A New Route to Anthraquinones

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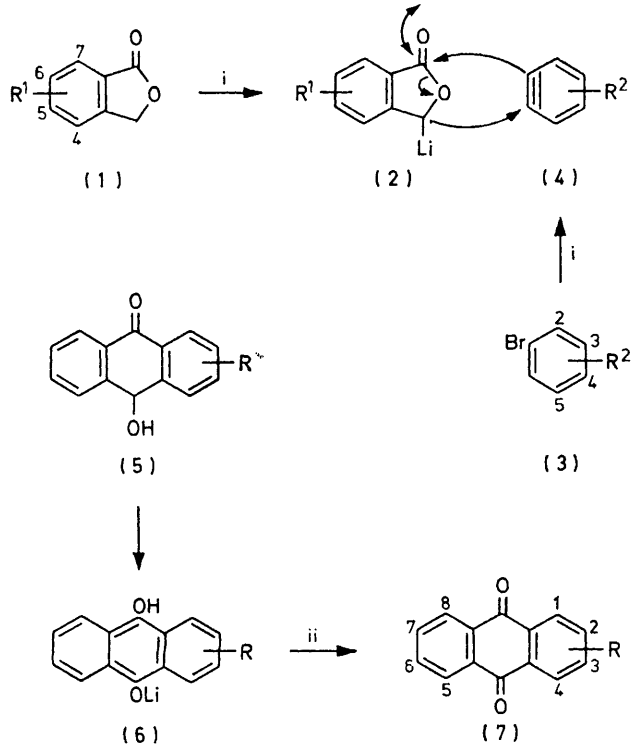
The lithium salts derived from position 3 of phthalides react with arynes to form adducts, which, upon aerial oxidation, produce anthraquinones in moderate to good yields. Substituted phthalides and arynes also participate in this general reaction. The addition to unsymmetrically substituted arynes shows regioselectivity, whilst the availability of a new general route to phthalides extends the scope of this reaction.

THE use of carbanions, derived from phthalides, in the synthesis of naphthalene and hydronaphthalene systems has recently been noted.[1] In this paper we report a general method for the extended utility of such species in the direct preparation of anthraquinones.[2] The method based on earlier observations on the reaction of dienolate anions with arynes.[3] In the present instance reaction of the lithium salts (2) of phthalides (1) with arynes (4), generated *in situ* from bromobenzenes (3), affords the adducts (5) (Scheme 1), which, after aerial oxidation and neutralisation readily produce anthraquinones. Formation of the anthraquinones (7) appears to proceed *via* salts of the 10-hydroxyanthrones (5), converted under basic conditions into the enol forms (6), which are subsequently oxidised to the observed products.



SCHEME 1 Reagents: i, lithium di-isopropylamide; ii, H_3O^+, air

In order to effect the desired transformation the phthalide anion is produced in the presence of an extra equivalent of base and the aryne precursor then added. For example, for the formation of anthraquinone itself, phthalide (1 equiv.) was treated with lithium di-isopropylamide (2.2 equiv.) in tetrahydrofuran at −60 °C to produce the orange carbanion. To the solution at −45 °C was added bromobenzene (1 equiv.) in tetrahydrofuran. Since the formation of arynes from bromobenzenes is relatively slow at low temperatures,[4] the reaction mixture was allowed to warm to room temperature, eventually in contact with air, before acidification and work-up. Oxidation occurred during the latter stages of this procedure and the product anthraquinone could be isolated, either by direct filtration or extraction. In some cases the yield of anthraquinone was considerably enhanced by using an excess of the benzyne precursor (see Table).

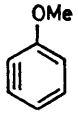
	Phthalide (1) R^1	Bromobenzene (3) R^2	Anthraquinone (7) R	% Yield
a	H	H	H	28.5,[a] 74.5[b]
b	4-MeO	H	1-MeO	51[b]
c	H	4-MeO	2-MeO	45[a]
d	6-MeO	H	2-MeO	31[b]
e	H	4-Me	2-Me	40[a]
f	5,6-$(MeO)_2$	H	2,3-$(MeO)_2$	32[a]
g	6,7-$(MeO)_2$	H	1,2-$(MeO)_2$	18[a]
h	H	2,5-$(MeO)_2$	1,4-$(MeO)_2$	46[a]
i	4-MeO	2-MeO	1,8-$(MeO)_2$	2[b]
			1,5-$(MeO)_2$	39.5[b]
j	6-MeO	2-MeO	1,7-$(MeO)_2$	41[b]
k	4-MeO	4-MeO	1,7-$(MeO)_2$ / 1,6-$(MeO)_2$	60[a,c]
l	6-MeO	2,5-$(MeO)_2$	1,4,6-(MeO)	64[b]
m	5,6-$(MeO)_2$	2,5-$(MeO)_2$	1,4,6,7-$(MeO)_4$	64[b]
n	H	2,3-benzo	1,2-benzo	62[a]
o	5,6-$(MeO)_2$	2,3-benzo	1,2-benzo-6,7-$(MeO)_2$	32[a]
p	H	2-MeO- 5-Me	1-MeO- 4-Me	16[b]
q	H	2-HO-5, MeO	1-HO- 4-MeO	26[a]
r	4-$PhCH_2O$	H	1-$PhCH_2O$	24[b]
			1-HO	4[b]
s	H	2-$PhCH_2O$, 5-MeO	1-$PhCH_2O$, 4-MeO	23.5[b]
			1-HO, 4-MeO	12[d]
t	7-MeO	1,4-$(MeO)_2$	1,4,5-$(MeO)_3$	50[a]

[a] 1 equiv. of aryne precursor used. [b] 2 equiv. of aryne precursor used. [c] Mixture not separated. [d] Other products not identified.

The use of substituted phthalides and substituted benzyne precursors permits the preparation of a wide range of

substituted anthraquinones, as listed in the Table. The variety of types prepared requires some comment. To date we have not encountered problems with the formation of isomeric carbanions from the phthalides produced by competing abstraction of an aromatic proton. Abstraction of such protons is generally relatively slow, and, at the temperatures used to form the phthalide anions, abstraction of the 3-proton by lithium dialkylamides proceeds rapidly.

The nature of the aryne species used is also of interest, since the substitution pattern can dictate the direction of aryne formation, *e.g.* in *meta*-substituted halogenobenzenes. Furthermore, addition of nucleophiles to substituted arynes can show regioselectivity.[5] An example in the present instance is the reaction of 4-methoxyphthalide with the aryne produced from 2-bromoanisole (Table, i). In this case two isomeric anthraquinones could be detected in the products. The major isomer was 1,5-dimethoxyanthraquinone (39%), as expected from the known tendency of nucleophiles to add to position 1 of the aryne (8); the minor isomer was

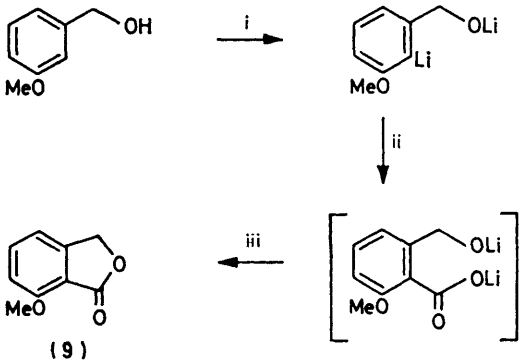


(8)

1,8-dimethoxyanthraquinone (2%), produced by the less favoured initial addition to position 2 of the aryne (8). A similar regioselectivity was observed with the addition of 6-methoxyphthalide to the aryne (8) (Table, j), from which only the 1,7-dimethoxyanthraquinone (41%) was isolated.

Arynes derived from brominated phenols also participate in this reaction; thus the aryne derived from 2-hydroxy-5-methoxybromobenzene reacted with the phthalide anion to yield 1-hydroxy-4-methoxyanthraquinone (26%) (Table, q).

A few exploratory reactions were conducted using



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SCHEME 2 Reagents: i, lithium di-isopropylamide; ii, CO_2; iii, H^+

benzyl groups to protect the phenolic functions. With these systems (Table, r and s) the desired anthraquinone products were isolated together with some debenzylated phenols; this protection method thus has only limited value. The benzyl protecting groups are readily removed, for example, with trifluoroacetic acid.

The utility of this route depends on the availability of a range of appropriately substituted phthalides. Since *ortho*-metallation of benzyl alcohols has been reported [6] we envisaged a method involving carboxylation of *ortho*-lithiated benzyl alcohols followed by acid-catalysed lactonisation of the product. For example, lithiation of *m*-methoxybenzyl alcohol followed by carboxylation, using carbon dioxide as reagent, produced, on work-up, 7-methoxyphthalide (9) (Scheme 2) in 45% yield. Stabilising groups, such as the *m*-methoxy-substituent, although beneficial, are not essential. Thus even benyzl alcohol itself reacted under these conditions to produce the phthalide, albeit in low yield (15%). Whilst these experiments were underway, Trost *et al.* reported similar findings.[7]

EXPERIMENTAL

Melting points were recorded with a Kofler hot-stage microscope or an Electrothermal heated-block apparatus and are uncorrected. U.v. spectra were measured with a Beckman DB-G spectrophotometer, i.r. spectra with a Perkin-Elmer 567 grating spectrophotometer, and ^1H n.m.r. generally in deuteriochloroform at 60, 90, or 100 MHz using tetramethylsilane as internal reference. Silica gel Merck 60 PF_{254} and PF_{366} was used for thin-layer (t.l.c.) and preparative-layer chromatography (p.l.c.) and the separated fractions are reported in order of increasing polarity. Solvents were dried and distilled under nitrogen or argon prior to use.

General Procedure for Anthraquinone Synthesis.—A solution of the phthalide in freshly distilled, dry tetrahydrofuran (THF) (5 ml per mmol) was added dropwise to a solution of lithium di-isopropylamide (2.2 equiv.) at −70 to −60 °C, the latter being prepared by the addition of 1.5M n-butyl-lithium in n-hexane to an equivalent amount of dry, redistilled di-isopropylamine in THF (5 ml per mmol) at −78 °C. The solution of the carbanion was stirred whilst being allowed to warm to *ca.* −35 °C before addition, dropwise, of a solution of the bromoarene in THF (5 ml per mmole). The mixture was allowed to warm slowly to 20 °C, stirred for a further 2 h, and then left in contact with air for 20 h before being poured over a mixture of ice and concentrated hydrochloric acid. The acidic mixture was filtered and the collected product recrystallised. In some instances, especially with systems giving mixtures of anthraquinones, the work-up procedure was by chloroform extraction of the acid-quenched mixture, followed by washing with water, drying ($MgSO_4$), and evaporation, the product anthraquinones being separated by silica gel column chromatography or p.l.c.

Anthraquinone.—(i) Phthalide (0.355 g, 2.5 mmol) in THF (10 ml) was treated in the normal way with lithium di-isopropylamide (5.5 mmol) and bromobenzene (0.40 g, 2.5 mmol). Work-up, by filtration and recrystallisation from benzene–diethyl ether, gave anthraquinone (7a) (0.10 g, 20%), m.p. 269—271 °C (subl.), identical with an authentic sample in its mixed m.p. and chromatographic behaviour.

(ii) Reaction as above, using phthalide (0.136 g, 1 mmol) with lithium di-isopropylamide (3.3 mol) and bromobenzene (0.33 g, 2.1 mmol), gave a higher yield of anthraquinone (0.155 g, 74.5%).

1-*Methoxy*-9,10-*anthraquinone*.—4-Methoxyphthalide [8] (0.164 g, 1 mmol) was treated with lithium di-isopropylamide (3.3 mmol) and bromobenzene (0.33 g, 2.1 mmol). Isolation by p.l.c. gave the anthraquinone (7b) (0.122 g, 51%), m.p. 175—176 °C (lit.,[9] 169.5 °C), $\nu_{max.}$ 1 673 cm^{-1}, δ 4.05 (3 H, s) and 7.32—8.33 (7 H, m).

2-*Methoxy*-9,10-*anthraquinone*.—(i) *From* 4-*bromoanisole*. Phthalide (0.134 g, 1 mmol) was treated with lithium di-isopropylamide (2.2 mmol) and 4-bromoanisole (0.187 g, 1 mmol). Isolation by p.l.c. ($CHCl_3$) afforded 2-methoxyanthraquinone (7; R = 2-MeO) (0.105 g, 45%) as yellow needles, m.p. 194—195 °C (lit.,[10] 195—196 °C), $\nu_{max.}$ 1 673 cm^{-1}, δ 4.04 (3 H, s) and 7.27—8.41 7 H, m).

(ii) *From* 6-*methoxyphthalide*.[11] Phthalide (0.164 g, 1 mmol) was treated with lithium di-isopropylamide (3.3 mmol) and bromobenzene (0.31 g, 2 mmol). Isolation by p.l.c. ($CHCl_3$) gave 2-methoxyanthraquinone (7; R = 2-MeO) (0.073 g, 31%), m.p. 194—195 °C.

2-*Methyl*-9,10-*anthraquinone*.—Phthalide (0.33 g, 2.5 mmol), lithium di-isopropylamide (5.5 mmol), and 4-bromotoluene (0.43 g, 2.5 mmol) gave, after direct recrystallisation from ethanol with charcoaling, the anthraquinone (7e) as pale yellow needles (0.121 g), m.p. 174—175 °C (lit.,[12] 175—176 °C), $\nu_{max.}$ 1 670 cm^{-1}, δ 2.54 (3 H, s) and 7.57—8.37 (7 H, m). Extraction of the aqueous phase with chloroform, and combination of the extract with the mother liquors from the recrystallisation gave, after p.l.c. ($CHCl_3$), more of the anthraquinone (0.10 g) (total yield 40%).

2,3-*Dimethoxy*-9,10-*anthraquinone*.—5,6-Dimethoxyphthalide [13] (0.465 g, 2.4 mmol), lithium di-isopropylamide (5.5 mmol), and bromobenzene (0.40 g, 2.5 mmol) afforded, after p.l.c. (CH_2Cl_2), the anthraquinone (7f) (0.18 g, 32%), m.p. 248—250 °C (lit.,[14] 237 °C), $\nu_{max.}$ 1 660 cm^{-1}, δ 4.13 (6 H, s), 7.80 (2 H, s), and 7.81—8.43 (4 H, m).

1,2-*Dimethoxy*-9,10-*anthraquinone*.—6,7-Dimethoxyphthalide [13] (0.194 g, 1 mmol) was treated with lithium di-isopropylamide (2.2 mmol) and bromobenzene (0.16 g, 1 mmol). Separation of the products by p.l.c. (CH_2Cl_2) gave, as a yellow-orange product, the anthraquinone (7g) (0.048 g, 18%), m.p. 220—221 °C (lit.,[15] 215 °C), $\nu_{max.}$ 1 668 and 1 654 cm^{-1}, δ 4.03 (6 H, s) and 7.28—838 (6 H, m).

1,4-*Dimethoxy*-9,10-*anthraquinone*.—Phthalide (0.134 g, 1 mmol) was treated with lithium di-isopropylamide (2.2 mmol) and 2-bromo-1,4-dimethoxybenzene (0.217 g, 1 mmol). Isolation of the major product by p.l.c. ($CHCl_3$) gave the orange anthraquinone (7 h) (0.124 g, 46%), m.p. 175—177 °C (subl.) (lit.,[16] 170—171 °C, subl.), $\nu_{max.}$ 1 670 cm^{-1}, δ 4.04 (6 H, s), 7.40 (2 H, s), and 7.7—8.28 (4 H, m).

1,5-*Dimethoxy*-9,10-*anthraquinone and* 1,8-*Dimethoxy*-9,10-*anthraquinone*.—4-Methoxyphthalide (0.33 g, 2 mmol), lithium di-isopropylamide (6 mmol), and 2-bromoanisole (0.75 g, 4 mmol) produced two major products. P.l.c. ($CHCl_3$–benzene, 5 : 1; 3 elutions) gave 1,8-dimethoxy-9,10-anthraquinone [7; R = 1,8-$(MeO)_2$] (0.012 g, 2%), m.p. (from MeOH) 223—224 °C (lit.,[17] 219 °C), $\nu_{max.}$ (KBr) 1 660 cm^{-1}, δ 4.05 (6 H, s) and 7.20—7.93 (6 H, m). The more polar material was 1,5-dimethoxy-9,10-anthraquinone [7; R = 1,5-$(MeO)_2$] (0.212 g, 39.5%), m.p. (from EtOH) 244—245 °C (lit.,[18] 238—240 °C), $\nu_{max.}$ (KBr) 1 660 cm^{-1}, δ 4.04 (6 H, s) and 7.20—7.93 (6 H, m).

1,7-*Dimethoxy*-9,10-*anthraquinone*. —6-Methoxyphthalide (0.33 g, 2 mmol), lithium di-isopropylamide (6 mmol), and 2-bromoanisole (0.75 g, 4 mmol) afforded, after p.l.c. ($CHCl_3$), 1,7-dimethoxy-9,10-anthraquinone (7j) (0.22 g, 41%), m.p. (from EtOH) 194—196 °C (lit.,[19] 191 °C), $\nu_{max.}$ 1 660 cm^{-1}, δ4.07 (3 H, s), 4.17 (3 H, s), and 7.17—8.30 (6 H, m).

Reaction of 4-*Methoxyphthalide with* 4-*Bromoanisole*.—4-Methoxyphthalide (0.166 g, 1 mmol), lithium di-isopropylamide (2.2 mmol), and 4-bromoanisole (0.187 g, 1 mmol) gave, after p.l.c. ($CHCl_3$), a yellow solid (0.16 g, 60%), m.p. 151—155 °C, δ 3.95, 4.03, and 7.10—8.21. High-performance liquid chromatography (Hypersil, 12.5 × 5 mm, CH_2Cl_2, 1.0 ml per min) indicated a mixture of two principal compounds, absorbance ratio 1.0 : 0.95, which was not separated on a preparative scale. The ^{1}H n.m.r. spectrum was consistent with a mixture of 1,6- and 1,7-dimethoxy-9,10-anthraquinones.

1,4,6-*Trimethoxy*-9,10-*anthraquinone*.—6-Methoxyphthalide (0.335 g, 2 mmol), lithium di-isopropylamide (6.6 mmol), and 2-bromo-1,4-dimethoxybenzene (0.86 g, 4 mmol) afforded one major product, isolated by p.l.c. ($CHCl_3$) to give the *anthraquinone* (7l) (0.38 g, 64%) as dark yellow needles, m.p. (from MeOH) 211—213 °C, $\lambda_{max.}$ (EtOH) 4.20 (ε 4 500), 267 (20 500), and 211 nm (23 800), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, δ 4.90 (3 H, s), 4.07 (6 H, s), and 7.10—8.27 (5 H, m) (Found: C, 68.2; H, 4.7. $C_{17}H_{14}O_5$ requires C, 68.45; H, 4.7%).

1,4,6,7-*Tetramethoxy*-9,10-*anthraquinone*.—5,6-Dimethoxyphthalide (0.39 g, 2 mmol), lithium di-isopropylamide (6.6 mmol), and 2-bromo-1,4-dimethoxybenzene (0.87 g, 4 mmol) gave, after purification by p.l.c. (CH_2Cl_2, 2 elutions) the *anthraquinone* (7 m) m.p. (from MeOH) 245—246 °C, $\lambda_{max.}$ (EtOH) 418 (ε 7 900), 277 (32 000), and 218 nm (36 300), $\nu_{max.}$ (KBr) 1 650, 1 580, and 1 215 cm^{-1}, δ 4.00 (6 H, s), 4.03 (6 H, s), 7.25 (2 H, s), and 7.53 (2 H, s) (Found: C, 65.7; H, 5.0. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%).

Benz[a]*anthracene*-7,12-*quinone*.—Phthalide (0.335 g, 2.5 mmol), lithium di-isopropylamide (5.5 mmol), and 1-bromonaphthalene (0.52 g, 2.5 mmol) were treated in the normal manner to give, after p.l.c. (CH_2Cl_2), benz[*a*]anthracene-7,12-quinone (7n) (0.4 g, 62%), m.p. (from acetic acid) 166—167 °C (lit.,[20] 168 °C).

9,10-*Dimethoxybenz*[a]*anthracene*-7,12-*quinone*.—5,6-Dimethoxyphthalide (0.39 g, 2 mmol), lithium di-isopropylamide (4 mmol), and 1-bromonaphthalene gave, after p.l.c. ($CHCl_3$), 9,10-*dimethoxybenz*[a]*anthracene*-7,12-*quinone* (7o) (0.20 g, 32%) as fine yellow needles, m.p. (from acetic acid) 236—237 °C (subl.), $\lambda_{max.}$ (EtOH) 368 (ε 1 500) 331 (2 700), 292 (23 700), 228 (11 500), and 209 nm (13 000); $\nu_{max.}$ (KBr) 1 650, 1 580, and 1 325 cm^{-1}; δ 4.13 (6 H, s) and 7.30—8.33 (8 H, m) (Found: C, 75.15; H, 4.6. $C_{20}H_{14}O_4$ requires C, 75.5; H, 4.4%).

1-*Methoxy*-4-*methyl*-9,10-*anthraquinone*.—Phthalide (0.27 g, 2 mmol), lithium di-isopropylamide (6 mmol), and 3-bromo-4-methoxytoluene (0.80 g, 4 mmol), afforded, after p.l.c. (CH_2Cl_2–benzene, 5 : 1), the anthraquinone (7p) (0.083 g, 16%), m.p. 131—133 °C (subl.) (lit.,[21] 128 °C), δ 2.67 (3 H, s), 4.00 (3 H, s), and 7.10—8.27 (6 H, m).

1-*Hydroxy*-4-*methoxy*-9,10-*anthraquinone*.—Phthalide (0.19 g, 1.4 mmol), lithium di-isopropylamide (3.3 mmol), and 2-bromo-4-methoxyphenol (0.20 g, 1.0 mmol) gave, after p.l.c. ($CHCl_3$, 2 elutions), the anthraquinone (7q) (0.09 g, 26%), m.p. 167—168 °C (subl.) (lit.,[22] 167—168 °C), $\nu_{max.}$ 1 655 and 1 633 cm^{-1}, δ 4.06 (3 H, s), 7.31—8.40 (6 H, m), and 13.08 (1 H, s, exchangeable with D_2O).

Reactions of 4-*Benzyloxyphthalide with Bromobenzene*.—4-Hydroxyphthalide (3.0 g, 20 mmol) in *NN*-dimethylformamide (DMF) (30 ml) was treated with potassium hydroxide (2.24 g, 40 mmol) in DMF (30 ml) at room tem-

perature before addition of a solution of benzyl bromide (10.3 g, 60 mmol) in DMF (20 ml). The mixture was heated at reflux for 3 h, poured over ice (100 g), acidified with concentrated hydrochloric acid, and extracted with chloroform (3 × 50 ml). The organic extracts were washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated to give a solid, which was recrystallised from aqueous ethanol to give 4-*benzyloxyphthalide* (2.6 g, 54%), m.p. 115—116° C, $\nu_{max.}$ (KBr) 1 770 and 1 280 cm^{-1}, δ 5.20 (2 H, s), 5.27 (2 H, s), and 7.03—7.53 (8 H, m) (Found: C, 75.1; H, 4.9. $C_{15}H_{12}O_3$ requires C, 75.1; H, 5.0%). Reaction of 4-benzyloxyphthalide (0.36 g, 1.5 mmol), lithium di-isopropylamide (4.5 mmol), and bromobenzene (0.47 g, 3 mmol) under the usual conditions gave, following work-up and p.l.c. (CH_2Cl_2–benzene, 5 : 1), 1-*benzyloxy*-9,10-*anthraquinone* (7; R = 1-$PhCH_2O$) (0.11 g, 24%), m.p. (from MeOH) 168—170 °C, $\lambda_{max.}$ (EtOH) 398 (ε 4 700), 249 (36 800), and 207 nm (31 500), $\nu_{max.}$ (KBr) 1 665 and 1 265 cm^{-1}, δ 5.37 (2 H, s) and 7.23—8.37 (12 H, m) (Found: C, 80.2; H, 4.5. $C_{21}H_{24}O_3$ requires C, 80.2; H, 4.5%).

Isolated as a slightly more polar material was 1-hydroxy-9,10-anthraquinone (7; R = 1-HO) (0.013 g, 4%), m.p. 192—194 °C (lit.,[23] 193—195 °C), $\nu_{max.}$ 1 680 and 1 650 cm^{-1}.

Treatment of 1-benzyloxy-9,10-anthraquinone (20 mg) with trifluoroacetic acid (1 ml) at room temperature for 1 h before dilution with water and extraction with chloroform afforded, after washing, drying, evaporation, and sublimation, 1-hydroxy-9,10-anthraquinone (11 mg, 77%) identical with the foregoing sample in its physical properties.

Preparation of 1-*Benzyloxy*-3-*bromo*-4-*methoxybenzene*.—A solution of bromine (3.0 g, 20 mmol) in chloroform (70 ml) was added dropwise to a stirred solution of *p*-benzyloxyphenol (4.0 g) in chloroform at 20 °C, and the solution stirred for a further 1 h. The solution was washed with aqueous sodium hydrogensulphite (0.1M; 3 × 50 ml), 1M-sodium hydroxide (3 × 50 ml), and water (3 × 50 ml) before drying ($MgSO_4$), filtering, and evaporation to give a solid. Recrystallisation from light petroleum gave 2-*bromo*-4-*benzyloxyphenol* (4.6 g, 83%), m.p. 72—73 °C, $\nu_{max.}$ (KBr) 3 500, 1 480, 1 200, and 1 020 cm^{-1}, δ 5.20 (1 H, s, exchangeable with D_2O), 4.97 (2 H, s), and 6.83—7.37 (8 H, m) (Found: C, 56.05; H, 4.0. $C_{13}H_{11}BrO_2$ requires C, 55.9; H, 4.0%).

2-Bromo-4-benzyloxyphenol (5.58 g, 20 mmol) in water (100 ml) was treated with a solution of potassium hydroxide (2.24 g, 40 mmol) in water (10 ml) and dimethyl sulphate (5.04 g, 40 mmol) and the mixture then heated to reflux for 2 h. The cooled solution was extracted with chloroform (3 × 50 ml), and the extract washed with water, dried ($MgSO_4$), and evaporated to give a solid residue which was recrystallised from aqueous ethanol to afford 1-*benzyloxy*-3-*bromo*-4-*methoxybenzene* (3.57 g, 61%), m.p. 85—86 °C, $\nu_{max.}$ (KBr) 1 500, 1 230, and 1 020 cm^{-1}, δ 3.83 (3 H, s), 5.00 (2 H, s), 6.83 (2 H, m), 7.22 (1 H, m), and 7.37br (5 H, s) (Found: C, 57.4; H, 4.45. $C_{14}H_{13}BrO_2$ requires C, 57.4; H, 4.5%).

Reaction of Phthalide with 1-*Benzyloxy*-3-*bromo*-4-*methoxybenzene*.—Phthalide (0.13 g, 1 mmol) was treated with lithium di-isopropylamide (3 mmol) and 1-benzyloxy-3-bromo-4-methoxybenzene (0.59 g, 2 mmol). Work-up, using ammonium chloride as quenching agent, afforded, after p.l.c. (CH_2Cl_2, 3 elutions), three products. The first, unidentified, was obtained as orange needles (0.044 g), m.p. 210—212 °C. The second was identified as 1-*benzyloxy*-4-*methoxy*-9,10-*anthraquinone* (7; R = 1-$PhCH_2O$, 4-MeO) (0.081 g, 23.5%), m.p. (EtOH) 156—158 °C, $\lambda_{max.}$ (EtOH) 416 (ε 3 500), 248 (17 200), and 207 nm (20 500), $\nu_{max.}$ (KBr) 1 665 and 1 255 cm^{-1}, δ 3.93 (3 H, s), 5.23 (2 H, s), and 7.27—8.27 (11 H, m) (Found: C, 76.5; H, 4.7. $C_{22}H_{16}O_4$ requires C, 76.7; H, 4.7%). The third product was 1-hydroxy-4-methoxy-9,10-anthraquinone (7; R = 1-HO, 4-MeO) (0.03 g, 12%), m.p. 166—168 °C (subl.) (lit.,[22] 167—168 °C), $\nu_{max.}$ (KBr) 1 655, 1 635, 1 355, and 1 245 cm^{-1}, δ 4.06 (3 H, s), 7.20—8.40 (6 H, m), and 13.0 (1 H, s, exchangeable with D_2O).

The benzyloxy-derivative could be debenzylated by treatment (20 mg) with concentrated hydrochloric acid (5 ml) in THF (10 ml) at room temperature for 15 h. Work-up, by chloroform extraction, gave, after sublimation, 1-hydroxy-4-methoxy-9,10-anthraquinone (0.015 g, 98%), m.p. 166—168 °C (subl.).

1,4,5-*Trimethoxy*-9,10-*anthraquinone*.—7-Methoxyphthalide (0.33 g, 2 mmol) was treated with lithium di-isopropylamide (4.4 mmol) and 2-bromo-1,4-dimethoxybenzene to afford, after column chromatography (acetone–$CHCl_3$, 1 : 9) the anthraquinone (7t) (0.30 g, 50%), m.p. (from EtOAc) 204—205 °C (lit.,[24] 209 °C), $\nu_{max.}$ 1 670 cm^{-1}, δ 3.95 (6 H, s), 4.00 (3 H, s), and 7.2—7.8 (5 H, m), *m/e* 298 (M^+, 100%), 283 (62), 281 (27), 209 (12), and 126 (18).

Preparation of 7-*Methoxyphthalide*.—To a solution of 3-methoxybenzyl alcohol (6.9 g, 50 mmol) in dry ether (100 ml) heated to reflux was added, dropwise over 30 min, n-butyl-lithium (hexane solution 1.5M; 67 ml), and heating continued for a further 24 h before cooling to −78 °C and adding dry ice (10 g). The mixture was allowed to warm to ambient temperature before acidification with dilute hydrochloric acid and the mixture stirred for a further 6 h, the ether removed, under reduced pressure, and the precipitate collected. Crystallisation from hexane–ethyl acetate afforded 7-methoxyphthalide (3.7 g, 45%), m.p. 107—108 °C (lit.,[25] 107—109 °C), $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1}, δ 4.0 (3 H, s), 5.21 (2 H, s), and 7.0—7.8 (3 H, m).

Preparation of Phthalide.—To benzyl alcohol (3.2 g, 30 mmol) in refluxing ether (100 ml) was added, dropwise, n-butyl-lithium (hexane solution, 1.6M; 38.2 ml) during 30 min and refluxing then continued for a further 24 h. After cooling to −78 °C, dry ice (5 g) was added and the mixture allowed to warm to ambient temperature before acidification with dilute hydrochloric acid and work-up in the manner described above, to afford phthalide (0.6 g, 16%), m.p. and mixed m.p. 74—75 °C.

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