[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Aminodibenzofurans and Derivatives

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In connection with studies on the correlation of physiological action with chemical constitution the following dibenzofuran derivatives were prepared: 2- and 4-β-aminoethyldibenzofuran, 2- and 3-fluorodibenzofuran, 4-dibenzofuryl-N-piperidinomethane, diethyl (3-dibenzofurylamino)ethylmalonate and diethyl (4-dibenzofurylamino)ethylmalonate. The synthesis of 3- and 4-(*p*-acetamidobenzenesulfonamido)dibenzofuran and of the corresponding amines was also carried out. The melting point of the 3-amide differed appreciably from previously recorded values. The interaction of 4-bromodibenzofuran with lithium dimethylamide and lithium diethylamide led to the rearrangement products: 3-dimethylaminodibenzofuran and 3-diethylaminodibenzofuran, respectively.

As early as 1922[1,2] investigators in the area of dibenzofuran chemistry sought to obtain physiologically active derivatives of this heterocycle. Lateral amino compounds and a nuclear amine were prepared and tested for morphine-like activity; such activity was absent.

Subsequently other aminodibenzofurans were prepared (and some tested) for evaluation as analgesics[3-10] as well as antimalarials[11,12] antituberculosis agents,[13] bacteriocides and bacteriostats,[14-18] and carcinogens.[19,20] We have prepared and are reporting here a variety of nuclear and lateral amino derivatives of dibenzofuran which contain groupings responsible for physiological activity in other molecules.

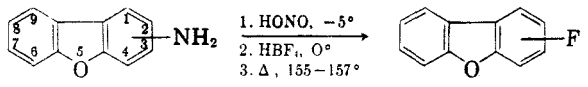
Of the sulfanilamide-type compounds reported here, only the two 4-substituted dibenzofurans are new. However, we have also included our directions for the preparation of the 3-isomers because of the discrepancy between our melting point for 3-(*p*-acetamidobenzenesulfonamido)dibenzofuran and the melting points previously reported[14,15] for this compound. Both 3-(*p*-aminobenzenesulfonamido)dibenzofuran and its 4-isomer were too insoluble for physiological testing.[21]

The β-aminoethyldibenzofurans were conveniently obtained by the Gabriel synthesis from the corresponding bromo compounds reported earlier.[5] These compounds as well as the 3-dimethylamino- and 3-diethylamino- compounds were prepared for general physiological screening.

Both 3-dimethylaminodibenzofuran and 3-diethylaminodibenzofuran have been reported previously. The earlier syntheses[5,22] involved the direct alkylation of 3-aminodibenzofuran. We are now reporting the preparation of these compounds by the amination (with rearrangement)[23] of 4-bromodibenzofuran with lithium dialkylamides.

2- and 3-Fluorodibenzofuran were prepared during the coarse of a search for antimalarial compounds. These are the first nuclear fluoro deriva-

(1) Mayer and Krieger, *Ber.*, **55**, 1659 (1922).
(2) von Braun, *Ber.*, **55**, 3761 (1922).
(3) Puetzer and Schoenhoefer, German Patent 550,327; *Chem. Abstr.*, **26**, 4062 (1932).
(4) Mosettig and Robinson, *J. Am. Chem. Soc.*, **57**, 902 (1935).
(5) Kirkpatrick and Parker, *J. Am. Chem. Soc.*, **57**, 1123 (1935).
(6) Mosettig and Robinson, *J. Am. Chem. Soc.*, **57**, 2186 (1935).
(7) Robinson and Mosettig, *J. Am. Chem. Soc.*, **58**, 688 (1936).
(8) Eddy, *J. Pharmacol. Exptl. Therap.*, **58**, 155 (1936).
(9) Burtner and Lehmann, *J. Am. Chem. Soc.*, **62**, 527 (1940).
(10) Miles Laboratories, Inc., British Patent 687,892; *Chem. Abstr.*, **48**, 4594 (1954).
(11) Wiselogle, *Survey of Antimalarial Drugs* 1941-1945, J. W. Edwards, Ann Arbor, Mich., 1946.
(12) Coatney, Cooper, Eddy, and Greenberg, *Survey of Antimalarial Agents*, Public Health Monograph No. 9, Federal Security Agency, U. S. Govt. Printing Office, Washington, D. C., 1953.
(13) Youmans, Doub, and Youmans, *The Bacteriostatic Activity of 3500 Organic Compounds for Mycobacterium Tuberculosis, Var. Hominis*, Review No. 4, National Research Council, Washington, D. C., 1953.
(14) Novelli, *Ciencia*, **1**, 260 (1940); *Chem. Abstr.*, **34**, 7903 (1940).
(15) Tani and Ohsaka, *J. Pharm. Soc. Japan*, **70**, 126 (1950); *Chem. Abstr.*, **44**, 5835 (1950).
(16) Puetzer, U. S. Patent 2,191,860; *Chem. Abstr.*, **34**, 4528 (1940).
(17) Bieber, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 665 (1953).
(18) Wenner, U. S. Patent 2,648,684; *Chem. Abstr.*, **48**, 9406 (1954).
(19) Miller, Miller, Sandin, and Brown, *Cancer Research*, **9**, 504 (1949).
(20) Buu-Hoï, *J. Chem. Soc.*, 2882 (1949).
(21) No test data were reported for Bieber's[17] 2-dibenzofuransulfonamides.
(22) Gilman, Jacoby, and Swislowsky, *J. Am. Chem. Soc.*, **61**, 954 (1939).
(23) This type of amination-rearrangement has been reported to occur in the treatment of 4-bromo-, 4-iodo-, and 4,6-diiodo-dibenzofuran with sodamide [Gilman and Avakian, *J. Am. Chem. Soc.*, **67**, 349 (1945)]. 3-Aminodibenzofuran was isolated in the first two cases; amination of the diiodo compound yielded 3,6-diaminodibenzofuran and 3-amino-6-iododibenzofuran. 1-Halonaphthalenes also yield rearrangement products with lithium dialkylamides [Gilman, Crounse, Massie, Benkeser, and Spatz, *J. Am. Chem. Soc.*, **67**, 2106 (1945)]. For a review of amination reactions see the pertinent sections in Levine and Fernelius, *Chem. Revs.*, **54**, 449 (1954).



tives[24] of dibenzofuran to be prepared and also apparently the only heterocyclic fluoro compounds other than derivatives of nitrogen-containing heterocycles to be prepared by the Schiemann reaction.[25]

Several other derivatives of dibenzofuran are also described in the experimental section of this paper.

EXPERIMENTAL[26]

3-(p-Acetamidobenzenesulfonamido)dibenzofuran. A solution of 9.6 g. (0.05 mole) of 3-aminodibenzofuran and 9.36 g. (0.04 mole) of *p*-acetamidobenzenesulfonyl chloride in 50 ml. of ethanol was refluxed for 5 hours. After dilution with ice-water, the solution was made alkaline with potassium hydroxide. Subsequent to extraction with ether, the aqueous layer was acidified. The precipitated product totaled 8.2 g. (54%), m.p. 199–203°. Several recrystallizations from dilute ethanol raised the melting point to 223–224°.[27] The yield of pure compound was 5.0 g. (39%).

Anal. Calc'd for $C_{20}H_{16}N_2O_4S$: N, 7.37. Found: N, 7.62.

Hydrolysis of the acetamido compound was effected by treatment with conc'd hydrochloric acid in ethanol. A 65% yield of 3-(*p*-aminobenzenesulfonamido)dibenzofuran was obtained, m.p. 245°.[28]

4-(p-Acetamidobenzenesulfonamido)dibenzofuran. By the method described for the preparation of the 3-isomer, a 41% yield of crude product was obtained, m.p. 210–214°. The yield of recrystallized material (from dil. ethanol) was 26.5%, m.p. 218°.

Anal. Calc'd for $C_{20}H_{16}N_2O_4S$: N, 7.37. Found: N, 7.06.

Hydrolysis of the acetamido compound yielded 73% of 4-(*p*-aminobenzenesulfonamido)dibenzofuran, m.p. 195°. The infrared spectrum of the compound showed the —NH (3.0 and 3.18 μ) and —SO_2— (7.30 and 8.65 μ) absorption bands.

2-β-Aminoethyldibenzofuran. (a). From 2-β-bromoethyldibenzofuran. An intimate mixture of 30.0 g. (0.108 mole) of 2-β-bromoethyldibenzofuran[5] and 25.0 g. (0.135 mole) of potassium phthalimide was heated without solvent for 6 hours at 185–200°. Following extraction of the reaction mixture with acetic acid, the solution was cooled, whereupon the substituted imide crystallized. This material was suspended in ethanol and after an excess of hydrazine hydrate was added, the mixture was refluxed until a gelatinous precipitate formed. The cooled reaction mixture was acidified with hydrochloric acid, heated to boiling, and filtered. The insoluble material was further extracted with dil. hydrochloric acid, and the filtrates were combined. The ethanol was distilled at reduced pressure and the remaining solution was made alkaline. Extraction with ether, drying of the ethereal solution, and removal of the ether by distillation gave a 46% yield of amine, b.p. 167–170°/2 mm. The free amine was extremely sensitive to atmospheric carbon dioxide. The compound was analyzed as the *hydrochloride*, m.p. 278°, prepared by passing dry hydrogen chloride into an ethereal solution of the amine.

Anal. Calc'd for $C_{14}H_{14}ClNO$: N, 5.67. Found: N, 5.64, 5.97.

(b). From 2-chloromethyldibenzofuran. To a solution of 84.0 g. (0.50 mole) of dibenzofuran in 100 ml. of petroleum ether (b.p. 75–115°) was added 25.0 g. (0.27 mole) of trioxymethylene and 20.0 g. of fused zinc chloride. Gaseous hydrogen chloride was passed at a rapid rate into the stirred suspension through a tube extending to the bottom of the flask. After 15–20 minutes the color of the reaction mixture darkened and the temperature began to rise. The reaction temperature was held at 55–60° for one hour, then the reaction mixture was poured onto ice. The organic layer and an ethereal extract of the aqueous phase were washed with sodium carbonate solution and dried over sodium sulfate.[29] After removal of the ether by distillation, 49.0 g. of crude 2-chloromethyldibenzofuran was distilled at 155–175°/4 mm. Redistillation yielded 41% of chloromethyl compound, b.p. 159–161°/3 mm., m.p. 78.5–79.5° after several recrystallizations from methanol.

Anal. Calc'd for $C_{13}H_9ClO$: Cl, 16.38. Found: Cl, 16.40, 16.63.

A small sample of the chloromethyl compound was oxidized to 2-dibenzofurancarboxylic acid by means of basic permanganate, thus indicating that chloromethylation like halogenation and sulfonation occurs *para* to the ether linkage.

2-Chloromethyldibenzofuran was converted to 2-cyanomethyldibenzofuran, b.p. 202–206°/2 mm., m.p. 102.5–103.5°,[30] by the method described in the literature.[31]

A solution of 13.0 g. (0.062 mole) of 2-cyanomethyldibenzofuran in 150 ml. of absolute ethanol was hydrogenated in a steam-heated vessel over 0.4 g. of Adams catalyst. After 1 hour, 10 lbs. of hydrogen had been absorbed. Filtration and evaporation of the solvent yielded 2-aminoethyldibenzofuran, b.p. 165–170°/2 mm. The hydrochloride melted at 278°, and a mixture melting point with a sample prepared by (*a*) was not depressed.

4-β-Aminoethyldibenzofuran. The amino compound was prepared by Gabriel synthesis from 4-β-bromoethyldibenzofurau[5] in the manner described for the preparation of the 2-isomer. A 61% yield of 4-β-aminoethyldibenzofuran was obtained, b.p. 165–166°/2 mm. The free amine did not react with atmospheric carbon dioxide.

The *hydrochloride* melted at 263° after two recrystallizations from water.

Anal. Calc'd for $C_{14}H_{14}ClNO$: N, 5.66. Found: N, 5.79.

2-β-Benzamidoethyldibenzofuran. To a solution of 2.0 g. (0.05 mole) of sodium hydroxide in 20 ml. of water were added 1.0 g. (0.005 mole) of 2-β-aminoethyldibenzofuran and 1.5 g. (0.01 mole) of benzoyl chloride. The reaction mixture was shaken for 15 minutes and then was heated for a short time on the steam-bath. The crystalline product which separated was filtered, washed, and dried to give 1.2 g. (89%) of crude amide, m.p. 177–180°. Recrystallization from glacial acetic acid raised the m.p. to 183.5–183.9°.

(24) Sawicki and Ray, *J. Am. Chem. Soc.*, **75**, 2266, (1953) have reported the preparation of the lateral fluoro compound, 3-trifluoroacetamidodibenzofuran.

(25) For a review of this reaction see Roe and Adams, *Org. Reactions*, **5**, Chap. 4 (1949).

(26) All melting and boiling points are uncorrected.

(27) Melting points of 242–243° [Rajogopalan and Ganapathi, *Proc. Indian Acad. Sci.*, **15A**, 432 (1942); *Chem. Abstr.*, **37**, 1125 (1943)], 242–244°[14] and 246–247°[15] have been reported previously.

(28) This compound has been reported to melt at 240–242°[14] and 246–247°.[15] In the case of the former reference, though the original article and *Chem. Abstr.* refer to a 2-derivative of dibenzofuran, it seems likely that the compound prepared was the 3-substituted dibenzofuran. In general, foreign publications use a numbering system for dibenzofuran in which the carbon atom *ortho* to the oxygen bridge is numbered 1.

(29) Dr. G. E. Brown has found that washing of the ethereal extract with ammonium hydroxide, hydrochloric acid, sodium bicarbonate solution, and water, in that order, prior to the drying step is effective in preventing the polymerization which may otherwise occur on distillation.

(30) A melting point of 89–90° [Wenner, *J. Org. Chem.*, **15**, 548 (1950)] has also been reported for this compound.

(31) Gilman and Avakian, *J. Am. Chem. Soc.*, **68**, 2104 (1946).

The infrared spectrum of this compound showed the anticipated —NH band at 3.1 μ and an amide carbonyl band at 6.18 μ.

No crystalline product could be obtained in cyclization attempts using phosphorus oxychloride in chloroform solution or phosphorus pentoxide in xylene.

3-Diethylaminodibenzofuran. Lithium diethylamide was prepared according to the method of Ziegler and Ohlinger.[32] *n*-Butyllithium[33] was prepared from 11 g. (0.08 mole) of *n*-butyl bromide and 1.4 g. (0.16 g.-atom + 20% excess) of lithium. To the ethereal solution of organometallic compound was added dropwise with stirring 5.85 g. (0.08 mole) of diethylamine in 25 ml. of anhydrous ether. The heat of reaction caused the mixture to reflux. After a 15-min. period of stirring, a solution of 10.2 g. (0.04 mole) of 4-bromodibenzofuran[34] in 50 ml. of dry ether was added slowly. After an additional 1 hour of stirring, the solution was allowed to stand overnight. The reaction mixture was hydrolyzed with 10 ml. of water and the ethereal layer was extracted with several portions of 5% hydrochloric acid. The combined extracts were refluxed with Norit, then filtered and made basic with ammonium hydroxide. The tertiary amine separated as a colorless oil. After the water-amine mixture had been heated in an open beaker until no odor of ammonia or diethylamine was detectable, the amine was separated from the aqueous phase and cooled overnight in the refrigerator. The white needles which formed were filtered, washed with water, dried, and taken up in anhydrous ether. Dry hydrogen chloride was passed into the ethereal solution. There was precipitated 3.35 g. (30%) of 3-diethylaminodibenzofuran hydrochloride, m.p. 227–228°. Since 3.5 g. of 4-bromodibenzofuran was recovered from the ethereal solution, the yield was 45% based on the amount of bromo compound actually consumed.

The free base, m.p. 68–69°, was obtained from the hydrochloride by treatment with ammonium hydroxide. A mixture melting point with an authentic sample[22] was 67–67.5°. The infrared spectra of the two samples were nearly superimposable.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.86. Found: N, 5.96.

3-Dimethylaminodibenzofuran. *n*-Butyllithium[33] was prepared from 0.4 g. (0.047 g.-atom + 20% excess) of lithium in 20 ml. of ether and 3.24 g. (0.023 mole) of *n*-butyl bromide in 15 ml. of ether. Lithium dimethylamide was prepared by the addition of 3.7 g. (0.023 mole) of dimethylamine in 20 ml. of ether to the solution of the organometallic compound. Then 3 g. (0.012 mole) of 4-bromodibenzofuran[34] was added and the mixture was allowed to stir overnight. After 3 days at room temperature without stirring, the reaction mixture was worked up in the manner described in the previous experiment. The crude 3-dimethylaminodibenzofuran weighed 1.61 g. (63%) and was slightly brown in color. Two recrystallizations from methanol (employing Norit) gave 0.6 g. (23.5%) of pure tertiary amine as colorless plates, m.p. 98–99°.

A mixture melting point with an authentic sample[5] was 95.5–97.5°. The infrared spectra of the two samples differed slightly; the variance in the positions of the bands was of a small enough degree to be ascribed to traces of impurities.

Anal. Calc'd for $C_{14}H_{13}NO$: N, 6.64. Found: N, 6.89.

3-Fluorodibenzofuran. A mixture of 23.4 g. (0.128 mole) of 3-aminodibenzofuran and 26.9 ml. (0.32 mole) of conc'd hydrochloric acid in 30 ml. of water was stirred at 75° for 1 hour. The mixture then was cooled to −5° and diazotized with a solution of 9.3 g. (0.128 mole) of sodium nitrite (95%) in 13 ml. of water. The mixture was stirred at 0° for 30 min. after a positive test for excess nitrous acid was obtained. A cold solution of fluoboric acid was added slowly from a copper beaker to the reaction mixture.

The fluoboric acid solution was prepared by dissolving 8.75 g. (0.14 mole) of boric acid in 21.4 g. (0.513 mole) of a cold 48% hydrofluoric acid solution. The mixture was stirred at 0° for 1 hour, then was filtered. The residue was immediately washed with 250 ml. of cold water, 50 ml. of cold methanol, and finally with 50 ml. of cold ether. The solid was quickly transferred to a vacuum desiccator and dried over sulfuric acid.

The 40.0 g. of crude diazonium fluoborate was decomposed at 155–157°, then the melt was distilled *in vacuo*. The material distilling at 125–140°/0.5 mm. amounted to 23.9 g. One recrystallization from ethanol gave 17.0 g. (80% based on the amine) of 3-fluorodibenzofuran, m.p. 88.5°. A mixture melting point with a sample of pure dibenzofuran (m.p. 82.5–83°) was 80°.

Anal.[35] Calc'd for $C_{12}H_7FO$: F, 10.21. Found: F, 10.01, 10.02.

2-Fluorodibenzofuran. In the manner described above, 11.3 g. (0.062 mole) of 2-aminodibenzofuran was diazotized. The diazonium salt was treated at 0° with a solution of fluoboric acid prepared from 5.7 g. (0.0925 mole) of boric acid in 10.3 g. (0.247 mole) of cold 48% hydrofluoric acid. The diazonium fluoborate was washed as above. From the decomposition of 10.0 g. of the complex was obtained 5.0 g. (44% based on the amine) of crude 2-fluorodibenzofuran. Recrystallization of this material from ethanol gave 4.4 g. (38.5%) of pure 2-fluorodibenzofuran, m.p. 88.5–88.8°. A mixture melting point with 3-fluorodibenzofuran was 80–81°.

Anal.[35] Calc'd for $C_{12}H_7FO$: F, 10.21. Found: F, 10.12.

4-Dibenzofuryl-N-piperidinomethane.[36] An ethereal solution of 20.0 g. (0.119 mole) of dibenzofuran was added to the *n*-butyllithium[33] prepared from 6.60 g. (0.952 g.-atom) of lithium and 50 ml. (0.476 mole) of *n*-butyl bromide in 400 ml. of anhydrous ether. A yellow-green color appeared almost immediately. Stirring was continued for 18 hours; at the end of this time a strong color test[37] for an organo-metallic compound was obtained.

The solution of 4-dibenzofuryllithium was added dropwise to an ethereal solution of 20.3 g. (0.119 mole) of *n*-butoxymethylpiperidine.[38] A white precipitate formed and some refluxing was observed during the addition. The yellow color which persisted was discharged by the addition of a small additional amount of *n*-butoxymethylpiperidine. The mixture was stirred for 10 hours, at the end of which time a negative color test was obtained. After the addition of 50 ml. of water, the undissolved solid was filtered off and extracted with ether. These extracts were combined with the ethereal layer from the filtrate and the whole was extracted with dil. hydrochloric acid. Treatment of the acid extract with ammonium hydroxide yielded a brown oil. This oil was separated and combined with the ethereal extract of the aqueous layer. Removal of the ether at reduced pressure was followed by vacuum distillation of the 4-dibenzofuryl-N-piperidinomethane at 175–180° at 0.5 mm. The yield was 7.8 g. (24.8%).

(32) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(33) Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(34) This compound, m.p. 69–70°, was prepared by the method of Gilman, Parker, Bailie, and Brown, *J. Am. Chem. Soc.*, 61, 2836 (1939).

(35) Fusion of the compound with sodium was accomplished by the method of Elving and Ligett, *Ind. Eng. Chem., Anal. Ed.*, **14**, 449 (1942). After precipitation of the fluoride as lead chlorofluoride according to the directions of Hawley, *Ind. Eng. Chem.*, **18**, 573 (1926), the precipitate was redissolved. The chloride was precipitated with silver nitrate and determined by the Volhard method; fluorine was calculated indirectly.

(36) Compound prepared by F. A. Yeoman.

(37) Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(38) Prepared in 66% yield, b.p. 91–93°/6 mm. by the method of Robinson and Robinson, *J. Chem. Soc.*, **123**, 532 (1923).

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.33, 5.41.

The *picrate*[39] melted at 177–178° after recrystallization from ethanol.

Anal. Calc'd for $C_{24}H_{22}N_4O_8$: N, 11.35. Found: N, 11.39, 11.30.

Diethyl (3-dibenzofurylamino)ethylmalonate. A mixture of 7.32 g. (0.04 mole) of 3-aminodibenzofuran and 5.34 g. (0.02 mole) of diethyl bromoethylmalonate[40] was heated on the steam-bath for 1 hour. The crude product was extracted with ether several times, then the ether was removed from the combined extracts by distillation. The residue was recrystallized from ethanol, then twice from petroleum ether (b.p. 60–68°) to give 51% of secondary amine, m.p. 99–100°.

Anal. Calc'd for $C_{21}H_{23}NO_5$: N, 3.79. Found: N, 4.02.

Diethyl (4-dibenzofurylamino)ethylmalonate. From 2.5 g. (0.014 mole) of 4-aminodibenzofuran and 1.87 g. (0.007 mole) of diethyl bromoethylmalonate the 4-isomer of the compound described above was prepared in 76.6% yield (1.9 g.), m.p. 75–76° after recrystallization from petroleum ether (b.p. 60–68°).

Anal. Calc'd for $C_{21}H_{23}NO_5$: N, 3.79. Found: N, 3.62.

Attempted preparation of diethyl (2-nitro-3-dibenzofurylamino)ethylmalonate. No reaction was effected between diethyl bromoethylmalonate and 2 equivalents of 2-nitro-3-aminodibenzofuran; the mixture did not melt at the temperature of the steam-bath. The use of toluene as a solvent was ineffectual in bringing about the reaction.

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We also wish to express our appreciation to Mr. John Eisch for assistance.

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(39) Prepared by Procedure 23A, Shriner and Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

(40) Prepared in 82% yield by the method of Ruhemann, *Ber.*, 26, 2357 (1893).