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FURAN MERCURIALS AND DERIVED TYPES

By

R. J. VanderWal

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

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College
1936

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TABLE OF CONTENTS

A. ORIENTATION IN THE FURAN NUCLEUS

Page

B. FURAN MERCURIALS AND DERIVED TYPES

A. ORIENTATION IN THE FURAN NUCLEUS

INTRODUCTION

In the study of the chemistry of furan it is of fundamental importance that the structures of a number of compounds be definitely known. These compounds may then be used as reference compounds, by means of which the positions of groups in other compounds may be determined (1).

In the investigation of the mercury compounds of furan it has been found that the most useful method for determining the position occupied by the mercury containing group is the replacement of this group by a halogen. But before this method can be of use it is necessary to know the position occupied by the halogen in the derived compound. The first section of this thesis will be devoted to such studies.

The subject of nuclear substitution and orientation of furan types has been well reviewed by Gilman and Wright (2) to the date of their publication. In this article certain views were expressed concerning the structure of some halogenated furans. The statement was made that the dibromofuroic acid, to the halogens of which Hill and Sanger (3) had assigned the 3,5-positions, was probably 4,5-dibromo-2-

(1) A series of publications on this subject has been published by Gilman and coworkers. The latest paper of this series is that by Gilman and Burtner, J. Am. Chem. Soc., 57, 909 (1935).
(2) Gilman and Wright, Chem. Reviews, 11, 323 (1932).
(3) Hill and Sanger, Proc. Am. Acad. Arts Sci., 21, 135 (1885).

furoic acid. Likewise, the χ-dichlorofuroic acid of Hill and Jackson(4) was probably, according to Gilman and Wright, 3,5-dichloro-2-furoic acid. These views have now been confirmed, as will be demonstrated in this thesis. Numerous other problems of orientation have also been solved and will be presented in their places.

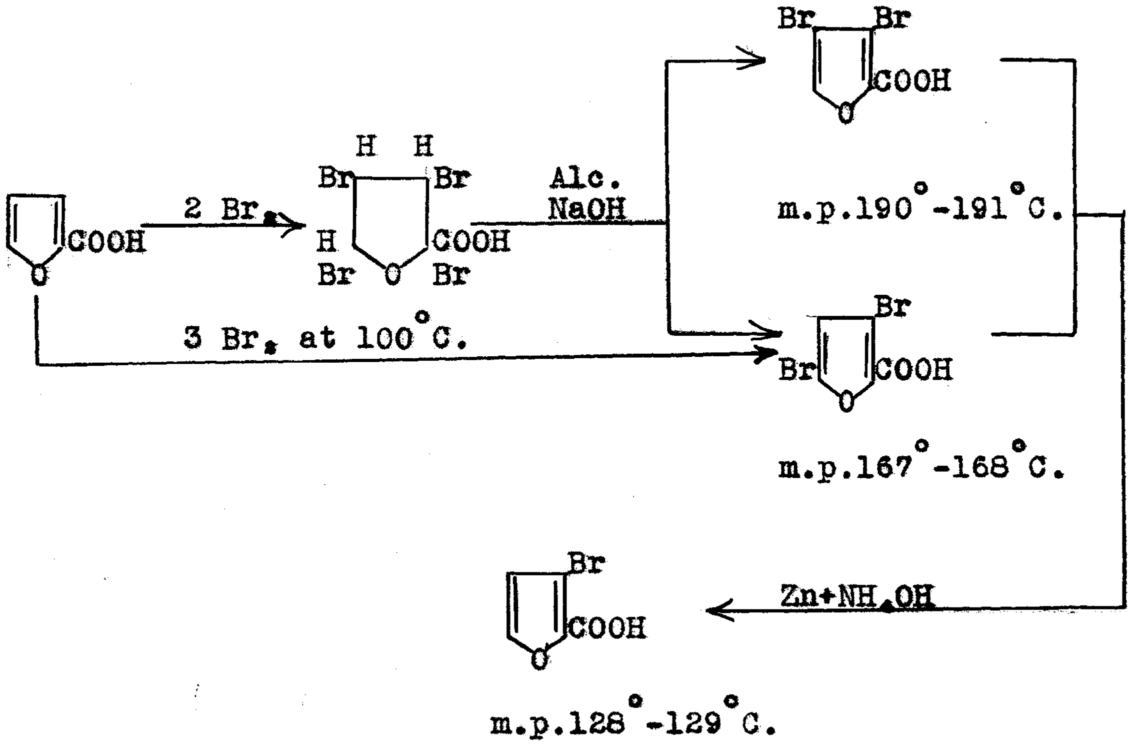
The β-Monohalogeno-2-furoic Acids and the Dihalogeno-2-furoic Acids.

Toennies (5) found the first dibromofuroic acid in the product of the action of alcoholic potassium hydroxide on 2,3,4,5-tetrabromotetrahydro-2-furoic acid. The melting point was given as 184°-186°C.

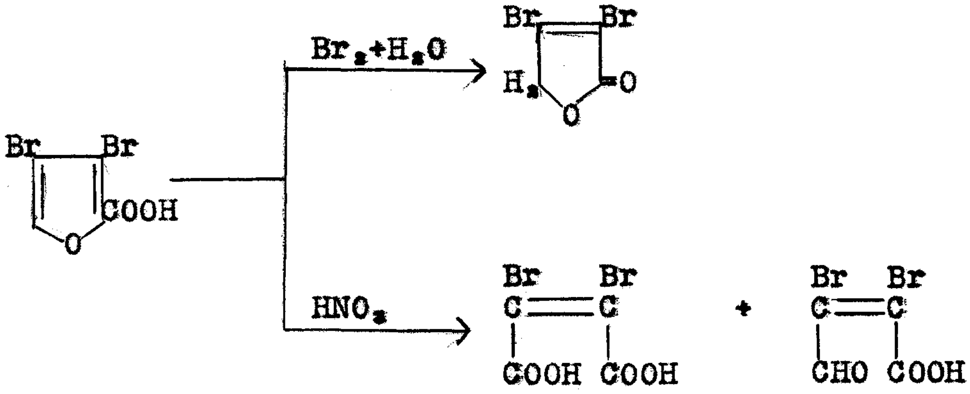
In 1884 Hill and Sanger (3) published a remarkably complete work on the subject of bromofuroic acids in which they describe two isomeric dibromofuroic acids obtained by the action of alcoholic alkalies on 2,3,4,5-tetrabromotetrahydro-2-furoic acid. One of these compounds melted at 190°-191°C. and they state that this one is identical with that of Toennies. To it they assign the structure of 3,4-dibromo-2-furoic acid. To the other acid, which melted at 167°-168°, they give the structure of 3,5-dibromo-2-furoic acid. This compound they also obtained by the direct action of three molecules of bromine on furoic acid at about 100°C. No other dibromo-2-furoic acid has ever been found.

(4) Hill and Jackson, Proc. Am. Acad. Arts Sci., 24,320 (1889).
(5) Toennies, Ber., 11, 1085 (1878); Ber., 12, 1202 (1879).

From both of the dibromofuroic acids, Hill and Sanger were able to obtain, by reduction with zinc and ammonium hydroxide, the same monobromofuroic acid melting at 128°-129°C. To this compound they assigned the structure of 3-bromo-2-furoic acid. The preparation of these compounds is summarized below. It should be stated here that some of the structures assigned by Hill and Sanger are erroneous, as will be shown later.



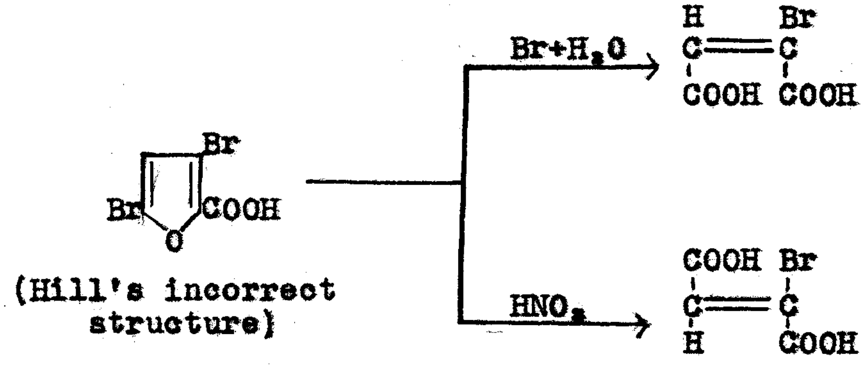
Hill and Sanger were correct in regard to the structure they assigned to the acid melting at 190°-191°C., which is 3,4-dibromo-2-furoic acid. This fact is well shown in their own work. Oxidation, by means of bromine water, produced α,β-dibromocrotonolactone; and oxidation by means of nitric acid, resulted in dibromomaleic and mucobromic acids.



Since all the oxidation products are compounds having a bromine atom on each of the 2,3-positions of a four carbon chain, it follows that the halogens could have been nowhere on the furan ring except in the 3,4-positions.

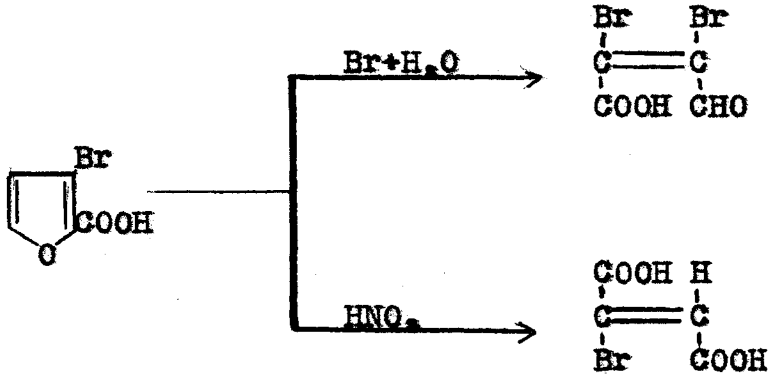
The structure assigned to the compound melting at 167°-168°C. was, however, not confirmed by any real evidence. Only two isomeric dibromo acids can be obtained by 1,2-elimination of hydrogen bromide from 2,3,4,5-tetrabromotetrahydro-2-furoic acid. These compounds are 3,4- and 3,5-dibromo-2-furoic acids. Since they had already assigned to one compound the 3,4-structure, they assumed that the compound melting at 167°-168°C. was 3,5-dibromo-2-furoic acid. They did not consider the alternative structure which might be obtained by a combination of 1,2- and 1,4-elimination of hydrogen bromide, namely, that of 4,5-dibromo-2-furoic acid, since that possibility was not deemed likely at that time.

Oxidation of this compound produces monobromomaleic acid when bromine water is used as the oxidizing agent, and monobromofumaric acid when nitric acid is used.


(Hill's incorrect structure)

These oxidation products show, only, that a bromine atom is in a β-position but give no indication as to which β-carbon atom is involved.

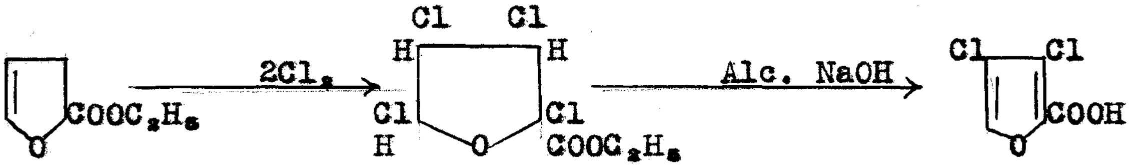
From the so-called 3-bromo-2-furoic acid Hill and Sanger obtained mucobromic and monobromofumaric acids by oxidation.



As before, these products indicate nothing as to which carbon atom is involved except that it is a β-carbon atom.

The β-monochloro- and the dichloro-2-furoic acids, although none of them is produced by the direct substitution of chlorine atoms, are nevertheless of great importance as reference compounds.

The three isomeric dichloro-2-furoic acids were all prepared by Hill and Jackson (4). They also prepared one of the β-chloro-2-furoic acids. The preparation of the other β-chloro-2-furoic acid will be described in this thesis. The source of all the compounds was ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate prepared by the addition of two molecules of chlorine to ethyl 2-furoate at 0°C. When this compound is decomposed by alcoholic sodium hydroxide, only one of the isomeric dichloro-2-furoic acids is obtained, namely, 3,4-dichloro-2-furoic acid.



It should be pointed out that two of the isomeric dibromo-2-furoic acids were obtained from furoic tetrabromide by the same method.

The structure of 3,4-dichloro-2-furoic acid was determined by Hill and Jackson by oxidation to mucochloric and dichloromaleic acids as in the case of the analogous bromo compound. Gilman and VanderWal (6) confirmed this structure

(4) Loc. cit., 3,4-dichloro-2-furoic acid was first prepared in 1884 by J. N. Garratt, working with Hill. The acid was not identified at that time, and the work was completed by Hill and Jackson.

(6) Gilman and VanderWal, Rec. trav. chim., 52, 267 (1933).

by half decarboxylation of 3,4-dichloro-2,5-furan dicarboxylic acid to form the identical 3,4-dichloro-2-furoic acid.

The remaining two isomeric dichloro-2-furoic acids were prepared by the decomposition of ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate by heat and subsequent separation of the esters by fractional distillation. The esters were then hydrolyzed to the acids. To that one of these compounds which melted at 155 -156 C., Hill and Jackson assigned the structure of 3,5-dichloro-2-furoic acid largely on the basis of analogy in physical properties and reactions with their so-called 3,5-dibromo-2-furoic acid.

To the last of the isomeric dichloro-2-furoic acids, known as χ-dichloro-2-furoic acid, no structure was immediately assigned, but Hill and Jackson suggested that it was either 4,5-dichloro-2-furoic acid or a geometrical isomer of 3,5-dichloro-2-furoic acid. Later Hill and Cornelison (7) assigned to it the first structure.

Only one β-monochlorofuroic acid was prepared by Hill and Jackson. Since it was obtained by removal of one halogen atom from either so-called 3,5-dichloro-2-furoic acid or 3,4-dichloro-2-furoic acid, these authors gave to it the

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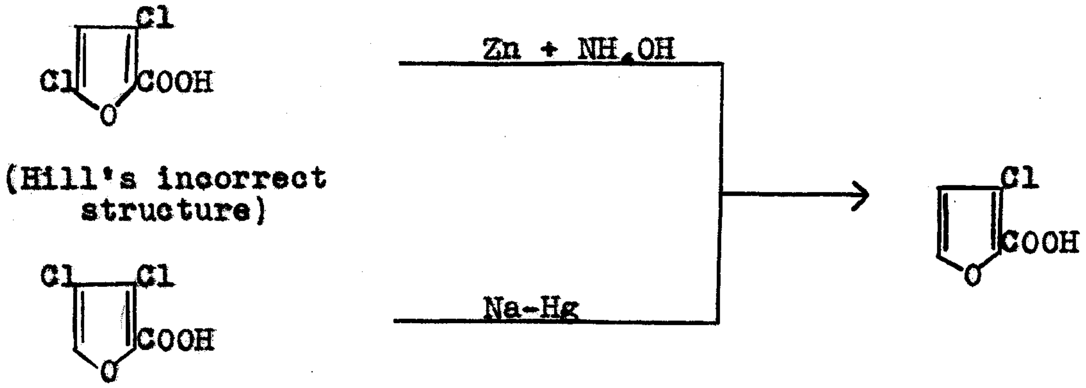
(7) Hill and Cornelison, *Am. Chem. J.*, *16*, 188 (1894).

structure of 3-chloro-2-furoic acid.



A study of the oxidation products of so-called 3,5-dichloro-2-furoic acid, χ-dichloro-2-furoic acid, and so-called 3-chloro-2-furoic acid in a manner similar to that used for the bromine compounds shows, only, that in all cases a halogen is on a β-carbon atom.

The last β-monochloro-2-furoic acid has now been prepared by removal of one of the halogens of χ-dichloro-2-furoic acid. It is entirely unlike the compound obtained by Hill and Jackson, and a mixed melting point of the two is greatly depressed.

The Halogenocrotonolactones(8) Obtained from Some Halogenated Furoic Acids.

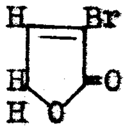
In a later article Hill and Cornelison (7) record further studies of the dichloro-, dibromo-, and the β-monobromo-2-furoic acids. There is a great deal of evidence to show that they were mistaken in the structures they assigned to some of their key compounds. When these apparent errors are corrected, their work in no way opposes the results of this investigation.

Hill and Cornelison found that when the dihalogen and β-monohalogen acids in question were treated according to certain procedures there were obtained various α,β-dihalogeno-, α-monohalogeno-, and β-monohalogenocrotonolactones. The reactions will be taken up in detail later in this thesis, but it is necessary at this point to digress sufficiently to present the argument for the belief that the

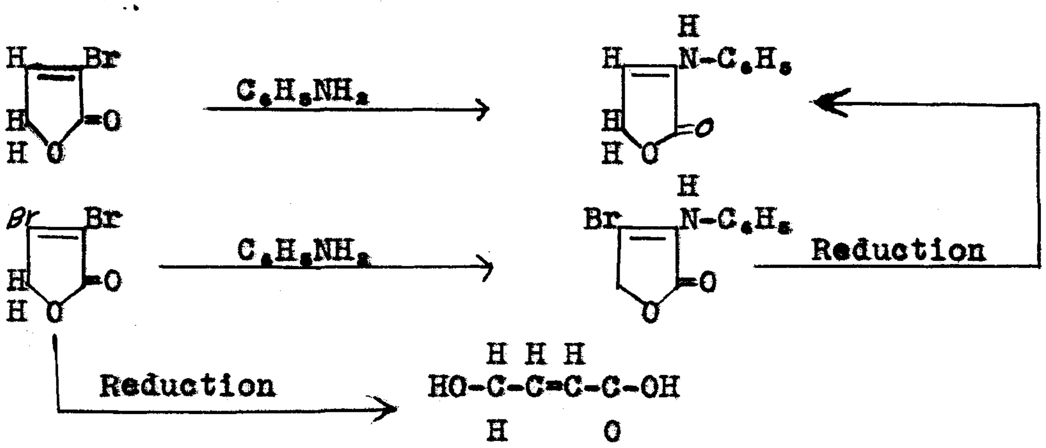
(8) To avoid further complication of an already complicated relationship, the names used by Hill and Cornelison for these compounds will be employed in this thesis. In a communication from Dr. E. J. Crane and Dr. Leonard T. Capell of the Editorial staff of Chemical Abstracts, these authorities state that the preferred method would be to name them as γ-lactones of substituted γ-hydroxycrotonic acids. They suggest, as alternative methods, naming them as derivatives of 2-furanone, or if it is desired to avoid questions of isomerism, as derivatives of γ-hydroxy-α-butenoic acid. Thus what is called in this thesis α-chlorocrotonolactone is better named (a) the γ-lactone of α-chloro-γ-hydroxycrotonic acid, (b) 3-chloro-2(5)-furanone and (c) the γ-lactone of α-chloro-γ-hydroxy-α-butenoic acid. The first name (a) is to be preferred.

structures assigned to the monohalogenocrotonolactones are in error.

To the bromine atom in the monobromocrotonolactone melting at 77° C., Hill and Cornelison assigned the α-position relative to the carbonyl group.

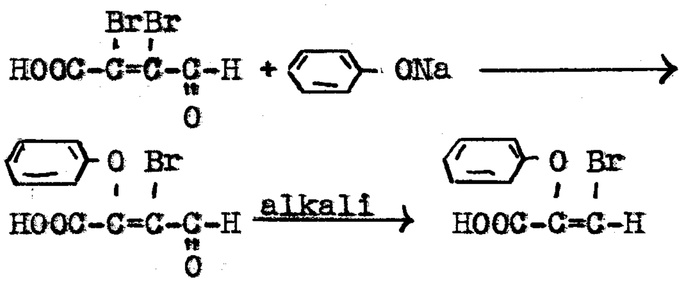


This structure was assigned on the basis of their belief that the α-halogen atom of an α,β-dihalogeno-α,β-unsaturated acid or lactone was the more reactive toward reagents such as aniline. They had derived the same so-called α-phenylamidocrotonolactone from this compound as they had obtained by reduction of the bromophenylamidocrotonolactone made by the interaction of aniline and α,β-dibromocrotonolactone.



Strong support for the assumption that the structure assigned to the dibromocrotonolactone is correct is found in the fact that it may be reduced to γ-hydroxycrotonic acid, as indicated above.

For their assumption that the aniline residue had been substituted for the α-bromine atom in the dibromolactone, Hill and Cornelison presented as evidence the conclusion of Hill and Stevens (9) that a phenoxy group, when substituted for one of the halogens in mucobromic acid, enters the α-position relative to the carboxyl group.



The conclusion of Hill and Stevens was fairly well confirmed when Hill and Palmer (10) found that the mucoxychloric acid obtained by the replacement of a halogen atom in mucochloric acid was decomposed by bromine to dibromochloroacetaldehyde. Thus it was shown that the chlorine atom had probably been originally on the β-carbon atom or had rearranged.

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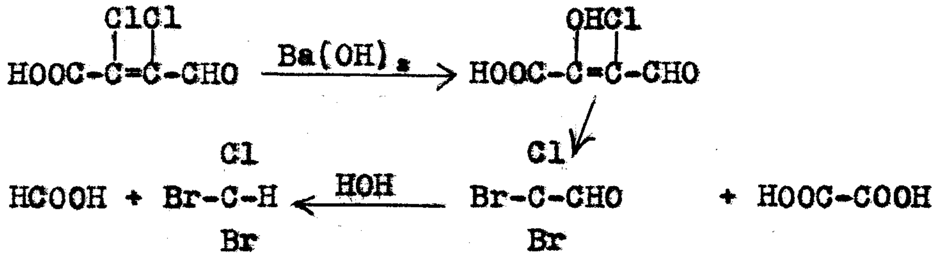
(9) Hill and Stevens, Proc. Am. Acad. Arts Sci., 19, 268 (1883).
(10) Hill and Palmer, Am. Chem. J., 9, 147 (1887).



$$\mathrm{HOOC{-}\overset{Cl}{C}{=}\overset{Cl}{C}{-}CHO} \xrightarrow{Ba(OH)_2} \mathrm{HOOC{-}\overset{OH}{C}{=}\overset{Cl}{C}{-}CHO}$$

$$\mathrm{HCOOH + Br{-}\underset{Br}{\overset{Cl}{C}}{-}H} \xleftarrow{HOH} \mathrm{Br{-}\underset{Br}{\overset{Cl}{C}}{-}CHO} \quad + \mathrm{HOOC{-}COOH}$$

The analogy between mucobromic or mucochloric acid and dihalogenocrotonolactones is not good insofar as the relative reactivity of the halogen atoms is concerned. In the first case highly activating carbonyl groups are situated on both sides of the carbon atoms holding the halogens, while in the lactones a carbonyl group is found on only one side with a less strongly activating group opposite.

Certain facts point to the probability that the structures assigned by Hill and Cornelison to some of the various crotonolactones are wrong. Lespieau and Viguier (11) obtained by treatment of γ-hydroxytetrolic acid with hydrogen bromide what is doubtless the same bromocrotonolactone, melting at 77°C., as was obtained by Hill and Cornelison, to the bromine atom of which Hill and Cornelison assigned the α-position.

Lespieau and Viguier assumed, as did Hill and Cornelison, that the bromine atom was attached to the α-carbon atom.

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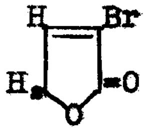
(11) Lespieau and Viguier, Compt. rend., 148, 420 (1910).

$$HO\text{-}CH_2\text{-}C{\equiv}C\text{-}COOH + HBr \longrightarrow$$

$$HO\text{-}CH_2\text{-}CH{=}CBr\text{-}COOH \longrightarrow$$



m.p. 77° C.

Upon examination the molecule of γ-hydroxytetrolic acid is observed to be a composite of propargyl alcohol and tetrolic acid.

$HO\text{-}CH_2\text{-}C{\equiv}CH$	$CH_3\text{-}C{\equiv}C\text{-}COOH$
(propargyl alcohol)	(tetrolic acid)

$$HO\text{-}CH_2\text{-}C{\equiv}C\text{-}COOH$$

(γ-hydroxytetrolic acid)

A number of investigators have found that hydrogen bromide and hydrogen chloride will add to the triple bond of tetrolic acid (12). That the chlorine atom of hydrogen chloride adds to the β-carbon atom is demonstrated by the fact that the same product has been synthesized from acetoacetic ester, using phosphorus pentachloride to replace the enolic hydroxyl group with chlorine (13).

(12) Friedrich, *Ann.*, *219*, 368 (1883).
Michael and Browne, *Am. Chem. J.*, *9*, 274 (1887); *J.prakt. Chem.* [2] *35*, 257 (1887).
Clutterbuck, *Ann.*, *268*, 108 (1892).
(13) Froelich, *Zeitschrift fur Chem.*, *5*, 270 (1869).
Geuther, *Zeitschrift fur Chem.*, *7*, 237 (1871).
Michael and Schulthess, *J. prakt. Chem.* [2] *46*, 236 (1892).

$$\underset{OH}{CH_3-C}=CH-COOC_2H_5 \xrightarrow{PCl_5} \underset{Cl}{CH_3-C}=CH-COOH$$

The corresponding bromine compound could not be thus prepared by Michael and Browne (12) but the bromocrotonic acid they prepared by the addition of hydrogen bromide to tetrolic acid was doubtless β-bromocrotonic acid, since hydrogen bromide would be expected to add in the same manner as does hydrogen chloride.

The halogen in β-chlorocrotonic acid is much more reactive than that of α-chlorocrotonic acid, since the former reacts easily with sodium ethoxide giving β-ethoxycrotonic acid (14). On the other hand, α-chlorocrotonic acid does not react with sodium ethoxide, even at 215° C. (14).

Hydrogen chloride or hydrogen bromide would be expected to add to propargyl alcohol in such a manner that the halogen atom would attach itself to the α-carbon atom relative to the hydroxymethyl group. This is in accord with Markownikoff's rule (15).

In both propargyl alcohol and in tetrolic acid, then, the halogen of a haloid acid would tend to go to the carbon atom which, in the composite γ-hydroxytetrolic acid would

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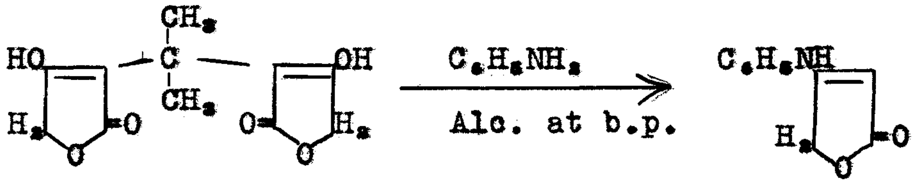
(14) Friedrich, Ann., 219, 322 (1883).
(15) Markownikoff, Ann., 153, 228 (1870).

be the β-carbon atom relative to the carbonyl group. It is entirely likely in view of these facts that the halogen of a haloid acid actually does go to the β-carbon atom when the haloid acid is added to γ-hydroxy tetrolic acid. If this be true, the bromolactone of Lespieau and Viguier, which is probably the same as the α-bromocrotonolactone of Hill and Cornelison, has its bromine atom attached to the β-carbon atom. The compound must then be β-bromocrotonolactone.

Added evidence that the positions assigned to the halogens in the α-halogenocrotonolactones are wrong is found in the work of Wolff and Schimpff (16). These authors report that the anilide of tetronic acid was obtained by treatment of propylidene bis-tetronic acid with aniline.

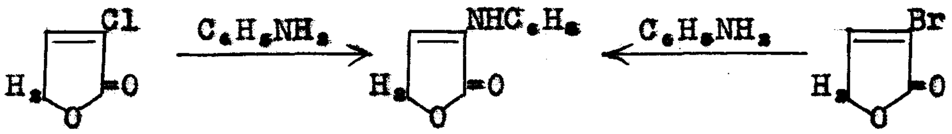


They also state that the same compound is formed by the direct action of aniline on tetronic acid. They give the melting point as 220°C. This compound, if their structure is correct, is β-phenylamidocrotonolactone. If Hill and Cornelison were wrong in the structures they assigned to their compounds, it should be identical with their so-called α-phenylamidocrotonolactone melting at 217°-218°C. A mixed

(16) Wolff and Schimpff, Ann., 315, 151 (1901).

melting point determination should settle this matter.

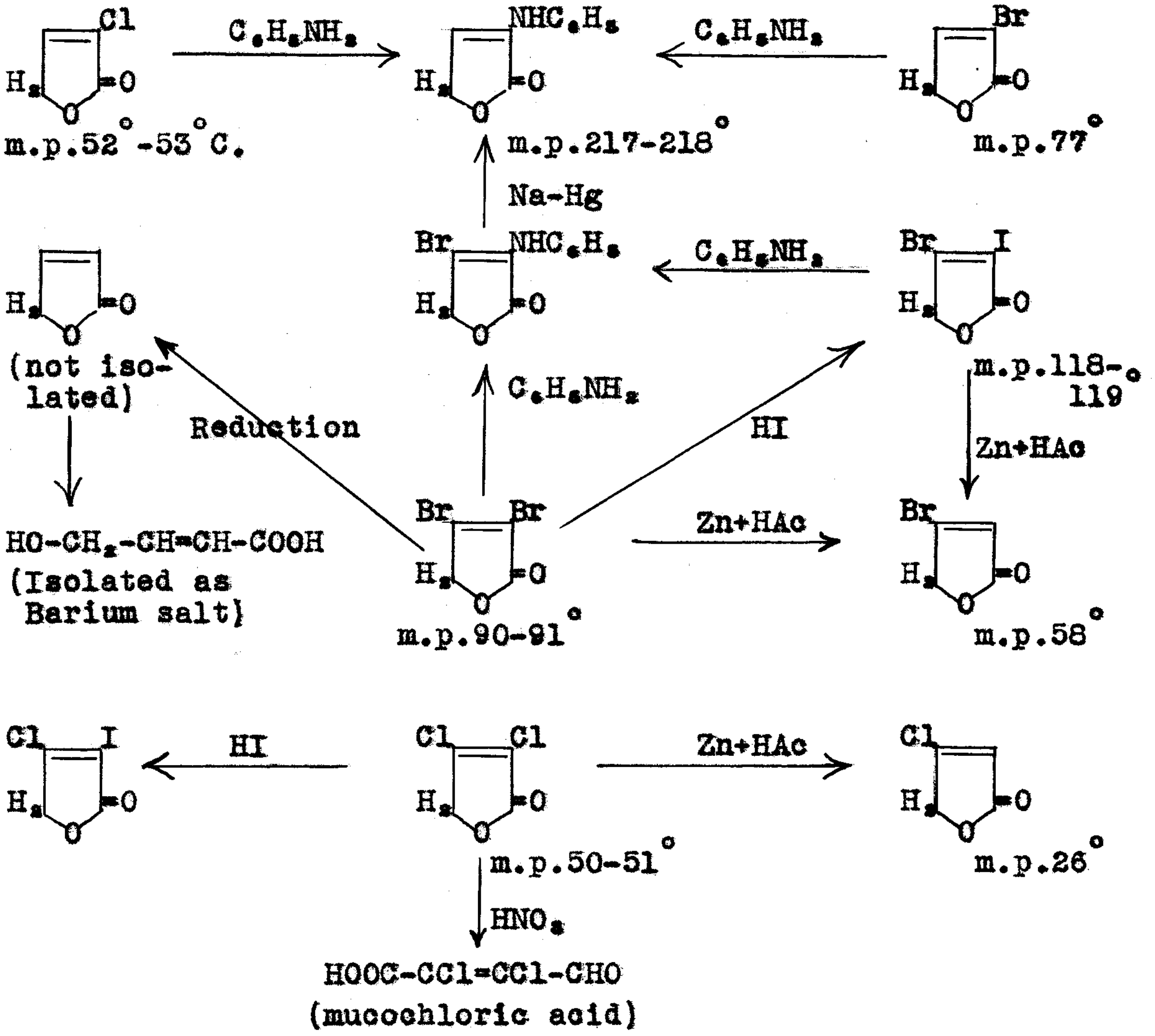
If the structure assigned by Hill and Cornelison to α-bromocrotonolactone is incorrect, the same must be true of the so-called α-chlorocrotonolactone. These authors have shown the compounds to be of similar structure by demonstrating the fact that they both produce the same phenylamidocrotonolactone by replacement of the halogen by a phenylamido group.



m.p. 52°-53°C.   m.p.217°-218°C.   m.p. 77°C.

(Hill's structures - probably incorrect)

If the structures of the so-called α-halogenocrotonolactones are incorrect, then those of the corresponding so-called β-halogenocrotonolactones are also in error. These compounds can be prepared by reduction of one of the halogens of the corresponding dihalogenocrotonolactone, the structure of which is known; therefore there can be little doubt that they are crotonolactones. Furthermore, the same phenylamidocrotonolactone as is produced by the action of aniline on so-called α-bromocrotonolactone can be obtained by the action of aniline on so-called α-iodo-β-bromocrotonolactone, and the reduction of the bromine atom on the resulting compound. This α-iodo-β-bromocrotonolactone can be derived by the action of hydriodic acid on α, β-dibromocrotonolactone. It can be reduced to the so-called β-bromocrotonolactone. The various interrelationships of these compounds are shown below (17).



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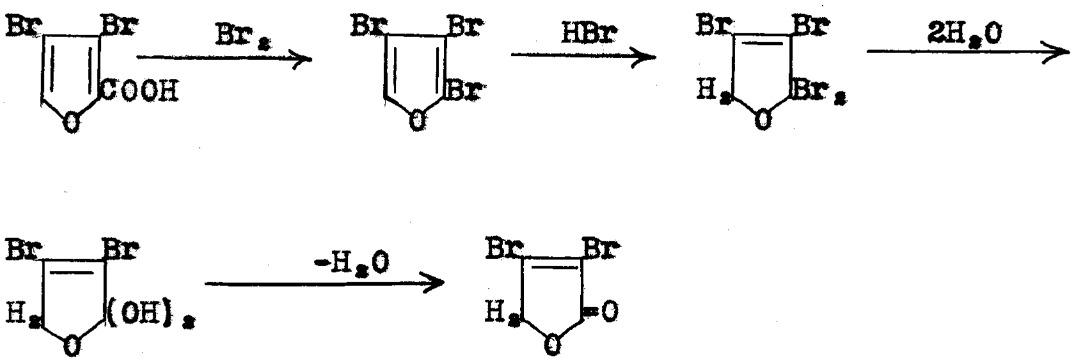
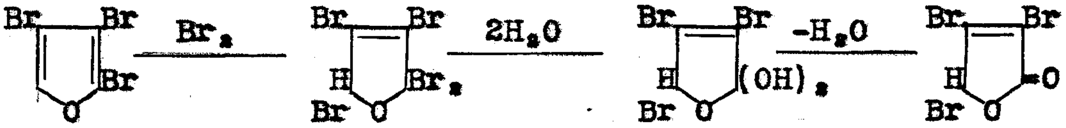
(17) The structures are those assigned by Hill and Cornelison (see reference (7)) and may be incorrect in some cases.

When Hill and Cornelison treated 3,4-dibromo-2-furoic acid with aqueous bromine at room temperature, they obtained a compound which melted at 90°-91° C. They identified this compound as α ,β -dibromocrotonolactone. This same compound had apparently been obtained by Toennies (5), who did not identify it as such. Hill and Sanger (3) had obtained it by the same method but also did not identify it.

Hill and Cornelison propose the following mechanism for the transformation.



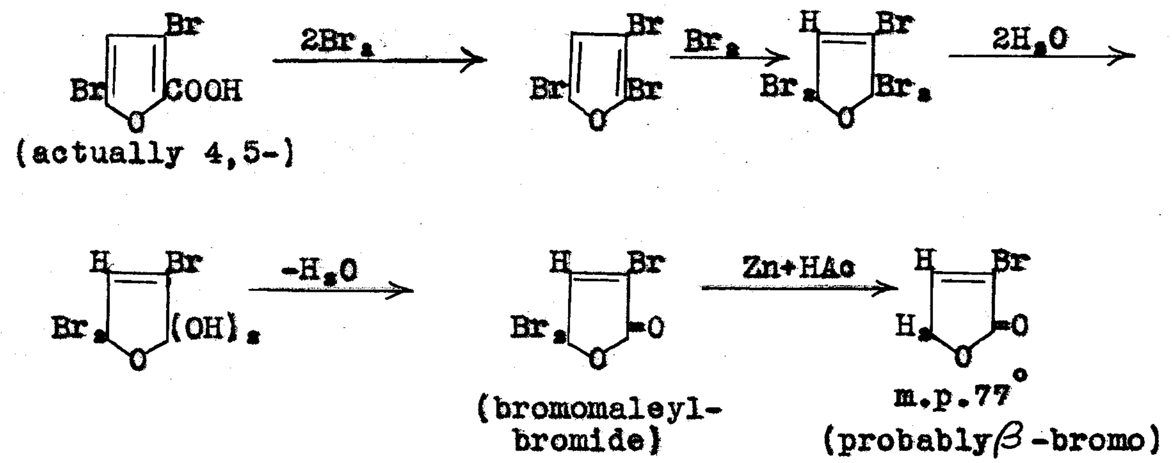
The fact that mucobromylbromide is formed simultaneously lends credence to the theory that the initial step is the formation of the tribromofuran indicated.



(mucobromylbromide)

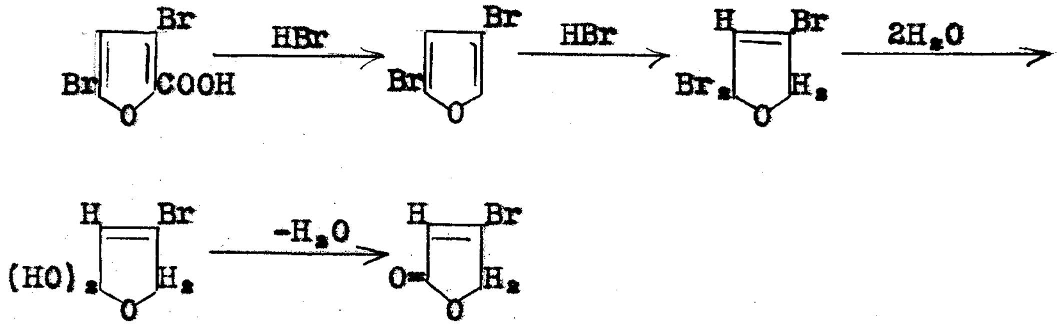
It has been indicated elsewhere in this thesis that the structure of 3,4-dibromo-2-furoic acid assigned to it by Hill and Sanger (3) is undoubtedly correct.

From their so-called 3,5-dibromo-2-furoic acid (really 4,5-) Hill and Sanger (3) had obtained a so-called α-bromomaleylbromide by treatment of the acid with an aqueous solution of bromine. By reduction of this compound with zinc and acetic acid Hill and Cornelison obtained what they called α-bromocrotonolactone, melting at 77° C. The following mechanism was proposed.



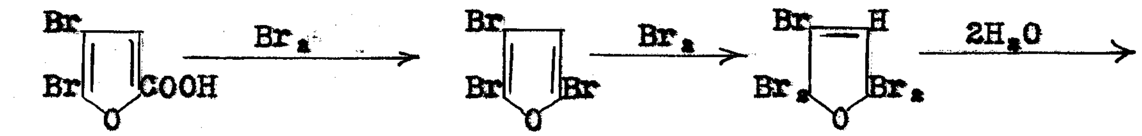
Evidence that the first step is actually the formation of the tribromofuran indicated is found in the fact that Hill and his coworkers (7) were able to isolate the intermediate tribromofuran and from it prepare the same bromomaleylbromide as was obtained from so-called 3,5-dibromo-2-furoic acid.

When the so-called 3,5-dibromo-2-furoic acid was boiled with concentrated hydrobromic acid, Hill and Cornelison found that what they called β-bromocrotonolactone was produced. They postulated the following mechanism.

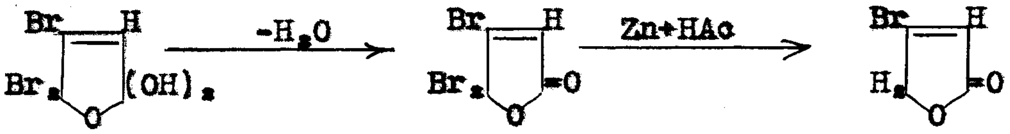


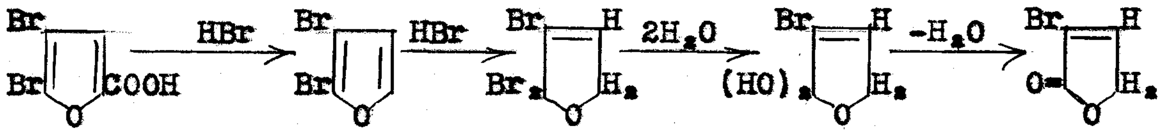
m.p.58°
(probably
α -bromo-)

If for the erroneous structure of the so-called 3,5-dibromo-2-furoic acid there be substituted the correct structure, which is that of 4,5-dibromo-2-furoic acid, then both α -bromocrotonolactone and β -bromocrotonolactone may be derived by the same general mechanisms as employed with the incorrect structures.

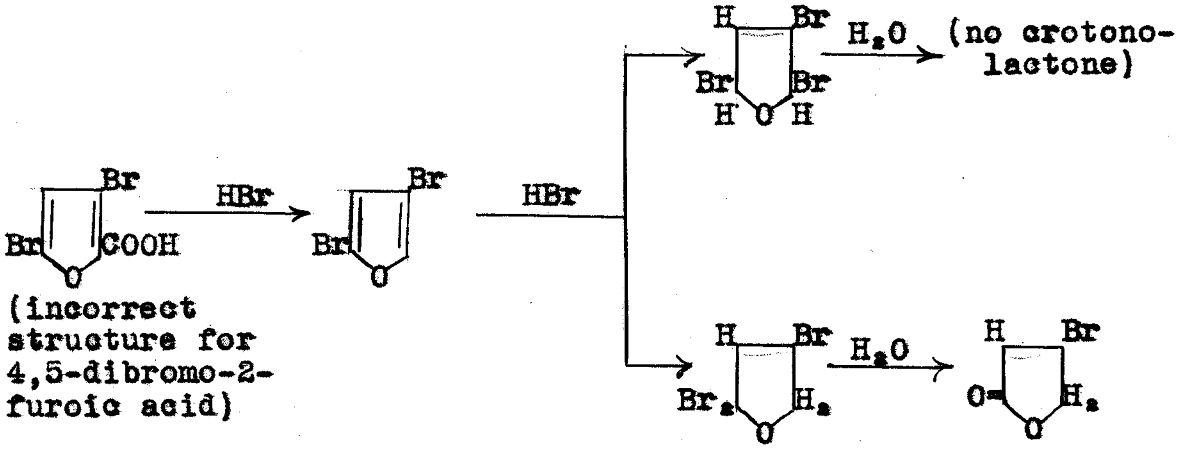


(correct structure
for so-called 3,5-
dibromo-2-furoic
acid)

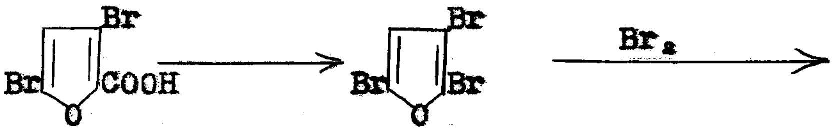




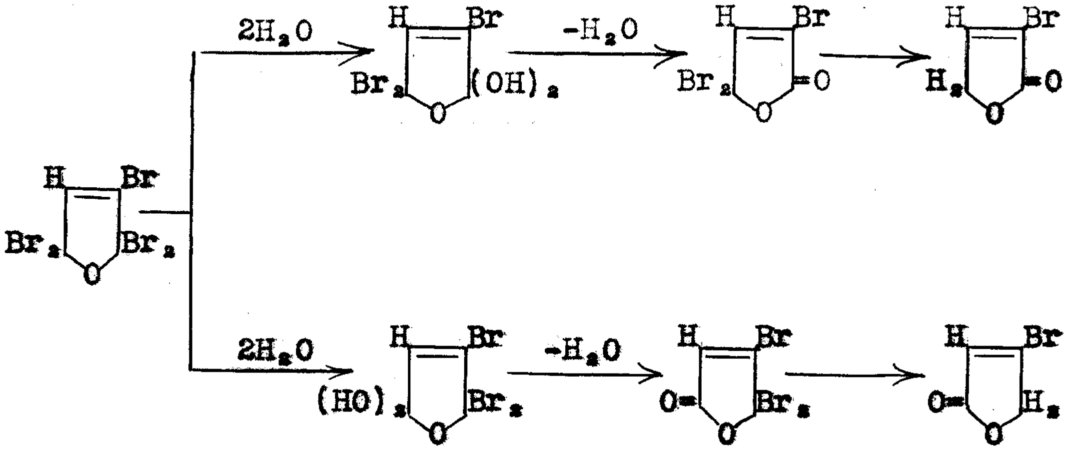
It must be kept in mind that what Hill and Cornelison called α-bromocrotonolactone is probably β-bromocrotonolactone and vice versa. Then it is obvious that their structure for the so-called 3,5-dibromo-2-furoic acid can not be made to follow their mechanism for its conversion by means of hydrobromic acid into what the author believes to be the true structure (α-bromo-) of the so-called β-bromocrotonolactone.



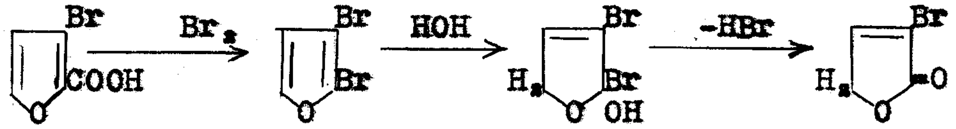
This criticism does not apply to the mechanism proposed for the reaction with bromine, since the tribromofuran postulated could be made to yield either α- or β- bromocrotonolactone by the same general mechanism.



(incorrect structure for so-called 3,5-dibromo-2-furoic acid)



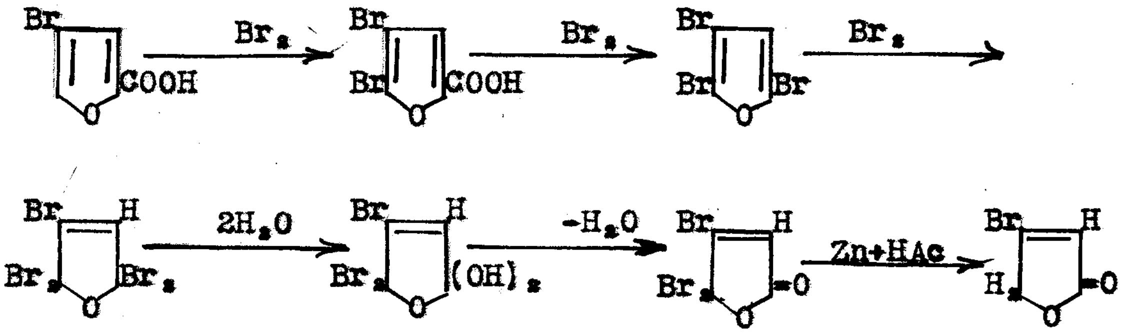
From the so-called 3-bromo-2-furoic acid (which is actually 4-bromo-2-furoic acid) Hill and Cornelison obtained by treatment with aqueous bromine the compound melting at 77° C. which they called α-bromocrotonolactone. Their proposed mechanism is as follows:



(incorrect structure of so-called 3-bromofuroic acid)

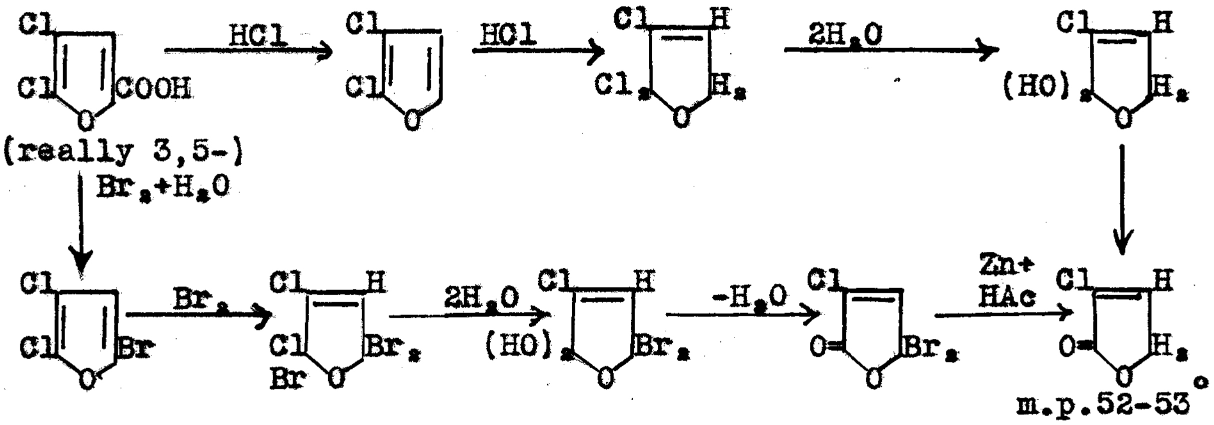
The starting compound is really 4-bromo-2-furoic acid and the end product is probably β-bromocrotonolactone.

The proposed mechanism, although it could be made to fit the corrected structures, is not tenable in the light of the fact that the β-monobromofuroic acid in question brominates in the 5-position with extreme ease (3). A better mechanism is as follows (using corrected structures):

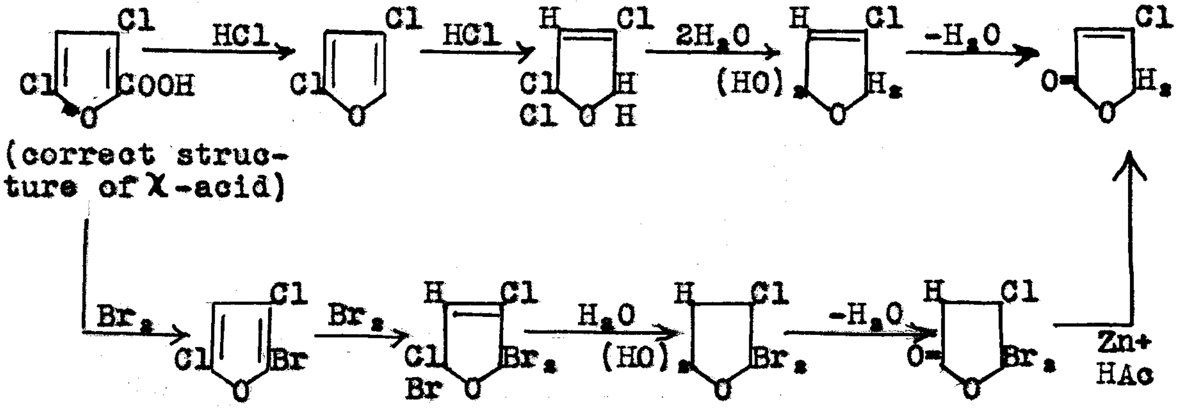


From 3,4-dichloro-2-furoic acid Hill and Cornelison obtained a compound which melted at 50°-51° C. and which was identified as α,β-dichlorocrotonolactone. The method of preparation and the mechanism proposed were the same as those employed in the case of the analogous bromine compound.

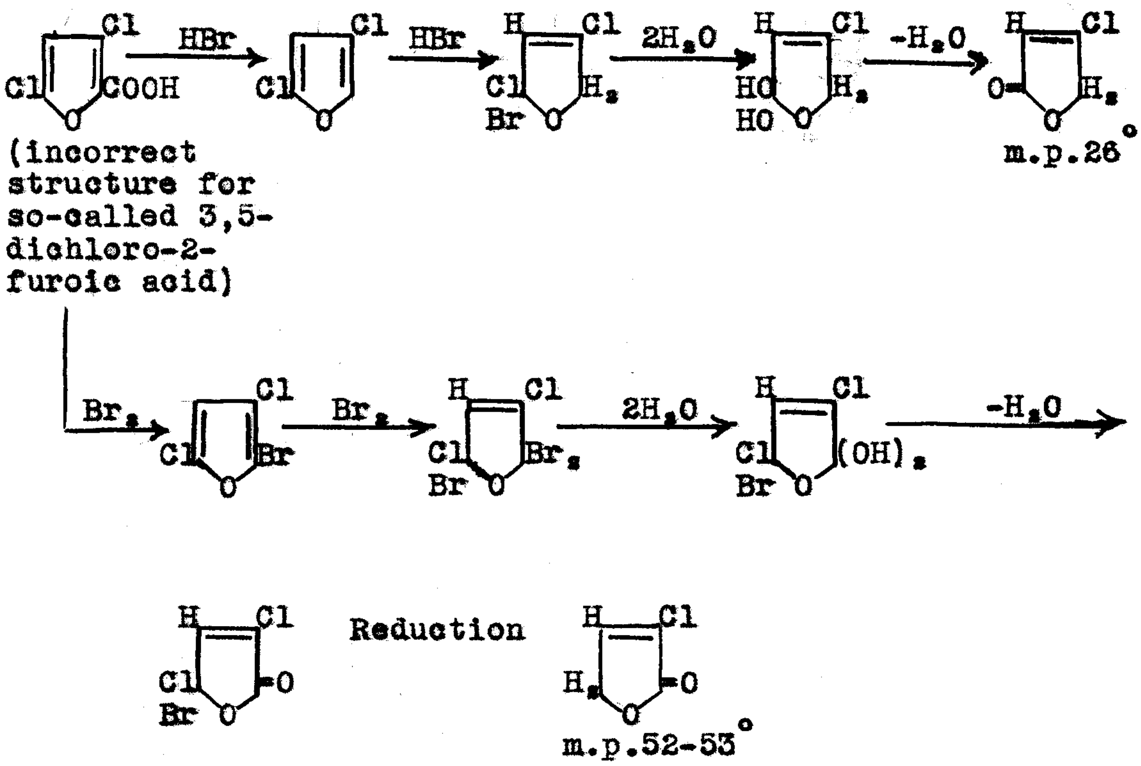
By treatment of χ-dichloro-2-furoic acid with both aqueous bromine, followed by reduction, and hydrochloric acid Hill and Cornelison obtained what they named α-chlorocrotonolactone. The proposed mechanism follows.



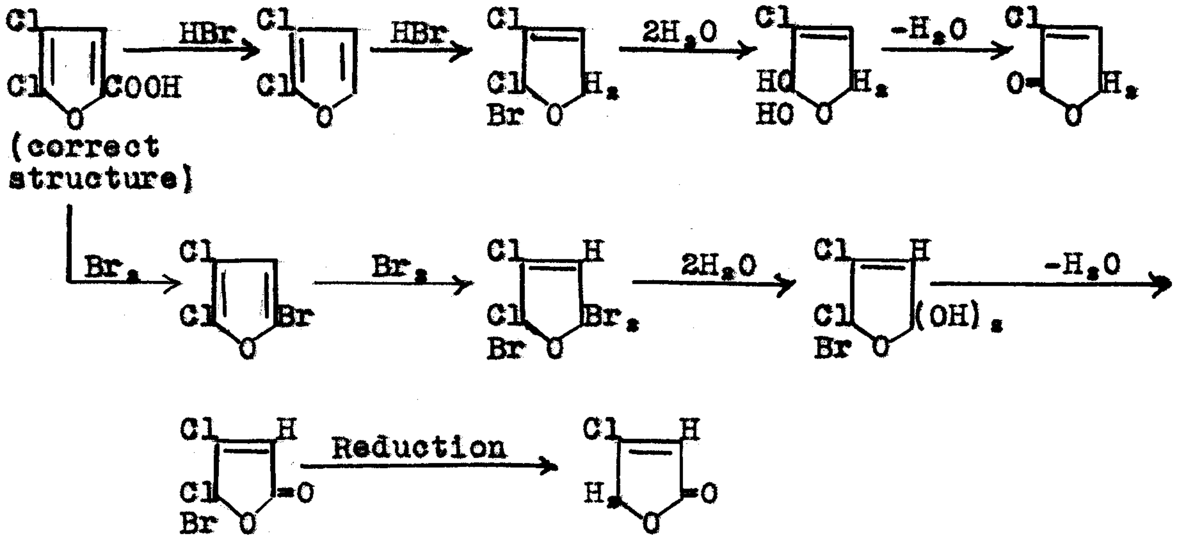
When the correct structure of χ-dichloro-2-furoic acid and the probable structure of the so-called α-chlorocrotonolactone are used, the same general mechanism may be employed to denote the reaction.



From the so-called 3,5-dichloro-2-furoic acid, melting at 155°-156° C., Hill and Cornelison obtained, by treatment with hydrobromic acid, what they supposed was β-chlorocrotonolactone. From the same acid they obtained the supposed α-chlorocrotonolactone by treatment with aqueous bromine and by reduction.

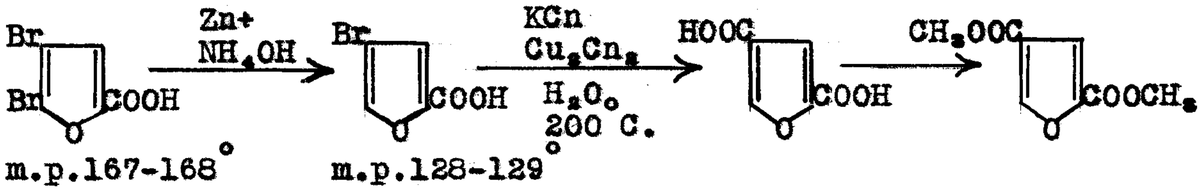


Using corrected structures, the reaction may be written thus:

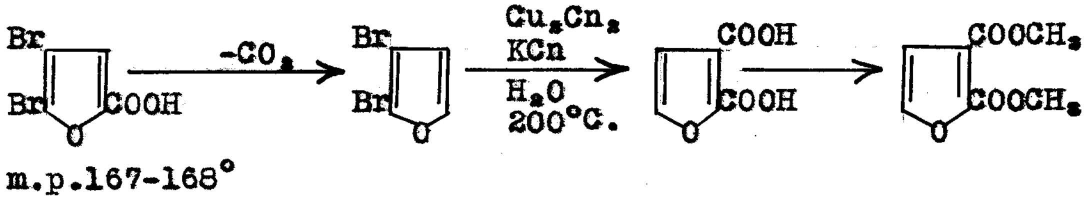


Proof of the Structure of Some Halogeno-2-furoic Acids.

That Hill and his coworkers were mistaken in the structure they assigned to the so-called 3,5-dibromo-2-furoic acid, which melted at 167°-168° C., has been demonstrated by the following reactions:



The procedure is that employed by Rosenmund and Struck (18) with benzenoid compounds. The end products, 2,4-furandicarboxylic acid and its methyl ester, are compounds of known structure. The so-called 3-bromo-2-furoic acid is shown by the same reaction to be 4-bromo-2-furoic acid. The above results are confirmed by the following series of reactions:



The structures of 2,3-furandicarboxylic acid and its ester are known. The same series of reactions also proves the structure of the 2,3-dibromofuran derived by decarboxylation of the acid.

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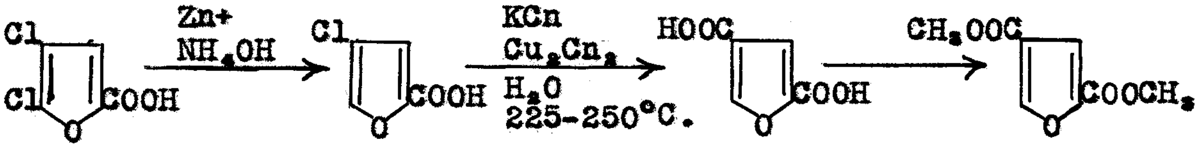
(18) Rosenmund and Struck, Ber., 52B, 1749 (1919).

The same method was used to derive 2,4-furandicarboxylic acid from the so-called 3,5-dichloro-2-furoic acid.



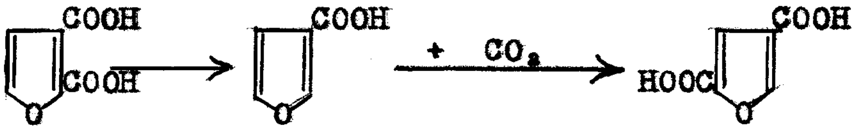
The reaction in this case went much less smoothly than in the case of the corresponding bromine compound. The yields were small (0.5-2%) but no other compounds were isolated and it was quite easy to purify the products. Furthermore, very pure materials were employed in two steps leading up to the preparation of 4-chloro-2-furoic acid. This compound was itself very carefully purified. The actual material used was prepared from highly pure 3,4-dichloro-2-furoic acid by removal of the chlorine atom in the 3-position, using sodium-amalgam at 100°C. A mixed melting point with a pure sample prepared from the so-called 3,5-dichloro-2-furoic acid showed no depression. The method of preparation is in itself a guarantee that only one β -chloro-2-furoic acid exists in the product. It was found that χ -dichloro-2-furoic acid was completely reduced to furoic acid by sodium-amalgam at room temperature. Hill and Jackson (4) also state that sodium-amalgam slowly reduces χ -dichloro-2-furoic acid to furoic acid. Since they make no mention of temperature, it is assumed that their experiment was carried out at room temperature. The only β-chloro-2-furoic acid which it is possible to obtain by treatment of 3,4-dichloro-2-furoic acid with sodium-amalgam at 100° C. is, then, the one which is derived also from so-called 3,5-dichloro-2-furoic acid and which is not derived from χ-dichloro-2-furoic acid. The 3,4-dichloro-2-furoic acid is apparently the only dichloro acid yet obtained in the reaction by which it is prepared. This is an added reason for the belief that the material used contained neither of the remaining isomeric dichloro-2-furoic acids.

A point to be considered is the possibility that the 2,4-furandicarboxylic acid, formed as the end product in the reaction of the β-chloro-2-furoic acid with cuprous cyanide, potassium cyanide, and water, was really derived by rearrangement of initially formed 2,3-furandicarboxylic acid. This reaction, if true, would prove that the β-chloro acid in question was 3-chloro-2-furoic acid rather than 4-chloro-2-furoic acid. That the rearrangement does not take place to an appreciable extent at about 200° C. is shown by the fact that each of the dicarboxylic acids was obtained in a different reaction, under the same conditions, in the course of the work on 4,5-dibromo-2-furoic acid which has been described. Only one dicarboxylic acid was isolated in each case. The temperature used in the present case was somewhat higher, however, (225-250°) and the heating period was longer.

These conditions might have been sufficient to cause rearrangement. The reaction doubtless takes place in the following steps:

The ammonium hydroxide formed would be sufficient to form the ammonium salt of one carboxyl group and would probably be a stabilizing factor. Large amounts of free copper were found at the end of the reaction and smaller quantities were found under the less stringent conditions used for the bromine compounds. It seems likely, therefore, that cyanogen was liberated, which, if present in excess, would quickly be hydrolyzed to form oxalic acid and ammonia. Decomposition of oxalic acid would increase the concentration of carbon dioxide, which might hinder the decarboxylation process but might promote carboxylation. The ammonia, if liberated, would probably help stabilize the organic acid.

No exact information is available on the relative stabilities toward decarboxylation of the various furandicarboxylic acids, and, owing to the peculiar configuration of the furan ring, no reasonable guess can be made. Complete decarboxylation and recarboxylation to form 2,4-furandicarboxylic acid need not be considered since substitution of a carboxyl group in the very difficultly reactive β-position is altogether unlikely. It seems probable then that if rearrangement did occur it could only take place by decarboxylation of a group in the 2-position of 2,3-furandicarboxylic acid and by carboxylation in the 5-position to form 2,4-furandicarboxylic acid.



In summation it may be said that the possibility of rearrangement exists, but that it is extremely unlikely that it occurs. The possibility of rearrangement is one that must often be faced in proof of structure reactions and is not one to be given much weight when reliable reactions and groups are concerned. The carboxyl group is not one with a reputation for wandering from one position to another.

There is a great deal of added evidence for the revised structures of the chloro acids in question, besides that already presented. Hill and Jackson had no doubt that the so-called 3,5-dichloro-2-furoic acid had a structure analogous to the so-called 3,5-dibromo-2-furoic acid (which has now been proved to be 4,5-dibromo-2-furoic acid). They based their conclusions partly on the resemblance in physical properties of the acids and numerous salts. As further evidence they cite the fact that the β-monochloro-2-furoic acid derived from both so-called 3,5-dichloro-2-furoic acid and 3,4-dichloro-2-furoic acid is similar in its physical properties to the β-monobromo-2-furoic acid derived in analogous manner from so-called 3,5-dibromo-2-furoic acid and 3,4-dibromo-2-furoic acid. Although the reduction method differed in the case of the 3,4-dichloro acid from that used for the 3,4-dibromo acid, there can be little or no doubt that the halogen atom in the same position was removed in each case. The resulting β-monochloro- and β-monobromo-2-furoic acids must, then, have the same structures, and since the latter is definitely known to be 4-bromo-2-furoic acid, the β-monochlorofuroic acid must be 4-chloro-2-furoic acid. Since the last named compound may be derived from so-called 3,5-dichloro-2-furoic acid, it follows that the latter is really 4,5-dichloro-2-furoic acid.

Another important piece of evidence is the fact that only the so-called χ-dichloro-2-furoic acid could be sulfonated by Hill and Jackson (4). It seems reasonable to suppose that sulfonation would be more likely to take place in a furan compound in which the 4-position is vacant, as seems probable in χ-dichloro-2-furoic acid.

Gilman and Brown (19) have successfully converted the so-called 3-sulfo-5-chloro-2-furoic acid of Hill and

(19) Gilman and Brown, unpublished data.

Hendrixson (20) to the so-called 3,5-dichloro-2-furoic acid by replacement of the sulfonic acid group with chlorine. They used phosphorus pentachloride in a sealed tube to effect the reaction. If the directly substituted sulfonic acid group has entered the same position in 5-chloro-2-furoic acid as do directly substituted acetyl- (21), sulfo- (21), bromo- (22), and acetoxymercuri (22) groups in similarly constituted compounds, it will go to the 4-position. If it does do so, then the so-called 3-sulfo-5-chloro-2-furoic acid was really 4-sulfo-5-chloro-2-furoic acid, and the compound derived by Gilman and Brown was 4,5-dichloro-2-furoic acid.

Gilman and Franz (23) have found that so-called ethyl 3,5-dichloro-2-furoate gives with phenylmagnesium bromide a chlorocrotonolactone. In this compound the chlorine atom occupies the same position as is occupied by the bromine atom in the analogous compound obtained from 4,5-dibromo-2-furoic acid (24). Such a compound could not occur unless the so-called 3,5-dichloro-2-furoic acid were actually 4,5-dichloro-2-furoic acid.

Finally, the fact that Hill and Cornelison found that the course of the reactions leading to halogenated crotono-

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(20) Hill and Hendrixson, Proc.Am.Acad.Arts Sci.,25,283 (1890).
(21) Gilman, Calloway and Smith, J.Am.Chem.Soc.,56, 220 (1934).
(22) This Thesis, Part B, page 86.
(23) Gilman and Franz, unpublished data.
(24) Gilman, VanderWal, Franz and Brown, J.Am.Chem.Soc., 57, 1146 (1935).

lactones was apparently the same for both so-called 3,5-dibromo- and so-called 3,5-dichloro-2-furoic acid, is a further measure of proof that their structures are the same. If this be true, the halogens in both compounds are in the 4,5-positions since this has been proved in the case of the bromo compound.

Consideration of all the direct and indirect evidence warrants the conclusion that the structures of the chloro acids in question, as defined by Hill and coworkers, are wrong; and that the true structures are as indicated in this thesis.

EXPERIMENTAL

Preparation of 4,5-Dibromo-2-furoic Acid.

This compound was prepared by Hill and Sanger (3) by the action of alcoholic sodium hydroxide on 2,3,4,5-tetrabromotetrahydro-2-furoic acid and also by the direct action of bromine on furoic acid. In the present work the modified procedure of Shepard, Winslow and Johnson (25) was employed, in which furoyl chloride is used in place of furoic acid. Purification was effected by distillation of the ethyl ester instead of by precipitation of the barium salt.

To 230 g. (1.76 moles) of furoyl chloride at room temperature there was added, with stirring, 750 g. (4.69 moles) of bromine over an interval of two hours. The resulting mixture was refluxed for eight hours in an oil bath, with constant stirring. The excess of bromine was removed by means of an air stream, and the mixture was added dropwise to 750 cc. of anhydrous alcohol with stirring. The resulting solution was refluxed for three hours and the alcohol was then distilled. The residue was diluted with ether and extracted with about 150 cc. of 10% sodium carbonate solution. The ether layer was filtered, the ether was distilled and the residue distilled under reduced pressure. A small fore-run

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

was discarded and the main portion was refluxed, with stirring, with 850 cc. of 10% aqueous sodium hydroxide for several hours. The solution was acidified with hydrochloric acid and the crystalline product was recrystallized once from water. The melting point was about 154°-158° C. and the yield was 120 g. or 25% of the theoretical quantity. This product was sufficiently pure for the purpose for which it was intended. (26)

Preparation of Ethyl 4-Bromo-2-furoate.

A 10 g. portion of the crude 4,5-dibromo-2-furoic acid, prepared as previously described, was dissolved in a mixture of 20 cc. of concentrated ammonium hydroxide and 70 cc. of water, and the solution filtered. It was cooled to 10° C., at which point crystals began to form. Five grams of zinc dust was added quickly and the flask rapidly shaken until the temperature rose to 30° C. This rise took place in only a few seconds. The mixture was filtered quickly by suction, acidified, heated to the boiling point, and cooled. A mixture of oil and crystals precipitated.

The accumulated products of three such runs and one which may have been over-reduced weighed 20 g. This material

(26) There is no doubt that the yield of this product could be much improved. The details recorded are those of the actual process by which the material was obtained for the critical experiments which follow. The yield and quality of the product are not to be regarded as typical of the procedure.

was esterified by passing dry hydrogen chloride into its solution in 100 cc. of anhydrous ethyl alcohol. The alcoholic solution after standing for some time was diluted with water and the oily precipitate was distilled. In order to dry the material, a portion of benzene was added and distilled first. The boiling point of the middle fraction was 119°-123°C. at 20 mm. pressure. The yield was 6 g. or 18.5% of the theoretical quantity based on pure 4,5-dibromo-2-furoic acid.

Preparation of 4-Bromo-2-furoic Acid.

The ethyl ester prepared as previously described was hydrolyzed by refluxing it with 60 cc. of 10% aqueous sodium hydroxide for three hours. The hot solution was acidified and sufficient water was added so that the precipitate was dissolved in the solution when heated. The acid which precipitated upon cooling melted at about 115°-124°C. After three recrystallizations from carbon tetrachloride, it melted at 128°- 129.5°C. The yield was 4 g. or 76.5% of the theoretical quantity. This method differs from that of Hill and Sanger(3) only in the techniques of purification and determination of the extent of reduction. The melting point of the product obtained by Hill and Sanger was 128°-129°C.

Conversion of 4-Bromo-2-furoic Acid to 2,4-Furandicarboxylic Acid.

Run 1. This transformation was made by the method of Rosenmund and Struck (18).

A mixture of 2 g. (0.0095 mole) of 4-bromo-2-furoic acid (m.p. 128°-129.5°C.), prepared as previously described, with 2 g. (0.03 mole) of potassium cyanide, 0.9 g. (0.005 mole) of cuprous cyanide, and 10 cc. of water was sealed in a tube 60 cm. long and 22 mm. in diameter (outside). The tube and contents were heated to 180°-200°C. for ten hours. After addition of 50 cc. of 10% aqueous sodium hydroxide, the mixture was warmed for two hours and filtered while warm. The solution was acidified with hydrochloric acid until the initially formed precipitate redissolved. The resulting solution was boiled with decolorizing carbon for a few minutes and filtered. After cooling, it was extracted with ether, this ether solution partially dried with sodium sulfate, and the solvent distilled. The solid residue was recrystallized from a little hot water. The product blackened at 264°C. and melted with decomposition at 264°-266°C. The yield was 0.45 g. or 30% of the theoretical amount. A mixed melting point was taken with a sample of 2,4-furandicarboxylic acid (m.p. 263°-264°C.) made from methyl bromocoumalate by the method of Feist (27). The mixture melted at 262°-264°C. A mixture with 2,3-furandicarboxylic acid prepared from 2-methyl-3-furoic acid (28) melted below 202°C.

(27) Feist, Ber., 34, 1992 (1901).
(28) Asahina, Acta Phytochim. (Japan), 2, 1 (1924).

As a further check on its identity, the acid was esterified by passing dry hydrogen chloride into the solution of the acid in anhydrous methanol. Dilution with water precipitated the ester. After recrystallization from water, it melted at 105°-107°C. The yield at this point was 0.1 g. or 19% of the theoretical amount based on 2,4-furandicarboxylic acid. One more recrystallization raised the melting point to 107°-108°C. A mixture with dimethyl 2,4-furandicarboxylate (m.p. 108°-109°C.) melted at 109°-110°C. The melting point of the diester is, according to Feist, 109°-110°C.

Run 2. A mixture of 1.0 g. (0.005 mole) of the same 4-bromo-2-furoic acid used in run 1, 1.0 g. (0.015 mole) of potassium cyanide, 0.45 g. (0.0025 mole) of cuprous cyanide, and 10 cc. of water was heated in a sealed tube for eight hours at 190°C. and for a few hours more at 160°C. The contents of the tube were warmed with 50 cc. of 5% aqueous sodium hydroxide for two hours, after which the solid was separated by filtration. The filtrate was acidified with hydrochloric acid, boiled with decolorizing carbon, filtered, and extracted with ether. The ether was distilled and the solid residue was esterified using anhydrous methanol and hydrogen chloride gas as before.

After dilution with water the mixture was extracted with ether. Distillation of the solvent left a residue which upon recrystallization from water yielded 0.07 g. of dimethyl

2,4-furandicarboxylate melting at 104°-106°C. A mixture with a known sample melted at 106°-108°C. The yield was 7.6% of the theoretical amount based on 4-bromo-2-furoic acid.

Decarboxylation of 4,5-Dibromo-2-furoic Acid.

Run 1. The procedure used was substantially the same as that employed by Shepard, Winslow, and Johnson (25) for the preparation of some halogenated furans.

Five grams of pure 4,5-dibromo-2-furoic acid (m.p. 168°-169°C.) was mixed with 10 cc. of quinoline and 1.0 g. of copper-bronze powder in a decarboxylation apparatus similar to that described by the above-mentioned authors. The temperature of the metal bath was raised to 250°C. and held there until several cubic centimeters of liquid had distilled. The tube was then partially cooled, 5 g. more of the acid was added, and the process repeated. A total of 15 g. (0.056 mole) was decarboxylated in this manner. After rapid gas evolution had stopped, following the last addition of acid, the temperature was raised to 280°C. and about two thirds of the quinoline distilled. The liquid distillate was diluted with a small amount of ether and extracted with 3% hydrochloric acid until the extractant was acidic. After removal of the solvent, the residue was distilled at atmospheric pressure. The product was fairly stable, darkening only slightly when kept over night in a refrigerator. The main portion distilled at 160.5°-162.5° C. The yield was 3.5 g., or 28% of the theoretical amount, of 2,3-dibromofuran. Other constants are:

n_D^{25} 1.5430(29); D_4^{26} 2.117;

MR_D(30) : calc'd 34.711, obs. 33.620.

Anal. Calc'd for $C_4H_2OBr_2$: Br, 70.80.

Found: Br, 71.09, 71.29.

Run 2. Another run was made in a similar manner. From 8 g. (0.0296 mole) of pure 4,5-dibromo-2-furoic acid (m.p. 166°-168° C.) there was obtained 2 g. of 2,3-dibromofuran boiling at 158°-161° C. This is 30% of the theoretical amount. The distilled product was colorless and was found to remain so for at least three weeks when kept, tightly

(29) The index of refraction was taken on material which had stood over night in a refrigerator and was slightly yellowish. The value given checks that found by Mr. E. V. Brown, using an entirely different sample.

(30) The molecular refractivity was calculated from the values of the atomic refractions given by Eisenlohr [Landolt-Börnstein, "Physikalisch-Chemische Tabellen," Julius Springer, Berlin, 5th Ed., Vol. II, 1923, p. 985 .] Two ethylenic double bonds and an ethereal oxygen were assumed. If the value for the molecular refractivity of 3-bromofuran as determined by Hughes and Johnson [*J. Am. Chem. Soc.*, **53**, 737 (1931)] is employed in the calculation, a better result is obtained. The molecular refractivity then is 33.633. It should be noted that the exaltation as calculated from the value derived by consideration of the atoms and bonds (-1.091) is very nearly that for 3-bromofuran as determined by Hughes and Johnson (-1.078).

stoppered, in a refrigerator. The refractive index then was n_D^{25} 1.5419.

Anal. Calc'd for $C_4H_2OBr_2$: Br, 70.80

Found: Br, 70.97, 71.04.

Conversion of 2,3-Dibromofuran to 2,3-Furandicarboxylic Acid.

Run 1. A mixture of 1.5 g. (0.007 mole) of the 2,3-dibromofuran prepared as described in run 2 of the previous section, with 2 g. (0.03 mole) of potassium cyanide, 0.9g.(0.005 mole) of cuprous cyanide, 7 cc. of water, and 2 to 5 cc. of ethyl alcohol was heated in a sealed tube. The capacity of the tube was 140 cc. and heating was carried out at 200°-205°C. for ten hours. When cooled, the tube was opened, the contents warmed for one half hour with 30 cc. of 5% sodium hydroxide solution, diluted to 75 cc. with distilled water and filtered. The filtrate was acidified with a large excess of concentrated hydrochloric acid. The initially formed precipitate was mostly redissolved in the excess of acid solution. The solution was boiled with decolorizing carbon for a few minutes in order to clarify it and to expel dissolved hydrogen cyanide, and then filtered while still warm. The filtrate was extracted with ether and the ether solution partially dried by shaking it with anhydrous sodium sulfate for a few minutes. The solvent was distilled from the filtered solution and the solid residue was recrystallized from a small amount of glacial acetic acid. The product melted at 216° C. but blackened at 210° C. After another recrystallization from acetic acid, it melted at 218°-220° C. A mixture with a sample of 2,3-furandicarboxylic acid melted at 219°-220° C. The melting point of the material of known constitution was 220°-221° C. The yield of the material melting at 216° C. was 0.1 g. or 10% of the theoretical amount.

Run 2. In this run 2 g. (0.009 mole) of 2,3-dibromofuran boiling at 158°-160° C. (n_D^{25} 1.5415) was heated in a sealed tube with 2 g. (0.03 mole) of potassium cyanide, 1 g. (0.006 mole) of cuprous cyanide, 7 cc. of water, and 3 to 5 cc. of ethyl alcohol. Temperatures ranging from 180°-207° C. were employed and the time of heating was nine hours. The contents of the tube were warmed for one half hour with 60 cc. of 5% sodium hydroxide solution. The mixture was filtered and the filtrate acidified. A yellow solid precipitated which was separated by filtration. The filtrate was thoroughly extracted with ether, the ether solution partially dried with anhydrous sodium sulfate, the ether distilled, and the residue recrystallized once from glacial acetic acid. The product was dried in air and melted at 216°-217° C. A mixture with known 2,3-furandicarboxylic acid, prepared by the method of Asahina (28), melted at 218°-219° C. The yield was 0.2 g. or 14.5% of the theoretical amount.

The 0.2 g. of acid thus produced was esterified by the use of anhydrous methanol and dry hydrogen chloride gas. The crude ester weighed 0.05 g. and when recrystallized once from water melted at 35°-36.5°C. The yield of crude product was 21% of the theoretical amount. A mixture with a sample of dimethyl 2,3-furandicarboxylate (m.p. 36.5°-37.5°C.) melted at 36°-37.5°C.

The Half Amide of 2,3-Furandicarboxylic Acid.

The small amount of yellow precipitate which was filtered from the cooled acidic solution of 2,3-furandicarboxylic acid, as recorded in the previous section, weighed 0.15 g. It melted at 261°-262°C. with decomposition, and after purification by reprecipitation from sodium hydroxide solution with hydrochloric acid, followed by extraction of the solid with hot chloroform and with hot ethyl alcohol, it melted at approximately 288°-293°C. with decomposition. The material contained no halogen but the proper amount of nitrogen for a mono amide of a furandicarboxylic acid.

Anal. Calc'd for $C_6H_5O_4N$: N, 9.03
Found: N, 8.94, 8.70, 8.72.

The remainder of the sample was hydrolyzed by refluxing it with 1 cc. of 5% aqueous sodium hydroxide for 2 hours. The solution was acidified with hydrochloric acid and extracted several times with ether. The ether was evaporated under reduced pressure and the solid recrystallized from glacial acetic acid. The product melted at 218°-220°C. with darkening. A mixture with pure 2,3-furandicarboxylic acid melted at 218.5°-219.5°C. with darkening. Esterification by means of diazomethane produced sufficient diester for two melting point determinations. The product melted at 36°-37.5°C. in one determination and at 36.5°-37.5°C. in the other. A mixed melting point taken with the material used in the last mentioned determination and dimethyl 2,3-furandicarboxylate was 36°-38°C. The unknown substance is probably either 2-carboxy-3-furoamide or 3-carboxy-2-furoamide.

Preparation of Ethyl 2,3,4,5-Tetrachlorotetrahydro-2-furoate.

This compound was prepared by the method of Hill and Jackson (4).

Dry chlorine was passed into a flask, fitted with a mechanical stirrer, containing 300 g. (2.14 moles) of distilled ethyl 2-furoate, the temperature being kept at 0°C. or below. Chlorine was absorbed and the ester liquefied. The addition of chlorine was stopped when the gain in weight was 290 g. or 95% of the theoretical amount required for the addition of four atoms. The product was partially purified by one distillation at reduced pressure, and the boiling range of the material retained for use was 150°-173°C. at 24 mm. pressure. In another run, which had absorbed only 85% of the theoretical amount of chlorine, there was produced a

78% yield of product boiling at 153°-157°C. at 16 mm. In another case it was found that the total amount of chlorine absorbed amounted almost exactly to 100% of the theoretical amount. This product was used for the preparation of 3,4-dichloro-2-furoic acid and was not distilled.

Thermal Decomposition of Ethyl 2,3,4,5-Tetrachlorotetrahydro-2-furoate.

One hundred grams of ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate, prepared in a manner similar to that described in the previous section, was distilled in a metal bath at atmospheric pressure. The liquid distilled over the range 215° to 266°C. A black carbonaceous residue weighed 11 g., and 72 g. of liquid distillate was obtained. This material was redistilled in a modified Claisen flask and all distillate boiling below 140°C. at 16 mm. pressure was set aside. The remainder (42 g.) was combined with 58 g. of fresh starting material and the process repeated until almost all the material boiled below 140°C. at 16 mm. pressure.

In some cases, instead of simply being distilled at atmospheric pressure, the ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate was refluxed for some time and then distilled. From such a run there was obtained 42 g. of product distilling below 140°C. at 16 mm. pressure, starting with 125 g. of the tetrachloro ester. This was a 22% yield, assuming the product was dichlorofuroic acid.

Separation of the Isomers.

The decomposition product obtained by distillation at atmospheric pressure of ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate was redistilled fractionally using a modified Claisen flask. Several fractions of various boiling points ranging from 115°C. at 16 mm. pressure to 163°C. at 15 mm. pressure showed a tendency to deposit crystals upon cooling in ice (31). These fractions were strongly cooled in ice-salt and filtered. Fractionation and cooling were continued until only small yields, if any, of the solid were obtained upon cooling. This solid consisted essentially of the so-called χ-dichlorofuroic acid (3,5-dichlorofuroic acid). Ethyl ester

Purification of Ethyl χ-Dichloro-2-furoate (Ethyl 3,5-Dichloro-2-furoate.

The crude ethyl 3,5-dichloro-2-furoate obtained by crystallization in an ice bath, as described in the last section, was recrystallized from ethyl alcohol. The melting point of the air-dry product was 70.5°-72.5°C. The yield was 8 g. This quantity was the total amount obtained, starting with 300 g. of ethyl 2-furoate. The yield was therefore

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(31) There seemed to be some variation in different runs as to which fractions deposited crystals. In one run fractions varying in boiling point from 115°C. to 160°C. at 16 mm. pressure deposited crystals while in another run only the fractions boiling between 135°C. and 163°C. at 15 mm. pressure would partially crystallize.

only about 2%.

Preparation of 3,5-Dichloro-2-furoic Acid.

Eight grams (0.038 mole) of the purified ethyl 3,5-dichloro-2-furoate (m.p. 70.5°-72.5°C.) was dissolved in 15 cc. of absolute ethyl alcohol and this solution poured with cooling and shaking into 3.5 g. (0.088 mole) of sodium hydroxide dissolved in 35 cc. of absolute ethyl alcohol. Ten cubic centimeters of absolute ethyl alcohol was added to dilute the thick mass, and the mixture was well stirred. The sodium salt was separated by filtration, dried in air, dissolved in water, and the solution acidified. The alcoholic filtrate and washings from the sodium salt were evaporated to dryness, the solid dissolved in water, and the solution acidified. The precipitate was combined with the main portion, the whole washed with dilute hydrochloric acid and then recrystallized from water. The product was dried in a vacuum desiccator over phosphorus pentoxide. It melted at 198°-201°C. The yield was about 5.5 g. or 80% of the theoretical amount.

Preparation of 4,5-Dichloro-2-furoic Acid.

The residues remaining after the ethyl 3,5-dichloro-2-furoate was separated by freezing and filtration, were saponified with alcoholic sodium hydroxide in a manner similar to that used for the saponification of ethyl 3,5-dichloro-2-furoate.

The crude acid was purified by precipitation of the calcium salt from ammoniacal solution. The salt was filtered, suspended in water, and acidified strongly with hydrochloric acid. The resulting precipitate was reprecipitated as the calcium salt, filtered, and acidified as before. After being recrystallized several times from chloroform and from carbon tetrachloride, the acid melted at 156°-157°C., the melting point having been raised from 155°-157°C. by the last recrystallization.

Preparation of 3,4-Dichloro-2-furoic Acid.

Six hundred and four grams (2.14 moles) of crude ethyl 2,3,4,5-tetrachlorotetrahydro-2-furoate was added in small portions to 3 l. of 10% absolute alcoholic sodium hydroxide solution with shaking and cooling to avoid excessive heating. After standing with occasional shaking for two and one-half hours the solid was separated by filtration and dried in air. This material was then dissolved with the assistance of some heating in about 2 l. of water. The solution was cooled to room temperature, acidified with hydrochloric acid, and the precipitate filtered from the cooled mixture and dried. After two recrystallizations from benzene (including decolorization by charcoal in one instance), the product melted at 169°-170°C. The yield at this point was 70 g. Another recrystallization from carbon tetrachloride raised the melting point to 170°-171°C. The yield at this point was

50 g.

From the various mother liquors a quantity of material was recovered which after a partial purification by reprecipitation from ammoniacal solution with acid, melted at 145°-163°C. (softened at 130°C.) and which was probably impure 3,4-dichloro-2-furoic acid. The total yield of purified and crude material was 137 g. or 35% of the theoretical amount.

Preparation of 4-Chloro-2-furoic Acid.

a. From 4,5-Dichloro-2-furoic Acid.

This acid was obtained by the method of Hill and Jackson (4).

Two grams (0.011 mole) of 4,5-dichloro-2-furoic acid, obtained as previously described and melting at 156°-157°C., was reduced with 2 g. of zinc dust, 15 cc. of water, and 15 cc. of concentrated ammonium hydroxide solution. The mixture was refluxed for ten and one-half hours, a few cubic centimeters of concentrated ammonium hydroxide having been added after about eight hours. The zinc was separated by filtration, a few drops of a solution of calcium chloride were added to the filtrate, and the calcium salt of the unreacted dichlorofuroic acid which precipitated was separated by filtering the mixture. The filtrate was acidified with hydrochloric acid. The precipitate was found to melt much too low. Accordingly, the precipitation procedure was carried out twice more, after which the crude acid melted at 143°-145°C. After one recrystallization from water this material melted at 147°-148.5°C. The yield was 0.054 g. or 3.5%. A mixture of this substance with the β-monochlorofuroic acid (m.p. 145°-146.5°C.) produced by reduction of 3,4-dichloro-2-furoic acid, as described later, melted at 145.5°-147°C.

The calcium salts separated by filtration were warmed with hydrochloric acid. The crude product melted at 151°-154.5°C. but softened at a much lower point. The yield was 0.42 g. The material was reduced with 0.5 g. of zinc dust and ammonium hydroxide as before, except that another 0.5 g. quantity of zinc dust was added together with more ammonium hydroxide after five hours, and refluxing was continued for ten hours more. A yield of 0.058 g. or 17% of the theoretical amount was obtained. The substance melted at 146°-147°C. and a mixture with the above mentioned material obtained from 3,4-dichlorofuroic acid melted at 144.5°-146°C. The residual material was sublimed in vacuum and melted at 146°-147°C. A mixture with the material prepared from 3,4-dichloro-2-furoic acid melted at 145.5°-147°C. The total yield from 2 g. of 4,5-dichloro-2-furoic acid was 0.11 g. or 7.0% of the theoretical amount.

b. From 3,4-Dichloro-2-furoic Acid.

This substance was also prepared by the method of Hill and Jackson (4).

Forty-five grams (0.25 mole) of pure 3,4-dichloro-2-furoic acid (m.p. 170°-171°C.) was reduced by heating the acid in 500 cc. of water with 1700 g. of 1% sodium-amalgam. The temperature was held almost at the boiling point for three hours by means of an oil bath. After the first hour the amalgam was slowly stirred. Stirring was allowed to continue for about two hours more while the mixture was cooling. The solution was separated from the amalgam, filtered, and acidified with hydrochloric acid. The crude product melted at 146.5°-148°C. The yield was about 25 g. or 68% of the theoretical amount. After one recrystallization from water (with decolorizing carbon) the product melted at 147°-148°C. One recrystallization from carbon tetrachloride raised the melting point only very slightly (147.5°-148.5°C.). The yield of this highly pure material was 15.5 g. or 42% of the theoretical amount. A mixture of this material and some obtained by the same method, with which the mixed melting points of the compounds derived from 4,5-dichloro-2-furoic acid were taken, melted at 146°-147°C.

Preparation of 3-Chloro-2-furoic Acid.

A number of attempts were made to prepare this material from 3,5-dichloro-2-furoic acid before a successful method was found.

a. Attempted reduction of 3,5-dichloro-2-furoic acid with zinc and ammonium hydroxide. Reduction with zinc and ammonium hydroxide solution for twenty-two hours was almost without effect, the melting point of a small amount of recovered product being lowered by only five degrees.

b. Attempted reduction of 3,5-dichloro-2-furoic acid with iron and acetic acid. A small amount of this ammoniacal solution was separated from the zinc, acidified with acetic acid, and refluxed with iron powder for three hours but was not further reduced.

c. Attempted reduction of 3,5-dichloro-2-furoic acid with sodium-amalgam. Another small portion (2 cc.) of the ammoniacal solution was allowed to stand over 10 g. of 2% sodium-amalgam at room temperature for four hours. The solution was then acidified and extracted once with an equal volume of ether. Evaporation of the ether left a residue which melted at 95°-120°C. A mixture with furoic acid melted at 124°-126°C. The solid was dissolved in a little water. Partial evaporation of a drop of this solution produced crystals which under the microscope showed a crystal structure quite similar to that of furoic acid similarly treated. The water solution was/

evaporated to dryness and the solid, when mixed with furoic acid, softened at 125 C. and melted at 128°-130.5°C.

d. Reduction of 3,5-dichloro-2-furoic acid with zinc and hydrochloric acid. Another small sample, when acidified with hydrochloric acid and refluxed with zinc dust, gave such encouraging results that the entire quantity was treated in this manner.

The ammoniacal solution, which had been refluxed for twenty-two hours with zinc dust, had originally contained 5.2 g. of pure 3,5-dichloro-2-furoic acid (m.p. 198°-201°C.). A considerable quantity of this solution had however been withdrawn for tests of various sorts. The total quantity of zinc which had been added was 10 g. The solution was acidified with 5 cc. of concentrated hydrochloric acid and refluxed for twenty-six hours, being kept distinctly acidic to Congo-red. The melting points of the solids obtained from small test samples were:

After 17 hours	129°-137°C.
After 20 hours	140°-147°C.
After 26 hours	142°-147°C.

The mixture was then acidified strongly, filtered hot, and extracted several times, with a total of about 200 cc. of ether. The ether was distilled and the residue recrystallized from a little hot water. The crystalline product melted at 149.5°-151°C. A second recrystallization from water raised the melting point to 150°-151.5°C. Two more recrystallizations from a mixture of benzene and ether (by evaporation of the ether) raised the melting point to 153°-154°C. and one more recrystallization from benzene and ether by the same method raised the melting point to 153.5°C. - 154.5°C. The yield of the highly purified material was about 0.6 g.

Anal. Calc'd for $C_5H_3O_3Cl$: Cl, 24.23
Found: Cl, 24.54, 24.79.

Reduction of 3-Chloro-2-furoic Acid.

In order to show that the halogen in this compound is readily affected by sodium-amalgam in water, 0.2 g. of this material, which melted at 152°-154°C. (m.m.p. with analyzed material, 153°-154°C.) was suspended in 10 cc. of water and the suspension allowed to remain in contact with 10 g. of 1% sodium-amalgam at room temperature. The mixture was shaken until all the acid had dissolved and then allowed to stand with occasional shaking until a total of about two hours had elapsed from the beginning of the reaction. The aqueous portion was separated, acidified with hydrochloric acid, and well extracted with ether. Evaporation of the solvent left 0.15 g. of a solid which melted at 102°-148°C. (mostly liquefied at 130°C.). Although pure furoic acid was not isolated, there is no doubt that the halogen was quickly removed by this reagent, even at room temperature.

Attempt to Prepare 2,3-Furandicarboxylic Acid from 3-Chloro-2-furoic Acid.

A mixture of 0.55 g. of the highly purified 3-chloro-2-furoic acid (m.p. 153.5°-154.5°C.), 1 g. of cuprous cyanide, 1 g. of potassium cyanide, and 5 cc. of water was sealed in a tube of about 100 cc. capacity. The tube was heated to a temperature of 200°-280°C. for 24 hours. No dicarboxylic furan was isolated, and it is possible that the temperature was too high. The experiment was not repeated because of lack of material and because later events showed it to be unnecessary.

Conversion of 4-Chloro-2-furoic Acid to 2,4-Furandicarboxylic Acid.

Run 1. The 4-chloro-2-furoic acid used in this run melted at 146.5°-147°C. and was prepared by reduction of crude 3,4-dichloro-2-furoic acid by means of sodium-amalgam in water at or near the boiling point.

A mixture of 1.4 g. (0.0096 mole) of the above-mentioned acid, 1.4 g. (0.0078 mole) of cuprous cyanide, 1.4 g. (0.021 mole) of potassium cyanide, and 10 cc. of water was heated in a sealed tube of 120 cc. capacity for twenty-seven hours at temperatures ranging from 210° to 250°C. Much apparently free copper was observed in the tube. After warming for about ten minutes with 30 cc. of 5% sodium hydroxide solution, the mixture was filtered. The filtrate was well extracted with ether and this solution dried by shaking with anhydrous sodium sulfate. The ether was distilled and the solid product was boiled with decolorizing carbon in a few cubic centimeters of water, filtered, the water evaporated, and the solid recrystallized from water. Since the melting point was quite low for 2,4-furandicarboxylic acid, the material was esterified with diazomethane to produce a solid melting at 98°-103°C. After one recrystallization from water, it melted at 107°-109°C. A mixture with pure dimethyl 2,3-furan dicarboxylate melted at 106.5°-109°C. The melting point of the known sample was 108°-109°C. The yield of pure ester was 0.006 g. This is a yield of 0.4%.

Run 2. The 4-chloro-2-furoic acid used in this run was prepared in a very careful manner. The ethyl furoate employed as starting material boiled over a range of one degree, and the 3,4-dichloro-2-furoic acid obtained from it was recrystallized twice from benzene and once from carbon tetrachloride. It melted then at 170°-171°C. The details of the preparation of this compound are given elsewhere in this thesis.

The 4-chloro-2-furoic acid produced from this material by reduction with sodium-amalgam was highly purified. The crude acid itself melted at 146.5°-148°C. and this was recrystallized from water and from carbon tetrachloride. The melting point was raised only very slightly by the last recrystallization. It was then 147.5°-148.5°C. The complete details of the preparation of this compound are to be found elsewhere in this thesis.

A mixture of 2 g. (0.0137 mole) of the highly purified 4-chloro-2-furoic acid just described, with 2 g. (0.011 mole) of cuprous cyanide, 2 g. (0.03 mole) of potassium cyanide, and 10 cc. of water was sealed in a tube of 130 cc. capacity. The mixture was heated intermittently at temperatures varying from 200° to 257°C. for a total of twenty-three hours. The tube was opened when cool, the contents were warmed for thirty minutes with 50 cc. of 5% sodium hydroxide solution, and filtered. The filtrate was acidified with concentrated hydrochloric acid until the initial precipitate redissolved. The solution was boiled with decolorizing carbon for a few minutes and filtered while hot. After cooling, it was extracted several times with a total of 400 cc. of ether. The ethereal solution was partially dried by being shaken with anhydrous sodium sulfate, filtered, and the solvent distilled. The residue was dissolved in 3 cc. of hot acetic acid, filtered, and partially evaporated by a stream of air. Decolorizing carbon was added, the solution was boiled a few minutes and filtered. Upon cooling in a refrigerator, crystals formed which were separated by filtration and carefully dried. The yield was 0.0355 g. of solid melting at 261°-265°C. with decomposition. It was however blackened at 243°C. A mixture with a sample of 2,4-furandicarboxylic acid (m.p. 266.5°-268°C. with dec.) melted at 265°-267°C. The yield amounted to 1.7% of the theoretical quantity. The dimethyl ester was prepared by means of diazomethane and after one recrystallization from water, melted at 106°-107°C. A mixture with known dimethyl 2,4-furandicarboxylate melted at 106°-109.5°C. The yield of ester was 0.0265 g. or 1% based upon 4-chloro-2-furoic acid.

DISCUSSION OF RESULTS

The establishment of the structures of the various dihalogenated and β-monohalogenated furoic acids culminates an extensive study by a number of investigators. Much that was done was unsuccessful but much of value was learned.

In this thesis are described the preparation and properties of the now definitely established 2,3-dibromofuran. Its constitution is known by its preparation from 4,5-dibromo-2-furoic acid.

The structure of 2-nitro-3-bromofuran derived from 2,3-dibromofuran by replacement of the bromine in the α-position may also be considered as established. That it was the α-bromine and not the β-bromine atom that was replaced requires no proof in view of the much greater reactivity of a halogen in the α-position (32).

The positions assumed by a number of chloromercuri groups are also now known as a result of their replacement by halogens and by comparison of the product with the corresponding halogen compounds. These reactions will be discussed later.

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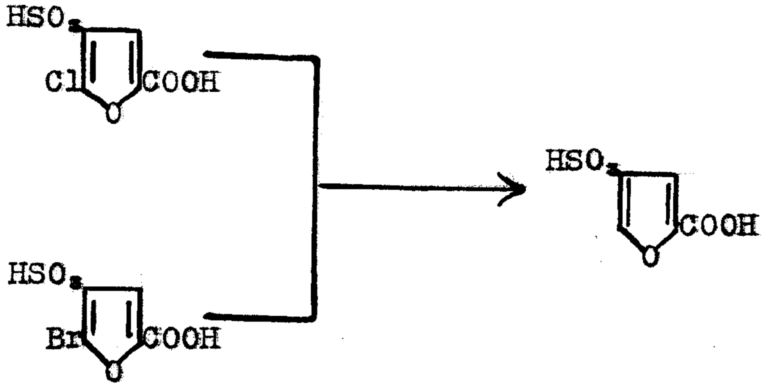
(32) Gilman, Burtner, and Wright, J. Am. Chem. Soc., 54, 1696 (1932); and Gilman, Mallory, and Wright, J. Am. Chem. Soc., 54, 733 (1932).

An extensive series of reactions has been carried out by Gilman and Brown (33). They have been able to convert 4-sulfo-5-chloro-2-furoic acid (20) into the known 4,5-dichloro-2-furoic acid by means of phosphorus pentachloride. Thus by direct substitution the sulfonic acid group enters the 4-position. Furthermore, Gilman and Brown have shown that the sulfonic acid group goes to the same position in 5-bromo-2-furoic acid (34), since they have obtained the identical 4-sulfo-2-furoic acid by reduction of the halogens from the two compounds.



The following series of transformations has also been accomplished by Gilman and Brown. The structures are established by the work presented in this thesis.

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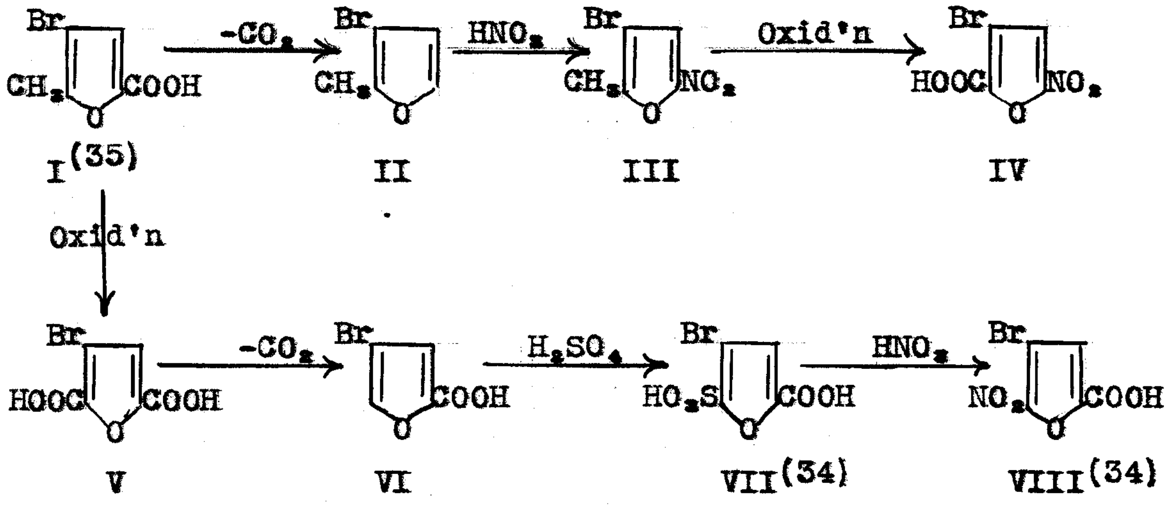
(33) Gilman and Brown, unpublished data.
(34) Hill and Palmer, Proc. Am. Acad. Arts Sci., 23, 188 (1888).



The key to this entire series is in the now known structure of 4-bromo-2-furoic acid (VI). In the sulfonation of this compound it may be safely assumed that the sulfo group has entered the 5-position in preference to the 3-position. Substitution in the α-position is in general much the more easily accomplished. Furthermore, according to Hill and Sanger (3), 4-bromo-2-furoic acid is so easily substituted in the 5-position that it forms 4,5-dibromo-2-furoic acid when merely exposed at room temperature to the vapors of bromine.

The ionization constants for the various chloro acids as determined by Catlin (36) show regular behavior in all but one case when the correct structures are used. The corrected series follows, together with the differences

(35) Hill and Jennings, Am. Chem. J., 15, 159 (1893).
(36) Catlin, Doctoral Thesis, Iowa State College Library (1934).

between successive values of -log K.

TABLE I

Correlation of Ionization Constants with Structure

Acid	-Log K	Difference	Calculated
2-Furoic	3.125		
5-Chloro-2-furoic	2.831	0.294	
4-Chloro-2-furoic	2.690	0.141	
3,5-Dichloro-2-furoic	2.604	0.086	2.539
4,5-Dichloro-2-furoic	2.423	0.181	2.396
3,4-Dichloro-2-furoic	2.398	0.025	

It may be seen that the ionization constant increases as one halogen atom moves nearer the carboxyl group, and when both halogen atoms are as near to it as possible the ionization constant is at the maximum for the series. It seems strange, however, that the value for 4,5-dichloro-2-furoic acid should fall above that for 3,5-dichloro-2-furoic acid. The very good relationship between the calculated and observed values presents strong evidence for the correctness of the data.

SUMMARY

1. The structures of the various dibromo-, dichloro-, β-monobromo-, and β-monochloro-2-furoic acids have been determined.

2. The structures of a number of other furan compounds are now known and can be used as reference compounds.

3. Added evidence is produced for the conclusion that orientation in the β-position in furan follows the rules governing orientation in benzenoid chemistry.

B. FURAN MERCURIALS AND DERIVED TYPES

INTRODUCTION

The discovery by Frankland, in 1850, of the first compound known to have a mercury atom attached directly to a carbon atom (1) was the beginning of a vast amount of investigation of the preparation and properties of such compounds. Although interest seems to have been directed largely to the effects of such mercury-containing organic compounds upon biological processes, they are, together with all other organometallic compounds, of interest as well to synthesists as intermediates for the production of metal-free organic compounds.

In the chemistry of furan, compounds having mercury attached to the nucleus are of both theoretical and practical importance. The ease with which furan has been mercurated has been a factor tending towards belief that furan has superaromatic properties (2). In a practical way they have been found to be excellent derivatives for the identification and stabilization of some furan compounds (2).

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(1) Frankland, J. Chem. Soc., 3, 322 (1850) and Ann., 77, 221 (1851).
(2) Gilman and Wright, J. Am. Chem. Soc., 55, 3302 (1933).

The history of furan mercurials is short and of recent beginning. That this should be true seems the more strange when it is recalled that thiophene was mercurated as far back as 1892, by Volhard (3).

The first compound in which mercury was known to be attached directly to a furan ring was made by Ciusa and Grillio (4). From furan and mercuric acetate they prepared tetraacetoxyfuran, and from it tetrachloromercurifuran. By replacement of the mercury-containing groups, they obtained tetraiodofuran.

Shepard, Winslow and Johnson (5) have prepared a mixture of mercuration products of furoic acid by means of the reaction with mercuric acetate in aqueous solution. The acetoxymercuri groups were converted to chloromercuri groups. These groups were replaced by iodine but the resulting mixture of iodofurans could not be satisfactorily separated.

Furfural diacetate was mercurated by means of mercuric acetate in acetic acid solution by Scheibler, Jeschke, and Beiser (6). They obtained triacetoxymercurifurfural diacetate in 82% yield but they state that the product was contaminated with an impurity which could not be removed by

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(3) Volhard, Ann. 267, 172 (1892).
(4) Ciusa and Grillio, Gazz. chim. ital., 57, 323 (1927).
(5) Shepard, Winslow and Johnson, J. Am. Chem. Soc. 52, 2083 (1930).
(6) Scheibler, Jeschke and Beiser, J. prakt. chem., 136, 232 (1933).

washing with water because the mercurial was decomposed. They converted the material into the chloride and were able to obtain this compound in a pure state. Replacement of the chloromercuri group by iodine produced a mixture of iodinated furaldehydes, but the only one isolated was a monoiodo compound which they thought might be 5-iodo-2-furaldehyde. There is good reason to doubt that the halogen is in the 5-position. If the original compound was pure trichloromercurifurfural diacetate, then to produce 5-iodo-2-furaldehyde one of three things must have occurred:

1. Two of the three chloromercuri groups must have been replaced by hydrogen atoms prior to the iodine treatment. That these should both be groups attached to β-positions while a group in the α-position remains untouched, is contrary to what is known of the relative ease of such scissions(2). Furthermore, no reagent of sufficient potency to effect this scission was present. Acetic acid has little or no effect upon such compounds unless heated to a high temperature under pressure (7).

2. Two of the three iodine atoms of triiodo-2-furaldehyde or the diacetate must have been replaced by hydrogen atoms. Again it is unlikely that this reduction should involve

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(7) Whitmore, "Organic Compounds of Mercury," The Chemical Catalog Co., Inc., New York, 1921, p. 41.

β-halogen atoms leaving a halogen atom in the more reactive α-position untouched.

3. The molecule must have been stripped to furfural or furfural diacetate and the product directly iodinated. Conditions for replacement of the chloromercuri groups were not present prior to the treatment with iodine, and accordingly no furfural or furfural diacetate was obtainable directly from the mercurial. If the initial reaction was the formation of triiodofurfural diacetate, it is very remotely possible that it might have been reduced to furfural, which was subsequently directly iodinated to form 5-iodo-2-furaldehyde. The conditions probably necessary for such direct iodination were, however, not present.

It seems more probable that the monoiodo compound of Scheibler and coworkers was 4-iodo-2-furaldehyde formed by reduction of triiodo-2-furaldehyde. That conditions for reduction were present is apparent when it is recalled that furfural itself is a reducing agent. By analogy with the behavior of chloro- and bromofuroic acids, the iodine atoms in the 3,5-positions would be the most easily reduced.

Wright (8) attempted to obtain 3,4-diiodofuran by splitting off the two α-chloromercuri groups of tetrachloro-

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(8) Wright, Doctoral Thesis, Iowa State College Library (1932), page 85.

mercurifuran with sodium cyanide and treating the product with iodine. He was not successful.

The most complete work on the mercurials of furan has been done by Gilman and Wright (2). These authors have prepared a variety of furan mercurials both by direct substitution of a hydrogen atom and by displacement of a carboxyl group by a mercury-containing group. They have, moreover, conducted an extended investigation of the reactions of such products as they have obtained. Among their accomplishments is the preparation of the first monomercurated furan having the mercury-containing group attached to a β-carbon atom. This result was accomplished by means of a rearrangement, the full nature of which is not yet fully elucidated. Their final products were pure and the structures proved.

The reactions of some furan mercurials with ketene were investigated by Gilman, Woolley, and Wright (9). This reagent was found to react with several simple furan mercurials to produce the corresponding ketone. These cases are possibly, according to these investigators, the first ones in which an organomercury compound has reacted with a carbonyl group by addition.

Burtner (10) prepared 2,5-dimethyl-3-chloromercurifuran

(9) Gilman, Woolley and Wright, _J. Am. Chem. Soc._, _55_, 2609 (1933).

(10) Burtner, Doctoral Thesis, Iowa State College Library (1933).

as a derivative of 2,5-dimethyl furan. From it he prepared 2,5-dimethyl-3-iodofuran and 2,5-dimethyl-3-bromofuran by replacement of the chloromercuri group by the corresponding halogens. The same author was unable to obtain a mercurial by treatment of 2,5-dimethyl-3,4-furandicarboxylic acid with mercuric acetate in water.

Gilman and VanderWal (11) used the method of Gilman and Wright (2) to prepare 2-chloromercuri-3,4-dichlorofuran from 3,4-dichloro-2-furoic acid.

The decarboxylation procedure of Gilman and Wright (2) was used by Gilman and Burtner (12) to prepare 2-bromo-3-furoic acid from 5-bromo-2,4-furandicarboxylic acid. What was probably the sodium salt of 2-chloromercuri-4-furoic acid was used by these authors as an intermediate in the preparation of 2-bromo-4-furoic acid. They also prepared 3-methyl-2-furylmercuric chloride from 3-methylfuran using the method of Gilman and Wright (2).

In connection with experiments on the structure of Carlina-oxide, Gilman, Van Ess and Burtner (13) prepared α-(γ-phenylpropyl)-α'-furylmercuric chloride from phenylfurylpropane by means of a buffered solution of mercuric chloride.

(11) Gilman and VanderWal, *Rec. trav. chim.*, *52*, 267 (1933).
(12) Gilman and Burtner, *J. Am. Chem. Soc.*, *55*, 2903 (1933).
(13) Gilman, Van Ess and Burtner, *J. Am. Chem. Soc.*, *55*, 3461 (1933).

Gilman and Calloway (14), by means of acetyl chloride, replaced the chloromercuri group of 2,5-dimethyl-3-chloromercurifuran by an acetyl group to obtain 2,5-dimethyl-3-furyl methyl ketone. The same authors prepared several 5-alkyl-2-chloromercurifurans which they report as being decomposed over a period of three months. They also prepared several other ketones from 2-chloromercurifuran and the corresponding acid chlorides.

Gilman, Calloway and Burtner (15) prepared both 3-isopropyl-2-chloromercurifuran and 4-isopropyl-2-chloromercurifuran by the general methods outlined by Gilman and Wright(2).

Gilman and Burtner (16) prepared 5-tertiarybutyl-2-chloromercurifuran from both 5-tertiarybutyl-2-furoic acid and 2-tertiarybutyl furan.

Lowe and Hamilton (17) employed furan mercurials in the preparation of some furan arsenicals.

Paul (18) mercurated some 2-alkylfurans with a buffered solution of mercuric chloride. His products were well characterized and could be titrated with iodine in ethyl acetate solution.

(14) Gilman and Calloway, J. Am. Chem. Soc., 55, 4197 (1933).

(15) Gilman, Calloway and Burtner, J. Am. Chem. Soc., 57, 906 (1935).

(16) Gilman and Burtner, J. Am. Chem. Soc. 57, 909 (1935).

(17) Lowe and Hamilton, J. Am. Chem. Soc., 57, 1081 (1935). See also Gilman and Kirkpatrick, Proc. Iowa Acad. Sci. 39, 176 (1932) [C.A. 28, 6714 (1934)] .

(18) Paul, Bull. soc. chim. [5], 2, 2220 and 2227 (1935).

Reddy (19) and Wilson and Reddy (20) have used mercury-containing substances involving the furan ring for seed treatment with some success. The true nature of the materials was not determined.

TECHNIQUE AND OBSERVATIONS

A fairly good method for the mercuration of some furan compounds is to fuse the material with mercuric acetate. The procedure is similar to that employed by Whitmore and Isenhour (21) in the mercuration of diethyl terephthalate. By this means several compounds have been mercurated in the less reactive β-position. Although polymercuration probably does occur, the yields of monomercurials have, for the most part, been fairly good when such products were desired. The method is applicable to esters, which are stable liquids at temperatures of 125°-150° C., and probably to other types of compounds which exhibit these characteristics. Those esters which have been successfully mercurated in this manner have all been esters of 5-substituted-2-furoic acids. Ethyl furoate apparently mercurates but the number and positions of substituents have not been determined.

Many furan mercurials, and in particular those α, α', β-trisubstituted furans in which the β-position is occupied by chloromercuri or acetoxymercuri groups, are very difficult

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(19) Reddy, Phytopathology, 20, 147 (1930).
(20) Wilson and Reddy, Phytopathology, 21, 1099 (1931).
(21) Whitmore and Isenhour, J. Am. Chem. Soc., 51, 2785 (1929).

to purify. No solvent is good in all cases but those that have been the most useful are acetone, acetone-water mixtures, ethyl alcohol and mixtures of it with water, n-propyl alcohol, n-butyl alcohol and, for acetoxymercuri compounds, acetic acid. In some cases purification can be effected by dissolving the mercurial in a suitable solvent such as acetone, partially precipitating it with water, filtering, and then completely precipitating the compound with more water. Chloromercuri compounds are, in general, more easily purified than the corresponding acetoxymercuri compounds. Poly chloromercurated furans are exceedingly insoluble in ordinary solvents. Poly acetoxymercuri compounds may, however, be somewhat soluble in acetic acid.

In replacing mercury-containing groups with halogens, the use of chlorine is to be avoided since it shows a great tendency to add to the unsaturated furan nucleus. Iodine and bromine show a less pronounced tendency to form addition compounds. Carbon tetrachloride is recommended as a solvent or suspension medium in the replacement of the mercury-containing group by bromine. Mercuric bromide is extremely insoluble in this solvent, while in many cases the halogenated furan compound produced is soluble. The mercury salts may be separated by filtration and the filtrate concentrated to secure the compound. The same solvent is useful for separation of mercuric iodide from iodinated furan compounds.

EXPERIMENTAL

Preparation of Ethyl 2-Methyl-4,5-dichloromercuri-3-furoate.

Forty grams (0.26 mole) of ethyl 2-methyl-3-furoate boiling at 80°-90°C. at 23 mm. pressure was dissolved in 100 cc. of 95% ethyl alcohol. This mixture was added slowly, with shaking, to 3500 cc. (0.7 mole) of a mercurating solution of mercuric chloride and sodium acetate (22) at a temperature of 35°-40°C. A white precipitate slowly formed which increased in amount overnight. The mixture was then heated to boiling on an oil bath and refluxed for ten hours. The following day the solid was filtered and sucked as dry as possible and then refluxed, with stirring, with 1500 cc. of 90% ethyl alcohol for 5 hours. After the mixture had cooled, the solid was filtered and dried in air. The yield was 158 g. or 97.5% of the theoretical amount. The product was white and rather fluffy.

A portion of the material, produced in approximately the same manner, the essential difference being a larger proportion of mercurating solution, was analyzed.

(22) This mercurating solution is similar to that used by Gilman and Wright, [J. Am. Chem. Soc., 55, 3302 (1933)] for the mercuration of furan and some of its derivatives and is made up as follows: To a solution of 135 g. of mercuric chloride in 1000 cc. of water, heated to dissolve and then cooled to about 40°C. or until crystallization begins, is added a solution of 272 g. of sodium acetate trihydrate in 400 cc. of water. After cooling and standing for a few hours, the solution is filtered and diluted to 2500 cc. with distilled water.

Anal. Calc'd for $C_8H_8O_3(HgCl)_2$: Hg, 64.26

Found: Hg, 69.68, 68.76.

Ten grams of the same material was extracted in a Soxhlet extractor for several hours with alcohol. Upon completion of this process, the residue was extracted with acetone and the product was analyzed for mercury.

Anal. Calc'd for $C_8H_8O_3(HgCl)_2$: Hg, 64.26

Found: Hg, 65.09, 64.87.

Preparation of Ethyl 2-Methyl-4,5-dibromo-3-furoate.

This compound was not isolated but was hydrolyzed directly to the corresponding acid. Occasionally it was partially purified by steam distillation but this procedure was not necessary. The details of a successful preparation follow:

To 160 g. (0.26 mole) of ethyl 2-methyl-4,5-dichloromercuri-3-furoate prepared as described above and suspended by rapid stirring in 1200 cc. of dry carbon tetrachloride, was added a solution of 79 g. (1 mole) of bromine (U.S.P.) in 300 cc. of dry carbon tetrachloride. The addition was completed in three hours. After being filtered, the carbon tetrachloride was distilled (a good column should be used) and the residue was steam distilled. The aqueous layer was extracted with ether and the ether solution was combined with the oil. The ether solution was again filtered and the ether was removed by distillation. The residue consisted of 25 g.

of clear brownish oil, which probably contained much of the desired ester. If it was pure ester, the yield was 31% of the theoretical amount. In some cases the oil was not steam distilled but was filtered from a white crystalline solid. This melted at 179°-180° C. and was not investigated further.

Preparation of 2-Methyl-4,5-dibromo-3-furoic Acid.

The crude ester described above was hydrolyzed, using alcoholic sodium hydroxide, to produce this material. The hydrolysis proved to be difficult and unreliable. The best method found was as follows:

Two and one-half grams of the crude ester was chilled in an ice bath and 10 cc. of 10% alcoholic sodium hydroxide was added quickly, with cooling and shaking. The mixture was then heated rapidly to 50° C. and held there for 20 minutes, with occasional shaking. To this was added 20 cc. of water, and the solution extracted with ether, shaken with decolorizing carbon (without heating), filtered, and acidified using concentrated hydrochloric acid, with shaking and cooling. The crude acid which precipitated was removed by filtration. The total yield from 20.5 g. of crude ester hydrolyzed in 2.5 to 8 g. portions was 5 g. of crude acid, which was completely melted at 175° C. This is a yield of 27% of the theoretical amount. The acid may be purified by recrystallization from benzene. The melting point of material thus purified was 186°-189° C.

Neutralization equivalent Calc'd for $C_6H_4O_3Br_2$: 284

Found: 280 and 286.

Anal. Calc'd for $C_6H_4O_3Br_2$: Br, 56.31

Found: Br, 56.51.

Preparation of 4,5-Dibromo-2,3-furandicarboxylic Acid.

The acid chloride of 2-methyl-4,5-dibromo-3-furoic acid was prepared by refluxing 8 g. (0.028 mole) of the acid with 50 g. (0.4 mole) of thionyl chloride for 10 hours. The excess thionyl chloride was distilled and the residue was washed with a little benzene into a 250 cc. corex three-necked flask. It was then subjected to a reduced pressure for about 45 minutes at 100° C. or above to eliminate the benzene. To this material was added, with rapid stirring, 5.0 g. (0.031 mole) of bromine at a temperature of 120°-140° C. (the temperature measured was that of the sulfuric acid bath) with a corex ultra-violet lamp within ten inches of the flask. The flask held a reflux condenser as well. The total time consumed by the addition of bromine was three hours. The oily product was then refluxed for one and one-half hours with 250 cc. of water, and the resulting mixture was extracted thoroughly with ether. Upon distillation of the ether a semi-solid remained.

To this material was added 250 cc. of water and the silver oxide from 22.5 g. of silver nitrate. This mixture, in a three-necked flask equipped with a mercury-sealed stirrer and a reflux condenser, was made alkaline with sodium bicarbonate and boiled for five hours. It was then made strongly alkaline and filtered, the filtrate shaken with decolorizing carbon, again filtered, and acidified with dilute sulfuric acid. The solution was extracted with ether and the ether distilled. The crude product weighed 3.5 g. It was purified by being dissolved in ether, followed by the addition of 20 cc. of benzene and by slow evaporation of the ether. After one such purification the product was white. The melting point was 242°-243°C. with decomposition. The product was dried in air.

Neutralization equivalent Calc'd for $C_6H_2O_5Br_2$: 157
Found: 161.

Anal. Calc'd for $C_6H_2O_5Br_2$: Br, 50.92
Found: Br, 51.36, 51.32.

Preparation of 2-Hydroxymethyl-4,5-dibromo-3-furoic Acid.

This compound was obtained in several cases when the acid chloride of 4,5-dibromo-2-furoic acid was treated with bromine. It doubtless resulted from the introduction of only one atom of bromine instead of two into the methyl group, with subsequent hydrolysis to the hydroxymethyl group instead of to the aldehyde group.

Method 1. Fourteen grams (0.046 mole) of the acid chloride of 2-methyl-4,5-dibromo-3-furoic acid, which boiled at 117°-137°C. at 4 mm. pressure, was treated with 14.5 g.

(0.09 mole) of bromine, the bromine being added dropwise over a four hour period. The temperature of the liquid was 130° C., and rapid stirring was kept up throughout the run. After the addition of the bromine, the heating and stirring were continued for one half hour. The reaction flask was furthermore subjected to ultra-violet light from a powerful source during the entire reaction. The product was hydrolyzed by boiling for three hours with 500 cc. of water, and the residue obtained by evaporation of an ether extract of this mixture solidified.

Since it was hoped that this material contained the desired 3-carboxy-4,5-dibromo-2-furfural, the solid residue was oxidized with the silver oxide from 37.1 g. (0.22 mole) of silver nitrate, in 400 cc. of alkaline solution. The mixture, kept alkaline with sodium carbonate, was boiled for four hours with stirring. After cooling, the filtered solution was acidified and the precipitated solid separated by filtration. It was combined with the residue obtained by evaporation of an ether extract of the mother liquor. The combined solids were redissolved in ether, 50 cc. of benzene added, and the ether evaporated. Five grams of a solid melting at 160°-165° C. was obtained. The melting point was raised to 195°-198° C. by the same method. The yield of this product was 2 g. or 14.5% of the theoretical amount.

Neutralization equivalent Calc'd for $C_6H_4O_4Br_2$, 300

Found, 295.

Anal. Calc'd for $C_6H_4O_4Br_2$: Br, 53.30

Found: Br, 54.26, 54.26.

Method 2. The same product was obtained when the acid chloride of 2-methyl-3-furoic acid is brominated, using ferric chloride and ultra-violet light as catalysts. The product in this case melted at 192°-195°C. and gave a neutral equivalent of 301. A mixture with the product obtained by Method 1 melted at 197°-200°C.

Preparation of 3-Carboxylic-4,5-dibromo-2-furfuryl Acetate.

Approximately one half gram of 2-hydroxymethyl-4,5-dibromo-3-furoic acid melting at 195°-198°C. was refluxed for one hour with 3 cc. of acetyl chloride. At the end of this time the solution was poured slowly into 50 cc. of water. The aqueous solution was extracted with ether, and the ether was distilled leaving the ester in acetic acid solution. The acetic acid was diluted with hot water and the compound crystallized upon cooling. The solid melted at 143°-146°C.

Anal. Calc'd for $C_8H_6O_5Br_2$: Br, 46.75

Found: Br, 46.64, 46.73.

Preparation of 2-Nitro-3-bromofuran.

Two grams of 2,3-dibromofuran boiling at 158°-162°C. was exposed to nitrous oxide vapors for eight hours at a temperature of about 40°C. The crystalline product was recrystallized twice from alcohol and then melted at 74.5° - 76° C. The yield was 0.5 g. or 34% of the theoretical amount. The compound crystallized from alcohol in short, thick, slightly yellowish needles.

Anal. Calc'd for $C_4H_2O_3NBr$: Br, 41.64
Found: 41.23, 41.51.

Preparation of Some Halogenated 2-Chloromercurifurans from the Corresponding Carboxylic Acids.

Several halogenated furan mercurials were prepared according to the method of Gilman and Wright (2) by refluxing a solution of the sodium salt of the corresponding halogenated 2-furoic acid with a solution of mercuric chloride. The products were recrystallized from alcohol.

TABLE I

Some Halogenated 2-Chloromercurifurans

Compound derived	M.P.	Acid used	Anal. % Hg		Yield
			Calc'd	Found	
3,4-Dichloro-2-chloromercurifuran	172°-173° C.	3,4-dichloro-2-furoic acid	53.93	55.10 54.93	69%
4,5-Dichloro-2-chloromercurifuran	182° - 182.5° C.	4,5-dichloro-2-furoic acid	53.93	54.34 54.42	46%
3,5-Dichloro-2-chloromercurifuran	123°-124° C.	3,5-dichloro-2-furoic acid	53.93	54.32 54.46	97%

Preparation of Methyl 4-Chloromercuri-5-bromo-2-furoate.

To 50 g. (0.244 mole) of methyl 5-bromo-2-furoate, which melted at 65°-67° C., in a three-inch test tube heated in an oil bath, was added 80 g. (0.25 mole) of mercuric acetate. The salt was added in small quantities over a period of one half hour. The temperature of the mixture was 145°-155° C. and it was stirred with a thermometer. It became quite thick when about three fourths of the salt was added. After the addition was completed, the mixture was heated for about five minutes more. It was then refluxed with 500 cc. of acetone in a flask equipped with a return condenser and a mechanical stirrer. The solution was separated by filtration and the residue reextracted with 350 cc. of acetone. The residue weighed 35 g.

To the combined filtrates was added, with shaking, a solution of 30 g. of calcium chloride dissolved in 125 cc. of 80% alcohol. A white solid precipitated from the acetone solution. The acetone was concentrated on a steam bath to about 400 cc. and diluted to 2 liters with water. The mixture was allowed to stand overnight in a refrigerator and filtered. The solid melted at about 200°-210° C. It was dissolved in 500 cc. of hot acetone, boiled with decolorizing carbon, and filtered. Addition of hot water until precipitation was incipient, filtration, and cooling produced 14 g. of a white solid precipitate melting at 233°-

235°C. Recrystallization of this material in the same manner raised the melting point to 234°-235°C. Dilution of the first mother liquor produced 18.5 g. of solid melting at 226°-228°C. The entire yield of material melting between 226°C. and 235°C. was 32.5 g. or 30% of the theoretical yield of mercurial.

Concentration of the acetone-water mother liquor in a vacuum produced 9 g. of what was probably impure methyl 5-bromo-2-furoate melting at about 59°-72°C.

<u>Anal.</u> Calc'd for $C_6H_4O_3HgClBr$: Hg, 45.59

Found: Hg, 45.74, 45.49.

<u>Conversion of Methyl 4-Chloromercuri-5-bromo-2-furoate to 4,5-Dibromo-2-furoic Acid.</u>

Eleven and one-half grams (0.026 mole) of the mercury compound melting at 233°-235°C. was suspended in 100 cc. of carbon tetrachloride in a mechanically stirred flask. To this suspension was added in one hour a solution of 4.2 g. (0.0525 mole) of bromine in 25 cc. of carbon tetrachloride. After the mixture had been stirred for two hours more, the solvent was separated by filtration and the residue washed with carbon tetrachloride. The filtrate and washings were extracted with sodium thiosulfate solution and most of the carbon tetrachloride removed by distillation at atmospheric pressure. The remainder was removed over a gentle heat at reduced pressure. The residual material was stirred for five minutes with 20 cc. of 10% alcoholic sodium hydroxide solution, 50 cc. of water was added, and the alcohol-water solution of the sodium salt was extracted with ether. The aqueous portion was strongly acidified with hydrochloric acid and the precipitated solid was separated by filtration and dried. The melting point of the crude acid was 161°-163° C. The yield was 3.5 g. or 50% of the theoretical amount. The melting point was raised by recrystallization from benzene to 166°-167° C. and a mixed melting point with a pure sample of 4,5-dibromo-2-furoic acid was not depressed.

Reaction of Methyl 4-Chloromercuri-5-bromo-2-furoate with Ketene.

Run 1. Eighteen and one-half grams of the mercurial, melting at 226°-228° C., was treated for five hours in 150 cc. of dry acetone with ketene produced at the rate of about one tenth mole per hour. Twelve grams of a solid melting at 205° C., which melted when mixed with pure mercurial at 218°-220° C. was recovered, together with 2 g. of a solid melting at 220° C., the mixed melting point being in this case 228°-229° C. These fractions were undoubtedly unchanged mercurial. The recovery amounted to 76%. No ketone was isolated.

Run 2. Ketene was generated at the rate of 0.1 mole per hour for four hours and liquefied in a solid carbon dioxide - ether mixture. The total gain in weight was 12.5 g. or 0.3 mole, but some of this material was probably acetone. The liquid was sealed in a tube containing 4.4 g. (0.01 mole) of the mercurial (m.p. 229°-231°C.) and allowed slowly to warm to room temperature in a beaker of chloroform cooled to -60°C. at the start. After seventeen hours the tube was opened and the contents steam distilled. No product separated in the distillate, which was not examined further. The solid residue was reprecipitated from acetone with water and melted from a point somewhat below 185°C. to 195°C. A mixture with pure mercurial melted at 195°-201°C. The yield was 1.5 g. and it was probably impure mercurial. The recovery was therefore 34%. No ketone was isolated.

Reaction of Methyl 4-Chloromercuri-5-bromo-2-furoate with Acetyl Chloride.

This experiment was carried out in the hope that the chloromercuri group would be replaced by an acetyl group. Actually the chloromercuri group was eliminated entirely and the bromine was replaced by chlorine.

Eight and eight-tenths grams (0.02 mole) of the dry mercurial melting at 229°-231°C. was sealed in a tube with 15.6 g. (0.2 mole) of reagent quality acetyl chloride and heated to 100°-125°C. for six hours. The contents of the tube were filtered and the residue washed several times with ether. The combined filtrate and washings were again filtered and the solvents distilled. Water was added to the residue and the mixture distilled with steam. An oily product separated from the distillate and then solidified. The crystals melted at 40°-42° C. and were identified by analysis as methyl 5-chloro-2-furoate. The yield was 1.5 g. or 47% of the theoretical amount.

<u>Anal</u>. Calc'd for $C_6H_5O_3Cl$: Cl, 22,09
Found: Cl, 22.09, 22.23.

The identity of the compound was confirmed by hydrolysis of the ester with aqueous sodium hydroxide to 5-chloro-2-furoic acid melting at 177°-178° C. A mixture with a known sample of 5-chloro-2-furoic acid melted at 177°-178° C. A mixture of some of the acid, produced similarly but in another run, with 5-bromo-2-furoic acid (m.p. 183°-185° C.) melted at 177°-179° C.

<u>Neutralization equivalent</u> Calc'd for $C_5H_3O_3Cl$: 146.5
Found: 152.

<u>Conversion of Methyl 5-Bromo-2-furoate to 5-Chloro-2-furoic Acid by Means of Acetyl Chloride and Mercuric Chloride.</u>

Four and one-tenth grams (0.02 mole) of the ester (m.p. 66 -68 C.) was sealed in a tube of 55 cc. capacity with 5.4 g. (0.02 mole) of mercuric chloride (U.S.P. powder) and 10 cc. (0.14 mole) of reagent quality acetyl chloride. The tube and its contents were heated to 110°-135° C. for five hours. The contents of the tube were washed out with ether and after the solvents were distilled, the residue was steam distilled. An oil separated in the distillate and solidified in an ice bath. The crystals melted at 42°-44°C., and this melting point was not depressed by admixture of methyl 5-chloro-2-furoate. The yield was 2.5 g. or 78% of the theoretical amount. The ester was hydrolyzed with 10% aqueous sodium hydroxide and produced 2 g. of 5-chloro-2-furoic acid melting at 178°-180°C. A mixture with 5-chloro-2-furoic acid melted at 179°-180°C.

In another run under approximately similar conditions except that a tube of 40 cc. capacity was used, there was produced 1.6 g., or 50% of the theoretical amount, of 5-chloro-2-furoic acid melting at 177°-179°C. Occasionally some 5-chloro-2-furoic acid was isolated directly from the reaction.

Reaction of Methyl p-Bromobenzoate with Acetyl Chloride and Mercuric Chloride.

Four and three-tenths grams (0.02 mole) of methyl *p*-bromobenzoate (m.p. 79°-81°C.) was heated in a sealed tube to about 175°-190°C. for several hours with 5.4 g. of mercuric chloride and 10 cc. of acetyl chloride. From the reaction there was recovered 3.5 g. of a solid melting at 247°-249°C., which was probably *p*-bromobenzoic acid(m.p. 251°C.). This corresponds to a recovery of 87%.

From another run of the same size heated at 140°C. for ten hours, there was recovered 1 g. of *p*-bromobenzoic acid and 2.5 g. of methyl *p*-bromobenzoate, which corresponds to a recovery of 83%.

It was found later that pressure plays a great part in this reaction. The capacities of the tubes used are not known so these experiments are not entirely conclusive.

Preparation of 4-Bromo-5-chloro-2-furoic Acid from 4,5-Dibromo-2-furoic Acid.

Three and six-tenths grams (0.0127 mole) of methyl 4,5-dibromo-2-furoate (prepared from pure 4,5-dibromo-2-furoic acid and melting at 57°-59°C.) was sealed in a tube with 3.5 g. of mercuric chloride (U.S.P. powder) and 10 cc. of reagent quality acetyl chloride. The capacity of the tube was 55 cc. The tube and contents were heated to 160°-165°C. for seven hours. The contents were then washed out with ether, the solvents distilled, and the residue steam distilled. The distillate was extracted with ether and the ether carefully evaporated. The residual oil was hydrolyzed with 10% alcoholic sodium hydroxide solution, care being taken to avoid much heating of the mixture. Upon dilution of the alcohol with water, followed by acidification, a solid precipitated which when recrystallized from water melted at 149.5°-151°C. The yield was 0.45 g. or 16% of the theoretical amount of 4-bromo-5-chloro-2-furoic acid. The melting point was later raised to 150°-152°C. by recrystallization from benzene. A mixed melting point of the material melting at 149.5°-151°C. with 4,5-dichloro-2-furoic acid (m.p. 155°-156°C.) was 151.5°-155°C. It was known from experience that certain halogenated furan compounds differing only in the identity of the halogen did not show a marked depression of the melting point when mixed. Therefore, the neutralization equivalent of the product derived from this reaction was determined. The molecular weight was thus found to be 233. Since the molecular weight of 4,5-dibromo-2-furoic acid is 269.8, that of 4,5-dichloro-2-furoic acid is 180.9 and that of 4-bromo-5-chloro-2-furoic acid is 225.4, it seemed likely that the compound corresponded to the last structure. This suspicion was strengthened by a mixed melting point of the highly purified compound with the compound obtained by replacement of the chloromercuri group of methyl 4-chloromercuri-5-chloro-2-furoate by bromine, followed by hydrolysis, as will be described later. This product should have the same structure and the melting point was 149.5°-150.5°C. The mixture melted at 150°-151.5°C.

Preparation of Methyl 4-Iodo-5-bromo-2-furoate.

To 20 g. (0.045 mole) of methyl 4-chloromercuri-5-bromo-2-furoate (m.p. 229°-232°C.) was added, with shaking, at room temperature a solution of 12.7 g. (0.05 mole) of iodine, and 16.6 g. (0.10 mole) of potassium iodide in 75 cc. of water. After standing for about one half hour, the excess of iodine was reduced by sodium thiosulfate. The mixture was steam distilled and 13.5 g. of crude solid was obtained. This was 91% of the theoretical amount. After several recrystallizations from methanol, the solid melted at 69°-69.5°C.

Anal. Calc'd for $C_6H_4O_3BrI$: Br, 24.15; I, 38.35
Found: Br, 24.61, 24.22; I, 38.11, 38.69.

Preparation of Methyl 4-Chloromercuri-5-chloro-2-furoate.

To 45 g. (0.28 mole) of methyl 5-chloro-2-furoate (m.p. 35°-38°C.) was added slowly 89 g. (0.28 mole) of mercuric acetate. The reaction took place in a 250 cc. beaker heated in an oil bath, and the mixture was stirred with a thermometer. The temperature of the reacting mixture was held at 142°-152°C. and the salt was added in seventeen minutes. Following completion of the addition, heating was continued for about five minutes. The cooled solid was extracted twice by boiling with 500 cc. of acetone and filtering the mixture while hot. The filtrate was kept warm to avoid premature crystallization. When both extractions were finished, a solution of 50 g. of calcium chloride in a small amount of water was added, with shaking, to the combined filtrates. Two layers were formed. The entire mixture was diluted to three liters with water and a solid precipitated. After two hours the solid was separated by filtration and recrystallized from acetone and water. The yield was 24 g. or 22% of the theoretical amount. The product was a white solid which melted at 213°-216°C., with darkening at 180°C. Another recrystallization from acetone and water raised the melting point to 215°-217°C. The compound was apparently not entirely pure since the analysis was not particularly good.

Anal. Calc'd for $C_6H_4O_3HgCl_2$: Hg, 50.71
Found: Hg, 51.99, 51.83.

Preparation of 4-Bromo-5-chloro-2-furoic Acid from 4-Chloromercuri-5-chloro-2-furoic Acid.

Eight grams (0.022 mole) of the mercurial (only partially purified, m.p. 204°-209°C.) was suspended in 25 cc. of carbon tetrachloride. A solution of 3.5 g. (0.044 mole) of bromine in 10 cc. of carbon tetrachloride was added and the mixture stirred. It was found necessary to add 15 cc. more carbon tetrachloride later because the mixture thickened. The solid was separated by filtration and the excess of bromine in the filtrate was discharged by washing with sodium bisulfite solution. After partial drying of the solution with calcium chloride, the solvent was distilled, the last small quantity being removed with an air stream. The residue was dissolved in alcohol and hydrolyzed with 5 cc. of 10% alcoholic sodium hydroxide. The mixture was allowed to react for only a few minutes. Upon dilution with water, followed by acidification, a solid precipitated which weighed 0.9 g. and melted at 147°-149°C. without purification. Recrystallization from benzene raised the melting point to 149.5 -150.5 C., and a mixed melting point with the product obtained by replacement of the α-bromine of 4,5-dibromo-2-furoic acid (23) with chlorine was 150°-151° C. Neither of these compounds has been analyzed but from the methods used for their preparation and the value of the neutralization equivalent there is little doubt of their identity.

Attempted Replacement of the Chloromercuri Group of Methyl 4-Chloromercuri-5-chloro-2-furoate by Chlorine.

A number of attempts to prepare 4,5-dichloro-2-furoic acid by this means was made. When equivalent quantities of chlorine and mercurial were employed, much apparently unchanged mercurial was recovered. When an excess of chlorine was used, the only product identified was trichlorofuroic acid, which was doubtless formed by decomposition of an addition product of methyl 4,5-dichloro-2-furoate and chlorine. Both carbon tetrachloride and acetic acid were used as solvents.

(23) This Thesis, page 92.

DISCUSSION OF RESULTS

When the carbon chain only of furan is considered, substituents in the 3-, 4-, and 5-positions may be considered as being situated with respect to a substituent in the 2-position, in what would be the ortho-, meta-, and para-positions respectively in benzene. Thus methyl 5-chloromercuri-2-furoate would correspond to methyl _p_-chloromercuribenzoate. In benzene certain groups have been found to direct entering groups to specific positions in the ring with such regularity that chemists have been able to predict the position which will be occupied by an entering group by a consideration of those groups already in the ring.

There has been a considerable amount of evidence produced for the belief that the positions entered by substituents in the β-positions of the furan ring are determined by the rules of orientation in benzenoid chemistry. A number of cases have been cited elsewhere in this thesis (24) in which substituents entering a furan ring holding a meta-orienting group in the 2-position and an ortho-para-orienting group in the 5-position have been directed to the 4-position. This would be in benzene the position meta to the meta-orienting group and ortho to the ortho-para-orienting group.

Mercuration provides probably another instance in which the rule holds good. The presence of the chloromercuri group in the 4-position in methyl 4-chloromercuri-5-bromo-

(24) This Thesis, Part A, page 37.

2-furoate has been unequivocally proved. This material was produced in 30% yield and no isomer was found although it was not sought. The ease with which pure product could be obtained is a strong indication that little or no isomer was present. The fact that isomers are seldom produced in significant amounts in reactions with furan compounds is another reason for this belief. That the purified material consisted of only one isomer is fairly well assured by the facts that the melting point was raised only slightly by the last recrystallization and that the crude product of the reaction with bromine consisted of 4,5-dibromo-2-furoic acid melting only a few degrees low. The yield was 50%. The chloromercuri group was derived from the directly substituted acetoxymercuri group under conditions which would be extremely unlikely to lead to rearrangement. The carbethoxy group is, in benzene, a group which orients substituents to the meta-position while the bromine atom orients an incoming group in benzene to the ortho- or para-positions.

The reaction of acetyl chloride and methyl 4-chloromercuri-5-bromo-2-furoate under pressure to produce methyl 5-chloro-2-furoate was utterly unexpected. It is probable that the carbon-mercury bond was first attacked by the small amount of hydrogen chloride likely to be present in the reagents. From this point the reaction is similar to that by which the bromine atom of methyl 5-bromofuroate was replaced by a chlorine atom by the use of acetyl chloride and mercuric chloride. Experiments to determine whether or not the mercuric chloride served as a catalyst were inconclusive. Pressure certainly plays a great part in the reaction, and it is recommended that in all reactions carried out in sealed tubes in which the pressure developed might depend on the capacity of the tube, this capacity be carefully recorded.

The fact that under certain conditions some hydrolysis took place to form 5-chloro-2-furoic acid suggests the use of the reaction as a method for preferential hydrolysis of compounds containing acetylated groups as well as ester groups.

In only one case was the reaction of bromine on 2-methyl-4,5-dibromo-3-furoic acid carried far enough to produce, ultimately, 4,5-dibromo-2,3-furandicarboxylic acid. Repeated attempts by the same general method but under conditions calculated to be even more favorable toward the substitution of two of the hydrogen atoms of the methyl group by bromine,produced only the corresponding hydroxymethyl compound obtained through substitution by bromine of only one atom of hydrogen followed by hydrolysis.

There is little comparable information on which to base a comparison of mercuration in furan with other substitution reactions. Furan nitrates rapidly and preponderantly in one α -position at -10°C., when an equivalent of nitrating agent is added, while polymercuration takes place slowly but in considerable degree at room temperature. However, the mercury salt is added all at once while the nitrating agent is never present in great excess. It can be said with considerable assurance that nitration in the α-position of furan proceeds more rapidly than does mercuration. Sulfonation may possibly be said to proceed less readily than mercuration since furfural diacetate is easily mercurated (6) while no product could be isolated in the case of sulfonation (25). The case may not be a fair one, however, since the furfural compounds are easily decomposed. Furoic acid is easily sulfonated at room temperature, as is also 5-bromo-2-furoic acid. No mercuration of furoic acid at room temperature by means of mercuric acetate was reported by Gilman and Wright (2) in the course of their preparation of 3-chloromercurifuran. These facts would indicate that sulfonation in either the α- or the β-positions by means of fuming sulfuric acid is more rapid than mercuration in water solution. Bromination of furfural diacetate takes place mainly in the α-position at 8°-10°C. even when more than one equivalent is present (25). As has been mentioned before, furfural diacetate mercurates readily in all three free positions when three equivalents of mercuric acetate are present. Bromina-

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(25) Wright, Doctoral Thesis, Iowa State College Library (1932).

tion then is probably less rapid in the β-position than is mercuration, although the ease of substitution in the α-position may be very nearly the same in both types of reaction.

SUMMARY

1. A number of new mercury compounds of furan have been prepared and some of their reactions investigated.

2. The fusion method of preparing mercurials has been successfully applied to furan.

3. Evidence has been added toward the conclusion that orientation in the β-positions of furan follows the same rules as apply to benzenoid chemistry.

4. An unusual replacement reaction of halogenated furan compounds has been studied.