

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

THE PREPARATION OF 2-(4"-HYDROXYBENZOYL)-4'-HYDROXYBENZOPHENONE¹

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The preparation of phenolphthalein dimethyl ether (4',4"-dimethoxydiphenylphthalide) was attempted from phthalic anhydride and 4-methoxyphenylmagnesium iodide. Bauer² prepared diphenylphthalide in good yield from phthalic anhydride and phenylmagnesium bromide³ and by the use of the anhydride mentioned above and 2-methoxyphenylmagnesium iodide Ferrario⁴ obtained 2',2"-dimethoxydiphenylphthalide which, upon demethylation, yielded fluorane.

From phthalic anhydride and 4-methoxyphenylmagnesium iodide, and also from the methyl ester of 2-(4'-methoxybenzoyl)-benzoic acid and the Grignard reagent, we obtained a product which melted at 157-159°; after demethylation the material melted at 225-226° and dissolved in alkali to form a pale yellow solution. The melting points of phenolphthalein dimethyl ether and of phenolphthalein are 102-103° and 254-255°, respectively. Since the data obtained from an analysis and a molecular weight determination of the product which melted at 157-159° corresponded to that calculated for phenolphthalein dimethyl ether, it was evident that a substance isomeric with the last-named compound had been formed.

A consideration of the possible ways in which phthalic anhydride and 4-methoxyphenylmagnesium iodide may combine shows that after the interaction of equivalent amounts of these substances with the formation of compound I, further reaction of the latter with the Grignard reagent may yield either the dimethyl ether of phenolphthalein (II) or the dimethyl ether of 2-(4"-hydroxybenzoyl)-4'-hydroxybenzophenone (III), a substance isomeric with phenolphthalein dimethyl ether.

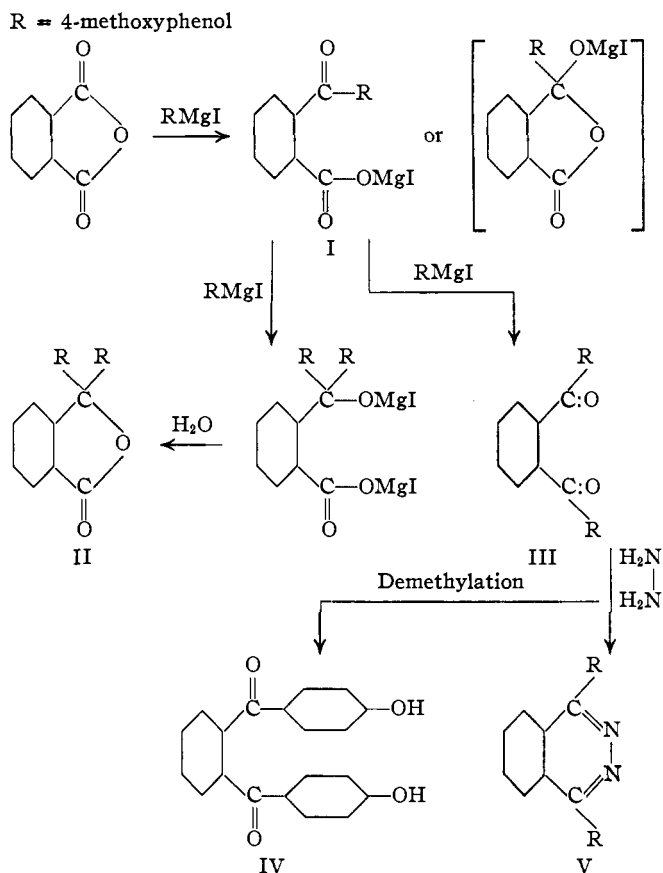
The chemical behavior of the compound (m. p. 157-159°) obtained conformed entirely with that of a substance of structure III. A 1,2-diazine-3,6-di-(*p*-methoxyphenyl)-4,5-benzopyridazine (V), obtained by the action of hydrazine, a dioxime and a diphenylhydrazone were prepared and analyzed. When the compound was fused with potassium hydroxide, 4-methoxybenzoic acid was obtained.

¹ This paper represents the second part of a dissertation submitted to the Graduate School by O. J. Weinkauff in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. O. J. Weinkauff was awarded The Upjohn Company Fellowship, 1928-1931.

² Bauer, *Ber.*, **38**, 240 (1905).

³ When 4-methoxyphenylmagnesium bromide was used this investigator isolated only gummy material as a reaction product.

⁴ Ferrario, *Gazz. chim. ital.*, **41**, I, 1 (1911).



Demethylation of III yielded 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone (IV). This substance, when fused with potassium hydroxide, yielded two molecular equivalents of 4-hydroxybenzoic acid.

A number of years ago Baeyer⁵ reduced diphenylphthalide (VI) to triphenylmethane-2-carboxylic acid (diphenylphthalin, VII). The latter, when treated with concentrated sulfuric acid, yielded a substance which, although it was not isolated in pure form nor was its structure suggested,⁶ upon oxidation was converted into 9-hydroxy-9-phenylanthrone-10 (IX). Since Haller and Guyot⁷ obtained this same compound (IX) from the action of phenylmagnesium bromide on anthraquinone, and these investigators,⁸ as well as Liebermann,⁹ were able to prepare the corresponding

⁵ Baeyer, *Ann.*, **202**, 100 (1880).

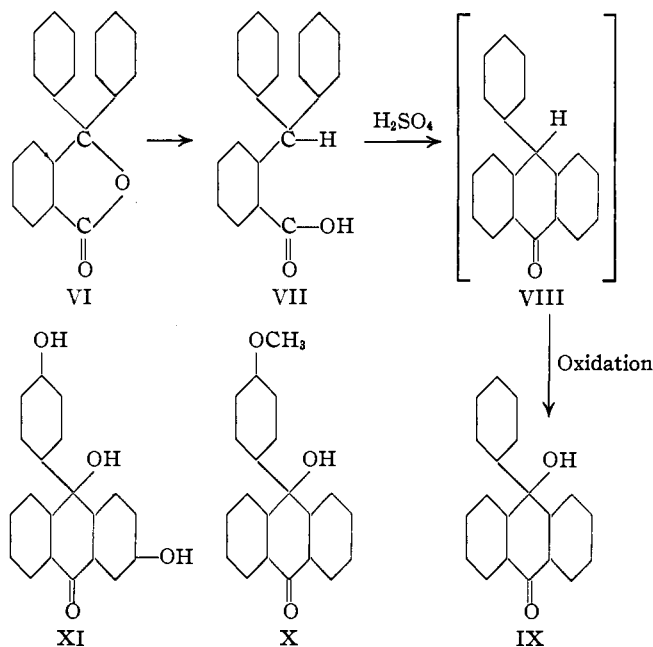
⁶ Presumably this material was 9-phenylanthrone-10 (VIII).

⁷ Haller and Guyot, *Bull. soc. chim.*, [3] **31**, 797 (1904).

⁸ Haller and Guyot, *Compt. rend.*, **121**, 102 (1895).

⁹ Liebermann, Glawe and Lindenbaum, *Ber.*, **37**, 3337 (1904).

carbinol chloride, there seems to be no doubt regarding the structure of this substance.

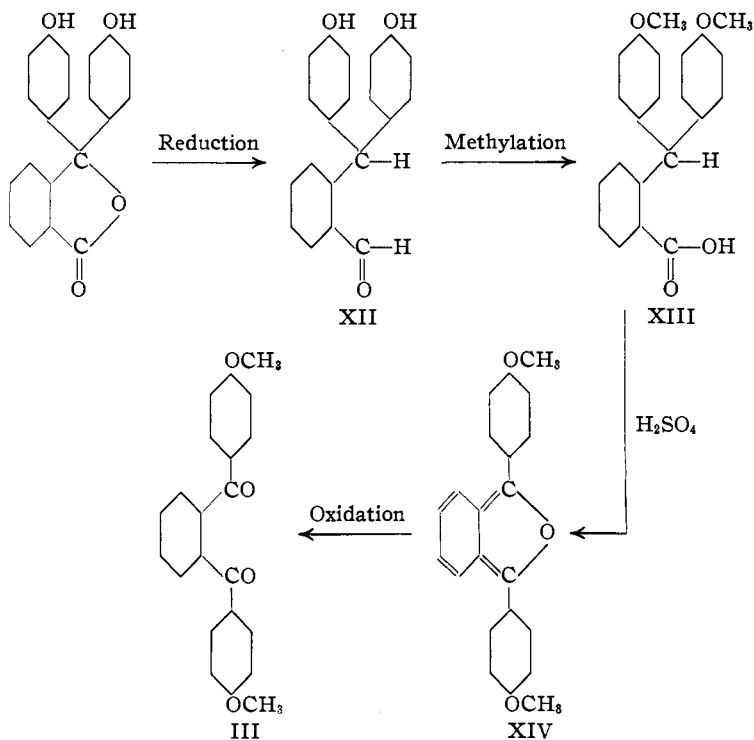


We found that 4-methoxyphenylmagnesium iodide reacts with anthraquinone, analogous to phenylmagnesium bromide, to form 9-(4'-methoxyphenyl)-9-hydroxyanthrone-10 (X).

It might be expected that phenolphthalein-4',4''-dihydroxydiphenylphthalide—when subjected to the same series of reactions applied in the case of diphenylphthalide, would yield a dihydroxy analog of IX, namely, 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10 (XI) and Baeyer⁵ considered the compound obtained by him from phenolphthalein to possess structure XI. However, since we found that the product obtained from phenolphthalein by Baeyer's method yielded neither a carbinol chloride nor a fuchsone when treated with hydrogen chloride, the structure previously assigned to the compound (XI) seemed questionable. It was discovered that Baeyer's compound¹⁰ is not an anthranol but is identical with 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone (IV).

When phenolphthalein was reduced to 4',4''-dihydroxytriphenylmethane-2-carboxylic acid (phenolphthalin, XII), the latter converted into the dimethyl ether (XIII) and then treated as described in the case of diphenylphthalin, the final reaction product was found to be identical with compound III. In this instance we were able to isolate the yellow

¹⁰ Named by him "dihydroxyphenylanthranol" according to the older nomenclature.



intermediate reaction product 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (XIV).¹¹

Experimental Part

2-(4'-Hydroxybenzoyl)-4'-hydroxybenzophenone. (a) From Phthalic Anhydride and 4-Methoxyphenylmagnesium Iodide.—4-Methoxyphenylmagnesium iodide was prepared from 18.8 g. of 4-iodoanisole, 2 g. of magnesium, 30 cc. of ether and 30 cc. of dry benzene. Four and seven-tenths grams of phthalic anhydride, dissolved in 100 cc. of benzene, was stirred rapidly and the Grignard reagent added to it. The mixture was heated for twelve hours. The precipitate which had formed was removed by filtration and decomposed with ice and ammonium chloride. The product was extracted with benzene and the benzene layer shaken with 10% sodium carbonate solution. After removal of the solvent the solid residue was recrystallized from toluene; m. p. 157-159°. This substance, the dimethyl ether of 2-(4'-hydroxybenzoyl)-4'-hydroxybenzo-

¹¹ The diphenyl analog of this substance has been prepared from phenylphthalide and phenylmagnesium bromide by Guyot and Catel [*Bull. soc. chim.*, [3] **35**, 1136 (1906)], Guyot and Vallette [*Ann. chim. phys.*, [8] **23**, 372, 388 (1911)] and by Seer and Dischendorfer [*Monatsh.*, **34**, 1495 (1913)]. It has been shown by Guyot and Haller [*Ann. chim. phys.*, [8] **19**, 297 (1910)] that 2-bis-(*p*-dimethylaminophenyl)-phthalide, upon reduction, treatment of the reduced material with acetic acid and finally oxidation of the reaction product, yields 2-(4'-dimethylaminobenzoyl)-4'-dimethylaminobenzophenone; hence the above-mentioned diarylphthalide behaves entirely analogous to phenolphthalein.

phenone, is somewhat soluble in hot alcohol and insoluble in ether. It was demethylated with hydrobromic acid in acetic acid solution.

2-(4'-Hydroxybenzoyl)-4'-hydroxybenzophenone, after recrystallization from acetic acid and then from dilute alcohol, melted at 225-226°. The material is insoluble in ether and benzene.

Anal. Calcd. for $C_{20}H_{14}O_4$: mol. wt., 318; C, 75.47; H, 4.40. Found: mol. wt. (alcohol),¹² 322; C, 75.31; H, 4.40.

(b) From the Methyl Ester of 2-(4'-Methoxybenzoyl)-benzoic Acid and 4-Methoxyphenylmagnesium Iodide.—The Grignard reagent, prepared from 11.7 g. of 4-iodoanisole, 1.2 g. of magnesium, 25 cc. of ether and 25 cc. of benzene, was added to 10.8 g. of the substituted benzoic acid dissolved in 30 cc. of benzene. The mixture was heated for four hours and then decomposed in the usual manner. The dimethyl ether obtained melted at 157-159°.

(c) From Phenolphthalein.—4',4''-Dihydroxytriphenylmethane-2-carboxylic acid (phenolphthalin) was prepared from U. S. P. phenolphthalein in 96% yield; m. p. 231-232°.¹³

Two hundred and fifty cubic centimeters of concd. sulfuric acid was poured into a beaker and stirred rapidly. Two hundred grams of finely powdered phenolphthalein was added in one portion. After the mixture had been stirred for five minutes the solid material had all dissolved. The solution was then poured into two liters of cold water which was stirred rapidly. The green, granular precipitate was filtered and washed with water. This product dissolved readily in acetone, alcohol, benzene and ether with the formation of solutions which exhibited a strong green fluorescence. The material was dissolved immediately in a mixture of 500 cc. of water and 80 g. of sodium hydroxide. The orange red solution was stirred and a solution prepared from 75 g. of potassium permanganate, 50 g. of sodium hydroxide and 1000 cc. of water was added. After five minutes the manganese salt was removed by filtration. The filtrate was stirred and treated with dilute hydrochloric acid. The precipitated material was filtered, washed with water, dried, recrystallized several times from acetic acid and then from dilute methyl alcohol. Since some of the product remains dissolved in the acetic acid mother liquors, the latter should be concentrated. The yield of the substituted benzophenone was 66 g.; m. p. 224-225°.¹⁴

(d) From 4',4''-Dimethoxytriphenylmethane-2-carboxylic Acid.—This acid,¹⁵ "prepared from phenolphthalein dimethyl ether," when subjected to the action of sulfuric acid in the manner described above, yielded an intensely yellow material, 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (XIV). After recrystallization from a mixture of acetone and alcohol the compound melted at 126-127°. The compound dissolves in ether, benzene and acetic acid to form solutions which possess a green fluorescence.

Anal. Calcd. for $C_{22}H_{18}O_3$: mol. wt., 330; C, 80.00; H, 5.45. Found: mol. wt. (benzene),¹³ 324; C, 79.78; H, 5.43.

The furan, when oxidized, yielded the dimethyl ether of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone. Six-tenths of a gram of the furan, dissolved in 10 cc. of hot acetic acid, was mixed with 1 g. of sodium dichromate, 10 cc. of acetic acid and 1 cc. of sulfuric acid. The mixture was heated for ten minutes on a steam-bath. Twenty

¹² Menzies method.

¹³ Baeyer, *Ann.*, **202**, 81 (1880).

¹⁴ Baeyer [*ibid.*, **202**, 102 (1880)] recorded the melting point as 212°. We obtained this melting point but after further purification the material melted at the temperature stated above.

¹⁵ Grande, *Gazz. chim. ital.*, **26**, I, 228 (1896).

cubic centimeters of hot water was added and the crystalline precipitate obtained was recrystallized from alcohol. The yield was 0.4 g.; m. p. 157–159°; mixed m. p. 157–159°.

Alkali Fusions.—One gram of 2-(4"-hydroxybenzoyl)-4'-hydroxybenzophenone was fused with 5 g. of potassium hydroxide. The residue was dissolved in a small amount of water, filtered and acidified. Sixty-two hundredths of a gram of 4-hydroxybenzoic acid precipitated; m. p. 209–211°. From the filtrate 0.18 g. more of the acid was obtained upon extraction with ether.

When the dimethyl ether of the substituted benzophenone was fused with potassium hydroxide, 4-methoxybenzoic acid was formed; m. p. 181–183°.

Derivatives of 2-(4"-Methoxybenzoyl)-4'-methoxybenzophenone. 3,6-Di-(*p*-methoxyphenyl)-4,5-benzopyridazine (V).—Three and five-tenths grams of the benzophenone was mixed with 20 cc. of acetic acid and to the hot solution there was added, in small portions, a solution prepared from 5 g. of 40% aqueous hydrazine hydrate and 10 cc. of acetic acid. The mixture was refluxed for two hours, an equal volume of water added, the solution cooled, the precipitate filtered and washed with water. Three and three-tenths grams of the diazine was obtained. After recrystallization from acetone the compound melted at 205–206°. It is insoluble in ether but soluble in warm benzene.

Anal. Calcd. for $C_{22}H_{13}O_2N_2$: C, 77.18; H, 5.30; N, 8.19. Found: C, 76.89; H, 5.30; N, 8.10.

Dioxime.—A solution prepared from 5 g. of hydroxylamine hydrochloride, 100 cc. of methyl alcohol and 10 g. of sodium hydroxide was added to 3.7 g. of the benzophenone dissolved in 100 cc. of methyl alcohol. The mixture was refluxed for two hours, cooled, the precipitate filtered and washed with 50% methyl alcohol. After recrystallization from ethyl alcohol there was obtained 2.3 g. of the oxime, which melted at 177–178° with decomposition. The compound is insoluble in ether and benzene.

Anal. Calcd. for $C_{22}H_{20}O_4N_2$: C, 70.20; H, 5.36; N, 7.45. Found: C, 70.61; H, 5.31; N, 7.79.

Diphenylhydrazine.—A solution prepared from 2.4 g. of the benzophenone, 4.3 g. of phenylhydrazine and 25 cc. of alcohol was refluxed for twelve hours. The solution was cooled, the precipitate filtered and washed with alcohol. After recrystallization from alcohol, 1 g. of material was obtained which melted with decomposition at 171–173°. The product is soluble in warm benzene but insoluble in ether.

Anal. Calcd. for $C_{34}H_{30}O_2N_4$: C, 77.53; H, 5.76; N, 10.64. Found: C, 77.37; H, 5.74; N, 10.83.

Summary

The dimethyl ether of 2-(4"-hydroxybenzoyl)-4'-hydroxybenzophenone has been prepared by four methods: (a) from phthalic anhydride and 4-methoxyphenylmagnesium iodide; (b) from the methyl ester of 2-(4'-methoxybenzoyl)-benzoic acid and the Grignard reagent mentioned above; (c) from phenolphthalein; (d) from 4',4"-dimethoxytriphenylmethane-2-carboxylic acid. The corresponding dihydroxy ketone was obtained by demethylation of the ether.

The compound described in the literature as "dihydroxyphenylanthranol," according to modern nomenclature 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10, is in reality 2-(4"-hydroxybenzoyl)-4'-hydroxybenzophenone.