NOTE TO USERS

DERIVATIVES OF 1-, 4-, 6-, AND 9-SUBSTITUTED DIBENZOFURANS

by

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for the Degree of

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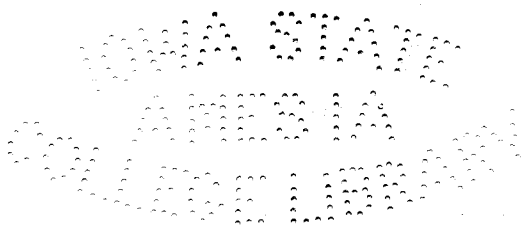

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Dean of Graduate College

Iowa State College

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A C K N O W L E D G M E N T

The author is sincerely grateful to Dr. Henry Gilman for his generous help and encouragement in the studies reported here.

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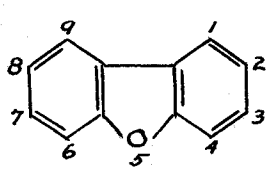
I N T R O D U C T I O N

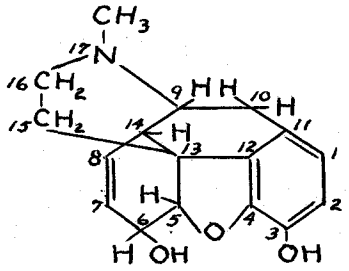
This is a report on a continuation of the work initiated in this laboratory several years ago (1) (2) on orientation and physiological studies of dibenzofuran and some of its derivatives. The original interest in dibenzofuran was the possibility of its use as an inexpensive source of some important furan compounds. It was hoped that these compounds could be formed by oxidative degradation of dibenzofuran (1). When dibenzofuran itself was found to be very resistant to attack, the introduction of positive substituents such as amino groups was planned in order to make the nucleus more susceptible to oxidation. A survey of the literature showed, however, that although dibenzofuran had been subjected to several substitution reactions, the positions of the substituents had not been determined in many of the compounds reported. Since dibenzofuran (I) plays such a prominent part in the morphine skeleton (II) it seemed desirable that these cases of questionable orientation be cleared up. At the same time it was felt that it would be of real value to test the

(1) Oatfield, Thesis, Iowa State College, 1933.
(2) Bywater, Smith, Brown and Gilman, Proc. Iowa Acad. Sci., 41, 166 (1934) /C. A., 29, 3674 (1935)/; Kirkpatrick and Gilman, ibid., 41, 173 (1934) /C. A., 29, 4007 (1935)/.

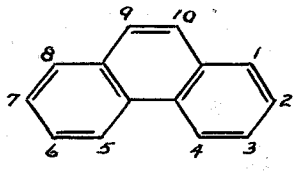
compounds prepared incidental to this work for morphine-like action. It was believed quite possible that a fragment of the morphine molecule, such as a simple dibenzofuran derivative, might be found that would have an analgesic action comparable to that of morphine but be devoid of the latter's habit forming properties. The successful substitution of procaine for novocaine in the field of local anesthetics may be cited as support for this type of reasoning. With this purpose in mind others (see discussion of Pharmacological Results) had already begun work on phenanthrene (III), which is also a part of the morphine skeleton.



I.



II.



III.

Accordingly, work was begun on proving unequivocally the structures of some of the compounds in which the positions of the substituents had been assigned arbitrarily or by analogy (3) (4) (5). At the same time other reactions

(3) Gilman, Smith and Oatfield, J. Am. Chem. Soc., 56, 1412 (1934).
(4) Gilman, Brown, Bywater and Kirkpatrick, ibid., 56, 2473 (1934).
(5) Gilman, Bywater and Parker, ibid., 57, 885 (1935).

of dibenzofuran were being investigated and the significant discovery was made that metalation, by means of mercuric acetate, organolithium compounds or organosodium compounds, involved the 4-position, a position which had hitherto not been attacked in any of the reactions studied (6). Di-metalation, involving the 4- and 6-positions, was effected by means of organosodium compounds, but could not be achieved by means of organolithium compounds (7) (8). Very recent studies (9) indicate that benzylsodium, prepared in one step from sodium, chlorobenzene, and toluene, may be the most efficacious metalating agent available at present, both from the points of view of cost and yields produced.

The 4- and 4,6-substituted dibenzofurans proved to be the key to the previously unsubstituted 1- and 9-positions. Bromination (10) (11) and nitration (12) of 4-acetaminodi-benzofuran were found to involve the 1-position and like reactions with 4-hydroxy- (10) (11) and 4-methoxydibenzo-furans (13) (14) introduced the substituent into the

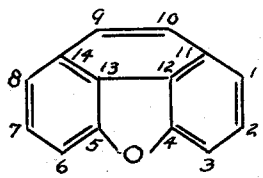
(6) Gilman and Young, Ibid., 56, 1415 (1934).
(7) Gilman and Young, Ibid., 57, 1121 (1935).
(8) Gilman and Young, J. Org. Chem., 1, 315 (1936).
(9) Unpublished studies by Messrs. H. A. Pacevitz and T. H. Cook, this laboratory.
(10) P. R. Van Ess, Doctoral Dissertation, Iowa State College, 1936.
(11) Gilman and Van Ess, J. Am. Chem. Soc., 61, 1365 (1939).
(12) This Thesis.
(13) Parker, Doctoral Dissertation, Iowa State College, 1937.
(14) Gilman, Jacoby and Swislowsky, J. Am. Chem. Soc., 61, 954 (1939).

1-position. The oxidation of 4,6-dibenzofurylenedisodium, even in the presence of butylmagnesium bromide, gave very poor yields of 4,6-dihydroxydibenzofuran (7). A method for the preparation of this important compound was worked out by Cheney (15) (16), who obtained 6-hydroxy-4-methoxydibenzofuran in approximately 30 per cent yield, along with the isomeric 3-hydroxy-4-methoxydibenzofuran, from the metalation of 4-methoxydibenzofuran with subsequent oxidation of the metalation products. The 4,6-dimethoxydibenzofuran prepared from this was found to direct substituents to the 1- and 1,9-positions in good yields and without the formation of isomers. However, the preparation of 4,6-dimethoxydibenzofuran is both costly and laborious.

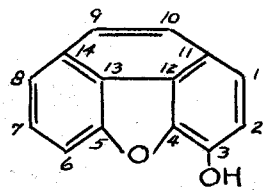
The purposes of this particular part of the work were: first, to study the nitration of 4-acetaminodibenzofuran and determine the structures of the products formed, and second, to evolve convenient methods for preparing 1,9-derivatives of dibenzofuran with the view that these might ultimately be used in bridging the 1- and 9-positions to form a phenanthrylene oxide type (IV). Syntheses of this kind to give phenanthrene derivatives from biphenyl

(15) Cheney, Doctoral Dissertation, Iowa State College, 1938.
(16) Gilman, Cheney and Willis, J. Am. Chem. Soc., 61, 951 (1939).

derivatives have been reviewed by Cheney (15). Phenanthrylene oxide itself has never been prepared (17) but a simple hydroxy derivative of it, morphenol (V), can be made in satisfactory yields by degradation of morphine (18).



IV.



V.

The importance of the 1-, 4-, 6-, and 9-positions in dibenzofuran, in relation to the latter's incidence in the morphine molecule, is readily apparent from an inspection of the two formulae (I) (II).

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

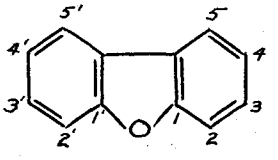
H I S T O R I C A L

In the pages which follow are tabulated all of the reported dibenzofuran derivatives with substituents in one or more of the critical (1-, 4-, 6-, or 9-) positions. The arrangement is: first, in sections according to the number of substituents, the monosubstituted dibenzofurans leading; second, alphabetically within each section and third, following the alphabetical arrangement within each section, according to the position of the first substituent mentioned. Thus, 1,4-diacetaminodibenzofuran precedes 3,4-diacetaminodibenzofuran, but 4-dibenzofurylacetic acid precedes both since it is a monosubstituted derivative and appears in an earlier section. Esters have been listed as individual compounds and not as derivatives of acids (e.g., 1-carbomethoxydibenzofuran and not methyl 1-dibenzofurancarboxylate). The letter "x" in place of a number signifies that the position of that substituent is indefinite. All compounds have been included which are listed in Chemical Abstracts or Chemisches Zentralblatt as dibenzofuran, diphenylene oxide, or biphenylene oxide derivatives. In addition an attempt has been made to include benzofuroquinolines (pyridodibenzofurans) and benzofurophenazines. The derivatives of some fused ring systems incorporating

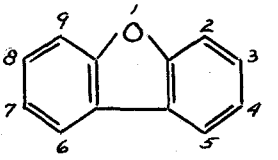
a dibenzofuran nucleus, such as the morphine alkaloids, dinaphthalene oxides, and brazans have been omitted. However, morphenol and a few of its simple derivatives have been included because of their close structural relationships to the compounds discussed here. In a few cases in which there is marked disagreement in the melting points reported, the ones which the writer believes less reliable are followed by a question mark.

At least four different numbering systems have been used for indicating the positions in the dibenzofuran nucleus. Mayer and Krieger (19) used the system (VI). Oatfield (1) used the system recommended at that time by authorities on nomenclature (VII). The system used by the English, German and Japanese chemists and in Chemical Abstracts for volumes up to Vol. 31 is shown in (VIII). The numbering system followed in this laboratory (IX) is that of the International Rules for Numbering of Organic Ring Systems (20). The numberings of the compounds listed in Table I have all been changed, when necessary, to conform with this system (21).

(19) Mayer and Krieger, Ber., 55, 1659 (1922).
(20) Patterson, J. Am. Chem. Soc., 47, 543 (1925).
(21) This is the numbering system used at present in the annual indices of Chemical Abstracts.



VI.



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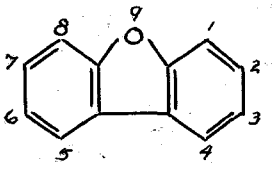
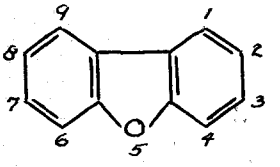


VIII.



IX.

TABLE I.

Dibenzofurans with Substituents in the 1-, 4-, 6-, and 9-Positions

Name of Compound	M. P.	Reference
MONOSUBSTITUTED DIBENZOFURANS		
1-Acetaminodibenzofuran	205	(10) (11)
4-Acetaminodibenzofuran	172.5	(22) (23)
	235-236 ?	(24)

(22) Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.
(23) Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1123 (1935).
(24) Yamashiro, J. Chem. Soc. Japan, 59, 945 (1938) /C. A., 33, 603 (1939)/.

TABLE I (continued)

Name of Compound	M. P.	Reference
4-Acetoxydibenzofuran	99-100	(25)
1-Aminodibenzofuran	74	(10) (11)
4-Aminodibenzofuran	84.5-85.5	(23) (26) (10) (12) (11)
	118-119 ?	(24)
4-β-Aminoethyldibenzofuran	b.p./2 mm. 165-166	(27) (22)
4-β-Aminoethyldibenzofuran hydrochloride	263	(27) (22)
Bi-(4-dibenzofuryl)	191	(15) (16)
1-Bromodibenzofuran	67	(28) (29) (10) (11)
4-Bromodibenzofuran	72	(30)
4-β-Bromoethyldibenzofuran	37-38	(23) (22)

(25) Unpublished work by Mr. T. H. Cook, this laboratory.
(26) Bywater, Doctoral Dissertation, Iowa State College, 1934.
(27) Kirkpatrick, Iowa State Coll. J. Sci., 75 (1936) /C. A., 31, 1800 (1937)/.
(28) P. R. Van Ess, ibid., 12, 164 (1937) /C. A., 32, 4981 (1938)/.
(29) Jacoby, Hayes and Van Ess, Proc. Iowa Acad. Sci., 43, 204-5 (1936) /C. A., 32, 4160 (1938)/.
(30) Unpublished work by Mr. G. E. Brown, this laboratory.

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Carbomethoxydibenzofuran	63	(29) (10) (11)
4-Carbomethoxydibenzofuran	93-94	(31) (32)
	95-96	(12)
4-β-Chloroethoxydibenzofuran	64-65	(23)
Diazomethyl 4-dibenzofuryl ketone	72-75	(13)
4-Dibenzofuranarsonic acid	186-188	(33)
1-Dibenzofurancarboxylic acid	232	(29)
	232-233	(10) (11)
4-Dibenzofurancarboxylic acid	209-210	(34) (35) (26)
4-Dibenzofurancarboxylic acid amide	181-182	(26) (23)
4-Dibenzofurancarboxylic acid chloride	118	(22) (23)
4-Dibenzofurancarboxylic acid dimethylamide	116.5	(36)

(31) Hayes, Thesis, Iowa State College, 1934.
(32) Gilman, Van Ess and Hayes, J. Am. Chem. Soc., 61, 643 (1939).
(33) Davies and Othen, J. Chem. Soc., 1236 (1936).
(34) Kruber, Ber., 65, 1382 (1932).
(35) Gilman, Willis and Swislowsky, J. Am. Chem. Soc., 61, 137 ~~0000~~ (1939).
(36) Unpublished work by Mr. H. B. Willis, this laboratory.

TABLE I (continued)

Name of Compound	M. P.	Reference
4-Dibenzofurylacetamide	211-212	(37) (13)
4-Dibenzofurylacetic acid	213.5-214.5	(37) (13)
4-Dibenzofurylmercuric acetate	199-200	(6)
4-Dibenzofurylmercuric chloride	235-238	(6)
4-Dibenzofuryl-triphenyllead	99-100	(5)
Di-4-dibenzofuryl ketone	172-173	(38) (32)
4-Diethylaminodibenzofuran	68-69	(12)
4-Diethylaminodibenzofuran hydrochloride	227-228	(12)
4-β-Diethylaminoethoxydibenzofuran	128.5-129.5	(23)
4-β-Diethylaminoethyldibenzofuran hydrochloride	184-185	(23)
1,4-Dihydro-6-hydroxydibenzofuran	116-117	(39) (40)
1,4-Dihydro-6-methoxydibenzofuran	54	(39) (40)

(37) Parker, Iowa State Coll. J. Sci., 12, 148 (1937) /C. A., 32, 2937 (1938)/.
(38) M. W. Van Ess, Doctoral Dissertation, Iowa State College, 1936.
(39) Bradley, Iowa State Coll. J. Sci., 12, 108 (1937) /C. A., 32, 2531 (1938)/.
(40) Bradley, Doctoral Dissertation, Iowa State College, 1937.

TABLE I (continued)

Name of Compound	M. P.	Reference
3,4-Dimethoxy-α-(4-dibenzofuryl-acetamino)-acetophenone	186-187	(37) (13)
3,4-Dimethoxy-α-(4-dibenzofuroyl-amino)-acetophenone	178-179	(37) (13)
4-Dimethylaminodibenzofuran	98-99	(13)
4-[γ-(Dimethylamino)-n-propyl]-dibenzofuran hydrochloride	168-169	(41)
4-[γ-(Dimethylamino)-n-propyl]-dibenzofuran picrate	148-149.5	(41)
1-Hydroxydibenzofuran	140.5	(29) (10) (11)
4-Hydroxydibenzofuran	101-102	(26) (32) (7) (15)
	125 ?	(42)
4-β-Hydroxyethyldibenzofuran	70-71	(23) (22)
4-Iododibenzofuran	71-72	(6)
4-(1-Isoquinolyl)-dibenzofuran	137-138	(37) (13)
4-Methoxydibenzofuran	52	(7)
4-Methyldibenzofuran	45	(34) (7)

(41) Mosettig and Robinson, J. Am. Chem. Soc., 57, 902 (1935).
(42) French patent 768,053 [C. A., 29, 475 (1935)].

TABLE I (continued)

Name of Compound	M. P.	Reference
4-Methyldibenzofuran picrate	94	(34)
1-Nitrodibenzofuran	121 91-93 ?	(12) (43)
4-Nitrodibenzofuran	138-139 ?	(24)
4-β-Piperidinoethoxydibenzofuran	210.5-212	(23)
1,2,3,4-Tetrahydrodibenzofuran-4-carboxylic acid	168	(44)
1,2,3,4-Tetrahydro-4-methoxydibenzofuran	39-39.5	(40)
1,2,3,4-Tetrahydro-6-aminodibenzofuran hydrochloride	228 (dec.)	(15)
1,2,3,4-Tetrahydrodibenzofuran-6-carboxylic acid	197	(44)
1,2,3,4-Tetrahydro-6-methoxydibenzofuran	39.5	(45)
Tri-4-dibenzofurylcarbinol	274-275	(12)
DISUBSTITUTED DIBENZOFURANS		
3-Acetamino-6-carbomethoxydibenzofuran	245-246	(38) (32)
1-Acetamino-4-methoxydibenzofuran	222-223	(37) (13)

(43) Yamashiro, J. Chem. Soc. Japan, 57, 714 (1936) /C. A., 30, 7575 (1936)/.
(44) Gilman, Smith and Cheney, J. Am. Chem. Soc., 57, 2095 (1935).
(45) Ebel, Helv. Chim. Acta, 12, 3 (1929).

TABLE I (continued)

Name of Compound	M. P.	Reference
3-Acetamino-4-methoxydibenzofuran	127	(25)
4-Acetamino-6-nitrodibenzofuran	251-252	(24)
2-Acetyl-6-carbomethoxydibenzofuran	174-175	(46)
2-Acetyl-6-dibenzofurancarboxylic acid	362-365	(46)
3-Acetyl-4-hydroxydibenzofuran	180-181.5	(25)
3-Acetyl-4-hydroxydibenzofuran oxime	234-236 (dec.)	(25)
1-Acetyl-2-methoxydibenzofuran	120-121	(12)
1-Acetyl-4-methoxydibenzofuran	134-134.5	(37) (13)
3-Acetyl-4-methoxydibenzofuran	70.5-72	(25)
1-Acetyl-4-methoxydibenzofuran oxime	176-177.5	(37) (13)
3-Acetyl-4-methoxydibenzofuran oxime	162.5-165	(25)
1-Allyl-2-hydroxydibenzofuran	82.5-83	(29) (28) (10) (11)
1-Allyl-2-methoxydibenzofuran	67-68	(29) (28) (10) (11)
1-Amino-4-acetaminodibenzofuran	202	(12)
3-Amino-4-acetaminodibenzofuran	236-237	(14)

(46) Unpublished work by J. C. Bailie.

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Amino-4-dibenzofuranarsonic acid	318 (dec.)	(47)
1-Amino-4-ethoxydibenzofuran	91	(14)
1-(α-Aminoethyl)-4-methoxydibenzofuran hydrochloride	267-269	(25)
3-(α-Aminoethyl)-4-methoxydibenzofuran hydrochloride	223	(25)
1-(α-Aminoethyl)-4-methoxydibenzofuran p-toluene-sulfonamide	172-173	(25)
4-Amino-6-hydroxydibenzofuran	191.5-192.5	(15)
1-Amino-4-methoxydibenzofuran	104	(14)
2-Amino-4-methoxydibenzofuran	127-127.5	(37) (13)
3-Amino-4-methoxydibenzofuran	75-76	(13) (14)
4-Amino-6-methoxydibenzofuran	109	(15)
4-Amino-6-methoxydibenzofuran hydrochloride	235-236	(15)
4-Amino-6-nitrodibenzofuran	183-184	(24)
1-Benzeneazo-2-hydroxydibenzofuran	165.5-166	(39) (48) (38)

(47) Hall and Hamilton, J. Am. Chem. Soc., 56, 1779 (1934).
(48) M. W. Van Ess, Iowa State Coll. J. Sci., 12, 167-9 (1937) /C. A., 32, 4980 (1938)/.

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Benzeneazo-4-hydroxydibenzofuran	174-175	(29) (48) (38)
1-Benzoyl-1,2,3,4-tetrahydropyrido-/2,3-c/dibenzofuran	158-159	(41)
Bi-(6-hydroxy-4-dibenzofuryl)	285-286	(15) (16)
Bi-(4-methoxy-1-dibenzofuroyl)	329	(15)
Bi-(6-methoxy-4-dibenzofuryl)	237-238	(15) (16)
2,4-Bis-(diethylaminoethylamino)-dibenzofuran	b.p./1 mm. 255	(49)
1-Bromo-4-acetaminodibenzofuran	228	(28) (10) (11)
1-Bromo-4-aminodibenzofuran	119-20	(28) (29) (10) (11)
2-Bromo-4-carbomethoxydibenzofuran	189-189.5	(16)
2-Bromo-6-carbomethoxydibenzofuran	166-167	(29) (31) (32)
	165-166	(38)
2-Bromo-4-dibenzofurancarboxylic acid	285-286	(16)

(49) German patent 550,327 /C. A., 26, 4062 (1932)/.

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Bromo-6-dibenzofurancarboxylic acid	363-364	(31) (32)
1-β-Bromoethyl-4-methoxydibenzofuran	91-91.5 ~~191-191.5~~	(13)
1-Bromo-2-hydroxydibenzofuran	123-123.5	(28) (29) (10) (11)
	121.5-122	(38)
1-Bromo-4-hydroxydibenzofuran	151.5-152	(28) (10) (11)
	150	(38)
4-Bromo-6-hydroxydibenzofuran	138-139	(15)
1-Bromo-2-methoxydibenzofuran	117-118	(28) (10) (11)
1-Bromo-4-methoxydibenzofuran	97-98	(13) (28) (10) (11)
2-Bromo-4-methyldibenzofuran	106-106.5	(38) (32) (16)
4-Bromo-6-methoxydibenzofuran	114	(15) (16)
1-Carbomethoxy-2-methoxydibenzofuran	99.5-100	(10) (11)
1-Carbomethoxy-7-(or 3-)-nitrodibenzofuran	216	(28) (29) (10)

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Chloroacetyl-4-methoxydibenzofuran	165-166	(15)
1-Chloro-8-hydroxydibenzofuran	---	(50)
1,4-Diacetaminodibenzofuran	307-308	(12)
2,6-Diacetaminodibenzofuran	265-266	(51)
3,4-Diacetaminodibenzofuran	257	(14)
4,6-Diacetaminodibenzofuran	297-298 323.5-323.5 ?	(15) (24)
3,4-Diacetoxydibenzofuran	104-105	(15)
4,6-Diacetoxydibenzofuran	177	(15)
2,6-Diaminodibenzofuran	138-140	(51)
4,6-Diaminodibenzofuran	152 151-152	(15) (24)
1,4-Diaminodibenzofuran dihydrochloride	322-323	(12)
4,6-Diaminodibenzofuran dihydrochloride	298	(15)
4,6-Diaminodibenzofuran picrate	213 (dec.)	(15)
Dibenzo[a,c]benzofuro[2,3-h]phenazine	277-278	(14)
4,6-Dibenzofurandicarboxylic acid	325	(7)
4,6-Dibenzofurandisulfinic acid	183-185	(7)

(50) British patent 470,021 [C. A., 32, 1487 (1938)].
(51) Yamashiro, J. Chem. Soc. Japan, 59, 186 (1938) [C. A., 32, 9084 (1938)].

TABLE I (continued)

Name of Compound	M. P.	Reference
4,6-Dibenzofurandisulfonic acid	300	(7)
4,6-Dicarbomethoxydibenzofuran	161-162	(7)
1-β-Diethylaminoethyl-4-methoxydibenzofuran hydrochloride	187 (dec.)	(37) (13)
1,4-Dihydroxydibenzofuran	217-218 (dec.)	(10) (11)
1,8-Dihydroxydibenzofuran	241-242	(52)
2,6-Dihydroxydibenzofuran	194-195	(52)
3,4-Dihydroxydibenzofuran	164-164.5	(15)
4,6-Dihydroxydibenzofuran	200-202 190	(15) (7)
4,6-Diiododibenzofuran	160	(7)
1,2-Dimethoxydibenzofuran	79	(10) (11)
1,4-Dimethoxydibenzofuran	78.5	(10) (11)
3,4-Dimethoxydibenzofuran	60-61	(15)
4,6-Dimethoxydibenzofuran	128-129	(15)
4,6-Dimethoxydibenzofuran picrate	161-162	(15)
Di-(4-methoxy-1-dibenzofuryl) ketone	234	(15)
1,9-Dimethyldibenzofuran	62 61-62	(53) (54)

(52) French patent 816,719 /C. A., 32, 2145 (1938)/.
(53) Sugii and Shindo, J. Pharm. Soc. Japan, 54, 829 (1934) /C. A., 29, 791 (1935)/.
(54) Mascarelli and Longo, Gazz. chim. ital., 68, 121 (1938) /C. A., 32, 6235 (1938)/.

TABLE I (continued)

Name of Compound	M. P.	Reference
4,6-Dimethyldibenzofuran	87 89	(7) (53)
4,6-Dinitrodibenzofuran	108.5-109.5	(24)
1,9-Diphenyldibenzofuran	154-155	(55)
1-Ethoxalyl-4-methoxydibenzofuran	113	(15)
2-Hydroxy-6-chlorodibenzofuran	167-169	(50) (52)
1-β-Hydroxyethyl-4-methoxydibenzofuran	96-96.5	(37) (13)
1-Hydroxy-2-methoxydibenzofuran	111-111.5	(10) (11)
1-Hydroxy-4-methoxydibenzofuran	155	(10) (11)
3-Hydroxy-4-methoxydibenzofuran	109-110	(15) (16)
4-Hydroxy-6-methoxydibenzofuran	111-112 109-110	(15) (16) (7)
1-Keto-1,2,3,4-tetrahydrobenzo[b]naphtho[1,2-d]furan	112-113	(56)
1-Keto-1,2,3,4-tetrahydrobenzo[b]naphtho[1,2-d]furan oxime	200-203	(56)

(55) Sako, Bull. Chem. Soc. Japan, 9, 55 (1934) [C. A., 28, 3730 (1934)]

(56) Robinson and Mosettig, J. Am. Chem. Soc., 61, 1148 (1939).

TABLE I (continued)

Name of Compound	M. P.	Reference
1-[α-(Methylamino)ethyl]-4-methoxydibenzofuran p-toluenesulfonamide	196-197	(25)
2-Methoxy-1-dibenzofurancarboxylic acid	156-157	(10) (57) (58) (11)
4-Methoxy-1-dibenzofurancarboxylic acid	279-280	(37) (13) (15)
4-Methoxy-1-dibenzofuryl-α-oxoacetic acid	187	(15)
4-Methoxy-1-dibenzofuryl-α-oxoacetic acid semicarbazone	211.5-212	(15)
6-Methyl-4-carbomethoxydibenzofuran	80-81	(7)
6-Methyl-4-dibenzofurancarboxylic acid	238-240	(7)
2-Methylpyrido[2,3-c]dibenzofuran	185-186	(22) (23)
1-Methyl-1,2,3,4-tetrahydropyrido[2,3-c]dibenzofuran	72-73	(41)
1-Methyl-1,2,3,4-tetrahydropyrido[2,3-c]dibenzofuran hydrochloride	227-229 208-209 (dec.)	(23) (22) (41)

(57) Bebb, Doctoral Dissertation, Iowa State College, 1938.
(58) Gilman and Bebb, J. Am. Chem. Soc., 61, 109 (1939).

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Propenyl-2-hydroxydibenzofuran	94-95	(10)
Pyrido/2,3-c/dibenzofuran	112	(23)
	105.5-106	(22)
	106-107	(41)
Pyrido/3,2-a/dibenzofuran	185-186 or 160.5-161.5	(22) (23)
Pyrido/2,3-c/dibenzofuran hydrochloride	292-294	(23)
	266-285	(41)
1-Nitro-4-acetaminodibenzofuran	216	(12)
3-Nitro-4-acetaminodibenzofuran	237-238	(12) (14)
1-Nitro-4-aminodibenzofuran	219-220	(12)
3-Nitro-4-aminodibenzofuran	185-186	(14)
2-Nitro-6-carbomethoxydibenzofuran	205.5	(29) (31) (32)
3-Nitro-6-carbomethoxydibenzofuran	158	(29)
	156-158	(31) (32)
7-(or 3-)-Nitro-1-carbomethoxydibenzofuran		(11)
2-Nitro-4-dibenzofuranarsonic acid	203-205	(47)
2-Nitro-6-dibenzofurancarboxylic acid	300-305 (dec.)	(31) (32)

TABLE I (continued)

Name of Compound	M. P.	Reference
3-Nitro-6-dibenzofurancarboxylic acid	160-165 (dec.) 260-265 ?	(31) (32)
7-(or 3-)-Nitro-1-dibenzofuran-carboxylic acid	297-298	(10) (11)
1-Nitro-4-ethoxydibenzofuran	135-135.5	(14)
3-Nitro-4-hydroxydibenzofuran	193	(14)
1-Nitro-4-methoxydibenzofuran	155 ---	(14) (29)
2-Nitro-4-methoxydibenzofuran	185-186	(37) (13)
3-Nitro-4-methoxydibenzofuran	129.5	(14)
Tetrahydropyrido[5,4-c]dibenzofuran	b.p./1-2 mm. 184	(27) (22)
1,2,3,4-Tetrahydropyrido[2,3-c] dibenzofuran	80-81	(41)
1,2,3,4-Tetrahydropyrido[2,3-c] dibenzofuran hydrochloride	247-248 225-235	(22) (23) (41)
Tetrahydropyrido[5,4-c]dibenzofuran hydrochloride	259	(27) (22)
TRISUBSTITUTED DIBENZOFURANS		
1-Acetamino-3,4-dimethoxydibenzo-furan	196-196.5	(15)

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Acetamino-4,6-dimethoxydibenzofuran	244-245	(15)
1-Acetamino-2-nitro-4-methoxydibenzofuran	244	(37) (13)
1-Acetyl-3,4-dimethoxydibenzofuran	90.5-91	(15)
1-Acetyl-4,6-dimethoxydibenzofuran	178-179	(15)
1-Acetyl-3,4-dimethoxydibenzofuran oxime	156-157	(15)
1-Acetyl-4,6-dimethoxydibenzofuran oxime	203-204	(15)
Acetylmorphenol	140	(59)
1-Amino-3,4-dimethoxydibenzofuran	162.5-163	(15)
1-Amino-4,6-dimethoxydibenzofuran	163-162.5	(15)
1-(α-Aminoethyl)-4,6-dimethoxydibenzofuran hydrochloride	255-257	(25)
1-(α-Aminoethyl)-4,6-dimethoxydibenzofuran p-toluenesulfonamide	177-178	(25)
1-Amino-2-nitro-4-methoxydibenzofuran	206-207	(37) (13)
1-Benzeneazo-4,6-dimethoxydibenzofuran	170	(15)
1-Benzeneazo-4-hydroxy-6-methoxydibenzofuran	175	(15)

(59) Small and Lutz, "The Chemistry of the Opium Alkaloids," Public Health Service Supplement No. 103, U. S. Government Printing Office, Washington, D. C., 1932, pp. 287-288.

TABLE I (continued)

Name of Compound	M. P.	Reference
Bi-(4,6-dimethoxy-1-dibenzofuroyl)	> 300	(15)
2-Bromo-3-acetamino-6-carbomethoxy-dibenzofuran	247-247.5	(38) (32)
1-Bromo-3-acetamino-4-methoxydi-benzofuran	178-179	(37) (13)
1-Bromo-3-amino-4-methoxydibenzo-furan	135-136	(37) (13)
1-Bromo-3,4-dimethoxydibenzofuran	108	(15)
1-Bromo-4,6-dimethoxydibenzofuran	152	(15)
1-Bromo-3-hydroxy-4-methoxydibenzo-furan	161-162	(15)
2-Bromo-3-nitro-6-carbomethoxy-dibenzofuran	205-206	(48) (38) (32)
2-Bromo-3-nitro-6-dibenzofuran-carboxylic acid	331-334	(38) (32)
1-Bromo-3-nitro-4-methoxydibenzo-furan	160-161	(37) (13)
Diazomethyl 4,6-dimethoxy-1-dibenzo-furyl ketone	151	(15)
Di-(4,6-dimethoxy-1-dibenzofuryl) ketone	254-255	(15)
1,x-Dinitro-4-acetaminodibenzofuran	288	(12)

TABLE I (continued)

Name of Compound	M. P.	Reference
3,x-Dinitro-4-acetaminodibenzofuran	277-278	(12)
x,x-Dinitro-4-carbomethoxydibenzofuran	230-231	(32)
3,8-Dinitro-4-hydroxydibenzofuran	225 (dec.)	(14)
3,8-Dinitro-4-methoxydibenzofuran	177	(14)
4,6-Dimethoxy-1-carbomethoxydibenzofuran	163	(15)
4,6-Dimethoxydibenzofuran-1-aldehyde	162-164	(25)
4,6-Dimethoxy-1-dibenzofurancarboxylic acid	297-298	(15)
4,6-Dimethoxy-1-dibenzofurylacetamide	210-211	(15)
4,6-Dimethoxy-1-dibenzofurylacetic acid	205.5-206.5	(15)
1-[α-(Methylamino)-ethyl]-4,6-dimethoxydibenzofuran p-toluenesulfonamide	189-190.5	(25)
2-Methyl-5-methoxydibenzofuro[1,2-d]imidazole	222-222.5	(13)
Methylmorphenol	65	(59)
Morphenol	145	(18) (59)
2,4,6-Trinitrodibenzofuran	260-261	(24)
TETRASUBSTITUTED DIBENZOFURANS		
1,9-Dibromo-2,8-diacetoxydibenzofuran	173-174	(12)

TABLE I (continued)

Name of Compound	M. P.	Reference
2,8-Dibromo-4,6-dibenzofurandicarboxylic acid	>350	(60)
2,8-Dibromo-4,6-dicarbomethoxydibenzofuran	273	(60)
1,9-Dibromo-2,8-dihydroxydibenzofuran	200-201	(12)
1,9-Dibromo-4,6-dihydroxydibenzofuran	239-240 (dec.)	(15)
1,3-Dibromo-4,6-dimethoxydibenzofuran	173.5-174	(15)
1,9-Dibromo-2,8-dimethoxydibenzofuran	196-197	(12)
1,9-Dibromo-4,6-dimethoxydibenzofuran	167-168	(15)
1,3-Dibromo-4-hydroxy-6-methoxydibenzofuran	177-178	(15)
1,9-Dicarbomethoxy-2,8-dimethoxydibenzofuran	129-130	(12)
2,8-Dimethoxy-1,9-dibenzofurandicarboxylic acid	271-272	(12)
1,9-Dimethyl-2,8-dihydroxydibenzofuran	168-169	(12)
1,9-Dimethyl-2,8-dimethoxydibenzofuran	106-107	(12)
Dinitro-2-bromo-6-carbomethoxydibenzofuran	259.5-260.5	(38) (32)
3,4,6,7-Tetraacetoxydibenzofuran	247-251	(61)

(60) Unpublished studies by R. E. Dickey.
(61) Nierenstein, Ann., 386, 318 (1912).

TABLE I (continued)

Name of Compound	M. P.	Reference
3,4,6,7-Tetrahydroxydibenzofuran	334-338	(61)
2,4,6,8-Tetramethyldibenzofuran	90-90.5	(62)
2,4,6,8-Tetranitrodibenzofuran	239-240	(63) (64)
	262-263	(24)
	252.5	(65)
7,8,12-Trimethoxybenzo[a]benzofuro[3,2-c]phenazine	261.5	(66)
x,x,x-Trinitro-4-carbomethoxydibenzofuran	208-210	(32) (31)
PENTASUBSTITUTED DIBENZOFURANS		
3,7-Dimethoxy-8-acetoxydibenzofuro-1,4-quinone	252-254	(67)
3,7-Dimethoxy-8-hydroxydibenzofuro-1,4-quinone	250	(67)
2-Hydroxy-3,7-dimethoxydibenzofuro-1,4-quinone	242-245	(68)
1,4,8-Triacetoxy-3,7-dimethoxydibenzofuran	232	(67)
1,3,9-Tribenzeneazo-4,6-dihydroxydibenzofuran	228 (dec.)	(15)

(62) Bamberger and Brun, Ber., 40, 1949 (1907).
(63) Van Alphen, Rec. trav. chim., 51, 179 (1932).
(64) Van Alphen, ibid., 51, 715 (1932).
(65) Borsche and Scholten, Ber., 50, 596 (1917).
(66) Pfeiffer and Böttcher, J. prakt. Chem., 148, 126 (1937).
(67) Erdtman, Proc. Roy. Soc. (London), A143, 177 [C. A., 28, 1338 (1934)].
(68) Erdtman, Svensk. Kem. Tids., 44, 135 (1932) [C. A., 26, 4804 (1932)].

TABLE I (continued)

Name of Compound	M. P.	Reference
1,3,9-Tribenzeneazo-4,6-dimethoxydibenzofuran	191-193	(15)
1,4,8-Trihydroxy-3,7-dimethoxydibenzofuran	210 (dec.)	(67)
1,4,8-Tri-p-nitrobenzoyloxy-3,7-dimethoxydibenzofuran	300	(67)
HEXASUBSTITUTED DIBENZOFURANS		
3,4,6,7-Tetraacetoxydibenzofuran-1,9-dicarboxylic acid	324-327	(61)
1,4,8,9-Tetraacetoxy-3,7-dimethoxydibenzofuran	255-266	(69)
3,4,6,7-Tetrabenzoyloxydibenzofuran-1,9-dicarboxylic acid	279-281 (dec.)	(61)
3,4,6,7-Tetrahydroxydibenzofuran-1,9-dicarboxylic acid	---	(61)
3,4,6,7-Tetramethoxydibenzofuran-1,9-dicarboxylic acid	242-244 (dec.)	(61)

Dibenzofuran was first prepared in 1866 by Lesimple (70) who obtained it from heating phenyl phosphate with lime. Its structure was elucidated by Hoffmeister and others (71). Dibenzofuran and its homologs make up about

(69) Erdtman, Ann., 513, 240 (1934).
(70) Lesimple, Ann., 138, 376 (1866).
(71) Hoffmeister, Ber., 3, 747 (1870); Tauber and Halberstadt, ibid., 25, 2745 (1892); Kraemer and Weissgerber, ibid., 34, 1662 (1901).

35 per cent of the coal tar fraction boiling between 270° and 330° (34), and this is one commercial source of the product (72). Another commercial preparation consists of passing phenol vapors over thorium oxide in a heated tube. Lead oxide may be used in this preparation, but lower yields are obtained (73). The remarkable stability of dibenzofuran, together with the ease with which it undergoes substitution reactions and its low cost (about fifty cents a pound), have given impetus to the investigation of it and some of its derivatives for a variety of uses. Among these are: as lubricants for engine cylinders at high temperatures (74), as dye intermediates (75), as bacteriocides (76), and as trypanocides (77).

The early work on the preparation of dibenzofurans by ring closures and by substitution reactions has been discussed elsewhere (1) (22) (26) (31). Oatfield (1) has given a complete chronological bibliography of the published work on dibenzofuran up to 1933. The bibliography at the end of this thesis supplements this and includes all of the work appearing in Chemical Abstracts, from January, 1933, to June, 1939.

(72) German patent 491,594 /C. A., 24, 2475 (1930)/.
(73) Cullinane, Davey and Padfield, J. Chem. Soc., 716 (1934).
(74) U. S. patent 1,867,968 /C. A., 26, 5201 (1932)/.
(75) German patent 591,213 /C. A., 29, 5671 (1935)/.
(76) Phatak and Leake, J. Pharmacol., 58, 155 (1936) /C. A., 31, 1068 (1937)/.
(77) Skiles and Hamilton, J. Am. Chem. Soc., 59, 1006 (1937).

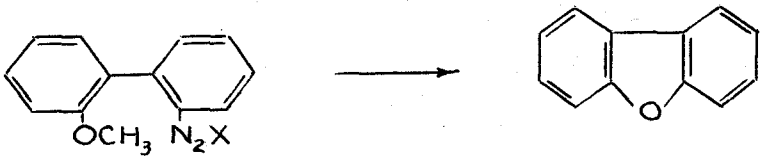
Methods of Preparing 1-, 4-, 6-, and 9-Derivatives

The preparation of the so-called critically substituted dibenzofurans has been effected both by means of ring closure reactions and by means of substitution reactions. The ring closure reactions are important for structural proofs but are generally less useful than the substitution reactions for synthesis because of the labor involved in preparing the substances to be used in the ring closures, and the poor yields usually obtained in the ring closure reactions. The ring closure reactions will be discussed from the point of view of the starting materials for the ring closure, i.e., the biphenyl type, the phenyl ether type, and the substituted-benzenes type. The substitution reactions will be treated under the headings: monosubstitution, homonuclear substitution, and heteronuclear substitution.

By ring closures

Ring closures of the biphenyl type. Biphenyls substituted in the 2,2'-positions by two hydroxyl groups, an amino and a hydroxyl, two amino groups, a chloro and a hydroxyl, or by two acetoxy groups have been converted into dibenzofurans. Thus 2,2'-dihydroxybiphenyl gives a 90 per cent yield of dibenzofuran on heating for fifty

hours at the boiling point. When phosphorus pentoxide is used the yield is increased to 95 per cent (78). In this manner, by heating the appropriately substituted dihydroxybiphenyls with zinc chloride or constant boiling hydrobromic acid in sealed tubes at 275°, Sugii and Shindo (53) prepared 4,6-dimethyldibenzofuran and 1,9-dimethyldibenzofuran. In an attempt to prepare 2-hydroxy-2'-iodobiphenyl from 2-hydroxy-2'-aminobiphenyl, the only product isolated was dibenzofuran (79). So strong is the tendency to go over into the stable aromatic ether type that often groups which are considered strongly bound are eliminated. Thus 2-methoxy-2'-diazobiphenyl gives a 90 per cent yield of dibenzofuran when boiled in water solution (79):



Tetrazotization of 2,2'-diamino-6,6'-dimethylbiphenyl (10 g.) followed by heating the tetrazonium salt on a water bath for two hours gave a small yield (0.12 g.) of 1,9-dimethyldibenzofuran (54). Sako (55) obtained 1,9-diphenyl-

(78) Cullinane and Davies, Rec. trav. chim., 55, 881 (1936).
(79) Mascarelli and Pirona, Gazz. chim. ital., 68, 117 (1938) /C. A., 32, 6235 (1938)/.

dibenzofuran, together with 4,5,9,10-dibenzopyrene and 2,2'-dihydroxy-6,6'-diphenylbiphenyl upon heating the tetrazonium sulfate of 2,2'-diamino-6,6'-diphenylbiphenyl. It should be noted that when the product formed is a substituted dibenzofuran and not dibenzofuran itself, the yield is often very much smaller.

A number of closures have been reported in the patent literature involving the treatment of substituted 2-chloro-2'-hydroxybiphenyls with alkali or alkali carbonates (50) (52) (80).

In this manner 2,6-dihydroxy-, 2,9-dihydroxy-, and 2-hydroxy-6-chlorodibenzofurans have been synthesized. No details as to the availability of the starting materials or yields have been given.

Some 2,2'-diacetoxybiphenyls are smoothly converted into dibenzofurans when heated either alone (63) (64), or with alkali carbonates or metallic oxides such as BaO, PbO

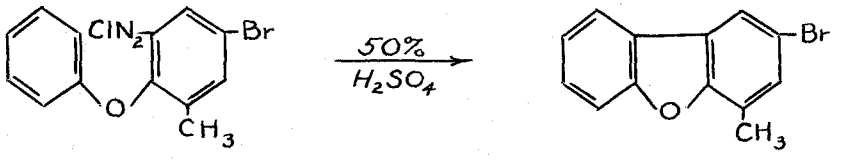
(80) British patent 472,170 /C. A., 32, 1380 (1938)/.

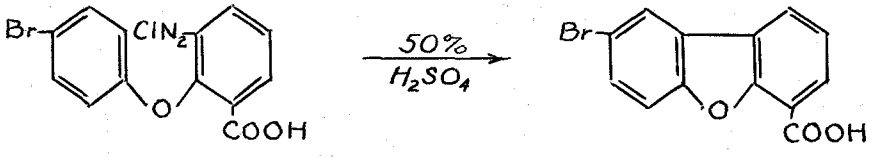
or ZnO (81) (24). Van Alphen reported a quantitative yield of 2,4,6,8-tetranitrodibenzofuran from heating 2,2'-diacetoxy-3,3',5,5'-tetranitrobiphenyl at 200-210° (63) (64). The reaction is by no means general, however, for the correspondingly substituted tetrabromo compound was unaffected by these conditions, and decomposed when heated more strongly, evolving HBr. Likewise the 5,5'-dinitro 2,2'-diacetoxybiphenyl could not be made to undergo ring closure by this method (64). The ring closure to form 2,4,6,8-tetranitrodibenzofuran was effected earlier by Borsche and Scholten (65) who heated the dihydroxy compound in the presence of p-toluenesulfonyl chloride or dimethylaniline. Yamashiro (81) (24) has reported closures with such compounds as 5,5'-dinitro-2-acetoxy-2'-methoxybiphenyl and 3,3'-dinitro-2,2'-diacetoxybiphenyl. The 4-amino-, 4-acetamino-, and 4,6-diacetaminodibenzofurans obtained from the corresponding nitro compounds have melting points so different from those of the authentic specimens prepared in this laboratory that there is considerable doubt concerning the structure of Yamashiro's compounds. It may be that he had the 4,4'-dinitro-2,2'-diacetoxybiphenyl as a starting material since the melting points of both his 4,6-diamino and 4,6-diacetamino

(81) Yamashiro, J. Chem. Soc. Japan, 59, 443 (1938) /C. A., 32, 9085 (1938)/.

compounds check within a degree the melting points of the 3,7-diamino- and 3,7-diacetaminodibenzofurans. The melting points reported by him for the 4-amino- and the 4-acetaminodibenzofurans do not coincide with those of any of the monoamino- and acetaminodibenzofurans, all of which are known.

Ring closures of the phenyl ether type. Only two successful ring closures of this type to yield critically substituted dibenzofurans have been reported. M. W. Van Ess (38) (32) prepared 2-bromo-4-methyldibenzofuran from 2-methyl-4-bromo-6-aminophenyl ether and 8-bromo-4-dibenzofurancarboxylic acid from 3-carboxy-6-amino-4'-bromophenyl ether, by diazotization of the amino groups and decomposition of the diazonium salts with 50 per cent sulfuric acid.

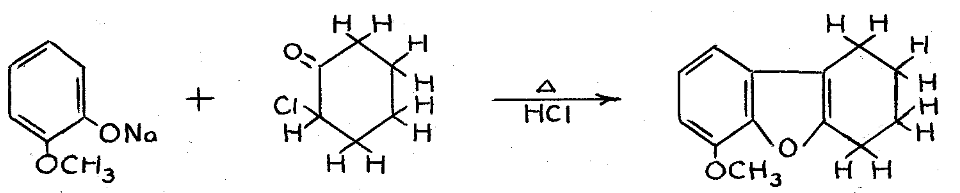




The observation has been made (38) (32) that in order for success to attend this method of ring closure, the amino

group, through which the ring is ultimately closed by diazotization and decomposition of the diazonium salt, must be in the same benzene nucleus as the group which is to be the 4-substituent in the final product. Two attempts in which these conditions were not met ended in failure: 2-chloro-6-aminophenyl ether could not be converted to 4-chlorodibenzofuran by this method (82), and an attempt to prepare 1,4-dimethoxydibenzofuran from 2,5-dimethoxy-6'-aminophenyl ether was likewise unsuccessful (10).

Direct closures from benzene derivatives. Ebel (45) has prepared 1,2,3,4-tetrahydro-6-methoxydibenzofuran by a novel synthesis: 2-chlorocyclohexanone and sodium guiacolate condense in the following manner upon being heated in the presence of hydrogen chloride.



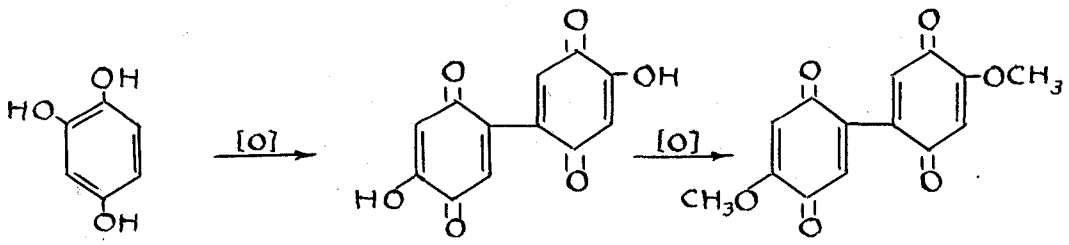
These tetrahydro compounds can be smoothly and quantitatively dehydrogenated by means of bromine to give the unreduced dibenzofuran derivatives (83).

(82) McCombie, MacMillan and Scarborough, J. Chem. Soc., 531 (1931).
(83) Smith, Doctoral Dissertation, Iowa State College, 1936.

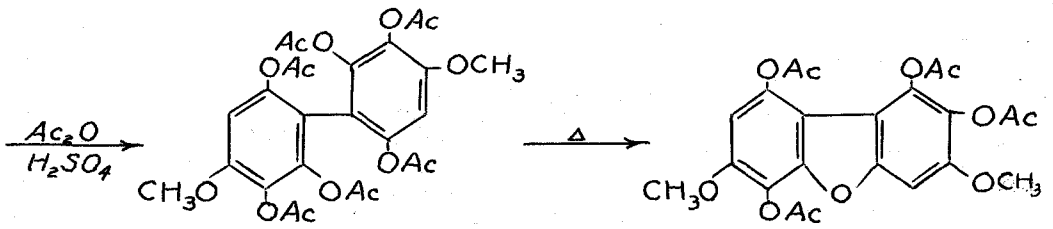
Hall and Hamilton (47) have obtained 2-nitro-4-dibenzofuranarsonic acid from 2-chloro-5-nitrophenylarsonic acid and o-chlorophenol.

Tsuzuki (84) reported that 1-hydroxy- and 1,9-dihydroxydibenzofuran are formed when resorcinol is passed over heated tungstic oxide. It was later shown (5) (85) that the monohydroxy compound is really 3-hydroxydibenzofuran, and the dihydroxydibenzofuran may, accordingly, be the 3,7- rather than the 1,9-isomer.*

Some very interesting syntheses of dibenzofuran derivatives have been discovered in the course of oxidation studies with polyhydroxybenzene derivatives. Erdtman has obtained some hydroxy derivatives of dibenzofuran-1,4-quinone (67) (68) in this way. A derivative of a hexahydroxydibenzofuran has been prepared by the following sequence of reactions (57):



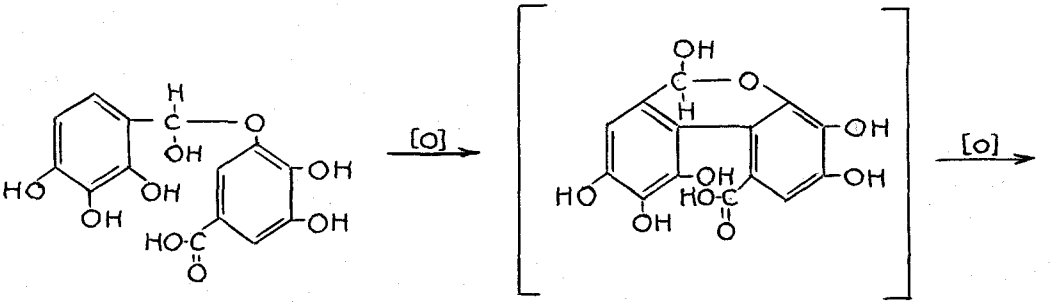
(84) Tsuzuki, Bull. Chem. Soc. Japan, 2, 79 (1927).
(85) Tatematsu and Kubota, Ibid., 9, 448 (1934).
* This has just been conclusively shown by the preparation of 1,9-dihydroxydibenzofuran (m.p., 215°) by another method. See, Simada and Hata, Sci. Papers Inst. Phys. Chem. Research (Tokyo), 35, 365 (1939) /C. A., 33, 4594 (1939)/.



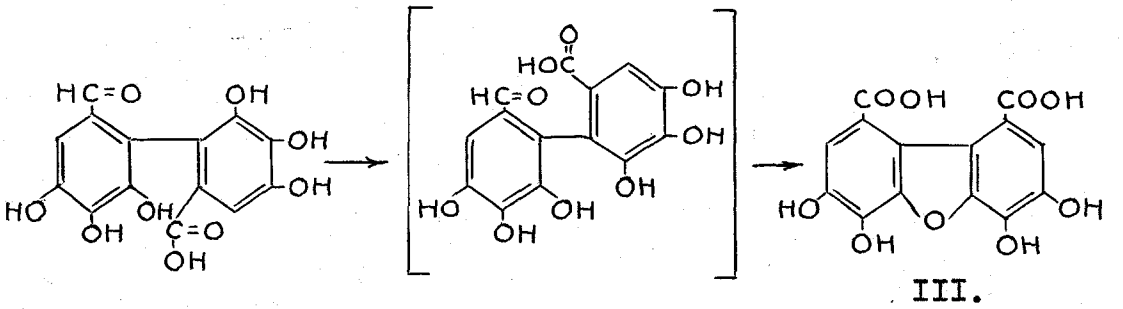
I.

The compound designated as [I] was converted to the corresponding octamethoxybiphenyl which was shown to be identical with the compound synthesized by the Ullmann reaction. The final step, which brings about the ring closure, is reminiscent of the closures of acetoxybiphenyls discussed earlier (p. 40). Bamberger and Brun (62) obtained 2,4,6,8-tetramethyldibenzofuran from the reaction of alcoholic sulfuric acid on 2,4-dimethylhydroquinone, followed by heating to effect the ring closures of the dihydroxybiphenyl formed.

Nierenstein (61), in the course of the investigation of tannin-like substances, prepared several very interesting dibenzofuran derivatives. Leucodigallic acid [II] upon oxidation gave the substance which he called "purpurotannin" [III], a derivative of 4,6-dihydroxydibenzofuran-1,9-dicarboxylic acid. The mechanism is postulated as follows:



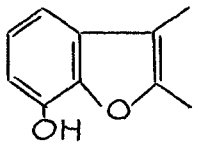
II.



III.

The acid [III] was smoothly decarboxylated by heating in a sealed tube with piperidine. Upon zinc dust distillation it yielded biphenylene, and treatment with hydriodic acid (d., 1.9) and phosphorus at 180° converted it to dibenzofuran. Thus the structure of [III] rests upon analyses and these rather drastic degradation reactions, and is uncertain to the extent that these reactions are uncertain. In connection with this a point which is not borne out by further work in this laboratory concerns the colors of some of these substances. Nierenstein's 3,4,6,7-tetrahydroxydibenzofuran is red, whereas the 2,3,7,8-tetrahydroxydibenzo-

furan prepared earlier by Schuler (86) is colorless. The 3,4,6,7-tetramethoxydibenzofuran of Nierenstein is yellow. Nierenstein was of the opinion that the color was connected with the peri-position of the hydroxyl to the ring oxygen. The 4-hydroxy- and the 4,6-dihydroxydibenzofurans



prepared in this laboratory (6) (7) are colorless, however. The yield of purpurotannin [III] from 25 g. of acetylleucodigallic acid was 8.42 g.

By nuclear substitution

Monosubstitution. Up to the present time direct substitution in the 1-position of dibenzofuran has not been accomplished. Direct substitution in the 4-position has been effected only through metalation (6). In fact, with a single exception, this is the only method by means of which the 4-position has been substituted. In the preparation of pyridodibenzofurans by the Skraup synthesis with 3-aminodibenzofuran, one of the isomers formed involves a ring closure in the 4-position (22) (23) (41). An Emde

(86) Schuler, Arch. Pharm., 245, 262 (1907).

degradation on this pyridodibenzofuran gave the 4-[δ-dimethylamino-n-propyl]-dibenzofuran hydrochloride (41). Yamashiro (43) has reported the isolation of 1-nitrodibenzofuran as an isomer formed in the preparation of 3-nitrodibenzofuran, but the melting point does not agree with that of the compound prepared in this laboratory by indirect methods (cf. Table I). Likewise Cullinane (87) has suggested that the 110° melting isomer isolated from this nitration is 4-nitrodibenzofuran. This supposed compound has been shown to be a mixture in which one of the components is 2-nitrodibenzofuran (5).

When dibenzofuran is heated with mercuric acetate or refluxed with a solution of it in glacial acetic acid, 4-acetoxymercuridibenzofuran is formed. The acetoxymercuri compound may then be converted to 4-iododibenzofuran by treatment with a solution of iodine in methanol. Other 4-dibenzofuryl-metal compounds are formed by refluxing dibenzofuran in ether with n-butyllithium, phenyllithium, n-butylsodium (6) or benzylsodium (9). The lithium compounds have been used most frequently for the introduction of other substituents into the 4-position. Thus, carbonation gives the corresponding acid together with some ketone; oxidation, the corresponding phenol together with

(87) Cullinane, J. Chem. Soc., 2267 (1930).

some coupling product; treatment with bromine vapor, the corresponding bromo compound; treatment with methyl sulfate, the corresponding methyl compound; and treatment with ethylene oxide, the corresponding β-hydroxyethyl compound (88). Still other substituents are introduced into the 4-position through the intermediary of these compounds. Thus the 4-amine has been prepared from the 4-acid by a Hofmann reaction on the amide, and by amination of the 4-bromo compound; and 4-dibenzofurylacetamide has been prepared from the 4-acid through the acid chloride and the diazomethyl ketone.

Metalation of 1,4-dihydrodibenzofuran yields 1,2-dihydro-2-dibenzofurancarboxylic acid, but in the mechanism postulated (89) 1,4-dihydro-4-dibenzofuryllithium is assumed to be the intermediate. When 4-methoxydibenzofuran is reduced catalytically, 1,2,3,4-tetrahydro-4-methoxydibenzofuran is produced (40). Reduction of 4-aminodibenzofuran, with sodium and alcohol, takes place in the unsubstituted nucleus and 1,2,3,4-tetrahydro-6-aminodibenzofuran is formed (15). Metalation of 1,2,3,4-tetrahydrodibenzofuran also utilizes the unsubstituted nucleus and upon carbonation 1,2,3,4-tetrahydro-6-dibenzofurancarboxylic acid is obtained (44).

(88) References to the preparations of these compounds may be obtained from Table I.
(89) Gilman and Bradley, J. Am. Chem. Soc., 60, 2333 (1938).

Homonuclear substitution. Groupings which are strong ortho and para directors in benzene direct substituents homonuclearly in dibenzofuran. Bromination of 2-hydroxy-, 3,4-dihydroxy-, 4-methoxy- and 4-acetaminodibenzofurans gives rise to the corresponding 1-bromo compounds. Likewise, bromination of 4,6-dihydroxy- and 4,6-dimethoxydibenzofurans leads to 1-bromo, and dibromination, to 1,9-dibromo compounds. That the hydroxyl group has a stronger directive influence than the methoxyl group is shown by the dibromination of 4-hydroxy-6-methoxydibenzofuran, in which the 1,3- and not the 1,9-dibromo derivative is formed. Bromination of 2-methoxydibenzofuran yields chiefly the 3-isomer and only a trace of 1-bromo-2-methoxydibenzofuran. Bromination of 1-hydroxydibenzofuran gives isomers which have not been identified (10).

In some instances nitration proceeds in a manner different from bromination. By proper choice of conditions either the 1-nitro- or the 3-nitro-4-acetaminodibenzofuran may be obtained from the nitration of 4-acetaminodibenzofuran. Nitration of 4-methoxydibenzofuran forms the 1-nitro isomer, but 4-hydroxydibenzofuran directs the nitro group to the 3-position. The strong directive influence of the acetamino group is brought out by some of these nitration experiments. With 1-acetamino-4-methoxydibenzofuran some of the 1-acetamino-2-nitro-4-methoxy derivative is formed;

however, with 1-bromo-4-methoxydibenzofuran, the sole product is the 1-bromo-3-nitro-4-methoxy compound.

Bromine is a rather weak ortho-para director and its presence alone in dibenzofuran usually gives rise to heteronuclear substitution. A notable exception, however, is metalation. When 2-bromodibenzofuran is refluxed in ether solution with n-butyllithium and the reaction mixture is then carbonated, 2-bromo-4-dibenzofurancarboxylic acid results. Under these same conditions the bromine in 2,8-dibromodibenzofuran is replaced by lithium and 2,8-dibenzofurandicarboxylic acid is obtained upon carbonation (35). With phenylcalcium iodide and 2,8-dibromodibenzofuran, metalation occurs instead of replacement, and the final product is 2,8-dibromo-4,6-dibenzofurandicarboxylic acid (60). The bromine in 4-bromodibenzofuran suffers replacement with n-butyllithium, but with methylmagnesium iodide neither metalation nor replacement occurs (35). Metalation of 2-methoxydibenzofuran yields chiefly 2-methoxy-1-dibenzofurancarboxylic acid upon carbonation, but some of the 3-acid is also formed.

Other homonuclear reactions of dibenzofuran derivatives are the coupling reactions with benzenediazonium salts and the Friedel-Crafts reactions. With 2-hydroxy-, 4-hydroxy-, and 4-hydroxy-6-methoxydibenzofurans excellent yields of the 1-benzeneazo compounds are obtained, and

these may be reduced to the 1-amines. Friedel-Crafts reactions have not been attempted with 3-methoxydibenzofuran, but with the 4-methoxy and 4,6-dimethoxy derivatives, acetyl and chloroacetyl groups have been introduced into the 1-position. Attempts to bridge the 1,9-positions by Friedel-Crafts reactions with oxalyl chloride on these methoxy compounds did not succeed (15). Attempts to prepare a phenanthrylene oxide type by a Friedel-Crafts reaction with 4,6-dimethoxy-1-dibenzofurylacetic acid chloride were likewise unsuccessful (15) (25).

Metalation of 4-methoxydibenzofuran occurs both homonuclearly and heteronuclearly. Upon oxidation of the reaction mixture, approximately equal amounts of 3-hydroxy-4-methoxy- and 6-hydroxy-4-methoxydibenzofurans are obtained.

Heteronuclear substitution. There are only a few examples of heteronuclear substitution in which one of the substituents in the final product occupies a 1-, 4-, 6-, or 9-position. The metalation of 4-methoxydibenzofuran mentioned just previously, and the metalation of 4-methyldibenzofuran, give 6-metal derivatives. Dimetalation of dibenzofuran, is achieved by means of organosodium and organopotassium compounds. If the 4,6-dibenzofurylenedisodium is carbonated, an excellent yield (77 per cent) of 4,6-dibenzofurandicarboxylic acid is obtained, but oxidation gives a very poor

yield (3 per cent) of the 4,6-dihydroxy compound (7). Metalation of 1,2,3,4-tetrahydrodibenzofuran involves the 6-position, but this can hardly be classed as a hetero-substitution since the reduced nucleus is unsubstituted.

Bromination of 4-carbomethoxydibenzofuran introduces a bromine into the 8-position, and nitration yields a 7-nitro and an 8-nitro derivative (32). Acetylation of 4-carbomethoxydibenzofuran gives a compound in which the acetyl group has been shown to be in either the 2- or 8-position (46). On the basis of the other substitution reactions of this ester, one might safely conclude that the acetyl group is in the 8-position. The structure of the compound resulting from the nitration of 1-carbo-methoxydibenzofuran has also not been definitely deter-mined. Hydrolysis and decarboxylation have shown that the nitro group is in either the 3- or the 7-position.

E X P E R I M E N T A L P A R T

Preparation of 4-Aminodibenzofuran

Bywater (32) first prepared 4-aminodibenzofuran from 4-dibenzofurancarboxylic acid amide (27.3% yield) and from 4-hydroxydibenzofuran (16.6% yield). The writer has found that the yield in the former reaction is markedly improved by the addition of ethanol. In the latter reaction ammonium bisulfite gives superior yields to zinc ammonium chloride. These modifications are described below.

A. By the Hofmann amide reaction. Twenty grams (0.0836 .095 mole) of 4-dibenzofurancarboxylic acid amide, suspended in 50 ml. of 95% ethanol and 100 ml. of 10% sodium carbonate solution was added gradually to an ice-cooled hypobromite solution prepared from 28.8 g. (0.18 mole) of bromine and 54 g. (1.35 mole) of sodium hydroxide in 300 ml. of water. After there was no further evidence of reaction, the mixture was warmed on a steam bath for three and one-half hours with occasional shaking, then cooled, the excess alkali partially neutralized with hydrochloric acid, and the brown product filtered with suction.

Acidification of the filtrate yielded one-half gram of crude 4-dibenzofurancarboxylic acid. The brown residue on the filter was extracted twice with 250-ml. portions of ether, and the combined ether extracts were dried over anhydrous sodium sulfate. The amine hydrochloride was precipitated from the dried ether solution by passing in dry hydrogen chloride. Then the hydrochloride was decolorized by refluxing for twenty minutes in 300 ml. of water, to which 10 ml. of concd. hydrochloric acid and 2 ml. of Norite had been added. Finally the free amine was precipitated from the above filtered solution by the addition of a mixture of equal volumes of concd. ammonium hydroxide and ethanol. The yield of pure amine was 9.5 g. or 55%. From the ether insoluble residue there was recovered 4 g. of the amide; accordingly, the yield was 68% if based on the amide actually used in the reaction.

B. By the Bucherer reaction with 4-hydroxydibenzofuran. This is an adaptation of the method used by Cheney (15) for the preparation of 4,6-diaminodibenzofuran. A mixture of 2 g. (0.0109 mole) of 4-hydroxydibenzofuran, 15 ml. of concd. ammonium hydroxide, and 7.5 g. of sodium metabisulfite dissolved in 15 ml. of water was heated for twenty hours at 185-195° in a sealed tube. When the tube was opened the product had settled to the bottom as a light

brown oily ball which solidified on shaking. This solid was separated by filtration, and extraction with 5% potassium hydroxide solution yielded 0.2 g. of 4-hydroxydibenzofuran on acidification (10% recovery). The alkali insoluble portion was extracted twice by refluxing with 50-ml. portions of 5% hydrochloric acid, and 0.9 g. (45% yield) of pure 4-aminodibenzofuran, m.p. 85-86°, separated when the combined extracts were made alkaline with ammonium hydroxide. Since 4-hydroxydibenzofuran is easily prepared in good yields, this method may perhaps be the one of choice for the preparation of pure 4-aminodibenzofuran.

Nitration of 4-Acetaminodibenzofuran

The 4-acetaminodibenzofuran used in these experiments was prepared according to the directions of Kirkpatrick and Parker (61).

A. In acetic anhydride at -10°. This compound has been described earlier (14) but since its preparation depends upon rigid adherence to an empirical procedure the directions are repeated here in somewhat greater detail. Two grams (0.0089 mole) of 4-acetaminodibenzofuran suspended in 10 ml. of acetic anhydride was cooled to -10°. Then 1 ml. (0.0238 mole) of fuming nitric acid (sp.g. 1.49) was added slowly, the temperature not being allowed to rise above -5°. Stirring was continued for thirty minutes after

the addition of the nitric acid, during which time the product had begun to separate in short blunt needles. The mixture was poured on cracked ice, filtered, and crystallized from glacial acetic acid. The pale yellow needles, which melted at 230° weighed 850 mg. (35% theory). Two recrystallizations from glacial acetic acid and one from ethanol raised the melting point to 238°. This compound was established as 3-nitro-4-acetaminodibenzofuran by conversion, through several steps, to a phenazine derivative (14).

B. In glacial acetic acid at 70°. One gram (0.0044 mole) of 4-acetaminodibenzofuran was dissolved in 15 ml. of glacial acetic acid and warmed to 70°. Two milliliters (0.0476 mole) of fuming nitric acid (sp.g. 1.49) was added dropwise with stirring, during a period of two minutes. The temperature rose to 85° momentarily, and then gradually became lower. The solution was maintained at a temperature of 65-75° for twenty minutes, and then approximately 25 ml. of water was added slowly, with stirring. The crystals which separated were recrystallized once from glacial acetic acid and once from 95% ethanol. The yield of light yellow needles melting at 216° was 0.7 g. (59% theory).

Anal. Calcd. for $C_{14}H_{10}O_4N_2$: N, 10.35. Found: N, 10.31.

This compound was shown to be 1-nitro-4-acetaminodibenzofuran by converting it, through reduction and acetylation to 1,4-diacetaminodibenzofuran, which, in turn, was prepared by amination and subsequent acetylation of authentic 1-bromo-4-acetaminodibenzofuran.

Hydrolysis of 1-Nitro-4-acetaminodibenzofuran

One-half gram of 1-nitro-4-acetaminodibenzofuran was refluxed for three hours with a mixture of 15 ml. of conod. hydrochloric acid and 15 ml. of 95% ethanol. The solution was cooled and the nitro-amine hydrochloride separated by filtration. The free 1-nitro-4-aminodibenzofuran, which was liberated by addition of ammonium hydroxide, melted at 219-220° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_8O_3N_2$: N, 12.28. Found: N, 12.23 and 12.39.

Preparation of 1-Nitrodibenzofuran

Four-tenths gram (0.00176 mole) of 1-nitro-4-aminodibenzofuran was placed in a solution of 2.5 ml. of 48% sulfuric acid and 12.5 ml. of 95% ethanol and warmed to 80° on a steam bath. Then a solution of 1.2 g. (0.0174 mole) of sodium nitrite in 2.5 ml. of water was added dropwise with stirring. After all of the sodium nitrite solution had been added, the mixture was refluxed gently

for fifteen minutes. The contents of the flask were then cooled, filtered out, and subjected to steam distillation. The compound which distilled over with steam melted at 120°. After recrystallization from ethanol the straw-colored needles melted at 120-121°. A recrystallization from glacial acetic acid did not change the melting point. The yield of purified 1-nitrodibenzofuran was 125 mg. or 33%.

Anal. Calcd. for $C_{12}H_7O_3N$: N, 6.57. Found: N, 6.75 and 6.78.

Preparation of 1-Amino-4-acetaminodibenzofuran

The reduction was carried out in an apparatus similar to that described in Organic Syntheses (90). One gram of 1-nitro-4-acetaminodibenzofuran was placed in a citrate bottle, and 50 ml. of 95% ethanol and about 1 g. of Raney nickel catalyst (91) added. The bottle was then placed in the jacket of the shaking machine, the hydrogen pressure set at 47 lbs. on the gauge (4 atmos.) and the outer jacket of the container heated with steam. The pressure dropped about a pound in a few minutes, but the shaking was continued for an hour in order to insure complete

(90) Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 55.
(91) Covert and Adkins, J. Am. Chem. Soc., 54, 4116 (1932).

reduction. The colorless solution was separated from the catalyst by filtration, and the product was precipitated quantitatively when 300 ml. of water was added slowly to the alcoholic solution. After one recrystallization from methanol the 1-amino-4-acetaminodibenzofuran melted at 202°. A further recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{14}H_{12}O_2N_2$: N, 11.68. Found: N, 11.64.

Preparation of 1,4-Diacetaminodibenzofuran

A. From 1-amino-4-acetaminodibenzofuran. One-half gram (0.00195 mole) of 1-amino-4-acetaminodibenzofuran was refluxed for thirty minutes in 15 ml. of benzene containing the calculated quantity of acetic anhydride. The starting material went into solution and precipitated out as the di-monoacetyl derivative in 80% yield. After two crystallizations from glacial acetic acid the product melted at 307-308°, and the melting point was not changed by further recrystallization.

B. From 1-bromo-4-acetaminodibenzofuran. Ten grams (0.044 mole) of 4-acetaminodibenzofuran was brominated in glacial acetic acid by the addition of 45 ml. of a molar bromine (in glacial acetic acid) solution, yielding 12 g.

(89% theory) of 1-bromo-4-acetaminodibenzofuran, m.p. 222°.

Into each of two Carius tubes was placed 150 ml. of concd. ammonium hydroxide and an intimate mixture of 3 g. of 1-bromo-4-acetaminodibenzofuran and 3 g. of cuprous bromide. The sealed tubes were heated in an electric furnace at 175° for thirty hours, after which the combined contents of the two tubes were extracted with four 50-ml. portions of benzene. The combined benzene extracts were dried overnight with anhydrous sodium sulfate, then shaken for a few minutes with Norite, and filtered. Seven milliliters of acetic anhydride was added, and after one hour the diacetamino compound which had separated was filtered off. Crystallization from glacial acetic acid gave 2.5 g. (45% yield) of white needles melting at 307-308°.

A mixed melting point determination of the compounds prepared by methods (A) and (B) showed no depression.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.99.

Preparation of 1,4-Diaminodibenzofuran Dihydrochloride

Two and one-half grams of 1,4-diacetaminodibenzofuran (m.p. 307-308°) was refluxed for two hours with 35 ml. of 95% ethanol and 35 ml. of concd. hydrochloric acid. The dihydrochloride was precipitated quantitatively when the reaction mixture was cooled. This was separated by

filtration and recrystallized from water to which a little hydrochloric acid had been added. Precipitation was made complete by passing hydrogen chloride gas into the aqueous solution. The pure white dihydrochloride melted at 323-333°.

Anal.* Calcd. for $C_{12}H_{12}OCl_2N_2$: N, 10.32. Found: N, 10.50.

The free amine, obtained by addition of concd. ammonium hydroxide to the solid dihydrochloride, melted at 86-87°. The free base was too sensitive to air oxidation to be recrystallized by ordinary procedures.

Nitration of 1-Nitro-4-acetaminodibenzofuran

One-tenth gram of 1-nitro-4-acetaminodibenzofuran suspended in 8 ml. of acetic anhydride was cooled to -10° and 0.5 ml. of fuming nitric acid (sp.g. 1.49) was added dropwise with stirring. The stirring was continued for twenty minutes following the addition of the nitric acid, during which time yellow needles separated. After recrystallization from glacial acetic acid the compound melted at 286-288°. Further recrystallization from acetone, and from glacial acetic acid raised the melting point to 288°.

Anal. Calcd. for $C_{14}H_9O_6N_3$: N, 13.35. Found: N, 13.46.

*The writer is grateful to Mr. H. B. Willis for this micro-Dumas analysis.

This compound is different from the nitration product of 3-nitro-4-acetaminodibenzofuran, and is probably 1,7-dinitro-4-acetaminodibenzofuran.

Nitration of 3-Nitro-4-acetaminodibenzofuran

One-tenth gram of 3-nitro-4-acetaminodibenzofuran was nitrated under the same conditions as those described above for the nitration of 1-nitro-4-acetaminodibenzofuran, with the exception that twice as much nitric acid was used. When only 0.5 ml. of fuming nitric acid was used, the dinitro compound was difficult to purify, and the yield was very low. In this reaction no product separated, and the reaction mixture was poured on cracked ice. After two crystallizations from glacial acetic acid, the dinitro-acetamino compound melted at 277-278°.

Anal. Calcd. for $C_{14}H_9O_6N_3$: N, 13.35. Found: N, 13.42.

A mixed melting point determination with the 1,7(?)-dinitro-4-acetaminodibenzofuran resulted in a depression to 259°.

Direct dinitration of 4-acetaminodibenzofuran gave a product which melted at 260-261° after recrystallization from glacial acetic acid and acetone. Since a further recrystallization from acetone did not change the melting point, the product was assumed to be pure and was analyzed.

Its analysis (N, 13.50) checked the theoretical value for a dinitro-4-acetaminodibenzofuran. Later, however, it was found that a recrystallization (with great loss) from a large volume of toluene raised the melting point to 284° and a mixed melting point determination with 1,7(?)-dinitro-4-acetaminodibenzofuran was 287°. The impurity in the product melting at 260-261° was probably another dinitro compound, possibly 3,8(?)-dinitro-4-acetaminodibenzofuran. It seems reasonable to conclude that the second nitro group entered the unsubstituted nucleus in these reactions, for nitration of 1-nitro-2-naphthol (92) gives 1,6-dinitro-2-hydroxynaphthalene, and the hydroxyl group is known to be a stronger ortho-para director than the acetamino group.

Preparation of 4-Diethylaminodibenzofuran

This method was suggested by a recent preparation of diethylaniline from lithium diethylamide and bromobenzene (93). Lithium diethylamide was prepared according to the method of Ziegler and Ohlinger (94) by adding dropwise, with stirring, 5.85 g. (0.08 mole) of diethylamine dissolved in 25 ml. of anhydrous ether to n-butyllithium prepared in the usual manner from 11 g. (0.08 mole) of n-butyl bromide

(92) German patent 670,358 /C. A., 33, 2916 (1939)/.
(93) Bergstrom, Wright, Chandler and Gilkey, J. Org. Chem., 1, 170 (1936).
(94) Ziegler and Ohlinger, Ann., 495, 84 (1932).

and 1.4 g. (20% excess over 0.16 g. atom) of lithium. Enough heat was evolved during this addition to cause a slight refluxing. Stirring was continued for fifteen minutes after which time 10.2 g. (0.04 mole) of 4-bromodibenzofuran (m.p. 69-70°) dissolved in 50 ml. of anhydrous ether was added slowly. No noticeable amount of heat was evolved, but the solution gradually turned darker. After another hour of stirring, the solution was allowed to stand overnight.

Ten milliliters of water was then added and the ether solution extracted with several portions of 5% hydrochloric acid. The combined extracts were refluxed for an hour with Norite, then filtered and made basic with ammonia. The product separated as a colorless oil. To remove any diethylamine the solution containing the oil was boiled in an open beaker until no odor of ammonia or diethylamine was perceptible, then most of the supernatant liquid was decanted and the residual oil, together with some of the water solution, was transferred to an Erlenmeyer flask and placed in the refrigerator overnight, during which time the oil crystallized into white needles.

The solid crystals were separated by filtration and washed with water to remove any inorganic salts, then dried and taken up in anhydrous ether from which 3.35 g. (30% theory) of pure white hydrochloride was precipitated

by passing in dry hydrogen chloride. From the original ether solution was recovered 3.5 g. of 4-bromodibenzofuran: accordingly, the yield was 45% of the theoretical if based on the amount of bromo compound actually used in the reaction.

The 4-diethylaminodibenzofuran hydrochloride melted at 227-228°; the free base obtained from it melted at 68-69°.

Anal. Calcd. for $C_{16}H_{17}ON$: N, 5.86. Found: N, 5.96.

Lithium diethylamide may be prepared in good yields directly from diethylamine and lithium metal if there is present as a catalyst an organic compound such as naphthalene, to which lithium adds to give a true organometallic compound (95).

Preparation of 4-Dimethylaminodibenzofuran

Lithium dimethylamide was prepared from n-butyllithium and anhydrous dimethylamine. To 0.4 g. (20% excess over 0.047 g. atom) of lithium in 20 ml. of ether was added, dropwise, 3.24 g. (0.023 mole) of n-butyl bromide in 15 ml. of ether. Stirring was continued for one-half hour after all of the halide had been added and then the solution was

(95) U. S. patent 2,141,058 /C. A., 33, 2538 (1939)/; also, unpublished work by N. N. Crounse, this laboratory.

filtered through a glass wool plug. To the filtered solution was added 3.7 g. (0.023 mole) of dimethylamine dissolved in 20 ml. of ether. The addition of the amine caused only a slight refluxing. Then 3 g. (0.012 mole) of 4-bromodibenzofuran was added and the mixture was allowed to stir overnight. The flask was stoppered and allowed to stand at room temperature for an additional three days, after which time the reaction was worked up as described in the preceding experiment. There was obtained 1.61 g. (63%) of crystalline basic material, slightly brown in color. Decolorization with Norite and two crystallizations from methanol gave 0.6 g. (23.5%) of pure 4-dimethylaminodibenzofuran, colorless plates melting at 98-99°.

Anal. Calcd. for $C_{14}H_{13}ON$: N, 6.64. Found: N, 6.89.

Reaction of n-Butyllithium with 4-Bromodibenzofuran

This reaction was first investigated by Willis (35) who obtained from it 4-dibenzofurancarboxylic acid in 57% yield upon carbonation after refluxing the mixture for seven and one-half hours. The exchange reaction takes place very rapidly, and the long refluxing is not necessary, as the experiments described below show.

n-Butyllithium, prepared from 1.25 g. of lithium metal (excess) and 5.18 g. (0.0378 mole) of n-butyl bromide, in 50 ml. of ether was added to 5 g. (0.0202 mole) of

4-bromodibenzofuran in 100 ml. of warm benzene. A heavy white precipitate formed immediately. The mixture was stirred and refluxed for five minutes, and was carbonated with solid carbon dioxide exactly ten minutes after the solutions were mixed. The yield of 4-dibenzofurancarboxylic acid was 42%, m.p. 204-205°.

When the above proportions were refluxed for twenty-five minutes the yield of 4-dibenzofurancarboxylic acid melting at 200-204° was 2.58 g. (60.1%). The neutral residue from this reaction weighed 1.0 g. and melted at 145-155°. Recrystallization from glacial acetic acid left undissolved 20 mg. of material melting at 268-270°, while the product which dissolved and separated on cooling melted at 165-168°. This was shown to be di-4-dibenzofuryl ketone (mixed melting point). The material which melted at 268-270° gave a purple color with concd. sulfuric acid and formed a compound which melted at 226-228° when treated with acetic anhydride and a drop of sulfuric acid. The latter product depressed the melting point of the starting material (268-270°) to 205-207°. These facts indicated a tertiary carbinol, and the compound melting at 268-270° was shown to be tri-4-dibenzofurylcarbinol by comparison with the specimen synthesized in the experiment which follows. The formation of carbinols on carbonation of organolithium

compounds is not a new observation (95) (96), but no instances have been reported of their formation at the temperature of solid carbon dioxide.

Preparation of Tri-4-dibenzofurylcarbinol

The 4-carbomethoxydibenzofuran was prepared in accordance with the directions of Hayes (31). Fifty grams of 4-dibenzofurancarboxylic acid was suspended in 300 ml. of methanol, the mixture saturated with dry hydrogen chloride at the reflux temperature, and then refluxed for an additional four hours. Upon cooling, 46.5 g. (87%) of long white needles, m.p. 95-96°, separated. Dilution of the mother liquor yielded 5.0 g. more of less pure material. The combined yield of ester was 96%.

Thirty grams of dibenzofuran was metalated with n-butyllithium prepared from 54.8 g. (0.40 mole) of n-butyl bromide and 5.6 g. (0.807 g. atom) of lithium in 250 ml. of ether. Then 5.02 g. (0.022 mole) of 4-carbomethoxydibenzofuran dissolved in 50 ml. of benzene was added dropwise. There was vigorous refluxing while the ester was being added, and a white crystalline precipitate formed simultaneously. The reaction was stirred and refluxed for an hour after the addition of the ester. The color

(95) Gilman and Van Ess, J. Am. Chem. Soc., 55, 1258 (1933).
(96) Wittig and Pockels, Ber., 72, 89 (1939).

test (97) for a C-metal linkage was strongly positive at this point. After cautiously hydrolyzing the mixture, the solid was filtered off and extracted with boiling ethanol to remove any unchanged ester and dibenzofuran. This treatment left 11.7 g. (99%) of a white crystalline powder which melted at 265-267°. Further extraction with acetone raised the melting point to 269-270°. A mixed melting point with the product melting at 268-270°, isolated from the carbonation of 4-dibenzofuryllithium, was not depressed. Recrystallization from a mixture of equal volumes of acetone and dioxane gave a final melting point of 274-275°.

Anal. Calcd. for $C_{37}H_{22}O_4$: C, 83.9; H, 4.18. Found: C, 83.8; H, 4.23.

Preparation of 2-Acetoxydibenzofuran

Sixteen grams (0.087 mole) of 2-hydroxydibenzofuran (m.p. 132°) was suspended in 50 ml. of acetic anhydride and 3 drops of concd. sulfuric acid added. Most of the solid went into solution when the acid was added, and the flask became warm. The mixture was refluxed for ten minutes to complete the reaction. Upon cooling, the liquid solidified to a crystalline mass, which was broken up by stirring, and filtered to yield 16 g. of white plates melting at 111-113°. Addition of water to the filtrate

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

gave another 5 g. of crystals. These were combined and recrystallized from propanol to give 17.4 g. (77% yield) of 2-acetoxydibenzofuran melting at 115-116°. A further recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.3; H, 4.46. Found: C, 74.2; H, 4.89.

Fries Rearrangement with 2-Acetoxydibenzofuran

The procedure was adapted from that described by Hey and Jackson (98) for the Fries rearrangement of 4-benzoyloxybiphenyl. Five grams (0.022 mole) of 2-acetoxydibenzofuran and 30 ml. of sym.-tetrachloroethane were placed in a 200-ml. flask equipped with a mercury-sealed stirrer, a condenser into the top of which a calcium chloride tube had been inserted, and a hopper for adding aluminum chloride. The contents of the flask were heated to about 60° while 3.2 g. (10% excess over 0.022 mole) of aluminum chloride was added in small amounts, after which the mixture was heated to 140° for one hour and allowed to stir at room temperature for seven hours. Following hydrolysis, the solvent was removed by steam distillation and the residue was separated from the water by filtration. This residue

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

was heated to boiling with 10% sodium hydroxide. Most of the material went into solution readily, but a part dissolved with difficulty, and precipitated out as bright yellow plates when the solution was cooled to room temperature. This, on acidification, yielded 1 g. (20%) of yellow crystals melting at 165-166.5°. Recrystallization from dilute ethanol and dilute propanol raised the melting point to 168-169°. Methylation and oxidation (see the following experiments) to 2-methoxy-3-dibenzofurancarboxylic acid showed this to be 3-acetyl-2-hydroxydibenzofuran. The color of this compound was not altered by distillation (b.p. 227°/7 mm.) or by repeated treatments with Norite in alcohol.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.35; H, 4.47. Found: C, 74.14; H, 4.43.

The alkali soluble portion of the residue on acidification yielded 2.4 g. of pale yellow solid melting at 105-110°. This contained the isomeric hydroxy-ketone together with 2-hydroxydibenzofuran formed as a result of hydrolytic cleavage by aluminum chloride. Since this crude material would not crystallize readily, a part of it was methylated as follows:

Eighteen milliliters of methyl sulfate, 1.5 g. of the crude 1-acetyl-2-hydroxydibenzofuran and 28 ml. of acetone were heated at the reflux temperature while 14 ml. of 60% potassium hydroxide was added dropwise with stirring.

Refluxing was continued for one-half hour after the addition of the alkali. Upon cooling, a colorless oil remained which was taken up in dilute ethanol and allowed to stand in the refrigerator for several weeks. About 0.1 g. of colorless cubic crystals, m.p. 114-118°, were deposited. These melted at 121-122° after recrystallization from petroleum ether (b.p., 60-68°).

Anal. Calcd. for $C_{15}H_{12}O_3$: Methoxyl, 12.91. Found: Methoxyl, 12.78.

Since the Fries rearrangement involves only ortho and para positions, and since the para position is blocked, by a process of elimination this compound can be only 1-acetyl-2-methoxydibenzofuran.

The colors of these o-hydroxy ketones may be explained on the basis of hydrogen bond formation, accompanied by quinoidation (99). Thus 2-methoxybenzophenone cannot undergo chelation and is colorless, while 2-hydroxybenzophenone can form a chelate ring and is pale yellow in color; 2,2'-dihydroxybenzophenone is bright yellow. Also, 3-acetyl-4-hydroxydibenzofuran is pale yellow in color, while its methyl ether is colorless (25).

Preparation of 2-Methoxy-3-acetyldibenzofuran

Seven-tenths gram (0.0032 mole) of the bright yellow

(99) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1639.

2-hydroxy-3-acetyldibenzofuran (m.p. 168-169°) was dissolved in a solution of 100 ml. of 3% sodium hydroxide and 40 ml. of acetone. To this was added 10 ml. (0.0588 mole) of dimethyl sulfate, and the mixture was allowed to stand overnight. During this time most of the product had separated as small white crystals. Water was added to insure complete precipitation and, after filtration, the crystals were warmed with 5% sodium hydroxide solution to destroy any remaining dimethyl sulfate and to remove any unchanged hydroxy compound. This treatment yielded 720 mg. (96% theory) of white 2-methoxy-3-acetyldibenzofuran which melted at 112-113°. Recrystallization from ethanol yielded white needles melting at 113-114°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.90; H, 5.03. Found: C, 74.60; H, 4.93.

Preparation of 2-Methoxy-3-dibenzofurancarboxylic acid

In accordance with the general procedure of Fuson and Tullock (100), to 0.1 g. of 2-methoxy-3-acetyldibenzofuran in 2 ml. of dioxane and 2 ml. of 10% sodium hydroxide, a solution of iodine in potassium iodide was added a few drops at a time with shaking, until a permanent iodine color resulted. The mixture was then acidified with hydrochloric acid and, after addition of a few crystals of

(100) Fuson and Tullock, J. Am. Chem. Soc., 56, 1638 (1934).

sodium bisulfite to remove excess iodine, was filtered. The yellow residue, which smelled strongly of iodoform, was extracted with dilute sodium hydroxide; the filtered alkaline solution upon acidification yielded very fine white needles which melted at 206-207° after recrystallization from 30% ethanol. A mixed melting point with the 2-methoxy-3-dibenzofurancarboxylic acid obtained by P. R. Van Ess from carbonation of the Grignard of 2-methoxy-3-bromodibenzofuran was not depressed.

Preparation of 2,8-Dibromodibenzofuran

This compound was first prepared by Hoffmeister (101). Its structure was proved by McCombie and others (82), who obtained it from a phenyl ether ring closure. Most of the dibromo compound used in the succeeding experiments was made by students in the undergraduate preparations course by a modification of Hoffmeister's procedure:

Thirty-four grams (0.20 mole) of dibenzofuran, 0.5 g. of iron filings, and 130 ml. of carbon tetrachloride were placed in a 500-ml. round-bottomed flask equipped with a reflux condenser and a dropping funnel. A rubber stopper, fitted with a glass tube, was inserted in the top of the condenser to carry away the hydrogen bromide generated in

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

the reaction. Through the dropping funnel, 24 ml. (0.45 mole) of bromine was added during a period of ten to fifteen minutes; at the same time the solution was stirred slightly by imparting a circulatory motion to the ring stand. After standing overnight, during which time a part of the product separated, the mixture was refluxed on a water bath until the bromine color disappeared. This usually required two to two and one-half hours. The crude product obtained by filtration, after washing with sodium bisulfite and water, melted at about 170° and weighed 51 g. (77%). Two crystallizations from toluene (2.4 ml. per gram of dibromo compound) gave 39 g. (59%) of lustrous plates, m.p. 187-189°. The 2,8-dibromodibenzofuran may be distilled without decomposition (b.p. 220°/8 mm.), but recrystallization is a more effective method of purification.

Preparation of 2,8-Dimethoxydibenzofuran

An intimate mixture of 100 g. (0.307 mole) of 2,8-dibromodibenzofuran (m.p. 185-189°), 200 g. of technical, flake sodium hydroxide (76% NaOH), and 24 g. of copper-bronze powder was poured onto a mat of 100 g. of copper turnings in a 600-ml. copper beaker, and 100 ml. of a copper sulfate solution containing 20 g. of $CuSO_4 \cdot 6H_2O$ added. The beaker and its contents were kept at 235-240°

for twelve hours in an electrically heated bomb (102). In working up, the contents of the beaker were diluted with 300 ml. of water, heated to boiling, and filtered through a fluted filter. This extraction procedure was repeated until a few drops of the filtrate gave no precipitate on acidification. About 1500 ml. of water was required for this treatment. The combined filtrates were made acid to Congo Red with hydrochloric acid, and the light tan product filtered with suction. The dried material weighed 67 g. and melted at 230-235°. The theoretical yield is 62 g. (the crude product contained occluded sodium chloride).

To 237.5 g. of crude 2,8-dihydroxydibenzofuran, prepared as described above and dissolved in a liter of water containing 103 g. of sodium hydroxide, was added 380 ml. of dimethyl sulfate, dropwise with stirring. Stirring was continued at room temperature for two hours after the addition of the dimethyl sulfate; then the mixture was stirred three hours more at the reflux temperature. At the end of that time, 30 g. of sodium hydroxide was added to destroy any remaining dimethyl sulfate. The yield of crude 2,8-dimethoxydibenzofuran was 221 g. or 81%. This was distilled (b.p. 187°/5 mm.) to give, after crystallization from 95% ethanol, 89 g. of white plates melting at 88-89°. (The

(102) The writer is grateful to Professor F. E. Brown for the use of his steel bomb.

product crystallizes as needles when a larger volume of solvent is used). An additional 15 g. of somewhat less pure material was obtained by concentrating the alcoholic mother liquor. The residue in the Claisen flask was extracted with several portions of ethanol to yield an additional 20 g. of product. This was combined with the 15 g. of material mentioned above and distilled (b.p. 173°/3 mm.) to give, after crystallization from ethanol, 24 g. of white needles melting at 88-89°. The total yield of pure 2,8-dimethoxydibenzofuran was 113 g. or 45.5% based on the weight of 2,8-dibromodibenzofuran required for its preparation.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.61; H, 5.30. Found: C, 73.65; H, 5.47.

The 2,8-dimethoxydibenzofuran can also be purified without distillation. The crude product may be extracted with petroleum ether (b.p. 60-68°), or ethanol, from which the 2,8-dimethoxydibenzofuran crystallizes readily. A number of crystallizations are required, however, to bring the melting point up to 88-89°.

Preparation of 2,8-Dimethoxydibenzofuran Picrate

To 0.5 g. (0.0022 mole) of 2,8-dimethoxydibenzofuran dissolved in 5 ml. of hot absolute ethanol was added a solution of 0.5 g. (0.0022 mole) of picric acid in 5 ml.

of hot absolute ethanol. The mixed solutions were boiled for one minute and then allowed to cool. It was necessary to concentrate the solution to about one-third its volume before the picrate would precipitate. The red needles melted at 117-118° after two crystallizations from absolute ethanol.

Anal. Calcd. for $C_{14}H_{12}O_3 \cdot C_6H_3O_7N_3$: Methoxyl, 13.55. Found: Methoxyl, 13.44.

This picrate is very soluble in ethanol and is decomposed by cold water.

Dibromination of 2,8-Dimethoxydibenzofuran

To 45.6 g. (0.20 mole) of 2,8-dimethoxydibenzofuran, dissolved in 1 liter of glacial acetic acid was added, dropwise, 400 ml. of a molar solution of bromine in glacial acetic acid. The reaction was carried out at room temperature and the solution was stirred mechanically. When about one-third of the bromine had been added, a white crystalline precipitate began to form; addition of the bromine required one and three-quarters hours. The mixture was allowed to stand overnight and then filtered with suction. The precipitated material weighed 54 g. and melted at 180-220°. The filtrate was treated with a few ml. of sodium bisulfite solution and then concentrated to about 250 ml., and this

on cooling yielded an additional 16 g. of product which also melted at 180-220°, thus making the combined crude yield 91% of the theoretical.

Two isomeric dibromo compounds were separated from this mixture. By treatment with boiling acetone, the more soluble and lower melting isomer, which comprised about two-thirds of the total, was dissolved. This formed long, white needles, which melted at 196-197° after recrystallization from acetone, ethanol and isopropanol, and is very probably 1,9-dibromo-2,8-dimethoxydibenzofuran (103).

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.45. Found: Br, 41.90.

A mixed melting point with the dibromo-dimethoxy compound obtained by methylation of the bromination product of 2,8-dihydroxydibenzofuran was not depressed.

The residue from the acetone extraction melted at 240°, and successive recrystallizations from benzene, dioxane and glacial acetic acid gave white needles which melted at 260-261°. This compound is probably 3,7-dibromo-2,8-dimethoxydibenzofuran.

(103) The structures of all of the 1,9-derivatives discussed here depend, for final proof, on the conversion of 1,9-dimethyl-2,8-dihydroxydibenzofuran to the authentic 1,9-dimethyldibenzofuran prepared by ring closure. This work is being carried out at the time of this writing.

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.45. Found: Br, 40.90.

Dimetalation of 2,8-Dimethoxydibenzofuran

Thirty grams (0.131 mole) of 2,8-dimethoxydibenzofuran was dissolved in 300 ml. of ether, and to this solution was added an excess over 2 moles of n-butyllithium, prepared from 9.8 g. (1.4 g. atoms) of lithium and 69 g. (0.6 mole) of n-butyl bromide in 300 ml. of ether. The mixture was refluxed gently for eight hours and then carbonated with an excess of solid carbon dioxide. After removal of the ether by distillation the residue was taken up in 300 ml. of water and the solution was refluxed with Norite, filtered, and acidified. The yield was 31 g. of yellow solid (m.p., 210-230°) which smelled strongly of valeric acid. This was pulverized and extracted at the reflux temperature with 240 ml. of acetone, which left behind 10.7 g. (25.7%) of white crystalline material which melted at 235-253°. Three recrystallizations from glacial acetic acid gave 5.45 g. (13.1%) of the pure 2,8-dimethoxydibenzofuran-1,9-dicarboxylic acid (103) which melted at 271-272°. A further recrystallization from dioxane did not change the melting point.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 60.70; H, 3.80; neutralization equiv., 158. Found: C, 60.5 and 60.8; H, 3.82 and 3.88; neutralization equiv., 156.

A mixed melting point of this acid with the acid obtained by treatment of 1,9-dibromo-2,8-dimethoxydibenzofuran with n-butyllithium and subsequent carbonation, was not changed. The identity of these two acids was confirmed by a mixed melting point of their methyl esters (see following experiment).

Preparation of 1,9-Dicarbomethoxy-2,8-dimethoxydibenzofuran

One gram of the di-acid obtained in the above experiment was treated in dry ether with an excess of diazomethane, and there was obtained a quantitative yield of the di-ester melting at 126-127°. Recrystallization from methanol raised the melting point to 129-130°. A further recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62.8; H, 4.69. Found: C, 62.44; H, 4.45.

A mixed melting point with the 1,9-dicarbomethoxy-2,8-dimethoxydibenzofuran obtained in several steps from 1,9-dibromo-2,8-dimethoxydibenzofuran was not depressed.

Preparation of 2,8-Dihydroxydibenzofuran

The crude 2,8-dihydroxydibenzofuran obtained from the alkaline hydrolysis of 2,8-dibromodibenzofuran does not crystallize readily and can be purified only with great loss. However, this crude material is easily converted

into the corresponding diacetoxy and dimethoxy derivatives which crystallize readily and which can be distilled at low pressures. The best method of obtaining pure 2,8-dihydroxydibenzofuran is from hydrolysis of the former or cleavage of the latter.

A. From hydrolysis of 2,8-diacetoxydibenzofuran. Eight and six-tenths grams (0.03 mole) of 2,8-diacetoxydibenzofuran (m.p., 150-151°) was refluxed for four hours with 30 ml. of concd. hydrochloric acid and 30 ml. of 95% ethanol. When the flask cooled to room temperature, the product crystallized out. The entire mixture was poured into 400 ml. of water to insure complete precipitation. This gave 5.8 g. or a 96% yield of white plates melting at 242-243°.

B. From demethylation of 2,8-dimethoxydibenzofuran. Five grams (0.022 mole) of 2,8-dimethoxydibenzofuran, in a flask fitted to a condenser through a ground-glass joint, was refluxed for ten hours with 20 ml. of glacial acetic acid and 25 ml. of constant-boiling hydrobromic acid. After being cooled to room temperature, the contents of the flask were poured into 400 ml. of water. This gave 4.28 g. or a 98% yield of nicely crystalline plates melting at 241-242°. A recrystallization from 30% ethanol raised the melting point to 242-243°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 71.97; H, 4.03. Found: C, 71.60; H, 4.16.

The 2,8-dihydroxydibenzofuran is readily soluble in ethanol. It is soluble in boiling water to the extent of 2.4 g. per liter, from which it precipitates out quantitatively when cooled to room temperature. With ferric chloride solution, it gives an intense green color.

Since this work was done, the preparation of this compound by another method has been reported in the patent literature. Treatment of 2,5,5'-trihydroxy-2'-chlorobiphenyl with alkalies yielded 2,8-dihydroxydibenzofuran melting at 243-244° (52).

Preparation of 2,8-Diacetoxydibenzofuran

From 200 g. of 2,8-dibromodibenzofuran there was obtained, in two runs, using the procedure and proportions described previously (p. 75) 139 g. of crude 2,8-dihydroxydibenzofuran. This was suspended in 250 ml. of acetic anhydride and 1 ml. of concd. sulfuric acid was added. The mixture was refluxed for an hour and then, after thorough cooling, about 20 ml. of water was cautiously added. There was vigorous boiling even though the water was added dropwise. When the addition of more water elicited no further evolution of heat, the solution was diluted to 1 liter and, after standing several hours, was

filtered. The yield was 117 g. (60.2%, based on the dibromo compound) of crude tan product which melted at 135°. This distilled smoothly (b.p., 212°/6 mm.) and was obtained as colorless plates after crystallization from ethanol. The yield was 77 g. (39.7%, based on the dibromo compound), m.p. 150-151°.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.5; H, 4.28. Found: C, 67.05; H, 4.30.

Preparation of 2-Acetoxy-8-methoxydibenzofuran

In some preliminary attempts to demethylate 2,8-dimethoxydibenzofuran with 17% hydrobromic acid in glacial acetic acid there was obtained some crude 2-hydroxy-8-methoxydibenzofuran which could be best purified through conversion to the acetoxy derivative:

Ten grams (0.044 mole) of 2,8-dimethoxydibenzofuran in 30 ml. of glacial acetic acid and 40 ml. of 30% hydrogen bromide in glacial acetic acid (Eastman Kodak Co.) was refluxed for twenty-five hours. Upon the addition of 200 ml. of water an oil separated, which on standing changed to a semi-solid gum that could be filtered. Treatment of this material with 10% sodium hydroxide dissolved the 2,8-dihydroxydibenzofuran and precipitated the sodium salt of 2-hydroxy-8-methoxydibenzofuran, which was obtained as lustrous tan plates on filtration. Acidification of the

alkaline filtrate yielded 6.5 g. of 2,8-dihydroxydibenzofuran melting at 220-230°. Hydrochloric acid was added to an aqueous solution of the sodium salt of the incompletely demethylated compound, and the 2-hydroxy-8-methoxydibenzofuran separated as an oil. This was acetylated in the usual manner with 10 ml. of acetic anhydride and 3 drops of concd. sulfuric acid, yielding 1.1 g. (9.8%) of the acetoxy compound which melted at 106-107°. Two recrystallizations from ethanol raised the melting point to 110°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.12 and 70.09; H, 5.02 and 5.09.

Preparation of 2-Hydroxy-8-methoxydibenzofuran

One gram of 2-acetoxy-8-methoxydibenzofuran was refluxed for three and one-half hours with 10 ml. of concd. hydrochloric acid and 10 ml. of 95% ethanol. When the solution was cooled and diluted with water, the product separated as an oil which crystallized upon standing overnight in the refrigerator. This solid, which weighed 720 mg. (86.2%) and melted at 85-86°, was recrystallized twice from petroleum ether (b.p., 60-68°) whereupon it melted at 90-91°.

Anal. Calcd. for $C_{13}H_{10}O_3$: Methoxyl, 14.49. Found: Methoxyl, 14.59.

Subsequently, the preparation of this compound from a biphenyl ring closure was reported in a patent (50), but no physical constants were given.

Preparation of 1,9-Dibromo-2,8-dihydroxydibenzofuran (103)

To a stirred suspension of 30 g. of 2,8-dihydroxydibenzofuran in 370 ml. of glacial acetic acid was added 296 ml. of a molar solution of bromine in glacial acetic acid, at a rate of 1 drop per second. The dihydroxy compound gradually went into solution as the bromine was added and was all dissolved by the time that half the bromine was dropped in. Upon standing overnight, 21.5 g. of dibromo compound, m.p. 180°, precipitated, and an additional 25.5 g., with the same melting point, was precipitated by dilution of the filtrate with water. The combined crude yield was 47 g. (89%). A portion was recrystallized from ethanol and from glacial acetic acid to a constant melting point of 201-202°.

Anal. Calcd. for $C_{12}H_6O_3Br_2$: Br, 44.7. Found: Br, 43.75.

Methylation of 1,9-Dibromo-2,8-dihydroxydibenzofuran

To a stirred solution of 35 g. (0.097 mole) of the crude 1,9-dibromo-2,8-dihydroxydibenzofuran (m.p., 180°) in 500 ml. of water containing 10 g. of sodium hydroxide, was added dropwise 30 ml. (0.202 mole) of dimethyl sulfate.

After all of the dimethyl sulfate was added the mixture was refluxed for three-quarters of an hour, then 10 g. of sodium hydroxide was added to destroy the unused ester and heating was continued for thirty minutes longer. The precipitated dimethoxy compound was separated by filtration, and since acidification of a few milliliters of the filtrate showed the presence of considerable phenolic material, the above treatment with alkali and dimethyl sulfate was repeated. The combined precipitates were dried and crystallized from 400 ml. of glacial acetic acid. Upon cooling there was obtained 24.5 g. (64.8%) of white needles which melted at 193-194°. Two recrystallizations from glacial acetic acid raised the melting point to 196-197°. This compound was found to be identical (mixed m.p.) with the compound melting at 196-197° obtained from direct dibromination of 2,8-dimethoxydibenzofuran.

Preparation of 1,9-Dibromo-2,8-diacetoxydibenzofuran (103)

Two and seven-tenths grams (0.0075 mole) of 1,9-dibromo-2,8-dihydroxydibenzofuran was suspended in 15 ml. (0.137 mole) of acetic anhydride and 5 drops of concd. sulfuric acid was added. The solution which formed was warmed on a steam bath for one and one-half hours, and then, after thorough cooling, the excess acetic anhydride was cautiously hydrolyzed with water. Recrystallization from a mixture of equal volumes of 95% ethanol and acetone

produced 2.3 g. (69.1%) of long white needles which melted at 173-174°. A second recrystallization from glacial acetic acid raised the melting point to 173.5-174°.

Anal. Calcd. for $C_{16}H_{10}O_5Br_2$: Br, 36.20. Found: Br, 36.40.

Conversion of 1,9-Dibromo-2,8-dimethoxydibenzofuran to 2,8-dimethoxydibenzofuran-1,9-dicarboxylic acid

To 1.5 g. (0.0039 mole) of 1,9-dibromo-2,8-dimethoxydibenzofuran dissolved in 130 ml. of benzene was added a solution of n-butyllithium, prepared from 2.5 g. of lithium and 13.6 ml. of n-butyl bromide in 60 ml. of ether. Within a minute after mixing the solutions a milky-white precipitate began to form. The mixture was heated at the reflux temperature (approximately 60°) for two hours and then carbonated by pouring on crushed solid carbon dioxide. After removal of the solvent by steam distillation, the residue was extracted with hot 5% potassium hydroxide solution. Acidification of the extraction liquor gave 820 mg. (66.6%) of acid melting at 210-220°. Two recrystallizations from glacial acetic acid raised the melting point to 270-271°, and a mixed melting point with the acid obtained from direct dimetalation of 2,8-dimethoxydibenzofuran followed by carbonation was not depressed.

One-tenth gram of the di-acid prepared above was dissolved in 5 ml. of methanol and refluxed for one hour while dry hydrogen chloride was passed into the solution. The di-ester precipitated in quantitative yield as needle-like clusters when the solution was cooled. Recrystallization from methanol gave needles melting at 128-129°, and a mixed melting point with the 1,9-dicarbomethoxy-2,8-dimethoxydibenzofuran obtained previously (p. 81) showed no depression.

Conversion of 3,7-Dibromo-2,8-dimethoxydibenzofuran to 2,8-dimethoxydibenzofuran-3,7-dicarboxylic acid

To 0.7 g. (0.0018 mole) of the dibromo-dimethoxydibenzofuran melting at 360-361° and tentatively designated as the 3,7-isomer (p. 79), dissolved in 60 ml. of benzene, was added a solution of n-butyllithium, prepared from 1.4 g. of lithium and 6.3 ml. of n-butyl bromide in 30 ml. of ether. The mixture was refluxed for seven hours and then carbonated by pouring on crushed solid carbon dioxide. Upon working up in the usual manner there was obtained 650 mg. of acidic material from which several tenths of a gram of benzoic acid was isolated by sublimation (mixed m.p.). This resulted from metalation of the solvent by the n-butyllithium as is shown in a following experiment. Three recrystallizations from glacial acetic acid gave

0.1 g. (17.5%) of white needles which melted at 290° with decomposition.

Anal. Calcd. for $C_{16}H_{12}O_7$: Methoxyl, 19.63. Found: Methoxyl, 19.62.

A mixed melting point with 2,8-dimethoxydibenzofuran-1,9-dicarboxylic acid (m.p., 271-272°) was depressed to 265°. Both of these acids melt with decomposition and different melting points can be obtained, depending upon the rate of heating. In taking the mixed melting points described here the two pure samples and the mixed sample were always heated together in the same bath.

Preparation of 3,7-Dicarbomethoxy-2,8-dimethoxydibenzofuran

Thirty milligrams of the di-acid melting at 290° was suspended in 4 ml. of methanol and esterified by saturating the solution with dry hydrogen chloride at the reflux temperature. When the solution was cooled 18 mg. (50%) of needles, m.p. 183-184°, separated.

Anal. Calcd. for $C_{18}H_{16}O_7$: Methoxyl, 36.05. Found: Methoxyl, 36.50.

A mixed melting point with 1,9-dicarbomethoxy-2,8-dimethoxydibenzofuran was depressed to 135°.

Metalation of Benzene with n-Butyllithium

It seemed logical to conclude that the benzoic acid,

isolated from the treatment of 3,7-dibromo-2,8-dimethoxydibenzofuran with n-butyllithium followed by carbonation (p. 89), resulted from a metalation of the benzene used as a solvent. Benzoic acid has been obtained in small yields from reactions of this type with the more reactive alkylsodium compounds (104). To show definitely that organolithium compounds can also metalate benzene the following experiment was carried out.

Sixty milliliters of benzene was added to a solution of n-butyllithium, prepared from 1.4 g. of lithium and 6.3 ml. of n-butyl bromide in 30 ml. of ether. During the first five minutes of heating a heavy white precipitate, which was probably lithium bromide, formed. Refluxing was continued for seven and one-half hours, and then the mixture was carbonated by pouring it on solid carbon dioxide. After removal of the solvent by steam distillation there was obtained on acidification, 30 mg. of benzoic acid, m.p. 116-120°. This is a 5.2% yield on the basis of a 50% yield of n-butyllithium. The crude acid melted at 121-123° after sublimation, and a mixed melting point with a sample of pure benzoic acid was not lowered.

Preparation of 1,9-Dimethyl-2,8-dimethoxydibenzofuran (103)

Five grams of 1,9-dibromo-2,8-dimethoxydibenzofuran

(104) Schorigin, Ber., 41, 2723 (1908).

(0.013 mole), dissolved in 75 ml. of warm benzene, was refluxed and stirred for twenty minutes with a solution of n-butyllithium, prepared from 1.2 g. of lithium and 6.9 ml. of n-butyl bromide in 37.5 ml. of ether. A white precipitate formed immediately upon the addition of the n-butyllithium. Then 5 ml. (6.54 g. or 0.052 mole) of dimethyl sulfate, dissolved in 10 ml. of ether, was added dropwise. The solution refluxed vigorously during the addition. Stirring was continued for four hours, and then after making a color test for organometallic compound (97) and finding it negative, water and potassium hydroxide were added and the mixture was refluxed for five minutes to insure complete removal of the excess dimethyl sulfate. The solution was filtered and the ether-benzene layer was separated and dried for a few minutes over anhydrous calcium chloride, and then the solvent was removed by distillation. The residue was taken up in petroleum ether (b.p., 60-68°), from which it crystallized in very small needles melting at 103-105°. The yield was 1.6 g. or 48.5%. A recrystallization from 95% ethanol raised the melting point to 106-107° and a further recrystallization from petroleum ether (b.p., 60-68°) gave long white needles with the same melting point.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.95; H, 6.29. Found: C, 75.20; H, 6.33.

Preparation of 1,9-Dimethyl-2,8-dihydroxydibenzofuran

Two and one-tenth grams of 1,9-dimethyl-2,8-dimethoxydibenzofuran was refluxed for ten hours with 20 ml. of glacial acetic acid and 25 ml. of constant boiling hydrobromic acid. When the solution had cooled to room temperature it was poured into 400 ml. of water, from which 1.85 g. (99%) of the dihydroxy compound, melting at 163-164.5°, separated. Recrystallization from dilute ethanol raised the melting point to 168-169°.

Anal.* Calcd. for $C_{14}H_{12}O_3$: C, 73.65; H, 5.30. Found: C, 73.50; H, 5.24.

Attempted Bucherer Reaction with 1,9-Dimethyl-2,8-dihydroxydibenzofuran

Six-tenths of a gram of 1,9-dimethyl-2,8-dihydroxydibenzofuran was heated in a sealed tube with 7.5 g. of sodium metabisulfite, 15 ml. of water and 15 ml. of concd. ammonium hydroxide at 180° for twenty hours. Only starting material (m.p., 163-165°) was recovered. There was no trace of basic material. Under these same conditions 2,8-dihydroxydibenzofuran gave an 80% yield of 2,8-diaminodibenzofuran.

*The writer is grateful to Mr. L. D. Apperson for this semi-micro analysis.

In a second experiment, 0.5 g. of the dimethyl-dihydroxy compound was heated with 10 g. of sodium metabisulfite and 25 ml. of concd. ammonium hydroxide at 185-190° for twenty hours, the water being omitted. Here, also, only starting material was recovered and there was no trace of basic material.

In a third experiment, 0.6 g. of the dimethyl-dihydroxy compound was heated with the 10 g. of sodium metabisulfite and 25 ml. of concd. ammonium hydroxide for 30 hours at 188° and for 20 hours at 220°. When the tube was opened, it was found that the contents had turned a brownish black and a strong odor of hydrogen sulfide was present. Not a trace of amine could be isolated, but some starting material was recovered.

The failure of this reaction to proceed as does the reaction with 2,8-dihydroxydibenzofuran may be explained on the basis of steric factors and fixity of bond structures (see Discussion).

Preparation of 2,8-Diaminodibenzofuran

A. By amination of 2,8-dibromodibenzofuran. One hundred grams (0.3065 mole) of 2,8-dibromodibenzofuran was intimately mixed with 50 g. of cuprous bromide and placed in a glass beaker fitted as a liner for an electrically heated steel bomb, and then 400 ml. of concd.

ammonium hydroxide was added. The mixture was heated at 165-195° for thirty hours. When the bomb was opened, 24 g. of the product had crystallized as long white needles at the top and sides of the beaker. The rest of the product was obtained by extracting the residue, after filtration, with boiling dilute hydrochloric acid and subsequent precipitation of the diamine by ammonium hydroxide. The yield of crude 2,8-diaminodibenzofuran was 40 g. (65%) which melted at 195-205°. Recrystallization from dilute ethanol raised the melting point to 212-213°. This is the same melting point as that reported by Borsche and Schacke (105) who obtained this diamine from hydrolysis of the Beckmann rearrangement product of the dioxime of 2,8-diacetyldibenzofuran. The diacetamino compound of Borsche and Schacke melted more than forty degrees lower (258° as compared with 299-300°) than the diacetamino compound obtained from the diamine whose preparation is described here. It was, therefore, thought advisable to analyze the diamine.

Anal. Calcd. for $C_{12}H_{10}ON_2$: N, 14.12. Found: N, 14.02.

B. By the Bucherer reaction with 2,8-dihydroxydibenzofuran. One gram of 2,8-dihydroxydibenzofuran was heated

(105) Borsche and Schacke, Ber., 56, 2506 (1923).

in a sealed tube with 7.5 g. of sodium metabisulfite, 15 ml. of concd. ammonium hydroxide and 15 ml. of water at 180° for twenty hours. There was obtained by filtration and washing with water, 0.8 g. of 2,8-diaminodibenzofuran as white needles, m.p. 209-210° (80.8%).

C. From 2,8-dibromodibenzofuran and sodamide in liquid ammonia. Bradley (40) found that 2-aminodibenzofuran could be smoothly and easily prepared in good yields from 2-bromodibenzofuran and sodamide in liquid ammonia. The method is much less satisfactory for the preparation of 2,8-diaminodibenzofuran, probably because of the lower solubility of 2,8-dibromodibenzofuran in liquid ammonia.

Sodamide was prepared according to the directions of Vaughn, Vogt and Nieuwland (106) from 10.1 g. (0.44 g. atom) of sodium and 0.3 g. of hydrated ferric nitrate in 400 ml. of liquid ammonia. Then 65.2 g. (0.20 mole) of 2,8-dibromodibenzofuran was added during a period of ten minutes. There was no vigorous reaction, and after three hours the excess sodamide was destroyed by the addition of ammonium chloride. The ammonia was allowed to evaporate and the solid was washed with water and then extracted with hot, dilute hydrochloric acid. The crude 2,8-diaminodibenzofuran obtained by addition of ammonium hydroxide to

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

the extraction liquors weighed 6.0 g. (15%). The neutral residue was recrystallized from toluene to give a good recovery of starting material. In a second experiment, the dibromo compound was added as a suspension in benzene, but the yield was not improved.

Preparation of 2,8-Diaminodibenzofuran Picrate

A solution of 1.1 g. (0.0048 mole) of picric acid (90%) in 50 ml. of hot absolute ethanol was added slowly to a boiling solution of 1 g. (0.005 mole) of 2,8-diaminodibenzofuran in 100 ml. of absolute ethanol. When about half the picric acid solution had been added, the picrate began to separate in very small plates. Refluxing was continued for several minutes after the addition was complete; then the solution was cooled and filtered. The product was insoluble in ethanol, petroleum ether, and benzene. The yield was 1.82 g. (98.4%) of bright yellow plates which turned black at about 260° and melted with decomposition at about 278°.

Anal. Calcd. for $C_{12}H_{10}ON_2 \cdot C_6H_3O_7N_3$: N, 16.39. Found: N, 16.36 and 16.58.

When the picrate was formed in a larger volume of ethanol (200 ml.) the plates were orange-red in color.

Preparation of 2,8-Diacetaminodibenzofuran

A. Five grams (0.025 mole) of 2,8-diaminodibenzofuran (m.p., 211-212°) was dissolved in 50 ml. of glacial acetic acid, and 50 ml. of water added. Then 6 ml. (0.06 mole) of acetic anhydride was added slowly with vigorous stirring. Six and nine-tenths grams (97%) of white needles melting at 298-299° separated. A recrystallization from glacial acetic acid raised the melting point to 299-300°. The 2,8-diacetaminodibenzofuran is only slightly soluble in ethanol, acetone, or toluene, but may be dissolved in glacial acetic acid or dioxane.

B. Forty grams of crude 2,8-diaminodibenzofuran (m.p., 190-210°), as obtained from the bomb reaction without purification, was dissolved in 400 ml. of glacial acetic acid and 50 ml. of acetic anhydride added with stirring. Then 400 ml. of water was added gradually, and the stirring continued for three hours. After filtration the crude diacetamino compound was refluxed with 200 ml. of acetone. The light-tan insoluble residue melted at 297-298° and weighed 35 g. (61%). Recrystallization from glacial acetic acid raised the melting point to 299-300°.

Anal. Calcd. for $C_{16}H_{16}O_3N_2$: N, 9.93. Found: N, 9.93.

This compound has been prepared by a Beckmann rearrangement of the dioxime of 2,8-diacetyldibenzofuran (105). No analysis was reported, however, and the melting point given (258°) is more than forty degrees too low.

Bromination of 2,8-Diacetaminodibenzofuran

Seven grams (0.0248 mole) of 2,8-diacetaminodibenzofuran was suspended in 500 ml. of glacial acetic acid and 45 ml. of a molar solution of bromine in acetic acid was added dropwise. Upon working up the reaction in the usual manner 3.2 g. of bromo compound melting at 247-257° was obtained. Isomers are probably formed in this bromination for the product did not crystallize well and was purified with great difficulty. After five recrystallizations from glacial acetic acid there was obtained 1.1 g. (12.3%) of 3-bromo-2,8-diacetaminodibenzofuran which melted at 259-260°.

Anal. Calcd. for $C_{16}H_{15}O_3N_2Br$: Br, 22.3. Found: Br, 22.4.

The structure of this compound was determined by hydrolysis and deamination to give 3-bromodibenzofuran (mixed m.p.).

Hydrolysis and Deamination of 3-Bromo-2,8-diacetaminodibenzofuran

To 1.0 g. (0.0028 mole) of 3-bromo-2,8-diacetaminodibenzofuran in 30 ml. of 95% ethanol was added 30 ml. of concd. hydrochloric acid and the mixture was refluxed. A clear solution resulted upon the addition of the hydrochloric acid, but a precipitate began to form after about thirty minutes. The refluxing was continued for six hours. The precipitated dihydrochloride was separated by filtration, and a small portion of it, tested for water solubility, was found to be completely soluble. The free amine obtained by addition of ammonium hydroxide to this solution darkened at 215° and melted with decomposition at about 235°.

To a boiling solution of 0.5 g. of the dihydrochloride in 3.3 ml. of water, 3.3 ml. of 48% sulfuric acid and 16.5 ml. of 95% ethanol was added, gradually, 1.6 g. of sodium nitrite. After thirty minutes of refluxing, the reaction mixture was steam-distilled. There was obtained 0.1 g. (28.4%) of 3-bromodibenzofuran which melted at 119-120° after recrystallization from ethanol. A mixed melting point with an authentic specimen* was not depressed.

*Kindly provided by Mr. H. B. Willis

Demethylation of 3,4-Dimethoxydibenzofuran

Some crude 3,4-dimethoxydibenzofuran* was purified by distillation (b.p., 186°/6 mm.) followed by a recrystallization from petroleum ether (b.p., 30-40°). This gave long white needles which melted at 60°. The distillation proceeded smoothly and there was no evidence of decomposition.

Nine and three-tenths grams (0.04 mole) of 3,4-dimethoxydibenzofuran was refluxed for ten hours with 40 ml. of constant boiling hydrobromic acid and 32 ml. of glacial acetic acid in a flask fitted to a condenser by means of a ground-glass joint. The contents of the flask were cooled to room temperature and slowly poured into 400 ml. of water. The product separated as white plates which melted at 161-164°. The yield was 8.1 g. (99%).

Bucherer Reaction with 3,4-Dihydroxydibenzofuran

Into each of two Carius tubes was placed 3.5 g. (0.0175 mole) of 3,4-dihydroxydibenzofuran, 10 g. of sodium metabisulfite and 25 ml. of concd. ammonium hydroxide. The tubes were then filled with nitrogen, sealed, and heated at 180-190° for twenty hours. When the tubes were opened there was present long colorless needles and a dark brownish

*Kindly provided by Mr. T. H. Cook.

black tar. Air was kept away from the contents by continuous sweeping with nitrogen, and the contents were extracted with boiling 5% hydrochloric acid. After decolorization with Norite 3.0 g. (41.5%) of the amine hydrochloride was precipitated from this solution by passing in dry hydrogen chloride. The hydrochloride turned dark at 300° and did not melt at 275°. Analysis showed it to be an amino-phenol hydrochloride and the compound is probably 3-amino-4-hydroxydibenzofuran hydrochloride.

Anal. Calcd. for $C_{12}H_{10}O_2NCl$: N, 5.95. Found: N, 5.96.

The free base is extremely sensitive to air and rapidly changes from green to purple to black when exposed to the atmosphere. It is soluble in alkali, and when 0.1 g. of the hydrochloride was treated with 5% potassium hydroxide and acetic anhydride in a nitrogen-filled test tube, the acetamino-acetoxy derivative, which melted at 209-210°, precipitated.

Anal.* Calcd. for $C_{16}H_{13}O_4N$: N, 4.94. Found: N, 5.02.

The sharp melting point of the acetamino-acetoxy derivative indicates a complete preferential reaction with one of the hydroxyl groups. Since both positions ortho

*The writer is grateful to Mr. T. H. Cook for this micro-Dumas analysis.

to the 4-hydroxyl are occupied, it is very unlikely that this group would undergo a Bucherer reaction easily, if at all (see Discussion). The structures of these compounds can be definitely ascertained by comparison of the acetamino-acetoxy compound with an authentic specimen of 3-acetamino-4-acetoxydibenzofuran. Mr. T. H. Cook has prepared 3-acetamino-4-hydroxydibenzofuran by a Beckmann rearrangement of the oxime of 3-acetyl-4-hydroxydibenzofuran. The required acetoxy derivative could easily be obtained from this.

Bucherer Reaction with 1-Bromo-2-hydroxydibenzofuran

Two grams (0.0076 mole) of 1-bromo-2-hydroxydibenzofuran was heated in a sealed tube with 7.5 g. of sodium metabisulfite and 25 ml. concd. ammonium hydroxide at 185-195° for twenty hours. The product was a brownish-black tar, which was washed with water and then extracted with three 50-ml. portions of 3% hydrochloric acid at the reflux temperature. Addition of ammonium hydroxide to the combined extracts yielded 400 mg. (20%) of almost colorless needles, which melted at 115°, and showed no halogen present on sodium fusion. A recrystallization from methanol raised the melting point to 125-126°, which is the melting point of 2-aminodibenzofuran. The compound was identified as 2-aminodibenzofuran by conversion to 2-acetaminodibenzofuran

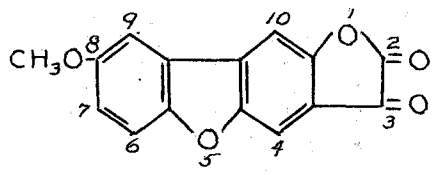
melting at 161-162°. The amorphous residue from the hydrochloric acid extraction gave a positive test for nitrogen, but a negative test for halogen on sodium fusion. No starting material was recovered.

The removal of the bromine in this reaction was unexpected, but can be explained if one assumes a fixed double bond between the 1- and 2-positions in 1-bromo-2-hydroxydibenzofuran (see Discussion).

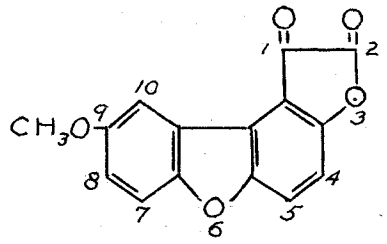
Friedel-Crafts Reaction with 2,8-Dimethoxydibenzofuran and Oxalyl Chloride

To a stirred solution of 4.56 g. (0.02 mole) of 2,8-dimethoxydibenzofuran and 5 ml. (6.7 g. or 0.053 mole) of oxalyl chloride in 50 ml. of sym-tetrachloroethane, cooled to 0° in an ice bath, was added, in small portions during a period of one hour, 6.20 g. (0.0465 mole) of aluminum chloride. The solution turned orange, then red, and finally a reddish black upon the addition of the aluminum chloride. The reaction was kept at the ice-bath temperature for six hours and then gradually allowed to rise to room temperature. After a total of twenty-four hours of stirring the solvent was removed by steam distillation and residue was treated with hot saturated sodium bisulfite solution; nothing separated when the solution was acidified with hydrochloric acid. The residue from this treatment was

refluxed with 10% sodium carbonate solution and this on acidification gave a red solid which, after crystallization from glacial acetic acid, melted at 235-250° and weighed 2.5 g. Four more recrystallizations from the same solvent gave 500 mg. (9.7%) of orange-red needles, m.p. 278°, with decomposition. Repeated treatments with Norite failed to remove the color. This compound gave a dark purple color with ferric chloride solution and is probably a lactone of one of the following structures:



8-Methoxybenzofuro[5,6-b]benzofuran-2,3-dione



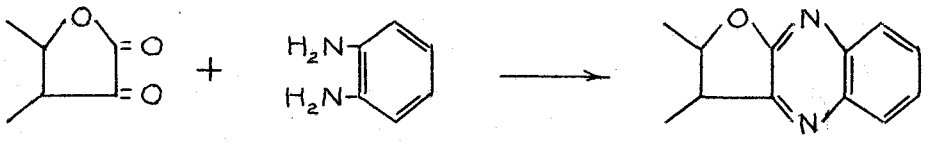
9-Methoxybenzofuro[5,4-b]benzofuran-1,2-dione

Anal. Calcd. for $C_{15}H_8O_5$: Methoxyl, 11.55; neutralization equiv., 268. Found: Methoxyl, 11.62 and 11.20; neutralization equiv., 266.

The carbon and hydrogen analyses, however, did not check this formula (Calcd.: C, 67.2; H, 3.02. Found: C, 64.2 and 64.3; H, 3.94 and 3.94), and should be repeated. The compound burns with difficulty (chars and "flashes") and this may be the reason for the anomalous result.

Staudinger (107) obtained a lactone of this type as the principle product in the reaction of 2,7-dimethoxy-naphthalene with oxalyl chloride and aluminum chloride.

When an acetic acid solution of the lactone was refluxed with an alcoholic solution of o-phenylenediamine, a very insoluble quinoxaline derivative precipitated as red needles, m.p. 323-325°.



Anal. Calcd. for $C_{21}H_{12}O_3N_2$: N, 8.24. Found: N, 8.12.

When an excess of o-phenylenediamine was added to the combined mother liquors from the recrystallizations of the lactone, 500 mg. of the same quinoxaline derivative precipitated after a few hours (mixed m.p.).

(107) Staudinger, Helv. Chim. Acta, 4, 334 (1921).

Six-tenths of a gram of the lactone was treated with an excess of diazomethane in dry ether. The ester obtained by evaporation of the ether and subsequent crystallization from acetic acid was deep yellow in color and melted at 206-207°. The yield of methyl 2,8-dimethoxy-1(or 3-)-dibenzofuryl-a-oxoacetate was 350 mg. (49.8%).

Anal. Calcd. for $C_{17}H_{14}O_6$: C, 65.00; H, 4.48. Found: C, 65.4 and 65.4; H, 4.25 and 4.10.

The ester was saponified by boiling for thirty minutes with 10% potassium hydroxide.

Carbon disulfide and nitrobenzene were found to be unsatisfactory as solvents in the reaction for the preparation of the lactone. In fact with the former solvent no appreciable reaction took place with three days of stirring at room temperature, and with the latter solvent no lactone was obtained. The only product appeared to be demethylated ketonic material.

In an orienting experiment it was found that 2,8-dihydroxydibenzofuran reacts with oxalyl chloride in tetrachloroethane under the same conditions as described for 2,8-dimethoxydibenzofuran. The quinoxaline obtained from the reaction product melted at 345-350° after recrystallization from dioxane.

Preparation of 5,5'-Dibromo-2,2'-dimethoxybiphenyl

To 34.4 g. (0.10 mole) of the dibromo-2,2'-dihydroxybiphenyl, prepared in accordance with the directions of Diels and Bibergeil (108) and dissolved in 106 ml. (0.265 mole) of 10% sodium hydroxide, was added, dropwise, 22 ml. (29.6 g. or 0.235 mole) of dimethyl sulfate. When all of the dimethyl sulfate had been added, the mixture was refluxed for an additional ninety minutes. Upon cooling, there was obtained 34 g. (92%) of soft white needles, m.p. 125-128°. Recrystallization from ethanol raised the melting point to 128-129°.

Anal. Calcd. for $C_{14}H_{12}O_2Br_2$: Br, 43.00. Found: Br, 43.04 and 43.17.

The structure of this compound will be definitely established when it is converted into the corresponding dimethyl-dimethoxybiphenyl of Sugii and Shindo (53).

Preparation of 5,5'-Dibromo-2,2'-diacetoxybiphenyl

Ten grams (0.029 mole) of the dibromo-2,2'-dihydroxybiphenyl was suspended in 25 ml. of acetic anhydride and 5 drops of concd. sulfuric acid was added. The resulting solution was heated for an hour on a steam bath, then thoroughly cooled, and finally slowly poured into 200 ml.

(108) Diels and Bibergeil, Ber., 35, 302 (1902).

of cold water. There was obtained, after recrystallization from ethanol 9.7 g. (78%) of the diacetoxy compound which melted at 105-106°.

Anal. Calcd. for $C_{16}H_{12}O_4Br_2$: Br, 37.40. Found: Br, 37.41 and 37.50.

The structure of this compound will be established automatically when that of the dibromo-dimethoxy compound is proved.

D I S C U S S I O N

Evidence for the Assigned Structures

The establishment of the structures of the compounds resulting from the Fries rearrangement with 2-acetoxydibenzofuran is presented schematically in Diagram I. The structure of 2-hydroxydibenzofuran followed from its preparation from 2-bromodibenzofuran. The two hydroxy ketones obtained in the rearrangement reaction were methylated, and the methoxy ketone which melted at 113-114° was oxidized by means of sodium hypoiodite to an acid, which was identical with the acid obtained by Gilman and Van Ess (11) by carbonation of the Grignard of 3-bromo-2-methoxydibenzofuran. Accordingly, this ketone was 3-acetyl-2-methoxydibenzofuran. The isomeric ketone then could be only 1-acetyl-2-methoxydibenzofuran, since the Fries rearrangement involves only ortho and para positions and the para position was blocked. The proof of structure of the 1-bromo-2-hydroxydibenzofuran from which 2-aminodibenzofuran was obtained by the Bucherer reaction has been presented in detail by Gilman and Van Ess (11).

DIAGRAM I. TRANSFORMATIONS INVOLVING ONE BENZENE NUCLEUS

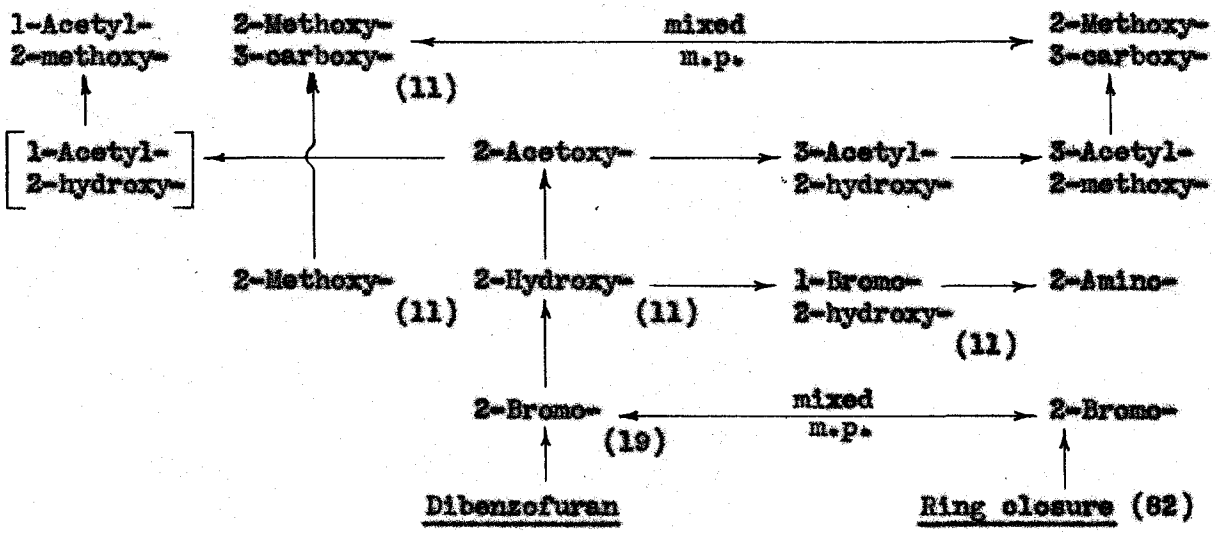


Diagram II presents the relationships between the 4-substituted dibenzofurans. The 4-methyldibenzofuran obtained by Kruber (34) by ring closure was found to be identical with the methyldibenzofuran obtained from metalation of dibenzofuran followed by treatment of the metalation product with dimethyl sulfate (7). Also, the acid obtained from oxidation of Kruber's 4-methyldibenzofuran was found to be identical with the acid obtained by metalation of dibenzofuran followed by carbonation (6). This definitely established the fact that metalation occurred in the 4-position, and the structures of all of the 4-monosubstituted dibenzofurans followed from their preparations from the metalation product, by direct or indirect means.

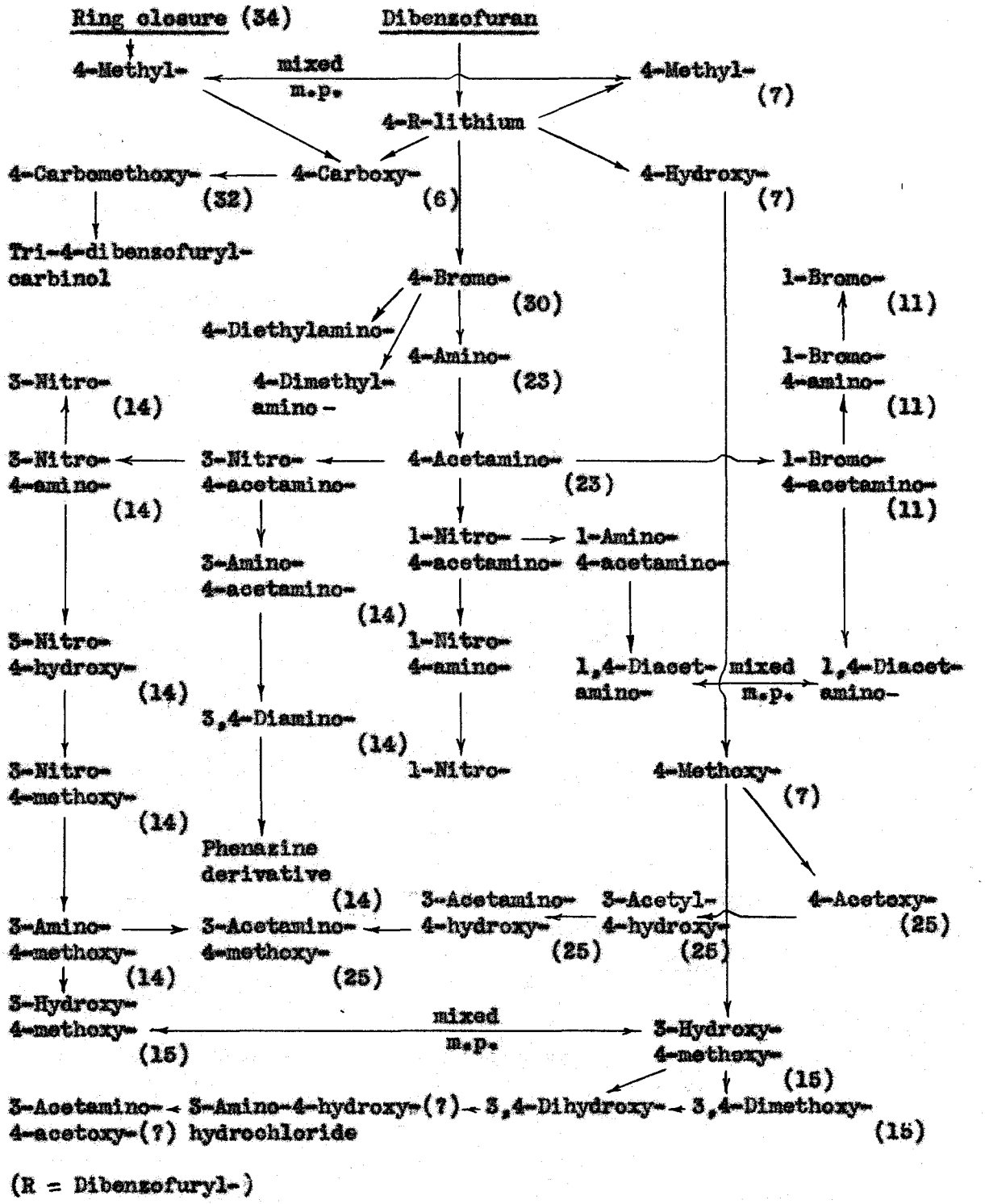
Nitration of 4-acetaminodibenzofuran at low temperatures gave 3-nitro-4-acetaminodibenzofuran. This structure was established as follows: The compound was hydrolyzed to the free nitro-amine, a part of which was deaminated to give 3-nitrodibenzofuran. Another portion was reduced to the diamine and treated with o-phenylenediamine. The formation of a phenazine derivative proved that the two amino groups were ortho to each other and that the original nitro group was in the 3- and not in the 7-position (14). The proofs of structure of all 3,4-substituted dibenzofurans rest on these reactions. Replacement of the amino group by hydroxyl in 3-nitro-4-aminodibenzofuran gave 3-nitro-4-hydroxydibenzofuran (14). This was methylated, reduced and diazotized, and the diazonium salt was hydrolyzed to yield 3-hydroxy-4-methoxydibenzofuran (15).

Nitration of 4-acetaminodibenzofuran at 70° in glacial acetic acid gave 1-nitro-4-acetaminodibenzofuran. The structure of this compound was established in the following way. Hydrolysis and deamination gave a mononitro-dibenzofuran different from the known 3-nitro- and 2-nitrodibenzofurans. Reduction and acetylation gave a diacetaminodibenzofuran which was the same as the compound prepared by amination and acetylation of 1-bromo-4-acetaminodibenzofuran. The structure of 1-bromo-4-acetaminodibenzofuran had been previously established by Van Ess (10), who had

removed the acetamino group and obtained a bromo-dibenzofuran different from the known 2-, 3-, and 4-bromodibenzofurans. A 9-bromo-4-acetaminodibenzofuran would show these same reactions, but the possibility of heterosubstitution was excluded on the basis of the known homonuclear directive influence of the acetamino group. This conclusion is supported by the behavior of 1,4-diaminodibenzofuran towards air. This diamine, like the 2,3- and 3,4-diaminodibenzofurans, colors rapidly in air. The heterosubstituted 2,7-, 3,7- and 2,8- diaminodibenzofurans are very stable in air.

The structure of the amino-hydroxy dibenzofuran which resulted from the Bucherer reaction with 3,4-dihydroxydibenzofuran requires one step for its final proof. The 3-acetamino-4-hydroxydibenzofuran prepared by Cook (25) may be converted to 3-acetamino-4-acetoxydibenzofuran, and this then compared with the acetamino-acetoxy dibenzofuran prepared from the above-mentioned product of the Bucherer reaction. The authentic 3-acetamino-4-hydroxydibenzofuran was prepared as follows: 4-acetoxydibenzofuran was subjected to a Fries rearrangement, and the oxime of the resulting hydroxy ketone was converted to the acetamino-hydroxy compound by means of a Beckmann rearrangement. Methylation of this acetamino-hydroxy compound gave the same compound as that formed by acetylation of 3-amino-

DIAGRAM II. TRANSFORMATIONS INVOLVING ONE BENZENE NUCLEUS cont'd.



(R = Dibenzofuryl-)

4-methoxydibenzofuran (25).

The basic compound for the transformations illustrated in Diagram III is 2,8-dibromodibenzofuran, which was first prepared by Hoffmeister (71), who dibrominated dibenzofuran in carbon disulfide solution. Its structure was established by a reliable phenyl ether ring closure (82). Amination, followed by acetylation, gave 2,8-diacetaminodibenzofuran, and this on bromination gave 3-bromo-2,8-diacetaminodibenzofuran. The structure of the latter compound was determined by hydrolysis and deamination to give 3-bromodibenzofuran. The structure of 3-bromodibenzofuran had been previously established by its synthesis from a phenyl ether ring closure (82).

Catalyzed hydrolysis of 2,8-dibromodibenzofuran with concentrated sodium hydroxide solution at 240° gave 2,8-dihydroxydibenzofuran. This on methylation gave 2,8-dimethoxydibenzofuran, which upon dibromination yielded two isomeric dibromo-dimethoxy compounds. On the assumption that, of the three theoretically possible isomers, these two were the symmetrical ones, the lower melting isomer was tentatively designated as 1,9-dibromo-2,8-dimethoxydibenzofuran and the higher melting isomer was tentatively designated as 3,7-dibromo-2,8-dimethoxydibenzofuran. This designation was in accord with the general observations of the melting

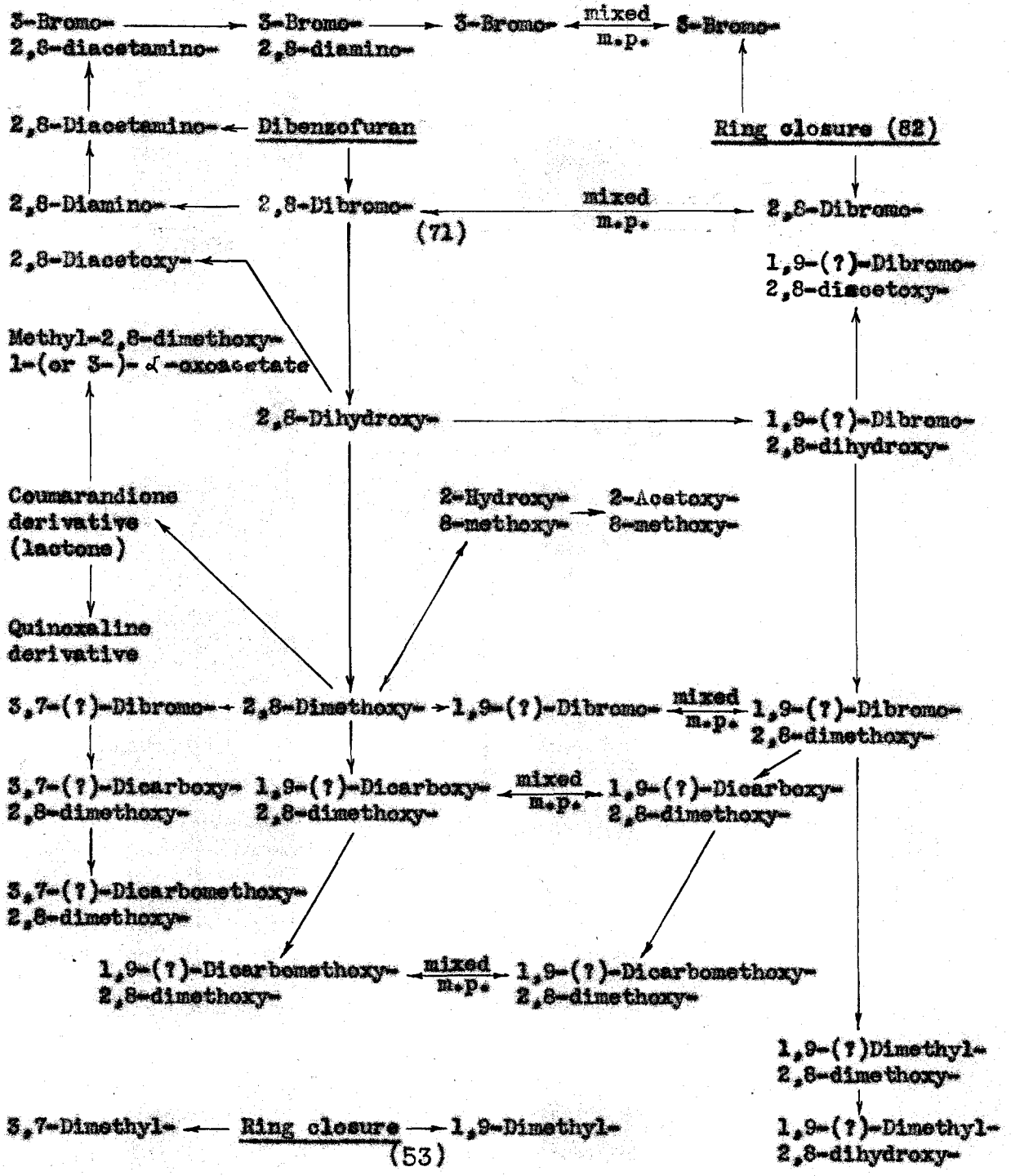
points of 1- and 3-isomers in dibenzofurans, and in particular, with the melting points of the isomeric 1- and 3-bromo-2-methoxydibenzofurans (10) (11). Direct dibromination of 2,8-dihydroxydibenzofuran, followed by methylation, gave as the sole product a compound identical with the lower melting (1,9-) isomer from the dibromination of 2,8-dimethoxydibenzofuran. This was in agreement with the earlier observation that 2-hydroxydibenzofuran directs bromine to the 1-position.

Dimetalation of 2,8-dimethoxydibenzofuran gave the same di-acid as that formed from the 1,9-(?)-dibromo-2,8-dimethoxydibenzofuran *via* the interconversion reaction ("metalation") and carbonation. The identity of these acids was confirmed by mixed melting points of the acids themselves and of their methyl esters. This dimetalation, too, was in accord with the fact that metalation of 2-methoxydibenzofuran yielded, as the principal product, the 1-metal derivative (58). The 3,7-(?)-dibromo-2,8-dimethoxydibenzofuran was converted into the corresponding di-acid *via* the interconversion reaction. The final proofs of structure of these compounds will be complete when the dibromo-dimethoxy compounds are converted to the corresponding dimethyldibenzofurans prepared by ring closure. With this purpose in view the 1,9-(?)-dibromo-2,8-dimethoxydibenzofuran has been treated with *n*-butyllithium, followed by dimethyl sulfate, to yield 1,9-(?)-dimethyl-2,8-dimethoxydibenzofuran. This

by demethylation gave 1,9-(?)-dimethyl-2,8-dihydroxydibenzofuran. The final step in this series will involve removal of the hydroxyl groups and comparison with an authentic sample of 1,9-dimethyldibenzofuran. At the present time attempts to remove the hydroxyls by distillation of the dimethyl-dihydroxy compound with zinc dust are in progress.

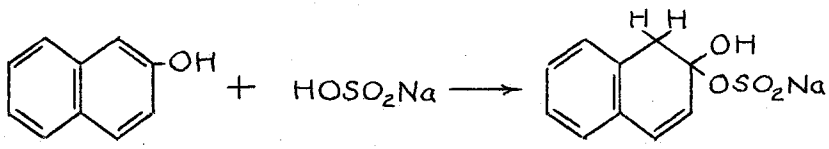
The coumaranedione derivative arising from the interaction of oxalyl chloride with 2,8-dimethoxydibenzofuran could result from substitution in the 1- or the 3-position. If cleavage of the methoxyl by aluminum chloride took place prior to substitution, the reaction probably involved the 1-position, for bromination of 2-hydroxydibenzofuran replaced the 1-hydrogen by bromine (11). In all instances which have been investigated with dibenzofuran, the Friedel-Crafts reaction has been found to take the same course as bromination. The Friedel-Crafts reaction has not been attempted, however, with 2-hydroxy- or with 2-methoxydibenzofuran. It will be possible to determine definitely the structures of the lactone and its derivatives when 2,8-dimethoxy-1- and 3-dibenzofurancarboxylic acids have been prepared. The methyl 2,8-dimethoxy-1-(or 3-)-dibenzofuryl-α-oxoacetate can then be converted to one of them by hydrolysis, decarboxylation and oxidation.

DIAGRAM III. TRANSFORMATIONS INVOLVING BOTH BENZENE NUCLEI

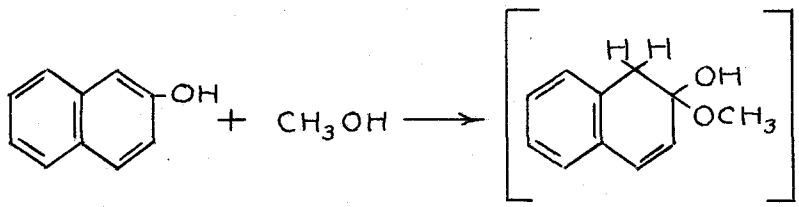


The Bucherer Reaction

Fieser (109) has postulated that the Bucherer reaction with β-naphthol takes place by preliminary addition of sodium bisulfite to the double bond between the 1- and 2-positions:



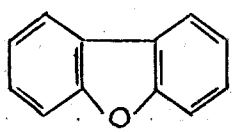
This addition complex then reacts with ammonia to give the naphthylamine. According to Fieser (109) a methyl group in the 1-position should inhibit the reaction, since the mechanism is analogous to that of etherification with alcohols:



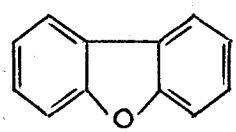
Fieser and Lathrop (110) have observed that this etherification was strongly inhibited by the presence of alkyl groups in the 1-position. Alkyl groups in the 3-position did not show this inhibitory effect.

(109) Page 87 of reference 99.
(110) Fieser and Lathrop, J. Am. Chem. Soc., 57, 1459 (1935).

Dibenzofuran resembles naphthalene more closely than it does benzene. For example, it undergoes substitution reactions such as sulfonation and nitration with great ease. Coupling of 2-hydroxydibenzofuran with benzenediazonium chloride involves the 1-position exclusively, as does the same reaction with β-naphthol. Furthermore, the hydroxydibenzofurans, such as 2,8-dihydroxydibenzofuran, undergo the Bucherer reaction readily and give high yields of amines. Phenol, under the same conditions, does not react. Fries (111) has expressed the view that the increased ease of reaction in naphthalene results from the restriction to the migration of the bonds. Although there is no conclusive evidence at present for a fixed bond structure in dibenzofuran (112), the structure [I] would best represent dibenzofuran if there is restriction to the migration of the bonds.



I.



II.

(111) Fries, Waller and Schilling, Ann., 516, 248 (1935).
(112) M. W. Van Ess (38) has shown that diazo coupling with 2- and 4-hydroxydibenzofurans involves the 1-position exclusively. This indicates double bonds between the 1,2- and 3,4-positions. However, coupling with 3-hydroxydibenzofuran involved the 2-position, indicating a double bond between the 2- and 3-positions. These observations indicate some fixity of bonds; the fixed structure assumed may depend upon the substituents present.

In structure [I] the ring systems benzene-furan-benzene are present, all of which are aromatic in character. In structure [II] the central aromatic ring has disappeared, and according to the Fries rule (113), dibenzofuran would have little tendency to exist in this form.

The failure of 1,9-dimethyl-2,8-dihydroxydibenzofuran to undergo the Bucherer reaction conforms with these ideas. The reaction of 3,4-dihydroxydibenzofuran with sodium bisulfite and ammonium hydroxide under these conditions resulted in the replacement of one of the hydroxyls by an amino group. To explain this reaction on the same basis it would be necessary to assume either that one of the hydroxyls does not exert a blocking effect or that there is a double bond between the 2- and 3-positions (112). The removal of the bromine in the Bucherer reaction with 1-bromo-2-hydroxydibenzofuran (p. 103) is in accord with the assumptions of a 1,2-double bond and the blocking effect of a substituent in the 1-position. The bromine in 1-bromo-2-naphthol is displaced in the coupling reaction with benzenediazonium salts. The mechanisms of the two reactions are believed to be similar.

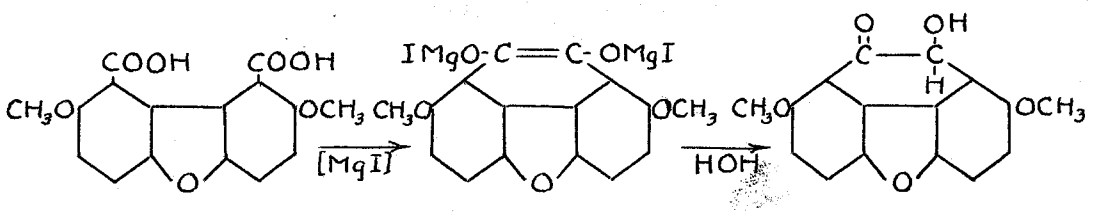
Some Possible Approaches to Bridging the 1- and 9-Positions

Cheney (15) has given a literature review of methods

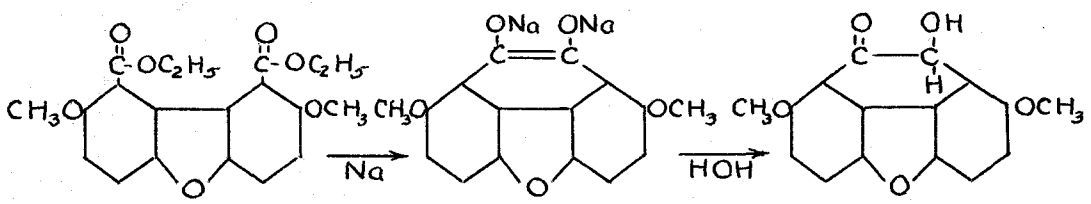
(113) Fries, Ann., 454, 121 (1927).
(114) Gomberg and Bachmann, J. Am. Chem. Soc., 50, 2762 (1928).

which might be used in effecting a bridge between the 1- and 9-positions in dibenzofuran. The recent availability of 2,8-dimethoxy-1,9-dibenzofurancarboxylic acid has suggested some new approaches. These are presented here.

Gomberg and Bachmann (114) have reported the formation of benzoins from the action of their binary system ($Mg + MgI_2$) on aromatic acids. The yields varied between 30 and 75 per cent. This reaction might be applied to 2,8-dimethoxy-1,9-dibenzofurandicarboxylic acid:



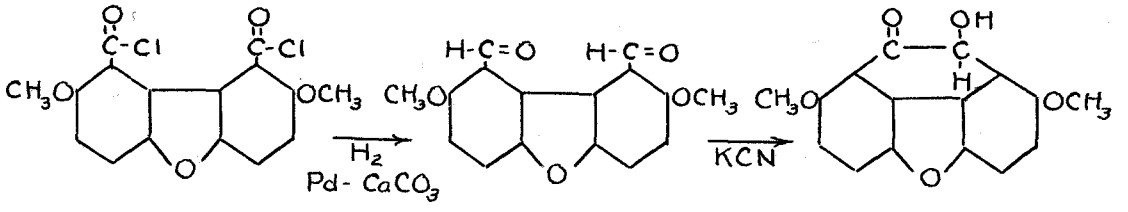
Another possible method would utilize the dimethyl ester of this acid:



Reductions of a somewhat similar nature have been described in Organic Syntheses (115).

(115) Organic Syntheses, Vol. XIII, John Wiley and Sons, Inc., New York, N. Y., 1933, p. 24.

A third method would involve the use of the di-acid chloride. This could be reduced to the di-aldehyde by the Rosenmund reaction, and the di-aldehyde could be subjected to a benzoin condensation:



Weitzenbock (116) transformed 2,2'-dialdehydobiphenyl into phenanthraquinone in 50 per cent yield by means of a benzoin condensation followed by oxidation.

There is at the present time insufficient data concerning the spatial distributions of the 1- and 9-positions in dibenzofuran to determine whether bridging reactions which are possible with biphenyls can be carried over to dibenzofuran compounds. Only a few physico-chemical measurements have been made on dibenzofuran. Bretscher (117) and Smythe and Walls (118) have determined the dipole moment of dibenzofuran. The absorption spectra (119), the Raman spectra (120) and the magnetic birefringence (121) of dibenzofuran have also been studied. An electron diffraction pattern

(116) Weitzenbock, Monatsh., 34, 193 (1913). See, also, Mayer, Ber., 45, 1105 (1912); ibid., 47, 406 (1914).
(117) Bretscher, Helv. Phys. Acta, 2, 257, (1929).
(118) Smythe and Walls, J. Am. Chem. Soc., 54, 3230 (1932).
(119) Charlampowicz and Marchlewski, Bull. intern. acad. polonaise, A, 376 (1930) [C. A., 25, 5096 (1931)].
(120) Donzelot and Chaix, Compt. rend., 202, 851 (1936).
(121) John, Trans. Faraday Soc., 34, 275 (1938).

of a compound like 1,9-dibromo-3,8-dihydroxydibenzofuran should furnish the additional data necessary for the construction of a model.

Pharmacological Tests*

Of the one hundred and seven derivatives of dibenzofuran which have been submitted from this laboratory to be tested for analgesic action, nineteen (6 per cent) have shown some analgesic activity. The compounds which have been submitted for testing have been listed in a series (HD) which includes also some other heterocycles such as dibenzothiophene, benzofuran, phenanthridine and phenoxthin. Parker (13) has tabulated the pharmacological data pertaining to the first seventy-eight compounds of the HD series, and Cheney (15) has presented the data on HD numbers of 79 to 106. The results with the other members of the series which have been tested to date are listed in Table II. In this table, M.L.D. (minimal lethal dose) is that dose which killed 50 per cent of the animals tested (white mice). The dose is expressed in terms of milligrams of substance per gram of body weight of the animal.

*These tests were carried out in the laboratories of Parke, Davis and Company, Detroit, Michigan.

(122) Eddy, J. Pharmacol., 58, 159 (1936). See, also, reference 17.

Eddy (122) has made a comparison of the analgesic effect on cats of analogous phenanthrene and dibenzofuran derivatives. The dibenzofuran analogs were found to be more analgesic, but also more toxic. The most active analgesic was found to be 3-aminodibenzofuran (No.7 in the HD series). When this comparison was carried over to include carbazole derivatives (123) 3-aminodibenzofuran was still the most active substance, although it was also more toxic and more emetic than the aminocarbazoles. Since 3-aminodibenzofuran (HD 7) and its N-ethyl derivative (HD 19) had been reported inactive in the tests with white mice it was thought advisable to resubmit them. In the repeated tests, the former was found to elicit a slight analgesic action, while with the latter it was questionable if any analgesic action was present at all. Both compounds were inactive towards guinea pigs in the repeated tests. Apparently cats respond differently to some substances than do white mice.

In the tests with carbazole derivatives (123) the introduction of a second amino group into the nucleus was found to decrease the analgesic activity of the aminocarbazoles. The opposite effect has been observed with dibenzofuran. Thus, 2-aminodibenzofuran (HD 3) is inert, while 2,8-diaminodibenzofuran (HD 106) and 2,7-diaminodibenzofuran (HD 113) show some analgesic action. Likewise, both 3,7-

(123) Eddy, J. Pharm. Exp. Therap., 65, 294 (1939).

(HD 111) and 2,7-diaminodibenzofurans appear to be more analgesic than 3-aminodibenzofuran (HD 7).

Some furan derivatives which have been tested for morphine-like action were found to be inert (134).

(134) Henecka, Med. u. Chem. Abhandl. med.-chem. Forschungsstätten I. G. Farbenind., 3, 403 (1936) /Chem. Zentr., I, 1146 (1937)/.

TABLE II.

HD No.	Name of Compound	M.L.D. in mg. per g.
7	3-Aminodibenzofuran hydrochloride	0.15*
19	3-Ethylaminodibenzofuran	0.09*?
107	2,8-Dimethoxydibenzofuran	----
108	2,3-Diaminodibenzofuran dihydrochloride	0.15
109	4-Diethylaminodibenzofuran hydrochloride	0.22
110	1,4-Diaminodibenzofuran dihydrochloride	0.30**
111	3,7-Diaminodibenzofuran dihydrochloride	0.25*
113	2-Bromo-3-aminodibenzofuran	0.15
113	2,7-Diaminodibenzofuran dihydrochloride	0.50*,**
114	1-Bromo-2-hydroxydibenzofuran	0.25
115	2-Amino-3-bromodibenzofuran	0.15
116	1-Allyl-2-methoxydibenzofuran	0.12
117	1-Bromo-4-aminodibenzofuran	0.15
118	Diazomethyl 4,6-dimethoxyl-1-dibenzofuryl ketone	0.15
119	1-α-Aminoethyl-4-methoxydibenzofuran hydrochloride	0.12
120	4-Dimethylaminodibenzofuran	0.18*
121	4-Dibenzofurancarboxylic acid amide	0.15

* Slight analgesic action in white mice.
*? Very slight, if any, analgesic action.
** Toxic to guinea pigs.

TABLE II (continued)

HD No.	Name of Compound	M.L.D. in mg. per g.
122	4-Bromodibenzofuran	0.12*
123	2-Bromodibenzofuran	0.18*,**

S U M M A R Y

I. The known 1-, 4-, 6- and 9-substituted dibenzofurans have been tabulated, and methods of preparing them have been reviewed.

II. The nitration of 4-acetaminodibenzofuran has been studied and the structures of the nitration products have been established.

III. Convenient methods have been worked out for the preparations of 2,8-dihydroxy- and 2,8-diaminodibenzofurans and some of their derivatives. Among these are 1,9-dibromo-2,8-dimethoxydibenzofuran and 2,8-dimethoxydibenzofuran-1,9-dicarboxylic acid.

IV. The evidence for restricted migration of bonds in dibenzofuran has been discussed.

V. The results of pharmacological studies with dibenzofuran derivatives have been listed.

B I B L I O G R A P H Y*, **

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*For references 1-81 see Oatfield (1). This supplements the bibliography for dibenzofuran begun by Oatfield and includes the published work up to July, 1939.

**The writer is grateful to Mr. H. B. Willis for his help in compiling this bibliography.

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