# Efficient Synthesis of Cytotoxic Quinones: 2-Acetyl-4*H*,9*H*-naphtho[2,3-*b*]furan-4,9-dione (**6**) and (±)-2-(1-Hydroxyethyl)-4*H*,9*H*-naphtho[2,3-*b*]furan-4,9-dione (**7**)



Cláudio C. Lopes, Rosangela S. C. Lopes, Antonio V. Pinto*, and Paulo R. R. Costa*

Núcleo de Pesquisas de Produtos Naturais Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco H, 21941 Rio de Janeiro, R. J., Brazil

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From the ethanol extract of the stem bark of *Tabebuia cassinoides* (Lam.) DC (Bignoniaceae), Kingston and Rao [1] isolated two new furonaphthoquinones **6** and **7** that showed activity in KB cell culture assay ($ED_{50}$ 1.0 and 2.0 μg/ml, respectively). These values may be significant since lapachol, which has an $ED_{50}$ value of 4.4 μg/ml in the same assay, showed sufficient *in vivo* activity to reach clinical trial at the National Cancer Institute of the United States. The syntheses of these compounds (**6** and **7**) were realized in 36% overall yield starting from furan and phthalic anhydride.

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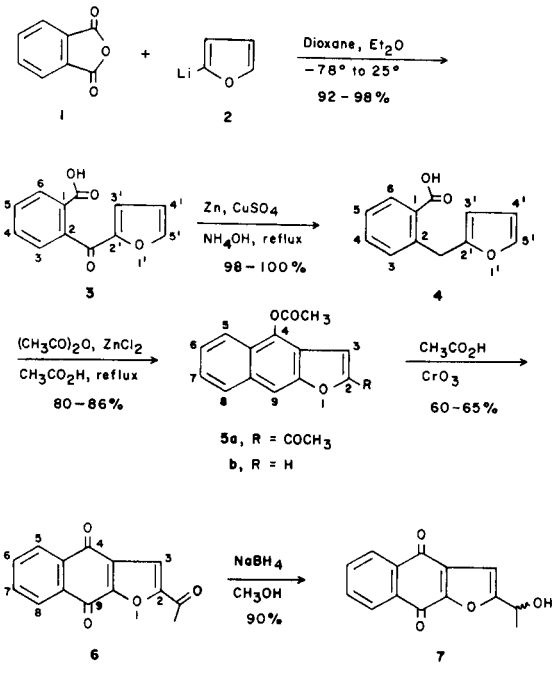
Compound **6** was first synthesized by acylation of the quinol diacetate of furo[2,3-*b*]naphthoquinone with acetyl chloride and aluminum chloride in very poor yield [2]. The position of the acetyl group in compound **6**, previously proposed on the grounds of the chemical shift of the proton in the 3-position, was firmly established by synthesis of this quinone from natural lapachol [3].

Since a mixture of **6** and **7** is available in low yield from the plant [1] and the overall yields of the published syntheses [2,3] of **6** are low, an efficient route leading to **6** and **7** is desirable. We now describe a simple and straightforward synthesis of **6** and **7**, starting from cheap raw materials, in 36% overall yield (Scheme I). To an ethereal suspension of **2** was added an equimolar solution of **1** in dioxane. The reaction was left at room temperature overnight and worked up to give **3**. The crude product was reduced by refluxing in aqueous medium with zinc, copper sulfate and ammonium hydroxide [4] affording acid **4** in 98-100% yield. Cyclization of **4** to a mixture of **5a** and **5b** (8:2 by $^1H$ nmr) was accomplished in 86% yield reaction in an acetic acid-acetic anhydride mixture containing zinc chloride [5]. Oxidation of this mixture with chromium trioxide in acetic acid furnished, after silica gel purification, pure **6** in 36% overall yield from **1**. Surprisingly, we were not able to isolate any products from the reaction of **5b**. In fact when pure **5b**, prepared by cyclization of **4** in the absence of zinc chloride, was oxidized with chromium trioxide in acetic acid a complex mixture of polar products were formed.

SCHEME I




Reduction of **6** with sodium borohydride in methanol affords, in 90% yield, (±)-**7**.

The synthesis of **6** and **7** as described here opens a new route to prepare other furanonaphthoquinone derivatives with potential biological activity.

## EXPERIMENTAL

The $^1H$ nmr spectra were recorded on an EM-360, XL-100 NMR spectrometer using tetramethylsilane as internal reference. Mass spectra were obtained on a VG M12-F spectrometer operating at a probe temperature 200° and an ionization voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer 257 gating spectrophotometer. All melting points are uncorrected and were taken on a Kofler hot-stage microscope. Evaporations were carried out under reduced pressure on a rotary evaporator. Yields of solids referred to products obtained prior to recrystallization, unless otherwise stated. Microanalyses were performed by Centro de Pesquisas da Petrobrás, R. J., Brazil.

2-(2-Furoyl)benzoic Acid (**3**).

To a solution of *n*-butyllithium (9.3 ml of 15% solution in hexane) in ether (12.0 ml) at −78° under nitrogen was added furan (2.5 ml, 0.034 mole). The resulting mixture was allowed to reach room temperature and

after 1.0 hour again cooled at −78°. To the white suspension obtained was added a solution of phthalic anhydride (1.48 g, 0.01 mole) in dioxane (12.0 ml). The reaction mixture was left at room temperature overnight, diluted with cooled water (770.0 ml), neutralized with 35% hydrochloric acid and extracted with ethyl acetate (300 ml). The organic layer was washed with saturated brine (120 ml), dried over sodium sulfate and evaporated giving **3** (2.12 g, 98%) as a brown solid. An analytical sample (white crystals) was obtained by recrystallization from chloroform, mp 152-153°; ir (potassium bromide): $\nu$ 3000 (R-COO*H*), 1686 (acid, C=O), 1667 (ketone, C=O) $cm^{-1}$; $^1$H-nmr (perdeuterioacetone): $\delta$ 8.03 (m, 1H aromatic), 7.80-7.40 (m, 3H aromatic), 7.51 (d, 1, J = 3.0 Hz, furan H-3'), 6.96 (d, 1, J = 4.0 Hz, furan H-5'), 6.60 (dd, 1, J = 4.0 Hz, J = 3.0 Hz, furan H-4'), 6.50 (br, 1H, exchangeable with dueterium oxide, $RCO_2H$) ppm; ms: m/e (%) 216 (75) ($M^{+\cdot}$) 199 (17), 149 (55), 95 (100).

*Anal.* Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.71; H, 3.78.

2-(2-Furyl)benzoic Acid (**4**).

To a solution of 0.338 g (0.00156 mole) of 2-(2-furyl)benzoic acid in 35.0 ml of concentrated ammonium hydroxide were added 0.01 g (0.00153 mole) of zinc dust and 0.14 g (0.0009 mole) of anhydrous cupric sulfate. The reaction mixture was heated at reflux for 24 hours with addition of 4.0 ml portions of concentrated ammonium hydroxide every 4.0 hours. At the end of the reflux period the reaction mixture was filtered, treated with 35% hydrochloric acid and extracted with chloroform (200.0 ml). The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated giving **4** (0.313 g, 99%) as a clear brown solid. An analytical sample (white crystals) was obtained by recrystallization from ethanol-water, mp 55-56°; ir (potassium bromide): $\nu$ 3000 (RCOO*H*), 1705 (acid C=O) $cm^{-1}$; $^1$H nmr (deuteriochloroform): $\delta$ 8.70 (br 1H, exchangeable with deuterium oxide $RCO_2H$), 8.02 (dd, 1H aromatic, J = 8.0 Hz, J = 2.0 Hz), 7.60-7.14 (m, 3H aromatic, 1, furan H-3'), 6.22 (dd, 1, J = 4.0 Hz, J = 3.0 Hz, furan H-4'), 5.95 (d, 1, J = 3.0 Hz, furan H-5'), 4.44 (s, 2H, aromatic $CH_2$ furan) ppm; ms: m/e (%) 202 (70) ($M^{+\cdot}$), 184 (61), 156 (100), 128 (83).

*Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28: H, 4.98. Found: C, 71.34; H, 5.02.

4-Acetoxynaphtho[2,3-*b*]furan (**5b**).

A solution of 0.120 g (0.00059 mole) of 2-(2-furyl)benzoic acid in acetic anhydride (0.4 ml) and acetic acid (2.0 ml) was refluxed for 1.0 hour and the solvent evaporated under reduced pressure. The residue was dissolved in chloroform (120.0 ml), washed with water (90.0 ml), dried over sodium sulfate and evaporated giving **5b** (0.121 g, 90%) as white solid, mp 137-139°; $^1$H nmr (deuteriochloroform): $\delta$ 8.20-7.40 (m, 5H aromatic), 7.75 (d, 1, J = 2.0 Hz, furan H-3), 6.85 (d, 1, J = 2.0 Hz, furan H-2), 2.50 (s, 3H, $CH_3CO$) ppm; ms: m/e (%) 226 (29) ($M^{+\cdot}$), 183 (100), 43 (46).

*Anal.* Calcd. for $C_{14}H_{19}O_3$: C, 74.33; H, 4.45. Found: C, 74.38; H, 4.49.

2-Acetyl-4-acetoxynaphtho[2,3-*b*]furan (**5a**).

A mixture of 0.24 g (0.00118 mole) of 2-(2-furyl)benzoic acid, acetic anhydride (0.8 ml), acetic acid (5.0 ml) and zinc chloride (0.1 g, 0.00073 mole) was refluxed for 3.0 hours and the solvent removed under reduced pressure. The residue was dissolved in chloroform (150.0 ml), washed with water (100.0 ml), dried over sodium sulfate and evaporated giving a mixture of **5a** and **5b** (8:2 by $^1$H nmr) as a viscous oil (0.306 g). An analytical sample of **a** was obtained by careful purification on silica gel; ir (film): $\nu$ 1729 (acetate, C=O), 1710 (ketone, C=O) $cm^{-1}$; $^1$H nmr (deuteriochloroform): $\delta$ 8.2-7.4 (m, 5H aromatic, 1, furan H-3), 2.60 (s, 3H, $CH_3CO$), 2.53 (s, 3H, $CH_3CO_2$) ppm; ms: m/e (%), 268 (14) ($M^{+\cdot}$), 226 (100), 211 (62), 43 (37).

*Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.50. Found: C, 71.72; H, 4.60.

2-Acetyl-4*H*,9*H*-naphtho[2,3-*b*]furan-4,9-dione (**6**).

To a solution of a mixture of **5a** and **5b** (0.180 g) in acetic acid (2 ml) was added chromium trioxide (0.244 g). After 0.5 hours 2-propanol (6.0 ml) was added followed by chloroform (100.0 ml). The organic layer was washed with aqueous 5% sodium bicarbonate until neutralization, saturated brine (140.0 ml), dried over sodium sulfate and evaporated giving **6** (0.090 g, 62%) as yellow solid. An analytical sample was obtained by crystallization from ethanol, mp 222-224°; uv (ethanol): $\lambda$ max (log $\epsilon$) 340 (3.5), 272 (4.26), 274.5 (4.32); ir (potassium bromide): $\nu$ 2890 ($CH_3$-R), 1695, 1623 (C=O, naphthoquinone) $cm^{-1}$; $^1$H nmr (deuteriochloroform): $\delta$ 8.22 (m, 2H aromatic), 7.80 (m, 2H aromatic), 7.59 (s, 1, furan H-3), 2.68 (s, 3H, $CH_3CO$) ppm; ms: m/e (%) 240 (57) ($M^{+\cdot}$), 225 (100), 43 (30).

*Anal.* Calcd. for $C_{14}H_8O_4$: C, 71.64; H, 3.36. Found: C, 71.70; H, 3.43.

2-(1-Hydroxyethyl)-4*H*,9*H*-naphtho[2,3-*b*]furan-4,9-dione (**7**).

To a solution of **6** (0.1 g, 0.004 mole) in methanol (5.0 ml) was added sodium borohydride (0.062 g, 0.0016 mole). After 2.0 hours the mixture reaction was acidified with 10% hydrochloric acid (2.0 ml) and extracted with chloroform (150.0 ml). The organic layer was washed with water until neutralization, dried over sodium sulfate and evaporated giving **7** (0.09 g, 90%) as yellow solid. An analytical sample was obtained by crystallization from ethanol, mp 139-140°; ir (potassium bromide) 3300 (R-OH), 1669, 1653 (naphthoquinone, C=O); $^1$H nmr (deuteriochloroform): $\delta$ 8.10 (m, 2H aromatic), 7.70 (m, 2H aromatic), 6.80 (s, 1, furan H-3), 5.03 (q, 1H, J = 6.0 Hz, RR'CHOH), 3.40 (br, 1H, OH, exchangeable with deuterium oxide), 1.65 (d, 3H, J = 6.0 Hz, $CH_3$-R) ppm; ms: m/e (%) 242 (40) ($M^{+\cdot}$), 227 (100).

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