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SYNTHESES OF CERTAIN FURAN
AND DIFURYL DERIVATIVES

by

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Approved

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In charge of Major work

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A. THE OXIDATION OF FURAN METHYL GROUPS

INTRODUCTION

Although oxidation in the furan series has been studied since 1873 when Limpricht (1) worked with furoic acid, no general method and few special methods have been reported for the oxidation of furan compounds without decomposition of the furan ring. Some of the agents that have been used for the oxidation of furan compounds to aliphatic acids such as fumaric, succinic, oxalic, etc. are:- aqueous bromine (2), dilute nitric acid (3), potassium permanganate (4), peracetic acid (5), sodium chlorate and vanadium pentoxide or osmium tetroxide (6), air and vanadium trioxide, vanadium pentoxide, or ammonium vanadate (7), oxygen and vanadium pentoxide (8), Caro's acid (9), and many others. There are a number of isolated cases of oxidation in which the furan ring is kept intact but only a few will be enumerated. Boeseken (10) and his coworkers using 70% peracetic acid in acetic acid solution, have obtained what they consider to be an oxide of furan. Furfural and other furan aldehydes have been oxidized to the corresponding acids by potassium permanganate (11), silver oxide (2), air (12), and other agents. The Cannizzaro reaction goes smoothly with a number of furan aldehydes. Furoin has been oxidized to furil by air (13) or electrolysis (14). Moureu, Dufraisse, and Johnson (15) have reported the supposed oxidation of furylbromoethylene with air to w-bromofuryl methyl ketone. Priebs (16) has oxidized 5-nitro-2-ethenyl nitrofuran to 5-nitro-2-furoic acid with chromic acid. Gilman and Wright (17) have oxidized 5-nitro-furfuryl alcohol to nitrofurfural by heating to 40-50° for two days with manganese dioxide and 50% sulfuric acid.

Methyl groups in the furan series have been oxidized (17a) by bromination to give the dibromide followed by hydrolysis to the aldehyde. The drastic conditions of this method, however, keep it from being general. B.L. Wooley (18) has oxidized sylvan to furfuraldoxime with NOCl, but it has been found impossible to extend this reaction to other furan methyl compounds. He has also oxidized sylvan to furoic acid with selenium dioxide but we have been unable to duplicate this reaction.

The oxidizing agent used in these studies is one that has been applied successfully by W.A. Noyes (19) to the benzene series, and appears to be general for the oxidation of furan methyl groups to carboxylic acids. This reagent, potassium ferricyanide, combines power with mildness in a way which makes it an ideal oxidizing agent in the furan series. With it such compounds as fufuryl alcohol and sylvan have been oxidized to furoic acid.

EXPERIMENTAL

Typical Oxidation for Most Types of Furan Compounds.

Oxidation in basic solution may be used for all compounds except the nitrofurans which are unstable in the presence of alkalies. A typical oxidation is outlined.

One gram of the compound, 25 g. of potassium ferricyanide, and 10 g. of potassium hydroxide were placed in a 300 cc. flask with 150 cc. of distilled water and refluxed three hours. The solution was filtered hot to remove iron oxide, and concentrated to one-half the original volume. On cooling a large quantity of potassium ferrocyanide crystallized and was filtered. This potassium ferrocyanide could be converted to potassium ferricyanide and used again. The filtrate was then acidified with hydrochloric acid in slight excess of that required to neutralize the base. It was not necessary to use enough hydrochloric acid to convert the potassium ferrocyanide to the acid as hydroferrocyanic acid was stronger than the organic acids prepared. The acid solution was extracted with ether. Removal of the ether left the impure organic acid which was purified by crystallization. In some cases where the yields were poor it was found advantageous after boiling two hours to add another 25 g. of potassium ferricyanide and 10 g. of potassium hydroxide and continue the boiling another two hours. Table I gives the amounts of reagents used and yields of acid in grams.

Oxidation of Groups in Furan Nitro Compounds.

In the case of the furan nitro compounds two equivalents, 34 g. of potassium acetate were used instead of the 10 g. of potassium hydroxide. The procedure was the same as before with this exception. The neutral type of reaction, using potassium acetate, was also tried with some of the other furan compounds.

TABLE I

Compds. oxidized	Sample grams	Grams potassium ferricyanide used	Acid obtained	Yield grams
Sylvan	1	50	furoic	.05
Dimethyl furan	1	25	dehydromucic	.01
Furyl methyl ketone	1	25	furoic	.51
Furylacrylic acid	1	25	not oxidized	
5-Methyl-2-furoic	1	25	dehydromucic	.35
Furfural	1	25	furoic	.22
5-Bromofuryl methyl ketone	1	25	5-bromofuroic	.45
Furyl methyl ketone*	1	25	furoic	.30
5-Nitrosylvan*	1	25	5-nitrofuroic	.54
Furfuryl alcohol	1	25	furoic	.21
Furfural acetone	1	25	furylacrylic	.10
Furfural acetone*	1	25	furylacrylic	.10
Furil	1/2	25	furoic	.41
2-Methyl-3-furoic acid	1	75	2,3-dicarboxy furan	.35
Tertiarybutyl furoic acid	1/2	50	dehydromucic	.01
Furyl ethylene	1	25	furoic acid	.02

*All of these were run in neutral (see above) solution.

The acids were characterized by m.p. and mixed m.p. with an authentic specimen.

In the case of dehydromucic acid which has no melting point, the acid was converted to the dimethyl ester and a m.p. and mixed m.p. were taken.

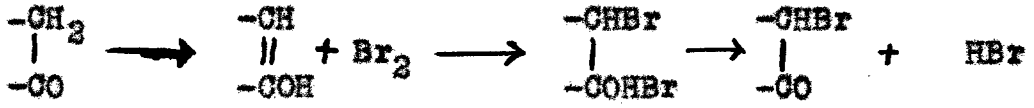
SUMMARY

1. An oxidizing agent which seems to be general for the oxidation of furan methyl groups has been reported. A number of furan compounds containing methyl groups have been oxidized. A number of other furan compounds have been oxidized using the same reagent.

B. THE BROMINATION OF FURYL METHYL KETONE

INTRODUCTION

The great tendency of furan to undergo nuclear substitution when treated with a reagent which can effect furan nuclear substitution has been demonstrated in the case of ethyl furylacrylate (20) and 2-furyl phenyl ketone (21). The only exception has been the addition of bromine to the side chain of furyl ethylene (22). In the bromination of furyl methyl ketone it has been shown that the bromine enters the side chain to give w-bromofuryl methyl ketone. This behavior may be explained by the theory of C. F. Ward (23). This theory assumes enolization of the carbonyl group and addition to the unsaturated linkage with a final removal of hydrogen bromide.



$$\begin{matrix}\mathrm{-CH_2}\\ |\\ \mathrm{-CO}\end{matrix} \longrightarrow \begin{matrix}\mathrm{-CH}\\ \|\\ \mathrm{-COH}\end{matrix} + \mathrm{Br_2} \longrightarrow \begin{matrix}\mathrm{-CHBr}\\ |\\ \mathrm{-COHBr}\end{matrix} \longrightarrow \begin{matrix}\mathrm{-CHBr}\\ |\\ \mathrm{-CO}\end{matrix} + \mathrm{HBr}$$

It was expected, however, that the second atom of bromine would substitute in the nucleus. This was shown not to be the case as the dibromination of furyl methyl ketone gives w,w-dibromfuryl methyl ketone in 90% yield. It was thought that this formation of a chain substituted compound was caused by the removal of hydrogen bromide from an addition product which may have contained bromine attached to the nucleus. To test this theory the bromination was carried out at low temperature and the product treated with alcoholic potassium hydroxide before it reached a point where hydrogen bromide was given off spontaneously. However, a careful examination of the reaction product failed to show a compound containing a bromine atom in the nucleus.

The nitration product of furyl methyl ketone (24) has been shown to be 5-nitro-2-furyl methyl ketone by comparison with the product from the reaction of diazomethane with 5-nitro-2-furfural (25). This ketone has been characterized by the preparation of the oxime.

EXPERIMENTAL

Monobromination of Furyl Methyl Ketone.

To 11 g. (0.8 mole) of furyl methyl ketone dissolved in 100 cc. of carbon disulfide (dried over calcium chloride) was added 16 g. (0.1 mole) of bromine in 500 cc. of carbon disulfide. The bromine was added dropwise with stirring at room temperature. The reaction mixture was stirred 15 minutes after the last addition of bromine. It was then poured into water and washed with sodium bicarbonate solution. The carbon disulfide layer was dried and most of the carbon disulfide removed. The residue was distilled under reduced pressure. The fraction boiling 120-5° C. at 20 mm. pressure was collected and redistilled. The yield of redistilled w-bromofuryl methyl ketone b.p. 121-3° C. at 20 mm. pressure was 16 g. This was 90% of the theoretical amount. The product thus obtained was a liquid and will not solidify on cooling. Other constants are:-

N_D^{25} 1.5783; D_4^{25} 1.5785.

MR_D: Calc'd 36.57, Obs. 39.75

However, if this oil were dissolved in petroleum ether at room temperature and then vigorously cooled crystals were deposited which after two crystallizations melted constantly at 36-7° C.

Anal. Calcd. for $C_6H_5O_2Br$: Br, 42.33

Found: Br, 42.26. 42.21

The above run was repeated except that the temperature was kept below -15° during the reaction and during the stirring after the reaction. No hydrogen bromide was evolved. A portion of the product was treated with alcoholic sodium hydroxide at 0° C. Another portion was treated with pyridine and the rest was allowed to come up to room temperature and evolve hydrogen bromide. From none of these fractions was any compound isolated which contained nuclear bromine.

Oxidation of w-Bromofuryl Methyl Ketone.

Two grams (0.01 mole) of w-bromofuryl methyl ketone and 4 g. of calcium hydroxide were suspended in ice water and 1 g. of potassium permanganate in water was added. The mixture was heated to boiling and filtered. The solution was then acidified and ether extracted yielding 0.4 g. of furoic acid. This was 35% of the theoretical amount. The furoic acid was identified by its melting point of 129-30° C. and a mixed melting point with an authentic specimen showed no depression.

Three grams (0.015 mole) of w-bromofuryl methyl ketone was treated with 3 cc. of pyridine in 50 cc. of dry ether and refluxed one hour. The reaction mixture was cooled and a layer of gummy material separated. A portion of this gummy material which was undoubtedly furacyl pyridinium bromide was then dissolved in water and treated with sodium hydroxide at 40°. The solution was then acidified and ether extracted to give furoic acid. The furoic acid was identified by its melting point 129-130° C. and by mixed melting point with an authentic specimen.

Bromofuryl Methyl Ketone from the Friedel-Crafts Reaction.

To 30 g. (0.24 mole) of aluminum chloride in 50 cc. of carbon disulfide was added 41 g. (0.2 mole) of bromacetyl bromide in 100 cc. of carbon disulfide at room temperature. To this mixture was added 14 g. (0.2 mole) of furan in 50 cc. of carbon disulfide. The reaction mixture was stirred for 15 minutes after the addition and then poured into ice-water to decompose it. The carbon disulfide layer was washed several times with sodium bicarbonate solution, dried, and the solvent was removed. The residue was distilled and the fraction boiling at 123-5° C. at 20 mm. was collected. The yield of w-bromofuryl methyl ketone was 7 g. This was 38% of the theoretical amount. The oily product was crystallized from petroleum ether. M.P. 36-37$_o$ C. It was shown to be the same compound as that derived from the bromination of furyl methyl ketone as there was no depression of the melting point when the two were mixed.

Dibromination of Furyl Methyl Ketone.

Thirty-two grams (0.2 mole) of bromine in 50 cc. of carbon disulfide was added dropwise with stirring at room temperature to 11 g. (0.1 mole) of furyl methyl ketone. When the hydrogen bromide evolution ceased the reaction mixture was poured into water, washed with sodium bicarbonate solution, dried, and the solvent removed. The residue was distilled under reduced pressure. The fraction boiling at 140-150° C. at 15 mm. pressure was collected. On refractionation the fraction boiling at 145-7° C. at 15 mm. pressure was collected. The yield of w,w-dibromofuryl methyl ketone was 24.5 g. This was 90% of the theoretical amount. Other constants are:-

N_D^{25} 1.6070. D_4^{25} 2.0040

M.R. Calcd. 76.2, Obsvd. 81.2

Anal. Calcd. for $C_6H_4O_2Br_2$: Br, 59.70

Found: Br, 59.30, 59.37.

Oxidation of w,w-Dibromofuryl Methyl Ketone.

Five grams of the ketone was refluxed in ether with 5 cc. of pyridine. No salt separated on cooling so the ether solution was extracted with water and the water extract treated with sodium hydroxide at 40° C. The solution was acidified and extracted with ether to give 0.5 g. of furoic acid m.p. 129-30° C. This was 20% of the theoretical amount. The acid was identified by mixed melting point with an authentic sample and showed no halogen test on fusion with sodium.

Five grams (0.02 mole) of the ketone and 10 g. of calcium hydroxide were suspended in ince-water and treated with 2.5 g. of potassium permanganate in solution. The mixture was heated, acidified and ether-extracted to give 1.4 g. of acid. This was 65% of the theoretical amount of furoic acid melting point 125-7°. The furoic acid was identified by mixed melting point with an authentic sample and showed no halogen test on fusion with sodium.

All the other fractions from a dibromination run were submitted to oxidation in the above manner but no trace of a compound containing nuclear halogen was found.

Bromination of 5-Bromofuryl Methyl Ketone.

Ethyl 5-bromofuroate (10) was converted to ethyl 5-bromofuroyl acetate by the Claissen condensation in 34% yield. The ethyl 5-bromofuroyl acetate was hydrolyzed by dilute sulfuric acid in 80% yield to give 5-bromofuryl methyl ketone. To 30 g. (0.16 mole) of 5-bromofuryl methyl ketone in 100 cc. of carbon disulfide was added 24 g. (0.15 mole) of bromine at room temperature with stirring. The reaction mixture was allowed to stir until the hydrogen bromide evolution ceased and was then poured into water. The carbon disulfide was washed with sodium bicarbonate solution, dried, and the solvent removed. The residue was distilled under reduced pressure. The fraction boiling 150-55° C. at 19 mm. pressure was collected. It solidified in the receiver and then was recrystallized to the constant melting point of 98.5-99.5° C. The yield was 21 g. of w, 5-dibromofuryl methyl ketone. This was 50% of the theoretical amount.

Anal. Calcd. for $C_6H_4O_2Br_2$: Br, 59.70
Found: Br, 59.91, 59.85.

Oxidation of w, 5-Dibromofuryl Methyl Ketone.

To 1 g. (0.004 mole) of the ketone and 2 g. of calcium hydroxide suspended in ice-water was added 0.6 g. of potassium permanganate in solution. The reaction mixture was heated, acidified, and ether-extracted to give 0.25 g. of 5-bromofuroic acid. This was 36% of the theoretical amount. The acid on recrystallization melted at 184° C. and a mixed melting point with an authentic specimen showed no depression.

To 1 g. (0.004 mole) of the ketone was added 1 cc. of pyridine in ether. The mixture was refluxed one hour and filtered. The residue was dissolved in water, treated with sodium hydroxide at 40°, acidified, and ether extracted to yield 0.5 g. of acid. This was 70% of the theoretical amount of 5-bromo-furoic acid. This acid was identified by its melting point and by a mixed melting point with an authentic specimen.

Nitrofuryl Methyl Ketone.

Nitrofuryl methyl ketone was prepared by the method of Rinkes (24). This compound was shown to be 5-nitro-2-acetyl furan by the following reaction. Diazomethane in ether was prepared by heating 45 g. (0.8 mole) of potassium hydroxide in 200 cc. of methyl alcohol with 25 g. (0.2 mole) of nitrosomethyl urethane in 300 cc. of ethyl ether and distilling the mixture of diazomethane and ether. To this solution was added 14.1 g. (0.1 mole) of 5-nitrofurfural (25). A rapid evolution of nitrogen took place and, after the completion of the reaction, the ether was removed and the product crystallized. Melting point of 5-nitro-2-acetylfuran 78-78.5° C. Mixed with the nitrofuryl methyl ketone of Rinkes 78-78.5° C.

Nitrofuryl Methyl Ketoxime.

Due to the sensitivity of the furan nitro group to alkali, this oxime was prepared in acid solution. To 5 g. (0.03 mole) of 5-nitrofuryl methyl ketone and 4 g. (0.06 mole) of hydroxylamine hydrochloride in alcohol solution was added one half cc. of concentrated hydrochloric acid. The mixture was heated to 100° for 2 hours in a closed vessel. The yield of 5-nitro furyl methyl ketoxime, melting point 167-8° C., was 5.1 g. This was 93% of the theoretical amount.

SUMMARY

1. It has been shown that in the bromination of 2-furyl methyl ketone the first bromine enters the side chain. It has been further shown that the second bromine will also enter the side chain.

2. In the bromination of 5-bromo-2 furyl methyl ketone the bromine enters the side chain.

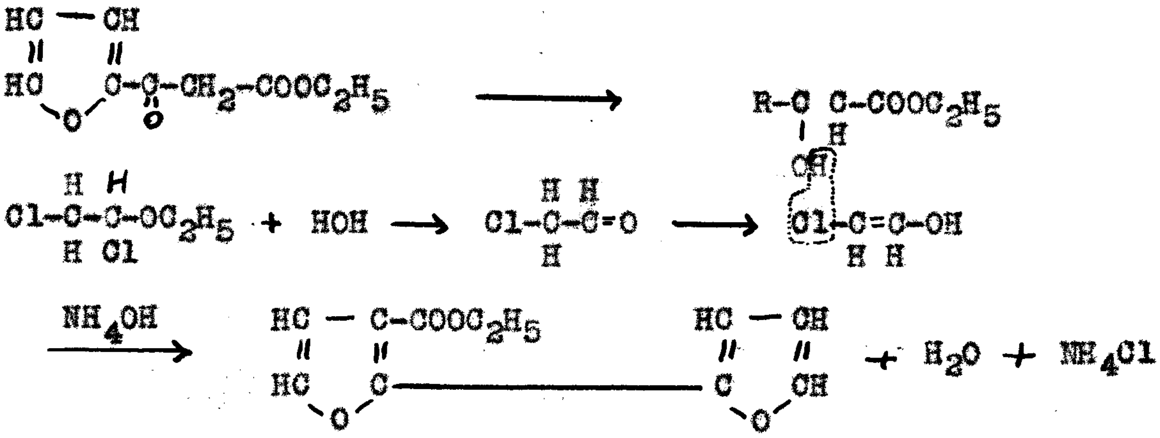
3. The nitrofuryl methyl ketone prepared by Rinkes has been shown to be 5-nitro-2-furyl methyl ketone.

C. SYNTHESES IN THE DIFURYL SERIES

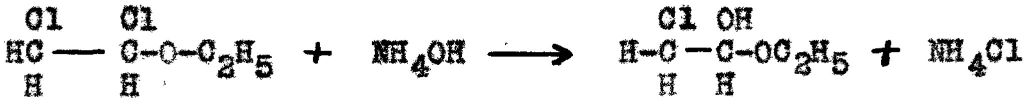
INTRODUCTION

It is significant that, although a large number of diphenyl compounds (26) and many phenylated heterocylic compounds have been prepared, very little work has been published concerning the difuryl series of compounds. The chemistry of the difuryls might be said to have started with Marquis (27), who isolated the first difuryl, 5, 5'-dinitro-2,2'-difuryl, as a by-product in the nitration of furan in 1905. The structure of this compound was not elucidated at this time. However, it was definitely proved to be 5,5'-dinitro-2,2'-difuryl by Rinkes (28) in 1931.

The first work directed toward the preparation of a difuryl type of compound was that of Kondo and Susuki (29) who used the Benary (30) method of ring closure. The Benary synthesis, which involves the condensation of arylacetic esters with reactive halogeno aliphatic ethers, aldehydes or ketones in the presence of a base, yields 2-aryl-3-furoic acids. The most logical reaction mechanism which may be gathered from the literature cited is shown as follows:



This mechanism appears plausible for two reasons. First, α, β-dichloroethyl ether reacts in the presence of water in the following manner (31):

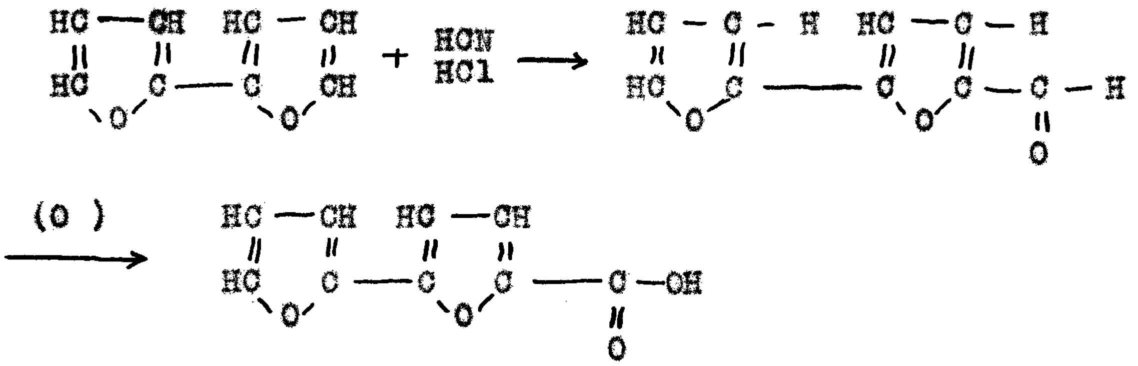


$$\underset{H}{\overset{Cl}{HC}}-\underset{H}{\overset{Cl}{C}}-O-C_2H_5 + NH_4OH \longrightarrow H-\underset{H}{\overset{Cl}{C}}-\underset{H}{\overset{OH}{C}}-OC_2H_5 + NH_4Cl$$

The ammonium hydroxide merely serves as a buffer to remove the hydrogen chloride from solution. If the reaction is unbuffered, the hemi-acetal readily breaks down to the corresponding aldehyde. Second, Plancer and Albini (32) as well as Nalterer (33) showed that chloracetaldehyde and ethyl acetoacetate react in the presence of ammonia in ether solution to form ethyl-2-methyl-3-furoate.

If dichloroethyl ether is used in this synthesis, obviously, the reaction must be carried out in aqueous solution. When the halogenated aldehydes or ketones are employed, anhydrous conditions must be maintained using ether as a solvent and gaseous ammonia as the condensing agent.

Kondo and Susuki (29) saponified the 3-carboethoxy-2,2'-difuryl to get 2,2'-difuryl-3-carboxylate which they decarboxylated to 2,2'-difuryl. Starting with this 2,2'-difuryl, Reichstein (34) has carried out the following series of reactions:



Wright (35) has tried the method of coupling the Grignard reagent with various compounds to prepare difuryl and its derivatives. The coupling of the Grignard reagent to the corresponding hydrocarbon gives varying yields, most of which are high. Phenylmagnesium bromide, for example, yields 98% of the theoretical amount of diphenyl when treated with anhydrous cupric chloride. When furylmagnesium iodide is treated in a like manner, the yield of difuryl is about 5 - 15%. Ferric chloride, azobenzene, and ethylene dibromide were tried as coupling agents without success. The difuryl prepared was nitrated in 1% yield to the 5,5'-dinitro-2,2'-difuryl of Marquis. 5-Iodo-2-furylmagnesium iodide was also successfully coupled to 5,5'-diodo-2,2'-difuryl with anhydrous cupric chloride. 2,5-Diodofuran did not react with sodium but exploded when heated to 140° C. in a sealed tube with copper powder.

Burtner (36) was unsuccessful in an attempt to use the Benary synthesis to prepare 5'-bromo-2,2'-difuryl-3-furoate. This synthesis was halted by inability to prepare ethyl 5-bromofuroyl acetate by the condensation of ethyl 5-bromo-2-furoate and ethyl acetate with sodium. A small amount of 5-bromo-2-furyl methyl ketone was the only product obtained.

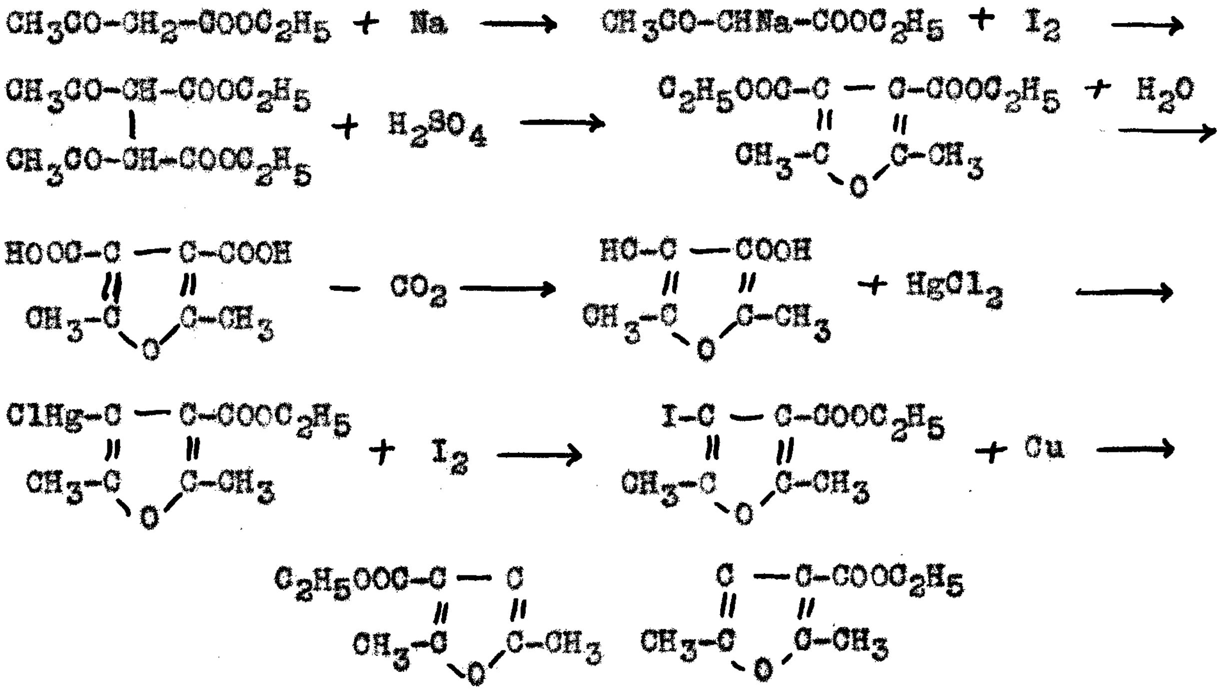
The following table lists in chromological order all of the difuryls known at the present time.

TABLE II

Compound	Method used	Source	Reference
5,5'-dinitro-2,2'-difuryl		Furan	Ann. Chim. phys., (8) 4, 233 (1905)
3-carboethoxy-2,2'-difuryl	Ring closure	Ethyl furoyl acetate	J. Pharm. Soc. Japan, 544, 501 (1927)
2,2'-difuryl-3-carboxylic acid	Saponification	3-Carboethoxy 2,2'-difuryl	Ditto
2,2'-difuryl	Decarboxylation	2,2'-difuryl-3-carboxylic acid	Ditto
5-furyl-2-furfuraldehyde	Gatterman	2,2'-difuryl	Helv. Chim. Acta, 15 1066 (1932)
5-furyl-2-furoic acid	Oxidation	5-furyl-2-furfulald	Ditto
5,5'-diodo-2,2'-difuryl	Coupling of RMgx	5-iodo-2-furyl Magnesium iodide	Wright, Doctoral Thesis. Iowa State College. 1932.
5,5'-dicarboethoxyl-2,2'-difuryl and acid	Coupling Cu	Ethyl 5-bromo-2-furoate	This Thesis
5,5'-dimethyl-2,2-dicarbomethoxy-4,4'-difuryl and acid	Coupling Cu	Methyl 5 methyl-4-iodo-2-furoate	This Thesis
2,2',5,5'-tetramethyl-3,3'-dicarboethoxy-4,4'-difuryl and acid	Coupling Cu	Ethyl 2,5-dimethyl 4 iodo-3-furoate	This Thesis

The method of coupling with copper using the organic halides affords a rough measure of the reactivity of the halogen compounds. This measure is of interest inasmuch as the compounds measured are not capable of forming Grignard reagents which is a property often used as a rough measure of activity.

One particular object in the studies on the difuryl types was to prepare a compound which would show optical activity. The method of Stanley and Adams (32) for determining which diphenyls would be resolvable was applied to the difuryl series. After a thorough consideration of all the resolvable difuryls possible, the only one that seems to offer a chance for successful preparation was 2,2',5,5'-tetramethyl-3,3'-difuryl-4,4'-dicarboxylic acid. The following series of transformations illustrates its synthesis:



Although optical studies on this compound are not completed, the results should throw some very interesting light on the structure of the furan ring.

EXPERIMENTAL

Study of 5-Bromo-2-furyl Methyl Ketone and Its Coupling Product.

Before undertaking the preparation of 5-bromo-2-furyl methyl ketone from 2-bromofuran it was thought advisable to study the optimum conditions for the preparation of furyl methyl ketone from the readily available furan.

Synthesis of 2-Furyl Methyl Ketone from Furan.

2-furyl methyl ketone has been prepared by Reichstein (38) from furan and acetyl chloride using anhydrous aluminum chloride, stannic chloride, ferric chloride, or zinc chloride as catalysts. In order to avoid the hydrogen chloride to which furan is quite unstable, it seemed best to use acetic anhydride (39) instead of acetyl chloride.

Run 1. A solution of 30 g. (0.4 mole) of aluminum chloride in 40 cc. of carbon disulfide was stirred and cooled to 0° C. A mixture of 10 g. (0.15 mole) of furan, 30 g. (0.3 mole) of acetic anhydride, and 30 cc. of carbon disulfide was added dropwise. The reaction was allowed to come to room temperature and stirred one hour. The reaction mixture was then decomposed by pouring onto cracked ice, neutralized with sodium hydroxide, and steam distilled. The distillate was ether extracted, the extract dried, and the ether removed. There remained 2.4 g. of furyl methyl ketone melting at 30-31° C. and boiling at 88-89° C. under 30 mm. pressure. This was 15% of the theoretical amount. The yield (39) using acetyl chloride was 11.9%.

Run 2. In this reaction 24 g. (0.18 mole) of anhydrous zinc chloride in 100 cc. of dry ether was treated with a mixture of 10 g. (0.15 mole) of furan, 30 g. (0.3 mole) of acetic anhydride, and 30 cc. of dry ether in the same manner as in the first run. The yield of 2-furyl methyl ketone was 5.2 g. or 32% of the theoretical amount. The yield (39) using zinc chloride and acetyl chloride was 34% of the theoretical.

Run 3. Another run was made in a similar manner except that 15 g. (0.1 mole) of ferric chloride in 50 cc. of carbon disulfide was treated with a mixture of 10 g. (0.15 mole) of furan, 20 g. (0.3 mole) of acetic anhydride and 50 cc. of carbon disulfide. The yield by this method was 34% of the theoretical.

Run 4. A mixture of 10 g. (0.15 mole) of furan with 25 cc. of benzene and 20 g. (0.3 mole) of acetic anhydride was cooled and treated with a solution of 40 g. (0.15 mole) of anhydrous stannic chloride in 40 cc. of benzene. After working up in the customary manner the yield of 2-furyl methyl ketone was 8 g. This was 50% of the theoretical amount. The yield using acetyl chloride (39) and stannic chloride was 15%.

Preparation of 2-Furoyl Chloride.

Two hundred and twenty-four grams (2 moles) of technical 2-furoic acid was added to 600 g. (5 moles) of technical thionyl chloride and the mixture was refluxed for eight hours. At the end of this time the excess thionyl chloride was removed by distillation at atmospheric pressure and the residue was vacuum-distilled. There was obtained 226 g. of 2-furoyl chloride boiling point 75° at 18 mm. pressure. This was 87% of the theoretical amount.

Preparation of 5-Bromo-2-furoic Acid.

One hundred and twelve cubic centimeters (2.2 moles) of dry bromine (40) was dropped during the course of an hour into 131 g. (1 mole) of furoyl chloride contained in a 1-liter round-bottomed flask provided with a ground-glass reflux condenser. The tube from the dropping funnel passed completely through the condenser and reached to within 10 mm. of the surface of the furoyl chloride. It was found advantageous to add the bromine at room temperature as the reaction mixture became warm during the course of the reaction, and the bromine refluxed during the addition.

After all of the bromine had been added the flask was immersed in an oil bath and heated at 100 - 110° C. for 4 hours. Approximately 250 cc. of water was added and the mixture poured into an excess of 20% sodium carbonate contained in a 3-liter flask. It was boiled under a reflux condenser until the oily layer completely disappeared. Then the solution was treated with Norit, boiled a short time, and filtered hot. The warm solution was poured into a mixture of concentrated hydrochloric acid and ice, and the precipitated acids filtered by suction. There was obtained 250 g. of mixed acids.

The mixture of 5-bromo-2-furoic and 4,5-dibromo-2-furoic acid was separated by the method of Hill and Sanger (41), which depends on the difference in solubilities of the barium salts in dilute adueous ammonia. One hundred grams of the mixed acid was dissolved in a liter of water containing 50-60 cc. of concentrated aqueous ammonia. An excess of a 10% solution of barium chloride was added, which caused precipitation of the barium salt of the 4,5-dibromo-2-furoic acid. This was separated by filtration and the acid regenerated by pouring the barium salt, in the form of a thick paste, into a boiling solution of 25 g. of anhydrous sodium sulfate in 500 cc. of water. A few grams of Norit was added, the solution filtered hot, and poured with stirring into a mixture of ice and concentrated hydrochloric acid. The 4,5-dibromo-2-furoic acid separated in light brown crystals which melted from 155-160 ° C.

The 5-bromo-2-furoic acid was obtained by boiling the filtrate from the barium chloride precipitation to remove excess ammonia, adding Norit, filtering, and pouring into cold concentrated hydrochloric acid. The crude acid melted 180-183° C.

When 1.1 moles of bromine was used with 1 mole of furoyl chloride the yield of 5-bromo-2-furoic acid was 75% and no 4,5-dibromo-2-furoic acid was isolated. When 0.6 mole of bromine to 1 mole of furoyl chloride was used, the yield of 5-bromo-2-furoic acid was 35%. Then using the directions of Johnson (40), 2.2 moles of bromine with 1 mole of furoyl chloride, the ratio of 4,5-dibromofuroic to 5-bromofuroic was 75% to 25%. Johnson (40) reported 100% yield which was improbable and has not been duplicated, our yields running between 70 and 75%. Using 2.7 moles of bromine to 1 mole of furoyl chloride, the ratio of 4,5-dibromofuroic to 5-bromofuroic acid was 85% to 15% and the total yield was found to be 71%. Therefore, it was thought advisable to try 3.3 moles of bromine with 1 mole of furoyl chloride and the ratio 4,5-dibromofuroic to 5-bromofuroic acid in this run was 100% to 0% and the total yield was 57%. Although this accomplished the purpose of getting all 4,5-dibromo-furoic and no 5-bromofuroic acid, there was too large an excess of bromine used and this cut the yield down to 57%.

From the above observations it can be seen that the correct amount of bromine for the reaction, when only 5-bromo-2-furoic acid was wanted, was 1.1 moles to 1 mole of furoyl chloride.

Preparation of 2-Bromofuran.

A suspension (42) of 19.1 g. (0.1 mole) of 5-bromo-2-furoic acid in a solution of 27 g. (0.1 mole) of mercuric chloride in 300 cc. of water was boiled in a distilling flask provided with a condenser, and the oil which steam distilled was separated, dried, and distilled to give 9.6 g. of 2-bromofuran (40) boiling at 102° C. at atmospheric pressure. This was 65.5% of the theoretical amount.

Preparation of 5-Bromo-2-furyl Methyl Ketone.

A mixture of 96 g. (0.65 mole) of 2-bromofuran with 100 cc. of dry benzene and 66 g. (0.65 mole) of acetic anhydride was cooled and treated with a solution of 170 g. (0.65 mole) of anhydrous stannic chloride in 200 cc. of dry benzene at room temperature. The reaction mixture was decomposed by pouring into ice-cold water, neutralized with sodium hydroxide, and steam distilled. There was obtained 80 g. of 5-bromo-2-furyl methyl ketone melting point 94° C. This is 67% of the theoretical amount.

Attempted Coupling of 5-Bromo-2-furyl Methyl Ketone.

Nineteen grams (0.1 mole) of 5-bromo-2-furyl methyl ketone was treated with 10 g. of copper powder and heated to 206° C. (inside temperature) at which point the material refluxed rapidly. The temperature was held at 206° C. for one-half hour. The contents of the flask were allowed to cool and were thoroughly extracted with ether and then with benzene. After removal of the solvents there was obtained only the original 5-bromo-2-furyl methyl ketone. No difuryl could be found.

Nineteen grams (0.1 mole) of the ketone was placed in a Carius tube with 10 g. of copper and 1 cc. of glacial acetic acid, sealed, and heated to 200° C. for one-half hour. This treatment completely decomposed the material and no product was isolated.

A third 19 g. (0.1 mole) of the ketone was heated to 206° C. and treated with small portions of activated copper (43). After treating this reaction mixture as in the first run no material other than the unchanged ketone was isolated.

Preparation of Ethyl 5-Bromo-2-furoate.

One hundred and thirty grams (1 mole) of furoyl chloride was brominated with 1.1 moles of bromine as prefiously reported. However, instead of decomposing with sodium carbonate solution, the reaction mixture was dropped slowly into a liter of anhydrous ethyl alcohol. After the last portion had been added, the alcoholic solution was refluxed for several hours. The solvent was removed under diminished pressure and the residue vacuum distilled. After redistilling in vacuum there was obtained 153 g. of pure ethyl 5-bromo-2-furoate. This was 70% of the theoretical amount. The boiling point was 133-134° C. at 31 mm. pressure.

Preparation of 5,5-Dicarboethoxy-2,2-difuryl.

Fifty grams (0.22 mole) of ethyl 5-bromo-2-furoate was refluxed 1 hour with 30 g. of copper powder while the temperature of the metal bath surrounding the flask was kept at 240° C. The contents of the flask were allowed to cool and were then thoroughly extracted with ether. After filtration the ether was removed under diminished pressure. The gummy residue remaining was shaken with cold methyl alcohol and filtered. The filtrate, after removal of the alcohol and distillation of the product, yielded 34 g. of the unchanged ester. From the residue, after crystallizing twice from ethyl alcohol using Norit, there was obtained 2.1 g. of 5,5'-dicarboethoxy-2,2'-difuryl. This was 70% of the theoretical amount after taking into consideration the recovered ester. It melted at 150-151° C. and the melting point was not raised by further crystallization.

Anal. Calc'd for $C_{14}H_{14}O_6$: C, 60.41; H, 5.07.

Found: C, 59.77, 60.00, 59.71.

H, 5.14, 5.11, 5.13.

Saponification of 5,5'-Dicarboethoxy-2,2'-difuryl.

Nine-tenths of a gram (0.0032 mole) of the above ester was treated with 5 g. of sodium hydroxide in 25 cc. of 30% ethyl alcohol. The mixture was refluxed 1 hour and poured into dilute hydrochloric acid. Seven-tenths of a gram or the theoretical amount of the acid was obtained. It has no melting point.

Neutralization equivalent. Calc'd for $C_{10}H_6O_6$, 111.0

Found, 111.5.

Attempted Preparation of 5'-Carboethoxy-2,2'-furyl-5-furoic Acid.

Two grams (0.01 mole) of 5,5'-dicarbethoxy-2,2'-difuryl was treated with 0.56 g. (0.01 mole) of potassium hydroxide in 100 cc. of absolute alcohol and refluxed until the solution was neutral to phenolphthalein. The alcohol was removed under diminished pressure, the salt dissolved in water, and the acid regenerated by acidifying with hydrochloric acid. The only products isolated were the unchanged ester and the dicarboxylic acid. Therefore, it seems impossible to form the half ester in this manner.

Decarboxylation of 2,2' Difuryl-5,5'-dicarboxylic Acid.

In a small flask containing 10 cc. of quinoline (40) was placed 0.56 g. (0.003 mole) of 2,2'-difuryl-5,5'-dicarboxylic acid and 2 g. of copper powder. The flask was heated to 200° C. and a large amount of carbon dioxide was evolved. After removing the copper and then the quinoline with dilute acid, there was obtained a trace of compound which was unstable to mineral acids. This was probably 2,2'-difuryl but the quantity did not permit an identification.

Preparation of Ethyl 5-Chloro-2-furoate (44).

Four and four-tenths grams (0.02 moles) of the previously described ethyl 5-bromo-2-furoate (45) was sealed in a Carius tube with 5.4 g. (0.02 mole) of mercuric chloride and 10 cc. (0.14 mole) of acetyl chloride. The tube and its contents were heated to 110 - 135° C. for 5 hours. At the end of this time, the tube was cooled and the contents extracted with ether. The ether was removed and the residue steam distilled to 2.6 g. of crude ethyl 5-chloro-2-furoate. This was 78% of the theoretical amount. The crude product was purified by saponification to the acid which was recrystallized. The melting point of 5-chloro-2-furoic acid was 179-180° C. The acid was then converted to the ester by treating with phosphorus pentachloride, dissolving in anhydrous ethyl alcohol, and distilling.

Attempted Coupling of Ethyl 5-Chloro-2-furoate.

Seventeen grams (0.1 mole) of ethyl 5-chloro-2-furoate was treated with 10 g. of copper powder and heated to 220° C. at which point the material refluxed rapidly. After being held at this temperature for 1 hour the material was extracted in the usual manner. No trace of a difuryl was found.

Another 17 g. (0.1 mole) of the ester was placed in a Carius tube with 10 g. of copper powder and 1 cc. of glacial acetic acid, sealed, and heated to 250° C. for one-half hour. After extracting and working up in the usual manner, no difuryl was obtained.

Preparation of Ethyl 4,5-Dibromo-2-furoate.

This ester was prepared by the bromination of 1 mole of furoyl chloride as previously described except that 2.7 moles of bromine were used instead of 1.1 moles as before. The brominated furoyl chloride was added to alcohol, refluxed over night and distilled. There was obtained 175 g. of ethyl 4,5-dibromo-2-furoate. This was 60% of the theoretical amount and melted 57-58° C.

Coupling of Ethyl 4,5-Dibromo-2-furoate.

Twenty grams (0.07 mole) of the ester and 10 gms. of copper were heated to 230° C. After the usual treatment only a trace of a possible difuryl was isolated. Temperatures as high as 260° in a sealed tube with 1 cc. of glacial acetic acid failed to give more than a trace of a compound which it was hoped would be diethyl 4,4'-dibromo-5,5'-difuryl-2,2'-dicarboxylate.

In the hope of getting this difuryl 2 g. (0.007 mole) of 5,5'-difuryl-2,2'-dicarboxylate was treated with 2 g. (0.014 mole) of bromine in carbon disulfide solution. However, careful fractionation of the resulting material resulted in the recovery of the original ester and no evidence of a dibromo compound.

This run was repeated using bromine in boiling carbon tetrachloride solution but no dibromo product could be identified.

Preparation of 2-Bromo-5-nitrofuran (28).

Twenty-eight grams of nitric acid of specific gravity 1.51 was dropped with stirring into 60 g. of acetic anhydride at a temperature from -10 to -5° C. A mixture of 9.5 g. of 5-bromo-2-furoic, prepared as previously described, with 50 g. of acetic anhydride was prepared by warming to dissolve the acid and then allowing the solution to cool. This left part of the acid precipitated but in a very finely divided state. The second mixture was added to the first in small portions, the temperature being kept as before. The material was allowed to stir one hour after the final addition and decomposed with a mixture of ice and water. This solution was extracted with three portions of ether and then the ether removed to leave a residue which was steam distilled. An oil was obtained which rapidly crystallized to give 3.5 g. of dry 2-bromo-5-nitrofuran. This was 45% of the theoretical amount. The product melted at 48° C. and its boiling point was 118° C. at 15 mm. pressure.

Preparation of 5,5'-Dinitro-2,2'-difuryl.

Method A. Eight grams (0.04 mole) of 2-bromo-5-nitrofuran was heated one-half hour with 10 g. of copper powder. The reaction tube was surrounded by a metal bath which was held at 200° C. The contents of the tube were washed with ether, dissolved in benzene and filtered. After removal of the benzene, there remained 0.4 g. of 5,5'-dinitro-2,2'-difuryl. This was 9% of the theoretical amount. After several crystallizations from benzene the product melted 213-214° C.

Method B. One hundred grams of furan (27) was nitrated in the usual manner. After decomposing the nitration mixture with water, there remained 1.5 g. of a product which was insoluble in ether. Several crystallizations from benzene brought the melting point of this product to 213-214° C. By the method of mixed melting points it was shown to be identical with the product prepared by the first method. The yield was 1% of the theoretical amount.

Preparation of α,β-Dichloroethyl Ether.

Chlorine gas was passed into 1500 cc. of anhydrous ether for 20 hours. The mixture was distilled on a water bath to 100° C. and the distillate was further chlorinated. The combined residues were fractionated. Boiling range 55-65° C. at 35 mm. pressure. A 2 degree fraction was taken on the second fractionation. The yield was 500 gm. of α,β-dichloroethyl ether.

Preparation of 2-Methyl-3-furoic Acid.

One hundred cubic centimeters of water was placed in a 1-liter 3-necked flask. One hundred and thirty grams (1 mole) of acetoacetic ester and 143 g. (1 mole) of α,β-dichloroethyl ether (46) (47) were placed in one dropping funnel and 142 g. (1.8 moles) of pyridine (48) was placed in the other. The two solutions were allowed to drop into the flask with stirring so as to finish simultaneously in 1½ hours. The mixture was allowed to stir for 16 hours at 45-50° C., extracted with ether, washed with 250 cc. of 20% hydrochloric acid, dried over sodium sulfate, and distilled. The fraction boiling 70-100° C. at 20 mm. pressure was saponified to give 45 g. of crude 2-methyl-3-furoic acid. It may be crystallized from water or converted directly to the ester by dissolving in anhydrous ethyl alcohol and saturating the solution with hydrogen chloride gas.

Bromination of 2-Methyl-3-furoic Acid.

In a 500 cc. 3-necked flask equipped with a dropping funnel, stirrer, and thermometer was placed 30 g. (0.235 mole) of 2-methyl-3-furoic (49) acid in 150 cc. of glacial acetic acid. A small amount of acetic anhydride was added to the glacial acetic acid to insure anhydrous conditions. To this was added dropwise at 5° C, 56 g. (0.35 mole) (18 cc.) of bromine in 50 cc. of glacial acetic acid. When all of the bromine had been added, the mixture was stirred for two hours and allowed to stand overnight at room temperature. The mixture was poured into ice-water, filtered, and dried to give 34.5 g. of 5-bromo-2-methyl-3-furoic acid melting 115-118° C. This is 70% of the theoretical amount.

Esterification of 5-Bromo-2-methyl-3-furoic Acid.

Sixty-one grams (0.3 moles) of 5-bromo-2-methyl-3-furoic acid was refluxed for 5 hours with 250 g. (2.2 moles) of thionyl chloride. The excess thionyl chloride was removed at atmospheric pressure. The residue was added slowly with stirring to 300 cc. of absolute ethyl alcohol, and refluxed 4 hours. There was obtained on distillation 58 g. of ethyl 5-bromo-2-methyl-3-furoate boiling 123-124° at 22 mm. pressure. This was 83% of the theoretical amount.

Saponification equivalent: Calc'd for $C_8H_9O_3Br$, 233.0

Found, 232.0

Other constants are:

N^{25}_{D} 1.4942; N^{20}_{D} 1.4970; D^{25}_{25} 1.388

MR_D Calc'd 47.47, Obs. 48.83.

Attempted Preparation of 5,5'-Dimethyl-3,3'-dicarboethoxy-2,2'-difuryl.

Fifty grams of ethyl 5-bromo-2-methyl-3-furoate was refluxed for one hour with 20 g. of copper powder keeping the bath temperature at 230° C. The reaction mixture was allowed to cool, extracted with ether, and distilled. Thirty-five grams of the unchanged ester was recovered. There remained a tarry substance which was saponified with alcoholic potassium hydroxide. Upon acidifying this solution no difuryl acid was obtained.

Mercuration of 2,5-Dimethylfuran (36).

A solution of 50 g. (0.52 mole) of dimethylfuran (50) in 250 cc. of ethyl alcohol was added to the mercurating solution prepared from 135 g. (0.5 mole) of mercuric chloride, 82 g. (1 mole) of anhydrous sodium acetate, and 500 cc. of water. Precipitation began within one minute and, after stirring for 2 days, the reaction was complete. The crude product, evidently a complex of the type described by Gilman and Wright (42), was filtered and refluxed with a liter of ethyl alcohol for 5 hours. The cooled filtrate yielded 80 g. of a light tan crystalline solid melting at 138-140°. This was 45% of the theoretical amount.

Preparation of 2,5-Dimethyl-3-iodofuran.

Eighty grams (0.25 mole) of the above mercurial was suspended in 500 cc. of water and stirred rapidly during the slow addition of a solution of 63 g. (0.25 mole) of iodine and 82 g. (0.5 mole) of potassium iodide in 500 cc. of water. After the last addition, the mixture was stirred for one hour, the excess of iodine was reduced with sodium thiosulfate, and the mixture steam distilled. The steam distillate was ether extracted. The ether extract was dried over anhydrous sodium sulfate and the ether removed. Fractionation of the residue in an atmosphere of nitrogen yielded 22 g. of 2,5 dimethyl-3-iodofuran (36) boiling at 64-65° at 10 mm. pressure. This was 40% of the theoretical amount.

Coupling of 2,5-Dimethyl-3-Iodofuran.

Twenty-two grams (0.1 mole) of the iodo compound and 10 g. of copper powder were sealed in a tube and heated to 180° C. for 1/2 hour. Complete decomposition took place and none of the expected 2,2',5',5-tetramethyl-3,3'-difuryl was isolated.

Preparation of 5-Methyl-2-furoic Acid. (51)

In a 12-liter round-bottomed flask fitted with a separatory funnel and a short fractionating column, 500 g. of technical stannous chloride crystals, 2000 g. of sodium chloride, and 4 liters of 12% sulfuric acid were mixed thoroughly and heated to boiling over a large gas plate using an oil bath. When vigorous ebullition began, a solution of 800 g. of sucrose, cane sugar, in 1 liter of hot water was added slowly through the separatory funnel over a period of 30 to 40 minutes. The 5-methyl-2-furfural distilled out as rapidly as it was formed, and an efficient condenser was necessary to avoid loss. The distillation was continued after all the sucrose had been added, until the distillate came over clear. The entire distillate was carefully neutralized with sodium carbonate, saturate with salt, and distilled. The distillate separated into two layers and contained 27-35 g. of 5-methyl-2-furfural. This is 10-13% of the theoretical amount.

One hundred and twenty-five grams of silver nitrate was converted to the oxide in a 2-liter round-bottomed flask by addition of one liter of 5% sodium hydroxide solution. The precipitate was allowed to settle and the solution of sodium nitrate was decanted in order to prevent serious bumping if it were left in the flask. The distillate containing the methyl furfural was then added along with a solution composed of 15 g. of sodium hydroxide and enough water to make 1 to 1 1/2 liters of solution. The contents of the flask was heated to boiling and boiled for 30 minutes with a reflux condenser. The sodium salt was then filtered and the solution concentrated to 250 cc. The concentrated solution was boiled with Norit a few minutes, filtered, and the acid formed by pouring into an excess of dilute hydrochloric acid. On filtration 32 g. of 5-methyl-2-furoic melting at 106-108° C. was isolated, which is sufficiently pure for most purposes. The yield was 11% of the theoretical amount based on the levulose residue of the sucrose.

Esterification of 5-Methyl-2-furoic Acid.

Sixty-three grams (0.5 mole) of 5-methyl-2-furoic acid was dissolved in 350 cc. of anhydrous methyl alcohol and the solution was saturated with hydrogen chloride gas. After standing over night the alcohol was removed under diminished pressure and the residual ester was fractionated in vacuum. There was obtained 60 g. of methyl 5-methyl-2-furoate boiling at 201-3° C. at atmospheric pressure. This is 85% of the theoretical amount.

Preparation of Methyl 5-Methyl-4-iodo-2-furoate.

Seventeen grams (0.12 mole) of methyl 5-methyl-2-furoate was shaken 24 hours in a solution containing 50 cc. of ethyl alcohol, 40 g. (0.12 mole) of mercuric acetate, and 800 cc. of distilled water. At the end of this time the solution was filtered and washed with several quantities of alcohol.

The crude mercurial thus obtained was suspended in 500 cc. of cold water and iodine-potassium iodide solution was added until no more iodine was absorbed after several minutes. The excess iodine was removed with sodium thiosulfate and the mixture ether extracted. After removing the ether, there was obtained 20 g. of methyl 5-methyl-4-iodo-2-furoate. This was 80% of the theoretical amount. After two crystallizations from methyl alcohol the melting point was constant at 55° C.

Anal. Calc'd for $C_7H_7O_3I$; I, 38.65.

Found; I, 38.30, 38.55.

Preparation of Dimethyl 5,5'-Dimethyl-4,4'-difuryl-2,2'-dicarboxylate.

Several trials were made to couple methyl 5-methyl-4-iodo-2-furoate with copper powder at atmospheric pressure and a temperature of about 200° C. Traces that were almost impossible to isolate were the only result of this method.

Therefore, it seemed advisable to try higher temperatures in a sealed tube.

Twenty grams (0.1 mole) of methyl 5-methyl-4-iodo-2-furoate was heated to 250° C. in a sealed tube with 10 g. of copper powder and 1 cc. of glacial acetic acid. The mixture was ether extracted and on removal of the ether there was obtained 4 g. of dimethy 5,5'-dimethyl-4,4'-difuryl-2,2'-dicarboxylate melting at 152-5° C. This was 30% of the theoretical amount. After two crystallizations from ethyl alcohol the melting point remained constant at 160° C.

<u>Anal</u>. Calc'd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.04.
Found: C, 60, 41; H, 5.25.

<u>Saponification of Dimethyl 5,5'-Dimethyl-4,4'-difuryl-2,2'-dicarboxylate</u>.

The ester was boiled with an excess of 20% alcoholic potassium hydroxide, the alcohol distilled, and the residue acidified to give the theoretical amount of 5,5'-dimethyl-4,4'-difuryl-2,2'-dicarboxylic acid. The melting point was over 300° C.

<u>Neutralization equivalent</u>. Calc'd for $C_{12}H_{10}O_6$, 125.0
Found, 124.7.

<u>Preparation of Ethyl 2,5-Dimethyl-3-furoate. (51)</u>.

<u>Method A</u>. One hundred and thirty grams (1 mole) of ethyl

acetoacetate, 102 g. (1 mole) of acetic anhydride, and 197 g. (1 mole) of potassium succinate in a 1-liter round-bottomed flask fitted with a reflux condenser was heated two hours in a water bath. The mixture was allowed to cool and was dissolved in water. The water solution was ether-extracted and then the ether solution was treated with sodium carbonate solution. This solution was acidified with cold dilute sulfuric acid and ether-extracted. The ether solution was dried over anhydrous sodium sulfate and distilled until the thermometer registered 100° at 30 mm. pressure. The residue in the flask was then treated with 20 g. of copper powder and heated to 240 - 260° C. in order to decarboxylate the acid. After decarboxylation the remaining material was distilled under diminished pressure. The fraction boiling at 83-85° C. at 6 mm. pressure, or 99-101° C. at 14 mm. was ethyl 2,5-dimethyl-3-furoate. The yield was 17 g. which was 10% of the theoretical amount.

Method 2. Twenty grams of sodium was reacted with ethyl acetoacetate (52) in the usual manner to form the sodium salt. This sodium salt was then coupled by means of iodine and there was obtained 50 g. of crude diethyl diacetosuccinate. The crude diethyl diacetosuccinate from the above run was dissolved in 100 cc. of concentrated sulfuric acid, cooled, and allowed to stand over night. The next day the mixture was poured with stirring into 2 liters of ice-water. The water solution was ether extracted and the ether extract was dried over calcium chloride. After removal of the ether, the product was distilled under diminished pressure, and the fraction boiling 158-163° C. at 20 mm. was collected. There was obtained 35 g. of diethyl 2,5-dimethyl-3,4-dicarboxylate. This ester was then treated with 25 g. of potassium hydroxide in 250 cc. of ethyl ether and brought to the boiling point. After removing the alcohol by distillation, the salt was dissolved in water and acidified with hydrochloric acid to give 25 g. of 2,5-dimethyl-3,4 dicarboxylic acid. The yield was practically quantitative. This acid was placed in a special flask having an enlarged side arm, 10 g. of copper powder was added, and the flask heated in a metal bath until decarboxylation was complete. The acid, which had sublimed into the side arm of the flask, was dissolved in sodium hydroxide and reprecipitated by acidifying. There was obtained 13.5 g. of 2,5-dimethyl-3-furoic acid melting 132-134° C. This was 71% of the theoretical amount. The acid from two of the above runs was dissolved in 200 cc. of anhydrous ethyl alcohol and saturated with hydrogen chloride gas. After standing over night, the alcohol was removed and the product distilled under diminished pressure. There was obtained 28 g. of ethyl 2,5-dimethyl-3-furoate boiling 83-85° C. at 6 mm. pressure. This was 85% of the theoretical amount.

Preparation of Ethyl 2,5-Dimethyl-4-iodo-3-furoate.

Seventeen grams (0.1 mole) of ethyl 2,5 dimethyl-3-furoate was treated with 50 g. (0.15 mole) of mercuric acetate in alcohol-water solution. Crystals appeared in 15 minutes but the reaction was allowed to shake 12 hours. There was obtained 42 g. of the crude mercurial. This product was suspended in a liter of water and treated with a solution of 27 g. (0.15 mole) of iodine and 50 g. (0.3 mole) of potassium iodide in 150 cc. of water. The reaction mixture was treated with sodium thiosulfate, ether extracted, and the ether removed. The solid thus obtained was contaminated with various inorganic mercury compounds. Therefore, the organic mercurial was dissolved in petroleum ether. After removal of this solvent, the ethyl 2,t-dimethyl-4-iodo-3-furoate was crystallized from ethyl alcohol. There was obtained 21 g. melting 42-43° C. This was 71% of the theoretical amount.

<u>Anal</u>. Calc'd for $C_9H_{11}O_3I$; I, 43.20

Found; I, 43.71, 43.50.

Preparation of 2,2',5,5'-Tetramethyl-3,3'-dicarboethoxy-4,4'-difuryl.

Eleven grams (0.037 mole) of ethyl 2,5-dimethyl-4-iodo-3-furoate was heated to 210° C. (outside temperature) with 10 g. of copper powder for 1/2 hour. The inside temperature rose to as high as 260° C. The reaction mixture was cooled, extracted with ether, and filtered. The ether was removed and the product crystallized from ethyl alcohol. There was obtained 3.5 g. of 2,2',5,5' tetramethyl-3,3'-dicarboethoxy-4,4'-difuryl melting 81-82.5°. This was 65% of the theoretical amount. After two further recrystallizations from ethyl alcohol, followed by a sublimation, the material melted 81.5-82.5° C.

<u>Anal.</u> Calc'd for $C_{18}H_{22}O_6$: C, 64.67; H, 6.60.
Found, C, 64.32; H, 6.56.

<u>Saponification of 2,2',5,5'-Tetramethyl-3,3'-dicarboethoxy-4,4'-difuryl.</u>

The previously described ester was saponified with strong alcoholic potassium hydroxide, the alcohol removed, the residue treated with water, and poured into an ice-hydrochloric acid mixture. The resulting acid was crystallized several times from alcohol and melted 280-281° C. The yield was practical quantitative.

<u>Neutralization equivalent.</u> Calc'd for $C_{14}H_{14}O_6$, 139.0
Found, 140.2

<u>Anal.</u> Calc'd for $C_{14}H_{14}O_6$: C, 60.40; H, 5.04.
Found: C, 59.80; H, 5.34.

SUMMARY

1. A number of new compounds in the difuryl series have been reported.

2. Incidental to the coupling reaction to form the difuryls, a study of the reactivity of some halogens attached to the furan ring has been made. The usual series $I > Br > Cl$ has been found to apply. Negative groups which increase the activity of the halogen in order of decreasing effect are: - $-COOC_2H_5 > NO_2 > - COCH_3$. One of these groups in a position adjacent to an halogen greatly increases its activity. These groups when in a 5-position from a 2-halogen increase its activity more than when in a 4-position.

3. In an attempt to find a difuryl which would show the diphenyl type of isomerism, 2,2',5,5'-tetramethyl-3,3'-difuryl-4,4'-dicarboxylic acid has been prepared. Optical studies on this compound will be of interest in elucidating the structure of the furan ring.

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