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Some correlations between hypnotic action and chemical constitution

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NOTE TO USERS

196

SOME CORRELATIONS BETWEEN HYPNOTIC ACTION AND CHEMICAL CONSTITUTION

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INTRODUCTION

A search of the literature reveals that the physiological action produced by certain synthetic drugs which cause sleep closely resembling natural sleep, but from which the individual cannot be easily aroused, is not limited to any one class of organic compounds. The aliphatic hypnotics which are used as sedatives in nervous cases, in pre- and post-operative medication and in rare cases for complete anesthesia are typified by the alcohols, amides, urethanes, barbituric acid derivatives, hydantoin derivatives and sulfones. The aromatic types have very definite hypnotic properties but their toxic properties make them unfit for practical use. A glance at this diverse group of compounds shows that it is impossible to correlate the structure of these compounds with their ability to produce narcotic action.

Theories of Hypnotic Action

The Meyer-Overton[1] theory is one of the several theories of hypnotic action which have been developed to explain the ability of this wide variety of compounds to produce narcosis. It is based on the assumption that all chemically inert substances which are solvents for fats must exert a narcotic action and the relative efficiency of such narcotic agents is dependent on their relative solubility in the fatty sub-

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1. Meyer, Arch. exper. Path. Pharm., 46, 338 (1899).

stances on one hand and water on the other hand. There is a certain degree of correlation since the olive oil-water partition coefficients agree fairly well for the barbituric acid derivatives,[2] although some derivatives do not follow this rule[3]. Baum[4] has found that the distribution coefficient decreases in the order: trional, tetronal, sulfonal, the latter being least active and of lowest molecular weight, while tetronal has the highest molecular weight and greatest activity. Ethyl urethane shows a higher distribution coefficient and greater activity than methyl urethane. These examples illustrate that there is some value to the theory; however, such compounds as caffeine and theobromine have a high distribution coefficient while physiologically they are stimulants. Another objection to the theory is that insoluble hypnotics require a greater length of time to cause action and last longer, probably because they are more slowly absorbed and eliminated. On this basis the Meyer-Overton theory and the Traube theory may be regarded as modes of transportation of the hypnotic and may be applied to the aliphatic hypnotics.

Increase of toxicity with increase of molecular weight

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2. Tabern and Shelberg, J. Am. Chem. Soc., 55, 328 (1932).
3. Shonle and Moment, ibid., 45, 243 (1923); Volwiler, Tabern and Shelberg, ibid., 53, 18 (1931); Dox and Hjort, J. Pharm. Exp. Ther., 31, 4 53 (1927).
4. Baum, Arch. exper. Path. Pharm., 42, 119 (1899).

in the alcohol series suggested to Traube[5] that the strength of a narcotic was proportional to the surface tension of its aqueous solution. Since solubility of these compounds is dependent on the number of carbon atoms within the molecule, this correlation holds except that the surface tension does not decrease with the higher homologues where there ceases to be any hypnotic action.

Bancroft and Richter[6] have re-opened the question of the old theory of coagulation of cell colloids as the cause of narcosis, and present experimental evidence to show that reversible cell coagulation can take place in the presence of an electrolyte *in vitro*, the lack of which proof had been the greatest objection to this theory. They divide narcotics into two groups: (1) direct narcotics which coagulate the cell colloids by direct action, and (2) indirect narcotics which interfere with some cell function such as oxidation, producing coagulation by the accumulated waste products. According to these workers, Verwon's "suffocation" theory[7] is explained not by the exclusion of oxygen from the cell, but by inhibition of oxidation by the narcotic and Warburg's[8] absorption theory is only a special case of the reversible

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5. Traube, *Arch. ges. Physiol.* (Pflügers), 153, 276 (1913); ibid., 160, 51 (1915); ibid., 161, 53 (1915).
6. Bancroft and Richter, *J. Phys. Chem.*, 35, 215 (1931).
7. Henderson, *Physiol. Rev.*, 10, 180 (1930).
8. Henderson, *Ibid.*, 10, 203 (1930).

cell coagulation theory.

Correlation Between Chemical Constitution and Hypnotic Action

Within each class of aliphatic hypnotics there is some correlation between structure and hypnotic action. The simpler amides cause no appreciable narcotic action, and only when valeramide is used is hypnotic activity shown. The lower members of the series are toxic[9] while with valeramide the harmful effects are practically non-existent. Branched-chain acid amides show more sleep producing action than the straight-chain amides. Bromination of diethyl acetamide to give 1-ethyl-1-bromovaleramide (neuronal) markedly increases the hypnotic action as compared with diethylacetamide itself. The urethanes produce a pronounced narcotic action. Ethyl urethane itself is a mild hypnotic[10]. Hedonal or 1-methylbutyl carbamate ($(CH_3CH_2CH_2)(CH_3)CHOCONH_2$) shows less hypnotic activity than ethyl urethane. Greater hypnotic action is shown by tert.-butyl carbamate, indicating that with branched-chain derivatives more activity is produced.

Simple substituted urea derivatives are without toxic or narcotic action; but the higher aliphatic branched-chain derivatives show hypnotic action, and a preponderance of ethyl groups favors the development of narcotic activity[11].

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9. Dyson, "Chemistry of Chemotherapy." E. Benn, London. 1928, pp. 86-87.
10. Wilcox, Proc. Roy. Soc. Med., 27, 489 (1934).
11. Ref. 9. p. 89.

The cyclic ureides have been the subject of wider investigation since they have proved to be of great value clinically. Hydantoin, itself, possesses no narcotic action, and the 5,5-dialkyl derivatives show only slight narcotic action[12]. Herbst and Johnson[13] have made a comparative study of 5-ethyl-5-phenyl-(nirvanol), 5-methyl-5-benzyl-, 5-ethyl-5-benzyl-, 5-methyl-5-β-phenylethyl-, 5-ethyl-5-β-phenylethyl- and 5,5-cyclopentamethylenehydantoin. They found that 5-methyl-5-β-phenylethylhydantoin shows the same hypnotic action as nirvanol with one-half the toxicity and that 5-methyl-5-benzylhydantoin produces convulsions in low doses. Hsueh and Marvel[14] have shown that the sequence of phenyl-, benzyl- and phenylethyl-groups differs in hypnotic action in the hydantoin and barbituric acid series.

Barbituric acid, 5-ethyl-, 5-propyl and 5,5-dimethyl-barbituric acid are without hypnotic action, but 5,5-diethyl-barbituric acid (veronal, barbital) has a pronounced hypnotic activity[15]. By replacing one ethyl group in veronal with a larger alkyl group, the hypnotic action is increased[16].

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12. Ref. 9, p. 92.
13. Herbst and Johnson, J. Am. Chem. Soc., 54, 2463 (1932).
14. Hsueh and Marvel, ibid., 50, 855 (1930).
15. Frankel, "Die Arzneimittel Synthese", Springer, Berlin. 1927, p. 508.
16. Dox and Yoder, J. Am. Chem. Soc., 44, 1578 (1922).

Shonle[17], in a discussion of the barbituric acids, states that introduction of an amino, hydroxyl, ethoxyl, carbonyl or carboxyl group in the alkyl chain destroys the hypnotic effect of 5, 5-disubstituted barbituric acids. Increase in molecular weight in the 5-ethyl-5-alkylbarbituric acids causes increase in narcotic action with maximum effect at about the amyl group. Branched-chain derivatives with the same molecular weight as straight-chain derivatives have the same narcotic power with less toxicity. Unsaturated groups produce an increase in narcotic action. Dox and Yoder[18] found that the 5-benzyl-5-alkyl barbituric acids produce convulsions and apparently have little value as hypnotics. Barlow, Duncan and Gledhill[19] have studied the comparative value of those barbituric acid derivatives used clinically. The branched-chain derivatives and those containing an unsaturated group have the widest safety range and greatest premedication value for nitrous oxide anesthesia. In general, it may be said that the barbituric acids all behave in the same manner and the difference in behavior, such as rate of absorption and elimination, duration of action and toxicity, is due to different groups substituted in the 5,5-positions. It has been reported that N-alkylated

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17. Shonle, Ind. Eng. Chem., 23, 1104 (1931).
18. Dox and Yoder, J. Am. Chem. Soc., 44, 1141 (1922).
19. Barlow, Duncan and Gledhill, J. Pharm. Exp. Ther., 41, 357 (1932).

disubstituted barbituric acids show less toxicity than those derivatives with no alkyl groups on a nitrogen atom[20].

With the exception of those coal tar derivatives classed as sedatives, no compounds with clinically valuable hypnotic properties are found in the aromatic series. A comparison of the unsubstituted aromatic hydrocarbons shows that phenanthrene is more narcotic towards tadpoles than naphthalene which in turn is more active than benzene. Benzene itself, has received considerable study because of its extensive use in industry. Experimental observations show that it causes respiratory failure[21,22], although comparatively large doses may be absorbed before these toxic symptoms appear.

Brissemoret and Joanin[23] first pointed out the value of studying the physiological action of phenanthrene. They postulated that there are two factors which play a part in the action of an alkaloid, the hydrocarbon residue and the ammonium residue, and since phenanthrene is obtained from morphine by zinc dust distillation[24] it may be considered the hydrocarbon residue. They investigated this hypothesis by injecting hexahydrophenanthrene intraperitoneally into a dog

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20. Ger. Pat. 531, 366 [C. A., 26, 1299 (1932)].
21. Ref. 15, pp. 51-2; ref. 9, p.22.
22. Nahum and Hoff, J. Pharm. Exp. Ther., 50, 336 (1934).
23. Brissemoret and Joanin, Compt. rend., 151, 1151 (1910).
24. Van Gererigten and Schrotter, Ann. 210, 396 (1881)

and found that it produced morphine-like narcosis. Eddy[25] observed that when administered orally to cats, phenanthrene itself produces a mild general depression similar to that following administration of a small dose of one of the barbiturates. Derivatives with a single substituent in the 2-, 3-, or 9- position such as the amino, hydroxyl, acetyl and carboxylic acid groups were also administered orally to cats. Those derivatives with the substituent in the 3-position showed definite analgesic action. All were rapidly absorbed in spite of their almost complete water insolubility.

Since there is present a reduced dibenzofuran nucleus as well as a reduced phenanthrene nucleus in morphine, the work of Eddy suggests that dibenzofuran derivatives may have similar analgesic or hypnotic action. The purpose of this study was to prepare monosubstituted dibenzofurans with substituents in the 1-, 2-, 3-, and 4-positions, for study of physiological action. The structural relationship between morphine (Gulland-Robinson formula[26]), 3-hydroxyphenanthrene and 4-hydroxydibenzofuran[27] is illustrated by formulas I, II and III:

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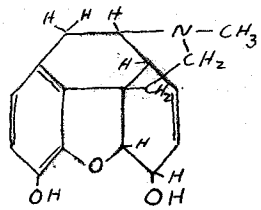
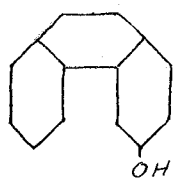
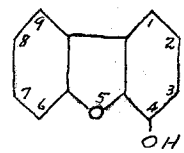
25. Eddy, J. Phar. Exp. Ther., 48, 183 (1933).
26. Small, "Chemistry of the Opium Alkaloids", Supp. 103, Public Health Reports, 1932, p. 143.
27. The system of numbers is that of the International Rules for Nomenclature. (Patterson, J. Am. Chem.Soc., 47, 543 (1925)).



I



II



III

These formulas illustrate that dibenzofurans with substituents in the 4- and 4,6- positions should prove most valuable in a study of physiological action, but a comparison of those substituted in 1-, 2-, 3- and 4-positions is essential for complete understanding of the part this molecule plays in morphine.

Very little work has been done on the physiological action of dibenzofuran and its derivatives. Subcutaneous injection of dibenzofuran in olive oil causes an increase in the amount of hippuric acid eliminated[28]. No hypnotic nor toxic action was reported and no o-hydroxyhippuric acid was found to be eliminated. Mayer and Krieger[29] found that γ-(2-dibenzofuryl)-n-propyl amine and γ-(2-tetrahydrodibenzofuryl)-n-propyl amine had no physiological action similar to that of morphine on warm blooded animals. Von Braun[30] first called attention to the structural resemblance between

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28. Chistomanos, Z. Physiol. Chem. 181, 182 (1929).
29. Mayer and Krieger, Ber., 55, 1659 (1922).
30. V. Braun, ibid., 55, 3761 (1922).

numerous compounds of morphine, codeine and thebaine and hydrogenated dibenzofuran. The uncommon ease of opening the ether linkage in morphine derivatives should be extended to hexahydrodibenzofuran. He found, however, that hexahydrodibenzofuran is stable toward sodium and alcohol, zinc and acetic acid, and phenylmagnesium bromide, all of which cause ring opening in thebaine. Aminohexahydrodibenzofuran and α-aminoethylhexahydrodibenzofuran were unaffected by dilute acids and in animal experiments were seemingly physiologically indifferent. It has been recorded that dibenzofuran and its derivatives[31] may be used as insecticides.

SUBSTITUTION IN DIBENZOFURAN

At the beginning of this work the only definitely determined direct nuclear substitutions were acetylation by the Friedel-Crafts reaction, bromination and nitration. No derivatives with substituents in the 1- or 4- positions had been definitely established[32] structurally except 4-methyldibenzofuran and 4-dibenzofurancarboxylic acid, synthesized by ring closure[33]. Consequently it was necessary to study nuclear substitution

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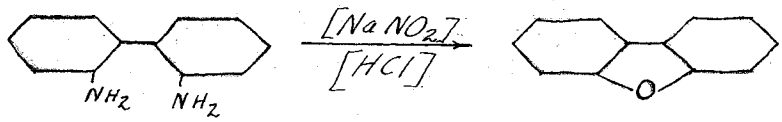
31. Ger. Pat. 355, 206 (Chem. Zentr., IV, 429 (1922)).
32. Tsuzuki, Bull. Chem. Soc. Japan, 2, 79 (1927), reported 1-hydroxydibenzofuran obtained by passing resorcinol over hot tungsten oxide. The orientation was based on similarity of absorption spectra curves for this derivative and 2-hydroxydiphenyl. However, see this thesis p. 49.
33. Kruber, Ber., 65, 1332 (1932).

of dibenzofuran in an attempt to prepare by easily accessible means 1- and 4- substituted dibenzofurans. During the course of this investigation metalation was found to involve the 4- position.[34]

METHODS OF SYNTHESIS OF DIBENZOFURANS

The structure of nuclear substitution products of dibenzofuran is based upon two general methods of synthesis by ring closure: (1) from diphenyl derivatives and (2) from diphenyl ether derivatives.

1. Synthesis of Dibenzofuran and its Derivatives from Diphenyl Derivatives. This method of synthesis demonstrates that the oxygen bridge in dibenzofuran is situated ortho to the diphenyl bond. Tauber and Halberstadt[35] and Cullinane, Davey and Padfield[36] have synthesized dibenzofuran itself from 2,2-diaminodiphenyl by tetrazotizing and then heating the diazonium solution with water or copper sulfate:



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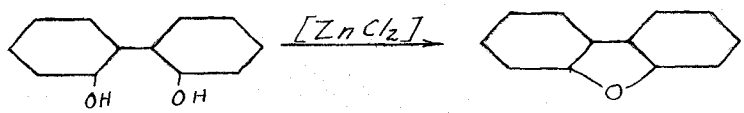
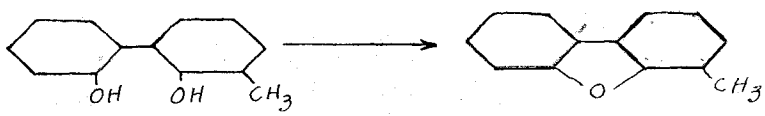
34. Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
35. Tauber and Halberstadt, Ber., 25, 2745 (1892).
36. Cullinane, Davey and Padfield, J. Chem. Soc., 716 (1934).

Sako[37] has synthesized 1,9-diphenyldibenzofuran in small yield by heating the tetrazonium salt of 2,2'-diamino-6,6'-diphenyldiphenyl with copper powder. Kraemer and Weissgerber[38] synthesized dibenzofuran by heating 2-2'-dihydroxydiphenyl with $ZnCl_2$:



The most important application of the latter method has been the preparation of 4-methyldibenzofuran by Kruber[33] from 2,2'-dihydroxy-3-methyldiphenyl:



2. Synthesis of Dibenzofuran Derivatives from Diphenyl Ethers. Synthesis by this method has proved to be the most fruitful means of proving the position of groups in nuclear substitution products of dibenzofuran. The method consists essentially of diazotizing 2-aminodiphenyl ether and heating the diazonium salt solution with 50% sulfuric acid[39].

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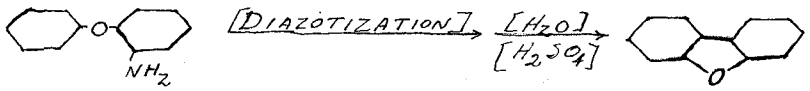
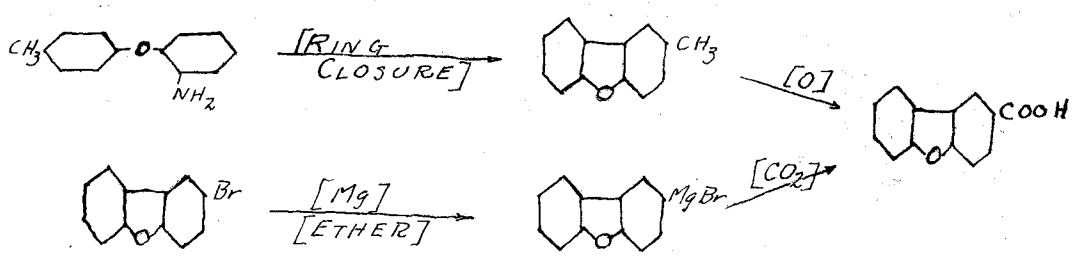
37. Sako, Bull. Chem. Soc. Japan, 9, 55 (1934).
38. Kraemer and Weissgerber, Ber., 34, 1662 (1901).
39. Grabe and Ullmann, ibid., 29, 1876 (1896).



Mayer and Krieger[29] first applied this method of ring closure to orientation problems. By synthesizing 2-methyldibenzofuran from 2-amino-4'-methyldiphenyl ether, they established the position of the bromine atom in monobromodibenzofuran since oxidation of 2-methyldibenzofuran and carbonation of the Grignard reagent from the halide both gave the same 2-dibenzofurancarboxylic acid:



This series of reactions definitely locates the bromine atom para to the oxygen bridge. McCombie, Macmillan and Scarborough[40] made unsuccessful attempts to prepare 1-chlorodibenzofuran using 2-amino-2'-chlorodiphenyl ether and this method of ring closure. They were, however, successful in synthesizing 2-chloro-, 2- and 3-bromo-, 2, 8-dichloro-. 2,8-dibromo-, 2,7-dibromo, 3-nitro- and 2-chloro-7-nitrodibenzofuran.

Ebel's synthesis of tetrahydrodibenzofuran from

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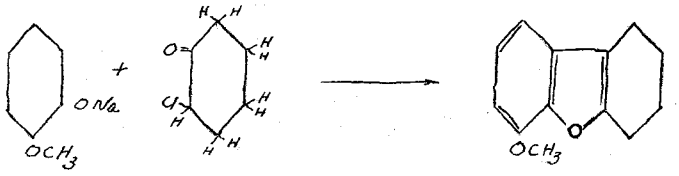
40. McCombie, Macmillan and Scarborough, J. Chem. Soc., 529 (1931).

chlorocyclohexanone and sodium phenate[41] may prove to be valuable for synthesizing 4- substituted dibenzofurans since tetrahydrodibenzofuran may be dehydrogenated by sulfur or selenium to give dibenzofuran, and the same reaction should be applicable to some substituted tetrahydrodibenzofurans. Ebel has synthesized 6-methoxy- 1, 2, 3, 4-tetrahydrodibenzofuran by this method:



Application of this method of synthesis for proving structure has not been thoroughly investigated.

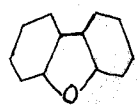
MONOSUBSTITUTION IN DIBENZOFURAN

The position assumed by substituents in monosubstitution of dibenzofuran is apparently governed not only by the inherent characteristics of the molecule, due to the diphenyl ether linkage and the diphenyl linkage, and to experimental conditions, but also by the type of entering group. The known o,p- directing influence of the diphenyl ether and diphenyl bonds makes substitution in the 1-, 2-, 3- and 4- positions competitive and highly probable.

Experimental observations demonstrate that actually the 2-, 3- and 4- positions are involved in direct nuclear substitution, but no direct substitution reaction has been reported which involves the 1- position. This phenomenon may be

41. Ebel, Helv. Chim. Acta, 12, 3 (1929).

attributed to the large oxygen angle between the two benzene nuclei, bringing the 1- and 9- positions close together, thus causing steric hindrance and preventing substitution in these positions. Bretscher[42] found that the dipole moment of dibenzofuran indicates a larger oxygen angle than that present in diphenyl ether. A reasonable structure of dibenzofuran then, may be illustrated by formula as follows:



Halogenation and Sulfonation

Monobromination of dibenzofuran to give 2-bromodibenzofuran was established, as has been shown by Mayer and Krieger[29], and was the first definitely determined nuclear substitution product of dibenzofuran. McCombie, Macmillan and Scarborough[40] synthesized 2-bromodibenzofuran by ring closure and confirmed Mayer and Krieger's work. Hoffmeister[43] studied the effect of phosphorus pentachloride on dibenzofuran and found that in an open vessel no reaction took place, but in a sealed tube a chloro- derivative was formed. Whitmore and Langlois[44] also obtained a chlorodibenzofuran by the same reaction. This derivative is 2-chlorodibenzofuran and is also formed by direct chlorination[45] with chlorine gas.

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42. Bretscher, Helv. Phys. Acta, 2, 265 (1929).
43. Hoffmeister, Ber. 3, 751 (1870); Ann., 159, 211 (1871).
44. Whitmore and Langlois, J. Am. Chem. Soc., 55, 1520 (1933).
45. Unpublished work by G. E. Brown of this laboratory.

Iodination of dibenzofuran gives 2-iododibenzofuran. The structure of 2-iododibenzofuran and 2-dibenzofuransulfonic acid was established by converting the sulfonic acid to 2-chloromercuridibenzofuran then to 2-iododibenzofuran[46]. The mercurial when treated with bromine gives the known 2-bromodibenzofuran. Zehenter[47] isolated a dibenzofuran monosulfonic acid from the reaction between 2,2'-dihydroxydiphenyl and concentrated sulfuric acid. The sulfonic acid group was assigned to the 2- or 4- position in the nucleus without definitely determining the structure.

Friedel-Crafts Reaction

Mono-acetylation with acetyl chloride by the Friedel-Crafts reaction was first attempted by Galewsky[48], who assumed that the diphenyl ether linkage was the greater orienting influence in the molecule and consequently called the product 2-acetyldibenzofuran. Mayer and Krieger[29] have shown this assumption to be correct by oxidizing the compound to 2-dibenzofurancarboxylic acid.

These reactions are good evidence that the diphenyl ether linkage is the greater directing influence in the molecule. The isologues of dibenzofuran do not strictly

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46. Gilman, Smith and Oatfield, J. Am. Chem. Soc., 56, 1412 (1934).
47. Zehenter, J. prakt. Chem., 131, 331 (1931).
48. Galewsky, Ann., 264, 187 (1891).

follow this rule. In carbazole the predominant orienting influence is the imino group[49] corresponding to the oxygen linkage in dibenzofuran. In nitration[50a], halogenation[50c,d] and sulfonation[50b,c,e] of fluorene and fluorenone substitution involves those positions para to the diphenyl bond. Very little has been done with nuclear substitution of dibenzothiophene, but the present status of the work indicates that substitution takes place as in dibenzofuran[51].

Nitration

Mononitration of dibenzofuran does not follow the general rule that the greater directing influence in the molecule is the oxygen bridge. Borsche and Bothe[52] first prepared mononitrodibenzofuran by the action of fuming nitric acid in glacial acetic acid. They suggested that possibly the nitro group had assumed the 2- position under the directing influence of the oxygen bridge, since the acid formed by reduction of the nitro group, followed by a Sandmeyer reaction

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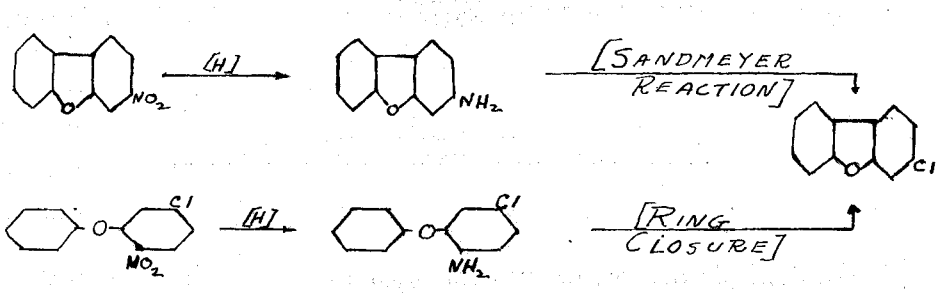
49. Cohn, "Die Carbazolgruppe" Thieme, Leipzig, 1919.
Chlorination p.77
Bromination p.79
Nitration p.83
Sulfonation pp.107-8

50. (a) Schultz, Ann., 203, 95 (1880); (b) Courtot and Geoffrey, Compt. rend., 178, 2259 (1924); (c) Courtot, Ann. Chim., (10) 14, 5 (1930); (d) Courtot and Vignati, Compt. rend. 184, 607 (1927), Bull. soc. chim., 41, 58 (1927); (e) Schmidt, Retzlaff and Haid, Ann., 390, 210 (1912).

51. Courtot and Pomonis, Compt. rend., 182, 931 (1926); Courtot and Chaix, Compt. rend., 192, 1667 (1931).

52. Borsche and Bothe, Ber., 41, 1940 (1908).

to the nitrile and hydrolysis, gave the same acid as oxidation of acetyldibenzofuran. Mayer and Krieger[29], however, found, by the method of mixed melting points, that their 2-dibenzofurancarboxylic acid was not identical with the acid prepared from mononitrodibenzofuran. Borsche and Schacke[53] then suggested that the main product of nitration was 3-nitrodibenzofuran. Cullinane definitely[54] determined the position of the nitro group by converting the corresponding amine to 3-chlorodibenzofuran synthesized by ring closure.



To explain the anomalous orientation of the nitro group Cullinane[55] has postulated that in a fused ring system containing one ring with an odd number of atoms, the result of nuclear substitution is dependent upon the route taken for electromeric changes. There are two paths which may be followed, both leading to substitution in the 3-position:

53. Borsche and Schacke, Ber., 56, 2498 (1923).
54. Cullinane, J. Chem. Soc., 2267 (1930).
55. Cullinane, Ibid., 2365 (1932).

That bromine enters the molecule para to the oxygen atom is explained as follows: "In all probability bromination is a more facile process and can take advantage of a smaller degree of polarization occurring more frequently than the activations of greater amplitude required to facilitate nitration." That dinitration gives 2,7-dinitrodibenzofuran, is due to the fact that the nitro group already present in the molecule prevents further electromeric changes in the substituted benzene ring so that substitution proceeds normally, i.e., the second nitro group enters the 2- position in the opposite ring[55].

Borsche and Bothe[52] isolated an isomeric mononitro-derivative melting at 110°. Borsche and Schacke[53] suggested that possibly this was 2-nitrodibenzofuran. Cullinane[55] then stated that it was 4-nitrodibenzofuran since 2-nitrodibenzofuran had been synthesized by ring closure[56], and had been obtained by successive hydrolysis and deamination of 3-acetamino-2-nitrodibenzofuran[57]. It has not been definitely established that the mononitro-derivative melting at 110° is or is not a mixture of isomers. An attempted purification and identification of this product of nitration is given in the experimental part of this thesis.

Ryan and Cullinane[58] have determined the efficiency of various nitrating agents with dibenzofuran. They believe that dibenzofuran is less easily nitrated than diphenyl ether, since

56. Ryan, Keane and McGahon, Pro. Royal Irish Acad., 37B, 368 (1927) C. A. 22, 70 (1928).
57. Brumberg, Doctoral Dissertation, Gottingen, 1925.
58. Ryan and Cullinane, Scientific Proc. Roy. Dublin Soc., 17 321 (1922-4)

cold concentrated nitric acid is almost without action on dibenzofuran. However, this is an isolated example for dibenzofuran with nitrogen peroxide and no solvent forms a dinitro-derivative, and in acetic acid yields a mononitro-derivative, as does diphenyl ether[59].

Metalation

The present knowledge that the 4- position is involved in nuclear substitution is limited to metalation (a term applied to direct replacement of hydrogen by a metal to give an organometallic compound)[34]. Mercuration of molten dibenzofuran with mercuric acetate produces 4-dibenzofurylmercuriacetate. This mercurial was concerted to the iodo compound and the Grignard reagent from the halide carbonated to give 4-dibenzofurancarboxylic acid[34], identical with that formed by oxidation of 4-methyldibenzofuran[33]. Carbonation of the organolithium, -sodium and -potassium compounds gives the same results.

Since other nuclear substitution reactions involve the 2- and 3- positions this result was unexpected, but may be used for easy access to one of the two important positions (4- and 4,6-), for comparative physiological study of dibenzofurans with morphine and phenanthrene. Indeed, it has been found that oxidation of 4-dibenzofuryl-lithium by air or oxygen gives 4-hydroxydibenzofuran[60].

59. Ryan and Drumm, Scientific Proc. Roy. Dublin Soc., 17, 313 (1922-24).
60. Unpublished work by R. V. Young of this laboratory. See also experimental part of this thesis.

DISUBSTITUTION

Heteronuclear Substitution

Heteronuclear substitution of dibenzofuran for the most part is concerned with the introduction of like substituents. Dibromination of dibenzofuran was first reported by Hoffmeister[43]. McCombie, Macmillan and Scarborough[40] found that this product was 2,8-dibromodibenzofuran by synthesizing it from 2-amino-5,5'-dibromodiphenyl ether. Dichlorination and diodination also yield 2,8-disubstituted dibenzofurans[45]. Hoffmeister[43] obtained a disulfonic acid by the action of concentrated sulfuric acid on dibenzofuran but made no attempt to determine the position of the sulfonic acid groups. Zehenter[47] sulfonated his monosulfonic acid and obtained a disulfonic acid. Gilman, Smith and Oatfield[46] proved the structure of this disulfonic acid by converting the corresponding disulfinic acid to dichloromercuridibenzofuran which with bromine gave 2,8-dibromodibenzofuran. Diacetylation by the Friedel-Crafts reaction gives 2,8-diacetyldibenzofuran[61]. Oxidation of this compound gives 2,8-dibenzofurandicarboxylic acid identical with the acid prepared by oxidation of 2,8-dimethyldibenzofuran, synthesized by ring closure.

Brumberg[57] first observed that nitration of 2-bromodibenzofuran produced a mixture of isomers, but did not resolve this product, and stated that no 2-bromo-3-nitrodibenzofuran

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61. Sugi and Sengoku, J. Pharm. Soc. Japan, 53T, 175 (1933).

was present since he was unable to replace the bromine atom by an amino group with alcoholic ammonia. This mixture of isomers has been separated into 2-bromo-7-nitro- and 2-bromo--3-nitrodibenzofuran[62]. Bromination of 3-nitrodibenzofuran also gives 2-bromo-7-nitrodibenzofuran[36,62]. These observations are further experimental evidence that in heteronuclear substitution the second substituent enters the unsubstituted benzene ring as it does in monosubstitution regardless of the group already present in the molecule. The only exception to this general rule is that of dinitration which gives 2,7-dinitrodibenzofuran[55].

Homonuclear Substitution

When acetaminodibenzofurans are nitrated or brominated, the o-, p- directing influence of the oxygen bridge is masked by the stronger o-, p- directing influence of the acetamino group and homonuclear substitution results.

First studies of this type were undertaken with the easily available 3- substituted dibenzofuran by Borsche and Schacke[53] who nitrated 3-acetaminodibenzofuran. Hydrolysis of this nitro-3-acetaminodibenzofuran followed by reduction of the nitro group gives a diamine which must have the amino groups ortho to each other for quinoxaline derivatives are formed. They suggested that the product was 2,3-diaminodibenzofuran. Unpublished work by Brumberg[57] confirmed this structure by

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62. This thesis p. 56.

first replacing the amino group by hydrogen and then successively reducing the nitro group to an amine, diazotizing, replacing the diazonium group by a cyano group and hydrolyzing to the known 2-dibenzofurancarboxylic acid. The structure of the 2,3-diaminodibenzofuran was confirmed by comparing quinoxaline derivatives of the diamine with those from the corresponding 2-bromo-3-amino[63] and 2-amino-3-bromodibenzofuran[64].

63. Gilman, Brown, Bywater and Kirkpatrick, J. Am. Chem. Soc., 56, 0000 (1934).
64. This thesis, p. 41

EXPERIMENTAL

Preparation of 2-Bromodibenzofuran

Monobromination of dibenzofuran was first carried out by Mayer and Krieger[29] in carbon disulfide. It has been found that carbon tetrachloride may be used as a solvent with good results. To 110 g. (0.654 mole) of technical dibenzofuran dissolved in 400 cc. of carbon tetrachloride, 33 cc. (105 g., 0.65 mole) of bromine was added with rapid stirring during a fifteen minute period. Stirring was continued for one hour, then the mixture was allowed to stand overnight. After refluxing for 5 hours, it was washed with saturated sodium bisulfite solution, followed by 10% sodium carbonate solution. Subsequent to the removal of the carbon tetrachloride by distillation, the product was distilled under reduced pressure to give 100 g. or a 62% yield of 2-bromodibenzofuran, melting at 98-102°. Pure 2-bromodibenzofuran (m.p. 108-109°) was obtained by recrystallizing from toluene or alcohol; but the loss was very great.

Preparation of 2-Aminodibenzofuran

This amine had been previously obtained by Brumberg[57] during the course of his investigation of nitration of 3-diacetaminodibenzofuran. Cullinane[55] prepared 2-aminodibenzofuran by partial reduction of 2,7-dinitrodibenzofuran to 2-nitro-7-aminodibenzofuran followed by removal of the amino group (via diazotization) then reduction of the remaining nitro group. These methods at best are long and tedious. A large amount of the amine was required for preparation of 2-hydroxydibenzofuran and for orientation studies; consequently an effort was made to determine the best method of preparation.

In accordance with the procedure used for the formation of some aromatic amines[65] and for the preparation of 2-aminofluorene from 2-bromofluorene[50c], 2-aminodibenzofuran was prepared by heating 2-bromodibenzofuran with ammonium hydroxide in the presence of cuprous chloride. In a preliminary experiment 1.5 g. (0.006 mole) of 2-bromodibenzofuran was heated with 25 cc. of 22% ammonium hydroxide (sp.gr. 0.9) and 1 g. of cuprous chloride at 220-235° for 17 hours. The product was extracted with ether; the ether dried over anhydrous sodium sulfate, and saturated with dry hydrogen chloride to give 0.87 g. (65%) of amine hydrochloride.

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65. Ullmann, Ber., 36, 2382 (1903); Ger. pat. 202, 170; [Chem. Zentr. II, 1221 (1908)].

The hydrochloride was converted to the free amine by heating with aqueous alcoholic ammonium hydroxide. On cooling, 0.6 g. (55%) of 2-aminodibenzofuran, melting at 127-128°, separated.

For preparation of larger amounts of this product an electrically heated steel bomb* of approximately 700 cc. capacity was used. In one run 17 g. (0.068 mole) of pure 2-bromodibenzofuran was heated at 200-225° for 12 hours with 11 g. of cuprous chloride and 300 cc. of 22% ammonium hydroxide (sp.gr. 0.9). The amine was isolated as the hydrochloride by dissolving the fused mass in ether-benzene and saturating with hydrogen chloride. The yield was 12.4 g. or 82%.

Concentrated ammonium hydroxide was found to react in a shorter time and give larger yields. When 48 g. (0.153 mole) of 2-bromodibenzofuran was heated at 200-210° for 10 hours with 35 g. cuprous chloride and 500 cc. of concentrated ammonium hydroxide (d. 0.89), the yield was 30 g. or 88.7% of 2-aminodibenzofuran hydrochloride.[66]

In order to be certain that no rearrangement had occurred during this reaction, 2 g. (0.0091 mole) of amine

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66. Shortly after this work was completed, a patent appeared which reported the same reaction. This gave melting points closely agreeing with those reported in this thesis for 2-amino-, 2-hydroxy- and 3-hydroxydibenzofuran. Ger. pat. 591,213; [C.A. 28, 2366 (1934)].

* The author is grateful to Dr. F. E. Brown for use of his steel bomb.

hydrochloride was diazotized by the method of Schoutissen,[67] and the diazonium solution poured into a solution of 1.3 g. (0.009 mole) cuprous bromide in 50 cc. of 10% hydrobromic acid. The mixture was steam-distilled to give 13.7% yield of 2-bromodibenzofuran which, after two recrystallizations from alcohol, melted at 108-109° alone or when admixed with an authentic sample of 2-bromodibenzofuran.

In an unsuccessful attempt to replace the bromine atom by an amino group, 5 g. (0.020 mole) of 2-bromidibenzofuran was heated at 250° for 5 hours with 0.79 g. (0.02 mole) of ground sodium amide. Some 2-bromodibenzofuran was lost by sublimation. The mass was covered with benzene, the sodium amide destroyed by water and the dried benzene solution saturated with hydrogen chloride. No precipitate of the desired amine hydrochloride separated. By concentration of the benzene solution, 3.4 g. (68%) of 2-bromodibenzofuran was recovered.

Preparation of 2-Acetamino- and 2-Diacetaminodibenzofuran

To confirm the identity of 2-aminodibenzofuran hydrochloride and for use in orientation studies,

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67. Schoutissen, J. Am. Chem. Soc., 55, 5432 (1932).

2-acetamino- and 2-diacetaminodibenzofuran were prepared.

a. 2-Acetaminodibenzofuran

This derivative was prepared by the method used by Sako[37] for 2-acetaminodiphenyl. To 7 g. (0.038 mole) of 2-aminodibenzofuran in 140 cc. of benzene was added 5.1 g. (0.05 mole) acetic anhydride. After standing for 2 hours to complete precipitation, 6.3 g. or 73.2% yield of white needles melting at 161-162.5° separated. Recrystallization from benzene raised the melting point to 162-163°. A mixed melting point with 2-acetaminodibenzofuran, isolated from the nitration of 2-diacetaminodibenzofuran[68], was not lowered.

b. 2-Diacetaminodibenzofuran

(1) Twenty-two grams (0.1 mole) of 2-aminodibenzofuran hydrochloride was reflexed 45 minutes with 22 g. of anhydrous sodium acetate and 75 cc. of acetic anhydride. After standing overnight, the acetic anhydride was destroyed with 300 cc. of cold water. The dark product was recrystallized from dilute acetic acid. On cooling, 11.5 g. of a mixture of mono-and di-acetaminodibenzofuran separated. By diluting the mother liquor with water, 11.1 g. of gray material melting at 120-126° precipitated. The precipitate was refluxed 24 hours with 22 cc. of acetic anhydride and

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68. This thesis p. 39.

40 cc. of acetic acid; cooled; the acetic anhydride destroyed with water; and the product recrystallized from dilute alcohol to give 6 g. of 2- diacetaminodibenzofuran melting at 125-128°. Brumberg[57] has reported the melting point as 127-128°.

Preparation of 2-Dibenzofurancarboxylic Acid

Mayer and Krieger[29] prepared 2-dibenzofurancarboxylic acid by carbonating 2-dibenzofurylmagnesium bromide prepared in anisole and ether. It has been found that the Grignard reagent may be prepared in ether alone by starting the reaction with reactivated copper-magnesium alloy.[69] The reaction was carried out in a one-liter three-necked flask with the usual equipment needed for preparation of a Grignard reagent. An ether suspension of reactivated magnesium prepared from 0.2-0.3 g. of the alloy, was added to 5.3 g. (0.22 mole) of magnesium turnings, and 2 g. of 2-bromodibenzofuran in 40 cc. of ether. The reaction apparently started immediately. The remainder of the halide (27.8 g. or a total of 0.122 mole) was dissolved in anhydrous ether and added to the flask. The reaction mixture was refluxed overnight. At the end of this time the color test was positive. The yield of Grignard

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69. Gilman, Peterson and Schultz, Rec. trav. chim., 47, 26 (1928).

reagent by titration was 68%. After carbonating with carbon dioxide gas and hydrolyzing with dilute sulfuric acid, the ether-acid mixture was filtered to facilitate separation from the heavy white insoluble material which was present. A 10% solution of sodium hydroxide used to extract the ether, was refluxed with the white solid to remove any undissolved acid. On acidification with dilute hydrochloric acid, 6.5 g., or 25.7% yield, of 2-dibenzofurancarboxylic acid separated, melting at 240°. Recrystallization from alcohol raised the melting point to 246°.

This acid may also be prepared as demonstrated by Oatfield[70] by hydrolysis of 2-dibenzofuronitrile. With small amounts of 2-bromodibenzofuran, good yields of the nitrile are obtained; but in larger molecular quantities the yield is lowered. In a typical run, 50 g. (0.202 mole) of 2-bromodibenzofuran was heated at 260-275° for 5 hours with 19.7 g. (0.22 mole) cuprous cyanide. The black product was extracted with hot alcohol to give 15.3 g. or 39.5% yield of 2-dibenzofuronitrile melting at 128-131°.

To hydrolyze the nitrile, 20 g. (0.103 mole) was refluxed 24 hours with 200 cc. of 25% methyl alcoholic

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70. Oatfield, Harold. Benzo- and Dibenzofurans. Unpublished thesis, Iowa State College. 1933. p. 29.

potassium hydroxide. The solution was diluted with water and filtered to remove a small amount of insoluble material, then acidified with dilute hydrochloric acid. The yield was 17.3 g. or 78.5% of acid; m.p. 244-246°.

For physiological tests the acid was converted to its sodium salt by dissolving it in a warm aqueous solution containing one equivalent of sodium hydroxide. In this manner, 9 g. of acid was converted to 3.5 g. of shiny white plates of the salt. It is easily soluble in water and difficultly soluble in alcohol. Acidification of the aqueous solution gives the pure acid, melting at 245-246°.

Preparation of 2-Hydroxydibenzofuran

Ivanoff[71] has found that the yields of phenol reported by others[72] from oxidation of phenylmagnesium bromide are increased if the oxidation is done in the presence of an alkylmagnesium halide. This method was attractive for the preparation of 2-hydroxydibenzofuran since 2-bromodibenzofuran was easily available.

In the usual set-up for preparation of Grignard

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71. Ivanoff, Bull. soc. chim., 39, 47 (1926).
72. See Gilman and Wood, J. Am. Chem. Soc., 48, 806 (1926) for a study of this oxidation and for pertinent references.

reagents, 7.2 g. (0.294 atom) of magnesium turnings and 36.5 g. (0.147 mole) of 2-bromodibenzofuran in 700 cc. of ether was refluxed for one-half hour with 5 drops of n-butyl bromide, sufficient n-butyl bromide to make one equivalent (19.1 g. or 0.147 mole) was then added so that gentle refluxing resulted. The solution was refluxed for one and one-half hours then cooled to -10° in an ice-salt bath while oxygen gas was passed over the surface of the solution at the rate of one bubble per minute. The 2-hydroxydibenzofuran is obtained by hydrolyzing the product with dilute hydrochloric acid, extracting the ether layer with sodium hydroxide, and acidifying the aqueous solution with dilute hydrochloric acid. The yield was 10 g. or 36.7% of crude product, melting at 129-131°. Two recrystallizations from aqueous alcohol gave the pure product, melting at 133-134°. The yield was 7.1 g. or 26.1% of the theoretical.

The same product is formed when 2-dibenzofuryldiazonium borofluoride (prepared by the method of Klieder and Adams[73]) is heated with acetic acid, according to the directions of Smith and Haller[74], and the resulting 2-acetoxydibenzofuran is hydrolyzed with dilute sodium hydroxide. The product melted at 132.75-133.5°. A mixed

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73. Klieder and Adams, J. Am. Chem. Soc. 55, 4219 (1933).
74. Smith and Haller, ibid., 56, 237 (1934).

melting point with that prepared above was not lowered.

Nitration of 2-Diacetaminodibenzofuran

Brumberg[57] nitrated 2-diacetaminodibenzofuran and isolated a nitro-2-acetaminodibenzofuran which, when hydrolyzed and the amino group removed by diazotization, gave 3-nitrodibenzofuran. The nitroamine was called 2-amino-3-nitrodibenzofuran, without, however, proving that the nitro group was in the same ring as the amino group. This work has been extended here, and Brumberg's assumption that it is 2-amino-3-nitrodibenzofuran established. Nitro-2-aminodibenzofuran has been reduced to a compound which must be 2, 3-diaminodibenzofuran because the diamine forms quinoxaline derivatives with benzil and phenanthraquinone. These derivatives definitely place the nitro group in the 3- position.

Nitration of 2-diacetaminodibenzofuran was effected in acetic acid by adding 25 cc. of fuming nitric acid (d. 1.5) to 25 g. of crude 2-diacetaminodibenzofuran in 125 cc. of glacial acetic acid. After stirring for 35 minutes at room temperature, the mixture was poured onto ice water and crystallized from alcohol to give 19.4 g. of crude product, melting at 165-183°. Recrystallization from dilute acetic acid gave 2.3 g. or 7.7% yield of

yellow needles melting at 206-208°. A mixed melting point with a sample of Brumberg's compound[75] (m.p. 207-209°) was not lowered. Unfortunately Brumberg has reported no yield so a comparison is not possible.

By diluting the acetic acid mother liquor resulting from crystallization, 4.8 g. of 2-acetaminodibenzofuran, melting at 160-162°, was recovered. Recrystallization from 90% alcohol raised the melting point to 161.5-162.5°.

Anal. Calc'd. for $C_{14}H_{11}O_2N$; N, 6.22.

Found: N, 6.18 and 6.20.

Further dilution of the mother liquor gave a gummy precipitate which was not investigated.

2,3-Diaminodibenzofuran from 2-Acetamino-3-Nitrodibenzofuran

Hydrolysis of 2-acetamino-3-nitrodibenzofuran with alcohol and hydrochloric acid gave a 66.6% yield of bright red 2-amino-3-nitrodibenzofuran. Reduction with tin and hydrochloric acid gave a 50% yield of 2,3-diaminodibenzofuran hydrochloride which was converted quantitatively to 2,3-diaminodibenzofuran melting at 158-160°. Several recrystallizations from dilute alcohol raised the melting point to 164-166°. The diamine darkens rapidly on exposure to air.

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75. A sample was kindly supplied by Professor Borsche.

To 0.1 g. of 2,3-diaminodibenzofuran in 8 cc. of alcohol, 0.1 g. of benzil was added and the whole refluxed for one-half hour. The yellow quinoxaline derivative separates on cooling. When recrystallized from alcohol, pale yellow needles, m.p. 184-185°, were obtained. A mixed melting point with the corresponding quinoxaline derivative from the diamine of 2-nitro-3-aminodibenzofuran[57,63] (m.p. 178.5-179.5°) was 178.5-181.5°; however, the two quinoxaline derivatives formed by interaction of phenathraquinone on the diamines melted at 302-303° alone or when admixed.

Bromination of 2-Diacetaminodibenzofuran

Formation of 2-acetamino-3-nitrodibenzofuran by nitration of 2-diacetaminodibenzofuran is not unexpected, since mononitration of dibenzofuran gives 3-nitrodibenzofuran. With the 2- position blocked, and with the o-directing influence of the acetamino group in mind, it was hoped that bromination of 2-diacetaminodibenzofuran would give 1-bromo-2-acetaminodibenzofuran and thus afford an entry to 1- substituted derivatives. Bromination, however, follows nitration and 2-acetamino-3-bromodibenzofuran is formed.

To 10 g. (0.037 mole) of 2-diacetaminodibenzofuran, dissolved in glacial acetic acid, 7 g. (0.0437 mole) of bromine was added. Dilution with ice water gave 10.3 g. of crude product which melted at 180-210°. This was digested with 300 cc. of alcohol, which left an insoluble white amorphous mass, melting at 203-216°. When recrystallized from 90% acetic acid, 2.5 g. (22.5% yield) of pure 3-bromo-2-acetaminodibenzofuran, melting at 240-241°, was isolated.

Anal. Calc'd for $C_{14}H_{10}O_2NBr$: N, 4.6. Found: N, 4.67 and 5.05.

In a second run, 15 g. (0.0555 mole) of 2-diacetaminodibenzofuran was dissolved in the minimum amount of cold acetic acid in a 200-cc. three-necked flask. To this solution 9 g. (2.8 cc.; 0.056 mole) of bromine was added to give 41% yield of once-recrystallized 2-acetamino-3-bromodibenzofuran melting at 203-216°.

The mother liquors from recrystallization when diluted with water gave 7.5 g. of pale pink needles melting at 138-161°. This product was not further investigated.

Hydrolysis of the 2-acetamino-3-bromodibenzofuran was effected by means of alcohol and hydrochloric acid to give a quantitative yield of crude 2-amino-3-bromodibenzofuran, which when recrystallized from

alcohol, melted at 172-173°.

Anal. Calc'd. for $C_{12}H_8ONBr$: N, 5.34.
Found: N, 5.45 and 5.64.

Identification of the bromoamine was done by two methods. First, it was converted to 2,3-diaminodibenzofuran which in turn gave a quinoxaline derivative with benzil identical with that prepared from the 2,3-diaminodibenzofuran previously described. Secondly, the amino group was removed by diazotization giving 3-bromodibenzofuran.

The same procedure for replacing the bromine atom was followed as with 2-bromodibenzofuran. One gram (0.0038 mole) of bromo-2-aminodibenzofuran was heated in a sealed tube at 165-175° for 2 hours then at 215° for 8 hours and worked up as before. The yield was 0.62 g. or 60% of diamine dihydrochloride. This was converted to the free amine with alcoholic ammonium hydroxide, 0.1 g. of which in 3 cc. of alcohol gave a quinoxaline derivative with benzil melting at 184-185°.

A 79.7% yield of crude 3-bromodibenzofuran was obtained by heating the diazonium salt solution of 2-amino-3-bromodibenzofuran with alcohol until no nitrogen was evolved. After recrystallizing from alcohol, the product melted at 118-119° either alone or when mixed with an

authentic sample of 3-bromodibenzofuran.[76]

Nitration of Dibenzofuran

A slight modification of the method of Borsche and Bothe[52] was used in an effort to prepare a large quantity of the 110° isomer reported by them. Speculations concerning this isomer and the possibility that it was 2-nitrodibenzofuran in an impure form, made it desirable to purify and identify this mixture.

The only difference in procedure was that, instead of allowing the temperature to rise to the point of refluxing while the nitric acid was being introduced, the solution of 168 g. (1 mole) of once-distilled technical dibenzofuran in 500 cc. of glacial acetic acid was maintained at 60-65° with vigorous stirring while 152 cc. of technical fuming nitric acid (d. 1.49-1.5)was added. The yellow product separated immediately and after cooling was filtered then washed with 125 cc. of glacial acetic acid and 200 cc. of water. The yield was 161.6 g. or 75.8% of pure 3-nitrodibenzofuran melting at 181-182°.

By diluting the acetic acid mother liquors with two volumes of water, 57 g. of light yellow needles separated. Purification was attempted by extraction with

76 . This was prepared by the Sandmeyer reaction from 3-aminodibenzofuran by Paul T. Parker.

petroleum ether (b.p. 60-68°), and recrystallization from methyl alcohol, dilute acetic acid, petroleum ether and benzene. The melting point of the product was raised from 92° to 107-110°. It could be purified no further.

Reduction of Low Melting Isomer From Nitration of Dibenzofuran

That fraction of the nitration product of dibenzofuran melting at 107-110° was reduced with tin and hydrochloric acid in 71% yield. The product was purified by recrystallization from dilute hydrochloric acid until a light gray hydrochloride was obtained. The amine hydrochloride was converted to the free amine by dilute alcoholic ammonium hydroxide. After three recrystallizations from dilute alcohol, pale pink plates melting at 103-112° separated.

Further purification was attempted through the acetamino-derivative prepared by dissolving 3 g. (0.0176 mole) of free amine in 175 cc. of benzene and, after filtering out a small amount of insoluble material, adding 1.8 g. (0.0176 mole) of acetic anhydride. After standing for one-half hour, the solution was concentrated by distillation then placed in the ice-box to facilitate crystallization. This procedure gave 1.9 g. or 51% yield of acetaminodibenzofuran melting at 141-149°. Purification was done by recrystallizing five times from dilute alcohol, extracting

once with petroleum ether (b.p. 60-68°), then recrystallizing five times from benzene. Fine white needles of 2-acetaminodibenzofuran melting at 162-162.5° (mixed m.p.) were obtained. This definitely proves that part at least of the 107-110° isomer from nitration is 2-nitrodibenzofuran.

Nitration of Dibenzofuran with Aluminum Nitrate in Acetic Anhydride

Bacharach and co-workers[77] found that aluminum nitrate with copper nitrate (or lithium nitrate alone) in acetic anhydride causes abnormal orientation in quinoline. Thus 7-nitroquinoline is formed rather than 5-nitroquinoline, the usual product obtained by nitrating with nitric-sulfuric acid. It was predicted that abnormal orientation with dibenzofuran would result in formation of 2- or 4-nitrodibenzofuran. Consequently 16.8 g. (0.1 mole) of once-distilled technical dibenzofuran in 165 cc. acetic anhydride was heated 2 hours on a water bath with 12.4 g. (0.033 mole) of aluminum nitrate and 2 g. of copper nitrate as a catalyst. The reaction product was then poured into water, whereupon 18.7 g. of crude product melting at 58-145° separated. Extraction with petroleum ether for 2 hours removed unchanged dibenzofuran. The

77. Bacharach, Haut and Caroline, Rec.trav.chim., 52, 413 (1933).

residue was treated with 75 cc. of warm glacial acetic acid and 3-nitrodibenzofuran filtered out. Dilution with water, extraction of the product with benzene and concentration of the benzene solution gave pale yellow needles melting at 132-133.5°. Recrystallization from 95% alcohol gave 0.3 g. of pale yellow needles melting at 132-133°. A mixed melting point with 2-nitrodibenzofuran prepared by Cullinane's method[55] (m.p. 147-149°) was 130.5-141.5°. This lowering of the melting point of the authentic 2-nitrodibenzofuran indicates that the product is not 2-nitrodibenzofuran and may be 1- or 4-nitrodibenzofuran.

Anal. Calc'd for $C_{12}H_7O_3N$: N, 6.57; Found N, 7.0.

In a second run 1.8 g. of the product from 0.5 mole dibenzofuran was obtained. The problem was not further investigated.

Preparation of 3-Hydroxydibenzofuran

Run 1. The necessary 3-aminodibenzofuran hydrochloride needed for the preparation of 3-hydroxydibenzofuran was made by reduction of 3-nitrodibenzofuran, using the method of Oatfield[70]. To a well stirred solution of 53 g. (0.25 mole) of 3-nitrodibenzofuran suspended in 375 cc. of concentrated hydrochloric acid, 100 g. of granulated tin was added in small portions. The suspension was heated one hour on the water bath, neutralized with

concentrated ammonium hydroxide and the white product extracted several hours with ether. Dry hydrogen chloride precipitated 3-aminodibenzofuran hydrochloride from the ether solution. The yield was 47.2 g. or 75.5% of the theoretical.

The directions of Klieder and Adams[73] were used for the preparation of the diazonium borofluoride; 17.5 g. (0.08 mole) of 3-aminodibenzofuran·HCl in 25 cc. of concentrated hydrochloric acid was diazotized at 0° with a saturated solution of sodium nitrite (starch-iodide test), then treated with 28 g. of hydrofluoroboric acid (prepared from 20 g. of 48% hydrofluoric acid and 8 g. of boric acid). After standing one hour, the yellow precipitate was filtered to give a quantitative yield of diazonium borofluoride.

The diazonium borofluoride was divided into two portions to determine the relative efficiency of acetic acid and acetic anhydride[74] in converting the salt to the acetoxy derivative. Twelve grams (0.0456 mole) of the borofluoride was cautiously heated with 75 cc. of acetic anhydride. The solution was concentrated by distillation, diluted with water, and neutralized with sodium carbonate. The brown precipitate was refluxed one hour with 50 cc. of 10% sodium hydroxide, filtered, then neutralized with sulfuric acid. After recrystallizing from dilute acetic acid then from hot water, 1.3 g. (24.1%) of shiny plates separated, melting at 138-139°.

Anal. Calc'd for $C_{12}H_8O$; C, 78.23; H, 4.38.
Found: C, 78.57, 78.71; H, 4.68, 4.64.
A Zerewitinoff determination gave 0.94 active hydrogen.

The remainder of the diazoniumborofluoride was heated cautiously with 150 cc. of glacial acetic acid, then worked up as before. From this 4.1 g. or 64% of crude yellow 3-hydroxydibenzofuran was isolated. Acetic anhydride is apparently the better reagent for converting a diazoniumborofluoride to the acetoxy derivative since the yield of crude product was quantitative.

Run 2. To 34 g. (0.113 mole) of 3-aminodibenzofuran hydrochloride suspended in 75 cc. of dilute hydrochloric acid, was added a solution of 11.1 g. (0.15 mole) sodium nitrite in 60 cc. of cold glacial acetic acid. After standing at room temperature for one hour, the clear diazonium solution was slowly added to 300 cc. of boiling glacial acetic acid. As soon as a black precipitate formed the heating was stopped and the acetic acid replaced by a fresh portion. The acetic acid was then made basic with 50% sodium hydroxide. From this filtered solution 2.7 g. (25% yield) of 3-hydroxydibenzofuran was precipitated when acidified with hydrochloric acid.

Run 3. Nitrogen trioxide from 30 g. of arsenic trioxide and nitric acid (sp.gr. 1.33) was passed into a suspension of 11 g.(0.051 mole) of 3-aminodibenzofuran in 200 cc.of

absolute alcohol. A small portion gave a positive test with β-naphthol. It was allowed to stand overnight then heated on a water bath for one hour. At the end of this time the color test was negative. Steam-distillation yielded only dibenzofuran (m.p. 78-79.5°). From the steam-distillation residue, 5.7 g. (51.8%) of 3-aminodibenzofuran hydrochloride was recovered. The only apparent reaction was reduction to dibenzofuran; otherwise it was unsuccessful.

Run 4. In an attempt to replace the amino group by a methoxyl group, 11 g. (0.051 mole) of the amine hydrochloride in 180 cc. of hot absolute methanol was slowly treated with 4 g. (0.058 mole) of solid sodium nitrite. Toward the end of addition, a brown precipitate began to separate. The mixture was heated on a steam bath for 4 hours then steam distilled. From the distillate 4.4 g., 51.7% yield, of dibenzofuran was recovered.

Tsuzuki[32] has re-examined the work of Kubata et al.,[78] and isolated a mono- and dihydroxydibenzofuran by passing resorcinol vapors over heated blue tungsten oxide. The mechanism of the reaction presented by Tsuzuki postulated the formation of 1- or 3-hydroxydibenzofuran and 1,9- or 3,7-dihydroxydibenzofuran. He has chosen 1-hydroxy-

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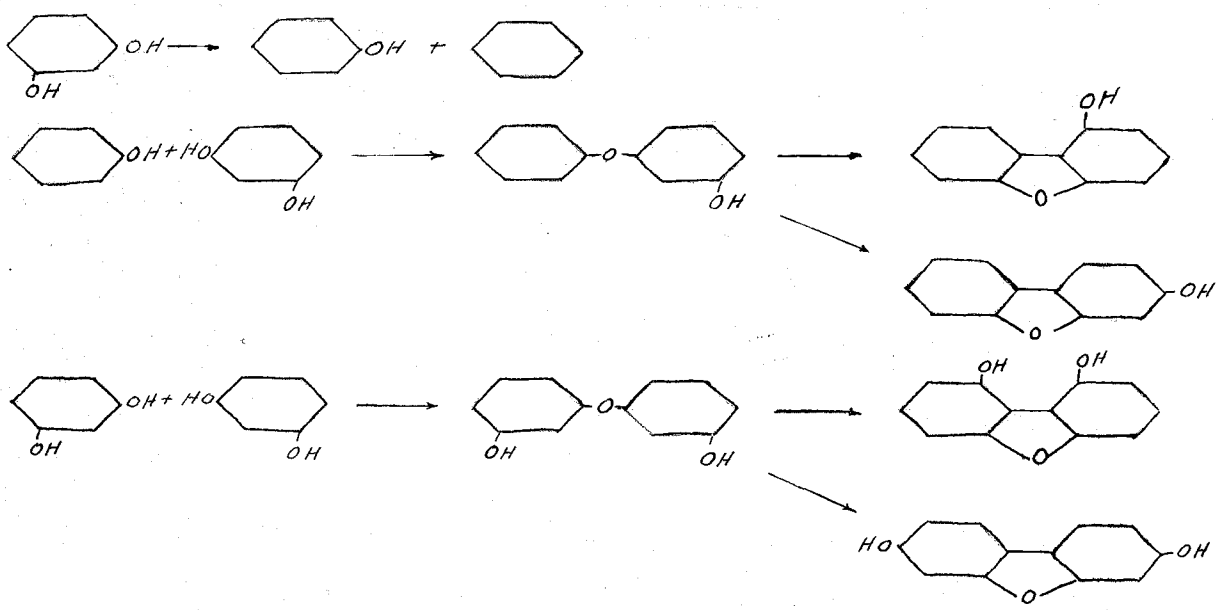
78. Kubota, Fujimura and Akashi, Scientific Papers Inst. Phys. Chem. Res. Tokyo, 2, 185 (1925).



dibenzofuran as the most probable form on the basis of similarity between absorption spectra curves of this compound and o-hydroxydiphenyl and because the hexahydro-derivative was oxidized to phenylmalonic acid. Formation of phenylmalonic acid cannot be used as a definite reason for assigning the hydroxyl group to any position, because phenylmalonic acid would be formed regardless of its position.

The close agreement between the melting point given by Tsuzuki (m.p.138-138.5°) and that obtained in this thesis for 3-hydroxydibenzofuran warranted re-examination of this reaction. It is obvious from the proposed mechanism that 3-hydroxydibenzofuran could be formed as easily as 1-hydroxydibenzofuran.

In accordance with the directions of Tsuzuki, alcohol vapors were passed over 12 g. of reprecipitated tungstic oxide heated at 290° in an ordinary combustion tube until the yellow oxide was reduced to the blue oxide.* Immediately, 12-15 g. of resorcinol was passed over the catalyst at 500-550°, and the product collected in an air condenser placed horizontally with a side arm projecting into a flask. The product was steam distilled until the distillate gave no precipitate with bromine water (phenol). The residue in the steam-distillation flask was then made strongly acidic with concentrated hydrochloric acid and the distillation continued until no solid separated in the condenser. The distillate was concentrated to approximately 50 cc., whereupon a white solid melting at 130° separated. The compound, after decolorizing with charcoal, separated in shiny white flakes which darkened slightly in air and melted at 137.5-138.5°. A mixed melting point with 3-hydroxydibenzofuran (m.p. 138-139°) was 137.5-138.5°, thus proving that Tsuzuki's compound is 3-hydroxydibenzofuran.

3-Dibenzofurancarboxylic Acid

This acid was prepared by the method of Borsche

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* The writer is grateful to Ralph L. Van Peursem for assistance.

and Bothe[52] and purified by sublimation and then recrystallized from alcohol. Some difficulty was experienced in freeing the acid from basic material. Hydrolysis with concentrated hydrochloric acid did not have this undesirable feature.

Preparation of 2-Bromo-7-Nitrodibenzofuran

A. From 3-nitrodibenzofuran.

Ten grams (0.047 mole) of 3-nitrodibenzofuran was suspended in 75 cc. of glacial acetic acid and heated to 70°. To this warm solution 3 cc. (9.6 g., 0.06 mole) of bromine was added while the suspension was vigorously stirred. The temperature was held at 65-70° for 4 hours. After cooling, precipitation was completed by the addition of 250 cc. of cold water. Thus, 12.3 g. of yellow needles, melting at 157-210°, were procured. Digestion with 225 cc. of glacial acetic acid left 2 g., or 14% yield, of 2-bromo-7-nitrodibenzofuran, melting at 246-249°. The pure compound can be obtained by recrystallizing from a large volume of acetone. M.p. 250.5-251.5°.

Anal. Calc'd for $C_{12}H_6O_3NBr$: Br, 27.37. Found: Br, 27.12 and 27.09.

When cooled, the glacial acetic acid filtrate yielded a fraction which melted at 169-228°. Digestion of this with

75 cc. of acetic acid left a small amount of crude bromo-nitro compound which melted at 222-237°. Fractional crystallization of the mother liquors resulted in the isolation of two fractions, m.p. 171-183° and 169-176°, neither of which was further investigated.

In a second run using 20 g. (0.094 mole) of 3-nitrodibenzofuran and 6 cc. of bromine (19.2 g. or 0.106 mole), 5 grams of product was obtained which melted at 238-242°. (18.3% yield).

B. From 2-bromodibenzofuran.

To 49.4 g. (0.2 mole) of 2-bromodibenzofuran in 175 cc. of glacial acetic acid, 40 cc. of fuming nitric acid was added. The mixture was heated at 70-75° for one-half hour whereupon a pale yellow precipitate began to form and a large quantity of nitrogen oxide fumes was given off. The reaction product (48.8 g. m.p 136-200°) was isolated by completing precipitation with water. Since 2-bromo-dibenzofuran is easily soluble in benzene, the mixture was heated with approximately 400 cc. of benzene which left 9.2 g. of insoluble material (m.p. 237-242°). On cooling the benzene solution, 5.4 g. more of bromonitro-dibenzo-furan, melting at 242-244° was procured. The total yield of crude product was 25%. When purified, this bromo-

nitro compound is identical with that prepared by method A (mixed m.p.). Cullinane, Davy and Padfield[36] have recently substantiated these results but have not reported isomers nor definitely proved the structure. Brumberg[57] obtained a mixture of isomers but did not resolve it. One isomer has been isolated as reported in the sequel.

Reduction of 2-Bromo-7-Nitrodibenzofuran

Two grams (0.0068 mole) of 2-bromo-7-nitrodibenzofuran was reduced with 5 g. of granulated tin and 25 cc. of concentrated hydrochloric acid. The reaction product was made alkaline with concentrated ammonium hydroxide; filtered; and the white solid extracted with ether. The hydrochloride was precipitated from the ether solution with hydrogen chloride, then converted to the free base by dissolving in hot alcoholic ammonium hydroxide. The yield was 0.1 g. of crude amine, melting at 128-130°. After one crystallization from alcohol, the melting point was raised to 133-134° and did not change on subsequent recrystallizations. A mixed melting point with 2-bromo-3-aminodibenzofuran[63] was lowered to 105°.

Anal.* Calc'd for $C_{12}H_8ONBr$: N, 5.34; Found: N, 5.33 and 5.32.

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* Analysis by George E. Brown.

Conversion of 2-Bromo-7-Aminodibenzofuran to 2,7-Dibromo-benzofuran

One gram of 2-bromo-7-aminodibenzofuran in dilute hydrobromic acid was diazotized and the diazonium solution treated with cuprous bromide in 10% hydrobromic acid to form 2,7-dibromodibenzofuran. Identification was established by a mixed melting point with an authentic sample kindly supplied by Professor McCombie[40].

Preparation of 2,7-Diaminodibenzofuran from 2-Bromo-7-Nitrodibenzofuran

One and one-half grams (0.005 mole) of 2-bromo-7-nitrodibenzofuran was heated in a sealed tube with 25 cc. of 22% ammonium hydroxide and 1 g. of cuprous chloride at 208-210° for 10 hours, then at 150-160° for 5 hours. The hard brown lumps were broken up and the mass extracted with ether-benzene. This extract was dried over sodium sulfate and saturated with hydrogen chloride to give 0.37 g. of the hydrochloride. The free base was obtained by warming the hydrochloride with 5 cc. of concentrated ammonium hydroxide then adding enough alcohol to cause solution. The amine separated as small brown glistening plates, melting at 143°. The yield was 0.13 g. or 10.8% of the theoretical.

This nitroamine was reduced with 1 g. of granulated

tin and 10 cc. of hydrochloric acid in the usual manner. The free amine crystallized from hot water in white plates which darkened on exposure to air and melted at 145-149°. It separated from 90% alcohol as fine needles melting at 147-148°. A mixed melting point of this product with 2,7-diaminodibenzofuran (m.p. 147°) prepared by reduction of 2,7-dinitrodibenzofuran[55], was not lowered.

Isolation of 2-Bromo-3-Nitrodibenzofuran

Concentration of the benzene solution from the nitration of 2-bromodibenzofuran to 175 cc. gave 10.5 g. (18%) of yellow glistening plates melting at 138-148°. Only one recrystallization from benzene is necessary to raise the melting point to 154.5-155.5°.

Anal. Calc'd for $C_{12}H_6O_3NBr$: N, 4.79. Found: N, 4.88 and 5.06.

Further concentration of the benzene solution gave 6 g. of slightly oily red material melting at 109-125°. Evaporation to dryness left 10.5 g. of residue.

Reduction of 2-Bromo-3-Nitrodibenzofuran

One gram of the isomer obtained by nitrating 2-bromodibenzofuran was reduced with tin and hydrochloric acid to give 0.35 g. of product which, when crystallized

from 50% alcoholic ammonium hydroxide, melted at 127-128° alone or when mixed with 2-bromo-3-aminodibenzofuran obtained by bromination of 3-diacetaminodibenzofuran[63].

Preparation of 4-Hydroxydibenzofuran

To 2.8 g. (0.2 equivalent) of lithium metal suspended in 140 cc. of anhydrous ether, 27 g. (0.2 mole) of n-butyl bromide was added after starting the reaction in the usual manner. The reaction mixture was refluxed with vigorous stirring for one and one-half hours, then decanted through glass wool in an atmosphere of nitrogen into a 500-cc. three-necked flask containing 20 g. (0.12 mole) of dibenzofuran. In order to complete the reaction between dibenzofuran and butyl-lithium, refluxing was continued for 4 hours. The resulting solution was oxidized with oxygen while the flask was cooled in an ice-salt bath, then hydrolyzed by pouring the mixture onto cracked ice. After extracting the ether in the usual manner with 10% sodium hydroxide and acidifying the basic solution, 3 g. or 13.6% yield of 4-hydroxydibenzofuran, melting at 97°, was isolated. Purification was completed by recrystallizing from dilute alcohol. The melting point of the pure material was 101-102°.

Preparation of 4-Dibenzofurancarboxylic Acid

This acid has been previously described by Gilman and Young[34] who prepared it by a longer process than that reported here. The method used in this work was developed from studies made by E. A. Zoellner on the relative ease with which organolithium compounds react with dibenzofuran. It has the advantage over other methods in that it requires less attention and is more easily manipulated since the filtration step in the preparation of dibenzofuryl-lithium from butyl-lithium may be eliminated. The yield of acid does not vary from 30-35%.

The reaction was carried out in the ordinary apparatus for preparation of a Grignard reagent in an atmosphere of nitrogen and was started in the usual manner. Phenyl-lithium from 94.2 g. (0.06 mole) of bromobenzene, and 8.4 g. (1.2 mole) of fine cut lithium metal in 520 cc. of anhydrous ether was refluxed 21 hours with 90.7 g. (0.54 mole) of dibenzofuran. The reaction product was carbonated by pouring it into a two-liter round-bottomed flask filled with solid carbon dioxide. Carbon dioxide gas was then passed into the flask to complete the reaction and to facilitate removal of the remaining ether. By extracting the residual solid with two 1500 cc. portions of hot water

and acidifying the filtrate with 10% hydrochloric acid, 41 g. or 35.6% yield of 4-dibenzofurancarboxylic acid separated. The crude product melts at 204-206° and is pure enough for most purposes.

Preparation of 4-Dibenzofurancarboxylic Acid Amide

Two methods were tried in preparing the acid amide. In the first, the acid chloride was slowly added to concentrated ammonium hydroxide; in the second, an ether-benzene solution of the crude acid chloride was saturated with ammonia gas. The amide prepared by the second method retains a slight yellow color which is difficult to remove by recrystallization. In neither preparation was any attempt made to isolate the acid chloride in a pure state.

Method 1. Run 1. The acid chloride was prepared by refluxing 16 g. (0.075 mole) of 4-dibenzofurancarboxylic acid with 70 g. (0.52 mole) of technical thionyl chloride for 2 hours. Excess thionyl chloride was removed under reduced pressure. The light yellow acid chloride was dried on a porous plate then added to 150 cc. of concentrated ammonium hydroxide (sp.gr. 0.89). The reaction is complete in a short time as indicated by disappearance of the yellow color. The crude product weighed 14.3 g. (89.9% yield) and melted at 168-176°. One recrystallization from alcohol

was sufficient to give a pure compound (54% of the theoretical yield), melting at 181-182°.

Anal. Calc'd for $C_{13}H_9O_2$ N: N, 6.63. Found: N, 6.73 and 6.46.

Run 2. In this run, 4-dibenzofurancarboxylic acid and thionyl chloride were refluxed only one hour after vigorous reaction had stopped. The acid chloride from 18 g. (0.085 mole) of acid was added to 400 cc. of concentrated aqueous ammonia (sp.gr. 0.89) and stirred for two hours. The yield was 16 g. or 89.4% of amide melting at 174°. Evidently these reactions are completed rapidly and longer time is not necessary.

Method 2. Twenty-three grams (0.108 mole) of 4-dibenzofurancarboxylic acid was refluxed in a 500-cc. round-bottomed flask with 85 g. (0.63 mole) of thionyl chloride for 3 hours. After removing the excess thionyl chloride with the aid of a water pump, the flask was swept out with nitrogen to remove traces of thionyl chloride, sulfur dioxide and hydrogen chloride. The crude acid chloride was dissolved in 200 cc. of ether-benzene and saturated with ammonia. Purification by recrystallizing from dilute alcohol using charcoal did not remove the yellow color present in the crude product. Yield: 14 g. Concentration of the ether-

benzene solution gave 2.6 g. more amide, melting at 179°. The total yield was 16.6 g. or 73%.

Preparation of 4-Aminodibenzofuran

This previously unknown amine was required for comparative physiological tests and for orientation studies. It has been prepared for the first time by two different reactions; namely, replacement of the hydroxyl group in 4-hydroxydibenzofuran by an amino group and by Hofmann rearrangement of 4-dibenzofurancarboxylic acid amide. These reactions establish its structure but in both cases it is obviously based on the fact that metalation takes place in the 4- position.

A. From 4-hydroxydibenzofuran.

Zinc ammonium chloride was prepared from fused zinc chloride by the method of Merz and Muller[79]. Six grams (0.035 mole) of this with 2 g. (0.037 mole) of ammonium chloride was heated in a sealed tube at 275-280° for 21 hours with 2.3 g. (0.0125 mole) of 4-hydroxydibenzofuran. The brown mass was removed from the tube by lixiviating with dilute hydrochloric acid and ether. The hydrochloric

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79. Merz and Müller, Ber., 19, 2902 (1886).

solution was neutralized with sodium hydroxide then extracted with ether. By passing gaseous hydrogen chloride into the ether solution, 0.45 g. (16.6% yield) of the amine hydrochloride was obtained. The hydrochloride was converted to the pure amine by dilute alcoholic ammonium hydroxide and it melted at 84.5-85.5°.

Anal. Calc'd for $C_{12}H_9ON$: N, 7.65; Found: N, 7.72 and 7.46.

B. From 4-dibenzofurancarboxylic acid amide by Hofmann rearrangement.

Run 1. Following the procedure Goldschmiedt[80] has used on 4-fluorenonecarboxylic acid amide, 4-dibenzofurancarboxylic acid amide was converted to the amine by the Hofmann reaction. A solution of potassium hypobromite was prepared by adding 3.4 cc. (10.9 g., 0.068 mole) of bromine to 23 g. (0.41 mole) of potassium hydroxide in 300 cc. of water. To this solution, 14 g. (0.0664 mole) of acid amide was introduced with shaking. At the end of three hours the mass had turned brown and shiny brown needles commenced to separate. The reaction was completed by allowing the mixture to stand 24 hours and then heating on the water bath for 2 hours. Following filtration, the brown material

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80. Goldschmiedt, Monatsh., 23, 890 (1902).

remaining in the funnel was extracted with dilute hydrochloric acid, filtered, and made alkaline with ammonium hydroxide. The yield was 2.3 g. of free amine; m.p. 77°. It was purified by re-precipitating the hydrochloride from ether then re-converting it to the amine by means of alcoholic ammonium hydroxide; m.p. 83.5-84.5°. A mixed melting point with the amine previously prepared was not lowered. By reerystallizing the dark brown residue from the hydrochloric acid extraction, 6 g. of 4-dibenzofurancarboxylic acid amide was recovered. The yield of free amine was 33.2% based on the acid amide actually used in the reaction.

Run 2. A hypobromite solution was prepared in a 500-cc. round-bottomed flask by adding 27.3 g. (8.6 cc) (0.152 mole) of bromine to 27 g. (0.67 mole) of sodium hydroxide in 150 cc. of water. To this solution, 16 g. (0.076 mole) of amide suspended in 50 cc. of 10% sodium carbonate was added while the flask was cooled in an ice-salt bath. The flask was allowed to warm up to room temperature then 25 cc. of ethanol was added. The amine hydrochloride was isolated in 27.3% yield, after heating for one hour on a water bath, by extracting with ether and precipitating with hydrogen chloride.

In this reaction the amount of bromine has been doubled with no apparent improvement in the yield.

SUMMARY

A review of theories of narcosis has been made, and some correlations between constitution and activity have been presented for the aliphatic hypnotics.

The close and important relationship of dibenzofuran and its derivatives to morphine has been discussed. The following derivatives of dibenzofuran have been prepared for use in physiological tests: 2-, 3-, and 4-amino-, 2- and 3-hydroxydibenzofuran, and 2- and 3-dibenzofurancarboxylic acids.

A necessary study of nuclear substitution in dibenzofuran has been made prior to the preparation of derivatives for physiological tests. It has been shown that homonuclear substitution results when 2-diacetaminodibenzofuran is brominated or nitrated. Heteronuclear substitution occurs when 3-nitrodibenzofuran is brominated. Both heteronuclear and homonuclear substitution take place when 2-bromodibenzofuran is nitrated.

The hydroxydibenzofuran formed by passing resorcinol over heated tungstic oxide has been shown to be 3-hydroxydibenzofuran; and, a low melting isomer formed during nitration of dibenzofuran has been found to consist, in part, of 2-nitrodibenzofuran. The significance of these two facts is discussed with reference to the space formula of dibenzofuran and purported anomalous substitutions.