

# Products of the condensation reaction of 2-(4-fluorobenzoyl)benzoic acid with *m*-cresol

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## Abstract

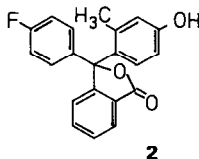
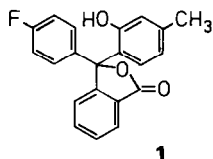
The preparation and structural elucidation of the new isomeric 3-(4-fluorophenyl)-3-(hydroxymethyl)phthalides made from *m*-cresol and 2-(4-fluorobenzoyl)benzoic acid are described.

## Introduction

In our investigations on 3,3-diarylphthalides [1–3], which have been obtained as intermediates for the syntheses of derivatives of 9-acetoxy-10-phenylanthracene [4, 5], we have prepared two new 3,3-diarylphthalides from *m*-cresol. These phthalides may have physiological activity and related anthracene compounds can be used as dye lasers [6] for generating electromagnetic waves over the range 360–410 nm.

## Results and discussion

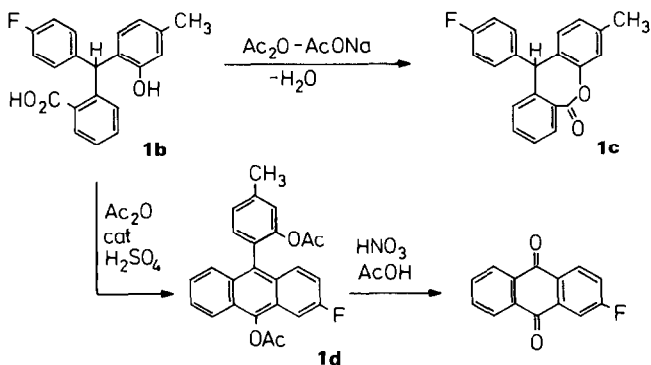
Condensing 2-(4-fluorobenzoyl)benzoic acid with *m*-cresol (method described in ref. 6) gave two new compounds: 3-(4-fluorophenyl)-3-(2-hydroxy-4-methylphenyl)phthalide (**1**) and 3-(4-fluorophenyl)-3-(4-hydroxy-2-methylphenyl)phthalide (**2**) in the ratio 32:48 (cf. analogues from the condensation of 2-benzoylbenzoic acid with *m*-cresol: ratio, 36:51 [1]).



Phthalides **1** and **2** on reaction with  $\text{Ac}_2\text{O}/\text{AcONa}$  gave the acetates **1a** and **2a**, and with Zn dust in 80% AcOH the corresponding derivatives of 2-

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benzhydrylbenzoic acid (**1b** and **2b**). Acid **1b** with  $\text{Ac}_2\text{O}/\text{AcONa}$  yielded its  $\epsilon$ -lactone **1c**, but in the presence of a catalytic amount of conc.  $\text{H}_2\text{SO}_4$ , the intracyclization of **1b** into 9-acetoxy-2-fluoro-10-(2'-acetoxy-4'-methylphenyl)anthracene (**1d**) occurred.



Scheme 1.

Under the same conditions as for **1b**, compound **2b** formed its acetate **2c**: the anthracene derivative was not obtained in crystalline form.

The structures of compounds **1**, **1a–1d**, **2** and **2a–2c** have been confirmed using chemical and spectral IR methods. Boiling compound **1d** with  $\text{HNO}_3$  in  $\text{AcOH}$  (cf. ref. 7) caused degradation to 2-fluoroanthraquinone, confirming that the  $\text{OAc}$  and  $\text{Me}$  substituents are not contained in the anthracene skeleton. The structures of **1c** and **1d** were additionally elucidated via their  $^1\text{H}$  NMR spectra; for **1c**:  $\delta$  2.30 (9-OAc); 5.02 ( $\geq\text{C}-\text{H}$ ) ppm; for **1d**:  $\delta$  2.64 (9-OAc); 1.34 (2'-OAc); 2.25 ( $\text{CH}_3$ ) ppm. For the model compounds [8]: 9-acetoxy-10-phenylanthracene:  $\delta$  2.65 ppm (9-OAc); and for 9-acetoxy-10-(2'-acetoxyphenyl)anthracene:  $\delta$  2.51 (9-OAc); 1.35 (2'-OAc) ppm. Comparison of the  $^1\text{H}$  NMR spectrum of **1d** with that of the model compound [8] elucidated the exact position of substituents in the phenyl ring. The  $^1\text{H}$  NMR shift for the  $\text{OCOCH}_3$  absorption in the 2'-position for compound **1d** confirmed the structure and hence also that of phthalide **1**.

## Experimental

All melting points have been corrected. Infrared (IR) spectra were recorded on a Specord Unicam SP 200 instrument. Values of  $\nu_{\text{max}}$  are reported only for characteristic groups.  $^1\text{H}$  NMR spectra of **1c** and **1d** were measured on a 80 MHz Tesla BS 787 C spectrometer in deuteriochloroform solution: tetramethylsilane (TMS),  $\delta$  0.00 ppm was applied as the internal standard.

The purities of compounds **1**, **1a–1d**, **2** and **2a–2c** were checked by TLC methods [kieselgel, benzene/ethyl acetate/acetic acid (32:8:1 v/v): iodine or conc.  $\text{H}_2\text{SO}_4$  were used for detection].

Compounds **1**, **1a–1d**, **2** and **2a–2c** are new. All physical data are presented in Table 1.

TABLE 1

Physical and spectral data for compounds 1-1d and 2-2c

No.	Compound	Formula <sup>a</sup> (molecular mass)	M.p. [°C]	Yield [%]	IR spectra [cm <sup>-1</sup> ]
<b>1</b>	3-(4-Fluorophenyl)-3-(2-hydroxy-4-methylphenyl)phthalide	C <sub>21</sub> H <sub>15</sub> O <sub>3</sub> F (334)	147-149 (AcOH)	32	1750 (s) (C=O, $\gamma$ -lactone); 1425 (m) (C-H, CH <sub>3</sub> ); 1245 (s) (C-O-C, $\gamma$ -lactone); 1165 (s) (C-O, phenol); 1130 (m) (C-F).
<b>1a</b>	Acetate of <b>1</b>	C <sub>23</sub> H <sub>17</sub> O <sub>4</sub> F (376)	142-143.5 (aq. EtOH)	83	1765 (s) (C=O of $\gamma$ -lactone and OCOCH <sub>3</sub> ); 1470 (m) (C-H, CH <sub>3</sub> ); 1370 (m) (CH <sub>3</sub> , acetate); 1200 (s) (C-O-C, acetate); 1110 (m) (C-F).
<b>1b</b>	2-(4-Fluoro-2'-hydroxy-4'-methylbenzhydryl)-benzoic acid	C <sub>21</sub> H <sub>17</sub> O <sub>3</sub> F (336)	174-177 (aq. EtOH)	89	2660 (mb) (OH, dimer COOH); 1700 (s) (C=O, COOH); 1410 (m) (C-H, CH <sub>3</sub> ); 1230 (s) (C-O, phenol); 1100 (m) (C-F).
<b>1c</b>	$\epsilon$ -Lactone of <b>1b</b>	C <sub>21</sub> H <sub>15</sub> O <sub>2</sub> F (318)	128-130 (aq. AcOH)	91	1710 (s) (C=O, $\epsilon$ -lactone); 1420 (w) (C-H, CH <sub>3</sub> ); 1230 (s) (C-O-C, $\epsilon$ -lactone); 1130 (s) (C-F).
<b>1d</b>	9-Acetoxy-2-fluoro-10-(2'-acetoxy-4'-methylphenyl)anthracene	C <sub>26</sub> H <sub>19</sub> O <sub>4</sub> F (402)	281-284 (AcOH)	87	1765 (s) (C=O of OCOCH <sub>3</sub> ); 1370 (s) (CH <sub>3</sub> , acetate); 1200 (s) (C-O-C, acetate); 1140 (m) (C-F).

(continued)

TABLE 1 (continued)

No.	Compound	Formula <sup>a</sup> (molecular mass)	M.p. [°C]	Yield [%]	IR spectra [cm <sup>-1</sup> ]
<b>2</b>	3-(4-Fluorophenyl)-3-(4-hydroxy-2-methylphenyl)phthalide	C <sub>21</sub> H <sub>18</sub> O <sub>3</sub> F (334)	109–111.5 (CCl <sub>4</sub> )	48	1730 (s) (C=O, $\gamma$ -lactone); 1465 (m) (C–H, CH <sub>3</sub> ); 1235 (m) (C–O–C, $\gamma$ -lactone); 1160 (m) (C–O, phenol); 1125 (m) (C–F).
<b>2a</b>	Acetate of <b>2</b>	C <sub>23</sub> H <sub>17</sub> O <sub>4</sub> F (376)	149–152 (aq. EtOH)	90	1770 (s) (C=O of $\gamma$ -lactone and OCOCH <sub>3</sub> ); 1465 (m) (C–H, CH <sub>3</sub> ); 1380 (m) (CH <sub>3</sub> , acetate); 1200 (s) (C–O–C, acetate); 1110 (m) (C–F).
<b>2b</b>	2-(4-Fluoro-4'-hydroxy-2'-methylbenzhydryl)-benzoic acid	C <sub>21</sub> H <sub>17</sub> O <sub>3</sub> F (336)	140.5–141.5 (aq. EtOH)	89	2530 (wb) (OH, dimer COOH); 1680 (s) (C=O, COOH); 1460 (m) (C–H, CH <sub>3</sub> ); 1250 (s) (C–O, phenol); 1100 (m) (C–F).
<b>2c</b>	Acetate of <b>2b</b>	C <sub>23</sub> H <sub>19</sub> O <sub>4</sub> F (378)	199–201 (EtOH)	85	2660 (mb) (OH, dimer COOH); 1760 (s) (C=O, OCOCH <sub>3</sub> ); 1690 (s) (C=O, COOH); 1420 (m) (C–H, CH <sub>3</sub> ); 1370 (m) (CH <sub>3</sub> , acetate); 1210 (s) (C–O–C, acetate); 1100 (m) (C–F).

<sup>a</sup>Satisfactory microanalyses: C  $\pm$  0.2; H  $\pm$  0.2.

### 3-(4-Fluorophenyl)-3-(hydroxymethylphenyl)phthalides (**1** and **2**)

Anhydrous  $\text{ZnCl}_2$  (22 g) was added to a mixture of 2-(4-fluorobenzoyl)benzoic acid (15.0 g, 0.06 mol; synthesized according to ref. 9) and *m*-cresol (10.5 g, 0.06 mol). The mixture was heated at 115–120 °C on an oil bath for 8 h. The brown melt was dissolved in hot acetic acid and poured into water. The yellowish amorphous precipitate was filtered off, washed with water and twice with 15% aq.  $\text{Na}_2\text{CO}_3$ , then again with water and dried. The yield was 18 g (88%) of isomers **1** and **2**.

The crude product (18 g) was dissolved in an aqueous solution of sodium hydroxide (144 cm<sup>3</sup> of 10% aq. NaOH) yielding a yellow solution. After some hours the white crystals of the sodium salt of 3-(4-fluorophenyl)-3-(2-hydroxy-4-methylphenyl)phthalide (**1**) was filtered off; yield 8.15 g; m.p., 241–247 °C (with decomposition). The salt of **1** was dissolved in water and aq. HCl was added. The white amorphous precipitates was filtered off and recrystallized from acetic acid to give colourless crystals of phthalide **1** (6.75 g).

The addition of water and then hydrochloric acid (1:2) to the filtrate resulting from the separation of the sodium salt of **1** afforded a white precipitate, which was filtered off, washed with water and dried: yield, 10 g. Recrystallization of the precipitate from  $\text{CCl}_4$  gave colourless, fine needles of phthalide **2**.

### Acetates **1a** and **2a** of phthalides **1** and **2**

A sample consisting of 0.005 mol of phthalide **1** [or **2**] was treated with 15 cm<sup>3</sup> of  $\text{Ac}_2\text{O}$  and c. 1.5 g of anhydrous AcONa, and heated for 3 h on an oil bath at 120 °C. The mixture was poured into water, the precipitate filtered off, washed with water and recrystallized several times from dilute ethanol; colourless crystals of **1a** [or **2a**] were obtained.

### 2-(4'-Fluorohydroxymethylbenzhydryl)benzoic acids (**1b** and **2b**)

A sample consisting of 0.01 mol of phthalides **1** and **2** was reduced with 5 g of Zn dust in 100 cm<sup>3</sup> of 80% AcOH for 7–10 h with heating under reflux until TLC showed the absence of phthalide. After filtration, the solution was poured into 800 cm<sup>3</sup> of water. The white, amorphous precipitate was filtered off, washed with water and recrystallized from dilute ethanol.

### $\epsilon$ -Lactone **1c**

To a solution of acid **1b** (0.002 mol) in 15 cm<sup>3</sup>  $\text{Ac}_2\text{O}$ , 2 g anhydrous AcONa was added. The reaction mixture was heated for 3 h at 120 °C. This mixture was then poured into 300 cm<sup>3</sup> of water. The crude precipitate yielded crystals after recrystallization from dilute acetic acid.

### Acetate **2c** of acid **2b**

Acetate **2c** was obtained from acid **2b** under the same conditions as described above for the  $\epsilon$ -lactone **1c**. Recrystallization of the crude compound from ethanol gave fine colourless crystals of **2c**.

*9-Acetoxy-2-fluoro-10-(2'-acetoxy-4'-methylphenyl)anthracene (1d)*

A mixture consisting of 0.02 mol of acid **1b**, 50 cm<sup>3</sup> of Ac<sub>2</sub>O and 1 drop of conc. H<sub>2</sub>SO<sub>4</sub> was heated on an oil bath at 120 °C for 1–3 h until TLC showed the absence of acid **1b**. The brown solution with blue–violet fluorescence was poured into 500 cm<sup>3</sup> of water. The crude product was recrystallized several times from acetic acid when yellow crystals were obtained.

Heating compound **1d** with conc. HNO<sub>3</sub> in AcOH gave 2-fluoroanthraquinone; m.p., 205–207 °C (lit. [9], 203–204 °C).

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