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Abnormal nucleophilic attack on the furan nucleus

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ABNORMAL NUCLEOPHILIC ATTACK
ON THE FURAN NUCLEUS

by

Wendell Clarence Overhults

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Physical-Organic Chemistry

Approved:



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Iowa State College

1954

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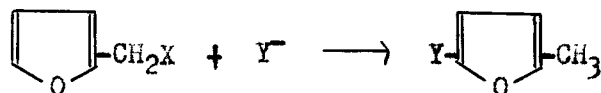
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INTRODUCTION

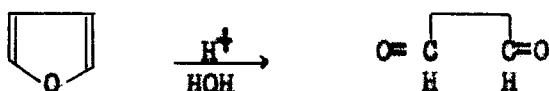
Abnormal nucleophilic displacement reactions on the furan nucleus have been noted previously, but have not been studied extensively. Displacement is considered to be abnormal when the nucleophilic agent is found to be bonded to a different atom in the product than the atom to which the displaced group was bonded in the original molecule. The most common examples of this attack are found in furfuryl derivatives, in which a group or atom bonded in the alpha position results in a product with the nucleophilic group bonded to the five position of the furan nucleus.



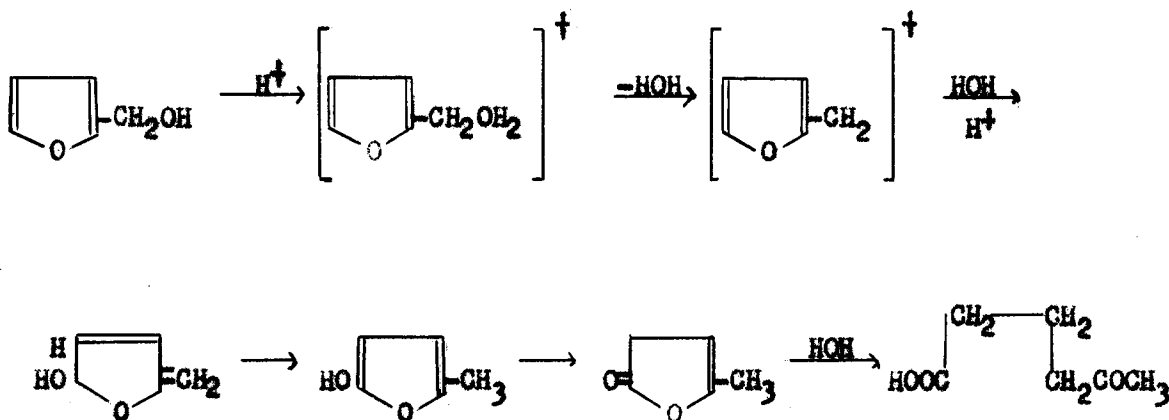
This work was instituted in an attempt to discover conditions which favor abnormal displacement and to learn more about the reaction mechanism or mechanisms which are involved in such displacements.

HISTORICAL REVIEW

Reaction schemes involving "abnormal" displacements by nucleophilic agents on the furan nucleus have been postulated to explain many reactions of furans, notably reaction involving opening of the furan ring. Since these reactions have been adequately reviewed recently,^{1,2} only a few examples will be discussed here. The product formed by the acidic hydrolysis of furan is the dialdehyde, succinaldehyde.



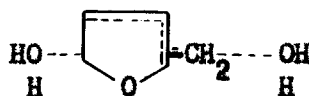
However, in the acidic hydrolysis of furfuryl alcohol, the keto-aldehyde, which analogously might be expected to form, is not isolated but instead levulinic acid is obtained. In an attempt to explain the formation of this compound, a reaction scheme in which a water molecule attacks "abnormally" in the five position of the furan nucleus has been proposed.²



¹T. D. Nevitt, Thesis (M.S. in Chemistry), Iowa State College. 1951.

²A. P. Dunlop and F. N. Peters. "The Furans", Reinhold Publishing Corporation, New York, N. Y. 1953.

The furfuryl carbonium ion may be actually pre-formed as shown above, or a water molecule could attack the furfuryl alcohol in the five position and simultaneously displace another water molecule from the protonated furfuryl alcohol, involving a transition state such as the one shown below.



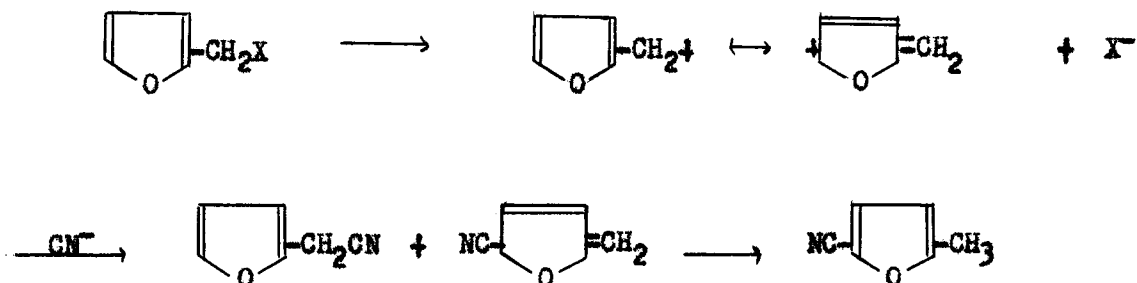
The best known and possibly the only authentic examples of abnormal nucleophilic displacement in furans involve the reaction of a furan with cyanide ion. The first of these reactions noted was the reaction of 2-furfuryl chloride with potassium cyanide to give 15 percent of the normal nitrile, furfuryl cyanide, and 85 percent of the "abnormal" nitrile, 5-methyl-2-cyanofuran.³ Other examples are the reaction of 3-furfuryl chloride⁴ and furfuryltrimethylammonium iodide⁵ with cyanide ion to give 90 percent normal, 10 percent abnormal, and 85 percent normal, 15 percent abnormal nitriles, respectively. These reactions can be explained by two general mechanisms. The first, or so-called S_N1 mechanism, involves the preliminary and rate determining ionization of the furfuryl compound to yield a furfuryl carbonium ion. This carbonium ion might be considered to be an allylic ion having the usual contributing resonance structures which

³(a) M. M. Runde, E. W. Scott and J. R. Johnson, J. Am. Chem. Soc., 52, 1284 (1930). (b) E. W. Scott and J. R. Johnson, ibid., 54, 2549 (1932). (c) T. Reichstein, Ber., 63, 749 (1930).

⁴E. Sherman and E. D. Amstutz, J. Am. Chem. Soc., 72, 2195 (1950).

⁵E. L. Eliel and P. E. Peckham, J. Am. Chem. Soc., 72, 1209 (1950).

would entail a partial positive charge in the five position.



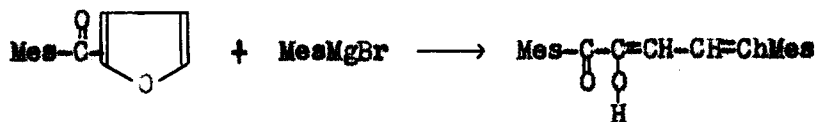
The allylic carbonium ion can then react with the cyanide ion to give a mixture of two products as is usual for ions of this type. The product formed by coordination of the cyanide in the five position can then undergo a proton shift to form the nitrile isolated.

The other reaction scheme would involve a combination of $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2^6$ reactions. The normal nitriles could be formed by a second order displacement of the chloride or trimethylammonium group by cyanide ion. The abnormal product would be formed by a second order displacement, with cyanide ion attacking in the five position and simultaneously displacing the leaving ion. This nitrile could then rearrange as postulated before in the $\text{S}_{\text{N}}1$ mechanism.

A recent reaction, not involving cyanide ion, which might be interpreted as an "abnormal" displacement on the furan nucleus is the reaction of mesitylmagnesium bromide with 2-mesitylfuran⁷ to form 1,5-dimesityl-2,3-pentadien-2-ol-1-one.

⁶R. E. Kepner, W. G. Young and S. Winstein, J. Am. Chem. Soc., 71, 115 (1949).

⁷R. C. Fuson and H. P. Wallingford, J. Am. Chem. Soc., 75, 5950 (1953).



In this reaction, 1,6 addition of the Grignard reagent takes precedence over the more common 1,4 addition to α, β unsaturated ketones. If the four and five positions of the ring are blocked as in 2-benzofuryl ketones,⁸ 1,4 addition does take place. This reaction is another example of preference for nucleophilic attack in the five position over that in the three position of the furan nucleus, although in this case reaction in the five position is also aided by coordination of the Grignard reagent with the adjacent oxygen atom.

Since the occurrence and relative importance of abnormal nucleophilic reactions seem to vary both with the type of furan and the type of nucleophilic reagent employed, a study of the conditions favorable for abnormal nucleophilic attack was instituted. This study involved two general phases, an attempt to discover other examples of abnormal attack, and a study of the kinetics of reaction of furfuryl chloride with various nucleophilic reagents.

⁸(a) R. C. Fuson, E. W. Kaiser and S. B. Speck, J. Org. Chem., 6, 845 (1941). (b) R. E. Lutz and W. G. Reveley, J. Am. Chem. Soc., 63, 3178 (1941).

EXPERIMENTAL

Materials

Furfuryl alcohol. Furfuryl alcohol, furnished by the Quaker Oats Company, was redistilled at reduced pressure using a nitrogen atmosphere shortly before use.

p-Toluenesulfonyl chloride. p-Toluenesulfonyl chloride (Eastman Kodak, white label) was distilled before use.

Calcium hydride. Calcium hydride was purchased from Metal Hydrides.

Sodium hydride. Sodium hydride was obtained from Metal Hydrides.

Silver nitrite. Mallinckrodt silver nitrite was used.

Acetone. Mallinckrodt "Analytical Grade" acetone was dried over Drierite for at least one week and distilled just before use.

Tetrabutylammonium hydroxide. This compound was prepared by the reaction of tetrabutylammonium iodide (Eastman Kodak, white label) and silver oxide.⁹

Lithium acetate. Lithium acetate was prepared by neutralizing lithium hydroxide with acetic acid. Most of the water was evaporated and the salt dried for 48 hours at 110°. The lithium acetate was 99.98 percent pure as shown by titration with perchloric acid.

Furfuryl chloride. Furfuryl chloride was prepared according to the directions of Kirner.¹⁰ The furfuryl chloride was distilled shortly before use under reduced pressure from sodium carbonate into a flask containing sodium carbonate, and diluted with dry ether.

⁹D. B. Paul and C. A. Kraus, J. Am. Chem. Soc., 62, 1140 (1940).

¹⁰W. R. Kirner, J. Am. Chem. Soc., 50, 1955 (1928).

Rhodanine. This compound was Eastman Kodak, white label.

Sodium hydroxide. Carbonate-free solutions were prepared by adding a saturated solution of sodium hydroxide to freshly boiled water. The solutions were standardized with potassium acid phthalate using phenolphthalein as indicator.

Hydrochloric acid. The solutions were prepared by diluting c.p. hydrochloric acid with freshly boiled water. The solutions were standardized by titration with standard sodium hydroxide.

Triethylamine. The solutions were prepared by adding freshly distilled triethylamine (Eastman Kodak, white label) to 90 percent aqueous acetone solution. The solutions were standardized by titration with hydrochloric acid using bromphenol blue as indicator.

Reactions

The attempted synthesis of α -furfuryl tosylate. To a solution of 14.7 grams (0.15 mole) of furfuryl alcohol in 100.0 milliliters of dry pyridine at -10° , was added gradually, with stirring, 28.7 grams (0.15 mole) of p-toluenesulfonyl chloride. After addition of the p-toluenesulfonyl chloride, which took approximately 30 minutes, the mixture was allowed to warm to 0° and stirring continued for 3 hours. About 30 minutes after the addition of tosyl chloride a white precipitate appeared and the solution became amber colored. The mixture was then poured into ice water from which a small amount of oil separated. The oil could not be crystallized from benzene, petroleum ether or dioxane. The above procedure was then repeated except the mixture was not poured into ice water. Instead, the

white precipitate was filtered. A partially dried sample did not melt at 120° (m.p. *p*-toluenesulfonyl chloride, 69° , pyridine hydrochloride, 69°). The compound which appeared to be hygroscopic was dried over phosphorous pentoxide in a vacuum desiccator overnight. The material decomposed, becoming dark and discolored. No accurate melting point could be taken and recrystallization was not successful. Evaporation of the original pyridine filtrate under reduced pressure gave a copious precipitate, originally white, but which decomposed when drying was attempted. The above procedure was essentially repeated except that only 0.15 mole of pyridine was used and 100.0 milliliters of dry benzene was used as solvent. Again the white precipitate obtained decomposed on drying over phosphorous pentoxide or paraffin. Recrystallization was not successful.

In another attempted preparation of furfuryl tosylate, the calcium salt of furfuryl alcohol was prepared by adding, with stirring, 1.96 grams (0.02 mole) of furfuryl alcohol to 0.842 gram (0.02 mole) of calcium hydride in 150.0 milliliters of dry ether. After addition of the alcohol, the mixture was stirred for 3 hours. Then 2.0 grams (0.01 mole) of *p*-toluenesulfonyl chloride was added in small portions, and the stirring continued for 2 hours. The solid material was filtered, and the ether removed under reduced pressure. After removal of the ether, the oil which remained darkened and decomposed quickly. Again recrystallization was not successful.

The sodium salt of furfuryl alcohol was prepared by the reaction of furfuryl alcohol with equivalent quantities of sodium or sodium hydride in ether. The reaction with sodium gave a pink colored product, but the

reaction with sodium hydride gave a white salt which appeared to be purer. The ethereal suspension was then allowed to react with an equivalent amount of *p*-toluenesulfonyl chloride. The sodium chloride formed was filtered and the ether removed leaving a white solid which decomposed as before.

The attempted synthesis of α -furfuryl methosylate. The preparation was attempted by adding *p*-methoxybenzenesulfonyl chloride¹¹ to the sodium salt of furfuryl alcohol as described previously with tosyl chloride. Attempted isolation of a solid product gave the usual dark, gummy mixture. The addition of a suspension of the sodium salt in ether to an equivalent amount of *p*-methoxybenzenesulfonyl chloride dissolved in ether gave the same result.

The reaction of the 2,4-dinitrophenyl ether of furfuryl alcohol with cyanide ion. A suspension of 2.0 grams of furfuryl 2,4-dinitrophenyl ether¹² was shaken with 8.0 grams of potassium cyanide in 10.0 milliliters of water at 70° for one hour. The solution became dark brown, but most of the ether appeared to be unaffected by this treatment. The solution was then extracted with ether, the ether evaporated and 20.0 milliliters of 25 percent potassium hydroxide added to the residue. After heating for one hour at 90°, the alkaline solution was extracted with ether and the aqueous layer cooled to 10° and neutralized with hydrochloric acid. No precipitate was formed. The procedure was repeated using 90 percent ethyl alcohol as solvent with the same result. The period of reaction was varied up to 96

¹¹M. S. Morgan and L. H. Critcher, J. Am. Chem. Soc., 70, 375 (1948).

¹²H. Normant, Ann. Chim., 17, 335 (1942).

hours with no result.

When the method was repeated using 90 percent aqueous acetone as solvent, a deep purple color was formed when the potassium cyanide solution was added to the acetone solution of the ether. The acetone solution was kept at 35° for 48 hours. The water-insoluble ether appeared to have reacted at this time since no solid precipitated when water was added to the solution. The acetone-water solution was then extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate. Removal of the ether gave a dark brown oil with a sweet odor. Fifty milliliters of 25 percent methyl alcoholic potassium hydroxide was added to the oil and the solution was refluxed for one hour. Water was added and the mixture was extracted with ether. The aqueous extract was neutralized with hydrochloric acid. A dark brown precipitate formed. The material darkened between 200° and 250°, but did not melt at 310° (m.p. 2-furylacetic acid, 67.3°-67.5°, 5-methylfuroic acid, 108°-109°).

The reaction of furfuryl p-nitrobenzoate with cyanide ion. To 2.0 grams of furfuryl p-nitrobenzoate¹³ dissolved in 75.0 milliliters of alcohol was added 2.5 grams of potassium cyanide in 15.0 milliliters of water. The solution was heated at 35° for 48 hours. Most of the alcohol was removed, water was added and the solution was extracted with ether. Addition of hydrochloric acid to the aqueous extract gave a white precipitate of p-nitrobenzoic acid. On evaporation of the ether extract a small amount of yellow oil remained. However, attempted hydrolysis of this oil with methyl

¹³R. D. Kleine and S. Freid, J. Am. Chem. Soc., 62, 3516 (1940).

alcoholic potassium hydroxide gave no acid product.

The reaction of furfuryl p-nitrobenzoate with ethoxide ion. Sodium ethoxide was prepared by adding 0.8 gram of sodium to 100.0 milliliters of absolute alcohol in a flask protected from moisture with a calcium chloride tube. Eight grams of the p-nitrobenzoate of furfuryl alcohol were then added to the flask and allowed to react for one hour. The alcohol was removed by distillation, water added, and the mixture extracted with ether. Neutralization of the aqueous extract gave a large amount of p-nitrobenzoic acid, indicating that most of the ester was cleaved. Distillation of the ether extract gave a small amount of liquid, b.p. 80° (25 mm.). This liquid reacted slowly with sodium. Attempts to prepare adducts with maleic anhydride were not successful. The material decomposed within 24 hours, and other means of identification were not successful.

Kinetics of the reaction of furfuryl p-nitrobenzoate and hydroxide ion.

Freshly distilled, commercial absolute alcohol was diluted with water to give an 85.4 percent by weight solution. The composition was determined by density measurements. Enough anhydrous lithium perchlorate was added to give an 0.0989 molar solution. Approximately 0.1 normal sodium hydroxide solution was prepared by adding a saturated solution of sodium hydroxide to part of the lithium perchlorate-alcohol-water solution. A weighed sample of furfuryl p-nitrobenzoate was dissolved in 90.0 milliliters of the reaction solvent and allowed to equilibrate for 30 minutes in a thermostated water bath. Ten milliliters of sodium hydroxide solution were pipetted into excess standard hydrochloric acid and back-titrated with sodium hydroxide using phenolphthalein as indicator.

Temp.	Conc. p-nitro-benzoate	Conc. hydroxide	Percent completion	$k_2 \times 10^2$
29.4°	0.00691	0.01097	92	9.08
20.9°	0.00995	0.01169	93	4.20
	0.00523	0.01672	93	4.52

Reaction of furfuryl chloride with silver nitrite. To 7.7 grams (0.05 mole) of silver nitrite in 50.0 milliliters of acetonitrile was added dropwise 0.05 mole of furfuryl chloride in 50.0 milliliters of acetonitrile. The silver chloride formed was filtered. The very dark brown solution was distilled to remove acetonitrile and recrystallization of the residue attempted without success. Basic extraction of the residue also was not successful. The reaction was not investigated extensively.

Attempted preparation of 3,4-diphenylfurfuryl methosylate. 3,4-Diphenyl-2-furyl carbinol was prepared by reduction of the methyl ester of 3,4-diphenyl-2-furoic acid¹¹ with lithium aluminum hydride. The sodium salt of the alcohol was prepared by the same procedure as with furfuryl alcohol and reacted with p-methoxybenzenesulfonyl chloride.¹¹ No pure solid product could be isolated.

Preparation of 3,4-diphenyl-2-furfuryl bromide. To 4.2 grams (0.017 mole) of 3,4-diphenyl-2-furyl carbinol in 200.0 milliliters of dry ether was added dropwise, with stirring, 13.5 grams (0.05 mole) of phosphorous tri-bromide. After one hour 3.0 milliliters of water was added dropwise and the ethereal solution washed quickly, first with 5.0 milliliters of 50

¹¹H. J. Backer and W. Stevens, Rec. Trav. Chim., 59, 423 (1940).

percent potassium hydroxide solution, then with water. The solution was dried over sodium sulfate and the ether distilled under reduced pressure, leaving a light colored liquid. The liquid was dissolved in Skelly B and the solution cooled to -40° . A white crystalline product was obtained which was recrystallized several times in this manner, m.p. 57° - 58° . Impure samples decomposed quickly and even the pure samples showed signs of decomposition after 72 hours in a vacuum desiccator.

Attempted preparation of 3,4-diphenyl-2-furylacetic acid. The acid chloride (m.p. 157° - 158°) of the acid was prepared using thionyl chloride. To a solution of diazomethane (0.048 mole) in ether was added in small portions at 0° , 4.5 grams (0.016 mole) of the acid chloride. After addition was complete the mixture was allowed to come to room temperature and stirring was continued for 12 hours. The ether was removed under reduced pressure and the yellow solid remaining recrystallized from benzene, m.p. 144° - 145° . Five grams (0.02 mole) of this compound was suspended in 75.0 milliliters of dioxane and added dropwise with stirring to a mixture of 5.0 grams of freshly prepared silver oxide and 5.0 grams of sodium thio-sulfate in 300.0 milliliters of water at 60° - 70° . The mixture was stirred at this temperature for 5 hours, then the temperature was raised to 90° for 15 minutes. The solution was cooled, diluted with water, filtered and acidified with hydrochloric acid giving a brown oily solid, m.p. 125° - 150° . Attempts at purification by recrystallization and by chromatography using an alumina column were not successful.

The preparation of 3,4-diphenyl-2-furylacetic acid was also attempted using the furfuryl rhodanine compound as an intermediate. The acid

chloride of 3,4-diphenyl-2-furoic acid was prepared as before and a Rosenmund reduction carried out using toluene as solvent and palladium on barium sulfate as catalyst, essentially according to the procedure of Gilman¹⁵ to prepare 4-carbomethoxy-2-furfuraldehyde. The toluene was removed under reduced pressure. The aldehyde was not purified because decomposition appeared to be taking place, but was dissolved in glacial acetic acid and rhodanine and sodium acetate added. The solution was refluxed for 30 minutes, poured in water, the crystals filtered, washed with water, alcohol and ether and recrystallized from acetone according to the method of Julian and Sturgis.¹⁶ The compound is a bright red and melts with decomposition at 308°-309°. The rhodanine compound was hydrolyzed with 15 percent sodium hydroxide to 3-(3,4-diphenyl-2-furyl)-2-thioketopropionic acid, m.p. 117°-118°. The thioketo acid was reacted with hydroxylamine according to method of Plucker and Amstutz¹⁷ to give 3-(3,4-diphenyl-2-furyl)-2-oximinepropionic acid, m.p. 144°-145°. The acid was simultaneously decarboxylated and dehydrated by heating with acetic anhydride. Steam distillation of the supposed nitrile was attempted but extensive polymerization took place and only a small amount of the material was distillable. This material was refluxed in 20 percent sodium hydroxide for 12 hours and on acidification with hydrochloric acid, a small amount of acid was precipitated. However, the acid product could not be

¹⁵H. Gilman, R. R. Burtman and E. W. Smith, J. Am. Chem. Soc., 55, 403 (1933).

¹⁶P. L. Julian and B. M. Sturgis, J. Am. Chem. Soc., 57, 1126 (1935).

¹⁷J. Plucker and E. D. Amstutz, J. Am. Chem. Soc., 62, 1512 (1940).

purified. The procedure was repeated except that distillation was not attempted. At this point the solution was extracted with ether, the ether removed and hydrolysis of the resulting oil attempted with 20 percent sodium hydroxide. After 7 days of refluxing only a very small amount of acid product was found and extensive decomposition had taken place. Repeating the process using alcoholic sodium hydroxide was not successful.

The attempted preparation and preparation of 3,4-diphenyl-5-methylfuroic

acid. In an attempt to prepare the acid, the metalation of 3,4-diphenyl-2-furoic acid was attempted. The acid was dissolved in dry ether and an ethereal solution of two equivalents of butyllithium¹⁸ was added dropwise. The reaction mixture was stirred for periods varying from one hour to three days. An equivalent of methyl iodide was then added and the mixture refluxed for periods varying up to three days. Upon working up the reaction mixture only unchanged acid was isolated and characterized, although some non-acidic material, probably a ketone, was isolated. Upon carbonation of the reaction mixture before the addition of methyl iodide, no di-acid could be isolated, indicating that the original acid had not been metalated.

An attempt to prepare the half-ester or half-acid chloride of 3,4-diphenyl-2,5-furandicarboxylic acid was made. Either of these compounds could be reduced with lithium aluminum hydride to the half-alcohol and then to the hydrocarbon. One equivalent of diazomethane was added dropwise

¹⁸H. Gilman, J. A. Bee, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, J. Am. Chem. Soc., 71, 1499 (1949).

to an ethereal solution of the acid at 0° . The mixture was allowed to stand two hours at room temperature. When the ether was removed only unreacted di-acid and di-ester could be isolated. Esterification using methyl alcohol and dry hydrochloric acid with excess methyl alcohol solvent or benzene as solvent gave the same products. Reaction of the di-acid with one equivalent of thionyl chloride gave only the di-acid chloride and unreacted di-acid.

The methylation of 3,4-diphenyl-2-furoic acid. To 5.0 grams of aluminum chloride in 100.0 milliliters of carbon disulfide was added dropwise with stirring, a carbon disulfide solution of 5.0 grams (0.018 mole) of methyl 3,4-diphenyl-2-furoate. The reaction mixture was cooled in an ice bath during addition. After addition was complete, the ice bath was removed and the mixture allowed to stand 24 hours. The mixture was poured into cracked ice and the aluminum hydroxide filtered. After removal of carbon disulfide, the solid product was sublimed, yielding a white solid, m.p. 121° - 122° . The infra-red spectrum of this compound was different from that of methyl 3,4-diphenyl-2-furoate.

Kinetics of the hydrolysis of furfuryl chloride. The reaction was carried out in a 250.0 milliliter rubber-stoppered Erlenmeyer flask. The rubber stopper was fitted with inlet tubes for a glass stirrer and a microburet. Forty-five milliliters of acetone and 5.0 milliliters of water were pipetted into the flask and allowed to equilibrate for 15 minutes in a thermostated bath at 30.8° . One milliliter of an ethereal furfuryl chloride solution and 5 drops of bromphenol blue indicator were added, the stirrer started, and a small amount of standard triethylamine solution

added. Zero time was taken when the indicator turned to its acid color. Another small portion of triethylamine was added and the time to indicator change was noted. No difference in rates under acid or basic conditions was noted as shown by runs in which the solution was allowed to be acid most of the time except for a few seconds following the addition of triethylamine. The reaction was followed to 90 percent completion. The initial concentration of furfuryl chloride was determined by adding 20.0 milliliters of water to the reaction at the completion of the measured run and titrating, after two hours, with triethylamine. A sample kinetic run is given below:

(Furfuryl chloride) = 0.009859 mole/liter.

(Triethylamine) = 0.1116 N.

Time	Milliliters tri-ethylamine added	$k_1 \times 10^5$ Sec. ⁻¹
0	0.000	
2'16"	0.040	3.34
4'58"	0.086	3.24
7'36"	0.130	3.19
10'30"	0.182	3.45
13'23"	0.230	3.22
15'58"	0.274	3.31
18'39"	0.324	3.50
21'30"	0.374	3.29
24'23"	0.424	3.34
27'18"	0.474	3.38
30'12"	0.524	3.39
32'47"	0.570	3.46
35'27"	0.616	3.34
...		
71'27"	1.212	3.43
...		
144'14"	2.464	3.39
...		
312'30"	4.404	3.50
...		
350'17"	<u>4.706</u>	3.48
Total	8.830	
Average		3.40

Kinetics of the reaction of furfuryl chloride with iodide ion. To a 90 percent aqueous acetone solution was added various amounts of potassium iodide and enough potassium chloride to almost saturate the solution. Twenty-five milliliter samples of this solution were pipetted into test tubes. The tubes were stoppered and allowed to equilibrate at 30.8° in a thermostated water bath. One milliliter of an ethereal solution of furfuryl chloride was added to each tube. The time of half-addition was taken as the zero time. The addition of furfuryl chloride caused potassium chloride to precipitate. The tubes were removed at intervals, and the contents filtered through a sintered glass Buchner funnel and washed with dry acetone. The precipitated chloride was then dissolved in water and a Volhard determination for chloride was made. The initial concentration of furfuryl chloride was determined by analysis of a tube which was allowed to react for 48 hours. A sample kinetic run is given below:

(Furfuryl chloride) = 0.03044 M. (Potassium chloride) = 0.0454 M.

(Potassium iodide) = 0.05061 M. (Silver nitrate) = 0.0292 N.

(Potassium thiocyanate) = 0.0297 N.

Time	$k_2 \times 10^2$	Milliliters AgNO ₃	Milliliters KCNS
9'27''	1.08	5.00	1.528
15'20''	1.01	5.00	0.090
22'16''	1.01	10.00	3.788
28'42''	1.30	10.00	2.422
38'36''	1.12	10.00	1.340
47'28''	1.10	10.00	0.784
56'19''	1.09	15.00	3.264
Average	1.10		

Kinetics of the reaction of furfuryl chloride with hydroxide ion. Ten milliliters of aqueous tetrabutylammonium hydroxide or potassium hydroxide was added to 90.0 milliliters of dry acetone in a 250.0 milliliter glass-stoppered Erlenmeyer flask. The use of tetrabutylammonium hydroxide was more satisfactory since larger concentrations of hydroxide could be obtained. The solution was equilibrated for 15 minutes at 30.8° in a thermostated water bath. One milliliter of ethereal furfuryl chloride solution was added. Ten milliliter samples were pipetted in 10.0 milliliters of Skelly B and the aqueous layer removed. The Skelly B solution was washed three times with 10.0 milliliter portions of ice water. The combined filtrates were extracted with hydrochloric acid using phenolphthalein as indicator. The initial concentration of furfuryl chloride was determined by adding a sample to 50.0 milliliters of water and titrating the base remaining after 6 hours. A sample kinetic run is given below:

(Furfuryl chloride) = 0.02127 mole/liter.

(Tetrabutylammonium hydroxide) = 0.02066 mole/liter.

(Hydrochloric acid) = 0.0270 N.

Time	$k_2 \times 10^3$	Milliliters HCl
11'02''	4.2	7.876
20'46''	5.5	7.263
31'00''	8.2	6.720
43'30''	4.8	6.054
55'23''	4.0	5.604
66'53''	4.7	5.264
82'51''	4.6	4.928
Average	4.6	

Kinetics of the reaction of furfuryl chloride with acetate ion. The same general procedure as used for hydroxide ion was used, except that the chloride content of the aqueous extracts was determined by the Volhard method. A sample kinetic run is given below.

(Furfuryl chloride) = 0.01302 mole/liter.

(Lithium acetate) = 0.03757 mole/liter.

Time	$k_2 \times 10^4$	Milliliters 0.02846 N. AgNO ₃	Milliliters 0.03219 N. KCNS
14'53''	6.46	5.00	3.264
29'14''	6.62	5.00	3.060
46'15''	7.22	5.00	2.870
59'45''	7.55	5.00	2.652
71'25''	6.39	5.00	2.352
85'54''	6.52	5.00	2.386
Final		10.00	2.042
Average	6.76		

Kinetics of the reaction of furfuryl chloride with thiosulfate ion. Since sodium thiosulfate is practically insoluble in 90 percent aqueous acetone, tetrabutylammonium thiosulfate which is more soluble was prepared by the reaction of tetrabutylammonium fluoride and calcium thiosulfate. The calcium fluoride formed was filtered leaving an aqueous solution of the salt. However, the tetrabutylammonium ion forms a complex with iodine so the thiosulfate concentration could not be determined by titration with iodine. Tetrabutylammonium chloride, fluoride and hydroxide also form this complex when iodine is added. The complex, originally yellow, darkens to a reddish brown as more iodine is added. Competitive reactions were then run using 50 percent and 64 percent aqueous acetone solutions. Five milliliters of furfuryl chloride in acetone was added dropwise to 50.0 milliliters of aqueous acetone of varying sodium thiosulfate concentration in a

thermostated water bath at 30.8° . After the solution had reacted for two hours, the thiosulfate remaining was determined by titration with iodine. The original thiosulfate concentration was determined by titrating 50.0 milliliters of the stock acetone-thiosulfate solution with iodine. The furfuryl chloride concentration was determined by hydrolyzing a 5.0 milliliter sample and determining the amount of acid formed. A sample kinetic run is given below:

$$(\text{Iodine}) = 0.0312 \text{ N.}$$

$$(\text{Sodium Hydroxide}) = 0.0309 \text{ N.}$$

Milliliters NaOH	Milliliters I_2 (Initial)	Milliliters I_2 (Final)
40.20	76.96	38.76

$$(\text{Furfuryl chloride}) = 0.001243 \text{ M.}$$

$$(\text{Thiosulfate})_0 = 0.02401 \text{ M.}$$

$$(\text{Thiosulfate})_f = 0.001209 \text{ M.}$$

$$\log \frac{k}{k_0} = 4.269.$$

Table 1
 Rate Constants for Reaction of Furfuryl Chloride with
 Nucleophilic Reagents at 30.8°*

Solvent	(Furfuryl chloride) M.	Nucleophile	(Nucleophile)	k_x^{**}	$\log \frac{k_x^{***}}{k_0}$
90% acetone-water	0.0266	I ⁻	0.0801	1.12×10^{-2}	3.25
"	0.0296	I ⁻	0.0506	1.08×10^{-2}	3.25
"	0.0134	OH ⁻	0.0260	4.0×10^{-2}	2.81
"	0.0080	OH ⁻	0.0309	3.9×10^{-3}	2.80
"	0.0207	OH ⁻	0.0212	3.8×10^{-3}	2.79
"	0.0130	OAc ⁻	0.0376	6.86×10^{-4}	2.05
"	0.0144	OAc ⁻	0.0446	6.72×10^{-4}	2.00

*A representative sample of kinetic runs is listed.

$$**k_x = \frac{k - k_{H_2O}}{[x]}$$

$$\text{where } k = \frac{2.303}{t} \log \frac{[\text{Furfuryl chloride}]_0}{[\text{Furfuryl chloride}]}$$

and $x = \text{OH}^-, \text{I}^-, \text{OAc}^-$.

$$***k_0 = \frac{k_{H_2O}}{[H_2O]}$$

Table 1 (continued)

Solvent	(Furfuryl chloride) M.	Nucleophile	(Nucleophile) M.	k_x	$\log \frac{k_x}{k_o}$
50% acetone-water	0.0248	S ₂ O ₃	0.0480	---	4.27*
"	0.0134	S ₂ O ₃	0.0148	---	4.34
64% acetone-water	0.0268	S ₂ O ₃	0.0420	---	4.00
90% acetone-water	0.00986	H ₂ O	--	3.40 x 10 ⁻⁵	--
"	0.0123	H ₂ O	--	3.42 x 10 ⁻⁵	--

$$*\log \frac{k_{S_2O_3}}{k_o} = \log \frac{[H_2O]^{2.303}}{[Furfuryl\ chloride]_o - [S_2O_3]_f} \log \frac{[S_2O_3]_o}{[S_2O_3]_f}$$

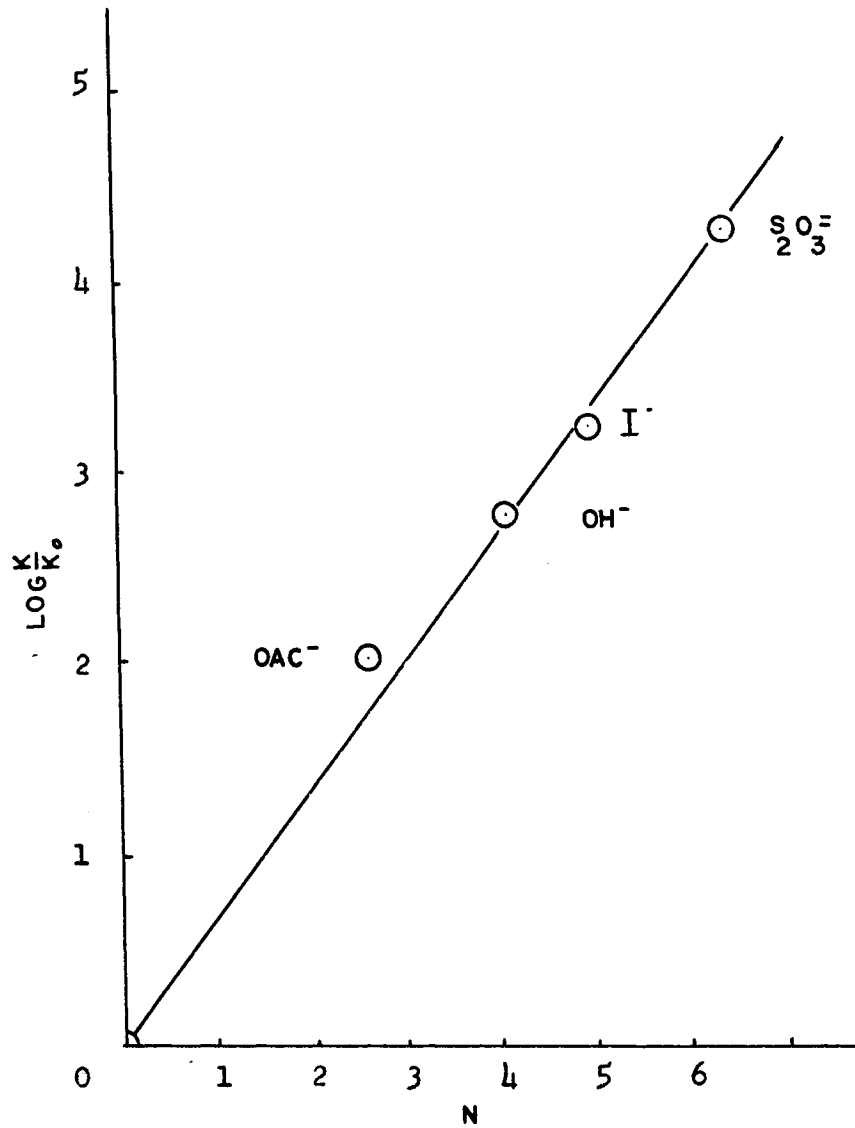


Fig. 1 Correlation of Rate Constants for Reaction of Nucleophiles with Furfuryl Chloride and n Values.

DISCUSSION OF EXPERIMENTAL RESULTS

In the first phase of the study, an attempt was made to discover other examples of abnormal nucleophilic displacement on the furan nucleus. The reaction of furfuryl halides with ethoxide,¹⁹ thiocyanate,²⁰ phenoxide,²¹ sodiomalonic ester,²⁰ thiourea²² and ammonia²³ have been reported to yield only normal products. However, the products were isolated only in amounts varying from 10 to 60 percent of the theoretical yield. The abnormal products may well have been formed and not isolated, and so account for the low yields. However, many other reactions of furans result in low yields. The abnormal product resulting from the attack of cyanide ion on furfuryl halides is more susceptible to the prototropic rearrangement necessary for



the formation of a stable product and, therefore, the product is more easily isolated than the products of reaction with other nucleophiles. The strongly negative cyano group causes the hydrogen of the adjacent carbon to be especially acidic. In the case of the other ions listed above, the

¹⁹W. R. Kirner, *J. Am. Chem. Soc.*, **50**, 1955 (1928).

²⁰W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).

²¹H. Paul and R. Normant, *Compt. rend.*, **204**, 1482 (1937).

²²J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **59**, 2439 (1937).

²³J. E. Zanetti and C. D. Beckmann, *J. Am. Chem. Soc.*, **50**, 2031 (1928).

hydrogen atom is not particularly activated by the adjacent group and this



intermediate, if formed, would be likely to either polymerize or undergo ring opening or other reaction and so not be isolated. Since the nitro group, like the cyano group, is also strongly negative, furfuryl chloride was allowed to react with silver nitrite in the hope that a stable product of substitution in the five position could be isolated. However, no pure product could be isolated and identified from the reaction. This reaction was not investigated extensively.

In another attempt to find reactions involving abnormal nucleophilic displacement, furfuryl derivatives other than the halides were prepared and tested for reaction with nucleophilic reagents. Often one of the aids to facile nucleophilic displacement is the formation of a stable, negative ion by the group being displaced by the nucleophilic agent. According to this principle, furfuryl 2,4-dinitrophenyl ether, with an incipient substituted phenoxy group, and furfuryl *p*-nitrobenzoate, with an incipient acid group, were prepared and allowed to react with potassium cyanide and sodium ethoxide.

Furfuryl 2,4-dinitrophenyl ether gave no discernible reaction with potassium cyanide in aqueous or alcoholic solution. However, when aqueous acetone was used as solvent, a deep purple color developed when potassium cyanide was added to a solution of the ether. This color developed gradually over a period of approximately five minutes. The materials were allowed to react at temperatures varying from room temperature to reflux

and for periods varying from 30 minutes to three days. The originally water-insoluble ether was converted to a more soluble compound which was not precipitated when water was added to the reaction solution. However, no nitrile or acid could be isolated from the reaction. The reaction product which was isolated polymerized readily and may have been formed by opening of the furan ring or reaction of the ether with acetone cyanohydrin ion. Furfuryl 2,4-dinitrophenyl gave no reaction with sodium ethoxide.

Similarly, furfuryl *p*-nitrobenzoate gave no reaction with potassium cyanide in aqueous, alcoholic and aqueous-acetone solutions. However, when the ester was reacted with sodium ethoxide in carefully dried ethyl alcohol, *p*-nitrobenzoic acid was isolated, indicating that abnormal cleavage of the ester had taken place, since the products of normal interchange would have been furfuryl alcohol and ethyl *p*-nitrobenzoate. The other product of abnormal cleavage, furfuryl ethyl ether, could not be isolated although a small amount of material having some ether-like characteristics was isolated. The abnormal cleavage might take place by means of a rate determining step involving ionization of the ester into a furfuryl carbonium ion and *p*-nitrobenzoate ion. Since such a reaction would be first order in the ester, a study of the kinetics of the reaction between the ester and hydroxide ion was made. Normal second order kinetics, that is, first order in ester and first order in hydroxide ion, were found. This result indicated that the cleavage did not take place by means of a furfuryl carbonium ion. However, it did not resolve the problem of whether abnormal cleavage of the ester had actually taken place. Since furfuryl ethyl ether was not isolated, the possibility still exists that

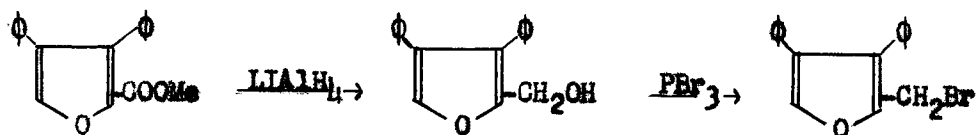
the *p*-nitrobenzoic acid was formed by some other process other than abnormal cleavage. Although the alcohol was very carefully dried and the reaction protected from the atmosphere with all precautions, water may have been present and so explain the formation of the acid.

The second method of attack was to prepare solid furfuryl derivatives which might be expected to have very similar reaction characteristics to those of the furfuryl halides. Solid compounds are more easily purified and tested for purity than liquids and hence are more suitable for kinetic and other measurements. Benzenesulfonates and substituted benzenesulfonates are often solid, whereas, the corresponding halides are liquids. These compounds react very similarly to the corresponding halides. Therefore, an attempt was made to prepare the *p*-toluenesulfonate, *p*-methoxybenzenesulfonate and *p*-bromobenzenesulfonate of furfuryl alcohol. The common method for synthesis of substituted benzenesulfonates, that is, reaction at 0° of an alcohol with the substituted benzenesulfonyl chloride either in pyridine or in benzene with an equivalent of pyridine present, gave only a salt-like material which decomposed quickly on standing and could not be purified further. This compound was probably the pyridinium salt formed by the reaction of the furfuryl benzenesulfonate with pyridine. Since benzyl tosylate is a much more reactive compound than benzyl chloride,²⁴ and furfuryl chloride is a much more reactive compound than benzyl chloride, it was to be expected that furfuryl tosylate would be an extremely reactive compound. Therefore, it is not too surprising that the

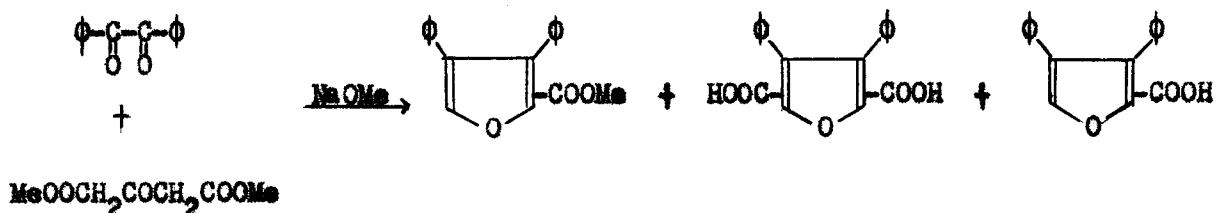
²⁴J. K. Kochi and G. S. Hammond, J. Am. Chem. Soc., 75, 3443 (1953).

tosylate could not be isolated under such conditions. In order to carry out the preparation without the presence of pyridine or other base, the sodium salt of furfuryl alcohol was prepared and allowed to react in ether with the substituted benzenesulfonyl chlorides. The product of the reaction decomposed quickly and attempts at purification were not successful. Since it was apparent that the substituted benzenesulfonates of furfuryl alcohol were very reactive and unstable compounds, this method of attack was abandoned.

The next procedure was an attempt to prepare substituted furfuryl halides which, having a higher molecular weight, might be expected to be solids. A solid bromide, 3,4-diphenyl-2-furfuryl bromide, was prepared. This compound is relatively stable although it decomposes quickly if impure, and even pure samples show signs of decomposition within 72 hours in a vacuum desiccator. The compound was prepared by reducing methyl 3,4-diphenyl-2-furoate with lithium aluminum hydride and treating the resulting alcohol with phosphorous tribromide.

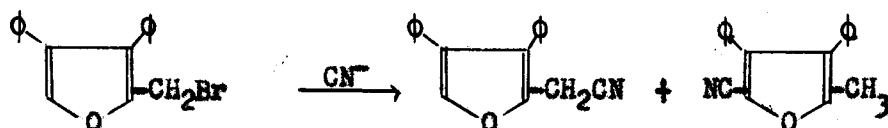


Another example of abnormal reaction in supposedly absolute alcohol was encountered in the preparation of methyl 3,4-diphenyl-2-furoate. This compound was prepared in absolute methyl alcohol by the condensation of benzyl and methyl diglycollate using sodium methoxide as catalyst.



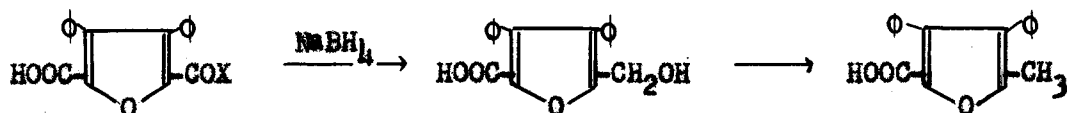
The principal product was the di-acid, with lesser amounts of the mono-acid and mono-ester. No di-ester could be isolated, indicating that the di-ester, if formed, must have been cleaved by some means in the supposedly water-free solvent.

The reaction of 3,4-diphenyl-2-furfuryl bromide with cyanide ion would be expected to give 3,4-diphenyl-2-furfuryl bromide and 3,4-diphenyl-5-cyano-2-methylfuran. Since these compounds had not been prepared previous-



ly, synthesis by independent means of the nitriles or their corresponding acids was necessary.

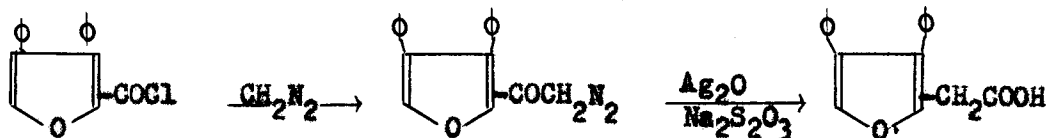
In an attempted preparation of 3,4-diphenyl-5-methyl-2-furoic acid, 3,4-diphenyl-2-furoic acid was treated with butyllithium in the expectation that five position of the furan nucleus would be metalated. The resulting organolithium could then have been treated with methyl iodide to give 3,4-diphenyl-5-methyl-2-furoic acid. However, the acid could not be metalated. Another possible synthesis was through the intermediate of the half-ester or half-acid chloride of 3,4-diphenyl-2,5-dicarboxylic furan. These compounds could then have been reduced with sodium borohydride to the half-methylol derivative, since sodium borohydride does not reduce acid groups but does reduce esters and acid chlorides.



The resulting methylol group could then have been reduced with phosphorous triiodide or other reagents to the methyl group. However, attempts to prepare the half-ester by reacting the acid with an equivalent of methyl alcohol or diazomethane gave only di-acid and di-ester. Similarly, when the acid was allowed to react with an equivalent of thionyl chloride, only di-acid chloride and unreacted di-acid were isolated.

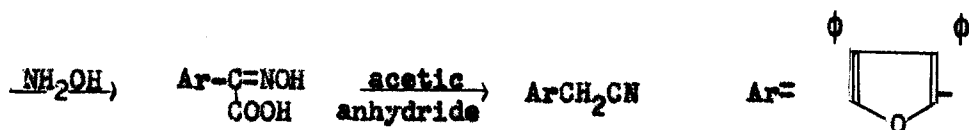
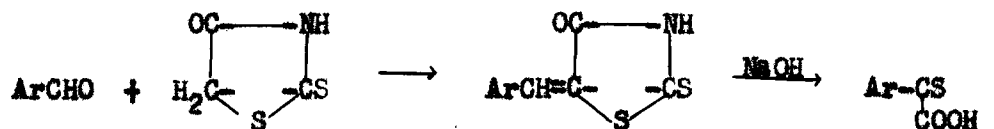
The final attempt at synthesis of the required acid appeared to be successful. Methyl 3,4-diphenyl-2-furoate was treated with methyl chloride using aluminum chloride as catalyst and carbon disulfide as solvent. The compound isolated, although having a very similar infra-red spectrum to that of methyl 3,4-diphenyl-2-furoate, differed in some important aspects. The compound is probably 3,4-diphenyl-5-methyl-2-cyanofuran, but no further structure proof was carried out.

The preparation of 3,4-diphenyl-2-furfuroic acid was attempted by means of the Arndt-Eistert reaction with 3,4-diphenyl-2-furoyl chloride. The acid chloride was reacted with diazomethane to yield the diazo ketone.



However, cleavage and rearrangement of the diazo ketone with silver oxide to the expected acid was not successful, possibly due to the steric hindrance of the benzene rings.

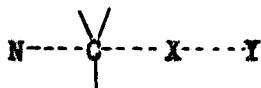
In an attempt to prepare 3,4-diphenyl-2-furfuryl cyanide, the following series of reactions was carried out:



The aldehyde was prepared by a Rosenmund reduction of the corresponding acid chloride. The synthesis, as outlined above, was apparently successful up to the last step, since stable compounds having the expected properties were isolated from the intermediate reactions. However, when 3-(3,4-diphenyl-2-furyl)-2-oximinopropionic acid was reacted with acetic anhydride in order to carry out simultaneous decarboxylation and dehydration to give the nitrile, an oily liquid resulted. This oil could not be distilled or recrystallized without polymerization and decomposition taking place. Basic hydrolysis of the supposed nitrile led to polymerization, and no acidic product could be isolated.

The reaction of 3,4-diphenyl-2-furfuryl bromide with cyanide ion also resulted in an oil which could not be purified or hydrolyzed to the acid. This oil acted very similarly to the product obtained above. Since so much difficulty was encountered in the synthesis of these nitriles and acids, an approach involving kinetic studies was instituted.

The next phase was suggested by some work of Swain²⁵ who has proposed a method of rating the nucleophilic or electrophilic character of various reagents. Swain has expanded a general theory of nucleophilic displacement which proposes that in displacement reactions by a nucleophilic agent, the reaction is also aided by an electrophilic reagent which helps to "pull" off the leaving group as the nucleophilic agent tends to "push" out this group. Since changes in the electrophilic character of reagents would



change the activation energy and hence the rate of reaction, Swain has proposed the following four parameter equation, where n and e are numbers

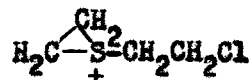
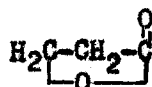
$$\log \frac{k}{k_0} = ns + es'$$

characteristic of the nucleophilicity and electrophilicity of the reagent, and s and s' are characteristic of the particular molecule being attacked. The parameter s may be considered as a measure of the selectivity or the ability of the substrate to discriminate among nucleophilic reagents. k and k₀ are rate constants for reaction of the substrate with water and with the reagent being studied. The values of n and e are thus defined as being zero for water. In carrying out his work, Swain used aqueous or partly aqueous solutions in which water was always the strongest electrophilic reagent present. With e equal to zero, therefore, $\log \frac{k}{k_0} = ns$. As a

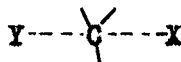
²⁵C. G. Swain and C. B. Scott, J. Am. Chem. Soc., 75, 141 (1953).

standard substrate he selected methyl bromide, and set \underline{s} equal to one for this substrate at 25°, using pure water as solvent. Values of \underline{n} were calculated from the rates of hydrolysis and reaction with other reagents of methyl bromide. Then using these \underline{s} values as secondary standards, \underline{n} values for reagents which had not, or could not, be reacted with methyl chloride were determined. In this way, \underline{n} values for ten nucleophiles and nine substrates were determined. Since most of the values used were taken from the previous literature, the solvents used varied from water to various acetone-water and dioxane-water mixtures. The temperatures used varied from 0° to 60°. However, these variations did not seriously affect the \underline{n} values as the mean value of the probable error of \underline{n} values is only 0.18 in a range of 6.36 in \underline{n} values. This means that $\frac{k}{k_0}$ or k can be estimated with a probable error of a factor of 1.5.

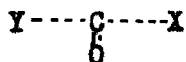
There were outstanding exceptions to this general agreement in the case of the reaction of hydroxide ion with β -propriolactone and with the mustard cation. Swain has proposed that hydroxide ion is unusually re-



active with β -propriolactone as compared with reaction with other substrates because hydroxide ion attacks the lactone ring at the carbonyl carbon while other nucleophilic reagents, both above and below hydroxide ion in \underline{n} values, attack the alkyl carbon. In attack by nucleophilic reagents, the transition state usually proposed is



When a nucleophile attacks a carbonyl group, a transition state such as



is likely. The negative charge produced is more dispersed and there is less repulsion between the negatively charged entering group and the negative charge developed in the molecule. Polarizable ions may distribute their charge so that this repulsion is lessened, but a non-polarizable ion such as hydroxide cannot distribute its charge. Swain reasons that when hydroxide reacts with a molecule which can distribute charge, it appears to be especially reactive as compared with the reaction of polarizable ions, which already being able to distribute their charge, are not aided so much by charge distribution in the molecule being attacked. Attack by a nucleophile in the five position of the furan nucleus might be considered analogous to attack at a carbonyl since the charge can be distributed in the ring. Therefore, hydroxide ion, if attacking in the five position, would be expected to show abnormal reactivity. However, by determining the rates of reaction of furfuryl chloride with water, acetate, hydroxide, iodide and thiosulfate ions and applying the Swain treatment to the results, no abnormally reactive ion was noted and a straight line plot was obtained by plotting $\log \frac{k}{k_0}$ against n . A further discussion of the reason that abnormalities would be detected by such a treatment now follows.

For the reaction of furfuryl chloride with nucleophilic agents, three modes of reaction are possible; namely, reaction all in position five, reaction all in the alpha position and reaction partly at both positions. Although the postulated abnormal product has never been isolated, the

hydrolysis and reaction of furfuryl chloride with hydroxide ion is known to give the normal product, furfuryl alcohol. Therefore, attack must not have been entirely at the five position and the first possibility is excluded.

In order to decide between the last two possibilities, a closer analysis of the Swain equation is required. If reaction takes place at both the alpha and five positions, $k = k_\alpha + k_5$, where k is the overall rate constant and k_α and k_5 are the rate constants for reaction at those positions. If it is assumed that \underline{n} and \underline{e} are truly characteristic of the particular species and are invariant,

$$\log \frac{k}{k_0} = s_\alpha n + s'_\alpha e \quad \text{and} \quad \log \frac{k_5}{k_0} = s_5 n + s'_5 e.$$

Then,
$$\frac{k_\alpha}{k_0} = e^{s_\alpha n + s'_\alpha e} \quad \text{and} \quad \frac{k_5}{k_0} = e^{s_5 n + s'_5 e}$$

and
$$\frac{k_\alpha + k_5}{k_0} = e^{s_\alpha n + s'_\alpha e} + e^{s_5 n + s'_5 e}.$$

Therefore,
$$\log \frac{k_\alpha + k_5}{k_0} = \log (e^{s_\alpha n + s'_\alpha e} + e^{s_5 n + s'_5 e})$$

or, since in aqueous solvent $e = 0$,

$$\log \frac{k_\alpha + k_5}{k_0} = \log (e^{s_\alpha n} + e^{s_5 n}).$$

A plot of $\log \frac{k}{k_0}$ against \underline{n} normally would not be expected to give a straight line plot. However, by proper choice of \underline{s} and \underline{s}_5 such a plot might be possible. Let $s_\alpha = as_5$,

$$\begin{aligned}
 \text{Then, } \log \frac{k_{\alpha} + k_{\beta}}{k_0} &= \log (e^{s_{\alpha} n} + e^{as_{\alpha} n}) \\
 &= \log [e^{s_{\alpha} n}(1 + e^{s_{\alpha} n(a-1)})] \\
 \log \frac{k_{\alpha} + k_{\beta}}{k_0} &= \log e^{s_{\alpha} n} + \log (1 + e^{s_{\alpha} n(a-1)}) \\
 \log \frac{k_{\alpha} + k_{\beta}}{k_0} &= s_{\alpha} n + \log (1 + e^{s_{\alpha} n(a-1)}). \quad (\text{I})
 \end{aligned}$$

This expression can give a straight line plot if the second term is either very small or approximately constant; that is, if a is either very small or approximately equal to one. If a is close to zero, then $s_{\beta} \gg s_{\alpha}$ and reaction takes place only at one position which is contrary to the experimental results. If a is approximately one, then reaction at the two positions is approximately equal. This occurrence cannot be excluded on the basis of experimental results presently available. Since the overall yields of reaction of furfuryl chloride with nucleophilic reagents are low and only the normal product was isolated in most cases, the possible relative percentages of the two products can only be guessed.

In order to exclude the last possibility of obtaining a straight line plot, the assumptions made in order to obtain equation I were reexamined. In order to obtain equation I in this form, the assumption was made that n is invariant and is dependent only on the character of the nucleophile. For the general case of two nucleophiles, A and B, which react at two different positions, the Swain equation for the four possible reactions would be

$$\log \frac{k_1^A}{k_0} = n_A s_1$$

$$\log \frac{k_1^B}{k_0} = n_B s_1$$

$$\log \frac{k_2^A}{k_0} = n_A s_2$$

$$\log \frac{k_2^B}{k_0} = n_B s_2$$

Where k_1^A refers to the rate constant for reaction of nucleophile A at reaction center one, n_A is the n value for the nucleophile, and s_1 is the s value for reaction at reaction center one, with similar symbols used for the other reactions. Then

$$\log \frac{k_1^A}{k_1^B} = s_1(n_A - n_B)$$

$$\log \frac{k_2^A}{k_2^B} = s_2(n_A - n_B).$$

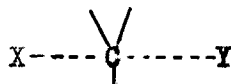
In order for n_A and n_B to be characteristic of the nucleophiles, $(n_A - n_B)$ must always be either positive or negative. No data are available for the relative rates of two nucleophiles reacting at two sites on the same molecule. However, data are available for displacement reactions by hydroxide ion and iodide ion on 2,4-dinitrochlorobenzene²⁶ and methyl chloride²⁷ in which it was found that for the first compound $\frac{k_{OH^-}}{k_{I^-}} > 1$ and for the second compound $\frac{k_{OH^-}}{k_{I^-}} < 1$. In the first case, since s values,

²⁶(a) A. K. Macbeth and J. R. Price, *J. Chem. Sec.*, 982 (1937).
 (b) G. M. Bennett and I. H. Vernon, *ibid.*, 1783 (1938).

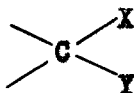
²⁷E. A. Moelwyn-Hughes, *Proc. Roy. Soc.*, 164, 295 (1938).

by definition, are always positive n_{OH^-} is greater than n_{I^-} , while in the second case n_{OH^-} is smaller than n_{I^-} . Therefore, a straight line plot could not be obtained using equation I since one of the fundamental postulates leading to this possibility is violated; that is, the invariance of n values.

The displacements on methyl chloride and 2,4-dinitrochlorobenzene, although both involving displacement of the same group by the same nucleophile, differ in the type of bonding for the carbon at the reaction center. The reaction center in methyl chloride may be considered to be "saturated" and in such cases the transition state for attack at the center involves the configuration²⁸



in which the C-X bond is partly formed, the C-Y bond partly broken and the bond distances are longer than normal covalent bonds. In attack at "unsaturated" centers such as in 2,4-dinitrochlorobenzene, however, the transition state is probably closer to



in which the new bond is nearly covalent.²⁹ In the first case, the polarizability of the nucleophilic agent is more important than in the second case since the bond distance in the transition state is shorter in the second case. Polarizable ions, such as iodide, thiosulfate and thiocyanate,

²⁸E. D. Hughes, Trans. Faraday Soc., 37, 603 (1941).

²⁹E. D. Hughes and C. K. Ingold, J. Chem. Soc., 608 (1941).

although less basic than ions with lower n values, have high n values because of the importance of polarisability of the nucleophile in displacements at saturated positions, which were used by Swain in determining n values.

The five position of furfuryl chloride is an unsaturated center, and is probably intermediate in character between the centers of methyl chloride and 2,3-dinitrochlorobenzene. In the transition state, the C-Cl bond should be approaching normal covalent distance.



In this case, if hydroxide were to attack in the five position, it should appear to be abnormally reactive as in the analogous case with β -propiolactone. Since hydroxide did not show abnormal reactivity, it is unlikely that reaction in the five position takes place in this reaction. Since acetate ion is also a non-polarizable or slightly polarizable ion, reaction by acetate ion in the five position is also unlikely.

SUMMARY

Attempts at finding abnormal nucleophilic displacement reactions other than the previously reported reactions of furfuryl halides with cyanide ion were not successful. A study of the kinetics of the reaction of furfuryl *p*-nitrobenzoate and hydroxide ion showed second order kinetics, indicating that cleavage of the ester did not take place by means of an intermediate carbonium ion. After several unsuccessful attempts to prepare solid furfuryl derivatives, which would be expected to have properties similar to furfuryl halides, such a solid compound, 3,4-diphenyl-2-furfuryl bromide, was prepared. Synthesis of the nitriles or of the corresponding acids which would be expected to be formed by reaction of this bromide with cyanide ion was partly successful. 3,4-Diphenyl-5-methyl-2-furoic acid was prepared, although a complete structure proof was not made. A study of the kinetics of the reactions of furfuryl chloride with water, iodide, thiosulfate, acetate, and hydroxide ions showed no abnormal reactivity for the slightly polarizable acetate or hydroxide ions. This result indicates that these ions do not attack furfuryl chloride in the five position of the furan nucleus.

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