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Some physiological properties of benzofuran and dibenzofuran derivatives

Earl Westley Smith
Iowa State College

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SOME PHYSIOLOGICAL PROPERTIES OF
BENZOFURAN AND DIBENZOFURAN DERIVATIVES

by

E. Westley Smith

A Thesis Submitted to the Graduate Faculty
for the Degree of

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Major Subject Organic Chemistry

Approved:

In charge of Major work

Head of Major Department

Dean of Graduate College

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BENZOFURAN

INTRODUCTION

Extensive work in this laboratory on the orientation and derivatives of the heterocyclic ring systems, furan and dibenzofuran, has lead very naturally to an investigation of benzofuran, a related oxygen heterocycle. In contrast to the comparatively large literature that has been built up of benzofuran derivatives through ring closure reactions, a surprisingly small amount of definite knowledge is known concerning the nuclear orientation of this heterocycle, or of its derivatives.

The presence of a partially reduced benzofuran nucleus (I) in the Gulland-Robinson structure of morphine (II) (1) suggested a study of the physiological properties of benzofuran and benzofuran derivatives in a manner similar to that carried out, for the same reason, on phenanthrene (III) (2) and dibenzofuran (IV) (3). The numbering of benzofuran that is used is indicated below in (I). This follows the rules suggested by Patterson's International Rules for Nomenclature (4).

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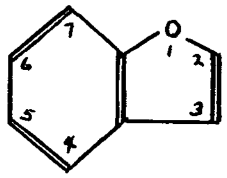
(1) Small, "Chemistry of the Opium Alkaloids", Supp. 103, Public Health Reports, 1932, p. 143.

(2) Chiefly by Eddy and co-workers. See Eddy, J. Pharmacol., 48, 183 (1933).

(3) Chiefly by Gilman and co-workers. See Bywater, Doctoral Dissertation, Iowa State College 1934, and Kirkpatrick, Doctoral Dissertation, Iowa State College 1935.

(4) Patterson, J. Am. Chem. Soc., 47, 543 (1925).



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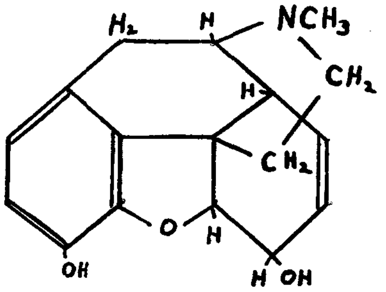

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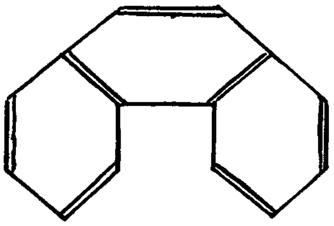

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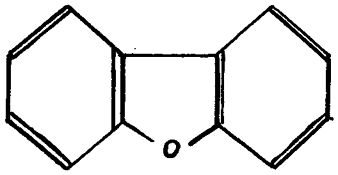

IV

Preparation of Benzofuran

The first derivatives of benzofuran were described in 1870 by Perkin (5). He obtained benzofuran-2-carboxylic acid by the action of aqueous potassium hydroxide upon 3-bromocoumarin or 3,4-coumarin dibromide. Perkin did not attempt to ascribe a structure to this acid though a year later he named it coumarilic acid (6), because of its method of preparation from coumarin. In this second paper he also described the formation of a compound, which was undoubtedly benzofuran, obtained by the distillation of his coumarilic acid. He did not inves-

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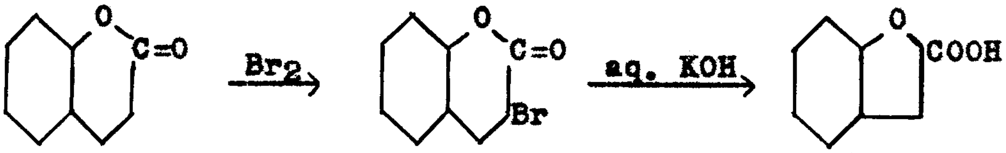
(5) Perkins, J. Chem. Soc., 23, 368 (1870).
(6) Perkins, J. Chem. Soc., 24, 37 (1871).

tigate this product further.



It remained for Fittig and Ebert (7) to describe, and assign a structure to benzofuran prepared by the decarboxylation of benzofuran-2-carboxylic acid in the following manner:

They prepared the benzofuran-2-carboxylic acid in the best yields by the treatment of coumarin dibromide with aqueous potassium hydroxide.

Excellent evidence for the proof of structure of benzofuran is obtained by the successful synthesis of this heterocycle from o-aldophenoxyacetic acid (8);

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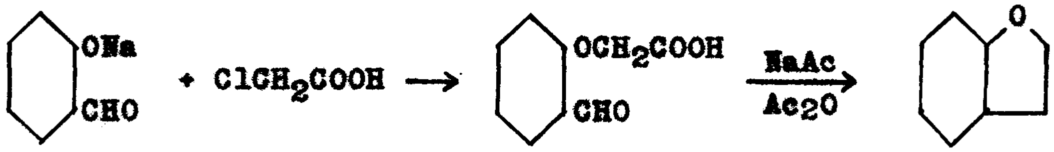
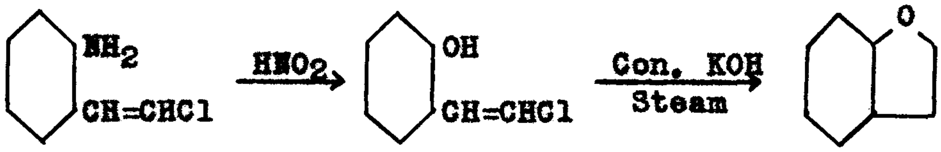
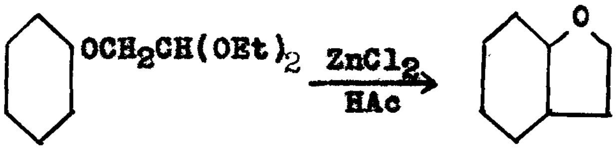
(7) Fittig and Ebert, Ann., 216, 162 (1883).
(8) Rössing, Ber., 17, 2988 (1884).



and from *o*-hydroxyphenyl-*beta*-chloroethylene (9).



The treatment of phenoxyacetal with anhydrous oxalic acid, or better, with anhydrous zinc chloride in glacial acetic acid gives benzofuran in good yields (10). The treatment of phenoxyacetaldehyde with zinc chloride in acetic acid also gives benzofuran, but in poorer yields (11).



Less important methods of preparation are those concerned with the decomposition of benzofuran derivatives, other than benzofuran-2-carboxylic acid, as indicated below (12, 13):

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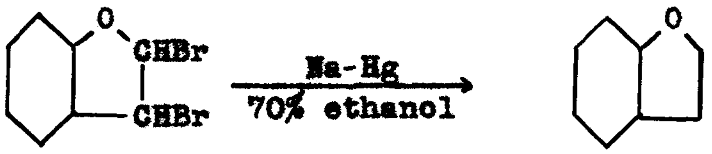
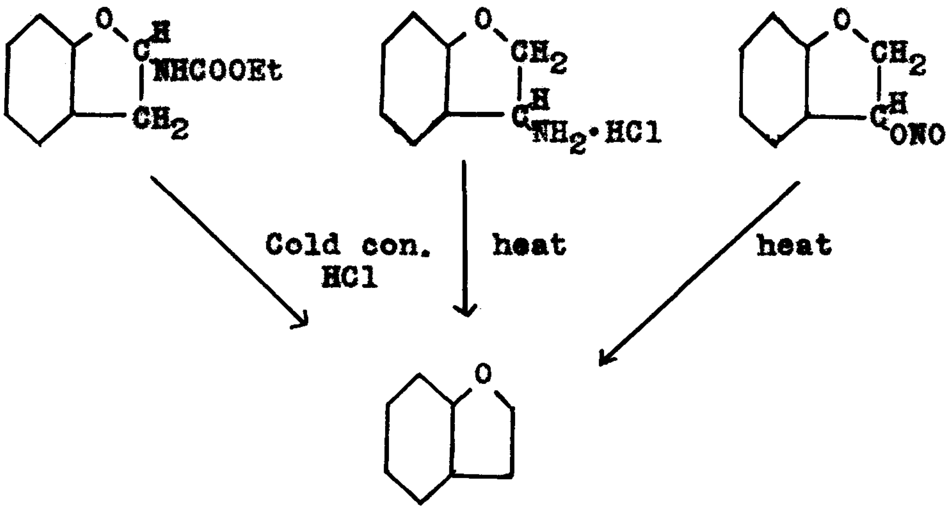
(9) Komppa, *Ber.*, **26**, 2968 (1893).
(10) Stoermer, *Ann.*, **312**, 237 (1900).
(11) Stoermer, *Ber.*, **30**, 1700 (1897).
(12) Stoermer, *Ber.*, **30**, 1711 (1897).
(13) Kraemer and Spilker, *Ber.*, **23**, 78 (1890).



and of dihydrobenzofuran derivatives (14).

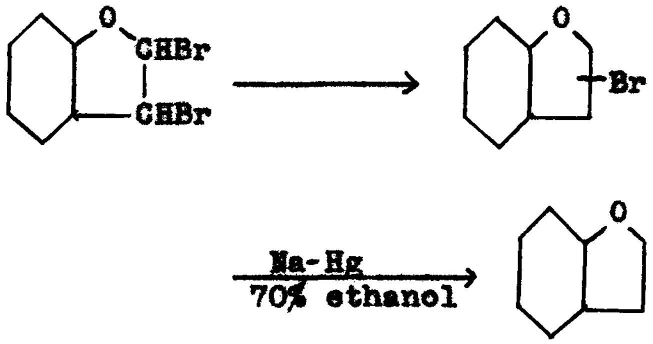


The most recent method of preparation of benzofuran, and probably the best for large quantities, is by the pyrolytic decomposition of coumarin at 860° in a tinned iron tube (15).

(14) Stoermer and König, Ber., 39, 492 (1906).
(15) Orlov and Tishchenko, Ibid., 63B, 2948 (1930).

Benzofuran is found in high boiling coal tar residues and various methods have been devised to separate this heterocycle from the polymethylbenzenes, phenols, and indenes also contained in the fraction which distills around 170°.

Kraemer and Spilker (13) brominated one kilo of the 168°-175° fraction of coal tar to obtain 80 g. of benzofuran dibromide. This compound was converted to bromobenzofuran with alcoholic potassium hydroxide, and to benzofuran by reduction with sodium amalgam in 70% alcohol.



The treatment of benzofuran in benzene with 80% sulfuric acid gives a benzene soluble resin whose formula has been found to be $(C_8H_6O)_4$. The destructive distillation of this resin yields benzofuran as a major product. Some phenol and ethylbenzene are formed, and a small quantity of o-ethylphenol, benzene, toluene, and dihydrobenzofuran isolated. This suggested the treatment of the 155°-185° fraction of coal tar with concentrated sulfuric acid, and the destructive distillation of the resulting resin. A mixture of benzofuran and hydroindene was obtained. The benzofuran was separated as the picrate (16). If sulfuric acid stronger than 80% is used to resinify benzofuran, a benzene insoluble resin is formed which contains a considerable amount of sulfur. The destructive distillation of this resin yields about the same products as the sulfur free product, and, in addition, sulfur, sulfur dioxide, and hydrogen sulfide (17). Indefinite results by means of this method of preparation were claimed by Burda and Sukacheva (18).

A patent has been issued that is based on a method in which the coal tar fraction is sulfonated with concentrated sulfuric acid in the presence of acetic anhydride, and the soluble benzofuransulfonic acid hydrolyzed with steam to benzofuran (19).

Methylbenzofurans have been identified in the 185° - 195° fraction of coal tar (20), 5,7-dimethylbenzofuran in the 215° - 225° fraction (20), and *beta*-naphthofuran (V) and *alpha*-naphthofuran (VI) in the 282° - 292° fraction (21).

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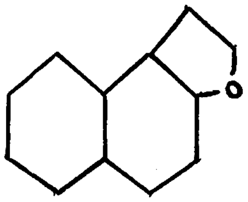
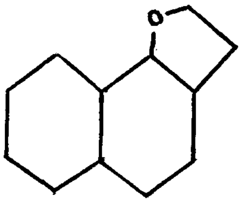
(16) Kraemer and Spilker, *Ber.*, *33*, 2257 (1900).
(17) Kraemer and Spilker, *Ibid.*, *34*, 1887 (1901).
(18) Burda and Sukacheva, *Ukrain. Khem. Zhur.*, *6*, Sci. pt. 169 (1931). [*C.A.*, *26*, 2192 (1932)]
(19) Kruber, Ger. *515*, 546. [*Chem. Zentr.*, *102 I*, 2537 (1931)]
(20) Stoermer and Boes, *Ber.*, *33*, 3013 (1900).
(21) Boes, *Z. öffentl. Chem.*, *8*, 151 (1902), [*J. Chem. Soc.*, *82 I*, 554 (1902)]



V

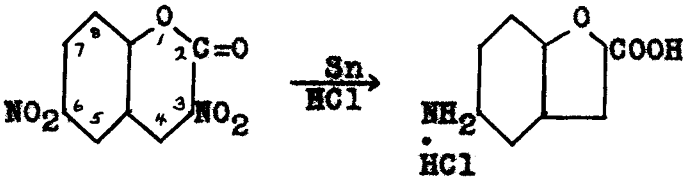


VI

Preparation of Benzofuran Derivatives

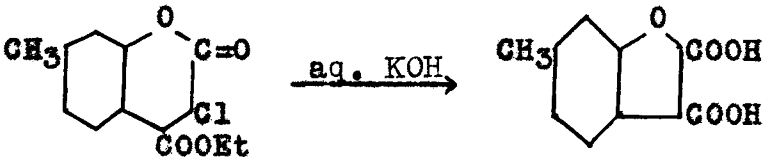
Benzofuran resembles furan much more closely than dibenzofuran in the fact that substitution is made remarkably difficult by reason of the ease of oxidation of the nucleus, and its sensitivity to acids, particularly sulfuric acid. Benzofuran enjoys the distinct advantage, however, of being the product of a number of facile and reliable ring closure syntheses. These reactions follow, in general, the methods used for the synthesis of unsubstituted benzofuran. The adaptability of these methods to the production of desired derivatives is demonstrated in the examples given of characteristic ring closure reactions which are available to yield benzofuran derivatives.

A halogen or amino group in the 3- position of coumarin, or a coumarin derivative, is necessary for the production of benzofuran derivatives by this method. In the former case a basic reagent, and in the latter case an acid reagent, is necessary to effect the ring closure. By this method is prepared 5-aminobenzofuran-2-carboxylic acid hydrochloride (22):



5-nitrobenzofuran-2-carboxylic acid (23):

and 6-methylbenzofuran-2,3-dicarboxylic acid (24).



The reaction of alpha-halogen ketones or acetates with salicylaldehyde or derivatives is used as a method of synthesis of benzofuran derivatives. By this method 2-acetylbenzofuran (12), and 5-bromobenzofuran-2-carboxylic acid (10) are made.

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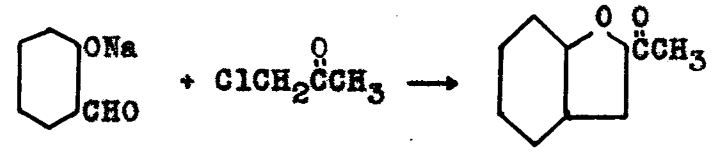
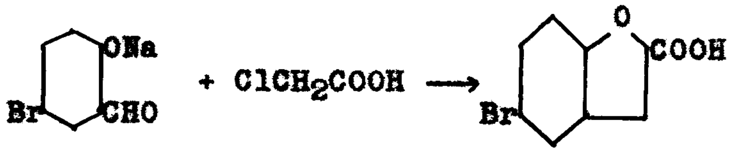
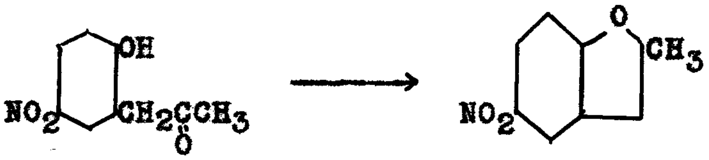
(22) Simonis, "Die Cumarin", Berlin, 1916, p.170 and 177.
(23) Dey and Row, J. Chem. Soc., 123, 3375 (1923).
(24) Dey, ibid., 107, 1606 (1915).





A related method of synthesis is used in the preparation of 2-methyl-5-nitrobenzofuran (25).



The two above general methods of synthesis are reliable in that the positions of fusion of the furan ring to the benzene nucleus are fixed. This is not always true in the third general method, which involves the ring closure of a phenyl ether, and certain restrictions must be observed if a benzofuran derivative of known structure is to be produced. Benzofuran derivatives have been prepared from the appropriate phenyl ethers through the elimination of either alcohol or

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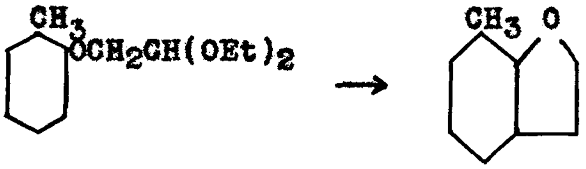
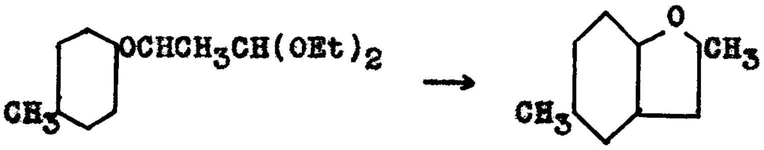
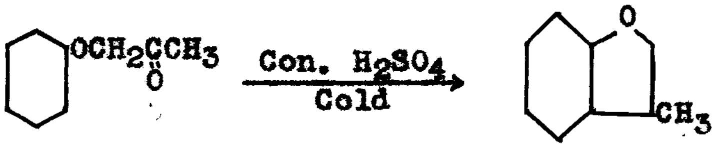
(25) Hale, Ber., 45, 1596 (1912).

water. Examples of the former are given in the following preparation of 7-methylbenzofuran from o-methyl-beta-phenoxyacetal (10), and of 2,5-dimethylbenzofuran from beta-(p-methylphenoxy)-propionacetal (10):





The elimination of water from phenyl ethers to yield benzofuran derivatives has resulted in the synthesis of such types as 3-methylbenzofuran (26), and ethyl 3-methyl-5-nitrobenzofuran-2-carboxylate (27).



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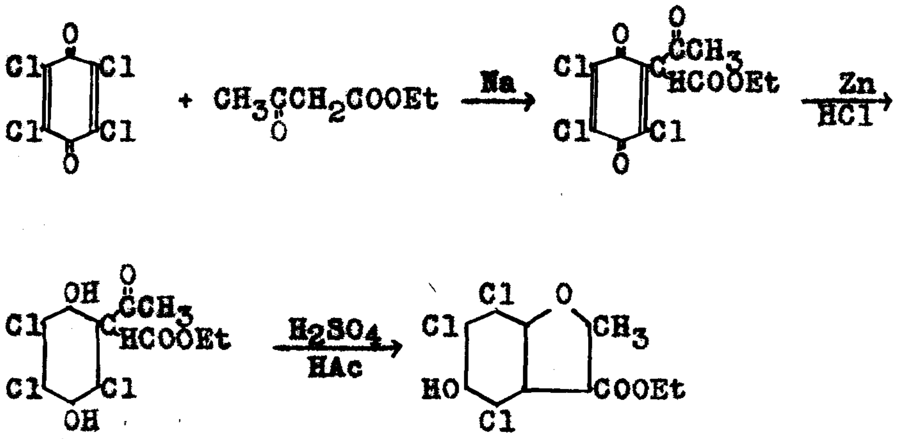
(26) Stoermer, Ber., 28, 1253 (1895).
(27) Huth, Ber., 20, 1332 (1887).

In connection with this last synthesis it is interesting to note that an attempted similar synthesis with m-nitrophenol gave a yield too minute to work with, and when o-nitrophenol was used the synthesis failed completely.

Ikuta (28) has devised a somewhat similar synthesis, involving the use of acetoacetic ester, that yields derivatives of 2-methylbenzofuran-3-carboxylic acid in contrast to the above Hantzsch (29) synthesis yielding derivatives of 3-methylbenzofuran-2-carboxylic acid.

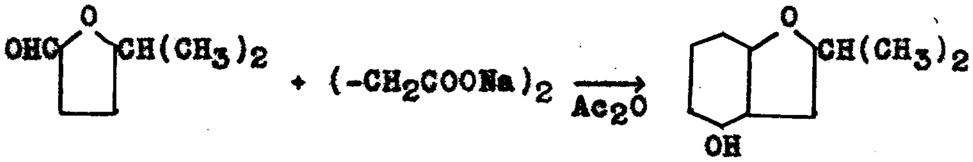


An interesting and useful synthesis is one which involves

(28) Ikuta, J. prakt. Chem., [2] 45, 65 (1892).
(29) Hantzsch, Ber., 19, 1290 (1886).

the distillation of *beta*-(2-furaldehyde)levulinic acid to yield 4-hydroxy-6-acetylbenzofuran as follows (30):

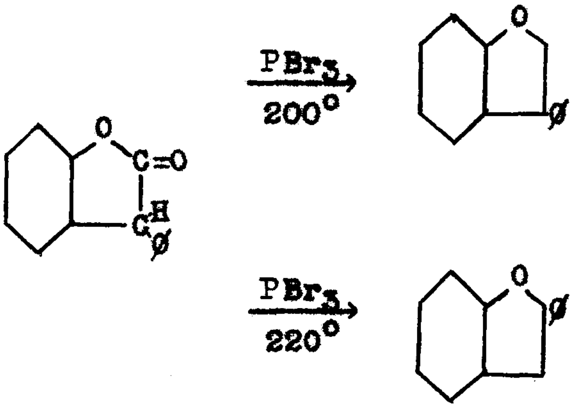
Sen and Roy (31) also obtained this product directly from furfural and levulinic acid by the use of hydrogen chloride. A similar synthesis from a furan derivative has been used by Reichstein and Hirt (32) to prepare the isotubanol of Takei (33).



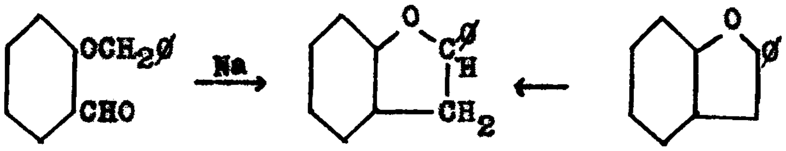
A patent has been based on the preparation of 2-methylbenzofuran by the action of an alkali upon *alpha*-halogen-*o*-allylphenols (34).

(30) Kehrer and Kleberg, *Ber.*, **26**, 345 (1893).
(31) Sen and Roy, *J. Indian Chem. Soc.*, **7**, 401 (1930). [*C.A.*, **24**, 4763 (1930)]
(32) Reichstein and Hirt, *Helv. Chim. Acta*, **16**, 121 (1933).
(33) Takei, *Ber.*, **61 B**, 1033 (1928).
(34) Ger. 293,956 [*Chem. Zentr.*, **87 II**, 618 (1916)]

In a few instances, benzofuran derivatives have been prepared from 2- and 3-keto-2,3-dihydrobenzofurans. Thus, by treatment with phosphorus tribromide at different temperatures, 2-keto-3-phenyl-2,3-dihydrobenzofuran is converted to 2- and 3-phenylbenzofuran (35).



The proof of this rather unusual reaction lies in the synthesis of the 2-phenylbenzofuran (36) and 3-phenylbenzofuran (35) by other ring closure syntheses. 3-Phenylbenzofuran is not converted to 2-phenylbenzofuran by heating with phosphorus tribromide.



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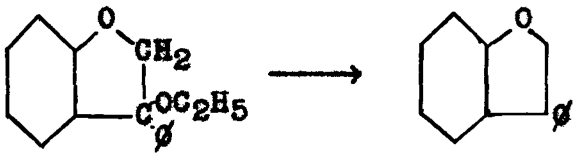
(35) Stoermer, Ber., **36**, 3986 (1903), Stoermer and Kippe, ibid., **36**, 3992 (1903).

(36) Stoermer and Reuter, Ber., **36**, 3979 (1903).



The use of a Grignard reagent upon 2-keto-2,3-dihydrobenzofuran resulted in the formation of 2-methylbenzofuran (37).

Although 2-keto- and 3-ketodihydrobenzofurans resemble aliphatic, rather than aromatic, ketones in their reactions, it has been determined that they are capable of enolization to 2-hydroxy- and 3-hydroxybenzofurans. This was shown by their reaction with sodium and potassium to yield salts of these elements, and by their ability to undergo the Zerevitinov reaction to the extent of 60% in the cold and 80-90% when heated (38).

The principal methods of synthesis of ketodihydrobenzofurans are from o-hydroxyphenylacetic acid (39), o-acetoxy-

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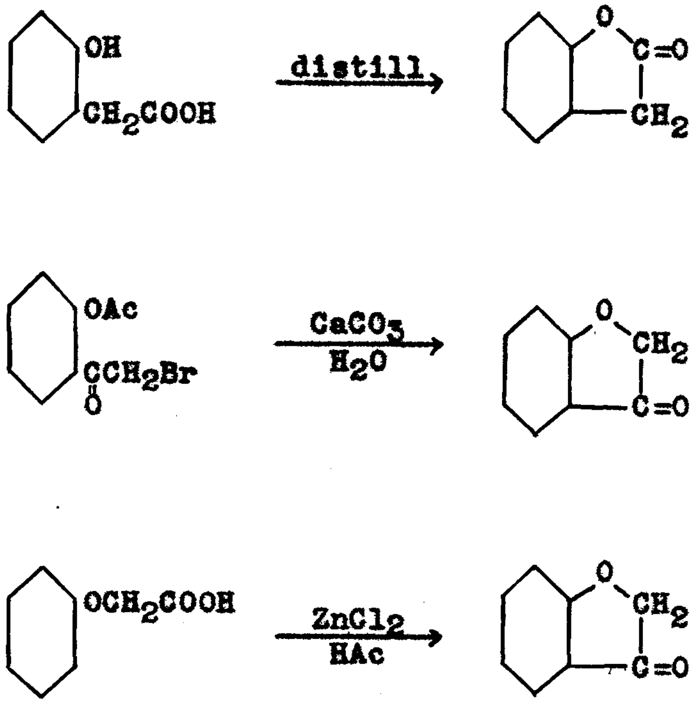
(37) Stoermer and Barthelmes, Ber., 48, 62 (1915).
(38) Löenbeim and Simonis with Lang and Jacobus, ibid., 57, 2040 (1924).
(39) Baeyer and Fritsch, ibid, 17, 973 (1884).

beta-bromacetophenone (40), and phenoxyacetic acid (12).



A number of ring closure syntheses have been developed for the preparation of 2,3-dihydrobenzofuran and derivatives. This nucleus is of particular importance from a physiological and pharmaceutical viewpoint as this particular reduced benzofuran nucleus is found in the structure of morphine.

The ring closure reactions that have been used for the preparation of unsubstituted 2,3-dihydrobenzofuran that close in a fixed position are; by the action of aqueous sodium car-

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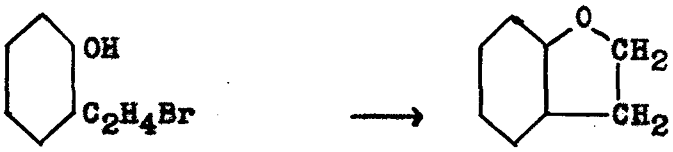
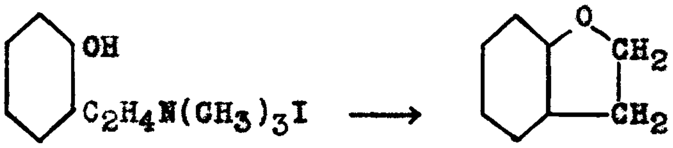
(40) Friedlander and Neudorfer, Ber., 30, 1077 (1897).

bonate upon *o*-hydroxyphenylethylene bromide (41), by the action of sodium upon *o*-bromophenoxyethylene bromide (42), and by the distillation of an aqueous potassium hydroxide solution of *beta*-(*o*-hydroxyphenyl)ethyltrimethylammonium iodide (43).

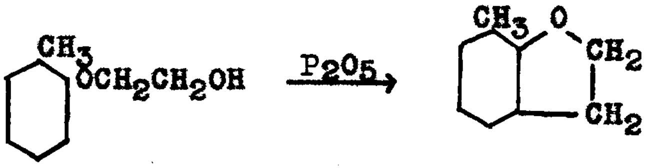




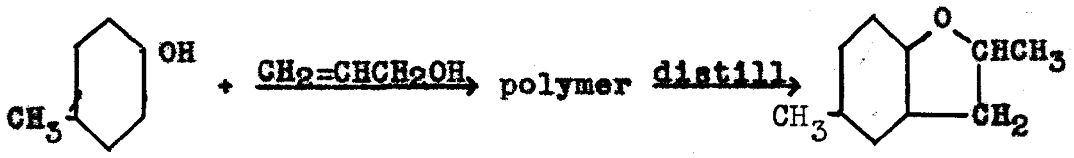
The action of anhydrous zinc chloride upon *beta*-hydroxy- and *beta*-bromoethylphenyl ether yields dihydrobenzofuran (44), and the action of phosphorus pentoxide upon *bz*-substituted *beta*-hydroxyethylphenyl ethers produces substituted dihydro-

(41) Stoermer and Kahlert, *Ber.*, *34*, 1806 (1901).
(42) Stoermer and Göhl, *ibid.*, *36*, 2873 (1903).
(43) Pshorr and Einbeck, *ibid.*, *38 I*, 2067 (1905).
(44) Rindfusz, *J. Am. Chem. Soc.*, *41*, 665 (1919).

benzofurans (45).



The first of the two best general methods for the ring closure preparation of dihydrobenzofuran derivatives is by the condensation of a phenol, or substituted phenol, with allyl alcohol in the presence of an acetic acid-sulfuric acid mixture, and the pyrolytic decomposition of the resulting polymer (46).



A related method is used to produce alkylated dihydrobenzofurans by the condensation of phenols and ketones. In

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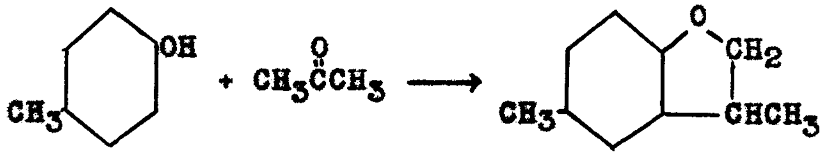
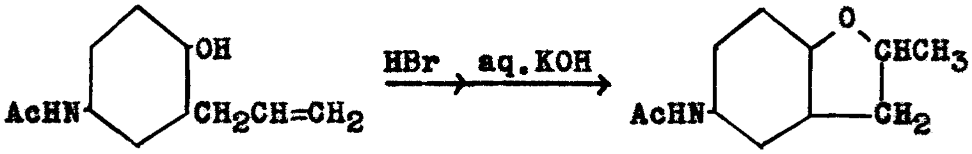
(45) Rindfusz, Ginnings, and Harnack, J. Am. Chem. Soc., **42**, 157 (1920).

(46) Niederl and Storch, ibid., **55**, 4549 (1933).

this way 3,5-dimethyl-2,3-dihydrobenzofuran is made from *o*-cresol and acetone (47).



The second, and most interesting, general method of synthesis of dihydrobenzofuran derivatives is that mentioned first in a patent in 1914 (48), and later developed in various modifications by other workers. By this method is prepared 2-methyl-5-acetamino-2,3-dihydrobenzofuran (49), and 2,5,7-trimethyl-2,3-dihydrobenzofuran (50).



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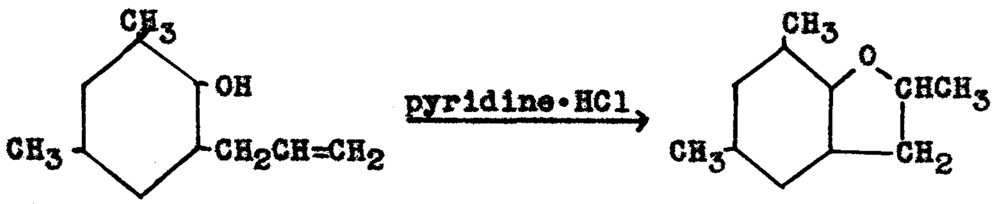
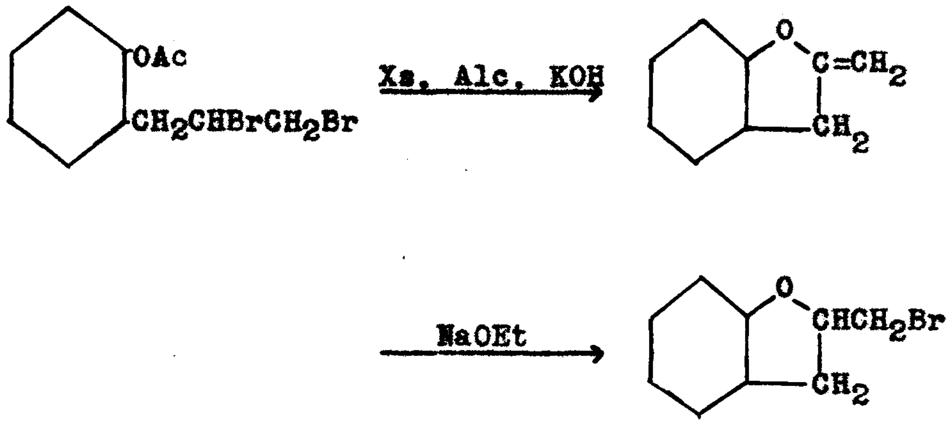
(47) Jordan, U. S. 1,679,664 [*Chem. Zentr.*, **100 I**, 2822 (1928)].
(48) Ger. 279,864 [*ibid.*, **85 II**, 1213 (1914)].
(49) Claisen and Kremers, *Ann.*, **418**, 104 (1919).
(50) Claisen and Tietze, *ibid.*, **449**, 81 (1926).

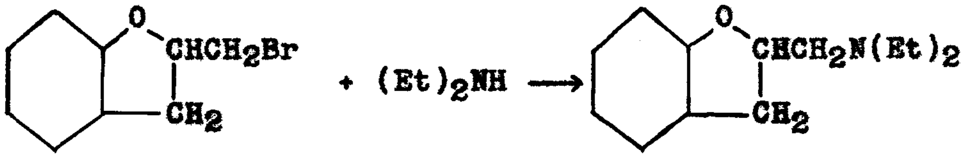


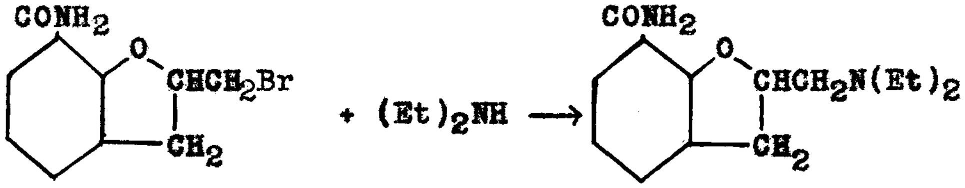
An interesting modification by Adams and Rindfusz (51) is used to synthesize 2-methylenedihydrobenzofuran and 2-bromomethyldihydrobenzofuran.



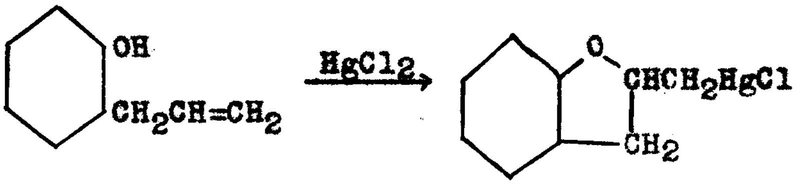
From this latter compound is prepared 2-diethylaminomethyldihydrobenzofuran through its reaction with diethyl amine (52), and from a similar derivative is synthesized 2-diethylaminomethyldihydrobenzofuran-7-carboxylic acid amide (53).

(51) Adams and Rindfusz, *J. Am. Chem. Soc.*, *41*, 648 (1919).
(52) Fourneau, Maderni, and de Lestrange, *J. pharm. chim.*, *18*, 185 (1933).
(53) Gomez, *ibid.*, *20*, 337 (1934).

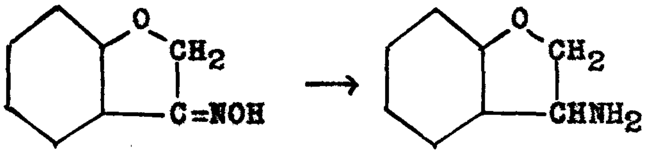




A mercurated dihydrobenzofuran is prepared by the action of mercuric chloride upon o-allylphenol (54).

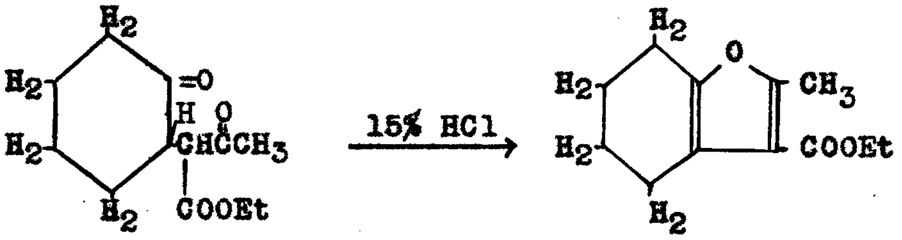


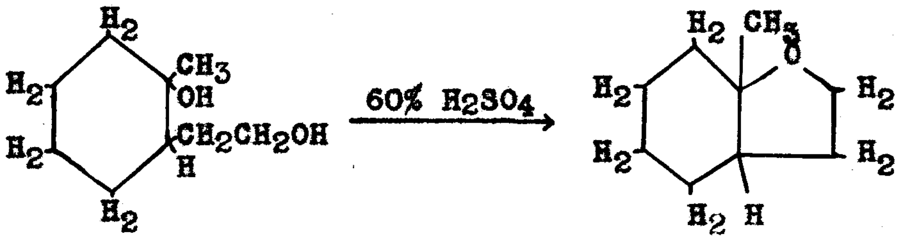
3-Amino-2,3-dihydrobenzofuran is prepared by the reduction of the oxime of 3-ketodihydrobenzofuran (37).



(54) Adams, Roman, and Sperry, J. Am. Chem. Soc., **44**, 1781 (1922).

More highly reduced benzofurans are represented by the formation of ethyl 2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (55), and 7a-methylperhydrobenzofuran (56) by means of the following syntheses:





Pharmacological Properties of Benzofuran Derivatives

Until very recently, no work on the physiological properties of benzofuran derivatives has been reported. Since 1934 a series of papers by Fourneau, Bovet, and co-workers has appeared, reporting on various physiological effects of a num-

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(55) Ebel, Huber, and Brunner, Helv. Chim. Acta., 12, 16 (1929).
(56) von Braun and Münch, Ann., 465, 52 (1928).

ber of derivatives of aminomethyl-2,3-dihydrobenzofurans (57, 58, 59, 60, 61, 62, 63, 64). The derivatives reported on are: 2-diethylamino- (878), 2-methylamino- (879), 2-dimethylamino- (911), 2-piperidino- (934), 7-methoxy-2-methylamino- (889), 7-methoxy-2-diethylamino- (890), 7-methoxy-2-piperidino- (991), 6-ethoxy-2-methylamino- (887), 6-ethoxy-2-diethylamino- (888), 5-ethoxy-2-methylamino- (881), 5-ethoxy-2-diethylaminomethyl-2,3-dihydrobenzofuran (880), and 2-diethylaminomethyl-2,3-dihydrobenzofuran-7-carboxylic acid amide (9009).

The reports on the dihydrobenzofuran derivatives are given quantitatively in only a few cases, but several interesting general observations are drawn. Compound (878) exercises a marked antagonism against adrenaline hyperglucemia in the rabbit (57, 58). It is a hypotensor, vasodilator, and increases the amplitude and tonus of intestinal contraction (58). The properties of the other derivatives are similar to this, but vary with the substituents. Thus, (911) and (879) are weaker hypotensors, and the intestinal action of all the diethylamino-

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(57) Blancher, *Compt. rend. soc. biol.*, **115**, 1185 (1934).
(58) Fourneau, Bovet, and Maderni, *ibid.*, **115**, 1215 (1934).
(59) Bovet and Simon, *ibid.*, **116**, 842 (1934).
(60) Bovet, *ibid.*, **116**, 1020 (1934).
(61) Bovet and Simon, *ibid.*, **117**, 958 (1934).
(62) Bovet, Simon, and Depierre, *ibid.*, **117**, 961 (1934).
(63) Bacq and Bovet, *ibid.*, **118**, 359 (1935).
(64) Bacq and Bovet, *Arch. intern. pharmacodynamie*, **50**, 315 (1935). /*C.A.*, **29**, 5921 (1935)/.

derivatives is more marked than that of the corresponding monomethylamino derivatives. The most active derivatives in this respect are (890) and (888). The ethoxy group seems to play a considerable role, this substituent in the 6- position being the most effective. Compound (888), together with (911), also has an enhanced antagonism against the effects of adrenaline (58). Compound (890), in the dog, has a very rapid and irregular action on the effects of adrenaline vasoconstriction of the kidney (59). Tests of the effects of the derivatives on the muscles of the bronchi of guinea pigs showed that the simplest derivatives had no effect, but that the more complex derivatives had a constrictive action (60). All the derivatives, and in particular (878), (887), and (1009), appeared to possess the property of prolonging considerably the duration of adrenaline contraction of the nictitating membrane of cats (63). The most interesting and encouraging report on the physiological properties of these aminodihydrobenzofuran derivatives was their action in sensibly prolonging the narcosis produced by Evipan in the rabbit. The effect of o-methoxy- derivatives in this respect was particularly marked (61). Further investigation showed that the aminomethyldihydrobenzofurans also possess distinct analgesic and sedative properties in themselves (62).

Orientation in Benzofuran

The little work that has been done on the nuclear orientation of benzofuran has been done chiefly on halogenation products of the unsubstituted nucleus. The 2,3- linkage of benzofuran resembles an aliphatic ethylenic linkage more closely than an aromatic compound by reason of its ready oxidation, reduction, and ease of halogen addition to form a stable dibromide and dichloride.

Fittig and Ebert (7) in 1883 first treated benzofuran with bromine to obtain a benzofuran dibromide addition product. A year later Ebert (65) regenerated benzofuran from the dibromide by boiling it with water, and obtained a monobromobenzofuran upon refluxing with alcoholic potassium hydroxide. The reduction of benzofuran dibromide with sodium amalgam in 70% alcohol yielded benzofuran (13). These results were later checked in substance (66, 10), though no evidence as to the orientation of the bromobenzofuran was brought forward until Stoermer and Kahlert (67) showed that the monobromobenzofuran (a liquid) obtained by the distillation of the dibromide addition product was different from the monobromobenzofuran (a

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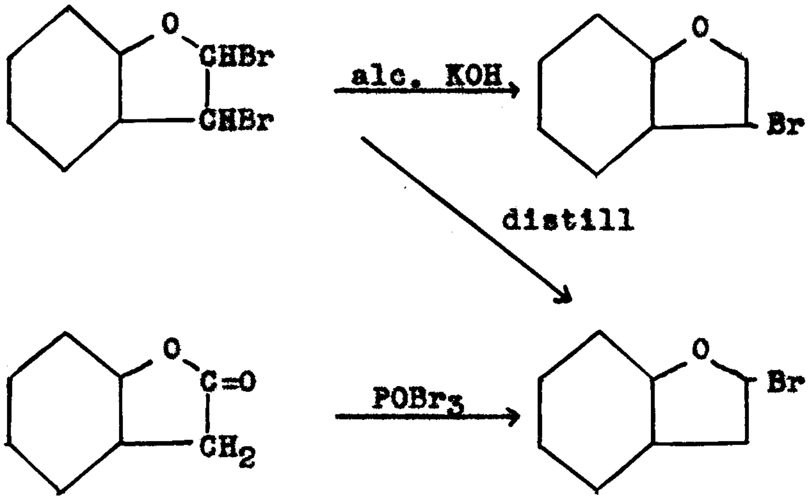
(65) Ebert, Ann., 226, 347 (1884).
(66) Dohme, Am. Chem. J., 13, 28 (1891).
(67) Stoermer and Kahlert, Ber., 35, 1633 (1902).

solid) obtained by the treatment of this same dibromide with alcoholic potassium hydroxide. The liquid product was shown to be 2-bromobenzofuran by comparison with the 2-bromobenzofuran obtained by the treatment of 2-keto-2,3-dihydrobenzofuran with phosphorus oxybromide. The 2-bromobenzofuran did not solidify when cooled with a solution of solid carbon dioxide in ether.



The reactions of the two monobromobenzofurans were also different. Treatment of 2-bromobenzofuran in an autoclave with alcoholic potassium hydroxide gave quantitative yields of o-hydroxyphenylacetic acid, and a similar treatment of 3-bromobenzofuran yielded a mixture of small amounts of o-hydroxyphenylacetic acid and o-ethoxyphenylacetic acid, and unidentified products. The treatment of 2-bromobenzofuran with nitrous anhydride gas yielded 2-nitrobenzofuran and a similar treatment of 3-bromobenzofuran gave a nitro-3-bromobenzofuran (67).

Previous attempts to prove the position of the bromo group through replacement by a methyl group, using methyl iodide and sodium, and dimethylzinc (10), failed, as did also the attempt to prepare authentic 2-bromobenzofuran through the replacement of the carboxylic group of benzofuran-2-carboxylic acid by bromine in an aqueous alkaline solution (68). In this case a tribromobenzofuran is formed which is the same as that obtained by Stoermers (10) bromination of 2,3-dibromobenzofuran.

Monobromobenzofuran was brominated by Stoermer, Richter, and Gralert (10), and by Simonis (69), to yield what is probably 2,3-dibromobenzofuran. The bromination of this compound yielded a tribromobenzofuran (10).

5-Bromobenzofuran (10) and 5,7-dibromobenzofuran (70, 71) were prepared by ring closure reactions and were both brominated to yield dibromide addition products (70, 71), according to the following reactions:

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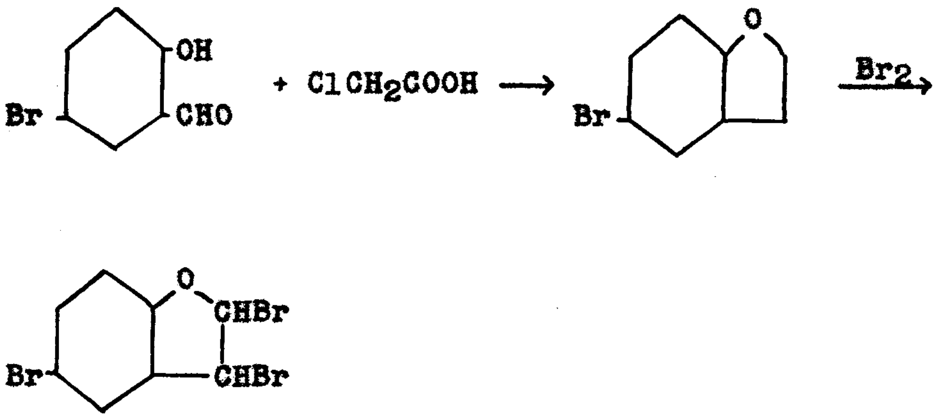
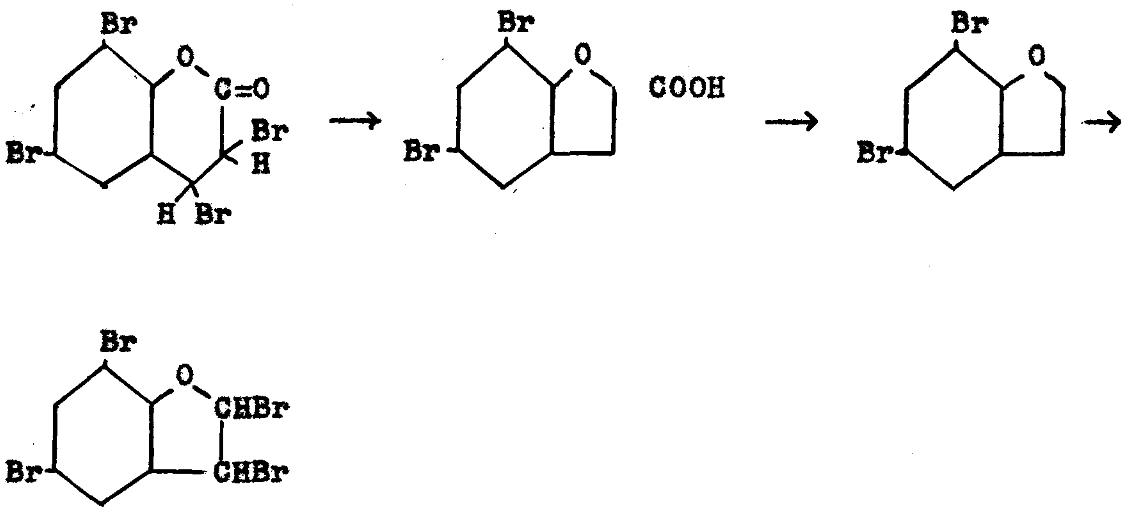
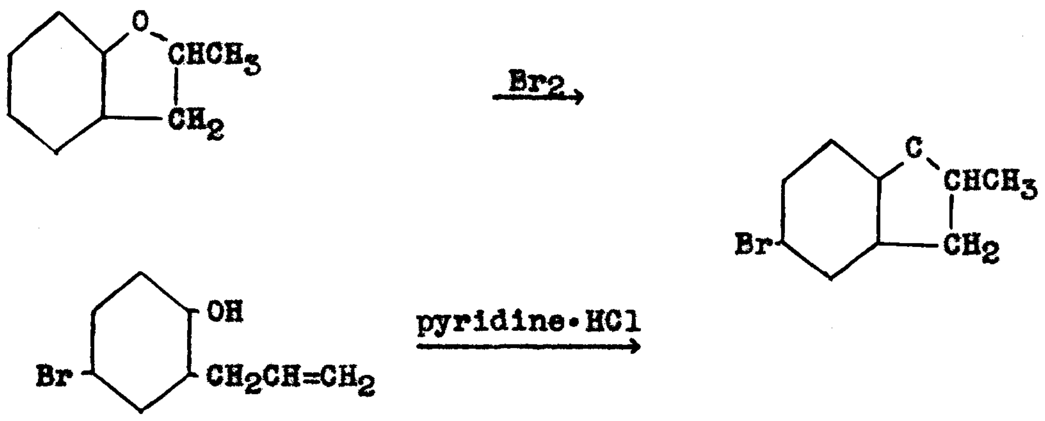
(68) Stoermer and Calov, Ber., 34, 770 (1901).
(69) Simonis, ibid., 34, 781 (1901).
(70) Simonis and Wenzel, ibid., 33, 421 (1900).
(71) Simonis and Wenzel, ibid., 33, 1961 (1900).





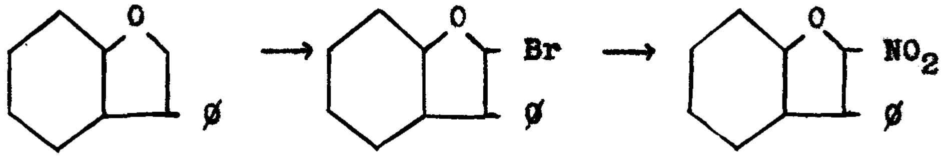
Treatment of the 5-bromobenzofuran dibromide with sodium ethylate yielded a dibromobenzofuran which brominated further to give a compound that is probably 2,3,5-tribromobenzofuran (71). This tribromobenzofuran is unlike the isomer mentioned in the preceding paragraph, formed by the bromination of 2,3-dibromobenzofuran.

The bromination of a dihydro-derivative of benzofuran, such as 2-methyl-2,3-dihydrobenzofuran, orients the entering group in the 5- position. This was shown by the preparation of the product through ring closure synthesis (51).



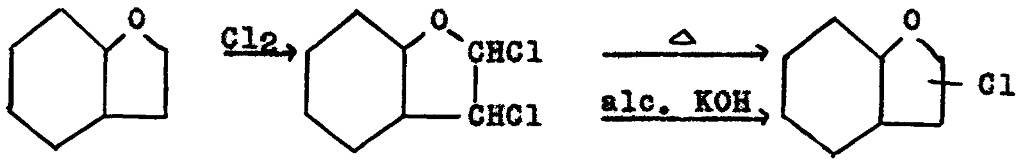
3-Phenylbenzofuran brominated to yielded a monobromo derivative whose bromo group is replaced by a nitro group through the medium of nitrous acid. 3-Phenyl-5-methyl- and 3-phenyl-6-methylbenzofuran also undergo this series of reactions (72). The work of Stoermer and Kahlert (67), who showed that a bromo group in the 2- position of benzofuran is easily replaceable by a nitro group, is accepted as evidence that this type has brominated to produce 2-bromo-3-phenylbenzofurans.

(72) Stoermer, *Ber.*, **44**, 1853 (1911).

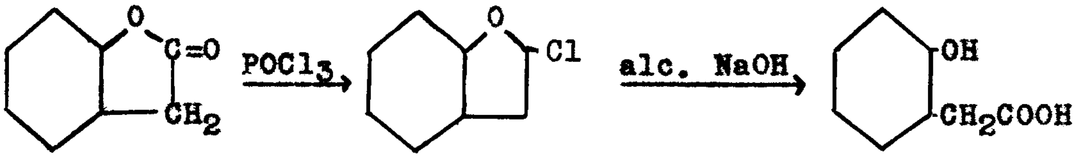


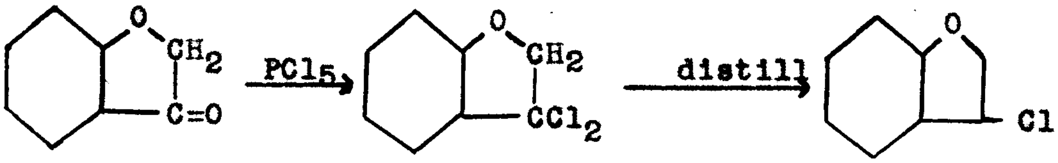
Bromine has no action upon benzofuran-2-carboxylic acid in ether or carbon disulfide. This compound also resists the polymerizing action of strong acids (7).

The status of the chlorination products of benzofuran is even less advanced than that of bromination. Kraemer and Spilker (13) chlorinated benzofuran, and obtained a dichloride addition product which they treated with alcoholic potassium hydroxide to yield a monochlorobenzofuran. A similar compound was prepared by the action of phosphorus pentachloride upon benzofuran (66). Later workers did not check the constants of Kraemer and Spilker for their monochlorobenzofuran, but did obtain a dichlorobenzofuran as a by-product that checked fairly closely the previous constants for the monochloro derivative (10). The decomposition of benzofuran dichloride by either distillation or alcoholic potassium hydroxide gave the same product (10).



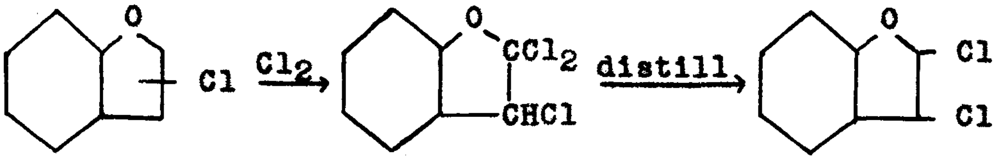
The action of alcoholic potassium hydroxide upon chlorobenzofuran in an autoclave yielded *o*-hydroxyphenylacetic acid as a principal product, and 3-keto-2,3-dihydrobenzofuran and 3-ethoxybenzofuran were isolated in minor amounts (73). This suggests that the chlorobenzofuran is a mixture of the 2- and 3- isomers. The two chlorobenzofuran isomers have been prepared by syntheses related to that employed for 2-bromobenzofuran, and it has been determined that the authentic 2-chlorobenzofuran yields only *o*-hydroxyphenylacetic acid upon treatment with alcoholic sodium hydroxide (73). The two isomeric chlorobenzofurans, as prepared in this way, have approximately the same boiling points.



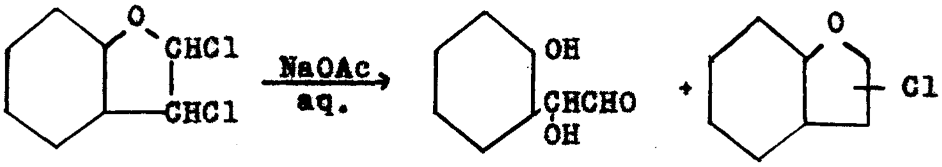


(73) Stoermer, *Ann.*, **313**, 79 (1900).

The addition of two atoms of chlorine to monochlorobenzofuran, and the subsequent splitting of hydrogen chloride by distillation, yielded a product which is probably 2,3-dichlorobenzofuran (10).



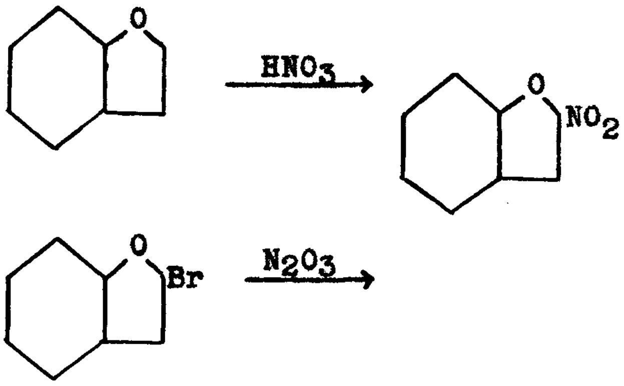
The treatment of benzofuran dichloride with a mild alkaline reagent, such as aqueous sodium acetate, resulted in the formation of o-hydroxymandelic aldehyde as well as chlorobenzofuran. This constitutes proof that the chlorine adds to the 2,3- ethylenic linkage in benzofuran (73).



The replacement of the chloro group by a nitro group in 2-chlorobenzofuran, through the use of nitrous anhydride, did not succeed (67).

Iodine does not react with benzofuran at ordinary temperatures, and at higher temperatures the mixture decomposes (13).

Benzofuran has been nitrated with concentrated nitric acid in acetic acid to give low yields of a mononitrobenzofuran. The isolation of 2-hydroxy-5-nitrobenzoic acid from the residues was at first considered evidence that benzofuran nitrated in the 5- position (74). 2-Hydroxy-3-nitrobenzoic acid was also isolated, but these products may be accounted for by assuming the oxidation of benzofuran to salicylic acid and the subsequent nitration of this product to yield the two isomeric nitrosalicylic acids. The treatment of 2-bromobenzofuran with nitrous anhydride to yield the same nitrobenzofuran as prepared by direct nitration is considered good evidence that the nitro group is oriented in the 2- position (67).



The reduction of 2-nitrobenzofuran with tin and hydrochloric acid resulted in the formation of *o*-hydroxyphenyl-

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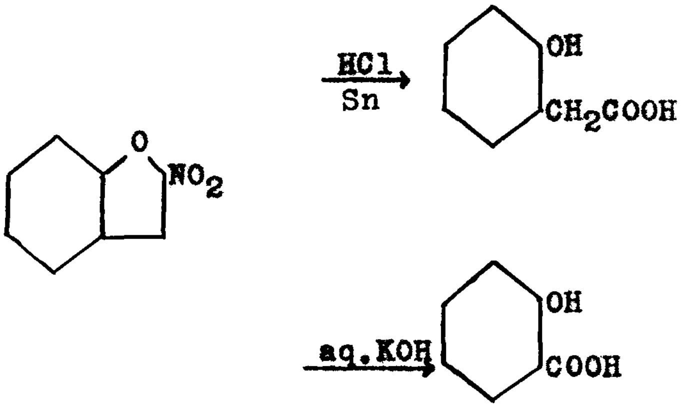
(74) Stoermer and Richter, *Ber.*, **30**, 2094 (1887).

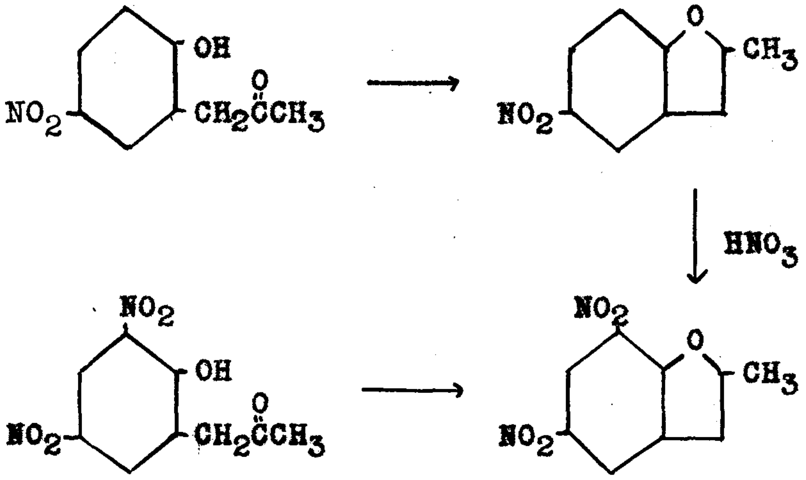
acetic acid, and the action of aqueous alkali yielded salicylic acid (75).



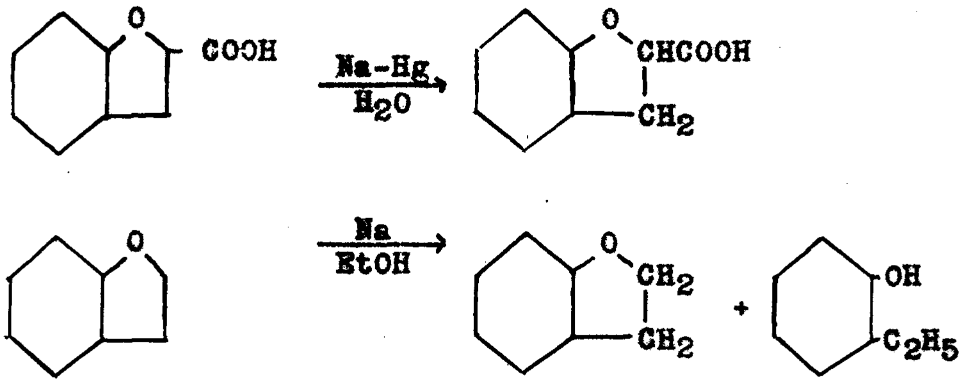
The nitrobromobenzofuran obtained by the nitric acid nitration of bromobenzofuran (74) is identical with the nitro-3-bromobenzofuran obtained by the treatment of 3-bromobenzofuran with nitrous anhydride (67). 2,3-Dibromobenzofuran has been nitrated to yield a nitro-2,3-dibromobenzofuran of unknown structure (10).

2-Methyl-5-nitrobenzofuran was nitrated to yield 2-methyl-5,7-dinitrobenzofuran. The identity of the product was established through ring closure synthesis (25).

(75) Stoermer and Kahlert, *Ber.*, *35*, 1640 (1902).

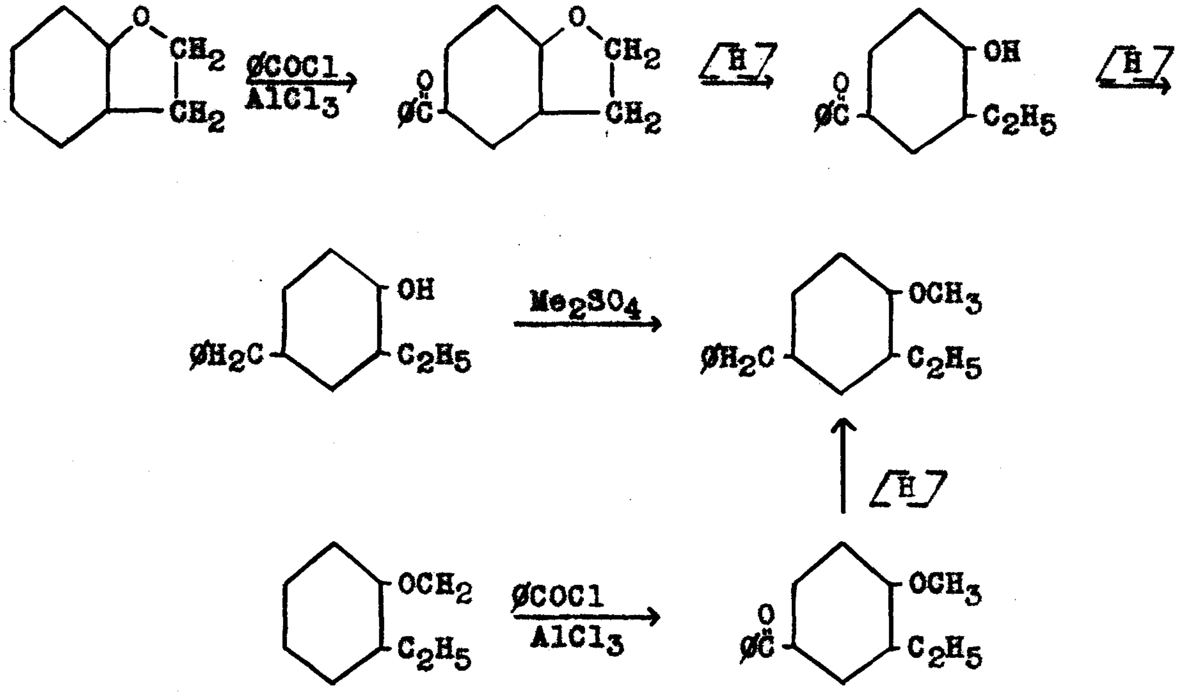


The action of sodium amalgam, in either alcohol or an alcohol-water mixture, had no effect upon benzofuran (7, 65). A large excess of sodium amalgam in an aqueous solution, however, reduced benzofuran-2-carboxylic acid to 2,3-dihydrobenzofuran-2-carboxylic acid (7). The treatment of benzofuran with sodium, in alcohol, resulted in the formation of 2,3-dihydrobenzofuran and <u>o</u>-ethylphenol (76).



(76) Alexander, <u>Ber.</u>, <u>25</u>, 2409 (1892).

The Friedel-Crafts reaction has not been attempted with benzofuran, but the reaction of benzoyl chloride with dihydrobenzofuran in the presence of aluminum chloride appears to orient the entering group in the 5- position (77). The somewhat involved proof of this structure is also submitted (78).



The addition of hypochlorus acid to benzofuran to yield chlorohydroxydihydrobenzofuran has been reported (79), as has also been the formation of a mercurial addition product, of the

(77) Kostanecki, Lampe, and Marschalk, <u>Ber</u>., <u>40</u>, 3660 (1907).
(78) Marschalk, <u>ibid</u>., <u>43</u>, 1695 (1910).
(79) Boes, <u>Apoth. Ztg</u>., <u>23</u>, 153 (1908). [<u>C.A</u>., <u>2</u>, 2845 (1908)].

formula $C_8H_6O \cdot 2\ HgSO_4 \cdot 2\ HgO \cdot H_2O$, by the action of a methanol solution of mercuric sulfate upon benzofuran (80).

Strong sulfuric acid polymerizes benzofuran. The action of concentrated sulfuric acid, in the presence of acetic anhydride, upon benzofuran contained in coal tar has been reported to yield a benzofuransulfonic acid. The sulfonic acid was not isolated, but was immediately converted to benzofuran by hydrolysis with steam (19). Dihydrobenzofuran has been sulfonated with concentrated sulfuric acid to yield a sulfonic acid of unknown structure. Derivatives were also made of this sulfonic acid (81).

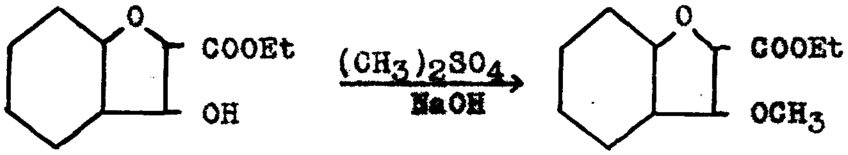
A rather interesting reaction of benzofurans characterized by a hydroxy group in the 2- or 3- position, is the apparent addition of methyl iodide to the 2,3- ethylenic linkage. This is another manifestation of the great reactivity exhibited by this linkage. An attempt to methylate ethyl 3-hydroxy benzofuran-2-carboxylate with methyl iodide gave, as a major product, ethyl 2-methyl-3-ketodihydrobenzofuran-2-carboxylate as follows (82):

(80) Boes, Pharm. Ztg., 46, 915 (1901). /Chem. Zentr., 72 II, 1347 (1901)/.

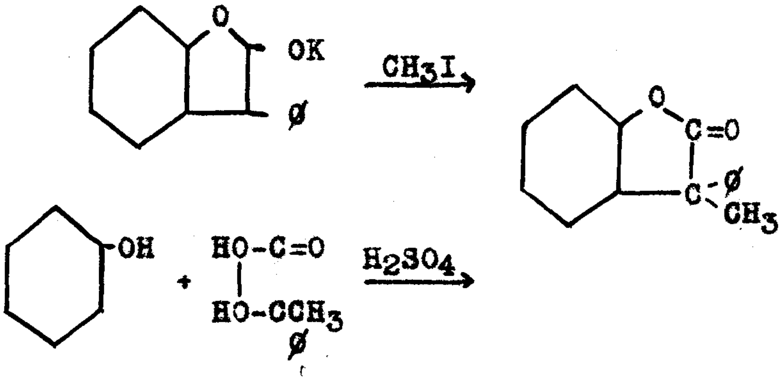
(81) Boes, Apoth. Ztg., 17, 422 (1902). /Chem. Zentr., 73 II, 370 (1902)/.

(82) Auwers, Ann., 393, 338 (1912).

The use of dimethyl sulfate as a methylating agent in this reaction gave a major yield of the expected ethyl 3-methoxybenzofuran-2-carboxylate (82).



A similar reaction with the potassium salt of 2-hydroxy-3-phenylbenzofuran yielded 2-keto-3,3-methylphenyldihydrobenzofuran, and the identity of the product was proved through ring closure (38).



These reactions can, of course, be explained on the basis that they are highly enolized ketones of the aceto-acetic ester type.

A summary of the nuclear orientation of benzofuran and derivatives reveals that amazingly little has been definitely accomplished along these lines at this time.

It is evident that halogens first add to the 2,3- double bond of benzofuran and then splits hydrogen halides to yield 2- and 3- substituted derivatives. The splitting of the dibromide through distillation yields 2-bromobenzofuran, and through refluxing with alcoholic potassium hydroxide gives 3-bromobenzofuran. The orientation of further brominated derivatives is not known. The boiling points of the 2-chloro- and 3-chlorobenzofurans are so nearly alike that they have not been differentiated as products of the decomposition of benzofuran dichloride. The specific gravity and index of refraction of these two isomers were not determined.

Benzofuran probably nitrates in the 2- position. The proof is dependent chiefly on the reliability of 2-bromobenzofuran as a reference compound, and the dependability of the reaction replacing the bromo group by a nitro group. The product obtained by the reduction of the nitrobenzofuran is supporting evidence. The fact that 2-methyl-5-nitrobenzofuran orients a second nitro group to the 7- position is definitely established.

Reduction hydrogenates the 2- and 3- positions.

Halogenation and Friedel Crafts reaction with dihydrobenzofuran and derivatives orient the entering group to the 5-position.

EXPERIMENTAL PART

Preparation of 3,4-Coumarin Dibromide

The addition of bromine to coumarin was carried out according to the general procedure of Perkin (5) (6).

A solution of 146 g. (1.0 mole) of coumarin and 168 g. (1.05 mole) of bromine in 500 cc. of dry carbon disulfide was allowed to stand 12 hours at room temperature and 24 hours at 4°. The carbon disulfide solution was decanted from the solid mass of large crystals and re-used as it was. The yields of crude 3,4-coumarin dibromide, dried at 45°, and melting at 107°-108°, ranged from 93% to quantitative.

Preparation of Benzofuran-2-carboxylic Acid

A. From salicylaldehyde and ethyl bromoacetate.

A solution of 0.5 mole of sodium ethylate, prepared from 11.5 g. (0.5 g. atom) of sodium in 300 cc. of absolute ethanol, was added in portions, with shaking, to a solution of 91 g. (0.5 mole) of salicylaldehyde and 83.5 g. (0.5 mole) of ethyl bromoacetate in 600 cc. of absolute ethanol. At the conclusion of the addition the mixture was gently refluxed 12 hours. A solution of 6.9 g. (0.35 g. atom) of sodium in 300 cc. of absolute alcohol was added, and the now strongly basic reaction mixture refluxed an additional 3 hours. A solution of 30 g. of potassium hydroxide in 400 cc. of water was added and the alcohol slowly distilled off. The residue was treated with Norite, filtered hot, cooled, and acidified. The dark, oily product was extracted with ether, and the ether extract extracted with 10% sodium carbonate solution. The basic extract was treated with Norite and acidified. A crude yield of 51 g., 62.8% of the theoretical, of benzofuran-2-carboxylic acid, air-dried at 45°, was obtained. Crystallization of the potassium salt once from 20% potassium hydroxide solution, and once from ethanol, yielded a free acid melting at 192°-193°.

B. From 3,4-coumarin dibromide.

The general procedure followed in this synthesis is that based on the method of Fittig and Ebert (7).

A suspension of 153 g. (0.5 mole) of 3,4-coumarin dibromide in 500 cc. of a 30% potassium hydroxide solution was refluxed four hours, cooled, filtered, and the resulting potassium salt dissolved in water, treated with Norite, acidified, and air-dried at 45°. Yields of crude benzofuran-2-carboxylic acid, melting within a degree of 185°, were obtained from 80% of the theoretical to quantitative. The use of 650 g. of 23% sodium hydroxide solution, under the same conditions, gave a yield of 71.5% of the theoretical, for an average of six runs, of a somewhat better product. The crude, air-dried product could be used in the preparation of the ester, but a crystallization from ethanol or benzene was necessary for the decarboxylation runs.

Preparation of Benzofuran

a). A mixture of 10 g. of benzofuran-2-carboxylic acid and 1 g. of copper-bronze was heated in a small distilling flask, by means of a metal bath, until no more distillate was obtained. The product which distilled over was principally the sublimed acid, and a considerable amount of resin remained in the flask.

b). A solution of 20 g. of benzofuran-2-carboxylic acid in 100 cc. of coal tar base boiling at 140°-210°/25mm. and one gram of copper-bronze catalyst was distilled at atmospheric pressure up to 255°. This is the boiling point of the coal tar bases at atmospheric pressure and no material distilled from the solution up to this point.

c). An intimate mixture of 25 g. of benzofuran-2-carboxylic acid and 50 g. of powdered calcium oxide was heated in a distilling flask until no more product distilled over. The distillate was taken up in ether, washed with 10% sodium hydroxide solution, dried over sodium sulfate, and distilled. A 23% theoretical yield of benzofuran boiling at 170°-173° was obtained. This procedure was in accordance of the general directions of Fittig and Ebert (7).

d). An intimate mixture of 20 g. of benzofuran-2-carboxylic acid, 20 g. of powdered calcium oxide, and one gram of copper-bronze was heated in a small distilling flask with a free flame until distillation had ceased. Crude yields of 83% to 93% of the theoretical quantities of benzofuran were obtained. Washing with 10% sodium hydroxide solution, drying over sodium sulfate, and distillation at atmospheric pressure yielded a product boiling at 167°-169°.

The picrate of this material was prepared by mixing hot solutions of 1.2 g. (0.01 mole) of benzofuran in 10 cc. of alcohol, and 2.3 g. (0.01 mole) of picric acid in 20 cc. of alcohol, and letting the mixture cool to room temperature. The long needles which precipitated were crystallized from alcohol and melted at 103°-104°. The picrate has been previously reported as melting at 102° (10). If the two solutions were refluxed for a few minutes before cooling, the mixture turned a yellow green color and the only material isolated was a small amount of unreacted picric acid. The picric acid appears to oxidize the benzofuran under these conditions.

Reduction of Benzofuran

A. With sodium and ethanol.

According to the general directions of Alexander (78) for the reduction of benzofuran, a solution of 11.8 g. (0.1 mole) of benzofuran in 150 cc. of absolute ethanol was treated with 23 g. (1.0 g. atom) of sodium in small pieces. The material was kept at the reflux temperature during the reduction. At the conclusion of the reaction the solution was diluted with water and the resulting oil allowed to settle before being removed by decantation. This oil was extracted with ether, washed with water, dried over sodium sulfate, and distilled at atmospheric pressure. The principal fraction boiled at 169°-185°, and was mostly unreduced benzofuran. A refractionation of the material boiling above 185° yielded 1.5 g., 12.5% of the theoretical, of 2,3-dihydrobenzofuran boiling at 186°-188°, n_D^{26} 1.545. A picrate, made in the usual manner, and precipitated from the alcoholic reaction mixture with water, melted at 76°-77° after crystallization from a water-alcohol mixture. It is evident that a great excess of sodium is necessary to carry this reduction to completion.

B. With hydrogen and platinum-palladium catalyst.

The reduction of 11.8 g. (0.1 mole) of benzofuran in 50 cc. of alcohol was carried out with hydrogen in the presence of 0.5 g. of platinum oxide-palladium oxide catalyst at 100° and 45 lbs./sq. in. pressure. Almost quantitative yields of 2,3-dihydrobenzofuran boiling at 190°-191°, n_D^{26} 1.5375, were obtained. This product is considerably purer than that obtained by the sodium-alcohol reduction of benzofuran. The picrate from this material melted at 76°-77° after crystallization from an alcohol-water mixture. A mixed melting point with the picrate of the 2,3-dihydrobenzofuran made by sodium-alcohol reduction of benzofuran showed them to be identical.

C. With hydrogen and Raney nickel catalyst.

A solution of 11.8 g. (0.1 mole) of benzofuran in alcohol was reduced with hydrogen in the presence of Raney nickel catalyst. A pressure of 2000 lbs./sq. in. at 200° was used. The theoretical amount of hydrogen to form perhydrobenzofuran was taken up. The alcohol and catalyst were removed and the residue fractionated at atmospheric pressure. An 85% yield of material boiling at 169°-173° was obtained. Redistillation yielded a fraction with a characteristic and pleasant terpene like odor boiling at 171°-172°, n_D^{25} 1.4635.

Anal. Calcd. for $C_8H_{14}O$: C,76.13; H,11.19. Found; C,75.75; H, 11.50 .

The boiling point of the benzofuran used was 170°-171°, n_D^{25} 1.560 .

Preparation of 2,3-Benzofuran Dibromide.

The directions used in this preparation were those suggested by Fittig and Ebert (7).

A solution of 16 g. (0.1 mole) of bromine in 10 cc. of dry carbon disulfide was added to a solution of 11.8 g. (0.1 mole) of benzofuran in 50 cc. of dry carbon disulfide at 0°. The bromine decolorized as rapidly as it was introduced. The clear solution was evaporated to dryness in a stream of dry air to give a quantitative yield of large yellow crystals of crude 2,3-benzofuran dibromide melting at 82°-83°. The crude material was used to prepare 2- and 3-bromobenzofuran.

Preparation of 3-Bromobenzofuran

The general procedure used for the preparation of 3-bromobenzofuran and 2-bromobenzofuran has been outlined by Stoermer and Kahlert (67).

a). A solution of 0.1 mole of crude 2,3-benzofuran dibromide, as made in the preceeding preparation, and 25 g. (0.45 mole) of potassium hydroxide in 150 cc. of absolute ethanol was allowed to stand at 0° four hours and at room temperature 10 hours. The alcoholic mixture was warmed to 60° for a few minutes before steam distillation. The distillate precipitated a colorless oil which was removed by decantation and steam distilled again. The distillate was extracted with ether, dried over sodium sulfate, and fractionated at atmospheric pressure. A 14 g. yield, 71% of the theoretical, boiling at 218°-220° was obtained. This material solidified readily in an ice bath.

b). An exactly similar run was made except that the powdered 2,3-benzofuran dibromide was added in portions to a hot solution of 25 g. of potassium hydroxide in 75 cc. of absolute ethanol. An 86.3% yield of 3-bromobenzofuran was obtained in this case.

Preparation of 2-Bromobenzofuran

One-tenth mole of crude dry benzofuran-2,3-dibromide, prepared as described above, was distilled at atmospheric pressure. A vigorous evolution of hydrogen bromide took place and the material distilling at 200°-225° was taken. This distillate was dissolved in ether, washed with water, 10% sodium carbonate solution, again with water, and dried over sodium sulfate. The ether was removed and the residue fractionated at atmospheric pressure. A 55% yield of 2-bromobenzofuran, boiling at 220°-225°, was obtained.

Preparation of 2,3-Dibromobenzofuran

This material was made according to the synthesis outlined by Stoermer, Richter, and Gralert (10).

A solution of 16.8 g. (0.085 mole) of 3-bromobenzofuran and 15.2 g. (0.095 mole) of bromine in 60 cc. of dry carbon disulfide was gently refluxed 3 hours. A vigorous reaction took place. The solvent, and a slight excess of bromine, were gently distilled from the bromination product and the residue fractionated at atmospheric pressure. Hydrogen bromide was evolved in considerable quantities. A crude yield of 19.5 g., 83% of the theoretical, of 2,3-dibromobenzofuran boiling at 260°-270° was obtained. Redistillation, after washing with 10% sodium hydroxide solution and water, yielded a product boiling at 266°-267°.

Attempted Preparation of Benzofuran-3-carboxylic Acid From 3-Bromobenzofuran

a). An attempt to prepare a Grignard reagent was made in the usual way from 2 g. (0.01 mole) of 3-bromobenzofuran and one g. of copper-magnesium alloy in 50 cc. of dry ether. A reaction apparently took place, though not readily. Iodine was decolorized immediately, but no color test was obtained. A considerable amount of white precipitate was formed in the solution. A few drops of n-butyl bromide was added to the reaction and allowed to react for a few minutes at the refluxing temperature of ether. No color test was obtained from this solution either, though the reagents were checked. The solution was allowed to reflux two hours, and poured on solid carbon dioxide. When the reaction had ceased, water and 10% sodium hydroxide was added, and the solution filtered and separated. The solid material was extracted with hot 5% sodium hydroxide solution and the alkaline extracts combined, concentrated, and acidified. No precipitate appeared.

b). An intimate mixture of 3 g. (0.015 mole) of 3-bromobenzofuran and 5 g. (0.028 mole) of cuprous cyanide was heated at the reflux temperature 5 hours. At the conclusion of this time the reaction products had become a solid mass. The material was broken up and refluxed with a solution of 20 g. of potassium hydroxide in 100 cc. of ethanol for 8 hours. The product was filtered, steam distilled, and the residue of the steam distillation treated with Norite. Acidification yielded no appreciable precipitate.

c). A mixture of 2 g. (0.01 mole) of 3-bromobenzofuran, 2 g. of potassium cyanide, 1 g. of cuprous cyanide, 5 cc. of ethanol, and 5 cc. of water was heated 10 hours in a sealed tube at 195°-205°. The product was refluxed with alcoholic potassium hydroxide several hours and the alcohol distilled off. The aqueous solution was treated with Norite and acidified. A minute yield of a thick oil appeared which soon hardened to a gummy mass. It was not investigated further.

Attempted Preparation of Benzofuran-2-carboxylic Acid From 2-Bromobenzofuran

A Grignard reagent was attempted in the usual manner from 4 g. (0.02 mole) of 2-bromobenzofuran and 1 g. of 40-60 mesh magnesium, plus a crystal of iodine, in 50 cc. of dry ether. No appreciable reaction took place. The solution was refluxed 24 hours, but no color test was obtained at the conclusion of this time. A Grignard reagent was prepared from 2.75 g. (0.02 mole) of *n*-butyl bromide and 1 g. of magnesium turnings, and added to the solution. This mixture was refluxed 24 hours and carbonated with gaseous carbon dioxide at -15° to an absence of the color test. The reaction was worked up in the usual way, but no carboxylic acid was isolated.

Attempted Preparation of 2-Aminobenzofuran

A mixture of 2 g. (0.01 mole) of 2-bromobenzofuran, 4 g. of cuprous bromide catalyst, and 15 cc. of concentrated ammonium hydroxide was heated in a sealed tube at 195° - 205° for 9 hours. The product was extracted with ether, and the ether extract dried over sodium sulfate. Saturation of the extract with dry hydrogen chloride did not yield a precipitate. Aromatic amine hydrochlorides are insoluble in ether when made in this fashion.

Attempted Preparation of 3-Aminobenzofuran

An exactly similar reaction as that in the preceeding paragraph was run, using 2 g. (0.01 mole) of 3-bromobenzofuran. The same negative results were obtained.

Attempted Iodination of Benzofuran

a). A mixture of 11.8 g. (0.1 mole) of benzofuran, 14 g. (0.11 mole) of iodine, 21.7 g. (0.1 mole) of yellow mercuric oxide, and 200 cc. of 77°-105° petroleum ether was refluxed 90 minutes. At the conclusion of this time the iodine color was gone from the solution. The mixture was filtered, and the solvent dried and distilled. A quantitative yield of benzofuran was recovered and no evidence of an iodinated product obtained. Petroleum ether takes up iodine fairly readily under these conditions.

b). A suspension of 21.7 g. (0.1 mole) of yellow mercuric oxide in a solution of 11.8 g. (0.1 mole) of benzofuran and 14 g. (0.11 mole) of iodine in 200 cc. of dry carbon tetrachloride was refluxed 3 hours. The suspension was filtered hot, and the filtrate washed with thiosulfate solution and dried over sodium sulfate. The solvent was removed and product fractionated at reduced pressure. A 55% recovery of benzofuran was made. Decomposition, accompanied by the distillation of iodine vapors, took place when an attempt was made to distill the residue at 18 mm.

Metalation of Benzofuran

a). A solution of 5.9 g. (0.05 mole) of benzofuran in 50 cc. of dry dioxane was refluxed 52 hours with 0.7 g. (0.1 g. atom) of lithium in small pieces. No color test was obtained at the conclusion of this time and no evidence of reaction was noticeable.

b). A solution of n-butyl-lithium was prepared in the usual manner from 27.4 g. (0.2 mole) of n-butyl bromide and 3.05 g. (0.44 g. atom) of metallic lithium in 150 cc. of dry ether. To this solution was added 11.8 g. (0.1 mole) of benzofuran in 70 cc. of dry ether. A reaction took place immediately, accompanied by the evolution of gas. The slightly colored solution was refluxed 12 hours and carbonated with solid carbon dioxide. The product was extracted with water to which had been added 25 cc. of 10% sodium hydroxide solution. The alkaline extract was separated, treated with Norite, and acidified. The product melted at 183°-186°, and 47.5% of the theoretical yield was obtained. The material was purified by crystallization of the potassium salt from 85% ethanol. A melting point of 193.5° was obtained for the free acid. A mixed melting point with authentic benzofuran-2-carboxylic acid was not depressed.

Acetylation of Benzofuran

Ten and two-tenths grams (0.1 mole) of acetic anhydride was added dropwise to a well stirred solution of 11.8 g. (0.1 mole) of benzofuran and 52.2 g. (0.2 mole) of stannic chloride in 100 cc. of dry benzene. The addition caused the solution to reflux gently and darken to a considerable extent. The mixture was gently refluxed 5 hours at the conclusion of the addition and poured on cracked ice. Ether was added and the ether-benzene layer separated. The solvent mixture was washed twice with 10% sodium hydroxide solution, once with water, and dried over anhydrous sodium sulfate. The solvent was removed and the residue fractionated at reduced pressure. The material boiling at 133°-134°/13 mm. weighed 4.9 g., 32.6% of the theoretical, and solidified when cooled to room temperature. It melted at 72° after two crystallizations from petroleum ether. A mixed melting point of this material with authentic 2-acetylbenzofuran, prepared according to the directions of Stoermer (12), showed them to be identical.

Oxidation of 2-Acetylbenzofuran

As additional orientation evidence, 2-acetylbenzofuran was oxidized to benzofuran-2-carboxylic acid.

A solution of 4.75 g. (0.0375 mole) of iodine in 75 cc. of potassium iodide solution was added to a solution of 2 g. (0.0125 mole) of 2-acetylbenzofuran, made by the acetylation of benzofuran, in 20 cc. of 10% sodium hydroxide solution and 50 cc. of dioxane. The iodine solution was added at room temperature, in portions, as fast as it was decolorized. The reaction was completed at 60°. The mixture was made strongly basic at the completion of the reaction with 25 cc. of 10% sodium hydroxide solution and cooled. The major portion of the precipitated iodoform was removed by decantation and the supernatant liquid acidified. The resulting milky liquid was extracted with ether. The ether solution was washed with sodium thiosulfate solution, water, and finally with 5% sodium hydroxide solution several times. The alkaline extract was treated with Norite and acidified. A 0.45 g. yield, 22.2% of the theoretical, of benzofuran-2-carboxylic acid was obtained. Crystallization of the potassium salt of this acid from alcohol gave a product which melted at 191°-192° as the free acid. A mixed melting point of this product with authentic benzofuran-2-carboxylic acid was not depressed.

Attempted Sulfonation of Benzofuran

a). Twelve and eight-tenths grams (0.11 mole) of chlorosulfonic acid was added, dropwise, with stirring, at 5° to 10°, to a solution of 11.8 g. (0.1 mole) of benzofuran in 75 cc. of dry carbon tetrachloride. At the completion of the addition the mixture was stirred at 25° for 3 hours. A considerable quantity of hydrogen chloride was evolved. The mushy mixture was poured on cracked ice, and the carbon tetrachloride layer separated. The residue was digested with 1.5 liters of water, treated with Norite, and neutralized with barium carbonate. The product was extracted thoroughly with hot water and the filtrate evaporated to dryness. A 12 gram yield of material was obtained. This was not benzofuransulfonic acid as attempts to prepare the p-toluidide and sulfonyl chloride derivatives failed completely.

b). A run exactly similar to a) was made, except that 200 cc. of carbon tetrachloride was used as a solvent and the reaction was run at 0° to 5°. The aqueous layer was separated from the carbon tetrachloride as usual and immediately neutralized with barium carbonate. The product was well extracted with hot water and the solution evaporated almost to dryness. A small amount of precipitate appeared. The solution was treated with just enough sulfuric acid to precipitate the barium, and evaporated carefully to dryness. The residue was negligible.

c). A similar reaction was attempted at -10° in the presence of 15 cc. of acetic anhydride. The product was stirred at room temperature an hour at the completion of the addition of the chlorosulfonic acid and poured upon cracked ice. The acetic acid was removed by steam distillation after the carbon tetrachloride layer had been separated. The residue of the steam distillation was concentrated to a small volume and cooled. No precipitate appeared. Treatment with barium carbonate in the usual manner yielded no soluble barium salt.

d). A solution of 10 cc. of concentrated sulfuric acid in 15 cc. of acetic anhydride was added, at -10° to -15°, to a solution of 11.8 g. (0.1 mole) of benzofuran in 35 cc. of acetic anhydride. At the conclusion of the addition the mixture was poured upon cracked ice and thoroughly extracted with ether. The aqueous solution was concentrated and cooled. No precipitate was formed. The acetic acid was removed by steam distillation and the residue concentrated again. No precipitate appeared upon cooling.

Preparation of Benzofuran-2-sulfonic Acid

a). A solution of n-butyl-lithium was prepared in the usual manner from 13.7 g. (0.1 mole) of n-butyl bromide and 1.46 g. (0.21 g. atom) of lithium in 125 cc. of dry ether, and filtered into a solution of 5.9 g. (0.05 mole) of benzofuran in 100 cc. of ether. The latter solution was refluxed gently 12 hours, cooled to -18° and saturated with dry sulfur dioxide gas to an absence of color test. The ether solution was poured upon cracked ice, made basic with 10% sodium hydroxide solution, and the layers separated. The aqueous layer was made strongly basic with 30 g. of potassium hydroxide and treated with 10% potassium permanganate solution until the color persisted. The solution was decolorized with alcohol, filtered hot, acidified with sulfuric acid, and neutralized with barium carbonate. This material, when worked up in the usual way, contained no soluble barium salt. As potassium permanganate completely and easily oxidizes benzofuran-2-carboxylic acid in a basic solution, it probably also oxidizes completely any benzofuransulfonic acid that is formed.

b). A similar run was made, with the exception that the precipitate resulting from the treatment of the 2-benzofuryllithium with sulfur dioxide was filtered from the ether solution, dissolved in water, and oxidized with an excess of 30% hydrogen peroxide. The product was boiled with Norite, filtered hot, cooled, and concentrated. A 0.7 gram yield of benzofuran-2-sulfonic acid as pearly flakes was recovered upon cooling. An extraction of the ether filtrate with a basic solution, and subsequent oxidation of the basic extract with hydrogen peroxide, gave a 2 g. yield of the same material upon acidification, concentration, and cooling. The total yield amounted to 27.4% of the theoretical. The preparation of the p-toluidide of this acid from 0.7 g. of this product and 1 g. of p-toluidine hydrochloride in 20 cc. of hot water yielded a derivative melting at 188°-189° after crystallization from hot water.

Anal. Calcd. for $C_{15}H_{15}O_4NS$: N, 4.53 . Found: N, 4.31 .

Attempted Mercuration of Benzofuran

a). A solution of 11.8 g. (0.1 mole) of benzofuran and 31.8 g. (0.1 mole) of mercuric acetate in 200 cc. of ethanol was kept at 30°-40° for 10 hours. At the conclusion of this time a quantitative yield of mercurous acetate was recovered. The alcoholic filtrate was concentrated to 100 cc. and 100 cc. of 10% sodium hydroxide solution added. The mixture was steam distilled until the condensate came over clear. The residue was filtered and acidified. A heavy brown oil resulted. The appearance of this alkali soluble organic compound, and the presence of the mercurous acetate, suggests the oxidation of the benzofuran nucleus by this reagent.

b). A suspension of 5.9 g. (0.05 mole) of benzofuran in a solution of 13.5 g. (0.05 mole) of mercuric chloride and 27.2 g. (0.2 mole) of sodium acetate in 300 cc. of water was shaken 5 days at room temperature. At the conclusion of this time no precipitate had formed and the benzofuran was recovered.

Esterification of Benzofuran-2-carboxylic Acid

This investigation was made in an effort to determine the most convenient method of preparing the large amounts of ester needed in the following reactions.

a). Two grams of pure benzofuran-2-carboxylic acid was treated with a slight excess of diazomethane in ether. The ether solution was filtered and evaporated to dryness. The resulting white crystals of methyl benzofuran-2-carboxylate melted at 54°-55°.

b). A mixture of 20 g. (0.123 mole) of benzofuran-2-carboxylic acid, 5.2 g. (0.13 mole) of sodium hydroxide, and 18.7 g. (0.15 mole) of dimethyl sulfate in 100 cc. of water was made by adding the dimethyl sulfate slowly to a solution of the other reagents at 10°. The mixture was refluxed 5 hours and allowed to cool. A small yield of methyl benzofuran-2-carboxylate solidified. This material was identified by comparison with the methyl benzofuran-2-carboxylate prepared in a). Acidification of the basic residue resulted in an almost quantitative recovery of benzofuran-2-carboxylic acid.

c). A solution of 25 g. of crude benzofuran-2-carboxylic acid in 100 cc. of absolute ethanol was saturated with dry hydrogen chloride at 0° and heated to gentle reflux for one hour. The solution was poured upon cracked ice, and the resulting precipitate filtered out. This product was dissolved in ether, washed with sodium carbonate solution, and dried over sodium sulfate. Distillation at atmospheric pressure gave an 80% yield of ethyl benzofuran-2-carboxylate boiling at 278°-280°. Failure to heat the saturated hydrogen chloride solution of the acid and alcohol reduced the yields. Smaller yields were also obtained when larger runs were tried by this method.

d). A solution of 25 g. of crude benzofuran-2-carboxylic acid in 75 cc. of absolute ethanol and 20 cc. of concentrated sulfuric acid was gently refluxed 10 hours. The brownish solution was poured upon cracked ice and the resulting precipitate dissolved in ether. The ether extract was washed with 10% sodium carbonate solution and water, and dried over sodium sulfate. Distillation at atmospheric pressure gave a 73.5% yield of ethyl benzofuran-2-carboxylate boiling at 278°-280°. A recovery of about 15% of the unchanged acid was made through acidification of the sodium carbonate extract. Runs of 100 g.

of the acid were successfully carried out by this method in about this yield.

Attempted Catalytic Reduction of Ethyl Benzofuran-2-carboxylate

The hydrogenation of 19 g. (0.1 mole) of ethyl benzofuran-2-carboxylate in ethanol, in the presence of Raney nickel catalyst, was attempted at 2500 lbs./sq in. and 215°. No appreciable amount of hydrogen was taken up. Twenty-five cc. of decahydronaphthalene was added and the alcohol removed. This solution was treated with hydrogen at 3100 lbs./sq. in. and 275°-280°. No hydrogen was taken up. A 91% recovery of ethyl benzofuran-2-carboxylate was made.

Attempted Bromination of Benzofuran-2-carboxylic Acid

A suspension of 8.1 g. (0.05 mole) of benzofuran-2-carboxylic acid and 8.8 g. (0.055 mole) of bromine in 100 cc. of dry carbon tetrachloride was refluxed 25 hours. A pinch of iron powder was added as a catalyst and the refluxing continued for 25 hours. At the conclusion of this time a great deal of the benzofuran-2-carboxylic acid was still in suspension. A few crystals of iodine and 25 cc. of glacial acetic acid was added and the refluxing continued for an additional 25 hours. Unreacted bromine was still present in the solution at this time. The reaction mixture was heated gently until the bromine, and most of the solvent, had been removed. The remainder was diluted with water, extracted with ether, and the ether extracted with

10% sodium hydroxide solution. Acidification of the alkaline extract yielded a quantitative recovery of impure benzofuran-2-carboxylic acid melting at 165°-172°. Crystallization from dilute acetic acid and a mixed melting point with authentic acid was the means of identification used.

Bromination of Ethyl Benzofuran-2-carboxylate

A solution of 9.5 g. (0.05 mole) of ethyl benzofuran-2-carboxylate, 8.8 g. (0.055 mole) of bromine, and a pinch of iron powder in 25 cc. of glacial acetic acid was refluxed until the evolution of hydrogen bromide ceased. The reaction was fairly rapid. The mixture was poured upon ice and made strongly basic with sodium hydroxide. The basic solution was refluxed 4 hours, treated with Norite, and concentrated until a precipitate formed in the hot solution. Cooling precipitated a 55% yield of crude sodium 5-bromobenzofuran-2-carboxylate. The free acid melted at 190°-210°. Two crystallizations of the sodium salt from 10% sodium hydroxide, and four crystallizations of the free acid from ethanol raised the melting point to 254°-255°. A mixed melting point of this material with authentic 5-bromobenzofuran-2-carboxylic acid showed no depression. The authentic derivative was prepared both from the 3,6-dibromocoumarin of Perkin (6) and by the action of 5-bromosalicylic acid upon ethyl bromoacetate. Stoermer (10) also prepared 5-bromobenzofuran-2-carboxylic acid by the reaction of 5-bromosalicylaldehyde and chloracetic acid.

An attempt to dibrominate ethyl benzofuran-2-carboxylate in the above manner, using two and one-half equivalents of bromine, resulted in a product from which was isolated 12% yields of 5-bromobenzofuran-2-carboxylic acid.

Preparation of 5-Bromobenzofuran-2-carboxylic Acid

A solution of sodium ethylate, prepared from 2.3 g. (0.1 g. atom) of sodium in 75 cc. of absolute ethanol, was added to a well stirred solution of 18.1 g. (0.09 mole) of 5-bromosalicylaldehyde and 16.7 g. (0.1 mole) of ethyl bromoacetate in 150 cc. of absolute ethanol, and the solution refluxed 8 hours. To the now acidic solution an additional 0.065 moles of sodium ethylate was added and the refluxing continued two hours. A solution of 10 g. of potassium hydroxide in 100 cc. of water was added and the alcohol distilled off slowly. The product was acidified and the resulting crystals filtered out. This organic acid was converted to the potassium salt by addition to an alcoholic potassium hydroxide solution. The potassium salt was filtered from the cold solution, acidified, and crystallized from ethanol. A 5.5 g. yield, 25% of the theoretical, of 5-bromobenzofuran-2-carboxylic acid, melting at 254°-255°, was obtained.

Nitration of Ethyl Benzofuran-2-carboxylate

Twenty-five cc. of fuming nitric acid was added dropwise, with stirring, to a solution of 19 g. (0.1 mole) of ethyl benzofuran-2-carboxylate and 20 cc. of concentrated sulfuric acid in 30 cc. of glacial acetic acid at 70°-80°. At the conclusion of the addition the mixture was stirred 30 min. at 75° and poured on cracked ice. The supernatant liquid was decanted from the resulting semi-solid mass, and the product extracted with ether and 10% sodium carbonate solution. The ethyl 5-nitrobenzofuran-2-carboxylate was not appreciably soluble in either reagent. Crystallization of this product from ethanol gave a 21.2% yield of product melting at 152°-153°. This agrees with the melting point of Dey and Row (23) for ethyl 5-nitrobenzofuran-2-carboxylate as prepared by a different method.

Acidification of the sodium carbonate extract gave a 19.3% yield of crude 5-nitrobenzofuran-2-carboxylic acid. From the ether extract was obtained an alkali insoluble material melting at 70°-105°. No fraction of a definite melting point was isolated from this material.

The hydrolysis of 0.5 g. of ethyl 5-nitrobenzofuran-2-carboxylate was carried out with 30 cc. of 10% sodium hydroxide solution. The solution was gently warmed until the solution was clear, cooled, and the resulting precipitate filtered out. The sodium salt was dissolved in water and acidified. A quantitative yield of 5-nitrobenzofuran-2-carboxylic acid, as described by Dey and Row (23), was obtained, melting at 274°-275° after crystallization from hot water. A mixed melting point showed them to be identical.

Oxidation of Ethyl 5-Nitrobenzofuran-2-carboxylate

A suspension of 0.5 g. of ethyl 5-nitrobenzofuran-2-carboxylate in a solution of 3 g. of sodium hydroxide in 30 cc. of water was gently heated until the solution was clear. The basic solution was oxidized with 5% potassium permanganate solution until no more decolorization took place. The mixture was filtered hot and the filtrate acidified. Crystallization of the product from hot water gave a quantitative yield of 5-nitrosalicylic acid melting at 227°-228°. A mixed melting point with an authentic specimen was the means of identification used.

Reduction of Ethyl 5-Nitrobenzofuran-2-carboxylate

A solution of 3.5 g. (0.015 mole) of ethyl 5-nitrobenzofuran-2-carboxylate in 10 cc. of ethanol was reduced with hydrogen in the presence of Raney nickel catalyst at 45 lbs./sq. in. and 100°. The calculated amount of hydrogen was quickly taken up. The catalyst was filtered from the solution, ether added to the alcoholic filtrate, and the mixture saturated with dry hydrogen chloride. A 45.5% yield of crude ethyl 5-aminobenzofuran-2-carboxylate hydrochloride was obtained. The crude material was crystallized from 2N hydrochloric acid to yield 5-aminobenzofuran-2-carboxylic acid hydrochloride melting at 253°.

Anal. Calcd. for $C_9H_8O_3NCl$; N, 6.56 . Found: N, 6.57 .

The preparation of 5-aminobenzofuran-2-carboxylic acid hydrochloride by another method has been described (22), but no constants or details are given.

Attempted Preparation of 5-Nitrobenzofuran-2-carboxylic Acid

A solution of 30.5 g. (0.18 mole) of ethyl bromoacetate in 100 cc. of absolute alcohol was added to a suspension of 33 g. (0.175 mole) of sodium 5-nitrosalicylaldehyde in 300 cc. of absolute alcohol, and the mixture refluxed until no longer basic to phenolphthalein. A solution of 0.13 mole of sodium ethylate in 150 cc. of absolute ethanol was added and the refluxing continued 4 hours. At the conclusion of this time a solution of 15 g. of potassium hydroxide in 200 cc. of water was added and the alcohol distilled from the solution slowly. The alkaline solution was concentrated, cooled, and filtered. The precipitate was sodium 5-nitrosalicylaldehyde. The filtrate was acidified, the sodium salt made of the product, and the sodium salt crystallized once from water. A yield of 1.9 g. of product melting at 202°-205° was obtained. Crystallization of this product from dilute acetic acid raised the melting point to 225°-226°, and a mixed melting point with 5-nitrosalicylic acid showed them to be identical.

Preparation of 3-Bromo-6-nitrocoumarin

a). The bromination of 9.5 g. (0.05 mole) of 6-nitrocoumarin in 200 cc. of glacial acetic acid with 8.2 g. (0.051 mole) of bromine failed to give any brominated product, and a 90% recovery of 6-nitrocoumarin was made.

b). A solution of 19 g. (0.1 mole) of 6-nitrocoumarin and 17.6 g. (0.11 mole) of bromine in 20 cc. of carbon tetrachloride was heated in a sealed tube at 165° for 6 hours. The crystalline product was crystallized twice from glacial acetic acid to yield 21.5 g., 80% of the theoretical, of 3-bromo-6-nitrocoumarin melting at 215°. This material has been previously prepared by the nitration of 3-bromocoumarin (22).

Acetylation of Ethyl Benzofuran-2-carboxylate

Eleven and eight-tenths grams (0.15 mole) of acetyl chloride was added rapidly to a well stirred solution of 19 g. (0.1 mole) of ethyl benzofuran-2-carboxylate and 20 g. (0.15 mole) of anhydrous aluminum chloride in 100 cc. of dry carbon disulfide. At the conclusion of the addition, the mixture was heated on the steam bath 4 hours and the carbon disulfide removed. The residue was hydrolyzed with an ice-dilute hydrochloric acid mixture and extracted with ether. The ether extract was thoroughly washed with 10% sodium hydroxide solution and water, and dried over anhydrous sodium sulfate. The ether was removed and the residue fractionated at reduced pressure. A 14.6 g. recovery of unchanged ethyl benzofuran-2-carboxylate was made, and a product boiling at 184°/3 mm. obtained. This is a 75% yield of ethyl 5-acetylbenzofuran-2-carboxylate on the basis of the ethyl benzofuran-2-carboxylate used. Four crystallizations from ethanol gave a product melting at 112.5°-114.5°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.21; H, 5.21 . Found: C, 67.52; H, 5.65 .

A similar run, using 40 g. (0.3 mole) of aluminum chloride, resulted in a yield of 5.6 g. of ethyl 5-acetylbenzofuran-2-carboxylate, but no appreciable amount of unchanged starting material was recovered.

Oxidation of Ethyl 5-Acetylbenzofuran-2-carboxylate

A suspension of 2 g. (0.01 mole) of ethyl 5-acetylbenzofuran-2-carboxylate in 50 cc. of 3% sodium hydroxide solution was heated gently until hydrolyzed. The solution was treated with 9.1 g. (0.0575 mole) of potassium permanganate, as a 5% solution in water, in portions, at room temperature. The colorless reaction mixture was filtered hot, concentrated, and acidified. The precipitate melted at about 288°. Crystallization from water raised the melting point to 305°. The reported melting point of 4-hydroxyisophthalic acid is 310° (83). A solution of 100 mg. of this product in 10 cc. of absolute methanol was saturated with dry hydrogen chloride at 0° and concentrated to 5 cc. by boiling. Cooling precipitated crude dimethyl ester of 4-hydroxyisopthalic acid melting at 96° after crystallization from dilute methanol. A mixed melting point with authentic dimethyl ester of 4-hydroxyisophthalic acid (84) showed them to be

(83) Graebe and Kraft, Ber., 39, 794 (1906)
(84) Jacobsen, Ber., 11, 374 (1878)

identical. The authentic 4-hydroxyisophthalic acid was prepared according to the directions of Jacobsen and Lönnies (85), and was esterified with absolute methanol and hydrogen chloride according to the above method.

Attempted Mercuration of Ethyl Benzofuran-2-carboxylate

a). A suspension of 4.75 g. (0.025 mole) of ethyl benzofuran-2-carboxylate was refluxed 30 hours with a solution of 8 g. (0.025 mole) of mercuric acetate in 200 cc. of water. At the conclusion of this time the only precipitates present in the reaction mixture were metallic mercury and mercuric oxide. Steam distillation gave a 70% recovery of ethyl benzofuran-2-carboxylate.

b). A solution of 4.75 g. (0.025 mole) of ethyl benzofuran-2-carboxylate, 8 g. (0.025 mole) of mercuric acetate, and 20 cc. of glacial acetic acid in 120 cc. of ethanol was refluxed 30 hours. At the conclusion of this time a yield of 1.3 g. of mercurous acetate was obtained. The alcohol was removed from the solution by distillation and the residue refluxed an additional 5 hours. A considerable further yield of mercurous acetate was obtained. Steam distillation of the reaction product recovered most of the ethyl benzofuran-2-carboxylate. An inappreciable amount of material was left as a residue of the steam distillation.

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(85) Jacobsen and Lönnies. Ber., 13, 1556 (1880).

c). Sixteen grams (0.05 mole) of powdered mercuric acetate was added in portions, with stirring, to 9.5 g. (0.05 mole) of ethyl benzofuran-2-carboxylate at 135°-150°. Acetic acid distilled from the mixture during the addition. At the conclusion of the addition the mixture was heated at this temperature one hour, cooled, and extracted with ether. Mercury, mercurous acetate, and mercuric acetate was identified in the ether insoluble portion. A small amount of an impure organic material containing mercury was also found in this ether insoluble portion. The yield was too impure and too slight to be investigated.

Preparation of 2,3-Dihydrobenzofuran

The beta-bromoethylphenyl ether used in this reaction was prepared in 20% yields by refluxing a solution of one mole of sodium phenolate and 1.5 mole of ethylene bromide for 12 hours in 350 cc. of absolute ethanol. The product was thrown out by dilution with water, dissolved in ether, washed with sodium carbonate solution and water, dried, and distilled at reduced pressure. The fraction boiling at 130°-140°/37 mm. was taken.

The general directions followed for the preparation of 2,3-dihydrobenzofuran from beta-bromoethylphenyl ether and beta-hydroxyethylphenyl ether, by the use of anhydrous zinc chloride, are those of Rindfusz (44).

A mixture of 40 g. of beta-bromoethylphenyl ether and 5 g. of freshly fused zinc chloride was heated under reflux at an oil bath temperature of 200°-210° for 2 hours. The product was dissolved in ether, washed thoroughly with 10% sodium carbonate solution and water, and dried over sodium sulfate. The ether was removed and the residue distilled at atmospheric pressure. A 26.8% yield of crude 2,3-dihydrobenzofuran boiling at 187°-191° was obtained.

The treatment of beta- hydroxyethylphenyl ether with zinc chloride in a similar manner yielded no appreciable amount of 2,3-dihydrobenzofuran. Rindfusz reported a 25% yield by means of this method.

The action of phosphorus pentoxide upon beta-hydroxyethyltolyl ethers has been reported to give 50% yields of the substituted 2,3-dihydrobenzofurans (45).

A solution of 69 g. (0.5 mole) of beta-hydroxyethylphenyl ether in 20 cc. of dry benzene was added in portions, with shaking, to a suspension of 35.5 g. (0.25 mole) of phosphorus pentoxide in 100 cc. of dry benzene. At the conclusion of the addition the solution was refluxed one hour and cooled. The reaction product was filtered, the precipitate washed with ether, and the ether and benzene solutions combined and dried over sodium sulfate. Distillation at atmospheric pressure yielded no fraction boiling in the vicinity of 190°, the boiling point of 2,3-dihydrobenzofuran.

Attempted Preparation of 2-Methyl-2,3-dihydrobenzofuran

The o-allylphenol used in this reaction was prepared according to the directions of Claisen (86). The ring closure procedure was that suggested by a patent (48).

Fifty grams of pyridine was cooled to 0° and dry hydrogen chloride run in until the mixture solidified. The pyridine hydrochloride was heated to 180° in an atmosphere of hydrogen chloride and 26.8 g. (0.2 mole) of o-allylphenol added. The reaction mixture was heated 8 hours at 220°-240°. The mass solidified upon cooling. The addition of water did not dissolve an appreciable amount of this material and steam distillation yielded no product. 2-Methyl-2,3-dihydrobenzofuran readily steam distills.

Preparation of o-Acetaminophenylallyl Ether

o-Aminophenol was acetylated in quantitative yields with one equivalent of acetic anhydride in benzene solution.

A suspension of 75.5 g. (0.5 mole) of o-acetaminophenol and 70.5 g. (0.51 mole) of powdered potassium carbonate in 350 cc. of dry acetone was vigorously stirred and 60.5 g. (0.5 mole) of allyl bromide added in portions. The mixture was refluxed 5 hours, some of the solvent removed, and the residue diluted with water. The precipitated thick oil was extracted with ether, washed

(86) Claisen, Ber., 45, 3157 (1912), Claisen. Ann., 401, 56 (1913)

thoroughly with 10% sodium hydroxide solution and water, and dried over anhydrous sodium sulfate. The ether was removed and the product dried at 45°. A 78.3% yield of crude *o*-acetaminophenylallyl ether melting at 47°-48° was obtained. The material melted at 51°-52° after crystallization from a benzene-petroleum ether mixture.

Anal. Calcd. for $C_{11}H_{13}O_2N$: N, 7.33 . Found : N, 7.54 .

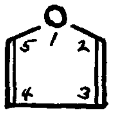
Preparation of *o*-Acetamino-*o*-allylphenol

A solution of 54.3 g. (0.25 mole) of crude *o*-acetaminophenylallyl ether in 50 cc. of dimethylaniline was refluxed 8 hours in an atmosphere of carbon dioxide. Ether was added to the cold reaction product and the dimethylaniline removed by extraction with 500 cc. of 3N sulfuric acid in three portions. The residual ether solution was thoroughly extracted with 10% sodium hydroxide solution and the alkaline extract acidified. The resulting precipitate of crude *o*-acetamino-*o*-allylphenol melted at 100°-103° and the yield was 49.7% of the theoretical. The product melted at 115° after two crystallizations from 50% acetic acid.

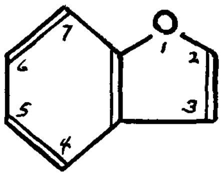
Anal. Calcd. for $C_{11}H_{13}O_2N$: N, 7.33 . Found : N, 7.41 .

DISCUSSION OF RESULTS

The results of this investigation indicate even more clearly the great similarity existing between furan and benzofuran. Furan (VII), and derivatives, with but one known exception, orients entering groups to the 2- or 5- positions (87), corresponding to the 2- position of benzofuran (I).



VII



I

The orientation of a nitro group in benzofuran to the position adjacent to the oxygen (67), and the addition of halogens to the 2,3- linkage (7)(13), are characteristic of furan (87). We have now two additional reactions which are oriented in the 2- position of benzofuran, metalation, by means of n-butyl-lithium, and acetylation, by means of acetic anhydride and stannic chloride.

The proof of the position assumed by the entering group in the metalation reaction was through carbonation of the intermediate 2-benzofuryl-lithium to the known benzofuran-2-carboxylic acid.

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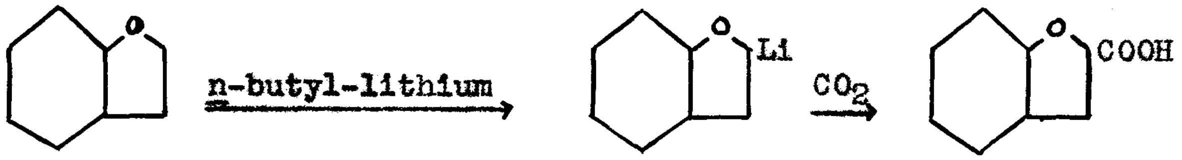
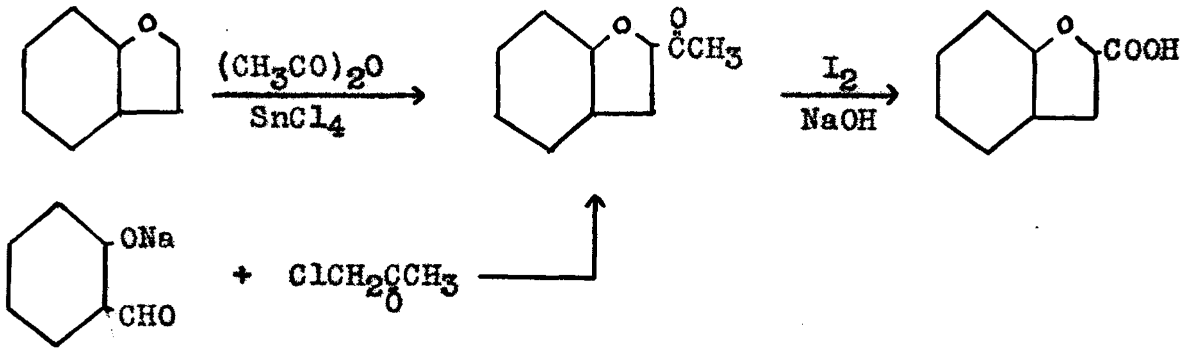
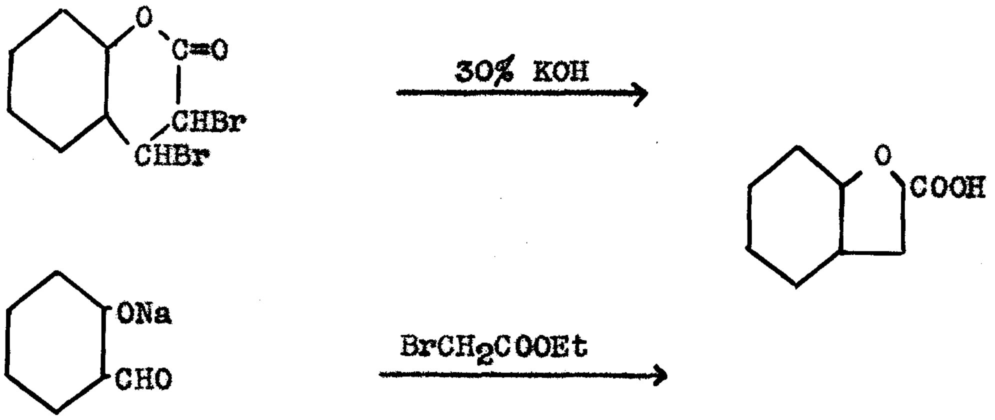
(87) Gilman and Wright, Chem. Reviews, 11, 323 (1932).



The acetylbenzofuran formed by the acetylation of benzofuran was also converted to benzofuran-2-carboxylic acid by means of mild oxidation, and, in addition, compared with 2-acetylbenzofuran prepared by the method of Stoermer (12).



The authentic benzofuran-2-carboxylic acid used as a reference compound in these two cases was prepared from 3,4-coumarin dibromide according to the method of Perkin (5), and from salicylaldehyde and ethyl bromoacetate.



The preparation of 2,3-benzofuran dibromide (7), 2-bromo- and 3-bromobenzofuran (67), and 2,3-dibromobenzofuran (10)(69) by various workers have been checked in substance, and details of procedure and yields given.

It has been shown that the preparation of a Grignard reagent from 2-bromo- and 3-bromobenzofuran can not be classed as an easy reaction, though it can not be classed as unavailable on the basis of the two runs tried. It is suggested that a Grignard reagent be attempted with 2,3-benzofuran dibromide. The aliphatic nature of this compound might be expected to activate the bromo group. The unreactivity of the bromobenzofurans have also been demonstrated in the failure of the reaction to synthesize benzofuran-2-carboxylic acid from 3-bromobenzofuran, *via* the benzofuran-3-nitrile. It is believed, however, that modifications of the sealed tube reaction (88) will result in an appreciable yield of this product. In view of the failure to obtain 2-aminobenzofuran by the reduction of 2-nitrobenzofuran (75) and of the difficulties encountered in obtaining aminofurans (87), it is not surprising that the attempted replacements of the bromo group by an amino group in 2-bromo- and 3-bromobenzofuran should fail. Methyl benzofuran-2-carbamate has been prepared by the action of sodium hypochlorite on

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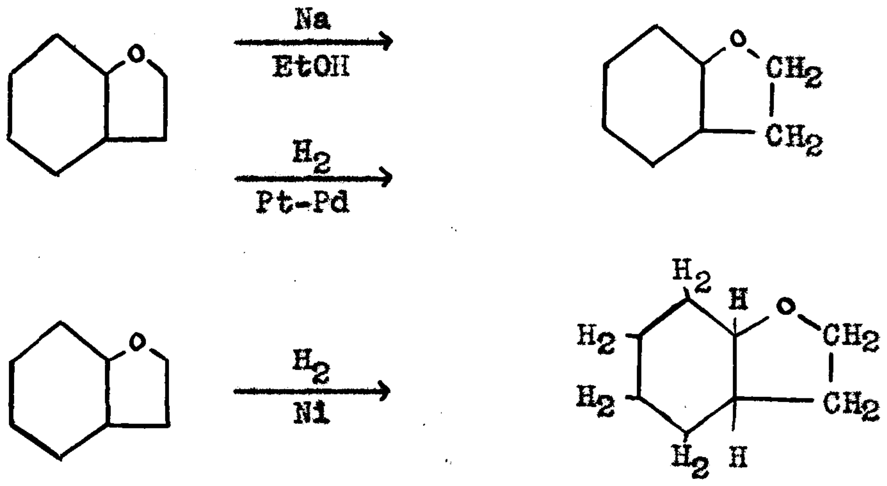
(88) This thesis, page 55.

benzofuran-2-carboxylic acid amide (89), and this compound is suggested as being of possible physiological value. Other amino compounds which have been synthesized previously and might well be tested are: the 3-amino-2,3-dihydrobenzofuran of Stoermer and co-workers (37)(14), the ethyl 2,3-dihydrobenzofuran-2-carbamate of Stoermer and König (14), and the 5-acetamino-2-methyl-2,3-dihydrobenzofuran of Claisen and Kremers (49).

The reduction of benzofuran by means of sodium and alcohol, and by means of catalytic reduction with noble metal catalysts, has been shown to yield the same product, 2,3-dihydrobenzofuran. The comparison was made through the picrates. The latter method gives a purer product. The high pressure-high temperature reduction of benzofuran with nickel catalyst readily yields perhydrobenzofuran.



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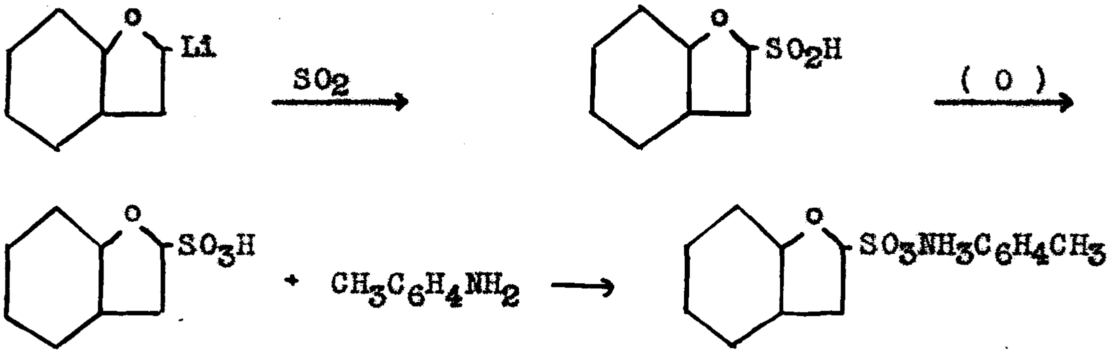
(89) Rinkes, Rec. trav. chim., 51, 349 (1932).

The failure to obtain iodination products of benzofuran is in accordance with a previous report (13). A more gentle treatment of the iodination product might be advisable in further attempts to prepare an iodobenzofuran.

A considerable amount of insoluble resinous material found in the attempted sulfonations of benzofuran indicates the difficulty which must be overcome in this synthesis. The particular sensitivity of benzofuran to sulfuric acid, and to hydrochloric acid to some extent, is probably responsible for the failure of the reaction under the conditions described. Benzofuran-2-sulfonic acid, and the *p*-toluidide derivative, was prepared as a reference compound by the action of sulfur dioxide upon 2-benzofuryl-lithium to form benzofuran-2-sulfinic acid, and the subsequent oxidation of this product to benzofuran-2-sulfonic acid.

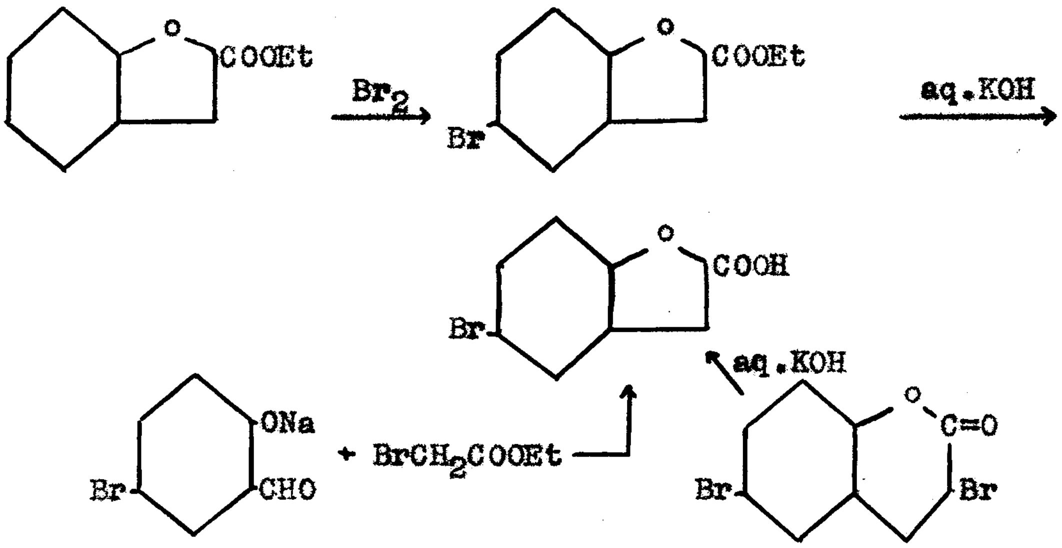


The attempted mercuration of benzofuran with mercuric acetate resulted, rather unexpectedly, in view of the ready mercuration of furan (90), in the oxidation of the benzofuran nucleus, and the recovery of a quantitative yield of mercurous acetate. Approximately 50% of the benzofuran was recovered. Refluxing an alcoholic benzofuran-picric acid solution for a few minutes also seemed to result in an oxidation of the benzofuran nucleus. The picrate is readily prepared, however, by mixing warm alcoholic solutions of the two reagents and allowing them to cool.

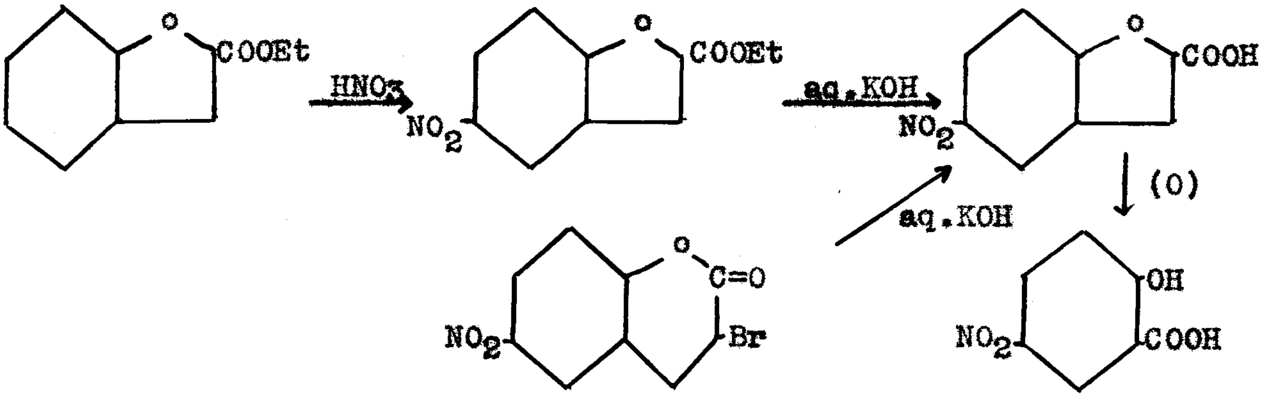
Bromination, nitration, and acetylation of ethyl benzofuran-2-carboxylate all orient the entering group in the 5-position. This is the position assumed by the nuclear substituents in the bromination of 2-methyl-2,3-dihydrobenzofuran (51), and the Friedel-Crafts reaction on 2,3-dihydrobenzofuran (76) (77).

The proof of the structure of the 5-bromobenzofuran-2-carboxylic acid obtained by the bromination of ethyl benzofuran-2-carboxylate, and hydrolysis of the product, is based on the synthesis of the product of the reaction by two separate ring closure reactions. The preparation from 3,6-dibromocoumarin has been described previously by Perkin (6).

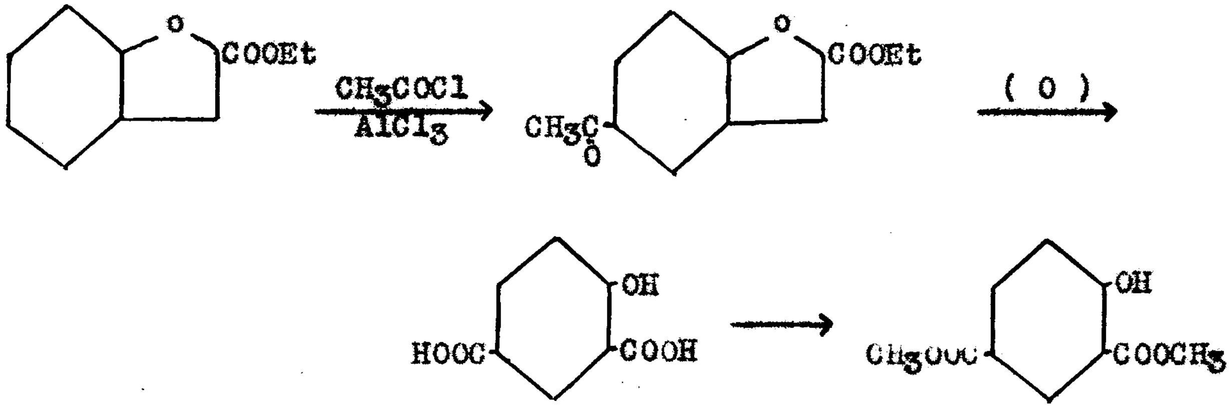
(90) Gilman and Wright, J. Am. Chem. Soc., 55, 3302 (1933).



Dey and Row (23) prepared 5-nitrobenzofuran-2-carboxylic acid by the action of aqueous potassium hydroxide on an alcohol solution of 3-bromo-6-nitrocoumarin. A comparison of this acid with the nitrobenzofuran-2-carboxylic acid formed by the hydrolysis of the nitration product of ethyl benzofuran-2-carboxylate showed them to be the same. As additional evidence, the oxidation of the nitration product, by means of alkaline potassium permanganate, gave 5-nitrosalicylic acid.



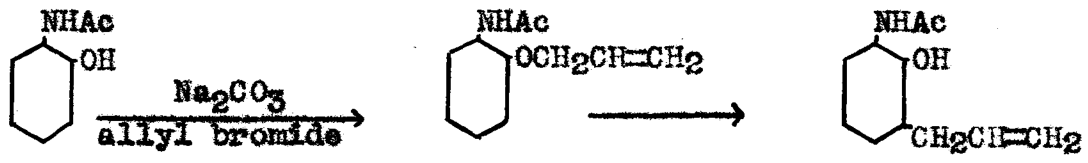
Ethyl 5-acetylbenzofuran-2-carboxylate was the product of the acetylation of ethyl benzofuran-2-carboxylate. The proof of this structure is shown by the isolation of 4-hydroxyisophthalic acid as an oxidation product. The product was compared with the authentic compound through the dimethyl ester.



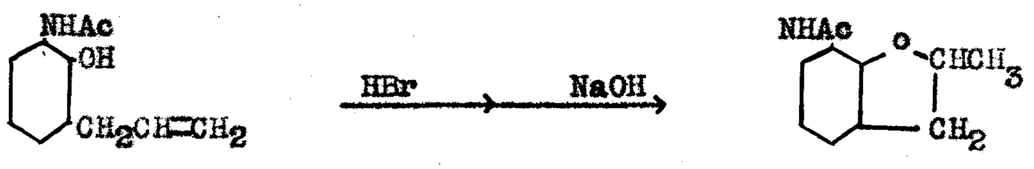
The high temperature-high pressure reduction of ethyl benzofuran-2-carboxylate with Raney nickel catalyst was expected to hydrogenate the unsubstituted benzene ring at least, in view of the ready hydrogenation of benzofuran. No hydrogen was taken up, however, and the starting material was recovered unchanged. The one trial made can hardly be used as a basis for discarding this reaction.

The presence of mercury and mercurous acetate in the products of attempted mercurations of ethyl benzofuran-2-carboxylate was a disappointing discovery as this means that an oxidation has taken place in the reaction, with the probable destruction of the benzofuran nucleus. No definite mercuration products were isolated from any of the attempted mercurations, but the presence of an organic compound containing mercury as a product in one of the reactions is indicative that some mercuration may have taken place.

Investigations upon the physiological properties of dibenzofuran derivatives (3) have indicated that an amino group adjacent to the ether linkage holds the most promise as a substituent in the search for analgesic properties. The preparation of *o*-acetaminophenylallyl ether and *o*-acetamino-*o*-allylphenol has been made towards the synthesis of 2-methyl-7-acetamino-2,3-dihydrobenzofuran, a similarly substituted benzofuran compound.



The contemplated last step is the ring closure method by which the isomeric 2-methyl-5-acetamino-2,3-dihydrobenzofuran (49) was formed.



Another suggested method for introducing groups in the critical 7- position of the benzofuran nucleus is by the metalation of 2,3-dihydrobenzofuran, or the more easily available 2-methyl-2,3-dihydrobenzofuran. Another compound of interesting pharmacological possibility is 7-methoxybenzofuran-2-carboxylic acid. This is prepared by the action of ethyl bromoacetate on the sodium salt of o-vanillin (91).

An aromatic amino derivative of this compound is suggested as a possibility for physiological study.

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(91) Reichstein, Oppenauer, Grüssner, Hirt, Rhyner, and Glatthaar, Helv. Chim. Acta, 18, 816 (1935).

SUMMARY

A review of the methods of preparation of benzofuran, and of the general methods for the ring closure synthesis of benzofuran derivatives has been made. A discussion of the pharmacological studies that have been made on benzofuran derivatives has been given, and a complete review and discussion of the nuclear orientation of benzofuran and benzofuran derivatives has been made.

Some similarities between benzofuran and furan have been pointed out. The nuclear substitution products of metalation and acetylation of benzofuran have been oriented in the 2- position.

Bromination, nitration, and acetylation of ethyl benzofuran-2-carboxylate have been found to have oriented the entering group in the 5- position of the benzofuran nucleus.

A few suggestions for future study of benzofuran derivatives of possible physiological activity have been made.

DIBENZOFURAN

INTRODUCTION

Complete reviews by previous workers upon the orientation (1) and physiological properties (2) of dibenzofuran and dibenzofuran derivatives makes a further discussion of this subject unnecessary in this paper, except when specifically related to investigations reported here.

One of the few unsolved problems on the orientation of dibenzofuran remaining in the literature concerns the structure of the dibenzofuransulfonic acid prepared by Zehenter (3) through the sulfonation of o-biphenol. The p-toluidide of this product has been compared with the p-toluidide of dibenzofuran-2-sulfonic acid prepared by the treatment of dibenzofuran with chlorosulfonic acid (4). The two derivatives were found to be identical on a basis of mixed melting points.

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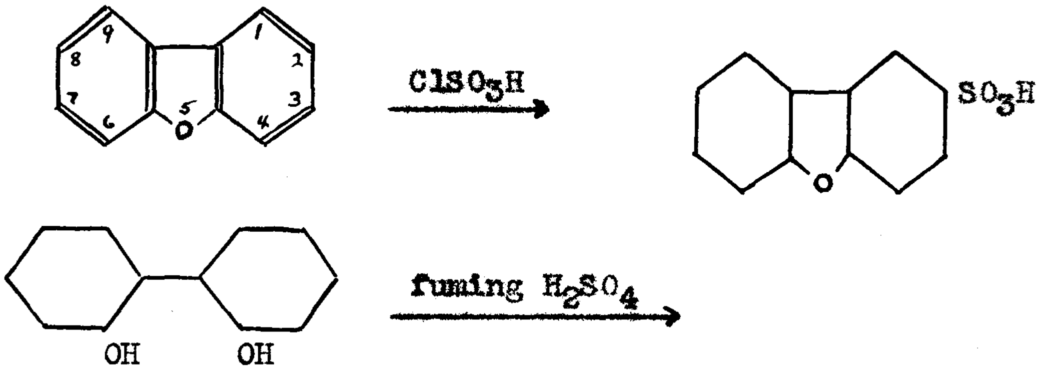
(1) Oatfield, Thesis, Iowa State College, 1933, Hayes, Thesis, Iowa State College, 1934, M. W. Van Ess, Doctoral Dissertation, Iowa State College, 1936, and P. R. Van Ess, Doctoral Dissertation, Iowa State College, 1936.

(2) Bywater, Doctoral Dissertation, Iowa State College, 1934, and Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.

(3) Zehenter, J. prakt. Chem., 131, 331 (1931).

(4) Gilman, Smith and Oatfield, J. Am. Chem. Soc., 56, 1412 (1934).



Zehenter predicted that his dibenzofuransulfonic acid would be oriented in the 2- or 4- position. He further sulfonated this monosulfonic acid to a dibenzofurandisulfonic acid which he claimed to be identical with the dibenzofurandisulfonic acid prepared by Hoffmeister (5) through the direct sulfonation of dibenzofuran. The rather tenuous basis for this claim was the fact that the barium salts of the disulfonic acids contained the same amount of water of crystallization. Later work has shown this assumption to be correct as the sulfonation of dibenzofuran-2-sulfonic acid yields the dibenzofuran-2,8-disulfonic acid of Hoffmeister (4).

Attempts were made to prove the orientation of the dibenzofuransulfonic acid prepared by the sulfonation of dibenzofuran with chlorosulfonic acid by means of replacement reactions designed to yield dibenzofuran derivatives of known structure.

(5) Hoffmeister, Ann., 159, 213 (1871).

The replacement of the sulfonic group by a nitro group was tried by means of reactions of increasing severity. In this case either no replacement, or the formation of nitro derivatives of unknown structure, was obtained. Similar attempted replacements of the sulfonic group by carboxylic group, bromo group, and chloro group also failed. The attempted replacement of the sulfinic group of dibenzofuran-2-sulfinic acid by a nitro group was made in an effort to make 2-nitrodibenzofuran more available. This reaction was suggested by the ready replacement of the sodium sulfinate group by the chloromercuri group in this same compound (4). The difficulties encountered in the preparation of 2-hydroxydibenzofuran (6) suggested an attempt at the synthesis of this compound through alkali fusion of dibenzofuran-2-sulfonic acid. No success was obtained either in this reaction or a similar reaction upon dibenzofuran-2,8-disulfonic acid.

The probable cause of the failure of the ring closure reaction to produce dibenzofuran-2-sulfonic acid is due to the comparatively easy hydrolysis of sulfonic groups under the conditions of the reaction. Dibenzofuran-2-sulfonic acid, the expected product, is hydrolyzed todbenzofuran by refluxing with 50% sulfuric acid. This is the conditions of the ring closure reaction attempted. The starting material would also probably be hydrolyzed. No attempt was made to isolate dibenzofuran in

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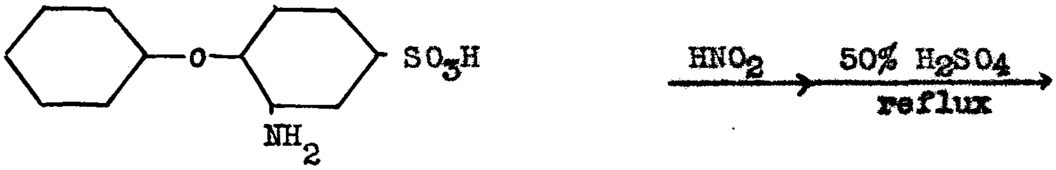
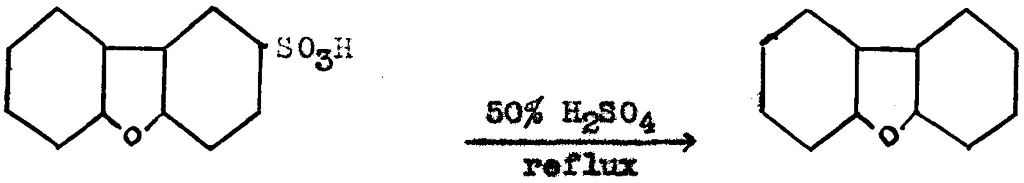
(6) Gilman, Bywater and Parker, *J. Am. Chem. Soc.*, *57*, 885 (1935)

these reactions.



no identified product



The good yields of dibenzofuran obtained by the sealed tube hydrolyses of dibenzofuran-2-sulfonic acid, dibenzofuran-2,8-disulfonic acid, and dibenzofurantetrasulfonic acid gave promise that this would be a general reaction. This hydrolysis reaction was expected to be a valuable tool, as the further substitution of dibenzofuran-2,8-disulfonic acid would be expected to orient entering groups in the critical 4- and 6- positions, and hydrolysis to remove the sulfonic groups. To this end the bromination, chlorination, and nitration of dibenzofuran-2,8-disulfonic acid was attempted. Halogenation gave reaction products that were powerful vesicants and could not be worked with. The nitration of dibenzofuran-2,8-disulfonic acid gave a nitrodibenzofuran-2-sulfonic acid whose nitro group was presumably oriented in the 8- position. All attempts at the hydrolysis of this compound to yield a nitrodibenzofuran failed.

Mercuration of dibenzofuran takes place ordinarily in the 4- position (7). The mercuration of sodium dibenzofuran-2-sulfonate was designed to produce a soluble dibenzofuran mercurial for germicidal tests. The position actually assumed by the acetoxymercuri group is not yet known.

An interesting application of the ability of dibenzofuran to orient nuclear substituents according to their kind is demonstrated in the iodination of dibenzofuran by means of nitric acid and iodine (8), and yellow mercuric oxide and iodine (9). In both cases the product is 2-iododibenzofuran. This product indicates that the role of the nitric acid and the mercuric oxide is purely one of an oxidizing agent. If the mechanism was one of preliminary nitration, or mercuration, followed by replacement by iodine, the product would be 3-iododibenzofuran in the case of the nitric acid iodination, and 4-iododibenzofuran in the case of the mercuric oxide iodination. Nitric acid orients the entering group almost exclusively to the 3- position (10) and dibenzofuran mercurates in the 4- position (7).

In order to further test this theory, the sulfonation and nitration of dibenzofuran was undertaken in the presence of

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(7) Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
(8) Gilman, Brown, Bywater and Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).
(9) Unpublished studies by R. V. Young. Iowa State College, 1936.
(10) Cullinane. J. Chem. Soc., 1930, 2267.

mercury salts. The results of the sulfonation showed that the presence of mercury and mercuric sulfate had little or no effect on the product. The nitration of dibenzofuran with nitric acid in glacial acetic acid, in the presence of mercuric acetate, gave a nitration product considerably different than that obtained by an exactly similar nitration in the absence of mercuric acetate. No nitrodibenzofurans isomeric with the usual product were isolated from this catalytic nitration, but it is beyond question that the presence of the mercury salt had a definite effect on the nitration reaction.

If the ease with which a compound undergoes the Gattermann-Koch reaction be an index of negativity, dibenzofuran is less negative than toluene. The failure of Gattermann-Koch reactions of varying severity to introduce an aldehyde group into dibenzofuran was rather unexpected. Toluene gave a fair yield of p-tolylaldehyde under the same conditions. Dibenzofuryl-2-aldehyde was prepared by a different method.

Cuprous cyanide was fused with a considerable excess of 2,8-dibromodibenzofuran, and the product hydrolyzed with alcoholic potassium hydroxide, in an effort to prepare 8-bromodibenzofuran-2-carboxylic acid. The only product isolated was dibenzofuran-2,8-dicarboxylic acid. An excess of cuprous cyanide was fused with 2,8-dibromodibenzofuran and the intermediate dibenzofuran-2,8-dinitrile hydrolyzed to a good yield of dibenzofuran-2,8-dicarboxylic acid by means of alcoholic potassium hydroxide. The dimethyl ester of this product was shown to be identical with authentic dimethyl dibenzofuran-2,8-dicarboxylate prepared in a different way (11).

The action of lead tetra-acetate upon dibenzofuran and tetrahydrodibenzofuran, and the subsequent hydrolysis of the expected acetoxy derivative, was made in an effort to prepare hydroxy derivatives of these nuclei. No appreciable reaction with dibenzofuran took place, and the action on tetrahydrodibenzofuran was that of an oxidizing agent, dibenzofuran being identified as a product.

The invariable identification of mercurous acetate as a product of attempts to mercurate tetrahydrodibenzofuran, by means of mercuric acetate under a variety of conditions, indicates that an oxidation has taken place in this reaction. Mercuration has undoubtedly also taken place, but the reaction mixture has so far defied efforts at separation. The iodination of tetrahydrodibenzofuran also yielded no identified product.

A number of attempts to oxidize 7-nitro- and 7-acetyl-1,2,3,4-tetrahydrodibenzofuran to compounds of known structure were made before success in these reactions was obtained by the use of bromine in glacial acetic acid (12).

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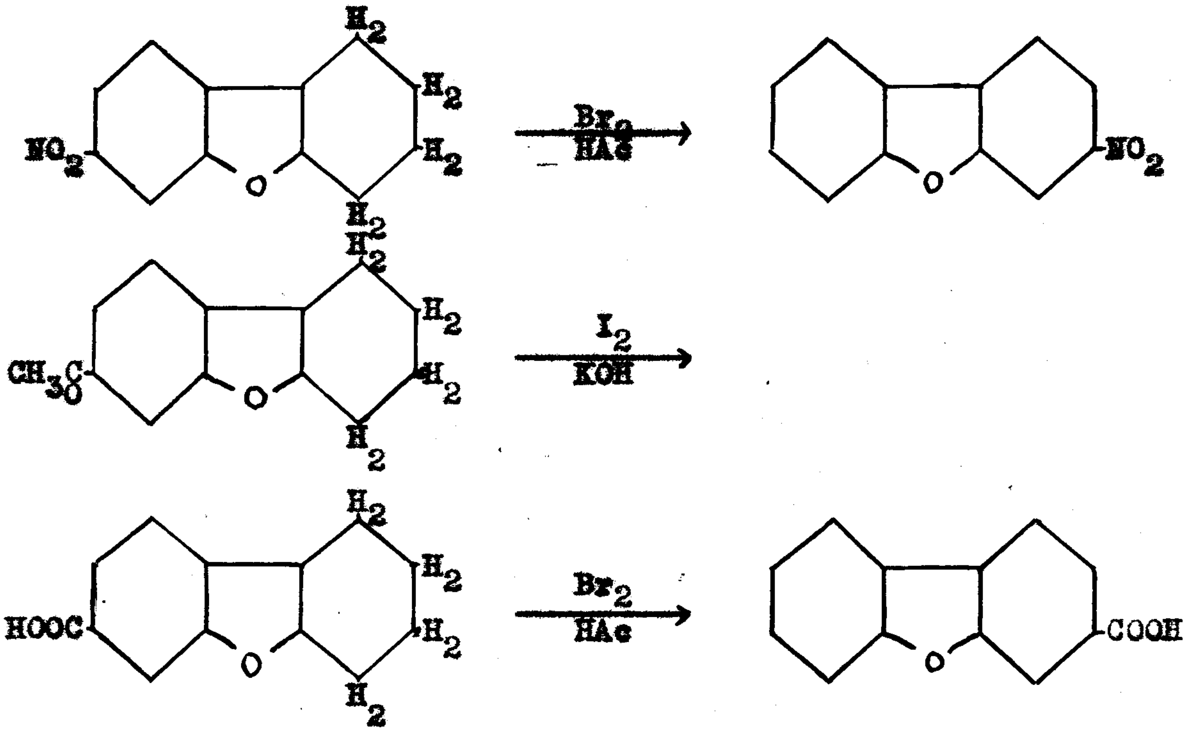
(11) Unpublished studies by J. C. Bailie, Iowa State College, 1936.
(12) Gilman, Smith and Cheney, J. Am. Chem. Soc., 57, 2095 (1935).


H2
H2
H2
H2
NO2
O
Br2
HAc
NO2
O
H2
H2
H2
H2
CH3C
O
O
I2
KOH
H2
H2
H2
H2
HOOC
O
Br2
HAc
COOH
O

EXPERIMENTAL PART

Preparation of o-Biphenol

In a typical preparation, a mixture of 100 g. of dibenzofuran, 50 g. of potassium hydroxide, and 50 g. of sodium hydroxide was heated at 360°-410° for 18 hours in an iron bomb. Extraction of the product with hot water and acidification yielded 46.7 g., 38.5% of the theoretical, of o-biphenol containing water of crystallization. The water of crystallization was removed by distilling a toluene solution of the crude product until the temperature rose to 111° and the distillate was clear. Cooling precipitated a quantitative yield of anhydrous o-biphenol melting at 108°-9°. A certain amount of leakage of dibenzofuran from the bomb caused the yields to be lowered.

Sulfonation of o-Biphenol

The sulfonation of 50 g. of o-biphenol with 13.2 g. of 20% fuming sulfuric acid at 180°-190° for 9 hours was carried out according to the directions of Zehenter (3). The product was treated with Norite, filtered hot and concentrated. The precipitate which resulted on cooling was filtered out. A 30% yield of the monosulfonic acid was obtained. A solution of 2 g. of this product in 75 cc. of water was made strongly acid with hydrochloric acid and heated to boiling. To this was added a hot solution of 1.5 g. of p-toluidine hydrochloride in 20 cc.

of water, and the solution heated for several minutes. Cooling precipitated colorless, glistening plates. Two crystallizations from hot water after treatment with Norite yielded colorless needles melting at 232°. A mixed melting point with the *p*-toluidide of authentic dibenzofuran-2-sulfonic acid, prepared in the same way, m.p. 232°-233°, showed them to be identical.

Attempted Replacements of Sulfonic Group by Nitro Group in Dibenzofuran-2-sulfonic Acid

The dibenzofuran-2-sulfonic acid used was prepared according to the directions of Gilmam, Smith, and Oatfield (4).

a). Twenty-five cc. of fuming nitric acid was slowly added, with shaking, to a suspension of 10 g. of sodium dibenzofuran-2-sulfonate in 75 cc. of concentrated sulfuric acid. A clear solution resulted which was heated on a steam bath for 25 minutes and poured upon cracked ice. The resulting precipitate melted at 225°-233° with softening beforehand, and weighed 5.3 g. Crystallization from glacial acetic acid gave a compound melting at 272°. This corresponds to no known nitro derivative unless it be the tetranitrodibenzofuran of Ryan and Cullianane (13) melting at 283°.

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(13) Ryan and Cullinane, *Sci. Proc. Roy. Dublin Soc.*, *17*, 321 (1924).

b). A mixture of 75 cc. of concentrated sulfuric acid and 30 cc. of concentrated nitric acid was cooled to -15° and 10 g. of sodium dibenzofuran-2-sulfonate added slowly with stirring. At the conclusion of the addition, which required five minutes, the reaction product was poured on cracked ice, diluted to 800 cc. with water, boiled a few minutes, cooled, and filtered. A yield of 1.1 g. of compound melting at about 180°-185° was obtained. After crystallization from glacial acetic acid it melted at 216°-218°. This corresponds to no known nitro derivative.

c). Fifteen hours exposure of 7.5 g. of dry powdered dibenzofuran-2-sulfonic acid to the fumes of nitrogen trioxide yielded only a water soluble product. It was not investigated further.

d). A suspension of 12.4 g. of dibenzofuran-2-sulfonic acid in 150 cc. of glacial acetic acid was treated with a total of 70 cc. of concentrated nitric acid at temperatures ranging from -15°to 100°. It was finally heated for 45 minutes on the steam bath. The product was water soluble and was not investigated further.

Attempted Replacement of Sulfonic Group by Carboxylic Group in Dibenzofuran-2-sulfonic Acid

An intimate mixture of 10 g. of sodium dibenzofuran-2-sulfonate and 10 g. of sodium formate was kept at the fusion temperature for ten minutes. An evolution of gas took place. The melt was extracted with a sodium carbonate solution, filtered, cooled, and acidified. The product was extracted thoroughly with ether. Removal of the ether yielded an inconsequential residue. A recovery of 7 g. of the sodium sulfonate was made.

Attempted Replacement of Sulfonic Group by Halogens in Dibenzofuran-2-sulfonic Acid

a). A mixture of 10 g. of sodium dibenzofuran-2-sulfonate and 10 g. of phosphorus trichloride was heated in a sealed tube for 3 hours at 250°- 280°. The black product was extracted with 10% sodium hydroxide solution. The oily, black, resinous residue was unworkable. Attempts at separation of products by steam distillation and crystallization from several solvents failed.

b). A mixture of 10 g. of sodium dibenzofuran-2-sulfonate and 10 g. of phosphorus tribromide was treated in a manner similar to a). The same sort of resinous product was recovered and the reaction was not investigated further.

Attempted Replacements of Sulfinic Group by Nitro Group in Dibenzofuran-2-sulfinic Acid

The dibenzofuran-2-sulfinic acid used was prepared according to the directions of Gilman, Smith and Oatfield(4).

a). A suspension of 10 g. of sodium dibenzofuran-2-sulfinate in 100 cc. of glacial acetic acid was treated with 10 cc. of concentrated nitric acid by dropwise addition at room temperature. After an additional 30 minutes stirring at room temperature the mixture was poured upon cracked ice, filtered, washed with water, and the precipitate crystallized from alcohol. The melting point of the small amount of product was 101°- 103°. This corresponds to no known nitro derivative.

b). A suspension of 5 g. of sodium dibenzofuran-2-sulfinate, 20 cc. of concentrated nitric acid and 50 cc. of glacial acetic acid was heated on the steam bath for 30 minutes. At the conclusion of this time the solution was clear. It was diluted and made basic with 10% sodium hydroxide solution. Heating again brought all the precipitate into solution. It was filtered hot, cooled, and the resulting precipitate filtered out. This precipitate was identified as dibenzofuran-2-sulfonic acid through the sulfonyl chloride.

c). A solution of 1.4 g. (0.02 mole) of sodium nitrate in 10 cc. of water was added with shaking at 0° to a suspension of 2.5 g. (0.01 mole) of sodium dibenzofuran-2-sulfinate in 100 cc. of 2N hydrochloric acid. At the conclusion of the addition 10 cc. more of concentrated hydrochloric acid was added and the mixture allowed to stand at 0° for 30 minutes. At the end of this time the considerable amount of precipitate was filtered off. This precipitate was probably the sulfonic acid as it had no melting point and gave a qualitative test for sulfur, but not for nitrogen.

d). A solution of 5 g. of sodium dibenzofuran-2-sulfinate, 25 g. of crystalline aluminum nitrate, and 200 cc. of water was refluxed for 15 min. The precipitate which appeared on cooling was readily soluble in dilute sodium hydroxide solution. Obviously no replacement of the sulfinic group had taken place as nitrodibenzofurans would not be soluble.

e). A suspension of 5 g. of sodium dibenzofuran-2-sulfinate, 20 g. of crystalline aluminum nitrate, and 200 cc. of acetic anhydride was placed in a flask equipped with a reflux condenser and the reaction started by gentle heating with a steam bath. The violent reaction was controlled for 10 minutes by the judicious use of an ice bath and then heated two hours on the steam bath. It was filtered hot, cooled, and the water soluble precipitate discarded. The filtrate was diluted with cracked ice and made basic with sodium hydroxide. All material went into solution so the products were not investigated further.

Attempted Preparation of Dibenzofuran-2-sulfonic Acid by Ring Closure Reactions

A. Attempted preparation of 2-nitro-4'-sulfodiphenyl ether (14)

An intimate mixture of 7.9 g. (0.05 mole) of 2-nitrochlorobenzene, 12.8 g. (0.06 mole) of potassium phenol-4-sulfonate, 2.8 g. (0.05 mole) of potassium hydroxide, 0.2 g. of copper bronze, and 50 cc. of absolute methanol was heated gently until the alcohol was removed, and the resulting cake heated at 185° for 6 hours. There was apparently no reaction.

B. Preparation of 2-nitro-4-sulfodiphenyl ether

A suspension of 27.5 g. (0.1 mole) of potassium 2-nitrochlorobenzene-4-sulfonate and 15 g. (0.11 mole) of potassium phenolate in 50 g. of phenol was heated 20 hours at 175°-190°. The product was dissolved in hot water, acidified, and the phenol removed by steam distillation. A quantitative yield of 2-nitro-4-sulfodiphenyl ether was obtained on cooling and filtration.

C. Preparation of 2-amino-4-sulfodiphenyl ether

A suspension of 20 g. of 2-nitro-4-sulfodiphenyl ether in 200 cc. of concentrated hydrochloric acid was treated with 30 g. of granulated tin, in small portions, with good stirring. At the conclusion of the addition the mixture was heated for three hours, with stirring, at 100°. The solution was diluted, made basic with ammonium hydroxide, and filtered hot.

(14) There is some doubt as to the correct nomenclature of this compound. The compound is a diphenyl ether with a nitro group in the 2- position and a sulfonic acid group in the 4'- position. It is named here as a diphenyl ether derivative.

The filtrate was treated with Norite, concentrated, and sodium carbonate added. The resulting precipitate was filtered out, dissolved in water, and acidified with hydrochloric acid. The resulting precipitate weighed 11 g., 54% of the theoretical.

Anal. Calcd. for $C_{24}H_{20}O_8N_2S_2Ba$: Ba, 20.64 . Found: Ba, 20.55 and 20.57 .

A similar reduction using 12 g. of 2-nitro-4-sulfodiphenyl ether, 250 cc. of concentrated hydrochloric acid, and 40 g. of iron filings gave a 61.5% theoretical yield of the hydrochloride of 2-amino-4-sulfodiphenyl ether.

D. Attempted ring closure of 2-amino-4-sulfodiphenyl ether to dibenzofuran-2-sulfonic acid.

a). A solution of 6.65 g. (0.025 mole) of 2-amino-4-sulfodiphenyl ether and 4.9 g. (0.05 mole) of sulfuric acid in 200 cc. of water was treated with a solution of 2.1 g. (0.03 mole) of sodium nitrite in 10 cc. of water at 0°. A beta-naphthol test for a diazo group was obtained immediately. The solution was stirred one hour at 0° and 3 hours at room temperature. The solution was filtered, and sufficient concentrated sulfuric acid added at 10° to bring the concentration up to 50%. The mixture was then dropped slowly on a refluxing solution of 50 cc. of 50% sulfuric acid and the refluxing continued 3 hours at the conclusion of the addition. No compound containing a sulfonic group was found in the product. The reaction products were not investigated for the presence of dibenzofuran.

b). A suspension of 6 g. (0.02 mole) of 2-amino-4-sulfodiphenyl ether hydrochloride in a mixture of 50 cc. of water and 2 cc. of concentrated hydrochloric acid was cooled to 0° and a solution of 1.4 g. (0.02 mole) of potassium nitrite in 5 cc. of water added slowly with stirring. The mixture was stirred for 4 hours at 0° and let stand 12 hours at room temperature. A good beta-naphthol test was obtained at this time. The mixture was slowly dropped on a boiling mixture of 50 cc. of concentrated sulfuric acid and 50 cc. of water, and the refluxing continued 15 minutes at the conclusion of the addition. No evidence for the presence of a sulfonic group was found in the products of this reaction. The insoluble residues were not investigated for the presence of dibenzofuran.

Hydrolysis of Dibenzofuransulfonic Acids

a). A solution of 20 g. of sodium dibenzofuran-2-sulfonate in 100 cc. of 50% sulfuric acid was refluxed 8 hours and steam distilled until the distillate was no longer turbid. Three-tenths of a gram of dibenzofuran, m.p. 81.5°-82°, was recovered from the distillate, and a quantitative recovery of the unchanged dibenzofuran-2-sulfonic acid from the cooled residue. To preclude the possibility that the dibenzofuran recovered was present as an impurity in the original sulfonic acid, the recovered sulfonic acid was refluxed for 24 hours with a solution of 50% sulfuric acid. A yield of 1.3 g. of dibenzofuran was obtained upon steam distillation of this reaction.

b). A solution of 20 g. of sodium dibenzofuran-2,8-disulfonate, 100 cc. of concentrated sulfuric acid and 100 cc. of water was subjected to 8 hours of constant concentration distillation. From the distillate was obtained 2.5 g. of dibenzofuran melting at 83°-84°, and from the residue dibenzofuran-2-sulfonic acid.

c). A solution of 3 g. of dibenzofuran-2,8-disulfonic acid, 10 cc. of concentrated sulfuric acid and 100 cc. of a saturated sodium sulfate solution was refluxed 4 hours. There was no appreciable hydrolysis.

d). A solution of 3 g. of sodium dibenzofuran-2,8-disulfonate in 100 cc. of concentrated hydrochloric acid was refluxed 4 hours. A very slow reaction took place. The amount of product was very slight and was not identified.

e). A solution of 10 g. of sodium dibenzofuran-2,8-disulfonate in 25 cc. of 6N hydrochloric acid was heated in a sealed tube at 190°-200° for 9 hours. A quantitative yield of dibenzofuran, melting at 84°-85° after crystallization from petroleum ether, was obtained.

f). Exactly similar results were obtained when 25 cc. of 6N sulfuric acid instead of hydrochloric acid was used under these conditions.

g). A solution of 10 g. of sodium dibenzofurantetrasulfonate in 25 cc. 50% acetic acid was heated 3 hours at 200° in a sealed tube. There was no perceptible hydrolysis.

i). Ten grams of sodium dibenzofurantetrasulfonate was heated 4 hours at 220° in a sealed tube with 25 cc. of 6N sulfuric acid. A small amount of dibenzofuran was isolated, but no charring had taken place. The soluble portion was neutralized with barium carbonate and extracted with four liters of boiling water. Concentration of the extract yielded no precipitate and a test of the concentrate with sodium sulfate showed the absence of any barium sulfonate group. This suggests that a hydrolysis of one or more of the sulfonic groups took place and that the barium salt of the sulfonic acid product was completely insoluble in hot water.

j). Ten grams of sodium dibenzofurantetrasulfonate in 25 cc. of 6N sulfuric acid was heated 2 hours at 220°- 230° and 4 hours at 240°-250°. A 73% yield of dibenzofuran melting at 83.5°-84.5° after crystallization from petroleum ether was obtained.

Alkali Fusions of Dibenzofuran Sulfonic Acids

a). A mixture of 30 g. of potassium hydroxide and 30 g. of sodium hydroxide was fused at 170°-200°, and 20 g. of powdered sodium dibenzofuran-2-sulfonate added in small portions. The temperature was raised to 300° and kept there one hour, followed by 5 minutes at 350°. The melt was cooled, dissolved in water, treated with Norite, and acidified. No appreciable precipitate appeared at this time, or after concentration and cooling.

b). Twenty grams of potassium hydroxide and 20 g. of sodium hydroxide was fused, and 15 g. of sodium dibenzofuran-2,8-disulfonate introduced in small portions with stirring. The melt was heated to 400° for 30 minutes, cooled, dissolved in water, and digested twice with Norite. The filtrate was strongly acidified and the slightly milky solution extracted with ether. Removal of the ether yielded no appreciable product.

c). A paste of 40 g. of potassium hydroxide, 25 g. of sodium dibenzofuran-2,8-disulfonate and 10 cc. of water was heated gently until the water was removed and then fused strongly for 30 minutes. Solution in water, treatment with Norite, and acidification yielded a brown gummy precipitate. This material was filtered out and boiled a few minutes with 10% sodium carbonate solution. The precipitate was apparently hydrolyzed by this treatment to a soluble product as subsequent strong acidification yielded no precipitate.

d). The water was driven from a mixture of 25 g. of potassium dibenzofuran-2,8-disulfonate, 25 g. of potassium hydroxide, and 10 cc. of water by gentle warming, and the residue strongly fused for 30 minutes. The product was treated twice with Norite after solution in water and the filtrate acidified. The resulting precipitate was purified by several reprecipitations and air dried. This material gave an excellent qualitative test for sulfur so was investigated no further.

e). A solution of 22.5 g. of potassium dibenzofuran-2,8-disulfonate, 50 g. of potassium hydroxide and 25 cc. of water was heated at 100° for 48 hours and gently fused for 4 hours. Dissolving in water, treatment with Norite, and acidification yielded a brownish precipitate. This precipitate was dissolved in a sodium carbonate-sodium hydroxide solution, treated again with Norite, filtered hot, cooled, and acidified. No precipitate appeared at this time or upon subsequent concentration and cooling.

Attempted Bromination of Dibenzofuran-2,8-disulfonic Acid

A solution of 16.4 g. (0.05 mole) of dibenzofuran-2,8-disulfonic acid, 20 g. (0.025 mole) of bromine, 1 g. of ferric chloride, a pinch of iron powder, and 100 cc. of glacial acetic acid was refluxed until the bromine color had been removed. The mixture was concentrated to some extent, diluted with water, and neutralized with barium carbonate. The soluble barium salts were extracted with hot water. The barium salts which appeared upon concentration and cooling of this extract were filtered off, converted to the acid with sulfuric acid, the barium sulfate removed, and refluxed in a 12N sulfuric acid solution. The material which steam distilled out was identified as dibenzofuran.

Other attempts to brominate dibenzofuran-2,8-disulfonic acid were made. The products were discarded as probable vesicants before definite results were obtained.

Chlorination of Dibenzofuran-2,8-disulfonic Acid.

A solution of 32.5 g. of dibenzofuran-2,8-disulfonic acid, a pinch of iron powder, and a few crystals of iodine in 200 cc. of glacial acetic acid was heated on a steam bath, and chlorine introduced for 20 hours. The evolution of hydrogen chloride was slow. At the conclusion of this time a precipitate had appeared in the solution, which was cooled and filtered. This material was crystallized from a large volume of ethanol. A yield of 4.6 g. melting at 155°-170° was obtained. Crystallization from chloroform and glacial acetic acid raised the melting point to 172°-74°. An elemental analysis showed the presence of chlorine and absence of sulfur. A mixed melting point with 2,8-dichlorodibenzofuran, m.p. 184°, was depressed to 150°.

This compound was not investigated further as it was strongly suspected of being a powerful vesicant.

Nitration of Dibenzofuran-2,8-disulfonic Acid

A suspension of 84 g. (0.5 mole) of dibenzofuran in 200 cc. of concentrated sulfuric acid was heated on a steam bath until the solution was complete. To this solution was added 102 g. (1.2 mole) of sodium nitrite in small portions with stirring. The mixture heated up to a considerable extent. It was stirred on the steam bath for two hours at the completion of the addition and poured in two liters of water. Cooling precipitated a white flocculent solid. This material was crystallized twice from small portions of water before use in attempted hydrolysis experiments. A 50 g. yield, 34.1% of the theoretical, of a compound analyzing for a nitrodibenzofuranmonosulfonic acid was obtained. This product gave qualitative tests for sulfur and nitrogen.

Anal. Calcd. for $C_{12}H_7O_6NS$: N, 4.78 . Found: N, 4.82 and 4.92 .

Attempted Hydrolysis of Nitrodibenzofuran-2-sulfonic Acid

a). Ten grams of air-dried nitrodibenzofuran-2-sulfonic acid and 25 cc. of 6N sulfuric acid were heated in a sealed tube at 180°-190° for 6 hours. The badly charred product was washed with water and extracted with hot glacial acetic acid. Concentration and dilution of the extract with water gave no precipitate.

b). A solution of 10 g. of nitrodibenzofuran-2-sulfonic acid in 25 cc. of 6N hydrochloric acid was heated 6 hours at 180°-190° in a sealed tube. The clear product was completely water soluble.

c). A run exactly similar to b) was made, heating the solution at 225° for 6 hours. The charred residue was filtered out, extracted with hot glacial acetic acid, concentrated, and diluted with water. The precipitate was sufficient to cloud the solution, but insufficient to investigate.

d). Another run similar to b) was made, heating the solution at 180°-210° for 3 hours. No charring took place and all the material was soluble in the clear yellow solution. The tube was resealed and heated 3 hours at 210°-20° and 3 hours at 220°- 230°. The charred product was washed with water and extracted with hot glacial acetic acid. Concentration and dilution of the extract yielded no precipitate.

Sulfonation of 2,7-Dinitrodibenzofuran

A mixture of 10 g. of 2,7-dinitrodibenzofuran and 50 cc. of 30% fuming sulfuric acid was heated 30 minutes on a steam bath with frequent stirring. The black liquid product was diluted with two liters of water and digested twice with Norite. Concentration to 250 cc., and cooling, precipitated straw colored needles which were filtered out. This product gave qualitative tests for sulfur and nitrogen.

Mercuration of Sodium Dibenzofuran-2-sulfonate

A solution of 54 g. (0.2 mole) of sodium dibenzofuran-2-sulfonate and 63.8 g. (0.2 mole) of mercuric acetate in 600 cc. of water was refluxed 12 hours. At the conclusion of this time no test for mercuric or mercurous ions was obtained in the solution. The clear solution was poured upon a hot solution of 200 g. of sodium chloride in 500 cc. of water and the pasty mass well stirred and allowed to digest a few minutes. The mixture was cooled, filtered, and the precipitate digested with 300 cc. of hot water, allowed to cool slowly to room temperature and filtered. A theoretical yield of crude sodium chloromercuridibenzofuran-2-sulfonate was obtained after drying 48 hours at 110°.

The sodium hydroxymercuridibenzofuran-2-sulfonate is obtained by digesting the sodium acetoxymercuri- or chloromercuridibenzofuran-2-sulfonate with 10% sodium hydroxide solution, cooling, and filtering.

Replacement of Chloromercuri Group by Bromine in Sodium Chloromercuridibenzofuran-2-sulfonate

A suspension of 20 g. of sodium chloromercuridibenzofuran-2-sulfonate in 50 cc. of glacial acetic acid was treated with a 25% bromine solution, in the same solvent, in small portions with shaking. When the solution no longer decolorized the bromine in a few minutes at 40°-45° it was diluted with water, the excess bromine removed with sodium bisulfite, and the solution neutralized with barium carbonate. The mixture was extracted with 7 liters of hot water and the extract cooled. A yield of 4.1 g., 25.5% of the theoretical, of the difficultly soluble barium salt was obtained. Concentration of the filtrate to one liter and cooling did not increase the yield a significant amount.

Anal. Calcd. for $(C_{12}H_6O_4BrS)_2Ba\cdot 2H_2O$: Ba, 16.64 . Found: Ba, 16.45, 16.34 and 16.41 .

Tetrasulfonation of Dibenzofuran

a). Eighty-four grams (0.5 mole) of dibenzofuran was dissolved in 300 cc of 30% fuming sulfuric acid and heated 6 hours at 100°. The product was diluted with water and neutralized with barium carbonate. The suspension was extracted with 5 liters of hot water and concentrated. The solubility of the barium salt recovered showed the presence of a considerable quantity of the disulfonate so this method was discarded.

b). A suspension of 190 g. of dry sodium dibenzofuran-2,8-disulfonate in 250 cc. of 30% fuming sulfuric acid was heated at 180°-190° for 7 hours. The reaction product was diluted with 7 liters of water, neutralized with barium carbonate, heated to boiling, and filtered hot. The clear filtrate was concentrated to 400 cc. and cooled. The barium salt which precipitated was filtered out, dissolved in water, and the barium precipitated with a very slight excess of sodium sulfate. The suspension was filtered hot and evaporated to dryness. A 97 g., 33% of the theoretical, yield of the dry sodium salt was obtained.

Anal. Calcd. for $C_{12}H_4O_{13}S_4Ba_2 \cdot H_2O$: Ba, 35.40 . Found: Ba, 35.29, 35.64 and 35.64 .

Attempts to prepare the p-toluidide of the tetrasulfonic acid, as a derivative, by the usual methods failed. The melting point of such a derivative would probably be too high to be of much value as the p-toluidide of dibenzofuran-2,8-disulfonic acid melts at 285°-286°. The same derivative of the monosulfonic acid melts at 233°-234°.

A 6.2 g. yield of dibenzofurantetrasulfonyl chloride was prepared by heating 20 g. (0.035 mole) of sodium dibenzofurantetrasulfonate with 31.2 g. (0.15 mole) of phosphorus pentachloride for 3 hours at 150°. The product was crystallized from benzene and xylene. The decomposition point of above 250° was too high to be of much use as a derivative.

Catalytic Sulfonation of Dibenzofuran

a). Thirty-three and six-tenths grams (0.2 mole) of dibenzofuran was added at room temperature to a suspension of 3.4 g. of mercuric sulfate in 100 cc. of concentrated sulfuric acid. The mixture was heated on the steam bath for one hour, diluted with two liters of water, and worked up in the usual fashion with barium carbonate. The sodium salt was separated into three fractions according to their order of appearance when a solution was concentrated. Treatment of the sodium salt with phosphorus pentachloride yielded only dibenzofuran-2,8-disulfonyl chloride.

b). A suspension of 3.4 g. of mercuric sulfate and 2 g. of mercury in 125 cc. of well stirred concentrated sulfuric acid was kept at 25°-35° and 33.6 g. (0.2 mole) of dibenzofuran added in small portions over a period of 90 minutes. At the conclusion of the addition the mixture was stirred at this temperature for three hours and diluted to 4 liters. The product was worked up by the usual barium carbonate method. Concentration of the filtrate of the barium salt to 1500 cc., and cooling, precipitated barium dibenzofuran-2,8-disulfonate. Identification was made by conversion to the disulfonyl chloride, through the sodium salt. The remainder of the barium salt in the filtrate was converted to the sodium salt and sulfonyl chloride in the usual manner and the product crystallized from toluene. The first crop of crystals was dibenzofuran-2,8-disulfonyl chloride. The second crop melted at 120°-155°. It was crystallized successively from carbon tetrachloride-petroleum ether, carbon tetrachloride, chloroform, and toluene-carbon tetrachloride solutions to yield a product melting at 128°-130°. A mixed melting point with dibenzofuran-2-sulfonyl chloride, m.p. 140°, melted at 102°-110°. The compound analyzed for the monosulfonyl chloride of dibenzofurandisulfonic acid.

Anal. Calcd. for $C_{12}H_7O_6S_2Cl$: S, 18.50 . Found: S, 18.86 and 18.65 .

Catalytic Nitration of Dibenzofuran

Thirty cc. of concentrated nitric acid was introduced dropwise, with stirring, at room temperature, to a solution of 33.6 g. (0.2 mole) of dibenzofuran and 10 g. of mercuric acetate in 100 cc. of glacial acetic acid. At the conclusion of the addition the mixture was heated on a steam bath. The greenish suspension became homogeneous and brown when heated. After 30 minutes of heating the mixture began to react fairly violently. Heating was discontinued until the reaction subsided and a sparse precipitate appeared. Heating was continued for 20 minutes and the solution cooled to -15° and filtered. The precipitate melted at 105°-125° and weighed 20 g. Extraction of this product with boiling ethanol yielded an insoluble residue which melted at 180° after several crystallizations from acetic acid and proved to be 3-nitrodibenzofuran. Chilling the alcohol extract yielded a precipitate melting at 113°-125°. Crystallizations of this material, a major product, from methanol, petroleum ether, ethanol, and glacial acetic acid yielded a product whose melting point range of 130°-140° could not be shifted by further crystallizations. This material was not investigated further.

As a means of comparison, a test run was made under exactly the same conditions and using the same quantities of reagents, with the exception of the mercuric acetate catalyst. In this case a heavy precipitate appeared after 15 minutes heating on the steam bath. The heating and stirring was continued for 15 minutes further and the product chilled to -15°. An 85.5% theoretical yield of 3-nitrodibenzofuran melting at 166°-174° was obtained.

Attempted Direct Carboxylation of Dibenzofuran

The catalyst used in a) and b) was the zinc oxide-cupric oxide-chromic oxide on asbestos of Kinney and Ward (15).

a). Three grams (0.0175 mole) of dibenzofuran, 3 g. of catalyst, and 3 g. (0.0682 mole) of solid carbon dioxide were sealed in a tube of 140 cc. (0.00625 mole) capacity. The reaction was heated at 300° for 50 hours. The calculated pressure was 23 atmospheres. The product was extracted with alkali and the alkaline solution well extracted with ether, decolorized, and filtered. Acidification yielded no carboxylic acid. A quantitative recovery of dibenzofuran was made.

b). An exactly similar reaction was attempted with the addition of 0.95 g. (0.009 mole) of sodium carbonate to the reaction mixture. The same results were obtained.

(15) Kinney and Ward, J. Am. Chem. Soc., 55, 3796 (1933)

c). A mixture of 10 g. of dibenzofuran, 6 g. of anhydrous aluminum chloride and 5.5 g. of solid carbon dioxide was sealed in a tube and heated at 220° for 9 hours. The calculated pressure was 35 atmospheres. A considerable amount of hydrogen chloride was evolved when the tube was opened and charring had taken place. Extraction of the product with alkali and subsequent acidification yielded but a trace of alkali soluble material. Five grams of pure dibenzofuran was recovered.

Attempted Preparations of Dibenzofurylaldehyde

a). Ten cc. of liquid hydrogen cyanide was added to a solution of 20 g. of anhydrous aluminum chloride and 10 g. of dibenzofuran in 100 cc. of dry ether cooled to -15°. Dry hydrogen chloride was passed into this solution for 90 minutes at this temperature, and the solution allowed to stand 12 hours at room temperature. The ether was removed and the product gently hydrolyzed. A quantitative recovery of pure dibenzofuran was made.

b). A mixture of dry carbon monoxide and dry hydrogen chloride in the ratio of two to one was passed through a well stirred solution of 10 g. of dibenzofuran, 15 g. of anhydrous aluminum chloride and 2 g. of cuprous chloride in 100 cc. of dry ether for 6 hours. At the conclusion of this time the mixture was poured on cracked ice, filtered, and dried. A quantitative recovery of pure dibenzofuran was made. This dibenzofuran, however, gave a slight test for an aldehyde with Schiff's reagent.

c). A similar reaction was run with 25 g. of dibenzofuran, 18.7 g. of anhydrous aluminum chloride, and 5 g. of cuprous chloride in the absence of a solvent. The starting temperature was 80°-90° and was gradually lowered to 40°-50° as the melting point of the mixture lowered. The reaction was run at this temperature for 5 hours and the syrupy, purple product decomposed with ice. No aldehyde test was obtained from the product. About half of the dibenzofuran was recovered, together with unidentified residues.

The reliability of the set-up and catalysts in b) and c) was demonstrated by the preparation of p-tolylaldehyde in a 45% yield from toluene.

Preparation of Dibenzofuryl-2-aldehyde

The aldehyde was successfully prepared from the nitrile, through the aldimine stannichloride, following the general directions of Stephen.(16).

A suspension of 13.75 g. (0.075 mole) of anhydrous stannic chloride in 150 cc. of dry ether was saturated with dry hydrogen chloride at 0° until two layers of liquid separated. A

(16) Stephen, J. Chem. Soc., 127, 1874 (1925)

suspension of 9.7 g. (0.05 mole) of dibenzofuran-2-nitrile in 50 cc. of ether was added and the mixture thoroughly shaken. The flask was tightly stoppered and the mixture allowed to react, with occasional shaking, for 6 days at room temperature. At the end of this time the resulting yellow precipitate was filtered and washed with ether. The crude aldimine stannichloride was immediately decomposed with 100 cc. of hot water and the oily product extracted with a small amount of ether. The ether solution was shaken with a saturated sodium bisulfite solution for an hour and let stand. The bisulfite complex was filtered out, thoroughly extracted with ether, and decomposed with dilute hydrochloric acid. A 50% yield of crude product melting at 66°-68° was obtained. After crystallization from dilute methanol it melted at 71°-72°.

Anal. Calcd. for $C_{13}H_8O_2$: C, 79.56 ; H, 4.11 . Found: C, 79.22 ; H, 4.23 .

The substitution of chloroform for ether as a solvent for the nitrile, in an effort to reduce the time requirement of the reaction, resulted in a poor yield of the aldehyde.

The oxidation of this aldehyde with basic permanganate gave dibenzofuran-2-carboxylic acid.

Hypochlorite Oxidation of 2-Acetyldibenzofuran

A suspension of 10 g. of 2-acetyldibenzofuran in 300 cc. of a solution made basic with sodium carbonate, and saturated with calcium hypochlorite, was heated at 90° for 15 hours. Fifteen grams of calcium hypochlorite was added at intervals during this period, and sufficient sodium carbonate introduced to keep the solution basic. The solution was filtered hot and the precipitate extracted with hot 5% sodium carbonate solution. The two extracts were cooled, acidified, and filtered. The product was crystallized from 500 cc. of hot alcohol. The precipitate which appeared on cooling melted at 255°-265°. Several crystallizations from ethanol and 60% acetic acid raised the melting point to 285°-290°. This compound gave qualitative tests for chlorine and was a chlorodibenzofuran-2-carboxylic acid. Neutral equivalent: calcd., 246.5; found, 248.7 . From the alcohol soluble product a 50% yield of dibenzofuran-2-carboxylic acid was obtained.

Attempted Preparation of 2-Bromodibenzofuran-8-carboxylic Acid

An intimate mixture of 5.4 g. (0.03 mole) of cuprous cyanide and 26 g. (0.08 mole) of 2,8-dibromodibenzofuran was heated for 6 hours at 275°-290°. The melt was powdered and extracted in a Soxlet 40 hours with methanol. Removal of the alcohol gave 5.5 g. of extract from which was recovered unchanged 2,8-dibromodibenzofuran and a product melting at 275°-285°. A 40 hour acetone extraction of the residue of the melt yielded an 8 g. total of unchanged 2,8-dibromodibenzofuran and the higher melting material. Basic hydrolysis of this unidentified product yielded only dibenzofuran-2,8-dicarboxylic acid as identified through the ester.

Preparation of Dibenzofuran-2,8-dicarboxylic Acid

An intimate mixture of 10 g. (0.03 mole) of 2,8-dibromodibenzofuran and 15 g. (0.085 mole) of cuprous cyanide was heated at 275°-295° for 6 hours. At the conclusion of the reaction the melt was powdered and hydrolyzed with 100 g. of potassium hydroxide in 300 cc. of methanol for 3 days. Water was added, the solution decolorized with Norite, filtered hot, and acidified. A 5.2 g., ~~88.7%~~ 62.2% of the theoretical, yield of crude dibenzofuran-2,8-dicarboxylic acid was obtained. Esterification of this acid by means of diazomethane, and subsequent crystallization of the ester from methanol yielded methyl dibenzofuran-2,8-dicarboxylate melting at 166°-167°. A mixed melting point with material prepared from 2,8-dibromodibenzofuran, <u>via</u> the Grignard reagent and carbonation, showed no depression.

Picrates of Dibenzofuran and Derivatives

a). A boiling solution of 2.3 g. of picric acid in 15 cc. of ethanol was added to a hot solution of 1.65 g. of dibenzofuran in 10 cc. of ethanol and heated together for two minutes. Cooling precipitated orange-yellow needles which melted at 99°-100° upon crystallization from ethanol. A mixed melting point of this derivative and the picrate of tetrahydrodibenzofuran, m.p. 98°-99°, melted at 85°-87°.

b). One gram of 4-methoxydibenzofuran in 10 cc. of hot alcohol was added to a solution of 1.2 g. of picric acid in 10 cc. of hot ethanol. The two solutions were allowed to react for two minutes and cooled. The orange precipitate melted at 98°-99° after crystallization from ethanol. Mixed melting points of this derivative with the picrates of both dibenzofuran and tetrahydrodibenzofuran, melting at 100° and 97°-98° respectively, were depressed.

c). A solution of 1.84 g. (0.01 mole) of 4-hydroxydibenzofuran in 10 cc. of ethanol was brought to reflux and a hot solution of 2.5 g. (0.011 mole) of picric acid in 15 cc. of ethanol added. It was necessary to concentrate the solution to some extent before cooling precipitated the picrate. Two crystallizations from petroleum ether yielded a picrate melting at 122°.

Reduction of 4-Hydroxydibenzofuran

A solution of 10 g. (0.055 mole) of 4-hydroxydibenzofuran in 100 cc. of absolute ethanol was brought to a reflux and 20 g. (0.87 g. atom) of sodium introduced in small portions. An additional 100 cc. of ethanol was added as needed to keep the material in solution. The reaction product was diluted with water to one liter and steam distilled until the alcohol was removed. Acidification of the residue yielded a heavy oil. Steam distillation of this oil yielded a solid in the distillate melting sharply at 116°. The residue was crystallized from water and gave a small amount of material melting at 111°-113°. The total yield of this product was less than 10%. No recovery of 4-hydroxydibenzofuran was made. The material was not investigated further.

Reaction of Lead Tetra-acetate and Dibenzofuran

A solution of 44.3 g. (0.1 mole) of lead tetra-acetate and 16.8 g. (0.1 mole) of dibenzofuran in 100 cc. of glacial acetic acid was heated in an atmosphere of nitrogen 10 hours at 75°-80°. There was no apparent reaction. A 91% recovery of dibenzofuran melting at 82°-83° was obtained.

Reaction of Lead Tetra-acetate and Tetrahydrodibenzofuran

A solution of 17.2 g. (0.1 mole) of tetrahydrodibenzofuran in 50 cc. of glacial acetic acid was heated to 70°, and 44.3 g. (0.1 mole) of lead tetra-acetate introduced. A reaction took place immediately, accompanied by evolution of gas and darkening of the solution. When the reaction had subsided it was heated at 70° for 6 hours. The reaction mixture was diluted with water, 100 g. of potassium hydroxide added, refluxed for 5 hours, and steam distilled until the distillate was clear.

The first distillate was chiefly impure dibenzofuran. The latter part of the distillate was an unidentified solid melting at 99°-101° after crystallization from petroleum ether. The basic residue was boiled with Norite for 5 hours, filtered, and acidified. No appreciable precipitate appeared.

Attempted Mercuration of Tetrahydrodibenzofuran

a). A solution of 5.15 g. (0.03 mole) of tetrahydrodibenzofuran and 9.9 g. (0.031 mole) of mercuric acetate in 125 cc. of a 75% solution of alcohol was refluxed 18 hours. Mercurous acetate formed immediately in the solution and increased with continued reflux. The removal of this product, and cooling of the filtrate, yielded an oil which was mainly tetrahydrodibenzofuran.

b). A solution of 17.2 g. (0.1 mole) of tetrahydrodibenzofuran and 31.9 g. (0.1 mole) of mercuric acetate in 100 cc. of glacial acetic acid was refluxed 14 hours. A considerable amount of metallic mercury as well as mercurous acetate was filtered out and the filtrate diluted with water. Ether extraction of the oil resulting from the dilution, and subsequent distillation of the ether extract yielded tetrahydrodibenzofuran and 3 g. of impure dibenzofuran.

c). A suspension of 8.6 g. (0.05 mole) of tetrahydrodibenzofuran in a solution of 13.5 g. (0.05 mole) of mercuric chloride, and 27.5 g. (0.05 mole) of sodium acetate in 150 cc. of water was gently refluxed 4 days. The heavy oil which resulted was extracted with ether, and the ether dried and distilled. Some mercurial was evidently present, as well as some recovered tetrahydrodibenzofuran, as metallic mercury appeared as a decomposition product of the distillation.

d), A solution of 34.4 g. (0.2 mole) of tetrahydrodibenzofuran and 63.8 g. (0.2 mole) of mercuric acetate in 300 cc. of absolute ethanol was refluxed for 30 hours and cooled. The mercurous acetate which had precipitated as it was formed was discarded. The alcoholic filtrate was warmed and treated with 40 g. (0.28 mole) of calcium chloride in 200 cc. of 80% ethanol. The resulting precipitate was filtered and air dried. It melted roughly at 140°-175° and weighed 62.5 g. Numerous fractionations of this product from acetone, alcohol, ether, and various strengths of acetic acid gave no material of definite or sharp melting point. It was quite soluble in acetone, and throwing out the precipitate with water did not appear to purify the product. It was also quite soluble in acetic acid, less so in alcohol, and but slightly soluble in ether. By repeated extractions with alcohol, a small amount of residue melting at 225°- 227° was obtained which a mixed melting point with 4-chloromercuridibenzofuran, melting at 235°-238°, did not depress. A mixed melting point of this sort is evidence, not proof, of identity. The original alcoholic filtrate was diluted with water, and the precipitated oil removed by decantation, and steam distilled. From this was recovered 10 g., 29% recovery, of tetrahydrodibenzofuran.

Three more runs by this method were made, altering conditions and methods of working up the product, but the results in all cases were essentially the same.

e). Seventeen and two-tenths grams (0.1 mole) of tetrahydrodibenzofuran was heated to 120° and 31.9 g. (0.1 mole) of powdered mercuric acetate was added in small portions, with stirring, over 30 minutes. The mixture was then heated, with occasional stirring, up to 145° for one hour. Acetic acid was given off in considerable quantities above 130°. If the temperature was raised to 155° an appreciable amount of decomposition took place. The melt was poured upon 100 cc. of ethanol, and 30 g. (0.37 mole) of calcium chloride in 150 cc. of 80% ethanol added. A heavy flocculent precipitate was formed immediately. The mixture was well shaken, cooled, and filtered. The precipitate was extracted with warm water and cold alcohol. A 32 g. yield of the air-dried product was obtained. Extractions and attempted crystallizations of this very impure material with acetone, ether, alcohol, and water yielded fractions of product, containing mercury, which melted in their lower range from 68° and in their upper range to 230°. No compounds of definite melting point were isolated. Tetrahydrodibenzofuran was recovered from the original alcoholic filtrate, and mercurous acetate was identified as a product.

Changes in time and temperature of heating, and methods of working up the products of this reaction yielded no significant difference in the product.

Attempted Iodination of Tetrahydrodibenzofuran

a). A suspension of 17.2 g. (0.1 mole) of tetrahydrodibenzofuran, 25.4 g. (0.1 mole) of iodine, 43.3 g. (0.2. mole) of yellow mercuric oxide, and 100 cc. of dry carbon tetrachloride was allowed to stand 12 hours at room temperature. At the end of this time the iodine color had vanished from the suspension. The reaction mixture was filtered hot, and the residue extracted with 100 cc. of boiling carbon tetrachloride. The two extracts were combined, dried over sodium sulfate, and distilled at 15 mm. A 76% recovery of dibenzofuran, characterized as the picrate, was made. Continued distillation of the higher boiling fraction at 15 mm. resulted in the violent decomposition of the product at 170° with the evolution of free iodine.

b). A suspension of 43.3 g. (0.2 mole) of yellow mercuric oxide, 21.8 g. (0.12 mole) of tetrahydrodibenzofuran, and 25.4 g. (0.1 mole) of iodine in 200 cc. of dry petroleum ether was allowed to stand at room temperature for two days. The iodine color had been removed at the conclusion of this time. The mixture was filtered, and the precipitate extracted with hot chloroform. The two solutions were combined, dried over sodium sulfate, and the solvents removed. The residue was subjected to steam distillation until the condensate came over clear. From the condensate was recovered most of the tetrahydrodibenzofuran, but no iodo compound. An iodotetrahydrodibenzofuran would be expected to steam distill. A small amount of yellow solid precipitated from the residue of the steam distillation. It melted at 140°-141° after crystallization from ethanol. A mixed melting point with 3-iododibenzofuran, m.p. 147°-147.5° , was depressed to 133°-140°.

Attempted Dehydrogenations of 7-Nitro-1,2,3,4-tetrahydrodibenzofuran

a). An intimate mixture of 1 g. of 7-nitrotetrahydrodibenzofuran and 2 g. of flowers of sulfur was heated slowly from 160° to 250° for 8 hours. The residue was extracted with hot glacial acetic acid. Cooling the extract precipitated only sulfur. Dilution of the extract with water gave a further yield of less pure sulfur.

b). An intimate mixture of 1 g. of 7-nitrotetrahydrodibenzofuran and 1 g. of sulfur was heated at 200°-220° until the evolution of hydrogen sulfide ceased. This required 90 minutes. The melt was extracted twice with hot 95% ethanol. The only product recovered by the concentration and dilution of the extract was a small amount of impure sulfur.

c). A suspension of 1 g. of 7-nitrotetrahydrodibenzofuran in a solution of 50 cc. of 15% potassium permanganate and 5 cc. of concentrated sulfuric acid reacted quite vigorously when mixed. The product was cooled to 15°, let stand 10 minutes, and filtered. The solid material was extracted twice with hot alcohol and allowed to cool. The starting material was the only product recovered.

d). The starting material only was isolated when 0.5 g. of 7-nitrotetrahydrodibenzofuran was refluxed 5 hours with a solution of 10 g. of ferric chloride in either 50 cc. of water, or 50 cc. of glacial acetic acid.

e). A solution of 10 g. of mercuric acetate and 0.5 g. of 7-nitrotetrahydrodibenzofuran in 60 cc. of 50% acetic acid was refluxed 6 hours. Cooling precipitated a yellow solid which was in part the starting material, and in part a compound insoluble in hot or cold concentrated hydrochloric acid or 10% sodium hydroxide solution, slightly soluble in acetone and alcohol, and quite soluble in acetic acid. The melting point was about 230° with decomposition from 185°. This material was not investigated further as this melting point is too high for mononitrodibenzofurans.

f). An intimate mixture of 1 g. of 7-nitrotetrahydrodibenzofuran and 2 g. of nickel oxide was heated at 200°- 250°for

3 hours. Extraction of the residue with hot alcohol yielded only the starting material.

g). A similar result was obtained by heating an intimate mixture of 1 g. of 7-nitrotetrahydrodibenzofuran and 3 g. of mercuric oxide for 90 minutes at 180°-200°.

Attempted Oxidation of 7-Acetyl-1,2,3,4-tetrahydrodibenzofuran

a). A suspension of 3 g. of 7-acetyltetrahydrodibenzofuran in a solution of 25 cc. of water and 6 g. of potassium hydroxide was treated in small portions at 60°-70° with the theoretical amount, 4.4 g., of potassium permanganate in 90 cc. of water. The solution was filtered hot and extracted with ether. The basic solution was treated with Norite, concentrated somewhat, acidified, and cooled. No precipitate appeared.

b). A suspension of 2 g. of 7-acetyltetrahydrodibenzofuran was refluxed 12 hours with a solution of 60 g. of potassium ferricyanide and 11 g. of potassium hydroxide in 300 cc. of water. The turbid solution was filtered hot and acidified. The resultant precipitate was extracted with ether, and the ether extracted with 100 cc. of 15% potassium hydroxide solution. Concentration of this basic extract gave the potassium salt of an acid. The sodium salt was made, crystallized twice from water, and acidified. The resulting acid melted at 145°-146°. The yield was 5%-10% and the product was not further investigated. It was not tetrahydrodibenzofuran-7-carboxylic acid or dibenzofuran-3-carboxylic acid, the known oxidation products. There is a possibility that this compound is a dihydrodibenzofuran derivative, but it is more likely a ring cleavage product.

c). One hundred cc. of 5% potassium permanganate solution was added in small portions to a suspension of 3 g. of 7-acetyltetrahydrodibenzofuran in a solution of 10 g. of potassium hydroxide and 30 cc. of water. The decolorized solution was filtered hot, cooled, and acidified. The semi-solid oil that separated was extracted with ether, and the ether extracted with 15% potassium hydroxide solution. As in b), concentration and purification through the sodium salt yielded the same acid melting at 145°-146°.

d). An intimate mixture of 2 g. of acetyltetrahydrodibenzofuran and 3 g. of sulfur was heated at 200°-260° until the evolution of hydrogen sulfide had ceased. The sublimed product was crystallized from petroleum ether and melted at 139°- 141°. This material gave a good elemental test for sulfur.

SUMMARY

The dibenzofuransulfonic acid of Zehenter has been identified as dibenzofuran-2-sulfonic acid.

The preparation of dibenzofuryl-2-aldehyde, dibenzofuran-2,8-dicarboxylic acid, and dibenzofurantetrasulfonic acid has been reported.

The acid hydrolysis of dibenzofuran-2-sulfonic acid, dibenzofuran-2,8-disulfonic acid, and dibenzofurantetrasulfonic acid to dibenzofuran has been described.

A number of negative, but significant, results in the dibenzofuran and tetrahydrodibenzofuran series has been mentioned.