

A re-examination of the condensation of 2-benzoylbenzoic acid with *m*-fluorophenol

J. Gronowska, P. Miecznik and K. Aleksandrak

Department of Organic Chemistry, Institute of Chemistry, N Copernicus University, 87 100 Toruń (Poland)

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Abstract

The condensation of 2-benzoylbenzoic acid with *m*-fluorophenol gives the new 3-phenyl-3-(4-fluoro-2-hydroxyphenyl)phthalide (**1**) and the known 3-phenyl-3-(2-fluoro-4-hydroxyphenyl)phthalide (**2**) in the ratio of 16:51.

Introduction

During the course of investigations into the synthesis of 9-acetoxyanthracene derivatives [1] from precursors such as 3-phenyl-3-arylphthalides [2], the preparation of amorphous material believed to be 3-phenyl-3-(2-fluoro-4-hydroxyphenyl)phthalide (**2**) was reported [3]. This reaction has now been re-investigated, and found to be more complicated.

Experimental

All melting points are corrected. Infrared (IR) spectra were recorded on a Specord Unicam SP 200 instrument. Values of ν_{\max} are reported only for characteristic groups. ^1H NMR spectra were recorded on a 80 MHz Tesla BS 787 C spectrometer in deuterochloroform solutions; tetramethylsilane (TMS), $\delta=0.00$ ppm was applied as the internal standard.

The purity of compounds **1**, **1a–1d**, **2** and **2a** was checked by TLC [Kieselgel, benzene/ethyl acetate/acetic acid (32:8:1 v/v); iodine or conc. H_2SO_4 were used for detection]. Compounds **1–1d** are new; all physical data are given in Table 1.

3-Phenyl-3-(fluorohydroxyphenyl)phthalides (1) and (2)

To a mixture of 2-benzoylbenzoic acid (11.3 g, 0.05 mol) and *m*-fluorophenol (5.5 g, 0.05 mol), was added 8 g of anhydrous ZnCl_2 . This mixture was heated on an oil bath at 115–120 °C for 8 h. The melt was dissolved in hot acetic acid and poured into water. The amorphous precipitate

TABLE I
Physical and spectral data for compounds 1-1d, 2 and 2a

No. Compound	Formula ^a (molecular mass)	M.P. (°C) from EtOH	IR spectra (cm ⁻¹)	¹ H NMR spectra (δ ppm)
1 3-Phenyl-3-(4'-fluoro-2'-hydroxyphenyl)phthalide	C ₂₀ H ₁₃ O ₃ F (320.3)	217.0-218.3	1735vs (C=O, γ -lactone); 1430s (C-O-C, γ -lactone); 1280s (O-H, phenol); 1130s (C-F)	2.85 (s, 1H; 2'-OH); 6.5-8.1 (m, 12H; aromat.)
2 3-Phenyl-3-(2'-fluoro-4'-hydroxyphenyl)phthalide	C ₂₀ H ₁₃ O ₃ F (320.3)	187.5-189.5 (CHCl ₃ -CCl ₄)	1730vs (C=O, γ -lactone); 1445m (C-O-C, γ -lactone); 1120s (C-F)	2.65 (s, 1H; 4'-OH)
1a Acetate of phthalide 1	C ₂₂ H ₁₅ O ₄ F (362.4)	131.0-131.5	1770vs (C=O, γ -lactone); 1370m (CH ₃ , acetate); 1200s (C-O-C, acetate); 1105s (C-F)	1.71 (s, 3H; 2'-OAc); 6.93-8.0 (m, 12H; aromat.)
2a Acetate of phthalide 2	C ₂₂ H ₁₅ O ₄ F (362.4)	117.0-118.0; ref. 3, 132.5-134.1	1765vs (C=O, γ -lactone); 1365m (CH ₃ , acetate); 1200s (C-O-C, acetate)	2.24 (s, 3H; 4'-OAc); 7.8-8.05 (m, 12H; aromat.)
1b 2-(4'-Fluoro-2'-hydroxybenzhydriyl)benzoic acid	C ₂₀ H ₁₅ O ₃ F (322.3)	amorphous	1 M	1 M
1c ϵ -Lactone of acid 1b	C ₂₀ H ₁₃ O ₂ F (304.3)	157.0-161.0	1690s (C-O, ϵ -lactone); 1275s (C-O-C, ϵ -lactone); 1140s (C-F)	5.4 (s, 1H; Ar ₃ CH); 6.69-7.9 (m, 12H; aromat.)
1d 9-Acetoxy-10-(2'-acetoxy-4'-fluorophenyl)anthracene	C ₂₄ H ₁₇ O ₄ F (388.4)	134.0-135.6	1770vs (C=O, acetate); 1365s (CH ₃ , acetate); 1200s (C-O-C, acetate); 1150s (C-F)	1.41 (s, 3H; 2'-OAc); 2.60 (s, 3H; 9-OAc); 7.0-8.13 (m, 11H; aromat.)

^aSatisfactory microanalyses: C \pm 0.3; H \pm 0.3.

was filtered off, washed three times with 15% aq. Na_2CO_3 , then with water and dried to afford a mixture (yield, 12.5 g; *c.* 77%) of isomers **1** and **2**.

This crude product was dissolved in an aqueous solution of sodium hydroxide (625 cm³ of 10% aq. NaOH) yielding a yellowish solution. After 3 weeks, the white powdered precipitate of the sodium salt of 3-phenyl-3-(4-fluoro-2-hydroxyphenyl)phthalide (**1**) was filtered off, dissolved in water and aq. HCl was added. The precipitated product was filtered off and recrystallized from ethanol to give phthalide **1** (2.7 g, 16%).

The addition of water and 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 recrystallized from acetone-ethanol to give phthalide **2** (8.2 g, 51%).

Acetates of phthalides 1 and 2; 1a and 2a

A mixture of phthalide **1** or **2** (1.5 g), Ac_2O (15 cm³) and anhydrous AcONa (3 g) was heated for 3 h at 120 °C. The solution was then poured into water. The resulting precipitate was filtered off, washed with water and dried. After recrystallization from aq. EtOH colourless crystals of acetate **1a** or **2a** were obtained. Yield, 0.85 g (75%).

2-(4-Fluoro-2-hydroxybenzhydryl)benzoic acid (1b)

Phthalide **1** (3 g), 80 cm³ of 80% aq. AcOH, and 5 g of Zn dust were heated under reflux for 8 h. After filtration, the filtrate was poured into 700 cm³ of water. The resulting white precipitate was filtered off, washed several times with water and dried in air. Yield of crude produced **1b**, 0.71 g (70%).

ε-Lactone (1c)

To a solution of acid **1b** (1 g) in Ac_2O (15 cm³), anhydrous AcONa (2 g) was added. The reaction mixture was heated for 3 h at 120 °C. This mixture was then poured into water giving a precipitate. Recrystallization of this product from EtOH afforded colourless crystals of **1c**. Yield, 0.66 g (60%).

9-Acetoxy-10-(2'-acetoxy-4'-fluorophenyl)anthracene (1d)

A mixture 0.5 g of crude acid **1b**, 30 cm³ of Ac_2O and 2 drops of conc. H_2SO_4 was heated under reflux for 1 h. The yellow solution with blue-violet fluorescence was then poured into 300 cm³ of water. The precipitate was filtered off and recrystallized from EtOH. Yield, 0.45 g (75%). Oxidative degradation of **1d** according to a described procedure [3] afforded anthraquinone.

Results and discussion

Structure (**2**), assigned to the phthalide obtained from the condensation of 2-benzoylbenzoic acid with *m*-fluorophenol, was based on the observation

The isomers were separated by a reported procedure [6]. The crude mixture was dissolved in 10% aq. NaOH (yellow colour) and left for 3 weeks. The white microcrystalline (or colloidal) precipitate was filtered off (or centrifuged), dissolved in water and acidified with aq. HCl. The white, amorphous precipitate was crystallized from ethanol to give **1**, m.p., 217.0–218.3 °C.

The alkaline filtrate after separation of the disodium salt of **1** was diluted with water and acidified. The precipitate was crystallized from chloroform–carbon tetrachloride to give phthalide **2**, m.p., 187.5–189.5 °C.

Acetylation of phthalides **1** and **2** with Ac₂O/AcONa gave the corresponding acetates **1a** and **2a**.

The structure of compound **1** was proved by chemical [7] and spectral [8] methods (see Scheme 1).

Reduction of **1** gave amorphous 2-(4-fluoro-2-hydroxybenzhydryl)benzoic acid (**1b**). Acetylation of **1b** gave a crystalline ϵ -lactone (**1c**), the ¹H NMR spectrum of which is given in Table 1.

9-Acetoxy-10-(2'-acetoxy-4'-fluorophenyl)anthracene (**1d**) was obtained from acid **1b** by a known method [3]. The structure of **1d** was confirmed by chemical and spectral methods: (i) oxidative degradation of **1d** gave anthraquinone (the substituents are therefore in the phenyl ring not in the anthracene skeleton) and (ii) a comparison of its ¹H NMR spectrum with those of related compounds [3] and model compounds [8]. The ¹H NMR shifts for the OCOCH₃ absorptions in the 2'-position for compound **1d** and in the 4'-position for *g*-acetoxy-10-(4'-acetoxy-2'-fluoro-phenyl)anthracene [3] confirmed the structures and hence those of phthalides **1** and **2** also.

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