

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

The Interaction of the Acid Chloride of 2-Benzoylbenzoic Acid with Phenols. II. Diarylphthalides¹

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It has been found³ that the acid chloride of 2-benzoylbenzoic acid reacts at ordinary temperature with potassium phenolate or with phenol in the presence of pyridine to yield compounds which are presumably the phenyl ester of the benzoylbenzoic acid and the isomeric phenylphenoxyphthalide; analogous results were obtained with other phenols.

In this investigation it has been shown that when the acid chloride and phenol alone or anisole is used 4'-hydroxy- and 4'-methoxydiphenylphthalide, respectively, are obtained. Certain other phenols and their methyl ethers act similarly; however, in the case of *o*-xenol, *p*-xenol and 4-bromophenol the addition of aluminum chloride is necessary, otherwise an ester or arylaryloxyphthalide is formed. It was not found possible to obtain from thiophenol a diarylphthalide which contained the mercapto group.⁴

In several instances the acid chlorides of 2-(4'-hydroxybenzoyl)- and of 2-(4'-methoxybenzoyl)-benzoic acid were used.

The diarylphthalides obtained are listed in Table I.

It seemed desirable to synthesize 2-(4''-hydroxybenzoyl)-benzophenone in order to compare its properties with those of the isomeric 4'-hydroxydiphenylphthalide, especially since the preparative procedures used for the latter substance, in themselves, do not offer rigid proof of the phthalide structure—2-benzoylbenzoic acid and its acid chloride react in the keto as well as in the lactoid form. Inasmuch as it was necessary to prepare 2-(4''-hydroxybenzoyl)-benzophenone in the form of its methyl ether and since the demethylation product of the latter could not be obtained in crystalline form, the properties of 2-(4''-methoxybenzoyl)-benzophenone were compared with those of 4'-methoxydiphenylphthalide. The melting point of the methoxy phthalide is

(1) This paper represents the second part of a dissertation to be submitted to the Graduate School by Mr. Swisher in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Part I. Blicke and Swisher, *THIS JOURNAL*, **56**, 902 (1934).

(4) Knapp [*Monatsh.*, **58**, 176 (1931)] tried unsuccessfully to prepare thiophenolphthalide (4',4''-thiomercaptodiphenylphthalide).

110–115°, that of the methoxy ketone 132–135°; the phthalide yields an orange solution with concd. sulfuric acid, the ketone a deep violet solution.

Various investigators have found it exceedingly difficult, by the use of procedures described hitherto, to obtain 4'-hydroxy-, 4'-methoxy- and 4-hydroxy-4''-methoxydiphenylphthalide in crystalline form. By means of the synthesis described in this paper these phthalides are obtained as crystalline products directly from the reaction mixtures in practically quantitative yields.

Experimental Part

Diarylphthalides.—To the acid chloride obtained from 0.1 mole of the benzoylbenzoic acid and thionyl chloride⁵ there was added 0.1 mole of the phenol or the aryl methyl ether, dissolved or suspended in 150 cc. of benzene. After thirty-six hours⁶ the mixture was filtered,⁷ the filtrate shaken with 10% sodium carbonate solution and then with 10% sodium hydroxide solution to extract the hydroxydiarylphthalide, which is subsequently obtained by acidification. If a methoxydiarylphthalide is formed it remains in the benzene layer; after removal of the solvent and treatment of the cooled residue with a small amount of ether, it practically always crystallized.

2-(4''-Methoxybenzoyl)-benzophenone.—A mixture of 100 g. of 2-benzoylbenzoic acid⁸ and 100 g. of lead thiocyanate⁹ was heated in a 250-cc. distillation flask in a bath at 200° for one hour and the mixture then distilled. The distillate (300–325°),¹⁰ combined with the large amount of material obtained by extraction of the residue in the distillation flask with benzene, was fractionated. The 2-cyanodiphenylmethane obtained boiled at 315–320°,¹¹ yield 40 g.

A crystalline precipitate formed when 15 g. of the

(5) The acid chloride of 2-benzoyl- and of 2-(4'-methoxybenzoyl)-benzoic acid was obtained in crystalline condition.

(6) In the case of phenol and α -naphthol the reaction was complete at the end of one-half hour.

(7) In some instances the phthalides separate spontaneously from the reaction mixture in crystalline form.

(8) Barnett, Cook and Nixon, *J. Chem. Soc.*, 508 (1927).

(9) Reed, *Am. Chem. J.*, **43**, 180 (1910).

(10) A small amount of crystalline material present was removed by filtration and recrystallized from benzene; m. p. 162–163°. This product, was undoubtedly, the acid amide of 2-benzoylbenzoic acid; Cassirer [*Ber.*, **25**, 3022 (1892)] stated that this compound melts at 163°.

(11) Cassirer [*Ber.*, **25**, 3021 (1892)] obtained the cyanide by another method and reported the boiling point to be 313–314°. In order to identify the cyanide prepared by us it was allowed to react with phenylmagnesium bromide whereupon 2-benzoyldiphenylmethane was formed [Seidel, *ibid.*, **61**, 2275 (1928)].

TABLE I
 DIARYLPHthalIDES

A = Acid chloride of 2-benzoylbenzoic acid
 B = Acid chloride of 2-(4'-hydroxybenzoyl)-benzoic acid
 C = Acid chloride of 2-(4'-methoxybenzoyl)-benzoic acid

Chloride	Phenol or ether	Phthalide	M. p., °C.	Color with ^a concd. H ₂ SO ₄
A	Phenol	(1) 4'-Hydroxydiphenyl	168-170	Orange
A	Anisole	(2) 4'-Methoxydiphenyl	110-115	Orange
A	4-Bromophenol ^b	(3) 2'-Hydroxy-4'-bromodiphenyl	210-211	Green, yellow-green
A	2,6-Dibromophenol ^b	(4) 4'-Hydroxy-3',5'-dibromodiphenyl	199-200	Orange-red
A	<i>o</i> -Xenol ^b	(5) Phenyl- <i>o</i> -hydroxyxyenyl	178-180	Orange-red
A	<i>o</i> -Xenyl methyl ether	(6) Phenyl- <i>o</i> -methoxyxyenyl	152-154	Orange-red
A	<i>p</i> -Xenol ^b	(7) Phenyl- <i>p</i> -hydroxyxyenyl	220-222	Green, brown
A	<i>p</i> -Xenyl methyl ether	(8) Phenyl- <i>p</i> -methoxyxyenyl	179-180	Green, brown
A	α -Naphthol	(9) Phenyl- α -hydroxynaphthyl	231-233	Purple, brown
A	α -Naphthyl methyl ether	(10) Phenyl- α -methoxynaphthyl	206-207	Purple, brown
A	β -Naphthol	(11) Phenyl- β -hydroxynaphthyl	234-236	Indigo, brown
A	β -Naphthyl methyl ether	(12) Phenyl- β -methoxynaphthyl	210-212	Indigo, brown
B	Phenol	(13) 4',4''-Dihydroxydiphenyl	253-256	Red
B	Anisole	(14) 4'-Hydroxy-4''-methoxydiphenyl	139-142	Red
C	Phenol	(14) 4'-Hydroxy-4''-methoxydiphenyl	139-142	Red
C	Anisole	(15) 4',4''-Dimethoxydiphenyl	97-99	Red

ANALYSES^c

Compound	Formula	Calcd., %			Found, %		
		C	H	OCH ₃	C	H	OCH ₃ ^d
2	C ₂₁ H ₁₆ O ₃	79.71	5.10	9.81	79.58	4.92	9.92
3	C ₂₀ H ₁₃ O ₃ Br	(Br, 20.97			(Br, 20.98)		
5	C ₂₆ H ₁₈ O ₃	82.51	4.80		82.31	4.76	
6	C ₂₇ H ₂₀ O ₃	82.62	5.14	7.91	82.47	5.03	8.28
7	C ₂₆ H ₁₈ O ₃	82.51	4.80		82.26	4.77	
8	C ₂₇ H ₂₀ O ₃	82.62	5.14	7.91	82.23	4.99	7.93
9	C ₂₄ H ₁₆ O ₃	81.79	4.58		81.62	4.49	
10	C ₂₆ H ₁₈ O ₃	81.93	4.96	8.47	81.70	4.87	8.52
11	C ₂₄ H ₁₆ O ₃	81.79	4.58		81.75	4.61	
12	C ₂₆ H ₁₈ O ₃	81.93	4.96	8.47	81.56	4.87	8.52

Compound 6, mol. wt. calcd. 392; found 395 (benzene, Menzies method).

^a The first color is obtained with cold acid, the second color with hot acid.

^b In the case of this compound the reaction was carried out in the presence of one mol. equiv. of aluminum chloride in tetrachloroethane; in the absence of the condensation agent the ester or arylaryloxypthalide is formed.

^c Prior to analysis all samples were dried at 125° under diminished pressure in a current of dry nitrogen.

^d In the methoxy determinations phenol was used as a solvent [Weishut, *Monatsh.*, **33**, 1165 (1912)].

COMMENTS

Compounds 1-13 inclusive were recrystallized from acetic acid, compound 15 from alcohol.

Compound 2. Meyer and Fischer [*Ber.*, **44**, 1953 (1911)] recorded the melting point as 86°. The compound appears to contain benzene of crystallization which is lost gradually at room temperature. When dried at an elevated temperature the material changes into a somewhat sticky mass. The identity of our compound was established by boiling 5 g. of the material for six hours with 40 cc. of acetic acid and 25 cc. of 48% hydrobromic acid; the 4'-hydroxydiphenylphthalide obtained melted at 168-170°, while Baeyer [*Ann.*, **354**, 173 (1907)] stated that this compound melts at 167°.

Furthermore, reduction of compound 2 to 4'-methoxytriphenylmethane-2-carboxylic acid was effected as follows: 10 g. of 4'-methoxydiphenylphthalide, dissolved in alcohol, was added to 200 cc. of 10% sodium hydroxide solution, the mixture diluted to 500 cc., 50 g. of zinc dust added

and the mixture heated for twelve hours on a steam-bath. The mixture was filtered, the acid precipitated from the filtrate, filtered, dissolved in 10% sodium carbonate solution, filtered and the acid again precipitated with hydrochloric acid. The crude, pasty product was dried at 100° for twelve hours and recrystallized from dilute alcohol; m. p. 146-147°.

Anal. Calcd. for C₂₁H₁₆O₃: C, 79.21; H, 5.70; equiv. wt., 318. Found: C, 79.22; H, 5.68; equiv. wt., 325.

When 1 g. of the acid was boiled for three hours with 8 cc. of acetic acid and 5 cc. of 40% hydrobromic acid the 4'-hydroxytriphenylmethane-2-carboxylic acid obtained melted at 209-210°¹² after recrystallization from dilute alcohol.

Compound 3. Upon reduction of this substance with zinc dust in alkaline solution, as described above, a bromine-free, bicarbonate-soluble product, undoubtedly

(12) V. Pechmann [*Ber.*, **13**, 1616 (1880)] recorded the melting point as 210°.

2'-hydroxytriphenylmethane-2-carboxylic acid, was obtained; m. p. 194-196° after recrystallization from dilute alcohol.

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.91; H, 5.30; equiv. wt., 304. Found: C, 79.18; H, 5.45; equiv. wt., 306.

To obtain the corresponding methyl ether, 2'-methoxytriphenylmethane-2-carboxylic acid, 5 g. of the material, dissolved in 15 cc. of 10% sodium hydroxide solution, was heated with 4 cc. of dimethyl sulfate for a short time; 2 g. of sodium hydroxide and 10 cc. of water were added and the mixture heated for three hours. The solution was acidified, the precipitate dissolved in 10% sodium carbonate solution, the acid precipitated with hydrochloric acid and recrystallized from alcohol; m. p. 191-193°.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.21; H, 5.70. Found: C, 78.96; H, 5.73.

Compound 4. This substance has been prepared by bromination of 4'-hydroxydiphenylphthalide by v. Pechmann [*Ber.*, 13, 1615 (1880), m. p. 196°] and by Acree and Slagle [*Am. Chem. J.*, 42, 138 (1909), m. p. 199°]. Our preparative method definitely establishes the positions occupied by the bromine atoms.

Compounds 5, 7, 9 and 11 upon methylation yielded the corresponding methyl ethers; from compounds 2, 6, 8 and 14 the corresponding hydroxy phthalides were obtained after demethylation.

Compounds 5 and 7 dissolve in alkali to form a yellow solution while compounds 9 and 11 yield an orange solution.

Compound 14. The melting point recorded in the table was obtained with material taken directly from the reaction mixture. Meyer and Spengler [*Ber.*, 38, 1328 (1905)] stated that the compound melted at 141-142°; Green and King [*ibid.*, 40, 3729 (1907)] recorded the melting point as 148-149°; see also Lund, *J. Chem. Soc.*, 1572 (1928).

Compound 15. Grande [*Gazz. chim. ital.*, 26, I, 224 (1896)] reported the melting point as 101-102°.

cyanide was heated with the Grignard reagent prepared from 38 g. of *p*-iodoanisole, 3.9 g. of magnesium, 60 cc. of benzene and 60 cc. of ether. The precipitate and the benzene-ether layer were decomposed separately in the usual manner and the gummy 2-(4'-methoxybenzoyl)-diphenylmethane obtained was steam distilled to remove anisole; m. p. 68-70° after recrystallization from alcohol.

To obtain 2-(4'-methoxybenzoyl)-benzophenone a mixture of 32 g. of the methane, 300 cc. of concd. nitric acid and 600 cc. of water was boiled for three hours, poured into water and the gummy product stirred with ether, whereupon it partially crystallized. It was filtered, washed with ether and recrystallized from acetic acid; m. p. 133-135°; yield 13 g. The solvent was removed from the ether solutions and the residue reoxidized; 12 g. more of the product was obtained.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.71; H, 5.10; mol. wt., 316. Found: C, 79.36; H, 5.11; mol. wt., 318 (benzene, Menzies method).

A diazine, 3-phenyl-6-(*p*-methoxyphenyl)-4,5-benzopyridazine, was formed when 3 g. of the ketone was boiled with 8 g. of 40% hydrazine and 30 cc. of acetic acid for five hours, the mixture poured into water and the precipitate recrystallized from acetone; m. p. 157-159°.

Anal. Calcd. for $C_{21}H_{18}ON_2$: C, 80.73; H, 5.17. Found: C, 80.86; H, 5.25.

The diphenylhydrazone precipitated when 2.4 g. of the ketone, 4.3 g. of phenylhydrazine and 25 cc. of alcohol were heated for twelve hours; m. p. 157-160° after recrystallization from alcohol.

Anal. Calcd. for $C_{33}H_{28}ON_4$: C, 79.80; H, 5.69. Found: C, 79.83; H, 5.68.

Incidentally it was noticed that 2-(2'-hydroxybenzoyl)- and 2-(2'-methoxybenzoyl)-benzoic acids taste slightly bitter while the corresponding 4'-hydroxy¹³ and 4'-methoxy¹³ compounds are sweet. Methyl 2-(2'-methoxybenzoyl)- and methyl 2-(4'-methoxybenzoyl)-benzoate are tasteless.

Summary

It has been found that the acid chloride of 2-benzoylbenzoic acid reacts readily, at ordinary temperature, with a variety of phenols and aryl methyl ethers to yield diarylphthalides; in a few instances it was necessary to add aluminum chloride to the reaction mixture.

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(13) Cohn, "Die organischen Geschmacksstoffe," Franz Siemenroth, Berlin, 1914, pp. 325, 327.