STUDIES OF METHODS FOR SYNTHESIZING
β -ALKOXYFURANS

A Thesis

by

Gabriel A. Baramki, M.A.
(American University of Beirut)

Submitted to the Faculty of Graduate Studies
and Research of McGill University in partial
fulfilment of the requirements for the
degree of Doctor of Philosophy

McGill University
September, 1959

ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude for the warm interest and valuable advice of

Dr. J. T. Edward

whose constant encouragement and enthusiasm made this work possible. The author wishes to acknowledge also Dr. Edward's assistance in writing the section on nuclear magnetic spectra.

Grateful acknowledgement is also made to:

Dr. A. Taurins for his instruction in the use of the infrared spectrophotometer;

to:

Professor R.U. Lemieux of the University of Ottawa, through whose kind hospitality the nuclear magnetic spectra determinations were made;

to:

The Ford Foundation for a special fellowship during the sessions 1957-1959;

to:

Bir-Zeit College (Jordan) for a furlough of two years during which this work was undertaken,

and to:

Mr. I. Puskas for his help in some experimental parts of this work; to my colleagues for many helpful discussions.

TABLE OF CONTENTS

page

INTRODUCTION

PART I

EXPERIMENTAL

PART II

EXPERIMENTAL

PART III

EXPERIMENTAL

LIST OF TABLES

TABLE page

PART I

PART III

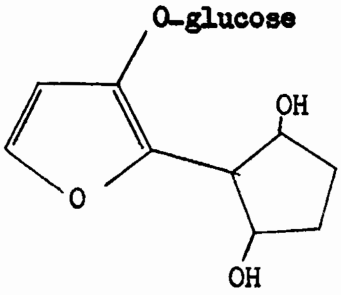
LIST OF FIGURES

FIGURE page

INTRODUCTION

I. Aucubin

Aucubin, a compound isolated from the leaves of Aucuba japonica and other plants(1), has been assigned the structure (1) by Karrer and Schmid(1). It is of interest as the first β-furanol derivative reported as a natural product. The evidence in support of a furan structure according to Karrer and Schmid may be summarized as follows:

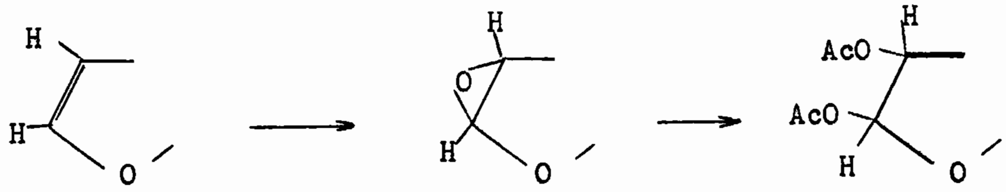


(1)

1. Hydrogenation of aucubin hexa-acetate yielded a tetrahydro product, indicating the presence of two double bonds in the molecule.

2. Out of the nine oxygen atoms in aucubin six could be acetylated. Two other atoms are involved in the glucosidic linkage and in the pyranose ring of glucose. The ninth atom was neither in a carbonyl group nor in a tertiary hydroxyl group, and the logical conclusion was that this oxygen atom should be in the form of an ether linkage.

3. Aucubin hexa-acetate (2) was treated with monoperphthalic acid to give the epoxide (3), which in turn gave dihydrodioxyoctaacetylaucubin (4) on treatment with acetic anhydride in pyridine.



(2) (3) (4)

Reagents: (a) peracid; (b) Ac_2O + pyridine.

Both (3) and (4) reduced Tollen's reagent. In the case of (4), this was explained on the assumption that at least one of the acetyl groups formed an easily hydrolyzable hemi-acetal acetate. This indicated that one of the double bonds was adjacent to the ether oxygen.

4. Treatment of aucubin hexa-acetate with bromine resulted in two isomeric mono-substitution products both stable towards silver acetate and to boiling with alkali. This indicated an aromatic character and was attributed to a furan nucleus.

5. The ease with which the acetate (4) was formed from the epoxide (3), indicated that the carbon atoms in the epoxy ring could not be tertiary. Hence the conclusion that the furan ring in aucubin was not fully substituted.

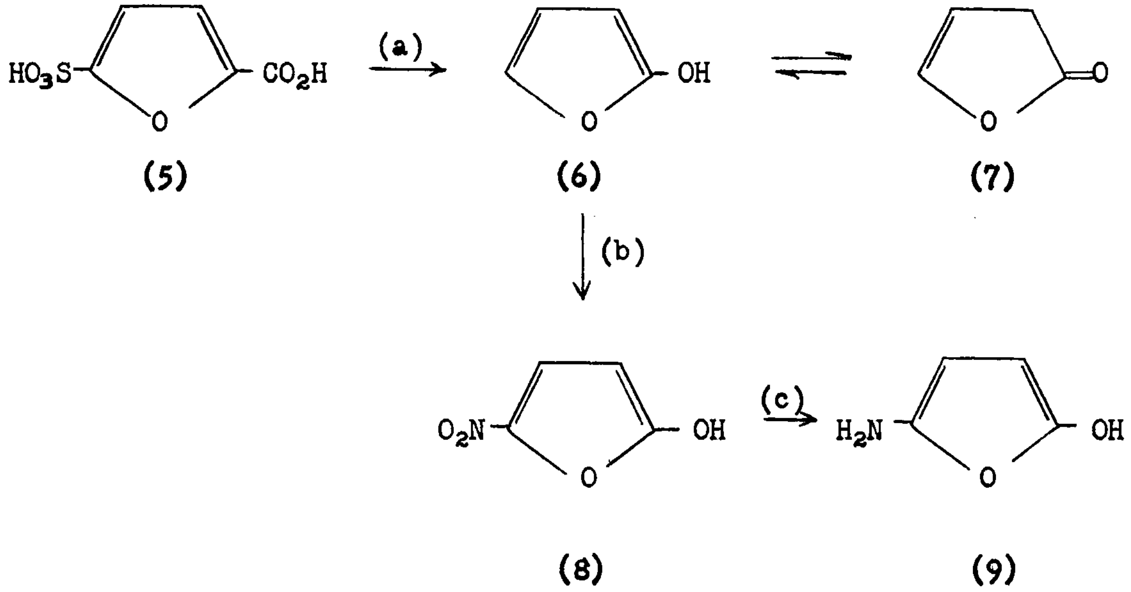
6. The ultraviolet spectrum of aucubin was compared with that

of furan and showed similar absorption in the region 230–200 mμ.

It can be seen from the above argument that the chemical evidence, though circumstantial, is not conclusive. In no case was controlled degradation to a compound of unequivocal structure carried out. Perhaps the weakest point is the lack of proper physical evidence (infrared and ultraviolet studies). IR and UV spectra of aucubin should be compared with those of β-alkoxy furans and derivatives rather than with furan itself for drawing reasonable conclusions from such spectra. The present work was initiated to discover general methods for preparing β-alkoxy furans with a view to using them as model compounds for such spectroscopic comparison.

II. α-Furanols

α-Furanol (6) could be considered as the enolic form of the γ-lactone (7). Hodgson and Davies$^{(2)}$ claimed to have prepared this compound by heating (200°) 5-sulfo-2-furoic acid (5) with strong, aqueous



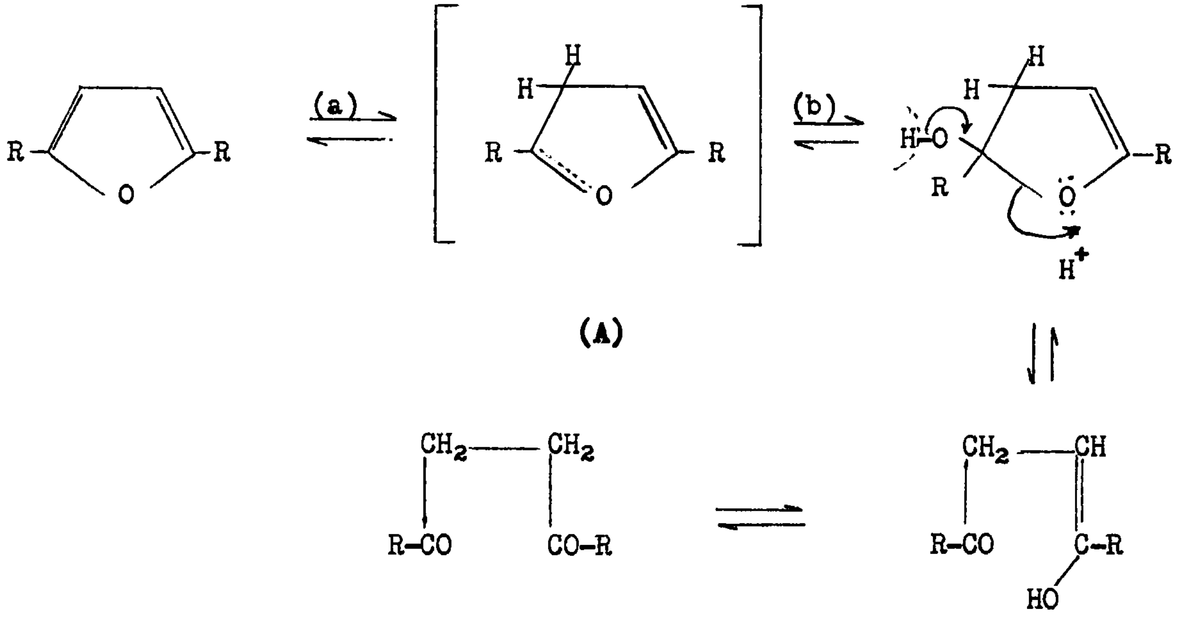
(5) (6) (7)

(8) (9)

Reagents: (a) NaOH + $KClO_3$; (b) H_2SO_4 + HNO_3 ; (c) Zn + HCl

sodium hydroxide in the presence of a small amount of potassium chlorate. The product was described as a colorless crystalline solid, m.p. 80°, which turned brown on keeping and resinified with great ease, especially during distillation with steam, in which it was volatile. Hodgson and Davies(3) also claimed to have nitrated the compound with nitric-sulphuric acid mixture to obtain 5-nitro-2-furanol (8). This was reduced to 5-amino-2-furanol (9) by dissolving it in alkali, then adding the salt to zinc and hydrochloric acid.

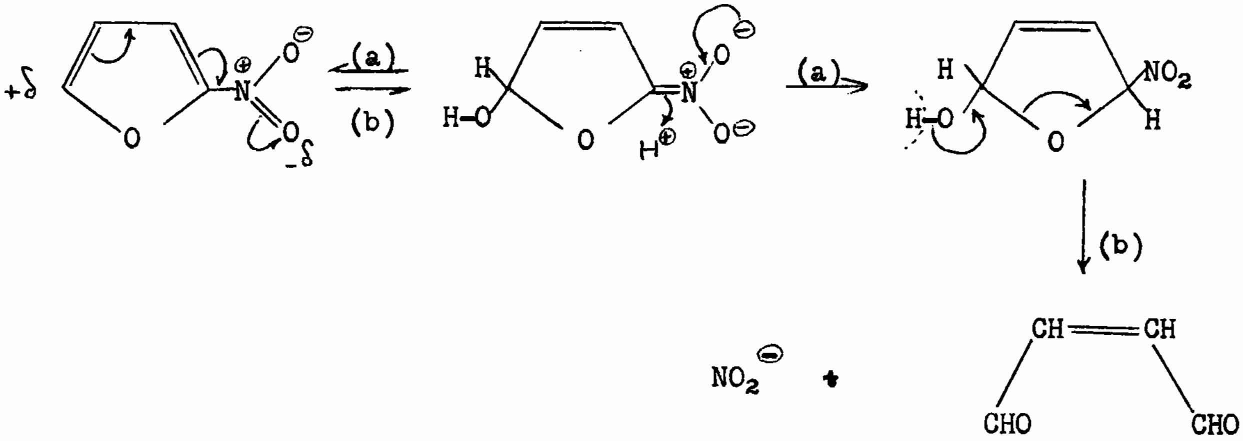
These findings are surprising in view of the usual instability of furans in the reagents employed. Furans may be cleaved in acidic or basic media(4 a). Acid hydrolysis probably involves protonation at a β-carbon atom, followed by attack of water at an α-carbon atom as shown:



Reagents: (a) H^+; (b) H_2O

The ease of formation of ionic intermediates of the type (A) will obviously depend on the ability of the original furan compound to act as an electron donor and on properties of the group(s) R. It may be expected, therefore, that furans possessing substituents which have an electron-withdrawing effect (e.g. nitro and carboxylic groups), would be more resistant to acid catalyzed cleavage. This is attested by the experience of many investigators(5).

In alkaline medium the picture changes. Furan and its homologs, in which the nucleus is relatively electron rich, are very stable towards aqueous or alcoholic alkali. However, furans with an electron-withdrawing group are subject to nuclear attack by suitable donor reagents. Thus α-nitrofurans are readily attacked by alkalies(6), in which they decompose to give nitrites and products possessing aldehyde characteristics:

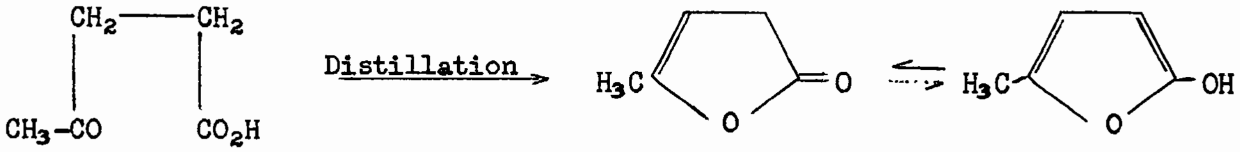


Reagents: (a) H^+; (b) OH^-

Besides showing differing stabilities to acidic or alkaline attack, furans differ widely in their tendency to oxidize or polymerize when stored in the dry state. The exact nature of the reaction causing the furans to form tars or resins is not known. However, as in the case of other aromatic compounds generally, electron attracting groups (e.g., CO_2H) stabilize the furan ring. So that electron releasing groups (e.g., OMe) may be expected to make it less stable.

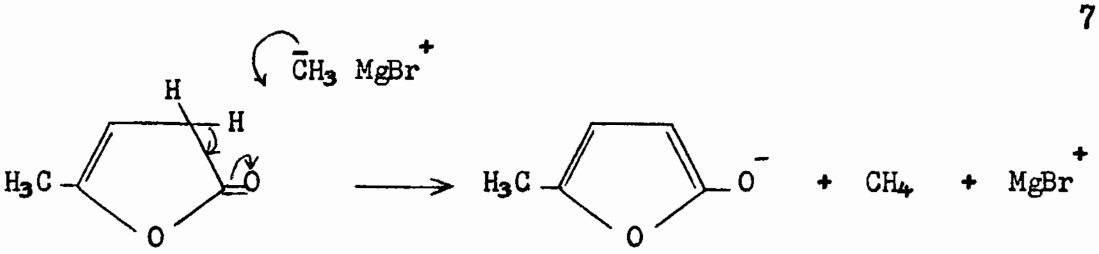
In view of the above discussion it would be difficult to explain the existence of compounds (6) and (9) in strong acidic media or the survival of (8) on treatment with strong alkali. Unfortunately, to date this work has not been confirmed.

The chemistry of the so-called α-angelica lactone (3-pentenoic-lactone) (10) offers little support for the existence of the enolic form (11) beyond the fact that a Zerewitinoff determination liberated approximately one third of a mole of methane for one mole of the lactone(7).



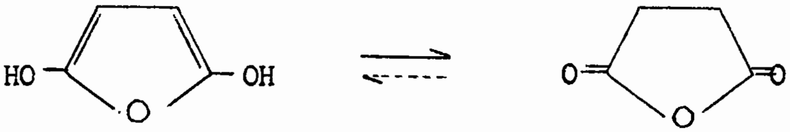
Levulinic acid (10) (11)

This test, however, is not a conclusive one for the presence of a hydroxyl group, and could be equally well explained on the basis of the lactone structure (10) as shown below:



The UV spectrum of α-angelica lactone was compared with that of furfuryl alcohol and a maximum of absorption at 2170 Å shown by both compounds was given as additional evidence for the presence of the enol form (11)(7). Here again, the conclusion cannot be a valid one since furfuryl alcohol has no real structural relationship with the enol form, and a more logical model compound would be α-methoxy furan.

Finally, succinic anhydride (13), which might be considered as the keto form of α,α'-difuranol (12), shows no evidence of existing in the latter form(4 b).

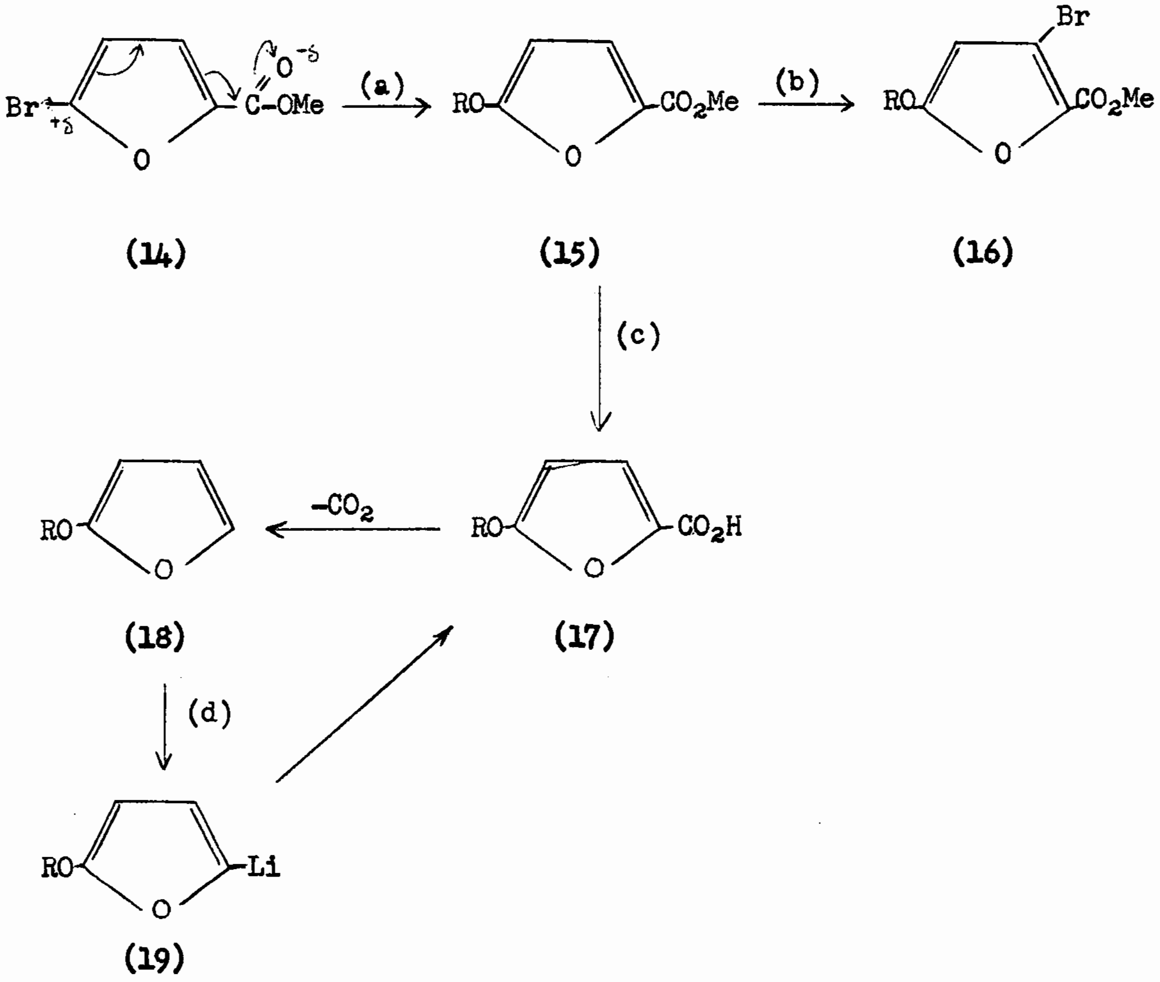


(12) (13)

III. α-Furyl Ethers and Esters

While the existence of α-furanols is doubtful, their ethers and esters have been obtained and are moderately stable.

A series of 2-alkoxy furans was prepared by Manly and Amstutz(8) by a direct Williamson synthesis. Because of the extreme inertness of aromatic halides such as 2-bromofuran(4 c), they used methyl 5-bromo-2-furoate which reacted with sodium alkoxides to give the corresponding ethers according to the scheme below:



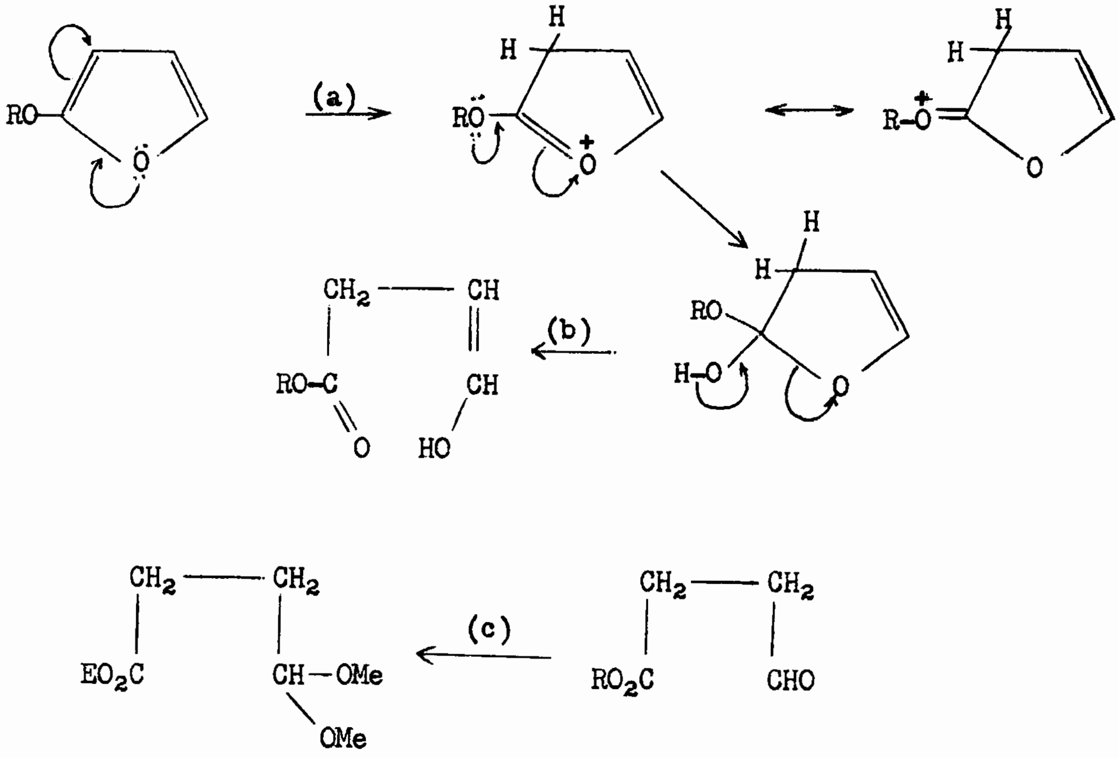
(R = CH_3-, C_2H_5-, i-C_3H_7-, C_6H_5-, n-C_8H_{12}, C_6H_{11})

Reagents: (a) RO-; (b) N-bromosuccinimide; (c) NaOH; (d) PhLi

The presence of the carboxyl group labilizes the α-bromine atom by creating a positive center for nucleophilic attack(9,10).

Attempted nitration of (17) was unsuccessful, and bromination of (15) produced considerable tar along with a small amount of the 4-bromo compound (16). However, the reaction proceeded smoothly and in somewhat better yield using N-bromosuccinimide as the brominating agent. The extreme sensitivity of the furyl ethers themselves is indicated in this paper, and ring opening in methanolic hydrogen chloride produces the dimethyl acetal of methyl-β-formyl propionate (21).

The great general reactivity of 2-furyl ethers was shown by the isolation of only the trimercurated product on mercuration. However, the unoccupied 5-position is the most reactive carbon in the ring toward metallation, as evidenced by the reaction of 2-phenoxy furan (18, R = Ph) with phenyl lithium followed by carbonation to give 5-phenoxy-2-furoic

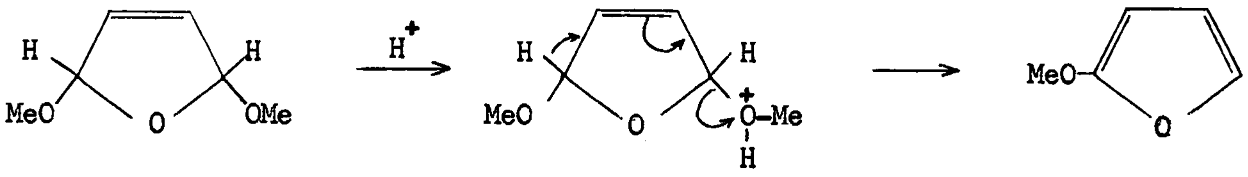


(21)

Reagents: (a) and (b) H^+; (c) MeO^-

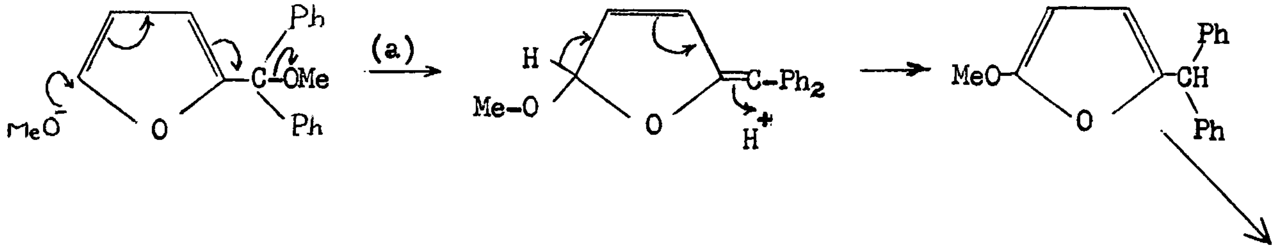
acid (17, R = Ph). All of the simple 2-furyl ethers reported seemed to be unstable to air oxidation, and over a period of several weeks became yellow and viscous on standing, even when stored under nitrogen in a sealed tube at ice temperatures.

2-Methoxy furan (23) was prepared also by heating 2,5-dihydro-2,5-dimethoxy furan⁽¹¹⁾(22), β-naphthalene sulfonic acid and n-butyl phthalate to 360°. The mechanism proposed for the acid catalyzed formation of (23) is shown below:



(22) (23)

Ushakov and Kucherov⁽¹²⁾ reported the preparation of 5-(diphenylmethyl)-2-methoxyfuran (26) by the action of methanolic hydrochloric acid on the methyl ether of diphenyl furyl carbinol (24), at mild temperatures. When reflux temperatures were used, 5,5-diphenyl-levulinic ester (27) was obtained.



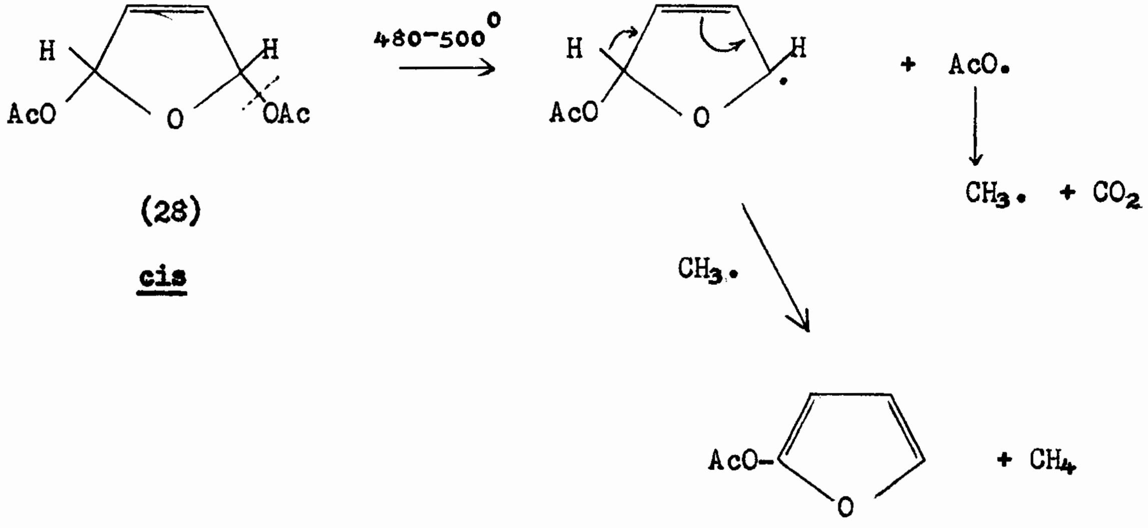
(24) (25) (26)

(27)

Reagents: (a) HCl + MeOH; (b) H^+ + MeOH (reflux).

The compound (25) was obtained in the mother liquor during the first step of the reaction, giving evidence for the reaction sequence shown.

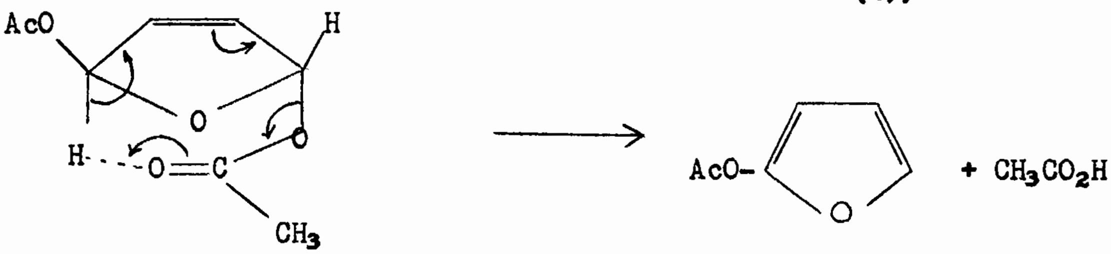
The only known ester of α-furanol, 2-acetoxy furan (29), was obtained in 7-35% yield by the vapor-phase pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran (28) at 480-500°$^{(13)}$; possible mechanisms are the following:



(28)

cis

(29)

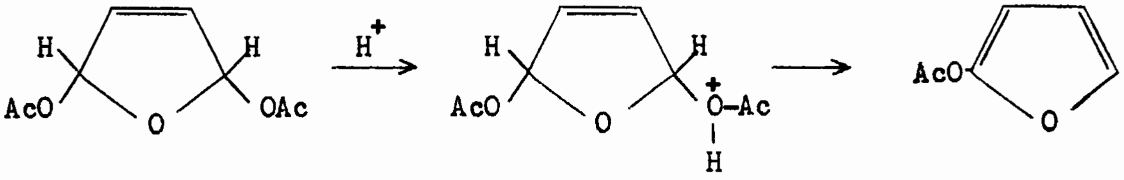


(28)

(29)

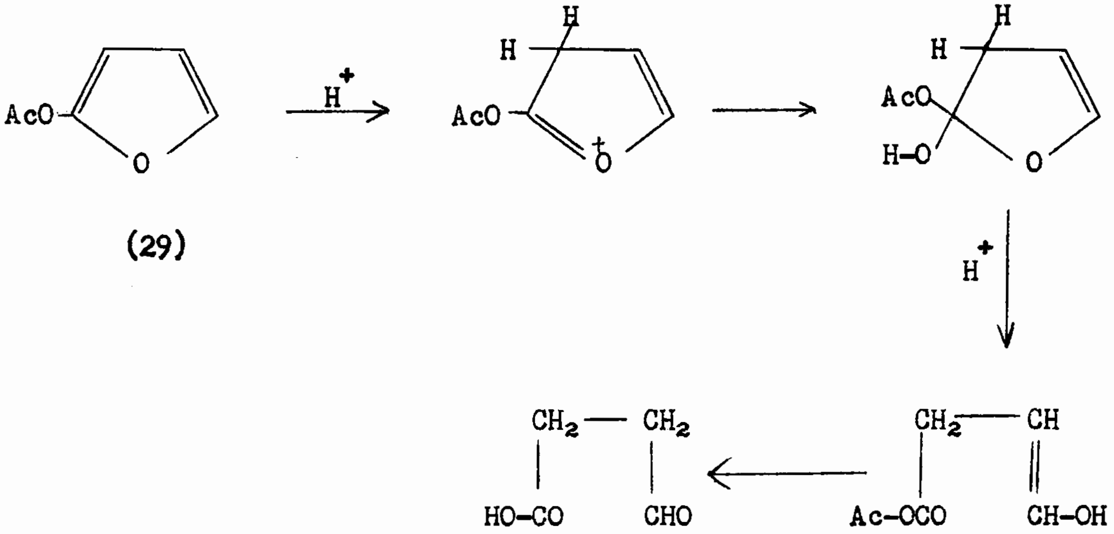
trans

A yield of 80% was reported by Cava et al.(11) by conducting the cracking in the liquid phase at 160-190° in the presence of a catalytic amount of acid, the reaction under these conditions probably following an ionic course:



(28) (29)

The ester (29) hydrolyzes easily in acid medium to β-formyl propionic acid (30) isolated as the 2,4-dinitrophenylhydrazone(13).

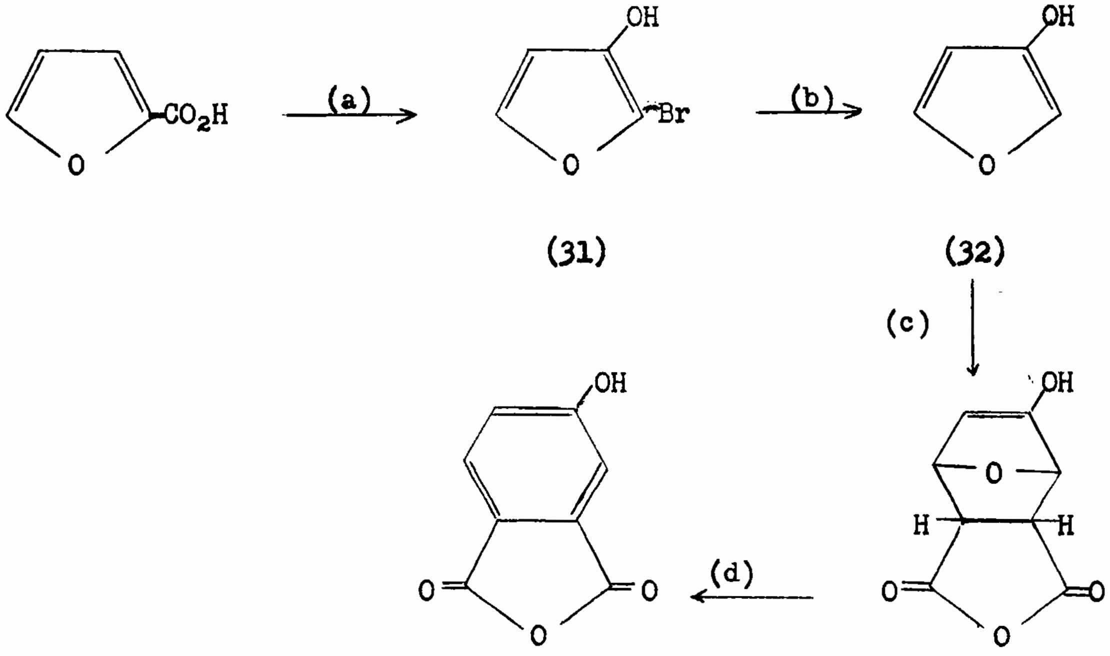


(29)

(30)

IV. β-Furanols and Derivatives

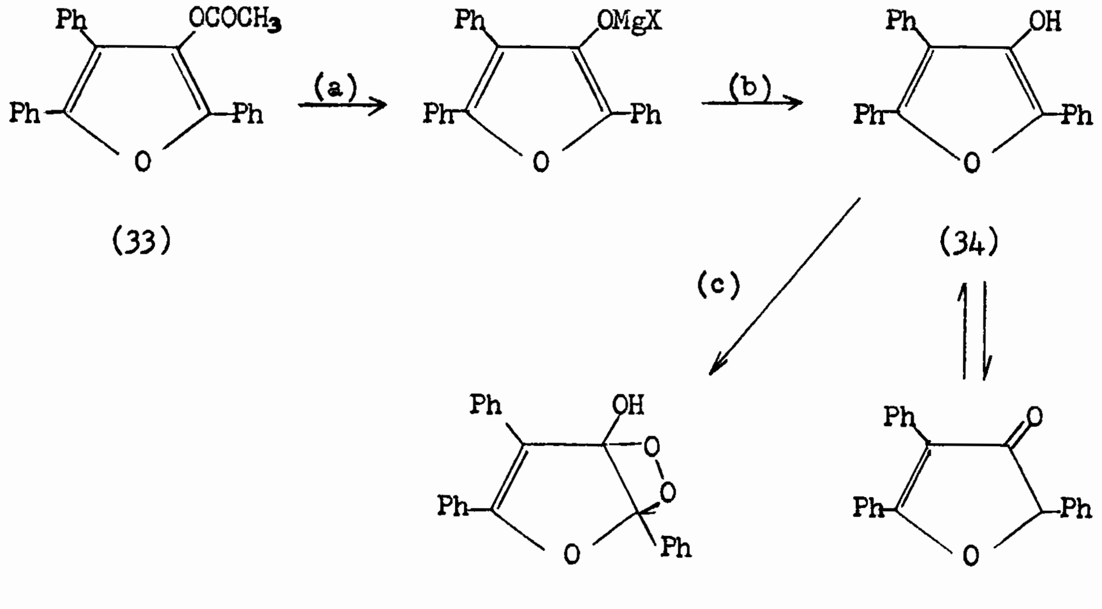
As in the case of the α-furanol, the only report in the literature of the preparation of β-furanol (32) is by Hodgson and Davies(2). They claimed to have prepared it by treatment of furoic acid with bromine in chloroform containing a specified amount of water, and subsequent reduction of the 3-hydroxy-2-bromofuran (31) with sodium amalgam. The β-furanol (32) was reported as a crystalline solid melting at 58°. Its structure was confirmed by the preparation of a maleic anhydride adduct which was then converted to the known 4-hydroxy phthalic acid.



Reagents: (a) Br_2 + H_2O and $CHCl_3$;(b) Na-Hg; (c) maleic anhydride; (d) HBr + AcOH

Nitration(3) of β-furanol (32) afforded 2-nitro-3-furanol, which was reduced to give the 2-amino-3-furanol, a compound seemingly stable enough to survive the strongly acidic conditions of the reduction. Unfortunately this work has to be viewed with scepticism, not only because the properties of (32) are inconsistent with the properties reported for other β-furanols, as will be seen below, but also because Baily and Waggoner(14) could not duplicate the first step in the synthesis, viz. the preparation of the hydroxy bromofuran (31) from furoic acid, despite numerous trials.

Kohler et al.(15) obtained solutions containing 2,4,5-triphenyl-3-furanol (34) by carefully removing the acetate group from (33) by the Grignard reaction and subsequent acidifying in an inert atmosphere. The solution was considered to contain the furanol (34) because it decolorized bromine instantaneously and absorbed oxygen from the air to give a sparingly soluble crystalline peroxide (35). An ether extract of the



(33)

(34)

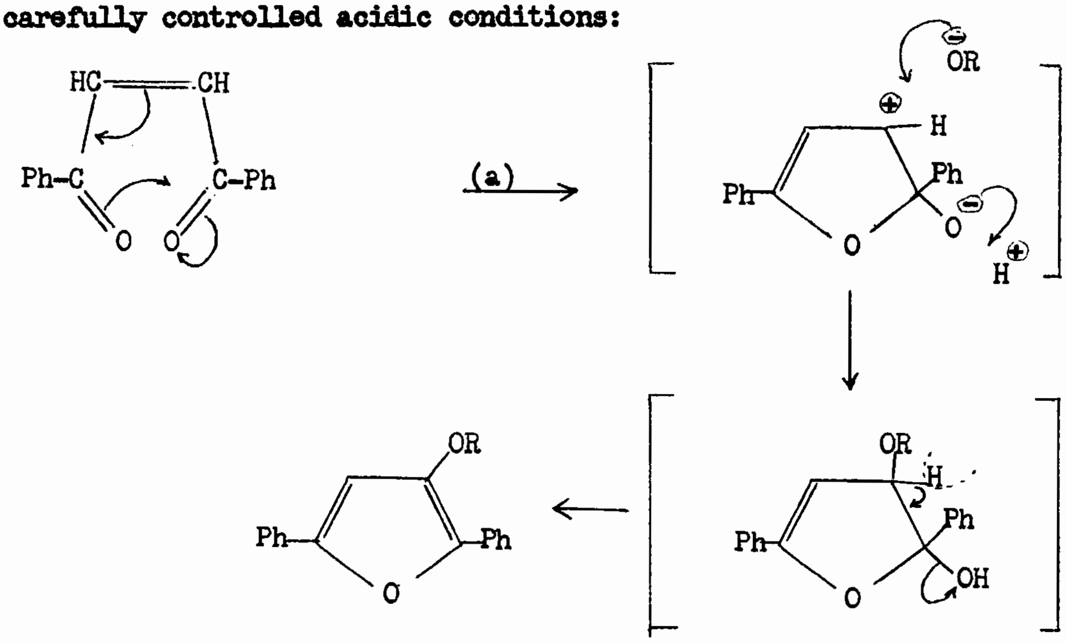
(35)

(36)

Reagents: (a) MeMgX; (b) H^+; (c) O_2

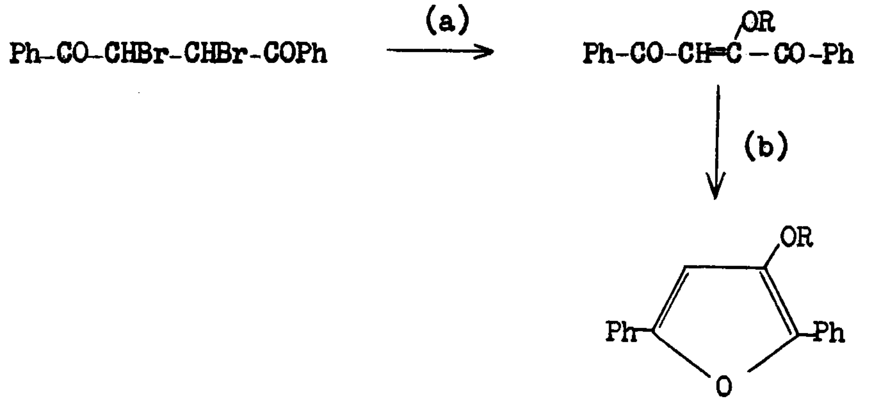
furanol (34) deposited colorless crystals which had the composition of the furanol, but were assumed to be the furanone (36) because solutions from which they had been separated as completely as possible still formed peroxide rapidly and in quantities far in excess of any that could be obtained from saturated solutions of the solid. Moreover, solutions of the solid formed peroxides much more slowly than those obtained from the acetate.

The starting material (33) as well as a number of heavily substituted ethers and esters were prepared by Lutz and others$^{(16,17)}$. Two more or less general methods were employed$^{(16)}$. In one method, an alcohol was added to the appropriate unsaturated 1,4-diketone under carefully controlled acidic conditions:



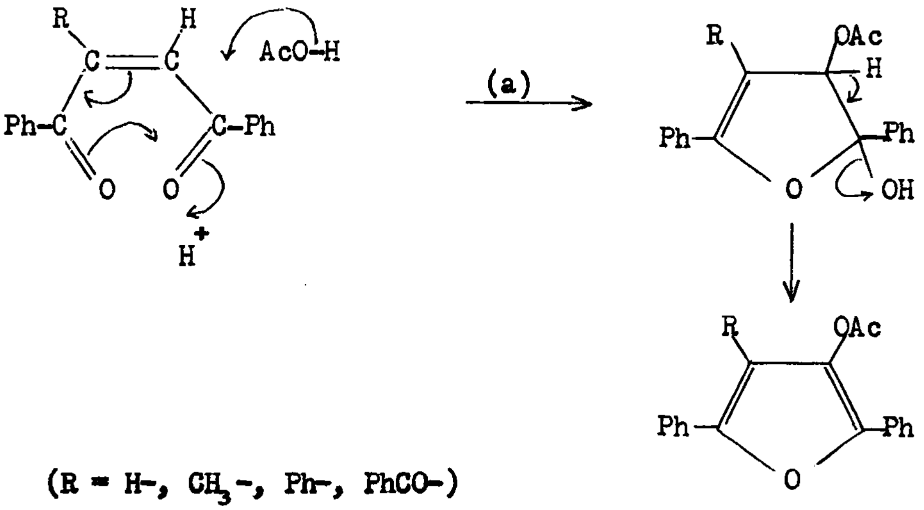
Reagents: (a) ROH + $R_3N.HCl$ (pH 2-3)

The other route was the reduction of an alkoxy derivative of the unsaturated 1,4-diketones.



Reagents: (a) NaOR; (b) Zn + AcOH or H_2/Pt

Esters of β-furanol derivatives were prepared(15) using similar methods; the <u>cis</u> compounds were shown to be much more susceptible than the <u>trans</u> compounds towards furanization.



(R = H-, CH_3-, Ph-, PhCO-)

Reagents: (a) $Ac_2O + H_2SO_4$

Unlike Kohler et al., Votocek and Malachta(18) claim to have isolated a β-furanol, 2-methyl-3-furanol (42), having some stability in the phenolic form. 5-Ketorhamnolactone(19) (37) on treatment with methanolic hydrogen chloride afforded a methoxy ester formulated as

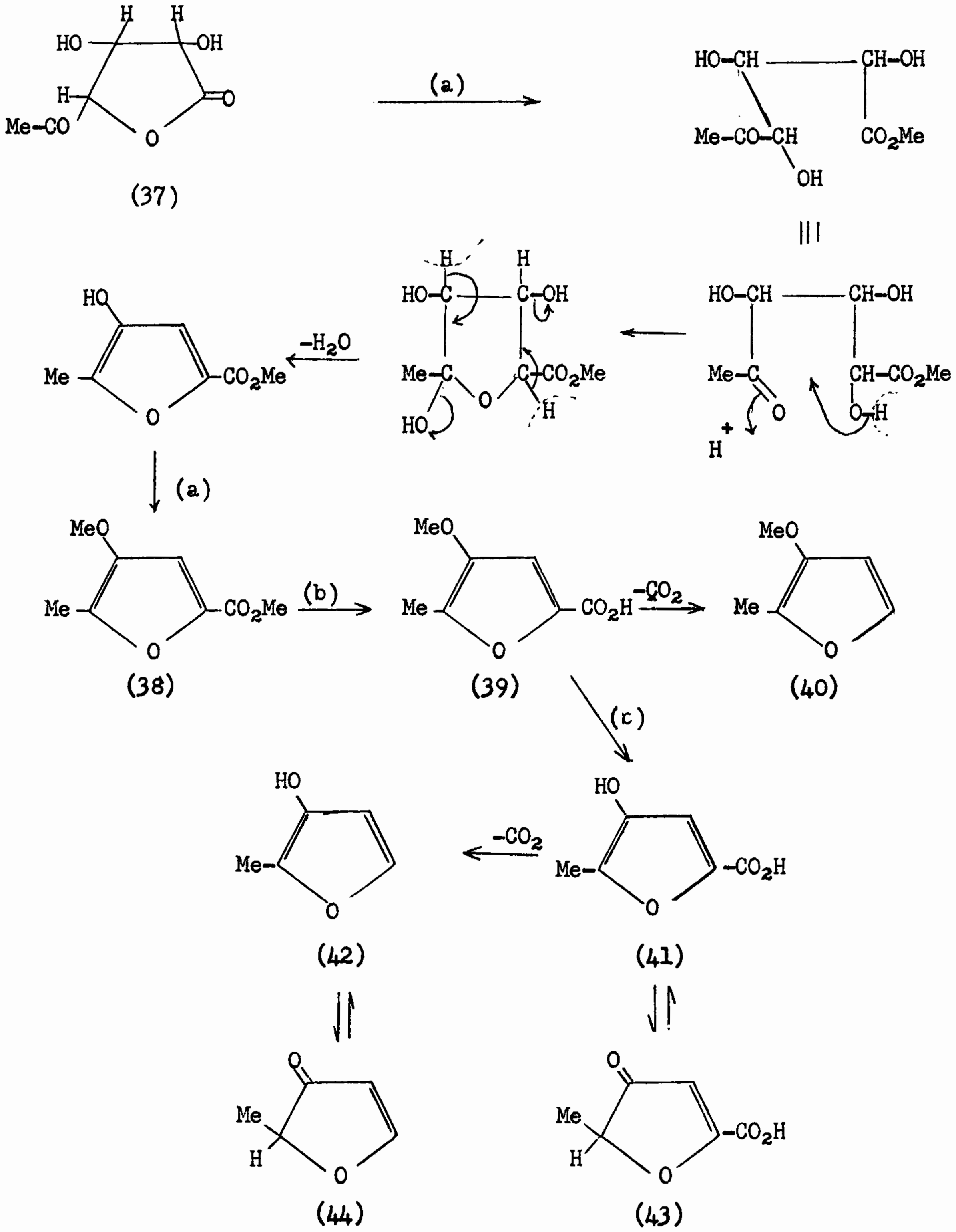
4-methoxy-5-methyl-2-carbomethoxyfuran (38); a possible mechanism for this reaction is shown below. The ester was hydrolyzed with alkali to give the acid (39) of which the methyl ether group was cleaved by refluxing with hydrochloric acid. From the resulting hydroxy acid (41) the methyl furanol (42) was obtained by decarboxylation.

Both (41) and (42) gave the ferric chloride test, but it is interesting to note that a Zerewitinoff determination on (42) gave 6.65% instead of the expected 17.37% active hydrogen, indicating that the equilibrium is shifted towards the keto form (44). This compares very well with the value obtained from α-angelica lactone which has the same grouping as (42) (cf. p. 6).

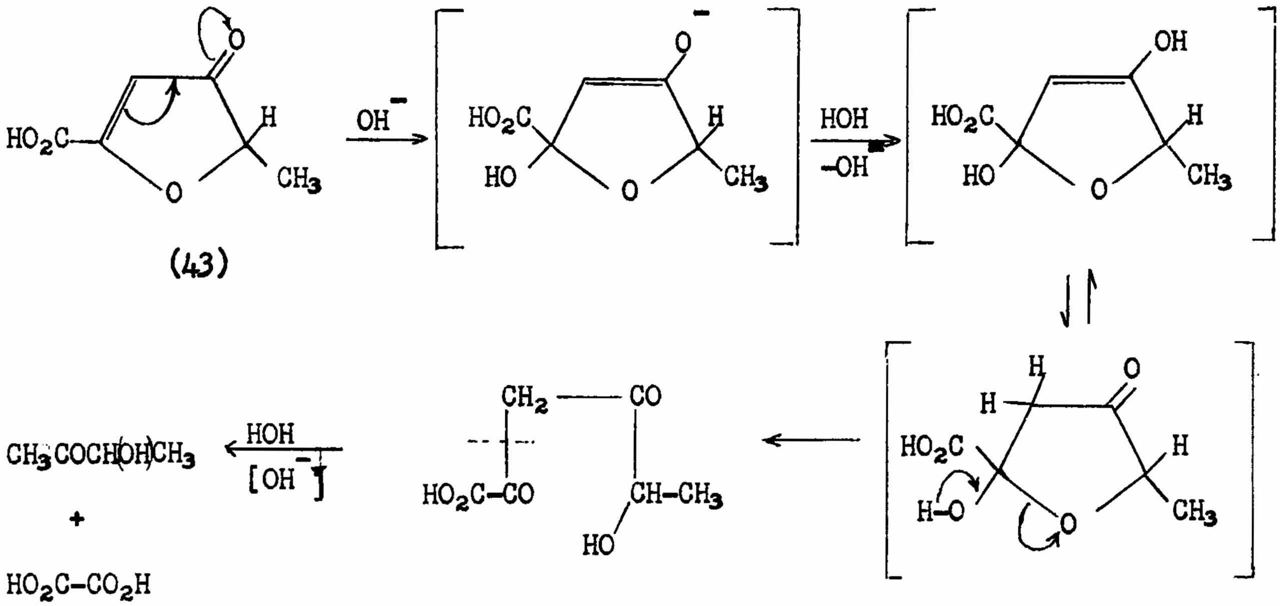
The compounds (43) and (44) are vinylogs of lactones. Consequently, as expected, they were cleaved by barium hydroxide to give acetoin. With sodium hydroxide and potassium iodide compound (43) gave the iodoform test. These cleavages established the positions of the various functional groups in the furan nucleus.

These tests indicate that, while compounds (41) and (42) were reported as β-furanols, the corresponding keto forms (43) and (44) probably exist in equilibrium with them. Unfortunately, no work has been done to establish the positions of the equilibria.

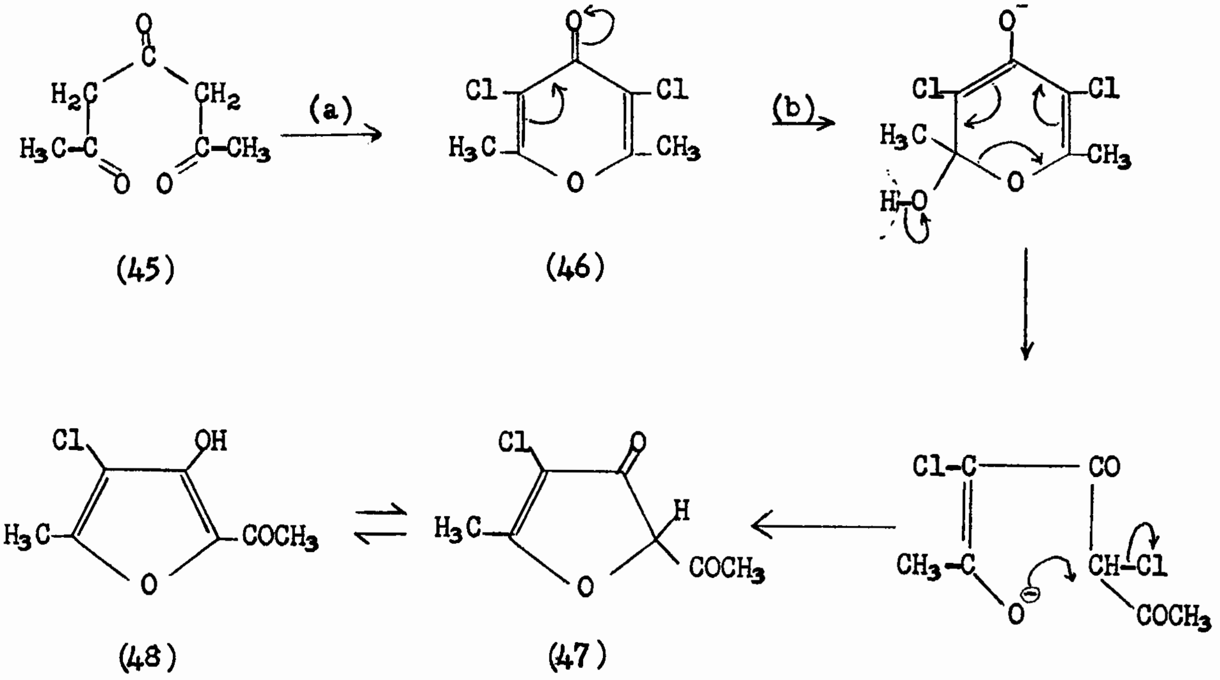
Morgan and Porter(20) reported the preparation of 5-acetyl-3-chloro-4-hydroxy-2-methylfuran (48) by treating 3,5-dichloro-2,6-dimethyl-γ-pyrone (46) with barium hydroxide. Compound (46) was obtained by the action of selenium tetrachloride on diacetyl acetone (45). The compound



Reagents: (a) MeOH + HCl; (b) KOH followed by H^+; (c) N/5 HCl, reflux



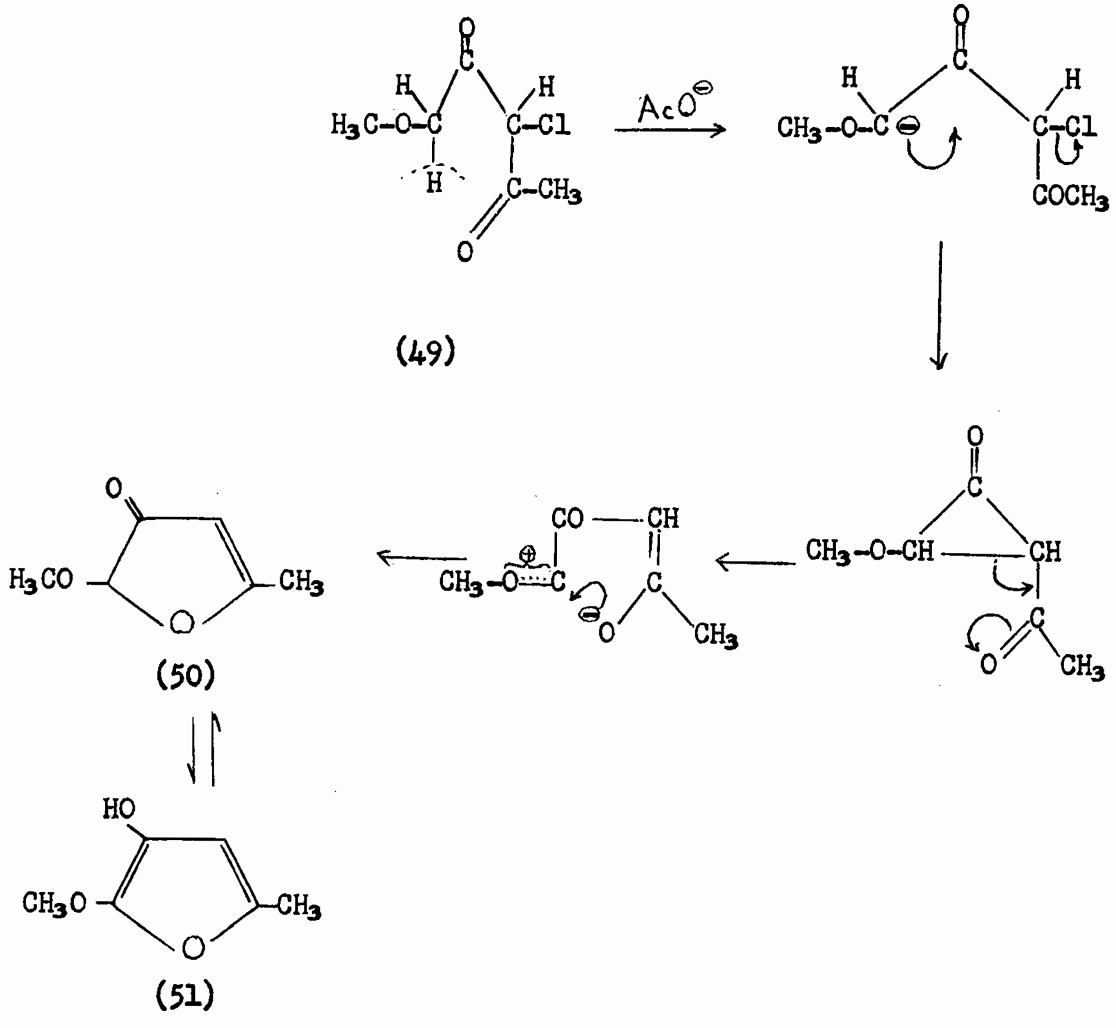
(48) was reported as a crystalline solid melting at 83-4°C, whose solutions gave a violet color with ferric chloride. The phenolic form (48) may well be favored over the keto form (47) in the present instance because of the 5-acetyl group (cf. p. 23).



Reagents: (a) $SeCl_4$; (b) OH^-

V. α,β-Dihydroxyfurans

α,β-Dihydroxyfurans have never been obtained, but a monomethyl derivative, 2-methoxy-5-methyl-3-furanol (51), was prepared by Henecka(21) by heating α-chloro-γ-methoxy acetylacetone (49) with acetic acid and potassium acetate. The mechanism of the reaction, modified from that proposed by Henecka is probably as shown below:



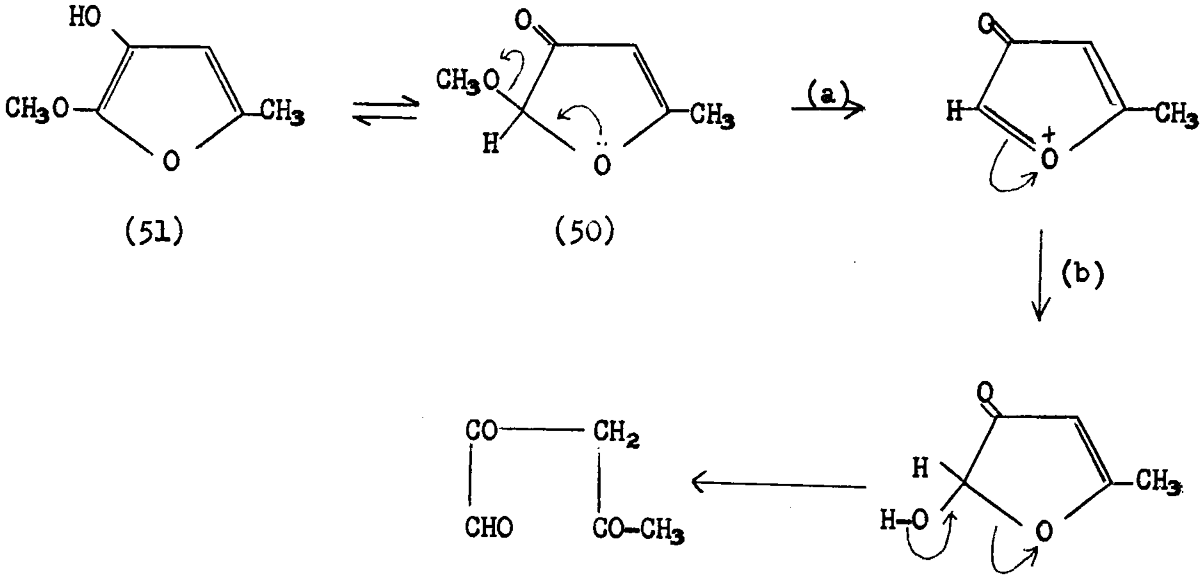
(49)

(50)

(51)

The furanol structure (51) was preferred by Henecka to the keto form (50). However, it seems likely that the compound existed mainly in the keto form, because solutions of it gave a color with ferric chloride only very slowly.

The compound was cleaved readily by dilute acids, so that the trisemicarbazone of 2,4-dioxopentanol (52) was obtained from solutions of (51) in semicarbazide hydrochloride.



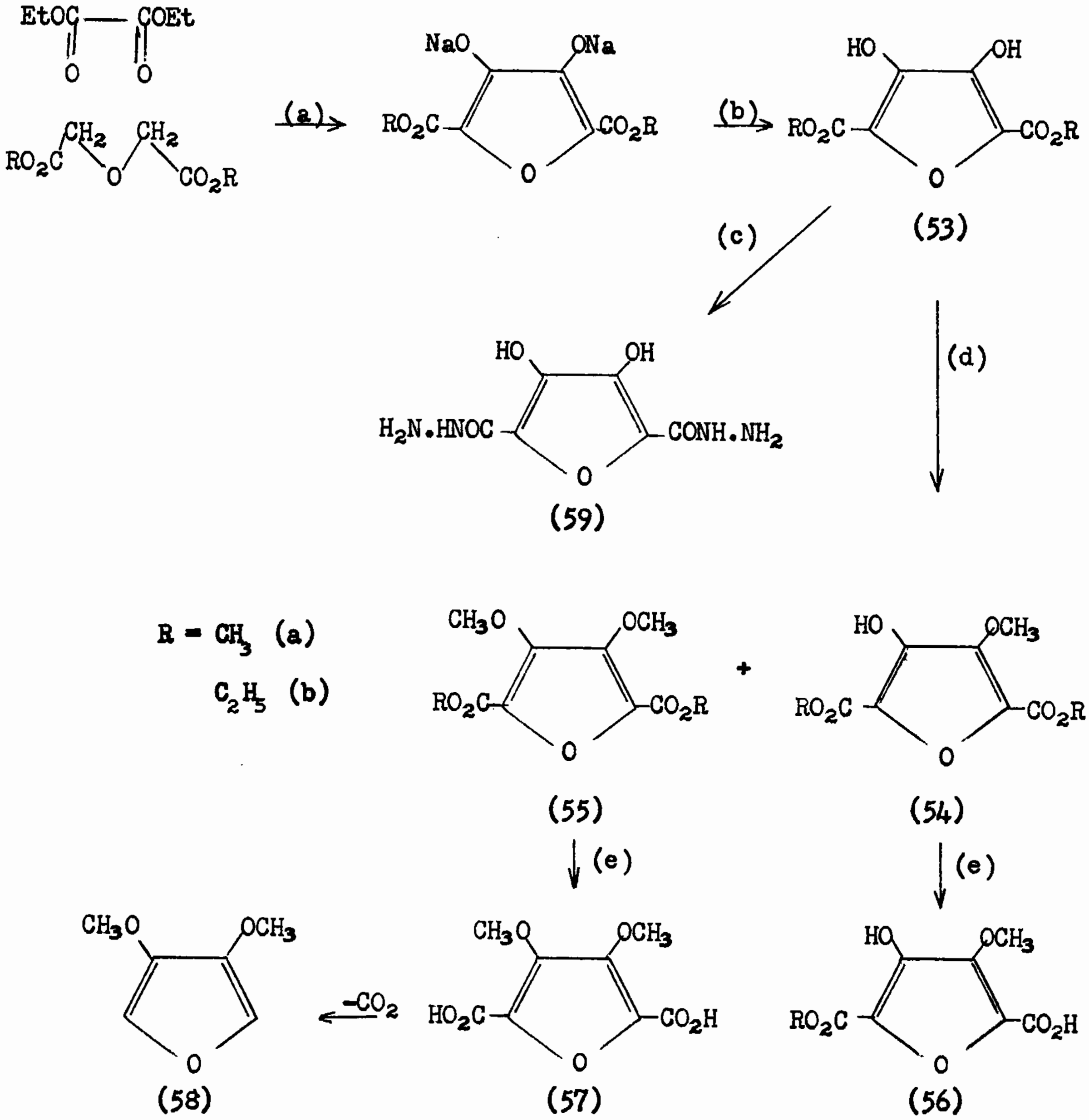
(51) (50)

(52)

Reagents: (a) H^+; (b) HOH

VI. β,β'-Dihydroxyfurans

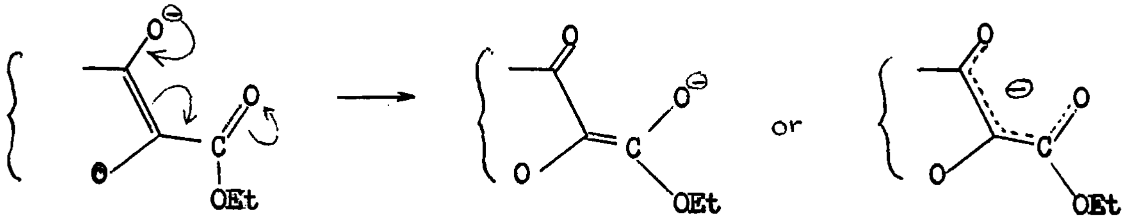
Diethyl and dimethyl 3,4-dihydroxy-2,5-furandicarboxylate (22,23,24) (53) were prepared by a Claisen condensation of ethyl oxalate with ethyl or methyl diglycolate in the presence of sodium ethoxide (or sodium methoxide when the methyl ester was used).



Reagents: (a) NaOR; (b) H^+; (c) N_2H_4; (d) NaOH, Me_2SO_4; (e) NaOH followed by H^+.

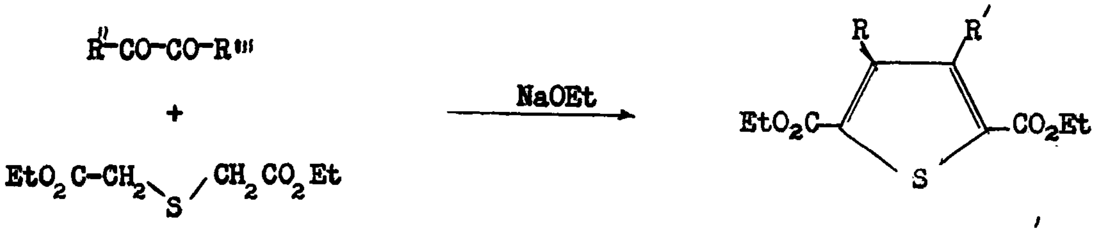
The fact that (53) reacted with hydrazine to give the hydrazide (59)$^{(25)}$ indicated that the compound was mostly in the enol form.

The dihydroxy ester (53) was highly resistant to saponification, probably because the negative charges from ionization of the hydroxyl groups were partially delocalized on the carbonyls of the ester groups. However, the ester groups of the dimethoxy compound (55) could be easily



saponified. In the case of the monohydroxy compound (54) only the ester group adjacent to the methoxy group can be saponified to give the product (56).

Similar work was carried out with esters of thiodiacetic acid(23) where condensations with various α-dicarbonyl compounds were performed as shown below.

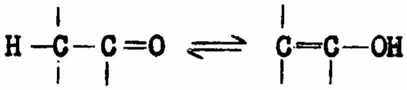


R, R' = C_6H_5- (benzil)
= $-OH$ (ethyl oxalate)
= $-H$ (glyoxal)
R = $-OH$
R' = CO_2Et (ethyl mesoxalate)

The attempted condensation of ethyl diglycolate with ethyl pyruvate failed(23). No attempts to prepare furanols by the condensation of ethyl diglycolate with other compounds of the type R.CO.CO.R' have been reported.

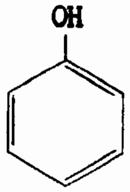
VII. Relative Stabilities of Keto and Enol Forms of Furanols

From the evidence above, furanols seem to exist in the keto rather than the enol forms, although more quantitative evidence would be desirable. In this respect furanols differ from phenol which shows no tendency to exist in the keto form. This difference is to be expected on theoretical grounds. Summation of the bond energies for the system

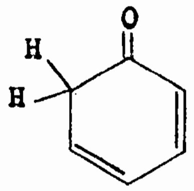


$$H-\overset{|}{\underset{|}{C}}-\underset{|}{C}=O \rightleftharpoons \overset{|}{\underset{|}{C}}=\underset{|}{C}-OH$$

shows(26) that the keto structure is more stable than the enol by ~ 18 Kcal/mole. In phenol this gain of energy of the keto form is offset by a greater loss in resonance energy (~ 35 Kcal/mole) in going from the benzenoid form (60) to the non-aromatic form (61).

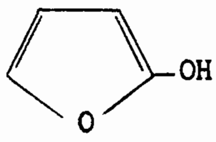


(60)

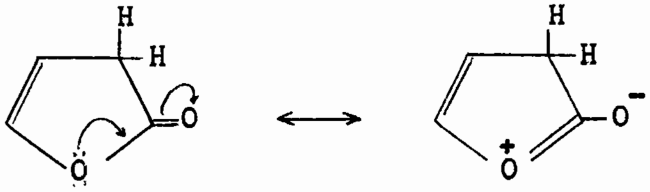


(61)

We now consider α-furanol. In going from the phenolic (6) to the keto (7) form, we lose the resonance energy due to the aromatic system, which will be slightly greater than that of furan itself (variously reported from 15.8 to 22.2 Kcal/mole: cf.(27)) because of the interaction of the



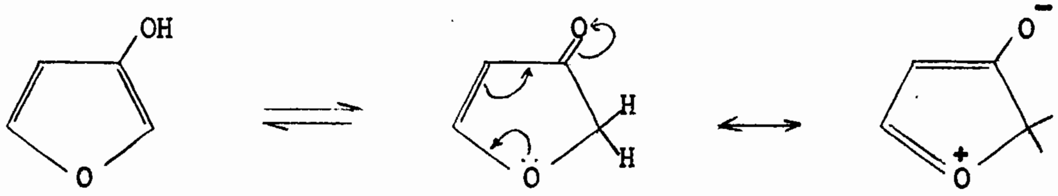
(6)



(7)

hydroxyl group with the aromatic ring. However, we gain the resonance stabilization characteristic of the ester group (about 21 Kcal/mole(28)) and of the vinyl ether group (about 2-3 Kcal/mole(28)). These calculations show that the large resonance effects which favour phenol (60) over its keto form (61) are not to be expected in α-furanol, but are too crude to indicate decisively the relative stabilities of the enol (6) and the keto (7) forms. In fact, the balance of experimental evidence outlined above indicates the keto form to be much more stable.

On the other hand, it is possible that β-furanol (32) is more stable relative to its keto form (32a).



(32) (32a)

The latter is the vinylog of an ester, and hence should be stabilized by resonance as shown; however, the greater separation of charges in the dipolar form of (32a) as compared with the dipolar form of (7) probably makes it less stable, and hence a less important contributor to the hybrid state of the molecule.

A similar difference has been noted with α- and β-thienols(29). The β-hydroxy compound exists in equilibrium with its keto tautomer, while the α-hydroxy compound is unstable and is known only in the keto form.

VIII. General Outline of Thesis

In the present work are outlined methods to discover more general routes to alkoxyfurans, and to characterize the products. We first describe (Part I) the direct formation of aromatic ethers by the reaction of organometallic compounds with dimethyl peroxide, and the application of this reaction to the furan series. The preparation of various furans from dimethyl and diethyl 3,4-dihydroxy-2,5-furandicarboxylate (53; R = Me and R = Et), including attempts selectively to reduce one of the hydroxyl groups in the nucleus are next described (Part II). Attempts to obtain monohydroxyfuran derivatives by related condensation reactions are also described. Finally, the characterization of furans by various physical methods are discussed in Part III, and some tentative conclusions regarding the structure of aucubin are made.

BIBLIOGRAPHY

1. Karrer, P. and Schmid, H., Helv. Chim. Acta, 29, 525 (1946).
2. Hodgson, H. and Davies, R., J. Chem. Soc., 1939, 806.
3. Hodgson, H. and Davies, R., J. Chem. Soc., 1939, 1013.
4. Dunlop, A. and Peters, F., "The Furans", Reinhold Publishing Corp., New York, 1953 (a) pp. 638-663. (b) p. 171. (c) p. 85.
5. Gilman, H. and Young, R.V., Rec. trav. chim., 51, 761 (1932).
6. Hill, H.B. and White, G.R., Am. Chem. J., 27, 193 (1902).
7. Langlois, D. and Wolff, H., J. Am. Chem. Soc., 70, 2624 (1948).
8. Manly, D. and Amstutz, E., J. Org. Chem., 21, 516 (1956).
9. Ingold, C.K., "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York, 1953, p. 804.
10. Bunnett, J.F., Quart. Revs. 12, 1 (1958).
11. Cava, M.P., Wilson, C.L. and Williams, C.J., Chemistry and Industry, 1955, 17.
12. Ushakov, M. and Kucherov, V., J. Gen. Chem. (U.S.S.R.), 14, 1073 (1944); C.A., 40, 7185 (1946).
13. Clauson-Kaas, N., Acta Chem. Scand., 6, 560 (1952).
14. Baily, P.S. and Waggoner, J., J. Org. Chem., 15, 159 (1950).
15. Kohler, E., Westheimer, F. and Tishler, M., J. Am. Chem. Soc. 58, 264 (1936).
16. Lutz, R.E. and McGinn, C.E., J. Am. Chem. Soc., 64, 2585 (1942).
17. Baily, P.S. and Lutz, R.E., J. Am. Chem. Soc., 69, 498 (1947).
18. Votocek, E. and Malachta, S., (a) Coll. Czech. Chem. Com., 1, 449 (1929). (b) Ibid., 4, 87 (1932).
19. Votocek, E. and Benes, L., Bull. soc. chim., 43, 1328 (1928).
20. Morgan, G. and Porter, C., J. Chem. Soc., 125, 1269 (1924).
21. Henecka, H., Ber., 82, 32 (1949).

22. Johnson, T.B. and Johns, C.O., Am. Chem. J., 36, 290 (1906).

23. Hinsberg, O., Ber., 45, 2413 (1912).

24. Hoehn, W.M., Iowa State Coll. J. Sci., 11, 66 (1936).

25. Darapsky, A. and Stauber, M., J. prakt. chem., 146, 209 (1936).

26. Branch, G. and Calvin, M., "The Theory of Organic Chemistry", Prentice Hall Inc., New York, 1947. p. 291.

27. Wheland, G., "Resonance in Organic Chemistry", John Wiley and Sons Inc., New York 1955, pp. 85,99.

28. Ingold, C.K., op. cit., pp. 116, 117.

29. Ford, M.C. and Mackay, D., J. Chem. Soc., 1956, 4985.

PART I

The Use of Dimethyl Peroxide for the Methoxylation of Organic Compounds

Little work has been done with dimethyl peroxide since it was first prepared and this could be mainly due to the difficulty in handling the compound, which was reported as an explosive gas, sensitive to shock. This difficulty has been overcome in the present work by using dilute solutions of the gas in cold ether.

The possibility of using dimethyl peroxide for the methoxylation of organic compounds has been explored. At first methoxylation by the use of organometallic compounds was investigated; a mechanism for this reaction has been proposed, and the limitations discussed. The nature of the reaction of dimethyl peroxide with sulfuric acid was next investigated with a view to using it as a possible analytical method for the determination of the peroxide. Finally, methoxylation of aromatic compounds was attempted with dimethyl peroxide under Friedel-Crafts conditions and under conditions in which the peroxide decomposed to methoxyl free-radicals.

1. The Reaction of Dimethyl Peroxide with Organometallic Compounds

In 1906 Wuyts(1) reported the preparation of thio-ethers from disulfides and Grignard reagents, and predicted a similar reaction with diselenides and probably with peroxides.

(1) $R\text{-}S\text{-}S\text{-}R + R'MgBr \longrightarrow R\text{-}S\text{-}R' + R\text{-}S\text{-}MgBr$.

Later, Oddo(2) obtained alcohols from hydrogen peroxide and Grignard reagents.

(2) $H\text{-}O\text{-}O\text{-}H + RMgBr \longrightarrow R\text{-}OH + Mg(OH)Br$.

In 1925 Gilman and Adams(3) reported the reaction between Grignard reagents and a number of organic peroxides including diethyl peroxide. They found that neither succinic peroxide nor triphenylmethyl peroxide underwent a reaction with Grignard reagents, but that both benzoyl peroxide and diethyl peroxide reacted according to the general equation

(3) $R\text{-}O\text{-}OR + R'MgX \longrightarrow R\text{-}O\text{-}R' + R\text{-}OMgX$.

In the reaction of diethyl peroxide with phenylmagnesium bromide, relatively large amounts of biphenyl (30%) were obtained along with phenetole (34%).

Much later, Campbell and co-workers(4) examined the reaction between di-t-butyl peroxide with phenylmagnesium bromide and some aliphatic Grignard reagents. They found that phenylmagnesium bromide and t-alkyl Grignard reagents failed to react with the peroxide, while t-butyl ethers were obtained with primary and secondary aliphatic bromomagnesium compounds. Strangely enough, this work and the work of Gilman and Adams was overlooked in monographs reviewing the reactions of Grignard reagents(5) and of peroxides(6).

In a paper just published, Lawesson and Yang(7) describe a rather similar reaction between t-butyl perbenzoate and Grignard reagents from which t-butyl ethers were obtained.

(4) $PhCO\text{-}O\text{-}O\text{-}Bu^t + R\text{-}MgX \longrightarrow R\text{-}O\text{-}Bu^t + PhCO\text{-}OMgX$

In the present work (which was begun before the work of Lawesson and Yang had been announced(8)) we have attempted to apply the reaction of Gilman and Adams to the preparation of furyl ethers. The peroxide used was dimethyl peroxide(9). This peroxide gave substantially higher yields of ethers, and lower yields of coupling products of the Grignard reagents, than did diethyl peroxide, as shown by the results in Table I.

TABLE I

Nature and Yields of Products from Reaction of Dimethyl Peroxide

	(a) With RLi		(b) With RMgX	
R	ROMe (% Yield)	R-R (% Yield)	ROMe (% Yield)	R-R (% Yield)
C_6H_5-	62	19	62	20
p-MeO.C_6H_4-	45	20	47	26
p-C_6H_5. C_6H_4-	65	11	53	trace
2- $C_{10}H_7$-	21	30	*-	-
2-furyl-	49**	....***		

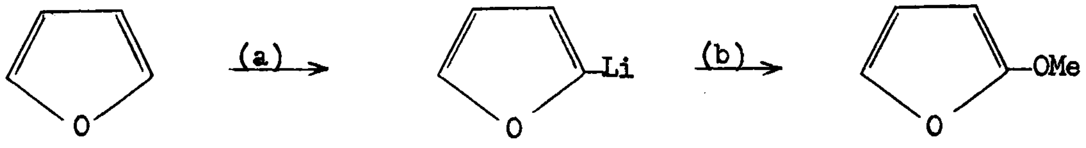
* Reaction not tried

** Product shows slight contamination with aliphatic material

*** Product not isolated.

The reaction of organolithium in place of organomagnesium compounds was next investigated, since the former compounds are often more easily prepared. The yields of methyl ethers using organolithium compounds were virtually the same as when the Grignard reagents were used (Table I).

Consequently, 2-furyllithium(10), prepared by the reaction of furan with n-butyllithium(11), was allowed to react with dimethyl peroxide.



(1) (2)

Reagents: (a) n-BuLi; (b) Me_2O_2.

A yield of 49% of a liquid boiling at 108.5°-111°, and having the same characteristics as the 2-methoxyfuran reported by Petfield and Amstutz(12), was obtained. The infrared spectrum of this compound (Fig. 1) showed characteristic furan bands as well as the band at 2850 $cm.^{-1}$ for the methoxyl group. The structure of this compound (2) follows conclusively from its NMR spectrum (Fig.37) which, however, showed it to be contaminated with aliphatic impurities. These are most probably methyl n-butyl ether (b.p. 70.3°) and n-butyl alcohol (b.p. 117.7°) produced by the reactions

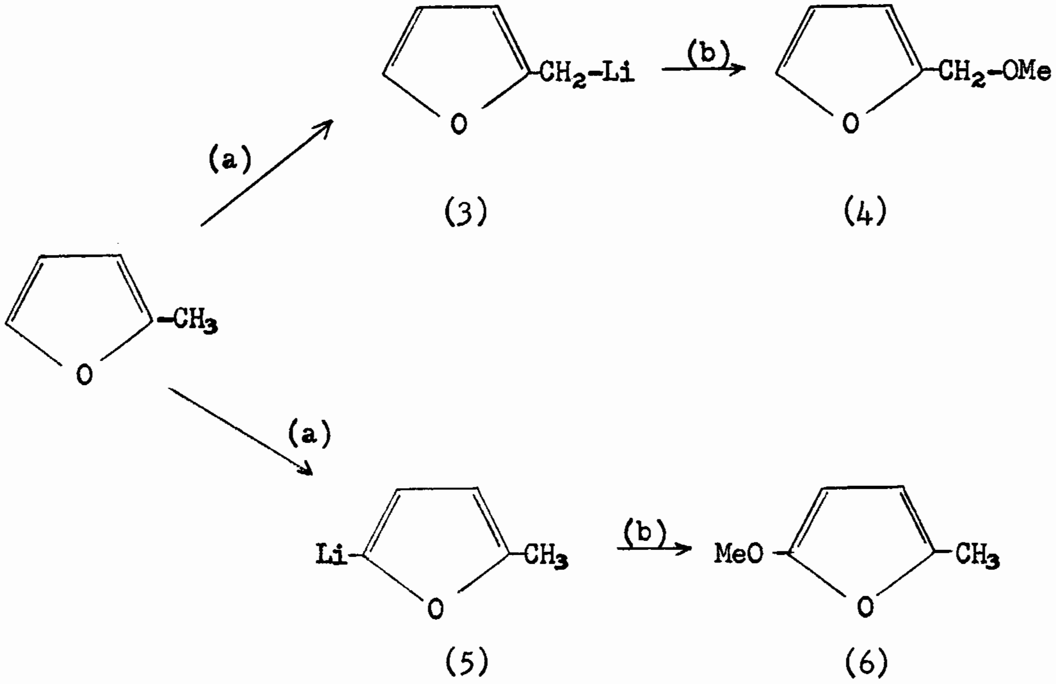
(5) $$BuLi + Me_2O_2 \longrightarrow Bu\text{-}O\text{-}Me + LiOMe$$

(6) $$2BuLi + O_2 \xrightarrow{H_2O} 2BuOH + 2LiOH$$

However, while the overall yield is slightly less than 49%, it is obviously much higher than the overall yields of 7.5% and 11.5% reported for the methods described on pp. 8 and 10.

It was next of interest to investigate the metallation of 2-

methylfuran, followed by treatment with dimethyl peroxide. In this case metallation might in theory afford either compound (4) or (6), although the evidence in the literature favours the latter(13). After reaction



Reagents: (a) n-BuLi; (b) Me_2O_2.

with dimethyl peroxide and working up in the usual way, a 6% yield of a liquid boiling at 128-130° was obtained. The NMR spectrum of this compound (Fig.38) showed it to be made up largely of the desired 2-methoxy-5-methyl furan (6), but again aliphatic impurities were evident. Methoxyl determination and analysis of the compound at different intervals gave different results and indicated the tendency of this compound to decompose at room temperature, besides confirming the presence of impurities (93% of the theoretical amount of methoxyl group). Characteristic furan bands were obtained in the infrared spectrum of this compound (Fig. 2), as well as the band at 2850 cm.$^{-1}$ for the methoxyl group.

The α-metallation of aromatic heterocycles with n-butyllithium is very general(10,14), and it is evident that subsequent reaction with dimethyl peroxide affords a very simple means of obtaining the corresponding methyl ethers. Of special interest are the good yields and the mild conditions under which the reaction takes place, for no external heating was used, and cooling was necessary in most cases. However, it is also evident that when these ethers are low boiling liquids, their separation from other products of the reaction may be difficult. Such an objection obviously does not hold for solids.

2. Mechanism of the Reaction

While organometallic compounds are generally considered to react by ionic mechanisms(15,16), free-radical mechanisms have occasionally been postulated(17). In the present instance the formation of coupling products, R-R, from Grignard reagents or organolithium compounds, might seem to offer some evidence for the intervention of free radicals.

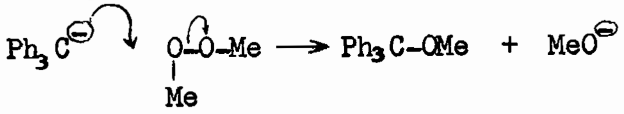
(7) $R\cdot + MeO{-}OMe \longrightarrow R{-}OMe + MeO\cdot$

(8) $MeO\cdot + RLi \longrightarrow MeOLi + R\cdot$

(9) $R\cdot + R\cdot \longrightarrow R{-}R.$

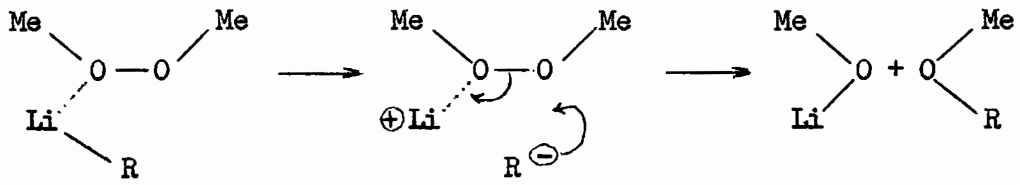
Consequently, an attempt was made to compare the reactivity of dimethyl peroxide towards a free radical and a carbanion, using triphenylmethyl radical and triphenylmethylsodium. Infrared examination of the products showed that only the latter gave methoxytriphenylmethane:

(10)



$$Ph_3C^{\ominus} + MeO{-}OMe \longrightarrow Ph_3C{-}OMe + MeO^{\ominus}$$

although it proved impossible to isolate the ether in crystalline form. Hence, the reaction of organolithium and organomagnesium compounds also probably involves a nucleophilic attack by the carbanion on the peroxide. This may involve a preliminary coordination of the metal atom by the unshared electrons of the oxygen, as is well known to happen with ethers (18a,b).

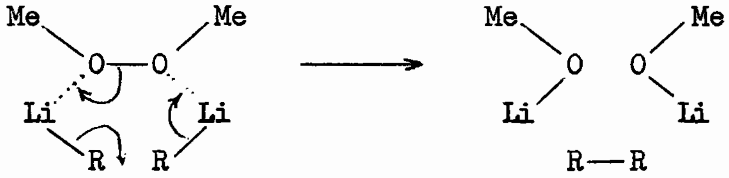


(7)

Such a coordination would facilitate the formation of an ion-pair (7) which then reacts as shown. The fact that phenylmagnesium bromide gives a lower yield of the ether with diethyl(3) than with dimethyl peroxide, and fails to react with di-t-butyl peroxide even when refluxed for twenty-four hours (4), is in agreement with this mechanism, since the approach of a phenyl group towards one oxygen will be sterically hindered to an increasing extent in the three cases. This behaviour is similar to that of disulfides. Disulfides in which the sulfur atom is linked to a secondary or a tertiary carbon atom(19), are particularly stable to S-S cleavage by most bases, including cyanide ion.

It is possible that the oxidative coupling to give R-R compounds

(Table I) occurs when two RLi molecules are coordinated by a peroxide molecule (cf. Kharasch and Reinmuth(20)).



3. Limitations of the Reaction

The reaction of dimethyl peroxide with organometallic compounds was found to be of general applicability whenever an organometallic compound could be prepared. However, there are certain limitations which stem from difficulties in obtaining such organometallic compounds. Two main limitations will be discussed below.

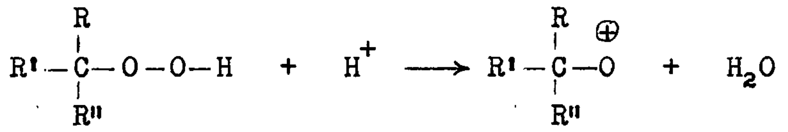
a) Difficulty of getting reactive compounds for metallation:- In attempting to prepare a Grignard reagent of a certain compound, a stable and reactive halide must first be obtained. In the furan series, ordinary or activated magnesium fails to react with 2-bromofuran(21); a highly activated magnesium-copper alloy is required to induce reaction(22). On the other hand, 2-iodofuran is sufficiently reactive to give a high yield (95%) of 2-furylmagnesium iodide with ordinary magnesium(23). However, 3-iodofuran is extremely unreactive and is recovered unchanged after heating with magnesium at 150° for sixteen hours(24). Treatment of this compound with sodium-potassium alloy at 115° for twenty-four hours gives on carbonation a small amount (0.5%) of 3-furoic acid(25). Gilman et al.(26,27) reported that 2,5-dimethyl-3-iodofuran reacted with magnesium to give the corresponding Grignard reagent, but no yields were given. We have found that amylpotassium, which was so effective in metallating benzene and other aromatic compounds(28), failed to react with 2,5-dimethylfuran, even after refluxing the mixture for twelve hours and then keeping it overnight with stirring. Thus it can be seen that failure to metallate furans in the β-position leads to difficulty in obtaining β-methoxyfurans by methoxylation with dimethyl peroxide.

b) Interference of other groups:- The fact that groups such as $-CO_2R$, $-CHO$, $CONH_2$ etc.(5) react with organometallic compounds, eliminates the possible use of compounds having these groups for the preparation of methoxy derivatives by the dimethyl peroxide method.

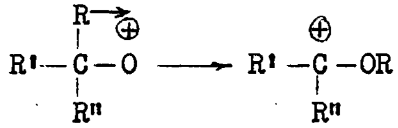
The above-mentioned difficulties in obtaining organometallic compounds led us to investigate two other modes of introducing the methoxyl group into the molecule, which are discussed in sections 5 and 6 below.

4. Reaction of Dimethyl Peroxide with Sulfuric Acid

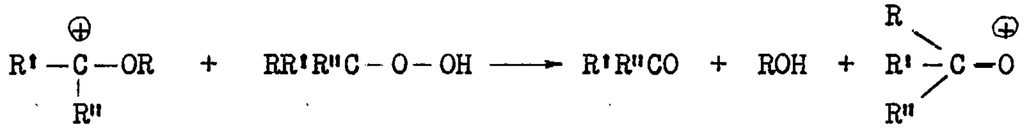
The decomposition of hydroperoxides was studied by Kharasch and his co-workers(29,30), who found that one mode of decomposition was that catalyzed by strong acids (in the Lewis sense). Thus with α-cumyl hydroperoxide the products were exclusively phenol and acetone. The following mechanism was suggested by these workers to elucidate the acid-catalyzed decomposition:

(11) 

$$R'-\underset{R''}{\overset{R}{C}}-O-O-H \quad + \quad H^+ \longrightarrow R'-\underset{R''}{\overset{R}{C}}-\overset{\oplus}{O} \quad + \quad H_2O$$

(12) 

$$R'-\underset{R''}{\overset{R\rightarrow}{C}}-\overset{\oplus}{O} \longrightarrow R'-\underset{R''}{\overset{\oplus}{C}}-OR$$

(13) 

$$R'-\underset{R''}{\overset{\oplus}{C}}-OR \quad + \quad RR'R''C-O-OH \longrightarrow R'R''CO \quad + \quad ROH \quad + \quad \underset{R''}{\overset{R}{R'}}\!\!>C-\overset{\oplus}{O}$$

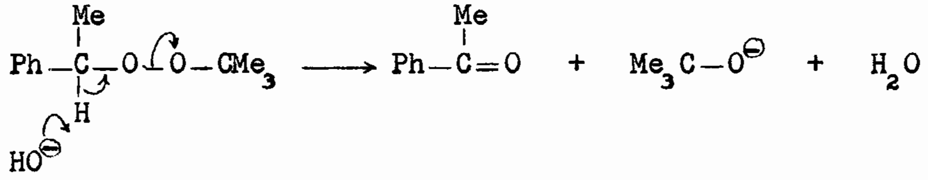
This decomposition was found to be general for tertiary, secondary and primary hydroperoxides, the migrating group predominantly being the most electronegative one. In order that the rearrangement in reaction (12) may take place readily, at least one of the groups R, R', R'' should be aromatic; t-alkyl hydroperoxides seem to be stable towards acids(30).

In the course of their study of the decomposition of hydroperoxides, Kharasch and Burt(30) suggest that unsymmetrical peroxides are subject to acid cleavage of the type.

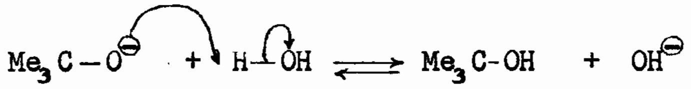
(14) $$R-O-O-R' \quad + \quad H^+ \longrightarrow R-O^{\oplus} \quad + \quad R'-OH$$

where the carbinol formed is predominantly or exclusively that derived from the less electronegative radical, but give no experimental examples of such reactions.

In contrast with the acid-catalyzed decomposition of peroxides and hydroperoxides, the base-catalyzed decomposition follows an E_2 mechanism and takes place equally well with peroxides and hydroperoxides with or without an aromatic nucleus, provided that one of the carbon atoms attached to the peroxide linkage is not tertiary(31).

(15) 

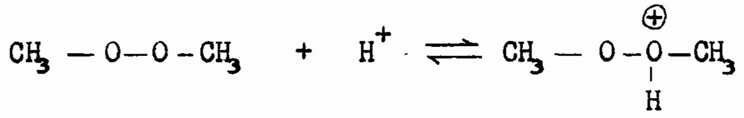
$$\mathrm{Ph-\underset{H}{\overset{Me}{C}}-O-O-CMe_3 + HO^{\ominus} \longrightarrow Ph-\overset{Me}{C}=O + Me_3C-O^{\ominus} + H_2O}$$

(16) 

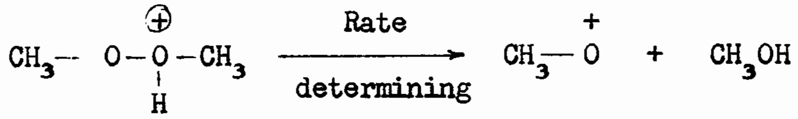
$$\mathrm{Me_3C-O^{\ominus} + H-OH \rightleftharpoons Me_3C\text{-}OH + OH^{\ominus}}$$

So far, no examples of a similar acid-catalyzed elimination reaction of symmetrical dialkyl peroxides have been reported.

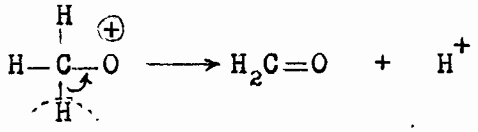
We have now found that decomposition of dimethyl peroxide to formaldehyde (and presumably methanol) takes place in 95%, but not in 85% sulfuric acid. This strong dependence on acid concentration indicates an E_1 mechanism as shown:

(17) 

$$\mathrm{CH_3-O-O-CH_3 + H^+ \rightleftharpoons CH_3-O-\underset{H}{\overset{\oplus}{O}}-CH_3}$$

(18) 

$$\mathrm{CH_3-O-\underset{H}{\overset{\oplus}{O}}-CH_3 \xrightarrow[\text{determining}]{\text{Rate}} CH_3-\overset{+}{O} + CH_3OH}$$

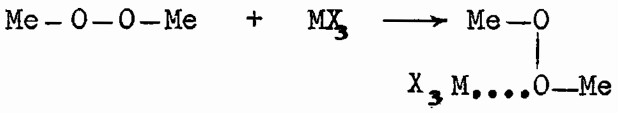
(19) 

$$\mathrm{H-\underset{H}{\overset{H}{C}}-\overset{\oplus}{O} \longrightarrow H_2C=O + H^+}$$

(An E_2 mechanism in which fission of the O-O bond was synchronous with the removal of a proton by a water molecule, would be expected to go faster in 85% than in 95% acid). The yield of formaldehyde from the reaction in 95% acid was only 25%, but the aldehyde is known to react with acid of this strength(32). This poor yield nullifies the usefulness of the reaction as a quantitative analytical method. However, since sensitive tests for formaldehyde are available, it might be used for the qualitative detection of dimethyl peroxide.

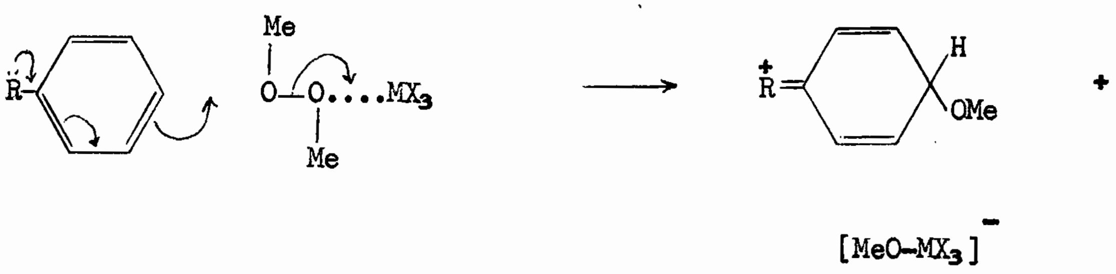
5. Attempted Methoxylation of Aromatic Compounds under Friedel-Crafts Conditions

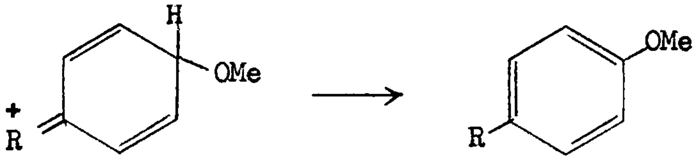
It was seen in the preceding section that the decomposition of dimethyl peroxide in sulfuric acid probably involves the formation of a methoxyl cation. Since the decomposition of hydroperoxides takes place in Lewis acids(29), it would be reasonable to assume that such Lewis acids might also catalyze the decomposition of a dimethyl peroxide into methoxyl cations, or form a peroxide-Lewis acid complex:

(20) 

$$\mathrm{Me-O-O-Me} + \mathrm{MX_3} \longrightarrow \begin{array}{r} \mathrm{Me-O} \\ | \\ \mathrm{X_3M\cdots O-Me} \end{array}$$

Hence, the reaction of dimethyl peroxide with various aromatic compounds in the presence of Lewis acids was next investigated in the hope that a Friedel-Crafts type of substitution (cf. Brown et al.(33,34)) might take place:





However, the formation of methoxy compounds could not be detected when dimethyl peroxide was introduced into solutions containing anisole and boron trifluoride, naphthalene and stannic chloride, and naphthalene and aluminum chloride, even by the use of sensitive infrared spectroscopic methods. It is uncertain whether this failure stems from the weakness of the Lewis acids in the solvents employed, or from the decomposition of the methoxyl cation to formaldehyde before it had time to attack the aromatic compounds.

6. Attempted Free-radical Methoxylation of Aromatic Compounds with Dimethyl Peroxide

Dimethyl peroxide decomposes at elevated temperatures to give methoxyl radicals(35,36), which can react with each other in a number of ways(36).

(21) $CH_3-O-O-CH_3 \longrightarrow 2CH_3O.$

(22) $CH_3O. + CH_3O. \longrightarrow CH_3\text{-}OH + H_2CO$

(23) $CH_3O. + H_2CO \longrightarrow CH_3\text{-}OH + HCO.$

(24) $CH_3O. + HCO. \longrightarrow CH_3OH + CO$

At 167° the decomposition should be very rapid(35,36). Since hydroxyl radical, generated from Fenton's reagent(37,38,39), attacks benzene(40), phenol(41) and naphthalene(42), to give small amounts of phenol, catechol and naphthols respectively, it was hoped that methoxyl radicals might similarly substitute aromatic compounds. Naphthalene was chosen because of its known reactivity to radical attack(42,43,44). However, the formation of methoxy compounds from the reaction of naphthalene and dimethyl peroxide at elevated temperatures could not be detected. Infrared studies of the reaction product (Fig. 3) showed absence of the band at 2815-2832 cm.$^{-1}$ characteristic of the methoxyl group(45) and present in 1- and 2-methoxynaphthalene at 2820 cm.$^{-1}$ (Fig. 4). Yet, in separate experiments (cf. p.57) it was shown that about 75% of the peroxide was being decomposed (presumably to methoxyl radicals). It would appear in consequence that, under these conditions, the methoxyl radical acts only as a dehydrogenating agent(46,47).

$$C_{10}H_8 + CH_3O\cdot \longrightarrow C_{10}H_7\cdot + CH_3OH$$

$$C_{10}H_7\cdot + C_{10}H_7\cdot \longrightarrow C_{10}H_7{-}C_{10}H_7\cdot$$

No attempt was made to isolate binaphthyl from the reaction.

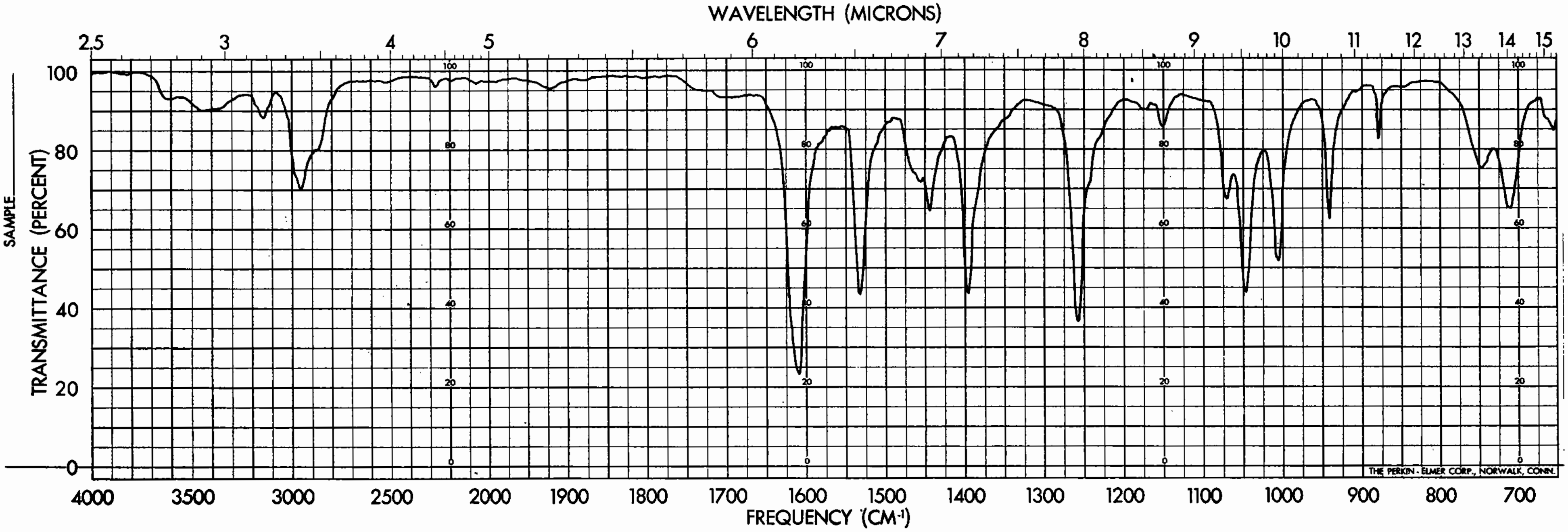


Figure 1. Infrared Absorption Spectrum of 2-Methoxyfuran.

(liquid film)

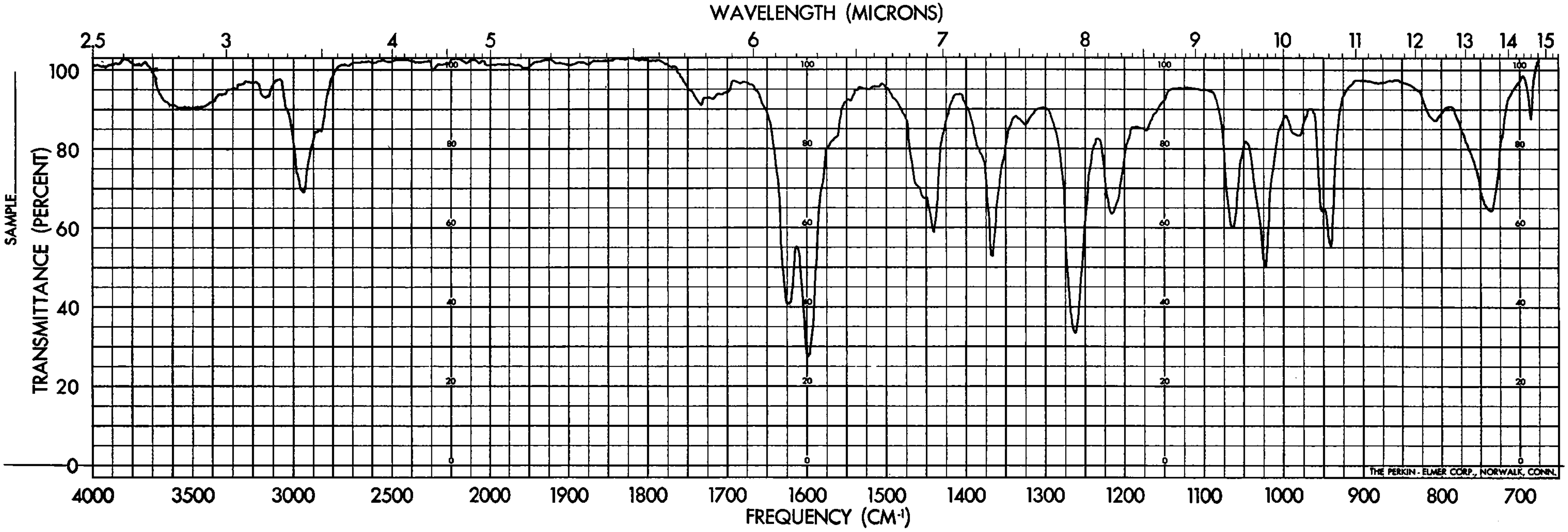
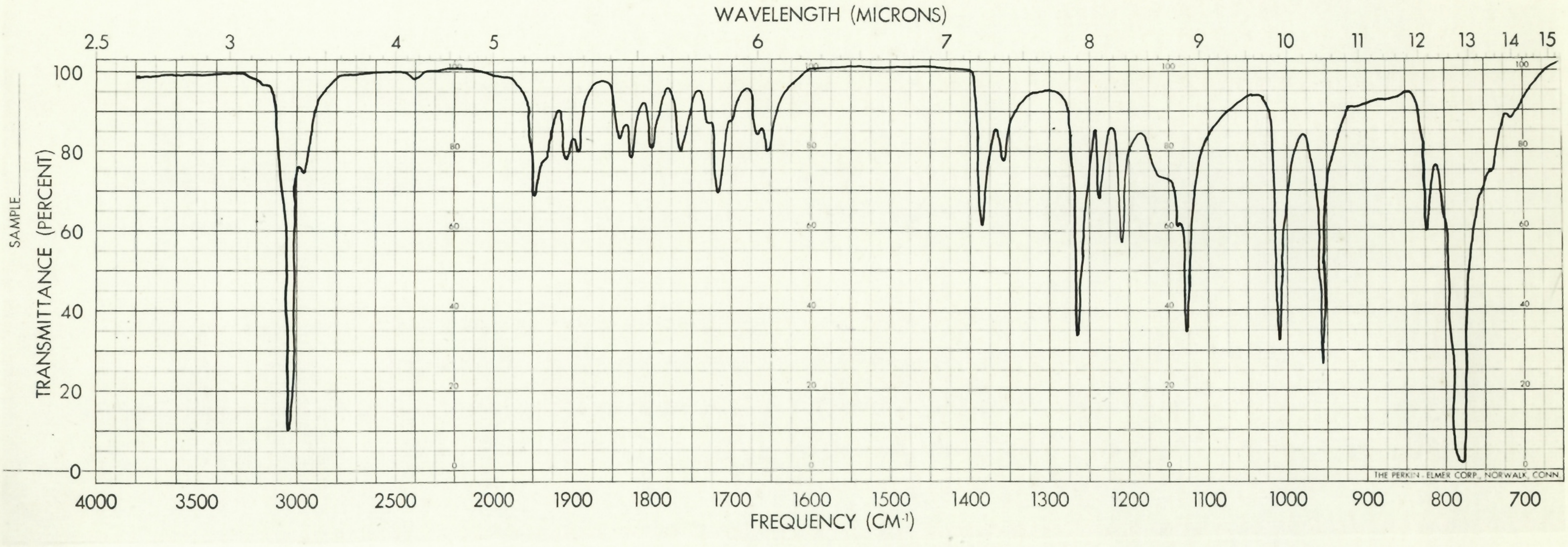


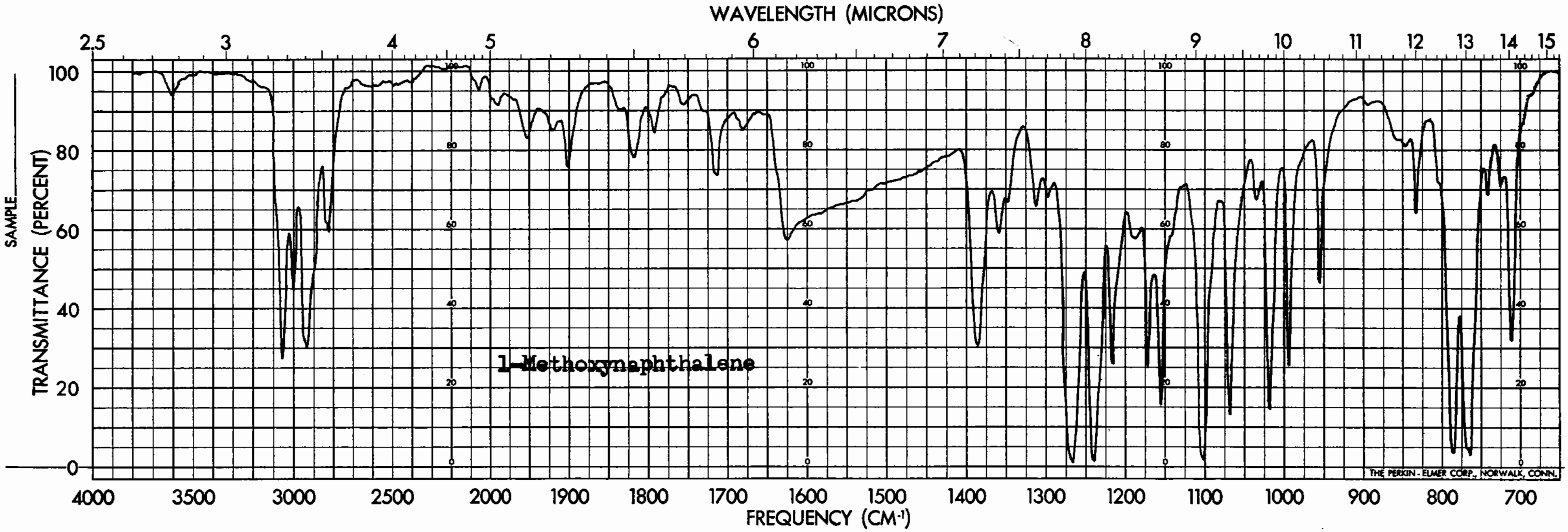
Figure 2. Infrared Absorption Spectrum of 2-Methoxy-5-Methylfuran.

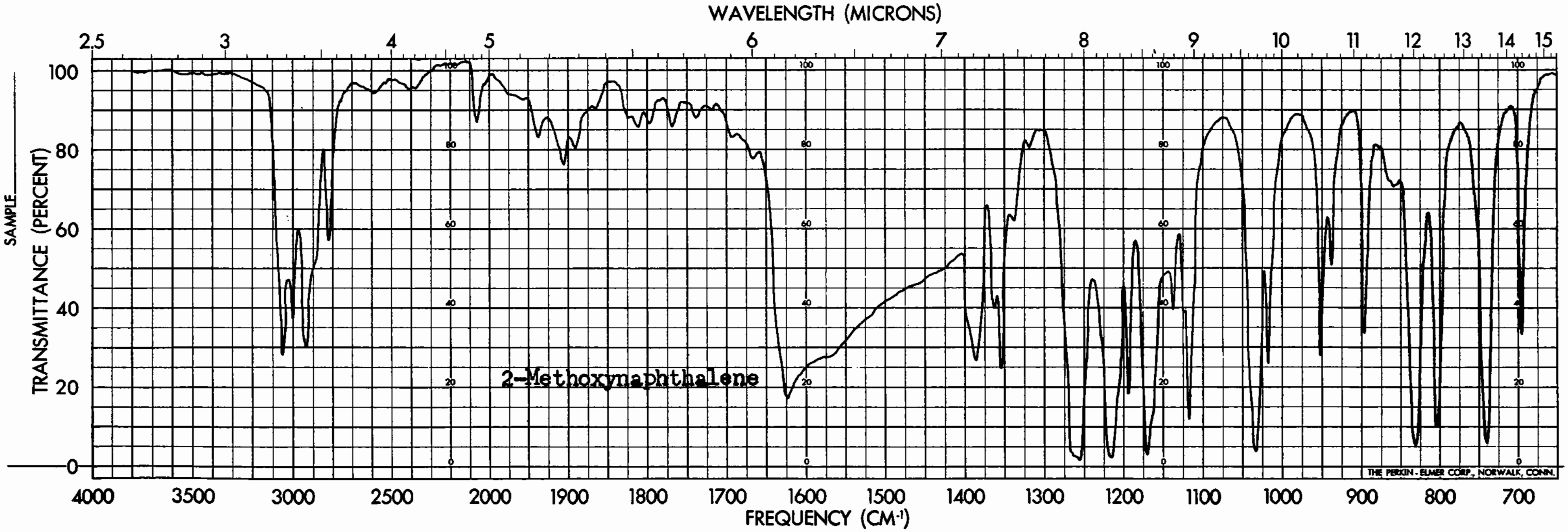
(liquid film)

FIGURE 3

Infrared spectrum of
Product of Reaction
between
Naphthalene and Dimethyl Peroxide
(In CS_2 solution)


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
11
12
13
14
15
SAMPLE
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM⁻¹)
THE PERKIN - ELMER CORP., NORWALK, CONN.


1-Methoxynaphthalene


2-Methoxynaphthalene

EXPERIMENTAL

Dimethyl Peroxide

Dimethyl peroxide was prepared according to the directions of Rieche(9) but, rather than collecting the pure compound, the peroxide, in a stream of nitrogen, was passed through a long Drierite column and then into dry ether cooled by dry ice-acetone mixture. The ether solution was safe to handle and could be stored in the ice-box without apparent deterioration.

Analysis of Dimethyl Peroxide

The method employed was a slight modification of Rieche's method(9). Dimethyl peroxide, prepared from 10 ml. of 10% hydrogen peroxide, 7.5 g. of dimethyl sulfate and 11 g. of potassium hydroxide in 15 g. of water, was carried by a stream of nitrogen into 100 ml. of dry ether (peroxide free) cooled in dry ice-acetone mixture. Ten ml. of the ether solution were then mixed with 5 ml. of standard aqueous stannous chloride solution, the flask stoppered tightly, and the contents stirred magnetically for two hours. The ether layer was separated and washed quickly with two 10 ml. portions of water, and the aqueous washings combined with the stannous chloride layer. Standard iodine solution (10 ml.) was added to the aqueous solution, which was then back titrated with standard thiosulfate solution. Such a titration indicated generally a yield of 71% of peroxide collected in the ether solution.

Infrared Absorption Spectra Determinations

A Perkin-Elmer Model 21 double beam recording infrared spectrophotometer equipped with a sodium chloride prism was used for the determination of infrared spectra. All spectra of liquid compounds were studied by preparing thin contact films of the liquids between two sodium chloride plates. This technique was also used with syrups. Solids were studied by preparing 2% solutions of them in "spectro grade" carbon tetrachloride or carbon disulfide. In some cases, when the solids were insoluble in the above-mentioned solvents, mulls in Nujol or Fluorolube were used.

In reporting the band intensities in infrared at the various frequencies, the following way was used: very strong (vs), strong (s), medium (m), weak (w), shoulder (sh) and broad (bd).

Reaction of Dimethyl Peroxide with Organometallic Compounds

General Procedure: The organometallic compound was prepared in the usual way in a three-necked flask equipped with an efficient reflux condenser, a nitrogen inlet tube, and a dropping funnel. Stirring was done magnetically. The mixture was cooled to -10° to 0° and the cold ethereal dimethyl peroxide solution was slowly added through the dropping funnel. The solution was gradually brought up to room temperature (20-30 minutes), then decomposed with cold dilute acid. In the case of furan compounds, the decomposition was done with ice water only. The ether layer was separated, and the aqueous layer extracted several times with ether. The combined ether extracts were dried and worked up in the usual way. The identification of the products of the reaction with various organometallic compounds is described below. The yields of the products were based on the quantity of peroxide used.

(a) With phenylmagnesium bromide:- The reagent from 0.2 moles of bromobenzene and 0.26 g.-atoms of magnesium reacted with 0.08 moles of peroxide. After removal of the ether, the remaining liquid was distilled using a 5 cm. Vigreux column. The fraction boiling at 150-155° was collected and weighed 5.3 g. On the basis of its refractive index (n^{24}_{D}1.5151), its nitro derivative (m.p. 86°) and its infrared spectrum ($\lambda_{max.}$ at: 3040 (s), 2960 (s), 2840 (s), 2000-1680 (w) bands, 1600 (s), 1500-1450 (s,bd), 1300 (s), 1250 (vs), 1175 (m) 1075 (m), 1040 (s), 880 (m), 785 (s), 750 (s) and 690 (m) cm.$^{-1}$, the compound was identified as anisole (b.p. 154°,n^{24}_{D}1.5152, dinitro derivative m.p. 86° and infrared spectrum identical with above). Mixed m.p. of dinitro derivative with nitro derivative above 86°. Yield, 62%. A second fraction was collected at 250°-260° and solidified in the receiver to give white crystals m.p. 69-70°. Mixed m.p. with authentic biphenyl 70-71°. Yield, 1.28 g. (20.3%).

(b) With phenyllithium:- The reagent prepared from 0.2 moles of bromobenzene and 0.42 g.-atoms of lithium reacted with 0.08 moles of dimethyl peroxide gas (carried into the solution by nitrogen and dried by means of a long Drierite column). The separation and identification of the products were the same as in (a). Yield of anisole: 5.41 g., (62.5%); yield of biphenyl: 1.5 g., (19.5%).

(c) With p-anisylmagnesium bromide: The reagent prepared from 0.1 mole of p-bromoanisole and 0.13 g.-atoms of magnesium reacted with 0.04 moles of peroxide in solution. A solid separated from the reaction mixture and was removed by filtration. The ether layer was then evaporated and the oil remaining was fractionally distilled under reduced pressure. A clear oil was collected at 88°-96°/6 mm. which solidified in the receiver to give plates, m.p. 54.5-55°, mixed m.p. with authentic p-dimethoxybenzene was 55°. The compound gave an identical infrared spectrum with that of p-dimethoxybenzene; $\lambda_{max.}^{CCl_4}$ at: 3000 (sh), 2940 (s), 2835 (m), 1610 (w), 1590 (w), 1500 (s), 1460 (s), 1440 (s), 1290 (s), 1215 (s), 1175 (s), 1100 (s), 1040 (s), 700 (w) cm.$^{-1}$ The solid that separated from the reaction mixture was recrystallized twice from alcohol to give white plates m.p. 172°. A similar solid was obtained from the residue of distillation on recrystallization from alcohol, m.p. 170°, mixed melting point with above solid 171.5°. Reported m.p. for 4,4'-bianisyl is 172°. Total yield: 2.25 g., (26.3%).

(d) With p-anisyllithium: The reagent(48) prepared from 0.1 mole of p-bromoanisole and 0.23 g.-atoms of lithium was treated with 0.04 moles of peroxide solution. The ether was removed and the residue was worked up as in (c). In this case the fraction boiling between 86°-96°/6 mm. did not solidify and gave a positive Beilstein test for halogens. By repeated chilling and quick filtration, pure p-dimethoxybenzene (4.7 g.; 45%) was obtained and identified as in (c) above. From the residue, 4,4'-bianisyl was obtained (1.73 g., 20.3%) by recrystallization from alcohol.

(e) With p-biphenylmagnesium bromide:- The reagent prepared from 0.1 mole of p-bromobiphenyl and 0.13 g.-atoms of magnesium was treated with 0.08 moles of peroxide solution. The ether was removed by evaporation leaving fine crystals m. p. 66°-70°. On recrystallization from petroleum ether, plates melting at 83.5°-85° were obtained. The mixed melting point with authentic p-methoxybiphenyl (actual m.p. 84-85°) was not depressed. The infrared spectrum was identical with that of p-methoxybiphenyl; $\lambda_{max.}^{CCl_4}$ at: 3040 (m), 2950 (m), 2840 (m), 1610 (s), 1485 (s), 1465 (m), 1443 (m), 1295 (s), 1270 (s), 1240 (s), 1175 (s), 1045 (s) and 690 (m) cm.$^{-1}$ Yield: 7.8 g., 53%. Only traces of a solid insoluble in ether (probably quaterphenyl) were obtained.

(f) With p-biphenyllithium:- The reagent prepared from 0.1 mole of p-bromobiphenyl and 0.23 g.-atoms of lithium was treated with 0.08 moles of peroxide solution. A solid, insoluble in both ether and water, separated and was recrystallized from nitrobenzene, m.p. 305-307°. No depression in melting point was observed when the solid was mixed with authentic quaterphenyl. Yield of crude compound: 1.4 g., (11.4%). On evaporation of the ether solution, 16 g. of a crude solid m.p. 65-70° were obtained. Recrystallization from petroleum ether gave 9.5 g. (65%) of pure crystals m.p. 83-84°. A mixed melting point and the infrared spectrum of the compound showed it to be p-methoxybiphenyl.

(g) With 2-naphthyllithium:- The reagent(48) from 0.1 mole of 2-bromonaphthalene and 0.23 g.-atoms of lithium was treated with 0.08 moles of peroxide solution. An insoluble solid separated from the ether solution, and was recrystallized from benzene giving white flakes melting at 180° (reported m.p. for 2,2'-binaphthyl is 187°). Yield of <u>crude</u> solid: 3.05 g. (30%). The ether solution was evaporated and the crude residue was purified by chromatography on alumina (neutral grade, activity one). Naphthalene came down with petroleum ether (67-69°), followed by pure 2-methoxynaphthalene (2.8 g.; 21%) on elution with benzene-petroleum ether 40:60. Melting point 72°, infrared spectrum identical with that of authentic 2-methoxynaphthalene (Fig. 4); $\lambda_{max.}^{CS_2}$ at: 3080 (s), 3020 (m), 2960 (s), 2840 (m), 1628 (vs), 1390 (s), 1355 (s), 1258 (vs), 1220 (vs), 1195 (s), 1170 (vs), 1120 (s), 1035 (vs), 1020 (s), 953 (s), 897 (s), 830 (vs), 805 (vs), 740 (vs) and 695 (s) cm.$^{-1}$

(h) <u>With 2-furyllithium</u>:- <u>n</u>-Butyllithium reagent(11) prepared from 0.5 moles of <u>n</u>-butyl bromide, was added with slight cooling to 0.6 moles of furan(10) and the mixture stirred and refluxed for six hours. To the resulting 2-furyllithium, 0.16 moles of dimethyl peroxide solution were added over a period of twenty minutes. The reaction product was then decomposed with ice water and extracted with ether (acid decomposition was avoided). The ether extract was dried overnight in the ice-box, the ether removed by distillation using a Vigreux column (2 by 20 cm.) and the residual transferred to a semi-micro distilling flask with a Vigreux column (1 by 5 cm.). The clear liquid boiling at 108.5-111°/761.4 mm. was collected. The product weighed 7.64 g. (49%), n_D^{20} 1.4380, d_4^{20} 1.0147. MR_D (calc.) 25.439. MR_D (found) 25.21. (Reported(12) MR_D 25.1). Maleic anhydride adduct m.p. 118° (decomp.) (reported(12) m.p. 120°). The infrared spectrum of the liquid film (Fig. 1) shows absorption maxima at: 3140 (w), 2960 (m), 2860 (sh), 1610 (s), 1445 (m), 1396 (s), 1258 (s), 1070 (m), 1047 (s), 1006 (s), 942 (m), 878 (w), 745 (m), 710 (m) and 655 (w) cm.$^{-1}$. Cava et al.(49) reported the peaks at 1535, 1396 and 1006 cm.$^{-1}$

(i) With 2-methyl-5-furyllithium: The reagent was prepared from 0.5 moles of sylvan (2-methylfuran) and n-butyllithium (prepared from 0.5 moles of n-butyl bromide) following the procedure above for 2-furyllithium, except that the time of reflux was reduced to three hours. The peroxide solution (0.16 moles of peroxide) was added to the metallation product during the period of thirty minutes and the ether solution distilled to remove the ether. The residue was then transferred to a semi-micro distilling flask and fractionated using a Vigreux column (1 by 5 cm.). The clear liquid boiling at 128-130°/761 mm. was collected and weighed 1.5 g. The compound was identified as 2-methoxy-5-methylfuran by its NMR spectrum (Fig.) and its infrared spectrum (Fig. 2) which showed characteristic furan C-H stretching frequencies at 3150 (w) and 3120 (w) cm.$^{-1}$, ring stretching frequencies at 1623 (s), 1597 (s), 1462 (sh) and 1387 (sh) cm.$^{-1}$, C-H in-plane deformation frequencies at 1215 (m), 1170 (sh) and 1065 (m) cm.$^{-1}$, ring breathing frequency at 1022 (m) cm.$^{-1}$, C-H out-of-plane deformation frequencies at 950 (sh), 940 (m) and 807 (w) cm.$^{-1}$ as well as characteristic frequencies for the methoxyl group at 2850 (sh) cm.$^{-1}$, for the ether linkage at 1262 (s) cm.$^{-1}$ and for the methyl group C-H stretching at 2960 (m) asymmetrical and 2880 (sh) cm.$^{-1}$ symmetrical vibration and C-H deformation at 1440 (m) asymmetrical and 1360 (m) cm.$^{-1}$ symmetrical vibrations.

(j) With triphenylmethylsodium:- The reagent, prepared according to "Organic Syntheses"(50) from 0.114 moles of triphenylchloromethane and 0.25 g.-atoms of sodium amalgam, was treated with 0.08 moles of peroxide. During the period of addition of the peroxide (20 minutes), the color of the triphenylmethylsodium solution changed from deep red to yellow. The syrup remaining after evaporation of the ether crystallized only with difficulty from petroleum ether to give crystals of triphenylmethane, but only intractable gums could be obtained on evaporation of the mother liquor. The infrared spectrum (Fig. 5) of the syrup however, showed clearly an absorption of medium intensity at 2825 cm.$^{-1}$ characteristic of the methoxyl group(45) and present in the spectrum of methoxytriphenylmethane (Fig. 6), as well as the 2880 cm.$^{-1}$ band for the C-H stretching vibration in triphenylmethane(51) (Fig. 7).

Another experiment was carried out with diethyl peroxide(52) and here again the infrared spectrum of the product (Fig. 8) showed the presence of an ether linkage at 1085 (s) cm.$^{-1}$ as well as CH_3 and CH_2 asymmetrical C-H stretching frequencies at 2980 (m) and 2940 (m) cm.$^{-1}$ (slight shift to higher frequencies) and C-H stretching for triphenylmethane at 2880 (m) cm.$^{-1}$

Reaction of Dimethyl Peroxide with Sulfuric Acid

Dimethyl peroxide (1.3 g., 0.02 moles) diluted with nitrogen was bubbled into 25 ml. of 95% sulfuric acid over a period of forty minutes. One ml. of the acid solution was then removed immediately and placed in a round-bottomed flask, diluted with water, and steam-distilled. The distillate was collected in a flask containing 75 ml. of saturated dimedone solution. The formaldehyde, determined according to the procedure of Yoe and Reid(53), amounted to 0.155 g. (25% yield).

A similar experiment using 85% sulfuric acid, gave only a trace of formaldehyde.

Attempted Methoxylation of Aromatic Compounds under Friedel-Crafts Conditions

An attempt was first made to obtain a solution of dimethyl peroxide in carbon disulfide. However, the peroxide formed a turbid mixture which exploded violently on slight shaking. The experiments were conducted, therefore, by passing the gas, carried by nitrogen, directly into the reaction mixture.

The aromatic compound, with or without a solvent, was contained in a two-necked round-bottomed flask equipped with an efficient reflux condenser and a gas inlet tube. Stirring was done magnetically using a teflon-covered stirring bar.

(a) Anisole and Boron trifluoride

Dimethyl peroxide (0.08 moles) in 25 ml. of dry ether, was added slowly to a cold mixture of anisole (108 g., 1 mole) and boron trifluoride etherate (0.2 moles). The mixture was left at room temperature overnight then fractionally distilled. Small amounts of phenol were obtained together with unchanged anisole. No dimethoxybenzene could be found in the tarry residue as shown by the absence of a peak in its infrared spectrum at 1150 cm.$^{-1}$ characteristic of p-dimethoxybenzene.

(b) Naphthalene and Stannic Chloride

Naphthalene (10.24 g., 0.08 moles) was dissolved in nitromethane (30 ml.) and mixed with stannic chloride (20.8 g., 0.08 moles) in a dry box. Dimethyl peroxide gas (0.08 moles) was passed through the mixture, which was cooled to 0°C. during the addition. Distillation of the nitromethane followed by chromatography on an alumina column (activity one) of the tarry residue, afforded only naphthalene. The absence of any methoxynaphthalene was shown by the absence of peaks at 2940, 2825, 1255, 1195, 1170 and 1155 cm.$^{-1}$ in the infrared spectra of the crude fractions from the column.

(c) Naphthalene and Aluminum Chloride

Naphthalene (10.24 g., 0.08 moles) was dissolved in carbon disulfide (50 ml.) and mixed with anhydrous aluminum chloride (13.3 g., 0.1 mole) in a dry box. Dimethyl peroxide gas (0.08 moles) was passed through the cooled mixture. Carbon disulfide was removed by distillation and the residue was chromatographed on an alumina column (activity one) from which naphthalene, identified by melting point, mixed melting point (82°) and infrared spectrum, was obtained by elution with light petroleum. The spectrum showed the absence of peaks between 3000 and 2800 cm.$^{-1}$ No other material could be obtained from the alumina column on elution with benzene. (In a trial separation it was found that 2-methoxynaphthalene came down in 40% benzene-light petroleum).

Attempted Free-radical Methoxylation of Aromatic Compounds with Dimethyl Peroxide

A. At elevated temperatures:- In a 500 ml. two-necked round-bottomed flask, equipped with a 60-cm. air condenser and a gas inlet tube, was placed 100 g. of naphthalene (0.78 moles). The naphthalene was heated to reflux temperature, and a total of 0.2 moles of dimethyl peroxide, in a stream of nitrogen, was bubbled through. Infrared analysis of the dried product (Fig. 3) showed the absence of peaks at 2940 cm.$^{-1}$, 2825 cm.$^{-1}$ (C-H vibration in methoxy group), 1255 cm.$^{-1}$, 1195 cm.$^{-1}$, 1170 cm.$^{-1}$ and 1155 cm.$^{-1}$ which would indicate the presence of any methoxynaphthalene.

The following variations of the above experiment were also tried:

(1) The naphthalene was heated to 120° only.

(2) The lower half of the air condenser was heated to 220°, while the naphthalene was refluxing.

(3) Boiling anisole was used instead of naphthalene.

Negative results were obtained in all cases as shown by infrared spectroscopy, no peaks for 1- or 2-methoxynaphthalene or p-dimethoxybenzene being observed.

Another experiment was done, with the dimethyl peroxide in nitrogen gas passing through boiling naphthalene then into 25 ml. of 95% sulfuric acid. One ml. of the acid solution was then steam-distilled as before (see preceding section), and gave 6.4% of the theoretical quantity of formaldehyde.

This indicated that about 75% of the peroxide was being destroyed in the naphthalene.

B. <u>At ordinary temperatures</u>:- To a solution of triphenylmethyl radicals(54) in benzene (prepared from 0.066 moles of triphenylchloromethane and 0.63 g.-atoms of zinc dust) was added 0.08 moles of peroxide in <u>benzene</u> solution. The solution thus obtained was stirred under nitrogen atmosphere for thirty minutes, then air was bubbled through to change the unreacted radical into the insoluble triphenylmethyl peroxide, which was identified by its melting point (186° (decomp.)) and infrared spectrum (peak at 895 $cm.^{-1}$ for peroxides(55)). The benzene solution was evaporated to dryness and the solid examined by infrared (Fig. 9). It showed no absorption in the region 3000-2800 $cm.^{-1}$ and coincided with the infrared spectrum of triphenylchloromethane. Recrystallization from benzene gave colorless plates m.p. 108-110°; mixed m.p. with an authentic sample of triphenylchloromethane was 109-110°.

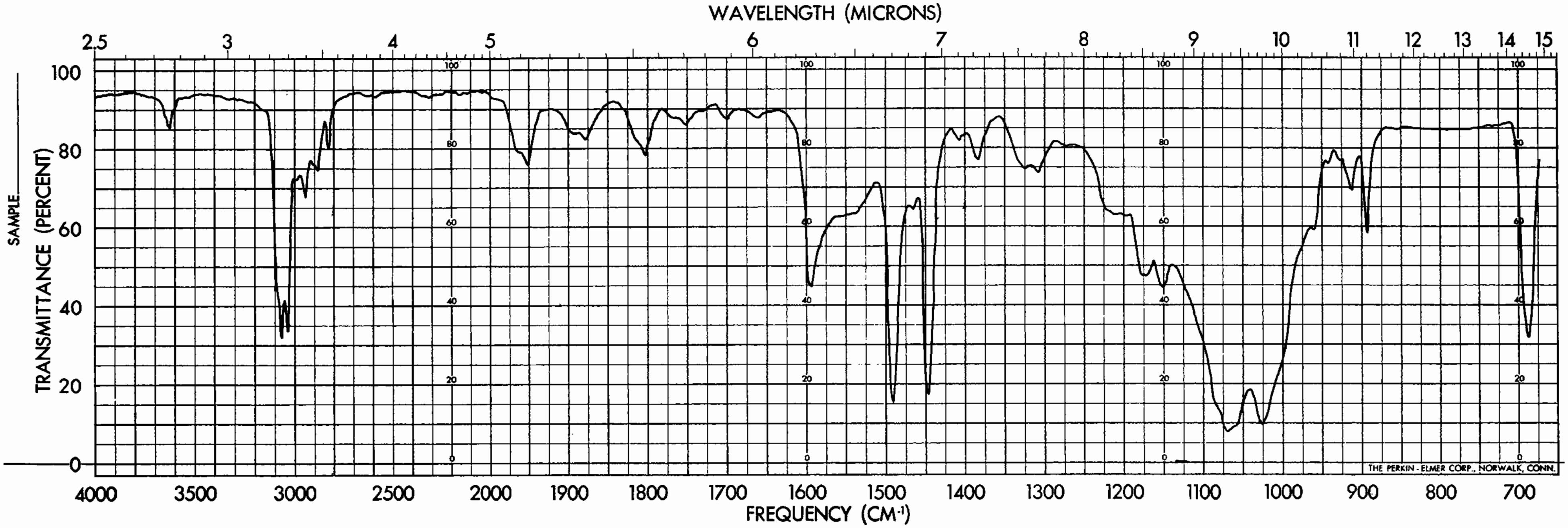


Figure 5. Infrared Absorption Spectrum of Product of Reaction between Triphenylmethylsodium and Dimethyl Peroxide.

(2% CCl_4 solution)

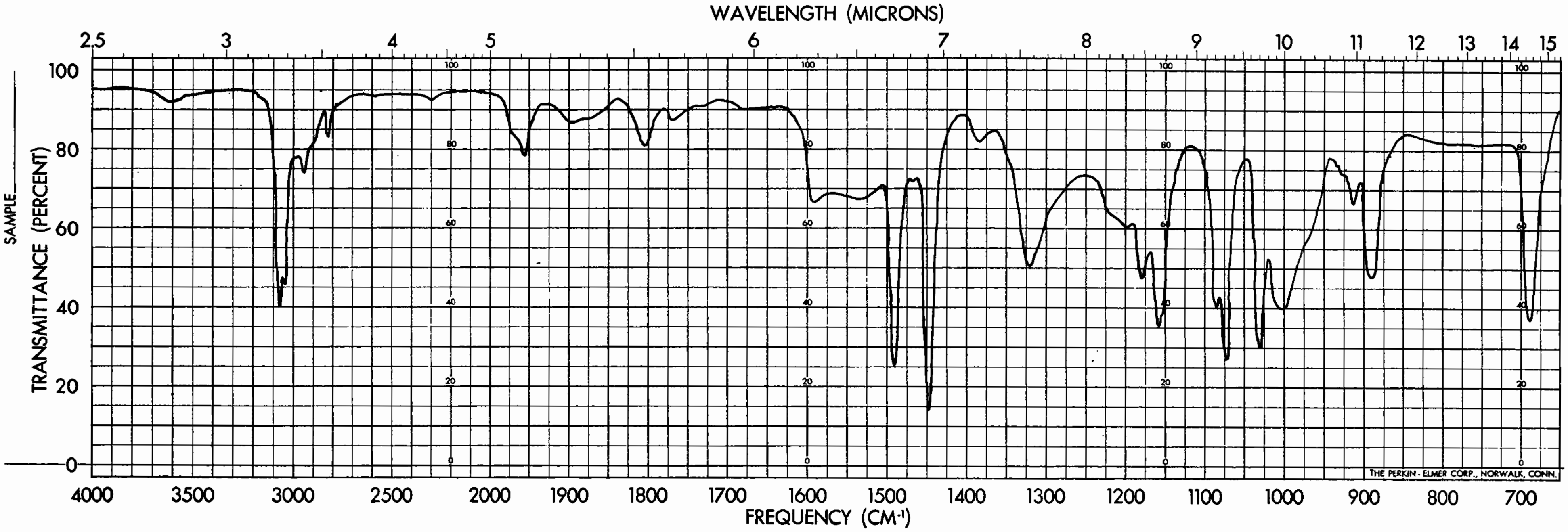


Figure 6. Infrared Absorption Spectrum of Methoxytriphenylmethane.

(2% CCl_4 solution)

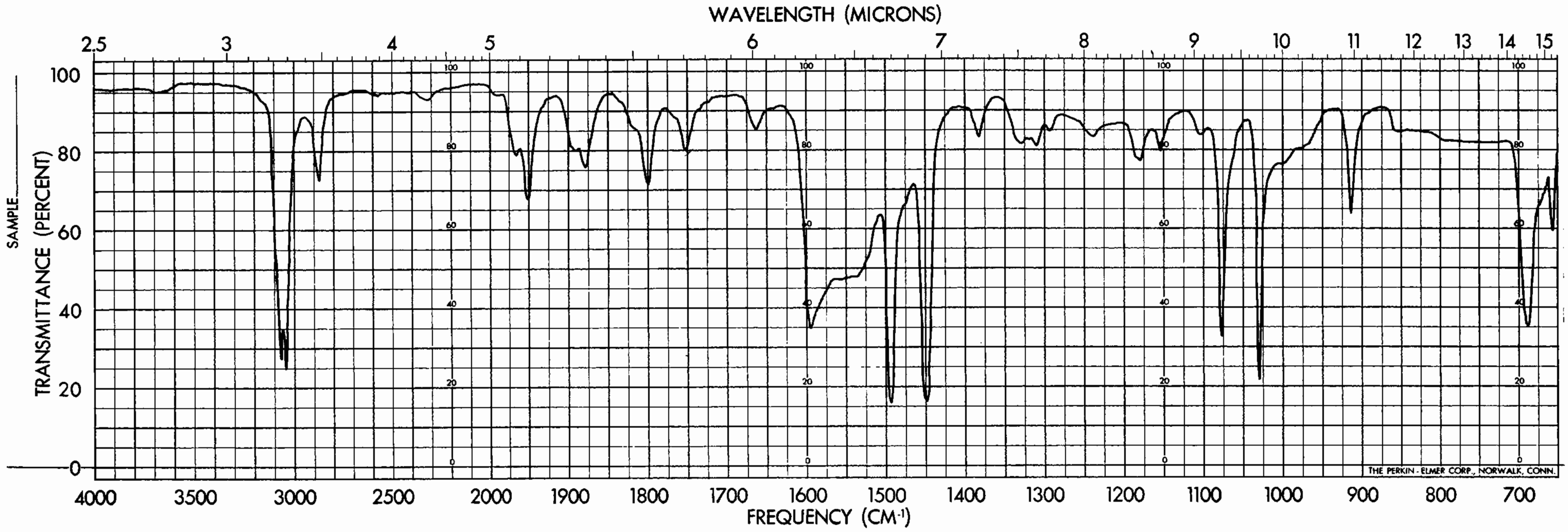


Figure 7. Infrared Absorption Spectrum of Triphenylmethane.

(2% CCl_4 solution)

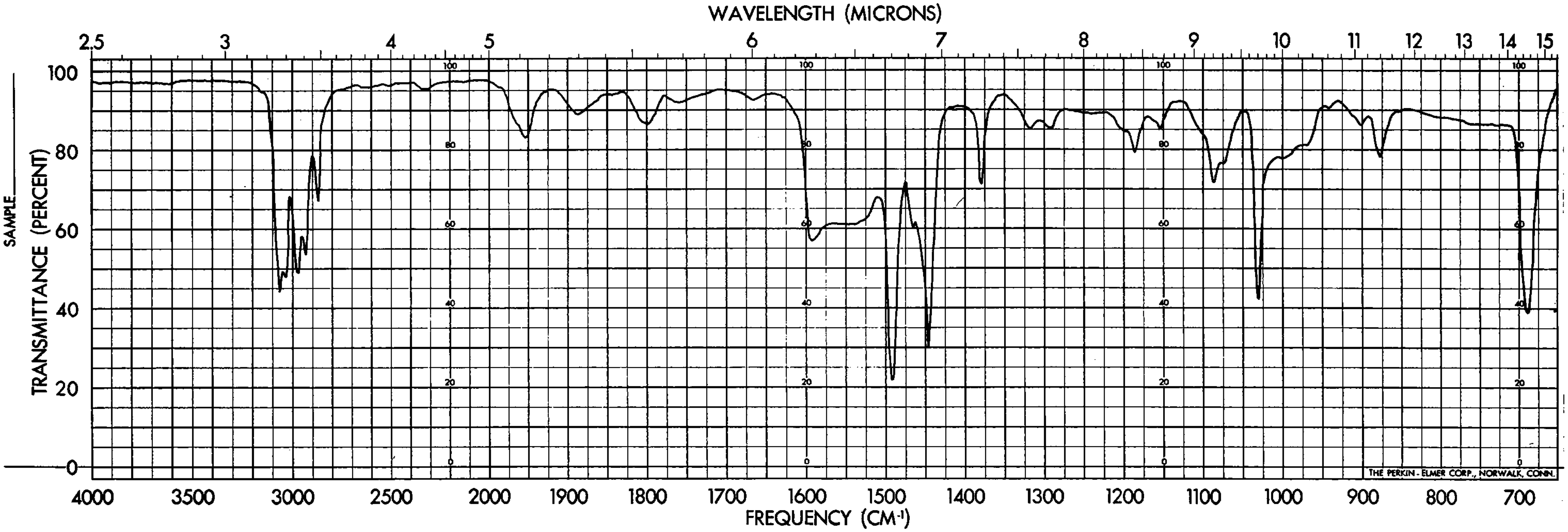


Figure 8. Infrared Absorption Spectrum of Product of Reaction between Triphenylmethylsodium and Diethyl Peroxide.

(2% CCl_4 solution)

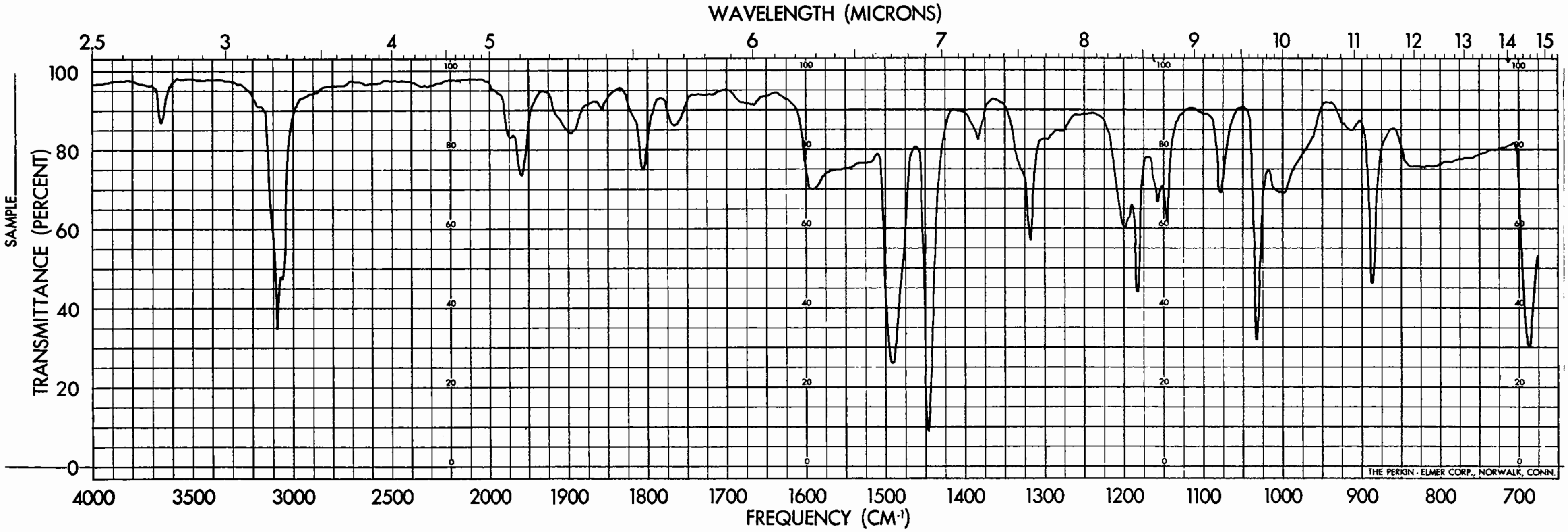


Figure 9. Infrared Absorption Spectrum of Product of Reaction between Triphenylmethyl Radicals and Dimethyl Peroxide.

(2% CCl_4 solution)

BIBLIOGRAPHY

1. Wuyts, H., Bull. soc. chim., [3], 35, 166 (1906).
2. Oddo, B. and Binaghi, R., Gazz. chim. ital., 54, 193 (1924).
3. Gilman, H. and Adams, C.H., J. Am. Chem. Soc., 47, 2816 (1925).
4. Campbell, T.W., Burney, W. and Jacobs, T.L., J. Am. Chem. Soc., 72, 2735 (1950).
5. Kharasch, M.S. and Reinmuth, O., "Grignard Reactions of Nonmetallic Substances", Prentice-Hall Inc., New York, 1954.
6. Tobolsky, A.V. and Mesrobian, R.B., "Organic Peroxides", Interscience Publishers, Inc., New York, 1954.
7. Lawesson, S. and Yang, N.C., J. Am. Chem. Soc., 81, 4230 (1959).
8. Lawesson, S., Yang, N.C. and Kharasch, M.C., Abstract of Papers - Am. Chem. Soc. Meeting, Chicago, 1958, p. 56P.
9. Rieche, H. and Brumshagen, W., Ber. 61, 951 (1928).
10. Truce, W. and Wellisch, E., J. Am. Chem. Soc., 74, 5177 (1952).
11. Gilman, H., Beel, J.A., Brannen, C.G., Bullock, M.W., Dunn, G.E. and Miller, L.S., J. Am. Chem. Soc. 71, 1499 (1949).
12. Petfield, R.J. and Amstutz, E.D., J. Org. Chem., 19, 1944 (1954).
13. Gilman, H. and Breuer, F., J. Am. Chem. Soc., 56, 1123 (1934).
14. Gilman, H., and Bebb, R., J. Am. Chem. Soc., 61, 109 (1939).
15. Schlenk, W. and Schlenk, W. Jr., Ber., 62, 920 (1929).
16. Evans, W.V., Pearson, R., J. Am. Chem. Soc., 64, 2865 (1942).
17. Kharasch, M.S. and Reinmuth, O., Op. Cit., pp. 116-132.
18. Tschelinzeff, W., (a) Ber., 37, 2081 (1904).
    (b) Ber., 39, 773 (1906).
19. Schoberl, A. and Ludwig, E., Ber., 70, 1422 (1937).
20. Kharasch, M.S. and Reinmuth, O., Op. Cit., p. 117.
21. Shepard, A.F., Winslow, N.R. and Johnson, J.R., J. Am. Chem. Soc., 52, 2083 (1930).

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

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

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

25. Gilman, H. and Wright, G.F., J. Am. Chem. Soc., 54, 2893 (1932).

26. Gilman, H., Burtner, R. and Wright, G.F., J. Am. Chem. Soc., 54, 1696 (1932).

27. Gilman, H. and Franz, R.A., Rec. trav. chim., 51, 991 (1932).

28. Bryce-Smith, D. and Turner, E.E., J. Chem. Soc., 1953, 861.

29. Kharasch, M.S., Fono, A. and Nudenberg, W., J. Org. Chem., 15, 745(1950).

30. Kharasch, M.S., and Burt, J.G., J. Org. Chem., 16, 150 (1951).

31. Kornblum, M. and DeLamare, H.E., J. Am. Chem. Soc., 73, 880 (1951).

32. Staudinger, H., Signer, R., Johner, H., Schweitzer, O. and Kern, W., Ann., 474, 254 (1929).

33. Brown, H.C. and Grayson, M., J. Am. Chem. Soc., 75, 6285 (1953).

34. Brown, H.C. and Jungk, H., J. Am. Chem. Soc., 78, 2182 (1956).

35. Takezaki, Y. and Takeuchi, C., J. Chem. Phys., 22, 1527 (1954).

36. Hanst, P.L. and Calvert, J.G., J. Phys. Chem., 63, 104 (1959).

37. Haber, F. and Willstätter, R., Ber., 64, 2844 (1930).

38. Weiss, J., Trans. Faraday Soc., 31, 1547 (1935).

39. Merz, J.H. and Waters, W.A., Discussions Faraday Soc., 2, 179 (1947).

40. Stein, G. and Weiss, J., Nature, 166, 1104 (1950).

41. Stein, G. and Weiss, J., J. Chem. Soc., 1951, 3265.

42. Boyland, E. and Sims, P., J. Chem. Soc., 1953, 2966.

43. Levy, M. and Szwarc, M., J. Am. Chem. Soc., 77, 1949 (1955).

44. Smid, J. and Szwarc, M., J. Am. Chem. Soc., 78, 3322 (1956).

45. Henbest, H.B., Meakins, G.D., Nichölls, B. and Wagland, A.A., J. Chem. Soc., 1957, 1462.

46. Rust, F.F., Seubold, F.H. and Vaughan, W.E., J. Am. Chem. Soc., 72, 338 (1950).

47. Bell, E.R., Raley, J.H., Rust, F.F., Seubold, F.H. and Vaughan, W.E., Discussions Faraday Soc., 10, 242 (1951).

48. Gilman, H., Zoellner, E.A. and Selby, W.M., J. Am. Chem. Soc., 54, 1957 (1932).

49. Cava, M.P., Wilson, C.L., Williams, C.J., Chemistry and Industry, 1955, 17.

50. "Organic Syntheses", 19, 83 (1939).

51. Fox, J.J. and Martin, A.E., Proc. Roy. Soc., A175, 208 (1940).

52. Harris, E.J. and Egerton, A.C., Proc. Roy. Soc., A168, 1 (1938).

53. Yoe, J.H. and Reid, L.C., J. Ind. Eng. Chem. (Anal.) 13, 238 (1941).

54. Vogel, A.I., "Practical Organic Chemistry", Longmans, Green and Co. Ltd., London, 1951, p. 822.

55. Bellamy, L.J., "The Infra-Red Spectra of Complex Molecules", John Wiley and Sons, Inc., New York, 1958, pp. 120-121.

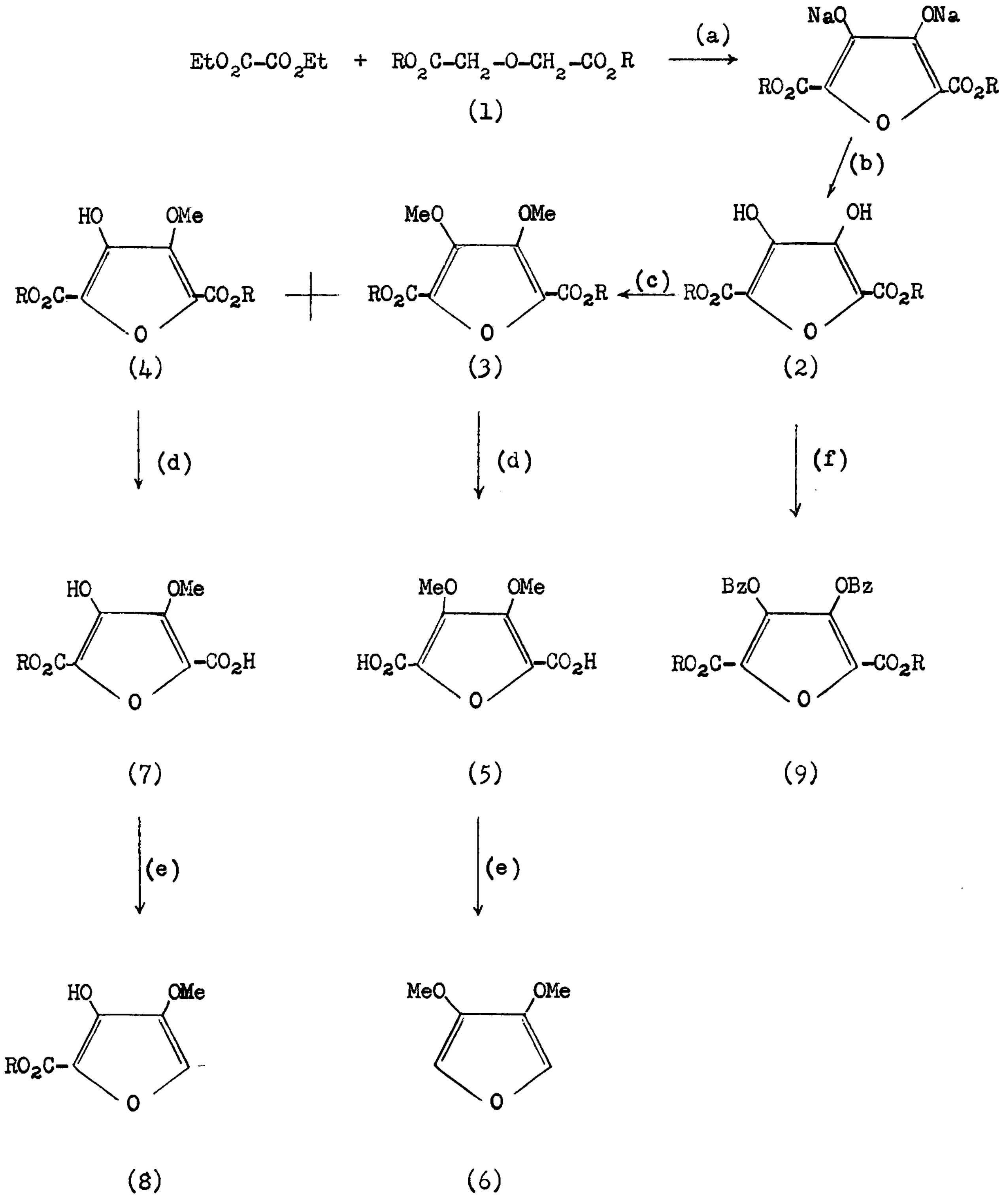
PART II

β-Methoxyfurans from the Condensation of Esters of Diglycolic Acid with 1,2-Dicarbonyl Compounds

The Claisen condensation of esters of the type X-CO-CO_2R with esters of diglycolic acid is expected to give β-hydroxyfurans (cf. p. 21). In the present work, such condensations were attempted with a view to preparing β-methoxyfurans, using diethyl oxalate (X = OEt), *n*-butyl glyoxylate (X = H) and diethyl mesoxalate (X = CO_2Et). Since diethyl oxalate gave a compound containing two hydroxyl groups, attempts were made selectively to remove one hydroxyl group.

1. Condensation with Diethyl Oxalate

The condensation of diethyl oxalate with diethyl diglycolate (1; R = Et) in the presence of sodium ethoxide affords on acidification diethyl 3,4-dihydroxy-2,5-furandicarboxylate(1,2,3) (2; R = Et). Starting with dimethyl diglycolate (1; R = Me), Hoehn(3) prepared the corresponding dimethyl ester (2; R = Me) and thence 3,4-dimethoxyfuran (6) by the series of steps shown, but his work was not published in detail and no yields were reported. We have repeated the preparation of 3,4-dimethoxyfuran in order to obtain its ultraviolet and infrared spectra. In general, our results for the intermediate compounds confirm those of Hoehn.



Reagents: (a) NaOR; (b) H^+; (c) Me_2SO_4; (d) NaOH; H^+; (e) decarboxylation;
(f) BzCl.

The preparation of dimethyl diglycolate (1; R = Me) was performed according to the procedure of Anschutz and Biernaux(4) which gave an overall yield of 85%. Several methods for the preparation of diethyl diglycolate (1; R = Et) are reported in the literature. Anschutz and Biernaux(4) prepared it by passing dry hydrogen chloride into an alcoholic solution of the acid, while Heintz(5) prepared it from ethyl iodide and silver diglycolate. However, neither in these methods, nor in other less practical ones(6,7,8), were any yields reported. In the present work, diethyl diglycolate was prepared by the azeotropic distillation method. This proved greatly superior to the above-mentioned methods in simplicity, and gave an 82% yield of ester.

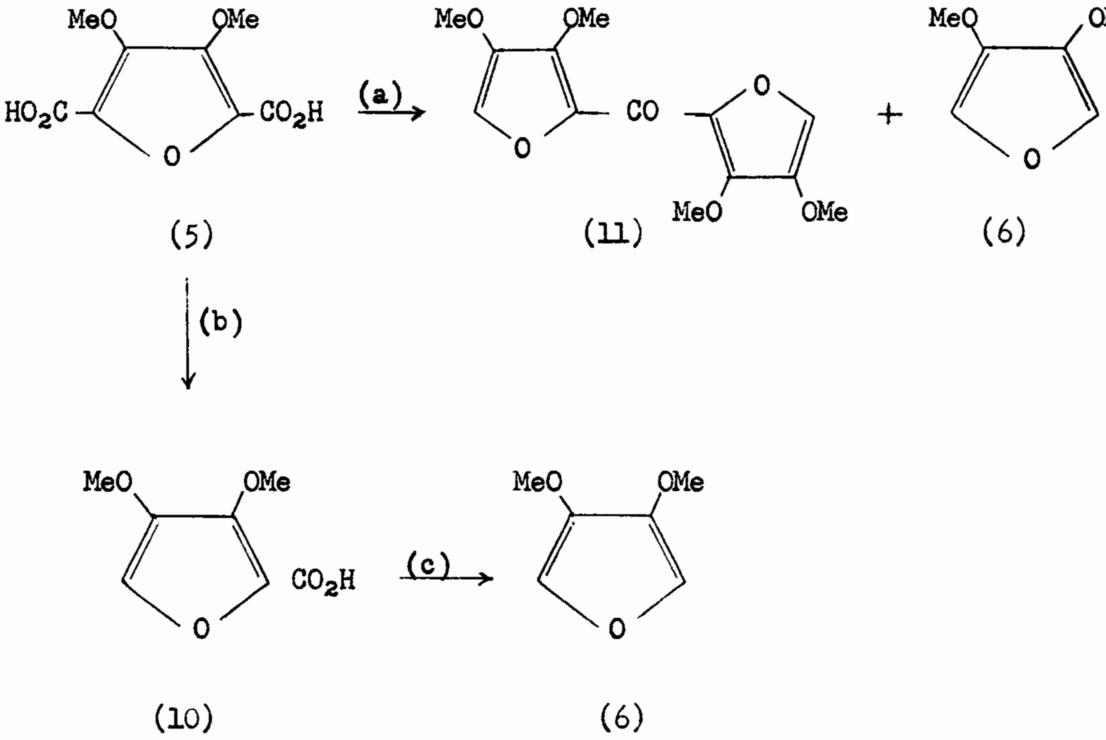
The preparation of the dihydroxy compound (2; R = Me and Et) was performed according to both Johnson and Johns' method(1), in which alcohol-free alkoxide was used, and Hinsberg's method(2), in which the alkoxide was dissolved in excess alcohol. Both methods gave the same yield of dihydroxy compound (77% for 2; R = Me, and 70% for 2; R = Et); however, the latter method was adopted for routine preparation as it was more convenient.

In proceeding to prepare 3,4-dimethoxyfuran (6), both esters (2; R = Me) and (2; R = Et) were utilized for the purpose. Hoehn(3) worked mostly with the methyl ester (2; R = Me). In the present work, a number of compounds (4, 7, 9, 12, 13 and 15; R = Et) derived from the ethyl ester (2; R = Et) has been prepared for the first time. It was noted that such ethyl derivatives (2, 3, 4, 7 and 8; R = Et) were more soluble generally than the corresponding methyl derivatives (2, 3, 4, 7 and 8; R = Me), and had melting points 30° to 70° lower. While the decreased solubility and the higher melting point made the methyl esters more easily separable from mixtures by crystallization, the increased general solubility of the ethyl esters was found to be useful when reactions requiring the esters in solution (as discussed in the next section) were involved.

The dimethoxy dimethyl ester (3; R = Me) was prepared from the dihydroxy compound (2; R = Me) in 49% yield, using dimethyl sulfate. The two ester groups in compound (3) were then easily saponified by 10% sodium hydroxide solution. This contrasted with the behaviour of the ester groups of the dihydroxy compounds (2; R = Me and R = Et), which were highly resistant to saponification even when the compound was boiled for two hours with 10% sodium hydroxide solution (cf. p. 23). The acid (5) from the saponification of the ester (3; R = Me) was obtained in 85% yield and from the ester (3; R = Et) in 95% yield.

Since there was no mention of the method of decarboxylation of the acid (5) in Hoehn's paper, several methods of decarboxylation were tried in this laboratory. Decarboxylation in quinoline took place readily, being over after a few minutes refluxing. However, the lack of efficient semi-micro fractionating equipment made the separation of the last traces of quinoline very difficult. Since 3,4-dimethoxyfuran of high purity was required for ultraviolet studies, decarboxylation in an inert liquid (to help even distribution of heat) was tried. The acid was placed in silicone oil together with a small amount of copper powder and heated for one hour. Distillation of the mixture afforded a pure sample of 3,4-dimethoxyfuran, but the yield was lower than that obtained in the previous case. The infrared absorption spectrum of the 3,4-dimethoxyfuran (Fig. 10) showed all the expected peaks for the furan ring (=C-H stretching vibration at 3150 cm.$^{-1}$ (w), ring stretching at 1630 cm.$^{-1}$ (s), 1575 cm.$^{-1}$ (s) and 1415 cm.$^{-1}$ (m), C-H in-plane deformation at 1216 cm.$^{-1}$ (s), 1147 cm.$^{-1}$ and 1026 cm.$^{-1}$ (s), ring breathing at 1010 cm.$^{-1}$ (s) and C-H out-of-plane deformation at 867 cm.$^{-1}$ (s) and 730 cm.$^{-1}$ (s)) as well as a sharp band at 2840 cm.$^{-1}$ (w) characteristic of the methoxyl group. The ultraviolet spectrum of the compound (Fig. 11) showed no absorption in the region 400-240 mμ and a shoulder at 213 mμ.

When decarboxylation of the acid (5) was tried by heating the solid acid above its melting point, a clear liquid was obtained which quickly turned brown when it came in contact with air. The infrared absorption spectrum of this liquid (Fig. 12) showed a peak of medium intensity at 1712 cm.$^{-1}$ indicating the presence of a carbonyl compound besides the 3,4-dimethoxyfuran. The ketone (11) which might be formed during decarboxylation seems at first sight an improbable source of the frequency above, being similar to a diaryl ketone. However, studies on 2,6-disubstituted aryl ketones(9) showed that the carbonyl frequency of such ketones is shifted toward the aliphatic frequency by steric inhibition of phenyl-carbonyl conjugation(10). Since construction of a Courtaulds model of the ketone (11) showed lack of coplanarity between the carbonyl group and either of the furan rings, the assignment of the 1712 cm.$^{-1}$ band to this compound was justifiable. Two other weak bands at 1340 (sh) and 1160 cm.$^{-1}$ (sh) which do not appear in the infrared spectrum of pure 3,4-dimethoxyfuran are attributed to the motion of the carbonyl group coupled with the rest of the molecule(11) and to the C-H in-plane vibration of



Conditions: (a) strong, fast heating; (b) slow heating; (c) further heating.

trisubstituted furans, respectively. Furthermore, the ultraviolet spectrum of this impure 3,4-dimethoxyfuran showed a peak at 258.5 mμ (Fig. 13), which must also be due to the ketone (11). A peak at this wavelength also indicates a lack of coplanarity in the molecule, since 2-furylmethyl ketone absorbs at 267 mμ(12) (the ultraviolet spectrum of di-2-furyl ketone which would be the one to compare with, is not reported). Other experiments on decarboxylation of the acid (5) in the solid state showed that the decarboxylation takes place in two stages as indicated by the isolation of 3,4-dimethoxy-2-furancarboxylic acid (10). This fact was overlooked by Hoehn(3), who obtained this acid from the monomethoxy compound (8; R = Me) by methylation of the hydroxyl group followed by hydrolysis of the ester group.

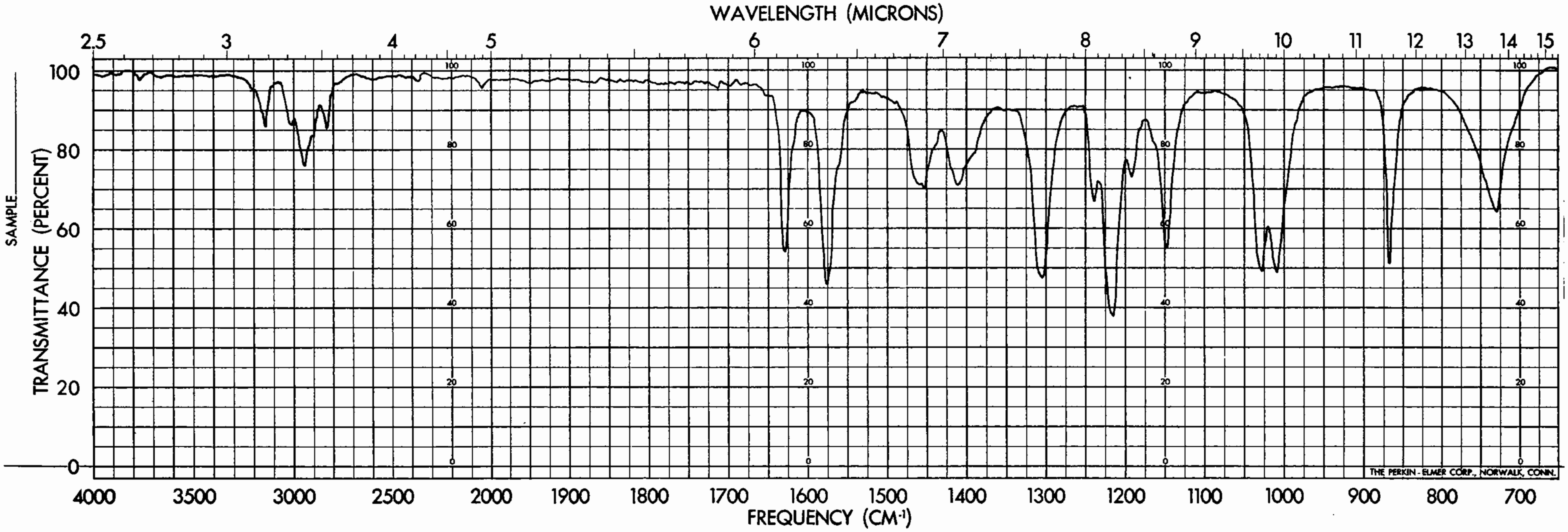


Figure 10. Infrared Absorption Spectrum of 3,4-Dimethoxyfuran

(liquid film)

FIGURE 11

Ultraviolet Absorption Spectrum of

3,4-Dimethoxyfuran

(0.095 mg./10 ml. of cyclohexane)

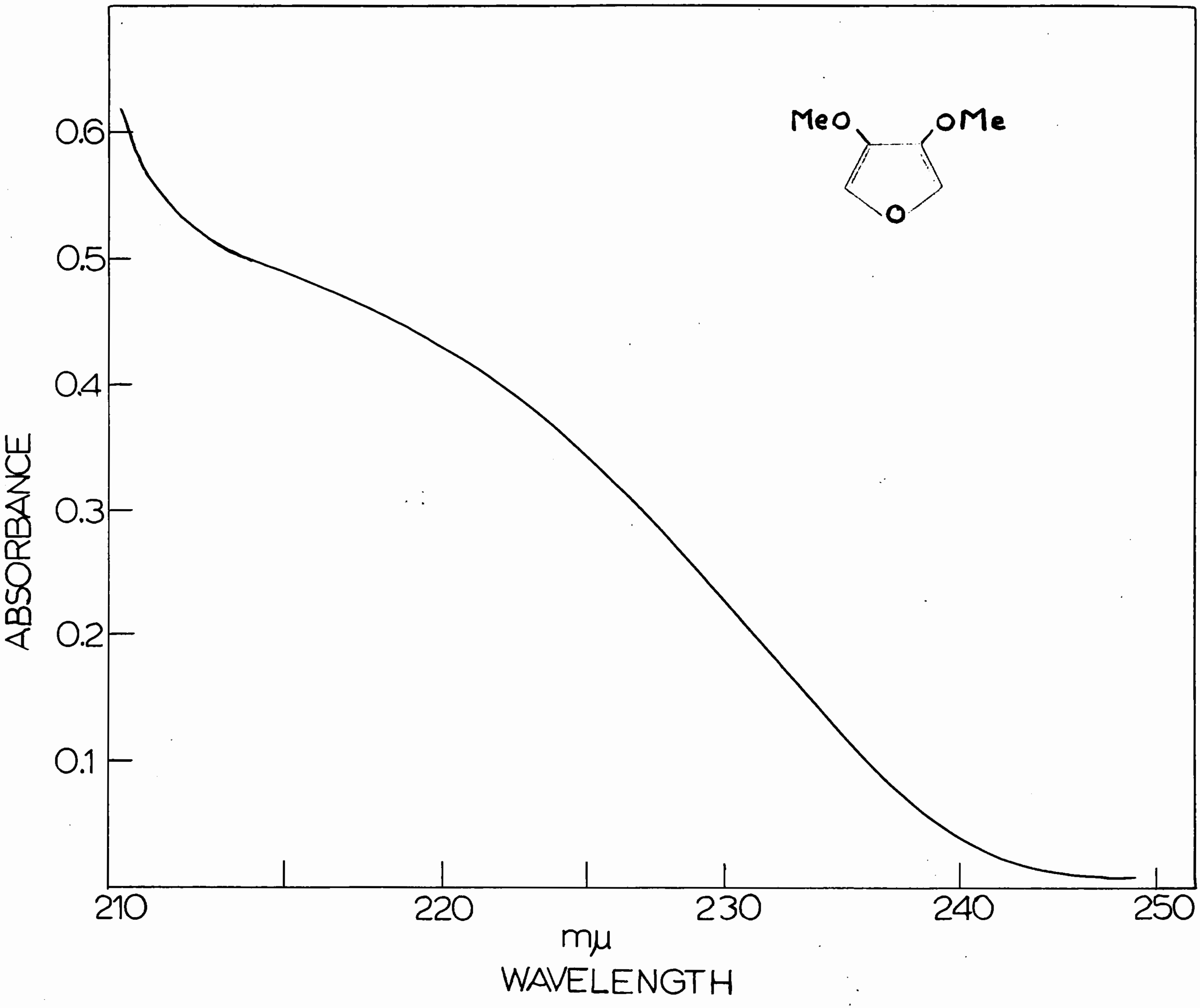

MeO
OMe
O
0.6
0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
250
mμ
WAVELENGTH

FIGURE 24

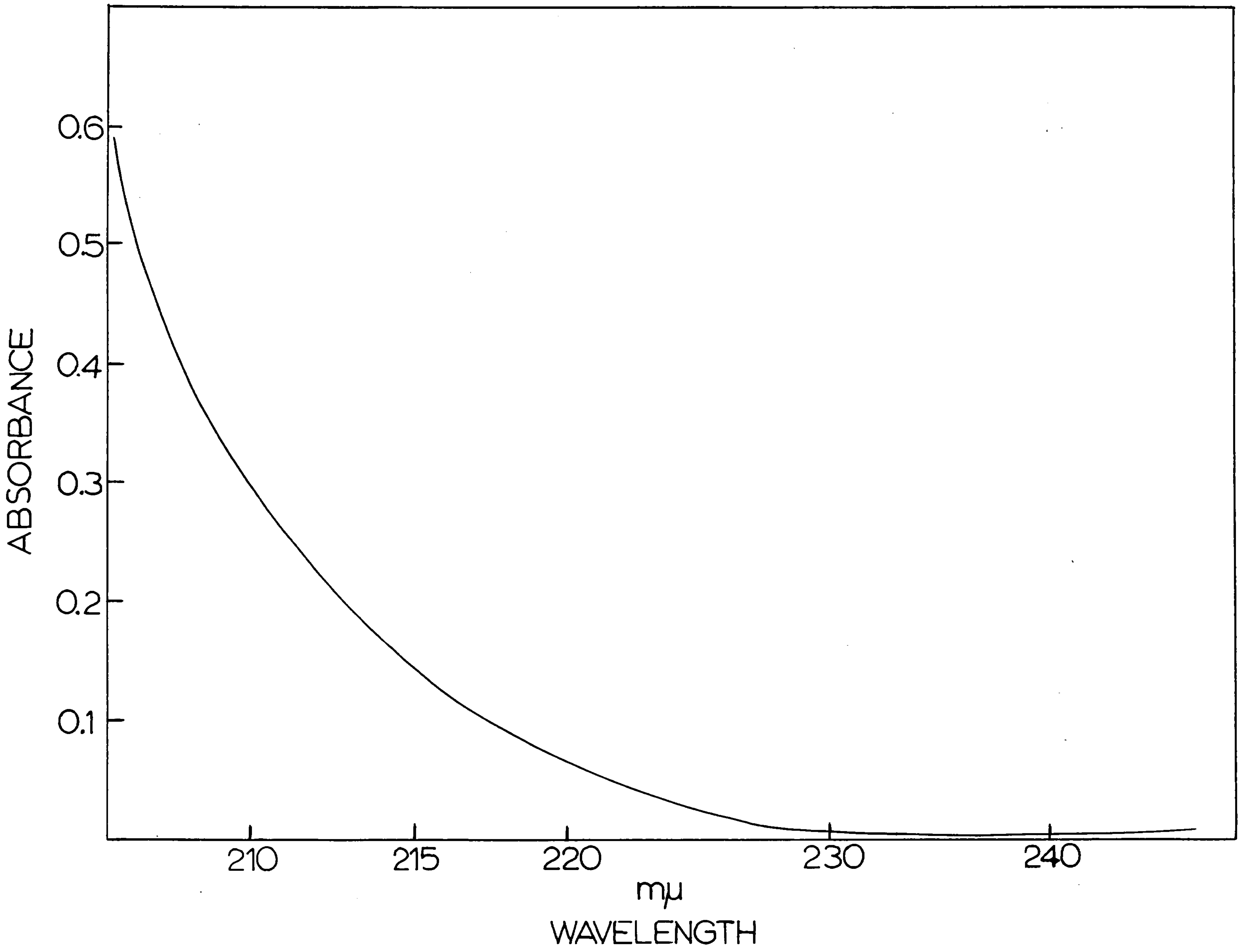
Ultrviolet Absorption

Spectrum

of

Aucubin

(lmg. in 25 ml. of water)


ABSORBANCE
0.6
0.5
0.4
0.3
0.2
0.1
210
215
220
230
240
mμ
WAVELENGTH

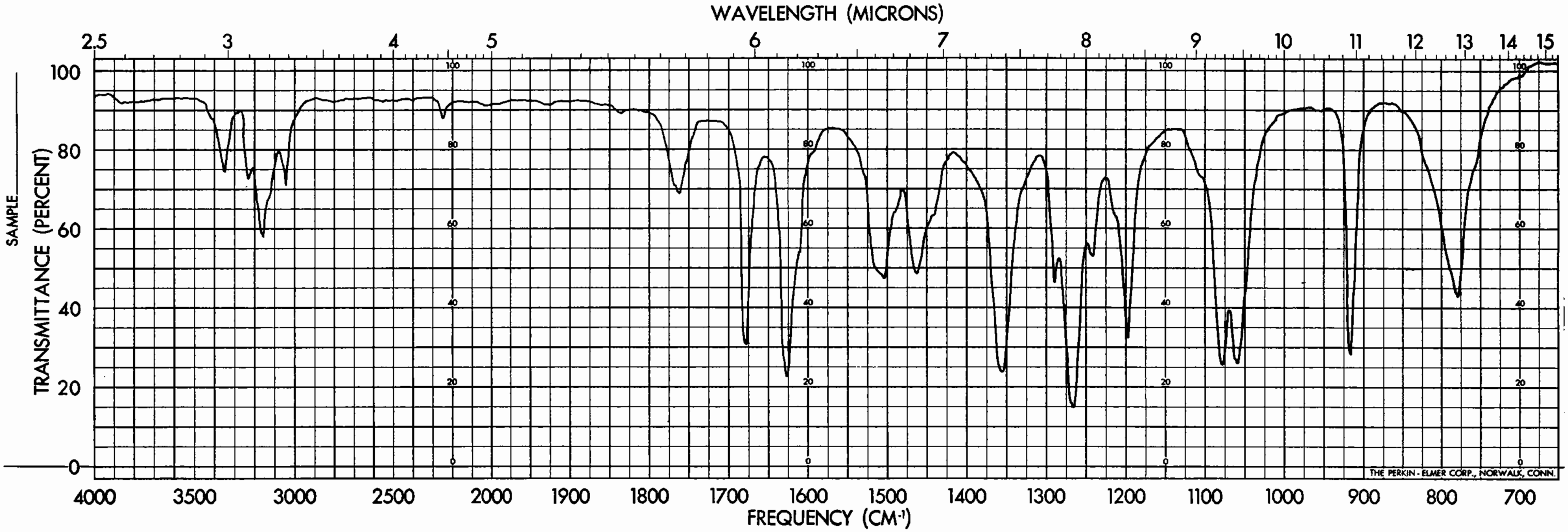


Figure 12. Infrared Absorption Spectrum of Mixture of 3,4-Dimethoxyfuran and Di-2-(3,4-Dimethoxyfuryl) Ketone.

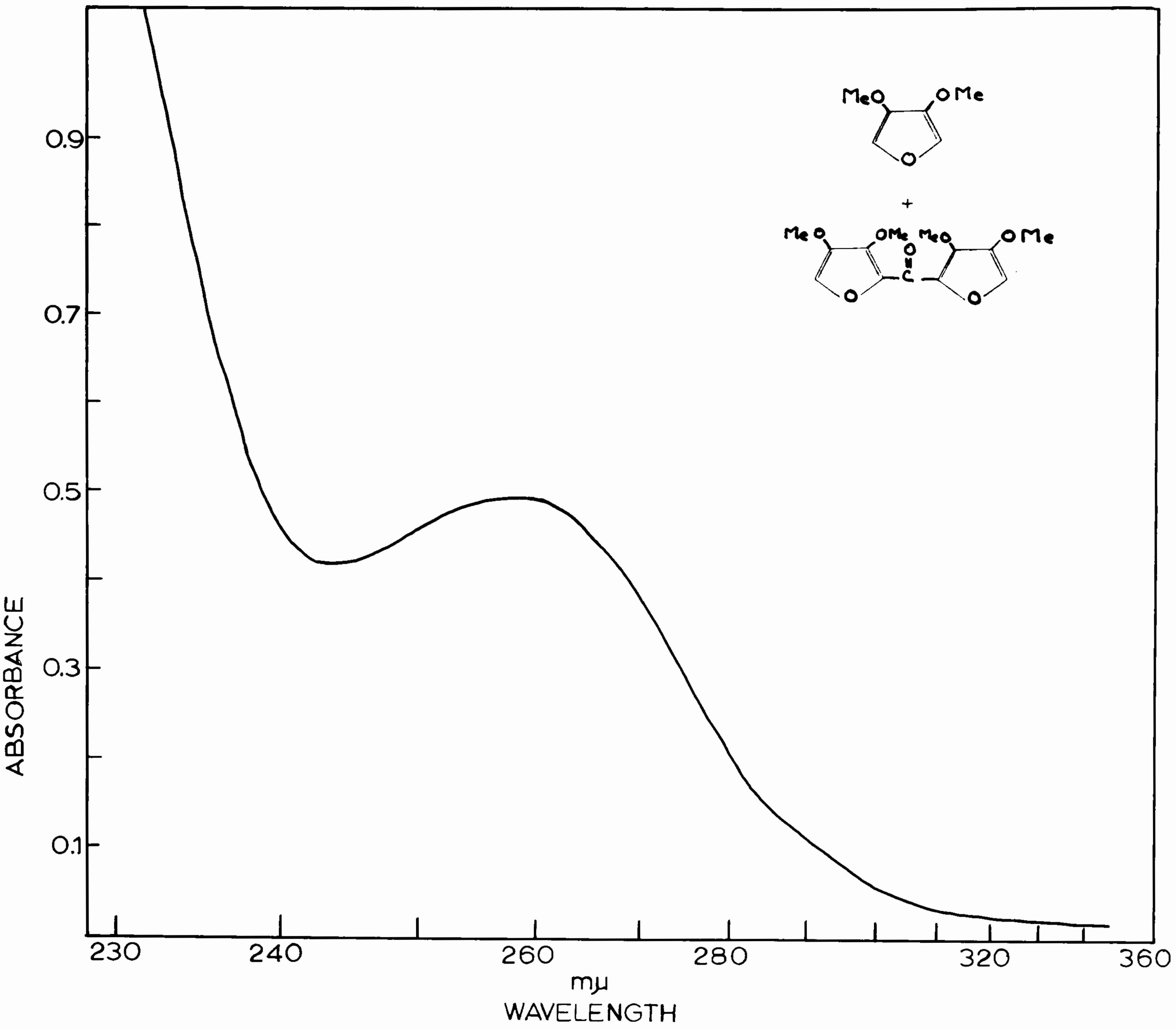
(liquid film)

FIGURE 13

Ultraviolet Absorption Spectrum of

3,4-Dimethoxyfuran and Di-2-(3,4-Dimethoxyfuryl) Ketone

(0.3 mg./25 ml. of cyclohexane)


MeO
OMe
O
+
MeO
OMe
MeO
OMe
O
C
O
O
0.9
0.7
0.5
0.3
0.1
ABSORBANCE
230
240
260
280
320
360
mµ
WAVELENGTH

2. Attempted Preparation of 3-Hydroxyfuran Derivatives from Dimethyl and Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate

Since the hydroxyl groups in the dihydroxy compound (2; R = Me or Et) were strongly phenolic in nature (cf. p.43), methods for removing the oxygen from aromatic phenols were sought. Sowa et al.(13, 14, 15) studied the cleavage of aromatic ethers by sodium and liquid ammonia, from which they obtained hydrocarbons and phenols. Studying the effect of substituents on the mode of cleavage, these workers observed that the carbon-oxygen cleavage took place at the ring with the most negative substituents:

$$\text{(i)} \qquad \text{Ar-O-Ar'} \xrightarrow{\text{Na/NH}_3} \text{Ar-H} + \text{Ar'-OH}$$

where Ar was an aromatic ring with a carboxyl or a nitro group.

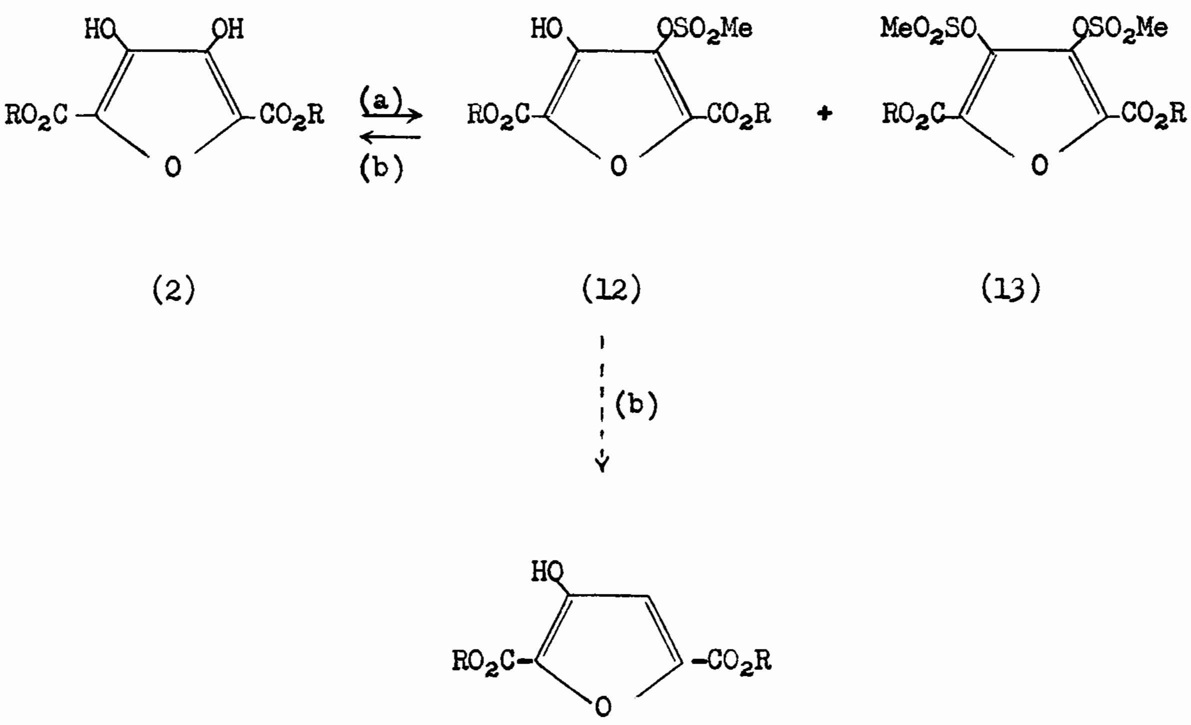
Birch(16), working with aralkyl ethers obtained phenols by utilizing the same reagent:

$$\text{(ii)} \qquad \text{Ar-O-R} \xrightarrow{\text{Na/NH}_3} \text{Ar-OH} + \text{R-H}$$

Cleavage to give phenols (rather than aromatic hydrocarbons) is also known to take place with aromatic methanesulfonates and p-toluenesulfonates on reduction with lithium aluminum hydride(17), as well as in the catalytic hydrogenation of alkyl p-toluenesulfonates(18). Furthermore, Bunnett and Bassett(19), in a recent paper, showed that aromatic 2,4-dinitro-p-toluenesulfonates, underwent both C-O and S-O scission with various nucleophilic reagents. They found that polarizability, rather than the overall nucleophilic reactivity, appeared to be the reagent characteristic to which the ratio of C–O to S–O scission was related. The reagents which gave the most C–O scission were a sulfur anion ($PhS^{\ominus}$) and a carbanion ($Ac\overset{\ominus}{C}HCO_2Et$); both types have high polarizability. The reagent which gave the most S–O scission was an oxygen anion ($MeO^{\ominus}$) whose polarizability was rather low. Since reduction by sodium in liquid ammonia is due to electrons from sodium attacking the aromatic compounds(13,20,21) (a nucleophilic attack by a reagent of low polarizability), reduction of p-toluenesulfonates and probably methanesulfonates with this reagent might in general be expected to give phenols rather than hydrocarbons.

On the other hand, Kenner and Williams(22) reported the successful reduction of some aryl methanesulfonates (p-methoxyphenyl and m-acetamidophenyl methanesulfonate) to the corresponding hydrocarbons using sodium or lithium in liquid ammonia, in which they were moderately soluble. Aromatic p-toluenesulfonates would have been the obvious choice according to these authors, but unfortunately they were insoluble in liquid ammonia. By the same method aryl phosphates were also reduced to the corresponding hydrocarbons, and the phosphate ester of methyl salicylate was reduced to methyl benzoate in 20% yield, in spite of the interfering reactions of the ester group with ammonia.

The successful results of Kenner and Williams with soluble methanesulfonates prompted an attempt to use their method on the dihydroxy compound (2; R = Me and Et) and the monohydroxy compound (4; R = Me and Et), since the methanesulfonates of these compounds were found to be quite soluble in liquid ammonia.



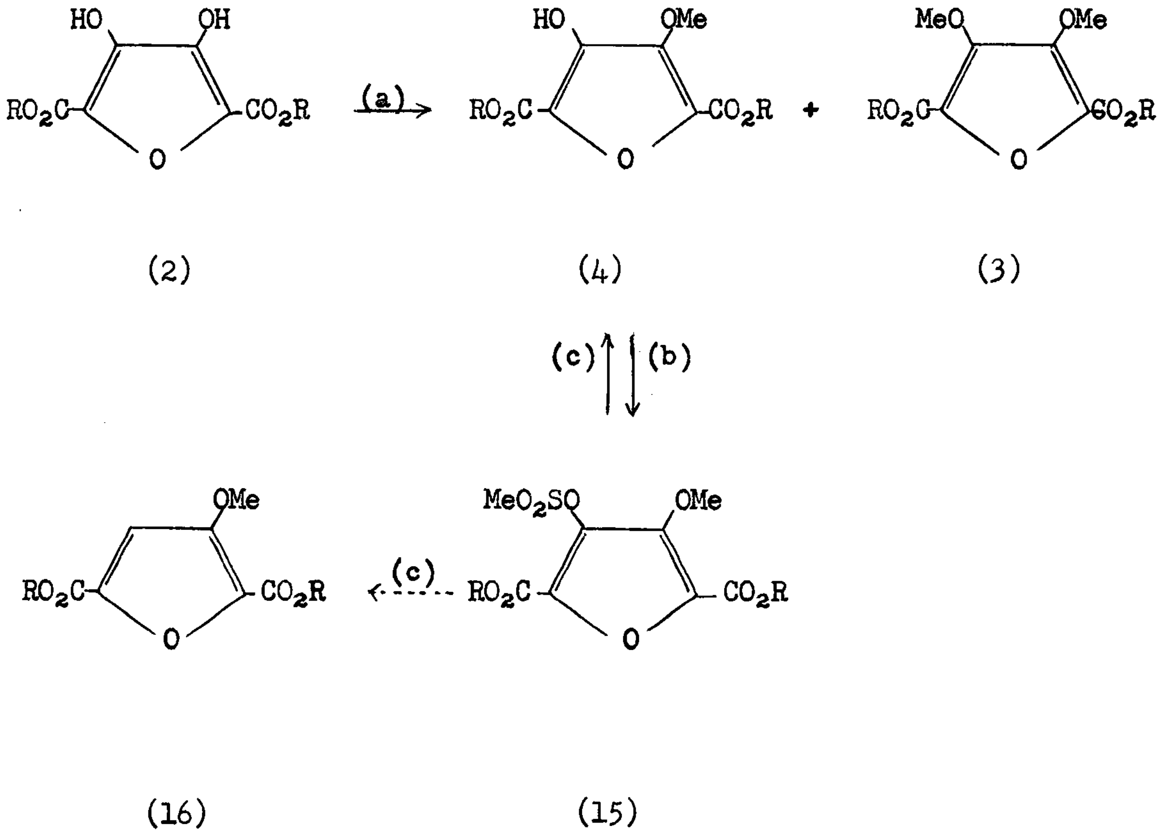
(2) (12) (13)

(14)

Reagents: (a) $MeSO_2Cl$; (b) Na/NH_3.

The monomethanesulfonate (12; R = Me) was obtained in 66% yield by treatment of the dihydroxy compound (2; R = Me) with one equivalent of methanesulfonyl chloride. A small amount of the dimethanesulfonate (13; R = Me) was also obtained (20% yield). The two compounds were easily separated, since the latter (13; R = Me) was neutral and precipitated from the alkaline solution, while the monomethanesulfonate (12; R = Me) remained in solution and was obtained on acidification. Reduction of the monomethanesulfonate (13; R = Me) by sodium in liquid ammonia, however, yielded only starting material (2; R = Me), reductive cleavage of the methanesulfonate group evidently taking place at the S-O linkage.

Because it seemed possible that C-O scission was not taking place because of the ionized hydroxyl group of the compound (12), a second route was attempted by preparing first the monomethoxy compound (15).



Reagents: (a) Me_2SO_4; (b) $MeSO_2Cl$; (c) Na/NH_3.

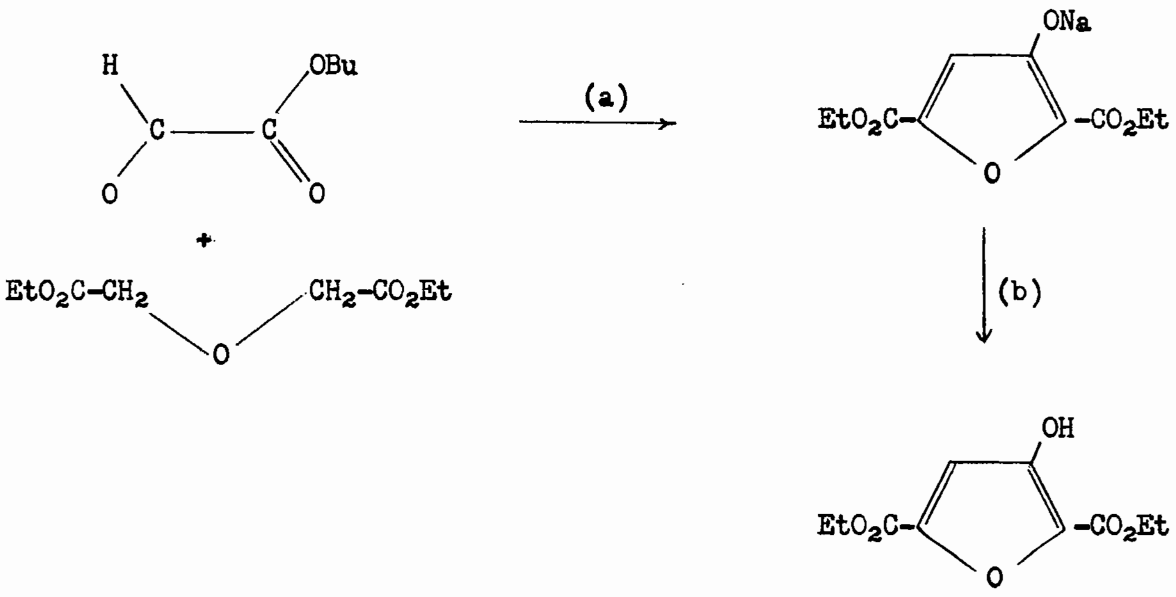
The monomethoxy compound (4) from which compound (15) was prepared, could not be easily obtained. The monosodium salt of the dihydroxy compound (2) from which the compound (4) could best be prepared by methylation, was insoluble in water, and therefore, the disodium salt had to be used with only one equivalent of dimethylsulfate. By this procedure, a mixture of the starting material (2) (35%) together with the monomethoxy compound (4) (48%) and the dimethoxy compound (3) ($< 5\%$), was obtained. The latter compound was easily removed by filtration and extraction of the alkaline solution with ether. However, the last traces of the starting material were hard to remove, since, even on careful acidification both the mono-(4) and di-(2) hydroxy compounds came out of solution together. Several attempts using diazomethane for methylation of compounds (2; R = Me and R = Et) failed. In subsequent experiments, the separation of compounds (2) and (4) was not attempted, and the methanesulfonation step was carried out directly on the crude product. By adding just one equivalent of methanesulfonyl chloride, only the neutral compound (15; R = Me or Et) separated as a solid, and any of the starting material (2) or its monosulfonate (12; R = Me or Et) remained in solution. The methanesulfonates were crystalline products and easy to purify.

The reduction of the methanesulfonates (15; R = Me or Et) again led to S-O rather than C-O fission, giving the monomethoxy compound (4; R = Me or Et) rather than the hoped for products (16; R = Me or Et). It is not immediately apparent why S-O fission occurred in the present cases, and not in those investigated by Kenner and Williams(22), and obviously further studies to define the scope of this reaction would be desirable.

3. Condensation with n-Butyl Glyoxylate

Because it was not found possible to remove one hydroxyl group from esters of 3,4-dihydroxy-2,5-furandicarboxylic acid, other condensation reactions, from which monohydroxy compounds might be expected directly were next investigated.

The simplest ester from which a monohydroxyfuran might be obtained is one of glyoxylic acid:



Reagents: (a) NaOEt; (b) H^+

However, the condensation of n-butyl glyoxylate with diethyl diglycolate produced only a small amount (~4%) of diethyl 3,4-dihydroxy-2,5-furandicarboxylate together with unidentified gums. The same product was obtained when ethanol-free alkoxide was used as the condensing agent. The formation of the dihydroxy compound above indicated that a Cannizzaro reaction had taken place to give an ester of oxalic acid, which had then condensed to give the dihydroxy compound.

Traube(23) showed that both glyoxylic acid and its esters undergo the Cannizzaro reaction in alkaline medium at 100°:

$$2OHC.CO_2Et \xrightarrow{KOH} EtO_2C.CO_2^- + HO.CH_2CO_2Et$$

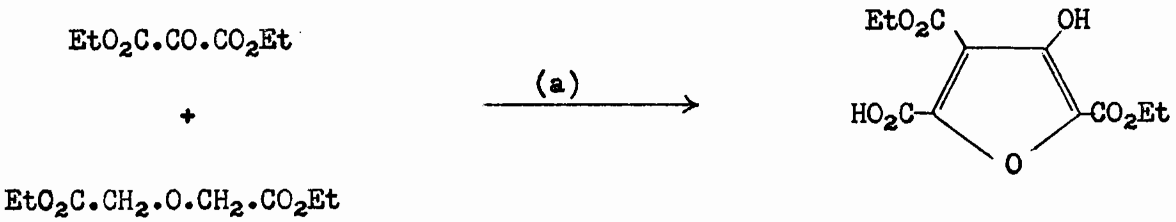
It is evident from the results above that the Cannizzaro reaction can also take place at room temperature; an alkaline catalyzed trans-esterification reaction can then cause the half-ester of oxalic acid to be transformed into a full ester:

$$EtO_2C.CO_2^- + HOCH_2CO_2Et \longrightarrow EtO_2C.CO_2Et \qquad HOCH_2CO_2^-$$

4. Condensation with Diethyl Mesoxalate

Hinsberg(2) reported a reaction between the esters of thiodiglycolic acid and mesoxalic acid, from which he obtained triethyl 3-hydroxy-2,4,5-thiophenetricarboxylate (cf. p. 23). However, the corresponding condensation with diglycolic ester was not reported.

The condensation of diethyl mesoxalate with diethyl diglycolate in the presence of sodium ethoxide gave diethyl 3,4-dihydroxy-2,5-furandicarboxylate as the major product (25% yield) together with a small quantity (7.5%) of a substance, which also gave a red color with ferric chloride, whose analysis corresponded to diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (17)



(17)

Reagents: (a) NaOEt then H^+

Detailed infrared studies (see Fig. 14) of the compound (17) are in good agreement with the proposed structure. The following regions were studied carefully and bands in them correlated with various groups in the molecule:

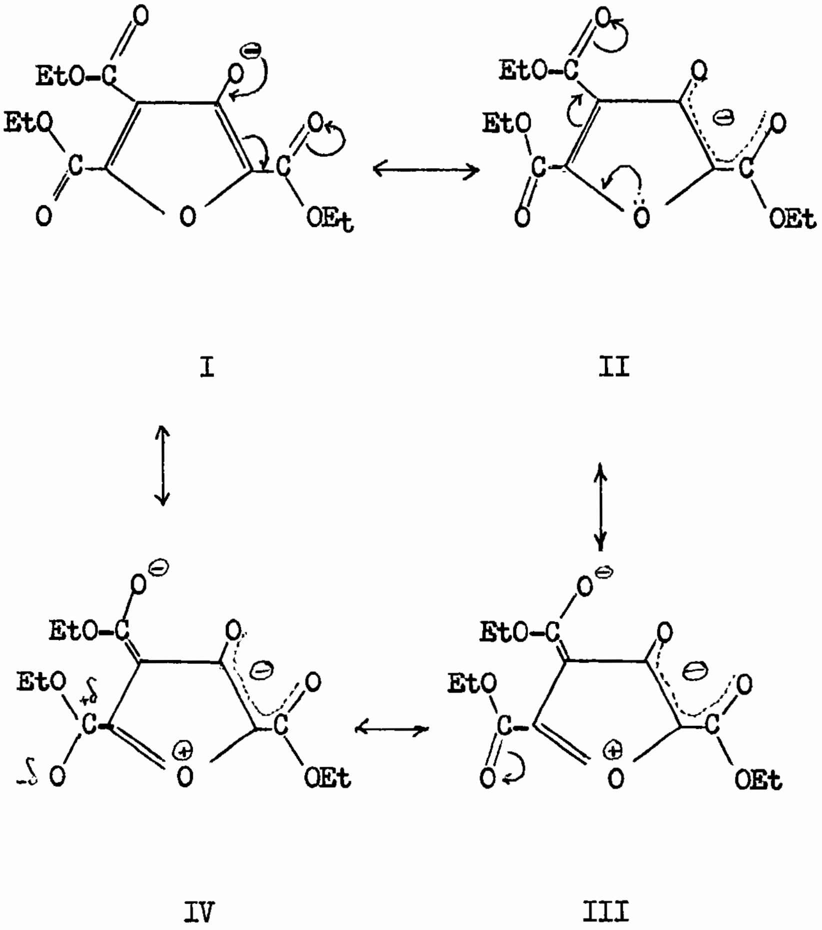
(1) The band at 3260 cm.$^{-1}$ (bd) with a shoulder at 3160 cm.$^{-1}$ and absorption continuing till 3020 cm.$^{-1}$ can be correlated with the enolic O-H stretching (chelate) and the O-H stretching of the carboxyl group. In the dihydroxy compound (2) a sharp band at 3360 cm.$^{-1}$ (s) is present (Fig. 15) and in the spectrum of the ethyl 3-carboxy-4-methoxy-5-hydroxy-2-furancarboxylate (Fig. 16) a band at 3100 cm.$^{-1}$ (w, bd) is due to the O-H stretching of the carboxyl group.

(2) There are four bands in the region 1750-1600 cm.$^{-1}$ The first of these bands is at 1726 cm.$^{-1}$ (s) and is attributed to the C=O stretching of the 4-carbethoxy group. This compares very

well with the absorption of the C=O of the 5-carbethoxy group in diethyl 3 hydroxy-4-methoxy-2,5-furandicarboxylate (where no chelation in the 5-position is possible). The second band appears at 1690 cm.$^{-1}$ (s) and is correlated with the C=O stretching of the 5-carboxy group. This is in agreement with the accepted figure for aryl or conjugated acids(24). The third band at 1640 cm.$^{-1}$ (s) is attributed to the C=O stretching of the 2-carbethoxy group after chelation with the adjacent 3-hydroxyl group. In the 3,4-dihydroxy compound (2) this band appears at 1655 cm.$^{-1}$ (s). The last band in this region appears at 1610 cm.$^{-1}$ (w) and this is correlated with the C=C stretching of the furan ring. This band appears at 1615 cm.$^{-1}$ (w) in the dihydroxy compound (2) (cf. p.114).

(3) The region 1320-1210 cm.$^{-1}$ shows three bands. Two of these bands at 1320 cm.$^{-1}$ and 1212 cm.$^{-1}$ are attributed to the C-O stretching of the 2- and 4-carbethoxy groups (the 2 and 5-carbethoxy groups of the dihydroxy compound (2) show absorption at 1315 cm.$^{-1}$ and 1237 cm.$^{-1}$). The third band at 1265 cm.$^{-1}$ is correlated with the C-O stretching of the 5-carboxyl group. As expected, this band is absent in the spectrum of diethyl 3,4-dihydroxy-2,5-furandicarboxylate.

While the infrared studies showed the presence of three different types of carbonyl groups in the compound (17), no clue could be obtained from these studies regarding the position of the carboxyl group in the molecule. For reasons discussed earlier (cf. p.23) we can assume that the free carboxyl group can either be in positions 4- or 5-, since the 2-carbethoxy group is not saponifiable, being adjacent to a hydroxyl group. If we consider carefully the resonance contributions of the sodium salt of triethyl 3-hydroxy-2,4,5-furantricarboxylate (I), it will become clear why the 5-carbethoxy group rather than the 4-carbethoxy group was assumed to be the one more liable to hydrolysis:



It can be seen from the above resonance forms that only the 4-carbethoxy group is involved in the form III. That means that the carbonyl carbon of the 5-carbethoxy group is more positive (IV) and hence more prone to nucleophilic attack by the OH^- group than the 4-carbethoxy group.

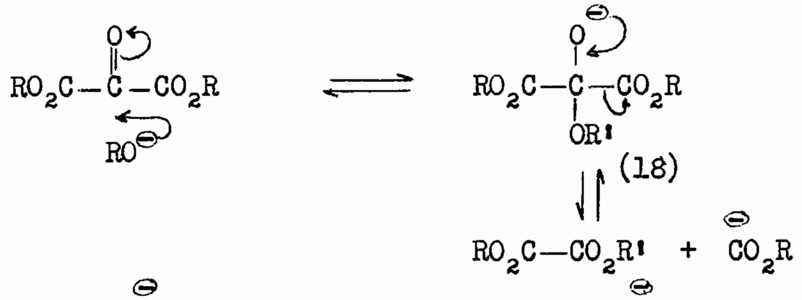
Further evidence for the furanoid nature of the condensation product comes from ultraviolet studies, to be described later (p134).

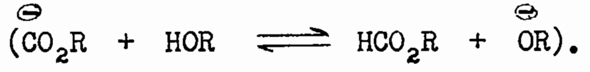
Methylation of the compound (17) followed by hydrolysis of the carbethoxy groups would lead to the formation of 3-methoxy-3,4,5-furantricarboxylic acid, which on decarboxylation would afford 3-methoxyfuran. Since the complete decarboxylation of the tricarboxylic acid was not expected to give good yields of the methoxyfuran, attempts were made to improve the yield of the compound (17).

The fact that diethyl 3,4-dihydroxy-2,5-furandicarboxylate, which is the normal product from the condensation with diethyl oxalate (see Section 1), was produced in the present case, indicates most probably that part of the diethyl mesoxalate was converted to diethyl oxalate under the conditions of the reaction. Denis(25) observed that mesoxalic acid changes quantitatively into oxalic and formic acids on boiling with concentrated alkali at 150°:

$$HO_2CO.CO.CO_2H \; + \; 3KOH \longrightarrow KO_2C.CO_2K \; + \; HCO_2K \; + \; 2H_2O$$

The formation of oxalic esters in the presence of alkoxides might proceed as follows





$$(\overset{\ominus}{C}O_2R \; + \; HOR \rightleftharpoons HCO_2R \; + \; \overset{\ominus}{O}R).$$

In trying to check the course of this side reaction, the following modifications were tried:

(a) Ethanol-free sodium ethoxide was used.

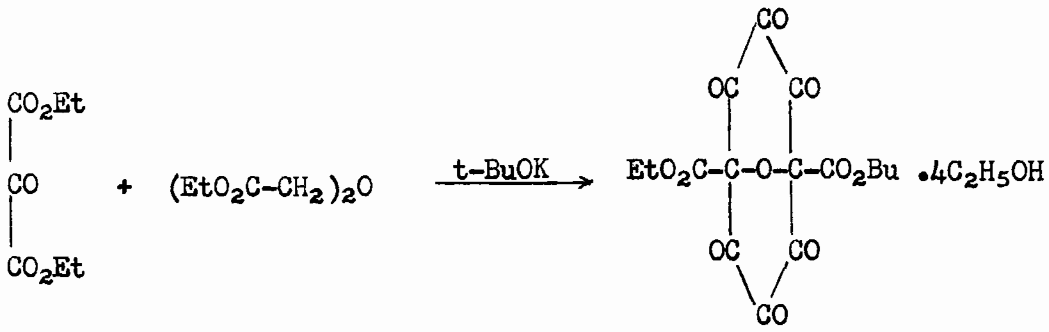
(b) The mode of addition of reagents was reversed, so that the alkoxide solution was gradually added to the mixture of esters.

(c) Potassium tert. butoxide was used as the condensing agent instead of sodium ethoxide.

The reason for the use of ethanol-free sodium ethoxide springs directly from the study of the mechanism of the Claisen (acetoacetic) condensation(26, 27, 28). Since the first step in the condensation involves the liberation of alcohol, the use of alcohol-free alkoxide was tried in the hope of shifting the equilibrium to the right, thus helping the normal reaction to compete favorably with the cleavage reaction. However, the normal condensation product (17) could not be obtained in this case.

Since the conversion of mesoxalic into oxalic ester seems to be catalyzed by alkali, the mode of addition of reagents was reversed so that the alkoxide was added gradually to the mixture of esters. It was hoped that this modification would cut down the time of exposure of the mesoxalic acid ester to excess alkali. Experimentally, this modification was used with dimethyl diglycolate and sodium methoxide as the condensing agent, and yet an even better yield (38%) of dimethyl 3,4-dihydroxy-2,5-furandicarboxylate was obtained, with no detectable amount of the normal condensation product.

Finally, potassium t-butoxide was used as the condensing agent. This would be expected to remove protons even more strongly than the corresponding methoxide or ethoxide ions, so that the condensation reaction would proceed normally. However, due to steric factors(29), the t-butoxide ion is expected to add much less readily to the carbonyl group. Since the cleavage of mesoxalic ester probably proceeds through the formation of an intermediate (18) by such an addition, as shown on page 87, this reaction may be expected to be suppressed by the use of potassium t-butoxide, thus allowing the normal condensation reaction to take place. However, the use of this reagent gave gummy reaction products with a minute amount of crystals melting at 77.5° and analyzing for $C_{24}H_{38}O_{15}$ ($C_{24}H_{14}O_{11}.4C_2H_5OH$). The compound gave no red color with ferric chloride and the infrared absorption spectrum (Fig. 17) showed no absorption in the region 4000-3000 cm.$^{-1}$ confirming the absence of an enolic OH. However, strong absorption in the region 3000-2800 cm.$^{-1}$ and the bands at 1465 (m), 1455 (m), 1390 (m) and 1370 cm.$^{-1}$ (s), indicate the presence of t-butyl group(s) in the molecule. In Nujol, a double headed peak appears at 1735-1720 cm.$^{-1}$ (s) which might indicate the presence of more than one carbonyl group. The absence of bands between 1700 and 1500 cm.$^{-1}$ (cf. p. 114) rules out the possibility of a furan ring, while strong absorption in the region 1320-1000 cm.$^{-1}$ (4 bands) indicates the presence of a number of C-O groups (probably from esters). A product of condensation of two molecules of diethyl mesoxalate with one molecule of diethyl diglycolate accompanied by ester exchange is one possibility:



The formation of oils in this case is probably due to the ester exchange, with the formation of t-butyl esters mixed with the ethyl esters. The t-butyl esters of the reaction products may be expected to have lower melting points than the methyl or ethyl esters, and hence their formation should make the reaction product more gummy and uncrystallizable.

From the experimental work reported above, it is evident that the yield of the 3-hydroxyfuran derivative (17) was low and capricious. It is unfortunate that the quantity of the compound available was too low to permit investigation of its transformation into other derivatives of furan.

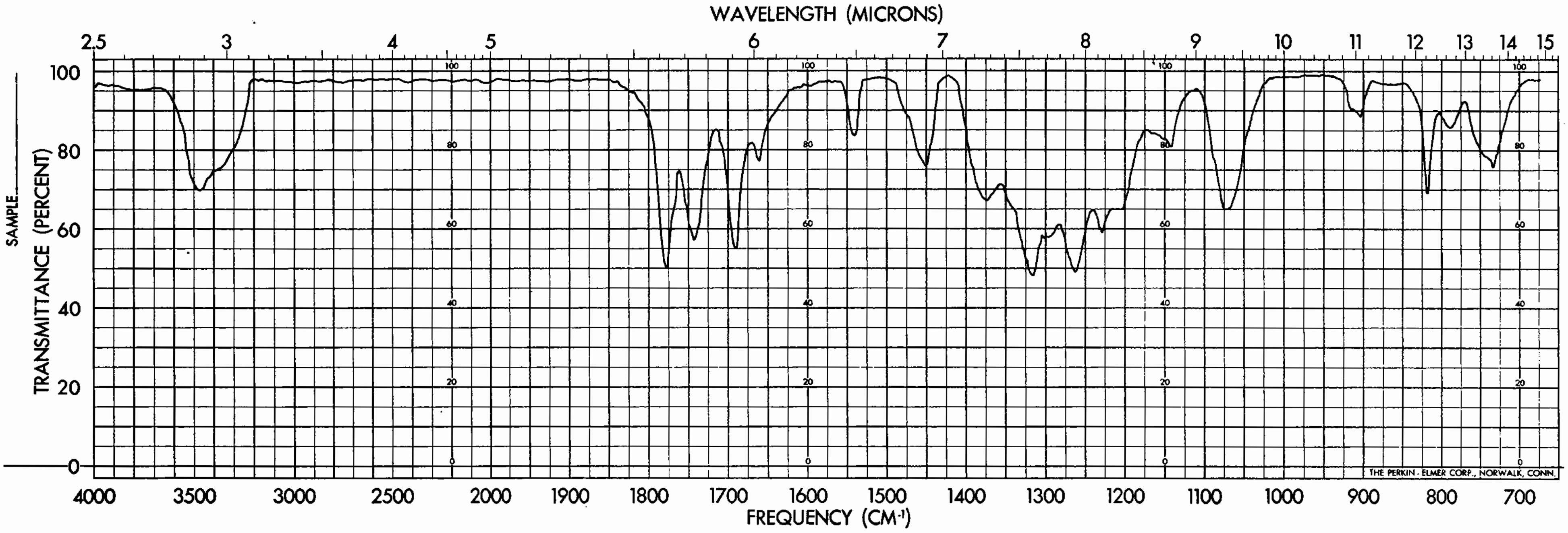


Figure 14. Infrared Absorption Spectrum of Diethyl 5-Carboxy-3-Hydroxy-2,4-Furandicarboxylate.

(Nujol mull)

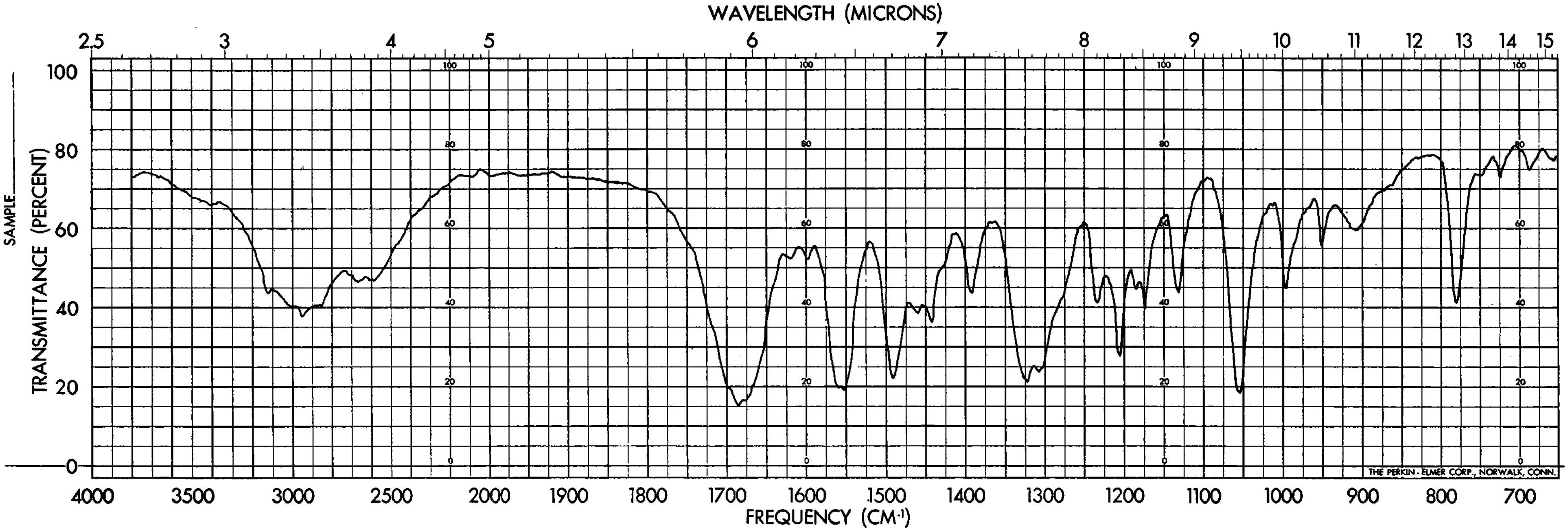


Figure 21. Infrared Absorption Spectrum of 3,4-Dimethoxy-2-Furancarboxylic Acid.

(KBr pellet)

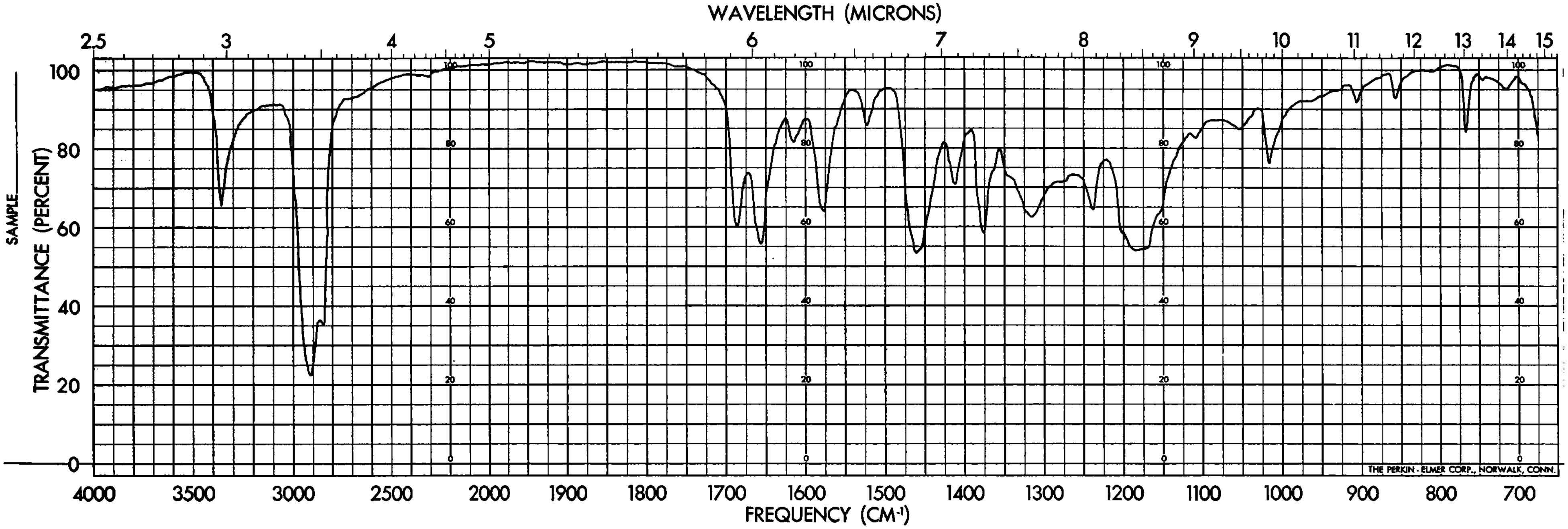


Figure 15. Infrared Absorption Spectrum of Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate.

(Nujol mull)

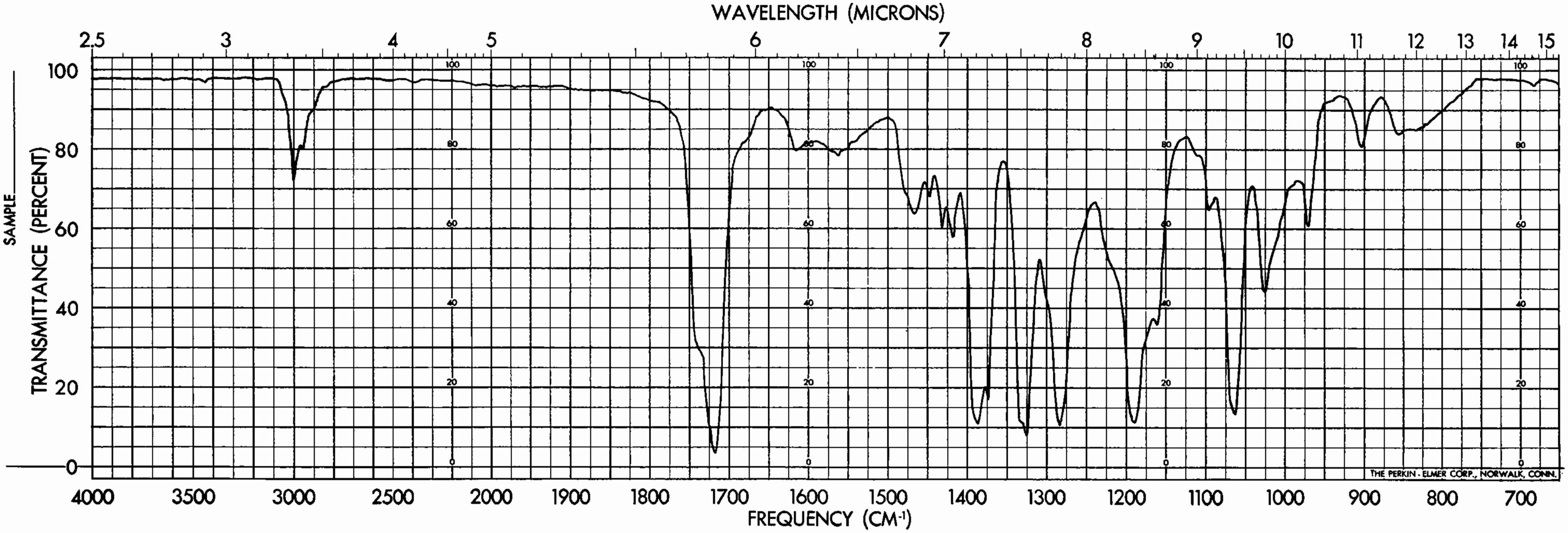


Figure 22. Infrared Absorption Spectrum of Diethyl 3-Methanesulfonyloxy-4-Methoxy-2,5-Furandicarboxylate.

(0.5% CCl_4 solution)

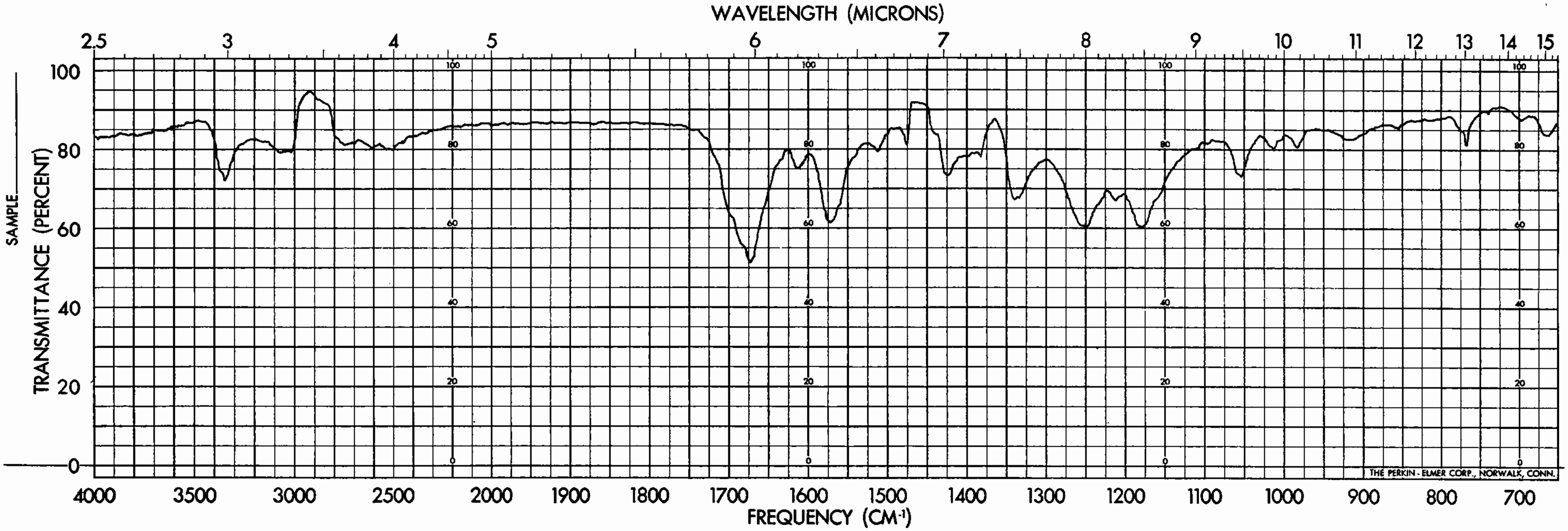


Figure 16. Infrared Absorption Spectrum of Ethyl 5-Carboxy-3-Hydroxy-4-Methoxy-2-Furancarboxylate.

(Nujol mull)

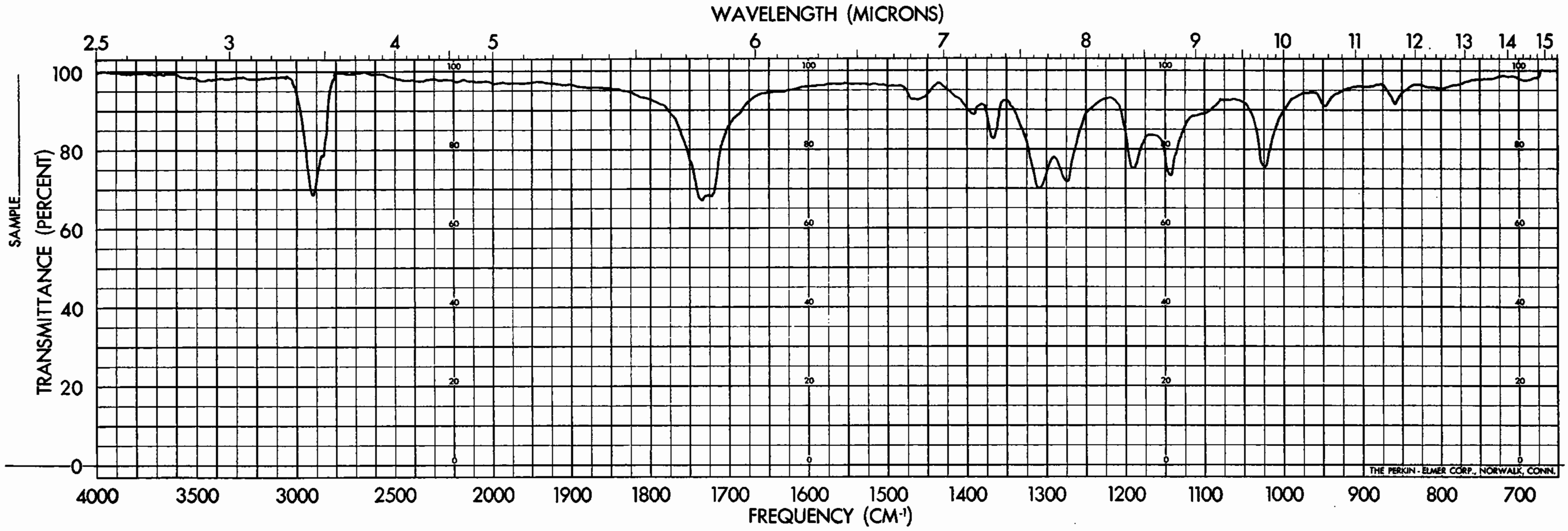


Figure 17. Infrared Absorption Spectrum of Product of Condensation of Diethyl Diglycolate with Diethyl Mesoxylate in the Presence of Potassium n-Butoxide.

(Nujol mull)

EXPERIMENTAL

Dimethyl Diglycolate (1; R = Me)

Dimethyl diglycolate was prepared by converting the acid to the acid chloride according to Anschutz and Biernaux(4), and then refluxing the crude acid chloride with the calculated amount of absolute methanol until hydrogen chloride ceased to be evolved. The mixture was then distilled at reduced pressure and the ester came off at 113°/9 mm. as a colorless oil, which solidified into white crystals m.p. 36-37° (reported (4) m.p. 36°). Overall yield of dimethyl diglycolate was 85%.

Dimethyl 3-Hydroxy-4-Methoxy-2,5-Furandicarboxylate (4; R = Me)

Dimethyl 3,4-dihydroxy-2,5-furandicarboxylate (21.6 g., 0.1 mole) prepared by Hinsberg's method(2) (77% yield), was dissolved in 150 ml. of water containing 8 g. (0.2 mole) of sodium hydroxide. Dimethyl sulfate (12.6 g., 0.1 mole) was added over a period of thirty minutes from a dropping funnel to the cooled, stirred solution. The mixture was then refluxed for one hour. A crystalline solid (mostly inorganic, probably sodium methyl sulfate) was removed from the mixture by filtration and the filtrate was extracted with ether (three 20 ml. portions). The dried ether extract yielded only a trace of dimethyl 3,4-dimethoxy-2,5-furandicarboxylate, as indicated by its sweet candy-like smell. The aqueous layer was then acidified to a pH of 5-6. The voluminous precipitate which formed was separated, washed with water, and dried. The filtrate was extracted five times with 20 ml. portions of ether, the combined ether extracts dried over anhydrous magnesium sulfate, and then the ether evaporated to yield a further amount of the crude dimethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (4; R = Me) (14.7 g.); m.p. 134-138°. Recrystallization from aqueous methanol raised the melting point to 145-147°. No further purification was attempted.

Hoehn(3) briefly reports obtaining this monomethoxy compound in 10% yield by extracting the methylation product of the dihydroxy compound (2; R = Me) with disodium hydrogen phosphate, and reports a melting point of 150-151°.

Dimethyl 3,4-Dimethoxy-2,5-Furandicarboxylate (3; R = Me)

Dimethyl 3,4-dihydroxy-2,5-furandicarboxylate (2; R = Me) (10.8 g., 0.05 mole) was dissolved in 70 ml. of water containing 4 g. (0.1 mole) of sodium hydroxide, then slowly, with stirring, dimethyl sulfate (12.6 g., 0.1 mole) was added, and the mixture refluxed for one hour after the addition. On cooling, a heavy precipitate was formed, which was separated and washed thoroughly with water to remove inorganic material. The filtrate was extracted six times with ether (20 ml. portions), the combined ether extracts dried, and the ether evaporated. The solid left after evaporation of the ether, combined with the original precipitate, was recrystallized from methanol giving white needles of dimethyl 3,4-dimethoxy-2,5-furandicarboxylate (6 g.; 49% yield) melting at 89-90°. Hoehn(3) gives a m.p. of 89.5-90°).

Methyl-5-Carboxy-3-Hydroxy-4-Methoxy-2-Furancarboxylate (7; R = Me)

Methyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (4.6 g. of crude compound, 0.02 mole) was boiled for ten minutes with 20 ml. of 10% sodium hydroxide solution. On cooling and acidification, white crystals were obtained, which were recrystallized from aqueous methanol to give needles of methyl-5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (3.8 g., (86%), m.p. 243-245° (decomp.). The same melting point was reported by Hoehn(3).

Methyl 3-Hydroxy-4-Methoxy-2-Furancarboxylate (8; R = Me)

Methyl-5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (1 g., 0.0046 mole) was placed in a small sublimation apparatus and heated to 260° at ordinary pressure. Decarboxylation took place together with sublimation of the compound. The liquid that collected on the upper side of the tube soon solidified on cooling into thick prisms, m.p. 98°. Recrystallization from aqueous methanol gave prisms of methyl 3-hydroxy-4-methoxy-2-furancarboxylate (8; R = Me), m.p. 100°. Hoehn(3) reports a melting point of 100-101°.

Diethyl Diglycolate (1; R = Et)

Diglycolic acid (134 g., 1 mole), absolute ethanol (360 ml., 6.2 moles), toluene (180 ml.), and concentrated sulfuric acid (1.5 g.), were placed in a one-liter round-bottomed flask equipped for downward distillation. The mixture was heated on an oil bath kept at 115°, and the distillate boiling at 78° was collected over anhydrous potassium carbonate, shaken well, and then returned to the original flask. The mixture was again heated until the temperature of the distillate reached 80°. The residue was transferred to a 500-ml. Claisen flask and distilled under reduced pressure. The colorless oil boiling at 130°/13 mm. was collected. Yield, 156 g. (82%); n_D^{20} 1.4267; d_4^{20} 1.115. MR_D (calc.), 43.92; found, 43.70.

Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate (2; R = Et)

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate was prepared in 70% yield according to Johnsons and Johns' method(1), which involved the condensation of diethyl oxalate with diethyl diglycolate in the presence of sodium ethoxide, in ether solution, and in the same yield by a condensation using sodium ethoxide in the presence of excess ethanol(2).

Diethyl 3,4-Dimethoxy-2,5-Furandicarboxylate (3; R = Et)

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate (15 g., 0.06 mole) was added to 120 ml. of water containing 4.9 g. (0.12 mole) of sodium hydroxide and shaken well until dissolved. Dimethyl sulfate (7.8 g., 0.06 mole) was slowly added with stirring and the mixture was then refluxed for one hour. An oily layer formed, which, after separation from the alkaline solution, solidified on standing. This solid was taken up in benzene and the solution shaken with 20 ml. of 10% sodium hydroxide solution. The benzene layer was dried with anhydrous magnesium sulfate and then concentrated, leaving long white needles of diethyl 3,4-dimethoxy-2,5-furandicarboxylate, (4 g.; 24% yield) melting at 54-55°. Hoehn(3) reported a melting point of 48°.

Ethyl 5-Carboxy-3-Hydroxy-4-Methoxy-2-Furancarboxylate (7; R = Et)

In the above experiment, the alkaline extract of the benzene solution gave on acidification a white crystalline solid, which was removed by filtration and washed with water. Yield of ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate was 2 g. (14%); m.p. 192-195° (decomp.). Recrystallization from ethanol raised the melting point to 202° (decomp.).

Analysis:

Calc. for $C_9H_{10}O_7$: C, 47.0; H, 4.35%.

Found: C, 47.2; H, 4.76%.

Diethyl 3-Hydroxy-4-Methoxy-2,5-Furandicarboxylate (4; R = Et)

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate (21.2 g., 0.085 mole) was dissolved in 150 ml. of water containing 7 g. (0.17 mole) of sodium hydroxide, then dimethyl sulfate (10.7 g., 0.085 mole) was added slowly, with stirring, and the mixture was refluxed for one hour after the addition. The solid formed (mostly inorganic) was removed by filtration, the aqueous solution extracted with ether, and the ether evaporated to give 2 g. (17%) of diethyl 3,4-dimethoxy-2,5-furandicarboxylate. The aqueous layer was acidified, and the precipitate washed well with water and recrystallized from aqueous ethanol to give plates (14.3 g.) having a melting point range of 70-100°. Further recrystallization from the same solvent brought down the range to 70-86°. Finally, distillation under vacuum* gave a product boiling at 118-119°/0.13 mm. which solidified directly in the receiver. Recrystallization from ligroin gave white plates of diethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate melting at 73.6-75.6°.

Analysis:

Calc. for $C_{11}H_{14}O_7$: C, 51.15; H, 5.46%.

Found: C, 51.02; H, 5.59%.

Diethyl 3,4-Dibenzoyloxy-2,5-Furandicarboxylate (9; R = Et)

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate was dissolved in the calculated amount of 10% sodium hydroxide solution and was benzoylated in the usual way with benzoyl chloride. The resulting solid ester was removed by filtration, washed with water, and recrystallized from aqueous ethanol to give white needles of diethyl 3,4-dibenzoyloxy-2,5-furandicarboxylate, m.p. 141-143°.

Analysis:

Calc. for $C_{24}H_{20}O_9$: C, 63.70; H, 4.42%.

Found: C, 63.61; H, 4.27%.

3,4-Dimethoxy-2,5-Furandicarboxylic Acid (5)

Dimethyl 3,4-dimethoxy-2,5-furandicarboxylate (2 g., 0.0082 mole) was dissolved in 15 ml. of 10% sodium hydroxide solution and boiled for half

---

* The author is grateful to Mr. I. Puskas who carried out the high vacuum distillation, and prepared the sample for analysis.

an hour. After cooling, the solution was acidified and the solid that formed was removed and washed with water. Recrystallization from aqueous methanol afforded white plates of 3,4-dimethoxy-2,5-furandicarboxylic acid (1.5 g.; 85%), m.p. 245° (decomp.). Hoehn$^{(3)}$ reported a melting point of 243-245° (decomp.) for this acid.

In the same manner as above, the acid (5) was obtained in 95% yield by hydrolysis of the diethyl 3,4-dimethoxy-2,5-furandicarboxylate (3; R = Et).

3,4-Dimethoxyfuran* (6)

3,4-Dimethoxyfuran was prepared by the decarboxylation of 3,4-dimethoxy-2,5-furandicarboxylic acid (5) in three different ways:

(a) Decarboxylation in Quinoline: 3,4-Dimethoxy-2,5-furandicarboxylic acid (2.5 g., 0.0116 mole) was suspended in 3 ml. of quinoline and the mixture refluxed until the solid particles had disappeared. Decarboxylation was very rapid as shown by the vigorous evolution of gas as soon as refluxing started. The mixture was then fractionated under vacuum and the fraction boiling at 96-98°/18 mm. was collected. Refractionation of this liquid gave 3,4-dimethoxyfuran as a clear oil (0.285 g., 19%), $n_D^{22.5}$ 1.4708 (n_D^{25} 1.4650 as reported by Hoehn$^{(3)}$). The slightly higher refractive index indicated a small amount of impurity (quinoline) whose presence was confirmed by ultraviolet study.

---

*The author wishes to express his thanks to Mr. I. Puskas for carrying out parts (a) and (b) of this experiment.

(b) Decarboxylation in Silicone Oil: 3,4-Dimethoxy-2,5-furandicarboxylic acid (5) (2 g., 0.0093 mole) was placed in 3 ml. of silicone oil (D.C. 550) and heated slowly with a micro-burner. The use of an inert liquid such as silicone oil was to allow even distribution of heat and to prevent superheating of the acid. Decarboxylation took place very slowly and 0.3 g. of copper powder was added to catalyze the process. After one hour of heating (using a reflux condenser to prevent any evaporation of the expected 3,4-dimethoxyfuran), the mixture was fractionated under vacuum. The clear liquid of 3,4-dimethoxyfuran was obtained in 10.2% yield (0.121 g.), n^{25}_{D} 1.4641. The clear liquid soon became yellowish on standing in air. A longer period of exposure to air resulted in darkening and hardening.

(c) Decarboxylation in the Solid State: 3,4-Dimethoxy-2,5-furandicarboxylic acid (1 g., 0.0046 mole) was placed in a semi-micro distilling apparatus and heated on a metal bath above its melting point (bath temperature 265°). A clear oil distilled off at 180°, which turned brown on coming in contact with air. The infrared spectrum of the compound (Fig. 12) showed the presence of a small amount of a carbonyl compound beside 3,4-dimethoxyfuran.

Other experiments on decarboxylation of the acid (5) in the solid state were carried out by heating the acid slowly and applying vacuum. From the oil that distilled off in such experiments, small crystals separated on cooling and were identified as 3,4-dimethoxy-2-furoic acid, m.p. 168-170° (Hoehn(3) reports a melting point of 170-171°).

Methanesulfonation of Dimethyl 3,4-Dihydroxy-2,5-Furandicarboxylate

Dimethyl 3,4-dihydroxy-2,5-furandicarboxylate (4.32 g., 0.02 mole) was dissolved in 30 ml. of water containing sodium hydroxide (1.6 g., 0.04 mole) then methanesulfonyl chloride (2.28 g., 0.02 mole) was added, and the mixture immediately shaken rapidly. After a few minutes, a yellow solution containing a pasty solid appeared. The solid was separated and recrystallized from methanol to give fine white needles of dimethyl 3,4-dimethanesulfonyloxy-2,4-furandicarboxylate (13; R = Me) (0.6 g.; 20% yield), m.p. 131.5°. It gave no red color with ferric chloride solution.

Analysis:

Calc. for $C_{10}H_{12}O_{11}S_2$: C, 32.20; H, 3.56; S, 17.15%.

Found: C, 32.09; H, 3.41; S, 17.09%.

The yellow solution above was acidified to give a voluminous precipitate, which was recrystallized from methanol. White needles of dimethyl 3-hydroxy-4-methanesulfonyloxy-2,5-furandicarboxylate (12; R = Me) (3.88 g.; 66% yield), m.p. 142-143°, were obtained. A violet color was produced with ferric chloride solution.

Analysis:

Calc. for $C_9H_{10}O_9S$: C, 32.20; H, 3.56; S, 17.15%.

Found: C, 32.09; H, 3.41; S, 17.09%.

Dimethyl 3-Methanesulfonyloxy-4-Methoxy-2,5-Furandicarboxylate (15; R = Me)

Dimethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (4.6 g. of crude compound, 0.02 mole) was dissolved in 50 ml. of water containing 0.8 g. (0.02 mole) of sodium hydroxide, then methanesulfonyl chloride (2.28 g., 0.02 mole) was added. The mixture was immediately shaken for a few minutes at the end of which, a grey pasty solid appeared. The solution was decanted, and the solid recrystallized from aqueous methanol. A second recrystallization from the same solvent yielded dimethyl 3-methanesulfonyloxy-4-methoxy-2,5-furandicarboxylate (3.35 g., 61% yield) in the form of white needles melting at 92.5°. It gave no red color with ferric chloride solution.

Analysis:

Calc. for $C_{10}H_{12}O_9S$: C, 38.95; H, 3.89; S, 10.4%

Found: : C, 38.98; H, 3.94; S, 10.19%

Methanesulfonation of Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate (24.4 g., 0.1 mole) was dissolved in 180 ml. of water containing 8 g. (0.2 mole) of sodium hydroxide. Methanesulfonyl chloride (11.4 g., 0.1 mole) was added quickly and the mixture was shaken vigorously by hand. After a few minutes a grey paste appeared which, on decantation of the supernatant liquid, crystallized into fine needles. On recrystallization from aqueous ethanol, white needles of diethyl 3,4-dimethanesulfonyloxy-2,5-furandicarboxylate (13; R = Et) (2 g.; 10% yield), m.p. 83-85° were obtained. The compound gave no red color with ferric chloride solution.

Analysis:

Calc. for $C_{12}H_{16}O_{11}S_2$: C, 36.00; H, 4.00; S, 16.00%

Found: : C, 36.26; H, 4.03; S, 15.94%

The supernatant liquid above was acidified and a heavy precipitate formed which, upon recrystallization from aqueous ethanol, gave white needles of diethyl 3-hydroxy-4-methanesulfonyloxy-2,5-furandicarboxylate (12; R = Et) (10 g.; 31% yield), m.p. 108-110°. A deep red color was obtained with ferric chloride.

Analysis:

Calc. for $C_{11}H_{14}O_9S$: C, 41.00; H, 4.35; S, 9.85%

Found: : C, 41.08; H, 4.38; S, 9.62%

Diethyl 3-Methanesulfonyloxy-4-Methoxy-2,5-Furandicarboxylate (15; R = Et)

Diethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (2.58 g. of crude compound, 0.01 mole) was dissolved in 25 ml. of water containing 0.4 g. (0.01 mole) of sodium hydroxide, then methanesulfonyl chloride (1.14 g., 0.01 mole) was added quickly and the mixture shaken vigorously. A white pasty solid appeared which crystallized into plates on decantation of the supernatant liquid. Recrystallization from aqueous ethanol yielded white plates of diethyl 3-methanesulfonyloxy-4-methoxy-2,5-furandicarboxylate (15; R = Et) (2.5 g.; 75% yield), m.p. 101-102°. No red color was obtained with ferric chloride solution.

Analysis:

Calc. for $C_{12}H_{16}O_9S$: C, 42.87; H, 4.76; S, 9.52%.

Found: C, 42.75; H, 4.70; S, 9.38%.

Reduction of Dimethyl 3-Hydroxy-4-Methanesulfonyloxy-2,5-Furandicarboxylate (12; R = Me)

The reduction was carried out according to the procedure of Kenner and Williams(22) with slight modification as follows:

Dimethyl 3-hydroxy-4-methanesulfonyloxy-2,5-furandicarboxylate (2.94 g., 0.01 mole) was dissolved in about 30 ml. of liquid ammonia, and then freshly-cut sodium (0.69 g., 0.03 g.-atom) was added gradually in small pieces, and the flask shaken occasionally by hand. The yellow solution slowly turned dark green on the addition of sodium, but no blue color appeared. When all the sodium dissolved, the solution was kept in the fume cupboard for three hours until all the ammonia evaporated. One ml. of ethanol was then added, and the dark brown residue was washed with ether. The ethereal solution yielded nothing on evaporation. The brown residue was then taken up in water and the solution acidified, whereby a white precipitate formed. On crystallization from methanol, white prisms (1.3 g.; 60% yield) were obtained which melted at 218-220°. Mixed melting point with authentic dimethyl-3,4-dihydroxy-2,5-furandicarboxylate was 219-220°.

Reduction of Dimethyl 3-Methanesulfonyloxy-4-Methoxy-2,5-Furandicarboxylate (15; R = Me)

Dimethyl 3-methanesulfonyloxy-4-methoxy-2,5-furandicarboxylate (6.16 g., 0.02 mole) was dissolved in 50 ml. of liquid ammonia, and then lithium metal (0.28 g., 0.04 g.-atom) was added slowly and the mixture shaken every now and then. As the addition of lithium proceeded more ammonia had to be added due to evaporation of the ammonia in the reaction flask. A total of about 120 ml. of liquid ammonia was added, and the reaction mixture turned dark green as in the case of sodium above. On evaporation of the excess ammonia, the green-brown residue was first washed with ether then dissolved in water, boiled for two minutes, and finally acidified to yield white crystals (2.5 g.; 58% yield), which on recrystallization from aqueous methanol melted at 243-245° (decomp.), and gave a red color with ferric chloride solution. Mixed melting point with authentic methyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (decomp.).

Reduction of Diethyl 3-Methanesulfonyloxy-4-Methoxy-2,5-Furandicarboxylate (15; R = Et)

Diethyl 3-methanesulfonyloxy-4-methoxy-2,5-furandicarboxylate (22 g., 0.065 mole) was reduced with sodium (3 g., 0.13 g.-atom) and liquid ammonia (about 120 ml.) in the same manner as above. On working up the residue, white crystals (6 g., 40% yield) were obtained; m.p. 195° (decomp.). These were identified as ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate by mixed melting point with an authentic sample.

Condensation of *n*-Butyl Glyoxylate and Diethyl Diglycolate

A mixture of *n*-butyl glyoxylate(30) (13 g., 0.1 mole) and diethyl diglycolate (19 g., 0.1 mole) was added slowly, with stirring, to a solution of sodium ethoxide (6.6 g. of sodium, 0.29 g.-atom in 100 ml. of absolute ethanol) in ethanol. The mixture was left for five days at room temperature under dry nitrogen, then poured into 150 ml. of water, acidified with dilute acid, and the acid solution extracted with chloroform. Concentration of the chloroform solution gave an oily residue together with some crystals. The crystals were separated by filtration and washed with a small amount of 50% aqueous ethanol, then recrystallized from aqueous ethanol to give white needles (< 0.5 g.) m.p. 185-186°. Both infrared spectroscopy and mixed melting point determination showed the compound to be diethyl 3,4-dihydroxy-2,5-furandicarboxylate. The oil was boiled with a 10% solution of sodium hydroxide for ten minutes, the alkaline solution extracted with ether, and then acidified, whereupon an oil was recovered on extraction of the acid solution with ether. An ill-defined infrared spectrum of the oil was obtained and showed no carbonyl frequencies above 1700 cm.$^{-1}$

Condensation of Diethyl Mesoxalate with Diethyl Diglycolate

(a) Using Sodium Ethoxide: A mixture of diethyl mesoxalate (8.7 g., 0.05 mole) and diethyl diglycolate (9.5 g., 0.05 mole) was added with stirring to an ice-cooled solution of sodium ethoxide (4.5 g. of sodium in 70 ml. of absolute ethanol) in ethanol. The mixture was left for five days at room temperature in a closed flask, then dissolved in water and acidified with dilute acid. The acidified solution was extracted with chloroform, and the dried extract on evaporation yielded a viscous oil which contained long white needles. On separation by filtration and recrystallization from aqueous ethanol, the crystals (3 g., 25% yield), which gave a red color with ferric chloride, were identified as diethyl 3,4-dihydroxy-2,5-furandicarboxylate by melting point and mixed melting point. The viscous oil which separated was left in a desiccator for six weeks whereupon it slowly solidified. On recrystallization from aqueous ethanol, tiny white flakes, m.p. 178-180°, were obtained and formulated as diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (1 g,; 7.4% yield). A deep red color was produced in the ferric chloride test, and the infrared spectrum of the compound (Fig. 14) indicated the presence of a carbonyl absorption band above 1700 cm.$^{-1}$ as well as carbonyl absorption below 1700 cm.$^{-1}$ indicating the absence of chelation in the first case and the presence of it in the second.

<u>Analysis</u>:

Calc. for $C_{11}H_{12}O_8$: C, 48.2; H, 4.41%.

Found: C, 48.7; H, 4.38%.

(b) <u>Using Sodium Methoxide</u>: The above experiment was repeated using dimethyl diglycolate (6.4 g.; 0.04 mole) and diethyl mesoxalate (6.8 g., 0.04 mole) with sodium methoxide (3 g. sodium in 60 ml. of absolute methanol). Acidification of the aqueous solution of the product gave a white crystalline precipitate which was separated by filtration. The filtrate was extracted with chloroform from which on evaporation a further amount of the same solid was obtained. The crystals (2.8 g.; 32% yield) gave a positive ferric chloride test and were identified as dimethyl 3,4-dihydroxy-2,5-furandicarboxylate by means of melting point and mixed melting point.

In a second experiment the solution of sodium methoxide (11 g. sodium, 0.48 g.-atom in 120 ml. of absolute methanol) in methanol was added to a mixture of dimethyl diglycolate (25.7 g., 0.16 mole) and diethyl mesoxalate (27.6 g., 0.16 mole) with stirring and cooling, over a period of 40 minutes. White crystals (10.146 g.; 30% yield), identified as dimethyl 3,4-dihydroxy-2,5-furandicarboxylate, were obtained. Further quantities (3 g.) of the crude product were obtained upon concentration of the aqueous layer, extraction with chloroform, and evaporation of the solvent.

(c) Using Potassium t-Butoxide: Potassium t-butoxide was prepared (31) from potassium metal (3.9 g., 0.1 g.-atom) and dry t-butyl alcohol (82 ml.). A mixture of diethyl mesoxalate (8.7 g., 0.05 mole) and diethyl diglycolate (9.5 g., 0.05 mole) was added to the solution of potassium t-butoxide with stirring, under nitrogen atmosphere. Stirring was continued for half an hour, then the reaction flask was stoppered and left for three days at room temperature. The contents were then dissolved in water and the solution extracted with ether to remove any starting material or neutral by-products. The aqueous layer was acidified and extracted with six 20-ml. portions of chloroform. On evaporation of the combined chloroform extracts, a red viscous oil containing a small amount of needle-like crystals, was obtained. The crystals (0.5 g.) were separated and recrystallized from aqueous ethanol, giving needles, m.p. 77.5°. They gave no red color with ferric chloride solution, and the absence of an enolic or phenolic hydroxyl group was confirmed by infrared spectroscopy (Fig. 17), which also showed the presence of a wide carbonyl absorption band at 1735-1720 cm.$^{-1}$

Analysis:

Found: C, 50.90; H, 6.57%.

Calc. for $C_{24}H_{38}O_{15}$: C, 50.85; H, 6.71%.

BIBLIOGRAPHY

1. Johnson, T.B. and Johns, C.O., Am. Chem. J., 36, 290 (1906).
2. Hinsberg, O., Ber., 45, 2413 (1912).
3. Hoehn, W.M., Iowa State Coll. J. Sci., 11, 66 (1936).
4. Anschütz, R. and Biernaux, F., Ann., 273, 64 (1893).
5. Heintz, W., Ann., 144, 95 (1868).
6. Heintz, W., Ann., 147, 144 (1868).
7. Curtius, T., J. prakt. chem., 2 , 38, 431 (1888).
8. Loder, D.L. (To E.I. du Pont de Nemours and Co.), U.S. Patent 2,405,967 (1946).
9. Schubert, W.M. and Sweeny, W.A., J. Am. Chem. Soc., 77, 4172 (1955).
10. Saunders, R.H., Murray, M.J. and Cleveland, F.F., J. Am. Chem. Soc., 63, 3121 (1941).
11. Hadzi, D. and Sheppard, N., J. Am. Chem. Soc., 73, 5460 (1951).
12. Abe, S., J. Chem. Soc. Japan, 59, 1117 (1938); C.A. 33, 2033 (1939).
13. Sartoretto, P. and Sowa, F.J., J. Am. Chem. Soc., 59, 603 (1937).
14. Kranzfelder, A., Verbanc, J. and Sowa, F.J., J. Am. Chem. Soc., 59, 1488 (1937).
15. Weber, F. and Sowa, F.J., J. Am. Chem. Soc., 60, 94 (1938).
16. Birch, A.J., J. Chem. Soc., 1947, 102.
17. Strating, J. and Backer, H.J., Rec. trav. chim., 69, 638 (1950).
18. Kenner, G.W. and Murray, M.A., J. Chem. Soc., 1950, 406.
19. Bunnett, J.F. and Bassett, J.Y., J. Am. Chem. Soc., 81, 2104 (1959).
20. Ingold, C.K., "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, p. 700.
21. Birch, A.J., Quart. Revs., 4, 69 (1950).
22. Kenner, G.W., and Williams, N.F., J. Chem. Soc., 1955, 522.

23. Traube, W., Ber., 42, 3295 (1909).

24. Bellamy, L.J., "The Infrared Spectra of Complex Molecules", John Wiley and Sons, Inc., New York, 1958, p. 168.

25. Denis, W., Am. Chem. J., 38, 561 (1907).

26. Hauser, C.R. and Renfrow, W.B., J. Am. Chem. Soc., 59, 1823 (1937).

27. Hauser, C.R., J. Am. Chem. Soc., 60, 1957 (1938).

28. Adams, R. Editor, "Organic Reactions", John Wiley and Sons, Inc., New York, 1942, Vol. I, pp. 267-270.

29. Newman, M.S., Editor, "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc., New York, 1956, pp. 73-77.

30. "Organic Syntheses", 35, 19 (1955).

31. Adams, R., Editor, Op. Cit., 1951, Vol. VI, p. 42.

PART III

Physico-chemical Studies

The infrared, ultraviolet, and nuclear magnetic resonance spectra of a number of furan derivatives prepared in the course of this work have been studied and correlations with the structure of these compounds have been made. The structure of α-angelica lactone has also been studied and some evidence regarding the absence of a furanol form is discussed. The strongly phenolic nature of some of the β-hydroxyfuran derivatives prepared in this laboratory was observed, and some potentiometric titrations were made, from which the dissociation constants of these phenols were obtained. Finally some conclusions regarding the structure of aucubin are discussed in the light of the data obtained in this study.

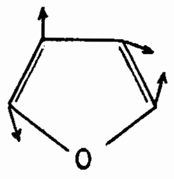
I - Infrared Absorption Spectra

A. The Furan Ring

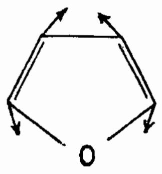
The infrared spectra of furan both in the liquid and vapor phase, have been studied in some detail by several investigators(1,2,3,4). However, the first attempts at a systematic infrared study of mono- and di-substituted furans were made fairly recently by Cross et al.(5) and slightly later by Daasch(6). Most recently, a thorough study of 2-mono-substituted furans has been made by Katritzky and Lagowski(7), who cleared up some controversial correlations given in previous work. Unfortunately, the work on tri- and fully substituted furans in the infrared region seems to be completely lacking. In the course of this work, the infrared spectra of a number of fully substituted furans, as well as some di- and trisubstituted furans, were examined and correlations with the structure of these compounds as well as comparison with the reported characteristic furan frequencies (5,6,7), have been attempted.

The instrument used for this study was a Perkin-Elmer Model 21 double-beam recording spectrophotometer equipped with a rock-salt prism. Such a prism is not expected to have a high resolving power(8) in the region 4000-2000 cm.$^{-1}$, and furthermore, the relative intensities of bands will be low(8). However, all the mono- and disubstituted furans examined showed a relatively weak band between 3152-3127 cm.$^{-1}$ (see Table I). This is probably the =C-H stretching vibration, since the band disappears in the fully substituted furans. Pickett(1) and Thompson and Temple(2) reported bands in this region at 3164 cm.$^{-1}$ and 3185 cm.$^{-1}$ respectively, for furan vapor, using fluorite prisms, and assigned them to =C-H stretching vibrations.

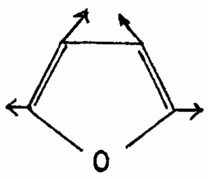
Furans generally absorb in the region 1600-1400 cm.$^{-1}$ Katritzky and Lagowski(7) attributed this absorption to the furan ring stretching frequencies (modes I - III). All the compounds examined here showed at



(I)



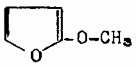
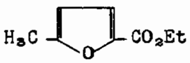
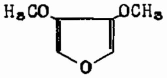
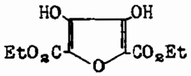
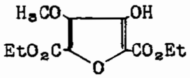
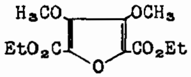
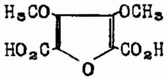
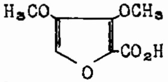
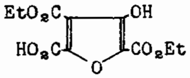
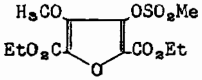
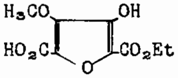
(II)



(III)

TABLE I

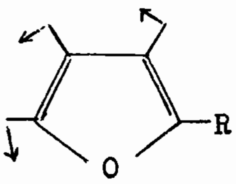
Characteristic Furan Frequencies

Compound	=C-H Stretching	Ring Stretching			H In-plane Deformation			Ring Breathing	H Out-of-plane Deformation		Technique	Figure
1. 	3140 (w)	1610 (vs)	1535 (s)	1396 (s)	1216 (sh)	1150 (w)	1070 (m)	1006 (s)	940 (m)	880 (m) 740 (m)	Liquid film	1
2. 	3145 (w)	1623 (s) 1597 (s)	1462 (sh)	1387 (sh)	1215 (m)	1170 (sh)	1065 (m)	1022 (m)	950(sh) 940 (m)	807 (w) 735 (m)	Liquid film	2
3. 	3127 (w)	1598 (m)	1527 (s)	1390 (sh)	1208 (s)	1170 (sh)	1092 (sh)	1018 (s)	962 (m) 945 (m)	860 (m) 756 (m)	Liquid film	23
4. 	3035 (w) 3152 (w)	1630 (s) 1578 (s)	1540 (sh)	1390 (sh) 1415 (m)	1216 (s)	1145 (s)	1070 (sh)	1010 (s)	-	868 (s)	Liquid film	10
5. 	-	1615 (w) 1577 (s)	1523 (w)	1410 (m)	-	-	-	1015 (m)	-	-	Nujol mull	15
6. 	-	1620 (w)	*	1400 (m)	-	-	-	1022 (m)	-	-	2% CCl_4 solution	18
7. 	-	1607 (w)	*	1392 (m)	-	-	-	1026 (s)	-	-	1% CCl_4 solution	19
8. 	-	1595 (m) 1562 (s)	1515 (sh)	1385 (sh)	-	-	-	983	-	-	KBr pellet	20
9. 	-	1597 (w) 1557 (s)	1492 (s)	1390 (m)	-	-	-	997 (m)	-	-	KBr pellet	21
10. 	-	1610 (m)	1490 (m)	1400 (m)	-	-	-	1020 (m)	-	-	Nujol mull	14
11. 	-	1612 (w)	*	1386 (s)	-	-	-	1025 (m)	-	-	0.5% CCl_4 solution	22
12. 	-	1612 (w) 1570 (m)	1512 (w)	1380 (w)	-	-	-	1015 (w)	-	-	Nujol mull	16

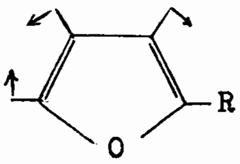
* Solvent absorption

least two bands in this region. In some cases, however, the presence of bands was obscured by the absorption of the solvent (CCl_4).

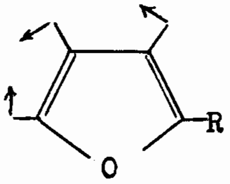
The hydrogen in-plane deformation frequencies (modes IV - VI) appear between 1200 and 1050 cm.$^{-1}$ according to Katritzky and Lagowski(7), while Cross et al.(5) correlate the bands at 1248-1218 cm.$^{-1}$ with the C-O-C asymmetric stretching vibration. Since in three of the fully substituted furans studied (compounds (1), (2) and (3) below), this band was completely absent (see Figs. 19,18 and 20), while in the other fully substituted furans strong bands in this region were correlated with other groups (ester and carboxylic groups) known to absorb in this region, we favor the correlation of Katritzky and Lagowski.



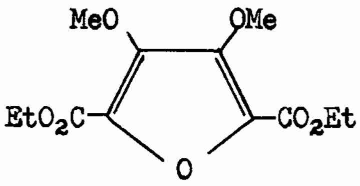
(IV)



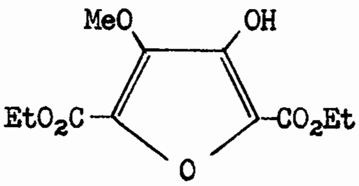
(V)



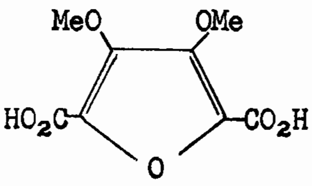
(VI)



(1)

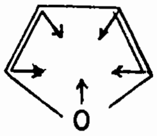


(2)



(3)

A band that consistently appeared between 1025 and 1006 $cm.^{-1}$ in all the compounds examined was attributed to ring breathing frequency (mode VII) by Katritzky and Lagowski(7). Jones et al.(9) correlated this frequency with the C-H bending mode of vibration. However, it is evident from this study that this cannot be the case, since fully substituted furans exhibit medium to strong absorption in this region (with the exception of 3,4-dimethoxy-2,5-furandicarboxylic acid).



(VII)

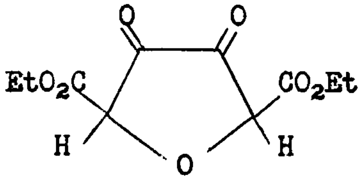
Absorption between 1000 and 700 $cm.^{-1}$ has been correlated with the C-H out-of-plane deformation vibration(5,7), and while most of the compounds examined here (including the fully substituted furans) showed a number of bands in this region, all the compounds having at least one hydrogen atom in the nucleus showed absorption bands in this region which may be attributed to this mode of vibration. Unfortunately, due to the limited number and variety of mono-, di-, and trisubstituted furans studied, no definite correlation between the position of substituent(s) and position of band in this region, as in the case of benzene(10), could be given.

Kubota(11) selected the bands around 3125 cm.$^{-1}$ (C-H stretching), 1563 and 1511 cm.$^{-1}$ (aromatic ring) and 885-869 cm.$^{-1}$ to be the characteristic absorption bands of the furan ring. It will be clear from the above discussion that the bands at 3125 and 885-869 cm.$^{-1}$ appear only when there are free hydrogen atoms in the furan nucleus and disappear in fully substituted furans and therefore cannot be taken as characteristic of the furan ring. Furthermore, the band around 1563 cm.$^{-1}$ seems to be at the lowest extreme of the range since all the furans examined in this laboratory and most of the furans examined by Katritzky and Lagowski absorb at higher frequencies (30-40 cm.$^{-1}$ higher in some cases). However, it must be understood that bands in this region are sensitive to the type of substituent, a shift towards lower frequencies taking place as a result of conjugation. On the other hand, the band at 1006-1025 cm.$^{-1}$ (ring breathing) seems to be the most consistently stable in position and is not affected by the type or number of substituents. It is evident therefore that such a band, rather than the bands at 3125 or 885-869 cm.$^{-1}$, should be taken as most characteristic of the furan ring.

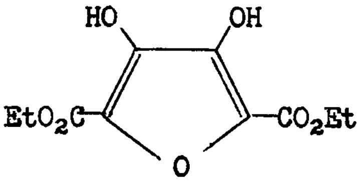
B. The Carbonyl Absorption Bands in Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate and Derivatives

The region 1640-1750 cm.$^{-1}$ was one of the most useful ones in the characterization of the compounds obtained from the condensation of diethyl diglycolate and other dicarbonyl compounds (Part II).

Diethyl 3,4-dihydroxy-2,5-furandicarboxylate was given the formula (4) by Johnson and Johns(12), but soon after, the formula (5) was suggested in favor of the formula (4) by Hinsberg(13) who found that the compound gave a positive ferric chloride test for enols.

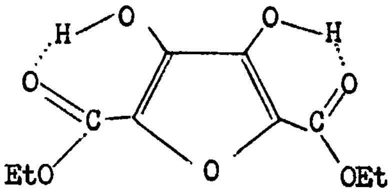


(4)



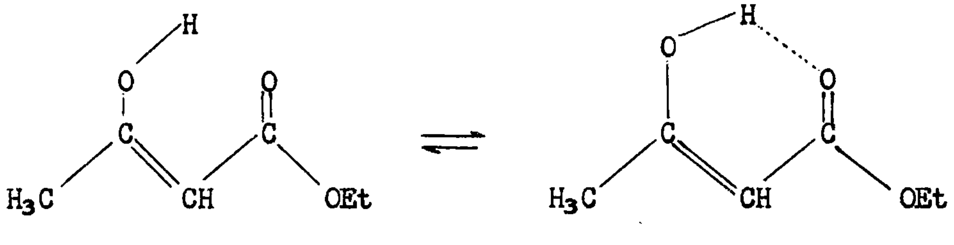
(5)

Later, Hoehn obtained derivatives of the enol form (2) but only one attempt (14) to obtain keto derivatives (with hydrazine) was reported. Infrared studies on this compound and a number of its derivatives show the absence of tautomerism, the compound being completely in the enolic form (5). Dunlop and Peters(15) suggest that the tendency of this compound to react in the enolic form is probably due to the stabilization of the latter form by chelation. Infrared studies indicate that this must be the case.



(6)

The formula (6) indicates that both carbonyl groups of the esters are involved in chelation with the two hydroxyl groups. Rasmussen and Brattain(16) reported that ethyl acetoacetate (7) showed a carbonyl band at 1653 cm.$^{-1}$ which they attributed to the ester carbonyl group after chelation with the enolic hydroxyl group in the tautomeric form (8).

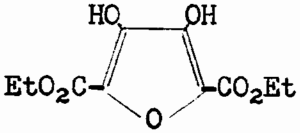
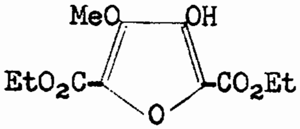
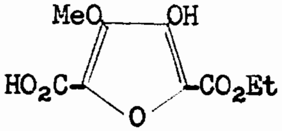
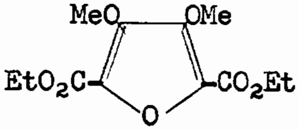
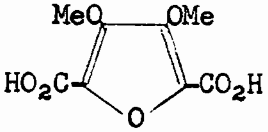
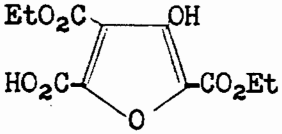
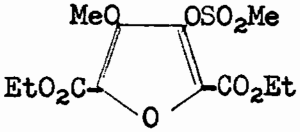


(7) (8)

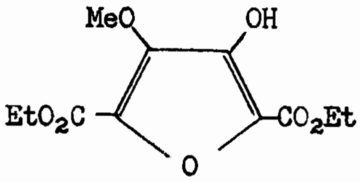
The similarity in structure between (6) and (8) can immediately be seen. Compound (6) shows two carbonyl absorption bands at 1687 and 1657 cm.$^{-1}$ (Table II). The presence of two peaks for the compound (3) with two identical carbonyl groups indicates probably the splitting of the band due to coupling(17) between the C=O vibrations in in-phase and out-of-phase modes as in the case of diacyl and diaroyl peroxides. Davison(17) considers that the mean of the two frequencies is acceptable as the unperturbed frequency of the individual C=O band. The mean frequency in the above case would be 1672 cm.$^{-1}$ and this is in excellent agreement with the carbonyl frequency of the 2-carbethoxy group in diethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (9), which falls at 1670 cm.$^{-1}$ (Table II).

TABLE II

Carbonyl and Hydroxyl Group Absorption of 3-Hydroxy-2-Furancarboxylic Acid Derivatives

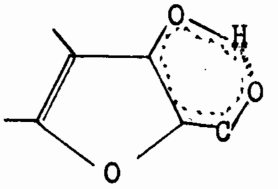
	Compound	Phenolic O-H Stretching (chelate)	Carboxylic O-H Stretching	Ester C=O Stretching (non-chelate)	Ester C=O Stretching (chelate)	Carboxylic C=O Stretching
1.		3360	-	-	1687 1657	-
2.		3360	-	1720	1670	-
3.		3350	3100-3000 2800-2500	-	1672	1692 (sh) 1682 (sh)
4.		-	-	1708 1717	-	-
5.		-	2950-2540	-	-	1700 (sh 1685 (sh) 1670
6.		3260	3160 (sh)	1727	1640	1690
7.		-	-	1740 (sh) 1720	-	-

The absence of any peaks above 1700 cm.$^{-1}$ rules out the possibility of the existence of structure (4) to any appreciable extent. Such a structure is expected to show characteristic frequencies for unconjugated esters (about 1740 cm.$^{-1}$) and α-diketones (about 1730 cm.$^{-1}$ (18)).

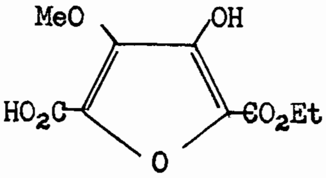


(9)

That chelation is responsible for the shift of the carbonyl frequency downwards, is attested by the fact that as soon as one of the hydroxyl groups is methylated, such as in diethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate (9), a new peak at 1720 cm.$^{-1}$ appears. This is due to the carbonyl vibration of the 5-carbethoxy group, which is expected to behave in a way similar to ordinary furoates (ethyl 5-methyl-2-furoate absorbs at 1715 cm.$^{-1}$). When both hydroxyl groups in the compound (6) are methylated the possibility of chelation exists no more and this is clearly seen in the spectrum of ethyl 3,4-dimethoxy-2,5-furandicarboxylate (1), which shows no carbonyl frequencies below 1700 cm.$^{-1}$, but only one double peak at 1708 and 1717 cm.$^{-1}$. This doubling is again probably due to coupling of the two identical carbonyl groups with the mean falling at around 1713 cm.$^{-1}$ which is the position expected for ordinary furoates, or conjugated esters in general(19). The position of the carbonyl band due to chelation seems to be lower in the compound (6) than in methyl salicylate where the band occurs at 1684 cm.$^{-1}$ (20). This is probably due to the stronger double-bond character(21,22) in the 2,3 bond of furan (84-86%(23)) as compared with the C=C bond in benzene (50%). The greater double-bond character would facilitate greater conjugation between the substituents on the 2,3-carbon atoms of furan with the result that a stronger intramolecular hydrogen bonding takes place (chelation) and a shift of both the O-H and the C=O stretching vibrations to lower frequencies.



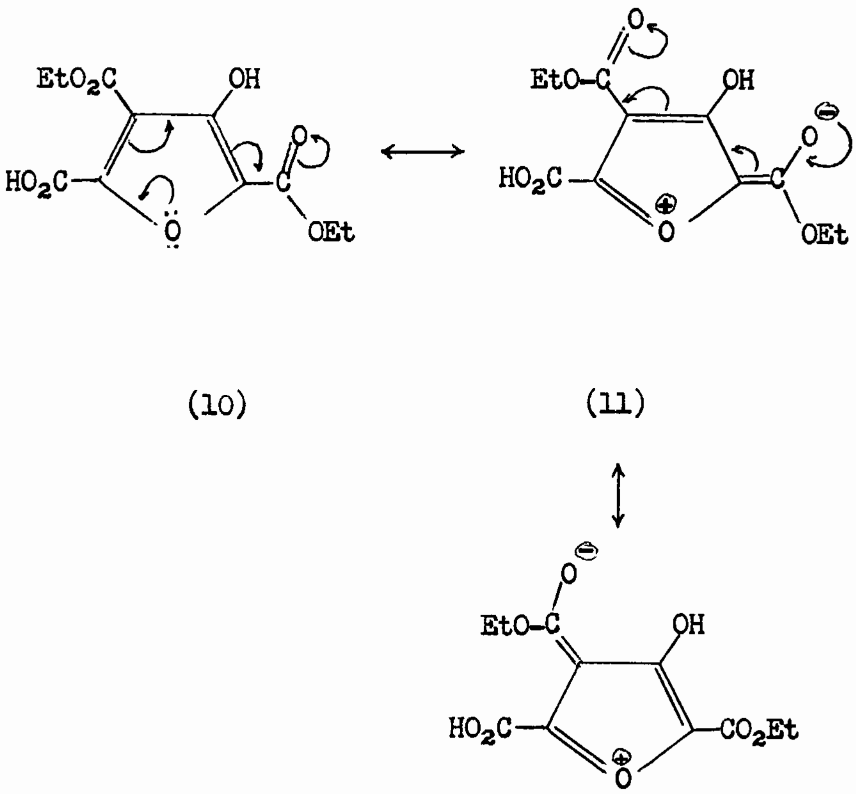
The band at 1672 cm.$^{-1}$ also occurs in the spectrum of ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (9a) in which chelation exists as in the dihydroxy compound (6). However, the free carboxyl group



(9a)

in the 5-position shows a normal absorption for aryl conjugated acids(24) at 1692 cm.$^{-1}$ Possible dimerization of the acid is indicated by the shoulder at 1682 cm.$^{-1}$ and by the absence of a band at 3560-3500 cm.$^{-1}$ for the O-H stretching of the free carboxylic OH group. A more acute case of association of carboxyl groups occurs in 3,4-dimethoxy-2,5-furandicarboxylic acid (2) which shows its stronger peak at 1670 cm.$^{-1}$ with shoulders at 1700 and 1685 cm.$^{-1}$ That this is due to dimerization, can be seen from the position of the carboxylic O-H which shows a weak but very broad band extending from 2950-2540 cm.$^{-1}$ Due to the insolubility of this acid in non-polar solvents, a Fluorolube mull was used and association could not be avoided.

In the case of diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (10) whose infrared spectrum was discussed in some detail in Part II, the chelate carbonyl group absorbs at 1640 cm.$^{-1}$ This seemingly low value for the chelate carbonyl absorption (as compared with 1670 cm.$^{-1}$ in the other compounds discussed above) may be explained on the increased double-bond character of the 2,3 linkage in this compound. This can be seen from the various resonance forms contributing to the resonance hybrid. In the 3,4-dihydroxy-compound (6) and derivatives the main contributing form would be one similar to form (11) below. However, the presence of the ester group in the β-position will now introduce the form (12) in which the double-bond character of the bond 2,3- is increased. The positions of the other two carbonyl groups in the molecule are in agreement with the expected positions for a conjugated acid (1690 cm.$^{-1}$) and a conjugated ester (1727 cm.$^{-1}$). The increased degree of chelation in this compound may also be seen from



(10)

(11)

(12)

the shift of the hydroxyl group stretching vibration from 3360 cm.$^{-1}$ in most of the chelate compounds discussed above, to 3260 cm.$^{-1}$

II - Ultraviolet Absorption Spectra

Changes in electronic spectra due to individual groups are modified by interaction with other groups present in the same molecule. Such interaction may be of three kinds, vibrational, electronic, or steric. Vibrational interaction causes no profound changes in the ultraviolet light absorption properties, except for alternations in the vibrational fine-structure or in the shape of the band envelope. Electronic interaction, on the other hand, can result in marked changes in transition energy and in large wavelength-displacements of the bands. Such interaction is particularly strong in the case of adjacent groups containing highly polarizable π- or p-electrons, and the classical term "conjugation" is given to such interaction. The term "chromophore" is given to unsaturated groups such as $C{=}C$ and $C{=}O$ (π-electron groups), while the term "auxochrome" is given to such groups as $-NR_3$ and $-OR$ (p-electron groups).

It is assumed that a molecule can absorb certain characteristic quanta of light energy which raise it to some electronically excited state. Absorption of light therefore brings about transition of the molecule from its ground state to an electronically excited state, and the difference in energy of these two states will determine the frequency of light absorbed. The more nearly the energy of the first excited state corresponds to the energy of the ground state, the longer is the wavelength of light absorption. Conjugation (π-π conjugation or π-p conjugation) generally results in closing-up of ground and excited electronic levels, i.e., a decrease in transition energy and band displacement to longer wavelength (bathochromic shift). If, on the other hand, resonance stabilizes the ground state more than it stabilizes the excited state, the difference between the two states increases and a shift towards shorter wavelength (hypsochromic shift) takes place. Steric interaction affects light absorption by influencing the stabilization of the molecule in the ground or excited states. If steric factors interfere with resonance stabilization of the excited state, the energy difference between the two states increases and a hypsochromic shift occurs (cf. p. 72).

In studying the ultraviolet spectra of the furan derivatives prepared in the course of this work, the effect of various substituents (auxochromes and chromophores), will be discussed.

A. α- and β-Methoxyfurans

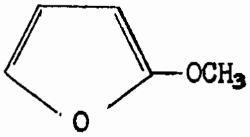
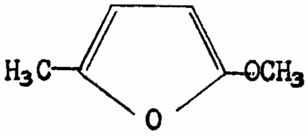
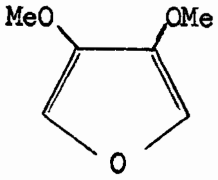
Furan shows very weak absorption above 220 mμ and only end absorption at 210 mμ(25). Recently, Pickett _et_ _al_.,(26) working with a fluorite prism in the vacuum ultraviolet region, obtained a peak for furan vapor at 205 mμ ($\varepsilon_{max.}$ 6,000). However, a small bathochromic shift is observed when alkyl groups are substituted (effect of hyperconjugation). Thus 2,5-dimethylfuran has a maximum of absorption(27) at 219.5 mμ ($\varepsilon_{max.}$ 8,000).

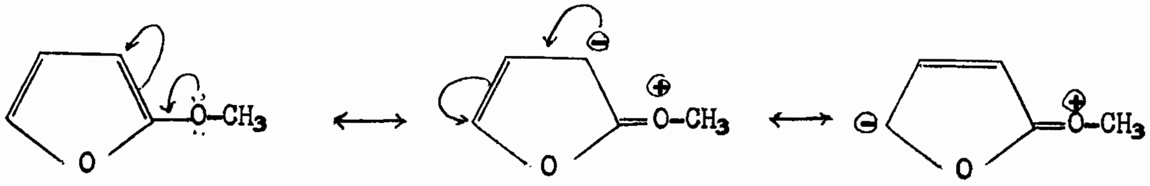
In the present work the effect of substituting methoxyl groups in the α- and β-position of furan was studied (Table III). The methoxyl group is considered as an auxochrome and as such is expected to cause a bathochromic shift when attached directly to an aromatic system(28,29). In furans, it was noticed that well-defined peaks appeared in the spectra of

2-methoxyfuran ($\lambda_{max.}$ 222.5, $\varepsilon_{max.}$ 4,500) and 5-methyl-2-methoxyfuran ($\lambda_{max.}$ 224, $\varepsilon_{max.}$ 5,600), while a shoulder at 213 mμ ($\varepsilon_{max.}$ 9,800) was obtained with 3,4-dimethoxyfuran. The greater bathochromic effect of the α-methoxy group may be explained on the basis of capability of such a group to conjugate (π-p-conjugation(30)) with the diene system of the furan nucleus as shown below (forms VIII and IX).

TABLE III

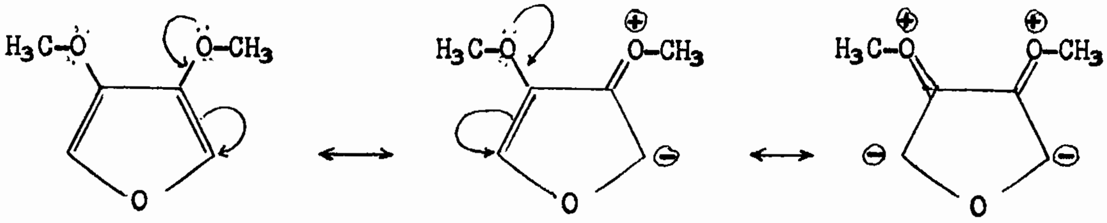
Ultraviolet Absorption Spectra of Methoxyfurans

	Compound	$\lambda_{max.}$	$\varepsilon_{max.}$	Figure
1.		222.5	4,500	24
2.		224	5,600	25
3.		213 (sh)	9,800	11



(VIII) (IX)

Resonance involving such polar forms as (IX) probably stabilizes the excited state more than it stabilizes the ground state, hence the bathochromic shift. On the other hand, the β-methoxy group can only conjugate with one double bond (forms X and XI).



(X) (XI)

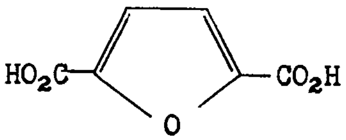
The increased intensity of absorption in the case of 3,4-dimethoxyfuran is probably understandable if we assume that the two methoxy groups work independently of each other and that these effects would be additive (cf. Gillam and Hay(31) on m-polyphenyl compounds).

B. 3-Hydroxy-2-Furancarboxylic Acid Derivatives

This part is concerned mainly with the study of the ultraviolet absorption spectra of the derivatives of 3,4-dihydroxy-2,5-furandicarboxylic acid and of diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (10), whose preparation was discussed in Part II. Six different compounds were chosen, five of which had at least one ionizable hydrogen (see Table IV). To measure the spectrum of the unionized compounds, a drop of concentrated hydrochloric acid was mixed with 25 ml. of each solution.

In contrast with the auxochromic effect of the methoxyl group on the furan diene system (cf. preceding section), the furan ring in the compounds discussed here furnishes a diene system to conjugate (π-π conjugation) with the carbonyl groups of the acids or esters and it is these peaks which appear most prominently in the spectra of these compounds.

Since all the compounds examined had the basic structure of 2,5-furandicarboxylic acid (13), their spectra were compared with that of the acid. The spectrum of the acid (13) was studied by several workers(32,33,34),

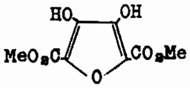
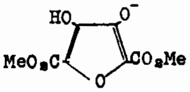
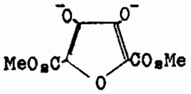
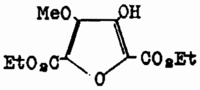
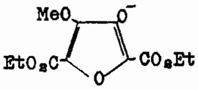
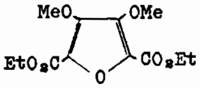
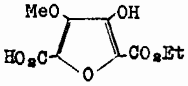
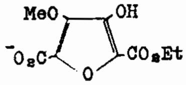
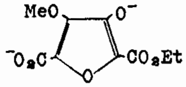
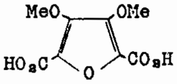
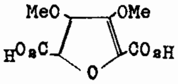
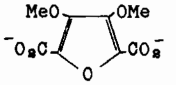
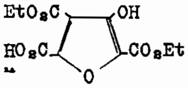
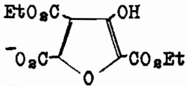
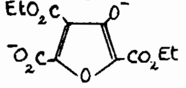


(13)

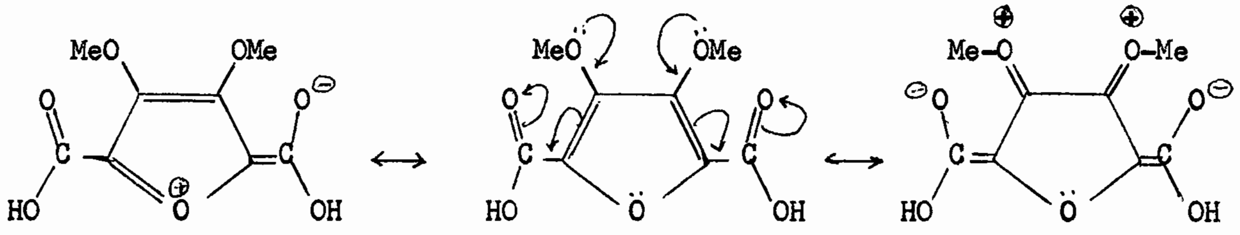
$\lambda_{max.}$ 263 mμ, $\varepsilon_{max.}$ 15,800

TABLE IV

Ultraviolet Absorption Spectra of 3-Hydroxy-2-Furancarboxylic Acid Derivatives

	Compound	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda'_{max.}$	$\varepsilon'_{max.}$	$\lambda''_{max.}$	$\varepsilon''_{max.}$	$\lambda'''_{max.}$	$\varepsilon'''_{max.}$
						mμ			
1.a)		280	21,700						
b)		336	6,970	288	15,700	225	10,000		
c) ×		350(sh)	7,300	320	15,700	225	>20,000		
2.a)		278	19,600						
b)		346	4,140	278	15,600	233	7,350		
3.		274.5	31,400						
4.a)		279	16,500						
b)		317(sh)	3,350	279	13,650				
c) ×		322	7,660	275	9,600	222	9,600		
5.a)		270	8,100						
b)		267.5	7,050						
c)		266.5	7,300						
6.a)		335	7,200	284.5	7,470	250 258(sh)	9,000 7,950	227	15,200
b)		406	6,450	311	4,550	274.5	18,800	230.5	9,350
c)		435	5,600	341	7,250	275	8,280	248	10,600

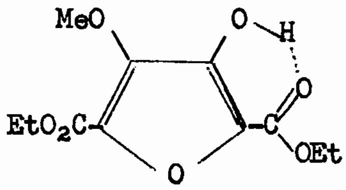
but only Andrisano and his co-workers(34,35) made a systematic study of the furan mono- and dicarboxylic acids and their esters. They found that the acid (13) and its dimethyl ester absorb at 263 mμ ($\varepsilon_{max.}$ 15,800). However, in the present case, all the compounds examined exhibited a bathochromic shift from the 263 mμ peak reported for the simple acid (13) and its methyl esters. Two factors may be responsible for this shift. The first is the auxochromic effect of the methoxyl group in the β-position and this is noticed in the case of 3,4-dimethoxy-2,5-furandicarboxylic acid (3), whose resonance hybrid might receive contributions from such a polar form as (15) beside the form (14) which exists usually in the



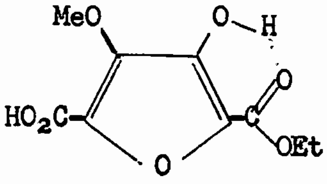
(14) (3) (15)

$\lambda_{max.}$ 270 mμ, $\varepsilon_{max.}$ 8,100

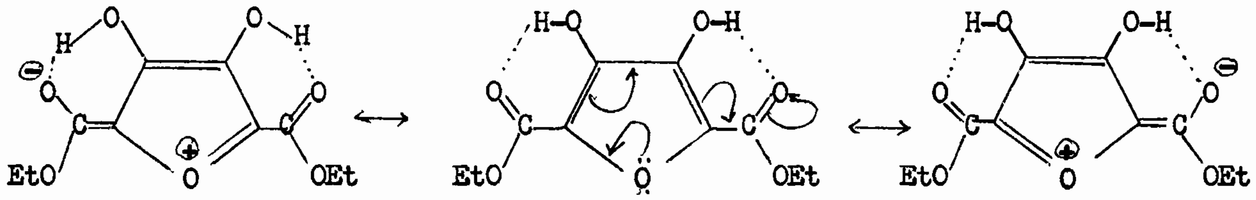
acid (13) itself. A second and more effective factor probably is chelation which appears in the dihydroxy ester (6) and its monomethoxy derivatives (2) and (16). Chelation obviously stabilizes such polar forms as (17) and (18) which contribute to the resonance of the excited state and hence there will be a smaller difference between the ground state and the first excited state than if chelation did not exist. The influence of chelation will be apparent as we examine the dihydroxy compound (6) and its dimethoxy derivative



(2)



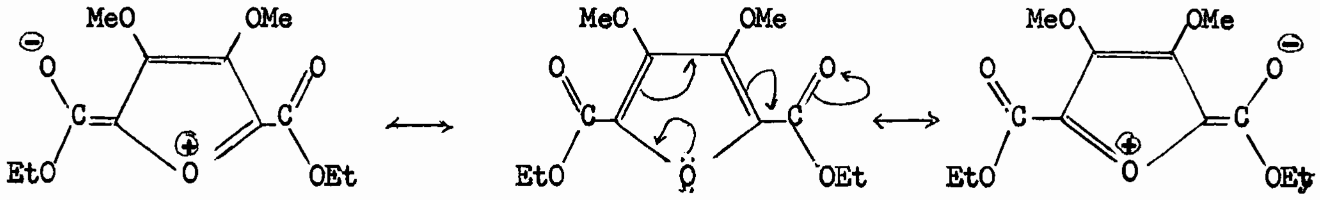
(16)



(18) (6) (17)

$\lambda_{max.}$ 282 mμ, $\varepsilon_{max.}$ 14,700

(1) where chelation is not possible (see Table IV), a hypsochromic shift of 7.5 mμ taking place.

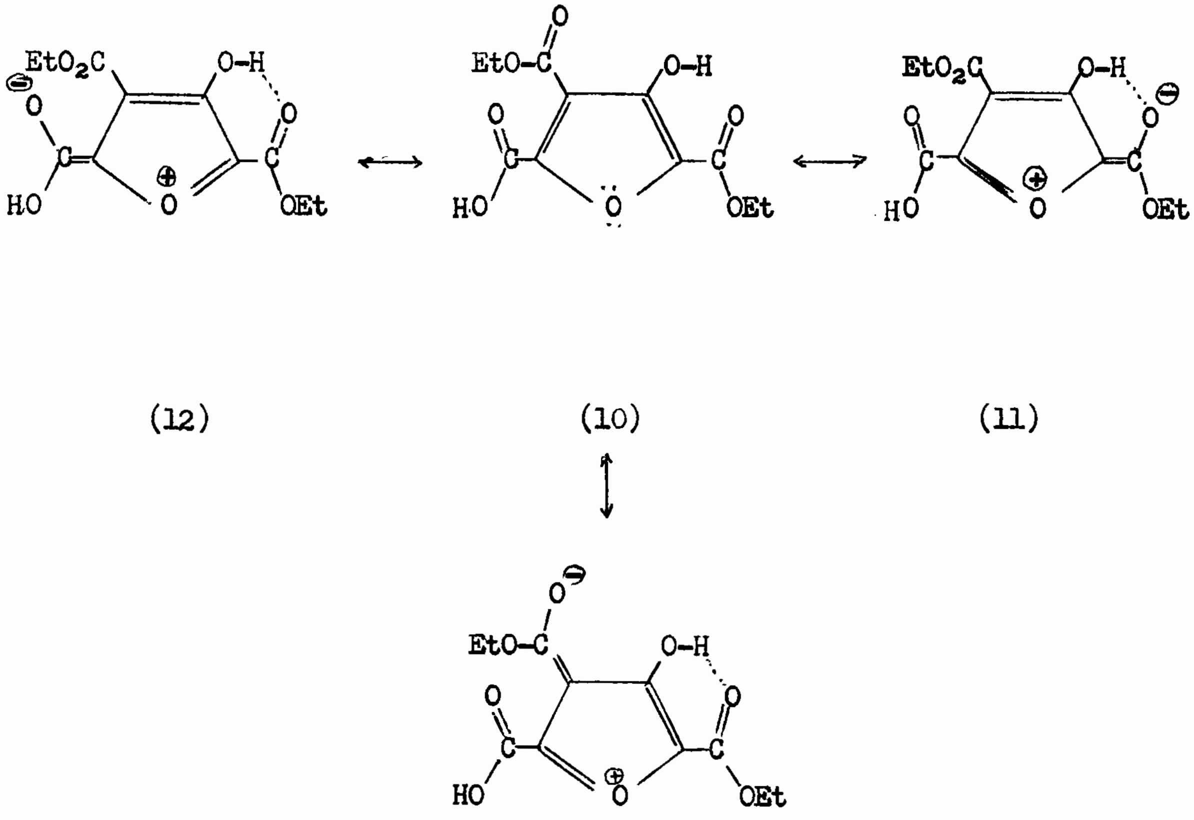


(1)

$\lambda_{max.}$ 274.5 mμ, $\varepsilon_{max.}$ 31,400

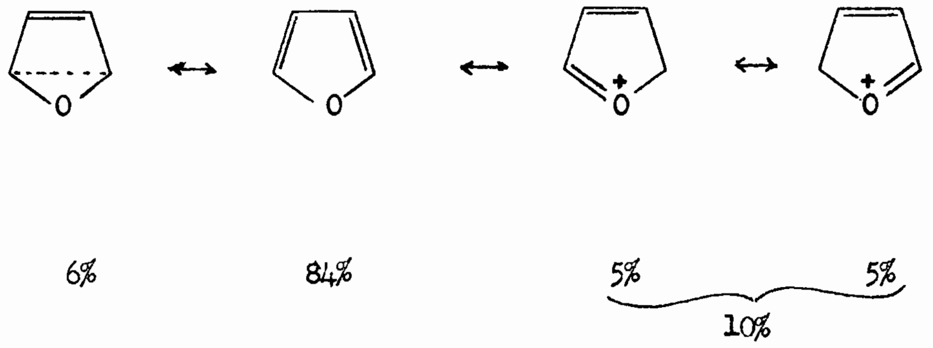
The bathochromic shift observed on going from the acid (3) to its diethyl ester (1) must be due to the influence of the ethyl groups, which is in agreement with the observation of Andrisano and co-workers(35,36) who observed a bathochromic shift of 1 mμ (as compared with 4.5 mμ in this case) on replacing the carboxylic group by carbethoxy groups in 2,5-furandicarboxylic acid. This small shift is probably due to the weak inductive effect of the ethyl group.

The ultraviolet spectrum of diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (10) requires special attention. This compound has an ester group on the β-position instead of the hydroxyl or methoxyl groups in the above-mentioned compounds. Two new peaks appear beside the one assigned for the general structure of the dicarboxylic acid (which appears here at 284.5 mμ). One strong peak at 250 mμ with a shoulder at 258 mμ and the other at 335 mμ. It would be rather difficult to judge on the basis of the resonance forms that contribute to the resonance hybrid (below), which form is responsible for each band. However, the observations of Andrisano and Pappalardo(35) regarding the effect of α- and β-substitution of carboxylic groups on the absorption of furoic acid might be of help here. A strong hypsochromic shift was observed when a second carboxyl group was substituted in the β'(4-) position and a still stronger shift was noticed when the second carboxyl group was placed in the β-(adjacent) position. The 4-carbethoxy group in compound (10) fulfils both descriptions in that it is adjacent to one carboxyl group and across the ring (β'-position) to the other, so that form (13) above is probably responsible mainly for the introduction of the band at 250 mμ. Form (13) not only interferes with the

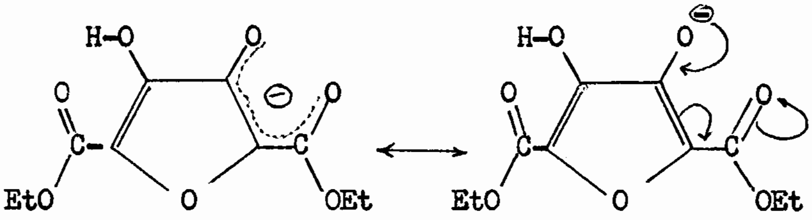

(12) (10) (11)

(13)

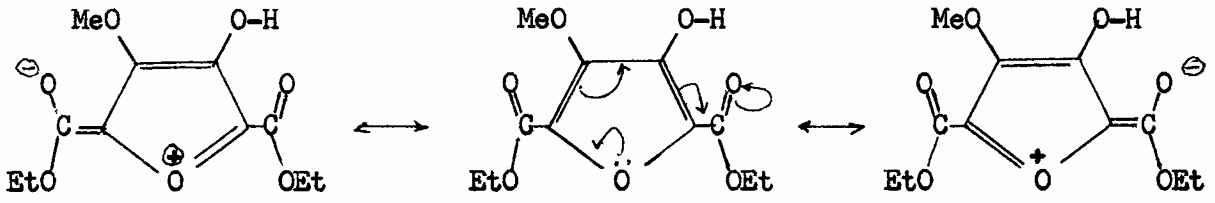
normal furan conjugation(23) but also with the more favored form (11) which would be stabilized by chelation.



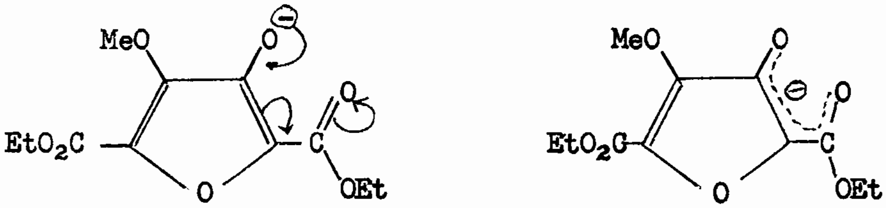
Ionization of the phenolic hydroxyl groups caused strong bathochromic shifts in the spectra of compounds (2), (6), (10) and (16). This is mainly due to the participation of the oxygen anion in the resonance of the compounds. The peak in this case shifts to 320 mμ. This change can be followed clearly if we take the example of the dihydroxy compound (6) whose monovalent anion showed peaks at 288 mμ and 336 mμ, the latter peak being due to the ionized hydroxyl group. When both hydroxyl groups are ionized the peak at 280 mμ disappears completely leaving only the peak at 320 mμ. When the monomethoxy compound (2) was used, ionization of the hydroxyl group introduces a new peak at 346 mμ while the peak at 278 mμ remains in the same position but decreases in intensity since it now has lost the contribution of one form (20). The most favored structure of the anion is probably as shown.



(6)



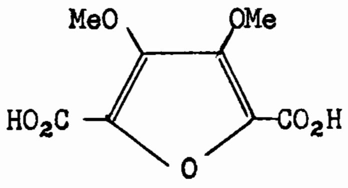
(20) (2) (19)



The most striking shift takes place with diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (10) where the peak shifts to 341 mμ, while the peak at 335 mμ shifts to 435 mμ. Such strong bathochromic shifts are observed in strong phenols such as p-nitrophenol(37) the acid strength of which is comparable with that of the furanols at present under discussion.

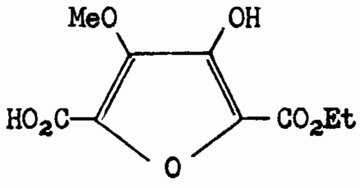
The behaviour of the carboxylic anions also is in agreement with that of such anions as p-hydroxybenzoate(37). In this case a hypsochromic shift was observed (see Table IV) for all three acids studied (Nos. 4, 5 and 6 in Table IV). The shift varies from 2.5 mμ for the first anion in 3,4-

dimethoxy-2,5-furandicarboxylate (3) to 10 mμ in the first anion of the compound.



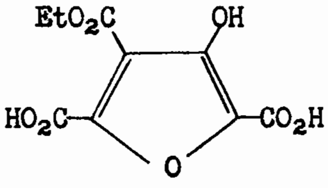
(3)

-Δλ2.5 mμ



(16)

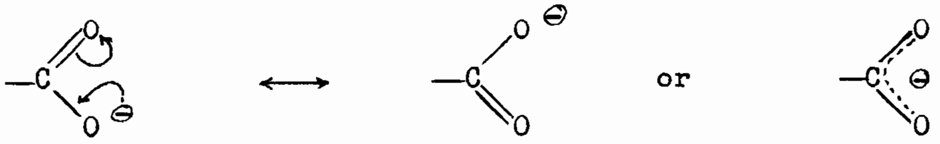
-Δλ4 mμ



(10)

-Δλ10 mμ

In p-hydroxybenzoic acid the hypsochromic shift for the first anion from that of the unionized compound is 10 mμ (from 255 to 245 mμ). This shift can be explained by the lessening of the electron attracting effect of the carboxyl group after ionization since now the following type of mesomerism takes place.



or in other words, the negative charge is now spread over all the carboxyl group and hence its need for electrons is considerably diminished.

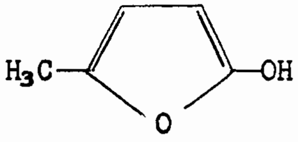
The fact that the peak at 284 mμ in diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate (10) undergoes a hypsochromic shift during ionization to the monovalent anion, and then remains unchanged with excess alkali is a further confirmation of the presence of a carboxyl group in the molecule, while the appearance of other bands at higher frequencies might indicate the presence of the phenolic hydroxyl group. The band at 250 mμ could be used as an indication of the presence of the 4-carbethoxy group.

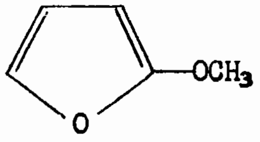
III - α-Angelica Lactone (4-Hydroxy-3-Pentenoic Acid γ -Lactone)

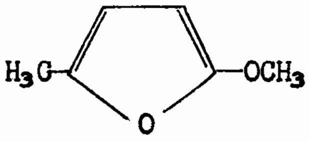
It was next of interest to investigate the structure of α-angelica lactone (21). Langlois and Wolff(38) claimed that this lactone exists partially in the enolic form (22) on the basis of a Zerewitinoff determination which gave one third of a mole of methane per mole of lactone.

(21) (22)

It was mentioned earlier (p. 7) that such a reaction could be equally well explained on the basis of the lactone structure (21). Additional evidence for the enolic structure (22) was claimed by those workers by comparing the ultraviolet spectrum of α-angelica lactone in neohexane with that of furfuryl alcohol in <u>water</u>. As mentioned earlier, furfuryl alcohol was a poor choice for such a comparison, since structure rather than molecular weight is the important factor in this comparison. Two compounds prepared in this work have been used for the spectroscopic comparison with α-angelica lactone. These are 2-methoxyfuran (23) and 5-methyl-2-methoxyfuran (24), the structural relationship with the form (22) being evident.


(22)


(23)


(24)

Both infrared and ultraviolet studies on these compounds indicate the absence of the form (22) in the α-angelica lactone.

The infrared spectrum of α-angelica lactone (Fig. 24) was reported by Rasmussen and Brattain(16), who attributed the peak at 3584 cm.$^{-1}$ to adventitious water. Charlesworth et al.(39) re-examined one of the lactones studied by those workers and reported that such a peak is undoubtedly the first overtone of the strong carbonyl absorption band. This is most probably the case with α-angelica lactone where the carbonyl absorption is observed at 1790 cm.$^{-1}$ and the first overtone should appear at 3580 cm.$^{-1}$ which is almost exactly where the peak in this region was observed. The position of this peak was unchanged when 5% and 2.5% solutions in carbon tetrachloride were examined. This indicates absence of a hydroxyl group which would be observed if the enol form (22) of the lactone were present. A peak would be expected to appear at about 3300 cm.$^{-1}$ for bridged hydroxyl groups which would shift toward higher frequencies on dilution (breaking the bridges, and forming more free hydroxyl groups). Furthermore, both compounds (23) and (24) show strong absorption in the region 1500-1625 cm.$^{-1}$ (two bands), which is attributed to the furan ring stretching (cf. Table I). No bands were observed in the spectrum of α-angelica lactone in the region 1500-1650 cm.$^{-1}$, which would indicate the absence of a furan ring. Information from other regions (H in-plane deformation and H out-of-plane deformation frequencies) cannot be utilized for comparison since the position of absorption in these regions is rather sensitive to type and position of substituents.

Additional evidence in favor of the structure (21) was obtained from spectroscopic comparison in the ultraviolet region. Both compounds (23) and (24) show well-defined peaks at 222.5 mμ ($\mathcal{E}_{max.}$ 4,500) and 224 mμ ($\mathcal{E}_{max.}$ 5,600) respectively (Table III), while α-angelica lactone in the same solvent (cyclohexane) shows a shoulder at 216 mμ ($\mathcal{E}_{max.}$ 1,360) (Fig. 27). In comparing the structure (22) with 2-methoxy-5-methylfuran (24), which has a methoxyl instead of the hydroxyl group of the enol (22), we notice a shift of about 8 mμ in the former while in the benzene series (37) phenol absorbs at about the same frequency (270 mμ) as anisole (269 mμ). While the difference in the two positions of absorption is not great, it might be considered enough to show the absence of a structure similar to that of either compound (23) or (24).

IV - Dissociation Constant Measurements

The ionizations of organic acids and bases are by far the simplest of reversible reactions which are available for study. The study of the effect of structure on the ionization of acids and bases has contributed considerable evidence for the importance of polar, steric, and resonance effects on these structures.

Since the ionization of an organic acid HA is an equilibrium reaction,

$$HA + H_2O \rightleftharpoons H_3O + A^-$$

the following expression may be written for the equilibrium constant K_a

$$K_a = \frac{[H_3O^+]\,[A^-]}{[HA]}$$

where the concentration of water is taken as unity. The strength of the acid may be expressed either in terms of the dissociation constant K_a or its negative logarithm

$$pK_a = \log K_a$$

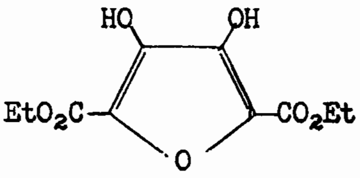
The pK_a has the same advantage as the pH in that it covers an enormous range of K_a values ($1 - 10^{12}$) on a convenient scale (0 - 12). However, the greatest value of the pK_a scale lies not in this convenience, but in the fact that the pK_a value is directly proportional to the free energy change ΔF for the ionization reaction:

$$pK_a = -\log K_a = \frac{\Delta F}{2,303\ RT}$$

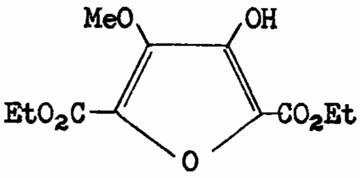
The glass electrode is frequently used as a convenient method for measuring pH. At half neutralization point, the ratio of $\frac{[HA]}{[A^-]}$ is approximately unity for a weak acid and its highly ionized salt, so that the pK_a value is equal to the measured pH^* value at that point.

$$pK_a = pH^*$$

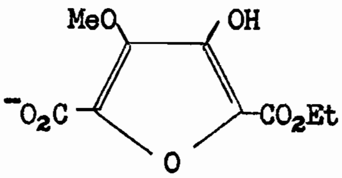
It was of interest, in the course of this work, to study the acidity of the hydroxyl group in the β-position of some of the compounds discussed earlier. Three different compounds were chosen:



(6)



(2)



(16)

The pK_a values for the first ionization in the dihydroxy compound (6) and that of the monohydroxy compound (2) were very close to 6.2 which is considerably higher than the *p*- or *o*- negatively substituted phenols. The closest value is obtained with salicaldehyde(40) (pK_a 6.79) which shows chelation similar to that taking place in the above-mentioned compounds. The hydroxy acid (16), as expected, has a higher pK_a value for the hydroxyl group (7.28) than the one obtained with the corresponding ester (2) and this is due probably to the negative charge already present in the molecule, which makes the removal of a hydrogen ion from the hydroxyl group more difficult. This again agrees with the data obtained from studies of p-hydroxybenzoic acid(41) and its ethyl ester(42), which have pK_a values for the hydroxyl group of 9.39 and 8.5 respectively.

The higher pK_a values obtained in the case of the compounds (2) and (6) are most probably due to the higher degree of chelation in these compounds than in the corresponding benzene compounds (cf. p. 123). Chelation in general is expected to weaken the oxygen-hydrogen bond of the hydroxyl group thus permitting easier removal of a hydrogen ion than if chelation were absent.

V - Nuclear Magnetic Resonance Spectra*

The measurement of the nuclear magnetic resonance spectra of organic molecules has recently proved a powerful method for determining structure(43,44). The nuclei of certain atoms behave as if they were spinning, and generate a magnetic field. When a compound containing such nuclei is placed in a magnetic pole gap, and subjected to the radiofrequency field of an oscillator, absorption of rf energy (resonance) occurs at particular combinations of the oscillator frequency and the magnetic field strength, and an rf signal is picked up by a detector.

For organic molecules, the resonance most generally measured is that of the various protons in the molecule. These will resonate at different applied fields because of the different degrees to which they are screened by their valency electrons. Protons from which the electrons are most removed by inductive, mesomeric, etc., effects resonate at the lowest fields. The difference in the field necessary for resonance of two different protons is termed the "chemical shift".

Under high resolution, the absorption bands due to various protons are sometimes found to be split into several peaks. This splitting is usually due to interaction with protons on neighboring atoms. The spin-coupling constant, J, which gives the separation of the peaks, varies with

---

*The author is extremely grateful to Dr. J.T. Edward for carrying out the nuclear magnetic resonance measurements reported here, and to Professor R.U. Lemieux of the University of Ottawa for providing the facilities for these determinations. Since the author has no experience in this field, he is further indebted to Dr. J.T. Edward for his help in writing this section.

the nature of the interacting protons; while the number of peaks is a function of the number of interacting protons.

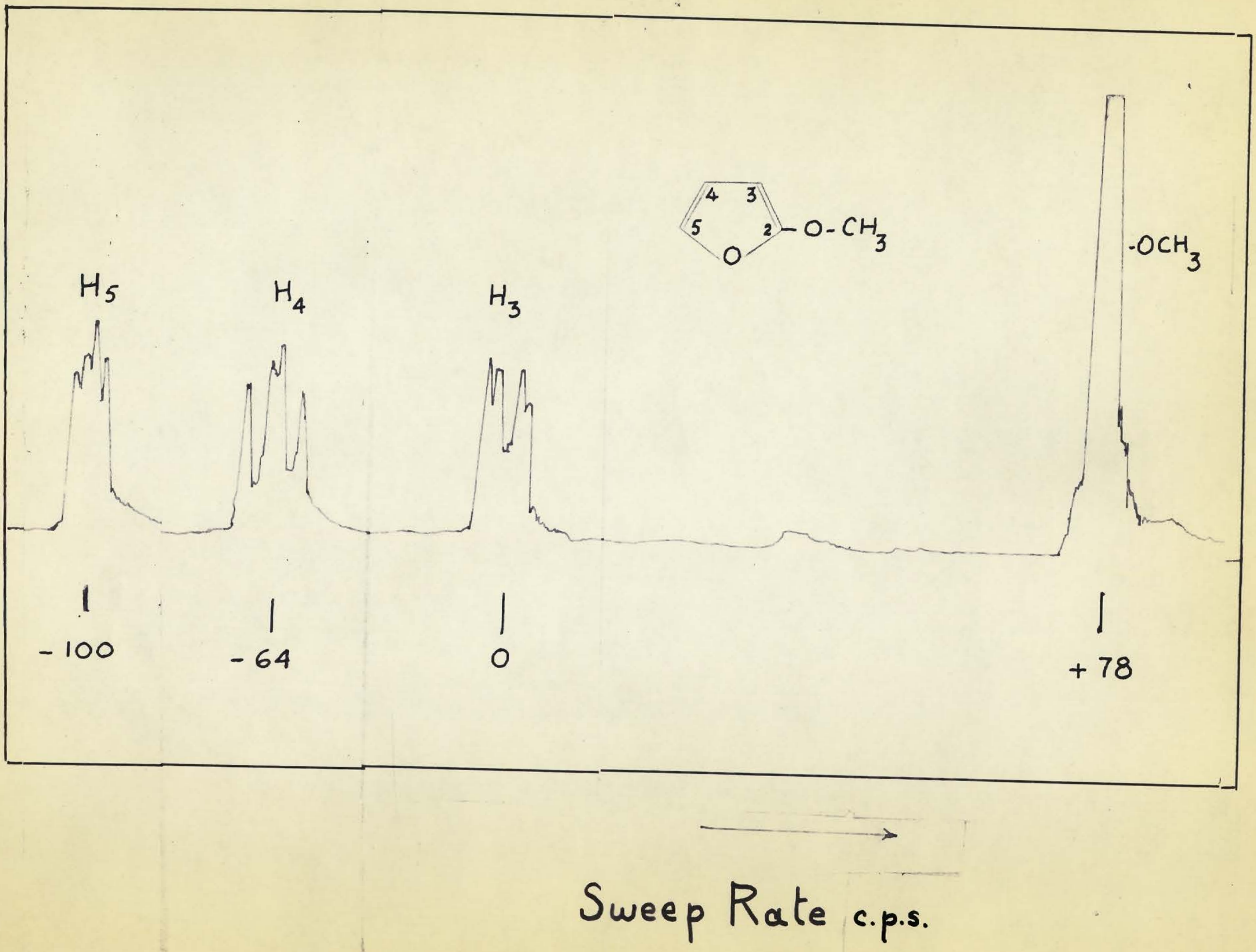
The proton resonance spectra of furans have proved particularly useful in indicating the presence of the furan nucleus, and in determining the positions at which it is substituted(45,46). Some results of Abraham and Bernstein, converted to those expected for a spectrometer operating at 60 Mc/s, are shown in Table V. It is evident that in furan itself the hydrogens at the α-positions, because of the inductive effect of the ring oxygen, resonate at a lower field than the β-hydrogens. This general effect is modified by substituents. The electron-releasing methyl group increases the screening of the protons, so that all peaks are shifted to higher fields, the effect being greatest at the 3- and 5-positions. On the other hand, the electron-withdrawing aldehyde group in furfural causes the peaks to be shifted to lower fields. The shift again is greatest at the 3- and 5-positions, as expected from a consideration of the mesomeric effects of this group.

The spectrum of 2-methoxyfuran is shown in Fig.37 . This and following spectra were obtained with a high-resolution spectrometer operating at 60 Me/s. The peaks in the spectrum may be assigned to the various protons in the molecule as indicated in the figure. The effect of the electron-releasing 2-methoxyl group in shifting the peaks to higher field being about twice as great as the effect of the 2-methyl group. Each hydrogen atom on the nucleus interacts with the other two hydrogen atoms, so that each peak is split into a quartet; the coupling constants derived from the separation of the peaks have the values expected (Table VI) from

FIGURE 37

Nuclear Magnetic Resonance Spectrum of

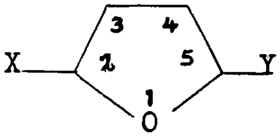
2-Methoxyfuran



4
3
5
2
O
-O-CH₃
H₅
H₄
H₃
-OCH₃
-100
-64
0
+78
Sweep Rate c.p.s.

TABLE V

Chemical Shifts for Furans (relative to water (c.p.s.))



Compound	X	Y	H_2	H_3	H_3	H_5	Other
Furan*	H	H	-132	- 69	-69	-132	
2-Methylfuran*	Me	H	-	- 35	-51	-112	Me+193
Furfural*	CHO	H	-	-114	-72	-141	
2-Methoxyfuran	OMe	H	-	0	-64	-100	OMe+78
5-Methyl-2-methoxyfuran	OMe	Me	-	0	-48	-	OMe+75 Me+168

*From Abraham and Bernstein(45)

TABLE VI

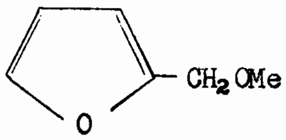
Coupling Constants for Furans (c.p.s.)

	J_{45}	J_{35}	J_{34}
Furan*	1.3	1.3	
2-Methylfuran*	1.7	1.1	3.5
Furfural*	1.5	0.9	3.4
2-Methoxyfuran	2.0	1.0	3.3
5-Methyl-2-methoxyfuran	-	-	3.0

*From Abraham and Bernstein(45)

the work of Abraham and Bernstein. This concordance confirms the assignment of the peaks to the different protons as shown.

The spectrum of 5-methyl-2-methoxyfuran shows four main peaks, due to the protons at the 4-position, the 3-position, the 2-methoxyl group, and the 5-methyl group. In addition to these main peaks, several peaks to higher field show the presence of other aliphatic groups, presumably present in impurities such as $C_4H_9OCH_3$ which were not separated in the fractionation procedure used. However, the spectrum indicates that the material is mainly 5-methyl-2-methoxyfuran. The fact that only two peaks are to be found in the general region expected for the nuclear hydrogens of furans eliminates possible isomeric structures as:



which have three nuclear hydrogens. The peak at lowest field (-48 c.p.s.) is due to H_4, because of its multiplet structures, the proton interacting with both H_3 and the hydrogens of the methyl group; Abraham and Bernstein found a similar fine structure for the peak of H_3 of 2-methylfuran. The next peak (0 c.p.s.) is due to H_3, as shown by its doublet structure. The peaks for the methoxyl and methyl groups are at about the values expected.

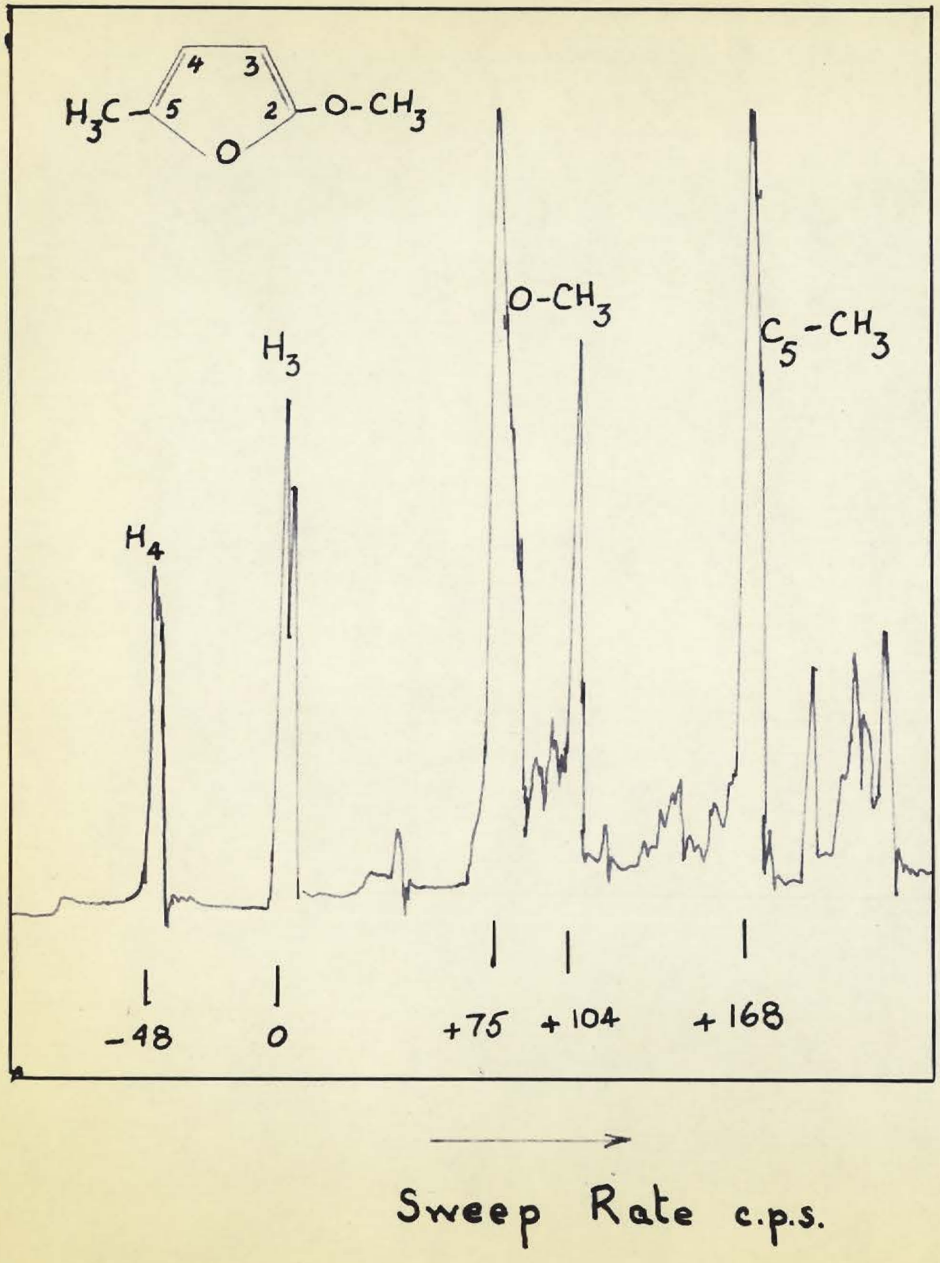
VI - Evidence Regarding the Structure of Aucubin

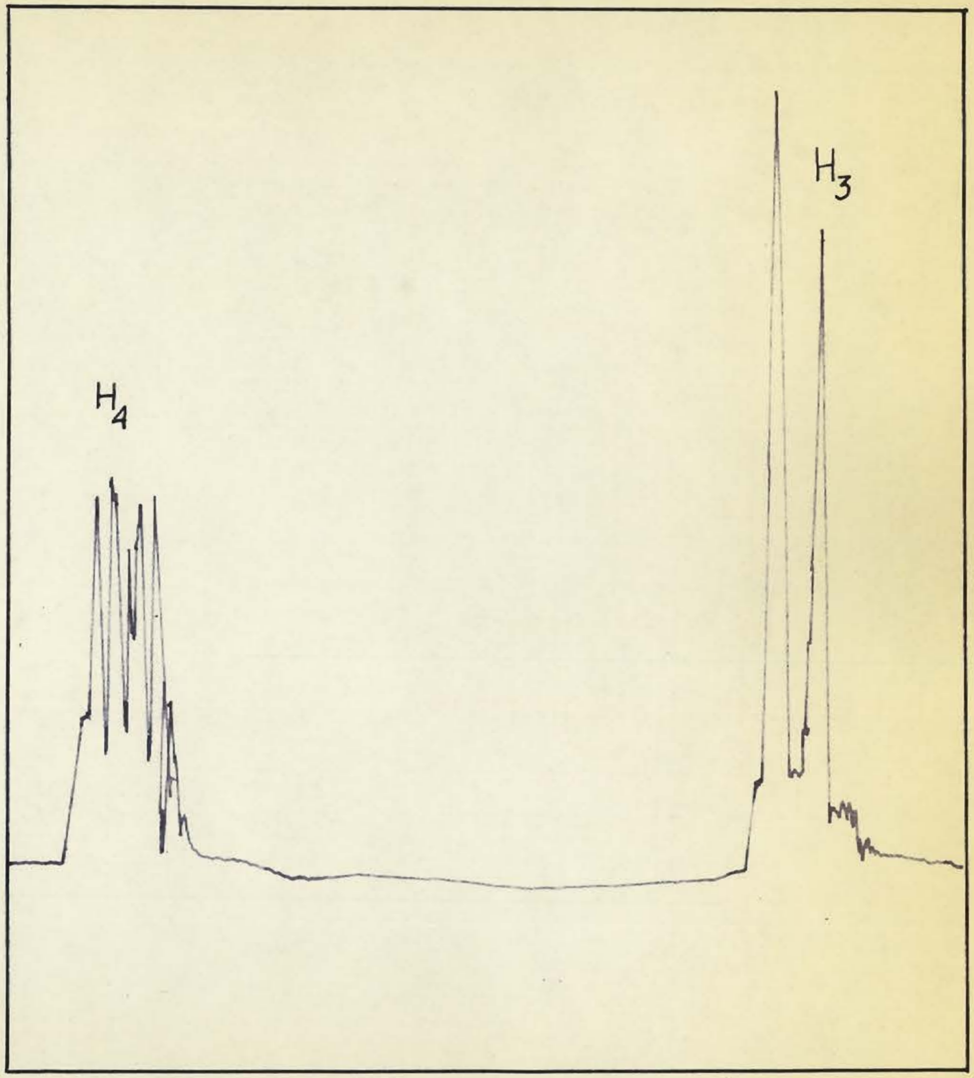
As mentioned previously (p. 1), the structure of aucubin as suggested by Karrer and Schmid(48) contains a furan ring with a glucosidic linkage in the β-position.

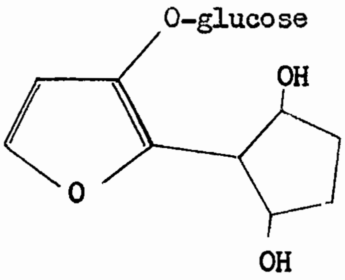
FIGURE 38

Nuclear Magnetic Resonance Spectrum of

5-Methyl-2-Methoxyfuran


4
3
H_3C-
5
2
$-O-CH_3$
O
H_4
H_3
$O-CH_3$
C_5-CH_3
-48
0
+75
+104
+168
Sweep Rate c.p.s.


H_4
H_3

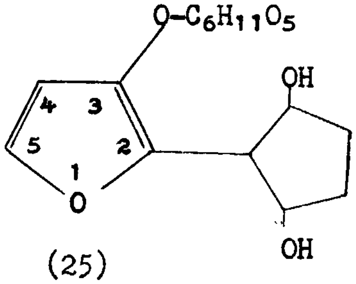


Evidence accumulating from studies on compounds with similar structure, however, indicates the absence of a furan ring. The evidence comes mainly from infrared, ultraviolet and NMR spectra and may be outlined as follows:

(a) Infrared Spectroscopy: Furan compounds examined by various workers as well as the compounds studied in this laboratory showed at least two bands of variable intensity in the region 1630-1490 cm.$^{-1}$ The spectrum of aucubin, however, shows no absorption in this region, which is assigned to the ring stretching vibration in furan (cf. p. 114). The band at 1645 cm.$^{-1}$ in aucubin is too high for a conjugated double-bond and is probably due to an isolated double-bond. Unfortunately, this is the only region where correlation can be made with certainty, since aucubin contains several aliphatic hydroxyl groups which absorb (C-O stretching and -OH deformation) in the region 1200-1000 cm.$^{-1}$ and thus would obscure the furan ring breathing band (1006-1025 cm.$^{-1}$) and the C-H in-plane deformation vibrations.

(b) Ultraviolet Spectroscopy: A number of methoxyfurans has been studied in the ultraviolet region, and the spectra of the α-methoxyfurans show well-defined peaks at 223-224 mμ while 3,4-dimethoxyfuran has a shoulder at 213 mμ. Aucubin shows no maximum of absorption above 210 mμ (Fig. 24).

(c) Evidence from Nuclear Magnetic Resonance: Unfortunately no model compound having a structure closely similar to that of aucubin was available for NMR studies. However, it can be predicted that a compound having the structure (25) should show peaks having the following chemical shifts (relative to the hydrogens of water):



(25)

(a) Two doublets in the range of about -150 to -30 c.p.s., for H_4 and H_5, each split by the same coupling constant (J_{45})

(b) A complex peak in the region -90 to -40 c.p.s. due to the hydrogen at C_1 of the glucose residue

(c) Peaks in the region of 0 c.p.s. for the secondary hydrogens of the glucose residue, and for the alcoholic hydrogens

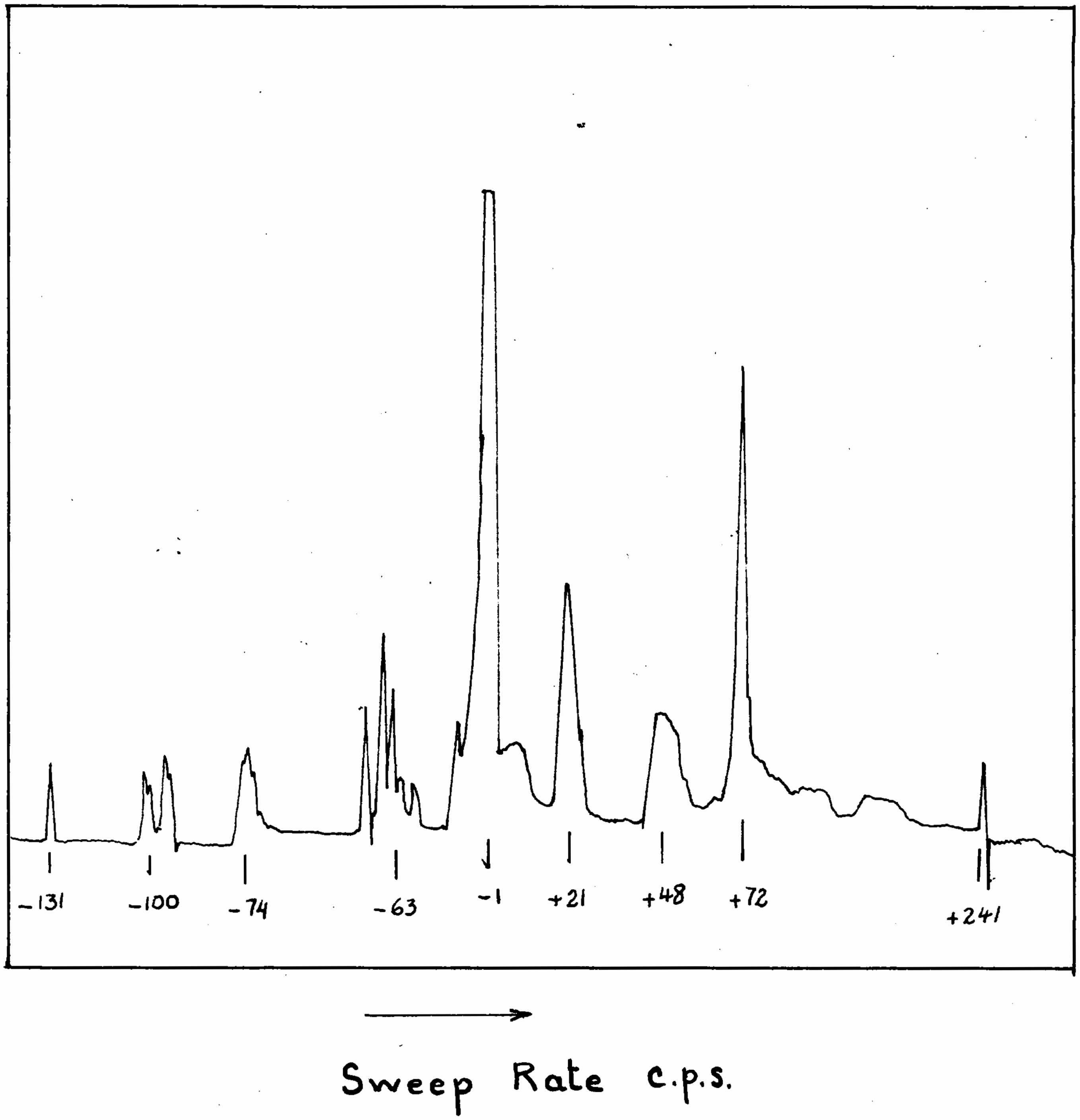
(d) Peaks at higher field strengths due to aliphatic hydrogens of various kinds.

In Fig. 39 is shown the NMR spectrum of aucubin, determined in deuterium oxide solution. It is evident that the first two peaks (at -131 and -100 c.p.s.) are in the expected region for hydrogens attached to furan, but do not have the type of splitting expected for the structure (25) or indeed for any disubstituted furan. One or both of them could be due to the α-

FIGURE 39

Nuclear Magnetic Resonance Spectrum of

Aucubin


-131
-100
-74
-63
-1
+21
+48
+72
+241
Sweep Rate c.p.s.

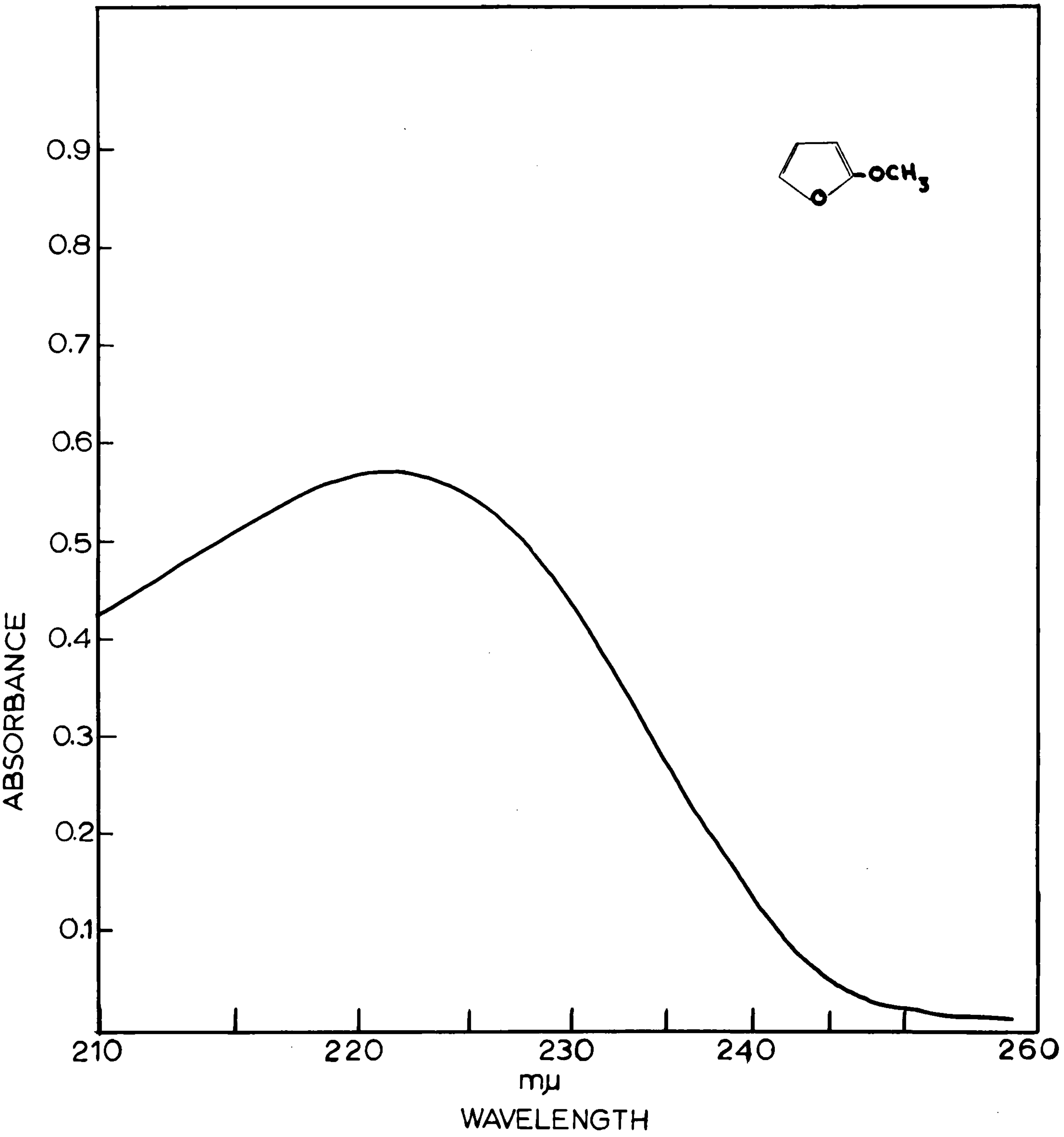
hydrogens of vinyl ethers(46), which in the few examples studied had chemical shifts of about -90 to -103 c.p.s. The third peak, at -74 c.p.s., seems most likely, from its position and general shape, to be due to the anomeric hydrogen of the glucose residue(47).

FIGURE 25

Ultraviolet Absorption Spectrum of

2-Methoxyfuran

(0.18 mg./25 ml. of cyclohexane)



O
-OCH$_3$
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
260
mμ
WAVELENGTH

FIGURE 26

Ultraviolet Absorption Spectrum of

5-Methyl-2-Methoxyfuran

(0.18 mg./25 ml. of cyclohexane)

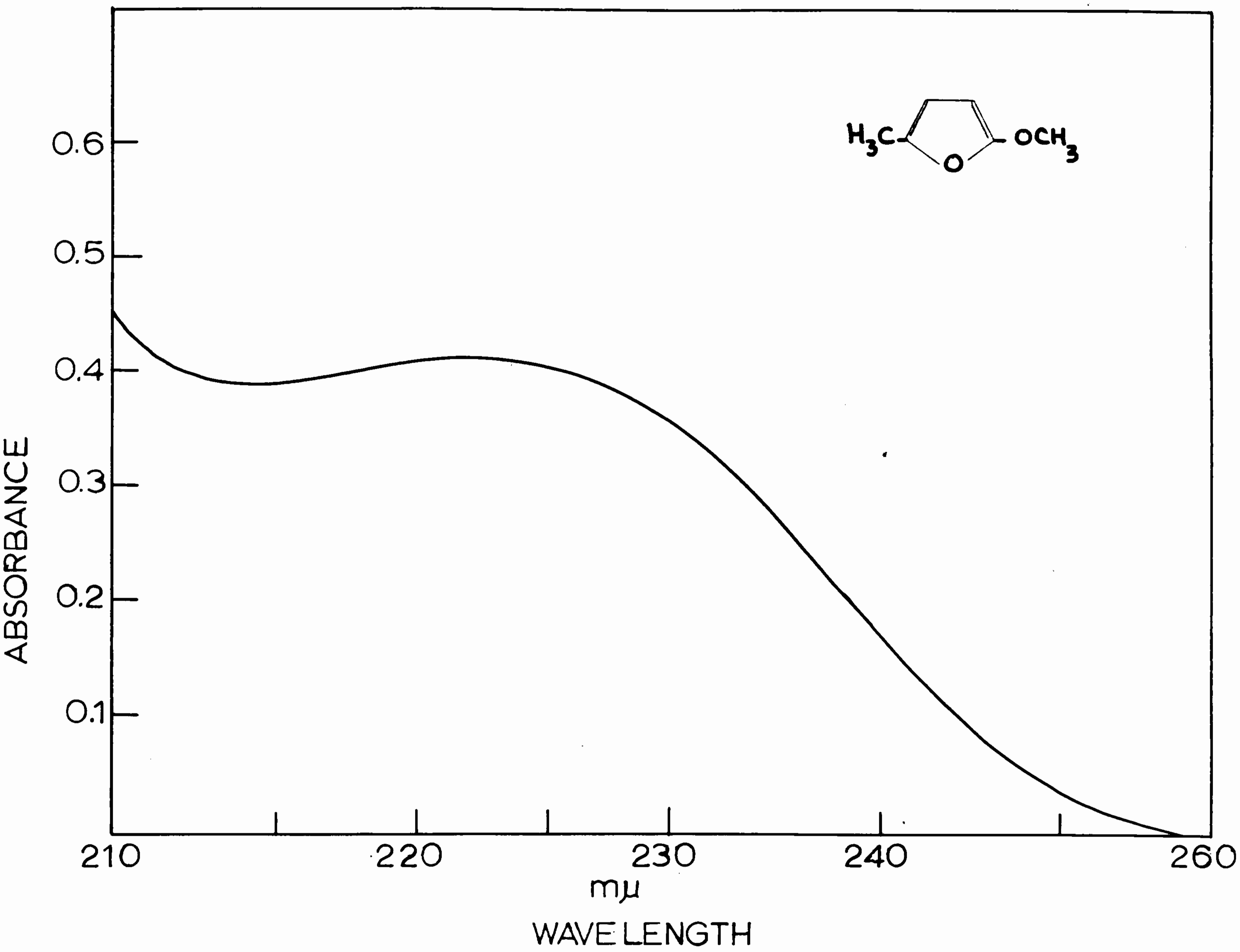
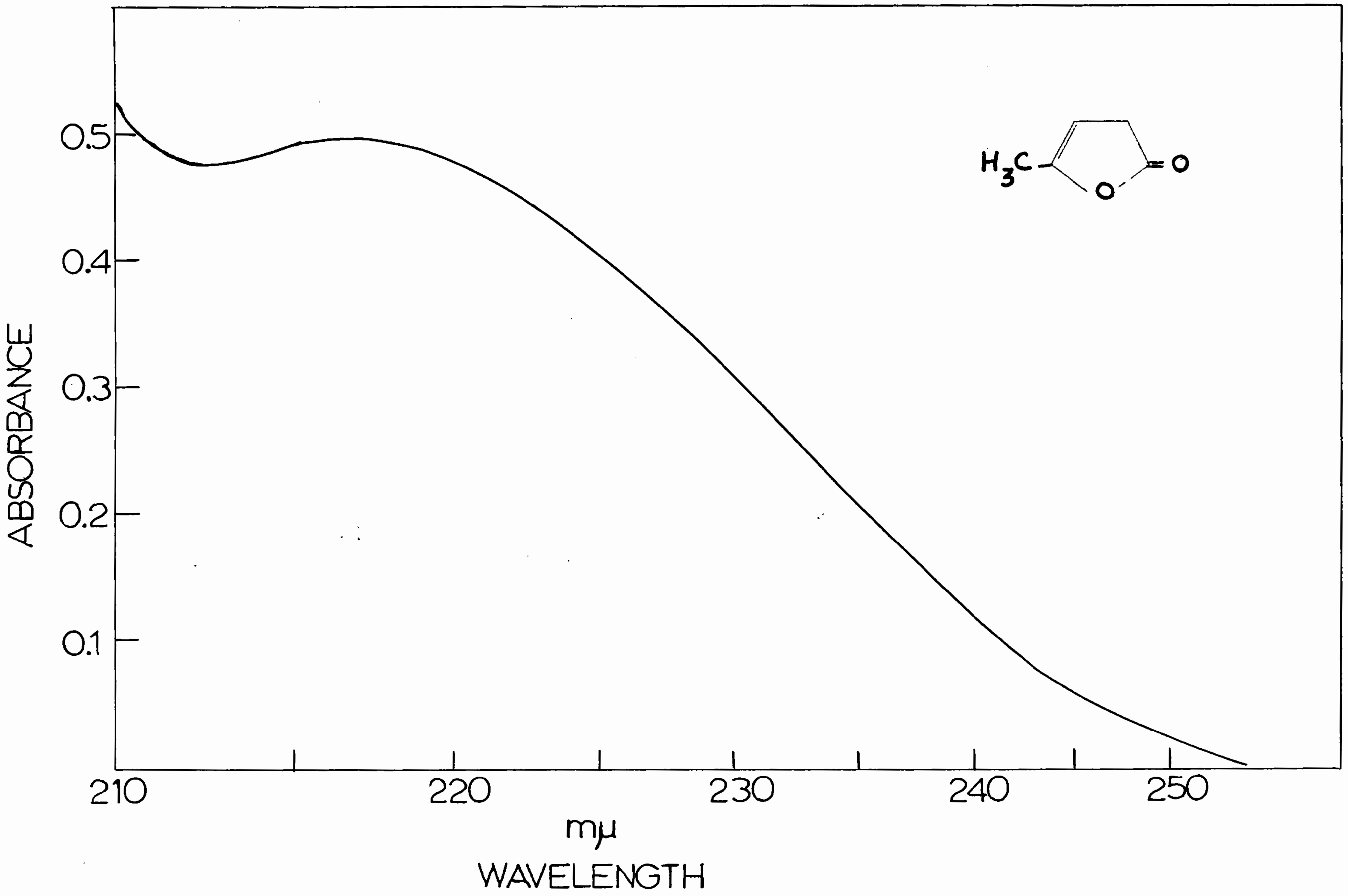

H$_3$C
O
OCH$_3$
0.6
0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
260
mμ
WAVE LENGTH

FIGURE 27

Ultraviolet Absorption Spectrum of

α-Angelica Lactone

(0.36 mg./10 ml. of cyclohexane)


0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
250
mμ
WAVELENGTH
H_3C
O
O

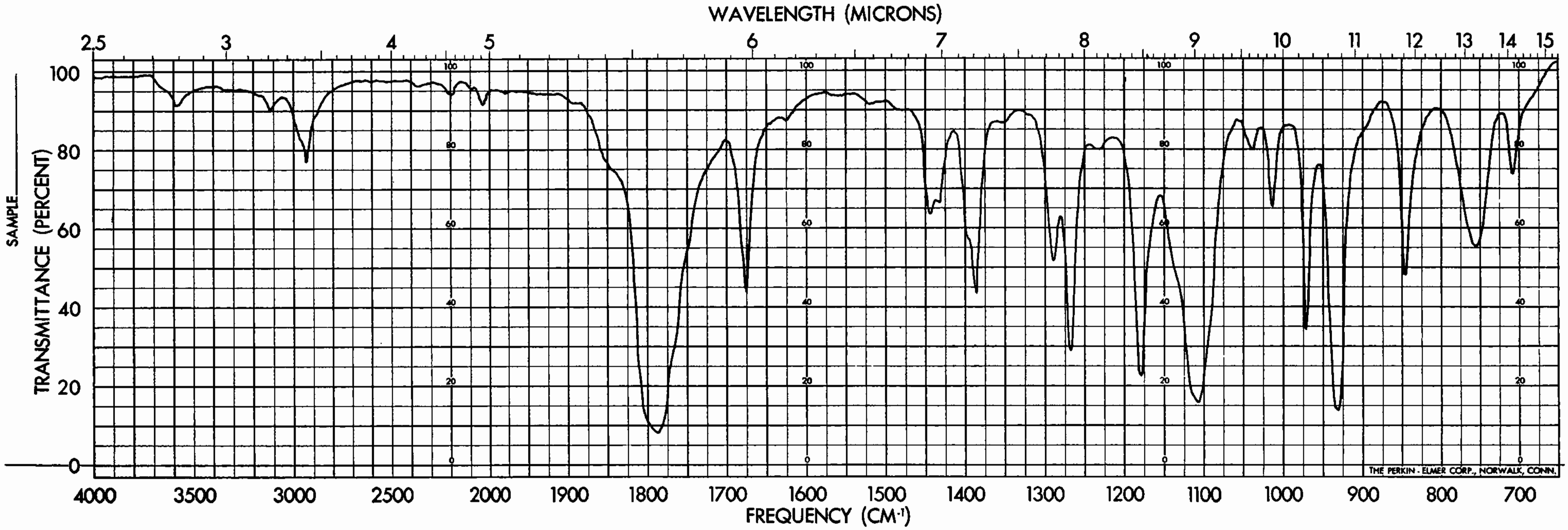


Figure 23. Infrared Absorption Spectrum of α-Angelica Lactone.

(liquid film)

FIGURE 28

Ultraviolet Absorption Spectra of

Dimethyl 3,4-Dihydroxy-2,5-Furandicarboxylate

and its mono- and disodium salts

(0.21 mg./25 ml. of absolute ethanol)

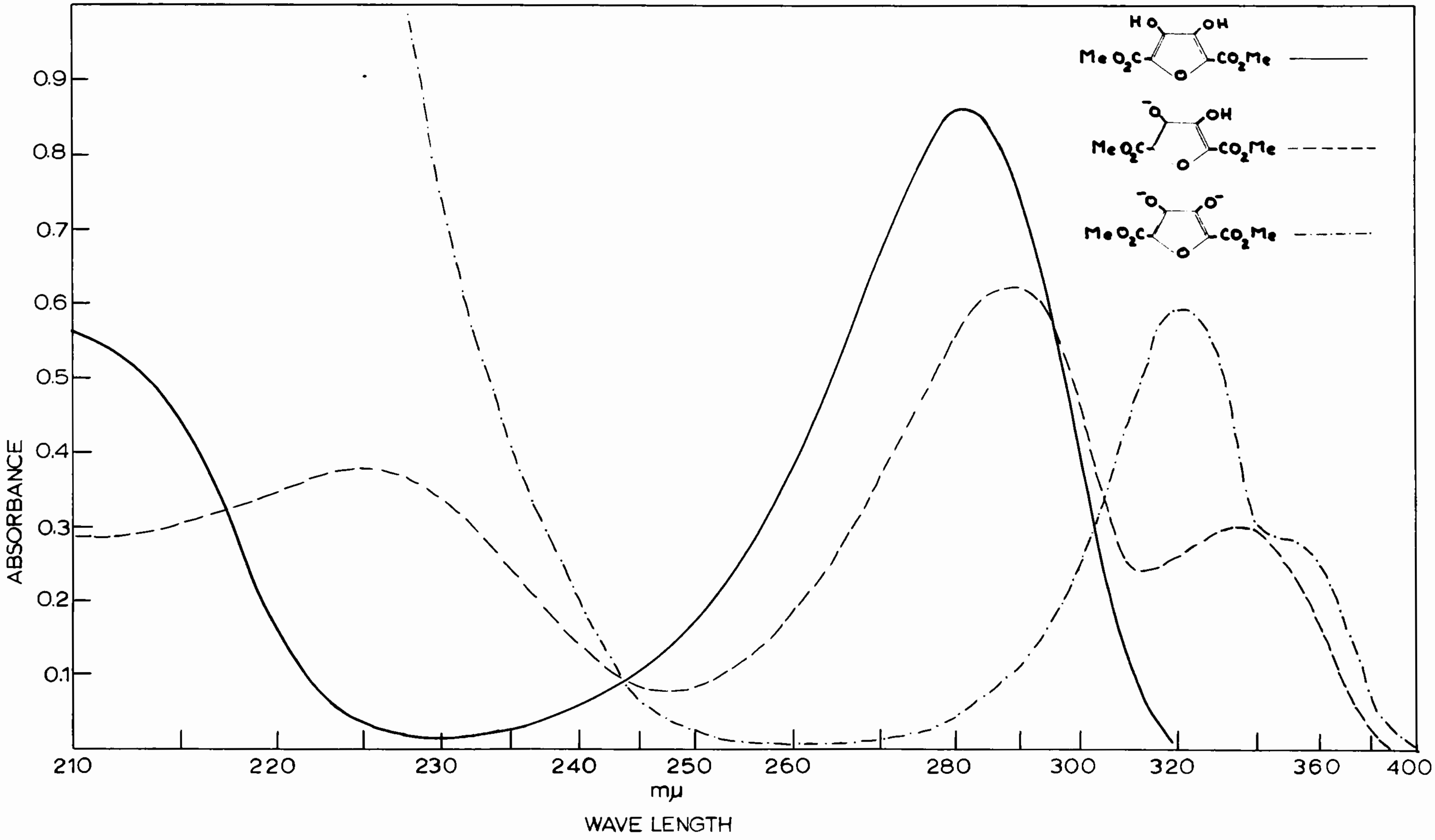

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
250
260
280
300
320
360
400
mμ
WAVE LENGTH
HO
OH
MeO2C
CO2Me
O
⁻O
OH
MeO2C
CO2Me
O
⁻O
O⁻
MeO2C
CO2Me
O

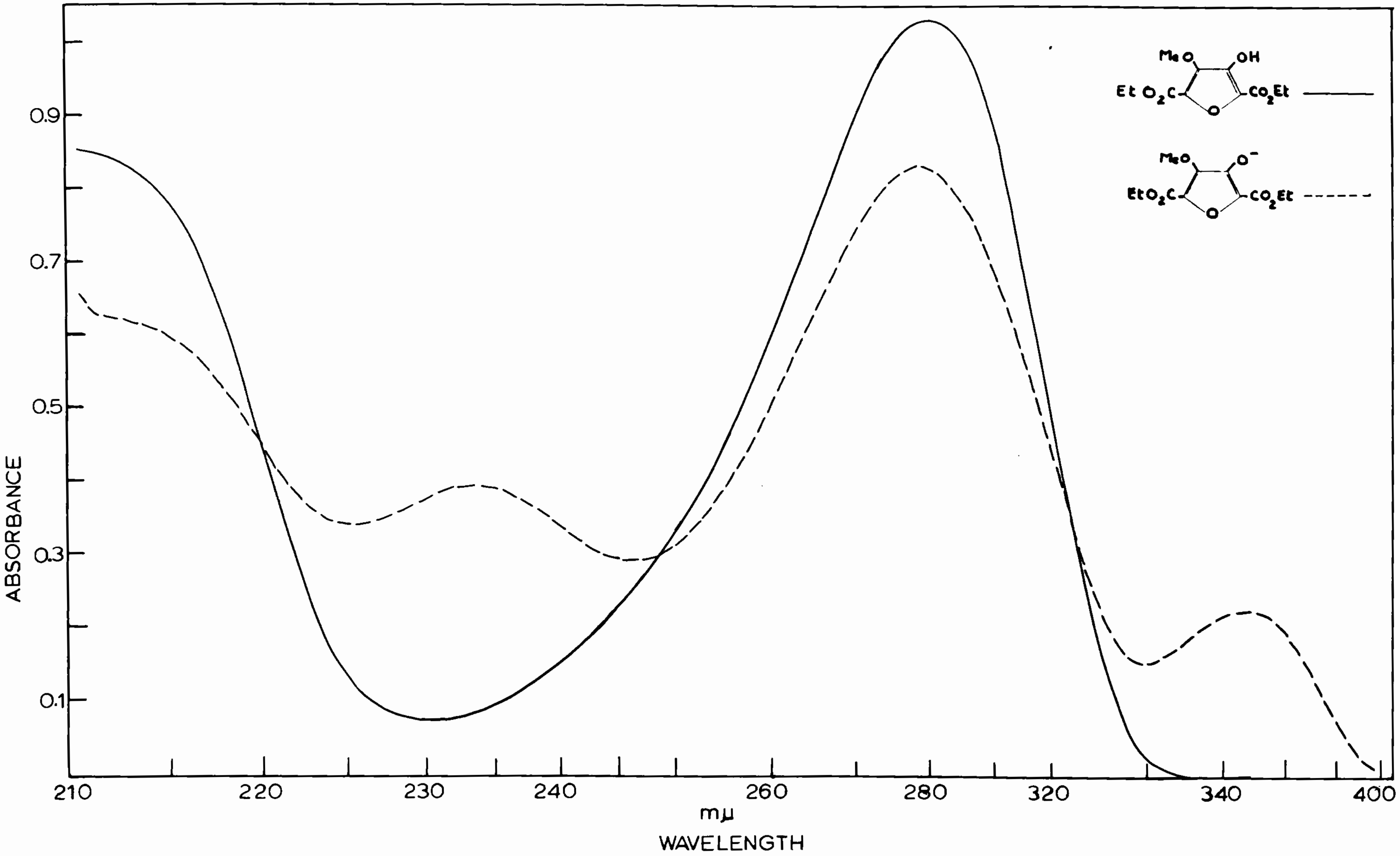
FIGURE 29

Ultraviolet Absorption Spectra of

Diethyl 3-Hydroxy-4-Methoxy-2,5-Furandicarboxylate

and its monosodium salt

(0.34 mg./25 ml. of absolute ethanol)


MeO
OH
EtO2C
CO2Et
O
MeO
O⁻
EtO2C
CO2Et
O
0.9
0.7
0.5
0.3
0.1
ABSORBANCE
210
220
230
240
260
280
320
340
400
mμ
WAVELENGTH

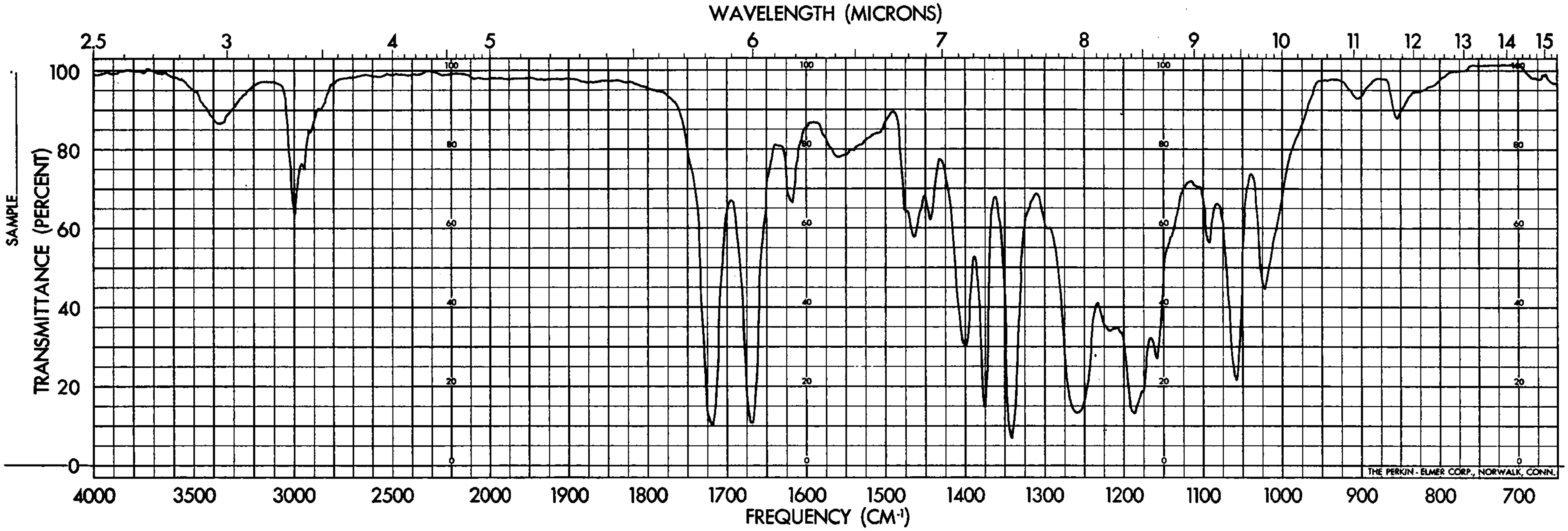


Figure 18. Infrared Absorption Spectrum of Diethyl 3-Hydroxy-4-Methoxy-2,5-Furandicarboxylate.

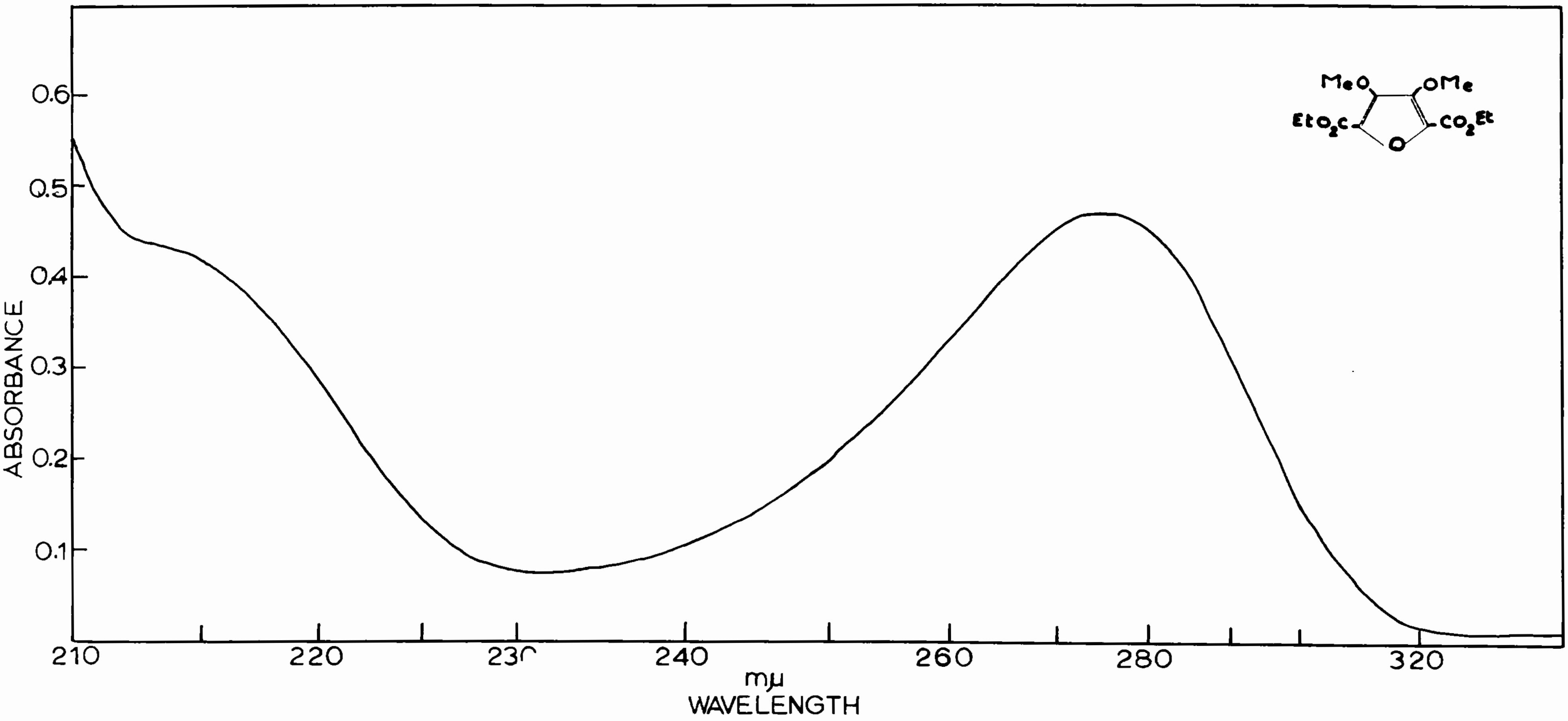
(2% CCl_4 solution)

FIGURE 30

Ultraviolet Absorption Spectrum of

Diethyl 3,4-Dimethoxy-2,5-Furandicarboxylate

(0.102 mg./25 ml. of absolute ethanol)


MeO
OMe
EtO2C
CO2Et
O
0.6
0.5
0.4
0.3
0.2
0.1
ABSORBANCE
210
220
230
240
260
280
320
mμ
WAVELENGTH

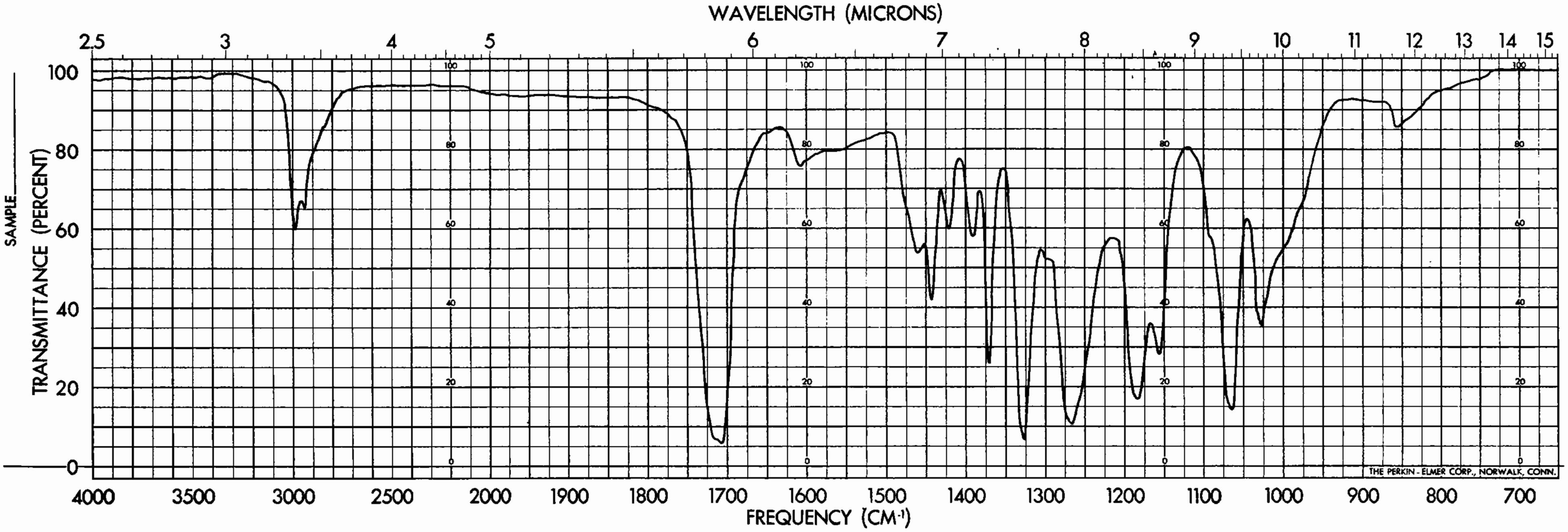


Figure 19. Infrared Absorption Spectrum of Diethyl 3,4-Dimethoxy-2,5-Furandicarboxylate.

(1% CCl_4 solution)

FIGURE 31

Ultraviolet Absorption Spectra of

Ethyl 5-Carboxy-3-Hydroxy-4-Methoxy-2-Furancarboxylate

and its mono- and disodium salts

(0.24 mg./25 ml. of absolute ethanol)

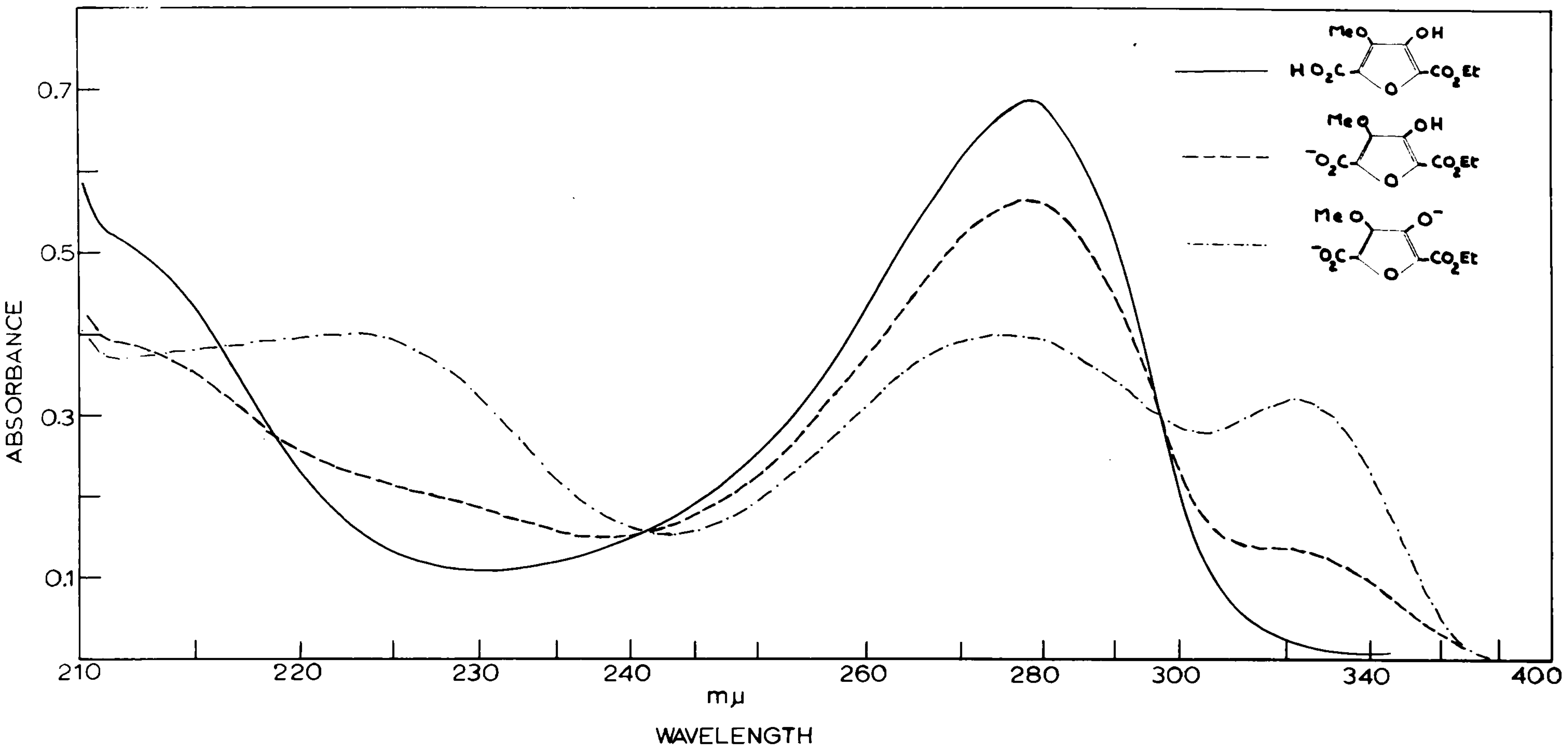
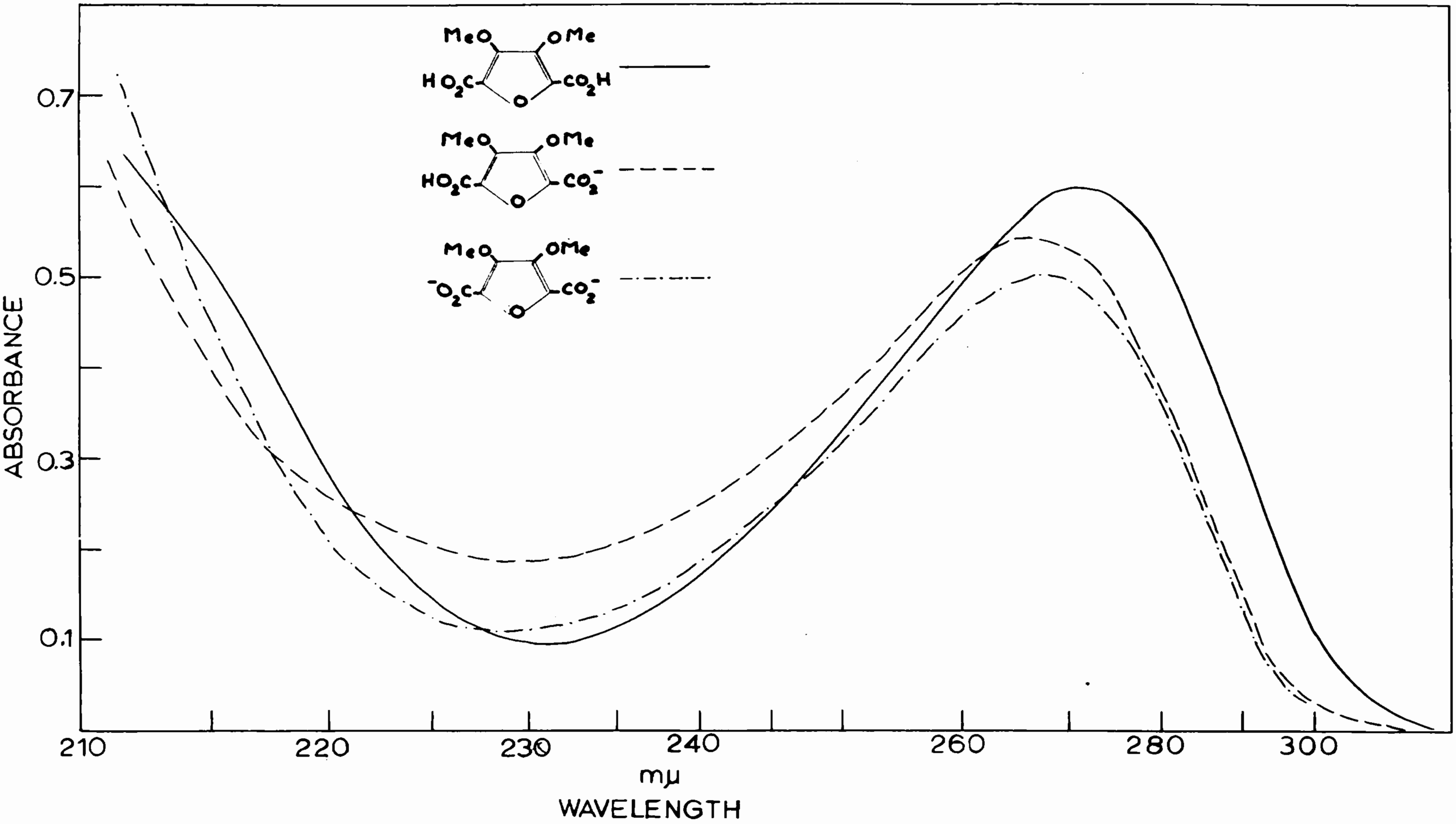

0.7
0.5
0.3
0.1
ABSORBANCE
210
220
230
240
260
280
300
340
400
mμ
WAVELENGTH
MeO
OH
HO_2C
CO_2Et
O
MeO
OH
^-O_2C
CO_2Et
O
MeO
O^-
^-O_2C
CO_2Et
O

FIGURE 32

Ultraviolet Absorption Spectra of
3,4-Dimethoxy-2,5-Furandicarboxylic Acid
and its mono- and disodium salts
(0.2 mg./25 ml. of absolute ethanol)


MeO
OMe
HO_2C
CO_2H
O
MeO
OMe
HO_2C
CO_2^-
O
MeO
OMe
^-O_2C
CO_2^-
O
ABSORBANCE
0.7
0.5
0.3
0.1
210
220
230
240
260
280
300
mμ
WAVELENGTH

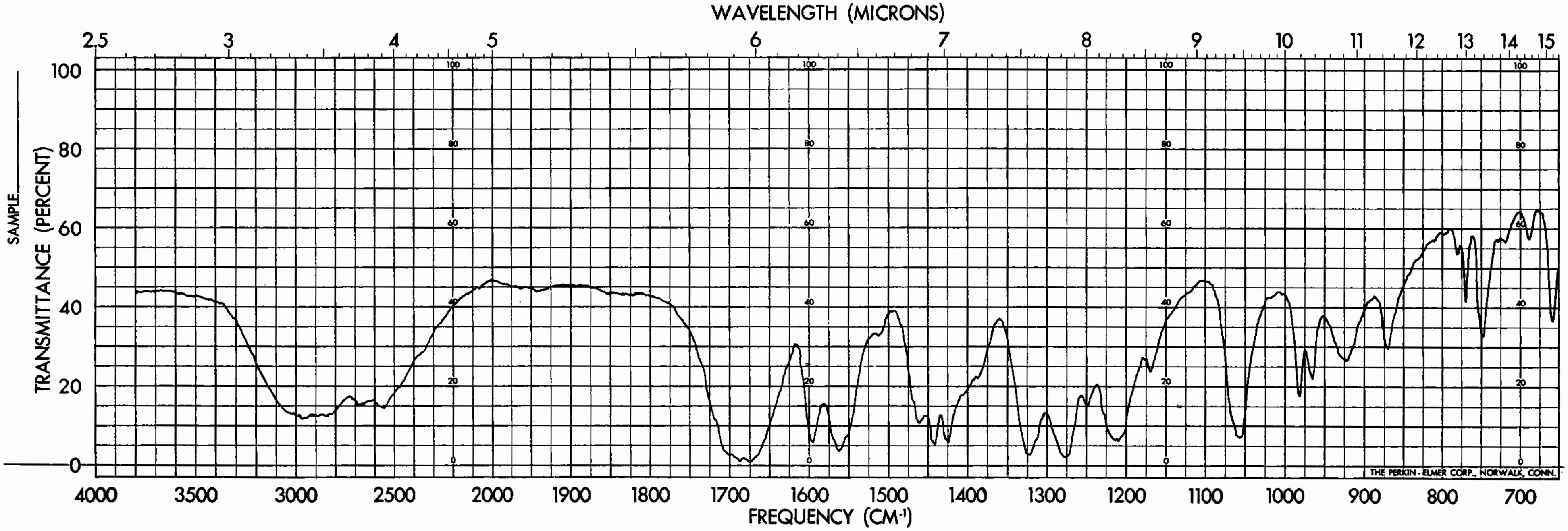


Figure 20. Infrared Absorption Spectrum of 3,4-Dimethoxy-2,5-Furandicarboxylic Acid.

(KBr pellet)

FIGURE 33

Ultraviolet Absorption Spectra of

Diethyl 5-Carboxy-3-Hydroxy-2,4-Furandicarboxylate

and its mono- and disodium salts

(0.29 mg./25 ml. of absolute ethanol)

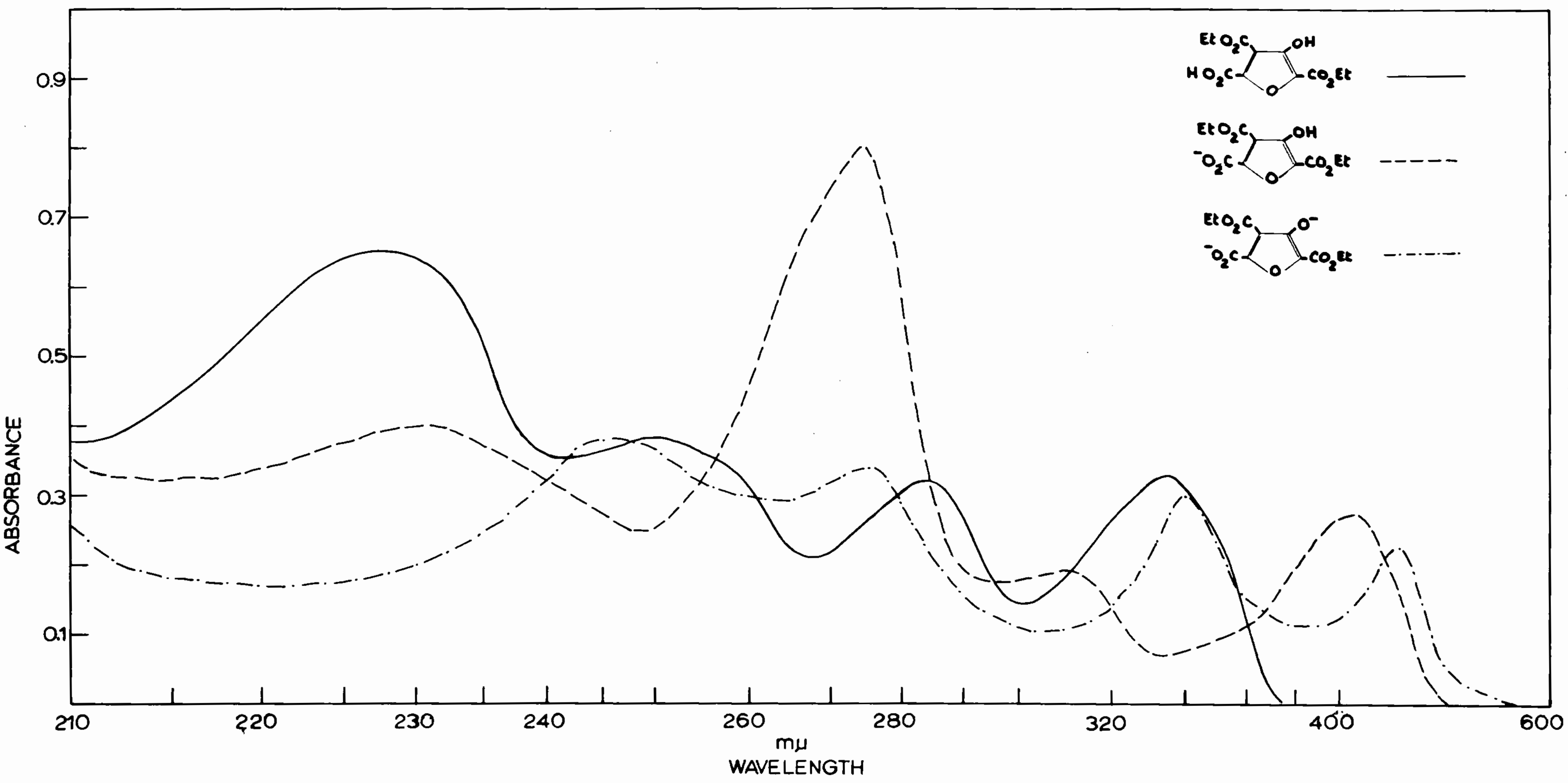

ABSORBANCE
0.9
0.7
0.5
0.3
0.1
210
220
230
240
260
280
320
400
600
mμ
WAVELENGTH
EtO2C
OH
HO2C
CO2Et
O
EtO2C
OH
-O2C
CO2Et
O
EtO2C
O-
-O2C
CO2Et
O

FIGURE 34

Potentiometric Titration Curve of

Diethyl 3,4-Dihydroxy-2,5-Furandicarboxylate

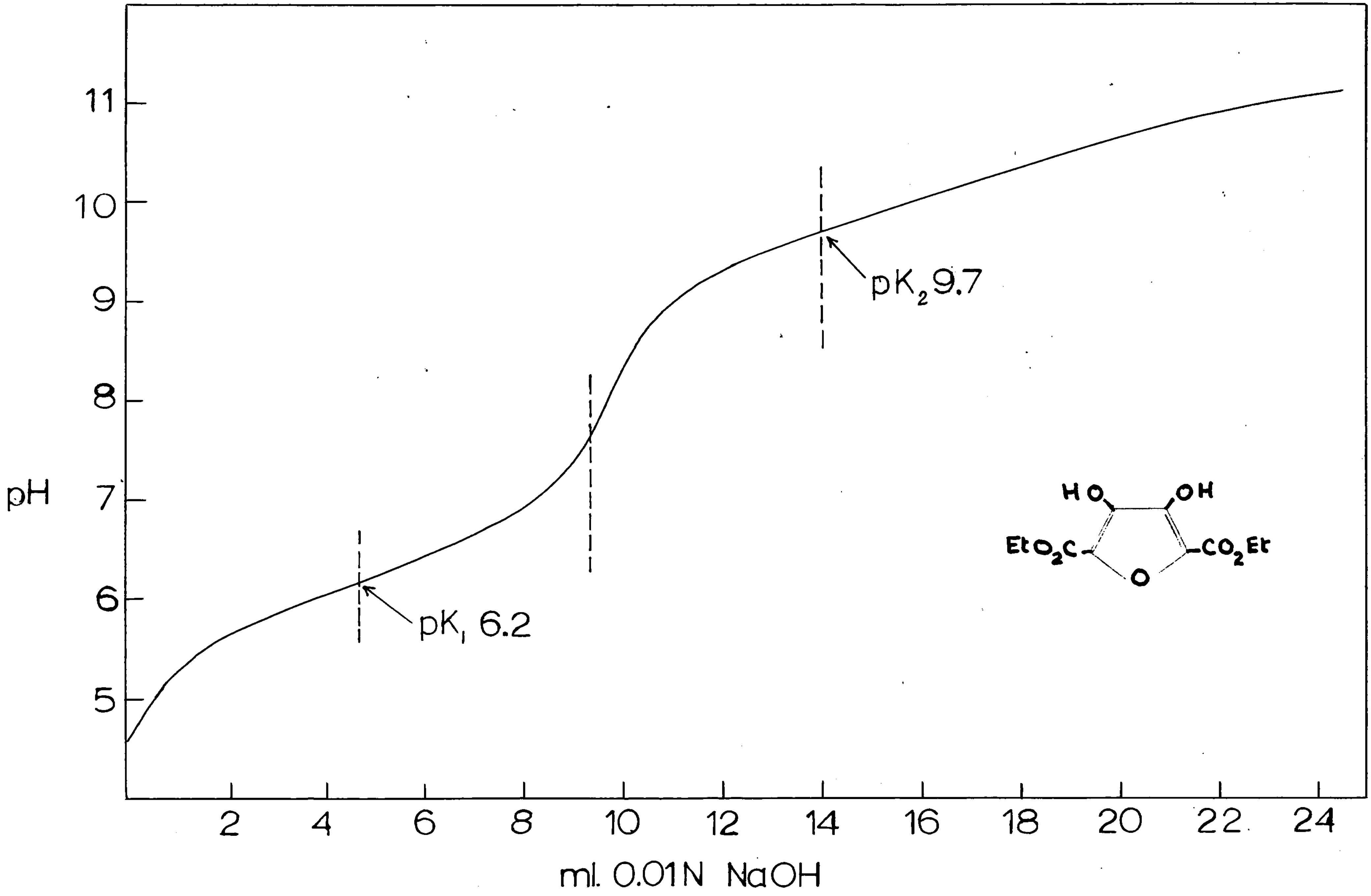

11
10
9
8
7
6
5
pH
2
4
6
8
10
12
14
16
18
20
22
24
ml. 0.01N NaOH
pK₁ 6.2
pK₂ 9.7
HO
OH
EtO₂C
CO₂Et
O

FIGURE 35

Potentiometric Titration Curve of

Ethyl 5-Carboxy-3-Hydroxy-4-Methoxy-2-Furancarboxylate

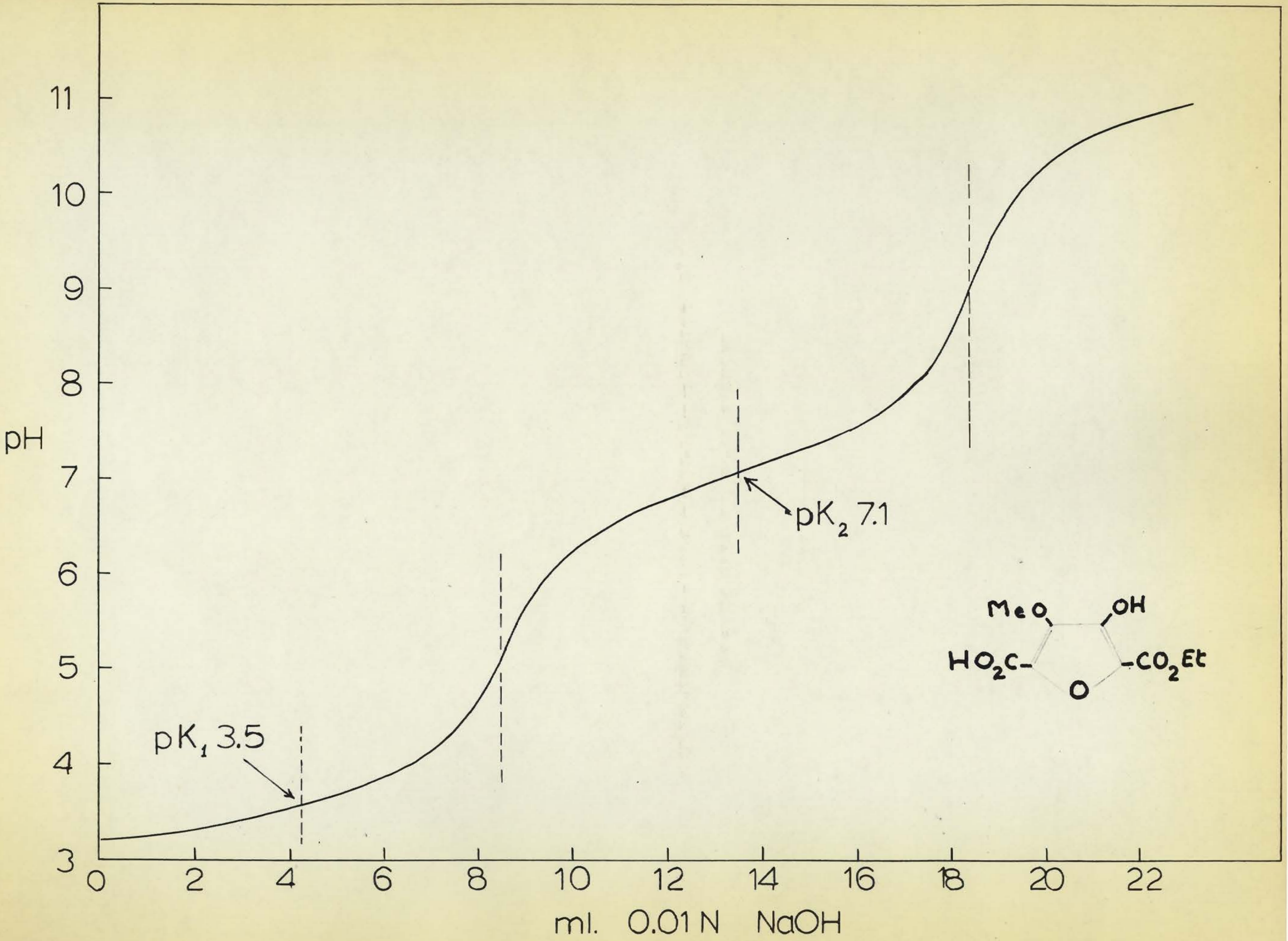
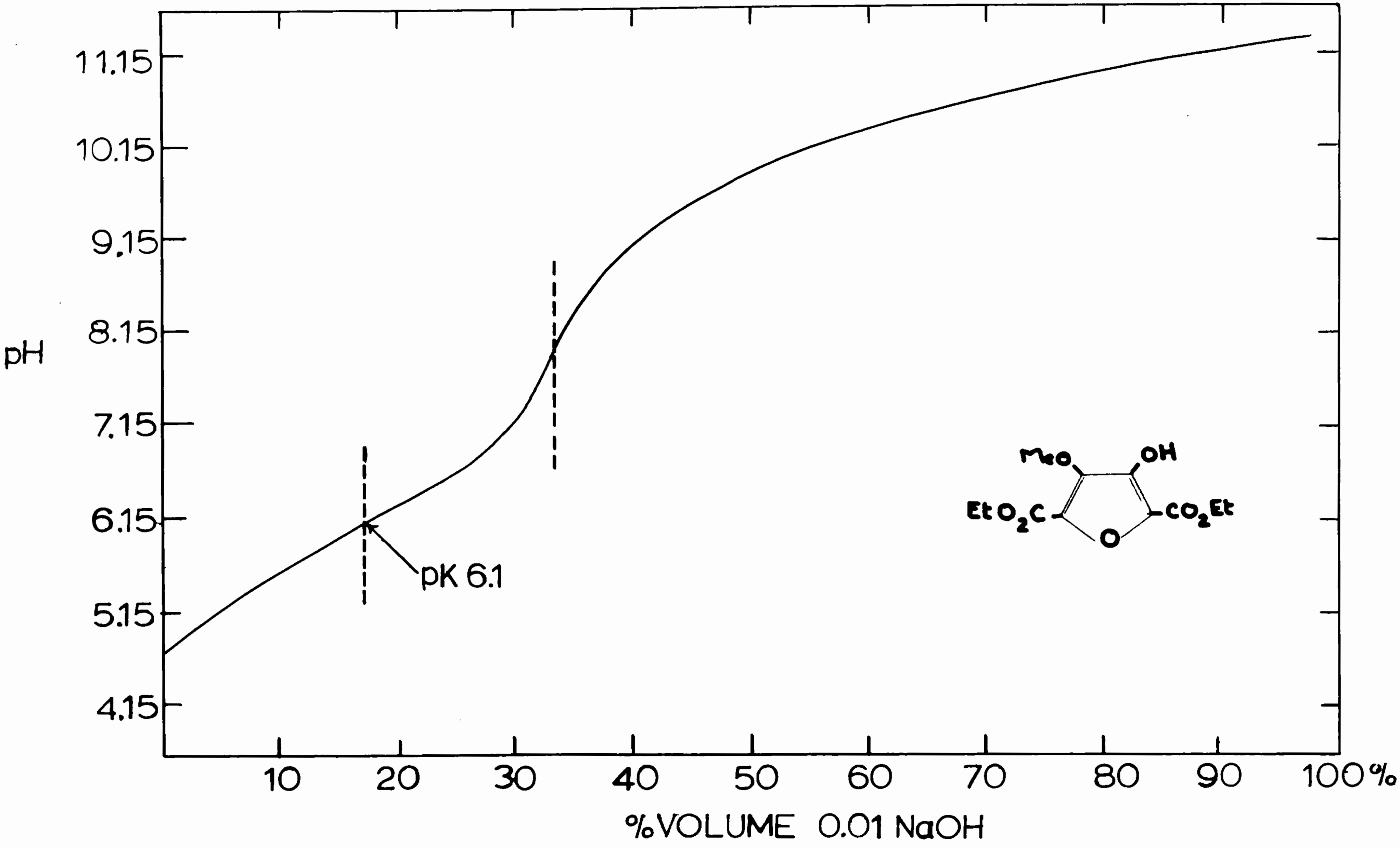

pH
11
10
9
8
7
6
5
4
3
0
2
4
6
8
10
12
14
16
18
20
22
ml. 0.01 N NaOH
pK₁ 3.5
pK₂ 7.1
MeO
OH
HO₂C-
-CO₂Et
O

FIGURE 36

Potentiometric Titration Curve of

Diethyl 3-Hydroxy-4-Methoxy-2,5-Furandicarboxylate


pH
11.15
10.15
9.15
8.15
7.15
6.15
5.15
4.15
pK 6.1
10
20
30
40
50
60
70
80
90
100%
%VOLUME 0.01 NaOH
MeO
OH
EtO$_2$C
CO$_2$Et
O

EXPERIMENTAL

Ultraviolet Absorption Spectra Determination

The ultraviolet absorption spectra were determined by means of a Beckman model DK2 recording spectrophotometer, using a scale of A 0-1 and a scanning time of three minutes. The concentrations of the solutions used for such studies were between 3.5×10^{-5} and 6×10^{-5} molar. Absorbance A was plotted directly against wavelength and the molar extinction coefficient $\mathcal{E}$ was obtained by means of the equation

$$\mathcal{E} = \frac{A}{cl}$$

where c is the concentration in moles/l. and l is the cell length (1 cm.).

Potentiometric titrations

A Radiometer automatic titrator model TTT1a was used for the titration of diethyl 3,4-dihydroxy-2,5-furandicarboxylate (Fig. 33) and ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (Fig. 34), proceeding as follows:

(a) Diethyl 3,4-dihydroxy-2,5-furandicarboxylate (22.78 mg., 0.093 mmoles) was dissolved in 25 ml. of absolute ethanol and then diluted with water to 50 ml. The whole solution was placed in the titrator and the pH of the solution recorded. The titrator was set so that readings of the burette containing 0.01N NaOH were taken at intervals of 0.2 pH increase. A graph was obtained on plotting the pH vs. volume and the first inflection point representing the first equivalent point coincided with that calculated. The pH at half neutralization was 6.2 and this is the pK_1 for this dihydroxy compound. However, the second inflection point was very faint and the theoretical value for the half neutralization of the second ionizable hydroxyl group was calculated, from which a pK of 9.7 was obtained. Since carbon dioxide was not excluded in this experiment, it is the most likely source for the absence of an inflection point, especially at around a pH of 9.

(b) Ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate (22.12 mg., 0.096 mmoles) was dissolved in 50 ml. of 50% ethanol and titrated as indicated above in (a). The graph showed two inflection points corresponding to the first and second neutralization points. The first inflection point from which the pK was obtained was slightly lower than the calculated equivalent point, while the second inflection point was slightly higher than the calculated equivalent point. The cause for such discrepancies is not exactly known, since neither carbon dioxide interference nor incorrect weighing can account for such discrepancies.

A self-recording automatic titrator was used in the case of diethyl-3-hydroxy-4-methoxy-2,5-furandicarboxylate using 0.1 ml. of an alcoholic solution containing 0.03408 g./10 ml. of alcohol. The graph obtained in this case had an inflection point which was in close agreement with the calculated point of equivalence. The pK obtained from such a graph was 6.1.

BIBLIOGRAPHY

1. Pickett, L.W., J. Chem. Phys., 10, 660 (1942).
2. Thompson, H.W. and Temple, R.B., Trans. Faraday Soc., 41, 27 (1945).
3. Garach, J. and Lacomte, J., Compt. rend., 222, 74 (1946).
4. Lacomte, J., Bull. soc. chim., 1946, 415.
5. Cross, A.H.J., Stevens, S.G.E. and Watts, T.M.E., J. Appl. Chem. (London), 7, 562 (1957).
6. Daasch, L.W., Chemistry and Industry, 1958, 1113.
7. Katritzky, A.R. and Lagowski, J.M., J. Chem. Soc., 1959, 657 .
8. Lothian, G.F., "Absorption Spectrophotometry", The Macmillan Company, New York, 1958, pp. 51-53.
9. Jones, L.A., Holmes, J.C. and Seligman, R.B., Anal. Chem., 28, 191 (1956).
10. Randle, R. and Wiffin, D., Molecular Spectroscopy (Inst. of Pet., 1955) p. 111.
11. Kubota, T., Tetrahedron, 4, 68 (1958).
12. Johnson, T.B. and Johns, C.O., Am. Chem. J., 36, 290 (1906).
13. Hinsberg, O., Ber., 45, 2413 (1912).
14. Darapsky, A. and Stauber, M., J. prakt. chem., 146, 209 (1936).
15. Dunlop, A. and Peters, F., "The Furans", Reinhold Publishing Corp., New York, 1953, p. 182.
16. Rasmussen, R.S. and Brattain, R.R., J. Am. Chem. Soc., 71, 1073 (1949).
17. Davison, W.H.T., J. Chem. Soc., 1951, 2456.
18. Thompson, H.W., Trans. Faraday Soc., 36, 988 (1940).
19. Bellamy, L.J., "The Infrared Spectra of Complex Molecules", John Wiley and Sons, Inc., New York, 1958, p. 181.
20. Hampton, R.R. and Newell, J.E., Anal. Chem., 21, 914 (1949).
21. Hunsberger, I.M., J. Am. Chem. Soc., 72, 5626 (1950).
22. Hunsberger, I.M., Ketcham, R. and Gurowsky, H.E., J. Am. Chem. Soc., 74, 4839 (1952).

23. Elderfield, R.C., Editor, "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, 1950, Vol. I, p. 138.

24. Bellamy, L.J., Op. Cit., p. 168.

25. Menczel, S., Z. physik. chem., 125A, 161 (1927).

26. Pickett, L.W., Hoeflich, N.J. and Liv, T., J. Am. Chem. Soc., 73, 4865 (1951).

27. Heilborn, I.M., Jones, E.R.H., Smith, P. and Weedon, B.C.L., J. Chem. Soc., 1946, 54.

28. Bowden, K., Braude, E.A. and Jones, E.R.H., J. Chem. Soc., 1946, 948.

29. Bowden, K. and Braude, E.A., J. Chem. Soc., 1952, 1068.

30. Braude, E.A. and Nachod, F.C., Editors, "Determination of Organic Structure by Physical Methods",

31. Gillam, A.E. and Hey, D.H., J. Chem. Soc., 1939, 1170.

32. Hausser, K.W., Kuhn, R., Smakula, A. and Deutch, A., Z. physik. chem., 29B, 378 (1935).

33. Sörensen, N.A., Ann., 546, 57 (1940).

34. Andrisano, R. and Tundo, A., Gazz. chim. ital., 81, 414 (1951).

35. Andrisano, R. and Pappalardo, G., Gazz. chim. ital., 83, 340 (1953).

36. Andrisano, R. and Passerini, R., Gazz. chim. ital., 80, 730 (1950).

37. Daub, L. and Vandenbelt, J.M., J. Am. Chem. Soc., 69, 2714 (1947).

38. Langlois, D.P. and Wolff, H., J. Am. Chem. Soc., 70, 2624 (1948).

39. Charlesworth, E.H., Campbell, H.J. and Stachiw, D.L., Can. J. Chem., 37, 877 (1959).

40. Pauly, H., Schubel, K. and Lockemann, K., Ann., 383, 288 (1911).

41. Jones, B. and Speakman, J.C., J. Chem. Soc., 1944, 19.

42. Sager, E.E., Schooley, M.R., Carr, H.S., and Acree, S.E., J. Research Natl. Bur. Standards, 35, 521 (1945).

43. Roberts, J.D., "Nuclear Magnetic Resonance", McGraw-Hill Book Co. Inc., New York, 1959.

44. Pople, J.A., Schneider, W.G. and Bernstein, H.J., "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co. Inc., New York, 1959.

45. Abraham, R.J. and Bernstein, H.J., Can. J. Chem., 37, 1056 (1959).

46. Corey, E.J., Slomp, G., Dev. S., Tobinaga, S. and Giazier, E.R., J. Am. Chem. Soc., 80, 1204 (1958).

47. Lemieux, R., Kullnig, R.K. and Moir, R.Y., J. Am. Chem. Soc., 80, 2237 (1958).

48. Karrer, P. and Schmid, H., Helv. Chim. Acta, 29, 525 (1946).

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The reaction between dimethyl peroxide, organolithium and organomagnesium compounds was investigated for the first time. The reaction affords a simple means of obtaining in high yields methyl ethers of compounds whose enols or phenols are not available or hard to obtain.

2. The reaction was shown to take an ionic rather than a free-radical course, since the peroxide reacted with triphenylmethylsodium but not with triphenylmethyl radicals.

3. In the furan series, the reaction proved superior to previous methods for the preparation of 2-methoxyfuran; 5-methyl-2-methoxyfuran was prepared for the first time by this method. The difficulty in metallating furans in the β-position limited the usefulness of this reaction for the preparation of β-methoxyfurans.

4. Attempts to use dimethyl peroxide as a methoxylating agent under Friedel-Crafts conditions failed.

5. Attempts at free-radical methoxylation of organic compounds with dimethyl peroxide at elevated temperatures failed, although separate experiments indicated the decomposition of dimethyl peroxide.

6. The nature of the reaction of dimethyl peroxide with sulfuric acid was studied. The strong dependence of the decomposition on acid concentration indicated an E_1 mechanism. This is the first example of the acid-catalyzed decomposition of dialkyl peroxides.

7. The Claisen condensation of diglycolic esters with diethyl oxalate to give dialkyl 3,4-dihydroxy-2,5-furandicarboxylates and the conditions for preparing the various derivatives from this reaction product, were studied.

8. The Claisen condensation of diethyl diglycolate with diethyl mesoxalate in the presence of sodium ethoxide afforded a small yield of a compound formulated as diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate.

9. The attempted condensation of n-butyl glyoxylate with diethyl diglycolate yielded only diethyl 3,4-dihydroxy-2,5-furandicarboxylate, indicating a Cannizzaro reaction of the n-butyl glyoxylate.

10. The reduction of the methanesulfonates of diethyl and dimethyl 3,4-dihydroxy-2,5-furandicarboxylate and derivatives with sodium or lithium in liquid ammonia proceeded by scission of the S-O rather than the C-O linkage of the methanesulfonate group.

11. The following compounds were prepared and characterized for the first time:
    (a) Diethyl 3-hydroxy-4-methoxy-2,5-furandicarboxylate.
    (b) Ethyl 5-carboxy-3-hydroxy-4-methoxy-2-furancarboxylate.
    (c) Dimethyl 3-hydroxy-4-methanesulfonyloxy-2,5-furandicarboxylate.
    (d) Dimethyl-3-methanesulfonyl-4-methoxy-2,5-furandicarboxylate.
    (e) Dimethyl 3,4-dimethanesulfonyloxy-2,5-furandicarboxylate.
    (f) Diethyl 3,4-dibenzoxy-2,5-furandicarboxylate.
    (g) Diethyl 3-hydroxy-4-methanesulfonyloxy-2,5-furandicarboxylate.
    (h) Diethyl 3-methanesulfonyl-4-methoxy-2,5-furandicarboxylate.

(i) Diethyl 3,4-dimethanesulfonyloxy-2,5-furandicarboxylate.
(j) Diethyl 5-carboxy-3-hydroxy-2,4-furandicarboxylate.
(k) 5-Methyl-2-methoxyfuran.

12. With the exception of α-angelica lactone, all the infrared spectra of the compounds mentioned in Parts II and III were recorded for the first time.

13. The ultraviolet spectra of 9 furan compounds were recorded for the first time, and correlations between the ultraviolet spectra and the structure of a number of the β-hydroxyfurans and their ions, were made.

14. The acidity constants of three β-furanols were determined for the first time using potentiometric titrations.

15. The nuclear magnetic spectra of three compounds were recorded for the first time and certain correlations with the structure of these compounds were made.

16. Evidence regarding the absence of a furan ring in aucubin was advanced on the basis of infrared, ultraviolet and NMR spectral studies.