Synthetic dibenzofurans structurally related to known analgesics

Frederick Albert Yeoman
Iowa State College

Follow this and additional works at: https://lib.dr.iastate.edu/rtd

Part of the Medicinal and Pharmaceutical Chemistry Commons, Medicinal Chemistry and Pharmaceutics Commons, Medicinal-Pharmaceutical Chemistry Commons, and the Organic Chemistry Commons

Recommended Citation
Yeoman, Frederick Albert, "Synthetic dibenzofurans structurally related to known analgesics" (1944). Retrospective Theses and Dissertations. 14954.
https://lib.dr.iastate.edu/rtd/14954

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.
NOTE TO USERS

This reproduction is the best copy available.
SYNTHETIC DIBENZOFURANS STRUCTURALLY
RELATED TO KNOWN ANALGESICS

by

Frederick Albert Yeoman

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

In Charge of Major Work

Head of Major Department

Dean of Graduate College

Iowa State College

1944
INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.
ACKNOWLEDGMENT

The author is sincerely grateful to Dr. Henry Gilman, whose valuable suggestions and encouragement have been of great assistance during the course of these studies.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL</td>
<td>5</td>
</tr>
<tr>
<td>Derivatives of Morphine</td>
<td>5</td>
</tr>
<tr>
<td>Derivatives of Phenanthrene, Dibenzo[1,4]furan, and Carbazole</td>
<td>12</td>
</tr>
<tr>
<td>Miscellaneous Pain-Relieving Compounds</td>
<td>20</td>
</tr>
<tr>
<td>Derivatives of Dibenzo[1,4]furan</td>
<td>25</td>
</tr>
<tr>
<td>EXPERIMENTARY</td>
<td>35</td>
</tr>
<tr>
<td>Nitration of 2,8-Dihydroxydibenzo[1,4]furan</td>
<td>35</td>
</tr>
<tr>
<td>Methylation of 1,3,7,9(1)-Tetranitro-2,8-dihydroxydibenzo[1,4]furan</td>
<td>36</td>
</tr>
<tr>
<td>Preparation of 1,9(1)-Dibromo-2,8-diacetoxydibenzo[1,4]furan</td>
<td>37</td>
</tr>
<tr>
<td>Methylation of 1,9(1)-Dibromo-2,8-diacetoxydibenzo[1,4]furan</td>
<td>38</td>
</tr>
<tr>
<td>Conversion of 1,9(1)-Dibromo-2,8-dimethoxydibenzo[1,4]furan to 2,8-Dimethoxydibenzo[1,4]furan-1,9(1)-dicarboxylic Acid</td>
<td>39</td>
</tr>
<tr>
<td>Attempted Bromination of 2,8-Dimethoxydibenzo[1,4]furan-1,9(1)-dicarboxylic Acid</td>
<td>40</td>
</tr>
<tr>
<td>Demethylation of 2,8-Dimethoxydibenzo[1,4]furan-1,9(1)-dicarboxylic Acid</td>
<td>41</td>
</tr>
<tr>
<td>Bromination of 2,8-Dihydroxydibenzo[1,4]furan-1,9(1)-dicarboxylic Acid</td>
<td>42</td>
</tr>
<tr>
<td>Attempted Decarboxylation of 2,8-Dihydroxy-3,7(1)-dibromodibenzo[1,4]furan-1,9(1)-dicarboxylic Acid</td>
<td>43</td>
</tr>
<tr>
<td>Attempted Amination of 1,9(?)-Dibromo-2,8-dimethoxydibenzofuran</td>
<td>44</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Attempted Amination of 1,9(?)-Dibromo-2,8-dimethoxydibenzofuran with Sodamide</td>
<td>45</td>
</tr>
<tr>
<td>Preparation of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde</td>
<td>46</td>
</tr>
<tr>
<td>Preparation of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde Dioxime</td>
<td>47</td>
</tr>
<tr>
<td>Oxidation of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde</td>
<td>48</td>
</tr>
<tr>
<td>Reaction of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde with Hydrazine</td>
<td>49</td>
</tr>
<tr>
<td>Reaction of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde with 2-Phenylenediamine</td>
<td>50</td>
</tr>
<tr>
<td>Dibromination of 2-Hydroxydibenzofuran</td>
<td>52</td>
</tr>
<tr>
<td>Acetylation of the Dibromination Product of 2-Hydroxydibenzofuran</td>
<td>53</td>
</tr>
<tr>
<td>Monobromination of 2-Hydroxydibenzofuran</td>
<td>53</td>
</tr>
<tr>
<td>Acetylation of 1-Bromo-2-hydroxydibenzofuran</td>
<td>54</td>
</tr>
<tr>
<td>Hydrolysis of 1-Bromo-2-acetoxydibenzofuran</td>
<td>54</td>
</tr>
<tr>
<td>Bromination of 1-Bromo-2-hydroxydibenzofuran</td>
<td>55</td>
</tr>
<tr>
<td>Acetylation of 1,-Dibromo-2-hydroxydibenzofuran</td>
<td>55</td>
</tr>
<tr>
<td>Hydrolysis of 1,-Dibromo-2-acetoxydibenzo-</td>
<td>56</td>
</tr>
<tr>
<td>furan</td>
<td></td>
</tr>
<tr>
<td>Monobromination of 2-Methoxydibenzofuran</td>
<td>56</td>
</tr>
<tr>
<td>Anomalous Demethylation of 2-Methoxy-3-bromo-</td>
<td>57</td>
</tr>
<tr>
<td>dibenzofuran</td>
<td></td>
</tr>
<tr>
<td>Monobromination of 2,-Dihydroxydibenzofuran</td>
<td>58</td>
</tr>
<tr>
<td>Acetylation of 1(?)-Bromo-2,-dihydroxydibenzofuran</td>
<td>60</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Methylation of 1(?)-Bromo-2,8-diacetoxydibenzofuran</td>
<td>60</td>
</tr>
<tr>
<td>Preparation of m-Butoxymethylpiperidine</td>
<td>61</td>
</tr>
<tr>
<td>Preparation of 4-Dibenzofuryl-N-piperidinomethane</td>
<td>61</td>
</tr>
<tr>
<td>Preparation of 4-Dibenzofuryl-N-piperidinomethane Picosrate</td>
<td>63</td>
</tr>
<tr>
<td>Preparation of m-Trifluoromethylaniline</td>
<td>63</td>
</tr>
<tr>
<td>Preparation of 1-(m-Trifluoromethylphenylazo)-2-hydroxydibenzofuran</td>
<td>64</td>
</tr>
<tr>
<td>Preparation of 1-(m-Trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran</td>
<td>65</td>
</tr>
<tr>
<td>Attempted Preparation of 1,9-bis-(m-Trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran</td>
<td>66</td>
</tr>
<tr>
<td>Attempted Preparation of Dibenzofuran-4-aldehyde</td>
<td>67</td>
</tr>
<tr>
<td>Bromination of Benzotrifluoride</td>
<td>70</td>
</tr>
<tr>
<td>Preparation of m-Trifluoromethylbenzaldehyde</td>
<td>71</td>
</tr>
<tr>
<td>Preparation of m-Trifluoromethylbenzaldehyde 2,4-Dinitrophenylhydrazone</td>
<td>73</td>
</tr>
<tr>
<td>Preparation of m-Trifluoromethylbenzaldoxime</td>
<td>74</td>
</tr>
<tr>
<td>Preparation of 3-(m-Trifluoromethylbenzal-amo)-benzotrifluoride</td>
<td>74</td>
</tr>
<tr>
<td>Preparation of 4-(m-Trifluoromethylbenzal-amo)-dibenzofuran</td>
<td>75</td>
</tr>
<tr>
<td>Preparation of N-(p-Acetaminophenyl)-2,5-dimethylpyrrole</td>
<td>76</td>
</tr>
<tr>
<td>Hydrolysis of N-(p-Acetaminophenyl)-2,5-dimethylpyrrole</td>
<td>77</td>
</tr>
<tr>
<td>Attempted Diazocoupling of N-(p-Aminophenyl)-2,5-dimethylpyrrole with 2-Hydroxydibenzofuran</td>
<td>78</td>
</tr>
<tr>
<td>Reaction Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Reduction of Tolu-p-quinone</td>
<td>79</td>
</tr>
<tr>
<td>Methylation of Toluhydroquinone</td>
<td>80</td>
</tr>
<tr>
<td>Iodination of Toluhydroquinone Dimethyl Ether</td>
<td>80</td>
</tr>
<tr>
<td>Conversion of 5-Iodotoluhydroquinone Dimethyl Ether to 2,5-Dimethoxy-p-toluic Acid</td>
<td>81</td>
</tr>
<tr>
<td>Attempted Preparation of the Grignard Reagent from 5-Iodotoluhydroquinone Dimethyl Ether</td>
<td>82</td>
</tr>
<tr>
<td>Preparation of 2,5-Dimethoxy-p-tolunitrile</td>
<td>83</td>
</tr>
<tr>
<td>Hydrolysis of 2,5-Dimethoxy-p-tolunitrile</td>
<td>83</td>
</tr>
<tr>
<td>Oxidation of 2,5-Dimethoxy-p-toluic Acid</td>
<td>84</td>
</tr>
<tr>
<td>Esterification of 2,5-Dimethoxyterephthalic Acid</td>
<td>85</td>
</tr>
<tr>
<td>Nitration of Toluhydroquinone Dimethyl Ether</td>
<td>85</td>
</tr>
<tr>
<td>Reduction of 5-Nitrotoluhydroquinone Dimethyl Ether</td>
<td>86</td>
</tr>
<tr>
<td>Acetylation of 5-Aminotoluhydroquinone Dimethyl Ether</td>
<td>87</td>
</tr>
<tr>
<td>Conversion of 5-Aminotoluhydroquinone Dimethyl Ether to 5-Iodotoluhydroquinone Dimethyl Ether</td>
<td>87</td>
</tr>
<tr>
<td>Nitration of 5-Iodotoluhydroquinone Dimethyl Ether</td>
<td>88</td>
</tr>
<tr>
<td>Nitration of 2,5-Dimethoxy-p-toluic Acid</td>
<td>89</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>90</td>
</tr>
<tr>
<td>Evidence for the Assigned Structures</td>
<td>90</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>100</td>
</tr>
</tbody>
</table>
INTRODUCTION

Several theories have been advanced in an attempt to explain something of the mechanism of analgesic action. The Meyer-Overton theory (1) suggests that a chemically inert substance which can serve as a solvent for fats must exert narcotic action. This observation appears to have merit in the consideration of such simple substances as diethyl ether and chloroform. It is evident, however, that the theory is not adequate for the explanation of the activity of complex aromatic substances.

The Traube theory (2) advances the contention that the strength of a narcotic is proportional to the surface tension of its aqueous solution. Among the members of a given series of homologues, this relation is quite possibly of value, but it would appear to be useless as a means of predicting relative activities of structurally unrelated compounds.

Bancroft and Richter (3) have presented evidence which indicates that reversible coagulation of cell colloids can occur within a living cell in the presence of an electrolyte. These workers suggest that narcotic activity may involve direct action by the narcotic substance resulting in the

2. Traube, Arch. ges. Physiol. (Pflügers), 155, 276 (1915); 
   ibid., 160, 51 (1915); ibid., 161, 53 (1915).
coagulation of cell colloids, or that the narcotic substance may act indirectly by inhibiting some cell function, and that the accumulation of waste products resulting brings about coagulation. Since nothing is known of the mechanism by which oxidation or other functions can be inhibited within living cells by chemical means, this information does not serve to advance our knowledge of correlation between chemical constitution and narcotic activity. The possible desirability of the presence of electrolytes during narcosis as indicated by the Bancroft-Richter theory might be construed as designating the use of salts, as amine hydrochlorides in place of free amines, but this is indicated in most instances by solubility considerations in any event.

In reviews on the subject of analgesia (4,5), and particularly in studies in the morphine series of alkaloids (6), attempts have been made to correlate molecular structure with analgesic activity on an empirical basis. As will be shown in the historical section, considerable success has attended these attempts at correlation when they are confined to a series of compounds possessing closely related structures. Very few if, indeed, any reliable generalizations have emerged from these studies.

Although the effects of small alterations in structure of the morphine molecule upon its analgesic activity have been thoroughly investigated (6), no information now available indicates specifically what group or groups are responsible for the analgesic power of morphine. Interest in the physiological properties of compounds containing phenanthrene (I), dibenzofuran (II), or isoquinoline (III) nuclei has been stimulated by the fact that all three nuclei in a partially reduced state form part of the morphine skeleton (IV).

![Chemical Structures](image)

It is to be noted that the partially reduced dibenzofuran nucleus in the morphine skeleton is substituted in the 4- and 6-positions and has a two-carbon bridge between the 1- and 9-positions. Synthesis of morphine-like compounds would be facilitated by preparation of dibenzofuran derivatives.
substituted in the 1-, 4-, 6-, and 9-positions. A few derivatives of this type are now available. The synthesis of 4,6-
dihydroxydibenzo-furan (7,8) has been improved by Cheney (9). The same author has established that monobromination of 4,6-
dimethoxydibenzo-furan yields 1-bromo-4,6-dimethoxydibenzo-furan.
The dibromination of 4,6-dimethoxydibenzo-furan was reported, and it is possible that the product is 1,9-dibromo-4,6-dimethoxy-
dibenzo-furan. Swislowsky (10) has reported the dibromination of 2,8-dihydroxydibenzo-furan and has tentatively designated the product as 1,9-dibromo-2,8-dihydroxydibenzo-furan. From the dibromination of 2,8-dimethoxydibenzo-furan, he obtained two isomeric dibromo compounds. One of these was identical with the methylation product of 1,9(?) dibromo-2,8-dihydroxy-
dibenzo-furan. The other has been designated tentatively as 3,7-dibromo-2,8-dimethoxydibenzo-furan, and the work of Willis (11) has strongly supported this belief.

A large part of the present work has been directed toward the establishment of the structure of the two isomeric dibromo-2,8-dimethoxydibenzo-furans just mentioned. In addition to these orientation studies, a number of compounds were prepared to be tested for pharmacological activity.

HISTORICAL

Since the isolation of morphine by Sertürner (12) in 1805, a vast amount of work has been carried out in an attempt to synthesize a compound possessing the analgesic activity of morphine but lacking its toxic and habit-forming properties. A significant part of this work has centered around rather simple alterations of the morphine molecule itself. Another approach to the problem has been through the preparation of numerous derivatives of phenanthrene, dibenzofuran, and carbazole. A considerable variety of aromatic isocyclic and heterocyclic compounds has been found to exhibit analgesic activity and many of these compounds have found commercial application. Despite the exhaustive search for a substitute, morphine remains probably the most important drug sold commercially. In 1936, its production was reported as 36.8 tons (13).

Derivatives of Morphine.

The Culland-Robinson (14) structure for morphine (IV) has found general acceptance. Treatment of morphine with reagents suited to replace the alcoholic hydroxyl group by halogen, as

thionyl chloride or phosphorus tribromide, results in the formation of halogenomorphides. Hydrolysis of a halogenomorphide with acetic acid yields three isomers of morphine, alpha, beta, and gamma isomorphines (V, VI, VII), but no morphine (15).

V. Alpha-isomorphine

VI, VII. Beta- and Gamma-isomorphines

The effect of methylation of the phenolic hydroxyl group upon toxicity and analgesic activity for morphine, alpha, beta-, and gamma-isomorphines, and the four corresponding dihydro derivatives was tested (6). In almost every instance, methylation of the phenol greatly increased toxicity and lowered analgesic activity. Similarly, if the phenolic hydroxyl group of morphine and its isomers is covered with an ethyl or a benzyl group, toxicity is increased and analgesic activity lowered. Methylation of the phenolic hydroxyl group of morphine alcoholic methyl ether (heterocodeine) results in lowering of analgesic activity and also in lowering of toxicity. The same result is obtained by methylation of

dihydroheterocodeine.

Desoxymorphine-C (VIII) has been prepared by elimination of hydrogen chloride from chlorodiopihromorphide (16). Dihydro-desoxymorphine-D (IX) was prepared by a controlled hydrogenation of a halogenomorphide (17). The corresponding codeine derivatives are made in like manner from chlorodihydrocodide and halogenocodides (18, 19).

\[
\begin{align*}
\text{VIII. Desoxymorphine-C.} & \quad \text{IX. Dihydrodesoxymorphine-D}
\end{align*}
\]

Desoxycodine-C and dihydrodesoxycodine D, the phenolic methyl ethers of VIII and IX, are less toxic than VIII and IX, but also show less analgesic activity. Similarly, the halogenocodides are poorer analgesics and also less toxic than the halogenomorphides (6).

In summary, then, it can be said that the effect of muzzling the phenolic hydroxyl group is nearly always to reduce analgesic action. Toxicity is not affected uniformly,

but it is increased more often than it is decreased.

A change in the configuration of the alcoholic hydroxyl group appears to have no uniform effect upon analgesic power, but alpha-isomorphine derivatives are in general less toxic than morphine derivatives, and gamma-isomorphine derivatives are much less toxic than beta-isomorphine derivatives. Beta- and gamma-isomorphine derivatives show considerably less analgesic activity than morphine and alpha-isomorphine derivatives (6).

Alkylation of the alcoholic hydroxyl group in morphine necessitates prolonged treatment with alkyl halides or sulfates. If the phenolic hydroxyl group and the tertiary nitrogen atom are not protected, their alkylation cannot be avoided. Mannich (20) solved the difficulty by covering the phenolic hydroxyl with a methoxymethyl group, and converting the tertiary nitrogen atom to the oxide. At the end of the alkylation, treatment of the product with sulfurous acid regenerates the phenolic group and the tertiary nitrogen atom. A number of alcoholic ethers of morphine have been prepared by this method (6). Almost without exception, methylation of the alcoholic hydroxyl group in morphine and its derivatives results in increased analgesic activity and also in increased toxicity. Similarly, ethyl and phenyl substitution of the alcoholic hydroxyl group increase both analgesic power and toxicity.

Acetyl substitution of the alcoholic hydroxyl group increases toxicity in nearly every instance, but has no uniform effect on analgesic activity.

Replacement of the alcoholic group by a ketonic oxygen at C-6 brings about some increase in analgesic activity, but also a very marked increase in toxic action (6). Replacement of the alcoholic hydroxyl group by hydrogen increases both analgesic action and toxicity, while replacement by halogen increases toxicity without having any uniform effect on analgesic power.

Surprisingly, the ether ring in the morphine skeleton is opened with extreme ease by reductive processes when a double linkage is present in the 6,7-position, or where halogen or ketonic oxygen is attached to the 6-carbon atom (21, 15). The general trend is toward decreased analgesic action and decreased toxicity when this reaction is carried out (6).

Hydrogenation of the 6,7- or 7,8-double bond in isomorphine or morphine derivatives usually causes a definite increase in analgesic power, but the effect upon toxicity cannot be predicted (6). Substitutions in the aromatic nucleus of the morphine series, as far as studied, appeared to result in decreased pharmacological activity. Introduction of a hydroxyl group, presumably at the 14-position, consistently decreased pharmacological effects. Change from tertiary to quaternary nitrogen in morphine decreased analgesic activity

and increased curare-like action.

A compound whose derivatives would merit extensive investigation if the compound itself were available in quantity is methylmorphhenol (XIV). In its skeleton are combined the nuclei of dibenzofuran and phenanthrene. Its preparation through the exhaustive methylation of morphine was reported long ago by Knorr (22) and Vongerichten (23). More recently, Mosettig and Meitzner (24) have improved Vongerichten's degradation process for morphine. These workers converted morphine to codeine methomethysulfate (X) by treatment with methyl sulfate and sodium ethoxide. Treatment of compound X with sodium hydroxide opens up the isoquinoline ring to yield alpha-methylmorphimethine (XI) which is rearranged to beta-methylmorphimethine (XII). Compound XII is treated with methyl sulfate to yield beta-methylmorphimethine methomethylsulfate (XIII) which breaks down upon heating at 120° with sodium cyclohexoxide to give methylmorphhenol (XIV). A diagrammatic representation of this series of transformations appears on the following page.

23. Vongerichten, ibid., 22, 65 (1896); ibid., 31, 51 (1898).
For the conversion of morphine to alpha-methylmorphimethine, Mosettig and Meitzner (24) report a yield of 67 to 72 per cent. No yields are reported for the rearrangement to
beta-methylmorphimethine or for the preparation of beta-methylmorphimethine methomethylsulfate. Conversion of the latter compound to methylmorphphenol is reported to go in 65 per cent yield. At best, the over-all yield of methylmorphphenol is no better than 45 per cent.

Only three compounds of this type have been tested for analgesic activity. They are 3-hydroxy-4,5-phenanthrylene oxide, 3-methoxy-4,5-phenanthrylene oxide, and 3-acetoxy-4,5-phenanthrylene oxide. Only morphenol itself (3-hydroxy-4,5-phenanthrylene oxide) showed activity and it was considerably weaker in action than 3-hydroxyphenanthrene (6). However, it is evident that the number of compounds tested in this series is too small to warrant the drawing of any conclusions regarding the value of morphenol derivatives.

Derivatives of Phenanthrene, Dibenzo furan, and Carbazole (25).

Prior to the series of studies in the dibenzo furan series carried out in these laboratories (26), the search for a synthetic morphine substitute had been directed primarily toward derivatives of phenanthrene. From the few dibenzo furan derivatives tested (6), it appears that dibenzo furans tend to possess stronger analgesic action than phenanthrene derivatives, but they are also more toxic. Carbazole derivatives are

25. Except for those statements attributed to others, the material presented in this section can be found in ref. 6.

26. More detailed discussion of this work will be found in that part of the historical section dealing specifically with dibenzo furan.
characterized by definite analgesic action and surprisingly low toxicity.

Phenantherene itself and its hydro derivatives manifest very little activity. The most effective compound studied is 9,10-dihydrophenanthrene which exhibits slight analgesic effect on cats in doses of 300 mg. per kg. Octahydrophenanthrene and phenanthrene are practically identical in their action.

Several hydroxyphenanthrenes and their methylation and acetylation products were studied. The only compound of this type exhibiting activity was 3-hydroxyphenanthrene, and its activity was destroyed by the "muzzling" of the hydroxyl group. No generalization can be made regarding the effect of the introduction of a second substituent into the phenanthrene nucleus, but it is of interest to note that 3,4-dihydroxyphenanthrene possesses far greater activity than 3-hydroxyphenanthrene.

Three aminophenanthrenes were studied along with some methylated and acetylated amines. Both 2- and 3-aminophenan-threnes exhibited limited analgesic activity, but the 9-amine possessed none. None of the acetylated or methylated amines exhibited activity, but 9-aminomethylphenanthrene was about as effective as the 2- and 3-amines.

The effect of partial reduction of the phenanthrene ring upon the activity of the aminophenanthrenes was studied, but unfortunately the most active compounds of this type prepared were 1- and 4-amino derivatives, and no data are available for
the activity of the unreduced 1- and 4-aminophenanthenes. For this reason no statement can be made concerning the effect of reduction of the ring upon the activity of the aminophenanthenes. 2-Amino-9,10-dihydrophenanthrene was found to possess about the same analgesic activity as 2-aminophenanthen. The most active compound of this type prepared was 1-amino-1,2,3,4-tetrahydrophenanthrene, which produced moderate analgesia in cats at a dosage of 20 mg. per kg.

In general, the aminohydroxyphenanthrenes and their ethers and acetylation products were found to be inactive. However, 3-hydroxy-4-aminophenanthen was about twice as effective as 3-hydroxyphenanthrene. Very few active compounds were found among the aldehydes, ketones, and carbinols of phenanthrene. The most active substance of the group was 3-phenanthryl methyl carbinol.

Of the phenanthroic acids studied, only the 3-acid exhibited activity. The amides and methyl esters of the phenanthroic acids were without activity, but the beta-diethylaminomethyl ester of 3-phenanthroic acid showed moderate activity in doses of 300 mg. per kg. The only reduced phenanthroic acid tried, 1,2,3,4,5,6,7,8-octahydro-9-phenanthroic acid exhibited moderate activity in doses of 150 mg. per kg.

Three amino ketones were examined. The most active, 3-phenanthryl dimethylaminomethyl ketone, possessed moderate analgesic activity in doses of 100 mg. per kg., and the corresponding diethylaminomethyl ketone was only slightly less
active. Only slight analgesic activity was exhibited by 3-phenanthryl N-piperidinomethyl ketone.

The most active phenanthrene derivatives found were the amino alcohols, of which a large number were studied. Of the amino alcohols of the ethanolamine type, the most active was 3-phenanthryl aminomethyl carbinol, which produced marked analgesia in injected doses of only 50 mg. per kg. The corresponding dimethylaminomethyl and diethylaminomethyl compounds exhibited only slight analgesic power. A number of amino alcohols of the ethanolamine type derived from reduced phenanthrenes were also tested. The most effective compound was 2-(9,10-dihydrophenanthryl) N-piperidinomethyl carbinol which brought about moderate analgesia in injected doses of 10 mg. per kg. This activity is on the order of that of codeine. Moderate analgesia at a dosage of 25 mg. per kg. was produced by 2-(9,10-dihydrophenanthryl) dimethylaminomethyl carbinol and the corresponding diethylaminomethyl compound was active to the same degree. The amino alcohols of the ethanolamine type derived from 1,2,3,4,5,6,7,8-octahydrophenanthrene possessed only slight analgesic activity.

The amino alcohols of the beta-propanolamine type (XV) are in general less active than the ethanolamine type of alcohol, and the latter type of compound is usually less active than the gamma-propanolamine type of alcohol (XVI).
XV. Beta-propanolamine type of amino alcohol.  

Of the compounds tested of the beta-propanolamine type, the most effective was alpha-(3-phenanthryl)-beta-diethylamino- 
propanol, which produced moderate analgesia in doses of 60 mg. 
per kg. The corresponding dimethyl amine showed only slight 
activity, and the unsubstituted amine was inactive. Hydrogena-
tion of the 9,10-double bond in alpha-(2-phenanthryl)-beta-
diethylaminopropanol resulted in a compound possessing only 
slight analgesic activity. However, the corresponding 
N-piperidino compound produced moderate analgesia in doses of 
30 mg. per kg. Of the amino alcohols studied which were 
derived from octahydrophenanthrene, the only compound exhibit-
ing appreciable activity was alpha-(5-(1,2,3,4,5,6,7,8-octa-
hydrophenanthryl)7-beta-diethylaminopropanol, which produced 
moderate analgesia in doses of 75 mg. per kg.

The most effective of the amino alcohols of the gamma-
propanolamine type prepared was alpha-(3-phenanthryl)-gamma-
(N-piperidino)-propanol which produced moderate analgesia in 
doses of 40 mg. per kg. No alcohols of this type derived from 
reduced phenanthrenes were prepared.
A number of cyclic amino alcohols derived from tetrahydrophenanthrene were studied and three compounds possessing considerable analgesic activity were found. Two of these, 3-(N-piperidino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene, and 3-diethylamino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene, brought about moderate analgesia in doses of 40 mg. per kg. The third compound, 3-dimethylamino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene, produced moderate analgesia in doses of 60 mg. per kg.

Only a few dibenzofuran derivatives have been tested by Small, Eddy, Mosettig, and Himmelsbach (6), and these investigators have stressed amino alcohols and amino ketones. Of the simple derivatives of dibenzofuran studied, the most effective compound was 3-aminodibenzofuran, which produced moderate analgesia in doses of 40 mg. per kg. This result does not agree with that reported for the 3-amine prepared in this laboratory (27). The latter compound was found to be inert when first tested. A later test (10) indicated slight activity. The discrepancy may lie in the fact that the compound prepared by Small was tested as the free amine, while the compound prepared in this laboratory was tested as the hydrochloride.

Two amino ketones derived from dibenzofuran were studied and found to possess only slight analgesic activity. The compounds were 2-dibenzofuryl dimethylaminomethyl ketone and

the corresponding diethylamino compound. Of the amino alcohols studied, the most effective were 2-dibenzofuryl N-piperidino- methyl carbinol and 2-dibenzofuryl ethylaminomethyl carbinol, both of which produced moderate analgesia in doses of 60 ml. per kg. The one partially reduced amino alcohol tested, 7-(1,2,3,4-tetrahydrodibenzofuryl)dimethylaminomethyl carbinol, exhibited only slight analgesic power.

In general, the amino alcohols derived from dibenzofuran appear to be more analgesic than the corresponding phenanthrene derivatives, but they are also more toxic and more convulsant, so that the ratio of analgesic to toxic dose is about the same for the two series of compounds.

A limited number of derivatives of carbazole (XVII) have been tested for analgesic activity.

![Chemical Structure](image)

XVII. Carbazole.

Carbazole itself exhibits no activity, and the simple amino derivatives of carbazole, N-methylcarbazole and N-acetylcocabazole, possess only slight activity. The preparation of a number of amino alcohols derived from carbazole has been reported by Ruberg and Small (28), and the results of pharmacological tests of these compounds were reported by

Eddy (29). Two compounds, 2-(3-diethylamino-1-hydroxy-η-propyl)-9-methylcarbazole and 1-hydroxy-2-dimethylaminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole, were reported to have a smaller minimum effective analgesic dose than any phenanthrene or dibenzofuran derivatives tested and also a more prolonged effect. Other compounds of this type tested and found to be active were 2-(3-dimethylamino-1-hydroxy-η-propyl)-9-methylcarbazole and 2-(3-tetrahydroisoquinolino-1-hydroxy-η-propyl)-9-methylcarbazole.

In a more recent paper, Ruberg and Small (30) report the preparation of some additional amino alcohols derived from carbazole, including 3-(3-dimethylamino-1-hydroxy-η-propyl)-9-methylcarbazole and the corresponding diethylamino and tetrahydroisoquinolino compounds. Also, a compound of the ethanolamine type, 2-(2-diethylamino-1-hydroxyethyl)carbazole, was reported. Unfortunately, the results of the pharmacological tests upon these compounds have not yet appeared.

No reliable generalizations can be set forth from the relatively small number of carbazole derivatives tested, but preliminary indications are that the carbazole derivatives are at least as strong in analgesic action as the corresponding phenanthrene and dibenzofuran derivatives, and they appear to be less toxic, although those tested to date possess the disadvantage of strong convulsant action.

Miscellaneous Pain-Relieving Compounds.

The majority of compounds to be mentioned in this classification are not analgesics in the strict sense of the word since their action is localized. Some are administered as spinal analgesics and others by injection into mucous membranes.

The first local anesthetic to find clinical use was cocaine (XVIII), which was introduced by Coller in 1884 (31). It is extremely effective as a pain-relieving agent, but its toxicity and habit-forming properties offer strong objections to its use. Legitimate world production declined from 6934 kg. in 1929 to 4010 kg. in 1933 (32), but illegitimate production is unofficially estimated at 15,000 to 20,000 kg. Hydrolysis of cocaine with acids or alkalis yields ecgonine, benzoic acid, and methanol. Ecgonine possesses no analgesic activity.

\[
\text{CH}_2-\text{CH}-\text{CH}-\text{COOCH}_3
\]

\[
\text{N}-\text{CH}_3
\]

\[
\text{CHO}_3
\]

\[
\text{CH}_2-\text{CH}-\text{CH}_2
\]

XVIII. Cocaine.

It is to be noted that cocaine is an ester of benzoic acid with a very complex amino alcohol. Attempts to prepare cocaine substitutes have very largely centered around compounds of this type. The most simple compounds of this type

which exhibit pain-relieving properties are new orthoform (methyl 3-amino-4-hydroxybenzoate), and anesthesin (ethyl p-aminobenzoate). In both cases, an amino acid rather than an amino alcohol is used, and it may be significant that both of these compounds possess only mild analgesic activity.

Better results were obtained by esterification of benzoic acid with acyclic amino alcohols (5). Two compounds of this type which have seen considerable clinical use are stovaine (XIX) and alypine (XX).

\[ \text{XIX. Stovaine.} \]

\[ \text{XX. Alypine.} \]

Still better results have been obtained through esterification of p-aminobenzoic acid with amino alcohols. The most widely used substitute for cocaine is novocaine, or procaine (XXI), which is diethylaminoethyl p-aminobenzoate. The compound was first reported by Högger (33) and its pharmacological action was described by Läwen (34). It exhibits very strong anesthetic power and is low in toxicity. Unfortunately it

pounds of this type are teracaine type compounds have been prepared.

The compounds have a better therapeutic index than novocaine.

Some of the amino ester has a pronounced chain in which the amino ester has been prepared

Activity and toxicity

Atom brought about a proportionate increase in anesthetic

Substitution of nitroalkyl groups on the tertiary

Activity, so that the therapeutic index was actually lowered.

The nitroalkyl derivatives. The latter series of compounds

Aminoethyl esters of p-aminoalcohol acid, and the corresponding

toxities of two series of procaine derivatives, the dextrorotatory
toxicities of two series of procaine derivatives, the dextrorotatory

the effectiveness of cocaine by preventing the rapid disappearance

does not possess the vasocorderative effect which increases

XXI. NOVOCAINE.

\[
\text{CH}_2-\text{CH}_2-\text{N}^+\text{C}_6\text{H}_5
\]

\[
\begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\]

\[
\text{C}_6\text{H}_5
\]

\[
\text{CH}_2-\text{CH}_2-\text{N}^+\text{C}_6\text{H}_5
\]
The fact that phenacetin, p-ethoxyacetanilide, possesses weak analgesic activity as well as antipyretic activity has long been recognized. Attempts to increase this activity led to the synthesis of holocaine (XXIV) (36) which has found limited clinical use. This substance is of particular interest because it contains the anil linkage which is not commonly found in analgesics. Diocaine is the corresponding diallyloxy compound. Another local anesthetic containing the anil linkage, this time in a quinoline ring, is percaine (XXV).

Percaine is a relatively new drug, but it has been adopted with unusual rapidity by the medical profession. The

first report on its pharmacological activity appeared in 1929 (37). In 1930, Popper (38) reported that it was likely to replace cocaine as a surface anesthetic. It is of interest to note that compounds in the percaine series show little analgesic activity until the alkyl group on the phenolic hydroxyl contains more than two carbon atoms (5). Percaine is reported to have about forty times the analgesic power of cocaine.

Probably the most recent drug to come into clinical use is dolantin (XXVI). It is a true analgesic in that its action is morphine-like (not localized). The first report on its pharmacological activity was made by Eisleb and Schaumann (39). The original purpose in its synthesis was the preparation of a drug with atropine-like action. Dolantin combines the spasmodic action of atropine and papaverine with the analgesic action of morphine. In tests conducted on mice, one-fifth of the lethal dose resulted in complete cessation of pain sensation. The lethal dose for mice by subcutaneous injection is 150 mg. per kg.

37. Lipschitz and Laubender, Klin. Wochenschr., 8, 1438 (1924)
/2A., 24, 3275 (1930)./
Derivatives of Dibenzofuran.

Dibenzofuran first occupied the attention of investigators in these laboratories in connection with some studies in the furan series. It was hoped that oxidation of dibenzofuran would provide a convenient source of supply for furan tetracarboxylic acid. When dibenzofuran itself proved extraordinarily resistant to oxidation (40), interest was directed toward substituted dibenzofurans containing amino or hydroxy groups which might facilitate the breaking of the ring. It was found that a considerable number of substituted dibenzofurans had been prepared, but the positions of the substituents had not been established in many instances. The need for orientation studies in the dibenzofuran series, together with the structural similarity between the dibenzofuran and morphine molecules, was largely responsible for initiation of the dibenzofuran studies now in progress in these laboratories.

Dibenzofuran was first synthesized in 1866 by Lesimple (41), who obtained it by heating phenyl phosphate with lime. Its isolation from coal tar was reported by Kraemer and Weissgerber (42) in 1901, and its structure was established by Hoffmeister and others (43). Dibenzofuran and its homologs comprise about 35 per cent of the coal tar fraction boiling...

42. Kraemer and Weissgerber, Ber., 34, 1662 (1901).
43. Hoffmeister, ibid., 3, 747 (1870); Tauber and Halberstadt, ibid., 25, 2745 (1892).
between 270° and 330° (44). Another commercial source for dibenzofuran is a synthesis in which phenol vapors are passed over heated thorium oxide (45).

An exhaustive survey of the literature of dibenzofuran compounds up to the end of 1942 has been made elsewhere (40, 10, 11, 46). One hundred and twenty-three dibenzofuran compounds have been submitted from this laboratory to be tested for analgesic activity (47). The results with the first seventy-eight compounds of the series have been tabulated by Parker (27), and Cheney (48) presented the data on the compounds with HD numbers 79 to 106. The results with HD numbers 107 to 123 were presented by Swislowsky (10), and Cook (49) tabulated the data for HD numbers 124 to 142. Nineteen of the compounds submitted for testing have exhibited at least slight analgesic activity.

The most active compound tested was 4-aminodibenzofuran which possessed ten per cent of the analgesic power of morphine and whose minimum lethal dose in white mice was 500 mg. per kg. It is of interest to note that none of the derivatives of 4-aminodibenzofuran tested exhibited activity of the same magnitude. Three derivatives, 4-acetaminodibenzofuran,

44. Kruber, Ber., 65, 1382 (1932).
47. The pharmacological tests were carried out in the laboratories of Parke, Davis and Company through the courtesy of Dr. Dox and Dr. Bywater.
4-dimethyaminodibenzofuran, and 4-aminoacetaminodibenzofuran, were found to possess slight analgesic action. The other derivatives of 4-aminodibenzofuran tested, all inert, were 4-amino-6-methoxydibenzofuran, 4-amino-6-hydroxydibenzofuran, 4,6-diaminodibenzofuran, 1,4-diaminodibenzofuran, 1-bromo-4-aminodibenzofuran, and 4-aminodibenzofuran-d-glucoside. Related compounds tested and found inert were 4-beta-diethylaminooethylidibenzofuran, 4-beta-diethylaminooethyloxydibenzofuran, 4-beta-N-piperidinoethyloxydibenzofuran, and 4-beta-aminooethyl-dibenzofuran.

In view of the structure of the morphine molecule, the desirability of observing the effect of bridging the 1- and 9-positions in dibenzofuran is obvious. Since 4,5-phenanthrylene oxide cannot be synthesized by dehydration of 4,5-dihydroxyphenanthrene, the most promising approach to compounds of this type is through dibenzofuran itself.

Derivatives of dibenzofuran substituted in the 1-, or 1- and 9-positions have been made by direct substitution in dibenzofuran compounds containing proper orienting groups, and also by means of syntheses involving ring-closure. In general, the latter method is not of practical synthetic value because of the labor involved in preparation of the intermediates used and the poor yields usually obtained in the ring-closure reactions themselves.

The direct substitution of the dibenzofuran nucleus in the 1-position has been accomplished only in instances where a
rather strong ortho-para directing group is present in either the 2- or the 4-position. Bromination of 4-hydroxy- and of 4-acetaminodibenzofurans has been shown by P. R. Van Ess (50) to involve either the 1- or the 9-position. The bromo-4-acetaminodibenzofuran obtained was hydrolyzed, diazotized, and the diazonium group replaced with a hydroxyl group to give a product identical with the compound obtained by direct bromination of 4-hydroxydibenzofuran. Parker (27) brominated 4-methoxydibenzofuran and obtained a compound identical with the methylation product of the bromohydroxy compound prepared by Van Ess. M. W. Van Ess (51) prepared the benzeneazo coupling product of 4-hydroxydibenzofuran. Reduction of this compound to the amine, followed by diazotization and replacement of the diazonium group with bromine, gave a bromohydroxy compound identical with that prepared by P. R. Van Ess by bromination of 4-hydroxydibenzofuran. This fact constitutes strong evidence in support of the assumption that bromination of 4-hydroxydibenzofuran involves the 1-position rather than the 9-position, since heteronuclear substitution is virtually excluded by the nature of the diazo coupling reaction.

Cheney (9) has shown that bromination of 4,6-dimethoxydibenzofuran, 3,4-dimethoxydibenzofuran, and 3-hydroxy-4-methoxydibenzofuran involves the 1-position in each case.

Similarly, acetylation of both 4,6-dimethoxydibenzofuran and

3,4-dimethoxydibenzofuran involves the 1-position. P. R. Van Ess (50) proved that bromination of 2-hydroxydibenzofuran gives 1-bromo-2-hydroxydibenzofuran, while the 3-bromo compounds result from the bromination of 2-methoxydibenzofuran and 2-acetaminodibenzo- 

Dibenzofuran derivatives substituted in the 1-position have also been prepared by rearrangement of 2-allyloxydibenzo- 

Swislowsky (10) dibrominated 2,8-dimethoxydibenzo- 

and provisionally designated the product as 1,9-dibromo-2,8- 

dimethoxydibenzo- 

Swislowsky to involve the same
positions as those occupied by the bromine atoms in the compound designated as 1,9-dibromo-2,8-dimethoxydibenzo-3-furan.

Swislowsky converted the latter compound to the corresponding dimethyl-2,8-dihydroxydibenzo-3-furan, and attempted removal of the hydroxyl groups by conversion to the diamine with the Bucherer reaction followed by deamination. The Bucherer reaction, however, was unsuccessful and only starting material was recovered. Attempted removal of the hydroxyl groups by means of zinc dust distillation likewise failed. If a method for removal of the hydroxyl groups could have been devised, the dimethyldibenzo-3-furan obtained could have been compared with the known 1,9-dimethyldibenzo-3-furan (52).

Later studies (53, 46) have indicated that the compound in question is probably not a 1,9-derivative. Failure of the Bucherer reaction on the dimethyl-2,8-dihydroxydibenzo-3-furan makes it appear probable that the methyl groups are in the 1- and 7-positions, since each hydroxyl group must have a methyl group in the position ortho to it in order to be protected from the Bucherer reagents. Hogg (53) has proved that one of the two methyl groups is actually in the 1-position.

Willis (11) has advanced strong evidence in support of the contention that the higher-melting isomer obtained from the dibromination of 2,8-dimethoxydibenzo-3-furan is actually

3,7-dibromo-2,8-dimethoxydibenzofuran. He demethylated and dehydrated the 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl reported by Erdtman (54) to obtain 2,8-dihydroxy-3,7-dimethyl-dibenzofuran which was found to be identical with the derivative prepared by Swislowsky from 2,8-dimethoxy-3,7-dibromo-dibenzofuran. Erdtman prepared his biphenyl compound through Ullmann coupling of 5-iodotoluhydroquinone dimethyl ether, a compound which he obtained from iodination of toluhydroquinone dimethyl ether. The position of iodination, however, does not appear to have been definitely established and consequently the structure of 2,8-dimethoxy-3,7-dibromodibenzofuran is uncertain to the extent that this iodination is uncertain.

Only a few syntheses of 1,9-substituted dibenzofurans from ring-closure reactions have been reported. Tetrazotization of 2,2'-diamino-6,6'-dimethylbiphenyl and heating produced a small amount of 1,9-dimethyldibenzofuran (55). The synthesis of the same compound by Sugii and Shindo has been mentioned (52). 1,9-Diphenyldibenzofuran has been prepared from 2,2'-diamino-6,6'-diphenylbiphenyl (56). The synthesis of 1,9-dihydroxydibenzofuran by ring closure of 2,2',6,6'-tetrahydroxybiphenyl has been reported (57).

55. Mascarelli and Tonge, Gazz. chim. Ital., 68, 121 (1938) [C.A., 32, 6235 (1938)].
Probably the most intensive attempts to bridge the 1,9-positions in dibenzofuran have been conducted by Cheney (48). He prepared 1-chloroacetyl-4-methoxydibenzofuran and attempted to convert it to a phenanthrylene oxide derivative through an intramolecular alkylation in the presence of aluminum chloride. Despite rather extensive variation in the conditions of reaction, no trace of either the desired compound or of an intermolecular reaction product was found. The same author carried out a Friedel-Crafts reaction with 4-methoxydibenzofuran and oxalyl chloride in the hope of obtaining a 4,5-phenanthrylene oxide quinone. No trace of the desired ortho-quinone could be found, but three products, 4-methoxy-1-dibenzofuranocarboxylic acid, di-(4-methoxy-1-dibenzo furyl) ketone, and bi-(4-methoxy-1-dibenzo furyl), were isolated. The isolation of the last-named product suggested that activation of both the 1- and 9-positions was necessary in order to realize the formation of the desired ortho-quinone. Accordingly the same reaction was carried out on 4,6-dimethoxydibenzofuran. Again no trace of ortho-quinone could be found, although bi-(4,6-dimethoxy-1-dibenzo furyl) was isolated in good yield.

Cheney also attempted cyclization of 4,6-dimethoxy-1-dibenzofurylacetic acid by conversion to the acid chloride followed by an intramolecular alkylation in the presence of aluminum chloride. No pure products could be isolated from the reaction mixture. Studies on this reaction were continued by Cook (49), who isolated no pure compound other than the
starting material from his reaction mixtures. The same author attempted to fuse a heterocyclic ring to the dibenzofuran nucleus across either the 1,2- or 1,9-positions by dehydration of (4-methoxy-1-dibenzofuryl)-mercaptoacetic acid. In several runs in which the dehydrating agent was varied, the only pure compound isolated from the reaction mixture was the starting material.

Swislowsky (10) carried out a Friedel-Crafts reaction with 2,8-dimethoxydibenzo furan and oxaly chloride. The structure of the product has not been established, but it is an ortho-quinone as evidenced by its formation of a quinoxaline derivative on treatment with 2-phenylenediamine. It is believed to be a lactone of one of the following structures:

![Structural formulas](image)

XXVII. 8-Methoxybenzofuro/5,6-\(\beta\)/benzofuran-2,3-dione.  
XXVIII. 9-Methoxybenzofuro/5,4-\(\beta\)/benzofuran-1,2-dione.

A more recent and possibly successful attempt at bridging the 1,9-positions is that carried out by Avakian (58). He proved that succinoylation of 4-methoxydibenzo furen involved the 1-position by oxidation of the keto-acid obtained to the

58. S. Avakian, unpublished studies.
known 4-methoxydibenzofuran-1-carboxylic acid. The keto-acid was reduced to \textit{gamma}-(4-methoxy-1-dibenzofuryl)-\textit{n}-butyric acid and the latter compound was dehydrated by treatment with 88 per cent sulfuric acid to yield a cyclic ketone which was characterized by preparation of the oxime. Oxidation of the ketone yielded a dibasic acid which was not identical with a sample of 4-methoxydibenzofuran-1,2-dicarboxylic acid prepared by Avakian. A cyclic ketone was prepared in similar manner from the succinoylation product of 4,6-dimethoxydibenzofuran. While it cannot be stated that the evidence now at hand constitutes conclusive proof for a 1,9-bridge, there is no denying that the presence of such a bridge in these two compounds is strongly indicated.
EXPERIMENTAL

Nitration of 2,8-Dihydroxydibenzofuran.

A solution of 4.6 g. (0.023 mole) of 2,8-dihydroxydibenzofuran (10) in 125 ml. of glacial acetic acid was warmed to 60°. To the warm solution was added slowly with stirring a mixture of 11.5 ml. of concentrated nitric acid and 11.5 ml. of glacial acetic acid. The reaction mixture was cooled occasionally during this addition by immersion in an ice bath in order to maintain the internal temperature at 60°. The deep red solution resulting from addition of all the nitrating mixture was stirred ten minutes and then poured into a 600 ml. beaker filled with cracked ice. When the ice had melted, the reddish-yellow precipitate remaining was filtered off and dissolved in acetone. Water was added slowly to the boiling acetone solution to incipient formation of a yellow precipitate. Upon cooling, the product crystallized out in yellow plates which melted at 246-247°. Recrystallization from dilute acetone did not alter the melting point. The yield of pure tetranitro-2,8-dihydroxydibenzofuran was 4.3 g. (49.2%). The structure of this compound has not been established definitely, but it is probably 1,3,7,9-tetranitro-2,8-dihydroxydibenzofuran, since, with the exception of meta-alation reactions, direct substitution in the 4- and 6-positions is rare.
Methylation of 1,3,7,9(?)-Tetranitro-2,8-dihydroxydibenzo-furan.

Four and three-tenths grams (0.0113 mole) of 1,3,7,9(?)-tetranitro-2,8-dihydroxydibenzo-furan was suspended in about 75 ml. of anhydrous ether in a 250 ml. Erlenmeyer flask. The mixture was cooled in an ice bath, and a 50 ml. distilling flask fitted with a medicine dropper and equipped with a long vertical side arm was so mounted that the side arm dipped into the mixture in the Erlenmeyer flask. In the distilling flask was placed 25 ml. of anhydrous ether and 13 ml. of ethyl N-nitroso-N-methylcarbamate. A 25% solution of potassium hydroxide in methyl alcohol was added dropwise to the ethyl N-nitroso-N-methylcarbamate solution by means of the medicine dropper. Addition was continued cautiously until evolution of diazomethane had stopped. The mixture in the diazomethane generator was then heated gently with a warm water bath to drive off any remaining diazomethane. During the course of the methylation, the reaction vessel containing the nitro compound was swirled frequently to obtain better retention of the diazomethane. When all the diazomethane had been driven out of the generator, the Erlenmeyer flask containing the reaction mixture was stoppered and allowed to stand in the refrigerator for a twenty-four hour period to ensure complete reaction.

The product was filtered out and dried. The crude yellow
Material obtained melted at 234-237° and weighed 4.1 g. (89%). The crude 1,3,7,9(?)-tetranitro-2,8-dimethoxydibenzofuran was extracted with a small amount of acetone to remove unreacted starting material. The residue melted at 244-245°. A recrystallization from acetone raised the melting point to 245-246°. A mixed melting point with 1,3,7,9(?)-tetranitro-2,8-dihydroxydibenzofuran was depressed to 218-219°.

**Anal.** Calcd. for C_{14}H_{8}O_{11}N_{4}: N, 13.72. Found: N, 13.74, 13.83.

**Preparation of 1,9(?)-Dibromo-2,8-diacetoxydibenzofuran.**

The dibromination of 2,8-dihydroxydibenzofuran was carried out in essential accordance with the procedure of Swiss (10) and Thirtle (46). Several attempts at dibrominating larger quantities of 2,8-dihydroxydibenzofuran served to indicate that optimum conditions prevail in a ten-gram run. The product obtained from the larger runs appeared to be more impure, and purification was difficult.

A suspension of 10 g. (0.05 mole) of 2,8-dihydroxydibenzofuran in 125 ml. of glacial acetic acid was brominated by the dropwise addition of 99 ml. of a molar solution of bromine in glacial acetic acid. The addition was carried out with constant stirring over a period of three hours. When about one-half of the bromine solution had been added, all the solid had gone into solution. After standing for several hours the reaction mixture became completely solid. Water was added, the
solid was broken up, and the resulting suspension was filtered. The dried, crude 1,9(?)-dibromo-2,8-dihydroxydibenzofuran melted at 181-185\(^\circ\) and weighed 17.5 g. (97.8\%). The crude product was acetylated without further purification.

One hundred and ten grams (0.308 mole) of crude 1,9(?)-dibromo-2,8-dihydroxydibenzofuran was suspended in 230 ml. of acetic anhydride in an Erlenmeyer flask. The mixture was thoroughly cooled in an ice bath, and then 1.0 ml. of concentrated sulfuric acid was added. The flask was swirled gently, and a violent, spontaneous reaction began almost immediately. After the reaction had subsided, the mixture was refluxed gently for fifteen minutes and then allowed to cool. Cautious dilution with water produced a white, crystalline precipitate. Two recrystallizations from alcohol resulted in 73.5 g. (54\%) of pure 1,9(?)-dibromo-2,8-diacetoxydibenzofuran melting at 173-174\(^\circ\).

**Methylation of 1,9(?)-Dibromo-2,8-diacetoxydibenzofuran.**

The use of a large flask for this reaction is imperative, because violent refluxing frequently occurs during the course of the methylation and material would be lost from a small reaction vessel. Seventy-three and one-half grams (0.166 mole) of 1,9(?)-dibromo-2,8-diacetoxydibenzofuran was suspended in 150 ml. of methyl alcohol in a 2-liter Erlenmeyer flask. To the suspension of diacetoxy compound was added 54.5 ml. of freshly distilled dimethyl sulfate, and the mixture was cooled to -10\(^\circ\). To the cold reaction mixture was added slowly and
with great caution a solution of 60 g. of sodium hydroxide in 60 ml. of water. The flask was swirled vigorously after the addition of each small portion of the sodium hydroxide solution. Vigorous refluxing on the walls of the flask took place following the addition of each portion of sodium hydroxide solution. After all the sodium hydroxide had been added and the reaction had subsided, the mixture was refluxed for thirty minutes. The cooled suspension was diluted and filtered. The crude product was recrystallized once from alcohol to yield 52.5 g. (82%) of pure 1,9(?)-dibromo-2,8-dimethoxydibenzofuran melting at 195-196°.

The foregoing series of reactions for the preparation of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran from 2,8-dihydroxydibenzofuran offers an improvement in yield over the method used by Swislowksy (10). His overall yield of somewhat impure material was 57.6%, compared with an overall pure yield of 44.3% by the above method. This author, however, obtained an overall yield of pure 1,9(?)-dibromo-2,8-dimethoxydibenzofuran of only 35.3% by Swislowksy's method.

Conversion of 1,9(?)-Dibromo-2,8-dimethoxydibenzofuran to 2,8-Dimethoxydibenzofuran-1,9(?)-dicarboxylic Acid.

The procedure used for the halogen-metal interconversion of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran has been modified slightly from that used by Swislowksy.

The n-butyllithium prepared from 7.2 g. (0.0525 mole) of
n-butyl bromide and 1.0 g. (0.149 g. atom) of lithium in 100 ml. of anhydrous ether was filtered under an atmosphere of dry nitrogen into a three-necked flask containing five grams (0.013 mole) of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran dissolved in 75 ml. of anhydrous ether. The mixture was stirred at its reflux temperature for fifteen minutes and then poured upon an excess of solid carbon dioxide.

When all the carbon dioxide had volatilized, the ethereal residues were extracted with 30 ml. of 10% potassium hydroxide solution and the aqueous layer was acidified with hydrochloric acid following filtration. The crude acid which precipitated weighed 4.08 g. (99%) and melted at 220-230°. Several recrystallizations from glacial acetic acid resulted in 2.0 g. (49%) of pure 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid which melted at 270-272°.

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

This bromination was also attempted by Thistle (46). In addition to the two experiments reported here, the method of Thistle which utilizes aluminum chloride was tried without success.

A solution of one gram (0.00317 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid in 50 ml. of glacial acetic acid was stirred constantly while 3.5 ml. of a molar solution of bromine in glacial acetic acid was added dropwise.
After having been stirred twenty hours, the reaction mixture still retained the bromine coloration. Sodium bisulfite solution was added to the mixture till the bromine color was discharged. Concentration of the mixture, followed by dilution with water and filtration yielded the unchanged starting material. The recovery was 90%.

Five-tenths of a gram (0.00158 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid was heated gently for one hour with 0.5 ml. of bromine in a test tube fitted with condenser. The bromine color was not discharged. Sodium bisulfite solution was added to complete decolorization of the bromine and the resulting mixture was acidified with hydrochloric acid and filtered. Again the unchanged starting material was recovered.

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

Five-tenths of a gram (0.00158 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dicarboxylic acid was suspended in a mixture of 6 ml. of glacial acetic acid and 7.5 ml. of constant-boiling hydrobromic acid. The reaction mixture was refluxed for ten hours in an all-glass apparatus. When it had cooled, the mixture was poured out into 50 ml. of water, and the resulting suspension was filtered. A yellowish-white amorphous product which weighed 0.44 g. and melted at 312-314° was obtained. Recrystallization from a mixture of glacial
I 3 i
[Image 0x0 to 822x610]

The reaction mixture was diluted with 100 ml. of water
allowed to stand over night.

After all the bromine had been added, the flask was stoppered and
allowed to stand over night.

The reaction had showed considerable
been added. After all the bromine had been added, the reaction had showed considerable
reactivity, but before the theoretical amount of bromine had
reacted. At first the bromine added was decomposed with great
vessels. At first the bromine added was decomposed with shaking of the reaction
temperature, 4°C. With a mortar solution of bromine in 10 ml. of

Pour reaction of a From (0.0125 mole) of 2,2'-dipyridoxal

Acid

Promotion of 2,2'-dipyridoxal[benzoyl]ene-T,3,7,9- 

bromate, 144, 145.

Analyzed. Calculated. For C<sub>48</sub>H<sub>38</sub>O<sub>7</sub>Br. Found.

At 313-314°,
dichloroalkyne-T,3,7,9-dipyridoxal[benzoyl]ene

Acetate and phthalate extracted 0.4 & 0.6 of pure 2,2'.
melted at 318-319°. Mixture of this product with a sample of 2,8-dihydroxydibenzofuran-1,9(?)-dicarboxylic acid, which melted at 313-314°, depressed the melting point to 296-297°.

Anal. Calcd. for C_{14}H_{16}O_{7}Br_{2}: neut. equiv., 223. Found, neut. equiv., 222, 223.

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

The procedure followed for the attempted decarboxylation was adapted from the method of Shepard, Winslow, and Johnson (59).

One-tenth of a gram (0.00022 mole) of 2,8-dihydroxy-3,7(?)-dibromodibenzofuran-1,9(?)-dicarboxylic acid was suspended in 5 ml. of quinoline and about 0.05 g. of finely powdered copper was added. The mixture was heated in an oil bath at 170-190° and during the heating, a gas, presumably carbon dioxide, was evolved sporadically. When evolution of gas had ceased at the end of thirty minutes, the mixture was cooled to room temperature and decanted from the copper powder. Acidification with excess hydrochloric acid produced a gray, flocculent precipitate which was filtered out. This material was recrystallized successively from alcohol and dilute acetic acid. Purification was not successful, however, and the crude product obtained melted at 160-190°.

A second attempt in which the reaction mixture was heated for one hour at $150^\circ$ was also unsuccessful. From the same reaction, Thirtle (46) has obtained a product melting at 220-230$^\circ$, which may be crude 2,8-dihydroxydibenzo- 

**Attempted Amination of $1,9(?)$-Dibromo-2,8-dimethoxydibenzo- 

The method used was adapted from the procedure of Swislowsky (10) for the amination of 2,8-dibromodibenzo- 
after mixing the reactants, the reaction was sealed in a Carius tube with 18 ml. of concentrated aqueous ammonium hydroxide and the tube was heated at $180^\circ$ for sixteen hours. At the end of that time, a brown, partially crystalline mass remained in the tube. 

As soon as the Carius tube was opened, a nitrogen tube was introduced into it to minimize exposure to oxygen. The
brown residue was extracted with six 50-ml. portions of ether to yield a reddish-brown solution which exhibited a blue-green fluorescence in the sunlight. To the combined ethereal extracts was added 25 ml. of glacial acetic acid and the ether was then distilled off. The resulting acetic acid solution was warmed to 40° for thirty minutes with 25 ml. of acetic anhydride. An additional 10 ml. of acetic anhydride was added and the solution was allowed to stand five hours at room temperature.

Dilution of the reaction mixture with water gave a tan precipitate which weighed 2.0 g. and melted at 80-110°. Recrystallization from alcohol, acetone, and acetic acid failed to bring about substantial alteration in the melting point. However, recrystallization from a large volume of acetic acid with an accompanying Norite decolorization yielded a small amount of white material melting at 175-177°.

Anal. Calcd. for C_{18}H_{16}O_5N_2: N, 8.18. Found: N, 8.35.

**Attempted Amination of 1,9(?)-Dibromo-2,8-dimethoxydibenzo-furan with Sodamide.**

The following procedure is taken from the method for amination presented by Vaughn, Vogt, and Nieuwland (60). To 100 ml. of liquid ammonia in a three-necked flask fitted with mechanical stirrer was added 0.394 g. (0.0171 g. atom) of sodium and 0.3 g. of Fe(NO_3)_3·9H_2O. This mixture was stirred for fifteen minutes and then a suspension of three grams

(0.0078 mole) of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran in 50 ml. of dry toluene was added. Stirring was continued for two and one-half hours, and when all the ammonia had evaporated, the mixture was heated to 60-70°. Finally, two grams of ammonium chloride was added to decompose the excess sodamide. Then 25 ml. of acetic anhydride was added and the reaction mixture was stirred and warmed gently for thirty minutes. Following addition of water to the solution, the toluene was steam-distilled off and a lumpy, brown solid remained after all the toluene had been removed. This substance proved to be unchanged starting material. The recovery was 90%.

Preparation of 2,6-Dimethoxydibenzofuran-1,9(?)-dialdehyde.

The procedure described below for the conversion of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran to the corresponding dialdehyde is adapted from that presented by Wittig (61) for the preparation of 2,6-dimethoxybenzaldehyde.

The n-butyllithium prepared from 5.5 ml. (0.052 mole) of n-butyl bromide and 0.72 g. (0.104 g. atom) of lithium in 300 ml. of ether was filtered under an atmosphere of dry nitrogen into a three-necked flask. To this solution was added a warm toluene solution of five grams (0.0129 mole) of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. The mixture was stirred at

room temperature for one hour and then 7.02 g. (0.052 mole) of N-methylformanilide was added. The reaction mixture immediately took on a bright yellow coloration and after five minutes the color test (62) for an organometallic compound was negative. Stirring was continued for thirty minutes and then 20 ml. of concentrated hydrochloric acid was added to the mixture.

Filtration of the reaction mixture yielded 2.3 g. (62%) of amorphous yellow aldehyde melting at 236-238°. Recrystallization from dioxane yielded pure 2,8-dimethoxydibenzofuran-1,9(?)-dialdehyde melting at 237-238°.

Anal. Calcd. for C_{16}H_{12}O_{5}: methoxyl, 21.82. Found: methoxyl, 22.03, 21.92.

Preparation of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde Dioxime.

A mixture of 0.5 g. (0.00176 mole) of 2,8-dimethoxydibenzo-
furan-1,9(?)-dialdehyde, 1.0 g. of hydroxylamine hydrochloride, 10 ml. of alcohol, 5 ml. of water, and 2.0 g. of potassium hydroxide was refluxed for twenty-four hours. At the end of this period, all the aldehyde had gone into solution. The cooled solution was acidified with concentrated hydrochloric acid and the resulting yellow precipitate was filtered out. The crude dioxime melted at 242-243° and weighed 0.49 g. (90%). Recrystallization from dioxane yielded pure 2,8-dimethoxy-
dibenzofuran-1,9(?)-dialdehyde dioxime melting at 243-244°.

Mixture of the diol with a sample of 2,8-dimethoxydibenzo-
furan-1,9(9)\(^{-}\)dialdehyde depressed the melting point to 206-
218°.

Anal. Calcd. for C\(_{16}\)H\(_{14}\)O\(_{5}\):  
N, 8.92; Found: N, 8.85.

Oxidation of 2,8-Dimethoxydibenzo-
furan-1,9(9)\(^{-}\)dialdehyde.

A few milligrams of the 2,8-dimethoxydibenzo-
furan-1,9(9)\(^{-}\)dialdehyde was suspended in 3 ml. of alcohol
and a solution of 0.3 g. of potassium permanganate in 3 ml. of
water was added. At the end of two and one-half hours of
refluxing, the permanganate color had been discharged. The
acid melted at 242-262°. Four recrystallizations from alcohol
raised the melting point to 271-272°. A mixed melting point
from alcohol, a nearly quantitative yield of 1.9(9)\(^{-}\)-dicarbo-
nyl-2,8-dimethoxydibenzo-furan was obtained. Mixture with an
authentic sample of 1.9(9)\(^{-}\)-dicarboxylic acid obtained from the
oxidation of the dialdehyde was esterified by treatment with diazomethane in ether. Upon
evaporation of the ether and recrystallization of the residue
the ester showed no depression. A few milligrams of the
2,8-dimethoxydibenzo-furan-1,9(9)\(^{-}\)-dicarboxylic acid obtained from the oxidation of the dialdehyde
was treated with 10% sodium amalgam to produce the
reduction mixture was dissolved slightly and filtered. Acid-
ification of the filtrate with hydrochloric acid precipitated an
acetate melting at 234-252°. A mixed melting point
Reaction of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde with Hydrazine.

The purpose of this reaction was to prepare a bridged compound of the type illustrated below. Any possibility for the formation of such a compound is of course based upon the assumption that the two aldehyde groups actually occupy the 1- and 9-positions.

![Chemical Structure](image)

Five-tenths of a gram (0.00176 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dialdehyde was suspended in 100 ml. of alcohol and just sufficient dioxane was added to effect complete solution. A slight excess of hydrazine hydrochloride was added to this solution, and the mixture was refluxed for one hour. Cooling and dilution of a sample of the reaction mixture produced very little precipitate. Accordingly, most of the solvent was distilled off and the small volume of solution remaining was diluted with water. A yellow flocculent precipitate melting at 290-295° was obtained. It was noted that the product tended to become red in color on prolonged exposure to air. Recrystallization from dioxane yielded a product melting at about 190°.

Analysis of the original high-melting material gave 8.77%
nitrogen, while analysis of the low-melting material obtained on recrystallization gave 4.48% nitrogen. The minimum nitrogen content to be expected in a possible product is 4.96% nitrogen, which is the composition of the following structure.

![Chemical Structure](image)

If a large number of dibenzofuran molecules were tied together by a series of intermolecular bridges, the composition of the polymer would approach that of the intramolecularly bridged compound (10.00% nitrogen) as the chain length approached infinity. Thus it appears likely that the original high-melting product which gave the higher nitrogen analysis was a relatively long-chain polymer, while the final product which gave a nitrogen analysis lower than the lowest possible theoretical result was a mixture of very short chain polymers with some regenerated aldehyde.

**Reaction of 2,8-Dimethoxydibenzofuran-1,9(?)-dialdehyde with o-Phenylenediamine.**

As in the previous reaction, the purpose of this reaction was the preparation of a compound possessing a bridge between the 1- and 9-positions. The desired product would have the following structure.
Five-tenths of a gram (0.00176 mole) of 2,8-dimethoxydibenzofuran-1,9(?)-dialdehyde was mixed intimately with 0.19 g. (0.00176 mole) of o-phenylenediamine and the mixture was heated at 120-140° for four hours. A reddish mass of rather glassy appearance resulted. This substance was dissolved in glacial acetic acid and the solution was refluxed thirty minutes with Norite and then filtered while hot. A sample of the filtrate gave no precipitate on dilution, but addition of sodium hydroxide resulted in the formation of a yellow, flocculent precipitate. The precipitate obtained in this manner from the entire body of filtrate was treated with warm, concentrated hydrochloric acid. The solution obtained was separated from a brown tarry substance which settled to the bottom. Treatment of the solution with alkali again precipitated a yellow floc which did not melt at 350°. Attempts at crystallizing the tarry material were unsuccessful.

Analysis of the yellow material gave 5.87% nitrogen. A dimer containing one o-phenylenediamine molecule and two unreacted aldehyde groups would contain 4.37% nitrogen. A very long chain polymer would approach a nitrogen content of 7.37%.
Thus it appears that the material obtained is a polymer of intermediate chain length.

**Dibromination of 2-Hydroxydibenzofuran.**

To a solution of five grams (0.0272 mole) of 2-hydroxydibenzofuran (50) in 50 ml. of glacial acetic acid was added dropwise with stirring 54.5 ml. of a molar solution of bromine in glacial acetic acid. Shortly after half of the bromine had been added, a granular precipitate began to form in the solution. Addition of all the bromine required one hour. When the bromination had been completed, the reaction mixture was allowed to stand one hour and was then filtered without dilution. The amorphous white product melted at 168-178° and weighed 3.4 g. (36.6%). The crude dibromo compound was acetylated without further purification as described in the following experiment.

Dilution of the filtrate obtained after removal of the crude dibromo-2-hydroxydibenzofuran produced 2.3 g. of amorphous white material melting at 108-132°. From steam distillation of this material was obtained 0.9 g. of a white, crystalline product melting at 122-123°. A mixed melting point determination with an authentic sample of 1-bromo-2-hydroxydibenzofuran showed no depression. The residue which did not volatilize with steam distillation melted at 167-175° and was very probably dibromo-2-hydroxydibenzofuran.
bromine in acetic acid. Over one and one-half hours was
addition with stirring of 5.2 ml. of a 25% solution of
in 100 ml. of 95% acetic acid and brominated by dropwise
10 g. atoms (0.045 mole) of 2-hydroxy benzene were dissolved
purified by recrystallization at 1-2°C. and then hydrolyzed.
in which the crude 1-bromo-2-hydroxy benzene, was acetylated.
used by Ven Rees. Recrystallization and purified procedure was repeated
of the crude 1-bromo-2-hydroxy benzene from the solution
experienced in obtaining a pure product by recrystallizations
procedure of Ven Rees (60). The crystals were
The bromination was carried out in accordance with the
M 00 bromination of 2-hydroxy benzene.

41.2, 41.4

Anal. Calcd. for C7H8O3Br2: Br, 41.7. Found: Br,
Pure compound crystallized in white prisms. The
1-bromo-2-acetoxy benzene which melted at 174-176°C. The
crystallizations from acetic acid. Yielded 7.6 g. (2) of pure
product which was obtained melted at 160-162°C. Two re-
preparations which were obtained, melted at 160-162°C.
and cautiously diluted with water. The white, crystalline
presumed. The mixture was refluxed for ten minutes, cooled,
and triturated and one drop of sulfuric acid was added to the susp.
2-hydroxy benzene was suspended in 15 ml. of acetic

Furum

Acetylation of the Bromination Product of 2-Hydroxy benzene.

- 25 -
required for the addition of all the bromine. When bromination had been completed, the reaction mixture was diluted to 1500 ml. with water and then filtered. The crude 1-bromo-2-hydroxydibenzofuran melted at 103-112° and weighed 12.5 g. (86.5%). It was used without further purification in the following experiment.

**Acetylation of 1-Bromo-2-hydroxydibenzofuran.**

Nine and two-tenths grams (0.035 mole) of crude 1-bromo-2-hydroxydibenzofuran was suspended in 15 ml. of acetic anhydride and two drops of concentrated sulfuric acid was added to the suspension. The mixture was refluxed for ten minutes, cooled to room temperature, and cautiously diluted with water. The crystalline product which melted at 133-135° was recrystallized twice from alcohol to yield 7.8 g. (73%) of pure 1-bromo-2-acetoxydibenzofuran melting at 135-136°.

**Anal. Calcd. for C_{14}H_{9}O_{3}Br: Br, 26.3 Found: Br, 26.1, 26.2.**

**Hydrolysis of 1-Bromo-2-acetoxydibenzofuran.**

Five and two-tenths grams (0.0170 mole) of 1-bromo-2-acetoxydibenzofuran was suspended in 20 ml. of alcohol and a solution of 2.04 g. of sodium hydroxide in 10 ml. of water was added. The mixture was refluxed for two hours and then acidified with hydrochloric acid. A white, amorphous precipitate of 1-bromo-2-hydroxydibenzofuran weighing 4.3 g. (96%) and
melting at 122-123° resulted. One recrystallization from 50% alcohol raised the melting point to 123-123.5°.

**Bromination of 1-Bromo-2-hydroxydibenzofuran.**

A solution of 3.3 g. (0.0125 mole) of 1-bromo-2-hydroxydibenzofuran in 100 ml. of glacial acetic acid was brominated by the dropwise addition of 12.5 ml. of a molar solution of bromine in acetic acid. The bromination was carried out with constant stirring over a period of two hours, and during the course of the reaction, a granular, white precipitate separated. When bromination was complete, the mixture was allowed to stand for one hour and was then filtered without dilution. The white, amorphous 1, x* - dibromo-2-hydroxydibenzofuran weighed 3.0 g. (70%) and melted at 180-182°. This product was acetylated without further purification. Dilution of the filtrate after removal of the crude dibromo compound produced an additional 1.1 g. of crude product melting at 168-178°.

**Acetylation of 1, x-Dibromo-2-hydroxydibenzofuran.**

Three grams (0.0088 mole) of 1, x-dibromo-2-hydroxydibenzo- 

The "x" is used to represent the position of the second bromine atom because its location has not yet been established.
melting at 151-153° was obtained. Two recrystallizations from alcohol produced 3.2 g. (95%) of pure 1,x-dibromo-2-acetoxydibenzofuran melting at 154-155°. A mixed melting point determination with a sample of the dibromoacetoxy compound prepared from direct dibromination of 2-hydroxydibenzofuran showed no depression. This proves that one of the two bromine atoms in the dibromination product is in the 1-position.

Hydrolysis of 1,x-Dibromo-2-acetoxydibenzofuran.

One and five-tenths grams (0.0039 mole) of 1,x-dibromo-2-acetoxydibenzofuran was suspended in a mixture of 10 ml. of alcohol and 5 ml. of concentrated hydrochloric acid. This mixture was refluxed for twenty hours. During the reflux period, the crystalline mass was altered gradually to an amorphous solid, but complete solution was never obtained. After cooling, the mixture was diluted and filtered. The amorphous, white 1,x-dibromo-2-hydroxydibenzofuran weighed 1.3 g. (97.5%) and melted at 181-182°. Recrystallization from alcohol did not alter the melting point.

Anal. Calcd. for C_{12}H_{6}O_{2}Br_{2}: Br, 46.2. Found: Br, 45.8, 45.9.

Monobromination of 2-Methoxydibenzofuran.

The procedure of Van Ess (63) for the preparation of 2-methoxy-3-bromodibenzofuran was followed. The yield

obtained was somewhat lower than that reported by Van Ess, and the discrepancy may be due to the fact that the reaction mixture was not diluted before removal of the crude product. It was hoped that avoiding of dilution would yield a crude product of better quality.

Seven and two-tenths grams (0.0364 mole) of 2-methoxy-dibenzofuran melting at 45-47° was dissolved in 70 ml. of glacial acetic acid and brominated by dropwise addition with stirring of 36.4 ml. of a molar solution of bromine in acetic acid. Thirty minutes was required for addition of all the bromine. Filtration of the reaction mixture without dilution yielded 3.6 g. of a white, granular material melting at 156-171°. The crude 2-methoxy-3-bromodibenzofuran was extracted with 20 ml. of boiling alcohol and the residue was recrystallized from benzene to yield 2.6 g. (25.8%) of pure 2-methoxy-3-bromodibenzofuran melting at 171.5-172.5°.

Anomalous Demethylation of 2-Methoxy-3-bromodibenzofuran.

Two and two-tenths grams (0.00795 mole) of 2-methoxy-3-bromodibenzofuran was suspended in a mixture of 9 ml. of constant-boiling hydrobromic acid and 10 ml. of glacial acetic acid. The resulting mixture was refluxed for seventeen hours, and then diluted and filtered. The product obtained on recrystallization from dilute alcohol melted at 168-170°. A sample of this material was found to dissolve readily in 10% sodium hydroxide solution, a fact which indicated the phenolic
nature of the compound. Mixture with a sample of 2-bromo-3-methoxydibenzofuran depressed the melting point to 139-144°. The product is obviously not 2-hydroxy-3-bromodibenzo-furan, since this compound, prepared from 2-bromo-3-aminodibenzo-furan, has been reported to melt at 143-144° (50).

The phenolic compound was methylated in methyl alcohol solution by treatment with dimethyl sulfate and sodium hydrox-ide. The white, alkali-insoluble product resulting was re-crystallized at considerable loss from benzene to yield a small amount of needles crystallizing in radiating clusters melting at 154-155°. This methylation product is obviously not 2-methoxy-3-bromodibenzo-furan. The material was not analyzed or further investigated.

**Monobromination of 2,8-Dihydroxydibenzofuran.**

A number of attempts were made to monobrominate both 2,8-dihydroxy- and 2,8-dimethoxydibenzo-furan by addition of a bromine-containing solution to a solution of the dibenzo-furan derivative. The solvents tried were glacial acetic acid and carbon tetrachloride. The only pure substances isolated from these reactions were the 1,9(?)-dibromo- derivatives and the unreacted starting materials. Entrainment bromination, however, in which the bromine was introduced by bubbling a stream of air containing bromine vapors through the reaction mixture, proved capable of yielding the desired monobromo derivative.

In a typical run, ten grams (0.05 mole) of
It was heated without further filtration at 17.7°C (91%)
filtered off, The crude 1,2'-bromo-2',6'-dihydroxybenzoin was
filtered with water, and the white, translucent precipitate was
diluted with water. When the reaction mixture was
completed, the reaction mixture was
where the bromine entered the reaction mixture.
remaining compound collected at the end of the gas intake tube
occasionally it was advisable to remove the solid
material which collected at the end of the gas intake tube
after about 16 hours. Stirring was maintained at all
times during the bromination, Which required about 16
or one bubble in two seconds. Stirring was maintained at a rate
passed over the bromine and into the reaction vessel at a rate
which during the course of the bromination. It upset was then
be of quite a large bore (about 15 mm) In order to avoid the
of an efficient stirrer. It was found that this tube must
be at the bottom of the flask, thus leaving ample space for the function-
the mass of the three-necked flask rather closer to the
mass was taken from the mass so shaped as to follow the contour
rather than with a gas delivery tube which was connected to a gas intake
which was connected to the surface of the bromine,
the brominator flask was fitted with a gas intake tube which
extended to within half an inch of the surface of the bromine.
the brominator flask was fitted with a 25 ml. (0.05 mole) or bromine.
two- or three-necked styper was placed 2.55 ml.
mechanical stirrer. In a small brominator flask fitted with
septum and in a 500 ml. three-necked flask fitted with
2,6-dihydroxybenzoin was dissolved in 200 ml. of
- 59 -
Acetylation of 1(?)-Bromo-2,8-dihydroxydibenzo[fluran.

Twelve and seven-tenths grams (0.0455 mole) of crude 1(?)-bromo-2,8-dihydroxydibenzo[fluran was suspended in 35 ml. of acetic anhydride, and 1.5 ml. of concentrated sulfuric acid was added. The mixture was refluxed two hours, cooled to room temperature, and cautiously diluted with water. The slightly gummy crude product was recrystallized several times from alcohol to yield 4.1 g. (24.8%) of pure 1(?)-bromo-2,8-di-acetoxydibenzo[fluran melting at 142-144°. The compound crystallized in white needles.

**Anal.** Calcd. for C_{16}H_{11}O_5Br: Br, 22.03. Found: Br, 21.9, 21.8.

Methylation of 1(?)-Bromo-2,8-di-acetoxydibenzo[fluran.

Three grams (0.00825 mole) of 1(?)-bromo-2,8-di-acetoxydibenzo[fluran was suspended in a mixture of 7.5 ml. of methyl alcohol and 2.8 ml. of dimethyl sulfate. The mixture was cooled to -10° and a solution of 3.0 g. of sodium hydroxide in 5 ml. of water was added. When the reaction had subsided, the mixture was refluxed for thirty minutes. The cooled reaction mixture was diluted and filtered. Three recrystallizations from alcohol yielded 1.9 g. (75%) of pure 1(?)-bromo-2,8-dimethoxydibenzo[fluran melting at 102.5-103.5°.

**Anal.** Calcd. for C_{14}H_{11}O_3Br: Br, 26.05. Found: Br, 25.7, 25.8.
Preparation of n-Butoxymethylpiperidine.

The following procedure is adapted from that of Robinson and Robinson (64). The piperidine used was the 105-112°C fraction taken from Eastman Kodak practical grade piperidine.

Forty-two and one-half grams (0.5 mole) of piperidine was added cautiously to 42 g. of a 37% formaldehyde solution. A temporary turbidity appeared after the addition of each portion of piperidine. After all the piperidine had been added, it was found necessary to add a small amount of formaldehyde to clear the solution.

To the clear solution was added 37 g. of n-butyl alcohol and sufficient anhydrous potassium carbonate was added to the resulting mixture to saturate it and leave a considerable portion undissolved. The reaction flask was stoppered and shaken vigorously at frequent intervals over a period of twenty-four hours. The mixture was then diluted with ether, and decanted from the potassium carbonate sludge which was then extracted with additional ether. The combined ether extracts were dried over potassium carbonate and then distilled at reduced pressure. The fraction boiling at 82-96°C at 3 mm. was collected and redistilled. The yield of pure n-butoxymethylpiperidine boiling at 91-93°C at 6 mm. was 56.5 g. (68%).

Preparation of 4-Dibenzofuranyl-N-piperidinomethane.

To the n-butyllithium prepared from 6.60 g. (0.952 g. atom)
of lithium and 50 ml. (0.476 mole) of \text{n}-butyl bromide in 400 ml. of anhydrous ether was added an ethereal solution of twenty grams (0.119 mole) of pure dibenzofuran. The reaction mixture assumed a yellow-green color almost immediately after the addition of the dibenzofuran. Stirring was continued for eighteen hours, and a strong color test (62) for an organometallic compound was obtained at the end of this time.

The solution of 4-dibenzofuryllithium was added dropwise to an ethereal solution of 20.3 g. (0.119 mole) of \text{n}-butoxy-methylpiperidine. A white precipitate formed and there was some refluxing during the course of this addition. At the end, the yellow color of the organometallic compound persisted and sufficient \text{n}-butoxy-methylpiperidine was added to discharge this color. The mixture was stirred for a period of ten hours and, at the end of this time, the color test was negative. About 50 ml. of water was added to the reaction mixture and the solid material remaining undissolved was filtered out and extracted with ether. The ethereal extracts were combined with the ethereal layer from the filtrate and the whole was extracted with dilute hydrochloric acid. Treatment of the acid extract with ammonium hydroxide precipitated a brown oil which was taken up in ether solution.

The ethereal extract was distilled at reduced pressure and a small amount of \text{n}-butoxy-methylpiperidine was collected following removal of the ether. The reaction product, 4-dibenzofuryl-N-piperidinomethane, appeared to have a very low
vapor pressure and part of the compound was decomposed in initial attempts to distill it. It was finally distilled successfully in an all-glass apparatus which was heated by an oil bath which covered it to within a centimeter below the side arm. The compound distilled at 175-180° at 0.5 mm. The yield of pure 4-dibenzofuryl-N-piperidinomethane was 7.8 g. (24.8%).

Anal. Calcd. for C_{18}H_{19}ON: N, 5.28. Found: N, 5.33, 5.41.

Preparation of 4-Dibenzofuryl-N-piperidinomethane Picrate.

One gram (0.0038 mole) of 4-dibenzofuryl-N-piperidinomethane was dissolved in 20 ml. of alcohol and 25 ml. of a saturated solution of picric acid in alcohol was added to the warm solution. A yellow, finely divided precipitate formed immediately. The suspension was heated to boiling and it was necessary to add additional alcohol to effect complete solution. The granular, yellow picrate which separated on cooling melted at 174-177°. Recrystallization from alcohol yielded 0.5 g. of pure 4-dibenzofuryl-N-piperidinomethane picrate melting at 177-178°.


Preparation of m-Trifluoromethylaniline.

Benzotrichloride was converted to m-trifluoromethyl-
Treatment of 300 g. of benzotrichloride with antimony trifluoride gave benzotrifluoride in 81.5% yield in a typical run. Nitration of the product with a mixture of concentrated sulfuric acid and fuming nitric acid at 30-40° gave crude m-nitrobenzotrifluoride in 99% yield. Reduction of the crude nitro compound with sulfuric acid and powdered iron metal gave a yield of pure m-trifluoromethylaniline of 88% (based upon the amount of benzotrifluoride originally nitratred).

**Preparation of 1-(m-Trifluoromethylphenylazo)-2-hydroxydibenzo-furan.**

The procedures used in this and the following coupling reactions were adapted from the procedure of M. W. Van Ess (51) for the preparation of 1-phenylazo-2-hydroxydibenzo-furan.

Three grams (0.0163 mole) of 2-hydroxydibenzo-furan was dissolved in 12.5 ml. of 15% potassium hydroxide solution and 50 ml. of water was added. The solution was cooled to 0° in an ice-HCl bath. Two and sixty-two-hundredths grams (0.0163 mole) of m-trifluoromethylaniline was treated with 4.1 ml. of concentrated hydrochloric acid and sufficient water was added to effect complete solution. This solution was cooled to 0° and then diazotized by the slow addition of a solution of 1.11 g. of sodium nitrite in 20 ml. of water. The temperature was not allowed to rise above 5° during the course of the diazotization.

The cold solution of diazonium salt was added in small
portions with vigorous stirring to the cold solution of 2-
hydroxydibenzofuran potassium salt. After all the diazonium
salt had been added, stirring was continued for thirty min-
utes. The crude orange coupling product, which had separated
at once, was filtered off and dried. It weighed 4.8 g. (82%)
and melted at 128-134°. Extraction of the crude coupling
product with boiling alcohol raised the melting point to 154-
158°. Two recrystallizations from glacial acetic acid yielded
2.7 g. (46.5%) of pure 1-(m-trifluoromethylphenylazo)-2-
hydroxydibenzofuran melting at 173-174°.

Anal. Calcd. for C_{19}H_{11}O_{2}N_{2}F_{3}: N, 7.36. Found: N,
7.94, 7.99.

Preparation of 1-(m-Trifluoromethylphenylazo)-2,8-dihydroxy-
dibenzofuran.

The procedure used was essentially that just described
for the preparation of 1-(m-trifluoromethylphenylazo)-2-
hydroxydibenzofuran. Six and forty-two-hundredths grams (0.04
mole) of m-trifluoromethylaniline was treated with 10.1 ml. of
concentrated hydrochloric acid and diazotized with a solution
containing 2.72 g. of sodium nitrite. The cold diazonium salt
solution was added to a cold solution of eight grams (0.04
mole) of 2,8-dihydroxydibenzoferan in 200 ml. of water con-
taining 6.7 g. of potassium hydroxide. A deep reddish-orange
precipitate separated immediately. Stirring was continued
for thirty minutes, and then the suspension was allowed to
stand over night to coagulate for better filtration.

The coupling product was filtered off and extracted several times with 50 ml. portions of boiling 5% potassium hydroxide solution. The solution was filtered hot after each extraction and the residue extracted with fresh alkali. Extraction was discontinued when acidification of a sample of the filtrate produced no appreciable precipitate. The combined extracts, which were deep red in color, were carefully acidified with hydrochloric acid, being made just acid to Congo Red. The dark red precipitate was filtered off and recrystallized from glacial acetic acid. The product crystallized out in fine orange-brown needles which melted at 256-257°. A second recrystallization from acetic acid did not alter the melting point. The yield of pure 1-(m-trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran was 3.0 g. (20.1%).

Anal. Calcd. for C_{19}H_{11}O_{3}N_{2}F_{3}: N, 7.53. Found: N, 7.49, 7.55.

**Attempted Preparation of 1,9-bis-(m-Trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran.**

The only alteration in procedure from the foregoing two reactions was that the diazonium salt solution was added very quickly and in one portion to the cold solution of phenolic salt. The quantities of materials used were eight grams (0.04 mole) of 2,8-dihydroxydibenzofuran, 18 g. of potassium hydroxide in 300 ml. of water, twelve and nine-tenths grams
(0.08 mole) of m-trifluoromethylaniline, 20.2 ml. of concentrated hydrochloric acid, and 5.45 g. of sodium nitrite. A voluminous red-orange precipitate separated immediately upon addition of the diazonium salt solution to the phenolic salt solution. After having been stirred for thirty minutes, the reaction mixture was filtered and attempts were made to purify the crude coupling product. The product was too insoluble in most solvents for successful recrystallization, and contact with acetic acid appeared to decompose it. No pure product could be isolated.

**Attempted Preparation of Dibenzofuran-4-aldehyde.**

To the n-butyllithium prepared from 10.3 g. (1.49 g. atom) of lithium and 79 ml. (0.746 mole) of n-butyl bromide in 500 ml. of anhydrous ether was added fifty grams (0.298 mole) of dry dibenzofuran of m.p. 83-85°. The solution immediately became green in color. It was stirred and refluxed for fourteen hours, during which time it gradually assumed a brown coloration. At the end of the reflux period, the reaction mixture gave a strong color test (62) for an organometallic compound.

To the reaction mixture was added cautiously 101 g. (0.746 mole) of N-methylformanilide. The mixture refluxed vigorously during this addition and about one hour was required to complete it. As the addition of N-methylformanilide was completed, the white precipitate which had been forming in the reaction mixture suddenly coagulated to a very sticky, viscous
mass which froze the stirrer. A color test on the supernatant liquor for an organometallic compound was negative. The ether was decanted off, and the viscous residue was treated with 200 ml. of six-normal hydrochloric acid. Considerable heat was evolved, and the solid mass gradually disappeared, leaving a yellow ethereal layer floating on the hydrochloric acid layer. The ether which had originally been decanted off was poured back in, and the entire mixture was transferred to a large separatory funnel and shaken vigorously. The ethereal layer was then separated and dried over anhydrous sodium sulfate. During these manipulations of the aldehyde-containing reaction mixture, all vessels were kept flushed out with nitrogen to prevent possible oxidation of the aldehyde.

The dried ethereal solution was concentrated into a Claisen flask and the last traces of ether were removed under the aspirator vacuum. Heating was continued under the aspirator vacuum, and all the material distilling below 155° was collected. About 10 ml. of N-methylformanilide was recovered. Distillation was then continued at a pressure of 1 mm. using the oil pump. About half of the material remaining in the flask distilled at 176-179°. Distillation was discontinued at 180°. The distillate was a mobile yellow oil from which a small amount of white powder separated on standing over night. The oil was decanted from the solid and found to weigh 27.5 g. (47%). Upon standing with Schiff's reagent a few minutes, a sample of the oil gave a positive test for an aldehyde. A
similar test on N-methylformanilide was negative.

The crude aldehyde was evidently very impure, because attempts to prepare the oxime and the anil with m-trifluoro-methylaniline resulted in products which could not be purified. On standing for several days, the yellow oil formed in part a white solid which was found to consist of microscopic needles melting at 81-83º. This substance was not further investigated, but it may have been dibenzofuran.

An attempt at preparation of the 2,4-dinitrophenylhydrazone of the crude aldehyde was successful, although a low yield was obtained. Three grams (0.0153 mole) of 2,4-dinitrophenylhydrazine was suspended in 150 ml. of alcohol and the suspension was heated to boiling. To the hot mixture was added a solution of three grams (0.0153 mole) of crude dibenzofuran-4-aldehyde in 50 ml. of alcohol. The yellow dinitrophenylhydrazone separated almost at once. The mixture was again heated to boiling and 4 ml. of concentrated hydrochloric acid was added. After a ten minute reflux period, the reaction mixture was cooled and filtered. The crude product crystallized in microscopic yellow needles which melted at 297-299º and weighed 2.2 g. (38.2%). Because of extreme insolubility, the 2,4-dinitrophenylhydrazone could not be crystallized from alcohol, but the crude product which had been extracted with hot alcohol melted at 299-300º. Two recrystallizations from a chloroform-dioxane mixture yielded pure dibenzofuran-4-aldehyde 2,4-dinitrophenylhydrazone melting at 301-302º.

It is thought likely that a more successful preparation of dibenzofuran-4-aldehyde could be carried out by cooling the solution of 4-dibenzofuryllithium to $-10^\circ$ before addition of the N-methylformanilide. This would make it possible to add the N-methylformanilide very rapidly and there would be less opportunity for dibenzofuran-4-aldehyde to react with 4-di-benzofuryllithium.

**Bromination of Benzotrifluoride.**

The bromination was carried out using essentially the procedure of Simons and Ramler (66). Two hundred and sixty-six grams (1.82 moles) of benzotrifluoride was placed in a three-necked flask with 4 g. of iron powder. To the mixture was added 6 ml. of bromine, and the oil bath surrounding the flask was heated to $70^\circ$ to start the reaction. As soon as the reaction had started, the bath was cooled to $56^\circ$ and 42 ml. of bromine was added dropwise with stirring over a period of two hours. Stirring was continued for a second two-hour period with the bath at $56^\circ$. An additional 50 ml. of bromine was added dropwise over a two-hour period, and then stirring was continued for two hours with the oil bath at $60^\circ$. The product was poured out into 800 ml. of water containing 30 g. of sodium bisulfite.

When the bromine color had disappeared, the mixture was steam distilled under the hood, a precaution which was necessitated by the sulfur dioxide fumes evolved. A colorless oily layer separated at the bottom of the distillate. Steam distillation was continued until a white solid (benzoic acid and \( m \)-bromobenzoic acid) began to come over with the distillate. The distillate was extracted with ether, and the combined ether extracts were washed twice with dilute potassium hydroxide solution. The ether layer was dried for four hours over anhydrous potassium carbonate, and then the ether was distilled off. A forerun, consisting principally of unreacted benzotrifluoride, followed, and then the product distilled at 151-153\(^\circ\). The yield of pure \( m \)-bromobenzotrifluoride was 221 g. \((54\%\)). Physical constants determined for this substance were: \( n_D^{20} \) 1.4749; and \( d^{29} \) 1.606.

**Preparation of \( m \)-Trifluoromethylbenzaldehyde.**

The following procedure was adapted from that of Smith and Bayliss (67) for the preparation of benzaldehyde from phenylmagnesium bromide. In a three-necked flask was placed 200 ml. of anhydrous ether and four and eight-tenths grams (0.2 mole) of magnesium turnings. The system was swept out with dry nitrogen, and a solution of forty-five grams (0.2 mole) of \( m \)-bromobenzotrifluoride in 50 ml. of anhydrous ether was placed in the dropping funnel. A crystal of iodine was added to the

mixture in the flask, and 5 ml. of the halide solution was allowed to flow in. The mixture was warmed gently and stirred until the reaction had started. The remainder of the halide solution was added dropwise with stirring over a period of one and one-half hours. Once started, the reaction proceeded smoothly, and the mixture took on a dark brown color which was so deep as to be almost black at the conclusion of the reaction. Stirring was continued for thirty minutes after addition of the halide was completed. All the magnesium turnings disappeared indicating virtually quantitative formation of the Grignard reagent.

The reaction mixture was cooled in an ice-bath and 27 g. (0.2 mole) of N-methylformanilide was added through the addition funnel as rapidly as possible. About three minutes was consumed by this addition. After five minutes, the color test for an organometallic compound was negative. Stirring, however, was continued for three hours, during which time a granular, yellow precipitate separated.

The mixture was again cooled in an ice-bath and a solution of 11 ml. of concentrated sulfuric acid in 55 ml. of water was added, very cautiously, with stirring. Stirring was continued for ten minutes after addition of all the acid and then sufficient water was added to dissolve all solids present. The ether layer was separated and washed twice with saturated sodium bicarbonate solution. After drying over calcium chloride for three hours, the ether solution was distilled in a
Preparation of 7,8-dinitrophenylhydrazone

The 7,8-dinitrophenylhydrazone was prepared in the usual manner in acetone solution from the tetra-tenine of a O.00287 mole of 3,4-dinitrophenylhydrazine. The crude 3,4-dinitrophenylhydrazide and 0.66 g. of 66-69°C (10 mm.)

and 6% 1.200 ° red. (25°C) of the pure 3,4-dinitrophenylhydrazide were 0.1.460 g., and the yield was read to 54%. Physical constants of the pure yellow material showed it to be 9-70°C. 10% of a mobile, light yellow oil distillated at 76.7°C.

This material gave a positive test with Schiffs reagent, and subsequent preparation of derivatives showed it to be 9-70°C.

In an atmosphere of 75 mm., posterior removal of the ether,
Preparation of m-Trifluoromethylbenzaldoxime.

Ten and eight-tenths grams (0.062 mole) of m-trifluoromethylbenzaldehyde was added to a mixture of 5.6 g. of hydroxylamine hydrochloride and 3.0 g. of sodium hydroxide in 20 ml. of water. Sufficient alcohol was added to this mixture to obtain complete solution and the resulting solution was refluxed for forty-five minutes. No product separated when the reaction mixture was cooled. Dilution with water produced a colorless oil which was separated from the aqueous layer. A small sample of the oil was found to be readily soluble in potassium hydroxide solution. The aqueous layer was extracted with benzene, and the benzene extracts were combined with the oil previously separated.

The benzene solution of the oxime was distilled at 15 mm. Following removal of the benzene and alcohol, the main fraction distilled at 108-110°. The yield of m-trifluoromethylbenzaldoxime was 7.6 g. (65%). Physical constants determined for the oxime were: n_D^20 1.5128; and d_29^2 1.305. Redistillation gave b.p. 102-104° (12 mm.).


Preparation of 3-(m-Trifluoromethylbenzalaminio)benzotrifluoride.

Five and three-tenths grams (0.0329 mole) of m-trifluoromethylaniline and five and forty-eight-hundredths grams (0.0315 mole) of m-trifluoromethylbenzaldehyde were dissolved in 50 ml.
of benzene. The solution was refluxed for one hour. The water formed in the reaction separated as an aqueous layer and was removed by use of a small separatory funnel. The benzene layer was dried over anhydrous potassium carbonate.

The benzene was distilled off at atmospheric pressure and the yellow oil remaining was fractionated at 3 mm. A forerun, undoubtedly representing unreacted starting materials, distilled at 76-90°. The main fraction distilled at 139-140° at 3 mm. and was a yellow oil weighing 4.2 g. (42%). On standing a few minutes, the oil crystallized to needles of crude 3-(m-trifluoromethylbenzalamino)-benzotrifluoride which melted at 49.5-51.5°.

In a second run, the same procedure was followed except that the reaction mixture was refluxed for five hours. The yield of crude anil was 62%. The crude products from the two runs were combined and recrystallized from petroleum ether (b.p., 28-38°). The yield of pure 3-(m-trifluoromethylbenzalamino)-benzotrifluoride, which crystallized in white needles melting at 50-51°, was 6.7 g. The melting point was not altered by a second recrystallization from the same solvent.


Preparation of 4-(m-Trifluoromethylbenzalamino)-dibenzofuran.

In 50 ml. of dry benzene was dissolved one gram (0.00545 mole) of 4-aminodibenzofuran (10) and ninety-five-hundredths of a gram (0.00545 mole) of m-trifluoromethylbenzaldehyde.
There was no evidence of reaction having occurred after eight hours of refluxing. The benzene was distilled off, and the residual red oil was heated in an oil bath at 120-130° for one hour. The mass solidified on cooling, and recrystallization from petroleum ether (b.p., 60-70°) yielded a tan amorphous product melting at 64-66°. Successive recrystallizations from benzene-petroleum ether (b.p., 28-38°), chloroform-petroleum ether (b.p., 28-38°), and anhydrous ethanol-petroleum ether (b.p., 28-38°) yielded 0.532 g. (28.8%) of pure 4-([m-trifluoromethylbenzalamino]dibenzoferan melting at 81-83°. Mixture with a sample of 4-aminodibenzoferan depressed the melting point to 61-65°.


Preparation of N-([p-Acetaminophenyl]-2,5-dimethylpyrrole.

Two identical runs were made. Twenty-five grams (0.166 mole) of Eastman technical p-aminoacetanilide was placed in an Erlenmeyer flask with nineteen grams (0.166 mole) of acetonylacetone. The mixture was heated on the steam bath for one hour. At first it fused and became completely liquid. Then water was evolved, and the liquid solidified. A white, crystalline material sublimed onto the walls of the flask above the main mass of product which was dark brown.

Half of the crude product from one of the two runs made was sublimed at 200° at 2 mm. The sublimed product melted
at 206-207° and was crystallized in minute white needles. Recrystallization from alcohol yielded white plates which altered to white needles at 198° and then melted at 207-208°. This melting point was not changed by a second recrystallization. Since considerable charring occurred during the sublimation, the main body of crude product was crystallized from alcohol without sublimation. The yield of pure N-(p-acetaminophenyl)-2,5-dimethylpyrrole melting at 207-208° was 41.5 g. (73%, based upon one and one-half times the amount of p-aminoacetanilide used in a single run). The material analyzed was the sublimed product.


**Hydrolysis of N-(p-Acetaminophenyl)-2,5-dimethylpyrrole.**

Thirty-five grams (0.154 mole) of N-(p-acetaminophenyl)-2,5-dimethylpyrrole was suspended in a mixture of 40 ml. of concentrated hydrochloric acid and 50 ml. of water. After three hours of refluxing, all the solid had dissolved and a deep red solution remained. From this solution there precipitated, upon cooling in the refrigerator, 9.1 g. of light tan plates which did not melt. This substance was undoubtedly an amine hydrochloride, since it was extremely soluble in water and contained chlorine.

Neutralization with excess sodium carbonate of the red solution from which the amine hydrochloride had been filtered
resulted in a voluminous pink precipitate of free amine. This compound was quite unstable and darkened very rapidly on exposure to air. The free amine was filtered off, pressed as dry as possible in a Büchner funnel, and quickly transferred to a vacuum desiccator in which it was dried over calcium chloride for two hours. The amine was used in the following experiment without further purification.

An analysis of the substance believed to be the hydrochloride of N-(p-aminophenyl)-2,5-dimethylpyrrole gave an anomalous result.

**Anal.** Calcd. for C_{12}H_{14}N_{2}: N, 15.04. Calcd. for C_{12}H_{14}N_{2}·HCl: N, 12.58. Calcd. for C_{12}H_{14}N_{2}·2HCl: N, 10.80. Found: N, 14.80, 14.91.

**Attempted Diazo Coupling of N-(p-Aminophenyl)-2,5-dimethylpyrrole with 2-Hydroxydibenzofuran.**

Seven and five-tenths grams (0.0403 mole) of crude N-(p-aminophenyl)-2,5-dimethylpyrrole was dissolved in 8 ml. of concentrated hydrochloric acid in 50 ml. of water, cooled to 0°, and diazotized with a solution of 3.5 grams of sodium nitrite. The cold diazonium salt solution was added slowly with stirring to a solution of seven and five-tenths grams (0.0407 mole) of 2-hydroxydibenzofuran in 75 ml. of water containing 3 g. of sodium hydroxide at 0°. At the outset, a red precipitate formed, but the mixture had become brown in color by the time all of the diazonium salt solution had been added.
Stirring was continued for thirty minutes with the temperature of the reaction mixture at 0°, and then the mixture was filtered. The brown solid obtained darkened rapidly to black on exposure to air. Attempts at purification by recrystallization from various solvents were unsuccessful.

Reduction of Tolu-p-quinone.

Tolu-p-quinone was reduced to toluhydroquinone with stannous chloride by a modification of the procedure of Russig (68) for the reduction of o-quinones. Thirty grams (0.246 mole) of tolu-p-quinone was suspended in 300 ml. of hot water and a warm solution of 60 g. of SnCl₂·2H₂O in 100 ml. of water was added slowly. The stannous chloride solution used contained just sufficient hydrochloric acid to prevent the formation of stannous hydroxide. The flask was swirled during the addition in order to obtain efficient mixing.

No appreciable precipitate separated when the reaction mixture was cooled, and consequently the cold mixture was extracted with ether. Distillation of the ether layer produced a dark brown residue which was extracted repeatedly with boiling benzene. A white, crystalline product separated from the cooled benzene extracts. Recrystallization from benzene yielded 24.5 g. (60%) of pure toluhydroquinone melting at 125-126°.

Methylation of Toluhydroquinone.

The methylation was carried out in accordance with the procedure of Perkin and Weizman (69) for the methylation of pyrocatechol. Treatment of 96.1 g. (0.775 mole) of toluhydroquinone with 406 g. of dimethyl sulfate in 235 ml. of methanol and then with 129 g. of sodium hydroxide in 322 ml. of water yielded 105.5 g. (89.5%) of pure toluhydroquinone dimethyl ether boiling at 138-141° at 3 mm.

Iodination of Toluhydroquinone Dimethyl Ether.

The procedure used for the preparation of 5-iodotoluhydroquinone dimethyl ether was adapted from that of Erdtman (54). In an Erlenmeyer flask was placed 25 g. (0.164 mole) of toluhydroquinone dimethyl ether and 41.4 g. (0.164 mole) of iodine. A small quantity of mercuric oxide was added to the mixture and it was stirred until a perceptible evolution of heat indicated that the reaction had started. It is important that the reaction be started before any considerable quantity of mercuric oxide is added since, otherwise, there is danger of a violent reaction in which iodine is volatilized from the reaction vessel and considerable decomposition occurs. Once the reaction was started, addition of mercuric oxide in small portions was continued until the total amount added was 35.8 g.

When the reaction mixture had cooled, a solid red mass

remained. This material was extracted with four 50 ml. portions of boiling benzene, which were filtered while hot. The combined benzene extracts were washed with aqueous sodium iodide solution to remove traces of free iodine. The benzene was then distilled off, leaving a reddish mass of crystals. Two recrystallizations from methanol yielded 18.3 g. (40%) of pure 5-iodotoluhydroquinone dimethyl ether which crystallized in slightly yellowish needles melting at 84-85°. This melting point was not depressed by mixture with a sample of the 5-iodotoluhydroquinone dimethyl ether prepared by Erdtman.

**Conversion of 5-iodotoluhydroquinone Dimethyl Ether to 2,5-Dimethoxy-β-toluic Acid.**

To the n-butyllithium prepared from 0.20 g. (0.0285 g. atom) of lithium and 1.52 ml. (0.0144 mole) of n-butyl bromide in 30 ml. of anhydrous ether was added with stirring a solution of two grams (0.0072 mole) of 5-iodotoluhydroquinone dimethyl ether in 20 ml. of ether. The mixture was stirred at room temperature for five minutes and then poured out onto a large excess of solid carbon dioxide.

When all the carbon dioxide had volatilized, additional ether was added, and the ethereal solution and residues were extracted with a solution of 0.9 g. of potassium hydroxide in 50 ml. of water. Acidification of the pinkish potassium hydroxide extract with hydrochloric acid produced a curdy, white precipitate. Solution and precipitate were cooled in an
ice-bath, and the crude acid was filtered from the cold solution. The crude acid weighed 0.57 g. and melted at 124-125°. Recrystallization from water yielded 0.50 g. (35.4%) of pure 2,5-dimethoxy-p-toluic acid melting at 125-126°.


Attempted Preparation of the Grignard Reagent from 5-Iodotoluhydroquinone Dimethyl Ether.

Two grams (0.0072 mole) of 5-iodotoluhydroquinone dimethyl ether was dissolved in 25 ml. of anhydrous ether. This solution was added with stirring to 0.18 g. (0.0075 g. atom) of magnesium turnings and a small amount of finely divided magnesium in 50 ml. of ether containing a crystal of iodine. After all the iodo compound had been added, the mixture was stirred and refluxed for eight hours. Although the iodine color disappeared, no color test for an organometallic compound was obtained at the end of this time.

Two drops of n-butyl bromide was then added to the reaction mixture and stirring and refluxing were continued for a second eight-hour period. At the end of this time, a very weak positive color test for an organometallic compound was obtained. The mixture was carbonated, and the ethereal solution, following carbonation, was extracted with aqueous potassium hydroxide solution. Acidification of the extract produced no precipitate.
Preparation of 2,5-Dimethoxy-p-tolunitrile.

Preparation of this compound was accomplished by application of the Rosenmund-von Braun nitrile synthesis to 5-iodotoluhydroquinone dimethyl ether using the procedure of Koelsch (70). An intimate mixture of three grams (0.0108 mole) of 5-iodotoluhydroquinone dimethyl ether and 2.12 g. of anhydrous cuprous cyanide was heated at 240°C for four hours in a system protected from moisture. After the reaction mixture had been cooled, the solid mass which remained was broken up and transferred to a Soxhlet extraction cup. The mass was extracted for one hour with acetone and then the acetone was distilled from the extract. The light yellow crude nitrile which remained was recrystallized from dilute alcohol to yield 1.4 g. (73%) of pure 2,5-dimethoxy-p-tolunitrile which crystallized in yellow needles melting at 130-131°C.

Anal. Calcd. for C_{10}H_{11}O_2N: N, 7.91. Found: N, 7.95, 7.98.

Hydrolysis of 2,5-Dimethoxy-p-tolunitrile.

One and two-tenths grams (0.0068 mole) of 2,5-dimethoxy-p-tolunitrile was dissolved in a solution of 0.8 g. of sodium hydroxide in a mixture of 9 ml. of water and 18 ml. of alcohol. The solution was refluxed for two hours and then evaporated almost to dryness. Most of the yellowish residue which remained was insoluble in water, indicating that reaction had not taken place. A solution of 5 g. of sodium hydroxide in 70. Koelsch, J. Am. Chem. Soc., 58, 1328 (1936).
30 ml. of alcohol was added, and the mixture was refluxed for nine hours. The reaction mixture was again concentrated nearly to dryness and the residue was taken up in hot water. A small insoluble fraction was filtered from the hot solution. Acidification of the cold filtrate produced a voluminous white floc which was filtered off. Recrystallization from water yielded 0.55 g. (41%) of pure 2,5-dimethoxy-p-toluic acid melting at 125-126°. A mixed melting point determination with the acid prepared from 5-iodotolyhydroquinone dimethyl ether by halogen-metal interconversion showed no depression. The rather low yield obtained in this reaction was probably due in part to steam distillation of unreacted nitrile during the initial concentration of the reaction mixture.

Oxidation of 2,5-Dimethoxy-p-toluic Acid.

To a solution of one gram (0.0051 mole) of 2,5-dimethoxy-p-toluic acid in 80 ml. of boiling water was added a solution of 1.6 g. of potassium permanganate in 40 ml. of water. A voluminous brown precipitate of manganese dioxide formed immediately and no violet color remained in the solution. An additional 0.5 g. of potassium permanganate was added to the mixture and refluxing was continued fifteen minutes. Decolorization was much less rapid, but was complete at the end of fifteen minutes. The mixture was filtered while still hot to remove suspended manganese dioxide and then concentrated to a volume of 50 ml. Excess hydrochloric acid was added to
precipitate the crude product which appeared as a yellow floc. The crude acid weighed 0.47 g. (40%) and melted at 210-239°. Purification was difficult, and the most effective procedure appeared to consist of very slow crystallization from a rather large volume of water. Pure 2,5-dimethoxyterephthalic acid was obtained in white needles which melted at 265-265.5° and weighed 30 mg.

**Anal.** Calcd. for C\textsubscript{10}H\textsubscript{10}O\textsubscript{6}: neut. equiv., 113. Found: neut. equiv., 114.

**Esterification of 2,5-dimethoxyterephthalic Acid.**

A small amount (about 8 mg.) of 2,5-dimethoxyterephthalic acid was suspended in 3 ml. of anhydrous ether and treated with the diazoethane prepared from 2 ml. of ethyl N-nitroso-N-ethylcarbamate and excess methyl alcoholic potassium hydroxide solution. The ethereal reaction mixture was allowed to stand for three hours in the refrigerator and then the ether was distilled off. The residue which remained melted at 91-96°. Two recrystallizations from alcohol yielded pure diethyl 2,5-dimethoxyterephthalate melting at 101-102°. The melting points obtained for both 2,5-dimethoxyterephthalic acid and its diethyl ester agree with those reported by Nef (71).

**Nitration of Toluhydroquinone Dimethyl Ether.**

The nitration of toluhydroquinone dimethyl ether was

carried out by the method of Erdtman (54). Treatment of 50 g.
(0.329 mole) of toluhydroquinone dimethyl ether with 25 ml. of
concentrated nitric acid in 350 ml. of glacial acetic acid
yielded 63.5 g. (98%) of pure 5-nitrotoluhydroquinone dimethyl
ether melting at 118-119°.

Reduction of 5-Nitrotoluhydroquinone Dimethyl Ether.

Nine grams (0.0456 mole) of 5-nitrotoluhydroquinone di-
methyl ether was dissolved in the minimum amount of hot alcohol
and the solution was placed in a glass hydrogenation bottle.
One gram of activated Raney nickel catalyst was added to the
solution, and the air space above the reaction mixture was
swept out with hydrogen. The hydrogen line was then connected
to the bottle and hydrogenation was allowed to proceed for
one hour with shaking at a temperature of 100° and a hydrogen
pressure of 45 lbs. The reaction mixture was cooled and then
filtered quickly from the Raney nickel. The alcohol was dis-
tilled from the colorless solution under reduced pressure.

Toward the end of the distillation, white needles of 5-amine-
toluhydroquinone dimethyl ether began to form in the solution
and a considerable white residue remained in the flask after
all the alcohol had been removed. The crude amine, which
melted at 108.5-109.5°, darkened very rapidly on exposure to
air. No attempt was made to purify the amine for analysis,
but it was acetylated, and the acetylation product was char-
acterized as described in the following experiment.
Acetylation of 5-Aminotoluhydroquinone Dimethyl Ether.

To the flask containing the 5-aminotoluhydroquinone dimethyl ether from the previous reaction was added 10 ml. of acetic anhydride. The mixture was heated gently to bring about solution of the amine, and the resulting light yellow solution was transferred to a small Erlenmeyer flask and was refluxed for one hour. Upon dilution and cooling of the reaction mixture, a white, granular precipitate of acetamino compound formed. Several recrystallizations from alcohol yielded 5.1 g. (53%, based on the amount of nitro compound reduced) of pure 5-acetaminotoluhydroquinone dimethyl ether which crystallized in white needles melting at 160-162°. It was noted that the white needles formed in the first two recrystallizations tended to turn green upon standing any length of time in the air, but the final product was stable in air.

Anal. Caled. for C_{11}H_{15}O_{3}N: N, 6.69. Found: N, 6.72, 6.75.

Conversion of 5-Aminotoluhydroquinone Dimethyl Ether to 5-Iodotoluhydroquinone Dimethyl Ether.

The amine resulting from the reduction of ten grams (0.0507 mole) of 5-nitrotoluhydroquinone dimethyl ether was transferred quickly to an Erlenmeyer flask and dissolved in a solution of 11 ml. of concentrated hydrochloric acid in 38 ml. of water. The resulting solution of amine hydrochloride was
water produced a yellow amorphous precipitate which melted

The solution with stirring. The mixture was stirred ten
and 5 ml of concentrated nitric acid was added dropwise to

Three grams (0.13 mole) of 5-iodo-4-nitrobenzoic acid were

Nitration of 5-Iodo-4-nitrobenzoic Acid Directly Reflected

Thus, the nitration of 5-iodo-4-nitrobenzoic acid showed no depression

A mixture melted point determined with an authentic sample

pure 5-iodo-4-nitrobenzoic acid had a melting point of 86-88°C.
The material recrystallized from acetic acid at a small amount of crystals formed at reflux temperature.

When attempts at purification by recrystallization were un-
successful, the black material was sublimed at reduced pressure.

- the black solid was filtered off, washed with potassium iodate
  the yellow material became bright red in color and then black,
  forming a thin white. The mixture was heated to boiling, whereupon
  of potassium iodate in 12 ml of water. A yellow precipitate

solution of 1.5% of sodium nitrite in 12 ml of water. To this

added to 0.5 and distilled with the slow addition of a solution

- 88 -
at 115-117°. Recrystallization from alcohol yielded 1.7 g. (80%) of pure 5-nitrotoluhydroquinone dimethyl ether melting at 118-119°. Mixture with an authentic sample of 5-nitrotoluhydroquinone dimethyl ether did not depress the melting point.

**Nitration of 2,5-Dimethoxy-p-toluic Acid.**

To a solution of three grams (0.0153 mole) of 2,5-dimethoxy-p-toluic acid in 25 ml. of glacial acetic acid was added slowly with stirring 5 ml. of nitric acid. The reaction mixture was stirred ten minutes at a temperature of 45° and was then cooled and diluted. The amorphous yellow precipitate which formed melted at 114-117°. Two recrystallizations from alcohol yielded 2.5 g. (83%) of pure 5-nitrotoluhydroquinone dimethyl ether melting at 118-119°. Mixture with an authentic sample of 5-nitrotoluhydroquinone dimethyl ether did not depress the melting point.
DISCUSSION

Evidence for the Assigned Structures.

A number of the compounds whose preparations are described in this thesis are derivatives of 1,9(?)-dibromo-2,8-dihydroxydibenzofuran. Their structures, therefore, are dependent upon the validity of the assumption made by Swislowsky (10) that dibromination of 2,8-dihydroxydibenzofuran yields 1,9-dibromo-2,8-dihydroxydibenzofuran. These compounds are included in Diagram I.

Swislowsky's tentative assignment of structure to the dibromination product of 2,8-dihydroxydibenzofuran was based on the known behavior of 2-hydroxydibenzofuran which yields 1-bromo-2-hydroxydibenzofuran on bromination. His attempts to prove the structure of his 1,9(?)-dibromo-2,8-dihydroxydibenzofuran have been mentioned in the historical section.

Thirle (46) and the present author undertook two series of reactions which were designed to prove that neither of the bromine atoms in 1,9(?)-dibromo-2,8-dihydroxydibenzofuran is in the 3- or the 7-position. In the first of these two series, it was hoped that nitration of 2,8-dihydroxy- or of 2,8-dimethoxydibenzofuran could be made to yield a 3,7-dinitro compound. The structure of such a compound could be proved by reduction to the corresponding diamine and conversion to
the known 2,8-dimethoxy-3,7-dibromodibenzo- 

furan. It was proposed then to dibrominate the 2,8-dimethoxy-3,7-dinitro dibenzo- 
furan, remove the nitro groups by reduction and deamination, 

and compare the resulting dibromo-2,8-dimethoxy dibenzo- 

furan

with 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. Identity of these two compounds would have proved the structure of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran if substitution in the 4- and 6-positions is ruled out. The same proof of structure might also have been accomplished through dinitration of 1,9(?)-dibromo-2,8-dimethoxydibenzofuran, simultaneous debromination and reduction of the nitro groups, and conversion to 2,8-dimethoxy-3,7-dibromodibenzo furan.

Nitration of 2,8-dihydroxydibenzo furan yielded a tetranitro compound whose methylation product proved identical with the compound obtained by Thirtle from the nitration of 2,8-dimethoxydibenzo furan. These compounds are assumed to be 1,3,7,9-tetranitro compounds on the basis of the ortho-directing influence of the two hydroxyl groups in the 2- and 8-positions and also because of the rarity of substitution in the 4- and 6-positions in dibenzo furan. Thirtle (46) was unable to effect dinitration of 1,9(?)-dibromo-2,8-dimethoxydibenzo furan in satisfactory yield and nitration of 1,9(?)-dibromo-2,8-dihydroxy-3(?)-nitrodibenzo furan also went in such poor yield as to render further work with the product impractical.

In the second of the two series of reactions which were attempted in order to eliminate the possibility of 3,7-substitution in 1,9(?)-dibromo-2,8-dihydroxydibenzo furan, 1,9(?)-dicarboxy-2,8-dimethoxydibenzo furan was cleaved to the corresponding dihydroxy compound, and the latter was
dibrominated to yield 1,9(?)-dicarboxy-2,8-dihydroxy-3,7(?)-
dibromodibenzofuran. No pure compound could be obtained on
decarboxylation, although Thirtle obtained a product which may
possibly have been crude 2,8-dihydroxydibenzofuran. Thirtle
also prepared 1,9(?)-dicarboxy-2,8-dimethoxy-3,7(?)-dibromo-
dibenzofuran and attempted decarboxylation without success.

Hogg (53) has proved that the monobromination product of
2,8-dihydroxydibenzofuran described in this thesis is actually
1-bromo-2,8-dihydroxydibenzofuran. The same investigator con-
verted this compound to 1-methyl-2,8-dihydroxydibenzofuran,
brominated, and converted the resulting bromo compound to
1,8-dimethyl-2,8-dimethoxydibenzofuran. The latter compound
proved identical by mixed melting point with Swislowsky's
1,9(?)-dimethyl-2,8-dimethoxydibenzofuran. Thus, it has been
proved that one of the bromine atoms in 1,9(?)-dibromo-2,8-
dihydroxydibenzofuran is in the 1-position.

Hogg (53) and Thirtle (46) have shown that the other of
the two bromine atoms in question is not in the 9-position,
but in the 3- or the 7-position. It therefore seems very
probable that Swislowsky's 1,9(?)- compounds are actually
1,7- compounds, since failure of the Bucherer reaction with
1,9(?)-dimethyl-2,8-dihydroxydibenzofuran indicates that a
methyl group is in a position ortho to each of the hydroxyl
groups.

On the basis of the above evidence, all the compounds in
Diagram I which are designated as being 1,9(?)- derivatives
The compound was an impure dihydroxyphenylurethan rather than a pure 2-<p>hydroxy-2'-p-hydroxyphenylurethan. The dihydroxyphenylurethan was prepared by one of the two bromine atoms in the dihydroxyphenylurethan product. Thus, a compound whose acetatization product was tentatively identified as a compound whose acetatization product was tentatively identified as the methyl ester of 2-<p>hydroxy-2'-p-hydroxyphenylurethan. The acetatization product of the compound was an impure dihydroxyphenylurethan rather than a pure 2-<p>hydroxy-2'-p-hydroxyphenylurethan. The acetatization was carried out on but which was not identical with the dihydroxyphenylurethan product of a compound which was isolated for a dihydroxyphenylurethan and converted the dihydroxyphenylurethan to isomer. Two additional isomers of 2-<p>hydroxy-2'-p-hydroxyphenylurethan (60) to yield 2-<p>hydroxy-2'-p-hydroxyphenylurethan was in the 2-<p>position by dihydroxyphenylurethan. When proved that one of the bromine atoms in this dihydroxyphenylurethan isomer is 79, the study was carried out in comparison with the work of concerned with the dihydroxyphenylurethan of 2-<p>hydroxyphenylurethan. Included in this is a series of transformations that do not hydroxyphenylurethan is 79, the study was carried out in comparison with the work of concerned with the dihydroxyphenylurethan of 2-<p>hydroxyphenylurethan. Included in this is a series of transformations that do not
Diagram II. Transformations Involving One Benzene Nucleus

4-Dibenzofuryl-\(\rightarrow\) Dibenzofuran
\[\text{N-piperidino-}\]
\[\text{methylmethane}\]

4-Dibenzofuryl-\(\rightarrow\) 2-Bromo-
\[\text{N-piperidino-}\]
\[\text{methylmethane picrate}\]
\[\text{(73)}\]

2,8-Dihydroxy-
\[\text{(10)}\]

1-Bromo-2,8-dihydroxy-
\[\text{2-hydroxy-}\]
\[\text{(50)}\]

1-Bromo-2,8-diacetoxy-
\[\text{1,3-Dibromo-}\]
\[\text{2-acetoxy-}\]

1-Bromo-2,8-dimethoxy-
\[\text{1,3-Dibromo-}\]
\[\text{2-acetoxy-}\]

Dibenzofuran

Benzotrichloride
\[\text{4-Lithio-}\]
\[\text{(74)}\]

Benzotrifluoride
\[\text{4-(m-Trifluoro-}\]
\[\text{4-Aminomethylbenzalalmine-}\]
\[\text{(10)}\]

m-Bromobenzotri-
\[\text{m-Trifluoromethyl}\]
\[\text{m-Trifluoromethyl-}\]
\[\text{benzaldehyde}\]
\[\text{benzaldoxime}\]
\[\text{2,4-Dinitro-}\]
\[\text{phenylhydrazone}\]
\[\text{3-(m-Trifluoromethylbenzalalmine-}\]
\[\text{benzotrifluoride}\]

by cleavage of authentic 2-methoxy-3-bromodibenzo-furan (50). The cleavage product was not identical with the 2-hydroxy-3-bromodibenzo-furan prepared by Van Ess (50) through diazotization of 2-amino-3-bromodibenzo-furan. Methylation of the cleavage product yielded a compound which was not 2-methoxy-3-bromodibenzo-furan. These two anomalous products were not further investigated, but it would appear likely that the cleavage split the ether bridge in the dibenzo-furan nucleus to yield a biphenyl compound. Had 2-hydroxy-3-bromodibenzo-furan been obtained, it was to have been brominated for comparison with the dibromination product of 2-hydroxydibenzo-furan.

The 4-substituted dibenzo-furan derivatives described, 4-dibenzofuryl-N-piperidinomethane, 4-(m-trifluoromethylbenzalamino)-dibenzo-furan, and dibenzo-furan-4-aldehyde 2,4-dinitrophenylhydrazone, are dependent for proof of structure upon the position of metatalation of dibenzo-furan by n-butyllithium. This metatalation was shown to involve the 4-position by Young (75).

The two coupling products prepared, 1-(m-trifluoromethylphenylazo)-2-hydroxydibenzo-furan, and 1-(m-trifluoromethylphenylazo)-2,8-dihydroxydibenzo-furan, have been assigned these structures by analogy with the diazo coupling reaction between benzenediazonium chloride and 2-hydroxydibenzo-furan which was shown by M.W. Van Ess (51) to involve the 1-position.

In Diagram III is presented schematically a series of reactions which serves to prove the structures of the iodination and nitration products of toluhydroquinone dimethyl ether described by Erdtman (54). The 5-ido derivative was converted to the corresponding nitrile which was hydrolyzed to 2,5-dimethoxy-p-toluic acid. The same acid was prepared from the iodo compound by halogen-metal interconversion followed by carbonation. The acid was oxidized to 2,5-dimethoxyterephthalic acid which was then converted to the diethyl ester. Since

Diagram III. Transformations in the Benzene Series.

\[
\begin{align*}
\text{Toluhydroquinone dimethyl ether} &\rightarrow 5\text{-Iodo} \\
5\text{-Nitro-} &\quad (54) \\
5\text{-Amino-} &\downarrow \\
5\text{-Acetamino-} &\rightarrow 5\text{-Iodo-} \\
&\quad (54)
\end{align*}
\]

the latter two compounds had melting points identical with those reported by Nef (71), the iodination of toluhydroquinone dimethyl ether has been shown to involve the 5-position. Nitration of toluhydroquinone dimethyl ether was shown to involve the same position by reduction of the nitro compound.
to the amine and conversion to 5-iodotoluhydroquinone dimethyl ether.

Willis (11) prepared 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl through Ullmann coupling of 5-iodotoluhydroquinone dimethyl ether in accordance with the procedure of Erdtman and then demethylated and dehydrated to obtain 2,8-dihydroxy-3,7-dimethyldibenzofuran. The latter compound was identical with the cleavage product of the dimethyl derivative prepared by Swislowsky from his 2,8-dimethoxy-3,7(?)-dibromodibenzofuran. Thus the structures of the 3,7- compounds described by Swislowsky have been proved.

The nitrations of 5-iodotoluhydroquinone dimethyl ether and of 2,5-dimethoxy-p-toluic acid were attempted in the hope of obtaining 5-nitro derivatives which would have been valuable as intermediates in a ring-closure synthesis of 1,9-dimethyl-2,8-dihydroxydibenzofuran. In each instance, however, the nitro group displaced the substituent already in the 5-position, as indicated by the formation of the known 5-nitrotoluhydroquinone dimethyl ether. Willis (11) brominated 5-nitrotoluhydroquinone dimethyl ether in the hope of obtaining a 3-bromo derivative. The structure of the product was not proved, but it was found to contain bromine and no nitrogen. This circumstance makes it probable that the bromine atom displaced the nitro group.

Such unusual lability of groups is difficult to explain on the basis of the normally weak activating influence of a
methyl group, but no other explanation is apparent, since all
three unsubstituted positions in toluhydroquinone dimethyl
ether have the same relation to the two methoxy groups.
SUMMARY

1. Some correlations between chemical constitution and analgesic activity have been discussed.

2. The preparation of a number of compounds of interest as intermediates in the proof of structure of the dibromination product of 2,8-dihydroxydibenzo-furan has been reported.

3. The structures of 5-iodotoluhydroquinone dimethyl ether and 5-nitrotoluhydroquinone dimethyl ether have been proved.

4. The remarkable lability of substituents in the 5-position of toluhydroquinone dimethyl ether has been noted.