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Derivatives of 2- and 2,8-substituted dibenzofurans

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DERIVATIVES OF 2- AND 2,8-SUBSTITUTED DIBENZOFURANS

by

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INTRODUCTION

The interest, in this laboratory, in dibenzofuran (I) chemistry[1] was first aroused in the quest for a convenient source of furan-tetracarboxylic acid. At first it was hoped that the oxidative degradation of dibenzofuran would furnish an inexpensive and convenient source of this compound. When dibenzofuran was found very resistant to attack by oxidizing agents, a search was instigated for dibenzofuran derivatives possessing amino or hydroxyl groups that might aid the ease of oxidation. In this search it was found that, while several substitution reactions had been carried out with dibenzofuran, structural proofs had never been established for many of the most common substitution products. Thus an urgent need was felt for fundamental orientation studies in view of the confused condition of the literature on dibenzofuran.

In addition, the occurrence of a dibenzofuran nucleus as an important part of the complex morphine molecule (II) suggested some dibenzofuran compounds might possess analgesic action. This hope of obtaining compounds which would possess a morphine-like action was also attended by the hope that these compounds would not be habit-forming. Derivatives of phenanthrene (III)[2], also an important portion of the

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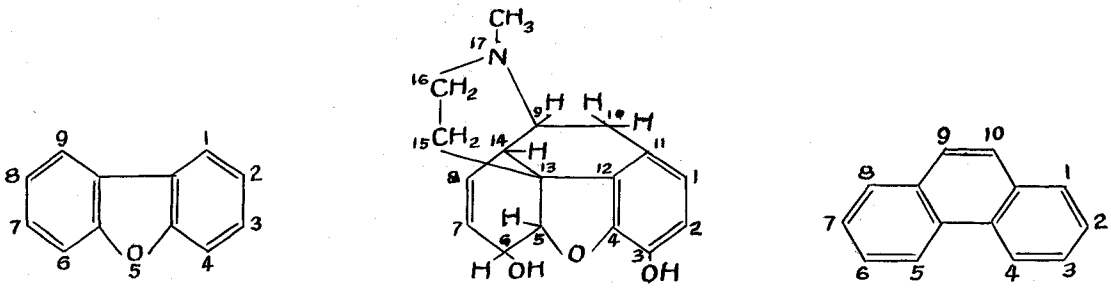
[1] Oatfield, Thesis, Iowa State College (1933).
[2] Eddy, J. Pharmacol., 48, 183 (1933).

morphine molecule, had already been shown to have analgesic action.



Two dibenzofuran derivatives had shown some analgesic activity.[3] It was hoped, furthermore, by a systematic examination of a number of dibenzofuran compounds for physiological action, that correlations between chemical constitution and physiological action might be formulated.[4]

The work in this field has been very satisfactorily reviewed by previous workers in these laboratories in orientation of dibenzofuran compounds[5,6,7,8,9] and studies on pharmacologically active dibenzofuran

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[3] Mayer and Krieger, Ber., 55, 1650 (1922).
[4] Bywater, Doctoral Dissertation, Iowa State College (1934).
[5] Hayes, Thesis, Iowa State College (1934).
[6] Van Ess, M.W., Doctoral Dissertation, Iowa State College (1936).
[7] Van Ess, P.R., Doctoral Dissertation, Iowa State College (1936).
[8] Cheney, Doctoral Dissertation, Iowa State College (1938).
[9] Swislowsky, Doctoral Dissertation, Iowa State College (1939).

compounds.[4,10,11,12,13,14]

Studies on dibenzofuran have shown that by direct nuclear substitution reactions the 2-, 3-, 7-, and 8-positions can readily be attacked. Metalation has provided the only method for introduction of a variety of substituents into the 4-, and 4,6-positions.[15] From the point of view of closer analogy to the morphine molecule the most important positions in the dibenzofuran nucleus are the 1-, 4-, 6-, and 9-positions.[8,9] Nitration[9] and bromination[16] of 4-acetamino-dibenzofuran involved the 1-position. These same reactions with 4-hydroxy-[16] and 4-methoxydibenzofuran[13,17] also introduced a substituent into the 1-position. An excellent method for introduction of substituents into the 1-, and 9-positions[8] involved the tedious and costly preparation of 4,6-dimethoxydibenzofuran.

To circumvent the difficulties of this method, Swislowsky[9] had studied the use of 2,8-derivatives as a source of 1-, or 1,9-derivatives. Bromination of 2,8-diacetaminodibenzofuran[9] gave only 2,8-diacetamino-3-bromodibenzofuran. However, Parker had shown that bromination of

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[10]Kirkpatrick, Doctoral Dissertation, Iowa State College (1935).
[11]Smith, Doctoral Dissertation, Iowa State College (1936).
[12]Bradley, Doctoral Dissertation, Iowa State College (1937).
[13]Parker, Doctoral Dissertation, Iowa State College (1937).
[14]Cook, Doctoral Dissertation, Iowa State College (1940).
[15]Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
[16]Gilman and Van Ess, ibid., 61, 1365 (1939).
[17]Gilman, Jacoby, and Swislowsky, ibid., 61, 954 (1939).

2-hydroxydibenzofuran gave 1-bromo-2-hydroxydibenzofuran.[13] Dibromination of 2,8-dihydroxydibenzofuran[9] yielded a product tentatively designated as 1,9-dibromo-2,8-dihydroxydibenzofuran. From the dibromination of 2,8-dimethoxydibenzofuran[9] were obtained two products. One was identical with the methylation product of the 1,9-dibromo-2,8-dihydroxydibenzofuran. The other was tentatively designated as 3,7-dibromo-2,8-dimethoxydibenzofuran.

The objectives of this work were to clarify the structures of these dibromination products; to prepare other derivatives of 2,8-substituted dibenzofurans; and to prepare certain derivatives of dibenzofuran which might possess pharmacological activity.

HISTORICAL

In the following pages are tabulated all of the 2- and 2,8-substituted dibenzofurans which have been reported. The arrangement is the same as that adapted by Swislowsky.[9] The compounds are arranged in sections according to the number of substituents, the mono-substituted derivatives being in the first section. In each section the compounds have been arranged in alphabetical order. The arrangement, following the alphabetical order, is according to the position of the first substituent mentioned. Wherever the exact position of a substituent is not known, this has been indicated by the letter "x" in place of a number.

Because of the task of compiling this table, only derivatives of dibenzofuran have been included. The more complex systems containing a dibenzofuran nucleus have been omitted. Only the major references to each compound are given. As far as possible references are given to the best available preparation of each compound and also to the proof of its structure.

The naming and numbering of all compounds have been made to conform with the usage in the latest annual indices of Chemical Abstracts.

Table 1. Dibenzofurans with Substituents in the 2- and 2,8-Positions

Name of compound	M.P.	Reference
MONOSUBSTITUTED DIBENZOFURANS		
2-Acetaminodibenzofuran	161.5-162.5	(18)
2-(γ-Acetamino-n-propyl)-dibenzofuran	120	(3)
2-Acetoxydibenzofuran	115-116	(19)
2-Acetyldibenzofuran	68 b.p. 220-228 /18 mm.	(20) (3, 21)
2-Acetyldibenzofuran oxime	167	(21)
2-Allyloxydibenzofuran	b.p. 178-180 / 4 mm.	(16)
2-ω-Aminoacetyldibenzofuran hydrochloride	254-255	(23)
2-Aminodibenzofuran	128	(22)
2-(α-Aminoethyl)-dibenzofuran hydrochloride	222-223	(24)

[18] Gilman, Brown, Bywater, and Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).
[19] Swislowsky, Iowa State Coll. J. Sci., 14, 92 (1939) [C. A., 34, 6273 (1940)].
[20] Galewsky, Ann., 264, 189 (1891).
[21] v. Braun, Ber., 55, 3761 (1922).
[22] German patent 591,213 [C. A., 28, 2566 (1934)].
[23] Mosettig and Robinson, J. Am. Chem. Soc., 57, 2186 (1935).
[24] Gilman, Parker, Bailie, and Brown, J. Am. Chem. Soc., 61, 2836 (1939).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-(β-Aminoethyl)-dibenzofuran	b.p. 167-170 / 2 mm.	(10, 25)
2-(β-Aminoethyl)-dibenzofuran hydrochloride	278	(10, 25)
(β-Amylaminoethyl) 2-dibenzofurancarboxylate	160	(26)
2-Arsenosodibenzofuran	>250	(27)
2-Benzoyl-x-carbomethoxydibenzofuran	189-190	(28)
2-Benzoyldibenzofuran	167-168 135-136	(29) (28)
2-Benzoyldibenzofuran benzoyloxime	248	(29)
2-Benzoyl-x-dibenzofurancarboxylic acid	265-266	(28)
2-Benzoyldibenzofuran oxime	234-235 182-183	(29) (28)
Bi-(2-dibenzofuryl)	201-202	(28)
Bis-(2-dibenzofuran)glycolic acid	248	(30)
Bis-(2-dibenzofuryl)-diketone	236-237	(30)

[25] Kirkpatrick, Iowa State Coll. J. Sci., 11, 75 (1938) [C. A., 31, 1800 (1937)].
[26] Burtner and Lehmann, J. Am. Chem. Soc., 62, 527 (1940).
[27] Skiles and Hamilton, J. Am. Chem. Soc., 59, 1006 (1937).
[28] This thesis.
[29] Borsche and Bothe, Ber., 41, 1940 (1908).
[30] Hinkel and Beynon, J. Chem. Soc., 778 (1937).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-(ω-Bromoacetyl)-dibenzofuran	106-107	(23) (31)
2-Bromodibenzofuran	110	(3) (32)
2-(β-Bromoethyl)-dibenzofuran	62-62.5 b.p. 179-180 / 2-3 mm.	(31)
2-(2-Carbomethoxybenzoyl)-dibenzofuran	99-103	(33)
2-Carbomethoxydibenzofuran	82-83	(34)
2-Carbomethoxy-7-nitrodibenzofuran	239-240	(24)
2-(2-Carboxybenzoyl)-dibenzofuran	203-204	(33) (35)
2-(2-Carboxybenzoyl)-dibenzofuran oxime anhydride	203-206	(33)
2-(2-Carboxybenzoyl)-dibenzofuran phenylhydrazone anhydride	221-223	(33)
2-(ω-Chloroacetyl)-dibenzofuran	109-110 b.p. 206-208 / 1-2 mm.	(31)
2-Chlorodibenzofuran	106	(18) (32)

[31] Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1123 (1935).
[32] Mac Combie, Mac Millan, and Scarborough, J. Chem. Soc., 529 (1931).
[33] Stümmer, Monatsch., 28, 411 (1907).
[34] Gilman, Langham, and Willis, J. Am. Chem. Soc., 62, 346 (1940).
[35] Borsche and Schacke, Ber., 56, 2498 (1923).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Chloromercuridibenzofuran	236.5-237	(36)
2-Chloromethyldibenzofuran	78.5-79.5	(10) (25)
(γ-Chloropropyl) 2-dibenzofurancarboxylate	85	(26)
2-Dibenzofuranacetonitrile	102.5-103.5	(10, 25)
2-Dibenzofuranacrylic acid	239-240	(30)
2-Dibenzofuranarsonic acid	350	(37)
2-Dibenzofuranarsonic acid monohydrate	213-214	(37)
2-Dibenzofuran-p,p'(-bis-dimethylamino)-diphenylmethane	172	(30)
2-Dibenzofuranbutyric acid	112-113	(3, 24)
2-Dibenzofuranbutyric acid amide	157	(3)
2-Dibenzofuranbutyric acid chloride	b.p. 270-272 / 10-12 mm.	(3)
2-Dibenzofurancarboxaldehyde	68	(30)
2-Dibenzofurancarboxaldehyde oxime	129	(30)
2-Dibenzofurancarboxaldehyde phenylhydrazone	162	(30)
2-Dibenzofurancarboxaldehyde semicarbazone	240	(30)

[36] Gilman, Smith, and Oatfield, J. Am. Chem. Soc., 56, 1414 (1934).
[37] Davies and Othen, J. Chem. Soc., 1236 (1936).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Dibenzofurancarboxanilide	131	(30)
2-Dibenzofurancarboxylic acid	246-247	(3)
2-Dibenzofurancarboxylic acid diethylamide	77-78	(28)
2-Dibenzofuran-γ-ketobutyric acid	184-185	(3, 24)
2-Dibenzofuran-γ-ketobutyric acid hydrazide	122-123	(3)
2-Dibenzofuranmethylenemalonic acid	213 dec.	(30)
2-Dibenzofuranphosphinic acid	125	(37)
2-Dibenzofuranpropylamine hydrochloride	219-220	(3)
2-Dibenzofuranpropylurethane	73-74	(3)
2-Dibenzofuransulfinic acid	-	(36)
2-Dibenzofuransulfonic acid	>300 dec.	(21, 36)
2-Dibenzofuransulfonyl chloride	140	(36)
2-Dibenzofuroyl-2-dibenzofurylcarbinol	130	(30)
6-(2-Dibenzofuryl)-4,5-dihydro-3-pyridazinone	199-200	(3)
6-(2-Dibenzofuryl)-3-pyridazone	259-260	(3)
2-Dibenzofuryl-triphenyllead	158.5-159.5	(38)
2-Dichlorophosphinodibenzofuran	b.p. 245-250 / 25 mm.	(37)

[38]Gilman, Bywater, and Parker, J. Am. Chem. Soc., 57, 885 (1935).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-(α-Diethylaminoethyl)-dibenzofuran picrate	173-174	(24)
Diethylaminoethyl 2-dibenzofuran-acrylate hydrochloride	185	(26)
2-(β-Diethylaminoethyl)-dibenzofuran hydrochloride	192-193 b.p. 169-170 / 2 mm.	(31)
1,2-Dihydro-2-dibenzofurancarboxylic acid	278-279	(39)
2-(β-Dimethylaminopropionyl)-dibenzofuran	88-89	(24)
2-(β-Dimethylaminopropionyl)-dibenzofuran hydrochloride	194-196	(24)
2-(γ-Dimethylaminopropyl)-dibenzofuran hydrochloride	195-197	(3)
2-(γ-Dimethylaminopropyl)-dibenzofuran methiodide	210-211.5	(40)
2-(γ-Dimethylaminopropyl)-dibenzofuran picrate	164-165	(40)
2-Ethyldibenzofuran	b.p. 310 b.p. 218-226 / 15 mm.	(35)
Ethyl 2-dibenzofuranbutyrate	b.p. 260 / 10 mm.	(3)

[39]Gilman and Bradley, J. Am. Chem. Soc., 60, 2333 (1938).
[40]Mosettig and Robinson, J. Am. Chem. Soc., 57, 902 (1935).

Table 1. (Continued)

Name of compound	M.P.	Reference	
Ethyl ether of chloromethyl-2-dibenzofurancarbinol	58-59 b.p. 204-206 / 6 mm.	(31)	
Ethyl ether of piperidinomethyl-2-dibenzofurancarbinol	175	(31)	
Ethyl 1,2,3,4-tetrahydro-8-dibenzofuranbutyrate	b.p. 253-255	(3)	
2-(Guanylguanido)-dibenzofuran	175	(41)	
1-Hydroxy-2-acetyl-4-methoxy-dibenzofuran	127.5-128	(14)	Di-subst.
1-Hydroxy-2-acetyl-4-methoxy-dibenzofuran acetyloxime	178-179	(14)	Di-subst
1-Hydroxy-2-acetyl-4-methoxy-dibenzofuran oxime	215-216	(14)	Di subst
2-(α-Hydroxy-β-aminoethyl)-dibenzofuran	132	(23)	
2-(α-Hydroxy-β-aminoethyl)-dibenzofuran hydrochloride	261 dec.	(23)	
2-(α-Hydroxy-β-chloroethyl)-dibenzofuran	b.p. 205-206 / 2 mm.	(31)	
2-Hydroxydibenzofuran	156	(16, 42, 43)	

[41] U.S. patent 2,191,860 [C. A., 34, 4528 (1940)].
[42] French patent 768,052 [C. A., 29, 475 (1935)].
[43] German patent 606,350 [C. A., 29, 1436 (1935)].

Table 1. (Continued)

Name of compound	M.P.	Reference
2-(α-Hydroxy-β-diethylaminoethyl)-dibenzofuran	75-76 b.p. 220 / 2-3 mm.	(23, 31)
2-(α-Hydroxy-β-diethylaminoethyl)-dibenzofuran hydrochloride	157-159	(23, 31)
2-(β-Hydroxy-γ-diethylaminopropyl)-dibenzofuran hydrochloride	145	(31)
2-(α-Hydroxy-β-dimethylaminoethyl)-dibenzofuran	88-89	(23)
2-(α-Hydroxy-β-dimethylaminoethyl)-dibenzofuran benzoate	99-100	(23)
2-(α-Hydroxy-β-dimethylaminoethyl)-dibenzofuran hydrochloride	173-174	(23)
2-(α-Hydroxy-β-ethylaminoethyl)-dibenzofuran	99.5-101	(23)
2-(α-Hydroxy-β-ethylaminoethyl)-dibenzofuran hydrochloride	219-219.5	(23)
2-(α-Hydroxyethyl)-dibenzofuran	63-64	(23)
2-(β-Hydroxyethyl)-dibenzofuran	67-67.5	(31)
2-(α-Hydroxy-β-piperidinoethyl)-dibenzofuran	116.5-117.5	(23)
2-(α-Hydroxy-β-piperidinoethyl)-dibenzofuran benzoate	119	(23)
2-(α-Hydroxy-β-piperidinoethyl)-dibenzofuran hydrochloride	250-251	(23)

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Iododibenzofuran	142 112	(29) (18)
(β-Isobutylaminoethyl) 2-dibenzofuran carboxylate hydrochloride	212	(26)
(1-Keto-4-aminobutyl)-dibenzofuran	b.p. 230-232 / 17-18 mm.	(3)
2-(α-Keto-β-aminoethyl)-dibenzofuran hydrochloride	254-256 dec.	(23)
2-(α-Keto-β-diethylaminoethyl)-dibenzofuran hydrochloride	204-206	(23, 31)
2-(α-Keto-β-dimethaminoethyl)-dibenzofuran	82-83	(23)
2-(α-Keto-β-dimethaminoethyl)-dibenzofuran hydrochloride monohydrate	212-235	(23)
2-(α-Keto-β-methylaminoethyl)-dibenzofuran hydrochloride	225-250	(23)
2-(α-Keto-β-piperidinoethyl)-dibenzofuran	97-100	(23)
2-(α-Keto-β-piperidinoethyl)-dibenzofuran hydrochloride	255-265	(23)
2-Methoxydibenzofuran	46-47 b.p. 164-165 / 6 mm.	(16)
Methyl-bis-(2-dibenzofuroylmethyl)-amine hydrochloride	235-245	(23)
2-Methyldibenzofuran	45 b.p. 160	(3, 44)

[44] Sugii and Shindo, J. Pharm. Soc. Japan, 53, 571 (1933) [C. A., 28, 151 (1934)].

Table 1. (Continued)

Name of compound	M.P.	Reference
Methyl 2-dibenzofuranacrylate	130	(30)
3-Methyl-5-methoxybenzofuro-[2,3-g]-1,2-benzisoxazole	171.5-173	(14)
2-Nitrodibenzofuran	110 b.p. 190-205	(35, 38)
Phenyl-2-dibenzofuransulfone	166	(45)
2-Propionyldibenzofuran	101.5-102.5	(23)
2-Propionyldibenzofuran semicarbazone	184-186	(23)
1,2,3,4-Tetrahydro-8-(γ-acetamino-propyl)-dibenzofuran	118	(3)
Tetrahydro-2-dibenzofuranbutyric acid	119-120	(3)
Tetrahydro-2-dibenzofuranbutyric acid hydrazide	125.5-126.5	(3)
Tetrahydro-2-dibenzofuran-γ-keto-butyric acid	152-152.5	(3)
Tetrahydro-2-dibenzofuranpropyl-amine	b.p. 220-230	(3)
Tetrahydro-2-dibenzofuranpropyl-amine hydrochloride	253-254	(3)
Tetrahydro-2-dibenzofuranpropyl-urethane	68-69	(3)

[45]German patent 701,954 [C. A., 36, 98 (1942)].

Table 1. (Continued)

Name of compound	M.P.	Reference
DISUBSTITUTED DIBENZOFURANS		
2-Acetamino-3-bromodibenzofuran	240-241	(18)
2-Acetamino-3-nitrodibenzofuran	206-208	(18)
2-Acetoxy-8-methoxydibenzofuran	110	(9, 19)
2-Acetyl-7-acetaminodibenzofuran	203	(24)
2-Acetyl-7-acetaminodibenzofuran oxime	203	(24)
2-Acetyl-7-aminodibenzofuran	158-159	(24)
2-Acetyl-6-carbomethoxydibenzofuran	174-175	(24)
2-Acetyl-6-dibenzofurancarboxylic acid	262-265	(24)
1-Acetyl-2-methoxydibenzofuran	121-122	(9, 19)
2-Acetyl-7-nitrodibenzofuran	212-213	(24)
2-Acetyl-x-nitrodibenzofuran	105	(35)
1-Allyl-2-hydroxydibenzofuran	83 b.p. 173 / 5 mm.	(16)
1-Allyl-2-methoxydibenzofuran	67-68	(16)
2-Aminobenzofuro-[2,3-f]-benzothiazole	268-269	(24)
2-Aminobenzofuro-[2,3-f]-benzothiazole hydrochloride	300 dec.	(24)
2-Amino-3-bromodibenzofuran	172-173 ~~122-123~~	(18)
2-Amino-4-dibenzofuranarsonic acid	218 dec.	(46)

[46] Hall and Hamilton, J. Am. Chem. Soc., 56, 1779 (1934).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Amino-7-dibenzofuranarsonic acid	>250	(27)
7-Amino-2-dibenzofuransulfonic acid	-	(35)
2-Amino-4-methoxydibenzofuran	127-127.5	(24)
1-Amino-2-nitro-4-methoxydibenzofuran	206-207	(24)
7-Amino-7,8,9,10-tetrahydrobenzo-[b]-naptho-[2,3-d]-furan hydrochloride	266-267	(24)
2,4-Bis-(diethylaminoethylamino)-dibenzofuran	b.p. 255 / 1 mm.	(47)
Bis-(diethylaminoethyl) 2,8-dibenzofurandicarboxylate dihydrochloride	251-252	(26)
2,7-Bis-(guanylguanido)-dibenzofuran	209	(48)
2-Bromo-3-acetaminodibenzofuran	194	(18)
2-Bromo-3-aminodibenzofuran	129	(18)
2-Bromo-7-aminodibenzofuran	133-134	(18)
2-Bromo-8-carboethoxydibenzofuran	130	(24)
2-Bromo-4-carbomethoxydibenzofuran	189-189.5	(49)
2-Bromo-6-carbomethoxydibenzofuran	166-167	(50)
2-Bromo-4-dibenzofurancarboxylic acid	285-286	(49)

[47] German patent 550,327 [C. A., 26, 4062 (1932)].
[48] U.S. patent 2,191,800 [C. A., 34, 4528 (1940)].
[49] Gilman, Cheney, and Willis, J. Am. Chem. Soc., 61, 951 (1939).
[50] Gilman, Van Ess, and Hayes, Ibid., 61, 643 (1939).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Bromo-6-dibenzofurancarboxylic acid	263-264	(50)
2-Bromo-8-dibenzofurancarboxylic acid	328	(24)
2-Bromo-3-(guanylguanido)-dibenzofuran	170	(48)
1-Bromo-2-hydroxydibenzofuran	123-123.5	(16)
2-Bromo-3-hydroxydibenzofuran	113-113.5	(51)
2-Bromo-8-methoxydibenzofuran	92.5	(16)
1-Bromo-2-methoxydibenzofuran	117-118	(16)
2-Bromo-4-methyldibenzofuran	106-106.5	(50)
2-Bromo-3-nitrodibenzofuran	154.5-155.5	(18)
2-Bromo-6-nitrodibenzofuran	231-232	(52)
2-Bromo-7-nitrodibenzofuran	250.5-251.5	(18, 53)
2-Bromo-8-nitrodibenzofuran	226-227	(52)
2-Chloro-7-nitrodibenzofuran	226	(32, 54)
2,7-Diacetaminodibenzofuran	290 dec. 265-265.5	(55) (56)
2,8-Diacetaminodibenzofuran	299-300	(9, 19)

[51] Tatematsu and Kubota, Bull. Chem. Soc. Japan, 9, 448 (1934) [C. A., 29, 1091 (1935)].
[52] Yamashiro, Bull. Chem. Soc. Japan, 16, 61 (1941) [C. A., 35, 5111 (1941)].
[53] Cullinane, Davy, and Padfield, J. Chem. Soc., 716 (1934).
[54] Cullinane and Padfield, J. Chem. Soc., 1151 (1935).
[55] Cullinane, J. Chem. Soc., 2365 (1932).
[56] Yamashiro, J. Chem. Soc. Japan, 59, 186 (1938) [C. A., 32, 9084 (1938)].

Table 1. (Continued)

Name of compound	M.P.	Reference
2,8-Diacetoxydibenzofuran	150-151 b.p. 212 / 6 mm.	(9, 19)
2,8-Diacetyldibenzofuran	140 b.p. 250-260 / 15 mm.	(35, 24)
2,8-Diacetyldibenzofuran dioxime	250 dec.	(35)
2,3-Diaminodibenzofuran	166	(18, 35)
2,6-Diaminodibenzofuran	138-140	(56)
2,7-Diaminodibenzofuran	152	(55)
2,8-Diaminodibenzofuran	212-213	(9, 19)
2,8-Diaminodibenzofuran picrate	278 dec.	(9, 19)
2,8-Dibenzofurandicarboxylic acid	300 >350 (58)	(57, 58)
2,8-Dibenzofurandisulfonic acid	-	(36)
2,8-Dibenzofurandisulfonyl chloride	218	(36)
2,3-Dibromodibenzofuran	150-150.5	(51)
2,7-Dibromodibenzofuran	176	(32)
2,8-Dibromodibenzofuran	195	(32, 59)
3,7-Dibromodibenzofuran	199-200	(52)

[57] Sugii and Sengoku, J. Pharm. Soc. Japan, 53, 951 (1933) [C. A., 29, 5444 (1935)].
[58] Gilman, Willis, and Swislowsky, J. Am. Chem. Soc., 61, 1371 (1939).
[59] Hoffmeister, Ann., 159, 191 (1871).

Table 1. (Continued)

Name of compound	M.P.	Reference
2,8-Dichlorodibenzofuran	190	(18, 32)
2,8-Dichloromercuridibenzofuran	-	(36)
Diethylaminoethyl 7-amino-2-dibenzofuran-carboxylate hydrochloride	255	(26)
Diethylaminoethyl 7-nitro-2-dibenzofurancarboxylate hydrochloride	161	(26)
γ-Diethylaminopropyl 2-dibenzofuran-carboxylate hydrochloride	185	(26) mon subst.
2,8-Diethyldibenzofuran	b.p. 334 b.p. 197-199 / 20 mm.	(35)
1,8-Dihydroxydibenzofuran	-	(60)
2,6-Dihydroxydibenzofuran	-	(60)
2,7-Dihydroxydibenzofuran	192-193	(61)
2,8-Dihydroxydibenzofuran	242-243	(9, 19)
2,8-Diiododibenzofuran	173	(18)
1,2-Dimethoxydibenzofuran	79	(16)
2,8-Dimethoxydibenzofuran	88-89 b.p. 187 / 5 mm.	(9, 19)
2,8-Dimethoxydibenzofuran picrate	117-118	(9, 19)
2,8-Dimethyldibenzofuran	64	(44)

[60] German patent 679,976 [C. A., 34, 636 (1940)].
[61] French patent 816,719 [C. A., 32, 2145 (1938)].

Table 1. (Continued)

Name of compound	M.P.	Reference
Dimethyl 2,8-dibenzofurandicarboxylate	167	(57)
1,8-Dinitrodibenzofuran	241-242	(52)
2,7-Dinitrodibenzofuran	245	(55)
2-Ethyl-x-nitrodibenzofuran	96 b.p. 218-226 / 15 mm.	(35)
2-(Guanylguanido)-3-hydroxydibenzofuran	-	(48)
2-Hydroxy-7-acetaminodibenzofuran	242-243	(61)
2-Hydroxy-3-acetyldibenzofuran	168-169 b.p. 227 / 7 mm.	(9, 19)
2-Hydroxy-7-aminodibenzofuran	200-201	(61)
1-Hydroxy-(2- or 4-)bromodibenzofuran	178	(16)
2-Hydroxy-3-bromodibenzofuran	143-144	(16)
2-Hydroxy-6-chlorodibenzofuran	167-169	(61)
2-Hydroxy-7-chlorodibenzofuran	167-168	(61)
2-Hydroxy-8-chlorodibenzofuran	177-178	(61)
2-Hydroxy-1-dibenzofurancarboxylic acid	209-214 dec.	(62)
1-Hydroxy-2-methoxydibenzofuran	111-111.5	(16)
2-Hydroxy-7-methoxydibenzofuran	151-152	(61)

[62]Gilman, Willis, Cook, Webb, and Meals, J. Am. Chem. Soc., 62, 667 (1940).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Hydroxy-8-methoxydibenzofuran	90-91	(9, 19)
2-Hydroxy-7-methyldibenzofuran	147-148	(61)
2-Hydroxy-8-methyldibenzofuran	160-161	(61)
2-Iodo-7-(guanylguanido)-dibenzofuran hydrochloride	234	(48)
7-Keto-7,8,9,10-tetrahydrobenzo-[b]-naptho[2,3-d]-furan	137	(24)
7-Keto-7,8,9,10-tetrahydrobenzo-[b]-naptho[2,3-d]-furan oxime	212-213	(24)
2-Methoxy-3-acetyldibenzofuran	113-114	(9, 19)
2-Methoxy-3-allyldibenzofuran	b.p. 158-159 / 4 mm.	(16)
2-Methoxy-3-bromodibenzofuran	171-172	(16)
2-Methoxy-1-dibenzofurancarboxylic acid	156-157	(16)
2-Methoxy-3-dibenzofurancarboxylic acid	206-207	(16)
2-Methyl-1-benzofuro-[2,3-f]-benzimidazole	270	(24)
2-Methyl-1-benzofuro-[2,3-f]-benzimidazole hydrochloride	>335	(24)
2-Methyl-8-carbomethoxydibenzofuran	103	(44)
2-Methyl-8-dibenzofurancarboxylic acid	>270	(44)
2-Nitro-3-acetaminodibenzofuran	196	(24)

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Nitro-3-aminodibenzofuran	222	(35)
2-Nitro-7-aminodibenzofuran	268	(55)
2-Nitro-7-arsenodibenzofuran	>250	(27)
1-Nitro-8-bromodibenzofuran	189.5-190.5	(52)
2-Nitro-6-carbomethoxydibenzofuran	205-205.5	(50)
2-Nitro-7-carbomethoxydibenzofuran	235-236	(24)
2-Nitro-3-diacetaminodibenzofuran	196	(18, 35)
2-Nitro-4-dibenzofuranarsonic acid	203-205	(46)
2-Nitro-7-dibenzofuranarsonic acid	>280	(27)
2-Nitro-6-dibenzofurancarboxylic acid	300-305 dec.	(50)
2-Nitro-7-dibenzofurancarboxylic acid	>330	(24)
7-Nitro-2-dibenzofurancarboxylic acid	300 dec.	(24)
7-Nitro-2-dibenzofurancarboxylic acid chloride	225	(26)
7-Nitro-2-dibenzofuransulfonamide	265 dec.	(35)
7-Nitro-2-dibenzofuransulfonic acid	-	(35)
7-Nitro-2-dibenzofurensulfonyl chloride	200 dec.	(35)
2-Nitro-7-dichloroarsenodibenzofuran	152	(27)
2-Nitro-4-methoxydibenzofuran	185-186	(24)
1-Phenylazo-2-hydroxydibenzofuran	165.5-166	(63)

[63]Gilman and Van Ess, J. Am. Chem. Soc., 61, 3146 (1940).

Table 1. (Continued)

Name of compound	M.P.	Reference
2-Phenylazo-3-hydroxydibenzofuran	177-178	(63)
2,3?-Phthaloyldibenzofuran	258	(35)
1-Propenyl-2-hydroxydibenzofuran	94-95	(16)
2-Thiocyano-3-aminodibenzofuran	175	(24)
TRISUBSTITUTED DIBENZOFURANS		
1-Acetamino-2-nitro-4-methoxydibenzofuran	244	(24)
2-Acetyl-7-acetamino-6-nitrodibenzofuran	270-271	(24)
2-Bromo-3-acetamino-6-carbomethoxydibenzofuran	245-246	(50)
2-Bromo-3-acetamino-6-dibenzofurancarboxylic acid	247-247.5	(50)
2-Bromo-3-nitro-6-carbomethoxydibenzofuran	205-206	(50)
2-Bromo-x-nitro-6-carbomethoxydibenzofuran	205-206	(50)
2-Bromo-3-nitro-6-dibenzofurancarboxylic acid	331-334	(50)
8-Bromopyridodibenzofuran	152	(31)
2,8-Diacetamino-3-bromodibenzofuran	259-260	(9, 19)
2,7-Diacetamino-3-nitrodibenzofuran	303.5-304	(56)
2,8-Diacetamino-3-nitrodibenzofuran	324.5-325.5	(56, 28)

Table 1. (Continued)

Name of compound	M.P.	Reference
2,7-Diamino-3-nitrodibenzofuran	286.5-287	(56)
2,8-Diamino-3-nitrodibenzofuran	291.5-292 212-213	(56) (28)
2,8-Dibromo-3-acetyldibenzofuran	157-157.5	(24)
1,4-Dimethoxy-2-acetaminodibenzofuran	169-170	(14)
1,4-Dimethoxy-2-acetyldibenzofuran	114-115	(14)
1,4-Dimethoxy-2-acetyldibenzofuran oxime	193.5-195.5	(14)
1,4-Dimethoxy-2-aminodibenzofuran	110-112	(14)
1,4-Dimethoxy-2-(α-aminoethyl)-dibenzofuran hydrochloride	234-236 dec.	(14)
8-Dimethylamino-7-keto-7,8,9,10-tetrahydro-[b]-naptho-[2,3-d]-furan hydrochloride	185-186	(24)
2,7-Dinitro-6-acetaminodbenzofuran	277-278	(9, 19)
3,8-Dinitro-4-hydroxydibenzofuran	225 dec.	(17)
3,8-Dinitro-4-methoxydibenzofuran	177	(17)
2-Hydroxy-3,8?-dinitrodibenzofuran	240 dec.	(17)
8-Methoxybenzofuro-[5,6-b]-benzo-furan-2,3-dione	278	(9, 19)
2-Methyl-8-acetyl-1-benzofuro-[2,3-f]-benzimidazole	298	(24)
2-Methyl-8-acetyl-1-benzofuro-[2,3-f]-benzimidazole hydro-chloride	> 325 dec.	(24)

Table 1. (Continued)

Name of compound	M.P.	Reference
Methyl 2,8-dihydroxydibenzofuran-1(or 3)-α-oxoacetate	206-207	(9, 19)
2-Nitro-3,7-diacetaminodibenzofuran	348 dec.	(64)
2-Nitro-3,7-Diaminodibenzofuran	276-277	(64)
2,3,8-Tribromodibenzofuran	202-203	(65)
1,3,8-Trinitrodibenzofuran	207-208	(52)
2,3,8-Trinitrodibenzofuran	236-237	(65)
2,4,6-Trinitrodibenzofuran	260-261	(64)
2,4,8-Trinitrodibenzofuran	311-312	(65)
TETRASUBSTITUTED DIBENZOFURANS		
3,7-Bis-(guanylguanido)-2,8-dimethyl-dibenzofuran	216	(48)
2-Bromo-x,x-dinitro-6-carbomethoxy-dibenzofuran	259.5-260.5	(50)
2.7-Diacetamino-3,8-dinitrodibenzo-furan	285.5-286	(56)
2,7-Diamino-3,8-dinitrodibenzo-furan	360.5-361.5 dec.	(56)
1,9?-Dibromo-2,8-diacetoxydiben-zofuran	173.5-174	(9, 19)

[64] Yamashiro, J. Chem. Soc., Japan, 59, 945 (1938) [C. A., 33, 603 (1939)].

[65] Yamashiro, Bull. Chem. Soc. Japan, 16, 6 (1941) [C. A., 35, 3640 (1941)].

Table 1. (Continued)

Name of compound	M.P.	Reference
2,8-Dibromo-4,6-diaminodibenzofuran	276.5-277.5	(65)
2,8-Dibromo-4,6-dicarbomethoxydibenzofuran	273	(66)
2,8-Dibromo-4,6-dibenzofurandicarboxylic acid	> 350	(66)
1,9?-Dibromo-2,8-dihydroxydibenzofuran	201-202	(9, 19)
1,9?-Dibromo-2,8-dimethoxydibenzofuran	196-197	(9, 19)
1,9?-Dicarbomethoxy-2,8-dimethoxydibenzofuran	129-130	(9, 19)
2,8-Dimethoxy-3,7-dibromodibenzofuran	260-261	(9, 19)
2,8-Dimethoxy-3,7-dicarbomethoxydibenzofuran	183-184	(9, 19)
2,8-Dimethoxy-1,9?-dibenzofurandicarboxylic acid	271-272 dec.	(9, 19)
2,8-Dimethoxy-3,7-dibenzofurandicarboxylic acid	290 dec.	(9, 19)
1,9?-Dimethyl-2,8-dihydroxydibenzofuran	168-169	(9, 19)
1,9?-Dimethyl-2,8-dimethoxydibenzofuran	106-107	(9, 19)
2,3,7,8-Tetraacetoxydibenzofuran	262	(67)

[66]Unpublished studies by R.E. Dickey.
[67]Erdtman, Proc. Roy. Soc. (London), A143, 191 (1933).

Table 1. (Continued)

Name of compound	M.P.	Reference
2,3,7,8-Tetrabromodibenzofuran	306-307	(65)
2,4,6,8-Tetrabromodibenzofuran	237-238	(65)
2,4,7,8-Tetrabromodibenzofuran	248-249	(65)
2,4,6,8-Tetramethyldibenzofuran	90-90.5	(68)
1,3,7,8-Tetranitrodibenzofuran	253-254	(52)
2,3,6,8-Tetranitrodibenzofuran	249-250	(65)
2,3,7,8-Tetranitrodibenzofuran	285-286	(65)
2,4,6,8-Tetranitrodibenzofuran	252.5	(69, 70)
PENTASUBSTITUTED DIBENZOFURANS		
3,7-Dimethoxy-8-acetoxydibenzofuran-1,4-quinone	252-254	(71)
3,7-Dimethoxy-8-hydroxydibenzofuran-1,4-quinone	250	(71, 72)
3,7-Dimethyl-8-hydroxydibenzofuran-1,4-quinone	218-220	(71)
1,3,4,7,8-Pentamethoxydibenzofuran	109-110	(71)

[68] Bamberger and Brun, Ber., 40, 1949 (1907).
[69] Borsche and Scholten, Ber., 50, 606 (1917).
[70] von Alpen, Rec. trav. chim., 51, 715 (1932). (1934)
[71] Erdtman, Proc. Roy. Soc. (London), A143, 223 (~~1933~~).
[72] Erdtman, Svensk. Kem. Tids., 44, 135 (1932) [C. A., 26, 4803 (1932)].

Table 1. (Continued)

Name of compound	M.P.	Reference
1,4,8-Triacetoxy-3,7-dimethoxydibenzofuran	232	(71)
1,4,8-Trihydroxy-3,7-dimethoxydibenzofuran	210 dec.	(71)
1,4,8-Trihydroxy-3,7-dimethoxydibenzofuran tri-p-nitrobenzoate	300	(71)
HEXASUBSTITUTED DIBENZOFURANS		
1,2,3,6,7,9-Hexamethoxydibenzofuran	126-127.5	(73)
1,2,6,9-Tetraacetoxy-3,7-dimethoxydibenzofuran	255-256	(73)

The first preparation of dibenzofuran was reported by Lesimple[74] in 1866, who obtained this compound by heating phenyl phosphate with lime. Later Hoffmeister and others[75] proved its structure. A major commercial source of dibenzofuran is coal tar.[76,77] This compound has also been prepared by passing the vapors of phenol over lead or thorium oxides.[53]

[73] Erdtman, Ann., 513, 240 (1934).
[74] Lesimple, Ann., 138, 376 (1866).
[75] Hoffmeister, Ber., 3, 747 (1870); Tauber and Halberstadt, ibid., 25, 2745 (1892); Kramer and Weissgerber, ibid., 34, 1662 (1901).
[76] Kruber, Ber., 65, 1382 (1932).
[77] German patent 491,594 [C. A., 24, 2475 (1930)].

The literature on dibenzofuran has been very thoroughly covered in a chronological bibliography by Oatfield[1] up to 1933. The further literature till June, 1939 has been supplemented by Swislowsky.[9] In this thesis this bibliography has been carried on up to January 1, 1943.

Methods of Preparing 2- and 2,8-Substituted Dibenzofurans

The preparation of 2- and 2,8-substituted dibenzofurans has been carried out chiefly by substitution reactions. Ring closure reactions have been used rather for structural proofs than as a source of compounds for further work. The substitution reactions will be discussed under the following headings: halogenation, nitration, metalation and halogen-metal interconversion, Friedel-Crafts reaction, amination, and sulfonation. The ring closure reactions will be discussed from the point of view of the type of ring closure and the starting material, as biphenyl ring closure, phenyl ether ring closure, and ring closures involving substituted benzene types.

By substitution reactions

Halogenation. In general, direct halogenation of dibenzofuran gives 2- and 2,8-substituted dibenzofurans in excellent yield. Chlorination of dibenzofuran yields 2-chlorodibenzofuran.[18] Further chlorination gives 2,8-dichlorodibenzofuran.[18] Bromination can likewise be readily controlled to yield either 2-bromodibenzofuran[3] or 2,8-dibromodibenzofuran.[59] Iodination, using nitric acid to remove

the liberated hydrogen iodide, gives, according to the conditions, 2-iododibenzofuran[18] or 2,8-diiododibenzofuran.[18]

Bromination has been more extensively studied than other halogenation reactions in dibenzofuran chemistry. A general rule is that monobromination of hydroxy- and acetaminodibenzofurans gives the ortho or para monobromo derivatives. Thus from 3-hydroxydibenzofuran is obtained 2-bromo-3-hydroxydibenzofuran.[51] In a similar manner 2-hydroxydibenzofuran gives 1-bromo-2-hydroxydibenzofuran.[16] The exact structure of the bromination product of 1-hydroxydibenzofuran is not known but is possibly the 2-bromo derivative.[16]

The acetaminodibenzofurans brominate very much like the hydroxy derivatives. Thus the monobromination product from 3-acetaminodibenzofuran is 2-bromo-3-acetaminodibenzofuran.[18] In exactly similar manner the bromination of 3-acetamino-6-carbomethoxydibenzofuran gives 2-bromo-3-acetamino-6-carbomethoxydibenzofuran.[50]

A totally different course is pursued in the bromination of the negatively substituted dibenzofurans. Heteronuclear bromination occurs in dibenzofuran derivatives having in one nucleus such groups as carboxyl, nitro, carbomethoxy, and the weakly negative bromine. If the dibenzofuran derivative has only one negative group, the entering bromine atom goes to the 8-position irrespective of the position of the other group. From 2-dibenzofurancarboxylic acid is thus obtained 2-bromo-8-dibenzofurancarboxylic acid.[24] The bromination of 3-nitro-

dibenzofuran proceeds smoothly to yield 2-bromo-7-nitrodibenzofuran.[18] From 4-carbomethoxydibenzofuran is obtained 2-bromo-6-carbomethoxydibenzofuran.[50] The bromination of 2-bromo-dibenzofuran has been discussed earlier.

Nitration. Nitration is one of the very interesting substitution reactions of dibenzofuran because it attacks positions not readily substituted in other ways. Direct nitration of dibenzofuran yields chiefly 3-nitrodibenzofuran,[35] but at the same time a small amount of 2-nitrodibenzofuran is formed.[35,38] The nitration of 3-acetaminodibenzofuran goes very smoothly to yield 2-nitro-3-acetaminodibenzofuran.[24] 1-Acetamino-4-methoxydibenzofuran gives, on nitration, 1-acetamino-2-nitro-4-methoxydibenzofuran.[24] The nitration of 2-acetyl-7-acetaminodibenzofuran gives 2-acetyl-7-acetamino-8-nitrodibenzofuran.[24]

Heteronuclear nitration takes place, however, if one nucleus contains a group such as carboxyl, nitro, or carbomethoxy. If the negative group is in the 3-position, the entering nitro group attacks the 8-position. If the negative group is in the 2, or 4-position the entering nitro group may go into either the 3-, or 4-position depending on the particular experimental conditions. Dinitration of dibenzofuran, or further nitration of 3-nitrodibenzofuran, yields 2,7-dinitrodibenzofuran.[55] From 3-bromodibenzofuran is obtained 2-nitro-7-bromodibenzofuran.[18] The nitration of 2-dibenzofurancarboxylic acid yields the 7-nitro-derivative[24] whereas the nitration of 4-carbomethoxydibenzofuran yields both the 7-nitro- and the 8-nitro-dibenzofuran derivatives.[50] Similar

to the nitration of 3-bromo- and 3-nitrodibenzofurans is the nitration of 3-carbomethoxydibenzofuran[24] to yield 2-nitro-7-carbomethoxydibenzofuran. Dinitration of 4-methoxydibenzofuran yields 3,8-dinitro-4-methoxydibenzofuran.[17] In the case of the 2-hydroxydibenzofuran, dinitration yields a product of unknown structure,[17] which may be 3,8-dinitro-2-hydroxydibenzofuran.

Metalation and halogen-metal interconversion. There is only one case of a dibenzofuran derivative which metalates in the 2-position.[78] The action of n-butyllithium on 1,4-dihydrodibenzofuran[39] yields 1,2-dihydro-2-dibenzofurancarboxylic acid, after carbonation. For the preparation of 4- and 4,6-substituted dibenzofurans, metalation is the method of choice.[8,9,15]

One of the most potent tools available for the preparation of 2- and 2,8-substituted dibenzofurans is halogen-metal interconversion. In the case of 2-bromodibenzofuran, halogen-metal interconversion gives, after carbonation, 2-dibenzofurancarboxylic acid.[34] In this particular example the halogen-metal interconversion may take a further course. If so, the product is 2-bromo-4-dibenzofurancarboxylic acid.[49] Since 2-bromodibenzofuran reacts smoothly with magnesium to form the Grignard reagent,[3] this interconversion reaction is not so important as it otherwise would be.

But, on the other hand, 2,8-dibromodibenzofuran reacts very sluggishly with magnesium to give a very low yield of 2,8-dibenzo-

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[78] If arsenic is considered a metal, then the direct arsonation of dibenzofuran[37] is a metalation that likewise gives a 2-substituted dibenzofuran.

furylenedimagnesium bromide.[24] 2,8-Dibromodibenzofuran and n-butyllithium, on the other hand, react very smoothly to give an excellent yield of 2,8-dibenzofurandicarboxylic acid after carbonation.[58]

As yet halogen-metal interconversion reactions with dibenzofuran derivatives are too new for the full scope of these reactions to have been exploited. By proper choice of organometallic compound, 2,8-dibromodibenzofuran may, after carbonation, be changed into 2,8-dibenzofurandicarboxylic acid, or to 2,8-dibromo-4,6-dibenzofurandicarboxylic acid.[66] To summarize the scope of these reactions in dibenzofuran chemistry, it has been found that halogen-metal interconversion takes place where a bromine atom is ortho, meta, or para to the oxygen bridge and ortho, meta, or para to a methoxy group in dibenzofuran.[79]

Friedel-Crafts reaction. Like halogenation, the Friedel-Crafts reaction gives 2-, and 2,8-substituted dibenzofurans. As a method of acylation, this reaction is indeed the one of choice. Using aluminum chloride and the appropriate acid anhydride or acid chloride, 2-substituted dibenzofurans have been prepared from acetic,[20,3,31] propionic,[23] succinic,[3,24] benzoic,[28,29] and phthalic[33] acids.

A number of substituted dibenzofurans have also been acylated. In most cases the entering group goes to the 8-position in the unsubstituted ring. Thus acylation of 3-nitrodibenzofuran gives 2-acetyl-7-nitrodibenzofuran.[24] The action of aluminum chloride and acetyl chloride with 4-carbomethoxydibenzofuran gives 2-acetyl-6-carbomethoxydibenzofuran.[24] In the same manner acylation of 2-bromo- and

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[79]Gilman, Swislowsky, and Brown, J. Am. Chem. Soc., 62, 348 (1940).

2-acetyldibenzofurans gives, respectively, 2-acetyl-8-bromodibenzofuran[24] and 2,8-diacetyldibenzofuran.[24,35]

In addition to its use for acylation, the Friedel-Crafts reaction has also been used for the preparation of arsenic and phosphorus derivatives of dibenzofuran. The reaction of arsenic trichloride with aluminum chloride and dibenzofuran yields, after hydrolysis, 2-arsenosodibenzofuran.[27] In a similar manner the action of phosphorus trichloride on dibenzofuran in the presence of aluminum chloride yields a dichlorophosphinodibenzofuran of unknown structure, but probably the 2-derivative.[37]

Amination. For the preparation of aminodibenzofurans by amination there are several excellent methods. 2-Aminodibenzofuran[12] has been prepared very smoothly from 2-bromodibenzofuran by means of sodamide in liquid ammonia. This same method failed completely with 2,8-dibromodibenzofuran, perhaps because of the insolubility of the latter compound.[9,19]

A second excellent method for the preparation of 2-aminodibenzofuran is the reaction of 2-bromodibenzofuran with ammonium hydroxide and cuprous bromide as catalyst[22] in a bomb. This method works excellently for the amination of the 2,8-dibromodibenzofuran as well.[9,19]

The Bucherer reaction has proved to be a very smooth reaction for the conversion of 2,8-dihydroxydibenzofuran to 2,8-diaminodibenzofuran.[9,19] However, the usefulness of this particular synthesis is limited because the 2,8-dihydroxydibenzofuran is generally prepared from 2,8-dibromodibenzofuran.[9,19]

It is interesting to note that no reaction occurred, even under rather drastic conditions, when an attempt was made to carry out a Bucherer reaction on 1,9(?)-dimethyl-2,8-dimethoxydibenzofuran.[9,19] A Bucherer reaction was successfully carried out with 1-bromo-2-hydroxydibenzofuran but the bromine was displaced. The product was 2-aminodibenzofuran.[9,19]

Sulfonation. Direct sulfonation of dibenzofuran, like halogenation and the Friedel-Crafts reaction, gives 2-, and 2,8-substituted dibenzofurans. From dibenzofuran is obtained 2-dibenzofuransulfonic acid.[21,36] Further sulfonation gives 2,8-dibenzofurandisulfonic acid.[36] Sulfonation of 3-nitrodibenzofuran gives 7-nitro-2-dibenzofuransulfonic acid.[35]

Ring closures of the biphenyl type. In general biphenyls substituted in the 2,2'-positions by two hydroxyl groups, two acetoxy groups, an amino and a hydroxy group, or a chloro and a hydroxy group have been converted into dibenzofurans.[9]

In some cases ring closure is surprisingly easy. Thus 2,4,6,8-tetranitrodibenzofuran was obtained in quantitative yield by heating 2,2'-diacetoxy-3,3',5,5'-tetranitrobiphenyl above its melting point.[70] This tetranitrodibenzofuran had been prepared previously by heating the dihydroxy-tetranitrobiphenyl with dimethylaniline and p-toluenesulfonylchloride.[69] It is interesting that 5,5'-dinitro-2,2'-diacetoxybiphenyl could not be made to undergo ring closure on heating.[70] Also that

2,2′-diacetoxy-3,3′,5,5′-tetrabromobiphenyl decomposed without undergoing ring closure when it was heated.

Ring closures of biphenyl derivatives similar to 2,5-dihydroxy-2′-chlorobiphenyl have been reported in the patent literature.[60] In these cases the hydroxydibenzofurans are prepared by melting the biphenyl compounds with alkali hydroxide or alkali carbonate. No data was given as to the yields of conditions for these reactions. In this manner 2,6-dihydroxy-, 1,8-dihydroxy-, and 2-hydroxy-6-chlorodibenzofuran have been prepared.[60]

Ring closures of the phenyl ether type. Ring closures of the phenyl ether type to yield 2- or 2,8-substituted dibenzofurans have been very successful. In general, a substituted o-aminodiphenyl ether is diazotized and heated with a strong mineral acid such as sulfuric or phosphoric acid. It has been observed in the preparation of 2,4- or 2,6-substituted dibenzofurans that the amino group, through which the ring is eventually closed by diazotization, must be in the same benzene nucleus with any substituent which is to be the 4-substituent in the final product.[50] Otherwise no ring closure takes place. Thus it has been found impossible to ring close 2-chloro-2′-aminodiphenyl ether to 4-chlorodibenzofuran.[32]

Treatment of the diazonium salt of 2-amino-4-chlorodiphenyl ether with 50 per cent sulfuric acid yields 2-chlorodibenzofuran.[32] The ring closure of 2′-amino-4-chloro-5′-nitrodiphenyl ether yields 2-chloro-7-nitrodibenzofuran.[32] In a similar manner 4,4′-dichloro-2-aminodiphenyl

ether is cyclicized to 2,8-dichlorodibenzofuran.[32] By using this type of ring closure 2-bromodibenzofuran,[32] 2,7-dibromodibenzofuran,[32] and 2,8-dibromodibenzofuran have been prepared.[32] The preparation of 2-bromo-4-methyldibenzofuran,[63] 2-bromo-6-carbomethoxydibenzofuran,[50] and 2-bromo-8-methoxydibenzofuran[16] involved phenyl ether type ring closures.

In all of the above ring closures 50 per cent sulfuric acid was used. 2-Hydroxydibenzofuran has been prepared by a diphenyl ether type ring closure using phosphoric acid but no details were given.[42,43]

Ring closures of substituted benzene types. This type of ring closure has been used far less than the two types mentioned previously for the preparation of 2- and 2,8-substituted dibenzofurans.

One of the best examples of this type of synthesis is the preparation of 2-nitro-4-dibenzofuranarsonic acid from 2-chloro-5-nitrophenylarsonic acid and o-chlorophenol.[46]

Several ring closures of this type were carried out by Erdtman in the course of his study of the oxidation of polyhydroxy-benzenes.[62,71,72,73] He found that the oxidation of pyrogallol, followed by a reductive acylation and ring closure, yields 1,2,6,8,9-tetraacetoxy-3,7-dimethoxydibenzofuran.[62] A somewhat similar reaction was the preparation of 2,4,6,8-tetramethyldibenzofuran from 2,4-dimethylhydroquinone and sulfuric acid.[68]

In general these reactions are too complex and the yields are much too low for them to be of much use as sources for general preparatory purposes.

EXPERIMENTAL

Metalation of dibenzofuran with n-butyllithium

A solution of n-butyllithium, prepared from 18.8 g. (0.14 mole) of n-butyl bromide and 2.8 g. (0.40 g. atom) of lithium in 60 cc. of ether was added to 8.4 g. (0.05 mole) of dibenzofuran in 40 cc. of ether. All the manipulations and reactions were carried under a nitrogen atmosphere. This solution was stirred and refluxed for 20 hours, then cooled and poured on crushed, solid carbon dioxide. After extraction of the acidic material with dilute potassium hydroxide solution, and acidification with dilute hydrochloric acid, there was obtained 6.5 g. (61%) of crude 4-dibenzofurancarboxylic acid, m.p. 200-204°. After recrystallization from dilute methyl alcohol the yield of pure 4-dibenzofurancarboxylic acid was 5.6 g. (53%), m.p. 208-209°.

In addition 2.0 g. (22%) of bi-4-dibenzofuryl ketone was obtained, m.p. 172-173° after crystallization from dilute ethyl alcohol. The identity of this product was confirmed by a mixed melting point with an authentic specimen.

In a second experiment using a very large amount of powdered, solid carbon dioxide, the yield of 4-dibenzofurancarboxylic acid was 8 g. (76%), m.p. 209-210°.

Metalation of dibenzofuran with phenyllithium

A solution of phenyllithium, prepared from 11 g. (0.07 mole) of bromobenzene and 1.4 g. (0.20 g. atom) of lithium in 60 cc. of ether, was added to 8.4 g. (0.05 mole) of dibenzofuran in 40 cc. of ether.

The solution was stirred and refluxed for 20 hours, then poured on solid, powdered carbon dioxide. The acidic material was extracted with dilute potassium hydroxide solution, then precipitated by the addition of dilute hydrochloric acid. The yield of crude 4-dibenzofurancarboxylic acid was 5.5 g. (52%), m.p. 190-200°. This crude product was recrystallized from 50 per cent ethyl alcohol to yield 4.2 g. (40%) of pure product, m.p. 209-210°.

In a second experiment the yield of crude acid was 6 g. (57%) and of pure acid was 4.9 g. (46%).

From the combined neutral residues was obtained 1.2 g. (6.6%) of bi-4-dibenzofuryl ketone, m.p. 172-173° after crystallization from ethyl alcohol. A mixed melting point with an authentic specimen showed no depression.

In addition about 0.5 g. of unknown material, m.p. 178-179°, was obtained. This material was insoluble in alcohol.

Metalation of dibenzofuran with methyllithium

A solution of methyllithium, prepared from 14.2 g. (0.10 mole) of methyl iodide and 2.1 g. (0.30 g. atom) of lithium in 60 cc. of ether, was added to a solution of 8.4 g. (0.05 mole) of dibenzofuran in 40 cc. of ether. This solution was stirred and refluxed for 20 hours. Then it was cooled and poured on crushed, solid carbon dioxide. The acidic product was extracted with dilute potassium hydroxide solution, and precipitated with dilute hydrochloric acid. The yield of crude acid

was 0.5 g. (4.7%). This product was recrystallized from 50 per cent ethyl alcohol to yield 0.3 g. (2.8%) of pure 4-dibenzofurancarboxylic acid, m.p. 209-210°.

In a second experiment carried out under the same conditions, the crude yield was 0.4 g. (3.8%), m.p. 206-207°. This product was recrystallized from 50 per cent ethyl alcohol to yield 0.3 g. (2.8%), m.p. 209-210°.

Metalation of 2-bromodibenzofuran with phenyllithium

A solution of phenyllithium, prepared from 1.96 g. (0.01 mole) of bromobenzene and 0.35 g. (0.05 g. atom) of lithium in 40 cc. of anhydrous ether, was added to 2.50 g. (0.01 mole) of 2-bromodibenzofuran in 20 cc. of ether. The solution was stirred at room temperature for 20 hours, then poured on powdered, solid carbon dioxide. The acidic product was extracted with very dilute potassium hydroxide solution, then precipitated by the addition of dilute hydrochloric acid. The crude 2-bromo-4-dibenzofurancarboxylic acid was recrystallized from glacial acetic acid to yield 0.6 g. (21%) of pure product, m.p. 284-285°.

In a second experiment the yield of pure acid was 0.5 g. (17%).

Two more experiments were run using the same conditions as above except that the concentration of the phenyllithium was doubled. The yields of pure product were 0.7 g. (23.6%), and 0.6 g. (21%).

Attempted preparation of 2-dibenzofuryllithium

To a solution of 12.35 g. (0.05 mole) of 2-bromodibenzofuran in 50 cc. of ether and 50 cc. of benzene in an atmosphere of dry nitrogen was added 1 g. (0.141 g. atom) of finely divided lithium. Even after many hours refluxing and stirring, the reaction mixture showed no sign of reaction. Since this unreactivity might be due to a coating of lithium nitride on the lithium, butane and helium were tried as inert atmospheres in place of the nitrogen. Pure ether was used as a solvent but there was no reaction even after 24 hours.

Under the same experimental conditions lithium did not react with 2-iododibenzofuran.

Preparation of 4-dibenzofuryllithium

To a solution of 1.38 g. (0.0056 mole) of 4-bromodibenzofuran in 20 cc. of ether was added 0.2 g. (0.029 g. atom) of lithium in small pieces. In 15 minutes this solution gave a positive color test. After one hour the solution was carbonated and hydrolyzed to yield 0.7 g. (58%) of 4-dibenzofurancarboxylic acid, m.p. 209-210° after crystallization from dilute ethyl alcohol.

Metalation of 2-bromodibenzofuran with methyllithium

A solution of methyllithium, prepared from 5.7 g. (0.04 mole) of methyl iodide in 20 cc. of ether and 0.7 g. (0.1 g. atom) of lithium

in 40 cc. of ether, was added to 5 g. (0.02 mole) of 2-bromodibenzofuran in 40 cc. of ether. This solution was refluxed for 20 hours, then cooled and poured on powdered, solid carbon dioxide. After carbonation, the solution was hydrolyzed and the acid was extracted with dilute potassium hydroxide solution. This alkaline solution was acidified with dilute hydrochloric acid to yield 2.3 g. (39.6%) of crude 2-bromo-4-dibenzofurancarboxylic acid, m.p. 255-265°. This crude acid also contained some inorganic salt. After crystallization from glacial acetic acid there was obtained 1.3 g. (24.2%) of pure 2-bromo-4-dibenzofurancarboxylic acid, m.p. 284-285°.

In a second experiment the yield of pure 2-bromo-4-dibenzofurancarboxylic acid was 1.6 g. (27.6%), m.p. 284-285°.

Attempted metalation of 2-dibenzofurylmagnesium bromide with n-butyllithium

To a solution of 10 g. (0.041 mole) of 2-bromodibenzofuran in 75 cc. of ether and 25 cc. of benzene was added 1.08 g. (0.045 g. atom) of magnesium and a crystal of iodine. This solution was stirred and refluxed for 4 hours, then filtered into a clean, dry flask.

In a separate flask was prepared a solution of n-butyllithium from 10.96 g. (0.16 mole) of n-butyl bromide in 25 cc. of ether and 3.15 g. (0.45 g. atom) of lithium in 50 cc. of ether. The n-butyllithium was filtered, and added to the solution of the 2-dibenzofurylmagnesium bromide. In addition 150 cc. of benzene was added to raise the boiling

point. When the two solutions were mixed together a white precipitate formed. After stirring and refluxing for 20 hours, the solution was cooled and poured on powdered, solid carbon dioxide. The product was extracted with dilute potassium hydroxide solution, then precipitated with dilute hydrochloric acid. The yield of crude product was 4.9 g., m.p. 220-225°. This crude acid was recrystallized from methyl alcohol to give pure 2-dibenzofurancarboxylic acid, m.p. 240-242°. The methyl ester was prepared from the acid and diazomethane in ether and melted at 81-82° after crystallization from dilute alcohol. A mixed melting point with an authentic sample was not depressed. No other product was isolated from this reaction.

Reaction of n-butylmagnesium bromide with 4-iododibenzofuran

A solution of n-butylmagnesium bromide, prepared from 1.20 g. (0.05 g. atom) of magnesium and 6.85 g. (0.05 mole) of n-butyl bromide in 50 cc. of ether and 25 cc. of benzene was allowed to stand several days. The clear ether solution was carefully filtered to remove any magnesium particles. This filtered solution was added to 4.50 g. (0.015 mole) of 4-iododibenzofuran in 25 cc. of benzene. This solution was stirred and refluxed for four hours, then carbonated by pouring it on powdered, solid carbon dioxide. The magnesium salts were dissolved in hydrochloric acid, then the acid was extracted from the ether solution with dilute potassium hydroxide and precipitated with dilute hydrochloric acid. The yield of 4-dibenzofurancarboxylic acid was 1.8 g. (55.6%), m.p. 207-208°.

In a second experiment carried out just as above the yield of 4-dibenzofurancarboxylic acid was 1.3 g. (37.5%).

Reaction of methyllithium and 4-iododibenzofuran

A solution of methyllithium, prepared from 5.7 g. (0.04 mole) of methyl iodide in 20 cc. of ether and 0.7 g. (0.10 g. atom) of lithium in 40 cc. of ether, was added to a solution of 2.94 g. (0.01 mole) of 4-iododibenzofuran in 40 cc. of ether. This solution was stirred and refluxed for 20 hours, then poured on powdered, solid carbon dioxide. The ether solution was extracted with dilute potassium hydroxide solution, then the 4-dibenzofurancarboxylic acid was precipitated by the addition of dilute hydrochloric acid. The crude yield was 0.7 g. (33%), m.p. 203-205°. After crystallization from 50 per cent alcohol the yield of pure acid was 0.5 g. (23.6%), m.p. 209-210°.

Interconversion of 1-bromo-2-hydroxydibenzofuran with n-butyllithium

A solution of n-butyllithium, prepared from 16.1 g. (0.12 mole) of n-butyl bromide in 20 cc. of ether and 2.8 g. (0.40 g. atom) of lithium in 70 cc. of ether, was filtered into a dry flask. Then a solution of 4.0 g. (0.015 mole) of 1-bromo-2-hydroxydibenzofuran in 20 cc. of ether was added from a dropping funnel at such a rate that gentle refluxing occurred. The solution was stirred and refluxed for thirty minutes following the addition of the 1-bromo-2-hydroxydibenzofuran solution. Next it was cooled and poured on powdered, solid carbon

dioxide. This ether solution was extracted with dilute potassium hydroxide, then the 2-hydroxy-1-dibenzofurancarboxylic acid was precipitated by the addition of dilute hydrochloric acid. The yield of the crude product was 2.5 g. (74%), m.p. 216° with decomposition. This melting point was not changed by recrystallization from ethyl alcohol. The melting point was found to vary on pure samples unless the bath was heated rapidly to about 210° and then heated more slowly until the compound melted.

Anal. Calcd. for $C_{13}H_8O_4$: Neut. equiv., 228. Found: Neut. equiv., 220.

Preparation of 2-aminodibenzofuran hydrochloride

A solution of 2-dibenzofurylmagnesium bromide was prepared from 5.94 g. (0.02 mole) of 2-bromodibenzofuran, 0.5 g. (0.024 mole) of magnesium, and a few drops of butylmagnesium bromide solution in 100 cc. of ether. The solution was refluxed for two hours, then cooled and filtered. A salt-ice bath was used to cool the reaction mixture while a solution of 0.28 g. (0.006 mole) of α-methylhydroxylamine[80] in 20 cc. of ether was added slowly. The reaction mixture was hydrolyzed after it had stood overnight. The ether solution was separated and dried over sodium sulfate. Then the ether solution was saturated with dry hydrogen chloride gas to yield 0.5 g. (38%) of 2-aminodibenzofuran hydrochloride.

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[80] Sheverdina and Kocheskov, J. Gen. Chem., U.S.S.R., 8, 1825 (1938). [C. A. 33, 5804 (1939)].

Preparation of 4-aminodibenzofuran

A solution of n-butyllithium was prepared from 134 g. (1 mole) of n-butyl bromide and 21 g. (3 g. atoms) of lithium in 650 cc. of ether. This solution was then added to a solution of 84 g. (0.5 mole) of dibenzofuran in 200 cc. of ether. After 20 hours, 9.9 g. (0.21 mole) of _-methylhydroxylamine in 60 cc. of ether was added.[80] The 4-dibenzofurylilithium solution was cooled in a salt-ice bath while the _-methylhydroxylamine solution was added very slowly. After two hours at reflux temperature the solution still gave a positive color test. Therefore refluxing was continued overnight. The color test was negative after 12 hours at reflux temperature. The solution was hydrolyzed carefully by the addition of ice water, and the ether was separated and dried over sodium sulfate. The dry ether extract was then saturated with dry hydrogen chloride gas. The 4-aminodibenzofuran hydrochloride was filtered off and dissolved in a liter of warm water. A small amount of dibenzofuran was filtered off, and then the solution was made alkaline. The yield of 4-aminodibenzofuran, m.p. 81-82°, was 21.3 g. (78.4%), based on the amount of dibenzofuran used in the reaction. In addition 59 g. (72%) of dibenzofuran was recovered.

Preparation of bi-2-dibenzofuryl

A solution of 15 g. (0.062 mole) of 2-bromodibenzofuran and 1.5 g. (0.062 g. atom) of magnesium in 150 cc. of ether with a crystal of iodine

was refluxed and stirred for four hours. Then the solution was cooled in an ice bath and 2.75 g. (0.02 mole) of cupric chloride suspended in 75 cc. of ether was added. The mixture was refluxed two hours, cooled, and hydrolyzed with ice water and concentrated hydrochloric acid. The ether layer was washed with sodium carbonate solution, then with water, and finally was dried over sodium sulfate. The ether was evaporated, and the crystalline product remaining was recrystallized from glacial acetic acid. The yield of pure bi-2-dibenzofuryl was 2.5 g. (25%), m.p. 201-202°.

Anal. Calcd. for $C_{24}H_{14}O_2$: C, 86.21; H, 4.22. Found: C, 86.03; H, 4.56.

Preparation of bi-3-dibenzofuryl

To a solution of 10 g. (0.041 mole) of 3-bromodibenzofuran in 200 cc. of ether was added 1.2 g. (0.05 g. atom) of magnesium metal and 2 cc. of n-butylmagnesium bromide solution as catalyst. The solution was refluxed for 14 hours, then 6.5 g. (0.049 mole) of cupric chloride was added. The solution was refluxed for two hours, then hydrolyzed and acidified. The product was so insoluble it was filtered off and recrystallized from glacial acetic acid. The yield of pure bi-3-dibenzofuryl, m.p. 245-246°, was 3 g. (41.8%). Recrystallization from dioxane did not raise the melting point.

Anal. Calcd. for $C_{24}H_{14}O_2$: C, 86.21; H, 4.22. Found: C, 86.54; H, 4.63.

Reaction of 2-Dibenzofuryllithium with benzonitrile

A solution of n-butyllithium was prepared from 6.7 g. (0.05 mole) of n-butyl bromide in 25 cc. of ether, 1.4 g. (0.2 g. atom) of lithium in 25 cc. of ether and was then added to a solution of 3 g. (0.012 mole) of 2-bromodibenzofuran in 50 cc. of benzene. This reaction mixture was stirred and refluxed for thirty minutes, then 2.06 g. (0.02 mole) of benzonitrile in 7 cc. of ether and 7 cc. of benzene was added. The solution was refluxed for an hour following this addition after which time the color test was negative.

The solution became bright red following the addition of the benzonitrile. After the period of refluxing, it was cooled and hydrolyzed with ice water followed by concentrated hydrochloric acid. The ether layer changed from red to pale yellow during the hydrolysis. The ether layer was dried and the ether was distilled off. The tarry material that remained was extracted several times with hot water, then recrystallized from alcohol. The yield of crude 2-benzoyldibenzofuran was 1.55 g. (42%), m.p. 129-132°. The yield of pure material was 1.3 g. (36.4%), m.p. 134-135° after two recrystallizations from alcohol. The identity of this material was confirmed when it did not depress the melting point of an authentic sample, m.p. 135-136°, prepared from benzoyl chloride and dibenzofuran by the Friedel and Crafts reaction.

Attempted mercuration of 2-bromodibenzofuran

A melt of 27 g. (0.11 mole) of 2-bromodibenzofuran heated at 140°

in a metal bath was mechanically stirred while 31.9 g. (0.1 mole) of mercuric acetate was added slowly. The mixture was stirred and heated for four hours. After cooling the product was like taffy. It was extracted several times with 250 cc. of boiling petroleum ether (b.p. 60-68°) to remove any unreacted 2-bromodibenzofuran. The remaining product was extracted for four hours in a Soxhlet with glacial acetic acid. This solution was then cooled and precipitated by the addition of petroleum ether, b.p. 60-68°. A brown oil separated that could not be induced to solidify by cooling or by the use of a variety of solvents.

Preparation of 2-(β-hydroxyethyl)-dibenzofuran

This compound was prepared from 2-dibenzofurylmagnesium bromide and ethylene oxide in 45 per cent yield in accordance with the directions of Parker[13] and Kirkpatrick.[10] In addition there was obtained 1 g. (1.2%) of bi-2-dibenzofuryl, m.p. 202-203° after crystallization from glacial acetic acid.

Preparation of 2-(β-bromoethyl)-dibenzofuran

This compound[10,13] was prepared in 60 per cent yield by the action of hydrogen bromide gas on 2-(β-hydroxyethyl)-dibenzofuran.

Preparation of 2-(β-aminoethyl)-dibenzofuran

This compound[10,13] was prepared in 15 per cent yield from 2-(β-bromoethyl)-dibenzofuran and the potassium salt of phthalimide.

Preparation of N-benzoyl 2-(β-aminoethyl)-dibenzofuran

To a solution of 2 g. (0.05 mole) of sodium hydroxide in 20 cc. of water was added 1 g. (0.005 mole) of 2-(β-aminoethyl)-dibenzofuran and 1.5 g. (0.01 mole) of benzoyl chloride. The mixture was shaken for 15 minutes, then heated shortly on a steam-bath to remove excess benzoyl chloride. A crystalline product separated. The precipitate was filtered and washed to yield 1.2 g. (89%) of crude product, m.p. 177-180°. After crystallization from glacial acetic acid the yield was 1.1 g. (78%) of pure product, m.p. 183.5-183.9°.

Attempted ring closure on N-benzoyl 2-(β-aminoethyl)-dibenzofuran

To a solution of 0.2 g. (0.0013 mole) of phosphorous oxychloride in 10 cc. of chloroform was added 0.1 g. (0.0003 mole) of N-benzoyl 2-(β-aminoethyl)-dibenzofuran. The solution was allowed to stand overnight. Only a gum resulted.

Similar attempts using xylene as a solvent and phosphorous pentoxide as a catalyst were likewise unsuccessful.

Attempted preparation of 2,3,8-triaminodibenzofuran

To a suspension of 3 cc. of Raney nickel catalyst in 50 cc. of n-propyl alcohol was added 0.7 g. (0.004 mole) of 2,8-diamino-3-nitrodibenzofuran. This suspension was hydrogenated at 100° and 45 pounds of hydrogen for two hours. Then the solution was cooled, filtered under nitrogen, and boiled up twice with Norite under nitrogen. The

alcohol was distilled off and ether was added. The amine hydrochloride was then precipitated by passing in dry hydrogen chloride gas. However, even the dry amine hydrochloride was unstable in the presence of light or air so it was not examined further.

Nitration of 2,8-diacetaminodibenzofuran

A solution of 1 g. (0.004 mole) of 2,8-diacetaminodibenzofuran in 20 cc. of boiling glacial acetic acid was quickly cooled and 1 cc. (0.02 mole) of fuming nitric acid (sp. g. 1.52) was added slowly. The solution was allowed to stand two hours at room temperature, then it was poured into 100 cc. of cold water. The precipitate weighed 0.9 g. (80%) and melted at 275-280°. After repeated crystallization from alcohol and from acetic acid, 0.1 g. (8.9%) of pure 2,8-diacetamino-3-nitrodibenzofuran was obtained, m.p. 322-324° with some softening at 312°.

Anal. Calcd. for $C_{16}H_{13}N_3O_5$: N, 12.92. Found: N, 13.22.

Preparation of 2,8-diamino-3-nitrodibenzofuran

To a mixture of 30 cc. of concentrated hydrochloric acid and 30 cc. of ethyl alcohol was added 2 g. (0.0074 mole) of 2,8-diacetamino-3-nitrodibenzofuran. This suspension was heated under reflux for two hours. The color changed from yellow to red and finally a clear red solution resulted. This solution was cooled, diluted with water, and made alkaline with ammonium hydroxide. The yield of 2,8-diamino-3-nitro-

dibenzofuran was 1.4 g. (76%), m.p. 212-213°, after recrystallization from alcohol.

Anal. Calcd. for $C_{12}H_9N_3O_3$: N, 17.28. Found: N, 17.47.

Preparation of 3-nitrodibenzofuran

In accordance with the directions of Cullinane[81] the amino groups were removed from the 2,8-diamino-3-nitrodibenzofuran. To a mixture of 5 cc. of water and 25 cc. of ethyl alcohol, was added 5 cc. of concentrated sulfuric acid and 0.5 g. (0.003 mole) of 2,8-diamino-3-nitrodibenzofuran and 2.5 g. (0.03 mole) of sodium nitrite in small amounts. The reaction mixture was refluxed for thirty minutes, then cooled and diluted with water and filtered. The precipitate was washed with dilute alkali, dilute acid, and then extracted with boiling acetone. This product was recrystallized from a 50-50 alcohol-acetone mixture. The pure 3-nitrodibenzofuran obtained then melted at 182-183°, and a mixed melting point with an authentic specimen showed no depression.

Preparation of 4-dibenzofurancarboxylic acid dimethylamide

To a suspension of 5 g. (0.022 mole) of 4-dibenzofurancarboxylic acid chloride in 20 cc. of anhydrous ether was added excess dimethylamine. The reaction was quite vigorous. After standing several hours at room temperature, the reaction mixture was washed with water. The ether layer was dried and the ether was distilled off. The product was recrystallized

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[81] Cullinane, J. Chem. Soc., 2267 (1930).

from petroleum ether (b.p. 60-68°) to yield 5.8 g. (73%) of shiny white crystals, m.p. 116.5°. Recrystallization from methyl alcohol failed to raise this melting point.

Anal. Calcd. for $C_{15}H_{13}NO_2$: N, 5.85. Found: N, 6.02.

Preparation of 2-dibenzofurancarboxylic acid diethylamide

To a solution of 5 g. (0.02 mole) of 2-dibenzofurancarboxylic acid chloride in 100 cc. of anhydrous ether was added an excess of anhydrous diethylamine. The ether solution was washed with sodium carbonate solution, and then with water, and was dried over sodium sulfate. The ether was removed, and the product was recrystallized from petroleum ether, b.p. 60-68°, to yield 3.5 g. (60%), m.p. 77-78°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: N, 5.24. Found: N, 5.05.

Metalation of 2-dibenzofurancarboxylic acid diethylamide

To a solution of 2 g. (0.0075 mole) of 2-dibenzofurancarboxylic acid diethylamide in 50 cc. of ether was added a solution of phenyllithium prepared from 0.3 g. (0.042 g. atom) of lithium and 1.5 g. (0.01 mole) of bromobenzene in 25 cc. of ether. The reaction mixture was refluxed 2 hours, then carbonated by pouring it upon powdered, solid carbon dioxide. The ether solution was extracted with alkali. On acidification the alkaline solution yielded 0.85 g. (38.5%) of 2-benzoyl-x-dibenzofuran-carboxylic acid, m.p. 265-266° after recrystallization from 50 per cent alcohol.

Anal. Calcd. for $C_{20}H_{12}O_4$: Neut. equiv., 317. Found: Neut. equiv., 315, 320.

From the ether solution was obtained a neutral gum that melted at 136-137° after recrystallization from ethyl alcohol. A mixed melting point with an authentic specimen of 2-benzoyldibenzofuran prepared from benzoyl chloride and dibenzofuran by the Friedel and Crafts reaction, was not depressed.

The methyl ester of the 2-dibenzofuran-x-carboxylic acid was prepared from the acid and diazomethane in ether. This ester melted at 189-190°, after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{21}H_{14}O_4$: OCH_3, 9.40. Found: OCH , 9.44.

Preparation of 2-benzoyldibenzofuran

To a mixture of 43.7 g. (0.26 mole) of dibenzofuran in 400 cc. of nitrobenzene was added slowly 53 g. (0.4 mole) of aluminum chloride. Then 59 g. (0.42 mole) of benzoyl chloride was added dropwise to the well-stirred solution. These additions were carried out while the reaction mixture was cooled in an ice bath. One hour after the addition was completed the flask was removed from the ice bath and allowed to come slowly to room temperature.

After two hours at room temperature 300 g. of ice and 100 cc. of concentrated hydrochloric acid were added cautiously. The nitrobenzene was steam-distilled. Because at this point the flask broke some of

the product was lost. The solid residue remaining after removal of the nitrobenzene was washed with acid, then with methyl alcohol, and extracted with glacial acetic acid. After crystallization from glacial acetic acid and from dioxane a pure product was obtained. The yield was 20.8 g. (30%), m.p. 135-136°.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.80. H, 4.40. Found: C, 84.03. H, 4.23.

The oxime was prepared in 85 per cent yield, m.p. 182-183° after crystallization from ethyl alcohol.

Anal. Calcd. for $C_{19}H_{13}NO_2$: N, 4.88. Found: N, 4.63.

Preparation of diethyl 3-aminodibenzofuran-N-ethylmalonate

This compound was prepared in accordance with the directions of Borsche and Schacke[35] for the preparation of the analogous compound from diethyl bromomalonate. A mixture of 7.32 g. (0.04 mole) of 3-aminodibenzofuran and 5.34 g. (0.02 mole) of diethyl bromoethylmalonate[82] was heated on a water bath for an hour without any solvent. The melt was then cooled and extracted several times with ether. The ether was removed and the product was recrystallized from alcohol to yield 0.6 g. (8.5%), m.p. 98-99°. By dilution of the alcohol with water and then recrystallization of the precipitate from petroleum ether (b.p. 60-68°) 3 g. more of product was obtained. The combined yield was 51 per cent of product that melted at 99-100° after one more

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[82]This compound was prepared in 82 per cent yield by the method of Ruhemann, Ber., 26, 2357 (1893).

recrystallization from petroleum ether (b.p. 60-68°).

Anal. Calcd. for $C_{21}H_{23}NO_5$: N, 3.79. Found: N, 4.02.

Preparation of diethyl 4-aminodibenzofuran-N-ethylmalonate

A mixture of 2.5 g. (0.014 mole) of 4-aminodibenzofuran and 1.87 g. (0.007 mole) of diethyl bromoethylmalonate was heated on a water bath one hour. The cooled melt was extracted with ether; the ether was removed and the residue was treated with Norite and recrystallized from petroleum ether (b.p. 60-68°). The yield was 1.9 g. (76.6%), m.p. 75-76°.

Anal. Calcd. for $C_{21}H_{23}NO_5$: N, 3.79. Found: N, 3.62.

Attempted preparation of diethyl 2-nitro-3-aminodibenzofuran-N-ethylmalonate

A mixture of 4.96 g. (0.019 mole) of diethyl bromoethylmalonate and 8.5 g. (0.037 mole) of 2-nitro-3-aminodibenzofuran was heated on the steam bath but this mixture did not melt. No reaction occurred. To this mixture was added 100 cc. of toluene and the heating was continued for an additional hour but there was still no reaction.

Preparation of 3-N^2-acetylsulfanilamidodibenzofuran

To a solution of 9.6 g. (0.05 mole) of 3-aminodibenzofuran in 50 cc. of absolute alcohol was added 9.36 g. (0.04 mole) of p-acetaminobenzenesulfonyl chloride. This reaction mixture was refluxed for five

hours, then it was cooled and poured into 400 cc. of ice water. The aqueous solution was made alkaline with potassium hydroxide and extracted with ether. The clear aqueous solution was then acidified and filtered to yield 8.2 g. (54%) of crude product, m.p. 199-203°. Several recrystallizations from dilute alcohol raised the melting point to 223-224°. The yield of pure compound was 5 g. (39%).

Anal. Calcd. for $C_{20}H_{16}N_2O_4S$: N, 7.37. Found: N, 7.62.

Preparation of 3-sulfanilamidodibenzofuran

A mixture of 4 g. (0.015 mole) of 3-N^2-acetylsulfanilamidodibenzofuran, 150 cc. of 95 per cent ethyl alcohol, and 150 cc. of concentrated hydrochloric acid was refluxed for five hours. The solution was then cooled and filtered to yield 3.2 g. (80%) of 3-sulfanilamidodibenzofuran hydrochloride. This amine hydrochloride was suspended in water and the free amine was liberated by the addition of dilute ammonium hydroxide. The yield was 2.7 g. (65%) of the amine, m.p. 245° after recrystallization from a large volume of ethyl alcohol.

Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: N, 9.46. Found: N, 9.21.

Preparation of 4-N^2-acetylsulfanilamidodibenzofuran

To a solution of 9.6 g. (0.05 mole) of 4-aminodibenzofuran in 50 cc. of absolute alcohol was added 9.4 g. (0.04 mole) of p-acetaminobenzenesulfonyl chloride. This solution was refluxed for five hours, then cooled and poured into 400 cc. of water. This solution was made alkaline

and extracted with ether. The clear alkaline solution was then acidified and filtered to yield 6.2 g. (41%) of product, m.p. 210-214°. This material was recrystallized from dilute alcohol to yield 4.0 g. (26.5%), m.p. 218°.

Anal. Calcd. for $C_{20}H_{16}N_2O_4S$: N, 7.37. Found: N, 7.06.

Preparation of 4-sulfanilamidodibenzofuran

A mixture of 4 g. (0.015 mole) of 4-N^2-acetylsulfanilamidodibenzofuran, 150 cc. of 95 per cent ethyl alcohol, and 150 cc. of concentrated hydrochloric acid was refluxed for five hours. Then the reaction mixture was cooled and filtered. The amine hydrochloride was converted into the free amine by treatment with ammonium hydroxide. The amine was recrystallized from ethyl alcohol to yield 3 g. (75%) of pure product, m.p. 196°.

Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: N, 9.46. Found: N, 9.39.

Attempted bromination of 2-nitro-3-acetaminodibenzofuran

To a solution of 1 g. (0.004 mole) of 2-nitro-3-acetaminodibenzofuran in 10 cc. of glacial acetic acid was added 0.3 g. (0.004 mole) of bromine. No reaction took place at room temperature after 12 hours. Even when the solution was heated to boiling, the starting material was recovered unchanged.

Attempted bromination of 2,8-diacetoxydibenzofuran

An attempt was made to brominate 2,8-diacetoxydibenzofuran by the method used for the bromination of 4-acetoxybiphenyl.[83] To a suspension of 5.96 g. (0.021 mole) of 2,8-diacetoxydibenzofuran in 30 cc. of glacial acetic acid was added 11.7 g. (0.063 mole) of bromine. A trace of iron filings was added and the solution was heated at 105° for 13 hours. This solution was then poured into 400 cc. of water, filtered, and the precipitate was recrystallized from alcohol. All that was isolated was the unchanged starting material, as shown by a mixed melting point.

Attempted Fries rearrangement on 2,8-diacetoxydibenzofuran

To a solution of 11.5 g. (0.04 mole) of 2,8-diacetoxydibenzofuran in 90 cc. of tetrachloroethane was added 11.97 g. (0.09 mole) of aluminum chloride. The solution was cooled in an ice bath during this addition. After the solution had stood at room temperature 45 hours, it was hydrolyzed by the careful addition of water. The solution was then acidified, the solvent steam-distilled, and the remaining water solution was cooled and filtered. The precipitate was heated with sodium hydroxide, then again cooled and filtered. The alkali insoluble product was unchanged 2,8-diacetoxydibenzofuran as shown by a mixed melting point. The portion soluble in the alkali was precipitated by

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[83]Hazlet and Kornberg, J. Am. Chem. Soc., 61, 3037 (1939).

the addition of acid and was found to be 2,8-dihydroxydibenzofuran as shown by a mixed melting point.

Preparation of 2-acetoxy-1-dibenzofurancarboxylic acid

To a suspension of 1.5 g. (0.007 mole) of 2-hydroxy-1-dibenzofurancarboxylic acid in 30 cc. of acetic anhydride was added one drop of concentrated sulfuric acid. The solution was warmed until the acid dissolved. After the solution had stood for 20 minutes, it was cooled and poured into 200 cc. of cold water. This solution was stirred vigorously until all the acetic anhydride was hydrolyzed. The product was filtered off. The crude yield was 1.6 g. (91.6%), m.p. 136-140°. This crude material was recrystallized from dilute alcohol to yield 1.3 g. (74.5%) of pure product, m.p. 151-152°.

Anal. Calcd. for $C_{15}H_{10}O_5$: Neut. equiv., 270. Found: Neut. equiv., 279.

Attempted preparation of 2-methoxy-1-dibenzofuranacetic acid

Following the procedure of Hill and Short[84] for the oxidation of an allyl group to the corresponding acetic acid, an attempt was made to prepare 2-methoxy-1-dibenzofurylacetic acid. A solution of 2.3 g. (0.01 mole) of 1-allyl-2-methoxydibenzofuran[85] in 4.32 g. (0.072 mole) of

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[84]Hill and Short, J. Chem. Soc., 260 (1937)

[85]Kindly supplied by P.R. Van Ess.

glacial acetic acid, 2.4 cc. of water, and 1.9 g. (0.012 mole) of potassium permanganate was refluxed for 72 hours. The permanganate was reduced to manganese dioxide but no acidic product was isolated.

Preparation of 2,8-dihydroxy-1,9(?)-bisphenylazodibenzofuran

The procedure for the azo coupling was taken essentially that used in coupling reactions with 2-hydroxydibenzofuran by M.W. Van Ess.[63]

A solution of 10 g. (0.05 mole) of 2,8-dihydroxydibenzofuran in 54 cc. of 15 per cent potassium hydroxide solution was diluted with 300 cc. of water and cooled in an ice bath. To this solution was added a diazonium solution prepared from 25 cc. of concentrated hydrochloric acid, 9.3 g. (0.1 mole) of aniline, 75 g. of cracked ice, and 7.25 g. (0.105 mole) of sodium nitrite in 20 cc. of water. The diazonium solution was added slowly over a half-hour period with constant shaking. The reaction mixture became dark red immediately after addition began. The solution was well shaken for one-half hour after the addition was completed, then it was allowed to stand at 0° for an hour. The red, alkali-insoluble product was filtered off and recrystallized from a liter of glacial acetic acid after treatment with Norite, followed by the addition of 200 cc. of water to the hot solution. The yield was 11.5 g. (56%), m.p. 165-166°. This compound decomposed at 240-250° with the evolution of gas. A second recrystallization from glacial acetic acid did not raise the melting point.

Anal. Calcd. for $C_{24}H_{16}N_4O_3$: N, 13.73. Found: N, 14.25.

Attempted preparation of 2,8-dimethoxy-1,9(?)-bisphenylazodibenzofuran

This preparation was carried out in essential accordance with the procedure used earlier[86] for the preparation of 4-hydroxy-6-methoxy-1-phenylazodibenzofuran. To a solution of 6.15 g. (0.015 mole) of 2,8-dihydroxy-1,9(?)-bisphenylazodibenzofuran in 60 cc. of acetone was added 28.6 g. (0.23 mole) of dimethyl sulfate. This solution was refluxed and stirred while a solution of 38.1 g. (0.68 mole) of potassium hydroxide in 30 cc. of water was added slowly. The solution was stirred and refluxed for an hour following this addition. Then it was diluted with water to 450 cc., cooled and filtered. There was obtained 5.8 g. (94%) of recovered starting material, melting point and mixed melting point 165-166°.

An attempt was made to prepare this compound by the use of sodium methylate and methyl iodide but it was likewise unsuccessful.

Reaction of 1,9-dibromo-2,8-dimethoxydibenzofuran with methyllithium

To a suspension of 1.8 g. (0.005 mole) of 1,9-dibromo-2,8-dimethoxydibenzofuran in 40 cc. of ether was added 0.01 mole of methyllithium. The solution was refluxed for 20 hours, then poured on powdered, solid carbon dioxide. The ether solution was hydrolyzed with water and extracted with potassium hydroxide solution. Acidification of the

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[86]Gilman and Cheney, J. Am. Chem. Soc., 61, 3149 (1939).

alkaline extract yielded 0.8 g. (54%) of crude acid. This crude product was recrystallized from glacial acetic acid after decolorization with Norite to yield white crystals melting at 270-271°. Thus this compound which was shown by a sodium fusion to contain no bromine was 2,8-dimethoxy-1,9-dibenzofurandicarboxylic acid. This same yield was obtained previously using n-butyllithium.[79]

Attempted preparation of 2-iodo-3,6-dimethoxy-4-nitrotoluene

To a mixture of 3.94 g. (0.02 mole) of 5-nitrotoluhydroquinol dimethyl ether[67] and 3.80 g. (0.03 g. atom) of iodine was added 8 cc. of concentrated nitric acid. There was a vigorous reaction and soon only tar remained.

In another attempt using the same quantities of reactants, the nitric acid was diluted with 50 cc. of water prior to addition. There was no reaction.

In another attempt using the above amounts of materials, the nitric acid was diluted with 100 cc. of glacial acetic acid. There was a reaction and the iodine was consumed after the solution had stood overnight. The solution was diluted to 400 cc. with water and washed with potassium iodide solution and with water. The yield was 0.7 g. of product that melted at 125-145° after recrystallization from alcohol. This yield was so discouraging further work was abandoned on this compound.

Attempted bromination of 5-nitrotoluhydroquinol dimethyl ether

To a solution of 3.94 g. (0.02 mole) of 5-nitrotoluhydroquinol dimethyl ether[67] in 25 cc. of carbon tetrachloride was added 3.2 g. (0.02 mole) of bromine. No reaction occurred so a trace of iron was added as a catalyst and the solution was refluxed several hours. When all of the bromine was consumed the solution was washed with sodium thiosulfate, and the carbon tetrachloride was distilled off. The yield was 2.4 g. of crude product. This product was recrystallized from ethyl alcohol to yield 1.5 g. of pure product, m.p. 168°. This compound contained bromine but no nitrogen.

By hydrolysis with hydrobromic acid in glacial acetic acid followed by acetylization with acetic anhydride the corresponding diacetoxy derivative was prepared, m.p. 253-254°. These compounds were not analyzed or further investigated.

Preparation of 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl

This compound was prepared in essential accordance with the procedure of Erdtman,[67] from 3 g. of copper and 3 g. of 5-iodotoluhydroquinol dimethyl ether.[67] The yield was 50 per cent of white crystals that melted at 134°. In a second run on a larger scale the yield was raised to 84 per cent.

Demethylation of 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl

A mixture of 4.5 g. of 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl, 20 cc. of glacial acetic acid, and 25 cc. of 42 per cent hydrobromic acid was refluxed 20 hours in an all glass apparatus. The solution was then poured into 400 cc. of water and filtered. The precipitate was dissolved in 50 cc. of 95 per cent ethyl alcohol and cooled. The few milligrams of product that crystallized out were sublimed under reduced pressure at 200°. The product from this sublimation melted at 232°. This is the melting point given by Nietzki[87] for his supposed 4,6-dimethyl-2,8-dihydroxydibenzofuran. However, the work of Erdtman[87] has established that Nietzki was mistaken in his suggested structure.

A mixed melting point was taken with the compound prepared as given above and the supposed 3,7-dimethyl-2,8-dihydroxydibenzofuran prepared by Jack Swislowsky.[19] There was no depression.

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[87]Nietzki, Ber., 11, 1278 (1878).

DISCUSSION

Evidence for Assigned Structures

Metalation[88] of dibenzofuran with organoalkali compounds followed by treatment with dimethyl sulfate gave a methyldibenzofuran identical with the 4-methyldibenzofuran prepared by Kruber[76] by a phenyl ether ring closure. Also the carbonation of the metalation product of dibenzofuran with organoalkali compounds gave an acid which was identical with the acid obtained by oxidation of the known 4-methyldibenzofuran.[15] All metalations of dibenzofuran have been referred back to this final proof of structure.

The structure of the interconversion product of 2-bromodibenzofuran with n-butyllithium was determined by the isolation of 2-benzoyldibenzofuran from the reaction of this interconversion product with benzonitrile. From the Friedel-Crafts reaction of benzoyl chloride with aluminum chloride and dibenzofuran there had previously been prepared an authentic specimen of 2-benzoyldibenzofuran. These two compounds were shown to be identical by a mixed melting point.

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[88]Gilman and Young, J. Am. Chem. Soc., 57, 1121 (1935).

Coupling reactions had been noted by Cheney[49] in the course of the oxidation of 4-dibenzofuryllithium to 4-methoxy-dibenzofuran. Coupling was noted in the case of the preparation of (β-hydroxyethyl)-dibenzofuran from 2-dibenzofurylmagnesium bromide and ethylene oxide. The structure of the bi-(2-dibenzofuryl) thus obtained was proved by its synthesis from 2-dibenzofurylmagnesium bromide and cupric chloride. By this same method pure bi-(3-dibenzofuryl) of known structure was obtained from 3-bromodibenzofuran.

From 2,8-dibromodibenzofuran was prepared 2,8-diaminodibenzofuran. This amine was acetylated to give 2,8-diacetaminodibenzofuran. Then this 2,8-diacetaminodibenzofuran was mono-nitrated. The nitro group was shown to be in the 3-position by deacetylating the 2,8-diacetamino-3-nitrodibenzofuran. Then the two amino groups were removed by diazotization. The resulting 3-nitrodibenzofuran was compared with a specimen of known structure by a mixed melting point and was found to be identical with the known compound. The authentic specimen was prepared by the direct nitration of dibenzofuran, but its structure was proved by a diphenyl ether ring closure.[81] In this ring closure 3-chlorodibenzofuran was prepared. The supposed 3-nitrodibenzofuran from direct nitration of dibenzofuran was reduced and diazotized to yield an identical sample of 3-chlorodibenzofuran. Yamashiro[56] has reported 2,8-diacetamino-3-nitrodibenzofuran, also; but, as in so many cases, the structure is based on assumptions with no structural proofs.

The structure of the 2,8-dihydroxy-3,7-dimethyldibenzofuran prepared

by Swislowsky[9,19] was proved by a biphenyl ring closure. Following the procedure of Erdtman,[67] toluhydroquinol dimethyl ether was iodinated with iodine and mercuric oxide. Erdtman[67] assumed that this iodination product was 5-iodotoluhydroquinol dimethyl ether. This assumption was proved to be correct by Yeoman[89] who converted the iodo compound into 2,5-dimethoxy-4-methylbenzoic acid by reaction with n-butyllithium followed by carbonation. By oxidation the 2,5-dimethoxy-4-methylbenzoic acid was converted into 2,5-dimethoxyterepthalic acid. The diethyl 2,6-dimethoxyterepthalic acid was then prepared and the melting point was found to be identical with an authentic specimen.[90]

The 5-iodotoluhydroquinol dimethyl ether was coupled by heating with copper powder to yield 2,2′-,5,5′-tetramethoxy-4,4′-dimethylbiphenyl.[67] This compound was treated with hydrobromic acid in glacial acetic acid to yield 2,8-dihydroxy-3,7-dimethyldibenzofuran. A mixed melting point with Swislowsky's 2,8-dihydroxy-3,7-dimethyldibenzofuran showed no depression. On the basis of this structural proof rests the proof for the structure of the other 2,8-dihydroxy-3,7-disubstituted dibenzofurans prepared by Swislowsky, all of which were derived originally from 2,8-dimethoxy-3,7-dibromodibenzofuran.

Metalation and Halogen-metal Interconversion

The direct metalation of dibenzofuran is the best method for the preparation of 4-substituted dibenzofurans. All the known examples of

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[89]Unpublished studies by F. Yeoman.

[90]Nef, Ann., 258, 297 (1890).

mono-metalation in dibenzofuran take place in the 4-position, whether the metalating agent is a metal,[15] a heavy metal salt like mercuric acetate[15] or thallic chloride,[91] an organo-alkali compound,[15,88] or an organo-metallic compound such as diethylstrontium[92] or diethylbarium.[92]

The metalation of other heterocycles is by no means so simple. The selective metalation of N-ethylcarbazole[93] demonstrates clearly that the particular nuclear hydrogen to be replaced depends on the organo-metallic agent employed. Another interesting example is the metalation of dibenzothiophene. Inorganic salts,[94] organo-alkali compounds,[94] and diethylstrontium[92] or diethylbarium[92] metalate dibenzothiophene in the 4-position. But phenylcalcium iodide replaces a hydrogen in the 3-position.[94] Also unexpected is the lateral metalation of methylphenyl sulfide by n-butyllithium.[95]

Cheney[8] has proposed a simple rule for the metalation of a variety of compounds with organo-alkali compounds: "All aromatic polynuclear compounds containing either ether or tertiary amine substituents can

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[91]Gilman and Abbott, J. Am. Chem. Soc., 65, 122 (1943).

[92]Unpublished studies by G. O'Donnell.

[93]Gilman and Kirby, J. Org. Chem., 1, 146 (1936).

[94]Gilman and Jacoby, J. Org. Chem., 3, 108 (1938).

[95]Gilman and Webb, J. Am. Chem. Soc., 63, 987 (1940).

be metalated with ease by organo-alkali compounds, and, in every case, the entering alkali metal will replace a hydrogen ortho to those substituents." No exceptions to this rule are known; calcium, and other alkaline earth metals, are not included in this rule.

Metalation of 2-methoxydibenzofuran[16] gives two products, both the 1- and 3-positions being involved. In a similar manner metalation of 4-methoxydibenzofuran gives substitution on both the 3- and 6-positions in about equal amounts.[86]

The metalation of 2,8-dibromodibenzofuran,[66] as well as 2-bromodibenzofuran,[49] suggests that, by choice of the proper organometallic reagent and proper conditions, one may, at will, bring about either metalation or halogen-metal interconversion. With further study other halogenodibenzofurans will probably be found to behave in a similar manner. In this manner 2,4- and 2,4,6,8-substituted dibenzofurans would be readily available which hitherto have been produced only in rare cases by ring closure reactions.

As yet very little has been done in dibenzofuran chemistry to utilize interconversion reactions for the stepwise conversion of halogen groups in polyhalogenated dibenzofurans. Thus it may prove possible to replace a single bromine atom from 2,8-dibromodibenzofurans as a step in the production of unsymmetrical dibenzofurans available now only by tedious ring closure reactions.

Only a few of the possible number of substituents have been used which can be introduced by the use of organolithium compounds. The

use of methylhydroxylamine is an excellent method of obtaining an amine directly from the organometallic compound. Methylformanilide[96] is a reagent that is very good for the introduction of aldehyde groups. There are many other similar reagents that permit the smooth introduction of functional groups directly from the organometallic reagent.

Sulfanilamide Derivatives

Many of the active sulfanilamide drugs have been prepared from heterocyclic compounds. No tests on derivatives of dibenzofuran have been reported. It seemed of interest to prepare and test some of these derivatives. However, it was found that both 3-sulfanilamidodibenzofuran[97] and 4-sulfanilamidodibenzofuran were too insoluble to be tested. More soluble derivatives might be obtained from such compounds as 2-amino-7-dibenzofuransulfonic acid, or other amino acids of dibenzofuran, the salts of which might be more soluble.

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[96] Smith and Bayliss, J. Org. Chem., 6, 437 (1940).

[97] Novelli, Ciencia, 1, 260 (1940) [C. A., 34, 7903 (1940)] reported the preparation of this compound but did not report the results of tests in vitro.

MISCELLANEOUS

Introduction

The metalation of dibenzofuran,[89] diphenyl ether,[98] dibenzothiophene,[94] and anisole[98] with n-butyllithium all take place ortho to the hetero element. A single exception is the metalation of methyl phenyl sulfide.[95]

The only compounds in which metalations take place in a meta or para position to the hetero element are those which contain, in addition, more strongly directing groups such as the methoxyl group. The metalation of 2-methoxydibenzofuran[16] with n-butyllithium yields, after carbonation, both 2-methoxy-1-dibenzofurancarboxylic acid and 2-methoxy-3-dibenzofurancarboxylic acid. Also, metalation of 4-methoxydibenzofuran takes place in both the 3- and 6-positions.

Since none of the compounds previously examined have all of the positions ortho to the hetero element blocked by alkyl groups, it is of interest to know whether the metalation of such a compound will take place laterally or in some position other than the ortho position.

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[98]Gilman and Bebb, J. Am. Chem. Soc., 61, 109 (1939).

Experimental

Methylation of 2,6-dimethylphenol

This methylation was carried by the procedure of Stevens and Tucker.[99] A solution of 74 g. (1.5 mole) of potassium hydroxide in 125 cc. of water was added slowly through a dropping funnel to a well-stirred solution of 25 g. (0.2 mole) 2,6-dimethylphenol, and 59 cc. (0.62 mole) of dimethyl sulfate in 35 cc. of acetone. After all of the potassium hydroxide was added, the solution was cooled and diluted to one liter with water. The aqueous solution was extracted with ether; the ether was distilled off, and the 2,6-dimethylanisole was distilled, b.p. 181-183°. The yield was 23.8 g. (85.5%). This compound was previously reported by Auwers and Markowitz.[100]

Metalation of 2,6-dimethylanisole

A solution of n-butyllithium, prepared from 26.8 g. (0.20 mole) of n-butyl bromide and 3.5 g. (0.50 g. atom) of lithium in 80 cc. of ether, was added to 6.8 g. (0.05 mole) of 2,6-dimethylanisole in 80 cc. of benzene. This solution was stirred and refluxed for 20 hours, then cooled and poured on powdered, solid carbon dioxide. The yield of

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[99] Stevens and Tucker, J. Chem. Soc., 123, 2140 (1923).

[100] Auwers and Markowitz, Ber., 41, 2339 (1908).

2-methoxy-3-methylphenylacetic acid was 0.6 g. (6.7%), m.p. 98-98.5°, after recrystallization from petroleum ether, b.p. 60-68°. The identity of this acid was confirmed by a mixed melting point with an authentic specimen. This same acid was previously reported by Hill and Short.[84]

Preparation of 2-hydroxy-3-methylphenylacetic acid

A solution of 0.1 g. of 2-methoxy-3-methylphenylacetic acid in 5 cc. of glacial acetic acid was demethylated by heating it with 4 cc. of 42 per cent hydrobromic acid for 16 hours. The product, m.p. 97.5° after recrystallization from dilute ethyl alcohol, gave a strong violet color with ferric chloride.

Anal. Calcd. for $C_9H_{10}O_3$: Neut. equiv., 167. Found: Neut. equiv., 160.

Introduction

Interconversion reactions, using n-butyllithium have been carried out very smoothly on a number of benzene,[101] biphenyl,[101] diphenyl ether,[101] and dibenzofuran compounds.[79] In general the halogens of these compounds can be smoothly replaced by lithium, but in the case of p-bromoanisole[34] an unexpected secondary reaction occurred. Not only p-methoxybenzoic acid, but also 2-methoxy-5-bromobenzoic acid was obtained. The same course of reactions has been found to occur in the metalation of 2-bromodibenzofuran.[49]

An interconversion reaction with 3-bromodibenzofuran yielded both 3-dibenzofurancarboxylic acid and 4-dibenzofurancarboxylic acid.[58] The similarities of other diphenyl ether and dibenzofuran interconversion reactions made it desirable to determine whether 3-iododiphenyl ether undergoes a smooth replacement of the halogen by n-butyllithium or whether a rearrangement occurs.

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[101] Gilman, Langham, and Moore, J. Am. Chem. Soc., 62, 2327 (1940).

Experimental

Halogen-metal interconversion on 3-iododiphenyl ether

A solution of n-butyllithium, prepared from 6.7 g. (0.05 mole) of n-butyl bromide and 1.4 g. (0.2 g. atom) of lithium in 50 cc. of ether, was added to 5.92 g. (0.02 mole) of 3-iododiphenyl ether in 50 cc. of benzene. This solution was stirred and refluxed for 15 minutes, then poured on solid carbon dioxide. After hydrolysis the acidic material was extracted with potassium hydroxide, and then precipitated by the addition of dilute hydrochloric acid. The yield of crude acid was 2.5 g. (50%), m.p. 142-165°. After two recrystallizations from dilute alcohol the pure compound was obtained, m.p. 144-145°. The identity of this compound was confirmed by a mixed melting point with an authentic sample of m-phenoxybenzoic acid prepared from 3-iododiphenyl ether and magnesium followed by carbonation. This acid was previously reported by Lock and Kempter.[102]

In addition 0.2 g. of an acidic compound was obtained that melted at 185° after recrystallization from dilute alcohol. This has not as yet been identified.

In a second experiment the yield of crude m-phenoxybenzoic acid was 56.7 per cent.

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[102] Lock and Kempter, Monatsch., 67, 2435 (1935).

Preparation of m-phenoxybenzoic acid

A solution of 1.0 g. (0.003 mole) of 3-iododiphenyl ether in 25 cc. of ether was stirred and refluxed 20 minutes with excess magnesium and a few drops of n-butyl bromide. The solution was cooled and poured on powdered, solid carbon dioxide. From the acidic portion extracted with potassium hydroxide and precipitated by dilute hydrochloric acid was obtained 0.6 g. (95%) of m-phenoxybenzoic acid, m.p. 145°.

SUMMARY

I. The preparation of 2- and 2,8-substituted dibenzofurans has been discussed.

II. Derivatives of 2- and 2,8-substituted dibenzofurans have been listed.

III. The structure of 2,8-dimethoxy-3,7-dibromodibenzofuran and related derivatives has been proved.

IV. The uses of metalation and halogen-metal interconversion reactions have been discussed.

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173. French patent 835,413 [C. A., 33, 4701 (1939)].

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