

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

HALOGEN DERIVATIVES OF DIARYLPHTHALIDES. II¹

BY F. F. BLICKE, F. D. SMITH AND J. L. POWERS

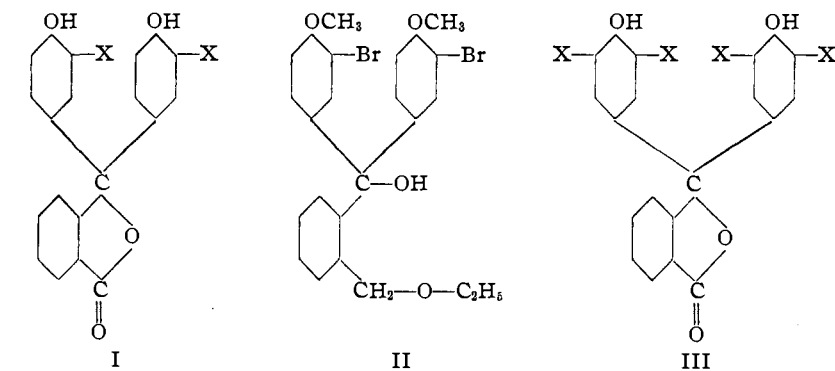
RECEIVED AUGUST 22, 1931

PUBLISHED APRIL 6, 1932

Some time ago² we described the products obtained by condensation of 4-fluoro-, 4-chloro-, 4-bromo-, 4-iodo and 3-iodophthalic anhydride with phenol.

We have studied now the interaction of 2-chloro-, 2-bromo, 2-iodo-, 2,6-dichloro- and 2,6-dibromoanisole with phthalyl chloride in the presence of aluminum chloride. The first three compounds reacted at ordinary temperature to form methyl ethers of phthalides of the general structure I in which halogen occupies the X positions; upon demethylation the phthaleins themselves were obtained, substances which dissolve in aqueous sodium hydroxide to form red-violet solutions which fade rapidly.³

Conclusive proof that the dimethyl ether of the dibromophthalein, and consequently the corresponding dimethyl ethers of the dichloro- and di-iodophthalein, really possessed structure I was obtained by the synthesis of 3',3''-dibromophenolphthalein dimethyl ether according to a method described previously⁴ for the preparation of diarylphthalides. 3,3'-Dibromo-4,4'-dimethoxybenzophenone reacts with 2-ethoxymethylphenylmagnesium bromide to form 2-ethoxymethyl-3',3''-dibromo-4',4''-dimethoxytriphenylcarbinol (II).

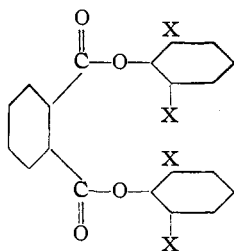


¹ This investigation was made possible by a grant from the American Pharmaceutical Association Research Fund and by the establishment of the Michigan State Pharmaceutical Association Research Fund and we wish to acknowledge our appreciation for the aid which has been given us.

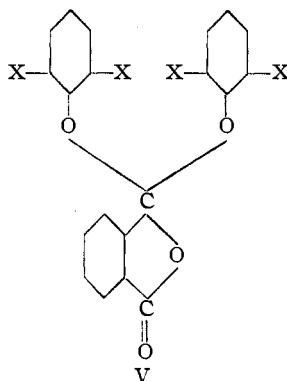
² Blicke and Smith, *THIS JOURNAL*, 51, 1865 (1929). This publication is to be regarded as the first paper of this series.

³ Recently Knapp [*Monatsh.*, 56, 106 (1930)] synthesized a dibromophenolphthalein dimethyl ether from phthalyl chloride, 4-bromoanisole and aluminum chloride. However, the positions of the bromine atoms in the phthalein molecule were not established.

⁴ Blicke and Weinkauff, *THIS JOURNAL*, 54, 1446 (1932).



IV



V

When this compound was subjected to oxidation the ethoxymethyl group was converted into carboxyl with the spontaneous elimination of water to form the phthalide, a substance which proved to be identical with the compound obtained from phthalyl chloride and 2-bromoanisole⁵ and also with the dibromo derivative formed by bromination of phenolphthalein dimethyl ether.⁶

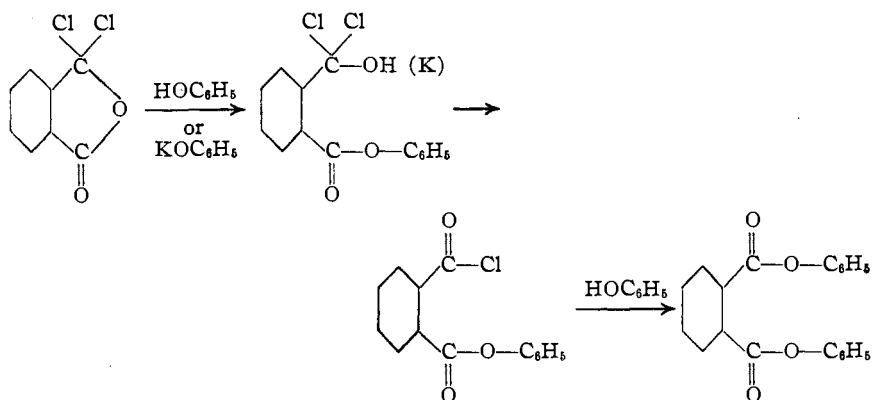
It was thought that from dihaloanisoles and phthalyl chloride methyl ethers of phthaleins of structure III might be produced. However, since it was found necessary in the case of the dihaloanisoles to heat the reaction mixture to the boiling point of the solvent employed, carbon disulfide, the dihaloanisoles were demethylated to a large extent by the aluminum chloride⁷ and the phenols formed reacted with the acid chloride to form tetrahalodiphenyl phthalates (IV) the structure of which was proved by their synthesis from phthalyl chloride and potassium 2,6-dihalophenolate. Before we had identified these esters with certainty, it was thought that tetrahalodiphenoxyphthalides of type V might have been produced; hence the synthesis of these compounds was attempted. Since such compounds apparently have not been prepared hitherto in the phthalein series, it was decided to prepare, first, the halogen-free diphenoxyphthalide from unsymmetrical phthalyl chloride and phenol. However, in the case of phenol, as well as potassium phenolate, we obtained diphenyl phthalate instead of diphenoxyphthalide. The following reaction mechanism is suggested to account for the formation of the ester. This mechanism gains support from the fact that phthalic anhydride and phenol react to yield the monophenyl ester of phthalic acid.⁸

⁵ Grande [*Gazz. chim. ital.*, **27**, II, 67 (1897)] condensed 2-bromoanisole with phthalyl chloride in the presence of aluminum chloride and obtained a dibromophthalein dimethyl ether which possessed the same melting point as the compound obtained by us.

⁶ Grande, *ibid.*, **26**, I, 230 (1896).

⁷ Hartmann and Gattermann [*Ber.*, **25**, 3531 (1892)] have shown that anisole is demethylated readily by aluminum chloride.

⁸ Bischoff and v. Hedenström, *ibid.*, **35**, 4092 (1902).



Finally, unsymmetrical phthalyl chloride, phenol and aluminum chloride were heated under various conditions but only diphenyl phthalate and a small quantity of phenolphthalein were produced. The latter may possibly have been formed as the result of a Friedel and Crafts reaction, or through the rearrangement of the diphenoxy compound, formed initially as a reaction product, or through the action of aluminum chloride on diphenyl phthalate.⁹

The monohaloanisoles were prepared by catalytic reduction of 2-nitroanisole to 2-anisidine, diazotization of the latter and conversion of the diazonium compound into the desired haloanisole.

2,6-Dichloro- and 2,6-dibromoanisole were obtained in the following manner. 4-Aminobenzoic acid was suspended in hot, dilute sulfuric acid and treated with sodium nitrite. 4-Hydroxybenzoic acid was obtained in 82% yield from a technical grade of the amino acid.¹⁰ By halogenation of the hydroxy acid we obtained 3,5-dichloro-, 3,5-dibromo- and 3,5-diiodo-4-hydroxybenzoic acid.

It was found that carbon dioxide could be eliminated from the dichloro- and dibromohydroxy acids merely by heating them with quinoline in an open flask¹¹ with a good yield of the corresponding dihalophenol. We were unable to obtain 2,6-diiodophenol by decarboxylation of 3,5-diiodo-4-hydroxybenzoic acid, since the phenol underwent decomposition during the process. Our efforts to prepare the phenol methyl ether from 3,5-diiodo-4-methoxybenzoic acid by elimination of carbon dioxide were also unsuccessful.

⁹ Csanyi, *Ber.*, **52**, 1792 (1919).

¹⁰ Although this method had been used previously by G. Fischer [*Ann.*, **127**, 145 (1863)], it was stated that considerable resin was formed and that the yield of hydroxy acid was not good.

¹¹ Several methods which require the use of sealed tubes have been described by Pope and Wood [*J. Chem. Soc.*, **101**, 1827 (1912)] for the elimination of carbon dioxide from 3,5-dibromo-4-hydroxybenzoic acid.

Methylation of the 2,6-dihalophenols with dimethyl sulfate yielded the desired anisoles.

Experimental Part

4-Hydroxybenzoic Acid.—A suspension prepared from 82 g. of 4-aminobenzoic acid (technical grade), 1000 cc. of water and 80 cc. of concd. sulfuric acid was heated to 80° and maintained at this temperature during the following operation. The mixture was stirred mechanically and 41.5 g. of sodium nitrite, dissolved in 300 cc. of water, was introduced slowly below the surface of the liquid. After all of the nitrite had been added, the solution was treated with charcoal, boiled and filtered. About one-half of the hydroxy acid separated from the filtrate when the latter was cooled. The remainder of the acid was obtained by extraction with ether. The crude hydroxy acid was dissolved in hot water and the solution boiled with charcoal until it was obtained, after filtration, in an almost colorless state. The yield was 67 g. or 82% of the calculated amount, m. p. 210–212°. ¹²

2,6-Dichloro- and 2,6-Dibromoanisole.—We prepared, first, 3,5-dichloro-¹³ and 3,5-dibromo-4-hydroxybenzoic acid.¹⁴ The dihalo acids were recrystallized from acetic acid and then thoroughly air-dried. One part of the respective 3,5-dihalo-4-hydroxybenzoic acid was heated in a flask, fitted with an air condenser, with two parts of freshly distilled quinoline until the evolution of carbon dioxide ceased; a bath temperature of 190–200° was required to effect the desired decomposition. The reaction mixture was cooled, treated with an equal volume of concd. hydrochloric acid and then extracted with ether. The ether solution was washed twice with water, separated, dried with fused sodium sulfate and the ether removed. The halophenols became solid when cooled and were recrystallized from petroleum ether (30–60°). The yield of pure product was 80–85%. The phenols were then methylated by the use of dimethyl sulfate.

TABLE I
2,5-DIHALOPHENOLS AND 2,6-DIHALOANISOLES

	M. p., °C.	B. p., °C.	Formula	Analyses, % ¹⁵	
				Calcd.	Found
C ₆ H ₃ Cl ₂ (OH)	68–70
C ₆ H ₃ Cl ₂ (OCH ₃)	Liquid	105–106 (20 mm.)	C ₇ H ₆ OCl ₂	Cl, 40.11	39.70
C ₆ H ₃ Br ₂ (OH)	55–57
C ₆ H ₃ Br ₂ (OCH ₃)	Liquid	129–130 (20 mm.)	C ₇ H ₆ OCl ₂	Br, 60.15	59.81

Condensation of Phthalyl Chloride with 2-Haloanisoles.—Two hundredths of a mole of phthalyl chloride was added to 0.05 mole of the respective 2-haloanisole, dissolved in 100 cc. of dry carbon disulfide. During the course of an hour 10 g. of aluminum chloride was added to the mixture. After twenty-four hours the carbon disulfide layer was decanted and the residue decomposed with ice and hydrochloric acid. The product was washed thoroughly with hydrochloric acid, then with sodium hydroxide solution and finally was recrystallized from acetic acid.

Dihalophenolphthaleins.—Two grams of the dimethyl ether of the dihalophenolphthalein was dissolved in 50 cc. of boiling acetic acid. Fifty cc. of 48% hydrobromic acid was added to the boiling solution in small portions in order to prevent precipita-

¹² Stohmann, Kleber and Langheim [*J. prakt. Chem.*, [2] **40**, 130 (1889)] recorded the melting point as 213°.

¹³ Zincke, *Ann.*, **261**, 250 (1891).

¹⁴ Robertson, *J. Chem. Soc.*, **81**, 1482 (1902).

¹⁵ Thompson-Oakdale method, *THIS JOURNAL*, **52**, 1195 (1930).

TABLE II
 DIMETHYL ETHERS OF 3',3"-DIHALOPHENOLPHTHALEINS

	M. p., °C.	Yield, ^a %	Analyses, %	
			Formula C ₂₂ H ₁₆ O ₄ X ₂	%
Dichloro	136-138	90	Cl, calcd., 17.08	Found, 17.18
Dibromo	161-162 ^b	85	Br, calcd., 31.70	Found, 31.40
Di-iodo	177-179	66	I, calcd., 42.47	Found, 42.40

^a The yield given is that of recrystallized material. ^b Grande [*Gazz. chim. ital.*, [II] 27, 68 (1897)] found the melting point to be 160-161°.

tion of the phthalein dimethyl ether. The mixture was refluxed for three hours. The hydrobromic and acetic acids were removed and the residue treated with 10% sodium hydroxide solution. The alkaline solution was filtered and then acidified with dilute hydrochloric acid. The phthalein precipitated in an amorphous condition. The iodo compound was obtained in the form of crystals by recrystallization from acetic acid. These dihalophenolphthaleins dissolved in alkali with the formation of red-violet solutions which fade with great rapidity.

 TABLE III
 3',3"-DIHALOPHENOLPHTHALEINS

	M. p., °C.	Analyses, %	
		Formula C ₂₀ H ₁₂ O ₄ X ₂	%
Dichloro	Amorphous ^a	Cl, calcd., 18.34	Found, 18.38
Dibromo	Amorphous ^b	Br, calcd., 33.61	Found, 33.82
Di-iodo	245-246	I, calcd., 44.56	Found, 44.41

^a Consonno and Apostolo [*Gazz. chim. ital.*, [I] 51, 63 (1921)] stated that they obtained an amorphous phthalein by condensation of phthalic anhydride with 2-chlorophenol but Thiel and Müller [*Ber.*, 55, 1313 (1922)], who repeated their process, were able to obtain only traces of the compound. Thiel and Diehl [*Sitzber. Ges. Beförder. ges. Naturw. Marburg*, 62, 536 (1927)] obtained the dichlorophthalein in very satisfactory yield from 2-(3'-chloro-4'-hydroxybenzoyl)-benzoic acid and phenol and also from 3',3"-diaminophenolphthalein. The melting point was recorded as 177°.

^b This product was obtained by Grande [*Gazz. chim. ital.*, [II] 27, 69 (1897)] in an amorphous form.

Condensation of Phthalyl Chloride with 2,6-Dichloro- and 2,6-Dibromoanisole.—The procedure used was the same as that described above except that the reaction mixture was refluxed for five hours. The compound obtained from 2,6-dichloroanisole, after recrystallization from alcohol, melted at 142-144°. The material obtained from 2,6-dibromoanisole melted at 216-218° after recrystallization from acetic acid.

Tetrachlorodiphenyl and tetrabromodiphenyl phthalate were prepared in the following manner. The potassium derivative was prepared from 2,6-dichlorophenol dissolved in absolute ether. After the addition of one-half of a molecular equivalent of phthalyl chloride the mixture was heated for one hour on a steam-bath. The potassium chloride and ether were removed and the oily residue washed with a small quantity of cold acetic acid. The crystalline material obtained, the 2,2',6,6'-tetrachlorodiphenyl ester of phthalic acid, was recrystallized from acetic acid; m. p. 142-144°. Mixed with the material obtained from 2,6-dichloroanisole the melting point was unchanged.

Anal. Calcd. for C₂₀H₁₀O₄Cl₄: mol. wt., 456; Cl, 31.14. Found: mol. wt. (camphor), 434; Cl, 31.42.

When the potassium derivative of 2,6-dibromophenol was used we obtained the 2,2',6,6'-tetrabromodiphenyl ester of phthalic acid. After recrystallization from acetic

acid the compound melted at 217–218°. The mixed melting point with the substance obtained from 2,6-dibromoanisole was 216–218°.

Anal. Calcd. for $C_{20}H_{10}O_4Br_4$: mol. wt., 633; Br, 50.44. Found: mol. wt. (camphor), 632; Br, 49.92.

One and twenty-six hundredths grams of the ester was hydrolyzed. There was obtained 1.00 g. of 2,6-dibromophenol and 0.30 g. of phthalic acid. The calculated amounts of phenol and acid are 1.00 g. and 0.33 g., respectively.

The products we hoped to obtain by condensation of phthalyl chloride with 2,6-dichloro- and 2,6-dibromoanisole were prepared by another method. 3',3'',5',5''-Tetrachloro¹⁶ and 3',3'',5',5''-tetrabromophenolphthalein¹⁷ were obtained by direct halogenation of phenolphthalein. The melting point of the latter compound was recorded by Baeyer as 220–230° but we found the melting point of tetrabromophenolphthalein to be 295–297°.¹⁸ These halophenolphthaleins were methylated with eight molecular equivalents of dimethyl sulfate in hot alkaline solution. After recrystallization from acetic acid, the dimethyl ether of tetrachlorophenolphthalein melted at 180–182° and the ether of the corresponding tetrabromo compound melted at 201–204°.¹⁹

Anal. Calcd. for $C_{22}H_{14}O_4Cl_4$: Cl, 29.21. Found: Cl, 29.17.

Preparation of 3',3''-Dibromophenolphthalein Dimethyl Ether with the Aid of the Grignard Reagent

2-Ethoxymethyl-3',3''-dibromo-4',4''-dimethoxytriphenyl Carbinol.—2-Ethoxymethylphenylmagnesium bromide was prepared from 4.3 g. of 2-ethoxymethylphenyl bromide, 0.48 g. of magnesium, 10 cc. of ether and 10 cc. of dry benzene. Six grams of 3,3''-dibromo-4,4''-dimethoxybenzophenone,²⁰ suspended in 25 cc. of benzene, was added and the mixture heated on a steam coil for two hours. After decomposition with ice and ammonium chloride the ether-benzene layer was separated. The crystalline residue, after recrystallization from carbon disulfide, weighed 5.6 g.; m. p. 148°.

3',3''-Dibromophenolphthalein Dimethyl Ether.—To 2.26 g. of the above tertiary carbinol, dissolved in 40 cc. of acetic acid, there was added 3.9 g. of finely powdered potassium dichromate. The mixture was heated with frequent agitation for four hours and then poured into 400 cc. of hot water. After the addition of 10 cc. of hydrochloric acid, the mixture was cooled. The crystalline product, after recrystallization from methyl alcohol, weighed 0.9 g.; m. p. 161–162°. The same melting point was obtained when the product was mixed with the dibromophthalein dimethyl ether produced in the condensation of phthalyl chloride with 2-bromoanisole.

Attempts to Obtain Diphenoxypthalide.—Two grams of unsymmetrical phthalyl chloride,²¹ 1.88 g. of phenol and 10 cc. of benzene were heated at 90° for thirty minutes, when the evolution of hydrogen chloride practically ceased. From the reaction mixture there was obtained 2.7 g. of diphenyl phthalate, which melted at 74–75° after recrystallization from alcohol. Complete conversion of the chloride into the ester would have yielded 3.28 g. of the material. No phenolphthalein was formed since the crude reaction product remained colorless when treated with alkali.

¹⁶ (a) Whiting, *THIS JOURNAL*, **42**, 2366 (1920); (b) Thiel and Diehl, *Sitzber. Ges. Beförder. ges. Naturw. Marburg*, **62**, 537 (1927).

¹⁷ Baeyer, *Ann.*, **202**, 78 (1880).

¹⁸ Thiel and Diehl^{16b} reported the melting point to be 286°.

¹⁹ Meyer, [*Ber.*, **40**, 2432 (1907)] recorded the melting point as 205–206°.

²⁰ Böslér, *ibid.*, **14**, 329 (1881).

²¹ Ott, *Ann.*, **392**, 274 (1912). In order to obtain this compound it is essential that the product obtained after rearrangement of the *sym.* acid chloride with aluminum chloride should be pulverized very finely before it is sifted on ice.

Potassium phenolate was prepared from 9.4 g. of phenol, dissolved in 150 cc. of absolute ether. Seven and five-tenths grams of the acid chloride was added and the mixture heated for thirty minutes. Eleven and three-tenths grams of diphenyl phthalate was isolated; the calculated amount of ester is 12.3 g.

Sixteen grams of aluminum chloride was added, in portions, to a mixture prepared from 10 g. of the acid chloride, 9.4 g. of phenol and 100 cc. of carbon disulfide. The mixture was refluxed for one-half hour, when the evolution of hydrogen chloride stopped. The carbon disulfide, which was found to be free from organic compounds, was decanted and the residue, after decomposition with ice and hydrochloric acid, steam distilled to remove any unchanged phenol. The amorphous reaction product weighed 8.2 g. Two and five-tenths grams of this material was treated with 100 cc. of 2% sodium hydroxide solution. Two grams of an alkali-insoluble product was obtained which proved to be diphenyl phthalate; m. p. 74-75°. Upon acidification of the alkaline solution, 0.2 g. of phenolphthalein precipitated which melted at 254° after recrystallization from acetic acid.

Summary

2-Chloro-, 2-bromo- and 2-iodoanisole react with phthalyl chloride in the presence of aluminum chloride to yield 3',3"-dihalophenolphthalein dimethyl ethers. Upon demethylation the phthaleins themselves were obtained.

From 2,6-dichloro- and 2,6-dibromoanisole, phthalyl chloride and aluminum chloride tetrahalodiphenyl phthalates were formed.

A practical method has been found for the preparation of 2,6-dichloro- and 2,6-dibromophenol.

Attempts to obtain diphenoxyphthalide are described.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]
**THE BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF -ONIUM
COMPOUNDS. IX. DERIVATIVES OF HOMOLOGS OF BETAINE¹**

BY R. R. RENSHAW AND M. E. MCGREAL²

RECEIVED AUGUST 22, 1931

PUBLISHED APRIL 6, 1932

The present paper deals with a continuation of the work³ being done in coöperation with Reid Hunt, in an attempt to get some light on the basis for the action of substances on the nervous system and, along with that, the problem of discovering substances with highly selective actions on such tissues. In the latter endeavor some success has been attained.

¹ This problem is being carried out in coöperation with Dr. Reid Hunt of the Harvard Medical School. The physiological data are the basis of another series of papers published elsewhere by him.

² This paper includes a portion of the material of a thesis presented by Martin E. McGreal, June, 1928, for the degree of Doctor of Philosophy at New York University.

³ Renshaw and co-workers: (a) *Science*, **62**, 384 (1925); (b) *THIS JOURNAL*, **47**, 1904, (c) 2989 (1925); (d) *ibid.*, **48**, 517, (e) 1726, (f) 2146, (g) 2698 (1926); (h) *ibid.*, **51**, 953 (1929).