

of a strong acid because of salt formation. The stability of the unprotected amines toward

chlorosulfonic acid was unexpected.

NEW YORK, N. Y.

RECEIVED FEBRUARY 7, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

## Dibenzofuran. XX. 2,3,7,8-Derivatives<sup>1</sup>

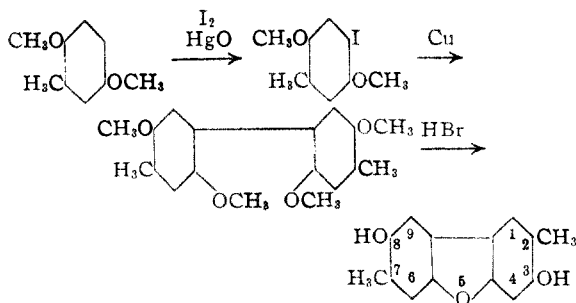
BY HENRY GILMAN, JACK SWISS, H. B. WILLIS AND F. A. YEOMAN

The present work is an extension of studies concerned with the bridging of the 1,9-positions. In an earlier paper,<sup>2</sup> the dibromination of 4,6-dimethoxydibenzofuran was reported. The structure of the resulting dibromo compound has not been definitely established, but it may possibly be 1,9-dibromo-4,6-dimethoxydibenzofuran.

We are now reporting the dibromination of 2,8-dimethoxydibenzofuran. From this reaction there resulted two isomeric dibromodimethoxydibenzofurans, one of m. p. 196–197°, and the other of m. p. 260–261°. The lower-melting isomer has been designated tentatively as 1,9-dibromo-2,8-dimethoxydibenzofuran, since it is known that 1-bromo-2-methoxydibenzofuran has a lower m. p. than the 3-bromo isomer.<sup>3</sup> However, it is possible that the spatial configuration of the dibenzofuran molecule is such that the 1- and 9-positions are in close proximity and simultaneous substitution of both positions by any large group or atom may, consequently, be very difficult. The 1,7-dibromo isomer is, therefore, a possibility not to be excluded from consideration.

The higher-melting isomer is now shown to be 3,7-dibromo-2,8-dimethoxydibenzofuran. This structure was established by conversion to 3,7-dimethyl-2,8-dihydroxydibenzofuran and comparison of this compound with an authentic sample prepared by a synthesis involving ring closure.

The series of transformations resulting in the formation of 3,7-dimethyl-2,8-dihydroxydibenzofuran through ring closure is schematically represented below.



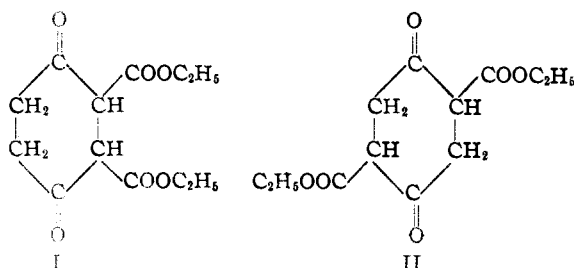
(1) Paper XIX: Gilman, Swiss and Cheney, *THIS JOURNAL*, **62**, 1983 (1940). The present address of Jack Swiss is Research Laboratories, Westinghouse Electric and Manufacturing Co., East Pittsburgh, Pa., and that of H. B. Willis is Fine Chemicals Division, Gelatine Products Co., Detroit, Michigan.

(2) Gilman and Cheney, *THIS JOURNAL*, **61**, 3149 (1939).

(3) Gilman and P. R. Van Ess, *ibid.*, **61**, 1365 (1939).

The iodination of toluhydroquinone dimethyl ether and the Ullmann coupling of the resulting iodo compound to give 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl have been reported by Erdtman.<sup>4</sup> The same investigator also reported the nitration of toluhydroquinone dimethyl ether, but the position in which the substituent enters the ring does not appear to have been finally proved for either the iodination or the nitration.<sup>5</sup> If the iodine atom entered the ring in the position ortho to the methyl group, the product obtained from the above series of reactions would be 1,9-dimethyl-2,8-dihydroxydibenzofuran. Hence, it was necessary to establish definitely the position of iodination.

Nef<sup>6</sup> has reported the synthesis of 2,5-dimethoxyterephthalic acid and of its diethyl ester from ethyl succinylsuccinate. The latter compound was first prepared by Hermann<sup>7</sup> who believed it to have the structure (I) and oxidized it to the corresponding benzene derivative. Ebert, however, has shown that the symmetrical structure (II) is the correct one.<sup>8</sup>



Accordingly, the iodination product of toluhydroquinone dimethyl ether was converted to 2,5-dimethoxyterephthalic acid by the following series of reactions.

The iodo compound was first converted to the corresponding nitrile by the method of Koelsch.<sup>9</sup>

(4) Erdtman, *Proc. Roy. Soc. (London)*, **A143**, 191 (1933).

(5) In a private communication, Dr. Erdtman stated, "I don't think the structure of this compound (5-iodotoluhydroquinone dimethyl ether) has been rigorously proved, but it follows, I believe, conclusively from the analogous reactivity of toluquinol and hydroxyquinol." The present authors have been unable to find any record of an investigation of this type having been carried out on toluhydroquinone or hydroxyhydroquinone. We are grateful to Dr. Erdtman for a sample of the 5-iodotoluhydroquinone dimethyl ether prepared by him. The material proved identical with the iodination product prepared in this Laboratory.

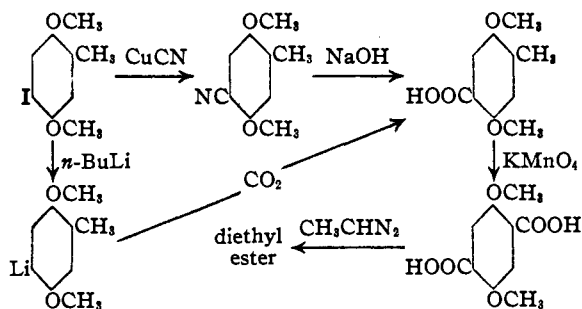
(6) Nef, *Ann.*, **258**, 297 (1890).

(7) Hermann, *ibid.*, **211**, 306 (1882).

(8) Ebert, *ibid.*, **229**, 45 (1885).

(9) Koelsch, *THIS JOURNAL*, **58**, 1328 (1936).

The resulting nitrile was hydrolyzed to give 2,5-dimethoxy-*p*-toluic acid which was oxidized to



2,5-dimethoxyterephthalic acid. The diethyl ester of the final acid was prepared. The melting points of both the 2,5-dimethoxyterephthalic acid and its diethyl ester agree with those reported by Nef. In addition to the method just mentioned, 2,5-dimethoxy-*p*-toluic acid was prepared from 5-iodotoluhydroquinone dimethyl ether by halogen-metal interconversion with *n*-butyllithium followed by carbonation.

Conversion of 3,7-dibromo-2,8-dimethoxydibenzofuran to 3,7-dicarboxy-2,8-dimethoxydibenzofuran and preparation of the dimethyl ester of this acid have already been reported.<sup>10</sup>

A number of attempts was made to prepare a compound from which 1,9-dimethyl-2,8-dihydroxydibenzofuran might be synthesized by ring closure. Such a compound could be prepared from toluhydroquinone dimethyl ether by introduction of a halogen atom into the 3-position.

First, the structure of the nitration product of toluhydroquinone dimethyl ether was established as being 5-nitrotoluhydroquinone dimethyl ether, in agreement with Erdtman's assumption, by reduction to the amine and conversion to the 5-iodo compound whose structure has been demonstrated.

Since the nitro group is a meta director, halogenation of 5-nitrotoluhydroquinone dimethyl ether might be expected to introduce the halogen atom into the 3-position. The nitro group could then be removed by stannous chloride reduction followed by diazotization. Bromination of the nitro compound proved difficult and the product obtained from the reaction was found to contain bromine, but no nitrogen. This substance has not been further investigated, but it seems likely that the nitro group was replaced by a bromine atom. Attempts at iodination of 5-nitrotoluhydroquinone dimethyl ether were unsuccessful.<sup>11</sup>

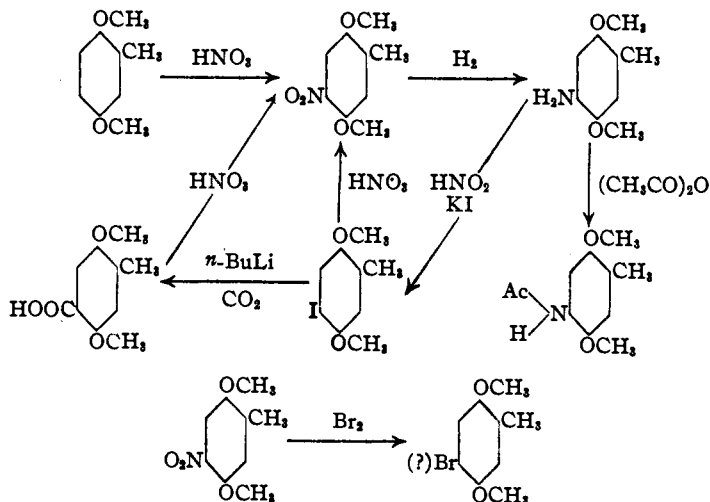
An additional substituent introduced into 2,5-

(10) Gilman, Swislow, and Brown, *THIS JOURNAL*, **62**, 348 (1940).

(11) Unpublished studies by F. A. Yeoman.

dimethoxy-*p*-toluic acid might also be expected to enter the position ortho to the methyl group, since the carboxyl group is a meta directing group. Nitration of 2,5-dimethoxy-*p*-toluic acid, however, resulted in replacement of the carboxyl group by the nitro group. Attempts at iodination of the same acid met with no success.

Nitration of 5-iodotoluhydroquinone dimethyl ether resulted in replacement of the iodine atom by a nitro group. A diagrammatic representation of the work done in attempting to synthesize an intermediate for the preparation of 1,9-dimethyl-2,8-dihydroxydibenzofuran appears below.



A striking feature of this series of reactions is the rather unusual exchange of groups occurring in the 5-position. The marked contrast between the reactivity of this position and that of the other two unsubstituted positions on the ring is difficult to explain on the basis of the normally rather weak directing influence of the methyl group, and yet all three positions bear the same relation to the two methoxyl groups.

### Experimental

**2,8-Dimethoxydibenzofuran.**—An intimate mixture of 100 g. (0.307 mole) of 2,8-dibromodibenzofuran (m. p. 185–189°), 200 g. of technical, flake sodium hydroxide (76% NaOH), and 24 g. of copper-bronze powder was poured onto a mat of 100 g. of copper turnings in a 600 ml. copper beaker, and 100 ml. of copper sulfate solution containing 30 g. of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  was added. The mixture was heated at 235–240° for twelve hours in an electrically heated bomb.<sup>12</sup>

The contents of the beaker were extracted with 300 ml. portions of boiling water until acidification of the filtrate gave no further precipitate. The combined filtrates were made acid to congo red with hydrochloric acid, and the light tan product was filtered. The dried product weighed 67 g. and melted at 230–235°. The theoretical yield is 62 g., but the crude product contained occluded sodium chloride.

To 237.5 g. of crude 2,8-dihydroxydibenzofuran, prepared as described above and dissolved in a liter of water

(12) The authors are grateful to Dr. F. E. Brown for the use of a steel bomb.

containing 103 g. of sodium hydroxide, was added 280 ml. of dimethyl sulfate, dropwise with stirring. The mixture was stirred two hours and then stirred and refluxed three hours. Excess dimethyl sulfate was destroyed by addition of 30 g. of sodium hydroxide. The yield of crude 2,8-dimethoxydibenzofuran was 221 g. (81%). This was distilled (b. p., 187° (5 mm.)) to give, after crystallization from 95% ethanol, 89 g. of white plates melting at 88–89°. Concentration of the mother liquor, and extraction of the residue in the Claisen flask yielded an additional 35 g. of impure material which gave on distillation and recrystallization 24 g. of pure product. The total yield of pure 2,8-dimethoxydibenzofuran was 113 g. (45.5% based on the weight of 2,8-dibromodibenzofuran required for its preparation).

*Anal.* Calcd. for  $C_{14}H_{12}O_2$ : C, 73.61; H, 5.30. Found: C, 73.65; H, 5.47.

**3,7-Dibromo-2,8-dimethoxydibenzofuran.**—To 45.6 g. (0.20 mole) of 2,8-dimethoxydibenzofuran dissolved in 1 liter of glacial acetic acid was added, dropwise, 400 ml. of a molar solution of bromine in glacial acetic acid. The bromination was carried out with stirring at room temperature and required one and three-quarters hours. The mixture was allowed to stand overnight and then filtered. The precipitated material weighed 54 g. and melted at 180–220°. Concentration of the filtrate after treatment with a little sodium bisulfite solution yielded an additional 16 g. of product, making the combined crude yield 91%.

Two isomeric dibromo compounds were separated from this mixture. Treatment with boiling acetone dissolved the lower-melting and more soluble isomer, which comprised about two-thirds of the total. Successive recrystallizations of the extracted material from acetone, ethanol, and isopropanol resulted in long white needles, which melted at 196–197°. This isomer is probably 1,9-dibromo-2,8-dimethoxydibenzofuran.

*Anal.* Calcd. for  $C_{14}H_{10}O_2Br_2$ : Br, 41.45. Found: Br, 41.90.

The residue from the acetone extraction was recrystallized successively from benzene, dioxane, and glacial acetic acid to give white needles which melted at 260–261°. This compound is 3,7-dibromo-2,8-dimethoxydibenzofuran.

*Anal.* Calcd. for  $C_{14}H_{10}O_2Br_2$ : Br, 41.45. Found: Br, 40.90.

**Conversion of 3,7-Dibromo-2,8-dimethoxydibenzofuran to 3,7-Dimethyl-2,8-dimethoxydibenzofuran.**—*n*-Butyllithium, prepared from 2 g. of lithium and 7 ml. of *n*-butyl bromide in 37 ml. of ether, was added to 4.6 g. (0.0119 mole) of 3,7-dibromo-2,8-dimethoxydibenzofuran in 75 ml. of benzene, and the mixture was refluxed with stirring for 30 minutes. The mixture was cooled for five minutes and 5 ml. of dimethyl sulfate in 10 ml. of ether was added dropwise. Stirring was continued for four hours.

Upon working up the product there was obtained 1.5 g. (49%) of a compound which melted at 140° after recrystallization from ethanol. A second recrystallization from the same solvent raised the melting point to 144–144.5°.

**Preparation of 3,7-Dimethyl-2,8-dihydroxydibenzofuran.**—To 0.1 g. (0.00039 mole) of 3,7-dimethyl-2,8-dimethoxydibenzofuran was added 2 ml. of glacial acetic acid and 2.5 ml. of constant boiling hydrobromic acid. The mixture was refluxed for seventeen hours in an apparatus fitted with ground-glass joints and then poured into 45 ml. of water. The crude dihydroxy compound which precipitated melted at 225–227°. This material was treated with Norite in boiling alcohol and then recrystallized from dilute alcohol. Light yellow plates, which sintered at 228° and melted at 231–232°, were obtained.

**2,2',5,5'-Tetramethoxy-4,4'-dimethylbiphenyl.**—This compound was prepared in essential accordance with the procedure of Erdtman<sup>4</sup> from 3 g. of copper and 3 g. (0.0108 mole) of 5-iodotoluhydroquinone dimethyl ether. The yield was 60% of white crystals that melted at 134°. In a second, larger run the yield was raised to 84%.

**Demethylation of 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl.**—A mixture of 4.5 g. (0.0149 mole) of 2,2',5,5'-

tetramethoxy-4,4'-dimethylbiphenyl, 20 ml. of glacial acetic acid, and 25 ml. of 42% hydrobromic acid was refluxed twenty hours in an all-glass apparatus. The solution was diluted to 450 ml. and filtered. The precipitate was recrystallized from 95% ethanol and then sublimed under reduced pressure. The few milligrams of product obtained melted at 232°. This is the melting point given by Nietzki<sup>13</sup> for his supposed 4,6-dimethyl-2,8-dihydroxydibenzofuran. However, the work of Erdtman<sup>4</sup> has shown that Nietzki was in error in his suggested structure.

The compound prepared by the above procedure did not depress the melting point of the compound prepared from the higher-melting dibromination product of 2,8-dimethoxydibenzofuran. This establishes the structure of this bromination product as 3,7-dibromo-2,8-dimethoxydibenzofuran.

**2,5-Dimethoxy-*p*-tolunitrile.**—5-Iodotoluhydroquinone dimethyl ether was converted to 2,5-dimethoxy-*p*-tolunitrile by the method of Koelsch.<sup>9</sup> An intimate mixture of 3.0 g. (0.0108 mole) of 5-iodotoluhydroquinone dimethyl ether and 2.12 g. of anhydrous cuprous cyanide was heated at 240° for four hours. The solid mass remaining was extracted with acetone and the yellow solid obtained was recrystallized from dilute ethanol. The pure nitrile crystallized in yellow needles which melted at 130–131° and weighed 1.4 g. (73%).

*Anal.* Calcd. for  $C_{10}H_{11}O_2N$ : N, 7.91. Found: N, 7.95, 7.98.

**2,5-Dimethoxy-*p*-toluic Acid.**—A solution of 1.2 g. (0.0068 mole) of 2,5-dimethoxy-*p*-tolunitrile in 5.8 g. of sodium hydroxide in a mixture of 5 ml. of water and 35 ml. of ethanol was refluxed ten hours and then evaporated nearly to dryness. The residue was extracted with boiling water and the cooled extract acidified with hydrochloric acid. The precipitate was filtered off and recrystallized from water. The pure acid crystallized in white needles which melted at 125–126° and weighed 0.55 g. (41%).

*Anal.* Calcd. for  $C_{10}H_{13}O_4$ : neut. equiv., 196. Found: neut. equiv., 197, 195.

Attempts at preparation of the Grignard reagent from 5-iodotoluhydroquinone dimethyl ether were unsuccessful.

A halogen-metal interconversion on the iodo compound using *n*-butyllithium was successful. To the *n*-butyllithium prepared from 0.20 g. (0.0285 mole) of lithium and 1.52 ml. (0.0144 mole) of *n*-butyl bromide in 30 ml. of ether was added with stirring a solution of 2.0 g. (0.0072 mole) of 5-iodotoluhydroquinone dimethyl ether in 20 ml. of ether. The mixture was stirred five minutes at room temperature and then carbonated. The crude acid obtained melted at 124–125° and weighed 0.57 g. Upon recrystallization from water, 0.50 g. of acid melting at 125–126° was obtained, representing a yield of 35%. The acid thus prepared did not depress the melting point of the acid prepared by hydrolysis of the nitrile.

**Oxidation of 2,5-Dimethoxy-*p*-toluic Acid.**—To a boiling solution of 1.0 g. (0.0051 mole) of 2,5-dimethoxy-*p*-toluic acid in 80 ml. of water was added a solution of 1.6 g. of potassium permanganate in 40 ml. of water. The permanganate was reduced almost instantaneously. A further 0.5 g. of potassium permanganate was added and the solution refluxed for fifteen minutes, at which time decolorization of the permanganate was again complete. The mixture was filtered hot, concentrated to 50 ml., and acidified with hydrochloric acid. The crude product resulting melted at 210–239°, and weighed 0.47 g., a crude yield of 40%.

Purification was difficult, but finally crystallization from a large volume of water yielded 30 mg. of pure 2,5-dimethoxyterephthalic acid of m. p. 265–265.5° in agreement with the melting point reported by Nef.<sup>8</sup>

*Anal.* Calcd. for  $C_{10}H_{10}O_6$ : neut. equiv., 113. Found: neut. equiv., 114.

A small amount (about 8 mg.) of 2,5-dimethoxyterephthalic acid was esterified by treatment with diazotethane in ether solution. The crude diethyl ester melted

(13) Nietzki, *Ber.*, **11**, 1278 (1878).

at 91–96°. Two recrystallizations from ethanol raised the melting point to 101–102° in agreement with that reported by Nef.

**5-Aminotoluhydroquinone Dimethyl Ether.**—In a glass hydrogenation vessel was placed a solution of 9.0 g. (0.0456 mole) of 5-nitrotoluhydroquinone dimethyl ether in the minimum amount of hot ethanol. One gram of activated Raney nickel catalyst was added. The mixture was hydrogenated at a hydrogen pressure maintained between 30 and 45 pounds gage pressure at a temperature of 100° for one hour. Constant shaking was maintained during this period.

After the mixture had been thoroughly cooled and the pressure released, it was filtered quickly to remove catalyst. A colorless filtrate resulted. The solution was concentrated under reduced pressure and, when nearly all the alcohol had been removed, white needles which melted at 108.5–109.5° precipitated. The amine darkened very rapidly upon exposure to air and, consequently, no attempt was made to purify it for analysis.

To the flask containing the crude 5-aminotoluhydroquinone dimethyl ether was added 10 ml. of acetic anhydride. The light yellow solution which resulted upon gentle heating was transferred to a small Erlenmeyer flask and refluxed one hour. Dilution and cooling resulted in a white, granular precipitate which was filtered off and recrystallized several times from an ethanol-water mixture. The pure 5-acetaminotoluhydroquinone dimethyl ether, which crystallized in white needles, weighed 5.1 g., and melted at 160–162°. This is a yield of 53% based upon the amount of 5-nitrotoluhydroquinone dimethyl ether originally reduced.

*Anal.* Calcd. for  $C_{11}H_{15}O_3N$ : N, 6.69. Found: N, 6.72, 6.75.

**Conversion of 5-Aminotoluhydroquinone Dimethyl Ether to 5-Iodotoluhydroquinone Dimethyl Ether.**—The 5-aminotoluhydroquinone dimethyl ether resulting from the reduction of 10.0 g. (0.0507 mole) of 5-nitrotoluhydroquinone dimethyl ether was transferred quickly to a one liter Erlenmeyer flask flushed out with nitrogen. A solution of 11 ml. of concentrated hydrochloric acid in 38 ml. of water was added and the resulting solution was cooled to 0°. To the chilled amine hydrochloride solution was added slowly with stirring a solution of 2.6 g. of sodium nitrite in 11 ml. of water. On slow addition of a solution of 6.4 g. of potassium iodide in 12 ml. of water to the above mixture, a yellow precipitate formed. Upon boiling, the color of the precipitate darkened through red to black. Attempts at crystallization of this material were unsuccessful, but sublimation at reduced pressure yielded a light tan solid which melted at 79–81°. Recrystallization from alcohol raised the melting point to 84–85° and removed virtually all the color. The pure product did not depress the melting point of an authentic sample of 5-iodotoluhydroquinone dimethyl ether.

**Bromination of 5-Nitrotoluhydroquinone Dimethyl Ether.**—To a solution of 3.94 g. (0.02 mole) of 5-nitrotoluhydroquinone dimethyl ether in 25 ml. of carbon tetrachloride was added 3.2 g. (0.02 mole) of bromine. A trace of iron was added as a catalyst and the solution was refluxed for several hours. When all the bromine had reacted, the mixture was washed with sodium thiosulfate solution and the carbon tetrachloride was distilled off. The yield was 2.4 g. of crude product. Recrystallization from ethanol gave 1.5 g. of pure product which melted at 168°. This compound contained bromine but no nitrogen.

The corresponding diacetoxy compound was prepared by hydrolysis of the above compound with hydrobromic acid in glacial acetic acid followed by acetylation with acetic anhydride. The diacetoxy derivative melted at 253–254°. These compounds were not analyzed or further investigated.

**Nitration of 2,5-Dimethoxy-*p*-toluic Acid.**—To a solution of 3.0 g. (0.0153 mole) of 2,5-dimethoxy-*p*-toluic acid in 25 ml. of glacial acetic acid was added slowly with stirring 5.0 ml. of concentrated nitric acid. The mixture was warmed to 45° for ten minutes and then cooled and diluted with water. An amorphous yellow precipitate which melted at 114–117° formed. Two recrystallizations from alcohol produced 2.5 g. (83%) of yellow plates melting at 118–119°. A mixed melting point with an authentic sample of 5-nitrotoluhydroquinone dimethyl ether showed no depression.

**Nitration of 5-Iodotoluhydroquinone Dimethyl Ether.**—A nitration was carried out on 3.0 g. (0.0107 mole) of 5-iodotoluhydroquinone dimethyl ether by the same procedure as that applied to 2,5-dimethoxy-*p*-toluic acid. Iodine vapors were given off during the course of the reaction. When the mixture was worked up, 1.7 g. (80%) of pure 5-nitrotoluhydroquinone dimethyl ether was obtained, as shown by a mixed m. p. with an authentic sample.

### Summary

Several 2,3,7,8-substituted derivatives of dibenzofuran have been prepared. Their structures have been demonstrated through a biphenyl ring closure.

The structures of the 5-iodotoluhydroquinone dimethyl ether and the 5-nitrotoluhydroquinone dimethyl ether reported by Erdtman have been established.

An unusual series of reactions involving exchange of groups substituted in the 5-position of toluhydroquinone dimethyl ether is reported.

AMES, IOWA

RECEIVED FEBRUARY 12, 1944