[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF INDIANA UNIVERSITY AND THE UNIVERSITY OF OREGON]

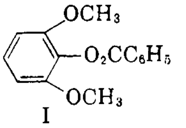
Benzoylation of 2,6-Dimethoxyphenol[1,2]

L. H. KLEMM, H. J. WOLBERT, AND B. T. HO[3]

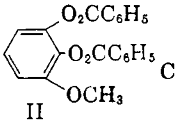
Received December 15, 1958

The effects of varying the solvent and the catalyst on the nature of the products formed from reaction of benzoyl chloride with 2,6-dimethoxyphenol were studied. It was found that, in general, as the reaction conditions are made increasingly strenuous one gets a transition from *O*-benzoylation (esterification) first to C-benzoylation (ring substitution) and then to demethylation plus O- or C-benzoylation. The structural assignment 2,3-dihydroxy-4-methoxybenzophenone was made to a yellow product previously reported as 3,4-dihydroxy-5-methoxybenzophenone by Mauthner. The undemethylated ketone 2,4-dimethoxy-3-hydroxybenzophenone was isolated for the first time.

Using unspecified reaction conditons Herzig and Klimosch[4] isolated two white crystalline compounds, 2,6-dimethoxyphenyl benzoate (I) and 2,3-dibenzoyloxyanisole (II), from treatment of 2,6-dimethoxyphenol (DMP) with benzoyl chloride. Later Mauthner[5] reported the formation of I and a yellow ketone (A), m.p. 168°, for which he suggested structure III, by treating the same reactants with aluminum chloride in nitrobenzene at 2–25°. To us, however, the color[6] of Mauthner's ketone, coupled with the fact that the production of his compound must involve both demethylation and ring benzoylation,[7] seemed inconsistent with structure III but readily correlatable with structure IV. It was the purpose of the present research to investigate further the benzoylation of DMP in order to clarify the structure of Mauthner's ketone and to develop, if possible, a method for benzoylation of the ring without accompanying demethylation.



I



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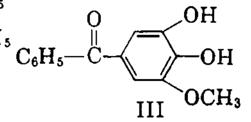
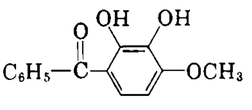
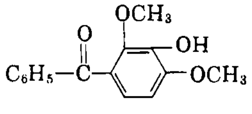


III



IV



VII

A search of the literature revealed that a bright yellow compound (B), m.p. 165°, assigned either the structure of IV or that of 2,4-dihydroxy-3-methoxybenzophenone (V),[8] had been reported both by Graebe and Eichengrün[9] and by Motylewski[10] as the product from limited[11] methylation of the known 2,3,4-trihydroxybenzophenone. The alternative that B was actually 3,4-dihydroxy-2-methoxybenzophenone was rejected by Motylewski on the basis that he could monomethylate B to 2-hydroxy-3,4-dimethoxybenzophenone (VI), of proved structure.[10,12]

We have now established that A and B are identical by repetition of the preceding syntheses and comparison of the resultant products by the criteria of melting points (same) and mixture melting point (undepressed). *Prima facie* this identity might be considered evidence in favor of structure IV for A (and B), inasmuch as formation of V *via* benzoylation would necessitate the migration of a methyl group during the process whereas formation of IV would not. More definite evidence for the correctness of structure IV was obtained by examination of the ultraviolet absorption spectrum

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[1] Abstracted (in part) from the M.A. thesis of H. J. Wolbert, Indiana University, August 1950.

[2] This investigation was supported (in part) by research grant No. CY-3097 from the National Cancer Institute, Public Health Service.

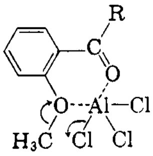
[3] Research assistant, 1957–1958.

[4] J. Herzig and K. Klimosch, *Monatsh.* **30**, 527 (1909).

[5] F. Mauthner, *J. prakt. Chem.*, **133**, 126 (1932).

[6] A check of I. Heilbron [*Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, pp. 211–212] indicates that of the twelve possible dihydroxybenzophenones only the 2,3- and 2,5- isomers are definitely yellow.

[7] C. A. Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corp., New York, 1941, pp. 727–28. It seems likely that the process of demethylation attendant to the acylation of an aromatic ring *ortho*- to a methoxy group is fostered by the formation of a chelate ring, thus



[8] *Cf. Beilsteins Handbuch der Organischen Chemie*, Julius Springer, Berlin, 1925, Vol. VIII, pp. 417–18.

[9] C. Graebe and A. Eichengrün, *Ann.*, **269**, 295 (1892).

[10] S. Motylewski, *Ber.*, **42**, 3148 (1909).

[11] There appears to be a typographical error in the directions of Motylewski, since he reported the formation of (a) a monomethyl derivative from treatment of 2,3,4-trihydroxybenzophenone with two molar quantities each of sodium hydroxide and dimethyl sulfate and (b) a dimethyl derivative from treatment of 2,3-dihydroxy-4-methoxybenzophenone with an equimolar quantity each of sodium hydroxide and dimethyl sulfate. On repetition of (a) we obtained 3,4-dimethoxy-2-hydroxybenzophenone.

[12] Proof of the structure of VI also established that of 2,3,4-trihydroxybenzophenone.

of the 2,4-DNP of A. This spectrum showed a $\lambda_{\max}^{\mathrm{CHCl_3}}$ of 396–398 mμ. On the basis of observations by Johnson[13] one would expect a $\lambda_{\max}$ of 398 mμ for IV.2,4-DNP but of only 392 mμ for V.2,4-DNP. It might be noted, in connection with Motylewski's thoughts, that the infrared absorption spectrum of A in dilute carbon tetrachloride solution exhibits bands at 2.72μ (free hydroxyl) and 3.05–3.07μ (presumably due to hydroxyl *ortho* to a carbonyl group).[14]

In a series of experiments on reaction of DMP with benzoyl chloride under various conditions (*cf.* Table I) it was found possible to prepare a fourth product, Z, m.p. 114°, alkali soluble, white, and with the elemental composition expected for a monohydroxydimethoxybenzophenone. Z is assigned structure VII on the basis of the following considerations: (1) Z can be methylated with aqueous sodium hydroxide and dimethyl sulfate to a neutral compound of m.p. 54°, consistent with that reported for 2,3,4-trimethoxybenzophenone.[4] This neutral compound, moreover, differs from authentic 3,4,5-trimethoxybenzophenone (m.p. 78°) prepared by reaction of phenylmagnesium bromide on the known 3,4,5-trimethoxybenzonitrile.[15] (2) Z differs from 3,4-dimethoxy-2-hydroxybenzophenone (m.p. 131°, obtained by methylation of IV) in that the latter will not undergo methylation under the conditions employed successfully with Z itself.[16] (3) The alternative structure of 2,3-dimethoxy-4-hydroxybenzophenone (though not excluded completely) would necessitate methyl migration during the benzoylation reaction.

TABLE I

REACTION OF 2,6-DIMETHOXYPHENOL WITH BENZOYL CHLORIDE[a]

Run No.[b]	Catalyst	Solvent	Yield of Product[c] (in %) IV	II	VII	I
1	$AlCl_3$	ϕNO_2-$Cl_2CHCHCl_2$	19[d]	16		
2[e]	$AlCl_3$	ϕNO_2	6–12			Much
3	$SnCl_4$	ϕNO_2-$Cl_2CHCHCl_2$			24	5
4	$SnCl_4$	ϕNO_2			28	18
5[f]	$AlCl_3$	CS_2				50
6	$SnCl_4$	CS_2			3	30
7	$SnCl_4$	ϕH				92

[a] Generally the dimethoxyphenol, benzoyl chloride, and catalyst were used in approximately equimolar quantities. The temperature was 0–5°. [b] Listed in approximate expected order of decreasing strenuousness of reaction conditions. [c] Isolated as crystals. [d] Crude crystals. [e] Experiment of Mauthner.[5] [f] Also 12% of dimethoxyphenol was recovered.

Observation of Table I shows that results of the benzoylation are apparently dependent on the strenuousness of the reaction conditions, as based on the solvent and catalyst used. Thus aluminum chloride, a strong Lewis acid, fosters benzoylation of the DMP ring and demethylation to a greater extent than occurs for stannic chloride, a milder Lewis acid. A polar solvent, nitrobenzene alone or with added tetrachloroethane, should favor the formation of ionic or polarized intermediates, probably of more importance in ring benzoylation than in esterification and of considerable importance in demethylation.[7] The nonpolar solvents, on the other hand, yield mainly esterification. In the latter regard the facile esterification occurring through catalysis by stannic chloride in benzene is especially noteworthy.

EXPERIMENTAL[17]

3,4,5-Trimethoxybenzophenone. To the cold Grignard reagent prepared from 2.7 ml. of bromobenzene, 0.6 g. of magnesium, and 15 ml. of anhydrous ether was added a solution of 3.7 g. of 3,4,5-trimethoxybenzonitrile[15] in 40 ml. of anhydrous toluene. The stirred mixture (containing a yellow precipitate) was heated gradually to 35–40°, which temperature was maintained for 3 hr. After 13 more hours at room temperature the mixture was poured into ice and concentrated hydrochloric acid. From the organic layer was recovered 1.0 g. of nitrile. The acid layer was refluxed for 2 hr. and extracted with chloroform. The washed (5% aqueous sodium hydroxide and then water) chloroform solution was dried (magnesium sulfate) and evaporated to leave 2 g. (38%) of product, m.p. 60–70°. Recrystallization from methanol gave needles, m.p. 77–78°; reported[18] needles, m.p. 78–79°. In carbon tetrachloride ($3 \times 10^{-4}M$) it showed a carbonyl band at 6.12μ (broad).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.40; H, 6.05.

The *2,4-dinitrophenylhydrazone*[19] formed orange needles from ethanol-ethyl acetate, m.p. 237–239°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ predicted[13] 396 mμ (log ϵ 4.5), found 395 mμ (log ϵ 4.48); reported[18] orange needles from alcohol, m.p. 200–202°.

Anal. Calcd. for $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; N, 12.39. Found: C, 58.35; H, 4.17; N, 12.14.

4,3,5(?)-Hydroxydimethoxybenzophenone. A solution of 0.8 g. of the preceding trimethoxybenzophenone (m.p. 70–71°) in 4 ml. of concentrated sulfuric acid was maintained at 40° for 17 hr. and then poured onto ice. Combined solids from filtration and extraction (chloroform) of the filtrate were recrystallized from 60% ethanol, yield 0.65 g. (85%), m.p. *ca.* 118°, soluble in 5% aqueous sodium hydroxide. Recrystallization from the same solvent gave needles, m.p. 124.5–126°; reported[18] plates from ether-ligroin, m.p. 124–126°. In carbon tetrachloride ($1 \times 10^{-3}M$) it showed strong absorption at 2.73μ.

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(13) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953). For this calculation additivity of the incremental effects on $\lambda_{\max}$ of substituents on the same phenyl ring in the basic structure of benzophenone.2,4-DNP is assumed. Such increments are 2 —OH, $\Delta\lambda$ = 2 mμ; 3 —OH = 3 —OCH_3, $\Delta\lambda$ = 0; 4 —OH, $\Delta\lambda$ = 3; 4 —OCH_3, $\Delta\lambda$ = 9.

(14) M. Tsuboi, *Bull. Chem. Soc. Japan*, **25**, 60 (1952).

(15) C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, **64**, 2085 (1942).

(16) In addition, the failure to effect methylation of 3,4-dimethoxy-2-hydroxybenzophenone by means of potassium hydroxide, methyl iodide, and methanol has been noted by Graebe and Eichengrün (ref. 9).

(17) Unless otherwise indicated microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet absorption spectra were determined by means of a Beckman DU instrument and infrared spectra by means of a Perkin-Elmer Infracord. Complete infrared spectra for three of the benzophenones taken in potassium bromide wafers are reported in the catalog of *Sadtler Standard Spectra.*

(18) C. F. Koelsch and R. N. Flesch, *J. Org. Chem.*, **20**, 1270 (1955).

(19) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951)

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.46; H, 5.58.

Methylation of 2,3,4-trihydroxybenzophenone.[11] A solution of 5 g. (0.022 mole) of 2,3,4-trihydroxybenzophenone[20] in 25 ml. of 4% aqueous sodium hydroxide was refluxed with 3 g. (0.024 mole) of dimethyl sulfate for 2 hr. The acidified solution was extracted with chloroform. The residue from evaporation of the chloroform was distilled (20 mm. pressure) and crystallized from methanol as bright yellow prisms of *2,3-dihydroxy-4-methoxybenzophenone*, yield 0.8 g. (15%), m.p. 166–167°, undepressed on admixture with the corresponding product from benzoylation of 2,6-dimethoxyphenol.

Repetition of the preceding methylation but with 8% aqueous sodium hydroxide and 6 g. of dimethyl sulfate gave pale yellow needles (from ethanol) of *3,4-dimethoxy-2-hydroxybenzophenone*, m.p. 130–131° [reported[21] prisms, m.p. 130–131°], undepressed on admixture with a sample from similar methylation of IV, obtained from benzoylation.

Benzoylation of 2,6-dimethoxyphenol. (a) *Using aluminum chloride in nitrobenzene-tetrachloroethane.* To the stirred cold (3–4°) solution of 100 g. (0.65 mole) of 2,6-dimethoxyphenol[22] in 475 ml. of purified[23] tetrachloroethane maintained in an atmosphere of nitrogen was first added, over a period of 1.5 hr., a solution of 78.5 g. of anhydrous aluminum chloride in 130 ml. of nitrobenzene and 200 ml. of tetrachloroethane and then, over a period of 2.5 hr., a solution of 78.5 g. (total 1.2 moles) of aluminum chloride and 92 g. (0.65 mole) of benzoyl chloride in 100 ml. of nitrobenzene and 240 ml. of tetrachloroethane. The reaction mixture was kept cold for 4 days, treated with 700 ml. of 1.7*M* hydrochloric acid, and steam distilled. The combined solid residues from the distillation flask and from evaporation of a chloroform extract of the distillate were pulverized and treated with methanol in a Soxhlet extractor. Crystallization of the insoluble portion from ethanol gave 35 g. (16%, based on dimethoxyphenol used) of *2,3-dibenzoyloxyanisole* (II), obtained as platelets, m.p. 154–156°; reported[4] m.p. 156–158°.

Anal.[24] Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.70; H, 4.83.

II was further identified by saponification to benzoic acid (more than a one-molar quantity isolated, m.p. 119–120°, undepressed on admixture with an authentic specimen) and other alkali-soluble crystals, m.p. 38–40°, presumably 2,3-dihydroxyanisole; reported[25] m.p. 38–41°.[26]

From the cold methanolic extract were deposited 30 g. of yellow crystals, m.p. *ca.* 165–169°. For further purification a 5-g. sample of the crystals, dissolved in chloroform, was added to a chromatographic column of silicic acid-Celite (3:1 by volume) and eluted with 30–60° petroleum ether-chloroform (4:1 by volume). The first fraction of effluent contained additional II. Recrystallization from methanol of the main fraction obtained by elution of the yellow zone, gave 3 g. of bright yellow needles of *2,3-dihydroxy-4-methoxybenzophenone* (IV), m.p. 167.5–168.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.87; H, 4.88.

The *2,4-dinitrophenylhydrazone*[19] was obtained as red needles from ethyl acetate, m.p. 265–266.5° (dec.); $\lambda_{max}^{CHCl_3}$ predicted[13] 398 mμ (log ϵ 4.5), found 396–398 mμ (log ϵ 4.47).

Anal. Calcd. for $C_{20}H_{16}N_4O_7$: C, 56.60, H, 3.80; N, 13.20. Found: C, 56.73; H, 3.98; N, 13.51.

(b) *Using stannic chloride in nitrobenzene.* To a cold (−10 to 0°), stirred solution of 20 g. (0.13 mole) of 2,6-dimethoxyphenol in 100 ml. of nitrobenzene was added slowly 20 ml. (0.17 mole) of anhydrous stannic chloride and then 20 g. (0.14 mole) of benzoyl chloride. After 3 more hours the mixture was allowed to warm to room temperature and was then treated with ice and concentrated hydrochloric acid (10 ml.). The residue from steam distillation of the mixture was extracted with ether. The ethereal extract was washed first with excess 5% aqueous sodium bicarbonate (discarded) and then with excess 5% aqueous sodium hydroxide. Evaporation of the ethereal solution yielded 6 g. (18%) of *2,6-dimethoxyphenyl benzoate*, (I) obtained as needles, m.p. 114–117°. Recrystallization from ethanol raised the m.p. to 116–117°, undepressed on admixture with an authentic specimen of the same compound, m.p. 117–118°, prepared by reaction of benzoyl chloride with 2,6-dimethoxyphenol in the presence of pyridine.[27]

Anal.[24] Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.93; H, 5.65.

The preceding sodium hydroxide wash was acidified with hydrochloric acid and extracted with chloroform. The residue from evaporation of the chloroform was recrystallized from methanol to yield 9.5 g. (28%) of tan *2,4-dimethoxy-3-hydroxybenzophenone* (VII), m.p. 107–109°. Further recrystallization from methanol gave white prisms, m.p. 113–114° [m.m.p. with 4,3,5(?)-hydroxydimethoxybenzophenone 103–112.5°]; strong absorption at 2.71μ (free hydroxyl), weak at 2.83μ (methoxy-bonded hydroxyl),[14] and strong at 5.80μ (carbonyl) in $1 \times 10^{-3}M$ solution in carbon tetrachloride.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.23; H, 5.27.

For further identification, a sample of the preceding ketone was methylated (using aqueous sodium hydroxide and dimethyl sulfate) to the neutral compound *2,3,4-trimethoxybenzophenone*, obtained as fluffy crystals from methanol, m.p. 53–54°; reported[4] prisms from dilute ethanol, m.p. 55°.

(c) *Using stannic chloride in benzene.* To a cold (1–5°) solution of 15.4 g. (0.1 mole) of 2,6-dimethoxyphenol in 100 ml. of anhydrous benzene was added dropwise, with shaking, first a solution of 11.7 ml. (0.1 mole) of anhydrous stannic chloride in 25 ml. of benzene and then a solution of 11.5 ml. (0.1 mole) of benzoyl chloride in 25 ml. of benzene. The almost colorless complex which had precipitated on addition of the stannic chloride turned red and partially dissolved upon addition of the acid chloride. Hydrogen chloride was evolved. The mixture was kept cold for 2 days and then poured into ice and dilute hydrochloric acid. The combined organic layer and benzene extracts of the aqueous layer were washed with 5% aqueous sodium hydroxide and then with water, dried (magnesium sulfate), and evaporated to yield 23.7 g. (92%) of cream colored *2,6-dimethoxyphenyl benzoate* (I), m.p. 114.5–116°, identified by recrystallization and mixture m.p. as in part (b).

Eugene, Ore.

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[20] German patent **54661**, *Ber.*, **24c**, 378 (1891).

[21] P. Bartolotti, *Gazz. chim. ital.*, **26 II**, 433 (1896).

[22] We are indebted to Cliffs Dow Chemical Co., Marquette, Mich. for a generous sample of this compound.

[23] L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed. D. C. Heath and Co., New York, 1941, p. 366.

[24] Analysis by Mrs. G. White.

[25] J. Herzig and J. Pollak, *Monatsh.*, **25**, 808 (1904).

[26] Herzig and Pollak (ref. 25) report a m.p. of 85–87° for 1,3-dihydroxy-2-methoxybenzene.

[27] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., J. Wiley and Sons, New York, 1956, p. 212.