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Nuclear substitution reactions of dibenzo-p-dioxin

Joseph Jacob Dietrich
Iowa State College

NUCLEAR SUBSTITUTION REACTIONS OF DIBENZO-p-DIOXIN

by

Joseph Jacob Dietrich

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Head of Major Department

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Dean of Graduate College

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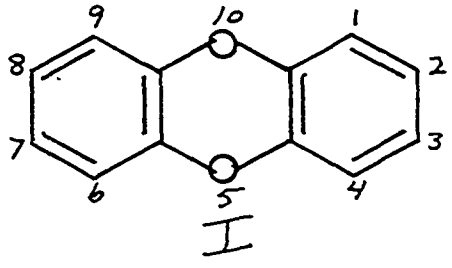
INTRODUCTION

Three numbering systems have been employed in the literature to describe derivatives of dibenzo-p-dioxin. The one adopted by Chemical Abstracts and also to be used in this dissertation is shown by I. The other two systems are illustrated by II and III.



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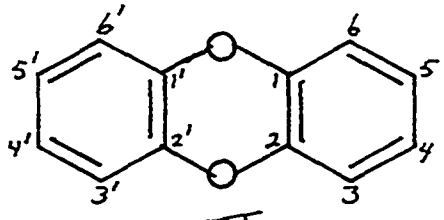

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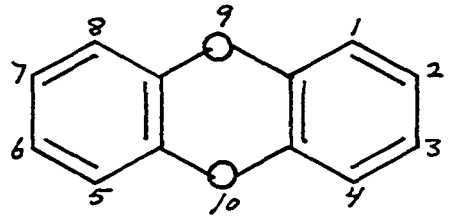

III

Even though the use of I is most common, a certain amount of confusion still exists due to the usage by some abstractors of II, which, because of the symmetry of the molecule, is not too ambiguous.

Diphenylene dioxide is the common name for dibenzo-p-dioxin and appears frequently in the literature. The Japanese workers still favor this name and have used it in recent

publications. Other names now rarely used are dibenzo-1,4-dioxin, p-dibenzodioxin, and phendioxin.

The planarity or non-planarity of dibenzo-p-dioxin is still undecided. It does not form a solid solution with phenoxathiin[1], a non-planar molecule, and was found to have a zero or nearly zero dipole moment when measured in carbon tetrachloride, cyclohexane, or benzene solutions.[2] The results obtained from x-ray studies are consistent with a planar molecule, but the other possibility cannot be excluded.[3] Higasi and Uyeo[4,5] reported dipole moments of 0.64 and 0.57 Debye units when dibenzo-p-dioxin was measured in benzene and cyclohexane, respectively. This was interpreted as showing the molecule to be folded about the O-O axis with the benzene rings lying at an angle of 160°. The oxygen valence angle is 117°. Using the same method, they also found 2,7-dimethyldibenzo-p-dioxin and 2,7-dichlorodibenzo-p-dioxin to have dipole moments of 0.61 and 0.62 Debye units, respectively. From the

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[1] N. Cullinane and W. Rees, Trans. Faraday Soc., 36, 507 (1940).

[2] G. Bennett, D. Earp, and S. Glasston, J. Chem. Soc., 1179 (1934).

[3] R. Wood and G. Williams, Phil. Mag., 31, 115 (1941) [C. A., 35, 2766 (1941)].

[4] K. Higasi, Sci. Papers Inst. Phys. Chem. Research, (Tokyo), 38, 331 (1940) [C. A., 35, 3496 (1941)].

[5] K. Higasi and S. Uyeo, J. Chem. Soc. Japan, 62, 396 (1941) [C. A., 33, 6103 (1939)].

evidence presented, it may be concluded that dibenzo-p-dioxin deviates only slightly, if at all, from a planar configuration. It forms crystals of the monoclinic holohedral class and contains four molecules per unit cell with a strong tendency for twinning.[3]

The substituted dibenzo-p-dioxin nucleus has been isolated from the degradation of some naturally occurring materials such as trilobine, isotrilobine[6], and micranthine.[7] Neither these nor dibenzo-p-dioxin itself has any pharmacological value at the present time.

Of the many dibenzo-p-dioxin derivatives tested for antibacterial activity, only 2,7-di(β-chloropropionyl)dibenzo-p-dioxin and its β substituted derivatives were effective (at a dilution of 1:160,000) for Mycobacterium tuberculosis, Staphylococcus aureas, and Es. coli.[8] Subcutaneous injections of dibenzo-p-dioxin and the hydrochloric acid salt of 2-aminodibenzo-p-dioxin were tried on mice, rabbits, and frogs. Both proved to be depressants and death was due to respiratory failure when a dosage of 50-100 mg. per kg. was used.[9]

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[6]M. Tomita and C. Tani, J. Pharm. Soc. Japan, 62, 468 (1942) [C. A., 45, 4728 (1951)].

[7]I. Bick and A. Todd, J. Chem. Soc., 1602 (1950).

[8]M. Tomita and W. Watanabe, J. Pharm. Soc. Japan, 71, 1198 (1951) [C. A., 46, 7617 (1952)].

[9]M. Okada and S. Frese, Japan J. Med. Sci. IV, Pharmacol. Trans., 9, 9 (1936) [C. A., 31, 8021 (1937)].

The present study was undertaken to elucidate the basic chemistry of dibenzo-p-dioxin. This necessarily led to the preparation of many derivatives and proof of their structures by both chemical and physical means. Direct nuclear substitution is especially attractive since the molecule contains two oxygen atoms capable of delivering their activating influence to eight positions, four of which are known to be susceptible to electrophilic attack.

In addition to elucidating the basic chemistry of dibenzo-p-dioxin, some of the dibenzo-p-dioxin derivatives are being tested for possible use in brain tumor therapy by Dr. Otho D. Easterday of the Brookhaven National Laboratory. Others have been evaluated as organic liquid solution scintillators by Drs. Wright H. Langham, F. Newton Hayes, and Donald G. Ott of the Los Alamos Laboratories.

HISTORICAL

The literature has been surveyed up to March, 1957, and will cover only derivatives that can conceivably be made by direct nuclear substitution and are pertinent to the elucidation and prediction of new nuclearly substituted products. Derivatives obtained by modification of functional groups attached to the ring will, however, be included in the table of compounds.

Dibenzo-p-dioxin

A general procedure for the production of dibenzo-p-dioxin involves heating the alkali salt of o-bromophenol or o-chlorophenol to 180-250° for a period of about 4 hr. with or without copper powder as a catalyst.[10-13] A variation of this method involves the heating of o-bromophenol or o-chlorophenol with anhydrous potassium carbonate under conditions similar to

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[10] German Patent 223,367 (May 26, 1909) [C. A., 4, 2981 (1910)].

[11] M. Tomita, J. Pharm. Soc. Japan, 52, 429 (1932) [C. A., 27, 724 (1933)].

[12] N. Cullinane and C. Davies, Rec. trav. chim., 55, 881 (1936).

[13] M. Tomita, T. Nakano, and K. Hirai, J. Pharm. Soc. Japan, 74, 934 (1954) [C. A., 49, 10964 (1955)].

those employed above.[11,14] The dry distillation of sodium o-chlorophenoxide afforded a 37% yield of dibenzo-p-dioxin[15] as compared to 15-25% for the heating of potassium o-chlorophenoxide[12,14] and 32-65% for the heating of potassium o-bromophenoxide.[13]

Ring closure of 2,2'-dihydroxydiphenyl ether with hydrobromic acid and a trace of red phosphorous is also possible, but has proved to be of little practical importance for the preparation of dibenzo-p-dioxin.[16]

Alkyl Derivatives

Ring closure of 2,2'-dihydroxy-4-methyldiphenyl ether with hydrobromic acid and red phosphorous produced 2-methyldibenzo-p-dioxin. Employing the aforementioned ring closure, the unsymmetrical 1,3-dimethyldibenzo-p-dioxin and 2,3-dimethyldibenzo-p-dioxin were prepared from 2,2'-dihydroxy-3,5-dimethyldiphenyl ether and 2,2'-dihydroxy-4,5-dimethyldiphenyl ether, respectively.[16]

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[14] H. Gilman and J. J. Dietrich, J. Am. Chem. Soc., 79, 1439 (1957).

[15] H. Gilman and C. G. Stuckwisch, J. Am. Chem. Soc., 65, 1461 (1943).

[16] M. Tomita, J. Pharm. Soc. Japan, 56, 814 (1936) [C. A., 32, 8426 (1938)].

Condensation of potassium 2-bromo-4,6-dimethylphenoxide yielded 1,3,6,8-tetramethyldibenzo-p-dioxin and condensation of potassium 2-bromo-4,5-dimethylphenoxide yielded 2,3,7,8-tetramethyldibenzo-p-dioxin.[17] This same method afforded 2,7-dimethyldibenzo-p-dioxin from potassium 2-bromo-4-methylphenoxide[18] and 2,7-diethyl-3,8-dimethyldibenzo-p-dioxin from potassium 2-bromo-4-ethyl-5-methylphenoxide.[19]

Friedel-Crafts reactions of t-butyl chloride on dibenzo-p-dioxin in carbon disulfide using aluminum chloride at room temperature formed the 2-t-butyl- and 2,7(8)-di-t-butyldibenzo-p-dioxins in 2.5 and 3.5% yields, respectively. Under the same conditions, isopropyl chloride, when used in the appropriate equivalents, produced 2-isopropyl-, 2,3-diisopropyl-, and 2,3,7,8-tetraisopropyldibenzo-p-dioxin in 9, 8, and 54% yields, respectively. An excess of isopropyl chloride under reflux condition afforded a hexaisopropyldibenzo-p-dioxin. By using anhydrous ferric chloride as the catalyst and one equivalent of benzyl chloride, the 2-benzyldibenzo-p-dioxin was obtained in 9% yield.[20]

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[17] M. Tomita, J. Pharm. Soc. Japan, 53, 775 (1933) [C. A., 28, 3391 (1934)].

[18] M. Tomita, J. Pharm. Soc. Japan, 52, 900 (1932) [C. A., 27, 724 (1933)].

[19] M. Tomita and C. Tani, J. Pharm. Soc. Japan, 62, 481 (1942) [C. A., 45, 5146 (1951)].

[20] H. Gilman and J. J. Dietrich, J. Org. Chem., 22, in press (1957).

Chloromethylation of dibenzo-p-dioxin produced 13% of the 2-chloromethyldibenzo-p-dioxin.[20]

Carbonyl Derivatives

Acylation of dibenzo-p-dioxin with acetyl chloride in carbon disulfide resulted in the formation of 2,7-diacetyldibenzo-p-dioxin. Likewise, acylation of 2,7-dimethyldibenzo-p-dioxin afforded 2,7-diacetyl-3,8-dimethyldibenzo-p-dioxin.[21] However, when β-chloroacetyl chloride was reacted with dibenzo-p-dioxin, both 2,7-di(β-chloroacetyl)dibenzo-p-dioxin and 2,8-di(β-chloroacetyl)dibenzo-p-dioxin were obtained.[22] In similar fashion, 2-(β-phthaliminoacetyl)-dibenzo-p-dioxin[23], 2,7-di(α-bromoisobutyryl)dibenzo-p-dioxin, 2,7-di(β-bromopropionyl)dibenzo-p-dioxin, 2,7-dipropionyldibenzo-p-dioxin, and 2,7-di(γ-chloropropionyl)-dibenzo-p-dioxin were all produced by reacting the appropriate acyl halide with dibenzo-p-dioxin. Reacting β-chloroacetyl chloride with 2,7-dimethyldibenzo-p-dioxin resulted in the formation of 2,7-di(β-chloroacetyl)-3,8-dimethyldibenzo-p-

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[21] M. Tomita, J. Pharm. Soc. Japan, 54, 885 (1934) [C. A., 31, 103 (1937)].

[22] M. Tomita, J. Pharm. Soc. Japan, 56, 906 (1936) [C. A., 31, 3484 (1937)].

[23] M. Tomita, J. Pharm. Soc. Japan, 57, 607 (1937) [C. A., 33, 2898 (1939)].

dioxin.[24] Treatment of dibenzo-p-dioxin in chlorobenzene at 10-15° with phthalic anhydride produced a 98% yield of dibenzo-p-dioxinoyl-o-benzoic acid. The chlorodibenzo-p-dioxinoyl-o-benzoic acid was obtained in the same yield.[25]

The Gattermann-Koch reaction on dibenzo-p-dioxin resulted in the formation of dibenzo-p-dioxin-2-carboxaldehyde in poor yield.[20]

Carboxyl Derivatives

Dibenzo-p-dioxin may be metalated with methyllithium in diethyl ether to produce dibenzo-p-dioxin-1-carboxylic acid after carbonation. When n-butyllithium was used instead, a mixture of 2 acids was obtained upon carbonation. These were presumably the 1,6- and 1,9-dicarboxylic acids.[15] Ring closure of the methyl ester of 2,2'-dihydroxy-4-carboxydiphenyl ether yielded dibenzo-p-dioxin-2-carboxylic acid after hydrolysis. Oxidation of 2,7-diacetyldibenzo-p-dioxin or condensation of the methyl ester of potassium 2-bromo-4-carboxyphenoxide followed by hydrolysis yielded dibenzo-p-dioxin-2,7-dicarboxylic

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[24] M. Tomita, J. Pharm. Soc. Japan, 58, 498 (1938) [C. A., 32, 7463 (1938)].

[25] German Patent 668,875 (December 13, 1938) [C. A., 33, 5006 (1939)].

acid.[26] The dibenzo-p-dioxin-2,8-dicarboxylic acid was obtained by the oxidation of 2,8-di(β-chloroacetyl)dibenzo-p-dioxin.[22]

Dithiocarboxylate Derivatives

Ethyl bromide failed to give the normal Friedel-Crafts product in carbon disulfide, but yields instead ethyl dibenzo-p-dioxin-2-dithiocarboxylate. Methyl iodide underwent the same reaction producing the methyl ester. Bubbling ethyl chloride into the reaction mixture resulted in the formation of diethyl dibenzo-p-dioxin-2,7-bis(dithiocarboxylate).[20]

Halogen Derivatives

2-Bromodibenzo-p-dioxin may be prepared by either using bromine in carbon disulfide[27] or using bromide-bromate in refluxing glacial acetic acid, the latter method giving a 40% yield.[14] The 2-bromodibenzo-p-dioxin may also be obtained from 2-aminodibenzo-p-dioxin via the Sandmeyer reaction.[27] Bromination of dibenzo-p-dioxin in glacial acetic acid using

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[26]M. Tomita, J. Pharm. Soc. Japan, 62, 476 (1942) [C. A., 45, 5146 (1951)].

[27]French Patent 799,627 (June 16, 1936) [C. A., 30, 7868 (1936)].

a 2:1 ratio of bromide-bromate[14] or in nitrobenzene using 2:1 ratio of bromine[28] produced the 2,8-dibromodibenzo-p-dioxin in 22% and an unspecified yield, respectively. When liquid bromine was employed in a 3:1 ratio, another dibromo compound was obtained and this was considered to be 2,7-dibromodibenzo-p-dioxin[14], but this has been shown to be in error.[29] Exhaustive bromination of dibenzo-p-dioxin in refluxing glacial acetic acid produced 2,3,7,8-tetrabromodibenzo-p-dioxin. Metalation of dibenzo-p-dioxin with phenyllithium followed by the addition of bromine produced 8% of 1-bromodibenzo-p-dioxin.[14]

Diazotization of 2-aminodibenzo-p-dioxin followed by addition of copper (I) chloride or direct chlorination of dibenzo-p-dioxin in glacial acetic acid resulted in the formation of 2-chlorodibenzo-p-dioxin. The latter method afforded an 18% yield of product. A small amount of 2,7-dichlorodibenzo-p-dioxin was also formed in the preparation of 2-chlorodibenzo-p-dioxin.[14] Condensation of sodium 2,4-dichlorophenoxide[30] or diazotization of 2,7-diaminodibenzo-p-dioxin followed by

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[28]Swiss Patent 238,627 (July 31, 1945) [C. A., 43, 4484 (1949)].

[29]See Experimental section of this thesis.

[30]M. Julia and M. Baillarg'e, Bull. Soc. Chim. France, 640 (1953).

addition of copper(I) chloride[31] was also used to produce 2,7-dichlorodibenzo-p-dioxin.

Diazotization of 2-aminodibenzo-p-dioxin followed by the addition of potassium iodide produced 2-iododibenzo-p-dioxin in low yield.

Hydroxy Derivatives

2-Hydroxydibenzo-p-dioxin was obtained from 2-aminodibenzo-p-dioxin via a diazotization reaction or from any 2-halodibenzo-p-dioxin via a basic hydrolysis under sealed tube conditions.[27] Hydrolysis of 2,7-dimethoxydibenzo-p-dioxin afforded 2,7-dihydroxydibenzo-p-dioxin.[17] It may also be obtained from 2,7-diamino-dibenzo-p-dioxin via a diazotization reaction.[32] The 1,6-dihydroxy-3,8-dimethyldibenzo-p-dioxin was obtained from the dimethoxy compound after hydrolysis.[21]

Methoxy Derivatives

Condensation of potassium 2-bromo-6-methoxyphenoxide produced both 1-methoxydibenzo-p-dioxin and 1,6-dimethoxydibenzo-

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[31] S. Uyeo, Bull. Chem. Soc. Japan, 16, 177 (1941) [C. A., 35, 7964 (1941)].

[32] M. Tomita, J. Pharm. Soc. Japan, 55, 1060 (1935) [C. A., 31, 6661 (1937)].

p-dioxin.[33] Employing similar conditions, it was possible to form 2,7-dimethoxydibenzo-p-dioxin[17], 3,8-diethyl-1,6-dimethoxydibenzo-p-dioxin[21], and 3,8-diethyl-4,9-dimethyl-1,6-dimethoxydibenzo-p-dioxin.[19] Degradation of trilobine and isotrilobine produced 3,8-diethyl-4,7-dimethyl-1-methoxydibenzo-p-dioxin as one of the products.[6]

Nitrogen Derivatives

Five nitro derivatives of dibenzo-p-dioxin have been reported. These consisted of 2-nitrodibenzo-p-dioxin, obtained by nitration of dibenzo-p-dioxin in glacial acetic acid at ice-bath temperature; 2,7-dinitrodibenzo-p-dioxin, obtained by nitration of dibenzo-p-dioxin in glacial acetic acid at room temperature; 2,8-dinitrodibenzo-p-dioxin, obtained by nitrating dibenzo-p-dioxin with warm, concentrated nitric acid; 2,3,7-trinitrodibenzo-p-dioxin, obtained by nitrating dibenzo-p-dioxin with warm, fuming nitric acid[32]; and 1,3-dinitrodibenzo-p-dioxin, obtained by heating picryl chloride with catechol.[34]

The aforementioned nitro compounds all yielded the corresponding amines when catalytically reduced.[32,35]

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[33]M. Tomita, Y. Inubushi, and M. Kozuka, Pharm. Bull., (Japan), 1, 360 (1953) [C. A., 49, 10990 (1955)].

[34]H. Hillyer, Am. Chem. J., 23, 126 (1900).

[35]H. Hillyer, Am. Chem. J., 26, 362 (1903).

Metallic Derivatives

Dibenzo-p-dioxin may be metalated with methyllithium to give the 1-lithiodibenzo-p-dioxin in 10% yield subsequent to carbonation. Using n-butyllithium, two dilithiodibenzo-p-dioxins were obtained which were considered to be the 1,6- and 1,9-dilithiodibenzo-p-dioxins. Carbonation of the dilithiodibenzo-p-dioxin mixture, esterification with methanol in the presence of dry hydrogen chloride, separation of the esters followed by hydrolysis resulted in the isolation of 20% of one acid and 7% of the other.[15]

Cleavage of dibenzo-p-dioxin with lithium was approximately 20 times faster in tetrahydrofuran than in diethyl ether. The product in both cases was 2-carboxy-2'-hydroxydiphenyl ether subsequent to carbonation in 56 and 23% yields, respectively.[36] Sodium in liquid ammonia cleaved dibenzo-p-dioxin to yield on work-up 2-hydroxydiphenyl ether. Under similar conditions, 2,7-dimethyldibenzo-p-dioxin remained "practically unchanged".[37]

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[36] H. Gilman and J. J. Dietrich, J. Org. Chem., 22, 0000 (1957).

[37] M. Tomita, Y. Inubushi, and H. Niwa, J. Pharm. Soc. Japan, 72, 203 (1952) [C. A., 47, 6428 (1953)].

Reduction of Dibenzo-p-dioxin

Catalytic reduction of dibenzo-p-dioxin with platinum(IV) oxide produced dodecahydrodibenzo-p-dioxin and cis-cyclohexenediol.[38]

Miscellaneous Derivatives of Dibenzo-p-dioxin

A series of compounds has been derived from the condensation of tetrahalo-o-quinone with tetrahalocatechol. Two examples of this type of derivative are 2,3-dione-2,3-dihydro-1,4,6,7,8,9-hexachlorodibenzo-p-dioxin[39] and 2,3-dihydroxy-1,4,6,7,8,9-hexabromodibenzo-p-dioxin.[40]

Condensation of the potassium salt of 1-bromo-2-hydroxynaphthalene yielded 1,2-dinaphtho-p-dioxin.[18] In similar manner it was possible to make 5,6-phenylenedioxyquinoline[41] and diquinoline-5,6-dioxide[41,42] from the appropriate sodium or potassium salts.

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[38] M. Tomita and C. Tani, J. Chem. Soc. Japan, 64, 972 (1943) [C. A., 41, 3802 (1947)].

[39] C. Jackson and R. MacLaurin, Am. Chem. J., 37, 7 (1914).

[40] J. Frejka, B. Sfranek, and J. Zika, Collection Czechoslav Chem. Commun., 9, 238 (1937) [C. A., 31, 7046 (1937)].

[41] E. Fujita, T. Saijoh, and N. Takao, J. Pharm. Soc. Japan, 73, 453 (1953) [C. A., 48, 5193 (1954)].

[42] M. Tomita and N. Yoshida, J. Pharm. Soc. Japan, 72, 718 (1952) [C. A., 47, 6419 (1953)].

Chemical Correlations

An excellent review of the chemistry of dibenzofuran, dibenzothiophene, phenoxathiin, thianthrene, and dibenzo-p-dioxin through 1950 has been compiled by Esmay.[43] This discussion covers the chemical behavior of these heterocycles under comparable conditions when this is possible.

Derivatives of Dibenzo-p-dioxin

In addition to the compounds reported in the literature as of March, 1957, Table 1 contains all of the new derivatives of dibenzo-p-dioxin appearing in the Experimental section of this dissertation. The compounds are arranged in alphabetical order using names consistent with Chemical Abstracts.

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[43] D. L. Esmay, Unpublished Ph. D. Thesis. Ames, Iowa, Iowa State College Library. 1950.

Table 1. Derivatives of dibenzo-p-dioxin

Name of Compound	M.P. °C	Ref.
2-Acetamidodibenzo-p-dioxin	184-186	29
2-Acetyldibenzo-p-dioxin	131-133.5	29
2-Acetyldibenzo-p-dioxin oxime	174-176	29
2-(β-Aminoacetyl)dibenzo-p-dioxin HCl salt	300	23
2-Amino-7-bromodibenzo-p-dioxin	180-183	29
2-Amino-X-bromodibenzo-p-dioxin	152-154	29
2-(β-Aminoethylamino)dibenzo-p-dioxin HCl salt	255 dec.	16
2-Aminodibenzo-p-dioxin	134-136, 157	29, 32
2-Aminodibenzo-p-dioxin HCl salt	288	32
2,2'-Azodibenzo-p-dioxin	239-241	29
2-Benzoyldibenzo-p-dioxin	140-145	29
2-Benzoyldibenzo-p-dioxin oxime	215-216	29
2-Benzyldibenzo-p-dioxin	106-108	20
1,1'-Bis(dibenzo-p-dioxin)	217-219	29
2,2'-Bis(dibenzo-p-dioxin)	235-236.5	29
2,8-Bis(β-dimethylaminoethyl)-3,7-diformyl-4-methoxydibenzo-p-dioxin		44
1-Bromodibenzo-p-dioxin	104-106	14

[44] H. Kondo and M. Tomita, Ann., 497, 90 (1932).

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
2-Bromodibenzo-p-dioxin	93-94.5, 90-92	14, 27
2-Bromo-7,X-dinitrodibenzo-p-dioxin	190-192	29
2-Bromo-7-nitrodibenzo-p-dioxin	215-217	29
2-t-Butyldibenzo-p-dioxin	95.5-97	20
7-Carboxy-2,3-diformyl-8-hydroxymethyl-4-methoxydibenzo-p-dioxin		44
2-Chlorodibenzo-p-dioxin	87-90	14
Chlorodibenzo-p-dioxinoyl-o-benzoic acid	215	25
2-Chloromethyldibenzo-p-dioxin	111-113	20
2,7-Diacetamidodibenzo-p-dioxin	356-357	29
2,8-Diacetamidodibenzo-p-dioxin	292	32
2,3-Diacetoxy-7,8-dichlorodibenzo-p-dioxin	218	40
2,3-Diacetoxy-1,4,6,7,8,9-hexabromodibenzo-p-dioxin	300	40
2,3-Diacetoxy-1,4,6,7,8,9-hexachlorodibenzo-p-dioxin	301, 282	40, 45
2,7-Diacetyldibenzo-p-dioxin	248, 255-260	21, 29

[45] C. Jackson and R. MacLaurin, Am. Chem. J., 38, 127 (1915).

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
2,7-Diacetyldibenzo-p-dioxin dioxime	265, 274-275	21, 29
2,7-Diacetyl-3,8-dimethyldibenzo-p-dioxin	211	21
2,7-Diacetyl-3,8-dimethyldibenzo-p-dioxin dioxime	255	21
2,7-Di(β-aminoacetyl)dibenzo-p-dioxin HCl salt	300	23
1,3-Diaminodibenzo-p-dioxin	198-200	35
2,7-Diaminodibenzo-p-dioxin	264-266, 249	29, 32
2,8-Diaminodibenzo-p-dioxin	178	32
2,8-Diaminodibenzo-p-dioxin acetate	292	32
Dibenzo-p-dioxin-1-boronic acid	296-304	28
Dibenzo-p-dioxin-2-carboxaldehyde	91-93	20
2,4-Dinitrophenylhydrazone of dibenzo-p-dioxin-2-carboxaldehyde	300-301	20
Dibenzo-p-dioxin-1-carboxylic acid	210, 217-219	15, 29
Dibenzo-p-dioxin-2-carboxylic acid	239-240, 245-246	26, 29
Dibenzo-p-dioxin-1,6(9)-diboronic acid	430	29
Dibenzo-p-dioxin-1,6(9)-dicarboxylic acid	335, 378	15, 29
Dibenzo-p-dioxin-1,9(6)-dicarboxylic acid	297-298	15

Table 1. (Continued)

Name of Compound	M.P., °C	Ref.
Dibenzo-p-dioxin-2,7-dicarboxylic acid	300	21, 26
Dibenzo-p-dioxin-2,8-dicarboxylic acid	300	22
Dibenzo-p-dioxin-X,Y-disulfonyl chloride	227.5-230	29
Dibenzo-p-dioxinoyl-o-benzoic acid	215	25
1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethanol	141-142	29
1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethene	123-125	29
2,7-Dibenzoyldibenzo-p-dioxin	244-246	29
2.7-Dibenzoyldibenzo-p-dioxin dioxime	253.5	29
2,8-Dibromodibenzo-p-dioxin	149-151, 145-150	14, 28
2,X-Dibromodibenzo-p-dioxin	174-176	14
2,7-Dibromodibenzo-p-dioxin	197-198	14, 29
2,8-Dibromo-3,8-dinitrodibenzo-p-dioxin	276-278	29
2,7-Di(α-bromoisobutyryl)dibenzo-p-dioxin	160-167	24
2,X-Dibromo-7-nitrodibenzo-p-dioxin	217-220	29
2,7-Di(β-bromopropionyl)dibenzo-p-dioxin	213	24
2,7(8)-Di-t-butyldibenzo-p-dioxin	226-228	20
2,7-Di(β-chloroacetyl)dibenzo-p-dioxin	282	22

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
2,8-Di(β-chloroacetyl)dibenzo-p-dioxin	202	22
2,7-Di(β-chloroacetyl)-3,8-dimethyl-dibenzo-p-dioxin	183-185	24
2,7-Dichlorodibenzo-p-dioxin	201-202, 207	14, 30 31
7,8-Dichloro-2,3-dihydroxydibenzo-p-dioxin		40
2,7-Di(γ-chloropropionyl)dibenzo-p-dioxin	211 dec.	24
2-[ε-(Diethylamino)amylamino]dibenzo-p-dioxin HCl salt	191	16
2-[δ-(Diethylamino)butylamino]-dibenzo-p-dioxin HCl salt	276 dec.	16
2-[β-(Diethylamino)ethylamino]-dibenzo-p-dioxin HCl salt	120 dec.	16
2-[δ-(Diethylamino)-α-methylbutyl-amino]dibenzo-p-dioxin HCl salt	248	16
2-[γ-(Diethylamino)propylamino]-dibenzo-p-dioxin HCl salt	161 dec.	16
Diethyl dibenzo-p-dioxin-2,7-bis(dithiocarboxylate)	174-176	20
2,7-Diethyl-3,8-dimethyldibenzo-p-dioxin		19
3,8-Diethyl-4,9-dimethyl-1,6-dimethoxydibenzo-p-dioxin	204-206	19
3,8-Diethyl-4,7-dimethyl-1-methoxydibenzo-p-dioxin	96-97	6

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
1,6-Diformyl-2,7-divinyl-4,9-dimethoxydibenzo-p-dioxin	300 dec.	7
3,7-Diformyl-2,8-dimethylethylamino-4-methoxydibenzo-p-dioxin	24	9
2,7-Dihydroxydibenzo-p-dioxin	269	17
2,7-Dihydroxydibenzo-p-dioxin phosphoric ester	236	46
2,3-Dihydroxy-2,3-dimethoxy-2,3-dihydro-1,4,6,7,8,9-hexachlorodibenzo-p-dioxin	218	45
1,6-Dihydroxy-3,8-dimethyldibenzo-p-dioxin	274	21
1,6-Dihydroxy-3,8-dimethyldibenzo-p-dioxin phosphoric ester	198	46
2,3-Dihydroxy-1,4,6,7,8,9-hexabromodibenzo-p-dioxin		40
2,3-Dihydroxy-1,4,6,7,8,9-hexachlorodibenzo-p-dioxin	290, 276	39, 40
2,7-Di(α-hydroxy-β-morpholylethyl)-dibenzo-p-dioxin	202	47
2,7-Di(α-hydroxy-β-morpholylethyl)-3,8-dimethyldibenzo-p-dioxin	242	47
2,7-Di(α-hydroxy-β-morpholylpropyl)-dibenzo-p-dioxin	220-232	47
2,7-Di(α-hydroxy-γ-morpholylpropyl)-dibenzo-p-dioxin	199	47

[46] M. Tomita, J. Pharm. Soc. Japan, 56, 490 (1936) [C. A., 30, 8214 (1936)].

[47] M. Tomita, J. Pharm. Soc. Japan, 59, 538 (1939) [C. A., 34, 1016 (1940)].

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
2,7-Di(α-hydroxy-β-piperidylethyl)-dibenzo-p-dioxin	168-170	47
2,8-Di(α-hydroxy-β-piperidylethyl)-dibenzo-p-dioxin	181	47
2,7-Di(α-hydroxy-β-piperidyl)-3,8-dimethyldibenzo-p-dioxin	211	24
2,7-Di(α-hydroxy-β-piperidylpropyl)-dibenzo-p-dioxin	215	24
2,7-Di(α-hydroxy-γ-piperidylpropyl)-dibenzo-p-dioxin	120 dec.	24
1,6(9)-Diiododibenzo-p-dioxin	216-218	29
2,3-Diisopropyldibenzo-p-dioxin	b.p. 128-131 (0.25 mm.)	20
1,6-Dimethoxydibenzo-p-dioxin	193.5-195.5	33
2,7-Dimethoxydibenzo-p-dioxin	131	17
1,3-Dimethyldibenzo-p-dioxin		16
2,3-Dimethyldibenzo-p-dioxin	113	16
2,7-Dimethyldibenzo-p-dioxin	116	18
Dimethyl dibenzo-p-dioxin-1,6(9)-dicarboxylate	202-204	15
Dimethyl dibenzo-p-dioxin-1,9(6)-dicarboxylate	142-143	15
Dimethyl dibenzo-p-dioxin-2,7-dicarboxylate	220, 245-246	23, 26
Dimethyl dibenzo-p-dioxin-2,8-dicarboxylate	167	22

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
3,8-Dimethyl-1,6-dimethoxydibenzo-p-dioxin	191	21
1,2-Dinaphtho-p-dioxin	125	18
1,3-Dinitrodibenzo-p-dioxin	192-192.5	34
2,7-Dinitrodibenzo-p-dioxin	270-273, 256	29, 32
2,8-Dinitrodibenzo-p-dioxin	190	32
2,3-Dione-2,3-dihydro-1,4,6,7,8,9-hexachlorodibenzo-p-dioxin	300	39
2,7-Di(α-oxo-β-morpholylethyl)-dibenzo-p-dioxin	195	47
2,7-Di(α-oxo-β-morpholylethyl)-dibenzo-p-dioxin HCl salt	300	47
2,7-Di(α-oxo-β-morpholylethyl)-3,8-dimethyldibenzo-p-dioxin	171	47
2,7-Di(α-oxo-β-morpholylpropyl)-dibenzo-p-dioxin	184	47
2,7-Di(α-oxo-γ-morpholylpropyl)-dibenzo-p-dioxin	176	47
2,7-Di(α-oxo-γ-morpholylpropyl)-dibenzo-p-dioxin HCl salt	280	47
2,7-Di(β-piperidylacetyl)dibenzo-p-dioxin	157	22
2,7-Di(β-piperidylacetyl)dibenzo-p-dioxin HCl salt	300	22
2,8-Di(β-piperidylacetyl)dibenzo-p-dioxin	161	22
2,7-Di(β-piperidylisovaleryl)-dibenzo-p-dioxin	161	24

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
2,7-Di(β-piperidylpropionyl)dibenzo-p-dioxin	185-186	24
2,7-Di(γ-piperidylpropionyl)dibenzo-p-dioxin	138	24
2,7-Dipropionyldibenzo-p-dioxin	241	24
2,7-Dipropionyldibenzo-p-dioxin dioxime	235	24
Diquinoline-5,6-dioxide	280 dec.	42
2,7-Disulfanilamidodibenzo-p-dioxin	300	48
Dodecahydrodibenzo-p-dioxin	b.p. 150-165 (18 mm.)	38
Ethyl dibenzo-p-dioxin-2-dithiocarboxylate	105-108	20
1,4,6,7,8,9-Hexachloro-2-hydroxy-2-methoxy-3-one-2,3-dihydrodibenzo-p-dioxin	198	45
Hexaisopropyldibenzo-p-dioxin	251-252	20
2-Hydroxydibenzo-p-dioxin	146-147	27
1-Iododibenzo-p-dioxin	114-115	29
2-Iododibenzo-p-dioxin	95-97	14
2-Isopropyldibenzo-p-dioxin	87.5-89	20
1-Methoxydibenzo-p-dioxin	127-128	33
2-Methyldibenzo-p-dioxin	54	16
Methyl dibenzo-p-dioxin-1-carboxylate	86	15
Methyl dibenzo-p-dioxin-2-carboxylate	107-108	26

[48] M. Tomita and G. Itah, J. Pharm. Soc. Japan, 65, 10 (1945) [C. A., 45, 7975 (1951)].

Table 1. (Continued)

Name of Compound	M.P. °C	Ref.
Methyl dibenzo-p-dioxin-2-dithiocarboxylate	121-123	20
2-Nitrodibenzo-p-dioxin	147-149, 141	23, 32
2-Phenyldibenzo-p-dioxin	108-110	29
5,6-Phenylenedioxyquinoline	127-129	41
6,7-Phenylenedioxyquinoline	184	49
6,7-Phenylenedioxyquinoline HCl salt	262	49
6,7-Phenylenedioxyquinoline methiodide	252	49
2-(β-Phthaliminoacetyl)dibenzo-p-dioxin	244	23
2-(β-Piperidylethylamino)dibenzo-p-dioxin HCl salt	244 dec.	16
2-(γ-Piperidylpropylamino)dibenzo-p-dioxin HCl salt	246 dec.	16
2-Sulfanilamidodibenzo-p-dioxin	224	48
2,3,7,8-Tetrabromodibenzo-p-dioxin	334-336	14
2,3,7,8-Tetrachlorodibenzo-p-dioxin	300-302	29
2,3,7,8-Tetraisopropyldibenzo-p-dioxin	b.p. 158-161 (0.5 mm.)	20
1,3,6,8-Tetramethyldibenzo-p-dioxin	138	17
2,3,7,8-Tetramethyldibenzo-p-dioxin	218	16
2,3,7,8-Tetranitrodibenzo-p-dioxin	334-335	29
2,3,7-Triaminodibenzo-p-dioxin	173	32
Phenanthrenequinone derivative of 2,3,7-triaminodibenzo-p-dioxin	339	32
2,3,7-Trinitrodibenzo-p-dioxin	226-228, 215-217	29, 32

[49] M. Tomita, J. Pharm. Soc. Japan, 56, 65 (1936) [C. A., 32, 5837 (1938)].

EXPERIMENTAL

All reactions involving organometallic compounds were run either in diethyl ether previously dried over sodium or tetrahydrofuran which was shaken with sodium hydroxide pellets, dried over sodium and finally distilled from lithium aluminum hydride prior to use. These reactions were all conducted under a dry, oxygen-free nitrogen atmosphere. A copper block was used for the determination of melting points which are uncorrected.

Derivatives

1-Iododibenzo-p-dioxin

A slight excess of phenyllithium was added to 9.2 g. (0.05 mole) of dibenzo-p-dioxin in 50 ml. of diethyl ether and refluxed for 7 hr. This metalation mixture was then slowly added to 12.6 g. (0.05 mole) of iodine in 100 ml. of diethyl ether at ice-bath temperature. The reaction mixture was allowed to warm to room temperature and then washed with an aqueous sodium bisulfite solution. Evaporation of the ether layer after drying over anhydrous sodium sulfate left a residue which was vacuum distilled to yield 3.6 g. of product, b.p. 144-145° (0.1 mm.). Two recrystallizations of this material

from ethanol produced 3.2 g. (20%) of fine, white needles, m.p. 114-115°.

Anal. Calcd. for $C_{12}H_7O_2I$: I, 40.96. Found: I, 41.11, 40.83.

1,6(9)-Diiododibenzo-p-dioxin

Seventy milliliters of diethyl ether containing 0.12 mole of phenyllithium was added to 9.2 g. (0.05 mole) of dibenzo-p-dioxin in 100 ml. of tetrahydrofuran and stirred at 42° for 1 hr. The resulting mixture was then slowly added to 27 g. (0.106 mole) of iodine in diethyl ether at ice-bath temperature. A sodium bisulfite solution was used to wash the ether layer before it was evaporated. Three recrystallizations of the residue from toluene yielded 2.9 g. (13%) of tan needles, m.p. 216-218°.

Anal. Calcd. for $C_{12}H_6O_2I_2$: I, 58.25. Found: I, 58.16, 58.31.

2-Iododibenzo-p-dioxin via diazotization

Nitrosylsulfuric acid was prepared by dissolving 0.8 g. (0.015 mole) of sodium nitrite in 8 ml. of sulfuric acid and gentle warming of the resulting mixture to 70°. A clear solution resulted. The temperature was then lowered to 10° after which 2 g. (0.01 mole) of 2-aminodibenzo-p-dioxin in

25 ml. of glacial acetic acid, cooled to 18°, was added with stirring at a controlled rate consistent with maintaining a temperature below 15°.[50] Stirring was continued for 15 min. after addition at which time the mixture was poured into a solution containing 2.5 g. (0.015 mole) of potassium iodide in 15 ml. of dilute sulfuric acid. The complex which formed was destroyed by heating the mixture to 80°. Dilution with water, filtration, and recrystallization from ethanol-water (Norit A) produced 1 g. of crude product melting 92-94.5°. Two recrystallizations from ethanol-water resulted in the isolation of 0.4 g. (13%) of white needles, m.p. 95-97°.

Anal. Calcd. for $C_{12}H_7O_2I$: I, 40.96. Found: I, 40.64, 40.40.

2-Iododibenzo-p-dioxin employing iodine monochloride

A solution of 9.2 g. (0.05 mole) of dibenzo-p-dioxin in 100 ml. of glacial acetic acid was stirred at room temperature while 8.1 g. (0.06 mole) of iodine monochloride was slowly added. After addition, the temperature was slowly raised to 80° over a period of 5 hr. The reaction was terminated after 2 hr. of reflux. Dilution with aqueous sodium bisulfite

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[50] This procedure was adapted from K. H. Saunders, "The Aromatic Diazo Compounds", Edward Arnold and Co., London, 1949, p. 13.

followed by filtration produced 14.5 g. of crude material which was vacuum distilled to yield 6.5 g. of product, b.p. 131-135° (0.25 mm.). Two recrystallizations of this material from ethanol-water produced 6.1 g. (40%) of product melting 91-94°.

2-Iododibenzo-p-dioxin (attempted)

Using directions for the preparation of 2-iododibenzofuran,[51] a mixture of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 4 ml. of concentrated nitric acid, 12.7 g. (0.05 mole) of iodine, and 50 ml. of chloroform was refluxed for 8 hr. The chloroform layer was washed with aqueous sodium bisulfite and then evaporated. Three recrystallizations of the residue from ethanol produced 2 g. of yellow needles melting 147-149°. A mixture melting point with authentic 2-nitrodibenzo-p-dioxin showed no depression.

A diiododibenzo-p-dioxin mixture

A solution of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 19.4 g. (0.12 mole) of iodine monochloride, and 100 ml. of glacial acetic acid was refluxed for 5.75 hr. After cooling, the dark solution was diluted with aqueous sodium bisulfite and

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[51] H. Gilman, G. E. Brown, W. G. Bywater, and W. H. Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).

the precipitate filtered off. Numerous recrystallizations of the material from ethanol-benzene or glacial acetic acid failed to alter the melting range of 184-205°. The crystalline form from both recrystallizing systems was shiny platelets. The infrared spectrum indicated this material to be a mixture of 2,7- and 2,8-diiododibenzo-p-dioxin, since there was a strong 1,2,4 trisubstitution band at 12.4μ and no 1,2 disubstitution band at 13.3μ.[52]

Anal. Calcd. for $C_{12}H_6O_2I_2$: I, 58.26. Found: I, 59.70.

2,3,7,8-Tetrachlorodibenzo-p-dioxin

Following the procedure of Silberrad,[53] a solution of 0.5 g. of sulfur monochloride in 33.6 g. (0.5 mole) of sulfuryl chloride was slowly added to a mixture of 0.25 g. of aluminum chloride and 9.2 g. (0.05 mole) of dibenzo-p-dioxin at room temperature. After 45 min., the reaction mixture became very viscous so 20 ml. of sulfuryl chloride was added. Stirring was continued for another 45 min. at room temperature and then the temperature was raised to 69° (reflux temperature of sulfuryl chloride) for an additional hour. Dilute hydrochloric

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[52]All infrared spectra were run on a Baird infrared spectrophotometer by E. M. Layton, Jr., of the Institute of Atomic Research.

[53]O. Silberrad, J. Chem. Soc., 121, 1015 (1922).

acid was added and a solid filtered from the reaction mixture. The crude solid was recrystallized four times from pyridine to yield 5.1 g. (32%) of cream colored needles, m.p. 300-302°. The infrared spectrum of this material was very similar to the spectrum of 2,3,7,8-tetrabromodibenzo-p-dioxin.

Anal. Calcd. for $C_{12}H_4O_2Cl_4$: Cl, 43.74. Found: Cl, 43.73, 43.62.

2-Cyanodibenzo-p-dioxin (attempted). Run I

Two grams (0.01 mole) of 2-aminodibenzo-p-dioxin was dissolved in 25 ml. of glacial acetic acid, cooled to 18°, and slowly added with stirring to a mixture of 8 ml. of concentrated sulfuric acid and 0.8 g. (0.014 mole) of sodium nitrite at 5°.[50] This mixture was then added to 2.5 g. of copper (I) cyanide dissolved in a solution of potassium cyanide. The resulting mixture was heated and then filtered, but no product was isolated. A duplicate run produced the same result.

Run II

Using the method of Koelsch and Whitney,[54] a mixture of 13 g. (0.05 mole) of 2-bromodibenzo-p-dioxin, 11 g. (0.06 mole)

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[54] C. Koelsch and A. Whitney, J. Org. Chem., 6, 795 (1941).

of copper (I) cyanide, as the dimer, and 50 ml. of dry quinoline was heated at 180° for 24 hr. The reaction mixture was boiled with 1:1 hydrochloric acid and the insoluble material filtered off and recrystallized four times from ethanol. This material proved to be 2 g. (15%) of 2-bromodibenzo-p-dioxin. No identifiable product was isolated from the combined mother liquors of the 2-bromodibenzo-p-dioxin.

2-Bromo-7-nitrodibenzo-p-dioxin. Run I

A mixture of 2 g. (0.0087 mole) of 2-nitrodibenzo-p-dioxin, 3.6 g. (0.029 mole) of potassium bromide, 1 g. (0.0058 mole) of potassium bromate, 5 ml. of water, and 50 ml. of glacial acetic acid was refluxed for 1.5 hr. The reaction mixture was then diluted with a sodium bisulfite solution and filtered. Three recrystallizations of the crude material from glacial acetic acid yielded 0.6 g. (23%) of yellow needles, m.p. 215-217°.

Anal. Calcd. for $C_{12}H_6O_4NBr$: N, 4.60. Found: N, 4.41, 4.32.

Run II

A solution of 1.5 g. (0.005 mole) of 2-bromodibenzo-p-dioxin, 2 ml. of concentrated nitric acid, and 20 ml. of glacial acetic acid was heated to 50-60° for 10 min. The

solution turned a green-yellow color. After cooling, the reaction mixture was diluted with water and filtered. Four recrystallizations of the material from glacial acetic acid resulted in the isolation of less than 0.1 g. of yellow needles, m.p. 214-216°. A mixture melting point of this material and that obtained in Run I showed no depression.

When the same reaction was run at 18° in 50 ml. of glacial acetic acid, there was a near quantitative recovery of starting material.

2-Amino-7-bromodibenzo-p-dioxin

A solution of 12 g. (0.041 mole) of anhydrous tin (II) chloride in 25 ml. of concentrated hydrochloric acid was slowly added to a hot solution of 4.3 g. (0.014 mole) of 2-bromo-7-nitrodibenzo-p-dioxin in 25 ml. of glacial acetic acid. The resulting solution was heated for 10 min. at which time the yellow color had disappeared. The mixture, now containing a white precipitate, was made strongly basic with aqueous potassium hydroxide and then filtered. Recrystallization of the crude material from ethanol-water (Norit A) produced 3 g. of material melting 150-170°. One gram of this material was recrystallized three times from benzene to yield 0.3 g. (23%) of white needles melting 180-183°. An infrared spectrum of this compound showed that total reduction had

taken place since the customary nitro band was absent from the spectrum.

Anal. Calcd. for $C_{12}H_8O_2NBr$: N, 5.04. Found: N, 4.90, 4.96.

2,7-Dibromodibenzo-p-dioxin. Run I

A solution of 2 g. (0.007 mole) of 2-amino-7-bromodibenzo-p-dioxin in 25 ml. of glacial acetic acid, cooled to 18°, was diazotized with 8 ml. of nitrosylsulfuric acid according to the procedure of Saunders.[50] The resulting mixture was stirred for 10 min. and then added at 5° to a hydrobromic acid solution of freshly prepared copper (I) bromide.[55] The mixture was heated to 80°, diluted with water, and filtered. After drying under a heat lamp, the crude material was dissolved in benzene and chromatographed on alumina. Evaporation of the excess eluate followed by two recrystallizations from benzene produced 0.6 g. (25%) of light yellow plates, m.p. 197-198°.

Anal. Calcd. for $C_{12}H_6O_2Br_2$: Br, 46.75. Found: Br, 46.31, 46.54.

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[55] W. C. Fernelius, "Inorganic Syntheses", Vol. 2, McGraw-Hill Book Company, Inc., New York, N. Y., 1951, p. 122.

Run II

A solution of 4.5 g. (0.021 mole) of 2,7-diaminodibenzo-p-dioxin in 50 ml. of glacial acetic acid was diazotized as in the preceding experiment. The mixture was stirred for 10 min. after addition and then added to a solution of copper (I) bromide[55] at 5°. A brown complex formed which was destroyed by heating the mixture to 80°. Dilution with water followed by filtration produced crude material which was dissolved in benzene and chromatographed on alumina. Evaporation of the eluate followed by four recrystallizations from glacial acetic acid yielded 1.2 g. (17%) of product, m.p. 195-197°. A mixture melting point with material from Run I melted 196-198°. Comparison of their infrared spectra served as an additional check.

2,8-Dibromo-3,7-dinitrodibenzo-p-dioxin

To a stirred solution of 50 ml. of concentrated nitric acid and 30 ml. of concentrated sulfuric acid was slowly added 1.5 g. (0.0044 mole) of 2,8-dibromodibenzo-p-dioxin at room temperature. Stirring was continued for 20 min. at room temperature, the temperature raised to 60°, and then allowed to cool. Dilution of the reaction mixture with water, followed by filtration, produced 1.5 g. of crude material. Four

recrystallizations of this material from glacial acetic acid yielded 0.5 g. (26%) of yellow needles, m.p. 276-278°.

Anal. Calcd. for $C_{12}H_4O_6N_2Br_2$: N, 6.48. Found: N, 6.51, 6.38.

2-Bromo-7,X-dinitrodibenzo-p-dioxin

To a solution of 50 ml. of concentrated nitric acid at ice-bath temperature was slowly added 1.3 g. (0.005 mole) of 2-bromodibenzo-p-dioxin. The yellow mixture was allowed to warm to room temperature, stirred for 10 hr., diluted with water, and filtered. Three recrystallizations of the crude material from ethanol produced 0.5 g. (28%) of yellow needles, m.p. 190-192°.

Anal. Calcd. for $C_{12}H_5O_6N_2Br$: N, 8.00. Found: N, 8.07, 8.11.

2,X-Dibromo-7-nitrodibenzo-p-dioxin

A solution of 2.7 g. (0.011 mole) of 2-nitrodibenzo-p-dioxin, 8 g. (0.05 mole) of bromine, and 50 ml. of glacial acetic acid was stirred and refluxed for 5.5 hr. The reaction mixture was diluted with a sodium bisulfite solution and filtered. Extraction of the crude material left a residue which was recrystallized three times from glacial acetic acid

to yield a small quantity of yellow crystalline material melting 217-220°. This range could not be altered even when other solvent systems were tried such as petroleum ether (b.p. 60-70°)-benzene. From a previous experiment (see 2-Bromo-7-nitrodibenzo-p-dioxin. Run I), it is assumed that some 2-bromo-7-nitrodibenzo-p-dioxin is present. The infrared spectrum was of no help in determining the impurity.

Anal. Calcd. for $C_{12}H_5O_4NBr_2$: Br, 41.45. Found: Br, 40.45, 40.69.

2-Amino-X-bromodibenzo-p-dioxin

A solution of 2 g. (0.01 mole) of 2-aminodibenzo-p-dioxin, 3.6 g. (0.02 mole) of bromine, and 100 ml. of carbon tetrachloride was stirred for 2.5 hr. at room temperature. The green solution was washed with aqueous sodium bisulfite and then dilute potassium hydroxide. Evaporation of the carbon tetrachloride layer followed by two recrystallizations of the residue from ethanol-water resulted in the isolation of 0.8 g. (28%) of fine, pink needles, m.p. 152-154°. The infrared spectrum has a sharp band at 13.3μ, indicating that both groups are in one ring. However, there was no simple way of determining the position of the bromine atom.

Anal. Calcd. for $C_{12}H_8O_2NBr$: Br, 28.77. Found: Br, 29.33, 29.37.

2,7-Diacetamidodibenzo-p-dioxin. Run I

A Beckmann rearrangement was run on 1.7 g. (0.006 mole) of 2,7-diacetyldibenzo-p-dioxin dioxime using 4.2 g. (0.02 mole) of phosphorous (V) chloride in 150 ml. of sodium dried benzene. During the slow addition of phosphorous (V) chloride, a yellow color developed. After addition, the mixture was stirred for 18 hr. at room temperature, hydrolyzed with a dilute sodium carbonate solution, and a yellow solid filtered from the benzene layer. Two recrystallizations of this solid from acetic acid-water produced 0.8 g. (47%) of tan needles, m.p. 354-356° dec.

Anal. Calcd. for $C_{16}H_{14}O_4N_2$: N, 9.40. Found: N, 8.88, 8.84.

Run II

A mixture of 1 g. (0.005 mole) of 2,7-diaminodibenzo-p-dioxin and 30 ml. of benzene was refluxed while 2 g. (0.02 mole) of acetic anhydride was slowly added. Refluxing was continued for 0.5 hr. at which time the mixture was cooled and filtered. The crude material, filtered from the benzene layer, was recrystallized twice from glacial acetic acid to yield 1 g. (66%) of tan needles, m.p. 356-357° dec. A mixture

melting point of this material with that obtained from Run I melted 354-356° dec.

2-Nitrodibenzo-p-dioxin

This compound had been prepared earlier by Tomita in unspecified yield with only general directions available in the abstracts.[32]

A solution of 18.4 g. (0.1 mole) of dibenzo-p-dioxin in 80 ml. of glacial acetic acid was cooled with an ice-bath until a slurry was formed. Then 40 ml. of concentrated nitric acid was slowly added and the stirring at ice-bath temperature continued for 0.5 hr. At that time, the reaction mixture was diluted with water, filtered, and the crude product recrystallized once from ethanol to yield 21.5 g. (94%) of yellow needles, m.p. 147-149° (lit. value 141°[32]).

2-Aminodibenzo-p-dioxin

This compound was reported by Tomita in unspecified yield with no directions available in the abstracts.[32]

To a hot solution of 21.5 g. (0.094 mole) of 2-nitrodibenzo-p-dioxin in glacial acetic acid was slowly added a solution of 80 g. (0.42 mole) of tin (II) chloride in 50 ml. of concentrated hydrochloric acid. An exothermic reaction

took place and the yellow color disappeared. The reaction mixture was cooled, made strongly basic with concentrated potassium hydroxide and filtered. One recrystallization of the crude amine from ethanol-water produced 16 g. (85%) of white needles, m.p. 133.5-135.5° (lit. value 157°[32]).

2-Acetamidodibenzo-p-dioxin

To a solution of 0.3 g. (0.0015 mole) of 2-aminodibenzo-p-dioxin in 10 ml. of dry benzene at reflux temperature was slowly added 0.5 g. (0.005 mole) of acetic anhydride. After refluxing the solution for 0.5 hr., the benzene was removed under reduced pressure and the residue recrystallized three times from ethanol-water to yield 0.2 g. (55%) of white needles, m.p. 184-186°.

Anal. Calcd. for $C_{14}H_{11}O_3N$: N, 5.54. Found: N, 5.50, 5.52.

2,7-Dinitrodibenzo-p-dioxin

Although reported by Tomita, no specific directions or percent yield were given for the preparation of this compound.[32]

To 330 ml. of concentrated nitric acid at ice-bath temperature was slowly added, with stirring, 18.4 g. (0.1

mole) of dibenzo-p-dioxin. The temperature was then raised to 90° over a period of 45 min. Cooling, diluting with water, and filtering the reaction mixture yielded, after two recrystallizations of the crude material from pyridine, 11 g. (30%) of yellow needles melting 270-273° (lit. value 256°[32]).

2,7-Diaminodibenzo-p-dioxin

The preparation of this compound has been reported by Tomita in unspecified yield with no directions available in the abstracts.[32]

To a hot mixture of 4 g. (0.015 mole) of 2,7-dinitrodibenzo-p-dioxin in 25 ml. of glacial acetic acid was slowly added a solution of 30 g. (0.16 mole) of anhydrous tin (II) chloride in 50 ml. of concentrated hydrochloric acid. The mixture was boiled for 15 min. to assure complete reduction, cooled, and made strongly basic with a concentrated potassium hydroxide solution. Filtration of this mixture followed by recrystallization of the crude material from ethanol-pyridine-water produced 2.2 g. (67%) of white plates, m.p. 264-266° dec. (lit. value 249°[32]).

2,3,7-Trinitrodibenzo-p-dioxin

The preparation of this compound has been reported by Tomita in unspecified yield with only general directions available in the abstracts.[32]

To a solution of 80 ml. of concentrated nitric acid and 20 ml. of fuming nitric acid at 40° was slowly added 3 g. (0.016 mole) of dibenzo-p-dioxin. The temperature was raised to 90° and held there until a clear solution resulted. Dilution with water after cooling, followed by filtration, produced 2.8 g. of crude material which, after dissolving in benzene and chromatographing on alumina, was recrystallized twice from glacial acetic acid to yield 1.6 g. (31%) of yellow needles melting 223-226° (lit. value 215-217°[32]).

Using the same conditions, 2,7-dinitrodibenzo-p-dioxin also yielded 2,3,7-trinitrodibenzo-p-dioxin.

2,3,7,8-Tetranitrodibenzo-p-dioxin. Run I

A solution consisting of 150 ml. of concentrated nitric acid and 100 ml. of concentrated sulfuric acid was cooled to ice-bath temperature while 9.2 g. (0.05 mole) of dibenzo-p-dioxin was added in small portions. After addition, the temperature was slowly raised to 90° over a period of 1 hr. and then allowed to cool. Dilution with water, filtration,

one recrystallization of the crude material from pyridine, and two recrystallizations from acetic anhydride produced 3.1 g. (17%) of red-brown needles, m.p. 334-335° dec.

The same product was obtained from the nitration of 2,7- and 2,3,7-trinitrodibenzo-p-dioxin.

Anal. Calcd. for $C_{12}H_4O_{10}N_4$: N, 15.38. Found: N, 14.79, 14.66.

Run II

A mixture of 1.7 g. (0.006 mole) of 2,7-dinitrodibenzo-p-dioxin, 50 ml. of concentrated nitric acid, and 50 ml. of fuming nitric acid was slowly warmed to 60° over a period of 2 hr. Dilution of the reaction mixture with water followed by filtration produced 1.9 g. of crude material which was recrystallized once from pyridine and three times from acetic anhydride to yield 0.4 g. (18%) of red-brown needles melting 330-333° dec. A mixture melting point with material from Run I showed no depression.

1,1'-Bis(dibenzo-p-dioxin)

A mixture consisting of 4 g. (0.015 mole) of 1-iododibenzo-p-dioxin and 4 g. of copper bronze was heated in an

oil-bath at 250° for 5 hr.[56] After cooling, the reaction mixture was pulverized, extracted with hot benzene, and filtered. Concentration of the benzene followed by dilution with ethanol produced 0.9 g. of product, melting 215-218°. Another recrystallization from ethanol-benzene yielded 0.6 g. (22%) of white plates, m.p. 217-219°.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.69; H, 3.82. Found: C, 78.36, 78.50; H, 4.24, 4.28.

2,2'-Bis(dibenzo-p-dioxin)

A mixture consisting of 4 g. (0.015 mole) of 2-iododibenzo-p-dioxin and 5 g. of copper bronze was heated at 240-250° for 4 hr.[56] After cooling, the reaction mixture was pulverized, extracted with hot benzene, and chromatographed on alumina. The eluate was concentrated and then diluted with ethanol to produce 0.7 g. of material, melting 225-230°. One further recrystallization from glacial acetic acid yielded 0.6 g. (22%) of white plates melting 227-230°.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.69; H, 3.82. Found: C, 78.40, 78.49; H, 4.08, 4.07.

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[56] D. A. Shirley, "Preparation of Organic Intermediates", John Wiley and Sons, Inc., New York, N. Y., 1951, p. 122.

2-Phenyldibenzo-p-dioxin

Nitrous fumes[57] were slowly bubbled through a solution consisting of 4 g. (0.016 mole) of 2-acetamidodibenzo-p-dioxin, 130 ml. of glacial acetic acid, and 20 ml. of acetic anhydride at 10° for 2.5 hr.[58] The yellow-green solution was poured into a liter of ice water and a bright yellow solid filtered off. This solid was air dried and then stirred for 8 hr. with 200 ml. of dry benzene. After 8 hr. at room temperature, the solution was warmed for 1 hr. and the bulk of the benzene distilled off. The concentrated benzene solution was chromatographed on alumina followed by evaporation of the eluate. Two recrystallizations of the residue from ethanol produced 0.7 g. (16%) of white plates, m.p. 108-110°. The infrared spectrum had bands indicative of 1,2,4 trisubstitution, 1,2-disubstitution, and mono substitution.

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.08; H, 4.61. Found: C, 82.64, 82.71; H, 4.64, 4.72.

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[57] J. Haworth and D. Hey, J. Chem. Soc., 361 (1940).

[58] W. E. Bachmann and R. A. Hoffman in R. Adams, "Organic Reactions", Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 249.

1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethanol

An excess of benzylmagnesium chloride was added to 5.76 g. (0.02 mole) of 2-benzoyldibenzo-p-dioxin in 100 ml. of diethyl ether over a period of 15 min. After addition, which caused gentle reflux, the reaction mixture was refluxed for another 1.75 hr. and then hydrolyzed with ice-ammonium chloride. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to produce 6 g. of crude material which after three recrystallizations from ethanol-water yielded 4.5 g. (60%) of white needles, m.p. 141-142°.

Anal. Calcd. for $C_{26}H_{20}O_3$: C, 82.10; H, 5.26. Found: C, 82.12, 82.15; H, 5.22, 5.48.

1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethene

A mixture of 3.5 g. (0.009 mole) of 1-(2-dibenzo-p-dioxinyl)-1,2-diphenylethanol, 45 ml. of benzene, and 15 ml. of Lucas reagent was refluxed for 2 hr. The benzene layer was separated and washed with dilute sodium carbonate solution. Evaporation of the benzene produced an oil which solidified when boiled with petroleum ether (b.p. 60-70°). Three recrystallizations of this material from ethanol-water yielded 1.1 g. (33%) of white needles, m.p. 123-125°.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.18; H, 4.97. Found: C, 86.18, 86.19; H, 4.83, 5.08.

2-Acetyldibenzo-p-dioxin

A mixture of 4.6 g. (0.025 mole) of dibenzo-p-dioxin, 11 g. (0.08 mole) of aluminum chloride, and 50 ml. of carbon disulfide was stirred at room temperature while 1.97 g. (0.025 mole) of acetyl chloride was added over a period of 5 min. The reaction mixture was stirred for 20 min. more, hydrolyzed with ice-hydrochloric acid, washed with sodium carbonate solution, and the carbon disulfide layer distilled. Three recrystallizations of the carbon disulfide residue from methanol-water produced 0.3 g. (5%) of white crystals melting 131-133.5°. An iodoform test on this material was positive producing dibenzo-p-dioxin-2-carboxylic acid which was identified. The infrared spectrum was also compatible with this structure.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.40; H, 4.43. Found: C, 73.86, 73.74; H, 4.19, 4.22.

2-Acetyldibenzo-p-dioxin oxime

A small amount of 2-acetyldibenzo-p-dioxin was mixed with 10 ml. of pyridine, 5 ml. of absolute ethanol, and an excess of

hydroxylamine hydrochloride.[59] After refluxing the reaction mixture for 1 hr., it was diluted with water and filtered. One recrystallization of the material from ethanol produced the pure product as tan needles, m.p. 174-176°.

Anal. Calcd. for $C_{14}H_{11}O_3N$: N, 5.82. Found: N, 5.75, 5.89.

2,7-Diacetyldibenzo-p-dioxin

This compound has been prepared in unspecified yield by Tomita using acetyl chloride with carbon disulfide as the solvent.[21]

A mixture consisting of 4.6 g. (0.025 mole) of dibenzo-p-dioxin, 26 g. (0.2 mole) of aluminum chloride, and 50 ml. of carbon disulfide was stirred at room temperature while 7 g. (0.06 mole) of acetic anhydride was slowly added. A vigorous reaction ensued, and it was refluxed for 2 hr. longer after addition had been completed. After hydrolysis with ice-hydrochloric acid, a white solid was filtered off and recrystallized twice from pyridine to yield 3.9 g. (55%) of white needles melting over the range of 255-260° (lit. value 248°[21]). Recrystallization of the product from glacial acetic acid did

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[59] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds", John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202.

not alter the melting point range. The infrared spectrum was in agreement with the given structure. Preparation of the dioxime in the following experiment produced only one product which was readily purified.

2,7-Diacetyldibenzo-p-dioxin dioxime

This compound has been prepared by Tomita.[21]

A mixture consisting of 3 g. (0.013 mole) of 2,7-diacetyldibenzo-p-dioxin, 3 g. (0.04 mole) of hydroxylamine hydrochloride, 35 ml. of pyridine, and 15 ml. of absolute ethanol was refluxed for 6 hr.[59] The product crystallized directly from the solution and was recrystallized once more from pyridine-ethanol to yield 2.9 g. (75%) of tan needles, m.p. 274-275° dec. (lit. value 265°[21]).

2-Benzoyldibenzo-p-dioxin. Run I

A mixture consisting of 4.6 g. (0.025 mole) of dibenzo-p-dioxin, 5 g. (0.038 mole) of aluminum chloride, 3.7 g. (0.025 mole) of benzoyl chloride, and 100 ml. of carbon disulfide was refluxed for 7 hr. The reaction mixture was hydrolyzed with ice-hydrochloric acid, washed with a dilute sodium carbonate solution, and dried over anhydrous sodium sulfate. Evaporation of the carbon disulfide produced 3.2 g. (44%) of white plates

melting 140-145°. Recrystallizing from three different solvents plus chromatographing on alumina, using benzene as the solvent, failed to alter the melting point range. The structure was in agreement with infrared data and previous knowledge of electrophilic substitution.

Anal. Calcd. for $C_{19}H_{12}O_3$: C, 79.10; H, 4.18. Found: C, 79.21, 79.16; H, 4.10, 4.36.

Run II

To a stirred mixture consisting of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 22 g. (0.16 mole) of aluminum chloride, and 50 ml. of chlorobenzene at 10° was slowly added 7 g. (0.05 mole) of benzoyl chloride. Stirring was continued for 50 min. at 10° and then the reaction mixture was hydrolyzed with ice-hydrochloric acid. Distillation of the chlorobenzene layer and recrystallization of the residue from glacial acetic acid produced 12 g. (83%) of product melting 140-145°.

Another run, using a 3:1 excess of benzoyl chloride, produced only 2-benzoyldibenzo-p-dioxin.

2-Benzoyldibenzo-p-dioxin oxime

A solution consisting of 0.4 g. of 2-benzoyldibenzo-p-dioxin, an excess of hydroxylamine hydrochloride, 10 ml. of

pyridine, and 5 ml. of absolute ethanol was refluxed for 1.5 hr.[59] The product was forced out with water and recrystallized once from ethanol to yield tan needles, m.p. 215° dec.

Anal. Calcd. for $C_{19}H_{13}O_3N$: N, 4.63. Found: N, 4.54, 4.68.

2,7-Dibenzoyldibenzo-p-dioxin

To a well stirred mixture of 4.6 g. (0.075 mole) of dibenzo-p-dioxin, 17 g. (0.13 mole) of aluminum chloride, and 100 ml. of carbon disulfide was added 8.4 g. (0.05 mole) of benzoyl chloride. The reaction mixture was refluxed for 5 hr., hydrolyzed with ice-hydrochloric acid, washed with a dilute sodium carbonate solution, and the insoluble solid filtered off. Four recrystallizations of this material from pyridine produced 3.6 g. (37%) of silver plates, m.p. 244-246°. Previous knowledge of electrophilic disubstitution (i.e., 2,7-diacetyldibenzo-p-dioxin) and infrared data are consistent with the given structure.

Anal. Calcd. for $C_{26}H_{16}O_4$: C, 79.55; H, 4.09. Found: C, 79.44, 79.33; H, 4.32, 4.37.

2,7-Dibenzoyldibenzo-p-dioxin dioxime

A mixture of 1 g. of 2,7-dibenzoyldibenzo-p-dioxin, an excess of hydroxylamine hydrochloride, 20 ml. of pyridine, and

10 ml. of absolute ethanol was refluxed 1.5 hr.[59] Dilution of the reaction mixture with water followed by two recrystallizations of the precipitate from ethanol-pyridine yielded the dioxime as tan needles, m.p. 253.5° dec.

Anal. Calcd. for $C_{26}H_{18}O_4N_2$: N, 6.64. Found: N, 6.56, 6.79.

Dibenzo-p-dioxin-1-carboxylic acid

This compound has been prepared in 10% yield using methyllithium in diethyl ether and subsequent carbonation.[15]

To a stirred solution of 9.2 g. (0.05 mole) of dibenzo-p-dioxin in 70 ml. of tetrahydrofuran was added 0.0514 mole of methyllithium in 60 ml. of diethyl ether over a period of 20 min. The temperature rose to 42° and was kept there for 0.5 hr. Filtration of the reaction mixture through glass wool into a Dry Ice-ether slurry produced 5 g. of crude acid. This was recrystallized twice from benzene to give 3 g. (26%) of product, m.p. 216-218° (lit. value 210°[15]).

Phenyllithium may also be used to mono metalate in better yield than methyllithium, but some di-metalated product was also formed which was troublesome to eliminate.

Dibenzo-p-dioxin-1,X-dicarboxylic acid

Preparation of this compound has been reported using n-butyllithium in refluxing diethyl ether to produce a 27% yield of two dicarboxy acids subsequent to carbonation. Separation of the two isomeric acids was accomplished through esterification. Subsequent hydrolysis yielded two pure acids melting 297-298° and greater than 335°.

To a stirred solution of 9.2 g. (0.05 mole) of dibenzo-p-dioxin in 100 ml. of tetrahydrofuran was added 0.11 mole of phenyllithium in 100 ml. of diethyl ether over a period of 15 min. The temperature rose to 42° during addition, but cooled to room temperature during the ensuing hour of stirring. Carbonation by the previously mentioned method produced 10.7 g. of crude acid. Since the acid was very insoluble, it was extracted with benzene and ethanol. A small portion was recrystallized from glacial acetic acid to give a white powder melting 378-380° dec. The amount of acid melting greater than 330° was 3.3 g. (24%).

From experience gained from later metalation reactions, it was found that the yield of di-metalated product was improved by maintaining a temperature of 42° for 45 min.

Diethyl ether may also be used for di-metalation with phenyllithium, but only a 2.1% yield of the acid was obtained subsequent to carbonation.

Dibenzo-p-dioxin-2-carboxylic acid

The preparation of this compound has been accomplished by ring closure of the methyl ester of 4-carboxy-2,2'-dihydroxydiphenyl ether.[26]

To 0.5 g. (0.021 g. atom) of magnesium in 20 ml. of diethyl ether was added 4 g. (0.015 mole) of 2-bromodibenzo-p-dioxin in 20 ml. of diethyl ether. A small quantity of iodine and ethyl bromide was used to catalyze the reaction, after which it was refluxed for 2 hr. and carbonated in the aforementioned manner. The reaction mixture was hydrolyzed with saturated ammonium chloride solution. Three recrystallizations of the acid from glacial acetic acid yielded 1 g. (29%) of white prisms, m.p. 245-247° (lit. value 239-240°[26]).

Dibenzo-p-dioxin-1-boronic acid

To a solution of 18.4 g. (0.1 mole) of dibenzo-p-dioxin in 100 ml. of tetrahydrofuran was added 0.11 mole of phenyllithium in 100 ml. of diethyl ether. The resulting mixture was stirred for 1 hr. at 42° and then added to 100 ml. (0.4 mole) of tri-n-butylborate in 300 ml. of diethyl ether at a -70° over a period of 30 min. An hour of stirring was followed by hydrolysis of the reaction mixture with 10% sulfuric acid and extraction of the boronic acid with dilute base. Removal

of the product from the crude acid by extracting it with benzene produced 5 g. (21%) of material melting 296-304°.

Anal. Calcd. for $C_{12}H_9O_4B$: C, 63.16; H, 3.94; B, 4.33; neut. equiv., 228. Found: C, 63.35; H, 4.09, 3.91; B, 4.94, 4.65; neut. equiv., 232.

Dibenzo-p-dioxin-1,X-diboronic acid

To a solution of 18.4 g. (0.1 mole) of dibenzo-p-dioxin in 170 ml. of tetrahydrofuran was added 0.22 mole of phenyllithium in 200 ml. of diethyl ether. The resulting solution was stirred for 1 hr. at 42° and then added over a period of 1 hr. to 100 ml. (0.4 mole) of tri-n-butylborate in 300 ml. of diethyl ether at a -70°. Hydrolysis of the mixture with 10% sulfuric acid followed by extraction of the acid with dilute base produced, after acidification, crude acid which was recrystallized from ethanol-acetone-water to yield 6.5 g. (24%) of white material, m.p. greater than 430°.

Anal. Calcd. for $C_{12}H_{10}O_6B_2$: C, 52.94; H, 3.67; B, 7.94; neut. equiv., 136. Found: C, 52.63; H, 4.15; B, 7.61; neut. equiv., 142.

Halogen-metal interconversion of 2-bromodibenzo-p-dioxin (attempted). Run I

To a stirred solution of 2 g. (0.004 mole) of 2-bromodibenzo-p-dioxin in 20 ml. of diethyl ether at -10° was added 4 ml. of 1.05 N n-butyllithium over a period of 5 min. The resulting mixture was stirred for 70 min. while the temperature was gradually raised to 10°. Termination of the reaction by carbonation followed by the usual work-up produced no acidic material and a 50% recovery of pure starting material.

Run II

The reaction was run at room temperature for 1 hr. employing the preceding quantities and then terminated by carbonation. No acidic material was isolated upon work-up, but 55% of pure starting material was recovered.

Run III

Six milliliters of 1.05 N n-butyllithium was added to a solution of 2 g. (0.004 mole) of 2-bromodibenzo-p-dioxin in 20 ml. of diethyl ether and stirred for 1 hr. at room temperature. Termination by carbonation and subsequent work-up

produced no acidic material. There was a 25% recovery of pure starting material.

Mercuration of dibenzo-p-dioxin (attempted). Run I

A mixture of 4.6 g. (0.025 mole) of dibenzo-p-dioxin, 11.3 g. (0.025 mole) of mercury (II) acetate, and 100 ml. of glacial acetic acid was stirred at room temperature for 8.5 hr. At that time, 0.1 mole of aqueous sodium chloride was added and stirring was continued for another 0.5 hr. Filtration of the diluted reaction mixture produced a near quantitative recovery of starting material.

Run II

In this experiment, the reaction mixture was kept at 50° for 15.5 hr. and then worked up as in Run I. Besides starting material, 0.2 g. of material, m.p. 327-329°, was obtained after two recrystallizations from glacial acetic acid. No analysis was run on this material, but qualitative tests showed it to contain mercury and chlorine.

Run III

During this reaction, the temperature was maintained at 80° for 10 hr. The usual work-up produced 1.5 g. of starting

material and 8 g. of insoluble material which contained chlorine and mercury, but could not be purified.

Run IV

A mixture of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 33 g. (0.105 mole) of mercury (II) acetate, and 200 ml. of glacial acetic acid was stirred and refluxed for 7.75 hr. An excess of aqueous sodium chloride was added to the hot solution, and the precipitate which formed was filtered off while the mixture was still hot. Cooling of the mother liquor produced 2.2 g. of material which was recrystallized twice from ethanol to yield 0.3 g. of white crystals, m.p. 210-212°. This material contained mercury and chlorine and analyzed correctly for a mono-mercurated dibenzo-p-dioxin, but it was not chemically identified. Subsequent reactions failed to produce a workable quantity of this material.

Anal. Calcd. for $C_{12}H_7O_2HgCl$: C, 34.40; H, 1.67. Found: C, 33.75, 33.62; H, 1.78, 1.71

The insoluble material filtered from the hot solution could not be purified.

2,2'-Azodibenzo-p-dioxin

A mixture consisting of 5 g. (0.022 mole) of 2-nitrodibenzo-p-dioxin, 70 ml. of methanol, 3.6 g. (0.05 mole) of zinc

dust, 4 g. (0.1 mole) of sodium hydroxide, and 50 ml. of water was stirred and refluxed for 23 hr.[60] The reaction mixture was diluted with water, filtered, and the precipitate washed with dilute hydrochloric acid. Two recrystallizations of the crude material from pyridine and twice from ethanol-benzene produced 0.2 g. (4%) of yellow crystals, m.p. 239-241°.

Anal. Calcd. for $C_{24}H_{14}O_4N_2$: N, 7.18. Found: N, 7.05, 7.06.

Dibenzo-p-dioxin-X,Y-disulfonyl chloride

A solution of 4.6 g. (0.025 mole) of dibenzo-p-dioxin in 50 ml. of chloroform was cooled to ice-bath temperature while 20 g. (0.21 mole) of chlorosulfonic acid was added over a period of 10 min.[61] The resulting solution was stirred for 2 hr. at 40-50° and then hydrolyzed with ice water. An insoluble material formed and was removed by filtration. Three recrystallizations of this material from chloroform yielded 0.3 g. (3%) of clear, granular crystals, m.p. 227.5-230°. A halogen test was positive and the infrared spectrum showed the characteristic sulfone band.

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[60] E. C. Horning, "Organic Syntheses", Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 103.

[61] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds", John Wiley and Sons, Inc., New York, N. Y., 1948, p. 189.

Anal. Calcd. for $C_{12}H_6O_6S_2Cl_2$: S, 16.84. Found: S, 17.07, 16.96.

Coupling of p-nitrobenzenediazonium chloride with dibenzo-p-dioxin (attempted)

To 6 ml. of water and 6 ml. of concentrated hydrochloric acid was added 2.8 g. (0.02 mole) of p-nitroaniline. The mixture was warmed to dissolve the salt and then cooled to 0° by addition of ice. Six milliliters of concentrated hydrochloric acid was added and the amine diazotized by the slow addition of 1.6 g. (0.022 mole) of sodium nitrite in 6 ml. of water keeping the temperature at 0-5° by addition of ice. After 10 min., the mixture was diluted with ice. Urea was then added to destroy the excess nitrous acid. The cold diazonium salt solution was filtered and added in one operation to a stirred solution of 3.6 g (0.02 mole) of dibenzo-p-dioxin in 100 ml. of glacial acetic acid maintained at 20°. The temperature dropped to 16° on addition of the diazonium salt. The white reaction mixture was stirred for 0.5 hr. and then 32 g. of anhydrous sodium acetate was added, keeping the temperature below 30°. Stirring was continued for 26 hr. at which time the solution was brown. Dilution with water followed by filtration produced 4.7 g. of crude material which upon purification was found to be starting material.

Coupling of 2,4-dinitrobenzenediazonium chloride with dibenzo-p-dioxin (attempted)

The 2,4-dinitroaniline was diazotized by adding a cold mixture of 3.6 g. (0.02 mole) of the amine in 40 ml. of glacial acetic acid to 11 ml. of concentrated sulfuric acid containing 1.6 g. (0.022 mole) of sodium nitrite at 10-15°. The mixture was allowed to stand 0.5 hr. before urea and 30 g. of ice were added. This mixture was filtered directly into a stirred solution of 4.6 g. (0.025 mole) of dibenzo-p-dioxin, 20 ml. of 10% sodium hydroxide, and 175 ml. of ethanol at room temperature. Addition took 45 min. and stirring was continued for another 5 hr. The orange reaction mixture was diluted with water and filtered to produce 3.5 g. of starting material after purification.

Cleavage of dibenzo-p-dioxin with hydriodic acid (attempted). Run I

A mixture of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 6.4 g. (0.05 mole) of 47% hydriodic acid, and 25 ml. of glacial acetic acid was heated and stirred at 90° for 1.5 hr. Dilution with aqueous sodium bisulfite followed by filtration produced 9 g. of crude dibenzo-p-dioxin.

Run II

A mixture of 9.2 g. (0.05 mole) of dibenzo-p-dioxin, 6.4 g. (0.05 mole) of 47% hydriodic acid, and 25 ml. of glacial acetic acid was refluxed and stirred for 4 hr. Dilution with aqueous sodium sulfite followed by filtration produced a near quantitative recovery of starting material.

DISCUSSION

General Elucidation of Structure

By intermolecular ring closure

The basic ingredient for this reaction is a substituted o-halophenol. Since strong alkali and elevated temperatures are used to effect the condensation, the number and nature of stable substituents possible on the o-halophenol are severely limited. This method is particularly useful for the preparation of symmetrical molecules; attempts to prepare unsymmetrical products give rise to complex separation problems. Even during symmetrical condensation, there is still the possibility of obtaining unsymmetrical substituted dibenzo-p-dioxins provided there exists a chance of removing functional groups during the reaction. However, since there is no known example of rearrangement, once a product is formed and analyzed, its structure is unambiguous provided the starting material was properly characterized.

By intramolecular ring closure

Although unambiguous, this reaction is limited by the availability of substituted 2,2'-dihydroxydiphenyl ethers.

In essentially all cases, the material to be used for the closure must be synthesized beforehand in anything but favorable yield. Also, not all substituents are stable under the conditions employed in the two steps necessary to reach the final product. Two distinct advantages over the intermolecular reaction are the possibility of preparing unsymmetrical derivatives and the milder reaction conditions employed.

By ring cleavage

Due to the complex diphenyl ether derivatives obtained, this method is of little practical importance. This stems from the fact that an o-hydroxydiphenyl ether derivative is obtained whether the cleavage is effected by a metal, an acid, or other known ring cleaving agents. Also, the substituent or substituents present on the nucleus must be of a nature whereby they will not react with the cleaving agent or the cleaved product in any way. Otherwise the whole purpose of the reaction is defeated.

By direct nuclear substitution

All available evidence indicates that only the 2, 3, 7, and 8 positions are susceptible to electrophilic substitution. In the case of disubstitution, the second equivalent of

electrophile has a choice of attacking the 3, 7, or 8 position. With the possible exception of bromination,[29] the point of entrance of the second group can usually be predicted using the general rules of ring activation. When the possibility of entering the 7 or the 8 position exists, proper choice of reaction conditions may yield a predominance of one isomer. Final identification is based on relating the above compounds by chemical and physical means to derivatives possessing definitive structures.

By indirect nuclear substitution

Starting from a known compound, it is often possible to use standard reactions to modify a substituent and obtain a new derivative which needs no further identification. A few examples are Grignard reactions, diazotization reactions, and metalation reactions. Metalation is unique in the respect that the substituent modified is hydrogen. Therefore, only after the position of metalation is determined may the organometallic compound be used as an intermediate to produce derivatives possessing unambiguous structures.

By physical means

Two common methods used in identification procedures are mixture melting points with an authentic specimen and study or

comparison of infrared spectra. The infrared spectra are of particular importance in determining relative positions when only 1 or 2 nucleophilic attacks have taken place on a molecule such as dibenzo-p-dioxin. Considerable importance may be attached to a particular spectrum if a suitable reference spectrum is available for comparison, allowances being made for band shifts occasioned by electron withdrawing or electron donating character of the substituents present.

Structural Assignments of the Experimental Section

1 Position

Substitution at this position was readily attainable through metalation of the parent heterocycle with an organolithium compound either in diethyl ether or tetrahydrofuran. The new organolithium derivative formed was then used as an intermediate. Since the product obtained from the organolithium compound was different from the only other mono substituted isomer possible with dibenzo-p-dioxin, the structure was readily established. Additional support was added by the general knowledge that organolithium compounds are known to metalate ortho to hetero atoms under normal

conditions[62], i.e. in diethyl ether at room temperature or reflux.

2 Position

Mono electrophilic attacks seem to take place exclusively at this position. The identity of 2-acetyldibenzo-p-dioxin was proved by converting it to dibenzo-p-dioxin-2-carboxylic acid. From the preceding evidence plus comparison of infrared spectra, the structure of 2-benzoyldibenzo-p-dioxin was assigned. Production of 2-iododibenzo-p-dioxin from 2-amino-dibenzo-p-dioxin established the structure of the material obtained when dibenzo-p-dioxin was mono iodinated with iodine monochloride.

2,3 Positions

A compound considered earlier to be the 2,7-dibromodi-benzo-p-dioxin[14] has been shown to be another isomer. This isomer may well be 2,3-dibromodibenzo-p-dioxin since its infrared spectrum, run in carbon disulfide, had a strong 1,2 disubstitution band at 13.3μ, indicating that one ring was

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[62] H. Gilman and J. W. Morton, Jr. in R. Adams, "Organic Reactions", Vol. 8, John Wiley and Sons, Inc., New York, N. Y., 1954.

unsubstituted. Chemical evidence presented in the previously mentioned paper[14] is also consistent with the proposed structure.

2,7 Positions

Nitration of 2-bromodibenzo-p-dioxin or bromination of 2-nitrodibenzo-p-dioxin produced the same product. The identity of this compound was established by reducing it to the amine and then forming the dibromo compound via a diazotization reaction. This dibromo compound proved to be the same as the dibromo compound obtained via the diazotization of 2,7-diaminodibenzo-p-dioxin, a known compound.[32] Also helping to tie all these compounds together was the Beckmann rearrangement carried out on the dioxime of 2,7-diacetyldibenzo-p-dioxin. This reaction produced a diacetamido compound identical with that obtained by acetylating 2,7-diaminodibenzo-p-dioxin. A large discrepancy between the reported melting points of 2,7-dinitrodibenzo-p-dioxin, 2,7-diaminodibenzo-p-dioxin[32], and the melting points, which were higher, obtained in the Experimental section for the same compounds made the last sequence of reactions imperative.

1,6(9) Positions

Metalation of dibenzo-p-dioxin with phenyllithium in either diethyl ether or tetrahydrofuran produced only one of three possible disubstituted isomers as contrasted to n-butyllithium which produced a mixture of two of the three possible isomers.[15] These possible isomers were the 1,4; the 1,6; and the 1,9. Since homonuclear di-metalation is less likely than heteronuclear di-metalation, the 1,4 isomer may be ruled out. This leaves the two aforementioned isomers, but does not tell which is the 1,6 and which is the 1,9. There is no simple chemical method to differentiate between the two products. However, symmetry tends to increase the melting point and the higher melting dibasic acid was formed when dibenzo-p-dioxin was metalated with phenyllithium at 42° for 45 min. and then carbonated. Also, phenyllithium is a weaker metalating agent than n-butyllithium and therefore would tend to be more selective in its second attack on dibenzo-p-dioxin. The difficulty encountered in di-metalating diphenyl ether with n-butyllithium in diethyl ether (i.e., 72 hr. at reflux) to obtain 2,2'-dilithiodiphenyl ether[63] may be used as an argument against 1,9 di-metalation in dibenzo-p-dioxin and a good case for 1,6 di-metalation.

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[63] K. Oita and H. Gilman, J. Am. Chem. Soc., 79, 339 (1957).

2,3,7 Positions

2-Nitrodibenzo-p-dioxin may be brominated to yield a dibromonitrodibenzo-p-dioxin. Likewise, 2-bromodibenzo-p-dioxin may be di nitrated. This, from bromination[14] and nitration[32] studies, fairly well limited the substituents to the 2,3,7 positions. Mono bromination of 2-nitrodibenzo-p-dioxin and mono nitration of 2-bromodibenzo-p-dioxin have been shown to yield the same compound. Therefore, only the position of the last group was in question. Working only with infrared data, the assignments of the two compounds in question were believed to be 2,3-dibromo-7-nitrodibenzo-p-dioxin and 2-bromo-3,7-dinitrodibenzo-p-dioxin. Both compounds had a 1,2,4 trisubstitution band at 12.2μ. This was consistent with the band found in the spectrum of 2-nitrodibenzo-p-dioxin at 12.2μ, but not with the band found in the spectrum of 2-bromodibenzo-p-dioxin at 12.4μ. Therefore, one ring must contain the nitro group which was responsible for the band at 12.2μ while the other ring contained the other two groups. Both assignments are theoretically sound when directive effects of the substituents already present are considered.

2,3,7,8 Positions

Exhaustive nitration of dibenzo-p-dioxin or 2,7-dinitrodibenzo-p-dioxin produced a tetranitro derivative which has

been designated 2,3,7,8 because the 2,3,7-trinitro derivative served as an intermediate.[32] Using 2,3,7,8-tetrabromodibenzo-p-dioxin and its infrared spectrum as analogies, the tetrachloro compound was assigned the same configuration. Since tetranitro- and tetrabromodibenzo-p-dioxin were formed directly, it seemed reasonable to assume that dinitration of 2,8-dibromodibenzo-p-dioxin would follow the same course. The derivative obtained in this manner was, therefore, designated as 2,8-dibromo-3,7-dinitrodibenzo-p-dioxin.

Melting Point Discrepancies

A number of known compound prepared in this Laboratory had melting points which were higher than the reported melting points (see Table 1). However, in all instances the compounds reported were shown to be the same as those prepared in this Laboratory, but of inferior quality.

Directive Influence of Substituents

For mono substituted dibenzo-p-dioxins, it is a general rule that electron withdrawing substituents will direct substitution into the other ring, whereas electron donating substituents will direct substitution into the same ring.

Bromination of 2-bromodibenzo-p-dioxin produces the 2,8 derivative along with a compound considered to be the 2,3 derivative, but none of the expected 2,7-dibromo derivative has been isolated.[14,27]

Isopropylation produces the 2,3 derivative and then the 2,3,7,8 derivative. If a bulky alkyl group, such as t-butyl, is in the 2 position, the second t-butyl group goes to the other ring.[20]

Acylation has so far, with the exception of -chloroacetyl chloride, produced only the 2,7 derivative.[21,29] β-Chloroacetyl chloride produces both the 2,7 and the 2,8 derivatives.[22]

Nitration is dissimilar to acylation but like chloroacylation in that both the 2,7 and the 2,8 derivatives are obtained.[32]

From a general consideration of the foregoing evidence, it is felt that proper conditions may well produce directly the 2,7-dibromo and the 2,8-diacyl derivatives in addition to those already reported.

With an electron withdrawing group initially present in the 2 position, the fact that a second substituent can still enter the 8 position leads to the conclusion that the directive influence of the oxygen para to the withdrawing group is scarcely affected under certain conditions.

Attempted Reactions

Mercuration

Mercuration at various temperatures gave at best only a trace of mono-mercurated product which, although analyzed, was never chemically identified. The reaction did not proceed at low temperatures. However at higher temperatures, above 80°, there was formed insoluble mercury (II) derivatives of unknown structures. Numerous attempts to identify these insoluble materials through conversion to be bromo or chloro derivatives met with no success.

Diazo coupling

In connection with compounds to be used in brain tumor studies, a number of attempts were made to couple various aryl diazonium salts with dibenzo-p-dioxin. It was hoped that this reaction might eventually lead to an azo-boronic acid which would be preferentially absorbed in brain tumors. Capture of slow neutrons by the ${}_5B^{10}$ present would then form ${}_5B^{11*}$ which disintegrates to ${}_2He^4$ (α particle) and ${}_3Li^7$, thus treating the tumor *in situ*. However, the electromeric effect of the oxygen atom in dibenzo-p-dioxin was not strong enough to cause coupling. These reactions were attempted after it was known

that some N substituted carbazoles coupled directly with strong diazonium salts such as p-nitrobenzenediazonium chloride.[64]

Hydriodic acid cleavage

Failure to cleave dibenzo-p-dioxin with hydriodic acid under the conditions described in the Experimental section was not surprising since dibenzo-p-dioxin is a very stable diaryl ether, comparable to diphenyl ether, with little or no strain on the oxygen linkage.

Liquid Solution Scintillators

In an attempt to count radioactive particle emanations, many different systems have been tried. Only the scintillation method will be mentioned. This method converts radioactive particle energy into visible or near-ultraviolet photon energy which is converted to electrical energy and then amplified by photomultipliers so the particles may be counted. This sequence starts when a nuclear particle interacts with an aromatic molecule causing an excited state. In returning to the ground state, the molecule liberates energy in the form of a photon.

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[64] H. Gilman and J. B. Honeycutt, Jr., J. Org. Chem., 22, 0000 (1957).

An investigation of liquid solution scintillators found p-terphenyl in toluene[65] and later 2,5-diphenyloxazole in toluene[66] to be very good. Both solutions are now used as standards. The best solute to date is 2-phenyl-5-(p-biphenylyl)-1,3,4-oxadiazole[67], but toluene still is the solvent of choice.

In an attempt to find more efficient scintillating solutes, a number of dibenzo-p-dioxin derivatives were prepared, but these all proved to be rather poor scintillators. Table 2 lists these compounds plus some others of interest. The values are relative to a 3 g./l. solution of 2,5-diphenyloxazole in toluene taken as unity.

Table 2 shows that 2,2'-bis(dibenzofuran) is a poorer scintillator than 2,2'-binaphthyl or 2,2'-bis(dibenzo-p-dioxin). Likewise, it can be seen that the relative pulse height for 1,1'-bis(dibenzo-p-dioxin) is greater than that of 4,4'-bis(dibenzothiophene). A general statement, borne out by the compounds in the table, may be made to the effect that linkage through the ortho position is less beneficial than linkage through the para position in polyphenyl compounds.

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[65] H. Kallman and M. Furst, Nucleonics, 8, No. 3, 32 (1951).

[66] F. N. Hayes, L. C. King, and D. E. Peterson, J. Am. Chem. Soc., 74, 1106 (1952).

[67] F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, Nucleonics, 13, 38 (1955).

Table 2. Evaluation of selected compounds as liquid solution scintillators

Compound	Relative Pulse Height
2,2'-Bis(dibenzofuran)[a]	0.14
6,6'-Dimethoxy-2,2'-bis-(dibenzofuran)[a]	0.46
4,4'-Bis(dibenzothiophene)[a]	0.12
1,1'-Binaphthyl[a]	0.87
2,2'-Binaphthyl[a]	0.25
Phenoxazine[a]	0.12
2,2'-Bis(dibenzo-p-dioxin)[b]	0.59
1,1'-Bis(dibenzo-p-dioxin)[b]	0.15
2-Phenyldibenzo-p-dioxin[b]	0.40
1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethene[b]	0.12
1-(2-Dibenzo-p-dioxinyl)-1,2-diphenylethanol[b]	0.12
Dibenzo-p-dioxin[b]	0.12

[a]From Dr. H. Gilman's Research Group, Iowa State College.

[b]This Thesis.

A striking exception is 1,1'-binaphthyl. No explanation has been given so far for this irregularity.

The two derivatives shown of dibenzo-p-dioxin, which do not have a direct phenyl linkage to the dibenzo-p-dioxin nucleus, are very poor scintillators. From this and the less than 0.12 values of dibenzo-p-dioxin and phenoxazine, the logical step is to attach aromatic nuclei directly to the parent heterocycle. The aforementioned bis compounds and 2-phenyldibenzo-p-dioxin show the increase in relative pulse height when this is done. Beneficial groups, such as dimethylamino and methoxy (i.e., compare 2,2'-bis(dibenzofuran) and 6,6'-dimethoxy-2,2'-bis(dibenzofuran), may also be added to the aromatic nuclei.

Since a phenyl group in the 2 position of dibenzo-p-dioxin showed a large increase, it would be interesting to prepare and test 2-(p-biphenylyl)dibenzo-p-dioxin and perhaps 2,7-diphenyldibenzo-p-dioxin.

Suggested Studies

The identity of the two isomers obtained when dibenzo-p-dioxin was di-metalated with n-butyllithium has not been rigorously established. This problem may well be resolved through physical rather than chemical means.

Chemical verification should be obtained for the structures of 2,(3)-dibromo-7-nitro- and 2-bromo-(3),7-dinitrodibenzo-p-dioxin since only infrared evidence was used as an aid in assignment of structure.

It would also be of interest to carry out a more extensive study on the mercuration and sulfonation of dibenzo-p-dioxin.

There is no logical explanation for the failure of 2-bromodibenzo-p-dioxin to halogen-metal interconvert. A thorough investigation of this reaction might prove worthwhile.

SUMMARY

The chemistry of dibenzo-p-dioxin has been reviewed with emphasis placed on functional groups. A table containing all the reported derivatives of dibenzo-p-dioxin up to this date is included.

Dibenzo-p-dioxin has been found to react in the expected manner when halogenated or benzoylated.

A series of bromo-nitro compounds was made in an effort to study directive effects of various substituents. Mono bromination of 2-nitrodibenzo-p-dioxin and mono nitration of 2-bromodibenzo-p-dioxin both yielded 2-bromo-7-nitrodibenzo-p-dioxin.

Several derivatives of dibenzo-p-dioxin have been made for the specific purpose of testing as scintillating solutes in connection with chemical correlation and scintillator activity. A table containing relative pulse heights for the dibenzo-p-dioxin derivatives tested and some other selected oxygen heterocycles is included.

A mono- and a diboronic acid of dibenzo-p-dioxin have been prepared for use in brain tumor studies.

Improved directions for the mono- and specific directions for the preparation of one of two possible di-metalated isomers were presented.

Unsuccessful attempts were made to obtain a mono-mercurated dibenzo-p-dioxin, to directly couple dibenzo-p-dioxin with a diazonium salt, and to cleave dibenzo-p-dioxin with hydriodic acid.

General methods for the preparation of dibenzo-p-dioxin derivatives have been discussed.

Structural assignments of the new derivatives of dibenzo-p-dioxin prepared were explained.

Melting point discrepancies, attempted reactions, directive influence of substituents, and liquid solution scintillators have been discussed.

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