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UNIVERSITY OF CINCINNATI

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I hereby recommend that the thesis prepared under my supervision by Robert J. Palchak

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be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

Approved by:

Jan R. MacGregor

Alfred H. Fuye

Joseph R. Lawrence

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Some Aspects of the Chemistry of 2-Hydroxy-5-phenylthiophene

A dissertation submitted to the

Graduate School of Arts and Sciences

of the University of Cincinnati

in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

1953

by

Robert Joseph Francis Palchak

B.S., Pharmacy, University of Pittsburgh, 1948

M.S. University of Pittsburgh, 1951

TABLE OF CONTENTS (CONTINUED)

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INTRODUCTION

During the fifty years beginning with the discovery and preliminary investigations of thiophene, research workers readily accepted the conclusion that thiophene and its many derivatives were strikingly similar to benzene and its analogous derivatives in a number of physical and chemical properties[1].

Thiophene is known to undergo a number of reactions characteristic of benzene and in many instances it forms derivatives resembling the corresponding phenyl compounds in both physical and chemical properties. In fact, it was just such a resemblance, that of boiling points[2], which prevented the earlier discovery of thiophene.

Perhaps the investigators most responsible for this analogy and by far the largest contributors to the chemistry of thiophene in this period have been Victor Meyer, who discovered thiophene in 1882 and who directed research which resulted in 106 publications, and his monograph Die Thiophengruppe[3], in the five years which followed, and Willhelm Steinkopf who directed investigations

1. A. Morton, The Chemistry Of Heterocyclic Compounds, McGraw-Hill Book Co., Inc., New York, 1946, p. 41, compares the properties of several benzene and analogous thiophene derivatives.
2. Boiling points of thiophene and benzene are 84.1° and 80.0° respectively.
3. V. Meyer, Die Thiophengruppe, F. Viewag und Sohn, Braunschweig, 1888.

which brought forth 65 lengthy publications during the period 1910-1941, and who culminated his lifetime of work in this field with his monograph, Chemie des Thiophens[4].

A new era in the development of thiophene chemistry began in the early 1940's with the discovery of an economically feasible synthesis of thiophene. A group of investigators at the Socony-Vacuum laboratories in New Jersey were studying the dehydrogenation of butane to butadiene, and on examining the process with sulfur observed that appreciable quantities of thiophene were being formed. The reaction was suitably modified to produce thiophene in quantity and a research team headed by Howard D. Hartough was organized to investigate potential commercial uses. The results published by this group, however, were chiefly of a fundamental nature and indicated that the similarities between thiophene and benzene are not as great as had been previously assumed. Hartough[5] has, in fact, recently indicated that this analogy is of the crudest type, and should perhaps be considered more the exception than the rule.

Two branches of thiophene chemistry which have not been investigated to any appreciable extent, and to which

4. W. Steinkopf, Chemie des Thiophens, T. Steinkopff, Dresden and Leipzig, 1941; lithoprinted by Edwards Bros., Ann Arbor, Michigan, 1944.

5. H. D. Hartough, Thiophene and its Derivatives, Interscience Publishers, Inc., New York, 1952, pp. 25, 26.

this analogy has not therefore been applied are those of the isosteres of phenol and of aniline. The meager information available concerning these compounds indicates that they are readily susceptible to air oxidation[6] and it is undoubtedly for this reason that they have been ignored.

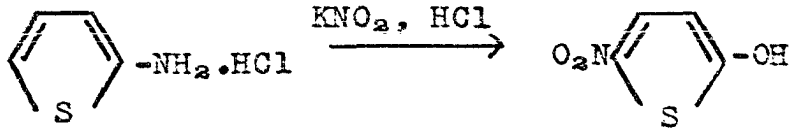
The research herein described was undertaken as a contribution to the fundamental knowledge of the chemistry of hydroxythiophenes, and to compare the observed properties with those of the benzene isologs, noting further the applicability or effectiveness of the generality which states that the properties of benzenes and thiophenes are similar.

The original intention of this investigation was to study the Claisen rearrangement of allyl thienyl ethers. 2-Hydroxy-5-phenylthiophene was the chosen intermediate, but because of the numerous experimental difficulties encountered in its synthesis - which included its very marked instability - only a few exploratory experiments were made in this direction.

6. H. D. Hartough, op. cit., pp. 288-294; Table, p. 303.

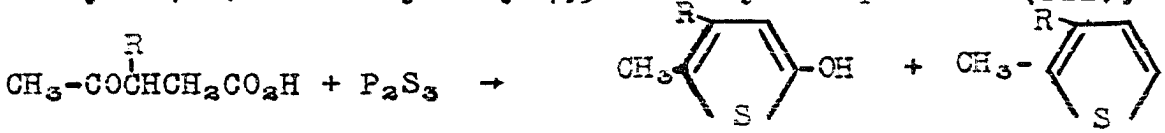
HISTORICAL

O. Stadler's synthesis of 2-hydroxy-5-nitrothiophene[7] (I) via the diazotization of 2-aminothiophene hydrochloride with potassium nitrite is the earliest recorded preparation



I

of an hydroxythiophene. Soon thereafter C. Paal et al. described the ring closure of levulinic and β-methyllevulinic acids with "phosphorus trisulfide" to produce 2-hydroxy-5-methyl- (II) and 2-hydroxy-4,5-dimethylthiophenes[8] (III),



II R = H
III R = CH_3

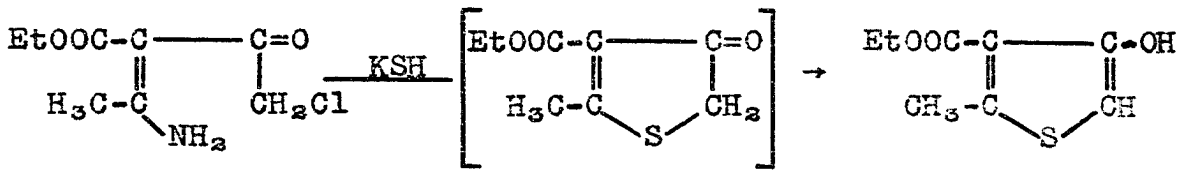
and E. Baumann and E. Fromm succeeded in preparing 3-hydroxy-5-phenylthiophene[9] (IV), by treating 5-phenyl-1,2-dithiacyclopenten-3-one (obtained by the action of sulfur on ethyl cinnamate) with chloroacetic acid in the presence of sodium sulfide, and hydrolyzing the acetate ester with

7. O. Stadler, Ber. 18, 2316 (1885) This procedure is doubtful since all attempts to repeat it have been unsuccessful, cf. W. Steinkopf, op. cit., p. 62, footnote 5.
8. a) C. Paal, Ber. 19, 551 (1886); b) W. Kues and C. Paal, ibid. 19, 556 (1886); c) C. Paal and A. Puschel, ibid. 20, 2557 (1887).
9. E. Baumann and E. Fromm, Ber. 30, 111 (1897) For a complete description of the various steps in this synthesis, see C. M. Selwitz, Ph. D. Dissertation, University of Cincinnati, 1953.

base.

No further interest was shown in the simpler thienols for some time, presumably due to their marked susceptibility to air oxidation.

In the first quarter of this century attention was turned to the synthesis of thienols containing other functional groups attached to the thiophene nucleus, perhaps with the hope that they would contribute to the stability of the molecule. Thus two syntheses of hydroxythiophenecarboxylic acids appeared simultaneously. The ring closure of Benary[10] involved the reaction between 2-chloroacetyl-3-aminocrotonic esters and similarly substituted compounds, and potassium hydrosulfide to yield

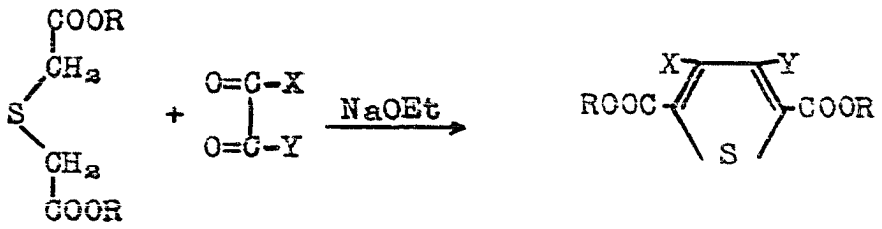


IV

products such as IV, which quite readily undergo dehydration, saponification, decarboxylation and condensation with aldehydes[10, 11]. The method of Hinsberg[12] consists of

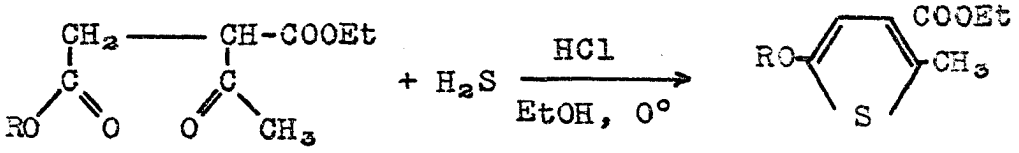
10. a) E. Benary, Ber. 43, 1943 (1910); b) E. Benary and A. Bavarian, ibid. 48, 593 (1915); c) E. Benary and L. Silberstrom, ibid. 52, 1605 (1919); d) E. Benary and W. Kerchkoff, ibid. B59, 2548 (1926).
11. H. D. Hartough, op. cit., pp. 405-410 summarizes reactions of this and similar materials.
12. a) O. Hinsberg, Ber. 43, 901 (1910); b) ibid. 45, 2413 (1912). See also H. D. Hartough, op. cit., pp. 410-412.

the base catalyzed condensation of thiodiglycollic acid or its esters with 1,2-dicarbonyl compounds. By the



proper choice of substituents X and Y, a variety of mono- or dihydroxythiophenes could be realized.

More recently, S. Mitra, N. K. Chakrabarty and S. K. Mitra[13] accomplished the ring closure of diethyl acetylsuccinate with hydrogen sulfide and hydrogen chloride in ethanol to form ethyl 2-methyl-5-ethoxy-3-thiophene-carboxylate (V) which may be saponified and cleaned with



V

hydrobromic acid to yield the substituted 2-hydroxythiophene.

Recently interest in the simpler thienols has been revived. C. Mentzer and Mlle. D. Billet[14] attempted to prepare the parent 2-hydroxythiophene by the action of phosphorus pentasulfide on succinaldehydic acid. They obtained a small amount of an uncrystallizable oil for

13. S. Mitra, N. K. Chakrabarty and S. K. Mitra, J. Chem. Soc. 142, 1116 (1939).
14. C. Mentzer and Mlle. D. Billet, Bull. Soc. Chim. France 12, 292 (1945).

which they recorded no physical constants and which they made no attempt to characterize. Credit for the first synthesis of this material must therefore be accorded to C. D. Hurd and K. L. Kreuz[15] who successfully treated the Grignard reagent made from 2-bromothiophene with oxygen. In addition these investigators prepared the highly unstable 3,5-dinitro-2-hydroxythiophene and 3-nitro-5-acetyl-2-hydroxythiophene (which undergo rapid decomposition at room temperature) by controlled hydrolysis of the corresponding chlorides.

The latest contribution to this field has been that of W. A. Steele[16], who prepared 2-hydroxy-5-phenylthiophene following the Grignard oxygenation process as described by Kreuz[15b], and the work herein primarily concerns itself with this substance.

The dihydroxythiophenes are perhaps worthy of brief comment at this point. V. Auger[17] accomplished the synthesis of the parent 2,5-dihydroxythiophene by treating succinoyl chloride with sodium sulfide. E. Benary[18] prepared a substituted thiotetronic acid (VI) by applying his ring closure technique to chloroacetylcyanoacetic ester.

15. a) C. D. Hurd and K. L. Kreuz, J. Am. Chem. Soc. 72, 5343 (1950); b) K. L. Kreuz, Ph. D. Dissertation, Northwestern University, 1948.
16. W. A. Steele, M. S. Thesis, University of Cincinnati, 1949.
17. V. Auger, Ann. Chim. Phys. [6] 22, 333 (1891).
18. E. Benary, Ber. 46, 2103 (1913).

VI

P. Karrer et al.[19] recently synthesized 3,4-dihydroxy-2-thiophenepropionic acid and 3,4-dihydroxy-2-thiophene-butyric acid by various cyclization procedures, and E. W. Fager[20] attempted the synthesis of the parent 3,4-dihydroxythiophene, applying the Hinsberg method[12] to diethyl thiodiglycollate and diethyl oxalate. The diol was described as being excessively unstable towards oxygen and was therefore not isolated. S. G. Turnbull[20b] succeeded in preparing and isolating the parent 3,4-dihydroxythiophene by decarboxylation of 3,4-dihydroxy-2,5-thiophenedicarboxylic acid in refluxing pyridine using an atmosphere of sulfur dioxide.

R. L. Holbrook[21] tried unsuccessfully to prepare 3- and 3,4-dihydroxythiophenes and derivatives by dehydrogenation of the corresponding thiophanes.

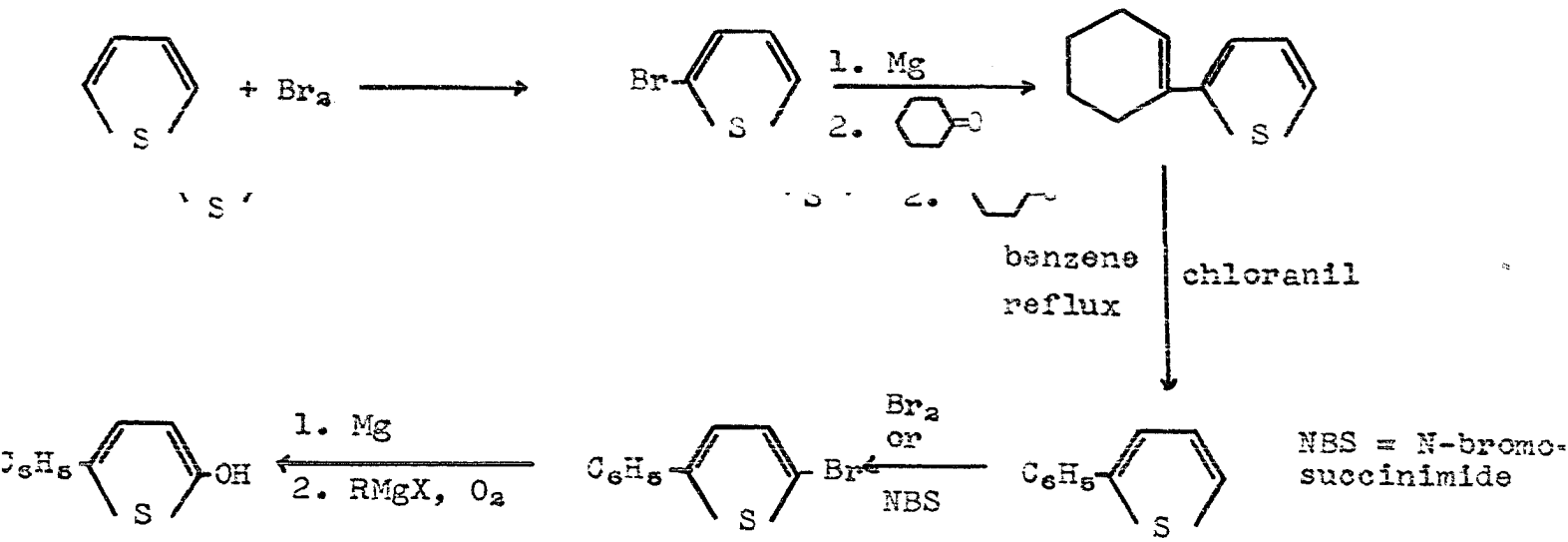
19. a) P. Karrer and F. Kehrer, Helv. Chim. Acta 27, 142-150 (1944); b) P. Karrer, R. Keller and E. Usteri, ibid. 27, 237-242 (1944).

20. a) E. W. Fager, J. Am. Chem. Soc. 67, 2217 (1945); b) S. G. Turnbull, Jr., U. S. Pat. 2,453,103 (1948).

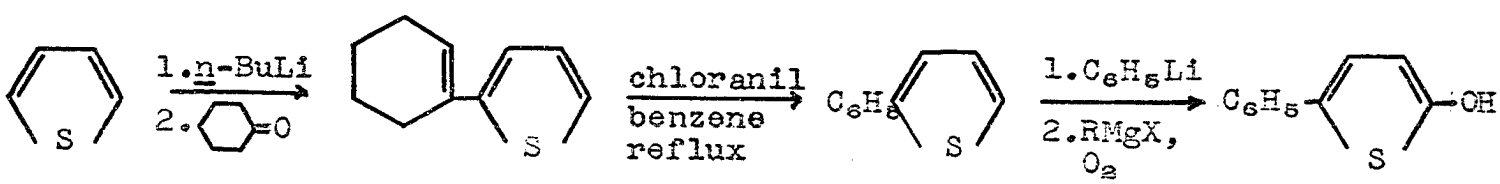
21. R. L. Holbrook, M. S. Thesis, University of Cincinnati, 1952.

DISCUSSION OF RESULTS

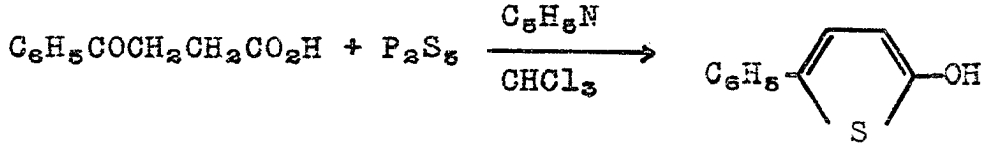
The synthesis of 2-hydroxy-5-phenylthiophene as described by Steele[16] is a long and cumbersome one. Starting with thiophene he prepared 2-bromothiophene, 2-thienyl-1-cyclohexene, 2-phenylthiophene, 2-bromo-5-phenylthiophene, and then 2-hydroxy-5-phenylthiophene.



In this study the method was improved and shortened by employing organolithium compounds and a new one-step



synthesis was developed starting with β-benzoylpropionic



acid. These syntheses and the preparation of intermediates involved numerous difficulties and are discussed below.

2-Bromothiophene has been prepared by the direct bromination of thiophene without a solvent[22], and in carbon tetrachloride[23], in glacial acetic acid[24], and in benzene[25]. However in addition to the desired monobromothiophene, varying quantities of the polybromothiophenes are inevitably obtained. Methods involving the use of brominating reagents include the reaction with N-bromosuccinimide without a solvent[26], N-bromoacetamide in acetone[27] at -5°, and cyanogen bromide in carbon disulfide or in benzene[28].

The direct bromination was selected in this study, primarily because of the ready availability of the reagents[29]. Using carbon tetrachloride as solvent and equimolar quantities of reactants, a 67% yield of the desired monobromothiophene was realized. This was always

22. V. Meyer, Ber. 16, 1465 (1883).
23. F. F. Blicke and J. H. Burckhalter, J. Am. Chem. Soc. 64, 477 (1942).
24. a) A. Tohl and K. Schultz, Ber. 27, 2834 (1894); b) E. Krause and G. Renwanz, Ber. B62, 1710 (1929).
25. R. Mozingo, et al., J. Am. Chem. Soc. 67, 2092 (1945).
26. Ng. Ph. Buu Hoi, Ann. 556, 1 (1944).
27. W. Steinkopf and A. Otto, Ann. 424, 61 (1921).
28. W. Steinkopf, H. Augestad-Jensen and H. Donat, Ann. 430, 78 (1923).
29. A generous sample of thiophene was supplied by the Organic Chemicals Division, Monsanto Chemical Co., St. Louis, Mo.

accompanied by the formation of appreciable quantities of 2,5-dibromothiophene and traces of the higher brominated isomers.

In an attempt to minimize the formation of the dibromothiophene, a bromination was conducted in glacial acetic acid using a 50% excess of thiophene. However the best yield of 2-bromothiophene obtainable was 45%, accompanied by 12.5% of 2,5-dibromothiophene and quantitative recovery of the excess thiophene.

Although a study of the addition of bromine to thiophene has never been reported the reaction undoubtedly occurs, because direct distillation of the brominated thiophene is accompanied by a copious evolution of hydrogen bromide. Previous investigators have met this situation by heating the reaction product with aqueous alkali prior to distillation[23-25], or by steam distillation of the brominated product from alkali[16, 30]. The latter method was employed in these syntheses.

The first recorded synthesis of 2-thienyl-1-cyclohexene was that of L. F. Fieser and J. Smuszkovicz[31], who obtained it in 91.5% yield by treating the Grignard reagent

30. H. D. Hartough to Socony Vacuum, U. S. Pat. 2,492,633, Dec. 27, 1949.

31. L. F. Fieser and J. Smuszkovicz, J. Am. Chem. Soc. 70, 3352 (1948); cf. reference 16.

of 2-bromothiophene with cyclohexanone. They are undoubtedly in error however in describing their material as a solid with a melting point of 132° and a boiling point of 89-91°/1 mm. The material obtained in this study, following their directions was a pale yellow liquid with a boiling point of 107-108°/7 mm. Our best yield was 80% based on 2-bromothiophene.

Since the supply of thiophene was limited and the synthesis of intermediates was time consuming and costly, attention was turned to methods which could be used to eliminate unnecessary steps in the synthesis. H. Gilman and D. A. Shirley[32] recently showed that thiophene could be metalated in high yields. Thus, they treated thiophene with n-butyllithium and then with Dry-Ice and obtained 87% of 2-thiophenecarboxylic acid. In this study, 2-lithiothiophene prepared by the method of Gilman and Shirley was treated with cyclohexanone. Hydrolysis of the reaction product followed by distillation yielded 84% of 2-thienyl-1-cyclohexene based on unrecovered thiophene, or 43% based on the total thiophene used.

Using anhydrous ether as a solvent, n-butyllithium has been prepared from n-butyl bromide and lithium at

32. a) H. Gilman and D. A. Shirley, J. Am. Chem. Soc. 71, 1870 (1949); b) R. A. Benkeser and R. B. Currie, J. Am. Chem. Soc. 70, 1780 (1948).

at temperatures below 0° in 80-90% yields[33], and from n-butyl chloride and lithium at the reflux temperatures in 60-70% yields[34]. The ether solutions of this reagent are unstable decomposing in three or four days when stored below 10° and in a few hours or sooner when allowed to stand at room temperature or if refluxed. Thus for optimum yields the reaction of n-butyl bromide with lithium at low temperatures has been recommended. In an effort to simplify the procedure and eliminate the cold bath, the reaction of a mixture of 1 mole of n-butyl bromide and 3 moles of n-butyl chloride at room temperature in dry ether was attempted. The reaction proceeded quite readily but the best obtainable yield was 47%. Using the same molar ratio of reactants and olefin-free petroleum ether (40-60°) as the solvent, the best yield which could be realized was 19%.

2-Phenylthiophene was prepared according to the method devised by Steele[16], viz., the dehydrogenation of 2-thienyl-1-cyclohexene with chloranil in refluxing benzene. Although he recommended a reaction time of

33. a) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, J. Am. Chem. Soc. 71, 1499 (1949); b) R. G. Jones and H. Gilman in Organic Reactions, R. Adams, Ed., John Wiley and Sons, Inc., New York, 1951, Vol. VI, Chapter 7, p. 351.

34. a) H. Gilman, E. A. Zoellner and W. M. Selby, J. Am. Chem. Soc. 54, 1957 (1932); b) H. Gilman, E. A. Zoellner, J. B. Dickey and W. M. Selby, J. Am. Chem. Soc. 57, 1061 (1935).

twenty four hours for optimum yields it was observed that reaction times of eight, twelve and twenty four hours produced no marked variations in yields, and with the shorter reaction time there was less tar formation.

A brief description of the material is noteworthy. 2-Phenylthiophene is a colorless crystalline material with a melting point of 35-36° and a boiling point of 113-114°/1 mm. It is best stored in stoppered bottles which are kept in the refrigerator, for on standing at room temperature, even in a desiccator over calcium chloride, it gradually decomposes, liquefying and turning brown.

2-Phenylthiophene has been readily brominated with cyanogen bromide[35] and with N-bromosuccinimide[16, 36] to produce 2-bromo-5-phenylthiophene in 85-90% yields. The 88% yield of 2-bromo-5-phenylthiophene obtained from the reaction between 2-phenylthiophene and N-bromosuccinimide is comparable to Steele's results, but a reflux time of seventy two hours was necessary for completion of the reaction. In addition 2-phenylthiophene was brominated directly with bromine in carbon tetrachloride to give an 85% yield of pale yellow crystals, m.p. 85-86°. In contrast to 2-phenylthiophene this material is stable at room temperature and has been stored for a period of two years in a screw cap bottle on the laboratory bench

35. W. Steinkopf, H. J. von Petersdorf and R. Gording, Ann. 527, 272 (1937).
36. cf. C. Djerassi, Chem. Revs. 43, 271 (1948).

without any change in appearance.

2-Hydroxy-5-phenylthiophene was prepared by a modification of the procedure utilized by Hurd and Kreuz[15] for the synthesis of 2-thienol and by the cyclization of β-benzoylpropionic acid with phosphorus pentasulfide in pyridine - chloroform solution.

The reaction between aromatic Grignard reagents and oxygen has generally been considered a poor preparative method for phenols. For example both Wuyts[37a] and Porter and Steele[37b] obtained considerable benzene, biphenyl and tars in addition to low yields (25%) of phenol when they treated phenylmagnesium bromide with oxygen. Porter and Steele proposed the following mechanism for the reaction:

$$\text{(A)}\quad RMgX + O_2 \rightarrow ROOMgX$$

$$\text{(B)}\quad ROOMgX + RMgX \rightarrow 2ROMgX$$

More recently Kharasch and Reynolds[38] observed that the conversion to phenols was markedly enhanced by the presence of alkylmagnesium halides. Taking this observation into account they modified the mechanism of Porter and Steele as follows:

$$ArMgBr + O_2 \rightarrow ArOOMgBr \qquad (I)$$

37. a) M. H. Wuyts, Compt. rend. 148, 930 (1909); b) C. W. Porter and C. Steele, J. Am. Chem. Soc. 42, 2650 (1920).

38. M. S. Kharasch and W. B. Reynolds, J. Am. Chem. Soc. 65, 501 (1943).

$$ArOOMgBr \begin{cases} \rightarrow Ar\text{-}Ar + tars & (IIa) \\ + ArMgBr \rightarrow 2ArOMgBr & (IIb) \\ + RMgBr \rightarrow ArOMgBr + ROMgBr & (IIc) \end{cases}$$

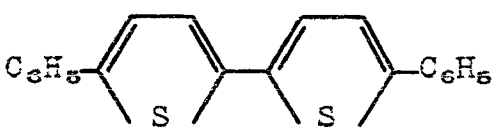
In the absence of an alkylmagnesium bromide the reduction (IIb) cannot successfully compete with the free radical decomposition (IIa) whereas in its presence reduction (IIc) predominates. As evidence of this, phenol has been prepared in yields of 70-74% by the oxidation of phenylmagnesium bromide in the presence of isopropyl- and cyclohexylmagnesium bromides[38]. Oxidation of phenylmagnesium bromide in the absence of alkylmagnesium halides has produced phenol in maximum yields of 25%[37b].

When applied to the synthesis of hydroxythiophenes however the results have been less gratifying. Thus Hurd and Kreuz found it necessary to use considerably more than one equivalent of isopropylmagnesium bromide in order to obtain what they described as "somewhat satisfactory" results in the oxidation of thienylmagnesium bromide. Even with this excess the best obtainable yields of 2-thienol were 20-25% plus considerable 2,2'-dithienyl, acidic resinous materials, tars and hydrogen sulfide.

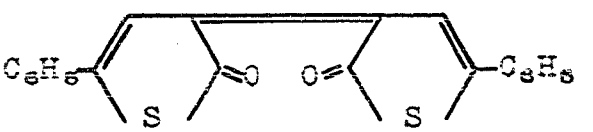
Steele[16] oxidized 5-phenyl-2-thienylmagnesium bromide in the presence of a 50% molar excess of isopropylmagnesium bromide. Patterning his procedure after that of Hurd and Kreuz he allowed the oxygenated solution to stand in

the refrigerator overnight. Subsequent decomposition of the cold organometallic solution with Dry-Ice and dilute sulfuric acid resulted in a 30% yield of 2-hydroxy-5-phenylthiophene.

Attempts to reproduce Steele's results in this study were largely unsuccessful. The reaction was erratic, for the most part exhibiting free radical decomposition (IIa) as represented above. Occasional low yields (1 - 5%) of 2-hydroxy-5-phenylthiophene were obtained but the desired product was inevitably accompanied by 5,5'-diphenyl-2,2'-dithienyl (VII) and the oxidative dimer 5,5'-diphenyl [$\Delta^{3,3'(2H,2'H)}$ bithiophene]-2,2'-dione[39] (VIII). The



VII



VIII

structure of VII was confirmed by elemental analysis and by a comparison of its physical properties with literature values recorded by earlier investigators. It has been reported[40] that hydroxythiophenes as a class readily

39. We are indebted to Mr. Russel Stemen of the Chemical Abstracts office for information as to the preferred name for this compound.

40. a) P. Friedlander and St. Kielbasinski, Ber. 45, 3389 (1912); b) W. Steinkopf and F. Thormann, Ann. 540, 1 (1939).

undergo oxidation to thioindigo structures of the type

By analogy, the structure VIII whose calculated percentage composition is in agreement with the observed values, was assigned to the crystalline product obtained on decomposition of 2-hydroxy-5-phenylthiophene.

One experiment along these lines is worthy of comment. After several unsuccessful oxidations it was concluded that the experimental conditions must have been too drastic. They were therefore modified to include the use of cyclohexylmagnesium bromide (which functioned best in the oxidation of phenylmagnesium bromide[37]) in place of isopropylmagnesium bromide, a much lower reaction temperature (Dry-Ice - acetone bath instead of an ice - salt bath) and only 5.5% of the theoretical amount of oxygen. The reaction gave a 23% yield of the desired 2-hydroxy-5-phenylthiophene (based on the oxygen) in addition to traces of 5,5'-diphenyl-2,2'-dithienyl and the isothioindigo (VIII).

In view of the time consumed in preparing intermediates and the low yields obtained, attention was next turned to the possibility of oxidizing 2-lithio-5-phenylthiophene, which could be prepared directly from 2-phenylthiophene. In an exploratory experiment 2-phenylthiophene

was treated with an equivalent amount of phenyllithium. The reaction mixture rapidly turned from pale amber to light olive green and when carbonated yielded (75%) 5-phenyl-2-thiophenecarboxylic acid.

A typical experiment involved the oxidation of 2-lithio-5-phenylthiophene with molecular oxygen in the presence of a 100% excess of cyclohexylmagnesium bromide at Dry-Ice - acetone temperature followed by overnight storage in a refrigerator. It was not necessary to measure the quantity of oxygen used; the gas was simply bubbled through the solution until the exothermic reaction ceased. In order to obtain reproducible results, the cyclohexylmagnesium bromide used was taken from a previously standardized stock solution[41].

Several attempts were made to extract the lithium salt of 2-hydroxy-5-phenylthiophene directly from the cold ether solution using water, but the best yields (30-34%) of the thienol were obtained when the oxidized solution was first acidified and then extracted with aqueous sodium hydroxide.

In an effort to further expedite the oxidation reaction, the effectiveness of n-butyllithium as an oxidation catalyst was investigated. An oxidation was

41. cf. H. Gilman and E. A. Zoellner, J. Am. Chem. Soc. 53, 1945 (1931) wherein the difficulties encountered in the preparation of cyclohexyl Grignard reagents are discussed.

conducted substituting a 40% excess of n-butyllithium in place of an alkylmagnesium bromide. However the only product was 5,5'-diphenyl-2,2'-dithienyl (VII) in 18% yield based on 2-phenylthiophene[42].

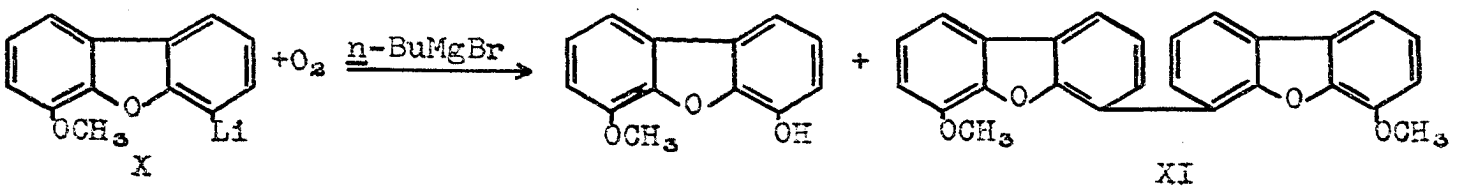
In a study of the reducing tendency of Grignard reagents, M. S. Kharasch and S. Weinhouse[43] presented evidence indicating that the reducing velocity of organomagnesium compounds should increase with a decrease in "electronegativity" of the organic portion of the molecule. Because of the low "electronegativity" of the allyl group[43] allylmagnesium bromide was used in one experiment to determine its effectiveness as a catalyst for reduction of the organometallic peroxide. However, even though it was present in 200% excess, the yield of 2-hydroxy-5-phenylthiophene was only 5%.

The coupled compound, 5,5'-diphenyl2,2'-dithienyl, always appeared as one of the products of this reaction. Porter and Steele[37b] found biphenyl to be present with the phenol they prepared by oxidation of phenylmagnesium bromide and attributed its formation to a Fittig type

42. a) This result in no way negates the effectiveness of lithium alkyls as promoters for the decomposition of organometallic peroxides (Step IIc of Kharasch and Reynolds' mechanism) since Kharasch and Reynolds (38) obtained the poorest yields of phenol when n-butylmagnesium bromide acted as the catalyst in their study. b) cf. also E. Muller and T. Topel, Ber. 72B, 273 (1939), who have conducted a thorough study of the action of oxygen on organolithium compounds.

43. M. S. Kharasch and S. Weinhouse, J. Org. Chem. 1, 209 (1936).

reaction between phenylmagnesium bromide and bromobenzene. Gilman, Cheny and Willis[44] likewise observed the coupled compound 6,6'-dimethoxy-4,4'-bis(dibenzofuran)(XI) among the products of the oxidation of 4-lithio-6-methoxydibenzofuran (X). Many additional examples wherein oxidation of



X XI

RM compounds gave appreciable quantities of coupling, or R-R compounds, may be found in the literature[42b, 45].

To determine at which stage coupling was occurring, a solution of Grignard reagent prepared from 25 millimoles of 2-bromo-5-phenylthiophene and 25 millimoles of cyclohexyl bromide was divided into two portions. One-half was carbonated to yield 61% of 5-phenyl-2-thiophenecarboxylic acid with no trace of coupled product. The other half, which was oxygenated, yielded 10% of VII and a trace of VIII. Thus coupling occurs in this case during oxygenation of the organometallic compound and not as a result of a Fittig type reaction.

The cyclization of γ-keto acids by fusion with the

44. H. Gilman, L. C. Cheney and H. B. Willis, J. Am. Chem. Soc. 61, 951 (1939).

45. cf. a) C. B. Wooster, Chem. Revs. 11, 21 (1932); b) L. M. Dennis, R. W. Work, E. G. Rochow and E. M. Chamot, J. Am. Chem. Soc. 56, 1047 (1934); c) H. Gilman and A. Wood, J. Am. Chem. Soc. 48, 806 (1926); d) R. Meyer and K. Togel, Ann. 347, 55 (1906); e) M. S. Kharasch, W. Goldberg and F. R. Mayo, J. Am. Chem. Soc. 60, 2004 (1938).

phosphorus sulfides is a satisfactory approach to those few hydroxythiophenes which are volatile enough to distill out of the reaction zone as they are formed[8]. The method is not applicable to the thienols of lower volatility. Thus although β-benzoylpropionic acid would be expected to form 2-hydroxy-5-phenylthiophene on fusion with a phosphorus sulfide, the only product which has previously been reported for this reaction is 2-phenylthiophene[46].

Recently Klingsberg and Papa[47] suggested the use of refluxing pyridine as a solvent for reactions involving the use of phosphorus pentasulfide. In this manner they readily replaced the oxygen atom of the carbonyl group by sulfur in acid amides.

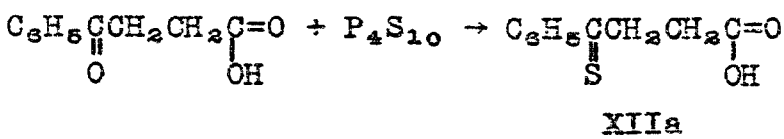
Following their procedure, a pyridine solution containing equimolar quantities of β-benzoylpropionic acid and phosphorus pentasulfide was refluxed for thirty minutes during which time the color changed from yellow to dark purple. Neutralization with hydrochloric acid and extraction with benzene resulted in a 13.6% yield of VIII. Further investigation revealed that when the reaction was conducted in a nitrogen atmosphere to minimize formation

46. a) W. Kues and C. Paal, Ber. 19, 3141 (1886); b) A. Chrzaszczewska, Roczniki Chem. 5, 1-3, 33-76 (1925); C. A. 20, 1078 (1926).

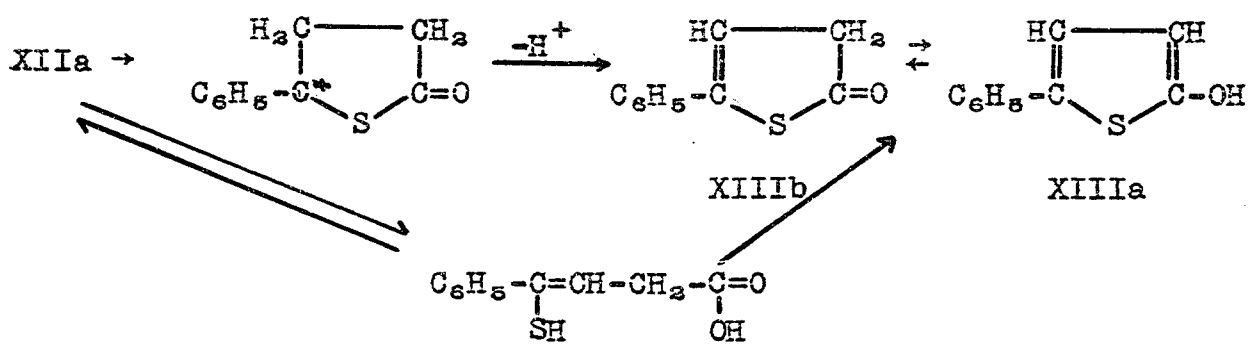
47. E. Klingsberg and D. Papa, J. Am. Chem. Soc. 73, 4988 (1951).

of VIII, and in a pyridine - chloroform mixture so that the organic materials remained in solution when the pyridine was neutralized, 2-hydroxy-5-phenylthiophene was obtained in 20% yields by extraction from the chloroform solution with aqueous sodium hydroxide, followed by acidification and crystallization.

Little if anything is known concerning the mechanism of the thiation reaction with the phosphorus sulfides. In the case of β-benzoylpropionic acid replacement of oxygen by sulfur may occur at either one of two carbon atoms. If replacement occurs at the carbonyl carbon atom, cyclization could occur by nucleophilic attack by sulfur on carbon displacing the hydroxyl group or by

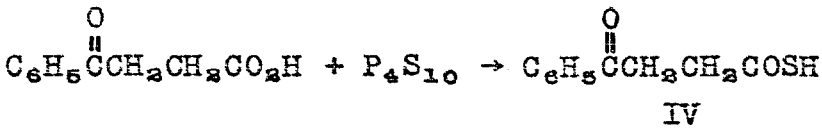


XIIa

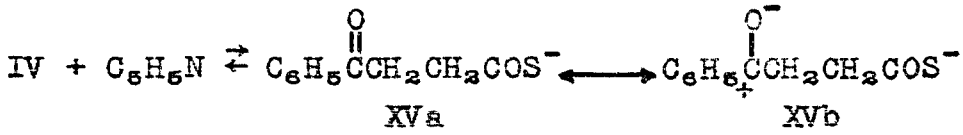


elimination of a proton from an enthiol and the hydroxyl

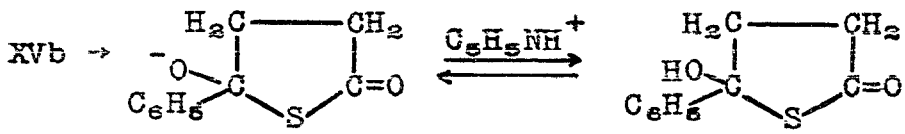
from the carboxyl group[48]. On the other hand if replacement of oxygen by sulfur occurs at the carboxylic acid group - cyclization could proceed by nucleophilic attack by sulfur on the carbonyl carbon followed by dehydration.



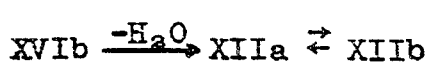
IV



XVa XVb



XVIa XVIb



Lack of experimental evidence however prohibits the assignment of a mechanism[49].

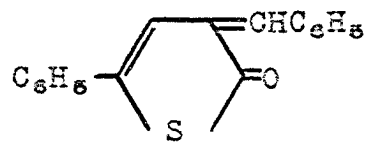
2-Hydroxy-5-phenylthiophene was isolated from the reaction mixtures as the sodium salt, precipitated with cold acid and crystallized from chloroform, ether or

48. cf. R. E. Cline, Ph. D. Dissertation, Indiana University, 1951, wherein E. Campaigne has been quoted as follows - "compounds possessing the reactive dienol system -C=C-C=C- in which X is -CH, -SH, -H, etc., and B
X BH
is O, S, etc., can easily be made to undergo cyclization to heterocycles by elimination of HX. In view of this one might also consider the gem diol $C_6H_5C(SH)=CH-CH=C(OH)-CH$ formed by enolization of the carboxyl group as the intermediate in the cyclization.

49. cf. however, R. Fuson, Advanced Organic Chemistry, John Wiley and Sons, Inc., New York, 1950, p. 86, where a mechanism for cyclization of β-benzoylpropionic acid to the lactol, and then the lactone is discussed.

methanol. This produced soft, blue-gray crystals with a metallic luster and a mild, characteristic odor, melting with decomposition at 81.2-81.6°, which were sufficiently pure for most purposes. Pure samples were prepared for spectroscopic analyses by the slow vacuum sublimation of the blue-gray crystals. This yielded colorless crystals m.p. 81.6-81.8° (with decomposition) which gradually acquired a green film, presumably VIII. A sample prepared in this manner and allowed to stand exposed in the laboratory showed no further change over an eight month period.

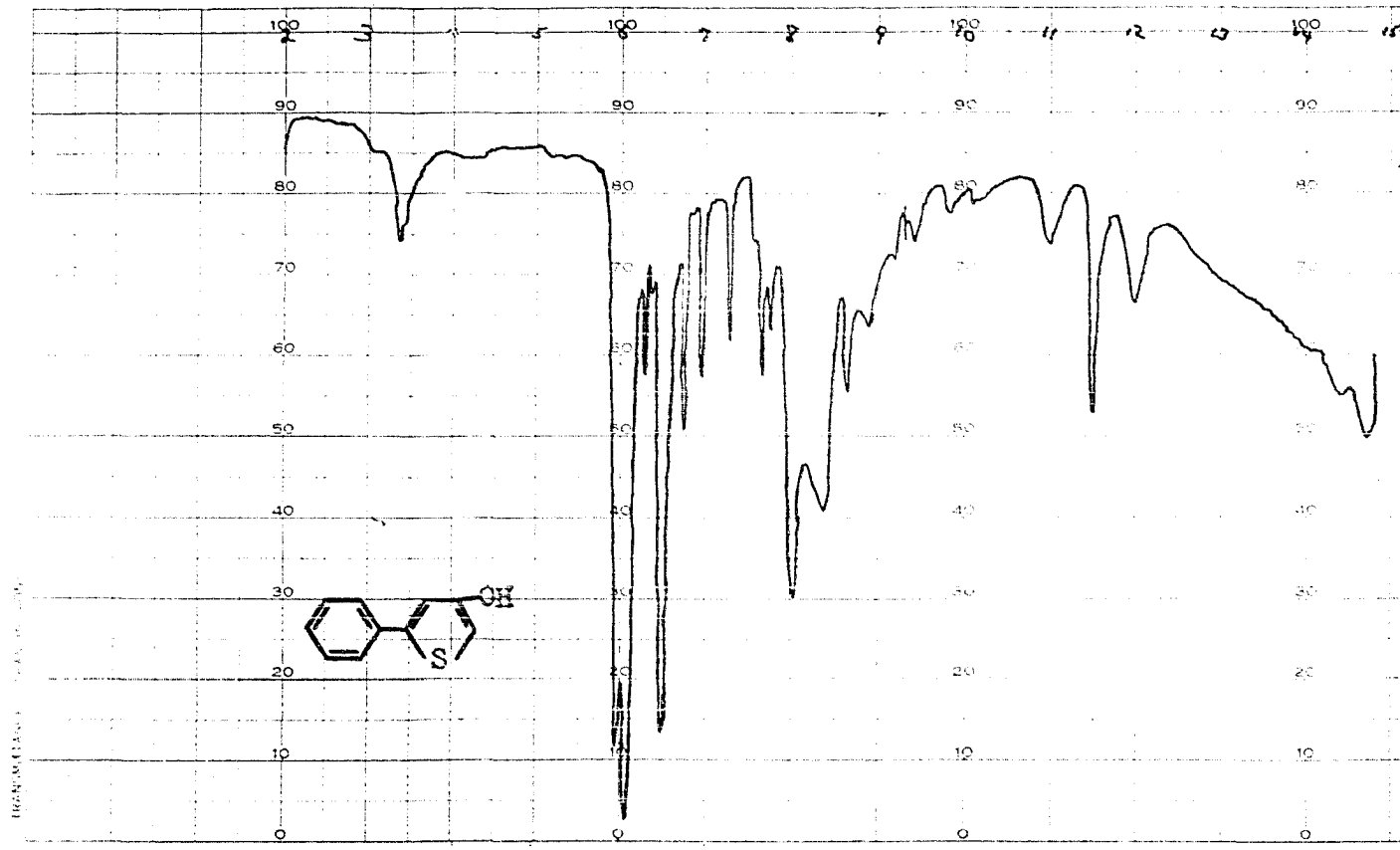
Evidence has been obtained which indicates that 2-hydroxy-5-phenylthiophene exists in equilibrium with a keto form which is a thiolactone. Thus it undergoes aldol condensation to yield the benzal derivative XVII. Also the infrared absorption spectrum of a chloform



XVII

solution of XIII contains an extremely weak band at 2.60-2.65μ and a strong band at 5.95μ (Fig. 1). These are in the hydroxyl and carbonyl regions respectively and indicate that in chloroform solution the equilibrium favors the keto form.

Figure 1 A



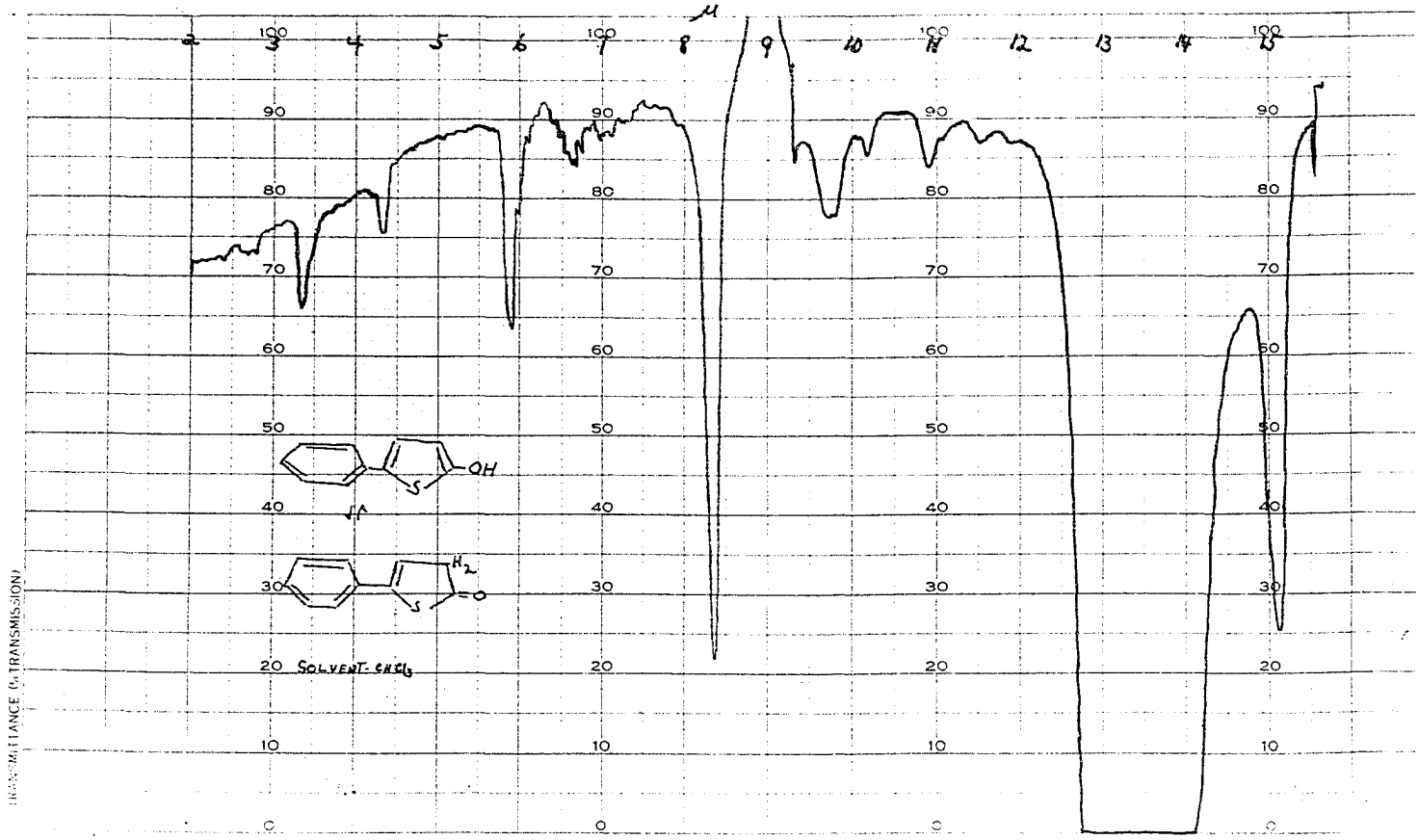
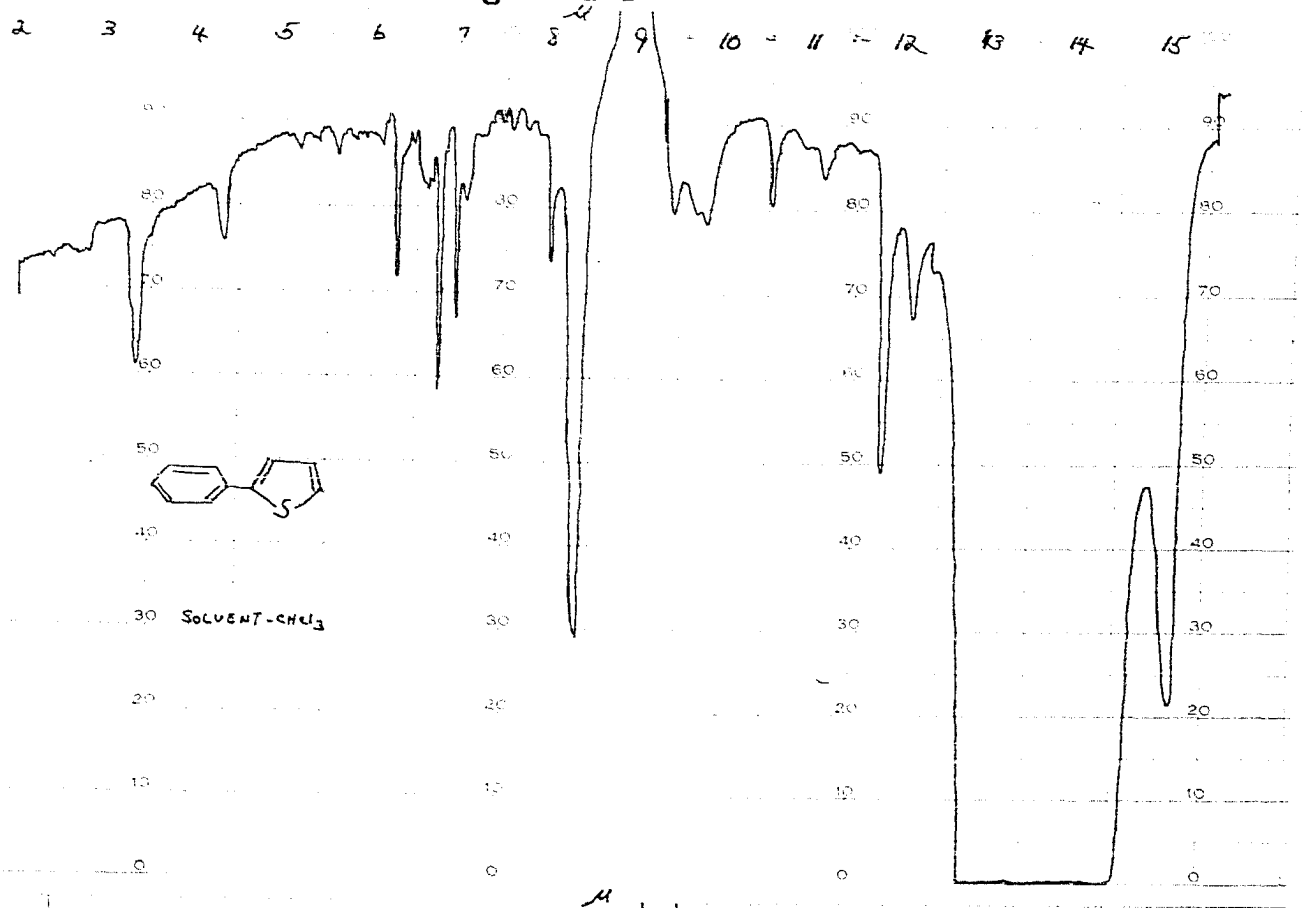
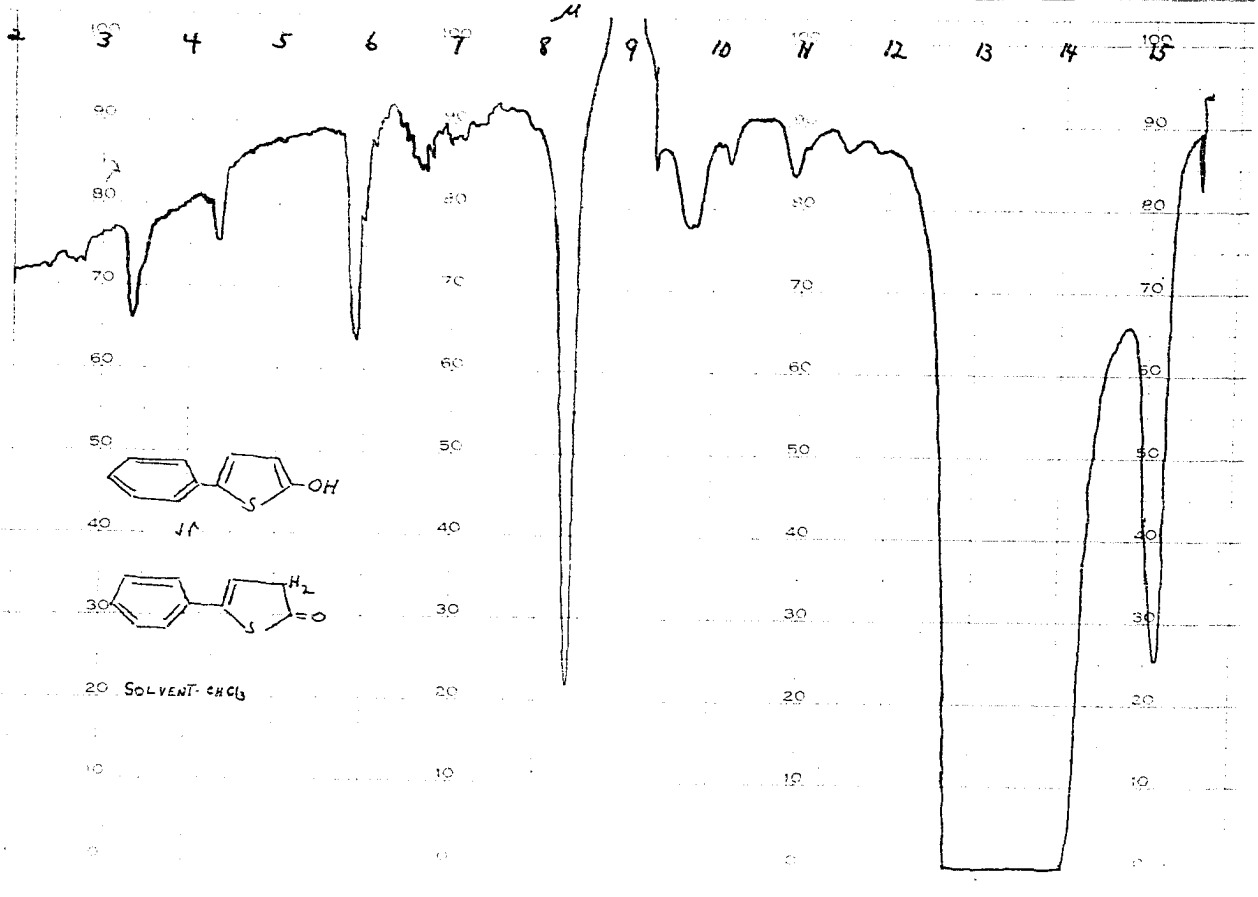


Figure 1 B





The infrared spectrum of the 3-hydroxy isomer in chloroform solution has no hydroxyl absorption band in the 3 micron region and has a much stronger carbonyl absorption band than (XIII) at 5.95-6.05μ (Fig. 1) indicating that in chloroform solution it too exists principally as the keto tautomer[50]. Chemical evidence for the existence of the keto structure for the 3-hydroxy isomer has been obtained by Selwitz[9b], who prepared the monooxime of 5-phenyl-2,3-thiophene quinone by nitrosation of 3-hydroxy -5-phenylthiophene.

The infrared spectrum of 2-phenylthiophene is included for purposes of comparison.

The infrared absorption spectrum of 2-hydroxythiophene in chloroform solution shows a weak hydroxyl band at 2.95μ and a strong carbonyl band at 5.95μ indicating that both keto and enol tautomers exist in equilibrium in chloroform solution.

The ultraviolet data for alcoholic solutions of 2-phenylthiophene, 2- and 3-hydroxy-5-phenylthiophenes and 2-methoxy-5-phenylthiophene are presented in Figure 2.

50. C. M. Selwitz[9b] interprets an absorption band at 8.03μ in the infrared absorption spectrum of the 3-hydroxy isomer as being due to an hydroxyl group. H. M. Randall *et al.*, Infrared Determination of Organic Structures, D. Van Nostrand, Inc., New York, 1949, p. 3, discuss the infrared absorption regions of the -OH group and make no mention of hydroxyl absorption in this region.

Figure 2 A

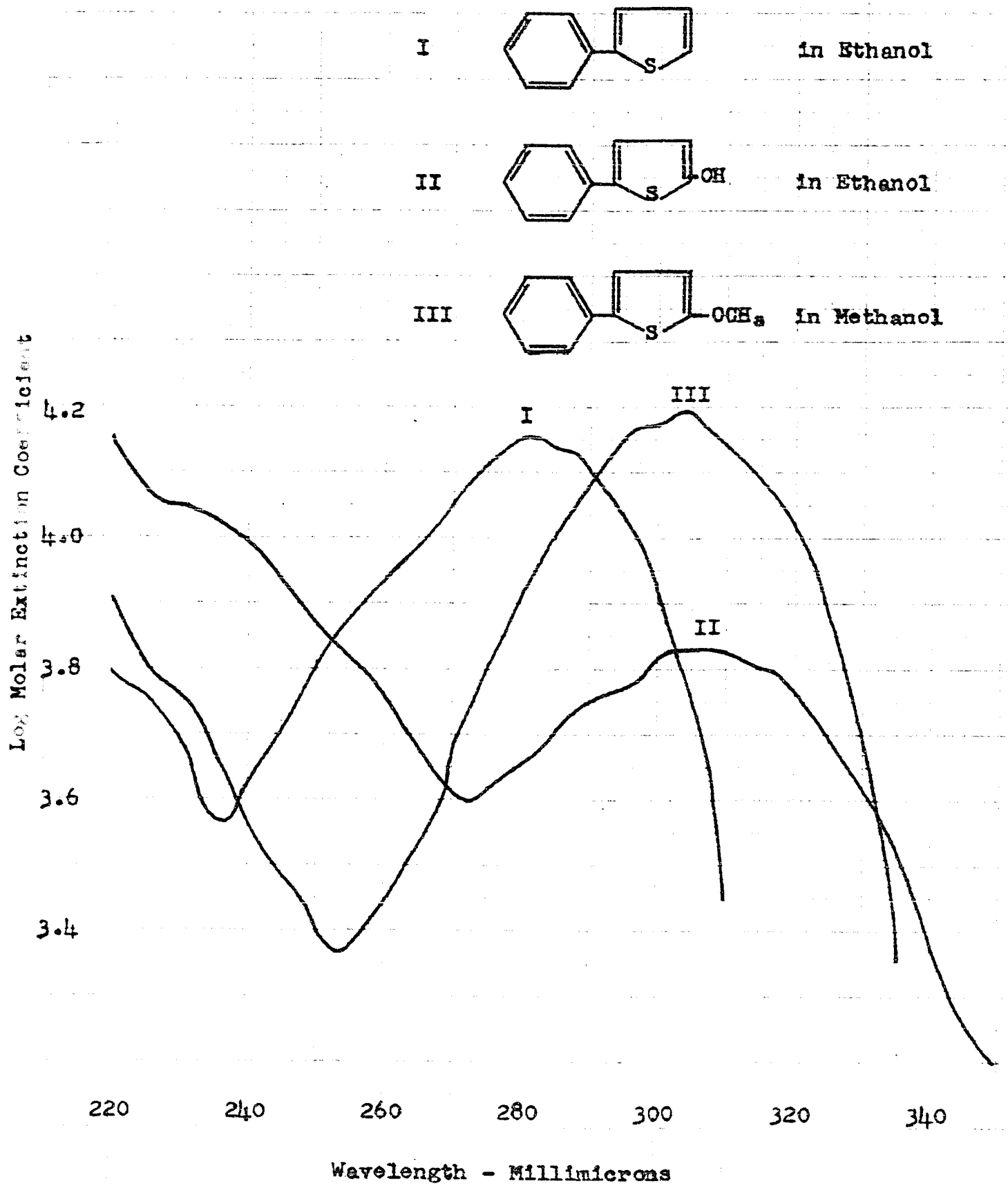
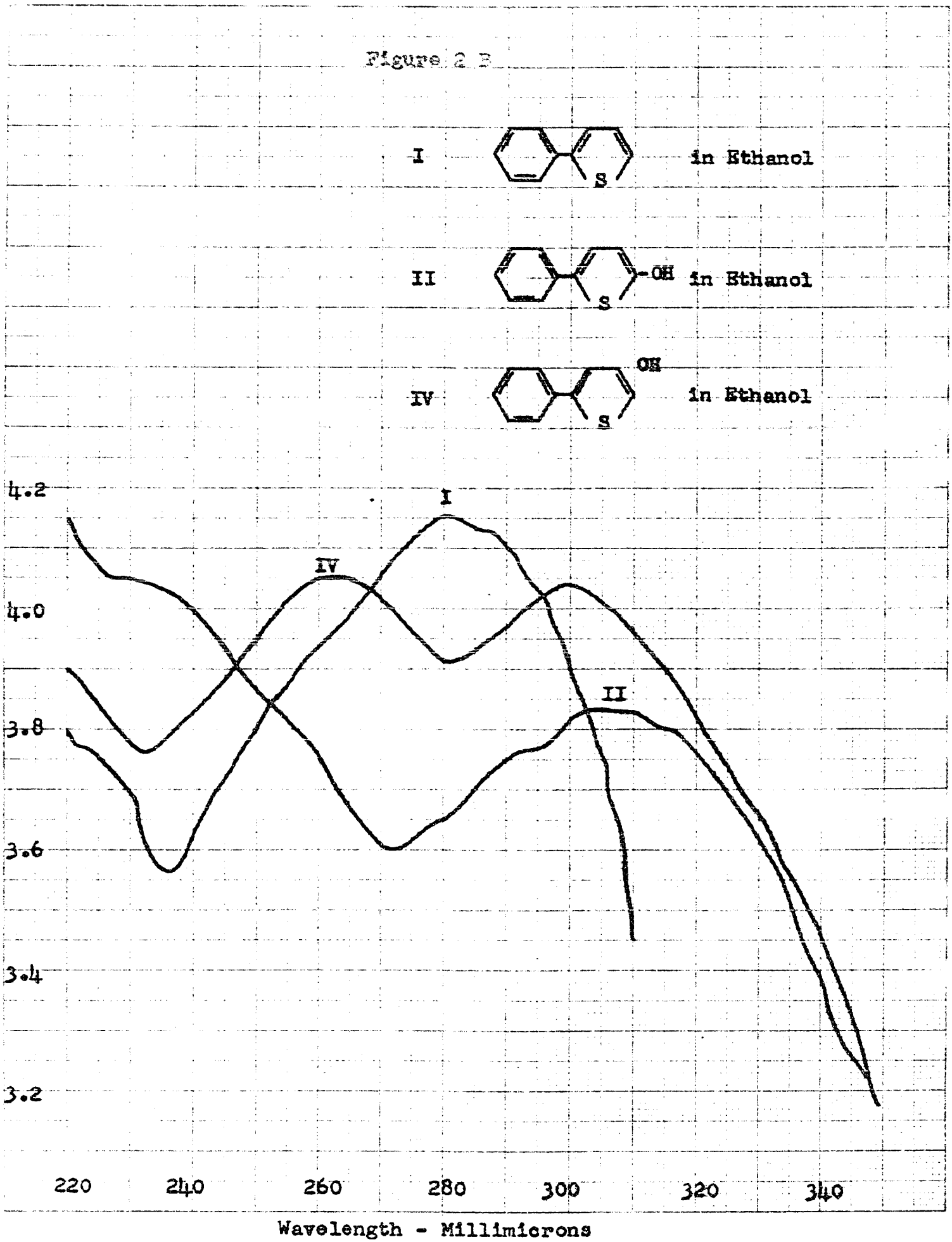


Figure 2 B



The introduction of a methoxyl or an hydroxyl group into 2-phenylthiophene promotes a shift of the maximum and the minimum towards higher wavelengths, which is not unexpected in view of the fact that two unshared electron pairs are introduced via the oxygen atom. The slight difference in the position of the maximum of (XIII) (308mμ) and of its methyl ether (305mμ) is significant, suggesting that in alcohol solutions (XIII) exists to a much greater extent in the enol form rather than in the keto form.

The ultraviolet spectra of 3-hydroxy-5-phenylthiophene (XVIII) and 3-methoxy-5-phenylthiophene (XIX) are similar in this respect[9b]. The curve for (XVIII) possesses two maxima (262mμ, 300mμ) which are almost identical with those of (XIX) (262mμ, 298mμ) indicating that in alcoholic solution (XVIII) exists principally as the enol tautomer.

The spectra of (XIII) and (XVIII) are compared in Figure 2. Although they each contain a maximum in the higher wavelength region (ca. 300mμ) (XVIII) exhibits a maximum at 262mμ which is not evident in the isomeric (XIII).

Hurd and Kreuz[15] observed a marked shift towards longer wavelengths in the spectrum of 2-thienol as compared to its methyl ether, and attributed the shift to the thiolactone structure, using the spectrum of the

methyl ether as the model for the enol structure. Chemical evidence for the enol structure is furnished by the ease with which 2-hydroxy-5-phenylthiophene undergoes acetylation and by the fact that in dilute alcoholic solution it gives a red color with ferric chloride.

It is worthy of comment at this point that where 2-hydroxy-5-phenylthiophene comes in contact with the skin it produces a reddened area which itches and blisters shortly thereafter, not unlike the symptoms produced by poison ivy. The blisters usually disappear in a week's time although the itching frequently persists for a while longer.

Solutions of 2-hydroxy-5-phenylthiophene are unstable, readily undergoing air oxidation with the formation of (VIII) and tars. Since it appeared that this decomposition occurred more readily in some solvents than in others, 1% solutions were prepared in 12 common laboratory solvents, and were allowed to stand loosely stoppered to observe the relative rates of decomposition (Table 1). The thienol seems to be least stable in the alcohols. It is not very soluble in petroleum ether and a reaction probably takes place with piperidine.

It is interesting to note that whereas 2-hydroxythiophene is more stable than its 3-isomer[15], (XIII) is more readily oxidized than is its 3-hydroxy isomer (XVIII).

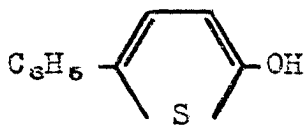
Table I[a]

Solvent	Time in Hours			
	0.0 hrs.	0.25 hrs.	3.5 hrs.	18 hrs.
Ether[b]	dissolves at once red-purple soln.[c]	no change	pink-purple soln.	solvent evaporated material recovered
Dioxane[d]	dissolves at once purple soln.	no change	red-purple soln.	dark red soln., no other change
Absolute ethanol	dissolves slowly purple soln.	completely dissolved no other change	amethyst soln. slight ppt.	liquid layer colorless, heavy ppt.
95% Ethanol	dissolves slowly purple soln.	completely dissolved slight ppt.	ppt. gives appearance of dark gray soln.	liquid layer colorless, heavy ppt.
Absolute methanol	dissolves slowly purple soln.	completely dissolved slight ppt.	amethyst soln. heavy ppt.	liquid layer colorless, heavy ppt.
Chloroform[e]	dissolves at once purple soln.	no change	amethyst soln.	red-purple soln. no other change
Ligroin (40-60°)[f]	incomplete solution pale purple	no change	pink-purple soln.	solvent evaporated material recovered
Carbon tetrachloride[g]	dissolves at once pink-purple soln.	no change	no change	no change
Benzene[h]	dissolves at once purple soln.	no change	no change	no change

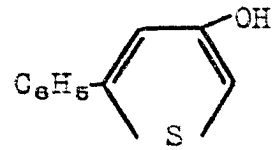
Table I (continued)

Solvent	Time in Hours			
	0.0 hrs.	0.25 hrs.	3.5 hrs.	18 hrs.
Carbon disulfide	dissolves at once red by reflected light, purple by transmitted light	no change	no change	no change
Pyridine	dissolves at once green-black soln.	no change	no change	no change
Piperidine	dissolves at once dark blue-green soln.	no change	no change	brown to red soln. white crystals about neck of flask

(a) The solutions were prepared all at once by adding 10 ml. of each solvent to 100 mgm. portions of 2-hydroxy-5-phenylthiophene contained in 25 ml. Erlenmeyer flasks which were then loosely stoppered with cotton wadding and set aside out of the path of direct sunlight. (b) Mallinckrodt's anhydrous ether stored over sodium. (c) 2-Hydroxy-5-phenylthiophene is colorless. The color of these solutions is due to the oxidative dimer (VIII). (d) Commercial grade, redistilled before use. (e) Merck's U.S.P. quality. (f) Commercial grade. Used as received. (g) Eimer and Amend, C.P. (h) Coleman and Bell anhydrous benzene stored over sodium.



XIII



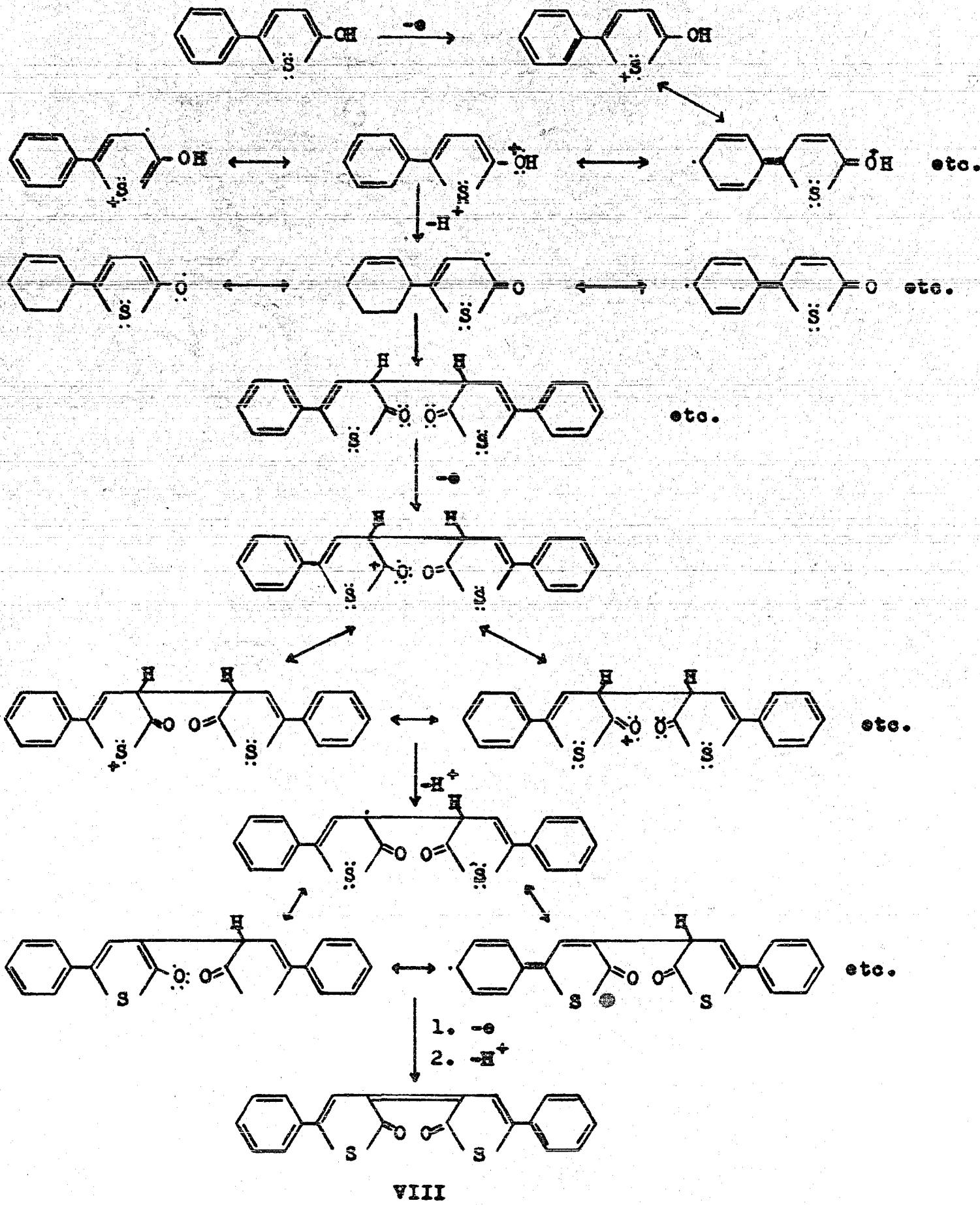
XVIII

The instability of (XIII) could be accounted for by assuming that oxidation proceeds by a series of steps each involving one electron[51]. In this manner the intermediates involved would be resonance stabilized quinoidal structures (See Fig. 3). This does not however explain the difference in stabilities between (XIII) and (XVIII) because the change in resonance energy between the thienol and the end products is the same in each case.

5,5'-Diphenyl-[$\Delta^{3,3'(2H,2'H)}$ - bithiophene]-2,2'-dione (VIII) is a dark green crystalline solid which is difficultly soluble in most of the common organic solvents and is best purified by recrystallization from boiling benzene or dioxane. Solutions are dichroic, appearing blue by transmitted light and red by reflected light. This phenomenon is most pronounced in carbon disulfide. (VIII) readily dissolved in morpholine and piperidine forming beautiful indigo-blue solutions. It reacted with these solvents at room temperature as indicated by a change in color of the solution from blue to brown to red. During this time sulfur-free crystals formed which

51. Michaelis' "principle of compulsory univalent oxidation". cf. a) L. Michaelis, Trans. Electrochem. Soc. 71, 107 (1937); b) L. Michaelis and E. S. Fetcher, J. Am. Chem. Soc. 59, 1246 (1937); c) R. B. Woodward and R. H. Eastman, ibid. 68, 2229 (1946).

Figure 3



VIII

were quite volatile, appearing on the upper portions of the flask which had not previously been in contact with the solution[52]. These products were not investigated.

Three moles of hydrogen per mole of (VIII) were consumed when a purple o-dichlorobenzene solution was subjected to low pressure hydrogenation over Adam's catalyst. The reduced solution was colorless but was rapidly reoxidized when exposed to the air. For this reason the hydrogenated material was never isolated.

The ultraviolet and infrared absorption spectra are presented in Figures 4 and 5, respectively.

The sodium salt of 2-hydroxy-5-phenylthiophene in methanol reacted with methyl sulfate to form 2-methoxy -5-phenylthiophene, which is a colorless to pale yellow liquid, b.p. 135-136°/1 mm., n^{25} 1.6308, which slowly decomposes, even when sealed in an ampule.

It is interesting to note that (XIII) could not be methylated with diazomethane in either ethyl ether or olefin-free petroleum ether (40-60°). The product of these reactions was a red-brown resin which was insoluble in aqueous alkali. Hurd and Kreuz[15] were unable to methylate 2-hydroxythiophene with diazomethane. They reported a yellow solid as the product, which was insoluble

52. cf. C. O. Guss and D. L. Chamberlain, Jr., J. Am. Chem. Soc. 74, 1342 (1952).

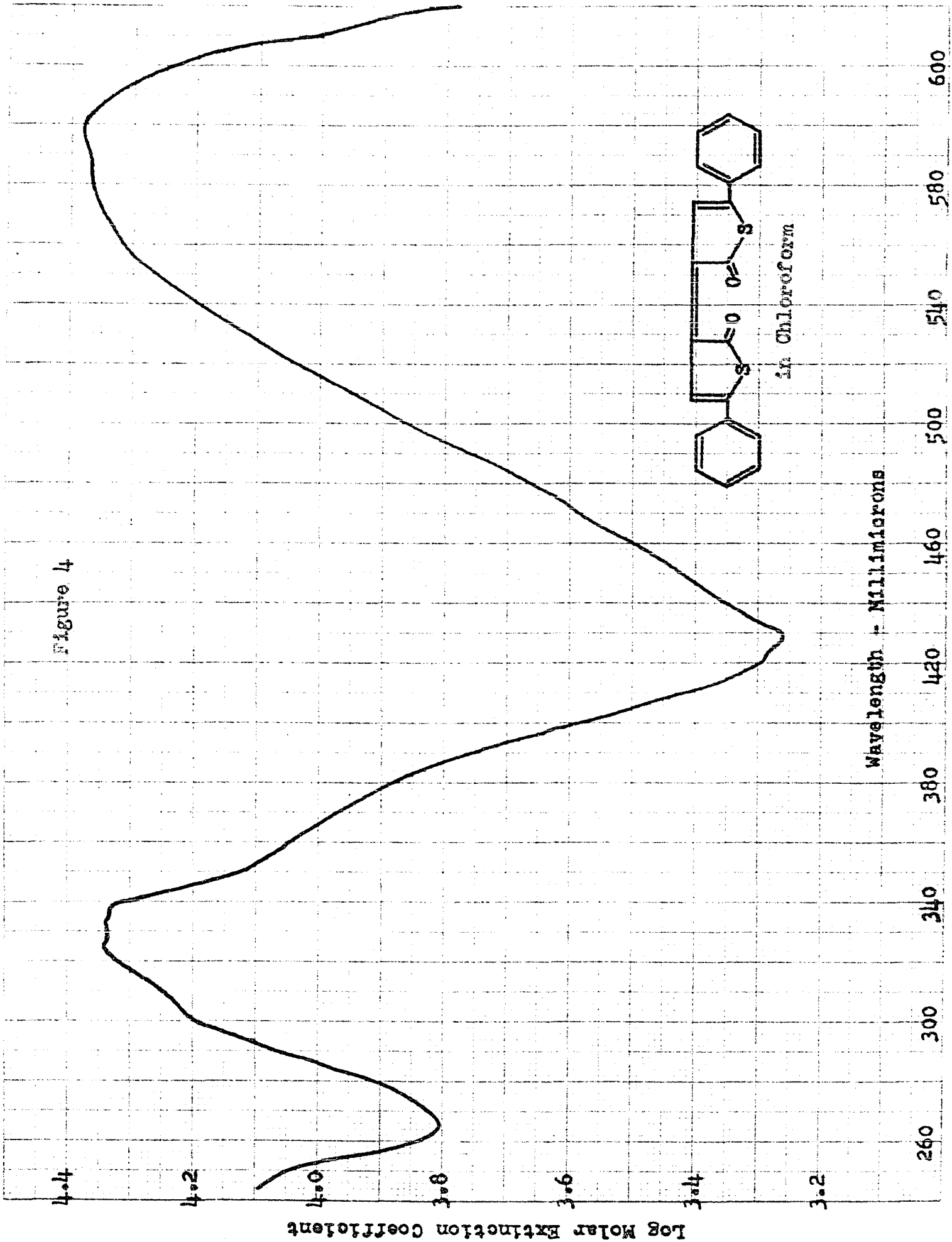
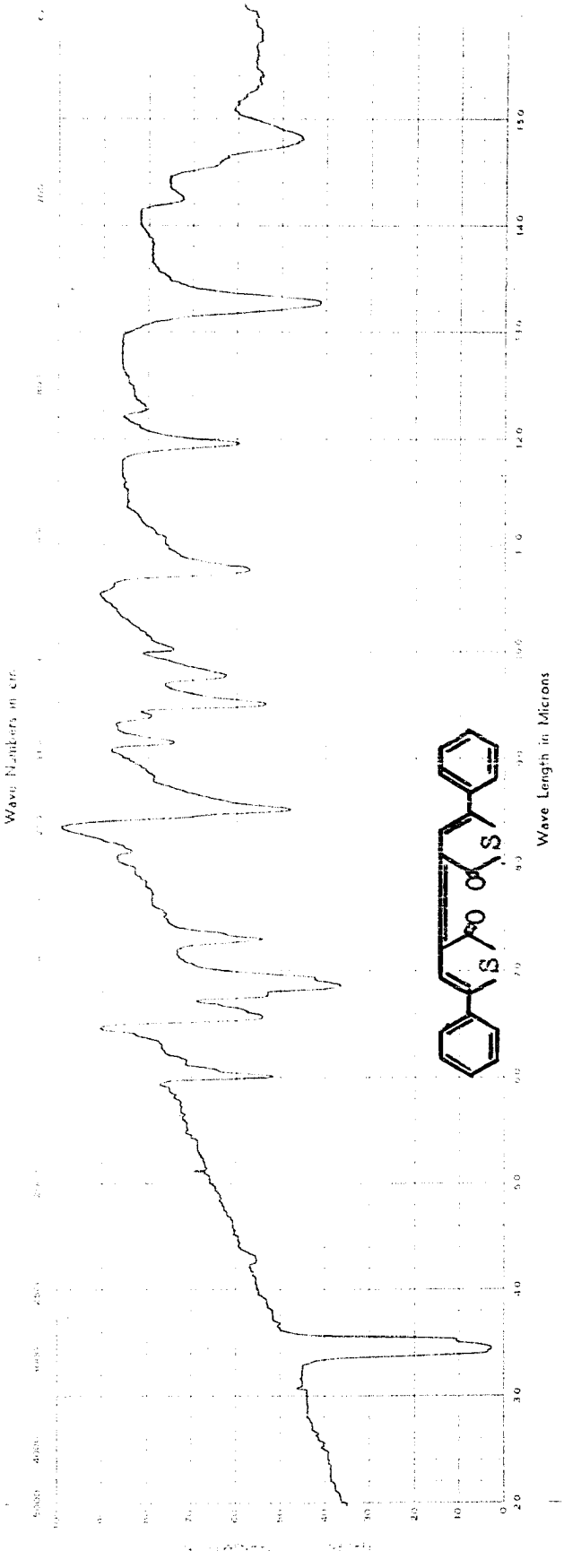


Figure 4

Figure 5



in the common solvents but which dissolved in warm alkali. The effect of diazomethane on 3-hydroxy-5-phenylthiophene is not known.

The reaction between the sodium salt of (XIII) and methyl iodide in methanol produced a blue-white powder which was only slightly soluble in the common organic solvents, insoluble in cold aqueous alkali and soluble in cold concentrated sulfuric acid in which it formed an orange solution. Since the elemental analysis did not correspond with the theoretical percentage composition calculated for the methyl ether, the product was not investigated further.

Because of the instability of 2-hydroxy-5-phenylthiophene, several attempts were made to prepare the methyl ether indirectly. The lithium salt, whether prepared by oxidation of 2-lithio-5-phenylthiophene or by reaction between 2-hydroxy-5-phenylthiophene and n-butyllithium would react with neither methyl sulfate nor methyl iodide. In these cases, extraction of the reaction products with alkali produced only the alkali salt of 2-hydroxy-5-phenylthiophene. No evidence of ether formation could be found in the neutral fraction which consisted mainly of tars and small amounts of the isothioindigo (VIII).

The original plan of this investigation included a

study of the Claisen rearrangement[53] of allyl ethers of hydroxythiophenes, but because of the numerous experimental difficulties encountered in the synthesis of 2-hydroxy-5-phenylthiophene only a few exploratory experiments were performed in this direction.

Realizing that a liquid ether would be difficult to purify, efforts were first directed toward the preparation of a cinnamyl ether which was expected to be a solid and could be purified by crystallization. The reaction between cinnamyl bromide and the alkali salt of 2-hydroxy-5-phenylthiophene in methanol failed to yield an ether. The only product was an alkali-insoluble light-red resin which dissolved in acetone but not in any of the other organic solvents.

A modification of the Williamson synthesis in which (XIII) was treated with silver acetate to form the silver salt, and then with cinnamyl bromide, was unsuccessful. Considerable oxidation occurred and an intractable tar was the major product.

The isomeric 3-hydroxy-5-phenylthiophene likewise failed to yield the cinnamyl ether. The reaction between the sodium salt of (XVIII) and cinnamyl bromide yielded

53. cf. D. S. Tarbell in Organic Reactions, R. Adams, Ed., John Wiley and Sons, Inc., New York, 1944 Vol. II, Chapter 1, p. 1.

a clear, tacky, red-brown resin which was insoluble in alkali and most of the organic solvents, with the exception of acetone.

Finally several attempts were made to prepare 2-allyloxy-5-phenylthiophene. Alkylation of the bromomagnesium salt of 2-hydroxy-5-phenylthiophene (prepared by oxidation of the Grignard reagent) with allyl bromide was unsuccessful. This was wholly unexpected in view of the known reactivity of allylic halides.

A. C. Cope[54] has studied the reaction ROMgBr + $(CH_3)_2SO_4$ and observed that ether formation only occurs under forced conditions and in the presence of a molar excess of methyl sulfate. This behavior was attributed to the formation of the dialkylmagnesium compound $(RO)_2Mg$,

$$2ROMgBr + 2(CH_3)_2SO_4 \rightarrow (RO)_2Mg + CH_3Br + Mg(CH_3SO_4)_2$$

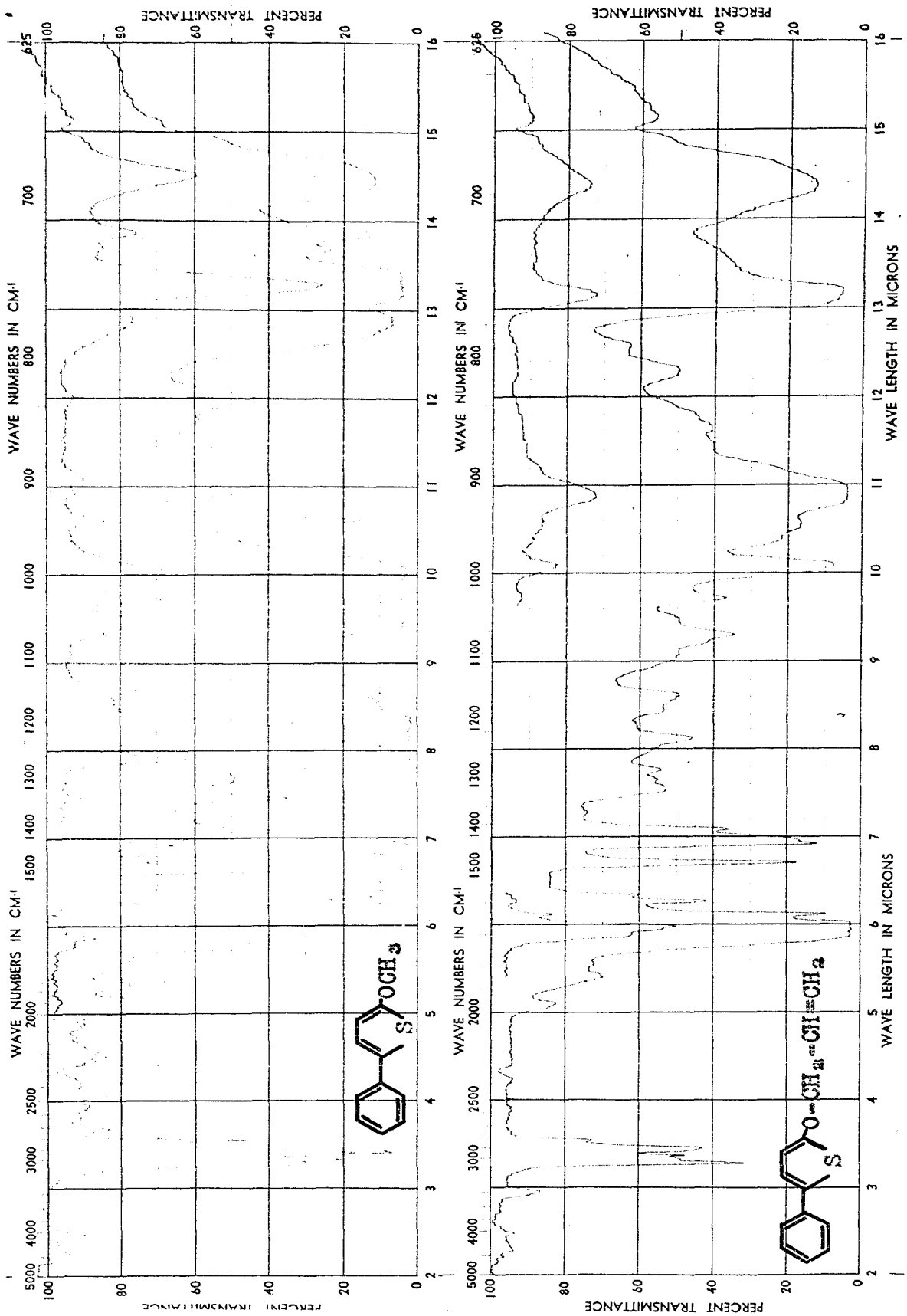
$$(RO)_2Mg + 2(CH_3)_2SO_4 \xrightarrow{C_6H_5CH_3} 2ROCH_3 + Mg(CH_3SO_4)_2$$

which is ordinarily considered to be unreactive. In view of these results, if an equilibrium existed between the bromomagnesium salt of 2-hydroxy-5-phenylthiophene and the diarylmagnesium derivative favoring the latter compound, the lack of reactivity could be understood.

54. A. C. Cope, J. Am. Chem. Soc. 56, 1342 (1934).

The reaction between the lithium salt of 2-hydroxy -5-phenylthiophene and allyl bromide in anhydrous ether produced a dark viscous liquid which resisted crystallization and vacuum distillation. A degree of success was obtained when the sodium salt was treated with allyl bromide in methanol. A pale yellow liquid was obtained, which although vacuum distilled to a constant refractive index was impure as indicated by the elemental analysis wherein the observed percentage composition neither agreed with the theoretical percentage composition nor could be assigned to a sensible formula. Furthermore the infrared spectrum (Fig. 6) possessed many broad bands and a sharp absorption in the carbonyl region and the ultraviolet absorption spectrum had neither maxima nor minima.

Figure 6



SUMMARY OF RESULTS

2-Hydroxy-5-phenylthiophene (XIII) has been synthesized by the cyclization of β-benzoylpropionic acid with "phosphorus pentasulfide" in pyridine - chloroform solution, and by the oxidation of 2-lithio-5-phenylthiophene, which is a modification of the procedure utilized by Hurd and Kreuz[15] for the synthesis of 2-hydroxythiophene and adapted by Steele[16] for the synthesis of (XIII).

Spectroscopic data indicate that in chloroform solution (XIII) exists chiefly as the keto tautomer whereas in alcoholic solution it exists chiefly as the enolic tautomer.

2-Hydroxy-5-phenylthiophene readily underwent acetylation but could be methylated only with difficulty. With diazomethane only tars resulted, with methyl sulfate and alcoholic alkali, 2-methoxy-5-phenylthiophene was formed in low yield.

The pure allyl ether could not be prepared *via* the Williamson synthesis and modifications thereof. All attempts to prepare the cinnamyl ether failed.

2-Hydroxy-5-phenylthiophene is extremely unstable oxidizing rapidly to yield tars and the isothioindigo, 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$ — bithiophene]-2,2'-dione (VIII). Furthermore it (XIII) is a vesicant, producing blisters and causing itching where it comes in contact with the

skin.

The isothioindigo (VIII) is quite stable and is insoluble in most of the common organic solvents but dissolves in and reacts with morpholine and piperidine forming sulfur-free crystalline materials which were not investigated. (VIII) absorbs three molar equivalents of hydrogen at low pressure, but the reduced product rapidly reoxidizes on exposure to the air.

EXPERIMENTAL

Experiments which were conducted in an atmosphere of dry nitrogen are indicated with an asterisk (*).

Microanalyses were performed at several laboratories. They are designated as follows:

(C) Clark Microanalytical Laboratories
104 1/2 West Main Street
P. O. Box 17
Urbana, Illinois

(S) Schwarzkopf Microanalytical Laboratory
Middle Village, Long Island
New York

(P) Microanalytical Laboratory
Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania

2-Bromothiophene[16]

(A) A 1 l. 3-necked flask equipped with a dropping funnel, stirrer and reflux condenser, was charged with a solution of 260 g. (3.1 moles) of thiophene dissolved in 300 ml. of carbon tetrachloride. A solution of 480 g. (3.0 moles) of bromine in 200 ml. of carbon tetrachloride was added dropwise, with stirring, over a period of eight hours. After stirring for an additional twenty hours, the solution was steam distilled from 400 ml. of a 10% sodium hydroxide solution. The organic portion was separated from the distillate, was dried over calcium chloride, filtered and fractionated to yield 325 g. (67%) of 2-bromothiophene, b.p. 151-151.5°.

(B) A solution of 513 ml. (1600 g., 10 moles) of bromine in 840 ml. of glacial acetic acid was added dropwise over a period of five hours to a stirred, well-cooled solution of 1260 g. (15 moles) of thiophene in 1850 ml. of glacial acetic acid. After the addition was completed the ice bath was removed and the solution was stirred for an additional hour. Three liters of cold water were added, the organic layer was separated, washed with a saturated sodium carbonate solution until effervescence ceased, and dried over a mixture of calcium chloride and anhydrous sodium carbonate. The material was filtered and distilled from sodium carbonate but there ensued an

evolution of hydrogen bromide, indicating the presence of bromine addition products of thiophene. The organic material was therefore steam distilled from a saturated sodium carbonate solution after which it was dried with calcium chloride and fractionated to yield 426 g. (5.08 moles) of unreacted thiophene, b.p. 84-85°; 729.5 g. (44.6% yield) of 2-bromothiophene, b.p. 153-154°; and 304 g. (12.5%) of 2,5-dibromothiophene, b.p. 65-70°/3 mm.

n-Butyllithium*

$$n\text{-}C_4H_9Br + 3n\text{-}C_4H_9Cl + 8Li \rightarrow 4n\text{-}C_4H_9Li + LiBr + 3LiCl$$

A mixture of 4.8 g. (0.035 mole) of n-butyl bromide and 10.65 g. (0.115 mole) of n-butyl chloride dissolved in 150 ml. of dry ether was added dropwise to bright lithium wire (2.3 g., 0.33 g. atoms) suspended in 80 ml. of dry ether. The reaction mixture became turbid and refluxing set in immediately and continued throughout the duration of the addition. The solution then was stirred for an additional half hour after which four 2 ml. aliquots were removed with the aid of a hypodermic syringe from the total volume of 225 ml. Two of the aliquots were added to 5 ml. portions of water and two were added to 5 ml. portions of allyl bromide. The latter two were hydrolyzed with 5 ml. of water each, and all four were titrated with 0.0483 N hydrochloric acid.

1. 2 ml. aliquot + H_2O = 20.95 ml. of 0.0483 N HCl
2. 2 ml. aliquot + H_2O = 20.94 ml. of 0.0483 N HCl
3. 2 ml. aliquot + allyl bromide + H_2O = 8.40 ml. of 0.0483 N HCl
4. 2 ml. aliquot + allyl bromide + H_2O = 7.90 ml. of 0.0483 N HCl

The yield was 47%. When conducted in olefin-free petroleum ether (40-60°) the best yield realized was 19%.

2-Thienyl-1-cyclohexene[31]

(A) A 2 l. 3-necked flask, equipped with a dropping funnel, mechanical stirrer and reflux condenser was charged with 53.5 g. (2.22 g. atoms) of magnesium turnings and 500 ml. of anhydrous ether. A solution of 362.0 g. (2.22 moles) of 2-bromothiophene in 100 ml. of dry ether was added dropwise to the stirred magnesium suspension at a rate which just maintained refluxing. The reaction mixture was stirred for fifteen minutes after the addition was completed, and then 208 g. (2.2 moles) of cyclohexanone diluted with 200 ml. of anhydrous ether was added, again at a rate which just maintained refluxing. This reaction mixture remained at room temperature for sixteen hours after the addition was completed, and then was hydrolyzed with a saturated ammonium chloride solution, care being taken to let the hydrogen sulfide which was evolved escape into the hood. The organic layer was separated, washed with a saturated sodium bisulfite solution, and dried

over anhydrous sodium sulfate. Vacuum distillation yielded 290 g. (80% yield) of pale yellow liquid, b.p. 107-108°/7 mm.

(B) A 2 l. 3-necked flask, fitted with a Dry-Ice - acetone cold finger, a mechanical stirrer and dropping funnel with nitrogen inlet was charged with 500 ml. of anhydrous ether and 14.6 g. (2.06 g. atoms) of lithium cut in cubes approximately 1 cm. on an edge. This flask was partially immersed in a Dry-Ice - acetone bath and 137 g. (1.0 mole) of n-butyl bromide, diluted with 100 ml. anhydrous ether, was added dropwise to the well-stirred lithium suspension at a rate which maintained refluxing. After the addition was complete, this cold solution of n-butyllithium was rapidly poured into a flask, similarly equipped, containing 101 g. (1.2 moles) of thiophene diluted with 200 ml. of ether. The thiophene, n-butyllithium mixture was stirred at room temperature for one-half hour, during which time the solution slowly turned green. This green solution was cooled in the Dry-Ice - acetone bath and 117.8 g. (1.2 moles) of cyclohexanone dissolved in 200 ml. of dry ether was added rapidly, since the cooling was efficient enough to keep the reaction under control. After all of the cyclohexanone was added, the cold bath was removed and the stirred solution gradually warmed up to room temperature after which a yellow-green solid appeared. This mixture was allowed to stand overnight,

was again cooled in a Dry-Ice - acetone bath, and was hydrolyzed with ice-cold hydrochloric acid. The organic layer was separated, washed with water, extracted with a saturated solution of sodium bisulfite, again washed with water and dried over sodium sulfate. The solution was filtered and then fractionated to yield 43.3 g. (43%) of unreacted thiophene, and 94.2 g. of 2-(1-cyclohexenyl)thiophene, b.p. 117-120°/5 mm., representing 84% yield based on unrecovered thiophene; 42.6% yield based on total thiophene.

2-Phenylthiophene[16]

A mixture of 120 g. (0.52 mole) of chloranil and 41 g. (0.25 mole) of 2-thienyl-1-cyclohexene in 150 ml. of commercial benzene was refluxed for twenty-four hours; after this time the product was cooled, vacuum-filtered, and extracted with 50 ml. portions of 12% sodium hydroxide solution until the alkaline washings were colorless. The benzene solution was then washed once with 100 ml. of water and dried over calcium chloride. Fractionation of the dried, filtered, benzene solution yielded 29.51 g. (74% yield) of 2-phenylthiophene, b.p. 113-114°/1 mm., m.p. 35-36°. Similar reactions with reflux times of eight and twelve hours showed no marked variation in the yields, which averaged 60-78%.

2-Bromo-5-phenylthiophene

(A) A mixture of 29.51 g. (0.185 mole) of 2-phenylthiophene, 46.25 g. (0.185 mole) of N-bromosuccinimide and 1 g. of benzoyl peroxide in 500 ml. of carbon tetrachloride was stirred and refluxed for seventy-two hours. Bromination was completed when no more N-bromosuccinimide remained on the bottom of the solution. The reaction mixture was cooled, filtered, extracted with five 50 ml. portions of 10% potassium hydroxide solution, washed twice with 50 ml. portions of water and dried over calcium chloride. The carbon tetrachloride solution was concentrated and the crude 2-bromo-5-phenylthiophene which separated was crystallized from ether to yield 40.23 g. (0.168 mole, 91%), m.p. 79-81°. One recrystallization from ether produced 38.7 g. of crystals, m.p. 85-86°, representing an 87.5% yield[36].

(B) A solution of 83 g. (26.6 cc., 0.518 mole) of bromine in 500 ml. carbon tetrachloride was added dropwise to a refluxing solution of 83 g. (0.518 mole) of 2-phenylthiophene in 500 ml. carbon tetrachloride. After the bromine had been completely added, the reaction mixture was allowed to stand for twelve hours. It was then washed with a solution of sodium bicarbonate, dried over calcium chloride, and distilled to yield 114 g. (90%) of a yellow-white solid, m.p. 56°. One recrystallization from

methanol gave 105 g. (85% yield) of pale yellow plates, m.p. 85-86°.

Metalation of 2-phenylthiophene*

A solution of 2-lithio-5-phenylthiophene was prepared by adding 8.0 g. (0.05 mole) of 2-phenylthiophene to an ether solution of phenyllithium prepared from 8.65 g. (0.055 mole) of bromobenzene and 0.763 g. (0.11 g. atom) of lithium. The 2-phenylthiophene was allowed to stand with the phenyllithium for one-half hour during which time the color of the solution had turned from red to yellow. This solution was then quickly poured over freshly broken Dry-Ice in an Erlenmeyer flask and was allowed to warm to room temperature. Extraction with sodium hydroxide solution and acidification yielded 7.67 g. (75.2%) of 5-phenylthiophene-2-carboxylic acid[55], m.p. 177-178°.

2-Hydroxy-5-phenylthiophene[16]

A solution of 9.6 g. (0.04 mole) of 2-bromo-5-phenylthiophene and 8.15 g. (0.05 mole) of cyclohexyl bromide in 150 ml. of dry ether was added dropwise, at a rate which just maintained refluxing, to 8 g. (0.33 g. atoms) of magnesium covered with a mixture of 60 ml.

55. W. Steinkopf and R. Gording, Biochem. Z. 292, 368 (1937).

of ether and 60 ml. of benzene contained in a 1 l. 3-necked flask equipped with a dropping funnel with nitrogen inlet tube*, stirrer, and reflux condenser fitted with a calcium chloride drying tube. When the addition was complete, the reaction mixture was stirred for an additional half hour, after which time the reflux condenser was replaced by a low temperature thermometer, and the dropping funnel was replaced by a gas dispersion tube, which just penetrated the surface of the solution. The reaction flask was then immersed in an ice - salt bath and when the temperature was approximately 0°, oxygen was admitted, the amount being measured by a flowmeter, until 0.025 moles had been absorbed. The reaction flask was then stoppered and allowed to stand in the refrigerator for sixteen hours. The solution was then treated with a hydrochloric acid - ice mixture. The organic layer, which immediately turned purple, was separated, washed once with 100 ml. water and extracted with five 40 ml. portions of 10% sodium hydroxide solution. This combined alkaline extract was filtered, acidified, and extracted with ether. The ether extract was dried with sodium sulfate, filtered and concentrated to yield 1 g. of 2-hydroxy-5-phenylthiophene, m.p. 80-81°, which represented 22.8% yield based on oxygen.

Oxygenation of 2-lithio-5-phenylthiophene

(A) To a 2 l. 3-necked flask charged with 0.225 mole

of n-butyllithium and 185 ml. of dry ether, and equipped with a dropping funnel and nitrogen inlet tube*, a mechanical stirrer and reflux condenser sealed with a calcium chloride drying tube was added 23.8 g. (0.149 mole) of 2-phenylthiophene. A vigorous evolution of butane ensued and the color changed from pale amber to yellowish green. Two hundred milliliters (0.4 mole) of an ether solution of cyclohexylmagnesium bromide was added, the condenser was replaced by a low temperature thermometer and a Bunsen valve, the dropping funnel was replaced by an oxygen inlet tube, the mixture was cooled to less than -50° (the lower limit of the thermometer) in a Dry-Ice - acetone bath, and oxygen was slowly bubbled in. (Oxygenation is exothermic and the rate of flow was adjusted so that at no time was the temperature permitted to rise above -20°.) When the reaction was complete, the flask was quickly stoppered and placed in the refrigerator for eighteen hours. This cold solution was rapidly filtered, acidified with 60 ml. of ice-cold concentrated hydrochloric acid, washed once with 100 ml. of cold water, and extracted with five 100 ml. portions of 12% sodium hydroxide solution. The dark brown-black alkaline extract was filtered, extracted with three 100 ml. portions of ether-benzene (50-50) and was then neutralized with 30 ml. of ice-cold concentrated hydrochloric acid. The precipitate was quickly taken up in ether and concentrated to yield 7.8 g.

(33.6%) of 2-hydroxy-5-phenylthiophene as brown plates, m.p. 81.2-81.6° (corr.). Vacuum sublimation yielded pure colorless diamond shaped crystals, m.p. 81.6-81.8° (corr.), which gradually acquired a thin green film, presumably the oxidation product, 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$-bithiophene]-2,2'-dione.

(B) 2-Lithio-5-phenylthiophene was prepared by adding 44.5 g. (0.278 mole) of 2-phenylthiophene to 310 ml. of a cold ether solution containing 0.316 mole of n-butyllithium, then stirring for forty minutes in a nitrogen atmosphere*, after which the reaction flask was equipped with a low temperature thermometer, a Bunsen valve, and a gas inlet tube, and allyl magnesium bromide (prepared from 80.47 g., 0.66 mole of allyl bromide) was added. The flask was then immersed in an ice - salt bath to maintain a temperature of less than 10°, and the contents was stirred while oxygen was slowly bubbled in until no more was absorbed. The flask was then stoppered and kept in the refrigerator for forty-eight hours after which the solution was filtered rapidly. The filtrate was acidified with 100 ml. of ice-cold concentrated hydrochloric acid, the ether layer was washed twice with 50 ml. portions of ice water, and was extracted with three 50 ml. portions of 12% sodium hydroxide solution. The dark-brown alkaline extract was washed with three 100 ml. portions of ether,

and then acidified with 50 ml. of ice-cold concentrated hydrochloric acid. The resulting precipitate was crystallized from ether to yield 2.41 g. (0.137 mole, 4.93%) of crude 2-hydroxy-5-phenylthiophene, m.p. 78-80°. No attempt was made to purify it further.

(C) 2-Phenylthiophene (15.2 g., 0.095 mole) dissolved in 10 ml. of ether was added to 0.0995 mole of n-butyllithium in 150 ml. of ice-cold ether. The color of the solution slowly changed from gray to pale yellow-green at room temperature. At the end of twenty-four hours this solution, which had finally become pale red-brown, was added to an additional 0.1425 mole of n-butyllithium, the entire mixture was cooled to -5° and oxygen (3.64 l., S.T.P., a 56% excess) was bubbled through. This oxygenated mixture was allowed to stand in the refrigerator for eighteen hours, after which time it was hydrolyzed and extracted with water until the aqueous layer was almost colorless. This aqueous layer was acidified and extracted with ether; the ether extract was concentrated using the water aspirator to yield 1 g. of dark, black-green, foul smelling tars. The original ether solution of the reaction mixture was filtered, and the precipitate crystallized from hot dioxane to yield 2.73 g. (18.1%) of 5,5'-diphenyl-2,2'-dithienyl, m.p. 230-231.5° (corr.).

Determination of the coupling step in the oxygenation experiment*

A mixture of 6 g. (25 millimoles) of 2-bromo-5-phenylthiophene and 5 g. (25 millimoles) of cyclohexylbromide dissolved in 250 ml. of dry ether and 50 ml. of dry benzene was converted to the Grignard reagent and the reaction mixture was divided into two parts. One half was poured over Dry-Ice and the other half was oxygenated, following the procedure previously described.

After the carbonated portion warmed up to room temperature, it was washed with cold, dilute hydrochloric acid, and then was extracted with sodium carbonate solution. Acidification yielded 2-phenylthiophene-5-carboxylic acid, which was crystallized from ether to yield 1.305 g. (60.8%), m.p. 177-178°[55]. No coupled product was present in the neutral portion.

The oxidized portion stood in the refrigerator overnight, and was then processed to yield 0.2 g. (10%) of 5,5'-diphenyl-2,2'-dithienyl, m.p. 243-244° (corr.)[56] and 0.06 g. of 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$-bithiophene]-2,2'-dione. No 2-hydroxy-5-phenylthiophene could be isolated.

Thiation of β-benzoylpropionic acid*

A solution of 46.70 g. (0.21 mole) of phosphorus

56. W. Steinkopf, Ann. 527, 278 (1937) reports a melting point of 237° for this compound.

pentasulfide in 275 g. of hot pyridine was added to a solution of 35.6 g. (0.20 mole) of β-benzoylpropionic acid in 100 g. of pyridine and 400 ml. of chloroform through which dry nitrogen was slowly being bubbled, and the mixture was refluxed for eighty minutes. At the end of this time 466 ml. of concentrated hydrochloric acid admixed with cracked ice was added rapidly, the aqueous layer was decanted from the chloroform layer and extracted with five 300 ml. portions of chloroform. All of the chloroform portions were combined and extracted with 6% sodium hydroxide solution until no base soluble material remained. The basic extract was frozen to a thick slurry on Dry-Ice, acidified with concentrated hydrochloric acid and filtered by vacuum. The precipitate was crystallized from ether and then from petroleum ether (equal parts of 40-60° and 70-90°) to yield 7.85 g. (21.7%) of 2-hydroxy-5-phenylthiophene, m.p. 80-81°.

Preliminary Investigations

(A) Sufficient anhydrous pyridine was added to a mixture of 8.9 g. (0.05 mole) of β-benzoylpropionic acid and 12.22 g. (0.055 mole) of phosphorus pentasulfide to bring about solution. The resulting mixture was refluxed for twenty-five minutes during which time the color had gradually changed from yellow to dark purple. Refluxing was stopped and the hot pyridine solution was poured into

550 ml. of hot water. The aqueous pyridine suspension cooled to room temperature, but no solid had settled out. Therefore enough cold hydrochloric acid was added to neutralize the pyridine and the resulting suspension was extracted with benzene. The purple benzene extract was dried over calcium chloride, filtered and concentrated to yield 1.19 g. (13.6%) of the dark green isothioindigo, 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$-bithiophene]-2,2'-dione, m. p. 304-305°.

(B) A solution of 8.9 g. (0.05 mole) of β-benzoylpropionic acid and 12.22 g. (0.055 mole) of phosphorus pentasulfide in 460 g. of pyridine was refluxed for three hours, after which it was poured over cracked ice and allowed to stand for one hour. This turbid solution, on further addition of water, yielded a white precipitate which, in a matter of a few minutes, turned blue. Extraction with ether and concentration of the ether extract produced 0.18 g. of the isothioindigo 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$-bithiophene]-2,2'-dione and residual black, foul smelling tarry material.

(C)* β-Benzoylpropionic acid (18 g., 0.1 mole) and 24 g. (0.11 mole) phosphorus pentasulfide were dissolved in separate 500 ml. quantities of boiling chloroform; 450 g. of pyridine was added and the mixture was refluxed for six hours. Approximately one half of the solvent was removed by distillation, and the remaining concentrate

was poured over a mixture of cracked ice and hydrochloric acid. This was transferred to a liquid-liquid extractor and continuously extracted with ether until the aqueous layer was practically colorless. The ether extract was shaken with two 50 ml. portions of 12% sodium hydroxide solution, which were combined, acidified, and extracted with ether. The ether extract, when concentrated, yielded only traces of a foul smelling tar.

2-Acetoxy-5-phenylthiophene

(A)[57] A mixture of 1 g. (5.67 mmoles) of 2-hydroxy-5-phenylthiophene, 6 ml. acetic anhydride, 1 g. zinc dust, and 2 drops of benzyl trimethylammonium hydroxide[58] was boiled until the colored material disappeared. Three drops of glacial acetic acid were added and the hot solution was filtered by gravity into a flask containing 1 ml. of boiling acetic acid, and then water was added dropwise to the boiling solution to hydrolyze the acetic anhydride. The cooled solution was extracted with ether, dried with sodium sulfate, decolorized with Darco, and concentrated to yield 0.95 g. of crude product, m.p. 45-51°. Vacuum sublimation yielded colorless needles, m.p. 55-57°.

Calc.: C, 66.0%; H, 4.6%; S, 14.7%

Found:(S) C, 66.2%; H, 4.7%; S, 14.4%

57. cf. L. F. Fieser, Experiments in Organic Chemistry, D. C. Heath and Co., Boston, 2nd ed., 1941, p. 399.

58. Sample courtesy of Rohm and Haas.

(B) Acetyl chloride (17.8 ml., 19.65 g., 0.25 mole) was added to a cold ether solution of the lithium salt of 2-hydroxy-5-phenylthiophene prepared by the oxygenation procedure [8.35 g. (0.055 mole) of bromobenzene, 0.764 g. (0.11 g. atom) of lithium, 8.0 g. (0.050 mole) of phenylthiophene and 110 ml. of 1.40 N (0.154 mole) cyclohexylmagnesium bromide] and this was allowed to stand at room temperature for six days. All attempts to isolate a crystalline solid were futile. The reaction mixture only yielded tars and a pleasant, fruity odor persisted, undoubtedly the odor of cyclohexyl acetate.

2-Methoxy-5-phenylthiophene

To a stirred, well-cooled solution of 8.8 g. (50 mmoles) of 2-hydroxy-5-phenylthiophene and 2.1 g. (50 mmoles) of sodium hydroxide in 50 ml. of water was added 6.3 g. (50 mmoles) of dimethyl sulfate. The reaction mixture, through which dry nitrogen was bubbling, was set aside at room temperature for twenty-four hours and then it was extracted with ether. The ether extract was washed twice with 20 ml. portions of 12% sodium hydroxide solution, once with 20 ml. of water and was dried over calcium chloride. It was then filtered, clarified with Darco, and concentrated with the aid of a steam bath to yield approximately 8 ml. of a dark-brown viscous liquid. Three vacuum distillations yielded 3.70 g. (19.45 mmoles)

of a pale yellow liquid representing a 39% yield of 2-methoxy -5-phenylthiophene, b.p. 135-136°/1 mm., n_D^{25} = 1.6308.

Calc. for $C_{11}H_{10}SO$: C, 69.5%; H, 5.3%; S, 16.8%
Found:(P) C, 69.6%; H, 5.5%; S, 16.0%

Unsuccessful Preparations

(A) A solution of 1.12 g. (20 mmoles) of potassium hydroxide in 15 ml. of distilled water was added to a solution of 2.0 g. (11.34 mmoles) of 2-hydroxy-5-phenyl-thiophene and 1.45 g. (11.34 mmoles) of dimethyl sulfate in 50 ml. of methanol[59]. The mixture was heated on a steam bath for forth-five minutes during which time the color changed from green to blue. Water was added and the mixture was allowed to stand overnight, after which it was boiled for an hour, cooled, and extracted with ether. The ether extract was concentrated on a steam bath and the residual liquid decomposed when subjected to vacuum distillation.

(B) A solution of 2 g. (11.34 mmoles) of 2-hydroxy -5-phenylthiophene was added to a cold ethereal solution of diazomethane, prepared from 2.4 g. (22.68 mmoles) of N-nitrosomethylurea. The solvent was removed in a nitrogen atmosphere to yield only a brown tar. The tar was put on

59. cf. W. J. Hickenbottom, Reactions of Organic Compounds, Longmans, Green and Co., Inc., New York, 1948, p. 94.

a column of Merck's alumina 4 1/2 cm. in diameter and 20 cm. high, previously washed with dry ether, and eluted with dry ether. Two fractions were obtained, a dark brown one which remained on the column (and which could not be appreciably removed with methanol) and a yellow-brown portion which readily washed through. Attempted vacuum distillation of this latter fraction only resulted in thick tar formation in the distilling flask, and no visible distillate.

(C) A solution of 5 g. (28.35 mmoles) of 2-hydroxy-5-phenylthiophene in 1 l. of dried, olefin-free petroleum ether (40-60°) was treated with diazomethane [prepared from 7.2 g. (68 mmoles) of N-nitrosomethylurea] which was generated in 300 ml. of the same solvent. This reaction mixture was allowed to stand for two and one-half hours in a nitrogen atmosphere, during which time no evolution of nitrogen was observed. The flask was then fitted with a capillary, which was attached to the nitrogen tank, and the solution was concentrated at a reduced pressure to a volume of 75 ml. This volume of reaction mixture yielded 2 g. of unreacted 2-hydroxy-5-phenylthiophene and intractable tars.

(D) A solution of 48.67 g. (0.31 mole) of bromobenzene was added with stirring to 4.30 g. (0.62 g. atom) of lithium suspended in 100 ml. of dry ether in a 2 l.

flask equipped with a mechanical stirrer, Dry-Ice - acetone cold finger, a low temperature thermometer and a dropping funnel*. After the reaction had subsided 48 g. (0.30 mole) of 2-phenylthiophene was added all at once and the mixture was allowed to stand at room temperature for twenty minutes. Then 1 mole of a 2.2 N ether solution of isopropylmagnesium bromide was added, the dropping funnel was replaced by a gas inlet tube, the cold finger was replaced with a Bunsen valve and the entire reaction mixture was cooled in a Dry-Ice - acetone bath. When the temperature reached -70°, oxygen was bubbled in beneath the surface at a rate such that the temperature never rose above -30°. When oxidation was finished (as evidenced by a constant low temperature), the flask was stoppered and placed in the refrigerator for sixteen hours. Then 39.1 g. (0.31 mole) of dimethyl sulfate was added and the mixture was placed on a steam bath to remove the solvent. The residue was treated with 200 ml. of cold water to use up the excess lithium and concentrated hydrochloric acid on cracked ice was added until the inorganic precipitates just dissolved. This mixture was rapidly extracted with ether, and the ether extract was shaken with five 30 ml. portions of 12% aqueous sodium hydroxide. Acidification of this alkaline extract yielded 3.1 g. (0.017 mole) of crude 2-hydroxy-5-phenylthiophene, m.p. 72-76°. The neutral portion was concentrated and distilled to yield 13.22 g. (0.123 mole) of anisole,

b.p. 34/1 mm., m.p. -30°; 17.12 g. (0.17 mole) of unreacted 2-phenylthiophene, b.p. 99-104°/1 mm., m.p. 35-36°; and a residue of undistillable high-boiling tar.

(E) A solution of 2.0 g. (11.34 mmoles) of 5-phenyl-2-hydroxythiophene in 70 ml. of dry ether was added to 20 ml. of a solution of n-butyllithium prepared from 3.10 g. (22.68 mmoles) of n-butyl bromide and 0.315 g. (0.4536 g. atom) of lithium. (A 50% conversion to n-butyllithium was assumed). This mixture was then treated with 2.41 g. (22.68 mmoles) of methyl iodide, the flask was stoppered, and allowed to stand at room temperature for twelve hours. The solution, which had turned purple, was washed with water, dried over calcium chloride, filtered, and fractionated to yield a mixture of ethyl ether and methyl iodide. A few drops of high boiling tar which would not vacuum distill remained in the distilling flask.

The aqueous wash was acidified, and extracted with ether. Crystallization yielded 1.37 g. (68.5%) of unreacted 5-phenyl-2-hydroxythiophene.

(F) A solution of 2.0 g. (11.34 mmoles) of 2-hydroxy-5-phenylthiophene in 75 ml. of dry ether (through which nitrogen was continuously being bubbled) remained in contact with 0.0787 g. (11.34 mgm. atoms) of lithium for twenty-four hours at room temperature. Then 1.45 g. (11.34 mmoles) of methyl sulfate in 75 ml. of dry ether

was added dropwise over a period of one-half hour. The mixture was allowed to stand for five hours, water was added to use up the lithium which still remained, and the mixture was extracted with ether, dried over calcium chloride and concentrated to yield a dark-brown tar.

(G) A solution of 2 g. (11.34 mmoles) of 2-hydroxy -5-phenylthiophene in 75 ml. of dry benzene (through which nitrogen was continually being bubbled) was refluxed on a steam bath for two hours with 78.7 mgm. (11.34 mgm. atoms) of lithium, dry benzene being added periodically to maintain the volume. Since there was no visible sign of a reaction having taken place; i.e., the unreacted lithium still remained, 10 ml. of ethanol was added, and the reaction mixture was further heated in the steam bath to dryness. A solution of 1.45 g. (11.34 mmoles) of methyl sulfate in 10 ml. of methanol was added, and the solution was heated to boiling, after which 10 ml. of water was added. The aqueous suspension was heated to boiling and then set aside to cool. The organic layer (a dark-brown tar) was taken up in ether, dried over calcium chloride and concentrated to yield a thick dark-brown tar.

(H) To a solution of the sodium salt of 2-hydroxy -5-phenylthiophene prepared from 50 ml. of absolute methanol, 0.26 g. (11.4 mmoles) of sodium and 2 g. (11.4 mmoles) of

2-hydroxy-5-phenylthiophene was added 2 g. (14 mmoles) of methyl iodide. The mixture was heated to reflux, stoppered, and set aside for twenty-four hours. It was then concentrated using the water aspirator and steam bath, to a volume of approximately 20 ml. and then poured into 200 ml. of water. The resulting aqueous suspension was extracted with ether; the ether extract was dried over sodium sulfate, filtered and set aside. In five days time a solid deposited which could not be readily redissolved in ether. Crystallization from hot benzene yielded a blue-white powder which darkened at 150°, and collapsed at 160° (D); when put in a bath preheated to 160° it darkened at 161° and melted at 163-163.2° (D).

Calc. for $C_{11}H_{10}SO$: C, 69.5%; H, 5.26%; S, 16.85%

Found:(S) C, 71.11%; H, 5.14%; S, 15.58%

The material was insoluble in 12% sodium hydroxide solution, and soluble in concentrated sulfuric acid in which it formed an orange solution.

(I) A mixture of 19.2 g. (0.10 mole) of methyl β-benzoylpropionate and 24.0 g. (0.11 mole) of phosphorus pentasulfide in 1 l. of pyridine was refluxed for thirty minutes, during which time the color of the solution slowly changed from yellow to orange-red. This mixture remained at room temperature overnight, and then the pyridine was neutralized with hydrochloric acid, and the residue was

dissolved in ether. The ether solution was washed with water, dried over sodium sulfate, filtered, and concentrated on the water bath. A trace of solid appeared which, when crystallized from ether, gave no sharp melting point, decomposing from 118-120°. When placed in the melting point bath, preheated to 120°, it collapsed with decomposition from 123-125°. The residue was distilled to yield 14.9 g. (74.6%) of unreacted methyl ester, b.p. 130-132°/3 mm.

Unsuccessful preparations of 2-cinnamyloxy-5-phenylthiophene

(A) 2-Hydroxy-5-phenylthiophene (2.0 g.; 11.34 mmoles) was dissolved in a solution of 11.34 mmoles of sodium methoxide in 50 ml. methanol, and to this was added 2.24 g. (11.34 mmoles) cinnamyl bromide. After standing overnight the solution was concentrated on a steam bath to about half its volume and water was added. This mixture was extracted with ether. The ether extract, when concentrated, yielded only a tar which would not solidify or separate from solution when placed on Dry-Ice.

(B) Two grams (11.34 mmoles) of 2-hydroxy-5-phenylthiophene was added to a solution of 0.0787 g. (11.34 mgm. atoms) of lithium in 120 ml. methanol, and to this was added 2.24 g. (11.34 mmoles) of cinnamyl bromide. The reaction mixture was heated on the steam bath for one hour, and was then allowed to stand for two days at room

temperature after which the methanol was removed under reduced pressure, the residue was extracted with ether, and the ether extract was concentrated to yield only a few drops of a viscous dark red-brown oil, which could neither be crystallized nor vacuum distilled.

(C) A solution of 1.0 g. (5.65 mmoles) of 2-hydroxy-5-phenylthiophene in 15 ml. of pyridine was added to a solution of 0.94 g. (5.65 mmoles) of silver acetate in 15 ml. of pyridine, (resulting in formation of a purple color), heated to boiling, and then poured into 175 ml. of ether. This was filtered and evaporated to dryness at reduced pressure. The residue, and the precipitate, both tarry semisolids, were mixed together in ethanol, 1.12 g. (5.65 mmoles) of cinnamyl bromide was added, and this mixture was refluxed for ninety minutes. The solution was cooled to room temperature, filtered and concentrated to near dryness. Ether was added, the solution was boiled with Darco, filtered, and concentrated to yield a dark-brown tarry mass.

Unsuccessful preparation of 3-cinnamyloxy-5-phenylthiophene

To a solution of 1.15 g. (0.05 mole) of sodium in 20 ml. of absolute methanol was added first a solution of 8.8 g. (0.05 mole) of 3-hydroxy-5-phenylthiophene in 35 ml. of methanol and then a solution of 9.9 g. (0.05 mole)

of cinnamyl bromide in 20 ml. methanol. The reaction mixture, which had become warm, was allowed to stand at room temperature for sixteen hours in a nitrogen atmosphere, after which it was poured into water and extracted with ether. The ether extract was washed once with 20 ml. of 6% sodium hydroxide, twice with 20 ml. portions of water, and was then dried over calcium chloride. The dried ether solution was boiled with charcoal yielding a red solution which was concentrated to an oily red residue which would not solidify on Dry-Ice. When subjected to vacuum distillation (1 mm.) the material began to decompose without distilling as evidenced by a copious evolution of brown vapors. No condensate was observed and heating was immediately stopped. Extraction of the residue with alkali yielded no base soluble material. Extractions with petroleum ether (40-60°) and methanol, in which the residue was only sparingly soluble, yielded nothing. When allowed to stand, it set to a tacky red-brown tar.

Attempted preparation of 2-allyloxy-5-phenylthiophene

(A) An ice cold solution of the sodium salt of 2-hydroxy-5-phenylthiophene, prepared from 17.6 g. (0.1 mole) of crude 2-hydroxy-5-phenylthiophene and 2.3 g. (0.1 g. atom) of sodium dissolved in methanol, was treated with 12.1 g. (0.1 mole) of allyl bromide dissolved

in 10 ml. of methanol. After completing the addition, the cold bath was removed and the reaction mixture was stirred at room temperature for 2 hours, and then allowed to stand for an additional hour. It was then poured into water and extracted with ether. The ether extract was treated twice with 10 ml. portions of 12% sodium hydroxide, once with water, and then dried over calcium chloride. Six one-plate vacuum distillations yielded 4.56 g. of a pale-yellow liquid, b.p. 168-170°/2 mm., n^{25} = 1.5805.

Calc. for $C_{13}H_{12}SO$: C, 72.3%; H, 5.6%; S, 14.8%
Found:(S) C, 73.25%; H, 5.79%; S, 10.72%

(B) Five grams (28.4 mmoles) of 2-hydroxy-5-phenylthiophene was added to a stirred ether solution of phenyllithium, prepared from 4.56 g. (0.03 mole) of bromobenzene and 0.403 g. (0.058 g. atom) of lithium, and refluxing immediately ensued. When the refluxing had stopped, 3.44 g. (29 mmoles) of allyl bromide was added, and the reaction mixture was allowed to stand for eighteen hours. (A nitrogen atmosphere was maintained throughout the above preparation.) Water was added, the two layers were separated, and acidification of the aqueous layer resulted in recovery of 2.06 g. (41%) of 2-hydroxy-5-phenylthiophene. The organic layer was dried with calcium chloride, filtered and concentrated to yield 10 ml. of a dark, viscous liquid

which could not be solidified in a Dry-Ice - acetone bath and which resisted vacuum distillation.

(C)* A 2 l. 3-necked flask, equipped with a dropping funnel with a nitrogen inlet tube, stirrer and reflux condenser fitted with a calcium chloride drying tube, was charged with 6.8 g. (0.28 mole) of magnesium turnings and 350 ml. of anhydrous ether. A mixture of 23.9 g. (0.1 mole) of 2-bromo-5-phenylthiophene and 18.4 g. (0.15 mole) of isopropyl bromide, diluted with 800 ml. of anhydrous ether was added dropwise to the stirred magnesium turnings at a rate which just maintained refluxing. After the reaction was complete, the flask was fitted with a low temperature thermometer, oxygen inlet tube, and Bunsen valve and was immersed in an ice - salt bath. When the temperature of the contents was approximately 0°, oxygen was admitted, the amount being measured by a flowmeter, until 0.25 mole had been absorbed. The reaction flask was then allowed to warm up to room temperature and 36.3 g. (0.30 mole) of allyl bromide, diluted with 150 ml. of anhydrous ether was added. The solution turned red-brown, and was stirred at room temperature for five hours. The flask was stoppered and the reaction mixture remained at room temperature for sixteen hours after which it was hydrolyzed. The ether solution was separated, dried over sodium sulfate, and concentrated to yield traces of

5,5'-diphenyl-2,2'-dithienyl, m.p. 240.5-241°, and traces of a dark green crystalline solid, 5,5'-diphenyl[$\Delta^{3,3'(2H,2'H)}$-bithiophene]-2,2'-dione, m.p. 304-305°.

Calc. for $C_{20}H_{12}S_2O_2$: C, 69.0%; H, 3.4%; S, 18.4%

Found:(P) C, 68.5%; H, 3.3%; S, 18.4%

This dark green solid is only very slightly soluble in most of the common laboratory solvents (See Table 1) and is purified by crystallization from hot dioxane, benzene or chloroform. It forms a brilliant green solution in cold, concentrated sulfuric acid and is rapidly decomposed when warmed with either dilute or concentrated aqueous or alcoholic alkali. Solutions in morpholine and piperidine are deep indigo blue, and gradually turn red on standing, depositing white crystals. The product obtained from the morpholine solution was isolated and purified by sublimation (90-95°), m.p. 103-104° (with bubbling). The odor of morpholine persists in the sublimed solid, and if allowed to stand open to the atmosphere this solid gradually disappears. Elemental analysis(S) yielded: C, 49.46%; H, 8.04%; S, 0%.

Several attempts were made to make the ether in this manner, varying the temperature and reflux time after addition of the allyl bromide, but none were successful.

Attempted rearrangement of 2-allyloxy-5-phenylthiophene

A solution of 0.81 g. (4.6 mmoles) of 2-allyloxy -5-phenylthiophene[60] in 15 ml. of dimethylaniline was heated to a temperature ranging between 170-216° for 10 hours in a nitrogen atmosphere. This reaction mixture was then cooled, poured into 13 ml. of ice cold concentrated hydrochloric acid and the resulting aqueous suspension was extracted with ether. The ether solution was extracted with six 10 ml. portions of 12% sodium hydroxide solution, and was then dried over calcium chloride. Ice-cold concentrated hydrcchloric acid was added dropwise to the alkaline extract until the solution was neutral to litmus, after which this aqueous solution was extracted with six 25 ml. portions of ether. The ether washings were evaporated to dryness, yielding nothing.

The original neutral, or alkaline-insoluble, organic portion was filtered, the ether was allowed to evaporate and the liquid residue was dissolved in 15 ml. dimethylaniline. This solution was refluxed in a nitrogen atmosphere for one hour at 274°, and then for 6 1/2 hours at 245°. This material was then worked up as described above, but yielded no alkaline soluble material. The neutral material decomposed when subjected to vacuum distillation.

60. The analysis received for this sample did not correspond to the calculated values within the limits of experimental error.