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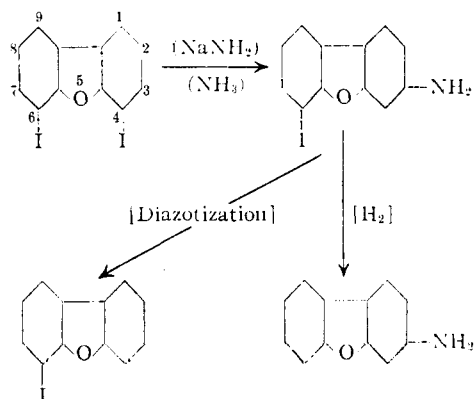
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## Dibenzofuran. XXIII. Rearrangement of Halogen Compounds in Amination by Sodamide<sup>1</sup>

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In connection with the preparation of 4,6-diaminodibenzofuran for antimalarial studies, an examination was made of the amination of 4,6-diiododibenzofuran. The products isolated were 4-aminodibenzofuran, 3-aminodibenzofuran, a diaminodibenzofuran and 3-amino-6-iododibenzofuran. The structure of the 3-amino-6-iodo compound was established as follows



A 3-amino-4-iododibenzofuran could also give 3-aminodibenzofuran and 4-iododibenzofuran by hydrogenolysis and diazotization, respectively, but a hetero-rearrangement is highly unlikely.

The diaminodibenzofuran is not the 4,6-compound which was prepared earlier<sup>2</sup> from 4,6-dihydroxydibenzofuran, ammonium hydroxide and sodium bisulfite. It is probable that the di-amino compound was formed from 3-amino-6-iododibenzofuran. Therefore, one of the amino groups must be in the 3-position and the other in either the 6, 7, 8, or 9-position. The 3,7- and the

3,8-diaminodibenzofurans were ruled out by comparison with authentic specimens. It is almost certain that our diamine is the 3,6-compound.

The 3,6-diaminodibenzofuran and 3-amino-6-iododibenzofuran were formed by amination with sodamide and liquid ammonia. Under corresponding conditions, but with ether also present, only 3-aminodibenzofuran was isolated (42% yield). In a high pressure amination with ammonium hydroxide and using cuprous bromide as a catalyst, 4-aminodibenzofuran was obtained in an 11% yield.

It was then shown that 4-iododibenzofuran when treated under corresponding conditions with sodamide in liquid ammonia gave 3-aminodibenzofuran. However, 2-bromodibenzofuran and 2,8-dibromodibenzofuran show no rearrangement in amination by sodamide in liquid ammonia.<sup>3</sup> Furthermore, 2-iodo- and 2,8-diiododibenzofuran are aminated without rearrangement under the selected experimental conditions. This suggested an amination of 4-bromodibenzofuran to determine whether the kind of halogen was a determining factor in the rearrangement. It was found that 4-bromodibenzofuran like the 4-iodo analog also reacted with sodamide in liquid ammonia to give the rearrangement product, 3-aminodibenzofuran.

Accordingly it appeared that the rearrangement takes place with any halogen *ortho* to an ether linkage. This found support in the formation of *m*-anisidine from *o*-iodoanisole, *o*-bromoanisole and *o*-chloroanisole. Also, 2-iododiphenyl ether gave, with sodamide in liquid ammonia, the 3-aminodiphenyl ether. Should the reaction be found later to be broad in scope, it may offer synthetic possibilities for the preparation of so-

<sup>1</sup> Paper XXII, Gilman and Swiss, THIS JOURNAL, 66, 1881 (1944).

<sup>2</sup> Gilman and Chemistry, *ibid.*, 61, 3119 (1939).

<sup>3</sup> Studies by C. W. Bealby and I. Swiss.

called abnormally oriented types like  $\beta$ -substituted aminofuran, etc. No study has as yet been completed on optimal conditions for the reaction, but orienting experiments with *o*-chloroanisole have shown that a 57.5% yield of *m*-anisidine can be obtained conveniently.

Finally, mention should be made of the fact that the catalyzed hydrolysis of 4,6-diiododibenzofuran proceeds normally to give 4,6-dihydroxydibenzofuran.

### Experimental

**4,6-Diiododibenzofuran.**—The following directions give a marked improvement in yield over the method described earlier.<sup>4</sup> First, phenylsodium was prepared by placing a mixture of 1200 cc. of toluene, 115 g. (5 g. atoms) of sodium sand, and 225 g. (2 moles) of chlorobenzene in a three-liter, 3-necked round-bottomed flask equipped with a Hopkins condenser having a nitrogen inlet, a mercury-sealed stirrer and a thermometer. A small crystal of iodine was added as a catalyst. Five minutes after the addition, the temperature began to rise and by appropriate cooling was not allowed to exceed 55° during the entire reaction period, which lasted about four hours.

A solution of 168 g. (1 mole) of dibenzofuran in 800 cc. of toluene was added directly to the organosodium mixture prepared above, and the temperature was raised to 100–105° by means of an oil-bath. The mixture was stirred at this temperature for twelve hours, then cooled in an ice-salt bath (–15°) and 635 g. (2.5 moles) of iodine was added at a rate to keep the temperature below 12°. The reaction was completed by heating at 60–65° for one hour; then the mixture was filtered, washed with 400 cc. of water containing 10 g. of sodium thiosulfate, and dried over calcium chloride. Concentration of the solution to 300 cc. yielded 290 g. of crude product melting at 155–158°. One crystallization from toluene gave 256 g. (60.1%) of colorless crystals melting at 160°. In three other preparations the yields were 59, 57 and 61%.

**Amination of 4,6-Diiododibenzofuran. [A] With Sodamide in Liquid Ammonia.**—Sodamide was prepared by the directions of Vaughn, Vogt and Nieuwland<sup>5</sup> from 10.1 g. (0.44 g. atom) of sodium and 0.3 g. of hydrated ferric nitrate in 400 cc. of liquid ammonia. Then 84 g. (0.2 mole) of 4,6-diiododibenzofuran was added over a period of fifteen minutes; the reaction was not vigorous, and after stirring for three hours the excess sodamide was destroyed by ammonium chloride. The ammonia was allowed to evaporate and the solid was extracted with one liter of ether. The amine was precipitated from the ether solution as the hydrochloride, which was subsequently treated in water with ammonium hydroxide. Two crystallizations from methanol yielded 37.8 g. of product melting at 143–144° and 2.1 g. of product melting at 154–155°. The lower melting compound is 3-amino-6-iododibenzofuran.

*Anal.* Calcd. for  $C_{12}H_9ONI$ : N, 4.53. Found: N, 4.52.

Six-tenths gram (0.002 mole) of the iodo-amine in 75 cc. of absolute ethanol was subjected to hydrogenation using a palladium-calcium carbonate catalyst, to yield 3-aminodibenzofuran (mixed m. p.).

In another experiment, 3 g. (0.01 mole) of the iodo-amine was diazotized to replace the amino group by hydrogen, and 4-iododibenzofuran (mixed m. p.) was obtained.

The iodine-free amine melting at 154–155° was shown by analysis to be a diamine, very probably 3,6-diaminodibenzofuran.

*Anal.* Calcd. for  $C_{12}H_{10}ON_2$ : N, 14.14. Found: N, 14.20.

(4) Gilman and Young, *THIS JOURNAL*, **57**, 1121 (1935). See also Gilman, Moore and Baine, *ibid.*, **63**, 2179 (1941), and Gilman, Paccvitz and Baine, *ibid.*, **62**, 1514 (1940).

(5) Vaughn, Vogt and Nieuwland, *ibid.*, **56**, 2120 (1934).

In an earlier experiment, the reaction products were acetylated by acetic anhydride to give two compounds, one of which melted at 321–322° and the other (containing iodine) at 268–269°. These compounds were shown to be identical with the acetylation products of the separate amines and, accordingly, are 3,6-diacetaminodibenzofuran and 3-acetamino-6-iododibenzofuran, respectively. The 3,6-diacetaminodibenzofuran crystallized from acetic acid as leaflets.

*Anal.* Calcd. for  $C_{16}H_{14}O_3N_2$ : N, 9.93. Found: N, 9.76.

The 3-acetamino-6-iododibenzofuran crystallized from ethanol as needles.

*Anal.* Calcd. for  $C_{16}H_{10}O_2NI$ : N, 4.10. Found: N, 4.02.

**[B] Amination with Sodamide in Liquid Ammonia and Ether.**—A solution of 21 g. (0.05 mole) of 4,6-diiododibenzofuran in 300 cc. of ether was added with stirring to a solution of 0.13 mole of sodamide in 200 cc. of liquid ammonia. Stirring was continued for twelve hours, and on working up the reaction mixture there was obtained 7.3 g. (42%) of 3-aminodibenzofuran.

**[C] Amination with Ammonium Hydroxide and Cuprous Bromide.**—A mixture of 42 g. (0.1 mole) of 4,6-diiododibenzofuran, 16 g. (0.11 mole) of cuprous bromide and 190 cc. of ammonium hydroxide was heated in a bomb at 180–185° for twenty-eight hours. The yield of 4-aminodibenzofuran (m. p. and mixed m. p., 84.5–85°) was 2 g. (11%).

**4,6-Dihydroxydibenzofuran. [A] From 4,6-Diiododibenzofuran.**—A mixture of 100 g. (0.238 mole) of 4,6-diiododibenzofuran, 22 g. of copper bronze and 200 g. of sodium hydroxide was placed in a copper beaker containing 100 g. of copper turnings and 30 g. of copper sulfate dissolved in 100 cc. of water. The mixture was heated in a bomb at 215–220° for fifteen hours. There was isolated, subsequent to dissolving in water and acidifying with hydrochloric acid, 35 g. (75%) of crude 4,6-dihydroxydibenzofuran melting at 145–150°. Recrystallization of 5 g. from benzene gave 4,6-dihydroxydibenzofuran (mixed m. p.), and the remaining 30 g. was converted to 4,6-dimethoxydibenzofuran.

**[B] From Oxidation of 4,6-Dilithiodibenzofuran.**—A solution of 8.4 g. (0.002 mole) of 4,6-diiododibenzofuran in 75 cc. of ether was added with stirring to 0.004 mole of *n*-butyllithium in ether. Then, in accordance with the procedure of Ivanoff,<sup>6</sup> 0.004 mole of *n*-butylmagnesium bromide in 50 cc. of ether was added to improve the yield of oxidation product. The reaction mixture was cooled below 0° by an ice-salt mixture, and oxygen (bubbled through sulfuric acid and passed over soda-lime) was swept over the surface of the well-stirred solution at a rate to maintain the temperature below 0° until a negative color test was obtained. The yield of pure 4,6-dihydroxydibenzofuran (mixed m. p.) was 5%.

**4,6-Dimethoxydibenzofuran.**—The procedure used was essentially that described for the methylation of 4-hydroxy-6-methoxydibenzofuran.<sup>2</sup> To a stirred and refluxed solution of 30 g. of crude 4,6-dihydroxydibenzofuran and 80 g. (0.682 mole) of dimethyl sulfate in 75 cc. of acetone was added a solution of 112 g. (2.8 moles) of potassium hydroxide in 80 cc. of water. After stirring at a reflux temperature for two hours, the product was poured into water. Crystallization from petroleum ether (b. p. 60–68°) gave 21 g. (61.4%) of 4,6-dimethoxydibenzofuran melting at 128–129°.<sup>2</sup>

**4-Iododibenzofuran.**—The following are improved directions for the preparation of 4-iododibenzofuran.<sup>8</sup> A solution of 16.8 g. (0.1 mole) of dibenzofuran in 50 cc. of ether was metallated by a slight excess of *n*-butyllithium in 75 cc. of ether, by refluxing and stirring for sixteen to eighteen hours in a nitrogen atmosphere. The reaction mixture was cooled in an ice salt bath and 25.4 g. (1.0 mole)

(6) Ivanoff, *Bull. Acad. Sci. Paris*, **39**, 47 (1926).

(7) Gilman and Scholtz, *THIS JOURNAL*, **47**, 2902 (1925).

(8) Gilman and Young, *ibid.*, **56**, 1115 (1934).

of iodine was added at a rate to keep the temperature below 5°. Subsequent to hydrolysis and drying of the ether layer, a reddish-brown solid melting at 63–65° was obtained when the ether was removed. Two recrystallizations from petroleum ether (b. p., 60–68°) gave 12 g. (42%) of product melting at 72–73°.

Amination of 29.4 g. (0.1 mole) of 4-iododibenzofuran by addition to a solution of sodamide (0.15 mole) in 600 cc. of ammonia, followed by four hours of rapid stirring, yielded 8.5 g. (47.5%) of pure 3-aminodibenzofuran (mixed m. p.). The compound was further identified by the preparation from it of 3-acetaminodibenzofuran (mixed m. p.).

**4-Bromodibenzofuran.**<sup>9a</sup>—Amination of 37 g. (0.15 mole) of 4-bromodibenzofuran by 0.2 mole of sodamide in 400 cc. of liquid ammonia gave 8.5 g. (31%) of 3-aminodibenzofuran. The melting point and mixed melting point with an authentic specimen was 97–98°.

**2-Iododibenzofuran.**<sup>9b</sup>—A solution of 29.4 g. (0.1 mole) of 2-iododibenzofuran in 70 cc. of dry benzene was added dropwise to a solution of 0.17 mole of sodamide in 400 cc. of liquid ammonia. The mixture was then stirred for one hour. The yield of 2-aminodibenzofuran (melting point and mixed melting point, 126–127°) was 6.2 g. (30%).

In another experiment, 29.4 g. (0.1 mole) of 2-iododibenzofuran, 0.15 mole of sodamide, and 400 cc. of liquid ammonia were allowed to react for two hours. After decomposing the excess sodamide by ammonium chloride, removing the solvent, and extracting the product with ether, the amine was precipitated as the hydrochloride. One crystallization of the free amine (obtained from the hydrochloride by treatment with ammonium hydroxide) from ethanol gave 3 g. (13%) of pure 2-aminodibenzofuran. In addition, there was recovered 6 g. of 2-iododibenzofuran.

**2,8-Diiododibenzofuran.**<sup>9b</sup>—From a reaction between 42 g. (0.1 mole) of 2,8-diiododibenzofuran and 0.3 mole of sodamide in 600 cc. of liquid ammonia, there was obtained (after stirring for four hours and then working up the product in a customary manner) 1.2 g. (6%) of 2,8-diaminodibenzofuran. From the reaction mixture was recovered 14 g. of 2,8-diiododibenzofuran.

**Amination of *o*-Iodo-, *o*-Bromo- and *o*-Chloroanisole.**—To a stirred solution of 0.7 mole of sodamide in 800 cc. of liquid ammonia was added dropwise 117 g. (0.5 mole) of *o*-iodoanisole. After stirring for two hours, the mixture was worked up in the usual manner and yielded 20.5 g. (33%) of *m*-anisidine distilling at 90–91° (0.5 mm.). The acetyl derivative was prepared, and a mixed m. p. determination with an authentic specimen of acetyl *m*-anisidine<sup>10</sup> showed no depression.

From the amination of 93.5 g. (0.5 mole) of *o*-bromoanisole and 0.7 mole of sodamide in 800 cc. of liquid ammonia (under the general conditions described for *o*-iodoanisole) there was obtained 20.5 g. (33%) of *m*-anisidine. This also was derivatized as the acetyl-*m*-anisidine (mixed m. p.).

From 40 g. (0.35 mole) of *o*-chloroanisole and 0.5 mole of sodamide in 700 cc. of liquid ammonia was obtained (after stirring for four and a half hours) 10 g. (23.2%) of *m*-anisidine (characterized by boiling point;  $n_D^{20}$  1.5810; and mixed m. p. of the acetamino derivative with an authentic specimen).

From 71.25 g. (0.5 mole) of *o*-chloroanisole, 0.7 mole of sodamide, 700 cc. of liquid ammonia and a one-hour period of stirring was obtained 31 g. (50%) of *m*-anisidine; b. p. 84–85° (0.3 mm.);  $n_D^{20}$  1.5812. From a parallel experiment in which the reaction mixture was stirred for fifteen minutes (after the twenty minutes required for addition), the yield of *m*-anisidine was 28 g. (45%);  $n_D^{20}$  1.5811.

A 57.5% yield (30 g.) of *m*-anisidine was obtained from a reaction between 60 g. (0.42 mole) of *o*-chloroanisole and 0.85 mole of sodamide in 800 cc. of liquid ammonia. The reaction mixture was stirred for one-half hour after the one-half hour period of addition.

**2-Iododiphenyl Ether.**<sup>11</sup>—From 15 g. (0.05 mole) of 2-iododiphenyl ether and 0.08 mole of sodamide in 250 cc. of liquid ammonia was obtained, after a fifteen-minute period of reaction, 3 g. of oily amino product. This on acetylation yielded 2.3 g. (22%) of 3-acetaminodiphenyl ether melting at 83–84°. A mixed m. p. with an authentic specimen<sup>12</sup> showed no depression. The authors are deeply grateful to Dr. Ray Q. Brewster for supplying the 2-iododiphenyl ether as well as the 3-acetaminodiphenyl ether.

## Summary

It has been shown that the amination of 4,6-diiododibenzofuran by sodamide in liquid ammonia gives 3,6-diaminodibenzofuran and 3-amino-6-iododibenzofuran. A similar rearrangement takes place with 4-iododibenzofuran and 4-bromodibenzofuran, but not with the 2-bromo-, 2-iodo-, 2,8-diiodo- or 2,8-dibromodibenzofuran.

The rearrangement appears to be general with *ortho*-halogenated ethers. *o*-Iodo-, *o*-bromo- and *o*-chloroanisole give *m*-anisidine; and 2-iododiphenyl ether gives 3-aminodiphenyl ether.

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(9) (a) Prepared in essential accordance with the directions of Gilman, Parker, Baile and Brown, *This Journal*, **61**, 2836 (1939).

(b) Gilman, Brown, Bywater and Kirkpatrick, *ibid.*, **56**, 2473 (1934).

(10) Korner and Weuder,  *Gazz. chim. Ital.*, **17**, 193 (1887).

(11) Clarkson and Gomberg, *This Journal*, **52**, 2885 (1930).

(12) Ullmann and Sponagel, *Ann.*, **350**, 83 (1901).