

Hydrolysis of the Filtrate.—The non-crystallizable filtrate (10.14 g.) was hydrolyzed and the products isolated as described for methylated gentiobiose. The crude tetramethylglucose weighed 5.44 g. After recrystallization from ligroin the melting point was 86° (uncorr.). A mixed melting point with an authentic sample of 2,3,4,6-tetramethylglucose showed no depression.

From the aqueous solution 3.31 g. of a thick sirup was obtained. Two and eight-tenths grams of this sirup was converted to the methylglucoside and the product distilled. A fraction weighing 1.53 g. and boiling at 139–143° (4 mm.) was collected. Upon seeding with crystals of 2,3,4-trimethyl- β -methylglucoside it crystallized readily.

A total of 0.27 g. of crystalline material was obtained. It was shown to be 2,3,4-trimethyl- β -methylglucoside by comparison with an authentic sample.

Summary

1. The non-fermentable material in "hydrol" has been methylated and heptamethyl- β -methylgentiobioside isolated and identified.

2. Evidence for the presence of 6- α -glucosidoglucose in the non-fermentable material has been obtained.

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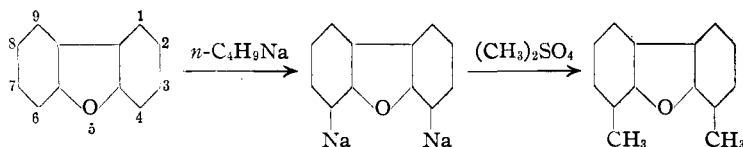
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Dibenzofuran. V. Dimetalation

BY HENRY GILMAN AND RICHARD V. YOUNG

Introduction

It was previously demonstrated that metalation of dibenzofuran proceeds anomalously to introduce a metal (lithium, sodium, potassium, mercury) in the 4-position.¹ Two of the most important positions, from a biological viewpoint, are 4 and 6. Dibenzofuran undergoes dimetalation to give a 4,6-dimetalated product. The constitution of the 4,6-disiododibenzofuran was established by the following sequence of reactions.



The 4,6-dimethyldibenzofuran was shown to be identical with an authentic specimen prepared by ring closure.²

The disodium compound undergoes the usual replacement reactions, yielding 4,6-diiododibenzofuran with iodine, 4,6-dibenzofurandicarboxylic acid on carbonation, 4,6-dihydroxydibenzofuran on oxidation, and 4,6-dibenzofurandisulfonic acid on oxidation of the disulfinic acid obtained by the action of sulfur dioxide on the disodium compound.

4-Methyldibenzofuran is metalated in the 6-position. The position of the metal was established by carbonating to a 4-methylcarboxylic acid, which on oxidation gave 4,6-dibenzofuran-

(1) THIS JOURNAL, 56, 1415 (1934).

(2) Sugii and Shindo, *J. Pharm. Soc. Japan*, 54, 149 (1934). The authors are grateful to Professor Sugii for a specimen of their 4,6-dimethyldibenzofuran.

dicarboxylic acid. 4-Methoxydibenzofuran is likewise metalated in the 6-position, the organometallic compound being oxidized to a 4-methoxyhydroxydibenzofuran, which on hydrogen iodide cleavage gave 4,6-dihydroxydibenzofuran. These two nuclear substitution reactions are significant from the point of view of orientation for, like dimetalation, they emphasize the essential independence of the benzenoid nuclei, and the highly developed acidities of the 4- and 6-hydrogens. On the basis of the activating effects of a methyl and a methoxyl group, one might have expected some homonuclear substitution, but in every case so far examined metalation takes place predominantly heteronuclearly if a 4-position be occupied.

Experimental Part

Mono- and Dimetalation.—Monometalation of dibenzofuran is effected satisfactorily by a miscellany of organo-alkali compounds, all preparations being carried out in a three-necked flask (in an inert atmosphere, preferably nitrogen) provided with a stirrer, condenser and dropping funnel. (a) *From n-butyl-lithium.*—The *n*-butyl-lithium solution in ether (prepared from 0.5 mole of *n*-butyl bromide) is filtered through a loose plug of glass wool directly into a flask containing 0.4 mole of dibenzofuran in ether. The resulting solution is then refluxed with stirring for four to five hours. (b) *From n-butylsodium.*—To a solution of 0.1 mole of dibenzofuran in 60 cc. of ether is added 0.032 mole of di-*n*-butylmercury and 2.3 g. or 0.1 atom of sodium. Reaction sets in almost immediately and is allowed to proceed with stirring for sixteen hours.

Dimetalation is best realized with *n*-butylsodium. To a solution of 0.032 mole of dibenzofuran in 75 cc. of ether

is added 0.08 atom of sodium and 0.032 mole of di-*n*-butylmercury. After the reaction has subsided, the mixture is refluxed for several hours.

It should be added that metalation (generally mono) has been carried out with ethylpotassium; ethylsodium prepared *in situ* from tetraethyllead and sodium chips or sodium powder; tetraethyllead and sodium-potassium alloy (good yields, and largely dimetalated product); and *n*-butylmagnesium chloride and sodium-potassium alloy. Several combinations can also be used for the metalation of *N*-alkyl carbazoles which, in accordance with studies by R. H. Kirby, give derivatives with the metals corresponding in positions observed with dibenzofuran (with the possible exception of mercuration).

4-Hydroxydibenzofuran.—4-Dibenzofurylsodium, prepared in the usual manner and separated from sodium amalgam by decantation, was oxidized at 0° and with vigorous stirring by dry air to give 10.3 g. or a 35% yield of impure 4-hydroxydibenzofuran melting at 92–93°. Purification by crystallization from petroleum ether (b. p. 65–75°) or hot water gave the phenol melting at 102°. An alcoholic solution gives a green color with ferric chloride.

Anal. Calcd. for C₁₂H₈O₂: C, 78.25; H, 4.35. Found: C, 78.03, 77.8 and 77.7; H, 4.52, 4.07 and 4.18.

Zerewitinoff analysis showed one active hydrogen, and benzylation by the Schotten-Baumann reaction gave the benzoate which melted at 91–92° after crystallization from alcohol.

The yield of phenol is erratic, and has reached 40%. In general, oxidation in the presence of an equivalent of *n*-butylmagnesium bromide is helpful.

4-Methoxydibenzofuran.—4-Hydroxydibenzofuran was methylated in 97% yield by dimethyl sulfate to give 4-methoxydibenzofuran distilling at 164–165° (5 mm.) and melting at 52° after crystallization from petroleum ether.

Anal. Calcd. for C₁₃H₁₀O₂: C, 78.8; H, 5.05. Found: C, 79.0; H, 5.13.

4-Methylidibenzofuran.—Methylation of the 4-sodium compound by means of dimethyl sulfate gave a 45% yield of 4-methylidibenzofuran. The identity of the compound was established by permanganate oxidation to the known 4-dibenzofurancarboxylic acid³ (comparison with an authentic specimen).

4,6-Dibenzofurandicarboxylic Acid.—4,6-Disodiobenzofuran [from 5.4 g. (0.032 mole) of dibenzofuran] was carbonated in the usual manner by solid carbon dioxide. The product was then filtered by suction, and the residue added slowly to about 500 cc. of water. When evolution of hydrogen ceased, the mixture was heated to boiling and filtered. From the filtrate, subsequent to cooling and acidification, there was obtained 5.2 g. or a 77% yield of the dibasic acid, which melts at 325° after crystallization from ethanol. *Neutral equivalent.*—Calcd., 128; found, 125.

The dibasic acid on esterification by methanol and hydrogen chloride gave dimethyl 4,6-dibenzofurandicarboxylate in 95% yield and melting at 161–162°.

Anal. Calcd. for C₁₆H₁₂O₆: C, 67.5; H, 4.25. Found: C, 67.26; H, 4.23.

(3) Krüger, *Ber.*, **65**, 1382 (1932).

4,6-Dimethyldibenzofuran.—The disodium compound (prepared by the use of a 10% excess of di-*n*-butylmercury to ensure complete dimetalation) was treated with dimethyl sulfate in ether to give a 90% yield of crude dimethyl compound. The 4,6-dimethyldibenzofuran melts at 87° after crystallization from ethanol, and showed no depression in a mixed melting point determination with an authentic specimen.²

4,6-Diiododibenzofuran.—The diiodo compound was prepared from the disodium compound and iodine in 19% yield, and melted at 160° after recrystallization from *n*-propanol.

Anal. Calcd. for C₁₂H₆OI₂: I, 60.4. Found: I, 60.8 and 60.7.

4,6-Dihydroxydibenzofuran.—Oxidation of 0.05 mole of the disodium compound suspended in ether was carried out in the presence of 0.1 mole of *n*-butylmagnesium bromide, in accordance with Ivanoff's procedure.⁴ When the color test for organometallic compound was negative, the mixture was allowed to warm up to room temperature over a period of several hours to prevent an explosion, which generally accompanies rapid warming. The 4,6-dihydroxydibenzofuran was separated from accompanying 4-hydroxydibenzofuran by its distinctly greater solubility in water. The yield of dihydroxy compound, which melts at 190°, was 3%. An aqueous solution of 4,6-dihydroxydibenzofuran gives a light green color with 10% ferric chloride solution.

Anal. Calcd. for C₁₂H₈O₃: C, 72.0; H, 4.0. Found: C, 72.25; H, 4.12.

Metalation of 4-Methyldibenzofuran.—Metalation was carried out in a customary manner, and carbonation gave a 46% yield of 6-methyl-4-dibenzofurancarboxylic acid melting at 238–240° after crystallization from ethanol. *Neutral equivalent.*—Calcd., 226; found, 221. Oxidation of the methyl acid by permanganate gave the 4,6-dibenzofurandicarboxylic acid, which was identified by conversion to the corresponding dimethyl ester (authenticated by mixed melting point).

Esterification of the methyl acid by methanol and hydrogen chloride gave methyl 6-methyl-4-dibenzofurancarboxylate, which melts at 80–81°.

Anal. Calcd. for C₁₃H₁₂O₃: C, 75.0; H, 5.0. Found: C, 74.7; H, 4.94.

Several attempts to oxidize methyl 6-methyl-4-dibenzofurancarboxylate to methyl 6-carboxy-4-dibenzofurancarboxylate gave the 4,6-dibenzofurandicarboxylic acid.

Metalation of 4-Methoxydibenzofuran.—Oxygen was admitted to a mixture of the metalated 4-methoxydibenzofuran and *n*-butylmagnesium bromide. On working up the product in a customary manner, 4-methoxy-6-hydroxydibenzofuran was isolated, and after numerous recrystallizations from petroleum ether (b. p. 65–75°) the hydroxy-methoxy compound melted at 109–110°.

Anal. Calcd. for C₁₃H₁₀O₃: C, 72.9; H, 4.67. Found: C, 72.8; H, 4.7.

The 4-methoxy-6-hydroxydibenzofuran was cleaved (by refluxing with hydrogen iodide) to 4,6-dihydroxydibenzofuran (mixed melting point).

(4) Ivanoff, *Bull. soc. chim.*, **39**, 47 (1926).

4,6-Dibenzofurandisulfonic Acid.—Sulfur dioxide was added to a suspension of the disodio compound in ether cooled to -18° . After the rapid and complete reaction, the suspension was filtered and the residue dissolved in water. The solution was heated to boiling, filtered, and the filtrate cooled and acidified to yield 90% of 4,6-dibenzofurandisulfonic acid which decomposes at $183-185^{\circ}$.

The disulfonic acid was oxidized by potassium permanganate to 4,6-dibenzofurandisulfonic acid, which was obtained in a 50% yield and which decomposes at about 300° .

Anal. Calcd. for $C_{12}H_8O_7S_2$: S, 19.5. Found: S, 19.16 and 19.21.

Summary

Dimetalation of dibenzofuran takes place in the 4,6-positions. The pronounced acidities of the 4- and 6-hydrogens are also reflected in the metalation of 4-methyldibenzofuran and 4-methoxydibenzofuran, each of which undergoes 6-metalation. The predominant, if not exclusive, metalation product is heteronuclear and not homonuclear, as might perhaps have been expected.

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Dibenzofuran. VI. Amino Derivatives

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Introduction

Some amino derivatives of dibenzofuran have been prepared in connection with a study of the physiological action of dibenzofurans. The hypnotic and analgesic properties will be reported by Dr. A. W. Dox and co-workers.

Experimental Part

Alkylated 3-Aminodibenzofurans.—3-Aminodibenzofuran was prepared, in accordance with the directions of C. W. Bradley, by the catalytic reduction of 3-nitrodibenzofuran using Adams catalyst. The corresponding dimethylamino and diethylamino compounds were made by means of dimethyl and diethyl sulfates. The methylamino and ethylamino derivatives were synthesized by alkylation (with dialkyl sulfates) of the *p*-toluenesulfonamides prepared *in situ*, followed by sulfuric-glacial acetic acid hydrolysis; and the *n*-propylamino compound was prepared from the 3-amine and *n*-propyl *p*-toluenesulfonate. The results are contained in Table I.

3-Piperidinodibenzofuran, $C_{12}H_{17}ONC_5H_{10}$.—A mixture of 26 g. (0.14 mole) of 3-aminodibenzofuran and 12 g. (0.05 mole) of pentamethylene bromide was heated for

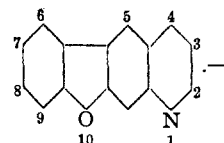
one hour on a water-bath, and the resulting solid was powdered and extracted with ether. The passage of hydrogen chloride into the solution gave a quantitative yield of the hydrochloride. The free base, obtained by the addition of ammonium hydroxide, melts at 111° on recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{17}H_{17}ON$: N, 5.57. Found: N, 5.54 and 5.55.

The hydrochloride, prepared in the usual manner from the base, melts at $258-260^{\circ}$.

Anal. Calcd. for $C_{17}H_{18}ONCl$: N, 4.87. Found: N, 4.89 and 4.90.

Pyrido-[3,2-*b*]-dibenzofuran,



From 3-Aminodibenzofuran.—A mixture of 60 g. (0.27 mole) of 3-aminodibenzofuran hydrochloride, 50 g. (0.21 mole) of arsenic oxide, 150 g. (1.62 moles) of glycerol and 80 g. (0.81 mole) of sulfuric acid was heated at 170° for four and one-half hours. The liquid was then poured into 1800 cc. of water, boiled with decolorizing carbon and

TABLE I

ALKYLATED 3-AMINODIBENZOFURANS

	°C.	B. p., Mm.	M. p., °C.		N Analyses, %	
					Calcd.	Found
3-Methylaminodibenzofuran ^a	190	4	48-49	$C_{12}H_{17}ONHCH_3$	7.10	6.90
Hydrochloride			245-247 dec.	$C_{12}H_{17}ONHCH_3 \cdot HCl$	6.03	6.06 6.15
3-Ethylaminodibenzofuran hydrochloride			^b	$C_{12}H_{19}ONHC_2H_5 \cdot HCl$	5.66	5.71 5.53
3- <i>n</i> -Propylaminodibenzofuran	203-205	1		$C_{12}H_{21}ONHC_3H_7$		
Hydrochloride ^c			190	$C_{12}H_{21}ONHC_3H_7 \cdot HCl$	5.36	5.53 5.32
3-Dimethylaminodibenzofuran ^d	211-212	4	96	$C_{12}H_{17}ON(CH_3)_2$	6.63	6.86 7.01
Hydrochloride			230-232	$C_{12}H_{17}ON(CH_3)_2 \cdot HCl$	5.66	5.90 5.86
3-Diethylaminodibenzofuran	205	2-3		$C_{12}H_{17}ON(C_2H_5)_2$		
Hydrochloride			203-205 dec.	$C_{12}H_{17}ON(C_2H_5)_2 \cdot HCl$	5.09	5.07 5.08

^a A Zerewitinoff analysis showed one active hydrogen.

^b The hydrochloride did not melt or decompose up to 315° .

^c The salt is hydrolyzed in water at room temperatures. ^d A Zerewitinoff analysis showed no active hydrogen.