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THE PHYSIOLOGICAL ACTION OF SOME FURAN COMPOUNDS

BY

Willard H. Kirkpatrick

A Thesis Submitted to the Graduate Faculty
for the degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

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INTRODUCTION

Physiologically, furan shows a great similarity to benzene. Koch and Cahan[1] have shown that while furan has some anesthetic and analgesic properties, its toxicity is so great as to eliminate it from consideration for therapeutic use. When given by inhalation it causes convulsions, apparently due to stimulation of the motor centers in the medulla and cord, which are followed by paralysis of the respiratory center and asphyxia. When administered in small doses orally it has a corrosive, solvent effect on the mucosa, causing a copious watery secretion. There is an increased permeability of the blood vessels, frequently producing extensive hemorrhages. Injection of 1.5 cc. into a ten kilogram dog caused immediate death with symptoms and post mortem changes similar to those seen in acute hydrocyanic acid poisoning. There is a marked hyperemic condition of the lungs, dilatation of the veins and a bright, cherry red coloring of the blood. Furan seems also to be a general protoplasm poison, completely inhibiting the growth of yeast. Johnston[2] has substantiated this work in that he has found that anesthesia produced in rats or cats by furan is associated with a great fall in blood pressure and by a high percentage of mortality.

1. Koch and Cahan, J. Pharmacol., 26, 281 (1925).
2. Johnston, J. Pharmacol., 43, 85 (1931).

Furfural appears to be quite toxic according to the work of McGuigan[3], who has found the phenol coefficient to be 0.26, measured from its bactericidal action. It is about one-half as toxic for gold fish as phenol and one-third as toxic as formaldehyde for the same animal. In large doses it has a paralytic action on frogs similar to that of chloral. Locally furfural is corrosive and anesthetic. In increasing doses it causes unsteady gait, inability to stand and finally paralysis in rabbits. The fatal dose by stomach is about 0.8 cc. per kilogram body weight. The action on white mice is similar to that on rabbits. When in five per cent solution, 0.6 cc. of pure furfural per kilogram body weight causes increased irritability, increased respiration, salivation and finally strychnine-like convulsions. In dogs the action is much the same.

Furfural, like the aliphatic aldehydes and benzaldehyde, possesses a narcotic action. Narcosis is produced in rabbits by 0.1 g. per kilogram body weight when injected subcutaneously, in cats and dogs by 0.2 g. After a short period of excitation, there follows a paralysis of the sensory nerves and a weakening of the respiration and heart functions. In stronger doses furfural produces clonic convulsions and finally coma followed by death. Orally, it is far less toxic; as one can give six to nine grams daily to a dog without producing any action. It produces a paralysis of short duration when

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[3] McGuigan, J. Pharmacol., 21, 65 (1923).

applied topically to muscle, nerve or mucous tissue. However, on account of its strong irritant action on membrane it can not be used as a local anesthetic[4].

The physiological action of 2-furancarbinol (furfuryl alcohol) is in most cases inhibitory and paralytic. Its dilute solution paralyzes the sensory nerves. This suggests that it has an anesthetic action; however, due to its extreme instability it is of no practical value. In general it resembles benzyl alcohol and represents an example where the physiological action of an organic compound depends greatly upon the side chain rather than upon the nucleus[5].

2-Furancarbinol acts as a mild narcotic; but, inasmuch, as it is far more toxic than benzyl alcohol it is of no therapeutic value. In rabbits, 0.5 g. per kilogram body weight produces a one to two hour sleep accompanied by a decrease in frequency of respiration and lowering of body temperature. Larger doses cause salivation, diuresis, and diarrhea. Death occurs as a result of disabling of the respiration centers and not because of any injury to the heart[6].

2-Furoic acid or pyromucic acid is without specific action. Similarly its amide is very indifferent as one can inject intravenously into dogs 4 g. per kilogram body weight without observing any changes.

These few reports constitute a brief summary of the phar-

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4. Cohn, Arch. exp. Path. Pharmakol., 31, 40 (1893); Lepine, Compt. rend. soc. biol., (1887), 437.
5. Okubo, J. Pharm. Soc. Japan, No. 539, 39, (1927).
6. Erdmann, Arch. exp. Path. Pharmakol, 48, 233 (1902).

macological data which are available on the simply substituted furan derivatives[7]. In benzene chemistry the literature is replete with physiological reports on many type compounds; such is not the case in furan chemistry. This paucity of information might be attributed to one of two reasons, or possibly a combination of both. First, it has only been in recent years that furan derivatives have been available in sufficient quantities to permit extensive studies. This has been made possible by the commercial production of furfural from oat hulls, so that today furfural is one of the cheapest aldehydes on the market. Second, furan compounds are very unstable, generally speaking. This fact in itself would tend to dissuade workers into more hopeful fields. The furan nucleus is also very sensitive to mineral acids.

The chemistry of furan has long been of major interest in this laboratory as a part of the problem on the utilization of agricultural waste. It is only natural that part of the work has been concerned with the synthesis of compounds which were hoped to be of physiological value. These furan derivatives were patterned after compounds that were known to be of use in therapy.

One of the most widely known local anesthetics is procaine or the hydrochloride of β-diethylaminoethyl ester of p-amino-

[7] A more detailed bibliography pertaining to the physiological action of complex furan derivatives can be found in the series of doctoral theses entitled "Furfural and Some of its Derivatives". These were published at Iowa State College by Hewlett in 1930, Dickey in 1930 and Brown in 1930.

benzoic acid. Because the related compounds without the *p*-amino grouping have considerable local anesthetic action, and because of the known inherent difficulties in introducing a free amino group in the furan nucleus, studies were made on compounds without any amino group attached to the nucleus, such as β-diethylaminoethyl 2-furoate. The series of compounds tested included the corresponding ester of 2-furylacrylic acid and the benzyl esters of the same two acids. The benzyl esters were apparently without action. The β-diethylaminoethylester of 2-furylacrylic acid has about seventy five per cent of the activity of β-diethylaminoethylbenzoate, and the corresponding ester of 2-furoic acid has only perceptible action[8]. This observation was somewhat surprising as Kamm, in unpublished work, had shown ethyl 2-furoate to have appreciable action. A possible explanation for this anomaly may be found in Kamm's hypothesis for the amino-ester class of local anesthetics which states that the carbonyl group of the ester must be attached to an unsaturated atom[9]. It is true, in this case, that the carbonyl group is attached to an unsaturated atom but the unsaturation is not a simple ethylenic double bond.

Having determined that certain furan derivatives were mild local anesthetics, it seemed of interest to determine whether or not a like correlation could be made with another

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[8] Gilman and Pickens, *J. Am. Chem. Soc.*, *47*, 245 (1925).

[9] Kamm, *J. Am. Chem. Soc.*, *42*, 1030 (1920).

physiological action: namely, hypnotic properties of mixed ketones. Acetophenone shows definite action in large doses and so was selected as the parent compound. Four compounds were prepared and tested: 2-Acetylfuran, 2-furyl-2-pyrryl ketone, 2-furyl-2-thienyl ketone, and 2-benzoylfuran. The pyrrole derivative produced a definite hypnosis in large doses, while the remainder of the compounds were very toxic[10]. The results of this study indicate that the phenyl and pyrryl nuclei are necessary for the hypnotic action; whereas, the furyl and thienyl nuclei apparently inhibit this property. One explanation for this behaviour involves the super-aromatic properties of furan and thiophene[11]. From these results one might conclude that the introduction of a super-aromatic nucleus into a ketone diminishes or even destroys the hypnotic action. However, such a conclusion cannot be drawn until a greater number of compounds has been tested. It is significant that the furan and thiophene compounds which were tested for local anesthesia were less effective than their phenyl and pyrryl analogs[8].

Besides these furan compounds possessing more or less desirable physiological properties, there are certain other derivatives which have very disagreeable action on man. These properties may be roughly classified as vesicants, lachrymators and sternutators. β-Chloroethyl-2-furfuryl sulfide, 2,5-dinitrofuran, and 5-chloromethyl-2-furaldehyde are vesicants. Furoyl chloride, 5-chlorofuroyl chloride and 2-chloromethylfuran are

10. Gilman, Rowe and Dickey, *Rec. trav. chim.*, *52*, 395 (1933).
11. Gilman and Towne, *Rec. trav. chim.*, *51*, 1054 (1932).

very irritant to the mucous membrane of the eyes, nose and throat. Powdered 2-furoic acid is irritating to mucous membrane and has distinct sneeze-provoking properties[12].

Early attempts in this laboratory to prepare furan arsenicals were not successful[13]. Later workers[14], to whom were made available a report of the unpublished work of Gilman and Kirkpatrick, were more successful and secured furylarsines. These compounds are very unstable and require pressures of 0.1 mm. before they can be distilled without decomposition. Physiologically, they are very offensive and extremely toxic. Work is being continued on other derivatives which might possess valuable properties in medicine.

In the course of the comprehensive investigation of furan and its derivatives being undertaken in this laboratory it became evident that furantetracarboxylic acid and the other polybasic furan acids would be exceedingly valuable compounds for clearing up cases of questionable orientation. When Sutter[15] in his work on diketoadipic acids, chanced to prepare 2,3,5-furantricarboxylic acid, it appeared that here by analogy was a possible expedient way to prepare the desired furan tetracarboxylic acid. With this in mind, dioxalsuccinic ester was prepared according to Sutter's directions[15] and subjected to ring closure. The resulting tetracarbethoxyfuran on acid hy-

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[12] Gilman, Hewlett and Dickey, Iowa State Coll. J. Sci., 6, 137 (1932).

[13] Gilman and Kirkpatrick, C. A., 28, 6714 (1934).

[14] Lowe and Hamilton, J. Am. Chem. Soc., 57, 1081 (1935).

[15] Sutter, Ann., 499, 47 (1932).

drolysis gave furantetracarboxylic acid in good yields.

This latter compound opened an avenue of approach, through decarboxylation, to furan carboxylic acids, both known and unknown. Consequently an attempt was made to carry out a stepwise decarboxylation of the tetrabasic acid. When this work was near completion, Reichstein[16] and co-workers published an account of parallel work. As a result the problem was not carried out in complete duplication.

Isolation of 3,4-furandicarboxylic acid, the last remaining unknown dibasic furan acid, and of 3-furoic acid gave further confirmation to the hypothesis that α-carboxyl groups are removed in preference to similar β-groups in the furan series. It appears that the decarboxylation of the tetrabasic furan acid is a more convenient source of β-furoic acid than those previously reported[17].

As this is written there is no unequivocal proof for the position of the nitro group in nitrofuran[18]. 3,4-Furandicarboxylic acid is admirably suited to give conclusive proof as to whether the nitro group enters in the α- or β-position. With both β-positions blocked an entering group would have to assume an α-position. The resulting compound could then be decarboxylated and the residuum compared with the known mononitrofuran.

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[16] Reichstein, Grüssner, Schindler and Hardmeier, Helv. Chim. Acta., 16, 276 (1933).
[17] Gilman and Burtner, J. Am. Chem. Soc., 55, 2903 (1933).
[18] Studies now in progress by Mr. James Straley may solve this problem. He is replacing the chloromercuri-group in 3-chloro-mercurifuran by the nitro o group; oxidation of the resulting product should give 2-nitrofuran.

It appeared that this dibasic acid in the form of its ester should undergo nuclear substitution with extreme ease because there are two α-positions available and α-positions are very reactive. But a number of attempted nitrations were carried out using a wide range of severity of experimental conditions. Either no reaction occurred or the furan nucleus was ruptured by oxidation resulting in the formation of oxalic acid. In the case of halogenation, where more strenuous conditions may be employed without accompanying breakdown of the reactants, dimethyl 3,4-furandicarboxylate was found to undergo bromination in a sealed tube at 160° in the absence of a solvent to give a compound of undetermined structure. Burtner[19] who checked a part of the experimental work, offered a possible explanation for these anomalous results.

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[19] Burtner, Doctoral Dissertation, Iowa State College, 1933 p. 49-51.

EXPERIMENTAL PART.

Preparation of Sodiooxalacetic Ester

In a one-liter balloon flask, 73 g. (0.5 mole) of freshly distilled ethyl oxalate and 260 cc. of dry ether were mixed. To this solution was added 11.5 g. (0.5 atom) of sodium in the form of wire. The flask was attached to a Knorr reflux condenser and cooled below room temperature by means of a water bath. To the cold solution, 260 cc. (roughly 3 moles) of ethyl acetate was introduced rapidly from the top of the condenser. The reaction began in a very few minutes and it was always necessary to have an ice-salt bath ready prior to the addition of the ethyl acetate. As soon as the foam which formed completely covered the surface of the liquid, the ice bath was applied to the flask. If this was not done in the initial stages of the reaction, it proceeded very violently and soon was beyond control.

Sometimes, it was necessary to control the rate of reaction for twenty minutes or even longer. Finally when the reaction has subsided, the material was permitted to cool and an orange colored mass separated. This was filtered and washed well with ether and when dry gave 75 g. of the pale yellow sodiooxalacetic ester which was a yield of 73%. Yields as high as 85% were secured but the average runs gave 70-75%.

Too much care could not be exercised in this preparation. In the hands of inexperienced chemists several serious fires occurred. These were caused by pieces of sodium being carried up in the ether vapor and out the reflux tube into the ice bath.

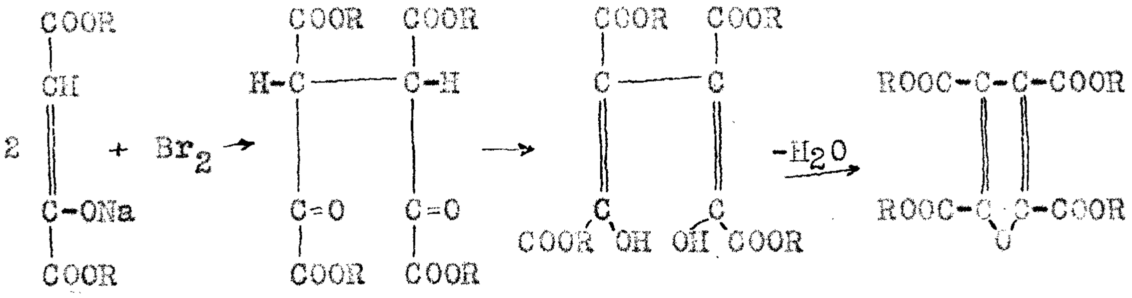
As an added caution it seemed advantageous to cover the ice bath with a dry towel.

Preparation of Dioxalsuccinic Ester

In a typical synthesis, 88 g. (0.41 mole) of sodiooxalacetic ester was suspended in 200 cc. chloroform and cooled with an ice salt bath. Then, gradually, a solution of 34 g. (0.2 mole) of bromine in 50 cc. of chloroform was added with efficient stirring. The bromine color disappeared immediately. Upon the addition of all the bromine, the flask was cooled for one hour. The reaction product was filtered to remove the unchanged ester and sodium bromide. The filtrate was then evaporated on the hot plate to one-third of its original volume. Sufficient ether was added so that the solvent layer would be lighter than the aqueous layer, and the solution was extracted twelve times with water to remove the last traces of inorganic salts. The upper layer was dried over calcium chloride and the chloroform-ether mixture evaporated. The residue, a yellow oil, quickly solidified, on cooling, to a crystal meal. The presence of any moisture apparently prevented the crystallization. The crystals were filtered and washed with cold ether; from these mother liquors two more crops of crystals could be procured. A yield of 39 g. or 56%, of dioxalsuccinnic ester, melting at 85°, was secured, which agreed with Sutter's[15] observation.

Preparation of Tetracarbethoxyfuran

In order for this compound to be secured from dioxalsuccinic ester, the following enolization must occur:



A solution of 18 g. (0.05 mole) of dioxalsuccinic ester was prepared in 30 cc. of concentrated sulfuric acid with cooling. The temperature was not permitted to rise above 50° as the resulting ester was sensitive to strong mineral acids at higher temperatures. The flask was then protected from the atmosphere by means of a calcium chloride tube, and placed in the ice box for fifteen hours. At the end of this time the dark colored syrup was poured on ice and a white oil separated which soon solidified. This was the crude tetracarbethoxyfuran. It was filtered and washed with ice-cold water. Upon crystallization twice from alcohol, the compound was secured pure for analysis, melting sharply at 32°. The yield was 11.6 g. or 84% of the theoretical. Reichstein and co-workers[16] secured a melting point of 34.5° after distillation under reduced pressure and several crystallizations from alcohol. Neutral equivalent: calcd., 89.0; found, 91.1 and 90.7.

Anal.[20] Calcd. for $C_{16}H_{20}O_9$: C, 53.93; H, 5.62. Found: C. 54.06; H, 5.48.

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[20] The author is indebted to Mr. H. [illegible]. Oatfield for this analysis.

Preparation of Furantetracarboxylic Acid

Ten grams (0.028 mole) of tetracarbethoxyfuran was heated to gentle reflux with 20 cc. of 20% hydrochloric acid in a small round-bottomed flask. Heating was continued until the oil droplets disappeared, a process which usually required from four to six hours. If after this time the hydrolysis was not complete, a few cc. of concentrated hydrochloric acid were added and the heating was continued. The solution was then chilled in an ice-salt bath; usually crystals separated at this point. If not, it was necessary to evaporate the solution under reduced pressure and then to place it in the ice box. A quantitative yield of the crude acid was secured which melted at 238°. It was very soluble in water and alcohol and only slightly soluble in benzene and acetone. Two crystallizations from water with the aid of decolorizing carbon raised the melting point to 247°, the value reported by Reichstein[16]. Neutral equivalent: calcd., 61; found, 63.0 and 62.7.

Anal. Calcd. for $C_8H_4O_9$: C, 39.35; H, 1.64. Found: C, 39.15 and 40.02; H, 1.60 and 1.88.

The ester could be hydrolyzed by boiling with water under reflux for 72 hours, but neither of these two procedures was satisfactory for the production of large quantities of the polybasic acid which were necessary for the studies on 3,4-furandicarboxylic acid. For this purpose, it was convenient to hydrolyze the ester in one-half mole runs. The ester was refluxed with 500 cc. of 20% hydrochloric acid for six hours. Then 100 cc. of concentrated hydrochloric acid and 100 cc. of acetic acid were added and the refluxing was continued for another six hours. The solution was transferred to a Claisen flask and three-fourths of the solvent distilled away at atmospheric pressure; the remainder was removed under reduced pressure, leaving a quantitative yield of the crude furantetracarboxylic acid, which was sufficiently good for decarboxylation.

At first, many attempts were made to hydrolyze the ester by means of an alkaline reagent. This appeared to be the most desirable method due to the inherent sensitivity of the furan nucleus toward mineral acid treatment. In each case the ester was successfully saponified to the salt but in no case could the free acid be liberated upon treatment with strong acid. From this action, it was evident that the mono-alkali salt of furantetracarboxylic acid was a very stable compound. These findings were in complete accord with the findings of Reichstein.[16]

In a typical experiment, 25.7 g. (0.072 mole) of tetracarbethoxyfuran was finely powdered and suspended in an equivalent amount of absolute alcoholic sodium hydroxide solution in a small balloon flask. The ester was saponified immediately and it was stirred well to insure complete reaction. It was then filtered and the salt dried. The dry powder was dissolved in as little water as was necessary and the flask was cooled in an ice bath; the solution was acidified with hydrochloric acid and a precipitate settled out. It was filtered and crystallized several times from water, yielding white crystals which melted with decomposition at 297°. The salt was insoluble in all organic solvents and only sparingly soluble in water.

Anal. Calcd. for $C_8H_3O_9Na$: C, 36.09; H, 1.12. Found: C, 35.2 and 35.8; H, 1.33 and 1.57.

Concerning the Furantricarboxylic Acids

Preliminary experiments to secure the 2,3,4-furantricarboxylic acid by removing one molecule of carbon dioxide from furantetracarboxylic acid were not successful. Before further work could be started, Reichstein and co-workers[16] published a report of identical experiments. They showed that the tribasic acid which they secured by decarboxylation and called 2,3,4-furantricarboxylic acid was identical with the acid which Sutter[15] prepared by ring closure and had assigned the structure 2,3,5-furantricarboxylic acid. Reichstein and Grüssner[21] later showed Sutter to be incorrect, by synthesizing 2,3,5-furantricarboxylic acid, a compound which was not identical with Sutter's acid. With this acid, all of the possible furancarboxylic acids have been prepared.

Preparation of 3,4-Furandicarboxylic Acid

If the hypothesis be true that α-carboxyl groups may be more easily removed from a furan nucleus than a similar β-group, then it is evident that the decarboxylation of furantetracar-

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21. Reichstein and Grüssner, *Helv. Chim. Acta.*, *16*, 555 (1933).

boxylic acid should give the hitherto unknown 3,4-furandicarboxylic acid. Experiments verified the hypothesis.

In a large pyrex test tube was placed 15 g. (0.061 mole) of the crude tetra-acid. This tube had air tight connections to a condenser, the outlet of which was attached to a eudiometer so that the volume of carbon dioxide evolved could be roughly measured. When all was in readiness, the pyrex tube containing the compound was heated in a metal bath to 280°. After the calculated volume for two equivalents of carbon dioxide had been displaced, the heating was stopped. The residue was then sublimed for 45 minutes at 280° under 5 mm. pressure. A 60% yield, or 5.5 g., of 3,4-furandicarboxylic acid could be removed from the walls of the test tube. This crude acid melted at 209° but when purified by several crystallizations from water the melting point was raised to 215-216°.[22] The acid was quite soluble in water. Neutral equivalent: calcd., 78.0; found, 77.9 and 78.3.

Anal. Calcd. for $C_6H_4O_5$: C, 46.15; H, 2.58. Found: C, 46.27 and 46.34; H, 2.64 and 2.55.

Worthy of mention is the fact that the same diacid was secured from the decarboxylation of the monosodium salt of furantetracarboxylic acid. The procedure in this case was much simpler than that used previously, but the method was only practical in small-sized runs. In a side-arm test

[22] Reichstein reported 217-218° upon crystallization from anisole.

tube was placed [illegible] g. (0.007 mole) of the salt, connecting the side-arm to a eudiometer. The compound was then heated in a metal bath to 280-300° until approximately two equivalents of carbon dioxide were driven off. The residue was boiled with dilute sodium hydroxide and treated with decolorizing carbon, filtered hot, cooled, and acidified. Crystals of 3,4-furandicarboxylic acid separated in a yield of 70%, which when dried melted at 213-214°.

Preparation of β-Furoic Acid

A small distillation flask was set up with a glass tube leading to within one inch of the bottom. The side-arm was connected to two Erlenmeyer flasks which were fitted to act as an absorption train. Ten cc. of crude tar base and 0.5 g. of copper bronze were placed in the flask. In each of the absorption flasks was placed 25 cc. of dilute sodium hydroxide. The apparatus was connected for operation after the glass tube was adjusted so that it was just above the surface of the liquid and then 1.56 g. (0.01 mole) of 3,4-furandicarboxylic acid was placed in the flask. A rapid stream of nitrogen was passed through the apparatus; this was to sweep the carbon dioxide and the sublimed acid into the alkaline solution. The flask was heated in a metal bath to 225° at which point the evolution of carbon dioxide began. The temperature was raised gradually to 275° over a period of forty minutes and was then stopped. The sodium hydroxide solution was washed well with ether to remove any tar base, acidified with hydrochloric acid, and the resulting solution cooled and extracted with ether. After the ether solution had been dried over sodium sulphate, the solvent was evaporated to give 0.7 g. of 3-furoic acid, which is a yield of 65%. The acid was crystallized twice from water and melted at 120-121°. A mixed melting point with an authentic sample of β-furoic acid showed no depression.

Substitution Reactions of 3,4-Furandicarboxylic Acid

It was demonstrated previously that nuclear substitution products of furan acids, were, in many cases, prepared with less difficulty if ester derivatives were chosen as starting materials[23]. Accordingly, the dimethyl 3,4-furandicarboxylate was synthesized; incidental to this synthesis, was the preparation of 3-carbomethoxy-4-carboxyfuran.

Preparation of Dimethyl 3,4-Furandicarboxylate

Dry hydrogen chloride was bubbled into a solution of 5.5 g. (0.035 mole) of the dibasic acid in the least possible amount of absolute methanol. After three hours the solution was poured on cracked ice whereupon a white crystalline material separated. It was filtered and washed with cold sodium bicarbonate solution. The filtrate and washings were extracted with ether; the ether layer was washed with sodium bicarbonate and dried over sodium sulphate. After the removal of the solvent, the oil was chilled and combined with the first crystals to give 5.6 g. of the ester, melting at 46°. This was identical with

23. Wright, Doctoral Dissertation, Iowa State College 1932.

the value reported by Reichstein[16]. Neutral equivalent: calcd., 92; found, 91.7 and 92.6.

Anal. Calcd. for $C_8H_8O_5$: C, 52.16; H, 4.38. Found: C, 52.47; H. 4.52.

In preliminary runs of esterification, the acid was refluxed with a mixture of methanol and sulfuric acid. In every case a compound resulted which melted at 123° when pure and it was not β-furoic acid. Analysis showed it to be 3-carbomethoxy-4-carboxyfuran; in other words, esterification had affected only one of the carboxyl groups. Neutral equivalent: calcd., 170; found, 175.

Anal. Calcd. for $C_7H_6O_5$: C, 49.41; H, 3.53. Found: C, 49.60; H. 3.72.

Attempted Nitrations of 3,4-Furandicarboxylic Acid and its Esters.

a). Into a small three-necked flask equipped with a mercury seal stirrer and a low temperature thermometer was placed 28 cc. of acetic anhydride. It was cooled to -5° and 12 g. of fuming nitric acid was added dropwise to the stirred solution, maintaining the temperature at -10° to -15°. Five grams (0.032 mole) of the furan acid was added in small portions, which occasioned no heat effect. Stirring was continued for an hour and the reaction product was filtered cold. The precipitate was crystallized from water, melted at 214°, was free of nitrogen and gave no depression in melting point when mixed with the starting material. This same proof was used in all cases below where the product was said to be identical with the original material. Other runs were made, using the same nitrating medium but varying the temperature, with the same results.

b). In a customary nitrating flask, 19 g. (0.07 mole) of the dibasic acid was added slowly to 30 cc. of fuming sulfuric acid, cooled to 0°. The resulting solution was permitted to stand in the cold for 18 hours. The flask was then cooled to -15° and 30 cc. of fuming nitric acid was added slowly, never letting the temperature rise above -8°. It was stirred for one hour and poured on cracked ice. The solution was extracted eight times with ether and the ether solution was washed well with water and dried over sodium sulphate. The solvent was evaporated and the last traces were removed under reduced pressure (20 mm.). This crude material melted at 95° to 105°, upon crystallization from water it melted sharply at 101°. A mixed melting point determination with oxalic acid showed no depression. Elementary analysis of the compound gave a negative nitrogen test and its water solution was acid and gave a precipitate with calcium chloride.

c). A small amount of 3,4-furandicarboxylic acid was added to 20 cc. of concentrated nitric acid. At first there was no sign of reaction but after twenty minutes there was a slight evolution of gas. After two hours a few crystals were isolated which proved to be the starting compound. The flask was then heated on a water bath for two hours. Oxalic acid and 3,4-furandicarboxylic acid were separated from the crystals secured on cooling.

d). Several other less common nitrating agents were tried on the dibasic acid. Baeyer[24] has successfully used potassium nitrate and sulfuric acid to effect nitration. Five grams (0.035 mole) of the dibasic acid was added to 36 g. of sulfuric acid in small portions with but slight heat effect. To the solution, 4 g. (0.04 mole) of finely powdered potassium nitrate was added, a few crystals at a time. It was then heated for two hours at 60-70° and poured on crushed ice, whereupon a solid separated out which was the unchanged dibasic acid.

e). In some cases mercuric nitrate has acted as a carrier in nitration reactions[25]. A small sample of the furan acid was heated in dilute nitric acid (sp. g. 1.3) to 60-70° with 0.25 g. of mercuric nitrate. After seven hours, the dibasic acid was recovered unchanged.

f). Other workers[26] have found that a compound may be dissolved in a suitable solvent and be nitrated with concentrated nitric acid. Two grams (0.035 mole) of 3,4-furandicarboxylic acid was dissolved in 40 cc. of acetone. This was added to 20 cc. of nitric acid in a flask equipped with a mechanical stirrer. The suspension was agitated for four hours. The emulsion was then poured on ice and the crystals which separated were identified as the original compound.

g). In the nitration of an acid, the entrance of a nitro group becomes difficult due to the electro-negative influence of the carboxyl groups present. This difficulty may be allevia-

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24. Baeyer, Ber., 12, 1315 (1879).
25. Brewster, C. A., 15, 3290 (1921); Chem. Centr., 1922, IV, 88.
26. Pschorr and Stöhrer, Ber., 35, 4393 (1902).

ted somewhat by esterification of the acid groups, thereby reducing the electro-negativity.

A solution of 2.2 g. (0.012) of dimethyl 3,4-furandicarboxylate in 5 cc. of acetic anhydride was prepared. In a small three-necked flask equipped with a stirrer and a pentane thermometer 16 cc. of acetic anhydride was introduced and cooled to -15°. To this, 8 cc. of fuming nitric acid was added cautiously, keeping the temperature below -10°. The solution of the ester was added dropwise with stirring, which was continued for one hour after all the ester was added. There was no heat effect noticeable. The reaction product was poured on ice and then the solution was brought almost to neutral with alkali. This homogeneous mixture was extracted well with ether and to the ether extract was added about 10 cc. of pyridine and then this solution was placed in the ice box for ten hours. The solvent was evaporated and the oil was acidified. This acid solution was extracted with ether and the ether solution dried over sodium sulphate. Upon removal of the solvent and the last traces of acetic acid under reduced pressure, there was obtained a small amount of solid which upon purification was found to be the unreacted ester, melting point 46°.

h). Seven grams (0.038 mole) of the diester was added in small portions to 25 cc. of fuming sulfuric acid contained in a small nitrating flask. The temperature was never permitted to rise above 5°. The solution was then placed in a refrigerator for 18 hours, whereupon it was cooled to -15° and 25 cc. of fuming nitric acid was added dropwise with stirring, maintaining the temperature between -15° and -10°. After addition was complete, the stirring was continued for one hour. The reaction mixture was poured on ice and the resulting solution was thoroughly extracted with ether and the ether solution dried over sodium sulphate. Distillation of the solvent left crystals which when purified, were identified as oxalic acid, melting at 101° and the anhydrous form at 189°. Mixed melting points were not depressed.

Heating of the ester with concentrated sulfuric and nitric acids for four hours at 70° failed to produce any change in the compound as 95% of the original material was recovered.

i). Employing the method of Brewster[25], 5 g. (0.027 mole) of the ester was added to the solution of 0.25 g. of mercuric nitrate in 20 cc. of nitric acid (sp. g. 1.2). It was then stirred for seven hours at 70-80°. The solution was cooled and extracted with ether; the ether extract was washed well with water and dried over sodium sulphate. The solvent was evaporated, leaving a residue which melted at 46° and which gave a mixed melting point determination with dimethyl 3,4-furandicarboxylate melting at the same point.

j). Five grams (0.027 mole) of the diester was added a little at a time to 40 g. of sulfuric acid maintaining the temperature at 20°. Addition of 3 g. (0.03 mole) of finely powdered potassium nitrate was made to the stirred solution over a period of 15 minutes. There was a slight heat effect and the solution was stirred for one hour. The reaction mixture was poured on ice and a solid separated which was identified as the starting material.

k). A nitrating mixture, consisting of 18 g. of fuming nitric acid and 20 g. of acetic anhydride, was prepared in the usual manner. A solution of 7 g. (0.041 mole) of 3-carbomethoxy-4-carboxyfuran in 10 g. of acetic anhydride, was added slowly to the nitrating mixture at -3° to 5°. Upon addition there was no temperature change noticed. The reaction was permitted to warm up to room temperature as the stirring was continued for one hour. The mixture was then poured on ice and extracted with ether. The ether solution was washed, dried over sodium sulphate and the solvent evaporated, leaving six grams of crystals which, when crystallized from aqueous alcohol, melted at 122-123°. They were identified as the unreacted ester-acid.

Attempted Bromination of 3,4-Furandicarboxylic Acid and its Esters.

a). Five grams (0.032 mole) of the 3,4-furandicarboxylic acid was dissolved in 100 cc. of carbon tetrachloride and the solution was placed in a small three-necked flask equipped with a mercury seal stirrer, a dropping funnel, and a Hopkins condenser. The solution was gently refluxed over an electric hot plate during the slow addition of 5.2 g. (0.032 mole) of bromine to the reactants. The carbon tetrachloride was refluxed with stirring for four to five hours and then was permitted to stand overnight. The greater portion of the solvent was evaporated and when the remainder of the solution was chilled, crystals separated which melted at 214° and were the unchanged acid.

b). Five grams (0.032 mole) of the diacid and 5.2 g. (0.032 mole) of bromine were sealed in a bomb tube and heated to 160° for six hours. After cooling and opening the product was dissolved in sodium hydroxide and boiled a few minutes with decolorizing carbon and filtered. Examination of the residue showed it to contain no furan derivative. The filtrate was cooled and acidified and due to its volume nothing precipitated. It was then extracted with ether and after desiccation and removal of solvent, crystals were obtained which melted at 204°. These were purified by crystallization from water and the melting point was raised to 214°. The compound was showed to be the unchanged acid.

c). In a reaction tube 5.1 g. (0.03 mole) of 3-carbomethoxy-4-carboxyfuran and 4.8 g. (0.03 mole) of bromine were sealed and heated to 140° for six hours in a Carius furnace. After cooling and opening the solid material was scraped out of the tube. It was fairly soluble in water and so was crystallized from that medium. The melting point was 204°. After several recrystallizations from water this physical constant was raised to 214°. A mixed melting point with an authentic sample of 3,4-furandicarboxylic acid was not depressed. Instead of undergoing nuclear substitution, the compound was hydrolyzed by the action of bromine to the corresponding dibasic acid.

d). A solution of 3.7 g. (0.02 mole) of dimethyl 3,4-furandicarboxylate in carbon tetrachloride was placed in a small three-necked flask equipped with a mercury seal stirrer, a dropping funnel, and a Hopkins condenser. As the solution was brought to the point of gentle refluxing, 3.2 g. (0.02 mole) of bromine was added slowly to the flask. It was then stirred for one hour at the boiling temperature. The solvent was removed by suction leaving an oil which solidified on cooling. Crystallization from alcohol gave a compound melting at 46° which was proved to be the diester.

A similar sized run was carried out in chloroform and the duration of refluxing was extended to 45 hours. When the reaction product was worked up, it was found that the bromine had hydrolyzed the diester to the ester-acid.

e). Into a reaction tube were placed 3.7 g. (0.02 mole) of the dimethyl ester and 3.2 g. (0.02 mole) of bromine. The tube was sealed and heated in a bomb furnace for six hours at 120°. After cooling and opening, the contents were transferred to a balloon flask containing 50 cc. of 10% alcoholic sodium hydroxide solution. It was then refluxed until saponification was complete, which required about three hours. The salt was filtered and dried, and dissolved in as little water as possible. The solution was acidified and yielded an acid which was showed to be identical with 3,4-furandicarboxylic acid.

f). In the only reaction that showed promise, 3.7 g. (0.02 mole) of dimethyl 3,4-furandicarboxylate and 3.2 g. (0.02 mole) of bromine were sealed in a pyrex tube and heated for eight hours at 160°. The tube was cooled and opened, and the residue was transferred to a small round-bottomed flask. Several small portions of 10% alcoholic sodium hydroxide solution were used to rinse the reaction tube and these were combined and added to the balloon flask. The contents were refluxed until saponification was complete. The salt was filtered and dried, and upon acidification yielded an acid which when purified by crystallization from water melted at 164°. The melting point was not raised by further crystallization from ethanol. However, neutralization equivalent and bromine analysis did not give values corresponding to a bromo-3,4-furandicarboxylic acid. After repeated purification by crystallization and sublimation under reduced pressure, elementary analysis showed the compound to contain bromine. Neutral equivalent: calcd. for $C_6H_3O_5Br$, 117.5, for $C_5H_3O_3Br$, 191.0, for $C_6H_2O_5Br$, 157; found, 106.

<u>Anal.</u> Calcd. for $C_6H_3O_5Br$: Br, 34.04,

$C_5H_3O_3Br$: Br, 41,88,

$C_6H_2O_5Br_2$: Br, 50.95.

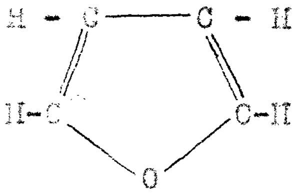
Found. Br, 17.42 and 17.25.

From these values it was evident that neither decarboxylation nor dibromination had occurred. The results of these analyses indicated that possibly the material was a mixture of the brominated acid and the unreacted acid which could not be separated by ordinary means. This problem was not investigated further.

Fluorescence Tests on Several Furan-polyacids.

It was thought that the comparison of the strengths of the fluorescein test on several furan polyacids might give some information as to the relative distance of the four carbon atoms in the furan nucleus. Accordingly a series of five furan acids and phthalic acid, as a control, was set up. The furan acids tested were: 2,3-; 2,4-; 2,5-; and 3,4-furandicarboxylic acids and furantetracarboxylic acid.

Into each of six test tubes was weighed accurately 0.01 g. of resorcinol. To these tubes was added 0.02 g. of the acid, each tube being carefully marked as to which acid it contained. Each sample was then moistened with one drop of sulfuric acid and the six tubes were immersed in an oil bath and heated to 140° for five minutes. They were then cooled and one cc. of water was added to each tube, followed by neutralization with sodium hydroxide solution. In order for a comparison of the resulting solutions to be made, a standard dilution was necessary. One drop of the solution from the phthalic acid tube was diluted to ten cc.; whereas, five drops of the solutions from the furan acids were diluted to ten cc. Comparison was then made on the colors and fluorescence by several observers. Even in its weaker concentration, phthalic acid was by far the strongest. Of the furan acids, the 2,3- and the 3,4-diacids were the strongest; 2, 4-furandicarboxylic acid showed some fluorescence while 2,5-furandicarboxylic acid and the furantetracarboxylic acid were negative. The failure of the tetra-acid to react and produce fluorescence was wholly unexpected and no explanation could be offered for its anomalous behavior. On this basis, it seemed not unlikely that a two-dimensional model of furan could be as represented in the figure below.



SUMMARY

Some pharmacological reports on the simple derivatives of furan have been presented.

Tetracarbethoxyfuran has been prepared and from it furantetracarboxylic acid. Through decarboxylation of the latter compound, other furan acids have been isolated. Among these was 3,4-furandicarboxylic acid, which was the last remaining unknown dibasic furan acid. A more convenient method for the synthesis of β-furoic acid has been described.

Nuclear substitution reactions of 3,4-furandicarboxylic acid and its esters have been attempted with little success.

INTRODUCTION

The exhaustive study of furan compounds in this laboratory led to the investigation of heterocyclic compounds which might possibly be degraded to yield furan derivatives that would clear up cases of questionable orientation. Dibenzofuran, a fused heterocycle consisting of a furan nucleus and two benzene nuclei, is such a substance. It appeared that the oxidation of suitable dibenzofuran derivatives would furnish furantetracarboxylic acid, a very desirable compound. It was also realized that a stepwise oxidation might occur to give substituted benzofurans.

There are very few reports of oxidation studies on dibenzofuran derivatives. Mayer and Krieger[1] have demonstrated that alkyl or aryl side chains in the 2-position may be oxidized in the customary manner with alkaline agents to the corresponding carboxylic acid. An oxidation of less importance was that reported by Hönigschmidt[2] with potassium permanganate upon tetrahydrodibenzofuran, converting it to dibenzofuran. Two examples in which one of the benzene nuclei in dibenzofuran had been broken have been reported. Von Braun[3] oxidized hexahydrodibenzofuran with chromic acid to δ-*o*-hydroxybenzolyvaleric acid. The scission of a benzene nucleus and a furan nucleus resulted upon oxidizing 1-hydroxyhexahydrodi-

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1. Mayer and Krieger, *Ber.*, *55*, 1659 (1922).
2. Hönigschmidt, *Monatsh.*, *22*, 561, (1901).
3. Von Braun, *Ber.*, *55*, 3761 (1922).

benzofuran. Tsuzuki[4] reported securing phenylmalonic acid as the final product.

Oatfield[5] considered that with an active group like the amino or the hydroxyl group substituted in the benzene nucleus to weaken it, oxidation might give a product with the furan ring unbroken. Since hydroxydibenzofurans are prepared with difficulty, the amino derivatives were chosen as suitable starting materials. Accordingly, they were prepared and attempts were made at oxidation, but with negative results. At first mild oxidizing agents, such as alkaline hydrogen peroxide, were tried; and when this failed, potassium permanganate, in aqueous and acetone solution, was used with similar results.

The subsequent preparation of furantetracarboxylic acid[6] in another manner has somewhat overshadowed the original interest in dibenzofuran. However, the studies of Oatfield have led to an even greater interest in this heterocycle due to the fact that the matter of orientation in the dibenzofuran ring system was in a vastly confused state, even for the most common simple substitution products. In addition, the research in this laboratory was concerned with the synthesis and study of physiologically active compounds; and since Von Braun[3] had called attention to the structural resemblance between numerous compounds of morphine, codeine and thebaine and hydrogenated dibenzofuran, it seemed advisable to test certain dibenzofuran

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[4] Tsuzuki, *Bull. Chem. Soc. Japan*, *2*, 79 (1927); [*C. A.*, *21* 2130 (1927)].

[5] Oatfield, Thesis, Iowa State College, 1933.

[6] This thesis, p. 18.

derivatives for hypnotic and analgesic action. As a consequence, this study has been concerned with the orientation of certain amino derivatives of dibenzofuran and the preparation of compounds which it was hoped would possess desirable physiological activity.

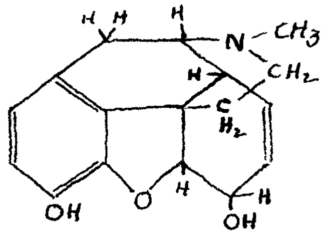
Few compounds in the aromatic series possess sufficient hypnotic properties to be of value in therapy. A comparison of the parent type hydrocarbons reveals that phenanthrene is more narcotic towards tadpoles than naphthalene which in turn is more active than benzene. This observation is in agreement with the suggestion offered by Dr. Dox in a private communication that the narcotic action of morphine and related types might be due to the compactness of the molecule.

Vongerichten and Schrötter[7] secured phenanthrene in about 30% yield by dry distillation of morphine over zinc dust. Brissemoret and Joanin[8] were the first to recognize the importance of studying the physiological action of phenanthrene, inasmuch as they postulated that the action of an alkaloid is influenced not only by the basic part of the molecule but also by the hydrocarbon nucleus. Accordingly, they injected hexahydrophenanthrene intraperitoneally into a dog and found that it produced morphine-like narcosis. At present, a great deal of research is being done on phenanthrene derivatives by a number of agencies having responsibility for the solution of

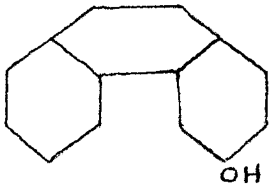
[7] Vongerichten and Schrötter, Ann., 210, 396 (1881).
[8] Brissemoret and Joanin, Compt. rend., 151, 1151 (1910).

the problem of drug addiction. Eddy[9] who is performing the pharmacological investigation for this group, has observed that phenanthrene when administered orally to cats produces a mild general depression. Of the substituted phenanthrene compounds, amino, hydroxy, acetyl, and carboxylic acid groups have been introduced in the nucleus in the 2-, 3-, and 9-positions, and these derivatives were also given orally to cats. Those compounds with the substituent in the 2-position were rapidly absorbed despite their almost complete water insolubility, and produced definite analgesic effects.

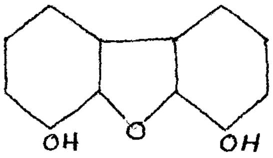
In addition to a reduced phenanthrene nucleus being present in the current interpretations of the structure of morphine[10], there is also a partially hydrogenated dibenzofuran nucleus. This suggested a study of dibenzofuran derivatives with substituents in all the available positions and their subsequent pharmacological testing. The structural relationship between morphine[10], 3-hydroxyphenanthrene, and 4,6-dihydroxydibenzofuran is illustrated in formulae I, II, and III:



I



II



III

9. Eddy, J. Pharmacol., 48, 183 (1933).
10. Small, "Chemistry of the Opium Alkaloids", Supp. 103 Public Health Reports, 1932 p. 143.

From these formulae, it is evident that the 4- and the 4,6-positions in dibenzofuran are the key positions and if there be any correlation between physiological action and chemical constitution, derivatives with substituents in these positions should prove most fruitful. However, it is highly important that dibenzofurans substituted in the 1-, 2-, and 3-positions be also examined. By so doing a comparison of the relative efficacies of the several positions may be determined, and in addition information imparted as to the rôle this molecule plays in morphine.

A survey of the literature of dibenzofuran and its derivatives revealed that very few compounds have been examined for physiological properties. Christomanos[11] reported that the subcutaneous injection of dibenzofuran in olive oil produced an increase in the amount of hippuric acid eliminated. Contrary to expectations no trace of _o_-hydroxyhippuric acid could be isolated. The injection of dibenzofuran was associated with no toxic or hypnotic effect. Von Braun[3] found that aminohexahydrodibenzofuran and α-aminoethylhexahydrodibenzofuran were physiologically inactive in animal experiments. Mayer and Krieger[1] reported that 2-(γ-aminopropyl)-dibenzofuran and [illegible]-(γ-aminopropyl)-tetrahydrodibenzofuran produced no morphine-like action on warm blooded animals. The compounds secured upon subjecting 3-aminodibenzofuran to the Skraup re-

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[11] Christomanos, _Z. Physiol. Chem._, _181_, 182 (1929)

action and simple derivatives of the resulting pyrido-compounds have been tested[12]. The physiological activity of this series increases progressively from the unreduced pyridodibenzofurans, through the tetrahydropyrido compounds to the maximum in the N-methyltetrahydropyrido compounds. No animals died with effective doses, and analgesia, general depression, muscular disturbance, emesis and temperature lowering were observed. The members of the series of the angular isomer were slightly more active than the corresponding linear series.

SUBSTITUTION IN DIBENZOFURAN

Dibenzofuran was first isolated in 1866 by Lesimple[13] in the course of heating phenyl phosphate and lime. From his analysis of the oily material secured on distillation, he calculated the empirical formula of the compound as $C_{12}H_{10}O$, and considered the compound to be either phenyl ether or the oxide of C_6H_5 called "benzyl". Hoffmeister[14] prepared the compound described by Lesimple and found it not to be identical with an authentic specimen of diphenyl ether. He purified the new compound and on analysis concluded that the correct empirical formula was $C_{12}H_8O$. From the facts that the substance was uncommonly stable and insoluble in potassium hydroxide, Hoffmeister stated that it was not a phenol but a true aromatic ether and he ascribed to it the structural formula which was

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12. Mosettig and Robinson, J. Am. Chem. Soc., 57, 904 (1935).
13. Lesimple, Ann., 138, 376 (1866).
14. Hoffmeister, Ber., 3, 747 (1860).

later proved beyond doubt by Kramer and Weissgerber[15] and also by Tauber and Halberstadt[16].

Dibenzofuran is found up to 12% in the fluorene fraction of coal tar. It has also been isolated from "stuppfett", a greasy mixture of hydrocarbons consisting mainly of phenanthrene and pyrene. The methods of preparation of dibenzofuran can be classified into three groups: from phenolic sources, from diphenyl derivatives, and from substituted diphenyl ethers. In the first class, it can be obtained by the distillation of phenyl phosphate with lime over some suitable metallic oxide such as zinc oxide or lead oxide. The commercial preparation of dibenzofuran consists of passing phenol vapors over thorium oxide in a heated tube. Other metallic oxides can be used, but they are less effective. The compound is also secured from the dry distillation of metallic phenolates. In general, the pyrogenic methods are not satisfactory because with a few exceptions the yields are low. Two derivatives of diphenyl can be used as starting materials in the synthesis of dibenzofuran. If 2,2'-diaminodiphenyl is tetrazotized in the usual manner, and the resulting tetrazonium salt is heated with water or copper sulfate, a good yield of dibenzofuran is secured. The same compound is formed when 2,2'-dihydroxydiphenyl is fused with zinc chloride. In the third class, diphenyl ether itself may be converted to dibenzofuran by passing its vapors through a heated glass tube. This pyrogenic synthesis, comparable to

[15] Kramer and Weissgerber, Ber., 34, 1662 (1901).
[16] Tauber and Halberstadt, Ber., 25, 2745 (1892).

the preparation of phenanthrene, fluorene, dibenzothiophene, and carbazole, gives low yields. Better yields of the compound can be obtained by diazotizing 2-aminodiphenyl ether and adding the diazonium solution to a boiling 50% sulphuric acid solution.

Dibenzofuran has been secured in sundry other reactions which are of passing importance only. Oxidation of diphenylene with nitric acid[17a], decomposition of xanthone at 880° [17b], thermal decomposition of mucic acid[17c], and heating phenoxthine with copper bronze[17d] produce varying amounts of dibenzofuran.

In the course of work on orientation of substituted dibenzofurans, it has been necessary to prepare certain reference compounds by ring closure, a reaction which is reliable for proof of structure. The two most important methods of establishing the constitution of dibenzofuran derivatives are syntheses from known diphenyls and diphenyl ethers.

As mentioned previously, the work of Kramer and Weissgerber[15], who prepared dibenzofuran by fusing 2,2'-diphenol with zinc chloride, established definitely that the oxygen bridge was situated <u>ortho</u> to the diphenyl bond. This same fact was demonstrated by Tauber and Halberstadt[16] in a slightly different manner, and some time later by Cullinane, Davey and Padfield[18].

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17. (a) Dobbie, Fox and Gauge, J. Chem. Soc., 103, 40 (1913).
    (b) Orlov and Tishenko, Ber., 63, 2948 (1930).
    (c) Klinkhardt, J. prakt. Chem., (2) 25, 45 (1882); Heinzelman, Ann., 193, 186 (1878).
    (d) Ferrario, Bull. soc. chim., (4) 9, 537 (1911).
18. Cullinane, Davey and Padfield, J. Chem. Soc., 716 (1934).

Following this procedure, 1,9-diphenyldibenzofuran has been prepared by Sako[19] by heating a solution of the tetrazonium salt of 2,2'-diamino-6,6'-diphenyldiphenyl with copper bronze. One of the most important utilizations of this type of synthesis has been the preparation of 4-methyldibenzofuran from 2,2'-dihydroxy-3-methyldiphenyl by Kruber[20].

Synthesis of dibenzofuran derivatives from diphenyl ethers has proved to be the most fruitful means of proving the position of groups in nuclear substitution products of dibenzofuran. The value of this method can best be illustrated by showing how the controversial orientation of the mononitrodibenzofurans was decided. The chief product of nitration of the parent compound was variously believed to be 2- or 3-nitrodibenzofuran. In 1927 Ryan, Keene and McGahon[21] prepared the 3-nitro derivative. Diazotization of 2-amino-4-nitrodiphenyl ether and refluxing of the resulting solution with 50% sulphuric acid gave a nitro compound, of which there could be no question concerning the position of the nitro group. This compound did not possess the same physical properties as the more common mononitro derivative. Cullinane[22] reduced the 182° melting isomer to the amine, diazotized, and prepared a chloro compound through the Sandmeyer reaction. He then synthesized 2-chlorodibenzofuran by

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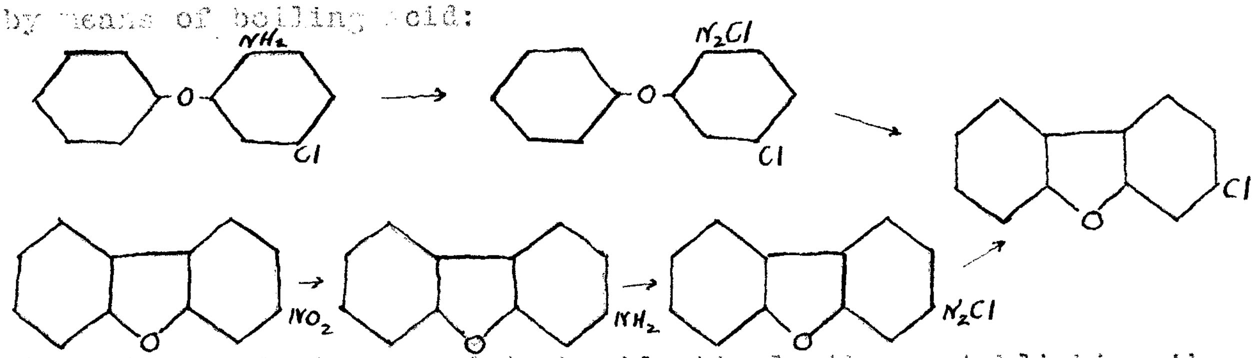
19. Sako, *Bull. Chem. Soc. Japan*, *9*, 55, (1934); [*C. A.*, *28* 3730 ~~5814~~ (1934)].
20. Kruber, *Ber.*, *65*, 1382 (1932).
21. Ryan, Keene and McGahon, *Proc. Roy. Irish Acad.*, *37B*, 368 (1927); [*C. A.*, *22*, 70 (1928)].
22. Cullinane, *J. Chem. Soc.*, 2276 (1930).

diazotizing 2-amino-5-chlorodiphenyl ether followed by coupling by means of boiling acid:



These two products proved to be identical, thus establishing the main product of nitration as 3-nitrodibenzofuran. A confirmatory synthesis of the 3-nitro compound from 2-amino-5-nitrodiphenyl ether was made by McCombie, Macmillan and Scarborough[23].

The first application of this method of ring closure to orientation problems was carried out by Mayer and Krieger[1]. They established the position of the bromine atom in monobromodibenzofuran by synthesizing 3-methyldibenzofuran from 2-amino-4'-methyldiphenyl ether. Since oxidation of 3-methyldibenzofuran and carbonation of the Grignard reagent from the halide both gave the same 3-dibenzofurancarboxylic acid, the position of the bromine atom was definitely proved to be *para* to the oxygen bridge.

McCombie, Macmillan and Scarborough[23] were successful in synthesizing 3-chloro, 2- and 3-bromo-, 2,8-dichloro-, 2,8-dibromo-, 2,7-dibromo-, and 3-chloro-7-nitrodibenzofuran by means of this type of ring closure. However, they were unsuccessful in attempts to prepare 1-chlorodibenzofuran from 2-amino-

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23. McCombie, Macmillan and Scarborough, *J. Chem. Soc.*, 529 (1931).

2'-chlorodiphenyl ether.

A limitation of the diphenyl ether method is that ortho substituted ethers have not undergone ring closure to give dibenzofuran derivatives; this is probably due to steric hindrance. Consequently a ready means of synthesizing compounds known to have substituents in the 1-, 4-, 6-, and 9-positions is not available.

A method which may prove of value in the synthesis of 4-substituted dibenzofurans has received only slight attention. In 1929 Ebel[24] synthesized tetrahydrodibenzofuran by condensing chlorocyclohexanone and sodium phenolate; similarly 6-methoxy-1,2,3,4-tetrahydrodibenzofuran was prepared using the sodium salt of guaiacol rather than phenol. Since it has recently been shown that tetrahydrodibenzofuran derivatives may be dehydrogenated by means of sulfur or bromine to give substituted dibenzofurans[25], it is logical to believe that this method of synthesis could be utilized in proof of structure.

Monosubstitution in Dibenzofuran.

The constitution of dibenzofuran is peculiar in that the nucleus possesses two distinct conflicting directive influences for nuclear substitution reactions. The position assumed by substituents in monosubstitution of dibenzofuran is apparently governed not only by the inherent characteristics of the molecule, due to the diphenyl bond and the diphenyl ether

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[24] Ebel, Helv. Chim. Acta., 12, 3 (1929).
[25] Gilman, Smith and Cheney, J. Am. Chem. Soc., 57, 000 (1935).

linkage, and to experimental conditions, but also by the type of entering group. Inasmuch as the diphenyl bond favors the 1- and 3-positions and the diphenyl ether linkage favors the 2- and 4-positions due to their strong *o*-, *p*- directing influence, it is not surprising that the substitution reactions of dibenzofuran are highly competitive and equally as uncertain.

At present, there has been no direct monosubstitution reaction which involved the 1-position. This apparent anomaly can possibly be explained by the work of Bretscher[26] who found that the dipole moment of dibenzofuran indicates a larger oxygen angle than that present in diphenyl ether. If this be correct, a large oxygen angle between the two benzene nuclei would force the 1- and 9-positions close together, causing steric hindrance and prohibiting nuclear substitution in these positions.

SULFONATION

Recently Wehenter[27], prepared a monosulfonic acid by the action of fuming sulfuric acid on 2,2'-dihydroxydiphenyl, and assigned the sulfonic group to either the 2- or the 4-position.

It has been found that sulfonation of dibenzofuran occurs with great ease and gives excellent yields. Gilman, Smith and Oatfield[28] have proved that the sulfonic acid group entered in the 2-position. Their method of proof consisted in conversion

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26. Bretscher, *Helv. Phys. Acta.*, *2*, 265 (1929).
27. Wehenter, *J. prakt. Chem.*, *131*, 331 (1931).
28. Gilman, Smith and Oatfield, *J. Am. Chem. Soc.*, *56*, 1412 (1934).

of the acid to the sulfonyl chloride, the reduction of the acid chloride, and the replacement of the resulting sulfinic acid group by iodine through the chloromercuri-compound. A Grignard reagent of the halide on carbonation gave an acid identical with 2-dibenzofurancarboxylic acid.

Confirmatory evidence for the 2-position was secured by replacing the chloromercuri-group in the mercurial with bromine to give 2-bromodibenzofuran, the structure of which was established by ring closure. Since dibenzofuran is known to undergo bromination in the 2-position, there is a possibility that the bromo-compound might have resulted as a consequence of initial cleavage of the mercurial by hydrogen bromide to give dibenzofuran. This possible difficulty was avoided by synthesizing 2-chloromercuridibenzofuran from the known 2-bromodibenzofuran *via* the Grignard reagent, and showing it to be identical with the mercurial obtained from the sulfonic acid.

HALOGENATION.

Fluorination is unknown and there are no known fluorine derivatives of dibenzofuran.

Hoffmeister[29] reported on the action of phosphorus pentachloride on dibenzofuran and found that there was no reaction when a mixture of the two substances was heated in an open vessel, but after ten hours heating at 220° in a sealed tube there resulted a compound containing chlorine. Whitmore and

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29. Hoffmeister, *Ann.*, *159*, 211 (1871).

and Langlois[30] also secured a chlorodibenzofuran in repeating this reaction. The compound was later shown to be undoubtedly 2-chlorodibenzofuran. Direct chlorination with chlorine gas led to a fair yield of 2-chlorodibenzofuran, which was shown to be identical with an authentic specimen prepared by ring closure[31].

The first definitely determined nuclear substitution product of dibenzofuran was 2-bromodibenzofuran. Mayer and Krieger[1] brominated dibenzofuran in carbon disulfide and established the position of the entering group by converting the bromo-compound successively through the Grignard reagent to the carboxylic acid. This acid was identical with the 2-dibenzofurancarboxylic acid which, as was mentioned previously, has been obtained by ring closure. McCombie and co-workers confirmed this proof by synthesizing 2-bromodibenzofuran from a diphenyl ether derivative.

Iodination of dibenzofuran gave 2-iododibenzofuran[31]. The Grignard reagent of the halide on carbonation gave the 2- acid. It is interesting to note that the iodo group entered the 2-position regardless of whether nitric acid or mercuric chloride was used as the carrier[32].

FRIEDEL-CRAFTS REACTION

An acetyl derivative of dibenzofuran was first prepared by Galewsky[33] in the customary manner by treating a carbon di-

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30. Whitmore and Langlois, *J. Am. Chem. Soc.*, *55*, 1520 (1933).
31. Gilman, Brown, Bywater and Kirkpatrick, *J. Am. Chem. Soc.*, *56*, 2473 (1934).
32. This thesis p. 54-55.
33. Galewsky, *Ann.*, *264*, 187 (1891).

sulfide solution of the compound with acetyl chloride and aluminum chloride. The position of this group was not determined but Galewsky postulated that the diphenyl ether linkage was the greater orienting influence and as a result assigned the structure of 2-acetyldibenzofuran to the compound. Later Mayer and Krieger[1] proved his assumption to be correct by oxidizing the acetyl derivative to the established 2-acid. The corresponding 2-benzoyldibenzofuran has been prepared in like manner[34].

These reactions are good evidence that the diphenyl ether linkage is the greater directing influence in the molecule. Bywater[35], who reviewed the literature on dibenzo-type compounds, found: "The isologues of dibenzofuran do not strictly follow this rule. In carbazole the predominant orienting influence is the imino group corresponding to the oxygen linkage in dibenzofuran. In nitration, halogenation, and sulfonation of fluorene and flourenone substitution involves those positions *para* to the diphenyl bond. Very little has been done with nuclear substitution of dibenzothiophene, but the present status of the work indicates that substitution takes place as in dibenzofuran".

NITRATION.

Dibenzofuran is one of the most easily nitrated compounds in organic chemistry. A solution of it in carbon tetrachloride or glacial acetic acid warmed with an excess of fuming nitric

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34. Borsche and Bothe, *Ber.*, *41*, 1940 (1908).
35. Bywater, Doctoral Dissertation, Iowa State College 1934. p. 21-22.

acid will give an almost quantitative yield of mononitrodibenzofuran melting at 182° with a trace of by-product which melts at 110°. To early workers, the constitutions of these materials were a source of dispute, and even today it has not been definitely established that the nitration product melting at 110° is or is not a mixture of isomers.

Borsche and Bothe[34] first nitrated dibenzofuran, and suggested that the nitro group had entered the 2-position due to the greater orienting influence of the oxygen bridge. Since the acid formed by reduction of the nitro group, followed by a Sandmeyer reaction to the nitrile and hydrolysis, was supposedly identical with the acid obtained by oxidation of acetyldibenzofuran, investigators were satisfied in calling the main product of nitration 2-nitrodibenzofuran. The work of Mayer and Krieger[1] however, invalidated this postulate, for they showed that their 2-dibenzofurancarboxylic acid was not identical with the acid secured from nitrodibenzofuran, by the method of mixed melting points. Conclusive proof as to the position of the nitro group in the 182° melting isomer, offered by Cullinane[22] was discussed previously[36]. Since mononitration involves predominantly the 3-position of dibenzofuran, it follows that there are exceptions to the general rule that the greater directing influence in the molecule is the ether linkage.

Modern electronic theory would lead one to predict that the oxygen bridge in dibenzofuran is o-, p- directing, yet the main product of nitration is the 3-derivative. It was sug-

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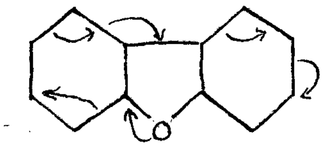
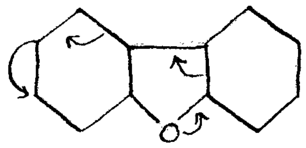
[36] This thesis, p. 49.

gested by Robinson[37] that this anomalous orientation is the result of the route selected for the electromeric changes. In a fused homocyclic aromatic nucleus such as naphthalene and phenanthrene, the same oriented compound is to be expected regardless of the route taken by electromeric changes. However, the situation is different when one of the fused rings contains an odd number of atoms, and the results obtained in nitration can be accounted for by the electromeric change in the course of the reaction taking the route indicated (A or B):



A



B

"In all probability bromination is a more facile process than nitration and can take advantage of a smaller degree of polarization occurring more frequently than the activations of greater amplitude required to facilitate nitration, dibenzofuran, therefore, is brominated normally to give the 2-bromodibenzofuran".

A by-product of usual nitration reactions is a so-called isomeric mononitro derivative, which was first isolated by Borsche and Bothe[34]. Borsche and Schacke[38] suggested that it

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37. Cullinane, *J. Chem. Soc.*, 2365 (1932).
38. Borsche and Schacke, *Ber.*, *56*, 2498 (1923).

was 2-nitrodibenzofuran. The reactions on which they based their assumption follows: 3-acetaminodibenzofuran formed by reduction of the 3-nitro derivative and acetylation of the amine produced, on nitration and subsequent hydrolysis and reduction yields a diamine. This is an *ortho* diamine for it combines with benzil and phenanthraquinone to give quinoxaline derivatives. Hence it must be a 2,3- or a 3,4-diaminodibenzofuran. Borsche and Schacke replaced the amino group of the nitroamine by hydrogen and secured a nitrodibenzofuran which they considered to be identical with the 110° melting compound.

More recently Cullinane[22] has proposed that the isomer is 4-nitrodibenzofuran, since 2-nitrodibenzofuran had been synthesized by ring closure[20] and had also been obtained by successive hydrolysis and deamination of 3-acetamino-2-nitrodibenzofuran[39].

Gilman, Bywater and Parker[40] did not believe, in view of their knowledge of dibenzofuran as well as information available on substitution reactions of more common benzenoid types, that the isomer was oriented in the 4-position. They suggested that the perplexity existed because previous investigators had assumed that the 110° substance was an individual compound. Accordingly, they showed by indirect methods that the supposed isomeric nitrodibenzofuran melting about 110° contained some 2-nitrodibenzofuran.

METALATION[41]

[39] Brumberg, Doctoral Dissertation, Göttingen, 1925.
[40] Gilman, Bywater and Parker, J. Am. Chem. Soc., 57, 885 (1935).
[41] A term proposed for those reactions which involve the replacement of hydrogen by a metal to give a true organometallic compound.

In general, metalation usually occurs with those nuclei having superaromatic characteristics. Since it had been demonstrated that dibenzofuran possesses a greater aromaticity than that of benzene[40] (by cleavage of 2-, 3-, and 4-dibenzofuryl-triphenyl-leads with hydrogen chloride), it was to be expected that dibenzofuran would metalate with relative ease. Gilman and Young[42] were successful in effecting metalation with salts, organometallic compounds and metals. Mercuration of molten dibenzofuran with mercuric acetate gave 4-acetoxymercuridibenzofuran. The orientation was established by converting the mercurial to the iodo compound; and the Grignard reagent from this halide on carbonation yielded 4-dibenzofurancarboxylic acid, the proof of which was offered by Kruber[20]. Carbonation of the organolithium, -sodium, and -potassium compounds, prepared in the normal manner, gave the same acid.

Inasmuch as other nuclear monosubstitution reactions involve the 2- and 3-positions exclusively, it was surprising to observe that metalation occurred in the 4-position. Nevertheless, it was exceedingly welcome for it provided a means of access to the physiologically important 4- and 6-positions.

Before considering the disubstitution reactions of dibenzofuran, it should be mentioned that the peculiar orienting influences of dibenzofuran can be utilized in securing information concerning some proposed mechanisms of nuclear substitution re-

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[42] Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).

actions. Since metalation involves the 4-position; nitration, the 3-position; and halogenation and sulfonation, the 2-position; it follows that the nature of the substituent in dibenzofuran determines to a large degree the position entered. It has been proposed that, in iodination by means of mercuric oxide and iodine, there is preliminary mercuration followed by the replacement of the mercuri group by iodine. Such a mechanism seems unlikely for Young has carried out this reaction on dibenzofuran and secured the 2-iodo compound; whereas, if mercuration had occurred the substituent would have been in the 4-position[31]. The mechanism which proposed nitration occurring prior to iodination has likewise been rejected in the case of dibenzofuran, for otherwise a 3- and not the observed 2-iododibenzofuran would have resulted.

DISUBSTITUTION WITH LIKE SUBSTITUENTS

No homonuclear disubstituted dibenzofuran derivative, resulting from direct nuclear substitution reactions, has been reported with like substituents. Hoffmeister[29] obtained a disulfonic acid by the action of concentrated sulfuric acid on dibenzofuran but made no attempt to determine the position of the sulfonic acid groups. The monosulfonic acid secured by Zehenter[27] through ring closure was sulfonated to give a disulfonic acid. Gilman, Smith and Oatfield[28] secured a disulfonic acid by sulfonating the 2-derivative which was identical with the acid obtained in accordance with Hoffmeister's directions. By a related series of transformations as was used in the case of the

2-acid, they demonstrated that the disulfonic acid had the two sulfonic acid groups in the 2,8-positions.

2,8-Dichlorodibenzofuran was obtained by passing chlorine gas into a solution of dibenzofuran in a suitable solvent[31]. The constitution of this compound was established by a mixed melting point determination with an authentic sample prepared by McCombie, Macmillan and Scarborough[23] through ring closure. These same authors proved that the product of dibromination of dibenzofuran, first reported by Hoffmeister, was 2,8-dibromodibenzofuran by synthesizing it from 2-amino-5,5'-dibromodiphenyl ether. As was to be expected, di-iodination led to 2,8-diiododibenzofuran, whose structure was established by comparison of the compound with that obtained by treating 2,8-dichloromercuridibenzofuran[28] with iodine.

Borsche and Schacke[38] were the first to prepare a diacetyldibenzofuran and assumed it to be a 2,8-derivative. Work in this laboratory has shown their assumption to be correct. The dicarbomethoxy compound prepared by oxidation of the diacetyl derivative and subsequent esterification was shown to be identical with the dimethyl 2,8-dibenzofurandicarboxylate obtained from 2,8-dibromodibenzofuran <u>via</u> the Grignard reagent and carbonation[44].

Confirmatory evidence for the structure of the diacetylated compound has been secured by Sugii and Sengoku[45] in a diff-

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44. Unpublished studies by Mr. R. [illegible]. Smith and Mr. J. C. Bailie.
45. Sugii and Sengoku, J. Pharm. Soc. Japan, 55, 175 (1935); [C. A., 29, 5444 (1935)].

erent manner. They oxidized the derivative with chlorinated lime and sodium carbonate to give a diacid. The dimethyl ester of this dicarboxylic acid, prepared by means of diazomethane, was found to be identical with an authentic specimen of dimethyl 2,8-dibenzofurandicarboxylate, the constitution of which had been established by fusing 2,2'-dihydroxy-5,5'-dimethyldiphenyl with zinc chloride and successively oxidizing and esterifying the resulting compound[46].

3-Nitrodibenzofuran yields on further nitration in acetic acid a dinitro derivative, which is also formed by the direct nitration of dibenzofuran with fuming nitric acid or nitrogen peroxide vapour. The introduction of the second nitro group was originally considered to involve a rearrangement unparalleled in organic chemistry, that of a nitro group shifting from carbon atom to carbon atom in the ring, giving a 2,8-dinitrodibenzofuran. Cullinane[37] later disproved this by showing the compound to be a 2,7-substituted compound. On reduction it yielded a diamine different from 3,7-diaminodibenzofuran. Partial reduction afforded a nitroamino compound which, on replacement of the amino group by hydrogen, yielded 2-nitrodibenzofuran. Since both nitro groups were not homonuclearly substituted as shown by the failure of the compound to form a quinoxaline derivative, it followed that the dinitro compound was a 2,7-derivative. Dinitration is the only reaction so far observed in which the second group enters the

46. Sugii and Shindo, *J. Pharm. Soc. Japan*, *53*, 97 (1933); [*C. A.*, *28*, 151 (1934)].

unsubstituted benzene ring in a position unlike that assumed in monosubstitution. It has been suggested[37] that the second nitro group orients normally because the positive field of the first nitro group inhibits any electromeric changes from passing out of the nucleus containing it.

Dimetalation in dibenzofuran is best realized with *n*-butylsodium to give a 4,6-disodio derivative. Gilman and Young[47] were able to prove the constitution of this compound by methylating it with dimethyl sulfate and comparing the resulting product with an authentic specimen of 4,6-dimethyldibenzofuran, synthesized by ring closure[48]. From the disodium compound there has been obtained 4,6-di-iododibenzofuran, 4,6-dibenzofurandicarboxylic acid, and 4,6-dihydroxydibenzofuran. These replacement reactions will undoubtedly be of considerable importance to future workers as they make available compounds with substituents in the biologically important 4- and 6-positions.

DISUBSTITUTION WITH UNLIKE GROUPS.

Homonuclear

Exceedingly little work has been reported on substitution of dibenzofuran derivatives which involve the already substituted benzene ring. Passing mention has been made of the work of Borsche and Schacke[38] who nitrated 3-diacetaminodibenzofuran and secured a product which on hydrolysis and reduction furn-

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[47] Gilman and Young, *J. Am. Chem. Soc.*, *57*, 1121 (1935).
[48] Suggi and Shindo, *J. Pharm. Soc. Japan*, *54*, 149 (1934); [*C. A.*, *29*, 790 (1935)].

ished an ortho diamine. This was stated by Cullinane[22] to be 3,4-diaminodibenzofuran on the basis of a statement by the previous authors that elimination of the amino group from the above nitroamino derivative gave a nitrodibenzofuran melting at 110°. However, this compound has been shown by Brumberg[39] in a publication, only recently available, to melt at 152°, and he established the constitution of the compound as follows: The amine formed on reduction was diazotized, and the diazonium group replaced by the cyano group. The crude nitrile was then hydrolyzed to give the known 2-dibenzofurancarboxylic acid. This proved conclusively that the compound was a 2,3-derivative. This has been confirmed in another manner and will be described in the experimental part of this thesis.

Bromination of 2-diacetaminodibenzofuran yielded a product which on hydrolysis gave 2-amino-3-bromodibenzofuran. Amination of this compound in a sealed tube furnished the known 2,3-diaminodibenzofuran; and, likewise, on diazotization and replacement by hydrogen there was obtained 3-bromodibenzofuran. Nitration gave a similarly oriented derivative. It is significant that 1-substituted products have not been isolated from either nitration or bromination of the acetylated 2-amino dibenzofuran. However, it is not altogether unlikely that they occur in view of the low yields reported[31] of the 2,3-isomer.

Work in this laboratory indicates that 4-acetaminodibenzofuran undergoes homonuclear substitution on bromination to give 1-bromo-4-acetaminodibenzofuran. The bromodibenzofuran secured from the bromo-acetamino compound does not correspond with any of the three previously described isomers. Likewise 4-methoxydibenzofuran directs bromine to the same position. Although a bromine atom in either the 1- or 9-position would satisfy these experimental observations, a substitution in the 9-position would be highly remote. It has also been observed that the coupling of 4-hydroxydibenzofuran with benzene-diazonium chloride gives the 1-phenylazo-4-hydroxydibenzofuran[49].

It was found by Tatematsu and Kubota[50] that the action of bromine on 3-hydroxydibenzofuran gave as a main product, 2-bromo-3-hydroxydibenzofuran. The constitution of this compound was established by showing it to be identical with the compound secured by replacing the amino group of 2-bromo-3-aminodibenzofuran by the hydroxyl group through the diazonium reaction. In a like manner Mr. P. R. Van Ess has proved the structure of the bromo-2-hydroxydibenzofuran obtained by the bromination of 2-hydroxydibenzofuran. He found that it was 3-bromo-2-hydroxydibenzofuran by comparison with the known compound resulting from the diazotization of 2-amino-3-bromodibenzofuran and subsequent replacement of the diazonium group by the hydroxyl group.

Brumberg[39] reported a mixture of isomers on nitration of 2-bromodibenzofuran, which was not resolved; and, on the basis of an unsuccessful attempt to replace the bromine by an amino group, by the use of alcoholic ammonium hydroxide, he concluded

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[49] Unpublished studies by P. R. and M. J. Van Ess.

[50] Tatematsu and Kubota, *Bull. Chem. Soc. Japan*, *9*, 448 (1904); [*C. A.*, *29*, 1091 (1935)].

that no 2-bromo-3-nitro derivative was present in the mixture. Recently[31], this homonuclear isomer has been isolated from the mixture, and on reduction furnished the previously mentioned 2-bromo-3-aminodibenzofuran.

Heteronuclear

The only conclusive evidence available to 1934 on heteronuclear disubstitution reactions was concerned with the introduction of like substituents. Since that time several reports have appeared which dealt with the substitution of unlike groups.

Cullinane[18] demonstrated that bromination of 3-nitrodibenzofuran and nitration of 2-bromodibenzofuran resulted in the same compound. He assigned the formula, 2-bromo-7-nitrodibenzofuran, without experimental proof. Gilman and co-workers[31] repeated these two substitution reactions and secured the same product. They showed it to be the suggested 2-bromo-7-nitrodibenzofuran by reducing, diazotizing the resulting bromoamine, and replacing the diazonium group by bromine. The 2,7-dibromodibenzofuran obtained in this manner was found to be identical with an authentic sample prepared by ring closure[23]. Confirmatory evidence for the correctness of the nitro-bromo structure was obtained by aminating the 2-bromo-7-amino derivative to the known 2,7-diaminodibenzofuran. Cullinane and Padfield[51] have recently observed that analogous results are obtained with chlorine derivatives. On nitration of 2-chlorodibenzofuran and

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51. Cullinane and Padfield, J. Chem. Soc., 1131 (1935).

on chlorination of 3-nitrodibenzofuran, they secured the identical product; and proved it to be 2-chloro-7-nitrodibenzofuran, by comparison with an authentic sample. No mention was made of the probability of isomers occurring in the nitration of the chloro compound.

Metalation of 4-methyldibenzofuran yielded an organometallic compound which on carbonation gave a carboxy-4-methyldibenzofuran. This derivative was oxidized to the known 4,6-dibenzofurandicarboxylic acid, thus proving that the metal had assumed the 6-position. 4-Methoxydibenzofuran was likewise metalated in the 6-position. This was established by oxidizing the sodio-compound to give a hydroxy-4-methoxydibenzofuran, which on cleavage by hydrogen iodide gave the known 4,6-dihydroxydibenzofuran. These two nuclear substitution reactions are significant for it would not have been surprising to have found homonuclearly substituted products, in view of the activating effects of the methyl and methoxyl groups.

Methyl 4-dibenzofurancarboxylate has been brominated and nitrated[52]. Conclusive evidence has not been obtained to prove the structure of the compounds secured. Upon decarboxylation of the acids obtained by hydrolysis of the substituted esters, 2-bromodibenzofuran and both 2- and 3-nitrodibenzofurans (it was found that nitration produced two isomers) were isolated. It seems likely that the 2-bromo- and the 3-nitrodibenzofurans

[52] Unpublished studies by Mr. D. M. Hayes.

resulted from hetero-substituted derivatives; whereas, the 2-nitrodibenzofuran came from a homo-substituted compound. These assumptions are based on the known orienting influences of dibenzofuran and the carbomethoxy group.

Mr. G. E. Brown, in unpublished work, has established the position assumed by the nitro group upon nitrating 3-bromodibenzofuran. The nitro-3-bromo compound was dehalogenated with hydrogen and palladium catalyst to give the known 3-aminodibenzofuran, reduction of the nitro group having occurred simultaneous with the removal of the bromine atom. From this result, it was evident that the starting compound was 3-bromo-7-nitrodibenzofuran.

It appears, on the basis of evidence available, that in heteronuclear substitution the second substituent enters the unsubstituted benzene ring as it does in monosubstitution regardless of the group already present in the nucleus. The only exception to this general rule is that of dinitration which gives 2,7-dinitrodibenzofuran.

EXPERIMENTAL PART

Preparation of 3-Nitrodibenzofuran

Early studies of the nitration of dibenzofuran led to somewhat inconsistent results. Borsche and Bothe[34] obtained a mononitro derivative, melting at 181-182° by the action of fuming nitric acid on a solution of dibenzofuran in glacial acetic acid. Mailhe[53] prepared the compound in the same manner and reported a melting point of 175°. Ryan and Cullinane[54] found that nitrogen peroxide vapor converted dibenzofuran in glacial acetic acid solution into a mononitrodibenzofuran, melting at 182° which was in agreement with the value first reported. The choice of solvent determined, to a large extent, the number of nitro groups which were introduced into the molecule. These authors determined that nitrations in carbon tetrachloride solutions gave higher nitro derivatives than those under similar conditions where the solvent was glacial acetic acid. It is significant that the tri- and tetra nitro compounds prepared by Ryan and Cullinane do not agree in physical properties with the similarly substituted compounds reported by Mailhe[53].

The observation has been made in this laboratory that dibenzofuran undergoes nitration when treated with concentrated nitric acid at 60° in the absence of a solvent. The resulting product is a mononitrodibenzofuran which was considered by Oatfield, in unpublished studies, to be unlike the known 3-nitrodibenzofuran. These experimental conditions have been repeated

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53. Mailhe, Compt. rend., 154, 1515 (1912).
54. Ryan and Cullinane, Sci. Proc. Roy. Dublin Soc., 17, 321 (1924); [C. A., 18, 1655 (1924)].

and in every case 3-nitrodibenzofuran has been obtained along with varying amounts of the dinitro derivative. The yield of the latter compound increased with the length of time of heating.

The most satisfactory method for preparing 3-nitrodibenzofuran was essentially that proposed by Borsche and Bothe. It was important to carry out the reaction in a hood because during the course of the reaction there was a continual evolution of nitrous oxides. A suspension of 168 g. (1 mole) of dibenzofuran in 600 cc. of glacial acetic acid was placed in a two liter, three-necked flask fitted with a mechanical stirrer and a dropping funnel. It was advisable to cover the stoppers with a thin protective layer of tin foil to prevent contamination of the product. Stirring was started and 152 cc. (3.6 moles) of fuming nitric acid (sp. g. 1.50) was added at a fairly rapid rate. By the time all the acid had been added much heat had been evolved, and the dibenzofuran was partially dissolved. It was usually necessary to heat the flask for three to five minutes on a steam bath to complete the reaction. The dibenzofuran dissolved entirely to give a dark red solution. Within a short time star-like clusters of yellow needles separated and the precipitate became so heavy that the stirrer was stopped. At this time, or preferably a moment sooner, the heating was discontinued. The entire contents of the flask formed a solid cake on cooling. This mass was broken up, filtered and washed free from acid with water. The crude

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60-65°
(water bath!

not catalytic

3-nitrodibenzofuran, melting at 172°, was air-dried and could be used satisfactorily for reduction. The yield was from 192 g. to 208 g. (90 to 95% of the theoretical). The crude product could be purified by crystallization from glacial acetic acid to give the pure compound melting at 181-182°.

Preparation of 3-Aminodibenzofuran

Oatfield[5] has made a comprehensive study of the relative efficacies of different reducing agents for the preparation of 3-aminodibenzofuran. After comparing zinc and hydrochloric acid, zinc and acetic acid, iron and acetic acid, sodium amalgam, and tin and hydrochloric acid, he concluded that tin and hydrochloric acid was the best reducing agent on the basis of ease of manipulation and yield of amine obtained. Accordingly, the 3-amine used in this study has been prepared by following Oatfield's procedure with a few minor modifications.

Recently it has been found that excellent yields of quite pure 3-amine can be obtained by the catalytic reduction of 3-nitrodibenzofuran[55]. An advantage of this type of reduction is that the amine can be obtained directly as the free base, whereas, in other methods the hydrochloride salt of the base is isolated.

In a large three-necked flask provided with an efficient mechanical stirrer were placed 54 g. (0.25 mole) of finely divided 3-nitrodibenzofuran and 540 cc. of concentrated hydro-

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[55] Studies by Mr. Bradley, *J. Am. Chem. Soc.*, *57*, 1123 (1935).

chloric acid. This stirred mixture was treated with 100 g. of tin (30 mesh was preferable) added in small portions. If the metal was added too rapidly, excessive foaming occurred with attendant loss of product. The reaction flask was heated on the steam bath for one hour after all the tin had been added. After cooling, the reaction mixture was poured into a large beaker and was made alkaline with ammonium hydroxide. A copious precipitate of stannous hydroxide and the free base resulted. The precipitate was removed by filtration and thoroughly dried on a steam plate. This grayish-brown material was powdered and extracted with ether in a Soxhlet apparatus. Gaseous hydrogen chloride was bubbled through the ether solution, which precipitated 52 g. of the 3-amine hydrochloride. This was a yield of [illegible]%. The salt was converted to the base by dissolving it in 1500 cc. of hot water to which a few cc. of hydrochloric acid had been added. This solution was boiled several minutes with decolorizing carbon and filtered hot. The cold solution was made alkaline, which threw down the free amine. There was secured 38 g., or a yield of 84%, of the 3-aminodibenzofuran. Crystallization from aqueous alcohol gave a product melting at 94-95°.

Preparation of 3-Diacetaminodibenzofuran

3-Diacetaminodibenzofuran was prepared, in accordance with the directions of Borsche and Bothe[34]. A suspension of 22 g. (0.1 mole) of the 3-amine hydrochloride and an equal weight of anhydrous fused sodium acetate in 100 cc. (1.0 mole) of acetic anhydride were refluxed for one hour with the open end of the condenser protected with a calcium chloride tube. On cooling the solution solidified to a dark colored mass. This solid was removed by filtration and attempts were made to crystallize from aqueous alcohol. About 6 g. of the desired compound was secured, melting at 83°, which was a yield of 23%.

A great deal of difficulty was encountered in this preparation and subsequent purification. Undoubtedly, the cause of this trouble was the formation of the monoacetamino derivative which produced a low melting mixture that frequently oiled out. No satisfactory means of separating the mixture was found.

Preparation of 3-Monoacetaminodibenzofuran

Borsche and Schacke[38] have described the product secured on mono-acetylating 3-aminodibenzofuran. Their method of synthesis was analogous to that previously described for the diacetyl derivative. Due to the obstacles encountered in the aforesaid reaction, a more facile method of preparation was desired. It appeared that the use of benzene and acetic anhydride, described by Sako[19] in the preparation of 2-acetaminodiphenyl, was such a method.

Accordingly, 45 g. (0.25 mole) of 3-aminodibenzofuran was dissolved in 700 cc. of benzene. To this solution was added 26 g. (0.27 mole) of acetic anhydride. After standing for two hours to complete precipitation, 42 g. or a 75% yield, of white or light pink needles melting at 175-176° separated. Recrystallization from benzene raised the melting point to 177-178°.

A mixed melting point with 3-acetaminodibenzofuran, isolated from the diacetylation of the 3-amine, was not depressed.

Nitration of 3-Diacetaminodibenzofuran

Borsche and Schacke[38] were the first to nitrate the diacetyl derivative. In accordance with their directions, 5.5 g. (0.02 mole) of 3-diacetaminodibenzofuran was dissolved in 30 cc. of glacial acetic acid. The solution was stirred and cooled, and 4 g. of fuming nitric acid (sp. g. 1.50) was added dropwise. After a short time yellow plates of the nitro compound began to separate. Stirring was continued for one-half hour and the reaction mixture was poured on crushed ice. After filtering and washing with a small amount of ice-cold acetic acid, the crude product melted at 185-188°. It was recrystallized from acetic acid three times, and the melting point was raised to 196°. The weight of the product obtained was 5.3 g. which is an 85% yield.

Nitration of 3-Acetaminodibenzofuran

Contrary to the statement of Borsche and Schacke[38], it was found that 3-acetaminodibenzofuran undergoes nitration. This nitration was effected in glacial acetic acid by adding 5 g. of fuming nitric acid to 10 g. (0.04 mole) of the 3-acetamino compound dissolved in 60 cc. of glacial acetic acid. After stirring for one hour at room temperature, the reaction mixture was poured on cracked ice, filtered, and crystallized from acetic acid. Eight grams, or a yield of 74%, of a product melting at 196° was obtained. Further crystallization failed to raise the melting point.

Anal. Calcd. for $C_{14}H_{10}O_4N_2$: N, 10.37. Found: N, 10.02 and 10.42.

A mixed melting point determination with the nitro derivative obtained from 3-diacetaminodibenzofuran was not lowered. This proved that nitration had hydrolyzed one of the acetyl groups in the 3-diacetamino compound. Brumberg[39] has reported similar findings in the nitration of 2-diacetaminodibenzofuran. Therefore, Borsche and Schacke's supposed 2-nitro-3-diacetaminodibenzofuran is in reality 2-nitro-3-acetaminodibenzofuran.

Preparation of 2,3-Diaminodibenzofuran

Seven grams (0.026 mole) of the nitro-acetamino compound was dissolved in 95% alcohol. To this solution was added 20 cc. of concentrated hydrochloric acid. After a short period of refluxing, the compound was deacetylated to give a bright orange-red nitro-amine. Most of the alcohol was removed under reduced pressure and the residue was cooled and filtered. The precipitate was crystallized from toluene to yield an almost quantitative amount of 2-nitro-3-aminodibenzofuran melting at 222°, the same value as reported by Borsche and Schacke[38].

A solution of 12 g. (0.05 mole) of the nitroamine in 100 cc. of hydrochloric acid was placed in a three-necked flask equipped with a mechanical stirrer, and was heated on a steam bath. To the stirred solution, 25 g. of granulated tin was added in small portions to avoid foaming. After stirring for one hour, the mixture was made alkaline, cooled, and filtered. The precipitate was dried and finely powdered. Extraction of this powder gave an ether solution from which, upon treatment with gaseous hydrogen chloride, there was obtained 11 g. of the hydrochloride of the diamine. The salt was made basic and crystallized from aqueous ethanol. After several crystallizations, the melting point was raised to 165-166°, the value reported by others[38]. The free base was not very stable as it soon darkened on exposure to light and air.

Preparation of 2-Nitrodibenzofuran

Five grams (0.02 mole) of the nitre-amine was dissolved in 6 cc. of concentrated hydrochloric acid diluted to 50 cc. with water. The solution was cooled and [illegible] g. of sodium nitrite was added in small portions with shaking. After the diazonium solution had stood in the cold for one-half hour, 10 cc. of alcohol was added and the resulting solution was refluxed until the diazonium compound was completely decomposed. The solution was filtered and the residue was crystallized many times from methanol. The product, isolated in 40% yield, was 2-nitrodibenzofuran which melted at 149°. The nitro compound was shown to be identical with a sample of Brumberg's[39], 2-nitrodibenzofuran, prepared by the same series of reactions, and kindly provided by Professor Borsche.

2-Chlorodibenzofuran from 2-Nitrodibenzofuran

To a suspension of 3 g. (0.014 mole) of 2-nitrodibenzofuran (obtained from previous experiment) in 35 cc. of hydrochloric acid was added 10 g. of granulated tin. The reduction and workup were carried out in the normal manner, for which adequate details have been given under the preparation of 2-aminodibenzofuran. The amine was crystallized from aqueous alcohol and melted at 125-126°. It was shown to be identical with an authentic sample of 2-aminodibenzofuran, prepared by amination of known 2-bromodibenzofuran, by means of a mixed melting point determination.

A small amount of the amine was dissolved in hydrochloric acid and cooled. Sodium nitrite was added, a few crystals at a time, until starch-iodide paper showed a definite excess of nitrous acid. The diazonium suspension was allowed to stand for fifteen minutes and was then added slowly to a boiling cuprous chloride-hydrochloric acid solution. The resulting solution was steam-distilled and a few crystals came over which melted at 93-95°. Recrystallization from aqueous alcohol raised the melting point to 102°. The 2-chlorodibenzofuran was found to be identical with an authentic specimen prepared by ring closure[32].

Bromination of 2-Acetaminodibenzofuran

To a solution of 10 g. (0.044 mole) of 2-monoacetaminodibenzofuran in 75 cc. of glacial acetic acid was added dropwise 7 g. (0.044 mole) of bromine. After a few minutes hydrogen bromide was evolved and the stirring was continued for one-half hour. The bromo compound which separated was filtered, washed well with water and crystallized from alcohol to give an

85% yield of product melting at 192°. Purification of the 2-bromo-3-acetaminodibenzofuran by recrystallization raised the melting point to 194°.

Anal. Calcd. for $C_{14}H_{10}O_2NBr$: N, 4.60. Found: N, 4.76 and 4.89.

3-Diacetaminodibenzofuran was brominated in like manner to give an 80% yield of the same 2-bromo-3-acetaminodibenzofuran.

Preparation of 2-Bromo-3-aminodibenzofuran

To a solution of 7 g. (0.024 mole) of 2-bromo-3-acetaminodibenzofuran in 75 cc. of ethanol was added 25 cc. of concentrated hydrochloric acid. After refluxing for one hour, the mixture was cooled and filtered. The hydrochloride which was formed was only slightly soluble in water, and was found to decompose at 236°. It is significant to note that in this reaction the hydrochloride salt was isolated; whereas, in the deacetylation of 2-nitro-3-acetamino under like conditions, the free base was obtained. The 2-bromo-3-aminodibenzofuran was secured quantitatively by adding an excess of ammonium hydroxide to a suspension of the hydrochloride in water, and melted at 129° after several recrystallizations from alcohol.

Anal. Calcd. for $C_{12}H_8ONBr$: N, 5.34. Found: N, 5.40.

2-Bromodibenzofuran from 2-Bromo-3-aminodibenzofuran

Nine grams (0.034 mole) of 2-bromo-3-aminodibenzofuran was suspended in 10 cc. of hydrochloric acid, diluted to 50 cc. with water. To the cold, well-stirred solution was added 2.5 g. (0.035 mole) of sodium nitrite in small portions. β-Naphthol gave a positive color reaction almost instantly. After the solution was stirred for one-half hour, the diazonium compound separated as a yellow solid. This mixture was refluxed with alcohol until reduction was complete. An oil separated which solidified on cooling and was removed by filtration. Crystallization of this residue from aqueous alcohol gave 2-bromodibenzofuran melting at 109-110°. This was compared with a sample of known 2-bromodibenzofuran and found to be identical by means of a mixed melting point.

2,3-Dibromodibenzofuran from 2-Bromo-3-aminodibenzofuran

The diazonium salt from 2 g. (0.007 mole) of 2-bromo-3-aminodibenzofuran was prepared in the customary manner. This solution was then added in small portions to a boiling solution of 1.5 g. (0.01 mole) of cuprous bromide in 10% hydrobromic acid solution. After the addition was complete, the mixture was refluxed for twenty minutes. From the solid residue which separated on cooling, there was obtained after extraction and crystallization from benzene a few crystals of pure 2,3-dibromodibenzofuran, melting at 153-154°. Tatematsu and Kubota[50], some time later, reported the same compound with melting point 151°. Since the two compounds were obtained by the same series of reactions, further amounts of the dibromo derivative were not prepared for analysis.

2,3-Diaminodibenzofuran from 2-Bromo-3-aminodibenzofuran

The 2-bromo-3-aminodibenzofuran (3 g. or 0.011 mole) and

2 g. of cuprous bromide suspended in 40 cc. of ammonium hydroxide were sealed in a pyrex tube and heated to 190° for twenty hours. After cooling and opening, the contents of the tube were extracted thoroughly with ether. After the ether extract had been dried, the hydrochloride of the diamine was precipitated with gaseous hydrogen chloride. This salt was filtered and treated with decolorizing carbon in its aqueous solution. The 2,3-diaminodibenzofuran was obtained from the salt solution by treatment with alkali. The base was crystallized from 75% alcohol to give a compound melting at 165-166°. It was shown to be identical with the diamine obtained from the reduction of 2-nitro-3-aminodibenzofuran.

Quinoxaline Derivatives of 2,3-Diaminodibenzofuran

A. From Benzil: In each of the two following experiments, two runs were made using samples of the diamine prepared from different sources: namely, 2-bromo-3-aminodibenzofuran and 2-nitro-3-aminodibenzofuran.

One-tenth gram of 2,3-diaminodibenzofuran was added to a solution of 0.1 g. of benzil in 8 cc. of alcohol contained in a 25 cc. Erlenmeyer flask. This solution was refluxed for one-half hour. Shortly after the heating was started, yellow platelets of the desired derivative began to separate. The flask was cooled in an ice-salt bath and the contents were filtered. The residue was recrystallized twice from a small amount of ethyl alcohol to give a compound melting at 179°. Borsche and Schacke[38] reported the same value for their derivative.

B. From phenanthraquinone: To a solution of 0.1 g. of phenanthraquinone in 5 cc. of a 50% mixture of glacial acetic acid and ethyl alcohol was added 0.1 g. of 2,3-diaminodibenzofuran. This solution was refluxed for thirty minutes to complete the condensation. In this reaction, the compound did not separate during the refluxing; however, when the flask was cooled in an ice-salt bath, the solution solidified to a crystalline mass. These crystals were removed by filtration and were recrystallized twice from glacial acetic acid. The pure derivative obtained in this manner melted at 297°, the same value reported by Borsche and Schacke[38].

Preparation of 3-Methylaminodibenzofuran

A series of alkylated 3-aminodibenzofurans was desired for purposes of pharmacological testing.

Following the directions for the preparation of methylaniline described by Ullman[56], 11 g. (0.05 mole) of the hydrochloride of 3-aminodibenzofuran was suspended in 15 cc. of water. Ten grams (0.05 mole) of freshly distilled *p*-toluenesulfonyl chloride and 40 cc. of 10% sodium hydroxide were added alternately to the suspension in small portions. After each addition, the reaction mixture was shaken vigorously; and when addition was complete, the flask was placed in a mechanical shaker for one hour. A sticky precipitate was formed. This *p*-toluenesulfonamide was treated *in situ* with 5 cc. of dimethyl sulfate. The resulting mixture was shaken and reaction occurred

[56] Ullman, *Ann.*, *327*, 110 (1903).

as evidenced by the evolution of heat. After standing overnight to complete the methylation, the product was filtered and washed with water. This oily residue was added to a mixture of 17 cc. concentrated sulfuric acid and 7 cc. of glacial acetic acid, and heated on a water bath for three hours and finally at 120° for a few minutes. This hydrolysis product was diluted with water and made alkaline with ammonium hydroxide. The basic solution was extracted with ether and the ether extract dried over sodium sulfate. Upon removal of the solvent, 3-methylaminodibenzofuran distilled at 190°/4mm. The methylamine could be crystallized from 75% alcohol to give white crystals melting at 48-49°.

Anal. Calcd. for $C_{13}H_{11}ON$: N, 7.10. Found: N, 6.90. A Zerewitinoff analysis showed the presence of one active hydrogen.

A small amount of the crystalline base was dissolved in sodium-dry ether. Gaseous hydrogen chloride was bubbled through the solution to precipitate the amine hydrochloride. The solid was filtered and crystallized from very dilute hydrochloric acid. The pure salt melted with decomposition at 245-247°.

Anal. Calcd. for $C_{13}H_{12}ONCl$: N, 6.03. Found: N, 6.06 and 6.15.

Preparation of 3-Ethylaminodibenzofuran

Nineteen grams (0.1 mole) of 3-aminodibenzofuran was suspended in [illegible] cc. of water. Freshly distilled p-toluenesulfonyl chloride (20.3 g. or 0.1 mole) and 85 cc. of 10% sodium hydroxide solution were added alternately to the flask with shaking. The flask was permitted to stand awhile and then 15.4 g. (0.1 mole) of freshly distilled diethyl sulfate was added with agitation. After standing for fifteen hours in an ice box, the solution deposited a dark oil. The supernatant liquid was decanted, and 54 cc. of sulfuric acid and 14 cc. of acetic acid were added to the flask, which was then heated for three hours on a water bath and for a short time at 120°. The resulting solution was cooled and made alkaline with ammonium hydroxide, which precipitated the free base as an oily sludge. This was removed and boiled with an excess of 5% hydrochloric acid and decolorizing carbon. After filtration, the clear solution gave 15 g., or a 60% yield of 3-ethylaminodibenzofuran hydrochloride. It was purified by crystallization from water to give a salt which did not melt up to 315°. Attempts to secure a crystalline free base were not successful. The hydrochloride is less than 0.2 g. soluble per 100 cc. of water or alcohol.

Anal. Calcd. for $C_{14}H_{14}ONCl$: N, 5.66. Found: N, 5.71 and 5.58.

Preparation of 3-*n*-Propylaminodibenzofuran

n-Propyl *p*-toluenesulfonate was prepared in accordance with directions described in Organic Syntheses[57]. A 65% yield was obtained which distilled at 145°/3mm.

The method which was found to be successful in the synthesis of *n*-propylaniline[58] was used to propylate 3-aminodi-

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[57] "Organic Syntheses", Coll. Vol., I, p. 139.

[58] Slotta, *Ber.*, *63*, 678 (1930).

benzofuran. A mixture of 22 g. (0.134 mole) of 3-aminodibenzofuran and 14 g. (0.067) of n-propyl p-toluenesulfonate was placed in a 300 cc. Erlenmeyer flask and heated in an oil bath for five hours at 110°. The residue was then removed from the flask and broken into small pieces. These were placed in a thimble and extracted with ether for 36 hours in a Soxhlet apparatus. The extraction was interrupted for a few minutes while the residue was pulverized, and then replaced and the extraction continued for another 12 hours. The ether extract was dried over sodium sulfate, filtered, and evaporated to leave an oil which distilled at 200-208°/1mm. On redistillation, it distilled at 203-205°/1mm., and would not crystallize, after remaining in a refrigerator for two days. This oil was dissolved in anhydrous ether and yielded 8.5 g. of the hydrochloride when treated with gaseous hydrogen chloride. This was a yield of 49%. The salt was crystallized from water and melted at 190°. Water hydrolyzed the hydrochloride apparently to the free amine. 3-n-propylaminodibenzofuran hydrochloride is soluble in alcohol to the extent of about 2 g. per 100 cc.

Anal. Calcd. for $C_{15}H_{16}ONCl$: N, 5.36. Found: N, 5.53 and 5.32.

Preparation of 3-Dimethylaminodibenzofuran

A suspension of 12 g. (0.1 mole) of the hydrochloride of 3-aminodibenzofuran in a solution of 8 g. (0.2 mole) of sodium hydroxide in 100 cc. water was placed in a three-necked flask provided with a mechanical stirrer. The flask was surrounded by an ice bath, and 24.4 g. (0.2 mole) of freshly distilled dimethyl sulfate was added to the stirred mixture. After stirring had been continued for ten hours, the reaction was heated on a water bath for one hour. After the reaction product had cooled, it was extracted well with ether and the extract dried over sodium sulfate. Upon removal of the solvent, twelve grams of 3-dimethylaminodibenzofuran was secured distilling at 211-212°/4mm, which was a 65% yield. A Zerewitinoff analysis showed the absence of any active hydrogen.

Anal. Calcd. for $C_{14}H_{13}ON$: N, 6.62. Found: N, 6.86 and 7.01.

The hydrochloride, prepared in the usual manner from the base, melted at 230-232°. It was less than 0.5 g. soluble in 100 cc. water and about 1 g. soluble in 100 cc. of alcohol.

Preparation of 3-Diethylaminodibenzofuran

The diethyl sulfate used in this experiment was washed with sodium bicarbonate solution and then with water. The pure ester distilled at 104°/9mm. To a cold suspension of 22 g. (0.1 mole) of 3-aminodibenzofuran hydrochloride in 150 cc. of water containing 8 g. (0.2 mole) of sodium hydroxide was added 15.4 g. (0.1 mole) of diethyl sulfate. After the mixture had been stirred for ten hours, it was heated on a water bath for thirty minutes. The cold reaction mixture was extracted with ether and the extract was dried over sodium sulfate. After the solvent had been evaporated, 15 g. of

3-diethylaminodibenzofuran was distilled at 201-210°/2-3mm. This distillate, which was obtained in a 62% yield, was redistilled and came over at 205°/2-3mm. Attempts were made to crystallize the hydrochloride which was prepared in the customary manner, but it was found that the salt was hydrolyzed by water at 80-90°. The hydrochloride, just as secured from the ether solution, melted at 203-205° and was difficultly soluble in water and alcohol.

Anal. Calcd. for $C_{16}H_{18}ONCl$: N, 5.09. Found: N, 5.07 and 5.08.

Preparation of 3-Piperidinodibenzofuran.

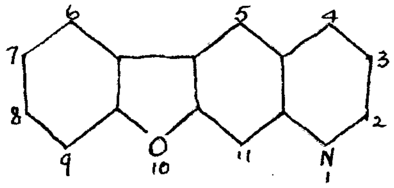
A mixture of 26 g. (0.14 mole) of 3-aminodibenzofuran and 12 g. (0.05 mole) of pentamethylene bromide was heated for one hour on a water bath, and the resulting solid was powdered and extracted with ether in a Soxhlet apparatus. The passage of hydrogen chloride into the ether solution gave a quantitative yield of 3-piperidinodibenzofuran hydrochloride. The free base, obtained by the addition of ammonium hydroxide, melted at 111° on recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{17}H_{17}ON$: N, 5.57. Found: N, 5.54 and 5.55.

The hydrochloride, prepared in the usual manner from the base, melted at 258-260°. The salt was hydrolyzed by water, but 100 cc. of ethanol dissolved about 5 g. of the compound.

Anal. Calcd. for $C_{17}H_{18}ONCl$: N, 4.87. Found: N, 4.89 and 4.90.

Preparation of Pyrido-[-3,2-b]-dibenzofuran[59]



A mixture of 60 g. (0.27 mole) of 3-aminodibenzofuran hydrochloride, 50 g. (0.21 mole) of arsenic oxide, 150 g. (1.62 moles) of glycerol and 80 g. (0.81 mole) of concentrated sulfuric acid was heated in an oil bath for four to five hours at 170°. The liquid was then poured into 1800 cc. of hot water, to which 85 cc. of 30% sodium hydroxide had been added, boiled with decolorizing carbon, and filtered hot. The cooled filtrate was made alkaline with ammonium hydroxide, extracted with ether and from the dried ether solution there was obtained 28 g. or a 49% yield of the pyridodibenzofurans which distilled at 203-215°/2-3mm. The mixture of the two isomers was dissolved in a small amount of ethanol and permitted to crystallize. The crystals were filtered and recrystallized from methanol. The pyrido-[3,2-b]-dibenzofuran melted at 167.5-168.5° and its structure was very recently established by Mosettig and Robinson[13].

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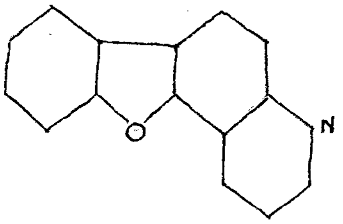
[59] For the principles used in naming certain parent ring systems, and especially in distinguishing isomeric forms by the use of bracketed numbers and letters in the middle of the name, see Patterson, J. Am. Chem. Soc., 50, 3074 (1928).

Anal. Calcd. for $C_{15}H_9ON$: N, 6.39. Found: N, 6.39.

The hydrochloride melts at 234-236°.

Preparation of Pyrido-[2,3-c]-dibenzofuran[59]



(a) From 3-Aminodibenzofuran: The mother liquors from the previous crystallization of the linear isomer was treated with an alcoholic hydrogen chloride solution. The resulting hydrochloride was filtered and washed with hot ethanol to remove last traces of the linear compound. The remaining precipitate was converted to the base by means of ammonium hydroxide. Crystallization from methanol gave the pure pyrido-[2,3-c]-dibenzofuran melting at 105.5-106°. This isomer, obtained also by fractional distillation under reduced pressure of the mixture of pyrido compounds, distilled at 209-210°/3mm.

Anal. Calcd. for $C_{15}H_9ON$: N, 6.39. Found: N, 6.41 and 6.49.

The hydrochloride melted at 292-294° and was quite insoluble in water.

Anal. Calcd. for $C_{15}H_{10}ONCl$: N, 5.49. Found: N, 5.60.

(b) From 3-Amino-2-bromodibenzofuran and (c) from 3-Amino-2-nitrodibenzofuran: The Skraup reaction was carried out with 0.1 mole of each of these substituted amines and in each case a small quantity of the pyrido-[2,3-c]-dibenzofuran was isolated, and shown to be identical with the pyrido compound prepared from 3-aminodibenzofuran.

Preparation of 1,2,3,4-Tetrahydropyrido-[2,3-c]-dibenzofuran.

The pyrido-[2,3-c]-dibenzofuran (17.5 g. or 0.08 mole) was refluxed for five hours with 20 g. of granulated tin and 350 cc. of concentrated hydrochloric acid. The cooled mixture was made alkaline with ammonium hydroxide and then filtered. The copious precipitate, consisting of hydrated stannous oxide and the free base, was dried, finely powdered and then extracted with ether. The passage of gaseous hydrogen chloride into the ether solution gave a quantitative yield of the hydrochloride melting at 247-248°. It was difficultly soluble in water and ethanol.

Anal. Calcd. for $C_{15}H_{14}ONCl$: N, 5.40. Found: N, 5.42 and 5.38.

Preparation of 1-Methyl-1,2,3,4-tetrahydropyridodibenzofuran.

A suspension of 10 g. (0.036 mole) of the compound described above in 100 cc. of water containing 2.9 g. (0.072 mole) of sodium hydroxide was placed in a round-bottomed flask provided with a mechanical stirrer. To the stirred, cold solution was added 5.1 g. (0.036 mole) of dimethyl sulfate. After all was added, the solution was refluxed for 1.5 hours. The cooled solution was extracted with ether. From the dried ether extract there was obtained an 83% yield of the hydrochloride of 1- or N-methyl compound. The salt melted with decomposition at 227-229°.

Anal. Calcd. for $C_{16}H_{16}ONCl$: N, 5.13. Found: N, 5.46.

Preparation of 2-Methylpyrido-[2,3-c]-dibenzofuran

A stirred mixture of 50 g. (0.22 mole) of the hydrochloride of 3-aminodibenzofuran and 135 cc. of concentrated hydrochloric acid was heated to 90-100° in a three-necked flask provided with a return condenser and a dropping funnel. Eighty grams of paraldehyde was added dropwise over a period of thirty minutes. Heating was continued for six hours on a water-bath. The resulting product was filtered, then made alkaline and extracted with ether. From the dried ether solution there was obtained 17 g. or a 30% yield of 2-methylpyrido-[2,3-c]-dibenzofuran which distilled between 200-210°/3mm. and melted at 185-186°, after recrystallization from ethanol. The other possible isomer was not investigated.

Anal. Calcd. for $C_{16}H_{11}ON$: N, 6.00. Found: N, 6.00 and 5.89.

The same compound, as established by a mixed melting point determination, was obtained by the action of methyl-lithium on pyrido-[2,3-c]-dibenzofuran.

A 0.15 mole run of methyl-lithium was prepared in the customary manner, the methyl iodide being added dropwise to a stirred suspension of finely divided lithium in anhydrous ether. When the formation of the organometallic compound was complete, the solution was filtered directly into a Schlenk tube which had previously been swept out with nitrogen. The pyrido compound (10.5 g. or 0.05 mole) was added, and the tube was sealed and heated for four hours at 90-100°. The cooled tube was opened and the material poured on crushed ice. After this solution had been extracted with ether, there was obtained from the dried ether extract a solid which distilled at 204°/3mm. Recrystallization from ethanol gave the 2-methylpyrido-[2,3-c]-dibenzofuran melting at 185-186°.

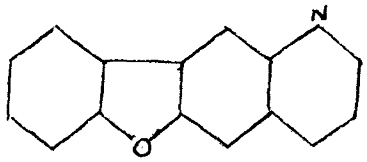
Preparation of 7-Bromopyridodibenzofuran

In 300 cc. of glacial acetic acid was suspended 53 g. (0.25 mole) of 3-nitrodibenzofuran. This mixture was stirred and heated to 65° and then 40 g. (0.25 mole) of bromine was added over a period of one-half hour. After an additional four-hour period of heating at 65-70°, the mixture was cooled and the filtered product was fractionally crystallized from acetic acid to give a 22% yield of 2-bromo-7-nitrodibenzofuran melting at 248°. Reduction of the nitro group was effected by tin and hydrochloric acid to give a 67% yield of the bromoamine hydrochloride.

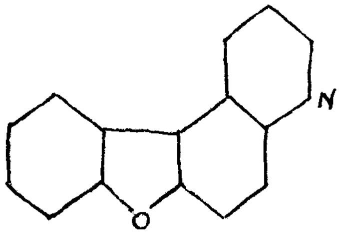
A mixture of 35 g. (0.12 mole) of this hydrochloride, 25 g. of arsenic oxide, 80 g. of glycerol, and 40 g. of sulfuric acid was heated under gentle reflux for five hours at 160°. The liquid was poured into 1500 cc. of hot water, and after the addition of 40 cc. of 33% sodium hydroxide and some decolorizing carbon, was boiled for a few minutes and filtered hot. After the cooled filtrate was made alkaline, a sludge formed which was filtered and crystallized from ethanol to give a 50% yield of the pure pyrido compound melting at 152°. The structure of this isomer was not established.

Anal. Calcd. for $C_{15}H_8ONBr$: N, 4.70. Found: N, 4.69.

Preparation of Pyrido-[2,3-b]-dibenzofuran and Pyrido-[3,2-a]-dibenzofuran[59]



Pyrido-[2,3-b]-dibenzofuran



Pyrido-[3,2-a]-dibenzofuran

The 2-aminodibenzofuran, necessary for this synthesis, was prepared by placing 48 g. (0.153 mole) of pure 2-bromodibenzofuran, 25 g. of cuprous bromide, and 500 cc. of ammonium hydroxide in an electrically heated steel bomb. The reaction was heated at 225-250° for twelve hours. The amine was isolated as the hydrochloride by dissolving the fused mass in ether-benzene and saturating with hydrogen chloride. The yield was 30 g. or 88% of the theoretical.

A Skraup synthesis on 22 g. (0.1 mole) of 2-aminodibenzofuran hydrochloride was carried out. The mixture was treated as in previous runs and the resulting solution was extracted with ether. The ethereal solution on desiccation, evaporation and distillation of the residue under reduced pressure gave a 39% yield of the mixed pyridodibenzofurans distilling at 240°/6mm. This distilled product was crystallized from ethanol; crystals separated which when purified by repeated crystallization from methyl alcohol melted at 185-186°.

Anal. Calcd. for $C_{15}H_9ON$: N, 6.39. Found: N, 6.35.

The alcohol mother liquors from the above crystallizations were combined and treated with an excess of alcoholic hydrogen chloride. The resulting hydrochloride was filtered and washed with hot ethanol, and converted to the free base by means of ammonium hydroxide. The isomeric pyrido compound was crystallized several times from methanol to give pure crystals melting at 160.5-161.5°.

Anal. Calcd. for $C_{15}H_9ON$: N, 6.39. Found: N, 6.49.

The hydrochlorides of these two isomers melted with darkening and decomposition at 307-310° and 296-298°, respectively.

The structures of these isomers were not determined.

Preparation of 2-Bromoacetyldibenzofuran

2-Acetyldibenzofuran was prepared by a Friedel-Crafts' reaction on dibenzofuran using acetyl chloride, aluminum chloride and carbon disulfide. A solution of 6.3 g. (0.03 mole) of the acetyl compound in 200 cc. of ether was cooled to 0°, and added to a solution of 4.8 g. (0.03 mole) of bromine in 200 cc. of ice-cold ether. The bromine color disappeared in about five minutes. After standing for one-half hour in an ice-bath, the solution was freed of hydrobromic acid by means of dry potassium carbonate. Upon removal of the solvent under reduced pressure, the residue was crystallized from methanol several times to give the pure 2-bromoacetyldibenzofuran, which melted at 106-107°.

Anal. Calcd. for $C_{14}H_9O_2Br$: Br, 27.68. Found: Br. 27.60 and 27.93.

Preparation of 2-Chloroacetyldibenzofuran

A mixture of 80 g. (0.6 mole) of aluminum chloride, 200 cc. of carbon disulfide, and 67.2 g. (0.4 mole) of dibenzofuran was placed in a three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel, and a return condenser. Forty-five grams (0.4 mole) of chloroacetyl chloride was added to the gently refluxing, stirred mixture. After heating for three hours the product was poured on cracked ice and extracted with ether-benzene. From the dried extract, there was secured 45 g. of twice-distilled 2-chloroacetyldibenzofuran which came over at 206-208°/1-2mm., in a 46% yield. The compound melted at 109-110° when recrystallized from aqueous alcohol.

Anal. Calcd. for $C_{14}H_9O_2Cl$: Cl, 14.35. Found: Cl, 14.46 and 14.39.

In order to be certain that the chloroacetyl group had oriented the same as the acetyl group under similar reaction conditions, a small sample of the compound was oxidized to an acid which was shown to be identical with an authentic specimen of 2-dibenzofurancarboxylic acid.

Preparation of 2-ω-Diethylaminoacetyldibenzofuran

In 150 cc. of absolute ether were dissolved 12 g. (0.05 mole) of 2-chloroacetyldibenzofuran and 7.3 g. (0.10 mole) of diethylamine. The solution was allowed to stand for 48 hours, after which time the precipitate of diethylamine hydrochloride was removed by filtration. The filtrate was evaporated to dryness and the residue dissolved in a minimum of absolute alcohol. To this solution there was added an ethereal solution of 0.05 mole of hydrogen chloride. The resulting hydrochloride was precipitated by diluting with a large volume of dry ether, filtered, and crystallized from ether-alcohol mixture to give a 20% yield of a salt melting at 204-206°.

Anal. Calcd. for $C_{18}H_{20}O_2NCl$: N, 4.41. Found: N, 4.37 and 4.61.

Preparation of Diethylaminomethyl-2-dibenzofurylcarbinol

Since some of the phenanthrene derivatives which contain the pharmacologically interesting hydroxyethylamino side chain produce in a cat a typical morphine-like excitement, dilatation of the pupils and marked analgesia[60], it seemed advisable to prepare analagous compounds in the dibenzofuran series.

Accordingly, an absolute ethanol solution of 20 g. (0.07 mole) of 2-ω-diethylaminoacetyldibenzofuran was reduced with

[60] Burger and Mosettig, J. Am. Chem. Soc., 56, 1745 (1934).

Adams catalyst. One equivalent of hydrogen was taken up in forty-eight hours. The free amine was distilled with difficulty at 220°/2-3mm and was obtained in a 30% yield.

Anal. Calcd. for $C_{18}H_{21}O_2N$: N, 4.92. Found: N, 4.90.

The hydrochloride was prepared with difficulty, generally coming down as an oil. However, some crystals were obtained by the use of one equivalent of alcoholic hydrogen chloride and extended standing in an ice box. The hydrochloride melted at 137° and darkened on standing.

Anal. Calcd. for $C_{17}H_{22}O_2NCl$: N, 4.38. Found: N, 4.39 and 4.36.

Preparation of 2-ω-Piperidinoacetyldibenzofuran

A mixture of 24.4 g. (0.1 mole) of 2-chloroacetyldibenzofuran and 17 g. (0.2 mole) of piperidine was placed in a small Erlenmeyer flask without solvent. A violent reaction occurred. When it had subsided and the mixture was cold, the residue was extracted with ether. The ether solution was filtered to remove the piperidine hydrochloride and the resulting filtrate was saturated with hydrogen chloride to give a quantitative yield of the desired hydrochloride. It was crystallized from ether-alcohol and melted at 270-271°. The salt is insoluble in water and only slightly soluble in ethanol.

Anal. Calcd. for $C_{19}H_{20}O_2NCl$: N, 4.24. Found: N, 4.34 and 4.07.

Preparation of Piperidinomethyl-2-dibenzofurylcarbinol

Thirteen grams (0.05 mole) of 2-ω-piperidinoacetyldibenzofuran was dissolved in 200 cc. of absolute ethanol. This solution was reduced with Adams catalyst, one equivalent of hydrogen being taken up in seven hours. After the removal of the solvent under reduced pressure, the residue was crystallized from aqueous ethanol to give a 25% yield of the free amine, melting at 103-104°. A Zerewitinoff analysis showed the presence of one active hydrogen.

Anal. Calcd. for $C_{19}H_{21}O_2N$: N, 4.74. Found: N, 4.69 and 4.74.

The hydrochloride prepared in the usual manner and crystallized from water melted at 242°.

Anal. Calcd. for $C_{19}H_{22}O_2NCl$: N, 4.22. Found: N, 4.32 and 4.32.

Preparation of Ethyl Ether of Piperidinomethyl-2-dibenzofurylcarbinol Hydrochloride

The ethyl ether of chloromethyl-2-dibenzofurylcarbinol was prepared by treating 0.2 mole of 2-dibenzofurylmagnesium bromide with 28.5 g. (0.2 mole) of α,β-dichloroethyl ether. The solution was refluxed for one hour with stirring, and after standing for another 12 hours was poured on ice and acidified. The ether layer was separated and the aqueous solution extracted with ether. The combined ether solution was dried and evaporated. The residue, the desired ethoxy compound, distilled with difficulty because of the excessive foaming (b. p. 204-206°/6mm.). The twice-distilled product could be crystallized from ethanol and melted at 58-59°.

Anal. Calcd. for $C_{16}H_{15}O_2NCl$: Cl, 12.77. Found: Cl, 12.36 and 12.42.

Twenty grams (0.08 mole) of this ethoxy derivative and 17 g. (0.2 mole) of piperidine were sealed in a pyrex tube and heated to 140-150° for four hours. After cooling and opening, the tube was washed free of solid material with water and ether. This mixture was made alkaline and thoroughly extracted with ether. The ether extract was evaporated and last traces of piperidine removed under reduced pressure. The remaining oil was dissolved in ether and the solution treated with gaseous hydrogen chloride. The hydrochloride separated as an oil; however, on extended standing in a ice box, the oil crystallized to give the hydrochloride melting at 175° after recrystallization from acetone.

Anal. Calcd. for $C_{20}H_{26}O_2NCl$: N, 4.02. Found: N, 4.15.

Preparation of Diethylaminomethyl-2-dibenzofurylmethylcarbinol Hydrochloride

A solution of 0.2 mole of the Grignard reagent obtained from 2-bromodibenzofuran in the usual manner was filtered through glass wool into a separatory funnel which was attached to a three-necked flask provided with a stirrer and a reflux condenser. A solution of 19 g. (0.2 mole) of epichlorohydrin in 150 cc. of sodium-dry ether was contained in the flask. The Grignard reagent was added dropwise to the stirred solution, which was refluxed for one hour after the addition was complete. Finally 200 cc. of the ether was distilled away, and then 200 cc. of dry benzene was added and the refluxing was continued for another two-hour period, after which the reaction was allowed to stand over night. The solution was hydrolyzed with ice and acid, and extracted with ether. From the dried ether solution, 6 g. or a 12% yield of chloromethyl-2-dibenzofurylmethylcarbinol was obtained, distilling at 205-206°/2 mm.

Anal. Calcd. for $C_{15}H_{13}O_2Cl$: Cl, 13.41. Found: Cl, 13.12 and 12.94.

Eleven grams (0.042 mole) of this carbinol, 11 g. (0.15 mole) of diethylamine, and 15 cc. of benzene were sealed in a Carius tube and heated at 140° for five hours. After cooling and opening, the contents were rinsed out with benzene, and after filtering the benzene solution to remove the diethylamine hydrochloride, the benzene and excess of diethylamine were removed under reduced pressure. The residue was dissolved in dry ether and this solution was treated with hydrogen chloride to give an oil. Some benzene was added to the solution and it was evaporated on a hot plate to the volume of 5-10 cc. This solution was cooled yielding a solid which when crystallized from acetone melted at 145°. A quantitative yield of diethylamin o methyl-2-dibenzofurylmethylcarbinol hydrochloride was obtained.

Anal. Calcd. for $C_{19}H_{24}O_2NCl$: N, 4.20. Found: N, 4.26 and 4.32.

Preparation of 2-β-Aminoethyldibenzofuran

A solution of 2-dibenzofurylmagnesium bromide was prepared from 500 cc. of anhydrous ether-benzene, 125 g. (0.51 mole) of 2-bromodibenzofuran and 13.5 g. (0.56 atom) of 40-

100 mesh magnesium. Into this solution was distilled 44 g. (1 mole) of ethylene oxide, and the reaction was carried out in essential accordance with the directions of Dreger[61] for the preparation of n-hexyl alcohol from n-butylmagnesium bromide. The 2-β-hydroxyethyldibenzofuran was secured in a 45% yield, and melted at 67-67.5° after recrystallization from petroleum ether (b. p. 60-68°).

Gaseous hydrogen bromide was bubbled at a moderate rate through 80 g. (0.377 mole) of molten 2-β-hydroxyethyldibenzofuran at 100° for two hours. The product was washed with water, allowed to solidify, dried and distilled under reduced pressure. The yield of the bromo compound was 93%, and it distilled at 179-180°/2-3mm. and melted at 62-62.5° on recrystallization from ethanol.

An intimate mixture of 30 g. (0.108 mole) of 2-β-bromoethyldibenzofuran and 25 g. (0.135 mole) of potassium phthalimide was heated without solvent at 185-200° for six hours. The product was extracted with acetic acid and the substituted imide crystallized on cooling and was removed by filtration. This crystalline material was suspended in alcohol and after the addition of an excess of hydrazine hydrate was refluxed until a gelatinous precipitate formed. The cooled reaction product was acidified with hydrochloric acid, boiled a few minutes and filtered hot. The residue was further extracted

[61] Dreger, "Organic Syntheses", Coll. Vol., I, p. 299, 1932.

with dilute acid solution and the filtrates combined. After the removal of the alcohol under reduced pressure, the acidic solution was made alkaline and extracted with ether. From the dried ether extract there was obtained a 46% yield of 2-β-aminoethyldibenzofuran distilling at 167-170°/2mm. The free amine was very sensitive to carbon dioxide. The hydrochloride prepared in the usual manner melted at 278°.

Anal. Calcd. for $C_{14}H_{14}ONCl$: N, 5.66. Found: N, 5.64 and 5.97.

2-β-Aminoethyldibenzofuran from 2-Chloromethyldibenzofuran

To a solution of 84 g. (0.5 mole) of dibenzofuran in 100 cc. of petroleum ether (b. p. 75-115°) contained in a three-necked flask, provided with a mechanical stirrer and a gas delivery tube extending to the bottom, was added 25 g. (0.27 mole) of trioxymethylene and 20 g. of fused zinc chloride. Gaseous hydrogen chloride was bubbled into the stirred suspension at a rather rapid rate. After fifteen or twenty minutes the color of the reaction darkened and the temperature began to rise but at no time was the reaction permitted to get hotter than 55-60°. After one hour of stirring at this temperature the reaction was poured on ice and extracted with ether. The ether extract was washed with sodium carbonate and dried over sodium sulfate. Upon the removal of the solvent 49 g. of crude 2-chloromethyldibenzofuran was secured distilling at 155-175°/4mm. On redistillation a 41% yield of the compound came over at 159-161°/3mm. This material was recrystallized several times from methyl alcohol and melted at 78.5-79.5°.

Anal. Calcd. for $C_{13}H_9OCl$: Cl, 16.20. Found: Cl, 16.40 and 16.63.

A small sample of this compound was oxidized to an acid which was shown to be 2-dibenzofurancarboxylic acid. This reaction gave proof that the compound was substituted in the 2-position.

An ethanol solution of 44 g. (0.2 mole) of 2-chloromethyldibenzofuran was added to a saturated aqueous solution of 30 g. (0.6 mole) of sodium cyanide and refluxed for five hours. The mixture was filtered hot and the solvent removed from the filtrate under reduced pressure. The residue was dissolved in ether and from the dried solution there was obtained 36 g., or a 87% yield, of 2-cyanomethyldibenzofuran distilling at 202-206°/2mm. After several crystallizations from methyl alcohol the pure compound melted at 102.5-103.5°.

Anal. Calcd. for $C_{14}H_9ON$: N, 6.76. Found: N, 6.75 and 6.96.

An absolute ethanol solution of 13 g. (0.062 mole) of 2-cyanomethyldibenzofuran was reduced with Adams catalyst. Two equivalents of hydrogen were taken up in one hour. After removal of the catalyst and evaporation of the solvent, an 80% yield of 2-β-aminoethyldibenzofuran distilling at 165-170°/2mm. was secured. The hydrochloride melted at 278°, and a mixed melting point with the hydrochloride secured from the phthalimide reaction showed no depression.

Preparation of 4-β-Aminoethyldibenzofuran

A solution of 4-dibenzofuryl-lithium was prepared from 168 g. (1 mole) of purified dibenzofuran, 137 g. (1 mole) of n-butyl bromide, 500 cc. of ether and 14 g. (2 atoms) of lithium. Into this solution was distilled 100 g. (2.27 moles) of ethylene oxide and the resulting solution refluxed for one hour. The reaction was hydrolyzed and worked up in the normal manner. A 45% yield of 4-β-hydroxyethyldibenzofuran distilling at 190-191°/4mm. was obtained. This compound melted at 70-71° after crystallization from petroleum ether (b. p. 60-68°).

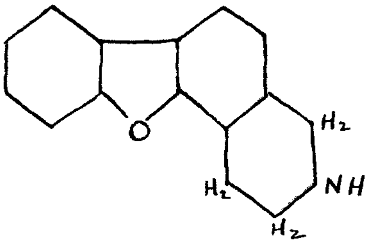
Dry hydrogen bromide was bubbled at a moderate rate through molten 4-β-hydroxyethyldibenzofuran (210 g. or 1 mole) at 100° for eight hours. The reaction product was dissolved in ether and washed with water and sodium carbonate. From the dried ether solution, there was secured an 88% yield of 4-β-bromoethyldibenzofuran, which distilled at 165-170°/2mm. and melted at 37-38°.

An intimate mixture of 30 g. (0.108 mole) of 4-β-bromoethyldibenzofuran and 25 g. (0.135 mole) of potassium phthalimide was heated for six hours at 190-200°. The resulting solid was broken up and boiled with alcohol for a few minutes, and then 15 cc. of hydrazine hydrate was added and the mixture refluxed until a heavy gelatinous precipitate formed. To the cooled solution was added an exce s of hydrochloric acid and the completion of reaction was insured by boiling for a few minutes and then filtering hot. The residue was extracted with four 250 cc. portions of dilute acid, and the filtrates combined and freed of alcohol under reduced pressure. The resulting acid solution was made alkaline and extracted with ether. From the dried ether extract there was secured 14 g., or a 61% yield, of 4-β-aminoethyldibenzofuran which distilled at 165-166°/2mm. The free amine did not react with the carbon dioxide of the atmosphere.

The hydrochloride prepared in the usual manner and twice crystallized from water melted at 263°.

Anal. Calcd. for $C_{14}H_{14}ONCl$: N, 5.66. Found: N, 5.79.

Preparation of Tetrahydropyrido-[5,4-c]-dibenzofuran[59]



A solution of 14 g. (0.066 mole) of 4-β-aminoethyldibenzofuran in a mixture of 27 cc. of glacial acetic acid and 10 cc. of hydrochloric acid was heated to 75° on a water bath. To this warm solution was added dropwise 6 cc. of freshly distilled methylal with shaking. Heating was continued at 75° for three hours. At first the addition of methylal produced cloudiness but as the heating progressed the turbidity disappeared. The clear solution was diluted with water, cooled, and made alkaline with ammonium hydroxide. The basic solution was extracted with ether and the ether extract dried over sodium sulfate. The anhydrous solution was evaporated and the residue distilled at 180-185°/1-2mm. The crude base was twice fractionally distilled under reduced pressure and 3 g. of tetrahydropyrido-[5,4-c]-dibenzofuran distilling at 183-184°/ 1-2 mm. was secured. This is a yield of 20% of pure product.

The hydrochloride, obtained by the saturation of an ethereal solution of the free amine with gaseous hydrogen chloride, melted at 259°.

Anal. Calcd. for $C_{15}H_{14}ONCl$: N, 5.40. Found: N, 5.55 and 5.61.

Preparation of 4-Acetaminodibenzofuran

The 4-dibenzofurancarboxylic acid was prepared in 50% yield by carbonating 4-dibenzofurylsodium. A quantitative yield of the crude acid chloride was obtained from 112 g. (0.52 mole) of 4-dibenzofurancarboxylic acid and 500 g. (4.2 moles) of thionyl chloride. The acid chloride was crystallized from ethyl alcohol, and finally purified by sublimation to melt at 118°.

Anal. Calcd. for $C_{13}H_7O_2Cl$: Cl, 15.22. Found: Cl. 15.24 and 15.11.

The acid chloride was converted quantitatively to the acid amide by treatment with ammonium hydroxide, and melted at 181-182° after crystallization from ethanol. A Hofmann reaction on the acid amide gave yields of 4-aminodibenzofuran ranging from 30 to 50%. The directions followed were those used by Goldschmiedt[62] in preparing 4-aminofluorenone.

To a benzene solution of 4.2 g. (0.023 mole) of 4-aminodibenzofuran was added 3 g. (0.03 mole) of acetic anhydride. This solution was allowed to stand for two hours at room temperature and was then placed in a refrigerator for ten hours. The crude derivative was filtered and washed with petroleum ether. The crude yield was 89%. On recrystallization from aqueous alcohol pure 4-acetaminodibenzofuran was obtained which melted at 172.5°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.16 and 6.21.

Preparation of 7-Amino-1,2,3,4-tetrahydrodibenzofuran

The reduced dibenzofuran was prepared according to the directions of Hönigschmidt. In a typical preparation 50 g. (0.3 mole) of dibenzofuran was reduced with 60 g. (2.6 atoms) of sodium and 400 cc. of absolute ethanol. This mixture was heated for four hours or until the sodium was completely decomposed and then it was diluted with 3 L. of water. The oil was separated, dried and distilled to give a 76% yield of tetrahydrodibenzofuran distilling at 268-272°.

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[62] Goldschmiedt, Monatsh., 23, 890 (1902).

Five grams (0.029 mole) of the reduced compound was placed in a 125 cc. Erlenmeyer flask and cooled to 0°. An ice-cold solution of 4 g. of concentrated nitric acid in 10 cc. of glacial acetic acid was added to the reduced dibenzofuran with agitation. Soon a violent reaction occurred and the nitration product was removed by filtration. On crystallization from alcohol there was obtained a 20% yield of 7-nitro-1,2,3,4-tetrahydrodibenzofuran melting at 124°. A mixed melting point of this compound and a sample of the so-called nitrohexahydrodibenzofuran kindly supplied by Professor Von Braun[3] showed no depression.

A mixture of 8 g. of tin, 75 cc. of hydrochloric acid and 1.3 g. (0.006 mole) of the above nitro derivative was refluxed for 12 hours. After the hydrolysis of the tin complex there was obtained a quantitative yield of the amine hydrochloride, which melted at 269°. The salt was converted to the free amine which, after several crystallizations from aqueous ethanol, melted at 55-56°. The supposed aminohexahydrodibenzofuran prepared by Von Braun[3] was reported to melt at 56°.

The picrate of the amine, prepared in the customary manner melted at 187-188°, which is in agreement with the value reported for the similar derivative of the aminohexahydrodibenzofuran.

The 7-acetamino-1,2,3,4-tetrahydrodibenzofuran was prepared by refluxing a mixture of 5 g. (0.05 mole) of acetic anhydride, 1 g. (0.005 mole) of 7-amino-1,2,3,4-tetrahydrodibenzofuran and 1 g. of fused sodium acetate. The reaction was poured on crushed ice and from the solid material after crystallization from aqueous ethanol there was secured some pure acetamino compound melting at 146°.

Von Braun reported[3] an acetyl derivative of his hexahydroamine to melt at 123°, but undoubtedly his compound was a mixture of the mono- and diacetmino compounds as the analysis was not given.

TABLE I

NAME OF COMPOUND	M. L. D.	M. E. D.	PHARMACOLOGY
Dibenzofuran	4 mg.	---------	Inert
Tetrahydrodibenzofuran	4 mg.	---------	Inert
2-Hydroxydibenzofuran+	2 mg.	---------	Inert
3-Hydroxydibenzofuran+	2 mg.	---------	Inert
4-Hydroxydibenzofuran+	3 mg.	---------	Inert
4,6-Dihydroxydibenzofuran+	12 mg.	---------	Inert
2-Dibenzofurancarboxylic Acid	6 mg.	---------	Inert
3-Dibenzofurancarboxylic Acid+	---------	---------	Inert
4-Dibenzofurancarboxylic Acid	10 mg.	---------	Inert
2-Aminodibenzofuran.HCl	10 mg.	---------	Inert
3-Aminodibenzofuran.HCl	2 mg.	---------	Inert
4-Aminodibenzofuran.HCl	15 mg.	---------	10% of Morphine Analgesia
Pyrido-/3,2-b/-dibenzofuran.HCl	No effect	in 50 and	100 mg./kg. doses
Pyrido-/2,3-b/-dibenzofuran.HCl	No effect	in 50 and	100 mg./kg. doses
Tetrahydropyrido-/3,2-b/-dibenzofuran.HCl	---------	---------	No morphine effect
7-Amino-1,2,3,4-tetrahydrodibenzofuran.HCl	---------	---------	No Morphine effect
2-β-Diethylaminoethyldibenzofuran.HCl+	6 mg.	2 mg.	----------
2-ω-Diethylaminoacetyldibenzofuran.HCl	8 mg.	4 mg.	----------
2-ω-Piperidinoacetyldibenzofuran.HCl	6-10 mg.	4 mg.	----------
Piperidinomethyl-2-dibenzofurylcarbinol.HCl	4-6 mg.	1-2 mg.	No morphine-like symptoms
4-Acetaminodibenzofuran	3.6 mg.	1.2 mg.	Analgesic
6-Tetrahydrodibenzofurancarboxylic Acid	9 mg.	4.5 mg.	----------

+ Prepared by other workers in this laboratory.

TABLE II

NAME OF COMPOUND	M. L. D.
6-Methoxy-1,2,3,4-tetrahydrodibenzofuran*	15 mg.
4-β-Diethylaminoethyldibenzofuran.HCl*	5 mg.
Diethylaminomethyl-2-dibenzofurylmethylcarbinol.HCl	6 mg.
4-β-Diethylaminoethoxydibenzofuran.HCl*	6 mg.
4-β-Piperidinoethoxydibenzofuran.HCl*	7.5 mg.
1-β-Diethylaminoethyl-4-methoxydibenzofuran.HCl*	6 mg.
2-β-Piperidino-α-ethoxyethyldibenzofuran.HCl**	4.5 mg.
Tetrahydropyrido-[3,4-c]-dibenzofuran.HCl	4.5 mg.
1,2,3,4-Tetrahydrodibenzofuran-7-carboxylic Acid*	4.5 mg.
2-β-Diethylaminoethyldibenzofuran.HCl*	4.5 mg.
4-β-Aminoethyldibenzofuran.HCl	3.7 mg.
2-β-Aminoethyldibenzofuran.HCl	6 mg.

Should be α

* Prepared by other workers in this laboratory.

** This compound was described in the Experimental Part as the Ethyl Ether of Piperidinomethyl-2-dibenzofurylcarbinol Hydrochloride.

Discussion of Pharmacological Results

In general the minimum lethal dose (M. L. D.) values were determined by intraperitoneal injection into mice, the value reported being an average of several determinations. The method used for evaluating the analgesic effect (M. E. D.) of the compounds consisted in observing the reflexes set up by pinching the tail or ear of the mouse or otherwise stimulating the animal. The evaluation is not quantitative but is believed to be satisfactory as a preliminary test especially when the work is done by experienced men who can make an excellent comparison with morphine from the knowledge of that substance. The weight reported in each instance is the number of milligrams per animal required to produce the desired result. The use of mice with dibenzofuran compounds has been very advantageous because of the slight solubility of the compounds and because only a small amount of material is required.

The limited number of compounds tested makes it difficult to draw valuable conclusions; however, a few generalizations may be made:

1. The reduction of the dibenzofuran nucleus to give tetrahydro derivatives seems to have little effect on the physiological action.

2. The increasing order of toxicity of the variously substituted amines is 4-, 2-, and 3-aminodibenzofuran.

3. The 4-hydroxydibenzofuran is less toxic than the corresponding 2-, and 3-derivatives, both of which possess the same

M. L. D. None of the hydroxyl compounds produces hypnosis or analgesia.

4. 4-Dibenzofurancarboxylic acid is less toxic than the 2-acid; no report of the 3-acid was made.

5. It appears that the introduction of a two-carbon chain between the dibenzofuran nucleus and the amino group increases the toxicity without increasing the physiological effect.

6. Apparently the reduction of a carbonyl group in a side chain to a carbinol increases the toxicity, but there is a favorable increase in the ratio of M. L. D. to M. E. D.

7. The only compounds to show appreciable analgesic action are the 4-amino- and 4-acetaminodibenzofurans.

It is significant that the 4-substituted derivatives are in general less toxic than the corresponding 2- and 3-isomers. To date there have been no biological tests made on 1-monosubstituted dibenzofurans.

The foregoing pharmacological reports have been made possible through the courtesy of Drs. Dox and Rywater of Parke, Davis and Company.

SUMMARY

A review of the substitution reactions of dibenzofuran has been made. Both mono- and disubstitution reactions have been considered. The orientation of the nitration product of 3-acetaminodibenzofuran has been confirmed; and the structure of the bromination product of the 3-acetamino derivative has been established.

Several N-substituted 3-aminodibenzofurans have been prepared for physiological tests. It has been shown that the Skraup reaction on aminodibenzofurans produces two isomeric pyrido-derivatives. Other derivatives in which the amino group was attached to side chains of various types in dibenzofuran have been synthesized and tested.

The pharmacological reports revealed that the dibenzofuran derivatives investigated in this study are relatively toxic and that they possess physiological action of meagre therapeutic importance. It is, however, significant that the 4-aminodibenzofuran and 4-acetaminodibenzofuran show analgesic action.