

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.

AMES, IOWA

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{CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE}

Dibenzofuran. VI. Amino Derivatives

BY WILLARD H. KIRKPATRICK AND PAUL T. PARKER

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, $C_{12}H_7ONC_5H_{10}$.—A mixture of 26 g. (0.14 mole) of 3-aminodibenzofuran and 12 g. (0.05 mole) of pentamethylene bromide was heated for

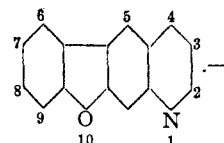
one hour on a water-bath, and the resulting solid was powdered and extracted with ether. The passage of hydrogen chloride into the solution gave a quantitative yield of the hydrochloride. The free base, obtained by the addition of ammonium hydroxide, melts at 111° on recrystallization from aqueous ethanol.

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	$C_{12}H_7ONHCH_3$	7.10	6.90
Hydrochloride			245-247 dec.	$C_{12}H_7ONHCH_3 \cdot HCl$	6.03	6.06 6.15
3-Ethylaminodibenzofuran hydrochloride			^b	$C_{12}H_7ONHC_2H_5 \cdot HCl$	5.66	5.71 5.53
3- <i>n</i> -Propylaminodibenzofuran	203-205	1		$C_{12}H_7ONHC_3H_7$		
Hydrochloride ^c			190	$C_{12}H_7ONHC_3H_7 \cdot HCl$	5.36	5.53 5.32
3-Dimethylaminodibenzofuran ^d	211-212	4	96	$C_{12}H_7ON(CH_3)_2$	6.63	6.86 7.01
Hydrochloride			230-232	$C_{12}H_7ON(CH_3)_2 \cdot HCl$	5.66	5.90 5.86
3-Diethylaminodibenzofuran	205	2-3		$C_{12}H_7ON(C_2H_5)_2$		
Hydrochloride			203-205 dec.	$C_{12}H_7ON(C_2H_5)_2 \cdot HCl$	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.

80 cc. of 33% sodium hydroxide, and filtered hot. The cooled filtrate was made alkaline, extracted with ether and from the dried ether solution there was obtained 30 g. or a 50% yield of the pyridodibenzofuran hydrochlorides from which there was obtained two isomers. The pyrido-[3,2-*b*]-dibenzofuran melts at 167.5–168.5°, and its structure was very recently established by Mosettig and Robinson.¹

Anal. Calcd. for C₁₆H₉ON: N, 6.39. Found: N, 6.39.

The hydrochloride melts at 234–236°.¹

Pyrido-[2,3-*c*]-dibenzofuran. (a) **From 3-Aminodibenzofuran.**—This isomer, obtained by fractional distillation under reduced pressure of the mixture of pyrido compounds, distills at 209–210° (3 mm.) and melts at 112°.¹

Anal. Calcd. for C₁₅H₉ON: N, 6.39. Found: N, 6.41 and 6.49.

The hydrochloride melts at 292–294°.¹

Anal. Calcd. for C₁₅H₁₀ONCl: N, 5.49. Found: N, 5.60.

(b) **From 3-Amino-2-bromodibenzofuran and (c) from 3-Amino-2-nitrodibenzofuran.**—The Skraup reaction was carried out with 0.1 mole of each of these substituted amines and in each case a small quantity of the pyrido-[2,3-*c*]-dibenzofuran was isolated, and shown to be identical with the pyrido compound prepared from 3-aminodibenzofuran.

1,2,3,4-Tetrahydropyrido-[2,3-*c*]-dibenzofuran.—The pyrido-[2,3-*c*]-dibenzofuran (17.5 g. or 0.08 mole) was refluxed for five hours with 20 g. of tin and 350 cc. of concd. hydrochloric acid. The cooled mixture was made alkaline with ammonium hydroxide and then filtered. The precipitate was dried and then extracted with ether. A quantitative yield of the hydrochloride (melting at 247–248°) was obtained from the ether solution.¹

Anal. Calcd. for C₁₅H₁₄ONCl: N, 5.40. Found: N, 5.42 and 5.53.

1-Methyl-1,2,3,4-tetrahydropyrido-[2,3-*c*]-dibenzofuran.—The tetrahydropyrido compound just mentioned was methylated by dimethyl sulfate, and the corresponding 1- or N-methyl compound obtained as the hydrochloride in 83% yield. The hydrochloride melts with decomposition at 227–229°.¹

Anal. Calcd. for C₁₆H₁₆ONCl: N, 5.13. Found: N, 5.46.

2-Methylpyrido-[2,3-*c*]-dibenzofuran.—A stirred mixture of 50 g. (0.22 mole) of 3-aminodibenzofuran hydrochloride, 125 cc. of concd. hydrochloric acid and 80 g. of paraldehyde was heated for six hours on a water-bath, then made alkaline and extracted with ether. From the ether solution there was obtained 17 g. or a 30% yield of the 2-methylpyrido-[2,3-*c*]-dibenzofuran which distilled between 200–210° (3 mm.) and melted at 185–186° after recrystallization from ethanol. The other possible isomer has not been investigated.

Anal. Calcd. for C₁₆H₁₁ON: N, 6.0. Found: N, 6.00 and 5.89.

The same compound, as established by a mixed melting point determination, was obtained by the action of methyl-

lithium on pyrido-[2,3-*c*]-dibenzofuran in a Schlenk tube for four hours at 90–100°.

7-Bromopyrido-dibenzofuran.—A mixture of 35 g. (0.12 mole) of 7-amino-2-bromodibenzofuran, arsenic oxide, glycerol and sulfuric acid was heated under gentle reflux for five hours at 160°. The bromopyrido compound melted at 152° after recrystallization from ethanol; yield, 50%. The structure of this isomer has not been established.

Anal. Calcd. for C₁₅H₈ONBr: N, 4.70. Found: N, 4.69.

Pyrido-[2,3-*b*] and [3,2-*a*] dibenzofurans were obtained from a Skraup synthesis on 22 g. (0.1 mole) of 2-aminodibenzofuran. The ethereal solution on evaporation and distillation of the residue under reduced pressure gave a 39% yield of the mixed pyridodibenzofurans distilling at 240° (6 mm.). From this mixture there was obtained an isomer melting at 185–186°.

Anal. Calcd. for C₁₅H₉ON: N, 6.39. Found: N, 6.35.

The hydrochloride melts with decomposition at 307–310°.

From the alcohol soluble portion there was obtained another isomer melting at 160.5–161.5°.

Anal. Calcd. for C₁₅H₉ON: N, 6.39. Found: N, 6.49.

The hydrochloride melts with darkening and decomposition at 296–298°.

The structures of these isomers have not been determined.

2-Bromoacetyldibenzofuran, C₁₂H₇OCOCH₂Br.—Bromination of a cold ether solution of 2-acetyldibenzofuran gave 2-bromoacetyldibenzofuran which melted at 106–107° after crystallization from methanol.

Anal. Calcd. for C₁₄H₉O₂NBr: Br, 27.68. Found: Br, 27.60 and 27.93.

2-Chloroacetyldibenzofuran.—A Friedel-Crafts reaction in carbon disulfide with 67.2 g. (0.4 mole) of dibenzofuran and chloroacetyl chloride gave a 40% yield of 2-chloroacetyldibenzofuran distilling at 206–208° (1–2 mm.) and melting at 109–110°.

Anal. Calcd. for C₁₄H₉O₂Cl: Cl, 14.35. Found: Cl, 14.46 and 14.39.

Oxidation of the 2-chloroacetyl compound gave pure 2-dibenzofurancarboxylic acid.

2-*ω*-Diethylaminoacetyldibenzofuran, C₁₂H₇OCOCH₂N(C₂H₅)₂, was prepared from 2-chloroacetyldibenzofuran and diethylamine. The hydrochloride, after crystallization from an absolute ethanol-ether solution, melts at 204–206°.

Anal. Calcd. for C₁₈H₂₀O₂NCl: N, 4.41. Found: N, 4.37 and 4.81.

Diethylaminomethyl-2-dibenzofurylcarbinol, C₁₂H₇OCH(OH)[CH₂N(C₂H₅)₂].—An absolute ethanol solution of 20 g. (0.07 mole) of 2-*ω*-diethylaminoacetyldibenzofuran was reduced with Adams catalyst. One equivalent of hydrogen was taken up in forty-eight hours. The free amine was distilled with difficulty at 220° (2–3 mm.), and was obtained in a 30% yield.

Anal. Calcd. for C₁₈H₂₁O₂N: N, 4.92. Found: N, 4.90.

(1) Mosettig and Robinson, *THIS JOURNAL*, **57**, 902 (1935).

The hydrochloride was prepared with difficulty, generally coming down as an oil. However, some crystals were obtained by the use of one equivalent of alcoholic hydrogen chloride and extended standing in an ice box. The hydrochloride melts at 137° and darkens on standing.

Anal. Calcd. for $C_{13}H_{22}O_2NCl$: N, 4.38. Found: N, 4.39 and 4.36.

Ethyl Ether of Chloromethyl-2-dibenzofurylcarbinol, $C_{12}H_7OCH(OC_2H_5)CH_2Cl$.—Reaction was effected between 2-dibenzofurylmagnesium bromide and α,β -dichloroethyl ether. The ethoxy product distills with difficulty because of excessive foaming; b. p. 204–206° (6 mm.); m. p. 58–59°.

Anal. Calcd. for $C_{15}H_{15}O_2Cl$: Cl, 12.77. Found: Cl, 12.36 and 12.42.

Ethyl Ether of Piperidinomethyl-2-dibenzofurylcarbinol Hydrochloride, $C_{12}H_7OCH(OC_2H_5)CH_2NC_5H_{10} \cdot HCl$.—This piperidinomethyl compound, prepared from the above chloromethyl ether and piperidine, melts at 175° after crystallization from acetone.

Anal. Calcd. for $C_{20}H_{26}O_2NCl$: N, 4.03. Found: N, 4.15.

Chloromethyl-2-dibenzofurylmethylcarbinol, $C_{12}H_7OCH_2CHOHCH_2Cl$.—This carbinol, prepared from 2-dibenzofurylmagnesium bromide and epichlorohydrin, distilled at 205–206° (2 mm.).

Anal. Calcd. for $C_{15}H_{13}O_2Cl$: Cl, 13.41. Found: Cl, 13.12 and 12.94.

Diethylaminomethyl-2-dibenzofurylmethylcarbinol Hydrochloride, $C_{12}H_7OCH_2CHOHCH_2N(C_2H_5)_2 \cdot HCl$, was obtained quantitatively from chloromethyl-2-dibenzofurylmethylcarbinol and diethylamine in a reaction carried out by heating a benzene solution at 140–150° for four to five hours. The hydrochloride melts at 145° after crystallization from acetone.

Anal. Calcd. for $C_{19}H_{24}O_2NCl$: N, 4.20. Found: N, 4.26 and 4.32.

2- ω -Piperidinoacetyldibenzofuran, $C_{12}H_7OCOCH_2NC_5H_{10}$, was prepared from 2-chloroacetyldibenzofuran and piperidine in a quantitative yield. The hydrochloride melts at 270–271° after recrystallization from an ether-alcohol mixture.

Anal. Calcd. for $C_{19}H_{20}O_2NCl$: N, 4.24. Found: N, 4.07 and 4.34.

Piperidinomethyl-2-dibenzofurylcarbinol, $C_{12}H_7OCH(OH)(CH_2NC_5H_{10})$, was prepared by the catalytic reduction of 2- ω -piperidinoacetyldibenzofuran. One equivalent of hydrogen was taken up in seven hours. The yield of compound melting at 103–104° was 25%. A Zerewitinoff analysis showed one active hydrogen.

Anal. Calcd. for $C_{19}H_{21}ON$: N, 4.74. Found: N, 4.69 and 4.74.

The hydrochloride melts at 242°.

Anal. Calcd. for $C_{19}H_{22}O_2NCl$: N, 4.22. Found: N, 4.32 and 4.32.

2- β -Hydroxyethylidibenzofuran, $C_{12}H_7OCH_2CH_2OH$.—A solution of 2-dibenzofurylmagnesium bromide was prepared from 600 cc. of ether, 200 cc. of benzene, 125 g. (0.51 mole) of 2-bromodibenzofuran and 13.5 g. (0.56

atom) of 40–100 mesh magnesium. Into this solution was distilled 33 g. (0.75 mole) of ethylene oxide and the reaction was carried out in essential accordance with the directions of Dreger² for the preparation of *n*-hexyl alcohol from *n*-butylmagnesium bromide. The 2- β -hydroxyethylidibenzofuran was obtained in a 47% yield, and melted at 67–67.5° after recrystallization from petroleum ether (b. p. 60–68°).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.21; H, 5.70. Found: C, 79.36; H, 5.82.

2- β -Bromoethylidibenzofuran.—Dry hydrogen bromide³ was bubbled at a moderate rate through 80 g. (0.377 mole) of molten 2- β -hydroxyethylidibenzofuran at 100° for one and one-half hours. The product was shaken with water, allowed to solidify, dried, and distilled under reduced pressure. The yield of bromide was 92%, and the compound distills at 179–180° (2–3 mm.) and melts at 62–62.5° on recrystallization from 95% ethanol.

Anal. Calcd. for $C_{14}H_{11}OBr$: Br, 29.06. Found: Br 28.71 and 29.29.

2- β -Diethylaminoethylidibenzofuran, $C_{12}H_7OCH_2CH_2N(C_2H_5)_2$.—The β -bromoethyl compound (80 g., 0.29 mole) and 72 g. (0.92 mole) of diethylamine were heated in a pressure bottle at 45–50° for twenty-two hours. The yield of 2- β -diethylaminoethylidibenzofuran was 82% (b. p. 169–170° (2 mm.)).

The hydrochloride, prepared from an ether solution of the base and hydrogen chloride, melted at 192–193° after crystallization from an ether-alcohol mixture.

Anal. Calcd. for $C_{18}H_{22}ONCl$: N, 4.63. Found: N, 4.72 and 4.96.

4- β -Hydroxyethylidibenzofuran.—This carbinol was synthesized from 4-dibenzofuryl-lithium (see preceding paper) and ethylene oxide in accordance with the directions for the preparation of 2- β -hydroxyethylidibenzofuran. The yield was 42% in a one mole run. The 4- β -hydroxyethylidibenzofuran distills at 190–191° (4 mm.) and melts at 70–71° after recrystallization from petroleum ether (b. p. 60–68°).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.21; H, 5.70. Found: C, 79.16; H, 5.71.

4- β -Bromoethylidibenzofuran.—This bromide was obtained in a 88% yield by the action of hydrogen bromide on the corresponding alcohol. The compound distills at 163–165° (2 mm.) and melts at 37–38°.

Anal. Calcd. for $C_{14}H_{11}OBr$: Br, 29.06. Found: Br, 29.24.

4- β -Diethylaminoethylidibenzofuran hydrochloride was obtained in a 27% yield as colorless needles melting at 184–185°. The procedure used was that described for the 2-isomer.

Anal. Calcd. for $C_{18}H_{22}ONCl$: N, 4.63. Found: N, 4.54 and 4.87.

4- β -Chloroethoxydibenzofuran, $C_{12}H_7O(OCH_2CH_2Cl)$.—A solution of 18.4 g. (0.1 mole) of 4-hydroxydibenzofuran (see preceding paper) in 150 cc. of water containing 5 g. of sodium hydroxide, and 25 g. of β -chloroethyl *p*-toluene-

(2) Dreger, "Organic Syntheses," Coll. Vol., I, p. 299.

(3) Ruhoff, Burnett and Reid, "Organic Syntheses," Vol. XV, p. 42.

sulfonate was heated on a water-bath for two and one-half hours with stirring. The chloroethoxy compound was separated from unaltered ester by shaking with a minimum quantity of petroleum ether. The yield was 75%, and the compound melted at 64–65° after crystallization from 95% ethanol.

Anal. Calcd. for $C_{14}H_{11}O_2Cl$: Cl, 14.38. Found: Cl, 14.53 and 14.51.

4- β -Diethylaminoethoxydibenzofuran, $C_{12}H_{17}O[OCH_2CH_2N(C_2H_5)_2]$, was prepared in a 22% yield by heating the chloroethoxy compound with diethylamine at 100° for eighteen hours. The impure base could not be distilled without significant decomposition. The hydrochloride formed by passing hydrogen chloride into a dry ether-acetone solution precipitated as an oil which crystallized after standing for several days and melted at 128.5–129.5° on crystallization from an ether-acetone solution.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.38. Found: N, 4.32 and 4.48.

4- β -Piperidinoethoxydibenzofuran, $C_{12}H_{17}O(OCH_2CH_2NC_5H_{10})$, was prepared by heating the chloroethoxy compound with piperidine on a steam-bath for twenty-four hours. The yield was 52%. The free amine distills at 213° (2 mm.) and the hydrochloride melts at 210.5–212°.

Anal. Calcd. for $C_{17}H_{23}O_2NCl$: N, 4.22. Found: N, 4.44 and 4.56.

4-Dibenzofurancarboxylic Acid Chloride, $C_{12}H_7OCOC_2H_5$.—The 4-dibenzofurancarboxylic acid was prepared in 30% yield by carbonation of 4-dibenzofuryl-lithium (prepared, in turn, through *n*-butyl-lithium and dibenzofuran); and in 50% yield by carbonating 4-dibenzofuryl-sodium. A quantitative yield of the crude acid chloride was obtained from 112 g. (0.52 mole) of 4-dibenzofurancarboxylic acid and 500 g. (4.2 moles) of thionyl chloride. The acid chloride was crystallized from ethanol, and finally purified by sublimation to melt at 118°.

Anal. Calcd. for $C_{13}H_7O_2Cl$: Cl, 15.22. Found: Cl, 15.24 and 15.11.

4-Dibenzofurancarboxylic acid amide was prepared by W. G. Bywater from the acid chloride and ammonium hydroxide, and melted at 181–182° after crystallization from ethanol.

Anal. Calcd. for $C_{13}H_9O_2N$: N, 6.63. Found: N, 6.73 and 6.46.

4-Aminodibenzofuran. (a) From 4-Hydroxydibenzofuran.—A mixture of 2.3 g. (0.0125 mole) of 4-hydroxydibenzofuran, 6 g. of fused zinc chloride and 2 g. of ammonium chloride was heated in a sealed tube at 275–280° for twenty-one hours. The brown mass was removed from the tube by lixiviating with dilute hydrochloric acid and ether. The acid solution was neutralized with sodium hydroxide and then extracted with ether. Hydrogen chloride then gave the amine hydrochloride in a 16% yield. The free amine, obtained from the hydrochloride by dil. alcoholic ammonium hydroxide, melts at 84.5–85.5°.

Anal. Calcd. for $C_{12}H_9ON$: N, 7.65. Found: N, 7.72 and 7.46.

(b) From 4-Dibenzofurancarboxylic Acid.—A Hofmann reaction on the amide of 4-dibenzofurancarboxylic acid gave yields of the amine ranging from 30 to 50%. The procedure was patterned after that described by Goldschmiedt⁴ with 4-fluorenoncarboxylic acid amide.

Both preparations of the 4-amine were made by W. G. Bywater.

4-Acetaminodibenzofuran.—A benzene solution of 4-aminodibenzofuran was acetylated by acetic anhydride to give an 89% yield of the 4-acetamino compound melting at 172.5°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.16 and 6.21.

Summary

Some amino derivatives have been prepared in connection with the physiological properties of dibenzofurans.

(4) Goldschmiedt, *Monatsh.*, **23**, 890 (1902).

AMES, IOWA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

Homoamines and Homoacids¹

BY PERCY L. JULIAN AND BERNARD M. STURGIS

This paper records details of a simple, relatively inexpensive and rapid method for preparation in good yield of β -arylethylamines (V) and arylacetic acids (VI), substances which are oft-needed tools in any laboratory, and especially one devoted to a study of natural products. The procedure has been employed successfully for preparation of homoveratrylamine, homopiperonylamine, homoanisylamine and the correspond-

ing homoacids, and indeed appears generally applicable.

The substituted benzaldehydes, which constitute starting material, are condensed with rhodanine in the initial reaction, and the remaining steps are indicated by formulas (I) \rightarrow (VI).

Condensation reactions of aldehydes with rhodanine have been beautifully worked out by Gränacher and his collaborators,² but these useful reactions have been overlooked as methods for

(1) Abstracted from the senior research of Bernard M. Sturgis at DePauw University and read before the American Chemical Society at the fall meeting in Chicago, 1933.

(2) Gränacher *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923).