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[Beta]-hydroxyfurans and some of their biological properties

Willard Max Hoehn
Iowa State College

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14
 **β -HYDROXYFURANS AND SOME OF THEIR BIOLOGICAL
PROPERTIES**

by

Willard Max Hoehn

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

Approved:

Signature was redacted for privacy.

In charge of Major work.

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Iowa State College
1936

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The author also takes this occasion to thank Doctor C. H. Werkman, of the Department of Bacteriology, for his aid and criticism on a portion of this investigation.

T5305

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INTRODUCTION

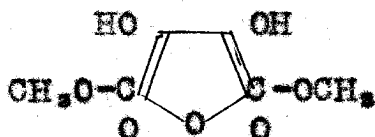
Although derivatives of hydroxyfurans are numerous and extremely important, there has been little investigation of hydroxyfurans themselves. Since β -hydroxyfurans seemed to be more stable than the α -forms, from a theoretical viewpoint, a study was made to ascertain some of the properties of this class of compounds.

All sugars having a furanose ring structure are tetrahydro- β, β' -dihydroxyfuran derivatives. When sugars of this type are treated with acids, furan derivatives such as furfural and methyl furfural are produced. Tetronic acids, which are not only closely related to hydroxy furans, but also to ascorbic acid, have recently been found present as metabolic products of Penicillium Charlesii G. Smith when grown on a medium containing glucose.

Some of the important problems which may receive some benefit from this investigation concerning the properties of hydroxyfuran include studies on lignin, degradation products of sugars, metabolic functions associated with ketogenesis, and others more closely related to sugar chemistry. Only recently have studies been made in an effort to produce erythrose and threose. The unsaturated derivatives of these two compounds - the hydroxyfurans - should show some of the properties, such as reducing power, ease of hydrolysis with acid, and the like, that these sugars exhibit.

An endeavor was then made to find a readily available source of a hydroxyfuran or a dihydroxyfuran and to study some of its chemical and biological properties.

Since compounds of the type $R-\overset{\text{OH}}{\text{C}}=\overset{\text{OH}}{\text{C}}-\overset{\text{O}}{\text{C}}-\text{OH}$ are known to be of importance biologically, 3,4-dihydroxy-2,5-dicarbomethoxyfuran was selected as a starting material for these investigations.



II. HISTORICAL

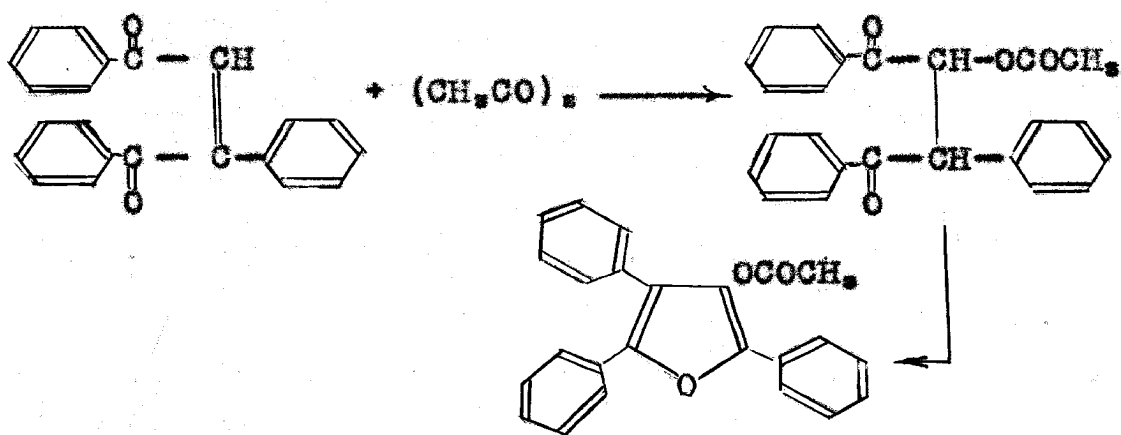
In 1887, Japp and Burton (1) prepared 3-acetoxy-2,4,5-triphenylfuran by treating the condensation product of benzil and acetophenone with acetic anhydride in the presence of a small amount of sulfuric acid. Later, Japp and Maitland (2) published an improved method for the preparation of dibenzoylstyrene.

The knowledge of hydroxyfurans will probably be of great benefit to investigators in the realm of cellulose chemistry. It is not surprising, then, that some of the first work published on hydroxyfurans was done by two outstanding workers in this field. Cross and Bevan (3) oxidized furfural, using hydrogen peroxide, and described certain reactions which they attributed to β -hydroxyfurfural. The hydroxy compound was not isolated as such, but obtained as the phenylhydrazone, melting at 150°. Since it precipitated gelatine, a phenolic group was said to be present. It is known that gelatine can be dehydrated, so that it precipitates, when the isoelectric point is reached. This work has never been substantiated. In 1900, Cross, Bevan and Briggs (4) found that the use of Caro's acid gave the same results. The treatment of benzoic acid with hydrogen peroxide or Caro's

- (1) Japp and Burton, J. Chem. Soc., 51, 430 (1887).
- (2) Japp and Maitland, J. Chem. Soc., 57, 673 (1890).
- (3) Cross and Bevan, J. Chem. Soc., 75, 747 (1899).
- (4) Cross, Bevan and Briggs, Ber., 33, 3132 (1900).

acid has yielded phenolic acids (5), so the work on the oxidation of furfural done by Cross and Bevan is possible.

Thiele, in 1898, (6) studied the action of acetic anhydride on the grouping $\cdot\text{CO}\cdot\text{C}:\text{C}\cdot\text{CO}\cdot$. By allowing dibenzoylstyrene to dissolve in acetic anhydride to which a little sulfuric acid had been added, Thiele obtained a product which was called triphenylfuranolacetate.

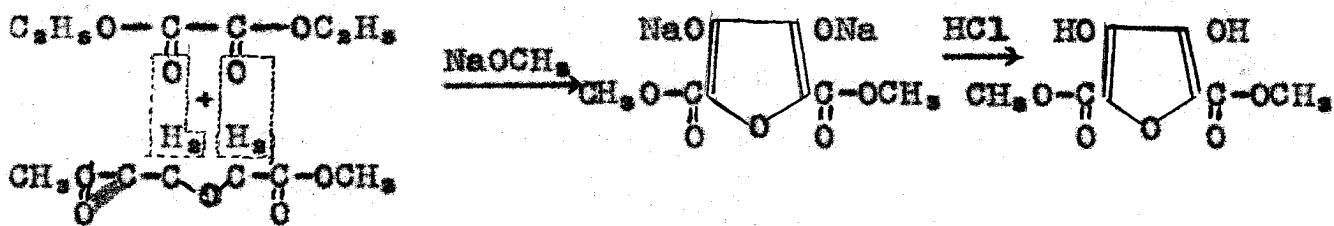


This material is the same as that obtained by Japp and Maitland (2). A green fluorescence was produced when a small amount of the compound was dissolved in concentrated sulfuric acid.

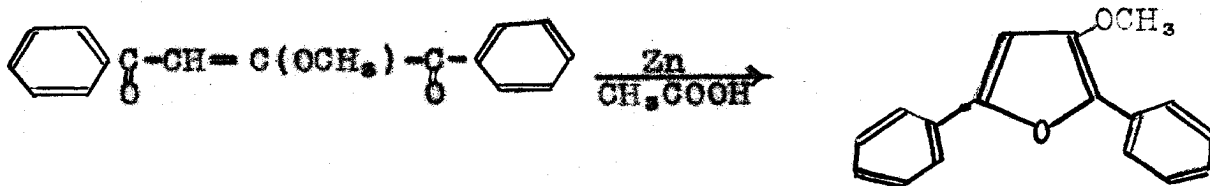
Hill and White (7) treated dinitrofuran with barium hydroxide solution and obtained in addition to barium nitrite, the barium salt of maleic acid. It is possible that during this hydrolysis some form of an α -hydroxyfuran existed.

- (5) Dakin and Herter, J. Biol. Chem., 3, 419 (1907).
- (6) Thiele, Ber., 31, 1247 (1898).
- (7) Hill and White, Am. Chem. J., 27, 193 (1902).

Johnson and Johns (8) condensed diethyl diglycolate with ethyl oxalate in the presence of sodium ethoxide and obtained a substance which at that time was called diethyl 3,4-diketo-2,5-dihydro-2,5-furandicarboxylate. Hinsberg (9) prepared the dimethyl ester and showed that phenolic groups were present since a ferric chloride color test was observed. Hinsberg's mechanism for the reaction was as follows:



It has already been inferred that β-hydroxyfurans and derivatives are best known, the α-form being demonstrated only in α-lactone structures. Conant and Lutz (10) published some work concerning the formation of β-hydroxyfuran compounds from 1,4-diketones. 2,5-Diphenyl-3-methoxyfuran was prepared by heating dibenzoylmethoxyethylene with zinc and acetic acid.

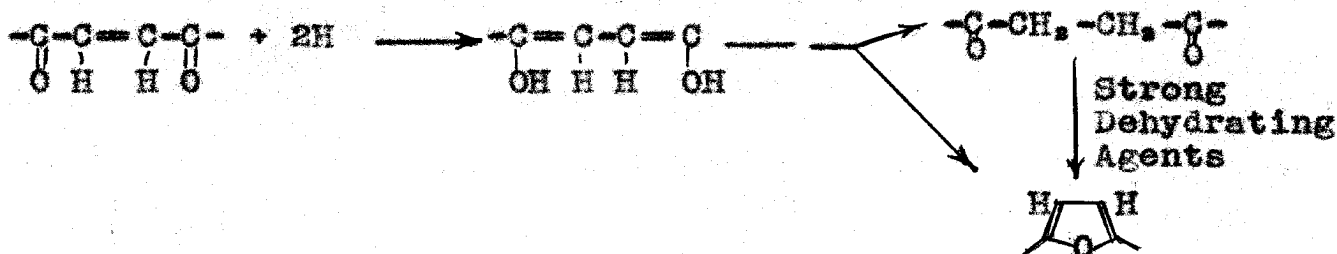


(8) Johnson and Johns, Am. Chem. J., **36**, 290 (1906).

(9) Hinsberg, Ber., **45**, 2413 (1912).

(10) Conant and Lutz, J. Am. Chem. Soc., **47**, 889 (1925)

Lutz (11) believes that the formation of compounds from the unsaturated 1,4-diketones is preceded by an intermediate dienol.



Other furan compounds which Lutz prepared at this time were:

- 2,5-Di(4-chlorophenyl)-3-methoxyfuran
- 2,5-Di(4-bromophenyl)-3-methoxyfuran
- 2,5-Diphenyl-3-phenoxyfuran
- 2,5-Diphenyl-3-(4 methylphenoxy) furan

Lutz and Eisner (12) found that the reaction of phosphorous pentachloride on 2,5-di(p-bromophenyl)-3-methoxyfuran gave 2,5-di(p-bromophenyl)-3-chlorofuran. When 2,5-diphenyl-3-methoxyfuran is used in the same reaction the starting material is recovered unchanged, (13). Saturated 1,4-diketones such as dibenzoylhydroxyethane and its acetate, are readily converted into furans; with acetic anhydride and sulfuric acid 2,5-diphenyl-3-acetoxymethoxyfuran is obtained, (14). By allowing 3-acetoxy-2,5-diphenylfuran to react with phosphorous pentachloride at 25-40°, these workers were able to obtain 3-acetoxy-4-

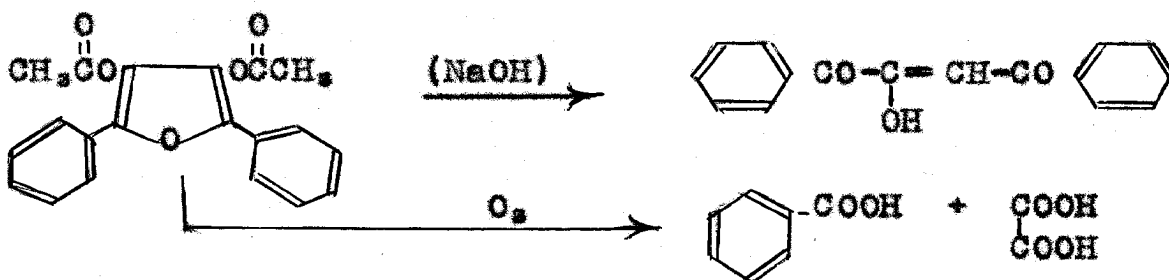
(11) Lutz, J. Am. Chem. Soc., 51, 3005 (1929)

(12) Lutz and Eisner, J. Am. Chem. Soc., 56, 2698 (1934).

(13) Lutz, Private communication.

(14) Lutz and Wilder, J. Am. Chem. Soc., 56, 2065 (1934).

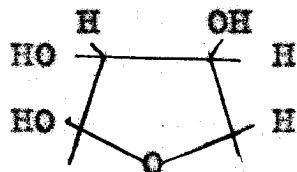
chloro-2,5-dibenzofuran. The acetoxy groups of 3,4-diacetoxy-2,5-dibenzofuran were also removed by chlorine yielding, at 25°-40°, a monochloro compound, while at 100° the 3,4-dichloro-2,5-diphenylfuran results, (15). Thionyl chloride has no such action on these compounds. When 3,4-diacetoxy-2,5-diphenylfuran was treated with acetyl chloride and sulfuric acid (16) one of the acetoxy groups was replaced by chlorine to give 3-acetoxy-4-chloro-2,5-diphenylfuran. Further treatment of this compound with phosphorous pentachloride yields 3,4-dichloro-2,5-diphenylfuran. Hydrolysis, of either 3,4-dimethoxy-2,5-diphenylfuran or the monoacetoxy compound, with sodium methoxide splits the ring giving the enol compound (17)



Some of the first furan compounds prepared were obtained from dehydration of sugars. Furan chemistry began with an experiment carried out by Döbereiner in 1830. In preparing formic acid by the action of manganese dioxide and sulfuric

- (15) Lutz and Wilder, J. Am. Chem. Soc., 56, 2145 (1934).
 (16) Lutz, Wilder and Parrish, J. Am. Chem. Soc., 56, 1980, 1987 (1934).
 (17) Lutz, J. Am. Chem. Soc., 48, 2916 (1926).

acid on sugar, some furfural was obtained, (18). Dehydration of the sugar molecule was involved and today most of the furfural is obtained from such a reaction using corn cobs, oat hulls or like materials in which furanose ring structures are contained. The furanose ring



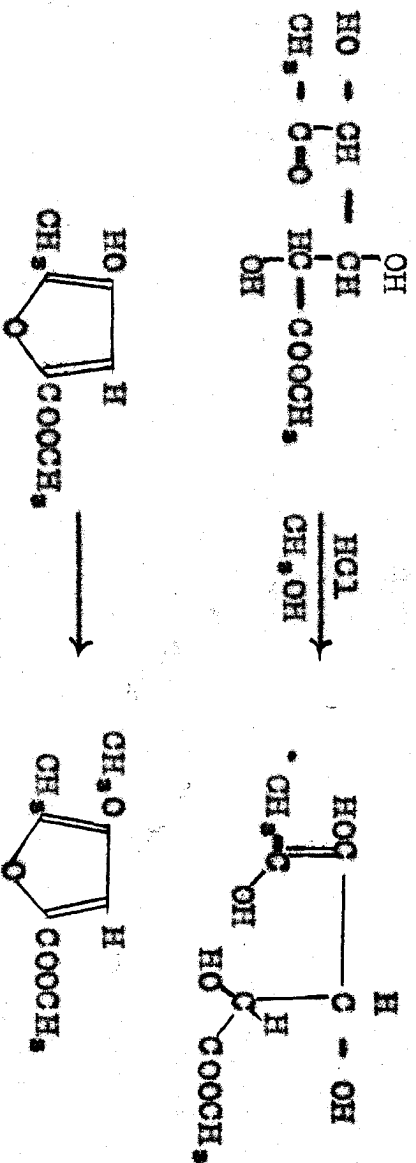
or a modification of it is found in erythrose, threose (19), (20, 21, 22, 23, 24). Votoček and Malachta prepared some very interesting compounds from the lactone of 5-ketorhamnic acid. This compound was suspended in methyl alcohol and dry hydrogen chloride gas passed through the mixture. Among other substances obtained in this experiment was methyl 4-methoxy-5-methyl-2-furoate. This compound was named incorrectly at first, but these workers corrected the error in 1932, (25). In their first paper, it was stated that ethyl ethoxycrotonate is readily formed when dry hydrogen chloride

- (18) Döbereiner, Ann., 3, 141 (1832).
- (19) Freudenberg, Ber., 64, 168 (1932).
- (20) Hockett, J. Am. Chem. Soc., 57, 2361 (1935).
- (21) Haworth and Niew, J. Chem. Soc., 1751 (1926).
- (22) Haworth and Porter, J. Chem. Soc., 151 (1930).
- (23) Haworth, Hirst and Leaner, J. Chem. Soc., 1040 (1927).
- (24) Votoček and Malachta, Collection Czechoslov. Chem. Communications, 1, 449 (1929).
- (25) Votoček and Malachta, Collection Czechoslov. Chem. Communications, 4, 87 (1932).

is passed through an alcoholic solution of ethyl acetacetate.



The mechanism for the ring closure followed from this reasoning.



The 4-methoxy-5-methyl-2-carbomethoxyfuran was studied further, (*loc. cit.*), and 3-hydroxy-2-methylfuran prepared. By the action of dilute hydrochloric acid on the ester, an oil was obtained which became a vitreous solid after being allowed to stand for an hour. The properties of this material are of extreme interest. The 4-hydroxy-5-methyl-2-furoic acid reduced Fehling's solution in the cold, gave an intensely red color with ferric chloride which was red in the presence of potassium hydroxide, and formed iodoform when treated with sodium hydroxide and iodine. An attempt was made to titrate the compound with alkali, but this proved to be hope-

less due to the development of a red color. The Zeisel determination for methoxyl gave a result of 1.72%, while the theory should have 19.75%. The material described is a mixture of hydroxy and methoxy compounds. When treated with barium hydroxide, the 4-hydroxy-5-methyl-2-furoic acid yielded oxalic acid and acetoin. Decarboxylation produced an oil which gave two fractions. The fraction boiling at 64°-65°/12 mm. gave an analysis for a hydroxyl group, by the Tschugaeff-Zerewitnoff method, of 6.65%, whereas the theoretical amount was 17.37%. Elementary analysis gave proof for an empirical formula of $C_6H_8O_5$. The second fraction boiled at 156-8°/12 mm. and gave a similar elementary analysis, and a Zerewitnoff value of 6.29% instead of 17.37%. This compound when treated with barium hydroxide gave acetoin. Diffused light decomposed the methyl 4-methoxy-5-methyl-2-furoate.

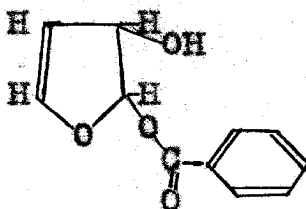
In 1934, Gilman and Wright (26) attempted to prepare a cyano compound from ethyl 4-amino-5-acetamino-2-furoate by a diazotization reaction, and obtained a compound of importance. It gave an analysis for $C_9H_{11}O_5N$ which corresponds to ethyl 4-hydroxy-5-acetamino-2-furoate. No ferric chloride color test was observed. The substance gave a precipitate with 2,4-dinitrophenylhydrazine.

There are several compounds described in the literature which should be discussed because of the possibility of their

(26) Gilman and Wright, Rec. trav. chim., 53, 13 (1934).

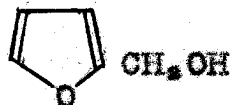
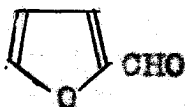
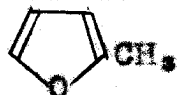
being hydroxyfurans or a derivative of a hydroxyfuran.

Böeseken and co-workers (27) have allowed furan and perbenzoic acid to react and obtained a compound to which they attributed the following structure:

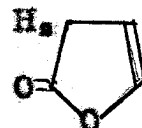
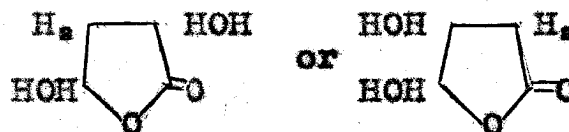
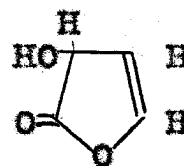


They also used peracetic acid on such compounds as furan, sylvan, furfural, and furfuryl alcohol. From methylfuran a hydroxy lactone was obtained; 2-furfuryl alcohol gave a lactone, while furfural gave a dihydroxylactone. The table below shows the reaction products and the compounds from which they are derived.

Compound treated with peracetic acid

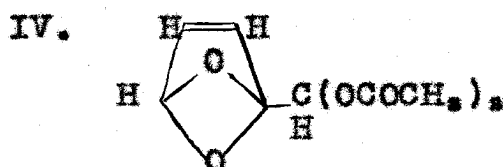
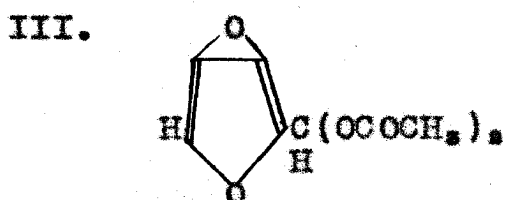
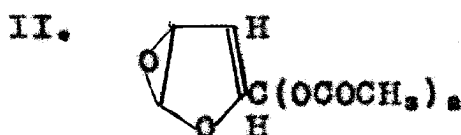
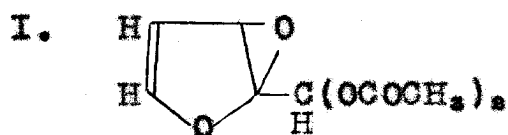


Product



(27) Böeseken, Vermij, Bunge and Meeuwen, Rec. trav. chim., 50, 1023 (1931).

The oxidation of certain furan derivatives has produced some very interesting results. Scheibler, Jeschke and Beiser (28) have presented evidence that furfural diacetate yields an oxide when treated with perbenzoic acid in chloroform solution. They propose the following structural formulae as possibilities for their product:



This compound reduces Fehling's solution and potassium permanganate. As yet the material has not been reduced catalytically.

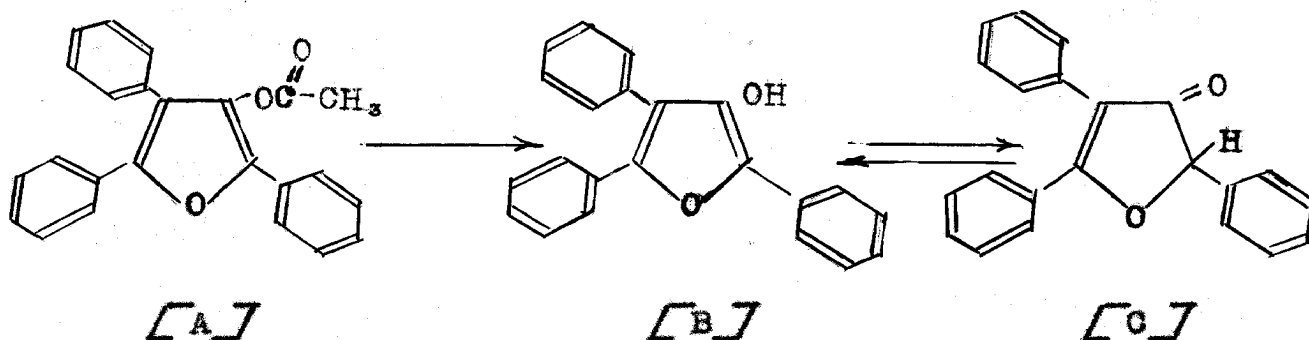
Work on the oxidation of furan compounds is still in progress, and much is yet to be found out on this subject. Milas, (29) was the first to make a systematic investigation of this problem.

Recently, the first of extensive studies on hydroxyfurans

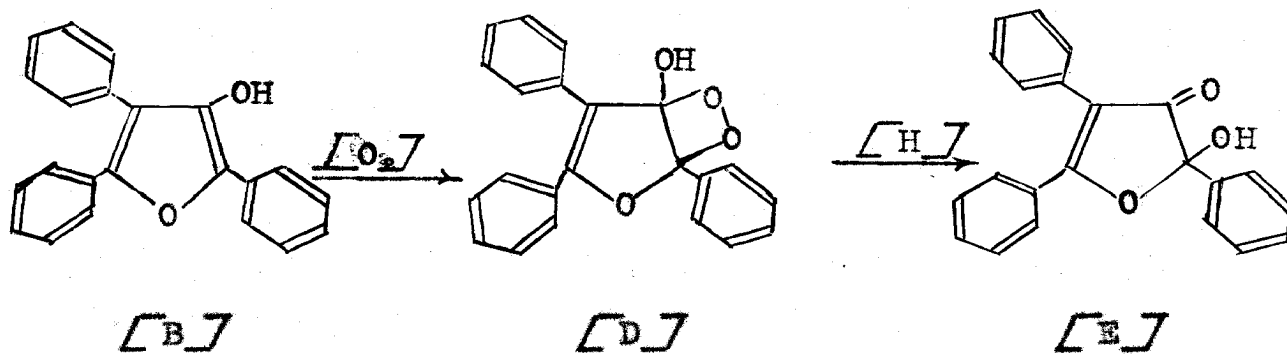
(28) Scheibler, Jeschke and Beiser, J. prakt. Chem., **137**, 322 (1932).

(29) Milas, J. Am. Chem. Soc., **49**, 2005 (1927).

has been published. Kohler, Westheimer and Tishler (30) took the 2,4,5-triphenyl-3-acetoxymfuran of Thiele and hydrolyzed it by means of either diluted sulfuric acid in an inert atmosphere or by the Grignard reagent. The resulting compound was the same with either reagent, 2,4,5-triphenyl-3-hydroxymfuran being isolated. This hydroxymfuran ketonizes and the stable form is the keto-isomer.



The hydroxy compound forms a peroxide when oxygen is passed through its ether solutions. On reductions of the peroxide formed, a so-called hydroxymfuranone is obtained

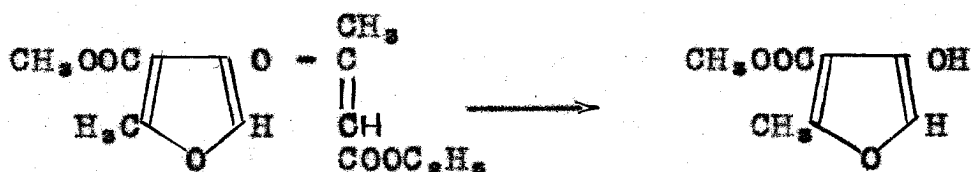


The reactions shown by this compound [E] demonstrated the

(30) Kohler, Westheimer and Tishler, J. Am. Chem. Soc., 58, 264 (1936).

presence of an aliphatic hydroxyl group.

West has recently studied the condensation of glucose with acetoacetic ester, and also of glucose with glyoxal. This work is being done in connection with a theory concerning antiketogenesis. In the condensation of glyoxal and acetoacetic ester, a product was isolated (31) which was earlier described by Polonowsky (32). This condensation on treatment with alkali gave a compound which Polonowsky isolated and found to melt at 75°. Acidic properties of the compound are attributed to the hydroxyl group in the β -position.



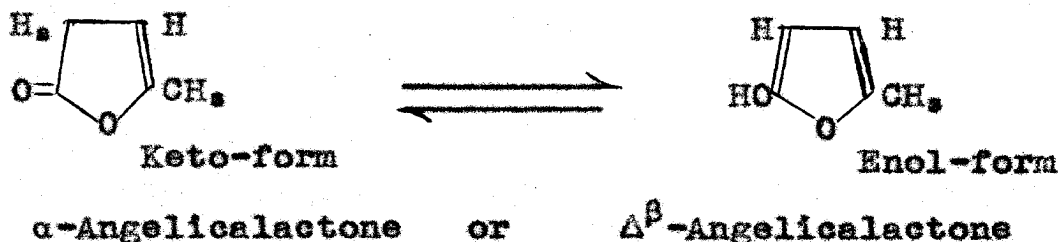
As will be seen, this compound is an isomer with that obtained by Votoček and Malachta (25).

(31) West, J. Am. Chem. Soc., 47, 2780 (1925).

(32) Polonowsky, Ann., 246, 1-32 (1888).

III. THEORETICAL

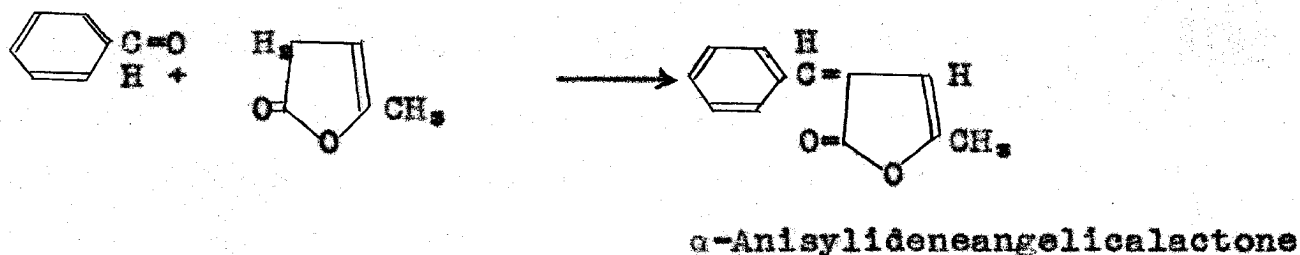
The question of the existence of α -hydroxyfurans has been a disturbing one. A compound of this type would be a hemiacetal, and although there is some evidence of a short-lived existence of several α -hydroxyfurans, none has been isolated as such. Some studies were made using the "Kohler" machine (33). The compounds tested for the presence of an active hydrogen were succinic anhydride and butyrolactone. No enolization was found to take place, using the methylmagnesium iodide reaction as a test reagent (34). α -Angelicalactone is another compound which would be an α -hydroxyfuran if any enolization occurred.



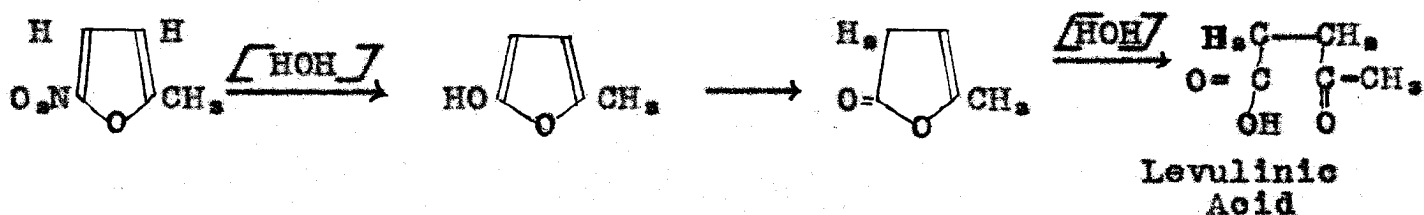
This lactone adds bromine very rapidly to give an unstable dibromolactone, which decomposes in the presence of moisture to monobromolevulinic acid. The addition of hydrogen chloride yields a compound which, in the presence of moisture, gives levulinic acid and hydrogen chloride. Hydrolysis

(33) Kohler, Stone and Fuson, J. Am. Chem. Soc., **49**, 3181 (1927).
(34) Gilman, Wright and Hoehn, Unpublished results

with a solution of barium hydroxide results in levulinic acid also (35). A phenylhydrazone is described for this isomer (36). Condensation products are obtained when α -angelicalactone is allowed to react with aromatic aldehydes. The aldehyde condenses with the methylene group, which is comparable to the reactions of tetrone acids (37).



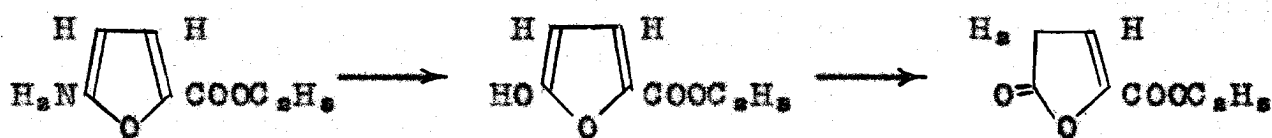
Studies on the hydrolysis of some α -nitro substituted furans have given some evidence of a transitory existence of α -hydroxyfurans. It has been shown that it is possible to hydrolyze certain members of this class of furan derivatives with water, while in other cases, barium hydroxide has been used. Levulinic acid can be isolated after boiling 5-nitrosylvan with water (38).



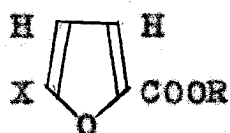
- (35) Wolff, Ann., 229, 249 (1885)
 (36) Thiele, Thisbein and Lossow, Ann., 319, 180 (1901)
 (37) Bredt, Ann., 256, 314 (1891).
 (38) Gilman and Van Ess, Unpublished results.

Hill and White (7) studied the hydrolysis with dinitrofuran using barium hydroxide solution.

Wright (39) has described an α -hydroxyfuran, which was formed when an attempt was made to diazotize ethyl 5-amino-2-furoate. This may be considered a hydrolysis reaction in which the amino group is replaced by a hydroxyl group. The resulting compound, undoubtedly, has a lactone structure.

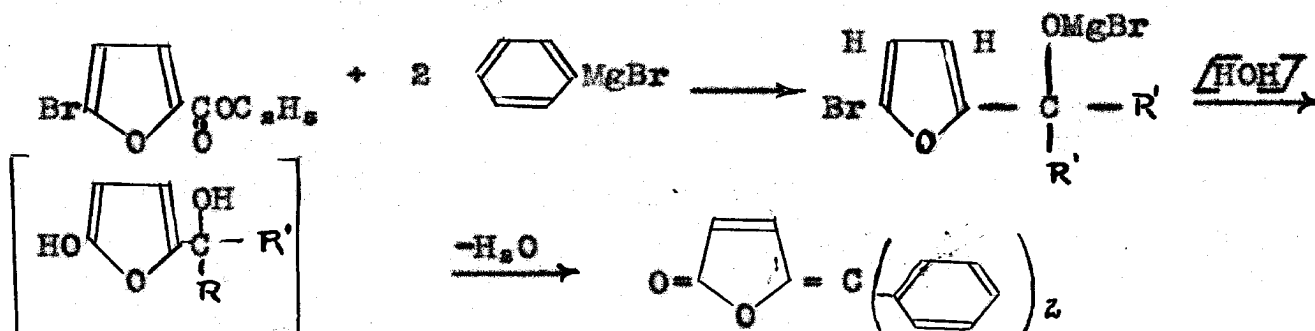


When compounds of the general type



X = Halogen
R = Alkyl Radical

are treated with two moles of phenylmagnesium bromide and subsequently hydrolyzed, a lactone derivative is obtained (40).

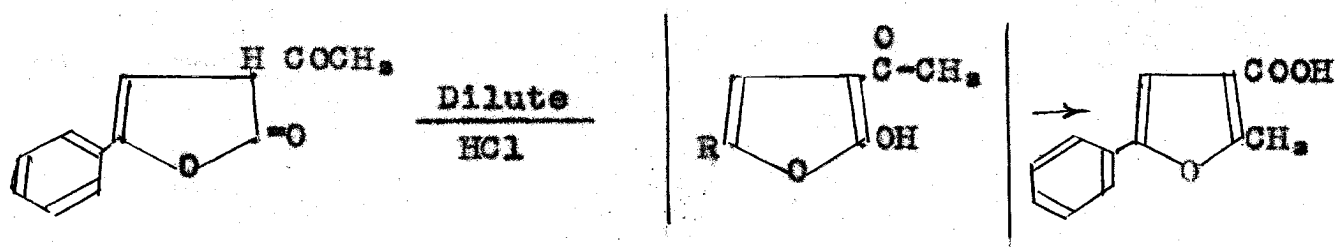


(39) Wright, Thesis, Iowa State College, 1933, p. 28.

(40) Franz, Unpublished results; cf. Gilman, Vander Wal, Franz and Brown, J. Am. Chem. Soc., 57, 1146 (1935).

Here, as in the above mentioned cases, a transitory existence of an α -hydroxyfuran is postulated.

Another interesting rearrangement, which apparently involves an α -hydroxyfuran, was studied by Borsche and Fels in 1906 (41). When γ -phenyl- α -acetyl angelicalactone is treated with dilute hydrochloric acid, the product obtained is 2-methyl-5-phenyl-3-furoic acid.



The table shows a somewhat restricted comparison of a furan compound with α -angelicalactone.

<u>Properties</u>	<u>Sylvan</u>	<u>α-Angelicalactone</u>
B.P.	65°-66°	56.5°/12 mm.
Bromination Product	Monobromo Compound	Dibromide
Hydrolysis Product	(Stable in H ₂ O)	Levulinic Acid
Reduction Product	Alcohol	Acid
Molecular Refractivity	Calc'd.: 23.799 Found: 23.377	Agrees within 1% Calc'd.: 24.28 Found: 24.20

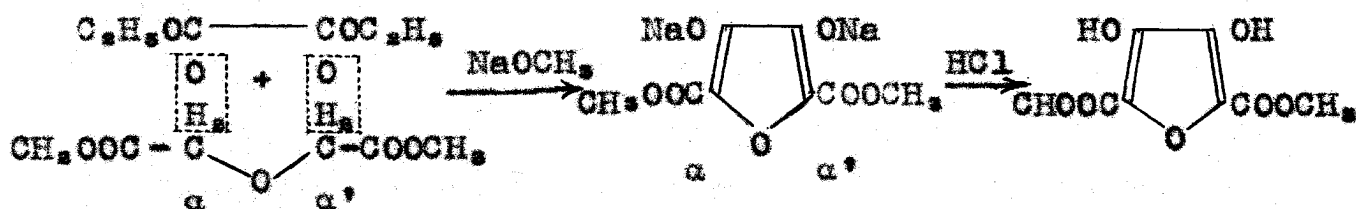
It is thought that although derivatives of α -hydroxyfurans may be isolated, one should not feel too confident in isolating α -hydroxyfurans themselves.

Votoček and Malachta (25) have published some work on 3-

(41) Borsche and Fels, Ber., 39, 1809.

hydroxysylvan and have found that when this compound was hydrolyzed with barium hydroxide, acetoin was obtained. This experiment shows the stability of a β -hydroxyfuran and is similar to that of an α -angelicalactone. The 3-hydroxysylvan ketonizes, which property will be discussed later.

When Johnson and Johns (8) studied the condensation between diethyl diglycollate and diethyl oxalate, a compound was obtained which they believed to be 3,4-diketo-2,5-dihydro-2,5-dicarbethoxyfuran. Hinsberg (9) later showed that the dimethyl ester of this type gave a ferric chloride color test. The mechanism was then postulated as follows:



In order to postulate such a mechanism, one must have evidence available which shows that the hydrogens attached to the carbon atoms linked to the oxygen are extremely active. After this condensation has taken place, the formation of the sodium salt must be explained.

From the knowledge at hand, it can be said that the hydrogens on carbon atoms α and α' are very reactive. When dimethyl diglycollate is dissolved in dry benzene and sodium added, there is a vigorous evolution of hydrogen (42). Since

(42) Hinsberg, Ber., 45, 901 (1910).

Hinsberg worked more successfully with thiodiglycollic esters, a discussion of some of these experiments would lend support to the case of the oxygen analogs. The condensation of glyoxal and dimethyl thiodiglycollate in the presence of sodium methoxide gave 2,5-dicarboxythiophene (9). This gives direct support to the fact that the carbonyl oxygens and the hydrogens on the α -carbon atoms combine to form water, establishing a double bond at the region of elimination. When one mole of diethyl thiodiglycollate was allowed to react with two moles of benzaldehyde, the condensation took place in a similar manner (43). Hinsberg put forth an idea that the negative atoms such as oxygen, sulfur and nitrogen exert an influence favoring very reactive hydrogens on the methylene group. This applies to oxygen linked to the methylene residue.

It is known, from studies concerning enol ethers, that the sodium enolate can be obtained from methyl or ethyl enol ethers when conditions are favorable. Lutz and his co-workers (44, 16) have shown that when the enol ethers of di-(trimethylbenzoyl) ethanol or dibenzoyl ethenol are treated with sodium methoxide in methyl alcohol, the enol salts are formed. These results are of interest since it has been observed in working with alkaline solutions of the compounds investigated that decomposition usually took place. Thus, in the preparation of

(43) Hinsberg, J. prakt. Chem., 84, 169 (1911).

(44) Lutz, J. Am. Chem. Soc., 56, 1590 (1934).

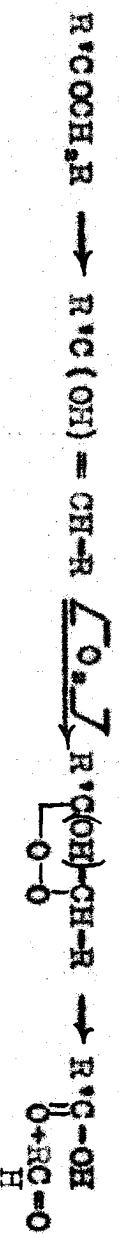
3,4-dimethoxy-2,5-dicarboxyfurane from the corresponding diester, there was a great amount of decomposition if the ester was refluxed in an alkaline solution over a long period of time. This decomposition occurs to a less extent in acid solution. Votocek and Malachta claimed that when methyl 4-methoxy-5-methyl-2-furoate is treated with dilute hydrochloric acid, the enol ether was also hydrolyzed, and 4-hydroxy-5-methyl-2-furoic acid was obtained.

The properties of the compounds studied may not apply to all hydroxyfurans. The main difference lies in the properties of the hydroxyl groups. From the evidence which has been collected in this investigation it seems reasonable to say that the hydroxyl groups in 3,4-dihydroxy-2,5-dicarbomethoxyfurane do not ketonize to a great extent. This is essentially different from the monohydroxyfurans which are known at present. It might be predicted from the work of Votocek and Malachta (25), Gilman and Wright (26), and Kohler, Westheimer and Tishler (30) that when one hydroxyl group is present in the β -position, ketonization is more likely to take place than when both β -positions are filled with hydroxyl groups. A list of the known and described hydroxyfurans is now in order, so that this generalization might be demonstrated. In every case that is known at present, when one of the β -positions is filled by a hydroxyl group, and the other by some group other than a hydroxyl or a derivative of it, the compound is capable of ketonization. The next step is to determine the enolic or

3,4-Dihydroxy-2,5-dicarb- ethoxyfuran	: No ketoniza- : tion shown	: Johnson and Johns(8)
:	:	:
3,4-Dihydroxy-2,5-dicarbo- methoxyfuran	: No ketoniza- : tion shown	: Hinsberg (9)
:	:	:
5-Methyl-4-hydroxy-2- carboxyfuran	: Capable of : ketonizing	: Votocek and : Malachta (25)
:	:	:
Ethyl 5-Acetamino-4(?) - hydroxy-2-furoate	: Capable of : ketonizing	: Gilman and Wright(26)
:	:	:
3-Hydroxy-2-methylfuran	: Capable of : ketonizing	: Votocek and : Malachta (25)
:	:	:
2,4,5-Triphenyl-3-hydroxy- furan	: Capable of : ketonizing	: Kohler, Westheimer : and Tishler (30)
:	:	:
3-Hydroxy-4-methoxy-2,5- dicarbomethoxyfuran	: No ketoniza- : tion shown	:
:	:	:
3-Hydroxy-4-methoxy-5-carb- oxy-2-carbomethoxyfuran	: No ketoniza- : tion shown	:
:	:	:
3-Hydroxy-4-methoxy-2- carbomethoxyfuran	: No ketoniza- : tion shown	:

phenolic status of these hydroxyl groups which do not ketonize. All the above compounds listed, which do now show any degree of ketonization, give a ferric chloride color test. Hydroxysylvan (5) and 5-methyl-4-hydroxy-2-carboxyfuran (3) also give a ferric chloride color test. Tschugaeff-Zerewitinoff analysis has shown that hydroxysylvan exists mostly in the keto-form. Kohler, Westheimer and Tishler (30) state that although the keto isomer is the stable form of 2,4,5-triphenyl-3-hydroxyfuran, it reacts with the Grignard reagent to give one mole of methane which indicates its ability to be transformed into the enol form.

There were some rather confusing conclusions stated in Kohler's paper concerning the properties of a β -hydroxyfuran. It is granted that the hydroxysilylan will ketonize and perhaps remain in the keto-form as the stable isomer. The evidence that peroxides are formed is not altogether convincing, but from what is known of active enols, such peroxide formations have been established. Thus benzyl-2-chlorophenylketone forms a peroxide which subsequently produces 2-chlorobenzoic acid and benzaldehyde (45). This reaction was explained thus:



After the peroxide of the 2,4,5-triphenyl-3-furanol is reduced by catalytic means, an aliphatic hydroxyl is produced at some point in the molecule, and all the reactions which are subsequently carried out are those of an aliphatic hydroxyl.

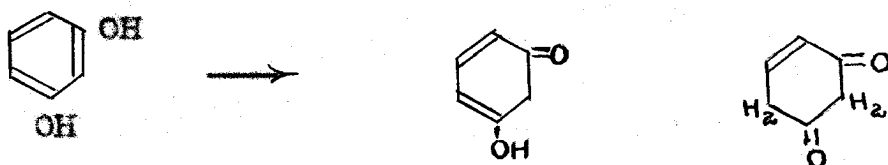
The question as to whether or not the compounds derived from 2,4,5-triphenyl-3-furanone showed aromatic properties was also considered in this paper. From the work done the evident conclusion could only be that this investigation showed that the properties of an aliphatic hydroxyl were demonstrated. The difference between the so-called aliphatic and aromatic hydroxyl groups should be clarified, if there is any dis-

(45) Jenkins, J. Am. Chem. Soc., 57, 2733 (1935).

tion. The behavior should be marked, if any classification of the two types is to be made.

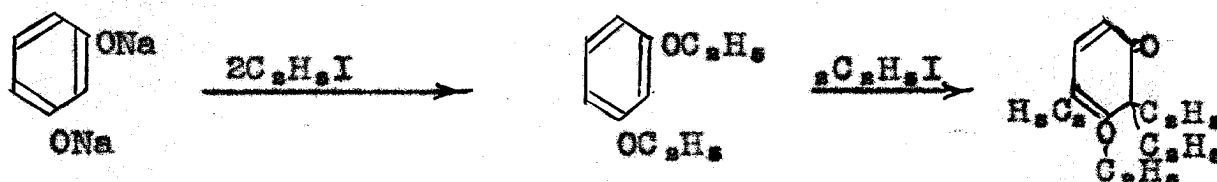
"Aromatic" properties may be possessed by hydroxyls attached to both chain and ring systems. Since aromaticity is usually a term associated with unsaturated ring systems, this type will be reviewed, and those "aromatic" hydroxyls of chain systems compared with their properties.

One of the outstanding properties of aromatic hydroxyls is their ability to give a ferric chloride color test. The phenols will usually dissolve in dilute potassium hydroxide or sodium hydroxide, but are precipitated when carbon dioxide is passed through the alkaline solution. A review of the work on diphenols reveals some interesting facts. Lead acetate will precipitate pyrocatechol, while Fehling's solution and ammoniacal silver nitrate are reduced by this diphenol. Its monomethyl ether, guaiacol, when heated with phosphorous pentachloride, yields o-chloroanisole. This is a case of a so-called aromatic hydroxyl being replaced by a halogen. Resorcinol is a meta-diphenol and is capable of keto-nizing. Fehling's solution or ammoniacal silver nitrate solu-



tion are reduced when warmed with resorcinol. The properties

shown by enolic hydroxyls, such as the one in acetoacetic ester, are demonstrated on methylation of resorcinol with alkyl iodides. It is possible to obtain C-ethers as well as O-ethers on methylation.



Phloroglucinol, a triphenol, shows a similar reaction when treated with dimethyl sulfate in alkaline solution. Phloroglucinol is the classical example of desmotropy of the phenols. When it is alkylated, it is possible to obtain the triether, while with hydroxyl amine, the trioxime is obtained. This triphenol has the ability to absorb oxygen from the air when in alkaline solution. There is no chemical evidence that ketonization takes place in pyrocatechol or guaiacol, and this diphenol and its monomethylether are analogous to the 3,4-dihydroxyderivatives of furan concerned in this problem (46).

Although tautomeric changes may not always be detected by chemical means, the use of chemico-physical methods has made this possible. Thiele (47) postulated the possibility of tautomerism in phenol itself, and compared its reactivity to that of the $>C=C(OH)-$ type of compounds, such as aceto-

(46) Meyer and Jacobson "Lehrbuch der Organischen Chemie", von Veit and Co., Leipzig, 1902, Vol. II, pt.1, pp. 408-27.

(47) Thiele, Ann., 306, 129 (1899).

acetic ester. Some excellent work was done a few years after this by Baly and his co-workers, which furnished proof of enolization in all the phenols where such tautomerism may take place (48). The absorption spectra of phenetole, anisole, and the methyl ethers of the cresols were found to be different from the absorption spectra of the phenols from which they are derived. This condition was accounted for by the tautomeric function concerning the hydroxyl group. Among other phenols, which were demonstrated to show this property, were phloroglucinol, catechol, and guaiacol.

From these considerations dealing with hydroxyls attached to the aromatic nucleus, it is readily seen that nearly all of these reactions could be applied to the enolic hydroxyl group. Some of the more common enol reagents are acetyl chloride, benzoyl chloride, ferric chloride, copper acetate, and phenyl isocyanate (49). Among the special reagents should be listed diazomethane. In general, diazomethane does not react with aliphatic hydroxyl groups (50). The enol form of tautomers reacts similarly to that of phenols (51). It is suggested that "aromatic" and enolic hydroxyl groups then be

- (48) Baly and Collie, J. Chem. Soc., 87, 1332 (1905); Baly and Miss Ewbank, J. Chem. Soc., 87, 1347 (1905).
(49) Houben, "Die Methoden der organischen Chemie", Georg Thieme, Berlin, 3rd Ed., Vol. III, 1930, p.22.
(50) K. Meyer, Monatsh., 26, 389 (1905); Clibbons and Nierenstein, J. Chem. Soc., 107, 1491 (1915); Biltz and Paetzold, Ann., 433, 86 (1923).
(51) Leuchs and Dziengl, Ann., 440, 149 (1924); Claisen, Ber., 59, 151 (1926); Weygand, Ber., 58, 1473 (1925).

determined by this reagent, since there is no tendency for the methyl group to migrate from the ether oxygen atom to an adjacent carbon atom. Migration of the carbon radicals sometimes takes place when alkylation is performed in alkaline solution with dimethyl sulfate as an alkylating reagent. Another reagent which has been used for the identification of phenols is monochloroacetic acid, which is added to an alkaline solution of the phenol to be identified, (52). Roll (53) has also listed the use of the Grignard reagent as a means of determining the presence of an enol, and where a strongly acidic enol is present, a titration method employing alkali may be used. An "aromatic" hydroxyl should be capable of reacting with all the enol reagents, and the one which is handled easily and from which the best results are obtained is diazomethane



Ferric chloride color tests are not always reliable in determining the presence of an "aromatic" hydroxyl group. There are substituted phenols known which give a negative reaction toward this reagent. Examples of such phenols are thymol, 1,4-xyleneol-2, picric acid, and mesitol (54). Kauf-

(52) Koelsch, *J. Am. Chem. Soc.*, 53, 304 (1933).

(53) Roll, L. J., *Thesis Abstract*, University of Illinois, 1931.

(54) Hans Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen", 5th Ed., Julius Springer, Berlin, 1931, Vol. I, p. 302.

mann and his co-workers (55) have found in their studies of keto-enol tautomerism, that certain forms give negative ferric chloride color tests. The researches concerned the tautomeric forms of diacetylsuccinic esters, dibenzoyl succinic esters, and phenylformylacetates. These examples illustrate the possibility of having negative ferric chloride color tests in the aliphatic series of compounds. Solubility in dilute alkali is likewise an unreliable criterion for establishing the presence of an "aromatic" hydroxyl group, as it is possible that stereo-effects from groups substituted adjacent to the hydroxy group may prevent solution (56). All of the substances designated as hydroxy compounds in this investigation of hydroxyfurans were alkali soluble.

The reactions shown by hydroxyl groups are found to be different as their position, in relation to unsaturation in the molecule, is changed. A hydroxyl group attached to a carbon atom which in turn is attached by a double bond to another carbon atom, is found to be extremely reactive (57).

(55) Kaufmann and Richter, Ber., 58, 216 (1925).

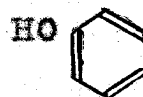
(56) Adams, J. Am. Chem. Soc., 41, 247-270 (1919).

(57) Reviews of the literature on this subject are found in some of the following handbooks. (a) Hans Meyer "Analyse und Konstitutionsermittlung organischer Verbindungen" 5th Ed., Julius Springer, Berlin, 1931, pp. 301-328; (b) Abderhalden, "Handbuch der biologischen Arbeitsmethoden", 2nd Ed., Urban and Schwarzenberg, Berlin, 1925, I, 1, pp. 291-462; Houben, "Die Methode der Organischen Chemie", 3rd Ed., Georg Thieme, Leipzig, 1931, 3, pp. 22-25 and 27-33.

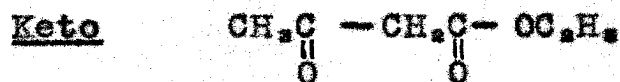
Examples of such a case are to be found in acetoacetic ester and phenol.



Acetoacetic ester



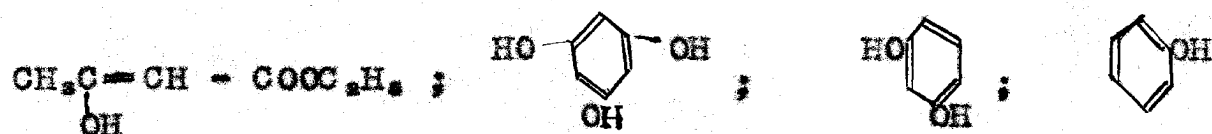
Phenol



The enol form of phenol is more stable than the keto form and phenol exists in the former state to a greater extent. The hydroxyl group of phenol and enol hydroxyl of acetoacetic ester react similarly. The difference in degree of reaction of the hydroxy is due to the residue to which they are attached. The aromatic compounds show a few reactions which concern the nucleus. One in particular is the reaction of phenols with benzenediazonium chloride. The ethers of the enols can be made by various methods. The ethers are more stable and possess the same reactivity as the enols themselves, excluding reactions in which the enolic hydroxyl takes part.

However, the difference in degree of reaction is marked. The enol ether of acetoacetic ester can be prepared by passing dry hydrogen chloride gas through its ethyl alcoholic solution. In a similar manner the dimethyl ether of phloroglucinol can be prepared (57a). The phenol methyl ether is difficult to prepare in this manner and sulfuric acid must be used as a cat-

alyst. The enolic hydroxyl group found in acetoacetic ester is similar to those found in phloroglucinol, and this similarity seems to decrease to a slight extent when di- and mono-phenols are considered. A tentative rating might be given to these hydroxylated compounds in the following manner:

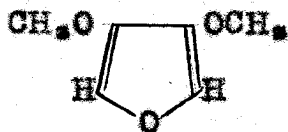


This series is by no means to be taken as final, but it is based on experimental evidence which proves the existence of keto-isomers. Thus, both keto and enol derivatives can be obtained for acetoacetic ester, phloroglucinol, and resorcinol. These three compounds also give analogous compounds, when alkylated in alkaline solution with dimethyl sulfate. The hydroxyl groups are different from those found in saturated alcohols. Diazomethane will not react with "aliphatic" hydroxyls, while it does so readily with the enol or "aromatic" hydroxyl group.

Enol ethers are very reactive compounds. An interesting example of an enol ether is furan. Furfural can be titrated with bromine much in the same way as an enol (58). One would expect the β -positions of the furan nucleus to be much more reactive than they are, but experimental evidence proves the

(58) Hughes and Acree, Ind. Eng. Chem., Anal. Ed., 6, 123 (1934).

greater reactivity of the α -positions. 3,4-Dimethoxyfuran should be a rather reactive compound, since it may be considered to be a dienol ether of a substance which is structurally an enol ether.



Dimethoxyfuran

It is resinified immediately when brought into contact with mineral acids. Mercuration took place immediately on addition of the mercurating solution, a dimercurial resulting. No detectable reaction was ascertained when 3,4-dimethoxyfuran was treated with ethylmagnesium bromide or with butyl-lithium.

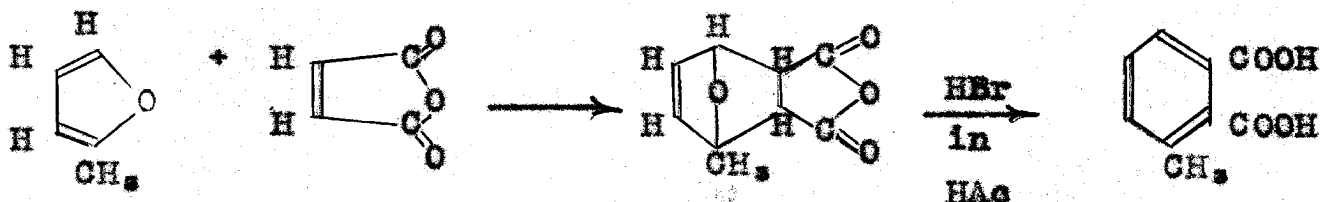
3,4-Dihydroxy-2,5-dicarbomethoxyfuran reduced Fehling's solution on warming, gave a positive test with Tollen's reagent, and reduced 2,6-dichlorophenol indophenol. When tested with ferric chloric, mercurous nitrate, acetyl chloride, diazomethane, benzoyl chloride and solubility in dilute alkali, the reactions were those to be expected from a phenol. 3-Hydroxy-4-methoxy-2-carbomethoxyfuran gave the characteristic phenol reactions with ferric chloride, acetyl chloride, benzoyl chloride, and solubility in dilute alkalies. The enol acetates were easily hydrolyzed in water which contained a few drops of acid.

As yet little has been said concerning the ring system

which was investigated. Some of the general characteristics of furan itself include instability toward acid, its relatively high stability toward alkali, and the ability to undergo halogenation, mercuration, the Friedel-Crafts reaction, nitration and sulfonation with a degree of smoothness that classes it as "superaromatic" in properties (59). Some work on hydrolysis has been discussed, and it can be said that the effect of certain types of substituents such as carboxyl, cyano and other negative groups tend to increase the stability of the ring in alkaline hydrolysis. The presence of the nitro group in the α -position in furan decreases the stability of the ring toward alkaline hydrolysis. The methyl group which tends to increase the stability of the ring toward acids, causes an action contrary to this when alkaline hydrolysis is investigated. In general, however, it may be said that the ortho,para-directing groups of the benzene series when substituted in an α -position in furan tend to decrease the stability of the ring towards acid. The fact that certain substituted furans will form maleic anhydride addition compounds proves the presence of a diene system. The statement has been made that this formation does not occur when a carbethoxy, cyano, nitro, or ethylenic group is attached to the ring, pre-

- (59) a. Gilman and Towne, Rec. trav. chim., 51, 1054 (1932).
b. Gilman and Calloway, J. Am. Chem. Soc., 55, 4197 (1933).
c. Gilman and Young, J. Am. Chem. Soc., 56, 464 (1934).
d. Gilman and Breuer, J. Am. Chem. Soc., 56, 1123 (1934).

sumably in the α -position. Johnson and Van Campen (60) obtained crystalline maleic anhydride addition compounds with 2-bromofuran, 3-bromofuran, furfurylmethyl ether, furfuraldiacetate, furfurylaceton and several others. These addition products are endoxy compounds which may later be converted to phthalic acid derivatives by treatment with hydrogen bromide in glacial acetic acid.



Even when an addition product is realized, proof that a diene system is present is not entirely complete until the proper phthalic acid derivative has been obtained. This method has only limited application, and some have been skeptical in accepting it as a procedure in orientation problems of furan (61).

The aminofurans have presented as difficult a problem as the hydroxyfurans (62, 26). If β -aminofuran were readily accessible, there would be a possibility of having a potential

- (60) Johnson and Van Campen, J. Am. Chem. Soc., 55, 431 (1933).
 (61) Gilman and Wright, Chem. Rev., 11, 352 (1932); Gilman and Dickey, Iowa State Coll. J. Sci., 6, 382 (1932).
 (62) Bloomquist and Stevenson, J. Am. Chem. Soc., 56, 146 (1934); Burtner, J. Am. Chem. Soc., 56, 666 (1934);

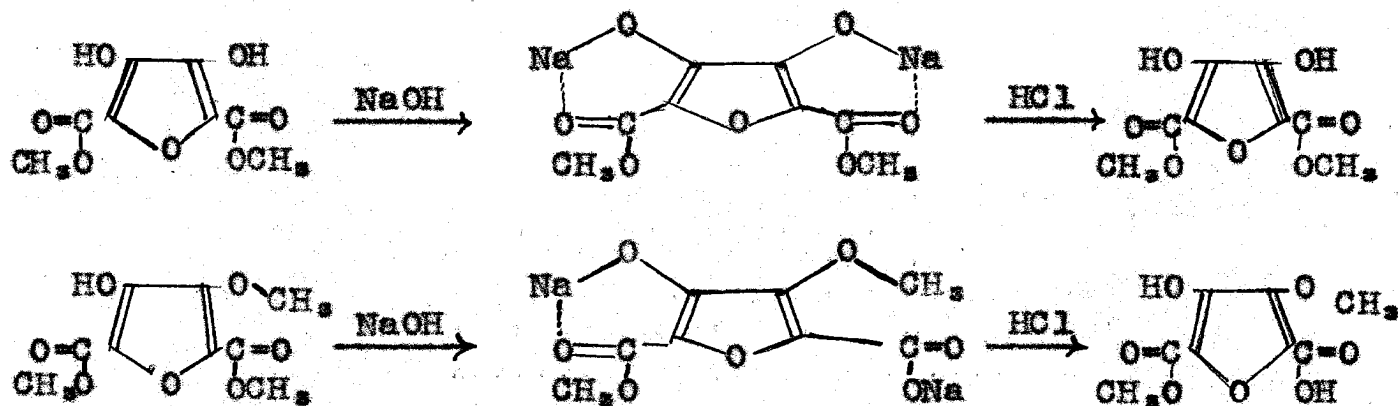
source of β -hydroxyfuran.

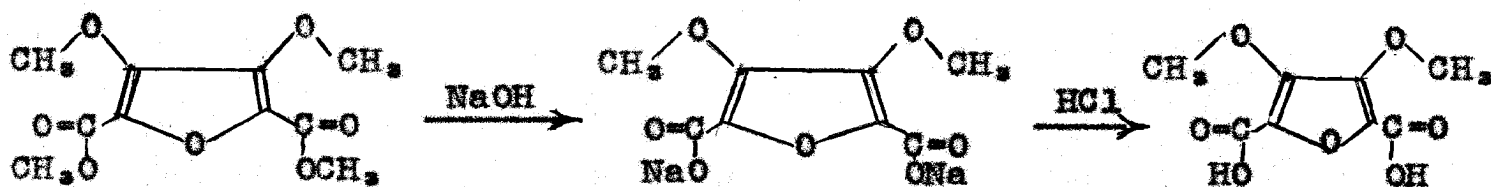
Removal and replacement of certain atoms or groups of atoms has aided in establishing many orientation problems of furan. If carboxyl groups are present, the process of decarboxylation can be used. Both acid and alkali hydrolysis were attempted. It was first thought possible that 3,4-dihydroxy-2,5-dicarbomethoxyfuran could be saponified, and in this way prepare 3,4-dihydroxy-2,5-dicarboxyfuran which on decarboxylation would yield 3,4-dihydroxyfuran. Due to the peculiar properties of the compound, this was found to be impractical, since saponification gave the dimetallic salt of the dienol at low temperatures, while at reflux temperatures this material was obtained among decomposition products. Acidification of the dienol salt reconverted it to the original dihydroxy-compound. The dimethyl ether was then prepared and when this compound was subjected to saponification, the 3,4-dimethoxy-2,5-dicarboxyfuran was obtained. An adequate explanation for this phenomenon cannot be made. Hinsberg (9) found that 3,4-dihydroxy-2,5-dicarbomethoxythiophene possessed similar properties. It might be possible to attribute some of this peculiarity to the formation of a ring system, which was visualized by Hantzsch (63) in accounting for chromoisomeric salts of the acetoacetic ester type.



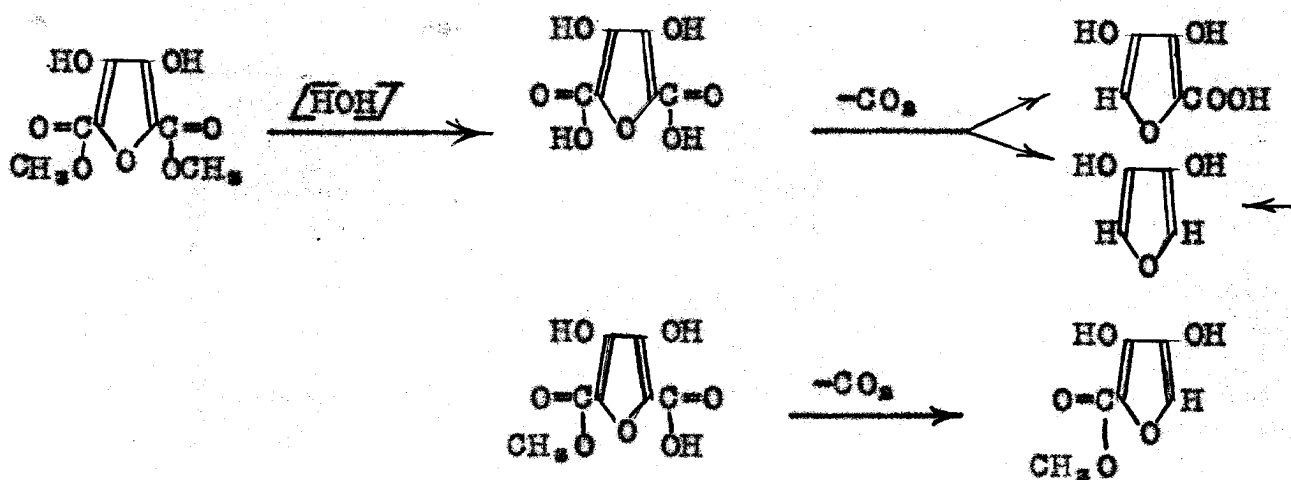
(63) Hantzsch, Ber., 48, 785 (1915).

Dihydroxydicarboxylic esters exhibit this effect, and such a property can be ascertained by the color of the monovalent salts contrasted to that of the divalent salts, or the difference in color of the salt in different solutions. When the disodium salt of 3,4-dihydroxy-2,5-dicarbomethoxyfuran was isolated from alcohol solution it was yellow, but when the dihydroxydiester was dissolved in aqueous alkali, a distinct red color was given to the solution. The effect would correspond to a formation such as (I), and in this state might hinder, to some extent, the saponification of the carboxyl group. If, however, the monomethyl ether was subjected to saponification, it was found possible to obtain a compound containing both a hydroxyl and a carboxyl group. Since it was found that 3,4-dihydroxy-2,5-dicarbomethoxyfuran could not be satisfactorily hydrolyzed, while 3,4-dimethoxy-2,5-dicarbomethoxyfuran was hydrolyzed to the dimethoxy-diacid, it was thought that the resulting compound of hydrolysis of the monomethyl ether was 3-hydroxy-4-methoxy-2-carbomethoxy-5-furcic acid,





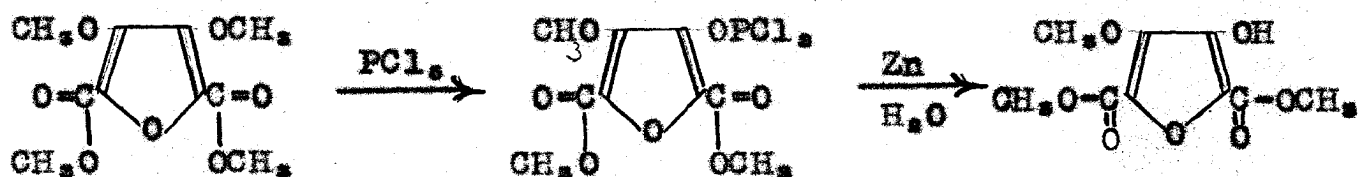
No hydrolysis takes place in cold acid solution, but on heating in dilute acid solution products of decomposition are apparent since tars and resins are formed to a slight extent. A large amount of the starting material is recovered. This might be explained by considering some hydrolysis to take place and the products, which are formed, to decarboxylate at the temperature necessary to bring about any hydrolysis.



Resins are very likely to form from such products.

From the work of Lutz (12), who found that phosphorous pentachloride reacted with 2,5-di(*p*-bromophenyl)-3-methoxyfuran, 2,5-di(*p*-bromophenyl)-3-acetoxyfuran to yield 2,5-di(*p*-bromophenyl)-3-chlorofuran, it was thought that replacement of the methoxyl or acetoxy groups in 3,4-dihydroxyfuran derivatives

would be effected. This would lead to known 3,4-dichlorofuran derivatives (64). When 3,4-dimethoxy-2,5-dicarbomethoxyfuran was allowed to react with phosphorous pentachloride, the chloro-derivative is not obtained. Instead, the 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran is obtained.



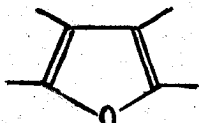
Other ether splitting reagents, such as benzoyl and acetyl chlorides, involve the use of a catalyst. Some of the catalysts used are stannic chloride, aluminum chloride and zinc chloride (65).

A survey of the evidence for the furan structure of these compounds should now be made. The parent 3,4-dihydroxy-2,5-dicarbomethoxyfuran has the empirical formula C₈H₈O₇. It was isolated as the disodium or diammonium salt of the dienol. The material reacted with acetyl chloride to give the diacetate, and with diazomethane to give the dimethylether. When the 3,4-dimethoxy-2,5-dicarbomethoxyfuran was saponified, the 3,4-dimethoxy-2,5-dicarboxyfuran, C₈H₈O₇, was obtained. Decarboxylation was performed. Decarboxylation of this compound yielded

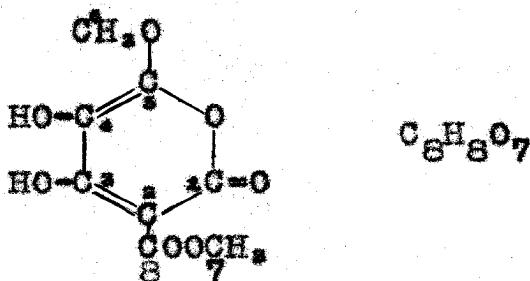
(64) Gilman and Vander Wal, Rec. trav. chim., 52, 267 (1933).

(65) Meerwein and Maier-Hüser, J. prakt. Chem., 134, 51 (1932).

a compound which has an empirical formula of $C_6H_8O_3$. Thus far, the presence of two methoxyl groups and two carboxyl groups has been shown. The residue, C_4O , which remained must be arranged in a diene system, since the 3,4-dimethoxy added maleic anhydride to give a compound $C_{10}H_{10}O_6$. The furan nucleus would fit these conditions.



From the data given by Hinsberg, (9, 42, 43), it is felt that the furan structure would account for all of these reactions, while other possible structures derived from the empirical formula, $C_8H_8O_7$, would not do so. An open chain formula would have to contain the diene system and also have present an enolic hydroxyl group. It is difficult to imagine such a compound, which would still retain two hydroxyl and two carboxyl groups, that could be successfully fitted to the facts. A pyrone type of compound might be adjusted to fit some of the facts concerned but not all of them.



In this formula one can account for two hydroxyls, which would give an enol test. The diene system is present. Acid hydroly-

ysis should split the acetal at carbon atom (*). The lactone should be split with little difficulty. Whether the diene system would remain intact, after two carboxyl groups were taken from this molecule is doubtful.

A readily available source of dimethyl and diethyl diglycollate was not at hand, and it was found necessary to discover a convenient method for their preparation. Barium diglycollate was prepared, according to the directions of Lossen (66). The diethyl ester was first prepared from the silver salt of the acid and methyl iodide (67). Heinz prepared the dimethyl ester by heating sodium carbonate with methyl chloroacetate at 180°-200° (68). Anschütz and his co-workers (69) prepared the methyl ester: (1) by treating the acid chloride with methyl alcohol, (2) by the action of methyl alcohol on the acid in the presence of dry hydrogen gas and (3) the action of a hydrogen gas saturated solution of methyl alcohol on the anhydride.

A great amount of time was consumed in converting the barium salt of diglycollic acid to the acid, and in the preparation of the desired ester from this acid. Procedures were developed so that the barium salt could be directly converted in-

- (66) Lossen, Ann., 342, 121 (1905); cf. Boeseken, Rec. trav. chim., 37, 132 (1918).
(67) Heinz, Ann., 144, 95 (1867).
(68) Heinz, Ann., 147, 200 (1868).
(69) Anschütz, Ann., 273, 65 (1892); Anschütz and Biermaux, Ber., 55B, 676 (1922).

to the desired ester.

In condensations of diglycollic esters with compounds containing the atomic grouping $\begin{array}{c} -\text{C}-\text{C}- \\ | \quad | \\ \text{O} \quad \text{O} \end{array}$ in the presence of alkali alkoxides, it was found that the alkoxide had a definite influence on the product isolated. Hinsberg has noted this earlier. When dimethyl thiodiglycollate was condensed with diethyl oxalate in the presence of sodium ethoxide, 3,4-dihydroxy-2,5-dicarbethoxythiophene was obtained (9). It was observed that the condensation of dibutyl diglycollate and diethyl oxalate in the presence of sodium ethoxide, yielded, instead of the expected 3,4-dihydroxy-2,5-dicarbobutoxyfuran, the 3,4-dihydroxy-2,5-dicarbethoxyfuran. It was found necessary, therefore, to choose the alkoxide which corresponded with the diglycollic ester used. This prevented the interchange of the alcohol radical of the ester group for that of the alkoxide radical.

The time of reaction could be shortened considerably, if the alcoholic solution of the alkoxide was diluted with some other inert solvent (8). The choice of this solvent seemed to depend on the compounds which were to undergo condensation. The condensation of benzil with dimethyldiglycollate in the presence of sodium methoxide in methyl alcohol was favorably improved by the addition of benzene (70). The use of a solution of a methyl alcohol, ether and sodium methoxide gave a very desirable condensation medium for the preparation of 3,4-

(70) Van Ess, Unpublished results.

3,4-dihydroxy-2,5-dicarbomethoxyfuran.

Besides studies concerning the condensation of diethyl oxalate and dimethyl diglycollate, investigations were carried out where these materials were replaced by other compounds. Ethyl pyruvate, ethyl acetopyruvate, diethyl oxomalonate and glyoxal were used instead of diethyl oxalate. A condensation was also attempted using benzyl ether and diethyl oxalate. No condensation products were obtained in the ethyl pyruvate, ethyl acetopyruvate and benzyl ether experiments. The compound from the condensation of diethyl oxomalonate and dimethyl diglycollate is, as yet, of undetermined constitution. A ferric chloride color test of deep blue to violet is observed when the material is freshly isolated, but on standing for some time, the ability to give such a test disappears.

The first directions for these condensation reactions stated that it was desirable to allow the condensation mixtures to stand for a period of from three to five days. This was found to be impractical, and the use of the solvent mixture of sodium alkoxide made it possible to isolate the condensation product after two to ten hours after the mixture of the starting compounds was made. These conditions apply only to condensations using diethyl oxalate and dialkyl diglycollates. The use of ether as a solvent for this reaction was introduced by Johnson and Johns (8). These authors stated that the yield of the disodium salt of 3,4-dihydroxy-2,5-dicarbomethoxyfuran was quantitative. Although the yields of 3,4-dihydroxy-2,5-dicar-

bomethoxyfuran are between 85-92%, as yet quantitative yields have not been obtained.

The mechanism to give the furan nucleus is substantiated by the condensation of glyoxal and dimethyl diglycollate to give dehydro mucic acid. The yields of the dehydromucic acid in these condensations were exceedingly small. The product from the condensation was therefore converted directly into the dimethyl ester by means of diazomethane and identification was made through this derivative.

The one reaction which aided greatly in carrying out this investigation was alkylation. Some of the alkylating reagents used were dimethyl sulfate in alkaline solution, ethyl chloro-carbonate, and diazomethane. The dimethyl sulfate was found to be satisfactory when fairly large amounts of material were to be methylated. When quantitative yields of rather pure products were required, diazomethane was used.

When 3,4-dihydroxy-2,5-dicarbomethoxyfuran was treated with one equivalent of alkali and one equivalent of dimethyl sulfate, a small amount of 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran was isolated. When 3,4-dihydroxy-2,5-dicarbomethoxyfuran was treated with two equivalents of dimethyl sulfate in alkaline solution, a mixture of products was obtained. This mixture consisted of the monomethyl and dimethyl ethers of the 3,4-dihydroxy-2,5-dicarbomethoxyfuran. Mr. P. R. Van Ess found that the 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran could be extracted from this mixture by the use of a lithium

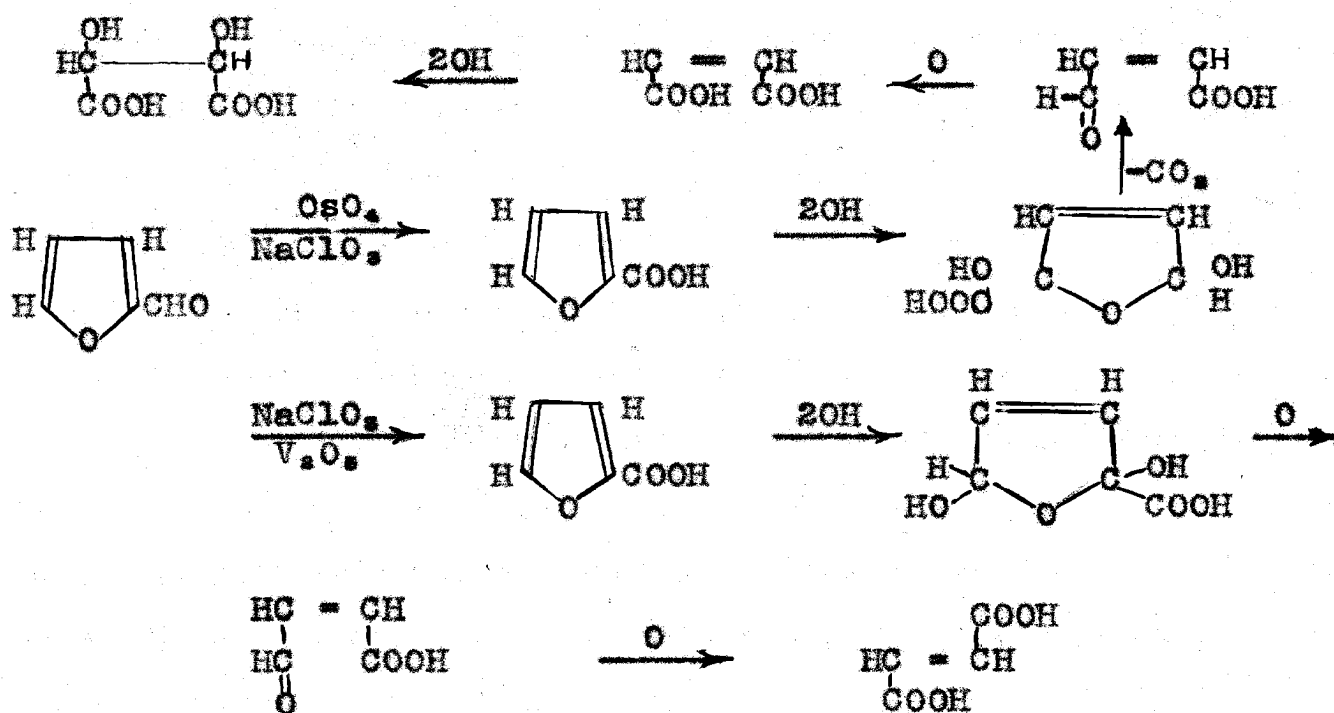
carbonate solution or by the use of secondary sodium phosphate solution. If one alkylated the mixture until no blue color appeared when tested with ferric chloride, only 3,4-dimethoxy-2,5-dicarbomethoxyfuran was obtained.

In order to show the presence of a hydroxyl group, which was not a part of a carboxyl group, the acetate and benzoate of 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran was prepared. By hydrolysis of the 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran in alkaline solution, a hydroxy-acid is obtained. This compound, from what has already been stated (page 40 in this thesis) is postulated as 3-hydroxy-4-methoxy-2-carbomethoxy-5-furoic acid. This material was converted to the acid chloride.

The use of diazomethane as an alkylating reagent is becoming popular due to the convenience of preparation, its mild but effective action on enol-type hydroxyl groups, and improvements in its preparation which have lessened the cost. Diazomethane may produce different results with acid chlorides, depending on the conditions under which it is used (71). The use of diazomethane for the preparation of methoxy-derivative made it possible to work with small amounts of material when necessary. Micro-Zeisel analyses were used frequently, since this gave an indirect method of finding the molecular weight of the compound.

(71) H. Meyer, "Analyse und Konstitutionsermittlung", Julius Springer, 1931, 5th Ed., I, pp. 410-412.

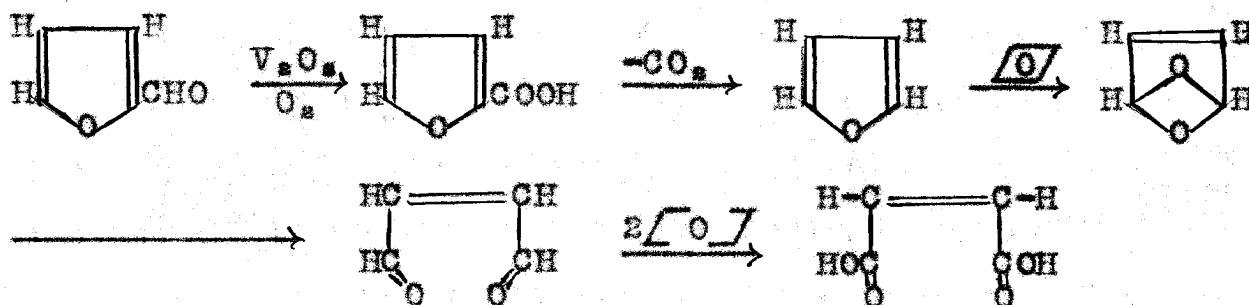
In the laboratories of Milas (78, 79) studies have been made of the catalytic oxidation of furan derivatives under various conditions in order to ascertain a mechanism for the formation of fumaric, mesotartaric, oxalic and maleic acids from them. Sessions (80) has also studied the oxidation of furfural, obtaining maleic acid as a product. The proposed mechanism of Milas, when furfural or furoic acid was oxidized using osmium oxide or vanadium oxide with sodium chlorate, was as follows:



The mechanism proposed, when the vapor phase oxidation was carried out, using furan, furfuryl alcohol, furfural and furoic

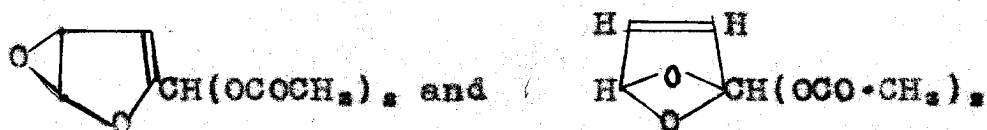
(80) Sessions, J. Am. Chem. Soc., 50, 1696 (1928).

acid, was as follows:

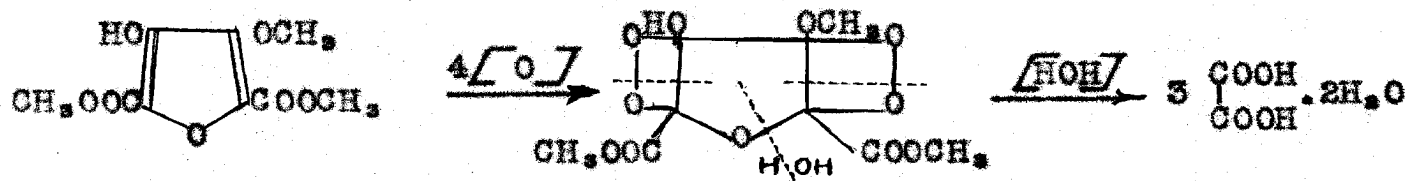


Wooley (81) has found that tars and resinous products were obtained when dimethylfuran was treated with vanadium pentoxide, vanadium pentoxide and sodium chlorate, silver peroxide, lead dioxide, lead tetracetate, hydrogen peroxide in either acidic or basic solution and nitrogen dioxide. Böseken and co-workers (27) have studied the effect of perbenzoic and peracetic acids on some substituted furans. In every case the furan or furan derivative had no substituent in one of the α -positions. This was invariably the point of attack in these oxidations, lactones being formed in each case. This work would then suggest that the product obtained by Scheibler, Jeschke and Beiser (28) would likewise be considered as some form of oxidation at the α -carbon atom. This narrows the possibilities to two compounds for the products isolated when furfural diacetate was treated with perbenzoic acid in chloroform.

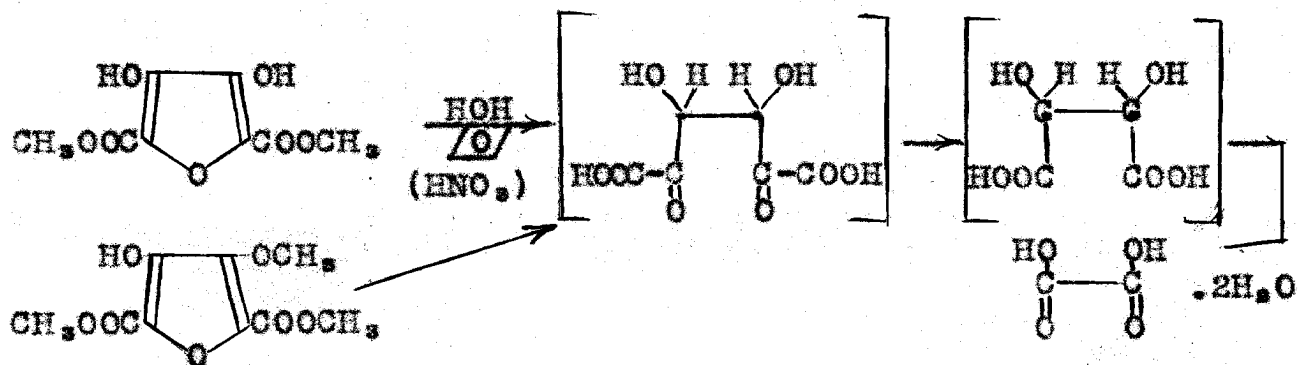
(81) Wooley (Unpublished results).



When 3-hydroxy-4-methoxy-2,5-dimethylfuran was treated with dilute nitric acid, the only product isolated was oxalic acid. This was likewise true when 3,4-dihydroxy-2,5-dimethylfuran was treated with dilute nitric acid. Since Kohler and co-workers (30) have found that peroxides are formed when oxygen came in contact with 2,4,5-triphenyl-3-furanol, one should consider the possibility of oxygen addition to the double bond. If such addition took place three molecules of oxalic acid should be obtained for each molecule of furan compound oxidized.



Only one molecule of oxalic acid was obtained for each molecule of the furan compound oxidized. The mechanism proposed is as follows:



Oxalic acid was the only one of the decomposition products which was formed that has been identified when 3,4-dihydroxy-2,5-dicarbomethoxyfuran was refluxed for some time in alkaline solution. The alkaline solutions of polyphenol compounds absorb free oxygen very readily, and this property has been used to advantage in gas analysis technique. It is known that when oxygen is absorbed by an alkaline pyrogallol solution that carbon monoxide is given off. There must be some decomposition of the ring system, and this is due to oxidation (82). This type of oxidation might be also considered possible in the alkaline hydrolysis of the dihydroxyfurans which were studied.

No peroxide formation could be detected by color test methods or mixed melting point determinations after 3-hydroxy-4-methoxy-2-carbomethoxyfuran or 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran were dissolved in ether and oxygen passed through.

Henninger has found that the reduction of erythritol yields as one of the main products, dihydrofuran. Furan was obtained from dihydrofuran by treating it with phosphorous pentachloride. When treated with hydroiodic acid and red phosphorous, dihydrofuran was converted to butyl iodide. Henninger (83) dehydrated erythritol with sulfuric acid and obtained erythrane, $C_4H_8O_3$. Hurd and Isenhour (84) were un-

(82) Drakeley and Nicol, J. Soc. Chem. Ind., 44T, 457 (1925).

(83) Henninger, Ann. chim. phys., 7, 224 (1886).

(84) Hurd and Isenhour, J. Am. Chem. Soc., 54, 317 (1932).

able to obtain this material when erythritol was treated with 7.5 N sulfuric acid.

The methylation of erythrane yielded a product which had physical properties somewhat in agreement with those found for the reduction product of 3,4-dimethoxyfuran.

C o m p o u n d	Sp. gr.	Index of Refraction	Molecular Refractivity	
			Cal'd.	Found
Methylated product from erythrane	1.089 ^{25°}	1.4395 ^{25°}	27.90	28.43
Reduction product of 3,4-dimethoxyfuran	1.051 ^{25°}	1.4378 ^{25°}	27.90	29.95

One would expect a much better comparison, and as yet it is not known to what this discrepancy is due. From the molecular refractivity, the fault appears to lie in the reduction product of 3,4-dimethoxyfuran. The reduction of the 3,4-dimethoxyfuran was carried out at a high pressure and a high temperature in the presence of Raney nickel. Under these conditions it is possible that an ether group was cleaved. The carbon and hydrogen analyses for the two compounds are in very good agreement, but they are low for the theoretical value.

This particular bit of work is of interest since it is probably the first example of reducing a furan compound to a sugar derivative. The literature holds many cases in which

furfural or methyl furfural has been obtained from certain sugars. As far as is known, however, no work has been done to build up furan derivatives to sugar derivatives.

Most of the investigations were carried on with the derivatives of 3,4-dimethoxyfuran, 3,4-dimethoxy-2,5-dicarbomethoxyfuran and 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran. All of these compounds were prepared from 3,4-dihydroxy-2,5-dicarbomethoxyfuran. A number of derivatives was prepared which illustrate the enolic properties of the hydroxyl groups of the 3,4-dihydroxy-2,5-dicarbomethoxyfuran.

Enol Derivatives

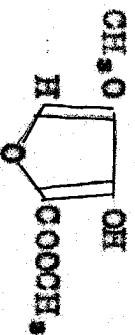
3,4-Diacetoxy-2,5-dicarbomethoxyfuran
3,4-Diacetoxycuproxy-2,5-dicarbomethoxyfuran
3,4-Diacetoxy-2,5-dicarbomethoxyfuran
3,4-Dibenzoxy-2,5-dicarbomethoxyfuran
The diammonium salt of 3,4-dihydroxy-
2,5-dicarbomethoxyfuran

The 3,4-dihydroxy-2,5-dicarbomethoxyfuran after methylation gave 3,4-dimethoxy-2,5-dicarbomethoxyfuran, which was converted to the diacid. 3,4-Dimethoxy-2,5-dicarbomethoxyfuran was then decarboxylated to give 3,4-dimethoxyfuran. 3,4-Dimethoxyfuran was found to be a very reactive compound, and when allowed to react with a solution of mercuric chloride, formed only the dimercurial. The addition of maleic anhydride, and maleic acid to the 3,4-dimethoxyfuran gave evidence of a furan structure. The treatment of this compound with hydrogen bromide

In glacial acetic acid decomposed the endoxy compound to a certain degree, and as yet m-hemipinic has not been identified.

The Gattermann-Koch reaction (85) with dimethoxyfuran, using hydrogen chloride and hydrogen cyanide in the presence of aluminum chloride, destroyed the 3,4-dimethoxyfuran. Bromocyanogen and aluminum chloride likewise destroyed the 3,4-dimethoxyfuran. However, when a modified Friedel-Crafts reaction was carried out with dimethoxyfuran, using stannic chloride and acetic anhydride, two products were formed. One of these was converted to 3,4-dimethoxy-2,5-dicarboxyfuran.

The 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran was decarboxylated, using copper bronze as a catalyst. When this reaction was performed in a vacuum sublimation chamber, the crude product sublimed out. The 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran gave a negative chloralide (86) reaction which does not necessarily prove the position of the hydroxyl group. The decarboxylated product should have the formula



which is 3-hydroxy-4-methoxy-2-carbomethoxyfuran. This compound was also obtained when 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran was treated with mercuric chloride in neutral solution. The reaction of 3-hydroxy-4-methoxy-2-carbomethoxy-

(85) Reichstein, Zohorke and Coere, Helv. Chim. Acta., 14, 1277 (1931).

(86) Wallach, Ber., 9, 546 (1876); Ann., 193, 35 (1878).

furan with diazomethane yielded 3,4-dimethoxy-2-carbomethoxyfuran. The rates of hydrolysis for these various β -hydroxyfurans and their derivatives were interesting. The ester groups of 3,4-dihydroxy-2,5-dicarbomethoxyfuran could not be hydrolyzed. One ester group of 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran could be hydrolyzed while both ester groups in 3,4-dimethoxy-2,5-dicarbomethoxyfuran could be hydrolyzed. In these latter two examples, where products of hydrolysis were obtained, the reactions were completed in one to three minutes after the addition of the compounds to alkali solution. The hydrolysis of 3,4-dimethoxy-2-carbomethoxyfuran required thirty to forty minutes of refluxing in alkaline solution before the reaction was completed.

3-Acetoxy-4-methoxy-2-carbomethoxyfuran was brominated and 3-hydroxy-4-methoxy-5-bromo-2-carbomethoxyfuran obtained. The reaction of diazomethane on 3-hydroxy-4-methoxy-2-carbomethoxyfuran produced the 3,4-dimethoxy-2-carbomethoxyfuran. Mercuration of this compound yielded the 3,4-dimethoxy-5-chloromercuri-2-carbomethoxyfuran. Alkaline hydrolysis of 3,4-dimethoxy-2-carbomethoxyfuran yielded the acid, which on decarboxylation yielded the 3,4-dimethoxyfuran. The maleic anhydride addition compound of the 3,4-dimethoxyfuran obtained in this reaction was identical with the derivative formed with the dimethoxyfuran from the decarboxylation of the diacid.

A maleic anhydride addition compound was obtained with 3,4-dimethoxy-2-carbomethoxyfuran. This is an example of

a furan-maleic anhydride addition product which does not fit the rule of Johnson and Van Campen (60), probably because of the marked activating effect of the two methoxyl groups in the β -positions.

The mercuration of 3,4-dimethoxy-2-carbomethoxyfuran produced a desirable derivative for this compound. The bromination of 3,4-dimethoxy-2-carbomethoxyfuran yielded an oil which gave a great deal of trouble. This bromo-compound was particularly desired since it might be converted to the nitro-compound which could subsequently be converted to a lactone by hydrolysis.

The chemical transformations of these compounds verify, to a certain extent, the structures assigned to them. All the chemical evidence at hand can be applied to the furan structure, whereas this does not hold for any other structural formulae which might be assigned to them.

IV. EXPERIMENTAL

Barium Diglycollate. (Lossen's method).

In a 5-liter round-bottomed flask were placed 2 liters of water and this was heated to boiling. Then 1580 g. (5 moles) of barium hydroxide (tech.) were added, and solution effected by stirring. This solution was allowed to cool to about 50° and 475 g. (5 moles) chloroacetic acid were added in 25-30 g. portions, stirring well after each addition. Care must be exercised in the addition of the chloroacetic acid to the barium hydroxide solution, as too rapid addition causes the reaction to become uncontrollable. The mixture rapidly heated to boiling and after all the chloroacetic acid was added the mixture was refluxed for one hour. On cooling to room temperature, the insoluble barium salt of diglycollic acid was filtered and washed with 500-700 ml. distilled water. The salt was placed in a flat pan and dried on a steam plate over night. The yield of barium salt was 620 g. or 43% of the theoretical yield based on chloroacetic acid.

Preparation of Dimethyl Diglycollate.

In a 1-liter E-flask were placed 400 ml. methyl alcohol and the flask and contents were cooled in an ice-bath to 5°-10°. To the alcohol were then added 80 ml. (1.49 mole) concentrated sulfuric acid (sp. gr. 1.83). Slow addition of the sulfuric acid insured minimum spattering, and even with slow addition the mixture warmed to 25°-30°. The solution was again cooled to 10° and 201 g. (0.70 mole) of finely

powdered barium diglycollate were added in 25°-30° g. portions, at such a rate that the temperature of the mixture never exceeded 30°. When all the salt had been added, the flask was stoppered and allowed to stand over night (10-12 hrs.). Then 500 ml. of water were added and the mixture shaken well. The mixture was neutralized with solid sodium carbonate. It was then extracted with three 300 ml. portions of benzene. An emulsion was sometimes formed during this extraction which was broken by the addition of ether. The benzene solution was dried by shaking and then standing for one-half hour with about 50 g. of anhydrous sodium sulfate. The benzene was distilled on a steam bath and the residue cooled in an ice-bath. The ester obtained is reasonably pure and melts at 37°. Recrystallization from benzene does not change this melting point. The yield is 60 g. or 52.9% of the theoretical yield based on barium diglycollate. Yields as high as 60% have been obtained, and the average was about 52%.

Preparation of Diethyl Diglycollate

Three hundred ml. of absolute ethyl alcohol were put into a 500 ml. 3-necked flask fitted with a condenser, mercury sealed stirrer and delivery tube for hydrogen chloride gas. Dry hydrogen chloride was then passed into the alcohol for two hours, during which time the flask and contents were cooled to 0°-10° in an ice-bath. To the saturated hydrogen chloride-alcohol solution was then added 50 g. (0.174 mole) of finely

powdered barium diglycollate (87). This mixture was stirred for another two hours, hydrogen chloride gas being passed over the mixture during this time. After standing over night at room temperature the liquid is filtered from the solid, and the solid residue washed with benzene. The filtrate was extracted with two 100 ml. portions of benzene. The benzene washings and extracts were combined and neutralized with 10% sodium carbonate solution. The neutral benzene solution was then washed with water, dried over sodium sulfate and then filtered into a Claisen distillation flask. The benzene was distilled on a steam bath, and the residue distilled under reduced pressure. A few ml. of liquid was collected at 120°-130°/20 mm. Nineteen g. of the diethyl diglycollate were collected at 138°/20 mm. This was 57.4% of the theoretical yield based on barium diglycollate. The yields usually range from 45-50% when large amounts of barium diglycollate are esterified in this manner. This sized run has given the best results. Mr. Van Ess has used larger amounts and found the yields to be slightly lower.

3,4-Dihydroxy-2,5-dicarbomethoxyfuran.

Thirty g. (0.185 mole) of dimethyl diglycollate and 28 g. (0.192 mole) of ethyl oxalate were diluted with 20 ml. of

(87) Fisher's method of preparing esters.
Fisher, "Anleitung zur Darstellung organischer Präparate",
8th Ed., Vieweg and Son, Braunscheig, 1908,
pp. 43-44.

sodium dried ether and added to 200 ml. of 5% sodium methoxide solution (88). This mixture, in a 1000 ml. E-flask, was then allowed to stand 10 hours at 30°-40°. The excess alcohol and ether were then distilled on a steam bath. The heating was continued 30 minutes longer after the distillation. The sodium salts so obtained are partially dissolved in 125 ml. water. The solution was then acidified with concentrated hydrochloric acid and 50 ml. in excess added. The mixture was cooled to room temperature under running tap water and filtered. The solid material was washed on the filter with water until no chloride test was obtained. It was dried on a glass plate in air. The yield was 36.6 g. or 91.5% of the theoretical yield based on dimethyl diglycollate. The compound was found to melt at 220°.

If, instead of distilling the solvents from the condensation product, water was added at this point, the yield was only slightly lower. The yield was usually 95-92%, and the product obtained was almost colorless, as compared to a buff colored compound obtained when the dried sodium salts were first isolated.

This compound was described by Hinsberg (9).

3,4-Dihydroxy-2,5-dicarbomethoxyfuran.

This condensation was carried out in a manner similar to that described in the procedure for the preparation of 3,4-dihydroxy-2,5-dicarbomethoxyfuran. The yields were slightly

(88) This solution was prepared by adding 50 g. of sodium to 800 ml. of methyl alcohol and then diluting to 1000 ml. by the addition of dry ether.

lower, being from 81-85% of the theoretical based on diethyl diglycollate.

This compound was described by Johnson and Johns (8)
Condensation of dibutyl diglycollate with diethyl oxalate in the presence of sodium ethoxide.

Ten g. (0.43 mole) sodium were added through a condenser to 150 ml. absolute ethyl alcohol which were contained in a 500 ml. round-bottomed flask. When the solution was cool, 50 ml. ether were added and the solution thoroughly mixed by shaking. A solution of 50 ml. ether, 20 g. (0.0813 mole) dibutyl diglycollate (89) and 13.5 g. (0.0924 mole) ethyl oxalate were then added and the resulting mixture shaken for a few minutes until a homogeneous solution resulted. This was allowed to stand for five days; then the solvents were evaporated from the resulting gelatinous mass. About 150 ml. water was added to the dry salt and this solution made acid to methyl red with hydrochloric acid. On evaporation under reduced pressure (70 mm.) from a water bath, 16 g. material were obtained which was found to melt at 177-180°. Recrystallization from water-alcohol solution (2:1) raised the melting point to 186°. A mixed melting point with 3,4-dihydroxy-2,4-dicarb-ethoxyfuran was found to give no depression of the melting point.

Anal. Calc'd for: $C_{10}H_{12}O_7$: C, 49.18; H, 4.92. Found: C, 49.10; H, 5.40.

(89) Prepared by Mr. P. R. Van Ess.

Condensation of Diethyl Oxomalonate with Dimethyl Diglycollate.

Thirty-five g. (0.2 mole) diethyl oxomalonate were mixed with 33 g. (0.2 mole) dimethyl diglycollate. This mixture added to a solution of 200 ml. sodium methoxide (.05 g. Na/ml methyl alcohol) (0.4 mole Na). It was then allowed stand for four days. No attempt was made to remove the excess solvent at this point. To the semi-solid mass was added 100 ml. water and it was acidified with nitric acid, 5 ml. nitric acid (1:1) being added in excess. The solution was then extracted with chloroform, and the chloroform solution dried over anhydrous sodium sulfate. After filtering the chloroform solution, the chloroform was distilled and the residue distilled under reduced pressure. The boiling point of the fraction, which had a constant range, was 206-8°/6mm. This material gave a blue color when tested with ferric chloride solution. After standing for a week in the ice-box, a solid was obtained which no longer gave a ferric chloride color test. Recrystallization of this solid from n-butyl alcohol yielded a compound which was found to melt at 80°-81°.

Anal. Found: C, 47.35 ; H, 5.42
47.40 5.43

The Condensation of Glyoxal and Dimethyl Diglycollate in the Presence of Sodium Methoxide.

Five g. of polymerized glyoxal (90) were depolymerized by mixing it with 5 g. of phosphorous pentoxide and heating it in

(90) The glyoxal was furnished to us by Dr. Hammer, of the Iowa State College Dairy Department. The writer is very grateful to Dr. Hammer for this cooperation.

a distillation flask connected to a condenser. A great deal of material was carbonized. About 1.5 g. impure glyoxal was obtained which was immediately dissolved in 5 ml. of methyl alcohol and 1 g. of dimethyl diglycollate was added. This solution was added to 10 ml. of a 5% sodium methoxide solution. The condensation mixture was allowed to stand for 28 hours. The solvent was distilled on a steam bath, and the dry salt neutralized with dilute hydrochloric acid. This mixture was evaporated to dryness and refluxed with 20 ml. of methyl alcohol for 10 minutes and then filtered. The alcohol was distilled on a steam plate and the residue, which was acidic, was treated with an excess of diazomethane in ether solution. The ether solution of the ester obtained was filtered and the ether distilled. The ester melted at 104-5°. This ester when mixed 50-50 with dimethyl dehydromucate melted at 106°-108°. Dimethyl dehydromucate melts at 108°-109°. Another condensation yielded a substance which was found to melt at 99°-101°.

Preparation of 3-Hydroxy-4-methoxy-2,5-dicarbomethoxyfuran.

To 20 g. (0.092 mole) 3,4-dihydroxy-2,5-dicarbomethoxyfuran were added 45 ml. potassium hydroxide methyl alcohol solution (0.107 mole) which contained 400 g. potassium hydroxide in 300 ml. methyl alcohol. Then 100 ml. water were added and the mixture was shaken for 30 minutes. As all the furan compound did not go into solution, it was thought feasible to heat it on a steam bath. After heating it for about 90 minutes,

the solution developed a deep red color, characteristic of that which was observed when the decomposition of 3,4-dihydroxy-2,5-dicarbomethoxyfuran occurred. The compound was now in solution, however. To this solution was then added 20 g. (0.16 mole) dimethyl sulfate and the mixture shaken for thirty minutes. Then 50 g. of ice were added and the mixture shaken for another ten minutes. About 3 g. of material was obtained which was found to melt at 87-89°. This was shown to be 3,4-dimethoxy-2,5-dicarbomethoxyfuran by mixed melting point with an authentic sample. The remaining solution was allowed to stand 4 days and then filtered. A solid material which was obtained had a melting point of 146°-150°. After one recrystallization from water, the compound was found to melt at 146°-7°. Sublimation and recrystallization gave a compound which was found to melt at 150-1°.

The compound proved to be identical with that one obtained from the mixture resulting from methylation of 3,4-dihydroxy-2,5-dicarbomethoxyfuran. The hydroxy compound was first extracted from this mixture by means of lithium carbonate or secondary sodium phosphate. (This was done by Mr. P. R. Van Ess).

The Reaction of Phosphorous Pentachloride with 3,4-dimethoxy-2,5-dicarbomethoxyfuran.

Ten g. (0.041 mole) of 3,4-dimethoxy-2,5-dicarbomethoxyfuran were mixed with 10 g. (0.048 mole) of phosphorous pentachloride and the resulting mixture put into carius tube. The

tube, after being sealed, was heated at 140°-150° for 1.5 hours. The tube and its contents were cooled to 30° and the tube then opened and the contents poured onto 200 g. of ice. One hundred ml. of ether were used to extract the viscous layer which separated. The ether extract was dried over sodium sulfate, the solution filtered and the ether distilled. The liquid which remained was distilled at 158°-160°/6-7 mm.

Anal. Calc'd. for $C_9H_9O_7Cl_2P$: Cl, 21.45

Found: Cl, 21.42; 21.40

The compound reacted with 10% silver nitrate solution in the cold within 2-5 minutes. When zinc dust and water were added to the compound, a vigorous reaction took place. An oily precipitate is formed by this reaction, and by recrystallization from alcohol a compound melting at 148°-150° is obtained. The latter substance, which gave an intense blue ferric chloride color test in alcohol solution, was mixed with an equal portion of 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran and was found to melt at 148°-150°.

3,4-Dimethoxy-2,5-dicarbomethoxyfuran.

Twenty g. (0.093 mole) 3,4-dihydroxy-2,5-dicarbomethoxyfuran were suspended in 100 ml. water in a 1000 ml. E-flask. Then 80 ml. of 10% methyl alcoholic sodium hydroxide solution were added. The flask and its contents were shaken vigorously until a homogeneous solution was obtained. To this solution were added 28 g. (0.22 mole) dimethyl sulfate, the flask stoppered, and it was shaken vigorously for 30 minutes. The

red color, which developed during solution of the dihydroxy compound, had faded to a light pink or turned to a light yellow. The solution was cooled to 10° by the addition of 300 g. ice. After standing an hour, the solid which crystallized out was filtered and washed with 500 ml. water. After recrystallization from methyl alcohol, the compound was found to melt at 89.5-90°. The yield is 19.2-20.5 g. or 85-90% of the theoretical yield, based on 3,4-dihydroxy-2,5-dicarbomethoxyfuran.

Anal. Calc'd. for $C_{10}H_{12}O_7$: C, 49.10; H, 4.91; OCH_3 , 50.80

Found: C, 48.80; H, 5.16; OCH_3 , 50.30.

One hundred and twenty g. (0.556 mole) of the 3,4-dihydroxy-2,5-dicarbomethoxyfuran were methylated in portions of 30 g. Twelve g. (0.30 mole) sodium hydroxide were dissolved in 100 ml. water and 30 g. (0.1388 mole) 3,4-dihydroxy-2,5-dicarbomethoxyfuran added. When all the furan compound had dissolved, a clear solution having a deep red color resulted. To this solution was added 50 ml. methyl alcohol. At this point a precipitate sometimes separated out, but regardless of that, 40 ml. (0.42 mole) dimethyl sulfate were added. This mixture was shaken well, and when the reaction became too vigorous, the flask was cooled under tap water. The red color gradually became lighter and at the end of the reaction a light yellow-colored solution remained. Usually this took place in about 10-15 minutes, and at this time no precipitate was evident. After this solution stood at room temperature for 2-3 hours, a precipitate was obtained, and in order to produce maximum sep-

aration, the contents of the flask were cooled to 10°. The solid, from the four reaction flasks, was filtered and washed with about 700 ml. water. Dried on a glass plate in air, there was obtained a yield of 110 g. or 83.5% of the theoretical yield, when considered as 3,4-dimethoxy-2,5-dicarbomethoxyfuran.

This solid material was then extracted with 10% secondary sodium phosphate solution. Three 200 ml. portions of the phosphate solution were used and each portion was shaken vigorously for ten minutes with the mixture of methylation products. A red supernatant liquid resulted, which, with each successive extraction, became lighter in color. This mixture was filtered. The extracts were combined and acidified with hydrochloric acid, which caused the solution to change from red to yellow in color. The solid, 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran was filtered, washed with water and dried in air on a glass plate. The yield was 10 g. or 9.1% of the mixture. The compound was found to melt at 150-1°.

The 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran gave a deep blue color when a drop of 10% ferric chloride solution was added to an alcoholic solution of it.

Anal. Calc'd. for $C_9H_{10}O_7$: C, 46.96; H, 4.35; OCH_3 , 40.43

Found: C, 46.71; H, 4.57; OCH_3 , 40.2 (91)

3-Acetoxy-4-methoxy-2,5-dicarbomethoxyfuran.

To 5.75 g. (0.020 mole) of 3-hydroxy-4-methoxy-2,5-dicarbo-

(91) These analyses were made by Mr. P. R. Van Ess.

methoxyfuran contained in a Carius tube was added 11.05 g. (0.141 mole) of acetyl chloride. The tube was sealed and then heated to 135°-140° for 4 hours. After cooling, the tube was opened. Large prisms were obtained from the tube. The acetate thus obtained was found to melt at 108-9°.

This material was also prepared by Mr. P. R. Van Ess, using acetic anhydride and sodium acetate.

Anal. Calc'd. for $C_{11}H_{12}O_8$: C, 48.50; H, 4.45

Found: C, 48.30; H, 4.60.

The yield of the acetoxy compound was considerably lowered when heated in a water solution for 20-30 minutes.

Preparation of 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxy-furan.

Twenty g. (0.087 mole) of 3-hydroxy-4-methoxy-2,5-dicarbo-methoxyfuran were made into a paste with 50 cc. water. To this was added a solution of 6.96 g. (0.174 mole) sodium hydroxide in 50 cc. water. The material dissolved within a minute when shaken vigorously. The solution became very deep red. When solution of solid material was complete, it was cooled under the tap until the temperature was about 15-°20°. The solution was acidified with hydrochloric acid (1:1) and filtered. The solid material which was collected was suspended in 500 cc. water and then filtered. After washing three times with water in this manner, the material was filtered by suction. It was then transferred to a glass plate and air-dried. When recrystallized from water, in which the acid was not very soluble,

it had a melting point of 245-6°. A mixed melting point with the 3,4-dimethoxy-2,5-dicarboxyfuran showed a depression of 11° (234°-245°). It gave a ferric chloride color test.

Anal. Calc'd. for $C_8H_8O_7$; OCH_3 , 28.70.

Found: OCH_3 , 28.65

This analysis was made by Mr. P. R. Van Ess.

3-Benzoxy-4-methoxy-2,5-dicarbomethoxyfuran.

3-Benzoxy-4-methoxy-2,5-dicarbomethoxyfuran was prepared by Mr. P. R. Van Ess by treating the hydroxy compound in lithium carbonate solution with benzoyl chloride. The compound formed was found to melt at 117°-8° after it was recrystallized from ether.

Anal. Calc'd. for $C_{16}H_{14}O_8$: C, 57.48; H, 4.22; OCH_3 , 27.80.

Found: C, 57.85; H, 4.76; OCH_3 , 27.93.

The Acid Chloride of 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran.

Two grams (0.868 mole) of 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran were suspended in 30 cc. thionyl chloride and this mixture was refluxed for ten hours. The flask was then connected for distillation and the excess thionyl chloride distilled. The compound thus obtained was suspended in petroleum ether (b.p. 68°-75°) and warmed to reflux. Five cc. benzene were added, and the mixture allowed to cool. By scratching the sides of the flask, the material began to crystallize. It was then filtered and washed with petroleum ether. This procedure of recrystallization was repeated four times

and the material then had a melting point of 132-133.5°. The yield was 2 g. or 98.0% of the theoretical yield based on 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyuran. The acid chloride of 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyuran gave a ferric chloride color test.

Anal. Calc'd. for $C_8H_7O_6Cl$; Cl, 14.95

Found: Cl, 15.01; 15.08.

3,4-Dimethoxy-2,5-dicarbomethoxyuran.

Ten g. (0.041 mole) 3,4-dihydroxy-2,5-dicarbomethoxyuran were allowed to react with an excess of diazomethane. After the reaction mixture had stood for an hour in the hood, the ether was distilled on a steam bath. The solid material was suspended in 200 ml. of hot water. It was filtered immediately and the residue washed with hot water. The liquid which settled to the bottom of the filtrate was separated, cooled in an ice-salt bath and the crystals filtered. The compound so obtained was found to melt at 45°. This material was then recrystallized from an alcohol-ethyl acetate-water mixture (1:1:2), and dried in a desiccator over barium hydroxide. The melting point of the recrystallized product was 48°. The yield was quantitative.

Two g. (0.00735 mole) of this compound were then suspended in water and 25 ml. 2% sodium hydroxide solution added. After this mixture was refluxed for five hours, it was cooled in an ice-salt bath. The solution was then acidified with hydrochloric acid (1:1) and the solid which precipitated was filtered,

washed with water, and dried on a clay plate. This compound was found to melt at 214°-225°. It was recrystallized from ethyl alcohol and found to melt at 232°-34°. A mixed melting point with 3,4-dimethoxy-2,5-dicarboxyfuran showed a melting point of 232°-34°. It was found necessary to recrystallize the compound from water and dry it on a clay plate before a mixed melting point of 243° was obtained for equal portions of the compound obtained and 3,4-dimethoxy-2,5-dicarboxyfuran.

The Reaction of Diazomethane with the Diacid Chloride of 3,4-Dimethoxy-2,5-dicarboxyfuran.

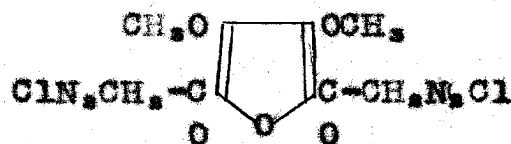
Six and five-tenths g. (0.0258 moles) of the diacid chloride of 3,4-dimethoxy-2,5-dicarboxyfuran were partially dissolved in 100 ml. of ether and cooled to -15°. A diazomethane (73) solution was poured in as rapidly as possible. The solution contained an excess amount of diazomethane necessary to complete the reaction. The reaction was allowed to stand for thirty minutes, during which time it was stirred vigorously. The product was filtered from the ether and dried over barium oxide in a vacuum desiccator. The melting point of this compound was 110°, using a rapidly rising bath. Recrystallization from carbontetrachloride yielded a compound which softened at 110° and melted at 119°. An elementary analysis showed the presence of nitrogen and chlorine. The yield was 6.6 g. or 76.6% of the theoretical yield based on the diacid chloride compound.

Anal. Calc'd. for $C_{10}H_{10}O_5N_4Cl_2$: N, 16.67

Found: N, 16.70.

This compound has been named 3,4-dimethoxy-2,5-di(diazonium chloride acetyl) furan.

Acids and boiling water decomposed the compound. It decomposed explosively when a small amount on a spatula was thrust over a flame. The diazonium compound decomposed slowly when it was placed in an ice-box during a period of two years. A mixture of products was obtained when the diazonium compound was treated with formic acid. The structure of the diazonium compound is postulated as follows



Oxidation of 3-Hydroxy-4-methoxy-2-carbomethoxy-5-furoic acid with Nitric Acid.

Five g. (.0232 mole) 3-hydroxy-4-methoxy-2-carbomethoxy-5-furoic acid were placed in 300 ml.-E-flask and 30 ml. of a solution of dilute nitric acid (1:2) added. The reaction mixture immediately became warm and it was found necessary to rotate the flask in order that the foam formed would be broken. When the foaming had stopped, the flask was set on a hot plate and allowed to evaporate to dryness. Oxalic acid was obtained as characterized by a microscopic examination using the manganese salt (92). The compound was found to melt at 98°-100° and on

(92) Chamot and Mason, "Handbook of Chemical Microscopy", John Wiley and Sons, Ind., New York, 1931, II, p. 134.

long heating at this point was converted to the anhydrous oxalic acid melting at 186° - 90° . The yield was 0.8 g. which, on the basis for the formation of one mole of oxalic acid for three moles of the starting compound (see page 52 of this thesis) is 82.5% yield.

Oxidation of 3,4-Dimethoxy-2,5-dicarboxyfuran with Nitric acid.

Five g. (0.021 mole) of 3,4-dimethoxy-2,5-dicarboxyfuran were placed in a 300 ml. E-flask and to this was added 30 ml. of a solution of dilute nitric acid (1:2). A reaction occurred almost immediately, brown fumes being given off, and it was accompanied by a great amount of foaming. After 5 minutes, the foaming had ceased and a clear solution remained. This solution was placed on a hot plate and evaporated to dryness. The material sublimed on the sides of the flask, and some of the compound was pressed onto a clay plate. The compound was found to melt at 190° (softened at 183°). This was found to be oxalic acid, since hydration gave the dihydrate of oxalic acid. The melting point for the dihydrate was found to be 98° - 100° . The microscopic test, using manganese chloride, was also positive.

Oxidation of 3,4-Dihydroxy-2,5-dicarbomethoxyfuran with potassium permanganate.

Ten ml. of 2% solution of potassium permanganate were added slowly to a suspension of 1 g. (0.0046 mole) 3,4-dihydroxy-2,5-dicarbomethoxyfuran in 10 ml. water. The mixture was then allowed to stand for an hour. Five ml. of 95% ethyl

alcohol were added. The solution was made acidic with glacial acetic acid. The precipitate formed was filtered and washed with water. It was not soluble in water or acetone. On addition of sulfuric acid and then a small volume of water, a little of the precipitate dissolved. When bromine water was added to a suspension of the precipitate, it was discolored. The compound did not melt, and on ignition it glowed throughout at first and left a fuzzy carbon residue. During the ignition the flame was somewhat luminous. As yet, this compound has not been identified.

The Effect of Alkali on 3,4-Dihydroxy-2,5-dicarbomethoxyfuran.

Two g. (0.0092 mole) 3,4-dihydroxy-2,5-dicarbomethoxyfuran were treated with 10 ml. of 50% sodium hydroxide solution (0.125 mole). Solution was incomplete, even after refluxing for 30 minutes. Twenty-five ml. water were then added and refluxing continued for another hour. The solution was then allowed to cool before it was neutralized by means of dry hydrogen chloride gas. When neutralization was complete, the flask was placed under running tap water and cooled. Acetone was then added and the solution filtered. The acetone was distilled and the liquid remaining cooled. A resinous material was obtained which could not be crystallized. The water was distilled from the aqueous solution under a pressure of 50 mm. at 70°. The residue was washed with 95% alcohol until the sodium chloride in the residue was colorless. Evaporation of the alcohol gave a solid which was dissolved in a small amount

of hot water. After standing over night, a precipitate came down which filtered and pressed on a clay plate. This compound was found to be oxalic acid by melting point, neutral equivalent, carbon and hydrogen analyses and mixed melting point with oxalic acid. It was found to melt at 100°, mixed with oxalic acid dihydrate, it was found to melt at 99°-100°. The manganese salt was prepared for microscopic examination. The neutral equivalent of the acid was found to be 63. The calculated value for the neutral equivalent was 63 or the acid had a molecular weight of 126.

Attempt to Form Peroxide of 3-Hydroxy-4-methoxy-2-carbomethoxyfuran.

Three-tenths g. (0.00174 mole) of 3-hydroxy-4-methoxy-2-carbomethoxyfuran in 50 ml. of ether was put into a 100 ml. suction flask. A stopper fitted with a delivery tube which reached the bottom of the suction flask was then adjusted in the flask and oxygen passed through the ether solution for five hours. As the ether evaporated, more was added in order to keep the compound in solution. After the time designated, the ether was distilled and the crystalline material pressed on a clay plate. This substance had a melting point of 100°-100.5° and when mixed with a known sample of 3-hydroxy-4-methoxy-2-carbomethoxyfuran, it was found to melt at 100°-100.5°. Twenty-nine hundredths g. or 97% of the original material was recovered.

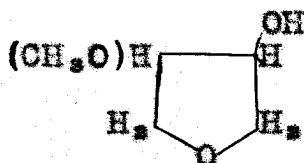
3-Hydroxy-4-methoxy-2,5-dicarbomethoxyfuran was treated in

a similar manner. The presence of a peroxide formation was tested by means of the cadmium iodide-potassium iodide test. The result was negative.

Reduction of 3,4-Dimethoxyfuran.

Eleven and five-tenths g. (0.089 mole) of 3,4-dimethoxyfuran were dissolved in 150 ml. of absolute alcohol and a 20 ml. suspension of the Raney nickel catalyst was added. This amount of suspension corresponded to about 1.0 g. of the catalyst. The beginning pressure was 1720 pounds. The temperature was raised to 200°-5° at which range the pressure was about 2750 pounds. This temperature was maintained for one hour. The bomb was cooled to room temperature and the pressure reading was now 1550 pounds. The catalyst was filtered and a clear alcohol solution remained. This solution was no longer discolored by mineral acids as was the 3,4-dimethoxyfuran. The alcohol was distilled on a water bath under 20 mm. of pressure. The liquid which remained was distilled at 118°/98 mm. with an outside bath temperature of 140-145°. The forerun, which consisted of 0.5 g. of material distilling at 115°/98 mm., was discarded. Less than a gram of liquid remained in the flask after the fraction was cut at 118°/98 mm. The main fraction was distilled at atmospheric pressure and the boiling point found to be 182°-3.5°. The ferric chloride color test was negative. The refractive index was found to be 1.4378 at 25° and the specific gravity at 25° was found to be 1.051. This compound probably has a structural formula cor-

responding to



Anal. $C_5H_{10}O_2$: C, 50.80 ; H, 8.40

Found: C, 50.01 ; H, 7.95

Erythrane (83)

Fifty g. (0.427 mole) of erythritol was added to a solution of 50 g. (0.93 mole) of sulfuric acid and 50 g. (2.77 mole) of water. The solution was gently refluxed for 10 hours. After standing for 12 hours the solution was diluted with two volumes of water and the resulting solution refluxed for an hour. The solution was neutralized with barium carbonate. The mixture was filtered and then distilled from the filtrate under diminished pressure. Twelve g. of material which distilled at 155° - 157° /18 mm. were obtained. The refractive index of erythrane was found to be 1.4748 at 25° , and the specific gravity was 1.267 at 25° . The molecular refractive was found to be 23.10 for a calculated value of 23.165.

Methylation of Erythrane (93)

Ten g. (0.0758 mole) of erythrane were dissolved in 15 ml. of water and this solution warmed to 70° by using a water bath. To this solution was added 180 ml. of 10% sodium hydroxide (0.454 mole) and 57 g. (0.454 mole) of dimethyl sulfate at

(93) Haworth, J. Chem. Soc., 107, 8 (1915).

such a rate that the solution is slightly alkaline at all times. This addition took 40 minutes. The solution was then kept in the water bath at the temperature of boiling water for an hour. The methylated product was extracted from the solution by means of chloroform. The chloroform extract was dried over sodium sulfate, filtered and the chloroform distilled. The residue which remained was distilled at atmospheric pressure. Four g. of material boiling at 170°-180°, and 4.5 g. of product boiling at 181°-183° were collected. The refractive index for the latter fraction was found to be 1.4395 at 25°. The specific gravity for this fraction was found to be 1.089 at 25°. The molecular refractivity was found to be 28.43 for a calculated value of 27.90.

Anal. Calc'd. for $C_5H_{10}O_3$; C, 50.80 ; H, 8.40

Found: C, 49.76 ; H, 7.61

The comparison of the physical constants of the reduction product of 3,4-Dimethoxyfuran and the alkylated product of erythrane shows that they are not identical. The effect of the presence of isomers is not known, but may have some influence on the properties of the two compounds. This method of showing that a furan nucleus exists in 3,4-dimethoxyfuran is far from ideal.

3,4-Diacetoxy-2,5-dicarbomethoxyfuran.

Fifteen g. (0.0695 mole) of 3,4-dihydroxy-2,5-dicarbomethoxyfuran were treated with a mixture of 200 ml. acetic anhydride and 20 g. of sodium acetate. The mixture was refluxed gently

for two hours. On cooling, a crystalline material separated which was filtered and washed with cold water. On successive suspensions in water, filtration and washing with water three times, it was sucked dry on the filter. The solid was then transferred to a clay plate and dried in the air. The yield was 19 g. or 95% of the theoretical yield based on the 3,4-dihydroxy-2,5-dicarbomethoxyfuran. The compound was found to melt at 138°. When recrystallized from hot water the compound decomposed to some extent. Hot alcohol decomposed it so that only a very small yield of the diacetoxy compound was obtained.

Anal. Calc'd. for $C_{12}H_{12}O_8$; C, 48.00; H, 4.00

Found: C, 48.13 ; H, 3.71

This compound was hydrolyzed by heating it in boiling water for 10-15 minutes. The 3,4-dihydroxy-2,5-dicarbomethoxyfuran crystallized when the water solution was cooled. A mixed melting point determination with an authentic sample was found to melt at 219-20°. The known 3,4-hydroxy-2,5-dicarbomethoxyfuran melted at 220°.

3,4-Diacetoxy-2,5-dicarbomethoxyfuran.

The condensation of 20 g. (0.14 mole) of diethyl oxalate and 19 g. (0.102 mole) diethyl diglycollate was carried out in the usual manner. The disodium salt of the resulting 3,4-hydroxy-2,5-dicarbomethoxyfuran was dried on a steam bath for an hour. To this dried salt were then added 25 g. (0.331 mole) of acetyl chloride and the mixture shaken well for about 5 minutes. The reaction mixture was cooled, which was necessary

because the temperature became very warm during the reaction. Two hundred ml. of ice water were added, which brought the temperature to 10°. The mixture was then filtered and the unreacted dihydroxy compound, which remained on the filter paper, was washed with water. The liquid which separated in the filtrate was extracted with ether, the ether extract separated and dried over sodium sulfate. The ether solution was then filtered into a Claisen distilling flask, the ether distilled on a steam bath and the residue distilled under a vacuum. The boiling point was 235°/35 mm. The liquid obtained was extremely viscous.

Anal. Calc'd. for $C_{14}H_{16}O_8$; C, 51.22; H, 4.33

Found: C, 51.01 ; H, 4.88.

The Di-Copper Acetate Salt 3,4-Dihydroxy-2,5-dicarbomethoxyfuran.

Three-tenths g. (.00139 mole) of 3,4-dihydroxy-2,5-dicarbomethoxyfuran were treated with 10 ml. of a saturated solution of copper acetate. The mixture was refluxed for one hour, after which it was cooled and filtered. A reddish yellow salt was obtained which was washed with water and dried in a desiccator over barium oxide.

Anal. Calc'd. for $C_{14}H_{12}O_{11}Cu$; Cu, 27.84

Found: Cu, 27.80, 28.07

This salt was suspended in water and the mixture made acidic with hydrochloric acid. Then hydrogen sulfide was passed into the suspension. Copper sulfide was precipitated, which was

filtered and washed with hot alcohol. The alcohol from these washings was diluted with water and a crystalline compound was obtained which was found to melt at 217-8°, and on recrystallization to melt at 219-20°. This compound, when mixed with 3,4-dihydroxy-2,5-dicarbomethoxyfuran, was found to melt at 219-20°. 3,4-Dibenzoxy-2,5-dicarbomethoxyfuran.

To 20 g. (0.082 mole) of 3,4-dihydroxy-2,5-dicarbomethoxyfuran were added 160 ml. of sodium ethoxide solution (0.05 g/ml.). The excess alcohol was distilled on a steam bath. Twenty-eight g. (0.2 mole) of benzoyl chloride were then added slowly and the flask shaken vigorously. When all the benzoyl chloride had been added, the mixture was set aside for 30 minutes. The reaction was now complete and the flask was cooled to 15° and 100 ml. water added. This mixture was filtered and the product collected was precipitated from water-alcohol-ethyl acetate solution (1:1:0.5). The compound was amorphous and colorless, melting at 146°. When 3,4-dibenzoxy-2,5-dicarbomethoxyfuran was treated with sodium hydroxide solution, benzoic acid and 3,4-dihydroxy-2,5-dicarbomethoxyfuran were obtained as the sodium salts.

Anal. Calc'd. for $C_{22}H_{20}O_9$: C, 63.70; H, 4.46; OC_6H_5 , 19.91.

Found: C, 63.32; H, 4.89; OC_6H_5 , 19.61

The Diammonium Salt of 3,4-Dihydroxy-2,5-dicarbomethoxyfuran.

One g. (0.0041 mole) of 3,4-dihydroxy-2,5-dicarbomethoxyfuran was dissolved in 10 ml. of ammonium hydroxide (sp. gr. 0.9) This was allowed to stand until all the liquid had evaporated. The

solid so obtained was heated with ethyl alcohol in which it eventually dissolved. On allowing this to stand at room temperature for two days, very beautiful feathery crystals were formed. These crystals, although they do not melt below 320°, decompose slowly at 200°.

Anal. Calc'd. for $C_{10}H_{18}N_2O_7$: N, 10.07 ;

Found: N, 10.00

When the diammonium salt was submitted to sublimation at 190° and 20 mm. pressure, the 3,4-dihydroxy-2,5-dicarbethoxyfuran was obtained as determined by a mixed melting point with a known sample of 3,4-dihydroxy-2,5-carbethoxyfuran.

3,4-Dimethoxy-2,5-dicarboxyfuran.

One hundred ten g. (0.45 mole) of 3,4-dimethoxy-2,5-dicarbomethoxyfuran were covered with a solution of 37 g. (0.925 mole) sodium hydroxide in 400 ml. water. The solution became warm, reaching a temperature of about 50° during the earlier part of the reaction. It was necessary to cool the mixture under tap water, shaking vigorously in order to maintain a good suspension of material. When all the compound had gone into solution, the flask and its contents were cooled in an ice bath to 5° and 100 ml. concentrated hydrochloric acid were added. The solution which had been deep red in color, gradually lost this color and a light yellow filtrate was obtained after filtration of the solid. This solid was suspended in 700 ml. water and filtered, and the process repeated three times. It was then dried on a glass plate in air. The com-

pound was found to melt at 235°-40° (decomposition) and after recrystallization from water, it melted at 243-5° (decomposition). The yield was 94 g. or 96% of the theoretical yield based on 3,4-dimethoxy-2,5-dicarbomethoxyfuran. The neutral equivalent was calculated as 108, and the value found was 108.2.

Anal. Calc'd. for $C_8H_8O_7$: C, 44.44; H, 3.77

Found: C, 44.68; H, 3.69

Diacid chloride of 3,4-dimethoxy-2,5-dicarboxyfuran. Thirty g. (0.138 mole) of a 3,4-dimethoxy-2,5-dicarboxyfuran were put into a 500 cc. distilling flask and 200 ml. of thionyl chloride were added. This mixture was gently refluxed for 20 hours after which time no suspended matter remained in the thionyl chloride solution. The excess thionyl chloride was then distilled on a water bath. To the solid residue which remained were added 30 ml. of carbon tetrachloride and then this solvent was distilled. In this manner, most of the thionyl chloride was distilled, and a fairly pure product remained in the flask. After recrystallization from ethyl acetate and low boiling petroleum ether, the compound was obtained in short colorless needles which were found to melt at 69°-70°. The yield was 31 g. or 94% of the theoretical yield based on the 3,4-dimethoxy-2,5-dicarboxyfuran. An additional 4 g. of the diacid chloride is obtained from the recrystallizing liquor. The compound did not possess lachrymatory properties and reacted very slowly with water. It decomposed slowly when kept in a glass-stoppered bottle during the period of a year.

Anal. Calc'd. for $C_8H_6O_5Cl_2$: Cl, 28.14

Found: Cl, 28.22

3,4-Dimethoxyfuran.

The method of Shepard, Winslow and Johnson (94) was used in the decarboxylation of 3,4-dimethoxy-2,5-dicarboxyfuran. Four g. (0.0185 mole) of the diacid were mixed with 1 g. copper bronze and added to 10 g. of coal tar base (b.p. 270°-310°) which was contained in the decarboxylation flask. The flask was heated in a metal bath to 200°. A stream of nitrogen was passed through the flask. A yellow liquid distilled at about 170°-180°. Five runs of four grams of 3,4-dimethoxy-2,5-dicarboxyfuran yielded 10 g. of 3,4-dimethoxyfuran after distillation at 172°-174°. This compound also boiled at 94-6°/18-20 mm. The yield was 84.4% of the theoretical yield, based on the 3,4-dimethoxy-2,5-dicarboxyfuran. The refractive index was 1.4650 at 25° and the specific gravity at 25° was 1.132. The molecular refractivity was found to be 31.28, while the calculated value was 31.70. This value was in the same order of error as those for other furan compounds (95).

Anal. Calc'd. for $C_6H_8O_3$; C, 56.25 ; H, 6.25

Found: C, 56.20; H, 6.28
56.60; 6.07

A much slower method was used which insured a product free from coal tar base. Thirty g. (0.139 mole) of 3,4-dimethoxy-

(94) Shepard, Winslow and Johnson, J. Am. Chem. Soc., 52, 2087 (1930).

(95) Johnson and Hughes, J. Am. Chem. Soc., 53, 743 (1931).

2,5-dicarboxyfurans were decarboxylated in 5 g. portions. Each portion was thoroughly mixed with 1 g. of copper bronze and put into a distilling flask which had the side arm set close to the bulb of the flask. The temperature of the metal bath in which the flask was placed was kept at 210°-220°. In this method of preparation, decarboxylation was carried out in an atmosphere of nitrogen at a reduced pressure of 20 mm. The distillate, from the 30 g. of 3,4-dimethoxy-2,5-dicarboxyfurans which were used, weighed 13.8 g. The distillate was taken up in ether and the ether solution washed with 50 ml. of 10% sodium hydroxide solution, and then with two 100-ml. portions of water. The ether solution was then dried over sodium sulfate, filtered and the ether distilled on a steam bath. The residue was distilled at 172°-174°. The yield was 12.0 g. or 63.8% of the theoretical yield based on 3,4-dimethoxy-2,5-dicarboxyfurans. 3,4-Dimethoxyfurans prepared by this procedure was free from coal tar base. The physical properties of samples of 3,4-dimethoxyfurans were the same regardless of the procedure used.

3,4-Dimethoxyfurans was extremely sensitive to mineral acids. This compound gave a positive pine splinter test, a green color being developed.

When hydrogen chloride was greatly diluted with air and passed over a small amount of 3,4-dimethoxyfurans, there was an immediate darkening, and resin formation. Hydrochloric acid diluted to .001 N had a similar effect. The other min-

eral acids, such as sulfuric and nitric, reacted in a similar manner. Organic acids, such as acetic and maleic acids, when dissolved in water, caused a definite darkening and resinous formation at room temperature or lower, and when heated caused rapid decomposition of the dimethoxyfuran. When heated with mineral acids, 3,4-dimethoxyfuran decomposed immediately to a carbonaceous residue.

3,4-Dimethoxy-2,5-di(chloromercuri)furan.

Six and four-tenths g. (0.05 mole) of 3,4-dimethoxyfuran were added to 100 ml. of 95% ethyl alcohol. To this solution were then added 250 ml. of mercurating solution containing 0.054 g. of mercuric chloride per milliliter (0.05 moles). After a lapse of 20 seconds, during which time the contents of the flask were thoroughly mixed, a flocculent precipitate began to appear.

The reaction flask was set aside for 30 minutes and the precipitate formed was filtered. The solid obtained was washed with 200 ml. of water. This solid was found to be soluble in hot alcohol and when recrystallized from this medium it was found to melt with decomposition at 208°. The yield was 10 g. or 33% of the theoretical yield. A search was made for the presence of a monomercurial. As yet the 3,4-dimethoxy-2-chloromercurifuran has not been prepared.

Anal. Calc'd. for $C_4H_6O_2Hg_2Cl_2$: Hg, 67.00; OCH_3 , 10.38
Found: Hg, 66.50; OCH_3 ; 10.53

The dimercurial is decomposed when heated with mineral acids.

3,4-Dimethoxy-2,5-diacetylfuran.

Four g. (0.0313 mole) of 3,4-dimethoxyfuran were dissolved in 5 ml. of benzene and added to 20 g. (0.077 mole) of stannic chloride in 75 g. (0.75 mole) of acetic anhydride. The mixture immediately darkened and became warm. The E-flask which contained the mixture was fitted to a condenser having a calcium chloride attached in order to exclude the water vapor of the air. The reaction stood for 16 hours at room temperature and it was then poured onto 200 g. of ice. The stannic chloride was decomposed by this procedure and the mixture was then ether extracted. The ether extract was washed three times with saturated sodium acetate solution, three times with a 10% solution of sodium bicarbonate, and finally three times with water. The ether extract was then dried with anhydrous sodium sulfate. The ether and benzene were distilled and the viscous residue distilled under reduced pressure. About 0.9 g. of material was obtained, which distilled at 157°-160°/8 mm. After standing for 10 days in an ice-box at 5°, a small amount of solid material precipitated which was found to melt at 48-9°. This solid, after it was dried on a clay plate, weighed 12 mg. Several recrystallizations from low boiling petroleum ether (b.p. 30-40°) gave a constant melting point at 58-9°. No further work was done on this solid. The liquid, 3,4-dimethoxy-2,5-diacetylfuran, now weighed 0.85 g.

which was 12.9% of the theoretical yield based on 3,4-dimethoxyfuran. The 3,4-dimethoxy-2,5-diacetylfuran had a refractive index of 1.5200 at 25°.

Anal. Calc'd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.66

Found: C, 56.40; H, 5.80

By using bleaching powder for the oxidizing agent, 0.5 g. (0.0024 mole) of 3,4-dimethoxy-2,5-diacetylfuran was converted to 3,4-dimethoxy-2,5-dicarboxyfuran as shown by a mixed melting point with an authentic sample.

3,4-Dimethoxy-2,5-diacetylfuran prepared from the diacid chloride of 3,4-dimethoxy-2,5-dicarboxyfuran boiled at 160°/8 mm. and had a refractive index of 1.5187 at 25°.

The Reaction between Maleic Anhydride and 3,4-Dimethoxyfuran.

Two and forty-five hundredths grams (0.025 mole) maleic anhydride were dissolved in 5 cc. dry benzene, (96). To this was added 3 gm (.025 mole) 3,4-dimethoxyfuran. The solution became warm and the benzene began to reflux. This solution was allowed to cool. When no crystals appeared after 24 hours, the benzene was distilled. A viscous residue remained which was recrystallized from ethyl acetate. The melting point of this material was 92-4°. Recrystallization from dioxan raised the melting point to 94°-95°.

Anal. Calc'd. for $C_{10}H_{10}O_6$; C, 53.10 ; H, 4.25

Found: C, 52.78; H, 4.56

(96) Diels and Alder, Ann., 490, 247 (1931).

To 5.36 g. (.0547 mole) maleic anhydride, which is dissolved in 25 ml. water, was added 7 g. (.0547 mole) dimethoxyfuran. This was allowed to stand for two days. The sides of the flask were scratched and some material crystallized out. This was filtered and washed with water, and then recrystallized from water. The substance softened at 168° and melted from 172°-174°.

Mol. wt. Calc'd. for $C_{10}H_{12}O_7$; 244; Found: 249

(Micro-Rast)

Anal. Calc'd. for $C_{10}H_{12}O_7$: OCH_3 , 25.40

Found: OCH_3 , 25.69

The Action of Benzoyl Chloride on 3,4-Dimethoxy-2,5-dicarbomethoxyfuran.

A study of splitting the ether groups was made as a preliminary step in obtaining the more sensitive hydroxyfurans.

Ten g. (0.041 mole) of 3,4-dimethoxy-2,5-dicarbomethoxyfuran were dissolved in 50 ml. of chloroform and 23.30 g. (0.174 mole) of benzoyl chloride were added. To this solution was then added 45.0 g. (0.175 mole) of stannic chloride. This mixture was allowed to reflux for 10 hours. The flask and its contents were cooled in an ice-bath to 10° and 200 g. of ice added to the mixture. By neutralizing with 10% sodium hydroxide and subsequent filtering, the insoluble tin compounds can be separated from the solution. The chloroform layer was separated and the aqueous layer again extracted with

chloroform. The two chloroform solutions were combined and dried over sodium sulfate. After filtering this chloroform extract, the chloroform was distilled and the product which remained in the flask was crystallized from hot 95% alcohol. It was necessary to crystallize the compound nine times before a constant melting point of 116.5-117.5° was obtained. A mixed melting point determination using 50-50 portions of the 3-benzyoxy-4-methoxy-2,5-dicarbomethoxyfuran (m.p. 117.5°) and the compound obtained in the reaction gave no depression. Hydrolysis in alkaline solution gave benzoic acid and 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran as determined by mixed melting points, using authentic samples of these two compounds.

Action of Hydrogen Cyanide and Hydrogen Chloride on 3,4-Dimethoxyfuran.

Ten g. (0.08 mole) 3,4-dimethoxyfuran and 2.1 g. (.08 mole) anhydrous hydrogen cyanide were dissolved in 175 ml. anhydrous ether. This solution was put into dry apparatus and precautions were taken to exclude water vapor of the atmosphere. Two and one-tenths g. (0.0158 mole) of aluminum chloride were added. Anhydrous hydrogen chloride was passed through this solution for 1.75 hour. The solution became extremely dark after the first 30 minutes. The solution was allowed to stand for 18 hours. The supernatant liquid was decanted, and the residue made alkaline to Congo paper with potassium hydroxide. It was then steam distilled. There was apparently nothing in

the steam distillate either when tested with fuchsin reagent or when an attempt was made to extract with ether. The residue which remained in solution was filtered, dissolved in acetone, treated with charcoal and filtered. The material, which precipitated on cooling, was filtered. It was found not to melt below 300°. No further work was done with this solid.

Action of Bromocyanogen and Aluminum Chloride on 3,4-Dimethoxyfuran.

Fourteen g. (0.109 mole) 3,4-dimethoxyfuran were mixed with 100 ml. of dry carbon disulfide and placed in a 3-necked flask fitted with a separatory funnel, reflux condenser and mercury sealed stirrer. Twenty g. (0.12 mole) of bromocyanogen (97) in 75 ml. dry carbondisulfide were added, followed by the addition of 20 g. (0.15 mole) aluminum chloride in 100 ml. dry carbon disulfide. There was an immediate darkening and carbon separated out on the sides of the flask. After 3 hours of stirring, the temperature being kept at 0°, the reaction mixture was allowed to stand over night at room temperature. The supernatant liquid, which was clear, was decanted, and the residue made alkaline to Congo paper and an additional 5 ml. 10% sodium hydroxide solution was added. This mixture was heated on a steam bath for two hours. After cooling, it was filtered and the filtrate acidified with dilute hydrochloric

(97) Marvel, "Organic Synthesis", John Wiley and Sons, Ind., New York, 1931, 11, p. 30.

acid (1:1) at which time hydrogen cyanide could be detected. Although it was cooled in an ice-bath, no precipitate formed. The solution was ether extracted, the extract dried over anhydrous sodium sulfate and after filtering, the ether was distilled. Nothing was obtained from the extract. Work was discontinued on this type of synthesis.

Decarboxylation of 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran by means of Mercuric Chloride.

Ten and a half grams (0.0486 mole) of 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran were added to a solution of 13.5 g. (0.05 mole) mercuric chloride (98) in 100 ml. water. A small amount of gas came off at the time of this addition. On refluxing and addition of 25 ml. of 10% sodium hydroxide solution, the evolution of gas was vigorous and at times it was necessary to cool the flask and its contents. When no more gas appeared to come from the solution, it was made alkaline and filtered. It was then acidified with hydrochloric acid (1:1) and saturated with hydrogen sulfide. The solution was boiled to expel the excess hydrogen sulfide and filtered while still hot. The filtrate was then cooled in an ice-bath and extracted with three 200-ml. portions of ether. The ether solution was dried with 25 g. sodium sulfate for 24 hours at 5°C. The ether was then distilled. A small amount of material was obtained which was sublimed in a vacuum of 10 mm. and at 100-110°. This material melted at

(98) Gilman and Wright, J. Am. Chem. Soc., 55, 3302 (1933).

100-100.5°. Another sublimation at the temperature of a water bath and 50 mm. pressure gave a substance of the melting point 101°. The 3-hydroxy-4-methoxy-2-carbomethoxyfuran gave a ferric chloride color test. The yield was 0.3 g. or 0.036%.

Anal. Calc'd for $C_7H_8O_5$: C, 48.81; H, 4.69; OCH_3 , 36.04.

Found: C, 49.10; H, 4.72; OCH_3 , 36.02.

Decarboxylation of 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran.

Ten g. (.0462 mole) of finely powdered 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran were mixed with 1 g. copper bronze until a uniform mixture was obtained. This material was then sublimed in portions of 0.4-0.5 g. at 200°-230° and 8-12 mm. The first sublimate consisted mostly of decarboxylated material, and on subliming this material at 100°-130° and 10-15 mm. the 3-hydroxy-4-methoxy-2-carbomethoxyfuran was obtained. This process, although tedious, yielded 5 g. of material after recrystallization from ether. This substance had a melting point of 100°-101° and a mixed melting point with a sample which was prepared by the mercuric chloride decarboxylation method of Gilman and Wright gave no depression. The yield was 62.9% of the theoretical yield based on 3-hydroxy-4-methoxy-5-carboxy-2-carbomethoxyfuran.

3-Acetoxy-4-Methoxy-2-carbomethoxyfuran.

One g. (0.00575 mole) of 3-methoxy-4-hydroxy-2-carbomethoxyfuran was put into a 50 ml. distilling flask and to this was

20 ml. of acetyl chloride and 1 ml. of acetic acid. The flask was connected to a condenser and warmed to 50°. It was kept at this temperature for 20 minutes, after which time the temperature was raised to 65°. When no more acetyl chloride distilled, the remaining liquid was poured into a mixture of 50 ml. of water and 10 g. ice. The solution was ether extracted as soon as the ice had melted. The ether extract was dried over sodium sulfate, filtered through a cotton wad and the ether distilled. The residue which remained was distilled at 138°-142°/5-8 mm. The compound obtained was yellow and very viscous. The yield was 0.98 g. or 74.5% of the theory. The compound gave no positive ferric chloride color test, as did the starting material.

Anal. Calc'd. for $C_9H_{10}O_6$; C, 50.47; H, 4.71

Found: C, 50.81; H, 4.94.

After standing for five days in the ice-box a waxy solid material was obtained which melted at 60°-70°. No further work was done on the crystallization of this substance.

The Bromination of 3-Acetoxy-4-methoxy-2-carbomethoxyfuran.

The acetoxy compound was prepared from 0.96 (.0056 mole) of the 3-hydroxy-4-methoxy-2-carbomethoxyfuran. The acetoxy compound was put into a 100 ml. Killinger flask and covered with 10 ml. carbon tetrachloride. Three-tenths ml. (required 0.28 ml. for .0056 mole) bromine in 10 ml. carbon tetrachloride was added dropwise. The solution was allowed to stand for 3 hours, warmed to 50° and the hydrogen bromide and carbon tetra-

chloride taken off by aspiration. The residue was taken in 50 ml. ether and washed with 50 ml. of a 10% sodium bicarbonate solution. The ether extract was then dried with sodium sulfate, filtered, the ether distilled and the residue cooled. By recrystallization from an alcohol-water solution, the composition of which is adjusted at the boiling point of the alcohol to just keep the material in solution, a compound which was found to melt at 125°-127° was obtained. Two more such recrystallizations did not raise the melting point. The yield of the crude material was 0.55 g. and after its purification 0.20 g. of the brominated material remained.

Anal. Calc'd. for $C_7H_7O_2Br$; C, 33.45; H, 2.81

Found: C, 33.04; H, 2.98
C, 33.33; H, 2.65

Mol. Wt. Calc'd for $C_7H_7O_2Br$: 251.15

Found (micro-Rast): 250.9

The material gave no ferric chloride color test. This compound was considered to be 3-hydroxy-4-methoxy-5-bromo-2-carbomethoxyfuran. The ease of hydrolysis of the enol acetate was illustrated in the recrystallization of this compound.

3,4-Dimethoxy-2-carbomethoxyfuran.

An excess amount of diazomethane was added to 0.45 g. (0.00256 mole) of 3-hydroxy-4-methoxy-2-carbomethoxyfuran. The reaction was vigorous and was complete in five minutes. The ether was then distilled. Dried on a clay plate in air, the compound had a melting point of 48-52°. The substance was

then recrystallized from methyl alcohol. The melting point of the compound so obtained was 54°-55°.

Anal. Calc'd. for $C_8H_{10}O_5$: C, 51.61; H, 5.30.

Found: C, 51.38; H, 5.80.

3,4-Dimethoxy-2-carboxyfurane.

One g. (.00538 mole) of 3,4-dimethoxy-2-carbomethoxyfurane was suspended in 3 ml. of water and 0.5 g. (.0125 mole) sodium hydroxide in 3 ml. water added. This material was refluxed until a homogeneous solution was obtained. The solution was filtered through cotton and then acidified with hydrochloric acid, 0.5 ml. in excess being added. The contents of the flask were cooled to 20°, filtered and the material washed on the filter paper with 10 ml. of water. The melting point of this material was 160°-163° (decomposition). After recrystallization from 70% alcohol, the melting point was found to be 170°-171° (decomposition). From 70% alcohol, the acid crystallized in prismatic needles which gave a purple dispersion when viewed under the microscope. The yield is 0.600 g. or 65.5% of the theoretical.

Anal. Calc'd. for $C_7H_8O_5$; C, 48.81; H, 4.69

Found: C, 48.36; H, 4.69.

Decarboxylation of 3,4-Dimethoxy-2-carboxyfurane.

Fifty mg. of the 3,4-dimethoxy-2-carboxyfurane were mixed with 50 mg. of copper bronze and placed in a micro-distillation flask. This was heated at atmospheric pressure to 190°-200°.

A liquid was obtained which had a boiling point of 170° (micro.). The liquid was sensitive to acids, and gave a maleic anhydride addition compound melting at 89°-91°. A mixed melting point with the material obtained by the condensation of 3,4-dimethoxyfuran and maleic anhydride was 90°-91°.

The Reaction between Maleic Anhydride and 3,4-Dimethoxy-2-carbomethoxyfuran.

To 1.02 g. (.00548) of methyl 3,4-dimethoxyfuran-2-carboxylate was added 3 ml. benzene which contained 0.51 g. (0.0052 mole) of maleic anhydride. The benzene was slowly evaporated by heating the flask to 60° and kept at this temperature for one hour. The crystalline material which separated was dissolved in 3 ml. dioxan and allowed to stand in the ice-box at a temperature of 5° until crystals were obtained. These crystals were allowed to dry on a clay plate, and a material was obtained which melted from 102-4°. A mixed melting point determination with the maleic anhydride addition compound of 3,4-dimethoxyfuran gave a melting range of 80-95°. The crystals were then washed with methyl alcohol and a compound melting at 109-111° was obtained. The yield was 0.1 g. after drying over phosphorous pentoxide at 60°.

Anal. Calc'd. for $C_{12}H_{12}O_8$: C, 50.68; H, 4.26

Found: C, 50.41; H, 4.40.

When an attempt was made to crystallize from alcohol, the addition compound decomposed to a very great extent. Some de-

composition takes place in dioxan.

Mercuration of 3,4-Dimethoxy-2-carbomethoxyfuran.

Twenty-two ml. of mercurating solution (98) (0.054 g. HgCl_2/ml) were added to 0.74 g. (0.0424 mole) of 3,4-dimethoxy-2-carbomethoxyfuran in a 100-ml. E-flask. The contents of the flask were shaken for 10 minutes and then warmed to 60° at which temperature it was kept for one hour. The material was allowed to cool, filtered, and the precipitate in the filter washed with 20 ml. water. The mercurial was taken up in 10 ml. acetone, and the acetone mixture refluxed for three minutes and 10 ml. water were then added.

The mixture was cooled to room temperature and filtered. The solid which was collected was dried in air on a glass plate and the compound was found to melt at $112-114^\circ$. Recrystallized once from alcohol and water (1:1) the melting point was $112^\circ-113.5^\circ$. The yield of 3,4-dimethoxy-2-carbomethoxy-5-chloro-mercurifuran was 0.65 g. or 38.2% of the theoretical yield.

Anal. Calc'd. for $\text{C}_8\text{H}_9\text{O}_5\text{HgCl}$: Hg, 47.56; OCH_2 , 22.14

Found: Hg, 48.00 ; OCH_2 , 22.53

Bromination of 3,4-Dimethoxy-2-carbomethoxyfuran

Three and nine-tenths g. (0.02 mole) of 3,4-dimethoxy-2-carbomethoxyfuran were dissolved in 50 ml. of carbon tetrachloride. To this solution was added 3.2 g. (0.02 mole) of bromine and the mixture allowed to stand for 30 minutes. During the bromination, dry nitrogen was passed over the solution

which aided in removing the hydrogen bromide which was formed. The carbon tetrachloride solution was poured into 200 ml. of water which was contained in a 500 ml. separatory funnel. After separation of the carbon tetrachloride layer, the process was repeated. The solvent extract was then washed with two 50-ml. portions of saturated sodium bicarbonate solution. The carbon tetrachloride layer, after washing once with water, was dried over sodium sulfate. Distillation of the carbon tetrachloride left an oil which could not be crystallized from low boiling petroleum ether, dioxan, benzene, butyl alcohol or ethyl acetate. This oil was then treated with 1 g. of zinc and 10 ml. of hot water. A vigorous reaction took place for a minute and then subsided. After filtering, the filtrate was cooled in the ice-box for 12 hours. The semi-solid mass which precipitated was filtered and crystallized from benzene. A constant melting point was found to be 115-6°. The yield was 12 mg. or 0.22% of the theoretical yield. The compound was considered to be 3,4-dimethoxy-5-bromo-2-carbomethoxyfuran.

Anal. Calc'd. for $C_8H_9O_5Br$: Br, 29.30

Found: Br, 29.24

Treatment of 3,4-Dihydroxy-2,5-dicarbomethoxyfuran with Hydroxylamine.

Four and thirty-two hundredths g. (0.02 mole) of 3,4-dihydroxy-2,5-dicarbomethoxyfuran were put into a 100-ml. E-flask and covered with water. To this water suspension was added

3.36 g. (0.04 mole) of sodium bicarbonate and the mixture was shaken until most of the material had dissolved. Then 2.76 g. (0.04 mole) of hydroxylamine hydrochloride was added. There was an evolution of gas for several minutes, and when this had subsided the flask and its contents were heated from 80°-90° for three hours. The solid, which was present, was filtered. This solid was a salt of 3,4-dihydroxy-2,5-dicarbomethoxyfuran. The salt did not melt below 360°, and on acidification with hydrochloric acid, gas was evolved, and 3,4-dihydroxy-2,5-dicarbomethoxyfuran was recovered. Acidification of the filtrate, from which the salt was filtered, also yielded 3,4-dihydroxy-2,5-dicarbomethoxyfuran. In both cases, a mixed melting point with an authentic sample of 3,4-dihydroxy-2,5-dicarbomethoxyfuran gave no depression.

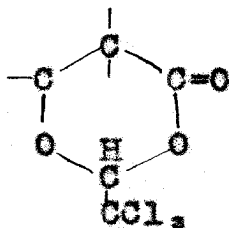
Negative results were also obtained with phenylhydrazine and 2,4-dinitrophenylhydrazine.

V. DISCUSSION

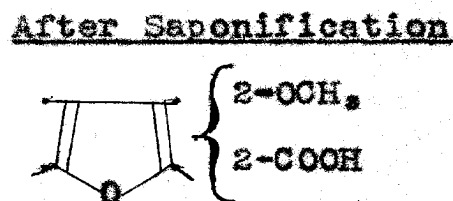
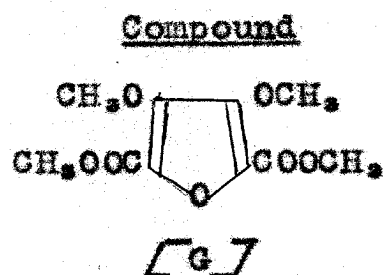
The β -hydroxyfurans were found to be very reactive compounds. This reactivity was attributed in some degree to the presence of the hydroxyl groups, and was best illustrated in the reactions of 3,4-dimethoxyfuran with (1) mercuric chloride, and (2) with maleic anhydride.

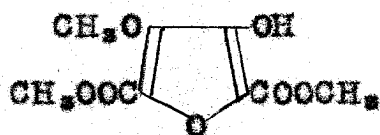
The mechanism of a ring formation was substantiated in some degree when glyoxal was condensed with dimethyl diglycolate to give an acidic substance which on treatment with diazomethane gave dimethyl dehydromucate. The reaction mechanism was considered to be essentially that given by Hinsberg (9). The general reactions, such as decarboxylation, bromination, mercuration, and Friedel-Crafts reactions were carried out with the same characteristic results as one finds with furan and furfural derivatives.

The postulated structure of 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxylfuran was based on two points. This material did not give a chloralide derivative. In compounds which have the grouping $\begin{array}{c} | \\ -C-C-CO \\ | \quad | \\ OH \quad OH \end{array}$, a reaction may be effected with chloral yielding a product of condensation,

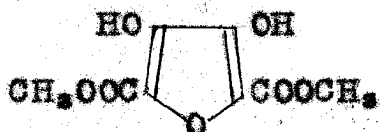


A negative chloralide reaction gave no substantial proof that the hydroxyl and carboxyl groups lie on the same side of the nucleus. The results obtained from the hydrolysis of several of these β -hydroxyfuran derivatives have given support to the structure of the hydroxy acid. It has already been pointed out that 3,4-dihydroxy-2,5-dicarbomethoxyfuran was recovered when treated with a dilute alkaline solution. When 3,4-dimethoxy-2,5-dicarbomethoxyfuran was saponified, the reaction proceeded rapidly and efficiently to yield 3,4-dimethoxy-2,5-dicarboxyfuran; that is, both ester groups were saponified. With one hydroxyl group free, the compound was called 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran for convenience. To be consistent, the free hydroxyl has been placed arbitrarily in the 3-position and all the derivatives of it have been named accordingly. When 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran was saponified, a compound containing one carboxyl group and one hydroxyl group was obtained.





[H]



[I]



Original Recovered

Since saponification did not change [I] and changed [G] and [H], the effect of the methoxyl groups was considered as the determining factor for the position of the hydroxyl group in [H]. With the hydroxyls free, the original was obtained, while the presence of the one methoxyl group made it possible to saponify one ester group. From these results, the ester group which was susceptible to saponification must lie on the same side of the nucleus as the methoxyl group. For these reasons, it was thought the compound should be named 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran.

The fact that keto derivatives were not obtained with the various β -hydroxyfuran derivatives studied does not mean that the keto-forms of these derivatives are entirely absent. It has been stated that a carbonyl group cannot always be detected (99). The ease with which enol derivatives were formed indicated to some degree that these compounds were more

(99) Lutz and Small, J. Am. Chem. Soc., 57, 2653 (1935).

stable in the enol form.

The properties of enolic and phenolic hydroxyl groups already have been surveyed. Both in structure and in reaction with specified reagents, the general properties of enols and phenols were found to be the same. It was pointed out that the hydroxyl groups present in 3,4-dihydroxy-2,5-dicarbomethoxyfuran were phenolic in character. Although no peroxide formation was observed in the investigation of the 3,4-dihydroxyfuran derivatives, it is a reaction to be expected of the highly active enol types. It may be that the resins and tars, which were obtained in alkaline or acid hydrolysis of some of the derivatives studied, were due to the addition of oxygen to the double bonds. The resulting peroxides then decomposed on hydrolysis yielding in some cases tars and resins. Oxalic acid was usually identified in these decomposition products. Since enol ethers have been found to be of the same order of reactivity of enols, and since furan may be considered to be an enol ether, peroxide formation should be expected with furan and its derivatives. This may account for the instability of these compounds. Much credit is due Kohler and his co-workers for observing this phenomenon (30).

The diene system in the molecule of 3,4-dimethoxyfuran was demonstrated by the fact that a maleic anhydride addition compound was obtained with it. The endoxy compound has not been changed as yet to the corresponding phthalic acid derivative.

The molecular refractivity of 3,4-dimethoxyfuran sub-

stantiates to some degree the structural formula assigned to the compound. Johnson and Hughes (95) have done some work on molecular refractivities of furan and certain of its derivatives. It was noted that for furan and some of the derivatives investigated, the observed molecular refractivity was lower than the value which was calculated. In these cases, the substituent did "not contain a double bond on the atom immediately attached to the ring in the α -position". 3-Bromofuran was also included in this group. This phenomenon was observed, too, in the case of 3,4-dimethoxyfuran. The value observed was within 1.4% of the calculated value. This lends support to the postulation that the furan nucleus was present in the compounds that were investigated.

The reduction of 3,4-dimethoxyfuran, which should have given a dimethoxytetrahydrofuran, produced a compound having a carbon and hydrogen analysis that indicated only one methyl was present. The greatest error, resulting from this hypothesis, was the large discrepancy of the calculated and observed values for the molecular refractivity. The observed molecular refractivity and carbon-hydrogen analysis for the methylated product of erythrane agreed with the calculated values to a fair degree. These two compounds should have been identical. The results of these experiments were not entirely satisfactory to the writer, and it was felt that an important link between furan chemistry and sugar chemistry can be developed through the β -hydroxyfuran derivatives.

The α -positions of the furan nucleus have been considered to be the most reactive positions. Substitution takes place at the α -positions before the β -positions are substituted. Due to the aromatic properties of furan, it would be expected that the nucleus would be brominated before any substitution took place in the alkyl groups of the ethers which were present in the β -positions. Since only one α -position was open on the nucleus, the product was 3,4-dimethoxy-2-carbomethoxy-5-bromofuran.

From the data obtained in this work and that found in the literature, a prediction of the properties of mono- β -hydroxyfuran might be made. The hydroxy group will probably show the characteristic enol-keto-tautomerism but may be more stable in the keto-form. The β -hydroxyfuran will be very reactive, and one may find it difficult to prepare a sample in the presence of oxygen. The compound will be extremely sensitive to mineral acids, and difficulty will be experienced when replacement of the hydroxyl group is attempted.

The β,β' -dihydroxyfuran will have most of the characteristic properties of the monohydroxyfuran. The dihydroxy may be expected to exist in the enol form, on the basis of what has been found from its derivatives. The study of aromatic properties of these furan derivatives should demonstrate the hypothesis that furan and its derivatives are aromatic or super-aromatic. Such a study may show that the furan derivatives have properties attributed to both the aliphatic and the aromatic compounds.

VI. BIOLOGICAL

Some of the hydroxyfurans and their derivatives were submitted to several biological tests. It is known that ascorbic acid, which has a γ -lactone structure (100), is important in metabolism. The l-isomer is commonly called Vitamin C. Derivatives of the tetronic acid series have been synthesized by Penicillium Charlesii G. Smith (101), and these acids are closely related in structure to ascorbic acid. West and his co-workers (31, 102) have contributed several papers in which evidence is given for a plausible theory of antiketogenesis. The work appears to show that a furan nucleus is involved. The investigation on "pantothenic acid" by Williams (103) and his collaborators indicates that this compound is of low molecular weight and acidic in character. This acid is a polyhydroxy compound. The substance is definitely a growth stimulant when present in a medium containing β -alanine (104). Although somewhat speculative, one may find the "pantothenic acid" molecule closely related to the hydroxyfurans and ascorbic acid. Clowes and Krahl (105) have recently reported that oxygen consumption of sea urchin eggs could be influenced by phenols other

- (100) Reichstein, Grüssner and Oppenauer, Nature, 132, 280 (1933);
Haworth and Hirst, J. Soc. Chem. Ind., 52, 645 (1933).
- (101) Clutterbuck, J. Soc. Chem. Ind., 55T, 55 (1936).
- (102) West, J. Am. Chem. Soc., 47, 2780 (1925).
J. Biol. Chem., 113, 43 (1936).
- (103) Williams and Moser, J. Am. Chem. Soc., 56, 169 (1934).
- (104) Williams and Rohrmann, J. Am. Chem. Soc., 58, 695 (1936).
- (105) Clowes and Krahl, Proceedings of the Thirteenth Meeting
of the Biological Chemists, March 25-28, 1936,
J. Biol. Chem., 114, XIX (1936).

than the nitrophenols. This seems to coincide, in some degree, with the idea of Popoff (106). The theory advanced by Popoff stated that all chemical compounds capable of stimulating cell function should possess the property of accelerating and increasing oxidation processes of the cell. Compounds which had a marked affinity for oxygen appeared to possess this property. It was found by Popoff that the action of phenols increased with the number of hydroxyl groups.

The compounds, which were tested in a Barcroft-Warburg respirometer in which Aerobacter aerogenes was used as a test organism were as follows:

1. Diammonium salt of 3,4-dihydroxy-2,5-dicarbomethoxyfuran,
2. 3,4-Dihydroxy-2,5-dicarbomethoxyfuran,
3. 3,4-Dimethoxy-2,5-dicarboxyfuran,
4. 3,4-Acetoxy-2,5-dicarbomethoxyfuran,
5. 3-Hydroxy-4-methoxy-2,5-dicarbomethoxyfuran,
6. 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran.

The organism was Strain N o. 23, obtained from Dr. Reynolds, of the Department of Bacteriology, at Iowa State College. The Aerobacter was grown on an agar slant medium and washed from this slant with a potassium acid phosphate buffer solution of pH 6.9. The heavy suspension of cells thus obtained was aerated by passing dry air through it for 30 minutes. This aerated suspension of cells was then used in the respirometer flask according to the usual technique. The buffer solution

(106) Popoff, J. Physiol. path. gén., 21, 482 (1923); cf., C.A., 14, 3912 (1920) and C.A., 15, 1269, 1982 (1921).

(pH = 6.9) was used as a solvent for the compounds tested and it contained 0.2% glucose. The hydroxyfurans which showed no inhibition and did show an increase in respiration, although not an exceedingly great increase, were as follows:

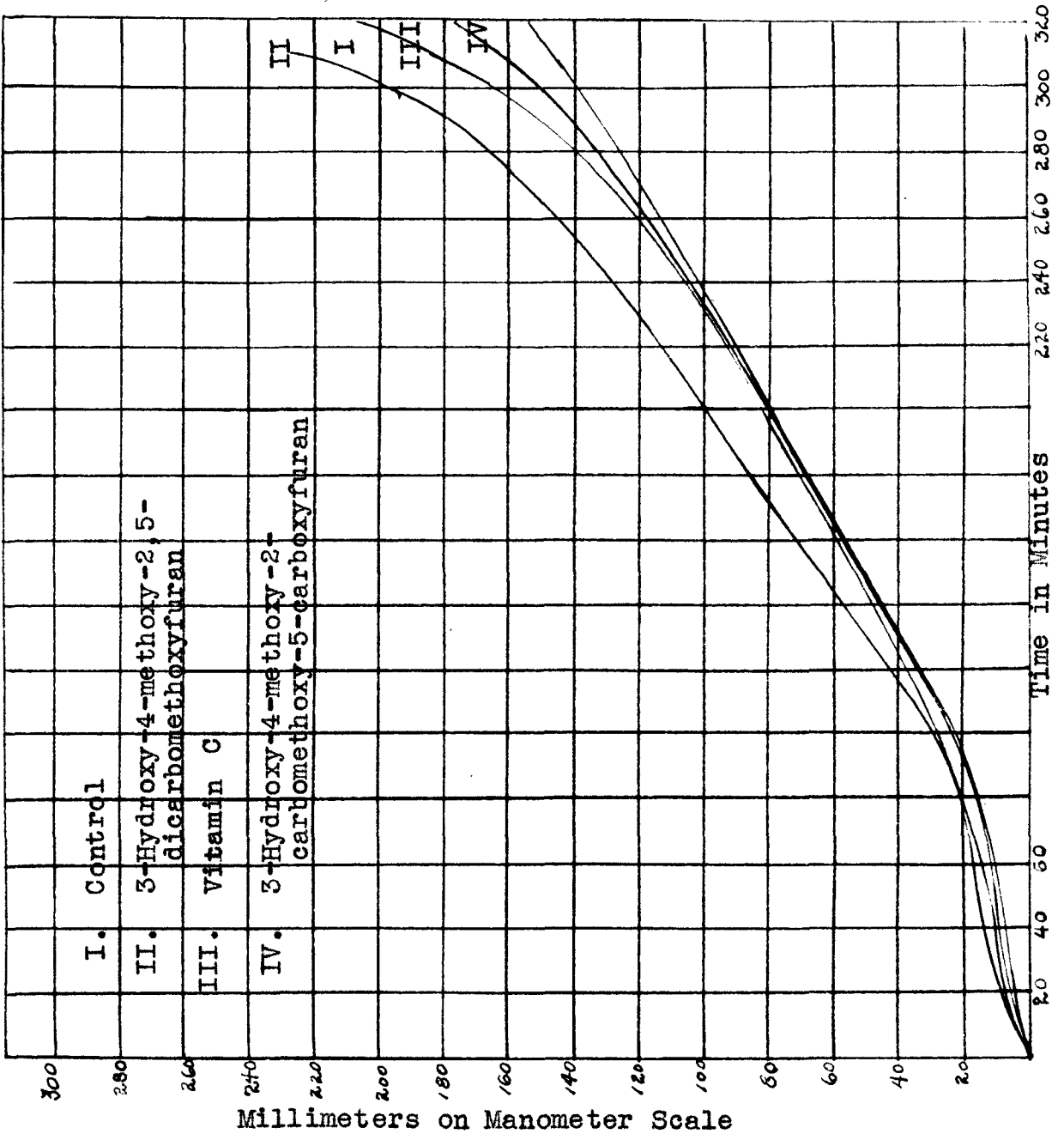
Diammonium salt of 3,4-dihydroxy-2,5-dicarbomethoxyfuran,
3-Hydroxy-4-methoxy-2,5-dicarbomethoxyfuran and
3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran.

The other materials tested with this organism showed an inhibitory reaction. (See Fig. 2.)

Zymin was also used as a test reagent for some of these various compounds. In these experiments 10 mg. of dry zymin were used in each test. 3-Hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran was definitely inhibitory, while ascorbic acid, 3,4-dimethoxy-2,5-dicarboxyfuran and 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran showed a very definite increase in metabolic rates. Again the rate of respiration was not extremely increased but check results were obtained in three different trials. The graphs show the relative relationships of the compounds tested. In each case the one compound which stood out by itself was 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran. (See Fig. 1)

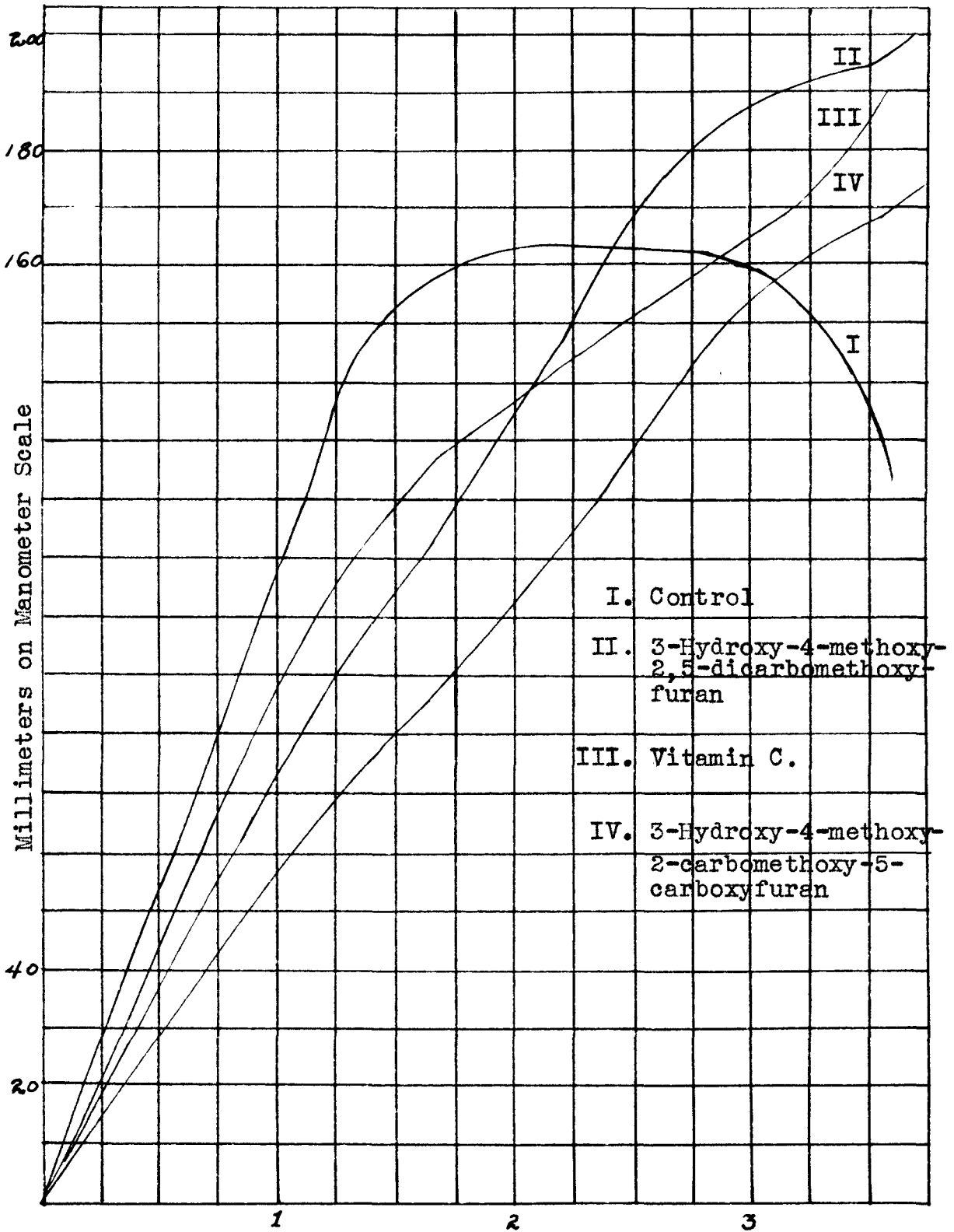
Mr. James Lesh tested the effect of this compound on yeast growth. The yeast cell count was found to be within experimental error. However, when viewed through the microscope, the control cells were smaller than those grown in the presence of

METABOLISM STUDIES WITH ZYMIN



Millimeters on Manometer Scale
Fig. 1

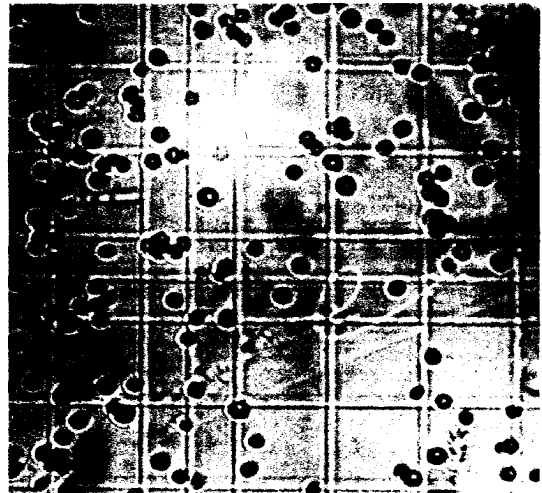
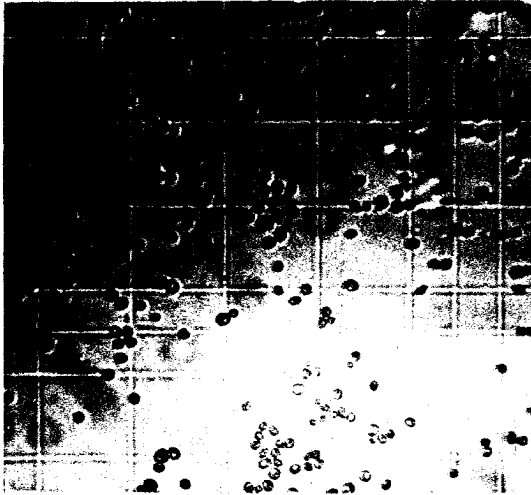
METABOLISM STUDIES WITH Aerobacter aerogenes



Time in Hours
Fig. 2

hydroxy compound. The American Type Culture Number 4226 was used in these tests. The photographs of the control and test samples are shown. (See Fig. 3)

S. cerevisiae



[Control]

[with 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran]

Fig. 3

Professor F. W. Went, of the California Institute of Technology, tested both the 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran and 3-hydroxy-4-methoxy-2-carbomethoxy-5-carboxyfuran. The Avenae and pea test did not show the characteristic curvature. Direct growth measurements of the elongation of tissue cylinders in solution showed no increase in growth. From these measurements it was concluded that these compounds cannot act as growth hormones or growth stimulants in higher plants. In root formation the action of these compounds was tested from

the apical as well as the basal end of the pea cuttings, and these tests were also carried out in the presence of auxin, and were likewise negative. From these experiments it was concluded that the compounds could not be local stimulants, hormones or co-stimulants.

Due to the low solubility of these compounds in water, the phenolic character of the compounds studied produced, in most cases, no harmful effects. The stimulation recorded for the 3-hydroxy-4-methoxy-2,5-dicarbomethoxyfuran may be considered to be closely related to that of the phenols. It is more like a poison in its action on the cell. One cannot accurately predict what the properties of the unsubstituted hydroxyfurans will be, but they should resemble their benzene analogs to a certain degree.

The writer is sincerely grateful to Dr. Went and to Mr. Lesh for their cooperation in this work.

VII. SUMMARY

A number of compounds derived from 3,4-dihydroxy-2,5-dimethoxyfuran have been prepared and studied in order to ascertain some of the properties of β -hydroxyfurans. The increased reactivity of these compounds in relation to furan itself was best illustrated by the reactions of 3,4-dimethoxyfuran with (1) mercuric chloride and (2) maleic anhydride. This activity can be attributed to the hydroxyl groups or their methyl ethers. The investigation has also made available some information on certain biological effects produced by β -hydroxyfuran derivatives. The hydroxyl groups have shown all the properties of phenolic hydroxyl groups.