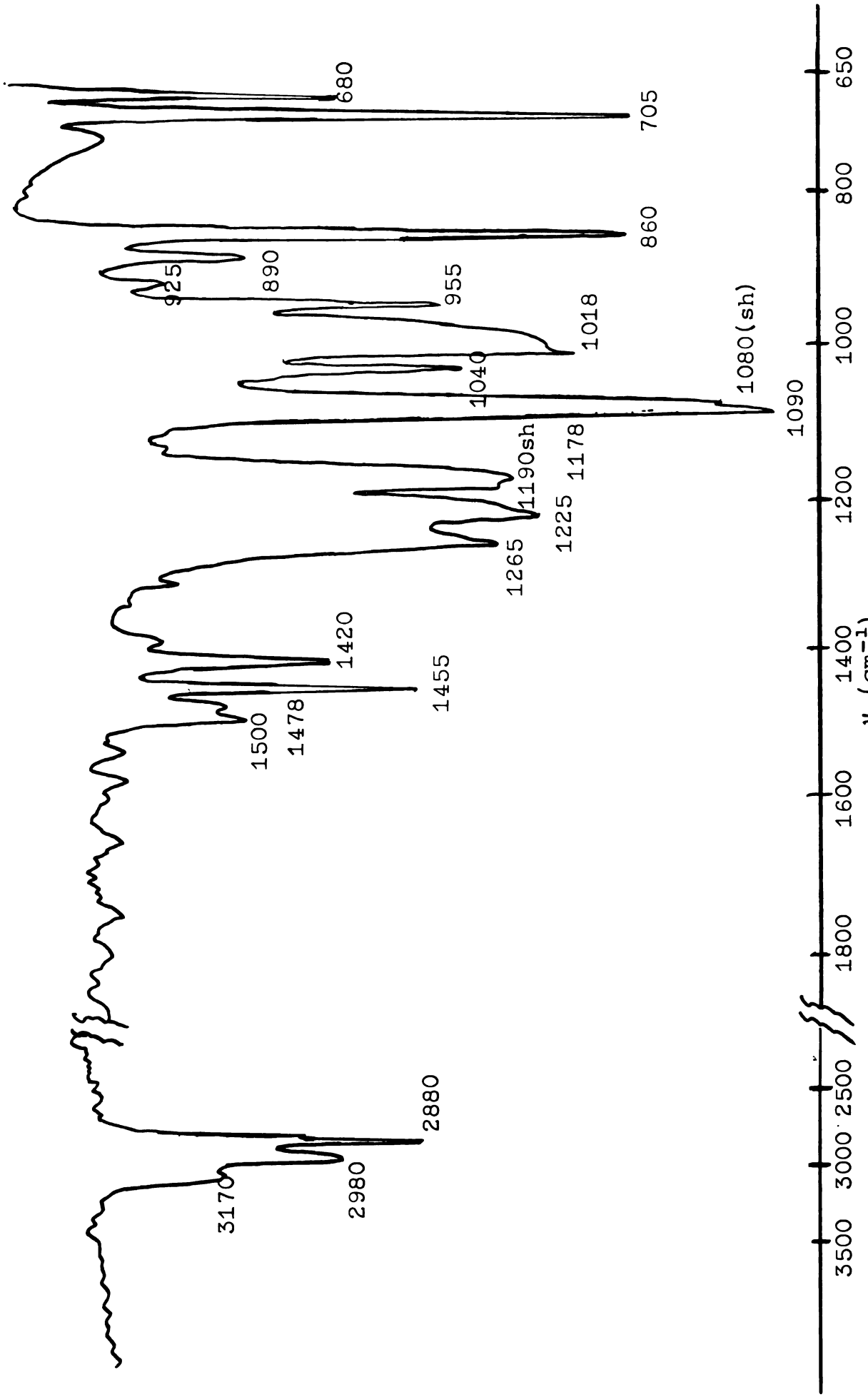


Figure 3. Infrared spectrum of 2-phenyl-2-(3'-thienyl)-1,3-dioxolane in CCl_4.

frequencies of 1090 cm^{-1} and 2880 cm^{-1}. The sterically larger phenyl group compared to the methyl group has created additional strain in the molecule, shifting the C-O-C stretching frequency to shorter wavelengths by approximately 40 cm^{-1}.

The UV spectra of 2-methyl and 2-phenyl-2-(3'-thienyl)-1,3-dioxolanes in ethanol showed maxima at 232 mμ (ε5840) and 236, 269 mμ (ε7490, 2760) respectively. Gronowitz (75) has reported that 2- and some 3-substituted thiophenes show two maxima, which are bathochromic shifts of maxima of unsubstituted thiophene, i.e., 215 mμ and 235 mμ (log ε3.5, 3.85) arising through a $\pi \longrightarrow \pi^*$ excitation. Many 3-substituted thiophenes show only a single maximum as in 2-methyl-2-(3'-thienyl)-1,3-dioxolane. This condition is thought to be due to a coalescing of these two maxima, or in this case a greater shift of the 215 mμ band than the 235 mμ band.

The NMR spectra of 2-methyl and 2-phenyl-2-(3'-thienyl)-1,3-dioxolanes showed the dioxolane hydrogens as a symmetrical A_2B_2 complex at 6.05-6.15 τ in either CCl_4 or CH_3CN solvents. The methyl group of the methyl dioxolane is observed at 8.40 τ and 8.44 τ respectively in CH_3CN and CCl_4, considerably more upfield than is the case with 3-acetothienone (i.e., 7.56 τ in CCl_4). A portion of the NMR spectrum is reproduced in Figure 4 for the aromatic region of 2-methyl-2-(3'-thienyl)-1,3-dioxolane in CCl_4 and CH_3CN solvents. The spectrum for the three aromatic protons in these solvents consisted of

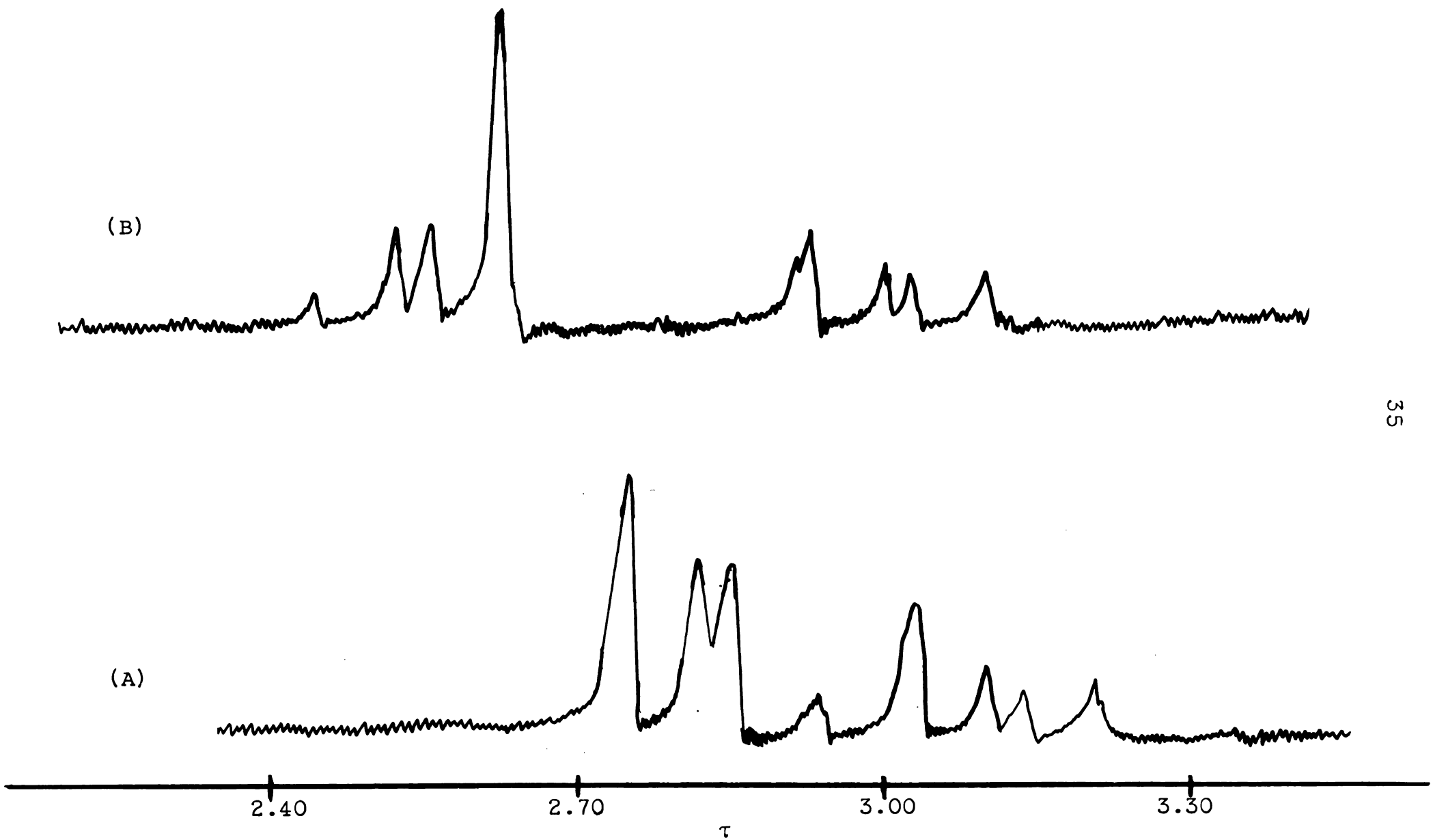


Figure 4. NMR spectrum of aromatic hydrogens of 2-methyl-2-(3'-thienyl)-1,3-dioxolane: (A) 20 w./v. % CCl_4; (B) 20 w./v.% CH_3CN.

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two quartets which are separable by use of a polar solvent, CH_3CN. If an assignment of the lower quartet could be made to hydrogen 2 of the thiophene ring, as in the case of 2-(3'-thienyl)-1,3-dioxolane, the observed splitting would be J=4.0 cps and J=2.8 cps. A value of J=4.0 cps would be acceptable for J_{25}. However, J=2.8 cps for J_{24} would be unusually large in light of all the examples studied by Gronowitz (ref. 3, p. 8). A large "singlet" appears to be associated with this downfield quartet. It is also interesting that the upfield quartet has the same coupling constants. Since the methyl group is unsplit, the thiophene protons will not show further coupling. Gronowitz (32) has indicated that the spectra of 2-(3')thienyl)-1,3-dioxolane was unusually complex (at 40 MC.). The NMR spectra of 2-phenyl-2-(3'-thienyl)1,3-dioxolane is complicated by the overlapping resonance of the phenyl protons and assignments for the thiophene hydrogens cannot be made unequivocally.

The introduction of the dioxolane ring system into the 3-acetyl and 3-benzoylthianaphthene, produced lower melting solids, 39.5-40.5° and 78-9° respectively, which were almost identical to the thiophene analogs. 2-Phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane represents a crystalline derivative of a "non-solid" 3-benzoylthianaphthene. The infrared spectra of 2-methyl and 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane are shown in Figures 5 and 6. These showed the absence of carbonyl stretching frequencies and the appearance


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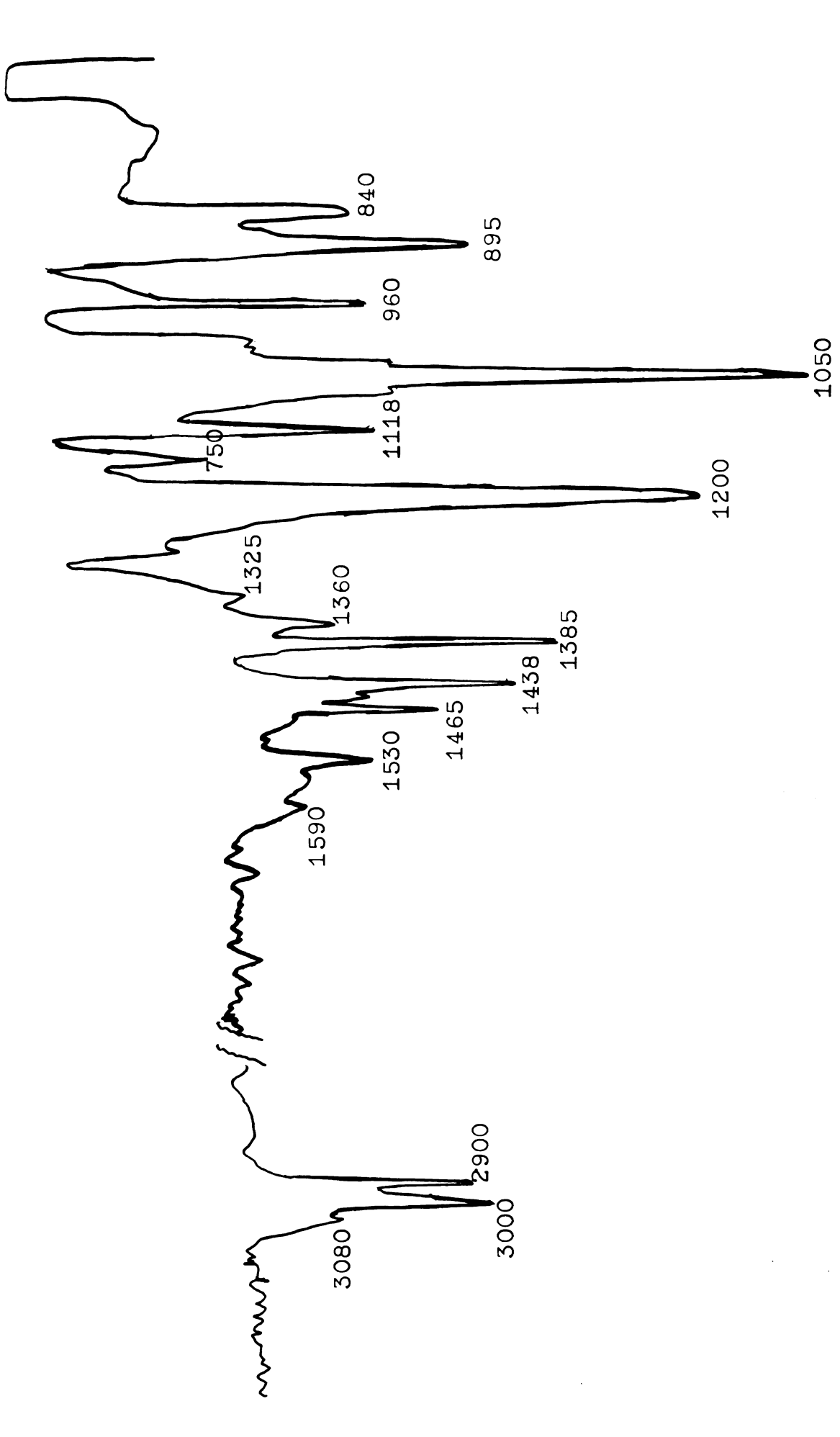

Figure 5. Infrared spectra of 2-methyl-2-(3'-thianaphthenyl)-1,3-dioxolane in CCl_4 (10 w./v.%).

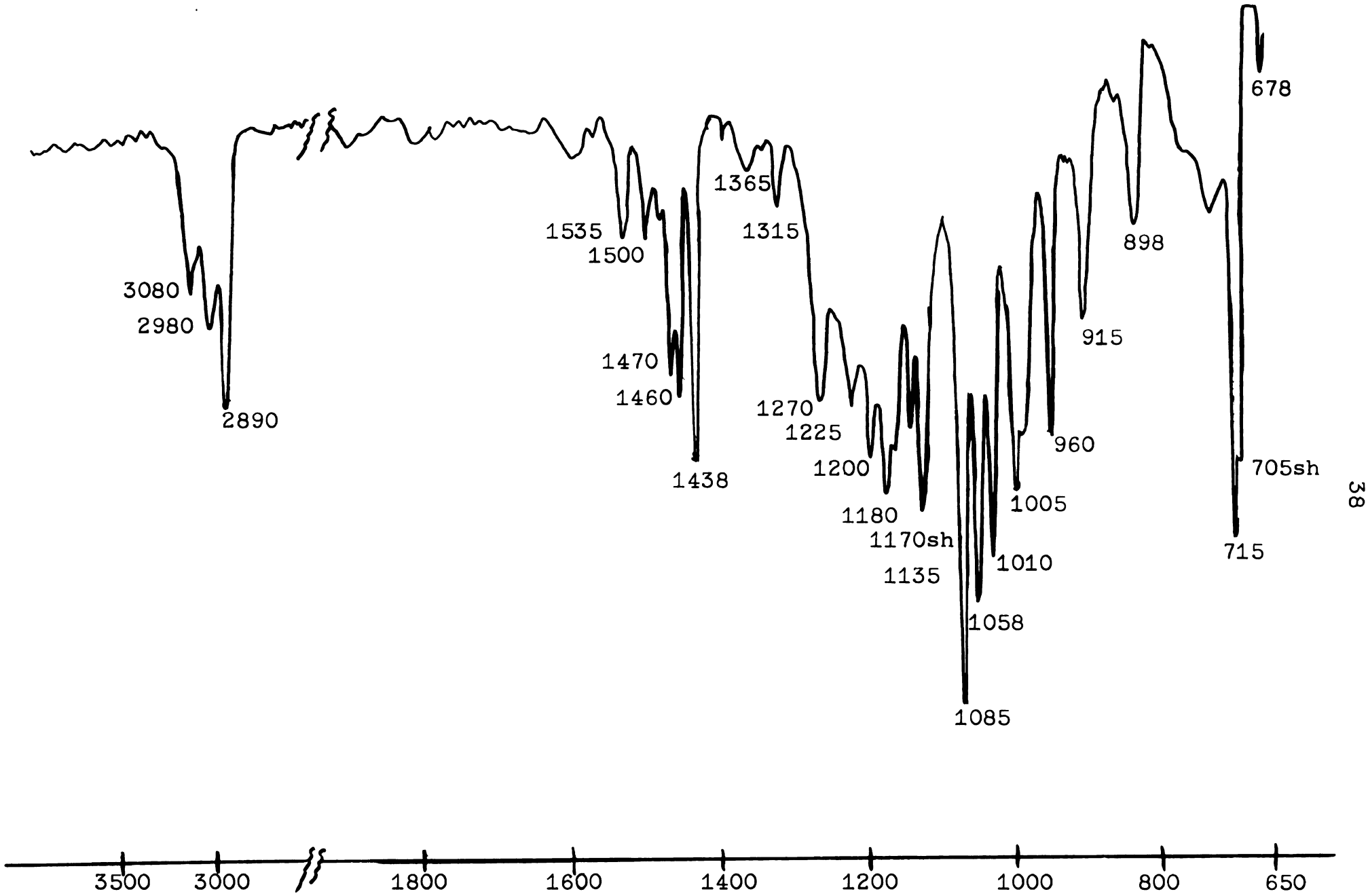

Figure 6. Infrared spectra of 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane in CCl_4

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of a dioxolane C-O-C and methylene carbon-hydrogen stretching frequencies respectively at 1050 cm^{-1} and 2900 cm^{-1} for the methyl derivative and at 1085 cm^{-1} and 2890 cm^{-1} for the phenyl derivative. These frequencies are essentially identical to those of the thiophene analogs, which have a similar shift to a shorter wavelength for the phenyl substituents. The UV spectra in ethanol for these two thianaphthenyl compounds, which appeared almost identical to unsubstituted thianaphthene, showed maxima at 220, 260, 280, 290 and 300 mμ with little change in extinction coefficients. As the 2-methyl-2-dioxolanyl and the 2-phenyl-2-dioxolanyl groups appeared to make a slight change in the UV spectra of the 3-substituted thianaphthene, these groups can be said to make only minimal contributions to the stabilization of the UV excited states of these molecules.

The NMR spectra of 2-methyl and 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolanes in CCl_4 (10 w./v. percent) showed absorption for the aromatic and dioxolane hydrogens at 1.97 τ - 2.94 τ, 6.22 τ and 2.26 τ - 3.00 τ, 6.06 τ respectively. The methyl group of the former compound appeared as a sharp singlet at 8.28 τ. The dioxolane hydrogens in 2-methyl-2-(3'-thianaphthenyl)-1,3-dioxolane appeared as a symmetrical A_2B_2 multiplet of approximately 50 cps in width, while the dioxolane hydrogens in the 2-phenyl derivative appeared as a sharp singlet. With the introduction of a sterically larger phenyl group to the dioxolane ring, which

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should assist rotation of the carbon-oxygen bonds, a zero average in the chemical shift of the four hydrogens in the dioxolane ring is observed. Models of dioxolane indicated a fairly rigid ring system with severe rotation about the carbon-carbon and carbon-oxygen bond (76). However, splitting of the A_2B_2 system of dioxolane was not observed (76).

Table 1 summarizes UV and IR spectral data of these thienyl and thianaphthenyl dioxolanes. Table 2 summarizes their NMR spectral data.

Syntheses of Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

In the preparation of larger amounts of 3-thenal, 3-acetothienone and 3-benzoylthiophene using the procedure of Taft (52), the direct preparation of n-butyllithium from two gram equivalents of lithium per equivalent of n-butyl bromide was economical, convenient and preferred. In the hydrogen-metal interchange reaction of smaller amounts (e.g., 10 mmoles) of 2-(3'-thienyl)-1,3-dioxolane, 2-methyl and 2-phenyl-2-(3'-thienyl)-1,3-dioxolanes and 2-methyl and 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolanes, the procedures of Gronowitz (40) and Pastour (49) were used to obtain the intermediate thienyl and thianaphthenyl lithiums. In this work, commercial n-butyllithium in hexane was found to be an excellent alternative to synthetic material, and gave identical yields of product when compared to the synthetic material used in the preparations of 3-thenal and 3-benzoylthiophene.

Table 1. UV and IR Spectral Data for Thienyl and Thianaphthenyl Dioxolanes

Compound	UV (Ethanol) λ_{max} (ϵ) (mμ)	Infrared Maxima $\nu_{C=O}$ (cm^{-1})	$\nu_{(C-O-C)}$* (cm^{-1})
3-Acetothienone	250 (12,050)		

Table 1. UV and IR Spectral Data for Thienyl and Thianaphthenyl Dioxolanes

Compound	UV (Ethanol) λ_{max} (ϵ) (mμ)	Infrared Maxima $\nu_{C=O}$ (cm^{-1})	Infrared Maxima $\nu_{(C-O-C)}$* (cm^{-1})
3-Acetothienone	250 (12,050)	1685	---
3-Benzoylthiophene	258 (15,890)	1656	---
2-Methyl-2-(3'-thienyl)-1,3-dioxolane	232 (5,840)	---	1053
2-Phenyl-2-(3'-thienyl)-1,3-dioxolane	236, 269 (7,490, 2,760)	---	1090
Thianaphthene**	228; 250; 260; 290; 298; (19,940; 6,310; 6,310; 1,990; 3,980)	---	---
2-Methyl-2-(3'-thianaphthenyl)-1,3-dioxolane	222, 260, 281, 290, 299 (49,300, 6,350, 2,035, 2,860, 3,660)	---	1050
2-Phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane	221, 260, 281, 290, 300 (33,100, 7,410, 2,280, 3,150, 3,710)	---	1085

*Primary band showing largest extinction.

**G. M. Badger, B. J. Christie, H. J. Rodda and J. M. Pryke, J. Chem. Soc., 1958, 1179.

Table 2. NMR Spectral Data for Thienyl and Thianaphthenyl Dioxolanes

Compound	Solvent	Aromatic	τ H(CH_3)	τ H(C-H)	τ H(OCH_2)$_2$	J (cps) J_{24}	J_{25}	J_{45}
2-(3'-Thienyl)-1,3-	CCl_4	2.75-2.98	--	4.22	6.16			

Table 2. NMR Spectral Data for Thienyl and Thianaphthenyl Dioxolanes

Compound	Solvent	Aromatic	τ			J (cps)		
			$H(CH_3)$	$H(C\text{-}H)$	$H(OCH_2)_2$*	J_{24}	J_{25}	J_{45}
2-(3'-Thienyl)-1,3-dioxolane	CCl_4	2.75-2.98	--	4.22	6.16	1.5	3.1	5.2
	CH_3CN	2.56-2.76	--	4.18	6.05	1.7	3.0	5.0
3-Acetothienone	CCl_4	2.00-2.75	7.56	--	--	1.5	2.9	5.1
2-Methyl-2-(3'-thienyl)-1,3-dioxolane	CCl_4	2.78-3.12	8.44	--	6.15	--	--	--
		2.54-3.02	8.40	--	6.12	--	--	--
2-Phenyl-2-(3'-thienyl)-1,3-dioxolane	CCl_4	2.40-3.03	--	--	6.12	--	--	--
	CH_3CN	2.33-3.00	--	--	6.05	--	--	--
2-Methyl-2-(3'-thianaphthenyl)-1,3-dioxolane	CCl_4	1.97-2.94	8.28	--	6.22	--	--	--
2-Phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane	CCl_4	2.26-3.00	--	--	6.06**	--	--	--

*A_2B_2 multiplet.

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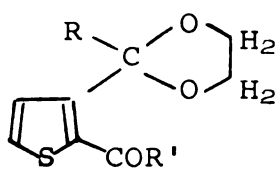
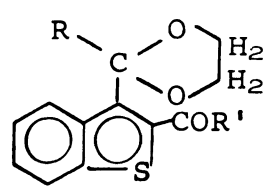
The dioxolane lithium mixtures in hexane-ether were treated at -30° with an equivalent amount of N,N-dimethylacylamide in ether over a ten minute period. Aqueous ammonium chloride readily accomplished the hydrolysis of the thienyl or thianaphthenyl lithium-N,N-dimethylacylamide complex without hydrolysis of the dioxolane ring. The hydrolysis to obtain 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane was accomplished with 10% aqueous hydrochloric acid without cleavage of the dioxolane ring. UV, IR and NMR spectra of these intermediates indicated 2,3-disubstitution of the thiophene ring (see discussion below).

These reactions usually produced, on removal of the solvent by distillation, dark brown semi-crystalline products. Particularly, dark intractable materials were obtained in the synthesis of 2-(2'-acetyl-3'-thienyl)-1,4-dioxolane, LIX, 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LX, 2-phenyl-2-(2'-formyl-3'-thienyl)1,3-dioxolane, LXIII, and 2-methyl-2-(2'-formyl-3'-thianaphthenyl)1,3-dioxolane, LXV. These



	R	R'
LVIII	H	H
LIX	H	CH_3
LX	H	C_6H_5
LXI	CH_3	H
LXII	CH_3	C_6H_5
LXIII	C_6H_5	H
LXIV	C_6H_5	C_6H_5



	R	R'
LXV	CH_3	H
LXVI	C_6H_5	H

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products were purified by a variety of procedures. For many of these products, repeated crystallizations from aqueous alcohols using activated charcoal was sufficient. 2-(2'-Formyl-3'-thienyl)-1,3-dioxolane, LVIII, and 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXI, were distilled under reduced pressure. 2-(2'-Acetyl-3'-thienyl)-1,3-dioxolane, LIX, was sublimed at 50-60^{o} under 0.5 mm. Hg. of pressure. 2-Phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LXIV, 2-methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, LXV, and 2-phenyl-2-(2'-formyl-3'-thianaphthenyl-1,3-dioxolane, LXVI, were unusual in that rather clean reaction products were obtained directly. The latter preparation was rather unusual in that the thienyl analog, i.e., 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXIII, was the most sensitive reaction to conduct in the entire series. 2-Phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane had to be isolated immediately from reaction residues, as prolonged contact with the reaction mixture appeared to cause complete conversion of the product within a week to resinous oils from which no product could be isolated.

The isolated yields of crystalline products varied from 32% for 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXIII, to 81% for 2-methyl-2-%2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, LXV. The majority of these preparations were greater than 50% in yield of isolatable products. As the substituent groups became larger, i.e., from hydrogen to

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methyl to phenyl, in 2-substituted-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, the yields decreased from 71% to 32% of isolatable product. The same results were found in comparing 2-methyl and 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolanes (81% and 57% respectively) and 2-hydrogen, 2-methyl and 2-phenyl-2-(2'-benzoyl-3'-thienyl)-1,4-dioxolanes (49, 38 and 32% respectively). Substitution of a thianaphthene ring for the thiophene moiety in 2-methyl and 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolanes improved the yield 10-20% with cleaner, less tar-like products.

While this work was in progress, Robba et al. (55) prepared 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane, LIX, and 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXI, by a method similar to the one reported in this work. Though the physical constants agreed with their report, they presented little spectroscopic evidence for these two compounds. Evidence for these two compounds, together with the remaining compounds, is presented below in the discussion on the spectral properties of carbonyl substituted thienyl and thianaphthenyl dioxolanes.

Spectral Properties of Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

The ultraviolet maxima together with carbonyl and C-O-C stretching frequencies are summarized in Table 3 for these carbonyl substituted thienyl and thianaphthenyl dioxolanes.

Table 3. UV and IR Spectral Data for Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

Compound	UV (EtOH) λ_{max} (mμ)	UV (EtOH) (ε)	IR (CCl_4) $\nu_{(C=O)}$ (cm^{-1})	IR (CCl_4) $\nu_{(C-O-C)}$ (cm^{-1})

Table 3. UV and IR Spectral Data for Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

Compound	UV (EtOH) λ_{max} (ϵ) (mμ)	IR (CCl_4) $\nu_{(C=O)}$ (cm^{-1})	IR (CCl_4) $\nu_{(C-O-C)}$ (cm^{-1})
2-(2'-Formyl-3'-thienyl)-1,3-dioxolane	268; 288(sh) (20,640; 10,980)	1660	1115, 1090
2-(2'-Acetyl-3'-thienyl)-1,3-dioxolane	268; 280(sh) (13,780; 12,340)	1672	1118, 1095
2-(2'-Benzoyl-3'-thienyl)-1,3-dioxolane	263, 287 (12,540; 11,190)	1650	1110
2-Methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane	270 (14,000)	1660	1050
2-Methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane	252; 284sh (15,420; 6,650)	1665	1055
2-Phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane	278 (10,512)	1688	1095, 1085 sh
2-Phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane	252 (14,420)	1665	1110
2-Methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane	233; 252; 302 (18,100; 15,040; 20,370)	1660	1055
2-Phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane	232; 250; 307 (15,870; 10,980; 15,320)	1640	1080

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The UV spectra of 2-(2-formyl, 2'-acetyl and 2'-benzoyl-3'-thienyl)-1,3-dioxolanes, LVIII, LIX and LX, show maxima respectively at 268, 268 and 263 mμ together with secondary bands which appear as shoulders in the former two compounds. These values compare to the maxima of 260, 260 and 263 mμ respectively for 2-thenal (75), 2-acetothienone (75), and 2-benzoylthiophene (77). Apparently, the introduction of the 2-dioxolanyl group into the 3' (or ortho) position of the thiophene ring has done little to interfere with resonance of the carbonyl function into the thiophene ring. The presence of the dioxolanyl ring gave a bathochromic shift of 8 mμ for 2-(2'-formyl and 2'-acetyl-3'-thienyl)-1,3-dioxolanes, in comparison to unsubstituted 2-thenal and 2-acetothienones (see Figure 7). The substitution of methyl and phenyl groups for hydrogen in the 2-position of the dioxolane ring in 2-(2'-formyl-3'-thienyl)-1,3-dioxolane shows an increased bathochromic shift; a shift of 10 mμ is observed in the latter case when a phenyl is substituted for hydrogen. The size of the 2-phenyl-2-dioxolanyl group in the 3-position of 2-thenal does not greatly affect the resonance ability of the carbonyl function with thiophene, or in other words, this group does not appear to stabilize the excited states observed in the UV spectrum (see Figure 8). The steric effect in hindering a carbonyl group's resonance is shown in 2-phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane where a hypsochromic shift of 11 mμ is observed in substituting the

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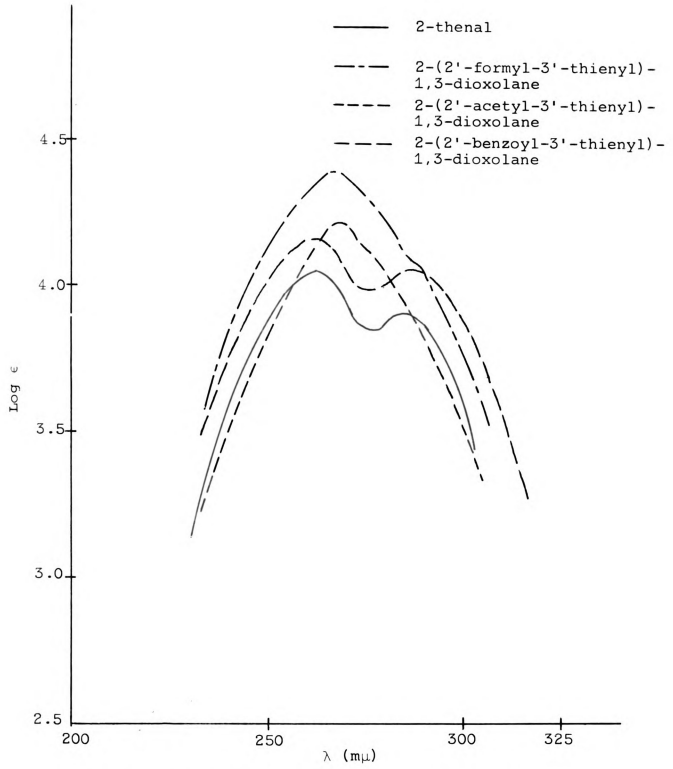

Figure 7. Ultraviolet spectra of 2-thenal and some 2-(2'-acyl-3'-thienyl)-1,3-dioxolanes.

Figure 8.

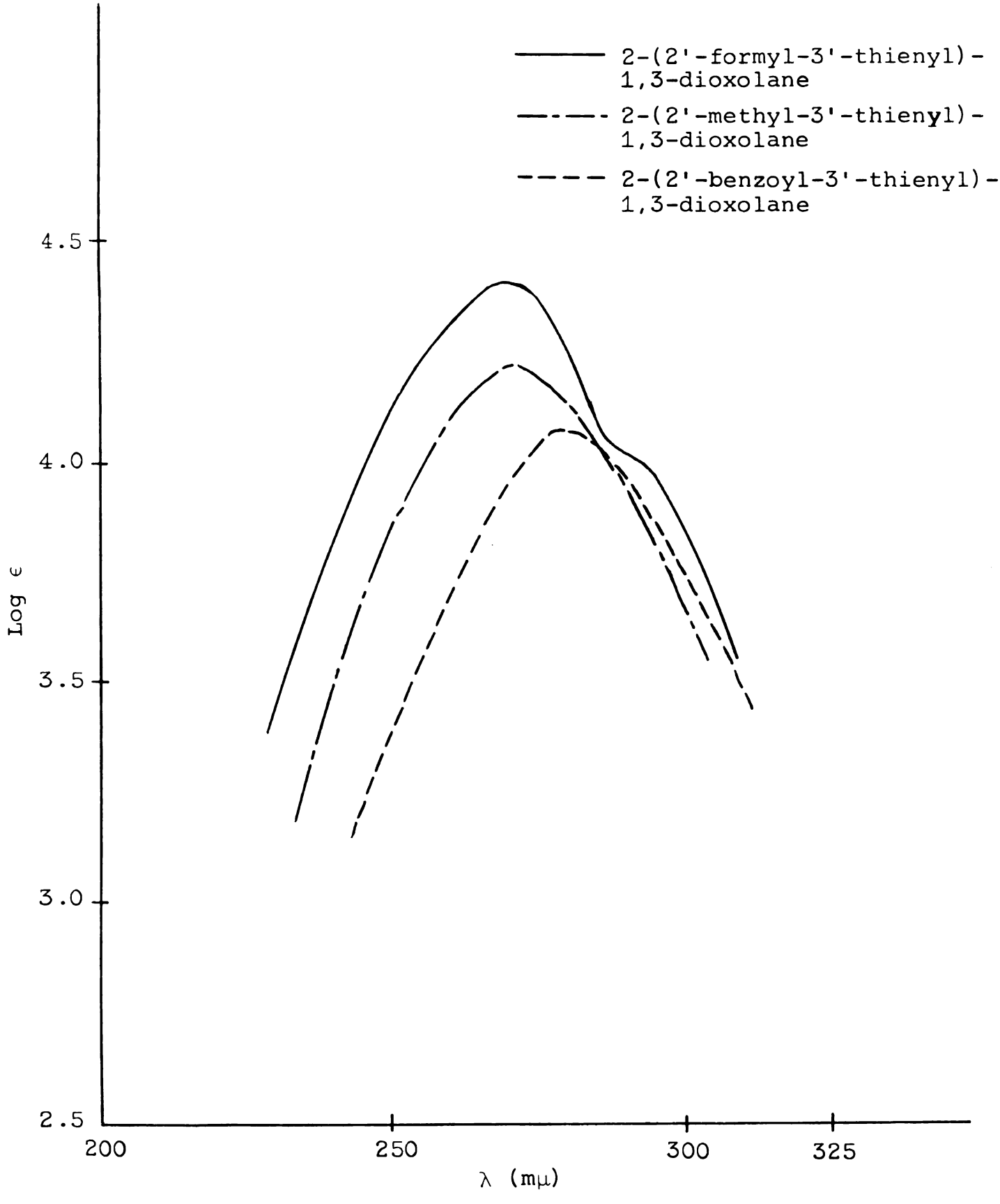

Figure 8. Ultraviolet spectra of some 2-substituted-2-(2'-formyl-3'-thienyl)-1,3-dioxolanes.

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2-phenyl-2-dioxolanyl in the 3-position of 2-benzoylthiophene (see Figure 9). In the case of 2-methyl and 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolanes, the latter four maxima at longer wavelengths of thianaphthene (see Table 1) are submerged by the higher extinction $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transitions, respectively at 250 mμ and 305 mμ, of the carbonyl group substituted in thianaphthene.

In the infrared spectra of the carbonyl substituted thienyl and thianaphthenyl dioxolanes, the effect of 2-hydrogen, 2-methyl and 2-phenyl-2-dioxolanyl groups in the 3-position of 2-thenal, 2-acetothienone and 2-benzoylthiophene follows the same general pattern as was shown in their UV spectra. For example, the carbonyl stretching frequency of 2-(2'-formyl-3-thienyl)-1,3-dioxolane and 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, shows a shift to longer wavelengths of approximately 10 cm^{-1} when compared to the carbonyl frequency of 1673 cm^{-1} for 2-thenal (78); it has shifted 13 cm^{-1} to shorter wavelengths in 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane. A similar effect is also seen in the successive substitution of the 2-dioxolanyl, 2-methyl-2-dioxolanyl and 2-phenyl-2-dioxolanyl groups in the 3-position of 2-benzoylthiophene, whereas shifts to higher frequencies of 30-51 cm^{-1} are observed from the monosubstituted 2-benzoylthiophene value of 1636 cm^{-1}. The opposite effect was found in 2-methyl and 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolanes where substitution of the

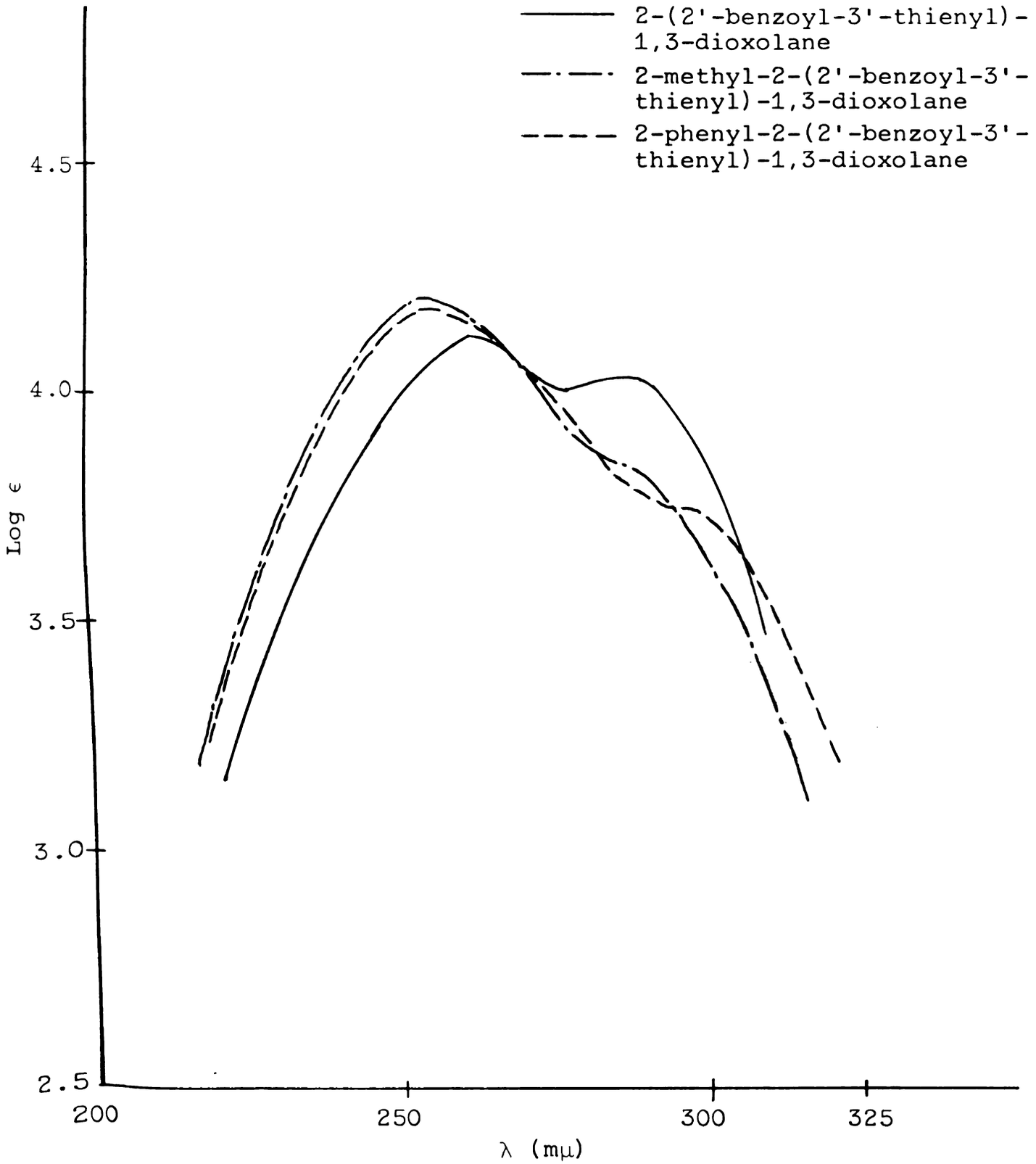

Figure 9. Ultraviolet spectra of some-2-substituted-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolanes.

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larger 2-phenyl-2-dioxolanyl group for the 2-methyl-2-dioxolanyl group gave a carbonyl frequency shift to longer wavelengths of 20 cm^{-1}.

Maxima observed for the dioxolane asymmetric C-O-C stretching are also given in Table 3. These maxima can appear as a multiplet of 4-5 bands, however in this study, only those bands with the largest extinction are listed. Little variation appears in the principal C-O-C stretching band by changing substituent groups in the 2-position of the dioxolane ring. However, the presence of a methyl rather than hydrogen or phenyl causes a shift to longer wavelengths of approximately 55-60 cm^{-1}. In general, as the steric requirement of a substituent or group becomes larger, a shift to shorter wavelengths is observed in the C-O-C stretching frequency of the dioxolanes. The infrared spectra of carbonyl substituted thienyl and thianaphthenyl dioxolanes determined as 10 (w./v.) percent solutions are reproduced in Figures 10-18.

The studies of NMR spectra of thiophenes has attracted considerable interest since substituted thiophenes contain only a few hydrogens, and as a consequence are readily analyzed giving information of electron distribution about chemically (or magnetically) non-equivalent hydrogen. From such information, considerable knowledge has been obtained and unequivocal structure assignments for the positions of substituents on the thiophene ring can be made based on the

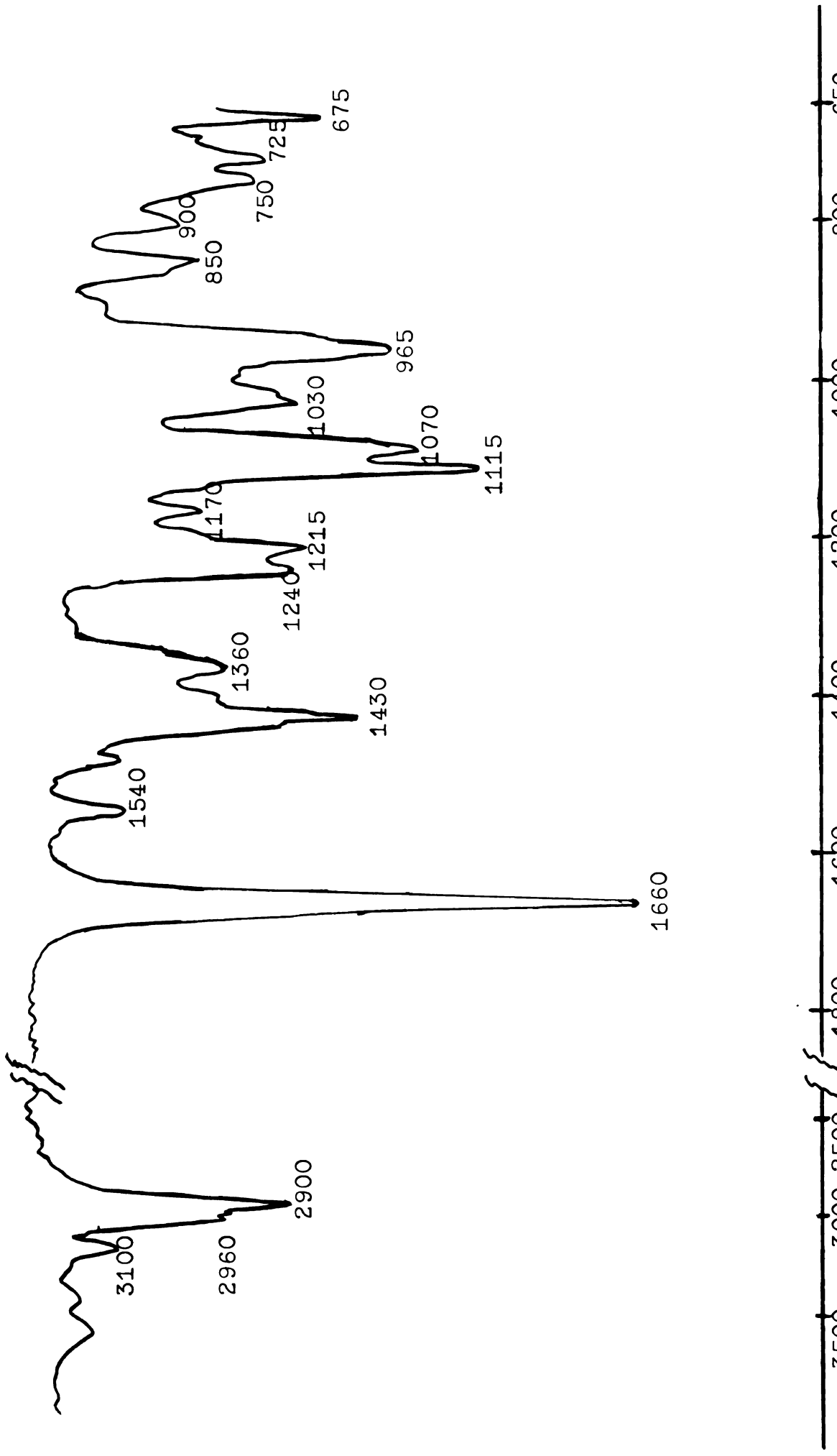

Figure 10. Infrared spectra of 2-(2'-formyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.


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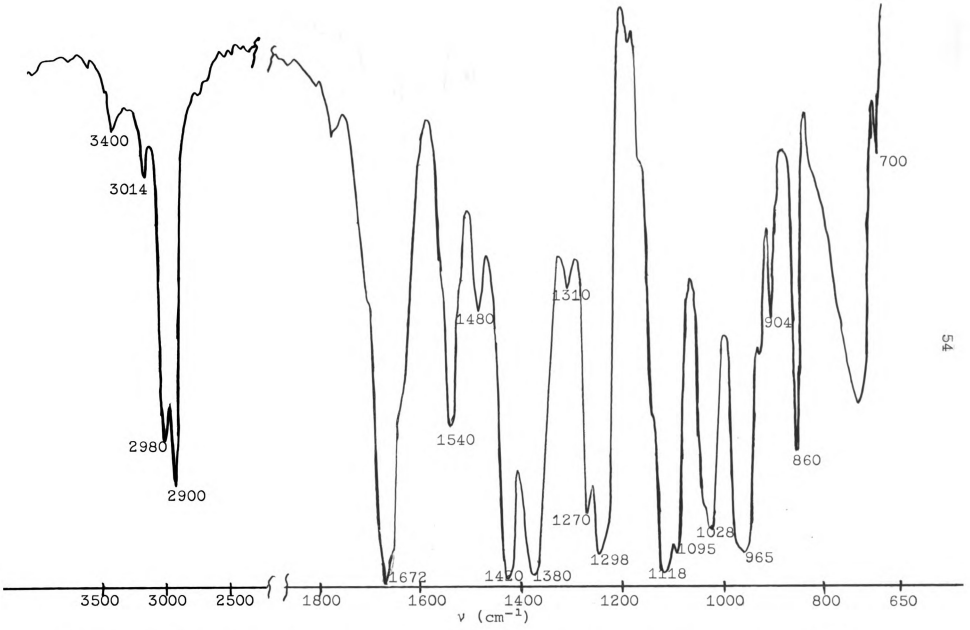


Figure 11. Infrared spectra of 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

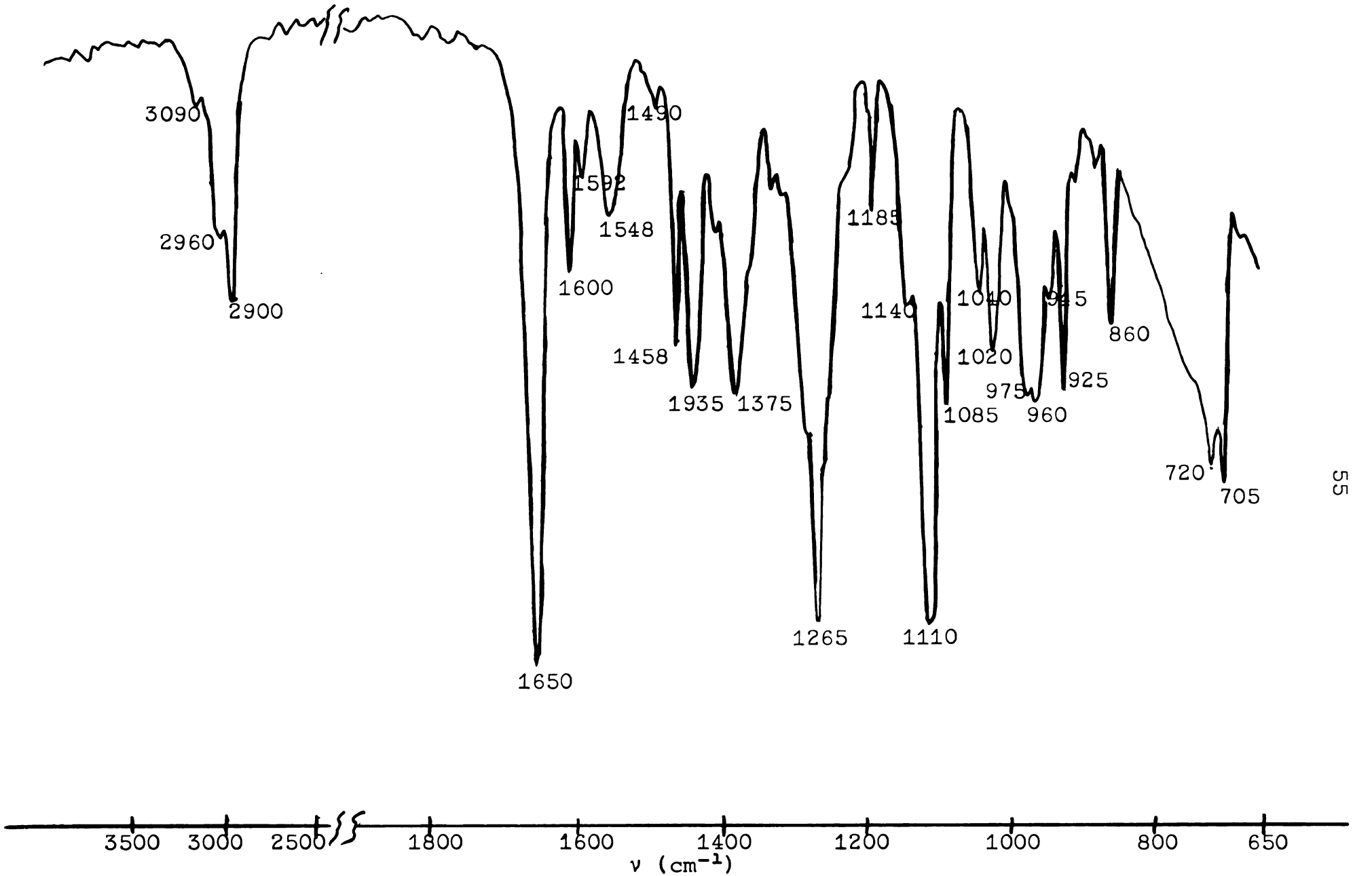


Figure 12. Infrared spectra of 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

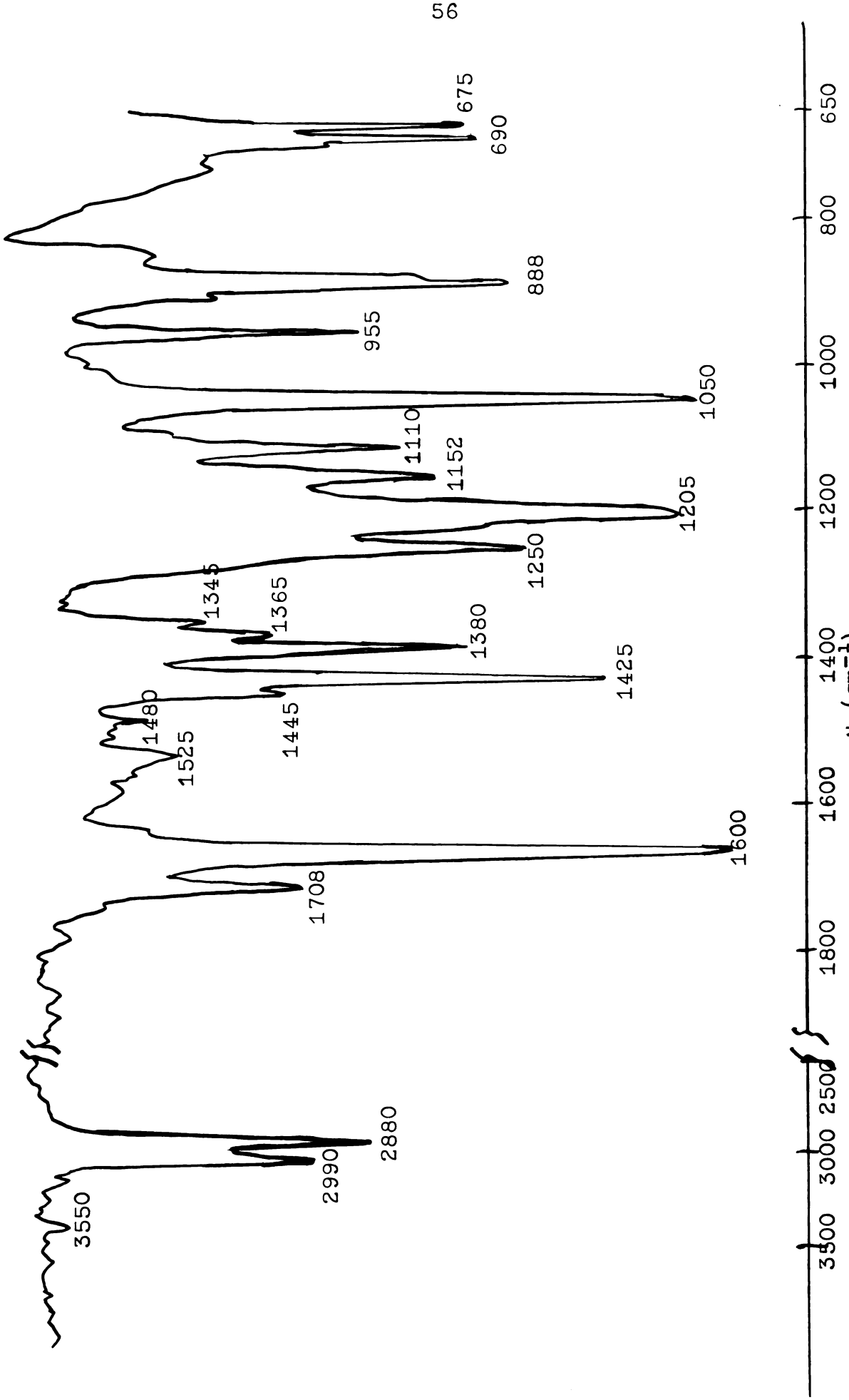


Figure 13. Infrared spectra of 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

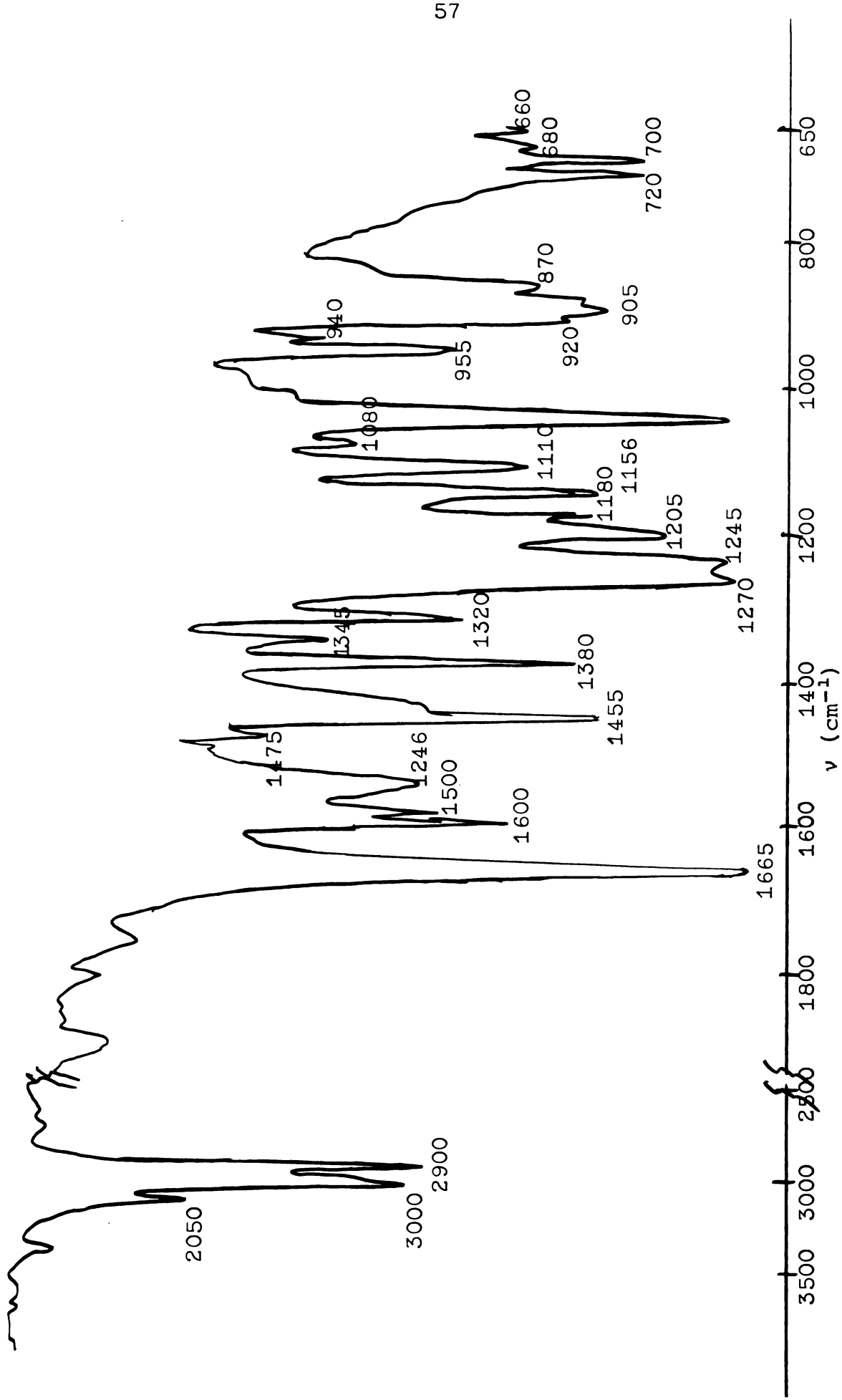


Figure 14. Infrared spectra of 2-methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

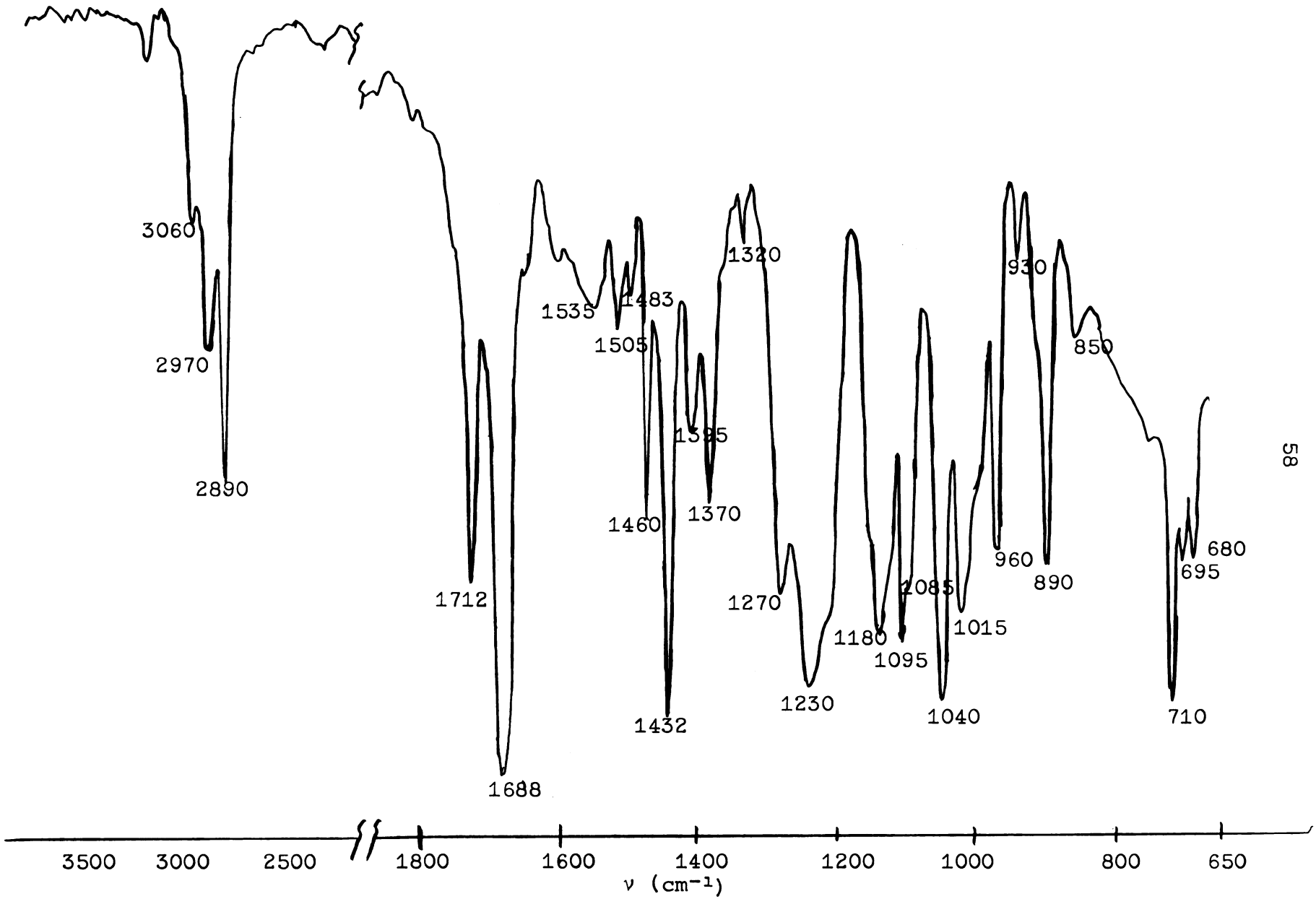


Figure 15. Infrared spectra of 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

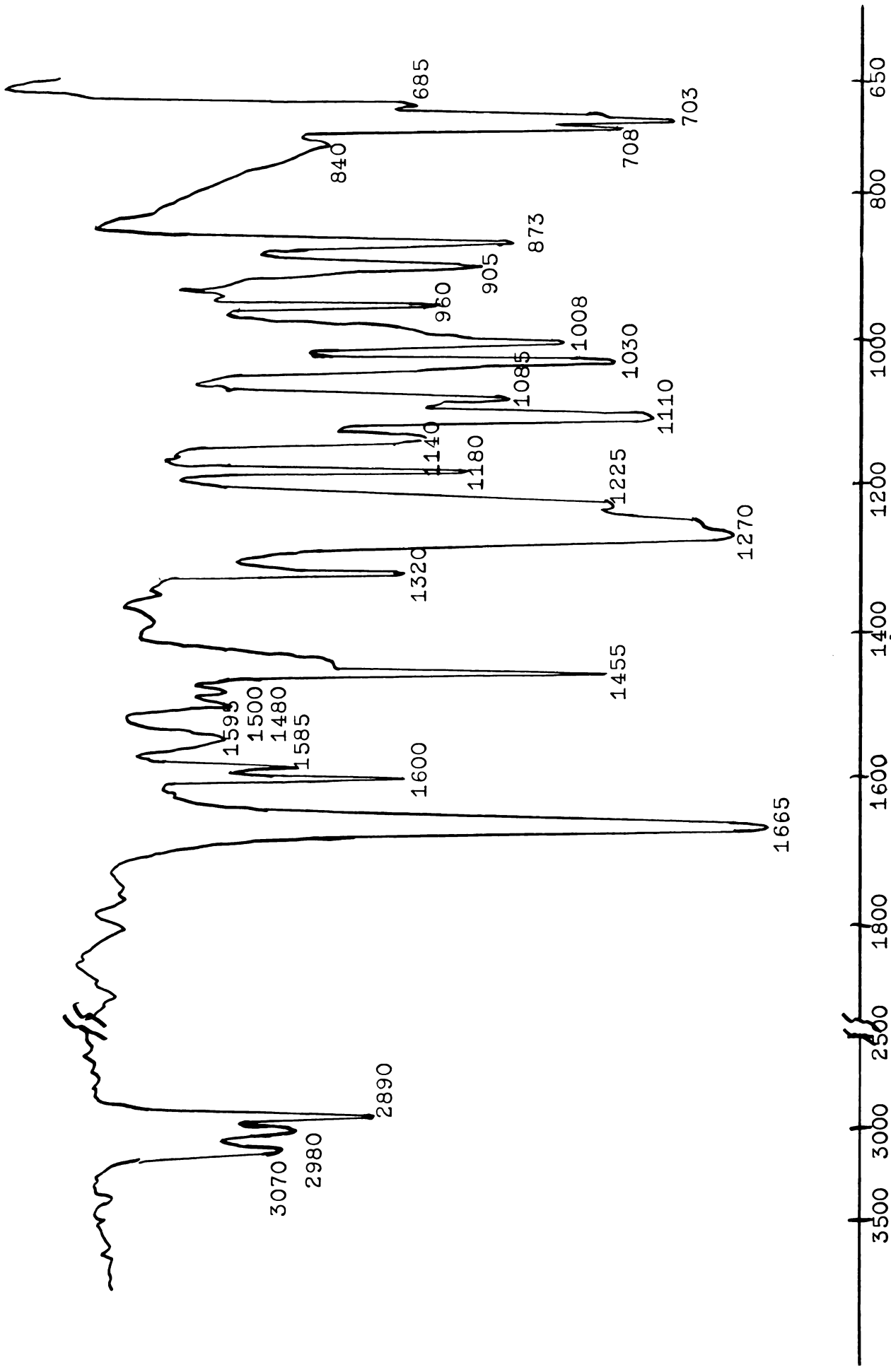


Figure 16. Infrared spectra of 2-phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane taken in CCl_4.

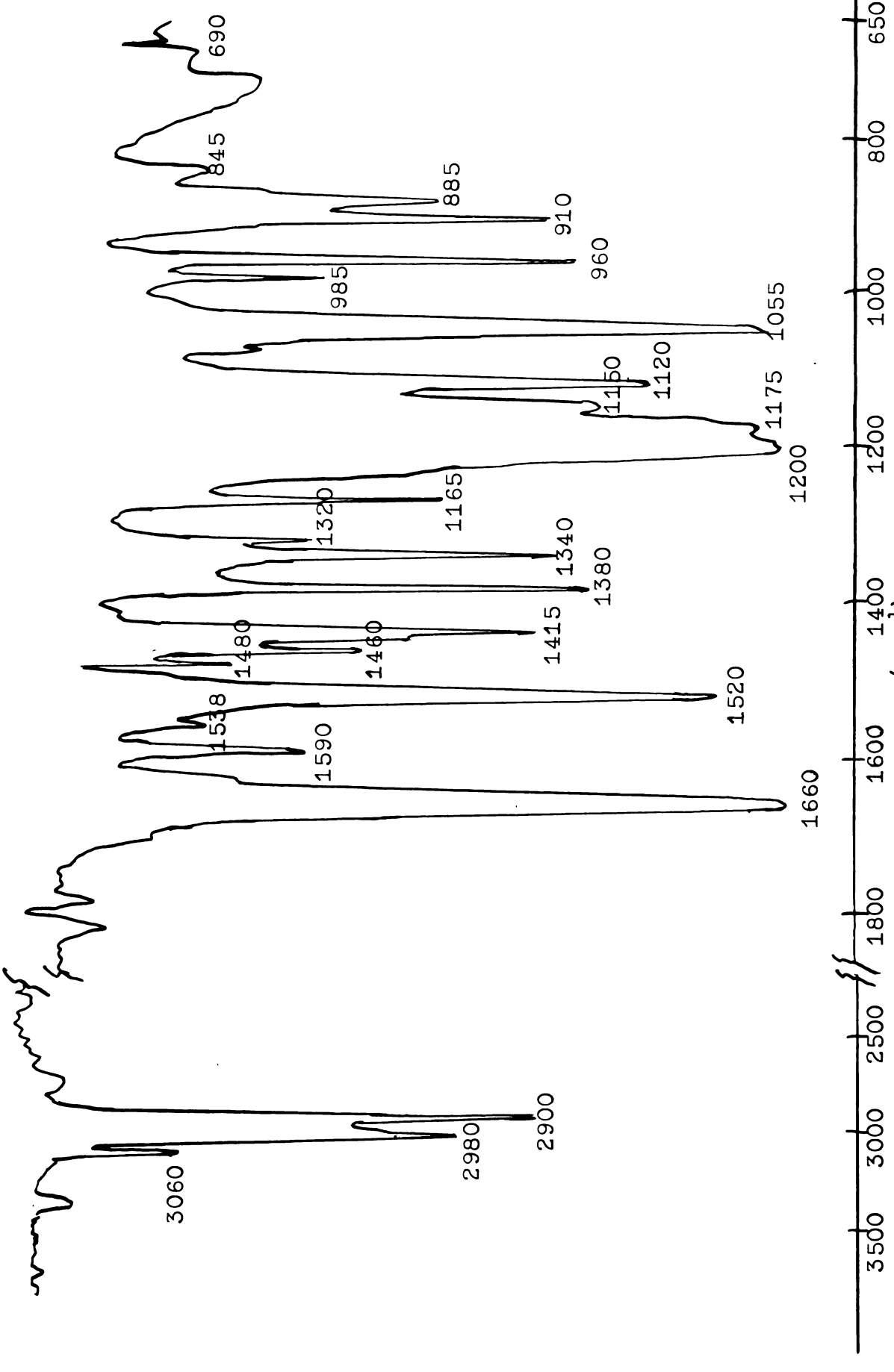


Figure 17. Infrared spectra of 2-methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane taken in CCl_4.

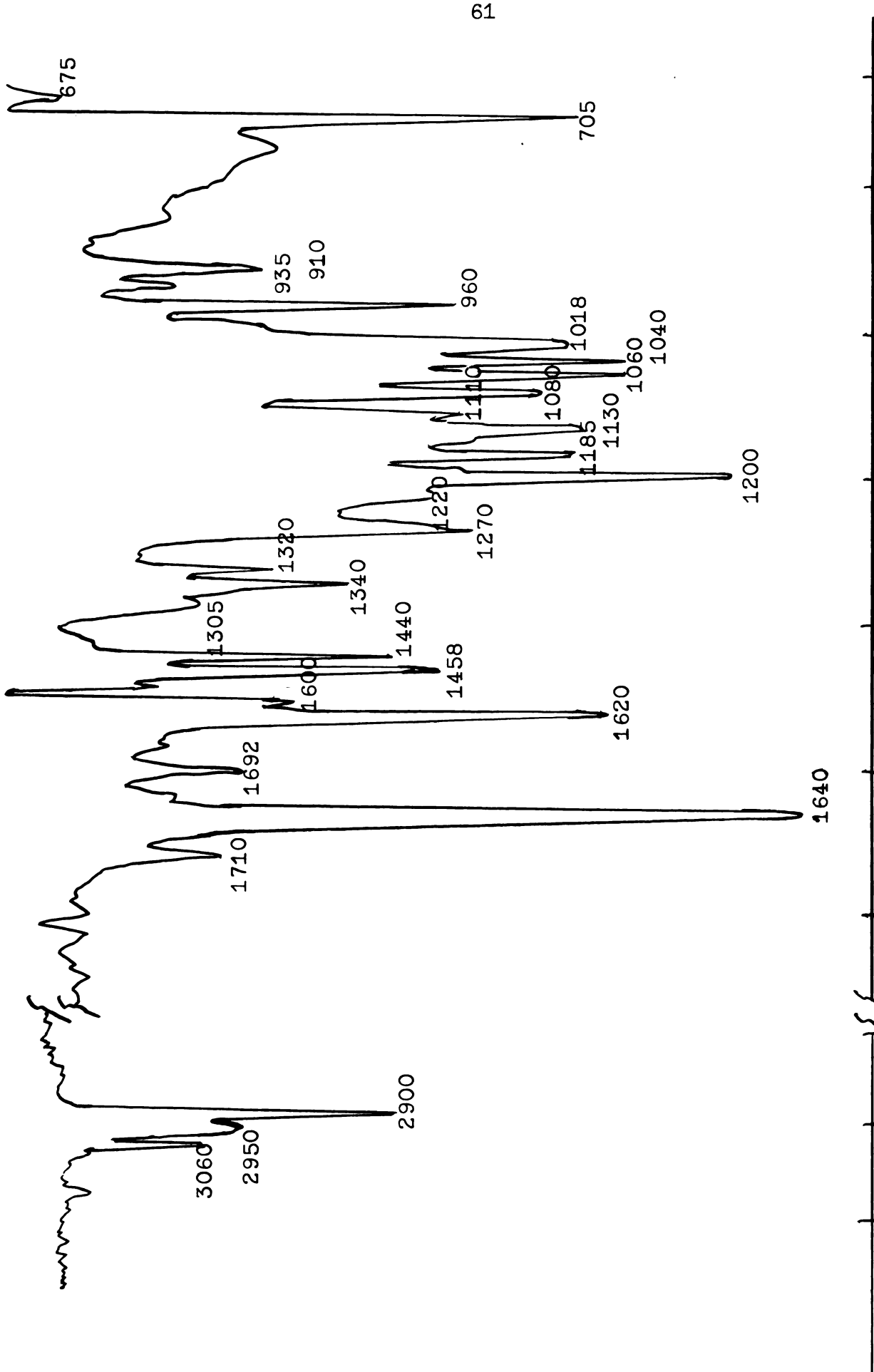


Figure 18. Infrared spectra of 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane taken in CCl_4.

splitting or coupling constants of the thiophene hydrogens. Gronowitz (ref. 3, p. 8) has observed, based on the study of 36 monosubstituted and 65 disubstituted thiophenes, that the coupling constants, all of equal sign, fall in four distinct regions: J_{35} = 1.25-1.70 cps; J_{25} = 3.20-3.65 cps; J_{34} = 3.45-4.35 cps and J_{45} = 4.90-5.80 cps. Structural assignments are made on the basis of these observations. Table 4 summarizes the NMR data on the carbonyl substituted thienyl and thianaphthenyl dioxolanes, prepared in the course of this investigation. One of the more interesting spectra, that of 2-(2'-formyl-3'-thienyl)-1,3-dioxolane in CH_3CN is shown as Figure 19 and demonstrated the applicability of the NMR to structure determination in these types of compounds. The coupling constant for the aldehydic proton at -0.24 τ (or 11.76 δ) is 1.2 cps and is coupled with hydrogen 5 of the thiophene ring. Hydrogen 5 is also split by hydrogen 4 (J_{24} = 5.15 cps); by the aldehydic hydrogen (J_{CHO_2-5} = 1.2 cps) and to a slight degree, it is split by the acetal hydrogen ($J \cong 0.3$ cps). It is interesting to note that by changing to a non-polar solvent, CCl_4, the latter slight coupling by the acetal hydrogen to hydrogen 5 disappeared. Hydrogen 4 shows coupling with hydrogen 5 plus coupling with the acetal hydrogen ($J_{CH-4} \cong 0.35$). Again this latter slight coupling also disappeared when the spectrum was determined in CCl_4. For this compound and 2-(2'-acetyl-3-thienyl)-1,3-dioxolane and 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, the

Table 4. NMR Spectral Data for Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

Compound	Solvent	τ* H_4	H_5	H_2	H_3	$H_{(OCH_2)_2}$**	J J_{45}	J_{CHO-5}	$J_{CH(OCH_2)_2-5}$
2-(2'-Formyl-3'-thienyl)-1,3-dioxolane	CCl_4	2.80	2.22	-0.20	3.86	6.01	5.10	1.2	-- --
	CH_3CN	2.70	2.22	-0.24	3.76	5.95	5.15	1.2	0.3 $J_{CH(OCH_2)_2-4}$ = 0.30
2-(2'Acetyl-3'-thienyl)-1,3-dioxolane	CCl_4	2.77	2.66	7.50 (CH_3)	3.68	6.02	5.20	---	0.3 --
	CH_3CN	2.66	2.38	7.38 (CH_3)	3.60	6.02	5.25	---	0.35 $J_{(CH)_3-4}$ = 0.25
2-(2'-Benzoyl-3'-thienyl)-1,3-dioxolane	CCl_4	2.66	---	---	3.93	6.10	5.25	---	---
	CH_3CN	2.70	---	---	3.90	6.05	5.20	---	---
2-Methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane	CCl_4	2.88	2.45	-0.33	8.28 (CH_3)	6.03	5.20	1.2	---
	CH_3CN	2.77	2.23	-0.39	8.28 (CH_3)	6.03	5.20	1.2	---
2-Methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane	CCl_4	3.00	(2.72)	---	8.40 (CH_3)	6.35	5.20	---	---
	CH_3CN	2.87	(2.48)	---	8.37 (CH_3)	6.32	5.10	---	---
2-Phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane	CCl_4	2.82	(2.50)	-0.35	---	5.97	5.20	1.3	---
	CH_3CN	2.73	(2.27)	-0.40	---	5.88	5.20	1.4	---
2-Phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane	CCl_4	3.12	---	---	---	6.33	5.20	---	---
	CH_3CN	2.98	---	---	---	6.27	5.20	---	---
2-Methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane	CCl_4	---	---	-0.68	8.20 (CH_3)	5.98	---	---	---
	CH_3CN	---	---	-0.75	8.13 (CH_3)	6.00	---	---	---
2-Phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane	CCl_4	---	---	-0.73	---	5.88	---	---	---
	CH_3CN	---	---	-0.87	---	5.92	---	---	---

*Tetramethyl silane used as a internal solvent.

**Center of A_2B_2 symmetrical multiplet.

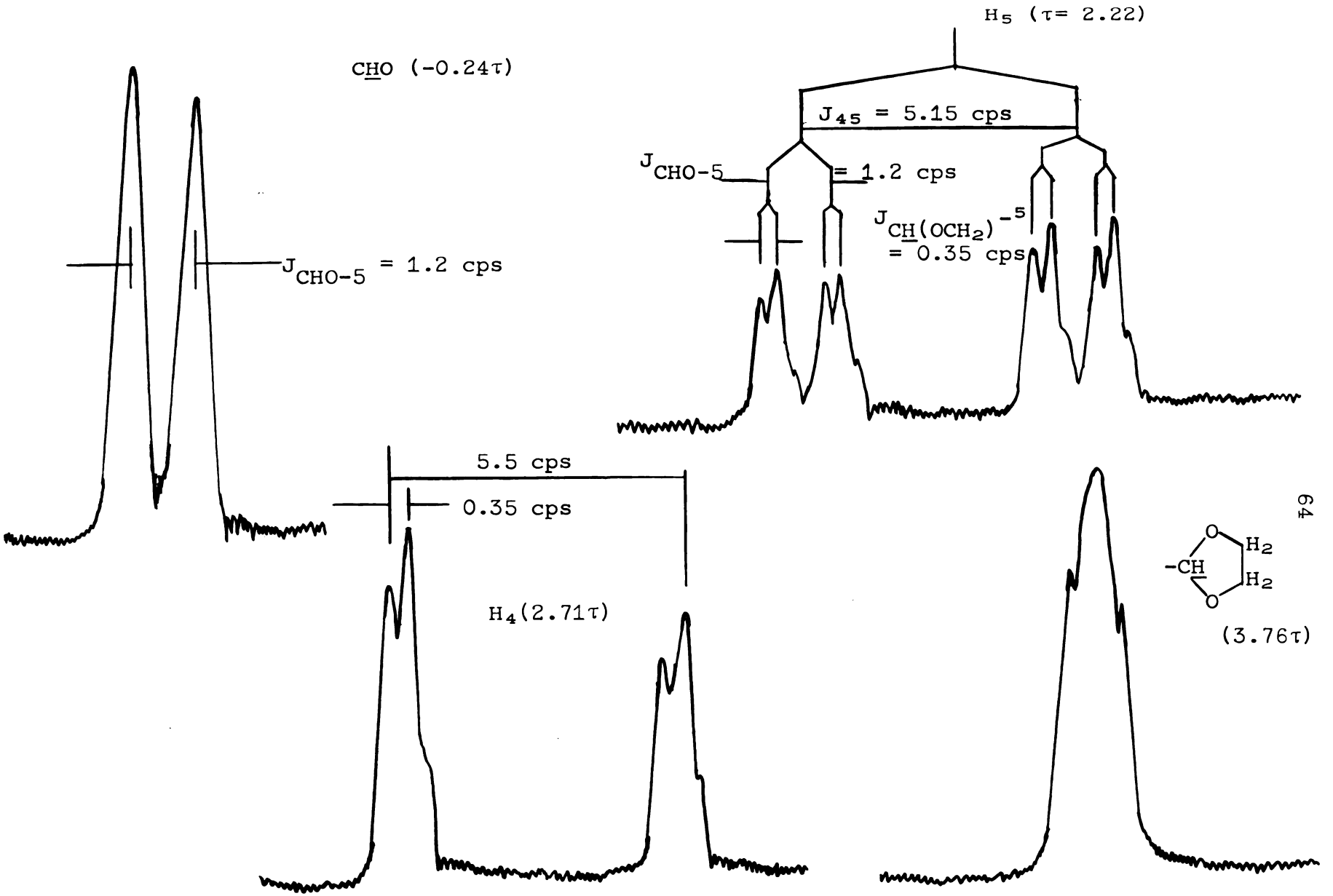


Figure 19. NMR spectra of 2-(2'-formyl-3'-thienyl)-1,3-dioxolane taken in CH_3CN.

coupling constants were found to be J_{45} = 5.10-5.25, J_{CHO-5} = 1.2, indicating these compounds are definitely 2,3-disubstituted thiophenes.

In these NMR studies, the appearance of the aromatic protons appeared between 2.00-3.5 τ and the acetal hydrogen appeared at 3.60 τ - 3.95 τ (generally as a singlet). The ketal methyl group at 8.28 τ - 8.40 τ (singlet) was considerably upfield from acetyl methyl which appeared as a sharp unsplit singlet at 7.38 τ - 7.50 τ. The dioxolane hydrogen appeared as a symmetrical A_2B_2 multiplet of varying band width; the center of these multiplets varied from 5.88 τ - 6.35 τ. The effect of changing the solvent from CCl_4 to a polar solvent CH_3CN, generally shifted the more "acidic" protons downfield.

The problem of assigning the τ values for thiophene hydrogens in compounds containing phenyl substituents is complicated by the overlapping resonances of the phenyl protons. Portions of the aromatic region in the NMR spectrum in CCl_4 and CH_3CN solvents are reproduced in Figures 20-23 respectively for 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LX, 2-methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LXII, 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXIII, and 2-phenyl-2-(2'-benzoyl-3'-thienyl)1,3-dioxolane, LXIV. A common NMR characteristic for these types of compounds, appears to be a doublet in the upfield portion of the aromatic region. This characteristic is quite evident in Figure 21 and 23. The couplings for these doublets are 5.10-5.20 cps

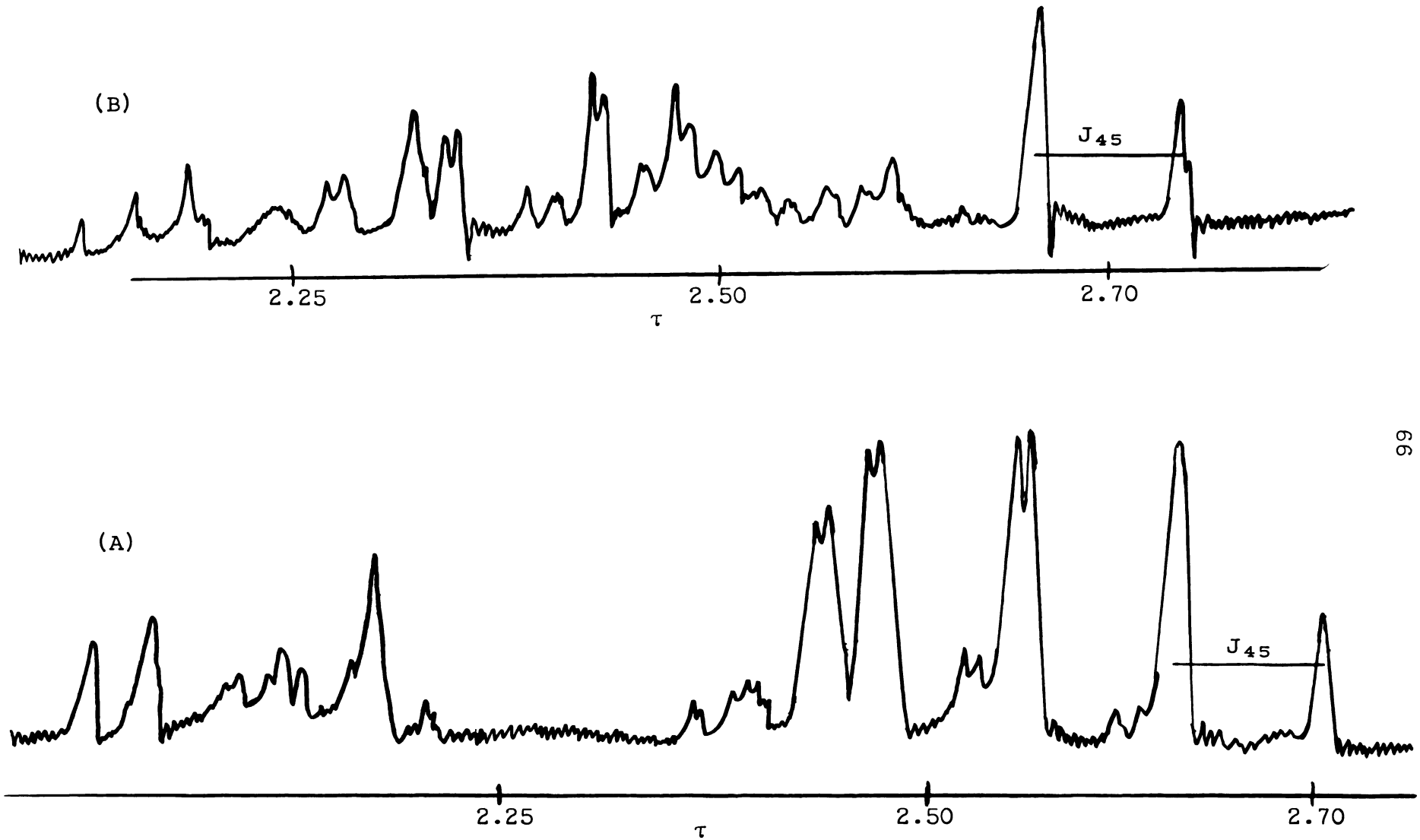


Figure 20. NMR spectrum of the aromatic hydrogens of 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane: (A) 20 (w./v.)% in CCl_4 solvent; (B) 20 (w./v.)% in CH_3CN solvent.

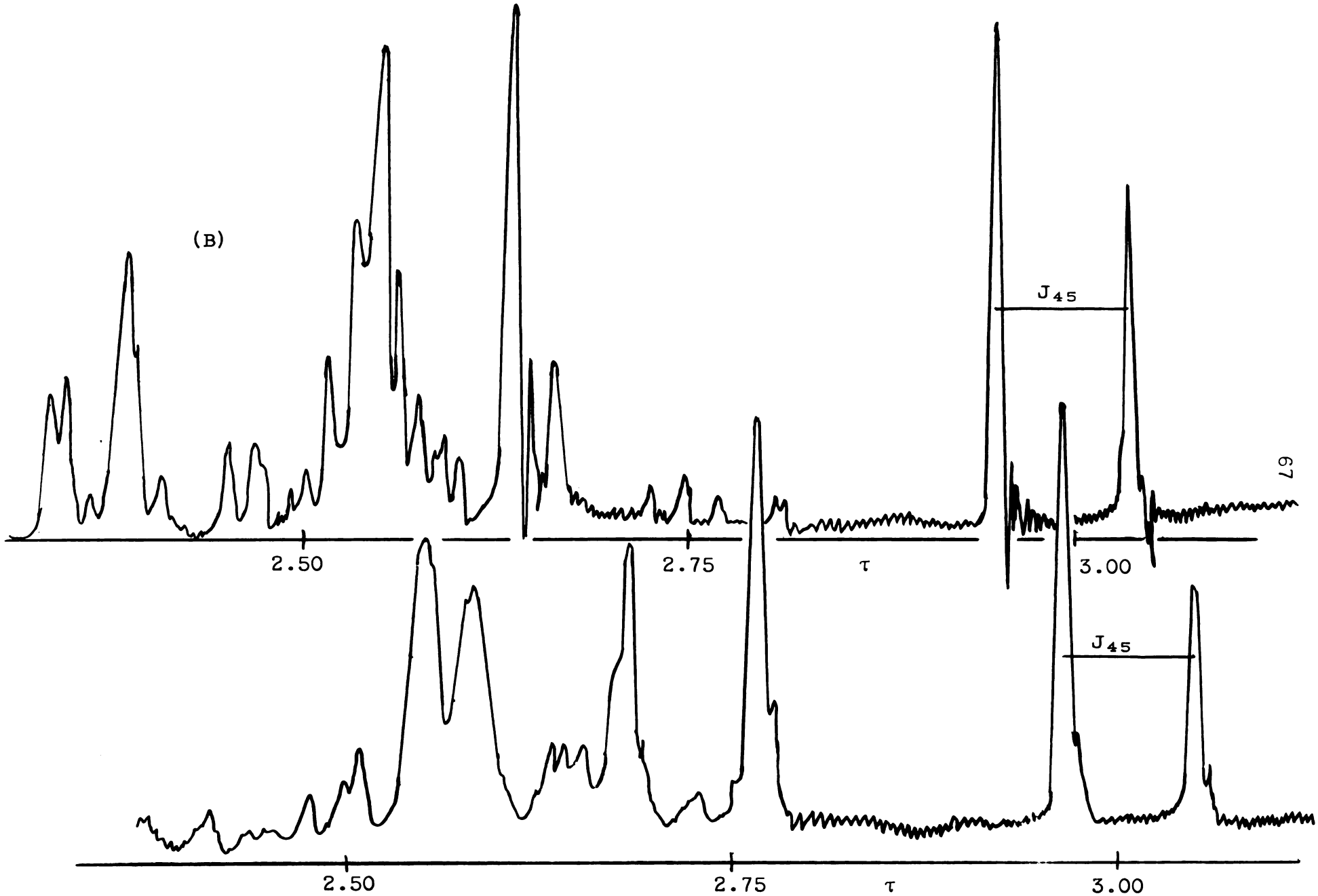


Figure 21. NMR spectrum of the aromatic hydrogens of 2-methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane: (A) 20 w./v.% in CCl_4; (B) 20 w./v.% in CH_3CN solvent.

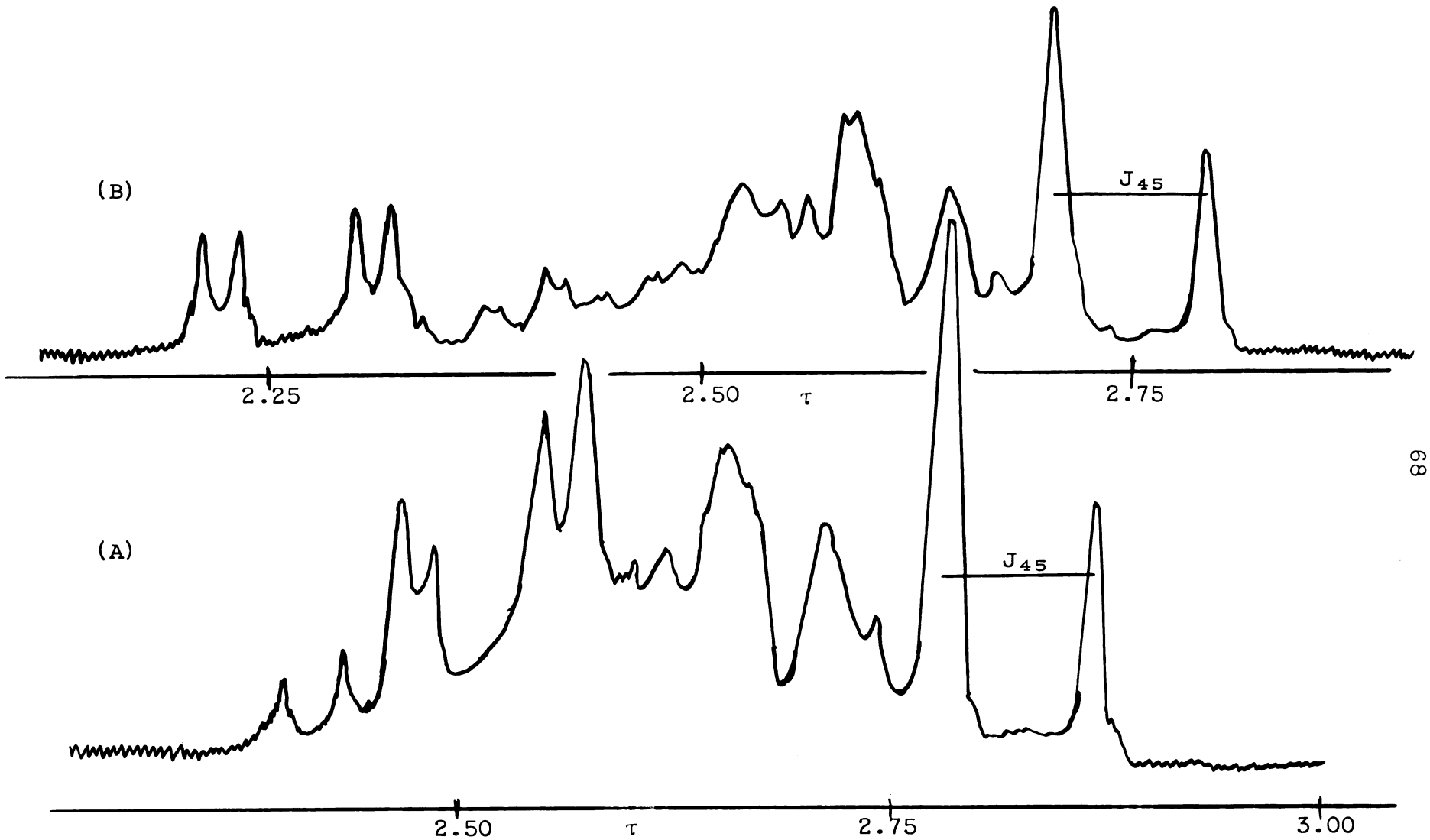


Figure 22. NMR spectrum of the aromatic hydrogens of 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane: (A) 20(w./v.)% in CCl_4; (B) 20(w./v.)% in CH_3CN solvent.

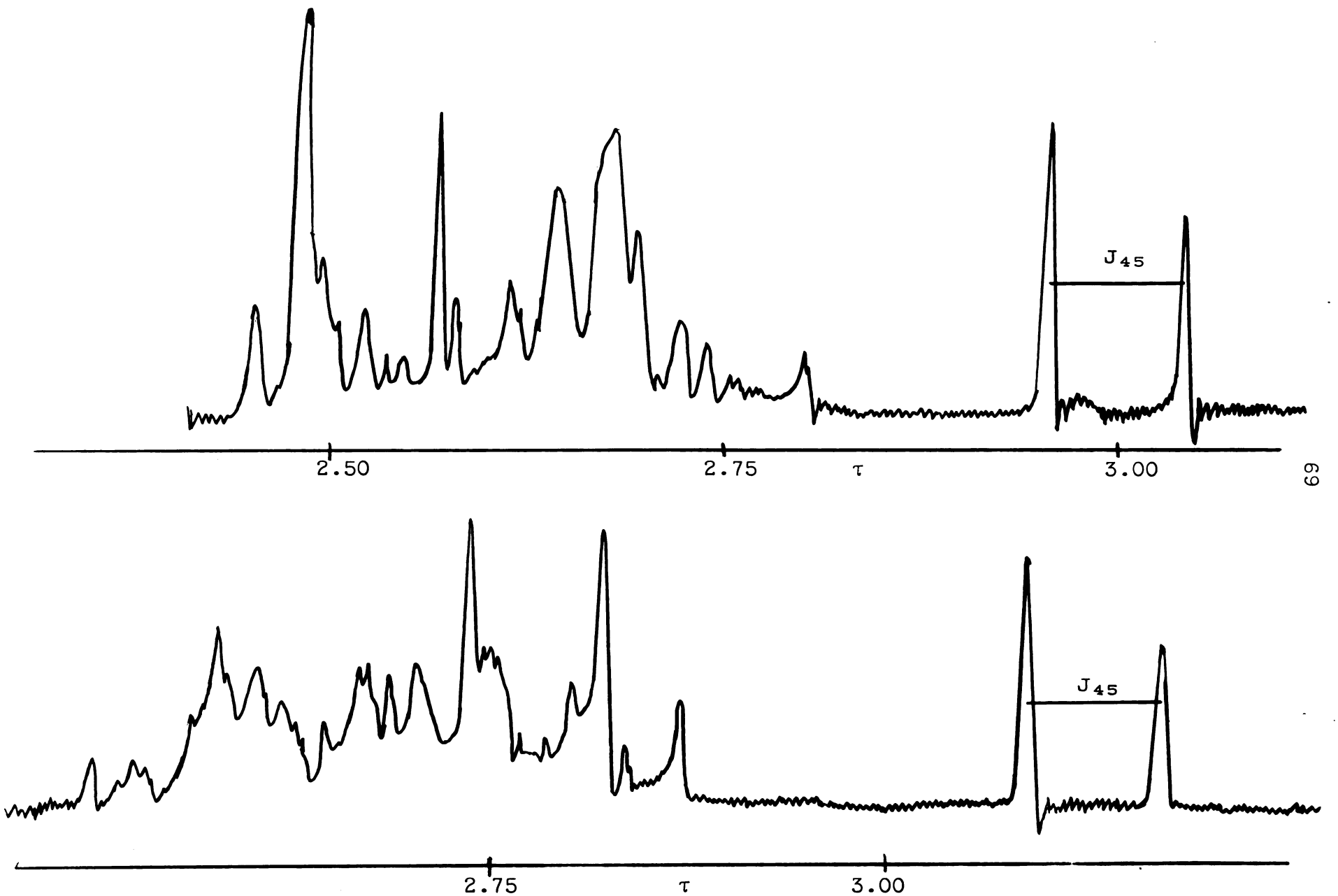


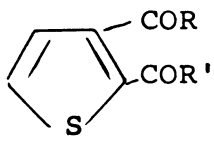
Figure 23. NMR spectrum of the aromatic hydrogens of 2-phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane: (A) 20(w./v.)% CCl_4 solvent; (B) 20(2./v.)% CH_3CN solvent.

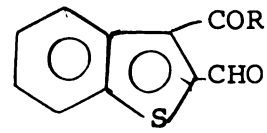
and are attributed to hydrogen 4 of the thiophene ring. The recent work of both Kaper et al., (79) and Martin et al., (80) have indicated that the chemical shift of hydrogen 4 of the thiophene ring of several 2-benzoylthiophenes was consistently observed in the upfield portion of the aromatic region of the NMR spectrum. The coupling constants were also found to be similar to those observed in this work, i.e., J = 5.0 - 5.4 cps. In Figure 22 the partial spectra of 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane in CH_3CN, the downfield quartet appears to be hydrogen 5 as the observed splitting is J = 1.4 cps and 5.2 cps. Though the evidence is not unequivocal in the case of these compounds, there are strong indications that these compounds are indeed 2,3-disubstituted thiophenes.

Both 2-methyl and 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolanes show the 2-aldehydic hydrogen at slightly downfield values (-0.68 τ to -0.78 τ) than their corresponding thienyl analogs. There is little reason to doubt the 2,3-disubstituted thianaphthene structure, due more so to chemical reasons, i.e., occurrence of metallation in the benzene part of thianaphthene appears unlikely when the 2-position of thianaphthene is available for hydrogen-metal interchange.

Hydrolysis of Carbonyl Substituted Thienyl and Thianaphthenyl Dioxolanes

Hydrolysis of the carbonyl substituted thienyl and thianaphthenyl dioxolanes to their corresponding 2,3-thienyl and 2,3-thianaphthenyl dicarbonyls was accomplished under rather mild conditions. For example, 80-100 ml. of a 0.5 molar solution of the carbonyl thienyl or thianaphthenyl dioxolane in acetone was stirred for two to two and one-half hours at ambient temperatures in contact with 5-10 ml. of 10% aqueous hydrochloric acid. This procedure was sufficient to hydrolyze all the dioxolanes in nearly quantitative yields with isolatable yields of 65-90%. The products obtained were clean crystalline materials with two exceptions, 2-benzoyl-3-formylthiophene, LXIX and 2-formyl-3-acetyl-thianaphthene, LXXIV.





	R	R'
LXVII	H	H
LXVIII	H	CH_3
LXIX	H	C_6H_5
LXX	CH_3	H
LXXI	CH_3	C_6H_5
LXXII	C_6H_5	H
LXXIII	C_6H_5	C_6H_5

	R
LXXIV	CH_3
LXXV	C_6H_5

The former compound was isolated from the hydrolysis reaction as a dark yellow-brown colored crystalline mass compared to the light yellow colors of other 2,3-thienyl dicarbonyls prepared in the course of this work. The use of activated charcoal in hexane-ether crystallization solvent gave an acceptable product. 2-Formyl-3-acetylthianaphthene was obtained from the hydrolysis mixture as a dark brown colored semi-crystalline mass. This thianaphthenyl dicarbonyl was readily purified by sublimination at 50-70^{o} and 0.1 mm. Hg. of pressure.

Two disappointing exceptions to these hydrolysis procedures were the attempted preparations of 2-formyl-3-benzoylthiophene, LXXII, and 2-formyl-2-benzoylthianaphthene, LXXV. Initial hydrolysis attempts yielded only very dark brown resinous oils. The NMR spectra of these oils showed the characteristic 4:1 integrated ratio of dioxolane and aldehyde protons in 2-phenyl-2-(2'-formyl-3'-thienyl or 3'-thianaphthenyl)-1,3-dioxolanes, indicating the absence of a dicarbonyl. With the presence of the latter group, the 4:1 ratio would be less than this or the appearance of another aldehyde peak would possibly have been noted. The continued hydrolysis of these two dioxolanyl aldehydes gave further reduction in the intensity of the 4:1 ratio of dioxolane-aldehyde proton peaks. Eventually, the only observable proton absorption in the NMR was in the aromatic region (2.2 τ - 3.0 τ). Apparently as both dicarbonyls were formed, they

were sufficiently unstable to prevent their isolation and their decomposition products did not show aldehydic protons in their NMR spectrum. It is also of interest to note that these final hydrolysis products did not show the presence of any carbonyl stretching frequencies in their infrared spectra. The disappearance of both IR carbonyl and NMR aldehyde-dioxolane bands could also be followed as a function of time. The use of a nitrogen atmosphere in these hydrolyses attempts did not improve the procedure and allow the isolation of the products. These dicarbonyl thiophenes and thianaphthene are all new materials, with the exception of the two isomers, 2-formyl-3-acetylthiophene, LXX, and 2-acetyl-3-formylthiophene, LXVIII. Robba et al., (55) had recently prepared these two compounds by acid hydrolysis from their respective dioxolane precursors, as described above. Again Robba et al., presented little spectroscopic evidence for these compounds; i.e., no ultraviolet or NMR data and little data on their infrared spectra. These data, obtained in this work, are discussed below.

3,4-Diformylthiophene

The synthesis of 3,4-diformylthiophene showed that this experimental approach may be applicable to the synthesis of other 3,4-thiophene dicarbonyls. The approach consisted of two consecutive bromine-metal interchange reactions with 3,4-dibromothiophene similar to the methods reported by

Gronowitz et al. (24,40,66) for the syntheses of 4-methylthio-3-thenal and 4-formyl-3-thenoic acid. Treatment with N,N-dimethylformamide at -70°, gave 3,4-diformylthiophene in a 54% yield based on 2-(4'-bromo-3'-thienyl)-1,3-dioxolane. The expected 2-(4'-formyl-3'-thienyl)-1,3-dioxolane was not obtained, which was unusual since the hydrolysis medium in this case was water. 3,4-Diformylthiophene is identical to the compound prepared by Trofimenko (51) by the reduction of 3,4-dicyanothiophene with diisobutyl aluminum hydride.

Spectral Properties of Thienyl and Thianaphthenyl Dicarbonyls

The summary of ultraviolet and infrared data is given in Table 5. Surprisingly, all the ultraviolet maxima recorded in ethanol showed little variation (272 mμ-280 mμ). In general, these maxima were all shifted to longer wavelengths by 10-15 mμ in comparison to the corresponding carbonyl substituted 3-thienyl dioxolanes. In the case of the single pair of thianaphthenyl derivatives, the shift to longer wavelengths was only 5 mμ. In the case of 3,4-diformylthiophene, an additional maximum appeared at 230 mμ having a high extinction coefficient. This could be the displaced 215 mμ primary band of thiophene caused by the dicarbonyl group. As groups ortho to each other become sterically larger, resonance becomes more difficult and hypsochromic shifts were seen; for example, the maxima for 2-benzoyl-3-acetylthiophene, LXXI, and 2,3-dibenzoylthiophene, LXXIII, appear respectively at 261 and

Table 5. UV and IR Spectral Data for Thienyl and Thianaphthenyl Dicarbonyls

Compound	UV Maxima λ_{max} (ϵ) (EtOH)	Infrared Maxima ν (C=O)
2,3-Diformylthiophene	272 (10,280)	1688(sh), 1680, 1675(sh)
3,4-Diformylthiophene	230; 278 (22,640; 12,940)	1692
2-Acetyl-3-formylthiophene	278; 310(sh) (10,430; 5,198)	1678
2-Benzoyl-3-formylthiophene	278 (12,720)	1690, 1650
2-Formyl-3-acetylthiophene	280 (11,650)	1680, 1665
2-Benzoyl-3-acetylthiophene	261; 290 (13,880; 7,740)	1710, 1682, 1670
2,3-Dibenzoylthiophene	264 (33,440)	1655, 1650(sh)
2-Formyl-3-acetylthianaphthene	234; 257; 307 (27,600; 10,670; 9,370)	1673

264 mμ (see Figure 24). 2-Formyl-3-acetylthianaphthene, LXXIV, shows a typical absorption for a carbonyl group substitution, i.e., two maxima at 257 mμ and 307 mμ which represent respectively the $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transitions of the carbonyl group. The band at 234 mμ is probably the high extinction primary band which occurs at 220 mμ in unsubstituted thianaphthene, shifted by the presence of the two carbonyl groups.

The infrared spectra of these thienyl and thianaphthenyl dicarbonyls (Figures 25-32) were characterized by maxima with smaller extinction coefficients than in spectra discussed previously. The one exception were the carbonyl stretching frequencies. The carbonyl frequencies range from 1690 cm^{-1} to 1650 cm^{-1}. Since carbonyls substituted in the 2-positions of thiophene have greater resonance capabilities with the thiophene ring compared to the 3-position (thus shifting to longer wavelengths), it is not surprising to find 2-benzoyl-3-formylthiophene, LXIX, and 2-formyl-3-acetylthiophene, LXX, with distinct doublets as carbonyl stretching frequencies. In these cases, the absorption at longer wavelengths was assigned to carbonyl at the 2-position. The spectrum of 3,4-diformylthiophene showed very few maxima, due to its high degree of symmetry. The spectrum of 2-benzoyl-3-acetylthiophene, LXXI, showed a strong peak at 1710 cm^{-1}. This most likely is not a carbonyl stretching frequency. Gronowitz (78) has explained these bands as Fermi resonance overtones of the

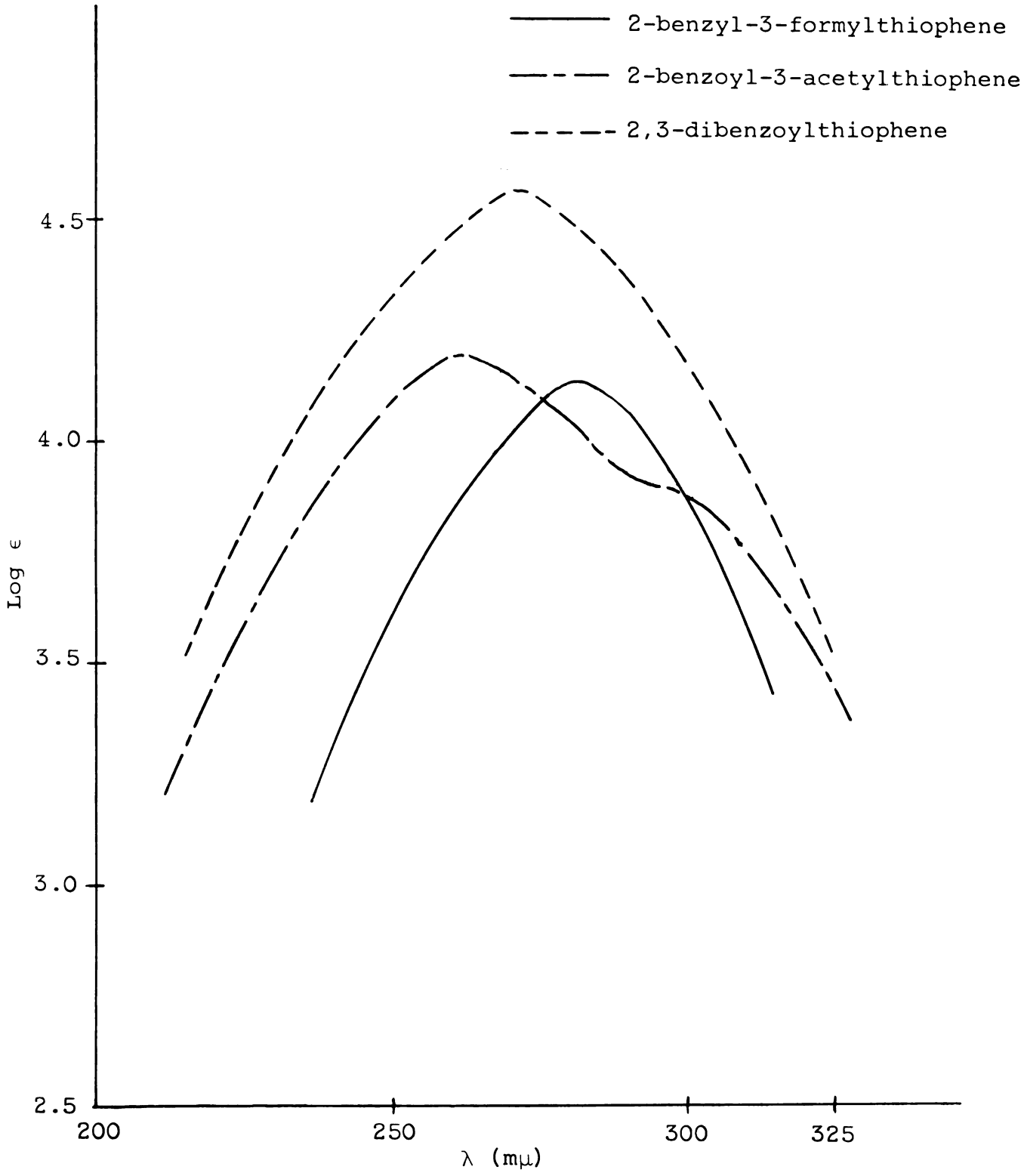


Figure 24. Ultraviolet spectra of some 3-acyl-2-benzoyl-thiophenes.

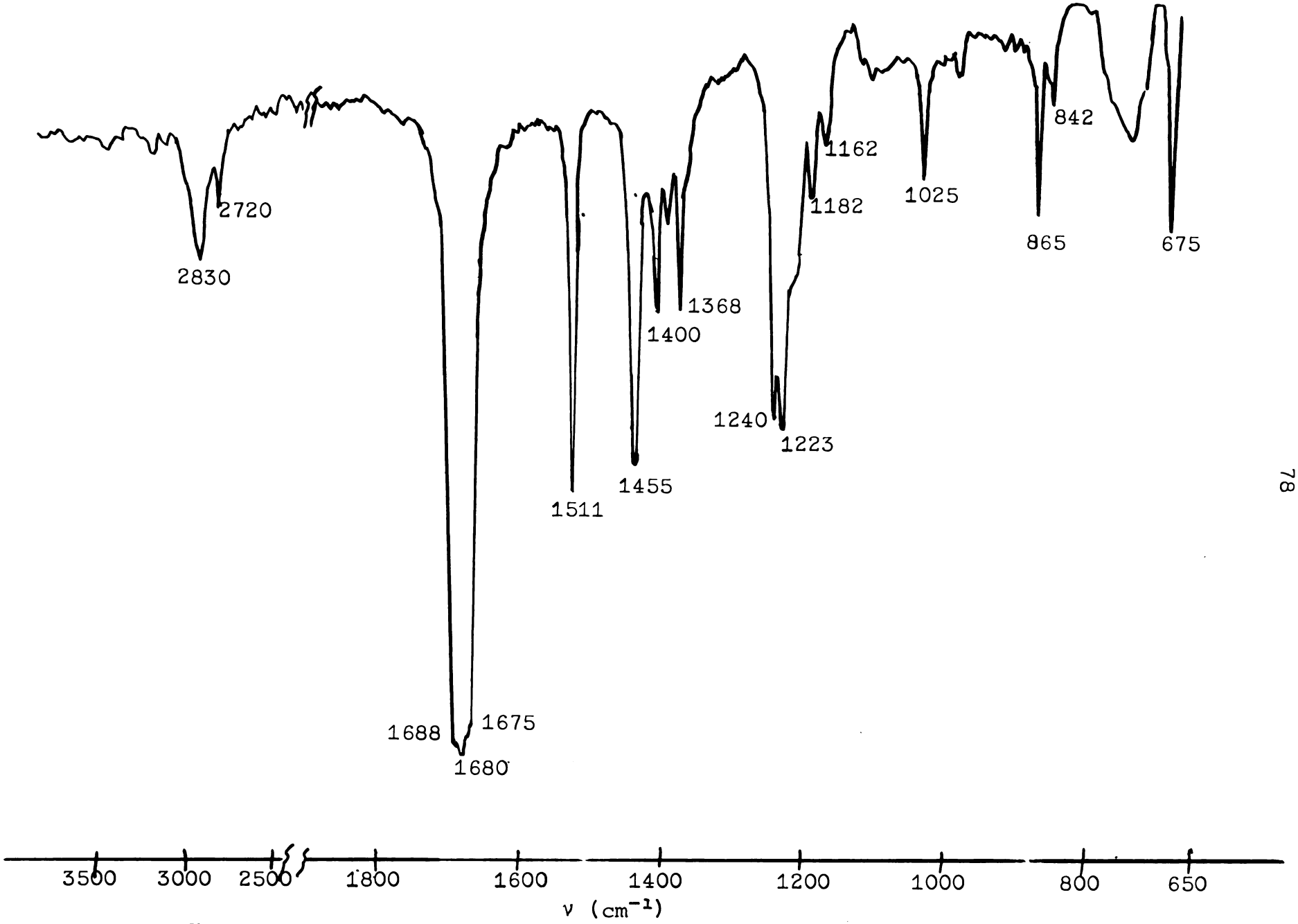


Figure 25. Infrared spectra of 2,3-diformylthiophene taken in CCl_4.

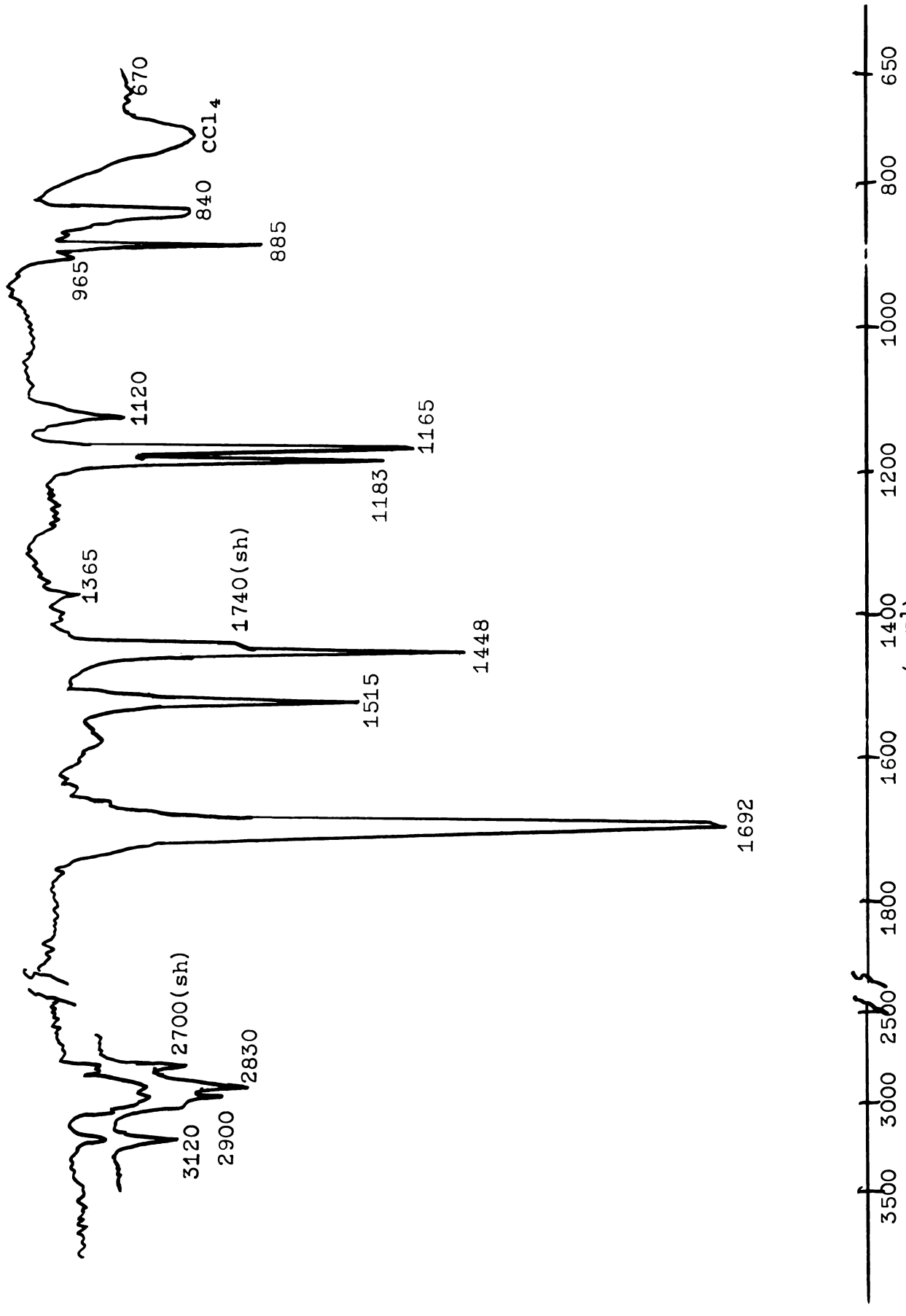


Figure 26. Infrared spectra of 3,4-diformylthiophene taken in CCl_4.

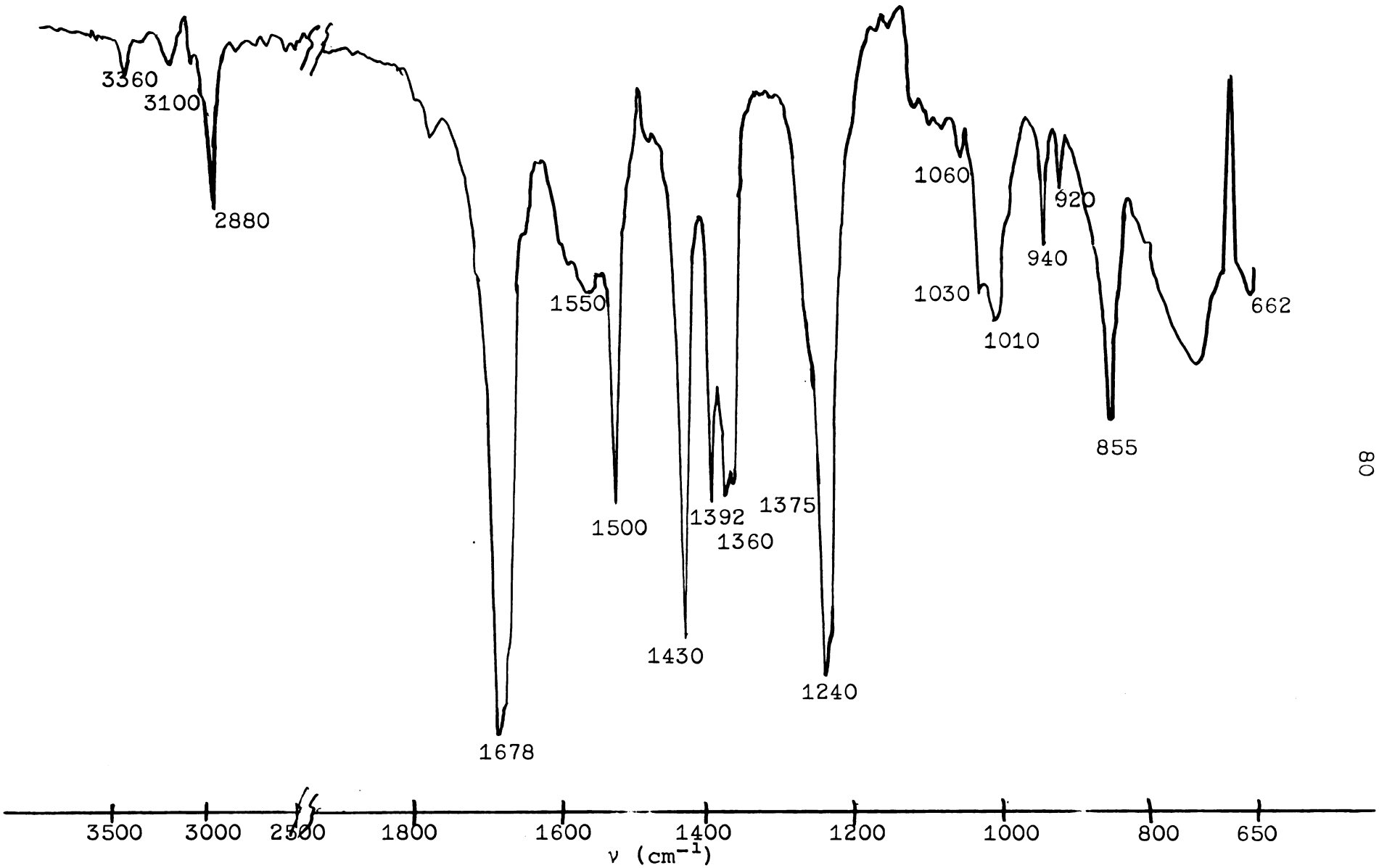


Figure 27. Infrared spectra of 2-acetyl-3-formylthiophene taken in CCl_4.

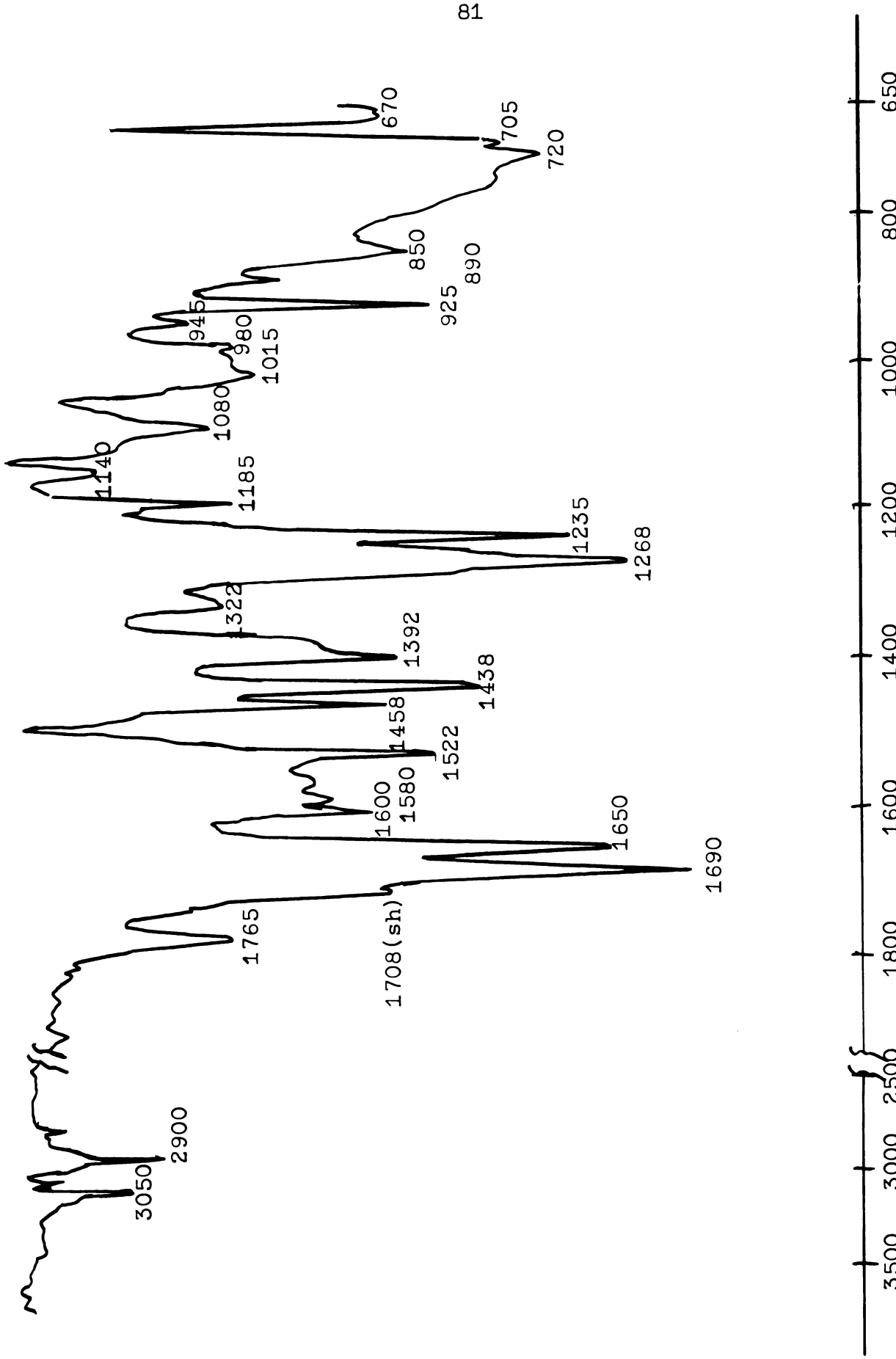


Figure 28. Infrared spectra of 2-benzoyl-3-formylthiophene taken in CCl_4.

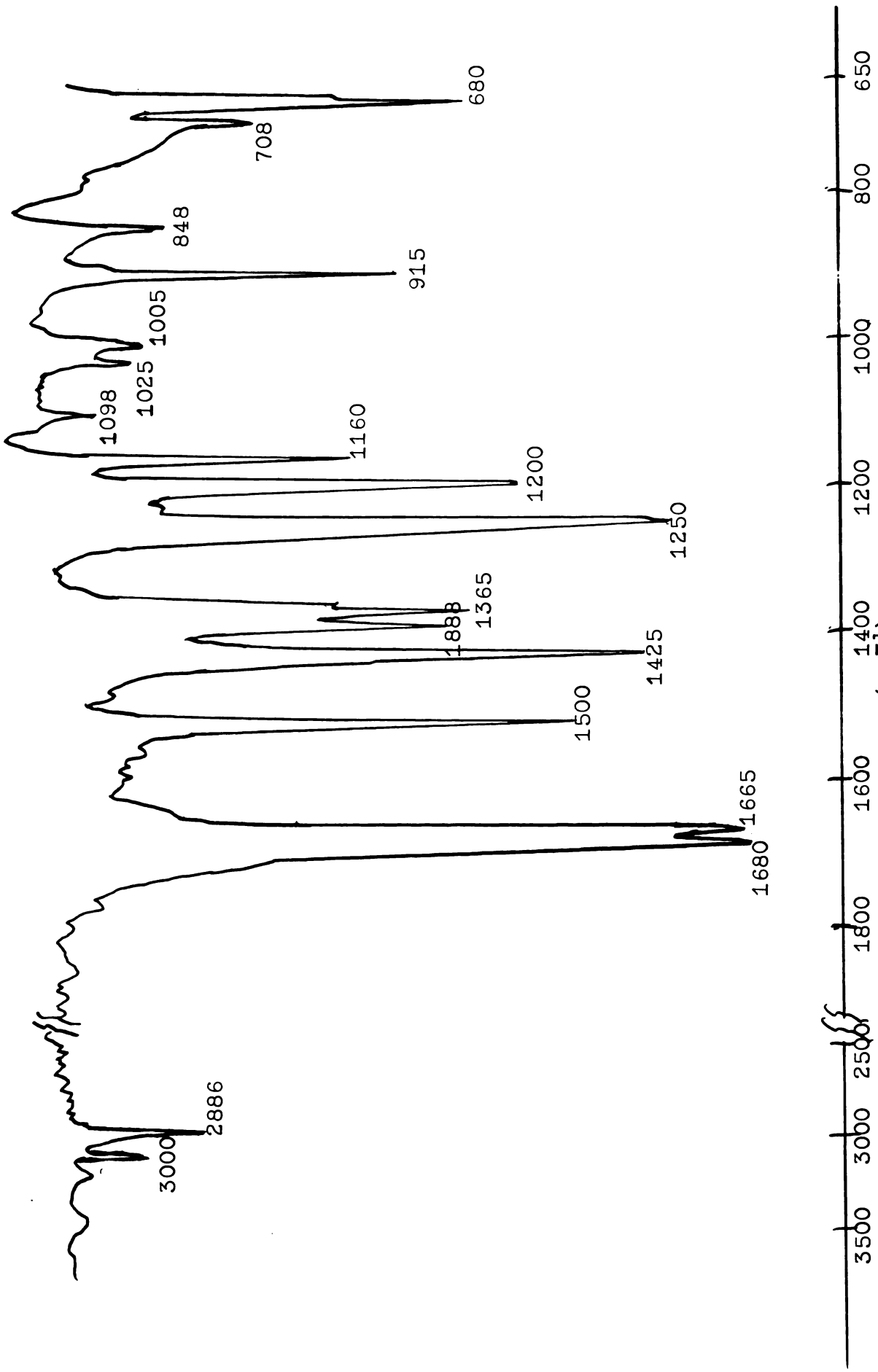


Figure 29. Infrared spectra of 2-formyl-3-acetylthiophene taken in CCl_4.

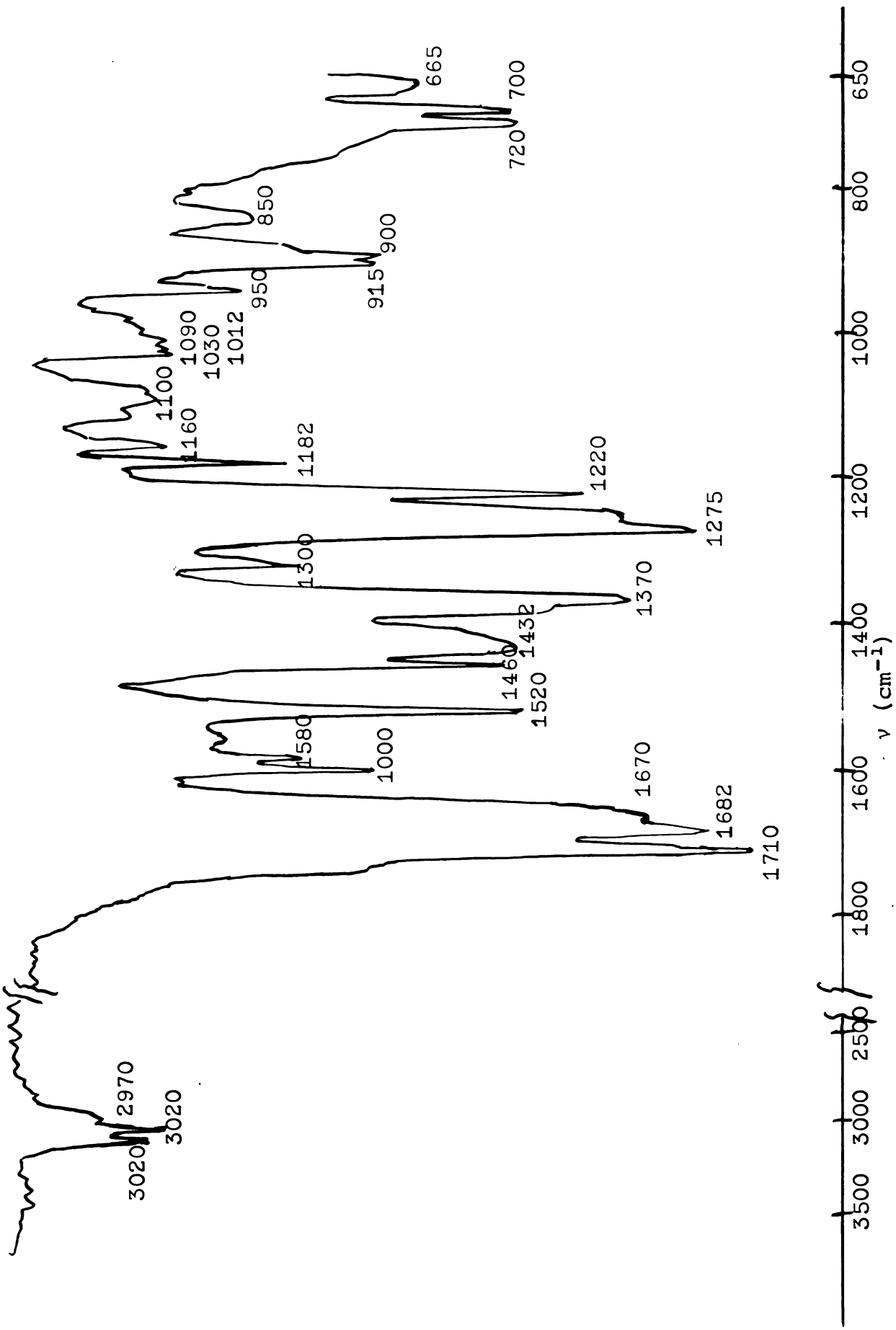


Figure 30. Infrared spectra of 2-benzoyl-3-acetylthiophene taken in CCl_4.

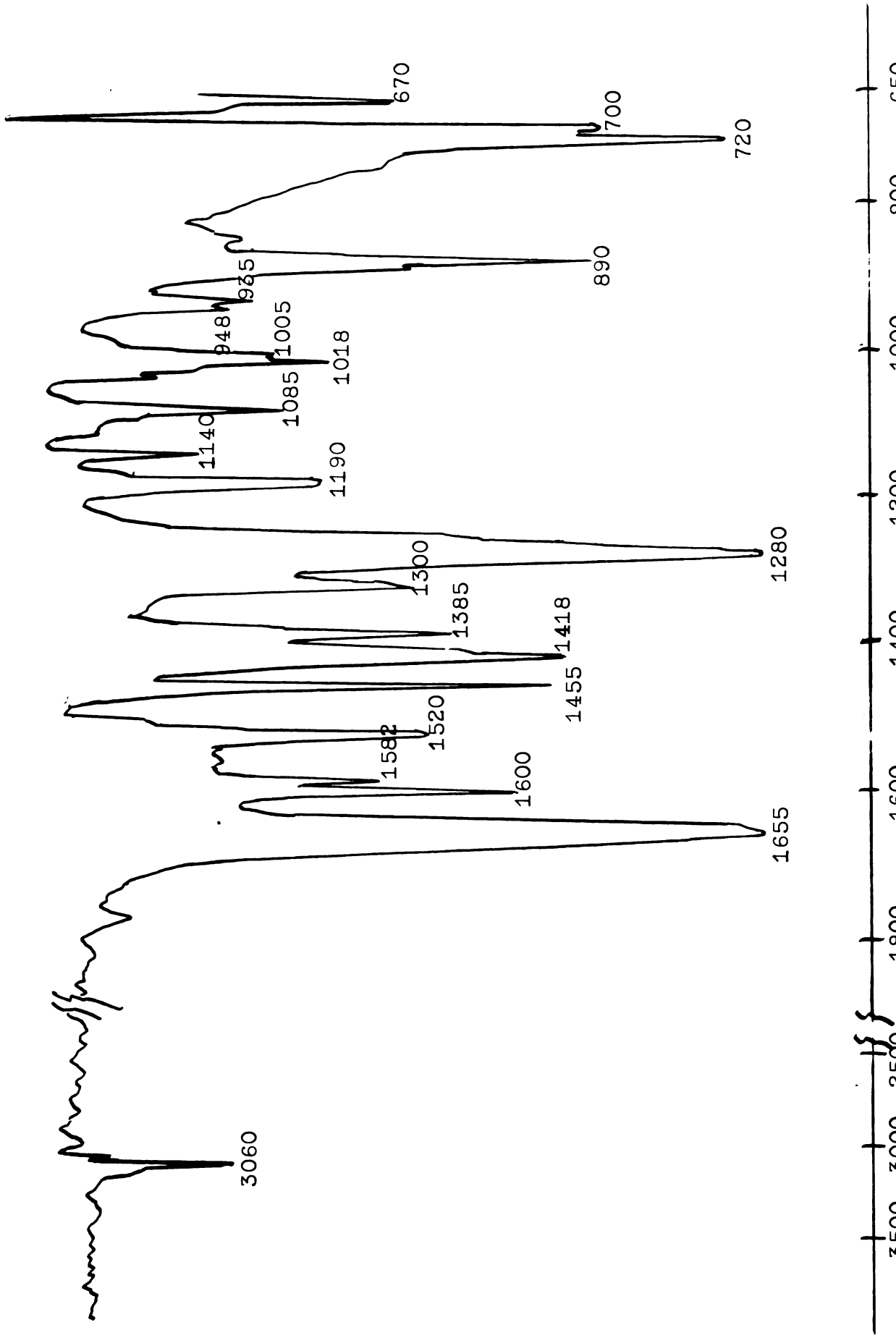


Figure 31. Infrared spectra of 2,3-dibenzoylthiophene taken in CCl_4.

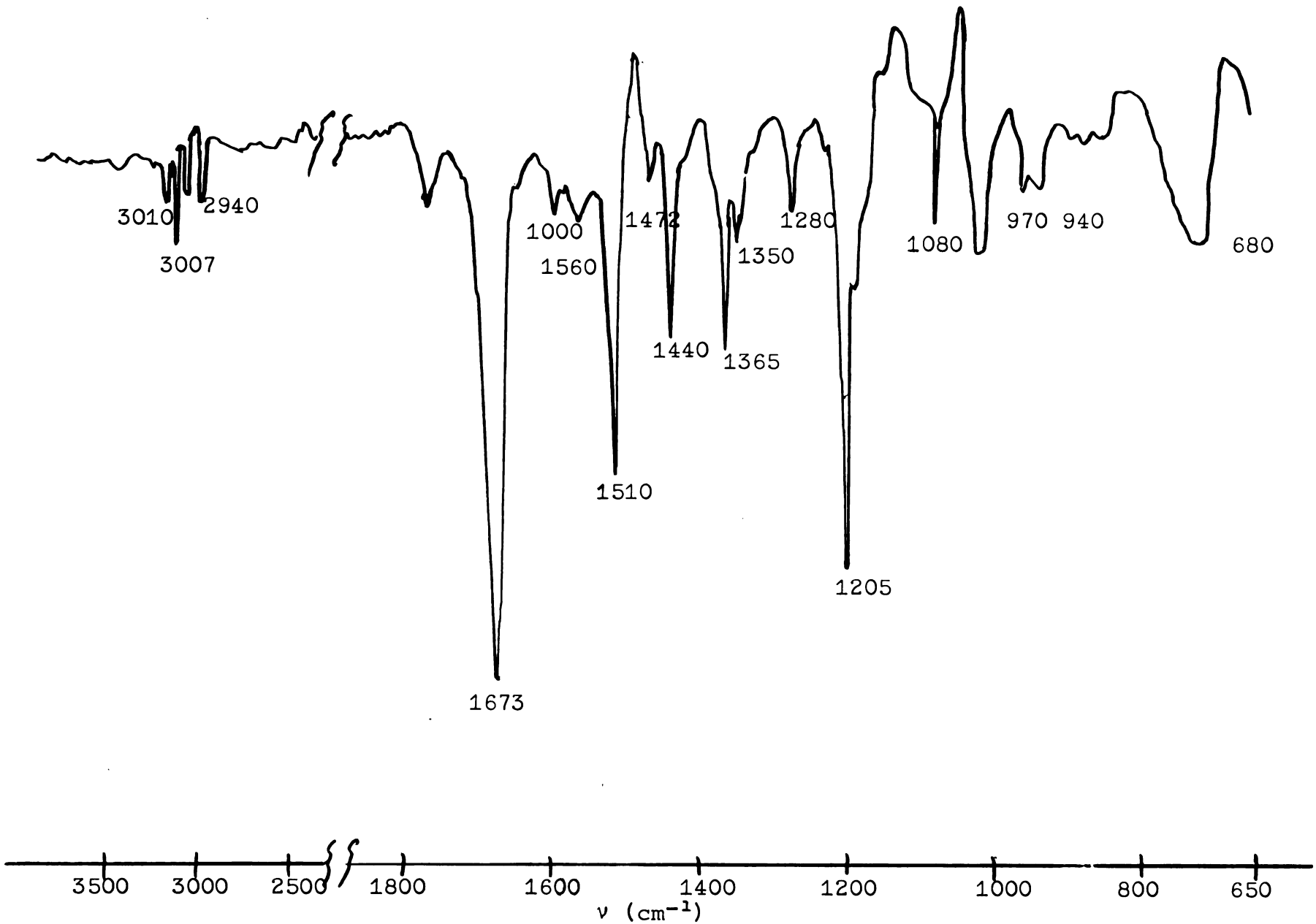


Figure 32. Infrared spectra of 2-formyl-3-acetylthianaphthene taken in CCl_4.

carbonyl band and bands appearing at 830 -850 cm^{-1}. These overtones are also found in the spectrum of 2-benzoyl-3-formylthiophene LXIX.

The NMR spectral data of these compounds are summarized in Table 6. In general, the τ values for the thiophene protons appear at somewhat lower values (2.00 - 2.70 τ) than in the corresponding carbonyl substituted thienyl and thianaphthenyl dioxolanes, due undoubtedly to the deshielding effect of an added carbonyl group present in the thiophene molecule. The methyl of the acetyl groups appeared at 7.22 - 7.71 τ and the aldehydic protons, being considerably more deshielded, appeared at -0.13 to -0.62 τ. The use of a polar solvent, CH_3CN as compared to CCl_4 for determining spectra, showed little effect on the τ values. The range of coupling constants found for these dicarbonyl compounds were: J_{45} = 5.10-5.20 cps, $J_{(CHO)_2-5}$ = 0.85-1.10 cps and $J_{(CHO)_3-5}$ = 0.30-0.70 cps. There was nothing unusual regarding the coupling constants, other than $J_{(CHO)_2-5}$ appeared somewhat smaller than in previous examples discussed. The dicarbonyls, which have a benzene moiety, did not show resolvable positions for the thiophene protons, due to deshielding of the 4 proton by the additional carbonyl at the 3-position of the thiophene ring. These values are given for the aromatic range in which aromatic protons appear.

Table 6. NMR Spectral Data for Thienyl and Thianaphthenyl Dicarbonyls

Compound	Solvent	τ					J (cps)		
		H_4	H_5	$H_{(CHO)_2}$	$H_{(CH_3)}$	$H_{(CHO)_3}$	J_{45}	$J_{(CHO)_2-5}$	$= J_{(CHO)_3-5}$
2,3-Diformyl-thiophene	CCl_4	2.36	2.29	-0.52	---	-0.38	5.20	0.85	0.30 $J_{(CHO)_2-4}$= 0.2
	CH_3CN	2.33	2.25	-0.53	---	-0.38	5.15	1.00	0.40 $J_{(CHO)_2-4}$= N.R. *
3,4-Diformyl-thiophene	CCl_4	---	1.81	---	---	-0.31	---	---	---
	CH_3CN	---	1.61	---	---	-0.29	---	---	---
2-Acetyl-3-formyl-thiophene	CCl_4	2.37	2.57	---	7.37	-0.50	5.20	---	0.70
	CH_3CN	2.39	2.54	---	7.45	-0.62	5.20	---	0.70
2-Benzoyl-2-formylthiophene	CCl_4	2.00	-2.58**	---	---	-0.13	---	---	0.70
	CH_3CN	1.98	-2.57**	---	---	-0.13	---	---	0.70
2-Formyl-3-acetyl-thiophene	CCl_4	2.52	2.40	-0.42	7.43	---	5.10	1.10	---
	CH_3CN	2.15	2.36	-0.39	7.40	---	5.10	1.10	---
3-Benzoyl-3-acetyl-thiophene	CCl_4	2.08	-2.73**	---	7.71	---	---	---	---
		2.10	-2.61**	---	7.61	---	---	---	---
2,3-Dibenzoyl-thiophene	CCl_4	2.32	-3.00	---	---	---	---	---	---
	CH_3CN	2.15	-2.98	---	---	---	---	---	---
2-Formyl-3-acetyl-thiophene	CCl_4	---	---	-0.30	7.22	---	---	---	---
	CH_3CN	---	---	-0.28	7.22	---	---	---	---

* Non-resolvable.

** Range of proton absorption in aromatic region.

Condensation Reactions of Thiophene biscarboxaldehydes under Hinsberg Conditions

A cursory attempt was made to investigate the condensation products of 3,4-diformylthiophene and 2,3-diformylthiophene with diethyl thiodiglycolate and dimethyl diglycolate as catalyzed by sodium methoxide. 3,4-Diformylthiophene and diethyl thiodiglycolate reacted in the presence of sodium methoxide in methanol at 10°, giving a base soluble compound which on the basis of elemental analysis and spectral properties has been assigned to structure, thieno[3,4-d]thiepin-2,4-dicarboxylic acid. Figure 33 shows the infrared spectra of this compound. It has bands in the hydroxyl (3500 cm^{-1}), carbonyl (1665 cm^{-1}) and olefinic (1595 cm^{-1}) regions. The spectra is of rather poor quality and was determined as a "mull" in CCl_4. The NMR spectrum of the material taken in N,N-dimethylacetamide showed three singlets of equal intensity at -0.89 τ (carboxyl hydrogens), 2.28 τ (6, .8 hydrogens) and 2.43 τ (1,5 hydrogens). The UV spectrum showed clearly defined maxima, well into the visible range. The bands are (ethanol): 218 mμ (14,300), 252 mμ sh (15,460), 284 mμ (34,100), 331 mμ (2,390), 348 mμ sh (2,070) and 368 mμ sh (1,180). The extension of the visible absorption is seen even into the infrared, where increasing transparency was observed from the 2 to the 6 micron region.

An attempt to prepare thieno[3,4-d]oxepin-2,4-dicarboxylic acid and thieno[2,3-d]thiepin-2,4-dicarboxylic acid were

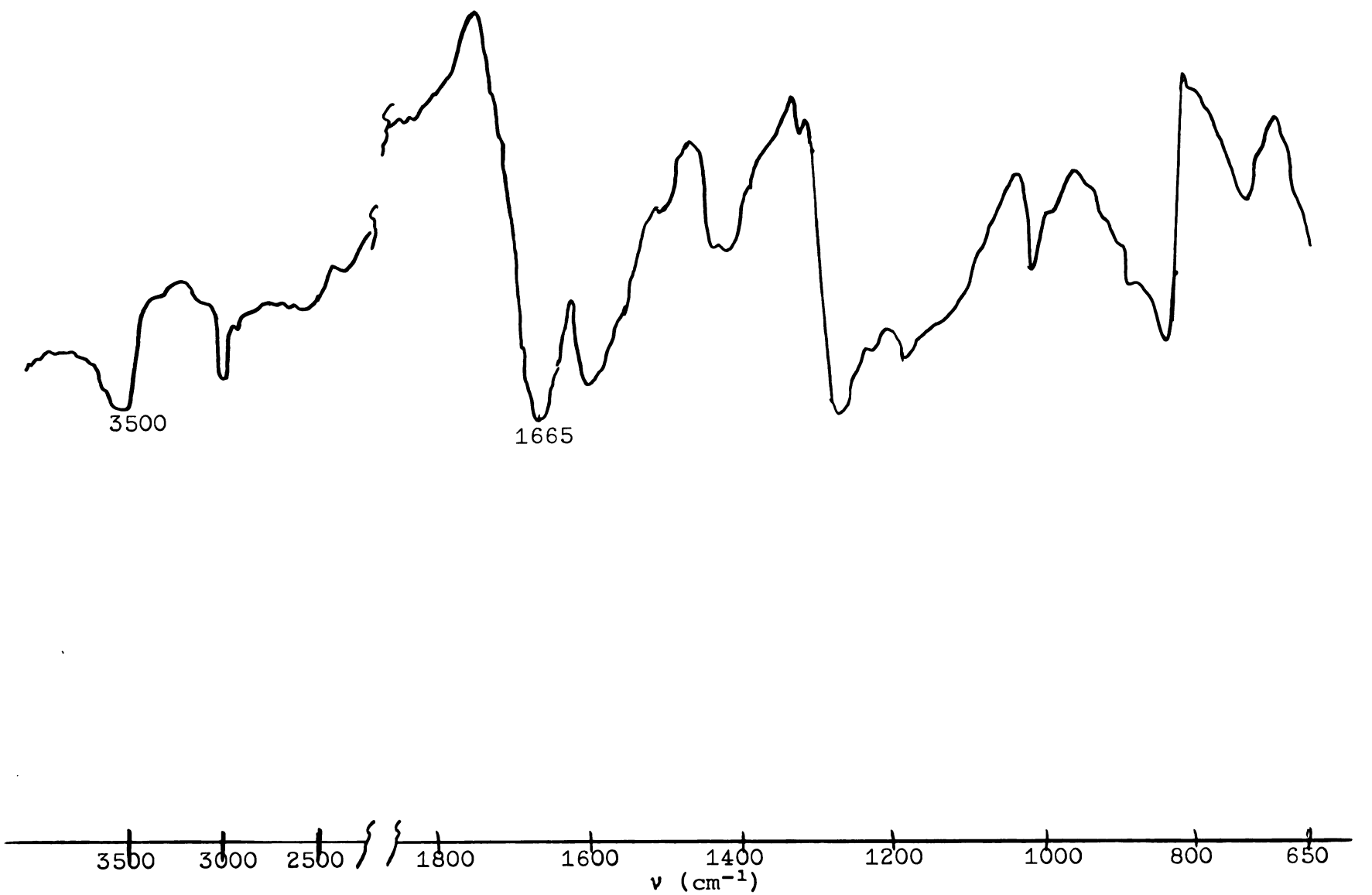


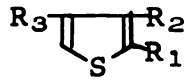
Figure 33. Infrared spectra of thieno[3,4-d]thiepin-2,4-dicarboxylic acid taken in CCl_4.

unsuccessful when conducted under similar experimental conditions. In the former case, a resinous polymeric product insoluble in a variety of solvents, e.g., CCl_4 and DMF, was obtained. In the latter case, a black intractable product was obtained and continued to form as the reaction proceeded, together with a strong odor of hydrogen sulfide evolution.

Microanalytical Data

All the compounds prepared in the course of this study were submitted for microanalytical analysis to Micro-Tech Laboratories, Skokie, Illinois. These analytical data are summarized in Tables 7 and 8. All results were within the accepted accuracy of 0.2% of the calculated values.

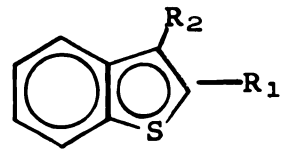
Table 7. Micro Analytical Data for Substituted Thiophenes[1]



				Calculated			Found		
R_1	R_2	R_3	Formula	Carbon	Hydrogen	Sulfur	Carbon	Hydrogen	Sulfur
-H	$-C(CH_3)(OCH_2)_2$	-H	$C_8H_{10}O_2S$	56.44	5.92	18.84	56.41	5.86	18.78
-H	$-CC_6H_5(OCH_2)_2$	-H	$C_{13}H_{12}O_2S$	67.21	5.21	13.80	67.13	5.29	13.91
-CHO	$-CH(OCH_2)_2$	-H	$C_8H_8O_3S$	52.16	4.38	17.41	52.11	4.41	17.29
$-COCH_3$	$-CH(OCH_2)_2$	-H	$C_9H_{10}O_3S$	54.52	5.08	16.18	54.41	5.16	16.38
$-COC_6H_5$	$-CH(OCH_2)_2$	-H	$C_{14}H_{12}O_3S$	64.59	4.65	12.32	64.42	4.61	12.49
-CHO	$-CCH_3(OCH_2)_2$	-H	$C_9H_{10}O_3S$	54.52	5.08	16.18	54.82	5.14	16.47
$-COC_6H_5$	$-CCH_3(OCH_2)_2$	-H	$C_{15}H_{14}O_3S$	65.43	5.49	11.65	65.55	5.16	11.54
-CHO	$-CC_6H_5(OCH_2)_2$	-H	$C_{14}H_{12}O_3S$	64.59	4.65	12.32	64.82	4.70	12.26
$-COC_6H_5$	$-CC_6H_5(OCH_2)_2$	-H	$C_{20}H_{16}O_3S$	71.40	4.79	9.53	71.43	4.86	9.48
-CHO	-CHO	-H	$C_6H_4O_2S$	51.42	2.89	22.88	51.67	3.15	22.73
$-COCH_3$	-CHO	-H	$C_7H_6O_2S$	54.52	3.92	20.80	54.67	4.00	20.56
$-COC_6H_5$	-CHO	-H	$C_{12}H_8O_2S$	66.65	3.73	14.83	66.75	3.84	15.03
-CHO	$-COCH_3$	-H	$C_7H_6O_2S$	54.52	3.92	20.80	54.37	3.96	21.01
$-COC_6H_5$	$-COCH_3$	-H	$C_{13}H_{10}O_2S$	67.80	4.38	13.93	67.74	4.37	14.08
$-COC_6H_5$	$-COC_6H_5$	-H	$C_{18}H_{12}O_2S$	73.95	4.14	10.97	73.87	4.21	10.97
H	-CHO	-CHO	$C_6H_4O_2S$	51.42	2.89	22.88	51.22	2.91	23.05
H_1	$-CH=C(CO_2H)-S-C(CO_2H)=CH-$		$C_{10}H_6O_4S_2$	47.23	2.38	25.22	47.25	2.65	25.04

[1]Analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Table 8. Micro Analytical Data for Substituted Thianaphthenes[1]



R_1	R_2	Formula	Calculated			Found		
			Carbon	Hydrogen	Sulfur	Carbon	Hydrogen	Sulfur
-H	$-CCH_3(OCH_2)_2$	$C_{12}H_{12}O_2S$	65.42	5.49	14.56	65.44	5.50	14.35
-H	$-CC_6H_5(OCH_2)_2$	$C_{17}H_{14}O_2S$	72.31	5.00	11.36	71.92	4.96	11.32
-CHO	$-CCH_3(OCH_2)_2$	$C_{13}H_{12}O_3S$	62.88	4.87	12.91	62.79	5.02	12.86
-CHO	$-CC_6H_5(OCH_2)_2$	$C_{18}H_{14}O_3S$	69.66	4.55	10.33	69.39	4.63	10.45
-CHO	$-COCH_3$	$C_{11}H_8O_2S$	64.68	3.95	15.70	64.96	4.05	15.59

[1]Analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

EXPERIMENTAL

Apparatus used with n-butyllithium solutions were flamed under a stream of dry nitrogen prior to start of a reaction. Dry nitrogen was obtained by passing "pre-purified" nitrogen through twin towers of sulfuric acid, a tower of solid potassium hydroxide and a final tower of anhydrous calcium sulfate. Thiophene was obtained from Pennsalt Chemicals Inc., Philadelphia, Penn., and the thianaphthene was secured from Columbis Organic Chemicals Inc., Columbia, S. C. These were purified by distillation through a glass helices packed column. Bromine was of a technical grade supplied by the Dow Chemical Co., Midland, Mich. N, N-Dimethylformamide and N,N-dimethylacetamide were obtained as practical grade chemicals from the Matheson, Coleman and Bell Co., Norwood, Ohio. These amides were treated initially with solid potassium hydroxide and then with calcium hydroxide, followed by distillation at reduced pressure.

NMR spectra were determined in a Varian A-60 high resolution spectrometer at 60 mc operating at room temperature. Infrared absorption spectra were determined with either a Beckman IR-5 or a Unicam SP-200 instrument. Ultraviolet spectra were determined with a Beckman DB instrument.

All melting points are uncorrected. Analyses reported were determined by Micro-Tech Laboratories, Skokie, Ill.

The Preparation of N,N-Dimethylbenzamide

A 100 g. (2.2 moles) quantity of gaseous dimethylamine was condensed into a one liter, three-necked flask at 30° (dry ice/isopropanol) equipped with a stirrer, dropping funnel and a suitable low temperature thermometer. The chilled amine, was dissolved in 100 ml. of anhydrous ether, and 140 g. (1.0 mole) of freshly distilled benzoyl chloride in 500 ml. ether were added dropwise during three hours to the ether solution of amine. The mixture was warmed to room temperature, then heated at its reflux temperature for fifteen minutes and poured into 800 ml. of water. The aqueous layer was extracted with two 200 ml. portions of ether. The combined organic layers were washed with 5% aqueous hydrochloric acid and dried over anhydrous magnesium sulfate. Distillation, after solvent removal in a Rinco evaporator, gave 148 g. (0.99 mole, 99% yield) of pure N,N-dimethylbenzamide boiling at 122°/5mm., m.p. 44.5-45.5° (recrystallized from hexane-ether). Literature value is: m.p. 45-45° (81).

3-Bromothiophene

Into a two liter, three-necked flask equipped with a stirrer, dropping funnel and reflux condenser fitted by a length of tubing which led to a suitable gas trap, were

placed 378 g. (4.5 moles) of freshly distilled thiophene. To the stirred thiophene, at room temperature, 2,196 g. (13.8 mole, 710 ml.) of bromine were added dropwise during nine hours at a rate sufficient to cause a steady ebullition of hydrogen bromide gas. Following the addition of the bromine, the reaction mixture was stirred for one day to purge the system of hydrogen bromide.

A solution containing 720 g. (12.8 moles) of potassium hydroxide in 1500 ml. methanol was prepared and placed into a five liter, three-necked flask equipped with a stirrer and reflux condenser. The brominated thiophene mixture was cautiously added to the alkaline methanol solution and the basic solution was refluxed for a three hour period. The organic residue was then exhaustively steam distilled until traces of tetrabromothiophene appeared in the condensate, at which point 1104 g. of an oily product had been collected.

The oil was placed in a five liter, three-necked flask equipped with two reflux condensers, 600 ml. of glacial acetic acid, 2700 ml. of water and 333 g. (5.1 g. atom) of zinc dust. The suspension became warm and after being set aside for one hour, the mixture was refluxed for one day. The reaction mixture was then steam distilled to obtain an oil which was washed with water, then with 5% aqueous sodium bicarbonate and again with water and then dried over anhydrous magnesium sulfate. The oil was fractionally distilled using a heated, 40 cm. glass spiral column to obtain 313.8 g.

(0.63 mmole, 42.8% based on the initial thiophene) of 3-bromothiophene boiling 70-71°/34mm., n_D^{20}= 1.5868. Literature values for 3-bromothiophene, b.p. 157-8°/1 atm; n_D^{20} 1.5861 (see ref. 1, p. 208).

A 267.3 g. (1.11 moles, 24.6% based on initial thiophene) of dibromothiophenes, presumably the 2,4 and 2,3-isomers, boiling at 93-96°/13 mm. were also obtained.

3-Thenal

A 14.0 g. quantity (2.0 g. atoms) of clean lithium metal (Fisher Scientific Co., Fairlawn, N. J.) was cut into chips (approx. 1 cm. x 1 cm. x 0.5 cm) and placed in 600 ml. anhydrous ether contained in a previously dried two liter, three-necked flask equipped with a dry nitrogen inlet tube, thermometer (-200° to 30°), a 500 ml. pressure equilibrating dropping funnel and a stirrer. A 165.0 g. quantity (1.2 moles) of n-butyl bromide in 250 ml. ether was added dropwise to the lithium-ether suspension precooled to -30 to -20° by immersion in a dry ice/isopropanol bath and stirred until the last traces of lithium had reacted (three to five hours). The etheral solution of n-butyllithium was thoroughly cooled to -70° and 163.0 g. (1.0 mole) of 3-bromothiophene in 200 ml. ether were slowly added to the alkyllithium and stirred for an additional fifteen minutes. To the cold 3-thienyllithium solution, 88.0 g. (1.2 moles) of freshly distilled N,N-dimethylformamide in 250 ml. ether were added during a period

of one hour and the stirred reaction solution was allowed to warm to room temperature overnight.

It was then poured into one liter of a saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted with 600 ml. ether. The combined extract organic layer was dried over anhydrous magnesium sulfate. Distillation of the residue after removal of the ether, gave 86.0 g. (0.76 mole, 76%) of 2-thiophenecarboxaldehyde: b.p. 79-80°/15 mm.; n_D^{20} 1.5875. Literature values for 3-thiophenecarboxaldehyde are; b.p. 72-78°/12 mm.; n_D^{20} 1.5860 (82).

3-Acetothienone

One mole of 3-thienyllithium was prepared in the manner previously described from 14.0 g. (2 g. atom) of freshly cut lithium metal, 165 g. (1.2 moles) n-butyl bromide, 163 g. (1.0 mole) of 3-bromothiophene and 600 ml. anhydrous ether. The addition of the acylating agent, 110.6 g. (1.2 moles) of N,N-dimethylacetamide, in 200 ml. ether was accomplished in one-half hour at -70°, after which the mixture was set aside at room temperature overnight.

The hydrolysis was done in the usual manner with 10% aqueous hydrochloric acid, followed by extraction of the aqueous layer once with ether. The combined organic layers were washed with 10% aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate and fractionated in vacuo. The product, 87.0 g. (0.68 mole, 68%) 3-acetylthiophene,

was obtained at 71-2° (3.0 mm. Hg): m.p. 56-7° (70% aqueous ethanol). Literature values for 3-acetylthiophene are: b.p. 88-9° (11 mm. Hg); m.p. 57.5-58.5° (70).

3-Benzoylthiophene

The preparation of 3-benzoylthiophene was accomplished in an identical manner to that used for the previous two syntheses, from 7.0 g. (1.0 g. atom) lithium metal, 82.5 g. (0.6 mole) n-butyl bromide, 81.5 g. (0.5 mole) 3-bromothiophene, 90.0 g. (0.6 mole) of N,N-dimethylbenzamide and 500 ml. anhydrous ether. Distillation of the reaction residue, after the removal of the solvent, gave 88.7 g. (0.47 mole, 94.3%) of 3-benzoylthiophene as a clear oil boiling at 113-20° (0.3 mm. Hg) which solidified upon being set aside overnight; m.p. 62-63.5° (70%, aqueous ethanol). Literature values for 3-benzoylthiophene are: b.p. 129-30° (3 mm. Hg); m.p. 63-4° (83).

2-(3'-Thienyl)-1,3-dioxolane, LIII

A 500 ml., one-necked flask equipped with a Dean and Stark water separator, reflux condenser and a calcium chloride drying tube, was charged with 86.0 g. (0.76 mole) 3-thiophenecarboxaldehyde, 75 ml. ethylene glycol, a few crystals of p-toluenesulfonic acid monohydrate and 250 ml. benzene. The contents were refluxed until no more water was obtained. The reaction mixture was poured into a solution of 10 g.

potassium carbonate and 200 ml. of water. The aqueous layer was extracted once with ether and the combined organic layers were dried over anhydrous magnesium sulfate. Distillation of the residue gave 77.6 g. (0.5 mole, 65%) of 2-(3'-thienyl)-1,3-dioxolane boiling at 108-9° (12 mm. Hg). The product exhibited no trace of carbonyl absorption, but showed intense ketal ether absorption at 1100 cm^{-1}. Literature value for the dioxolane is: b.p. 103-4°/10 mm Hg. (32).

The Synthesis of 2-Methyl-2-(3'-thienyl)-1,3-dioxolane, LIV

Into a 500 ml., single-necked flask equipped with a Dean and Stark water separator and reflux condenser were placed 40 g. (0.3 mole) of 3-acetylthiophene, 40 ml. ethylene glycol, 0.3 g. p-toluenesulfonic acid monohydrate and 300 ml. of benzene. The contents of the flask, heated at its reflux temperature for eight hours, were then cooled to room temperature. The contents were slurried over 20 g. of potassium carbonate. Three hundred milliliters of water were added, the organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate. Distillation of the crude product gave 45 g. of a liquid boiling at 103-4° (20 mm. Hg) which partially solidified upon cooling. Three crystallizations from an ethanol-water mixture (with refrigeration) removed the last traces of ketone. A 35 g. (0.21 mole, 68%) quantity of pure 2-methyl-2-(3'-thienyl)-1,3-dioxolane was

obtained in the form of fine needles: m.p. 33-4°; λ_{max} (ethanol) 232 mm. (ϵ 5840); ν $(cm^{-1})_{max}$ (CCl_4) 3003, 2875, 1600, 1483, 1433, 1420, 1380, 1250, 1203, 1190, 1110, 1090, 1053, 960, 890, 860, 670.

Anal. Calc'd for $C_8H_{10}O_2S$: C, 56.44; H, 5.92; S, 18.84.

Found: C, 56.41; H, 5.86; S, 18.78.

2-Phenyl-2-(3'-thienyl)-1,3-dioxolane, LV

A 500 ml., single-necked flask equipped with a Dean and Stark water separator and reflux condenser was charged with 40 g. (0.21 mole) of 3-benzoylthiophene, 2.0 g. of p-toluenesulfonic acid monohydrate, 70 ml. ethylene glycol and 300 ml. benzene. The mixture was refluxed for thirty-six hours and then poured over 30 g. potassium carbonate and then water added. The mixture layers were separated and the aqueous layer was extracted into ether. The combined organic layers were dried over anhydrous magnesium sulfate. The solvents were removed in a Rinco evaporator and the residue crystallized upon being set aside overnight. The residue was crystallized from 70% aqueous ethanol (plates) to yield 38.2 g. (0.17 mole, 81%) of pure 2-phenyl-2-(3'-thienyl)-1,3-dioxolane: m.p. 78.5-80.0°; λ_{max} (ethanol) 236 and 269 mμ (ϵ 7490 and 2760 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3170, 2980, 2880, 1500, 1478, 1455, 1420, 1265, 1225, 1190(sh), 1178, 1090, 1080(sh), 1040, 1018, 955, 925, 880, 860, 705, 680.

Anal. Calc'd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21; S, 13.80.

Found: C, 67.13; H, 5.29; S, 13.91.

2-Methyl-2-(3'-thianaphthenyl)-1,3-dioxolane, LVI

This ketal was prepared from 50.0 g. (0.28 mole) of pure 3-acetylthianaphthene (64) (m.p. 63.5-65.0°), 35 ml. ethylene glycol and 1.0 g. p-toluenesulfonic acid monohydrate using the experimental procedure described for the synthesis of 2-phenyl-2-(3'-thienyl)-1,3-dioxolane. The crude product, 57.0 g. (0.26 mole, 93%) was crystallized from 95% ethanol, after distillation (107-8° at 0.5 mm. Hg) to obtain 51.5 g. (0.23 mole, 84%) pure 2-methyl-2-(3'-thianaphthenyl)-1,3-dioxolane: m.p. 39.5-40.0°; λ_{max} (ethanol) 222, 260, 281, 290 and 299 mμ (ε 49,300, 6,350, 2,035, 2,860 and 3,660 respectively), ν $(cm^{-1})_{max}$ (CCl_4) 3080, 3000, 2900, 1590, 1530, 1465, 1438, 1385, 1360, 1325, 1200, 1150, 1118, 1050, 960, 895, 840.

Anal. Calc'd for $C_{12}H_{12}O_2S$: C, 65.42, H, 5.49; S, 14.56.

Found: C, 65.44; H, 5.50; S, 14.35.

2-Phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane, LVII

3-Benzoylthianaphthene was prepared in a 58% yield by the method of Badger and Christie (67): b.p. 164-5° (0.4 mm. Hg), liquid. Literature values are: b.p. 220° (12 mm. Hg), liquid (68).

Ketalization was effected in the usual manner using 70.0 g. (0.30 mole) 3-benzoylthianaphthene, 70 ml. ethylene glycol and 2.0 g. p-toluenesulfonic acid monohydrate until

water separation from the reaction mixture was completed (ninety-six hours). After prolonged storage (three hours), the distilled produce (191-200° at 0.1 mm. Hg) solidified. It was washed briefly with cooled 95% ethanol and the remaining solid was recrystallized from aqueous ethanol to obtain 50 g. (0.17 mole, 57%) of pure 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane: m.p. 78-9°; λ_{max} (ethanol) 221, 260, 281, 290 and 300 mμ (ε 33,100, 7,410, 2,280, 3,150 and 3,710 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3080, 2980, 2890, 1535, 1500, 1470, 1460, 1438, 1365, 1315, 1270, 1225, 1200, 1180, 1170(sh), 1150, 1135, 1085, 1058, 1040, 1005, 960, 915, 848, 715, 705(sh), 678.

Anal. Calc'd for $C_{17}H_{14}O_2S$: C, 72.31; H, 5.00; S, 11.36.
Found: C, 71.92; H, 4.96; S, 11.32.

2-(2'-Formyl-3'-thienyl)-1,3-dioxolane, LVIII

To a solution containing 20.0 g. (0.13 mole) of 2-(3'-thienyl)-1,3-dioxolane and 300 ml. of anhydrous ether in a dry 500 ml., three-necked flask equipped with a dry nitrogen inlet tube, magnetic stirrer, dropping funnel and reflux condenser, 88 ml. of a 1.6N solution of n-butyllithium in hexane (Foote Mineral Corp., Exton, Penn.) were added dropwise at -30° (dry ice/isopropanol) during fifteen minutes. The mixture was stirred at this temperature for an additional fifteen minutes, then warmed to room temperature and finally heated at its reflux temperature for fifteen minutes.

The mixture was recooled to -30°, 10.4 g. (0.14 mole) of freshly distilled N,N-dimethylformamide in 25 ml. anhydrous ether were added during ten minutes and the mixture was again heated at its reflux temperature for fifteen minutes to complete the reaction. The initial reaction product was hydrolyzed with a 10% aqueous ammonium chloride solution. Product isolation by procedures already described gave 17.2 g. (0.11 mole, 81%) of pure 2-(2'-formyl-3'-thienyl)-1,3-dioxolane: b.p. 125-32° (1.5 mm. Hg); m.p. 30.0-30.4° (methanol in dry ice) in the form of long, fine needles; λ_{max} (ethanol) 267 and 288(sh) mμ (ε 20,640 and 10,980 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3100, 2960, 2900, 1660, 1540, 1430, 1360, 1240, 1215, 1170, 1115, 1090, 1030, 965, 850, 800, 750, 725, 675.

Anal. Calc'd for $C_8H_8O_3S$: C, 52.16; H, 4.38; S, 17.41.
Found: C, 52.11; H, 4.41; S, 17.29.

2-(2'-Acetyl-3'-thienyl)-1,3-dioxolane, LIX

To a previously dried 300 ml., three-necked flask equipped with a magnetic stirrer, reflux condenser and a pressure equilibrating dropping funnel, was added a solution containing (31.6 mmoles) of 2-(3-thienyl)-1,4-dioxolane in 75 ml. anhydrous ether. The solution was precooled to -30° using a dry ice/isopropanol bath and 21.5 ml. of a 1.6N solution of n-butyllithium in hexane were added during fifteen minutes. The reaction mixture was stirred for five

minutes at room temperature and then heated under reflux ten minutes. After recooling the mixture to -30°, 3.05 g. (35 mmoles) of N,N-dimethylacetamide in 25 ml. anhydrous ether were added dropwise followed by stirring at room temperature (five minutes), followed by again heating it under reflux for fifteen minutes. Hydrolysis of the resulting mixture was accomplished with 10% aqueous hydrochloric acid. The etheral layer was separated and washed twice with 10% aqueous sodium bicarbonate, once with water and then it was dried over anhydrous magnesium sulfate. The NMR spectrum (vide infra) of the solution product indicated that conversion in 70.5% of the acetal-ketone had occurred.

After removal of the solvent, following the usual product isolation procedure employing 10% aqueous ammonium chloride as the hydrolysis media, the residue was distilled to remove some starting material. The remaining black residue, which failed to distill, crystallized on being set aside overnight. The crystalline residue was purified readily by sublimation during ywenty-four hours at a vacuum of 0.5 mm. Hg. Recrystallization twice of the greenish-yellow sublimate from methanol gave 2.3 g. (11.6 mmoles, 37%) of pure 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane as small white needles: m.p. 59.0-60.5°; λ_{max} (ethanol) 268 and 280(sh) mμ (ϵ 13,780 and 12,340 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3400, 3014, 2980, 2900, 1672, 1540, 1480, 1430, 1380, 1310, 1270, 1248, 1118, 1095, 1028, 965, 904, 860, 700. Literature

value for 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane is: m.p. 60° (55).

Anal. Calc'd for $C_9H_{10}O_3S$: C, 54.52; H, 5.08; S, 16.18. Found: C, 54.41; H, 5.16; S, 16.38.

2-(2'-Benzoyl-3'-thienyl)-1,3-dioxolane, LX

A 63 millimolar mixture of 2-(3'-thienyl)-1,3-dioxolane-2'-lithium was prepared in a 300 ml., three-necked flask equipped with magnetic stirrer, reflux condenser and a pressure equilibrating dropping funnel as described in the previous synthesis from 10.0 g. (63 mmoles) of 2-(3'-thienyl)-1,3-dioxolane in 100 ml. anhydrous ether and 43.0 ml. of a 1.6N n-butyllithium solution in hexane.

To the stirred mixture precooled to -30°, 10.3 g. (69 mmoles) of N,N-dimethylbenzamide in 50 ml. ether was added dropwise during ten minutes. Following the addition of the amide, the mixture was stirred an additional fifteen minutes, after which it was heated for five minutes at reflux to complete the reaction. The mixture was poured slowly into 200 ml. of a saturated aqueous ammonium chloride solution and stirred until two clear phases separated. The organic phase combined with two 100 ml. ethereal extracts of the aqueous phase, were washed twice with two 150 ml. portions of water and dried over anhydrous magnesium sulfate. Removal of the solvent under an air stream produced a dark brown, crystalline residue. This was recrystallized twice from

methanol using activated charcoal to obtain 8.0 g. (31 mmoles, 49%) of 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane as very pale yellow colored white short needles; m.p. 84.5-85.0°; λ_{max} (ethanol) 263 and 287 mμ (ε 12,540 and 11,190 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3090, 2960, 2900, 1650, 1600, 1592, 1548, 1490, 1458, 1435, 1375, 1265, 1185, 1140(sh), 1110, 1085, 1040, 1020, 975, 960, 945(sh), 860, 720, 705.

Anal. Calc'd for $C_{14}H_{12}O_3S$: C, 64.59; H, 4.65; S, 12.32.

Found: C, 64.42, H, 4.61; S, 12.49.

2-Methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXI

To a 500 ml., three-necked flask equipped with a magnetic stirrer, pressure equilibrating dropping funnel and reflux condenser, 85 ml. of a 1.6N n-butyllithium in hexane were added dropwise to a precooled (-40° dry ice/isopropanol) solution of 20.0 g. (0.12 mole) of 2-methyl-2-(3'-thienyl)-1,3-dioxolane in 100 ml. of anhydrous ether. The mixture was stirred for an additional ten minutes followed by heating under reflux for ten minutes.

The mixture was recooled to -25° and 10.0 g. (0.14 mole) of N,N-dimethylformamide in 30 ml. ether were added during ten minutes. The stirred mixture was set aside overnight at room temperature. The usual product isolation was accomplished by hydrolysis with a saturated aqueous ammonium chloride solution. Removal of the solvent followed by distillation in vacuo gave 2.09 g. (12 mmoles, 10% recovery) of

unreacted dioxolane distilling at 53-4° (0.5 mm. Hg) and 14.33 g. (72 mmoles, 61%) of 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane: b.p. 103-4° (0.5 mm. Hg), which solidified on being cooled. The dioxolane-aldehyde was recrystallized from methanol in dry ice. Its properties were: m.p. 34.7-35.0°; λ_{max} (ethanol) 270 mμ (ε 14,000); $\nu\ (cm^{-1})_{max}$ (CCl_4) 3330, 2990, 2880, 1708, 1660, 1525, 1480, 1445, 1425, 1380, 1365, 1345, 1250, 1205, 1150, 1110, 1050, 955, 888, 690, 675. Literature values for 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane are: b.p. 120-4° (1 mm. Hg); m.p. 40° (55). This slight discrepancy on the melting point is unexplainable.

Anal. Calc'd for $C_6H_{10}O_3S$: C, 54.52, H, 5.08; S, 16.18.

Found: C, 54.82; H, 5.14; S, 16.47.

2-Methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LXII

A 29 millimolar mixture of 2-methyl-2-(3'-thienyl)-1,3-dioxolane-2'-lithium was prepared in a 300 ml., three-necked flask equipped with a magnetic stirrer, pressure equilibrating dropping funnel and a reflux condenser, as described in previous similar synthesis, from 5.0 g. (29.4 mmoles) of 2-methyl-2-(3'-thienyl)-1,3-dioxolane and 20.0 ml. of a 1.6N n-butyllithium in pentane.

To the chilled (-25° dry ice/isopropanol) stirred mixture, 4.82 g. (33 mmoles) of N,N-dimethylbenzamide in 25 ml. ether were added dropwise and the solution was stirred overnight.

The reaction mixture was then hydrolyzed by pouring it over saturated aqueous ammonium chloride and isolating the product by the standard procedure. Removal of the solvent after drying the mixture over anhydrous magnesium sulfate yielded a crystalline residue which was recrystallized three times from methanol to obtain 3.02 g. (11 mmoles, 38%) of pure 2-methyl-2-(2'-benzoyl-2-thienyl)-1,3-dioxolane: m.p. 91.5-92.0°; λ_{max} (ethanol) 252 and 284(sh) mμ (ε 15,420 and 6,650 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3050, 3000, 2900, 1665, 1600, 1580, 1540, 1475, 1455, 1380, 1345, 1320, 1270, 1245, 1205, 1180, 1150, 1110, 1080, 1055, 955, 940, 920, 905, 870, 720, 700, 680, 660.

Anal. Calc'd for $C_{15}H_{14}O_3S$: C, 65.43; H, 5.49; S, 11.65.

Found: C, 65.55; H, 5.16; S, 11.54.

2-Phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, LXIII

Into a 300 ml., three-necked flask equipped with a magnetic stirrer, reflux condenser and pressure equilibrating dropping funnel, 5.0 g. (21.6 mmoles) of 2-phenyl-2-(3'-thienyl)-1,3-dioxolane and 70 ml. anhydrous ether were placed and cooled to -30°. To the dioxolane ether solution was added 15.6 ml. of a 1.6N n-butyllithium in pentane. The reaction mixture was stirred for five minutes and then heated under reflux for fifteen minutes. The stirred reaction mixture was recooled to a temperature of -20°, 2.0 g. (26 mmoles) of N,N-dimethylformamide in 10 ml. anhydrous ether

was added and the mixture was stirred overnight at room temperature. Product isolation was accomplished from the homogeneous mixture in the usual manner following its hydrolysis with aqueous ammonium chloride solution. Following solvent removal, distillation of the residue gave a tacky, brown material which solidified in forty-eight hours. This was easily recrystallized from methanol on refrigeration of the solution to yield 1.82 g. (7.0 mmoles, 32%) of 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane as light yellow colored crystals: m.p. 55-7°; λ_{max} (ethanol) 278 mμ (ϵ 10,512); ν $(cm^{-1})_{max}$ (CCl_4) 3060, 2970, 2890, 1712, 1688, 1535, 1505, 1483, 1460, 1432, 1395, 1370, 1320, 1270, 1230, 1130, 1095, 1085, 1040, 1015, 960, 930, 890, 850, 710, 695, 680.

Anal. Calc'd for $C_{14}H_{12}O_3S$: C, 64.59; H, 4.65; S, 12.32.
Found: C, 64.82; H, 4.70; S, 12.26.

2-Phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane, LXIV

A 300 ml., three-necked flask equipped with a magnetic stirrer, reflux condenser and dropping funnel was charged with 5.0 g (22 mmoles) of 2-phenyl-2-(3'-thienyl)-1,3-dioxolane dissolved in 75 ml. of anhydrous ether.

To the cooled solution (-25°), 13.5 ml. (25 mmoles) of a 1.6N n-butyllithium solution were added dropwise followed by heating the reaction mixture under reflux for ten minutes.

The resulting solution of 2-phenyl-2-(3'-thienyl)-1,3-dioxolane-2'-lithium in ether was recooled to -25°, and 3.5 g. (25 mmoles) of N,N-dimethylbenzamide in 20 ml. ether were slowly added. The reaction was completed by heating under reflux for ten minutes. The reaction was hydrolyzed with a saturated aqueous ammonium chloride solution and the product isolation was conducted in the usual manner.

Removal of the solvent from the dried (anhyd. magnesium sulfate) solution produced a crystalline mass. This was recrystallized twice from methanol to obtain 3.5 g. (10.4 mmoles, 47.3%) of pure 2-phenyl-2-(2'benzoyl-3'-thienyl)-1,3-dioxolane: m.p. 101.5-102°; λ_{max} (ethanol) 252 mμ (ϵ 14,420; ν $(cm^{-1})_{max}$ (CCl_4) 3070, 2980, 2890, 1665, 1600, 1585, 1545, 1500, 1480, 1455, 1320, 1270, 1225, 1180, 1140, 1100, 1085, 1030, 1008, 960, 905, 873, 840, 708, 702, 685.

Anal. Calc'd for $C_{20}H_{16}O_3S$: C, 71.40; H, 4.79; S, 9.53.

Found: C, 71.43; H, 4.86; S, 9.48.

2-Methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, LXV

A 500 ml., three-necked flask equipped with a magnetic stirrer and 100 ml. dropping funnel, were charged with 10.0 g. (45 mmoles) of 2-methyl-2-(3'-thianaphthenyl)-1,3-dioxolane in 100 ml. anhydrous ether. To the cooled (-25°, dry ice/isopropanol) solution, 31.4 ml. (50 mmoles) of a 1.6N n-butyllithium in pentane was slowly added. The resulting cold mixture, was stirred for an additional one-quarter hour

and 3.65 g. (50 mmoles) of N,N-dimethylformamide in 25 ml. anhydrous ether were added dropwise. The mixture was then set aside, at room temperature overnight with continuous stirring.

Hydrolysis of the reaction metal complex was accomplished using 100 ml. of a saturated ammonium chloride solution. Removal of solvent from the dried (anhyd. magnesium sulfate) solution produced a crystalline mass. Recrystallization of this twice from 95% ethanol gave 9.01 g. (36.3 mmoles, 80.8%) of pure 2-methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane: m.p. 110-11°; λ_{max} (ethanol) 233, 252 and 302 mμ (ε 18,100, 15.040 and 20,370 respectively); ν_{max} (CCl_4) 3.28(sh), 3.36, 3.45, 6.01, 6.62, 6.99, 7.27, 7.50, 7.61, 7.91, 8.40, 8.54, 9.00, 9.61, 10.54, 11.22, 11.52, 14.80 and 14.92(sh) u.

Anal. Calc'd for $C_{13}H_{12}O_3S$: C, 62.88; H, 4.87; S, 12.91.

Found: C, 62.79; H, 5.02; S, 12.86.

2-Phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, LXVI

A 500 ml., three-necked flask was equipped with a magnetic stirrer and a 100 ml. dropping funnel and charged with 11.3 g. (40 mmoles) of 2-phenyl-2-(3'-thianaphthenyl)-1,3-dioxolane in 100 ml. anhydrous ether. To the cooled solution (-20°), 25.3 ml. (40 mmoles) of a 1.6N n-butyllithium solution in hexane was slowly added. Following an additional stirring of the mixture for one-half hour, 2.3 g. (40 mmoles)

of N,N-dimethylformamide were added dropwise and the mixture was set aside at room temperature overnight. Following the hydrolysis of the organo lithium complex using saturated aqueous ammonium chloride, removal of the solvent produced an oil which slowly crystallized during two days. Recrystallization of the crude product twice from 95% ethanol using activated charcoal, gave 7.06 g. (22.8 mmoles, 57%) of 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane as light yellow, short needles; m.p. 111.0-12.5°; λ_{max} (ethanol) 232, 250 and 307 mμ (ε 15,870, 10,980 and 15,320 respectively); $\nu\ (cm^{-1})_{max}$ (CCl_4) 3060, 2950, 2900, 1710, 1640, 1692, 1620, 1600, 1458, 1440, 1365, 1340, 1320, 1270, 1220, 1200, 1185, 1130, 1110, 1080, 1060, 1040, 1018, 960, 935, 910, 705, 675.

Anal. Calc'd for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55; S, 10.33.

Found: C, 69.39; H, 4.63, S, 10.45.

The Hydrolysis of 2-(2'-Formyl-3'-thienyl)-1,3-dioxolane

An 88 ml. volume of acetone and 20 ml. of 10% aqueous hydrochloric acid, together with 12 g. (65.2 mmoles) of 2-(2'-formyl-3'-thienyl)-1,3-dioxolane were placed in a 250 ml. Erlenmeyer flask. The contents were stirred for two hours at room temperature. The acetone was removed by evaporation under a gentle stream of air leaving a crystalline mass. This was dissolved in 50 ml. of ether, separated from the residual water and dried over anhydrous magnesium sulfate. Removal of the ether and recrystallization of the

residue from CCl_4 yielded 8.2 g. (58.6 mmoles, 90%) of pure thiophene-2,3-dicarboxaldehyde, LXVII: m.p. 77.5-78.0°; λ_{max} (ethanol) 272 mμ (ε 10,280); ν $(cm^{-1})_{max}$ (CCl_4) 2830, 2720, 1688(sh), 1680, 1575(sh), 1511, 1435, 1400, 1368, 1240, 1223, 1182, 1162, 1025, 865, 842, 675.

Anal. Calc'd for $C_6H_4O_2S$: C, 51.42; H, 2.89; S, 22.88.

Found: C, 51.67; H, 3.15; S, 22.73.

The Hydrolysis of 2-(2'-Acetyl-3'-thienyl)-1,3-dioxolane

A 50 ml. Erlenmeyer flask was charged with 15 ml. of acetone and 2 ml. of 10% aqueous hydrochloric acid together with 1.08 g. (5.5 mmoles) of 2-(2'-acetyl-3'-thienyl)-1,3-dioxolane. The reaction was stirred for two hours and the acetone was removed by evaporation. The residual semi-solid mass was treated in the manner described previously to obtain 0.78 g. (5.1 mmoles, 92%) of 2-acetyl-3-formylthiophene, LXVIII, as pale greenish-white crystals. The product was further purified by recrystallization from methanol: m.p. 46-7°; λ_{max} (ethanol) 278 and 310(sh) mμ (ε 10,430 and 5,198 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3360, 3000, 2880, 1678, 1550, 1520, 1430, 1392, 1375, 1360. 1240, 1060, 1030, 1010, 940, 920, 855, 662. Literature values for 2-acetyl-3-formylthiophene are: m.p. 48°; ν $(cm^{-1})_{max}$ doublet 1688 and 1670 (55).

Anal. Calc'd for $C_7H_6O_2S$: C, 54.42; H, 3.92; $_2$, 20.80.

Found: C, 54.67; H, 4.00; S, 20.56.

The Hydrolysis of 2-(2'-Benzoyl-3'-thienyl)-1,3-dioxolane

Acetone (50 ml.) and 10 ml. of 10% aqueous hydrochloric acid were used to hydrolyze 4.0 g. (15.4 mmoles) of 2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane by the procedure just described. The time required for hydrolysis was two hours. The usual product isolation procedure using 50 ml. of ether yielded 3.0 g. (13.9 mmoles, 90.3%) of crude 2-benzoyl-3-formylthiophene, LXIX. This was recrystallized twice from hexane-ether using activated charcoal to obtain a pure material, in the forms of off-white colored short needles: m.p. 53.5-54.0°; λ_{max} (ethanol) 278 mμ (ε 12,720); ν $(cm^{-1})_{max}$ (CCl_4) 3050, 2900, 1765, 1708(sh), 1690, 1650, 1600, 1580, 1522, 1458, 1438, 1392, 1322, 1268, 1235, 1185, 1140, 1080, 1015, 980, 945, 925, 890, 850, 720, 705, 670.

Anal. Calc'd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83.

Found: C, 66.75; H, 3.84; S, 15.03.

The Hydrolysis of 2-Methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane

A 125 ml. Erlenmeyer flask was charged with 80 ml. acetone, 20 ml. of 10% aqueous hydrochloric acid, and 7.8 g. (39.4 mmoles) of 2-methyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane. The contents were stirred at ambient temperatures for six hours.

After the acetone had been removed under a gentle stream of air, the residue was dissolved in 50 ml. ether, separated

from the aqueous material and dried over anhydrous magnesium sulfate. Removal of the ether and recrystallization of the crude product from methanol gave 5.2 g. (33.7 mmoles, 85.5%) of 2-formyl-3-acetylthiophene, LXX, in the form of short pale greenish-white needles: m.p. 61-2°; λ_{max} (ethanol) 280 mμ (ε 11,650); ν $(cm^{-1})_{max}$ (CCl_4) 3000, 2880, 1680, 1665, 1520, 1425, 1388, 1365, 1250, 1200, 1160, 1090, 1025, 1005, 915, 848, 708, 680. Literature values for 2-formyl-3-acetylthiophene are: m.p. 61°; ν $(cm^{-1})_{max}$ 1671 (55).

Anal. Calc'd for $C_7H_6O_2S$: C, 54.52, H, 3.92; S, 20.80. Found: C, 54.37; H, 3.96; S, 21.01.

The Hydrolysis of 2-Methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane

The hydrolysis of 1.77 g. (6.5 mmoles) of 2-methyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane required 25 ml. acetone, 10 ml. water and 3 ml. of 10% aqueous hydrochloric acid. The hydrolysis solution was stirred for five hours at room temperature and the product was isolated in the manner previously described. The crude product was crystallized from CCl_4 (using refirgeration) to obtain 1.25 g. (5.43 mmoles, 84%) of pure 2-benzoyl-3-acetylthiophene, LXXI, in the form of small needles: m.p. 87.3-87.7°; λ_{max} (ethanol) 261 and 290 mμ (ε 13,880 and 7,740 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3080, 3020, 2950, 1680, 1660, 1600, 1582, 1515, 1483, 143-, 1408, 1383, 1358, 1320, 1273, 1255(sh), 1182, 1090, 1035, 1028, 945, 905, 900, 720, 700.

Anal. Calc'd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.93.

Found: C, 67.74; H, 4.37; S, 14.08.

The Hydrolysis of 2-Phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane

A 50 ml. Erlenmeyer flask was charged with 10 ml. of 10% aqueous acetone, a few drops of concentrated hydrochloric acid and 1.0 g. (2.97 mmoles) of 2-phenyl-2-(2'-benzoyl-3'-thienyl)-1,3-dioxolane. The hydrolysis mixture was stirred for two hours at ambient temperature, and the acetone was removed under a gentle stream of air. The residue was dissolved in ether, washed with 5% aqueous sodium bicarbonate and water and the ether solution was dried over anhydrous magnesium sulfate. Removal of the ether left a crystalline mass which was recrystallized twice from 95% ethanol to obtain 0.6 g. (2.05 mmoles, 69.2%) of pure 2,3-dibenzoylthiophene, LXXIII, in the form of short prisms: m.p. 80.5-81.0°; λ_{max} (ethanol) 264 mμ (ϵ 33.440); ν $(cm^{-1})_{max}$ (CCl_4) 3096, 3077, 3040, 1665, 1600, 1582, 1520, 1455, 1418, 1385, 1322, 1280, 1190, 1140, 1085, 1018, 1005(sh), 948(sh), 935, 890, 720, 700(sh), 670.

Anal. Calc'd for $C_{18}H_{12}O_2S$: Sc, 73.95; H, 4.14; S, 10.97.

Found: C, 73.87; H, 4.21; S, 10.97.

The Hydrolysis of 2-Methyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane

In a 125 ml. Erlenmeyer flask, a mixture of 5.32 g. (2.14 mmoles) of 2-methyl-2-(2'-formyl-3'-thianaphthenyl)-

1,3-dioxolane, 40 ml. of acetone and 5 ml. of 10% aqueous hydrochloric acid was stirred at room temperature for ten hours. Removal of the acetone was accomplished with a gentle stream of air to obtain a dark brown residue. The residue was dissolved in ether, washed with 5% aqueous sodium hydroxide and then with water. The ether solution was dried over anhydrous magnesium sulfate. Removal of the ether, followed by vacuum sublimation of the residue (0.1 mm Hg, 50-70°) yielded a semi-solid crystalline material which on recrystallization from methanol yielded 2.81 g. (1.37 mmoles, 64.2%) of pure 2-formyl-3-acetylthianaphthene, LXXIV, in the form of long pale green-white needles: m.p. 107-8°; λ_{max} (ethanol) 234, 257, and 307 mμ (ε 27,600, 10,670 and 9,370 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3010, 3007, 2940, 1673, 1600, 1560, 1510, 1472, 1440, 1365, 1350, 1280, 1205, 1080, 970, 940, 890, 870, 680.

Anal: Calc'd for $C_{11}H_8O_2S$: C, 64.68; H, 3.95; S, 15.70.
Found: C, 64.96; H, 4.05; S, 15.59.

The Synthesis of Thiophene-3,4-biscarboxaldehyde

The preparation of the necessary intermediates for the synthesis of this heterocyclic were carried out first. 3,4-Dibromothiophene was prepared from thiophene via the tetrabromothiophene following the method of Gronowitz, Moses and Häkansson (66). 4-Bromo-3-thiophenecarboxaldehyde was prepared from 3,4-dibromothiophene by the method of Gronowitz,

Moses, Hornfeldt and Häkansson (24). The bromo-aldehyde was readily converted to the corresponding ethylene acetal as described by Gronowitz, Biezais and Mathiasson (40). The synthesis of the thiophenedicarboxaldehyde was then conducted as follows.

A one liter, three-necked flask was equipped with a mechanical stirrer, dry nitrogen inlet tube and a dropping funnel. This flask was connected by a small length of Tygon tubing to a second two-liter, three-necked flask using rubber stoppers fitted with small glass tubes. This two liter flask was also equipped with a mechanical stirrer and a drying tube. The apparatus was thoroughly dried by flaming it with a Bunsen burner while continuously purging the apparatus with dry nitrogen.

The liter flask was charged with 312 ml. (0.5 mole) of a 1.6N n-butyllithium solution in hexane and cooled to -70° (dry ice/isopropanol bath). To the cold stirred solution of n-butyllithium, 100 g. (0.43 mole) of 2-(4'-bromo-3'-thienyl)-1,3-dioxolane in 150 ml. of anhydrous ether were added slowly to avoid any excessive rise in the reaction temperature (forty-five minutes). Following the addition of the dioxolane solution, the heavy white mixture was stirred an additional fifteen minutes.

A two liter flask was charged with 55.0 g (0.75 mole) of N,N-dimethylformamide and 150 ml of anhydrous ether and its contents were cooled to -70° by immersion in a

dry ice/isopropanol bath. The mixture in the one liter flask containing 2-(3'-thienyl)-1,3-dioxolane-4'-lithium was slowly poured through the Tygon tubing into the N,N-dimethylformamide-ether solution, during ten minutes. Cold, dry ether was used to wash the last solid residue from the one liter flask into the two liter flask. The combined mixture in the two liter flask was stirred overnight at room temperature.

The resulting clear green solution was poured into an equal volume of water and two phases were separated. The aqueous phase was extracted twice with 100 ml. portions of ether. The combined organic phases were washed twice with 5% aqueous hydrochloric acid, once with 10% aqueous sodium bicarbonate and finally with water, and then dried over anhydrous magnesium sulfate. After filtering, the ether was removed to yield a solid residue. This was crystallized from hexane-ether to obtain 32.0 g. in the form of long white needles (0.23 mole, 54% based on the bromo-acetal) of pure thiophene-3,4-biscarboxaldehyde: m.p. 79-80°; λ_{max} (ethanol) 230 and 278 mμ (ε 22,640 and 12,940 respectively); ν $(cm^{-1})_{max}$ (CCl_4) 3120, 2900, 2830, 2700(sh), 1692, 1515, 1448, 1740(sh), 1365, 1183, 1165, 1120, 905, 885, 840, 670.

Anal. Calc'd for $C_6H_4O_2S$: C, 51.42, H, 2.89; S, 22.88.

Found: C, 51.22; H, 2.91; S, 23.05.

Trofimenko (48) reported only a m.p. of 78-80° and NMR values of -0.36 τ and 1.69 τ for thiophene-3,4-biscarboxaldehyde.

The Synthesis of Thieno[3,4-d]thiepin-2,4-dicarboxylic acid

A solution of 9.00 g. [43.7 mmoles] of diethyl thiodiglycolate and 6.13 g. [43.7 mmoles] of thiophene-3,4-biscarboxaldehyde in 20 ml. absolute methanol was added dropwise into a 300 ml., three-necked flask equipped with a magnetic stirrer, dropping funnel and dry nitrogen inlet, containing a cold (0-5°) sodium methoxide solution prepared from 4.2 g. (0.176 g. atom) of freshly cut sodium in 60 ml. of absolute methanol. The rate of the addition of the sodium alkoxide solution was regulated to hold the reaction temperature below 8°. The mixture was stirred an additional two hours at ice bath temperatures, then concentrated to a total volume of 40 ml. using a water aspirator at room temperature. The mixture was then diluted with 90 ml. of water and acidified with 18% aqueous hydrochloric acid under rigorous stirring until no further precipitation occurred. The precipitate was recovered by filtration and dried in a vacuum desiccator over sulfuric acid for twenty-four hours to obtain 5.7 g. (22.4 mmoles, 51.3%) of crude thieno[3,4-d]thiepin-2,4-dicarboxylic acid.

Recrystallization of the crude product was accomplished in two equal portions by adding each to 200 ml. of boiling 80% aqueous ethanol and stirring rapidly for thirty seconds. Concentrated hydrochloric acid (4 ml.) was added and the solution was again stirred vigorously. Before the last traces

of residue had dissolved, the solutions were quickly filtered into flasks immersed in an ice bath. After setting the filtrate aside in a refrigerator for one-half hour, the products were then collected by filtration and dried. By this procedure, 1.8 g. of pure thieno[3,4-d]thiepin-2,4-dicarboxylic acid were collected and an additional quantity of 0.54 g. product were obtained by concentration of the mother liquor. The melting point of the product was stable at 250°, showed initial decomposition at 280° and had undergone decomposition at 295°. The crystalline material was a deep, velvet red in color, insoluble in carbon disulfide, carbon tetrachloride, water and cold ethanol but was soluble in aqueous base, dimethylsulfoxide, N,N-dimethylformamide and N,N-dimethylacetamide: λ_{max} (ethanol) 218, 252, 284, 331, 348 and 368 mμ (ε 14,300, 15,460, 34,100, 2,390, 2,070 and 1,180 respectively); max (CCl_4) 2.90, 3.20, 3.38, 3.80, 6.00, 6.22, 6.70, 8.02, 7.10, 7.78, 7.91, 8.16, 8.38, 9.87, 11.15, 11.54, 12.21, 13.05, 13.26, 13.77, 14.17, 14.83, and 15.66 u.

Anal. Calc'd for $C_{10}H_8O_4S_2$: C, 47.23; H, 2.38; S, 25.22.

Found: C, 47.25; H, 2.65; S, 25.04.

Attempted Hydrolysis of 2-Phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane

A 50 ml., Erlenmeyer flask was charged with 1.3 g. (5.0 mmoles) of 2-phenyl-2-(2'-formyl-3'-thienyl)-1,3-dioxolane, 2 ml. of 10% aqueous hydrochloric acid and 20 ml. of acetone. The reaction solution was stirred under a nitrogen atmosphere

at room temperature for two hours. The acetone was removed under a gentle stream of air and the residue was dissolved in ether, washed twice with water and dried over anhydrous magnesium sulfate. Removal of the ether yielded an oil which was shown to be identical to starting material by its identical infrared and NMR spectra. This oil was redissolved in 20 ml. of acetone and 2 ml. of 10% aqueous hydrochloric acid and allowed to stir an additional twelve hours under a nitrogen atmosphere. Following a product isolation procedure as described above, a brownish black "tarry" residue was obtained. An NMR spectrum of the residue in carbon tetrachloride, exhibited only complex absorption in the aromatic region (2.2 τ - 3.0 τ) and an aldehydic proton and ketal proton absorption (1:4 ratio) which together approximated less than 5% of the total proton absorption.

The Attempted Hydrolysis of 2-Phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane

In a 125 ml. Erlenmeyer flask were placed, 4.68 g. (1.5 mmoles) of 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, 40 ml. of acetone and 15 ml. of 10% aqueous hydrochloric acid. The reaction mixture was stirred for twelve hours under a nitrogen atmosphere. The acetone was removed by an air stream. The residue was dissolved in 20 ml. of ether, washed twice with water and dried over anhydrous magnesium sulfate. Removal of the ether gave a residue which was shown to be identical to the starting material.

The hydrolysis procedure was repeated under identical conditions for an additional twenty-four hours (total thirty-six hours) to yield a "tarry" brown residue which resembled the starting material as indicated from its NMR spectrum. To a 100 ml., three-necked flask equipped with a reflux condenser and nitrogen inlet gas tube was charged with 2.4 g. (0.8 mmole) of 2-phenyl-2-(2'-formyl-3'-thianaphthenyl)-1,3-dioxolane, 40 ml. acetone and 10 ml. of 10% aqueous hydrochloric acid. The contents were heated under reflux in a nitrogen atmosphere for eighteen hours. Product isolation procedures were carried out in the previously described manner. Removal of the ether left a tarry residue. Determination of its NMR spectrum in CCl_4 showed a complex absorption of protons in the aromatic region (2.2-3.0 τ). Proton absorption attributable to the aldehyde and ketal hydrogens in a 1 to 4 ratio compared to aromatic protons indicated that the reaction had progressed to the extent of approximately 90%.

The Attempted Synthesis of Thieno[3,4-d]-oxepin-2,4-dicarboxylic acid

To a 300 ml., three-necked flask equipped with a magnetic stirrer, dry-nitrogen gas inlet and a pressure equilibrating dropping funnel capped with an attached drying tube of calcium sulfate, a solution of 6.13 g. (43.7 mmoles) of dimethyl diglycolate in 20 ml. anhydrous methanol was added to a vigorously stirred solution of sodium ethoxide prepared from 4.2 g. (0.18 g. atom) of freshly cut sodium in 60 ml.

absolute methanol. The rate of addition of the alkoxide was adjusted to maintain the reaction temperature below 10°. The light yellow reaction mixture was stirred an additional two hours at 5° and overnight at ambient temperature to complete the reaction. The reaction solution was concentrated to 40 ml. volume under vacuum (water aspirator) and 50 ml. water was added to partially dissolve the residue. The contents of the flask were filtered to yield a clear filtrate. This on acidification with concentrated hydrochloric acid produced a precipitate which when collected by filtration and dried, could not be dissolved in methanol, ethanol, acetone, dimethylsulfoxide or N,N-dimethylformamide. The precipitate was redissolved in 10% aqueous sodium hydroxide. The original insoluble material, obtained on concentration of the reaction solution, could not be dissolved in any of the aforementioned solvents. Both precipitates exhibited melting points with initial decomposition at 295° and severe darkening at 310-315°. The base soluble precipitate (7.2 g.) was subjected to carbon-hydrogen analysis.

Anal. Calc'd for $C_{10}H_4O_5S$: C, 50.42; H, 2.54; S, 13.46.

Found: C, 48.74; 48.73; H, 3.99, 3.87; S, 9.88.

No ash or residue was reported.

The Attempted Synthesis of Thieno[2,3-d]-thiepin-2,4-dicarboxylic acid

A 300 ml., three-necked flask was equipped with a magnetic stirrer, dry-nitrogen gas inlet and a pressure

equilibrating dropping funnel. A sodium ethoxide solution containing 2.1 g. (0.09 g. atom) of freshly cut sodium in 40 ml. anhydrous methanol was prepared in the flask under dry nitrogen and cooled to 0°. To the chilled alkoxide solution, a mixture of 4.5 g. (21.9 mmoles) of diethyl thiodiglycolate and 3.00 g. (21.4 mmoles) of thiophene-2,3-biscarboxaldehyde in 40 ml. anhydrous methanol was added dropwise during one-quarter hour. No turbidity or precipitate was noted initially, as was also true with thieno[3,4-d]thiepin-2,4-dicarboxylic acid where an orange disodium salt was observed. However, as the reaction progressed at $0\text{-}5^{\circ}$, globules of dark brown-black resinous material was formed and deposited in the reaction vessel. After twelve hours, this material had partially solidified. This material (0.42 g.) was recovered by filtration and found to be insoluble in N,N-dimethylacetamide, dimethylsulfoxide, carbon tetrachloride, water and 10% aqueous base and acid. A strong odor of hydrogen sulfide was noted toward the end of the reaction period. The filtrate was acidified using concentrated hydrochloric acid. Reduction of the volume followed by addition of water produced no precipitate.

LITERATURE CITED

1. H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, 1952.

2. H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, 1954.

3. S. Gronowitz, Adv. Heterocyclic Chem., 1, 1 (1963).

4. M. Janda and F. Dvorak, Czech. 105,005 (Sept. 15, 1962); Chem. Abstr., 60, 1704a (1964).

5. P. Courtot and D. H. Sachs, Bull. Soc. Chim. France, 2259 (1965).

6. B. J. Herold and M. E. Miranda Faustino, Terahedron Letters, 467 (1968); B. J. Herold, Rev. Port. Quim., 3, 101 (1961); Chem. Abstr., 60, 13204d (1964).

7. R. E. Buntrock and E. C. Taylor, Chem. Rev., 68, 209 (1968).

8. R. Zahradnik, Adv. Heterocyclic Chem., 5, 1 (1965).

9. W. M. Mock, J. Amer. Chem. Soc., 89, 1281 (1967).

10. M. Rajsner, J. Metys and M. Protiva, Collect. Czech. Chem. Commun., 32, 2854 (1967); Chem. Abstr., 67, 90902r (1967).

11. SPOFA United Pharmaceutical Works, Brit. 1,081,360 (Aug. 31, 1967); Chem. Abstr., 68, 95849z (1968).

12. R. H. Schlessinger and G. S. Ponticello, J. Amer. Chem. Soc., 89, 7138 (1967).

13. M. J. Jorgenson, J. Org. Chem., 27, 3224 (1962).

14. H. Hofmann and H. Westernacher, Angew. Chem., 79, 238 (1967).

15. K. Dimroth and G. Lenke, Chem. Ber., 89, 2608 (1956); Ibid., Angew. Chem., 68, 519 (1956).

16. J. D. Loudon and A. D. B. Sloan, J. Chem. Soc., 3262 (1962).

17. G. P. Scott, J. Amer. Chem. Soc., 75, 6332 (1953).

18. H. Gilman and D. A. Shirley, J. Amer. Chem. Soc., 71, 1870 (1949).

19. S. Gronowitz, Arkiv Kemi, 7, 361 (1954).

20. Ibid., 13, 295 (1958).

21. D. J. Klinke, Ph. D. Thesis, Michigan State Univ., 1963.

22. D. A. Shirley and K. R. Barton, Tetrahedron, 22, 515 (1966); S. Cronowitz and K. Halvarson, Arkiv Kemi, 8, 343 (1955).

23. S. Gronowitz and B. Gestblom, Arkiv Kemi, 18, 513 (1962).

24. S. Gronowitz, P. Moses, A. B. Hornfeldt and R. Hakansson, Arkiv Kemi, 17, 165 (1961).

25. Ya. L. Gol'dfarb, M. A. Kalik and M. L. Kirmalova, J. Gen. Chem. (USSR), 29, 2003 (1959); English Translation.

26. Ibid., 29, 3592 (1959); English Translation.

27. J. Sice, J. Amer. Chem. Soc., 75, 3697 (1953).

28. S. Gronowitz, Arkiv Kemi, 12, 239 (1958).

29. Ibid., 16, 363 (1960).

30. J. Sice, J. Org. Chem., 19, 70 (1954).

31. C. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 61-90.

32. S. Gronowitz, B. Gestblom and B. Mathiasson, Arkiv Kemi, 20, 407 (1963).

33. S. O. Lawesson, Arkiv. Kemi, 11, 317 (1957).

34. Ibid., 11, 325 (1957).

35. P. Moses and S. Gronowitz, Arkiv Kemi, 18, 119 (1961).

36. S. Gronowitz, Arkiv Kemi, 7, 267 (1954).

37. S. O. Lawesson, Arkiv Kemi, 11, 337 (1957).

38. S. Gronowitz, Adv. Heterocyclic Chem., 1, 76 (1963).

39. S. Gronowitz, Arkiv Kemi, 12, 115 (1958).

40. S. Gronowitz, A. Biezais and B. Mathiasson, Arkiv Kemi, 21, 265 (1963).

41. L. Gatterman, Ann., 393, 230 (1912).

42. S. Gronowitz and A. Rosenberg, Arkiv Kemi, 8, 23 (1955).

43. M. Vaysse and P. Pastour, Bull. Soc. Chim. France, 469 (1964).

44. C. Sone. Bull. Soc. Chem. Japan, 37, 1197 (1964); Chem. Abstr., 61, 14620h (1964).

45. V. I. Rogovik and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., Akad. Nauk Latv. S.S.R., 657 (1957); Chem. Abstr., 64, 14156h (1966).

46. S. F. Thames and J. E. McCleskey, J. Heterocyclic Chem., 3, 104 (1966).

47. A. V. El'tsov and A. A. Ginesina, Zh. Org. Khim., 3, 191 (1967); Chem. Abstr., 66, 94851r (1967).

48. K. Dimroth, G. Pohl and H. Follman, Chem. Ber., 99, 634 (1966).

49. P. Pastour, P. Savalle and P. Eymry, Compt. Rend., 260, 6130 (1965).

50. Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein and B. V. Lopatkin, Zh. Obshch. Khim., 34, 969 (1964); Chem. Abstr., 61, 629c (1964).

51. S. Trofimenko, J. Org. Chem., 29, 3046 (1964).

52. D. D. Taft, Ph. D. Thesis, Michigan State Univ., 1963.

53. E. E. Campaign and W. O. Foye, J. Amer. Chem. Soc., 70, 3941 (1948).

54. B. Ostman, Arkiv Kemi, 22, 551 (1964).

55. M. Robba, B. Roques and M. Bonhomme, Bull. Soc. Chim. France, 2495 (1967).

56. B. P. Fedorov and F. M. Stoyanovich, U.S.S.R. 162,154 (Apr. 16, 1964); Chem. Abstr., 61, 9525h (1964).

57. M. Robba, R. C. Moreau and B. Roques, Compt. Rend., 259, 3568 (1964).

58. M. Winn and F. G. Bordwell, J. Org. Chem., 32, 1610 (1967).

59. D. A. Shirley and M. D. Cameron, J. Amer. Chem. Soc., 72, 2788 (1950).

60. D. A. Shirley and M. J. Danzig, J. Amer. Chem. Soc., 74, 2935 (1952).

61. W. Reid and H. Bender, Chem. Ber., 89, 1574 (1956).

62. K. Dimroth and H. Freyschlag, Chem. Ber., 89, 2602 (1956); Ibid., Angew. Chem., 68, 518 (1956).

63. K. Dimroth and H. Freyschlag, Angew. Chem., 69, 95 (1957).

64. R. Huisgen, E. Laschtuvka, I. Ugi and A. Kammermeier, Ann., 630, 128 (1960).

65. G. Eglinton, I. A. Lardy, R. A. Raphael and G. A. Sim, J. Chem. Soc., 1154 (1964).

66. S. Gronowitz, P. Moses and R. Hakensson, Arkiv Kemi, 16, 267 (1960).

67. S. Gronowitz, Acta Chem. Scand., 13, 1045 (1959).

68. M. W. Farrar and R. Levine, J. Amer. Chem. Soc., 72, 4433 (1950).

69. S. Gronowitz, Arkiv Kemi, 8, 441 (1955).

70. Ibid., 12, 533 (1958).

71. M. Sulzbacher, E. Bergman and E. R. Pariser, J. Amer. Chem. Soc., 70, 2827 (1948).

72. R. L. Gay, S. Beatman and C. R. Hauser, Chem. Ind., 1789 (1965).

73. G. M. Badger and B. J. Christie, J. Chem. Soc., 3435 (1948).

74. N. P. Buu Hoi and P. Cagniant, Rec. Trav. Chim., 67 64 (1948).

75. S. Gronowitz, Arkiv Kemi, 13, 239 (1958).

76. E. Caspi, T. A. Wittstruck and D. M. Piatek, J. Org. Chem., 27, 3183 (1962).

77. H. H. Szmant and A. J. Basso, J. Amer. Chem. Soc., 73, 4521 (1951).

78. S. Gronowitz, Arkiv Kemi, 13, 295 (1959).

79. L. Kaper, J. U. Veenland and T. J. deBoer, Spectrochimica Acta, 23A, 2605 (1967).

80. M. L. Martin, C. Andrieu and G. L. Martin, Tetrahedron Letters, 921 (1966).

81. B. Bottcher and F. Bauer, Ann., 568, 218 (1950).

82. E. E. Campaign, R. C. Bourgeois and W. C. McCarthy, Organic Syntheses, 33, 93 (1953).

83. B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy and J. H. Williams, J. Org. Chem., 18, 138 (1953).