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I hereby recommend that the thesis prepared under my supervision by Charles Myron Selwitz

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Thiophenequinone Derivatives

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INTRODUCTION

I

When Victor Meyer made his amazing discovery of thiophene in benzene[1] he found that this new compound was remarkably similar to benzene in chemical and physical properties and that both compounds often formed derivatives which had corresponding similarities[2]. In addition many of the reactions which benzenoid compounds undergo are also distinctive reactions of thiophene and its derivatives. These reactions include the typical substitution reactions of benzene itself - nitration, bromination, chlorination, acylation and alkylation - and substitution reactions such as chloromethylation, mercuration and others which require a benzene ring whose reactivity is enhanced by the proper substitution. These analogies can be drawn to a remarkable degree, and unfortunately often led to incorrect conclusions about the chemistry of thiophene. With more and more work in this field the extent of the analogies became more clearly defined, and the important differences between these two types of compounds became more evident[3].

(1) V. Meyer, Die Thiophenegruppe, Braunschweig, 1888, p.1.

(2) W. Steinkopf, Die Chemie des Thiophens, Theodor Steinkopff, Dresden and Leipzig, 1941, pp. 15, 74.

(3) H. D. Hartough, The Chemistry of Heterocyclic Compounds, Thiophene and its Derivatives, Interscience Publishers, New York, 1952, pp. 156-157.

The relationships between benzenoid aromatic compounds and their non-aromatic oxidation derivatives, quinoidal compounds, have been extensively studied and well established. These same relationships between the normal aromatic thiophene derivatives and compounds analogous to quinone derivatives are less well known. Friedländer[4] prepared 5-phenyl-2,3-thiophenequinone-2-oxime and unsuccessfully tried to prepare a quinone from this compound. Benary and Silberstrom[5] prepared 4-carbethoxy-5-methyl-2,3-thiophenequinone-2-oxime and also failed in their attempt to obtain the parent quinone. There has been therefore very little data with which to draw comparisons between benzoquinones and benzoquinone derivatives on one hand, and thiophenequinone and its derivatives on the other. The synthesis of thianaphthaquinone has been realized[6] and this compound behaves like a typical aromatic ortho quinone[7,8,9,10]. The thiophenequinone analogous to para-benzoquinone would be thiomaleic anhydride. This compound has not been prepared, however

(4) P. Friedländer and St. Kielbasinski, Ber. 45, 3389 (1912).
(5) E. Benary and L. Silberstrom, Ber. 52, 1605 (1919).
(6) A. Bezdrik, P. Friedländer, and P. Koeniger, Ber. 41, 227 (1908).
(7) C. Candea, Bull. Sci. Ecole Polytech. Timisoara (Review) 8, 191-228 (1938); C.A. 33, 4986[4] (1939).
(8) J. Harley-Mason and F. Mann, J. Chem. Soc. 404 (1942).
(9) W. Grassman and K. v. Armin, Ann. 519, 198 (1935).
(10) A. Schönberg, R. Moubasher, and A. Mostafa, J. Chem. Soc. 176, (1948).

the 1,3-isothianaphthaquinone has been prepared and inasmuch as its properties are entirely those of a thioanhydride[11,12] it is to be expected that "para"-thiophenequinone would possess mainly the properties of an unsaturated thioanhydride, and not those of a quinone.

The key to the synthesis of quinones is the hydroxy compound. One of the striking differences between the thiophene series and the benzene series is the instability of the hydroxythiophenes and the resultant difficulty in synthesizing these compounds[13]. The few attempts at synthesizing thiophenequinones followed the successful preparation of highly substituted hydroxythiophenes which were obtained in satisfactory yields by rather specific cyclization procedures[4,5]. It seems likely that the scarcity of investigation in this field is in part due to the lack of a general method for the introduction of the hydroxyl group into the thiophene ring. In 1950 the discovery that hydroxythiophenes could be prepared by the oxidation of thienyl magnesium bromide in the presence of isopropyl magnesium bromide led to the preparation of 2-hydroxythiophene[14], 3-hydroxythiophene[14], and 5-phenyl-2-hydroxythiophene[15] for the first time.

(11) Y. Gabel and L. Shpeier, J. Gen. Chem. (USSR) 17, 2277 (1947).

(12) R. Kitamura, J. Pharm. Soc. Japan 58, 24 (1938); C.A. 32, 3759[8] (1938).

(13) Ref. 3, p. 287.

(14) C. D. Hurd and K. L. Kreuz, J. Am. Chem. Soc. 72, 5543 (1950).

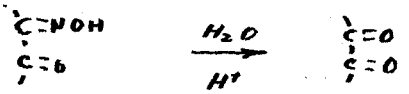
(15) W. A. Steele, "Synthesis of 5-phenyl-2-hydroxythiophene", Dissertation, Univ. of Cincinnati, 1951.

We were thus encouraged to study the question of thiophenequinone derivatives.

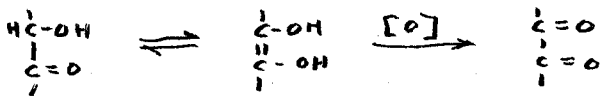
II

The first portion of this investigation was concerned with the synthesis of substituted thiophenequinones. The 1,2-dicarbonyl grouping in the alicyclic series may best be obtained in the following ways(16):

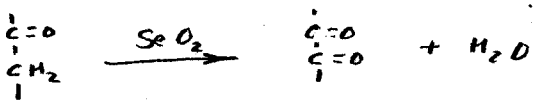
1. From the monoxime, obtained by the action of nitrous acid on the monoketone, by hydrolysis with dilute sulfuric acid, alkyl nitrites, etc.



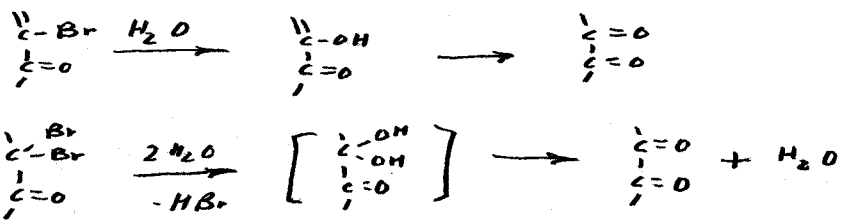
2. By the oxidation of the alpha-ketols, or ortho dihydroxy compounds.



3. By the oxidation of ketones with selenium dioxide.

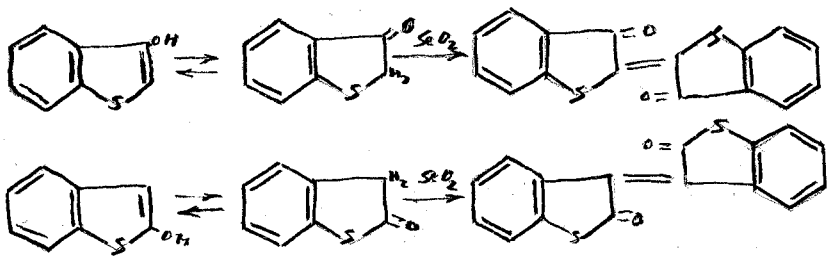


4. By the hydrolysis of bromoketones.



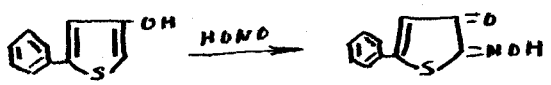
(16) E. H. Rodd, Chemistry of Carbon Compounds, Elsevier, Amsterdam, 1951, p. 719.

These methods were all considered. Chovin[17] showed that oxidation of hydroxythianaphthenes with selenium dioxide yielded the corresponding thioindigo dimer and this procedure was not further investigated. The



oxidation of dihydroxy compounds and the hydrolysis of haloketones required the synthesis of compound types not previously prepared. These were investigated and found to be too unstable to merit further study.

The most promising course of synthesis was the hydrolysis of quinone monoximes. In the course of Friedländer's work on thioindigo dyes[4] he synthesized 5-phenyl-3-hydroxythiophene, and found that when this compound was treated with nitrous acid an almost quantitative yield of 5-phenyl-2,3-thiophenequinone-2-oxime was obtained. Friedländer failed to obtain the quinone



by reduction of the oxime with zinc and acetic, or mineral, acids, and subsequent oxidation with ferric chloride.

(17) R. Chovin, Bull. Soc. Chim. France [5] 11, 91 (1944).

This procedure was successful for the preparation of the analogous thianaphthaquinone from its monoxime. The hydrolysis of the oxime is an obvious route to the quinone, but Friedlander does not mention any reactions of this type. Inasmuch as he does describe a number of other unsuccessful procedures it seems likely that he did not try hydrolysis. In any event a large number of hydrolytic and carbonyl exchange procedures for the regeneration of a carbonyl from the oxime grouping have been developed since these original experiments and this most promising course of action was extensively investigated by us for the preparation of thiophenequinones.

In the investigation of carbonyl exchange reactions it was found that refluxing the oxime in benzaldehyde led to the formation of 2,5-diphenylthiene[4,5-b]oxazole. The

literature shows that fused ring oxazoles have been produced by refluxing ortho-quinones with benzaldehyde and ammonia or ammonium acetate in acetic acid solution[18], and by treating ortho-quinone monoximes with benzaldehyde in the presence of hydrochloric acid and reducing the oxazole-N-oxides thus formed[19]. The use of

(18) S. Kreps and A. R. Day, J. Org. Chem. 6, 140 (1941).

(19) W. Dilthey and J. Friedrichsen, J. prakt. Chem. [2] 127, 292 (1930).

benzaldehyde as solvent, reactant, and reducing agent has not previously been described. The procedure was investigated with a variety of aromatic and aliphatic aldehydes. This second portion of the work was also concerned with the study of the course of this reaction with a number of acyclic, alicyclic, and aromatic diketone monoximes. Finally the reaction of benzaldehyde and the oxime was itself studied in some detail. The effect of catalysts, atmosphere, and reaction time on the yield of oxazole was investigated in order to learn more about the nature and mechanism of this reaction.

A quinone dioxime of thiophene was prepared for the first time. The third portion of this problem deals with a study of the chemistry of 5-phenyl-2,3-thiophenequinone-2,3-dioxime. The behavior of the dioxime grouping as a typical ortho-quinone dioxime was checked using reactions such as furazan formation, complex formation, and regeneration of carbonyl groups. In addition the dioxime was subjected to the hydrolytic procedures used on the monoxime, and to the benzaldehyde-oxazole reaction. Lastly it was noted that the compound, in the course of a number of its reactions, lost sulfur, and several degradation products of unusual structure were isolated and investigated.

Finally it seemed to us that this investigation would best be rounded out by the synthesis of 5-phenyl-2,3-thiophenequinone-3-oxime, and a comparison of this

compound with the "2-oxime". We were especially interested in oxime hydrolysis, dioxime formation, and oxazole formation. Nitrosation of 5-phenyl-2-hydroxythiophene, obtained by the oxidation of phenylthienyl lithium, was the route taken to this compound, but we were unable to isolate more than traces of material which might have been the desired compound, and could not carry out the desired experiments.

DISCUSSION OF RESULTS

I. Attempted Quinone Synthesis

Friedländer's[4] novel and ingenious route to 5-phenyl-3-hydroxythiophene may be summarized as follows:

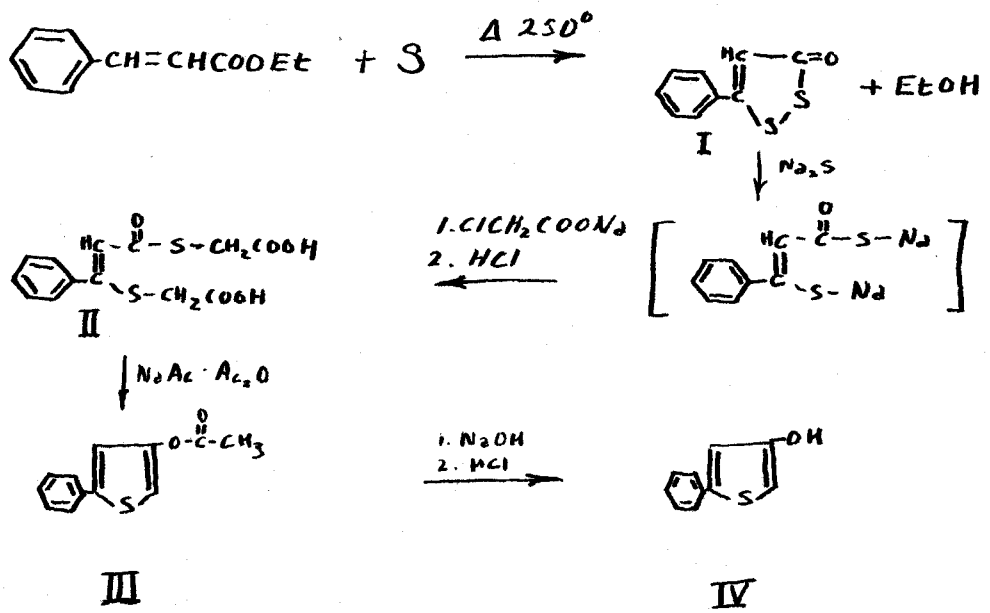


Fig. 1

The directions given by Friedländer are vague and incomplete and it was found necessary to develop a procedure, and sometimes modify the directions, for each step of the synthesis. The 5-phenyl-1,2-dithiacyclopentene-3-one (I) was first prepared by Baumann and Fromm[20] from sulfur and ethyl cinnamate. The unpleasant use of large quantities of boiling fifty per cent acetic acid for the

(20) E. Baumann and R. Fromm, Ber. 30, 111 (1897).

isolation of the cyclic disulfide from the tars and unreacted sulfur was avoided by an extraction procedure using ethanol and acetone. In the conversion of (I) to 4-keto-6-phenyl-3,7-dithia-5-cis-nonenedioic acid (II) the dithione was added to molten sodium sulfide nonahydrate; this cleaved disulfide solution (IIa) was added to a solution of sodium chloroacetate, unreacted dithione precipitated and was filtered from the solution. The filtrate was acidified and an oil formed which crystallized after standing for several days. In several runs the unreacted dithione did not precipitate and acidification of the solution gave a copious precipitate of sulfur from which no products could be isolated. This was found to occur when the ratio of sodium sulfide to dithione was too high. On the other hand when a large excess of the dithione was dissolved in the molten inorganic salt the unreacted material did precipitate and could be used again without purification to give a high overall conversion to the diacid. Partial hydrolysis of the chloroacetic acid during the preparation of its sodium salt was a troublesome side reaction which could be largely obviated by addition of solid sodium carbonate to a concentrated aqueous solution of the acid at 0°. Some hydrolysis always occurred as evidenced by the acidic reaction of the solution after the stoichiometric amount of base had been added.

The diacid (II) was converted to 5-phenyl-3-acetoxythiophene (III) by heating with acetic anhydride and sodium acetate. The addition of ice water to the reaction mixture caused the ester to separate as a dark, crystalline product. The ester was best isolated in pure form by extracting the reaction product with ligroin at room temperature and allowing the ligroin to evaporate. The 5-phenyl-3-hydroxythiophene (IV) was obtained by saponification of the ester. A solution of III in alcohol was warmed with the stoichiometric amount of five per cent sodium hydroxide solution. Completeness of saponification was tested for by adding one drop of the reaction mixture to several milliliters of water. The absence of turbidity indicated that the water-insoluble ester had been completely hydrolyzed. Hydrolysis took only a few minutes; prolonged heating caused dimerization to V.

5-Phenyl-3-hydroxythiophene is a colorless solid that melts at 75-76°. When the compound or its solutions are exposed to oxygen the thienol gradually decomposes and the red dimer 5,5'-diphenyl-[$\Delta^{2,2'(3H,3'H)}$-bithiophene]-3,3'-dione, (V), is formed. The hydroxythiophene appears

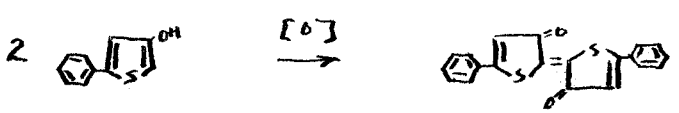


Fig. Ia

to give a red coloration with ferric chloride but this

is obscured by precipitation of the dimer which is also red. When a 1 per cent solution in 33 per cent ethanol was treated with 10 per cent ferric chloride a red coloration and a red precipitate formed. A 1 per cent solution in absolute ethanol gave a red-blue color; upon dilution with water a precipitate formed. A one and a half per cent solution of thienol in warm water yielded an immediate red precipitate, while a suspension of 0.15 g. of the hydroxythiophene in one ml. of cold water was not affected by ferric chloride.

5-Phenyl-3-methoxythiophene was produced in 60 per cent yield by treating a solution of the hydroxythiophene in base with dimethyl sulfate. This compound was prepared by Friedländer but was not investigated by him. The ether is a colorless liquid which boils at 141-142° (3 mm.). It appeared to gradually decompose on standing; however, distillation of a dark red sample which had discolored over a period of several months yielded most of the original material in colorless form. The ether gave a negative ferric chloride test and was completely insoluble in dilute base.

When treated with bromine, 5-phenyl-3-hydroxythiophene formed a tribromo derivative as was earlier reported[4]. We failed to prepare a semicarbazone by the use of standard procedures.

The hydroxythiophenes as a class are unstable[21]. They are readily oxidized and their decomposition may be due to oxidation and polymerization[15]. Functional groups which lower the electron density of the ring stabilize the molecule. Both 5-phenyl-2-hydroxythiophene and 5-phenyl-3-hydroxythiophene are more stable than the parent 2- and 3- hydroxythiophenes; but, whereas the 2-hydroxythiophene is more stable than its 3- isomer, the 3-hydroxy-phenylthiophene is more stable than the 2-hydroxy-phenylthiophene. For example, dilute alcoholic solutions of 2-hydroxy-phenylthiophene prepared for ultra-violet analysis rapidly became colored and deposited dimer, while similar solutions of 3-hydroxy-phenylthiophene remained colorless for over 24 hours. In the attempted preparation of a semicarbazone, pure 3-hydroxy-phenylthiophene was refluxed briefly in aqueous alcohol and was reobtained on cooling as light brown needles, melting point 75-76°. Furthermore the pure 3- isomer could be isolated from a mixture of tar, dimer and compound by extracting with petroleum ether (b.p. 40-60°) in a Soxhlet apparatus. This hydroxy compound was carried over and concentrated in the solvent flask and was recovered as pink, almost colorless crystals. However when the same procedure was applied to the 2- isomer the hydroxy compound

(21) H. D. Hartough, The Chemistry of Heterocyclic Compounds, Thiophene and its Derivatives, Interscience, New York, 1952, pp. 288-293.

was removed from the dimer and tars and concentrated in the flask but it decomposed during the extraction to a dark tar.

The greater stability of 5-phenyl-3-hydroxythiophene can be explained if we assume that the oxidation proceeds by a series of steps none of which involves transfer of more than one electron[22]. The thienol will, on loss of an electron from sulfur, for example, yield a radical with various possibilities of resonance stabilization. The further loss of a proton from the charged fragment will give a new species which may eventually lead to the dimeric product through two more one electron transfers.

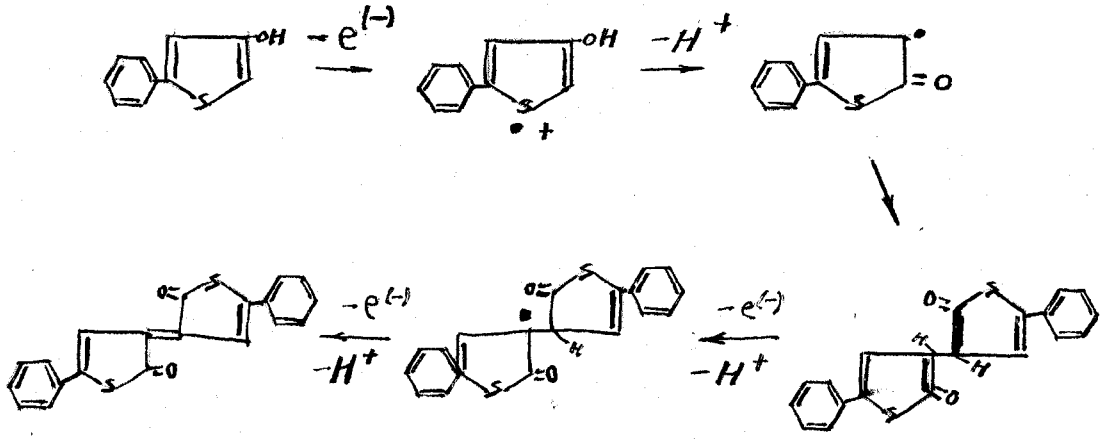


Fig. 2

The necessity of extracting an electron from the ring for oxidative decomposition is in agreement with the statement previously made that functional groups which lower the

(22) L. Michaelis, Trans. Electrochem. Soc. 71, 107 (1937); cf. also L. Michaelis and E. S. Fletcher, J. Am. Chem. Soc. 59, 1246 (1937); R. B. Woodward and P. Eastman, ibid., 68, 2229 (1946).

electron density of the ring stabilize the molecule. The intermediates involved in the oxidation of 5-phenyl-2-hydroxythiophene are stabilized by resonance forms involving quinonoid structures for the phenyl group which cannot contribute to the corresponding intermediates from 5-phenyl-3-hydroxythiophene.

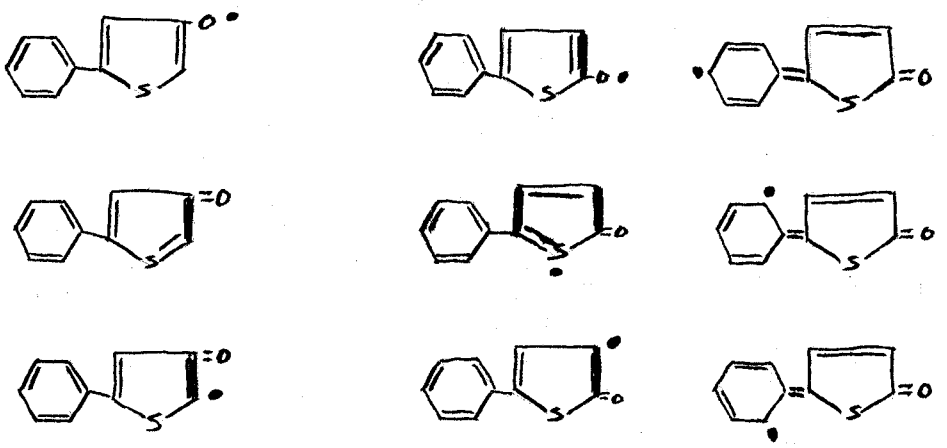


Fig. 3

Inasmuch as hyperconjugation structures (Fig. 4) of 5-methyl-2-hydroxythiophene should contribute little compared to the quinonoid structures[23] illustrated in Fig. 3, the resonance stabilization of the oxidation intermediates should be about the same as 5-phenyl-3-hydroxythiophene. This compound must be heated with ferric chloride to form the indigoid derivative[24].

Fig. 4

(23) C. Deasy, Chem. Revs. 36, 145 (1945).
(24) W. Steinkopf and A. Thormann, Ann. 540, 1 (1939).

Physical evidence indicates that 5-phenyl-3-hydroxythiophene exists in both keto and enol forms, although

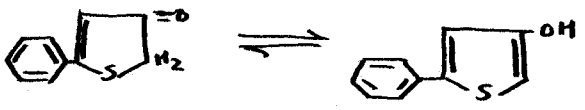


Fig. 5

the enol form predominates. The ultra-violet spectra of the 3-thienol and its ether in ethanol and of the thienol in chloroform are given in Fig. 6. The spectra of the two alcohol solutions are almost identical, while there is a shift to higher wave lengths in the spectrum of the thienol in chloroform. This suggests that the 5-phenyl-3-hydroxythiophene exists to a very great extent as the enol in alcohol, but that in chloroform, the keto form becomes of greater importance. The infra-red spectrum (Fig. 7) of the hydroxythiophene in chloroform shows absorption in the hydroxyl region, 8.03μ, and in the carbonyl region, 5.96μ, while in the ether spectrum there is no absorption in the carbonyl region, and the appearance of strong bands at 7.20, 9.62, and 9.67 microns is indicative of an aromatic ether.

5-Phenyl-3-hydroxythiophene IV was the basic compound through which we sought to prepare a thiophene quinone. The synthesis of thianaphthaquinone was achieved

Figure 6
Ultraviolet Spectra

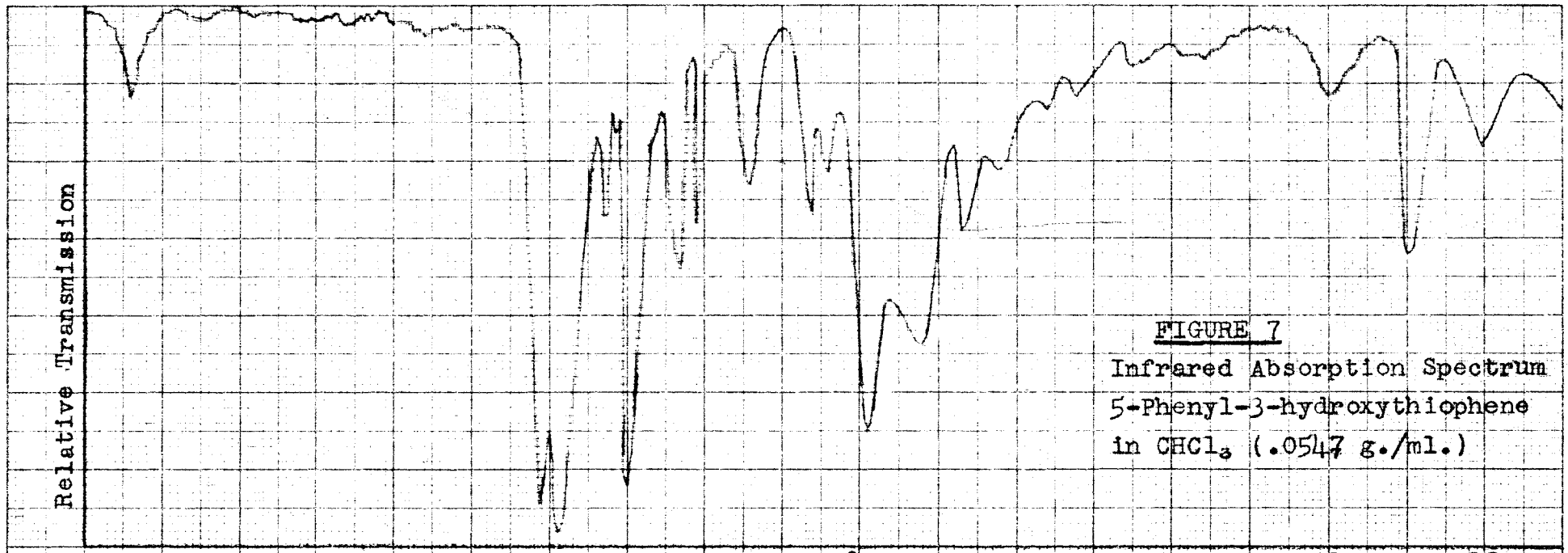


FIGURE 7

Infrared Absorption Spectrum
5-Phenyl-3-hydroxythiophene
in $CHCl_3$ (.0547 g./ml.)

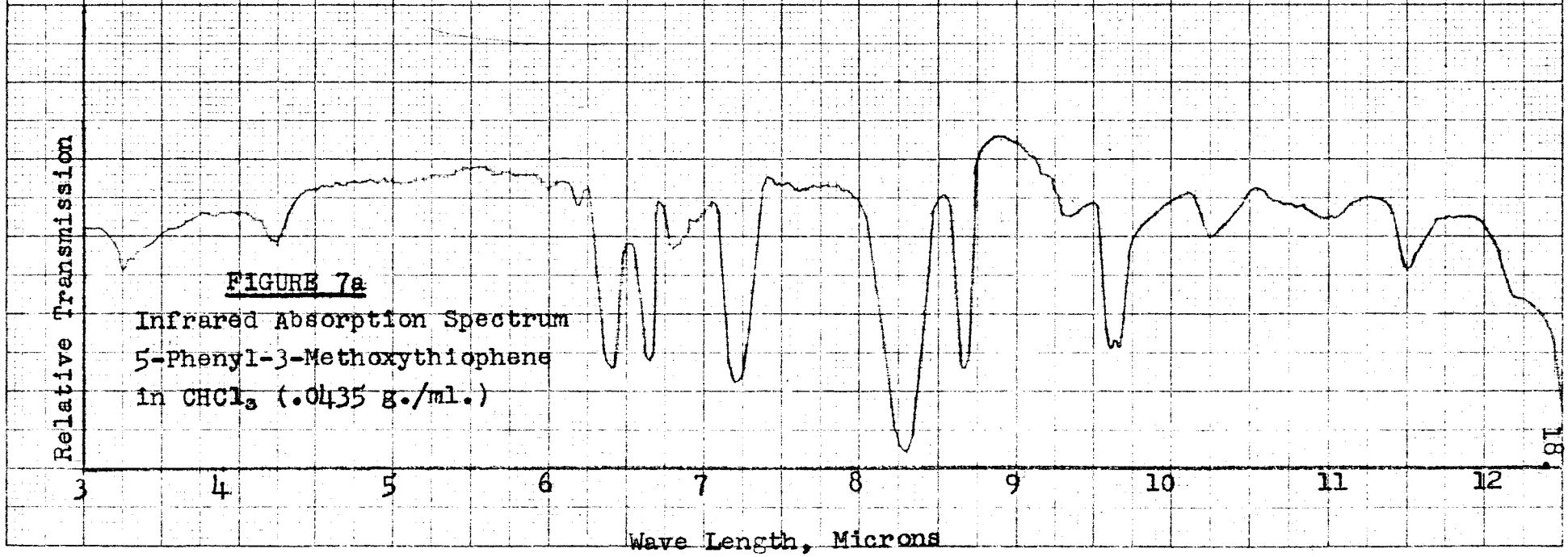


FIGURE 7a

Infrared Absorption Spectrum
5-Phenyl-3-Methoxythiophene
in $CHCl_3$ (.0435 g./ml.)

by condensing the hydroxy compound with nitroso-N,N-dimethylaniline, and hydrolyzing the resulting anil with acid(25).

Fig. 9

We attempted to condense the 5-phenyl-3-hydroxythiophene with para-nitroso-N,N-dimethylaniline in order to obtain the analogous anil, and we hoped to be able to hydrolyze this compound. The condensation did not occur without a basic catalyst. When a solution of thienol and the nitroso compound in ethanol was warmed with five milliliters of a 33 per cent solution of benzyl trimethylammonium hydroxide in methanol there was formed and isolated .56 g. of a dark red powder which gradually blackened and decomposed on standing. This route was not further investigated.

The preparation of an ortho-quinone by hydrolysis of the bromo ketone was considered. Friedländer had obtained a tribromo derivative of 5-phenyl-3-hydroxythiophene when the compound was treated with bromine directly and he unsuccessfully attempted to form the anil of this compound by condensation with aniline.

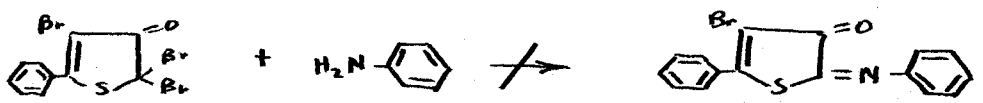


Fig. 10

(25) R. Pummerer, Ber. 43, 1370 (1910).

We investigated the bromination of 5-phenyl-3-methoxythiophene and 5-phenyl-3-hydroxythiophene with N-bromosuccinimide. It was our intention to prepare and hydrolyze a monobromo compound. The bromination of these compounds with molar quantities of N-bromosuccinimide went readily in the cold to give products which were too unstable to work with. The bromo derivative of the methyl ether was the more stable; it was isolated, and crystallized from petroleum ether as a colorless solid, m.p. 45-47°. The material, even when sealed under nitrogen, slowly decomposed at room temperature, liberated hydrogen bromide, and yielded a dark purple solid in a few hours. The product of bromination of the hydroxythiophene was even less stable. The bromination was carried out at 0°. At the conclusion of the reaction the carbon tetrachloride was removed by distillation at reduced pressure. When the product was flushed with nitrogen to maintain an inert atmosphere, hydrogen bromide was swept from the flask in considerable amount. When this ceased, a black, tarry reaction product remained from which there was isolated 5,5'-diphenyl-[$\Delta^{2,2'(3H,3'H)}$-bithiophene]-3,3-dione.

5-Phenyl-3-hydroxythiophene can be nitrosated to give a quantitative yield of 5-phenyl-2,3-thiophenequinone-2-oxime. This compound was the center of our investigation

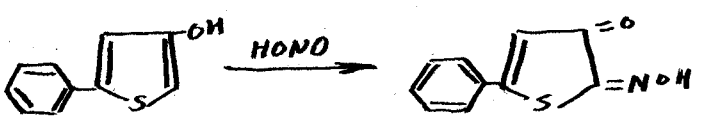


Fig. 11

into the quinonoid nature of thiophene, and was extensively studied as the subject of hydrolytic and carbonyl exchange procedures for the preparation of thiophenequinones. The oxime was generally prepared directly from the 3-acetoxy-5-phenylthiophene without isolating the hydroxy compound. Sodium nitrite was added to the solution of the ester as it was being hydrolyzed, and the reaction mixture was poured into excess iced dilute hydrochloric acid. The yellow precipitate was recrystallized several times from ethanol and with the aid of Darco treatment was obtained as yellow-orange needles with a melting point of 214-216° when heated at the rate of 2° per minute. The overall yield from ethyl cinnamate was thirteen per cent. The quinone monoxime was completely stable in air and gave a negative ferric chloride test. The compound has a solubility of 0.35 g. per liter in water at 100°. It is acidic in nature and dissolves in base although the alkali salt is only moderately soluble. The oxime complexes inorganic cations. A series of spot tests was made with aqueous solutions of a large number of inorganic salts at a concentration of 0. 1 mg. per ml. A 0.25 per cent solution of the oxime in ethanol gave yellow precipitates with Ag^{+}, Hg_2^{++}, and Pb^{++}. The oxime forms insoluble salts with many other metals at less dilute concentrations.

Esterification of the oxime can be accomplished

with mineral acids and glacial acetic acid, or with base and acetic anhydride. The acetate ester is a yellow solid melting at 149-150°. When the ester was refluxed with dilute caustic soda for thirty seconds it was saponified and the oxime was reobtained. We prepared a dioxime, colorless needles, m.p. 126.4-126.8° and a 2,4-dinitrophenylhydrazone which was obtained as dark brown needles. The latter compound melted at 232.0-232.5° when heated at the rate of 2.5 degrees per minute, or 226.0-227.0° when heated at the rate of 1.0 degree per minute. We did not succeed in preparing a semicarbazone of either the oxime, or the oxime acetate by means of standard procedures for preparing these derivatives. Fused thiophene oxazoles were obtained by refluxing the oxime with various aromatic aldehydes, but not with aliphatic aldehydes. The same oxazoles could not be made from the oxime by procedures that worked for other alpha-diketonemonoximes. This will be discussed in greater length in the next section.

These reactions may be summed up:

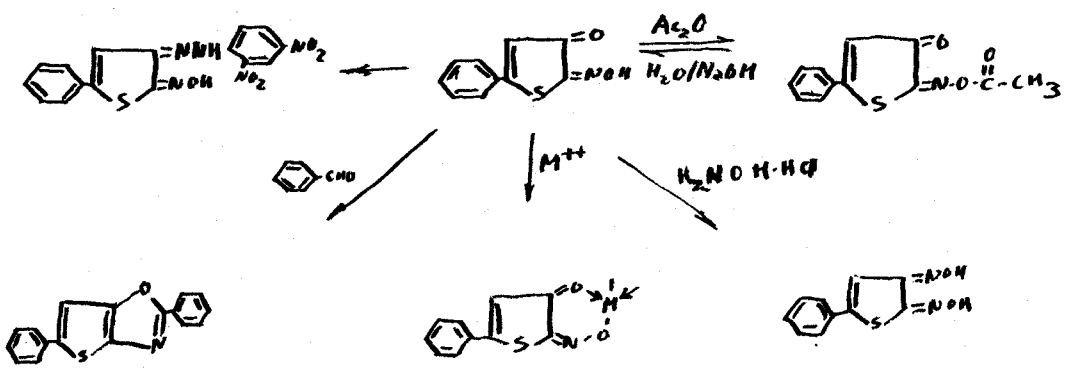


Fig. 12

It can immediately be seen from the preceeding chart that in no reaction was there a separation of the oxime nitrogen from the thiophene nucleus. The reactions which were tried and studied in order to accomplish this may be outlined in the following manner:

a. Solvent and salt action

b. Strong mineral acids

c. Carbonyl exchange

d. Mineral acids and carbonyl compounds in combination

e. Nitrous acid and nitrous acid derivatives.

f. Oxidative procedures.

Preliminary experiments showed that the oxime is stable and is not destroyed by water or water-acetic acid solutions, or by salt action, during the course of attempted hydrolysis. Refluxing the oxime in water for six days resulted in a 96 per cent recovery of the starting material; the action of 8 per cent acetic acid for one hour was without effect; and the compound was recovered unchanged when heated with 4 per cent sodium sulfite solution(26).

Cleavage was attempted with strong mineral acids without the aid of auxiliary reagents. The oxime was heated with hydrochloric, sulfuric, or phosphoric acid for various lengths of time. Inasmuch as quinones may very

(26) L. Kletz and A. Lapworth, J. Chem. Soc.,1254 (1915).

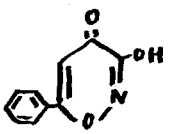
frequently be isolated in good purity by steam distillation (e.g. thianaphthaquinone)[27], and inasmuch as the conditions of hydrolysis were usually more severe than those of steam distillation, the reaction was generally worked up in this manner. The reaction product was first steam-distilled, the residue liquid was filtered, cooled, re-filtered, and extracted with ether. Typical runs are described in the experimental section. A degradation of the oxime did occur and the extent of this degradation was most obviously dependent on the length of time the reaction was allowed to run. The dependence on concentration and temperature was less clearly observed. As the reaction time increased the amount of undissolved material, and hence unreacted oxime decreased. In no reaction was there any material other than acetophenone and sulfur isolated from the distillate.

Two reactions are worthy of comment. In one reaction, the oxime in ethanol solution was added dropwise to 200 ml. of sulfuric acid (1:1) through which superheated steam was being passed. It was felt that this would be the best procedure for the isolation of a steam volatile, but acid sensitive, quinone. The distillate contained only acetophenone in 12 per cent yield. In the other experiment a solution of 2 g. of oxime in 20 ml. of ortho-dichlorbenzene

(27) W. T. Summerford and D. N. Dalton, J. Am. Chem. Soc. 66, 1330 (1944).

was refluxed with 20 ml. of concentrated hydrochloric acid. In this case it was hoped that the organic layer would dissolve any quinone formed and thus prevent acid decomposition. It was found that the ortho-dichlorobenzene had no effect on the course of the reaction, the decomposition of the oxime proceeded as it did in concentrated hydrochloric acid alone.

In all the reactions which were run for a sufficient length of time to give an isolable quantity of degradation product there was obtained a colorless compound which, when recrystallized from benzene, had a melting point of 156-157°. The compound was not benzoylpyruvic acid (melting point 156-158°). On the basis of elemental analysis and a study of its properties the compound was assigned the structure of 3-hydroxy-6-phenylexazine-4-one. When the reaction ran until the oxime was completely decomposed about a 50 per cent yield of the oxazinone was isolated in each case. In the distillate there was isolated acetophenone which was identified by means of the melting point of its 2,4-dinitrophenylhydrazone and mixed melting point with an authentic sample.*



3-hydroxy-6-phenyl-oxazine-4-one

Fig. 13

More frequently quinones are regenerated from their monoximes by the use of a carbonyl compound in combination

* A discussion of the oxazine structure is given on page 28.

with a mineral acid, rather than by the use of acids alone[28,29]. Lapworth[30] showed that the cleavage reaction of oximes in concentrated hydrochloric acid is a reversible one. In fact with an excess of hydroxylamine the oxime could often be formed quite readily from the parent carbonyl compound in concentrated acid solutions. With the less stable oximes the equilibrium is such that reaction with acids alone is sufficient to generate the ketone; however, when the position of equilibrium is less favorable, hydroxylamine must be removed from the product side of the reaction.

The hydroxylamine may be destroyed by oxidation or reduction, or tied up in another carbonyl compound. Lapworth found that he could prepare camphorquinone from the monoxime only by the use of formaldehyde, or benzaldehyde, and concentrated hydrochloric acid. The reaction would not occur without the carbonyl compound. The oxidation procedures are more severe but have been used successfully for the preparation of stable para-benzoquinones.

Cleavage of the oxime was attempted with acetone, formaldehyde, and benzaldehyde employing various concentrations of hydrochloric and sulfuric acids. The oxime was either recovered unreacted, e.g. when the reaction time was short or when acetone was present in sufficient

(28) C-L. Tseng, M. Hu, and E. Chu, J. Chinese Chem. Soc. 247 (1934); C.A. 28, 3730[8] (1934).

(29) W. T. Sumerford and W. Hartung, J. Am. Pharm. Assoc. 29, 65 (1940).

(30) A. Lapworth, J. Chem. Soc. 91, 1137 (1907).

quantity to maintain a low reflux temperature, or was decomposed by the acid in the previously discussed manner. The carbonyl compounds did not enhance quinone formation but were a complicating factor in determining the nature and the course of the reaction. They were either acted upon themselves by the acid, and for the most part yielded tars, or they reacted with the unreacted oxime molecule, or with the oxime degradation products. In general, the use of acetone or formaldehyde led to tars. The use of benzaldehyde gave more varied results. When a dilute solution of the oxime, concentrated hydrochloric acid, and benzaldehyde in isopropyl alcohol was refluxed for 4 hours there was recovered 93 per cent of the starting material. When the oxime was refluxed without other solvent using a twenty to one ratio of benzaldehyde to concentrated hydrochloric acid, a 23 per cent yield of 2,5-diphenyl-thieno[4,5-b]oxazole was isolated, when the ratio was one to one the oxime decomposed, the benzaldehyde reacted with the product of decomposition, and a tetronic acid (<u>vide infra</u>) was formed:

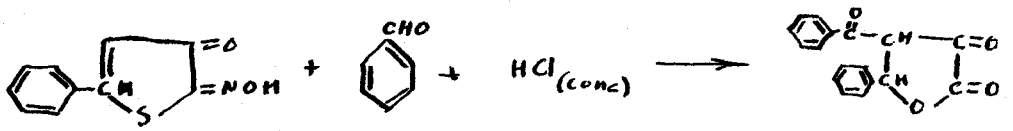


Fig. 14

The chief degradation product of the oxime during acid hydrolysis is a colorless solid that melts at 157-158°. Benzoylpyruvic acid also melts at this temperature and would appear to be an obvious degradation product of the oxime:

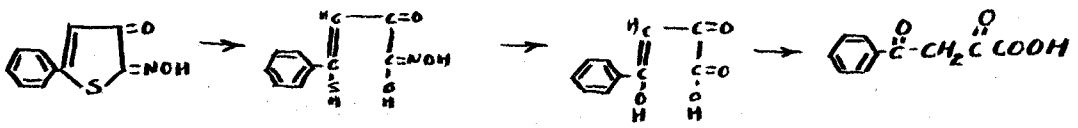


Fig. 15

We were surprized, therefore, when mixed melting points of the two compounds continually gave sizable depressions. In addition the degradation product formed when the oxime was decomposed in the presence of benzaldehyde was identical with the tetronic acid formed by the condensation of benzaldehyde and benzoylpyruvic acid in the presence of hydrochloric acid.

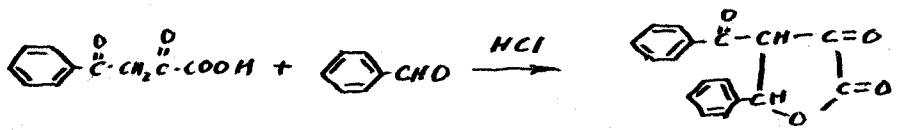


Fig. 16

The identity of the tetronic acid was proven by mixed melting point determinations, and by the preparation and determination of the melting point of the known anil.

Furthermore acetophenone was found in the acid decomposition of both the oxime and the benzoylpyruvic acid, and identified as the 2,4-dinitrophenylhydrazone.

We were certain that the degradation product and benzoylpyruvic acid were different compounds when we prepared an anil of the oxazine and found that it melted at 177-178°, 10 degrees higher than the similarly prepared aniline derivative of benzoylpyruvic acid. In addition the mixed melting points of the two anils showed a thirty five degree depression. The compound is weakly acidic, and is highly soluble in ethanol, moderately soluble in water and benzene. Elemental analysis indicated that the empirical formula was $C_{10}H_7O_3N$. Perhaps the most important clue we have to the structure of this compound is the structure of its precursor and the course of degradation. We can postulate an oxazine structure and explain its formation, as well as that of the acetophenone and the tetronic acid, if we assume that the oxime first hydrolyzes to a hydroxamic acid, part of which cyclizes to an oxazine derivative while the remainder is further hydrolyzed and forms benzoylpyruvic acid. Benzoylpyruvic acid is not stable in hot acid solution and either decomposes to acetophenone, carbon monoxide, and carbon dioxide, or condenses with benzaldehyde to form the tetronic acid, depending on the conditions of the reaction.

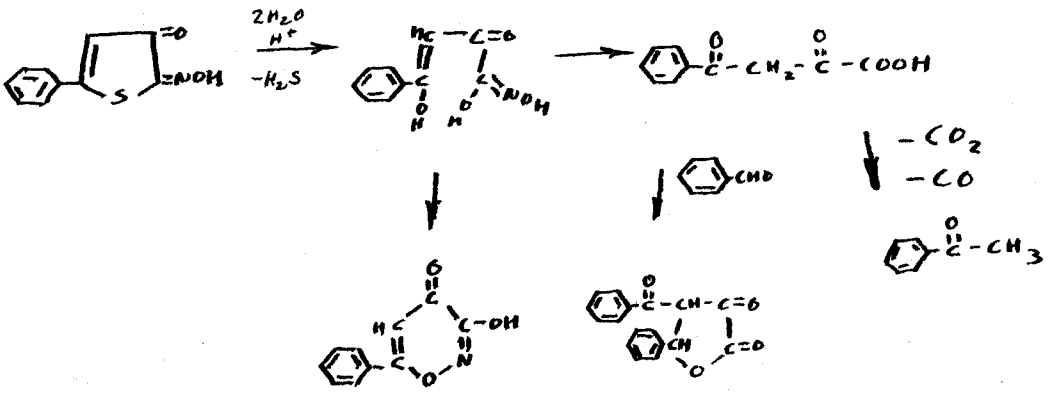


Fig. 17

The use of nitrous acid in oxime cleavage reactions is extensively described in the literature[31,32,33]. In one procedure nitrous acid is generated in the presence of hydrochloric acid, the hydrochloric acid causes a partial hydrolysis and a reaction of nitrous acid with the hydroxylamine formed causes the equilibrium to shift[34]. Another procedure using glacial acetic acid and sodium nitrite is postulated to go through a different mechanism[34].

We were unable to split the oxime linkage using nitrous acid and hydrochloric acid in combination on aqueous-alcoholic solutions of the oxime. In one experiment nitrogen oxide gases evolved from the addition of hydro-

(31) L. Claisen and O. Manasse, Ber. 22, 530 (1889).

(32) M. L. Wolfrom, L. W. Georges, and S. Soltzberg, J. Am. Chem. Soc. 56, 1744 (1934).

(33) St. Goldschmidt and W. L. C. Veer, Rec. trav. chim. 65, 796 (1946).

(34) St. Goldschmidt and W. L. C. Veer, Rec. trav. chim. 66, 258 (1947).

chloric acid to solid sodium nitrite were passed into a refluxing solution of oxime in ethanol. Nine normal hydrochloric acid was added and the solution was refluxed for 23 minutes. Upon cooling a 67 per cent recovery of the oxime occurred. In another experiment oxime and sodium nitrite were refluxed for three hours in methanol that was saturated with hydrogen chloride. Ninety seven per cent of the oxime was recovered.

A series of reactions was conducted in which sodium nitrite was added to a solution of the oxime in glacial acetic acid and the length of reflux time was varied. In the first reaction sodium nitrite was added to the solution at room temperature. Upon diluting the product with water a small quantity of red solid was thrown down which had a melting point above 260°. This material was not again encountered in similar, subsequent reactions. After the removal of the red solid, a yellow solid, which had a melting point of 149-150°, slowly precipitated in the body of the solution. This compound was the oxime acetate. In the second reaction sodium nitrite was added without further heating to the oxime-acetic acid solution which had been heated. The cooled solution was eventually diluted with water and a 45 per cent yield of the same ester was obtained. The third reaction was refluxed for thirty minutes and while hot diluted with water. There was recovered 40 per cent of

unreacted oxime, the rest of the material being a tarry decomposition product. The same procedure carried out for three hours with periodic additions of sodium nitrite led to complete decomposition.

In a slightly different reaction the sodium nitrite was added to a solution of oxime in aqueous acetic acid. This was refluxed for thirty minutes, water was added, and upon cooling a 70 per cent yield of pure oxime precipitated. These reactions may be interpreted in the following way. In glacial acetic acid the oxime was esterified and upon prolonged heating with nitrous acid deep-seated decomposition of the thiophene compound took place, possibly through the intermediacy of the quinone. When water was added to the hot solution of the ester in the hope of obtaining crystals on cooling hydrolysis occurred and the oxime was isolated instead of the ester. The esters of oximes are known to be hydrolyzed to the oxime by aqueous alkalis and acids with great ease[35]. The addition of water to the cold solutions did not cause hydrolysis of the ester and this compound was obtained.

The ester was a yellow solid which was slightly soluble in cold water, and moderately soluble in hot water. The same ester was also obtained by treating the sodium

(35) N. V. Sidgwick, Organic Chemistry of Nitrogen, Clarendon Press, Oxford, 1937, p. 173.

salt of the oxime with acetic anhydride, and a mixed melting point of the two showed no depression. When the ester was refluxed for thirty seconds in 6 N sodium hydroxide solution the oxime was reobtained.

We attempted to cleave the oxime using a nitrite ester, isoamyl nitrite. Concentrated hydrochloric acid was added to a solution of oxime and isoamyl nitrite in aqueous ethanol and this solution was refluxed for an hour. There was isolated 90 per cent of the oxime unreacted. The addition of 2,4-dinitrophenylhydrazine to the oxime-freed filtrate gave a large quantity of a red precipitate, melting point 122-123°. We expected this to be the 2,4-dinitrophenylhydrazine of isoamylaldehyde (melting point 123°) but the two compounds gave a sizable depression in melting point on admixture. Since the compound failed to give an elemental test for sulfur, and was much too weighty to be a derivative of the unrecovered thiophene compound, it was not further investigated.

Hershberg[36], and Mattox and Kendell[37] have recently described procedures for using pyruvic acid as an exchange reagent in cleavage reactions, although Sidgwick[38] a number of years ago recognized that

(36) E. B. Hershberg, J. Org. Chem. 13, 542 (1948).

(37) V. R. Mattox and E. C. Kendell, J. Am. Chem. Soc. 70, 882 (1948).

(38) Sidgwick, "Organic Chemistry of Nitrogen, Clarendon Press, Oxford, 1910, p. 247.

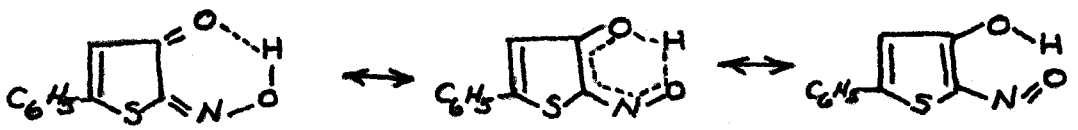
pyruvic acid in aqueous medium was a particularly effective exchange ketone. The oxime however was found to be completely resistant to the action of pyruvic acid. A solution of oxime in acetic acid and water containing equimolar amounts of pyruvic acid and sodium acetate was refluxed for three hours. Upon cooling 85 per cent of the oxime was recovered. Another solution of the oxime in pyruvic acid, benzaldehyde, and concentrated hydrochloric acid was shaken mechanically overnight. Most of the oxime was recovered unchanged. The driving of cleavage reactions to completion by the destruction of hydroxylamine has been done very successfully using oxidizing agents such as sulfuric acid and potassium dichromate, or 30 per cent hydrogen peroxide[39,40]. These reagents work well for the relatively stable alkyl para-benzoquinones but would readily destroy the thiophene nucleus. Summerford and Dalton[27] have developed a procedure using cuprous oxide as the oxidizing agent and have found it superior to the methods using much stronger oxidizing agents. Their method consists of either shaking or refluxing the oxime in a mixture of methyl cellusolve, hydrochloric acid (1:1), cuprous oxide, and acetone, and distilling the product from the mixture with steam. Both procedures were followed

(39) H. Henrich, S. Taubert, and T. Birkner, Ber. 45, 303 (1912).

(40) P. Karrer and O. Hoffmann, Helv. Chim. Acta 22, 654 (1939).

exactly with 5-phenyl-2,3-thiophenequinone-2-oxime but neither method yielded any product.

The resistance to cleavage and the retention of the oxime grouping under the most severe conditions indicates that 5-phenyl-2,3-thiophenequinone-2-oxime possesses remarkable stability for a molecule of its type. One possible explanation for this is that the acid hydrogen in the oxime structure is positioned in such a manner as to vastly increase the resonance stabilization of the molecule. If this picture



is valid, then we have a bicyclic structure possessing some degree of aromatic character in the ring fused to the thiophene nucleus. This increase in resonance energy would considerably enhance the stability of the molecule.

The objection has been raised with other molecules of this type that the two oxygens are too far apart to permit anything more than hydrogen bonding to one of the oxygens. The O-H....O bond is usually found to be about 2.5 - 2.8 A in length, which is considerably more than twice the ordinary oxygen-hydrogen distance of 0.96 A[41]. However the possibility cannot be ruled out that the hydrogen may be centered in some bonds, and not in others[41]. The

(41) G. W. Wheland, The Theory of Resonance, John Wiley and Sons, New York, 1949, pp. 50, 51.

bond distances in the thiophene ring are somewhat smaller than in the benzene ring, and a calculation using the best available values for bond angles and bond lengths puts the hydrogen 1.04Å from each oxygen at an angle of 105°.

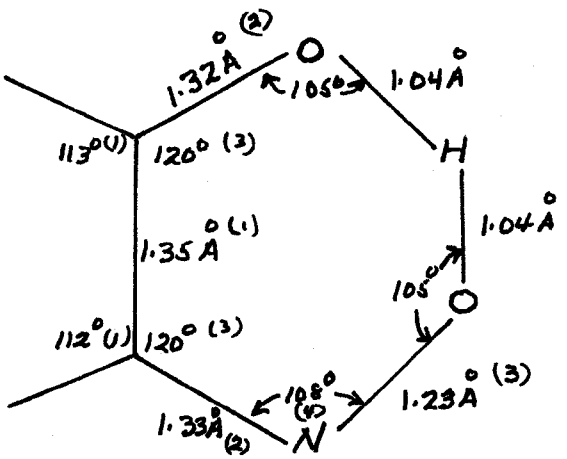


FIG. 17

(1) Angles = 112, 113°
thiophene -C-C = 1.35 Å (42)

(2) C-O based on partial double, single bond character. Dimeric formic acid C-O = 1.29 Å.

C-N based on partial double single bond character. Melamine C-N = 1.33 Å (41)

(3) N-O based on partial double, single bond character (43)

(4) Angle C-N-O based on ammonia 108°

(5) Angles O-C-C, N-C-C assumed to be 120°

(42) R. Schoemaker and L. Pauling, J. Am. Chem. Soc. 61, 1769 (1939).

(43) H. J. Bernstein, J. Chem. Phys. 15, 284 (1947).

II. The Oxazole Reaction

In the attempted synthesis of the quinone from 5-phenyl-2,3-thiophenequinone-2-oxime a carbonyl exchange type reaction was tried. The oxime was refluxed in benzaldehyde for a period of 24 hours in the hope that the benzaldehyde would remove the N-O-H group from the thiophene nucleus. The solution was cooled and, after re-

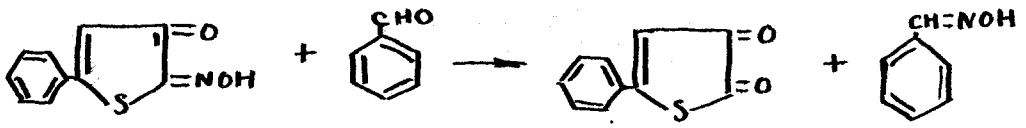


Fig. 20

crystallization from dioxane and then from ethanol, a colorless, neutral compound was obtained that had a melting point of 176.2-176.8°. The compound was not 5-phenyl-2,3-thiophenequinone but 2,5-diphenylthiene[4,5-b] oxazole.

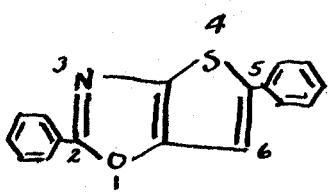


Fig. 21

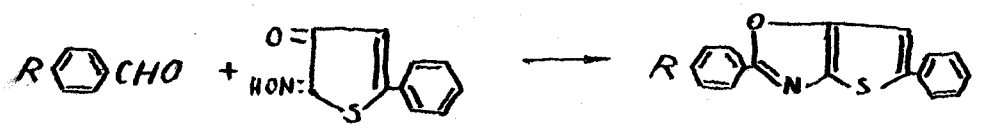
This reaction was called the oxazole reaction. When the oxime was refluxed in benzaldehyde for eighteen hours a 50 per cent yield of the oxazole was isolated by removal of the benzaldehyde at reduced pressure and crystallization

of the residue. When the oxime was refluxed in a 33 per cent solution of benzaldehyde in xylene there was isolated under the same conditions a 37 per cent yield of oxazole. However when 0.15 g. of oxime was refluxed in 10 per cent benzaldehyde in benzene for 15 hours there was recovered 0.13 g. of unreacted oxime. The temperature and the concentration of benzaldehyde are therefore important factors in the oxazole reaction. The latter factor was kept constant in the course of investigating this reaction by using excess benzaldehyde as solvent. This permitted the use of reaction temperatures up to 180° and also had the advantage of giving the best yields. The thienooxazoles were colorless or very lightly tinted compounds. They were insoluble in water, difficultly soluble in alcohol, but readily soluble in chloroform and carbon tetrachloride. Because of the unusual structure of these compounds we considered the possibility of screening them for pharmacological activity. The solubility in 10 per cent acetone-water of 2,5-diphenylthieno[4,5-b]oxazole was found to be 0.033 g. per liter and the entire class of compounds was considered too insoluble for this purpose. When exposed to ultra-violet light the thienooxazoles exhibited a purple-blue fluorescence. They were effectively separated from tarry impurities by elution from an alumina column with carbon tetrachloride. The compounds were readily followed through the column by means of their fluorescence under ultra-violet light and this made the separation from

reaction tars and the purification extremely easy. The oxazoles did not form an addition compound with 2,4,7-trinitrofluorinone[44].

The structure of this compound was assigned principally by a consideration of the reactants and the empirical formulae. The carbon, hydrogen and nitrogen values checked well (see experimental section) for $C_{17}H_{11}ONS$. We had difficulty in getting a good analysis for sulfur which should be 11.6 per cent of the molecule by weight. One laboratory found values of 8.7 and 8.9 per cent. A sample was sent to another laboratory and they returned a value of 12.2 per cent. These analyses in any event permit only one sulfur atom in the molecule. That the material fluoresces is consistent with the structure which possesses a long conjugated chain[45].

The oxime was heated with a number of aromatic aldehydes and one aliphatic aldehyde. Anisaldehyde gave



R = H, CH_3, CH_3O, $(CH_3)_2CH$

Fig. 23

an 18 per cent yield after three hours, and a 24 per cent

(44) M. Orchin and E. O. Woolfolk, J. Am. Chem. Soc. 68, 1727 (1946).

(45) J. Weiss, Nature 145, 744 (1940).

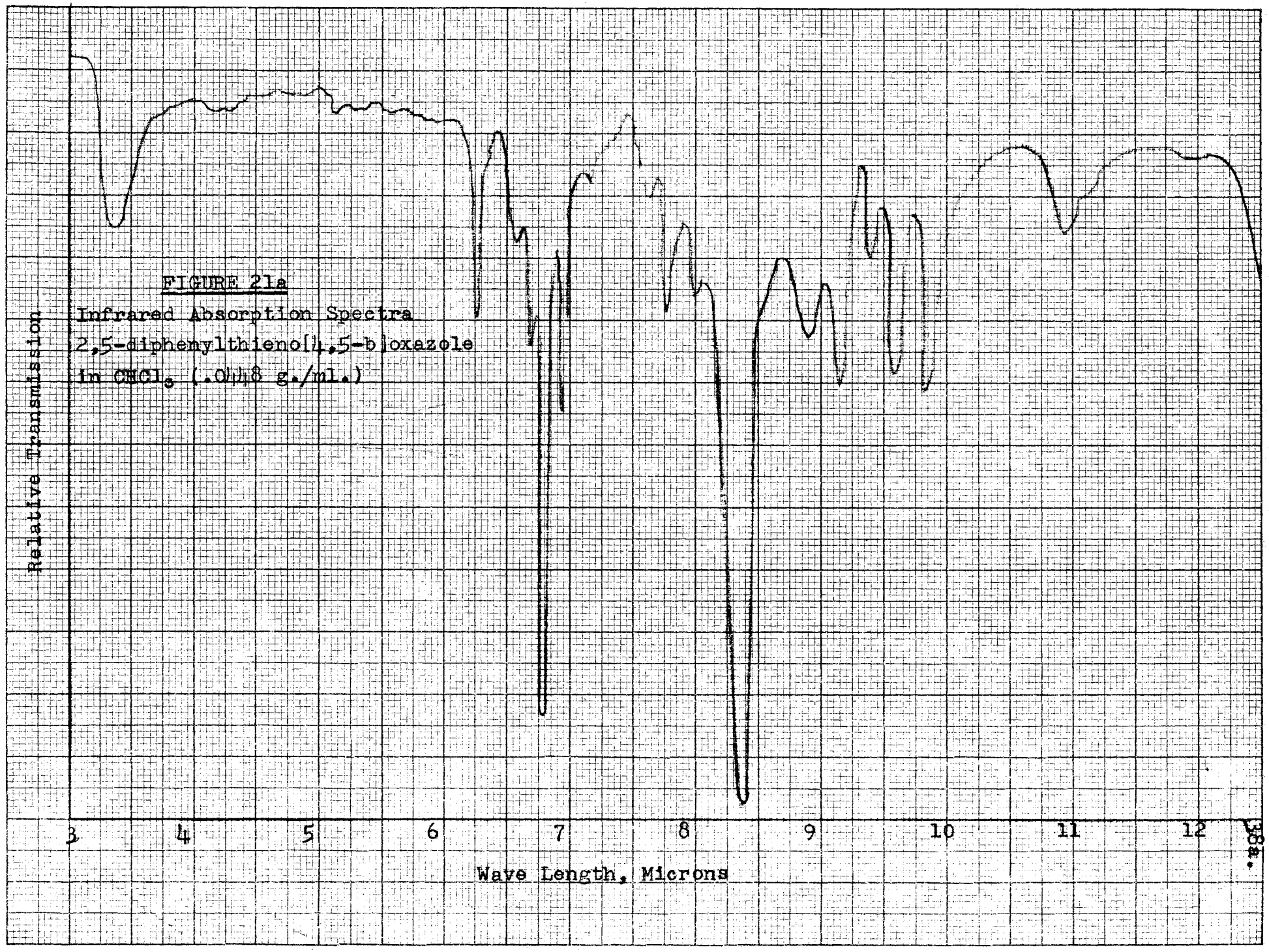


FIGURE 21a

Infrared Absorption Spectra

2,5-diphenylthieno[4,5-b]oxazole

in $CHCl_3$ (.0448 g./ml.)

yield, after eight hours at 150°, of colorless needles, which melted at 166.6-166.9°. Cuminaldehyde gave a 9 per cent yield of very pale green flakes, melting between 131.8-132.6°, and tolualdehyde gave yields of 30 per cent of pale tan crystals, which had a melting point of 101.0-101.2°. The reaction was also carried out with cinnamaldehyde; in the chromatographic purification two fluorescent bands, one blue, the other purple, formed. These yielded 0.08 g. and 0.04 g. of impure material respectively. From the larger quantity of product there was obtained by recrystallization from alcohol enough yellow crystalline material for one melting point, 173-175°. The same results were obtained on repeating the reaction. Possibly we have low yields of cis and trans isomers formed.

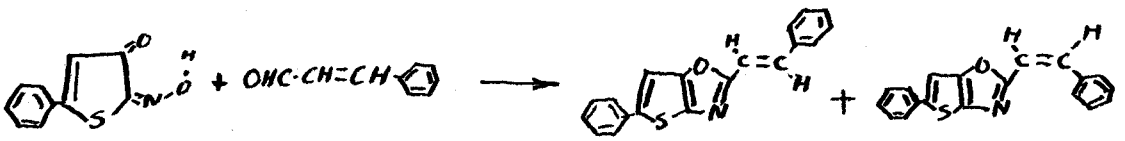


Fig. 22

The one aliphatic aldehyde investigated was caproaldehyde, but no crystalline product could be isolated from the reaction mixture.

Investigation into the nature of the oxazole formation was made by carrying out a large number of carefully controlled reactions between 5-phenyl-2,3-thiophenequinone-2-oxime and benzaldehyde and studying the effect of

changing certain variables. Any mechanism must explain the catalysis of the reaction by whatever catalyzes it and conversely an understanding of the nature of a reaction can be had only when the catalysts, if any, are known. Therefore we were especially interested in determining what compound types would catalyze the oxazole reaction and accordingly a number of different materials which are commonly used as catalysts for different purposes was added to reaction runs. The reaction was carried out by stirring 0.50 g. of the oxime in 5.0 ml. of benzaldehyde at 150° for eight hours under an atmosphere of nitrogen. To this was added such catalysts as trichloroacetic acid, benzoyl peroxide, hydroquinone, and dibenzyl amine. The reaction mixture was worked up by first removing benzaldehyde under reduced pressure, and then dissolving the residue in chloroform, and separating it into base-soluble and base-insoluble portions. The base-soluble material was separated into a water-soluble (benzoic acid) and a water-insoluble (unreacted oxime) portion. The base-insoluble portion was dissolved in carbon tetrachloride and chromatographed, and the oxazole was isolated, dried, and weighed.

The results are outlined in Fig. 24. No clear indication of catalytic action can be seen. Hydroquinone does not appear to hinder the reaction, nor does benzoyl peroxide have any marked effect and it thus seems likely

Run	Aldehyde	Temperature	Tme	Atmosphere	Oxime	Catalyst	Base Wt.	Solubles M.P.	Base Insoluble Wt.
1.	Benzaldehyde	150±3°	8hr	Nitrogen	0.50g.	Hydroquinone 0.02g.	0.11g.	120-155°	0.47g.
2.	Benzaldehyde	154±3°	8	Nitrogen	0.50	Benzoyl peroxide 0.01g.	0.14	106-200°	0.44
3.	Anisaldehyde	150±3°	8	Nitrogen	0.50	Benzoyl peroxide 0.01g.	0.24		0.68
4.	Benzaldehyde	150±3°	8	Nitrogen	0.50	Trichloroacetic 0.02g.	0.15		0.46
5.	Benzaldehyde	150°	8	Nitrogen	0.50	none	0.15		
6.	Benzaldehyde	150±3°	8	Air	0.50	none	0.32		0.37
7.	Benzaldehyde	150±3°	8	Air	0.50	none	0.44		0.40
8.	Benzaldehyde	150±3°	8	Nitrogen	0.50	Dibenzyl amine 0.1g.	0.07		
9.	Tolualdehyde	150± °	8	Nitrogen	0.50	none			
10.	Benzaldehyde	150±3°	1.83	Nitrogen	0.50	none	0.38		0.28
11.	Benzaldehyde	155°	2	Nitrogen	0.50	none	0.40		0.25
12.	Benzaldehyde	150°	2	Nitrogen	0.50	none	0.49		0.17
13.	Benzaldehyde	151±1.2	2	Nitrogen	0.50	none	0.49		0.15
14.	Benzaldehyde	150°	2	Nitrogen	0.50	none	0.38		0.36
15.	Benzaldehyde	150°	2	Nitrogen	0.50	Benzoyl peroxide 0.05g.	0.56		0.29
16.	Benzaldehyde	150°	2	Nitrogen	0.50	Benzoyl peroxide 0.05g.	0.52		0.21
17.	Benzaldehyde	150°	2	Nitrogen	0.50	$AlCl_3$ 0.05g.	0.23		0.56
18.	Benzaldehyde	150°	5	Nitrogen	0.50	none	0.36		0.34
19.	Benzaldehyde	150°	1	Nitrogen	0.50	none	0.35		0.09

Fig. 24

that the reaction is not a free radical one.

Several reactions were carried out for only two hours, since by running the reaction for shorter periods of time the uncatalyzed reaction does not go to completion and the effect of "catalysts" on rate can be determined. We were, however, unable to obtain reproducible results in the uncatalyzed two hour runs which severely limits the interpretation of the data obtained in these reactions. The failure to detect catalysis in these reactions is in part due to the lack of precise methods of working up the reaction. However it is likely that none of the materials tested was of high catalytic activity, and, inasmuch as the oxazole is stable once it is formed, if a potent catalyst had been tried it probably would have been recognized.

Dilthey and Friedrichsen[46] and Diels and Riley[47] have prepared oxazoles from alpha-diketonemonoximes and benzaldehyde. Their preparation was a two step reaction requiring the intermediate formation of an oxazole-N-oxide. The alpha diketone monoxime and benzaldehyde were dissolved in glacial acetic acid and hydrogen chloride passed through the solution. The addition of anhydrous ether precipitated the oxazole-N-oxide hydrochloride.

(46) W. Dilthey and J. Friedrichsen, J. prakt. Chem. [2] 127, 292 (1930).

(47) O. Diels and F. Riley, Ber. 48, 897 (1915).

The oxazole-N-oxide may also be prepared by shaking the oxime with benzaldehyde and concentrated hydrochloric acid and subsequently reducing the nitrogen oxide compound.

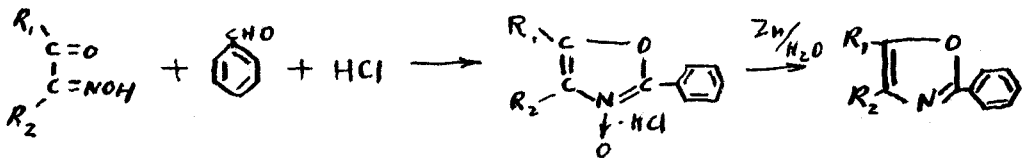


Fig. 25

We investigated these reactions to see whether the thienooxazole might have been formed in this manner with the benzaldehyde itself functioning as the eventual reducing agent. Benzil monoxime and biacetyl monoxime were synthesized and the known 2-phenyloxazole-N-oxide hydrochlorides of these compounds were prepared in yields of 62 and 27 per cent respectively. In addition, 1,2,3-cyclohexanetrione-1,3-dioxime was synthesized from the reaction of cyclohexanone, ethylnitrite and hydrochloric

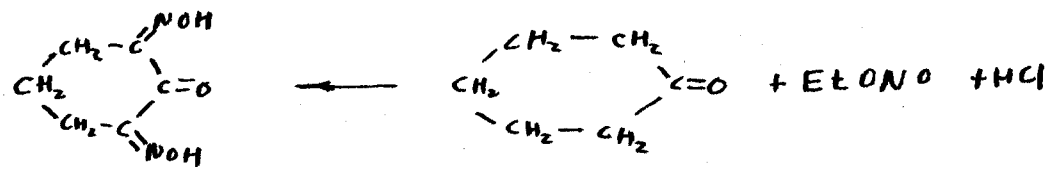


Fig. 26

acid and this compound was also treated with benzaldehyde and hydrogen chloride in glacial acetic acid. A 35 per cent yield of the oxazole-N-oxide hydrochloride was obtained,

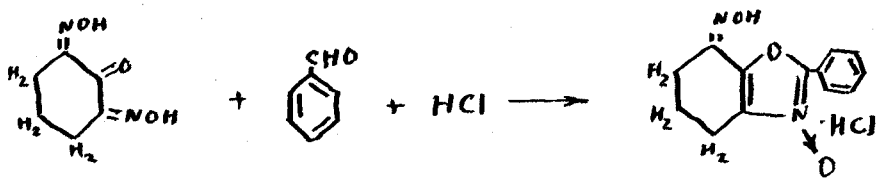


Fig. 27

which had a melting point of 165-170°. Upon heating the salt in methanol the free base was formed and one recrystallization from petroleum ether yielded a colorless solid with a melting point of 130.5-132.0°.

With this background in the preparation of oxazole-N-oxides we attempted to make this derivative of 5-phenyl-2,3-thiophenequinone-2-oxime. Hydrogen chloride was passed

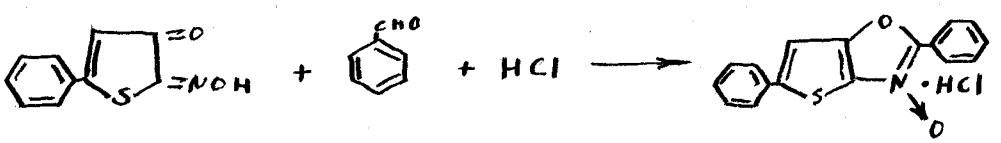


Fig. 28

into a mixture of the oxime and benzaldehyde in glacial acetic acid. At the end of the reaction unreacted, undissolved oxime was recovered. The addition of anhydrous ether did not cause any precipitation. Finally the solvents were removed and a brown-black residue remained from which there was isolated more oxime. The other procedure was no more successful. A mixture of 2 g. of oxime in 92 g. of benzaldehyde and 200 ml. of concen-

trated hydrochloric acid was shaken for three days. Most of the oxime was recovered.

We were next interested in investigating the benzaldehyde-oxazole reaction with these aliphatic alpha-diketone monoximes and with other ortho-quinone monoximes in order to determine the generality of oxazole formation under these conditions. Biacetyl monoxime was refluxed with benzaldehyde for twenty four hours. After standing at 0° for six days the liquid was distilled at reduced pressure and unreacted biacetylmonoxime was recovered. We did not succeed in identifying any products in the sizable amount of distillation residue. The 1,2,3-cyclohexanetrione-1,3-dioxime decomposed completely when refluxed with benzaldehyde for eighteen hours under nitrogen. When a mixture of the compound in benzaldehyde was stirred for three days, the dioxime was recovered unchanged.

The reaction between benzil monoxime and benzaldehyde produced triphenylimidazole,lophine. In one experiment

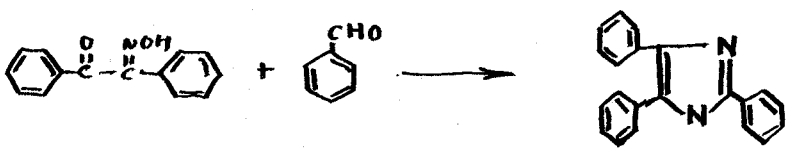


Fig. 29

three grams of benzil monoxime was refluxed in 10.3 grams of benzaldehyde for one hour under a stream of nitrogen. The crude product eventually isolated weighed 2.0 grams

which based on nitrogen represents an almost quantitative conversion to lophine. This compound was insoluble in acetone and after washing once with this solvent had a melting point of 268-270°. Mixed melting points of an authentic sample of lophine and the compounds prepared in this way from a number of runs did not, in any case, show a depression. If the reaction was allowed to go for longer periods of time oils formed which made the isolation of the lophine much more difficult.

The reaction of benzilam-N-oxide and benzaldehyde produced a small amount of lophine. The product which

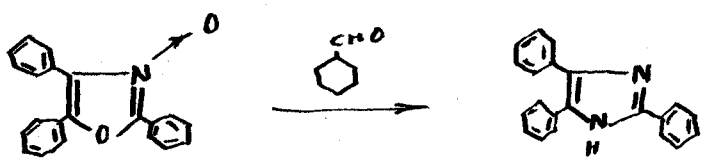


Fig. 30

remained after the removal of benzaldehyde from the non-basic residue by vacuum distillation was dissolved in ether and freed of acidic impurities by extraction with base. This left a gummy solid which after recrystallization from benzene, and then ethanol had a melting point of 228-230° (benzilam, melting point 115-116°). This compound was not identified.

The reaction of an ortho-quinone monoxime with benzaldehyde also produced an imidazole. When 1 g. of phenanthraquinone monoxime was heated in benzaldehyde at

150° for eight hours there was isolated 0.25 g. of 2-phenylphenanthrimidazole which after one crystallization from ethanol had a melting point of 310-313° (lit. 312-313°)[48].

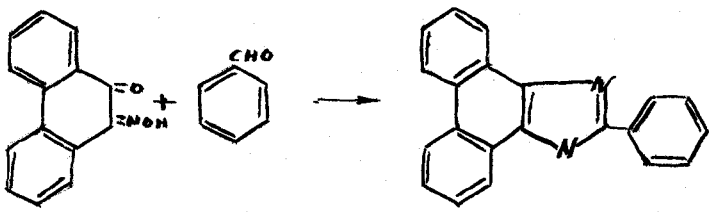


Fig. 31

The picrate was prepared, this compound melted at 280-282° (lit. 280°)[48].

The transformation of the alpha diketone monoxime to an imidazole involves the transfer of a nitrogen atom from one molecule to another, the reduction of oxime groups, and carbon-nitrogen condensation and cyclization. A number of mechanisms may be postulated for each operation and the total of the combinations and permutations of these gives a vast number of possible routes. It is not possible with the data at hand to do more than speculate on the most likely total mechanisms. One of these is discussed in the following paragraphs.

It is likely that the first step of the reaction involves a disproportionation of the diketone monoxime.

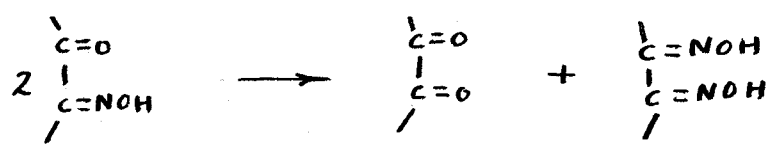


Fig. 32

(48) E. A. Steck and A. R. Day, J. Am. Chem. Soc. 68, 771 (1946).

Lapworth[30] showed the reaction between hydroxylamine and carbonyl compounds to be a reversible one in concentrated hydrochloric acid.

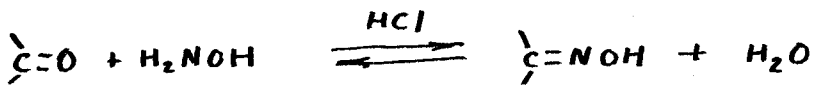


Fig. 33

Furthermore Ponzio[49] found that alpha diketone monoximes in hydrochloric acid did disproportionate and form diketones and dioximes. Equilibrium between the carbonyl group and the oxime group is also established when oximes are heated with aldehydes and ketones under anhydrous conditions and exchange with an excess of some ketone or aldehyde in non-aqueous solvents has frequently been used in the steroid field to obtain a ketonic compound from its oxime or semicarbazone[31]. If the disproportionation products are of lower energy content than the monoxime, as the work of Ponzio in aqueous medium would indicate, and equilibrium can be created between the moieties then disproportionation should occur no matter what the path of the reaction is. Hence in the reaction with benzaldehyde it is logical to postulate the formation of a dioxime without the use of hydrochloric acid. This is consistent with the observation that benzil dioxime forms an imidazole.

(49) G. Ponzio, Gazz. chim. ital. 60, 429 (1930).

The reaction mechanism must include at some point, the reduction of the oxime group. The failure of 5-phenyl-2,3-thiophenequinone-2-oxime to form the oxazole-N-oxide under conditions which produced this compound with all other monoximes investigated strongly suggests that the synthesis of thienooxazoles does not go through the formation of oxazole-N-oxides. Furthermore the action of

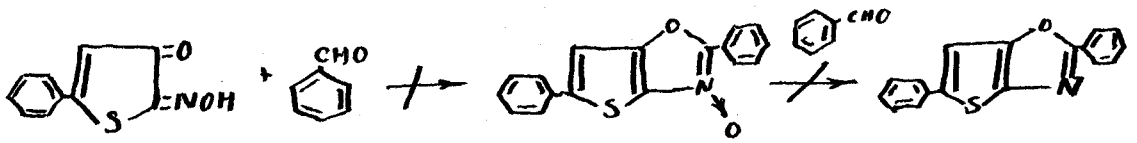


Fig. 34

benzaldehyde on benzilam-N-oxide did not produce the oxazole, benzilam, but instead a small amount of lophine and an unidentified product which was not triphenyloxazole. The possibility that these products were formed from benzilam can be excluded on the basis of studies carried out by Kreps and Day[50]. They found the oxazoles such as phenanthroxazole resisted the transformation into phenanthrimidazole or any other compound when heated with benzaldehyde and ammonia under severe hydrolytic conditions.

As the second step in the mechanism we propose the reduction of the dioxime to the di-imine. If one postulates the reduction of the oxime group by the aromatic aldehyde there is the problem of explaining how the benzaldehyde

(50) S. Kreps and A. R. Day, J. Org. Chem. 6, 140 (1941).

functions as a reducing agent. We tentatively advance the following mechanism.

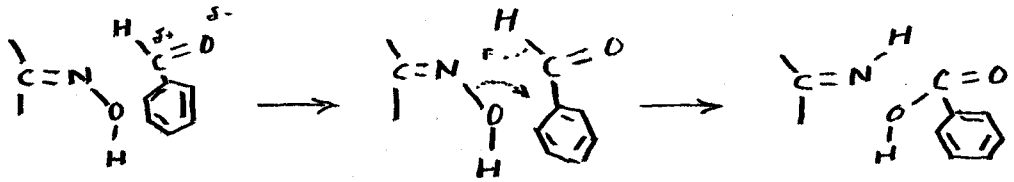


Fig. 35

McCoy and Day[51] have made a comprehensive study of ortho condensations which lead to oxazole or imidazole formation. They concluded that it was possible to represent many, if not all, ortho condensations which lead to oxazole or imidazole formation by a common intermediate. Whether oxazole or imidazole results is determined by the nature of the groups X and Y. In our case (i.e. the reaction of phenanthraquinone monoxime and benzaldehyde)

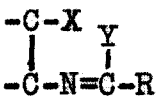


Fig. 36

X would be NH_2 and Y would be OH and this has been found to lead to imidazoles. Steck and Day[52] prepared 2-substituted phenanthrimidazoles from phenanthraquinone di-imine and aldehydes. The following mechanism which goes through this type of intermediate is postulated

(51) G. McCoy and A. R. Day, J. Am. Chem. Soc. 65, 2159 (1943).
(52) E. A. Steck and A. R. Day, J. Am. Chem. Soc. 65, 452 (1943).

by McCoy and Day[51]:

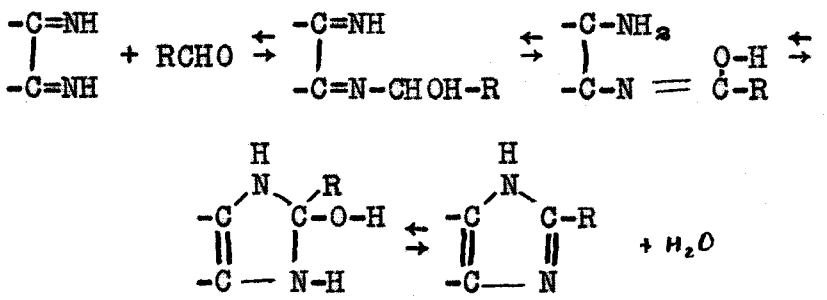


Fig. 37

The overall mechanism would be:

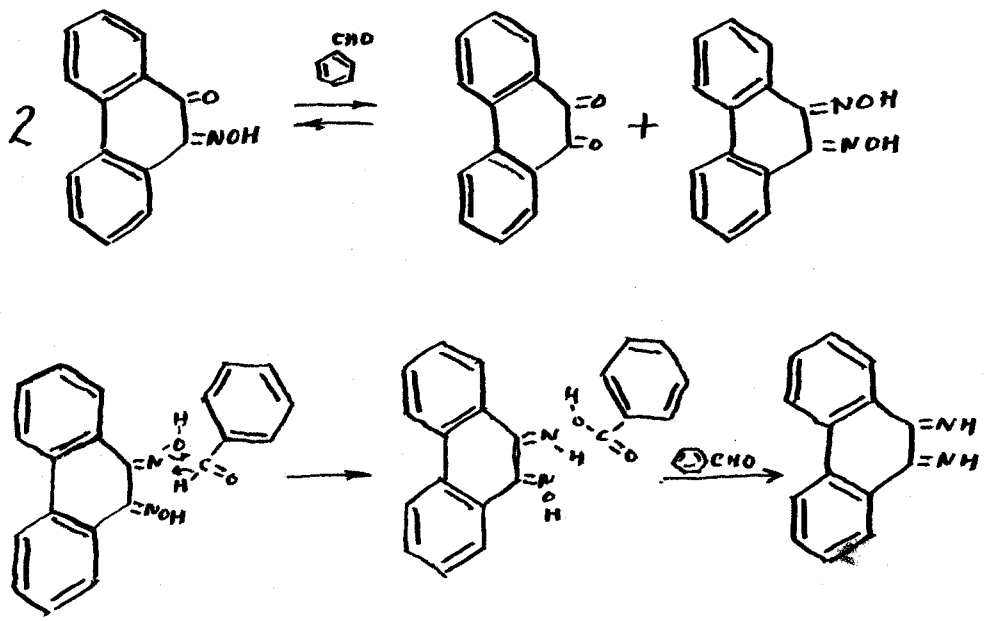


Fig. 38

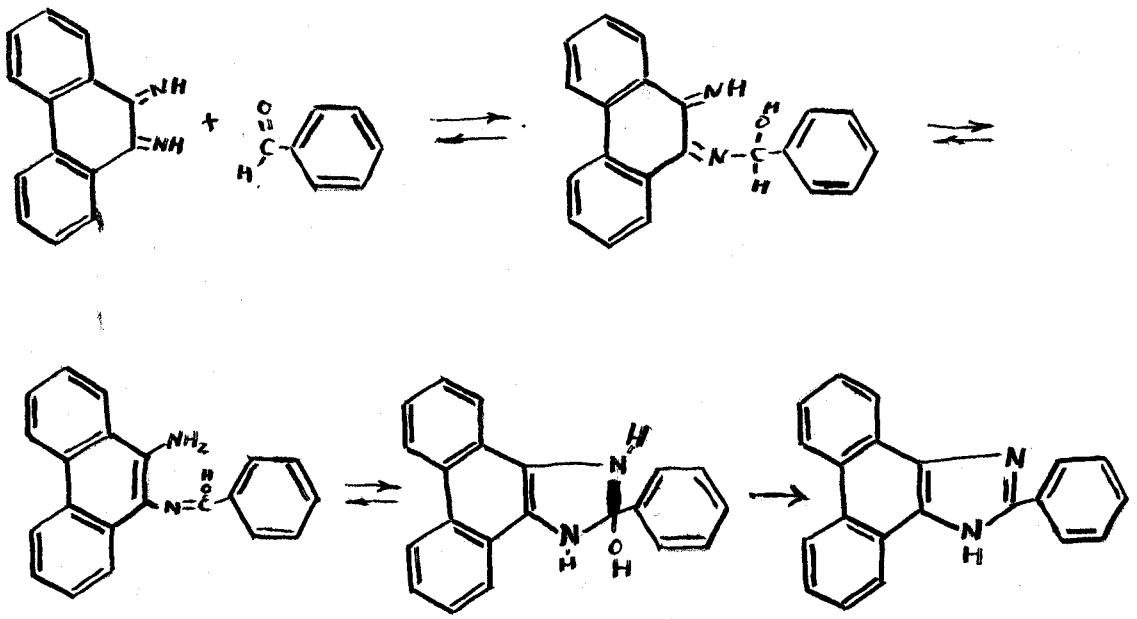


Fig. 39

In the reaction of the 5-phenyl-2,3-thiophenequinone-2-oxime with benzaldehyde the extraordinary stability of the oxime grouping is again manifested. Disproportionation does not occur. The dioxime has been found to decompose irreversibly in benzaldehyde at 100° to yield an isoxazole nitrile. This compound would have been encountered in the course of working up the oxazole had the dioxime formed. The failure to isolate this compound means therefore that the dioxime did not form. If we eliminate the first step in the imidazole formation we have a similar series of reactions which explain oxazole formation. In this

case the X and Y groups in the mechanism postulated by McCoy and Day[51] are both hydroxyl groups. Stein and Day[52a] have shown that the interaction of phenanthraquinone monoimine with an aldehyde proceeds through this intermediate to give 2- substituted oxazoles. On this basis we tentatively suggest the following possible explanation for oxazole formation:

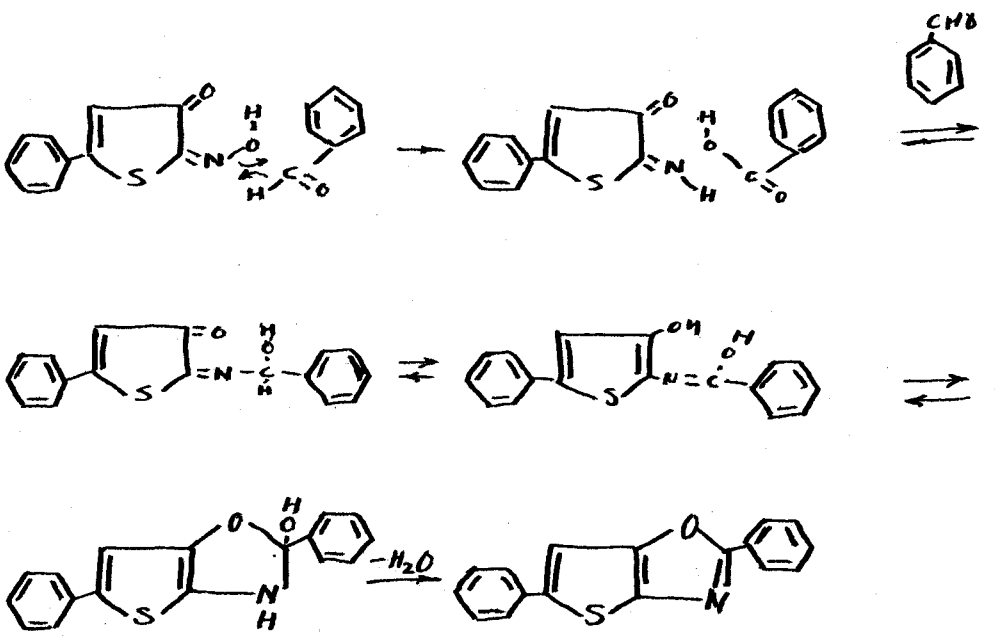


Fig. 40

(52a) C. W. C. Stein and A. R. Day, J. Am. Chem. Soc. 64, 2567 (1942).

III. Dioxime: 5-phenyl-2,3-thiophenequinone-2,3-dioxime

The dioxime of 5-phenyl-2,3-thiophenequinone was synthesized by the method of Kehrmann and Messinger[53]. Solutions of the monoxime and hydroxylamine in aqueous sodium hydroxide at room temperature were mixed and allowed to stand with stirring for from thirty minutes to six hours. When the solution was finally acidified the

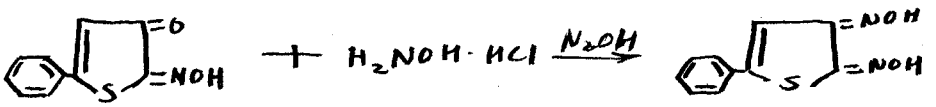


Fig. 40

dioxime would precipitate very slowly and was collected in crops over the course of several days. When the reaction had proceeded for less than an hour some unreacted monoxime precipitated at the beginning of the reaction. In all cases as the final quantities of material came out of solution in each particular run the monoxime precipitated with the dioxime in an ever increasing proportion. It is not known what that property of the dioxime is which would cause it to come out of solution slowly and continuously. The monoxime has repeatedly been shown to precipitate immediately upon acidification of its basic solution. Its isolation in the tail crops of the dioxime

(53) F. Kehrmann and J. Messinger, Ber. 23, 2816 (1890).

is therefore probably due to acid hydrolysis of the existent dissolved dioxime. The carbon atom at which hydrolysis of the dioxime occurred was not known and there existed the possibility that the 3-oxime isomer might have been formed.

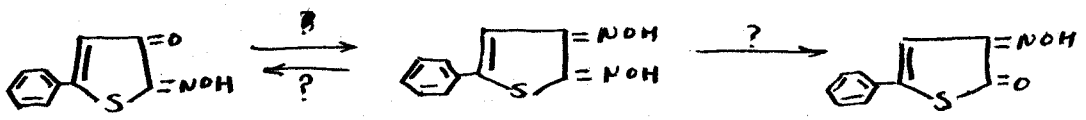


Fig. 41

To check this the yellow product obtained at the end of the dioxime synthesis was recrystallized from ethanol and the ultra-violet absorption spectra of material from a first and a second crop of crystals were determined along with that of the small amount of base soluble material isolated in a nitrosation of 5-phenyl-2-hydroxythiophene. The three curves were compared with the curve of a pure, authentic sample of 2-oxime. The two dioxime product curves were very similar to the monoxime curve, although not identical. The absorption curve of the nitrosation product of 5-phenyl-2-hydroxythiophene was shifted very much to the left. The hydrolysis product was therefore the 2- and not the 3- oxime. (See Fig. 41A)

The following yields were obtained after various lengths of reaction time before acidification: Thirty

FIGURE 41A

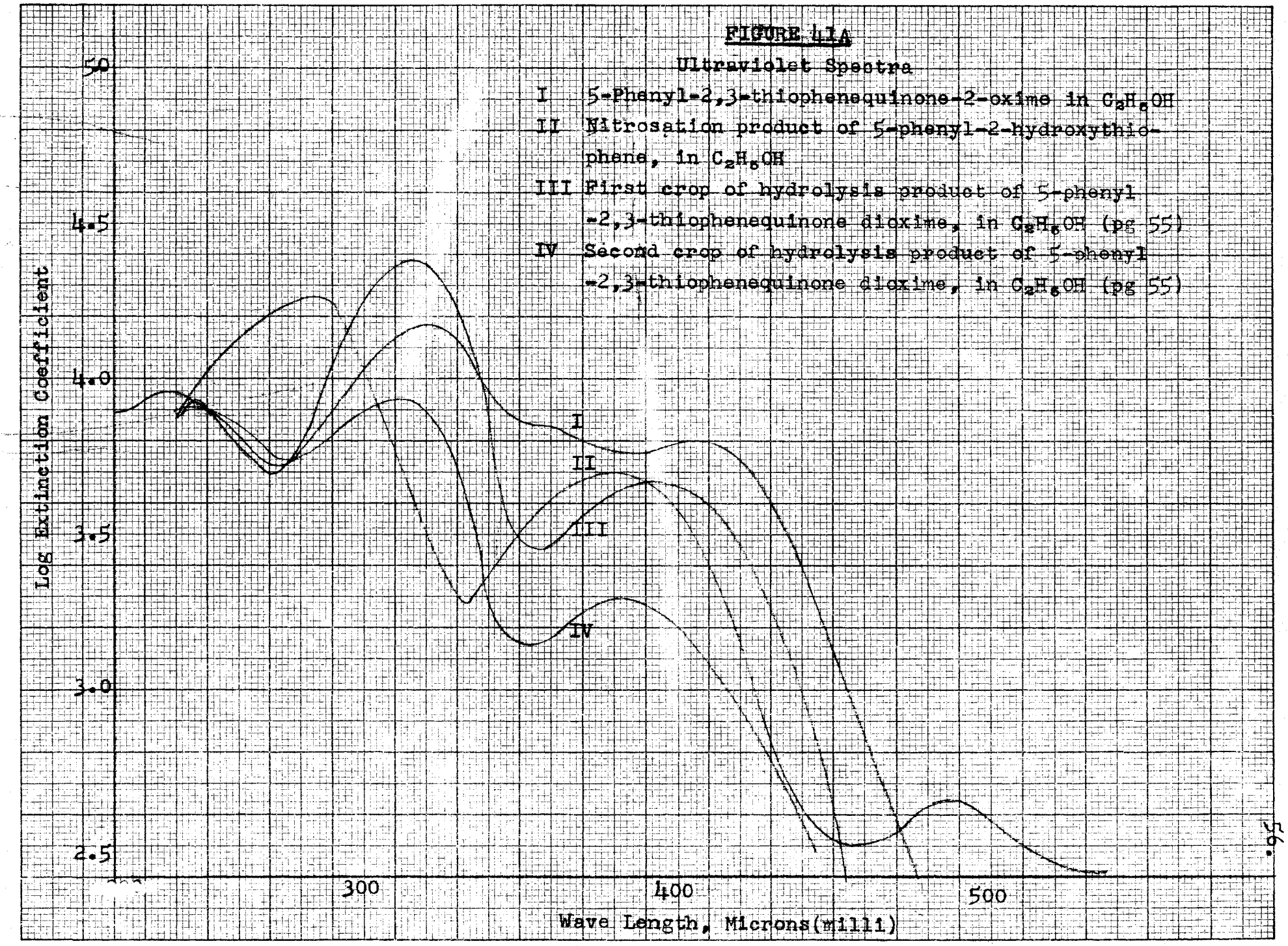
Ultraviolet Spectra

I 5-Phenyl-2,3-thiophenequinone-2-oxime in C_2H_5OH

II Nitrosation product of 5-phenyl-2-hydroxythiophene, in C_2H_5OH

III First crop of hydrolysis product of 5-phenyl-2,3-thiophenequinone dioxime, in C_2H_5OH (pg 55)

IV Second crop of hydrolysis product of 5-phenyl-2,3-thiophenequinone dioxime, in C_2H_5OH (pg 55)



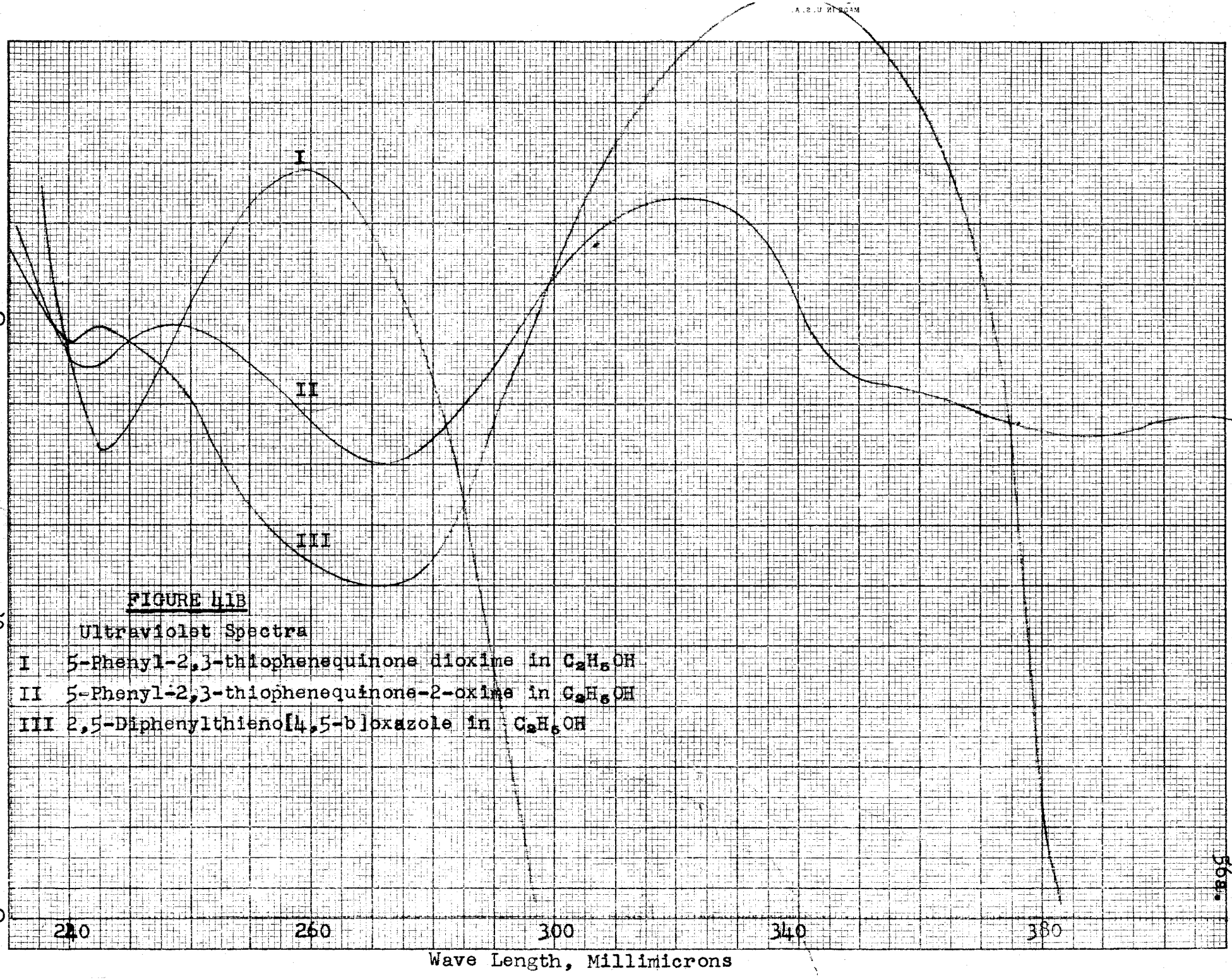


FIGURE 41B

Ultraviolet Spectra

I 5-Phenyl-2,3-thiophenequinone dioxime in C_2H_5OH

II 5-Phenyl-2,3-thiophenequinone-2-oxime in C_2H_5OH

III 2,5-Diphenylthieno[4,5-b]oxazole in C_2H_5OH

minutes, dioxime 35 per cent, monoxime 60 per cent; one hour, dioxime 49 per cent, monoxime 27 per cent; six hours, dioxime 71 per cent, monoxime 5 per cent.

The dioxime can best be removed from the monoxime by extracting with warm benzene, and purified by recrystallization from the same solvent. The dioxime is a colorless, crystalline solid that melts at 126.4-126.8°. It is extremely soluble in ethanol and ether, moderately soluble in benzene, and insoluble in petroleum ether. The compound gives the characteristic red precipitate, characteristic of alpha dioxime groups, with nickel. As in the case of the monoxime a series of spot tests was made with aqueous solutions of a large number of inorganic salts at a concentration of 0.1 mg. per ml. A 0.25 per cent solution of the dioxime gave a red precipitate with Ni^{++}, a dark blue-black precipitate with Fe^{+++}, a brown-yellow precipitate with Cu^{++}, and a pink color with Co^{++}. The precipitate with iron was much darker and heavier than the copper or nickel precipitates. The dioxime gave a positive, blue-grey spot test for iron at a concentration of five parts per million of ferric chloride; this test was used throughout the investigation of the dioxime to indicate the presence or absence of this compound.

One of the typical reactions of ortho-quinone

dioximes is the formation of furazans(54). Green and Rowe prepared the furazan of ortho-naphthaquinone dioxime by the steam distillation of this compound from base. A

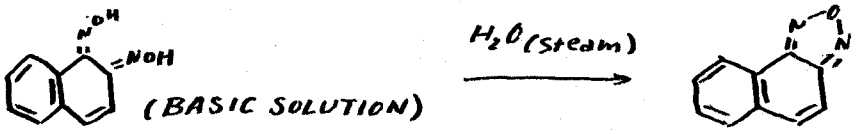


Fig. 42

solution of the thiophenequinone dioxime in 1 per cent sodium hydroxide solution was steam-distilled with superheated steam. Eighty five per cent of the dioxime was recovered unchanged. The distillate upon ether extraction was found to contain 9 per cent of a foul-smelling oil. The preparation of the furazan was then attempted by

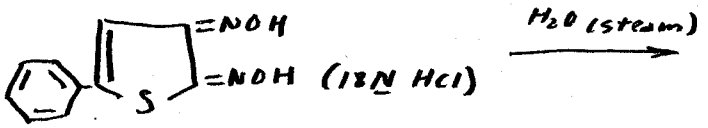


Fig. 43

distillation of 1 g. of the dioxime with superheated steam from 18 N hydrochloric acid. The distillate contained 0.33 g. of a colorless solid which after repeated recrystallization from petroleum ether had a melting point of 93.6-94.1°, and 0.02 g. of sulfur. From the pot liquid

(54) A. G. Green and F. M. Rowe, J. Chem. Soc. 111, 617 (1917).

there was isolated 0.17 g. of 5-phenyl-3-hydroxyoxazine-4-one which showed no melting point depression on admixture with the hydrolysis product of the monoxime, 0.12 g. of the monoxime which was identified by melting point and mixed melting point with an authentic sample, and 0.06 g. of a non-base soluble material which might possibly have been the amide described below.

The identification of the material isolated from the distillate proved to be an interesting problem. Samples crystallized from ethanol and from low boiling petroleum ether were analyzed and found to have the formula $C_{10}H_6N_2O$. No suitable compound bearing such an empirical formula and melting near 93° could be found in the literature. Assuming that the phenyl group remained intact we could describe our molecule as $C_6H_5-C_4N_2OH$. It seemed possible that the highly unsaturated C_4N_2OH grouping might contain a nitrile group. The compound was subjected to two reaction procedures which are typically applied to nitriles. The first was hydrolysis in refluxing 50 per cent sulfuric acid, which hydrolyzes nitriles to carboxy acids. This gave an acid which melted from 176.5-177.8°. Analysis showed its formula to be $C_{10}H_7NO_3$.

$$C_6H_5C_3NOH\text{-}CN \rightarrow C_6H_5C_3NOH\text{-}COOH$$

$$C_{10}H_6N_2O \rightarrow C_{10}H_7NO_3$$

Fig. 44

In the second experiment the unknown was stirred in concentrated hydrochloric acid at room temperature for eighteen hours. Partial hydrolysis generally occurs with nitriles under these conditions and amides are produced. From the unknown there was obtained in this manner a colorless, non-acidic solid melting at 203.0-203.5°. Analysis showed that this substance had the empirical formula $C_{10}H_8N_2O_2$.

$$C_{10}H_6N_2O \rightarrow C_{10}H_8N_2O_2$$

$$C_6H_5C_3NOH\text{-}CN \rightarrow C_6H_5C_3NOH\text{-}CONH_2$$

Fig. 45

Furthermore when it was refluxed with dilute hydrochloric acid the acid, $C_{10}H_7NO_3$, was produced. Thus it was established that our molecule was $C_6H_5\text{-}C_3NOH\text{-}CN$. Assuming that the three unaccounted for carbons formed a chain linking the phenyl group and the nitrile, and keeping in mind that the compound is soluble in neither acid nor base, only two structures are possible, A and B. Although

Fig. 46

neither of these compounds is described in the literature both of the derived acids are. The acid from compound A

melts at 162°, that of compound B melts at 177-178° and the nitrile was assigned the structure of 3-phenyl-5-cyanoisoxazole, B.

We did not attempt to synthesize this compound and thus do not have unequivocal proof of its sturcture. It should be noted that the 5-phenyl-3-cyanoisoxazole is the expected derivative but we obtained instead the isomer

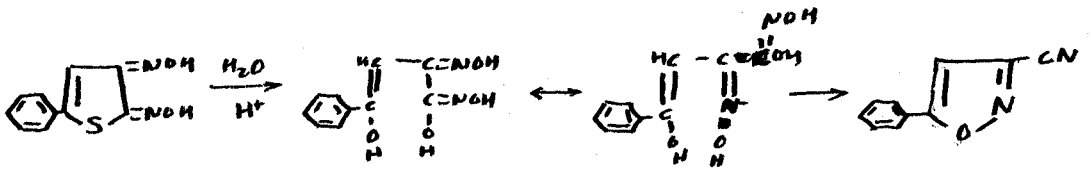


Fig. 47

in which the oxazole nitrogen is adjacent to the phenyl group. The easiest explanation for the formation of the opposite isoxazole is that there is an acid catalyzed transfer of the oxime group from the alpha carbon atom of the hydroxamic acid to the gamma carbon. In view of the disproportionation of the alpha diketone monoximes in concentrated hydrochloric acid previously discussed, this step is not too extraordinary. The cyclization of beta diketone monoximes to isoxazoles is a well established reaction[55,56].

(55) L. Claisen, Ber. 24, 3900 (1891).

(56) N. V. Sidgwick, The Organic Chemistry of Nitrogen, Clarendon Press, Oxford, 1937, p. 171.

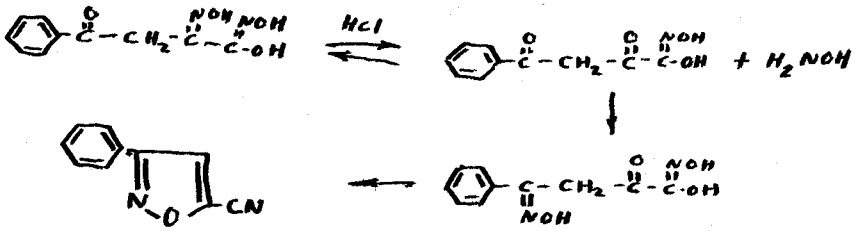


Fig. 51

A completely analogous series of reactions was carried out by Benary and Silberstrom[3]. Ethyl 5-methyl-2,3-thiophenequinone-2-oximino-3-hydrazino-4-carboxylate was refluxed in alcohol containing hydrochloric acid and ethyl 1-phenyl-3-methyl-5-cyanopyrazine-4-carboxylate was formed. Benary also found it necessary to hydrolyze

Fig. 52

the nitrile to the acid in order to identify his compound and he found to his surprise that his phenyl diazo grouping was in the reverse of the expected order just as we had obtained a reversal of the expected nitrogen oxygen linkage in the isoxazole. He explained this by postulating acid cleavage of the phenyl hydrazone, recombination at the gamma carbonyl and then cyclization. The following mechanism was proposed.

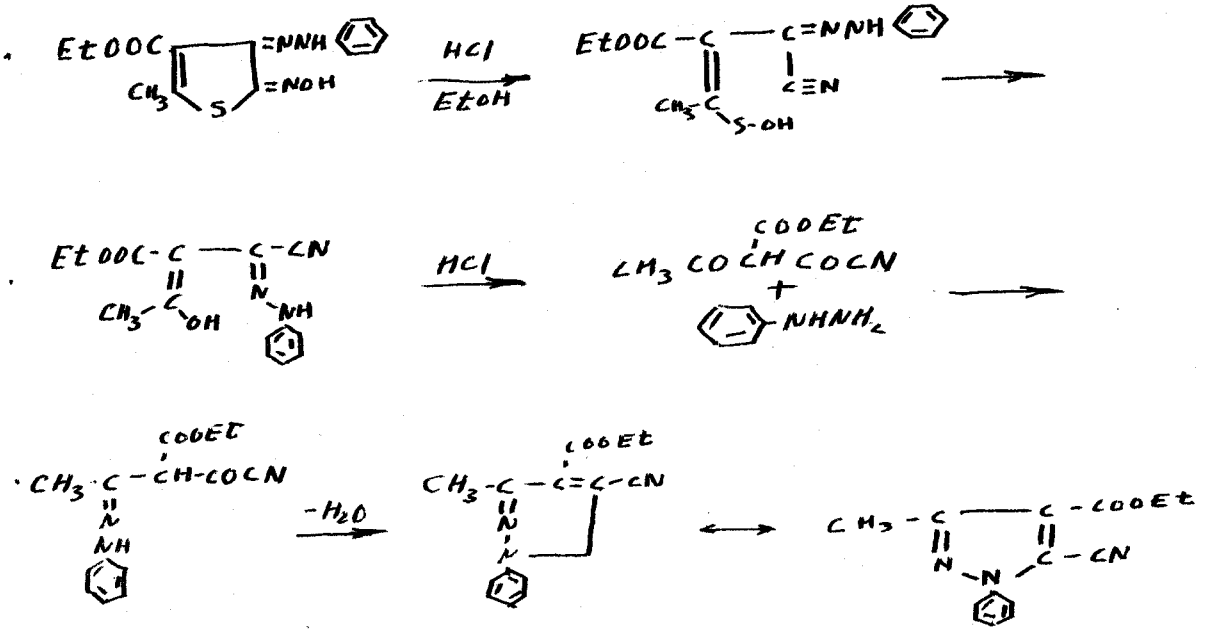


Fig. 53

The preparation of the furazan again was attempted, this time by heating the dioxime in an anhydrous solvent. Two g. of the compound was refluxed in toluene (boiling point 111°) for two hours. There was isolated 0.63 g. of unreacted dioxime and 0.65 g. of a base-insoluble, tan solid, melting point 147-155°. By recrystallizing from alcohol with the use of Darco there was obtained colorless crystals melting point 205-206°. We expected this compound to be the furazan but its analysis failed to agree with the calculated values and the nature and structure of this compound remain uncertain.

We were interested in cleaving the C=N linkages of the dioxime in order to see which oxime group was the more labile. The acidic steam distillation had yielded the 2- oxime in 12 per cent yield, and in addition the

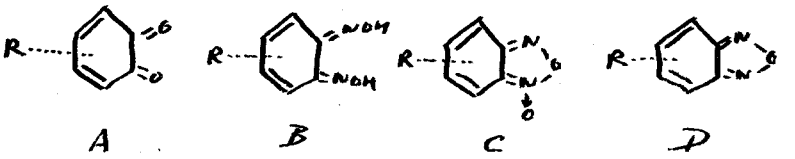
dioxime apparently was hydrolyzed to this monoxime upon standing in dilute hydrochloric acid for several days. The use of pyruvic acid as an exchange reagent appeared to be the most promising hydrolytic tool for removing the oxime group without cleaving the ring. A mixture of 1 g. of the dioxime and 1.5 ml. of pyruvic acid in 26 ml. of 75 per cent acetic acid was refluxed for four hours. Eight-hundredths of a gram (55%) of sulfur precipitated. There was also isolated 0.46 g. (60%) of 3-phenyl-5-cyanoisoxazole. In contrast to this, in a similar reaction with the monoxime 85 per cent of the starting material was recovered. This illustrates the difference in the stability of these two compounds.

The benzaldehyde-oxazole reaction (cf. p.36) was attempted with the dioxime. Since the dioxime decomposed when heated above 126° the benzaldehyde solution was kept at 100° instead of 150° for twenty four hours instead of eight. There was isolated from 0.5 g. of dioxime, 0.04 g. of a base-soluble solid, and 0.28 g. of impure base-insoluble material which proved to be the 3-phenyl-5-cyanoisoxazole.

Tappi and Forni[57] studied the bactericidal activity of heterocyclic derivatives of ortho-quinones of the

(57) G. Tappi and P. V. Forni, Ann. Chim. Applicata 38, 602 (1948); C. A. 45, 9804f(1951).

following types:



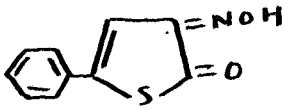
A B C D

Fig. 53 A

The activity of type B was the greatest in the series and the activity of C, and D was postulated to be due to the formation of B. The 5-phenyl-2,3-thiophenequinone-2,3-dioxime at the present time is being considered for pharmacological testing.

IV. 5-Phenyl-2,3-thiophenequinone-3-oxime

As a final phase of this study we attempted to prepare 5-phenyl-2,3-thiophenequinone-3-oxime, I. We



I

were interested in this compound because of its relationship to the 2-oxime. It would be especially desirable to learn how this compound would respond to cleavage reactions, what the degradation products would be, and what would happen if it were refluxed in aromatic aldehydes. The preparation of the dioxime from the 3-oxime would have rounded out the two series of oxime syntheses and would have been strong additional evidence for the structures of all the compounds involved.

As in the preparation of the 2-oxime, the corresponding hydroxythiophene was prepared and then nitrosated. Instead of the desired product, decomposition and dimerization occurred and in a series of reactions carried out under various conditions only trace quantities of a material which might have been the 3-oxime were isolated.

The following route to the oxime was investigated.

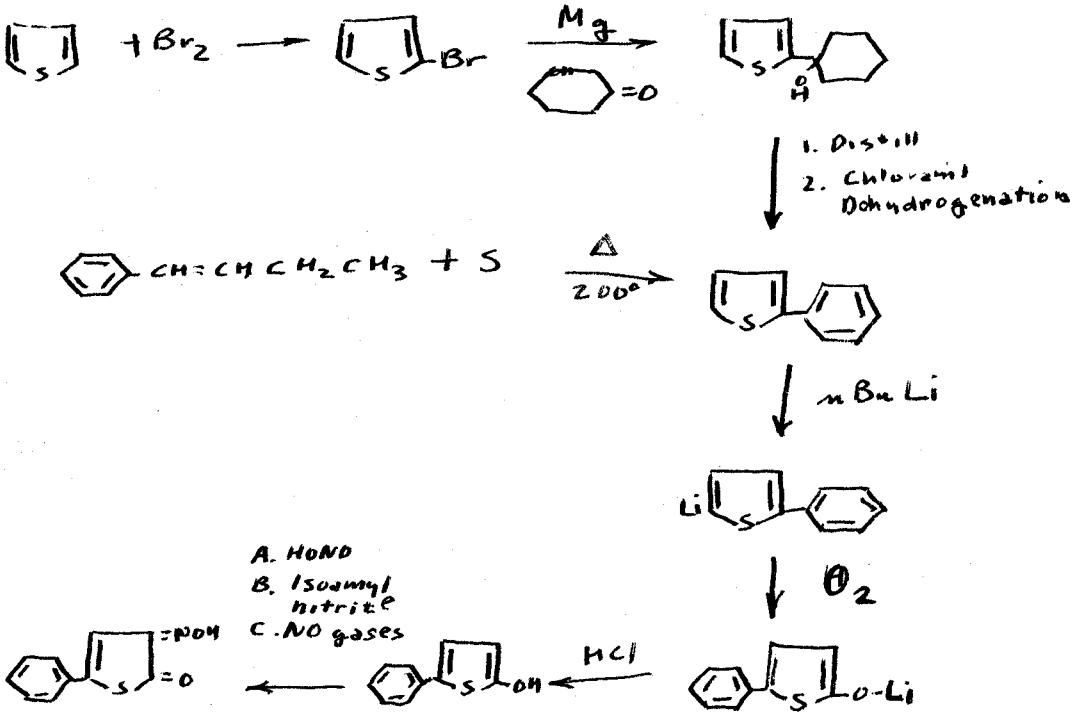


Fig. 48

Phenylthiophene was prepared by the method developed by Steele[15] in this laboratory from thiophene and cyclohexanone. We also attempted to prepare this compound by heating 1-phenylbutene-1 with sulfur. The olefin was synthesized from phenylmagnesium bromide and n-buteraldehyde via a Grignard reaction. The propyl

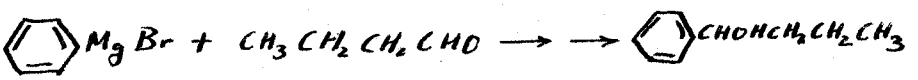


Fig. 49

phenyl carbinol obtained in the Grignard reaction was dehydrated during fractional distillation of the pure

olefin from a mixture of carbinol and 85 per cent phosphoric acid at reduced pressure under nitrogen. The dehydration

Fig. 50

went in 66 per cent yield, the overall yield from phenyl magnesium bromide was 35 per cent.

Brown and Voronkov[58] described the preparation of phenylthiophene from the reaction between 1-phenylbutene-1 and sulfur. The olefin was heated with sulfur for 15 hours at 200-250° and there was distilled from the reaction product a 35 per cent yield of crude product boiling between 80 and 105° (3 mm). We attempted the same procedure with larger quantities. The reaction did not go as described. Phenylbutene boils at 190-193° and we could not get the temperature above 200°. After 13 hours a considerable amount of decomposition had occurred. We eventually obtained 5.0 grams (4.1 per cent) of phenylthiophene. Horton[59] prepared 1-phenylthiophene in 19 per cent yield by adding 1-phenylbutadiene dropwise to molten sulfur at 340° at a pressure of 300 mm. The phenylthiophene distilled from the reaction mixture as it was formed. The same procedure was followed exactly

(58) M. G. Voronkov and A. C. Brown, J. Gen. Chem. (USSR) 19, (81) 1356 (1949).

(59) A. W. Horton, J. Org. Chem. 14, 761 (1949).

with 1-phenylbutene-1. Sixty three per cent of the olefin was recovered unreacted and a yield of 4.5 per cent of pure phenylthiophene (based on unrecovered phenylbutene) was obtained.

The 5-phenyl-2-hydroxythiophene was prepared by a modification of the method of Hurd and Kreuz[14].

Phenols may be prepared by the oxidation of arylmagnesium halides, although the yields are generally poor and with thienylmagnesium halides are particularly unsatisfactory[14]. Kharasch and Reynolds[60] found that the presence of an alkylmagnesium halide facilitates the conversion of the arylmagnesium bromides to phenols with a considerable increase in yield. The explanation is advanced that a peroxide is first formed which is rapidly reduced to the desired salt by the alkylmagnesium halide. In the absence of the alkylmagnesium halide the peroxide

$$ArMgBr + O_2 \rightarrow ArOOMgBr \xrightarrow[fast]{RMgBr} ArOMgBr + ROMgBr$$

is slowly reduced by another molecule of arylmagnesium halide and a competing decomposition to dimer and tars seriously lowers yields.

$$ArOOMgBr \begin{cases} \longrightarrow \text{tars, biaryls} \\ \xrightarrow[slow]{ArMgBr} 2.ArOMgBr \end{cases}$$

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

Hurd and Kreuz[14] found that the use of a large excess of isopropylmagnesium halide made possible the synthesis of 2-hydroxythiophene in 20-25 per cent yield. Palchak[61] improved the procedure by using the thienyllithium type of organo metallic compound which was prepared from phenylthiophene and butyllithium and thus avoided the intermediate preparation of the bromide. A three molar excess of cyclohexylmagnesium bromide was added and oxygen was rapidly bubbled into the reaction mixture, cooled to -50° in a Dry Ice-acetone bath, until

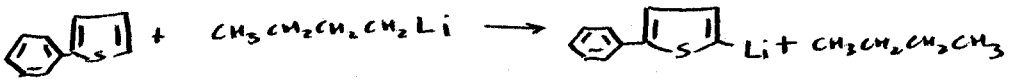


Fig. 54

absorption no longer occurred. This procedure gave 5-phenyl-2-hydroxythiophene in 30 per cent yield.

We attempted to prepare 5-phenyl-2,3-thiophenequinone-3-oxime by nitrosation of the 2-thienol with nitrous acid, with isoamyl nitrite, and with nitrogen oxide gases. In no procedure were we able to isolate any more than traces of a base-soluble solid which might possibly have been the desired compound. In the procedure patterned after the preparation of 2-oxime, a solution of 5-phenyl-2-hydroxythiophene in ethanol was added to a solution of sodium nitrite in 50 per cent ethanol. The addition of

(61) R. J. F. Palchak, Research currently in progress at the University of Cincinnati.

this to excess, dilute hydrochloric acid at 0° gave a sky-blue precipitate from which was isolated 40 per cent of the original compound as 5,5'-diphenyl-[$\Delta^{3,3}$ (2H,2H')-bithiophene]-2,2'-dione and 15 per cent as a base-insoluble tar, and about 40 per cent as a base-soluble tar. In one case only was there isolated a sufficient quantity of yellow solid from the base-soluble tar to obtain a melting point (196-198° recrystallized from petroleum ether) and ultra-violet absorption curve (Fig. 41A).

The procedure of Hodgson and Davies[62] for the nitrosation of the 2- and 3- hydroxyfurans was tried. An aqueous solution of the sodium salt of 5-phenyl-2-hydroxythiophene and sodium nitrite was added dropwise to a stirred, ice-cold, dilute solution of hydrochloric acid. This procedure yielded almost no base-soluble material, but did give the dimer in high conversion.

Nitrosation with isoamyl nitrite and hydrogen chloride[63] under anhydrous conditions yielded 27 per cent of dimer, 20 per cent of base-soluble tar, and 37 per cent of base-insoluble tars. Nitrogen oxide gases, evolved from the reaction of hydrochloric acid with sodium nitrite, were passed through calcium chloride and

(62) H. H. Hodgson and R. R. Davies, J. Chem. Soc., 1014 (1939).

(63) I. A. Barltrop, A. J. Johnson, and G. D. Meakins, J. Chem. Soc., 181 (1951).

then bubbled through an anhydrous solution of 5-phenyl-2-hydroxythiophene in ether at 0°. A considerable amount of dimer formed together with a red, base-soluble oil which we were not successful in identifying.

SUMMARY

We have prepared 3-hydroxy-5-phenylthiophene by improved procedures based on Friedländer's synthesis, and have investigated its properties. It is a colorless solid which can be readily oxidized to a thioindigo dimer. The ultra-violet spectrum in ethanol is almost identical with that of the methyl ether which serves as a model for the enol form. In chloroform the spectrum is different, a minor maximum at 330 mμ occurs which is characteristic of the C=C-C=O system. Therefore it is likely that the enol form predominates in alcoholic solution, the ketonic in chloroform. From 3-hydroxy-5-phenylthiophene there can be prepared a methyl ether, acetate ester, a 2-nitroso compound, and a tribromo derivative. The thienol did not form a semicarbazone nor yield isolable base-catalyzed condensation products with p-nitroso-N,N-dimethylaniline. The monobromo compound of the methyl ether was prepared by the Wohl-Ziegler reaction, but decomposed at room temperature in a few hours. A similarly prepared derivative of the hydroxythiophene apparently decomposed as it was formed.

We attempted to hydrolyze the oxime grouping of 5-phenyl-2,3-thiophenequinone-2-oxime by a variety of procedures with mineral acids, and carbonyl compounds, alone or in combination, in order to prepare the quinone

of phenylthiophene. The carbon-nitrogen bond was extraordinarily stable and rupture of the ring occurred before oxime hydrolysis. Prolonged heating of the oxime with acids led to the following transformations:

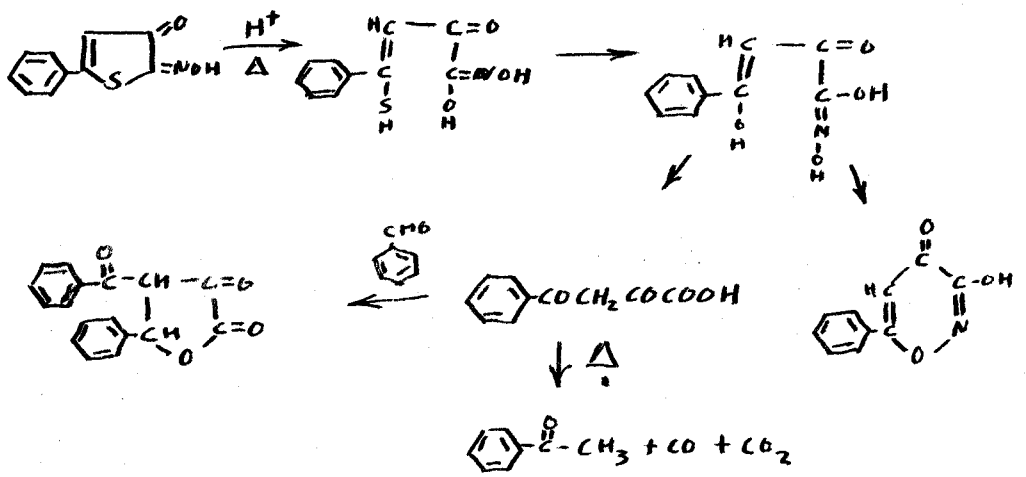


Fig. 55

The action of carbonyl compounds and nitrous acid derivatives as cleavage agents was negligible. From the 5-phenyl-2,3-thiophenequinone-2-oxime we prepared an acetate ester, a 2,4-dinitrophenylhydrazone, a dioxime, and substituted thienooxazoles. The monoxime entered into complex formation with extremely dilute solutions of Group I cations.

Refluxing the oxime in aromatic aldehydes led to substituted thienoxazoles. The reaction did not work

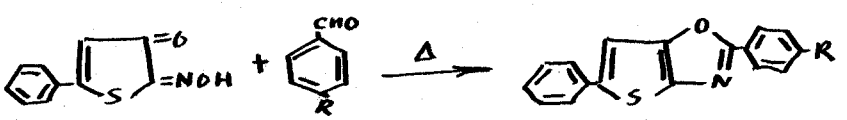


Fig. 56

with aliphatic aldehydes. A semi-quantitative study of this reaction did not disclose what materials, if any, catalyze this reaction. The oxime did not form an oxazole-N-oxide when a solution with benzaldehyde in glacial acetic acid was treated with hydrogen chloride as did other alpha diketone monoximes as well as 1,2,3-cyclohexanetrione-1,3-dioxime. Benzil monoxime and phenanthrenequinone monoxime on refluxing in benzaldehyde gave 2-phenylimidazole derivatives instead of the oxazoles.

The dioxime was obtained from the reaction between the monoxime, and hydroxylamine in cold, strongly alkaline solution. It is a colorless solid which characteristically gives a red precipitate with Ni^{++} ions and will detect Fe^{+++} ions at a concentration of five parts per million. The dioxime was stable in dilute base but in 18 normal hydrochloric acid was hydrolyzed partly to the monoxime and partly to 3-phenyl-5-cyanoisoxazole.

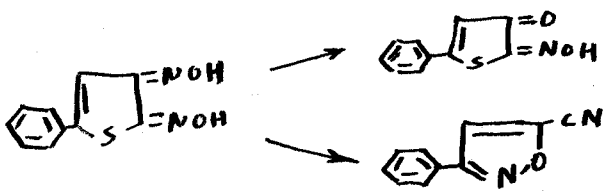


Fig. 57

The isoxazole was identified by hydrolysis to a known acid, and the intermediate amide was also isolated. This compound is interesting because its formation involves a rearrangement of the nitrogen-oxygen atoms of the expected

isoxazole. The isoxazole was also formed when the dioxime was heated in benzaldehyde, or refluxed in aqueous acetic acid containing pyruvic acid. Heating the dioxime in toluene gave a non-acidic unidentified compound.

We investigated the following route to 5-phenyl-2,3-thiophenequinone-3-oxime:

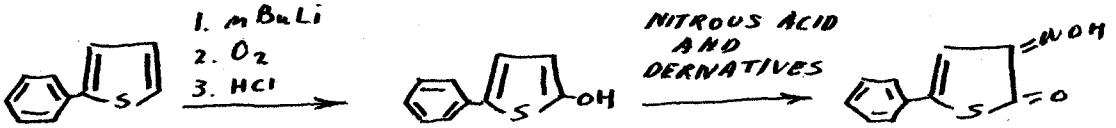


Fig. 58

Phenylthiophene was prepared by the method of Steele. The reaction described by Broun and Voronkov between 1-phenyl-butene-1 and sulfur gave less than five per cent yield instead of the 35 per cent reported. The 2-hydroxyl-5-phenylthiophene was prepared by the procedure of Kreuz and Hurd, i.e. oxygenating a mixture of thienylmagnesium halide and alkylmagnesium halide but phenylthienyllithium was used instead of the magnesium compound; this avoided the preparation of the bromide. We were unsuccessful in our attempts to nitrosate 2-hydroxy-5-phenylthiophene. The use of nitrous acid, nitrogen oxide gases or isoamyl nitrite and hydrogen chloride gave only dimer and tars.

EXPERIMENTAL

3-Phenyl-1,2-dithiacyclopentene-3-one-5

The reaction products from two runs of 484 g. (2.75 moles) of ethyl cinnamate and 500 g. of sulfur heated together for four hours at 250° were combined and extracted first with three 500 ml. portions of boiling ethanol, and then with seven 500 ml. portions of boiling acetone. From the ethanol there was formed upon cooling a reddish-brown solid. A further, smaller quantity of product was isolated from the ethanol by concentration of the solution, but it was necessary to recrystallize this batch from ethanol. The ethyl alcohol had extracted only a portion of the cyclic disulfide, but all of the tar and therefore the acetone extractions contained nearly pure disulfide and the product in these extractions was recovered by total evaporation of the solvent. A total of 505 g. (47.3%) of disulfide was obtained. Recrystallization of a sample from methanol yielded light yellow crystals, m.p. 116-116.8° (lit. m.p. 117°)(64).

4-Keto-6-phenyl-3,7-dithia-5-cis-nonenedioic acid

To an iced solution of 250 g. (2.64 moles) of monochloroacetic acid, neutralized with an equimolar quantity of solid sodium carbonate, in 1.5 liters of

(64) A. Luttringhaus, H. B. Konig and B. Bootcher, Ann. 560, 209 (1948).

water was added a solution of 170 g. (0.88 mole) of cyclic disulfide in 484 g. of molten sodium sulfide nonahydrate. Unreacted disulfide precipitated during the addition and was recovered and dried. The clear, filtered solution of the sodium salt of the diacid was acidified with hydrochloric acid (1:1) until it turned Congo red paper blue-black and the oil thus formed was allowed to stand until it had crystallized. The procedure was repeated twice with equal portions of the remainder of the original 500 g. of disulfide and twice with recovered, dried disulfide. After three days the oils had crystallized, these were filtered, combined, and dried to constant weight, 450 g. (56.0%), melting point 155-156°, a sample recrystallized from 50 per cent glacial acetic acid melted at 155.0-156.0°.

A good amount of product remained dissolved in the 10 liters of filtrate but this was not recovered.

5-Phenyl-3-acetoxythiophene

A finely ground mixture of 200 g. (0.64 mole) of diacid and 200 g. (2.44 moles) of anhydrous sodium acetate was heated in 600 ml. (651 g., 6.36 moles) of acetic anhydride for four hours on a water bath. The reaction was carried out in a 3 l. beaker so arranged in a well-vented hood that at the end of this time most of the excess acetic anhydride had been removed. Three liters of cracked

ice and water was added and the mixture was allowed to stand overnight. The dark brown, crystalline product was isolated by filtration, washed with cold water, and extracted repeatedly by stirring with 200 ml. portions of petroleum ether (b.p. 90-120°), without heating, until spontaneous evaporation of the solvent from a test quantity of solution indicated no further material was being extracted. The petroleum ether was decanted into a large crystallizing dish and the solvent was allowed to evaporate. The product was dried to constant weight in a vacuum desiccator and 112 g. (90.2%) of a slightly yellow, nearly colorless powder was obtained, m. p. 72-75°.

5-Phenyl-3-hydroxythiophene

Five grams of 5-phenyl-3-acetoxythiophene was dissolved in 200 ml. of 95% ethanol and 10% sodium hydroxide solution (ca. 10 ml.) was added to the solution being warmed on a hot plate until ester was completely saponified. This was tested for by adding one drop of the reaction mixture to several ml. of water. The absence of turbidity indicated that the water insoluble ester had been completely hydrolyzed. Hydrolysis took only a few minutes, prolonged heating caused dimerization. A large excess of ice water was added and the solution was acidified with dilute hydrochloric acid. A pink precipitate, contaminated with darker material, formed very slowly. It

was recrystallized from petroleum ether (b. p. 40-60°) as light yellow crystals that weighed 2.4 g., melting point 78°. The yield was 59%.

5-Phenyl-2,3-thiophenequinone-2-oxime

Ninety grams of 5-phenyl-3-hydroxythiophene acetate (0.414 mole) was dissolved in a solution of 400 ml. of 5% sodium hydroxide (0.50 mole) in 1 l. of ethanol. The solution was warmed on a water bath until hydrolysis was complete and this was checked by adding a drop of the solution to several ml. of distilled water. The formation of turbidity indicated unsaponified ester, for when only the thienolate ion existed in solution no precipitation occurred. At this point a solution of 55 g. (0.8 mole) of sodium nitrite in water was quickly added, the mixture was immediately poured into excess, iced, dilute hydrochloric acid and the light yellow precipitate was isolated, dried, recrystallized from ethanol and recrystallized a second time from this solvent (Darco treatment). The filtrates were reworked several times and there was eventually isolated 52 g. (61%) of yellow needles, m.p. 214-215°.

Reactions with ferric chloride

a. 5-Phenyl-3-hydroxythiophene

For these tests the thienol, freshly recrystallized from petroleum ether (40-60°) and obtained as colorless

crystals was used. The following preparations containing hydroxythiophene were treated with two drops of 10% ferric chloride solution.

I. A solution of 0.02 g. of thienol in 1.05 ml. of ethanol and 2 ml. of water. Red coloration and red precipitate occurred.

II. A solution of 0.03 g. of thienol in 2 ml. of ethanol. A dark red-blue color developed; upon dilution with water a precipitate formed.

III. A solution of 0.015 g. of thienol in 1 ml. of warm water. The solution took on a red, turbid appearance.

IV. A suspension of 0.01 g. of thienol in cold water. There occurred no color change.

Simultaneous control tests were made with phenol and a positive reaction, indicated by a deep purple color, was noted in each case.

b. 5-Phenyl-3-methoxythiophene

Two drops of the ether was dissolved in 2 ml. of alcohol, sufficient water was added to cause turbidity, then enough alcohol was added to restore the clear solution. A 10% ferric chloride solution was added dropwise until the solution again became cloudy, and clarity was then again obtained by the addition of alcohol. At no point

was there any color change.

c. 5-Phenyl-2,3-thiophenequinone-2-oxime

To the following preparations containing the oxime, two drops of 10% ferric chloride solution was added:

I. A suspension of oxime in water.

II. A saturated solution of oxime in boiling water (Solubility = 0.03 g/100 ml.).

III. Three ml. of a warmed solution of 0.02 g. of oxime in 5 ml. of ethanol and 14 ml. of water.

IV. A solution of 0.04 g. of oxime in 5 ml. of alcohol; water was added until the oxime started to precipitate.

No color change occurred in any test. A control with phenol gave positive results in each case.

5-Phenyl-3-methoxythiophene

Five grams of 3-hydroxy-5-phenylthiophene was placed in a 100 ml. three-necked flask, and after a solution of 1.6 g. of potassium hydroxide in 20 ml. of distilled water was added, 3 ml. of dimethyl sulfate was added dropwise over a period of one hour to the stirred solution. An atmosphere of nitrogen was maintained. The flask was immersed in an ice-salt bath during addition of the methylating agent, and at the conclusion of the addition the solution was refluxed for 20 minutes. The organic

layer was separated from the aqueous phase which was extracted with ether twice and all the organic portions were combined. Drierite was added and allowed to act for two hours, then it was removed, the solvent was evaporated from the product, and the thienol ether was distilled under nitrogen, b.p. 128-134° (2 mm.), 3.15 g. (60%). The ether was redistilled twice and was finally obtained as a colorless liquid, b.p. 141-142° (3 mm.), m.p. -3 to +3°.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.5; H, 5.3; S, 16.8

Found: C, 69.9; H, 5.5; S, 16.8 (Manser)

Attempted preparation of the semicarbazone of 3-hydroxy-5-phenylthiophene

To a solution of 1 g. of the thienol in ethanol was added sufficient water to just cause turbidity and then 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate were added. After the mixture was heated to reflux and then allowed to cool, light brown needles were obtained, m.p. 75-76°. 5-Phenyl-3-hydroxythiophene (m.p. 75-76°) when treated with nitrous acid yields 5-phenyl-2,3-thiophenequinone-2-oxime (m.p. 214-216°) and when the product of the semicarbazone reaction was nitrosated a similar yellow compound, m.p. 215-216°, was obtained. This was interpreted as showing that the 5-phenyl-3-hydroxythiophene was recovered unchanged.

Attempted condensation of 5-phenyl-3-hydroxythiophene with p-nitroso-N,N-dimethylaniline

a. A solution of 1 g. (5.7mmoles) of the thienol and 0.5 ml. of benzyltrimethylammonium hydroxide in methanol (33%) was added to a filtered solution of 1.5 g. (8.43 millimoles) of p-nitroso-N,N-dimethylaniline[65] in 40 ml. of alcohol. The resulting dark red solution was heated to the boiling point, cooled in a Dry Ice-acetone mixture, and a product precipitated which was isolated as a dark red powder (0.56 g.) that gradually turned black.

b. A solution of 1 g. (0.00568mmole) of the hydroxythiophene in 15 ml. of absolute ethanol added to a solution of 1.5 g. of nitroso-N,N-dimethylaniline in 25 ml. of absolute ethanol was warmed slightly on a hot plate, and then cooled with Dry Ice whereupon a small amount of black solid was isolated. This material when heated with 15% hydrochloric acid formed a tar. The filtrate from the initial reaction stood for several days at room temperature and a small amount of dark, reddish-brown solid formed. The solid gradually decomposed when heated and finally melted between 230-235°. Because of its extreme solubility in all solvents except water the small amount of material was not purified.

The reaction of 5-phenyl-3-hydroxythiophene and bromine

To a solution of 0.2 g. (1.15 mmole) of the thienol

(65) R. Adams and G. H. Coleman, Organic Syntheses, Coll. Vol. 1, John Wiley and Sons, Inc. New York, 1932 (1st ed.), p. 208.

in 7 ml. of chloroform was added 0.5 ml. (1.5 g., 9 mmole) of bromine at room temperature. Hydrogen bromide was evolved. The solvent and excess bromine were allowed to evaporate and brownish-red crystals remained, 0.47 g. (100%), m.p. 114-120°. After two crystallizations from carbon disulfide yellow granular crystals were obtained, m.p. 133-134°. This compound was not further investigated.

2-Bromo-3-methoxy-5-phenylthiophene

A slurry of 3.2 g. (0.0168 mole) of the hydroxythiophene methyl ether and 2.8 g. (0.0158 mole) of N-bromosuccinimide in 20 ml. of carbon tetrachloride was stirred at room temperature for three hours whereupon the reaction appeared to be complete and succinimide was removed by filtration. The solvent was removed by evaporation under reduced pressure and left a purple oil, which upon washing with 95% ethanol crystallized. A colorless solid (m.p. 45-47°) was obtained by extracting this with petroleum ether (b.p. 40-60°). This material when sealed under nitrogen at room temperature slowly decomposed, liberating HBr and yielding a dark purple solid, within a few hours. A small quantity was recrystallized from ethanol with the aid of Dry Ice, m.p. 47-48°.

The reaction of 5-phenyl-3-hydroxythiophene with N-bromosuccinimide

A solution of 5.0 g. (0.0284 mole) of the thienol in 140 ml. of carbon tetrachloride, and 4.8 g. (0.0270 mole)

of N-bromosuccinimide, were stirred for two hours at 0° under a nitrogen atmosphere. After the solution was filtered, the solvent was removed at 18° by vacuum evaporation, and the flask was cooled to 0° and flushed with nitrogen to remove the last traces of carbon tetrachloride from a tarry residue. This also flushed out sizable quantities of grey, choking fumes that were probably HBr. When the fumes were completely flushed out the flask was stoppered and stored in a refrigerator overnight. A mixture of dark brown solid material, and tar was finally obtained and this was washed with methanol until the tar was removed. The red-brown undissolved material was only slightly soluble in ethanol, methanol or acetone. A dilute acetone solution when cooled in Dry Ice gave a reddish-brown powder; this gave a negative Beilstein test for halogen and when recrystallized from dioxane had a melting point of 280°.

5-Phenyl-2,3-thiophenequinone-2-oxime acetate

To a solution of 0. 1 g. (2.5 mmoles) of sodium hydroxide in 50 ml. of water was added 0.5 g. (2.5 mmoles) of oxime. About 40 g. of crushed ice and 0.5 ml. of acetic anhydride were added to the warmed, filtered solution. The mixture was vigorously shaken and a yellow precipitate formed very rapidly. The product was recrystallized from isopropyl alcohol; yield 0.40 g. (60%); m.p. 149-150°;

mixed melting point with the compound formed in the reaction between the oxime and nitrous acid in glacial acetic acid (m.p. 149-150°) showed no depression.

After a solution of 0.3 g. (1.5 mmoles) of the oxime acetate in 15 ml. of ethanol and 5 ml. of 6 N sodium hydroxide had been refluxed for thirty seconds, it was acidified with 6 N hydrochloric acid and then excess water was added. The yellow precipitate was recrystallized from ethanol, yield 0.1 g. (40%); m.p. 217-219°.

Reaction of 2,4-dinitrophenylhydrazine with 5-phenyl-2,3-thiophenequinone-2-oxime

A solution of 0.3 g. (1.5 mmole) of oxime in 26 ml. of heated ethanol was added to 7 ml. of a standard 2,4-dinitrophenylhydrazine solution in ethanol and sulfuric acid[66]. Upon cooling dark brown needles formed, and were isolated, recrystallized twice from ethanol and dried. They had a melting point of 232.0-232.5 when heated at the rate of 2.5° per minute, or 226.0-227.0 when heated at one degree per minute.

Anal. Calcd. for $C_{16}H_{11}N_6O_5S$: C, 49.8; H, 2.85
Found: C, 49.6; H, 2.78 (Clark)

(66) R. L. Shriner and R. C. Fuson, The Systematic Identification of Organic Compounds, John Wiley and Sons, Inc., New York, 1948, p. 171.

Attempted preparation of the semicarbazone of 5-phenyl-2,3-thiophenequinone-2-oxime

To a solution of 0.6 g. (3 mmole) of oxime in 21 ml. of ethanol and 10 ml. of water was added 0.6 g. (6 mmoles) of semicarbazide hydrochloride and 1 g. (0.020 moles) of sodium acetate. The clear solution was refluxed for one minute and upon cooling a yellow precipitate formed which was recrystallized twice from ethanol, m.p. 211°, mixed melting point with oxime (m.p. 209-209.5°), 209-209.5°.

Attempted preparation of the semicarbazone of 5-phenyl-2,3-thiophenequinone-2-oxime acetate

To a solution of 0.6 g. (3 mmoles) of oxime acetate in 21 ml. of ethanol and 10 ml. of water was added 0.6 g. (6 mmoles) of semicarbazide hydrochloride and 1 g. of sodium acetate. The clear solution was refluxed for one minute and then stood several days at room temperature without yielding a precipitate. The addition of water caused the precipitation of yellow solid, m.p. 213-215°.

Action of water on 5-phenyl-2,3-thiophenequinone-2-oxime

A suspension of 0.3 g. (1.5 mmoles) of oxime in 200 ml. of water was refluxed for six days. The undissolved oxime was filtered from the hot solution, and dried, weight 0.23 g., m.p. 212-216°, and when the filtrate was cooled to room temperature, a further quantity of yellow

precipitate was isolated, 0.06 g., m.p. 212-216°.

Complex formation of 5-phenyl-2,3-thiophenequinone-2-oxime and 5-phenyl-2,3-thiophenequinonedioxime

Solutions of 0.010 g. of 5-phenyl-2,3-thiophenequinone-2-oxime in 5 ml. of ethanol and of 0.010 g. of 5-phenyl-2,3-thiophenequinone dioxime in 5 ml. of ethanol were prepared. To two drops of cation solution at a concentration of 0.1 mgm. per ml. on a 1 cm. spot plate was added two drops of organic reagent. The following results were obtained.

Cation	Monoxime	Dioxime
Ag^{+}	yellow ppt.	-
Ba^{++}	-	-
Bi^{+++}	-	-
Ca^{++}	-	-
Cd^{++}	-	-
Co^{+}	-	pink color
Cr^{+++}	-	-
Cu^{++}	-	yellow-brown ppt.
Fe^{++}	-	-
Fe^{+++}	-	dark black ppt.
Al^{+++}	-	-
Hg^{++}	yellow ppt.	-
Hg_2^{++}	yellow ppt.	-
Mn^{++}	-	-
Mg^{++}	-	-
Ni^{++}	-	red ppt.
Zn^{++}	-	-
Pb^{++}	yellow ppt.	-
Sn^{++}	-	-

The monoxime was found to give a yellow-orange precipitate with Group I metals, Ag^{+}, Pb^{++}, and Hg^{++}. The dioxime gave a red precipitate with nickel and a heavy dark blue-black precipitate with Fe^{+++}. One ml. of the Fe^{+++} solution was diluted to 200 ml. The concentration of Fe^{+++} was 0.5 parts per million. One drop of this solution was added to one drop of dioxime solution on a spot plate, there resulted a blue-grey coloration.

Action of aqueous acetic acid on 5-phenyl-2,3-thiophenequinone-2-oxime

A solution of 1.01 g. (5 mmoles) of oxime in 20 ml. of glacial acetic acid and 6 ml. of water was refluxed for 50 minutes and then cooled. Reddish-orange needles were isolated and dried at 75° for twelve hours, 0.80 g., m.p. 214-216°. The addition of water precipitated another 0.10 g. of oxime, total recovery was 90%.

Action of aqueous salt solution on 5-phenyl-2,3-thiophenequinone-2-oxime[26]

To 1 g. (5 mmoles) of oxime suspended in 50 ml. of water heated in a water bath was added 2 g. (0.016 mole) of sodium sulfite and after heating for several minutes the undissolved material was removed by filtration, the solution was cooled and extracted with ether. The ether contained only oxime, m.p. 220°.

Action of mineral acids on 5-phenyl-2,3-thiophenequinone-2-oxime (28,29,30)

a. A solution of 0.5 g. (2.5 mmoles) of oxime dissolved in 15 ml. of 95% ethanol and 10 ml. of sulfuric acid (1:1) was refluxed for five minutes and the black solution was poured into excess water. The yellow precipitate was dried, 0.48 g., m.p. 209-210°.

b. A solution of 1.5 g. of 5-phenyl-2,3-thiophenequinone-2-oxime (0.0073 mole) in 30 ml. of ethanol was added dropwise to 200 ml. of sulfuric acid (1:1) through which superheated steam was being passed. One liter of distillate, collected during the course of the addition, was saturated with sodium chloride, cooled, and extracted with ether, which yielded 0.12 g. (0.0010 mole - 14%) of acetophenone.

The pot liquor was diluted to 1 l. with water, saturated with sodium chloride, and extracted with three 100 ml. portions of ether which after washing with sodium carbonate solution was found to contain no solute. The sodium carbonate solution contained an undissolved solid, weight 0.29 g., (0.00135 mole) which proved to be the sodium salt of the oxazinone. It was dissolved in water, the solution was acidified and extracted with ether, which yielded 0.15 g. of a colorless solid, m.p. 155-158°, after one crystallization from benzene it had a melting point of 155-156°.

In addition to the undissolved sodium salt of 3-hydroxy-6-phenyl-oxazine-4-one the sodium carbonate washings contained a further quantity of the oxazine in solution which was isolated by acidification and ether extraction; 0.25 g. (1.3 mmoles, 19%) of a yellow solid, melting point 139-145°, which recrystallized once from benzene yielded colorless needles melting at 152-154°. This material showed no depression when a mixed melting point was taken with the solid first isolated, but a mixed melting point with benzoylpyruvic acid had a depression of 25°.

c. A mixture of 2.0 g. (0.010 moles) of oxime, 20 ml. of o-dichlorobenzene and 20 ml. of concentrated hydrochloric acid was refluxed for sixteen hours. The layers were separated and the aqueous layer was extracted with ether which was added to the organic portion. The combined organic portions were extracted with sodium carbonate solution and the addition of concentrated sodium hydroxide solution to this caused the precipitation of 2.0 g. of solid. The filtrate from the isolation of this solid yielded 0.3 g. of unreacted oxime upon acidification. The solid was extracted twice with boiling 50 ml. portions of ethanol; from these was eventually isolated another 0.2 g. of oxime, melting point 214°; mixed melting point with a known sample showed no depression. Acidification with dilute hydrochloric acid of the alcohol insoluble residue dissolved in boiling water caused the evolution of a gas,

indicating that some of the solid was sodium carbonate. Upon cooling light yellow needles were obtained, 0.15 g., m.p. 140-148°, which after one recrystallization from benzene melted at 155-156°. Another 0.13 g., m.p. 150-154°, was extracted from the last filtrate with ether. After one recrystallization from benzene it had a melting point of 152-153°; mixed melting point of the two portions 155-156.5°.

Anal. Calcd. for $C_{10}H_6NO_3$: C, 63.5; H, 3.7; N, 7.4
Found: C, 63.1; H, 4.2 (Manser) N, 7.0 (Schwarzkopf

A solution of 0. 15 g. of the oxazinone and 0.15 g. of aniline in ethanol was heated on a water bath for three hours and upon cooling light cream colored, almost colorless needles were formed, m.p. 177-178°. The known anil[67] of benzoylpyruvic acid was similarly prepared by warming a solution of 0.1 g. of benzoylpyruvic acid and 0.1 g. of aniline in ethanol on a water bath for three hours. When the solution was cooled the addition of petroleum ether caused the formation of an oil which soon solidified to yield 0.13 g. of the anil, m.p. 156-159°. A final crystallization from ligroin (b.p. 40-60°) gave light tan needles, m.p. 168-169°, m.m.p. with oxazinone anil, 134-140°.

d. Three-tenths of a gram (1.5 mmole) of oxime in

(67) L. Claisen and H. Bromme, Ber. 21, 1134 (1888).

25 ml. of sulfuric acid (1:1) was heated to boiling and immediately steam-distilled whereupon a small quantity of a yellow oil was obtained in the distillate which solidified to a brown solid, m.p. 108°-112°. The material burned with the odor and characteristic blue color of burning sulfur. From the still pot was isolated 0.3 g. of solid, m.p. 212°.

e. One half gram (2.5 mmole) of oxime in 20 ml. of 18 N hydrochloric acid was refluxed for two hours; very little of the material appeared to react or go into solution and 20 ml. of glacial acetic acid was added and refluxing was maintained for an additional six hours. The solution was finally filtered, and a small amount of residue was isolated and dried, m.p. 216-220°. Although the addition of a large quantity of ice to the filtrate caused no precipitation, the remainder of the organic material was isolated as a tar by ether extraction.

f. A solution of 0.5 g. (2.5 mmole) of oxime in 20 ml. of ethanol and 10 ml. of 85% phosphoric acid was refluxed for several minutes. Water was added to isolate the product, m.p. 212-214°.

g. A solution of 1 g. (5.0 mmole) of oxime in 150 ml. of concentrated hydrochloric acid and 150 ml. of distilled water which had been refluxed for sixteen hours was neutralized with solid sodium carbonate and then reacidified.

It was then extracted with three 100 ml. portions of ether which, after drying with Drierite, yielded 0.44 g. of a red solid. This residue was recrystallized from benzene to give brown, granular crystals, m.p. 156-158°. To the benzene solution was added 50 ml. of ether and this organic phase was extracted with three 15 ml. portions of 5% sodium hydroxide solution and 25 ml. of distilled water. The benzene and ether were allowed to evaporate and the non base-soluble residue was dissolved in methanol. To this 2,4-dinitrophenylhydrazine solution[66] was added. The resultant red precipitate was recrystallized from methylcellusolve and melted at 246-248°; mixed melting point with an authentic sample of the 2,4-dinitrophenylhydrazone of acetophenone (m.p. 249-251°) showed no depression.

Benzoylpyruvic acid was synthesized by the method of Bromme and Claisen[67]. A solution of 1 g. of benzoylpyruvic acid in 150 ml. of concentrated hydrochloric acid and 150 ml. of distilled water was refluxed for sixteen hours. The solution was neutralized with base and reacidified with dilute hydrochloric acid. This was extracted with three 100 ml. portions of ether and when the ether was removed a liquid with the odor of acetophenone remained. Its 2,4-dinitrophenylhydrazone had a melting point of 247-249°, m.m.p. 250-251°(with an authentic sample).

The action of carbonyl compounds and acids on 5-phenyl-2,3-thiophenequinone-2-oxime (28,29,30)

a. One half gram (2.5 mmole) of oxime, dissolved in 10 ml. of hydrochloric acid (1:1), and 20 ml. of acetone were refluxed for eight hours. The red solution was steam-distilled using superheated steam and a trace of yellow oil came over. A solid residue formed in the still pot; this recrystallized from ethanol as a yellow powder, m.p. 222°.

b. One half gram (2.5 mmoles) of oxime dissolved in 12 ml. of sulfuric acid (1:1) and 20 ml. of acetone was refluxed for eight hours. After cooling for an hour the viscous tarry product was steam-distilled and a small quantity of yellow oil was obtained that had the odor of mesitylene.

c. One half gram (2.5 mmoles) of oxime in 20 ml. of acetone and 5 ml. of sulfuric acid (1:1) was steam-distilled directly. After twenty minutes all the acetone had distilled and the distillate had taken on a yellow, opalescent color. The residue proved to be the unchanged oxime.

d. A mixture of 0.3 g. (2.5 mmoles) of oxime, 20 ml. of sulfuric acid (1:1) and 2 ml. of acetone was refluxed for one hour. The reaction mixture contained no steam-distillable product.

e. A mixture of 0.3 g. (1.5 mmoles) of oxime, 20 ml. of acetone and 2 ml. of sulfuric acid (1:1) was refluxed for one hour. The oxime was recovered unreacted.

f. A mixture of 0.3 g. (1.5 mmoles) of oxime, 20 ml. of 40% formaldehyde solution and 1 ml. of concentrated sulfuric acid was refluxed for one hour. When the clear red solution was cooled, 0.140 g. of oxime crystallized, m.p. 212°.

g. A mixture of 0.3 g. (1.5 mmoles) of oxime, 10 ml. of concentrated hydrochloric acid and 10 ml. of 40% formaldehyde solution was refluxed for one hour. A black scum which apparently contained most of the organic matter formed on the sides of the flask; dilution of the supernatant liquid with water caused no precipitation.

h. A mixture of 0.250 g. (1.2 mmoles) of oxime, 10 ml. of formalin, and 1 ml. of concentrated hydrochloric acid was refluxed for 1 hour, then 10 ml. of concentrated hydrochloric acid was added to the cooled solution, and refluxing was continued for another 45 minutes. A tar had formed along the sides of the flask while a trace of pink precipitate (m.p. 120-122°) formed in the body of the solution. The compound had a formaldehyde-like odor, was soluble in water and ether, and gave a negative Beilstein test for halogen.

i. A solution of 1.5 g. (7.5 mmoles) of oxime, 6 ml. of benzaldehyde, and 6 ml. of concentrated hydrochloric acid in 75 ml. of isopropyl alcohol was refluxed for four hours. The solution was cooled in an icebox overnight, and orange crystals were isolated, weight 1.12 g. The filtrate was condensed and a second crop of crystals was obtained, 0.27 g., total recovery amounted to 93%, m.p. 210-212°.

j. A solution of 0.68 g. (3.4 mmoles) of oxime in 15 ml. of concentrated hydrochloric acid and 30 ml. of acetone was refluxed for six hours. The solution became dark and tarry and had an unpleasant sour odor. The acetone was cautiously evaporated and the residue was extracted with seven 75 ml. portions of ether, which were combined and washed twice with water, thrice with 5% sodium carbonate solution, with saturated salt solution, and finally dried with calcium chloride for three hours. The ether was removed and left a black, tarry residue which was heated with boiling ligroin (b.p. 90-120°). The extraction liquid was decanted and quickly cooled in a Dry Ice bath and a small amount of brown powder was isolated. Neither this nor the unextracted material, which was the bulk of the product, yielded to further purification and this reaction was not further investigated.

k. A solution of 2.0 g. (0.010 mole) of oxime in 20 ml. of benzaldehyde and 20 ml. of concentrated hydrochloric acid was refluxed for eighteen hours. The organic layer was separated from the aqueous layer and the aqueous portion was washed with two 25 ml. quantities of ether which were added to the benzaldehyde. The organic layer was extracted with 25 ml. portions of 10% sodium carbonate until their acidification no longer gave a precipitate. The total precipitate was collected and dried over sodium hydroxide in a vacuum desiccator, weight 0.5 g. After three recrystallizations from ethanol it had a melting point of 221.2-222.0°; mixed melting point with an authentic sample of 2,3-diketo-4-benzoyl-5-phenyltetrahydrofuran 220-221°. The authentic sample of 2,3-diketo-4-benzoyl-5-phenyltetrahydrofuran was synthesized by adding to a warm solution of 0.2 g. of benzoylpyruvic acid and 0.1 g. of benzaldehyde dissolved in 10 ml. of ethanol 6 N hydrochloric acid dropwise until the solution became cloudy. Sufficient alcohol was added to restore a clear solution which was heated on the water bath for five hours. The solution was concentrated, then cooled, to give colorless needles, m.p. 218-220°.

A solution of 0.1 g. of this compound and 0.03 g. of aniline was refluxed in ethanol for three hours. Upon cooling, yellow crystals were obtained which melted from 171-173° (Lit. for 2,3-diketo-4-benzoyl-5-phenyltetrahydro-

furan-3-anil, 171-172°)[68].

The action of nitrous acid and nitrous acid derivatives on 5-phenyl-2,3-thiophenequinone-2-oxime (31,32,33)

a. To a solution of 1 g (5 mmoles) of oxime in 40 ml. of heated glacial acetic acid was added 3.0 g. (43 mmoles) of sodium nitrite with no further heating. One hundred and fifty milliliters of water was added and a yellow precipitate formed slowly which when isolated weighed 0.49 g., m.p. 135-138°. After recrystallization to constant m.p. it melted at 149-150°.

Anal. Calcd. for $C_{12}H_6SNO_3$: C, 58.2; H, 3.7
Found: C, 57.9; H, 3.8 (Clark)

b. One half gram of oxime was dissolved in 18 ml. of acetic acid and 0.5 g. of sodium nitrite was added slowly. One hundred milliliters of water was added to the dark red solution and a small amount of red solid formed which was recrystallized from ethanol. The melting point was above 260° and was not more closely determined. After removal of the red solid, a yellow precipitate gradually formed in the filtrate and after twenty four hours the compound was isolated and recrystallized from ethanol, m.p. 144-145°, recrystallized from isopropyl alcohol, m.p. 149-150°.

(68) S. Ruhemann, J. Chem. Soc. 89[a], 1243 (1906).

c. To a solution of 1 g. (5.0 mmoles) of oxime in 20 ml. of boiling glacial acetic acid was added gradually 0.5 g. (7.2 mmoles) of sodium nitrite. After the dark red solution had been refluxed for thirty minutes, an equal quantity of water was added and the solution was stored in an icebox for several hours whereupon three tenths of a brown solid, m.p. 210-215° was isolated. A large excess of water was added to the filtrate which was allowed to stand overnight and a dark colored gum formed from which 0.1 g. or orange powder, m.p. 200-210°, was isolated. Ether extraction of the remaining material yielded unpromising brown tar.

d. To a solution of 1 g. (5.0 mmoles) of oxime in 20 ml. of boiling glacial acetic acid was added 0.5 g. of sodium nitrite. After refluxing for thirty minutes another 0.5 g. of sodium nitrite was added. A final 0.5 g. (total 0.022 moles) of sodium nitrite was added after another hour and the solution was refluxed for another hour and a half, a total of three hours altogether. A black liquid, with a sour odor indicative of extensive decomposition was formed. When a large excess of water was added and the solution had stood for several hours a gum formed which could not be crystallized from ethanol.

e. A solution of 0.7 g. (3.3 mmoles) of oxime in 20 ml. of glacial acetic acid and 5 ml. of water was

refluxed while 0.5 g. (7.2 mmoles) of sodium nitrite was added. After the light red solution had refluxed for thirty minutes, water was added until it became turbid, and then the solution was cooled. A total of 0.50 g. of oxime was isolated, m.p. 216-217°.

f. A mixture of 37.1 g. of methanol, 2.0 g. of dry hydrogen chloride gas, 0.84 g. (4.1 mmoles) of oxime and 2.5 g. (32 mmoles) of sodium nitrite was refluxed for three hours, filtered from undissolved salts and stored in the icebox overnight. The precipitated solid was isolated and dried, recovery of oxime was 0.81 g. (97%), m.p. 220°.

g. Nitrogen oxide gases evolved by the addition of hydrochloric acid to sodium nitrite were passed into a refluxing solution of 3 g. of oxime in 95 ml. of ethanol. A solution of 4 ml. of concentrated hydrochloric acid in 13 ml. of water was added and the ethanol solution was refluxed for an additional twenty three minutes. The liquid became a red-black color and was stored in an icebox under nitrogen for seven days. The solution was concentrated and 2.0 g. of a reddish-brown precipitate was obtained, m.p. 212°.

h. To a stirred solution of 1.0 g. (5 mmole) of 5-phenyl-2,3-thiophenequinone-2-oxime in 20 ml. of ethanol

was added 3 ml. (22 mmole) of isoamylnitrite. To this a solution of 3 ml. of concentrated hydrochloric acid in 20 ml. of ethanol and 10 ml. of water was added dropwise over a one hour period. During these additions the reaction mixture was heated on a water bath. Finally an additional 10 ml. of water was added and the solution was refluxed for one hour. The solution was stored in Dry Ice until the process of crystallization appeared to be complete. There was recovered 0.80 g. of orange-yellow needles, m.p. 216-217°. A mixed melting point with an authentic sample of oxime showed no depression.

The filtrate had a volume of 60 ml. Five milliliters was treated with 2,4-dinitrophenylhydrazine solution and yielded 0.69 g. of a brick-red crystalline precipitate, m.p. 117-121°. After two recrystallizations from methanol, the compound had a melting point of 122-123°. A mixed melting point with an authentic sample of isovaleraldehyde-2,4-nitrophenylhydrazone (Lit. 123°)[69], showed a sizable depression, m.p. 85-90°. Elemental analysis of the hydrazone was negative for sulfur, although positive for nitrogen. The remaining 55 ml. of solvent was allowed to evaporate and yielded 0.30 g. of a yellow solid, m.p. 160-200°. One recrystallization from ethanol gave 0.1 g. of orange needles, m.p. 214-215.

(69) Ref. 66, p. 229.

Attempted hydrolysis of 5-phenyl-2,3-thiophenequinone-2-oxime with pyruvic acid (36)

a. A solution of 0.83 g. (4.1 mmole) of oxime in 20 ml. of glacial acetic acid, 10 ml. of water and 1 ml. (10 mmole) of pyruvic acid was refluxed for three hours. After this time sodium acetate was added, the solution was allowed to cool and the precipitate which formed was isolated and dried. It weighed 0.70 g. (85% recovery), m.p. 214-217°.

b. A mixture of 0.3 g. (1.5 mmole) of oxime, 1 ml. (10 mmole) of pyruvic acid, 1 ml. of benzaldehyde, and 2 ml. of hydrochloric acid (1:1) was shaken mechanically overnight. The solution was cooled to 0° and orange crystals were isolated which, when dried, melted at 214-215°.

Oxidative cleavage of 5-phenyl-2,3-thiophenequinone-2-oxime with cuprous oxide (27)

a. A mixture of 0.3000 g. (1.5 mmole) of oxime, 10 ml. of butylcellosolve, 1 ml. of acetone, 0.5 g. of cuprous oxide and 1.5 ml. of concentrated hydrochloric acid was shaken mechanically for seventy five minutes. The mixture was steam-distilled; it yielded no product.

b. A mixture of 0.300 g. of oxime, 10 ml. of butylcellosolve, 1 ml. of acetone, 0.5 g. cuprous oxide, 1.5 ml. of concentrated hydrochloric acid and 2 ml. of

water was refluxed for one hour and then steam-distilled. The distillate was extracted with ether which upon evaporation yielded no appreciable residue.

2,5-Diphenylthieno[4,5-b]oxazole

a. A solution of 1.22 g. (6.1 mmole) of oxime in 5 ml. of benzaldehyde was refluxed for twenty four hours. The precipitate which formed on cooling the benzaldehyde solution was isolated; the benzaldehyde was further concentrated and a second quantity of solid was isolated. The total yield was 0.5 g. (23%), m.p. 176-177°; recrystallization from ethanol gave colorless needles, m.p. 176.2-176.8°.

Anal. Calcd. for $C_{17}H_{11}ONS$: C, 73.7; H, 4.0; N, 5.1; S, 11.6

Found: C, 73.4 (Clark; 74.1 (Pittsburgh)
H, 4.1 (Clark); 4.1 (Pittsburgh)
N, 5.2 (Clark); 5.2 (Pittsburgh)
S, 8.7, 8.9 (Pittsburgh); 12.2 (Manser)

The solubility of the oxazole in a solution of 90 ml. of water and 10 ml. of acetone was determined at 29°. Excess exazole was stirred in this solvent for 10 minutes and the undissolved solid was filtered. The filtrate was extracted with ether, the ether evaporated and the residue dried. Weights of 0.0035 g. and 0.0031 g. were obtained in successive runs.

b. After a solution of 0.36 g. (1.8 mmole) of the oxime in 10 ml. (0.1 mole) of benzaldehyde had been refluxed for eighteen hours, the benzaldehyde was removed by distillation and the residue was dissolved in chloroform, washed with sodium carbonate solution and dried with Drierite. Upon removal of solvent and drying agent there was obtained 0.51 g. of a brown crystalline solid. Recrystallization from alcohol yielded two batches of crystals together weighing 0.24 g., m.p. 175-177°.

c. One gram (5 mmole) of oxime in 5 ml. (50 moles) of benzaldehyde and 10 ml. of m-xylene was refluxed overnight. There was no precipitate formed upon cooling the solution. The xylene and benzaldehyde were extracted with base before being removed by vacuum distillation. The residue was recrystallized from dioxane and yielded 0.5 g. (37%) of oxazole, m.p. 172-175°.

d. A mixture of 0.15 g. (0.7 mmole) of oxime, 50 ml. of benzene and 5 ml. (50 mole) of benzaldehyde was refluxed for fifteen hours. The solution was cooled to room temperature and 0.1 g. of yellow needles was isolated, m.p. 214-216°. Another 0.03 g. of oxime was extracted from the solution with base. Total recovery amounted to 87%.

e. A solution of 1 g. of oxime (5 mmole), and 0.5 g. of benzaldehyde (5 mmole) in 20 ml. of absolute alcohol was refluxed for two hours. When the solution was cooled 0.65 g. of oxime, m.p. 218-220°, was isolated.

f. A solution of 1.0 g. (5 mmole) of oxime and 2.0 ml. (20 mmole) of benzaldehyde in 50 ml. of diisopropyl ether

was refluxed for four hours. After standing at room temperature overnight oxime precipitated, but the mixture was cooled to -70° to further aid crystallization and 0.95 g. of oxime (m.p. 215-218°) was isolated by filtration.

g. A solution of 1.3 g. (6 mmole) of oxime in 10 ml. (0.1 mole) of benzaldehyde and five drops of concentrated hydrochloric acid was refluxed for ten hours. The product was stored at 0° for twenty four hours, filtered, and the solid thus isolated was washed with dioxane and vacuum dried. There was obtained 0.4 g. of light brown needles, m.p. 165-170°.

Study of the benzaldehyde-oxazole reaction

The oxazole reactions, using 5 ml. quantities of aromatic aldehydes, were carried out in side neck test tubes. A stirring rod and nitrogen inlet tube were introduced through a two hole rubber stopper. The temperature was followed by means of a 100-170° Anschutz thermometer which was enclosed in the test tube and was suspended from its edge by means of a copper wire hook. The side neck led to an upright semi-micro condenser and from the top of the condenser, glass tubing led into a bubble trap. When the reaction was carried out under nitrogen the flow of this gas through the reaction tube and the condenser was determined noting the stream of bubbles in the trap. The oxime was stirred with various aromatic aldehydes at temperatures close to 150° while time, quantity, catalyst, or atmosphere were varied. At the end of the run the product was transferred to a 25 ml. distilling flask and the solvent was distilled under nitrogen at reduced

pressure. The residue was dissolved in chloroform and extracted with dilute base. When the base soluble portions were investigated they were acidified with dilute hydrochloric acid and extracted with ether. The ether was allowed to evaporate and the total weight of the acidic portion was determined. This was extracted initially with 25 ml. and then with 10 additional ml. of boiling water. The water soluble material was isolated from these aqueous solutions by ether extraction and weighed after evaporation of the ether. The water insoluble material (oxime) was also dried and weighed.

The oxazole portions were worked up by allowing the chloroform to evaporate and first determining the total weight of oxazole and tar. This material was then dissolved in carbon tetrachloride and passed through a 4x18 cm. column of activated alumina (Merck). The oxazoles possessed a blue or blue-violet light and when washed through the column were separated from the very strongly adsorbed tars and could be followed by means of the fluorescence. Carbon tetrachloride gave an excellent separation and usually about a liter of this solvent was required to elute all of the fluorescent material. The solvent was removed with a take-off condenser and the oxazole was washed onto a Petri dish with carbon tetrachloride, which was then allowed to evaporate. The oxazole was weighed and its melting point determined. The results using this procedure are given in Figure 24, page 41.

2-(4-methoxyphenyl)-5-phenylthieno[4,5-b]oxazole

A solution of 1.3 g. (6 mmole) of oxime in 30 ml. (.25 mole)

of anisaldehyde was heated at 150±5° for three hours. The product was dissolved in 100 ml. of chloroform and extracted with sodium carbonate solution until acidification of the base no longer gave a precipitate. The precipitate was extracted with boiling water whereupon 0.74 g. of oxime was left. The chloroform solution was dried overnight with Drierite and after removal of the desiccant and solvent the anisaldehyde was removed by distillation at 1 mm., b.p. 87°, under nitrogen. The residue was crystallized from chloroform and then ethanol, wt. 0.15 g. (18%). The material was recrystallized to constant melting point from ethanol, colorless micro-crystals, m.p. 166.6-166.9°.

Anal. Calcd. for $C_{18}H_{13}O_2NS$: C, 70.4; H, 4.2; N, 4.5; S, 10.4
Found: C, 70.4; H, 4.2; N, 4.6; S, 11.2 (Manser)

Reaction of 2,5-diphenylthiene[4,5-b]oxazole with trinitrofluorenone

Seven-tenths of a gram (2.5 mmole) of oxazole and 0.8 g. of trinitrofluorenone (2.5 mmole) were each heated in sufficient quantities of benzene to just dissolve the compounds at the boiling point. The two pale yellow soluwions were combined; the mixture had a red color, but no precipitation occurred.

2-(4-Isopropylphenyl)-5-phenylthieneo[4,5-b]oxazole

Cuminaldehyde* was purified by extraction with 10% sodium carbonate solution followed by distilled water. After drying the aldehyde with Drierite, it was distilled under nitrogen, b.p. 77.8° (2.6 mm.). A solution of 2 g. (10 mmoles) of the oxime in 30 ml. (0.2 mole) of cuminaldehyde

* The cuminaldehyde was a gift of the Hilton-Davis Company, Cincinnati, Ohio through the courtesy of Dr. N. Crounse.

was heated between 150-170° for eight hours under nitrogen without stirring. The aldehyde was removed by vacuum distillation, b.p. 88° (3 mm.) and the residue was purified in the standard manner via chromatography. There was isolated 0.27 g. of an orange solid which after two recrystallizations from methanol was obtained as colorless needles, m.p. 131.8-132.6°.

Anal. Calcd. for $C_{20}H_{17}NOS$: C, 75.2; H, 5.3; N, 4.4

Found: C, 74.9; H, 5.2; N, 4.7 (Manser)

Para-xylyl bromide

Para-xylyl bromide was prepared by the method of Brewster[70]. A mixture of 106 g. (1.0 mole) of p-xylene, 800 ml. of carbon tetrachloride, 300 ml. of water and a few crystals of iodine was gently refluxed while 126 g. (4.76 mole) of bromine in 500 ml. of carbon tetrachloride was added dropwise. An ultra-violet lamp was placed against the reaction flask and its rays were directed into the reaction during the addition of the bromine. The solution was at first reddish-brown but after a few minutes became colorless, and then again turned yellow. The refluxing was stopped when the mixture had again become colorless whereupon the carbon tetrachloride layer was separated and the solvent removed by distillation. The remaining yellow oil was distilled and yielded 99 g. (54%) of p-xylyl bromide, b.p. 95-105° (8 mm.) and the residue was probably in large part α,α' dibromo-p-xylene. This method is comparable to the direct

(70) J.F. Brewster, J. Am. Chem. Soc. 40, 406 (1918).

bromination of p-xylene at 130° (71) which yields 46% of the p-xylyl bromide and 48% of the dibromo compound.

Para-tolualdehyde

Para-tolualdehyde was prepared from p-xylene and chromyl chloride by the method of Perkin and Law[72,73] in 22% yield.

Para-tolualdehyde was also prepared from p-xylyl bromide and the sodium salt of 2-nitropropane[74] in 57% yield.

2-(p-tolyl)-5-phenylthieneo[4,5-b] oxazole

A solution of 1 g. (5 mmole) of oxime in 7 ml. (.058 mole) of p-tolualdehyde was stirred at 150 ±5° under nitrogen for seven hours. The aldehyde was removed by vacuum distillation and the residue was chromatographed twice on a 4.5x18 cm. colum of alumina using carbon tetrachloride as the eluting agent. There was thus isolated 0.45 g. of a light tan solid which after three recrystallizations from methanol had a melting point of 101.0-102.0°.

Anal. Calcd. for $C_{18}H_{14}NOS$: C, 74.3; H, 4.5; N, 4.7

Found: C, 73.7; H, 4.73; N, 4.9 (Manser)

2-(ω-styryl)-5-phenylthieno[4,5-b]oxazole

A stirred solution of 1.0 g. (5 mmole) of oxime in 5 ml. (.041 mole) of cinnamaldehyde was heated at 150° in a

(71) E.F.J. Atkinson and J.F. Thorpe, J. Chem. Soc. 91, 1697 (1907).
(72) F.M. Perkin and H.D. Law, J. Chem. Soc. 91, 263 (1907).
(73) H.H. Sisler, Inorg. Synthesis 2, 205 (1946).
(74) H.G. Hass and M.L. Bender, Org. Syntheses 30, 99 (1950).

nitrogen atmosphere for eight hours. The cinnamaldehyde was removed by distillation at reduced pressure under nitrogen. The residue was subjected to chromatography through an 18x4.5 cm. column of activated alumina. Carbon tetrachloride was initially used as the eluting agent, but petroleum ether (40-60°) was used to separate the fluorescent layer from a mobile brown layer. The petroleum ether solution of the product was condensed and rechromatographed. Carbon tetrachloride was again used in order to effect a separation of fluorescence into an upper light blue band, and a lower dark purple band.

The purple layer yielded 0.04 g. of an oily residue. The blue layer contained 0.08 g. of an impure brown solid. The latter was recrystallized from ethanol and yielded a very small quantity of yellow needles, m.p. 173-175°.

The reaction was repeated and again yielded trace quantities of oily residues from two fluorescent layers.

Attempted preparation of 2-pentyl-5-phenylthiene[4,5-b]oxazole

A solution of 0.5 g. (2.5 mmole) of oxime in 20 ml. (0.167 mole) of n-hexaldehyde was refluxed at 140° for seven hours. The hexaldehyde was removed by distillation at 35 mm. and the residue was chromatographed on a 4x20 cm. column of alumina. No part of the column fluoresced when exposed to ultra-violet light. A yellow layer was washed through the column with carbon tetrachloride and on removal of this solvent a red oil was obtained which had the odor of hexaldehyde. The 2,4-dinitrophenylhydrazone gave a melting point of 102-104°, a mixed melting point with an authentic sample also occurred at 102-104°. The alumina column was

extruded and 0.42 g. of a reddish-brown oil was extracted from the brown layer at the top of the column. We did not succeed in getting this oil to crystallize from ethanol, benzene, chloroform, petroleum ether (b.p. 40-60°), or dioxane.

2-Phenyl-4,5-dimethyloxazole-N-oxide hydrochloride

Four grams (0.04 mole) of biacetylmonoxime (75) and 4 ml. (0.04 mole) of benzaldehyde were dissolved in 100 ml. of glacial acetic acid and dry hydrogen chloride was bubbled in over a two hour period. A large excess of ether was added and colorless crystals precipitated. These were isolated and dried in an amber desiccator, m.p. 189-191° (Lit., 188°)(46). The yield was 2.3 g. (27%).

Triphenyloxazole-N-oxide hydrochloride

Into a solution of 4.5 g. of 2-benzilmonoxime (0.02 mole), m.p. 136-138°, and 2 ml. (0.02 mole) of benzaldehyde in 30 ml. of glacial acetic acid anhydrous hydrogen chloride was bubbled. The clear solution was saturated with hydrogen chloride and after a few minutes solidified into a colorless crystalline mass. After standing for two days the product developed a light tan color. One hundred ml. of anhydrous ether was added and it became a mass of snow white micro-crystals which weighte 4.30 g. (61.7%). Recrystallization from benzene yielded the free base, m.p. 169-172°. (Lit., m.p. 170-171°)(46).

(75) W. L. Semon and V. R. Damerell, Organic Syntheses, Coll. Vol. 2, 204 (1943).

1,2,3-Cyclohexanetrione-1,3-dioxime

The same procedure described in Organic Syntheses[64] for the preparation of biacetyl monoxime was used in the preparation of cyclohexatrione dioxime. Ethyl nitrite was passed into a mixture of cyclohexanone and hydrochloric acid. The reaction mixture was cooled and a dark red product was removed by filtration. This was washed with acetone and then crystallized from acetone using a Darco to decolorize the material. The compound decomposed spontaneously at 205°. The compound was obtained as fine yellow needles from methanol which upon standing exposed to the atmosphere deformed to an amorphous yellow powder. The phenylhydrazine derivative melted at 180.0-182.5°. The literature[76] states that the dioxime decomposes above 200° and forms a triphenylhydrazone derivative with phenylhydrazine which melts at 182-183°.

4,5-(b-oximinocyclohexenone)-2-phenyloxazole-N-oxide hydrochloride

One gram (6.5 mole) of 1,2,3-cyclohexanetrione-1,3-dioxime was dissolved in 100 ml. of glacial acetic acid. Six milliliters (0.06 mole) of benzaldehyde was added. Anhydrous hydrogen chloride was passed in until the solution became saturated, whereupon the color changed from pale yellow to brown. When the weight of hydrochloric acid absorbed became constant (7.0 g.), the flow was discontinued and a crystalline precipitate started to form at this point. After standing for two days a colorless precipitate formed and was isolated and dried over potassium hydroxide in a vacuum desiccator.

(76) W. Borsche, Festschrift Otto Wallach, 301 (1909); Brit. Abstr. 98[1], 178 (1910).

It weighed 0.45 g., m.p. 165-170°. Recrystallization from methanol yielded the free base, m.p. 125-130°, recrystallized from petroleum ether, m.p. 130.5-132°. The following facts indicate that the salt precipitated, and the free base was obtained by crystallization from methanol.

a. Benzilam-N-oxide hydrochloride easily looses hydrogen chloride when recrystallized from benzene or alcohol[46].

b. The salt, compound with m.p. 165-170° was completely insoluble in petroleum ether.

c. Beilstein test for chlorine was negative on original dioxime, positive from compound m.p. 165-170°, negative for compound m.p. 130-132°.

Attempted preparation of 2,5-diphenylthieno[4,5-b]oxazole-N-oxide hydrochloride

a. Four grams (0.02 mole) of the thiophenequinone monoxime and 2 ml. of benzaldehyde were placed in 150 ml. of glacial acetic acid. Not all of the oxime dissolved. Dry hydrogen chloride gas was passed into the solution for four hours. The product was filtered, and 3.0 g. of undissolved oxime was recovered. A large excess of anhydrous ether was added to the filtrate, no precipitate occurred. The solvents were evaporated, a brown-black residue remained. Recrystallization from ethanol with the assistance of Darco gave 0.2 g. of yellow, orange needles, m.p. 218-220°.

b. Three grams (0.015 mole) of oxime, 15 ml. of benzaldehyde (0.15 mole), and 25 ml. of 37% hydrochloric acid were shaken two and a half hours, and then stirred for five hours. The unreacted, undissolved oxime weighed 2.45 g. The benzaldehyde layer was separated from

the aqueous layer which was made basic but no precipitation occurred. To the benzaldehyde portion 100 ml. of 37% hydrochloric acid and another 0.5 g. of oxime were added, and the mixture was refluxed for four hours. The aqueous portion of the cooled reaction mixture was washed with ether, and then made basic. No precipitation occurred.

c. A mixture of 2.0 g. (0.01 mole) of oxime, 0.92 g. (0.9 mole) of benzaldehyde and 200 ml. of 37% hydrochloric acid was shaken at room temperature for three days. The aqueous layer was separated and neutralized with ammonia. A trace of yellow material formed; this was of insufficient amount to be isolated and in the process of filtration was absorbed by the paper. In a similar, but smaller run, enough yellow solid was obtained for a melting point, 108-110° and it was not further identified. The majority of the oxime was extracted from the organic layer with aqueous carbonate solution.

Reaction of biacetyl monoxime with benzaldehyde

Ten grams of biacetyl monoxime (0.1 mole) in 15 ml. (0.15 mole) of benzaldehyde was heated to reflux, and an additional 15 ml. of benzaldehyde was added to bring all the solid into solution. The solution was refluxed for twenty hours and was then stored in a refrigerator for six days. No precipitation occurred. The benzaldehyde was removed by vacuum distillation under nitrogen. The distillation was continued and a yellow solid, biacetyl monoxime, came over, b.p. 85° (2.5 mm.), m.p. 75-76°. The tarry residue was dissolved in benzene, washed three times with 25 ml. of 10% sodium carbonate solution, and twice with 25 ml. portions of

distilled water, and finally dried over Drierite. Concentration of the solvent eventually left a non-crystalline orange tarry oil. Dioxane was added in attempt to crystallize but this was not successful. The tar was dissolved in a large quantity of ethanol, boiled with Darco, filtered, condensed and cooled. This procedure was also unsuccessful. The last traces of ethanol were removed by vacuum and the procedure was repeated with ether, carbon tetrachloride, and acetic acid. None of these enabled us to further identify the product.

Reaction of cyclohexanetrione dioxime with benzaldehyde

Five grams (0.32 mole) of 1,2,3-cyclohexanetrione-1,3-dioxime in 25 ml. (0.23 mole) of benzaldehyde was stirred under a nitrogen atmosphere for three days. The mixture consisted of a yellow solid in a brown liquid. The mixture was cooled and the solid was isolated by filtration under nitrogen. The solid proved to be unreacted dioxime; this was shown by the preparation of the known phenylhydrazone derivative by heating the yellow solid on a water bath with a few drops of phenylhydrazine and several ml. of ethanol. The mixture was heated to allow the ethanol and excess phenylhydrazine to evaporate and from the red sludge, orange needles were obtained from ethanol, m.p. 180.0-182.5°. The dioxime forms a triphenylhydrazone derivative, m.p. 182-183°.[65] The original filtrate was refluxed for four hours, cooled, and the solid which came down was isolated and recrystallized from methanol, m.p. 215° with sudden decomposition - typical of this dioxime.

When 1.0 g. (6 mmole) of the dioxime in 7 ml. (0.07 mole) of benzaldehyde was refluxed under nitrogen for eighteen hours the material completely decomposed to a charry, black solid.

Reaction of benzil monoxime with benzaldehyde

a. Three grams (0.013 mole) of 2-benzilmonoxime and 10.25 g. (0.10 mole) of benzaldehyde were refluxed for one hour under a nitrogen atmosphere. The stream of nitrogen during this time carried off 8.90 g. of benzaldehyde, and the remainder of the aldehyde was removed by distillation under nitrogen. The residue weighed 2.90 g. This was distilled at 15 mm.; 0.80 g. of material boiling up to 240°, was obtained and this distillate was recrystallized from petroleum ether (b.p. 40-60°) to give colorless crystals, m.p. 119-120°, mixed melting point with an authentic sample of benzoic acid was 121-122°. The final residue weighed 2.00.

b. A solution of 8 g. (0.035 mole) of benzil monoxime in 30 ml. (.3 mole) of benzaldehyde was refluxed for fifteen hours. The solid form, isolated by filtration, was recrystallized from water. It proved to be benzoic acid. The filtrate was condensed by boiling off benzaldehyde at atmospheric pressure. Upon cooling a yellow-orange solid separated and was isolated by filtration. The solid was dissolved in ether, washed with potassium carbonate solution, water, and was then dried over calcium chloride. Removal of the ether and desiccant left a small amount of residue which appeared to be benzaldehyde and some solid. The solid was recrystallized from benzene, m.p. 268-271°. More solid formed in the benzene filtrate and after removal of most of the benzene

the residue was crystallized from ethanol and water. This gave a gummy precipitate which did not improve in physical character by drying under vacuum. In an oven at 80° it eventually dried to a soft powder, m.p. 240-245°, recrystallized from acetone it had a melting point of 273-274°, a mixture with an authentic sample of lophine had a melting point of 272-274°.

Reaction of benzil dioxime with benzaldehyde

Three grams (0.0125 mole) of benzil dioxime in 20 ml. (0.2 mole) of benzaldehyde was refluxed for seventeen hours. The product was cooled at 0° for one day and 0.45 g. of benzoic acid was isolated by filtration, m.p. 114-118°. The remaining benzaldehyde was removed by distillation at reduced pressure, 12.75 g., b.p. 54° (6 mm.). The residue (6.1 g.) was a colorless solid with a tarry orange impurity. It was extracted with 100 ml. of 5% sodium carbonate solution and with two 150 ml. portions of boiling ether, and finally washed with ether. The residue weighed 0.31 g., m.p. 271-273°; it was recrystallized from ethanol, m.p. 275-277°.(77) A total of 1.11 g. of benzoic acid, m.p. 120-121°, was extracted from the ether with base and 3.4 g. of an oily orange solid remained. This was extracted repeatedly with petroleum ether (b.p. 40-60°) until no more material dissolved and left an oily solid which was separated into 0.42 g. of a dark, petroleum ether insoluble oil and 0.18 g. of lophine, m.p. 271-273°. The red, slightly soluble oil weighed 1.40 g. Over a period of months more solid appeared to form in these oils.

(77) D. Davidson, M. Weiss, and Murray Jelling, J. Org. Chem. 2, 319 (1938).

Reaction of benzil-N-oxide with benzaldehyde

A solution of 1 g. (3 mmole) of benzilam-N-oxide in 7 ml. of benzaldehyde (0.070 moles) was heated for eight hours at 140°. The solution was dissolved in ether and the ether extracted with dilute hydrochloric acid. The acid solution was made basic and extracted with ether. The ether yielded a small quantity of colorless solid which, after one recrystallization from ethanol, had a melting point of 273-274°. A mixed melting point with an authentic sample of lophine showed no depression.

The ether was removed from the original organic solution, and the benzaldehyde was distilled at 1 mm. The residue was dissolved in ether and washed with base, and the ether wasthen removed. This gave 0.54 g. of a gummy, orange-white solid which was recrystallized from benzene and then from ethanol, m.p. 229-230°. Evaporation of the benzene filtrate left a red, gummy residue which was extremely soluble in ethanol, chloroform, benzene, methanol, ethyl acetate, and ether and was not further characterized.

Phenanthraquinone monoxime

A solution of 10.0 g. (0.05 mole) of phenanthraquinone and 4.5 g. (0.065 mole) of hydroxylamine hydrochloride in 100 ml. of absolute methanol and 15 ml. of chloroform was refluxed for two hours. There was obtained 10.70 g. (100%) of yellow needles, m.p. 154-157° (Lit., m.p. 158°)[78].

The reaction of phenanthraquinone monoxime with benzaldehyde

A solution of 1 g. of phenanthraquinone monoxime (4.5 moles) in 7 ml. (0.07 mole) of benzaldehyde was heated at 150° for eight hours. Tan crystals weighing 0.50 g. were isolated

(78) H. Goldshmidt, Ber. 16, 2178 (1883).

from the cooled solution. These were dissolved in ether, the ether was washed with two 25 ml. portions of 16% sodium hydroxide solution, and then with 25 ml. of distilled water, and was then removed. There remained 0.25 g. of cream-colored crystals. Recrystallization from ethanol gave a compound with a melting point of 310-313°; the picrate of this melted at 280-282°. (Lit., 2-phenanthrimidazole, m.p. 312-313°; picrate, m.p. 280°)[48].

The benzaldehyde filtrate of this reaction was combined with that of a duplicate run. Benzaldehyde was removed by distillation at 1 mm. The brown-black gummy residue was dissolved in ether and left an amorphous brown solid that weighed 0.13 g., m.p. 196-203°. Attempted recrystallization from benzene yielded a black gum. The gum was dissolved in benzene and this was passed through a column of alumina. A blue-violet fluorescent band was washed through the 12x2 cm. column with this solvent. Removal of the benzene yielded a trace of yellow solid.

The ether solution was washed with dilute sodium carbonate solution, and this left 1.57 g. of a brown-black semi-solid dissolved in the ether. Recrystallization was unsuccessfully attempted from 50% ethanol-acetone (Darco treatment); recrystallization from methanol yielded 0.20 g. of a brown-red powder upon initial concentration, m.p. 146-156°. The products were not investigated beyond this point.

5-Phenyl-2,3-thiophenequinone dioxime

To a solution of 10 g. (0.05 mole) of 5-phenyl-2,3-thiophenequinone-2-oxime and 2.5 g. (0.062 mole) of sodium hydroxide in 200 ml. of water was added a solution of 15 g.

(0.216 mole) of hydroxylamine hydrochloride and 15 g. of sodium hydroxide in 150 ml. of water. The total volume was brought to 700 ml. by the addition of water and the solution was stirred at room temperature for one hour. Undissolved monoxime salt (0.75 g.) was removed by filtration; the solution was acidified with iced hydrochloric acid and allowed to stand for two days, and 7 g. of light brown solid was isolated. The solid was heated with three 300 ml. portions of benzene until the remaining bright yellow powder no longer gave a blue coloration with an alcoholic solution of ferric chloride. This yellow solid was monoxime, m.p. 214-216°, and weighed 2 g. The benzene was condensed to give a crop of cream-colored needles, yield 4.5 g. Further concentration of the benzene yielded 0.5 g. of less pure dioxime. The total yield of dioxime was 49%, of monoxime unreacted 27%. The dioxime when recrystallized from benzene was obtained as colorless crystals, m.p. 126.4-126.8°.

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.6; H, 3.64

Found: C, 54.7; H, 3.7 (Manser)

In a similar reaction run for 6 hours 71.4% of dioxime, 5 % of unreacted oxime, and 3% of unidentified material were isolated. When the reaction mixture was acidified the product precipitated very slowly. In another reaction the basic solution of 1 g. of monoxime and 1.5 g. of hydroxylamine hydrochloride was acidified after thrity minutes. The precipitate was isolated at one day intervals:

First precipitate	.30 g.	m.p. 125-164°. This was recrystallized from ethanol, m.p. 210-212°; m.m.p. with monoxime 213-215°
Second precipitate	.38 g.	m.p. 127-128°. Recrystallized from benzene and ligroin (b.p. 70-90°) 127.0-127.3°
Third precipitate	.11 g.	m.p. 125-278°
Fourth precipitate Fifth precipitate	.18 g.	Combined, recrystallized from methanol, yellow needles, m.p. 214-216°; m.m.p. (monoxime) 214-216°
Final precipitate	trace	m.p. 206-208°

The ultra-violet absorption spectrum of an ethanol solution of the first crop of yellow needles, determined with a Beckmann model DU quartz ultra-violet spectrophotometer, had the following values: λ max. 248 mμ (logϵ 3.72), λmin. 357 mμ (logϵ 3.45). A second crop of yellow needles was obtained by concentrating the original ethanolic solution, and the ultra-violet spectrum in ethanol was obtained; λ max. 246 mμ (logϵ 3.91), λmax 315 mμ (logϵ 3.95), λmax 382 mμ (logϵ 3.31), λmin. 276 mμ (logϵ 3.74), λmin. 353 mμ (logϵ 3.15)

Steam distillation of 5-phenyl-2,3-thiophenequinone dioxime

A solution of 1 g. (4.5 mmole) of the dioxime in 30 ml. of 4% sodium hydroxide solution and 120 ml. of water was steam-distilled using superheated steam. A total of 2100 ml. of distillate was collected. This was extracted with two 130 ml. portions of ether. The ether was dried over Drierite and then removed by evaporation. An unpleasant smelling oil, 0.09 g., remained, and attempted crystallization from benzene was unsuccessful. The basic pot liquid was extracted with ether and thus yielded less than 0.01 g. of residue. The solution was acidified with dilute hydrochloric

acid, whereupon there was the precipitation of cream-colored solid. The solution was extracted with ether, 29% (0.85 g.) of material was obtained, m.p. 124-126°. The ferric chloride test was positive.

Steam distillation of 5-phenyl-2,3-thiophenequinone dioxime from acid

One gram of 5-phenyl-2,3-thiophenequinone dioxime (4.5 mmole) was added to 75 ml. of concentrated hydrochloric acid and 75 ml. of distilled water and superheated steam was passed through this mixture until a total of 1300 ml. of distillate was collected. This contained a straw-colored solid, 0.28 g., m.p. 90-94°, negative $FeCl_3$ test, the majority of which came over at the start of the distillation. Upon solution in ethanol, 0.02 g. of undissolved material remained which proved to be sulfur. The ethanol solution yielded large colorless plates, m.p. 93.0-93.6°, which were recrystallized from petroleum ether (b.p. 40-60°) and dried at 1 mm. for eight hours, m.p. 93.6-94.1°.

Anal. Calcd. for $C_{10}H_6N_2O$: C, 70.6; H, 3.5; N, 16.5

Found: (ethanol) C, 70.9; H, 3.7; N, 16.0 (Manser)
(ligroin) C, 70.1; H, 3.6; N, 16.7 (Manser)

The distillate was extracted with ether and yielded 0.07 g. of a red solid, m.p. 83-85°, which was recrystallized from ethanol, mp. 90-92°.

The nondissolved material in the cooled pot liquor was a mixture of brown amorphous substance and yellow crystalline material and the total weight was 0.32 g. Some of the latter was isolated manually and had a melting point of 156-160°. The filtrate was extracted with ether and yielded

0.07 g. of a yellow solid, m.p. 155-157°. The solids were combined and extracted with three 20 ml. portions of boiling water. In this way 0.17 g. of water soluble solid, m.p. 148-154° and 0.18 g. of water insoluble solid, m.p. 182°, were isolated.

The water soluble material was crystallized twice from benzene, m.p. 158-161°. Simultaneous melting points with benzoylpyruvic acid and the oxazinone gave the following results:

A.	Benzoylpyruvic acid	m.p. 158-159°
	Dioxime product	m.p. 158-161°
	M.m.p.	136-141°
B.	Oxime hydrolysis product	m.p. 149-154°
	Dioxime hydrolysis product	m.p. 148-153°
	M.m.p.	151-158°

The water insoluble portion was dissolved in ether and extracted with small quantities of 5% sodium hydroxide until acidification with dilute hydrochloric acid no longer caused the precipitation of material. The acidified solution containing the precipitate was extracted with ether and after drying a yellow solid was isolated which weighed 0.12 g., m.p. 210-212°. This was recrystallized from ethanol, and with the aid of a small amount of Darco bright yellow needles were obtained, m.p. 214-215°, mixed melting point with an authentic 5-phenyl-2,3-thiophenequinone-2-oxime, 214-215°.

The base insoluble material was separated into a benzene insoluble yellow solid and a dark-colored benzene solution. The benzene solution yielded black crystals, m.p. 110°. These were eluted in a 1x8 cm. column of alumina with 200 ml. of benzene and yielded colorless crystals, m.p. 111-113°,

which proved to be sulfur.

Attempted preparation of 5-phenylthiophenequinone furazan

A solution of 2 g. (0.09 mole) of dioxime in 50 ml. of toluene was refluxed for two hours. The solution yielded 0.63 g. of cream-colored precipitate, m.p. 120-122°. The toluene was concentrated to15 ml., 0.27 g. of a red-brown powder, m.p. 170° (dec.) was obtained. Evaporation of the remaining toluene left 0.77 g. of a brown, somewhat crystalline residue. The last two portions were combined and dissolved in 80 ml. solution of ether. The ether solution was washed with two 50 ml. portions of 10% sodium hydroxide and two 50 ml. portions of distilled water and the ether was evaporated to yield 0.65 g. of a tan solid, m.p. 147-155°. After one recrystallization from alcohol (treated with Darco) and a recrystallization from benzene, a colorless crystalline solid was obtained, m.p. 205.5-206.0°.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.5; H, 3.0

Found: C, 63.5; H, 4.0 (Schwarzkopf)

The aqueous portion was acidified with hydrochloric acid and extracted with three 25 ml. portions of ether. Removal of the ether gave 0.41 g. of a red and black solid tar. Attempted recrystallization from benzene was unsuccessful and the material was not further investigated.

Reaction of 5-phenyl-2,3-thiophenequinone dioxime with benzaldehyde

A solution of 0.5 g. (2.2 mmoles) of 5-phenyl-2,3-thiophenequinone-2,3-dioxime was heated at 100° with 5 ml.

(0.05 moles) of benzaldehyde for twenty four hours. The reaction mixture was dissolved in 14 ml. of ether and extracted with two 20 ml. portions of 5% sodium hydroxide solution and 35 ml. of distilled water. The basic solution was acidified and extracted with ether. Evaporation of the ether left an orange-yellow, oily solid. This was dissolved in 20 ml. of ether and to this solution was added 100 ml. of petroleum ether Pb.p. 40-60°). A yellow precipitate was formed which weighed 0.04 g., m.p. 102-125°, negative ferric chloride test. The diethyl ether-petroleum ether solution was evaporated to dryness. This operation yielded only a negligible quantity of solid.

The original ether solution contained the non-base soluble products. After evaporation of the ether the benzaldehyde was removed by distillation under reduced pressure. The residual red oil was dissolved in ether and extracted with base to remove any benzoic acid. Evaporation of the ether yielded 0.28 g. of an impure solid. Further purification was attempted by chromatography. The product was washed through an 18x4 column of activated alumina with 1 l. of carbon tetrachloride, then a fraction was collected with 0.4 liter of carbon tetrachloride and finally with 1 l. of benzene. These fractions yielded 0.08 g. of yellow needles, m.p. 91-116°; 0.03 g. of colorless plates with red contamination, m.p. 116-126°, and a quantity of oily residue, respectively. The first product was recrystallized from ethanol, m.p. 92-93°, mixed melting point with phenylcyanoisoxazole from steam distillation of 5-phenyl-2,3-thiophenequinone dioxime showed no depression. The second solid was

recrystallized from petroleum ether, m.p., 124-125°.

Cleavage of 5-phenyl-2,3-thiophenequinone dioxime with pyruvic acid

A mixture of 1 g. of dioxime, (4.5 mmole), 1.5 ml. (0.017 mole) of pyruvic acid, 15 ml. of 50% acetic acid, water and 11.0 ml. of glacial acetic acid was refluxed for four hours. A colorless granular solid (0.08 g.) was isolated which ignited with the characteristic odor and color of burning sulfur. Two hundred ml. of ice-water was added to the filtrate, and a red solid, weight 0.46 g., m.p. 65-75°, was isolated, and recrystallized from petroleum ether, m.p. 91-92°.

Phenylthiophene

Phenylthiophene was prepared by the dehydrogenation of cyclohexenylthiophene. The cyclohexenylthiophene was prepared by another investigator in this laboratory* from the reaction of thienylmagnesium bromide and cyclohexanone. The tertiary alcohol thus formed was dehydrated by distillation, b.p. 128-130° (13 mm.). A stirred mixture of 139 g. (0.85 mole) of cyclohexenylthiophene, 430 g. (1.75 moles) of chloranil and sufficient benzene to make a total volume of 1.3 liters was refluxed for twelve hours. The benzene solution was removed from the tetrachlorohydroquinone by filtration, washed with base, washed with water and then dried over calcium chloride. After removal of the calcium chloride and benzene the phenylthiophene was distilled at reduced pressure, b.p. 95-105° (1-2 mm.). Redistillation of the product gave a pale yellow liquid, b.p. 109-110° (4 mm.). The crude yield of

* We are indebted to Mr. R. Palchak for this material.

phenylthiophene was 88 g. (65%).

A second similar run was heated for twenty hours. The product was distilled and yielded 78 g. (87%) of a colorless solid resembling naphthalene, b.p. 96-107° (1.5 mm.), m.p. 35.0-37.0°[59].

1-Phenylbutene-1

To 1.1 mole of phenylmagnesium bromide[79] at 0° was added a solution of 72 g. (1.0 mole) of n-buteraldehyde in 75 ml. of anhydrous ether at a rate sufficient to cause vigorous refluxing. The addition took fourteen minutes, after which the reaction stood at room temperature for four hours and was then refluxed for two hours. The flask was cooled externally with ice and water and 50 g. of ammonium chloride in 150 ml. of water was added dropwise to the stirred solution. The ether was decanted from the gelatinous residue, the residue was washed with 100 ml. portions of ether and these were combined. The ether was flash-distilled from the carbinol and the carbinol was collected in a 300 ml. flask equipped with a side arm for vacuum distillation. To this was added 40 g. (0.33 moles) of 85% phosphoric acid. The flask was placed under an 18 inch packed fractionating column and the product was distilled at reduced pressure under a nitrogen atmosphere. A fore-run was collected at 27° (6 mm.), n_D^{17} = 1.5575 (bromobenzene, n_D^{20} = 1.5604). The phenylbutene distilled at 67-69° (5 mm.); n_D^{17} = 1.5384. (Lit.[80] n_D^{17} = 1.5381; b.p. 71-72° (8 mm.)) The yield was 46 g. (35%).

(79) C. F. Allen and S. Converse, Organic Synthesis, Coll. Vol. 1, John Wiley and Sons, Inc., New York, 1932, (1st ed.), p. 221.

(80) J. Levy and M. Drobeitzka-Gombinska, Bull. Soc. Chim. France 49, 1769 (1931).

In another run the product from 118 g. (0.79 mole) of propylphenyl carbinol and 40 g. of 85% phosphoric acid was similarly fractionally distilled at a higher temperature and the yield was 89 g. (87%), b.p. 94° (32 mm.). There was water in this portion and it was therefore dried over calcium chloride for two days and then refractionated, b.p. 94-95° (32 mm.). The yield was 70 g. (66%).

The reaction of phenylbutene and sulfur

a. To a stirred solution of 500 g. (15.6 g. atoms) of molten sulfur at 340° was added 63 g. (0.477 mole) of 1-phenylbutene-1 dropwise[59]. The flask was equipped for vacuum distillation, a pressure of only 270-330 mm. was maintained during the reaction and 56.0 g. of a light orange-colored liquid was collected. By fractionation in a 2x50 cm. column packed with triple turn helices this was separated into 39 g. of a forerun of unreacted olefin, b.p. 45-48° (2 mm.), 1.75 g. of a fraction containing phenylthiophene, b.p. 48-80° (2 mm.), and a dark brown residue. The second portion was recrystallized from 85% ethanol and yielded 1.24 g. of colorless needles, m.p. 35-38°.

b. A mixture of 101 g. (0.765 mole) of 1-phenylbutene-1 and 70.5 g. (2.2 g. atoms) of sulfur was heated between 195-200° for thirteen hours[58]. This was then distilled at reduced pressure. The first fraction weighed 14.30 g., b.p. 47° (3 mm.) and the second fraction weighed 9.90 g.,

b.p. 80-120° (3 mm.). Redistillation of the second fraction gave 5.0 g. (4.2%) of phenylthiophene as a colorless solid, b.p. 96-98° (2 mm.), m.p. 36-38°.

5-Phenyl-2-hydroxythiophene *

Into a 1 l. flask equipped with a mechanical stirrer, Dry Ice condenser and a dropping funnel with a nitrogen inlet tube was placed 2.22 g. (0.32 g. atom) of freshly washed (ether) sheet lithium cut into small pieces and 150 ml. of anhydrous ether. A nitrogen atmosphere was maintained. Thirty milliliters of a solution of 20.6 g. (1.5 moles) of n-butyl bromide in 150 ml. of anhydrous ether was added at one time to the stirred lithium and reaction was initiated by heating the flask momentarily with a water bath heated to 85°. This was replaced by an ice and water bath and the remainder of the butyl bromide was added at a rate such as to maintain refluxing. The cloudy solution was stirred for an additional thirty minutes.

It was assumed that the yield of butyllithium was 50%(81).

To the butyllithium solution was added all at one time a solution of 12.8 g. (0.08 mole) of 2-phenylthiophene in 40 ml. of ether and butane was evolved. The yellow-colored solution was stirred at room temperature for an

(81) R. G. Jones and H. Gilman, Organic Reactions, Vol. VI, John Wiley and Sons, Inc., New York, 1951, p. 353.

* Private communication; experimental as developed by Robert J. F. Palchak, University of Cincinnati.

additional thirty minutes.

The flask was cooled to below -50° in a Dry Ice-acetone bath. The condenser was replaced with an alcohol thermometer whose bulb was below the surface of the ether while the dropping funnel was replaced with a 1 cm. diameter gas inlet tube whose end also was placed into the liquid. This tube was connected to an oxygen supply through a 1 l. erlenmeyer trap and a large mercury T trap. After 200 ml. of ether containing 0.25 mole of cyclohexylmagnesium bromide was added to the reaction mixture oxygen was bubbled as rapidly as possible into this stirred solution at -50°. When the absorption was complete the oxygen would either force its way out of a flask outlet, or through the mercury trap and the flask was then stoppered and stored at 0° for twenty four hours.

The reaction product was acidified with cold dilute hydrochloric acid and the ether was separated and extracted with 5% sodium hydroxide solution. The basic solution was in turn acidified with dilute, cold hydrochloric acid, and extracted with ether which was dried over Drierite for two hours and then removed by distillation at reduced pressure under an atmosphere of nitrogen. The solid black residue was recrystallized from petroleum ether (b.p. 40-60°) to yield 4.2 g. (30%) of light brown-grey plates, m.p. 84-85°[15].

Nitrosation of 5-phenyl-2-hydroxythiophene

a. To a solution of 0.73 g. (4.1 mmoles) of 5-phenyl-2-hydroxythiophene (m.p. 66-74°) in 30 ml. of ethanol was added a solution of 0.43 g. (6.2 mmoles) of sodium nitrite in 10 ml. of water and 10 ml. of ethanol. The solution was stirred by hand for about thirty seconds and then poured with stirring into excess cold, dilute hydrochloric acid. The sky blue-colored product was extracted with three 100 ml. portions of ether which was washed with sodium carbonate solution, filtered from a black precipitate and dried over Drierite. Removal of the desiccant and solvent left 0.41 g. of a red solid from which 0.31 g. of a black solid was extracted with 500 ml. of boiling ethanol. The first black precipitate weighed 0.14 g., m.p. 265°; recrystallization from dioxane gave green-black needles, m.p. 310-313°. This was similar to a compound isolated for the first time by other workers[61] in our laboratory as an oxidation by-product in reactions involving 5-phenyl-2-hydroxythiophene. They found this compound to give green-black needles from dioxane, m.p. 303-304° and analysis showed it to have the correct empirical formula for the thioindigo dimer.

Anal. Calcd. for $C_{20}H_{12}O_2S_2$: C, 69.0; H, 3.4; S, 18.4

Found: C, 68.5, 68.8; H, 3.3, 3.3; S, 18.4, 18.4

(Pittsburgh)

The sodium carbonate solution was acidified with iced, concentrated hydrochloric acid and extracted with

three 70 ml. portions of ether. The ether was removed and the residue was vacuum dried. A dark oily solid weighing 0.30 g. remained. This was recrystallized from 200 ml. of ethanol and a small amount of Darco was used to decolorize the product. The solution was concentrated nearly to dryness before precipitation occurred. The product, a tract of yellow solid, was extremely soluble in dioxane and benzene, and was recrystallized from petroleum ether (b.p. 70-90°), yellow granular crystals, m.p. 196-198°. The ultraviolet spectrum of this compound was determined with the remaining 2.1 mg. of solid, λ_{max} 285 mμ (logε 3.28) λ_{max} 380 mμ (logε 3.70), λ_{min} 333 mμ (logε 3.28).

b. One gram (5.7 mmoles) of 5-phenyl-2-hydroxythiophene was dissolved in 50 ml. of water by adding the necessary amount of 5% sodium hydroxide solution. One gram of sodium nitrite (0.0145 mole) was added and the solution was slowly run into an iced, stirred solution of 6 N hydrochloric acid. About a minute after the initial addition a flocculent blue precipitate appeared. The mixture was stirred for five minutes and then extracted with ether which was in turn extracted with base. The base upon acidification, gave a turbid solution which was extracted with ether and evaporation of the ether left a trace of brown resinous material. Most of the material precipitated as a blue-black solid in the original ether extract.

c. The solution of 5-phenyl-2-hydroxythiophene in ether obtained in the last isolation step of the synthesis of this compound from 12.8 g. of phenylthiophene was cooled to 0° in an ice bath. Into this stirred solution were bubbled the nitrogen oxides evolved by dropping concentrated hydrochloric acid on 63 g. of sodium nitrite. The gases were dried by passing them through a tube of Drierite. A considerable amount of green dimer formed. The solution was extracted with ether and the ether was dried with Drierite. Removal of the desiccant and the ether yielded 0.47 g. of a red oil. After the oil was treated with Darco in boiling ethanol, attempts to obtain crystals by alternate concentration and cooling of the solution failed and finally a red oil was reobtained on total removal of the ethanol. We also failed to crystallize this oil from petroleum ether (b.p., 70-90°).

d. Isoamylnitrite (4 ml., 0.03 mole) in dry ether was added dropwise over a period of one hour to an ice-cold, stirred solution of 1.5 g. (8.5 mmoles) of 5-phenyl -2-hydroxythiophene in 500 ml. of dry ether. Dry hydrogen chloride was passed in simultaneously and an atmosphere of nitrogen was maintained throughout. Stirring and the flow of hydrogen chloride were continued for an additional half hour by which time there had formed 0.41 g. of dimer. There was isolated from the ether 0.30 g. of a brown, base-soluble tar, and 0.55 g. of a base-insoluble tar.

Neither of these yielded to attempts to crystallize them from the usual organic solvents.

Investigation of the degradation products of the dioxime

A solution of 0.1 g. (0.59 mmoles) of 5-cyano-3-phenylisoxazole was refluxed for four hours in a mixture of 5 ml. of water, 5 ml. of concentrated sulfuric acid, and 0.5 g. of sodium chloride[82]. The product was dissolved in base and reprecipitated with acid and it was recrystallized from this solution and then twice recrystallized from distilled water, colorless needles, m.p. 176.5-177.8°. (Lit. m.p. for 5-carboxy-phenylisoxazole is 177-178°[83]).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.5; H, 3.7; N, 7.4

Found: C, 63.6; H, 3.9; N, 8.1 (Schwarzkopf)

One-tenth of a gram (0.059 mmole) of 5-cyano-3-phenylisoxazole was stirred in 10 ml. of concentrated hydrochloric acid overnight[84]. The product, which was not soluble in base, weighed 0.08 g. and was recrystallized from chloroform to give very small colorless needles, m.p. 203.0-203.5°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.2; N, 14.8

Found: C, 63.6; H, 4.1; N, 14.1 (Schwarzkopf)

The 5-carboxamide-3-phenylisoxazole was refluxed in 20 ml. of 5% hydrochloric acid for three hours. The

(82) Reference 66, p. 205.
(83) A. Quilico and G. Speroni, Gazz. chim. ital. 76, 164 (1946).
(84) Reference 16, p. 597.

product was obtained on cooling as colorless crystals, melting point 178-179°. The mixed melting point with the sulfuric acid product occurred at 178-179°.

Spectra

The following ultraviolet absorption spectra, not previously described in the experimental section, were measured on a Beckmann DU spectrophotometer. We are indebted to Mr. Jack Delaney* for the measurements of the ethanolic solutions of 5-phenyl-3-hydroxythiophene and 5-phenyl-3-methoxythiophene. All determinations were made of ethanol solutions unless otherwise noted.

5-Phenyl-3-hydroxythiophene in chloroform (p. 17, I)

This material was recrystallized from petroleum ether (b.p., 40-60°), λ_{max} 271 mμ (logϵ 4.19), λ_{max} 335 mμ (logϵ 3.86), λ_{min} 308 mμ (logϵ 3.68).

5-Phenyl-3-hydroxythiophene (p. 17, II)

This material was recrystallized from petroleum ether (b.p., 40-60°), λ_{max} 262 mμ (logϵ 4.05), λ_{max} 300 mμ (logϵ 3.97), λ_{min} 234 mμ (logϵ 3.76), λ_{min} 380 mμ (logϵ 3.91).

5-Phenyl-3-methoxythiophene (p. 17, III)

The ether had a boiling point of 139-140° (3 mm.),

*Hilton-Davis Company, Cincinnati, Ohio.

λ_{max} 260 mμ (logϵ 4.04), λ_{max} 298 mμ (logϵ 3.98), λ_{min} 280 mμ (logϵ 3.86).

5-Phenyl-2,3-thiophenequinone dioxime (p. 56a, I)

The compound was recrystallized from benzene and had a melting point of 126.4-126.8°, λ_{max} mμ (logϵ 4.24), λ_{min} 226 mμ (logϵ 3.77).

5-Phenyl-2,3-thiophenequinone-2-oxime (p. 56a, II)

The monoxime was recrystallized from ethanol and had a melting point of 214-216°, λ_{max} 236 mμ (logϵ 3.98), λ_{max} 350 mμ (logϵ 4.19), λ_{max} 407 mμ (logϵ 3.83), λ_{min} 223 mμ (logϵ 3.91), λ_{min} 272 mμ (logϵ 3.75), λ_{min} 388 mμ (logϵ 3.80), λ_{infl} 363 mμ (logϵ 3.86).

2,5-Diphenyl-thieno[4,5-b]oxazole (p. 56a, III)

This compound had a melting point of 176.2-176.8°, λ_{max} 225 mμ (logϵ 3.98), λ_{max} 338 mμ (logϵ 4.53), λ_{min} 230 mμ (logϵ 3.95), λ_{min} 272 mμ (logϵ 3.55).