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DERIVATIVES OF BENZOYLRESORCINOL

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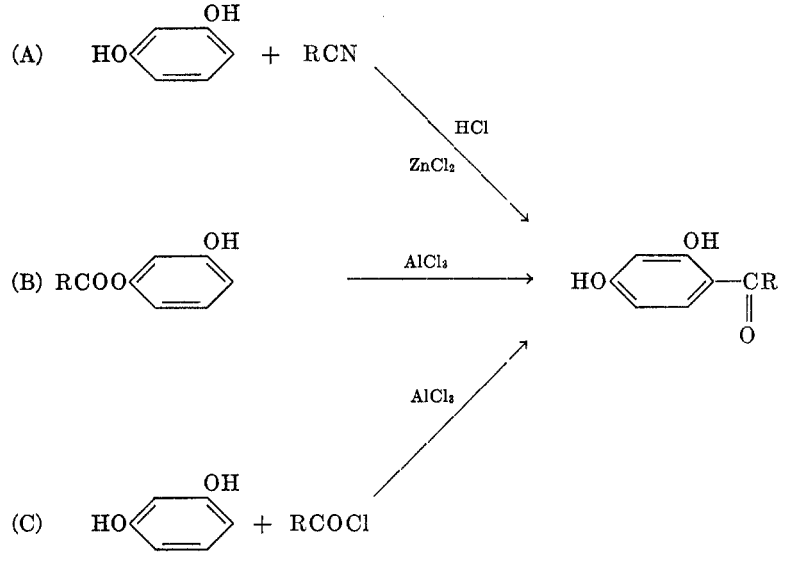
It is known that 4-benzoylresorcinol and its derivatives have good ultraviolet-absorbing properties (1). For this reason it is desirable to determine some of the factors that govern the ultraviolet absorption of 4-benzoylresorcinol. A number of related compounds have been synthesized and their ultraviolet absorption spectra determined. An examination of the literature shows that the acylation of resorcinol has been accomplished by the Hoesch reaction (A) (2, 2a), the Fries rearrangement (B) (2a), or by the Friedel-Crafts reaction (C); the last may introduce one (3), two (4, 5), or three (6) acyl groups.

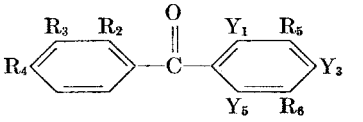


The Hoesch reaction requires a comparatively expensive nitrile and is rather slow. The Friedel-Crafts and the related Fries rearrangement require the use of an acid chloride and nitrobenzene.

The reaction of choice for the preparation of 4-benzoylresorcinol and its derivatives is the condensation of an aromatic acid in tetrachloroethane solution with resorcinol in the presence of an equivalent of boron trifluoride. The yields are usually between 80–90%. Hydrogen fluoride is also a satisfactory condensing agent, but is less desirable because of its corrosive action and the necessity of using pressure equipment. Data concerning the physical properties of the materials used in this work are collected in Table I. Where the substance was prepared by a known method, the literature reference is indicated in Table I by a number. One of the compounds prepared, 5-ethyl-2,4-dihydroxybenzophenone, disagrees in properties with the literature report (7). The product we obtained melts 40° higher and is, in our opinion, more likely to be genuine.

TABLE I

SOME BENZOYLRESORCINOLS



R_2	R_3	R_4	R_5	R_6	Y_1	Y_2	Y_5	M.P., °C.	Method	Empirical Formula or Lit. Reference	Analyses			
											Calc'd		Found	
											C	H	C	H
[a]		CH_3			OH	OH	[a]	139	A	$C_{14}H_{12}O_3$	72.7	5.3	73.0	5.2
		OCH_3			OH	OH		165	B	(15)				
		Cl			OH	OH		151	B	(2)				
		C_5H_{11}[b]			OH	OH		[c]	A	$C_{18}H_{23}O_3$	75.0	8.0	74.9	7.9
	Cl	Cl			OH	OH		188	A	$C_{13}H_8Cl_2O_3$	55.0	2.8	55.2	2.9
SO_3H					OH	OH		dec.		(16)				
				C_2H_5	OH	OH		109	A	$C_{15}H_{14}O_3$	74.3	5.7	74.0	5.7
				n-C_6H_{13}	OH	OH		81–82	A	$C_{19}H_{22}O_3$	76.7	7.7	76.4	7.3
				C_6H_{11}[d]	OH	OH		164	B	$C_{19}H_{20}O_3$	77.0	6.8	77.0	6.8
					OH	[a]	OH	135		(17)				
			C_6H_5CO[e]		OH	OH		105		(4)				
			C_6H_5CO[e]	C_6H_5CO[e]	OH	OH		185		(6)				
				C_6H_5CO[e]	OH	OH		145		(5)				
	NO_2			n-C_6H_{13}	OH	OH		85		$C_{19}H_{21}NO_5$	66.6	6.4	66.1	6.0
					OCH_3	OCH_3		88		(19)				
	NO_2				OCH_3	OCH_3		100		$C_{15}H_{12}NO_5$	62.3	4.2	62.2	4.3
		OCH_3			OH	OCH_3		130		(20)				
					OH	OCH_3		66		(19)				
						OH		134		(25)				
		OH				OH		206		(26)				
OH		OH			OH	OH		193–195		(27)				
			CH_3		OH	OCH_3		124–125		(24)				
4-Phenacylresorcinol								119		(18)				

[a] Where there are no entries in the table the substituent is hydrogen. [b] sec-Amyl. [c] B.p. 235–240° (0.75 mm). [d] Cyclohexyl. [e] Benzoyl.

TABLE II

ABSORPTION SPECTRA DATA

No.	Compound	λ_{max}	log ϵ	λ_{max}	log ϵ	λ_{max}	log ϵ	Reference[b]
I	R•Ph[a]	250	4.30	—	—	333	1.85	(9)
II	*4*•HO•R•Ph	248[c]	4.00	289	4.17	—	—	
III	*4*•HO•R•Ph•OH•*4*	—	—	295	4.28	—	—	
IV	*2*•HO•R•Ph	251	4.04	—	—	342	3.20	(9)
V	*2*•MeOR•Ph	251	4.04	—	—	342	3.20	(9)
VI	*3*•MeOR•Ph	256	4.05	—	—	—	—	(9)
VII	PhCHO	240	4.12	278	3.02	320	1.70	
VIII	PhCOMe	240	4.12	—	—	320	1.70	(22)
IX	*4*•R•Y[a]	242	3.94	290	3.96	338	4.12	
X	*2*•R•Y	250	4.07	280	3.74	—	—	
XI	*2,4*•$(R)_2$•Y	248	4.30	290	3.90	348	4.34	
XII	*4,6*•$(R)_2$•Y	258	4.27	275	4.26	338	4.15	
XIII	*2,4,6*•$(R)_3$•Y[d]	258	4.30	280	4.53	330	3.91	
XIV	*4*•(*4*•MeOR)•Y	256	4.16	285	4.29	325	4.14	
XV	*4*•(*4*•MeR)•Y	250	3.93	290	4.07	340	4.09	
XVI	*4*•(*4*•ClR)•Y	250	4.08	290	4.02	325	4.04	
XVII	*4*•(*3,4*•Cl_2R)•Y[d]	252	3.98	290	4.10	325	3.96	
XVIII	*4*•[*2,4*•$(OH)_2$R]•Y	242	3.80	283	3.96	352	4.17	
XIX	*4*•$PhCH_2CO$•Y	230	3.88	280	4.00	322	4.01	
XX	*4*•MeCO•Y	232	3.90	275	4.16	315	3.84	(14)
XXI	*2,4*•$(MeO)_2$Ph•R	245	4.18	280	3.86	310	3.78	
XXII	*2*•OH•*4*•MeO•PhR	—	—	289	4.13	322	3.96	
XXIII	*2*•OH•*4*•MeOPh•*4*•MeOR	—	—	285	4.20	320	4.12	
XXIV	*2*•HO•*4*•MeO•*3*•MePhR	250	3.89	300	4.27	—	—	

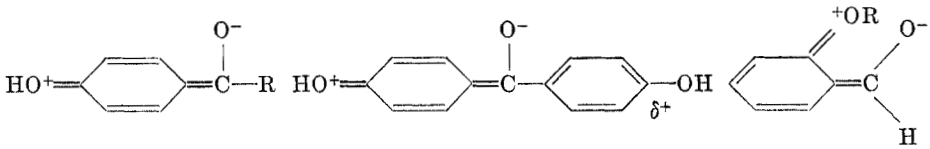
[a] Ph = phenyl; R = benzoyl; Y = resorcinol. [b] Where reference is missing, this work. [c] Inflection. [d] Dioxane as solvent. All other compounds were run in methanol as a solvent using a Cary Model 11 recording spectrophotometer.

4-Benzoylresorcinol undergoes the Mannich reaction readily, and can be easily sulfonated; several derivatives prepared by these reactions are also listed in Table I.

The ultraviolet absorption spectra. The longer-wavelength absorption band of benzophenone (I, Fig. 1) is typical of an aromatic ketone group (8, 9). The introduction of a 4-hydroxyl group, as in 4-hydroxybenzophenone (II), produces a significant change in the absorption spectrum as compared to I, *i.e.*, the development of a strong band at λ_{max} 290 mμ (log ϵ 4.17) and the disappearance of the carbonyl band, due probably to greater resonance contribution from polar structures of Type A (*cf.* Ref. 9, p. 168). A second hydroxyl in the 4′-position, as in 4,4′-dihydroxybenzophenone (III), produces little further change in the spectrum, indicating that there is little resonance contribution from structures of Type B. This result is not unexpected, since the barrier to planarity is considerable (8).

If a hydroxyl or methoxy group is introduced *ortho* to the carbonyl group of I, as in 2-hydroxy- (IV) or 2-methoxy-benzophenone (V) (see Table), there is

a large increase of intensity of the long-wavelength band. 3-Methoxybenzophenone (VI) shows no such effect (9). These results may be correlated by assuming a conjugate chelation of Type C to be operative in the *ortho* derivatives (10). Thus, benzaldehyde (VII), acetophenone (VIII), and I have only a very weak carbonyl band, compared to IV and V.



A B C

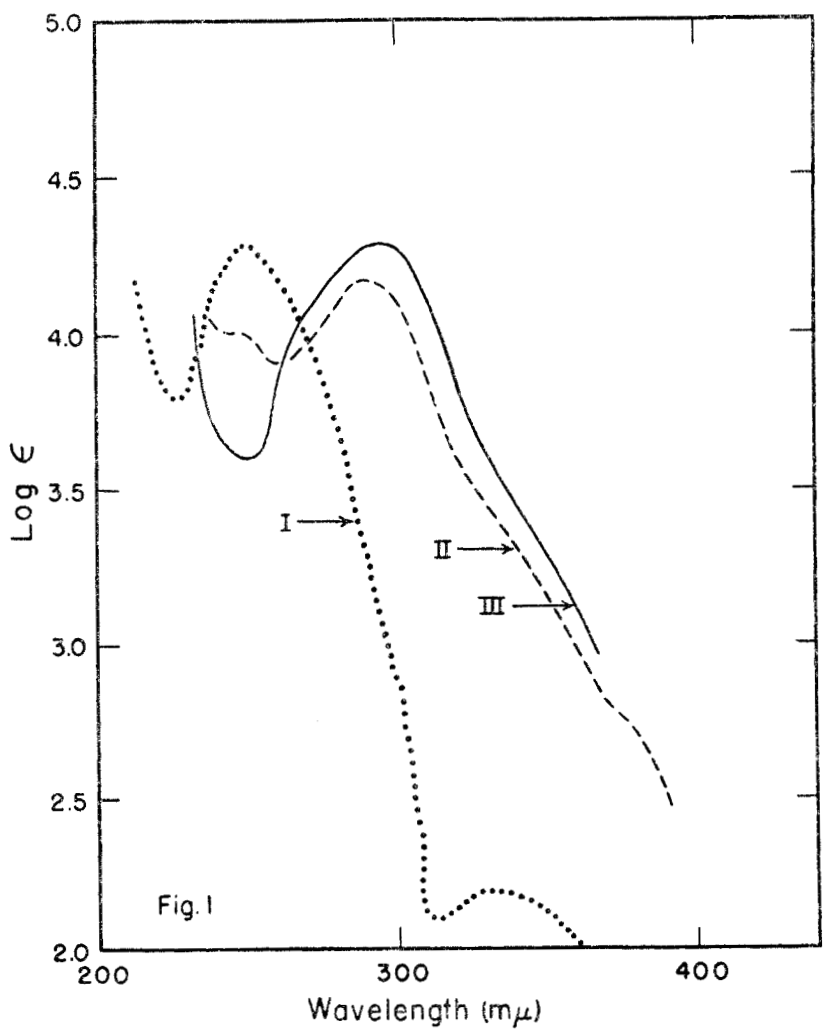


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF: I, Benzophenone; II, 4-Hydroxybenzophenone; and III, 4,4′-Dihydroxybenzophenone.

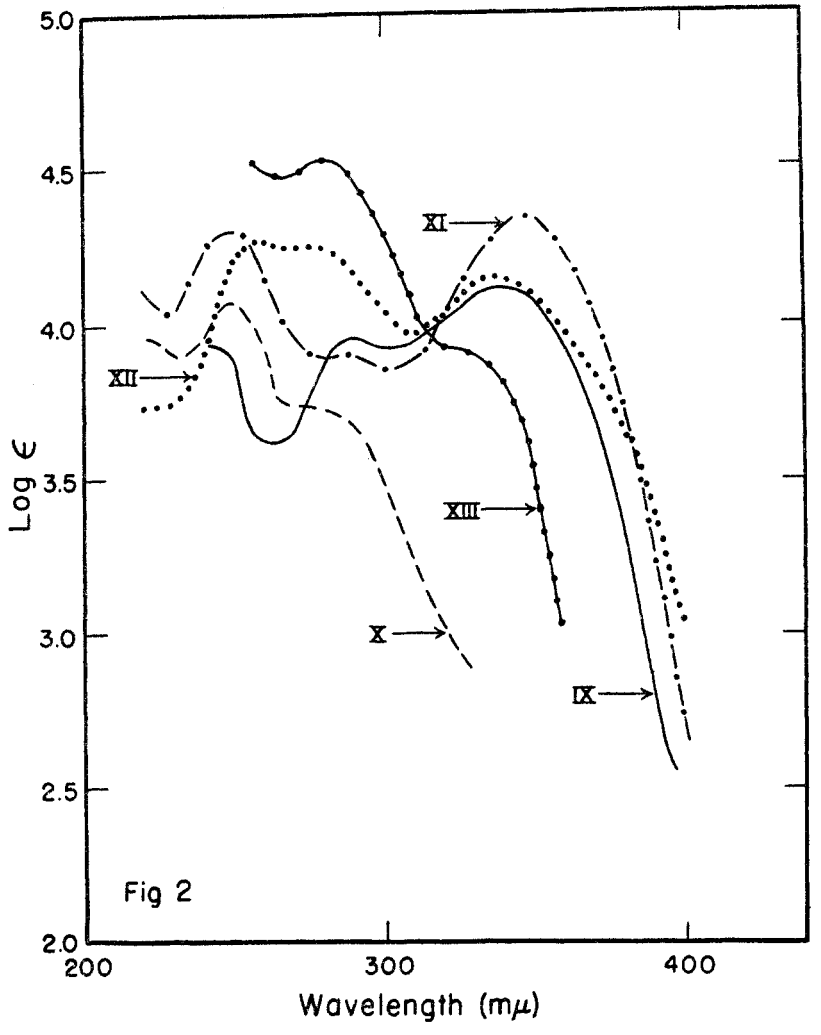


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA OF: IX, 4-Benzoylresorcinol; X, 2-Benzoylresorcinol; XI, 2,4-Dibenzoylresorcinol; XII, 4,6-Dibenzoylresorcinol; and XIII, 2,4,6-Tribenzoylresorcinol.

Hydroxy groups in both the 2- and 4-positions produce a characteristic spectrum in which there are three distinct maxima, which, for convenience in describing derivatives, are designated as the "a" band, 245–255 mμ; "b" band, 280–290 mμ; and "c" band, 335–345 mμ. These are clearly shown in Figure 2. The "a" band is constant in position and in intensity, and is probably benzenoid in origin. The "b" band probably arises from contributors of Type A, and the "c" band is assumed to be associated with the conjugate chelation of Type C. Variations of the parent 4-benzoylresorcinol (IX) have been made to determine the effects on its ultraviolet spectrum. In the spectrum of 2-benzoylresorcinol (X), the "c" band has disappeared. We consider this to be a consequence of

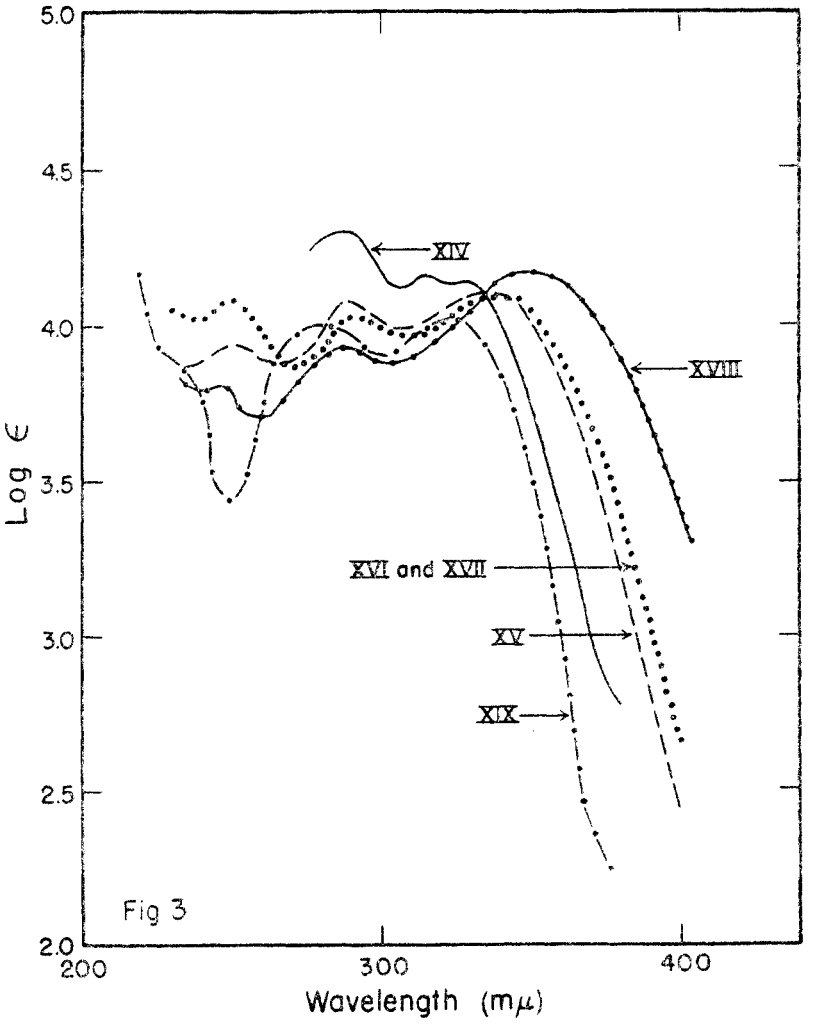


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED BENZOYLRESORCINOLS: XIV, 4′-Methoxy-; XV, 4′-Methyl-; XVI, 4′-Chloro-; XVII, 3′,4′-Dichloro-; and XVIII, 2′,4′-Dihydroxy-. Also, 4-phenacylresorcinol, XIX.

steric hindrance in the conformation of Type C. The spectra of 2,4- (XI) and 4,6-dibenzoylresorcinol (XII) are quite similar to IX, although the "b" band of XII is only an inflection. 2,4,6-Tribenzoylresorcinol (XIII) has a unique spectrum, a result of the distortion which must exist in this molecule.

Further examples of these three bands are shown in Figure 3. Substitution in the nonphenolic residue, as in 4′-methoxy- (XIV), 4′-methyl- (XV), 4′-chloro- (XVI), 3′,4′-dichloro- (XVII), and 2′,4′-dihydroxy-benzoylresorcinol (XVIII), increases slightly the intensity of the "b" band, and, in addition, produces a bathochromic shift (14 mμ) in the case of XVIII in the "c" band as compared to IX. Insulation of the phenyl group with a methylene group, as in 4-phenacyl-

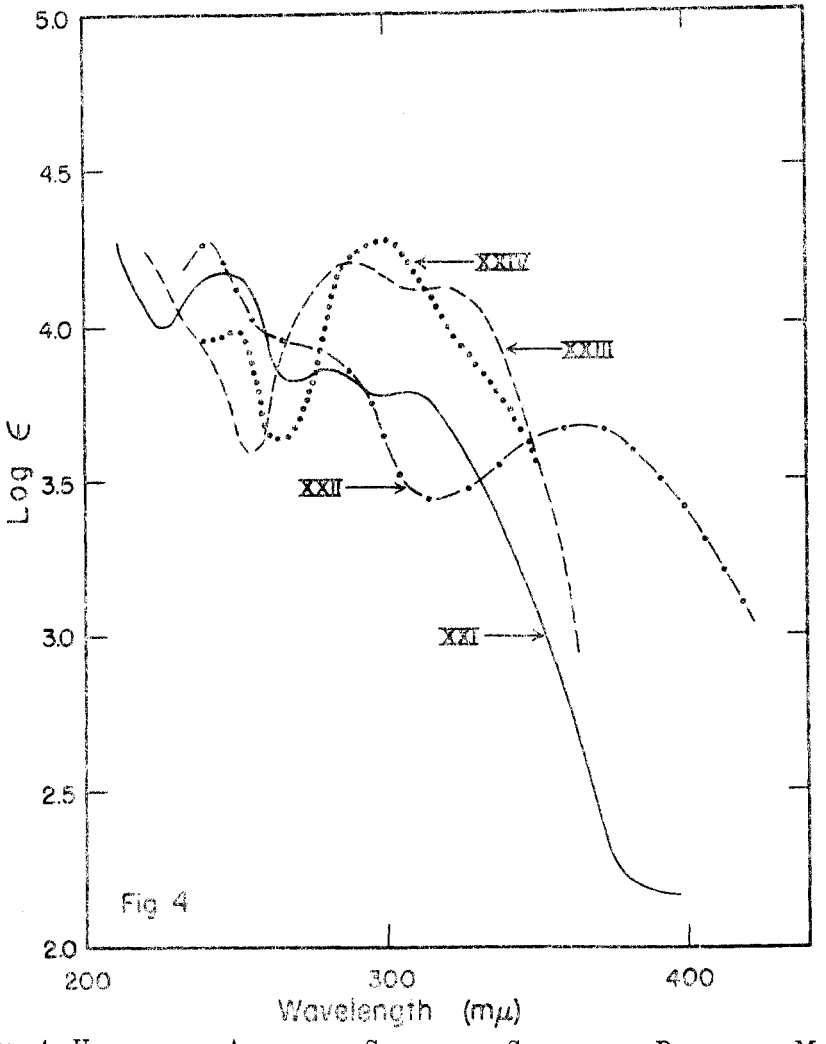


FIG. 4. ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED RESORCINOL METHYL ETHERS: XXI, 2,4-Dimethoxybenzophenone; XXII, 2-Hydroxy-4-methoxybenzophenone; XXIII, 2-Hydroxy-4,4′-dimethoxybenzophenone; and XXIV, 2-Hydroxy-4-methoxy-3-methylbenzophenone.

resorcinol (XIX), produces a hypsochromic shift of both "b" and "c" bands, and XIX is quite similar to 2,4-dihydroxyacetophenone (XX).

Methyl ethers have the spectra shown in Figure 4. The methylation of IX to 2,4-dimethoxybenzophenone (XXI) produces a large (28 mμ) hypsochromic shift, and a decrease in intensity of the "c" band. This parallels the finding of Buroway and Chamberlain (11) on the effects of methylating phenols. This effect is also found in the partially methylated benzoylresorcinols, 2-hydroxy-4-methoxy- (XXII) and 2-hydroxy-4,4′-dimethoxy-benzophenone (XXIII), but not to such a large extent. It is known (11) that when both *ortho*-positions to a

hydroxy are occupied by Cl, Br, Me, etc., there is a hypsochromic shift of the absorption spectrum, owing to the intramolecular steric hindrance involving these substituents. This is the case in 2-hydroxy-4-methoxy-3-methylbenzophenone (XXIV), as is evidenced by its spectrum. The characteristic spectra of the benzoylresorcinols are absent in XXIV, being replaced by one more closely resembling II. Apparently the *meta*-methyl group exerts considerable steric inhibition to coplanarity, possibly by buttressing effect (12). It is well established (13) that such steric effects result in hypsochromic shifts and a decrease in intensity of ultraviolet spectra.

EXPERIMENTAL

The following examples are typical of those used in this work.

I. *2,4-Dibenzoyl-6-n-hexylresorcinol* (*Friedel-Crafts method*). 6-Hexylresorcinol, 38.8 g. (0.2 mole), was added to a complex consisting of 50 ml. (0.4 mole) of benzoyl chloride and 55 g. (0.4 mole) of aluminum chloride in 125 ml. of nitrobenzene, and the mixture was allowed to stand for 2 hours. The mixture was heated at 80–90° for 3 hours, allowed to stand overnight, and decomposed with dilute hydrochloric acid. The nitrobenzene solution was extracted three times with 5% sodium hydroxide solution, the sodium salt of the product remaining in the nitrobenzene. The nitrobenzene was evaporated and the residue was washed with benzene, dissolved in methanol, precipitated with dilute acetic acid, and the supernatant liquids were decanted. The residue was slurried with cold methanol and then recrystallized from methanol. The yield of white needlelike crystals was 42 g. (52%), m.p. 68–69°.

2,4-Dihydroxy-4'-methoxybenzophenone (*Method A*). In a 250-ml., 3-necked flask, equipped with a stirrer and inlet tube, and protected from moisture by a drying tube, were placed 22 g. (0.2 mole) of resorcinol, 30 g. (0.2 mole) of anisic acid, and 50 ml. of tetrachloroethane. Gaseous boron trifluoride was then introduced until the increase in weight was 18 g. The mixture was stirred and heated on a steam-bath for 4 hours, then poured into 300 ml. of water containing sodium acetate (55 g.). The mixture was filtered and the precipitate (57 g.) dissolved in 400 ml. of 5% sodium hydroxide. Carbon dioxide was passed into this alkaline solution until the solution was weakly alkaline. The mixture was filtered and the precipitate dried. The yield was 44 g. (90%), m.p. 158–160°. The crude product was dissolved in 150 ml. of hot methanol, Norit (10 g.) was added, and the solution was filtered. Water (50 ml.) was added, and after 4 hours, the white crystalline precipitate was filtered and dried. The recovery was 39.5 g. (81%), m.p. 165°.

5-Ethyl-2,4-dihydroxybenzophenone (*Method B*). A mixture of 4-ethylresorcinol (25 g.), benzoic acid (25 g.), and 200 ml. of hydrogen fluoride gas was heated to 100° in a stainless-steel bomb. The excess hydrogen fluoride was vented and the residue was taken up in dilute alkali and precipitated with carbon dioxide. The precipitate was collected in benzene, the solvent removed, and the residue distilled; b.p. 240–250° (1 mm.). The distillate was recrystallized from benzene-ligroin; yield 21 g.; m.p. 104°.

II. *Sodium 2,4-dihydroxybenzophenone-5-sulfonate.* Benzoylresorcinol (43 g.) was slowly added, with stirring, to 20% oleum (200 g.) at a temperature of 15–20° and the solution was allowed to stand for about 0.5 hours. The mixture was poured on 1500 g. of ice, whereupon the sulfonated product separated out. The mixture was then redissolved by heating to 40–45°, and 5 g. of Nuchar and 5 g. of Filter Cel were added. After filtering, 1000 g. of saturated salt solution was added, precipitating the sodium salt of the product. It was filtered and dried; yield 56 g.

4-Benzoyl-6-dimethylaminomethylresorcinol hydrochloride. Benzoylresorcinol (21.4 g.; 0.1 mole), 10 g. (0.2 mole) of trioxymethylene, 20 g. (0.2 mole) of dimethylamine hydrochloride, and 150 ml. of 3A alcohol[1] were refluxed for 5 hours, and the mixture then was

[1] A denatured ethyl alcohol.

chilled in the ice chest. The white crystalline precipitate was removed by filtration, washed with alcohol, and dried. Yield, 21.0 g.; m.p. 210–212°. The product was recrystallized from ethanol as white platelike crystals, m.p. 215°.

4-Benzoyl-6-piperidinomethylresorcinol hydrochloride was prepared in a similar manner, m.p. 222°.

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: C, 64.4; H, 6.6.
Found: C, 64.3; H, 6.2.

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SUMMARY

The long-wavelength absorbing band of 4-benzoylresorcinol and its derivatives seems to be associated with the conjugate chelation which can occur between the *ortho*-hydroxy- and the carbonyl group. This conjugation can be reinforced by suitably placed electron sources or suppressed by steric effects.

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