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FURFURAL AND SOME OF ITS DERIVATIVES

BY

George F. Wright

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

Approved

Signature was redacted for privacy.

In charge of Major work

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The writer wishes to thank Doctor Henry Gilman. Under his direction the work has been a distinct pleasure, and his advice and encouragement have proved to be an invaluable stimulus.

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INTRODUCTION

The sudden advent of cheap furfural about 1920 immediately stimulated an interest in the compound. Prior to that time there had been comparatively little work done on furfural and its derivatives (1). Furfural was discovered in 1832 by Döbereiner (2). A survey of the literature shows that, following that time, the work was intermittent. For a time interest would be stimulated, only to die out when the investigation seemed well begun. This is easily explained by one who has worked in furan chemistry. The instability of many of the really important furan types discouraged many, and the tendency was naturally to turn to work more productive of results. Consequently it has been found that most of the literature is concerned with reactions not directly related to the furan nucleus itself.

Such an attitude was not blameworthy; indeed it might be termed good judgment to cease work on a branch of chemistry which was relatively unimportant when that chemistry was not easily elucidated. But, for economic reasons, the attitude cannot persist when the basis of the chemistry, furfural, has become cheap and readily available. Hence, it is to be expected that furan chemistry should have been given a great impetus in the last ten years.

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(1) The most complete bibliography, published in 1928 by The Miner Laboratories, Chicago, Illinois, lists but 1530 references.

(2) Döbereiner, Ann., 3, 141(1832).

It was found early in the work at Iowa State College that there were certain differences between the furan series and its near relative, the benzene series. For several years these difficulties served to confound the worker who applied analogous reactions to furan compounds. Gradually it became apparent that these differences must be carefully elucidated before the application of furan compounds to economic uses could be intelligently carried out.

It is the purpose of this thesis to point out the variance between furan and the true aromatic type, as well as to show the particular laboratory methods of handling furan compounds. Since the nuclear reactions have been, heretofore, the most incongruous, they are given the most attention. Hence, the thesis is divided into a study of nuclear substituents, for example, halogenation and the halogenated furans, nitration and the reactions of the nitro furans, and the like.

The basis of the difficulty in working with furan compounds is this: whereas, the ring substituents behave like typically aromatic groups, the nucleus itself has none of the unity of, for example, the benzene or thiophene ring. Hence, treatment strenuous enough to induce reaction all too frequently demolishes the ring. The bromine in bromofuran is so firmly attached that it will not react with sodium (3), yet the compound is totally destroyed by attempted nitration and has

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

a short life alone under laboratory conditions. This duality of properties is entirely the rule.

This condition is not entirely hopeless; indeed, by observing certain precautions, much can be done to avoid ring splitting and so retain the furan nucleus. A prime necessity is to recognize the classification of positively and negatively substituted furans. This classification, important in benzene chemistry, is accentuated in furan chemistry by the decided difference in stability. The positive substituents such as methyl, bromo, chloro, iodo, amino, and other saturated groups tend to decrease the stability of the nucleus, just as they do when attached to benzene, but to a much greater degree. For example, furan is fairly stable in cold dilute hydrochloric acid while 2-methylfuran is less so, and 2,5-dimethylfuran is instantly split to acetonyl acetone. The negative substituents, carboxyl, nitro, formyl, ethylideno and the like tend to stabilize the ring to a considerable extent, but, as would be expected, lower its reactivity in like degree.

Of all the agents capable of splitting the furan ring, mineral acids seem to be the most potent. Hence it is important to avoid every possibility of a high acid concentration. Where it is the custom to wash laboratory glassware in a hot acid bath, great care must be taken to remove all traces of the acid. With very sensitive compounds it is necessary to steam out the apparatus, or to wash with dilute alkali in order to remove the acid film which persists on the surface of the glassware. Where acid is unavoidable, as in halogenations, the maintenance of anhydrous condition is necessary. Every solvent must be thoroughly dried. The characteristic color of furan decomposition is green and this is often an indication of the presence of water. Since the furan ring contains an oxygen atom there is always the disturbing possibility that water is formed from a side reaction. To avoid this difficulty, it is often advantageous to use such a solvent as acetic anhydride which tends to take up the water formed. Again, when it is necessary to neutralize a solution with acid, a cold solution and a dilute addendum should be used whenever possible. This is especially necessary with some of the furan acids and is accentuated by the fact that the furoic acids decarboxylate quite readily. Sometimes it is even necessary to use a buffer such as sodium acetate in such neutralizations. When halogen substituted furans start to decompose, halogen acid is formed; consequently, when these compounds are kept over a period of time, they are best stored under a large volume of water. This also serves to exclude oxygen of the air which seems to have a catalytic effect on furan decompositions. Because of the latter factor, it is advisable that in vacuum distillations, the pressure be always released under an inert atmosphere. The use of stabilizing agents such as hydroquinone and urea is also beneficial. Lastly it is our belief that when mineral acid must be used in furan reactions, other acids than the hydrogen halides are to be preferred.

With negatively substituted furans the problem is not so acute. Furoic acid and its congeners are quite as stable as benzene derivatives so long as they retain their identity. Their ease of decarboxylation sometimes renders them difficult to handle, but the large amount of work done on them points to their stability. Nitrofurans are likewise unusually stable toward many reagents, notably acids, but here there is an unequivocal rule; they decompose completely with ring splitting in thepresence of alkalies. Such weak bases as sodium bicarbonate or pyridine and quinoline may be employed in their reaction but alkaline media such as ammonia, sodium or calcium hydroxide or the like are to be avoided. The furan substituted with less negative groups, like furfural and furylacrylic acid have a stability intermediate between the two extreme classifications discussed.

All furan compounds are to some degree thermally unstable, the tendency being toward resinification. Very little has been studied of these evident polymers, but of their formation there is no doubt. To avoid them it is necessary to maintain low temperatures; a customary procedure is to remove a solvent, especially the last portion, under reduced pressure.

Crystallizations are conducted so as to avoid long heating periods and oftentimes the hot boiling solvent is poured on the substance, solution is attained at once, and filtration follows in the shortest possible time. When tars or resin have formed, the fact that they are not volatile with steam may be utilized, and as a last resort, a steam distillation is always in order. A steam distillation is often advantageous before a distillation in vacuum is carried out, since the presence of polymers will so raise the temperature of the distilling liquid so as to incite decomposition. Another important phase of this thermal instability involves the storing of furan compounds. There are a great number of examples of compounds which will decompose in several weeks in the laboratory, but which will keep indefinitely in the refrigerator. The absence of light may also be a contributory factor. At any rate it is best to store these compounds in a cold place.

Thus a few precautions as to handling of furan compounds are noted. They are not unusual and most certainly not original, but the significant fact is that they are not usually associated with aromatic chemistry. The necessity for observance of them will be noted, however, in the discussion which follows and which is conveniently divided into several types of nuclear reactions.

I SULFONATION

Introduction

Sulfonation in the furan series has been confined entirely to the furoic acids (4). These compounds are formed with ease and are quite stable. We sought to use furfural as a type of less stable furan compound and to attempt its sulfonation. The investigation resulted in failure. It was found that furfural was unusually unstable toward even concentrated sulfuric acid. A number of milder sulfonating agents were tried, but when these were mild enough so as not to decompose the compound, they would not sulfonate.

Sulfonation was then tried on furfural when the aldehyde group was blocked. These were equally unsuccessful except in the case of sulfonation of furfuraldiacetal, and in this case, when the product is freed from its barium salt, nothing can be isolated, nor does the analysis of the salt conform to any expected product.

The decomposition seems to be caused by dehydration of the furfural. In a preliminary experiment, sulfuric acid was added dropwise to a stirred aqueous solution of furfural. No evidence of decomposition was noted until the concentration reached about 50%. Sulfuryl chloride, which is not a desiccating agent of the order of sulfuric or chlorosulfonic acids does not readily decompose furfural.

(4) Schwanert, Ann., 116, 257(1860)
Hill and Palmer, Am. Chem. J., 10, 373(1888)
Hill and Palmer, Am. Chem. J., 15, 145(1895)

Experimental

Action of sulfonating agents on furfural and furfural diacetate.

1. A cooled solution of sulfuric acid in absolute alcohol causes complete decomposition with furfural. The diacetate is more stable in the cold reagent, but sulfonation does not take place.

2. No reaction could be obtained upon heating furfural with either potassium pyrosulfate or potassium bisulfite.

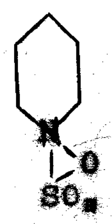
3. Complete decomposition takes place when an acetic anhydride solution of furfural diacetate is added to an acetic anhydride solution of concentrated sulfuric acid at -8°C.

4. Ethyl chlorosulfate causes decomposition of furfural diacetate to a jelly-like tar.

5. Chlorosulfonic acid causes complete decomposition of a chloroform solution of either furfural or furfural diacetate.

Sulfonation of Furfural with N-pyridinium Sulfonic Acid

The sulfonating agent in this series of runs was N-pyridinium sulfonic acid. This compound in reality is the anhydride.



It is most easily prepared from chlorosulfonic acid. It is not very stable and was usually not isolated but was used directly in these reactions. The compound has been used in the sulfonation of naphthalene.

Preparation of N-pyridinium Sulfonic Acid (5)

One hundred and fifty-eight grams (2 moles) of pyridine were dissolved in three hundred cc. of dry carbon tetrachloride and placed in a one liter balloon flask equipped with dropping funnel, thermometer, and breather. To this were slowly added 116 g. (1 mole) of chlorosulfonic acid. Manual shaking or stirring was necessary because of the heavy precipitate formed. When addition was completed, the flask was let stand for a few hours and was then filtered by suction.

The precipitate was stirred vigorously into 1 1/2 liters of ice and water. The ice was skimmed off; the large lumps were thoroughly broken up and the white product was collected by suction filtration and washed thoroughly with ice water. It was dried in the vacuum desiccator over phosphorous pentoxide. Yield was 31 g. or 19% of the theoretical amount.

Sulfonation of Furfural.

Thirty-nine and five-tenths grams (0.5 mole) of pyridine were dissolved in 100 cc. of carbon tetrachloride in a 200 cc. three-necked flask equipped with stirrer, dropping funnel, and thermometer and immersed in an ice-salt freezing mixture.

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(5) Baumgarten, Ber., 59,1166(1926); 59,1976(1926).

Twenty-nine grams (0.25 mole) of chlorosulfonic acid were slowly added. The sulfonating mixture was let stand overnight; twenty-four grams (0.25 mole) of furfural were then added and the solvent was distilled off. The residual mixture was heated to 134°C. for five hours. There was some darkening, but no apparent decomposition. The temperature was then raised to 154°C. for four hours. At the end of the period, the mixture had decomposed to a black jelly.

When 19.8 g. (0.1 mole) of furfural diacetate (45) and 15.9 g. (0. 1 mole) of N-pyridinium sulfonic acid were heated together for seven hours at 95°-100° considerable decomposition occurred. The mixture was poured into ice and water and the solution was filtered to remove 2.3 g. of carbonaceous material. The filtrate was worked up in the customary manner, but no product could be obtained.

In a similar trial with ethyl furylacylate and N-pyridinium sulfonic acid, most of the ester was recovered unchanged.

When furfural was refluxed with a chloroform solution of N-pyridinium sulfonic acid, no reaction occurred and the furfural was recovered unchanged.

Sulfonation of Furfural-Sodium Bisulfite Complex.

Eighteen grams (0.1 mole) of the furfural-bisulfite complex were added very slowly over a period of two hours to 160 g. of fuming (15%) sulfuric acid to which had been added a trace of of boric acid (6). After twenty-four hours the reaction mixture was poured on 500 g. of cracked ice. The solution was extracted twice with ether. Evaporation of the ether left a brownish powdery residue which was crystallized from chloroform to melt at 154°C. (soften at 151°C.). The compound contained no sulfur.

The extracted water solution was neutralized with barium carbonate, filtered and evaporated to a volume of 40 cc. Upon chilling, 1.9 g. of barium salt precipitated. This was crystallized from water-alcohol solution. Exact precipitation of the barium with dilute sulfuric acid and subsequent evaporation of the filtrate yielded no product. The salt was probably barium sulfite.

Sulfonation of Furfural Diethylacetal.

Thirty-four g. (0.2 mole) of furfural diacetal (7) were added dropwise over a two hour period to 102 g. of fuming (15%) sulfuric acid. The reaction was stirred and the temperature was held between 25° and 30°C. The charring or blackening was not very great. Next day the reaction was poured over cracked ice. The resulting solution was neutralized with barium carbonate. The mixture was heated and then filtered by suction and the filtrate evaporated by means of a dry air stream across the surface of the liquor. This extraction of the barium sulfate precipitate was repeated twice.

(6) Engel, J. Am. Chem. Soc., 52, 2835(1930).
(7) Claisen, Ber., 40, 3903(1907).

In this way evaporation of the solution yielded 23 g. of a salt which was purified by dissolving in water and reprecipitating with alcohol. The water of crystallization was removed by heating to 110°C. for one hour.

% water of crystallization 0.539%
0.552%

Analysis of anhydrous salt;

Calc'd. for $C_{18}H_{28}O_{14}S_2Ba$; Ba, 20.42%; Found; Ba, 39.70%, 39.63%, 39.53%, 39.67%.

It is quite evident that the salt here analyzed was not that of sulphofurfural diacetal.

II THE NITRO FURANS

Introduction

A number of furan compounds have been nitrated. These are tabulated as follows:

Table I

Source	Nitrating Agent	Product	Worker	Reference
#Dehydromucic acid	Nitric-Sulfuric	Nitrofuroic acid	(8) Klinkhardt	J. Prakt. Chem., 25, 41(1882)
#Furylnitroethylene	Fuming Nitric	Nitrofuroic acid	(9) Priebs	Ber., 18, 1362(1885)
#Ethylcyano furylacrylate	Fuming Nitric	Ethyl nitrocyano furylacrylate	(10) Heuck	Ber., 28, 2256(1895)
#Furyl cyano acrylic acid	Fuming Nitric	Nitrofuryl cyanoacrylic acid		
#Furfural malonitrile	Fuming Nitric	Nitro-furfural malonitrile		
#Furfuralmalonic ester	Fuming Nitric	Nitro-furfural malonic ester		
#5-Sulphofuroic acid	Fuming Nitric	5-nitrofuroic acid+nitrofuransulfonic acid + dinitro furan	(11) Hill and White	Am. Chem. J., 27, 193(1902)
# Furoic acid	Nitric and Sulfuric	Dinitrofuran and nitrofuroic acid	(11) Hill and White	Am. Chem. J., 27, 193(1902)
#5-Sulpho-3-bromo-2-furoic acid	Fuming Nitric	5-nitro-3-bromo-2-furoic acid	(12) Hill and Palmer	Am. Chem. J., 27, 10, 373(1888)
#3,4-dibromo-5-sulpho-2-furoic acid	Fuming nitric	3,4-dibromo-5-nitro-2-furoic acid	(12) Hill and Palmer	Am. Chem. J., 10, 373(1888)
#Ethyl Furoate	Fuming nitric and acetic anhydride	Ethyl nitrofuroate	(13) Marquis	A$\overset{n}{m}$. Chem. Phys. (8), 4, 196 (1905)
# Furan	Fuming nitric and acetic anhydride	Nitrofuran		

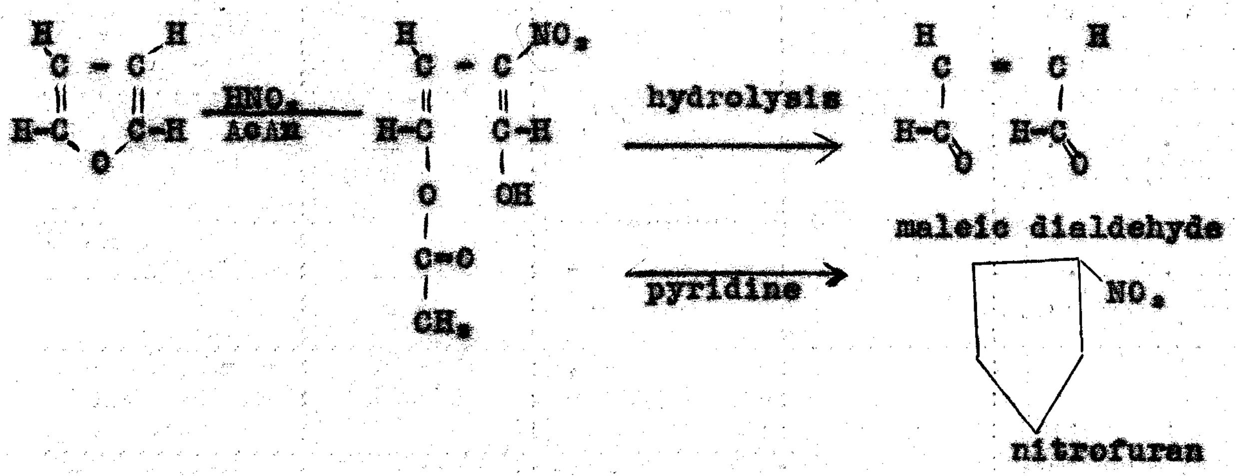
Table I (con'td.)

Source	Nitrating Agent	Product	Worker	Reference
*Furfural diacetate and furfural	Fuming Nitric and acetic anhydride	Nitrofurfural diacetate	(14) Gilman and Wright	J. Am. Chem. Soc., 52,2550 (1930) 52,4165(1930)
*Furylacrylic acid	Fuming nitric and acetic anhydride	Nitrofurylacrylic acid		
*Ethyl furylacrylate	Fuming nitric and acetic anhydride	Ethyl nitrofurylacrylate		
2-methylfuran	Fuming nitric and acetic anhydride	5-nitro-2-methyl furan	(15) Rinkes	Rec. trav. chim. 49,1118(1930)
5-methyl-2-furoic acid	Fuming nitric and acetic anhydride	5-nitro-2-methyl furan and 5-methyl-4-nitro-2-furoic acid		
methyl 5-methyl-2-furoate	Fuming nitric and acetic anhydride	Methyl 4-nitro-5-methyl 2-furoate		
3-methyl-2-furoic acid	Fuming nitric and acetic anhydride	2-nitro 3-methylfuran		
* Furoic acid	Fuming nitric and acetic anhydride	Nitro furan and nitrofuroic acid	(16) Rinkes	Rec. trav. chim. 49,1169(1930)
*Methyl furoate	Fuming nitric and acetic anhydride	Methyl nitrofuroate	(17) Freure and Johnson	J. Am. Chem. Soc., 53,1169(1930)
* 5-bromo furoic acid	Fuming nitric and acetic anhydride	5-bromo-2-nitrofuran	(18) Rinkes	Rec.trav.chim., 50,981(1931)
5-methyl-4-nitro-2-furoic acid	Nitric and sulfuric	2,4-dinitro-5-methylfuran	(18) Rinkes	Rec.trav.chim., 50,981(1931)
2-nitro-5-methyl furan	Nitric acid Sp.Gr. 1.2	2,5-dinitro-3-methyl furan		

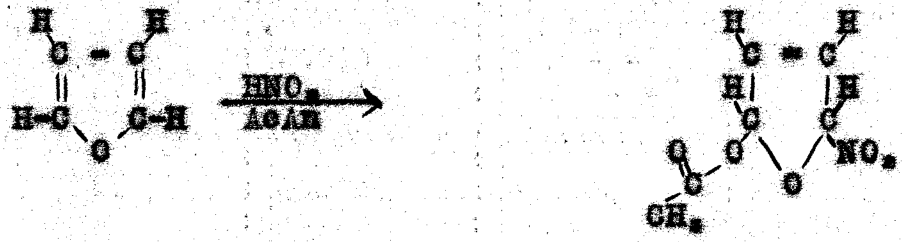
Table I (con'td.)

Source	Nitrating Agent	Product	Worker	Reference
Ethyl-3-methyl-2-furoate	Fuming nitric and acetic anhydride	Ethyl-5-nitro-3-methyl-2-furoate	(18) Rinkes	Rec.Trav.chim., <u>50</u>, 981(1931)
*Furfuryl-acetate	Fuming nitric and acetic anhydride	5-nitrofurfuryl alcohol	(19) Gilman and Wright	J. Am. Chem. Soc., <u>53</u>, 1925(1931)
Furyl methyl ketone	Fuming nitric and acetic anhydride	Nitrofuryl methyl ketone and nitrofuran	(20) Rinkes	Rec. Trav. Chim., <u>51</u>, 349(1932)
Ethyl 5-acetamino-furoate	Fuming nitric and acetic anhydride	Ethyl 4-nitro-5-acetamino furoate	(21) Gilman and Wright	Ia. State Coll. J. Sci., <u>5</u>, 85(1931)

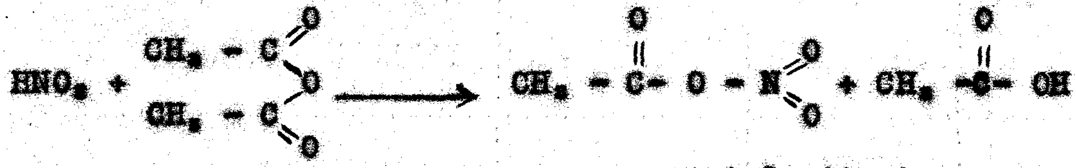
There has been some controversy over the position of the nitro group. While Hill (11) considered that replacement of the carboxyl and sulpho groups in dehydromucic and sulphofuroic acid established the product as 5-nitrofuroic acid, Marquis (13) on the other hand considered that from the intermediate which he postulated the nitro group must be in the beta position.



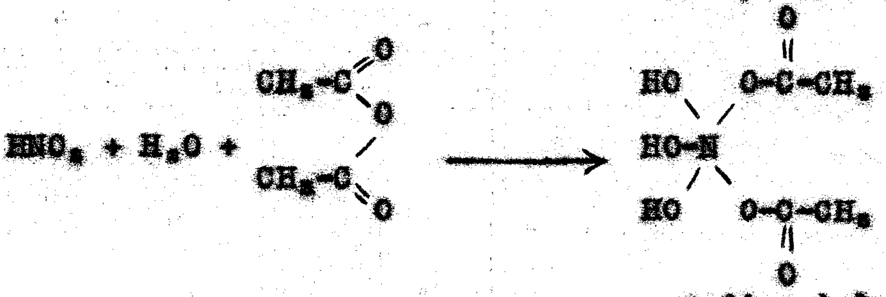
Since he felt that the nitro and acetyl group could not exist on the same carbon atom. This argument has been circumvented by Freure and Johnson (17) who offer the following mechanism:



The formulation of these intermediates depends on the two factors: first, that when acetic acid is split, nitrofuran is formed; second, decomposition with weak barium hydroxide or hot water yields maleic dialdehyde and nitrous acid. We are not inclined to accept either of these proposed structures. A reasonable explanation seems to be that since the intermediate is formed only when acetic anhydride and nitric acid are used for nitrating, it is derived from the acetyl nitrate (22) or o-diacetylnitric acid (23) present in this mixture.

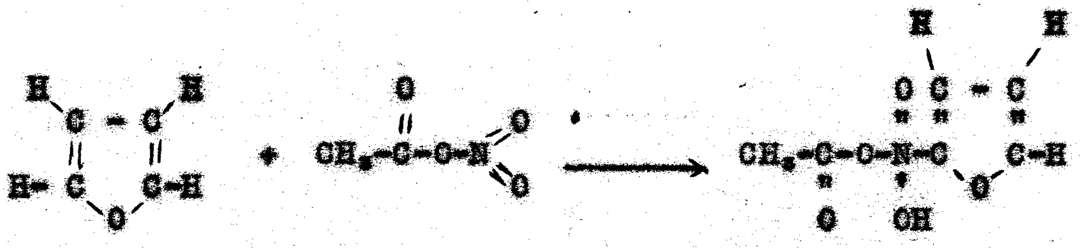


acetyl nitrate

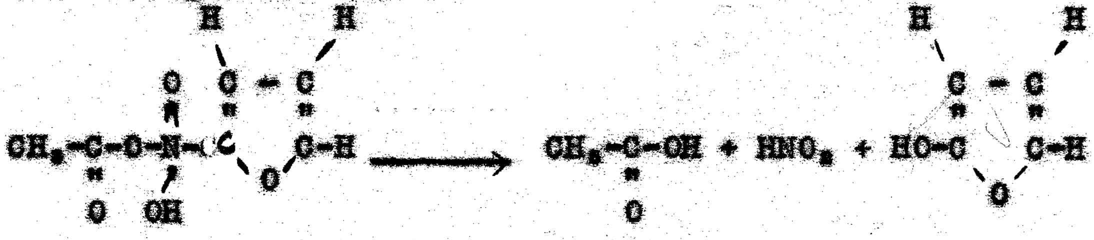


o-diacetylnitric acid

This would react as follows:



The intermediate would very easily split out acetic acid to give the nitrofuran. On the other hand when heated with water or barium hydroxide the compound would decompose between the nitrogen and carbon.



The hydroxy furan is not known (24). It will be observed that it is an isomer of maleic dialdehyde. Our attempts to prepare the compound have met with failure; when furylmagnesium-iodide was oxidized, neither a hydroxy furan nor an aldehyde could be isolated.

It may be said that the reaction between acetyl nitrate and furan as formulated should not be accompanied by a very great heat reaction. Actually the evolution of heat is considerable. Again the carbon-nitrogen split may seem not to be orthodox; however there is evidence that this split actually occurs during alkaline decomposition of nitro furans (11).

(22) Pictet and Khotinsky, Ber., 40, 1163(1907)
(23) Pictet and Genequand, Ber., 35, 2526(1902)
(24) Boeseken, Vermij, Bunge, and Van Meeuwen, Rec. trav. chim., 50, 1023(1931) have reported a compound of this empirical formula but have offered no proof as to its constitution.

The structure proposed by Marquis is doubtful because the intermediate will not add bromine, and this objection likewise applies to the structure of Freure and Johnson. On the other hand a true furan ring with nitro substituent should not add bromine. Our experience has shown that the one compound which should give the intermediate nitration product is furylacrylic acid, since this is the only furan compound which definitely adds two atoms of bromine to the nucleus (25). But nitrofurylacrylic acid is obtained directly by precipitation in the reaction mixture. Therefore, whatever may be the faults of our proposed structure, it explains the facts as well as any yet promulgated and it assigns the nitro group to the alpha position.

We have sought to establish the position of the nitro group by conversion of furyl methyl ketoxime into acetaminofuran, but have failed. It was also hoped that diazotization of ethyl aminofuroate would yield a derivative which would fix this position. Diazotization, however, was unsuccessful, both with substituted and unsubstituted ethyl aminofuroate.

Those members of the table given above which are interrelated insofar as position of the nitro group is concerned have been marked by an asterisk. We have succeeded in converting nitrofurfural to nitrosylvan and thus extended this list.

As another means of allocating the nitro group, attempts were made to nitrate 3,4,5-tribromofuran and ethyl 3,4-dibromo-

(25) Gilman and Wright, J. Am. Chem. Soc., 52,3349(1930)

2-furoate. Both of these compounds were too inert and were recovered unchanged. It was thought that some light might be thrown on the question by studying the orientation; consequently bromofuran was nitrated, and nitrofuran was brominated. Both of these reactions were unsuccessful, the first because of unstability and the second because of the unusual difficulty of substitution.

When it was found that the nitrofuran could not be prepared by methods which definitely located the position, we tried to prepare 3-nitrofuran. Since halogen substituents are removed with little difficulty when attached to furan nucleus, nitration of ethyl 5-bromo-2-furoate,2,5-dibromofuran, 2,5-diiodofuran and ethyl 3,5-dibromo-2-furoate was attempted. The first three decomposed in the reaction mixture and the latter was recovered unchanged.

Experimental

The Beckmann Rearrangement with Furyl Methyl Ketoxime.

As a means of definitely allocating the nitro group in the known nitrofurans, the Beckmann rearrangement seemed to be a reliable method. In this way furyl methyl ketoxime would be converted to acetaminofuran. A number of reagents capable of effecting this conversion were tried, but all proved to be too strenuous. This is, no doubt, due to the instability of the desired acetaminofuran.

The furyl methyl ketoxime was prepared by the method of

(26) Sandelin, Ber., 33,493(1900)

Sandelin (26) and was crystallized from hot water to melt at 104°-105°.

(1) One and twenty-five hundredths grams (0.01 mole) of furyl methyl ketoxime were dissolved in 15 cc. of anhydrous ether in a 50 cc. three-necked flask equipped with stirrer, dropping funnel, and thermometer. The temperature was maintained at -15°C. while a solution of 2.08 g. (0.01 mole) of phosphorus pentachloride in 35 cc. of dry carbon disulfide was slowly added. When addition was finished, the reaction mixture was stirred for a short time; then 10 cc. of cold water were added. The ether-carbon disulfide solution was separated and the aqueous layer was washed five times with ether. The combined non-aqueous extracts were dried with anhydrous sodium carbonate and evaporated under reduced pressure. The resinous residue was extracted with hot benzene, but no product could be obtained.

(2) Precisely the same conditions were used in this run employing thionyl chloride instead of phosphorus pentachloride. The results were likewise negative.

(3) The sodium salt of furyl methyl ketoxime was prepared by dissolving 1.25 g. (0.01 mole) of the oxime in 50 cc. of anhydrous ether. Twenty-three thousandths of a gram (0.01 mole) of sodium was added in flakes. After 24 hours the slight excess of sodium was removed and 1.76 g. (0.01 mole) of benzenesulphonyl chloride were then added. The sodium salt immediately dissolved

and flocculent sodium chloride appeared. After two hours this was filtered off and the filtrate evaporated under reduced pressure. A crystalline solid remained which melted at 85°C. and decomposed at 87°C. to a blackish purple tar. The solid was exposed for three hours to the ultra-violet light (27). It still melted at 85°C. The solid was then boiled for a few minutes with chloroform. A brown tar was found which could not be crystallized.

(4) Boiling with acetic anhydride did not affect the ketoxime. Acetyl chloride completely decomposed the compound.

The Reduction of Ethyl Nitrofuroate.

Five 18.5 g. portions (0.1 mole) of very pure ethyl nitrofuroate were each dissolved in 200 cc. of absolute alcohol. One-tenth gram platinic oxide ($PtO_2.2H_2O$) was added to each. They were then reduced by absorption of 22-23 pounds of hydrogen per tenth mole quantity using the catalytic hydrogenator described by Adams and Shriner (28). It is important that the temperature does not exceed 40-45°C. during reduction. This has been managed by directing a compressed air stream on the shaker bottle. When reduction was completed (about thirty to forty-five minutes for each tenth mole) the reaction mixture was filtered by suction and 800 cc. of the solvent were distilled

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(27) For details of the method of rearrangement, consult Kuhara, "On the Beckmann Rearrangement", edited by Shigeru Komatsu, Kyoto, 1926.

(28) Adams and Shriner, J. Am. Chem. Soc., 45, 2171 (1923)

under reduced pressure. One thousand cubic centimeters of benzene were then added and distillation under reduced pressure again resumed until 1000 cc. of distillate had come over. The residue was then heated until liquefaction was complete and transferred to an Erlenmeyer flask. This was cooled very slowly, finally seeded and then allowed to crystallize in the refrigerator. After filtering off the first crop of crystals, the liquor was concentrated to one-half of its volume and when cool was again seeded. The combined yield of the ethyl aminofuroate was 37.5 g. or 48.5% of the theoretical amount. The filtrate from the last crystal crop was diluted with 100 cc. of acetic anhydride and heated to 100°-110° C. for five to ten minutes. On cooling, 13.5 g. of ethyl acetaminofuroate crystallized.

If only ethyl acetaminofuroate is desired, the original reaction mixture is distilled under reduced pressure until all the alcohol is gone. Two hundred and seventy cubic centimeters of acetic anhydride are then added directly to the residue in the distilling flask. The flask is heated on the water bath for ten to fifteen minutes. Boiling water is then cautiously added until all the acetic anhydride has decomposed. On cooling, 46 g. of ethyl acetaminofuroate crystallized out melting at 168°C. This is 47% of the theoretical amount.

A more convenient method of reduction for large runs consists in admitting the hydrogen at atmospheric pressure. Hydrogen is bubbled through the violently stirred solution of ethyl nitrofuroate in absolute alcohol. A temperature of 40° C. to 45° C.

is maintained and 0.2 g. of platinic oxide is used per tenth mole of ester. An excess of hydrogen does no harm. The run is worked up as is described above yielding 47% of the theoretical amount of ethyl acetaminofuroate.

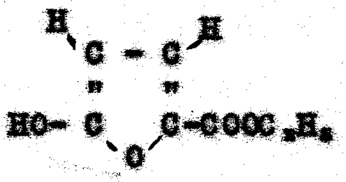
Diazotization of Ethyl Aminofuroate.

Three and one-tenth grams (0.02 mole) ethyl aminofuroate were dissolved in 9 g. of concentrated sulfuric acid. This was chilled and cracked ice was added until the volume was 50 cc. This was maintained at 0°C. A 10% solution of 1.38 g. (0.02 mole) of sodium nitrite was then added very slowly over a twenty-four hour period. After a short time a precipitate appeared which persisted over the entire reaction period. Finally it was filtered and the filtrate tested with *beta*-naphthol for presence of diazonium salt. The test was negative.

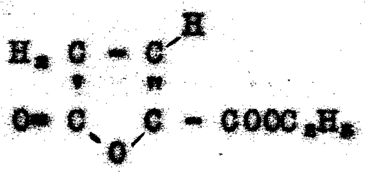
The precipitate was crystallized from alcohol-petroleum ether (B.P. 30°-60°C.) solution. It then melted at 91°C. It was slightly soluble in water. A qualitative test showed absence of nitrogen or sulfur.

Anal. Calc'd. for $C_7H_8O_4$: C,53.84%; H,5.13%: Found; C,54.28%; H,5.41%.

These results have not yet been duplicated although several trials have been made. It will be observed that analysis conforms with the empirical formula of ethyl hydroxyfuroate:



or



Unfortunately we have been unable to determine the constitution because of lack of material.

Attempted Diazotization of Ethyl Aminofuroate.

(1) Three and one-tenth grams (0.02 mole) of ethyl aminofuroate were dissolved in 40 cc. of absolute alcohol. Through this solution at 0°C., nitrous acid (generated from nitric acid and arsenious anhydride) was bubbled for three hours. The resulting solution was treated with warm cuprous chloride solution. No product was obtained.

(2) Three and one-tenth grams (0.02 mole) of ethyl amino furoate were dissolved in 6 g. (0.1 mole) of glacial acetic acid in a 25 cc. three-necked flask equipped with stirrer, dropping funnel and thermometer. The reaction was maintained at +10°C. while 2.35 g. (0.02 mole) of amyl nitrite were slowly added (1 drop every three seconds). After a subsequent stirring period of one-half hour, the contents of the flask were poured into ice water. A reddish oil precipitated which soon solidified. The aqueous solution was filtered off and was added to an equal volume of cuprous bromide solution. This was allowed to stand for two hours and was then heated to 80°C. on the water bath for fifteen minutes. Evolution of nitrogen oxides was noted and no bromofuroic acid or ester could be found. An identical reaction with methyl anthranilate gave a 25% yield of orthobromobenzoic acid.

(3) This diazotization was carried out on a mer-

curic chloride-ethyl aminofuroate complex, which was prepered by pouring a solution of 5.5 g. (0.02 mole) of mercuric chloride into a solution of 3.1 g. of ethyl amino furoate in 20 cc. of alcohol. After one minute a heavy white precipitate seperated, which, after five days was filtered off. It melted at 180°C. and weighed 1.5 g. The filtrate was poured into water, yielding 0.5 g. more compound. This precipitate was suspended in an iced solution of 10% hydrochloric acid while 0.2 mole of a 10% solution of sodium nitrite was added. The absorption of nitrous acid, as indicated by starch-iodide paper was very slow. At the end of the addition there was no color reaction with *beta*-naphthol but 0.5 g. of ethyl aminofuroate was recovered.

The Preparation of Ethyl ?-Bromo-5-Acetamino-2-Furoate(29)

Nineteen and seven-tenths grams (0.1 mole) of ethyl acetaminofuroate were dissolved in a mixture of 250 cc. of carbon disulfide and 250 cc. of chloroform. To this stirred solution were added 20 g. (0.125 mole) of bromine dissolved in 100 cc. of carbon disulfide. After a one hour addition period, the reaction mixture was refluxed for two and one-half hours. The remainder of the solvent was removed under reduced pressure. The residue was crystallized from benzene yielding 22.1 g. of crude product melting at 109°C. This is

(29) For a preliminary report of the work see Gilman and Wright, Iowa State Coll. J. of Sci., 5,85(1931).

80% of the theoretical amount. Another crystallization from the same medium raised the melting point to 112°C.

<u>Anal.</u> Calc'd. for $C_9H_{10}O_4NBr$: Br, 28.95%; Found; Br, 28.49%.

An attempted hydrolysis with 10% alcohol solution of sulfuric acid yielded only ammonium sulfate. A cold hydrolysis with the same reagent gave, after twelve days, a precipitate melting at 255°C. This was not investigated further.

<u>Preparation of Ethyl 5-acetamino-beta-nitro-2-furoate.</u>

A nitrating mixture was prepared by adding 350 g. (5.4 moles of fuming nitric acid to 1500 cc. of acetic anhydride. The temperature was kept below -5°C. throughout the reaction. One hundred and ninety-seven grams (1 mole) of ethyl 5-acetamino-2-furoate were added in small amounts over a four hour period. There was almost no evidence of heat evolution. Two hours after all the solid was added, the reaction mixture was filtered through a chilled Büchner funnel and into two liters of cracked ice. The precipitate was well washed with water. The oil which came through the filter and into the ice soon solidified and was likewise filtered. This latter precipitate was then added slowly to 250 cc. of cold pyridine, the reaction being very violent. Next day this was diluted with water, the precipitate filtered out and thoroughly washed with water. This precipitate and that obtained by the first filtration comprised a yield of 128 g. melting at 156°C. This is 53% of the theoretical amount. The compound when crystallized from alcohol melted at 138°C.

Anal. Calc'd. for $C_9H_{10}O_6N_2$: C,44.63%; H,4.14%: Found; C,44.66%; H,4.25%.

This compound was found to be soluble in dilute sodium carbonate, from which solution it could be reprecipitated with dilute acid. When it was heated in a sealed tube with water for one and one-half hours, hydrolysis took place and the ethyl 5-amino-beta-nitro-2-furoate was obtained together with some decomposition.

Preparation of Ethyl 5-Amino-beta-nitro-2-furoate.

One hundred and twenty-one grams (0.5 mole) of ethyl 5-acetamino-beta-nitro-2-furoate were suspended in a solution of 100 g. of concentrated sulfuric acid in one liter of absolute ethyl alcohol. This mixture was refluxed for one and one-half hours. It was filtered hot and allowed to cool slowly, finally being chilled to -15°C. Filtration yielded 76.5 g. of the amine. The filtrate was concentrated under reduced pressure yielding 9.5 g. of the compound. The yield is 86% of the theoretical amount of compound melting at 148°-150°C. Two crystallizations from a water-alcohol solution raised this to 153°C.

Anal. Calc'd. for $C_7H_8O_5N_2$: C,42.00%; H, 4.00%: Found; C,42.15%; H,4.12%.

When a water solution of the amine was treated with a barium hydroxide solution, a red precipitate was formed. Dilute sodium hydroxide destroys the compound. Its ether solution

solution when treated with dry hydrochloric acid gas will not form the hydrochloric, but it may be recovered from the treatment unchanged. When 2 g. of the amine were heated to 175°C. with 15 cc. of water for one and one-half hours, 1.45 g. of the compound were recovered unchanged.

Attempted Diazotization of Ethyl 5-Amino-beta-nitro-2-furoate.

Most of these trials failed to give any indication of diazotization. In each the criterion was a color test with alkaline beta-naphthol.

(1) Two grams (0.01 mole) of the ester were dissolved in 9.8 g. (0.01 mole) of concentrated sulfuric acid. This was immersed in an ice-water bath and 25 cc. of alcohol were slowly added, causing precipitation of the ester. The suspension was then chilled with an ice-salt freezing mixture while a solution of 1.03 g. (0.01 mole) of butyl nitrite in 3 cc. of alcohol was slowly added. One-half hour after the addition was terminated, the reaction showed presence of nitrous acid, but a test portion gave no precipitate with alkaline beta-naphthol. After standing twelve hours at room temperature, the reaction mixture was filtered yielding 1.62 g. of unchanged ester melting at 153°C.

(2) Six grams (0.04 mole) of the ester were dissolved in 20 g. (0.2 mole) of concentrated sulfuric acid. Ice was added until the volume was 100 cc. Then 0.04 mole of

a 10% solution of sodium nitrite was added. Much foaming took place, but the solution gave no beta-naphthol test. None of the amine was recovered.

(3) Two grams (0.01 mole) of the amine were intimately ground with 1.2 g. (0.01 mole) of potassium bisulfite in a mortar. This was slowly added to stirred fuming nitric acid (5 cc.) at the temperature of an ice-salt freezing mixture. There was no charring or evidence of violent reaction. When addition was complete, a test portion gave no red coloration with alkaline beta-naphthol. When poured into ice and water no precipitate appeared.

(4) A nitrosyl sulfate solution was prepared by adding 0.8 g. (0.012 mole) of sodium nitrite to 160 g. of sulfuric acid monohydrate. This solution was chilled to -5°C. while 2 g. (0.01 mole) of ethyl 5-amino-beta-nitro-2-furoate, dissolved in 160 g. of acetic acid, were added over a two hour period. When addition was complete, a solution of 1.44 g. (0.01 mole) of beta-naphthol in 20 cc. of acetic acid was added. The solution immediately became green in color and the presence of a volatile acid was detected by fuming with ammonium hydroxide. Following the addition the reaction was stirred for fifteen minutes and then poured into cracked ice. The greenish precipitate which appeared was filtered off. It seemed to be rather unstable. Its color when dry was a distinct green, but when dissolved in hot alcohol an intense red color was observed. When the alcohol solution was precipitated with water, the red color entirely disappeared. The compound melts

at about 70°C. and is completely soluble in ether.

(5) A nitrosyl sulfate solution consisting of 0.7 g. of sodium nitrite in 50 g. of sulfuric acid monohydrate was added dropwise to a solution of 2.0 g. of ester in 75 cc. of acetic acid at +15°C. When all the nitrosyl sulfate was added, 200 cc. of ethyl alcohol were poured into the flask and the resulting solution was heated to 70°C. for one hour. A steady evolution of nitrogen accompanied the heating process. The reaction was then poured into water and extracted with carbon disulfide. Evaporation of the dried carbon disulfide solution under reduced pressure yielded a small amount of yellow solid that melted roughly at 200°C.

The Preparation of Nitrosylvan (5-nitro-2-methylfuran). In the report by Rinkes (30) on the preparation of nitrosylvan, the position of the nitro group was reported as "5-" on the assumption that nitration of a furoic acid replaced the carboxyl group by the nitro group in the identical position. It was thought that this assumption should be verified, especially since this was the first case where a furan ring containing a true positive substituent (31) was nitrated.

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(30) Rinkes, Rec. trav. chim., 49,1118(1930)

(31) Although furfural diacetate (Gilman and Wright, J. Am. Chem. Soc., 52,2550(1930)) appears to have a positive substituent, the reaction solvent, acetic anhydride, would probably tend to make this substituent negative. A similar case is that of aniline sulfate in sulfuric acid.

Hence, reactions intended to prove the structure of this compound were carried out in order that the mode of substitution in the furan series should be elucidated.

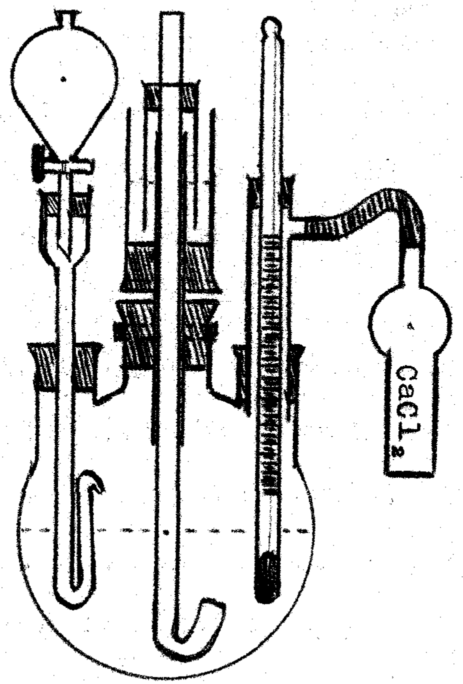
The nitration of sylvan is a difficult reaction. We were unable to increase Rinkes' low yield of 20% although by use of a device for pre-cooling the added solution, we were able to adapt the method to large size runs. Some other variations intended to raise the yield show interesting features of the furan nitrations. The addition of urea to remove nitrous acid had no effect on the yield; nor did the use of an inert atmosphere cause any change. Most significant of all was the observation that reaction temperatures as low as -50°C. did not raise the yield.

Numerous attempts to oxidize nitrosylvan to the known nitrofuroic acid led to unsatisfactory results. When, finally, a product was obtained in very low yield, it was found not to be 5-nitrofuroic acid. An attempt to brominate under the influence of ultra-violet light likewise led to failure.

At this point, it was fortunately discovered that the denitridation of a hydrazone (Wolff reaction) could be accomplished without the use of alkali catalysts. In this way nitrofurfural was converted to nitrosylvan and the fact was established that, regardless of the nature of the original substituent, nitration will only substitute the <u>alpha</u> position if such position be open.

Nitration of Sylvan

A nitrating mixture was prepared by adding 325 g. (5 moles) of fuming nitric acid (sp. gr.=1.52) to 510 cc. of acetic anhydride at -5°C. To this mixture was added dropwise a solution of 82 g. (1 mole) of sylvan in 175 cc. of acetic anhydride using the device illustrated and holding the temperature between -5°C. and -10°C.



The hook shaped addition tube should slide in its stopper easily so that the height may be adjusted as the volume of the reaction mixture increases. In this manner the added solution was maintained at the same temperature as the nitrating mixture. When addition was complete, the reaction mixture was poured on four liters of cracked ice. The resulting liquor was extracted three times with ether. This ether solution was neutralized with a suspension of sodium bicarbonate. The aqueous layer was then separated and also extracted with ether. The combined ether extracts were treated with pyridine until no further heat reaction was observed. After twenty-four hours the ether was distilled off at atmospheric pressure and then the pyridine was removed under reduced pressure. The residue was steam distilled, yielding 25 g. of nitrosylvan melting at 43°C. This is 19.7% of the theoretical amount. The residual steam distillation liquors yielded a small amount of solid melting at 115°-117°C. which when crystallized from water melted at 125°C. This is not maleic acid.

Attempted Oxidation of Nitrosylvan.

An attempted oxidation with chromic acid (sodium dichromate and sulfuric acid) resulted in a quantitative recovery of nitrosylvan. When nitrosylvan was refluxed with potassium permanganate, total decomposition occurred, and an acid permanganate oxidation using potassium permanganate and sulfuric acid, did not affect the nitrosylvan. A reaction was obtained when a chloroform solution of nitrosylvan was refluxed during a slow addition of three equivalents of bromine in a quartz test tube using a strong source of ultra-violet light, but no product could be obtained. In general these oxidations show the stability of nitrosylvan and especially the stabilizing influence of the nitro group.

When 6.34 g. (0.05 mole) of nitrosylvan were heated with 40 cc. of 50% sulfuric acid and 10 g. of manganese dioxide to

80°-140°C. for thirty-six hours, a reaction took place. Repeated ether extractions yielded a residue which, when crystallized from benzene, melted at 158°C. This compound contained nitrogen. The yield was 0.2 g. No further work was done upon it. Although 5-nitro-2-furoic acid melts at 183°C., a mixed melting point was taken and this was lowered 20°C.

Reduction of Nitrofurfural to Nitrosylvan.

Fourteen and one-tenth grams (0.1 mole) of nitrofurfural were dissolved in 50 cc. of methyl alcohol. This solution, chilled to 0°C. was added at once to a solution of 10 g. (0.2 mole) of hydrazine hydrate in 150 cc. of methyl alcohol, likewise chilled to 0°C. After twelve hours, the precipitate was filtered off and dissolved in 30 cc. of quinoline. Five grams of copper bronze were added and the mixture was heated to 90°-100°C. for four hours. The evolution of nitrogen was very slow. Finally the reaction mixture was dissolved in ether, transferred to a steam distillation flask, and the ether being removed by distillation, the residue was chilled by addition of ice and hydrochloric acid was added until the solution was acid. It was then steam distilled yielding upon acidification of the distillate 0.82 g. of nitrosylvan melting at 43°C. The identity with Rinkes' nitrosylvan was established by mixed melting point. The yield was 6.5% of the theoretical amount.

Bromination of Nitrofuran.

Five and sixty-five hundredths grams (0.05 mole) of nitrofuran were dissolved in 100 cc. of carbon disulfide. This solution was placed in a 200 cc. three-necked flask equipped with stirrer, dropping funnel, and reflux condenser. Twenty-six and four tenths grams (0.33 mole) of bromine were added dropwise. The first few drops of bromine were not absorbed even when the solution was refluxed. The remainder of the bromine was added and various catalysts (ferric chloride, mercuric chloride, stannic chloride) were added successively with no effect. A few pieces of silica gel caused a very slight evolution of hydrobromic acid. The solution was then refluxed for twenty-four hours. Only unchanged nitrofuran and a few crystals of sulfur could be found in the reaction mixture. The run was repeated using 5 g. of freshly reactivated silica gel and a forty-eight hour period of reflux. The results were again negative.

Nitration of 2-Bromofuran.

Twenty-seven grams (0.184 mole) of 2-bromofuran, prepared by decarboxylation of bromofuroic acid, (32) were dissolved in 35 cc. of acetic anhydride. This was added drop by drop to a nitrating mixture composed of 65 g. (1 mole) of fuming nitric acid in 102 g. of acetic anhydride. The temperature was maintained at -5°C. The color of the reaction mixture was reddish orange, but showed no abnormal signs of decomposition. When addition was complete and the reaction had been stirred for an additional half hour, the solution was poured on 1.5 kilos of cracked ice. Sodium hydroxide was added cautiously

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(32) Shepard, Winslow, and Johnson, J. Am. Chem. Soc., **52**, 2083(1930).

to facilitate the precipitation of the oil. This oil was separated and combined with a subsequent ether extract of the aqueous layer. A suspension of sodium bicarbonate was added to this ether solution until it was almost neutral. The ether solution was then treated cautiously with pyridine. An immediate darkening took place with decided heat evolution and nitrogen oxides were evolved. One hundred and thirty cubic centimeters of pyridine were quickly added and the solution strongly cooled with ice water. After twelve hours the ether was distilled off, the pyridine was removed under 20 mm. pressure, and the residue was steam distilled. No product could be obtained. A duplicate run gave similar results.

Nitration of Tribromofuran.

A solution of 5.8 g. (0.019 mole) of 3,4,5-tribromofuran (33) in 5 cc. of acetic anhydride was added dropwise to a nitrating mixture consisting of 1.89 g. (0.03 mole) of fuming nitric acid dissolved at 0°C. in 10 cc. of acetic anhydride. A temperature of -5°C. was maintained during the addition. After a three hour period of stirring, the reaction mixture was poured on 200 g. of cracked ice and the resulting mixture was thoroughly extracted with ether. This ether solution was then treated with 50 cc. of pyridine. After twenty-four hours the ether was distilled off, the residue diluted with water, and acid added until the pyridine was just neutralized. The

(33) Prepared by the method of Hill and Sanger, Proc. Am. Acad. Arts Sci., 21, 135(1885); Ann., 232, 42(1885)

suspension was then steam distilled. The oil in the steam distillate was collected with ether. The ether solution, dried and distilled, yielded 2.86 g. of tribromofuran boiling at 109°-111°C. at 35 mm. No other product could be found.

Nitration of 2,5-Dibromofuran.

This run was carried out using conditions identical with those used for nitration of 3,4,5-tribromofuran. The 2,5-dibromofuran was prepared by the method of Hill and Hartshorn (34). After the final steam distillation, only a trace of material melting below 20°C. was found in the distillate. An almost quantitative yield of fumaric acid was found in the residual steam distillation liquors.

Nitration of Ethyl 5-Bromofuroate.

The conditions used were similar in every respect with those employed in the two previous runs. As was observed with 2,5-dibromofuran, additions to the nitrating mixture caused an intense reddish brown coloration of the solution. After the customary hydrolysis with ice water, the oil was slowly added to cold pyridine. A violent reaction occurred and the resulting solution yielded only an unworkable tar.

Nitration of 2,5-Diiodofuran.

To a nitrating mixture consisting of 17.5 g. (0.25 mole) of fuming nitric acid dissolved at -5°C. in 25.5 g. (0.25 mole) of acetic anhydride, there was added dropwise at -5° to -10°C.

(34) Hill and Hartshorn, Ber., 18,448(1885).

a solution of 16 g. (0.05 mole) of 2,5-diiodofuran in 51 g. (0.5 mole) of acetic anhydride. At the addition of each drop, the solution became an intense red color. For a while the color was reabsorbed, but finally it became permanent. When the halide was all added, the reaction was stirred for three hours and was then filtered by suction through a chilled Büchner funnel into cracked ice. The precipitate was found to be 11.2 g. (almost dry) of iodine. This is 87.5% of the total iodine content of the reaction. The filtrate, having been mixed with about 250 g. of ice was extracted twice with ether. The ether solution was first washed with a 10% solution of sodium thiosulfate, then neutralized with a suspension of sodium bicarbonate. Finally the solvent was removed under reduced pressure. <u>No pyridine was used in this reaction.</u> The residue weighed 0.5 g. and melted at 72°C. Analysis showed this to be a nitro-iodofuran; the yield is then 4%. This substance was crystallized from a mixture of benzene and petroleum ether. It then melted at 76°-77°C. This is a powerful lacharymator, sternutator and vesicant; the presence of this half gram made the entire atmosphere of the room unbearable. A very small amount accidentally spilled on the palm of the hand caused a vicious blister which was several weeks in healing.

<u>Anal</u>. Calc'd. for $C_4H_2O_3NI$: I, 53.14%; Found: I, 53.20%.

<u>Nitration of 2,5-Diiodofuran.</u>

Seventeen grams (0.1 mole) of silver nitrate were suspended in 50 cc. of carbon tetrachloride and chilled to -15°C. To this stirred solution was added dropwise 14 g. (0.1 mole) of benzoyl chloride dissolved in 50 cc. of carbon tetrachloride. In this way benzoyl nitrate (35) was prepared. To this solution at -10°C. was slowly added 32 g. (0.1 mole) of diiodofuran dissolved in 50 cc. of carbon tetrachloride. The reaction mixture was allowed to warm up to 10°C. after addition. At no time during the process was there any evidence of heat evolution. The mixture was then filtered to remove silver chloride. The filtrate was washed with sodium thiosulfate to remove the iodine and the solvent removed under reduced pressure. The residue after washing with more thiosulfate was found to be 18 g. of unchanged diiodofuran.

<u>Nitration of Diiodofuran</u>.

A solution of 32 g. (0.1 mole) of diiodofuran in 75 cc. of carbon tetrachloride was placed in a 200 cc. three-necked flask equipped with stirrer, dropping funnel and thermometer. The temperature was maintained at -5°C. to -10°C. while a solution of 16.3 g. (0.1 mole) of o-diacetylnitric acid (36) in 50 cc. of carbon tetrachloride was added dropwise. There was no apparent heat evolution, but a gradual darkening of the solution was observed. Following addition the reaction was stirred for several hours and was then filtered yielding 8 g. of iodine. The filtrate when washed with 10% sodium thiosulfate

(35) Francis, J. Chem. Soc., 89,1(1906)
(36) Pictet, Ber., 35,2526(1902)

and evaporated under reduced pressure yielded 18.7 g. of unchanged diiodofuran. No other product could be obtained.

Nitration of Ethyl 3,4-Dibromofuroate and Ethyl 3,5-Dibromofuroate.

These two esters were prepared according to directions of Hill and Sanger (33). They were nitrated by adding dropwise a solution of 26.8 g. (0.09 mole) of the ester in 20 g. of acetic anhydride to a nitrating mixture made up from 35 g. of fuming nitric acid in 56 g. of acetic anhydride. The temperature of the reaction was maintained at -5° C. throughout. The recovery of the two esters was quantitative.

An attempt to nitrate these esters by dissolving in sulfuric acid and slowly adding fuming nitric acid to the reaction mixture at low temperature resulted in each case, in total decomposition.

III THE HALOGENOFURANS

The halogenation reactions of furan compounds are among the first mentioned and are, perhaps, the most numerous. Unfortunately, they have been confined to but a few types, notebly the furoic acids. After some preliminery, rather indefinite work by several chemists, Hill and his co-workers studied at length the halogenation of furoic acid (37). Henninger (38) reported the direct bromination of furan. However, the greater number of simple halogen derivatives of furan were prepared by decarboxylation of the corresponding furoic acids (39). Furylacrylic acid (40,41) was brominated, but the products were not studied to any great extent.

The chlorination (42) and bromination (43) of furfural diacetate have been reported from this laboratory, as well as some investigations of the brominated furylacrylic acids (44). We have made a number of attempts to improve the synthesis of chlorofurfural, with no success. An improved preparation of

(37) For chlorofuroic acids, see Am. Chem. J., 12,112 (1890); Ber., 20,252(1883)
For bromofuroic acids, see Ann., 232,42(1885); Am. Chem. J., 32,185(1904); Am. Chem. J., 15,159(1893); Ibid., 15,130(1893); Ber., 18,448(1885); Ber., 18, 1130(1885).

(38) Henninger, Ann. chim. phys., (6) 7,209(1886)

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

(40) Gibson and Kahnweiler, Ann. Chem. J., 12,314(1890)

(41) Moureu, Dufraisse and Johnson, Ann.,chim., (10) 7, 1(1927)

(42) Gilman and Wright, Rec. trav. chim., 50,833(1931)

(43) Gilman and Wright, J. Am. Chem. Soc., 52,1170(1930)

(44) Gilman and Wright, J. Am. Chem. Soc., 52,3349(1930)
Gilman, Hewlett and Wright, Ibid., 53,4192(1931)
Gilman and Wright, Rec. trav. chim., 49,195(1930)

bromofurfural is, however, included, as well as a discussion of the mechanism of the bromination reaction.

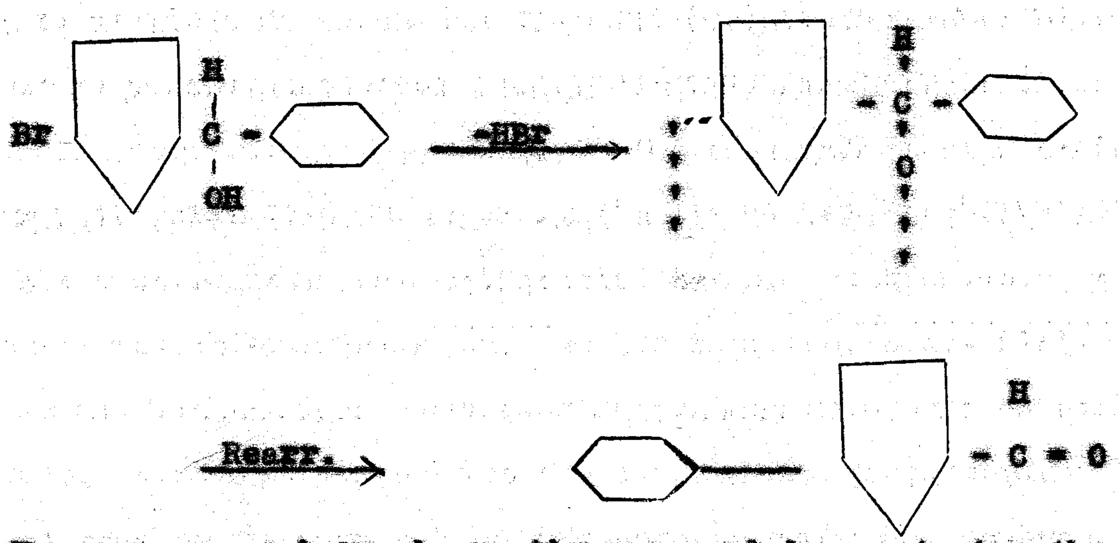
The reactions of bromofurfural and some of its derivatives are quite interesting. Whereas chlorofurfural was easily reduced to chlorosylvan, when this reaction was carried out with bromofurfural, such abnormalities arose that we are forced to report the work without being able to offer a real solution for it. However, the low percentage of halogen indicates that, as will be shown later, this alpha halogen possesses a peculiar lability and is, in part, removed from the molecule.

This removal of the alpha halogen was noted by Hewlett (45). When he prepared 5-chlorofuryl phenylcarbinol and 5-bromofuryl phenylcarbinol, he found these compounds to be unstable, splitting out halogen acid with great ease and resulting in a halogen-free compound. He was unable to adduce the nature of this compound. We have investigated the substance in the hope of throwing some light on the problem of bromofurfural, but have been likewise unsuccessful.

Recently Reichstein (46) and Runde, Scott and Johnson (47) have reported a rearrangement which takes place when furfuryl chloride is treated with aqueous sodium cyanide.

(45) Hewlett, Thesis "Furfural and Some of Its Derivatives", Iowa State College, (1930).
(46) Reichstein, Ber., 63, 749(1930)
(47) Runde, Scott and Johnson, J. Am. Chem. Soc., 52, 1284(1930)

we thought it possible that a reaction of this kind might have taken place with these carbinols resulting in a phenyl furfural.



However, as we have shown, the compound does not give the reactions of 5-phenyl furfural.

However, it was thought best to test this type of reaction further. Hewlett (48) had already found that chloro or bromo-furfuryl alcohol could not be prepared because of its extreme instability. 5-Chlorofurfurylamine was then prepared by reduction of the oxime. We were much surprised to find that this compound is quite stable. A twenty-four hour reflux period with alcohol failed to change the compound.

Returning to furfuryl chloride, a number of attempts were

(48) Hewlett, Unpublished results.

made to prepare the Grignard reagent. This would be expected to rearrange as does the nitrile reaction. Unfortunately, furfuryl chloride will not react with ordinary magnesium. This is probably due to the fact that it is impossible to obtain the compound in a pure state. The ether solution is never perfectly clear; a crystalline compound can be isolated from a solution chilled to -80°C. The halide reacts easily with reactivated magnesium, or with a magnesium-magnesium iodide complex, but the reaction is consistently one of coupling to the extent of 35-40%.

We have made a study of the simple iodo derivatives of furan. Prior to this study only 2,5-diiodofuran was known, having been prepared by Phelps and Hale (49). Both 2-iodofuran and 3-iodofuran have been prepared; the former by iodination of furoic acid and the latter by reduction of tetraiodofuran.

The diiodofuran would not react with ordinary magnesium; with reactivated magnesium or reactivated 12 3/4% copper-magnesium alloy it reacted readily giving 5-iodo-2-furylmagnesium iodide. No trace of a di-Grignard reagent could be obtained. Carbonation of the Grignard reagent gave 5-iodo-2-furoic acid. An attempt to prepare iodosylvan from iodofurylmagnesium iodide failed because, contrary to expectation, the dimethyl sulfate caused hydrolysis. A good yield of iodofuran was obtained.

(49) Phelps and Hale, Am. Chem. J., <u>25</u>,445(1901)

The preparation of 2-iodofuran was effected by treating an excess of boiling sodium furoate with solid iodine (50). A solution of iodine in potassium iodide when slowly added to the boiling solution of sodium furoate gave no product whatsoever. The product was quite unstable when first obtained and had to be used at once. When the compound was treated with magnesium, furylmagnesium iodide was obtained in 90-95% yield. When this Grignard reagent was treated with anhydrous cupric chloride, only a small yield of difuryl was obtained. The iodofuran which was recovered from the reaction was found to be much more stable than the original compound.

When 3-iodofuran was prepared by treating tetraiodofuran with aluminium amalgam, the compound was found to be unusually stable as compared to the 2-iodofuran. It was also decidedly inert, and would not react with magnesium under any circumstances. This was not surprising since 3-bromofuran would not react with reactivated copper-magnesium alloy.

The halogenation reactions of furylacrylic acid were of interest because of the analogies which might be drawn with the peculiar reaction of the bromo cinnamic acids. Many of these reactions have already been reported. (44).

The bromination of ethyl furylacrylate proceeded smoothly and in better yield than with the acid. Upon careful purification of the ethyl 5-bromofuryl-alpha-beta-dibromo propionate an isomer was discovered in small amount which was much

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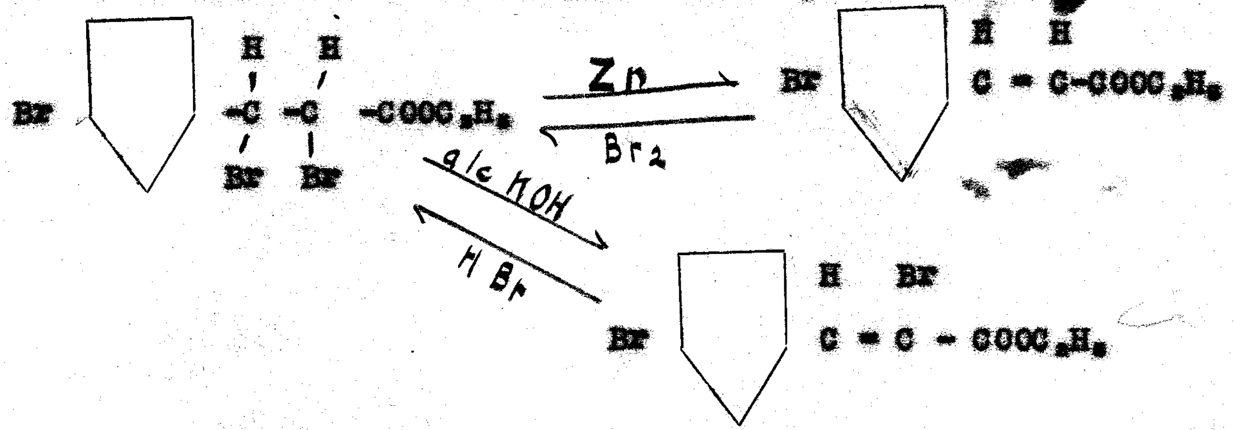
(50) Gilman, Mallory and Wright, J. Am. Chem. Soc., 54, 733(1932)

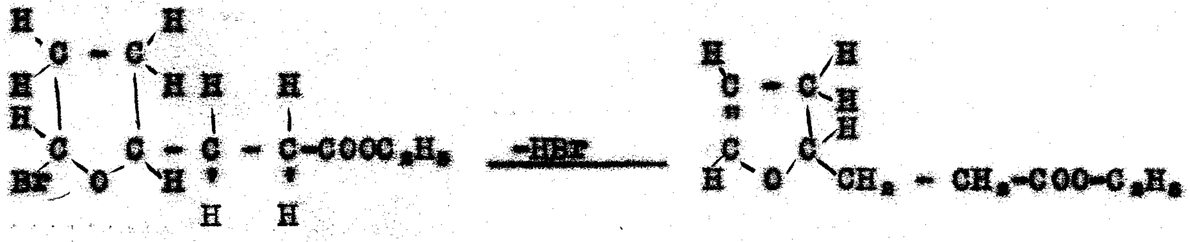
more stable than the customary form.

As in the case of the 5-bromofuryl-dibromopropionic acid (40), this ester was easily decomposed into ethyl 5-bromofurylacrylate and ethyl 5-bromofurylbromoacrylate. Both of these esters could be reconverted to the parent form.



A number of derivatives of these two esters are described. These were prepared from the 5-bromofurylacryloyl chloride and the 5-bromofurylbromoacryloyl chloride.

The reduction of either 5-bromofurylacrylic acid or its ester gives an ethyl 5-bromotetrahydrofurylpropionate which cannot be isolated. Hydrobromic acid splits out with great ease giving what is probably ethyl 2,3-dihydrofuryl-2-propionate.



Experimental

The Preparation of 5-Bromofurfural.

Three methods were originally submitted for the preparation of 5-bromofurfural (43). Of these the first method is of interest only because of the polybromo compound obtained when an amount of bromine greater than two equivalents is used. A typical run is given:

In a one liter three-necked flask equipped with reflux condenser, stirrer, and dropping funnel and gas inlet were placed 133.5 g. (0.674 mole) of furfural diacetate (45) in 300 cc. of carbon disulfide (dried with anhydrous calcium chloride). The flask was swept out for several hours with dry carbon dioxide. Then 240 g. (1.5 moles) of bromine (dried by shaking with sulfuric acid) were added dropwise with stirring; evolution of hydrobromic acid commenced during the addition. After addition was complete, the reaction was refluxed for four hours. The solvent was removed under reduced pressure and the residue was refluxed with carbon dioxide atmosphere for thirty minutes. The mixture was then neutralized with sodium carbonate and steam distilled. The first fraction was 5-bromofurfural, weighing 11 g. Toward the end of the distillation, 8.5 g. of substance melting at 125°-132°C. This was crystallized from benzene to melt at 134°-135°C.

Anal. Calc'd. for $C_5H_2O_2Br_2$: Br, 62.99%; Found; Br, 63.68%.

This compound could not be oxidized with alkaline permanganate at room temperature, being recovered unchanged. It had a decided vesicant effect. About 10 mg. in 5 cc. of alcohol when applied to the skin in 1 drop quantity caused a red spot in four hours and a painful blister in twenty-four hours. The blisters heal rapidly. After two years this compound, although seemingly unchanged, had lost its vesicant properties. The analysis approximates that required for dibromofurfural.

The second method outlined for preparation of 5-bromofurfural has been improved so that it is easier and more reliable. A solution of 640 g. (4.0 moles) of bromine in 200 cc. of carbon disulfide was added dropwise over a four and one-half hour period to a stirred solution of 396 g. (2.0 moles) of furfural diacetate (45) in 800 cc. of carbon disulfide maintained at 8°-10°C. After standing three or four hours (or overnight) at this temperature, the reaction mixture was filtered, yielding 48.5 g. of the solid compound, the nature of which is discussed later. The filtrate was poured into five liters of water and the carbon disulfide distilled off slowly over a three hour period. The residue was then steam distilled yielding 86 g. of 5-bromofurfural melting at 80°C. This is 25% of the theoretical yield.

If the solid by-product is $C_7H_8O_4Br_2$, the yield is only 7.6% of the amount which might theoretically be formed. This may be raised significantly by using acetic anhydride as the solvent instead of carbon disulfide. The yield of 5-bromofurfural is, however, lowered. The presence of a large quantity of acetyl bromide is substantiated by conversion to acetanilide. The yield of the compound melting at 159°C. was 30% of the theoretical, whether one or two equivalents of bromine were added. The yield of 5-bromofurfural was 15.9% using one equivalent of bromine.

Composition of By-Product Obtained in Bromination of Furfural Diacetate.

The compound was found to contain carbon, hydrogen, and bromine. It was insoluble in benzene and alcohol, but slightly soluble in chloroform and carbon tetrachloride. It was soluble in hot acetic acid, but decomposed in the solvent at 100°C. The crude compound melting at 151°-154°C. was crystallized from chloroform or carbon tetrachloride, then melting at 169°C. When washed with cold acetic acid, the melting point was raised to 172°C.

Anal. Calc'd. for $C_7H_8O_4Br_2$: Br, 50.65%; C, 26.58%; H, 2.55%; Found: Br, 50.46%; 50.90%, 50.97%; C, 25.89%, 24.80%; H, 2.56%, 2.75%.

Refluxing an ether suspension of the compound for eight hours with silver acetate produced no change, showing that the bromine atoms are not laterally situated (51). No product could be isolated by alkaline permanganate oxidation. A test with vanillin-hydrochloric acid solution (52) and with aniline acetate were both negative.

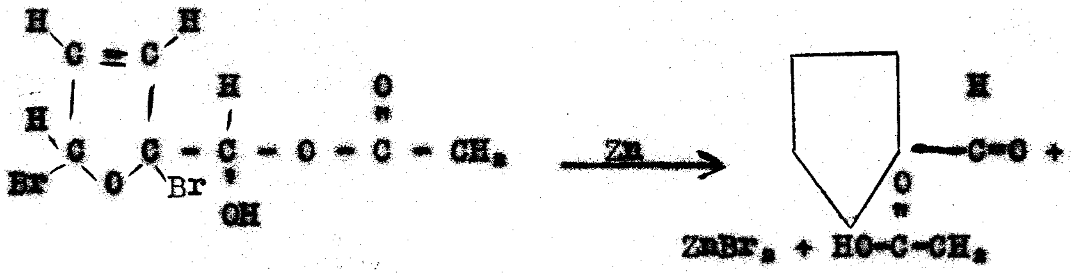
The bromine atoms were removed by suspending 31.6 g. (0.1 mole) of the compound in 300 cc. of methyl alcohol. Thirteen grams (0.2 mole) of zinc dust were added and the mixture was refluxed with stirring for three hours. It was then filtered by suction and the filtrate was poured in a saturated solution

(51) Adams and Vollweiler, J. Am. Chem. Soc., **40**, 1732(1918)

(52) Asahina, Acta Phytochim.(Japan), **2**, 1(1924-26)

of calcium chloride. The solution was extracted four times with ether. Since the solution still showed a positive aniline acetate test, it was further extracted with two 100 cc. portions of chloroform. The extracts were combined and washed three times with 100 cc. portions of saturated sodium carbonate solution. The solvent was then distilled off after drying with anhydrous calcium chloride. The residue was distilled at 79°C. and this is 15.7% of the theoretical amount. The furfural was converted to the phenyl hydrazone. A mixed melting point of the latter with a specimen prepared from furfural showed no depression.

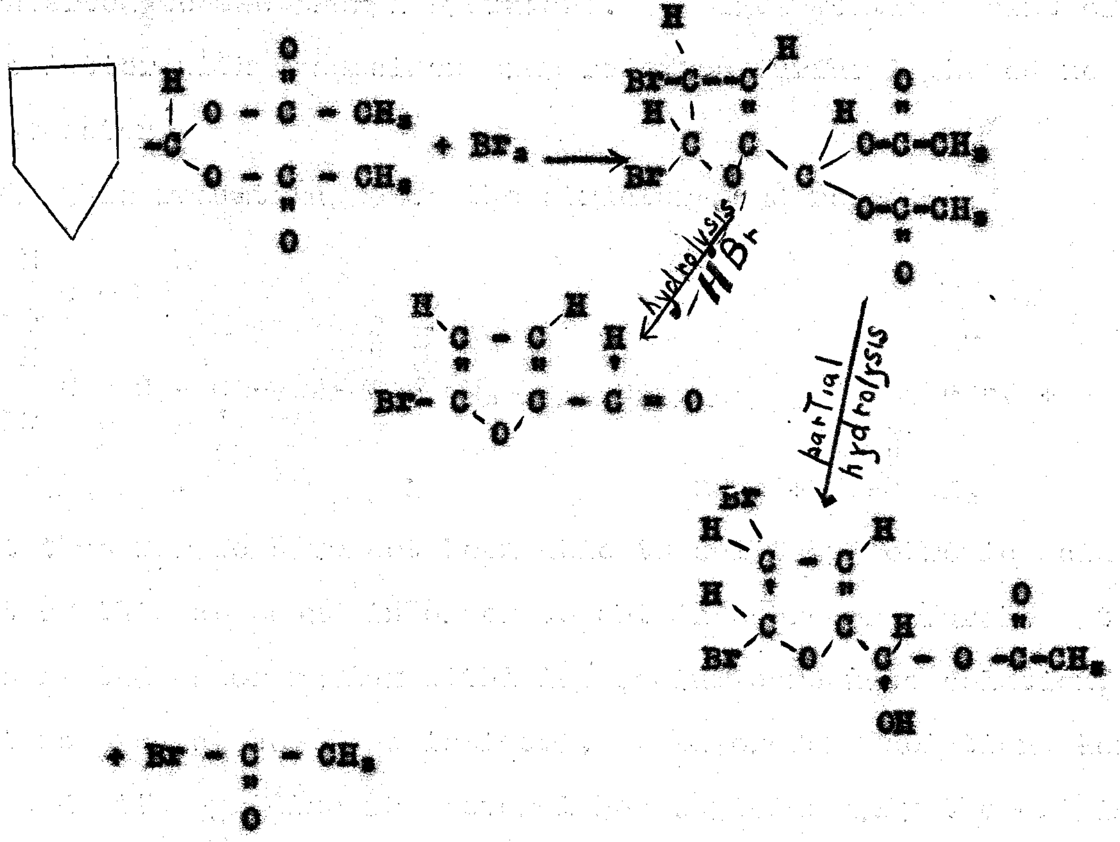
This result suggests the structure and reaction:



but thus far we have not been able to split hydrobromic acid out of this compound in order to obtain 5-bromofurfural. It was heated under reflux with 10% sodium carbonate solution, but no product could be isolated. A chloroform solution when heated with pyridine for several hours yielded only the original compound, slightly purer than before.

An attempt to split out the acetic acid fragment also met with failure. Ten grams of the compound were boiled with normal sulfuric acid under carbon dioxide atmosphere until solution was attained. A little alcohol was added to facilitate solution. Upon cooling no solid precipitated. A test portion with sodium carbonate solution likewise gave no precipitate. Ether extraction gave no workable product.

Since the use of acetic anhydride as a solvent increased the yield of this compound, it is improbable that the compound is itself an intermediate in the bromination reaction. It is, however, probably derived from the intermediate addition product in the following manner.



This is supported by the fact that acetyl bromide may be isolated from this reaction. It was identified by treating the distillate (B.P. 48°C. at 68 mm.) with an excess of aniline. The acetanilide was identified by mixed melting point. It may be noted that the bromine addition has been indicated as both 1,2- and 1,4-. Either is possible.

Preparation of 5-Chloro-2-Methylfuran.

Sixty-five grams (0.5 mole) of 5-chlorofurfural (53) were dissolved in 250 cc. of methyl alcohol and cooled to 5°C. To this solution was rapidly added 48 g. (0.96 mole) of hydrazine hydrate. A slight precipitate was formed. After one hour 56 g. (1.0 mole) of pellet potassium hydroxide were added. Frequent cooling was necessary in order to keep the reaction from becoming too strenuous. After twelve hours the reaction mixture was completely distilled. The distillate was washed with saturated calcium chloride and extracted with ether after the precipitated oil had been drawn off. The oil and three ether extracts were combined and dried with anhydrous sodium sulfate. The ether was distilled off. The residue was carefully fractionated, yielding 21 g. of 5-chlorosylvan boiling at 108°-110°C. This yield is 36.2% of the theoretical amount. In addition, a small amount of distillate boiled at 110°-125°C. The following physical constants were determined: $n_D^{20} = 1.4619$; $D_4^{20} = 1.118$; B.P., 110°C.

Anal. Calc'd. for C_5H_5OCl; Cl, 30.4%; Found; Cl, 30.60%, 29.91%.

The compound would not react with either ordinary or reactivated magnesium in ether. Its action with sodium in ether

(53) Gilman and Wright, Rec. trav. chim., 50, 833(1931)

solution was strenuous. The products are being investigated. The product is quite stable if left in the cold and absence of light.

The Action of Hydrazine Hydrate on 5-Bromofurfural.

(1) Product obtained using normal conditions for Wolff reaction.

One hundred and sixty-seven and two-tenths grams (0.95 mole) of 5-bromofurfural were dissolved in one liter of methyl alcohol and this solution was cooled to about 5°C. One hundred grams (2 moles) of pure hydrazine hydrate were added directly thereto. After standing overnight, the solvent was removed under reduced pressure. When practically all the solvent was gone, the residue separated into two layers. The upper layer contained the excess hydrazine hydrate. The bottom layer was separated, diluted with 250 cc. of methyl alcohol and 112 g. (2 moles) of pellet potassium hydroxide were added. After about six hours of gentle heating with a water bath all of the nitrogen had evolved. The reaction mixture was then distilled until the temperature reached 85°C. The liquer was distilled under 20 mm. until the temperature of the oil bath reached 200°C. The residue in the flask was then <u>quickly</u> steam distilled and the oil in the distillate was combined with that obtained from the vacuum distillation. (They were first shown to be identical.) This oil was diluted with ether, washed with strong calcium chloride solution and dried with anhydrous sodium sulfate. After removal of the solvent, the substance distilled at 102°-104°C. under 19 mm. pressure. The yield was 159.2 g. The refractive index was $n_D^{20} = 1.4863$. The compound did not contain nitrogen. The analysis does not conform with that required by bromofurfural dimethylacetal.

Anal. Calc'd. for $C_7H_9O_3Br$: Br, 36.38%; C, 38.18%; OCH_3, 28.18%; H, 3.63%: Found: Br, 33.89%, 33.92%, 33.44%, 32.90%; C, 35.50%, 35.25%; OCH_3, 27.52%, 27.66%; H, 1.83%, 1.92%.

When the preparation was carried out using ethyl alcohol instead of methyl alcohol, the nitrogen solution was normal, but no product could be isolated. Again, using methyl alcohol, bromofurfural, and hydrazone hydrate, but no potassium hydroxide, this reaction mixture was distilled under reduced pressure. Before the temperature of the oil bath reached 100°C., violent decomposition occurred.

(2) Hydrolysis of the above compound

Twelve and six-tenths grams (0.05 mole) of the compound were refluxed for forty-five minutes with 50 cc. of water; following this treatment, it was steam distilled. Seven and five-tenths grams of bromofurfural were obtained; This is 85% of the theoretical amount. Because of the interfering bromofurfural, the presence of methyl alcohol could not be established.

(3) Modified procedure for treatment of bromofurfural with hydrazine hydrate.

Since, in the preparation described above, there was always a small amount of low boiling fraction preceding the distillation of the product, it was thought that this might be bromosylvan. Inasmuch as the solvent had been shown to enter into the former reaction, the alcohol was eliminated as follows:

Forty-four grams (0.25 mole) of bromofurfural were dissolved in 500 cc. of anhydrous ether in a one liter three-necked flask equipped with stirrer, dropping funnel and thermometer. To this stirred solution were slowly added 15 g. (0.3 mole) of hydrazine hydrate. The latter was insoluble in the ether, but was gradually absorbed except for the excess. When addition was finished, the ether solution was decanted from this excess into a one liter distilling flask. Fifty-six grams (1 mole) of pellet potassium hydroxide were added. Since no nitrogen evolution occurred, 200 cc. of methyl alcohol were now added. The ether was distilled off and then nitrogen evolution commenced. When this evolution was complete, the alcohol was distilled off. The residue was steam distilled, but nothing came over in the distillate. The alcoholic distillate was washed with strong calcium chloride solution and the oil which separated was collected in ether. This ether solution was dried with anhydrous calcium chloride and after the solvent was evaporated, the residue was distilled under 27 mm. pressure. Fourteen grams of compound boiled at 45.5°C. The constants were determined as follow: n_D^{20} = 1.4869, n_D^{25} = 1.4845, D_4^{20} = 1.325, M_r = 55.8 calc'd. for bromosylvan, 59.16 found for the compound, B. P. 61°C. at 58 mm. pressure, 51°C. at 34 mm. pressure. The compound did not contain nitrogen.

Anal. Calc'd. for C_5H_5OBr: C, 37.27%; H, 3.10%; Br, 49.69%: Found: C, 39.90%; H, 3.83%, 3.75%; Br, 34.22%, 35.43%.

(4) Properties.

This compound was refluxed for several hours with water but the compound did not undergo any change. A carefully distilled fraction would not react with magnesium in ether. The compound was much less stable than that formed using methyl alcohol as the solvent. It should be noted that the refractive indices of the two products of this investigation are almost identical.

Preparation of Bromofurfural Azin (BrC.H.ON:NCH.C.Br)

Three and three-tenths grams (0.05 mole) of hydrazine hydrochloride were added to a solution of 2.8 g. (0.05 mole) of potassium hydroxide in 6.5 cc. water. To this stirred solution cooled to 0°C.; 8.8 g. (0.05 mole) of 5-bromofurfural were added in small portions. When addition was complete, the reaction was let stand for several hours and was then made slightly alkaline with potassium hydroxide and was refluxed for one hour. After cooling the flask, the precipitate was filtered off. It melted at 168°-170°C. and weighed 8.5 g. or 98% of the theoretical amount. When crystallized from alcohol, it melted at 172°-173°C.

Anal. Calc'd. for $C_{10}H_6O_2N_2Br_2$: Br, 46.24%: Found; Br, 46.39%, 46.49%.

This compound was not changed by boiling with 20% potassium hydroxide solution. Fusing with potassium ethylate did not eliminate nitrogen.

Studies on 5-Bromo and 5-Chlorofuryl phenylcarbinol.

The compounds, 5-bromofuryl-2-phenyl carbinol and 5-chlorofuryl-2-phenylcarbinol which were reported by Hewlett (45) were prepared and his reported yields were checked. It must be emphasized that these products are quite unstable and the bromo compound especially should not be prepared in runs larger than 0.1 mole. If the chlorofurfural is available and the chlorofuryl phenylcarbinol is a suitable product, it should be chosen rather than the very unstable bromofuryl phenylcarbinol. In one run with bromofurfural the order of addition was reversed and the ether solution of bromofurfural was added to a filtered solution of phenylmagnesium bromide. No advantage was gained by this variation. In order to determine the effect of removing the phenyl group from the carbinol linkage, benzyl magnesium chloride was added to a solution of bromofurfural. This run completely decomposed upon hydrolysis. In general, no improvement could be made over the procedure. However an account of a typical run is outlined.

Preparation of 5-Bromofuryl-2-Phenylcarbinol.

Three and six-tenths grams (0.15 mole) of magnesium turnings were suspended in 20 cc. of anhydrous ether in a one liter three-necked flask fitted with stirrer, dropping funnel, and reflux condenser. Eighteen and eight-tenths grams (0.121 mole) of bromobenzene in 150 cc. of ether were slowly added in order to minimize the formation of diphenyl. When this halide had been added, the solution was refluxed for twenty minutes. A solution of 17.6 g. (0.1 mole) of bromofurfural in 250 cc. of ether was then added over a period of one and one-half hours. After a two hour period of reflux, the reaction mixture was poured into acetic acid. This hydrolysate was let stand for two hours. The ether layer was then separated and washed twice with sodium bisulfite solution. The ether was distilled off and the residue rapidly steam distilled until darkening started to occur. The steam distillation flask was then quickly chilled and when cold was extracted with ether. This ether extract was dried with potassium carbonate and evaporated under reduced pressure. The residue was crystallized from petroleum ether. The yield was 7.2 g. of material melting at 110°C., or 29.8% of theoretical amount.

Decomposition of 5-Bromofuryl-2-Phenylcarbinol and 5-chlorofuryl Phenylcarbinol.

Two methods of splitting out of hydrobromic acid are used, both giving practically quantitative yields. The carbinol may be refluxed in 5% potassium carbonate until solution is complete. Crystallization is very slow after filtering the solution. A more rapid method consists in refluxing for one hour in alcohol and then pouring the solution into water. This product is not so pure as the former one and must be crystallized from alcohol from which it metls at 85°C. Hewlett's analyses were checked.

Anal. Calc'd. for $C_{11}H_8O_2$: C, 76.74%; H, 4.69%: Found: C, 76.72%, 76.96%; H, 4.97%, 5.02%.

Reactions of Decomposition Product.

(1) Oxidation.

One and one-tenth grams (0.02 mole) of calcium oxide were suspended in 5 cc. of water. After the suspension was cool, 1.72 g. (0.01 mole) of the decomposition product were added. The mixture was kept in an ice bath while 1.1 g. (0.007 mole) of potassium permanganate in 50 cc. of water were slowly added. When addition was complete, the mixture was heated to boiling, filtered by suction and cooled, filtered, and acidified with dilute sulfuric acid. The solution was extracted twice with ether and the solvent removed under reduced pressure. The residue was dissolved in 10% sodium hydroxide solution, heated with Norite, filtered, cooled and very carefully acidified with 2% sulfuric acid solution. A white solid separated which melted at 134°C. A mixed melting point with furoic acid was lowered twenty degrees. The neutralization equivalent was 211.

(2) Formation of oxime

Treatment of the decomposition product with hydroyxlamine hydrochloride in alkaline solution did not form an oxime. Most of the compound was recovered unchanged.

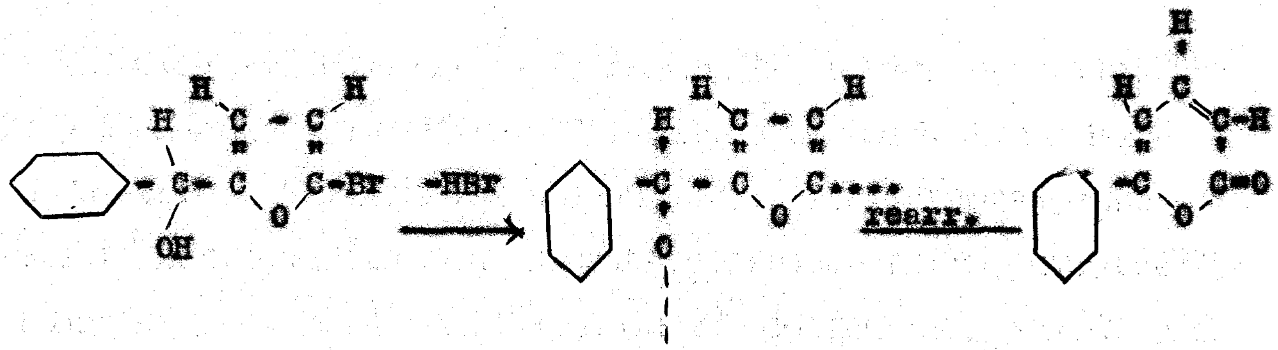
(3) Formation of phenyl hydrazone.

Treatment of a water-alcohol solution of the decomposition product with phenyl hydrazine failed to yield a phenyl hydrazone.

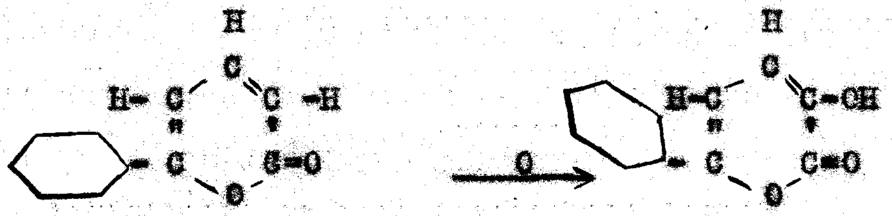
(4) Reaction with acetyl chloride.

The reaction with undiluted acetyl chloride was very strenuous and no product could be isolated. A solution of 0.5 g. of the decomposition product in 5 cc. ether was treated with metallic sodium for three weeks. An excess of acetyl chloride was then added and was allowed to react for twenty-four hours. The solution was then diluted with water and the ether was extracted with sodium bicarbonate solution. Evaporation of this ether solution left a gummy mass which yielded the original compound after crystallization from water-alcohol solution.

This series of reactions discounts the possibility that the compound might be 5-phenyl-2-furfural. Even in the event that the aldehyde group might not react to form an oxime or phenyl hydrazone, it is inconceivable that it could withstand a three weeks treatment with metallic sodium. A possible course of the decomposition reaction might be the following:



oxidation of this lactone (*alpha* pyrone) should give



Preparation of 5-Chlorofurfuryl Amine.

5-Chlorofurfuraldoxime (53) was reduced according to the procedure described for furfuraldoxime (54). Seven and twenty-five hundredths grams (0.05 mole) of the oxime were dissolved in 100 cc. of alcohol. This solution was stirred while 237 g. of 2 1/2% sodium amalgam solution and 15.5 g. of acetic acid were added independently and intermittently over a period of one hour. The reaction mixture was decanted off the mercury, diluted with water and extracted thrice with ether. If the extracted solution is not distinctly acid, acetic acid must be added. After these extractions, the solution was filtered and then made alkaline with sodium hydroxide. This alkaline solution was then extracted three times using ether. The ether solution was dried with anhydrous sodium sulfate and, after the solvent was evaporated, distilled under 25 mm. pressure. The boiling point of the amine was 50°-55°C. at this pressure. Yield was 5 g. or 76.3% of the theoretical amount. The first ether extract yielded a compound which when crystallized from petroleum ether melted at 135°-137°C. The compound contained nitrogen, was soluble in dilute sodium hydroxide, but insoluble in dilute hydrochloric acid. It was not investigated further.

The amine was analyzed as the chloroplatinate which formed very easily.

<u>Anal</u>. Calc'd. for $C_5H_6ONCl.H_2PTCl_6$: PT, 29.00%: Found, PT, 29.21%.

This amine was refluxed for twelve hours in alcohol solution. The solution was then diluted with water. The oil which separated was equal in volume to that introduced into the reaction. It was dissolved in hydrochloric acid and chloroplatinic acid was added. The chloroplatinate showed an analysis identical with that of the chlorofurfurylamine chloroplatinate.

<u>Anal</u>. Calc'd. for $C_5H_6ONCl.H_2PTCl_6$: PT, 29.00%: Found; PT, 29.00%.

Hence no rearrangement was detected either in the formation of the amine, or in a long period of heating. The stability of the compound is notable as compared with the nonexistent chlorofurfuryl alcohol. A great many attempts have been made to prepare this latter compound, total decomposition resulting in every case.

There is, of course, the possibility that the compound

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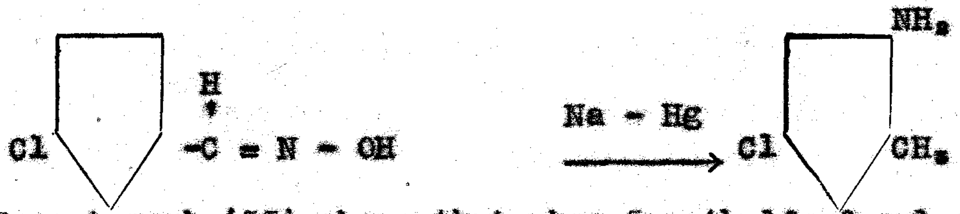
(54) Goldschmidt, Ber., <u>20</u>,728(1887)

obtained is not 5-chlorofurfuryl amine. Supposing an allylic rearrangement we might expect the following:



Recent work (55) shows that when 5-methylfurfuryl chloride is treated with sodium cyanide, the nitrite is found in the usual manner, without rearrangement. There is, then, no reason to expect it here.

The Reaction Between 2-Furfuryl Chloride and Magnesium.

Although the preparation of furfuryl chloride has been described several times (56), it is considered advisable to describe the large size runs used through this work.

One hundred and ninety-six grams (2 moles) of furfuryl alcohol (freshly distilled under reduced pressure) were dissolved in 250 cc. of dry ether, together with 190 g. (2.4 moles) of pyridine. This was placed in a two liter three-necked flask fitted with stirrer, dropping funnel, and thermometer. To this solution held at 6° C. to 10°C. were added 261.8 g. (2.2 moles) of thionyl chloride in 250 cc. of dry ether. The rate of addition was one drop every two seconds. When addition was completed, the solution was decanted from the solid residue.

(55) Reichstein and Zschokke, Helv. Chim. Acta., 15, 249(1932)
Scott and Johnson, J. Am. Chem. Soc., 54, 2549(1932)
(56) Kirner, J. Am. Chem. Soc., 50, 1955(1928). See also Reichstein, Ber., 63, 749(1930).

The residue was washed twice with ether. The combined ether solutions were chilled and added in small portions to ice cold 50% potassium hydroxide solution in a two liter separatory funnel, shaking after each addition. When the neutralization was completed, the ether solution was separated, dried with anhydrous sodium carbonate, and the solvent removed under reduced pressure. The residual liquid was distilled at 49°C. under 26 mm. pressure. Yield was 110 g. or 47% of the theoretical amount.

When this product was diluted with ether, a white cloudiness appeared. Redistillation of the halide accentuated this turbidity. It is possible that this turbidity was caused by distillation (sublimation or mechanical inclusion) of a crystalline residue remaining with the furfuryl chloride after removal of the original solvent under reduced pressure. This decomposed in alkaline solution.

Repeated trials showed that furfuryl chloride in absolute ether would not react with ordinary magnesium. Its action with reactivated magnesium-copper alloy, reactivated magnesium, and a magnesium-magnesium iodide system, all resulted in coupling to the extent of 35-40%. The results with the first two forms of magnesium were identical, so only one is described.

<u>2-Furfuryl Chloride with Reactivated Magnesium</u>.

The magnesium used was activated according to the method used by Gilman and Kirby (57) for the magnesium-copper alloy.

(57) Gilman and Kirby, Unpublished results.

Thirty grams of magnesium were suspended in 200 cc. of benzene and 20 cc. of ether. This was treated with 6 g. of iodine until the color disappeared. The solvent was distilled off and the residue was allowed to "spoil" in air for twenty minutes. Before it was used, it was reactivated by heating until all the inflammable gas was expelled, and the iodine commenced to sublime.

Twenty-nine and two tenths grams (1 mole) of reactivated magnesium were suspended in 50 cc. of dry ether in a one liter three-necked flask equipped with stirrer, dropping funnel, reflux condenser, and dry nitrogen inlet. The latter was used throughout the reaction. To this was added, dropwise, 11.7 g. (0.1 mole) of doubly distilled furfuryl chloride dissolved in 400 cc. of dry ether. The reaction started vigorously with immediate clouding. It continued until all the halide was added. A color test toward the beginning and end of the reaction proved to be negative. Nevertheless, the solution was chilled and carbon dioxide was passed over the chilled, stirred solution for several hours. The reaction was then filtered and the filtrate was treated with cold 50% sulfuric acid followed by an extraction with water. The mass of unused magnesium which was filtered from the reaction mixture was washed with ether-benzene solution, since the carbonation product might be insoluble in ether alone. However, no substance other than magnesium iodide was found in the last extractant. Both solutions were washed with normal potassium hydroxide solution.

Acidification of these alkaline extracts yielded no trace of either furylacetic or methyl furoic acid.

The ether solution having been alkali extracted was dried with anhydrous sodium sulfate and the ether distilled off. The residue distilled at 82°-85°C. under 8 mm. pressure. The yield of difuryl ethane was 3.1 g. or 38% of the theoretical amount.

This run was also carried out using reactivated 12 3/4% copper-magnesium alloy. The yield of difuryl ethane was 36.2% of the theoretical amount. The product boiled at 100°-105°C. at 17 mm. pressure. In another trial a carbon dioxide atmosphere was maintained throughout the reaction. No methyl furoic nor furyl acetic acids were obtained thereby.

Since the conditions used in the preceding runs were necessarily condusive to coupling of an active halide (58), the nearest approach to the ideal conditions were employed. Ordinary magnesium did not react; an equivalent amount of magnesium iodide was then added. This initiated reaction.

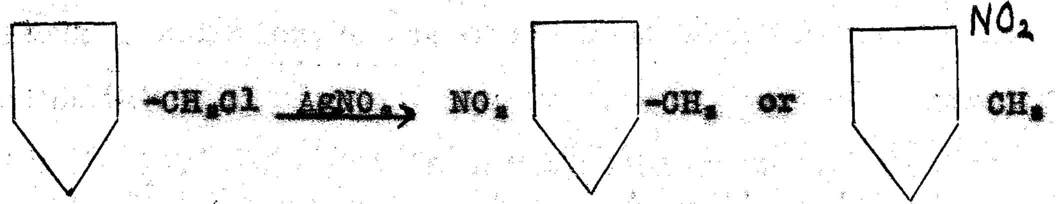
Seventy-two and nine-tenths grams (3 moles) of magnesium (80 to oo mesh) were suspended in 200 cc. of anhydrous ether in a two liter three-necked flask fitted with stirrer, dropping funnel, and reflux condenser. To this were added 25.6 g. (0.1 mole) of furfuryl chloride dissolved in 600 cc. of ether over an eighteen hour period. From time to time a color test was taken which was always negative. Finally the run was carbon-

(58) Gilman and Zoellner, J. Am. Chem. Soc., <u>52</u>, 3984(1930)

-ated and then worked up in the manner prescribed for the previous runs. No furan acids were obtained. Distillation of the ether solution yielded 3.61 g. of difuryl ethane boiling at 92°-94°C. under 15 mm. pressure. This is 44.7% of the theoretical amount.

The reactivity of furfuryl chloride was further tested by its reaction with methylmagnesium iodide. The Grignard reagent was prepared from 4.8 g. (0.2 mole) of magnesium and 28.4 g. (0.2 mole) of methyl iodide in 75 cc. of ether. A solution of 11.6 g. (0.1 mole) of furfuryl chloride in 100 cc. of ether was added dropwise to this reagent. A vigorous reaction followed each addition. Finally the reaction was hydrolyzed with 10% ammonium chloride. The ether layer was separated, washed with water, and dried with anhydrous sodium sulfate. The solvent was fractionated very carefully, but no light fraction (sylvan) was found up to 150°C. The residue was distilled at 94°C. under 16 mm. pressure. The yield was 4.23 g. of difuryl ethane or 52.2% of the theoretical amount.

In order to test the reactivity of this compound, as well as to find a possible rearrangement, furfuryl chloride was treated with silver nitrite, in the hope of effecting the reaction,



although there was little hope of isolating furfuryl nitrate.

But when 11.6 g. (0.1 mole) of furfuryl chloride dissolved in 30 cc. of benzene were refluxed with 23.1 g. (0.15 mole) of silver nitrite under nitrogen atmosphere, no reaction seemed to take place and no nitrosylvan could be isolated by steam distillation of the reaction mixture.

In order to definitely establish the identity of the difuryl ethane obtained in these reactions, the compound was nitrated. This was compared with dinitrodifurylethane prepared by reduction (59) of difuryl ethylene and subsequent nitration.

To a nitrating mixture consisting of 34 g. (0.538 mole) of fuming nitric acid in 51 cc. of acetic anhydride was added dropwise a solution of 8.71 g. (0.0538 mole) of difuryl ethane in 8.75 cc. of acetic anhydride. A temperature below -5°C. was maintained throughout the reaction. When about one-third of the solution had been added, a bronze-like precipitate appeared in the reaction mixture. When addition was completed, the mixture was stirred for two hours and was then filtered through a chilled Büchner funnel into cracked ice. The precipitate was washed several times with water. The filtrate contained a gummy lump which, when treated with pyridine, diluted with water several hours later, and finally acidified with dilute hydrochloric acid yielded more of the compound obtained directly from the reaction mixture. The total yield was 7.85 g. melting at 152°C. or 57.8% of the theoretical amount. This was crystallized from 400 cc. of alcohol to a constant melting point, 158°C.

Anal. Calc'd. for $C_{10}H_8O_6N_2$: C, 47.62%; H, 3.17%; Found: C, 48.42%; H, 3.94%.

The Reactions of 5-Iodofuryl-2-Magnesium Iodide (60).

The preparation of diiodofuran from dehydromucic acid presented two main difficulties. First, the preparation of dehydromucic acid from mucic acid (the most economical source) could be effected only in small runs. We have not been able to improve the method of Yoder and Tollens (61). Second, the directions of Phelps and Hale (62) for preparation of diiodofuran were so indefinite as to be valueless as a mode of preparation of working quantities of the substance. The Grignard reagent was prepared by following the method used with bromofuran (63). The consistent 29% yield could not be improved. Chemiluminescence tests suggested that the reagent was unreactive toward oxygen. In general, after this reagent was prepared, it was found to be of little value for further synthetic purposes. Its reaction with dimethyl sulfate was abnormal, yielding iodofuran instead of iodosylvan. When cupric chloride was used for coupling, a very small yield of diiododifuryl was obtained.

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(59) Reichstein, Helv. Chim. Acta., 13, 345(1930)
(60) Gilman and Wright, Ia. State Coll. J. Sci., 5, 85(1931)
(61) Yoder and Tollens, Ber., 34, 3447(1901)
(62) Phelps and Hale, Am. Chem. J., 25, 445(1901)
(63) Shepard, Winslow and Johnson, J. Am. Chem. Soc., 52, 2083(1930)

(1) Preparation of dehydromucic acid.

Fifty grams (0.238 mole) of mucic acid and 100 g. (1.02 moles) of concentrated sulfuric acid were mixed in a 500 cc. three-necked flask equipped with stirrer and thermometer. This was slowly heated on an oil bath to 130°-133°C. and maintained at this temperature for forty minutes. When this temperature was reached, considerable reaction took place and the inside thermometer registered 140°-145°C. It is this quick reaction with subsequent temperature rise that makes the larger runs completely decompose. When the reaction mixture had cooled, 200 cc. of water were added and the mixture was heated for ten to fifteen minutes on the water bath. After twenty-four hours (optional period), it was filtered and washed with water. The precipitate was suspended in 800 cc. of boiling water. Solid barium hydroxide was added until the reaction was distinctly alkaline. It was then filtered and washed with hot water. This process was repeated on the black precipitate using 250 cc. of boiling water and an appropriate amount of the base. The combined filtrates were acidified with hydrochloric acid. It is best to let this acidified solution stand twenty-four hours to insure complete precipitation. The precipitate was dissolved in ammonium hydroxide and water (350 cc. volume) and boiled three or four minutes with Norit; filtering and subsequent acidification yielded 9.4 g. of dehydromucic acid. This is 25.4% of the theoretical amount. The neutralization equivalent was found to be 157, which is exactly the calculated value.

Runs up to one mole size may be made, but are unreliable.

A number of variations were tried for this reaction; they all resulted in failure. The most disappointing was a run wherein the dry mucic acid was slowly added to a stirred sulfuric acid bath at 140°C. No product was obtained. The amount of sulfuric acid used seemed to have little effect on the yield of the reaction. Phosphoric acid used under the same conditions gave no yield at all.

(2) Preparation of Diiodofuran.

Ninety-three and six-tenths grams (0.6 mole) of dehydromucic acid were suspended in 1200 cc. of water. Eighty-two and eight-tenths grams (0.6 mole) of potassium carbonate were added and the solution was heated until the evolution of carbon dioxide was complete. One hundred and twenty grams (0.72 mole) of potassium iodide were added at once, followed by 101.5 grams (0.8 mole) of iodine. This was stirred until solution was completed. The resulting mixture was heated to 160°C. under 90 pounds pressure (steam) in an autoclave for one hour. The steel autoclave was not noticeably damaged by this treatment. After the autoclave was slowly cooled, the reaction mixture was treated with 10% sodium thiosulfate to disperse the excess of iodine and was then twice steam distilled. The yield of diiodofuran was 112 g. or 70% of the theoretical amount, melting at 47°C.

In order to obtain this compound dry enough for reaction with magnesium, it was either distilled (B.P. 98°-99°C/13 mm.), or dissolved in ether, the solution dried with anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The latter procedure is to be recommended unless the reagent is to be used at once.

(5) Preparation of Iodofurylmagnesium Iodide.

It was first determined definitely that the compound would not react with ordinary magnesium even when the reaction was started by the addition of a small amount of the reactivated alloy. The compound would, however, react with a large excess of reactivated magnesium-copper alloy, or with reactivated magnesium. Twenty-eight and eight-tenths grams (0.8 mole) of 12 3/4% copper-magnesium alloy were activated by the method of Gilman and Kirby. This metal was then reactivated and placed in a 200 cc. three-necked flask fitted with stirrer, gas inlet, dropping funnel and reflux condenser. The flask had been previously swept out with dry, pure nitrogen. Fifty cubic centimeters of ether were added; a solution of 32 g. (0.1 mole) of diiodofuran in 100 cc. of ether was then added fairly rapidly. When about one-half of the solution was in the flask, reaction started, but did not become violent. Addition was continued at such a rate as to maintain a refluxing temperature. Following the addition the reaction was refluxed by external heating for three hours. It was then filtered into a dry nitrogen filled container. The yield, determined by titration was 29% (64). It gave a strong color test.

The reagent was carbonated by bubbling dry, cold carbon dioxide through the chilled solution for one and one-half hours. The reaction mixture was hydrolyzed with cold, dilute hydrochloric acid and allowed to stand overnight. If it is to be worked up at once, a stronger hydrolyzing agent must be used. The ether solution was then separated and the aqueous hydrolysate was extracted twice with 50 cc. portions of ether. The combined ether solutions were washed with water followed by normal potassium hydroxide. The washed ether solution was then dried and evaporated under reduced pressure. There were recovered 10.3 g. of unchanged diiodofuran, or 33% of the amount originally taken. This recovery is consistent and varies between 30% and 40%. The three alkaline washings were combined and heated with Norit until the ether was expelled. The solution was filtered, cooled and acidified with 50% sulfuric acid. The precipitate of 5-iodofuroic acid weighed 5.1 g. and melted at 192°C. This was 21.4% of the molar proportion of diiodofuran. The neutralization equivalent was found to be 235, the calculated value being 238.

<u>Anal</u>. Calc'd. for $C_5H_3O_3I$: I, 53.36%; Found: I, 52.89%.

We were unable to isolate any diiododifuryl from this

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(64) This was titrated by the method of Gilman, Wilkinson, Fischel and Meyers, J. Am. Chem. Soc., <u>45</u>,150(1923). The value should not be taken too seriously, however, since a reaction mixture showing no positive Grignard color test also gave this titration value. Gilman and Zoellner (unpublished results) have shown that when the reactivated magnesium-copper alloy is digested in ether no hydroxyl ion can be titrated. We are at a loss to explain this discrepancy.

reaction, but since, as will be shown, this compound is insoluble in ether, it would be left behind with the unreacted magnesium. This residual magnesium was transferred to a Soxhlet extractor, but the extract decomposed during the long period of heating.

(4) Preparation of diiododifuryl.

An identical run which gave a titration value of 29% RMgX was slowly added to a suspension of 13.4 g. (0.1 mole) of anhydrous cupric chloride in 50 cc. of ether. The temperature was held below 0°C. When addition was complete, the reaction mixture was refluxed for several hours. It was then decanted from the residue which was washed with ether. The ether solution upon evaporation yielded 40% of the original diiodofuran. The residue in the flask was rapidly washed with boiling alcohol. This alcohol precipitated crude diiododifuryl when water was added. A small amount of this was found to sublime, giving white crystals melting at 142°C. The bulk of the precipitate was crystallized from an aqueous acetic acid solution, from which it melted at 136°C. Repeated crystallization from this medium failed to raise the melting point; consequently a satisfactory analysis could not be obtained.

Anal. Calc'd. for $C_8H_4O_2I_2$: I, 65.75%; Found; I, 64.33%, 64.34%.

Attempts to prepare this compound by other methods resulted in failure. An ether solution of diiodofuran reacted easily with sodium, but only an amorphous red powder, insoluble in acetic acid, was obtained. When diiodofuran was heated with copper bronze in a sealed tube to 140°C., it exploded.

(5) Action of dimethyl sulfate on iodofurylmagnesium iodide.

A solution containing 29% of Grignard reagent was prepared from 0.1 mole of diiodofuran and 0.1 mole of reactivated magnesium. This chilled solution was treated dropwise with 12.6 g. (0.1 mole) of freshly distilled dimethyl sulfate in 30 cc. of ether. The action was vigorous. When it was finished, the reaction mixture was hydrolyzed with 10% ammonium chloride and distilled therefrom. The fraction boiled at 54°C. under 26 mm. pressure and weighed 4.04 g. Thus the yield of iodofuran was 72% of that which could theoretically be obtained from the 29% yield of iodofurylmagnesium iodide.

This iodofuran was identified by treating its solution in 5 cc. of ether with an excess of magnesium. When reaction had subsided, the solution was treated with 1.19 g. (0.01 mole) of phenyl isocyanate added dropwise as a solution in 5 cc. of ether. This mixture was hydrolyzed by adding cold 10% ammonium chloride solution. The ether layer was separated and the solvent evaporated off. The residue was steam distilled and the liquor remaining in the steam distillation flask precipitated a solid which when crystallized from alcohol melted at 122°C. A mixed melting point with furoyl anilide showed no depression.

This peculiar reaction must be explained on the basis that a hydrolyzing agent is formed. There is no doubt that the dimethyl sulfate was pure. Hence, we must suppose that this reagent, by disrupting the unchanged diiodofuran has given rise to an active hydrogen which in turn has hydrolyzed the Grignard reagent.

(6) The action of the binary system (Mg - MgI_2) on diiodofuran.

A dry ether solution of 0.1 mole of diiodofuran was added to a suspension of magnesium in ether, to which had been added 0.1 mole of iodine. No reaction took place although the concentration (0.1 mole per 150 cc. of ether) was precisely that used in the former runs. When. however 0.1 mole of reactivated magnesium was added, a strenuous action was observed, and the resulting solution gave a normal 29% yield of Grignard and a positive color test. If this halide is otherwise normal, then it appears that the catalytic effect of the reactivated metal is due to some other factor than the mere presence of magnesium halide.

<u>The Preparation of Difuryl</u>.

This investigation was started because of a misconception arising from an incorrect abstract of the preparation of difuryl by Kondo and Suzuki (65). The mistake was discovered by

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(65) Kondo and Suzuki, J. Pharm. Soc., Japan, <u>544</u>, 501 (1927). See also C. A., <u>21</u>, 3362(1927).

reference to the original article, and it was found that the boiling point was reported as 65°-67°C. at 7 mm. pressure instead of 240°C. at 7 mm. pressure as given in the abstract. By this time the problem had become so interesting that it was continued.

The coupling of Grignard reagents to the corresponding hydrocarbon gives varying yields, but most of the yields are high. Phenylmagnesium bromide, for example, yields 96% of diphenyl when treated with anhydrous copper chloride. When furylmagnesium iodide was treated in like manner, the yield was about 5% to 15%.

(1) Reduction of furylmagnesium iodide to difuryl.

A solution of 19.4 g. (0.1 mole) of freshly distilled iodofuran in 100 cc. of dry ether was slowly added to 4.8 g. (0.2 mole) of magnesium turnings suspended in 20 cc. of ether. The reaction started in a few seconds and was refluxed for one-half hour. After addition was completed, the resulting Grignard reagent was chilled with an ice-salt freezing mixture while 16.2 g. (0.12 mole) of anhydrous cupric chloride were added over a two hour period. The reaction was allowed to slowly rise to room temperature and was then refluxed for one-half hour. A Grignard color test (66) was negative. The reaction mixture was filtered and well washed with ether. The filtrate was washed with water, whereupon <u>a strenuous heat</u>

(66) Gilman and Schulze, J. Am. Chem. Soc., <u>47</u>,2002(1925)

reaction took place. After an another washing with water, the ether solution was dried with anhydrous sodium sulfate and the solvent was distilled off. The residue when distilled at 17 mm. pressure, yielded a first fraction of 1 g. of iodofuran boiling at 42°-43°C. and a higher fraction of 0.42 g. of difuryl boiling at 73°C. This is 6.1% of the theoretical amount.

In a similar run, where the cupric chloride was added as a suspension in ether, the yield was 0.98 g. or 14.6% of the theoretical amount. In every case it was noted that the recovered iodofuran was much more stable than the original halide. Whereas the ordinary distilled compound had a life of about fifteen minutes in the air, this recovered iodofuran was let stand several hours with only a slight discoloration.

Other coupling agents were tried with no result. Ferric chloride caused the formation of a reddish brown amorphous infusible powder which could be dissolved in acetic acid and reprecipitated with water. Refluxing with azobenzene or ethylene dibromide had no action on the Grignard reagent.

(2) Identification of difuryl

Since the boiling point obtained for difuryl did not yet agree with that obtained by Kondo and Suzuki, we sought to identify the compound by nitration to the known dinitrodifuryl (67). A nitrating mixture was prepared by adding 4.41 g. (0.07 mole) of fuming nitric acid (Sp. Gr. 1.52) to 7 cc. of

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(67) Rinkes, Rec. trav. chim., (50, 981(1931).

acetic anhydride at -5°C. To this solution was added dropwise at -20° to -30°C. ninety-eight hundredths of a gram (0.0073 mole) of difuryl in 2 cc. of acetic anhydride. Addition of this compound caused an intense green color in the reaction mixture. Finally it was let stand for three hours and was then poured on ice. The semi-solid tarry material was collected with a stirring rod and dissolved in pyridine. Next day this solution was diluted with water and acidified with hydrochloric acid. Filtration yielded about 0.02 g. of 5,5'dinitro-2,2'difuryl melting at 205°C. This is 1.2% of the theoretical amount. It was dissolved in benzene and crystallized by vacuum evaporation of the solvent. The crystallized product melted at 210°C. A mixed melting point with the dinitrodifuryl furnished by Doctor Rinkes showed no depression.

Preparation of 3-Iodofuran.

Since 2-iodofuran was prepared and its properties noted (68), the investigation of 3-iodofuran was desirable. After an unsuccessful attempt to remove the alpha-chloromercuri groups from tetrachloromercurifuran, with subsequent iodination, the compound was prepared from tetraiodofuran. The resulting 3-iodofuran was considerably more stable than its isomer; whereas the 2-iodofuran would totally decompose in air in fifteen minutes, the 3-iodofuran was stable over an

(68) Gilman, Mallory and Wright, J. Am. Chem. Soc., 54, 733(1932)

equal number of days. Its inertia toward reaction with magnesium is most unusual. When it was subjected to the conditions (69) used for the production used for phenylmagnesium chloride, the compound was not affected.

(1) Attempted preparation of 3,4-diiodofuran.

The directions of Ciamician and Cisua (70) were followed for preparation of the mercurial. Seventeen grams (0.25 mole) of furan were added dropwise to a stirred solution of 330 g. (1.04 moles) of mercuric acetate in 1300 cc. of water. After twelve hours, the precipitate was filtered off and suspended in 1500 cc. of water in which were dissolved 58 g. (1 mole) of sodium chloride. After two hours stirring, the tetrachloromercurifuran was filtered off and thoroughly washed. This compound was suspended in a solution of 32.5 g. (0.5 mole) of potassium cyanide in one liter of water. The precipitate soon became black; after two hours, it was filtered and washed. This precipitate was suspended in one liter of water and stirred while 139.7 g. (0.55 mole) of iodine were added in a solution of 182.6 g. of potassium iodide in 800 cc. of water. Finally, a very slight excess of iodine was dispersed with a 10% solution of sodium thiosulfate. A few grams of diiodofuran were steam distilled, but no other product was obtained, either in the distillate or residue. The crude diiodofuran melted at 46°C.

(69) Gilman and Brown, J. Am. Chem. Soc., 52,3330(1930)
(70) Ciamician and Ciusa, Gazz. Chim. ital.,55,385(1925)

Since it is contrary to experience to expect alpha substituted groups to be less labile than beta substituents, we can only conjecture that the tetrachloromercurifuran is easily and entirely split to furan and mercuric halide by the action of either potassium cyanide or potassium iodide. It is unfortunate that difficulty of purification made a stepwise analysis of the reaction impracticable.

(2) Preparation of tetraiodofuran.

Sixty-eight grams (1 mole) of furan were added dropwise tp a stirred solution of 1320 g. (4.32 moles) of mercuric acetate in 5000 cc. of water. After five hours this mixture was filtered and washed thoroughly with water. The wet precipitate was then stirred into a solution of 293 g. (5 moles) of sodium chloride in six liters of water. After two hours the precipitate was filtered off, washed with water, and suspended in four liters of water. A solution of 1024 g. (4 moles) of iodine and 1340 g. (8 moles) of potassium iodide in eight liters of water was prepared. When 6200 cc. of this solution had been added dropwise to the stirred suspension, a permanent test for iodine was obtained. The slight excess was dispersed with sodium thiosulfate solution. The reaction mixture was then extracted three times with ether and the ether extracts evaporated to about 300 cc. Enough petroleum ether (B.P.45°C.) was added to complete precipitation of the mercuric iodide. The latter compound was filtered off and the filtrate evaporated. This yielded 160 g. of crude tetraiodofuran melting

148°C. This is 27.7% of the theoretical amount.

(3) Preparation of 3-iodofuran.

One hundred and sixty grams (0.28 mole) of tetraiodofuran were partially dissolved in a solution of 750 cc. of ether and 100 cc. of methyl alcohol. This was contained in a two liter Erlenmeyer flask. Twenty-two and ninety-five hundredths grams (0.85 mole) of aluminium strips measuring 20 mm. x 4 mm. x 0.5 mm. were amalgamated by a saturated solution of mercuric chloride. After a thorough washing with alcohol and ether, the metal couple was added to the solution of tetraiodofuran. At first slight cooling under the tap water was necessary. After three days the reaction mixture was filtered by suction and the precipitate was well washed with ether. The filtrate was distilled until all the ether was removed and the residue was steam distilled. The heavy oil was separated from the aqueous layer of the steam distillate and was placed in a 75 cc. Claisen distilling flask. Anhydrous calcium chloride was added and the substance was distilled from this under 14 mm. pressure. The 3-iodofuran boiled at 42°-43°C. and weighed 16 g., or 29% of the theoretical amount. The residue in the flask was diluted with ether; the calcium chloride was filtered off, and the ether was distilled off. The residue distilled at 112°-114°C. at 20 mm. pressure. It weighed 28.2 g. and is probably 3,4-diiodofuran. It was not further investigated, but was dissolved in 250 cc. of ether and 2.37 g. (0.088 mole) of aluminium amalgam. The reaction was let stand four days and was then worked up as before. The yield was 9.4 g. of 3-iodofuran, boiling with superheating at 134°-140°C. Since the amount of 3,4-diiodofuran was 0.088 mole, the yield is 55% of the theoretical amount.

The entire yield of 3-iodofuran, based on the tetraiodofuran used is 46.05% of the theoretical amount. The boiling point of the pure product is 134°C. at atmospheric pressure. Other constants are $n_D^{20°}$= 1.5610; n_D^{25} = 1.5592; $D_4^{20°}$= 2.045.

<u>Anal.</u> Calc'd. for C_4H_3OI; I, 65.46%; Found; I, 65.69%; 65.57%.

The pure compound would not react with either ordinary or reactivated magnesium in ether. Similar results were obtained using reactivated 12 3/4% copper-magnesium alloy. A 0.05 mole portion was sealed with an excess of fine magnesium under 30 mm. pressure. By this technique (69) phenylmagnesium chloride was obtained at 140°C. The sealed tube was heated for three hours at 75°C., then the temperature was raised to 150°C. and maintained for sixteen hours. No apparent change occurred, the halide being only slightly colored. The magnesium was bright and clean. The reaction was then heated at 175°C. for one hour; at the end of this time it exploded.

The stability of the halide was likewise determined by its action with aluminium amalgam in ether-alcohol solution. After a week's reaction period, the 3-iodofuran was recovered unchanged.

The Treatment of 3-Bromofuran with Magnesium.

Twelve and one-tenth grams (0.0825 mole) of bromofuran (63) dissolved in 40 cc. of dry ether, were added to a suspension of 15 g. (0.5 mole) of reactivated 12 3/4% copper-magnesium alloy. No reaction occurred after four hours of refluxing. A small piece of sodium was added and the reaction was let stand for a month. At the end of this time no reaction occurred and the 3-bromofuran was recovered unchanged.

Preparation of Ethyl 5-Bromofuryl-alpha,beta-dibromopropionate.

One hundred and sixty-six grams (1 mole) of ethyl furylacrylate were diluted with 400 cc. of dry carbon disulfide in a one liter balloon flask. Three hundred and twenty grams of bromine, diluted with 100 cc. of carbon disulfide were slowly added. Care must be taken that the reaction be not too vigorous. When addition was complete, the reaction was refluxed over a water bath for three and one-half hours. It was then chilled in an ice-salt freezing mixture, filtered and the filtrate concentrated under reduced pressure. The concentrated filtrate yielded 61.5 g. while the original precipitate weighed 260.5 g. The yield was therefore 322 g. melting at 106°-107°C., or 79.5% of the theoretical amount. When crystallized from benzene, this melted at 108°C.

Anal. Calc'd. for $C_9H_9O_3Br_3$: Br, 59.25%; Found; Br,59.68%.

This ester is formed when dry hydrobromic acid is bubbled through an ether solution of ethyl 5-bromofurylbromoacrylate, cooled with ice. The conversion is only 16.7% of the theoretical amount, the remainder of the original ester being recovered unchanged.

Ethyl bromofuryldibromopropionate was also formed in 86.4% yield when 24.5 g. (0.1 mole) of ethyl 5-bromofurylacrylate were dissolved in 25 cc. of carbon disulfide and 16 g. (0.1 mole) of bromine in 25 cc. of carbon disulfide were added thereto. The reaction mixture was stirred constantly and the temperature held at +5°C. Each drop of bromine was absorbed instantly. When addition was completed, the reaction solution was chilled with an ice-salt bath and filtered, yielding 35 g. of product melting at 108°C.

This ester is fully saturated with bromine at room temperature as shown by the fact that a dilute carbon disulfide solution of bromine is not decolorized by the ester.

Crystallization of the ester from alcohol yields an isomer. When 14.2 g. of ester were dissolved in 125 cc. of hot 95% alcohol, filtered and cooled, there was a slight precipitation of white needles. The solution was concentrated under reduced pressure until 1.72 g. of the isomer had precipitated. This melted at 169°C. When crystallized from benzene and carbon disulfide, the substance melted at 174°-175°C.

Anal. Calc'd. for $C_9H_9O_3Br_3$: Br, 59.25%; Found: Br, 59.01%.

An alcohol solution of this stable isomer did not react with zinc powder. In general, it was much more stable than the lower melting isomer.

Preparation of Ethyl 5-Bromofurylacrylate.

Two hundred sixty and five-tenths grams (0.64 mole) of ethyl 5-bromofuryldibromopropionate were dissolved in 500 cc. of methyl alcohol in a one liter Erlenmeyer flask and 41 g. (0.64 mole) of zinc dust were slowly added. The reaction was vigorous. When addition was completed, the reaction mixture was filtered and the filtrate poured into 2.5 liters of cold water. The water layer was decanted, the oil was dissolved in ether, dried with anhydrous sodium sulfate and distilled under 6 mm. pressure. The fraction boiling at 144°-146°C. weighed 92.5 g. or 59% of the theoretical amount. After redistillation, it melted at 42°C.

The ester is also obtained when 5-bromofuryldibromopropionate is treated with alcoholic potassium hydroxide. In this run almost equimolar proportions of the mono and dibromo furylacrylic esters are obtained. To a solution of 101 g. (0.25 mole) of ethyl 5-bromofuryldibromopropionate in 500 cc. of alcohol were added 14 g. (0.25 mole) of potassium hydroxide in 250 cc. of alcohol. The potassium bromide which formed was filtered off and dissolved in water leaving an insoluble residue which proved to be the modification of ethyl 5-bromofuryldibromopropionate melting at 175°C. It weighed 1.12 g. The alcoholic filtrate was diluted with water; the oil was separated, after which the aqueous layer was extracted with chloroform. The oil combined with the chloroform extract was dried with anhydrous sodium sulfate and distilled under 3 mm.

pressure. Three fractions were cut between 140° and 160°C. The first and last fractions partially solidified upon chilling. Their liquid portions, together with the middle fractions, were combined and refractionated. In this way 14.2 g. of ethyl 5-bromofurylacrylate and 20 g. of ethyl 5-bromofurylbromoacrylate were obtained. The first melted at 39°C. and the latter at 53°C. and were purified by crystallization to melt at 42°C. and 56°C., respectively. The yield of the monobromo ester was 23% of the equivalent amount; that of the dibromo ester was 25%.

Preparation of Methyl 5-Bromofurylacrylate.

The reaction between a sodium alcoholate and an acid chloride was used in the preparation of this ester in order to determine whether the bromine atoms in the molecule were active enough to interfere with normal esterification. It was found the ester was formed in the normal manner.

Two and three-tenths grams (0.1 mole) of sodium were dissolved in an excess of methyl alcohol. To this alcoholate was slowly added a solution of 23.5 g. (0.1 mole) of bromofurylacrylyl chloride in 50 cc. ether. After one hour, the sodium chloride was filtered off and the filtrate concentrated by evaporation. This yielded 15.5 g. of crude ester melting at 62°-63°C., or 70% of the theoretical amount. When crystallized from hot benzene, it melted at 64°C.

Anal. Calc'd. for $C_8H_7O_3Br$: Br., 34.63%: Found: Br.,34.31%.

Preparation of n-Butyl 5-Bromofurylbromoacrylate.

A solution of 39.5 g. (0.126 moles) of bromofurylbromoacryloyl chloride and 14.4 g. (0.15 mole) of n-butyl alcohol in 75 cc. dry benzene was refluxed for four hours. After removing the solvent under reduced pressure, the residue was distilled under 9 mm. pressure. The distillate boiling at 180°-185°C. was chilled and the solidified portion separated by filtration on a chilled Büchner funnel. The yield was 15 g. or 53.9% of the theoretical amount. This melted at 36°C. and after crystallization from hot alcohol melted at 37°C.

Anal. Calc'd. for $C_{11}H_{12}O_3Br_2$: Br, 45.45%; Found, Br, 45.50%.

Preparation of Anilides, p-Phenetidides, and Amides of Substituted Furylacrylic Acids.

This series of compounds was prepared to ascertain whether reaction between amines and the halogenated furylacryloyl chlorides was normal. It was found almost impossible to obtain these compounds in the pure state. This situation was eventually traced to the fact that the acid chlorides used were not pure, it being difficult to fractionate the 5-bromfurylacrylyl chloride from the 5-bromofurylbromoacryloyl chloride.

The procedure of preparation was as follows: Four-hundredths of a mole of the amine was diluted with 30 cc. of dry benzene and placed in a 200 cc. three-necked flask equipped with dropping funnel, stirrer, and thermometer. The acid chloride (0.02 mole) diluted with 10 cc. of benzene was added slowly, keeping the reaction mixture below 5°C. with an ice bath. The reaction was stirred for three hours, finally warming it to room temperature. One hundred cubic centimeters of water were then added and the reaction mixture was stirred violently for a few minutes. It was then separated, extracted again with water, separated and the benzene, after drying with sodium sulfate was concentrated and then frozen. The compound which separated was crystallized from alcohol. The results are shown in Table II.

Preparation of Diethylaminoethyl Bromofurylbromoacrylate (Hydrochloride)

Seventy-nine grams (0.25 mole) of 5-bromofurylbromoacryloyl chloride, dissolved in 50 cc. of benzene were added slowly with stirring to 25.7 g. (0.22 mole) of beta-diethylaminoethyl alcohol in 300 cc. of benzene. The reaction was kept at room temperature. After a two hour addition period, the reaction was heated to 40°-45°C. on the water bath for two hours. Filtration of this mixture yielded 84 g. of vacuum dried hydrochloride. After crystallization, first from 95% alcohol and finally from absolute alcohol, it melted at 189°C. Yield was 80% of the theoretical amount.

Anal. Calc'd. for $C_{13}H_{18}NBr_2Cl$: N., 3.24%. Found: N., 3.24%.

Reduction of 5-Bromofurylacrylic Acid.

The bromofurylacrylic acid for this run must be very pure, crystallization from alcohol to a sharp melting point of 178°C. being necessary. Fifty-four and two tenths grams (0.25 mole) of this acid is dissolved in 250 cc. of absolute alcohol. To this is added 0.25 g. of platinum oxide prepared by the method

Table II

Compound	g. Amine	g. Acid Chloride	Yield g. %	Crude m.p.	Pure m.p.	Analysis % Br.Calc	Found
5-bromofurylacryloyl anilide	3.7 g. aniline	4.7 g. bromofurylacryloyl chloride	56%	118°C.	118°C	27.40%	26.08%
5-bromofurylacryloyl p-phenetidide	5.5 g. Phenetidine	4.7 g. bromofurylacryloyl chloride		131°-133°	135°-137°	23.81%	23.78%
5-bromofurylbromoacryloyl anilide	3.7 g. aniline	6.3 g. bromofurylbromoacryloyl chloride	2.44 g. 53%	110°	110.5°	43.13%	42.94%
5-bromofurylbromoacryloyl p-phenetidide	5.5mg. phenetidine	6.3 g. bromofurylbromoacryloyl chloride		108°-110°	109°-110°	38.55%	40.04%
5-bromofurylbromoacryloyl amide (71)					153°-154°	54.2%	55.29%

(71) This amide was prepared by pouring bromofurylbromoacryloyl chloride into 28% ammonium hydroxide and letting stand twenty-four hours.

of Adams and Shriner (72). The mixture was then reduced very slowly. Four reactivations of the catalysts were necessary; finally 0.1 g. of fresh catalyst were added. In this manner 59.2 pounds of hydrogen were absorbed (0.75 mole of hydrogen is equivalent to 56.7 pounds in this appartus). The catalyst was filtered off and the alcoholic filtrate was poured into water. The oil which separated was combined with an ether extract of the aqueous layer, dried with anhydrous sodium sulfate and distilled at 8 mm. pressure. The fraction boiling at 84°-110°C. was collected. The distillation is rather slow since hydrobromic acid is split off in the process. Twenty-one grams of product were collected which analysis shows to be ethyl 2,3-dihydrofurylpropionate. This is 50% of the theoretical amount. At the end of the distillation about one gram of furylacrylic acid distilled. It was identified by mixed melting point with the known acid.

The product was redistilled and the fraction boiling at 98°-102°C. at 6 mm. pressure was collected.

Anal. Calc'd. for $C_9H_{14}O_3$: C, 63.53%; H, 8.30%: Found: C, 63.49%, 63.99%; H, 8.12%, 7.59%. (See note 73).

The saponification equivalents were not satisfactory, but were found to be 164 and 158. The calculated value is 170.

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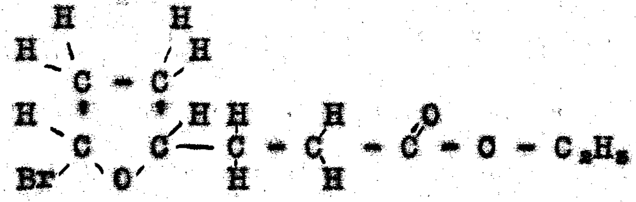
(72) Adams and Shriner, J. Am. Chem. Soc., 45, 2171(1923)

(73) These analyses were taken on two different fractions; the first boiled at 135°C./32 mm. while the second was a preliminary fraction.

The latter was run on a fraction boiling at 127°-150°C. at 32 mm. pressure.

In another run the ethyl 5-bromofurylacrylate was used instead of the acid. This was very unsatisfactory, twelve reactivations and four additions of catalyst over a period of three days being necessary. Evidently the hydrobromic acid which is freed in the reaction must be taken up by the ester formation.

In order to determine the actual amount of addition product



which was present at the end of the reaction, the alcoholic solution after removal of the catalyst was treated slowly with alcoholic potassium hydroxide until no more immediate precipitate was formed. This precipitate was found to weigh 26 g., and a solution of this salt in a minimum of water yielded no precipitate upon acidification, although extraction of the acidified solution with ether and subsequent evaporation showed a slight amount of compound to be present. The theoretical amount of potassium bromide to be obtained is 29.7 g.

The product from this reaction had a most pleasant and penetrating odor resembling mangoes or coconuts. It was more stable than ethyl furylacrylate as shown by the fact that a sample exposed to laboratory light and temperature turned only a slight red after two years exposure in a corked test tube.

SUMMARY

A number of reactions involving sulfonation, nitration, and halogenation have been carried out, first for the purpose of providing some derivatives of furfural which will serve as the basis of future research in this field; second, to elucidate a technique for such reactions. It has been shown, especially, that avoidance of ring splitting is a necessary precaution to be observed if work in furan substitution is to be successful. The investigations of furan substitutions in the past have largely dealt with the more stable furan compounds (furoic acids and the like). This work has extended substitution reactions to less stable but more significant types.