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Condensation of *o*-Phthalaldehydic Acid with Dihydroxy Benzenes, Part VII: Synthesis of 3-(Dihydroxyphenyl) Phthalides and their Nitration Reactions

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The condensation of *o*-phthalaldehydic acid (1) with hydroquinone, resorcinol and catechol in 30–55% H_2SO_4 afforded the corresponding 3-arylphthalide (2a, b, 3a) respectively, while with more concentrated acid > 70% they afforded the unisolated 1,3-diaryl isobenzofuran of type (4). Nitration of compound 2a–b, 3a–c with aqueous nitric acid/acetic acid mixture gave the corresponding mono-nitro derivative (5, 6a–d), but in one case the dinitro derivative (6e) was isolated. Some of these mono-nitro derivatives show acid-base indicator behaviour. The structures of isolated products were confirmed from their spectral and analytical data.

INTRODUCTION

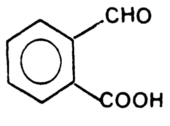
Phthalides, from *o*-phthalaldehydic acid (1) are known to possess some biological activity;[1–3] on the other hand, 3-arylphthalides have been used as a precursor in the synthesis of some biologically active compounds like islandicin, adrimycine, the antitumor daunomycine[4] and for anthraquinones and anthracyclone systems.[5] For these and other reasons, the synthesis of new 3-aryl phthalides and the study of their properties became of interest.

Reaction of (1) with phenols, substituted phenols and anisoles has been studied by the author[6] and by Gupta *et al.*[7] under different acidic conditions. With phenols and anisoles in 60–65% H_2SO_4 the main condensation products are 3-arylphthalides, while with concentrated H_2SO_4 or H_3PO_4, 1,3-diarylisobenzofurans are the main products.[8] This indicates that the type of the product depends upon the reactivity of the aromatic compound and upon the kind of acid and its concentration. Highly reactive aromatic molecules require low acid concentration to afford 3-arylphthalides, but unreactive aromatic compounds like nitrophenols need high acid concentration and longer reaction time, conditions which favour the formation of 1,3-diarylisobenzofurans.

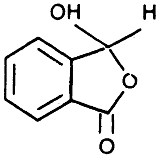
For these reasons, our interest was concentrated on the reaction of the reactive dihydroxybenzenes with (1), and on the preparation of nitro aryl phthalides, products which are difficult to prepare by direct condensation.

RESULTS AND DISCUSSION

Since *o*-phthalaldehydic acid (1) has been found to exist in the lactol form (7), we thought that (1) will generate the phthalidyl cation (8) in acidic medium, which will behave as an electrophile.



(1)



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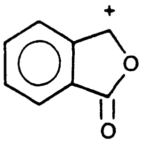

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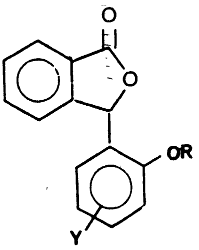
TABLE-1
PREPARATION AND PROPERTIES OF 3-ARYL PHTHALIDE (2a, 2b, and 3a), THEIR DERIVATIVES (2c–d, 3d–e) AND (6a–6e)

Comp. No.	m.p. (°C)	Yield %	Solvent of crystallization	IR absorption (cm^{-1})	Colour	Analyses % found (calcd)		
						C	H	N
2a	108–110	73	benzene	3200, 1720	White	69.50 (69.42)	4,35 (4.16)	—
2b	132–133	75	ethanol H_2O	3300, 1720	White	69.56 (69.42)	4.32 (4.16)	—
2c	93–95	90	ethanol H_2O	1750	Brown	73.46 (73.52)	4.76 (4.83)	—
2d	108–110	81	ethanol H_2O	1750	Pale yellow	73.30 (73.52)	4.76 (4.83)	—
3a	183–184	82	ethanol H_2O	3500, 3300, 1720	Off white	69.60 (69.42)	4.30 (4.16)	—
3d	123–124	91	ethanol H_2O	1750, 1730	White	73.27 (73.52)	4.70 (4.83)	—
3e	145–146	85	benzene	1750, 1740	Off white	70.36 (70.20)	6.42 (6.38)	—
5	140–142	80	benzene-Pet-ether	3300, 1780. 1530, 1370	Orange	58.33 (58.53)	3.30 (3.15)	5.06 (4.88)
6a	Oily	—	—	—	—	—	—	—
6b	110–112	80	benzene-Pet-ether	3350, 1770, 1520, 1520, 1360	Brown	58.39 (58.53)	3.27 (3.15)	5.01 (4.88)
6c	150–152	80	benzene-Pet-ether	3400, 1765, 1540, 1360	Yellow	62.06 (61.99)	3.26 (3.35)	4.99 (5.10)
6d	147–149	90	benzene-Pet-ether	1760, 1545, 1350	Yellow	62.92 (63.15)	3.75 (3.86)	4.96 (4.91)
6e	178–180	60	benzene-Pet-ether	3450, 1760, 1530, 1330	Yellow orange	54.86 (54.9)	2.52 (2.61)	9.31 (9.15)

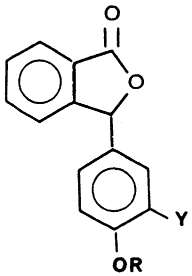
This was the case, when (1) was allowed to react with hydroquinone and resorcinol (2a, b) in the presence of >70% H_2SO_4 at room temperature; a very deep red colouration occured which after hydrolysis gave a highly coloured gummy material. The IR spectra of the crude products show the presence of a strong absorption at 1180–1130 cm^{-1} but no absorption in the range 1770–1730 cm^{-1}.

Many attempts to isolate a pure product failed, mainly because the products were light sensitive and showed a tendency to light catalysed oxidation,[9] suggesting the crude products to be 1,3-dihydroxyphenyl isobenzofurans of type (4).

On the other hand the reaction of (1) with catechol afforded a solid product. The IR spectrum shows the presence of a strong absorption at 1725 cm^{-1} due to the lactonic group. Furthermore the ^1H-nmr spectrum shows a sharp singlet at δ 6.45 integrating for one proton and assigned to H-3. This chemical shift suggests that H—3 is unaffected electronically or sterically by any substituent on the aryl group, confirming that the condensation was regioselective at the *para* position to one hydroxyl of the catechol affording compound[10] (3a).



2 ; a , R = H ; Y = 5-OH
b , R = H , Y = 4-OH
c , R = $COCH_3$; Y = 5-$OCOCH_3$
d , R = $COCH_3$, Y = 4-$OCOCH_3$



3 ; a ; R = H , Y = OH
b ; R = H , Y = H
c ; R = Me , Y = H
d , R = $COCH_3$, Y = $OCOCH_3$
e ; R = $COBu^t$, Y = $OCOBu^t$

Furthermore the structure of compound 3a was converted to the diacetate and dipivaloate derivatives (3d and 3e) respectively (see Table-2 for their spectral data).

It was realised that the condensation of (1) with hydroquinone and resorcinol to afford the required 3-arylphthalides could be achieved using 30–35% H_2SO_4. With hydroquinone the white solid product melts at 108–110°C; its IR spectrum shows two strong absorptions at 3500–3200 cm^{-1} due to highly hydrogen bonded OH and at 1735 cm^{-1} due to the lactone system. On the other hand its NMR spectrum in d-acetone shows a sharp singlet at δ 6.6 and in $CDCl_3$ at δ 6.72, integrating one proton due to H-3, suggesting the structure of the product to be (2a). Such product is entirely different from structure (9) suggested by Raoof[11], since H-3 of such compound should absorb at δ 7.1–7.3. Furthermore compound (2a) was easily converted to the diacetate (2c) through its reaction with acetylchloride-pyridine mixture. (See Table 2 for spectral data.)

The reaction of (1) with resorcinol gave the expected product (2b). Its IR spectrum shows a strong absorption at 3400, 3200 cm^{-1} due to OH groups and at 1720 cm^{-1} due to the lactone group, while its NMR in d-acetone shows a singlet at δ 6.78 due to H-3. The deshielding of H-3 in compounds (2a–d) can be attributed to the electronic effect caused by the hydroxyl or acetoxy group at position 2′ of the aryl group.

TABLE-2

^{1}H-NMR SPECTRAL DATA OF COMPOUNDS (2a–d) AND (3a, d, e)

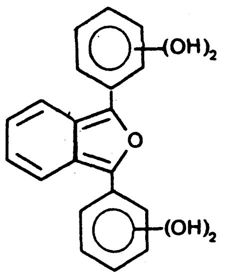
Compd. No.	H-3	H-7	H-4	H5 + H6	H2′ + 3′ + 4′ + 5′ + 6′	Others
2a[1]	s, 6.71	m, 7.85 $J_1 = 7.7$ $J_2 = 1.7$	dd 7.32	m, 7.4–7.7	m, 6082	b, 3.5, 2 OH
2b[2]	s, 6.78	m, 7.82	m, 7.53	m, 7.64	d, 6.7 $J_1 = 9.5$ H-6; d, 6.4, $J_1 = 9.5$ H-5′, 6.3, H-3′	B, 8.74, 2 OH
2c[1]	s, 6.80	m, 7.80	m, 7.4	m, 7.62	s, 7.0 g	s, 2.28, 2 $COCH_3$
2d[1]	s, 6.71	dd, 7.94, $J_1 = 8.0$ Hz $J_2 = 2.0$ Hz	dd, 7.61	m, 7.4–7.6	m, 7.03–7.13	s, 2.14, $COCH_3$, s, 2.25, $COCH_3$
3a[2]	s, 6.45	d, 7.8, $J_1 = 7.5$ Hz	d, 7.40 $J_1 = 7.5$	dd, 7.6, $J_1 = 8.0$ Hz $J_2 = 2.0$ Hz	s, 6.72 H-3′, ABq, 6.85 J = 8.0 Hz	s, 8.05, OH, s, 6.8, OH
3d[1]	s, 6.38	d, 7.92 $J_1 = 7.8$ Hz	d,7.43 J = 7.8	dd, 7.60 $J_1 = 7.8$, $J_2 = 2.0$ Hz	m, 7.15–7.26	S, 2.27, 2$COCH_3$
3e[1]	s, 6.37	d, 7.92 $J_1 = 8.0$ Hz	d, 7.42 J=7.8 Hz	dd, 7.66 $J_1 = 7.8$ Hz	s, 7.14	s, 1.32, CO But

[1]in $CDCl_3$. [2]in d-acetone.

As with other compounds, product (2b) was converted to the diacetate derivative (2d) (see Table-2 for spectral data).

The condensation of (1) with nitrophenols was found to be difficult to achieve at ordinary temperature and it required either a high temperature or stronger acids; both can cause loss of selectivity and possibly the formation of isobenzofuran derivatives.[11] It was realised that nitration of already prepared 3-aryl phthalides might give the desired products.

Thus when 3-(4-hydroxyphenyl) phthalide (3b) and 3-(4-methoxyphenyl) phthalide (3c) were nitrated with a mixture of aqueous acetic acid and nitric acid[12] at room temperature for 1 h, they afforded the corresponding nitro derivatives (6c and 6d); compound (6d) separated out from the reaction mixture after about 15 min, while under reflux conditions compound (3b) only afforded the corresponding 3,5-dinitro derivatives (6e). The IR spectra of compounds (6c–e) show the presence of a lactone group at 1760–1740 cm^{-1}. On the other hand their NMR spectra show H-3 as a sharp singlet in the range of δ 6.40–6.84. The



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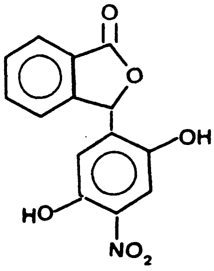
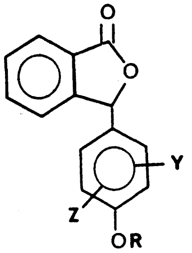
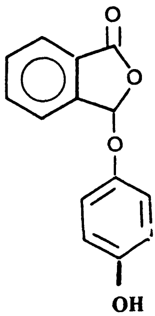


(5)

slight deshielding of H-3 in some cases could be attributed to the highly electron withdrawing nitro group. Furthermore the UV spectra of compounds (6c and 6e) show red shift under basic conditions suggesting that they can have some acid-base character. We are investigating this point and results will be communicated later[14]



6 ; a , R = H , Y = 3-OH , Z = 5-and r6-NO_2
b , R = H , Y = 2-OH , Z = 5-NO_2
c , R = H , Y = 3-NO_2 , Z = H
d , R = Me , Y = 3-NO_2 , Z = H
e , R = H , Y = 3-NO_2 , Z = 5-NO_2



(9)

Nitration of compounds (2a, 2b and 3a) under similar conditions[12] afforded in the first two cases solid mononitro derivatives (5) and (6a) respectively, while with (3a), an oily mixture was obtained.

The structures of the products tentatively proposed on the basis of the most probable nitration position and on the spectral data (see Table-3). Nitration of 3-phenyl phthalide afforded a mixture of 3-(2-and 4-nitrophenyl) phthalide.[13] It was realised that nitration of (2a) will afford compound (5), in which the nitration occurs at carbon *ortho* to the hydroxyl and *para* to the alkyl. On the other side, nitration of (2b) will give exclusively compound (6d), while in nitration of (3a), a mixture of products was formed and this can be supported by the formation of oil rather than a solid.

TABLE 3

^{1}H NMR SPECTRAL DATA OF NITRO COMPOUNDS 5 AND 6b–e IN d-ACETONE

Compd No.	H-3	H-7	H-4	H-5 + H-6	H-2′,3′,4′,5′,6′	Others
5	s, 7.19	m, 7.91		8.01	s, 7.95, H3′, s, 7.31, H6′	b, 10.3, OH
6b	s, 6.90	m, 7.60		7.90	s, 8.14, H6′, s, 7.3, H3′	b, 10.2, OH b, 3.6, OH
6c	s, 6.71	dd, 7.85 J_1 = 7.5 Hz J_2 = 1.9 Hz	m, 7.52	m, 7.62–7.74	d, 8.2, J = 1.9 Hz, H6′, m, 7.5 , H2′, d, 7.24, J = 8.7 Hz, H5′	b, 10.53, OH
6d	s, 6.40	m, 7.5	m, 7.50	m, 7.62–7.7	d, 8.0, J = 2.0 Hz, H6′, m, 7.4 H2′, m, 7.3 H5′	b, 3.9, OCH_3
6e	s, 6.84	m, 7.8	m, 7.80	ABq, 7.72, J = 8.0	s, 8.42, H2′, 6′	b, 10.2, OH

All IR spectra of the mononitro products show strong absorptions in the range of 3450–3300, ν(OH), 1780–1760, ν(CO) and 1540–1520, 1370–1330 cm^{-1} due to the nitro group, while the NMR spectra of compounds (5) and (6b) show a sharp singlet in the range of δ 6.90–7.19 due to H-3; again the deshielding could be attributed to electronic effect and to prochirality.[10]

Oxidation of compounds (2a) and (3a) to the corresponding quinones has been carried out and results will be communicated later.

EXPERIMENTAL

All melting points were measured on electrothermal melting point apparatus and were uncorrected, infrared (IR) spectra were measured using pye-Unicam SP-300 spectrophotometer as a potassium bromide disc. ^1H NMR were measured using a Bruker WP 80 SY spectrometer. Elemental analyses were measured at M.H.W. Laboratories, Pheonix, Arizona, USA.

Reaction of *o*-phthalaldehydic acid with disubstituted benzene (General method)

To a mixture of 3.75 g *o*-phthalaldehydic acid in 50 mL dilute H_2SO_4(< 70%) was added 2.75 g of dihydroxybenzene. The mixture was stirred at room temperature for about 15 h; in certain cases a solid starts to appear. The mixture was then added to 100 mL ice-water. Filteration, washing the precipitate with water (2 × 25 mL), saturated $NaHCO_3$ (2 × 10 mL), then water. After drying the solid was crystallized from the mentioned solvent. According to this procedure, 3(2,5-dihydroxyphenyl) phthalide (2a), 3(2,4-dihydroxyphenyl) phthalide (2b) and 3(3,4-dihydroxyphenyl) phthalide (3a) were prepared. See Table-1 for physical data and Table-2 for NMR data.

Nitration Reactions

To a mixture of 1.0 g hydroxyphenyl phthalide in 15 mL acetic acid and 9 mL H_2O, 3 mL of conc. HNO_3 was added dropwise with stirring for 2–3 h; the temperature of the reaction never reached boiling point. The resulting red or deep brown solution was added to100 mL ice-water. The solid that formed was filtered, washed with water (3 × 25 mL), dried and crystallized from the mentioned solvent (see Table-1 for physical data and Table-3 for NMR data). The compounds that were prepared according to this procedure are 3(2,5-dihydroxy-5-nitrophenyl) phthalide (5), 3(3,4-dihydroxy-5 or 6-nitrophenyl) phthalide (6a), 3(2,4-dihydroxy-5-nitrophenyl) phthalide (6b), 3(4-hydroxy-3-nitrophenyl) phthalide (6c) and 3(4-methoxy-3-nitrophenyl) phthalide (6d).

3(4-hydroxy-3,5-dinitrophenyl) phthalide (6e) was prepared using the same procedure with excess HNO_3 and under refluxing conditions for about 2–3 h.

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