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14

THE PROBLEM OF BRIDGING THE 1- AND 9-POSITIONS OF DIBENZOFURAN

by

John Alexander Hogg

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

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TABLE OF CONTENTS

INTRODUCTION

The interest in dibenzofuran chemistry in these laboratories has gone through a very logical metamorphosis. The earliest investigations were carried out by Oatfield[1] in the hope of clearing up certain problems of orientation in the furan series through the preparation of furan-tetracarboxylic acid by the oxidative degradation of derivatives of dibenzofuran less resistant to attack than the parent nucleus itself.

However, derivatives of dibenzofuran, suitable for the above mentioned purpose, were not unknown at that time. Monosubstituted derivatives, prepared by halogenation,[2] nitration,[3,4] acetylation,[5,2] and sulfonation,[6] had been reported and their structures established, except in the case of sulfonation. Certain heteronuclear substituted derivatives were also known, and the structure of some of them had been established. Dibromination had been reported by Hoffmeister[7] and the structure of this compound had only recently been

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[1] Oatfield, Thesis, Iowa State College, 1933.
[2] Meyer and Krieger, Ber., 55, 1659 (1922).
[3] Borsche and Bothe, ibid., 41, 1940 (1908).
[4] Cullinane, J. Chem. Soc., 2267 (1930).
[5] Galewsky, Ann., 264, 187 (1891).
[6] Hoffmeister, ibid., 159, 211 (1871).
[7] Hoffmeister, Ber., 3, 751 (1870).

determined.[8] Hoffmeister[7] had prepared a dibenzofuran-disulfonic acid, but made no attempt to determine the position of the sulfonic acid groups. 2,8-Diacetyldibenzofuran[9] had been prepared by the Friedel-Crafts reaction and its structure shown by oxidation to the dicarboxylic acid. Brumberg[10] had nitrated 2-bromodibenzofuran, recognizing only that a mixture of isomers was produced, and left the ultimate resolution and structure clarification to later investigators.[11] In addition, some homonuclear disubstitution products had been prepared by Borsche and Schacke,[12] as a result of the nitration of 3-acetaminodibenzofuran. The product was designated 2-nitro-3-acetaminodibenzofuran. Brumberg[9] confirmed this structure.

Thus, the earlier work done in this particular series of dibenzofuran publications[13,14,15] was devoted to the confirmation of provisional formulas and to improvements in the

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[8] McCombie, Macmillan, and Scarborough, J. Chem. Soc., 529 (1931).

[9] Sugi and Sengoku, J. Pharm. Soc. Japan, 53T, 175 (1933).

[10] Brumberg, Doctoral Dissertation, Göttingen, (1925).

[11] Bywater, Doctoral Dissertation, Iowa State College, 1934.

[12] Borsche and Schacke, Ber., 56, 2498 (1923).

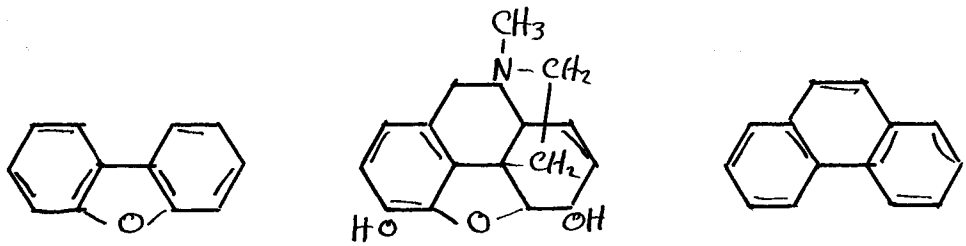
[13] Gilman, Smith and Oatfield, J. Am. Chem. Soc., 56, 1412 (1934).

[14] Gilman, Brown, Bywater, and Kirkpatrick, ibid., 56, 2473 (1934).

[15] Gilman, Bywater, and Parker, ibid., 57, 885 (1935).

preparation of these basic derivatives of dibenzofuran. Efforts to obtain the desired furan-carboxylic acids proved fruitless, and the interest in dibenzofuran chemistry had become established.

A study of the morphine (II) molecule, as proposed by Gulland and Robinson,[16] shows that dibenzofuran (I) and phenanthrene (III) are two common aromatic nuclei which are similar to portions of the morphine skeleton:



I II III

Although the search for a synthetic morphine substitute had been directed primarily toward derivatives of phenanthrene[17] at that time, the dibenzofuran molecule offered an inviting new field for new analgesics.[18,19] As work in this field progressed, it was discovered that metalation of dibenzofuran by means of

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[16] Gulland and Robinson, Mem. Proc. Manchester Lit. Phil. Soc., 69, 79 (1925).

[17] Small, Eddy, Mosettig, Himmelsbach, "Studies on Drug Addiction", U. S. Pub. Health Repts., Suppl. No. 138, Washington, D. C. (1938).

[18] Parker, Doctoral Dissertation, Iowa State College, 1938.

[19] Cheney, Doctoral Dissertation, Iowa State College, 1938.

mercuric acetate, benzylsodium, or organolithium compounds involved the 4-position[3] and that, by the use of benzylsodium,[20] dimetalation was effected, involving the 4- and 6-positions.[21,22] Cheney[19,23] worked out a better, although more difficult, approach to the preparation of 4,6-dimethoxydibenzofuran than by the oxidation of 4,6-dibenzofurylenedisodium,[21] through the stepwise introduction of methoxy-groups, using n-butyllithium as the metalating agent, followed by oxidation of the organometallic compound with subsequent methylation. It was shown that the bromination and nitration of 4-methoxydibenzofuran[18,24] involved the 1-position and that similar reactions with 4-acetaminodibenzofuran[25,26,27] also involved the 1-position. The deamination of 1-bromo-4-aminodibenzofuran resulted in 1-bromodibenzofuran.[25] Thus, each of the four

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[20] Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).

[21] Gilman and Young, ibid., 57, 1121 (1935).

[22] Gilman and Young, J. Org. Chem., I, 315 (1936).

[23] Gilman, Cheney, and Willis, J. Am. Chem. Soc., 61, 957 (1939).

[24] Gilman, Jacoby, and Swislowsky, ibid., 61, 954 (1939).

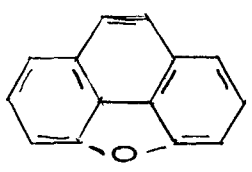
[25] Van Ess, P. R., Doctoral Dissertation, Iowa State College, 1936.

[26] Gilman and Van Ess, J. Am. Chem. Soc., 61, 1365 (1939).

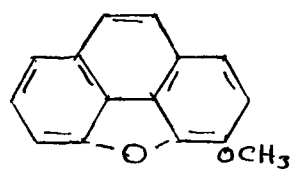
[27] Swislowsky, Doctoral Dissertation, Iowa State College, 1939.

positions of dibenzofuran had been reached and it was surmised that the dibromination of 4,6-dimethoxydibenzofuran[19] and 2,8-dihydroxydibenzofuran[27] involved the 1- and 9-positions as well as the 3- and 7-positions in the latter case. A great part of the work of this thesis is devoted to the clarification of the bromination products of 2,8-dimethoxydibenzofuran and 4,6-dimethoxydibenzofuran.

The acquisition of these new dibenzofuran compounds substituted in the 1-position and a promise of derivatives substituted in both the 1- and 9-positions stimulated interest in more nearly approximating the structure of morphine by establishing a two-carbon bridge between the 1- and 9-positions, thus incorporating both the phenanthrene and dibenzofuran molecules into a new nucleus, the derivatives of which would be very likely to show analgesic activity and would possibly be devoid of habit-forming tendencies. This new nucleus would be called phenanthrylene oxide (IV) and would be similar to methylmorphenol (V), a simple known derivative of it.



IV



V

This thesis is devoted to the discussion of dibenzofuran derivatives which might possibly be synthetic precursors to the above molecules (IV, V) or derivatives of them and to orientation work on some of these compounds which had previously been designated as 1, 9-derivatives. New and previous attempts to bridge the 1- and 9-positions are recorded and discussed.

HISTORICAL

The nature of the indifferent oxygen atom of methylmorphenol (V), prepared by the exhaustive methylation of morphine,[28] was made clear in 1897 by Vongerichten.[29] This was shown by fusion of morphenol with potassium hydroxide at elevated temperatures to yield 3,4,5-trihydroxyphenanthrene. The same material was prepared for comparison by mixed melting points through the method of Pschorr for the synthesis of derivatives of phenanthrene.

This accomplishment has shown that the completely aromatized nucleus of morphine can exist with the oxygen bridge between the 4- and 5-positions, but gives no clue to molecular strain and valence angles. Bywater[11] has pointed out that the tendency for dibenzofuran to form direct substitution products in all but the 1- or 9-positions may be the result of steric hindrance, attributed to the large oxygen angle between the two benzene nuclei, bringing the 1- and 9-positions close together and into the same plane. Through dipole moment studies of dibenzofuran, Bretscher[30] has found that an oxygen angle larger than in diphenyl ether is indicated.

---

[28] Mosettig and Meitzner, J. Am. Chem. Soc., 56, 2738 (1934).

[29] Vongerichten, Ber., 30, 2439 (1897); 31, 3198 (1898); 33, 352 (1900).

[30] Bretscher, Helv. Phys. Acta., 2, 265 (1929).

Smythe and Walls[31] have also determined the dipole moment of dibenzofuran. Other physical data on dibenzofuran are the absorption spectra,[32] the Raman spectra,[33] and the magnetic birefringence.[34] However, no electron diffraction patterns of dibenzofuran or any of its derivatives have been prepared, and, hence, no exact information regarding the spatial relationships of the 1- and 9-positions is available.

The dehydration of 3,4,5-trihydroxyphenanthrene to morphenol has never been accomplished, although Schmidt and Kämpf[35] tried a number of dehydrating agents. Dibenzofuran is formed quite readily from 2-2'-dihydroxybiphenyl[36]. This comparison is indicative of the strain which must be overcome in forming the phenanthrylene oxide nucleus. Since the choice of methods from 4,5-substituted phenanthrenes is quite limited, it is better to proceed with derivatives of dibenzofuran substituted in the 1- and 1,9-positions.

---

[31] Smythe and Walls, J. Am. Chem. Soc., 54, 3230 (1932).

[32] Charlampowiez and Marchlewskâ, Bull. Intern. Acad. Polonaise, A, 376 (1930). [C. A., 25, 5096 (1931)].

[33] Donzelot and Chaix, Compt. rend., 202, 851 (1936).

[34] John, Trans. Faraday Soc., 34, 275 (1938).

[35] Schmidt and Kämpf, Ber., 36, 3745 (1903).

[36] Cullinane and Davies, Rec. Trav. Chim., 55, 881 (1936).

Survey of Known 1- and 1,9-Derivatives

Since the problem of bridging the 1- and 9-positions of dibenzofuran is to some extent still one of obtaining suitable derivatives with substituents in either or both of these positions, a brief survey of known 1- and 1,9-derivatives is desirable.

The literature on dibenzofuran chemistry up to 1933 is well covered by Oatfield.[1] Swislowsky[27] has made a thorough survey of dibenzofuran up to 1939 and has tabulated all 1-, 4-, 6- and 9-substituted dibenzofuran compounds. Willis[37] has continued this review, bringing dibenzofuran chemistry up to date in late 1942, and has tabulated all dibenzofurans with substitution in the 2- and 2,8-positions. Thirtle[38] has reviewed all additional work up to January, 1943.

Many of the compounds listed in the following table are included in the above mentioned tables of Swislowsky[27] and Cheney,[19] and a few in the tables of Willis.[37] This table is designed to include only those derivatives that are known with certainty to contain at least one group in either the 1- or the 9-positions, and care has been taken to exclude compounds which would obviously be of little value as precursors to the actual incorporation of the 1,9-bridge. In addition, this table

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[37] Willis, Doctoral Dissertation, Iowa State College, 1943.

[38] Thirtle, Doctoral Dissertation, Iowa State College, 1943.

is intended to bring up to date recent additions to the category of 1- and 1,9-substituted derivatives. The literature references are not intended to be complete, and only major references are included.

TABLE I

Derivatives of Dibenzofuran with Substituents in the 1- and 1,9-Positions

Name of Compound	M. P.°	Reference
Monosubstituted Dibenzofurans		
1-Acetaminodibenzofuran	205	25
1-Aminodibenzofuran	74	25
1-Bromodibenzofuran	67	25 39 26 40 23
1-Carbomethoxydibenzofuran	63	40 25 26
1-Dibenzofurancarboxylic acid	232-233	25
1-Hydroxydibenzofuran	140.5	25
1-Nitrodibenzofuran	121	27
α-Phenyl-α(1-dibenzofuryl) acetone	101-102	41

[39] Van Ess, P. R. Iowa State College J. Sci., 12, 164 (1937) [C. A., 32, 4981 (1938)].

[40] Jacoby, Hayes, and Van Ess, Proc. Iowa Acad. Sci., 43, 2045 (1936). [C. A., 32, 4160 (1938)].

[41] This thesis.

TABLE I (Continued)

Name of Compound	M. P.°	Reference
Disubstituted Dibenzofurans		
1-Acetamino-4-methoxydibenzofuran	222-223	18
1-Acetyl-2-methoxydibenzofuran	120-121	27
1-Acetyl-4-methoxydibenzofuran	134-134.5	18
1-Allyl-2-hydroxydibenzofuran	82.5-83	39 40
1-Allyl-2-methoxydibenzofuran	67-68	39 40
1-Amino-4-acetaminodibenzofuran	202	27
1-Amino-4-ethoxydibenzofuran	91	24
1-Amino-4-methoxydibenzofuran	104	19
1-Benzeneazo-2-hydroxydibenzofuran	165.5-166	42
1-Benzeneazo-4-hydroxydibenzofuran	174-175	42
1-Bromo-4-acetaminodibenzofuran	228	25
1-Bromo-2-aminodibenzofuran	120-121	41
1-Bromo-4-aminodibenzofuran	119-120	25
1-β-Bromoethyl-4-methoxydibenzofuran	131-131.5	18
1-Bromo-2-hydroxydibenzofuran	123-123.5	25 26
1-Bromo-4-hydroxydibenzofuran	151.5-152	25 26
1-Bromo-2-methoxydibenzofuran	117-118	25 26

[42] Van Ess, M. W., Doctoral Dissertation, Iowa State College, 1936.

TABLE I (Continued)

Name of Compound	M. P.°	Reference
1-Bromo-4-methoxydibenzofuran	97-98	25 26
1-Carbomethoxy-2-methoxydibenzofuran	99.5-100	25 26
1-Chloroacetyl-4-methoxydibenzofuran		43
1-Chloro-8-hydroxydibenzofuran	165-166	19
1,4-Diacetaminodibenzofuran-dihydrochloride	322-323	27
1,4-Dihydroxydibenzofuran	217-218 (dec.)	25 26
1,8-Dihydroxydibenzofuran	241-242	44
1,2-Dimethoxydibenzofuran	79	25 26
1,4-Dimethoxydibenzofuran	78.5	25 26
1,9-Dimethyldibenzofuran	61-62	45
1,9-Diphenyldibenzofuran	154-155	46
1-Ethoxyalyl-4-methoxydibenzofuran	96	18 ?
1-Hydroxy-2-methoxydibenzofuran	111-111.5	25 26

[43] British Patent 470,021 [C. A., 32, 1487 (1938)].

[44] French Patent 816,719 [C. A., 32, 2145 (1938)].

[45] Sugii and Shindo, J. Pharm. Soc. Japan, 54, 829 (1934) [C. A., 29, 791 (1935)].

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

TABLE I (Continued)

Name of Compound	M. P.°	Reference
4-Methoxydibenzofuran-1-aldehyde	104-105	41
1-(4-Methoxydibenzofuryl) acetic acid	220	47
1-(4-Methoxydibenzofural) acetic acid	281-282	41
β-[1-(4-Methoxydibenzofuryl)] propionic acid	177-178	41
γ-[1-(4-Methoxydibenzofuryl)] butyric acid	165	48
1-(4,6-Dimethoxydibenzofuryl) acetic acid	205.5-206.5	19 (Incorrect)
1-Methyl-2-acetoxydibenzofuran	80-81	41
1-Methyl-2-hydroxydibenzofuran	135-136	41
1-Methyl-2-methoxydibenzofuran	60-61	41
1-Nitro-4-aminodibenzofuran	216	27
1-Nitro-4-aminodibenzofuran	219-220	27
1-Nitro-4-ethoxydibenzofuran	135-135.5	24
1-Nitro-4-methoxydibenzofuran	155	24
1-Propenyl-2-hydroxydibenzofuran	94-95	25
1-Succinoyl-4-methoxydibenzofuran	224-225	48

[47] Burger and Avakian, J. Am. Chem. Soc., 62, 226 (1940).

[48] Avakian, Doctoral Dissertation, Iowa State College, 1944.

TABLE I (Continued)

Name of Compound	M. P.°	Reference
Trisubstituted Dibenzofurans		
1-Acetamino-~~4,6~~ 3,4-dimethoxydibenzofuran	196-196.5	19
1-Acetamino-4,6-dimethoxydibenzofuran	244-245	19
1-Acetamino-2-nitro-4-methoxydibenzofuran	244	18
1-Acetyl-3,4-dimethoxydibenzofuran	90.5-91	19
1-Acetyl-4,6-dimethoxydibenzofuran	178-179	19
1-Amino-3,4-dimethoxydibenzofuran	162.5-163	19
1-Amino-4,6-dimethoxydibenzofuran	162-162.5	19
1-Amino-2-nitro-4-methoxydibenzofuran	206-207	18
1-Benzeneazo-4,6-dimethoxydibenzofuran	170	19
1-Benzeneazo-4-hydroxy-6-methoxydibenzofuran	175	19
1-Bromo-3-acetamino-4-methoxydibenzofuran	178-179	18
1-Bromo-3-amino-4-methoxydibenzofuran	135-136	18
1-Bromo-2,8-dimethoxydibenzofuran	102-103.5	41
1-Bromo-3,4-dimethoxydibenzofuran	108	19

TABLE I (Continued)

Name of Compound	M. P.°	Reference
1-Bromo-4,6-dimethoxydibenzofuran	152	19 ~~41~~
1-Bromo-3-hydroxy-4-methoxydibenzofuran	161-162	19
1-Bromo-3-nitro-4-methoxydibenzofuran	160-161	18
1-Carboxy-4,6-diaminodibenzofuran	183-184° ~~160-161~~	41
1-Carboxy-2,8-dimethoxydibenzofuran	194-195	41
1-Carboxy-4,6-dihydroxydibenzofuran	278-280	41
1,3-Dibromo-4-methoxydibenzofuran	139-140	41
4,6-Dimethoxydibenzofuran-1-aldehyde	163-164	41 49
1-Ethyl-2,8-dihydroxydibenzofuran	142-143	41
1-Ethyl-2,8-dimethoxydibenzofuran	71-72	41
1-Methyl-2,8-dihydroxydibenzofuran	187-188	41
1-Methyl-2,8-dimethoxydibenzofuran	85-86	41
1-Methyl-2-hydroxy-8-aminodibenzofuran hydrochloride	220 (dec.)	41
1-Succinoyl-4,6-dimethoxydibenzofuran	241-242	48

[49] Cook, Doctoral Dissertation, Iowa State College, 1940.

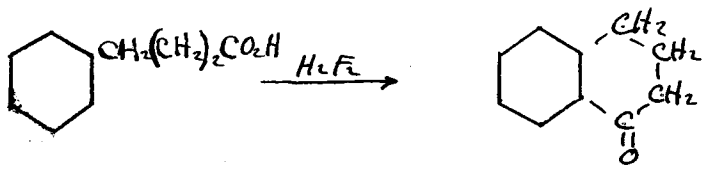
TABLE I (Continued)

Name of Compound	M. P.°	Reference
Tetrasubstituted Dibenzofurans		
1-Bromo-7-succinoyl-4,6-dimethoxydibenzofuran	200-201	41 48
1,7-Dibromo-2,8-diacetoxydibenzofuran	173-174	27
1,7-Dibromo-2,8-dihydroxydibenzofuran	200-201	27
1,7-Dibromo-4,6-dihydroxydibenzofuran	239-240	19
1,3-Dibromo-4,6-dimethoxydibenzofuran	173.5-174	19
1,7-Dibromo-2,8-dimethoxydibenzofuran	196-197	27
1,7-Dibromo-4,6-dimethoxydibenzofuran	167-168	19
1,3-Dibromo-4-hydroxy-6-methoxydibenzofuran	177-178	19
1,7-Dicarbomethoxy-2,8-dimethoxydibenzofuran	129-130	27
1,7-Dimethyl-2,8-dihydroxydibenzofuran	168-169	27
1,7-Dimethyl-2,8-dimethoxydibenzofuran	106-107	27
1-Ethyl-7-bromo-2,8-dimethoxydibenzofuran	116-117	41
1-Methyl-7-bromo-2,8-dimethoxydibenzofuran	144-145	41
1-Methyl-7-ethyl-2,8-dimethoxydibenzofuran picrate	144-145.5	41

Reactions Potentially Applicable to Bridging the 1- and 9-Positions of Dibenzofuran

Aside from the uncertainty surrounding the space relationships of the 1- and 9-positions of dibenzofuran, there is every reason to believe, by analogy, that a method for bridging the 1- and 9-positions might be found among the many reactions observed in the literature. Cheney[19] has covered the literature up to 1938. Swislowsky[27] has suggested a number of reactions which might be applicable to the derivatives of dibenzofuran arising from the compound which was then thought to be 1,9-dibromo-2,8-dimethoxydibenzofuran. This section is devoted to reactions which have been developed since that time.

The advent of anhydrous hydrogen fluoride as a condensing agent has resulted in the addition of a powerful new reagent for cyclization reactions with various types of acids:[50]



[50] Fieser and Hershberg, J. Am. Chem. Soc., 61, 1272 (1939).

Other methods of cyclization have many limitations. One of the most generally useful procedures is an application of the Friedel-Crafts reaction, which consists in treating the acid in benzene, nitrobenzene, or chlorobenzene with phosphorbus pentachloride, followed by aluminum chloride.[51] The use of thionyl chloride in place of phosphorous pentachloride is even less desirable because, if not removed before treating with the condensing agent, unwanted side-reactions take place.[52] Stannic chloride can be used where a more reactive aromatic nucleus is present.[53] The acid chloride method has the disadvantage of giving rise to tars and products of dehydrogenation and has failed completely in some cases, for example, with γ-(4-methoxy-3-biphenyl)butyric acid.[54] Cyclization by heating the free acid or the acid chloride with the above mentioned condensing agents seldom proceeds smoothly. The cyclization of α-naphthylpropionic acid with stannic chloride, or by heating the acid chloride with aluminum chloride, has resulted in a dehydrogenation action.[55]

Cyclization of certain γ-aryl butyric acids has been

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[51] Brown, Blessing, and Cahn, Ber., 57, 908 (1924).

[52] Fieser and Desreux, J. Am. Chem. Soc., 60, 2253 (1938).

[53] Fieser, Hershberg, Long, and Newman, ibid., 59, 475 (1937).

[54] Fieser and Bradsher, ibid., 58, 1738 (1936).

[55] Cook and Hewitt, J. Chem. Soc., 398 (1933).

accomplished with phosphorous pentoxide in organic solvents such as benzene or toluene,[56] or in syrupy phosphoric acid,[57] but the method is not a general one.

The method of cyclodehydration with 85-95% sulfuric acid[58] is very desirable since there is little tendency for tar formation, and it quite frequently gives good yields. Often, however, much material is lost by sulfonation. This is particularly true when one tries to force the reaction.

The catalytic cyclization with zinc chloride in acetic anhydride has been applied successfully to some acids of the type, $Ar(CH_2)_n-CO_2H$, giving ketones.[59] Frequently the acid is recovered unchanged. The cyclization of a γ-arylbutyric acid with hydriodic acid has been reported by R. Robinson and Walker.[60]

The use of anhydrous liquid hydrogen fluoride by Fieser and Hershberg[50] as an agent for cyclodehydration shows a marked contrast with the above mentioned methods. In general, the reactions were carried out in an open platinum vessel in a good hood by dissolving the acid in commercial anhydrous liquid hydrogen fluoride, without stirring of any kind, for

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[56] Haberland and co-workers, Ber., 71, 470, 2619 (1938).

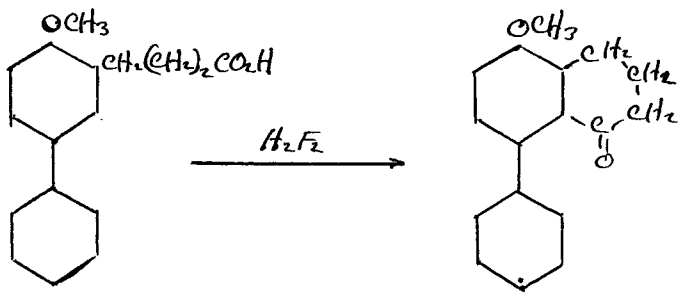
[57] Koebner and R. Robinson, J. Chem. Soc., 1994 (1938).

[58] Haworth, ibid., 1125 (1932).

[59] Fieser and Hershberg, J. Am. Chem. Soc., 59, 1028 (1937).

[60] R. Robinson and Walker, J. Chem. Soc., 183 (1938).

a period of a few hours or overnight. Pure γ-phenylbutric acid gave pure α-tetralone in 92% yield and hydrocinnamic acid gave α-hydrindone in 72% yield, while α-tetralone is prepared only in poor yield by the sulfuric acid method, and α-hydrindone cannot be prepared by the use of sulfuric acid.[61] In the case of γ-(4-methoxy-3-biphenyl)butyric acid (I), no cyclization could be effected by either the sulfuric acid or acid chloride method.[54] However, there was no difficulty in obtaining the ketone (II) with hydrogen fluoride.



I II

Anhydrous hydrogen fluoride seems to have little destructive effect on sensitive products or upon starting materials. Attempts to acylate several aromatic hydrocarbons with hydrogen fluoride and organic acids throw some light on the absence of intermolecular condensation products in cyclodehydrations of this type. Of the many aromatic hydrocarbons tried, condensation was realized only with the very

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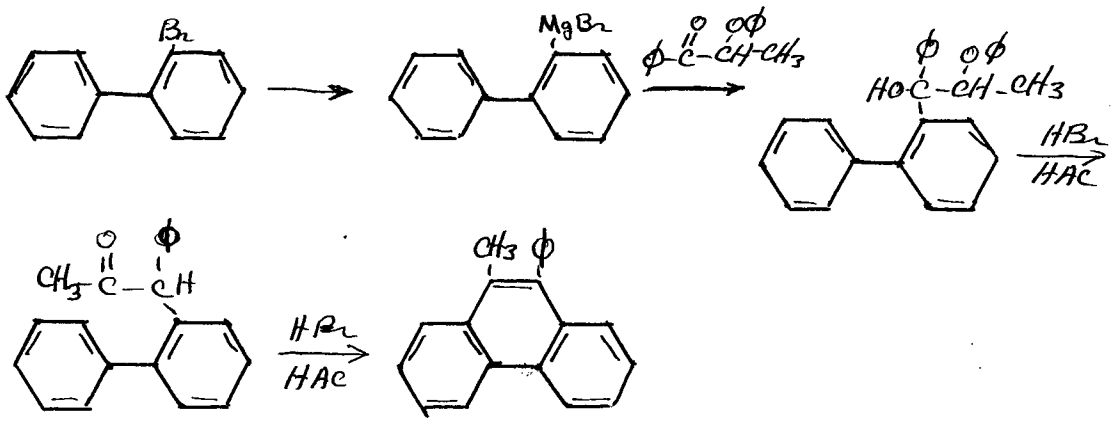
[61] W. V. Miller and Rohde, Ber., 23, 1887 (1890).

active acenaphthene. Acetylation yielded 94% of mixed acetoacenaphthenes after treating with acetic acid and a large amount of hydrogen fluoride for three days. Benzoylation resulted in a 62% yield after only two and one-half hours. Attempts to acylate benzene, naphthalene, anthracene, phenanthrene, 1,2-benzanthracene, and dihydrophenanthrene resulted in failure. All attempts to cyclodehydrate the arylbutyric and propionic acids with hydrogen fluoride have met with success.

Another significant discovery of Fieser and Hershberg[50] is that hydrogen fluoride sometimes orients differently from the parallel Friedel-Crafts reaction. The mixture of acetoacenaphthenes was shown to contain 25% of the previously unknown 1-acetoacenaphthene, while other methods of acetylation had produced only 3-acetoacenaphthene. This tendency could possibly prove useful in ring closure between the 1- and 9-positions when other reagents oriented differently.

In general, it can be said that the use of anhydrous hydrogen fluoride is free of the tendency to form tars, the chief disadvantage of the Friedel-Crafts type of reaction. In the case of two competing reactions, where one is required to overcome some stress, as is likely in bridging the 1- and 9-positions of dibenzofuran, the other is likely to predominate. It is evident from the work of Fieser and Hershberg[50] and others that anhydrous hydrogen fluoride is slow to promote intermolecular condensation.

In 1939, Bradsher and co-workers introduced a series of reactions, similar in type, for the synthesis of phenanthrene and its derivatives from o-bromobiphenyl. Bradsher and Rosher[62] have prepared 9,10-substituted phenanthrenes in good yields by the following series of reactions:



The ketone was postulated as the intermediate but was never isolated. The actual cyclization is believed to be a result of the dehydration of the enol form of the ketone. The yields in this type of reaction were as follows:

Alkyl radical		Yield
R=	$-CH_3$	72%
R=	$-CH_2-CH_3$	70%
R=	phenyl	62%

Another method of preparing hydrocarbons with the phenanthrene nucleus was devised by Bradsher.[63] By this

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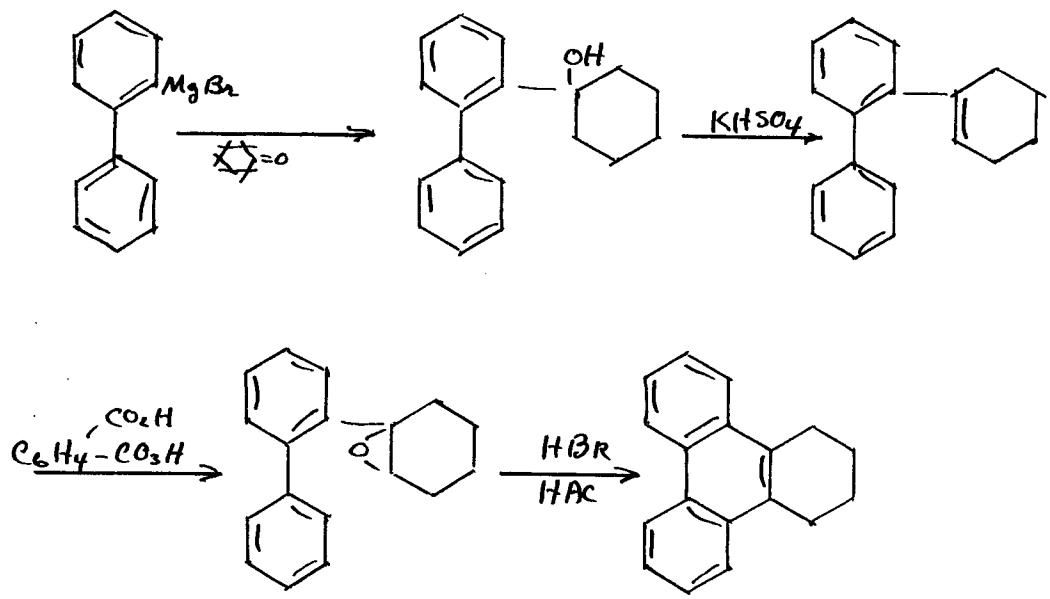
[62] Bradsher and Rosher, J. Am. Chem. Soc., 61, 1524 (1939).

[63] Bradsher, ibid., 61, 3131 (1939).

method 9,10-cyclopentenophenanthrene and 9,10-cyclohexenophenanthrene were prepared in 30% yield, based on the ketone. 2-Biphenylmagnesium bromide was treated with the appropriate ketone, the carbinols were dehydrated with potassium bisulfate, and the resulting 1-(2-biphenyl)cyclopentene-1 and 1-(2-biphenyl)cyclohexene-1 were oxidized with monoperphthalic acid, with ultimate ring closure by refluxing with hydrobromic acid and acetic acid.



Geissman and Tess[64] have carried out a series of reactions for the preparation of phenanthrene-9-carboxylic acid and phenanthrene-9,10-dicarboxylic acid anhydride from 2-aminobiphenyl which substantiates the theory of an enol intermediate proposed by Bradsher and Rosher.[62] This

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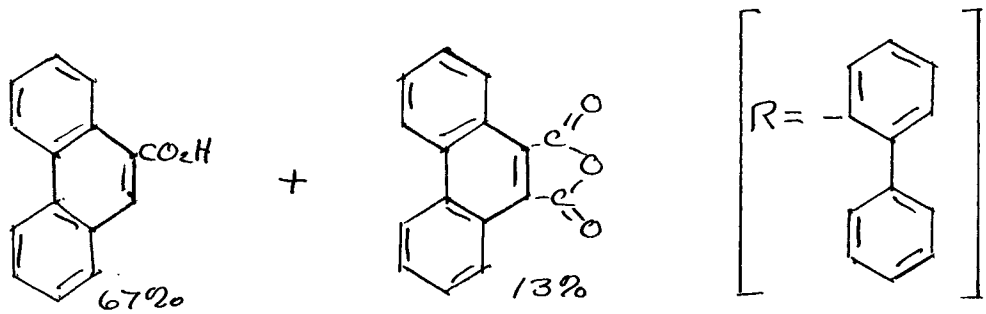
64 Geissman and Tess, J. Am. Chem. Soc., 62, 514 (1940).

synthesis employs the following series of reactions:

$$RNH_2 \longrightarrow RCN \longrightarrow RCH_2NH_2 \longrightarrow RCH_2OH \longrightarrow$$

$$RCH_2Cl \longrightarrow RCH_2CN \longrightarrow RCH_2CO_2(C_2H_5) \longrightarrow R\text{-}CH(COCO_2Et)\text{-}CO_2Et$$

$$\longrightarrow \left[\begin{matrix} R\text{-}C\text{-}CO_2Et \\ \| \\ HO\text{-}C\text{-}CO_2Et \end{matrix}\right] \xrightarrow[HAC]{HBR}$$



That the ethyl 2-biphenyloxalylacetate exists to some extent in the enol form is shown by the fact that it gives a positive enol test with ferric chloride. The ethyl 2-biphenyloxalylacetate was not isolated in pure form but was refluxed as an oil with hydrobromic acid and glacial acetic acid for a period of twenty-four hours to effect the cyclodehydration. The over-all yield of phenanthrene derivatives in this case is 80%, as compared to the yield of Bradsher and Rosher[62] of 72%. The oily residue, after separating the above acids, was shown to be unreacted ethyl 2-biphenyloxalylacetate.

Bradsher and Tess[65] worked out another and somewhat similar method of preparing 9-methylphenanthrene. None of the yields proved to be exceptionally good. However, the

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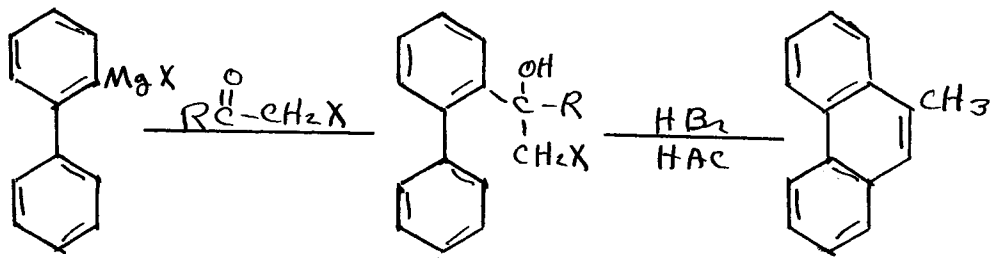
[65] Bradsher and Tess, J. Am. Chem. Soc., 61, 2184 (1939).

scope of this type of reaction is indicated. By the addition of the Grignard reagent of o-bromobiphenyl to several derivatives of acetone in the following general procedure, Bradsher and Tess[65] were able to obtain 9-methylphenanthrene in each case.



The final ring closure in this series is brought about by the use of hydrobromic acid and glacial acetic acid. The following table is a summary of the results of this paper.

R	X	% Yield
CH_3-	$-OCH_3$	30
"	$-O-\phi$	32
"	$-OC_{10}H_7(\beta)$	23
"	$-N(Et)_2$	10
"	-Cl	$\angle 1$

In a later paper Bradsher[66] worked out another modification of the above procedure. o-(α-Methoxyaceto)biphenyl was prepared and reduced to the alcohol by means of aluminum

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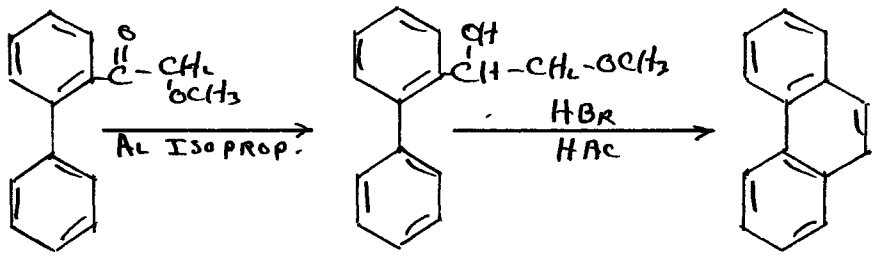
[66] Bradsher, J. Am. Chem. Soc., 62, 2806 (1940).

isopropylate. The ring closure was carried out, as usual, with hydrobromic acid and acetic acid.



The yield of pure phenanthrene from the method was 46%. The author has suggested that o-biphenylacetaldehyde might well yield phenanthrene under the same treatment.

Bradsher and Amore[67] have obtained methylphenanthrene by still another method. The Grignard reagent from o-bromobiphenyl was treated with acetone, the resulting carbinol dehydrated with potassium bisulfate, and the isopropenyl derivative oxidized to the oxide with perbenzoic acid, whereupon 9-methylphenanthrene was formed after refluxing for a few hours with hydrobromic acid and glacial acetic acid. The yield was 30% of the theoretical, based on the amount of o-bromobiphenyl used.

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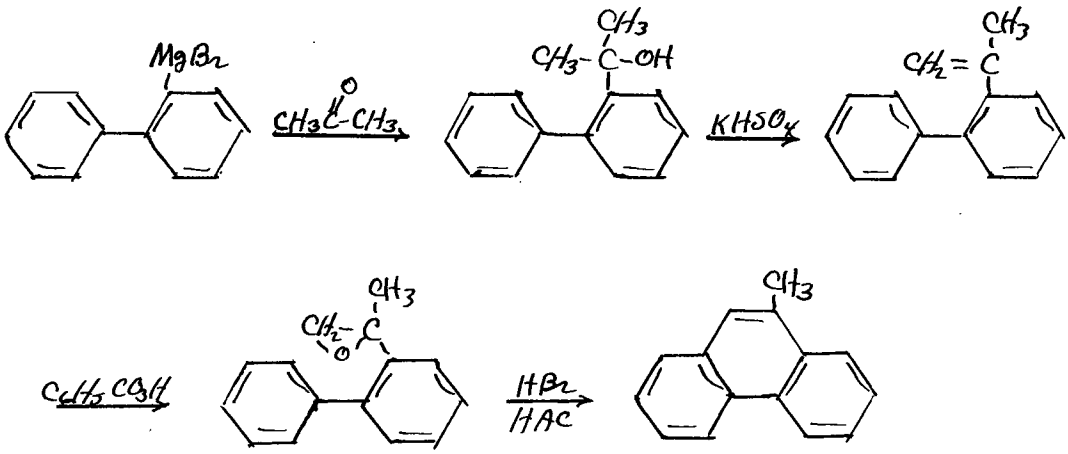
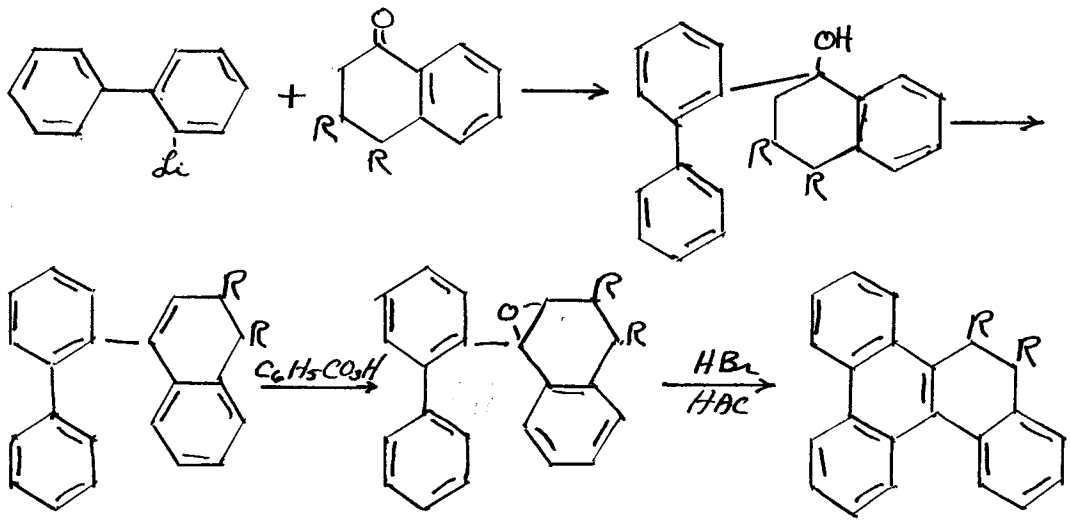
[67] Bradsher and Amore, J. Am. Chem. Soc., 65, 2016 (1943).



The method has been extended to the preparation of more complicated products by Bradsher and Rapoport.[68] The basic principles involved are essentially the same except that a more active organometallic derivative of biphenyl is used. In the following case the yield was 37%:



In nearly all of this series a ketone precursor to the ultimate phenanthrene product is postulated. In the presence

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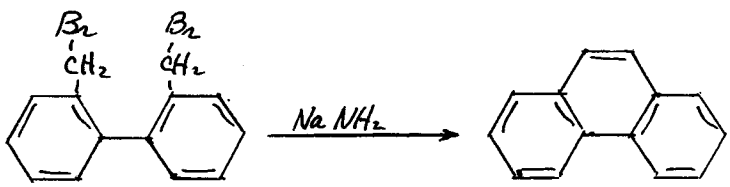
[68] Bradsher and Rapoport, J. Am. Chem. Soc., 66, 1291 (1944).

of the reagents used either cyclodehydration occurs, or the starting materials are recovered, except where peroxide oxidation is used. This indicates that there are no side-reactions competing with the desired trend. Hence, this type of reaction may well be considered a fair test of the expected ease of bridging the 1- and 9-positions of dibenzofuran.

Kharasch, Nudenberg, and Fields[69] have worked out an interesting synthesis of phenanthrene, using sodamide as a condensing agent on o-dibromomethylbiphenyl, according to the following reaction:



The yield of a very pure phenanthrene was 80%. This would certainly be an excellent method of bridging the 1- and 9-positions should a 1,9-dibromomethyl derivative of dibenzofuran ever be realized, either by direct substitution in the dibenzofuran nucleus or by ring closure.

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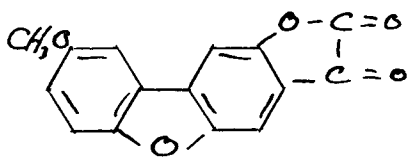
[69] Kharasch, Nudenberg, and Fields, J. Am. Chem. Soc., 66, 1276 (1944).

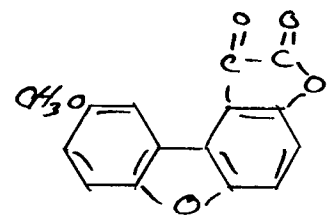
Previous Attempts to Bridge the 1- and 9-Positions of Dibenzofuran

The achievement of a 1,9-bridge in dibenzofuran has as yet not been realized. However, various attempts have been made by Swislowsky,[27] Cheney,[19] Cook,[49] Avakian,[48] Burger and Avakian,[47] and Yeoman.[70]

Swislowsky[27] treated 2,8-dimethoxydibenzofuran with oxalyl chloride and aluminum chloride, and concluded that his product had one of the following structures:



8-Methoxybenzofuro-(5,6-b) benzofuran-2,3-dione



9-Methoxybenzofuro-(5,4-b) benzofuran-1,2-dione

This conclusion was based essentially upon the formation of a dark red quinoxaline derivative with o-phenylenediamine.

Several interesting procedures were investigated by Cheney.[19] One of these was the treatment of 4-methoxydibenzofuran with aluminum chloride and α-chloroacetyl chloride with the hope of obtaining a 4,5-phenanthrylene oxide derivative through an intramolecular alkylation. Only 1-chloroacetyl-4-methoxydibenzofuran could be isolated, in spite of attempts to force the reaction, and no intermolecular

[70] Yeoman, Doctoral Dissertation, Iowa State College, 1944.

condensation occurred. This compound is of interest, however, in that it might be used to test the method of Bradsher[66] in the field of dibenzofuran.

Cheney[19] and Cook[49] also tried the Friedel-Crafts reaction of 4-methoxydibenzofuran and 4,6-dimethoxydibenzofuran with oxalyl chloride. Good yields of the dimolecular condensation products, bi-(4-methoxy-1-dibenzofuroyl) and bi-(4,6-dimethoxy-1-dibenzofuroyl), were obtained. Three attempts to synthesize a 4,5-phenanthridene oxide derivative from 1-acetamino-4,6-dimethoxydibenzofuran by means of the Bischler-Napieralski reaction[71] resulted in failure.

The synthesis of 4,6-dimethoxy-1-dibenzofurylacetic acid by Cheney[19] afforded a promising compound for bridging the 1- and 9-positions by the methods known at that time. One attempt with this compound, utilizing the Friedel-Crafts reaction with the acid chloride, yielded an oil from which no pure material could be isolated. Cook[49] prepared the same compound and gave it a thorough test, using sulfuric acid, zinc chloride, and stannic chloride as agents for condensation. The desired results were not obtained, even though conditions of time and temperature were varied.

Cook[49] attempted to form a seven-membered ring with a three-atom bridge between the 1- and 9-positions of dibenzofuran by treating 1-dibenzofurylmercaptoacetic acid with

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[71] Bischler and Napieralski, Ber., 26, 1903 (1893).

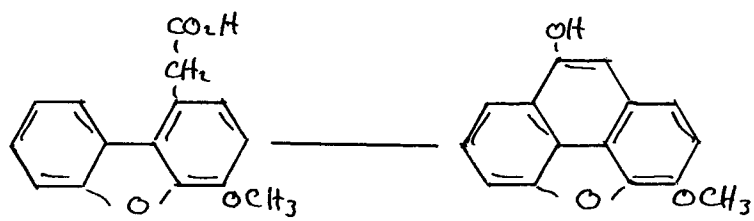
chlorosulfonic acid, acetic anhydride, and phosphorous pentoxide.

Avakian[48] has attempted to prepare a derivative of dibenzofuran with an eight-membered ring involving the 1- and 9-positions by cyclization of γ-(4-methoxy-1-dibenzofuryl)butyric acid in 88% sulfuric acid and γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid, using stannic chloride on the acid chloride. In each case a ketone was obtained. Although nothing is known about the latter compound, Avakian has oxidized the resulting 1,2,3,4 tetrahydro-7-methoxy-1-oxocycloöcta (klm) dibenzofuran to the dibasic acid and found it to be different from another dibasic acid of 4-methoxydibenzofuran, which might possibly be 1,2-dicarboxy-4-methoxy dibenzofuran. That one of the carboxy-groups of this compound is in the 1-position is questionable since the only evidence is that of analogy. 2-Bromo-4-methoxydibenzofuran was brominated, and it was assumed that the bromination involved the 1-position since succinoylation was definitely shown to involve that position.[48] This 1,2(?)-dibromo-4-methoxydibenzofuran was converted to the corresponding 1,2(?)-diacid by halogen-metal interconversion with n-butyllithium and carbonation of the resulting lithio derivative.

Yeoman[70] prepared the dialdehyde from the compound that was thought at that time to be 1,9-dibromo-2,8-dimethoxydibenzofuran and treated this compound with hydrazine and

o-phenylenediamine, but could isolate no pure crystalline material.

Burger and Avakian[47] have prepared 4-methoxy-1-dibenzofurylacetic acid and tried several methods for its cyclodehydration to a derivative of methylmorphenol. The reagents tried were concentrated sulfuric acid, 88% sulfuric acid, anhydrous liquid hydrogen fluoride at room temperature, and stannic chloride. In no case was the expected phenolic product obtained.



This paper records the first attempt to use hydrogen fluoride in bridging the 1- and 9-positions of dibenzofuran.

EXPERIMENTAL

The Entrainment Monobromination of 2-Aminodibenzofuran

Four grams (0.0218 mole) of 2-aminodibenzofuran, prepared according to the directions of Bywater,[11] was dissolved in 100 cc. of glacial acetic acid in a 250 cc. three-necked flask. The flask was equipped with a motor-driven stirrer, an inlet tube of 12 mm. diameter, placed beneath the surface of the solution, and an outlet tube arranged to trap any escaping hydrogen bromide. Two grams of sodium carbonate was added to avoid the formation of amine hydrobromides. Three and three-tenths grams (o.0218 mole) of bromine was entrained by passing a slow stream of air over the bromine in a small Erlenmeyer flask and was then introduced through the inlet tube beneath the surface of the rapidly stirred solution. The stream of air was adjusted so that three and one-half hours were required to introduce all of the bromine.

After the addition of all of the bromine the solution was diluted and filtered, yielding four grams of material melting mainly between 100° and 114°. A small portion was found to be insoluble in methanol and was filtered from the hot solution. Recrystallization of this insoluble portion from a larger volume of 95% ethanol yielded 0.5 g. of product

melting at 180-181°. A mixed melting point determination showed it to be identical with the dibromo-2-aminodibenzofuran prepared by John R. Thirtle[38] by the dibromination of 2-aminodibenzofuran. The main body of material crystallized from the methanol solution. After two purifications from the same solvent 1.75 g. (30.7%) of a monobromo-2-aminodibenzofuran melting at 120-121° was obtained.

Anal. Calcd. for $C_{12}H_8ON\,Br$: Br^{N}, 5.34.
Found: Br^{N}, 5.31.

Deamination of 1-Bromo-2-aminodibenzofuran

The hydrochloride of 0.5 g. (0.0019 mole) of monobromo-2-aminodibenzofuran was prepared by boiling with 6 cc. of concentrated hydrochloric acid in 75 cc. of water. On cooling in an ice-bath the amine hydrochloride crystallized as fine needles. To this suspension of the hydrochloride 0.138 g. (0.0019 mole) of sodium nitrite dissolved in 10 cc. of water at 0° was added dropwise with stirring. After one-half hour the hydrochloride went into solution as the slightly yellow diazonium salt. Then 4 cc. of 50% hypophosphorous acid was added to the cold solution and the mixture was allowed to stand in the ice box for twelve hours whereupon a tan precipitate formed. The precipitate was dissolved in a minimum of petroleum ether (b.p., 60-86°) and filtered to remove an

insoluble brown portion. Cooling in an icebox gave prisms which, after two subsequent purifications, melted at 64-65°. The yield was 0.2 g. or 50% of the theoretical.

A mixed melting point of the above product with an authentic sample of 1-bromodibenzofuran[25] was not depressed. Thus, the monobromo-2-aminodibenzofuran can be designated 1-bromo-2-aminodibenzofuran if the probability of heteronuclear substitution in the 9-position is waived.

Monobromination of 1-Bromo-2-aminodibenzofuran

To 0.7 g. (0.00267 mole) of 1-bromo-2-aminodibenzofuran dissolved in 40 cc. of glacial acetic acid was added dropwise with stirring 2.67 cc. of a molar solution of bromine in acetic acid. A product began to settle out before all of the bromine had been added. After the addition of all of the bromine the flask was heated to dissolve the precipitate and then allowed to cool. Seven-tenths of a gram of needles melting at 180-181° formed. The yield was 76.5%.

A mixed melting point of this material with the dibromo derivative of 2-aminodibenzofuran prepared by Thirtle[38] was not depressed. This demonstrates that one of the bromine atoms in this dibromo-2-aminodibenzofuran is in the 1-position.

Preparation of 2,8-Dihydroxydibenzofuran

This procedure is essentially the same as that used by Swislowsky[27] and is included for the sake of recording certain modifications which have made the preparation less difficult.

Three hundred grams (0.915 mole) of 2,8-dibromodibenzofuran (student prep.) was thoroughly dried and pulverized in a large mortar. It is essential that the pulverizing step be done very carefully to ascertain that the material be well suspended in the fusion mixture later on. To this powdered material was added 500 g. of commercial flake sodium hydroxide. Ninety grams of copper sulfate in 200 cc. of water was then added with stirring. Then 70 g. of copper-bronze powder was stirred into the paste until the color was uniform. There was a considerable evolution of heat when the water contacted the sodium hydroxide. The consistency at this point should be a thick paste to assure minimum settling of the ingredients. The reaction mixture just filled a 600 cc. copper beaker, which was placed in an electrically heated bomb at 240° for twelve hours. The beaker was removed and its contents transferred before cooling to three or four liters of water. The water was warmed to assure complete solution of the phenolic materials. When a copper mat was used to avoid settling, the extractions became tedious. The sodium salt solution was filtered, decolorized with charcoal, and then precipitated.

The method of purification of the crude product was essentially that of Swislowsky.[27] The yields varied from 80 g. to 92.8 g. (35-40%) of pure 2,8-dihydroxydibenzofuran. The yield of 2,8-diacetoxydibenzofuran reported by Swislowsky[27] was 39.7% based on the 2,8-dibromodibenzofuran used.

Preparation of 1-Bromo-2,8-dihydroxydibenzofuran

This method is a modification of that employed by Yeoman.[70]

Twenty grams (0.10 mole) of 2,8-dihydroxydibenzofuran and 200 cc. of glacial acetic acid were placed in a 500 cc. three-necked flask. The flask was equipped with an air-tight stirrer with smooth action. Sixteen grams (0.1 mole) of bromine was entrained in a stream of air and passed into the space above the solution. A piece of 12 mm. tubing with a bulb-trap attached was fitted tightly into the flask with a rubber stopper and barely immersed into the stirred solution, thus allowing the air to escape only after all of the bromine had been absorbed on the surface of the solution. The escape tube can be adjusted to allow the escaping gas to bubble rather smoothly. The flow of air was adjusted to one or two bubbles every second (as shown by a sulfuric acid bubbler).

The entrainment unit was a flask with an inlet tube

close to the bromine and an all-glass connection to the three-necked flask. The addition of bromine required six to seven hours. The free flow of gas was occasionally blocked in the delivery tube by the formation of a red crystalline material which was most likely an addition compound between bromine and acetic acid. It decomposes in contact with bromine-free air. After the bromine had all passed through, the solution was diluted to two liters and the crude product filtered. This material did not purify by crystallization from acetic acid and weighed 28 g. (theoretical weight). The crude product was purified through the diacetoxy derivative.

Preparation of 1-Bromo-2,8-diacetoxydibenzofuran

To 28 g. (0.1 mole) of crude 1-bromo-2,8-dihydroxydibenzofuran was added 80 cc. of acetic anhydride and a few drops of concentrated sulfuric acid. The evolution of heat was immediate. The mixture was refluxed for fifteen minutes and then treated cautiously with water to decompose the excess acetic anhydride and then further diluted and filtered. The ultimate purification required from two to six crystallizations from a 30% mixture of toluene in petroleum ether (b.p., 60-86°), and the yields of 1-bromo-2,8-diacetoxydibenzofuran[70] varied from 7.5 g. to 14 g. (20% to 60% of the

theoretical). However, a yield of 30% was more often the case. The product melts at 143-145°.

Methylation of 1-Bromo-2,8-diacetoxydibenzofuran

To a cooled solution of 59 g. (0.163 mole) of 1-bromo-2,8-diacetoxydibenzofuran in 350 cc. of methanol and 50 cc. of methyl sulfate was slowly added 40 g. of sodium hydroxide in 50 cc. of water. The temperature was kept below the boiling point of methanol in an ice-bath. When the main reaction appeared to be complete, the mixture was shaken for ten minutes and then diluted and filtered. Recrystallization from 95% ethanol yielded 39 g. (78%) of pure 1-bromo-2,8-dimethoxydibenzofuran[70] melting at 102-103°.

Preparation of 1-Bromo-2,8-dimethoxydibenzofuran by Vacuum Distillation of Methylated Crude 1-Bromo-2,8-dihydroxydibenzofuran

Since large quantities of 1-bromo-2,8-dimethoxydibenzofuran were needed, a method for obtaining better yields was sought.

Twenty grams (0.1 mole) of 2,8-dihydroxydibenzofuran was monobrominated by the entrainment method in the usual manner (Page 37). The crude 1-bromo-2,8-dihydroxydibenzofuran was dissolved in 200 cc. of water and 10 g. of sodium hydroxide.

To this rapidly stirred and refluxing solution 40 cc. of methyl sulfate was added dropwise. Heating and stirring was continued for one hour after the addition of the last portion of methyl sulfate. Ten grams of sodium hydroxide was then added and heating was continued for ten minutes to assure the complete destruction of the excess methyl sulfate. After cooling, the solid product was filtered, washed with water, and thoroughly dried.

This crude product was distilled at 182-184°/1 mm. Crystallization of this material from 160 cc. of ethanol gave 17 g. (55%) of small needles melting at 101-103°.

In one run a yield of 60% of the theoretical was obtained (based on the amount of 2,8-dihydroxydibenzofuran used).

Preparation of 1-Methyl-2,8-dimethoxydibenzofuran

To 39 g. (0.127 mole) of 1-bromo-2,8-dimethoxydibenzofuran in 250 cc. of sodium-dried benzene was added 0.127 mole of n-butyllithium in ether solution. This entire process was carried out under nitrogen. There was some evolution of heat during the addition of the organometallic compound. After twelve minutes with rapid stirring 25 cc. of methyl sulfate in 50 cc. of ether was added dropwise with considerable evolution of heat. After about one-half of the methyl sulfate had been added, a white precipitate began to settle out. The

solution was stirred and refluxed for an additional four hours and then allowed to stand overnight. At this time the color test[72] for an organometallic compound was negative.

The solution was filtered free of the gray-white precipitate and washed with a 10% solution of sodium hydroxide to remove excess methyl sulfate. The solution was then dried over sodium sulfate and the solvents removed by distillation. The amber liquid residue soon solidified when placed in a crystallizing dish. The total product was dissolved in 50 cc. of 95% ethanol and cooled slowly. The solution was finally cooled in the icebox. The yield of crystals melting at 77-85° was 20 g. (66%). After two crystallizations from 95% ethanol there were 17 g. (56%) of pure 1-methyl-2,8-(?) dimethoxydibenzofuran melting at 85-86°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.5; H, 5.80.
Found: C, 74.3; H, 5.91.

Demethylation(?) of 1-Methyl-2,8-dimethoxydibenzofuran

Twelve grams (0.056 mole) of 1-methyl-2,8-dimethoxydibenzofuran was refluxed for 8 hours in a mixture of 35 cc. of glacial acetic acid and 40 cc. of 47% hydrobromic acid. The acetic acid solution was diluted and cooled overnight in the icebox. The crude yield represented 97% of the theoretical

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[72] Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

and melted at 183-187°. One purification from 33% ethanol yielded 10 g. (93%) of pure 1-methyl-2,8-dihydroxydibenzofuran melting at 187-188°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 73; H, 4.67.

Found: C, 72.2; H, 4.67.

Preparation of 1-Methyl-2-methoxydibenzofuran

The 1-bromo-2-methoxydibenzofuran used in this experiment was prepared according to the directions of P. R. VanEss.[25]

To 4.7 g. (0.0154 mole) of 1-bromo-2-methoxydibenzofuran in 75 cc. of dry benzene under an atmosphere of nitrogen was added 0.0154 mole of n-butyllithium. The exact quantity of the organometallic compound used was determined by the double titration method of Gilman and Haubein.[73] There was an immediate evolution of heat with the development of a slightly reddish color. After 15 minutes of vigorous stirring 10 cc. of methyl sulfate was added dropwise. The addition was carried out as rapidly as the condenser was able to handle the refluxing solvent. After two hours of stirring and subsequent standing overnight, the white precipitate which formed on the addition of methyl sulfate was filtered. The filtrate

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[73] Gilman and Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

was washed with a 10% sodium hydroxide solution and then with water. Evaporation of the solvent by distillation, after drying over sodium sulfate, yielded an oil which soon solidified. The crude product was taken up in petroleum ether (b.p., 60-86°) and after two subsequent purifications from the same solvent yielded 2 g. (61%) of pure product melting at 60-61°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.2; H, 5.67.
Found: C, 79.1; H, 5.73.

Demethylation of 1-Methyl-2-methoxydibenzofuran

The demethylation of 1-methyl-2-methoxydibenzofuran was effected by refluxing 1.5 g. (0.007 mole) of this material in a mixture of 10 cc. of 47% hydrobromic acid and 10 cc. of glacial acetic acid for 10 hours. On dilution the product came down as an oil, but soon solidified. Recrystallization from petroleum ether (b.p., 60-86°) gave 0.9 g. (65%) of needles melting at 135-136°. The crude yield of product melting at 130-135° was 95%.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.7; H, 5.05.
Found: C, 78.5; H, 5.00.

Acetylation of 1-Methyl-2-hydroxydibenzofuran

In accordance with the general method of acetylating phenols, 0.7 g. (0.0035 mole) of 1-methyl-2-methoxydibenzofuran was refluxed for one-half hour with 5 cc. of acetic anhydride and two drops of concentrated sulfuric acid. Two recrystallizations from petroleum ether (b.p., 60-86°) yielded crystals melting at 80-81°. The yield was 75% of pure 1-methyl-2-acetoxydibenzofuran.

This material was acetylated in order to compare it later with a sample prepared from the product of deamination of 1-methyl-2-hydroxy-8-aminodibenzofuran.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.1; H, 5.00.

Found: C, 75.6; H, 4.9.

Bucherer Reaction with 1-Methyl-2,8-dihydroxydibenzofuran

A mixture of 1.54 g. (0.0072 mole) of 1-methyl-2,8-dihydroxydibenzofuran, 7.5 g. of sodium metabisulfite, 15 cc. of water, and 15 cc. of concentrated ammonium hydroxide was sealed in a Carius tube. The tube was placed in an electrically heated oven at 180° for twenty hours. When the tube was cooled and opened, beautiful white crystals were found. These were filtered and dissolved in a dilute solution of hydrochloric acid. A small amount of insoluble

matter was filtered off and the amine hydrochloride allowed to crystallize. The amine salt began to decompose at about 220°. The yield of 1-methyl-2-hydroxy-8-amino-dibenzofuran hydrochloride was 1.2 g. (66.5%).

Anal. Calcd. for $C_{13}H_{11}O_2NCl$: N, 5.64.

Found: N, 5.59.

Deamination of 1-Methyl-2-hydroxy-8-aminodibenzofuran

The amine hydrochloride (1.1 g. or 0.00428 mole) was dissolved in 50 cc. of water and 2 cc. of concentrated hydrochloric acid. Then 0.37 g. (0.00428 mole) of sodium nitrite in 5 cc. of water was added to the above cooled solution in a dropwise manner with rapid stirring. An insoluble orange-yellow diazonium salt formed. The suspension was stirred for one hour to insure complete diazotization, and then 5 cc. of 50% hypophosphorous acid was added. The flask was then placed in the ice-box for 50 hours after which it showed little change in appearance. Some reaction appeared to occur after the mixture had stood for four hours at room temperature. The flask was finally heated for 15 minutes on a steam-bath. The brown product which formed was filtered and found to weigh 0.75 g. in crude form. The purification was carried out by acetylating this crude material in 9 cc. of acetic anhydride and two drops of concentrated sulfuric

acid. This solution was heated on the steam bath for 20 minutes, and the excess acetic anhydride was destroyed with water. Dilution yielded an oil which resisted attempts at purification. A microvacuum distillation yielded 0.3 g. of material which solidified readily and melted at 61-74°. Three subsequent crystallizations from petroleum ether (b.p., 60-86°) yielded 50 mg. of material melting sharply at 80-81°.

This product was identified as 1-methyl-2-acetoxydibenzofuran by a mixed melting point (80-81°) with an authentic sample[41] prepared for this purpose from the known 1-bromo-2-methoxydibenzofuran.[25]

Preparation of 1-Ethyl-2,8-dimethoxydibenzofuran

To 46 g. (0.150 mole) of 1-bromo-2,8-dimethoxydibenzofuran in 200 cc. of dry thiophene-free benzene under an atmosphere of nitrogen was added 0.150 mole of n-butyllithium in ether solution. The concentration of n-butyllithium was determined by the double titration procedure of Gilman and Haubein.[73] The interconversion required about ten minutes and gave a reddish color. Then 40 cc. of freshly distilled ethyl sulfate (b.p., 67°/1 mm.) was added dropwise as rapidly as the rate of reflux would permit. The usual white precipitate began to form at once. The solution was stirred for one hour after all of the ethyl sulfate had been added and

was then filtered. The white precipitate was washed with benzene to extract every possible trace of product. The excess ethyl sulfate was destroyed by washing the filtrate with a 10% solution of sodium hydroxide, and it was then washed once with water. After drying over sodium sulfate the solvent was distilled and the residue placed in a crystallizing dish. Since no crystallization could be induced, the material was distilled under vacuum. Four fractions were taken at 5° intervals between 170° and 190° under 1 mm. of pressure. The first and second fractions (b.p., 170-175° and 175-180°) solidified at once and crystallization from 95% ethanol yielded 7.6 g. (20%) of pure 1-ethyl-2,8-dimethoxydibenzofuran. No pure crystalline material could be isolated from the two higher boiling fractions.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75; H, 6.36.

Found: C, 75.2; H, 6.42.

Demethylation of 1-Ethyl-2,8-dimethoxydibenzofuran

A mixture of 7.6 g. (0.0297 mole) of 1-ethyl-2,8-dimethoxydibenzofuran, 30 cc. of glacial acetic acid, and 30 cc. of 47% hydrobromic acid was refluxed over a hot-plate for 8 hours. Part of the product oiled out on dilution to 400 cc., and crystals formed from the solution after it had stood in the icebox overnight. In spite of the high melting

point, the product persisted in coming down as an oil when recrystallized from 50% ethanol. The yield of pure 1-ethyl-2,8-dihydroxydibenzofuran melting at 142-143° was 3.9 g. (57.7%).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.4; H, 5.68.

Found: C, 73.8; H, 5.90.

Bromination of 1-Methyl-2,8-dihydroxydibenzofuran

An attempt to monobrominate 1-methyl-2,8-dihydroxydibenzofuran by the dropwise method resulted only in the formation of a compound melting at 191-192°, with the recovery of some starting material. Analysis of this compound after methylation showed that dibromination had taken place.

Anal. Calcd. for $C_{13}H_8O_2Br_2$: Br, 44.53

Found: Br, 44.3.

The monobromination of 1-methyl-2,8-dihydroxydibenzofuran was accomplished through the method of entrainment bromination. The apparatus used was the same as that employed in the monobromination of 2-aminodibenzofuran (see Page 33). To 4.0 g. (0.0175 mole) of 1-methyl-2,8-dihydroxydibenzofuran dissolved in 50 cc. of glacial acetic acid was introduced, in a stream of air, 3.33 g. of bromine. After all of the bromine had been introduced, the solution was diluted and filtered. Methylation of this mixture was accomplished by dissolving it in 50 cc. of water containing 2 g.

of sodium hydroxide. To this solution 10 cc. of methyl sulfate was added with rapid stirring, and the mixture was then refluxed for one-half hour. On cooling the product solidified and was filtered. This material was taken up in the minimum of acetic acid and allowed to cool, yielding 1.3 g. of product melting at 191-192°. This was shown to be identical with the dibromination product above. The mother liquor was concentrated and the crystals formed were further purified in acetic acid to yield 0.5 g. (8.3%) of needles melting at 143-145°. Later work indicates that this compound is probably 1-methyl-7-bromo-2,8-dimethoxydibenzofuran.

Anal. Calcd. for $C_{15}H_{13}O_3Br$: Br, 24.9.

Found: Br, 25.19.

Monobromination of 1-Ethyl-2,8-dihydroxydibenzofuran

To 4 g. (0.0175 mole) of 1-ethyl-2,8-dihydroxydibenzofuran in 50 cc. of acetic acid was added 2.80 g. (0.0175 mole) of bromine by the method of entrainment described for the preparation of 1-bromo-2-aminodibenzofuran (see Page 33). The acetic acid solution was diluted and filtered. The crude product was taken up in 40 cc. of a 5% sodium hydroxide solution, and to this solution was added 10 cc. of methyl sulfate in the usual dropwise manner. The mixture was refluxed for one-half hour and cooled. The product solidified and was

filtered. Four crystallizations from ethanol yielded 1.0 g. (17%) of a pure product melting at 116-117°.

Anal. Calcd. for $C_{16}H_{15}O_3Br$: Br, 25.0

Found: Br, 25.5.

By analogy with the monobromination of 1-methyl-2,8-dihydroxydibenzofuran, this compound is provisionally designated as 1-ethyl-7-bromo-2,8-dimethoxydibenzofuran.

Preparation of 1,7-Dimethyl-2,8-dimethoxydibenzofuran from 1-Methyl-7-bromo-2,8-dimethoxydibenzofuran

A 50 ml. three-necked flask was thoroughly dried and swept out with nitrogen. A solution of 300 mg. (0.000932 mole) of 1-methyl-7-bromo-2,8-dimethoxydibenzofuran in 10 cc. of thoroughly dried thiophene-free benzene was introduced. To this solution 0.0012 mole of n-butyllithium in ether was added. This is a slight excess. After ten minutes of rapid stirring, 0.5 cc. of methyl sulfate was added quite rapidly. After three hours, with stirring, the white precipitate was filtered and the filtrate washed with 5% sodium hydroxide solution. The solution was washed once with water and then dried over sodium sulfate. Removal of the solvent yielded an oil which melted at 75-90° after solidification. Four recrystallizations from 95% ethanol yielded 25 mg. of plate-like crystals melting at 104-106°.

A mixed melting point of this material with the compound designated as 1,9-dimethyl-2,8-dimethoxydibenzofuran by Gilman, Swiss, Willis, and Yeoman[74] showed no depression. This demonstrates that the step-wise introduction of bromine involves the same positions as in the case of the direct dibromination.

Preparation of 1-Methyl-7-ethyl-2,8-dimethoxydibenzofuran in the Form of the Picrate

To 300 mg. (0.000932 mole) of 1-methyl-7-bromo-2,8-dimethoxydibenzofuran in 10 cc. of dry benzene in a 50 ml. three-necked flask under an atmosphere of nitrogen was added 0.000932 mole of n-butyllithium in 1.55 cc. of ether. Ten minutes with rapid stirring was allowed for the interconversion, and then 0.66 cc. of ethyl sulfate was added dropwise. Stirring was continued for one and one-half hours. The grayish precipitate was filtered and the excess ethyl sulfate destroyed by washing the benzene solution with dilute sodium hydroxide solution. The oil remaining after removal of the solvent would not solidify on cooling. Attempts to purify from 95% ethanol were fruitless.

The total solvents were removed and the residue taken up in the minimum of chloroform. Then 0.001 gm. of picric

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[74] Gilman, Swiss, Willis, and Yeoman, J. Am. Chem. Soc., 66, 798 (1944).

acid in 1 cc. of hot chloroform was added to the chloroform solution of 1-methyl-7-ethyl-2,8-dimethoxydibenzofuran. The solution immediately turned red, and red needles formed on cooling. The crude picrate melted at 125-138°. Four additional purifications from chloroform yielded 20 mg. of the pure picrate melting at 144-145.5°.

Anal. Calcd. for $C_{23}H_{21}O_{10}N_3$: N, 8.42.

Found: N, 8.3.

Attempted Preparation of 1-Ethyl-7-methyl-2,8-dimethoxydibenzofuran

This reaction was carried out simultaneously with the previous preparation, using the same reagents and n-butyllithium solution.

An ether solution of 0.0012 mole of n-butyllithium was added to 300 mg. (0.000932 mole) of 1-ethyl-7-bromo-2,8-dimethoxydibenzofuran in 10 cc. of dry benzene. After filtration the solution was washed in the usual manner with sodium hydroxide and water. After removal of the solvent the residue failed to solidify. All attempts to induce crystallization met with failure.

Hence, an attempt was made to prepare the picrate. A red color formed immediately in chloroform solution, but prolonged efforts failed to produce anything but a dark red oil.

This entire procedure was repeated with similar results. It is possible that the picrate is a very low melting solid or an oil.

Metalation of 1-Methyl-2,8-dimethoxydibenzofuran

It was thought that the metalation of 1-methyl-2,8-dimethoxydibenzofuran might involve the same position as in the bromination of 1-methyl-2,8-dihydroxydibenzofuran. This would have facilitated the preperation of 1-methyl-7(?)-ethyl-2,8-dimethoxydibenzofuran.

Six grams (0.0248 mole) of 1-methyl-2,8-dimethoxydibenzofuran was dissolved in 125 cc. of sodium-dried ether and placed in a 250 cc. three-necked flask equipped with a stirrer and attached to a nitrogen train. To this solution 0.0248 mole of n-butyllithium was added, and stirring was continued for eight hours. The solution turned orange after a few minutes with the formation of an orange precipitate before the metalation was complete. Ten cc. of methyl sulfate was added dropwise and the mixture stirred for one hour. The precipitate was filtered. The ether solution was washed once with sodium hydroxide and once with water. The residue, after evaporation of the ether, was taken up in 95% ethanol from which it oiled out on cooling. The mother liquor after standing yielded white needles which melted at 129-131°. The yield of product melting at 129-131° was 1.4 g. (22%). No

other product could be isolated.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.25.

Found: C, 74.7; H, 6.21.

This compound may be either 1,9- or 1,7-dimethyl-2,8-dimethoxydibenzofuran.

Monobromination of 2,8-Dimethoxydibenzofuran

Twelve grams (0.0526 mole) of 2,8-dimethoxydibenzofuran was dissolved in 250 cc. of glacial acetic acid and 8.4 g. (0.0526 mole) of bromine was added to the rapidly stirred solution by the entrainment method.

After all of the bromine had passed over, the solution was diluted with water and filtered. An attempt to dissolve this crude material showed that a portion of it was fairly insoluble in alcohol. This insoluble portion was filtered and resolved by crystallization in acetic acid into two products melting at 196-197° and 262-263°. These were shown by the method of mixed melting points to be identical with the products obtained by Swislowsky[27] in the dibromination of 2,8-dimethoxydibenzofuran.

The alcohol filtrate was concentrated and cooled in the icebox. Three crystallizations of the product which came down yielded 1 g. (6.2%) of needles melting at 115-116°. A mixed melting point of this material with the product

obtained by Thirtle[38] in the debromination of the supposed 1,9-dibromo-2,8-dimethoxydibenzofuran showed no depression. Analysis by Thirtle[38] shows that this compound is a monobromo-2,8-dimethoxydibenzofuran.

Monobromination of 3-Bromo-2,8-dimethoxydibenzofuran

To 0.55 g. (0.00178 mole) of 3-bromo-2,8-dimethoxydibenzofuran in 20 cc. of glacial acetic acid was added 1.8 cc. of a 1-molar bromine solution in a dropwise manner. The product crystallized from the vigorously stirred solution before all of the bromine had been added. The solution was cooled and filtered. This crude product melted at 196-260°. Four crystallizations were carried out in acetic acid, giving 150 mg. of pure crystals melting at 262-263°. A mixed melting point of this material with an authentic sample of 3,7-dibromo-2,8-dimethoxydibenzofuran[27, 37] showed no depression. This identifies the monobromo derivative of 2,8-dimethoxydibenzofuran as 3-bromo-2,8-dimethoxydibenzofuran.

The mother liquors from the first and second crystallizations above were concentrated and found to yield, on subsequent recrystallization, 50 mg. of needles melting at 196-197°. A mixed melting point of this material with a sample of the supposed 1,9-dibromo-2,8-dimethoxydibenzofuran prepared by Swislowsky[27] showed no depression.

The identity of these two compounds establishes the fact that the compound previously designated as 1,9-dibromo-2,8-dimethoxydibenzofuran is either 1,7- or 1,3-dibromo-2,8-dimethoxydibenzofuran.

Monobromination of 1-Bromo-2,8-dimethoxydibenzofuran

Seventy milligrams (0.000228 mole) of 1-bromo-2,8-dimethoxydibenzofuran was dissolved in 10 cc. of glacial acetic acid and to this solution was added 0.228 cc. (0.000228 mole) of a molar solution of bromine in glacial acetic acid. The product was crystallized from the same acetic acid by redissolving and cooling to 0°. The yield of pure 1,7-dibromo-2,8-dimethoxydibenzofuran melting at 196-197° was 80 mg. (93%).

A mixed melting point with an authentic sample of the supposed 1,9(?)-dibromo-2,8-dimethoxydibenzofuran was not depressed.

Formylation of 2,8-Dimethoxydibenzofuran

A mixture of 5 g. (0.022 mole) of 2,8-dimethoxydibenzofuran, 12 g. of phosphorous oxychloride, and 12 g. of N-methylformanilide in an Erlenmeyer flask was heated for two and one-half hours on the steam bath with frequent shaking. The reaction was slow to start as indicated by the tardiness in the appearance of the red color characteristic of this type of reaction. The contents of the flask were treated with 50 cc. of 10% ammonium chloride. Shaking and cooling resulted in the formation of a solid suspension in the flask. This crude product was filtered and dissolved in a rather large volume of 95% ethanol. Cooling resulted in the formation of 3.5 g. of crystals melting at 150-155°. A second purification from the same solvent yielded 2.5 g. (45.5%) of pure 2,8-dimethoxydibenzofuran-3-aldehyde melting at 166-167°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.70.

Found: C, 70.1; H, 4.68.

Preparation of 2,8-Dimethoxydibenzofuran-1-carboxylic acid

A solution of 1 g. (0.00326 mole) of 1-bromo-2,8-dimethoxydibenzofuran in 25 cc. of dry ether was placed in a 50 cc. three-necked flask under an atmosphere of nitrogen,

and 0.00326 mole of n-butyllithium in 8 cc. of ether was added rapidly with vigorous stirring. After ten minutes, to allow for complete halogen-metal interconversion, the ether solution was cautiously poured onto freshly crushed dry ice in an Erlenmeyer flask and allowed to stand for one hour with occasional shaking. At the end of this time all of the carbon dioxide had disappeared, and the salt of the acid was treated with a dilute solution of hydrochloric acid. The crude acid formed was taken up in dilute sodium hydroxide and filtered. The acid was precipitated by acidification with hydrochloric acid. Two purifications from 95% ethyl alcohol yielded 0.3 g. (33.9%) of long needles melting at 193-195°.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.2; H, 4.42.

Found: C, 66.50; H, 4.45.

Preparation of 2,8-Dimethoxydibenzofuran-3-carboxylic acid

This reaction was performed at the same time as the above reaction, using the same reagents and the same n-butyllithium.

A halogen-metal interconversion was carried out on 1 g. (0.00326 mole) of 3-bromo-2,8-dimethoxydibenzofuran in 25 cc. of dry ether under nitrogen by the addition of 0.00326 mole of n-butyllithium in 8 cc. of ether. After ten minutes with vigorous stirring, the solution of the organometallic compound

was carbonated by pouring onto powdered dry ice in an Erlenmeyer flask. After all of the dry ice had evaporated, the product was hydrolyzed with a 50% hydrochloric acid solution. The acid was taken up in base, filtered, and acidified. The free acid was filtered and purified from a hot ethanol solution. The yield of pure 2,8-dimethoxydibenzofuran-3-carboxylic acid melting at 170-171° was 0.2 g. or 22.6% of the theoretical.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.2; H, 4.42.

Found: C, 66.15; H, 4.39.

Oxidation of 2,8-Dimethoxydibenzofuran-3-aldehyde

One gram (0.0039 mole) of the product formed by the action of N-methylformanilide and phosphorous oxychloride on 2,8-dimethoxydibenzofuran was refluxed in suspension in a neutral solution of 1 g. of potassium permanganate for five hours. The excess permanganate was destroyed by adding sodium bisulfite, and the manganese dioxide was filtered off. Acidification of the filtrate precipitated the acid. The acid was purified by crystallization from a 50% ethanol solution. The yield was 0.3 g. (33.9%) of beautiful needles melting at 169.5-171°.

A mixed melting point of this acid with the authentic 2,8-dimethoxydibenzofuran-3-carboxylic acid showed no depression.

Preparation of 4-Hydroxydibenzofuran

Large quantities of 4-hydroxydibenzofuran were prepared in essentially the same manner as described by Cheney.[19] At that time it was assumed that the yields of n-butyllithium corresponded with the findings of Gilman, Zoellner, and Selby.[75] However, accurate determinations of yield in the preparation of n-butyllithium according to the procedure of Gilman and Haubein[73] have demonstrated that these yields are often lower.

From 150 g. of finely divided lithium in 3 l. of dry ether in a 5 liter three-necked flask and 1100 cc. of freshly distilled n-butyl bromide was prepared 5.00 mole of n-butyllithium. The 5 liter flask was immersed in an ice-salt bath during the addition of n-butyl bromide. This corresponds to a yield of 50% of the theoretical. In nearly all cases, where n-butylithium was prepared by this writer, the yield seldom fell below 50% and more frequently approached the 60% mark where smaller runs were made.

The n-butyllithium was strained through a glass wool plug into a 12 l. three-necked flask containing a solution of 850 g. (5 mole) of dibenzofuran in 2 l. of ether. The procedure described by Cheney[19] was followed throughout the remainder of the preparation. It is essential to thoroughly

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[75] Gilman, Zoellner, and Selby, J. Am. Chem. Soc., 55, 1252 (1933).

cool the solution of 4-dibenzofuryllithium before adding an equivalent amount of n-butylmagnesium bromide[76] and to allow one hour with stirring before proceeding with the oxidation. Better results were obtained when it was made very certain that the temperature of the solution did not rise above 0-5° during the oxidation. The yield of crude 4-hydroxydibenzofuran was 458 g. or 52.5% of the theoretical. In two other runs comparable in size, the yields were 50% and 51%.

Preparation of 3-Bromo-4,6-dimethoxydibenzofuran

The 4,6-dimethoxydibenzofuran used in this preparation and in subsequent preparations was prepared according to the procedure of Cheney.[19] The added precautions mentioned in the procedure above were used in the preparation of 4-hydroxy-6-methoxydibenzofuran. The yield of 4-hydroxy-6-methoxydibenzofuran[23] was 29%, and 29.5% in the case of the isomeric 3-hydroxy-4-methoxydibenzofuran.[23]

Ten grams (0.044 mole) of 4,6-dimethoxydibenzofuran was dissolved in 100 cc. of dry ether in a 250 cc. three-necked flask supplied with an atmosphere of nitrogen. To this was added 0.050 mole of n-butyllithium in 80 cc. of ether. This

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[76] Ivanoff, Bull. Soc. Chem., 39, 47 (1926).

solution was stirred and refluxed for 5-6 hours. A deep purple color developed. Not quite all of the 4,6-dimethoxydibenzofuran dissolved at the beginning.

Into the above rapidly stirred solution was passed 0.044 mole of bromine gas entrained in a stream of dry nitrogen. Stirring was continued for 15-20 minutes. The ether solution was washed with a dilute sodium hydroxide solution and dried over sodium sulfate after being washed once with water. The ether was removed by distillation, leaving an oil that would not crystallize readily. Several purifications from 95% ethanol yielded 1 g. (8%) of needles melting at 117.5-119°. This product is believed to be 3-bromo-4,6-dimethoxydibenzofuran.

Anal. Calcd. for $C_{14}H_{11}O_3$: Br, 27.05.

Found: Br, 26.95.

Conversion of 3-Bromo-4,6-dimethoxydibenzofuran into 3,4,6-Trimethoxydibenzofuran

To 0.4 g. (0.0035 mole) of 3-bromo-4,6-dimethoxydibenzofuran dissolved in 10 cc. of dry ether under an atmosphere of nitrogen was added 0.0037 mole of n-butyllithium. Stirring was continued for ten minutes. At the end of this period 0.0035 mole of butylmagnesium bromide was added to

the solution, and the flask was cooled in an ice-salt bath prior to oxidation.

Into the space above the rapidly stirred and well cooled solution was passed a slow stream of well dried oxygen gas. At the end of two hours a negative test for an organometallic compound[72] was obtained. After acidification with dilute hydrochloric acid the ether layer was washed with water and extracted with a 5% solution of sodium hydroxide. The 3-hydroxy-4,6-dimethoxydibenzofuran was precipitated with hydrochloric acid and recrystallized from a ten percent mixture of benzene in petroleum ether (b.p., 77-115°). The yield was 150 mg. (40%) of chunky crystals melting at 140-141°.

Anal. Calcd. for $C_{14}H_{12}O_4$; C, 68.8; H, 4.92.

Found: C, 68.4; H, 4.89.

The methylation of this phenol was carried out by dissolving it in a solution of 0.2 gram of sodium hydroxide in 10 cc. of water and adding 2 cc. of methyl sulfate dropwise. This mixture was refluxed for 15 minutes, the excess methyl sulfate was destroyed with 1 gram of sodium hydroxide, and the solid product which formed after cooling was filtered off. Recrystallization from 95% ethanol yielded 140 mg. (40%) of needles melting at 126-127°.

Anal. Calcd. for $C_{15}H_{14}O_4$; C, 69.6; H, 5.44.

Found: C, 69.0; H, 5.64.

Attempted Preparation of 3,4,6-Trimethoxydibenzofuran from 3,4-Dimethoxydibenzofuran

Using the usual nitrogen atmosphere when dealing with organometallic compounds, 3.8 g. (0.0167 mole) of 3,4-dimethoxydibenzofuran was dissolved in 75 cc. of dry ether, and 0.0167 mole of n-butyllithium was introduced rapidly. The solution was stirred for six hours, maintaining an atmosphere of nitrogen. An equivalent amount (0.0167 mole) of n-butylmagnesium bromide was added, and into the cooled mixture was passed a stream of dry oxygen. Only two or three hours were required to bring about a negative test for an organometallic compound.[72] After acidification the ether solution was separated, washed with water, and extracted. The sodium hydroxide extract was acidified. Only an oil was obtained. All attempts to isolate a crystalline product resulted in failure. There was no base insoluble phenolic product as was obtained in the metalation and subsequent oxidation of 4-methoxydibenzofuran. It is possible that isomeric products are not formed and that metalation involved the 2-position yielding a very low melting solid. The preparation was repeated with similar results. Petroleum ether (b.p., 60-86°) and methanol were tried as solvents for purification.

Monobromination of 1-Bromo-4,6-dimethoxydibenzofuran

Seventy milligrams (0.000228 mole) of 1-bromo-4,6-dimethoxydibenzofuran was dissolved in 10 cc. of glacial acetic acid and to this solution was added 0.228 cc. (0.000228 mole) of a molar solution of bromine in glacial acetic acid. After cooling the product was filtered and recrystallized once more from acetic acid. The yield was 60 mg. (72%) of pure 1,7-dibromo-4,6-dimethoxydibenzofuran melting at 173-174°.

A mixed melting point with an authentic sample of the supposed 1,9(?)-dibromo-4,6-dimethoxydibenzofuran was not depressed.

Monobromination of 3-Bromo-4,6-dimethoxydibenzofuran

To a solution of 0.4 g. (0.0013 mole) of 3-bromo-4,6-dimethoxydibenzofuran in 20 cc. of glacial acetic acid was added 1.3 cc. of a molar bromine solution in glacial acetic acid. The product began to crystallize before all of the bromine had been added. The bromine was absorbed very rapidly. Purification was effected by heating and then cooling the reaction mixture. The needles that formed were filtered and found to weigh 0.45 g. or very nearly a quantitative yield. The melting point was 167-168° and was not depressed when the material was mixed with a sample of the product obtained by Cheney[19] in the direct dibromination of 4,6-dimethoxydibenzofuran. This compound is probably 1,7-dibromo-4,6-dimethoxydibenzofuran.

Bucherer Reaction with 1-Bromo-4-hydroxydibenzofuran

The following experiment was performed in order to observe the action of sodium metabisulfite and concentrated ammonium hydroxide on a bromine atom para to a phenol-group in the dibenzofuran nucleus. In the case of 1-bromo-2-hydroxydibenzofuran only the 2-aminodibenzofuran was obtained.[27]

The 1-bromo-4-hydroxydibenzofuran used in this

experiment was prepared according to the directions of P. R. Van Ess.[26]

A mixture of 1.5 g. (0.057 mole) of 1-bromo-4-hydroxydibenzofuran, 7.5 g. of sodium metabisulfite, 15 cc. of concentrated ammonium hydroxide, and 15 cc. of water was sealed in a Carius tube. The tube was then placed in an electrically heated oven at 180° for 20 hours. After the tube was cooled and removed from the oven, a black ball of solid product was observed at the bottom of the liquid present. The black material was extracted with ether and dried over sodium sulfate, and the amine was precipitated as the hydrochloride by passing a stream of dry hydrogen chloride gas into the solution. The hydrochloride was dissolved in water and neutralized with ammonium hydroxide. The product which separated was purified in a 25% ethanol mixture. The yield of pure needles melting at 84-85° was 0.2 g. (19%). A mixed melting point of this material with an authentic sample of 4-aminodibenzofuran was not depressed.

Since the conditions of the Bucherer reaction have the effect of removing bromine atoms from an aromatic ring containing a phenolic group, this reaction cannot be used to prepare 1-bromo-4,6-diaminodibenzofuran as was hoped.

Demethylation of 4,6-Dimethoxydibenzofuran-1-carboxylic Acid

The 4,6-dimethoxydibenzofuran-1-carboxylic acid used in this reaction was prepared according to the directions of Cheney.[19] The 1-bromo-4,6-dimethoxydibenzofuran required was also prepared according to Cheney.[19]

Five grams (0.0182 mole) of 4,6-dimethoxydibenzofuran-1-carboxylic acid was dissolved in one liter of acetic acid, and 15 cc. of 47% hydrobromic acid was added to the refluxing solution. The mixture was refluxed for 8 hours after the addition of the hydrobromic acid. The darkened solution was concentrated by distilling the greater portion of the solvent. Dilution with water yielded a material melting at 260-270°. Attempts to purify this product in various solvents yielded only a compound of the same melting point. Purification was achieved by vacuum sublimation. In this way 1.9 g. (42.8%) of material melting sharply at 278-280° was obtained.

Anal. Calcd. for $C_{13}H_8O_5$: C, 64; H, 3.28.

Found: C, 63.7; H, 3.30.

Bucherer Reaction with 4,6-Dihydroxydibenzofuran-1-carboxylic Acid

One and one-half grams (0.0616 mole) of 4,6-dihydroxydibenzofuran-1-carboxylic acid was sealed in a Carius tube

with 7 g. of sodium bisulfite and 25 cc. of concentrated ammonium hydroxide. The tube was placed in an electrically heated oven at 160° for 16 hours. After cooling and opening, the contents of the tube were washed into a 100 cc. beaker and made just acid to litmus. This was filtered, taken up in ether, and precipitated from the dried ether solution with dry hydrogen chloride gas. The hydrochloride was filtered, dissolved in hot water, and barely neutralized with ammonium hydroxide. The liberated 4,6-diaminodibenzofuran-1-carboxylic acid was recrystallized three times from ethanol, yielding 0.66 g. (43.8%) of darkened needles melting at 183-184°.

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: N, 9.42.

Found: N, 9.31.

Deamination of 4,6-Diaminodibenzofuran-1-carboxylic Acid

To a solution of 0.44 g. (0.0018 mole) of 4,6-diaminodibenzofuran-1-carboxylic acid in 30 cc. of water and 4 cc. of concentrated hydrochloric acid cooled to 0° was added 0.552 g. of sodium nitrite in 10 cc. of water at 0°. The addition was carried out in a dropwise manner. The solution turned a deep red color, and the diazonium salt crystallized out as dark red needles. To this suspension of the diazonium salt was added 5 cc. of 50% hypophosphorous acid. This

mixture was placed in the icebox for 24 hours and then heated for 1 hour on the steam bath after coming to room temperature. The residue was taken up in a 5% sodium hydroxide solution and filtered. The acid was liberated with dilute hydrochloric acid. Purification from 50% ethanol yielded a small amount of crystals melting at 232°. A mixed melting point of this material with an authentic sample of dibenzofuran-1-carboxylic acid was not depressed.

Preparation of 4,6-Dimethoxydibenzofuran-1-aldehyde

The procedure in this experiment was patterned after that of Fieser and Jones[77] in the N-methylformanilide synthesis of aldehydes.

A mixture of 5 g. (0.0219 mole) of 4,6-dimethoxydibenzofuran, 12 g. of N-methylformanilide, and 12 g. of phosphorous oxychloride was heated for 1.5 hours on a steam bath with occasional shaking. The solution turned a deep red color, and considerable foaming occurred. The excess phosphorous oxychloride was destroyed by treating with a 10% solution of sodium acetate. A solid red material settled out on cooling. This crude product was recrystallized from a minimum quantity of 95% ethanol, yielding crystals melting at 155-160°. A second crystallization from ethanol yielded 3.5 g. (62.5%) of white crystals melting at 162-164°.

[77] Fieser and Jones, J. Am. Chem. Soc., 64, 1666 (1942).

A mixed melting point of this compound with an authentic sample of 4,6-dimethoxy-1-aldehyde was not depressed.

From the standpoint of yield and ease of preparation, this method is superior to that of Cook,[49] who prepared 4,6-dimethoxydibenzofuran-1-aldehyde in 41% yield from the action of zinc cyanide, dry hydrogen chloride gas, and aluminum chloride on 4,6-dimethoxydibenzofuran.

Action of N-Methylformanilide on 4,6-Dimethoxydibenzofuran-1-aldehyde

A mixture of 1 g. (0.0039 mole) of 4,6-dimethoxydibenzofuran-1-aldehyde, 1.5 g. of N-methylformanilide, and 1.5 g. of phosphorous oxychloride was heated on the steam bath for two hours. There was no evolution of heat at the beginning and the red color characteristic of this type of reaction did not appear for some time. Treatment with a sodium acetate solution and purification of the resulting solid product in ethyl alcohol yielded crystals melting at 162-164° which proved to be starting material. It was hoped that 4,6-dimethoxydibenzofuran-1,9-dialdehyde would be formed. Such a compound would be valuable in attempting to bridge the 1- and 9-positions.

Attempts to Chloromethylate 4-Methoxydibenzofuran

The first attempt to chloromethylate 4-methoxydibenzo-

furan was carried out by Cook.[49] Further attempts by varying the conditions are recorded here.

(1) Twenty grams (0.101 mole) of 4-methoxydibenzofuran was powdered and placed in a three-necked flask with 200 cc. of concentrated hydrochloric acid and 5 g. of paraformaldehyde. The mixture was rapidly stirred while a stream of hydrogen chloride gas was passed through. No heat was evolved at first so the flask was heated to 75° and the addition of hydrogen chloride gas continued for 3-4 hours. An oily ball was formed.

Extraction of this oil with 95% ethanol left a precipitate which was very nearly insoluble in all of the common solvents. Small crystals of melting point 235-240° were formed from a large volume of petroleum ether (b.p., 60-86°). An elemental test showed the presence of halogen. This material could not be further purified and is likely a mixture of polychloromethylation products.

Crystalline material could not be induced to form from the original alcohol extract. An attempt to remove the solvent by distillation resulted in polymerization.

(2) Treatment of 20 g. (0.101 mole) of 4-methoxydibenzofuran in 200 cc. of acetic acid with 3 g. of zinc chloride, 5 g. of paraformaldehyde, and a stream of hydrogen chloride gas for four hours yielded on dilution with water a crude material which behaved exactly as the product in the first attempt.

(3) The reaction was repeated with 20 g. (0.101 mole) of 4-methoxydibenzofuran in 200 cc. of concentrated hydrochloric acid with 5.2 g. of paraformaldehyde at a temperature of 0°. Hydrogen chloride gas was passed through for 5 hours. The resulting oil was taken up in ether and thoroughly dried since it was thought that the material might be sensitive to water. Distillation of the ether on a water bath yielded an amorphous thermoplastic product. Apparently, heat aids its polymerization.

(4) In another attempt ten grams (0.05 mole) of 4-methoxydibenzofuran was dissolved in 100 cc. of absolute ethanol with 2.5 g. of paraformaldehyde. The solution was cooled to 0° and a stream of hydrogen chloride gas passed through for three hours. After dilution the resultant oil was taken up in chloroform in which it was readily soluble. The addition of petroleum ether (b.p., 60-86°) resulted in the formation of crystals (this method was employed in order to avoid the use of heat). This material melted from 60-145°. However, all attempts to further purify this product were futile.

(5) A final attempt was carried out with 10 g. (0.05 mole) of 4-methoxydibenzofuran and 2.5 g. of paraformaldehyde in 150 cc. of dry ether cooled to 0°. A stream of hydrogen chloride was passed into the stirred solution for 3 hours.

Careful removal of the ether in a hood resulted in a solid material (8 g.) melting in the range 60-150°. Its purification could not be effected.

Preparation of 4-Methoxydibenzofuran-1-aldehyde

In a typical run 7 g. (0.0375 mole) of 4-methoxydibenzofuran was placed in a 125 cc. Erlenmeyer flask with 9 g. of freshly distilled phosphorous oxychloride and 9 g. of N-methylformanilide. This mixture was heated on a steam bath for 1.5 hours with occasional shaking. The excess phosphorous oxychloride was destroyed with a 10% solution of sodium acetate. The product solidified on cooling and was filtered off. Crystallization from a 50% methanol solution yielded 5 g. (63%) of white needles melting at 104-105°.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.5; H, 4.43.

Found: C, 75.2; H, 4.71.

Oxidation of 4-Methoxydibenzofuran-1-aldehyde

One gram (0.0044 mole) of the aldehyde was suspended in a water solution (neutral) of 1 g. of potassium permanganate and refluxed until the color of the potassium permanganate did not show up when a drop of the solution was placed on a piece of filter paper. The manganese dioxide was removed by

filtration and the acid precipitated by acidifying with hydrochloric acid. A white gelatinous precipitate formed which was twice recrystallized from ethanol, yielding well formed needles of a product melting at 280-281°. The yield was 0.5 g. (47%).

A mixed melting point of this acid with an authentic sample of 4-methoxydibenzofuran-1-carboxylic acid showed no depression. This demonstrates that the formylation of 4-methoxydibenzofuran involves the 1-position.

Preparation of 4-Methoxy-1-dibenzofuralacetic Acid

Thirteen grams (0.055 mole) of 4-methoxydibenzofuran-1-aldehyde, prepared as just described, was placed in an Erlenmeyer flask with 13 g. of pure malonic acid and 15 cc. of dry pyridine. The mixture was well stirred and then placed on the steam bath for 2.5 hours. After a few minutes the mixture turned into a homogeneous liquid phase and soon began to evolve carbon dioxide. Very shortly, the entire solution solidified into a yellow cake which continued to swell as more carbon dioxide was liberated. Water was then added and the insoluble product filtered. The cake-like material was then dissolved in 200 cc. of a hot 5% solution of sodium carbonate and filtered after cooling. The clear and colorless basic solution was then acidified with hydro-

chloric acid, and the pale yellow precipitate which formed was filtered. This crude product was dissolved in the minimum amount of hot glacial acetic acid which yielded, on cooling, 9.5 g. (64.5%) of beautiful light yellow needles melting at 281-282°.

Anal. Calcd. for $C_{16}H_{12}O_4$: neut. equi., 268.

Found: neut. equi., 266.

Preparation of β-[1-(4-Methoxydibenzofuryl)]propionic Acid

The following is a typical preparation:

One and one-half grams (0.0055 mole) of 4-methoxy-1-dibenzofuralacetic acid was dissolved in 0.2 g. of sodium hydroxide in 75 cc. of water and two grams of Pd-$CaCO_3$ catalyst added. Treatment of this solution with hydrogen under 20 pounds of pressure for two hours resulted in the absorption of the theoretical quantity of hydrogen. The catalyst was filtered and the product precipitated from the basic solution with hydrochloric acid. The crude product weighed 1.5 g. and melted at 165-175°. One crystallization from 95% ethanol yielded thick needles melting at 176-178°. The yield of pure β-[1-(4-methoxydibenzofuryl)]propionic acid was 1.3 g. or 90% of the theoretical.

Anal. Calcd. for $C_{16}H_{14}O_4$: neut. equiv., 270.

Found: neut. equiv., 265 and 269.

Cyclization of β-[1-(4-Methoxydibenzofuryl)]-propionic Acid

(I) With 88% sulfuric acid.

A solution of 1.2 g. (0.00445 mole) of β-[1-(4-methoxydibenzofuryl)]propionic acid was allowed to stand at room temperature for fifteen minutes. The mixture was poured onto cracked ice and filtered. The filtrate was completely dissolved in a solution of sodium hydroxide indicating that no cyclization occurred.

(II) With anhydrous hydrogen fluoride.

Into 75 cc. of anhydrous liquid hydrogen fluoride in a round-bottomed copper flask was introduced 1.5 g. (0.0055 mole) of β-[1-(4-methoxydibenzofuryl)]propionic acid. The acid readily dissolved and was allowed to stand in the open vessel at room temperature for two and one-half hours. The remaining solution was poured on cracked ice, neutralized with ammonium hydroxide, and filtered. The white product was extracted with a 5% solution of sodium hydroxide and then purified by crystallization from 95% ethanol. The yield of pure product melting at 192-193° was 1 g. or 73% of the theoretical.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.77.

Found: C, 76.00; H, 4.77.

Oxidation of 5-Methoxy-1-benz[b]indeno[4,5-d]furan-3(2)-one

The oxidation of 0.5 g. (0.002 mole) of the cyclic ketone obtained in the previous experiment was accomplished by refluxing with 2 g. of potassium permanganate in neutral solution for four hours. At the end of this time the color of potassium permanganate had disappeared. The manganese dioxide formed was filtered and the filtrate acidified. After cooling the acid was filtered and directly methylated for purification. The 200 mg. of crude acid obtained was suspended in dry ether, and an excess of diazomethane in ether solution was added. Stirring was continued until the evolution of nitrogen had ceased and all of the acid was in solution. The ether was evaporated and the residue taken up in a minimum of methanol. On cooling, this solution yielded 150 mg. (24%) of pure product melting at 175-176°.

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 65.00; H, 4.46.

Found: C, 64.5; H, 4.38.

The mixed melting point of this di-acid ester with the di-acid ester prepared by Avakian[48] by the oxidation of 1,2,3,4-tetrahydro-7-methoxy-1-oxocycloocta(klm)dibenzofuran was not depressed, indicating that this cyclization involved the same position as the cyclization by Avakian[48] with γ-[1-(4-methoxydibenzofuryl)]butyric acid. This product

is either 4-methoxy-1,9-dicarbomethoxydibenzofuran or 4-methoxy-1,2-dicarbomethoxydibenzofuran.

Reduction of 5-Methoxy-1-benz[b]indeno[4,5-d]furan-3(2)-one to 4-Methoxy-1,2-cyclopentenodibenzofuran

One gram (0.004 mole) of the ketone was dissolved in 50 cc. of ethyl alcohol and 20 g. of zinc amalgam placed in the flask. To this refluxing mixture was added 25 cc. of concentrated hydrochloric acid in 5 cc. portions. After four hours a second portion of 25 cc. of concentrated hydrochloric acid was added, and the reaction mixture was refluxed overnight. The solution was decanted from the zinc, concentrated by distillation, and diluted with water, producing an oil which did not solidify in the icebox. The oil was taken up in a minimum of petroleum ether (b.p., 60-68°) and cooled to 0° for two or three days. One-half gram of chunky prisms was formed. The product melted at 66-68°. This represents a yield of 52.5%.

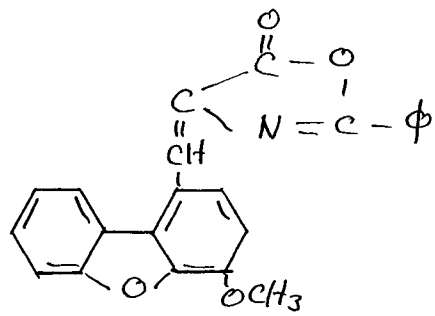
Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.8; H, 5.88.

Found: C, 80.5; H, 6.0.

Attempted Oxidation of 5-Methoxy-1-benz[b]indeno[4,5-d]-furan-3(2)-one with Selenium Dioxide

A solution of 0.6 g. (0.0021 mole) of ketone and 0.3 g. of selenium dioxide was refluxed overnight in 75 cc. of 95% ethanol. Red selenium metal precipitated during the course of the reaction. After cooling the solution deposited small powdery crystals of material which proved to be very impure starting material.

Condensation of 4-Methoxydibenzofuran-1-aldehyde with Hippuric Acid



The procedure used in this preparation is essentially that employed in Organic Syntheses.[78]

A mixture of 18 g. (0.08 mole) of 4-methoxydibenzofuran-1-aldehyde, 16 g. (0.08 mole) of hippuric acid, 6.5 g. of

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[78] Blatt. "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, New York, (1943) p. 55.

freshly fused sodium acetate, and 50 cc. of acetic anhydride was placed in a 150 cc. flask. The reacting mixture was cautiously heated on a steam plate until a yellow precipitate formed. The paste was thoroughly mixed and transferred to a steam bath. Caution was taken to avoid the formation of a deep red color by overheating. At no time did the mixture form a completely liquid phase. After one and one-half hours on the steam bath 50 cc. of 95% ethanol was added cautiously to destroy the excess acetic anhydride. The product was filtered, washed with 50 cc. of 95% ethanol, and then washed with 100 cc. of boiling water. This material was dried and found to weigh 20 g. (68%). The melting point of this crude material was found to be 240-245°. A sample was purified from acetic acid for analysis. The pure material melted at 245-246°.

Anal. Calcd. for $C_{23}H_{15}\Phi_4N$: N, 3.79.
Found: N, 3.71.

Preparation of 4-Methoxy-1-dibenzofurylacetic Acid

This preparation is patterned after a similar preparation in Organic Syntheses.[79]

Twenty grams (0.0542 mole) of the azlactone, prepared as just described, was refluxed gently with 100 cc. of a 10%

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[79] Blatt. "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, New York, (1943) p. 333.

sodium hydroxide solution for 15 hours. The insoluble material in suspension was filtered. Sulfur dioxide gas was passed into the solution to precipitate the benzoic acid. This acid was filtered off through an asbestos filter pad with suction. The solution of the sodium salt of 4-methoxy-1-dibenzofurylpyruvic acid was oxidized by the addition of 8 cc. of 30% hydrogen peroxide. After standing for several hours the solution was acidified. The crude acid which precipitated melted at 200-215° and resisted purification from solvents. The weight of crude acid was 4 g. Purification was effected by esterification with diazomethane in ether. The ether was distilled, and 2.0 g. of pure product was formed after one crystallization from dilute ethanol. The ester melted at 95-96°.

The ester was hydrolyzed by refluxing for one hour in 15 cc. of 5% sodium hydroxide solution. Acidification yielded 1.5 g. (10.8%) of pure 4-methoxy-1-dibenzofuryl-acetic acid melting at 220°.

Attempt to Prepare 4-Methoxy-1-dibenzofurylpyruvic Acid

Eight grams (0.022 mole) of the azlactone of α-benzoylamino-β-(4-methoxydibenzofuryl)-acrylic acid was refluxed for 5 hours with 100 cc. of a 10% sodium hydroxide solution. The solution was neutralized with hydrochloric acid and the

yellow acid filtered. Several crystallizations from acetic acid yielded 3 g. of material melting at 235-237° with decomposition. According to the following analysis, the compound is not the desired product.

Anal. Calcd. for $C_{16}H_{12}O_6$: neut. equiv., 284.

Found: neut. equiv., 200 and 198.

Attempted Cyclodehydration of 4-Methoxy-1-dibenzofurylacetic Acid

(I) With hydrogen fluoride at room temperature.

A solution of 0.15 g. (0.00058 mole) of 4-methoxy-1-dibenzofurylacetic acid in 20 cc. of anhydrous liquid hydrogen fluoride was sealed in a small 50 cc. copper bomb and allowed to stand at room temperature for 6 hours. The bomb was then heated on the steam bath for one hour and allowed to stand overnight before opening. After the bomb was opened, the contents were poured over cracked ice in a copper beaker, and the hydrogen fluoride was neutralized with ammonium hydroxide. The product dissolved in hot water. However, cooling produced needles of acid melting at 221° which was identical with the starting material.

(II) With hydrogen fluoride at 100°.

A solution of 0.1 g. (0.00039 mole) of acid in 20 cc. of anhydrous liquid hydrogen fluoride was sealed in a small

copper bomb as before and heated on a steam bath for four hours. After cooling the tube was opened, and the contents were poured over cracked ice in a copper beaker. The residue was filtered and found to be insoluble in a dilute solution of sodium hydroxide. The basic extract was treated for phenolic material by passing carbon dioxide gas into it. No precipitate formed. Acidification with hydrochloric acid produced no acidic material. The insoluble residue could not be crystallized and was probably a mixture of intermolecular condensation products.

Attempted Preparation of 9-Methyl-10-phenyl-4,5-phenanthrylene Oxide

The 1-bromodibenzofuran used in this experiment was prepared according to the directions given by P. R. Van Ess.[25] The α-phenoxypropiophenone was prepared as directed by Bradsher and Rosher.[62] The entire procedure was patterned after that of Bradsher and Rosher[62] in the preparation of 9-methyl-10-phenylphenanthrene.

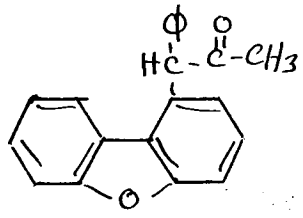
1-Dibenzofurylmagnesium bromide was prepared by dissolving 10 g. (0.04 mole) of 1-bromodibenzofuran in a mixture of 200 cc. of dry ether and 200 cc. of dry benzene containing 2 g. of magnesium turnings. The reaction was initiated by introducing 0.5 cc. of n-butyl bromide and a small crystal

of iodine. It was necessary to reflux the solution to complete the reaction of the magnesium with 1-bromodibenzofuran. The disappearance of the iodine indicated that the reaction had started. One hour of refluxing was required to complete the reaction, and then 13 g. of α-phenoxypropiophenone in 50 cc. of ether was added quite rapidly. After 15 minutes of stirring the solution was washed with dilute hydrochloric acid and then with water. The ether and benzene were distilled, leaving an oil which did not solidify.

The oil thus prepared was refluxed for 48 hours with a mixture of 60 cc. of 47% hydrobromic acid and 60 cc. of glacial acetic acid. Dilution of this solution produced an oil which was taken up in 95% ethanol. The crystals which formed were purified once more from petroleum ether (b.p., 60-68°) and found to melt at 103-105°. An exhaustive search for another product led only to the recovery of more material melting at 103-105°. The combined yield was 4 g. (36.5%) of pure product.

Another run using 12 g. of 1-bromodibenzofuran gave similar results.

Since the crystals melting at 103-105° readily formed an oxime, the material was supposed to be α-phenyl-α-(1-dibenzofuryl)acetone.



The analysis substantiates this conclusion.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 84.00; H, 5.34.

Found: C, 84.2; H, 5.30.

The oxime was prepared by dissolving 0.5 g. of the ketone in 20 cc. of ethyl alcohol with 0.2 g. of sodium hydroxide, and 0.3 g. of hydroxylamine hydrochloride was added to the hot solution. The oxime crystallized immediately. Crystallization from 95% ethanol yielded needles melting at 204-206°.

Anal. Calcd. for $C_{21}H_{17}O_2N$: N, 4.45.

Found: N, 4.42.

It was thought that a more powerful dehydrating agent might cause the ring closure to occur. Several procedures were carried out using the following reagents:

(I) Hydrobromic acid and acetic acid.

Prolonged heating of the ketone (0.5 g.) intermediate with this reagent resulted only in the recovery of 0.35 g. of starting material.

(II) 88% sulfuric acid.

A solution of 0.5 g. (0.00167 mole) of the ketone in 60 cc. of 88% sulfuric acid was allowed to stand at room temperature for twenty minutes. After pouring on cracked ice and filtering the product, it was found that the small amount of product recovered was starting material. Apparently considerable sulfonation had occurred.

(III) Phosphorous pentoxide.

Heating 0.5 g. (0.00167 mole) of the ketone with 1 g. of phosphorous pentoxide in a small tube immersed in a metal bath at 150° resulted in the formation of a yellow polymer which was insoluble in all of the common solvents.

(IV) Anhydrous hydrogen fluoride at room temperature.

A solution of 0.4 g. (0.00134 mole) of ketone in 20 cc. of anhydrous liquid hydrogen fluoride was placed in an open copper beaker in a good hood and allowed to stand until all of the hydrogen fluoride had evaporated. The residue was taken up in a small amount of hot petroleum ether (b.p., 60-86°) and cooled. Crystals of melting point 103-105° were formed. This product proved to be identical with the starting material.

(V) Anhydrous hydrogen fluoride at 100°.

One-half gram (0.00167 mole) of the ketone was placed in a small copper bomb with 20 cc. of liquid hydrogen fluoride and sealed. The bomb was allowed to stand overnight

at room temperature and was then heated to 100° on a steam bath for 2 hours. The bomb was opened and its contents were poured into a copper beaker with cracked ice. The acid was neutralized with ammonium hydroxide and the residue filtered. One crystallization from petroleum ether (b.p., 60-86°) produced chunky crystals melting at 95-100°. A second crystallization from the same solvent raised the melting point to 103-105°.

Since this product was impure, an exhaustive search was made for a second product. No other material could be found.

Succinoylation of 1-Bromo-4,6-dimethoxydibenzofuran

To a solution of 11.2 g. (0.0365 mole) of 1-bromo-4,6-dimethoxydibenzofuran and 3.65 g. (0.0365 mole) of succinic anhydride in 200 cc. of tetrachloroethane and 60 cc. of dry nitrobenzene cooled to 0° in an ice bath was added 14 g. of anhydrous aluminum chloride in small portions. After the addition of the aluminum chloride the mixture was stirred at 0° for 24 hours. The aluminum chloride complex was then hydrolyzed by pouring the solution on an ice-hydrochloric acid mixture. The tetrachloroethane layer was separated, washed with water, and the solvents were removed

by steam distillation. The residue from the steam distillation was extracted with a 10% solution of sodium carbonate. The insoluble residue was found to weigh 2.5 g. Acidification of the sodium carbonate extract with hydrochloric acid precipitated 12 g. of crude acid melting at 175-180°. One crystallization from acetic acid gave 9 g. of product melting at 186-188°. The yield at this point was 61% of the theoretical. This material could not be further purified using toluene as a solvent. This is attributed to the fact that the impurity was less soluble than the main product. The acid material melting at 186-188° was extracted with toluene in a Soxhlet extractor. The residue weighed 1 g. and melted at 235-240°. One crystallization from glacial acetic acid produced crystals melting at 240-241°. A mixed melting point of this material with an authentic sample of 1-succinoyl-4,6-dimethoxydibenzofuran was not depressed.

Further purification of 2.5 g. of the material melting at 186-188° from acetic acid yielded 1.5 g. of needles melting sharply at 200-201°. Another crystallization from the same solvent failed to raise the melting point. This corresponds to a yield of 36%. An elemental test for bromine was positive. This compound is provisionally designated as 1-bromo-7-succinoyl-4,6-dimethoxydibenzofuran.

Anal. Calcd. for $C_{18}H_{15}O_6Br$: neut. equiv., 408;
Br, 19.55.
Found: neut. equiv., 400; Br, 19.75.

The Debromination of
1-Bromo-7(?)-succinoyl-4,6-dimethoxydibenzofuran

To a solution of 0.5 g. (0.00122 mole) of 1-bromo-7(?)-succinoyl-4,6-dimethoxydibenzofuran in 150 cc. of 95% ethanol was added 3 g. of palladium-calcium carbonate catalyst, and the entire mixture was shaken for 20 minutes with hydrogen under a pressure of 35 pounds. The catalyst was filtered from the solution. Dilution, followed by cooling in the icebox, produced 0.2 g. of crude product. This material was dissolved in a small amount of 5% sodium carbonate solution and filtered. The basic solution was acidified, and the product filtered. One crystallization from 95% ethanol gave 0.15 g. (24%) of product melting at 164-166°. Subsequent crystallization raised the melting point to 167-168°.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.9; H, 4.93;
neut. equiv. 329.
Found: C, 66.4; H, 5.05; neut. equiv. 326.

Since substitution in the 2-position is improbable, the compound is most likely 3-succinoyl-4,6-dimethoxydibenzofuran.

Preparation of 1,3-Dibromo-4-methoxydibenzofuran from 1-Bromo-3-amino-4-methoxydibenzofuran

Thirteen grams (0.0445 mole) of 1-bromo-3-amino-4-methoxydibenzofuran prepared according to the directions of Parker,[80] was boiled with 75 cc. of 48% hydrobromic acid in 1.5 liters of water to form a suspension of the hydrobromide. The suspension was cooled to 0° and diazotized by the dropwise addition of 3.5 g. of sodium nitrite in 25 cc. of water. Stirring was continued for one-half hour. Yellow crystals of the diazonium salt slowly formed. Ten grams of cuprous bromide in 50 cc. of 48% hydrobromic acid cooled to 0° was added slowly. The red-brown complex which formed was decomposed by heating to 75°. The crude product was dissolved in acetic acid and the insoluble portion removed by filtration. On cooling, 6 g. of 1,3-dibromo-4-methoxydibenzofuran melting at 135-140° was obtained. Further purification from the same solvent produced long silky needles melting at 139-140°. The yield was 5 g. or 31.5% of the theoretical.

Anal. Calcd. for $C_{13}H_8O_2Br_2$: Br, 44.69

Found: Br, 44.71.

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[80] Gilman, Parker, Baillie, and Brown, J. Am. Chem. Soc., 61, 2836 (1939).

Dibromination of 4-Hydroxydibenzofuran

Seventeen grams (0.0187 mole) of 4-hydroxydibenzofuran was dissolved in 75 cc. of acetic acid, and to this solution was added 187 cc. of a molar bromine solution. The bromine was added rapidly from a dropping funnel. Bromine was absorbed more slowly near the end of the reaction. The resulting solution was diluted, filtered, and the crude product was directly methylated.

Since the sodium salt of this phenol was insoluble in water, the procedure employed by Stevens and Tucker[81] was used.

The crude phenol was dissolved in 50 cc. of acetone and 40 cc. of methyl sulfate. To this rapidly stirred and refluxing solution was added dropwise 50 g. of potassium hydroxide in 50 cc. of water. Stirring and refluxing was continued for one-half hour. The solution was diluted, filtered, and the crude product was recrystallized from glacial acetic acid, yielding 22 g. (62%) of long silky needles melting at 139-140°.

A mixed melting point of this material with 1,3-dibromo-4-methoxydibenzofuran was not depressed.

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

Anomalous Reaction of 1,3-Dibromo-4-methoxydibenzofuran in an Attempt to Prepare 1,3-Dimethyl-4-methoxydibenzofuran.

To 10 g. (0.028 mole) of 1,3-dibromo-4-methoxydibenzofuran dissolved in a mixture of 150 cc. of dry ether and 150 cc. of dry thiophene-free benzene was added 0.028 mole of n-butyllithium in 130 cc. of ether. The solution was stirred for ten minutes, and 10 cc. of methyl sulfate was added dropwise. Stirring was continued for one hour after the addition of the methyl sulfate. The white precipitate which formed was filtered, and the solution was washed with a 10% sodium hydroxide solution. After washing once with water the solution was dried over sodium sulfate, and the solvents were removed by distillation. The residue was taken up in ethyl alcohol from which it crystallized in fine long needles. The yield was 3.0 g. (47.5%) of pure material melting at 86-87°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.7; H, 6.2.

Found: C, 64.8, 64.3, 64.5, and 63.4; H, 4.43, 4.42, 4.23, and 4.46.

The product obtained was evidently not the desired one. Coupling products and various products resulting from autometalation were considered, but none of them fits the above analyses.

Anomalous Reaction of 1,3-Dibromo-4,6-dimethoxydibenzofuran in an Attempt to Prepare 1,3-Dimethyl-4,6-dimethoxydibenzofuran

The 1,3-dimethyl-4,6-dimethoxydibenzofuran used in this reaction was prepared according to the directions of Cheney[19] from 4-hydroxy-6-methoxydibenzofuran.

One gram (0.0025 mole) of 1,3-dibromo-4-methoxydibenzofuran was dissolved in 50 cc. of dry ether and 50 cc. of dry benzene, and to this solution was added 0.0025 mole of n-butyllithium. The solution assumed a bluish color almost immediately, and after ten minutes of stirring, 3 cc. of methyl sulfate was added in a dropwise manner. After 2 hours the while precipitate was filtered and the solution washed once with a sodium hydroxide solution and once with water. Evaporation of the solvent left an oil which crystallized in white needles from 95% ethanol. The yield of product melting at 115-116° was 0.2 g. (31.5%).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25.

Found: C, 64.3, 64.9; H, 4.23, 4.30.

These analyses show that the desired 1,3-dimethyl-4,6-dimethoxydibenzofuran was not obtained. No theoretical compound could be found to fit the analyses.

Nitration of 5,6-Dibromohydrindene

The 5,6-dibromohydrindene used in this experiment was prepared according to the directions of Borsche and Bodenstein.[82] The 5-acetylhydrindene used in the preparation of 5,6-dibromohydrindene was prepared according to the directions of Braun, Kirschbaum, and Schumann[82a] in 90% yield by means of the Friedel-Crafts reaction with hydrindene and acetyl chloride. This is the yield reported by Braun, Kirschbaum, and Schumann[82a]. The 5-acetylhydrindene was converted to the oxime in 85% yield (m.p., 114°). No yield was reported in the original work of Borsche and Bodenstein[82]. This oxime was converted in 75% yield to 5-acetaminohydrindene by means of the Beckmann rearrangement. Bromination gave a 75% yield of 5-acetamino-6-bromohydrindene. These same yields were reported by the original authors.[82] Deacetylation gave a nearly quantitative yield of 5-amino-6-bromohydrindene which was converted *via* the diazonium salt into 5,6-dibromohydrindene in 25% yield.

Several attempts to nitrate 5,6-dibromohydrindene with two equivalents of nitric acid both in acetic acid and acetic anhydride at room temperature resulted in failure. The reaction did not occur even at 100°.

The nitration was finally carried out in concentrated sulfuric acid and nitric acid. Six grams (0.0217 mole) of

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[82] Borsche and Bodenstein, *Ber.*, *59*, 1926 (1912).

[82a] Braun, Kirschbaum, and Schumann, *Ber.*, *53*, 1155 (1920).

5,6-dibromohydrindene was placed in a 125 cc. Erlenmeyer flask with 10 cc. of concentrated sulfuric acid and cooled under the tap. To this mixture was added 5 cc. of concentrated nitric acid in 5 cc. of concentrated sulfuric acid. The temperature was allowed to rise slowly, whereupon the reaction started, and heat was evolved. The reaction mixture was mechanically agitated and kept below 40-50° by cooling under the tap. The flask was then warmed for 15 minutes on the steam-bath. The contents of the flask were then poured on cracked ice and the crude product filtered. Two crystallizations from acetic acid gave 2.5 g. (28%) of pure yellow needles melting at 139-140°. The yields were the same in three other identical preparations.

Anal. Calcd. for $C_9H_7O_2NBr_2$: N, 4.36.

Found: N, 4.40.

Since the two positions available for substitution are identical, this compound is most probably 4-nitro-5,6-dibromohydrindene.

Attempted Preparation of 4-Nitro-5-phenoxy-6-bromohydrindene

Seven grams (0.0187 mole) of 4-nitro-5,6-dibromohydrindene was intimately mixed with 2.5 g. (0.021 mole) of sodium phenoxide by grinding in a mortar. The ingredients were carefully dried before mixing. This mixture was heated for 2 hours at 170° in a small Erlenmeyer flask immersed in a metal-bath. The 4-nitro-5,6-dibromohydrindene proved to be very sensitive,

and complete charring occurred under these conditions. The successful preparation of 4-nitro-5-phenoxy-6-bromohydrindene would have led to an attempt to prepare 4-bromo-1,2-cyclopentenodibenzofuran *via* the diazonium salt of the reduced 4-nitro-5-phenoxy-6-bromohydrindene.[25, 42] The 4-bromo-1,2-cyclopentenodibenzofuran could then have been converted to 4-methoxy-1,2-cyclopentenodibenzofuran through a halogen-metal interconversion with *n*-butyllithium, followed by the oxidation of this organometallic derivative and subsequent methylation. This compound was to be compared with the product prepared on Page 79 of this thesis by the reduction of the cyclization product of β-[1-(4-methoxydibenzofuryl)]propionic acid. The identity of these two compounds would have shown that the cyclization involved the 2-position. The dissimilarity of the two compounds would have indicated that ring closure occurred in the 9-position.

Preparation of 4-Hydroxy-5-nitro-*o*-cresyl Methyl Ether

Sixty grams (0.33 mole) of 5-nitrotoluhydroquinone dimethyl ether[83] prepared according to the directions of Erdtman was placed in a flask containing 400 cc. of acetic acid and 100 cc. of 42% hydrobromic acid. The solution was refluxed for five hours. The solution was then diluted with water and cooled with ice. The precipitate was filtered and extracted

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[83] Erdtman, Proc. Roy. Soc. (London), A143, 191 (1933).

by boiling with a 10% sodium hydroxide solution. This red basic solution was filtered while hot and neutralized with hydrochloric acid. The orange precipitate was recrystallized from petroleum ether (b.p., 60-86°). The yield was 17 g. (33%) of orange needles melting at 100-101.5°.

Anal. Calcd. for $C_8H_9O_4N$: OCH_3, 16.9.

Found: OCH_3, 17.1.

The product is probably 4-hydroxy-5-nitro-o-cresyl methyl ether. This compound was to be used in an attempt to show the structure of the dibromination product of 2,8-dihydroxydibenzofuran.[27] The method was discarded in favor of a more promising procedure.

DISCUSSION

Evidence for Assigned Structures

The series of transformations illustrated in Diagram I was designed to confirm the structure of the supposed 1,9(?)-dibromo-2,8-dimethoxydibenzofuran first prepared by Gilman, Swislowsky, and Brown[84] through the dibromination of 2,8-dihydroxydibenzofuran. The success of this method of proof was dependent upon the actual existence of the complete structural symmetry of this dibromo-2,8-dimethoxydibenzofuran. On this assumption the plan involved the step-wise introduction of methyl- and ethyl-groups into 2,8-dihydroxydibenzofuran by the expedient of introducing a bromine atom into the molecule and then replacing the bromine atom with the desired alkyl-group through a halogen-metal interconversion with n-butyllithium and subsequent treatment with the proper alkyl sulfate. The hydroxyl-groups were protected by methylation in all cases where halogen-metal interconversions were employed, and all brominations were carried out with free hydroxyl-groups in the 2- and 8-positions to assure the same directive influence as in the direct dibromination of 2,8-dihydroxy-

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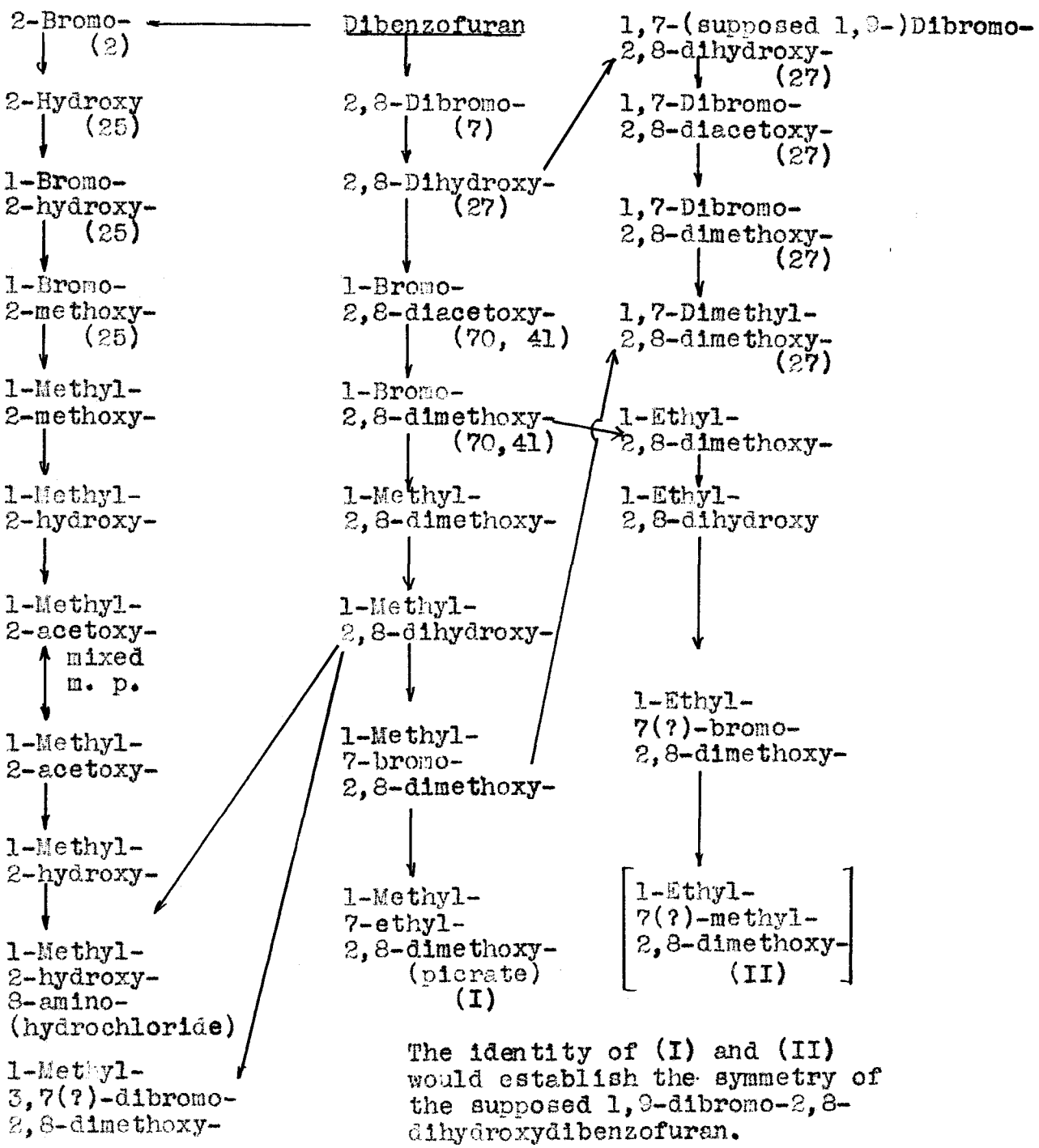
[84] Gilman, Swislowsky, and Brown, J. Am. Chem. Soc., 62, 348 (1940).

Diagram I

Transformations Involving the Supposed 1,9(?)-Dibromo-2,8-dimethoxydibenzofuran



The identity of (I) and (II) would establish the symmetry of the supposed 1,9-dibromo-2,8-dihydroxydibenzofuran.

dibenzofuran. The acquisition of the same products by the step-wise introduction of methyl- and ethyl-groups in reverse orders would have established the fact that symmetrical substitution had occurred.

The first monobromination of 2,8-dihydroxydibenzofuran was accomplished by Yeoman.[70] This compound was methylated and its structure proved by converting it into 1-methyl-2,8-dimethoxydibenzofuran *via* the interconversion reaction and cleaving this compound to the corresponding 1-methyl-2,8-dihydroxydibenzofuran, which was then subjected to a Bucherer reaction to form 1-methyl-2-hydroxy-8-aminodibenzofuran. The deamination of this compound and subsequent acetylation to form a product which was identical by a mixed melting point determination with a sample of 1-methyl-2-acetoxydibenzofuran prepared from authentic 1-bromo-2-methoxydibenzofuran also *via* the interconversion reaction[25] definitely established the structure of this compound to be 1-bromo-2,8-dimethoxydibenzofuran.

The introduction of a single bromine atom into 1-methyl-2,8-dihydroxydibenzofuran was accompanied by some dibromination. This dibromo-compound is likely 1-methyl-2,8-dihydroxy-3,7-dibromodibenzofuran. That the bromine atom and the methyl-group in this monobromo-1-methyl-2,8-dihydroxydibenzofuran occupy the same positions as the two atoms of bromine introduced into 2,8-dihydroxydibenzofuran was shown by converting it

into the corresponding dimethyl-2,8-dimethoxydibenzofuran by methylation, halogen-metal interconversion with n-butyllithium, and subsequent treatment with methyl sulfate. A comparison of this compound with a sample of the supposed 1,9-dimethyl-2,8-dimethoxydibenzofuran prepared by Swislowsky[27] showed them to be identical.

This bromo-1-methyl-2,8-dimethoxydibenzofuran was then converted into an ethyl-1-methyl-2,8-dimethoxydibenzofuran by halogen-metal interconversion with n-butyllithium and subsequent treatment with ethyl sulfate. The product was purified as the picrate (m.p., 144-145°).

By the same procedure 1-bromo-2,8-dimethoxydibenzofuran was converted into 1-ethyl-2,8-dihydroxydibenzofuran. Bromination of this, followed by methylation, gave a monobromo-1-ethyl-2,8-dimethoxydibenzofuran. An attempt to convert this to a methyl-1-ethyl-2,8-dimethoxydibenzofuran picrate resulted only in a red oil. A crystalline product of melting point other than 144-145° (see previous paragraph) would lead one to suspect that the dibromo-2,8-dimethoxydibenzofuran in question is not a symmetrical compound. This oily picrate may be just as significant since it is possible that the pure product is a very low melting solid or even an oil.

Aside from the dibenzofuran derivatives of Diagram I which involve the proof of structure of 1-bromp-2,8-dimethoxy-

dibenzofuran, the structure of the compounds included in this diagram depend upon the definite proof of the supposed 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. The evidence supplied by the series of transformations included in Diagram II establishes the fact that this compound is either 1,7- or 1,3-dibromo-2,8-dimethoxydibenzofuran. Hence, the compound resulting from the monobromination and subsequent methylation of 1-methyl-2,8-dihydroxydibenzofuran is provisionally designated as 1-methyl-7-bromo-2,8-dimethoxydibenzofuran. There is no evidence to show that the compound resulting from the monobromination and subsequent methylation of 1-ethyl-2,8-dihydroxydibenzofuran is substituted in the same position involved in the monobromination of 1-methyl-2,8-dihydroxydibenzofuran. The compound, however, is probably 1-ethyl-7-bromo-2,8-dimethoxydibenzofuran.

Thirtle,[38] working on the assumption that the 1,9(?)-dibromo-2,8-dimethoxydibenzofuran in question was a symmetrically substituted dibenzofuran, set out to make use of the newly established 1-bromo-2,8-dimethoxydibenzofuran. His work involved the removal of one of the bromine atoms in 1,9(?)-dibromo-2,8-dimethoxydibenzofuran by treating this compound with one equivalent of n-butyllithium and adding water to the resulting organometallic derivative of dibenzofuran. The acquisition of 1-bromo-2,8-dimethoxydibenzofuran in better

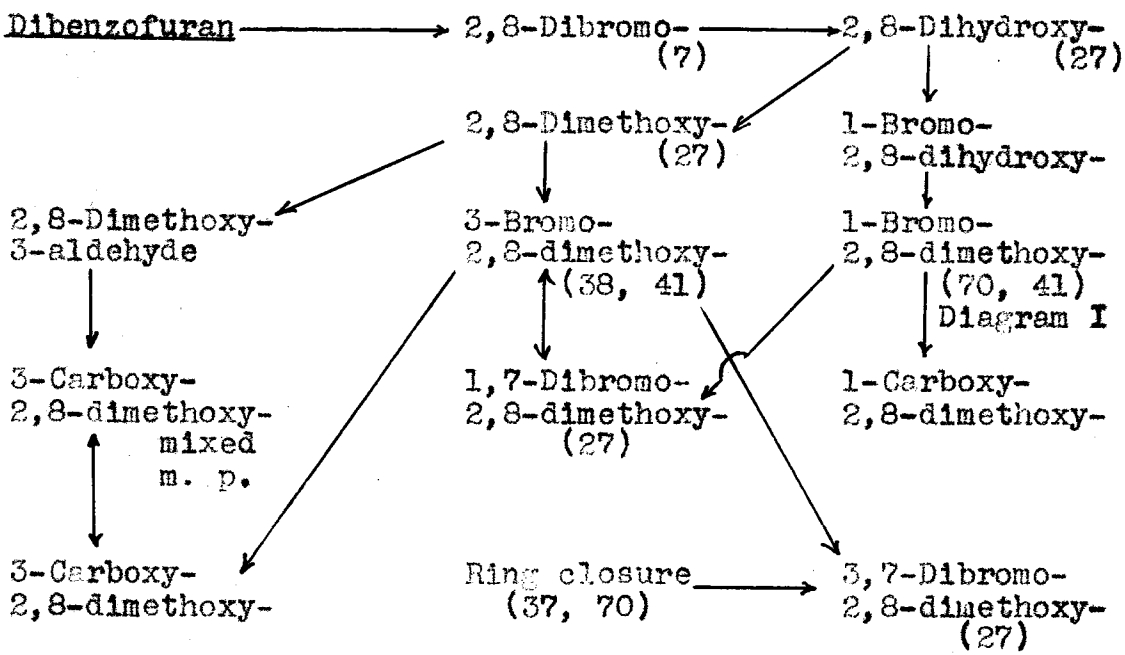
than a 50% yield would have established the symmetrical nature of this 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. However, 1-bromo-2,8-dimethoxydibenzofuran was not obtained. Instead, a small yield of a pure product which analyzed for a monobromo-2,8-dimethoxydibenzofuran was isolated. Thirtle[38] also carried out a halogen-metal interconversion with 1,9(?)-dibromo-2,8-dimethoxydibenzofuran and treated this organometallic derivative with methyl sulfate. This compound was shown by a mixed melting point determination to be identical with the 1-methyl-7-bromo-2,8-dimethoxydibenzofuran of Diagram I. This tieup with the work of Diagram I showed that the monobromo-2,8-dimethoxydibenzofuran prepared by Thirtle[38] was not the product of an anomalous reaction. It was immediately suspected to be 3-bromo-2,8-dimethoxydibenzofuran.

Diagram II includes a series of transformations which further clarify the structure of 1-9(?)-dibromo-2,8-dimethoxydibenzofuran. The work of Thirtle[38] encouraged the monobromination of 2,8-dimethoxydibenzofuran in the hope of obtaining a monobromo-2,8-dimethoxydibenzofuran different from the known 1-bromo-2,8-dimethoxydibenzofuran and identical with the supposed 3-bromo-2,8-dimethoxydibenzofuran obtained from the 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. 3-Bromo-2,8-dimethoxydibenzofuran identical with the compound

prepared by Thirtle[38] was obtained by this method and its structure was shown as such by further bromination to the known 3,7-dibromo-2,8-dimethoxydibenzofuran.[74] The bromination of 3-bromo-2,8-dimethoxydibenzofuran also produced a fraction of pure material identical with the

Diagram II

Transformations in the Proof of Structure of 1,7-Dibromo-2,8-dimethoxydibenzofuran



supposed 1,9(?)-dibromo-2,8-dimethoxydibenzofuran. From the evidence at hand it can now be definitely stated that the latter compound is either 1,7- or 1,3-dibromo-2,8-dimethoxydibenzofuran.

There is considerable evidence supplied by a number of Bucherer reactions on hydroxyl-derivatives of dibenzofuran in favor of 1,7-dibromo-2,8-dimethoxydibenzofuran. Bucherer reactions have been carried out successfully with the following phenolic dibenzofurans: 4-hydroxydibenzofuran,[19] 4,6-dihydroxydibenzofuran,[19] 1-carboxy-4,6-dihydroxydibenzofuran,[41] 1-bromo-4-hydroxydibenzofuran,[41] and 1-bromo-2-hydroxydibenzofuran.[27] In the latter two compounds the bromine atoms were removed, and the corresponding amines were obtained. In none of these compounds were there any substituents in positions ortho to the hydroxyl-groups to inhibit the reaction, except in the case of 1-bromo-2-hydroxydibenzofuran, and the bromine atom here was apparently removed before the reaction could proceed.

The 1,7- or 1,3-dibromo-2,8-dimethoxydibenzofuran[84] was converted by Gilman, Swiss, Willis, and Yeoman[74] to 1,7- or 1,3-dimethyl-2,8-dihydroxydibenzofuran.[27] A number of attempts to run a Bucherer reaction on this compound met with failure.

In striking contrast to this group of compounds without ortho substituents which reacted favorably and the one compound, 1,3- or 1,7-dimethyl-2,8-dihydroxydibenzofuran, which

failed to react even under more drastic conditions, we have the results of the Bucherer reaction on 1-methyl-2,8-dihydroxydibenzofuran[41] in which one hydroxyl-group is free and the other is ortho to a methyl-group. The yield of 1-methyl-2-hydroxy-8-aminodibenzofuran in this case was 66.5%. It was only the free hydroxyl-group which reacted. This evidence is certainly powerful support for the existence of heteronuclear methyl-groups in positions ortho to the hydroxyl-groups in the 1,3- or 1,7-dimethyl-2,8-dihydroxydibenzofuran.

From the combined evidence the supposed 1,9(?)dibromo-2,8-dimethoxydibenzofuran[84] can be designated with reasonable certainty to be 1,7-dibromo-2,8-dimethoxydibenzofuran.

The structures of 2,8-dimethoxydibenzofuran-1-carboxylic acid and 2,8-dimethoxydibenzofuran-3-carboxylic acid naturally follow from the proof of structure of the corresponding monobromo-2,8-dimethoxydibenzofurans. The structure of 2,8-dimethoxydibenzofuran-3-aldehyde was determined by oxidation to 2,8-dimethoxydibenzofuran-3-carboxylic acid.

The results of the investigation on the structures of the dibromination products of 2,8-dimethoxydibenzofuran[38, 41] placed some doubt upon the validity of the structure which had been provisionally assigned to the dibromination product of 4,6-dimethoxydibenzofuran.[85] It was thought to be 1,9-dibromo-

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

4,6-dimethoxydibenzofuran, and its structure had been assigned by analogy with the reactions of 4-hydroxydibenzofuran with bromine[26] and benzenediazonium chloride[86] involving the 1-position.

Diagram III includes a series of transformations designed to reveal the true structural identity of this dibromination product of 4,6-dimethoxydibenzofuran.

The monobromination of 4,6-dimethoxydibenzofuran was thought to involve the 1-position.[85] This was established as a fact by the following series of transformations: The 1-bromo-4,6-dimethoxydibenzofuran was converted into 1-carboxy-4,6-dimethoxydibenzofuran by a halogen-metal interconversion with n-butyllithium and subsequent carbonation. The acid was converted into 1-carboxy-4,6-dihydroxydibenzofuran by refluxing with 47% hydrobromic acid. A Bucherer reaction on 1-carboxy-4,6-dihydroxydibenzofuran resulted in 1-carboxy-4,6-diaminodibenzofuran which gave 1-carboxydibenzofuran upon deamination. This final product was compared with an authentic sample of 1-carboxydibenzofuran.[25,26]

Cheney[19] observed that the metalation of the methyl-ethers of phenolic derivatives of dibenzofuran with n-butyllithium has always involved positions ortho to the methoxy-groups or ortho to the dibenzofuran oxygen atom. The

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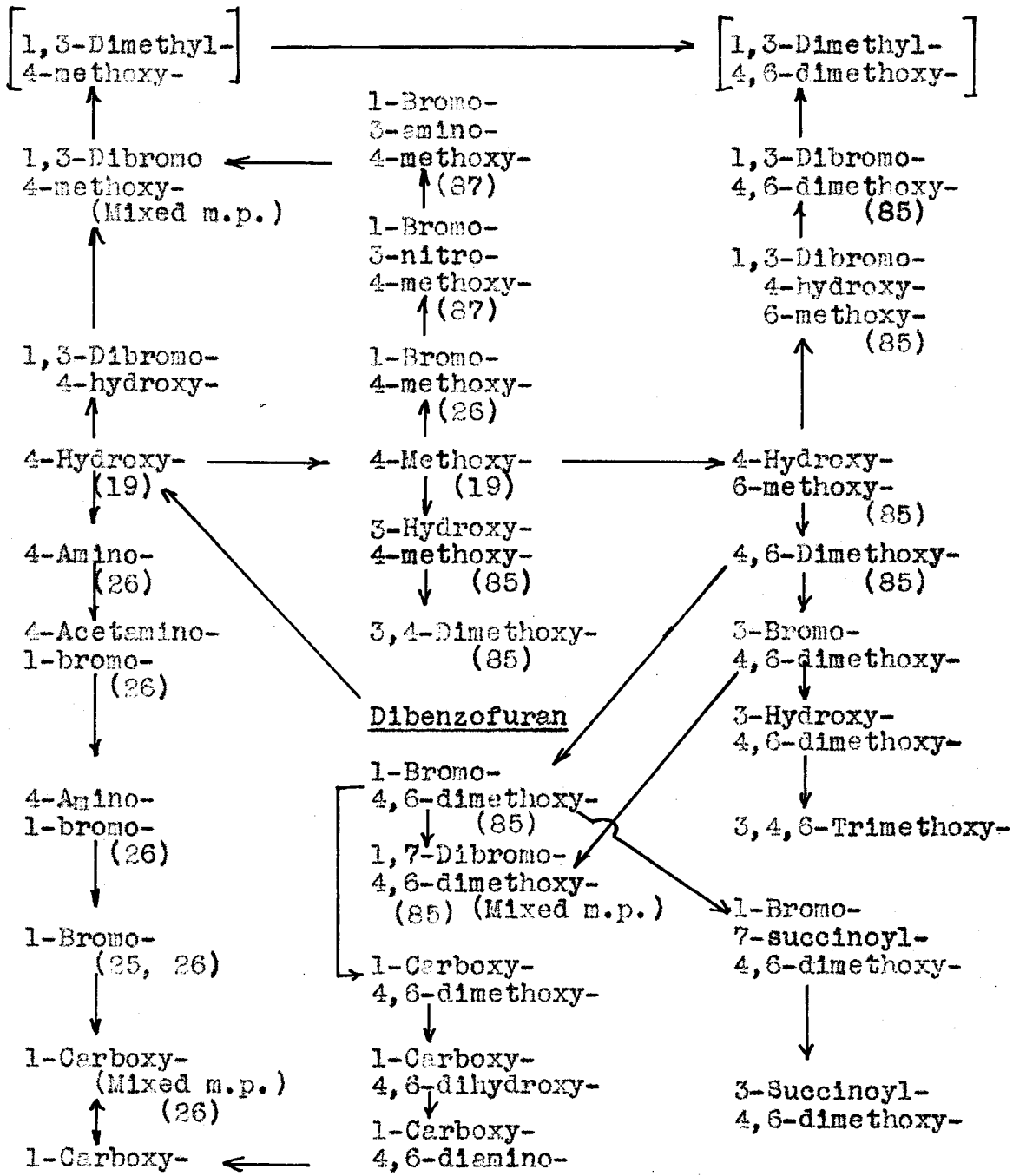
[86] Gilman and H. W. Van Ess, J. Am. Chem. Soc., 61, 3146 (1939).

Diagram III

Transformations Involved in the Structure Clarification of Some Derivatives of 4-Methoxy- and 4,6-Dimethoxydibenzofuran



[87] Gilman, Parker, Bailie, and Brown, J. Am. Chem. Soc., 61, 2836 (1939).

metalation of 4,6-dimethoxydibenzofuran with n-butyllithium with subsequent introduction of bromine yielded a monobromo-4,6-dimethoxydibenzofuran which was not identical with 1-bromo-4,6-dimethoxydibenzofuran.[85] Since there are only three possible monobromo-4,6-dimethoxydibenzofuran compounds possible, and since metalation in the 2-position is very highly improbable, this compound is most probably 3-bromo-4,6-dimethoxydibenzofuran. There is no certainty that the bromine atom occupies the position involved in metalation. 3-Bromo-4,6-dimethoxydibenzofuran was converted into 3,4,6-trimethoxydibenzofuran through a halogen-metal interconversion with n-butyllithium, followed by oxidation of the resulting organometallic derivative and subsequent methylation of the phenol. An attempt to prepare the same compound from 3,4-dimethoxydibenzofuran by a process of metalation with n-butyllithium, oxidation, and methylation was unsuccessful.

3-Bromo-4,6-dimethoxydibenzofuran was monobrominated to yield the supposed 1,9(?)-dibromo-4,6-dimethoxydibenzofuran. This evidence definitely establishes the fact that the dibromo-4,6-dimethoxydibenzofuran in question is not a 1,9-derivative and suggests that it is either 1,3- or 1,7-dibromo-4,6-dimethoxydibenzofuran.

Gilman and Cheney[85] dibrominated 4-hydroxy-6-methoxydibenzofuran and, after methylation, designated the compound as 1,3-dibromo-4,6-dimethoxydibenzofuran. Since definite confirmation of this structure would eliminate one of the two most probable structures of the supposed 1,9(?)-dibromo-4,6-

dimethoxydibenzofuran, the following series of transformations was performed (Diagram III): 1,3-Dibromo-4,6-dimethoxydibenzofuran, prepared according to the directions of Gilman and Cheney, was treated with n-butyllithium and the resulting organometallic derivative of 4,6-dimethoxydibenzofuran was treated with methyl sulfate. A product analyzing for the desired 1,3-dimethyl-4,6-dimethoxydibenzofuran was not obtained. A similar anomalous reaction occurred with 1,3-dibromo-4-methoxydibenzofuran. The 1,3-dibromo-4-methoxydibenzofuran was prepared by the direct dibromination and subsequent methylation of 4-hydroxydibenzofuran. The structure of this compound was confirmed by its preparation from the known 1-bromo-3-amino-4-methoxydibenzofuran[85] through replacement of the amino group with bromine via the diazonium salt. The intention was to convert 1,3-dimethyl-4-methoxydibenzofuran into 1,3-dimethyl-4,6-dimethoxydibenzofuran by metalation with n-butyllithium, oxidation of the metalation product, and methylation of the resulting phenol. This would have established the structure of 1,3-dibromo-4,6-dimethoxydibenzofuran.

Since the monobromination of 4-hydroxy-6-methoxydibenzofuran[85, 41] parallels the monobromination of 4-hydroxydibenzofuran, it is quite likely, in view of the greater orienting influence of the hydroxyl-group over the methoxyl-group, that the dibromination of 4-hydroxy-6-methoxydibenzofuran[85] would also parallel the dibromination of 4-hydroxydibenzofuran.[41]

The structure of the supposed 1,9(?)-dibromo-4,6-dimethoxydibenzofuran is then most likely 1,7-dibromo-4,6-dimet oxydibenzofuran.

Avakian[48] succinoylated 1-bromo-4,6-dimethoxydibenzofuran and obtained a product melting at 188-189°. Debromination of this product with palladium-calcium carbonate and hydrogen gave him a compound melting at 240° which was shown to be 1-succinoyl-4,6-dimethoxydibenzofuran[48] by comparison with an authentic sample. This evidence indicates a true 1,9-substituted derivative of dibenzofuran. Since the introduction of a bromine atom into 1-bromo-4,6-dimethoxydibenzofuran and 1-bromo-2,8-dimethoxydibenzofuran[41] has been shown to involve a position other than the 9-position, it was difficult to understand why the succinoylation of 1-bromo-4,6-dimethoxydibenzofuran should result in a 1,9-substituted derivative of dibenzofuran.

This writer repeated the succinoylation of 1-bromo-4,6-dimethoxydibenzofuran and obtained a product melting at 186-188° (melting point of 188-189° reported by Avakian[48]) which could not be purified further using toluene or 95% ethanol as solvents. These were the solvents used by Avakian.[48] However, by the use of glacial acetic acid as a solvent the melting point was raised to 200-201°. This compound showed the presence of bromine in an elemental test by sodium fusion and analyzed correctly for a monosuccinoyl-1-bromo-4,6-di-

methoxydibenzofuran. The quantitative tests were for bromine and the neutral equivalent. This shows that the product melting at 186-188° was impure. The portion of this material melting at 186-188° which did not dissolve in a small quantity of boiling toluene was further purified from glacial acetic acid. This product melted at 240-241°, and was found to be identical with an authentic sample of 1-succinoyl-4,6-dimethoxydibenzofuran.[48] Some succinoylation had evidently occurred by the replacement of the bromine atom.

The debromination of 1-bromo-7(?)-succinoyl-4,6-dimethoxydibenzofuran by hydrogenation using palladium-calcium carbonate catalyst yielded a pure monosuccinoyl-4,6-dimethoxydibenzofuran melting at 166-167°. Since it is unlikely that succinoylation would involve the 2-position, and since the 1-succinoyl-4,6-dimethoxydibenzofuran is known,[48] the product is probably 3-succinoyl-4,6-dimethoxydibenzofuran. The compound resulting from the succinoylation of 1-bromo-4,6-dimethoxydibenzofuran is most likely 1-bromo-7-succinoyl-4,6-dimethoxydibenzofuran.

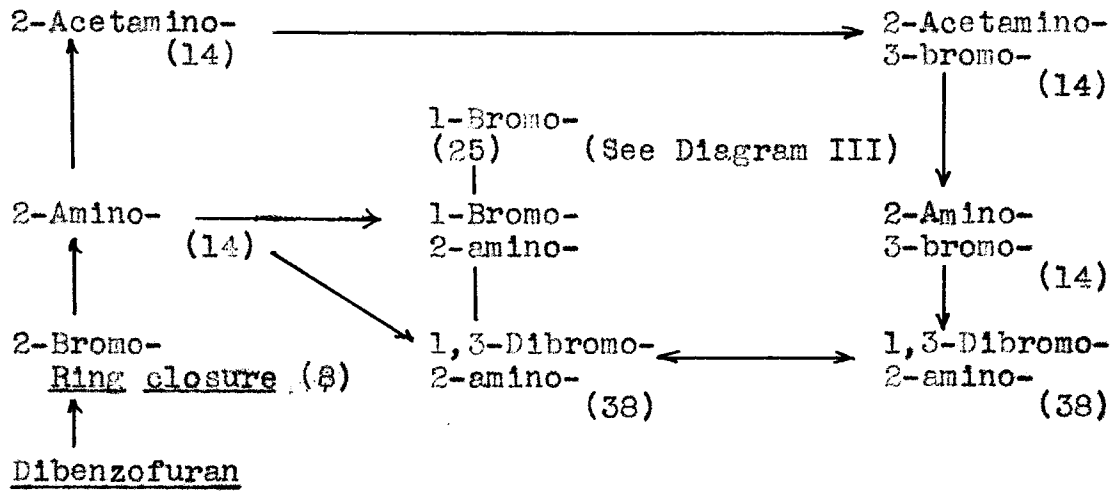
1-Succinoyl-4,6-dimethoxydibenzofuran[48] is much less soluble in 95% ethanol than 3-succinoyl-4,6-dimethoxydibenzofuran.[41] The presence of 1-succinoyl-4,6-dimethoxydibenzofuran in the material melting at 186-188° resulting from the succinoylation of 1-bromo-4,6-dimethoxydibenzofuran has been demonstrated.[48] It is quite probable, then, that Avakian

isolated this 1-succinoyl-4,6-dimethoxydibenzofuran instead of the 3-succinoyl-4,6-dimethoxydibenzofuran because of its greater insolubility.

Diagram IV includes a series of steps involving the bromo-derivatives of 2-aminodibenzofuran. Thirtle[38] brominated 2-aminodibenzofuran by the ordinary drop-wise addition of bromine and obtained only a dibromo-2-aminodibenzofuran.

Diagram IV

Some Derivatives of 2-Aminodibenzofuran



Thirtle[38] also demonstrated that one of these bromine atoms was in the 3-position when he obtained the same compound by the bromination of 2-amino-3-bromodibenzofuran.[14] This writer prepared a new monobromo-2-aminodibenzofuran by the entrainment bromination of 2-aminodibenzofuran. Deamination

of this product to 1-bromodibenzofuran[25] showed the compound to be 1-bromo-2-aminodibenzofuran. It is unlikely that 2-aminodibenzofuran would brominate in the 9-position and, hence, 9-bromo-2-aminodibenzofuran is ruled out. This provides a new method for the synthesis of 1-bromodibenzofuran.[26] Further bromination of 1-bromo-2-aminodibenzofuran yielded the same dibromo-2-aminodibenzofuran obtained by Thirtle.[38] This demonstrates that the dibromination product of 2-aminodibenzofuran is 1,3-dibromo-2-aminodibenzofuran.

Attempts to Bridge the 1- and 9-Positions of Dibenzofuran

A study of the various attempts* to bridge the 1- and 9-positions of dibenzofuran reveals that in nearly every approach the efforts were rewarded only with blackened oils and products of polymerization from which no pure crystalline products could be isolated. This was not true in the case of the cyclization of γ-[1-(4-methoxydibenzofuryl)] butyric acid by Avakian.[48] In this latter case, however, there are two possible cyclization products in addition to the possibility of intermolecular condensation.

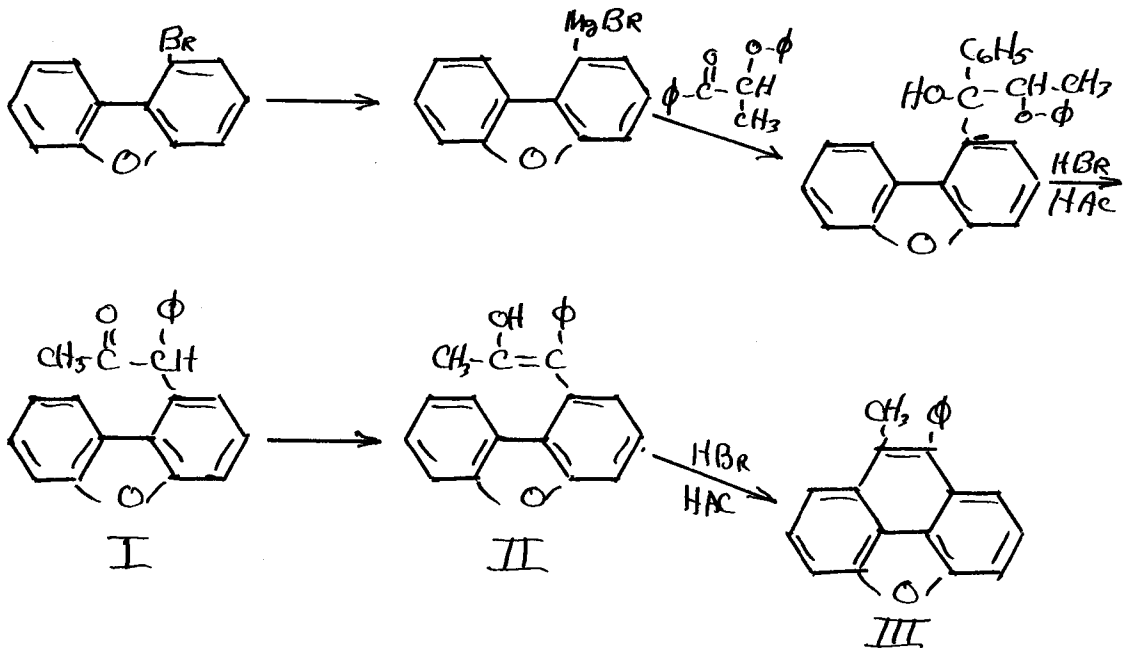
The method of Bradsher and Rosher[62] ** for the

*Refer to the Historical section of this thesis, p.17.

**See p.22, this thesis.

preparation of 9, 10-substituted derivatives of phenanthrene seemed to fulfill all of the desirable requirements of the reaction which would most adequately test the ease of bridging the 1- and 9-positions of dibenzofuran. Such a reaction would not tend to give intermolecular condensation products and would react intramolecularly in just one way. To be able to recover the starting material or some precursor to the actual 1,9-bridge is highly desirable since it enables one to have a definite indication of the effect of the methods employed. The method of Bradsher and Rosher[62] proved, indeed, to be just such a reaction.

1-Bromodibenzofuran (see Diagram III, p. 108) prepared according to the directions of P. R. Van Ess[25] was employed in the following series of reactions:



The Grignard reagent prepared from 1-bromodibenzofuran[26] was treated with α-phenoxypropiophenone, and the resulting oil was refluxed for 24 hours with 48% hydrobromic acid in glacial acetic acid. A pure crystalline product was isolated which readily formed an oxime. The analysis for carbon and hydrogen on this compound and for nitrogen on the oxime indicated the expected structure I. No other product could be isolated.

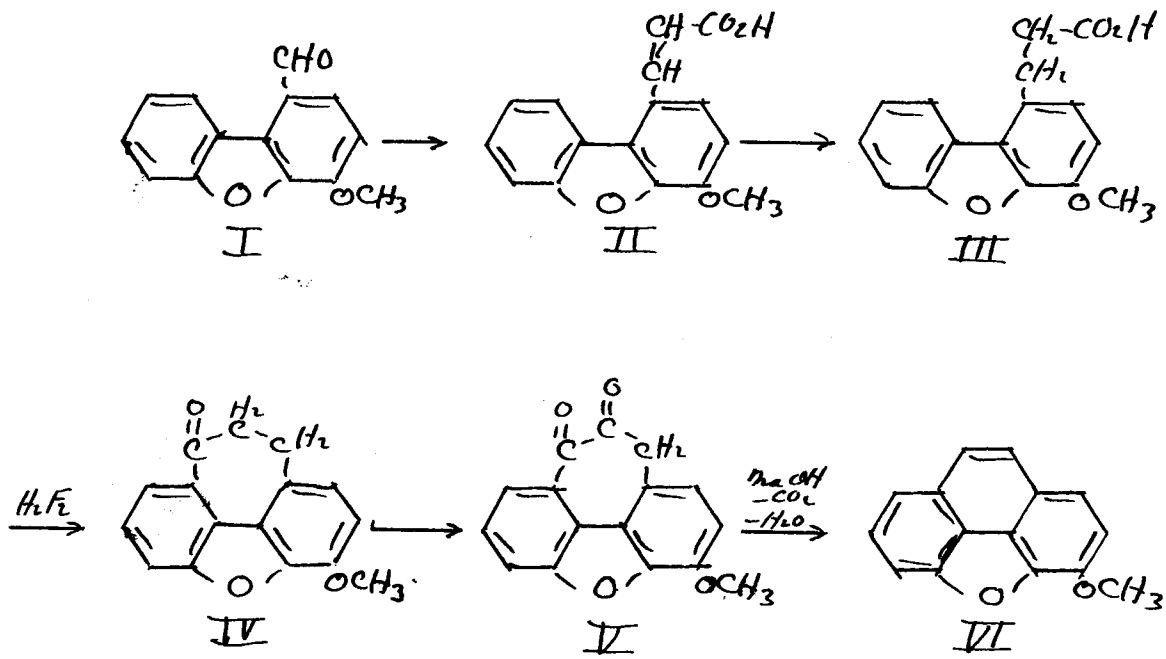
The mechanism for this type of reaction was postulated by Bradsher and Tess[65] to involve the cyclodehydration of the enol-form II to give the desired 9-methyl-10-phenyl-4,5-phenanthrylene oxide (III). Hence, the ketone (I) was refluxed for a prolonged period (48 hours) with 48% hydrobromic acid and glacial acetic acid. Only the ketone (I) was recovered.

It was thought that other dehydrating agents might effect the cyclodehydration. Anhydrous liquid hydrogen fluoride at room temperature and at 100° was tried. Sulfuric acid and phosphorous pentoxide were employed. The starting material (I) was obtained in each case except with phosphorous pentoxide. This powerful reagent caused polymerization. Pyrolysis had no effect upon the ketone (I).

This work indicates that the bridging of the 1- and 9-positions involves more than the discovery of a suitable type of reaction. It is quite likely that a certain amount of energy of activation involving the strain that would naturally be expected in a compound containing the 4,5-phenanthrylene

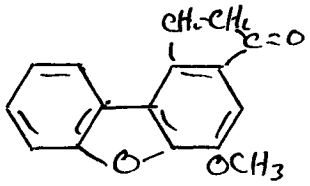
oxide nucleus must be generated before reaction can occur. Also it is possible that 9-methyl-10-phenyl-4,5-phenanthrylene oxide, which has assumed complete aromatic character, is of a much higher energy level than the ketone II where there is a possibility of fixed bond structure. Swislowsky[27] has discussed the likelihood of a fixed bond structure in dibenzofuran. Although dibenzofuran is definitely similar to naphthalene in some of its reactions, it cannot be stated with certainty that the bond structure is fixed.

The following series of reactions was designed with the hope of incorporating a three-carbon bridge between the 1- and 9-positions which might then be reduced to a two-carbon bridge by a process of ring contraction:



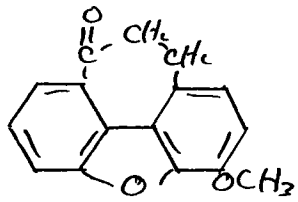
4-Methoxydibenzofuran-1-aldehyde was prepared by the N-methylformanilide synthesis[77] using N-methylformanilide and phosphorous oxychloride on 4-methoxydibenzofuran. Its structure was shown by oxidation to the known 4-methoxydibenzofuran-1-carboxylic acid.[13] The structures of compounds II and III depend upon the structure of 4-methoxydibenzofuran-1-aldehyde. 1-(4-Methoxydibenzofural)acetic acid (II) was obtained by the action of malonic acid and dry pyridine on the aldehyde (I). The reduction of II gave β-[1-(4-methoxydibenzofuryl)] propionic acid (III). It was hoped that the cyclization of III would involve the 9-position and that the resulting ketone (IV) could be oxidized to the di-ketone (V) with selenium dioxide. The successful preparation of V might possibly lead to methyl morphenol (VI) by the use of the benzilic acid rearrangement, followed by decarboxylation and dehydration. The selenium oxide oxidation of IV (?) gave no pure product.

The cyclization of β-[1-(4-methoxydibenzofuryl)] propionic acid was accomplished by the use of anhydrous liquid hydrogen fluoride. The following are the possible structures of this cyclodehydration product:



I

5-Methoxy-1-benz(b)indeno-* [4,5-d]furan-3(2)-one



II

2,3-Dihydro-6-methoxy-1-* oxo-1-cyclohepta(klm)dibenzofuran

The oxidation of this cyclic ketone, followed by the methylation of the resulting di-acid, gave the same di-acid ester obtained by Avakian[48] by the oxidation and esterification of the cyclic ketone prepared by the cyclization of γ-[1-(4-methoxydibenzofuryl)]butyric acid. This indicates that the ring closure in both cases involved the same position. A compound thought to be 1,2-dibromo-4-methoxydibenzofuran prepared by Avakian[48] was converted by him into 1(?),2-dicarbomethoxy-4-methoxydibenzofuran. This compound was not identical with the di-acid ester obtained by oxidation and esterification of the ring-closure products. Until the structure of 1(?),2-dicarbomethoxy-4-methoxydibenzofuran[48] is definitely established the course of the ring closure will be unknown.

A theoretical consideration of the course of the

* See note on nomenclature from Dr. Leonard Capell included at the end of this thesis.

cyclization of β-[1-(4-methoxydibenzofuryl)] propionic acid favors ring closure in the 2-position. By the use of sulfuric acid this writer was unable to obtain the ketone represented by either formula I or II from β-[1-(4-methoxydibenzofuryl)] propionic acid. Avakian,[48] however, was able to effect cyclization of γ-[1-(4-methoxydibenzofuryl)] butyric acid by the use of 88% sulfuric acid. In comparison, α-tetralone cannot be prepared from hydrocinnamic acid by the sulfuric acid method, while γ-arylbutyric acids are known to undergo cyclodehydration under these conditions.[61] If the ring closures of Avakian[48] and this writer involved the 9-position, it would seem that there would be little difference in the ease of formation of a seven- or eight-membered ring by the sulfuric acid method.

By the use of anhydrous liquid hydrogen fluoride α-tetralone and α-hydrindone can be prepared in excellent yields from γ-phenylbutyric acid and hydrocinnamic acid under exactly the same conditions used in the cyclization of these dibenzofuran derivatives. It would seem, then, that isomeric products would be obtained if the same conditions are sufficient to cause ring closure in both the 2- and 9-positions. No isomeric products were obtained in either case.

A final consideration involves the accessibility of the 9-positinn of dibenzofuran derivatives already substituted

in the 1-position. The bromination of 1-bromo-4,6-dimethoxydibenzofuran and 1-bromo-2,8-dimethoxydibenzofuran has been shown to involve positions other than the 9-position.[41] Succinoylation of 1-bromo-4,6-dimethoxy dibenzofuran does not involve the 9-position.[41] The explanation for this behavior is most likely steric hindrance. The 9-position is partially blocked by the substituent in the 1-position. Cyclization from the 1-position to the 9-position would be, essentially, the substitution in the 9-position of a 1-substituted dibenzofuran, and there is no reason to believe that it would not encounter the same type of interference. This would be true only of acid chains longer than two carbon atoms in the 1-position.

The compound resulting from the cyclodehydration of β-[1-(4-methoxydibenzofuryl)] propionic acid may be provisionally designated as 5-methoxy-1-benz(b)indeno[4,5-d]-furan-3(2)-one (I) until further evidence is obtained.

1-(4-Methoxydibenzofuryl)acetic acid[47] was prepared from 4-methoxydibenzofuran-1-aldehyde[41] by the hydrolysis and oxidation with hydrogen peroxide of the azlactone formed by the condensation of this aldehyde with hippuric acid in the presence of acetic anhydride. Attempts to cyclodehydrate this compound at room temperature with anhydrous liquid hydrogen fluoride had no effect on the compound. Prolonged heating at 100° with hydrogen fluoride promoted the formation

of a non-acidic product which could not be purified. This material is probably the product of intermolecular condensation, since ring closure would probably give a ketone which would likely enolize to the phenol. However, this is not certain, and similar investigation using a larger amount of this acid or of 1-(4,6-dimethoxydibenzofuryl)acetic acid would not be unwise.

The Accessibility of the 9-Position of 1-Substituted Dibenzofurans

The probability of steric hindrance in connection with substitution in the 1- or 9-positions of dibenzofuran was first mentioned by Bywater.[11] Although later work[25] has shown that at least one of these positions is free when the proper orienting groups are present in the nucleus, it is now known that the presence of one substituent in either the 1- or 9-position prevents the introduction of a second group into the remaining of these two positions in spite of strong orientation influences.[38, 41] The bromination of 1-bromo-2,8-dimethoxydibenzofuran and 1-bromo-4,6-dimethoxydibenzofuran and the succinoylation of 1-bromo-4,6-dimethoxydibenzofuran have been shown to involve either the 3- or the 7-position. The 7-position is preferred.

Overcoming this steric effect by the introduction of smaller groups may have some merit. However, the

dimetalation of 2,8-dimethoxydibenzofuran with n-butyllithium by Swislowsky[27] with subsequent carbonation yielded 1,7-dicarboxy-2,8-dimethoxydibenzofuran. From this evidence it is possible that atoms as small as lithium can sterically hinder the introduction of a second atom. The first hydrogen replaced by lithium in 2,8-dimethoxydibenzofuran is probably in the 1-position, since the metalation of 2-methoxydibenzofuran involves mainly the 1-position.[88] The second metal atom would then tend to enter the 9-position if there were no hindrance.

It may be possible to introduce useful groups into the 1- and 9-positions of a compound such as 3,7-dimethyl-2,8-dimethoxydibenzofuran.

Some General Considerations for Dibenzofuran Research

The recent developments[38, 41] in the effort to introduce substituents into the 1- and 9-positions of dibenzofuran by direct substitution give very definite indications that the task will not be an easy one, if at all possible. 1,9-disubstituted dibenzofurans could most probably be prepared more easily by ring closure methods.[11] The synthesis of 1,9-dichloromethyldibenzofuran would provide a valuable compound as a precursor to the preparation of phenanthrylene oxide by

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

using sodamide.[69] It would likely be necessary to prepare a 1,9-derivative by ring closure which could then be converted into the 1,9-dichloromethyl derivative.

Until 1,9-substituted dibenzofurans are available, there are many reactions which might be applied (see Historical of this thesis) in obtaining the 1,9-bridge using 1-substituted dibenzofurans. It would be interesting to try the method of Bradsher and Rosher[62] for the preparation of 1-methyl-9-phenyl-4,5-phenanthrylene sulfide from 1-bromodibenzothiophene.[89] The spatial relationship of the 1- and 9-positions of dibenzothiophene should be more favorable to the accomplishment of a 1,9-bridge than in dibenzofuran because of the greater size of the sulfur atom as compared to the oxygen atom in dibenzofuran.

Another expedient which has as yet not been investigated is that of preparing a suitable derivative of a partially reduced dibenzofuran which might be induced to undergo cyclodehydration by virtue of reduced strain to form a 1,9-bridge. Such a compound might be 1-(4-methoxy-1,2,3,4-tetrahydrodibenzofuryl)acetic acid. This acid could probably be prepared by the hydrogenation of 1-(4-methoxydibenzofuryl)-acetic acid.[48, 41] Bradley[90] was able to obtain 1,2,3,4-tetrahydro-4-methoxydibenzofuran in 41% yield by the hydrogenation of 4-methoxydibenzofuran using nickel as the catalyst.

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

[90] Bradley, Doctoral Dissertation, Iowa State College, 1937.

SUMMARY

1. The structures of some mono- and dibromination products of 2,8-dimethoxydibenzofuran have been clarified.

2. Some additional evidence on the structure of the dibromination product of 4,6-dimethoxydibenzofuran has been given. The structure of 1-bromo-4,6-dimethoxydibenzofuran has been proven.

3. The structures of the mono- and dibromination products of 2-aminodibenzofuran have been proven. A new source of 1-bromodibenzofuran has been found.

4. Some new 1-substituted dibenzofuran derivatives have been prepared.

5. Some new attempts to bridge the 1- and 9-positions of dibenzofuran have been made. The actual course of these reactions has been discussed.

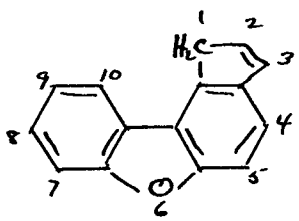
6. The effect of this work on the course of future dibenzofuran research has been discussed.

This letter is the reply received from Dr. Leonard T. Capell following an inquiry on the correct nomenclature of the cyclization product of β-[1-(4-methoxydibenzofuryl)]-propionic acid:

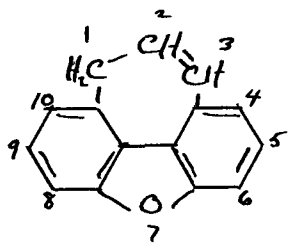
Mr. John A. Hogg
Iowa State College
Ames, Iowa

Dear Mr. Hogg:

The ring systems represented in the suggested structures for your compound are new systems. The least hydrogenated forms are:



I



II

These rings should be numbered as shown. I can be called 1-benz[b]indeno[4,5-d]furan. The 1- indicates the position of the extra H atom which is necessary for the existence of the ring. Your compound is the 2,3-dihydro-5-methoxy-3-oxo derivative which can also be named 5-methoxy-1-benz[b]indeno[4,5-d]furan-3(2)-one. II should be named 1-cyclohepta[klm]dibenzofuran. The compound should be called 2,3-dihydro-6-methoxy-1-cyclohepta[klm]dibenzofuran-1-one or 2,3-dihydro-6-methoxy-1-oxo-1-cyclohepta[klm]dibenzofuran.

Sincerely yours,

(Signed) Leonard T. Capell

LTC:MW