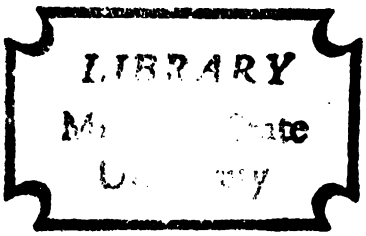
THE SYNTHESIS AND REACTIONS OF SOME THIENYL FURANS

Thesis for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY

David J. Klinke

1963



ABSTRACT

THE SYNTHESIS AND REACTIONS OF SOME

THIENYL FURANS

by David J. Klinke

The purpose of this investigation was to study the chemical behavior of some mixed heterocyclic biaryls. 2-(2'-Thienyl)-furan and 3-(2'-Thienyl)-furan were prepared by the ring closure methods of Benary and Burness respectively. Although these compounds were found to be air oxidizable, they were quite stable under a nitrogen atmosphere.

These biaryls were subjected to metalation, acylation, and free radical bromination. Preferential coordination of the metalating agent with the sulfur hetero atom prior to hydrogen metal interchange controls the location of substitution, only that α position which is proximate to the sulfur atom undergoing metalation. Acylation and bromination occur preferentially in the less aromatic furan nucleus. Substitution occurring in the α position ortho to the thienyl substituent thus characterizing that substituent as an ortho para director.

Product structures were assigned with the aid of the characteristic spin-spin coupling constants of the aromatic protons, which in this work were found to be (c.p.s.): thiophene, J_{23} = 4.5-5.3; J_{24} = 1.2-1.9; J_{34} = 3.4-4.1; furan, J_{23} = 1.6-2.1, J_{24} = 0.7-0.9, J_{25} = 1.5-1.7, J_{34} = 3.4-3.9.

The Campaigne and Hinsberg methods of ring closure are discussed. The attempted conversion of 2-nitro-thiophene to 3-thenoic acid via a Von Richter reaction is also outlined.

THE SYNTHESIS AND REACTIONS OF SOME THIENYL FURANS

By

David J. Klinke

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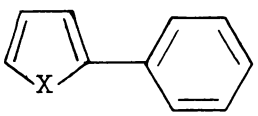
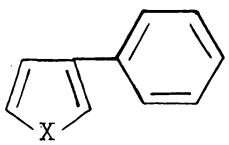
INTRODUCTION AND HISTORICAL

The directing influence of a substituent on an aromatic nucleus on a subsequent substitution on the ring is well known. The directive influences of many substituents in arene hydrocarbons have been determined and are familiar knowledge. However, the orienting effects of the heteroaromatics furan, pyrrole, and thiophene as substituents have been more difficult to ascertain experimentally. Due to the greater reactivity of the heterocyclics relative to benzene, compounds such as I' or II' undergo further



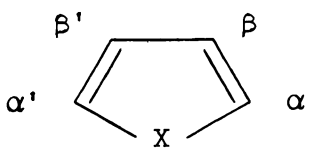
I'



II'

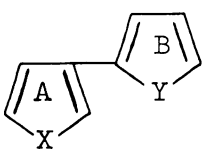
X = O, S, or NH

substitution in the hetero ring, which gives no information on the directing effect of the hetero ring as a substituent. Thus, if the directing influence of a hetero ring in substitution reactions is to be determined it must be used as a substituent on a more reactive nucleus. In a search for such a nucleus the possibility of using another heterocyclic ring immediately suggests itself. Substitution reactions of the heterocyclic aromatic compounds, furan, pyrrole, and thiophene are known to occur preferentially in a position α to the heteroatom when that position is open.

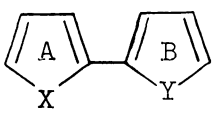


X = O, S, or NH

When one of the β positions is substituted moreover, this β substituent directs the incoming group to the adjacent α or opposite α' position in a manner similar to that found in the benzene system. Thus, ortho, para directing substituents direct the incoming group to the adjacent α position, while a meta director leads to substitution at the alternate α' position. Therefore, the substitution reactions of compounds of types III' and IV', where the reactivity of ring A is greater than, or equal to



III'



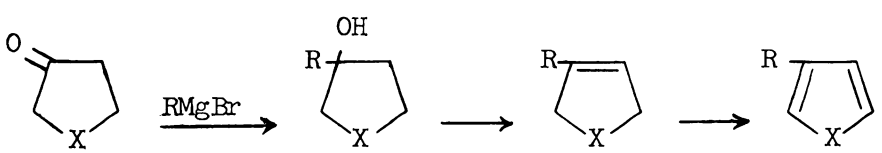
IV'

that of ring B, should yield important information regarding the directive influence of ring B to substitution reactions on ring A.

Methods of preparation of heterocyclic biaryls.

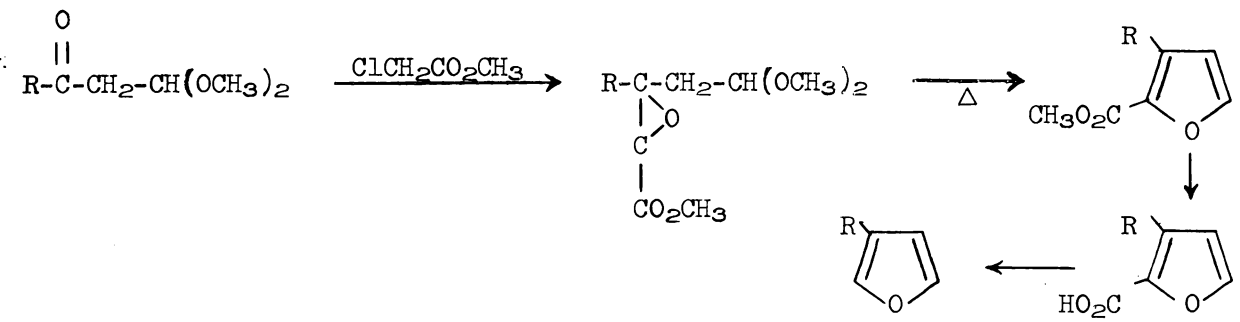
(a) β substituted compounds.

Wynberg has developed synthetic procedures (2,3) for the preparation of compounds of structure type III'.

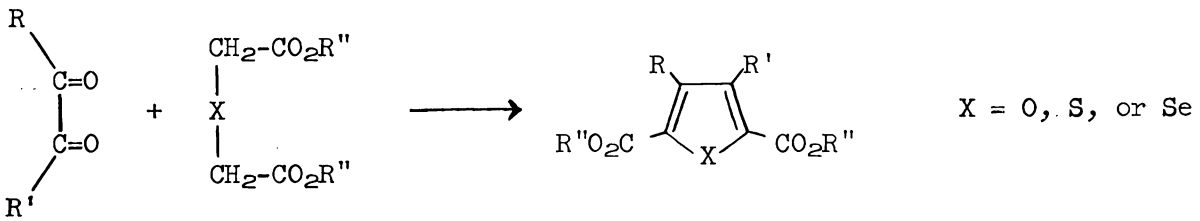


X = O or S

In this, or a similar manner he has prepared compounds where X=Y=S, (2) X=S and R=ϕ, (2) X=O and R=ϕ (3) and in unpublished work (1,4) the compound where X=O and Y=S. Burness has also developed an excellent route (5,6,7) to the β substituted furans.



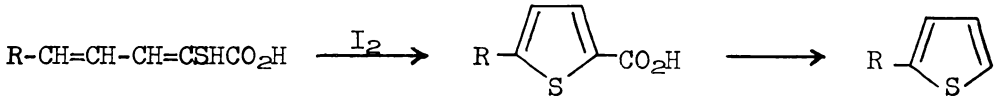
He has shown this reaction to be quite general by utilizing it to prepare compounds where R = methyl or phenyl. Alternatively Hinsberg's (15) studies of the reaction between α-dioxo compounds and diglycolic or thiodiglycolic acids or their esters,



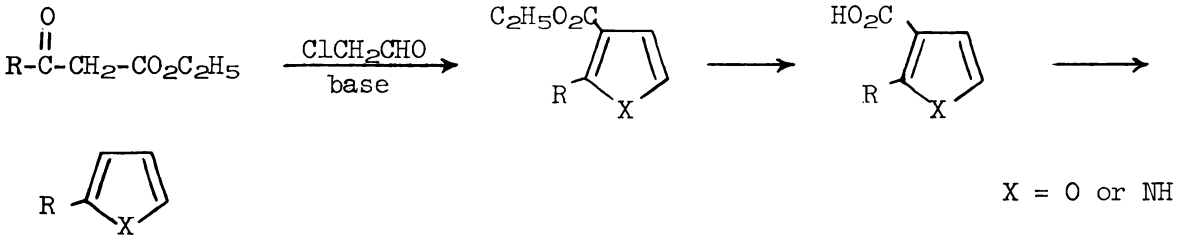
may give a third method for the synthesis of type III' structures. While Becker and Stevens (16) used this procedure to prepare the 3,4-diphenyl-furan, - thiophene, and -selenophenes, Dodson (9) utilized it to prepare the β,β'-di-α-thienyl-thiophene.

(b) α substituted compounds.

Compounds of type IV' on the other hand should be capable of preparation by the method of Campaigne (8),



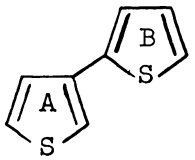
who used this method to prepare the R = phenyl compound. Dodson (9) has prepared the R = α-thienyl compound by the same procedure. An alternative procedure for the preparation of a type IV' structure could be adaptation of the method developed by Benary (10,11,12) for the preparation of α-substituted β-furoates and pyrrole carboxylates.



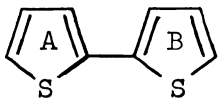
While Gilman (12) used this method to prepare the 2-methyl-3-furoate, Kondo and Suzulsi (13) used it to prepare the 2-phenyl-3-furoate. Johnson (14) however while using this and other methods reported that the 2-phenyl furans which they prepared turned dark on standing, indicating a degree of instability of aromatic substituted furans.

Reactions of heterocyclic biaryls.

Reactions of 2-3' bithienyl V', and 2-2' bithienyl VI', . .

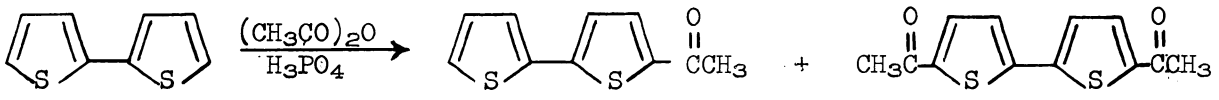


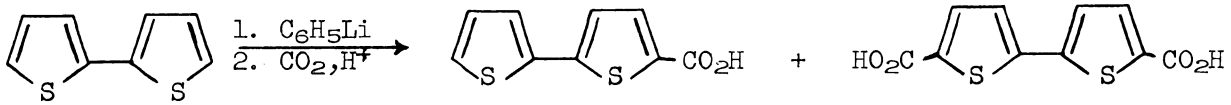
V'



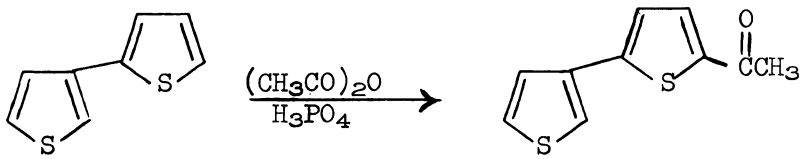
VI'

i.e., structures III' and IV' where X = Y = S, have been studied by Wynberg (1). While both acylation (17) and metalation of compound VI' resulted in mono- and di-substitution in the 5 and 5' positions as expected,

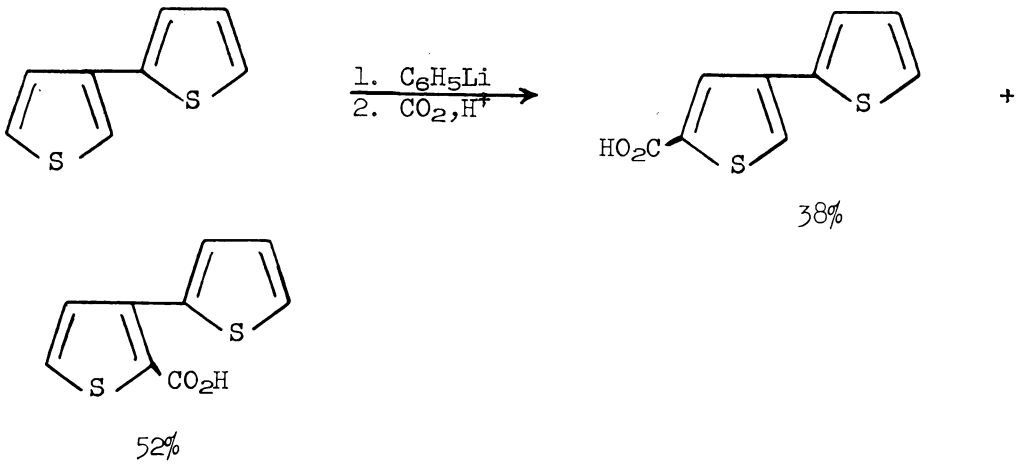




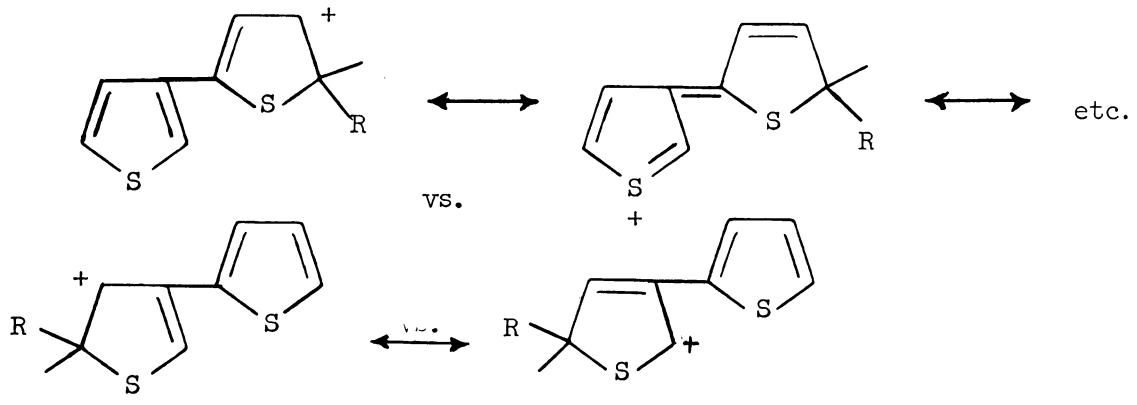
acylation of V' resulted in substitution into the open 5 position of ring B. Attempted acylation of ring A by using more drastic methods resulted in the formation of an intractable polymer.



Metalation of V', however, resulted in substitution at either the 2' or 5' position of ring A.

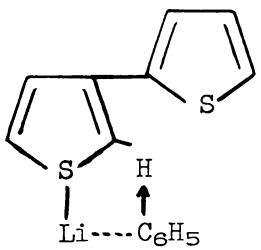


Wynberg ascribes the electrophilic attack at the 5 position in V' to steric interference by the ortho thiophene to substitution at the 2' position and to conjugative interactions with the other ring which are possible for substituion at the 5 position but which cannot easily be formulated if initial attack occurs at the 5' position.

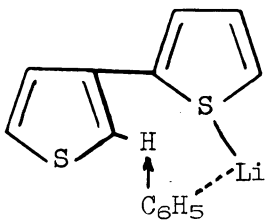


These results give little information as to the directive influence of a thiophene ring to electrophilic substitution.

The results of the hydrogen metal interchange were ascribed to: (a) greater electronegativity of the 5 position, as illustrated by the electrophilic substitution, than that of the 5' position, (b) the electron attraction of thiophene as an ortho substituent, (c) possibility of coordination of the lithium atom with the sulfur atom of either ring prior to exchange, and

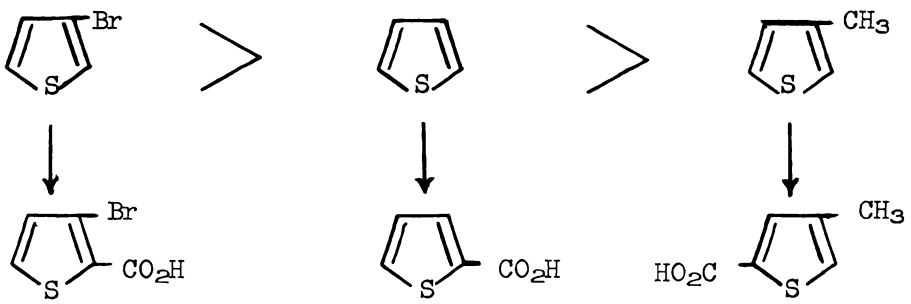


and



(d) a decrease in basicity of the sulfur atom in ring B, therefore, a decrease in ability to coordinate with the lithium atom, caused by electron attraction by thiophene. The work of Gronowitz (23,24,25) on electrophilic aromatic substitutions has shown metalation to occur at a position ortho to a substituent which contains a pair of unshared electrons, independent of the directing influence of that substituent. Thus, the initial step in metalation of thiophenes is a coordination of the metal of the metalating agent with the unshared electron pair of the sulfur atom. By reactions on unsubstituted, 3-bromo, and 3-methyl thiophenes, Gronowitz determined that

the orientation and reaction rates were the same as would be predicted by inductive effect, i.e.,



These results are consistent with additional work (26) in which the same investigator metalated thiophene with n-butyl lithium in trace amounts of thiophene-2-t, and observed a kinetic isotope effect of $K_H/K_T = 5.9$. These facts have been interpreted by Gronowitz to indicate that the rate determining step is a nucleophilic attack on H by the carbanion, a mechanism similar to that proposed by Wynberg and discussed previously.

Assignment of product structures.

Nuclear magnetic resonance studies (20) have been made on several substituted furans, pyrroles (22) and thiophenes (18,19,21). The data obtained indicate that these heterocycles have characteristic proton spin-spin coupling constants which are quite consistent regardless of the substituent which may be present. Gronowitz (18), in a study of twenty, 2 and 3 substituted thiophenes, has found this ring's proton spin coupling constants to be (c.p.s.): $J_{23} = 5.4 \pm 0.6$; $J_{34} = 3.8 \pm 0.3$; $J_{25} = 2.5 \pm 0.4$; $J_{35} = 1.6 \pm 0.3$. In another study (27) of twenty, 2 substituted and sixteen, 3 substituted thiophenes, Gronowitz attempted to establish the influence of

the anisotropic susceptibilities of the substituents on the chemical shifts. These were found to contribute only in a minor degree to the chemical shifts. Thus, he decided that the shifts are largely determined by local contributions and as such are directly related to the electron densities on the various hydrogens. The shift data were discussed in terms of inductive effects and by using simple resonance theory. Smaller shifts of the 4 position compared to those of the 2 position, in 3 substituted thiophenes, and the larger shifts of the 2 position, in 3 substituted thiophenes, compared to the shifts of the 3 position, in 2 substituted thiophenes, were also interpreted in these terms. Evidence was given for a more extensive conjugation of mesomeric substituents to the 3 position than to the 5 position and for an alternating inductive effect in 2-substituted thiophenes. He also determined some ring coupling constants in nineteen, 2,5-, seventeen 2,3-, eighteen 2,4- and eleven 3,4-disubstituted thiophenes. They are: J_{34} = 3.45 - 4.35; J_{45} = 4.90 - 5.80; J_{35} = 1.25 - 1.70; J_{25} = 3.20 - 3.65 all $\pm$ 0.15 c.p.s.

Bernstein (20) moreover in a summary of several studies has reported the following ring proton spin coupling constants (c.p.s.).

Table I

	J_{12}	J_{13}	J_{23}	J_{24}	J_{34}	J_{25}
Furan			1.80 (.09)	0.80 (10)	3.53 (.13)	1.55 (.1)
Pyrrole	2.43 (.16)	2.43 (.24)	2.63 (.03)	1.44 (.05)	3.42 (.42)	
Thiophene			5.2 (.3)	1.3 (.3)	3.6 (.3)	2.7 (.3)

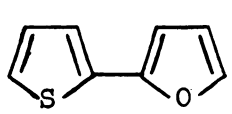
In his paper Bernstein also concludes from data for 2-substituted furans in acetone (Table II), that the chemical shift of a proton signal is dependent on two factors: (a) the electronegativity of a substituent being greater than that of hydrogen caused a shift of all signals to a lower field, the closest proton to the substituent being shifted the greatest; the effect being attenuated as the distance from the substituent increases; and (b) because of its ability to donate or withdraw electrons from "aromatic" rings, the substituent can cause the signals to move to high or low field, respectively. This mesomeric effect probably behaves in a fashion analogous to that in the parent compound, affecting all positions in the same qualitative way (i.e., all increase in π electron density or all decrease). Thus, in a semi-quantitative way he distinguishes between the effect of electron donating and withdrawing substituents. In the case of the former, the electronegativity of the substituent shifts the signals to low field but the mesomeric effect increases the π electron density, causing greater shielding which causes the signal to move to higher field. In the case of electron withdrawing substituents, however, both the electronegativity and mesomeric effect operate to shift the signals to a low field. All substituents which he studied were of greater electronegativity than methyl, which due to its donor property and low electronegativity caused a shift to a high field relative to furan, and thus these substituents caused the proton signals to be found at a lower field than in 2-methyl furan. With stronger electron withdrawing substituents the proton signals appeared at increasingly lower fields. He also observed that the effect of multiple substitution is very nearly additive.

Table II. Substituent effects in the ring-proton chemical shifts of furans (results are given in parts per 10^7).

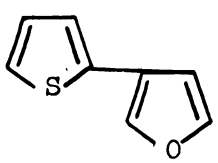
	δ_3	δ_4	δ_5
2-methylfuran	+ 4.35	+ 1.53	+ 2.05
2-furfurylamine	+ 2.42	+ 1.00	+ 1.37
2-furfurol	+ 1.51	+ 0.76	+ 0.89
furan	0.00	0.00	0.00
2-furanacrylic acid	- 4.08	- 1.44	- 1.36
2-furan acrolein	- 5.51	- 2.09	- 2.26
ethyl furoate	- 7.74	- 1.83	- 2.26
2-furoic acid	- 7.95	- 1.81	- 2.20
furfurol	- 9.87	- 2.94	- 3.66
2-nitro furan	-10.65	- 4.02	- 3.18
2-furoyl tri fluoromethyl ketone	-11.98	- 3.73	- 4.54

(a) results were determined at 60 Mc/s in 10% solutions of acetone using the acetone signal as reference, the reproducibility from three independent spectra for each solution was $\pm$ 0.2 c.p.s., i.e., $\pm$ 0.03 parts per 10^7. (b) actual furan value -54.82 (α protons); -43.58 (β protons).

With this information on the directing influence, and the n.m.r. spectra characteristics of substituted furans, pyrroles, and thiophenes, it was decided to synthesize the compounds VII' and VIII'. It was anticipated that



VII'



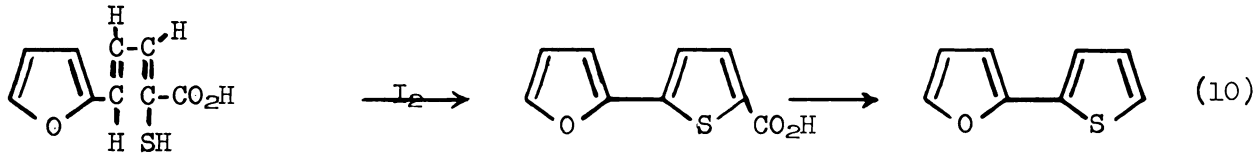
VIII'

these compounds should facilitate the determination of the directive influence of a five membered heterocyclic ring on the substitution reactions which another aromatic nucleus might undergo. The differences in chemical shift of the thiophene protons versus the furan protons, plus the characteristic spin-spin coupling constants of substituted thiophenes and furans of known structure, could be used as a convenient method for the assignment of the structures of compounds resulting from substitution reactions which biaryls VII' and VIII' would undergo.

RESULTS AND DISCUSSION

2-(2'-Thienyl)-furan(IV).

In an attempt to gain an entry into the α-furyl-α-thiophene biaryl system, the Campaigne (8) procedure for the preparation of 5-substituted-2-thenoic acids was used to obtain the compound 2-(2'-furyl)-5-thenoic acid(III). (Equation 10, Fig. 1,2,3).



I III IV (10)

Although acid III was obtained in rather low yield, it was found to be quite stable and was subsequently stored in the open with no precautions to exclude oxygen or sunlight. The bright yellow white fluorescence which resulted from exposure of the compound to ultraviolet light was consistent with its high extinction coefficient (Table IV). Decarboxylation of III gave the unsubstituted, biaryl IV (Fig. 4) in high yield. Like 2-phenyl-furan (14) which turns dark upon standing, 2-(2'-thienyl)furan(IV) turned to a dark blue-black color upon exposure to the atmosphere at room temperature. This biaryl IV, however, was stored for several weeks in the cold under nitrogen without the occurance of significant decomposition. Although III and IV were prepared through the use of the Campaigne method of ring closure, this route to the α-α' biaryl system was found to be awkward experimentally and therefore an alternate route was sought.

The Benary (11,12) method of preparation of α-substituted-β-furoates was subsequently used to prepare ethyl 2-(2'-thienyl)-3-furoate (V, Fig. 5) from ethyl 3-(2-thienyl)-3-oxopropanoate in a 33% yield (equation 11).

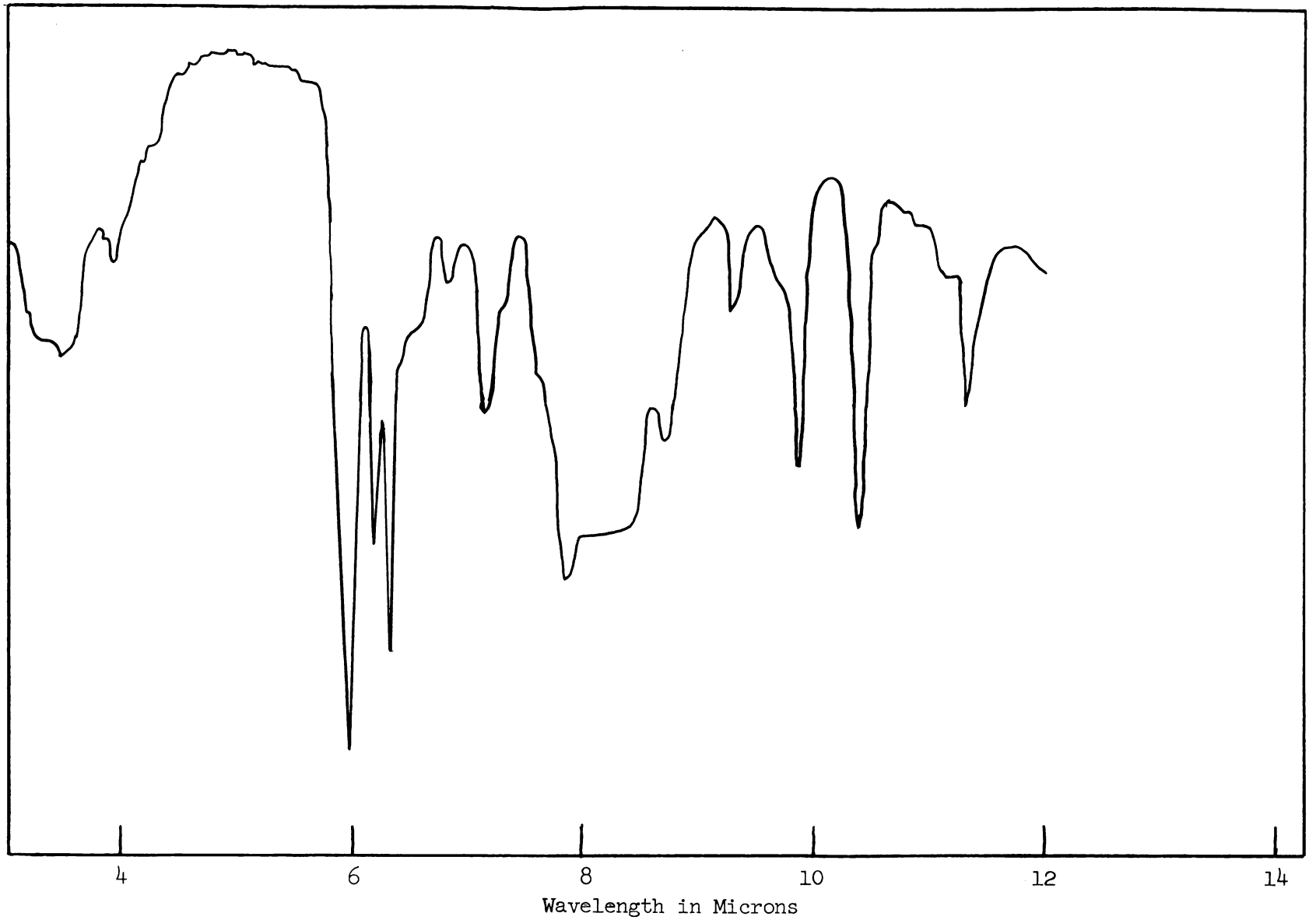


Figure 1. Infrared Spectrum of 5-(2'-Furyl)-2-mercapto-2,4-pentadienoic Acid (I) taken in Chloroform

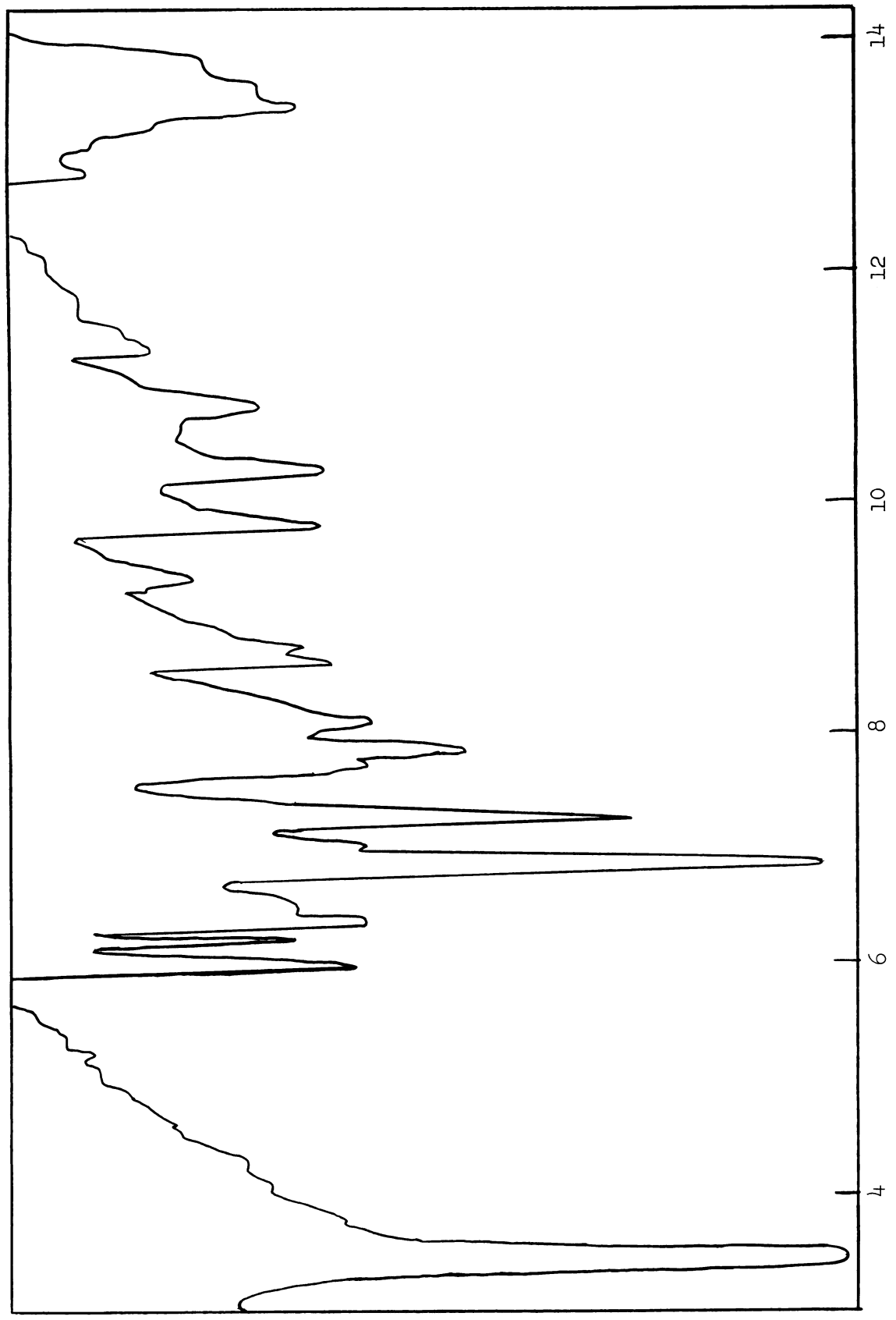


Figure 2. Infrared Spectrum of 2,2'-Dithiobis[5-(2"-furyl)-2,4-pentadienoic Acid] (II) taken as Nujol Mull

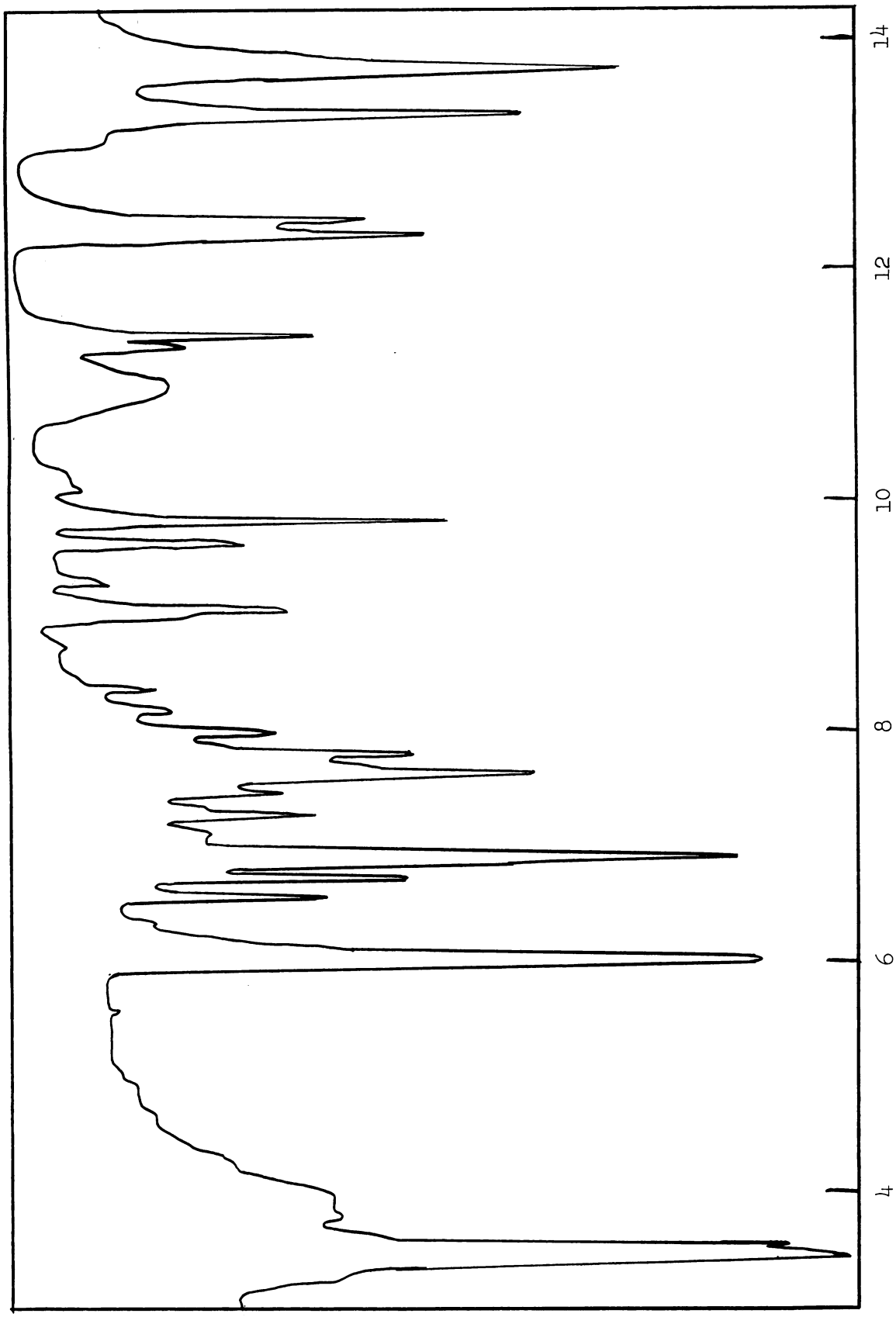


Figure 3a. Infrared Spectrum of 2-(2'-Furyl)-5-thenoic Acid (III) taken as Nujol Mull

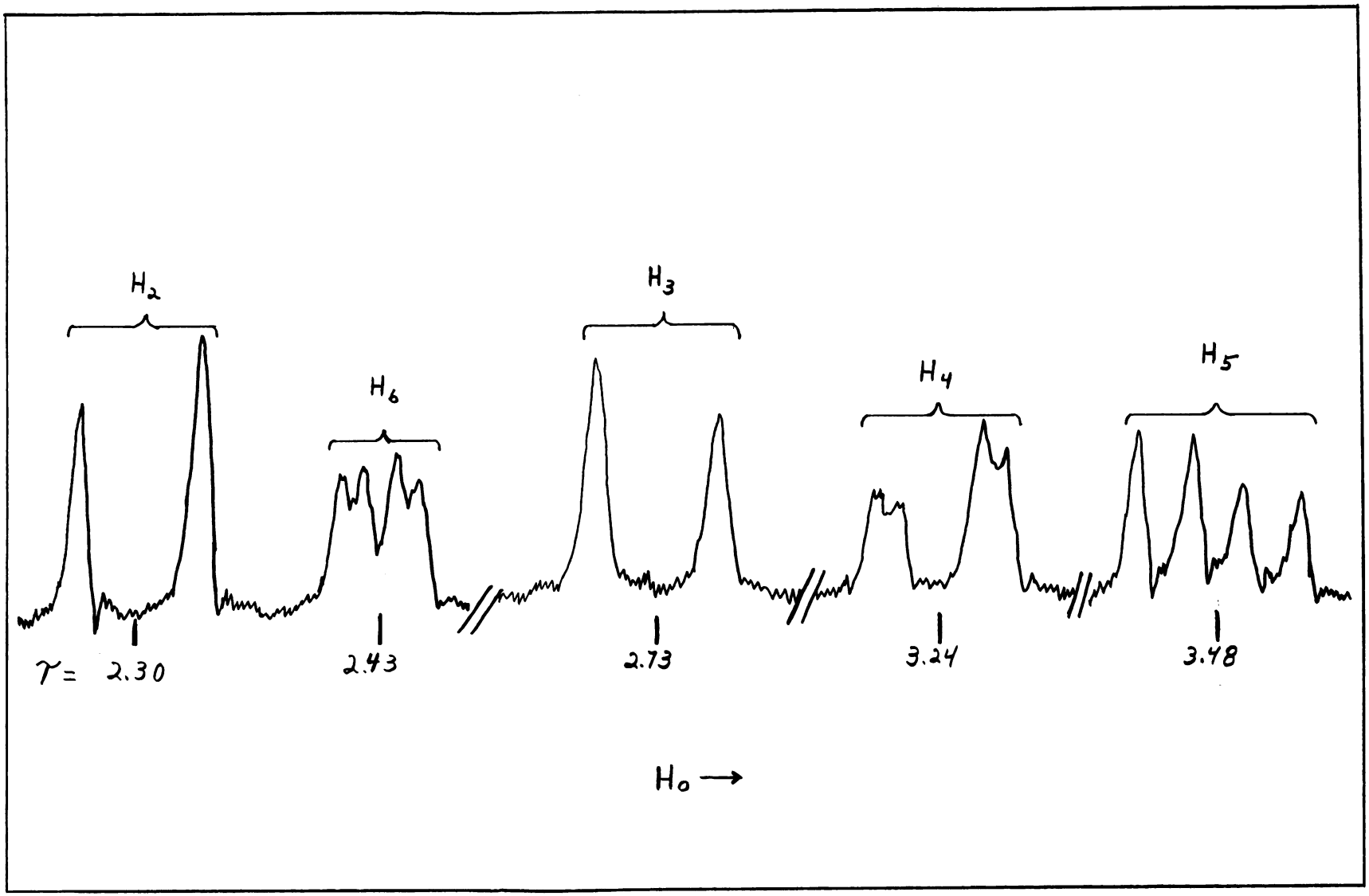


Figure 3b. N.m.r. Spectrum of 2-(2'-Furyl)-5-thenoic Acid (III) in Dioxane taken at sweep width of 100 c.p.s.

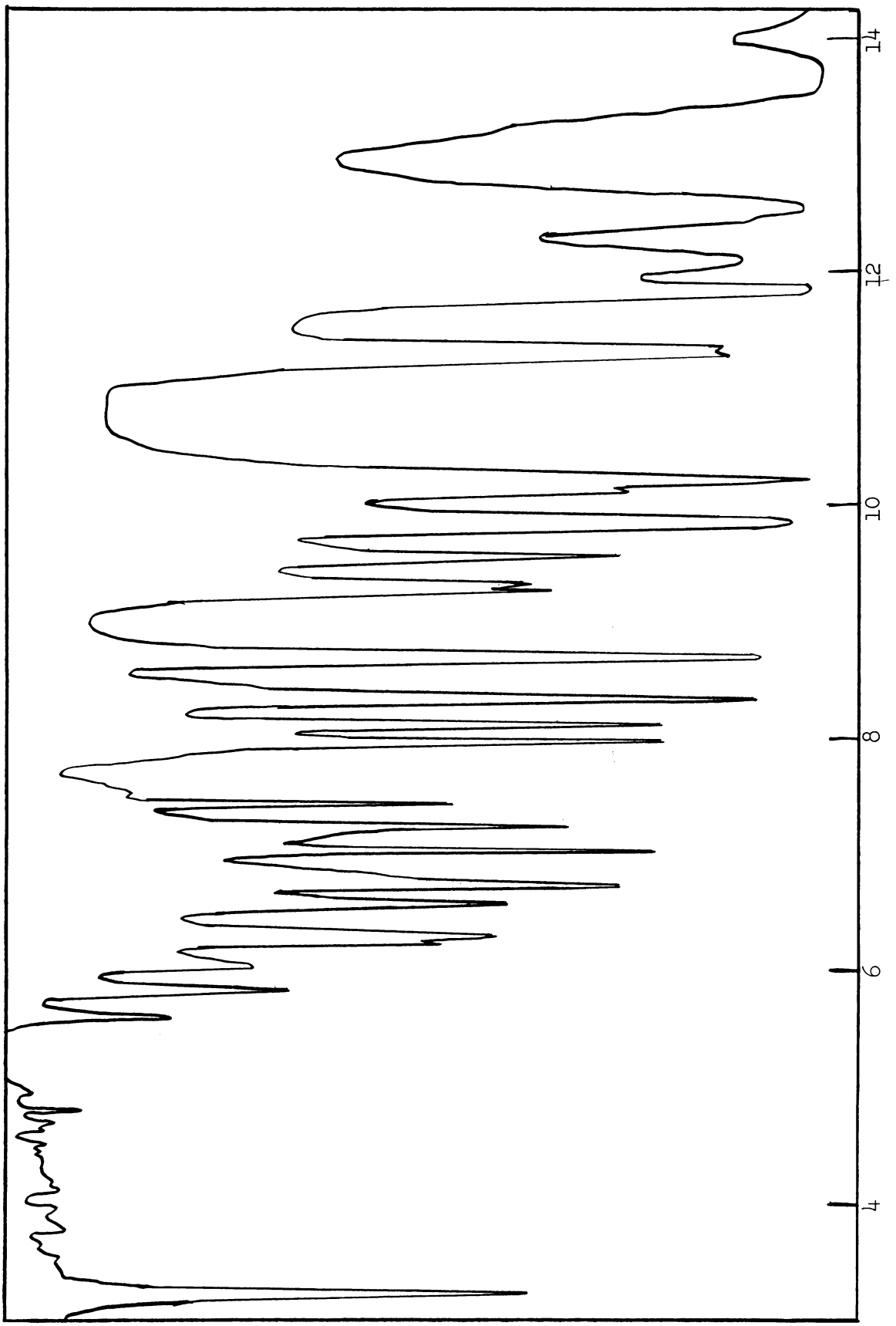


Figure 4a. Infrared Spectrum of 2-(2'-Thienyl)-furan (IV)

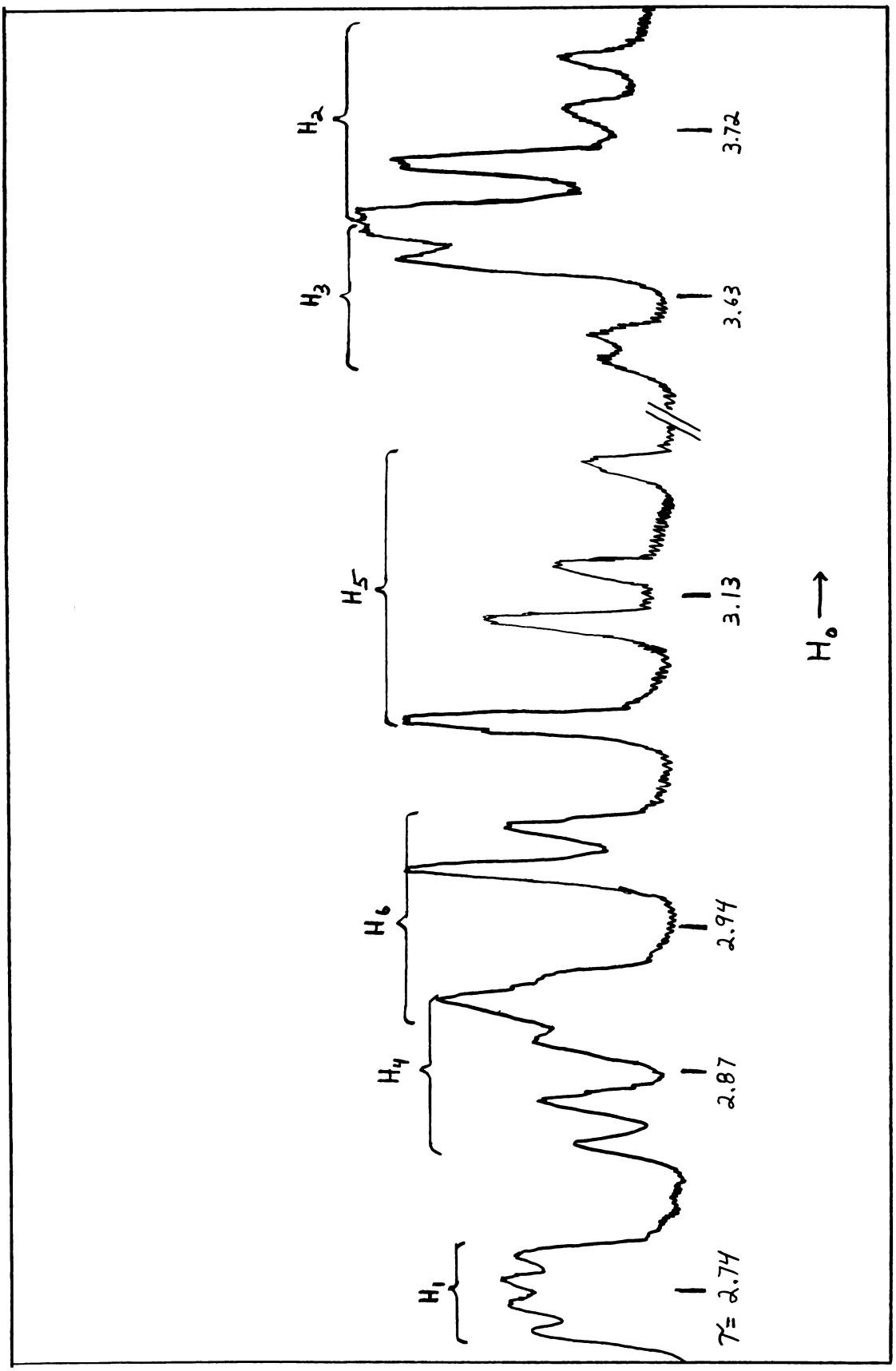


Figure 4b. N.m.r. Spectrum of 2-(2'-Thienyl)-furan (IV) in CCl_4 taken at sweep width of 100 c.p.s.

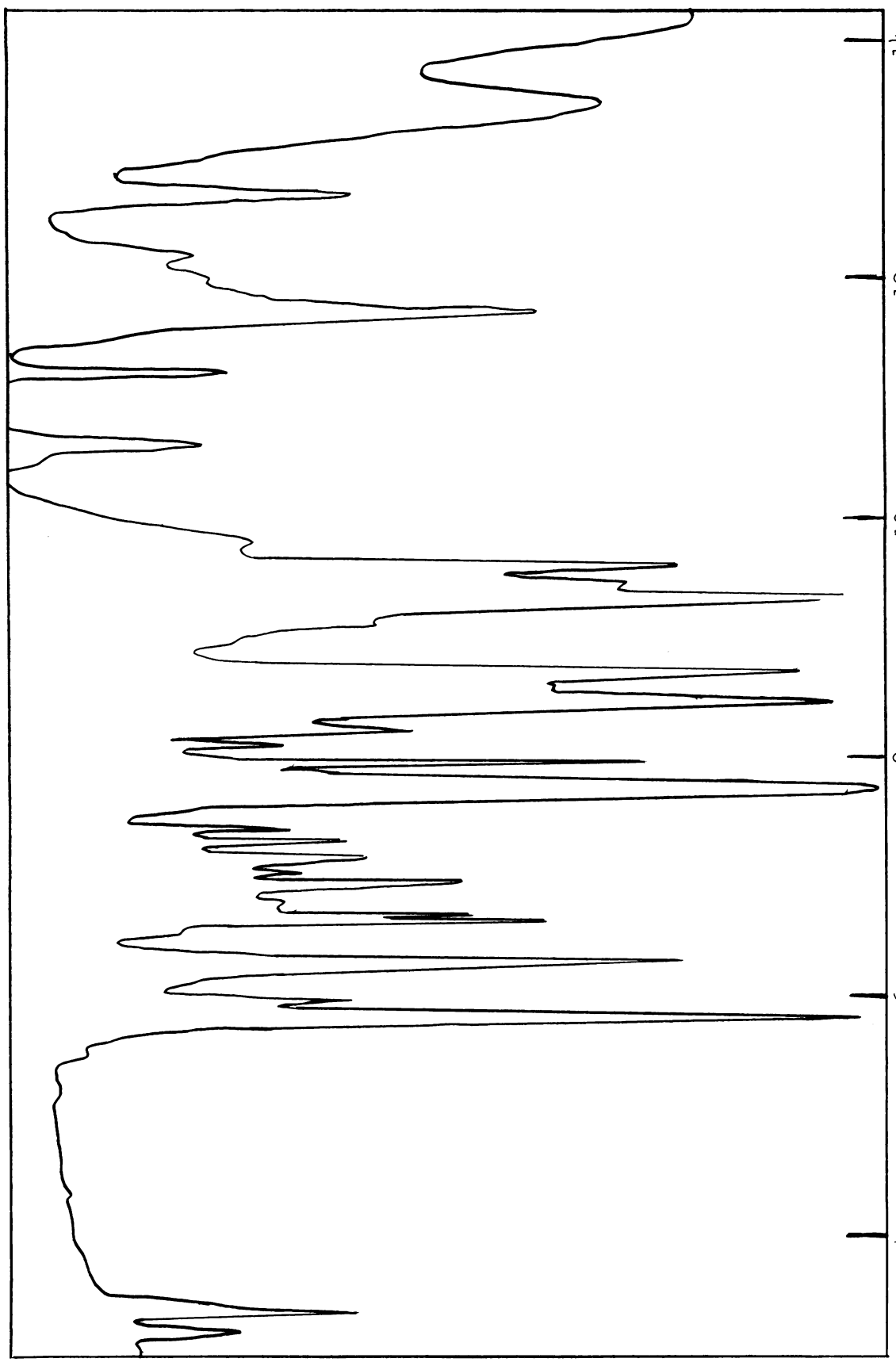
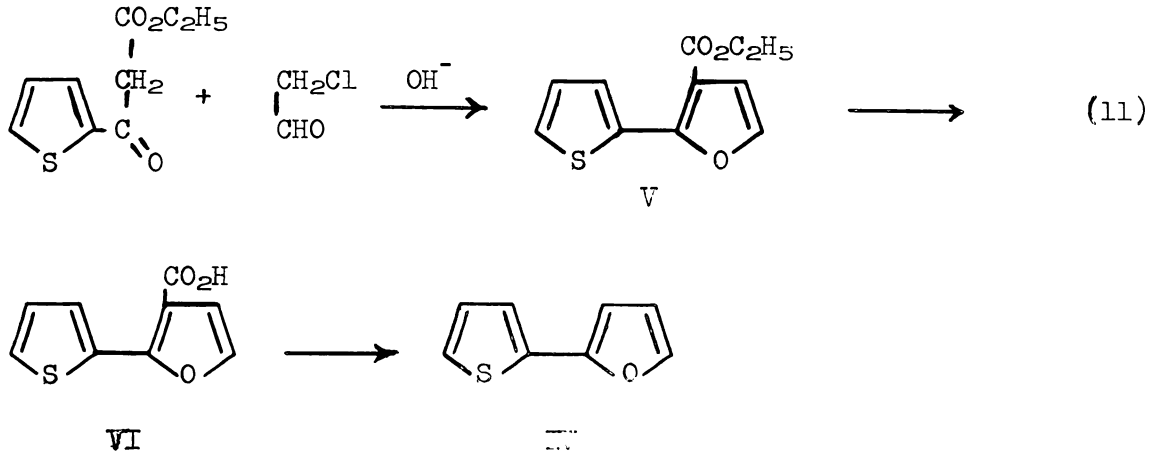


Figure 5. Infrared Spectrum of Ethyl 2-(2'-Thienyl)-3 furoate (V).



(11)

V

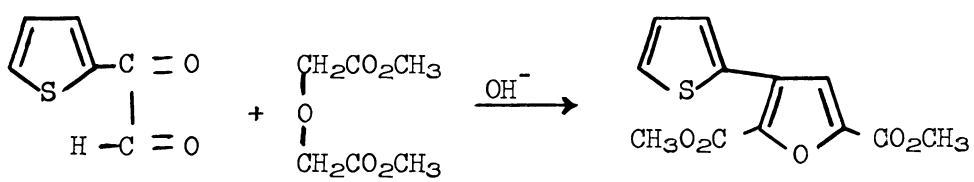
VI

Although V was also found to be readily air oxidized to a blue-black color, it was stable to storage under nitrogen in the cold. Saponification of this ester gave the stable acid VI (Fig. 6) and subsequent decarboxylation of this acid produced IV in good yield. This product was shown to be identical to that made previously by the Campaigne procedure, by comparison of ultraviolet, infra red and n.m.r. spectra.

The Benary procedure which, therefore, gave the substituted biaryl V in 10% overall yield in three clean steps from thiophene was preferred over the more awkward Campaigne method which yielded the biaryl III in an 8% overall yield through four steps from furfural.

3-(2'-Thienyl)-furan(XVII).

The synthesis of 3-(2'-thienyl)-furan was first attempted through the base catalyzed condensation of thienyl glyoxal with methyl diglycolate (equation 12).



(12)

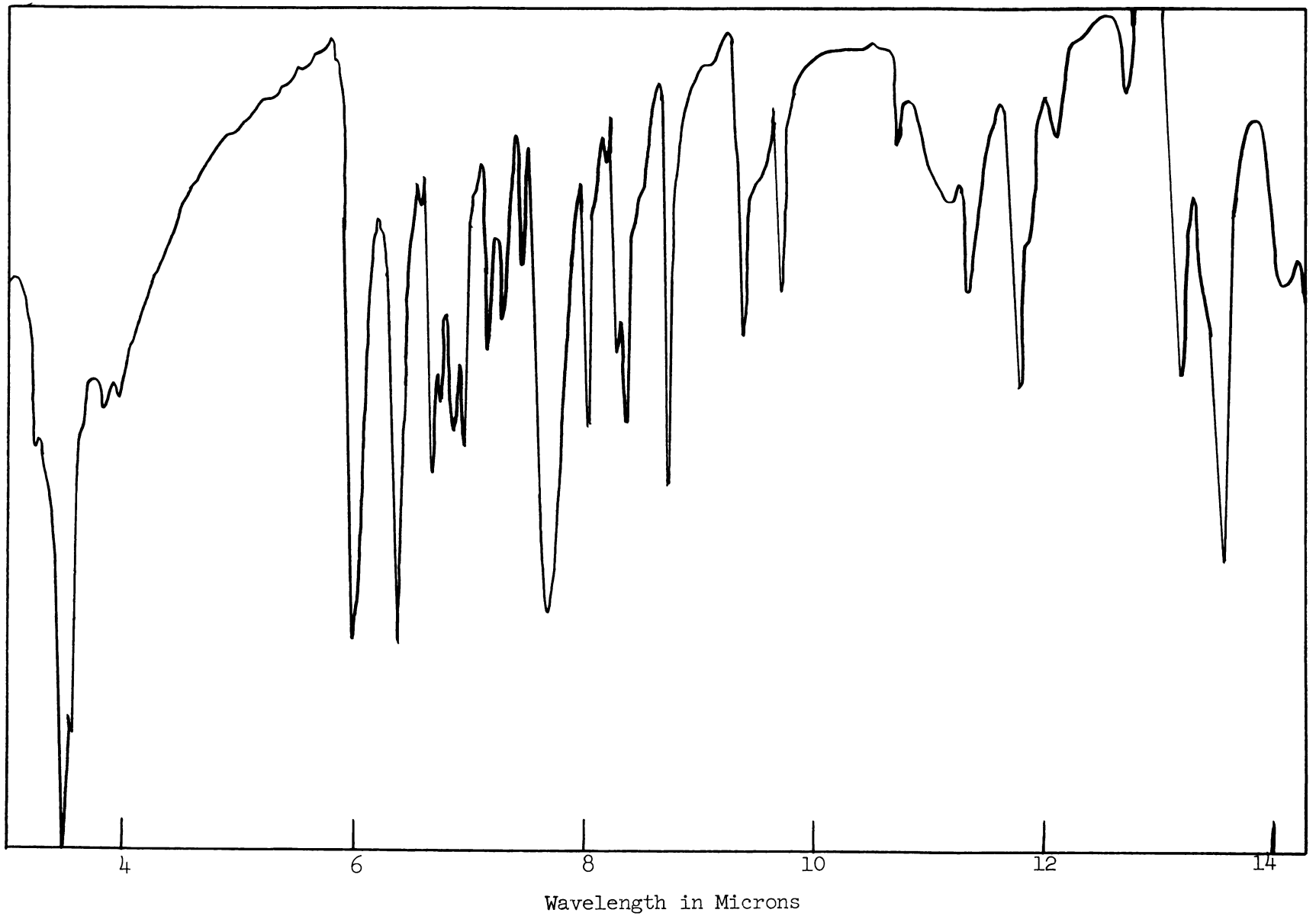
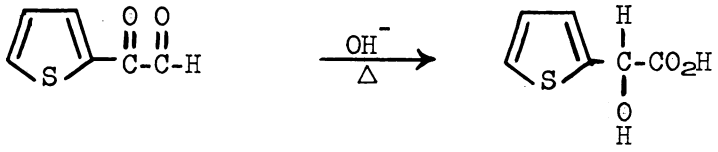


Figure 6. Infrared Spectrum of 2-(2'-Thienyl)-3-furoic Acid (VI) taken as Nujol Mull.

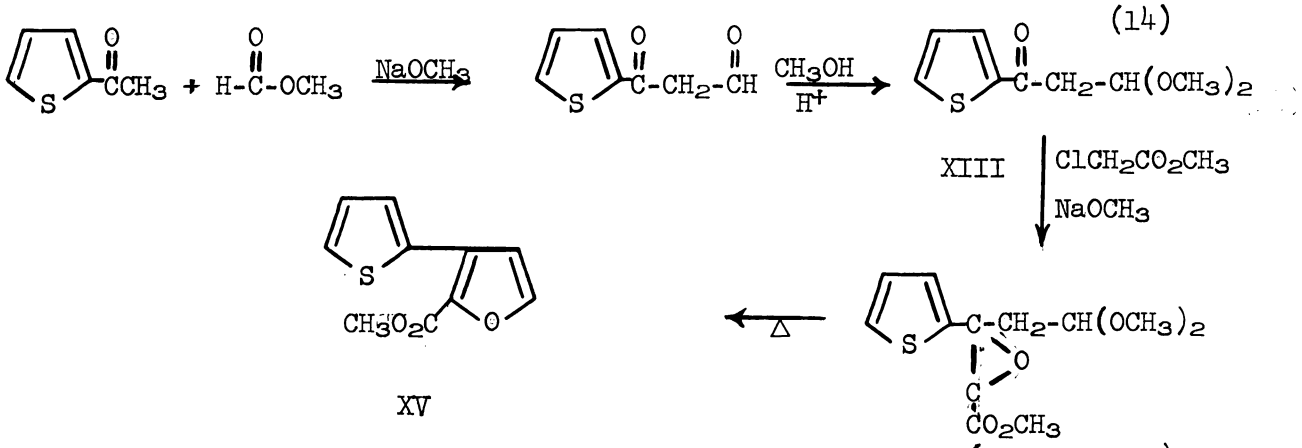
Although thienyl glyoxal is known (39) to react with base under reflux to give a quantitative yield of (2-thienyl)-glycolic acid (equation 13),



(13)

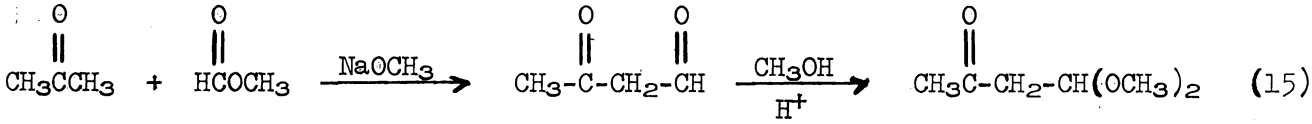
it was thought that the competing reaction with methyl diglycolate might yield some biaryl as indicated by equation 12. A variety of reaction conditions in several attempts to achieve the condensation failed, however, to effect any conversion to isolatable biaryl. At this point due to the possibility of an alternate procedure the Hinsberg method was set aside.

The methods of Royals (34) and Burness (5,7) were then used to prepare methyl 3-(2'-thienyl)-2-furoate (XV) (equation 14).



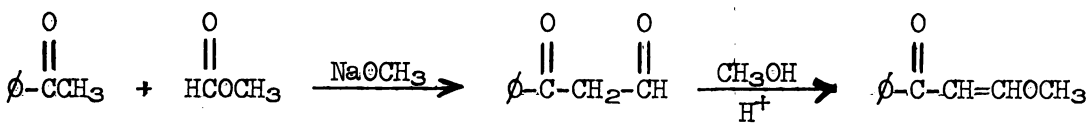
(14)

Although Royals was able to prepare 1,1-dimethoxy-3-butanone (equation 15),



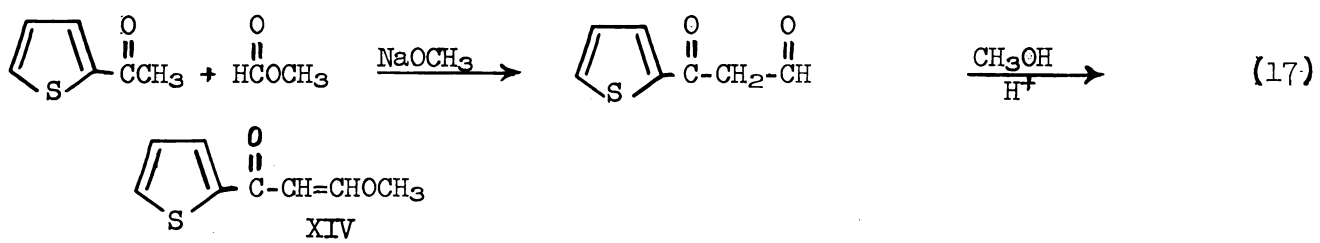
(15)

the same procedure, however, led to the formation of a vinyl ether (equation 16) when a synthesis of the analogous phenyl ketone acetal was attempted.



(16)

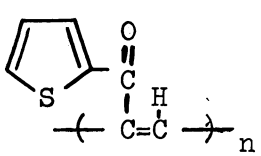
In our hands, an attempted preparation of the thienyl ketone acetal by Royals' procedure led similarly (equation 17) to the vinyl ether (XIV, Fig. 7) in 10% yield.



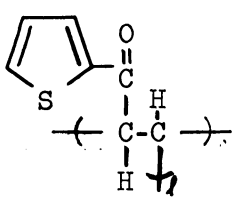
(17)

XIV

The distillation residue from this reaction also yielded a large quantity of a crystalline material in the empirical formula $C_7H_{4.6}SO$. It had a low solubility in organic solvents and also had a rather high melting point, i.e., m.p. 209.5-211.5°. This material is thought to have been produced by a base catalyzed polymerization of the vinyl ether to give a polymer with the possible unit structures IX' and X'.



IX'



X'

Unit IX' being formed from XIV by a normal polymerization mechanism (equation 18) followed by a base catalyzed loss of methanol.

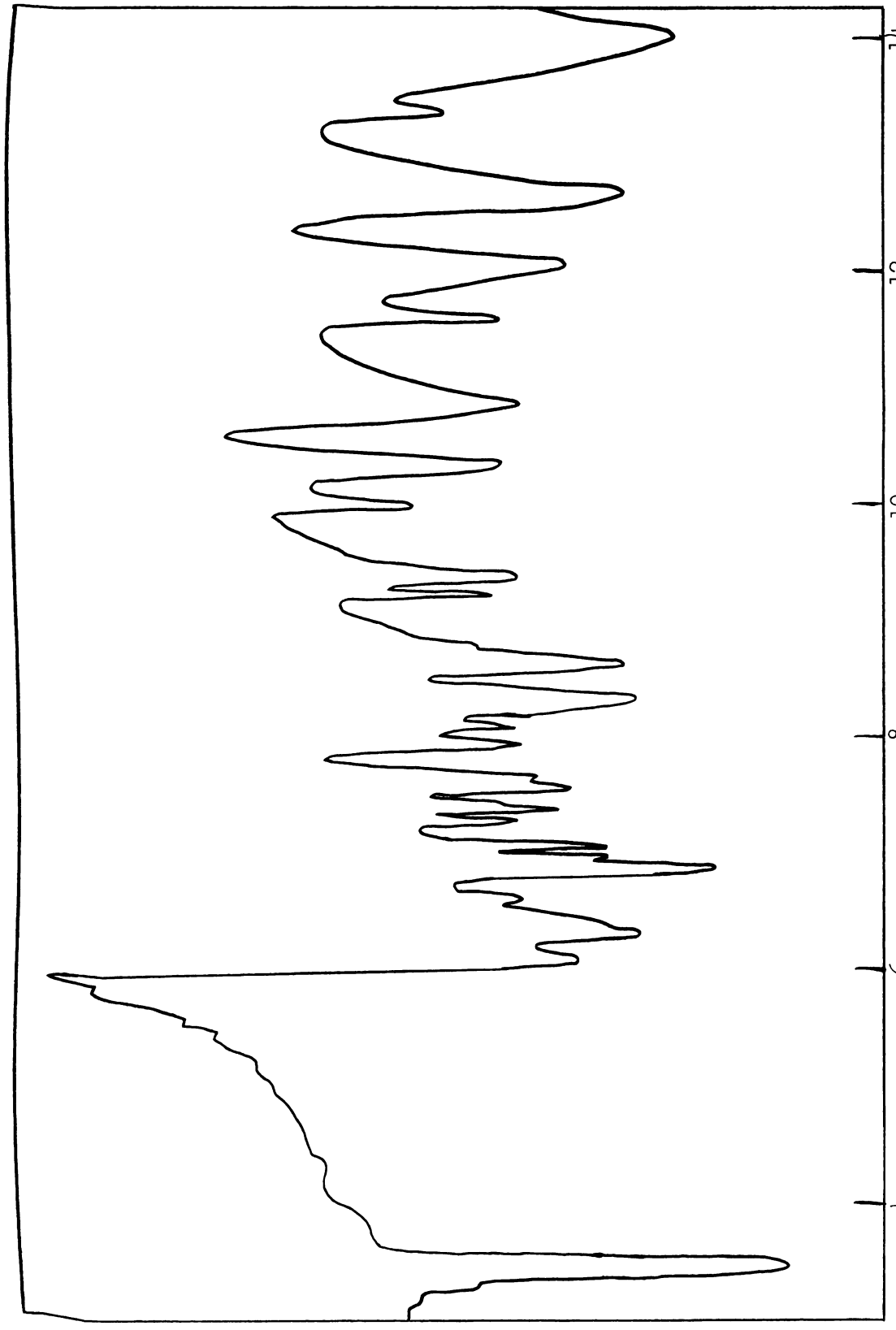
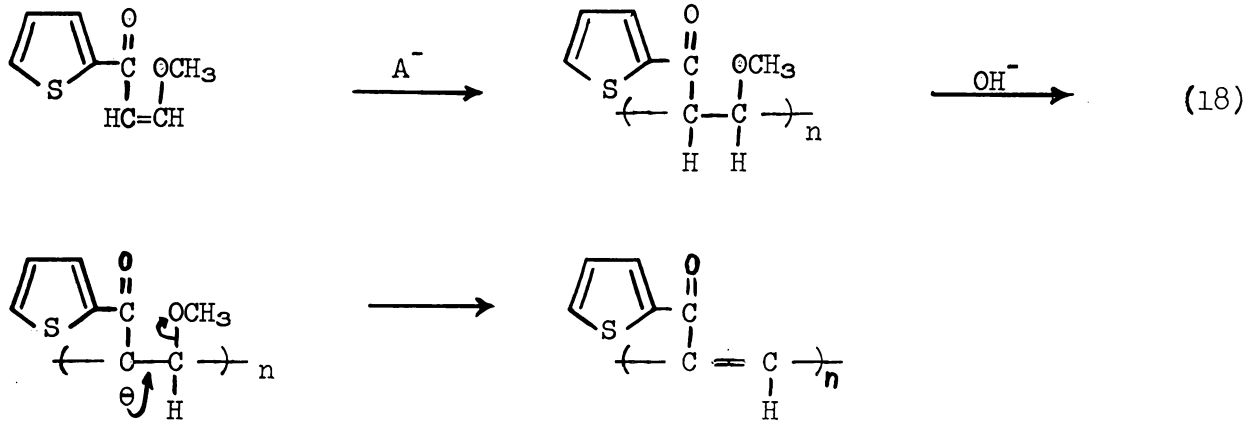
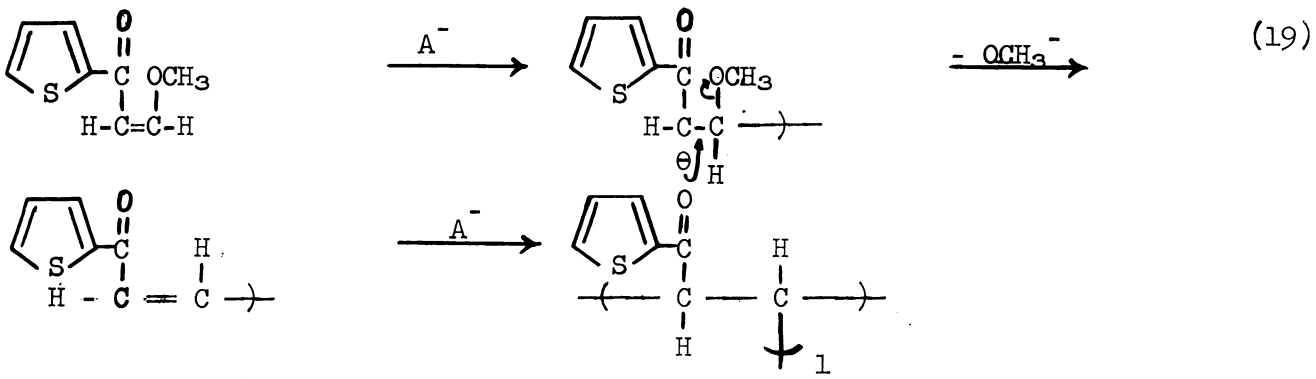


Figure 7. Infrared Spectrum of 1-Methoxy-3 oxo-3-(2'-Thienyl)-1-propene (XIV) taken as Nujol Mull.



(18)

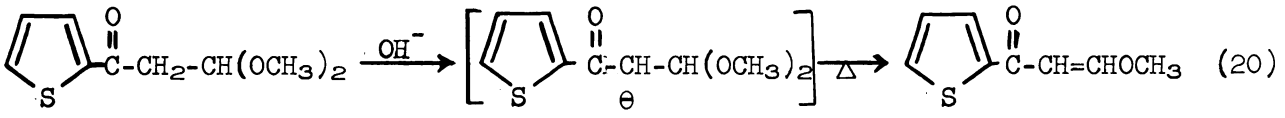
Unit X', however, might be formed by the loss of methoxide ion from the semi stable anion (equation 19) causing chain termination.



(19)

The alkene (XI') thus formed would also be subject to attack by another anion leading to chain branching. This hypothesis is supported by the infra red spectrum (Fig. 8) and by its low solubility in organic solvents which prohibited n.m.r. or mass spectrum studies.

Since Royals' procedure involved neutralization of the acidic acetal mixture until basic to litmus before distillation of the acetal product, it was thought that the slight excess of base could be deprotonating the acetal ketone with subsequent loss of methanol (equation 20) upon distillation.



(20)

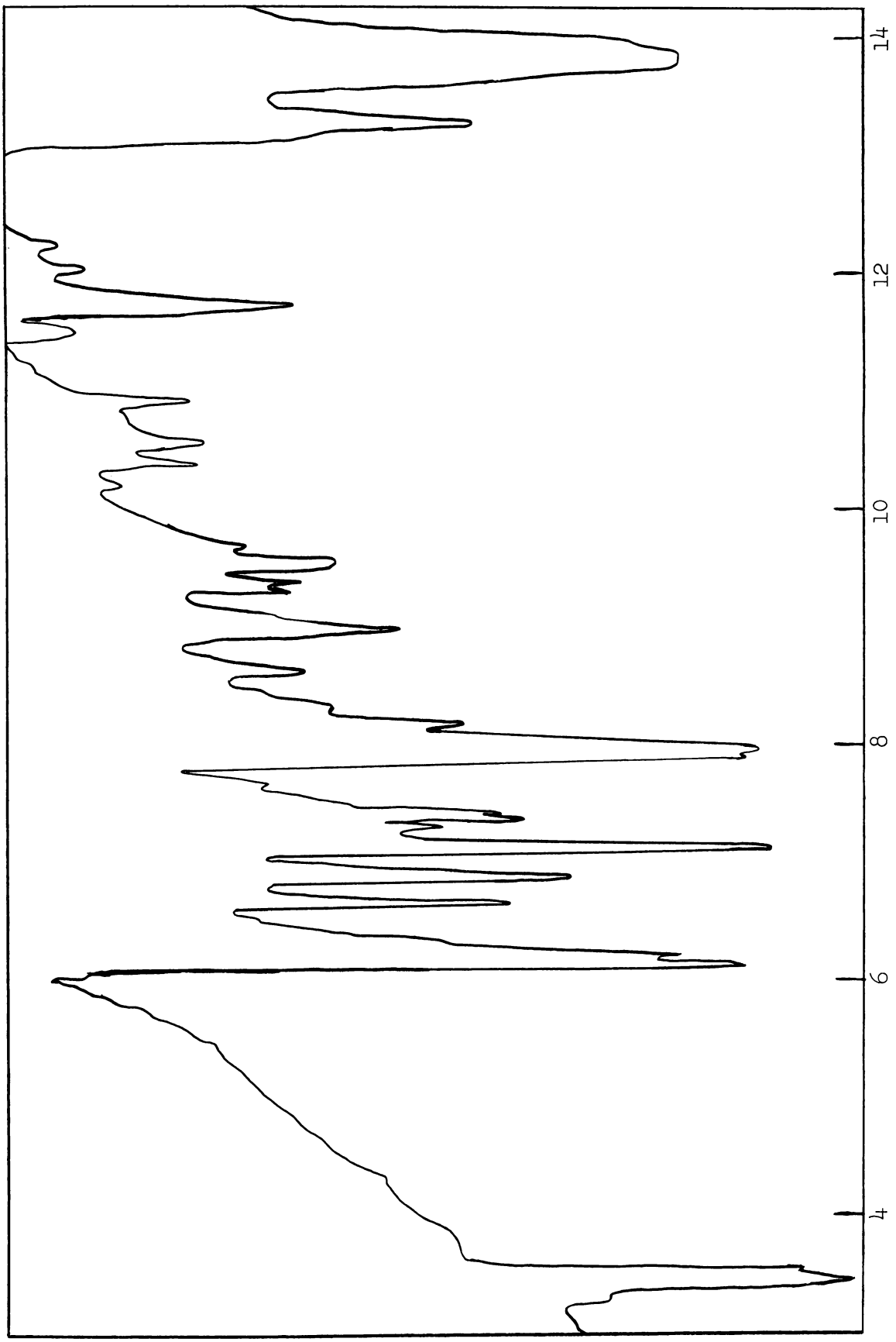


Figure 8. Infrared Spectrum of Purified Residue from the Preparation of XIV taken as a Nujol Mull.

Support for this was found in the change in color of the acetal mixture, during neutralization of the excess acid, from a bright yellow to an intense blood red near a pH of 7. Subsequent neutralization of the acidic acetal mixture, however, only to a pH of 6 and distillation of the acetal (Fig. 9) gave XIII in 70% yield from 2-aceto-thienone.

Subsequent preparation of the glycidic ester was followed by heating to 135° causing methanol to distill from the mixture while ring closure was affected. Vacuum distillation then yielded the biaryl ester XV (Fig. 10) in 17% overall yield from thiophene. Upon standing XV was quite readily air oxidized to a red viscous oil. However, its storage in the cold under nitrogen gave no decomposition. Saponification and decarboxylation gave successively XVI (Fig. 11) and XVII (Fig. 12) in high yield. Although the acid XVI was stable to the atmosphere, XVII reacted in a manner similar to XV in the air and thus had to be stored under nitrogen in the cold.

Reactions of 2-(2'-Thienyl)-furan(IV).

2-(2'-Thienyl)-furan was subjected to metalation, acylation, and free radical bromination.

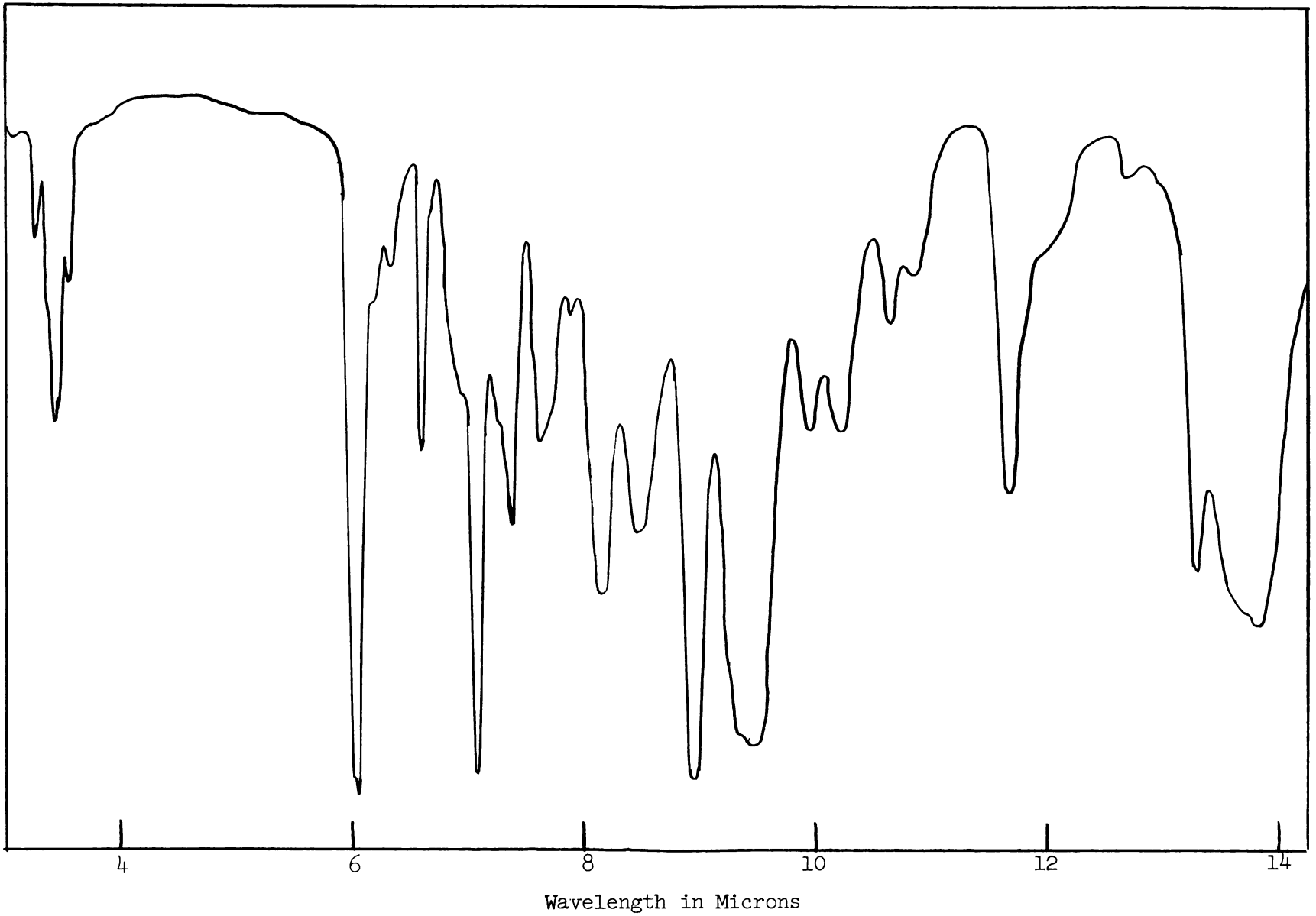


Figure 9. Infrared Spectrum of 1,1-Dimethoxy-3-oxo-3-(2'-thienyl)-propane (XIII).

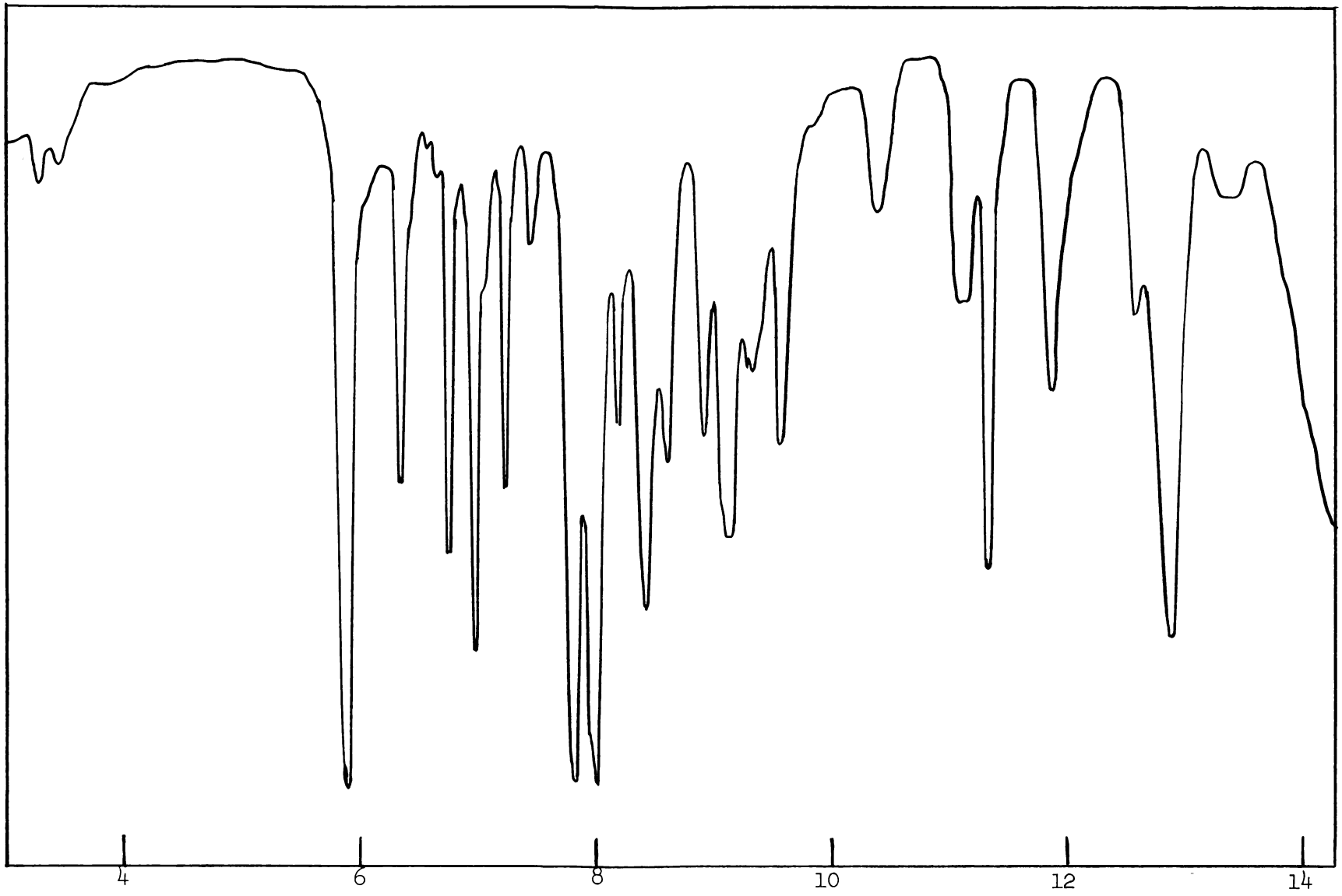


Figure 10. Infrared Spectrum of Methyl 3-(2'-Thienyl)-2-furoate (XV).

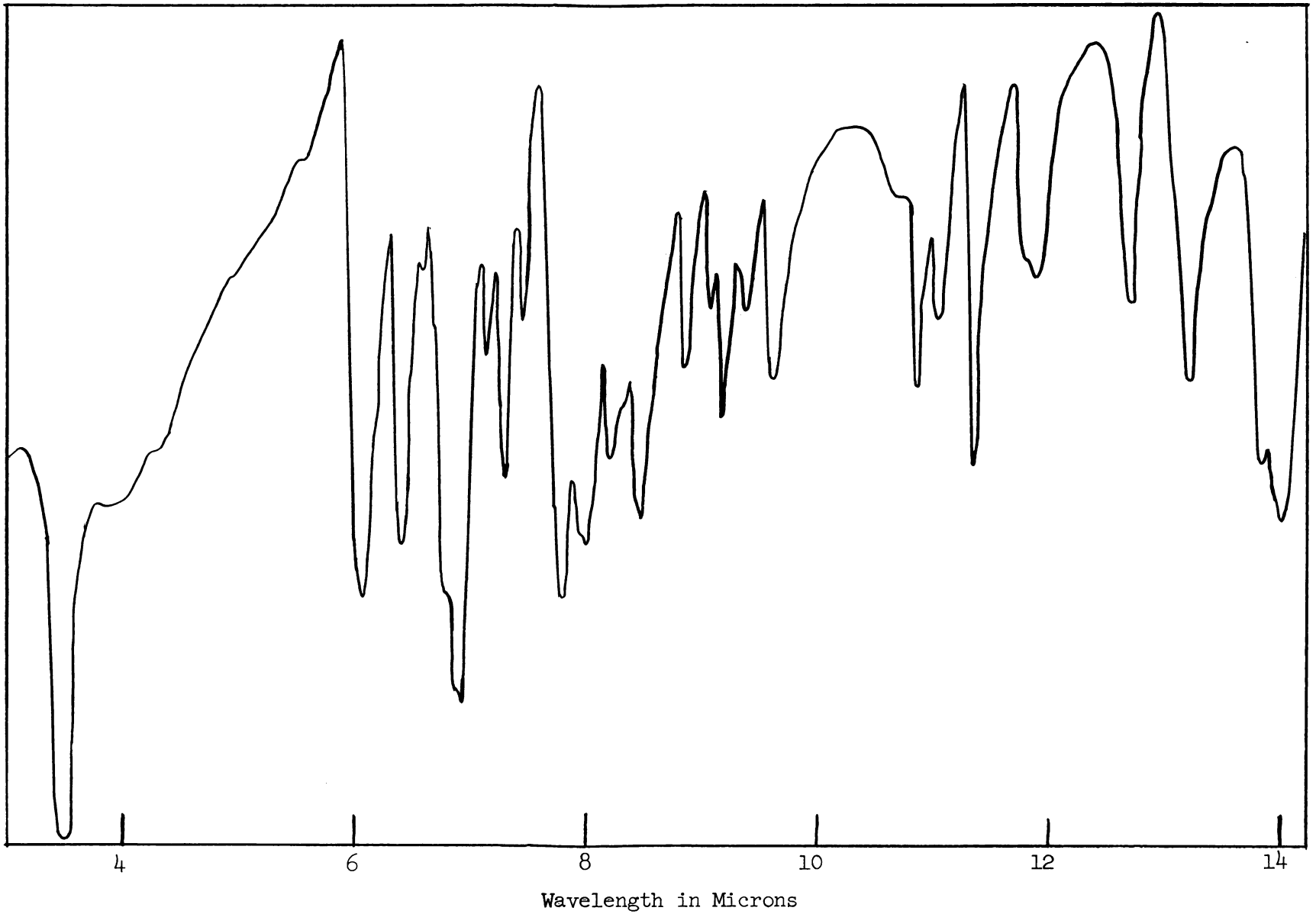


Figure 11. Infrared Spectrum of 3-(2'-Thienyl)-2-furoic Acid (XVI) taken as a Nujol Mull.

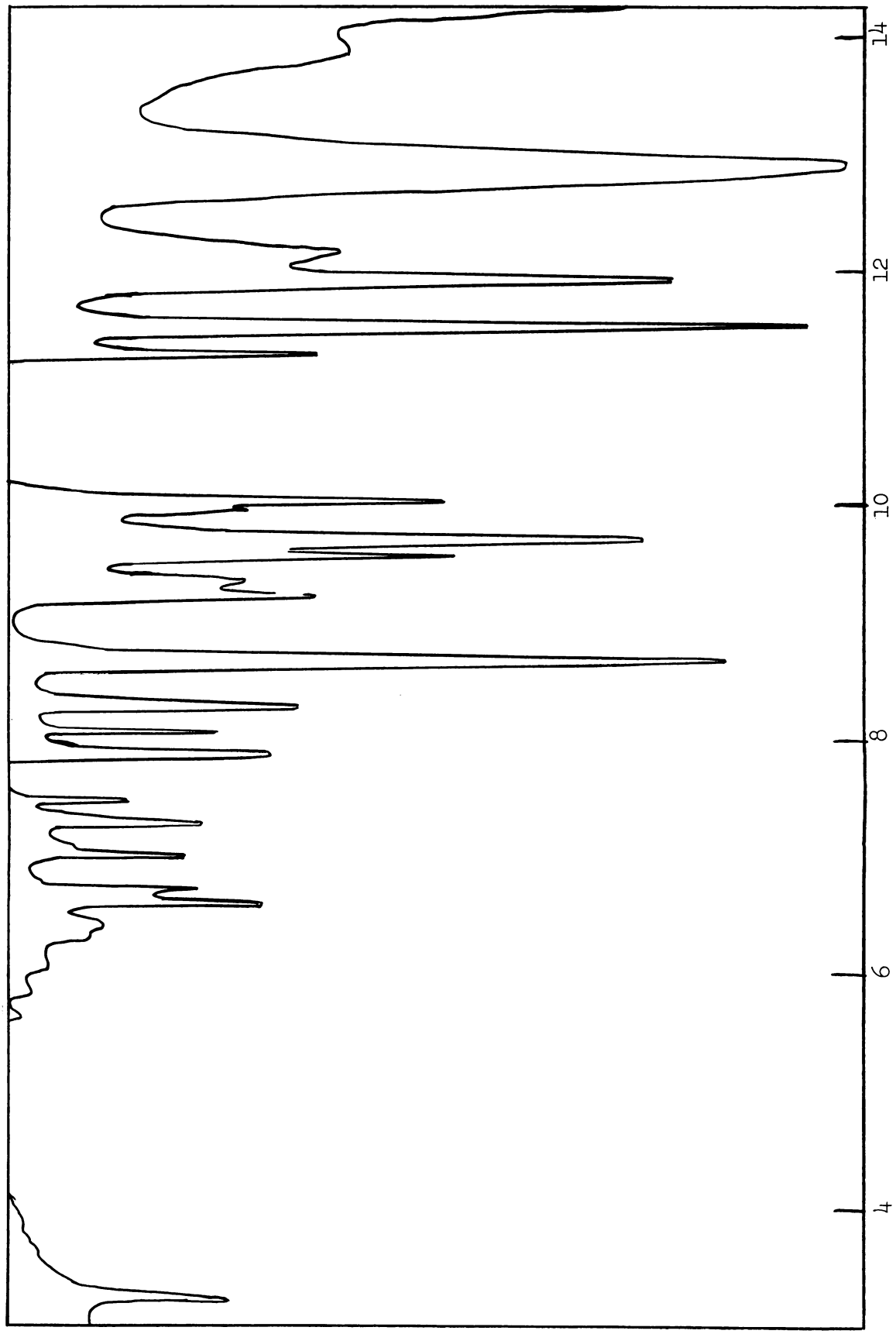


Figure 12a. Infrared Spectrum of 3-(2'-Thienyl)-furan (XVII).

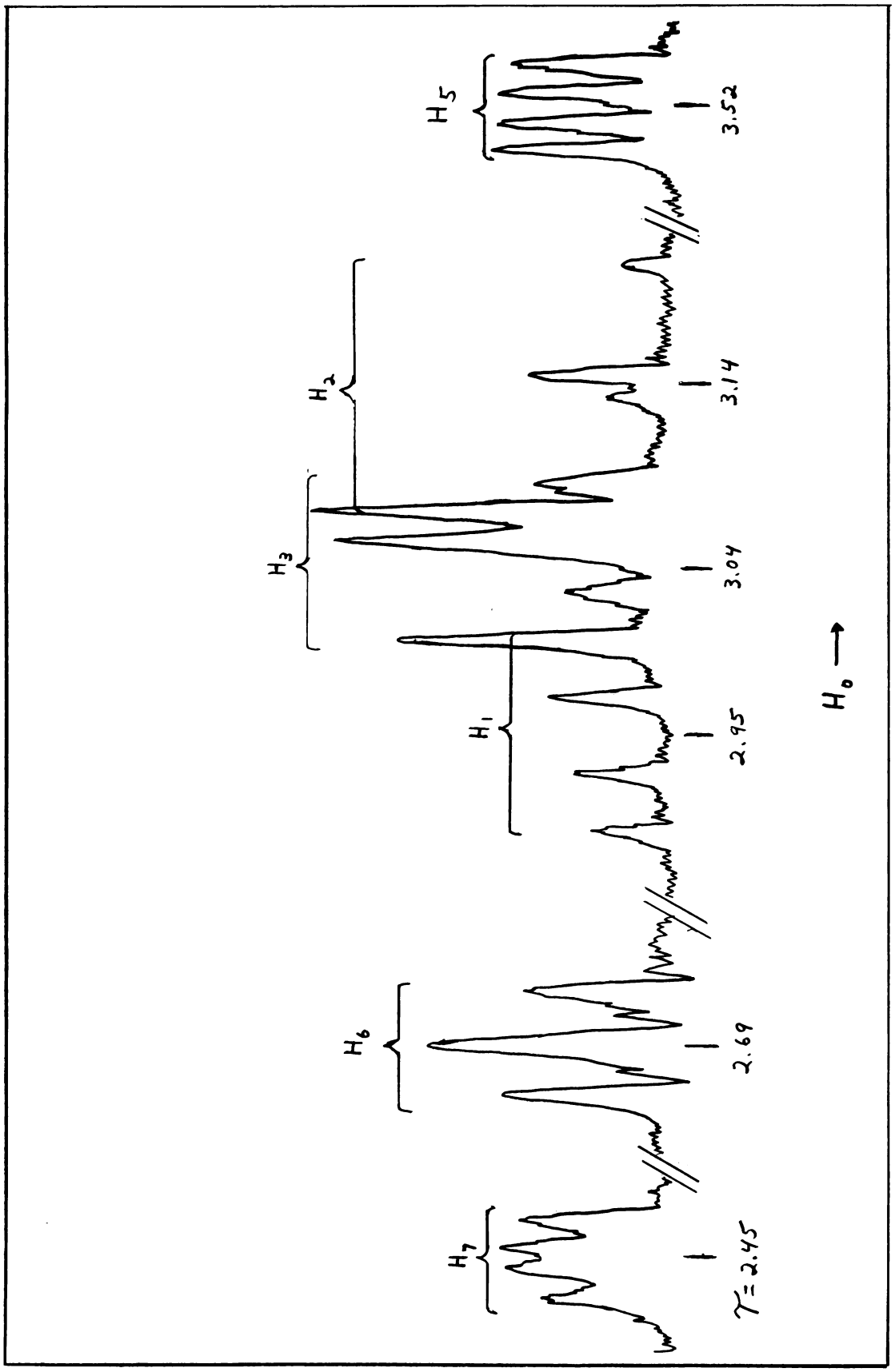
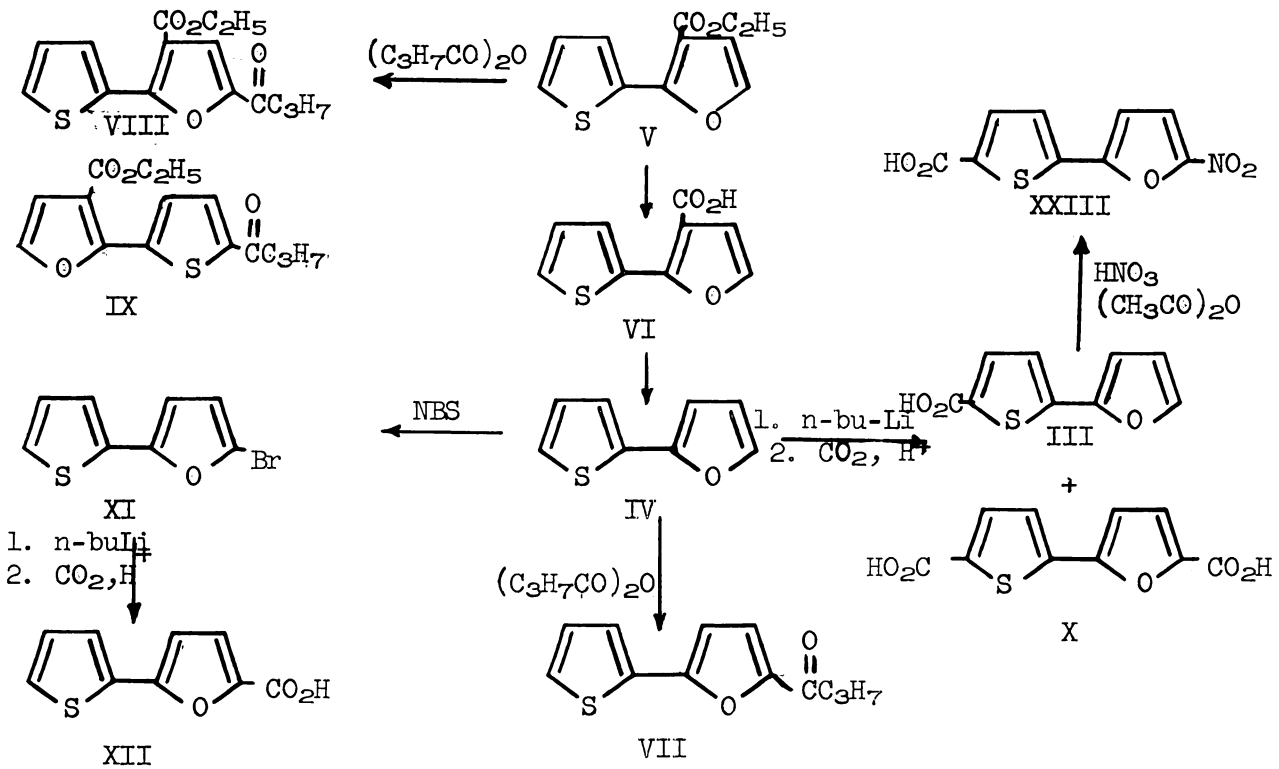
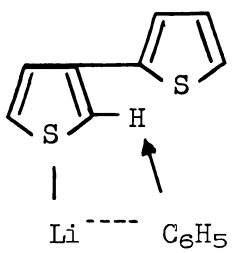


Figure 12b. N.m.r. Spectrum of 3-(2'-Thienyl)-furan in CCl_4 taken at a sweep width of 100 c.p.s.



Hydrogen metal interchange followed by carbonation was found to yield 2-(2'-furyl)-5-thenoic acid (III) (identical to a previously prepared sample by u.v., IR, n.m.r. and m.p.), and the dicarboxylic acid X (Fig. 13). Although the open α-position on the furan nucleus in IV has a lower electron density than the corresponding open α thiophene position, as predicted by the appearance of this α-furyl hydrogen atom farther downfield (τ = 2.74) in the n.m.r. spectrum than the corresponding hydrogen atom (τ = 2.94) in the thiophene nucleus, hydrogen metal interchange was found to occur only in the thiophene ring. This result, however, is consistent with the mechanism proposed by Wynberg (1) where the metalating agent coordinates with the hetero atom prior to hydrogen metal exchange.



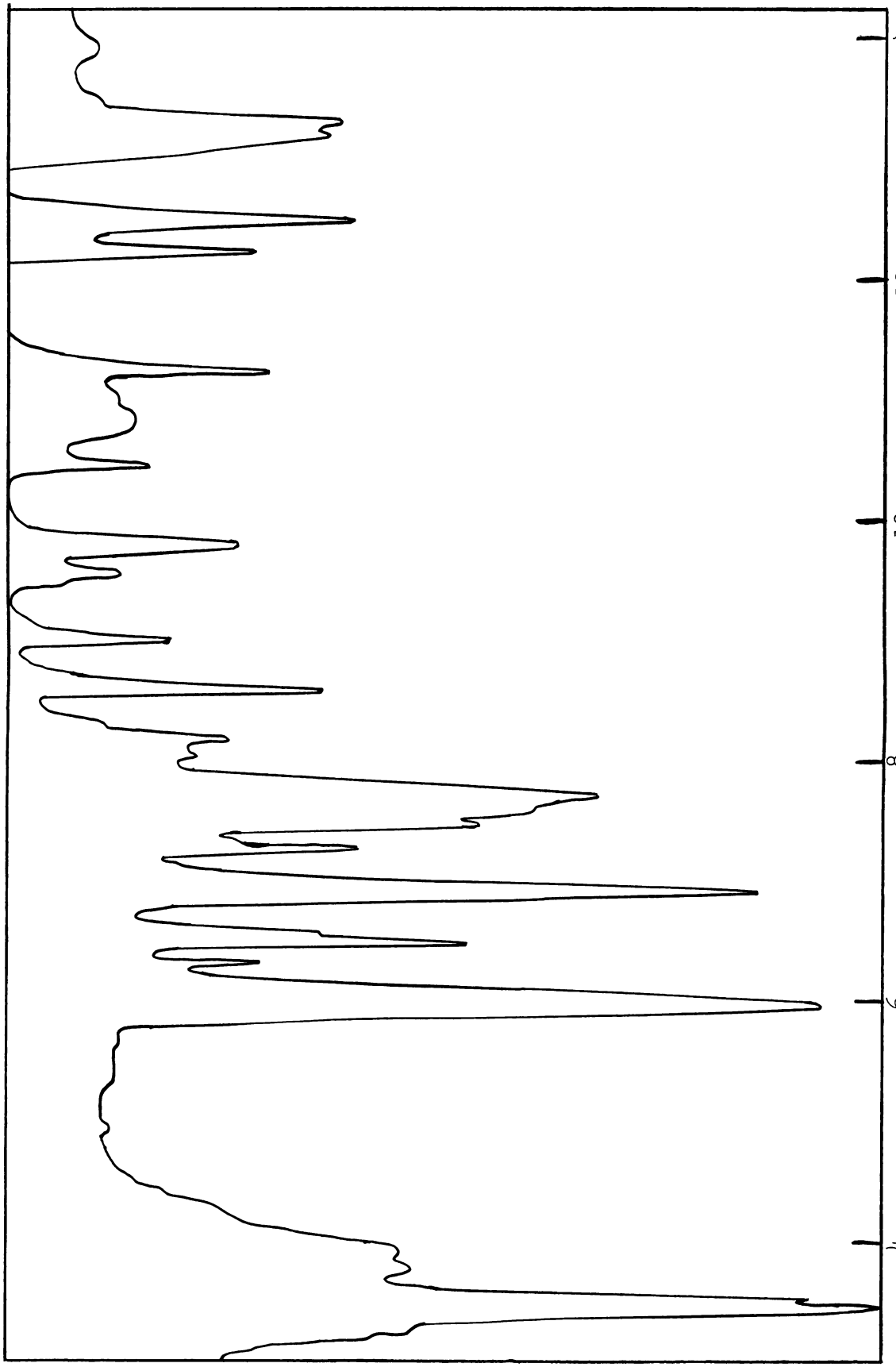


Figure 13. Infrared Spectrum of 2-(5'-Carboxy-2'-thienyl)-5-furoic Acid (X) taken as Nujol Mull.

With IV, therefore, coordination must occur only with the more available electrons on the sulfur atom allowing proton abstraction at a position α to the sulfur atom only. When coordination occurs, the electron density at the α position is decreased and hydrogen abstraction by the n-butylide anion is facilitated. Secondary metalation of the molecule to yield X (Fig. 13) can then occur because of the increased electron density at the oxygen hetero atom, due to the presence of a now less electronegative metalated thienyl substituent, facilitating coordination with the n-butyl lithium.

Acylation with n-butyric anhydride on the other hand occurred only on the furan nucleus to yield VII (Fig. 14). Though a lower electron density might be present in the position α to the oxygen atom than would be evident in the alternate α thiophene position, the lower aromaticity of the furan ring relative to that of the thiophene ring would lower the activation energy of the transition state leading to substitution in the furan ring. Acylation of the ester V, however, led to substitution in both rings, in 60% yield. The furan nucleus having been sufficiently deactivated by the carboethoxy substituent to cause 60% furyl acylation and 40% substitution in the thiophene ring*

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*As determined by integration of the n.m.r. spectra of the crude and distillate mixtures (the two keto esters were not isolated from each other).

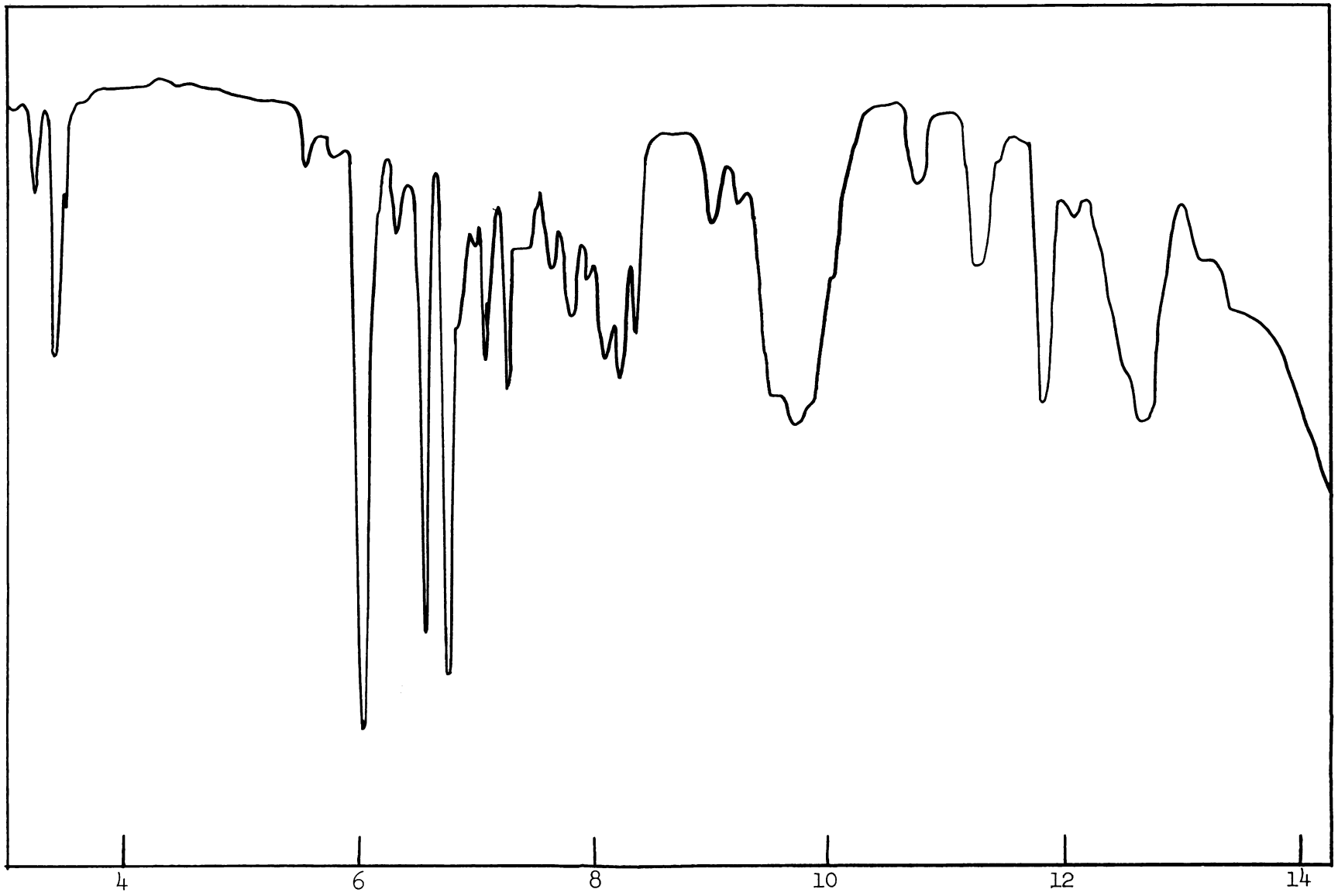
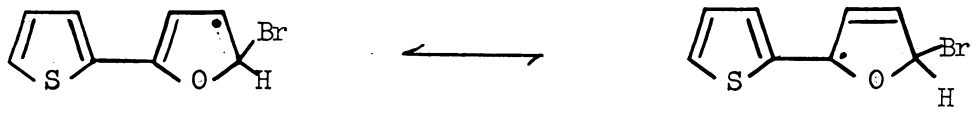


Figure 14. Infrared Spectrum of 5-Butyryl-2-(2'-thienyl)-furan (VII).

Bromination of IV with N-bromo-succinimide led quantitatively (no trace of IV was present in the n.m.r. spectrum of the crude reaction mixture after 2.5 hrs. of reflux) to 5-bromo-2(2'-thienyl)-furan (XI, Fig. 15). Again the furan nucleus with lower aromaticity requires less activation energy for substitution than does the thiophene nucleus.



The thienyl-bromo-furan (XI), like other bromo furans, was found to be quite unstable upon isolation. When the carbon tetrachloride reaction solvent was removed from the crude XI the bromide began to decompose within a few minutes with a seemingly self catalyzed spattering and fuming to form an amorphous tar. However, XI was stable in solution and although metal halogen interchange could not be effected by either lithium or magnesium at 140°, the interchange was effected at -70° by reacting the bromide with n-butyl lithium, for a limited time to reduce the possibility of metalation of the thiophene ring. Carbonation of this biaryl lithium produced thienyl furoic acid XII (Fig. 16).

Reactions of 3-(2'-Thienyl)-furan (XVII).

The biaryl XVII was also subjected to metalation, acylation, and free radical bromination.

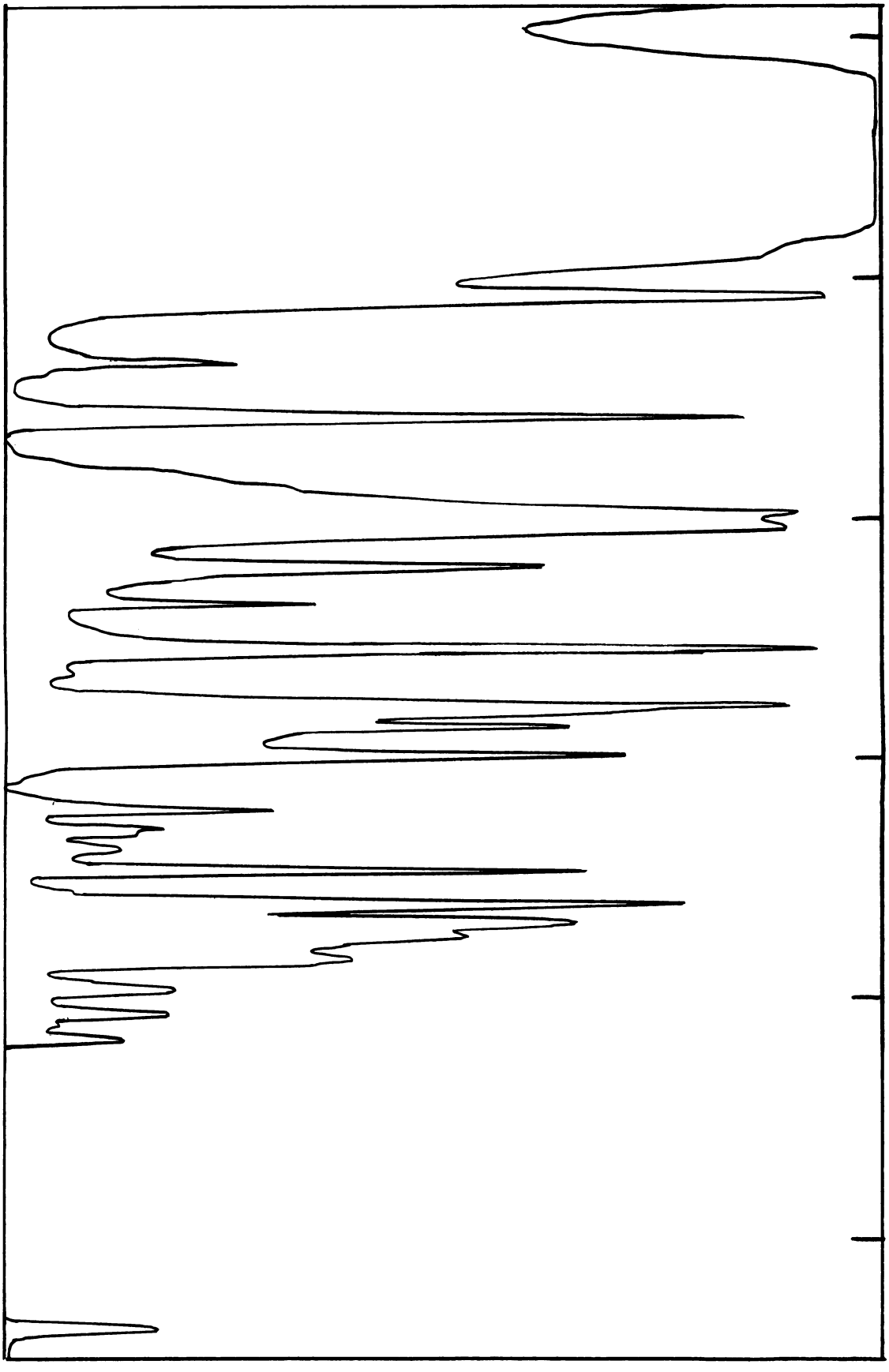


Figure 15. Infrared Spectrum of 5-Bromo-2-(2'-thienyl)-furan (XI) taken in Carbon Tetrachloride.

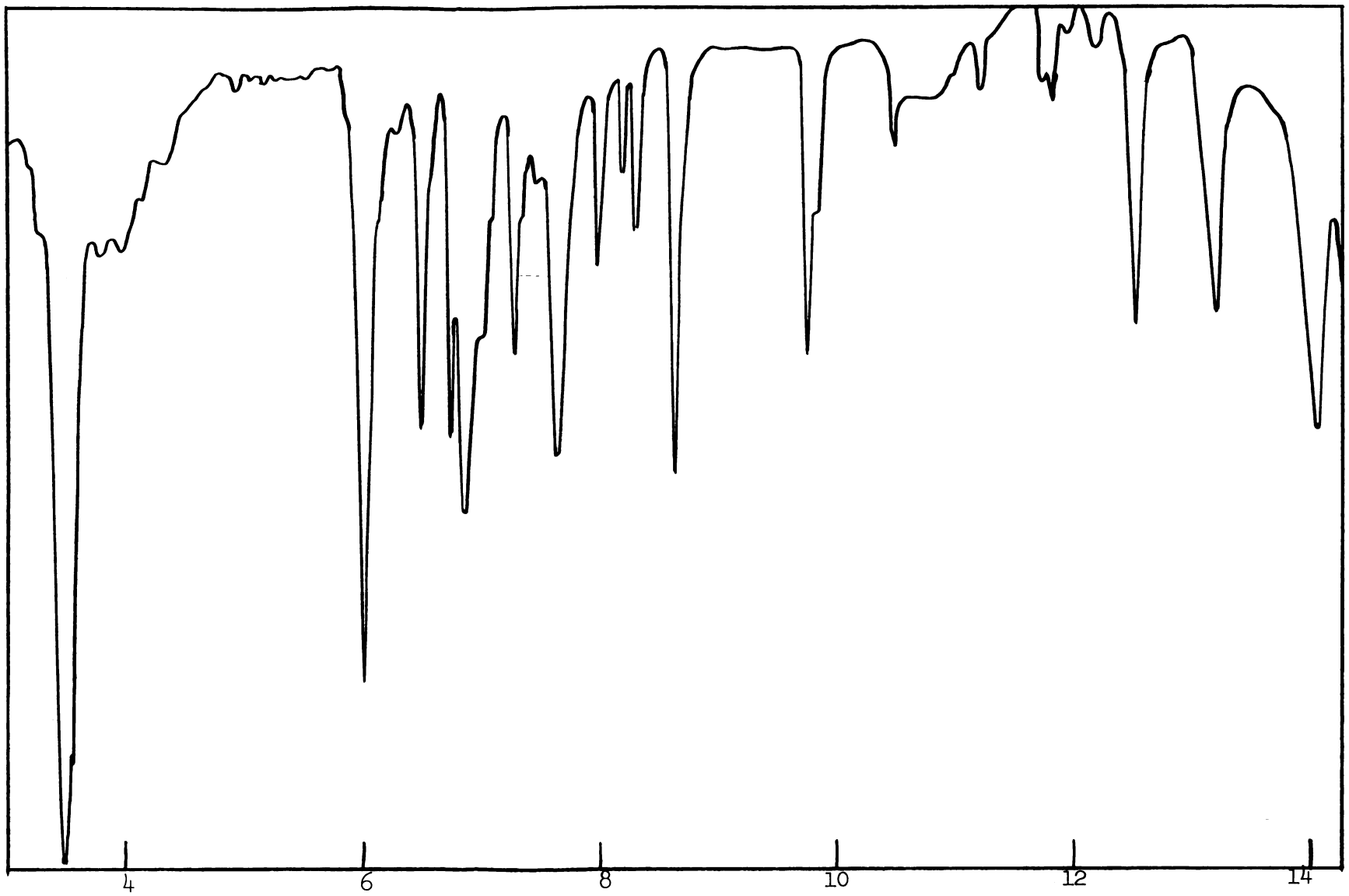


Figure 16a. Infrared Spectrum of 2-(2'-Thienyl)-5-furoic Acid (XII) taken as Nujol Mull.

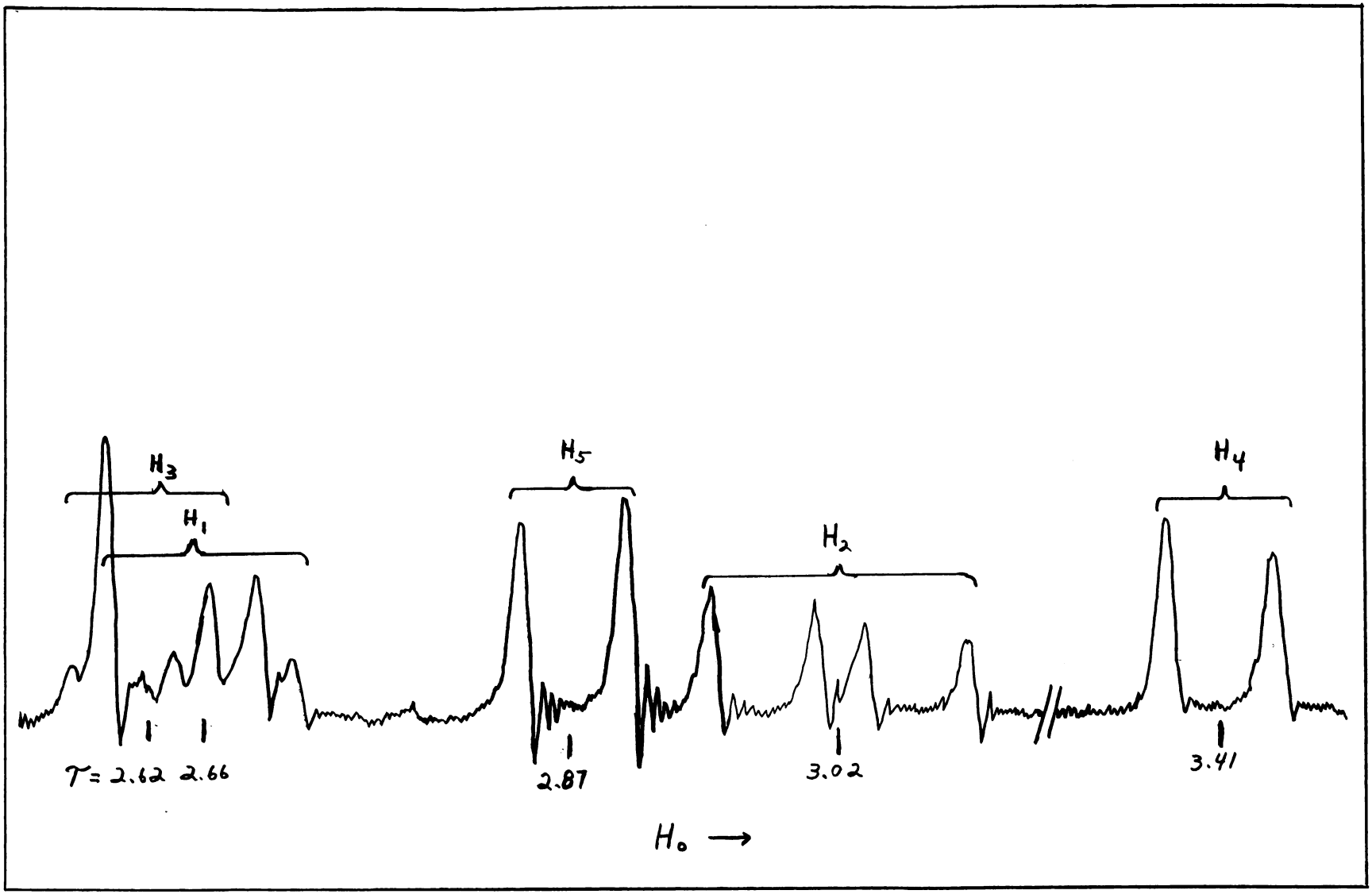


Figure 16b. N.m.r. Spectrum of 2-(2'-Thienyl)-5-furoic Acid (XII) in dioxane taken at a sweep width of 100 c.p.s.

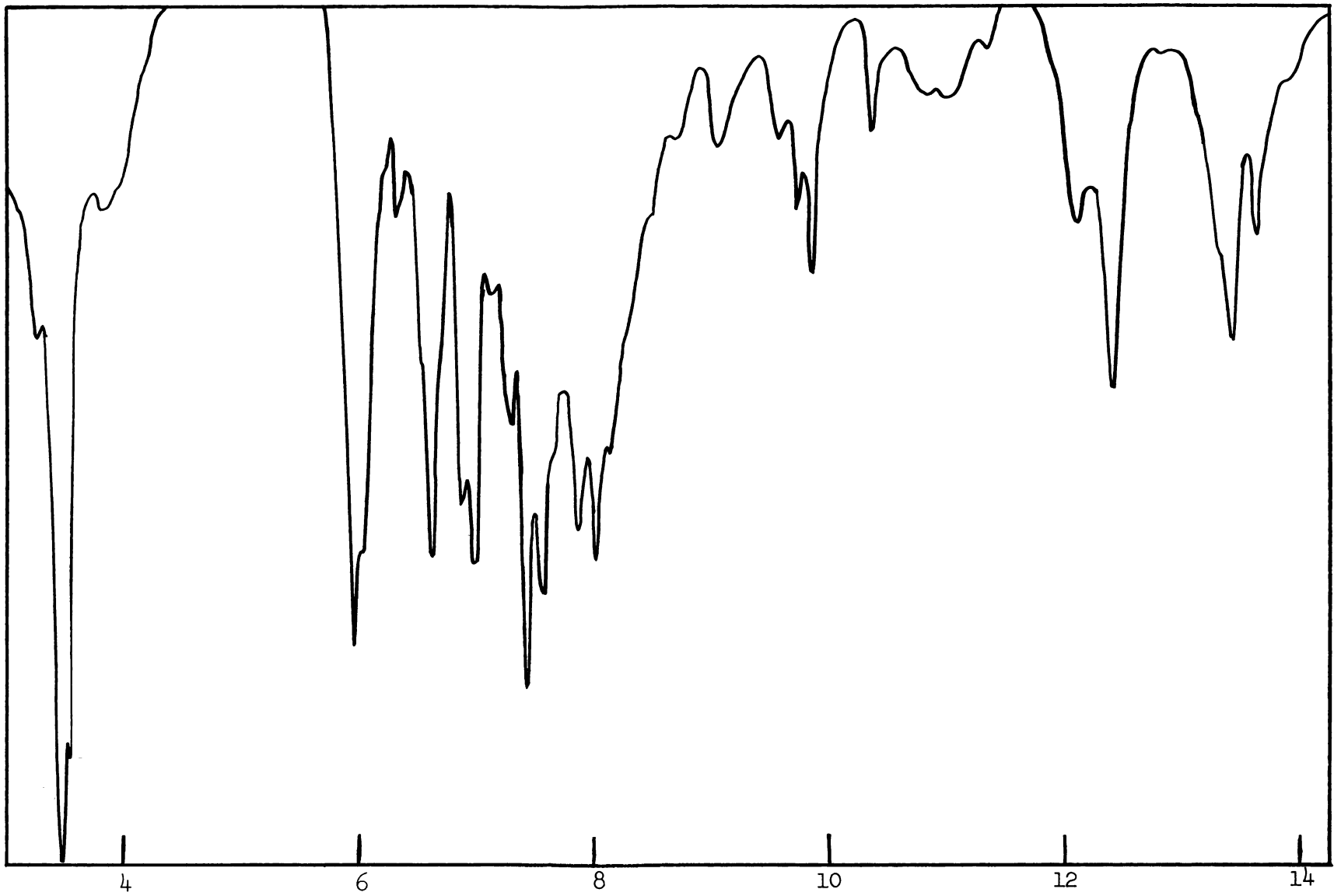
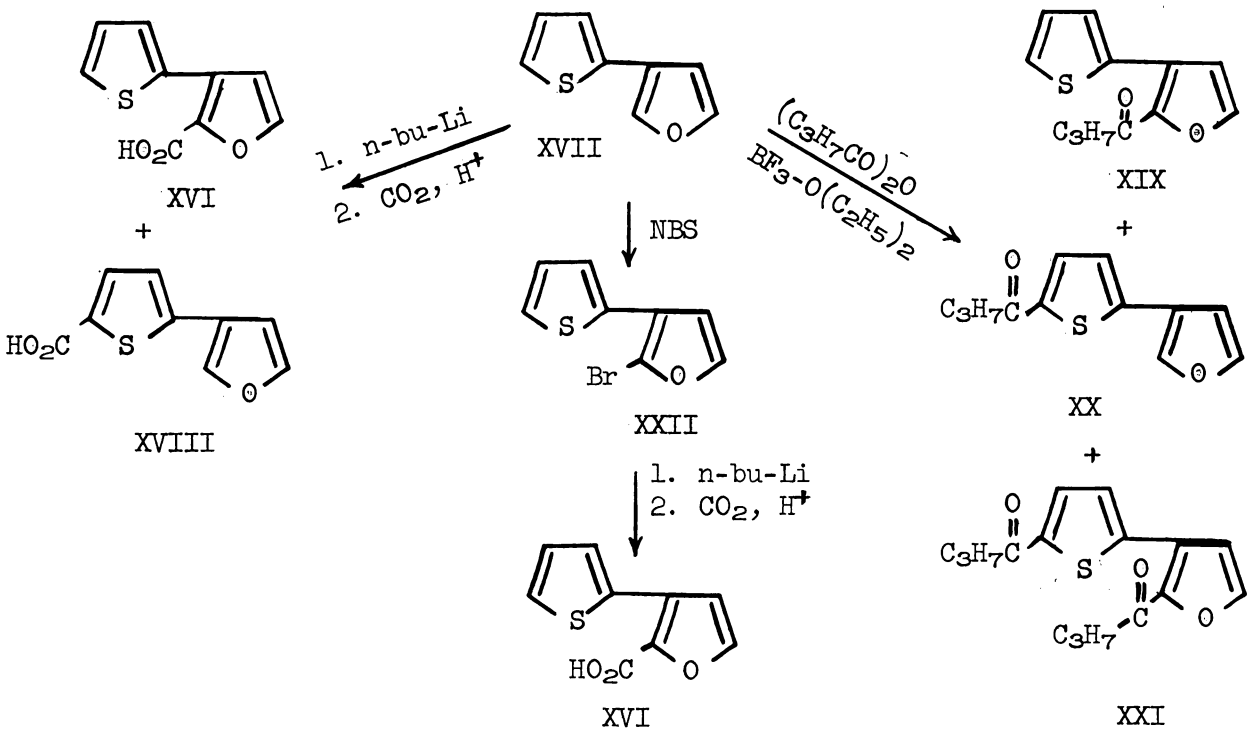
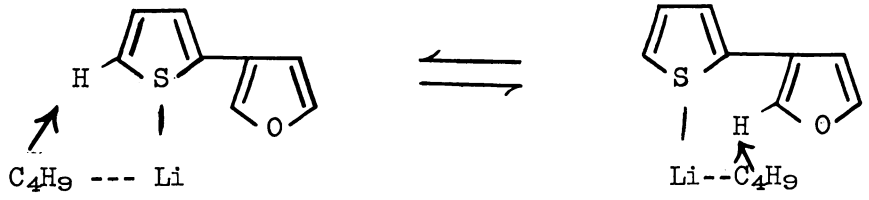


Figure 17. Infrared Spectrum of 5-Nitro-2-(5'-carboxy-2'-thienyl)-furan (XXIII) taken as a Nujol Mull.

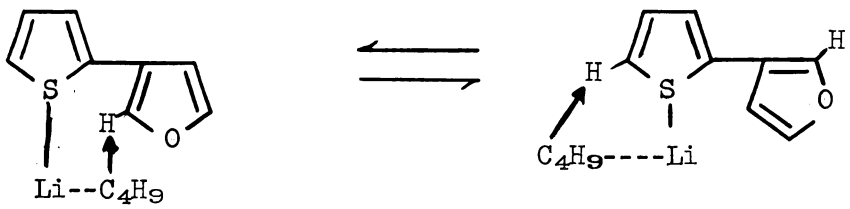


Metalation of XVII with n-butyl lithium gave a mixture of mono acids in 90% yield, consisting of 43% XVI and 57% XVIII (as determined by integration of the n.m.r. spectrum of the crude mixture, Fig. 20). Again coordination of the metalating agent before proton abstraction appears to be the rate determining factor. Coordination occurring only with the sulfur hetero atom, however, there are now two protons in the correct proximity for abstraction by the carbanion.



Although the n.m.r. spectrum of XVII shows the furan hydrogens to be at lower field, therefore having a lower electron density and probably therefore more prone to abstraction, the hydrogen α to the sulfur atom is abstracted

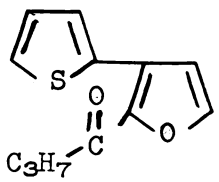
the most readily (57% vs. 43%). However, although this hydrogen atom is always in close prosimity to the butyl carbanion due to metal coordination with the sulfur, any rotation of the molecule about the thienyl furan carbon-carbon bond, removes the competing furan α hydrogen from the vicinity of the butyl carbanion,



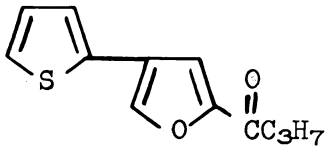
thereby reducing its possibility of abstraction. Considering the relative infrequency of the proper conformation for abstraction (a 7 center transition state is required) the amount of furan α-hydrogen abstraction is quite high.

Acylation of XVII produced two mono-acylated biaryls and one diacylated biaryl in 45% and 14% yields respectively. Of the mono-acylated material, electrophilic attack on the furan nucleus at the α position ortho to the thienyl substituent, was favored over attack on the open thiophene α position. Furan acylation gave XIX (79%), while thiophene substitution produced XX (21%) (as determined by integration of the n.m.r. spectra of the crude and distillate mixtures, the mono ketones were not separated from each other). Again the lower aromaticity of the furan nucleus leading to predominant substitution on that ring. The presence of the bulky ortho thienyl substituent however reduces the reactivity of this site to the extent that substitution on the thiophene ring becomes competitive. It should be noted, however, that substitution on the furan nucleus occurs only at the α position ortho to the thienyl substituent (XIX), thus characterizing the thienyl substituent as an ortho-para director, in that a meta director would in turn have led to substitution

at the alternate α position on the furan ring (XXIV).



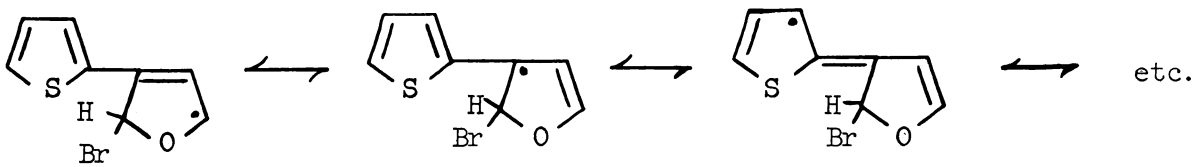
XIX



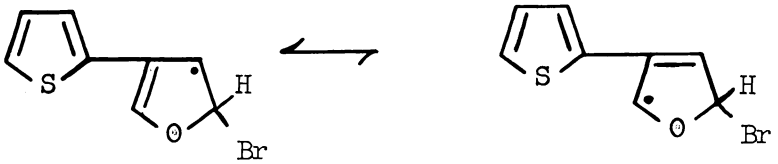
XXIV

A second acylation of either XIX or XX in turn gives the diketone XXI (Fig. 18).

Bromination of XVII with NBS, with or without benzoyl peroxide present, led to a single substitution product (XXII, Fig. 19). Again the lower aromaticity of the furan nucleus allowing a lower activation energy than would be found for substitution in the thiophene ring. The α position ortho to the thienyl substituent being attacked because of the possibility of conjugative interactions between that substituent and the α position ortho to it,



while such interactions cannot be incorporated in a structure where attack occurs meta to the thienyl substituent.



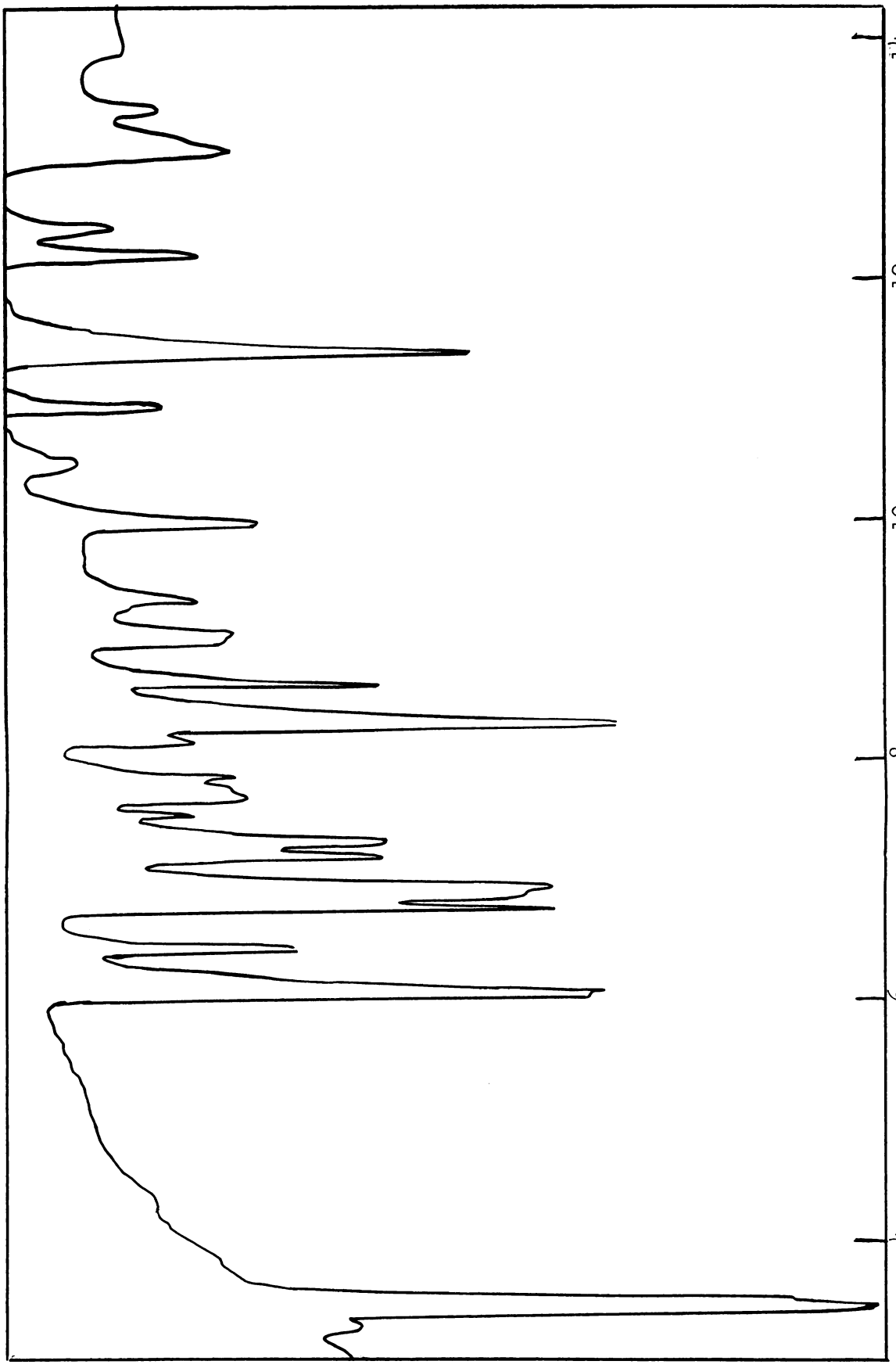


Figure 18. Infrared Spectrum of 2-Butyryl-3-(5'-butyryl-2'-thienyl)-furan (XXI) taken as a Nujol Mull.

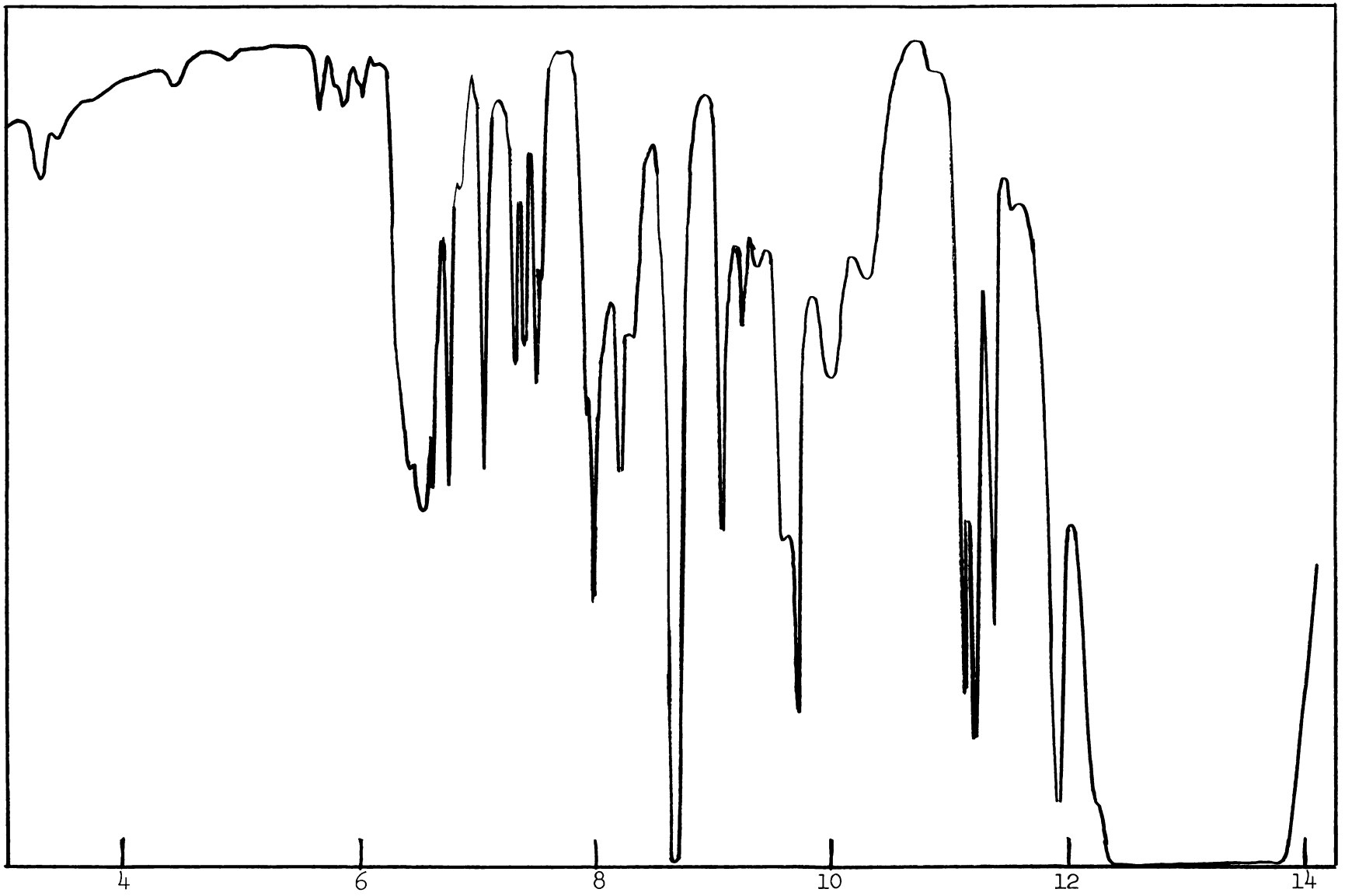


Figure 19. Infrared Spectrum of 2-Bromo-3-(2'-thienyl)-furan (XXII) taken in Carbon Tetrachloride.

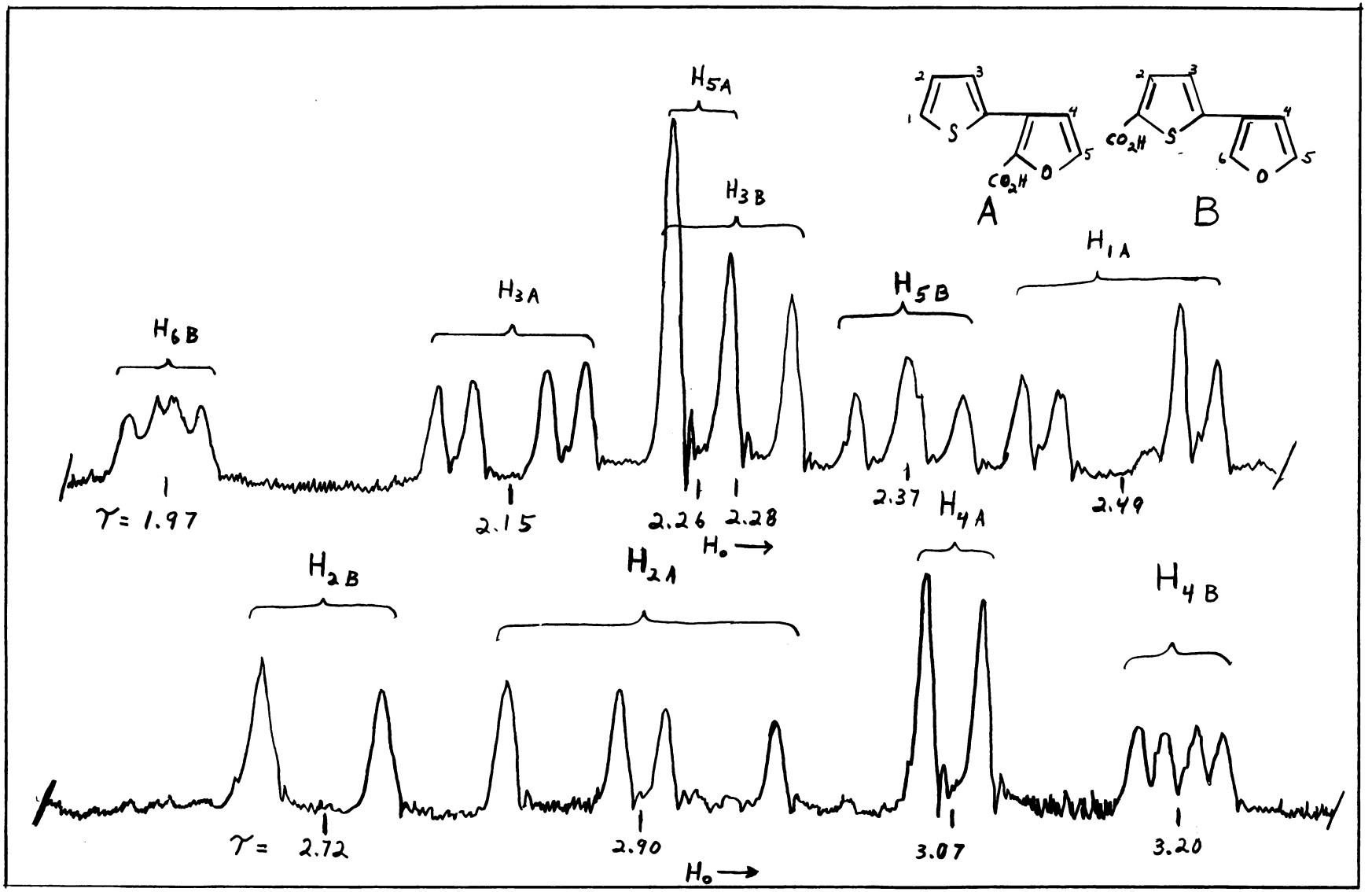


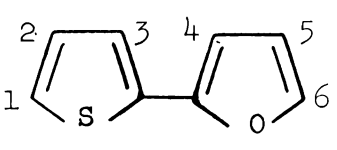
Figure 20. N.m.r. Spectrum of Crude Mixture of 57% XVI (A), and 43% XVIII (B) in Acetone taken at Sweep Width of 100 c.p.s.

The bromide XXII was found to have a stability similar to that of XI, and was therefore not isolated but was instead subjected to halogen metal interchange in order to obtain the corresponding acid XVI.

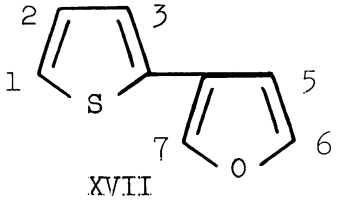
Studies of the Nuclear Magnetic Resonance Spectra.

The structure assignments of the thienyl-furans prepared and studied in this work were made through a first approximation of the n.m.r. spectra to first order splitting. The proton spin-spin coupling constants for these biaryls are: thiophene, J_{23} = 4.5 - 5.3; J_{24} = 1.2 - 1.9; J_{34} = 4.1; furan, J_{23} = 1.6 - 2.1; J_{24} = 0.7 - 0.9; J_{25} = 1.5 - 1.7; J_{34} = 3.4 - 3.9 (c.p.s.). These results were found to be quite consistent with the coupling constants obtained by Gronowitz (18,27) and Bernstein (20). The chemical shifts of the aromatic protons (Tables V and VI) of the substituted biaryls were also found to be dependent upon the inductive character of the substituents on the rings. The effect of a substituent on one ring is in turn felt by the protons on the other ring.

The n.m.r. spectra of the unsubstituted biaryls were of particular interest. While the absorption signals of protons 3 and 4 in IV, and 5 and 7 in XVII were found at lower field than are those



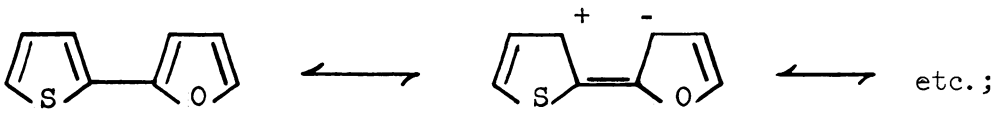
IV



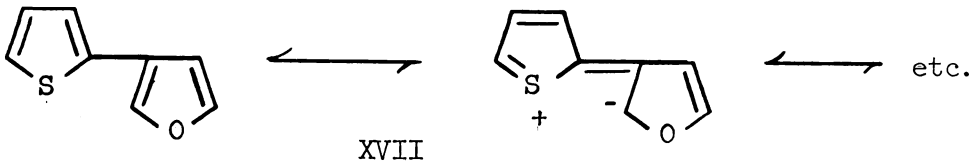
XVII

of the corresponding protons in the unsubstituted heterocycles (40),

the signals of the remaining protons have been shifted to a higher field. To the extent that structures involving interconjugation between the two coupled heterocyclic rings contributes to the ground state of IV or XVII,

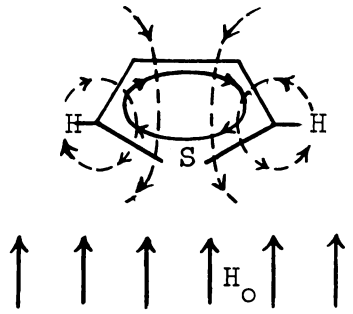


IV



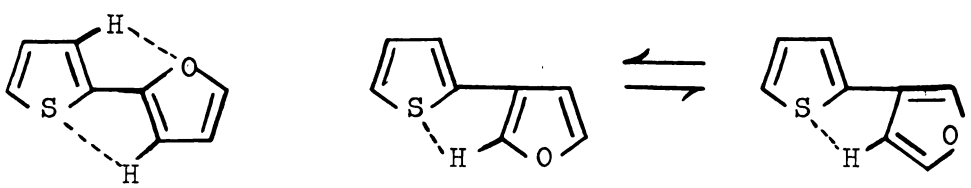
XVII

the loops of electrons in the aromatic rings are disturbed with a subsequent reduction of deshielding as caused by the inter atomic diamagnetic term.



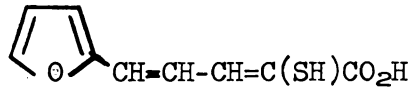
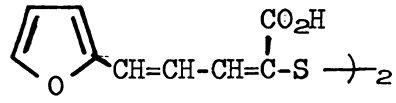
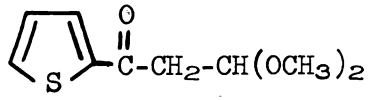
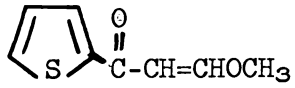
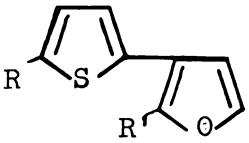
Although this reduction in interatomic diamagnetic effect would cause a shift of the absorption signals of all of the aromatic protons to a higher field, any protons capable of hydrogen bonding (i.e., protons 3 and 4 in IV, and 5 and 7 in XVII) are deshielded and their absorption signals are, therefore, found at a lower field strength. (Fig. 4b, 12b).

The proximity of these protons to the adjacent heterocyclic ring also can lead to additional deshielding due to the diamagnetic effect of the other ring. However, the extent of this diamagnetic term appears to be of minor consequence as is indicated by a lack of deshielding of the proton at position 3 in XVII, which though it can not hydrogen bond, should be influenced by the anisotropic effect of both rings.



IV

Table III

Compound			(95% EtOH) λ max. mμ	log ε	M.p.	B.p.	n_D^{20}
I			255 355	3.73 4.43	148-150°	----	---
II			208 343	3.89 4.28	191-193°	----	---
XIII			261 285	4.04 3.95	----	95° (0.07 mm)	1.5413
XIV			298*	4.29	72.5-73.5°	----	----
		R	R'				
XV		H	CO_2CH_3	238 266 303	4.06 3.86 4.02	----	136° (0.7 mm)	1.6098

Continued

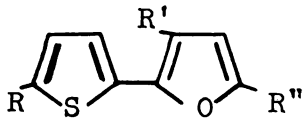
TABLE XLI — Continued

Table III - Continued

Compound			(95% EtOH) λ. max. mμ	log. ε	M.p.	B.p.	n_D^{20}
XVI	H	CO_2H	236 297	4.07 4.01	167-168°	----	---
XVII	H	H	220 224 271	4.03 4.04 3.97	----	84° (4.2 mm)	1.5924
XVIII	CO_2H	H	---	----	----	----	---
XIX	H	O C-(n-pr)	---	----	----	103-122° (0.06 mm)	---
XX	O C-(n-pr)	H	---	----	---	103-122° (0.06 mm)	---
XXI	O C-(n-pr)	O C-(n-pr)	220 267 340	4.03 4.26 4.24	109-110°	----	---
XXII	H	Br	280	----	---	----	---

*Nonresolvable shoulder at shorter wave length.

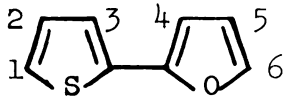
Table IV



Compound	R	R'	R"	(95% EtOH) λ max. mμ	log ε	M.p.	B.p.	n_D^{20}
III	CO_2H	H	H	226 328	3.84 4.30	186.5- 187.5°	----	---
IV	H	H	H	296	4.19	----	97.5° (10 mm) 75° (3.8 mm)	1.6201
V	H	$CO_2C_2H_5$	H	242 319	3.60	----	116° (0.09 mm)	1.5941
VI	H	CO_2H	H	241 316	3.54 4.15	155-155.5°	----	---
VII	H	H	O ‖ C-(n-pr)	230 263 340	3.80 3.61 4.33	32-33°	103° (0.08 mm)	1.6152
VIII	H	$CO_2C_2H_5$	O ‖ C-(n-pr)	---	----	----	141-145° (0.03 mm)	---
IX	O ‖ C-(n-pr)	$CO_2C_2H_5$	H	---	----	----	141-145° (0.03 mm)	---
X	CO_2H	H	CO_2H	334	4.39	302-304	----	---
XI	H	H	Br	---	----	----	----	---
XII	H	H	CO_2H	312	4.31	166-167	----	---

Table V. Spin-Spin Coupling Constants (c.p.s.)*; Chemical Shifts of Aromatic Protons

Table V. Spin-Spin Coupling Constants (c.p.s.)‡; Chemical Shifts of Aromatic Protons*

Compound	J_{12}	J_{13}	J_{23}	J_{45}	J_{46}	J_{56}	J_{67}	Solvent[a]	H_1	H_2	H_3	H_4	H_5	H_6	H_7
															
IV (unsubst.)	5.2	1.4	3.4	3.4	0.8	1.8	---	CCl_4	2.94	3.13	2.87	3.63	3.72	2.74	----
III (1-CO_2H)	---	---	4.0	3.4	0.7	1.9	---	acetone	----	2.30	2.67	3.16	3.44	2.40	----
III "	---	---	4.1	3.6	0.7	1.9	---	dioxane	----	2.30	2.73	3.24	3.48	2.43	----
III "	---	---	3.8	3.4	0.8	1.7	---	5% NaOH	----	3.16	2.76	3.65	3.76	2.80	----
V (4-$CO_2C_2H_5$)	5.2	1.3	3.9	---	---	1.6	---	CCl_4	2.70	3.00	1.92	----	3.31	2.78	----
VI (4-CO_2H)	5.2	1.3	3.9	---	---	2.0	---	acetone	2.40	2.84	1.84	----	3.11	2.42	----
VII (6-$CCH_2CH_2CH_3$)	5.0	1.2	3.5	3.6	---	---	---	CCl_4	2.80	3.10	2.73	3.56	2.99	----	----
VIII (4-$CO_2C_2H_5$-6-$CCH_2CH_2CH_3$)	5.0	1.2	3.8	---	---	---	---	CCl_4	2.58	3.02	1.92	----	2.78	----	----
IX (4-$CO_2C_2H_5$-1-$CCH_2CH_2CH_3$)	---	---	4.0	---	---	1.9	---	CCl_4	----	2.55	2.13	----	3.35	2.71	----

Continued

Table V — Continued

Table V - Continued

Compound	J_{12}	J_{13}	J_{23}	J_{45}	J_{46}	J_{56}	J_{67}	Solvent[a]	H_1	H_2	H_3	H_4	H_5	H_6	H_7
X (1-CO_2H-6-CO_2H)	---	---	3.8	3.5	---	---	---	5% NaOH	----	3.03	2.80	3.61	3.24	----	----
XI (6-Br)	5.2	1.3	3.3	3.4	---	---	---	CCl_4	2.97	3.17	2.93	3.73	3.83	----	----
XII (6-CO_2H)	5.1	1.2	3.5	3.6	---	---	---	dioxane	2.66	3.02	2.62	3.41	2.87	----	----
XXIII (1-CO_2H-6-NO_2)	---	---	4.0	3.9	---	---	---	dioxane[b]	----	2.30	2.49	3.11	2.56	----	----

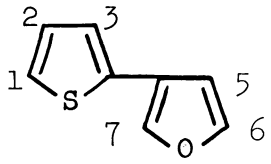
[a] Concentrations used were 10-20% except as noted.

[b] Concentration unknown due to low solubility.

‡ Accuracy of J value determinations is ± 0.2 cycles.

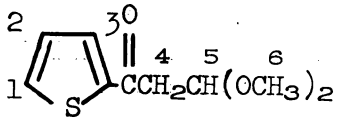
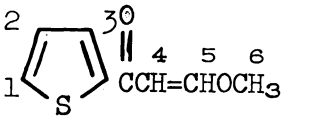
*Tetramethylsilane was used as an internal standard, τ = 10, accuracy of chemical shift determinations is ± 0.04 p.p.m.

Table VI. Spin-Spin Coupling Constants (c.p.s.)‡; Chemical Shifts of Aromatic Protons*

Compound	J_{12}	J_{13}	J_{23}	J_{45}	J_{57}	J_{56}	J_{67}	Solvent[a]	H_1	H_2	H_3	H_4	H_5	H_6	H_7
															
XVII (unsubst.)	4.9	1.4	3.8	---	0.9	1.9	1.6	acetone	2.77	3.02	2.84	----	3.33	2.50	2.20
XVII (unsubst.)	4.5	1.9	3.7	---	0.9	1.9	1.7	CCl_4	2.95	3.14	3.04	----	3.52	2.69	2.45
XVI (7-CO_2H)	5.3	1.3	3.8	---	---	1.9	---	acetone	2.48	2.88	2.13	----	3.06	2.25	----
XV (7-$CO_2C_2H_5$)	5.3	1.3	3.8	---	---	1.9	---	CCl_4	2.72	3.03	2.28	----	3.37	2.61	----
XVIII (1-CO_2H)	---	---	4.0	---	0.9	1.9	1.5	acetone	----	2.72	2.28	----	3.20	2.37	1.97
XIX (7-$CCH_2CH_2CH_3$)	5.2	1.2	3.8	---	---	1.9	---	CCl_4	2.75	3.03	2.08	----	3.30	2.65	----
XX (1-$CCH_2CH_2CH_3$)	---	---	4.0	---	0.9	1.9	1.6	CCl_4	----	3.04	2.56	----	3.47	2.65	2.32
XXI (1-$CCH_2CH_2CH_3$- 7-$CCH_2CH_2CH_3$)	---	---	4.0	---	---	2.0	---	acetone[b]	----	2.29	2.17	----	3.03	2.28	----

Continued

Table VI - Continued

Compound	J_{12}	J_{13}	J_{23}	J_{45}	J_{57}	J_{56}	J_{67}	Solvent[a]	H_1	H_2	H_3	H_4	H_5	H_6	H_7
XXII (7-Br)	5.3	1.4	3.5	---	---	2.1	---	CCl_4	2.80	3.02	2.72	----	3.42	2.61	----
XIII 	5.2	1.2	3.9	5.7	---	---	---	CCl_4	2.42	2.95	2.36	6.95	5.14	6.70	----
XIV 	5.2	1.2	3.9	12.4	---	---	---	CCl_4	2.48	2.96	2.39	2.33	3.83	6.25	----

[a] Concentrations used were 10-20%, except as noted.

[b] 5% due to low solubility.

* Tetramethylsilane was used as an internal standard, τ = 10.00, accuracy of chemical shift determination is ± 0.04 p.p.m.

‡ Accuracy of J value determinations is ±0.2 cycles.

EXPERIMENTAL*

5-(2'-Furyl)-2-mercapto-2,4-pentadienoic Acid (I).

A 7.1 g. (0.03 mole) quantity of the rhodanine derivative (28) of 2-furylacrolein (29) and 60 ml. of 10% NaOH were placed in a 250 ml. flask. The alkaline reaction mixture was heated until solution was complete (10-15 min.), then cooled in ice water and acidified by the addition of 40 ml. of 10% HCl in one portion. The precipitated mercapto-acid was recovered by filtration, washed with water and dried to obtain 4.4 g. (0.022 mole), 75%, of I. A portion for analysis was purified by sublimation in order to obtain light yellow needles which melted at 148-150°.

Anal.

Calc'd. for $C_9H_8SO_2$: C, 55.09; H, 4.11; S, 16.34.

Found: C, 54.94; H, 4.35; S, 16.40.

2,2'-Dithiobis-[5-(2"-furyl)-2,4-pentadienoic Acid] (II).

To a stirred solution of 0.5 g. (0.0025 mole) of crude I dissolved in a minimum of absolution ethanol at 0° was added 0.35 g. (0.0014 mole) of iodine. The oxidation was allowed to continue for an hour at 0°; the mixture was filtered and the disulfide precipitate washed with a minimum of cold ethanol. Recrystallization of the crude disulfide from an ethanol water

---

*All reactions were conducted under dry nitrogen. N.m.r. spectra were obtained on a Varian A-60 high resolution spectrometer, infrared spectra from a Perkin-Elmer model 21, and ultraviolet spectra were obtained on either a Beckman DK-2 or a Cary model 11.

mixture yielded the pure product II (0.35 g., 0.0018 mole, 70%) as an orange colored crystalline solid melting at 191 to 193°.

Anal.

Calc'd. for $C_{18}H_{14}S_2O_6$: C, 55.37; H, 3.61; S, 16.43.

Found: C, 55.22; H, 3.86; S, 16.63.

Neutralization equivalent. Calc'd.: 195. Found: 196.

2-(2'-Furyl)-5-thenoic Acid (III).

A 6 g. (0.03 mole) quantity of I was added to a stirred solution prepared from 7.5 g. (0.03 mole) of iodine dissolved in 100 ml. of absolute ethanol and contained in a 250 ml. Erlenmeyer flask. The temperature of the flask was maintained at 75° for 5 hrs. after which the contents were poured into a liter of water. Unreacted iodine was destroyed by adding excess granular $NaHSO_3$. Powdered charcoal was then added, the mixture was warmed to effect solution of the organic material, and the hot mixture was filtered through fluted filter paper. The cooled filtrate was extracted with one 200 ml. and two 100 ml. portions of ether. The combined ether extracts on evaporation yielded 1.6 g. (0.0082 mole, 27%) of crude III. A sample for analysis was purified by recrystallization from an ethanol-water mixture and then sublimed at 110° (0.08 mm.) to obtain a pale yellow solid in the form of needles which melted at 186.5 to 187.5°

Anal.

Calc'd. for $C_9H_6SO_3$: C, 55.66; H, 3.12; S, 16.51.

Found: C, 55.39; H, 3.34; S, 16.57.

Neutralization equivalent. Calc'd.: 194. Found: 197.

2-(2'-Thienyl)-furan (IV).

Into a 25 ml. three neck flask equipped with a nitrogen inlet tube, and a 20 cm. vacuum insulated vigereaux column attached to a distilling head were placed 5.6 g. (0.029 mole) of III, 0.5 g. powdered copper, and 10 g. of purified quinoline. The reaction mixture was heated to its reflux temperature while the flask was swept with nitrogen until CO_2 evolution had ceased (2 hours). The resulting thienylfuran-quinoline mixture was subjected to vacuum distillation, the portion boiling at 90-110° (10 mm.) being collected. The distillate was dissolved in 20 ml. of ether and the ether solution was washed twice with 5 ml. portions of water, and dried. The ether was removed and the residue distilled in vacuo to obtain 2.55 g. (0.017 mole, 59%) of IV, b.p. 97.5° (10 mm.), n_D^{20} 1.6201, which was readily oxidized by air.

Anal.

Calc'd. for C_8H_6SO: C, 63.97; H, 4.03; S, 21.34.

Found: C, 64.10; H, 4.11; S, 21.29.

Ethyl 2-(2'-Thienyl)-3-furoate (V) (11).

Into a liter three necked flask containing a nitrogen inlet tube, mechanical stirrer, and a dropping funnel, were placed 56.5 g. (0.286 mole) of ethyl 3-(2'-thienyl)-3-oxopropionate (31), 50 g. (0.315 mole) of 1,2-dichloroethylethyl ether, and 300 ml. of ether. The vigorously stirred mixture was cooled to 0° and a solution of 35 g. KOH dissolved in 200 ml. of ethanol was added to it over a period of an hour. The reaction mixture was stirred for an additional hour and then 50 ml. of 10% HCl was added to it. The insoluble salt (KCl) was removed by filtration, followed by removal of the ether on a rotary evaporator. The heavier, lower, organic layer was

separated, dried and distilled in vacuo, and the fraction boiling in the range 60-140° (0.5 mm.) was collected. The distillate was diluted with four times its volume of ether, chilled in ice, and washed five times with 50 ml. portions of 2% NaOH, then with dilute HCl, and finally with water and dried. Vacuum distillation of the resulting ethereal solution of essentially pure ester gave 20.71 g. (0.093 mole, 33%) of V, b.p. 115-119° (0.09 mm.), n_D^{20} 1.5941.

Anal.

Calc'd. for $C_{11}H_{10}SO_3$: C, 59.42; H, 4.53; S, 14.43.

Found: C, 59.45; H, 4.46; S, 14.49.

2-(2'-Thienyl)-3-furoic Acid (VI).

A 5 g. (0.0225 mole) quantity of ester (V) was saponified by heating at its reflux temperature a solution of the ester with 2 g. (0.036 mole) of KOH, dissolved in 75 ml. of 65% ethanol, under a nitrogen atmosphere for 20 min. The ethanol was removed from the aqueous acid salt of VI by vacuum distillation with a water aspirator, concentrating the alkaline solution to a volume of 15 to 20 ml. A 100 ml. volume of water was then added to the concentrated solution and the basic solution was cooled. Acidification with 20 ml. of 10% HCl, followed by filtration, washing of the precipitate with copious quantities of ice water, and drying, gave 4.4 g. (0.022 mole), 98%, of a stable colorless organic acid, VI. Sublimation of a portion of the acid for analysis at 100° (0.08 mm.) gave colorless needles melting at 155 to 155.5°.

Anal.

Calc'd. for $C_9H_6SO_3$: C, 55.66; H, 3.12; S, 16.51.

Found: C, 55.92; H, 3.34; S, 16.41.

2-(2'-Thienyl)-furan (IV).

2-(2'-Thienyl)-3-furoic Acid (IV) was decarboxylated by the procedure utilized for the decarboxylation of 2-(2'-furyl)-5-thenoic acid (III). A 17.7 g. (0.091 mole) quantity of VI yielded 12.9 g. (0.086 mole) of IV. The latter was shown to be identical to the material obtained by the decarboxylation of III by infrared, n.m.r., b.p., and refractive index determinations.

Nitration of 2-(2'-Furyl)-5-thenoic Acid.

Following the experimental procedure outlined by H. Gilman (37), 9.7 g. (0.05 mole) of 2-(2'-furyl)-5-thenoic acid (III) was added in portions at -15° to a well stirred nitrating mixture prepared from 18.3 g. of fuming nitric acid (sp. gr. 1.51) dissolved in 39 ml. of acetic anhydride. The reaction mixture was stirred for an hour at -15° and then poured into 300 ml. of ice water. The precipitated nitro acid was recovered by filtration to obtain 5.7 g. (0.024 mole) of the crude acid XXIII. Sublimation of a portion of the acid for analysis gave orange colored needles of pure acid which melted at 262-263°, and had a low solubility in most organic solvents.

Anal.

Calc'd. for $C_9H_5NO_5S$: C, 45.19; H, 2.11; S, 13.41; N, 5.86.

Found: C, 45.20; H, 2.28; S, 13.63; N, 5.84.

Acylation of 2-(2'-Thienyl)-furan (32).

Into a 10 ml. flask which had been fitted with a reflux condenser, a drying tube, a thermometer, a magnetic stirring bar, and a nitrogen inlet tube, were placed 2.73 g. (0.0182) mole) of IV and 3.30 g. (0.029 mole) of butyric anhydride. To this solution was added 0.25 g. (0.30 ml.) of BF_3-etherate while nitrogen was passed over the stirred mixture. The temperature of the dark blue solution immediately rose and was maintained at 110° for 2 min. The solution was then allowed to cool while stirring was continued for an additional 30 min., and the reaction was then quenched by the addition of 2 ml. of water. A saturated aqueous solution of Na_2CO_3 was then added to the reaction mixture until it was basic to litmus. The mixture was extracted with ether and the combined organic extracts were dried with Na_2SO_4. Removal of the ether and vacuum distillation of the residue yielded 1.0 g. (0.0045 mole) of the ketone VII, b.p. 103° (0.08 mm.), m.p. 32-33°, n_D^{40} 1.6152, (28% based on unreclaimed IV).

Anal.

Calc'd. for $C_{12}H_{12}SO_2$: C, 65.45; H, 5.45; S, 14.55.

Found: C, 65.21; H, 5.70; S, 14.45.

Acylation of Ethyl 2-(2'-Thienyl)-3-furoate.

Acylation of ethyl 2-(2'-thienyl)-3-furoate (V) was accomplished by the procedure outlined for IV above. By reacting 2.22 g. (0.01 mole) of V with 1.82 g. (0.0115 mole) of butyric anhydride and 0.14 g. (0.165 ml.) of BF_3-etherate, 1.7 g. (0.0077 mole) of a product, b.p. 141-145° (0.03 mm.), 60% was obtained, consisting of a mixture of keto-esters VIII and IX, melting at

59-62°. This mixture was subjected to elemental analysis.

Anal.

Calc'd. for $C_{15}H_{16}SO_4$: C, 61.64; H, 5.48; S, 10.96.

Found: C, 61.92; H, 5.67; S, 10.77.

Metalation of 2-(2'-Thienyl)-furan.

A mixture of 0.30 g. (0.0433 mole) of lithium metal pellets and 10 ml. of anhydrous ether was placed under nitrogen in a 25 ml. 3 neck flask which was equipped with a magnetic stirrer, a -100 to + 30° thermometer and a pressure equalizing dropping funnel. A solution of 2.74 g. (0.02 mole) of n-butyl bromide dissolved in 3 ml. of anhydrous ether was placed in the dropping funnel and a few drops of the latter mixture were added to the lithium mixture. The stirrer was started and after 5 to 10 minutes, the liquid in the flask became cloudy and bright spots appeared on the lithium. The temperature of the reaction mixture was lowered to -20° by immersion of the reaction flask in a dry ice acetone bath, and the remainder of the bromobutane was added at an even rate during approximately an hour. The mixture was stirred for an additional hour while the temperature was allowed to rise to +10°. The unreacted lithium was removed and the remaining solution was cooled to -30°. A solution of 3.0 g. (0.02 moles) of thienylfuran (IV) in 3 ml. of anhydrous ether was placed in the dropping funnel and this mixture was allowed to drop into the reaction flask during a half hour while the temperature of the reaction mixture was maintained below -20°. The reaction mixture was stirred for an additional hour while the temperature was allowed to rise to 0°, at which point it was poured into a slurry of 25 g. of dry ice in 15 ml. of ether. The dry ice was allowed to evaporate and the remaining

ether mixture was washed three times with 20 ml. portions of water. The combined water extracts were washed once with 10 ml. of ether, placed in a flask and acidified to a pH of 4.2 (pH meter) to obtain the mono-acid III, 2.5 g. (0.0129 mole), 65%, (identified by comparison of m.p., and n.m.r. and infrared spectra with data for previously prepared III). The filtrate was treated with norite and further acidification yielded 0.3 g. (0.0015 mole), 6%, of pure dicarboxylic acid X melting at 302-304°.

Anal.

Calc'd. for $C_{10}H_6SO_5$: C, 50.42; H, 2.54; S, 13.46.

Found: C, 50.34; H, 2.61; S, 13.77.

Bromination of 2-(2'-Thienyl)-furan (33).

Into a 100 ml. 3 neck flask equipped with a reflux condenser, a nitrogen inlet tube, and a magnetic stirrer, was placed 3 g. (0.02 mole) of IV dissolved in 40 ml. of purified CCl_4. To this solution was added 3.5 g. (0.02 mole) of N-bromosuccinimide and the resulting mixture was heated at its reflux temperature for 2.5 hrs., then cooled and the succinimide removed by filtration. The filtrate was washed twice with 10 ml. portions of water and dried with Drierite. Infrared and n.m.r. spectra taken of this solution showed the reaction to be essentially quantitative. Evaporation of the solvent on a rotary evaporator gave a greenish-yellow colored liquid which decomposed with a seemingly self-catalyzed spattering and fuming, commencing about 5 minutes after removal of the CCl_4, producing a black amorphous tar.

2-(2'-Thienyl)-5-furoic Acid (XII).

5-Bromo-2-(2'-thienyl)-furan (approx. 0.02 mole) in CCl_4, from the previous reaction was placed in a 100 ml. 3 neck flask which had been fitted with a nitrogen inlet tube and a vigereaux column with distilling head attached. A 40 ml. quantity of dry di-n-butyl ether was added and the CCl_4 was removed from the mixture by distillation until the vapor temperature reached 40° (30 mm.). The di-n-butyl ether solution was cooled and added in one portion to 0.02 mole of n-butyl-lithium dissolved in 30 ml. of diethyl ether at -70°. The resulting mixture was stirred for 2.5 minutes and the reaction mixture was then poured into a slurry consisting of 25 g. of dry ice in 25 ml. of anhydrous diethyl ether. The excess dry ice was allowed to vaporize and the remaining ether mixture was washed 3 times with 50 ml. portions of water. The combined aqueous portions were extracted once with 20 ml. of ether and then acidified with 10% HCl. The crude organic acid was separated by filtration (1.89 g., m.p. 162-164°), and again dissolved in aqueous base, treated with Norite and reacidified. Filtration of the resulting white flocculant acid and drying gave XII which melted at 166-167°. The 41% yield based on IV, should be increased by longer reaction time as considerable unreacted bromide remained in the ether layer. A portion of the acid for analysis was sublimed with no further improvement in melting point.

Anal.

Calc'd. for $C_9H_6SO_3$: C, 55.66; H, 3.12; S, 16.51.

Found: C, 55.46; H, 3.26; S, 16.32.

1,1-Dimethoxy-3-oxo-3-(2'-thienyl)-propane (XIII) (34).

Into a dry 2 liter 3 neck flask, equipped with a reflux condenser with an attached drying tube, A Hirshberg stirrer, a vacuum take off, and a nitrogen inlet tube, was placed 250 ml. of anhydrous methanol. To this was added 23 g. (1 mole) of sodium metal chips. After the reaction was complete the excess methanol was removed by vacuum distillation from the stirred mixture until powdering was complete.* A 1.5 liter volume of anhydrous ether was then added to the cooled flask and a solution of 126 g. (1 mole) of acetothienone dissolved in 72 g. (1.2 mole) of methyl formate (distilled from P_2O_5) was added at a rate sufficient to maintain a gentle refluxing (30 min.) of the well stirred thickening yellow-white mixture. The reaction mixture was stirred for an additional 1.5 hrs., at which point most of the ether was removed by vacuum distillation from the very thick mass (stirring was continued for as long as practical). Methanol (6 moles) was then added to the solid sodium hydroxymethylene ketone followed by the addition of a solution of 2 moles of anhydrous HCl dissolved in 4 moles of methanol. The temperature of the mixture rose on addition of acid and was lowered to 20° by cooling. The acidified mixture was stirred for an additional 2 hrs. at 20°. A solution of KOH dissolved in a minimum of methanol was then added, while the stirred reaction mixture cooled in an ice bath, until a pH of 6 (moistened Hydrion Paper) was attained. A mixture of 200 ml. of CCl_4 and

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*Commercial sodium methylate would not catalyze the desired condensation.

450 ml. of water was then added and the resulting aqueous brine layer was removed and washed with two 50 ml. portions of CCl_4. The organic layers were combined and washed twice with 150 ml. portions of a half saturated brine solution. The organic layer was separated and dried with $MgSO_4$, and the solvent was removed by means of a rotary evaporator and vacuum distillation of the residue from a simple distillation flask gave XIII (141 g.) 70%, b.p. 95° (0.07 mm.) (oil bath temperature 115°).

Anal.

Calc'd. for $C_9H_{12}SO_3$: C, 53.97; H, 6.04; S, 16.01.

Found: C, 54.18; H, 5.94; S, 16.24.

1-Methoxy-3-oxo-3-(2'-thienyl)-1-propene (XIV) (34).

The procedure for the preparation of XIII was followed with the following modifications. The acidic methanolic acetal solution was neutralized with a saturated solution of KOH dissolved in methanol until the mixture was basic to litmus. At this point the coloration of the mixture had changed from a yellow to a blood red color. Filtration of the precipitated inorganic salts, followed by vacuum distillation of the filtrate from a simple distillation flask, resulted in the isolation of 10 g. of distillate, b.p. 120° (0.7 mm.), consisting of a mixture of XIII and XIV, which solidified in the collection flask. Recrystallization of this solid distillate four times from CCl_4 with Norite treatment resulted in the isolation of 4.0 g. of pure XIV, m.p. 72.5-73.5°.

Anal.

Calc'd. for $C_8H_8SO_2$: C, 57.12; H, 4.79; S, 19.07.

Found: C, 56.61; H, 4.66; S, 19.35.

Methyl 3-(2'-Thienyl)-2-furoate (XV).

The procedure outlined by Burness (5,7) for the preparation of β-substituted methyl α-furoates was utilized for the synthesis of XV. In this manner 200 g. (1 mole) of XIII was converted to (66 g.) of XV, 32%, b.p. 136° (0.7 mm.), n_D^{20} 1.6098 by distillation from a simple distillation flask without purification of the glycidic ester intermediate.

Anal.

Calc'd. for $C_{10}H_8SO_3$: C, 57.67; H, 3.87; S, 15.40.

Found: C, 57.42; H, 3.92; S, 15.22.

3-(2'-Thienyl)-2-furoic Acid (XVI).

The procedure followed has been outlined for the saponification of V. By this method 100 g. (0.48 mole) of ester was converted to 84 g. (0.43 mole), 90%, of crude, cream colored acid melting at 168-169°. A 4.0 g. portion of the acid for analysis was dissolved in base, treated with Norite at 25°, and acidified to obtain 3.2 g. of colorless acid melting at 171-172° on a Kofler block.

Anal.

Calc'd. for $C_9H_6SO_3$: C, 55.66; H, 3.12; S, 16.51.

Found: C, 55.63; H, 3.16; S, 16.71.

3-(2'-Thienyl) furan (XVII).

By the method used above for the conversion of VI to IV, 61 g. (0.315 mole) of acid XVI was converted to 42.1 g. (0.28 mole), 89%, of XVII, b.p. 84° (4.2 mm.), n_D^{20} 1.5924.

Anal.

Calc'd. for C_8H_6SO: C, 63.97; H, 4.03; S, 21.34.

Found: C, 64.50; H, 3.92; S, 21.00.

Acylation of 3-(2'-Thienyl)-furan (XVII).

By the procedure used above for the acylation of IV, 9 g. (0.06 mole) of XVII, 10.92 g. (0.069 mole) of n-butyric anhydride, and 0.99 ml. of BF_3-etherate were allowed to react for 5 minutes at 110° and the solution was then allowed to cool while stirring was continued for an additional hour. A 12 ml. volume of water was added and the solution was made basic by the addition of a saturated Na_2CO_3 solution. Ether (10 ml.) was then added and the crystals of almost colorless diketone XXI (2.4 g., 14%) were recovered by filtration and rinsed with ether. Sublimation of a portion of the crude XXI gave cubic crystals melting at 109-110°.

Anal.

Calc'd. for $C_{16}H_{18}SO_3$: C, 66.18; H, 6.25; S, 11.04.

Found: C, 66.28; H, 6.36; S, 11.14.

The filtrate after isolation of XXI was extracted with ether and the organic layer was dried over $MgSO_4$. Removal of the ether and vacuum distillation of the residue gave a mixture (5.9 g., 45%) of ketones consisting of 79% XIX and 21% XX, b.p. 103-122° (0.06 mm.) with XX predominating at the higher temperature.

Anal.

Calc'd. for $C_{12}H_{12}SO_2$: C, 65.45; H, 5.45; S, 14.55.

Found: C, 66.01; H, 5.75; S, 14.50.

Metalation of 3-(2'-Thienyl)-furan (XVII).

By the procedure previously discussed for the metalation of IV, a 6 g. (0.04 mole) quantity of XVII was converted to 3.95 g. (2.04 mole), 51%, of a crude acid (90% based on unreacted XVII). Sublimation of a portion of the acid for analysis at 110° (0.05 mm.) yielded a mixture of monoacids consisting of 43% XVI and 57% XVIII.

Anal.

Calc'd. for $C_9H_6SO_3$: C, 55.66; H, 3.12; S, 16.51.

Found: C, 55.83; H, 3.16; S, 16.78.

Bromination of 3-(2'-Thienyl)-furan (XVII).

By the procedure outlined earlier for the bromination of IV, a 3 g. quantity (0.02 mole) of XVII was allowed to react with 3.5 g. of NBS in 40 ml. of CCl_4, to yield quantitatively (as determined by n.m.r.) in 1.5 hrs., 2-bromo-3-(2'-thienyl)-furan (XXII). Due to the instability of XXII it was converted to the corresponding acid XVI (2.25 g., 58%) by the previously described procedure to convert XI to XII.

Bromination of XVII in the presence of benzoyl peroxide.

In a manner similar to that above, 3 g. (0.02 mole) of XVII was allowed to react with 3.5 g. (0.02 mole) of NBS, and 0.2 g. of benzoyl peroxide in 40 ml. of purified CCl_4. Again XVII was converted quantitatively (by n.m.r.) in 1.5 hrs. to XXII, at the reflux temperature of the reaction mixture.

Attempted condensation of thienyl glyoxal with methyl diglycolate.

The Hinsberg (16,30) method for the preparation of substituted furans was used in an attempt to prepare a substituted 3-(2'-thienyl)-furan. Utilizing this previously described experimental method 3.5 g. (0.025 mole) of thienyl glyoxal (35,36) and 4.05 g. (0.025 mole) of methyl diglycolate dissolved in 20 ml. of anhydrous methanol were added to a solution containing 7.25 g. (0.113 mole) of freshly prepared sodium methylate dissolved in 45 ml. of anhydrous methanol. The resulting mixture was set aside under nitrogen at room temperature for 7 days. The dark blue reaction mixture was then poured into water and concentrated by heating on a steam bath. Acidification of the cooled alkaline mixture gave an aqueous suspension of a dark amorphous material from which no substituted furoic acid could be isolated. Modifications of this procedure were also attempted. The reaction mixture was heated at its reflux temperature under nitrogen for 4 hrs., poured into water and then concentrated on a steam bath. The brown basic mixture was acidified and the isolation of any resulting furoic acid was again unsuccessful.

A 7 g. (0.05 mole) quantity of thienyl glyoxal and 8.1 g. (0.05 mole) of ester were dissolved in a mixture of 75 ml. of ether and 25 ml. of methanol. This solution was cooled to 0° and a second solution containing 14.5 g. (0.225 mole) of freshly prepared sodium methylate in 67 ml. of methanol was slowly added to the stirred mixture. The cold mixture was stirred for an additional 2 hours, then poured onto ice, and the resulting mixture extracted three times with ether. The organic layers were combined, washed with dilute acid, then with water and dried. The ether was evaporated and the residue was distilled in vacuo. The starting material

which distilled at 85° (0.1 mm.), consisted mainly of methyl diglycolate, the remaining material was undistillable, at a pressure of 0.1 mm., although the still bath temperature was raised to 200°. Attempted isolation of ester or acid from this residue was unsuccessful. A 7 g. (0.05 mole) quantity of thienyl glyoxal and 8.1 g. of methyl diglycolate were dissolved in 20 ml. of dimethyl sulfoxide and 1 ml. of triethylamine was added. The resulting dark blue mixture was stirred at room temperature for 30 hrs., and 40 ml. of 10% NaOH solution was then added. The basic mixture was heated at its reflux temperature for 15 minutes. The triethylamine was removed by vacuum distillation from the mixture and 200 ml. of water was added. The resulting solution was treated with Norite, and then acidified. Attempted isolation of a thienyl-furoic acid from the resulting dark colored mixture gave no positive results.

Attempted Von Richter reaction on 2-nitrothiophene.

The Von Richter (17,38) reaction conditions were used in an attempt to convert 2-nitro thiophene to 3-thenoic acid. In this manner 4 g. of 2-nitrothiophene was combined with 15 g. of KCN in 75 ml. of 48% ethanol. The resulting mixture was refluxed for 1.5 hrs., and then poured into 100 ml. of water and made strongly basic with NaOH. The ethanol was removed by steam distillation and the residue was acidified. Steam distillation of the acidic solution gave a cloudy distillate, which was extracted with ether. Evaporation of the solvent from the ether extract yielded no 3-thenoic acid. In a subsequent attempt to carry out the Von Richter reaction with 2-nitrothiophene, CuCN was used in place of the KCN with no positive results; and the KCN

aqueous ethanol solution was buffered with KH_2PO_4 to a pH of 7.8. In neither of these modifications of the reaction conditions was any 3-thenoic acid isolated.

SUMMARY

The mixed biaryls 2-(2'-thienyl)-furan and 3-(2'-thienyl)-furan were prepared, and though air oxidizable, they were quite stable under a nitrogen atmosphere. These biaryls were subjected to metalation, acylation, and free radical bromination. While coordination of the metalating agent with the sulfur hetero atom controlled the position of hydrogen metal exchange, acylation and bromination occurred preferentially in the less aromatic furan nucleus. Substitution took place in the α position ortho to the thienyl substituent in the β substituted furans, and in the alternate α (para) position in α substituted furans.

Product structures were assigned with the aid of the characteristic spin-spin coupling constants of the various aromatic protons, which in this work were found to be: thiophene - $J_{23} = 4.5 - 5.3$; $J_{24} = 1.2 - 1.9$; $J_{34} = 3.4 - 4.1$; furan - $J_{23} = 1.6 - 2.1$; $J_{24} = 0.7 - 0.9$; $J_{25} = 1.5 - 1.7$; $J_{34} = 3.4 - 3.9$ (c.p.s.).

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