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Synthesis and Spectra of Some New Phthalein Dyes

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ABSTRACT

A new series of analogues of phthalein dyes has been synthesised by the condensation of 2-(4′-ethyl-3′-nitrobenzoyl)benzoic acid with various mono-, di- and trihydroxyphenols, using concentrated sulphuric acid as the condensing agent. Similar to most γ-oxoacids, 2-(4′-ethyl-3′-nitrobenzoyl) benzoic acid exhibits keto–lactol tautomerism, and in the presence of concentrated sulphuric acid, undergoes condensation with phenols through its cyclic lactol tautomeric form. The resulting compounds are unsymmetrically substituted phthalides in which the central triphenylmethane carbon is attached to two different phenyl rings. Electronic spectra data in ethanol (neutral and alkaline) are compared to those of some known phthaleins. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Phthaleins have many applications, such as analytical reagents and colourants. Tetraiodofluorescein has been used as a photographic dye and also as a colouring matter for foodstuffs, and tetraiodophenophthalein has found use as a skiagraphic chemical.[1] Some metal complexes of fluorescein have been reported to possess antiseptic,[2] and antibacterial[3] properties. A large number of phenolphthalein derivatives exhibit cathartic activity,[4] and have been used in pharmaceutical preparations. In view of these applications of phthalein dyes, it was thought worthwhile to synthesise some new analogues by condensing a γ-oxoacid, viz. 2-(4′-ethyl-3′-nitrobenzoyl) benzoic acid, with various phenols.

It has been noted that γ-oxoacids generally exist in keto-acid (chain) and lactol (ring) tautomeric forms[5–9]. The conversion of the open keto-acid form

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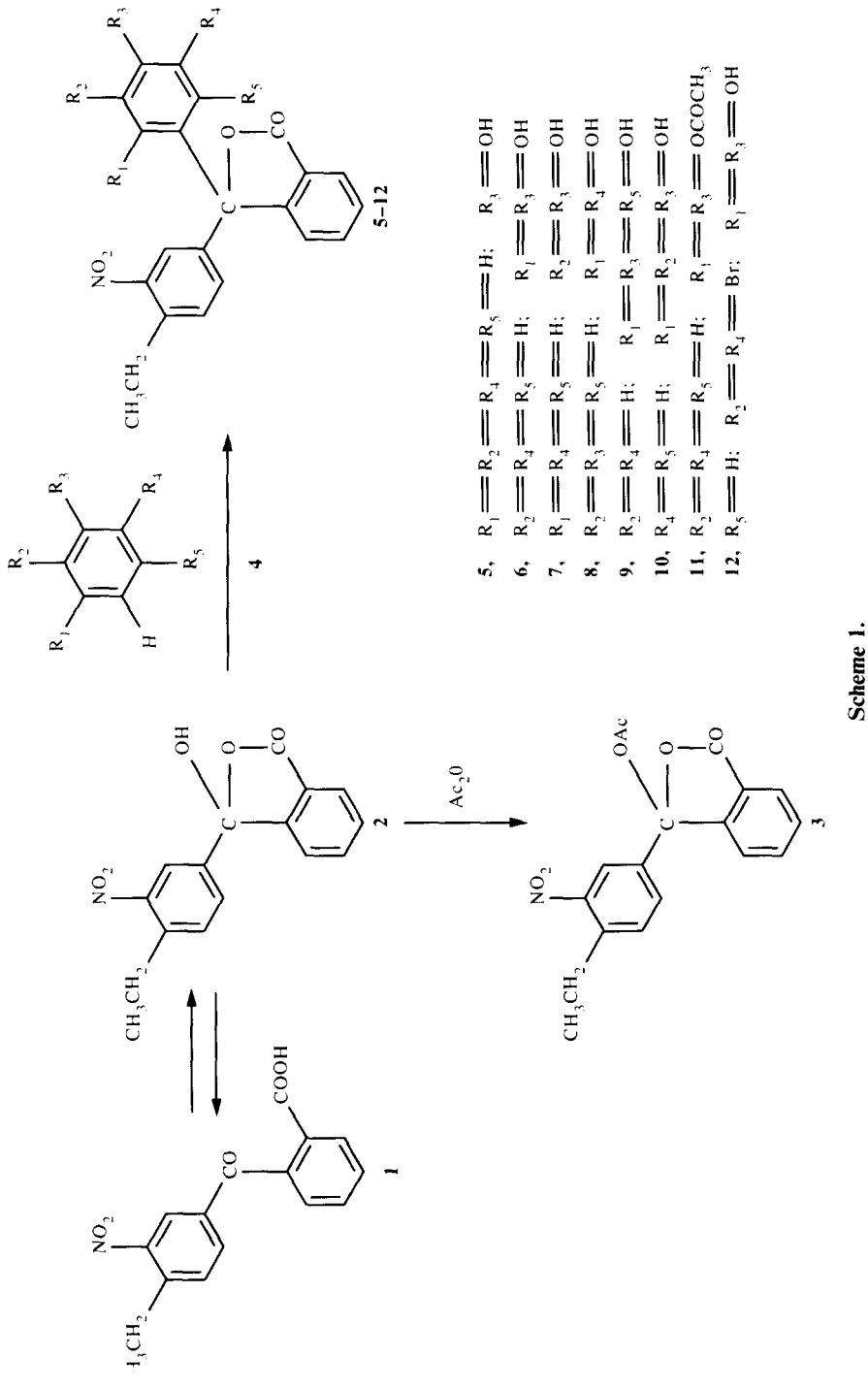
into the cyclic lactol form (or vice versa) is effected by the action of basic and acid catalysts, by specific reagents and on heating.[6] The lactols of γ-oxoacids form crystalline acetyl derivatives[10–12] possessing a cyclic lactonic structure. The formation of cyclic derivatives, such as pseudo-chlorides[13] and pseudo-esters,[14–16] has been reported to take place through the cyclic lactol form. There are many chemical reactions of γ-oxoacids which take place due to their cyclisation to the lactol form.[17–23] Instrumental methods, viz. IR,[15,24] Raman[16] and NMR[25] spectroscopy, also support the formation of cyclic isomers.

RESULTS AND DISCUSSION

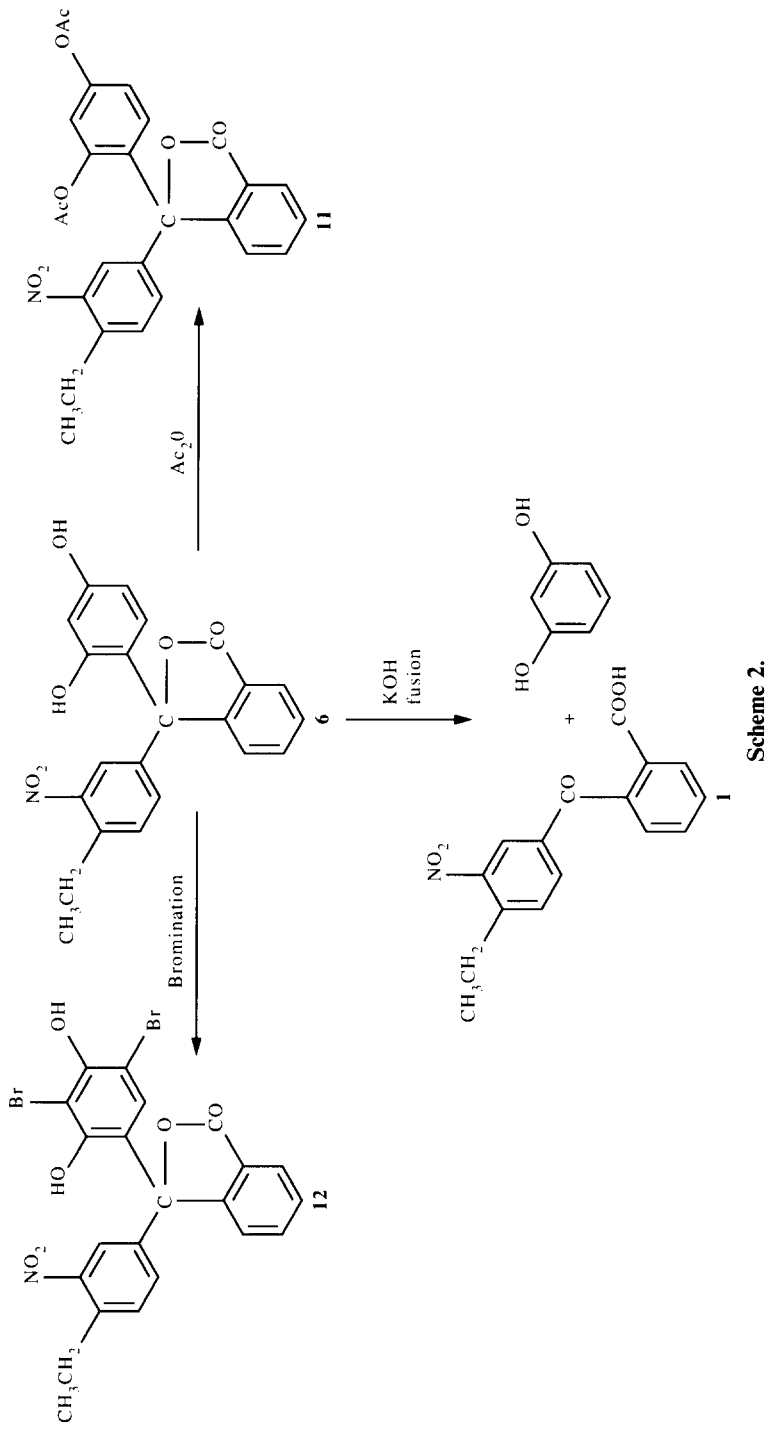
The γ-oxoacid, used in this investigation, i.e. 2-(4′-ethyl-3′-nitrobenzoyl)-benzoic acid, has been found spectroscopically to exist as a mixture of its keto-acid (**1**) and lactol (**2**) tautomeric forms. On refluxing with acetic anhydride in the presence of anhydrous sodium acetate, it gave a cyclic acetyl derivative (**3**). The IR spectrum of the acid (KBr) showed absorption bands at 1690, 1650 and 1760 cm^{-1} (weak) characteristic of carboxyl CO, diaryl ketonic CO and lactonic CO groups, respectively. A broad band between 2500–2700 cm^{-1} and a weak band at 3400 were assigned to carboxyl and lactol OH groups, respectively. The acetyl derivative (**3**) of the oxoacid **1** showed sharp peaks at 1780 and 1750 cm^{-1}, which are relatable to lactonic carbonyl and acetyoxyl carbonyl stretching vibrations, respectively. The ^1H NMR spectrum (DMSO - d_6) of the acid showed a multiplet in the region between δ 7.1 and 8.0, which is assignable to aromatic protons. Protons of the ethyl group appeared at δ 2–2.3 as a multiplet. A singlet of low intensity at δ 2.5 could be ascribed to the hydroxy proton of the lactol form of the acid. The acetyl derivative (**3**) of the acid ($CDCl_3$) exhibited a multiplet at δ 7.1–8, assigned to the aromatic protons. The protons of the ethyl group and of the acetoxyl group formed a complicated multiplet between δ 2 and 2.4. There was no signal at δ 2.5, as observed in the spectrum of the acid. These spectral data indicate that the acetyl derivative (**3**) exists in a cyclic lactonic structure, the formation of which takes place through the lactol form (**2**) of the γ-oxoacid (**1**) as shown in Scheme 1.

2-(4′-Ethyl-3′-nitrobenzoyl)benzoic acid (**1**) was reacted with phenols (**4**) in the presence of concentrated sulphuric acid to give the new phthalein dyes (**5–10**). These compounds are unsymmetrically substituted phthalides, in which the central triphenylmethane carbon is attached to two different phenyl rings. The formation of the phthalides (**5–10**) occurs through a condensation reaction via the lactol form (**2**) of the acid **1** and with excess of phenols (**4**) the acid reacts entirely through the lactol form (Scheme 1). The



5, $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$
6, $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OH$
7, $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = OH$
8, $R_2 = R_3 = R_5 = H$; $R_1 = R_4 = OH$
9, $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = OH$
10, $R_4 = R_5 = H$; $R_1 = R_2 = R_3 = OH$
11, $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OCOCH_3$
12, $R_5 = H$; $R_2 = R_4 = Br$; $R_1 = R_3 = OH$

Scheme 1.


OAc
AcO
O
CO
C
NO2
CH3CH2
11
Ac2O
OH
HO
6
KOH
fusion
COOH
CO
1
Bromination
Br
12

Scheme 2.

structures of the synthesised products were established on the basis of elemental analysis, acetylation, bromination, KOH degradation and IR spectral studies (Scheme 2). The formation of the diacetyl (**11**) and dibromo (**12**) derivatives supported the presence of only one resorcinol molecule in **6**. On KOH fusion, **6** was degraded to **1** and resorcinol (Scheme 2).

IR spectra of the dyes **5–10** and **12** showed a strong and broad band in the region 3200–3450, due to OH stretching vibrations. The broad nature and low frequency of this band indicated that OH groups are involved in strong hydrogen bonding or tautomeric shifts. There was no band between 3200 and 3450 cm^{-1} in the IR spectrum of **11**, but an intense band was present at 1750 cm^{-1}, assignable to the carbonyl stretching in a phenolic acetate moiety. All the dyes (**5–12**) exhibited a strong band between 1740 and 1780 cm^{-1}, which could be attributed to lactonic carbonyl stretching. The presence of this band is in accord with the proposed lactonic structure.[26] The stretching vibrations (vc-c) of the aromatic rings led to the bands near 1590–1605, 1570–1580, 1490–1500 and 1440–1470 cm^{-1}. The nitro group attached to phenyl ring gave rise to three sharp bands at about 1520–1555 cm^{-1} (asymmetric N–O stretching), 1330–1370 cm^{-1} (symmetric N–O stretching) and 830–850 cm^{-1} (C–N stretching). The spectra of all the dyes showed one intense band at 750–765 cm^{-1} and a weaker band at 700–715 cm^{-1}, both of which are characteristic of an o-disubstituted phthalein ring [27].

The colours and absorption maxima of the unsymmetrically substituted phthalides were recorded in ethanol (neutral and alkaline) and compared to those of some analogous known phthaleins (Table 1). In alkaline medium, the maxima were significantly shifted towards the longer wavelength. This bathochromic shift indicates that, like true phthaleins, in an alkaline medium the lactonic structure of these dyes (**5–12**) also undergoes transformation into the corresponding quinonoid configuration. The phthalides reported here could be of potential interest as dyes, analytical reagents and therapeutic agents. This aspect is the basis of our ongoing studies.

EXPERIMENTAL

General

Melting points are uncorrected. Homogeneity of the products was checked by TLC; IR spectra were run (KBr) on a Perkin-Elmer 137 spectrophotometer and ^1H NMR spectra on a Varian FT-80A. Chemical shifts are expressed in δ ppm relative to tetramethylsilane as internal standard. Electronic spectra were recorded in ethanol (neutral and alkaline) on a Perkin-Elmer Lambda 15 UV/VIS spectrophotometer.

TABLE 1
Colours and Absorption Maxima of Phthalides Prepared and those of some Known Phthaleins

Phthalide	Colour in ethanol		Colour with 2% NaOH	λ max (nm)	
	Neutral	Alkaline		Netural	Alkaline
5	Reddish yellow	Dark red	Dark red	410	540
6	Light yellow	Orange red	Orange red	340	453, 480
7	Yellowish brown	Dark brown	Dark brown	–[a]	–[a]
8	Yellowish brown	Brown	Dark brown	–[a]	–[a]
9	Yellowish red	Red	Dark reddish brown	450	500
10	Yellowish brown	Dark brown	Dark brown	–[a]	–[a]
11	Light yellow	Orange red	Colourless	360	453, 480
12	Brownish red	Brownish red	Dark brownish red	425, 520	520, 600
Phenophthalein	Colourless	Pink	Pink	–	550
Flurescein	Yellowish red	Red[b]	Reddish pink[b]	480	500
Eosin	Light pink[b]	Orange pink[b]	Orange pink[b]	530	530

[a]Correct λmax could not be measured, probably because of decomposition of these phthalides.
[b]Green fluorescence.

The synthesis of 2-(4′-ethyl-3′-nitrobenzoyl)benzoic acid (**1**) was carried out by nitration of 2-(4′-ethylbenzoyl) benzoic acid.[28] The phenols (phenol, resorcinol, catechol, quinol, phloroglucinol and pyrogallol) were taken in slight excess over the acid (**1**), and concentrated sulphuric acid (4–5 drops) was used as condensing agent throughout. By analogy with phthaleins,[29] the condensation is assumed to have taken place as shown in Scheme 1.

*2-(4′-Ethyl-3′-nitrobenzoyl)benzoic acid (**1**)*
2-(4′-Ethylbenzoyl)benzoic acid (38.1 g) was dissolved in concentrated nitric acid (*d* 1.42, 200 ml) and the resulting solution was refluxed for 1 h and then cooled in an ice bath. The separated solid was filtered and washed with water and dried. Crystallisation of the product (ethanol) gave 2-(4′-ethyl-3′-nitrobenzoyl)benzoic acid as yellowish-white crystals (28.75 g, 65.9%); m.p. 151–152°C, IR: ν = 3400, 2500–2700 (broad), 1760, 1690, 1650, 1600, 1580, 1500, 1450, 1520, 1340, 840 cm^{-1}. ^1H NMR: δ = 7.1–8(m), 2.5(s), 2–2.3(m) ppm. Found: C, 64.3; H, 4.4; N, 4.7%. $C_{16}H_{13}NO_5$ requires C, 64.2; H, 4.3; N, 4.7%.

*3-Acetoxy-3-(4′-ethyl-3′-nitrophenyl)phthalide (**3**)*
The acetyl derivative (**3**) of the oxoacid **1** was prepared using previously reported acylation conditions for similar compounds.[12] The acid (**1**) (1 g) was mixed with fused sodium acetate (0.5 g) and acetic anhydride (10 ml). The mixture was refluxed on a steam bath for 4 h and then poured into ice-cold water (50 ml). The reaction mixture was allowed to stand, with occasional stirring, until excess of acetic anhydride had hydrolysed. The precipitate was filtered and then treated with hot potassium carbonate. The mixture was cooled and extracted repeatedly with ether. On evaporation of the ether, the residue was recrystallised from acetone, giving white crystals (0.47 g); m.p. 146–147°C, IR: ν = 1780, 1750, 1590, 1500, 1450, 1530, 1360, 870 cm^{-1}. ^1H NMR: δ = 7.1–8 (m), 2–2.4 (m) ppm. Found: C, 63.5; H 4.35; N, 4.2%. $C_{18}H_{15}NO_6$ requires C, 63.3; H, 4.4; N, 4.1%.

Synthesis of various phthalides (5–10). General procedure

The acid (**1**) (0.015 mole) was intimately mixed with the appropriate phenolic compound (**4**) (0.02 mole) and the resulting mixture heated at 130–165°C to obtain a homogeneous liquor. Concentrated H_2SO_4 (4–5 drops) was then added carefully with stirring, and the temperature raised by 10°C. Heating was continued for a further 1–6 h at this temperature, after which a hard, brittle mass was obtained on cooling. The product thus obtained was crushed and washed thoroughly with water to remove excess of the phenols. In the synthesis of **5**, the unreacted phenol after the condensation was

removed by steam distillation. The condensation product was then extracted with 2% aqueous NaOH and filtered. Dyes (**5**–**10**) were precipitated from the filtrate by gradual addition of dilute HCl with stirring. They were finally purified by repeated crystallisation from ethanol. Relevant data is given below.

3-(4′-Ethyl-3′-nitrophenyl)-3-(4′-hydroxyphenyl)phthalide (**5**): pinkish brown crystals, m.p. 105–106°C, yield 72.2%. Found: C, 70.5; H, 4.6; N, 3.7%. $C_{22}H_{17}NO5$ requires C, 70.4; H, 4.5; N, 3.7%. IR: 3200, 1760, 1590, 1500, 1470, 1555, 1330, 840, 750 and 700 cm^{-1}. UV-VIS: see Table 1.

3-(4′-Ethyl-3′-nitrophenyl)-3-(2′,4′-dihydroxyphenyl)phthalide (**6**): yellowish-brown crystals, m.p. 155–156°C, yield 72%. Found: C, 67.7; H, 4.4; N, 3.6%. $C_{22}H_{17}NO_6$ requires C, 67.5; H, 4.3; N, 3.6%. IR: 3300, 1750, 1600, 1570, 1455, 1525, 1345, 840, 765 and 715 cm^{-1}. UV-VIS: see Table 1.

3-(4′-Ethyl-3′-nitrophenyl)-3-(3′,4′-dihydroxyphenyl)phthalide (**7**): dark brown crystals, m.p. 168–170°C, yield 64.1%. Found C, 67.4; H, 4.4; N, 3.5%. $C_{22}H_{17}NO_6$ requires C, 67.5; H, 4.3; N, 3.6%. IR: 3300, 1750, 1600, 1580, 1460, 1520, 1340, 840, 760 and 700 cm^{-1}. UV-VIS: see Table 1.

3-(4′-Ethyl-3′-nitrophenyl)-3-(2′,5′-dihydroxyphenyl)phthalide (**8**): brown crystals, m.p. 130–132°C, yield 68.2%. Found C, 67.5; H, 4.3; N, 3.6%. $C_{22}H_{17}NO_6$ requires C, 67.5; H, 4.3; N, 3.6%. IR: 3200, 1740, 1600, 1575, 1455, 1520, 1350, 850, 760 and 700 cm^{-1}. UV-VIS: see Table 1.

3-(4′-Ethyl-3′-nitrophenyl)-3-(2′,4′,6′-trihydroxyphenyl)phthalide (**9**): reddish-brown crystals, m.p. 165–166°C, yield 67.5%. Found: C, 65.1; H, 4.2; N, 3.4%. $C_{22}H_{17}NO_7$ requires C, 64.9; H, 4.2; N, 3.4%. IR: 3300, 1780, 1600, 1580, 1440, 1520, 1340, 840, 750 and 720 cm^{-1}. UV-VIS: see Table 1.

3-(4′-Ethyl-3′-nitrophenyl)-3-(2′,3′,4′-trihydroxyphenyl)phthalide (**10**): dark brown crystals, m.p. 173–175°C, yield 67.5%. Found C, 64.6; H, 4.2; N, 3.5%. $C_{22}H_{17}NO_7$ requires C, 64.9; H, 4.2; N, 3.4%. IR: 3200, 1765, 1600, 1570, 1455, 1520, 1350, 840, 765 and 715 cm^{-1}. UV-VIS: see Table 1.

Acetylation of 6

The phthalide **6** (1 g) was mixed with acetic anhydride (15 ml) and fused sodium acetate (2 g) and the mixture heated at 130–140°C for 3 h to give the brown diacetyl derivative **11**. This was crystallised from acetone as pale brown crystals (0.9 g), m.p. 130–132°C. Found: C, 65.8; H, 4.5; N, 2.8%. $C_{26}H_{21}NO_8$ requires C, 65.7; H, 4.4; N, 2.9%. IR: 1775, 1750, 1605, 1580, 1490, 1470, 1525, 1350, 830, 760 and 700 cm^{-1}. UV-VIS: see Table 1.

Bromination of 6

The phthalide **6** (1 g) was dissolved in the minimum quantity of ethanol, and bromine (2 ml) was added to it dropwise with stirring. After standing

overnight at room temperature, the dark brown dibromo compound **12** precipitated. This was crystallised from 80% aqueous ethanol as reddish brown crystals (1.02 g), m.p. 123–124°C. Found: Br, 29.2%. $C_{22}H_{15}NO_6Br_2$ requires Br, 29.1%. IR: 3450, 1770, 1595, 1580, 1490, 1460, 1525, 1370, 830, 760 and 700 cm^{-1}. UV-VIS: see Table 1.

Caustic potash fusion of 6

The phthalide (**6**) (1 g) was mixed with a paste of KOH pellets (10 g) and the mixture was heated at 250°C for 3 h, until the colour of the dye had faded completely. The fused mass was cooled, dissolved in water and filtered. The filtrate was neutralised with dilute HCl, giving a yellowish brown solid (**A**), which was filtered and washed with water. The filtrate was further acidified by adding excess HCl, and then allowed to stand for a few hours, during which time a yellowish-white solid deposited (**B**); this was filtered and washed thoroughly with water. The filtrate was extracted with ether, and on evaporation of the ether a brownish-red residue (**C**) was obtained. Compounds **A**, **B** and **C** were identified as unreacted phthalide **6**, the oxoacid **1** and resorcinol, respectively, by direct comparison (m.m.p., co-TLC and co-IR) with authentic samples.

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