to 0°. Hydrogen chloride was introduced into the stirred and cooled solution at such a rate that the temperature remained below 10°; hydrogen chloride absorbed, 400 g. After standing for twelve hours at 0° the solution was poured into a water suspension of excess sodium bicarbonate and this solution was concentrated to dryness under reduced pressure at 50°. After dehydration with ethanol, the material was extracted with hot absolute ethanol (1 liter total) in portions, followed by removal of most of the inorganic salts by filtration. The ethanol was removed by concentration under reduced pressure and the resultant sirup was acetylated for twelve hours at room temperature with pyridine (350 cc.) and acetic anhydride (700 cc., initial cooling). This solution was concentrated under reduced pressure at 55° and the resultant thin sirup (260 g.) was poured into ice and water (1.5 liters) containing excess sodium bicarbonate. After stirring for thirty minutes, the aqueous solution which contained some insoluble sirup was extracted with several portions of chloroform. The chloroform solution (1 liter) was washed with sodium bicarbonate solution and with water, dried with calcium chloride and concentrated under reduced pressure; yield 182 g. of a light yellow sirup.

The sirup was distilled at approximately 1-mm. pressure through a 15-cm. fractionating column, 11 mm. in diameter, equipped with a nichrome wire spiral of about 1 turn per centimeter. The fraction (41.8 g.) boiling between 120–130° at a bath temperature of 70–80° was dissolved in an equal volume of ether and allowed to stand for twelve hours at 15°. The first crop of crystalline material (0.45 g.) melted at 200–208°. It was recrystallized from methanol and identified as trimethylenesorbitol; yield 0.27 g., m. p. 210–214°, $[\alpha]^{20}D$ −32° (*c* 2.5, chloroform). Ness, Hann and Hudson[13] cite as constants for 1,3:2,4:5,6-trimethylenesorbitol: m. p. 212–216°, $[\alpha]^{20}D$ −31° (*c* 1.2, chloroform).

A second crop of crystals was obtained when the ethereal mother liquor was treated with petroleum ether to incipient opalescence and allowed to stand for several weeks at 0°; yield 3.4 g. Pure material was obtained on further crystallization from ether–petroleum ether; yield 2.5 g., m. p. 107.5–108°, $[\alpha]^{26}D$ −61° (*c* 2.5, chloroform).

Anal. Calcd. for a diformal desoxyhexitol monoacetate ($C_8H_{13}O_5$-$COCH_3$): C, 51.72; H, 6.95; CH_3CO, 4.3 cc. 0.1 *N* sodium hydroxide per 100 mg. Found: C, 51.86; H, 6.92; CH_3CO, 4.3 cc.

This substance was identified as dimethylene-2-desoxysorbitol monoacetate by comparison with a synthetic product of known structure. An amount of 0.5 g. of dimethylene-2-desoxysorbitol, the synthesis of which is described below, was acetylated with pyridine and acetic anhydride and the product recrystallized from ethanol; m. p. 107–108° unchanged on admixture with the isolated product, $[\alpha]^{22}D$ −61° (*c* 4.5, chloroform).

Dimethylene-2-desoxysorbitol (Synonym Dimethylene-2-desoxy-D-mannitol).—2-Desoxysorbitol (10 g.) was treated at 0° with 40% formalin (50 cc.) and hydrogen chloride (44 g.) as described above. Neutralization and ethanol extraction of the dried mixture of sirup and sodium chloride yielded crystalline material (4 g.) after ethanol removal. Pure dimethylene-2-desoxysorbitol was obtained on further crystallization from acetone–petroleum ether; m. p. 148–149°, $[\alpha]^{28}D$ −17.5° (*c* 5. chloroform).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.57; H, 7.43. Found: C, 50.64; H, 7.69.

Summary

1. D-Mannitol and 1-desoxy-D-mannitol (D-rhamnitol) have been isolated in crystalline condition from a commercial product manufactured by the electroreduction of D-glucose at *p*H 10–13 and below 30°.

2. Identification of 1-desoxy-D-mannitol was made by periodate oxidation and by the preparation of its crystalline dibenzylidene and monotrityl derivatives.

3. 2-Desoxysorbitol (synonym 2-desoxy-D-mannitol) was isolated from the same source as crystalline dimethylene-2-desoxysorbitol monoacetate, identification being effected by comparison with a synthetic product of known structure.

4. The above results are in harmony with an enolic mechanism of sugar interconversion under reducing conditions.

COLUMBUS, OHIO RECEIVED JANUARY 4, 1946

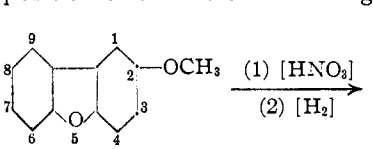
(13) A. T. Ness, R. M. Hann and C. S. Hudson, THIS JOURNAL, **66**, 665 (1944); *cf.* M. Schulz and B. Tollens, *Ann.*, **289**, 20 (1896).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

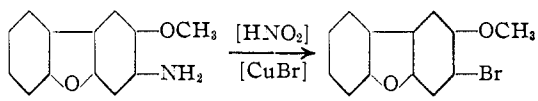
Dibenzofuran. XXIV. Some Dialkylaminoalkylamino Derivatives[1]

BY HENRY GILMAN AND S. AVAKIAN

The availability of some aminodibenzofurans suggested an examination of the corresponding dialkylaminoalkylamino derivatives for antimalarial action. One of the mono-substituted aminodibenzofurans used in this study was prepared by way of the nitration of 2-methoxydibenzofuran. The following reactions were used to establish the position of the nitro or amino group.



(1) Paper XXIII: Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).



A second amino derivative used in this study, 1-amino-3,4-dimethoxydibenzofuran, is most conveniently prepared by reduction of 1-nitro-3,4-dimethoxydibenzofuran which was obtained in a 96% yield by nitrating an acetic acid solution of 3,4-dimethoxydibenzofuran with fuming nitric acid. The structure of the nitro compound was established by reduction to an amine which was shown to be identical with an authentic specimen of 1-amino-3,4-dimethoxydibenzofuran prepared from the known 1-bromo-3,4-dimethoxydibenzofuran.

Of the several γ-diethylaminopropylaminodibenzofurans tested the only one which showed any activity, and this was slight, was 1-bromo-3-γ-diethylaminopropylamino - 4 - methoxydibenzofuran. This was the only compound examined which contained two different nuclear substituents in addition to the dialkylaminoalkylamino group. It is interesting to note that less than two additional nuclear substituents are sufficient for activity in some polynuclear heterocycles. An illustration chosen from a recent study of "open models" patterned after atabrine[2] is the continued activity when the chlorine in 6-methoxy-2 - (3′ - chlorophenyl) - 4 - [(α - methyl - δ - diethylaminobutyl)-amino]-quinoline is replaced by hydrogen. It is likely that compounds containing the basic side-chain *meta* to the methoxyl group, as in plasmochin, and a methyl or chloro group in the other ring of dibenzofuran may be active.

The dibenzofuran molecule was first examined as a possible source of antimalarials by the I. G. Farbenindustrie.[3] No pharmacological assays are available on their compounds which contained no nuclear substituents apart from the amino side-chain. More recently, Adams and co-workers[4] prepared several substituted aminobenzofuroquinolines, and these were shown to be inactive.

Experimental

3-γ-Diethylaminopropylamino-6-iododibenzofuran.—A mixture of 12.36 g. (0.04 mole) of 3-amino-6-iododibenzofuran[5] and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride[6] was heated for three and one-half hours in a bath kept at 160–165°. The heavy oil was dissolved in 350 cc. of hot water; the cooled solution was made alkaline with concd. ammonium hydroxide, extracted with ether, and the residue (obtained after removing the dried ether) was distilled under reduced pressure. The yield of heavy yellow liquid distilling at 290–295° (0.5 mm.) was 11.5 g. (68.1%).

Anal. Calcd. for $C_{19}H_{23}ON_2I$: N, 6.62. Found: N, 6.70.

3-γ-Diethylaminopropylaminodibenzofuran.—The reduction of 3-nitrodibenzofuran was carried out more conveniently in acetic acid with stannous chloride and hydrochloric acid than with tin and hydrochloric acid.[7] A solution of 85 g. (0.38 mole) of hydrated stannous chloride in 100 cc. of concd. hydrochloric acid was added to a solution of 25.6 g. (0.12 mole) of 3-nitrodibenzofuran in 300 cc. of glacial acetic acid and the mixture warmed on a steam-bath for twenty minutes. The brown precipitate which separated was filtered, then titrated with an excess of 10% sodium hydroxide solution, washed and filtered. One crystallization from dilute ethanol yielded 20 g. (91%) of pure 3-aminodibenzofuran.

From 12.1 g. (0.066 mole) of 3-aminodibenzofuran and 18.6 g. (0.1 mole) of γ-diethylaminopropyl chloride hydrochloride, heated at 165° for three hours, was obtained 12 g. (61.7%) of a light yellow oily product distilling at 260–261° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.66. Found: N, 9.61.

2-Bromo-3-γ-diethylaminopropylaminodibenzofuran.—From 8 g. (0.0305 mole) of 2-bromo-3-aminodibenzofuran[8] and 7.5 g. (0.0405 mole) of γ-diethylaminopropyl chloride hydrochloride, heated at 150–155° for three and one-half hours, was obtained 4.6 g. (40%) of a yellow oil with a green fluorescence which distilled at 190–195° at a pressure less than 0.5 mm.

Anal. Calcd. for $C_{19}H_{23}ON_2Br$: N, 7.46. Found: N, 7.38.

The same product was obtained in a yield of 0.5 g. (6.6%) by heating a mixture of 5.2 g. (0.02 mole) of 2-bromo-3-aminodibenzofuran, 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride and 5 g. of potassium carbonate in 200 cc. of propanol at the reflux temperature for twenty-four hours.

2-Nitro-3-hydroxydibenzofuran.—To a solution of 25 g. (0.1 mole) of 2-nitro-3-aminodibenzofuran[8] in 300 cc. of warm acetic acid was added 100 cc. of concd. hydrochloric acid. After the diazonium solution (formed by the addition of 8 g. of sodium nitrite) had stood for two hours in the cold, 50 g. of copper sulfate dissolved in 800 cc. of 2% sulfuric acid was added, and the resulting solution was refluxed for twenty-five minutes. Crystallization of the product from benzene gave 12 g. (52.4%) of 2-nitro-3-hydroxydibenzofuran melting at 162–163°.

Anal. Calcd. for $C_{12}H_7O_4N$: N, 6.11. Found: N, 6.03.

In an attempted methylation in acetone with dimethyl ulfate, the nitro-hydroxy compound was recovered.

2-Nitro-3-iododibenzofuran.—By a conventional diazotization procedure, 25 g. (0.1 mole) of 2-nitro-3-aminodibenzofuran yielded 19 g. (56%) of 2-nitro-3-iododibenzofuran which melted at 189–189.5° after crystallization from ethanol.

Anal. Calcd. for $C_{12}H_6O_3NI$: N, 4.16. Found: N, 4.10.

(2-Nitro-3-dibenzofuryl)-(4′-methoxyphenyl)-amine.—A mixture of 16.9 g. (0.05 mole) of 2-nitro-3-iododibenzofuran, 8.25 g. (0.05 mole) of acetyl-*p*-anisidine, 150 cc. of xylene, 10 g. of potassium carbonate and 1 g. of copper bronze was stirred and refluxed for twelve hours. The mixture was filtered hot, and from the cooled filtrate there precipitated a brown solid which, on crystallization from ethanol, melted at 154–155° and weighed 14.1 g. (74.5%). This acetyl compound was hydrolyzed by refluxing with ethanolic potassium hydroxide to yield 11 g. (89%) of (2-nitro-3-dibenzofuryl)-(4′-methoxyphenyl)-amine which crystallized from ethanol as needles melting at 173–174°.

Anal. Calcd. for $C_{19}H_{14}O_4N_2$: N, 8.38. Found: N, 8.49.

2,7-Bis-(γ-diethylaminopropylamino)-dibenzofuran.—A 92% yield of 2,7-diaminodibenzofuran was obtained by the stannous chloride reduction of 2,7-dinitrodibenzofuran.[9] A mixture of 7 g. (0.0356 mole) of the diamine and 18.6 g. (0.1 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a nitrogen atmosphere at 160–165° for three hours. The product was obtained in a yield of 10.1 g. (66.8%) as a yellow, fluorescent oil distilling at 285–290° (0.1 mm.).

Anal. Calcd. for $C_{28}H_{40}ON_4$: N, 13.20. Found: N, 13.40.

2,8-Bis-(γ-diethylaminopropylamino)-dibenzofuran.—A mixture of 7 g. (0.0356 mole) of 2,8-diaminodibenzofuran,[10] 14.9 g. (0.1 mole) of γ-diethylaminopropyl chloride, 300 cc. of propanol and 5.2 g. (0.72 mole) of fused sodium acetate was stirred and refluxed for 24 hours. The solution was diluted with water, made acid with 10 cc. of concd. hydrochloric acid, and the propanol removed under partially reduced pressure. From the ether extract, after

(2) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).

(3) I. G. Farbenindustrie A.-G., British Patent 373,624 (Aug. 20, 1931 [*Brit. C. A.*, **B**, 912 (1932)].

(4) Adams, Clark, Kornblum and Wolff, THIS JOURNAL, **66**, 22 (1944).

(5) Gilman and Avakian, *ibid.*, **67**, 349 (1945).

(6) Prepared in essential accordance with the directions of Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(7) Cullinane, *J. Chem. Soc.*, 2267 (1930).

(8) Gilman, Brown, Bywater and Kirkpatrick, THIS JOURNAL, **56**, 2473 (1934).

(9) Cullinane, *J. Chem. Soc.*, 2365 (1932).

(10) Prepared in accordance with the unpublished directions of Jack Swiss by the amination of 2,8-dibromodibenzofuran.

making basic with ammonium hydroxide, was obtained 8.2 g. (54.1%) of a reddish oil distilling at 240–245° (0.1 mm.).

Anal. Calcd. for $C_{26}H_{40}ON_4$: N, 13.20. Found: N, 12.99.

2-Bromodibenzofuran.—The following is an improved procedure, in time and yield, for the preparation of 2-bromodibenzofuran. A solution of 168 g. (1.0 mole) of dibenzofuran in 600 cc. of carbon tetrachloride was exposed to the radiation from a quartz jacketed H-4 mercury-vapor lamp and 160 g. (1.0 mole) of bromine was added with stirring over a three-hour period. Irradiation was continued for 2 more hours at room temperature, and then for one hour at the reflux temperature. Subsequent to the removal of the carbon tetrachloride by distillation, the product was distilled under reduced pressure to give 151 g. (61%) of compound melting at 102–106°. One crystallization from petroleum ether (b. p., 60–68°) yielded 128 g. (51%) of 2-bromodibenzofuran melting at 108–109°.

2-γ-Diethylaminopropylaminodibenzofuran.—From a mixture of 12.1 g. (0.066 mole) of 2-aminodibenzofuran,[8] 14.9 g. (0.1 mole) of γ-diethylaminopropyl chloride, 250 cc. of propanol and 7 g. of fused sodium acetate was obtained, after stirring and refluxing for eighteen hours, 11 g. (64%) of a reddish oil distilling at 185–190° (2 mm.).

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.46. Found: N, 9.57.

2-Acetamino-3-bromodibenzofuran.—The following are improved directions for the preparation of this compound.[8,11] To a solution of 22.5 g. (0.1 mole) of 2-acetaminodibenzofuran in 300 cc. of chloroform was added, at room temperature, 100 cc. of a molar solution of bromine in chloroform. After standing for two hours, the precipitate was filtered and the solution diluted with 300 cc. of ethanol. The precipitates were combined and recrystallized from acetic acid to give 11 g. (36%) of compound melting at 240–241°.

2-γ-Diethylaminopropylamino-3-bromodibenzofuran.—From a mixture of 8 g. (0.0305 mole) of 2-amino-3-bromodibenzofuran[12] and 7.5 g. (0.0405 mole) of γ-diethylaminopropyl chloride hydrochloride which was heated at 166–170° for three hours, was obtained 3.4 g. (30%) of a reddish, fluorescent oil distilling at 200–210° under a pressure of less than 0.5 mm.

Anal. Calcd. for $C_{19}H_{23}ON_2Br$: N, 7.46. Found: N, 7.51.

The same product was obtained in a very low yield (5%) by refluxing the reactants with sodium acetate in absolute ethanol for fifteen hours.

2-Methoxy-3-nitrodibenzofuran.—To a solution of 10 g. (0.05 mole) of 2-methoxydibenzofuran[11] in 150 cc. of glacial acetic acid cooled to 15° was added 8 cc. of fuming nitric acid (sp. g., 1.49), dropwise and with stirring. The mixture was kept at 15–18° for ten minutes and then filtered. The precipitate was washed with a little acetic acid, and the yield of product melting at 185–186° was 9 g. (73%). Crystallization from ethanol raised the melting point to 186–186.5°.

Anal. Calcd. for $C_{13}H_9O_4N$: N, 5.76. Found: N, 5.73.

2-Methoxy-3-aminodibenzofuran.—A suspension of 20 g. (0.0816 mole) of 2-methoxy-3-nitrodibenzofuran in 300 cc. of acetic acid was reduced by warming for an hour with a solution of 59.5 g. (0.268 mole) of hydrated stannous chloride in 70 cc. of concd. hydrochloric acid. The yield of 2-methoxy-3-aminodibenzofuran, melting at 92–92.5° after crystallization from methanol, was 15 g. (87%).

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.62.

By diazotization of 1 g. (0.005 mole) of 2-methoxy-3-aminodibenzofuran, followed by treatment with cuprous bromide in 10% hydrobromic acid solution, was obtained 2-methoxy-3-bromodibenzofuran. The melting point and mixed melting point with an authentic specimen[11] was 172°.

2-Methoxy-3-γ-diethylaminopropylaminodibenzofuran.—From 11 g. (0.0518 mole) of 2-methoxy-3-aminodibenzofuran and 15 g. (0.1 mole) of γ-diethylaminopropyl chloride, after heating in a nitrogen atmosphere at 150–155° for four hours, was obtained 12 g. (71%) of yellow oil distilling at 210–213° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.52.

1-Amino-2-methoxydibenzofuran.—This compound was prepared by the reaction of the Grignard reagent of 1-bromo-2-methoxydibenzofuran with α-methylhydroxylamine. The α-methylhydroxylamine was made by adding 39 cc. of 60% potassium hydroxide to 21 g. (0.25 mole) of α-methylhydroxylamine hydrochloride suspended in 400 cc. of ether. The ether–amine solution distilled over at 34–36°. A few grams of the methylhydroxylamine came over at 49–50°, after all of the ether had distilled. The two fractions were mixed and the ethereal solution was dried over anhydrous sodium sulfate.

The Grignard reagent from 33 g. (0.12 mole) of 1-bromo-2-methoxydibenzofuran[11] was prepared by reaction with 6.3 g. (0.25 g. atom) of magnesium turnings in a mixture of 150 cc. of ether and 150 cc. of dry benzene, using a little methyl iodide as a catalyst. To the RMgBr solution, cooled to 0°, was added over a ten-minute period 1.9 g. (0.04 mole) of α-methylhydroxylamine dissolved in 65 cc. of ether. After customary hydrolysis procedures, hydrogen chloride was added to the dried extracts to precipitate the amine hydrochloride. The free amine (obtained from the hydrochloride by the addition of dilute ammonium hydroxide) was recrystallized from dilute ethanol to give 5.8 g. (68% based on the α-methylhydroxylamine) melting at 92.5°.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.65.

1-γ-Diethylaminopropylamino-2-methoxydibenzofuran.—After heating a mixture of 5.5 g. (0.0258 mole) of 1-amino-2-methoxydibenzofuran and 7 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride at 150–155° for three hours and then at 165° for one hour, there was obtained 6.7 g. (80%) of a yellow, fluorescent oil which distilled at 205–207° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.54.

4-γ-Diethylaminopropylaminodibenzofuran.—The necessary 4-aminodibenzofuran was prepared by reaction of 4-dibenzofuryllithium with α-methylhydroxylamine, in accordance with unpublished directions of H. B. Willis. A mixture of 6 g. (0.033 mole) of 4-aminodibenzofuran and 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride was heated in a nitrogen atmosphere at 145–150° for three hours. The yield of light yellow oil distilling at 210–213° (0.5 mm.) was 8 g. (82%).

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.46. Found: N, 9.64.

1-Bromo-4-γ-diethylaminopropylaminodibenzofuran.—After heating a mixture of 8 g. (0.0305 mole) of 1-bromo-4-aminodibenzofuran[11] and 7.5 g. (0.04 mole) of γ-diethylaminopropyl chloride hydrochloride at 160–165° for three hours, there was obtained 4.5 g. (40%) of a light yellow oil with a green fluorescence which distilled at 212–215° at a pressure of less than 0.1 mm.

Anal. Calcd. for $C_{19}H_{23}ON_2Br$: N, 7.46. Found: N, 7.50.

1-Nitro-4-methoxydibenzofuran.—The following are improved directions for the preparation of 1-nitro-4-methoxydibenzofuran,[13] the yield being increased from 18 to 53%. To a solution of 27.7 g. (0.14 mole) of 4-methoxydibenzofuran in 200 cc. of glacial acetic acid cooled to 20° was added 20 cc. of fuming nitric acid (sp. g., 1.49) with stirring and over a ten-minute period. The mixture was kept at 18–20° for fifteen minutes and filtered. After washing the precipitate with 25 cc. of acetic acid and then with

(11) Gilman and Van Ess, THIS JOURNAL, **61**, 1365 (1939).

(12) Prepared by the alkaline hydrolysis of 2-acetamino-3-bromodibenzofuran (ref. 11).

(13) Gilman, Jacoby and Swislowsky, THIS JOURNAL, **61**, 954 (1939).

water, the yield of dry product melting at 152–153° was 18 g. (53%). One crystallization from ethanol gave the pure compound melting at 153.5–154° (mixed m. p.[13]).

1-γ-Diethylaminopropylamino-4-methoxydibenzofuran.—The 1-amino-4-methoxydibenzofuran was prepared by adding a solution of 60 g. (0.267 mole) of hydrated stannous chloride in 70 cc. of concd. hydrochloric acid to a warm suspension of 18 g. (0.0741 mole) of 1-nitro-4-methoxydibenzofuran in 250 cc. of acetic acid. After twenty minutes a clear solution resulted; the heating was continued for an additional thirty minutes, and on cooling a precipitate separated. This was filtered, treated with an excess of 25% sodium hydroxide solution, and the precipitate was recrystallized from dilute ethanol. The yield of pure product melting at 103–104° was 14.5 g. (92%). The compound was prepared earlier[13] by another method.

From 5.5 g. (0.0258 mole) of 1-amino-4-methoxydibenzofuran and 7 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride was obtained, after heating in a nitrogen atmosphere at 160–165° for five hours and then at 170° for one-half hour, 6.5 g. (80%) of a yellow oil distilling at 211–215° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.66.

1-Bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran.—A mixture of 8.8 g. (0.03 mole) of 1-bromo-3-amino-4-methoxydibenzofuran[14] and 7.5 g. (0.04 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a nitrogen atmosphere at 160–165°. After three hours, the dark brown oil was poured into water; the water was brought to a boil, and the mixture filtered from a considerable amount of insoluble matter. The cold filtrate was made basic with concd. ammonium hydroxide and extracted with two liters of ether. A considerable quantity of black ether-insoluble material was removed by filtration, and from the dried ether extract was obtained 3.2 g. (25.8%) of a dark red oil distilling at 245–250° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{25}O_2N_2Br$: N, 6.94. Found: N, 6.96.

3-γ-Diethylaminopropylamino-4-methoxydibenzofuran.—From a mixture of 2.3 g. (0.013 mole) of 3-amino-4-methoxydibenzofuran[14] and 5 g. (0.026 mole) of γ-diethylaminopropyl chloride hydrochloride, which was heated at 150–155° for three hours, was obtained 2 g. (50%) of a red oil distilling at 231–234° (0.3 mm.). This compound has not as yet been tested.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.71.

1-Nitro-3,4-dimethoxydibenzofuran.—To a solution of 9 g. (0.0394 mole) of 3,4-dimethoxydibenzofuran[15] in 100 cc. of acetic acid was added 9 cc. of fuming nitric acid (sp. g., 1.49) with stirring and cooling, over a five-minute period. From the heavy yellow precipitate was obtained, subsequent to crystallization from acetic acid, 10.5 g. (96%) of compound melting at 146–147°.

Anal. Calcd. for $C_{14}H_{11}O_5N$: N, 5.12. Found: N, 5.11.

1-Amino-3,4-dimethoxydibenzofuran.—A solution of 8 g. (0.0292 mole) of 1-nitro-3,4-dimethoxydibenzofuran in 200 cc. of absolute ethanol was catalytically reduced by Raney nickel at room temperature and under 40-pounds gage pressure. The catalyst was filtered, and the filtrate saturated with hydrogen chloride to give a quantitative yield of the amine hydrochloride. A suspension of the salt in water was heated with concd. ammonium hydroxide to yield [after one crystallization from petroleum ether (b. p., 60–68°)] 6.5 g. (92%) of pure product melting at 162–163°. A mixed melting point with an authentic specimen prepared by another procedure[15] showed no depression.

1-γ-Diethylaminopropylamino-3,4-dimethoxydibenzofuran.—A mixture of 5.1 g. (0.025 mole) of 1-amino-3,4-dimethoxydibenzofuran and 7 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a nitrogen atmosphere at 150° for one hour and then at 175° for three hours. The product distilled at 240–243° under a pressure of less than 0.1 mm., as a light yellow oil with a green fluorescence, and in a yield of 4.5 g. (50%). The compound is oxygen-sensitive and turns blue on exposure to air.

Anal. Calcd. for $C_{21}H_{28}O_3N_2$: N, 7.88. Found: N, 7.97.

In addition to the dialkylaminoalkylamino compounds described, 2-cyanodibenzofuran[16] was also tested and found to be inactive.

Attempted Direct Condensations with Nuclear Halogen Types.—A mixture of 8.8 g. (0.03 mole) of 2-iododibenzofuran[8] and 9.6 g. (0.06 mole) of 1-diethylamino-4-aminopentane was heated at 180–200° for forty-eight hours. The 2-iododibenzofuran was recovered quantitatively.

A mixture of 8.8 g. (0.03 mole) of 4-iododibenzofuran and 9.6 g. (0.06 mole) of 1-diethylamino-4-aminopentane was heated at 180–200° for thirty-six hours. The recovery of 4-iododibenzofuran was 7.6 g.

Acknowledgment.—The authors are grateful to Dr. Richard J. Porter and Dr. L. T. Coggeshall, of the University of Michigan, for the antimalarial tests, the results of which will be reported in detail elsewhere.

Summary

Several γ-diethylaminopropylaminodibenzofurans have been prepared and tested in experimental avian malaria. The only compound showing any activity, and this was slight, was 1-bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran. None of the other compounds examined had two different nuclear substituents in addition to the amino side-chain. The structure of 2-methoxy-3-aminodibenzofuran (prepared by way of the nitration of 2-methoxydibenzofuran), and of 1-amino-3,4-dimethoxydibenzofuran (prepared by way of the nitration of 3,4-dimethoxydibenzofuran) were established by a series of reactions leading to authentic types.

AMES, IOWA RECEIVED DECEMBER 20, 1945

(13) Prepared in essential accordance with the directions of Gilman, Parker, Bailie and Brown, THIS JOURNAL, **61**, 2836 (1939).

(14) Prepared in accordance with the directions of Gilman and Cheney, *ibid.*, **61**, 3149 (1939).

(15) Prepared in accordance with the directions of Gilman and Cheney, *ibid.*, **61**, 3149 (1939).

(16) Prepared by Harold Oatfield.