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CONDENSATION REACTIONS OF FURFURAL AND ITS DERIVATIVES

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BY

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Approved

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TABLE OF CONTENTS

PART II

Page

CONDENSATION REACTIONS OF FURFURAL AND ITS DERIVATIVES

OBSERVATIONS AND DISCUSSION OF RESULTS

EXPERIMENTAL

INTRODUCTION

Furfural has had a paradoxical history. Although it is the most plentiful and most easily available cyclic aldehyde, it has been little studied. The sudden transition of furfural from a laboratory curiosity to an industrial commodity ten years ago, flooded the markets with an aldehyde that was little understood. Immediately a hope arose that some technical value might be placed on the new industrial substance. The early attempts to develop the substance commercially met severe obstacles. These obstacles were attributable to one fact. Obviously, the daily output of tons of furfural from waste cellulosic and carbohydrate industries could not be utilized as the simple unaltered aldehyde.

When attempts were made to produce substances using furfural as a parent material, the disturbing fact was noted that little was known of the behavior of the compound. Excepting a few scattered researches, the work on furfural had consisted largely of studies of the aldehyde group, not of the ring, even as late as 1925. The demand then was for more knowledge of the inherent properties of the ring which gave the characteristic behavior to furfural.

Undoubtedly, the two greatest early drawbacks to a detailed study of furfural and the furan ring were the facts that, first, the materials were difficult and tedious to obtain, and, second, the disheartening behavior and apparent sensitiveness of the furan nucleus. The early literature of furfural and furan compounds was one of tars, gums and resins. Under the slightest provocation these compounds decomposed to yield intractable substances which were indefinite and altogether undesirable to handle. It is no wonder then that as late as 1935 furfural found itself in an embarrassing position among a host of well understood and intensively studied compounds.

The first of these obstacles was removed when it was found that carbohydrate and cellulosic agricultural wastes could be cheaply and efficiently converted to furfural. The second obstacle remained but it had to be met and dealt with determinedly.

Although the early work led to a few developments in the use of furfural as a base for polymeric and resin substances, it proved to be a detriment to rapid progress. It was an unduly emphasized warning to beware of drastic treatment, and many investigators discarded all hope of carrying out certain reactions where the treatment was drastic and intensely forced.

The last few years have seen much of this regard reduced and under certain well defined conditions it has been found that furfural and its derivatives are highly stable and undergo a series of transformations easily and with definiteness.

Among the ordinary reactions which many classes of compounds undergo, particularly the aromatic compounds, are the nuclear condensation reactions such as the Friedel-Crafts and the Gattermann-Koch reactions. At the time that the present work was begun neither of these reactions, as they concern nuclear substitution in furan compounds, had been studied. The alkylated and acylated products from these reactions would not only be of value, but they would also be necessary to a completion of the chemistry of furan. It would further offer a means of going from crude products or their derivatives to valuable alkyl or acyl compounds containing the furan nucleus.

Not only do these two condensations require the use of highly active substances, but they required active metal halides as condensing agents and the mineral acids liberated during reaction had been found to polymerize and resinify furan compounds. The problem resolved itself into one of determining methods whereby the sensitive furfural derivatives could be brought into contact with the necessary condensing agents without complete decomposition.

Therefore, it was desirable to know the conditions under which furan compounds were stable and to define the conditions and concept of decomposition to obviate needless waste and difficulties.

For this reason this work is divided into two parts. The first is concerned with the conditions under which furan compounds are stable and the effect on stability of the various substituents in the ring. There is also included the attempt to develop a color reaction for the furan nucleus. If successful, a color test would give a ready means for determining the presence of a furan ring after a series of strenuous transformations in which the ring might open with great facility.

The second part has to do with the actual condensations and the products obtained from a series of reactions under various conditions.

Finally, an attempt is made to interpret the results of the work in the light that it sheds on the constitution of the furan nucleus.

Even a cursory review of the recent literature emphasizes the fact that the hope of furan chemistry is by no means dismal. For out of the chaos of a multitude of reactions that have been developed during the last few years has evolved a definite and expanding furan chemistry. In some respects furan chemistry is novel and unprecedented.

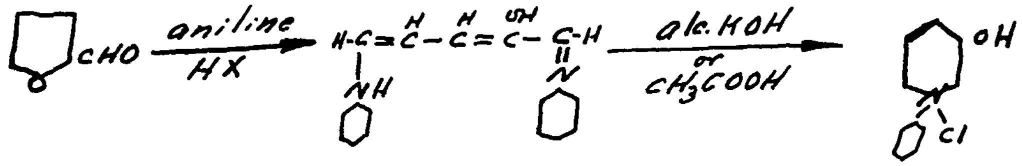
PART I

COLOR REACTIONS, POLYMERIZATION AND STABILITIES OF FURFURAL AND ITS DERIVATIVES.

HISTORICAL

Color Reactions.

It is of interest that the first furan compound definitely described was furfural, although furoic acid had been noted earlier by Scheele (1a). When Döbereiner (1b) distilled bran with dilute sulfuric acid, he obtained an oil which he noted but did not investigate. Five years later Stenhouse (2) studied the preparation and characterization of furfural. In working with the compound, Stenhouse carried out a series of condensations. One of these condensations was with aniline salts (3). He noted an intense red color when aniline salts and furfural were allowed to react in aqueous medium. This red compound was termed a furfuraniline or furalanil. No definite knowledge of the constitution of this red dye was obtained until Zincke and Mühlhousen (4) in 1905 found that the compound was not furalanil but an open chain compound. This work led to the conclusion that the red compound was the result of the following reaction:



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(1) (a) Scheele, Mém. acad. roy. sciences Stockholm (1780), p. 70.
(b) Döbereiner, Ann., 3, 141 (1832).

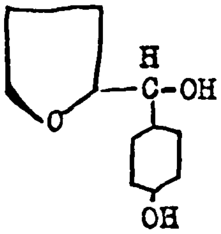
(2) Stenhouse, J. prakt. Chem., 12, 120 (1837); Ann., 35, 301 (1840).

(3) Stenhouse, Ann., 156, 197 (1870).

(4) Zincke and Mühlhousen, Ber., 38, 3824 (1905).

This red dianilide of hydroxyglutaconaldehyde condensed in alcoholic potassium hydroxide or acetic acid solution to yield β-hydroxy-N-phenylpyridinium chloride. These studies were confirmed by others (5). This work explained the color bases of Stenhouse (6) and Schiff's bases (7) prepared from furfural by condensation with aniline and some of its derivatives.

Meanwhile Baeyer (8) had described a color reaction of furfural. He found that in general furfural gave indigo blue colors with resorcinol and pyrogallol in the presence of hydrogen chloride. The blue compounds were an intense green when placed in water. Baeyer immediately suggested that perhaps these green bodies were related to chlorophyll. Under certain conditions (9) of condensation these green compounds possessed an absorption spectrum similar to chlorophyll. He suggested (9) that the green compound produced with phenol and furfural possessed the following structure:



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(5) Dieckmann and Beck, *Ber.*, *38*, 4122 (1905); Konig, *J. prakt. Chem.*, *72*, 555 (1905), also *ibid.*, *88*, 193 (1913); Fischer et al, *J. prakt. Chem.*, *100*, 105 (1919).
(6) Stenhouse, *Ann.*, *156*, 197 (1870).
(7) Schiff, *Ann.*, *201*, 355 (1880).
(8) Baeyer, *Ber.*, *5*, 26 (1872).
(9) Baeyer, *Ber.*, *10*, 355 (1877).

It is noteworthy that two of his suggestions have since been at least partially justified. First, that chlorophyll does contain a five membered heterocyclic ring; and secondly, that the primary condensation product of furfural and phenol is undoubtedly as he suggested (10), although the final products are probably a group of open chain aldehydes condensed with phenol. These open chain aldehydes resulted from the ring opening of furfural in the presence of hydrochloric acid.

These pronounced color reactions of furfural stimulated a search for a typical color reaction of the furan ring. The value of such a reaction is inestimable. The difficulty of demonstrating the presence of a furan ring after a series of strenuous transformations is in many cases of enormous proportions. For example, in the introduction of groups by vigorous reactions such as the Friedel-Crafts reaction, it is often desirable to demonstrate that the ring is intact. There is no simple method for this. The only course is to resolve the unknown product to a known furan derivative. This is well nigh impossible in some cases since suitable reference compounds are lacking or there is no method of resolving the products in question. Furthermore, there are times when a preliminary knowledge of the substance in question is of first importance. This fact is especially true now that the furan nucleus or a

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(10) Parai, Koshitz, Kudryovtzer and Mashkileison, Kunstoffe, 23, 97 (1933) [C.A., 27, 3709 (1933)].

derivative of it is being found often in naturally occurring products, notably the so-called fish poisons (11) such as rotenone and similar substances.

So far all attempts to develop a color reaction have been unsuccessful. The much used color reaction of furfural with aniline acetate has been found not to be without exception, that is, there are other substances which will give similar red colors (12). However, the color reactions of furfural and its derivatives have been used for a variety of practical tests and for a diverse group of color indicators for various purposes, such as the detection of adulteration in honey (13), bile acids (14), and proteins (15), as well as indole, pyrrole, thiophene and carbazole (15).

Attempts to develop color reactions for furan compounds in general have met uniform defeat, either because there was no universal test or because other substances gave the same reaction. Attempts have been made to use vanillin (16), dimethyl barbituric acid (17), and pine splints (18) to develop a color reaction for furan compounds. None of these reactions gave a

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(11) LaForge, Haller and Smith, *Chem. Rev.*, *12*, 181 (1933); Spath *et al*, *Ber.*, *66*, 749 (1933).

(12) Middendorp, *Rec. trav. chim.*, *38*, 47 (1919); von Raumer, *ibid.*, *17*, 115 (1909); Ekenstein and Blanksma, *Chem. Weekblad*, *6*, 217 (1909); Erdmann, *J. prakt. Chim.*, *56*, 156 (1897) Footnote.

(13) Fiehe, *Zeit. Untrsuch. Nahrund. Genussmittel*, *16*, 75 (1908)[*C.A.*, *3*, 83 (1909)]

(14) Villet and Derrien, *Comp. rend. Soc. Biol.*, *66*, 175 (1909) [*C.A.*, *3*, 1180 (1909)].

(15) Fleig, *ibid.*, *65*, 283 (1908)[*C.A.*, *3*, 429 (1909)].

(16) Asahina *et al*, *Acta Phytochim.*, *2*, 22 (1924)[*Chem. Zent.*, *95* [3] 1694 (1924)].

(17) Akabori, *Proc. Imp. Acad.* (Japan), *3*, 342 (1927)[*C.A.*, *21*, 3185 (1927)].

(18) Meyer-Jacobson, "Lehrbuch der organischen Chemie". Vol. 2, part 3, p. 50 (1920). Walter DeGruyter Co., Leipzig.

suitable test for all furan compounds nor were any of them of such a nature that certain non-furanic compounds would not give identical or closely related colors.

Throughout the experimental portion of the present work observations were constantly made in an attempt to find a color reaction that might be generally applicable to furan compounds.

Polymerization and Stability.

The great ease with which furfural and certain of its derivatives polymerized attracted early attention. Many attempts to industrially develop the enormous annual potential supply (19), estimated to be over a hundred million tons, had for their basis the formation of gums and resins. These were the so-called polymerized furfural substances. In truth they were not polymerized substances but they were products which resulted when the starting material was decomposed. That is, these so-called polymerized substances upon various treatment as heating do not regenerate the original material. Indeed, the entire furanic skeleton may be destroyed. Evidence tends to indicate that there is a high degree of probability that the furan ring undergoes decomposition.

On attempts to handle some furan compounds,as furfural and furfuryl alcohol, it was early observed that the material decomposed seriously under certain conditions to yield intractable tars and gums. Limpricht (20) reported the resinification

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(19) Barry, Ind. Chem., 6, 479 (1930).
(20) Limpricht, Ann., 165, 300 (1872).

of furfuryl alcohol on attempts to distill it and on standing. He was able to isolate an oil from resinified furfuryl alcohol which on analysis suggested the following reaction:

$$3(C_5H_6O_2) - H_2O \longrightarrow C_{15}H_{16}O_5$$

This seemed to indicate that the substance gradually underwent resinification with loss of water. He noted its extreme sensitiveness to mineral acids.

Erdmann (22) was the first to point out the unusual phenomenon of two forms of furfuryl alcohol. One he found was soluble in water to the extent of five per cent. The other was miscible with water in all proportions. This water soluble form appeared to be the unstable isomer since it was observed to change to the insoluble form on standing either alone or in a water solution.

The unusual ease with which furfural and furfuryl alcohol underwent resinification to hard substances, attracted the attention of the resin and gum industry (19, 21). Many patents have been taken out to cover various processes for preparing moldable and permanent resinified material. These have been prepared generally from furfural or some close derivative or in some cases from a furan compound together with a substance as phenol or formaldehyde. These transformations have been

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(21) Miner Laboratory Bulletin No. 2 (1928). This is the only publication in the nature of a bibliography of furfural and its derivatives that has been published. It is excellent for leading references.

(22) Erdmann, Ber., 35, 1846 (1902).

brought about largely through mineral acids or anhydrous salts such as aluminum chloride, ferric chloride or zinc halides.

However, no definite attempts were made to find the conditions under which furfural and its derivatives were stable or to discover what groups accelerated, one way or another, the decomposition.

It seemed hardly fair to conclude that these decompositions occurred without system or reason. Indeed, it has been found that there are definite rules for the behavior of furfural even when it is decomposing.

EXPERIMENTAL

Technique Used.

In studying the conditions under which the various substances were stable or were decomposed, observations were made on the color changes that occurred.

The method of study used here was similar to that of Staudinger and Bruson (23). It consisted essentially of placing a small portion of material under study in a test tube closed by a stopper bearing a tube of soda lime. The polymerizing substance was added to this and the observations were made as detailed.

The necessity of using clean apparatus can not be over emphasized. All pieces were cleaned in an acid bath, washed five times with water, then steamed out to remove all acids.

Polymerization of Furfural, Inorganic, Reactants.

The furfural used was freshly distilled material. It was dried by placing it in a desiccator over sulfuric acid.

One cc. of furfural was placed in a clean test tube which was closed by a stopper bearing a tube of soda lime.

The polymerizing substance was then added and the observations were made as shown in Charts I and III. One drop of the liquid reactant was added to the furfural from a pipette. A small fragment, about 0.01 gram, of the solid substance was added by means of a small spatula.

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(23) Staudinger and Bruson, Ann., 447, 113 (1926).

Effect of Dilution of Inorganic Reactants. Chart II.

In order to determine the effect of dilution, one drop of the reactant was dissolved in 1 cc. of dry, redistilled chloroform. Where the material was insoluble in chloroform the smallest piece of solid material which would cause a discoloration in five minutes was added. Only the more vigorous resinifying agents were employed in these studies. The chloroform solutions were added to the furfural (1 cc.) from a pipette.

Effect of Various Organic Substances on Furfural. Chart III.

This was studied in exactly the same way as for the inorganic substances.

Effect of Various Reagents on Furfuryl Alcohol. Chart IV.

This was studied in a way similar to the studies on furfural. Freshly distilled material was used.

Effect of Dilution of Reagents on Furfuryl Alcohol. Chart V.

These reactions were carried out by the method used with furfural.

Time as a Factor in the Stability of Furfural and its Derivatives. Stabilizing Agents.

It is a general observation that many furan compounds, particularly the more sensitive types as furfural and furfuryl alcohol, darken on standing and in many cases decompose completely if they stand for a sufficiently long period of time.

A series of studies was made to ascertain under what conditions and over what period of time these compounds decompose.

All compounds were freshly purified, colorless materials. It had previously been shown (24) that sensitive compounds might be protected against oxidation by certain easily oxidizable substances as hydroquinone and pyrogallol.

In the present study a series of substances was studied in an attempt to find one which efficiently prevented blackening and decomposition.

Observations were also made in an attempt to determine what groups stabilized the furan nucleus in such a way that long periods of standing caused little or no decomposition.

In each case the material was placed in a tube and either sealed with or without air present or allowed to stand in the laboratory protected from fumes. Charts VI, VII, VIII, show the various conditions used, the compounds studied and the observations made.

Effect of Various Groups on the Stability of the Furan Ring. Chart IX.

In order to develop systematically the concept of stability and instability it was essential to learn the effect of various groups when they were introduced into the furan ring. To accomplish this 0.5 gram of thirty-two variously substituted furans was placed separately in test tubes and treated with

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(24) Moureu and Dufraisse, Chem. Ind., 47, 819 (1928).

0.1 gram of reactant. Five reactants were used throughout to render the observations uniform. All of these substances had been found to decompose vigorously furfural and furfuryl alcohol under similar conditions. Observations were first made in the cold, then the contents of the tubes were heated to boiling and the observations were repeated.

Note on Cleaning Containers.

It is imperative that all glassware for handling furfural or furfuryl alcohol, in particular, and furan compounds in general, be clean and free from mineral acids particularly damp hydrogen halides. It has been observed that dry hydrogan chloride is without action on some sensitive furans. To ascertain this, a benzene solution of hydrogen chloride was added to 1 cc. each of furfural and furfuryl alcohol. After two hours only slight darkening had occurred. This is striking when compared with the violent decomposition that occurred when aqueous hydrogen chloride was used. To insure cleanliness, glassware from the acid bath was washed five times with water. It was then either steamed out or washed well with dilute alkali. In either case it was rinsed, drained and allowed to dry, protected from fumes.

Chart I.

Effect of Various Reagents on Furfural.

Inorganic Reagents.

One drop of reactant was added to 1 cc. of furfural.

Periodic Table Groups	Substance	Effect
Group 1	sodium chloride	none
	sodium bromide	none
	sodium iodide	rapidly darkened to yellow, 6 hours.
	sodium nitrate	none
	sodium sulfate	none
	sodium hydroxide	gradually dark, one hour.
	potassium chloride	none
	potassium bromide	none
	potassium iodide	none
	potassium sulfate	none
	potassium nitrate	none
	potassium hydroxide	gradually dark, one hour.
	cupric chloride	rapidly darkened to yellow.
	cuprous chloride	none
	cupric nitrate $6H_2O$	slight in 24 hours
	cupric sulfate	none
Group 2	calcium chloride (anhyd.)	none
	calcium nitrate $4H_2O$	none
	calcium chlorohypochlorite	very slight clouding.
	strontium chloride $6H_2O$	none
	strontium nitrate $4H_2O$	none
	barium hydroxide	none
	barium chloride $2H_2O$	none
	cadmium iodide	none
	cadmium chloride $2H_2O$	none
	cadmium bromide	none
	cadmium nitrate $4H_2O$	slight in 24 hours.
	mercuric chloride	none
	magnesium chloride $6H_2O$	none
	zinc chloride (anhyd.)	black in 24 hours.
	zinc chloride	none
Group 3	aluminum nitrate $9H_2O$	slight in 3 hours. Red in 24 hours.
	aluminum chloride $6H_2O$	none
	aluminum chloride (anhyd.)	black in 30 seconds, resinous.
	aluminum iodide	black instantly, resinous.
	boron trichloride	immediately black with solid particles.

Inorganic Reagents, Cont.

Periodic Table Groups	Substance	Effect
Group 4	stannic chloride $10H_2O$	dark 1 minute.
	stannic chloride (anhyd.)	black at once.
	stannous chloride $2H_2O$	dark 2 minutes.
	stannic bromide	light brown to green, black in 24 hours.
	stannic iodide	light brown, black in 18 hrs.
	plumbous chloride	none
	plumbous iodide	yellow in 24 hours.
	silicon tetrachloride	black immediately, solid in 24 hours.
	titanium tetrachloride	black at once
	carbon tetrachloride	no action.
Group 5	phosphorus trichloride	green to black resin immed.
	phosphorus pentachloride	dark 3 minutes, black 15 minutes, resin.
	phosphorus tribromide	green at first, black resin immediately.
	phosphorus oxychloride	purple 1 minute, resin 24 hrs.
	phosphorus pentoxide	dark 2 minutes, black 24 hrs.
	phosphorus diiodide (PI_2)	black immediately, black 24 hours.
	arsenic tribromide	red immediately, purple 3 minutes, resin.
	antimony trichloride	deep blue immediately, black 18 hours, resin.
	antimony pentachloride	black immediately
	antimony tribromide	green at once, black liquid 24 hours.
	antimony triiodide	dark 15 minutes, black 1 hour.
	bismuth triiodide	brown at once, brown 18 hours.
Group 6	chromium trichloride	darkened in 24 hours.
	chromium trioxide	very slight clouding 24 hours.
	sulfur monochloride	black resin 48 hours.
	chlorosulfonic acid	violent decomposition, fumes, resin
Group 7	bromine	black at once
	iodine	dark at once
Group 8	cobaltous chloride $6H_2O$	dissolved, blue solution
	ferric chloride $6H_2O$	dissolved, black 24 hours.

Chart II.

Effect of Dilution of Inorganic Reagents on Furfural

(1 cc. furfural)

Reactant	Effect
phosphorus pentachloride	0.001 g. darkened furfural in 5 minutes
phosphorus tribromide	3 drops slight brown 5 minutes[1]
phosphorus trichloride	5 cc. darkened (purple in 5 minutes)
phosphorus oxychloride	0.15 cc. dark yellow 5 minutes
sulfur monochloride	3 drops deep yellow 5 minutes
chlorosulfonic acid	0.5 cc. brown in 5 minutes
aluminum iodide	0.001 g. dark (brown) in 5 minutes
arsenic tribromide	0.5 cc. purple in 5 minutes
antimony pentachloride	5 drops red in 5 minutes
antimony tribromide	5 drops brown in 5 minutes
boron trichloride	10 drops brown in 5 minutes
silicon tetrachloride	2 cc. brown in 5 minutes

[1] Volumes given here refer to volumes of chloroform solution. To 1 cc. of chloroform was added 1 drop of the reactant. In cases where the reactant was insoluble in chloroform, the smallest piece which produced blackening in five minutes was used.

Chart III.

Effect of Various Organic Reagents on Furfural.

Reagent	Effect, Undiluted[1]	Effect in Chloroform[2]
acetic acid	none	none
acetamide	none	none
arsanilic acid	red-brown 24 hrs.	slight
benzaldehyde	no change	none
benzoic acid	none	none
benzoyl chloride	black 1 hr.	none
chloroacetic acid	black 24 hrs.	very slight
chloramine-T	none	none
dimethylamine	black 24 hrs.	dark
ethyl mercaptan	none	none
diethyl sulfide	yellow 24 hrs.	none
formic acid	black 24 hrs.	dark 24 hrs.
glycine	none	light brown 24 hrs.
o-nitrobenzene sulfonic acid	purple 2 minutes. black viscous 24 hrs.	light brown 24 hrs. black
p-bromodimethylaniline	light brown 24 hrs.	slight yellow
picryl chloride	white precipitate after 24 hrs.	none
quinoline	light yellow at once no change 24 hrs.	none
sodium acetate	light yellow 24 hrs.	none
sodium formate	light yellow 24 hrs.	none
sulfanilic acid	none	none
thiophenol	dark yellow 24 hrs.	dark yellow 24 hrs.
urea	brown jell mass	none

[1] One drop of the undiluted reactant was added to 1 cc. of furfural.

[2] One drop of a chloroform solution was added to 1 cc. of furfural. This solution was made by dissolving 1 drop of the reactant in 1 cc. of chloroform.

Chart IV.

The Effect of Reagents on Furfuryl Alcohol.

One drop of reactant was added to 1 cc. of furfuryl alcohol. In case of solids, a very small piece was used.

Reagent	Effect
arsenic tribromide	light brown
bismuth triiodide	yellowed immediately
chromic oxide	none
phosphorus trichloride	deep crimson, violent decomposition at once.
phosphorus tribromide	green, violent decomposition, 1 min.
sodium bromide	brown
sulfur monochloride	green, violent reaction at once
stannic chloride (hydrated)	brown 1 hr.
stannous chloride (hydrated)	red 2 hrs.
zinc chloride (hydrated)	none
plumbous iodide	none

Chart V.

Effect of Dilution of Reagents in Their Action on Furfuryl Alcohol.[1]

Reagent	Effect
aluminum triiodide	0.005 gram
arsenic tribromide	10 drops
bismuth triiodide	0.005 gram
ferric chloride (anhydrous)	0.005 gram
phosphorus trichloride	3 drops
phosphorus tribromide	2 drops
phosphoryl trichloride	3 drops
sulfur monochloride	1 drop
silicon tetrachloride	1 drop
stannic chloride (hydrate)	0.005 gram
stannous chloride (hydrate)	0.005 gram

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[1] The quantities here represent the amount of reactant required to darken 1 cc. of furfuryl alcohol in five minutes. For the substances soluble in chloroform, 1 drop was dissolved in 1 cc. of dry chloroform. For the substances insoluble in chloroform the smallest piece which would darken the furfuryl alcohol in five minutes was used.

Chart VI.

Stabilizers for Furfural.

Ten cc. of furfural was used, and 0.1 gram of stabilizer was added.

Tubes Stoppered[1] Only. A.

Stabilizer	Effect	Time
arsanilic acid	black	11 weeks
p-aminobenzoic acid	black	11 weeks
benzyl alcohol	black	11 weeks
hydroquinone	red	11 weeks
benzaldehyde	black	11 weeks
pyrocatechol	red	11 weeks
[control]	black	11 weeks

[1] Cork stoppers were used.

Tubes Sealed. B.

Stabilizer	Effect
hydroquinone	brown 10 weeks, black 160 weeks.
pyrogallol	brown 10 weeks, black 160 weeks.
pyrocatechol	brown 10 weeks, black 160 weeks.
nitrogen (gas)	yellow 10 weeks, clear light brown 172 weeks.
air	brown 10 weeks, brown 172 weeks.

Chart VII.

Stabilizers for Furfuryl Alcohol.

One-tenth gram of stabilizer was added to 10 cc. of furfuryl alcohol.

Stoppered Tubes. A.

Reagent	(4 months) Effect
pyrocatechol	yellow
urea	black
hydroquinone	orange
pyrogallol	orange
/control7	black

Sealed Tubes. B.

Reagent	Effect		
	12 Weeks	30 Weeks	150 Weeks
pyrocatechol	colorless	golden	amber
hydroquinone	colorless	golden	amber
pyrogallol	colorless	golden	amber
/control7	colorless	golden	amber

Chart VIII.

Observations on Time Stability of a Miscellany of Furan Compounds.[1]

Compound	Orig. Color	Time	Final Color
furfural	colorless	30 days	black
furfural diacetate	colorless	112 days	black
furfuryl alcohol	colorless	30 days	black
furfuryl acetate	colorless	540 days	light brown
furfuryl methyl ether	colorless	540 days	yellow
alkyl furoates	colorless	1000 days	straw yellow
alkyl 2-nitrofuroates	yellow	1000 days	yellow
nitrofurfural diacetate	yellow	1000 days	red
furyl alkyl ketones	colorless	100 days	brown-black
2-alkylfuroic acids.	colorless	1000 days	colorless
2-furoic acid	colorless	100 days	colorless
chlorofurfural	colorless	300 days	black
bromofurfural	colorless	300 days	black
n-butylfuran	colorless	10 days	brown-viscous
furan	colorless	1000 days	yellow
sylvan	colorless	1000 days	brown yellow
iso-butylenylfuran	colorless	1 day	brown-viscous
chloromercurifuran	colorless	90 days	brown (insoluble)
methyl alkyl furoates	colorless	1000 days	straw yellow
nitrofurfuryl alcohol	yellow	300 days	yellow-red
5-acetamino-2-furoic acid	colorless	540 days	colorless
furfural diacetate	(sealed in nitrogen)	80 days, brown	150 days, black
	(sealed in air)	80 days, black	

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[1] These compounds were allowed to stand in stoppered containers in the laboratory. They were thereby exposed, more or less, to the definitely acid atmosphere. This acidic nature of the air was shown by a piece of moist blue litmus paper which turned pink.

Chart IX.

Stability of Other Furan Types.

/C = cold; H = heated to a boil; decomp. = decomposition7

Reagent	Furan Compounds				
	chlorofurfural	bromofurfural	nitrofurfural	bromofurfural oxime	b a
phosphorus tribromide	dark in 5 min.	C - no change H - yellow	H and C no change	C - no change H - yellow	C H
silicon tetrachloride	H and C no change	C - light green H - no change	H and C no change	C - yellow H - no change	C H
phosphorus trichloride		H and C no change	H and C no change	H and C no change	H n
sulfur monochloride	H and C no change	H and C no change	H and C no change	C - no change H - orange	C H
arsenic tribromide	H and C no change	C - dark H - black	no C - change H - red	C - no change H - darkening	C H

Reagent	Compounds (Cont.)				
	dinitrofuran	ethyl aminofuroate	ethyl furylacrylate	ethyl nitrofuroate	
phosphorus tribromide	C and H no change	C - no change H - orange	C - black H	C and H no change	C
silicon tetrachloride	C and H no change	C) (no change H)	C - dark H - no change	C and H no change	C) H(
phosphorus trichloride	C and H no change	C - no change H - no change	C - no change H - no change	C and H no change	C H
sulfur monochloride	C and H no change	C - no change H - red to black	C - vigorous reaction	C and H no change	C
arsenic tribromide	C and H no change	C) (no change H)	C - brown H - black	C - green H - black	C H

	bromofuryl-acrylic acid	*n*-butyl furoylacetic ester	*n*-butyl furylacrylate	diethyl dehydromucate	dehydromucic acid
nge	C - no change H - brown	C - no change H - black	C - brown H - black	C - no change H - slightly yellow	C and H no change
nge	C - pink H - no change	C - pink H - red	C - red H - brown	C - no change H - no change	C and H no change
	H and C no change	C) H) no change	C) H) no change	C and H no change	C and H no change
age	C - no change H - brown	C - no change H - red	C - no change H - black	C and H no change	C and H no change
age ing	C - darkening H - darkening	C - no change H - brown	C - brown H - black	C - no change H - black	C - no change H - yellow

ro-	furan	nitrofurfuramide	furfural diacetate	furfural hydrazone	furfuryl acetate
e	C - black	C and H no change	C - brown	C - black	C - purple H - black
e	C) H) no change	C and H no change	C - black around crystals	C - no change H - black	C - black
e	C - yellow H - green	C and H no change	C - yellow with blackening	C - red H - dark	C - red H - violent decomp.
e	C - violent reaction black	C and H no change	C - no change H - no change	C - violent reaction	C - black violent
n k	C - ppt. forms H - no change	C - no change H - brown	C - black	C - deep red H - black	C - red to black

Stability of Other Furan Types (Cont.)

Reagent	Furan Compounds				
	furfuryl methyl ether	furfuramide	furoamide	furoic acid	fu acet
phosphorus tribromide	C - white ppt. formed H - black	C - blackens H - vigorous decomp.	C) H) no change	C - no change H - yellow	C - H -
silicon tetrachloride	C - red H - no change	C - black	C) H) no change	C - yellow H - no change	C - H -
phosphorus trichloride	C) H) no change	C - blackens	C) H) no change	C) H) no change	C) H)
sulfur monochloride	C - darkened H - red	C - no change H - brown	C) H) no change	C - no change H - light brown	C - H -
arsenic tribromide	C - no change H - brown	C - brown H - vigorous decomp.	C - no change H - darkened	C - no change H - brown	C - H -

Reagent	Compound				
	monoethyl dehydromucate	nitrofurfural diacetate	nitrofurfuryl alcohol	sylvan	trif am
phosphorus tribromide	C) H) no change	C - no change H - no change	C - gas, red H - blackened	C - yellow	C - crys H -
silicon tetrachloride	C) H) no change	C - no change H - brown	C - light brown H - gas, brown	C) H) no change	C - H -
phosphorus trichloride	C) H) no change	C) H) no change	C - gas, heat H - no change	C - no change H - no change	C - H -
sulfur monochloride	C) H) no change	C) H) no change	C - no change H - no change	C - vigorous decomp.	C -
arsenic tribromide	C) H) no change	C - no change H - black	C - darkened H - strong decomp.	C - yellow	C - H -

	furoyl acetic ester	furylacrylic acid	pseudo furyl *n*-amyl ketone[1]	furyl methyl ketone	furyl propyl alcohol
ange w	C - no change H - black	C - no change H - no change	C - no change H - black	C - black	C - violent decomp. red
ow hange.	C - red gas H - no change	C - red H - no change	C - red H - no change	C - red	C - violent decomp. red.
hange	C} H} no change	C} H} no change	C} H} no change	C - no change	C - violent decomp. red.
hange t brown	C - gas, clear H - black	C - red H - no change	C - darkened H - red	C - vigorous reaction, heavy liquid formed	C - violent decomp. red
hange n	C - no change H - red	C - no change H - red	C - no change H - brown	C - black	C - red

	trifuryl amine	furonitrile	nitrofuran		
ow	C - red brown crystals formed H - black	C - no change H - yellow	C} H} no change		
ange	C - no change H - darkened	C - no change H - yellow	C} H} no change		
hange hange	C - heat given off H - no change		C} H} no change		
rous mp.	C - violent reaction	C} H} no change	C - no change H - yellow		
ow	C - yellow mass H - black	C - no change H - yellow	C - no change H - brown		

[1] See page 44

OBSERVATIONS AND DISCUSSION

Color Reactions.

Throughout the experiments on furan compounds, color reactions were recorded as shown in the preceding charts. It was observed that there was no one reagent or related group of reagents that caused a uniform color change. In some cases no apparent reaction occurred at all. Some of the more sensitive furan compounds as furfural, furfuryl alcohol and furfuryl acetate showed a color reaction when treated with various substances. A glance at Chart I, Group 5, shows that furfural gave a green color with phosphorus tribromide. Chart IV shows the same color reaction for furfuryl alcohol with phosphorus tribromide, but furfuryl acetate, Chart IX, gave a distinct purple with the same reagent. Dinitrofuran and dehydromucic acid gave no reaction at all with phosphorus tribromide.

Similar studies by Levine and Richman (25) were not successful in developing a color reaction. These investigators attempted to use antimony trichloride to develop color reactions for compounds containing five-membered heterocyclic rings. They noticed that certain furan compounds gave color reactions, but they were not uniform nor were they general for all furan types. Certain substances, as furfural, gave an indistinct greenish brown or blue reaction. Furfuralacetophenone gave a lemon yellow while furonitrile yielded no color. Certainly such a variety

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(25) Levine and Richman, _J. Biol. Chem._, _101_, 373 (1933).

of color changes for various furanic substances could not be offered as a test for the presence of a furan ring.

Levine and Richman further noticed that negatively substituted furans, as furoic acid or certain derivatives of it, gave no color reaction. This appeared to be a general behavior of the negatively substituted furan compounds studied.

In the present work, the report of Levine and Richman has been essentially verified. Although the work was not repeated with antimony trichloride, similar halides were used. The active halides of phosphorus, silicon, sulfur, and arsenic were utilized.

The results may be briefly summarized. First, the colors developed in the reactions varied from none through the shades of the spectrum to black. Secondly, there was no uniformity of color change; that is, compounds with certain groups produced one color while another compound with the same or similar groups developed entirely different colors. Thirdly, generally the highly negatively substituted furans as furoic acid or dinitrofuran and related compounds showed no color reaction.

As will be developed later, the color reactions undoubtedly appear subsequent to opening of the furan ring. Loewenstein (26) has recently examined earlier work on ring opening in the formation of the Stenhouse-Shiff color bases of furfural. In extending this work, Loewenstein confirms earlier views that the

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(26) H. Loewenstein, Inaugral Dissertation, "Ueber die Einwirkung von primären aromatischen Aminen auf Furfurol". Friedrich-Wilhelms-Universität, Berlin (1931).

furan nucleus has opened when the colors appear.

Although definite color changes with active metal halides might suggest the presence of a furan nucleus, it would be a matter of chance if one were found. Certainly there is no color test that is even approximately reliable. Many sensitive compounds nonfuranic in nature yield sharp color changes when treated in various ways such as with active halides of the metals and metalloids (25). Unfortunately, there is no color test for the furan ring that may be considered an indication of its presence.

The Polymerization of Furfural. Inorganic Reactants.

The term polymerization is used very loosely here to denote a change in the physical appearance of the substances in question. Generally, the substance was said to polymerize furfural if the material became dark colored, thick, or solid. Otherwise only the color changes are reported.

Chart I shows that the substances utilized as polymerizing agents naturally fall into groups when classified on the basis of their action on furfural. Incidentally these groups may be divided into subgroups according to the Periodic Table. Grouping not only simplifies a consideration of the results, but it also emphasizes the definite Periodic Groups and Families of compounds that show marked action on furfural. Thus all group references refer to Periodic Table Groups.

In Group 1 there was essentially no action on furfural after twenty-four hours with three exceptions. Sodium iodide darkened furfural slightly. Alkali bases and cupric chloride had a similar effect.

In Group 2 only anhydrous zinc chloride caused a blackening and thickening which finally formed a hard resin. The other substances were without action.

In Group 3, salts of two elements were studied. These were aluminum and boron. The hydrated aluminum salts were quite mild in their action, while the anhydrous substances were vigorous polymerizing agents. The resins formed were hard, brittle substances. Boron trichloride caused a vigorous decomposition.

On the whole, the halides of Group 4 caused vigorous and apparently complete decomposition. The furfural became black and set to hard masses. In this connection, it is interesting to note that carbon tetrachloride is the only neutral, non-polar, stable halide. Incidentally, this is one of the idiosyncrasies of the carbon atom.

The halides of Group 5 behaved in a manner similar to those of Group 4. In every case the furfural was decomposed and yielded hard, black solids as the final material. Varied colors developed when the reactants were first added, but the ultimate products were alike.

The substances derived from elements of Group 6 varied in their action. Chromic oxide was feeble in its effect. Chlorosulfonic acid and sulfur monochloride caused violent decomposition.

The elementary substances of Group 7 are represented by bromine and iodine. They both caused vigorous decompositions.

In Group 8, cobaltous chloride (hydrated) and ferric chloride (hydrated) were used. The cobaltous chloride caused no decomposition. It quietly dissolved to form a blue solution. Hydrated ferric chloride caused a blackening after twenty-four hours.

The most reactive substances toward furfural appear to be derived from elements of the middle of the Periodic Table. The halides of the elements of Groups 3, 4 and 5 were found to be the most reactive. This seems to be particularly true of the B Families of these groups.

Effect of Dilution of Inorganic Reactants on Furfural.

Chart II shows the effect of diluting the more reactive reagents. Sulfur monochloride and aluminum iodide appear to be the most reactive substances toward furfural. The halides of the B Family of Group 5 were found to be the most reactive class of substances.

Effect of Various Organic Reactants on Furfural.

Chart III shows that in general organic substances are mild in their action on furfural. The active substances were found to be those substances which contained (1) active halogens as benzoyl chloride (27) or chloroacetic acid, (2) the

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(27) Adams and Vollweiler, J. Am. Chem. Soc., 40, 1732 (1918). This article discusses the action of acid chlorides on furfural.

derivatives of mineral acids as o-nitrobenzenesulfonic acid, (3) those substances which condense with furfural as urea. It is interesting to note that sulfanilic acid was neutral and had no effect on furfural. This is in contrast with arsanilic acid which caused a brown color to develop. This brown color may have developed as a result of condensation of furfural with the amino group in the more basic arsanilic acid.

Effect of Inorganic Reagents on Furfuryl Alcohol.

The effect of the various reagents on furfuryl alcohol was quite similar to the effect on furfural. Chart IV shows that the furfuryl alcohol decomposed vigorously and it generally behaved in a more violent manner than furfural. This indicates its extreme sensitiveness. It is apparently less stable than furfural.

Effect of Dilution of Reagents on Furfuryl Alcohol.

The dilution of the reactants only emphasized the sensitiveness of furfuryl alcohol. From Chart V it is apparent that only minute quantities of the various substances were required to produce a discoloration.

Stabilizers for Furfural.

The interesting fact is observed from Chart VI, that the value of a stabilizer depends on the conditions under which the compound is placed. Furfural stoppered with arsanilic acid, p-aminobenzoic acid, benzyl alcohol, benzaldehyde and without a stabilizer was found to turn black in eleven weeks. Hydroquinone and pyrocatechol allowed the furfural to darken to a red color.

However, as Chart VI, B, shows, the stabilizers found to be of value in stoppered tubes were found to be of no value in sealed tubes. They actually accelerated decomposition over a long period of time. This fact is emphasized when it is considered that furfural sealed with air decomposed less than furfural sealed with the stabilizing agents. An atmosphere of nitrogen, or other inert gas, appears as the best method of stabilizing furfural.

However, the polyhydroxybenzenes as hydroquinone, pyrogallol and pyrocatechol are evidently the best stabilizers for laboratory purposes when the material must remain in constant use and unsealed.

Stabilizers for Furfuryl Alcohol.

Chart VII shows that observations made for furfural stabilizers hold for furfuryl alcohol. Unsealed furfuryl alcohol quickly blackens. Pyrogallol, hydroquinone and pyrocatechol markedly prevent discoloration. Pyrocatechol appears to be the best stabilizer.

When the same stabilizers were sealed with furfuryl alcohol no effect was noted. There was neither increased decomposition nor was there any stabilizing effect. It is evident from this that furfuryl alcohol may be adequately kept by sealing in clean containers. It must be protected from acid fumes when opened.

Time as a Factor in the Stability of Furan Compounds.

Chart VIII shows the striking facts that, first, some compounds which have been regarded as traditionally unstable are in fact stable over long periods of time, for example, furfuryl methyl ether; secondly, that the converse is true, namely, that some compounds, which have been used for various reactions because of their stability under certain conditions, are quite unstable when stored for long periods. An example of this latter type is furfural diacetate. These facts, which appear peculiar at first, are understandable when it is considered that the conditions under which the observations are made are necessary to an appreciation of the concept of stability.

Although furfural diacetate undergoes halogenation (28a) and nitration (28b) it is relatively unstable when stored over any length of time. Even when furfural diacetate was sealed with nitrogen, it decomposed more rapidly than did furfural or furfuryl alcohol under similar conditions. See, Charts VI and VII.

In general the negatively substituted furans are the most stable. Apparently, the alkenylfurans and furfuryl chloride (32) are the least stable of all the observed furan compounds. Similar observations have been made before. Moureu, Dufraisse and Johnson (29) observed the extreme instability of furyl-

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(28) ✓(a) Gilman and Wright, J. Am. Chem. Soc., 52, 1170 (1930);
✓(b) Gilman and Wright, ibid., 52, 4165 (1930).

(29) Moureu, Dufraisse and Johnson, Bull. soc. chim., 43, 586 (1928).

ethylene when it was stored without a stabilizer. From an examination of Chart VIII, it seems that, in general, 2-nitro- and 2-carboxyfurans and derived compounds as the nitrile are the most stable groups of furanic substances, when time is considered a factor of decomposition. In certain cases, the disubstituted furans are more stable than the monosubstituted furans. There may be exceptions to the rule that all di-alpha substituted furans are more stable than the corresponding monosubstituted furans. In cases where highly active groups, as the formyl residue, are attached to quite unstable furan radicals as in bromofurfural the decomposition may be accelerated. These facts were observed, however. First, that for a relatively short time as 60 or 70 days, bromofurfural showed less discoloration than furfural, but secondly, once decomposition started in the case of bromofurfural, it was much more rapid and complete than in furfural. This seemed to indicate that decomposition resulted from secondary effects such as evolution of hydrogen halide.

Effect of Various Groups on the Stability of the Furan Ring.

Chart IX shows the result of treating a miscellany of furan compounds with various substances known to decompose vigorously furfural and furfuryl alcohol. In this way it was possible to reach a comparative basis for the concept of decomposition by acidic substances. Such a scheme of treatment yielded definite results.

As Gilman and Wright (30) have shown that the nitro group markedly increased the stability of furfural, it was to be expected that the effect of negative groups on the whole would be one of increased stability. This was found to be the case. Unsaturation increases stability toward time and acidic substances. On the basis of this reasoning, halogens become weakly negative groups. This is not unreasonable since halogens generally increase negativity as measured by ionization constants and dissociation values in general. Recent evidence introduced by Kharasch and co-workers (31) would seem to place halogens as weakly negative groups considering attached halogens as groups, according to their influence on the ease of scission of halogenophenyl nuclei from organo-mercury compounds.

From Chart IX and the evidence obtained from the other Charts, the various groups may be arranged in a series according to their effect in increasing the stability of furan compounds. This series is known to be valid only for the alpha-substituted furans, but in all probability it is valid not only for the alpha series of substituted furans but for the beta-substituted compounds as well. This series refers to stability toward acidic substances as used in the studies represented in Chart IX. The groups are arranged in the order of their increasing effect in

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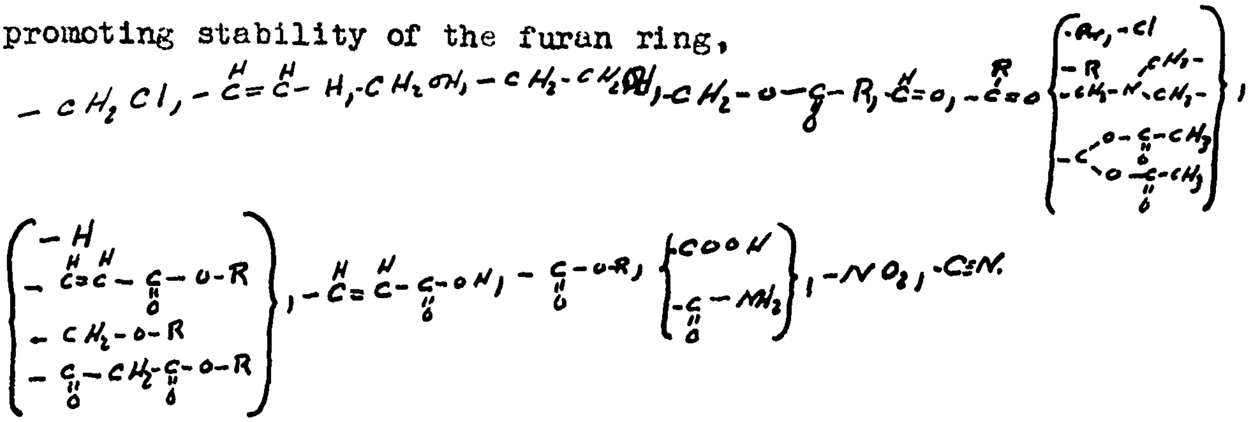
(30) Gilman and Wright, _J. Am. Chem. Soc._, _52_, 2550 (1930).
(31) Kharasch and Flenner, _J. Am. Chem. Soc._, _54_, 674 (1932). Leading references on "negativity series" may be obtained from this article.

promoting stability of the furan ring,



$$-CH_2Cl,\ -\overset{H}{C}=\overset{H}{C}-H,\ -CH_2OH,\ -CH_2-CH_2OH,\ -CH_2-O-\underset{O}{\underset{\|}{C}}-R,\ -\overset{H}{C}=O,\ -\overset{R}{C}=O\ \left\{\begin{array}{l} -Br,\ -Cl \\ -R \\ -CH_2-N\begin{array}{l}CH_3- \\ CH_3-\end{array} \\ -C\begin{array}{l} O-\underset{O}{\underset{\|}{C}}-CH_3 \\ O-\underset{O}{\underset{\|}{C}}-CH_3\end{array}\end{array}\right\},$$

$$\left(\begin{array}{l} -H \\ -\overset{H}{C}=\overset{H}{C}-\underset{O}{\underset{\|}{C}}-O-R \\ -CH_2-O-R \\ -\underset{O}{\underset{\|}{C}}-CH_2-\underset{O}{\underset{\|}{C}}-O-R\end{array}\right),\ -\overset{H}{C}=\overset{H}{C}-\underset{O}{\underset{\|}{C}}-OH,\ -\underset{O}{\underset{\|}{C}}-O-R,\ \left\{\begin{array}{l}-COOH \\ -\underset{O}{\underset{\|}{C}}-NH_2\end{array}\right\},\ -NO_2,\ -C\equiv N.$$

where R = alkyl groups.

free valence on carbon indicates attachment of furan ring.

The series is interesting. It will be observed that the hydroxyl-containing side chains occur at the end of the series which represents the most unstable compounds. It is generally true that the methylene group attached to the furan ring causes an unusual instability. Since furfuryl methyl ether showed a stability greater than furfural or furfuryl alcohol, it may be that the unusual instability of some compounds is in part explained by a tendency to rearrange. This tendency has been observed for furfuryl chloride (32). That is, the furfuryl alcohol and acetate may show this same tendency to rearrange while furfuryl methyl ether does not. This assumed lack of rearrangement tendency for furfuryl methyl ether may result from the greater strength of the bonds in the ether linkage. From the fact that furfuryl alcohol and furfuryl acetate may be kept for long periods of time, it is apparent that no rearrangement

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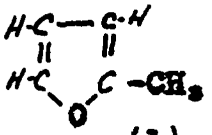
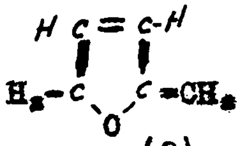
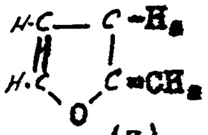
(32) (a) Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2552 (1932); Reichstein and Zschokke, *Helv. Chim. Acta.*, **15**, 1124 (1932); also, see, Kirner, *J. Am. Chem. Soc.*, **50**, 1955 (1928).
(b) Kizhner, *J. Gen. Chem.* (U.S.S.R.), **1**, 1212 (1931)[*C.A.*, **26**, 5299 (1931)].

is actually occurring, but it is possible that under the proper conditions rearrangement may occur. This is the case with furfuryl chloride. It does not rearrange spontaneously but upon proper treatment, such as subjection to aqueous potassium cyanide, some of the products are those of rearrangement. This theory is not necessarily valid. However, it has the advantage of having more of a basis than the alternative theory which says simply that the ring is weakened. The theory offered here attempts to use the meager facts at hand to explain an observed behavior. In this connection it is interesting to note that Kizhner (32b) has recently described an unstable isomer of sylvan. It appears that on reduction of furfural by the Wolff-Kizhner method two forms of sylvan may be obtained. One of these is the customary methylfuran (1). The other compound appears to be a mixture of 2-methylene-2,5-dihydrofuran (2) and 2-methylene-2,3-dihydrofuran (3).


(1)


(2)


(3)

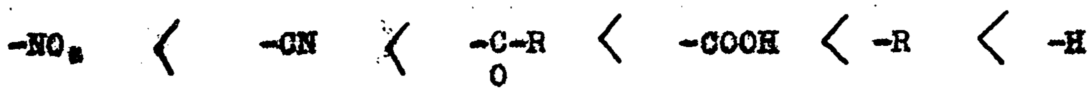
The unstable forms (2) and (3) easily isomerize to (1)

In the center portion of the series of the stabilizing groups, the order becomes hazy and indistinct. Nevertheless, the general scheme is valid. It will be observed that furfural diacetate is more stable than furfural and that the weakly unsaturated groups as acrylic radicals are definitely on the side of the series with the groups which give great stability. As was to be expected the carboxyl group when attached to the furan ring gives great stability to the compound.

Kharasch and co-workers (31) found that the nitrile group was one of the most negative in their series of electronegativities. In the present work it has been found that the nitrile group gives great protection to the furan nucleus. It is difficult to place the nitrile group as the most efficient protecting group but it appears to rank with, if not above, the nitro radical in its protecting influence.

In making this series, it was borne in mind that the arrangement of the series holds only for the present study. Another series of experiments might entirely change the arrangement. Indeed, it has not been overlooked that the nitro group, which appears to give great stability in this series, is the most sensitive group to alkaline reagents. This is discussed at greater length in the second portion of this work under the heading of "Removal of the Nitro Group".

It has been noticed that certain furan compounds tend to undergo decomposition with alkali. Furan and dimethylfuran have been observed to show marked stability toward bases. On the contrary, nitrofurans, α-furyl ketones and ketofuroic acids, and furoic acid show instability in the presence of alkalies. Thus parts of the preceding table of stabilizing groups would be reversed if basic media were used as the test criteria. Arranged in order of their stabilizing effect in basic media the groups should fall in line as follows:



$$-NO_2 < -CN < -\underset{O}{C}-R < -COOH < -R < -H$$

where R is an alkyl group. The free valence bond shows attachment of furyl group. This appears to be a reverse of the series for stabilities in acidic media. It is not complete and it should be further verified by very careful tests.

Perhaps the use of the stability of furan compounds reached its height in the identification of the compound in Chart IX labeled pseudo-furyl n-amyl ketone. In the course of the preparation of furyl n-amyl ketone by the acid hydrolysis of n-butyl furoylacetic ester, a product was obtained which appeared to be the desired furyl n-amyl ketone. Upon treatment as shown (Chart IX), it was observed to be too stable for the predicted behavior of furyl n-amyl ketone, but identical in its behavior with that of known n-butyl furoylacetic ester. Subsequent reëxamination disclosed the fact that the compound was indeed unchanged n-butyl furoylacetic ester. This points to the value that might be derived from use of a table of stabilities of furan compounds.

General Consideration of the Color Reactions and Stability of Furan Compounds.

Although there is no reaction which is a definite indication of the presence of a furan ring in an unknown compound, there is a sufficient number of recorded color changes at hand to aid in the identification of most known furan compounds by a comparison with a combination of color changes of a known specimen of the substance.

Many attempts have been made to develop color reactions for a certain group of furan compounds. Sohst and Tollens (33) found as Klinkhardt (34) had earlier found that dehydromucic acid yielded a red gelatinous precipitate with ferric chloride. Sohst and Tollens (33) also observed that 2-furoic acid gave a similar reaction. Unfortunately, however, Reichstein and co-workers found that the test was not general, and that it did not apply to beta-furoic acids (35) or certain polycarboxy-furans as furan tetracarboxylic acid (36). Another attempt to use a color reaction for certain furoic acids was unsuccessful. V. Meyer (37) used isatin and sulfuric acid to indicate the presence of thiophene. He found, however, that similar colors were developed by furoic acid. In a further study of this color reaction, Yoder and Tollens (38) found that although the violet color formed might be indicative of the presence of the furan ring, other compounds as calcium arabinate gave similar purples. Incidentally, it may be that the calcium arabinate underwent ring closure in the sulfuric acid, under the condition of temperature used (160 degrees), to yield a furan compound which then gave the typical violet of the isatin sulfuric acid test. However, the disqualifying fact still remains that thiophene gives a similar color.

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(33) Sohst and Tollens, Ann., 245, 20 (1888).
(34) Klinkhardt, J. prakt. Chem., 25, 46 (1882).
(35) Reichstein and Zschokke, Helv. Chim. Acta, 15, 268 (1932).
(36) Reichstein, Grussner, Shindler and Hardmeier, Helv. Chim. Acta, 16, 279 (1933).
(37) V. Meyer, Ber., 16, 1477 (1883).
(38) Yoder and Tollens, Ber., 34, 3461 (1901).

Thus, it appears that the attempts to develop color reactions for certain classes of furan compounds as acids have failed. Certainly, in the present work nothing was observed that would indicate a color reaction for any particular class of furan compounds.

The variety of colors that have been recorded in the various attempts to develop color reactions for furanic compounds has been one of the greatest handicaps to the successful solution of the problem. These varieties of colors are particularly noticeable in the attempt made by Asahina (16) to use vanillin and concentrated hydrochloric acid to yield red, yellow and violet colors, and in the attempt made by Reichstein (39) to develop the pine-splint reaction for furan compounds. This latter method utilizes concentrated hydrochloric acid. The colors obtained varied from green through permanganate to red.

These varieties of colors probably result because the furan ring is opened. The substances which yield the most pronounced colors are the more sensitive furan types. In general, the quite stable compounds do not yield a color test. An exception is apparent in the case of the furan α-carboxylic acids. These α-furoic acids yield salt-like substances with ferric chloride. The nucleus remains intact.

The unreliability of the aniline acetate test probably arises from the fact that the ring opens to yield quite similar

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(39) Reichstein, Helv. Chim. Acta, 15, 1110 (1932).

substances in methylfurfural, hydroxymethylfurfural and furfural (4, 5, 12, 26). Blanksma and Van Eckenstein (12) definitely showed that furfural and hydroxymethylfurfural yielded the same red color. In this test the ring has been shown definitely to open (26). Since strong mineral acids or highly active compounds are generally used in color tests for furanic compounds, it is undoubtedly the substances which result from the opening of the furan ring that yield the colors by either undergoing condensation and development of chromophore groups with foreign material as aniline, vanillin, constituents of the pine-splint, phenol or isatin on the one hand, or by development of chromophore groups in themselves on the other hand.

The color reactions, therefore, depend on the instability of the compound. It has been shown that the furan ring opens with uncommon ease under certain diverse conditions, such as in the presence of hydrochloric acid (40), in hydrogenations (41), and in forced reactions with hydrazine hydrate (42). In the drastic conditions generally utilized for production of colors in tests for the furan ring, the unstable furanic substances undoubtedly decompose to yield open chain products. In general, the more stable highly negatively substituted furans do <u>not</u> yield a color reaction until they are placed under conditions in which

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(40) H.P. Teunissen, Dissertation, Leiden, Holland (1929) "Snelheidsmetingen Bij De Opening Van Den Furaanring in Het Oxymethylfurfurol".

(41) Kaufman and Adams, <u>J. Am. Chem. Soc.</u>, <u>45</u>, 3029 (1923). See also, R. Takamoto, <u>J. Pharm. Soc. Japan</u>, <u>48</u>, 686 /<u>C.A.</u>, <u>23</u>, 387 (1928)/.

(42) Seka and Preissecker, <u>Monatsh.</u>, <u>57</u>, 81 (1931)/<u>C.A.</u>, <u>25</u>, 1826 (1931)/.

they are known to decompose. It seems now that any hope for developing a general color reaction for the furan nucleus must have as one of its bases conditions in which all furan compounds are known to decompose to yield substances which are capable of producing definite uniform colors when these decomposition products are subjected to the proper treatment. At the present time this requirement appears rather hopeless of realization.

The question of stability of furan compounds revolves about the ease with which the furan ring opens. It has been shown that the aldehyde group of furfural does not oxidize in air nor in oxygen. To show this, air and oxygen were slowly bubbled separately through two 25 gram portions of furfural for two weeks after the gas had been dried over sulfuric acid and passed over solid sodium hydroxide. The clear furfural became black and viscous. When the reaction was stopped the material was taken up in ether and extracted with dilute sodium hydroxide solution. On acidification after concentration and cooling of the aqueous portion, no acidic material precipitated. Five grams of furoic acid similarly treated yielded a quantitative recovery of the acid. However, benzaldehyde oxidizes practically quantitatively to benzoic acid under the same conditions.

An attempt to recover the furfural from the ether extract yielded only 10 grams of furfural. This result indicates that oxidation occurred at the ring in preference to oxidation at the aldehyde group. Anisaldehyde shows a similar behavior in that it does not undergo oxidation to the corresponding anisic acid as readily as benzaldehyde.

Thus any stabilizing substance must act in such a way as to stabilize the ring and thereby prevent oxidation and ring scission. In extended studies, Moureu and co-workers (24, 29, 43) found that easily oxidized substances as hydroquinone, pyrogallol and resorcinol, as well as the thioethers and certain compounds of cobalt, effectively stabilized the ring. If the theory of oxidation as propounded by Moureu and Dufraisse (24) is correct then the antioxidants act by "accepting" the oxygen and then releasing it. If such a continual cycle of reaction be granted, then it is easy to understand why the antioxidants are without effect in sealed tube studies such as have been reported here. See, Charts VI and VII. If there is no tendency toward oxidation, and there can be none in the absence of oxygen as in sealed tubes, then the supposed antioxidant is left free to either react with the substance under study as it does in the case of furfural thereby hastening decomposition or the antioxidant remains idle as it does in the case of furfuryl alcohol.

The highly negatively substituted furans are quite resistant to oxidation and ring opening and therefore they are stable under laboratory conditions.

The polymerization of furan compounds is quite indistinctly understood. The only definite, true case of polymerization of a furan compound has been described by Gilman and Hewlett (44).

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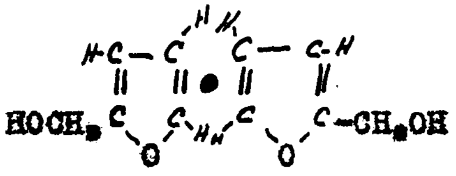
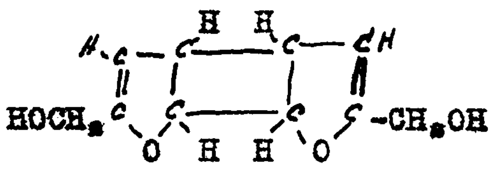
(43) Moureu, Dufraisse and Lotte, *Compt. rend.*, *180*, 993 (1925); Moureu, Dufraisee and Badoche, *ibid.*, *187*, 157 (1928); also see, Dufraisse and Nakae, *ibid.*, *194*, 880 (1932).

(44) Gilman and Hewlett, *Iowa State Coll. J. Science*, *5*, 19 (1930).

This is termed a true reversible polymer since by heating the original material, 2-furfuryl mercaptan, was regenerated. All other cases of polymerization appear to be either decomposition products or polymers of such a nature that they are not reversible. With sensitive compounds as furfural and furfuryl alcohol, the reactive aldehyde and carbinol groups, respectively, probably enter into the polymerization. It was shown that for furfuryl alcohol the disturbance is more deepseated than simple molecular addition (1) or attachment through the addition of double bonds (2).

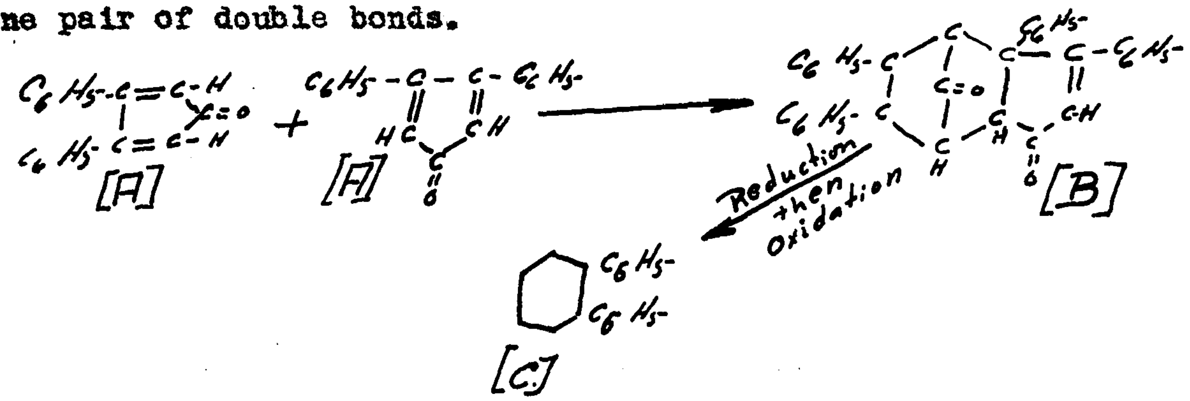


(1)



(2)

Allen and Spanagel (45) have quite recently shown that certain unsaturated cyclic compounds, as cyclopentadienone (A), undergo dimerization to yield a polymer (B) consisting of two molecules of the original cyclopentadienone connected through one pair of double bonds.



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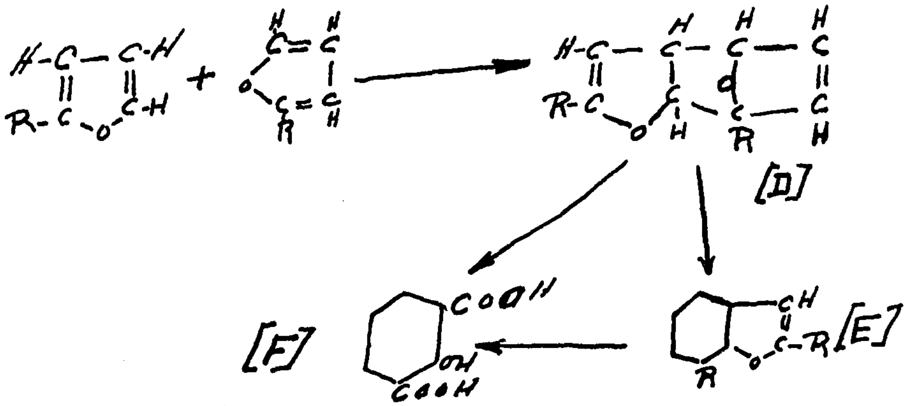
(45) Allen and Spanagel, J. Am. Chem. Soc., 55, 3773 (1933).

The structure of (B) was ultimately proven by converting the dimer to <u>ortho</u>-diphenylbenzene (C).

It is entirely possible that in the polymerization of furan compounds a similar dimerization may occur. Such a transformation would occur, perhaps, as follows for an alkylfuran:



It should be possible to establish this type of dimerization by converting (D) into either the coumaron (E) or the hydroxy-isophthalic acid (F). It is admitted that the chances for this type of dimerization to occur in furan are minimized by the fact that it appears that a diene and α,β-unsaturation to a carbonyl group are necessary for a polymerization as above to occur. That is, as Allen (45) points out, a compound displaying such a behavior is undergoing a diene synthesis with itself. Furan possesses an active diene structure (47). However, whether or not furan possesses a double bond of sufficient activity to behave as does the ethylenic unsaturation of maleic anhydride in the Diels-Alder Synthesis (47) is not known. It is possible, however, that both rings might add to each other in the 2,5-position.

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(47) Diels and Alder, <u>Ber.</u>, <u>62</u>, 557 (1929).

A Condensation Product of Furfuryl Alcohol.

In order to determine the nature of the change that occurred in furfuryl alcohol, several studies were made. When furfuryl alcohol was sealed for a long period of time, there were no apparent changes in the alcohol except that its solubility in water markedly decreased (46).

Fifteen grams of furfuryl alcohol was placed in a small flask. The flask was closed by means of a cork stopper. After three months the material in the flask had become thick and viscous. Solid particles were visible in the oily material. The resinous material was diluted with ether and filtered. A small quantity of a light brown solid was obtained. This solid was insoluble in water, ether and alcohol. It was soluble in acetone. Purification was effected by solution in acetone and precipitation by dilution of the solvent with alcohol. The melting point finally reached 118-122°. An attempt to distil the material to regenerate furfuryl alcohol led to complete decomposition.

By dilution with ether, this same substance was obtained from the residues from the distillation of furfuryl alcohol and from furfuryl alcohol that had been treated with a little 5 per cent aqueous hydrochloric acid. By extracting with acetone and

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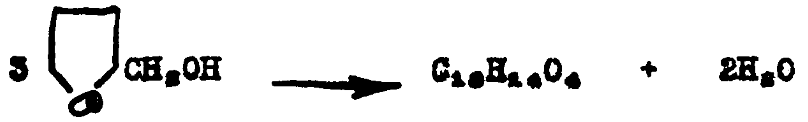
(46) As mentioned on page 14, this illusive problem of the change of water soluble furfuryl alcohol to water insoluble furfuryl alcohol was first shown by Erdmann (22). The other properties of the alcohol apparently do not change. It may be a phenomenon of dimorphism similar to the one observed by Zanetti and Kerr (J. Am. Chem. Soc., 48, 797 (1926)) for furfuryl furoate.

diluting with alcohol, this same substance was obtained from the solid cake that formed when furfuryl alcohol was exposed to the acid laboratory atmosphere for two years.

<u>Anal</u>. Calcd. for $C_{15}H_{14}O_4$: C, 69.74; H, 5.46. Found: C, 69.56, 69.27; H, 5.56, 5.33.

The analysis shows two definite things. First, it shows that three molecules of furfuryl alcohol combined by splitting out two molecules of water:



The molecular weight of the resulting compound was not taken since the main interest was an indication of the mode of decomposition. Secondly, the analysis shows that at least part of the decomposition is not a true polymerization. That is, the decomposition is not a molecular addition of any type or if it is, the addition is immediately followed by an elimination of water.

This observation is in line with that of Limpricht (20) as has been pointed out above (see page 13 of this thesis). He found that the oily resinous material from furfuryl alcohol had a composition which might result from the union of three molecules of furfuryl alcohol with the elimination of <u>one</u> molecule of water. The observation of Limpricht (20), together with the one here, would seem to indicate that the alcohol progressively split out water <u>after</u> union of three molecules of furfuryl alcohol. The reservation is made, however, that there is a possibility that the material reported here did not result from the intermediate compound reported by Limpricht.

SUMMARY AND CONCLUSIONS

1. A review of the literature shows that there is no adequate color test for the furan ring.

2. An attempt to develop one has not been successful, although an indication may be obtained by a combination of color tests.

3. Polymerization in furan chemistry is indistinct.

4. The stabilities of furan compounds may be systematized and made orderly.

5. Decomposition of furan compounds may be checked by use of appropriate stabilizers or by adequate sealing in inert atmospheres.

6. Furfuryl alcohol decomposes in such a manner that water is eliminated.

PART II

CONDENSATION REACTIONS OF FURFURAL AND ITS DERIVATIVES

HISTORICAL

As typical condensations, the Friedel-Crafts and Gattermann-Koch reactions have become of value in synthesizing alkyl and acyl derivatives of various substances. The original conception was that only aromatic hydrogens took part in a Friedel-Crafts (48) or a Gattermann-Koch (49) reaction. The flood of relatively recent work on the Friedel-Crafts reaction has shown that the hydrogens which enter into this reaction need not be attached to the aromatic nucleus.

However, the Friedel-Crafts reaction remains typically a reaction of aromatic compounds, judging from yields, ease of substitution and smoothness of reaction. This is true in spite of the fact that a miscellany of classes of compounds has been utilized in the Friedel-Crafts synthesis. The reaction has been applied with varying success to substitution in open chain aliphatic compounds (50), olefins (51), unsaturated cycloparaffins (52), saturated cycloparaffins (53), and the heterocyclic compounds as quinoline (54), pyrrole (55) and thiophene (56).

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(48) Ashdown, *J. Ind. Eng. Chem.*, *19*, 1063 (1927).

(49) Gattermann and Koch, *Ber.*, *30*, 1622 (1897); Gattermann, *ibid.*, *31*, 1149 (1898).

(50) Unger, *Ber.*, *65*, 467 (1932); von Braun and Kuhn, *ibid.*, *45*, 1267 (1912).

(51) Krapivin, *Bull. Soc. Imp. Nat. Moscow*, *1*, 176 (1908); /*Chem. Zentr.*, *1910*, I, 1335/; Norris and Couch, *J. Am. Chem. Soc.*, *42*, 2329 (1920).

(52) Wieland and Bettag, *Ber.*, *55*, 2246 (1922).

(53) Hopff, *Ber.*, *65*, 482 (1932) and *ibid.*, *64*, 2739 (1931).

(54) Matsumura, *J. Am. Chem. Soc.*, *52*, 4433 (1930).

(55) Fischer and Schubert, *Z. Physiol. Chem.*, *155*, 99 (1926).

(56) Steinkopf, *Ann.*, *430*, 78 (1923); Stadnikoff, *Ber.*, *61*, 2341 (1928).

The Gattermann-Koch reaction has not been as intensively studied as the Friedel-Crafts reaction. In truth, the Gattermann-Koch reaction is a special case of the Friedel-Crafts reaction by means of which formyl groups are introduced into aromatic nuclei (49) using either the hypothetical formyl chloride or formimine chloride (hydrocyanic acid with hydrogen chloride) with or without a condensing agent. Quite unscientifically and altogether inaccurately, the Friedel-Crafts reaction has come to mean the introduction of alkyl or acyl groups into all types of compounds by a variety of condensing agents and in a miscellany of solvents. It would be much more nearly correct to speak of the *class* of Friedel-Crafts *reactions*. There seems to be no end to the variety of transformations that may be effected by means of vigorous condensing agents like aluminum chloride (57). This halide was the original Friedel-Crafts condensing agent, but it is now one of a number of substances that may be used for efficient condensations. The confusion that has developed concerning the Friedel-Crafts reaction is an excellent example of the danger involved in naming reactions after their discoverers.

Throughout the present work the term Friedel-Crafts reaction will be used to indicate either alkylation or acylation. The exact conditions will be indicated where necessary. The Gattermann-Koch reaction is understood to indicate the introduction of formyl groups by either formyl chloride or formimine chloride.

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(57) G. Kränzlein, "Aluminiumchlorid in der Organischen Chemie", Verein Deutscher Chemiker, Berlin, 1930.

Previous Work on Furan Compounds.

Historically it is worthy of note that the first Friedel-Crafts reaction was probably carried out with a furan compound in 1894. Magnanini and Bentivoglis (58) synthesized 2,5-dimethyl-3-acetylfuran from succinic acid, acetic anhydride and zinc chloride. These authors believed that the complete condensation occurred simultaneously to yield the desired product. Actually, the succinic acid may have condensed with the acetic anhydride to yield a 1,4-diketone dicarboxylic acid which immediately split out water and carbon dioxide to yield 2,5-dimethyl furan. This furan compound and acetic anhydride then underwent condensation in the presence of zinc chloride to yield the 2,5-dimethyl-3-acetyl furan.

In 1901, Hill, Phelps and Hale (59) utilized dehydromucyl chloride to synthesize α,α'-dibenzoyl furan. Benzene was used as a solvent and aluminum chloride was the condensing agent. King (60), in 1927, attempted to condense benzene with furoic acid. He obtained a product which he described as 3-phenyl-2,3-dihydro-2-furoic acid.

The first well defined work on substitution in the furan nucleus by means of the Friedel-Crafts reaction was accomplished as recently as 1930 by Reichstein (61). In a single short article he described the synthesis of several furan ketones.

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(58) Magnanini and Bentivoglis, *Gazz. chim. ital.*, *24*, 435 (1894).
(59) Hill, Phelps and Hale, *Am. Chem. J.*, *25*, 457 (1901).
(60) King, *J. Am. Chem. Soc.*, *49*, 565 (1927).
(61) Reichstein, *Helv. Chim. Acta*, *13*, 356 (1930).

By his method he was able to isolate furyl methyl ketone (yield 13 to 34 per cent), 2-methylfuryl-5-methyl ketone (yield 15 per cent) and a minute quantity of difuryl ketone. Simultaneously, Reichstein (62) reported a series of aldehyde syntheses in furan compounds. He found that in general the formyl group would enter the furan nucleus easily if the ring did not contain a negative group or two α-substituents. More recently Reichstein has utilized this Gattermann-Koch reaction to synthesize 3,5-dimethyl-2-furoic acid and 3-methyl-2-furoic acid (63) as well as 5-isopropyl-2-furoic acid (64).

In general, this earlier work tended to disfavor hope of utilizing the Friedel-Crafts reaction for the preparation of large quantities of acyl or alkyl furan. In fact, no attempts were made to alkylate a furan by means of the Friedel-Crafts reaction. All attempts to utilize this reaction were attempts to acylate furan compounds.

Recently, Gilman and Calloway (65) have shown that the furyl alkyl ketones may be obtained in good yields by means of the Friedel-Crafts reaction. The novel and surprising observation was reported that furan ketones, aldehydes and esters undergo acylation and alkylation. The analogous reactions have not been reported for the corresponding unsubstituted benzene compounds. This work is discussed at great length under the heading

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(62) Reichstein, Helv. Chim. Acta, 13, 345 (1930).
(63) Reichstein, Zschokke and Georg, ibid., 14, 1277 (1931).
(64) Reichstein, Zschokke, Gehring and Rona, Helv. Chim. Acta, 15, 1118 (1932).
(65) Gilman and Calloway, J. Am. Chem. Soc., 55, 4197 (1933).

"Observations and Discussion".

All in all, the history of the carefully studied condensation reactions of furfural and its derivatives, such as the Friedel-Crafts and Gattermann-Koch reactions, has been a short one. The results are meagre and far from complete.

OBSERVATIONS AND DISCUSSION OF RESULTS

Friedel-Crafts Reaction with Furan.

Acylation. It was found that furan could be acylated to yield alkyl ketones in yields of 50 per cent and better. Various condensing agents have been found of value but ferric chloride and aluminum chloride gave superior yields. Aluminum chloride is undoubtedly the best condensing agent to use for acylation of furan by acyl halides. It is easily handled, gives excellent results, and it is easily washed from the mixture which results from the reaction. Aluminum chloride is cheap and it utilizes acyl halides in acylations. Acyl halides are cheaper than the anhydrides used with the less agreeable ferric chloride. E. V. Brown (66) in recent studies has found that ferric chloride gives excellent yields (50 per cent) of 2-furyl methyl ketone. By this means, furan is condensed with acetic anhydride in carbon disulfide. It was not possible to introduce the carboxyl group into furan using ethyl chlorocarbonate. Neither was it possible in the present study to synthesize difuryl ketone or furoic acid using phosgene.

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(66) E. V. Brown, Unpublished Work.

It was not possible to acylate furan using phthalic anhydride or phthalyl chloride.

Physiological Action of Furyl Alkyl Ketones.

By the method previously described (65) a series of 2-furyl alkyl ketones was synthesized. These ketones were found to be generally water insoluble and without hypnotic action although they were toxic to the experimental animals (65). The ketones studied were the furyl ketones with the following alkyl groups: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *n*-amyl. For the water solubility of these ketones see experimental part. The behavior shown here was not like that of the phenyl alkyl ketones which are hypnotics.

Gilman, Rowe and Dickey (67) have recently determined that certain aromatic ketones have no hypnotic effect. Methyl pyrryl ketone was weakly hypnotic in large doses. The corresponding furyl methyl and thienyl methyl ketones were without action. These latter ketones were found to be toxic to the test animals (dogs).

The synthesis of furyl chloromethyl ketone was effected in order to determine its lachrymatory action. It was found to be a powerful, persistent lachrymator. It approaches but is not equal to furoyl chloride in this respect, if one may judge from a crude comparison.

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(67) Gilman, Rowe and Dickey, *Rec. trav. chim.*, 52, 395 (1933).

Alkylation of Furan.

It was found impossible to isolate an alkylated furan in any of the many attempts made to alkylate directly unsubstituted furan. The failure may be in part due to a brown coating which always formed on the condensing agent when attempts were made to alkylate furan. In one case, an attempt was made to use furan as a solvent, but the difficulties were not removed. No product was obtained and 80 per cent of the furan was recovered.

The Acylation of Methyl Furoate.

As has already been reported (65), methyl furoate may be acylated in benzene by acid anhydrides and stannic chloride. The benzene as a solvent in this case is interesting. It has been found that the benzene is actually acylated but very slowly. The methyl furoate is acylated much more rapidly. However, an attempt to acylate methyl furoate with aluminum chloride and acetyl chloride was not successful even when the reaction was refluxed for 5 hours. It was not possible to acylate methyl furoate with phthalic anhydride under the conditions used.

The Alkylation of Methyl Furoate.

As has been reported (65), methyl furoate alkylates in the 5-position to yield alkylfuroic esters. The yields are good and the reaction is a simple one. This offers a means of obtaining the alkylated furoic acids in quantity from a simple furan derivative. There are some limitations to this synthesis, however. All attempts to introduce an alkyl group with less than three carbon atoms were not successful. There is no ready explanation for this peculiarity. However, it may be a function of the nature of the complex which formed between the aluminum chloride, alkyl halide and the alkyl furoate. All attempts to synthesize methyl 2-methyl- or 2-ethylfuroate were futile. The attempt to synthesize an alkylated product of methyl furoate, by alkylating it with ethylene bromide was likewise unsuccessful. Another limitation to this synthesis is the strong tendency for the alkyl halide to rearrange to highly branched compounds so that it is difficult if not impossible to obtain normal-chain compounds. This is undoubtedly the result of the action of the active metal halides. The rearrangement tendency prohibits the synthesis of *n*-alkyl compounds. There is a possibility that these normal-chain compounds are formed in very small yields and were not observed in the fractionations.

By means of these alkylations of the alkyl esters followed by hydrolysis to the corresponding acid, an approach is obtained to the simple alkyl furans. By decarboxylation according to Johnson's (65) method the alkylfurans may be obtained in good yields. Methyl benzoate will not alkylate under similar conditions.

These alkylated furoic acids were found to have germicidal action. Of a large group of substances tested, the alkylfuroic acids gave promise as the best furan germicides. The *tert*. (?)-5-amyl-2-furoic acid possessed a phenol coefficient of 22. It was observed that as the side-chain became longer the more efficient was the acid as a germicide. The high degree of branching in the side chain undoubtedly lowered the germicidal activity. Similar observations on the effect of length and isomerization of the side chain have been made for antiseptics in general (68).

Methyl furoate was also alkylated with butylene.

The Acylation of Furfural and Furfural Diacetate.

All attempts to acylate furfural were unsuccessful. Complete decomposition occurred and no furfural was recovered. The same failures attended the attempts to acylate furfural diacetate.

Alkylation of Furfural.

The attempt to alkylate furfural was more successful than the attempt to acylate it. In a previous report (65) it has been mentioned that a product was isolated which analyzed for an alkyldihydrofurfural or an opened ring product. Evidence recently obtained tends to show that the product may be neither of these.

The compound obtained upon oxidation of the aldehyde with silver oxide was an acid. It contained neither aldehyde, ketone nor hydroxyl group. Its analysis was close to that expected for a dihydroisopropylfuroic acid. However, the acid took up one atom of bromine with evolution of hydrogen bromide. This

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(68) Ishiwara, *Z. Immunitäts.*, *40*, 429 (1924) [*C.A.*, *19*, 999 (1925)]; Tilley and Schaffer, *J. Bact.*, *12*, 303 (1925); V. Leonard, *J. Am. Med. Assoc.*, *83*, 2005 (1924).

bromine was not removable by boiling alcoholic potassium hydroxide.

It has been shown by Hill and co-workers (59) that dihydro furoic acids will add bromine to the remaining double bond. This fact minimizes the chance that the acid concerned in this work is a dihydro compound. The fact that the bromine atom was not removable by hot alcoholic potassium hydroxide is evidence that the bromine atom is nuclear. The absence of ketone, aldehyde or hydroxyl groups minimizes the chances of this product being an opened ring substance since analysis shows that no carbon or oxygen was lost in the transformations. It is far removed from the present ideas regarding substitution in furan compounds, to believe that the acid here is *beta*-isopropyl-2-furoic acid, but such a structure is possible.

Acylation and Alkylation of Nitrofuran and Methyl Nitrofuroate.

It is general knowledge that the nitro group notoriously prohibits substitution in the benzene ring by means of a Friedel-Crafts reaction. The success that was obtained in introducing groups into carboxyfurans and aldehydofurans as well as in ketofurans (65), led to hopes that the same ease of substitution would be observed for nitrofurans. Unfortunately, this was not true. Of a large number of reactions with various condensing agents only one gave a definite product. In some cases the nitrofuran was partly recovered unchanged. In the one case that a definite reaction did occur, it was found that the condensing agent used, titanium tetrachloride, had removed the nitro group and had introduced a chlorine atom in its place. This chlorofuran then underwent a normal acylation to yield as the final product a chlorofuryl alkyl ketone.

All attempts to alkylate nitrofuran were futile.

Attempts to duplicate the above acylation with methyl nitrofuroate were unsuccessful.

Removal of the Nitro Group.

The removal of the nitro group of nitrofuran led to attempts to determine how general the phenomenon was. As mentioned above methyl 5-nitro-2-furoate resisted attempts to remove the nitro group when the substance was treated with titanium tetrachloride and propionyl chloride in carbon disulfide solution. Even boiling failed to show any effect on the nitro group.

Similar attempts to react nitrobenzene, *p*-nitroanisole or α-nitronaphthalene were unsuccessful.

The furan nitro group has been generally observed to be labile. It is removed from dinitrofuran with uncommon ease by alkali to yield nitrites and maleic acid as the principal products (69). The observation that it is removed from nitrofuran at 0° by titanium tetrachloride was quite a surprise. Generally the nitro group is considered stable and difficult to remove or replace (70). In this connection it is to be observed that E. V. Brown (71) has recently found that the

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(69) Hill and White, *Am. Chem. J.*, *27*, 198 (1902).
(70) De Lange, *Rec. trav. chim.*, *46*, 20 (1926).
(71) E. V. Brown, unpublished work.

nitro group is removed from ethyl 5-nitro-2-furoate at high temperatures by phosphorus pentachloride. The lability of the nitro group attached to the furan nucleus is of more than passing importance. This lability undoubtedly results from the extreme negativity of the furan ring.

Acylation of 3,4-Dicarbomethoxyfuran.

3,4-Dicarbomethoxyfuran was found to acetylate to yield a 2-acetyl-3,4-dicarbomethoxyfuran. This was of interest since all attempts to carry out other substitution reactions on this ester have been futile (72).

Acylation and Alkylation of 2,5-Dicarboethoxyfuran.

All attempts to force a substitution by means of the Friedel-Crafts reaction with 2,5-dicarboethoxyfuran failed. This ester that is notoriously resistant to substitution in such reactions as nitration not only failed to alkylate or acylate but it was recovered practically quantitatively.

The Friedel-Crafts Reaction with di-alpha-Substituted Furans.

Sanborn (73) found that 2,5-dimethylfuran would acylate to yield ketones when ferric chloride was used as a condensing agent. In the present study in an attempt to utilize stannic chloride to condense 2,5-dimethylfuran and acetic anhydride, it was found that the yield was 50 per cent. when no particular

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(72) Unpublished studies by Kirkpatrick and Burtner.
(73) See, Gilman and Calloway, J. Am. Chem. Soc., 55, 4204 (1933).

caution was used to obtain optimum yields. The yield, no doubt, can be increased markedly.

In an attempt to determine the orientation when a substituent was introduced into a di-alpha-substituted furan with unlike substituents, Gilman, Calloway and Smith (74) found that the acyl group entered a position contiguous to a substituent with ortho directing influence in benzene. It was shown that on acylating ethyl methylfuroate the acyl group entered the beta-position adjacent to the methyl group. Oxidation of the acetyl compound to the corresponding methyl-dibasic acid and subsequent decarboxylation yielded 2-methyl-3-furoic acid. This last mentioned compound proved the orientation definitely. An attempt to acylate ethyl 5-bromo- or chloro-2-furoate was not successful.

Acylation and alkylation of Furfuryl Methyl Ether.

All attempts to acylate or alkylate furfuryl methyl ether were unsuccessful. The reaction mixture became black and hard. No acylated or alkylated product was obtained.

Acylation and Alkylation of Furfuryl Acetate.

From several runs, nothing was isolated except a hard black tar and a small portion of unchanged material.

The Gattermann-Koch Reaction.

Attempts were made to introduce the formyl group using

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(74) Gilman, Calloway and Smith, J. Am. Chem. Soc., 56, 0000 (1934)/January/.

liquid hydrogen cyanide and gaseous hydrogen chloride with and without a condensing agent. Several runs were made on 2-methyl-3-furoic acid, ethyl 2-methyl-3-furoate and 2,5-dimethylfuran. No aldehyde compounds were isolated although reaction appeared to occur in some cases. This confirms the views of Reichstein (62) that negatively substituted furans and di-alpha-substituted furans do not undergo acylation by the Gattermann-Koch reaction.

The Relative Strengths of Various Condensing Agents.

If one were to judge from general consideration of the Friedel-Crafts reaction in furan compounds, the following series of condensing agents may be considered to be arranged in order of their decreasing activity in acylations.

$$SnCl_4 > FeCl_3 > AlCl_3 > TiCl_4$$

As alkylating agents the reverse order probably holds, as follows:

$$AlCl_3 > FeCl_3 > SnCl_4$$

It must be admitted that these series probably are not rigid. As is true with any series of activities, they may vary with varying reactants as well as with diverse conditions. There is not enough material available to make any predictions concerning the effect of the various substances in decomposing the reactants. There appears to be material to favor the view that ferric chloride has a less deleterious effect on the sensitive furan compounds than has aluminum chloride. This view is far from being verified.

It is an established fact (see, part I of this thesis) that similar compounds may exhibit different stabilities when treated with either the same substance or a variety of substances that cause decomposition.

A series of condensations was carried out to determine what other metal halides might be used to effect a Friedel-Crafts condensation with furan. Some free metals were also used. It was found that of the substances tried, mercuric chloride, titanium tetrachloride, metallic zinc and tin were the only effective ones. Sodium chloride, calcium chloride and silicon tetrachloride were without effect.

Wertyporoch (75a) has recently reported a study on the various metal halides as condensing agents in the Friedel-Crafts reaction. He found that in alkylation of benzene, mercuric chloride, titanium tetrachloride and stannic chloride among others were without effect even when the reactions were heated.

In the present case it is interesting to notice that certain metals are of value. The two metals which proved of value in this instance were tin and zinc. The halides of both these metals are of value as condensing agents in the Friedel-Crafts reaction. Peculiarly, aluminum was without effect.

Relative Ease with which Various Groups are Introduced by the Friedel-Crafts Reaction.

It appears that in general it is easier to alkylate furan compounds than to acylate them. This is true in spite of the fact that furan itself does not alkylate. The conditions for alkylation are in general milder than the corresponding conditions for acylation. For example, methyl furoate undergoes

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(75a) Wertyporoch, Ber., 66, 1232 (1933).

certain alkylations (65) in good yield at 0°. It does not undergo ready acylation at that temperature.

The difficulty of introducing an alkyl group apparently increases with increasing molecular weight of the alkyl halide. The isopropyl halides enter with much greater ease than do the amyl or hexyl halides.

The short-chain alkyl groups have another advantage. As has been pointed out above, the entering alkyl groups tend to isomerize to highly branched chains. It is apparent then that the fewer the carbon atoms the smaller the number of isomers than can form.

Relative Inhibiting Effect of Various Groups Present in Furan on the Friedel-Crafts Reaction.

As is well known the carbonyl group generally prohibits substitution in the benzene nucleus by the Friedel-Crafts reaction. The nitro group has an even more marked prohibitory action. That this action is not one of complex formation is shown by the fact that furanic esters, aldehydes and ketones undergo the Friedel-Crafts reaction (65). Furthermore, certain benzenoid types containing carbonyl groups and activating groups as the hydroxyl (65, 75b) undergo the Friedel-Crafts reaction. Certain derivatives of anisic acid are examples of this latter class of compounds.

(75b) Unpublished work.

These observations fall in line with those of Kharash and co-workers (31). These investigators point out the previously observed fact that such groups as the carboxyl and nitro groups hinder substitution while groups such as amino and hydroxyl promote substitution.

It seems ~~that~~ from a consideration of the general ease of furan substitution by the Friedel-Crafts reaction that the following order represents the relative "interference value". This series is arranged in order of decreasing inhibiting action.

$$-\mathrm{NO_2} \;>\; -\mathrm{COOR} \;>\; \left\{\begin{array}{l} -\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-\mathrm{R} \\ -\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-\mathrm{H} \end{array}\right\} \;>\; \left\{\begin{array}{l} -\mathrm{Br} \\ -\mathrm{Cl} \end{array}\right\} \;>\; -\mathrm{R} \;>\; \left\{\begin{array}{l} -\mathrm{NH_2} \\ -\mathrm{OH} \end{array}\right.$$

[marked inhibition] [activation]

The R represents an alkyl group.
The free valence represents attachment of furan ring.

The hydroxyl and amino groups were not studied in this series, but it is wise to include them since the hydroxy (76a) and aminofurans (76b) and their derivatives are now becoming accessible.

It will be noticed that the nitro group is the most inhibiting group present. Thus on the left hand side of the table the action of the group is entirely prohibitory. No Friedel-Crafts reaction has ever been reported with an aromatic nucleus containing the nitro group. The right hand end of the series represents actual activation of the nucleus.

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(76)(a) Unpublished work by Hoehn.
(b) Unpublished work by Burtner.

Super-aromaticity of Furan as Indicated by Condensation Reactions.

The recent suggestion that furan has super-aromatic properties (77, 65, 78, 79) has found support in the alkylation and acylation of furan compounds (65). The evidence first offered (77) was the relative ease with which furyl nuclei are removed from furyl-phenyl-lead compounds. The second list of evidence obtained was the ease with which furan compounds such as methyl furoate undergo alkylation. Combined with this latter fact were the facts that furyl phenyl ketone alkylated on the furan nucleus and that furan compounds could be acylated in good yields using benzene as the solvent (65).

More recently (78) the relative ease of nitration in the furan nucleus as compared to the benzene ring in a symmetrical compound like furyl phenyl ketone has been offered as additional evidence of the super-aromaticity of furan. Further evidence has been found in the ease with which sodium displaces the alpha-hydrogens (79).

The point of interest in the present work is the fact that in the studies on the acetylation of furan in benzene as a solvent, there is formed a small quantity of acetophenone. It points to the well known case of relative rates of reaction. In the previous use of benzene as a solvent for Friedel-Crafts

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(77) Gilman and Towne, Rec. trav. chim., 51, 1054 (1932).
(78) Gilman and Young, J. Am. Chem. Soc., 56, 0000 (1934).
(79) Gilman and Breuer, J. Am. Chem. Soc., 56, 0000 (1934).

reactions in synthesis of furan (61) and thiophene (80) compounds no mention has been made of the slight reaction of benzene. This slow acylation of benzene proves definitely that there is nothing particularly specific about the acylation of furan compounds with stannic chloride and acetic anhydride and that the furan compounds react more rapidly than unsubstituted benzene. This latter fact indicates that there is nothing inherently peculiar about the rapid and easy substitution in furan compounds. Super-aromaticity as observed in substitution reactions becomes entirely a matter of relative rates of reaction.

In this connection, it is interesting to note that Stenhouse (81) was probably the first person to apply the term aromatic to furan compounds.

Orientation and Reliability of the Friedel-Crafts Reaction with Furan Compounds.

The general observation in furan chemistry that substituents always enter an alpha-position if one is open applies to substitution by means of the Friedel-Crafts reaction. In every authentically determined orientation in a substance resulting from alkylation or acylation of a mono-alpha-substituted furan, the entering group has been found to enter the open alpha-position except possibly in the alkylation of furfural.

The orientation of entering groups in di-alpha-substituted

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(80) Stadnikov and Goldfarb, Ber., 61, 2341 (1928).
(81) Stenhouse, Ann., 35, 303 (1840).

furans has been discussed above.

No case of nuclear rearrangement has been observed in condensation reactions of furan compounds. The Friedel-Crafts and Gattermann-Koch reactions appear entirely reliable in substitution reactions as far as reliability concerns the position of the entering groups. The only noted rearrangement (65) occurred in attempts to alkylate furan compounds. The rearrangement, however, confined itself to a change in the branching of the alkyl groups. The alkyl group introduced was always found to have the most branched configuration possible. (See, Alkylation of Methyl Furoate, page 62) No movement or isomerization of a group already present has been found. In no case was it observed that the alkyl portion of an acyl halide or anhydride rearranged. These observations are in line with the one recently made (82) that the Friedel-Crafts reaction is often abused in regard to its unreliability.

It is only fair to mention here that the solvent used in these studies with aluminum chloride was carbon disulfide. This liquid seems to be a somewhat specific solvent for the Friedel-Crafts reaction. It appears to limit and inhibit rearrangement (82), besides giving excellent yields of product as compared to other solvents on the whole.

< (82) Ruzicka, Pieth, Reichstein and Ehmann, <u>Helv</u>. <u>Chim</u>. <u>Acta</u>, **16**, 275 (1933).

EXPERIMENTAL

General Technique.

Unless otherwise stated the following general set-ups for the apparatus were used.

Set-up No. 1. An appropriate sized three-necked round-bottomed flask was selected so that it would be approximately half-filled with reaction mixture. The flask was supported by a ringstand. One neck of the flask bore a reflux condenser which led through a 6 inch calcium chloride tube to a suitable trap. The middle neck carried a mercury sealed mechanical stirrer. The third neck was fitted with a dropping funnel or other suitable means of adding the reactants.

Cooling was effected by an ice bath. Heating was obtained by means of a water bath on a warm hot plate.

Warning. There is extreme danger of fire in handling certain solvents as carbon disulfide near hot objects.

Set-up No. 2. The reaction was placed in a suitably sized wide-mouthed Erlenmeyer flask closed by a rubber stopper bearing a calcium chloride tube. It was found that heating at a constant temperature for a long period of time could be effected easily by placing the flask on a drying oven. The flask was placed on the necessary and suitable heat insulation, as asbestos squares and cork rings.

In every case where the Erlenmeyer flask was used, benzene was the solvent. The procedure used was as follows: The required amount of benzene was placed in the flask and the other reactants added. The condensing agent, stannic chloride in these cases, was added last with or without cooling as the case demanded. The flask was shaken during the rapid addition of the condensing agent. It was added from a dropping funnel mounted in a two-holed rubber stopper which carried a calcium chloride tube.

The Acylation of Furan.

Preparation of Furyl Alkyl Ketones.

The preparation of the furyl alkyl ketones was carried out as recently described (83). The furan was prepared in accordance with the newly described rapid method (84). It was dried over calcium chloride and distilled. Incidentally, furan may be distilled from phosphorus pentoxide.

The following preparation of 2-furyl chloromethyl ketone gives the general directions for acylation of furan with acyl halides.

Using set-up No. 1, 22.6 grams (0.2 mole) of freshly distilled chloroacetyl chloride was added dropwise with stirring to 26.6 grams (0.2 mole) of aluminum chloride in 250 cc. of carbon disulfide previously dried with calcium chloride. After the reaction had stirred at room temperature for 20 minutes, the flask was cooled to 10° C, and 13.6 grams (0.2 mole) of furan was added over a ten minute period with stirring. There was a

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(83) Gilman and Calloway, J. Am. Chem. Soc., 55, 4200 (1933).
(84) Gilman and Lousinian, Rec. trav. chim., 52, 156 (1933).

vigorous evolution of hydrogen chloride. The ice bath was removed and the mixture was stirred for 5 minutes at room temperature. The material was then poured over cracked ice (hood) and the solid material was quickly filtered off by suction. The residue on the filter was washed with two portions of carbon disulfide. The carbon disulfide layer was rapidly separated from the aqueous portion; dried over sodium sulfate; and the solvent was removed by distillation on a water bath.

The residual oil was fractionated under reduced pressure. There was obtained 6 grams of an oil which boiled at 127-129°/27 mm. This was 20.7 per cent of the theoretical amount. d_{25}^{25}, 1.340; n_D^{25}, 1.5091. It solidified in the ice box.

Anal. Calcd. for $C_6H_5O_2Cl$: Cl, 24.56. Found: Cl, 24.99.

This substance is a powerful lachrymator. It produces intense burning of the membranes of the eyes and of the nose. It burns the skin without blistering.

Following the same general directions, attempts were made to acylate furan using phthalyl chloride, phthalic anhydride, and ethyl chlorocarbonate. These reactions were unsuccessful. In the case of the phthalyl chloride and phthalic anhydride, an almost quantitative yield of phthalic acid was obtained. With ethyl chlorocarbonate a small quantity of the acyl halide was obtained.

Attempts to acylate furan using ethyl chlorocarbonate with the following condensing agents were also futile: stannic chloride, ferric chloride, and phosphorus pentoxide (85).

Attempted Preparation of Difuryl Ketone.

In an attempt to acylate furan with carbonyl chloride to give either or both difuryl ketone or furoic acid no acylated product was found. Using set-up No. 1 in a tenth-mole run as above, to the aluminum chloride and carbon disulfide, carbonyl chloride was introduced for 20 minutes at 0° C. The furan was then added dropwise. The reaction became brown. There was no evolution of hydrogen chloride. After four hours at room temperature the reaction was worked up by hydrolizing with cracked ice. The separated, washed and dried carbon disulfide left no residue when distilled from a water bath.

A re-run using benzene as the solvent and stannic chloride as the condensing agent had the same outcome as the previous run.

In another run using 200 cc. of dry furan as the solvent and one-tenth mole of aluminum chloride as the condensing agent, 160 cc. of furan was recovered. No higher fractions or solid appeared.

Solubility of the Furyl Alkyl Ketones.

A series of furyl alkyl ketones was prepared according to the above directions which are essentially those recently published (65) for the same ketones. The solubilities were determined in a relatively crude style but it was an attempt to

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x (85) Steinkopf, Ann., 430, 105 (1923).

determine a limiting factor for use in studies on physiological action of the ketones.

One-tenth gram of the various ketones was placed in a 1 x 7 inch test tube. Water at 30°C was added until the ketone disappeared on shaking. The solubilities expressed in per cent are as follows: furyl methyl ketone, 1.25; furyl ethyl ketone, 1.0; furyl *n*-propyl ketone, 0.5; furyl isopropyl ketone, 0.5; furyl *n*-butyl ketone, 0.2; furyl *n*-amyl ketone, 0.05.

It was hoped that as the alkyl group became longer and water solubility decreased the increased lipoid solubility would promote hypnotic action. The results were disappointing. Although the toxicity of these ketones (see, page 60) indicates physiological action, it is not a hypnotic effect.

The Alkylation of Furan.

All attempts to alkylate furan were futile. It was found that in attempts to alkylate furan no alkyl group could be introduced whether it contained a completely saturated carbon chain, as in the butyl halides, or an unsaturated portion, as a carbomethoxy group as in ethyl chloroacetate.

Using set-up No. 1, 18.5 grams (0.2 mole) of *n*-butyl bromide and 13.6 grams (0.2 mole) of furan were added together to 26.6 grams (0.2 mols) of aluminum chloride under 200 cc. of carbon disulfide cooled to -15°C. Addition was dropwise and with constant stirring. No hydrogen chloride was evolved. The ice-salt bath was removed and the reaction was allowed to stand at room temperature for 2 hours.

There seemed to be a pellicle formation around the particles of aluminum chloride. This was apparently a complex of a probable polymeric structure. It was brown in color and did not show any change on subsequent hydrolysis of the reaction. It decomposed leaving a residue when heated to a high temperature.

The contents of the flask were poured over 200 grams of cracked ice, and made alkaline. The mixture was then placed in a 2 liter round-bottomed flask and the volatile liquids were removed by distillation by the steam generated in the flask. The organic solvent layer was separated from the aqueous layer and dried over sodium sulfate.

Fractionation through a 12 inch column yielded only a liquid which boiled between 43-48°. It was impossible to separate any fractions on repeated fractionation. The last portion, 5 cc., of the distillate was added to 10 grams of mercuric chloride, 15 grams of sodium acetate and 200 cc. of water and 15 cc. of alcohol, shaken vigorously, and allowed to stand for 24 hours. No precipitate formed. This was a good indication that there were no mono alkyl furan bodies present. Evidently no alkylation occurred in this reaction.

<u>Alkylation of Furan using Furan as a Solvent</u>.

A similar set-up was used as for the previous run. A large surplus of furan served as the diluent.

To 100 cc. of furan, in a (set-up No. 1) three-necked balloon flask surrounded by an ice bath there was added 9.25 grams (0.1

mole) of n-butyl chloride. Thirteen and three-tenths grams (0.1 mole) of aluminum chloride was then added in small portions with vigorous stirring. No hydrogen chloride was evolved.

The ice bath was removed when all of the aluminum chloride had been added and the reaction was heated on the water bath for two hours at a gentle reflux. There was a neglible evolution of hydrogen chloride.

The mixture was worked up as in the previous run. Practically all the liquid fractionated below 33°. There was a small quantity, 4 grams, which boiled 45-77°/atm. This was butyl halide, probably rearrangement products. These yielded the wide range of boiling points.

No fraction which might have been a butylfuran was isolated. Attempts to prepare mercurials of the higher fraction were futile.

Alkylation of Furan by Ethyl Chloroacetate.

In the usual set-up there was placed 26.6 grams (0.2 mole) of aluminum chloride and 75 cc. of carbon disulfide. To this was added 12.6 grams (0.1 mole) of ethyl chloroacetate. An oily complex formed.

There was now added dropwise (with cooling to 15°) 6.8 grams (0.1 mole) of cold furan. The reaction turned black and evolved a very small quantity of hydrogen chloride. As soon as the furan was added, the reaction mixture was poured over 200 grams of cracked ice and worked up as in the runs with methyl furoate. Two grams of ethyl chloroacetate were recovered.

Three attempts were made to reduce the activity of the aluminum chloride by using nitrobenzene (86). One run was made as in the latter case except that 0.2 mole of nitrobenzene was allowed to react with the aluminum chloride. To this mixture was added 0.2 mole of furan and 0.2 mole of butyl halide. No alkylated product resulted.

The quantities of nitrobenzene were increased until the solvent used was pure nitrobenzene. This did not help matters. No alkylated furan was obtained in any case.

Preparation of Methyl Furoate.

Although several methods have been described for the preparation of alkyl esters of furoic acid (87, 88, 89), there was no method which gave rapid results on a large scale continuous process. As the result of 28 experiments the following was found to give the best, quick results for large quantity preparations of ethyl and methylfuroates.

Two hundred and twenty-four grams (2 moles) of commercial furoic acid was mixed with 480 grams (15 moles) of methyl alcohol. Fifty grams (0.5 mole) of concentrated sulfuric acid was added and the mixture was refluxed for five hours. The condenser was closed by a calcium chloride tube. After cooling, the mixture was steam distilled. The excess alcohol was saved

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x (86) Rosenmond and Schulz, <u>Arch. Pharm.</u>, <u>265</u>, 308 (1927).
(87) Hill and Sylvester, <u>Am. Chem. J.</u>, <u>32</u>, 204 (1904).
x (88) Zanetti and Beckmann, <u>J. Am. Chem. Soc.</u>, <u>48</u>, 1067 (1926).
x (89) Gennari, <u>Gazz. chim. ital.</u>, <u>24</u>, 246 (1894).

to be re-used after drying. The ester was separated from the aqueous portion of the distillate and dried over sodium sulfate. The drying agent was filtered off. The ester amounted to 57 to 65 per cent of the theoretical amount. It was constant boiling so that redistillation was unnecessary.

In case it is desirable to distill the ester, it may be distilled either under diminished pressure or at atmospheric pressure. It boils at 181°/760 mm. It is not necessary to dry the ester if it is to be distilled. The moisture passes out with a small quantity of ester as the first fraction. This fraction may be combined with the next run.

In the case of ethyl furoate the distillate was cooled and the solid ester was filtered off and dried over sulfuric acid in a desiccator.

Acylation of Methyl Furoate.

It was found impossible to acylate methyl furoate by acyl halides and aluminum chloride or by acid anhydrides and aluminum chloride. A typical run follows:

Using set-up No. 1, 0.1 mole of acid chloride or acid anhydride was added dropwise with stirring to 26.6 grams (0.2 mole) of aluminum chloride in 250 cc. of dry carbon disulfide. After the reaction stood for 20 minutes there was added dropwise 12.6 grams (0.1 mole) of methyl furoate. The reaction was allowed to stir for two hours. It was then heated to a boil for from five hours to two days. There was a very slow evolution of a small quantity of hydrogen chloride. The material was poured over cracked ice and the aqueous layer separated and discarded after extracting with carbon disulfide. The solvent layer was washed with water and sodium bicarbonate solution. It was then dried over sodium sulfate. Removal of the carbon disulfide by distillation on a water bath yielded methyl furoate which boiled at 80-83°/17 mm.

Attempts were made to acylate methyl furoate with aluminum chloride as follows.

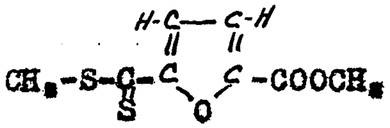
Acyl reactant	Number reactions	Product per cent
acetyl chloride	5	methyl furoate 70-95
acetic anhydride	2	methyl furoate 80-90
propionyl chloride	1	methyl furoate 90
propionic anhydride	2	methyl furoate 80
benzoyl chloride	1	methyl furoate 90
furoyl chloride	2	methyl furoate 85
ethyl chlorocarbonate	2	methyl furoate 95
carbonyl chloride	2	methyl furoate 90
phthalic anhydride	1	methyl furoate 80 phthalic acid 60

It was finally found thatferric chloride and stannic chloride would acylate esters of furoic acid (65). The stannic chloride was superior to the ferric chloride.

Alkylation of Methyl Furoate.

As has been reported (65), it was found that alkyl halides containing more than two carbon atoms alkylate methyl furoate with ease. In some cases the alkylated products were obtained in good yields.

Methyl and ethyl halides were found to yield red residues but no alkylated esters. In the case of methyl furoate this red product was worked up. All indications were that it had the following structure (65).



A7

In all, six experiments were carried out using the following reagents with aluminum chloride and methyl furoate.

Alkyl halide	Solvent	Product	Recovered methyl furoate
methyl chloride	CS_2	A7 above	30 per cent
methyl chloride	60° pet. ether	--	70 per cent
methyl bromide	CS_2	A7 above	40 per cent
ethyl chloride and bromide	CS_2	red gum	35 per cent
ethylene bromide	CS_2	red gum	40 per cent

Alkylation of Methyl Furoate with Butylene.

Alkylation of methyl furoate by butylene to yield a small quantity of methyl 5-*tert*.-butyl-2-furoate (65) was carried out along the general lines for related reactions in benzene chemistry (90, 91a). Four check runs were made varying minor details. However, the essentials are represented as follows:

Using set-up No. 1, 13.6 grams (0.22 mole) of technical butylene (91b) was slowly distilled through anhydrous calcium chloride into a rapidly stirred mixture of 200 cc. of dry carbon disulfide, 26.6 grams (0.2 mole) of aluminum chloride and 12.6 grams (0.1 mole) methyl furoate. When all the butylene was added the material in the flask was hydrolized by cracked ice and the carbon disulfide layer separated. The solvent layer was washed with water and sodium bicarbonate solution, dried over sodium sulfate and distilled. After the carbon disulfide was removed, the remaining oil was fractionated through a column at reduced pressure. There resulted from this distillation, by three fractionations, 1.5 grams of an ester boiling at 109-115°/15 mm. Hydrolysis by potassium hydroxide yielded a small quantity of an acid which melted at 96-98°. A mixed melting point of this acid with known 5-*tert*.-butyl-2-furoic acid gave a melting point of 101-102°. The melting point for 5-*tert*.-butyl-2-furoic acid is 104°.

From the mother liquors of recrystallization of the above acid there was obtained a few crystals of an acid which melted at 87-89°. This may have been an *iso*-, *sec*.-, or *n*-butyl-2-furoic acid.

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x (90) Balsohn, *Bull. soc. chim.*, /2/ *31*, 539 (1879).

x (91) (a) Milligan and Reid, *J. Am. Chem. Soc.*, *44*, 206 (1922); (b) Ohio Chemical and Manufacturing Co., Cleveland, Ohio.

The Alkylation of Methyl Furoate with Ethyl Chloroacetate.

Using the set-up No. 1, 12.6 grams (0.1 mole) of methyl furoate and 12.3 grams (0.1 mole) of ethyl chloroacetate were added rapidly to 40 grams (0.3 mole) of aluminum chloride in 100 cc. of carbon disulfide. The reaction was stirred rapidly during the addition of the halide and the ester.

After standing for twenty-four hours the material in the flask was refluxed for eight hours. The reaction mixture was then poured upon cracked ice and the carbon disulfide layer separated. The aqueous portion was extracted twice with carbon disulfide. The combined extracts were washed with water, then with sodium becarbonate and finally dried over sodium sulfate. After removing the solvent by distillation the residual oil was fractioned. There was obtained 6 grams of methyl furoate, B.P. 80-85°/19 mm. and 3 grams of ethyl chloroacetate, B.P. 144-147°/atm. pressure. No higher fractions were obtained.

The Acylation of Furfural.

In an apparatus according to set-up No. 1, 100 grams (0.33 mole) of stannic chloride was added dropwise over a four hour period to 500 cc. of dry, thiophene free benzene containing 153 grams (1.5 moles) of acetic anhydride and 48 grams (0.5 mole) of furfural. The contents of the flask were kept at 0° C. The solution became black at once and showed a progressive decomposition until at the end of the reaction, the flask was filled with a black, hard resin. This resin was scraped from the flask and vigorously agitated with cracked ice. The aqueous portion was separated after filtering off the tarry material. The benzene layer was washed with water and sodium acetate solution. After drying, the benzene was distilled off. It left approximately 0.5 gram of oily residue which did not oxidize with silver oxide. Another run produced similar results. A run using furfural diacetate in place of furfural gave the same negative result.

The Alkylation of Furfural.

As has been previously shown (65) furfural gives an anomalous result when alkylated with an alkyl halide and aluminum chloride. The product appears to be a case of abnormal orientation. That is, the alkyl group evidently has entered a beta-position although an alpha-position was open. The investigation is being continued. The results will appear elsewhere.

The Acylation and Alkylation of Nitrofuran. Removal of the Nitro Group.

The nitrofuran used in these experiments was prepared from furan (84), nitrated according to the directions of Marquis (92). Set-up No. 1 was used throughout these experiments. One typical run is given. The other runs are summarized for sake of brevity.

×(92) Marquis, Bull. soc. chim., 29, 276 (1903).

Using set-up No. 1, 13.3 grams (0.07 mole) titanium tetrachloride was added dropwise with vigorous stirring to 8 grams (0.07 mole) of nitrofuran and 6.5 grams (0.07 mole) propionyl chloride in 100 cc. of carbon disulfide. The reaction was kept at 0°C during the addition of the titanium tetrachloride. While the condensing agent was being added, hydrogen chloride was evolved and brown vapors were given off. The brown vapors were nitrogen tetroxide.

When the reaction subsided, the mixture was allowed to stir at room temperature for ten minutes. It was then poured upon cracked ice, acidified with hydrochloric acid, and the aqueous layer separated, extracted once with carbon disulfide and discarded. The combined carbon disulfide layers were washed with water and then with sodium bicarbonate solution. The solvent was removed by steam distillation. The residual oil was steam distilled to yield 2 grams of white crystals. After recrystallization from alcohol and water these crystals melted at 52-54°. The melting point became constant at 55°C.

It was found that these crystals contained no nitrogen. They contained chlorine and a ketone group.

<u>Anal</u>. Calcd. for $C_7H_7O_2Cl$: Cl, 22.4. Found: Cl, 22.9.

Since the analysis agreed for a chlorofuryl ethyl ketone, the 5-chlorofuryl-2-ethyl ketone was prepared as follows.

Five grams (0.034 mole) 5-chloro-2-furoic acid prepared by the method of Hill and Jackson (93) was decarboxylated according to the method of Johnson to obtain 5-chlorofuran (94). To avoid loss, the 5-chlorofuran was not isolated. It was taken up in 100 cc. of benzene. The benzene solution was washed three times with water, once with sodium bicarbonate solution and then dried over anhydrous sodium sulfate at 0°C. After drying the sodium sulfate was filtered off, and the benzene was placed in an apparatus according to set-up No. 2. The solution was chilled to 0° C. To the cold solution was added 5.2 grams (0.04 mole) of propionic anhydride and later 10.4 grams (0.04 mole) of stannic chloride. The ice bath was removed and the reaction was allowed to stand at room temperature for 3 hours. It was then poured upon cracked ice and the benzene layer separated. After washing with water and sodium bicarbonate solution, the benzene was removed by steam distillation. The residue on steam distillation yielded 1 gram of a ketone melting at 55°. A mixed melting point with the ketone prepared from nitrofuran by titanium tetrachloride showed no depression.

Using other condensing agents and various conditions, all attempts to acylate or alkylate nitrofuran were futile. A summary of these follows.

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(93) Hill and Jackson, Proc. Am. Acad. Arts. Sci., 24, 320 (1888).

x (94) Shepard, Winslow and Johnson, J. Am. Chem. Soc., 52, 2083 (1930).

Condensing agent	Halide or anhydride	Product	Per cent
aluminum chloride	acetyl chloride	nitrofuran	30
aluminum chloride	propionyl chloride	nitrofuran	10
aluminum chloride	isopropyl chloride	none	none
stannic chloride	acetic anhydride	none	none
stannic chloride	propionic anhydride	none	none
mercuric chloride	propionyl chloride	nitrofuran	70

In order to determine whether or not this removal of the nitro group by titanium tetrachloride was general for furan compounds, a run was made using 17.1 grams (0.1 mole) of methyl nitrofuroate. The run was carried out as for the run above with titanium tetrachloride, nitrofuran and propionyl chloride except the reaction was refluxed for three hours. Sixteen grams or 94 per cent of the methyl nitrofuroate was recovered.

A further comparison was made to determine if the corresponding benzene types behaved in a similar manner. Runs were made using titanium tetrachloride on the following compounds containing the nitro group.

Compound	Isolated after reaction
p-nitroanisole	93 per cent p-nitroanisole
α-nitronaphthalene	94 per cent α-nitronaphthalene
nitrobenzene	95 per cent nitrobenzene

Acylation of 3,4-Dicarbomethoxyfuran.

The 3,4-dicarbomethoxyfuran was prepared according to recent directions of Reichstein and co-workers (36).

Using set-up No. 2, 39.0 grams (0.15 mole) of stannic chloride was added with shaking to 100 cc. of dry, thiophene free benzene which contained 9.2 grams (0.05 mole) of 3,4-dicarbomethoxyfuran and 5.1 grams (0.05 mole) of acetic anhydride. The reaction was allowed to stand at 0°C for one hour. It was then poured upon cracked ice and the benzene layer was separated. Three portions of benzene used to extract the aqueous portion were combined with the original benzene layer. The entire benzene extract was washed with water, then with sodium bicarbonate solution. The benzene was distilled off and the residue was recrystallized from hot water to a constant melting point of 108°C after boiling with a <u>small</u> quantity of charcoal. The yield was poor. Two grams of material was obtained.

<u>Anal</u>. Calcd. for $C_{10}H_{10}O_6$: C, 53.07; H, 4.47. Found: C, 52.82, 52.63; H, 4.20, 4.15.

Three smaller runs with minor variations failed to improve the yield. No attempt was made to alkylate 3,4-dicarbomethoxyfuran.

<u>Acylation and Alkylation of 2,5-Dicarboethoxyfuran</u>.

These attempts were futile.

Two attempts to alkylate this ester with isopropyl chloride according to directions for alkylation of methyl furoate ended in a 90 per cent recovery of 2,5-dicarboethoxyfuran. The reactions were refluxed. Aluminum chloride was used.

An attempt to acylate this compound using the directions for acylation of methyl furoate (65), except the reaction was heated for four days at 65° C, yielded 70 per cent recovery of 2,5-dicarboethoxyfuran.

Acylation of Ethyl 5-Chloro-2-furoate.

Using set-up No. 2, an attempt was made to acylate ethyl 5-chloro-2-furoate (93) according to the directions for the acylation of 3,4-dicarbomethoxyfuran except that the reaction was heated to 60° for 18 hours. The product was worked up the same way except the material which remained after removal of the benzene was distilled. It boiled at 104-110/15 mm. Fifty-three per cent of the ester was recovered. Hydrolysis of the ester yielded an acid which when recrystallized once from hot water melted at 176°. A mixed melting point with known 5-chloro-2-furoic acid showed depression. The liquors from which the acid was crystallized were extracted with ether. The acid obtained when the ether was removed melted at 172°. Vacuum sublimation failed to yield a fraction which was not 5-chloro-2-furoic acid by mixed melting point.

Ethyl 5-bromo-2-furoate behaved the same way (71).

alpha-Furfuryl Methyl Ether, Aluminum Chloride and n-Butyl Chloride.

In a 500 cc. three-necked balloon flask there was placed 13.3 grams (0.1 mole) of aluminum chloride in 50 cc. of carbon disulfide.

This was cooled to 0° by means of an ice bath. Eleven and two-tenths grams (0.1 mole) of alpha-furfuryl methyl ether and 9.25 grams (0.1 mole) of *n*-butyl chloride were added dropwise from a dropping funnel to the reaction mixture over a period of one hour. The reaction was stirred vigorously by means of a motor stirrer with a mercury seal. The third neck of the flask was occupied by a Hopkins condenser closed by a calcium chloride tube.

There was no evolution of hydrogen chloride and the reaction became black.

After two hours, the material was scraped from the flask and poured over cracked ice. The mixture was then extracted three times with 200 cc. portions of ether. The ether extract was then dried over sodium sulfate and the ether was removed by distillation. There was obtained 1.3 grams of a liquid boiling at 132-136°/atm. pressure. It was alpha-furfuryl methyl ether.

The exact same run was repeated except stannic chloride was used instead of aluminum chloride, and benzene was used as the solvent. Nothing was recovered on distillation except benzene.

alpha-Furfuryl Acetate, Aluminum Chloride and n-Butyl Chloride.

This run was made exactly as for the corresponding run with alpha-furfuryl methyl ether except 100 cc. of carbon disulfide was used.

Two grams of alpha-furfuryl acetate were recovered. Boiling point 174-180°.

alpha-Furfuryl Methyl Ether, Aluminum Chloride and Acetyl Chloride.

Using the ordinary set-up as described for the above runs, 7.9 grams (0.1 mole) of acetyl chloride was added to 13.3 grams (0.1 mole) of aluminum chloride under 100 cc. of carbon disulfide. After allowing the reaction to stir for 15 minutes, there was added 11.2 grams (0.1 mole) of alpha-furfuryl methyl ether, dropwise, after cooling the reaction flask and its contents to -15°. The alpha-furfuryl methyl ether was added over a period of 30 minutes.

There was an evolution of hydrogen chloride.

The reaction was allowed to stir for 15 minutes. It was then poured over cracked ice and the mixture was steam distilled.

The distillate was extracted with ether. The ether was dried over sodium sulfate and removed by distillation. Nothing was obtained except one drop of acetic acid. Boiling point approximately 120°.

The residue from the steam distillation was likewise extracted and treated. Nothing was isolated.

alpha-Furfuryl Acetate, Aluminum Chloride and n-Propionyl Chloride.

This was run exactly as in the preceding experiment.

One gram of furfuryl acetate was obtained, and it distilled between 175-180°.

The Gattermann-Koch Reaction.

In an attempt to introduce the formyl group into several disubstituted furans, the Gattermann-Koch reaction was utilized.

Using set-up No. 1, 10.1 grams (0.3 mole) of hydrogen cyanide was added dropwise to 23.1 grams (0.15 mole) of ethyl 2-methyl-3-furoate and 39.9 grams (0.3 mole) aluminum chloride in 300 cc. of carbon disulfide. Dry hydrogen chloride gas was passed into the flask during the entire reaction. The delivery tube barely touched the carbon disulfide. After allowing the reaction to stir at 0° for one hour, it was stirred at room temperature for two hours. The mixture was then poured onto cracked ice and the carbon disulfide layer separated, washed with water and sodium bicarbonate solution, dried over sodium sulfate and the solvent removed. There resulted an oil which did not give an aniline acetate test nor yield a complex with sodium bisulfite. Hydrolysis yielded an acid which melted at 100-101°. The mixed melting point with known 2-methyl-3-furoic acid was 101° C.

A duplicate run was made with the same result. One run was made with stannic chloride. No aldehydo compound was obtained.

In a run using 2-methyl-3-furoic acid, an oily product was obtained. It possessed a penetrating odor and it was a powerful lachrymator. Upon boiling with water this oil yielded 2-methyl-3-furoic acid. This oil may have contained the 2-methyl-3-furoyl chloride. In a run using the acid with stannic chloride only a gummy intractable material was obtained.

In three attempts to acylate 2,5-dimethylfuran no products were obtained except a small quantity of 2,5-dimethylfuran.

This reaction, however, gave promise of yielding an acylated product if the proper conditions were found.

Activity of the alpha-hydrogens.

Since furan compounds underwent the Friedel-Crafts reaction with such ease, it was thought possible to find a condensing agent that would be quite mild. It was suggested that possibly furan would undergo acylation without a condensing agent. This idea resulted from the connection between ease of substitution in the alpha-position and activity of the corresponding hydrogens. Actually it is not known how closely connected the two phenomena are. In the present study it was found that certainly a condensing agent was necessary and only one was found to be of value that could be classed as mild in action. It was not studied further.

Using a battery of acetylation flasks with ground mouths to accommodate reflux condensers, a series of runs was made. In each flask was placed 50 cc. of furan, 9.3 grams (0.1 mole) of propionyl chloride was added and the condensing agent (0.1 mole) was added. If no reaction occurred the reaction was refluxed for one hour. After hydrolysis by cracked ice, the material was steam distilled from an alkaline solution. The furan was caught for future use. Any higher fractions were saved and treated with semicarbazide hydrochloride and sodium acetate. If a semicarbazone formed it was filtered off and identified by melting point and mixed melting point with furyl ethyl ketone semicarbazone (65). The following condensing agents were studied and the results are shown:

Of value	No value
mercuric chloride	mercurous chloride
titanium tetrachloride	silicon tetrachloride
metallic zinc	sodium chloride
metallic tin	calcium chloride
	plumbous chloride

[All salts were anhydrous]

After refluxing for 2 days it was found that no ketone was formed in a run using propionyl chloride and furan with the above directions except no condensing agent was used. A similar run without a condensing agent in which propionic anhydride was used was likewise fruitless.

Acetylation of Benzene by Stannic Chloride.

Although several papers have appeared in which benzene was used as a solvent for acetylating furan (61) and thiophene (80) compounds, no mention has been made of the small quantity of acetophenone which forms. It was noticed in the present work that the odor of acetophenone was always prevalent when working up a run in which benzene had been used as a solvent. A run was made to determine whether or not stannic chloride would acetylate benzene.

Using set-up No. 2, 10.2 grams (0.1 mole) of acetic anhydride was added to 25 cc. of benzene. To this mixture was added 52 grams (0.2 mole) of stannic chloride. The reaction was heated to 60° for 8 days. The mixture was then poured into water. The benzene layer was separated, washed with water, sodium acetate solution and sodium bicarbonate; dried over sodium sulfate; and the benzene removed by distillation on a water bath. The residue was distilled. One gram of material was obtained. It boiled at 200-202°/atm. pressure. It yielded a semicarbazone which recrystallized from alcohol-water to melt at 198° with decomposition. Mixed melting point with known acetophenone semicarbazone: 198-202°.

SUMMARY

A study of the Friedel-Crafts and Gattermann-Koch reactions as applied to furfural and its derivatives has led to rules of definite behavior for these substances. The surprising fact is noticed that although furan compounds, on the whole, are notoriously sensitive to mineral acids and drastic treatment, they generally withstand the conditions used in condensation reactions as studied here.

An interesting phase of this work is the meagre information that is available on the constitution of furan. As has been discussed before (95) there are possible formulas which ascribe great unsaturation to the nuclear oxygen atom. The evidence garnered in the present work tends to show that if this oxygen

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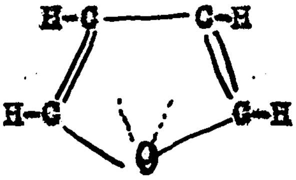
(95) Gilman and Wright, Chem. Rev., 11, 324 (1932).

is unsaturated, the unsaturation is turned toward the center of the ring. It is general knowledge that ethers form complexes readily with such substances as anhydrous aluminum-, ferric- or stannic chloride. It appears that the ring oxygen in furan compounds has no such effect. It was found that one mole of aluminum chloride was added molecularly to an ester such as methyl 2-furoate. This is evidence that the nuclear oxygen does not add the metal halide, since all known ester groups will readily add one mole of aluminum chloride. On the assumption that the aluminum chloride adds only to the lateral functional groups as carbonyl, the evidence points to an absence of effective unsaturation on the bridge oxygen. This would perhaps give credence to the view that the structure of furan may be represented as follows:



That is, the unsaturation of the oxygen is turned toward the center of the ring.

The general observations on the Friedel-Crafts and Gattermann-Koch reactions are summarized as follows:

1. Furan may be acylated in good yields, but it has not been directly alkylated.

2. Methyl furoate undergoes ready acylation and alkylation.

3. Furfural may be alkylated, but it has not been successfully acylated.

4. The sensitive furfuryl methyl ether and furfuryl acetate have not been acylated or alkylated.

5. Substitution can be effected in the beta-position.

6. Nitrofuran undergoes acylation simultaneously with replacement of the nitro group by a halogen atom. Nitrofuran resisted all attempts to acylate or alkylate it when the nitro group was not removed.

7. A highly negatively substituted furan as 3,4-dicarbomethoxyfuran undergoes acylation while 2,5-dicarboethoxyfuran does not.

8. Negatively substituted or di-alpha-substituted furans do not undergo the Gattermann-Koch reactions.