

1943

# 1,9-derivatives of dibenzofuran

John Robson Thirtle  
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1,9-DERIVATIVES OF DIBENZOFURAN

by

John Robson Thirtle

A Thesis Submitted to the Graduate Faculty  
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

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Dean of Graduate Collegé

Iowa State College

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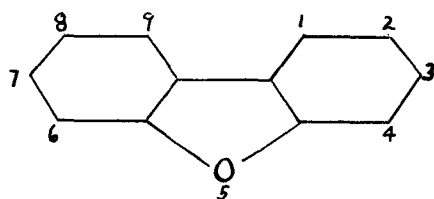
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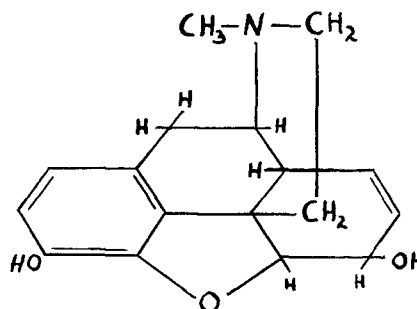
## INTRODUCTION

Several years ago (1,2,3) it was found that certain orienting groups promote substitution in the 1- and 9-positions of the dibenzofuran (I) nucleus. This thesis is primarily a study of the derivatives and substitution products of the compound provisionally designated as 1,9-dibromo-2,8-dimethoxydibenzofuran (3,4).

The importance of the 1,9-derivatives of dibenzofuran is not to be minimized, since it is evident that the dibenzofuran nucleus forms a major part of the morphine skeleton (II) and these derivatives open new approaches to the synthesis of morphine-like compounds.



I



II

1. Gilman and P. R. Van Ess, J. Am. Chem. Soc., 61, 1365 (1939).
2. Gilman and Cheney, ibid., 3149 (1939).
3. Gilman, Swislowsky, and Brown, ibid., 62, 348 (1940).
4. Swislowsky, Doctoral Dissertation, Iowa State College (1939); Iowa State Coll. J. Sci., 14, 92 (1939) [C. A., 34, 6273 (1940)].

The synthesis of morphine itself is not particularly to be desired because of its habit-forming properties and other harmful effects. It is possible, however, that a compound of similar structure, formed by bridging the 1,9-positions in dibenzofuran, may be an effective narcotic or be an intermediate in the preparation of drugs of highly superior qualities.

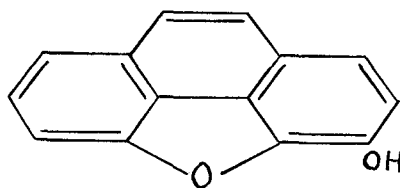
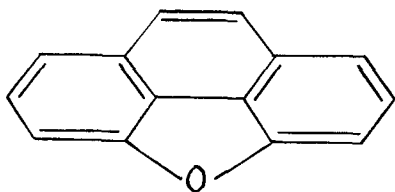
Furan, benzofuran, and dibenzofuran derivatives have been tested for pharmaceutical value. Some furan derivatives have been tested and found to be inert in morphine-like action (5). In tests on 142 compounds (6) of which 124 were dibenzofuran derivatives only 4-aminodibenzofuran showed distinct analgesic activity (10% that of morphine) on white mice. Eighteen others showed slight or doubtful activity. The first 78 compounds in the series (HD) were tabulated by Parker (7). Cheney (8) presented data on HD numbers 79 - 106. Swislowsky (4) listed test results on the compounds through HD 123 and Cook (9) continued the list through HD 142. The series included 18 compounds of related

5. Henecka, Med. u. Chem. Abhandl. med.-chem. Forschungsstätten I. G. Farbenind., 3, 403 (1936) / Chem. Zentr. I, 1146 (1937) /.
6. The tests were carried out by Parke, Davis and Company by courtesy of Dr. Bywater of that company.
7. Parker, Doctoral Dissertation, Iowa State College (1937).
8. Cheney, Doctoral Dissertation, Iowa State College (1938).
9. Cook, Doctoral Dissertation, Iowa State College (1940).

structure such as derivatives of dibenzothiophene, benzofuran, phenanthridine and phenoxathiin.

While there are many unexplored possibilities for pharmaceuticals in the dibenzofuran nucleus, there is still greater promise in a compound of the phenanthrylene oxide type (III) which might be formed by bridging the 1- and 9-positions in dibenzofuran.

Some methods of linking the 1- and 9-positions in dibenzofuran have been proposed by Cheney (8) and by Swislowsky (4) and some of these methods have been tried without success. Phenanthrylene oxide has never been synthesized (10) but morphenol (IV), 3-hydroxyphenanthrylene oxide, has been prepared in about 50% yield by degradation of morphine (11).



10. Small, Eddy, Mosettig, and Himmelsbach, "Studies on Drug Addiction", Public Health Reports Supplement No. 138, Government Printing Office, Washington, D. C. (1938), p. 41.
11. Mosettig and Meitzner, J. Am. Chem. Soc., 56, 2738 (1934).

## HISTORICAL

Dibenzofuran was first synthesized by Lesimple (12) in 1866 by heating phenyl phosphate with lime. Hoffmeister and other workers determined its structure (13). Coal tar is a major commercial source (14) of dibenzofuran, it and its homologs making up about 35% of the fraction boiling between 270 and 350<sup>o</sup> (15). Dibenzofuran is also made commercially by passing phenol vapors over thorium oxide or lead oxide in a heated tube (16).

Dibenzofuran was first used in these laboratories in an attempt to synthesize furan derivatives by oxidative degradation (17). When dibenzofuran and some of its derivatives were found to be resistant to attack, interest was aroused in dibenzofuran itself. Until then, although many derivatives had been made, the position of the substituents had, to a large extent, remained in doubt. Dibenzofuran, therefore, was practically unexploited and this fact, together with its

12. Lesimple, Ann., 138, 376 (1866).
13. Hoffmeister, Ber., 3, 747 (1870); Tauber and Halberstadt, Ber., 25, 2745 (1892); Kraemer and Weissgerber, Ber., 34, 1662 (1901).
14. German patent 491,594 [C.A., 24, 2475 (1930)].
15. Kruber, Ber., 65, 1382 (1932).
16. Cullinane, Davy, and Padfield, J. Chem. Soc., 716 (1934).
17. Oatfield, Thesis, Iowa State College (1933).

close similarity to morphine, greatly stimulated research.

A thorough survey of the literature up to 1933 of all types of dibenzofuran compounds was made by Oatfield (17). The literature to June, 1939, was reviewed by Swislowsky (4) and to late 1942 by Willis (18). The literature to the end of 1942, including any omissions in the previous surveys, is reviewed at the end of this thesis.

The literature of the 1-, 4-, 6- and 9-substituted dibenzofuran derivatives has been adequately covered up to the middle of 1939 by Swislowsky (4). Since then little work has been published on dibenzofuran, much less on the 1- and 9-derivatives.

In general, 1- and 9-substituted dibenzofuran derivatives have been made by direct substitution of dibenzofuran nuclei having the proper orienting groups. There are a few cases in which ring-closure reactions have been effective in preparing 1,9-derivatives but only in poor yield. Tetrazotization of 2,2'-diamino-6,6'-dimethylbiphenyl and heating gave a small yield of 1,9-dimethyldibenzofuran (19).

1,9-Diphenyldibenzofuran (20) has been made from 2,2'-diamino-6,6'-diphenylbiphenyl. One other important synthesis is that

18. Willis, Doctoral Dissertation, Iowa State College (1943).
19. Mascarelli and Tongo, Gazz. chim. ital., 68, 121 (1938). [C.A., 32, 6235 (1938)]/.
20. Sako, Bull. Chem. Soc. Japan, 9, 55 (1934) [C.A., 28, 3730 (1934)]/.

of 1,9-dihydroxydibenzofuran (21) by ring-closure of 2,2',6,6'-tetrahydroxybiphenyl.

Direct substitution to synthesize 1- and 9-derivatives is the most effective method for obtaining satisfactory yields. The desired compounds are generally formed when strong ortho and para directive groups are in the 2-, 2,8-, 4-, or 4,6-positions of the dibenzofuran nucleus.

#### Substitution in the 1- or 9-Position

There is as yet no method of direct substitution in the 1- or 9-position of dibenzofuran except possibly nitration. Yamashiro (22) reported that 1-nitrodibenzofuran, melting at 91 - 93<sup>o</sup>, was obtained as an isomer in the preparation of 3-nitrodibenzofuran. Recently (23) he reported in the nitration of dibenzofuran a 70% yield of 3-nitro, 10% of 2-nitro, and 1% of 1-nitrodibenzofuran. However, the 1-nitro-derivative is reported in the latter publication to melt at 126 - 126.5<sup>o</sup>. This melting point compares favorably with that obtained by Swislowky (4) on his 1-nitrodibenzofuran (m.p. 120 - 121<sup>o</sup>) prepared by deamination of authentic

21. Simada and Hata, Sci. Papers Inst. Phys. Chem. Research (Tokyo), 35, 365 (1939) [C.A., 33, 4594 (1939)]/.
22. Yamashiro, J. Chem. Soc. Japan, 57, 714 (1936) [C.A., 30, 7575 (1936)]/.
23. Yamashiro, Bull. Chem. Soc. Japan, 16, 61 (1941) [C.A., 35, 5111 (1941)]/.



1-nitro-4-aminodibenzofuran. The following transformations, however, prove the compounds are not identical. Reduction of Yamashiro's 1-nitro- compound gave, he reported, the 1-amino- derivative, melting at 113.5 - 114.5<sup>o</sup>. The corresponding acetamino- compound melted at 259 - 260<sup>o</sup>. 1-Aminodibenzofuran (1,24) prepared in these laboratories from authentic 1-bromo- dibenzofuran melted at 74<sup>o</sup> and the 1-acetamino- compound melted at 205<sup>o</sup>. There is no doubt of the authenticity of the latter compounds, and, thus, Yamashiro's work would seem to be in error.

Substitution in the 1- or 9-position of the otherwise substituted dibenzofuran molecule was first accomplished in these laboratories (1,2,3,4,24,25,26,27). P. R. Van Ess (24) definitely proved that bromination of 4-hydroxy- and 4-acetaminodibenzofuran involved the 1- or 9-position. Later, Parker (7) brominated 4-methoxydibenzofuran to obtain the same product which Van Ess obtained by methylation of his bromohydroxy- compound. It was also shown by Parker that the Friedel-Crafts reaction acylates either the 1- or the 9-position when a methoxyl- group is in the 4-position.

24. P. R. Van Ess, Doctoral Dissertation, Iowa State College (1936).
25. Gilman, Jacoby, and Swislowsky, J. Am. Chem. Soc., 61, 954 (1939).
26. Gilman, Parker, Bailie, and Brown, ibid., 2836 (1939).
27. Gilman and M. W. Van Ess, ibid., 3146 (1939).

Nitration of 4-methoxydibenzofuran gives 1- or 9-nitro-4-methoxydibenzofuran (25). It is interesting to note that nitration of the 4-hydroxy-derivative gives the 3-nitro-4-hydroxy-derivative (25). An interesting reaction in which the position of the substituent is dependent upon the experimental conditions is the nitration of 4-acetaminodibenzofuran. Nitration in acetic anhydride at  $-10^{\circ}$  gave a 35% yield of 3-nitro-4-acetaminodibenzofuran (25). On the other hand, nitration in glacial acetic acid at  $70^{\circ}$  gave 1- or 9-nitro-4-acetaminodibenzofuran in 59% yield (4). Bromination of 4-acetaminodibenzofuran gives the 1- or 9-bromo-derivative in almost quantitative yield (1).

It was found by M. W. Van Ess (27) that the benzeneazo coupling reaction with 4-hydroxydibenzofuran gives a product which, based on the nature of diazo coupling reactions, was assumed to be substituted in the same ring. The substitution could have occurred either ortho, to give the 3-benzeneazo-4-hydroxydibenzofuran, or para, to give 1-benzeneazo-4-hydroxydibenzofuran. Reduction to the amine, diazotization, and replacement of the diazonium group with bromine gives the same bromohydroxy-compound obtained by bromination of 4-hydroxydibenzofuran. Since, as it has been mentioned, azo coupling is a homonuclear reaction, the compounds noted previously as either 1- or 9-derivatives are thus proved to be 1-derivatives.

It was found that the dibenzofuran molecule substituted by a strong ortho-para directing group in the 4-position directs halogen to the 1-position even when some other substituents are present. For example, 3-hydroxy-4-methoxy-dibenzofuran brominates in the 1-position (2) in spite of the fact that the hydroxyl group is a strong ortho directing substituent and might presumably direct substitution to the 2-position. As would be expected, 3,4-dimethoxydibenzofuran also brominates in the 1-position (2).

While it has been found that an ortho-para directing group in the 4-position strongly activates the 1-position, the same groups in the 2-position have anomalous effects. For example, 2-acetaminodibenzofuran brominates and nitrates in the 3-position. 2-Methoxydibenzofuran, likewise, brominates in the 3-position almost exclusively. On the other hand, 2-hydroxydibenzofuran gives the 1-bromo-2-hydroxy- derivative together with a small amount of the 3-bromo- compound (1). M. W. Van Ess (27) suggested the possibility of an enolic double bond between the 1- and 2-positions of 2-hydroxydibenzofuran since the latter compound couples with diazo compounds almost quantitatively in the 1-position. This theory would require a double bond also between the 3- and 4-positions. However, the same experimenter found that 3-hydroxydibenzofuran couples in the 2-position, indicating a double bond between positions 2 and 3, and, yet,

4-hydroxydibenzofuran couples in the 1-position, indicating either that there is no fixity of the double bonds in dibenzofuran or that other directive factors, such as the biphenyl or biphenyl ether linkages, play a prominent part.

Dibenzofuran derivatives having groups in the 2-position which form a phenolic group by rearrangement generally rearrange to the 1-position. 2-Allyloxydibenzofuran, under the influence of heat, gives 1-allyl-2-hydroxydibenzofuran (1). 2-Acetoxydibenzofuran, on the other hand, gives a 20% yield of 3-acetyl-2-hydroxydibenzofuran and a smaller amount of 1-acetyl-2-hydroxydibenzofuran when rearranged with aluminum chloride (4).

Ortho-para directing groups in both the 4- and 6-positions activate the 1- or 9-position for monosubstitution. Thus, 4,6-dimethoxydibenzofuran acylates and brominates in the 1- or 9-position (2). Diazo coupling of 4-hydroxy-6-methoxydibenzofuran takes place in the 1-position (2). The same reaction with 4,6-dihydroxydibenzofuran, however, gives a tribenzeneazo- compound. Likewise, bromination of 4,6-dihydroxydibenzofuran has not been controlled to give a monobromo- derivative, a dibromo- compound resulting (2).

It has recently been demonstrated that 2,8-hydroxydibenzofuran can be monobrominated (28) and it has been proved

28. F. A. Yeoman, unpublished studies.

(29) that bromination occurs in the 1-position.

#### Substitution in Both the 1- and 9-Positions

Dibromination of 2,8-dihydroxydibenzofuran (3,4) gives a product which was provisionally designated as 1,9-dibromo-2,8-dihydroxydibenzofuran. This designation is logical, since 2-hydroxydibenzofuran gives the 1-bromo- derivative. Dibromination of 2,8-dimethoxydibenzofuran gives two isomers one melting at 196 - 197<sup>o</sup> and the other at 260 - 261<sup>o</sup>. The former is identical with the product obtained by methylation of the compound designated as 1,9-dibromo-2,8-dihydroxydibenzofuran. The isomer melting at 260 - 261<sup>o</sup> was then provisionally named 3,7-dibromo-2,8-dimethoxydibenzofuran and has since then proved as such (30). Proof of the structure of the so-called 1,9-derivatives has been under study and experimentation for several years. Swislowsky converted the dibromo- derivative to the dimethyl-2,8-dihydroxy- compound and attempted to effect a Bucherer reaction. It was planned to deaminate the resulting 1,9-dimethyl-2,8-diamino- compound to the known 1,9-dimethyldibenzofuran. The Bucherer reaction failed, and zinc dust distillation was, likewise, ineffective. The failure of these reactions may be attributed

29. J. A. Hogg, unpublished studies.

30. Dr. H. B. Willis and F. A. Yeoman, unpublished studies.

to steric factors. It has been demonstrated that 1-methyl-2,8-dihydroxydibenzofuran does undergo a Bucherer reaction in the 8-position but not in the 2-position where a methyl group is ortho (29).

Dimetalation (4) of 2,8-dimethoxydibenzofuran was found to involve the same positions assumed by the bromine atoms in the compound designated as 1,9-dibromo-2,8-dimethoxydibenzofuran.

Recent experiments have indicated that, while one of the bromine atoms in the compound designated as 1,9-dibromo-2,8-dimethoxydibenzofuran is in the 1-position (29), the other is probably in the 7-position (29,31). Until conclusive proof of the position of the second bromine atom is forthcoming, the compounds under consideration will be designated in this thesis as 1,9(?)-derivatives.

This recent work raises doubts about the dibromination products of 4,6-dihydroxy- and 4,6-dimethoxydibenzofuran which were designated as 1,9-derivatives. The monobromination products of these 4,6-derivatives were proved to be 1-bromo-derivatives. Proof of the location of the second bromine atom is lacking. There is reason to believe (28,29,31) that substitution of either the 1- or the 9-position by bromine sterically hinders substitution in the other position. This

31. This thesis.

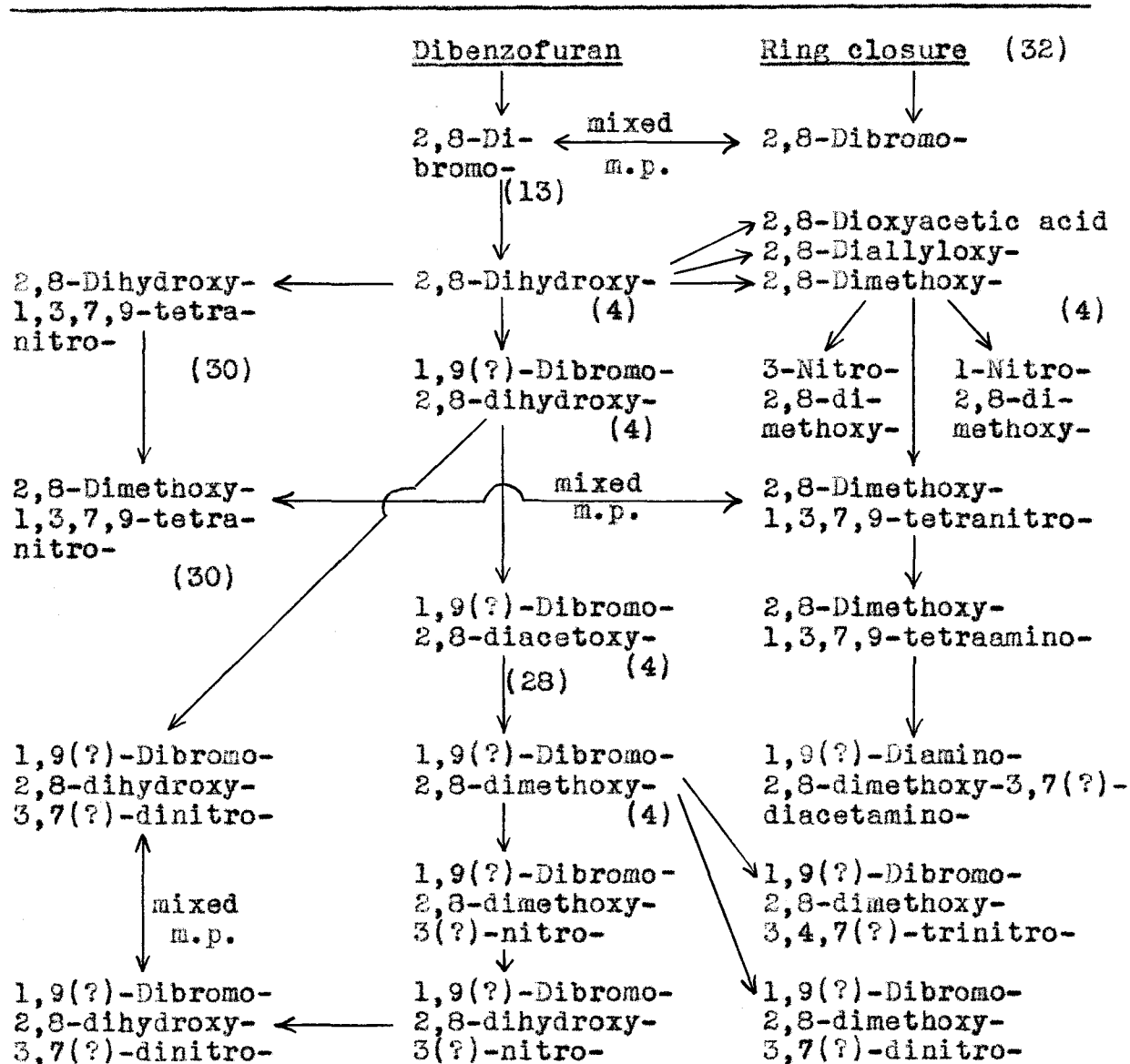
opinion does not apply where smaller groups, such as the nitro-group, are the substituents in question.

An interesting compound is 4-hydroxy-6-methoxydibenzofuran. Dibromination gives a product which, after methylation of the phenolic group, is different from the direct dibromination product of 4,6-dimethoxydibenzofuran. The latter dibromo- derivative is the same as that obtained by bromination, followed by methylation, of 4,6-dihydroxydibenzofuran. The anomalous behavior of the monohydroxymonomethoxy- compound may be a result of steric hindrance in the 9-position after the 1-position is occupied. The most likely place for substitution is then the 3-position, ortho to the hydroxyl- group. This placement would result in 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran. 4,6-Dihydroxy- and 4,6-dimethoxydibenzofuran would be expected to dibrominate heteronuclearly.

The historical development of the 1,9(?) - derivatives of dibenzofuran has, thus, been outlined. The importance of the dibenzofuran nucleus substituted in the 1- and 9-positions has been mentioned (p. 1); its value in a possible synthesis of morphine-like drugs is evident.

EXPERIMENTAL

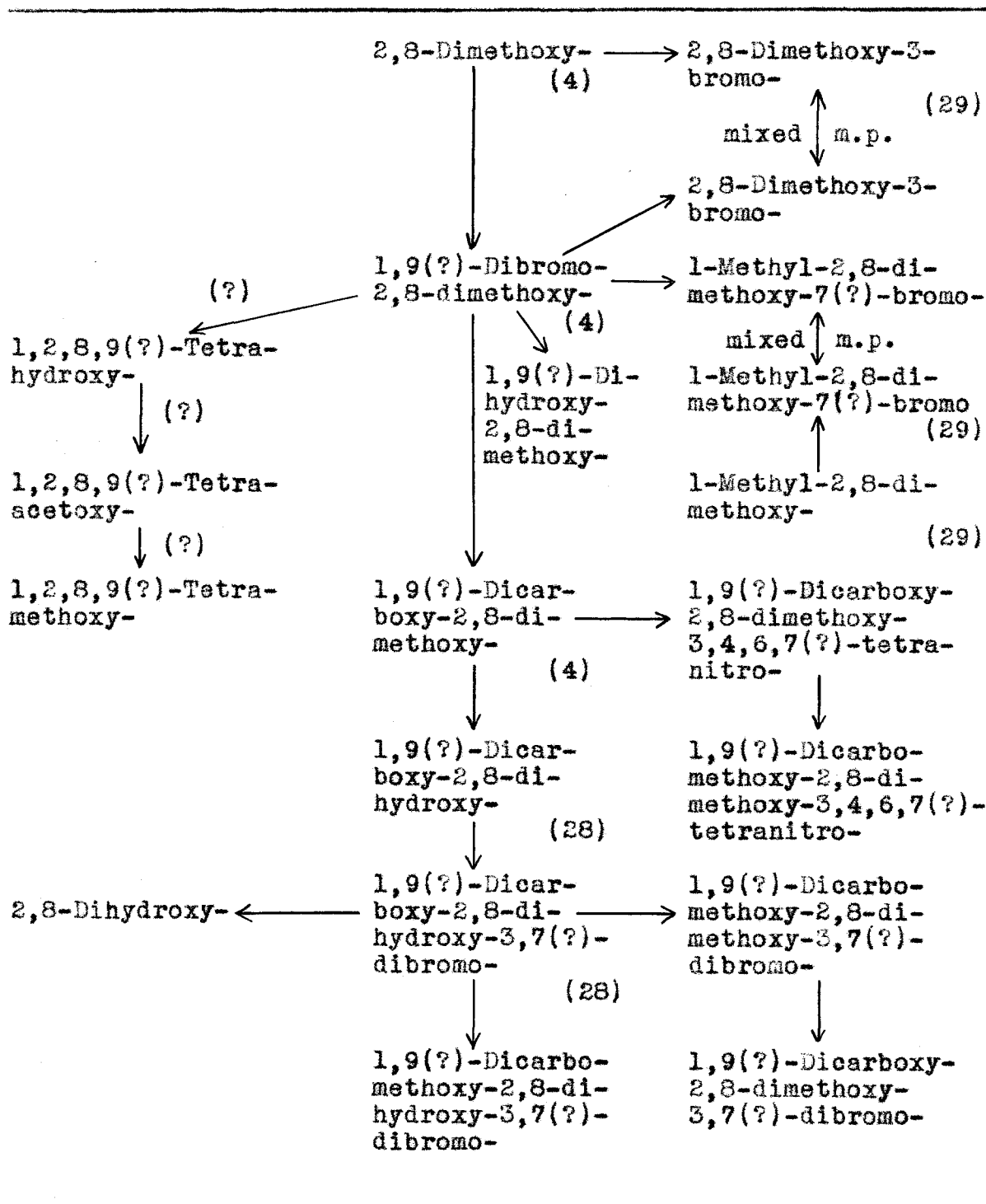
Diagram I. Transformations Involving Both Benzene Nuclei



32. McCombie, MacMillan, and Scarborough, *J. Chem. Soc.*, 531 (1931).



Diagram I. (continued)



#### Deacetylation of 2,8-Diacetoxydibenzofuran

Following the directions of Swislowsky (4), 38.6 g. (0.136 mole) of 2,8-diacetoxydibenzofuran was refluxed for 4 hours with 135 cc. of concentrated hydrochloric acid and 135 cc. of 95% ethanol. The material had not all dissolved at any time. When cooled to room temperature, the entire mixture was poured into 2 l. of water to insure complete precipitation. The dry product weighed 26.2 g. (96.5%), melted at 241 - 242<sup>o</sup>, and was, therefore, pure 2,8-dihydroxydibenzofuran.

#### Bromination of 2,8-Dihydroxydibenzofuran

Ten grams (0.05 mole) of 2,8-dihydroxydibenzofuran was suspended in 125 cc. of glacial acetic acid. While stirring, 99 cc. of a molar bromine solution in glacial acetic acid was added at the rate of one drop per second. The solid gradually went into solution and all was dissolved when about one-half of the bromine solution had been added. After standing for 2 hours, the reaction mixture was transferred to a 2 l. beaker and a liter of water was added with stirring. The dry product of two preparations as described weighed 37.3 g. (103%). This material was not purified but was converted at once into 1,9(?)-dibromo-2,8-diacetoxydibenzofuran.

Preparation of 1,9(?) - Dibromo-2,8-diacetoxy-  
dibenzofuran

The 37.3 g. (0.104 mole) of crude 1,9(?) - dibromo-2,8-dihydroxydibenzofuran described in the preceding preparation was suspended in 225 cc. of acetic anhydride and 0.5 cc. of concentrated sulfuric acid was added. The resulting solution was heated on a boiling water bath for 1 1/2 hours. The solution was well chilled in an ice bath and 50 cc. of water was added through the condenser a few drops at a time at first and with shaking. The product was then poured into a liter of water and the lumps were broken to complete hydrolysis of the acetic anhydride. The dry, white crystalline product weighed 43 g. and melted at 164 - 169°. Crystallization from a mixture of 300 cc. of acetone and 300 cc. of ethanol gave 31.5 g., melting at 167 - 170°. A third crystallization, from 200 cc. of glacial acetic acid, gave 23.8 g. melting at 171 - 173°. A final crystallization from 800 cc. of ethanol gave long white needles melting at 173 - 174°. The yield was 24.0 g. (54.4% based on the weight of 2,8-dihydroxydibenzofuran).

1,9(?) - Dibromo-2,8-diacetoxydibenzofuran has been converted to 1,9(?) - dibromo-2,8-dimethoxydibenzofuran in 82% yield (28). These reactions give a better yield of pure 1,9(?) - dibromo-2,8-dimethoxydibenzofuran than is obtained by direct methylation of the crude 1,9(?) - dibromo-2,8-dihydroxydibenzofuran.

Preparation of 1,9(?) - Dibromo-2,8-dimethoxy-  
3(?) - nitrodibenzofuran

To a solution of 7.72 g. (0.02 mole) of 1,9(?) - dibromo-2,8-dimethoxydibenzofuran in 1.0 liter\* of glacial acetic acid at 85° was added with stirring 50.0 cc. of fuming nitric acid over a period of 10 minutes. Crystals began to form in a few minutes. The reaction mixture was allowed to stir while cooling to room temperature. Six and twenty-eight hundredths grams (73% yield) of product was obtained after filtering and washing, first with glacial acetic acid and then with water. The product was in the form of pink needles and melted at 238 - 241°. After crystallizing from 600 cc. of glacial acetic acid, 6.2 g. of pale yellow needles was obtained melting at 242 - 243°. A second recrystallization of a small portion gave a product melting at 243 - 244°.

Anal. Calcd. for  $C_{14}H_9Br_2NO_5$ : N, 3.25. Found: N, 3.42 and 3.57.

The same product was obtained using acetyl nitrate in acetic anhydride. Nitration is believed to have occurred in the 3-position.

\* A large volume of acetic acid is necessary in this reaction.

Attempted Nitration of 1,9(?) - Dibromo-2,8-  
dimethoxy-3(?) - nitrodibenzofuran

In an attempt to obtain the dinitro- derivative, 0.43 g. (0.001 mole) of 1,9(?) - dibromo-2,8-dimethoxy-3(?) - nitrodibenzofuran was dissolved in 100 cc. of glacial acetic acid at 100°. A solution of 5 cc. of concentrated sulfuric acid in 30 cc. of glacial acetic acid was added with stirring, followed by an acetic acid solution containing 0.001 mole of nitric acid. The temperature was maintained at 100° for 20 minutes, stirring constantly. On cooling, most of the starting material crystallized out. Therefore, another 0.001 mole of nitric acid was added and the reaction mixture was maintained at 100° for 2 hours longer. When cool, 0.14 g. (33%) of the starting material was recovered by filtration. The filtrate was diluted with 200 cc. of water, giving 0.22 g. of yellow material which melted at 175 - 210°. Crystallization from an ethanol and acetone mixture gave 0.070 g. of yellow crystals melting at 205 - 215°. Dilution of the ethanol filtrate gave a yellow material melting at 185 - 190°. Neither of these products could be purified further.

An attempted nitration using acetyl nitrate in acetic anhydride at -15° gave a quantitative recovery of starting material.

Dinitration of 1,9(?) - Dibromo-2,8-dimethoxy-  
dibenzofuran

In an attempt to dinitrate 1,9(?) - dibromo-2,8-dimethoxy-  
dibenzofuran, 3.86 g. (0.01 mole) of this material was  
dissolved in 100 cc. of glacial acetic acid and heated to re-  
flux temperature in a stirring apparatus. Eighty-four  
hundredths of a cubic centimeter (0.02 mole) of fuming nitric  
acid in 25 cc. of glacial acetic acid was added over a period  
of 35 minutes. Stirring and refluxing was continued for one  
hour in addition, the solution becoming a clear ruby red and  
the condensing droplets losing the yellow color of oxides of  
nitrogen. After cooling, a precipitate formed which was  
filtered, washed with glacial acetic acid and then with water.  
This product weighed 2.30 g. and melted at 227 - 233<sup>o</sup>.  
Crystallization from 200 cc. of glacial acetic acid raised the  
melting point to 237 - 239<sup>o</sup>. Further recrystallization gave  
the product previously designated as 1,9(?) - dibromo-2,8-  
dimethoxy-3(?) - nitrodibenzofuran, melting at 243 - 244<sup>o</sup>.  
From the filtrate, on standing, 0.27 g. of yellow  
material settled out. This melted at 200 - 204<sup>o</sup>. Crystalliza-  
tion twice from toluene raised the melting point to 220 - 222<sup>o</sup>.  
A further crystallization from xylene gave a pale yellow  
powder melting at 222 - 223<sup>o</sup>. This product analyzed for two

nitro groups and is probably 1,9(?) -dibromo-2,8-dimethoxy-3,7(?) -dinitrodibenzofuran.

Anal. Calcd. for  $C_{14}H_8Br_2N_2O_7$ : N, 5.88. Found: N, 5.66.

Dilution of the filtrate after removal of the dinitro-derivative gave 1.17 g., melting from 115 to 160<sup>o</sup>. Efforts to isolate a pure product from this material were fruitless.

Trinitration of 1,9(?) -Dibromo-2,8-dimethoxydibenzofuran

In a 50 cc. Erlenmeyer flask was placed 0.50 g. (0.0013 mole) of 1,9(?) -dibromo-2,8-dimethoxydibenzofuran, and a solution of 5 cc. of glacial acetic acid and 5 cc. of fuming nitric acid was added. After heating on a steam bath for one hour, the reaction mixture was poured over crushed ice. When the ice had melted, the pale yellow product was filtered by suction and washed with water. The product weighed 0.26 g. and melted at 190 - 196<sup>o</sup>. After crystallizing twice from dilute acetone .09 g. was obtained melting at 212.5 - 214<sup>o</sup>. This analyzed for three nitro groups per molecule and is, probably, 1,9(?) -dibromo-2,8-dimethoxy-3,4-7(?) -trinitrodibenzofuran.

Anal. Calcd. for  $C_{12}H_7O_9Br_2N_3$ : N, 8.07. Found: N, 8.26.

Preparation of 2,8-Dimethoxy-1,3,7,9(?)  
tetranitrodibenzofuran

Five grams (0.0219 mole) of 2,8-dimethoxydibenzofuran was heated on a steam bath with 30 cc. of fuming nitric acid for one hour. Yellow crystals formed in about 10 minutes. After dilution to 200 cc., 5.66 g. (81.3% yield) of product was obtained melting at 245 - 246<sup>o</sup>. Recrystallization from acetone diluted with water raised the melting point to 246 - 247<sup>o</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>8</sub>N<sub>4</sub>O<sub>11</sub>: N, 13.7. Found: N, 13.6.

This compound proved to be identical (mixed m.p.) with the product made by Dr. H. B. Willis and F. A. Yeoman from 2,8-dihydroxydibenzofuran by nitration and methylation (30). The yield by the method described above is much superior. Because of the strong ortho-directing influence of the hydroxyl- groups and the relatively small size of the nitro- groups compared to bromine atoms, it is believed that these compounds are actually substituted in the 1- and 9-positions by nitro- groups.

Attempted Bromination of 2,8-Dimethoxy-  
1,3,7,9(?) - tetranitrodibenzofuran

To 0.10 g. (0.00025 mole) of 2,8-dimethoxy-1,3,7,9(?) - tetranitrodibenzofuran was added 10 cc. (0.01 mole) of 1 M



bromine solution in carbon tetrachloride. After refluxing for 3 hours, the reaction mixture was cooled and the solid filtered out. There was recovered 0.09 g. (90%) of the starting material, identified by an undepressed mixed melting point.

An attempted bromination of 0.10 g. of the tetranitro-derivative by 2 g. (large excess) of bromine in 20 cc. of boiling acetic acid was, likewise, ineffective even after refluxing for 6 hours.

These experiments were repeated using iron filings, aluminum chloride, and strong sunlight individually and collectively. No bromination occurred, the starting material being recovered in each case.

Preparation of 2,8-Dimethoxy-1,3,7,9(?)  
tetraaminodibenzofuran

Two grams (0.0049 mole) of 2,8-dimethoxy-1,3,7,9(?)  
tetranitrodibenzofuran was suspended in 50 cc. of ethanol and was completely reduced in one hour using Raney nickel at a hydrogen pressure of 40 pounds. After filtering off the catalyst by suction, a stopper was placed in the neck of the suction flask and the solvent was removed without heating. There remained 1.4 g. (99% yield) of grayish-white crystals melting at 181 - 182<sup>o</sup> with decomposition. The product is very unstable when moist or in solution.

Anal. Calcd. for  $C_{14}H_{16}N_4O_3$ : N, 19.4. Found: N, 19.5.

The hydrochloride (1.81 g.; 86% yield) melted at  $242^{\circ}$  with decomposition. Diazotization by the method of Schoutissen (33) to obtain the bromide was unsuccessful.

Acetylation of 2,8-Dimethoxy-1,3,7,9(?)  
tetraaminodibenzofuran

The amine prepared from 2.0 g. (0.0049 mole) of 2,8-dimethoxy-1,3,7,9(?)-tetranitrodibenzofuran by reduction was dissolved in a mixture of acetone and benzene and 2 cc. of acetic anhydride was added. Most of the solvent was removed by distillation. On cooling, a gray precipitate formed which melted at  $235 - 243^{\circ}$ . Two crystallizations from ethanol gave a product melting at  $295 - 296^{\circ}$  (d).

Analysis indicated incomplete acetylation had occurred, giving a diamino-diacetamino compound.

Anal. Calcd. for  $C_{18}H_{20}N_4O_5$ : N, 15.1. Found: N, 15.4, 15.1.

It is believed that steric hindrance prevented acetylation in the 1- and 9-positions and that the compound is 1,9-diamino-2,8-dimethoxy-3,7-diacetaminodibenzofuran.

Preparation of 1,9(?) -Dibromo-2,8-dihydroxy-3(?) -nitrodibenzofuran

Eight grams (0.0186 mole) of 1,9(?) -dibromo-2,8-dimethoxy-3(?) -nitrodibenzofuran was dissolved in a liter of boiling glacial acetic acid. One hundred cubic centimeters of 47% hydrobromic acid was added very slowly\*. The reaction mixture was refluxed for 22 hours and 100 cc. more hydrobromic acid was added and refluxing was continued for 6 hours longer. After cooling, 5.30 g. (70.6% yield) melting at 265 - 266<sup>o</sup> was obtained. Recrystallization from glacial acetic acid raised the melting point to 267 - 268<sup>o</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>5</sub>Br<sub>2</sub>NO<sub>5</sub>: N, 3.48. Found: N, 3.48, 3.73.

Nitration of 1,9(?) -Dibromo-2,8-dihydroxy-3(?) -nitrodibenzofuran

One-tenth of a gram (0.00025 mole) of 1,9(?) -dibromo-2,8-dihydroxy-3(?) -nitrodibenzofuran was dissolved in 20 cc. of glacial acetic acid at 60 - 70<sup>o</sup>. With stirring, 0.70 cc. (0.00025 mole) of a glacial acetic acid solution containing 0.02 g. of nitric acid per cubic centimeter was added. After about one minute the solution turned ruby red. The

\* Slow addition is necessary to maintain solution.

temperature was maintained at 60 - 70° for 10 minutes longer. No precipitate formed when the reaction mixture cooled to room temperature, even after a few cubic centimeters of water had been added. After diluting to 300 cc. and allowing to stand overnight at 0°, 0.030 g. of a bright red solid formed which melted at 201 - 208°. Crystallization from acetic anhydride gave red clusters melting at 204° which did not depress the melting point of the product of the following experiment. The products are, thus, identical.

Nitration of 1,9(?) - Dibromo-2,8-dihydroxy-  
dibenzofuran

One gram (0.00345 mole) of 1,9(?) - dibromo-2,8-dihydroxy-dibenzofuran was dissolved in 15 cc. of glacial acetic acid at 50°. A solution of 0.441 g. (0.007 mole) of nitric acid in 15 cc. of glacial acetic acid was added and, after standing for 10 minutes, the reaction mixture was chilled in an ice bath. After the acetic acid had melted 0.17 g. of bright red crystals melting at 199 - 201° was obtained. In an attempt at acetylation of 0.05 g. of the product in 1 cc. of acetic anhydride, red crystal clusters were obtained after standing for 48 hours at 0°. These melted at 204° with decomposition and were non-acetylated material.

Analysis indicated that dinitration had occurred. The

product is probably 1,9(?)-dibromo-2,8-dihydroxy-3,7(?)  
dinitrodibenzofuran.

Anal. Calcd. for  $C_{12}H_4Br_2N_2O_7$ : N, 6.25. Found: N,  
6.38.

Mononitration of 2,8-Dimethoxydi-  
benzofuran

To a stirring solution of 1.14 g. (0.005 mole) of 2,8-  
dimethoxydibenzofuran in 20 cc. of glacial acetic acid was  
added 0.636 cc. (0.01 mole) of 69.8% nitric acid in 5 cc. of  
glacial acetic acid over a period of one-half hour. After  
stirring for 15 minutes longer, the reaction mixture was  
cooled to 20° and poured over crushed ice. The dry product  
weighed 1.36 g. (99.6%) and melted at 126 - 155°. The  
material was dissolved in boiling ethanol and allowed to cool  
slowly to room temperature. The precipitate, 0.54 g. (40%),  
was filtered off and melted at 168 - 174°. Crystallization  
from dilute acetone gave a product melting at 172 - 174°  
which analyzed for one nitro- group.

Anal. Calcd. for  $C_{14}H_{11}NO_5$ : N, 5.12. Found: N, 5.13.

From the filtrate, after standing overnight, was  
obtained 0.19 g. of needles melting at 148 - 155°. Two  
crystallizations from dilute acetone gave 0.13 g. (10%) melt-  
ing at 158 - 159°. A mixed melting point with the product  
melting at 172 - 174° was depressed to 128 - 153°. This

compound likewise analyzed for one nitro- group.

Anal. Calcd. for  $C_{14}H_{11}NO_5$ : N, 5.12. Found: N, 5.02.

Chilling the filtrate gave 0.37 g. and concentration of all other liquors gave 0.29 g. of product. These crude materials melted at 128 - 155<sup>o</sup> and a repetition of the fractional crystallization process was not made.

The position of nitration has not yet been definitely proved, but it has been shown that the 1-substituted isomer generally has a lower melting point than the 3-substituted isomer. Pending proof, the compound melting at 172 - 174<sup>o</sup> is assumed to be 3-nitro-2,8-dimethoxydibenzofuran, and the compound melting at 158 - 159<sup>o</sup>, 1-nitro-2,8-dimethoxydibenzofuran.

Attempted Bromination of 2,8-Dimethoxydibenzofuran-1,9(?)-dicarboxylic Acid

To 0.5 g. (0.00156 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid (4) in 50 cc. of dry carbon tetrachloride was added 0.05 g. of aluminum chloride and 0.512 g. (0.0032 mole) of bromine in 25 cc. of carbon tetrachloride. The reaction mixture was kept at the reflux temperature for 22 hours without bromination having had occurred. The starting material was recovered unchanged.

A similar experiment in which glacial acetic acid was the solvent was, likewise, unsuccessful. Iron filings were

added, causing a deepening of the color of the reaction mixture, but unreacted starting material was recovered.

Bromination does occur, however, to give a dibromo-derivative when the methoxyl- groups are cleaved (28).

Preparation of 2,8-Dimethoxy-3,7(?) -dibromo-  
1,9(?) -dicarbomethoxydibenzofuran

One and two-tenths of a gram (0.0027 mole) of 2,8-dihydroxy-3,7-dibromodibenzofuran-1,9(?) -dicarboxylic acid (28) was suspended in 50 cc. of ether and an ethereal solution of diazomethane prepared from 2.0 g. of N-nitrosomethyl-urea was added. After standing for 20 hours, the insoluble material was filtered off. It weighed 0.52 g. (38%) and melted at 200 - 210<sup>o</sup>. Crystallization from dioxan raised the melting point to 230 - 231<sup>o</sup> with considerable loss.

Anal. Calcd. for  $C_{18}H_{14}Br_2O_7$ : Br, 31.9. Found: Br, 32.0.

Evaporation of the ether layer gave a resinous material from which only a small quantity of the pure product could be isolated.

Preparation of 2,8-Dihydroxy-3,7(?) -dibromo-  
1,9(?) -dicarbomethoxydibenzofuran

Ten milligrams of 2,8-dihydroxy-3,7(?) -dibromodibenzo-furan-1,9(?) -dicarboxylic acid was dissolved in 1.0 cc. of

dioxan. Ten cubic centimeters of methanol was added and the solution was saturated with dry hydrogen chloride. After refluxing for 2 hours, fine needles had formed. A quantitative yield of product was obtained melting at 268 - 269<sup>o</sup>.

De-esterification of 2,8-Dimethoxy-3,7(?)  
dibromo-1,9(?) -dicarbomethoxydibenzofuran

A solution of 0.050 g. (0.001 mole) of 2,8-dimethoxy-3,7(?) -dibromo-1,9(?) -dicarbomethoxydibenzofuran in 10 cc. of methanol, 10 cc. of a saturated sodium methoxide solution in methanol, and 10 cc. of water was refluxed for 4 hours. Acidification to Congo Red gave white flocs. After dilution to 500 cc. with water, 0.045 g. (95%) of 2,8-dimethoxy-3,7(?) -dibromodibenzofuran-1,9(?) -dicarboxylic acid was obtained melting at 322 - 324<sup>o</sup> with loss of carbon dioxide. A mixed melting point with 2,8-dihydroxy-3,7(?) -dibromodibenzofuran-1,9(?) -dicarboxylic acid (m.p. 318 - 319<sup>o</sup>) was depressed to 295 - 305<sup>o</sup>, indicating that cleavage of the ether linkages had not occurred. The product is very insoluble in glacial acetic acid. It is soluble in hot dioxan.

Anal. Calcd. for C<sub>16</sub>H<sub>10</sub>Br<sub>2</sub>O<sub>7</sub>: neut. equiv., 237.  
Found: neut. equiv., 236.



Attempted Decarboxylation of 2,8-Dimethoxy-3,7(?)  
dibromodibenzofuran-1,9(?)-dicarboxylic Acid

One-tenth of a gram of 2,8-dimethoxy-3,7(?)  
dibromodibenzofuran-1,9(?)<sup>o</sup>-dicarboxylic acid was heated at the melt-  
ing point in a vacuum sublimation apparatus. Repeated sub-  
limations were not successful in isolating a pure decarbox-  
ylated product although some of the sublimed crystals melted  
at 264<sup>o</sup>. Isolation of the proved compound 2,8-dimethoxy-  
3,7-dibromodibenzofuran would partially prove the structure  
of the 1,9(?)<sup>o</sup>-substituted dibenzofuran compounds.

Decarboxylation of 2,8-Dihydroxy-3,7(?)  
dibromodibenzofuran-1,9(?)<sup>o</sup>-dicarboxylic  
Acid

Using the method of Johnson (34) for decarboxylation of  
acids, 0.15 g. of 2,8-dihydroxy-3,7(?)<sup>o</sup>-dibromodibenzofuran-  
1,9(?)<sup>o</sup>-dicarboxylic acid was heated with 1 cc. of quinoline  
and 0.1 g. of copper powder ("Naturkupfer") at 200<sup>o</sup> for one  
hour and at the boiling point for 15 minutes. The quinoline  
was removed by extraction with hot 6 N hydrochloric acid.  
The residue was extracted with hot 5% potassium hydroxide.

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

Acidification of the alkaline extract gave 0.12 g. of compound. The latter was redissolved in the minimum amount of potassium hydroxide solution, diluted to 200 cc., and the solution was saturated with carbon dioxide. A brown solid appeared. Extraction with ether, and distillation of the ether gave a residue which, on solution in 10 cc. of ethanol and dilution, was reprecipitated yielding 0.050 g. of yellow solid melting at 220 - 230°. This product was apparently crude 2,8-dihydroxydibenzofuran (m.p. 240 - 241°), the material being debrominated as well as decarboxylated under these conditions. 2,8-Dihydroxy-3,7-dibromodibenzofuran (m.p. 260 - 261°) is only very slightly soluble in ether and alcohol.

Tetranitration of 2,8-Dimethoxydibenzofuran-  
1,9(?) -dicarboxylic Acid

To 0.316 g. (0.001 mole) of 2,8-dimethoxydibenzofuran-1,9(?) -dicarboxylic acid was added 1 cc. of fuming nitric acid. After standing for 2 minutes, the solution was poured over crushed ice. Filtration gave 0.20 g. of compound melting at 233 - 240°. Two crystallizations from dilute acetone raised the melting point to 247 - 249° and yielded 0.095 g. Analysis indicated the product to be impure, a mixture of the trinitro- (9.33% N) and the tetranitro- (11.30% N) derivatives.

A value of 9.60% N was obtained. Esterification, however, gave a pure product as indicated in the following preparation.

Preparation of 2,8-Dimethoxy-3,4,6,7(?) -tetra-  
nitro-1,9(?) -dicarbomethoxydibenzofuran

The 0.095 g. of product obtained above was refluxed in methanol while passing dry hydrogen chloride into the solution until saturation. After cooling, 0.060 g. of crystals formed which melted at about 200°. After crystallization from dilute acetone the melting point was 199.5 - 200°.

Anal. Calcd. for  $C_{18}H_{12}N_4O_{15}$ : N, 10.68. Found: N, 10.73.

Nierenstein (35) and Erdtman (36) have formed hexa-substituted dibenzofuran compounds by ring closure reactions. This is, however, the first completely substituted dibenzofuran compound.

Reaction of 2,8-Dimethoxydibenzofuran-1,9(?) -  
dicarboxylic Acid with Acetyl Chloride

Many attempts were made to form an anhydride linkage between the 1- and 9-positions in the substituted dibenzofuran molecule. Failing this it was hoped that a diacidanhydride

35. Nierenstein, Ann., 386, 318 (1912).

36. Erdtman, Ann., 513, 240 (1934).

might form which would, on losing a molecule of acetic anhydride, cyclicize to give the desired bridge. The following is a representative experiment.

Five-tenths of a gram (0.0016 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid was refluxed with 10 cc. of acetyl chloride. Solution was effected within one hour and refluxing was continued for 5 hours longer. Colorless plates formed toward the end of the refluxing period. The reaction mixture was chilled in an ice bath and filtered, washing the crystals with ether. The crystals weighed 0.45 g. and melted at 132<sup>o</sup> with decomposition when heated rapidly. The product was insoluble in cold sodium carbonate and cold potassium hydroxide solution. It dissolved in hot potassium hydroxide solution and did not precipitate out when cooled. Acidification of the alkaline solution precipitated 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid. An attempted recrystallization of the crystals melting at 132<sup>o</sup> from glacial acetic acid gave a product melting at 247 - 250<sup>o</sup>. A second crystallization gave a product melting at 258 - 260<sup>o</sup>. Evidently the anhydride, if formed, is not stable and decomposes to give the starting material, 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid, m.p. 271 - 272<sup>o</sup>.

Caustic Fusion of 1,9(?) - Dibromo-2,8-  
dimethoxydibenzofuran

An intimate mixture of 11.58 g. (0.03 mole) of 1,9(?) - dibromo-2,8-dimethoxydibenzofuran, 40 g. of technical sodium hydroxide, 2.4 g. of copper powder, 10 g. of copper turnings, and 15 cc. of an aqueous solution containing 3 g. of  $\text{CuSO}_4 \cdot 6\text{H}_2\text{O}$  was heated in a copper beaker in a bomb at 230 - 240 for 12 hours. The reaction mixture was extracted with three 50 cc.-portions of water. After filtering, the extract was acidified to Congo Red. A tarry precipitate formed. This precipitate, 2.45 g., was refluxed for one hour with 10 cc. of acetic anhydride and 2 drops of concentrated sulfuric acid. After hydrolysis of the excess acetic anhydride and cooling 2.38 g. of brown solid was obtained. A portion of this product decomposed on attempted vacuum distillation. No purification method succeeded in isolating a pure material.

The acid filtrate was extracted several times with ether giving a total of 400 cc. of a red solution. The ether distilled off to about 20 cc. Twenty cubic centimeters of toluene was added and the remaining ether was removed and water was distilled out with toluene, about 2 cc. of toluene remained over a tarry black residue which hardened on cooling. The toluene was decanted off and the residue was refluxed with

3 cc. of acetic anhydride and 2 drops of sulfuric acid for 2 hours. After hydrolysis of the excess acetic anhydride, 0.235 g. of buff colored crystals was obtained melting at 172 - 174°. Vacuum sublimation gave white needles melting at 174.5 - 175.5°. It was supposed that this compound was 1,2,8,9(?) -tetraacetoxydibenzofuran, but the following reaction negated that supposition.

One-tenth of a gram of the supposed 1,2,8,9(?) -tetraacetoxydibenzofuran was dissolved in 2 cc. of dimethyl sulfate and 5 cc. of methanol. With cooling and stirring, 4 cc. of 50% sodium hydroxide solution was added. After standing for 2 hours, the reaction mixture was diluted and filtered. There was obtained 0.060 g. (83%) of product melting at 99 - 100.5°. Crystallization from methanol gave white crystals melting at 100 - 101°.

Anal. Calcd. for  $C_{16}H_{16}O_5$ :  $OCH_3$ , 43.1. Found:  $OCH_3$ , 38.25, 38.13.

The analysis indicated that the product was not 1,2,8,9(?) -tetramethoxydibenzofuran. It probably is a biphenyl derivative, but this has not been definitely established.

Attempted Preparation of 1,9(?) - Dihydroxy-2,8-  
dimethoxydibenzofuran

A filtered solution of n-butyllithium, made from 2.0 g. (0.29 atom) of lithium and 13.0 g. (0.095 mole) of n-butyl bromide in 10 cc. of dry ether, was added with stirring to a solution of 7.72 g. (0.02 mole) of 1,9(?) - dibromo-2,8-dimethoxydibenzofuran in 400 cc. warm dry toluene. The mixture was maintained at the reflux temperature for 15 minutes and was then cooled to  $-5^{\circ}$ . A nitrogen atmosphere was maintained.

A solution of n-butylmagnesium bromide, made from 3.42 g. (0.025 mole) of n-butyl bromide and 0.73 g. (0.03 atom) of magnesium in 30 cc. of ether, was added and a stream of dry oxygen was passed over the surface of the stirring reaction mixture. A tan color was noted almost immediately. After 2 hours color test I was negative. The process was continued for one hour longer.

The reaction mixture was steam distilled to remove ether and toluene. The aqueous residue was filtered, removing 4.3 g. of a gray solid. This material was refluxed with 100 cc. of 5% potassium hydroxide solution for 2 hours and filtered hot. The filtrate was acidified to Congo Red, giving 0.20 g. of material of indefinite melting point. No pure

product was isolated from this material.

The alkaline filtrate from the steam distillation was acidified to Congo Red giving a tarry precipitate. This was filtered and dried and extracted with boiling petroleum ether (b.p. 77 - 115°). After standing at 0°, 0.31 g. (6.0%) of white crystals was obtained melting at 111 - 118°. Recrystallization from petroleum ether gave a melting point of 113 - 117°. From methanol colorless needles melting at 133 - 140° (some at 121°) were obtained. Analysis indicated that the desired product, 1,9(?) - dihydroxy-2,8-dimethoxydibenzofuran had, probably, been obtained though in crude state.

Anal. Calcd. for  $C_{14}H_{12}O_5$ :  $OCH_3$ , 23.85. Found:  $OCH_3$ , 24.36.

The product is probably a mixture of 1(?) - hydroxy- and 1,9(?) - dihydroxy-2,8-dimethoxydibenzofuran.

Reaction of 1,9(?) - Dibromo-2,8-dimethoxydibenzofuran  
with n-Butyllithium (1 Equiv.) and Water

To a refluxing and stirring solution of 1.0 g. (0.0026 mole) of 1,9(?) - dibromo-2,8-dimethoxydibenzofuran in 100 cc. of dry ether and 50 cc. of dry benzene was added dropwise 7.7 cc. (0.0026 mole) of 0.34 N n-butyllithium diluted with 25 cc. of ether. The addition required 10 minutes. After an equal length of time 1.0 cc. of water was added and



the milky solution became clear. The ether-benzene layer was dried over anhydrous calcium sulfate and filtered. Evaporation of the solvent left a pasty solid containing some needles. The material was transferred to a test tube and refluxed with 7 cc. of 95% ethanol for 20 minutes. After filtering hot, the residue weighed 0.20 g. and melted at 185 - 190°. Recrystallization from 7 cc. of glacial acetic acid gave long needles melting at 195 - 196°, evidently starting material (m.p. 196 - 197°).

The alcoholic filtrate was allowed to cool slowly and then was kept at 0° for 2 hours. The 0.06 g. of solid which had formed was filtered off and melted at 140 - 170°. It was crude starting material. The filtrate was heated to boiling and water was added until a slight cloudiness persisted. On shaking in an ice bath, a yellowish oil separated out. The clear solution above the oil was decanted and cooled further and white crystals began to form. After a few minutes the latter were filtered and 0.08 g. (10% yield) of product melting at 100 - 104° was obtained. Crystallization from 2 cc. of 95% ethanol gave white needles melting at 117.5 - 118°. Since this compound is not 1-bromo-2,8-dimethoxydibenzofuran (m.p. 102 - 103°) it would seem that it is 2,8-dimethoxy-3-bromodibenzofuran.

Anal. Calcd. for  $C_{14}H_{11}BrO_3$ : Br, 26.1. Found: Br,

25.9, 26.2.

Exhaustive search was made for 1-bromo-2,8-dimethoxy-dibenzofuran (m.p. 102 - 103<sup>o</sup>) but none was isolated. The crude product seemed to be contaminated by 2,8-dimethoxy-dibenzofuran (m.p. 89<sup>o</sup>).

Recently, Mr. John A. Hogg (29), encouraged by the above work, monobrominated 2,8-dimethoxydibenzofuran and obtained the compound melting at 117.5 - 118<sup>o</sup>. A mixed melting point was not depressed.

These experiments cast doubt on the provisional location of the bromine atoms in the 1- and 9-positions (see Discussion, p. 74).

Reaction of 1,9(?) - Dibromo-2,8-dimethoxydibenzo-  
furan with n-Butyllithium (1 Equiv.) and  
Dimethyl Sulfate

To a stirring solution of 3.86 g. (0.01 mole) of 1,9(?) - dibromo-2,8-dimethoxydibenzofuran in 100 cc. of dry benzene at 65<sup>o</sup> was added 34 cc. (0.01 mole) of a 0.294 N n-butyllithium solution over a period of 15 minutes. Five cubic centimeters (6.5g., 0.052 mole) of dimethyl sulfate in 10 cc. of ether was added slowly. The reaction was vigorous, causing refluxing. After stirring for 30 minutes and finding

color test I (37) negative, 5 cc. of water was added and then 3 g. of potassium hydroxide to destroy the excess dimethyl sulfate. After 5 minutes the ether-benzene layer was dried over calcium chloride. The solvent was removed by distillation, finally using a water pump while heating by a boiling water bath. An oil remained which became a pasty solid on standing. Extraction with three 15 cc.-portions of boiling ethanol left a tan solid which was crude starting material. The ethanol extract showed a tendency to oil out. The supernatant liquid was decanted and cooled under running water, shaking vigorously. A tan gummy precipitate formed and the supernatant liquid was again decanted. Cooling the solution for one hour at 0° gave 0.53 g. of a white solid melting at 100 - 120°. One crystallization from ethanol raised the melting point to 134 - 137°. Two more crystallizations gave tiny white needles melting at 144 - 145°.

Since the preceding experiment showed that the halogen in the 1-position is the more reactive, the compound described above is probably 1-methyl-7-bromo-2,8-dimethoxydibenzofuran.

37. Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

Anal. Calcd. for  $C_{15}H_{13}Br_2O_3$ : Br, 24.9. Found: Br, 25.0, 24.8.

A mixed melting point with the compound melting at 143 - 145<sup>o</sup> obtained by Mr. John A. Hogg (29) by monobromination of authentic 1-methyl-2,8-dimethoxydibenzofuran was not depressed. This fact proves the location of the methyl group in the 1-position of the compound described above.

Attempted Preparation of 1,9-Diamino-  
2,8-dimethoxydibenzofuran

Sodamide was prepared by the procedure of Vaughn, Vogt, and Nieuwland (38).

To 100 cc. of liquid ammonia was added 0.394 g. (0.0171 atom) of sodium and 0.3 g. of  $Fe(NO_3)_3 \cdot 9H_2O$ . To this stirring solution was added 3.0 g. (0.0078 mole) of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran in 50 cc. of dry toluene. After stirring for 2 1/2 hours the reaction mixture was heated to 60 - 70<sup>o</sup> and stirring was continued for 3 hours longer. Ammonium chloride was added to destroy the excess sodamide and 25 cc. of acetic anhydride was added to react with the diamine. After stirring at 60 - 70<sup>o</sup> for 3 hours the reaction mixture was filtered hot and, on cooling, the original material crystallized out.

38. Vaughn, Vogt, and Nieuwland, J. Am. Chem. Soc., 56, 2120 (1934).

### Bromination of 2,8-Diaminodibenzofuran

This experiment was performed in search of 1,9-dibromo-2,8-diaminodibenzofuran. Removal of the amino-groups would give the 1,9-dibromo-derivative which could be converted to 1,9-dimethyldibenzofuran, a known compound, and conversion of 1,9-dibromo-2,8-diamino to 1,9-dibromo-2,8-dihydroxydibenzofuran would prove the latter. The following is a representative attempt to obtain the desired compound.

To 0.50 g. (0.0025 mole) of 2,8-diaminodibenzofuran suspended, by stirring, in 50 cc. of chloroform was added 5.0 cc. (0.0050 mole) of a molar bromine solution in chloroform over a period of 15 minutes. After one hour the tan solid was filtered. It turned gray on drying. The product weighed 0.97 g. (10% above the theoretical) and did not melt below 300°. The fact that an amount of product greater than the theoretical had been obtained indicated that some of the hydrogen bromide which had formed had reacted with the amino-groups. The product was, therefore, refluxed with 1 cc. of 12 N hydrochloric acid in 50 cc. of water, filtered, and the filtrate was made alkaline with ammonium hydroxide. There was obtained thus 0.34 g. of a white solid which melted at 152 - 160° with decomposition. This material was dissolved in 5 cc. of ethanol and diluted with an equal volume of water. After filtration and reheating, the solution was

allowed to cool, giving 0.27 g. of crude crystals melting at 155 - 159°. The same process was repeated except that when white crystals began to form (0.09 g., m.p. 157 - 170°), the supernatant liquid was decanted and cooled, giving 0.11 g. of product melting at 160 - 170°. Dilution of the filtrate with water gave 0.03 g. of product melting at 162 - 164° (?). The latter, however, melted at 174 - 180° when recrystallized from ethanol. No pure product was isolated from this reaction.

When 2,8-diaminodibenzofuran was dissolved in glacial acetic acid and an acetic acid solution of bromine was added, there was an immediate precipitation of a non-melting product such as that described above.

When bromine was carried in a stream of air into a solution of 2,8-diaminodibenzofuran in glacial acetic acid there was a rapid darkening of the solution. In this case, although 4 molecules of bromine were used per molecule of 2,8-diaminodibenzofuran, 15% of the diamino- compound was recovered unreacted.

#### Preparation of 2,8-Diallyloxydibenzofuran

The procedure used in the preparation of 2-allyloxydibenzofuran (1) was followed. A mixture of 20 g. (0.1 mole) of 2,8-dihydroxydibenzofuran, 30.4 g. (0.22 mole) of anhydrous potassium carbonate, 26.6 g. (0.22 mole) of allyl bromide and 50 cc. of acetone was refluxed for 10 hours. The reaction

mixture was poured into 500 cc. of water with stirring. The oil droplets which appeared soon solidified. The product was drawn dry on a suction filter and crystallized from 200 cc. of ethanol giving 21.6 g. (77.2%) of product melting at 70 - 71°.

Anal. Calcd. for  $C_{18}H_{16}O_3$ : C, 77.2; H, 5.71. Found: C, 77.0; H, 5.60.

#### Attempted Rearrangement of 2,8-Diallyloxydibenzofuran

Ten grams (0.0357 mole) of 2,8-diallyloxydibenzofuran was heated in a test tube in a metal bath until the temperature inside the test tube was 220°. An exothermic reaction occurred and the temperature rose rapidly to 275°. The temperature of the bath was raised to 250° and was held there while the internal temperature dropped. When the internal temperature had decreased to 252° (15 minutes), the temperature of the bath was raised to 260° and held there for 20 minutes. On cooling, the contents of the tube set to a glassy solid. The material was scraped out of the test tube and treated with 200 cc. of hot 5% potassium hydroxide solution. The insoluble material was filtered out and the filtrate was acidified to Congo Red with 6 N hydrochloric acid. A brown gummy precipitate (8.0 g.), covered by a milky supernatant liquid, was formed. Attempts to isolate a pure product were fruitless. The product seemed to be a polymer and formed a gummy precipitate from ethanol. No crystals were obtained.

### Preparation of 2,8-Dibenzofuryloxyacetic Acid

By the method of Houben (39) for the preparation of phenoxyacetic acid a solution of 5.5 g. (0.0275 mole) of 2,8-dihydroxydibenzofuran in 25 cc. of 33% sodium hydroxide solution was added to 25 cc. of a 50% aqueous solution of chloroacetic acid. Ten cubic centimeters of water was used to wash the remainder of the alkaline solution into the reaction mixture. After heating on a boiling water bath for 1 1/4 hours and adding 10 cc. of water to redissolve the crystals which formed, the solution was acidified to Congo Red with 6 N hydrochloric acid while still hot. A quantitative yield (8.7 g.) of the product was formed as a white crystalline precipitate. After cooling in an ice bath the product was filtered. It shrinks at 265° and melts at 271 - 273°, losing carbon dioxide slowly.

Anal. Calcd. for  $C_{16}H_{12}O_7$ : neut. equiv., 158. Found: neut. equiv., 155.

### Attempted Fries Rearrangement of 2,8-Diacetoxydibenzofuran

The procedure was essentially that described by Hey and Jackson (40) for the Fries rearrangement of 4-benzoyloxybiphenyl.

39. Houben, Ber., 46, 3988 (1913).

40. Hey and Jackson, J. Chem. Soc., 802 (1936).



Five grams (0.0176 mole) of 2,8-diacetoxydibenzofuran (4) and 30 cc. of sym.-tetrachloroethane were placed in a 200 cc. flask equipped with an efficient sealed stirrer, a condenser protected by a calcium chloride tube, and a hopper for adding aluminum chloride. The contents were stirred at 60° while 5.2 g. (0.039 mole, 10% excess over 0.035 mole) of aluminum chloride was added in small quantities. The reaction mixture thickened considerably. The temperature was raised to 140° for one hour and the reaction mixture was then allowed to stir at room temperature for 6 hours. Following hydrolysis by ice and hydrochloric acid, the solvent was removed by steam distillation and the residue was filtered. The solid material was extracted with hot water and added to the filtrate. The filtrate gave, on cooling, 0.35 g. of pale yellow material melting at 185 - 235°. Recrystallization from ethanol raised the melting point to 240 - 241° and a mixed melting point with 2,8-dihydroxydibenzofuran (m.p. 240 - 241°) was not depressed.

The residue after the extraction with water weighed 2.5 g. and melted at about 145° after crystallization from ethanol. Recrystallization twice more from ethanol raised the melting point to 150 - 151° and a mixed melting point with 2,8-diacetoxydibenzofuran (m.p. 150 - 151°) was not depressed.

There was evidently little, if any, rearrangement. Swislowky (4) reported a 20% crude yield of 2-hydroxy-3-acetyl- and a much smaller yield of 1-acetyl-2-hydroxydibenzofuran

using this procedure.

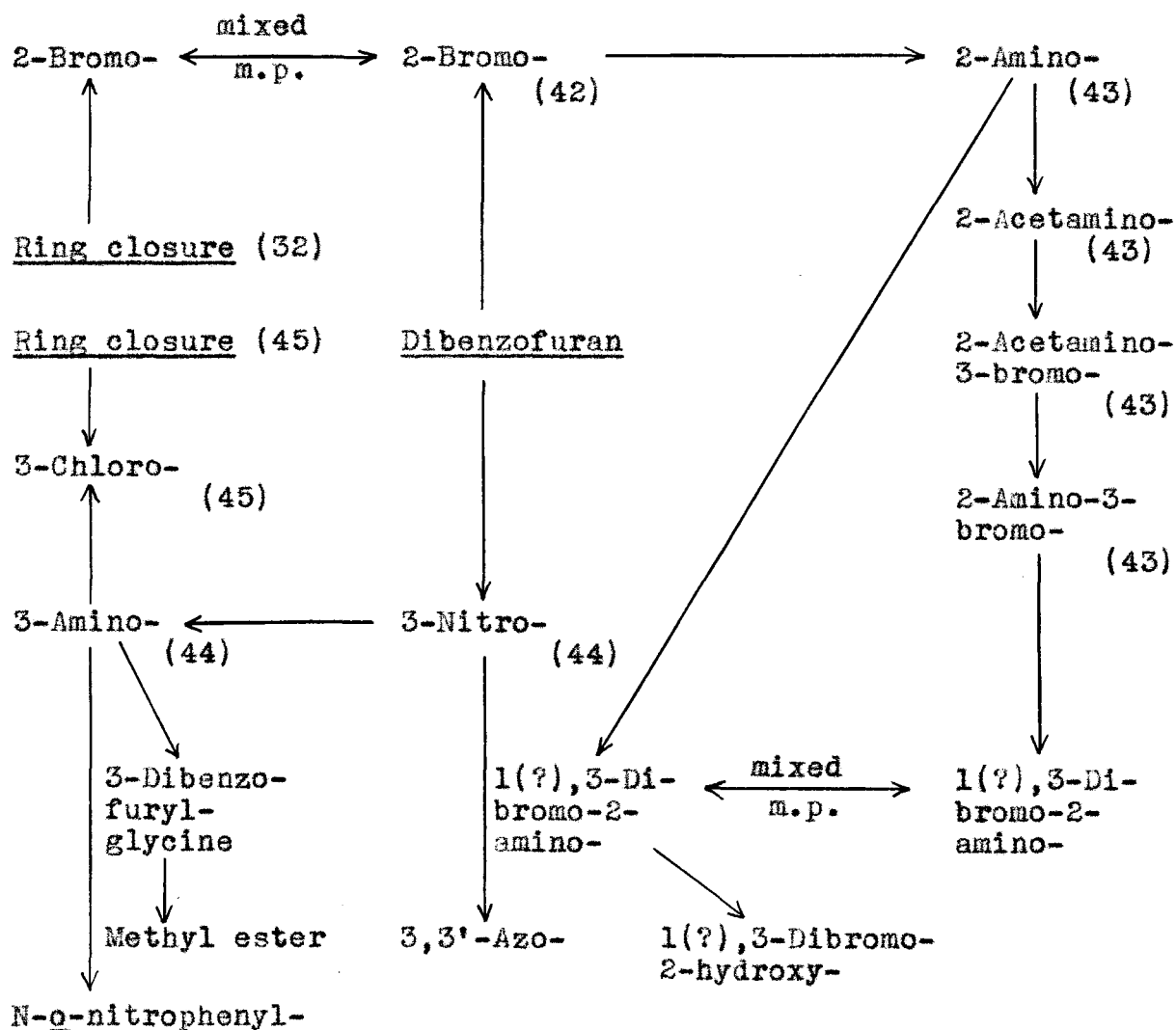
In another experiment, using a procedure adapted from that of Rosenmund and Schnurr (41), 2.84 g. (0.01 mole) of 2,8-diacetoxydibenzofuran was stirred in a test tube immersed in an oil bath at 160°. To the stirring mixture was added 3.32 g. (0.025 mole, 25% excess) of aluminum chloride. The mixture thickened and mechanical stirring had to be discontinued. After stirring manually for 20 minutes, the reaction mixture was cooled to room temperature. The material was removed from the test tube and ground to a powder. It was then suspended in 30 cc. of water and allowed to stand overnight. After filtering and drying, 2.6 g. of material was obtained which melted at 123 - 135°. Crystallization of 1.6 g. from ethanol raised the melting point to that of 2,8-diacetoxydibenzofuran (undepressed melting point at 150 - 151°). The 1.0 g. remaining was allowed to stand for 5 minutes in 10 cc. of 10% sodium hydroxide solution. The solid material was filtered off and found to melt at 134 - 141°. Crystallization from ethanol proved this to be crude 2,8-diacetoxydibenzofuran. The alkaline filtrate was acidified giving a product melting at 240 - 241°. A mixed melting point with authentic 2,8-dihydroxydibenzofuran was not depressed.

This latter experiment indicated that some hydrolytic cleavage of 2,8-diacetoxydibenzofuran had occurred giving

41. Rosenmund and Schnurr, Ann., 460, 56 (1928).

2,8-dihydroxydibenzofuran and that the latter was the only phenolic compound present. Thus, no rearrangement had occurred.

Diagram II. Transformations Involving One Benzene Nucleus



42. Mayer and Krieger, *Ber.*, 55, 1659 (1922).  
 43. Gilman, Brown, Bywater, and Kirkpatrick. *J. Am. Chem. Soc.*, 56, 2473 (1934).  
 44. Borsche and Bothe, *Ber.*, 41, 1940 (1908).  
 45. Cullinane, *J. Chem. Soc.*, 2267 (1930).

### Bromination of 2-Aminodibenzofuran

To a stirring solution of 1.83 g. (0.01 mole) of 2-aminodibenzofuran and 1.0 g. of sodium acetate dissolved in 50 cc. of glacial acetic acid at room temperature was added 10 cc. of 1 M. bromine (0.01 mole) in acetic acid at the rate of one drop per second. After about half of the bromine had been added, a precipitate began to form. The reaction mixture was allowed to stir for 15 minutes after all of the bromine had been added. Filtration gave 1.64 g. of white solid melting at 157 - 153°. The filtrate was made alkaline and 0.87 g. of unreacted 2-aminodibenzofuran was recovered. The 1.64 g. was dissolved with difficulty by 150 cc. of hot ethanol. Cooling gave 0.85 g. (47.5% of dibromination product based on reacted 2-aminodibenzofuran) melting at 178 - 181°. Recrystallization from 150 cc. of ethanol gave colorless needles melting at 181.5 - 182°. The product turns buff colored on exposure to air. Analysis indicated the presence of two bromine atoms. The location of one in the 3-position is proved by the following experiment. The other is believed to be in the 1-position and the product is, therefore, probably 1,3-dibromo-2-aminodibenzofuran.

Anal. Calcd. for  $C_{12}H_7Br_2NO$ : N, 4.11. Found: N, 4.18.

In a small-scale experiment 0.183 g. (0.001 mole) of 2-aminodibenzofuran was dissolved in 3 cc. of glacial acetic

acid, and, with stirring, 1 cc. (0.001 mole) of a molal bromine solution in glacial acetic acid was added. There was an immediate separation of a white solid. The product weighed 0.160 g. and melted at 125 - 135°. Without further purification, this material was dissolved in 5 cc. of benzene, and 0.5 cc. of acetic anhydride was added. After refluxing for one hour, the reaction mixture was hydrolyzed with a few cubic centimeters of water. The solid was filtered out and was found to melt at 195 - 220°. Recrystallization from 2 cc. of ethanol raised the melting point to 254 - 258° and yielded 0.11 g. of product. The product was not purified further or analyzed.

This experiment, which preceded that described above, indicated that bromination of 2-aminodibenzofuran and acetylation did not give 2-acetamino-3-bromodibenzofuran (m.p. 240 - 241°) and prompted further investigation. The product isolated was probably 1,3-dibromo-2-acetaminodibenzofuran.

#### Bromination of 2-Amino-3-bromo-dibenzofuran

A solution of 1.13 g. (0.005 mole) of 2-amino-3-bromo-dibenzofuran (43) in 100 cc. of glacial acetic acid was stirred at room temperature while 25 cc. of an acetic acid solution containing 0.005 mole of bromine was added dropwise.

The addition of bromine was regulated so that the yellow color did not permeate the entire reaction mixture. A white crystalline solid began to form after the first few drops had been added. The reaction mixture was stirred for one-half hour after the last of the bromine had been added. Filtration gave 1.45 g. (85%) of product melting at 176 - 179<sup>o</sup>. Crystallization from 200 cc. of ethanol gave 1.21 g. (71%) melting at 181 - 182<sup>o</sup>. A mixed melting point with the product of direct bromination of 2-aminodibenzofuran was not depressed. The compound is believed to be 1,3-dibromo-2-aminodibenzofuran.

Diazotization of 0.262 g. (0.00077 mole) of the amino-dibromo- compound was effected by the procedure of Misslin (46). The diazonium group was replaced by hydroxyl by adding to a boiling solution of 30 g. of copper sulfate (47) in 125 cc. of water. There was obtained 0.025 g. (9.5%) of product (m.p. 111 - 113<sup>o</sup>) which was volatile with steam. Recrystallization from ethanol raised the melting point to 112 - 113<sup>o</sup>.

Anal. Calcd. for  $C_{12}H_6Br_2O_2$ : Br, 46.8. Found: Br, 47.3, 47.0.

The compound is probably 1,3-dibromo-2-hydroxydibenzofuran.

46. Misslin, Helv. Chim. Acta, 3, 626 (1920) [C.A., 15, 61 (1921)]/.
47. Tatematsu and Kubota, Bull. Chem. Soc. Japan, 9, 448 (1934) [C.A., 29, 1091 (1935)]/.

### Abnormal Reduction of 3-Nitrodibenzofuran

During some reductions of 3-nitrodibenzofuran to 3-amino-dibenzofuran using Raney nickel and hydrogen, reduction stopped at an intermediate stage. From 18 g. of the reaction product of incomplete reduction of 20.0 g. of 3-nitrodibenzofuran was obtained, by crystallization from acetic acid, 2.0 g. of fine, bright yellow needles melting at 268 - 270<sup>o</sup>. This product was very insoluble in most general solvents. It was believed to be 3,3'-azodibenzofuran.

Anal. Calcd. for C<sub>24</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: N, 7.74. Found: N, 7.81.

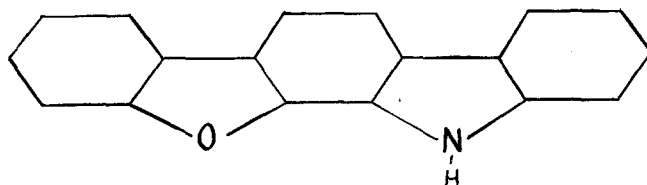
Borsche and Schacke (48) reported the formation of 3,3'-azodibenzofuran (m.p. 282<sup>o</sup>) by reduction of 3-nitrodibenzofuran with sodium and amyl alcohol.

### Attempted Preparation of *o*-Nitrophenyl-3-dibenzofurylamine

Many attempts were made to prepare derivatives of 3-aminodibenzofuran which could be cyclicized to give a combined dibenzofuran and carbazole nucleus (V), derivatives of

48. Borsche and Schacke, Ber., 56, 2498 (1923).





V

which might have desirable analgesic properties. This experiment is representative of the unsuccessful work.

A mixture of 4.0 g. (0.022 mole) of 3-aminodibenzofuran, 3.0 g. (0.022 mole) of *o*-nitroaniline, and 0.1 g. of iodine crystals was heated in a metal bath at 250 - 260° for 5 hours. The evolution of ammonia, noted at the start, gradually diminished as the heating was continued. The temperature was raised to 285 - 290° for 2 hours longer. The solid was extracted with ether and dry hydrogen chloride was passed into the ether solution to precipitate any amine as the hydrochloride. One-tenth of a gram of amine hydrochloride was obtained, which melted at 240 - 245°. When dissolved in water and made alkaline with ammonium hydroxide a yellow precipitate which melted at 89 - 92° was obtained. Insufficient product was obtained for identification. The material was probably crude 3-aminodibenzofuran (m.p. 98°). No pure material could be isolated from the ether-extracted solid.

Preparation of o-Nitrophenyl-3-dibenzofurylamine

A mixture of 5.5 g. (0.03 mole) of 3-aminodibenzofuran, 1.6 g. (0.01 mole) of o-chloronitrobenzene, 0.7 g. (0.01 equiv.) of anhydrous potassium carbonate, 0.05 g. of copper bronze ("Naturkupfer") and 17 cc. of nitrobenzene, which had been neutralized by shaking with potassium carbonate, was refluxed for 22 hours under a steam-heated condenser. The heated condenser allowed the water formed during the course of the reaction to escape but retained the nitrobenzene.

The nitrobenzene was distilled off with steam, and the residue was extracted repeatedly with 3 N hydrochloric acid. From the latter, on treatment with ammonium hydroxide, was obtained a small amount of 3-aminodibenzofuran, melting at 98 - 99°. The residue from this extraction was dissolved in hot toluene. Cooling gave 1.0 g. (30%) of crude yellow product melting at 130 - 135°. Recrystallization from toluene gave 0.31 g. (10.2%) of bright orange crystals, melting at 139.5 - 140°. Analysis indicated that the desired product had been obtained.

Anal. Calcd. for  $C_{18}H_{12}N_2O_3$ : N, 9.21. Found: N, 9.31.

Insufficient product was obtained in these experiments to warrant further work.

### Preparation of 3-Dibenzofurylglycine

The procedure for the preparation of phenylglycine by Houben (39) was followed.

To a solution of 0.95 g. (0.01 mole) of chloroacetic acid and 0.40 g. (0.01 mole) of sodium hydroxide in 8 cc. of water was added 1.83 g. (0.01 mole) of 3-aminodibenzofuran. The mixture was refluxed on a hot-plate. The 3-aminodibenzofuran melted and, after a few minutes, a white solid began to form. After 30 minutes all of the 3-aminodibenzofuran seemed to have reacted. Refluxing was continued, however, until one hour had elapsed. After cooling in an ice bath, the white crystalline material was filtered by suction and washed with ice-water. The product darkened to a buff color on drying and weighed 2.20 g. (91.5%). The product melted at 139 - 142<sup>o</sup> with loss of carbon dioxide above 142<sup>o</sup>. The product was unusually insoluble in alkali. It was insoluble in ether and benzene, slightly soluble in acetone, and soluble in glacial acetic acid.

The succeeding experiment, esterification, indicated that this product was impure and probably contained some 3-dibenzofurylammonium  $\alpha$ -chloroacetate as well as some sodium chloride. The preparation of the glycine derivative was not repeated, however.

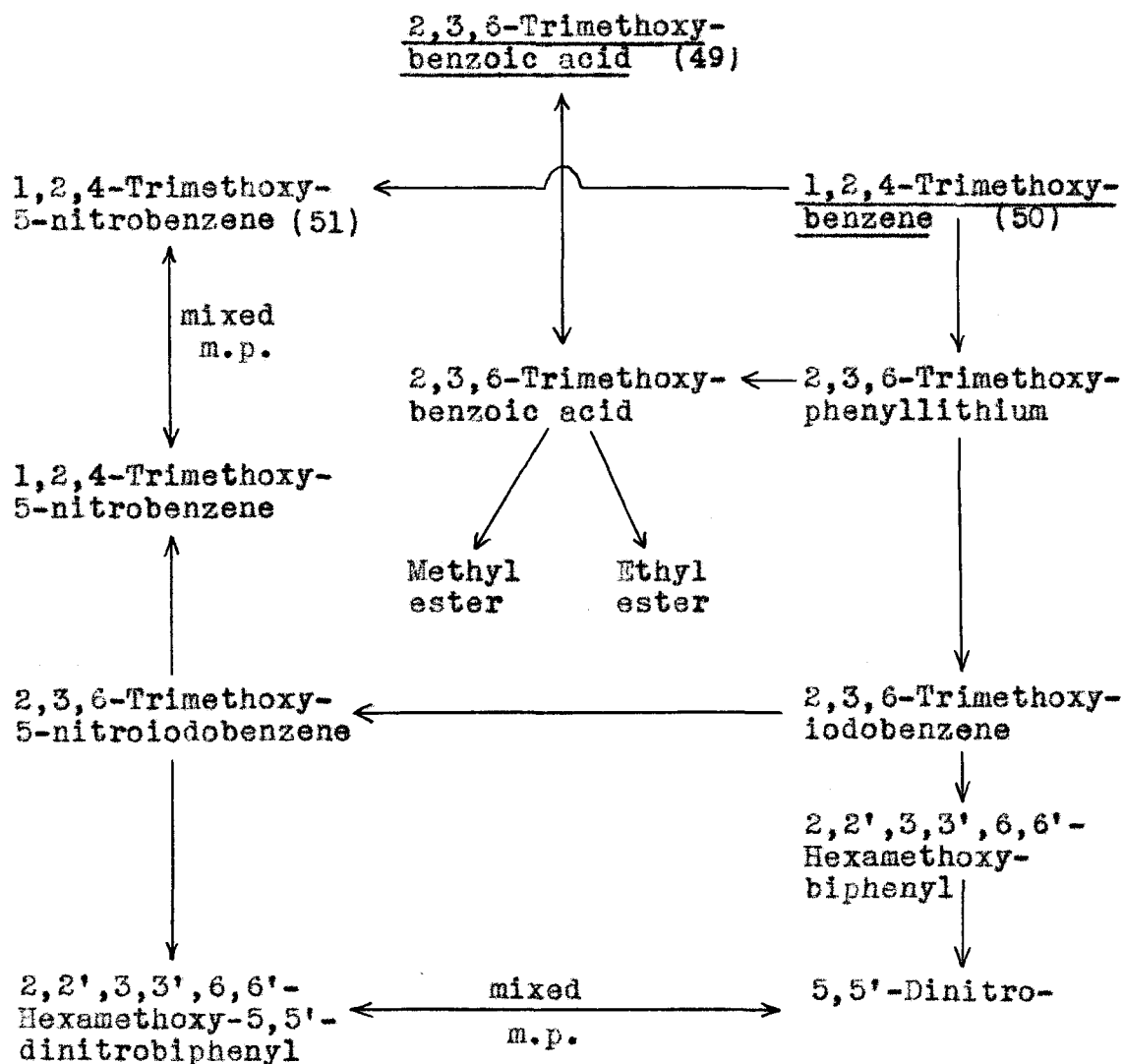
Preparation of 3-Dibenzofurylglycine  
Methyl Ester

One and two-tenths of a gram (0.005 mole) of crude 3-dibenzofurylglycine was covered with 5 cc. of ether and an ethereal solution of diazomethane made by decomposition of 1.0 g. of N-nitrosomethylurea. After standing overnight, ether was added to increase the volume to 20 cc. and the insoluble material was filtered out by suction. The filtrate was evaporated, leaving a clear viscous syrup. Ethanol dissolved the syrup but was inefficient as a crystallizing medium. From dilute methanol was obtained 0.15 g. (12%) melting at 121 - 123<sup>o</sup>. Recrystallization from methanol raised the melting point to 123 - 124<sup>o</sup>.

Obviously the dibenzofurylglycine was impure, possibly containing a considerable quantity of the 3-dibenzofuryl-ammonium salt of chloroacetic acid.

Anal. Calcd. for  $C_{15}H_{13}NO_3$ : N, 5.49. Found: N, 5.85.

Diagram III. Transformations in the Biphenyl System



49. Smith and LaForge, J. Am. Chem. Soc., 53, 3072 (1931).  
 50. Bargellini and Martegiani, Gazz. chim. ital., 41 II, 448 (1911) [Chem. Zentr. II, 1026 (1911)].  
 51. Schuler and Thoms, Arch. Pharm., 245, 267, 276 (1907) [Chem. Zentr. II, 806 (1907)].

### Preparation of 2,3,6-Trimethoxyiodobenzene

To a stirring and refluxing solution of 9.8 g. (0.0583 mole) of 1,2,4-trimethoxybenzene (50) in 100 cc. of dry ether was added 0.0655 mole of n-butyllithium dissolved in 100 cc. of ether. The reaction mixture was refluxed with stirring for 2 hours. The system was allowed to cool under nitrogen, and a Gooch adapter was placed between the reaction flask and the reflux condenser. A Soxhlet thimble was charged with 17.8 g. (0.14 atom) of iodine and was supported in the adapter by means of a piece of clay plate. Stirring was continued and heating was regulated in such a manner that the iodine was dissolved slowly. The reaction of the iodine with the organolithium compound was very vigorous at the start. As the reaction heat diminished, heating was regulated to extract the iodine more rapidly. The entire extraction required 45 minutes. Toward the end a distinct yellow to orange color due to excess iodine was noted and the white, insoluble, organolithium compound had disappeared, a clear solution resulting.

The ether solution was extracted with dilute sodium bisulfite to remove iodine and lithium iodide. After drying over calcium chloride, the ether was evaporated, leaving 10.6 g. (61.5% crude yield) of somewhat oily crystals. Crystallization from 40 cc. of ethanol gave 8.7 g. (51%)

melting at 107 - 108<sup>o</sup>. A second crystallization raised the melting point to 108 - 108.5<sup>o</sup>.

Anal. Calcd. for  $C_9H_{11}IO_3$ :  $OCH_3$ , 31.63. Found:  $OCH_3$ , 31.61, 31.61.

The compound was proved indirectly to be 2,3,6-trimethoxyiodobenzene. Carbonation of the metalation product, described in the next experiment, gave a monobasic acid melting at 149 - 150<sup>o</sup>. This acid, previously synthesized by Smith and LaForge (49) by a lengthy procedure and in very poor yield, was described as melting at 145 - 146<sup>o</sup>. A mixture of equal portions of this latter acid\* with the acid obtained from 1,2,4-trimethoxybenzene melted at 146 - 149<sup>o</sup>, indicating their identity except in purity. Furthermore, the methyl and ethyl esters of the acid obtained by carbonation proved different from those of the other possible products, 2,3,5-trimethoxybenzoic acid (m.p. 105<sup>o</sup>) and the 2,4,5-trimethoxybenzoic acid (m.p. 144<sup>o</sup>). The esters of 2,3,6-trimethoxybenzoic acid have not been reported previously.

Since the acid and the iodo- compound were formed from the same intermediate, the iodo- compound is, thus, proved to be 2,3,6-trimethoxyiodobenzene.

\* The author is indebted to Dr. LaForge and Mr. Smith for this melting point sample.

### Preparation of 2,3,6-Trimethoxybenzoic Acid

To a stirring solution of 6.72 g. (0.04 mole) of 1,2,4-trimethoxybenzene in 150 cc. of dry ether at the reflux temperature was added 100 cc. of 0.4 N n-butyllithium solution. The addition required one-half hour and refluxing was continued for one-half hour longer. The resulting suspension was poured over an excess of "dry ice". Hydrolysis of any excess organometallic was effected with water of which a total of 400 cc. was added. The aqueous layer was acidified to Congo Red and boiled to drive off ether. After cooling thoroughly 4.0 g. (47% yield) of white crystals melting at 148 - 149<sup>o</sup> was obtained. Crystallization from water raised the melting point to 149 - 150<sup>o</sup>.

Anal. Calcd. for  $C_{10}H_{12}O_5$ : neut. equiv., 212. Found: neut. equiv., 219.

The structure of this acid was proved by a mixed melting point determination with an authentic sample (49).

### Preparation of Methyl 2,3,6-Trimethoxybenzoate

2,3,6-Trimethoxybenzoic acid was esterified with great difficulty. One gram was dissolved in 10 cc. of methanol and saturated with dry hydrogen chloride. After refluxing for one hour and cooling no crystals formed. Evaporation left an



oil. The oil was dissolved in ether and washed twice with 10% sodium carbonate solution. The ether layer was dried over anhydrous sodium sulfate and evaporated to dryness. There was obtained 0.3 g. (28% yield) of white crystals melting at 54 - 56°. Crystallization from petroleum ether (b.p. 60 - 68°) raised the melting point to 57 - 57.5°.

Anal. Calcd. for  $C_{11}H_{14}O_5$ :  $OCH_3$ , 54.87. Found:  $OCH_3$ , 54.88.

#### Preparation of Ethyl 2,3,6-Trimethoxybenzoate

One gram of 2,3,6-trimethoxybenzoic acid was dissolved in 6 cc. of ethanol and 1 cc. of concentrated sulfuric acid. After refluxing for one-half hour the reaction mixture was poured into 20 cc. of water. A milky suspension resulted which gave a solid precipitate on standing at 0°. The solid was dissolved in ether and shaken with dilute sodium carbonate solution. After drying the ether layer over anhydrous potassium carbonate, the ether was evaporated, leaving an oil which crystallized on agitation. The crude product melted at 38 - 41°. Crystallization from petroleum ether (b.p. 60 - 68°) raised the melting point to 42.5 - 43°.

Anal. Calcd. for  $C_{12}H_{16}O_5$ : alkoxy, 57.50. Found: alkoxy, 57.41.

Preparation of 2,2',3,3',6,6'-Hexa-  
methoxybiphenyl

The copper powder used in this preparation was of the "Naturkupfer" type. It was purified by the method of Kleiderer and Adams (52). Fifty grams was treated first with a solution of 4 g. of iodine in 200 cc. of acetone for 10 minutes then with a solution of 6 cc. of 6 N hydrochloric acid in 100 cc. of acetone. After drying, an intimate mixture was made with 17.3 g. (0.0588 mole) of 2,3,6-trimethoxyiodobenzene. The mixture was placed in a flask which was attached to an air condenser. While slowly circulating nitrogen above the reaction mixture, heating was effected by an oil bath at 185 - 190° for 3 hours. The temperature was finally raised to 210 - 215° for 15 minutes.

Extraction in a Soxhlet apparatus was effected in one and one-half hours using 250 cc. of acetone. Concentration of the extract to a small volume and dilution with water gave 9.5 g. (97% yield) of crystals melting at 122 - 124°. Crystallization from 30 cc. of hot acetone diluted with water until crystals began to form gave 7.5 g. (76.4%) of product melting at 125.0 - 125.5°.

Anal. Calcd. for  $C_{18}H_{22}O_6$ :  $OCH_3$ , 55.69. Found:  $OCH_3$ , 55.50, 55.68.

52. Kleiderer and Adams, J. Am. Chem. Soc., 55, 4219 (1933).

Attempted Ring Closure of 2,2',3,3',6,6'-  
Hexamethoxybiphenyl

Two-tenths of a gram (0.006 mole) of 2,2',3,3',6,6'-hexamethoxybiphenyl was dissolved in 5 cc. of glacial acetic acid and refluxed for 6 hours with 0.43 cc. (slight excess over 6 moles) of constant boiling hydrobromic acid. The reaction mixture began to darken in a few minutes. A positive test for phenolic material was obtained with ferric chloride. Two cubic centimeters of acetic anhydride and 2 drops of concentrated sulfuric acid were added and refluxing was continued for 2 hours longer. A purple-colored precipitate formed but no pure product could be isolated. Evidently, the polyhydroxy-compound is very unstable. Refluxing 0.1 g. of the hexamethoxy-compound with 2.0 cc. of constant boiling hydriodic acid for one hour resulted in the formation of a great deal of tar.

Two-tenths of a gram of the hexamethoxy-compound was refluxed in 5 cc. of glacial acetic acid with 0.3 cc. of 12 N hydrochloric acid for 6 hours. Ferric chloride gave no red color and dilution with water to 25 cc. and cooling gave an 85% recovery of starting material.

Preparation of 2,2',3,3',6,6'-Hexamethoxy-5,5'-dinitrobiphenyl

It was found that the hexamethoxybiphenyl compound formed an unstable polyhydroxy- compound when cleaved by hydriodic or hydrobromic acid. Since methoxy- groups ortho to nitro- groups are more readily cleaved by acid than those meta or para, the hexamethoxybiphenyl was dinitrated, hoping to obtain the 5,5'-dinitro- derivative. This compound was obtained and its structure was proved.

This preparation is similar to that used by Van Arendonk, Cupery, and Adams (53) for the preparation of 2,2',6,6'-tetramethoxy-3,3'-dinitrobiphenyl. Only one-gram quantities of material were nitrated in shell vials because of the explosibility of the nitrating reagent, acetyl nitrate.

One gram (0.003 mole) of 2,2',3,3',6,6'-hexamethoxybiphenyl was dissolved in 10 cc. of acetic anhydride and 0.5 cc. of concentrated nitric acid. The latter was made by warming fuming nitric acid until colorless. The mixture was heated gently on a hot-plate to start the reaction and then removed from the heat. When boiling had ceased, heating was continued at incipient boiling for 5 minutes. When cool, the product was isolated as follows: Six reaction mixtures were combined in an

53. Van Arendonk, Cupery, and Adams, J. Am. Chem. Soc., 55, 4225 (1933).

Erlenmeyer flask. Ten cubic centimeters of boiling acetic acid was used to rinse all of the shell vials. The crystals which formed were redissolved by slight warming, and 10 cc. of water was added dropwise to hydrolyze the excess acetic anhydride. The solution was kept at 0° overnight giving 6.9 g. (90.5% yield) of yellow crystals melting at 149 - 150°. Crystallization from ethanol raised the melting point to 151 - 151.5°.

Anal. Calcd. for  $C_{18}H_{20}N_2O_{10}$ :  $OCH_3$ , 43.87. Found:  $OCH_3$ , 43.91, 43.77.

The structure was proved by the following experiments.

#### Preparation of 2,3,6-Trimethoxy-5-nitroiodobenzene

2,3,6-Trimethoxyiodobenzene was nitrated desiring to obtain the 5-nitro- derivative which could be coupled by the Ullmann reaction to give 2,2',3,3',6,6'-hexamethoxy-5,5'-dinitro-biphenyl, thus proving the structure of the hexamethoxy-dinitro- derivative obtained in the preceding reaction.

A solution of 3.34 g. (0.0114 mole) of 2,3,6-trimethoxyiodobenzene in 12 cc. of glacial acetic acid at 60° was stirred while 6 cc. of concentrated nitric acid in 20 cc. of acetic acid was added over a period of 5 minutes. Stirring was continued at 60° for 15 minutes longer. After cooling, the crystals were filtered and washed with acetic acid and with water. Two and nine-tenths grams (75.3%) of pale yellow

needles melting at 119.5 - 120<sup>o</sup> was obtained. Dilution of the filtrate gave 0.8 g. melting at 115 - 118<sup>o</sup>. Crystallization from acetic acid gave 0.45 g. more pure product. Dilution of the filtrate again and crystallization from dilute acetic acid gave 0.27 g. more. The total yield of pure product was 3.62 g. (94.1% yield).

Anal. Calcd. for  $C_9H_{10}INO_5$ :  $OCH_3$ , 27.43. Found:  $OCH_3$ , 27.25.

The position of the nitro- group was proved by removal of the iodine atom by hydrogen and palladium-calcium carbonate catalyst. Two-tenths of a gram of the compound was shaken with 1 g. of the catalyst in 20 cc. of absolute ethanol at 15 pounds pressure of hydrogen for 30 minutes. After filtering and noting that no precipitate formed when a small portion was saturated with dry hydrogen chloride, another small portion was evaporated to dryness and gave crystals of the starting material, m.p. 119 - 120<sup>o</sup>. Consequently, the remainder of the filtrate was shaken with 1 g. of catalyst for 2 hours at 30 pounds pressure of hydrogen. After filtering, concentrating to small volume, and cooling, crystals formed which melted at 125 - 127<sup>o</sup>. Recrystallization from ethanol raised the melting point to 128 - 129<sup>o</sup> and a mixed melting point with an authentic sample of 2,4,5-trimethoxynitrobenzene (51), prepared by nitration of 1,2,4-trimethoxybenzene, was not depressed.

Ullmann Coupling of 2,3,6-Trimethoxy-5-nitroiodobenzene

An intimate mixture of 2.0 g. (0.0059 mole) of 2,3,6-trimethoxy-5-nitroiodobenzene and 6.0 g. of specially prepared copper powder (see p. 64) was placed in a Pyrex test tube, covered with a thin layer of copper powder, and protected from air by a closely-fitting cork stopper placed just above the reaction mixture. The tube was placed in a heating bath at 210°. After 5 minutes the stopper rose slightly. Heating was continued at 210° for one hour and 10 minutes. The temperature was raised to 230° and held there for 30 minutes.

The reaction mixture was placed in a Soxhlet apparatus and extracted with 100 cc. of acetone. Evaporation of the acetone gave 0.9 g. of a tarry material. Extraction of this product with boiling petroleum ether (b.p. 60 - 68°) gave 0.2 g. of yellow crystals melting at 142 - 149°. Recrystallization from dilute acetic acid raised the melting point to 147 - 149°. A recrystallization from ethanol gave pale yellow crystals melting at 149.5 - 151° and a mixed melting point with 2,2',3,3',6,6'-hexamethoxydinitrobiphenyl (p. 66) was not depressed. The positions of the nitro-groups in the biphenyl compound are thus proved to be 5,5'.

Attempted Ring Closure of 2,2',3,3',6,6'-  
Hexamethoxy-5,5'-dinitrobiphenyl

Since hydrochloric acid was without effect on hexamethoxybiphenyl, it was hoped that it would preferentially cleave the methoxyl-groups ortho to the nitro-groups in 2,2',3,3',6,6'-hexamethoxy-5,5'-dinitrobiphenyl. Consequently, 0.2 g. of the hexamethoxydinitrobiphenyl was refluxed with 1.0 cc. of 12 N hydrochloric acid and 5 cc. of glacial acetic acid for 2 hours. A negative test for phenolic material was obtained with ferric chloride.

A solution of 1.06 g. (0.0025 mole) of the hexamethoxydinitrobiphenyl compound in 2 cc. of glacial acetic acid was refluxed with 0.58 cc. of constant boiling hydrobromic acid for 5 hours. After pouring over ice, a bright yellow precipitate, weighing 0.95 g., was obtained. The latter was treated with dilute sodium hydroxide to dissolve phenolic material and filtered. The insoluble material weighed 0.1 g. and melted at 148 - 160<sup>o</sup>. The filtrate was acidified giving a yellow solid melting at 66 - 74<sup>o</sup>. No pure product could be isolated; therefore, 0.4 g. was treated with 2 cc. of acetic anhydride and one drop of concentrated sulfuric acid and refluxed for 2 1/2 hours. A tarry material, which could not be purified, resulted.



## DISCUSSION

### Evidence for the Assigned Structures

Many of the compounds synthesized in the course of the work on this thesis were made in approaches to a proof of structure of 1,9(?) -dibromo-2,8-dihydroxydibenzofuran. Their structures, therefore, depend on the structure assigned to 1,9(?) -dibromo-2,8-dihydroxydibenzofuran.

The following transformations are illustrated on Diagram I, pages 14 and 15. 1,9(?) -Dibromo-2,8-dihydroxydibenzofuran was dinitrated to give the same compound that is obtained from 1,9(?) -dibromo-2,8-dimethoxydibenzofuran by mononitration, cleavage of the methoxyl- groups, and further nitration. The compound is probably 1,9(?) -dibromo-2,8-dihydroxy-3,7(?) -dinitrodibenzofuran.

The structures of 2,8-dibenzofuryloxyacetic acid and 2,8-diallyloxydibenzofuran are based on the structural proof of 2,8-dihydroxydibenzofuran.

2,8-Dimethoxydibenzofuran was mononitrated, giving two isomers. By analogy with previous experience, the lower melting isomer is named the 1-nitro- derivative and the higher melting the 3-nitro- derivative. Reduction to the corresponding amines which could be converted to the known bromo-

derivatives would prove the structures of the nitro- compounds.

2,8-Dimethoxydibenzofuran was tetranitrated to obtain the same compound that is given when 2,8-dihydroxydibenzofuran is nitrated and then methylated. By virtue of the strong directive influence of the hydroxyl- groups the assigned structure is 1,3,7,9-tetranitro-2,8-dimethoxydibenzofuran. Moreover, reduction gave a tetraamino- compound which could be only diacetylated, indicating steric hindrance. The latter compound, then, is probably 1,9-diamino-2,8-dimethoxy-3,7-diacetaminodibenzofuran.

2,8-Dihydroxy-3,7(?) -dibromodibenzofuran-1,9(?) -dicarboxylic acid synthesized by Yeoman was converted to the dimethyl ester and, also, to 2,8-dimethoxy-3,7(?) -dibromo-1,9(?) -dicarbomethoxydibenzofuran. The latter was saponified to 2,8-dimethoxy-3,7(?) -dibromodibenzofuran-1,9(?) -dicarboxylic acid. The structures of these compounds will depend for proof upon the structural proof of the starting material.

2,8-Dimethoxydibenzofuran-1,9(?) -dicarboxylic acid was tetranitrated to give, probably, 2,8-dimethoxy-3,4,6,7(?) -tetranitrodibenzofuran-1,9(?) -dicarboxylic acid whose structure depends on the proof of the starting material.

1,9(?) -Dibromo-2,8-dimethoxydibenzofuran was fused with caustic in an attempt to obtain 1,2,8,9-tetrahydroxydibenzofuran. The compound isolated as the acetoxy- derivative and

converted to the methoxy- derivative was not, according to analysis, a tetrahydroxy- compound of dibenzofuran.

1,9(?) -Dibromo-2,8-dimethoxydibenzofuran was monointer-converted and hydrolyzed to give 2,8-dimethoxy-3-bromodibenzofuran which was identified by a mixed melting point with an authentic sample prepared by Hogg (29). Similarly, monointer-conversion and treatment with methyl sulfate gave a bromomethyl-2,8-dimethoxy- derivative which did not depress the melting point of the product of bromination of 1-methyl-2,8-dimethoxydibenzofuran (29). Since the bromine atom which remained after the hydrolysis of the organolithium compound was in the 3-position, the methylbromo- compound is, presumably, 1-methyl-2,8-dimethoxy-7-bromodibenzofuran.

2-Aminodibenzofuran (see Diagram II, page 50) was dibrominated obtaining the same product that was obtained when 2-amino-3-bromodibenzofuran was brominated. Thus, one of the bromine atoms was proved to be in the 3-position. The compound is probably 1,3-dibromo-2-aminodibenzofuran. The proof of structure of 1(?),3-dibromo-2-hydroxydibenzofuran prepared from the amino- compound depends on the latter.

The structures of N-o-nitrophenyl-3-dibenzofurylamine, 3-dibenzofurylglycine, the methyl ester of the latter, and 3,3'-azodibenzofuran depend upon the proved structures of 3-amino- and 3-nitrodibenzofuran.

1,2,4-Trimethoxybenzene (see Diagram III, page 59) was metalated and carbonated to give 2,3,6-trimethoxybenzoic acid and a mixed melting point with an authentic sample (49) was not depressed. The methyl and ethyl esters are, thus, also proved. The 2,3,6-trimethoxyphenyllithium was treated with iodine. The position of the iodine atom is proved by the proof of the acid. 2,3,6-Trimethoxyiodobenzene was coupled to give 2,2',3,3',6,6'-hexamethoxybiphenyl whose proof of structure is based on that of the iodo- compound. 2,3,6-Trimethoxyiodobenzene was nitrated and the product was proved to be 2,3,6-trimethoxy-5-nitroiodobenzene by removal of the iodine atom by hydrogen. The resulting 1,2,4-trimethoxy-5-nitrobenzene was identical (mixed m.p.) with that prepared by direct nitration (51) of 1,2,4-trimethoxybenzene. 2,3,6-Trimethoxy-5-nitroiodobenzene was coupled to give 2,2',3,3',6,6'-hexamethoxy-5,5'-dinitro-biphenyl. The same compound was prepared by direct nitration of 2,2',3,3',6,6'-hexamethoxybiphenyl. A mixed melting point showed no depression.

#### Validity of 1,9-Derivatives

When Swislowsky (4) isolated from the bromination of 2,8-dihydroxydibenzofuran a dibromo- derivative, it appeared that, by analogy with the bromination of 2-hydroxydibenzofuran (1), the 1,9-dibromo- derivative had been formed. Methylation

gave a product which was provisionally designated as 1,9(?)  
dibromo-2,8-dimethoxydibenzofuran. The same product, together  
with the 3,7-dibromo- derivative, was formed when 2,8-dimethoxy-  
dibenzofuran was dibrominated. The compound designated as  
2,8-dimethoxy-3,7-dibromodibenzofuran has since been proved by  
ring closure by Willis (18) and Yeoman (28). Swislowsky (4)  
converted the 1,9(?)-derivative to 1,9(?)-dimethyl-2,8-dihydroxy-  
dibenzofuran and attempted to make 1,9(?)-dimethyl-2,8-diamino-  
dibenzofuran by the Bucherer reaction. This compound, by  
deamination, would give 1,9-dimethyldibenzofuran, a known  
compound. Unfortunately, the Bucherer reaction failed to occur.  
Likewise, a zinc dust distillation was unsuccessful.

Since a dibenzofuran molecule substituted in the 1- and  
9-positions is a very important compound, possibly as an inter-  
mediate in a synthesis of a morphine-like molecule, a great  
deal of time and effort was expended in various approaches to  
a proof of its structure. Some of these approaches are des-  
cribed in this thesis.

1,9(?)-Dibromo-2,8-dimethoxydibenzofuran was nitrated  
(see Diagram I, p. 14) with the hope of obtaining the 3,7-  
dinitro- derivative. A dinitro- derivative was obtained in  
very small yield and was not used in further reactions. Hydro-  
genation would have given a diamino-2,8-dimethoxy- compound  
which could have been converted to a dibromo-2,8-dimethoxy-  
derivative. If the original bromine atoms had been in the

1- and 9-positions, the resulting dibromo- compound would probably have been the 3,7-dibromo-2,8-dimethoxy- derivative.

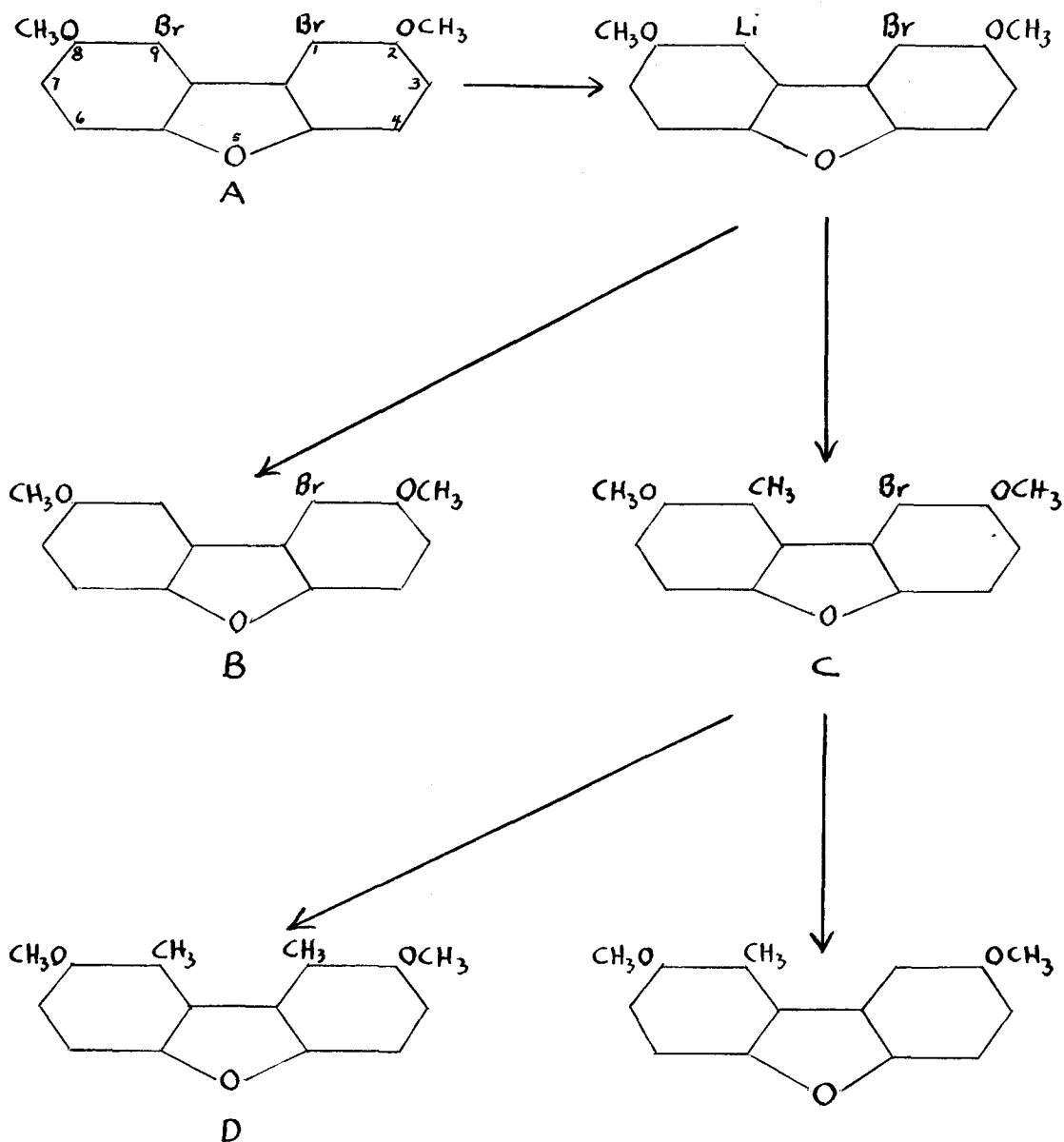
In another approach, 2,8-dimethoxydibenzofuran-1,9(?) -dicarboxylic acid was nitrated (Diagram I, page 14) hoping to get the 3,7-dinitro- derivative. The latter could be decarboxylated and the resulting 2,8-dimethoxy-3,7-dinitro- compound converted to 2,8-dimethoxy-3,7-dibromodibenzofuran. In this case, however, the only product isolated was 2,8-dimethoxy-3,4,6,7(?) -tetranitrodibenzofuran-1,9(?) -dicarboxylic acid.

A third approach was by a ring closure synthesis of 1,2,8,9(?) -tetrahydroxydibenzofuran. Although the proper biphenyl derivative was synthesized (Diagram III, page 59) the ring closure was not successful.

Another approach was that of bromination of 2,8-diaminodibenzofuran. Swislow (4) brominated 2,8-diacetaminodibenzofuran and obtained the 3-bromo- derivative. Bromination of the diamino- compound, like that of 2,8-dihydroxydibenzofuran, was expected to give the 1,9(?) -dibromo- derivative. Polyhalogenation seemed to occur, however. 2-Aminodibenzofuran brominated very rapidly to give 1(?),3-dibromo-2-aminodibenzofuran (31), and thus, polybromination probably occurred when 2,8-diaminodibenzofuran was treated likewise.

The most marked gains were made in the proof when

Yeoman (28) monobrominated 2,8-dihydroxydibenzofuran and Hogg (29) proved that the bromine entered the 1-position. To utilize this information, the author set out to perform the reactions indicated below.



If the reactions had occurred as designated and in good yield the compound (A) would have been proved as drawn, namely, 1,9-dibromo-2,8-dimethoxydibenzofuran. However, compound (B) was not 1-bromo-2,8-dimethoxydibenzofuran as drawn but did, nevertheless, analyze for a monobromo-2,8-dimethoxy- derivative. This led to the opinion that one of the bromine atoms was in neither the 1- nor the 9-position. Recently Hogg (29) monobrominated 2,8-dimethoxydibenzofuran and obtained the same monobromo- derivative and proved that substitution had occurred in the 3-position. Thus, the compound obtained by monointerconversion and hydrolysis of 1,9(?) -dibromo-2,8-dimethoxydibenzofuran was 3-bromo-2,8-dimethoxydibenzofuran. Compound (C) proved to be identical with the product of bromination of 1-methyl-2,8-dimethoxydibenzofuran (29). Hydrogenation was, thus, unnecessary to prove the position of the methyl- group.

Replacement of the bromine atom in (C) by a methyl-group would have given the 1,9(?) -dimethyl- derivative but not the actual 1,9-dimethyl- compound designated by (D) since it was shown that the bromine atom was not in the 1-position.

These reactions quite definitely prove that, though one bromine atom is in the 1-position, the other is not in the 9-position. There remain, then, two possibilities, excluding direct substitution into the 4- or 6-position. The compound designated as a 1,9(?) -derivative could be a 1,3(?) -derivative



or a 1,7(?)-derivative. The former would be likely to undergo a Bucherer reaction in the 8-position. However, Swislowsky recovered his starting material unreacted. If there is to be interference with both hydroxyl- groups in the dimethyl-2,8-dihydroxy- compound, then the methyl- groups must be ortho to both of the hydroxyl- groups. This allows only three possible arrangements, 1,9-, 3,7-, or 1,7-dimethyl-2,8-dihydroxydibenzofuran. The first possibility is excluded by the proof that one of the bromine atoms is in neither the 1- nor the 9-position. The second possibility is a known compound which is different from the compound in question. By exclusion, then, the derivative provisionally designated as 1,9(?)-dibromo-2,8-dihydroxydibenzofuran is shown to be, probably, 1,7-dibromo-2,8-dihydroxydibenzofuran.

It has been concluded by Hogg, Yeoman, and this writer that the entrance of a second bromine atom in the 9-position is sterically hindered by the bromine atom already in the 1-position. This theory may apply also to the derivatives previously described as 1,9-dibromo-4,6-dihydroxy- and 1,9-dibromo-4,6-dimethoxydibenzofuran (2). The structure of 1-bromo-4,6-dimethoxydibenzofuran is definitely established. That of the dibromo- derivative has not been proved. Doubt that these are 1,9-derivatives is aroused by the behavior of 4-hydroxy-6-methoxydibenzofuran toward bromine (2). When

4,6-dihydroxydibenzofuran was brominated and methylated the product was the same as that obtained by direct bromination of 4,6-dimethoxydibenzofuran (2). Van Ess (1) showed that bromination of 4-acetaminodibenzofuran gave the 1-bromo-derivative. Likewise, the 4-methoxy- (7) and 4-hydroxy- (1) compounds gave substitution in the 1-position. Therefore, it was assumed that the dibrominated products obtained from 4,6-dihydroxy- and 4,6-dimethoxydibenzofuran were 1,9-derivatives. However, when 4-hydroxy-6-methoxydibenzofuran was dibrominated and methylated, the product was not the so-called 1,9-dibromo-4,6-dimethoxydibenzofuran.

This anomalous behavior seems to be attributable to the hydroxyl- group, and Cheney (2) postulated what is probably the correct structure, 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran. With this in mind it is difficult to understand why the yield of the compound designated as 1,9-dibromo-4,6-dihydroxydibenzofuran was almost quantitative. One would expect some 1,7- and, possibly, 1,3-dibromo- derivative if the hydroxyl- group directs bromine to the ortho position so strongly as is indicated by the 4-hydroxy-6-methoxy- compound.

On the basis of the theory of steric hindrance by bromine already in the 1-position these disagreeing results can be explained. In the bromination of 4,6-dihydroxydibenzofuran, the first bromine can enter the 1-position without interference.

The second bromine is, however, hindered and can enter the 8-position, para to the biphenyl ether linkage, or the 7-position, ortho to the 6-hydroxyl- group. Since the hydroxyl- group exerts greater directive influence than the ether linkage, the second bromine atom probably enters the 7-position. The same reasoning holds for the dibromination of 4,6-dimethoxydibenzofuran.

When 4-hydroxy-6-methoxydibenzofuran is brominated, however, the first bromine should enter the 1-position. The second can then enter the 8-, 7-, or the 3-position. Since the hydroxyl- group is the most powerful directing agent in the molecule, the second bromine probably enters ortho to it in the 3-position, giving 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran. The reported yields may also give some insight into this theory. 4,6-Dihydroxydibenzofuran dibrominated quantitatively, giving a single product; 4,6-dimethoxydibenzofuran gave a 74% yield of the dibromo- derivative; 4-hydroxy-6-methoxydibenzofuran, however, gave only a 58.6% yield of the so-called 1,3-derivative. The latter yield may indicate that at least some of the bromine entered the other ring, possibly in the 7-position.

If these are not 1,9-derivatives, the outlook is still not hopeless. It is felt that groups smaller than the bromine atom or with greater freedom of rotation can be substituted in

both positions. Also, when 2,8-dimethoxydibenzofuran is tetranitrated, two of the nitro- groups probably enter the 1- and 9-positions. Reduction to the tetraamino- derivative and acylation gave a diaminodiacetamino-2,8-dimethoxy- compound, indicating that two of the amino- groups were sterically hindered from acylation (31). These two groups are probably in the 1- and 9-positions. 2,8-Dimethoxydibenzofuran can be mononitrated giving two isomers, probably the 1- and the 3-nitro- derivatives (31). It may be possible, then, to nitrate 1-bromo-2,8-dimethoxydibenzofuran to obtain 1-bromo-9-nitro-2,8-dimethoxydibenzofuran. Such a compound could be converted into a number of 1,9-derivatives which might be useful intermediates in the synthesis of a morphine-like structure.

SUMMARY

1. The preparation of 1- and 1,9(?) -substituted dibenzofuran compounds has been discussed.
2. Nitration of 1,9(?) -derivatives has been studied.
3. The 1,9(?) -derivatives have been proved to be not 1,9- as designated, and evidence has been given that they are, probably, 1,7-derivatives.
4. Evidence for steric hindrance in the 1- and 9-positions has been discussed.

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\* For references 1 - 81 see Oatfield (17), for references 82 - 168 see Swislowsky (4), and for references 169 - 203 see Willis (18). This bibliography supplements the previous compilations and includes the published work up to January, 1943.