

(0.184 mole). After stirring and refluxing for 20 hours Color Test II<sup>4</sup> was only weakly positive. The temperature of the solution was then maintained below 5° by means of an ice-bath while 24.0 g. (0.15 mole) of bromine was admitted by entrainment in a slow stream of nitrogen. Bromine vapor was plainly visible going into the reaction flask, but at no time was there evidence of bromine vapor above the reaction mixture. After addition of the bromine was completed (4.5 hours) the mixture was hydrolyzed by pouring into an equal volume of water. The ether and water layers were separated and the aqueous layer washed with ether. The combined ether layers were washed first with sodium bisulfite solution and then with water. Removal of the solvent from the dried ether layer left an oily residue which was crystallized from ethanol to yield 13.3 g. (33.6%) of crude 4-bromodibenzothiophene melting at 70–73°. Fractional crystallization from ethanol and diluted ethanol with simultaneous digestion with Norit-A gave 8.4 g. (21.3%) of pure product; m.p. 83–84°. The infrared spectrum showed absorption bands at 13.35 and 13.5  $\mu$  characteristic of 1,2,3- and 1,2-substitution of the benzene rings, respectively.

*Anal.* Calcd. for C<sub>12</sub>H<sub>7</sub>BrS: Br, 30.4. Found: Br, 29.9, 30.2.

**3-Bromodibenzothiophene<sup>5</sup> (Attempted).**—Phenylcalcium iodide was prepared in 74.4% yield by the reaction of calcium with iodobenzene in ether. In accordance with the previously published procedure<sup>6</sup> 0.373 mole of phenylcalcium iodide in 450 ml. of ether was run into a stirred solution of 27.6 g. (0.15 mole) of dibenzothiophene in 250 ml. of ether. The mixture was then refluxed for 17 hours, stirred at room temperature for 11 hours, and cooled in an ice-bath. Bromination and product work-up were carried out as described above. The only materials isolated were unreacted dibenzothiophene (56.5% recovery), a small amount of 2,8-dibromodibenzothiophene, and a liquid tentatively identified as either bromobenzene or iodobenzene.

**2,8-Dibromodibenzothiophene-5-dioxide.**—A stirred suspension of 27.4 g. (0.08 mole) of 2,8-dibromodibenzothiophene<sup>1</sup> in 350 ml. of glacial acetic acid was heated to just below reflux temperature without obtaining complete solution. To the hot suspension was added 40 ml. (0.32 mole) of 30% aqueous hydrogen peroxide. The mixture was then stirred and refluxed for 1.5 hours during which time the suspended material became very finely divided and much denser. An additional 20 ml. (0.16 mole) of peroxide was then added and stirring and refluxing were continued for 1.5 hours more. The mixture was cooled and the white product filtered off and dried. The slightly impure 2,8-dibromodibenzothiophene-5-dioxide<sup>7</sup> weighed 28.5 g. (95.3%) and melted at 357–360°. The product was digested one hour with boiling dioxane, then cooled slowly. Filtration yielded 26.5 g. (88.6%) of white, finely divided, pure dioxide, m.p. 360–361°. The infrared spectrum showed absorption bands at 8.59 and 12.5  $\mu$  characteristic of the sulfone group and 1,2,4-substitution of the benzene ring, respectively.

**2,8-Dibromo-3,7-dinitrodibenzothiophene-5-oxide.**—Eighty ml. of fuming nitric acid (90%) was added to 6.8 g (0.02 mole) of 2,8-dibromodibenzothiophene.<sup>1</sup> The resulting mixture was warmed slowly to 50° and heated at this temperature for one hour. After pouring upon crushed ice, filtration yielded 7.8 g. (86.7%) of product melting at 283–292°. Two recrystallizations from glacial acetic acid gave 5.0 g. (55.6%) of pure 2,8-dibromo-3,7-dinitrodibenzothiophene-5-oxide. The infrared spectrum showed absorptions at 9.7 and 11.5  $\mu$ , characteristic of the sulfoxide group and of a tetrasubstituted benzene ring, respectively. Bands indicating the presence of a sulfone group were absent.

*Anal.* Calcd. for C<sub>12</sub>H<sub>4</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S: Br, 35.7. Found: Br, 35.6, 35.6.

tion higher yields of 4-dibenzothiophenecarboxylic acid. In addition, washing of the crude acid with water gives a much purer product from the *n*-propyllithium reaction due to the greater solubility of butyric acid over valeric acid.

(4) H. Gilman and J. Swiss, *THIS JOURNAL*, **62**, 1847 (1940).

(5) G. Illuminati, J. F. Nobis and H. Gilman, *ibid.*, **73**, 5887 (1951).

(6) H. Gilman, A. L. Jacoby and H. A. Pacevitz, *J. Org. Chem.*, **3**, 120 (1938). The reported preparation of 3-dibenzothiophenecarboxylic acid was satisfactorily checked prior to attempting the preparation of 3-bromodibenzothiophene.

(7) C. Courtot and C. Chaix, *Compt. rend.*, **192**, 1667 (1931).

**Nitration of 2,8-Dibromodibenzothiophene-5-dioxide (Attempted).**—Essentially a quantitative recovery of starting material was obtained from an attempt to nitrate 2,8-dibromodibenzothiophene-5-dioxide with fuming nitric acid as in the above procedure. Use of a mixture of concentrated sulfuric acid and concentrated nitric acid as the nitrating agent yielded a very small amount of yellow material melting at 331–333° which gave a melting point depression when admixed with starting material. However, no pure compound was isolated or identified.

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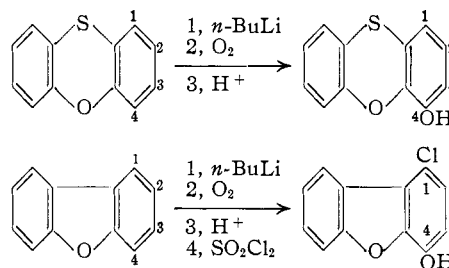
## Hydroxy Derivatives of Dibenzofuran, Phenoxathiin and Thianthrene

BY HENRY GILMAN AND DONALD L. ESMAY

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The excellent antiseptic properties of phenols<sup>1</sup> in general have long been known. In addition, halogenated phenols as a rule are more active as antiseptics than the unsubstituted phenols. Hexachlorophene, 2,2'-dihydroxy-3,5,6,3',5',6'-hexachlorodiphenylmethane, is an example of a halogenated phenol which has achieved considerable importance as a useful bactericide.<sup>2</sup>

As dibenzofuran, phenoxathiin and thianthrene have been shown to possess the power to kill various organisms,<sup>3</sup> it seemed of interest to prepare representative hydroxyl derivatives for bactericidal tests. This Note describes the preparation of 1-chloro- and 1,3-dichloro-4-hydroxydibenzofuran, 4-hydroxyphenoxathiin and 1-hydroxythianthrene. The results of tests for bactericidal activity will be reported elsewhere.



### Experimental<sup>4</sup>

**1-Chloro-4-hydroxydibenzofuran.**—4-Hydroxydibenzofuran<sup>5</sup> was prepared in a 45% yield (57.5% based on unrecovered dibenzofuran) by metalation of dibenzofuran with *n*-butyllithium in diethyl ether followed by oxidation with molecular oxygen in the presence of *n*-butylmagnesium bromide. To a solution of 9.2 g. (0.05 mole) of 4-hydroxydibenzofuran and 0.1 g. of iodine in 200 ml. of chloroform

(1) For a comprehensive review of the relation between the structure and bactericidal action of phenols, see C. M. Suter, *Chem. Revs.*, **28**, 269 (1941).

(2) M. John, *J. Am. Pharm. Assoc. Pract. Pharm. Ed.*, **10**, 488 (1949).

(3) For example, see L. E. Smith and R. Melvin, *J. Econ. Entomol.*, **36**, 475 (1943), and J. P. Linduska, F. A. Morton and W. C. McDuffie, *ibid.*, **41**, 43 (1948).

(4) All melting points are uncorrected.

(5) H. Gilman, L. C. Cheney and H. B. Willis, *THIS JOURNAL*, **61**, 951 (1939).

contained in a 500-ml. flask equipped with a motor stirrer, a dropping funnel and a reflux condenser closed with a calcium chloride tube was added dropwise a solution of 6.8 g. (0.05 mole) of sulfuryl chloride in 50 ml. of chloroform (15 min.). The color of the solution gradually changed during the addition of the sulfuryl chloride from a deep red to a light amber. After stirring at room temperature for 45 minutes the solution was allowed to stand overnight (red color returned), and then refluxed 1.5 hours. The solvent was removed by distillation leaving a pink solid which was dissolved in 35 ml. of boiling methanol. The solution was digested with Norit A, filtered hot, diluted with water and cooled. Filtration yielded 8.3 g. (85.3%) of white 1-chloro-4-hydroxydibenzofuran melting over the range of 85–105°. Purification was effected by fractional recrystallization from carbon tetrachloride. A total of 1.5 g. (11.8%) of pure product was obtained which melted at 154–155°. The infrared spectrum showed an absorption band at 3.0  $\mu$ , characteristic of the hydroxyl group.

*Anal.* Calcd. for  $C_{12}H_7ClO_2$ : Cl, 16.2. Found: Cl, 16.2, 16.2.

This compound was considered to be 1-chloro-4-hydroxydibenzofuran as bromination of 4-hydroxydibenzofuran has been shown to give 1-bromo-4-hydroxydibenzofuran.<sup>6</sup>

**1,3-Dichloro-4-hydroxydibenzofuran.**—A solution of 8.6 ml. (0.10 mole) of sulfuryl chloride in 50 ml. of chloroform was added dropwise over a period of 30 minutes to a stirred solution of 9.2 g. (0.05 mole) of 4-hydroxydibenzofuran in 200 ml. of chloroform. The solution was stirred at room temperature for 3 hours, then refluxed for 1.5 hours (until there was no further evidence of hydrogen chloride evolution). After the solvent was removed by distillation, the remaining gray residue was taken up in the minimum amount of refluxing carbon tetrachloride (250 ml.), and the resulting solution was digested with Norit A, filtered hot and allowed to cool slowly. The copious precipitate of white needles was filtered off yielding 6.6 g. (52.0%) of product melting at 158–159.5°. One recrystallization from carbon tetrachloride gave 4.6 g. (36.2%) of pure 1,3-dichloro-4-hydroxydibenzofuran, m.p. 160–161°. The infrared spectrum showed an absorption band at 3.15  $\mu$ , characteristic of the hydroxyl group.

*Anal.* Calcd. for  $C_{12}H_6Cl_2O_2$ : Cl, 27.8. Found: Cl, 27.5, 27.8.

Similar chlorination of the 1-chloro-4-hydroxydibenzofuran gave a 92.0% yield of 1,3-dichloro-4-hydroxydibenzofuran, m.p. 160–161°. A mixed m.p. of the two products showed no depression.

This compound was considered to be 1,3-dichloro-4-hydroxydibenzofuran since nitration of 1-bromo-4-methoxydibenzofuran has been shown to yield 1-bromo-3-nitro-4-methoxydibenzofuran.<sup>7</sup>

**4-Hydroxyphenoxathiin.**—4-Phenoxathiinylithium<sup>8</sup> was prepared by adding 0.1 mole of *n*-butyllithium<sup>9</sup> in 72 ml. of ether to a stirred suspension of 20.0 g. (0.1 mole) of phenoxathiin in 50 ml. of ether. After stirring and refluxing for 24 hours, the mixture was cooled in an ice-salt-bath. One-tenth mole of *n*-butylmagnesium bromide in ether was then added at such a rate that the temperature did not rise above  $-2^\circ$ . The resulting mixture was stirred and cooled for one hour, then oxygen was swept over the surface until a Color Test I<sup>10</sup> was negative (12 hours). Hydrolysis was carried out with iced 6 *N* hydrochloric acid. The acid layer was extracted well with ether and the resulting combined ether layer was extracted with 5% sodium hydroxide until an acidified sample gave no precipitate. Acidification of the combined alkaline solution and filtration gave 10.1 g. (46.7%) of light tan product melting over the range of 85–91°. Repeated recrystallizations from methanol and petroleum ether (b.p. 77–115°) raised the melting point to 98–99° and gave a final pure yield of 3.5 g. (15.5%).

*Anal.* Calcd. for  $C_{12}H_8O_2S$ : S, 14.83. Found: S, 14.75, 14.97.

(6) H. Gilman and P. R. Van Ess, *THIS JOURNAL*, **61**, 1365 (1939).

(7) H. Gilman, P. T. Parker, J. C. Bailie and G. E. Brown, *ibid.*, **61**, 2836 (1939).

(8) H. Gilman, M. W. Van Ess, H. B. Willis and C. G. Stuckwisch, *ibid.*, **62**, 2606 (1940).

(9) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *ibid.*, **71**, 1499 (1949).

(10) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

**1-Hydroxythianthrene.**—1-Thianthrenyllithium<sup>11</sup> was prepared by adding 0.11 mole of *n*-butyllithium<sup>9</sup> in 92 ml. of ether to a stirred suspension of 21.6 g. (0.1 mole) of thianthrene in 50 ml. of ether. After stirring and refluxing for 22 hours, the mixture was cooled in an ice-salt-bath. One-tenth mole of *n*-butylmagnesium bromide in ether was added at such a rate that the temperature did not rise above  $-2^\circ$ ; and the resulting mixture was cooled and stirred for one hour. While maintaining the internal temperature below  $-2^\circ$ , oxygen was swept over the surface of the reaction mixture until Color Test I<sup>10</sup> became negative (11 hours). The mixture was hydrolyzed with iced hydrochloric acid, the layers were separated, the acid layer was washed well with ether and the combined ether layer was extracted with 5% sodium hydroxide until no precipitate appeared when a test portion was acidified. Acidification of the combined alkaline layer and filtration gave 5.0 g. (21.6%) of 1-hydroxythianthrene melting over the range of 74–82°. Repeated recrystallizations from petroleum ether (b.p. 77–115°) raised the melting point to 117–118°.

*Anal.* Calcd. for  $C_{12}H_8OS_2$ : S, 27.60. Found: S, 27.62, 27.71.

Removal of the solvent from the reaction mixture ether layer yielded 6.8 g. of unreacted thianthrene (31.5% recovery) melting at 151–153°. Based on the unrecovered thianthrene, the crude yield of 1-hydroxythianthrene was 31.5% and the pure yield was 2.5%.

**Acknowledgment.**—The authors are grateful to Dr. Velmer A. Fassel and Mr. Marvin Margoshes and to the Ames Laboratory for the infrared absorption measurements.

(11) H. Gilman and C. G. Stuckwisch, *ibid.*, **65**, 1461 (1943).

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### Some Derivatives of 2-Amino-3-bromotetrahydropyran

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During the course of investigation of the preparation of nucleotide-like compounds a number of derivatives of 2-amino-3-bromotetrahydropyran were prepared.

Dihydropyran was quantitatively converted to 2,3-dibromotetrahydropyran (I), according to the direction of Paul.<sup>2</sup> Treatment of I with silver cyanate resulted in a 92% yield of 3-bromo-2-tetrahydropyranyl isocyanate (II). The action of aqueous ammonia on II gave the corresponding urea III; the disubstituted urea, 1,3-bis-(3-bromo-2-tetrahydropyranyl)-urea (IV), could be obtained by the hydrolysis of II, whereas the reaction of II with absolute ethyl alcohol afforded the urethan V. Furthermore, when II reacted with ethyl glycinate, ethyl 3-bromo-2-tetrahydropyranylhantoate (VI) was obtained, but attempts at ring closure to the corresponding hydantoin by means of 25% hydrochloric acid were unsuccessful.

Efforts to prepare similar derivatives of 3-bromo-2-tetrahydropyranyl isothiocyanate met with failure. The reaction of 2,3-dibromotetrahydropyran with silver thiocyanate gave upon distillation a liquid boiling at 107–110° (2 mm.) (VII). The conclusion that VII was the thiocyanate rather than the isothiocyanate was based on observations that the compound did not yield the substituted thiourea

(1) Parke, Davis and Co., Detroit 32, Michigan.

(2) R. Paul, *Compt. rend.*, **198**, 375 (1934).