The Chemistry Of 2-alkoxyfurans And The Kinetics Of Nucleophilic Displacement Of 2-halofurans.

Citation

MANLY, DONALD GEORGE. *The Chemistry Of 2-Alkoxyfurans And The Kinetics Of Nucleophilic Displacement Of 2-Halofurans.* 1956, https://preserve.lehigh.edu/lehigh-scholarship/graduate-publications-theses-dissertations/theses-dissertations/chemistry-2-0.

DOCTORAL DISSERTATION SERIES

Publication No.: 19,365

AUTHOR: Donald George Manly, Ph. D., 1956
Lehigh University

TITLE: THE CHEMISTRY OF 2-ALKOXYFURANS AND THE KINETICS OF NUCLEOPHILIC DISPLACEMENT OF 2-HALOFURANS

University Microfilms, Ann Arbor, Michigan

The Chemistry of 2-Alkoxyfurans

and

The Kinetics of Nucleophilic Displacement of 2-Halofurans

by

Donald G. Manly

A DISSERTATION

Presented to the Graduate Faculty
of Lehigh University
in Candidacy for the Degree of
Doctor or Philosophy

Lehigh University
1956

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

April 20, 1956
(Date)

E D Amstutz
Professor in Charge

Special committee directing the doctoral work of Mr. Donald George Manly

E D Amstutz Chairman

B. W. Parker

Robert C. West Jr.

Charles G. Dodd

ACKNOWLEDGEMENTS

The author is sincerely grateful to Dr. E. D. Amstutz for suggesting and directing the research work involved in this dissertation and for his helpful advice and criticism. The author is indebted to The Quaker Oats Company for their financial support of this work and to Mr. Andrew P. Dunlop for his advice, cooperation, and above all his understanding which permitted this to be a truely academic problem.

The author would also like to express his heartfelt gratitude to his wife for her never ending love and encouragement, her many hours of worry and concern, and her efforts in typing and proof reading this dissertation.

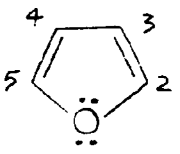
The author would also like to express his appreciation to the members of his committee for their helpful criticisms and to many of his colleagues among the graduate students.

TABLE OF CONTENTS

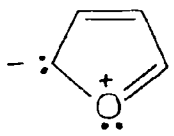
INTRODUCTION

Although the chemistry of furan began at nearly the same time as that of benzene, there are many simple furan compounds which have not been successfully prepared and characterized. For ease of presentation and for the convenience of the reader a brief discussion of the chemical and physical properties of furan will be given followed by a survey of the classes of compounds grouped according to the element which is bonded directly to the furan ring. Those compounds containing furan to carbon bonds, such as alkyls, aryls, aldehydes, ketones, acids, and others, have been fairly well studied and will not be included here. The size and scope of the chemical industry involving these furan compounds is indicated by The Quaker Oats Company which produces many furan chemicals derivable from furfural. There is, however, a considerable void in our knowledge of compounds containing furan bonded to atoms other than carbon while the chemistry of the analogous benzene compounds is on a sound experimental and theoretical basis.

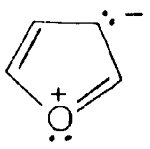
The chemistry of furan differs considerably from that of benzene even though comparisons are often made. In an extremely simplified view, furan may be thought of as a benzene ring with an oxygen atom substituted for one of the carbon to carbon double bonds. This is a very misleading concept, however, since benzene is a symmetrical molecule containing six mobile π electrons and six equivalent nuclei whereas in furan the π electrons are considerably more localized on non-equivalent nuclei. The actual furan resonance hybrid may be represented by the following structures and their mirror images.



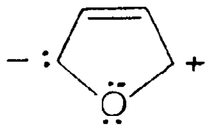
I 90%



II 8%



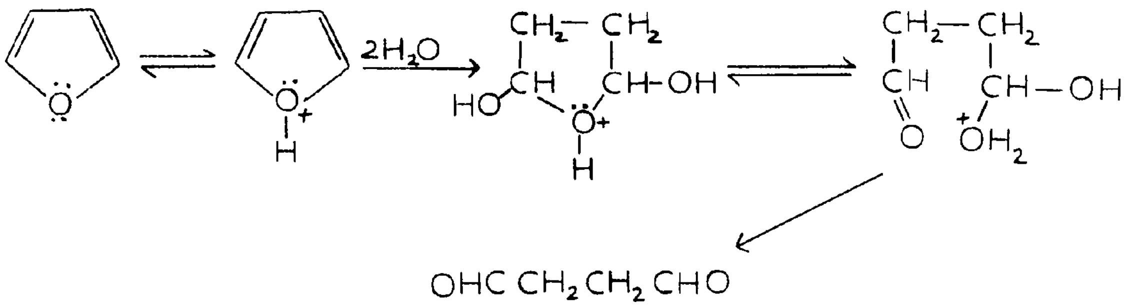
III 2%



IV

Structures I and II are generally considered to be the major contributing forms (1) since the furan alpha or 2-position is the position attacked during electrophilic substitution even when a "meta" director is present in the α'-position. Similarly the butadiene character of furan is indicated by its ready condensation in Diels-Alder reactions. This reaction together with many others, notably the addition of bromine in methanol (2), occur by 2, 5-addition. The butadiene character is also indicated by the addition of chlorine which under proper conditions produces a hexachloro derivative.

The extreme sensitivity of furan to acid is readily understood. The highly basic center, oxygen, is available for coordination with any cation thereby promoting ring opening as outlined below:



As might be expected many of the simple furans are cleaved in the presence of aqueous acids leading to the formation of compounds similar to the above which react further to form polymers. Many of the furans are being investigated commercially for possible use in plastics.

Furan to Nitrogen:

The two classes of compounds included in this category are the analogues of nitrobenzene and aniline, nitro- and aminofurans. The nitrofurans have been well investigated in spite of difficulties encountered in preparation and both the simple 2-nitro and 3-nitrofurans are known. The interest in nitrofurans as potential pharmaceuticals has been the driving force behind the thorough investigation. For example the 5-nitro-2-furfural semicarbazone (Furacin) and related compounds such as the 5-nitro-2-furylacrylic acids are active against various gram-positive and gram-negative organisms. Furacin has found considerable use against bacteria which have become resistant to penicillin and sulfathiazole.

The aminofurans, on the other hand, are known only to a very limited extent. It is virtually impossible to reduce nitrofurans to the corresponding amines due to the great sensitivity of furans to acidic reagents. There is no report of the synthesis of 2-aminofuran, but 2-methyl-3-aminofuran and 2, 5-dimethyl-3-aminofuran have been characterized (3). Both of these compounds are highly unstable and are attacked by acids, strong aqueous bases, and air. The hydrolytic deamination which occurs readily has been the source of the difficulty encountered by many workers in attempts to prepare aminofurans. This is not wholly unexpected by comparison with imino esters which suggest that the aminofurans exist mainly in the ketimine form (V).

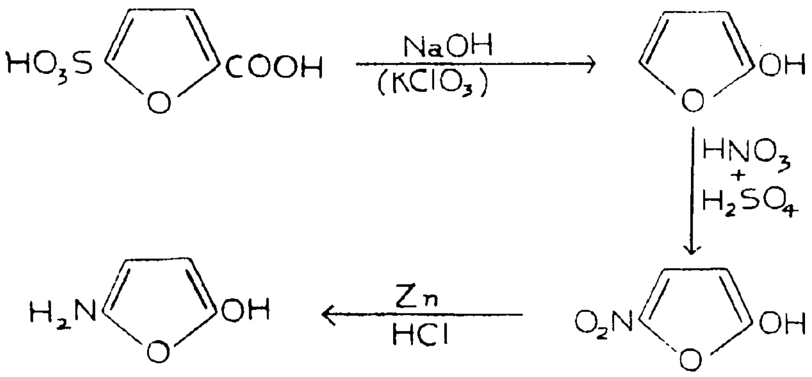
V

The successful isolation of the 3-aminofurans was possible only after the development of special techniques designed to provide minimum contact with aqueous hydrolytic reagents.

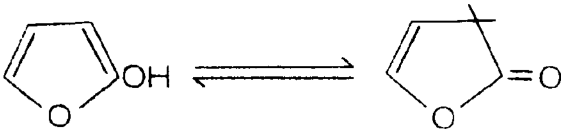
Furan to Oxygen:

The many attempts to prepare simple hydroxyfurans have been uniformly fruitless although a number of di- and tri-substituted 3-furyl ethers (4) have been synthesized from non-furan intermediates. A very controversial report (5) of the synthesis of 2-hydroxyfuran and 3-hydroxyfuran has appeared in the literature which has prompted Dunlop and

Peters (6) to discuss the evidence quite thoroughly. By comparison with the very low melting, highly unstable 2-hydroxythiophene (7) it is quite surprising to find that 2-hydroxyfuran has a reported melting point of 80° and is capable of being nitrated with mixed acid as shown in the following diagramatic representation of the work of Hodgson and Davies.



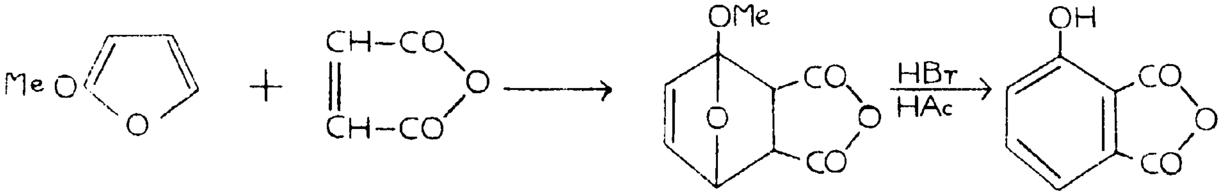
In view of the extreme sensitivity of furans to acids it is also extremely unlikely that the nitrofuranol could be reduced to a stable aminofuranol with zinc and hydrochloric acid as reported. By comparison with the thiophene analogue, the failure of other authors (8) to repeat even the first step of this work, and from the previous discussion it must be concluded that simple hydroxyfurans have not yet been prepared. That Hodgson and Davies reported strong phenolic properties for hydroxyfuran is completely unexpected since other evidence would suggest the keto form (VI). 2, 5-Dihydroxyfuran might be considered as the enol



VI

form of succinic anhydride, but its properties are completely described by the anhydride structure. Similarly α -angelica lactone shows very little indication that it exists as 5-methyl-2-hydroxyfuran and coumaran-2-one is consistent with the lactone form rather than 2-hydroxybenzofuran. Since Hurd (7) has shown that 2-thienol exists as a mixture of both tautomers by infrared, ultraviolet, and boiling point, it would be strange if 2-hydroxyfuran did not exist almost completely in the lactone form.

Assuming the lactone form, the remaining class of compounds, ethers, would not be expected to be available by etherification of the hydroxyfuran. However, while investigating the kinetics of nucleophilic displacement of halofurans, Petfield and Amstutz (9) were able to isolate and prove the structure of 2-methoxyfuran, the first known simple 2-furyl ether. The compound was prepared by displacement of the halogen of methyl 5-bromo-2-furoate with sodium methoxide followed by saponification and decarboxylation of the resulting methoxyfuroic acid. The structure proof is shown below:



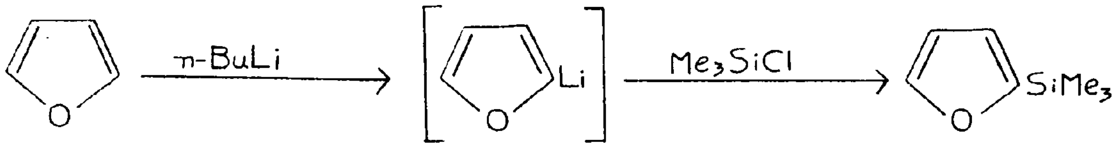
This derivative of 2-hydroxyfuran had the expected acid sensitivity, instability, and physical properties when compared with 2-methoxythiophene (7, 10). Almost immediately following this report the compound was synthesized by pyrolysis of 2, 5-dimethoxy-2, 5-dihydrofuran (11) thereby providing additional proof of structure. The synthesis of the first simple furan ether has aroused further interest in the investigation of the chemistry of this type of compound and in the completion of a previous gap in our knowledge of simple furans.

Furan to Sulfur:

The known compounds in this class consist entirely of sulfonic acids (12) with no reports of simple furan sulfones, sulfoxides, sulfides, or mercaptans as might be expected from the previous discussion of the corresponding oxygen compounds. The difficulties involved in sulfonation of simple furans which do not possess a stabilizing group are similar to those encountered in nitration. However, the development of the fairly mild reagent, pyridine-sulfur trioxide, has permitted the direct sulfonation of furan itself.

Furan to Silicon or Metals:

Perhaps the best known derivatives of furans are the furan mercurials. Many of the chloromercurifurans (13) are known and afford some of the best solid derivatives available. However, these derivatives do not form with furan carboxylic acids or aldehydes and the reaction with mercuric chloride has, in fact, been used as a method of decarboxylation. For example 5-bromo-2-furoic acid when treated with mercuric chloride is not mercurated in the 3- or 4-position, but instead undergoes decarboxylation resulting in the formation of 5-bromo-2-chloromercurifuran. Similarly furfural is not mercurated as expected but apparently forms a complex with the aldehyde oxygen in a manner which has not been fully investigated. The chloromercurifurans are used mainly to prepare the otherwise unobtainable iodofurans. The only other metallofurans which have been prepared to any great extent are the arsenicals because of their potential therapeutic use although compounds of antimony, lead, boron, and the alkali metals are known (13). In view of the recent interest in silicon compounds it is surprising to find that only one simple compound, 2-furyltrimethylsilane (14), has been prepared. The method used is outlined below:



<u>Furan to Halogen:</u>

The halofurans (15) have been studied more completely from a synthetic standpoint than any of the other classes previously mentioned, but these compounds need much fundamental and theoretical study. The 2-halofurans are colorless sweet-smelling liquids which show increasing ease of autoxidation from chloro to bromo to iodo. Although the mechanism of the autoxidation is not understood, it probably occurs by elimination of traces of iodine or hydriodic acid which then causes rapid decomposition accelerated by oxygen. Since the halofurans are much more prone to this oxidation than furan, it is only possible to store them in solution over a base such as quinoline. 2-Iodofuran turns dark and resinous with the liberation of iodine and hydriodic acid almost immediately on exposure to air.

The 2-halofurans are generally considered to contain inert carbon to halogen bonds since they are not affected by (16) aqueous sodium hydroxide, sodium cyanide, metallic sodium, dimethylmercury, or dimethylzinc. Similarly it has been reported (17) that magnesium metal does not react with chloro or bromofuran and that it reacts with iodofuran to about the same extent as does chlorobenzene. In order to obtain the Grignard reagent from bromofuran, Gilman (18) found it necessary to use a highly activated magnesium-copper alloy but the reagent when once prepared reacted normally. In view of this "inertness" it was surprising to Petfield and Amstutz (9) to find that the activation energy for nucleophilic displacement of bromofuran was not abnormally high and in fact was lower than that of the corresponding benzene compound using piperidine as the attacking reagent. From a consideration of their kinetic data there would not seem to be any evidence for the so-called "inertness" of the 2-halofurans. Unfortunately, because of undesirable side reactions (19), it has been impossible to obtain the activation energy for 2-bromothiophene from which Sice (10) prepared 2-methoxythiophene by reaction with sodium methoxide.

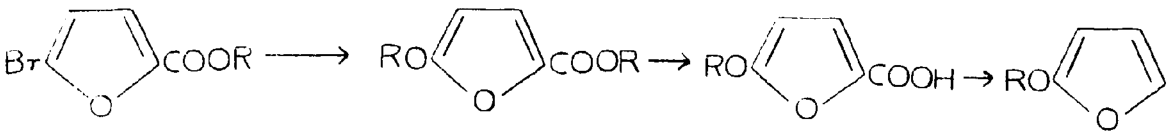
The work reported here was an effort to supply information for a few of the many voids in our knowledge of furan derivatives. By using slight modifications of the method of Petfield and Amstutz (9), the synthesis of a series of alkoxyfurans and alkoxyfuroic acids as well as a member of the hitherto unknown classes of thioalkoxyfurans and furylsulfones was accomplished. In order to complete the chemistry of alkoxyfurans a number of illustrative reactions were carried out on both the alkoxyfurans and the corresponding alkoxyfuroic acids and esters. The ultraviolet spectra of many of the new compounds along with many of the compounds used as intermediates were taken. From these spectra and those of the corresponding benzene compounds it has been possible to draw many parrallelisms and learn more about the effect of the furan ring. Since the preparation of the alkoxyfurans involves the nucleophilic displacement of halofurans, the kinetics of this type of reaction was also investigated thereby completing the much desired study of the kinetics of halofurans.

DISCUSSION

Alkoxyfurans and Their Derivatives - Syntheses, Reactions, Properties

The isolation of 2-methoxyfuran (9, 11) and its structure proof (9) (see Introduction p. 6) has opened a previously unknown field of furan chemistry. Methoxyfuran is the furan analogue of anisole in the benzene series. The alkoxyfurans are of great interest theoretically since they may be considered as derivatives of the unknown 2-hydroxyfuran. A thorough investigation of the chemistry of alkoxyfurans and their derivatives should provide a reliable background from which predictions of the reactivity and properties of hydroxyfuran might be made.

Sicé (10) recently reported the synthesis of 2-methoxythiophene by reaction of either 2-bromo or 2-iodothiophene with sodium methoxide in the presence of a cupric oxide catalyst. It was felt that this method might also be applicable to the synthesis of alkoxyfurans although neither of the reported methods involved it. The fact that 2-bromofuran presumably underwent normal nucleophilic displacement of the halogen with sodium methoxide (9) even though no product was isolated, indicated that the halofurans were not as "inert" as previously reported (17, 18) and that 2-iodofuran should react as easily as does the thiophene analogue. However, repeated attempts to complete this reaction under the conditions used by Sicé and at temperatures up to 100° led only to recovery of the starting material. This then provided further evidence for the unexpected "inertness" of 2-halofurans and necessitated the adoption of another method of preparation. Since the method used by Cava and co-workers (11) involving the pyrolysis of 2, 5-dimethoxy-2, 5-dihydrofuran is quite difficult to carry out and would be expected to be extremely difficult for the preparation of any compound other than the methoxyfuran, it was decided to use essentially the method of Petfield and Amstutz (9). They found that the activation energy for nucleophilic displacement of the halogen with methoxide was lowered by about 12 kcal by a carbomethoxyl group in the 5-position. This large energy decrease would be expected to make the reaction of 5-bromo-2-furoates with a sodium alkoxide an entirely feasable reaction for synthetic purposes. The sequence of steps used is as follows:



(1)

VII VIII IX X

Since furoic acid is a readily available starting material, the series of reactions must be begun at this point. Because the previously reported methods of brominating methyl furoate or furoic acid either involve long reaction time, dangerous conditions, or poor yields, it was necessary to develop a new method which has resulted in the rapid direct bromination of methyl 2-furoate. Adding bromine dropwise to rapidly stirred methyl 2-furoate at 100° gave a 43-50% yield of methyl 5-bromo-2-furoate (VII, R = Me) and 18-20% of 5-bromo-2-furoic acid as a by-product. This method is also easily adaptable to large scale preparations. As might be predicted the method is equally applicable to most other esters of furoic acid. The conversion of these bromo-esters (VII) to the alkoxyesters (VIII) is accomplished by reaction with the appropriate sodium alkoxide in excess alcohol as solvent. Since it was found that traces of moisture caused saponification and other undesirable side reactions, it was necessary to maintain completely anhydrous conditions during the course of the reaction and the alcohols used were therefore distilled from sodium before use. In all cases the reaction was carried out at temperatures of 100° or higher, either in sealed tubes if necessary or at reflux. The compounds prepared by this method are shown in Table 1. A study of the reaction of sodium methoxide with methyl 5-bromo-2-furoate at 100° proved that a maximum yield was obtained after 1.5 hours since a shorter reaction time produced incomplete reaction whereas a longer time led to excessive decomposition. No attempt has been made to obtain the maximum yield for the other reactions reported and a number of attempts to prepare the tert-butyl compound failed.

Since it would be more convenient to have a general procedure leading directly to the alkoxy-acid (IX), other compounds have been prepared from methyl 5-bromo-2-furoate using excess of the sodium alkoxide rather than preparing each individual bromo-ester. In these cases the products were not isolated, but were saponified directly to the acid after removal of the solvent under vacuum. This method provides the most convenient route to the 5-alkoxy-2-furoic acids without any apparent decrease in yield from a common starting material. These acids, shown in Table 2, have yields marked with an asterisk to indicate that it is an overall yield from methyl 5-bromo-2-furoate rather than merely a yield of saponification.

Table 1

5-Ethers of 2-Furoic Esters
($RO-C_4H_2O-COOR$)

No.	R	Yield	T(°C)	t(hrs)	b. p.	m. p.
VIIIa	Methyl (9)	42	100*	1.5	121-122/15	51-53
VIIIb	Ethyl	22	100*	3.0	149-150/27	40-41
VIIIc	Isopropyl	37	100*	5.0	146-147/20	liquid
VIIId	Phenyl	20	145	2.0	192-194/0.3	52-53

*In a sealed citrate bottle

The 5-alkoxy-2-furoic acids are all white powders which melt with decomposition and are decarboxylated by hot water. Although only the octyloxy (IXe) and amyloxy (IXh) acids were recrystallized, it appears that all could be recrystallized if necessary from an inert solvent such as petroleum ether as long as the temperature was kept well below the melting point. However in the course of this work it was found that the acids could be obtained in sufficiently pure form by

Table 2

5-Ethers of 2-Furoic Acid
($RO-C_4H_2O-COOH$)

No.	R	Yield	m. p.
IXa	Methyl (9)	65	136-141
IXb	Ethyl	99	140-141
IXc	Isopropyl	71	118-119
IXd	Phenyl	98	122-123
IXe	n-Octyl	18*	125-126
IXf	Cyclohexyl	23*	138-139
IXg	Thiophenyl	73*	139-141
IXh	n-Amyl	12*	93-95

acidification of the saponification mixture followed by washing with copious amounts of ice-water until essentially an acid-free filtrate was obtained.

Decarboxylation of the alkoxyfuroic acids (IX) gave the desired alkoxyfurans (X) whose physical properties are given in Table 3. The process of decarboxylation is normally carried out using a copper powder catalyst enabling the use of lower temperatures and quinoline or other high boiling coal tar base to remove any acids which may form during the reaction. It was found that even better results are obtained if enough quinoline is added to act as solvent. However, it was also found that all but the methoxy (Xa), ethoxy (Xb), and isopropoxy (Xc) compounds could not be decarboxylated in the presence of quinoline since the boiling points of the products were too close to that of quinoline to permit effective separation. Since the mixture of alkoxyfuran and quinoline could only be separated by extraction of an ethereal solution with aqueous acid which destroys most of the furan, the quinoline was omitted from the reaction mixture. The decarboxylation of these compounds was accomplished by heating the acid slightly above the melting point, attaching a vacuum, and then heating further until the product distilled. Immediate redistillation of the products gave the alkoxyfurans (X) as shown. The deviations in the molar refractions are not at all unusual with furan derivatives since no account is made for the exaltation due to the furan ring itself and most furan compounds have deviations of about one to three units.

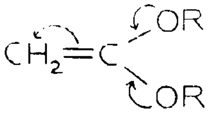
Table 3

2-Alkoxyfurans

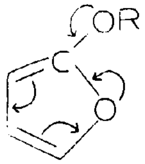
($RO-C_4H_2O$)

No.	R	maleic anhydride adduct (m. p.)	b. p.	M_r		yield(%)
				calc.	obs.	
Xa	Methyl (9)	121-122	110-111	25.44	25.14	36
Xb	Ethyl	132-134	125-126	30.06	30.56	56
Xc	Isopropyl	134-135	135-136	34.68	34.41	52
Xd	Phenyl	132-134	105-106/18	45.03	45.72	74
Xe	n-Octyl	137-138	129-130/18	57.91	57.39	36
Xf	Cyclohexyl	138-139	118-119/18	45.33	46.73	53
Xg	Thiophenyl	139-140	119-120/8	51.25	52.96	50

The 2-alkoxyfurans were found to be extremely sensitive to acids as would be predicted from a consideration of the ketene acetal structure and the nature of the furan ring itself. A comparison of the

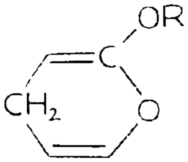


ketene-acetal XI



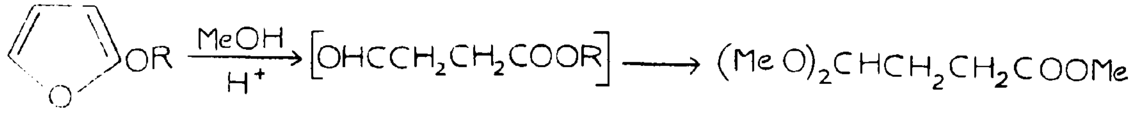
alkoxyfuran XII

two structures shown will serve to show the great similarity to be expected in chemical reactions. The arrows drawn help to indicate the type of polarization existing in the molecule. The effect normally occurring with ketene-acetals would be expected to be reinforced by the normal electronic interaction of the furan ring oxygen. The presence of the conjugated double bonds in the furan ring would be expected to lead to a much higher electron density at the 5-position than at the 3-position. In order to further illustrate the similarity of ketene-acetals and alkoxyfurans, a glance at alkoxypyrans will quickly show that these compounds would fit between structures XI and XII. The chemical reactions of ketene-acetals have been investigated intensively by McElvain (20) who has found that they are rapidly hydrolyzed by water or alcohol in the presence of a trace of acid.



2-alkoxypyran XIII

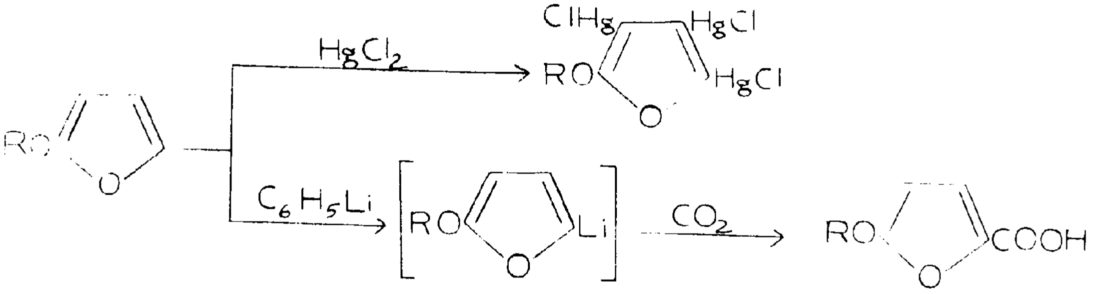
Similarly the 2-alkoxyfurans are cleaved rapidly by methanolic hydrochloric acid to produce the dimethyl acetal of methyl β -formyl propionate as shown in reaction 2. Reaction of this product with the



(2)

2,4-dinitrophenylhydrazine reagent gave the same product, the 2,4-dinitrophenylhydrazone of ethyl β -formylpropionate, as that obtained directly with the reagent from 2-phenoxyfuran. A further indication of the structure of the cleaved product is given by the hydrolysis of 2-methoxypyran (XIII R = Me) which is reported (21) to form methyl γ -formylbutyrate. Although the alkoxyfurans were clear colorless liquids, they all became yellow and viscous after exposure to air for a few days while the non-aromatic 2-methoxypyran oxidizes almost immediately on exposure to air.

Attempted bromination of 2-methoxyfuran with N-bromosuccinimide resulted in an unidentified high molecular weight compound as might be predicted from the action of bromine on ketene-acetals (20). However, it is in direct contrast with 2-methoxythiophene which is reported (10) to give a good yield of 5-methoxy-2-bromo-thiophene under identical conditions. This might be expected since the thiophene derivatives have considerably more aromatic character and therefore would behave somewhat differently than the ketene-acetals. The greater general reactivity of 2-methoxyfuran over its thiophene analogue was indicated by mercuration (equation 3). Treatment with mercuric chloride gave only 2-methoxy-3, 4, 5-trichloromercurifuran whereas 2-methoxythiophene is reported to be mercurated in the 3 and 5-positions. However the unoccupied 5-position of alkoxyfuran is the most reactive carbon of the ring toward metallation (equation 4) as evidenced by the reaction of 2-phenoxyfuran with phenyllithium which upon carbonation gave 5-phenoxy-2-furoic acid (IXd).



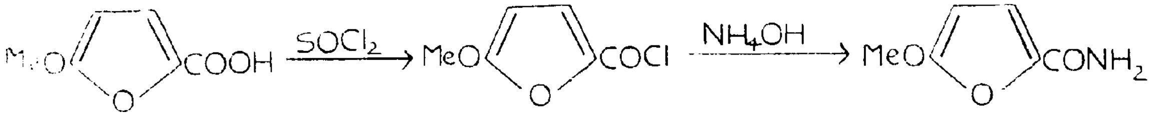
(3)

(4)

Thiophenoxyfuran is a member of the previously unknown class of furyl sulfides. It reacted readily with hydrogen peroxide to form a representative of another unknown class of furan chemicals, the furyl sulfones. As might be expected the phenyl furyl sulfide is more stable than the corresponding phenoxyfuran since the sulfur atom is more able to transmit any resonance effects between the two rings. Similarly the electron-withdrawing effect of the sulfone group leads to a decrease in basicity of the furan ring thereby adding considerable stability to the compound.

Phenyl 2-furyl sulfone was prepared from the sulfide by oxidation with hydrogen peroxide and recrystallized from ethanol to stable white needles. That the stabilizing effect of the sulfone group is not as great as that due to a carboxyl group was indicated by bromination which did not substitute on the furan ring but split the sulfur-furan bond to produce benzene sulfonyl bromide along with some tar due to destruction of the furan ring.

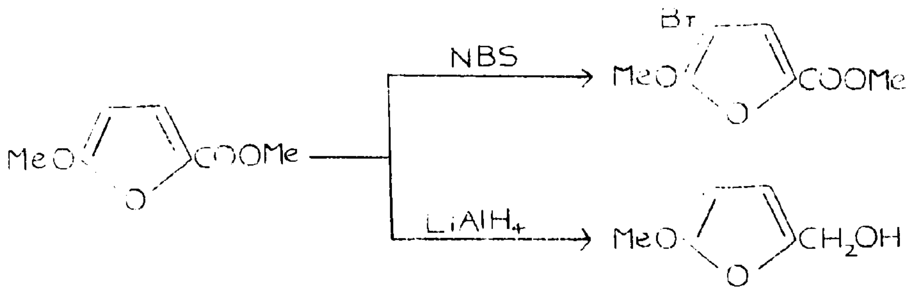
The stabilizing effect of a carboxyl group in the 5-position of 2-alkoxyfurans is demonstrated by the reaction of 5-methoxy-2-furoic acids with the strongly acidic compound, thionyl chloride, to produce the acid chloride with only slight tar formation. The methoxyfuroyl chloride hydrolyzed rapidly in air and reacted with concentrated ammonium hydroxide to produce 5-methoxy-2-furamide (equation 5)



(5)

This amide was also produced in good yield by direct ammonolysis of methyl 5-methoxy-2-furoate. The instability caused by the alkoxyl group is not removed completely by the presence of a carboxyl group however, since 5-methoxy-2-furoic acid, on attempted nitration, gave a high molecular weight compound which could only have arisen from ring opening and polymerization, while 5-bromo-2-furoic acid forms 5-bromo-2-nitrofuran and 5-nitro-2-furoic acid on nitration (22).

Similarly direct bromination of methyl 5-methoxy-2-furoate resulted in considerable tar formation along with a small amount of methyl 4-bromo-5-methoxy-2-furoate. This compound was produced smoothly and in somewhat better yield using N-bromosuccinimide as the brominating agent (equation 7). In contrast to reactions involving acidic conditions, the reduction of methyl 5-methoxy-2-furoate with lithium aluminum hydride gave a good yield of 5-methoxy-2-furfuryl alcohol (equation 8). This alcohol was even more unstable than furfuryl alcohol and decomposed rapidly on standing.



(7)

(8)

Kinetics

As previously stated the 2-halofurans reportedly (16, 17, 18) have relatively inert carbon to halogen bonds although the kinetic study by Petfield and Amstutz (9) did not show any physical basis for this inertness. Virtually all the reactions which have led to this idea of inertness have involved nucleophilic displacement of the halogen and indeed the methods employed in the synthesis of the alkoxyfurans reported here have utilized this same type of reaction. Attempts to prepare 2-methoxyfuran directly from sodium methoxide and 2-bromo- or 2-iodofuran have failed thereby indicating the "inertness" of the halogen-carbon bond. On the basis of a comparison with α-halo-ethers this inertness is unexpected. The normal prediction of reactivity would be halobenzenes less than halothiophenes which should be less than halofurans. Perhaps the best method for obtaining quantitative experimental and theoretical evidence of the properties of halocompounds is by kinetic studies. A considerable amount of this type of work has been carried out on substituted halocompounds (23, 24) and also this laboratory has been the scene of many investigations on unsubstituted halocompounds (9, 25, 26). The fact that Sicé (10) successfully isolated 2-methoxythiophene by reaction of 2-bromo- or 2-iodothiophene with sodium methoxide while the halofurans will not react under identical conditions has further emphasized the need for kinetic studies. Unfortunately both Petfield (19a) and Blood (24) were unable to show that 2-bromothiophene underwent a pseudo-unimolecular reaction with piperidine, thereby making it impossible to calculate a free energy of activation for the compound so that no quantitative comparison is available between the thiophene and furan analogues. The erratic results observed may be due to ring opening and the formation of 1,4-dipiperidino-2-butene which has been reported (19) to form at high temperatures. However the benzene compounds have been studied kinetically and their chemistry is well-known so that a comparison is possible.

Because of the difficulty in using methoxide as a nucleophilic reagent, piperidine has been used as an alternate. This choice was made not only for convenience but also so that comparisons with other compounds, investigated with piperidine, might be made and also to avoid the possibility of reduction of the halo compounds which has been reported (27) to occur with methoxide at 150°. In a series of papers on the molecular orbital theory of organic chemistry, Dewar (28) has claimed that the activation energy is equal to a constant, c, characteristic of the reagent and ΔE_π, the differences in π-electron binding energy between the initial and transition states, so that for a given type of reaction involving only different reagents the activation energy should change only by a constant. According to Dewar's theory then an activation energy measured using piperidine is directly translatable into an activation energy in terms of methoxide so that no theoretical disadvantage should be introduced by using one reagent rather than another and only practical considerations need limit the choice.

Since previous work (24, 25, 26) has dealt with similar compounds involving similar mechanisms, only the energy and entropy of activation have been considered. This is not strictly valid because the free energy of reaction is actually the rate controlling factor as shown by equation 8 of Appendix A. In this work there is a considerable difference in entropies of activation and therefore free energy will be used when discussing reactivity.

The activation energy is considered to be the energy required to raise the reactants in the ground state to the more energetic transition state. Any of the references cited in Appendix A give a comprehensive treatment of the theory of the transition state and this will not be discussed here other than to say that it is the transient species which "exists" when the bond to the nucleophilic reagent is forming and the bond to the halide group is breaking. The entropy of reaction is a much more vague term (25a), but may generally be considered to be a steric factor. The entropy of reaction then is that extra factor slowing the rate of reaction due to steric effects. For almost all bimolecular reactions the entropy of reaction, ΔS^*, is negative and for similar compounds undergoing the same type of reaction the more negative ΔS^* corresponds to the smaller steric factor. Naturally log pZ as defined in Appendix A is directly related to ΔS^* and has the same meaning. The free energy of reaction, ΔF^*, being the actual rate controlling factor is, as expected, the sum of the energy and entropy of reaction as shown by the following equation:

$$\Delta F^* = \Delta E^* - T \Delta S^*$$

Since both ΔF^* and ΔS^* are temperature dependent care must be taken that only values calculated at the same temperature are compared. This obvious disadvantage of these quantities has been one of the major reasons for comparing only activation energies which are theoretically temperature independent. Since all of the compounds necessary for this discussion have been investigated in the immediate vicinity of 200°C all of the temperature-dependent quantities have been calculated at this temperature. Table 4 contains the various kinetic values obtained for 2-chloro and 2-bromofuran along with these reported for chloro and bromobenzene (26).

Table 4

Compound	ΔE^* (kcal)	ΔS^*(e. u.)	ΔF^*(kcal)
2-chlorofuran	21.89 ± 0.36	-42.1 ± 1.5	41.23 ± .03
2-bromofuran	21.69 ± 0.33	-39.1 ± 1.3	39.38 ± .02
chlorobenzene (26)	26.8 ± 1.4	-42.4 ± 3.0	43.25
bromobenzene (26)	24.2 ± 0.4	-42.3 ± 1.0	41.43

Although the values for the furans are consistent within themselves as are the benzene values, ΔF^* and ΔE^* are smaller for the furans than the benzenes. Similarly the steric factor appears to be greater for the furan derivatives. Since it has not been possible to isolate the products from the reaction of halofurans with piperidine, there is no conclusive proof that both types of compounds proceed by the same mechanism. On the basis of the theory that two different mechanisms are involved no valid comparison of the kinetic data can be made. However there is no other reason to make this assumption and therefore other possible explanations must be examined. Since the halogen atoms have the same size regardless of the ring to which they are attached and the geometry of the rings would indicate a larger size for the benzene ring, the discrepancies in steric factors, ΔS^*, are not to be expected. As discussed previously and in the section on ultra violet spectra, the furan oxygen atom is a highly "basic" center. It is quite possible that this highly electron rich center at a neighboring position causes this entropy factor by exerting a strong repulsive force on any approaching nucleophilic reagent. The activation energy is directly related to the ease of production of a partial positive charge on the carbon bearing the halogen atom. In order to accomplish this with a benzene derivative a considerable amount of resonance energy must be overcome. With furan derivatives, on the other hand, the process should be much less energetic due to the diene contribution to the overall mesomer. However the energy would also be increased somewhat by an inductive neutralization of the charge by the unshared electrons of the furan oxygen. It is therefore conceivable that the activation energy of halofurans would be less than that of halobenzenes while the steric factor, ΔS^*, would be greater for the furan derivatives. Since ΔF^* is a composite function of both the energy and entropy of reaction it is not surprising that the values are nearly equal for both types of compounds. Although the general non-reactivity of the furan derivatives is demonstrated by the results, there is no indication that the halofurans are more "inert" than the halobenzenes. In fact the ΔF^* values seem to show that the halofurans are slightly more reactive towards piperidine.

Calculation of the kinetic values for 5-chloro-2-furoyl piperidide gives an activation energy of 17.22 ± 0.85 kcal, ΔF^* of 31.05 kcal, and ΔS^* of -37.1 e. u. The rate constants were erratic showing a definite increase with time which was shown not to be due to piperidine-hydrochloride catalysis. Because definite trends were observed, valid comparative results probably can not be obtained. Blood (24) has found an activation energy of 18.1 kcal for the 5-bromo-2-furoyl piperidide which corresponds to a decrease of 3.7 kcal due to the carboxypiperidide group while in the benzene series the decrease is only 1.2 kcal. The effect of the substituent on the activation energy is therefore three times greater in the furan series than in the benzene series. To apply this figure to other substituents is admittedly of rather dubious validity since the comparisons are not available for other groups.

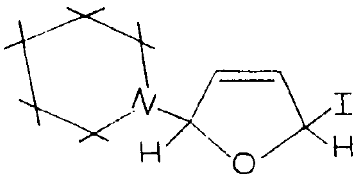
While completing the study of the 2-halofurans the following results were obtained on 2-iodofuran:

$$\Delta E^* = 30.85 \pm 0.38 \qquad \Delta S_{200} = -18.8 \pm 1.2 \qquad \Delta F^*_{200} = 38.74 \pm 0.02$$

These results do not fit in with the expected trends at all as may be seen from Table 4 and the following results reported for iodobenzene (29):

$$\Delta E^* = 23.6 \qquad \Delta S^*_{200} = -38.2 \qquad \Delta F^*_{200} = 40.7$$

The tremendous increase in activation energy in going from bromo to iodofuran and the large difference in entropy is entirely unexpected. The lower ΔF^* is consistent with the faster rate of reaction. These differences immediately suggest a different reaction mechanism possibly involving two or three steps before the elimination of iodide ion. The fact that the rate of reaction is faster while the activation energy is higher is quite unusual and implies a multi stage reaction leading to a false high energy of activation or a "furyne" type intermediate such as that reported by Roberts et. al. (52) for the reaction of chlorobenzene and potassium amide. This type of intermediate might involve even more unfavorable geometrical considerations than the corresponding benzyne and would be expected to lead to extremely high energies of activation. The well-known ability of furan compounds to add reagents 2, 5 (2, 22) suggests the possibility of a similar type reaction with piperidine perhaps proceeding through a metastable intermediate such as:



Further attack by another molecule of piperidine then might lead to the elimination of iodide ion. The resulting product might remain as such or further undergo stabilization by elimination of piperidine to form the expected product of the reaction, piperidinofuran. The proof of such a hypothesis is not likely to be obtained from product isolation since no products of this type are isolatable from furans. By blocking the 5-position, however, reasonable kinetics should be obtained corresponding to standard nucleophilic displacement of the halogen. Therefore 5-methyl-2-iodofuran was prepared and investigated with the following results:

$\Delta E^* = 26.65 \pm 0.75$ $\Delta S^* = -29.1 \pm 2.4$ $\Delta F^* = 39.47 \pm 0.3$

The deactivating effect of the methyl group has been demonstrated by Berliner and Monack (30). The entropy of activation of 5-methyl-2-iodofuran appears to be consistent with nucleophilic displacement and the free energy of activation is likewise consistent with the deactivation of the methyl group. The fact that all of the above data are not in serious disagreement with the expected values indicates that 2-iodofuran did undergo a multi stage reaction similar to that which is proposed here rather than nucleophilic displacement. Complete proof can not be given until the reaction mechanism has been thoroughly investigated and other compounds such as 5-methyl-2-bromofuran and 5-bromo-2-iodofuran have been investigated kinetically.

The results obtained in the kinetic study are listed in tabular form below:

Table 5

Compound	ΔE^*	ΔS^*_{200}	ΔF^*_{200}
2-Chlorofuran	21.89 ± .36	-42.1 ± 1.5	41.23 ± .03
2-Bromofuran	21.69 ± .33	-39.1 ± 1.3	39.08 ± .02
2-Iodofuran	30.85 ± .38	-18.8 ± 1.2	38.74 ± .02
5-Methyl-2-iodo furan	26.65 ± .75	-29.1 ± 2.4	39.47 ± 0.3
5-Chloro-2-furoyl piperidide	17.22 ± .85	-37.1 ± 2.2	31.05 ± 0.3
5-Bromo-2-furoyl piperidide (24)	18.1 ± 1.1	-40.3 ± 2.3	32.05
Chlorobenzene (26)	26.8 ± 1.4	-42.4 ± 3.0	43.25
Bromobenzene (26)	24.2 ± 0.4	-42.3 ± 1.0	41.43
Iodobenzene (29)	23.6	-38.2	40.7

Calculation of activation energy, entropy and free energy

Activation energies were calculated from the integrated Arrhenius equation:

$$\log\frac{k_1}{k_2} = \frac{\Delta E^*}{2.3R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

A preliminary plot of -log k vs. $\frac{1}{T}$ was made in order to determine which points should be used for the calculation of ΔE^*.

The calculation of ΔF^* was made on the basis of the

Absolute Reaction Rate Theory equation (eq'n 8 Appendix A)

$$k_r = \left(\frac{kT}{h}\right) e^{-\Delta F^*/RT}$$

which after inserting the proper numerical constants reduced to the following equation:

$$\Delta F^* = 4.576\ T(13.877 + \log T - \log k_r) \tag{1}$$

Similarly ΔS^* was calculated from equation 9 of Appendix A

$$k_r = \left(\frac{kT}{h}\right) e^{\Delta S^*/R}\, e^{-\Delta E^*/RT}$$

which reduced to $\Delta S^* = \dfrac{\Delta E^*}{T} - 4.576\ (\log T + 14.312 - \log k_r)$ (2)

Equation 3 of Appendix A also is reducible to the following simple equation:

$$\log pZ = \log k + \frac{\Delta E^*}{4.576\,T} \tag{3}$$

In order to obtain values of ΔF^* and ΔS^* which are temperature dependent, it was necessary to calculate a rate constant at some chosen temperature (200°C) which is readily available by a mathematical extrapolation of the best straight line of the Arrhenius plot.

Calculation of pseudounimolecular rate constants were made according to the readily derivable equation:

$$k_r = \frac{\ln\left(\frac{a}{a-x}\right) - \ln\left(\frac{a}{a-x_0}\right)}{t}$$

where a = ml. of $AgNO_3$ required for 100% reaction.

$$= \frac{\text{N sample} \quad \text{V sample}}{N_{AgNO_3}}$$

x = ml. $AgNO_3$ required after time t.

x_0 = ml. $AgNO_3$ required at time t = o.

Calculation of second order rate constants were made according to the following:

$$k_T = \frac{1}{Nt}\left[\frac{a}{a - x} - \frac{a}{a - x_0}\right]$$

where a = ml. of $AgNO_3$ required for 100% reaction.

x = ml. of $AgNO_3$ required after time t.

x_0 = ml. of $AgNO_3$ required at time t = o.

N = normality of sample.

Rate constant errors: Ten possible sources of error have been given by Brower (25a) of which only temperature variations and titration errors were concluded to be significant under the procedure used. In this work the temperature variation also has been reduced to a negligible value by using an especially constructed thermoregulator (designed and constructed by K. R. Brower) which controls the temperature variation to less than 0.05°C at temperature ranges between 60° and 230°. The average deviation of titrations of identical samples has been determined to be 0.072 ml. which corresponds to a deviation in the first order rate constant of about 0.00092 units. In general every pseudounimolecular rate determination which has been made in the course of this work with the exception of those on 5-chloro-2-furoyl piperidide has resulted in average deviations in k of less than 0.00092 units so that the error involved in the rate constants is quite probably due to errors in titration. The possible errors involved in letting the sample sit before dilution, after dilution but before acidification, and after dilution and acidification have been quantitatively determined and found to be less than the limit of precision of titration for times up to twenty minutes while the total time actually required from the time of removal of the sample from the bath to the completion of the titration is not more than twelve minutes. Any purely systematic error may effect the true value of k but will not effect any of the energies of activation since it is constant throughout.

Estimation of error in the activation energy, entropy, and free energy

Errors in ΔF^* were calculated assuming a negligible error in T for reasons mentioned previously. By calculating the average percentage error in log k, an average error to be expected in log k at some other temperature may be obtained which on application of equation 1 gives the error in ΔF^* Because this error is much less than that in ΔE^* the correction based on rate constant error may be neglected in the calculation of ΔS^*. The error in ΔS^* was obtained from equation 2 using the error in ΔE^*. Similarly errors in log pZ may be determined from equation 3 by a similar procedure. The errors in ΔE^* were calculated to include at least 95% of all ΔE^* values. For each point used in the determination an average deviation in log k, $\overline{\log k_d}$, was determined by summing the deviation of each log k and dividing by the total number of points. Using the two points corresponding to the two extreme temperatures, provided that they fall exactly on the best straight line, a maximum and minimum slope may be calculated according to the following equations:

$$\text{slope}_{\text{max}} = \frac{\left(\log k_1 - \overline{\log k_d}\right) - \left(\log k_2 + \overline{\log k_d}\right)}{1/T_1 - 1/T_2}$$

$$\text{slope}_{\text{min}} = \frac{\left(\log k_1 + \overline{\log k_d}\right) - \left(\log k_2 - \overline{\log k_d}\right)}{1/T_1 - 1/T_2}$$

$$\text{where} \quad \frac{1}{T_1} < \frac{1}{T_2}$$

The calculation of activation energies from both of these slopes gives the maximum and minimum values possible on the basis of the points observed. An average of these two slopes gives the slope of the best straight line through the experimental points from which ΔE^* is calculated. Making the entirely reasonable assumption that the activation energies show a normal distribution about the best straight line, ΔE^*, it is possible to apply a few of the principles of statistics (51). Since the limits of error which have been calculated are maximum values the area under the normal curve corresponding to these limits is at least $\pm 3.9\sigma$ where σ is the standard deviation from the mean. From this value, σ, it is possible to calculate $\pm 1.96\,\sigma$ which represents the error including at least 95% of all values of ΔE^* and the most probable error, $\pm 0.97\,\sigma$, which includes two-thirds of all values of ΔE^*. These statistical values show that the most probable error is approximately one-half of the error which includes 95% of all ΔE^* values which is in turn one-half of the maximum possible error.

The experimental procedure and equipment used have been thoroughly discussed by Brower (25) and will not be included in this work.

The Ultraviolet Spectra of Furan Derivatives

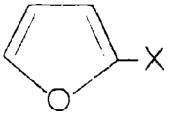
Since there is very little information in the literature on the ultraviolet spectra of simple furan derivatives and because many different types of these compounds have been prepared in the course of this work, a fairly complete compilation of the data has been made. The λ_{max}, $\log \epsilon$, and $\Delta\lambda$ values are recorded in Tables 5 and 6, and the curves are shown in Appendix C. For convenience the compounds have been divided into two classes, 2-substituted furans (Table 5) and methyl 5-substituted-2-furoates (Table 6). In each table the corresponding benzene or methyl p-substituted benzoate $\Delta\lambda$ values are included which are designated as $\Delta\lambda_{Ph.}$ In order to calculate $\Delta\lambda$ values a λ_{max} for furan was assumed to occur at 208 $m\mu$. Since no work has been reported for furan in the far ultraviolet, an exact value was not available but could be obtained by an extrapolation of the experimental curve which could be plotted to 213 $m\mu$ at which point the cut off of 95% ethanol occurred. However the extrapolation appears to be valid since a vapor spectrum was obtained of almost identical shape in which the maximum was displaced to 222 $m\mu$.

The concept of $\Delta\lambda$ was introduced and applied briefly by Doub and Vandenbelt (32) on a few benzene derivatives. Since their values were obtained for a water solution, the values have again been determined in 95% ethanol unless otherwise noted. The value, $\Delta\lambda$, is defined as the difference between the maximum wave length of absorption of the first primary band and the wave length of maximum absorption of the unsubstituted nucleus, λ_0 . The primary bands are of strong intensity usually with $\epsilon > 6000$ and the first primary band is that which shows the greatest bathochromic shift from that of the unsubstituted nucleus. The $\Delta\lambda$ values are expected to be a measure of the electronic interaction of the group with the aromatic system to which it is attached. As is well known in aromatic organic chemistry, there is considerable difficulty is assigning qualitatively the electronic effect of a group since most of the methods available involve chemical reactions, the isolation of products, and the proof of structure. In fact the relative degrees of ortho-para or meta- directing power of a group may only be determined after isolating all of the products and separating the isomers. This process in itself suffers from many inaccuracies and indeed is apt to vary from reaction to reaction. Because the method utilized here does not involve electronic polarizations induced by attacking reagents, it is felt that this method is superior to the others for evaluating, at least qualitatively, the amount of electronic interaction between groups. By first separating the substituents into those which are ortho-para directing and those which are meta-directing and then arranging each group in order of increasing $\Delta\lambda$, the following results are obtained:

$$C_6H_5S > C_6H_5O \geqslant MeO > Br > Cl > H$$

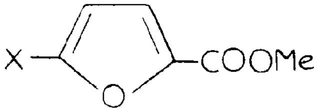
$$NO_2 > MeOOC > C_6H_5SO_2 > H$$

Table 5



X	λ_{max}(mμ)	log ε	$\Delta\lambda^{a}$	$\Delta\lambda^{b}_{Ph}$
H-	(208)	(3.9)	0	0
Br-	215.5	3.99	7.5	6.5*
MeO-	221.0	3.82	13.0	13.5*
C_6H_5O-	222.0	4.06	14.0	23.2
C_6H_5S-	241.5	4.21	33.5	28.3
$C_6H_5SO_2$-	249.5	4.13	41.5	32.8
MeOOC-	252.1	4.13	44.1	26.3

Table 6



X	λ_{max}(mμ)	log ε	$\Delta\lambda^{a}$	$\Delta\lambda^{b}_{Ph}$
H-	252.1	4.13	44.1	26.3
Cl-	260.5	4.23	52.5	37.5*
$C_6H_5SO_2$-	261.7	4.33	53.7	39.0
Br-	264.1	4.23	56.1	41.5
MeOOC-	264.6**	4.19	56.6	38.5
C_6H_5O-	275.0	4.25	67.0	54.5
MeO-	279.0	4.10	71.5	53.0
C_6H_5S-	291.8	4.33	83.8	89.7
O_2N-	295.4	4.08	87.4	55.0

a) $\lambda_{max} - \lambda_o$ where $\lambda_o = 208$

b) $\lambda_{max} - \lambda_{o\,Ph}$ where $\lambda_{o\,Ph} = 203.5$

* Taken from Doub and Vandenbelt (32)

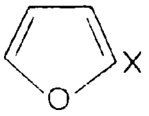
** Taken from literature (33)

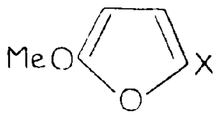
These results agree qualitatively with the degree of directing power observed in various aromatic electrophilic substitution reactions as evidenced by the polarizing force of the groups as calculated by Price (34) and the substituent constants (35). However, as previously stated by Braude (36), there is no direct theoretical relationship between ultraviolet absorption maxima and basicities, ionization potential, or other simple parameters.

The fact that $\Delta\lambda$ and $\Delta\lambda_{Ph}$ do not agree quantitatively shows that the difference between the energy of the first spectrally excited states for furan and benzene is appreciable. Since the first excited states occur at longer wave length and lower energy with furan derivatives, the resonance interaction between furan and its substituents must be greater than is the case in benzene derivatives. This is not wholly unexpected because any interaction with the benzene ring must be sufficiently energetic to interfere with the benzene π-electron resonance whereas in furan the groups may serve as a sink for the electrons of the oxygen thereby resulting in an overall increase in aromatic character of the ring.

Table 7 contains various derivatives of 2-methoxyfuran and from an inspection of these values it may be seen that the methoxyl group causes absorption at a wave length approximately 24 $m\mu$ longer than that of the parent compound.

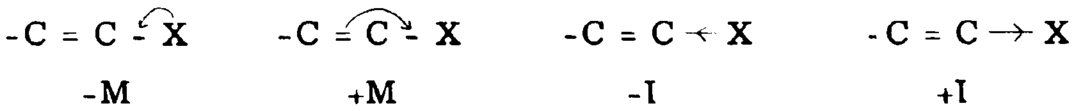
Table 7



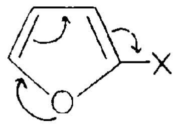


X	λ_{max}(mμ)	log ε	λ_{max} (mμ)	log ε
H-	(208)	(3.9)	221	3.82
$HOCH_2$	208 (37)	3.8	228.5	3.87
NH_2OC-	255 (38)	4.09	276.0	4.18
MeOOC-	252.1	4.13	279.5	4.10

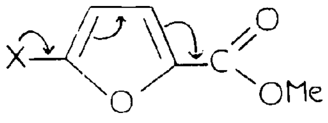
To examine these results further it is necessary to consider the mesomeric and inductive effects using the following sign convention:



Since the furan oxygen atom may be considered as a basic center, the ability of a group to accept these electrons should lead to an "acid-base" interaction. The greater the "acidity" of the group the greater should be the interaction and the wave length maximum would be expected to occur at longer wave lengths. The types of interaction involved in the furan compounds investigated may be written diagrammatically as:



A

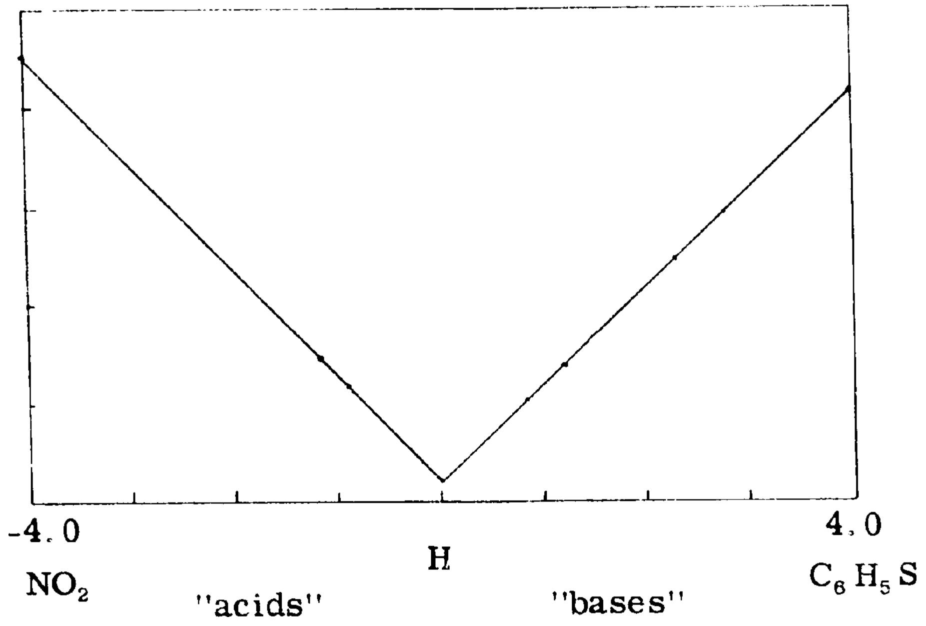


B

For compounds of type A (shown in Table 5) the only two electronic effects which exert any appreciable effect are +M and +I and the observed order is easily explained on this basis. The carbomethoxyl group, having a strong +M effect is a stronger "acid" than the phenyl sulfonyl group since the electron attracting power of the S-O bonds (or partial positive sulfur) could be decreased by interaction with the π-electrons of the phenyl ring. Waight (39) has found considerable evidence which he discussed quite thoroughly for conjugation in sulfones using the d orbitals of sulfur. The thiophenoxy group is a still weaker electron attracting group but is somewhat greater than the phenoxy group since the sulfur atom has d orbitals available for conjugation which, of course, the oxygen does not. Since oxygen is more electronegative than bromine, 3.5 and 2.8 respectively, on the Pauling scale, the alkoxyl group shows a stronger +I effect and therefore causes absorption at a longer wave length than the bromo-group. Thus on the basis of considering +M and +I effects the observed order of "acid-base" interaction is as predicted. Effectively then this spectral approach has led to at least a qualitative measure of the relative magnitudes of the summation of +M and +I effects for compounds of type A. The $\Delta\lambda$ values are therefore a measure of the electron attracting power or electronegativity of each group.

Although at present the exact theoretical relationships involving $\Delta\lambda$, log ϵ, and λ_{max} are not known so that no exact scale based on such measurements can be established, a qualitative empirical scale may be derived. In Figure 1 $\Delta\lambda$ is plotted against an arbitrary scale of "Acidity" and "Basicity".

Figure 1

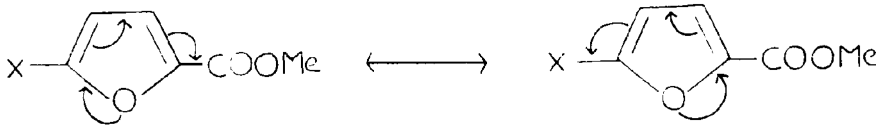


In this plot the meta directors are the "acids" and the ortho-para directors are the "bases". By choosing the units running from -4 to +4 a convenient scale of "acidity-basicity" or electronegativity is obtained. On this strictly empirical scale the following electronegativities are obtained:

O_2N	-4.0	H	0.0	C_6H_5O	+2.3
MeOOC	-1.2	Cl	+0.8	MeO	+2.8
$C_6H_5SO_2$	-0.9	Br	+1.2	C_6H_5S	+4.0

With compounds of type B the longest wave length of absorption would be expected to occur with the substituent possessing the greatest electron releasing power or "basicity". The observed series is considerably more complicated than those obtained for type A compounds due to the effect of the carbomethoxyl group. Disregarding the sulfone, carbomethoxyl, and nitro derivatives for the moment which are all "meta" directors in the benzene series, the remaining substituents fall into the same order as that obtained for type A compounds. The halogens would be expected to be the weakest electron donors with Cl being less than Br since the operative effects are -M and +I which are opposed and are probably of nearly the same intensity. Likewise with the alkoxy derivatives the -M and +I effects are opposed but in this case the -M effect must be large enough to overcome the +I effect. The thiophenoxy group shows a weaker +I effect than the oxygen compound due to the difference in electronegativity and an even stronger -M effect is allowed since sulfur may easily "expand its valence shell" and use d orbitals for conjugation. As before these compounds again appear to fall into the expected order by considering the -M and +I effects and the relative magnitudes must be a measure of the algebraic sum of both effects.

For the remaining compounds, the sulfone, carbomethoxyl, and nitro furoates, it is not possible to predict where they should fit in this series but it is possible to explain the fact thay they do not absorb at even shorter wave lengths than the halogens as might be expected since all of these groups are electron attracting. This anomalous position of the "meta" directors has also been noted by Doub and Vandenbelt (32) for nitrobenzenes. An examination of the $\Delta\lambda$ and $\Delta\lambda_{Ph}$ values given in Table 6 shows that all three groups absorb at relatively longer wave lengths in the furan series than in the benzene series. This is significant in that it implies that the difference is due to the basicity of the furan ring and most probably the oxygen atom. The unshared electrons of the oxygen atom may participate in the resonance of each group as:



In all of the compounds under consideration the most important effect is a +M effect. If the oxygen atom of the furan ring may participate in the resonance as illustrated above, the actual mesomeric structure would be expected to show a longer conjugated system than either extreme structure alone. Therefore absorption should occur at much longer wave lengths than expected. Naturally this effect may also occur in the benzene derivatives by conjugation of one of the double bonds. The fact that these compounds show a larger $\Delta\lambda_{Ph}$ than might be expected is sufficient evidence that the process definitely does occur. However, as previously shown, there is a great tendency for furan to conjugate with groups by donating the unshared electrons of the oxygen atom. This is exactly the explanation for the greater stability of furans containing electron withdrawing groups. Therefore it is quite reasonable to expect that the process would be much more important for furan derivatives than for the corresponding benzene derivatives and therefore the $\Delta\lambda$ values should be greater than the $\Delta\lambda_{Ph}$ values.

Appendix A

On the basis of the van't Hoff equation relating equilibrium constant with temperature, the famous Arrhenius equation was derived.

$$\frac{d \ln k_r}{dT} = \frac{\Delta E_a}{RT^2} \tag{1}$$

From this equation Arrhenius suggested that an equilibrium exists between the normal molecules and an activated molecule, now called the transition state, and that ΔE_a measures the difference in energy between the two states. Assuming a Boltzmann distribution of energy and introducing a frequency factor, A, representing the total frequency of encounters between two reactant molecules, equation 2 was derived.

$$k_r = Ae^{-\Delta E_a/RT} \tag{2}$$

On the basis of the collision theory it was found that the frequency factor, A, is equivalent to the collision number, Z. However, for certain simple reactions for which Z could be calculated it was found that equation 2 did not agree with the theoretical value of Z and an empirical value, p, was introduced and called the probability or steric factor giving the following equation:

$$k_r = pZe^{-\Delta E_a/RT} \tag{3}$$

In view of the empirical nature of this equation it is desirable to make use of a concept having better theoretical justification namely the absolute reaction rate theory. This theory is based on the statistical mechanical partition function. Assuming again an activated complex lacking one degree of freedom it is possible to arrive at the elementary equation $k_r = \left(\frac{kT}{h} \right) K^*$ where K^* is similar to an (4) equilibrium constant between non-activated and activated molecules. Because of the similarity of K to an equilibrium constant it is permissible to define certain functions analogous to those of thermodynamics as

The free energy of activation $\Delta F^* = - RT \ln K^*$ (5)

The heat of activation $\Delta H^* = RT^2 \frac{d\ln K^*_p}{dT}$ (6)

The entropy of activation $\Delta S^* = \frac{\Delta H^* - \Delta F^*}{T}$ (7)

From equations 4 and 5 it follows then that the basic rate equation is

$$k_r = \left(\frac{kT}{h} \right) e^{- \Delta F^*/RT} \tag{8}$$

which is also

$$k_r = \left(\frac{kT}{h} \right) e^{\Delta S^*/R} \quad e^{- \Delta H^*/RT} \tag{9}$$

For reactions in solution it may be shown that

$$\Delta H^* = \Delta E_a - RT \tag{10}$$

and that strictly speaking $\Delta H^* < \Delta E_a$.

However, since RT = PV and this term is negligible as compared with ΔE_a for reactions in solution, it is usually assumed that $\Delta H^* = \Delta E_a$. Since equations 8 and 9 have been derived on the basis of gaseous reactions, it is necessary to add a correction factor when applied to liquid reactions. The empirical validity of the Arrhenius equation, 3, makes a comparison of the two theories quite desirable. In order to do this and to extrapolate to liquid reactions it is necessary to assume that pZ is temperature independent and that the partition functions are not altered due to liquid-liquid interactions. These assumptions have been discussed by Brower (25a) who arrived at the conclusion that these assumptions do not effect the validity of the results to any appreciable extent and in fact may have some theoretical justification. Combining equations 3 and 9 and assuming $\Delta H^* = \Delta E_a$ the following equation is obtained

$$pZ = \left(\frac{kT}{h} \right) e^{j} e^{\Delta S^*/R} \qquad (11)$$

where $j \simeq 1$

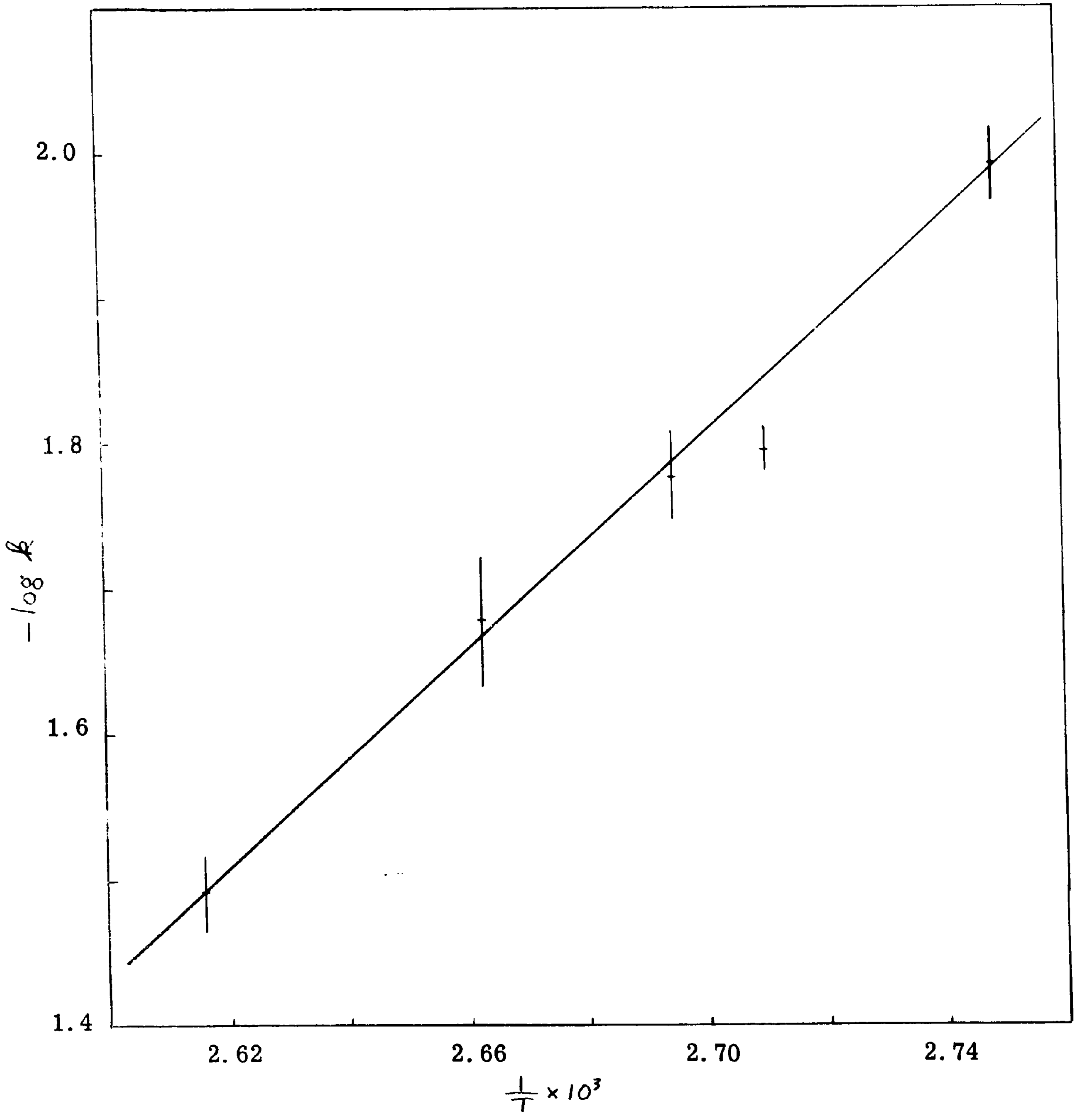
It follows from this equation that as ΔS^* becomes more positive, pZ becomes larger and that the two quantities are directly related. Further considerations show that for a series of similar reactions the more negative ΔS^* corresponds to the smaller steric factor.

For a more complete theoretical discussion the reader is referred to Frost and Pearson (48) and others (49, 50).

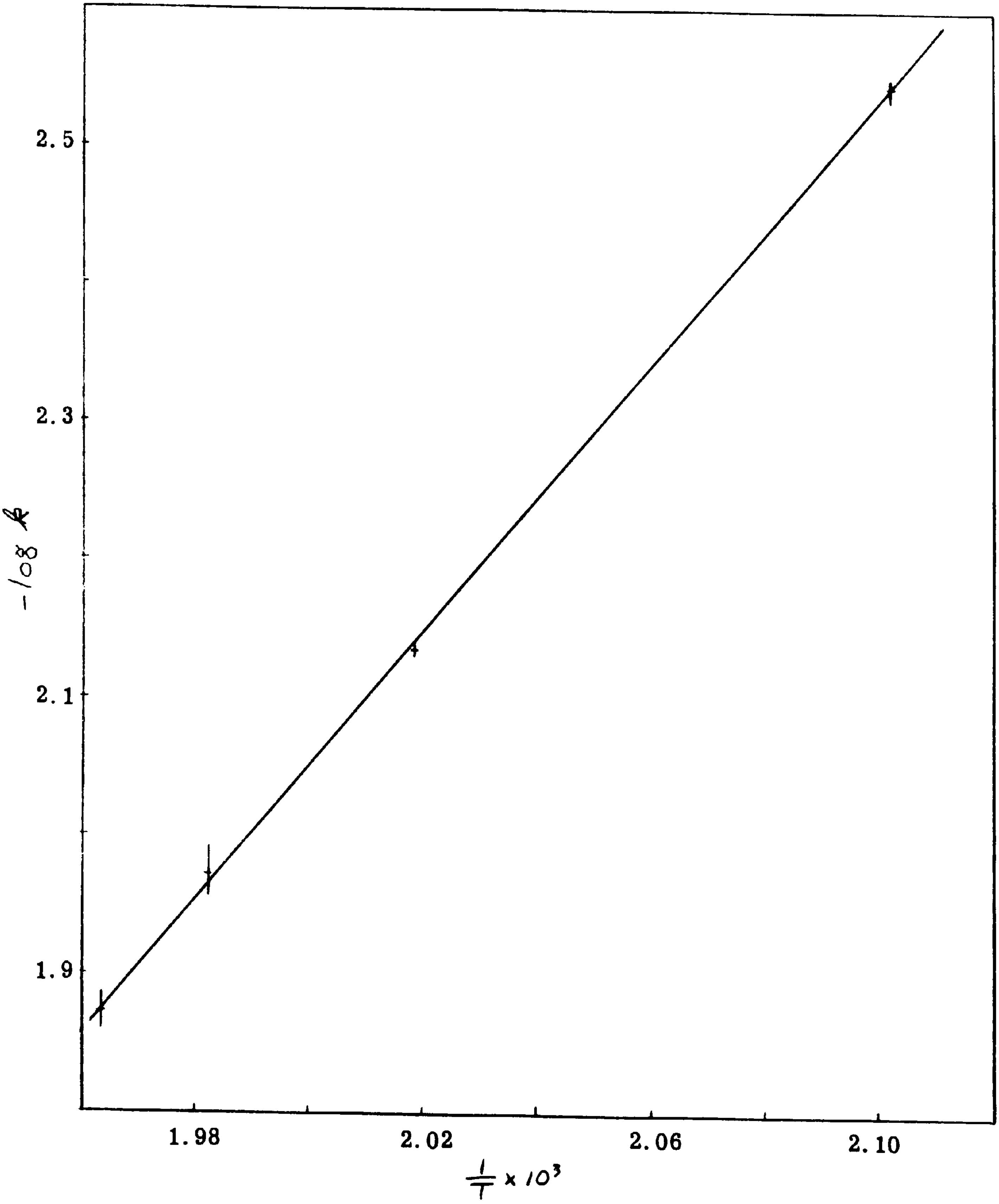
APPENDIX B

Graphic Representation of the Kinetic Studies

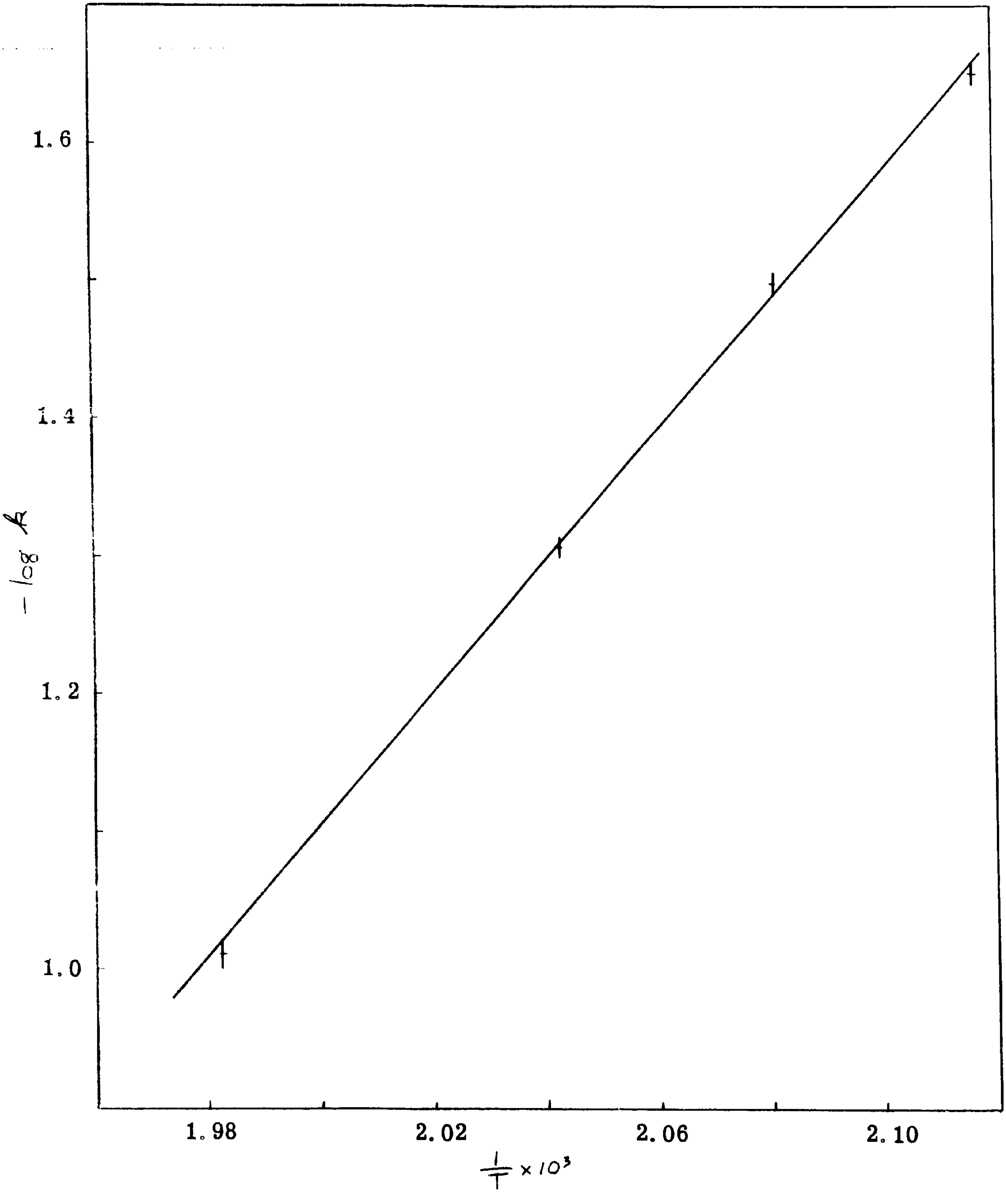
5-Chloro-2-furoyl piperidide



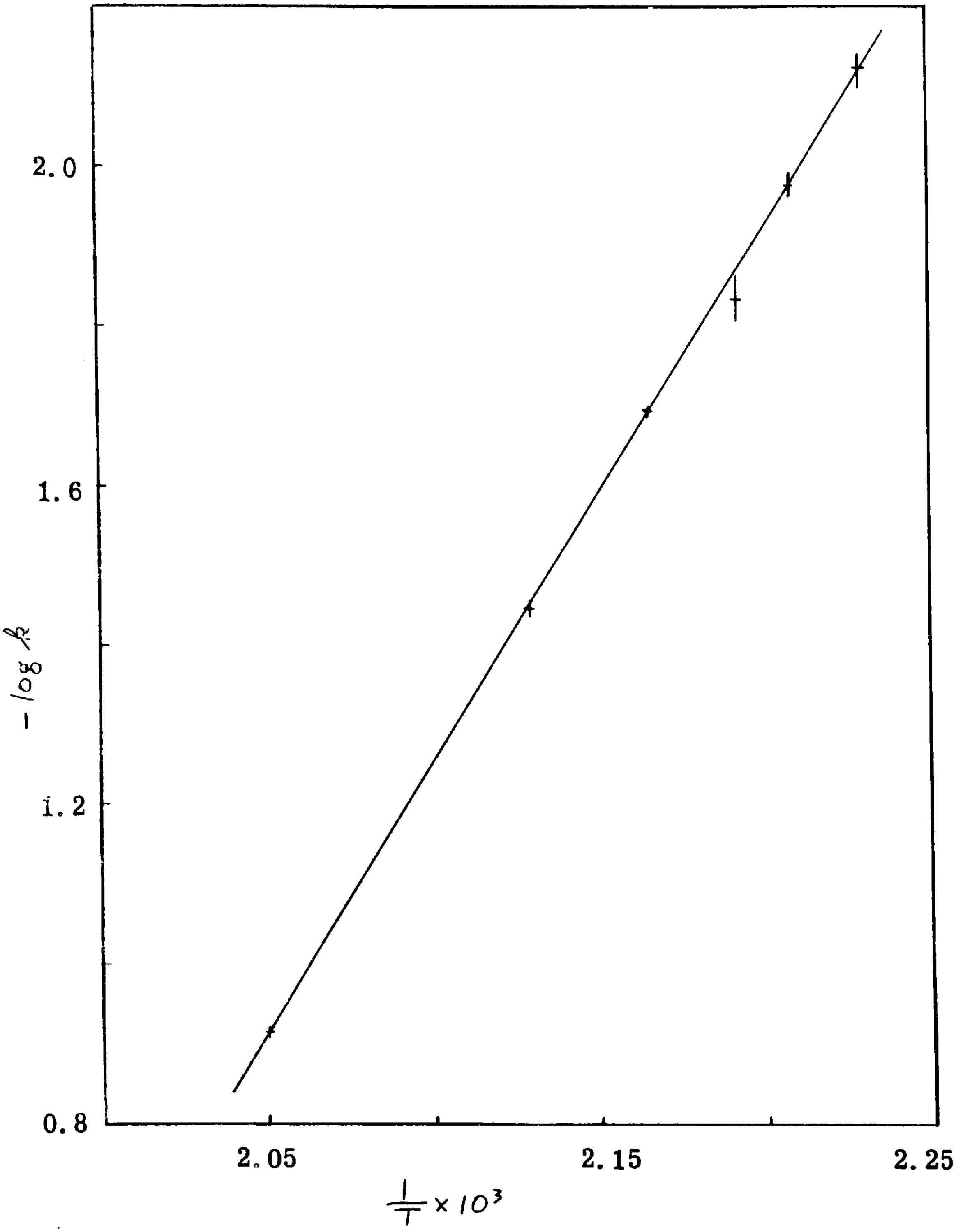
2-Chlorofuran



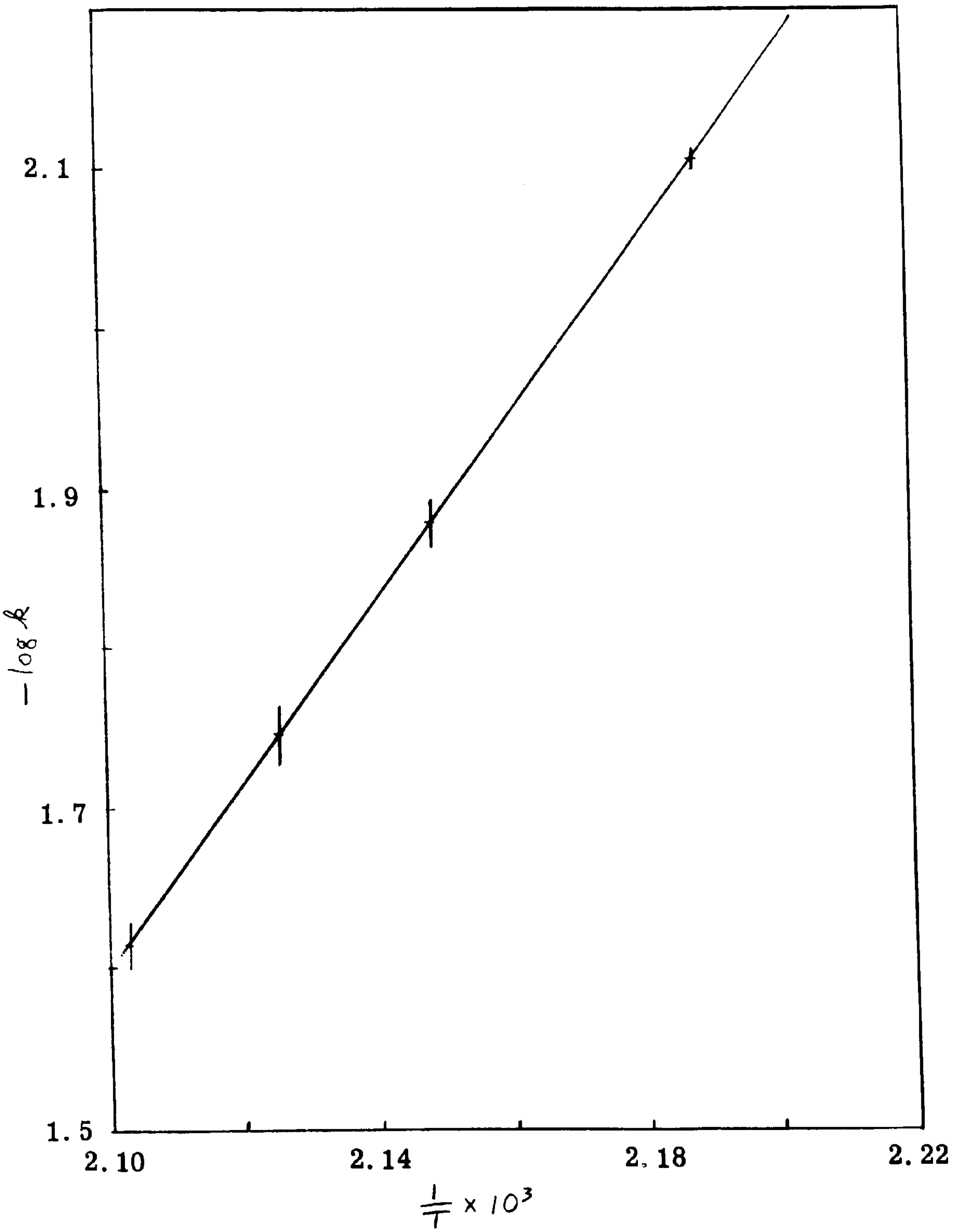
Bromofuran



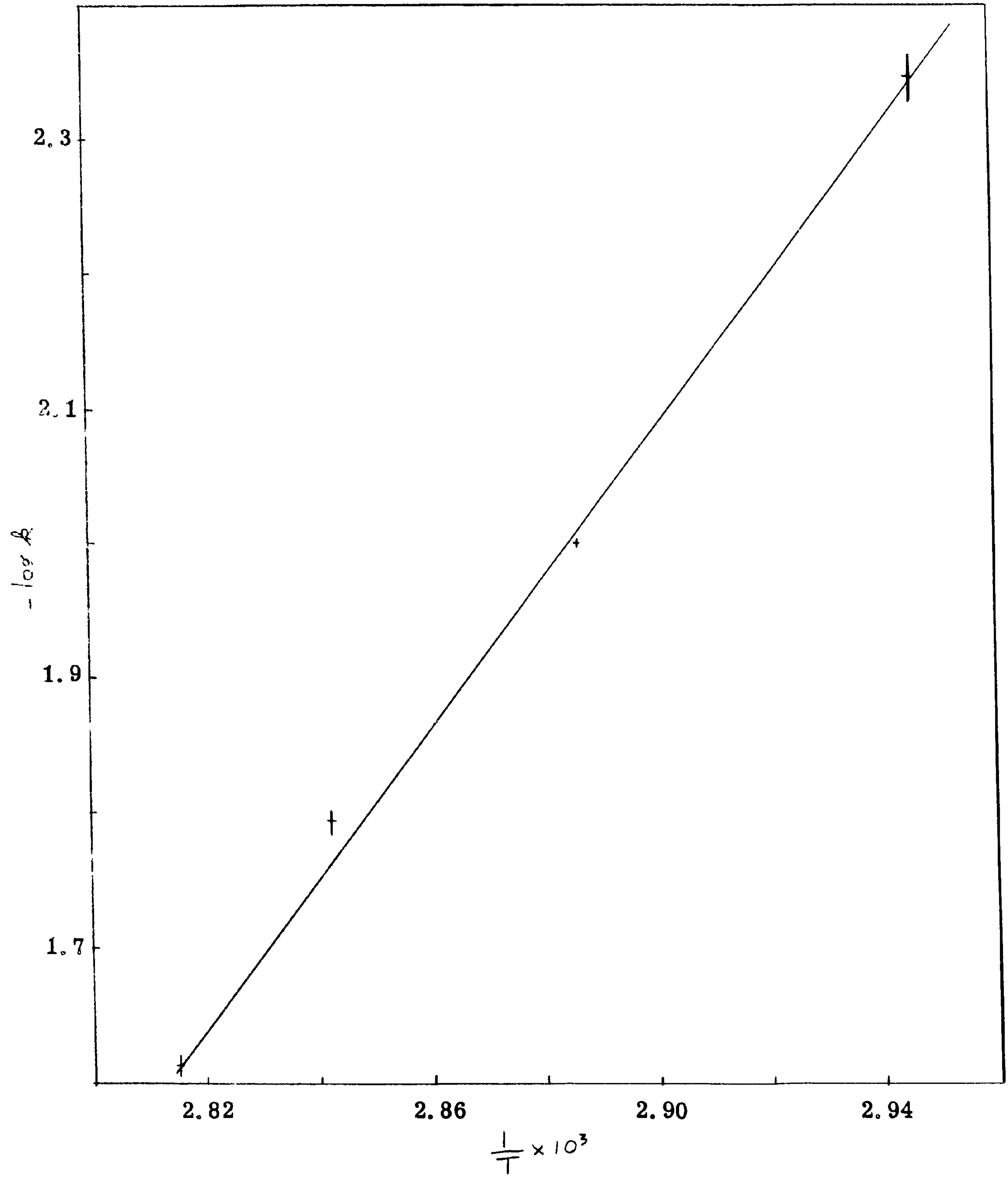
2-Iodofuran



5-Methyl-2-iodofuran



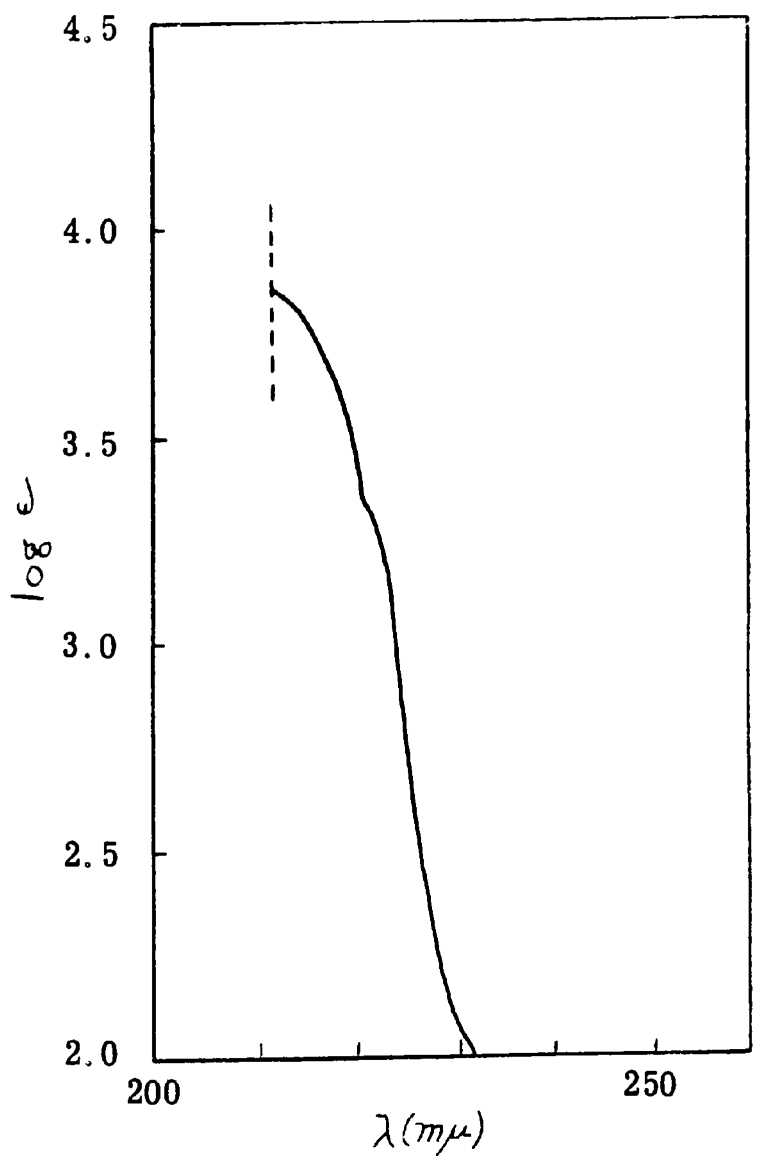
Methyl 5-chloro-2-furoate



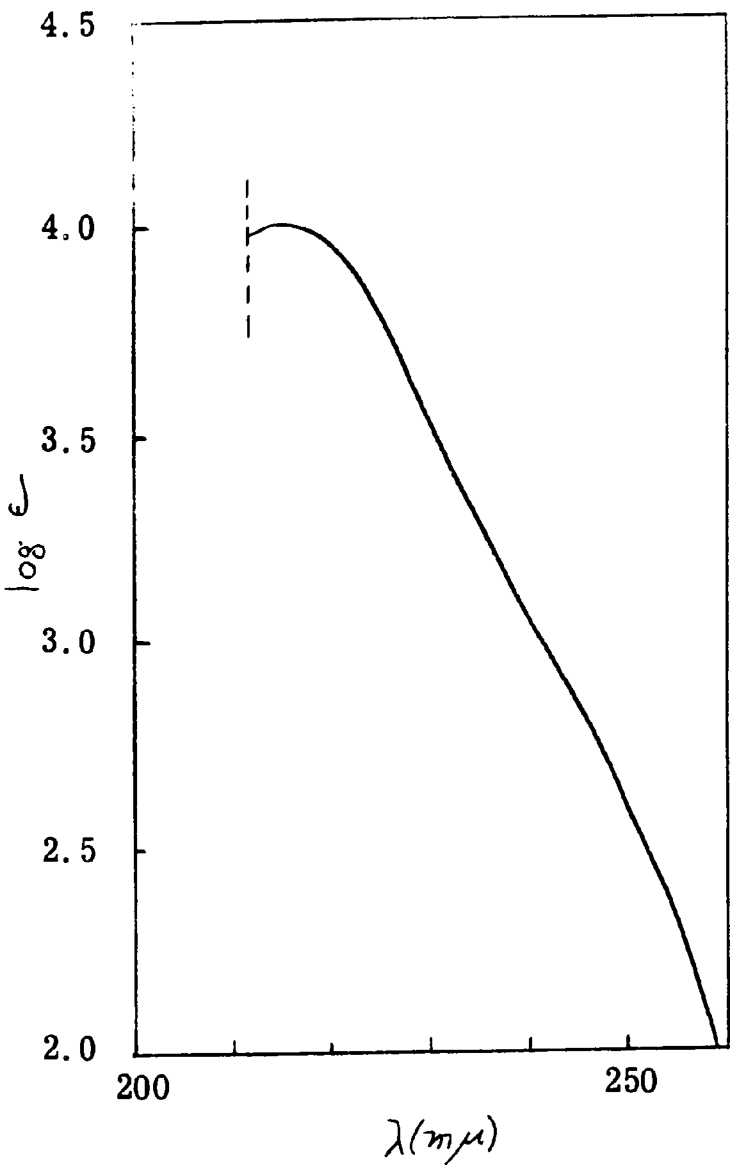
APPENDIX C

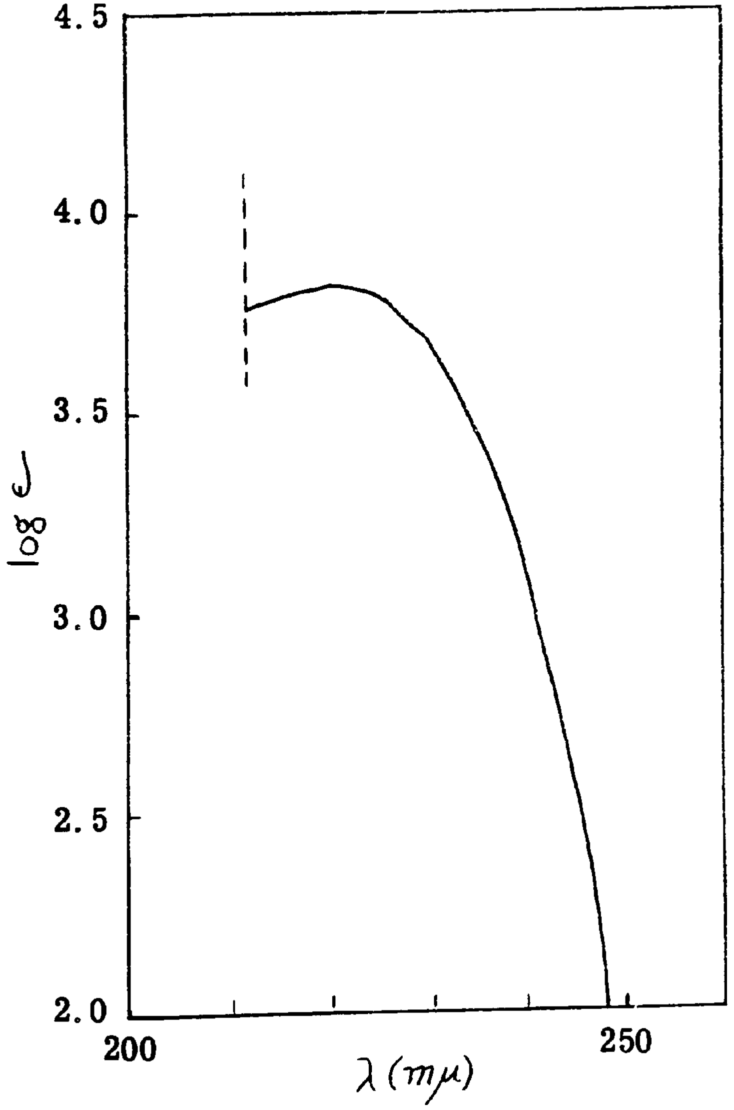
Ultraviolet Spectral Curves

Furan

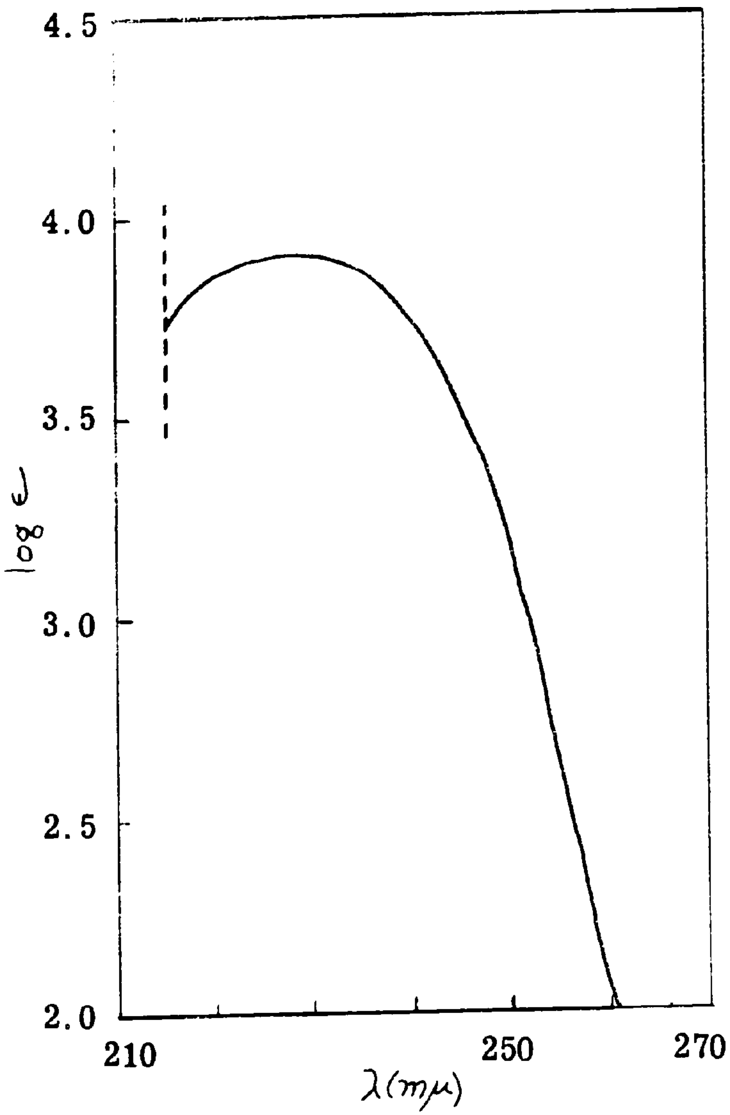


Bromofuran



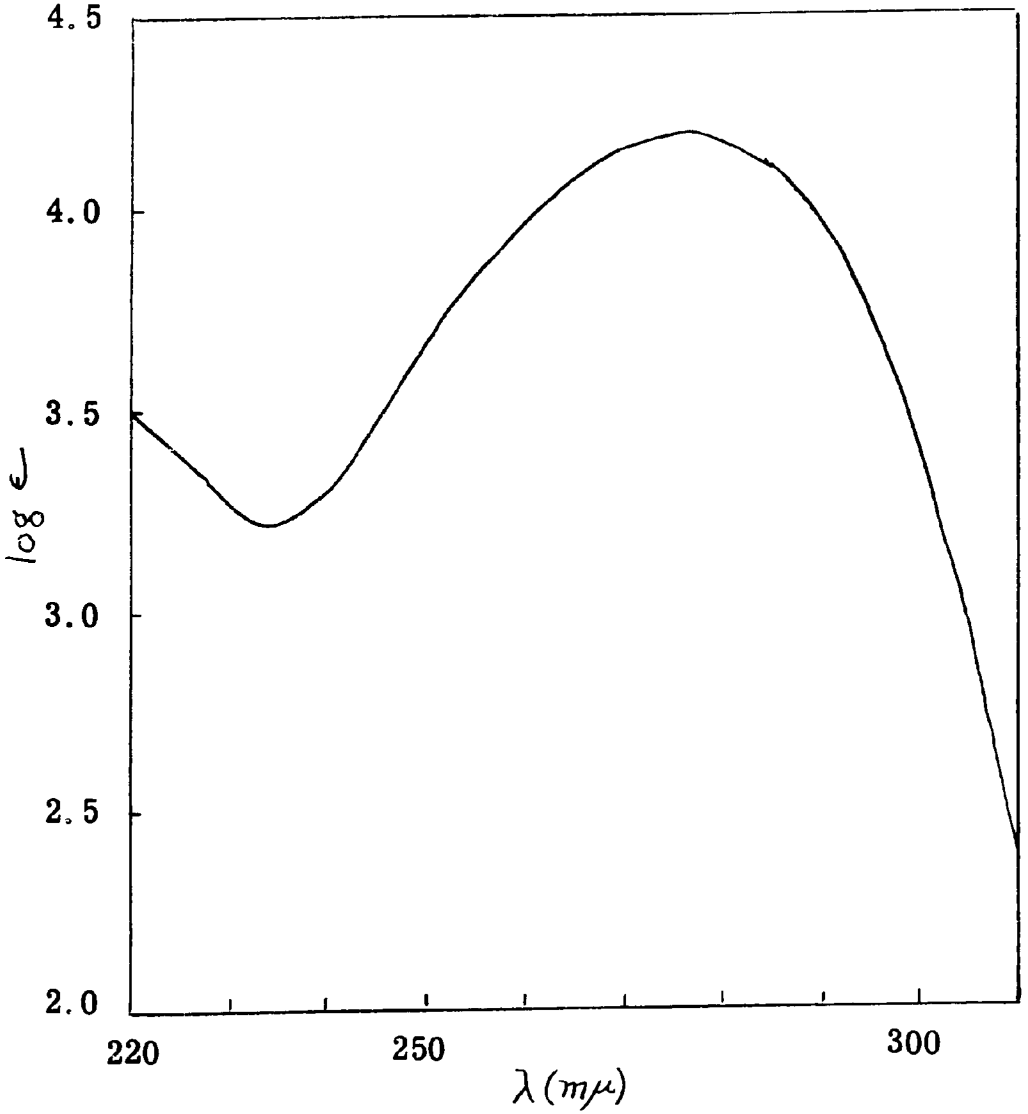


2-Methoxyfuran

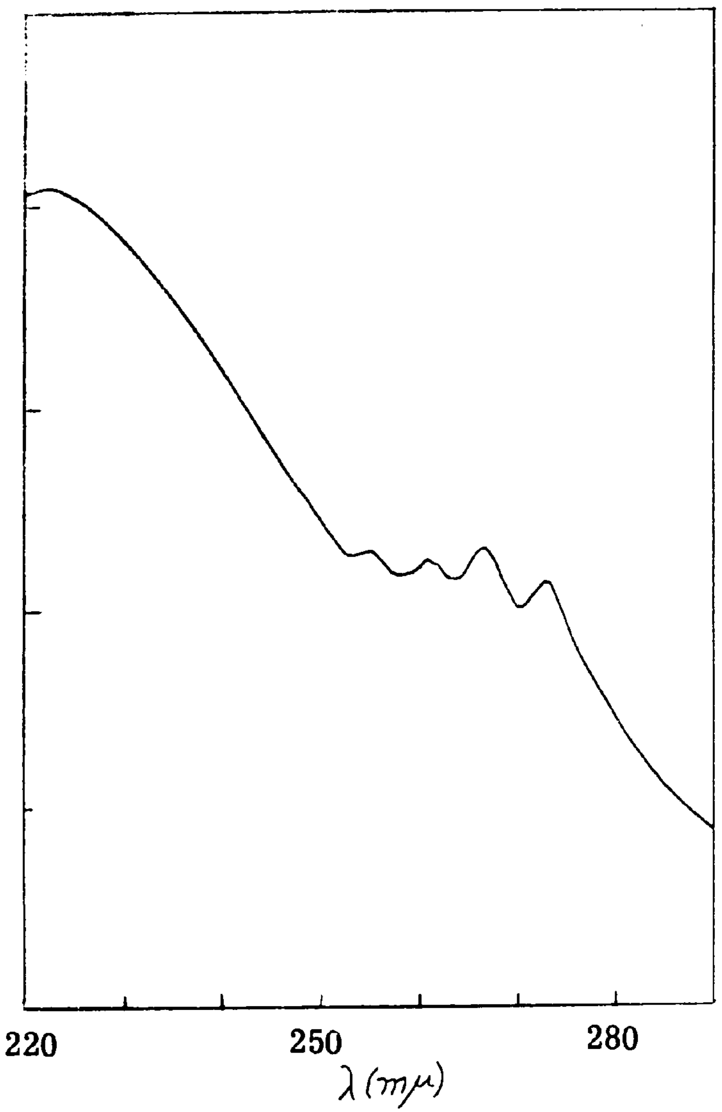


5-Methoxy-2-furfuryl alcohol

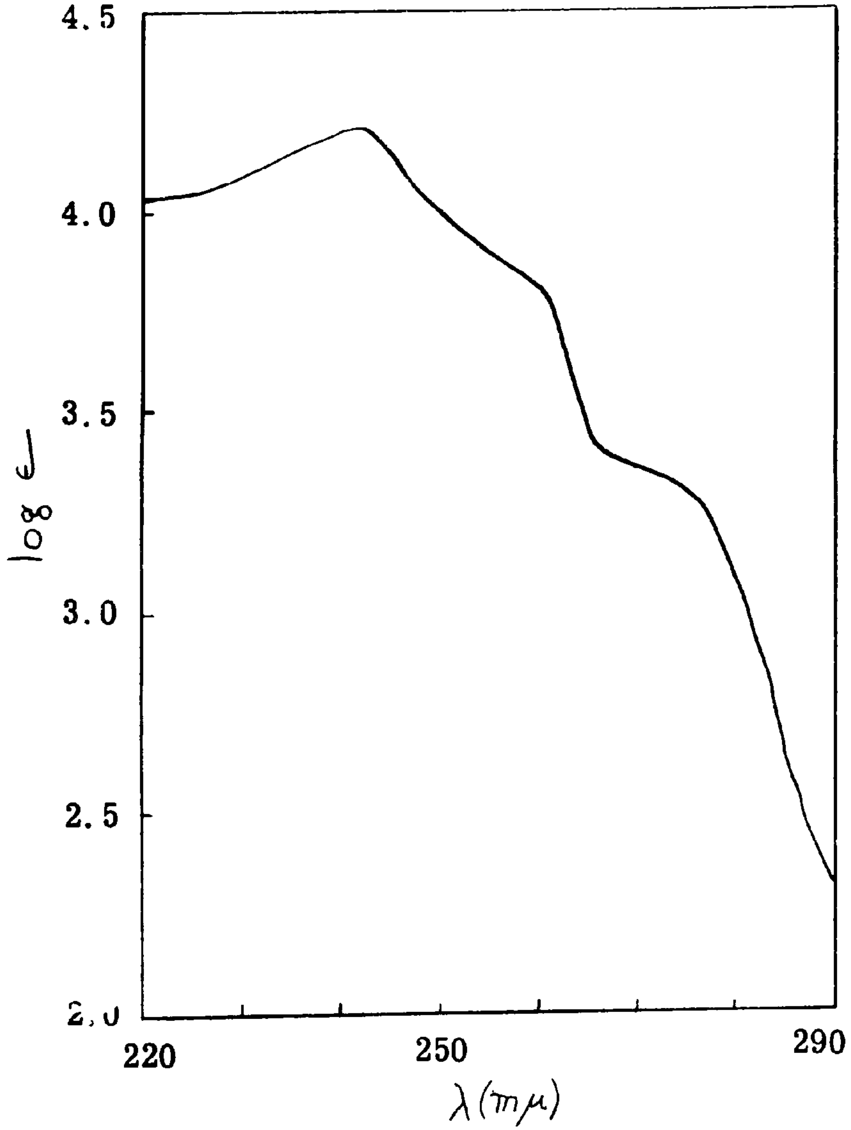
5-Methoxy-2-furamide



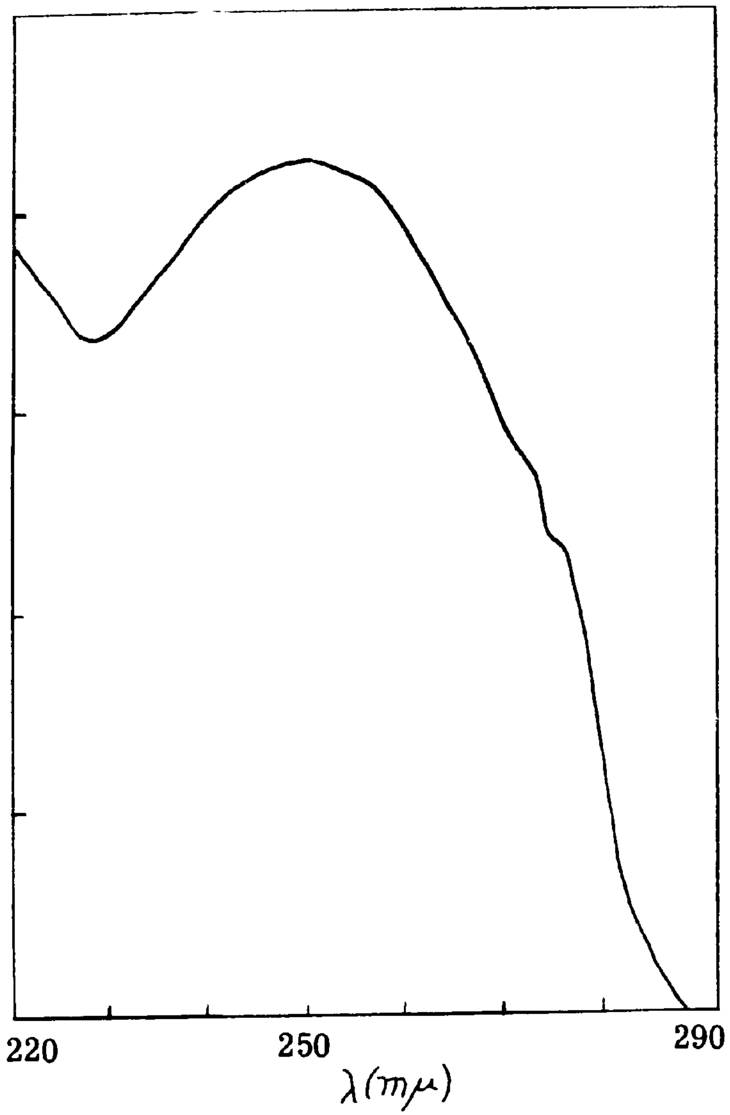
2-Phenoxyfuran



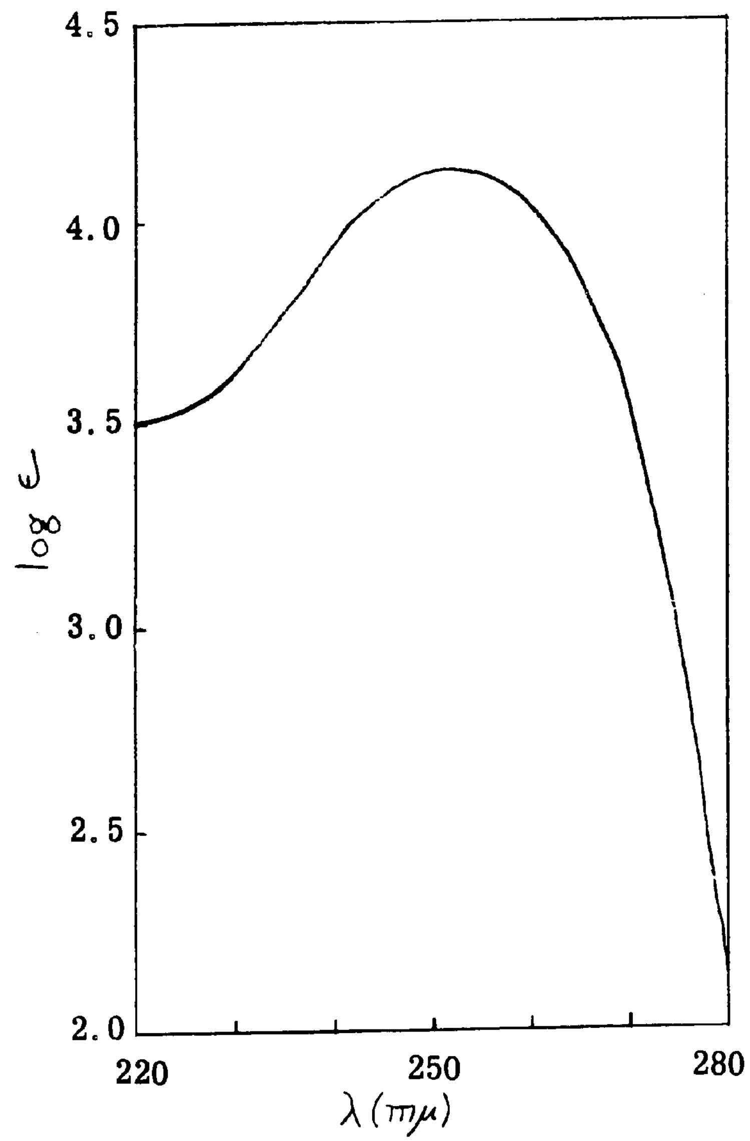
2-Thiophenoxyfuran



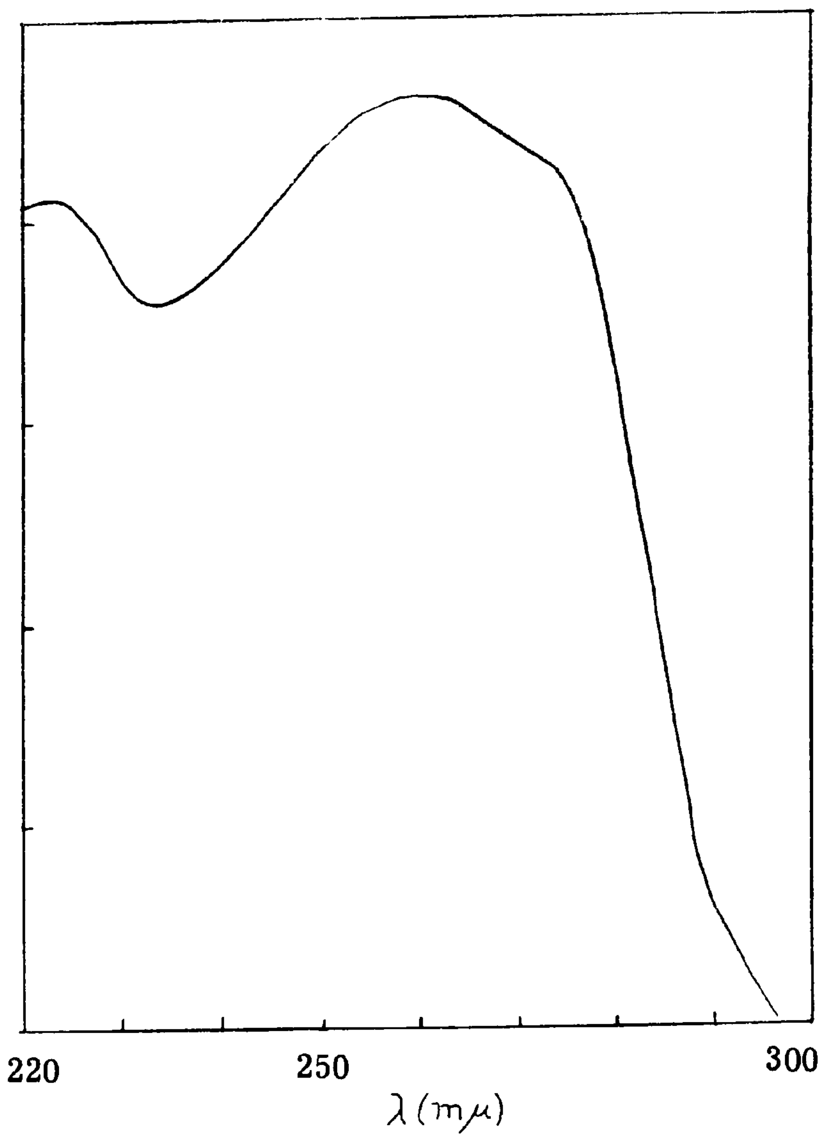
Phenyl 2-furyl sulfone



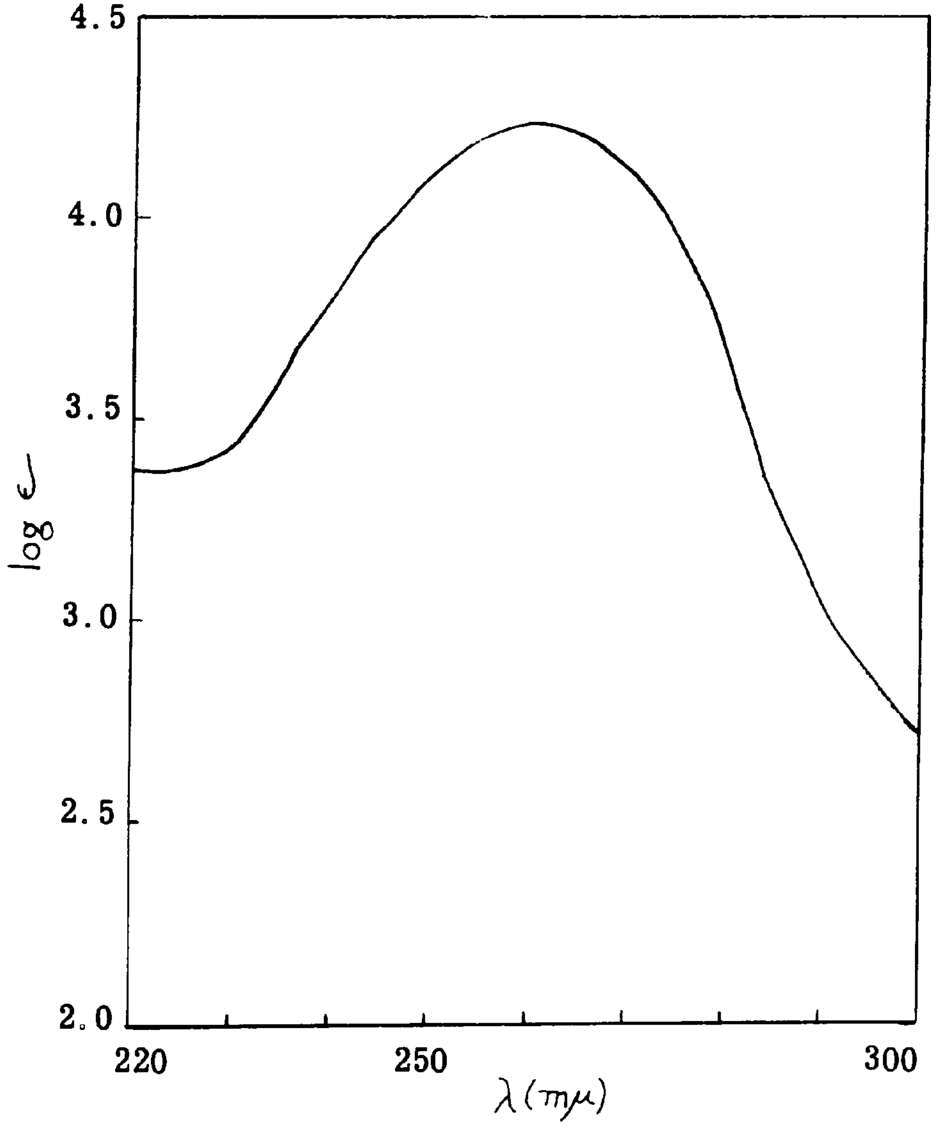
Methyl 2-furoate



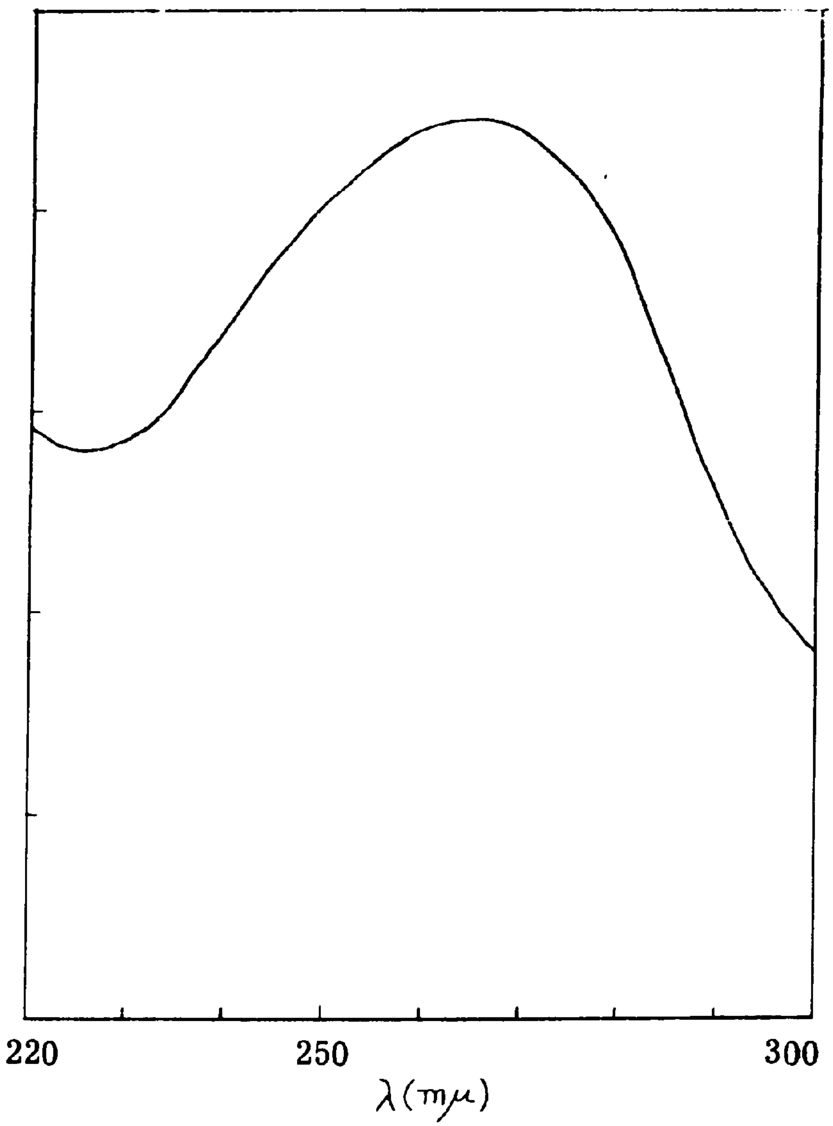
Phenyl 2-(5-carbomethoxyfuryl)sulfone



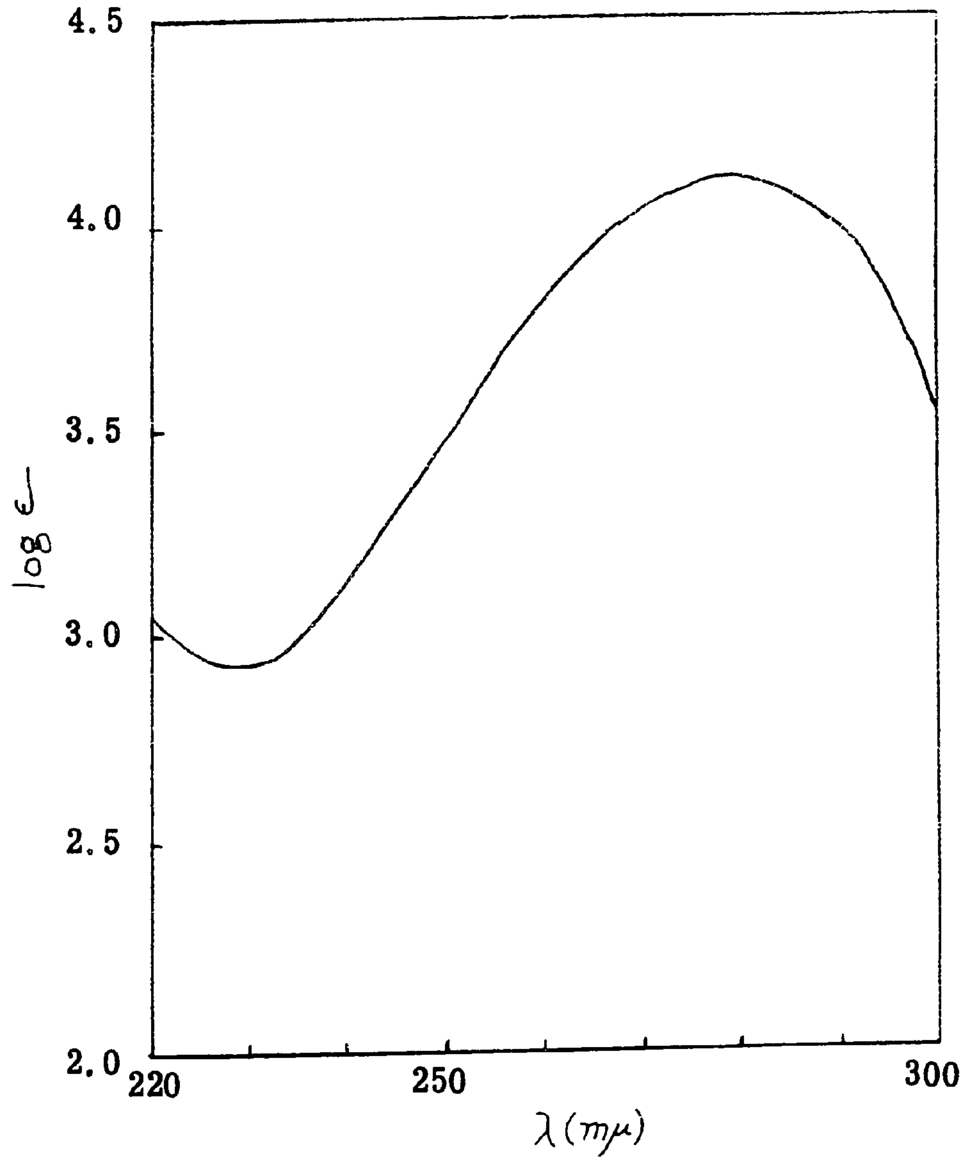
Methyl 5-chloro-2-furoate



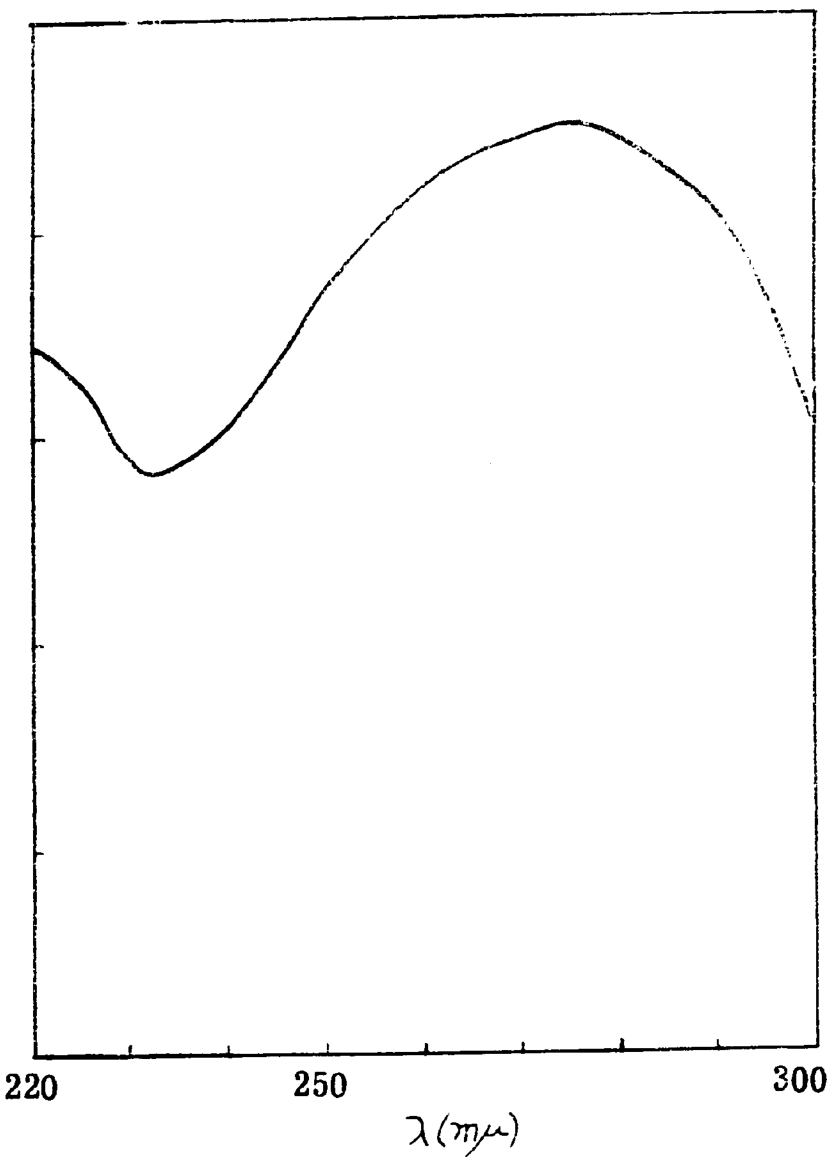
Methyl 5-bromo-2-furoate



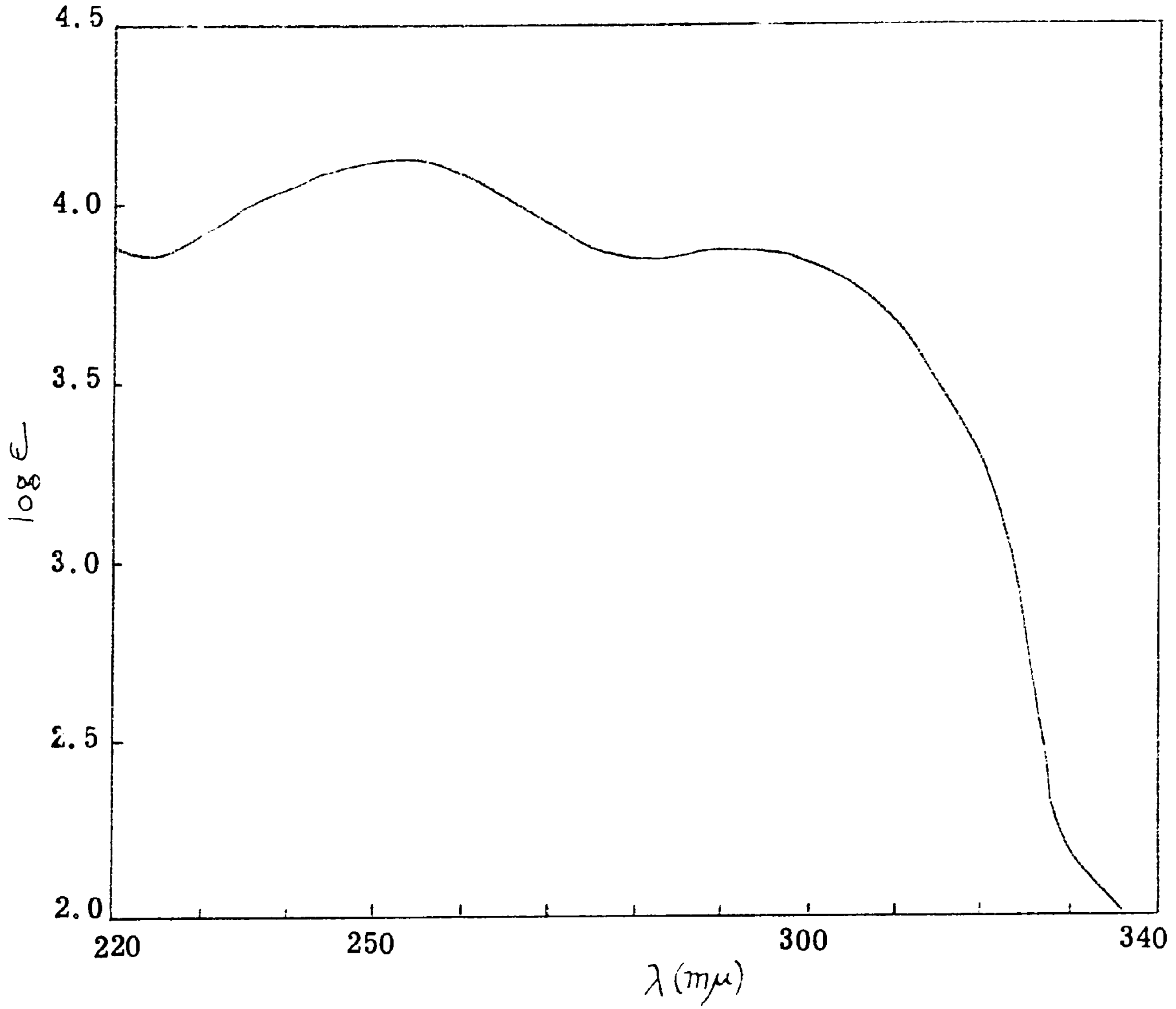
Methyl 5-methoxy-2-furoate



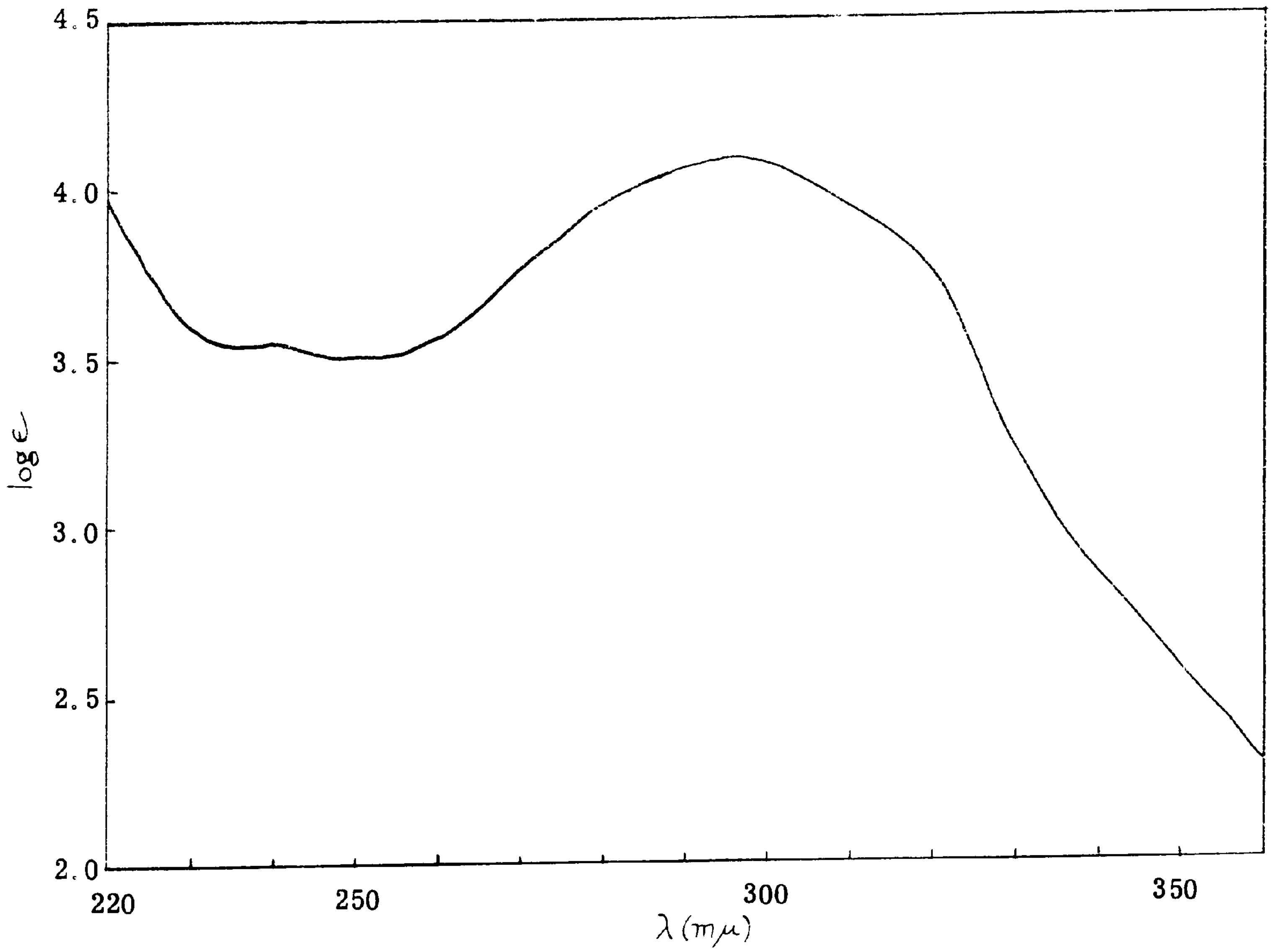
Methoxy 5-phenoxy-2-furoate



Methyl 5-thiophenoxy-2-furoate



Methyl 5-nitro-2-furoate



EXPERIMENTAL*

Furoic acid was a technical grade (m.p. 129-133°) which was generously supplied by The Quaker Oats Company and was used without further purification.

5-Bromo-2-furoic acid was prepared by the method of Raiford and Huey (40) and recrystallized from water to a melting point of 187-189° (reported 185, 190-191°).

5-Bromo-2-furoyl chloride was prepared by reacting the acid with 100% excess of thionyl chloride at reflux for two hours. Removal of excess thionyl chloride and subsequent vacuum distillation afforded the product in 76% yield boiling at 108-112°/15 mm (lit. 89°/8mm.).

Methyl 2-furoate, isopropyl 2-furoate and methyl 5-bromo-2-furoate was prepared by esterification of one mole of the appropriate acid using 13 moles of the alcohol and 35 ml. of concentrated sulfuric acid.

Methyl 5-chloro-2-furoate was prepared by passing chlorine into rapidly stirred methyl 2-furoate at 150° for three hours. After

---

* All melting points were taken with Anshutz Thermometers. All temperatures in the rate studies were taken with thermometers having National Bureau of Standards Certifications and were corrected for partial immersion according to standard equations.
All ultraviolet spectra were taken in 95% ethanol at a concentration of 10 mg./liter on a Warren Recording Spectrophotometer.
All alcohols used in the preparation of the alkoxyfurans were refluxed and distilled from sodium.

extraction with water and aqueous sodium bicarbonate, the fraction boiling at 89-92°/12 mm was recrystallized from petroleum ether (b. p. 30-60°) to a melting point of 40-41°; yield 42% .

Methyl 5-bromo-2-furoate: Methyl furoate (126 g. 1 mole) was placed in a one liter 3-necked flask equipped with dropping funnel, stirrer and condenser. To this rapidly stirred liquid, 160 g. (51.3 ml.) of bromine was added dropwise while heating on a steam bath. After stirring an additional ten minutes and cooling, the contents of the flask solidified and were washed thoroughly with cold water and steam distilled to give 94.1 g. (49.2%) of the product. The residue from steam distillation on recrystallization from water afforded 34 g. of 5-bromo-2-furoic acid melting at 188-190°.

Isopropyl 5-bromo-2-furoate was prepared in 32.5% yield, b. p. 132-133°/28 mm., by bromination of isopropyl 2-furoate as above.

Phenyl 5-bromo-2-furoate and t-butyl 5-bromo-2-furoate were prepared by adding 30 g. (0.134 mole) of 5-bromo-2-furoyl chloride carefully to a previously cooled solution of 3.5 g. (0.15 mole) of sodium in 80 g. of the alcohol. After heating at gentle reflux (phenyl, 1 hr.; t-butyl, 3 hours), the mixture was poured into cold water, decanted, extracted twice with boiling water, and vacuum distilled. t-Butyl 5-bromo-2-furoate was obtained in 38% yield; b. p. 123-128°/16 mm. Phenyl 5-bromo-2-furoate was obtained in 63% yield; b. p. 190-195°/14 mm and m.p. 50-52°.

The 5-ethers of 2-furoates, VIII, were prepared by adding 0.06 mole of the appropriate ester of 5-bromo-2-furoic acid to a previously prepared solution of 1.61 g. (0.072 mole) of clean sodium in 75-100 g. of the alcohol and heating for the time and temperatures shown in Table 1. The residue, after removing the solvent under vacuum, was poured into 300 ml. of water and extracted with ether. Vacuum distillation gave the products in the yields shown in Table 1. Attempts to prepare the t-butoxy compound were carried out at 100° and using a time of 2 hrs., 5 hrs., and 5 hrs. in the presence of 1 g. of cupric oxide and 1 g. of potassium iodide. In all three cases the t-butyl 5-bromo-2-furoate was recovered. The analyses of the other compounds are shown in Table 8.

Table 8

	Anal.			
	Calc'd		Found	
Compound	C	H	C	H
VIIIa Methyl 5-methoxy-2-furoate	53.8	5.16	53.8	5.34
VIIIb Ethyl 5-ethoxy-2-furoate	58.6	6.57	58.2	6.64
VIIIc Isopropyl 5-isopropoxy-2-furoate	62.3	7.60	62.3	7.85
VIIId Phenyl 5-phenoxy-2-furoate	72.8	4.32	72.8	4.52

Methyl 5-methoxy-2-furoate from methyl 5-chloro-2-furoate:

I: Ten grams of the chloroester in a solution of 2.6 g. of sodium in 100 ml. of absolute methanol was heated in a sealed citrate bottle at 100° for three hours. Removal of the methanol under vacuum and treatment with cold water precipitated 2.0 g. (21%) of methyl 5-methoxy-2-furoate. Saponification gave 5-methoxy-2-furoic acid melting at 140-142°.

II: A repeat experiment using 9.3 g. of the chloroester at 100° for seven hours gave 2.3 g. (25%) of the product.

The 5-Ethers of 2-furoic acid, IX, a through d were prepared by refluxing the ester 3 hours in 10% sodium hydroxide followed by acidification at temperatures below 10°. The n-Octyloxy (e), Cyclohexyloxy (f), and n-Amyloxy (h) were prepared as described above for the esters from methyl 5-bromo-2-furoate. After removing the solvent by vacuum distillation, the crude residue was saponified as above. The thiophenoxy compound (g) was prepared in the same manner from phenyl 5-bromo-2-furoate. The acids were purified by washing with ice-cold water until nearly acid free to give the analyses shown in Table 9.

Table 9

Compound	Neutralization Calc'd	Equivalent Found
IXa 5-methoxy-2-furoic acid (9)	142	145
IXb 5-ethoxy-2-furoic acid	156	155
IXc 5-isopropoxy-2-furoic acid	170	174
IXd 5-phenoxy-2-furoic acid	204	205
IXe 5-octyloxy-2-furoic acid	240	237
IXf 5-cyclohexyloxy-2-furoic acid	210	208
IXg 5-thiophenoxy-2-furoic acid	220	217

2-Methoxy-, 2-Ethoxy-, and 2-Isopropoxy-furan (X a, b, c) were obtained by heating the acid in the presence of a small amount of copper powder and enough quinoline to make a solution until a liquid distilled. Immediate redistillation gave the alkoxyfurans shown in Table 3 having the analyses shown in Table 10.

2-Phenoxy-, 2-octyloxy-, 2-cyclohexyloxy-, and 2-thiophenoxy furan (X d, e, f, g) were prepared by heating the acid in the presence of copper powder until the acid began to melt. At this point a vacuum was attached and heating was continued until the product distilled. Immediate redistillation gave the products shown in Table 3 with the analyses shown in Table 10.

Table 10

	Anal.			
	Calc.d		Found	
Compound	C	H	C	H
Xa 2-Methoxyfuran (9)	61.2	6.17	61.1	6.32
Xb 2-Ethoxyfuran	64.2	7.14	63.6	7.11
Xc 2-Isopropoxyfuran	66.6	7.91	66.8	7.99
Xd 2-Phenoxyfuran	75.5	5.00	75.1	5.08
Xe 2-Octyloxyfuran	73.6	10.2	73.3	10.3
Xf 2-Cyclohexyloxyfuran	72.2	8.43	72.0	8.56
Xg 2-Thiophenoxyfuran	68.2	4.55	67.8	4.46

Methyl 5-phenoxy-2-furoate was prepared by reaction of 5-phenoxy-2-furoic acid with an etherial solution of diazomethane until no further nitrogen was evolved. b. p. 133-135°/0.3 mm. Yield 98%.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 66.1. H, 4.62

Found: C, 66.1. H, 4.63

Methyl 5-Thiophenoxy-2-furoate was prepared by reaction of the acid with diazomethane in 98% yield. b.p. 146-148°/0.5mm. m.p. 39-40°.

Anal. Calc'd for $C_{12}H_{10}O_3S$: C, 61.5. H, 4.30

Found: C, 61.5. H, 4.36

Phenyl 2-furylsulfone: Two grams of thiophenoxyfuran was dissolved in 5 ml. of glacial acetic acid and 6 ml. of 30% hydrogen peroxide was added along with enough glacial acetic acid to form a homogeneous solution. After standing at room temperature for five days, the mixture was vacuum distilled to one half its volume and diluted with four times its volume of water. The resulting oily solid was recrystallized twice by dissolving it in 95% ethanol and adding water to the cloud point. The final product (2.1 g.) was a white crystalline solid melting at 68.8-69.2°.

Anal. Calc'd for $C_{10}H_8O_3S$: C, 57.7. H, 3.85

Found: C, 57.8. H, 4.09.

Phenyl 5-carbomethoxy-2-furyl sulfone was obtained in quantitative yield by reaction of methyl 5-thiophenoxy-2-furoate with excess 30% hydrogen perioxide in glacial acetic acid as above. Recrystallization from methanol-water gave white needles melting at 102-103°.

Anal. Calc'd for $C_{12}H_{10}O_5S$: C, 54.1, H, 3.79

Found: C, 54.1. H, 3.90.

Bromination of phenyl 2-furyl sulfone: To 300 mg. of the sulfone which was heated in a boiling water bath was added 0.3 g. of bromine. After heating 30 minutes the mixture was extracted six or seven times with cold water and dissolved in ether. Evaporation left a residue which distilled to give 0.3 g. of a red liquid boiling at 140-145°/ 16 mm. When heated with concentrated ammonium hydroxide a cream colored solid was obtained which melted at 155-156°. A mixed melting point with benzene sulfonamide showed no depression.

Nitration of 5-methoxy-2-furoic acid: A solution of the acid (10 g.) in 72 ml. of acetic anhydride was prepared and cooled to -10°. Nitration of this solution using the procedure of Rinkes (22) gave a yellow solid which on recrystallization from petroleum ether (b. p. 90-100°) melted at 154-156°. A calculated empirical formula is $C_{10}H_{10}O_{10}N$ which could arise only from a ring opened and polymerized product.

Anal. Calc'd for $C_{10}H_{10}O_{10}N$: C, 38.6. H, 3.40. N, 4.62.

Found: C, 38.6. H, 3.50. N, 3.94.

5-Methoxy-2-furoyl chloride: 5-Methoxy-2-furoic acid (10 g.) and thionyl chloride (10 ml.) were mixed and a vigorous endothermic reaction took place followed by the evolution of hydrogen chloride for thirty minutes. After heating at 50°, the excess thionyl chloride was removed under vacuum and the remaining dark red residue was vacuum distilled to give 5 g. (44%) boiling at 108-110°/18 mm.

The distillate solidified (m. p. 75-78°) on cooling and rapidly decomposed while standing in air.

5-Methoxy-2-furoyl amide: I: Addition of 5 g. of the acid halide to 45 ml. of concentrated ammonium hydroxide produced 1.5 g. (35%) of the amide which melted at 124-126° after recrystallization from water. II: Methyl 5-methoxy-2-furoate (5 g.) and 50 ml. of concentrated ammonium hydroxide were heated in a sealed tube for 2 hrs. at 60°. After filtration and recrystallization from water 4 g. (80%) of the product was obtained melting at 123-126°. A mixed melting point showed no depression.

Anal. Calc'd for $C_6H_7O_3N$: N, 9.93

Found: N, 10.21

5-Methoxy-2-furoyl -2,4-dinitrophenylhydrazide was obtained by heating methyl 5-methoxy-2-furoate in methanol with the 2,4-dinitrophenylhydrazine reagent. m.p. 95-97°.

Anal. Calc'd for $C_{12}H_8O_7N_4$: N, 17.5.

Found: N, 17.8.

5-Methoxy-2-furfuryl alcohol: A solution of methyl 5-methoxy-2-furoate (6 g.) in 25 ml. of dry ether was added dropwise to a rapidly stirred solution of lithium aluminum hydride (1.84 g.) in 60 ml. of dry ether. After refluxing 1.5 hours, 4 ml. of water was added cautiously followed by 25 ml. of 20% sodium hydroxide. After extraction of the aqueous layer with ether, the combined ether extracts were vacuum distilled to give 2.7 g. (55%) of a colorless liquid boiling at 112-115°/14 mm.

Anal. Calc'd for $C_6H_8O_3$: C, 56.2. H, 6.26

Found: C, 56.5. H, 6.56

Methyl 5-methoxy-4-bromo-2-furoate: A solution of 5.9 g. of N-bromosuccinimide and 5.2 g. of methyl 5-methoxy-2-furoate in 10 ml. of carbon tetrachloride was refluxed for 30 minutes. Extraction of the residue with ether followed by vacuum distillation of the combined ether carbon tetrachloride solutions gave 1.2 g. of a pale yellow oil boiling at 100-140°/4 mm. This oil solidified on cooling and was recrystallized from methanol-water (60 : 40) to give white needles melting at 63-64°. Direct bromination of methyl 5-methoxy-2-furoate required 2 hours heating time and gave a liquid in poor yield which was distilled and recrystallized to a melting point of 63-64°.

Anal. Calc'd for $C_7H_7O_4Br$: C, 35.5. H, 2.98

Found: C, 35.5. H, 3.24.

5-Methoxy-4-bromo-2-furoic acid was obtained as a white powder melting at 188-190° by saponification of the methyl ester.

Neut. Equiv.: Calc'd for $C_6H_5O_4Br$: 221

Found: 218.

Ring opening of phenoxyfuran: Refluxing phenoxyfuran in methanol containing one drop of concentrated hydrochloric acid for 30 minutes followed by vacuum distillation gave an oil boiling at 120-170°/14 mm. Reaction of this phenyl ester of the dimethyl acetal of β-formyl propionic acid with 2, 4-dinitrophenylhydrazine reagent in ethanol gave red needles melting at 101-102°. The reaction of phenoxyfuran directly with this reagent gave the same product.

Anal. Calc'd. for $C_{12}H_{14}O_6N_4$: C, 46.5. H, 4.52. N, 18.1

Found: C, 46.6. H, 4.67. N, 17.9

Refluxing phenoxyfuran in methanolic hydrochloric acid for six hours gave the dimethyl acetal of methyl β-formylpropionate boiling at 96-97°/18 mm.

Anal. Calc'd for $C_7H_{14}O_3$: C, 57.5. H, 9.60.

Found: C, 57.7. H, 9.40.

Bromination of methoxyfuran with N-bromosuccinimide in carbon tetrachloride gave a yellow viscous oil boiling at 160-170°/20 mm. Analysis of this product gave results which did not appear to fit any simple formula.

Anal. Found: C, 51.5. H, 5.38.

Mercuration of methoxyfuran: A solution of 4.61 g. (0.017 mole) of mercuric chloride and 9.25 g. (0.068 mole) of sodium acetate trihydrate in 102 ml. of water was prepared. Addition of a solution of 1.7 g (.017 mole) of methoxyfuran in 7 ml. of ethanol with rapid stirring caused a yellow solid to separate. After standing overnight the tri chloromercurimethoxyfuran melted at 206-210°.

Anal. Calc'd for $C_5H_3O_2Hg_3Cl_3$: C, 7.37. H, 0.38.

Found: C, 7.01. H, 1.39

5-Phenoxy-2-furyl lithium: A solution of phenyl lithium was prepared by adding a solution of 2.36 g. of bromobenzene in 10 ml. of ether to 0.21 g. of lithium shavings in 25 ml. of ether and stirring 30 minutes. Then 2.0 g. of 2-phenoxyfuran in 10 ml. of ether was added dropwise. After stirring an additional five minutes, the reaction mixture was poured onto crushed dry ice with stirring. Extraction with water followed by acidification of the aqueous extracts produced a solid melting at 95-105°. Recrystallization from ethanol-water gave 0.6 g. of 5-phenoxy-2-furoic acid melting at 121-123°(N. E., 201). The ether extract on distillation gave 1.2 g. of recovered 2-phenoxyfuran. The yield of 5-phenoxy-2-furoic acid based on the amount of phenoxyfuran used was 82%.

2-Bromofuran was prepared by decarboxylation of 5-bromo-2-furoic acid using copper powder and quinoline and the fraction boiling at 101-102° was collected.

2-Chlorofuran was obtained in 31% yield boiling at 77.1-77.6° by decarboxylation of 5-chloro-2-furoic acid using quinoline and copper powder.

Diazomethane was prepared according to the previously published (41) procedure.

2-Furan mercuric chloride: The following three solutions were prepared separately: 1) 462 g. of mercuric chloride in 6850 ml. of water, 2) 931 g. of sodium acetate trihydrate in 3450 ml. of water, and 3) 150 g. of furan in 700 ml. 95% ethanol. To each of three four liter bottles was added 2250 ml. of the mercuric chloride solution and 1350 ml. of sodium acetate solution. To this mixture with rapid stirring was added one-third (287 ml.) of the furan solution. After standing two days the solid was collected by filtration and recrystallized from 95% ethanol.

5-Methyl-2-furan mercuric chloride was prepared in exactly the same manner as above using 140 g. of 2-methoxyfuran. After recrystallization from ethanol 255 g. (44%) of the product was obtained.

2-Iodofuran: 2-Chloromercurifuran (56.0 g.) in 500 ml. of water in a 2 liter flask was rapidly stirred while a solution of 44.8 g. of iodine and 58.1 g. of potassium iodide in 250 ml. of water was added dropwise. After stirring one hour the solution was let stand overnight and then filtered. The solid was washed with ether and the solution, after making it basic with bicarbonate, was extracted with ether. After extracting the ether with sodium bicarbonate solution and decolorizing by extraction with sodium thiosulfate solution, the ether solution was dried over magnesium sulfate, 10 ml. of quinoline was added and the solution distilled. The highly unstable 2-iodofuran boiled at 61-62°/57 mm and weighed 14 g. (43%).

5-Methyl-2-iodofuran was prepared by the same method as above using 180 g. of 5-methyl-2-chloromercurifuran in 2 liters of water and a solution of 145 g. of iodine and 189 g. of potassium iodide in 1.5 liters of water. Distillation from quinoline gave 53.5 g. (46%) boiling at 56-57°/20 mm.

Reaction of 2-bromofuran with sodium methoxide: 2-Bromofuran (10 g.) and 2.5 g. of copper oxide powder in a solution of 1.56 g. of clean sodium in 80 ml. of methanol was refluxed four days. The mixture was filtered, diluted with water to 500 ml., and extracted with ether. After drying and evaporating the residue was distilled to give 8 g. of 2-bromofuran boiling at 101-102°.

Reaction of 2-iodofuran with sodium methoxide: I: Reaction of 13 g. of 2-iodofuran as above for 48 hours gave only 7.8 g. of recovered 2-iodofuran boiling at 136-137° at atmospheric pressure. II: Reaction of 6 g. of 2-iodofuran in a sealed tube at 100° for 31 hours again gave only unreacted 2-iodofuran boiling at 136-137°.

5-Bromo-2-furfural: Freshly distilled furfural (9.7 g.) in 40 ml. of carbon tetrachloride was heated to 70-75° in a 3-necked flask equipped with stirrer and condenser. N-bromosuccinimide (17.8 g.) was added portionwise with rapid stirring over one hour. After heating an additional 15 minutes, the contents were cooled, extracted twice with cold water, and steam distilled to give 4.0 g. (23%) of 5-bromofurfural melting at 80-82°.

The structure was established by adding 5-bromofurfural to a boiling suspension of copper oxide containing a trace of silver oxide in 10% sodium hydroxide. Filtration, acidification, and recrystallization from water gave 5-bromo-2-furoic acid melting at 185-187°. A mixed melting point with an authentic sample melted at 185-188°. The semicarbazone prepared in the usual manner decomposed at 183°. The phenylhydrazone prepared in the usual manner melted at 81°.

5-Bromofurfural azine: 5-Bromofurfural (5.25 g.) was dissolved in 15 ml. of absolute methanol, 2.88 g. of 100% hydrazine hydrate was added, and the solution was allowed to stand in an icebath for one hour. Removal of the solvent under vacuum left a solid residue which was recrystallized from a dioxane-water mixture and then from 95% ethanol to give 4.5 g. (87%) of yellow plates melting at 152.2-152.4°.

Anal. Calc'd for $C_{10}H_6O_2N_2Br_2$: N, 8.09.
Found: N, 8.29

This compound was isolated in all attempts to prepare 5-bromofurfural hydrazone. The ultraviolet spectrum in 95% ethanol showed maxima at 348 $m\mu$ ($\log \epsilon$ = 4.56) and 270 $m\mu$ ($\log \epsilon$ = 3.85).

Attempted preparation of 5-methoxy-2-methyl furan: 5-Methyl-2-iodofuran (12.5 g.) was added to a solution of 1.5 g. of sodium in 100 ml. of absolute methanol and the mixture was heated at 186° in sealed tubes for 21 hours. The resulting mixture was poured into water and extracted with ether. Evaporation of the ether gave no products boiling below 150°.

Attempted preparation of 5-phenoxy-2-methylfuran: I: After cooling a previously prepared solution of 1.5 g. of sodium in 40 g. of hot phenol, 12.5 g. of 5-methyl-2-iodofuran was added and the solution was heated at a bath temperature of 165-170° for 28 hours. When cool it was poured into 400 ml. of cold water and the dark red oil extracted with ether. After extraction of the ether layer with thiosulfate, drying over magnesium sulfate, and distilling, 9.1 g. of 5-methyl-2-iodofuran was recovered. II: Five grams of sodium phenoxide and 8 g. of 5-methyl-2-iodofuran were heated in a sealed tube at 185-190° for four hours The resulting material was a tar from which no identifiable product could be obtained.

5-Chloro-2-furoic acid: Methyl 5-chloro-2-furoate (34 g.) was saponified by heating 3 hours with 200 ml. of 10% sodium hydroxide. Acidification gave a white powder which was recrystallized from ethanol-water (40 : 60) to give 26 g. (85%) of white needles melting at 180-181°.

5-Chloro-2-furoyl chloride: After refluxing 100 ml. of thionyl chloride and 16 g. of 5-chloro-2-furoic acid for 2 hours, the excess thionyl chloride was removed and the residue distilled under vacuum to give 16.6 g. (89%) of the product boiling at 85-86°/16 mm and melting at 29-30°.

5-Chloro-2-furoyl piperidide: Piperidine (17.9 g.) in 22 ml. of ether was added dropwise to a rapidly stirred solution of 16.5 g. of 5-chloro-2-furoyl chloride in 40 ml. of ether which was cooled in an ice bath. After stirring an additional hour, the solution was diluted with 25 ml. of ether and filtered. The ether filtrates were evaporated and distilled to give 18 g. (89%) of crude product boiling at 140-142°/4 mm. This product was dissolved in 75 ml. of ether, washed twice with 20 ml. of 10% hydrochloric acid, three times with 25 ml of water, once with 20 ml. of 10%sodium hydroxide, twice with 25 ml. of water, dried over magnesium sulfate and distilled. The product boiled at 137-139°/3 mm.

Anal. Calc'd for $C_{10}H_{12}O_2NCl$: C, 56.3. H, 5.67. N, 6.58.

Found: C, 56.5. H, 5.87. N, 6.32.

Reaction of N-iodosuccinimide with methyl 2-furoate: NIS (22.5 g.) was added slowly over 2 hours to 20 g. of methyl furoate at 150° with stirring. After maintaining the temperature at 150° for an additional 2 hours, the mixture was cooled and dissolved in ether. The ether layer was extracted with water and thiosulfate, filtered to remove tar, and distilled. Only methyl furoate was recovered.

Reaction of methyl 2-furoate with iodine monochloride: Iodine monochloride (32.4 g.) was added dropwise over 30 minutes to rapidly stirred methyl furoate (31.2 g.) at 100°. It was cooled, poured into water, and extracted with ether. After extraction with water and thiosulfate the ether solution was distilled to give mainly methyl furoate and 0.5 g. of methyl 5-chloro-2-furoate. A mixed melting point with an authentic sample of the chloro ester showed no depression.

Attempted mercuration of furfural (42) I: A mixture of 42.8 g. of mercuric chloride, 30.8 g. of potassium acetate, and 50 g. of furfural were heated with stirring at 140-150° for 7 minutes and then steam distilled to remove excess furfural. The residue was extracted with 250 ml. of boiling water. The crystals which separated were recrystallized from 1 : 1 ethanol-chloroform to give 1.1 g. melting at 115-120° (lit. 218-219). II: A repeat experiment using one drop of glacial acetic acid and a heating time of five minutes gave only an oil which could not be solidified. III: A repeat experiment using an equivalent quantity of mercuric acetate rather than mercuric chloride and potassium acetate also gave no product.

Oxidation of 5-methyl-2-iodofuran with hydrogen peroxide in 10% sodium hydroxide, potassium permanganate, and potassium ferricyanide in potassium hydroxide gave no iodofuroic acid.

2, 5-Diiodofuran (43): Polymercurated furan was obtained as the residue left after extraction of the usual mercuration product with one liter of ethanol per 92 g. of solid. This polymercurated furan (53.6 g.) was suspended in 700 ml. of water and rapidly stirred as a solution of 50.8 g. of iodine and 120 g. of potassium iodide in

750 ml. of water was added dropwise. After stirring one hour, the solution was made basic with sodium bicarbonate, let stand overnight, decolorized with thiosulfate, and steam distilled. The distillates were extracted with ether, washed with thiosulfate, and distilled. A red liquid portion boiling at 120-125°/24 mm was collected, dissolved in ether, washed with thiosulfate, and dried. Evaporation of the ether left a residue of 16 g (50%) which was dissolved in dry ether (25 ml.)

Reaction of 2, 5-diiodofuran with butyl lithium: A butyl lithium solution prepared as usual from 2.86 g. n-butyl bromide in 120 ml. of ether was filtered and added dropwise to a solution of 6.0 g. of 2, 5-diiodofuran in 25 ml. of ether over 45 minutes at 0°. After allowing the solution to warm to 10-15° over one hour, the orange solution was poured onto 50 g. of crushed dry ice. The resulting dark red solution was extracted with sodium bicarbonate and water. A careful acidification of the aqueous extracts gave no solid and a continuous extraction of this solution with ether gave no iodofuroic acid on evaporation.

2, 5-Diiodofuran with activated magnesium-copper alloy (44): The copper magnesium alloy (1.54 g.) which had been rasped from a solid rod was heated with 0.31 g. of iodine in a vacuum of 30 mm. at 300° for 10 minutes. After exposing the catalyst to air for 20 minutes, it was heated until no further evolution of fumes occurred (5 min.). This catalyst was then covered with 10 ml. of dry ether and a solution of 10 g. of diiodofuran in 20 ml. of ether was added dropwise with stirring at reflux. After refluxing an additional hour, it was cooled and about 20 g. of crushed dry ice was added. It was poured into 100 ml. of 10% sulfuric acid and the ether layer separated. Evaporation of the ether layer gave a brown solid which was dissolved in methanol and treated with charcoal. The addition of water caused 0.2 g. (2.7%) of iodofuroic acid to separate which melted at 185-188° (lit. 192°).

Reaction of methyl 5-bromo-2-furoate with sodium iodide in acetone at 160° gave no exchange and only the bromo ester could be isolated.

Attempted mercuration of methyl 2-furoate gave a product only after reflux for 5 hours. Iodination of this solid gave only tetraiodofuran after recrystallization from methanol which melted at 156-158°.

Methyl 5-nitro-2-furoate (45) (m.p. 79-80°) was prepared by esterification of 5-nitro-2-furoic acid obtained by acid hydrolysis of ethyl 5-nitro-2-furoate donated by Eaton Laboratories, Norwich, N. Y.

Methyl p-phenoxybenzoate: The p-phenoxy acid (46) melting at 158-159° was prepared by carbonation of the Grignard reagent prepared from p-bromophenyl phenyl ether (Eastman). The acid was esterified directly with methanol and sulfuric acid to give the product which was recrystallized from 95% ethanol to a melting point of 56-57°. The ultraviolet spectrum showed a maximum at 258.0 mμ (log ε = 4.26)

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.7. H, 5.30

Found: C, 73.5. H, 5.05.

Methyl p-thiophenoxybenzoate: p-Thiophenoxybenzoic acid (47) was prepared by adding a cold solution of diazotized p-aminobenzoic acid to a solution of thiophenol in dilute sodium hydroxide. The acid was obtained in poor yield and after two recrystallizations from 95% ethanol had a melting point of 170-174° (lit. 177). The acid was esterified in the usual manner with methanol and sulfuric acid. After recrystallization from 95% ethanol the ester had a melting point of 69-70°. The ultraviolet spectrum showed a maximum at 293.2 $m\mu$ ($\log \epsilon = 4.23$).

Anal. Calc'd for $C_{14}H_{12}O_2S$: C, 69.0. H, 4.57.

Found: C, 68.9. H, 4.74.

Phenyl p-carbomethoxyphenyl sulfone: A solution of methyl p-thiophenoxybenzoate in glacial acetic acid containing excess 30% hydrogen perixode was allowed to stand five days. Dilution with water caused a solid to precipitate which on recrystallization from 95% ethanol melted at 145-146°. The ultraviolet spectrum showed a maximum at 242.5 $m\mu$ ($\log \epsilon = 4.29$).

Anal. Calc'd for $C_{14}H_{12}O_4S$: C, 60.9, H, 4.38

Found: C, 60.8. H, 4.26.

Diphenyl ether boiling at 129.5°/12 mm showed a maximum at 226.7 $m\mu$ ($\log \epsilon = 4.01$).

Diphenyl sulfide (Eastman) boiling at 151-153°/15 mm. showed maxima at 231.8 (3.80), 250.4 (4.07), and 275.0 (3.28).

Diphenyl sulfone (Eastman) melting at 128-130° showed a maximum at 236.3 mμ ($\log \epsilon = 4.17$).

Methyl benzoate boiling at 85°/15 mm. showed a maximum at 229.8 mμ (4.08).

Methyl p-bromobenzoate melting at 77-78° showed a maximum at 245.0 mμ (4.26).

Methyl p-anisate melting at 47-48° showed a maximum at 256.5 mμ (4.43).

Methyl p-nitrobenzoate melting at 95-96° showed a maximum at 259.0 mμ (4.12).

Dimethyl terephthalate melting at 139-140° showed a maximum at 242.0 mμ (4.47).

The furan used was a DuPont sample boiling at 31.5°.

5-Bromo-2-furyl mercuric chloride (43): Sixteen grams (.084 mole) 5-bromo-2-furoic acid was dissolved in a solution of 3.35 g. (.084 mole) of sodium hydroxide in 60 ml. of water. This was added at once to a solution of 24.3 g. (.09 mole) of mercuric chloride in 400 ml. of water. After standing one hour, the mixture was filtered and the filtrate was heated to reflux for about 20 minutes at which time the evolution of carbon dioxide stopped. When cool, the solid was filtered, washed with water, and then washed with about 50 ml. of ethanol. Drying gave 22 g. (69%) of the product melting at 177-178° (lit. 177°).

Methyl 2-furoate used for spectra determination boiled at 83.5°/25mm.

5-Bromo-2-iodofuran: A solution of 14 g. of iodine and 29.6 g. of potassium iodide in 150 ml. of water was added dropwise to a rapidly stirred suspension of 21 g. (.055 mole) of 5-bromo-2-chloromercurifuran in 200 ml. of water. After stirring an additional hour the mixture was made basic with sodium bicarbonate solution and extracted with ether. The ether solution was extracted with water and thiosulfate, 10 ml. of quinoline was added, and the solution was dried over magnesium sulfate, b. p. 104-106°/36 mm.

Kinetic data (pseudounimolecular with piperidine):

Compound	$T_{corr.}$ (°C)	k	- log k
5-chloro-2-furoyl piperidide:			
	90.60	.01015 ± .00059	1.9935 ± .0245
	95.73	.01599 ± .00057	1.7962 ± .0150
	97.84	.01666 ± .00122	1.7783 ± .0307
	102.45	.02091 ± .00223	1.6797 ± .0441
	109.04	.03213 ± .00193	1.4931 ± .0253
2-chlorofuran			
	202.50	.00285 ± .00005	2.5452 ± .0076
	222.19	.00731 ± .00100	2.1361 ± .0059
	231.29	.01064 ± .00048	1.9731 ± .0192
	235.90	.01336 ± .00041	1.8742 ± .0131
2-Bromofuran (9) recalculated values			
	199.3	.02234 ± .00037	1.6509 ± .0071
	207.7	.03171 ± .00054	1.4988 ± .0073
	216.3	.04937 ± .00090	1.3065 ± .0078
	231.2	.09735 ± .00254	1.0117 ± .0112

Compound	$T_{corr.}$ (°C)	k	-log k
2-Iodofuran			
	175.24	.00756 ± .00033	2.1215 ± .0186
	179.57	.01053 ± .00034	1.9776 ± .0136
	182.81	.01474 ± .00100	1.8315 ± .0285
	188.49	.02033 ± .00017	1.6919 ± .0036
	196.31	.03572 ± .00078	1.4471 ± .0094
	214.38	.12093 ± .00075	0.9175 ± .0034
5-Methyl-2-iodofuran			
	183.96	.00783 ± .00012	2.1062 ± .0066
	192.06	.01326 ± .00048	1.8775 ± .0155
	197.25	.01795 ± .00077	1.7459 ± .0182
	202.30	.02428 ± .00081	1.6147 ± .0142

Kinetics of 5-chloro-2-furoyl piperidide containing piperidine hydrochloride:

N = 0.1999 for 5-chloro-2-furoyl piperidide

$T_{corr.}$ = 101.10°C

		x		k		
tube	time (hr)	A	B (x-.722)	A	B	Δk
blank	-	.210	.216	-	-	-
2	0.5	.510	.372	.01820	.00932	.00888
3	1.0	.795	.734	.01801	.01618	.00183
4	1.5	1.128	1.047	.01881	.01753	.00128
5	2.0	1.457	1.393	.01924	.01861	.00063

A not containing piperidine hydrochloride

B containing piperidine hydrochloride at a concentration of .00451N

Kinetics of Methyl 5-chloro-2-furoate (second order with sodium methoxide):

$T_{corr.}$ (°C)	k_2	$-\log k_2$	$-\log k_1$
66.26	.0450 ± .0018	2.3468 ± .0171	2.0458
73.38	.0998 ± .0019	2.0009 ± .0082	1.6990
78.69	.1607 ± .0032	1.7940 ± .0082	1.4935
82.10	.2437 ± .0046	1.6131 ± .0083	1.3125

N = 0.200 for both reagents

BIBLIOGRAPHY

1. Shomaker, V. and Pauling, L., J. Am. Chem. Soc., 61, 1769 (1939).

2. Clauson-Kaas N., Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd, 24, 18 (1947). Che. Abst., 42, 1930 (1948).

3. Stevenson H. and Johnson J., J. Am. Chem. Soc., 59, 2525 (1937).

4. Dunlop A. P. and Peters F. N., "The Furans", Reinhold Publishing Co., New York, 1953, p. 177.

5. Hodgson H. and Davies R., J. Chem. Soc., 1939, 806, 1013.

6. Ref. 2 pp 173-175.

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

8. Bailey P. and Waggoner, J., J. Org. Chem., 15, 159 (1950).

9. Petfield R. and Amstutz E., J. Org. Chem., 19, 1944 (1954).

10. Sicé J., J. Am. Chem. Soc., 75, 3697 (1953).

11. Cava M., Wilson C., and Williams C., Chemistry and Industry, 1955, 17.

12. Ref. 2 p72, 126, 509.

13. Ref. 2 Chapter 6.

14. Benkeser R. and Currie R., J. Am. Chem. Soc., 70, 1780 (1948).

15. Ref. 2 Chapter 3.

16. Shepard A., Winslow N., and Johnson J., J. Am. Chem. Soc., 52, 2083 (1930).

17. Gilman H., Mallory H., and Wright G., J. Am. Chem. Soc., 54, 733 (1932).

18. Gilman H., Peterson J., and Schulze F., Rec. trav. chim., 47, 19 (1928).

19. Tohl A., Ber., 28, 2217 (1895).

19a. Petfield R. J., unpublished work.

20. McElvain S., Chem. Rev., 45, 453 (1949) and more recent.

21. McElvain S. and McKay G., J. Am. Chem. Soc., 77, 5601 (1955).

22. Rinkes I., Rec. trav. chim., 50, 981 (1931).

23. Bunnet J. and Zahler R., Chem. Rev., 49, 273 (1951).

24. Blood C. A., Ph. D. Thesis, Lehigh University, June 1956.

25a. Brower K., Ph. D. Thesis, Lehigh University, October 1953.

25b. Young T. and Amstutz E., J. Am. Chem. Soc., 73, 4773 (1951).

25c. Brower K. and Amstutz E., J. Org. Chem., 18, 1075 (1953).

25d. Brower K., Samuels W., Way J., and Amstutz E., J. Org. Chem., 18, 1648 (1953).

25e. Brower K. and Amstutz E., J. Org. Chem., 19, 411 (1954).

25f. Brower K., Way J., Samuels W., and Amstutz E., J. Org. Chem., 19, 1830 (1954).

26. Richardson A., M. S. Thesis, Lehigh University, June 1955.

27. Blau A., Monatsh., 7, 621 (1886).

28. Dewar M. J. S., J. Am. Chem. Soc., 74, 3341-3364 (1952).

29. Berliner E., Quinn M., and Edgerton P., J. Am. Chem. Soc., 72, 5305 (1950).

30. Berliner E. and Monack L., J. Am. Chem. Soc. 74, 1574 (1952).

31. Beach R., M. S. Thesis, Lehigh University, in progress.

32. Doub L. and Vandenbelt J., J. Am. Chem. Soc., 69, 2714 (1947).

33. Andrisano R. and Pappalardo G., Gazz. chim. Ital., 83, 340 (1953).

34. Price C. C., Chem. Rev., 29, 37 (1941).

35. Jaffe H. H., Chem. Rev., 53, 191 (1953).

36. Braude E., "The Determination of Organic Structures by Physical Methods", p154, Academic Press, Inc. New York 1955.

37. Menczel C., Z. physik. Chem., 125, 161 (1927).

38. Mackinney G. and Temmer O., J Am Chem. Soc., 70, 3586 (1948).

39. Waight E. S., J. Chem. Soc., 1952, 2440.

40. Raiford L. and Huey W., J. Org. Chem., 6, 858 (1941).

41. Berenbom M. and Fones W., J. Am. Chem. Soc., 71, 1629 (1949).

42. Irie T. and Wakayama S., Science (Japan), 18, 328 (1948), Chem. Abst., 45, 4213 (1951).

43. Gilman H. and Wright G., J. Am. Chem. Soc., 55, 3302 (1933).

44. Gilman H., Iowa State Coll. J. Sci., 5, 85 (1931).

45. Freure B. and Johnson J., J. Am. Chem. Soc., 53, 1142 (1931).

46. Langham W., Brewster R., and Gilman H., J. Am. Chem. Soc., 63, 545 (1941).

47. Weedon W. and Doughty H., Am. Chem. J., 33, 424 (1905).

48. Frost and Pearson, "Kinetics and Mechanism", Chapter 5, John Wiley and Sons, 1953.

49. Glasstone S., "Textbook of Physical Chemistry", Chapter XIII, D. Van Nostrand, 1946.

50. Glasstone S., Laidler K., and Eyring H., "The Theory of Rate Processes", Chapters IV, VIII, McGraw-Hill Book Co., 1941.

51. Waugh A. E., "Elements of Statistical Methods", p. 168, McGraw-Hill Book Co., New York, 1943.

52. Roberts J., Simmons H., Calsmith L., and Vaughan C., J. Am. Chem. Soc., 75, 3290 (1953).

VITA

Donald George Manly, son of George and Clarice Manly, was born October 7, 1930 in Cleveland, Ohio. However, after the first year of his life, he resided in the town of Pascoag, Rhode Island and graduated from Burrillville High School in 1948 taking the classical course and participating in football and class activities.

In September of 1948 he entered Brown University under a new curriculum for chemists and was graduated in June 1952 with a Bachelor of Science in Chemistry Degree. In his senior year he served as President of the Chemistry Club and carried out a research project on "Stable and Unstable Forms of Menthol Methyl Xanthate" under Dr. H. R. Nace.

After working the summer at Brown University in the Biology Department, he entered Lehigh University in September of 1952. Research was carried out under the Vale Chemical Company Fellowship until June of 1953 when he was given the Wm. S. Merrell Fellowship. On completion of this work, entitled "An Investigation in the Chemistry of Pyrophthalones", he was graduated with a Master of Science Degree. The research was directed by Dr. E. D. Amstutz and work toward the doctorate under the same director was begun immediately on The Quaker Oats Company Fellowship.

Mr. Manly presented a paper on Alkoxyfurans to the Delaware Valley Regional Meeting of the American Chemical Society on February 16, 1956 and has had a paper entitled "Simple Furan Ethers II: 2-Alkoxy- and 2-Aryloxy-furans" accepted by the Journal of Organic Chemistry for publication.

Mr. Manly was married on December 27, 1952 to the former Miss Patricia Varey also of Pascoag, Rhode Island.

Index of New Compounds

Compound	page	m. p. or b. p.*
5-n-Amyloxy-2-furoic acid	15, 69	93-95°
5-Bromo-2-furfural azine	79	152°
5-Bromo-2-iodofuran	87	104-106/36mm
5-Chloro-2-furoyl piperidide	81	137-139/0.3mm
2-Cyclohexyloxyfuran	16, 70	118-119/18mm
5-Cyclohexyloxy-2-furoic acid	15, 69	138-139°
2-Ethoxyfuran	16, 70	125-126/760mm
5-Ethoxy-2-furoic acid	15, 69	140-141°
5-Methoxy-4-bromo-2-furoic acid	74	188-190°
5-Methoxy-2-furamide	73	124-126°
5-Methoxy-2-furfuryl alcohol	73	112-115/14mm
5-Methoxy-2-furoyl chloride	72	75-78°
2-Methoxy-3, 4, 5-trichloromercurifuran	75	206-210°
Methyl 5-methoxy-4-bromo-2-furoate	74	63-64°
Methyl p-phenoxybenzoate	84	56-57°
Methyl 5-phenoxy-2-furoate	70	133-135/0.3mm
Methyl p-thiophenoxybenzoate	85	69-70°
Methyl 5-thiophenoxy-2-furoate	71	146-148/0.5mm
2-Octyloxyfuran	16, 70	129-130/18mm
5-Octyloxy-2-furoic acid	15, 69	125-126°
2-Phenoxyfuran	16, 70	105-106/18mm
5-Phenoxy-2-furoic acid	15, 69	122-123°
Phenyl 5-bromo-2-furoate	67	50-52°
Phenyl 2-(5-carbomethoxyfuryl)sulfone	71	101-102°
Phenyl p-carbomethoxyphenyl sulfide	85	69-70°
Phenyl p-carbomethoxyphenyl sulfone	85	145-146°
Phenyl 2-furyl sulfone	71	69°
Phenyl 5-phenoxy-2-furoate	14, 68	57-58°
2-i-Propoxyfuran	16, 70	135-136/760mm
5-i-Propoxy-2-furoic acid	15, 69	118-119°
i-Propyl 5-bromo-2-furoate	67	132-133/28mm
i-Propyl 5-i-propoxy-2-furoate	14, 68	146-147/20mm
2-Thiophenoxyfuran	16, 70	119-120/8mm
5-Thiophenoxy-2-furoic acid	15, 69	139-141°

*Boiling points show temperature and pressure. Melting points show only temperature.