

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

A NEW METHOD FOR THE PREPARATION OF DIARYLPHTHALIDES¹

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During a study of synthetic laxatives it became necessary to obtain a supply of phenolphthalein (4',4''-dihydroxydiphenylphthalide) entirely free from the by-products which result during the manufacture of this substance. Certain of these by-products—presumably some type of anthraquinone—are extremely potent cathartics and yellow phenolphthalein, that is, phenolphthalein which has not been subjected to a thorough purification process and which is contaminated with a small quantity of a yellow, alkali-soluble, resinous material, is used extensively as a laxative.²

Furthermore, we wished to obtain a sample of isophenolphthalein (2',4''-dihydroxydiphenylphthalide) in order that its physiological properties might be reinvestigated. In a preliminary report by Hatcher³ it is recorded that isophenolphthalein exhibits no cathartic action on humans. In view of the fact that this substance differs from phenolphthalein only in the respect that it is a 2',4''-dihydroxy instead of a 4',4''-dihydroxy derivative, it would be conceivable that the material might be less active than phenolphthalein but it seemed very strange that the compound should have been found to be entirely inert. Although our tests were carried out only on a very limited scale, the results obtained with the isophenolphthalein prepared by us agreed with those of Hatcher. Administered, mixed with milk sugar, in the form of gelatine capsules, no laxative effect was obtained with human subjects even with doses as large as four grains.

One of the objectionable features of many of the syntheses described hitherto is that in addition to the desired phthalide, by-products such as isomeric phthalides or anthraquinone derivatives are usually formed.

It seemed to us that the following method might be a very satisfactory one, not only for the synthesis of phenolphthalein and isophenolphthalein but also for a variety of diarylphthalides, since only one phthalide could be produced and the formation of an anthraquinone would be impossible; moreover, due to the procedure employed, the positions of any substituents in the phthalide molecule would be known with certainty.

Benzophenone should yield the MgBr derivative of 2-methyltriphenyl-

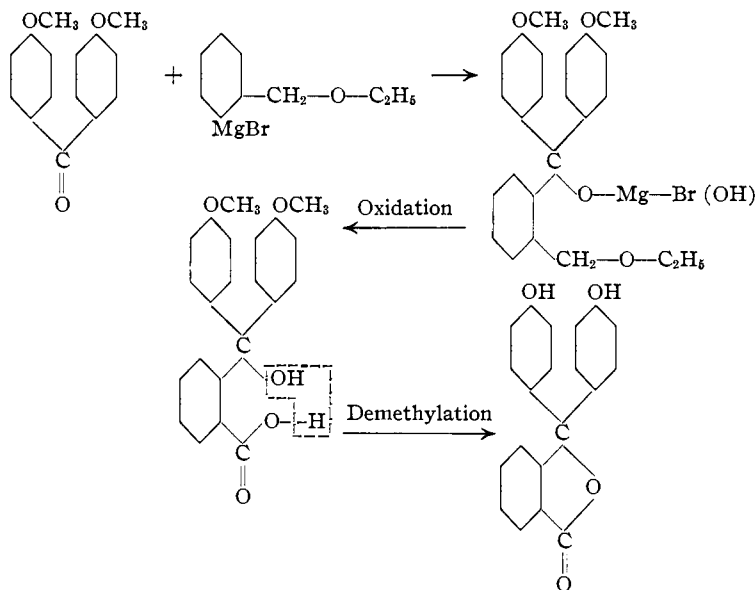
¹ This paper represents the first part of a dissertation submitted to the Graduate School by O. J. Weinkauff in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. We wish to take this opportunity to acknowledge our indebtedness to The Upjohn Company, who have made this investigation possible by the grant of a fellowship.

² Pasternack, U. S. Patent, 1,681,361 (1928).

³ Hatcher, see Orndorff and Barrett, *THIS JOURNAL*, **46**, 2487 (1924).

carbinol when treated with 2-methylphenylmagnesium bromide. Upon hydrolysis of this compound to the carbinol and oxidation of the methyl group to carboxyl, with spontaneous elimination of water from the molecule, diphenylphthalide should be formed. Although we were able by this method to obtain diphenylphthalide from benzophenone, and fluoran from 2,2'-dimethoxybenzophenone, the yields of the phthalides were low due to the difficulty encountered in the oxidation of the methyl group. However, by a slight modification of the above procedure, namely, the use of the Grignard reagent prepared from 2-ethoxymethylphenyl bromide instead of that from 2-methylphenyl bromide, it was found possible to prepare diphenylphthalide, phenolphthalein, isophenolphthalein and fluoran in fairly good yields.

The following series of reactions illustrates the process for the preparation of phenolphthalein⁴



We attempted to prepare isophenolphthalein by the method of Orndorff and Barrett.⁵ According to these investigators this product was obtained

⁴ We have not been able by the use of the method described above to prepare certain mono- and dihydroxydiarylphthalides although the syntheses of the corresponding tertiary carbinols have been described in the experimental part of the paper; in some cases the compounds seemed to decompose during the oxidation of the side chain, in others during demethylation. The applicability of the procedure for the preparation of a number of other substituted diarylphthalides is under investigation and it has been found, so far, that 3',3''-dibromophenolphthalein can be obtained from 3,3'-dibromo-4,4'-dimethoxybenzophenone.

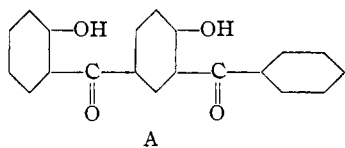
⁵ Orndorff and Barrett, *THIS JOURNAL*, **46**, 2488 (1924).

by them in 87% yield from the condensation of 2-(2'-hydroxybenzoyl)-benzoic acid with phenol in the presence of stannic chloride at 100–110°. Although the procedure was repeated a number of times and various condensation agents were used, we were unable to isolate any of the desired product. Instead there was obtained *phenolphthalein* in 40% yield, a small quantity of fluoran and a tar. It is possible, of course, that the latter may have contained some isophenolphthalein. Orndorff and Barrett make no mention of phenolphthalein as a reaction product. The formation of the latter was entirely unexpected and it was thought that the 2-(2'-hydroxybenzoyl)-benzoic acid used might possibly have been contaminated with 2-(4'-hydroxybenzoyl)-benzoic acid, although the amount of the latter, even if present, could hardly have been great enough to produce phenolphthalein in the yield stated above. 2-(2'-Hydroxybenzoyl)-benzoic acid was subjected to a very thorough process of purification but when the highly purified acid was used phenolphthalein was obtained again in a yield approximately that given above.

Experimental Part

2-Hydroxybenzophenone.—Salicylic acid was converted into the methyl ether of methyl salicylate,⁶ the latter was hydrolyzed to the methyl ether of salicylic acid and the acid was then treated with thionyl chloride.⁷ The crude acid chloride, obtained from 80 g. of the methyl ether, was dissolved in 400 cc. of thiophene-free benzene and 80 g. of aluminum chloride was added, in portions, during the course of an hour. After several hours the mixture was decomposed with ice and hydrochloric acid, the benzene layer separated, dried and the excess benzene removed. After the oil had remained at ordinary temperature for several months, 10 g. of crystalline material had formed. The latter was separated and the oil, which consisted to a large extent of 2-hydroxybenzophenone, was distilled with superheated steam; the oily distillate, which solidified when cooled, was recrystallized from alcohol. Sixty grams of 2-hydroxybenzophenone was obtained, m. p. 40–41°.

The crystalline material mentioned above melted at 131–132° after recrystallization from alcohol. It was found to be soluble in aqueous sodium hydroxide, benzene and hot acetic acid and was slightly soluble in ether. It dissolved in concd. sulfuric acid with the formation of a yellow solution. One gram of the material was fused with potassium hydroxide. There was obtained 0.43 g. of a compound which after recrystallization from water melted at 147–148°. This substance proved to be 2,4'-dihydroxybenzophenone, mixed m. p. 147–149°. An analysis and a molecular weight determination of the compound which melted at 131–132° yielded data which correspond to those calculated for C₂₀H₁₄O₄. The material is probably 2-hydroxy-5-(2'-hydroxybenzoyl)-benzophenone,⁸ (A) formed by the further re-



⁶ Graebe, *Ann.*, **340**, 210 (1905); Sachs and Herold, *Ber.*, **40**, 2718 (1907).

⁷ E. Fischer and Slimmer, *ibid.*, **36**, 2585 (1903).

⁸ As a by-product from the synthesis described above Graebe and Ullmann [*ibid.*, **29**, 824 (1896)] obtained a substance which melted at 127° and stated that the analytical results checked most closely to those calculated for a dihydroxybenzophenone.

action of the acid chloride on the primary reaction product, 2-methoxybenzophenone, and subsequent demethylation by the aluminum chloride.

Anal. Calcd. for $C_{26}H_{14}O_4$: mol. wt., 318; C, 75.46; H, 4.40. Found: mol. wt. (diphenyl),⁹ 320; C, 75.35; H, 4.50.

The 4-nitrobenzyl ether of the hydroxy ketone was prepared in the following manner: one hundredth mole of 2-hydroxybenzophenone and 0.01 mole of 4-nitrobenzyl bromide were dissolved in 15 cc. of acetone. One hundredth mole of crystalline sodium hydroxide and 5 cc. of water were added and the mixture heated on a steam-bath for one hour. The ether, which separated in crystalline form, melted at 124–125° after recrystallization from acetone.

4-Hydroxybenzophenone.—Twelve and two-tenths grams of benzoic acid, 9.4 g. of phenol and 26 g. of stannic chloride were placed in a flask connected with a reflux condenser and the mixture was heated in a bath at 120° for eighteen hours. After the addition of about 20 cc. of hydrochloric acid, the mixture was filtered. The solid material was treated with 10% aqueous sodium carbonate, which dissolved the benzoic acid and the hydroxybenzophenone. Carbon dioxide was passed into the alkaline solution, whereupon the hydroxy ketone precipitated. The yield of the latter was 4 g.; 6.5 g. of benzoic acid was recovered. After recrystallization of the hydroxy ketone from water, it melted at 135–136°.¹⁰ When an equivalent amount of phenyl benzoate was used in place of benzoic acid, there was obtained 1.5 g. of the ketone and 5 g. of unchanged ester.

2,4'-Dihydroxybenzophenone.—(a) A mixture prepared from 10.6 g. of salol and 13 g. of stannic chloride was heated under reflux for eighteen hours at 115–120° in an oil-bath. The reaction product was treated with hot hydrochloric acid in order to remove unchanged stannic chloride, cooled and filtered. After recrystallization from water the hydroxy ketone melted at 147–149°,¹¹ yield 5.8 g.

(b) Thirteen grams of salicylic acid, 9.4 g. of phenol and 26 g. of stannic chloride were heated under reflux for eighteen hours at 120°. There was obtained 5.5 g. of 2,4'-dihydroxybenzophenone and 4.5 g. of salicylic acid; in one instance we were able to isolate a small quantity of 4,4'-dihydroxybenzophenone.¹²

The dimethyl ether of 2,4'-dihydroxybenzophenone melted at 99–100°.¹³

3,4'-Dimethoxybenzophenone.—One hundred thirty-five grams of 3-methoxybenzoic acid¹⁴ was treated with 330 g. of thionyl chloride. After twenty-four hours the excess thionyl chloride was removed under diminished pressure and the acid chloride distilled, b. p. 122–123° under 16 mm. pressure. The yield was 118 g. Eighty-five grams of the acid chloride was dissolved in 50 cc. of tetrachloroethane and added, drop by drop, to a mixture of 65 g. of anisole, 85 g. of aluminum chloride and 100 cc. of tetrachloroethane. After forty-eight hours the reaction mixture was decomposed with ice and hydrochloric acid and the tetrachloroethane and excess anisole removed by steam distillation. The oily product was shaken with 10% sodium hydroxide solution, whereupon it became solid. After recrystallization from alcohol it melted at 58–59°. The yield was practically quantitative.¹⁵

⁹ Purified according to the method of Chipman and Peltier, *Ind. Eng. Chem.*, **21**, 1106 (1929).

¹⁰ Döbner, *Ann.*, **210**, 251 (1881).

¹¹ Several investigators have reported that this substance melts at 142–144° although Baeyer [*Ann.*, **354**, 178 (1907)] stated that the compound melts at 150–151°.

¹² Michael, *Am. Chem. J.*, **5**, 83 (1883); Baeyer, *Ann.*, **354**, 177 (1907).

¹³ Stoermer, *Ber.*, **41**, 323 (1908).

¹⁴ Graebe, *Ann.*, **340**, 211 (1905).

¹⁵ Lea and Robinson [*J. Chem. Soc.*, 2355 (1926)] obtained only a 40% yield of

2-(2'-Hydroxybenzoyl)- and 2-(4'-Hydroxybenzoyl)-benzoic Acids.—These compounds were prepared according to the method of Ullmann and Schmidt¹⁶ but we obtained much higher yields and different relative amounts of the two acids. The average result from a number of experiments was as follows. From the interaction of 40 g. of pure phthalic anhydride, 40 g. of phenol and 120 g. of aluminum chloride there were isolated 36 g. of the 4'-hydroxy acid which melted at 205–207°, 16 g. of the 2'-hydroxy acid, m. p. 171–173°, and 4 g. of crude phenolphthalein.

Attempts to Prepare Isophenolphthalein from 2-(2'-Hydroxybenzoyl)-benzoic Acid.—In order to obtain 2-(2'-hydroxybenzoyl)-benzoic acid entirely free from the 4'-hydroxy isomer, the former acid was recrystallized four times from methyl alcohol, converted into the ethyl ester and the latter hydrolyzed; the acid obtained melted at 171–173°.

The pure 2-(2'-hydroxybenzoyl)-benzoic acid, prepared as described above, was condensed with phenol according to the method of Orndorff and Barrett.¹⁷ There was obtained phenolphthalein in 40% yield, a small amount of fluoran and a tar. When the phenolphthalein was fused with potassium hydroxide, 4,4'-dihydroxybenzophenone was isolated in 85% yield.

Methylation of Phenolphthalein and Demethylation of Phenolphthalein Dimethyl Ether.—Fifteen grams of phenolphthalein was dissolved in 200 cc. of 10% sodium hydroxide solution and 35 cc. of dimethyl sulfate was added, in portions, while the mixture was shaken vigorously. Ten grams of sodium hydroxide was added and the solution heated for one-half hour under reflux. An oil separated which became solid when cooled. After recrystallization from alcohol the phenolphthalein dimethyl ether¹⁸ melted at 101–102°; yield 14.7 g. or 90% of the calculated amount.

Demethylation was effected in the following manner. Five grams of the ether, 40 cc. of acetic acid and 25 cc. of 48% hydrobromic acid were refluxed for five hours in a flask fitted to a reflux condenser by means of a ground-glass connection. Most of the hydrobromic and acetic acid was removed by distillation under diminished pressure. The yield of crude phenolphthalein was 3.8 g.; after recrystallization from dilute alcohol it melted at 252–253°.

The ether can also be demethylated if a mixture, prepared from 1 g. of the material, 30 cc. of dry thiophene-free benzene and 2.2 g. of aluminum chloride, is refluxed for two hours.

Preparation of Tertiary Carbinols.—The tertiary carbinols were prepared by the action of 2-methylphenylmagnesium bromide and 2-ethoxymethylphenylmagnesium bromide, respectively, on various ketones. 2-Ethoxymethylbromobenzene, necessary for the preparation of the Grignard reagent, was obtained in the following manner. Two hundred and fifty grams of pure 2-bromotoluene was brominated in a flask connected to a reflux condenser by means of a ground-glass connection.¹⁹ The 2-bromobenzyl bromide, which boiled at 130–136° under 16 mm. pressure, was used for the subsequent procedure. One hundred and twenty-six grams of 2-bromobenzyl bromide was added to a cold solution of sodium ethylate prepared from 250 cc. of absolute alcohol and 14 g. of the ketone, possibly due to the fact that carbon disulfide was used as a solvent; they reported the melting point to be 55°.

¹⁶ Ullmann and Schmidt, *Ber.*, **52**, 2106 (1919). See also Thiel and Müller, *ibid.*, **55**, 1314 (1922).

¹⁷ Orndorff and Barrett, *THIS JOURNAL*, **46**, 2488 (1924).

¹⁸ This compound has been obtained by Grande, *Gazz. chim. ital.*, **26**, I, 223 (1896); Underwood and Barker, *THIS JOURNAL*, **52**, 4084 (1930), and by Herzig and Meyer, *Monatsh.*, **17**, 430 (1896).

¹⁹ Jackson, *Am. Chem. J.*, **1**, 101 (1879–1880).

TABLE I
 TERTIARY CARBINOLS

The letter in parentheses before the ketone indicates the Grignard reagent used: A, 2-methylphenylmagnesium bromide; B, 2-ethoxy-methylphenylmagnesium bromide.

Carbinol obtained, ^a -triphenylcarbinol	Grignard reagent and substituted benzophenone	Color with H ₂ SO ₄	M. p., °C.	Formula	Calcd., % C H	Found, % C H
1 2-Methyl-	(A) Benzophenone	Yellow	100-101 ^b	C ₂₀ H ₁₈ O
2 2-Methyl-2',4"-dimethoxy-	(A) 2,4'-Dimethoxy-	Orange	152-154	C ₂₂ H ₂₂ O ₃	79.04 6.59	78.89 6.67
3 2-Methyl-4',4"-dimethoxy-	(A) 4,4'-Dimethoxy- ^c	Orange	109-110	C ₂₂ H ₂₂ O ₃	79.04 6.59	78.70 6.75
4 2-Ethoxymethyl-	(B) Benzophenone	Yellow	81- 82	C ₂₂ H ₂₂ O ₂	83.02 6.92	83.10 6.88
5 2-Ethoxymethyl-2'-methoxy-	(B) 2-Methoxy-	Green turns to red	108-109	C ₂₃ H ₂₄ O ₃	79.27 6.90	79.26 6.90
6 2-Ethoxymethyl-3'-methoxy-	(B) 3-Methoxy- ^d	Oily	C ₂₃ H ₂₄ O ₃	79.27 6.90
7 2-Ethoxymethyl-4'-methoxy-	(B) 4-Methoxy-	Orange	100-101	C ₂₃ H ₂₄ O ₃	79.27 6.90	79.10 6.98
8 2-Ethoxymethyl-2',2"-dimethoxy-	(B) 2,2'-Dimethoxy- ^e	Blue turns to purple	103-104	C ₂₄ H ₂₆ O ₄	76.19 6.88	76.06 6.94
9 2-Ethoxymethyl-2',4"-dimethoxy-	(B) 2,4'-Dimethoxy-	Red	107-108	C ₂₄ H ₂₆ O ₄	76.19 6.88	75.97 6.93
10 2-Ethoxymethyl-4',4"-dimethoxy-	(B) 4,4'-Dimethoxy-	Orange-red	74- 76	C ₂₄ H ₂₆ O ₄	76.19 6.88	75.80 6.67
11 2-Ethoxymethyl-3',4"-dimethoxy-	(B) 3,4'-Dimethoxy-	Orange-red	83- 84	C ₂₄ H ₂₆ O ₄	76.19 6.88	75.82 7.10
12 9-(2'-Methylphenyl)-xanthrydrol ^f	(A) Xanthone	Yellow	165-166	C ₂₀ H ₁₆ O ₂	83.33 5.56	83.40 5.65
13 9-(2'-Ethoxymethylphenyl)- xanthrydrol	(B) Xanthone	Yellow	153-154	C ₂₂ H ₂₀ O ₃	79.52 6.02	79.44 6.06

^a Carbinols 1, 2, 7, 9 and 12 were recrystallized from a mixture of benzene and petroleum ether (30-60°); 4 and 5 from a mixture of high (90-120°) and low boiling petroleum ether (30-60°); 8 and 11 from methyl alcohol, 13 from benzene and 3 and 10 from alcohol. ^b Bistrzycki and Gyr, *Ber.*, **37**, 1248 (1904), recorded the melting point as 98°. ^c Baeyer and Burkhardt, *Ann.*, **202**, 126 (1880); Zincke and Birschell, *ibid.*, **362**, 226 (1908); Blicke and Smith, *THIS JOURNAL*, **51**, 1872 (1929). ^d Ullmann and Goldberg, *Ber.*, **35**, 2814 (1902). ^e Richter, *J. prakt. Chem.* [2] **28**, 285 (1883); Graebe and Feer, *Ber.*, **19**, 2610 (1886). ^f Decker and Fellenberg, *Ann.*, **356**, 309 (1907), obtained a compound from xanthone and 2-tolylmagnesium bromide which they claimed was 9-(2'-methylphenyl)-xanthrydrol. Their material consisted of "pseudo crystals" which melted at 150.5°. The product obtained by us consisted of well-defined colorless glistening crystals.

sodium. The mixture was heated for two hours on a steam-bath. The sodium bromide was removed and the greater part of the alcohol distilled. The residue was poured into water and the oil which separated was treated successively with a concd. sodium bisulfite solution,²⁰ water and dilute aqueous sodium carbonate. The oil was dried and distilled; b. p. 108–109° under 13 mm. pressure.

To the Grignard reagent prepared from 0.1 mole of 2-methylbromobenzene or 2-ethoxymethylbromobenzene, 0.1 mole of magnesium, a few crystals of iodine and a mixture composed of 25 cc. of ether and 25 cc. of dry benzene, there was added 0.07 mole of the ketone, dissolved or suspended in 50 cc. of dry benzene. During the preparation of the Grignard reagent a stream of dry nitrogen was passed over the top of the condenser. The mixture was heated on a steam-bath for three hours and then decomposed with ice and ammonium chloride. The crude carbinols were subjected to steam distillation for several hours, then dried and purified by recrystallization.

The carbinols which were prepared are listed below. The method of preparation is indicated in Table I.

Oxidation of Tertiary Carbinols to Dimethyl Ethers of Diarylphthalides.—In many instances the oxidation of the methyl group to carboxyl in the carbinols which contained a tolyl nucleus did not take place readily and we were able, only in a few cases, to prepare the desired phthalide from such carbinols. The oxidation of 9-(2'-methylphenyl)-xanthidrol to fluoran was accomplished as follows. A solution prepared from 0.50 g. of the carbinol, 20 cc. of concd. sulfuric acid and 50 cc. of water was heated to the boiling point. Five-tenths of a gram of sodium dichromate, dissolved in 5 cc. of water, was added to the hot solution. The latter was stirred thoroughly and boiled for ten minutes. The mixture was cooled, water was added and the solid material removed by filtration.

TABLE II
DIMETHYL ETHERS OF DIARYLPHTHALIDES

Carbinol	Oxidation product ^a	M. p., °C.
1, 4	Diphenylphthalide	114–115 ^b
5	2'-Methoxydiphenylphthalide	127–128
6	3'-Methoxydiphenylphthalide	Gum
7	4'-Methoxydiphenylphthalide	Gum ^c
8	2',2''-Dimethoxydiphenylphthalide	151–152 ^d
9	2',4''-Dimethoxydiphenylphthalide	127–128 ^e
10	4',4''-Dimethoxydiphenylphthalide	101–102 ^f
11	3',4''-Dimethoxydiphenylphthalide	200–201 ^g
12, 13	Fluoran	182–183 ^h

^a All of the ethers were recrystallized from alcohol except the compound obtained from carbinol 11; this substance was recrystallized from toluene. ^b V. Pechmann [*Ber.*, **14**, 1866 (1881)] recorded the melting point as 115°. ^c H. Meyer and O. Fischer [*ibid.*, **44**, 1953 (1911)] stated that this compound melts at 86°; they experienced difficulty in obtaining it in crystalline form. ^d Ferrario [*Gazz. chim. ital.*, **41**, I, 1 (1911)] stated that this substance melts at 145–146°. ^e Orndorff and Barrett [*THIS JOURNAL*, **46**, 2490 (1924)] found the melting point to be 122°. ^f Grande [*Gazz. chim. ital.*, **26**, I, 224 (1896)] recorded the melting point as 101–102°. ^g This compound is insoluble in ether, soluble in hot toluene and dissolves in concd. sulfuric acid with the formation of a violet solution. *Anal.* Calcd. for C₂₂H₁₈O₄: C, 76.29; H, 5.24. Found: C, 75.94; H, 5.17. ^h Ferrario [*Gazz. chim. ital.*, **41**, I, 10 (1911)] recorded the melting point as 182°.

²⁰ To remove any aldehyde present; Errera, *Gazz. chim. ital.*, **17**, 204, 208 (1887).

TABLE III
HYDROXYDIARYLPHTHALIDES

Prepared by demethylation of the oxidation products (dimethyl ethers of diarylphtthalides) listed in Table II.^a

		M. p., °C.
7 ^b	4'-Hydroxydiphenylphtthalide	Amorphous
8	Fluoran	182-183 ^c
9	Isophenolphthalein	198-199 ^d
10	Phenolphthalein	254-255 ^e
11	3',4"-Dihydroxydiphenylphtthalide	Amorphous ^f

^a Demethylation was effected with hydrobromic acid in the manner described in the case of phenolphthalein dimethyl ether. ^b These numbers refer to the tertiary carbinols from which the hydroxydiarylphtthalides were obtained. ^c Ferrario [*Gazz. chim. ital.*, **41**, I, 10 (1911)] recorded the melting point as 182°. ^d Orndorff and Barrett [*THIS JOURNAL*, **46**, 2485 (1924)] stated that the compound melted at 200°. ^e Bebie [*J. Am. Pharm. Assoc.*, **19**, 372 (1930)] reported the melting point as 262.8° (corr.). ^f This material dissolved in alkali to form a red solution.

After recrystallization from alcohol, there was obtained 0.22 g. of crystalline fluoran; mixed m. p. 181-182°.

The oxidation of the ethoxymethyl group to carboxyl is illustrated by the conversion of 2-ethoxymethyl-4',4"-dimethoxytriphenylcarbinol into the dimethyl ether of phenolphthalein. Five grams of the carbinol, 10.5 g. of finely powdered sodium dichromate and 100 cc. of acetic acid were refluxed for two hours. The mixture was treated with 400 cc. of hot water and after some time the gummy precipitate was removed and recrystallized from alcohol. Three and one-tenth grams of material was obtained which melted at 97-99°. After further recrystallization the phenolphthalein dimethyl ether melted at 101-102°; yield 70% of the calculated amount.

The yields obtained in the oxidation of other carbinols varied from 40-60%. In the case of some of the dimethoxydiarylphtthalides considerable difficulty was experienced in their purification.

The oxidation products obtained from other carbinols are recorded in Table II.

Summary

It has been found that the interaction of 2-ethoxymethylphenylmagnesium bromide with the methyl ethers of various hydroxybenzophenones yields tertiary carbinols in which the ethoxymethyl group can be oxidized to carboxyl with the spontaneous formation of methyl ethers of diarylphtthalides. Upon demethylation hydroxydiarylphtthalides are obtained.

This method is of advantage in that phtthalides so formed cannot be contaminated with isomeric phtthalides or anthraquinone compounds and, due to the method of synthesis, the positions of any substituents in the phtthalide molecule are known with certainty.

This procedure has been found satisfactory for the preparation of diphenylphtthalide, phenolphthalein, isophenolphthalein and fluoran.

Preliminary tests indicate that isophenolphthalein has no laxative effect on humans.