Reactions of 3-(1-Hydroxyalkyl)phthalides with Acids: Synthesis of (*Z*)-3-Alkylidenephthalides and 3-Alkyl-8-hydroxyisocoumarins†

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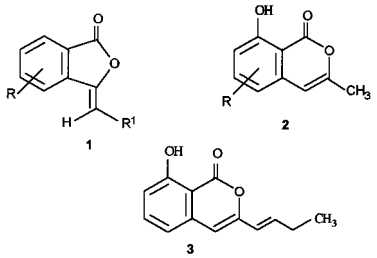
A new acid-catalyzed method for the synthesis of (*Z*)-3-butylidenephthalides **5** and a novel and general route to 3-alkyl-8-hydroxy/methoxyisocoumarins **6**−**8** from phthalides **9** is described. The hydroxyphthalides **4** and **10** were obtained by condensation of the phthalide anion with butyraldehyde and acetaldehyde. Reaction of hydroxyphthalides **4** with a mixture of orthophosphoric acid and formic acid gave the (*Z*)-3-butylidenephthalides **5**, while the hydroxyphthalides **4** and **10** on reaction with *p*-toluenesulfonic acid provided the 3-alkylisocoumarins **6**−**8**. The present approaches permit variation of the 3-substituent in isocoumarin and the pattern of functionalization on the aromatic rings of both isocoumarins and alkylidenephthalides.

A number of 3-alkylidenephthalides[1] **1** and 3-substituted 8-hydroxy isocoumarins[2] **2** have been isolated from natural sources. Most of the 3-substituted 8-hydroxyisocoumarins have a methyl substituent at the 3-position, while 8-hydroxyartemidin[3] (**3**) has a 1-butenyl group at the 3-position. The alkylidenephthalides have antispasmodic, herbicidal, and insecticidal activities.[4] They are also attractive intermediates[5] for the synthesis of a variety of heterocyclic and carbocyclic compounds including some aromatic 1,4-dicarbonyl compounds. The 3-substituted 8-hydroxyisocoumarins are important secondary metabolities obtained from various fungi[2] and have a wide range of biological activities.[2,6] They are useful intermediates[7] for the synthesis of various natural products such as canesin, α- and *β*-sorigenin methyl ethers, and 3,4-dihydro-3-alkylisocoumarins including some isoquinoline alkaloids.[8]



In view of the biological activity and synthetic utility, as intermediates, of the 3-alkylidenephthalides[9] and the 3-substituted 8-hydroxyisocoumarins,[7,10,11] several methods have been reported for their synthesis. We have reported two methods for the synthesis of the 3-alkylidenephthalides: one by dehydroiodination of the iodolactone obtained by iodolactonization[12] and the other by dehydrobromination of the 3-bromo-3-alkylphthalides, obtained by heteroatom directed lithiation[13] of *N*-meth-

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† Dedicated to Professor M. S. Wadia on the occasion of his 60th birthday.

(1) (a) Zhigui, L.; Yongtion, W.; Wenlie, W.; Wangun, C.; Xiaoyang, W. *Zhongeaoyao* (China) **1982**, *13*, 17; *Chem. Abstr.* **1982**, *97*, 17444r. (b) Wang, P.; Gao. X.; Wang, Y.; Fukuyama, Y.; Miyura, I.; Sugawara, M. *Phytochemistry* **1984**, *23*, 2033. (c) Kobayashi, M.; Fujita, M.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1984**, *32*, 3770. (d) Kaouadji, K.; Pauget, C. *J. Nat. Prod.* **1986**, *49*, 184. (e) Kobayashi, M.; Fujita, M.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1987**, *35*, 1427. (f) Kimura, M; Kimura, I; Ogawa, Y.; Naito, T.; Hosaka, K.; Mihashi, H. Jpn. Kokai Tokkyo Koho JP 04,208,278, 1992; *Chem. Abstr.* **1993**, *118*, 191531m.

(2) (a) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229. (b) Turner, W. B. *Fungal Metabolites*; Academic Press: London, 1971; Chapter 5. (c) Hill, R. A. *Progress in the Chemistry of Organic Natural Products*; Wien-Springer-Verlag: New York, 1986; Vol. 49. (d) Deangelis, J. D.; Hodges, J. D.; Nebeker, T. E. *Can. J. Bot.* **1986**, *64*, 151. (e) Ayer, W. A.; Browne, L. M.; Feng, M. C.; Orszanska, H.; Saeedi-Ghomi, H. *Can. J. Chem.* **1986**, *64*, 904. (f) Ayer, W. A.; Attah-Poku, S. K.; Browne, L. M.; Orzanska, H. *Can. J. Chem.* **1987**, *65*, 765. (g) Hegde, V. R.; Wittreich, H.; Patel, M. G.; Horan, A. C.; Hart, R. F.; Troyanvich, J. J.; Puar, M. S.; Gullo, V. P. *J. Ind. Microbiol.* **1989**, *4*, 209. (h) Gremaud, G.; Tabacchi, R. *Nat. Prod. Lett.* **1994**, *5*, 95. (i) Benz, G. *Arkiv Kemi* **1959**, *14*, 511; *Chem. Abstr.* **1960**, *54*, 10056h. (j) Lin, J. Y.; Yoshida, S.; Takahashi, N. *Agric. Biol. Chem.* **1971**, *35*, 363.

(3) (a) Greger, H.; Bohlmann, F.; Zdero, C. *Phytochemistry* **1977**, *16*, 795. (b) Greger, H. *Phytochemistry* **1979**, *18*, 1319.

(4) (a) Lacova, M.; Paulov, S.; Paulovova, J. Czech. Cs. 190,783, 1981; *Chem. Abstr.* **1982**, *97*, 67833v. (b) Lacova, M.; Brondos, M. *Chem. Zvesti* **1982**, *36*, 245; *Chem. Abstr.* **1982**, *97*, 92054z. (c) Ko, W. C.; Lin, L. C.; Lin, S. H.; Hwang, P. Y.; Hsu, C. Y.; Wang, G. Y.; Chang, C. W. *Tai-wan Yao Hsueh Tsa Chih* **1983**, *35*, 155; *Chem. Abstr.* **1984**, *101*, 48511y.

(5) (a) Dodsworth, D. J.; Caliagno, M. P.; Ehramann, U. E.; Sammes, P. G. *Tetrahedron Lett.* **1980**, *21*, 5075 and references therein. (b) Patil, P. A. Ph.D. Thesis, *Synthesis of Natural products*, University of Pune, Pune, 1987. (c) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *27*, 171. (d) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1989**, *30*, 5323. (e) Gore, V. G.; Chordia, M. D.; Narasimhan, N. S. *Tetrahedron* **1990**, *46*, 2483. (f) Chordia, M. D.; Narasimhan, N. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 371. (g) Ciattini, P. G.; Mastropietro, G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1993**, *34*, 3763.

(6) (a) Claydon, N. *J. Invertbr. Pathol.* **1979**, *33*, 364. (b) Tamoaki, O. *Kagaku to Seibutsa* **1987**, *19*, 365. (c) Hiroyuki, K.; Masahide, A.; Hiroshi, N.; Sawa, T.; Masaaki, I.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 440.

(7) (a) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1977**, *99*, 4533 and references therein. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1977**, *42*, 4155. (c) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (d) Hauser, F. M.; Pogany, S. A. *J. Heterocycl. Chem.* **1978**, *15*, 1535. (e) Mashelkar, U. C.; Usgaonkar, R. N. *Indian J. Chem.* **1979**, *18B*, 301. (f) Barber, J.; Carter, R. H.; Garson, R. J.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2577. (g) Hill, R. A.; Carter, R. H.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2570. (h) Beugelmans, R.; Ginsburg, H.; Bois-Choussy, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1149. (i) Lewis, C. N.; Staunton, J.; Sunter, D. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 747. (j) Minami, T.; Nishimoto, A.; Nakamura, Y.; Hanaoka, H. *Chem. Pharm. Bull.* **1994**, *42*, 1700. (k) Nomoto, S.; Mori, K. *Liebigs Ann.* **1997**, 721.

(8) (a) Kanevskaya, S. I.; Malinina, S. I. *J. Gen. Chem. (USSR)* **1956**, *25*, 727. (b) Jones, J. B.; Pinder, A. R. *J. Chem. Soc.* **1958**, 2612. (c) Tirodkar, R. B.; Usgaonkar, R. N. *Indian J. Chem.* **1972**, *10*, 1060; *Curr. Sci.* **1976**, *45*, 832.

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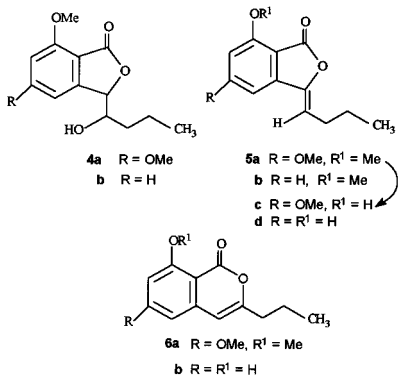
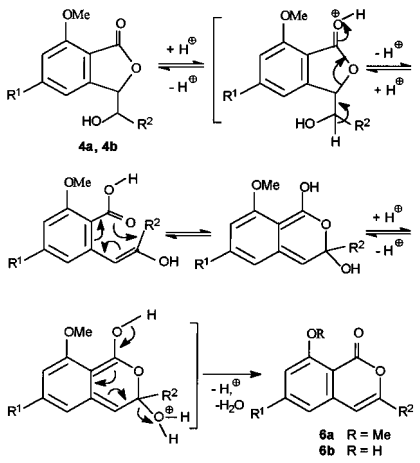
ylbenzamides. The literature methods reported for the synthesis of isocoumarins involve multistep reaction sequences and require harsh conditions. They lack flexibility and are overall inefficient.

In search of an alternate acid-catalyzed method for the 3-alkylidenephthalides, specifically (*Z*)-3-butylidene-5,7-dimethoxyphthalide (**5a**) and (*Z*)-3-butylidene-7-methoxyphthalide (**5b**), which have been used as antiarteriosclerotic agents and prostaglandin $F_{2\alpha}$ inhibitors,[14] we planned to obtain the corresponding hydroxyphthalides **4a** and **4b** and dehydrate them under acidic conditions.



The hydroxyphthalides **4a** and **4b** were prepared by the phthalide anion approach developed in our laboratory.[15] The hydroxyphthalides **4a** and **4b**, on treatment with a mixture of orthophosphoric acid and formic acid, gave the alkylidenephthalides **5a** and **5b** in 78 and 76% yields, respectively. The alkylidenephthalide **5a** was converted to the antiarteriosclerotic agent,[1f] (*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide (**5c**), by demethylation with $AlCl_3$ in methylene chloride solution at room temperature. The conversion of **5b** into (*Z*)-3-butylidene-7-hydroxyphthalide (**5d**), a natural product isolated from the dried rhizome of *Ligusticum wallichi*, has already been reported from our laboratory.[12a]

Scheme 1



The hydroxyphthalides **4a** and **4b**, on dehydration under milder conditions by refluxing with *p*-TsOH in benzene solution, gave no reaction even after 10 h. They were then refluxed with *p*-TsOH in toluene solution. To our surprise, the reaction gave the isocoumarins **6a** and **6b** in 76 and 72% yields, respectively. In **6b**, the 8-methoxy group had also been demethylated. Demethylation with *p*-TsOH is unprecedented.

The formation of the alkylidenephthalide is a simple acid-catalyzed dehydration. The formation of the isocoumarin, by the ring expansion reaction observed above, is interesting. The mechanistic aspects of the latter reaction are not clear. It is not through the alkylidene phthalide, since the latter is not converted to the isocoumarin on refluxing with *p*-TsOH in toluene solution. A possible mechanism for the formation of the isocoumarin is as shown in Scheme 1.

To establish the generality of the ring-expansion reaction, it was extended to obtain other natural 3-alkyl-8-hydroxyisocoumarins **7a**−**g**, directly or through their methyl ethers **8**, which could then be demethylated to the naturally occurring compounds (Scheme 2).

The starting compounds, e.g., hydroxyphthalides **10a**−**d**, were synthesized by a previously developed method from the corresponding phthalide anion, which in turn were obtained from phthalides **9a**−**d** by treatment with LDA. Reaction of the phthalide anion with acetaldehyde in THF at −78 °C gave the hydroxyphthalides **10a**−**d** in 75, 78, 80, and 76% yield, respectively. On refluxing in toluene solution with *p*-TsOH for 2 h, the hydroxyphthalide **10a** gave 8-hydroxy-3-methylisocoumarin (**7a**) in 82% yield. When the hydroxyphthalide **10a** was heated with *p*-TsOH in the absence of the solvent at 110 °C for 1.5 h, the isocoumarin **7a** was obtained in 62% yield, along with 8-methoxy-3-methylisocoumarin (**8a**, 22% yield). The hydroxyphthalide **10b** on reaction with *p*-TsOH in refluxing toluene for 4 h gave the isocoumarin **8b** in 76%

(9) (a) Mowry, D. T.; Ringwald, E. L.; Rennol, M. *J. Am. Chem. Soc.* **1949**, *71*, 120. (b) Gold, H. J.; Wilson, C. W. *J. Food Sci.* **1963**, *28*, 488; *Chem. Abstr.* **1964**, *61*, 2399h. (c) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635 and references therein. (d) Napolitano, E; Spinelli, G.; Fiachi, R.; Marsili, A. *Synthesis* **1985**, 38. (e) Ogawa, Y.; Hosake, K.; Chin, M.; Mitsuhashi, H. *Heterocycles* **1991**, *32*, 1737. (f) Watanabe, M.; Ijichi, S.; Morimoto, S.; Nogami, K.; Furukawa, S. *Heterocycles* **1993**, *36*, 553. (g) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1994**, *39*, 47. (h) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587. (i) Li, S.; Wang, Z.; Xiaoping, F.; Yating, Y.; Li, Y. *Synth. Commun.* **1997**, *27*, 1783.

(10) (a) Matsui, M.; Mori, K.; Arasaki, S. *Agric. Biol. Chem.* **1964**, *28*, 896. (b) Lin, J.-Y.; Yoshida, S.; Takahashi, N. *Agric. Biol. Chem.* **1972**, *36*, 506. (c) Chatterjea, J. N.; Bhakta, C.; Vakula, T. R. *J. Indian Chem. Soc.* **1972**, *49*, 1161 and references therein. (d) Carter, R. H.; Colyer, R. M.; Hill, R. A.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1438. (e) Belgaonkar, V. H.; Usgaonkar, R. N. *Indian J. Chem.* **1979**, *17B*, 430. (f) Nozawa, K.; Nakajima, S.; Yamada, M.; Kawai, K.-I. *Chem. Pharm. Bull.* **1980**, *28*, 1622. (g) Sinha, N. K.; Sarkhel, B. K.; Srivastava, J. N. *Indian J. Chem.* **1986**, *25B*, 640. (h) Sinha, J.; Singh, R. P.; Srivastava, J. N. *J. Indian Chem. Soc.* **1986**, *63*, 907. (i) Lewis, C. N.; Spargo, P. L.; Staunton, J. *Synthesis* **1986**, 944. (j) Hauser, F. M.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 4676 and references therein. (k) Kendall, J. K.; Fisher, T. H.; Schultz, H. P.; Schultz, T. P. *J. Org. Chem.* **1989**, *54*, 4218.

(11) (a) Loewenthal, H. J. E.; Pappo, R. J. *J. Chem. Soc.* **1952**, 4799. (b) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329. (c) Bhide, B. H.; Gupta, V. P.; Shah, K. K. *Chem. Ind.* **1980**, *84*. (d) Bhide, B. H.; Brahmbhatt, D. I. *Proc. Indian Acad. Sci.* **1980**, *89*, 525. (e) Batu, G.; Stevenson, R. J. *J. Org. Chem.* **1980**, *45*, 1532 (f) Chatterjea, J. N.; Bhakta, C.; Mukherjee, S. K. *Indian J. Chem.* **1981**, *20B*, 992. (g) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. (h) Bhide, B. H.; Brahmbhatt, D. I. *Proc. Indian Acad. Sci.* **1989**, *101*, 301. (i) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711 and references therein.

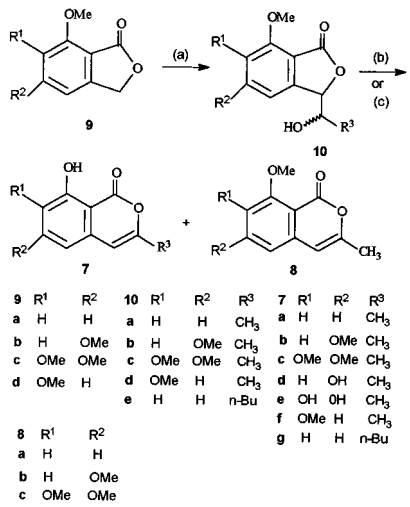
(12) (a) Mali, R. S.; Patil, S. R. *Synth. Commun.* **1990**, *20*, 167. (b) Mali, R. S.; Patil, S. R.; Kulkarni, B. K.; Yeola, S. N. *Indian J. Chem.* **1990**, *29B*, 319.

(13) Mali, R. S.; Jagtap, P. G. *J. Chem. Res., Synop.* **1993**, 184.

(14) (a) Bjedanes, L. F.; Kim, I. S. *J. Food Sci.* **1978**, *43*, 143; *Chem. Abstr.* **1978**, *88*, 69108. (b) Ko, W. C. *Jpn. J. Pharmacol* **1980**, *30*, 85; *Chem. Abstr.* **1980**, *92*, 208863r. (c) Ogawa, Y.; Hosa, K.; Chin, M. Jpn. Kokai Tokkyo Koho JP 04,208,278, 1992; *Chem. Abstr.* **1992**, *117*, 69721. (d) Ogawa, Y.; Wakamatsu, T.; Maruno, M.; Isono, M. Jpn. Kokai Tokkyo Koho JP 07206,844, 1995; *Chem. Abstr.* **1995**, *123*, 256503d.

(15) Mali, R. S.; Jagtap, P. G.; Patil, S. R.; Pawar, P. N. *J. Chem. Soc., Chem. Commun.* **1992**, 883.

Scheme 2[a]



[a] Reagents: (a) (i) LDA/THF, −78 °C, (ii) R^3CHO/THF, −78 °C; (b) *p*-TsOH, toluene, reflux; (c) *p*-TsOH, heat, 110 °C.

yield, **10c** gave the isocoumarins **7c** and **8c**, and **10d** gave the isocoumarin **7f**. Additionally, compounds corresponding to the methoxyl group demethylation, i.e., isocoumarins **8a** and **8c**, were also observed. The conversion of 6,8-dimethoxyisocoumarin **8b** into the corresponding natural isocoumarins **7b** and **7d** has already been reported in the literature.[7g,i] The reaction thus completes the total synthesis of the naturally occurring isocoumarins **7a** and **7c** and constitutes formal syntheses of **7b** and **7d**. The isocoumarins **7a** and **7e** have also been converted[7g,10a] to the corresponding 8-hydroxy- and 6,8-dihydroxy-3,4-dihyro-3-methylisocoumarins (mellein and 6-hydroxymellein), which have been isolated from natural sources.[2c]

A similar transformation of 3-(1-hydroxybutyl)-7-methoxyphthalide to 8-methoxy-3-propylisocoumarin has been reported very recently[16] by Wang et al. The authors, however, observed no demethylation, which had to be carried out separately using $AlCl_3$ in refluxing benzene to obtain the 8-hydroxy-3-propylisocoumarin.

The interesting feature of ring expansion and demethylation was capitalized in a first synthesis of dihydro-8-hydroxyartemidin (**7g**) as shown in Scheme 2. Thus, the treatment of the hydroxyphthalide **10e**, obtained by the condensation of the anion of **9a** with valeraldehyde, on heating with *p*-TsOH at 110 °C for 2 h gave dihydro-8-hydroxyartemidin (**7g**) in 89% yield.

In conclusion, it may be stated that a concise route to the 3-alkyl-8-hydroxyisocoumarins has been achieved from the easily available 7-methoxyphthalides. The present approach for the synthesis of 3-methyl(or 3-alkyl)-8-hydroxy(or methoxy)isocoumarins, which permits variation of the 3-substituent and the functionalization pattern on the aromatic ring, is better than the literature methods.

Experimental Section

General Methods. Melting points are uncorrected. Chemical shifts are expressed in units (ppm) downfield from TMS. *n*-Butyllithium (prepared) was 1.25 M solution in *n*- hexane, whose exact titer was determined by titration using diphenylacetic acid.[17] THF was distilled over $LiAlH_4$ before use. Phthalides **9a**−**d** were prepared according to the literatrure procedure.[18]

General Procedure for the Synthesis of 3-(1-Hydroxyalkyl)phthalides (4a,b and 10a−e). A solution of the phthalide **9** (2 mmol) in THF (10 mL) was added to a stirred solution of LDA (2.2 mmol) in THF (10 mL) at −78 °C under nitrogen atmosphere. The reaction mixture was stirred at −78 °C for 20 min, and a solution of the alkylaldehyde (2.2 mmol) in THF (5 mL) was added. After being stirred at −78 °C for 30 min, the mixture was allowed to warm to rt over a period of 1 h and quenched by addition of ice-cold water. THF was removed in vacuo and the aqueous solution extracted three times with $CHCl_3$. The combined organic layer was washed with water and dried over Na_2SO_4. The gummy mass, obtained after evaporation of solvent, was chromatographed on silica gel using 30% EtOAc/hexane as eluent to give the hydroxyphthalides **4a**, **4b**, and **10a**−**e**.

3-(1-Hydroxybutyl)-5,7-dimethoxyphthalide (4a). The phthalide **9b** (0.390 g, 2 mmol) and butyraldehyde (0.159 g, 2.2 mmol) afforded the hydroxyphthalide **4a** (0.416 g, 78%) as a thick liquid: IR ν 3441, 1746 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.84 (tr, J = 6.3 Hz, 3H), 1.10−1.63 (m, 4H), 1.87 (bs, 1H, exchangeable with D_2O), 3.92 (s, 3H), 3.93 (s, 3H), 4.17−4.74 (m, 1H), 5.23 (d, J = 6.3 Hz, 1H), 6.43 (s, 1H), 6.57 (s, 1H).

Anal. Calcd for C_{14} H_{18} O_5: C, 63.14; H, 6.81. Found: C, 63.03; H, 6.88.

3-(1-Hydroxybutyl)-7-methoxyphthalide (4b). The phthalide **9a** (0.328 g, 2 mmol) and butyraldehyde (0.159 g, 2.2 mmol) afforded the hydroxyphthalide **4b** (0.424 g, 90%) as a thick liquid: IR ν 3417, 1747 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92, 0.96 (2 × tr (3:1), J = 6.8 Hz, 3H), 1.40−1.67 (m, 4H), 1.90 (bs, 1H, exchangeable with D_2O), 3.89−3.97 (m, 1H), 3.99 (s, 3H), 5.32−5.34 (m, 1H), 6.95 (d, J = 7 Hz, 1H), 7.07, 7.11 (2 × d (3:1), J = 7 Hz, 1H), 7.61, 7.64 (2 × tr (3:1), J = 7 Hz, 1H).

Anal. Calcd for C_{13} H_{16} O_4: C, 66.08; H, 6.83. Found: C, 66.26; H, 7.07.

3-(1-Hydroxyethyl)-7-methoxyphthalide (10a). The phthalide **9a** (0.328 g, 2 mmol) and acetaldehyde (0.096 g, 2.2 mmol) afforded the phthalide **10a** (0.275 g, 75%) as a thick liquid: IR ν 3417, 1747 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.24, 1.37 (2 × d (3:1), J = 5.4 Hz, 3H), 2.05, 2.09 (2 × s (3:1), 1H, exchangeable with D_2O), 4.04 (s, 3H), 4.05−4.21 (m, 1H), 5.28, 5.35 (2 × d (3:1), J = 5.4 Hz, 1H), 7.0 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H).

Anal. Calcd for C_{11} H_{12} O_4: C, 63.45; H, 5.81. Found: C, 63.24; H, 6.11.

3-(1-Hydroxyethyl)-5,7-dimethoxyphthalide (10b). The phthalide **9b** (0.390 g, 2 mmol) and acetaldehyde (0.096 g, 2.2 mmol) afforded the phthalide **10b** (0.375 g, 78%) as a thick liquid: IR ν 3452, 1731 cm^{-1}; ^{1}H NMR (200 MHz), δ 1.22, 1.34 (2 × d (3:1), J = 5.3 Hz, 3H), 2.06, 2.09 (2 × s (3:1), 1H, exchangeable with D_2O), 3.88 (s, 3H), 3.92 (s, 3H), 4.0−4.17 (m, 1H), 5.19, 5.23 (2 × d (3:1), J = 5.1 Hz, 1H), 6.41 (s, 1H), 6.56 (s, 1H).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.33; H, 5.75.

3-(1-Hydroxyethyl)-5,6,7-trimethoxyphthalide (10c). The phthalide **9c** (0.450 g, 2 mmol) and acetaldehyde (0.096 g, 2.2 mmol) afforded the phthalide **10c** (0.430 g, 80%) as a thick liquid: IR ν 3457, 1729 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.28,1.36 (2 × d (1:1), J = 6.1 Hz, 3H), 2.07 (bs, 1H, exchangeable with D_2O), 3.87 (s, 3H), 3.95 (s, 3H), 4.03−4.13 (m, 1H), 4.14 (s, 3H),5.18, 5.20 (2 × d (1:1), J = 6.1 Hz, 1H), 6.76, 6.77 (2 × s (1:1), 1H).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.04; H, 6.21.

3-(1-Hydroxyethyl)-6,7-dimethoxyphthalide (10d). The phthalide **9d** (0.390 g, 2 mmol) and acetaldehyde (0.096 g, 2.2

(16) Wang, Z.; Li, S., Li, Y. *Bull. Soc. Chim. Belg.* **1996**, *105*, 787; *Chem. Abstr.* **1997**, *126*, 117840k.

(17) Kofron, W. G.; Baclawski, M. L. *J. Org. Chem.* **1976**, *41*, 1879.

(18) (a) Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. K.; Gupta, P. K. *Indian J. Chem.* **1983**, *22B*, 1257. (b) Mali, R. S.; Jagtap, P. G.; Tilve, S. G. *Synth. Commun.* **1990**, *20*, 2641.

mmol) afforded the phthalide **10d** (0.363 g, 76%) as a thick liquid: IR ν 3417, 1747 cm^{-1}; ^1H NMR (90 MHz) δ 1.27 (d, J = 6.4 Hz, 3H), 2.08 (s, 1H, exchangeable with D_2O), 3.97 (s, 3H), 4.0 (s, 3H), 4.05−4.15 (m, 1H), 5.32 (d, J = 5.14 Hz, 1H), 7.3 (bs, 2H).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.76; H, 6.06.

3-(1-Hydroxypentyl)-7-methoxyphthalide (10e). The phthalide **9a** (0.328 g, 2 mmol) and *n*-valeraldehyde (0.189 g, 2.2 mmol) afforded the phthalide **12** (0.430 g, 86%) as a thick liquid: IR ν 3312, 1766 cm^{-1}; ^1H NMR (300 MHz), δ 0.89, 0.92 (2 × tr (3:1), J = 6.9 Hz, 3H), 1.33−1.78 (m, 6H), 1.98 (bs, 1H, exchangeable with D_2O), 3.90−3.97, 4.22−4.25 (2 × m (3:1), 1H), 3.99 (s, 3H), 5.32−5.34 (m, 1H), 6.88, 6.95 (2 × d (1:3), J = 7 Hz, 1H), 7.04, 7.10 (2 × d (1:3), J = 7 Hz, 1H), 7.60, 7.63 (2 × tr (1:3), J = 7 Hz, 1H).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.01; H, 7.48.

(*Z*)-3-Butylidene-5,7-dimethoxyphthalide (5a). A mixture of the hydroxyphthalide **4a** (0.266 g, 1 mmol), formic acid (2 mL), and H_3PO_4 (2 mL) was stirred and heated at 80 °C for 8 h. The reaction mixture was allowed to cool to rt, poured in ice-cold water, and then extracted two times with CH_2Cl_2. The combined organic layer was washed with water and dried over Na_2SO_4. The residue, obtained after removal of solvent, was chromatographed on silica gel using 5% EtOAc/hexane as eluent to give 3-butylidenephthalide **5a** (0.203 g, 82%) as a colorless thick liquid: IR ν 1760, 1606 cm^{-1}; ^1H NMR (90 MHz) δ 0.84 (tr, J = 6.3 Hz, 3H), 1.15−1.88 (m, 4H), 3.87 (s, 3H), 3.94 (s, 3H), 5.37 (tr, J = 6.3 Hz, 1H), 6.47 (d, J = 2.5 Hz, 2H).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.93; H, 6.58.

(*Z*)-3-Butylidene-7-methoxyphthalide (5b). Following the procedure described for **5a**, but heating for 10 h, the phthalide (**4b**) 0.236 g (1 mmol) provided 3-butylidenephthalide **5b** (0.187 g, 86%) as a colorless thick liquid (lit.[12a] bp 200−203 °C (bath)/1 mm). The compound was found to be identical (co-TLC, superposable IR, PMR) with an authentic sample of the phthalide **5b** synthesized in our laboratory.[12a]

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.40; H, 6.74.

(*Z*)-3-Butylidene-7-hydroxy-5-methoxyphthalide (5c). A suspension of anhydrous $AlCl_3$ (0.162 g, 1.2 mmol) in dry CH_2Cl_2 was stirred for 20 min, and a solution of butylidenephthalide **5a** (0.1 g, 0.4 mmol) was added. The reaction mixture was stirred at rt for 3 h and poured into ice-cold HCl (1:1, 15 mL). The organic layer was separated and the aqueous layer extracted two times with CH_2Cl_2. The combined organic layer was washed with water and dried over Na_2SO_4. The residue, obtained after removal of solvent, was chromatographed on silica gel using 2% EtOAc/hexane as eluent to give phthalide **5c** (0.062 g, 65%): mp 102 °C; IR ν 3290, 1743 cm^{-1}; ^1H NMR (90 MHz) δ 0.91 (tr, J = 6.3 Hz, 3H), 1.16−1.85 (m, 4H), 3.84 (s, 3H), 5.28 (s, 1H, exchangeable with D_2O), 5.46 (tr, J = 6.3 Hz, 1H), 6.47 (s, 2H).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.87; H, 6.27.

Reaction of the Hydroxyphthalides 4a, 4b, and 10a−d with *p*-TsOH in Toluene as the Solvent. General Procedure. A solution of the hydroxyphthalides **4a**, **4b**, and **10a−d** (0.5 mmol) in dry toluene (5 mL) containing *p*-TsOH (0.237 g, 1.25 mmol) was refluxed for varying periods (until disappearance of the starting compound as monitored by TLC). The reaction mixture was cooled, diluted with water, and extracted three times with CH_2Cl_2. The combined organic layer was washed with water and dried over Na_2SO_4. The residue, obtained after removal of solvent, was chromatographed on silica gel using 5% EtOAc/hexane as eluent to give the isocoumarins **6a**,**b**, **7a**,**c**,**f**, and **8b**.

6,8-Dimethoxy-3-propylisocoumarin (6a). The phthalide **4a** (0.1 g, 0.375 mmol) provided the isocoumarin **6a** (0.070 g, 76%) as a white solid: mp 103−105 °C; IR ν 1720 cm^{-1}; ^1H NMR (90 MHz) δ 0.94 (tr, J = 7.6 Hz, 3H), 1.47−1.83 (m, 2H), 2.43 (tr, J = 7.6 Hz, 2H), 3.87 (s, 3H), 3.95 (s, 3H), 6.06 (s, 1H), 6.30 (s, 1H), 6.40 (s, 1H).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.84; H, 6.71.

8-Hydroxy-3-propylisocoumarin (6b). The phthalide **4b** (0.1 g, 0.423 mmol) gave the isocoumarin **6b** (0.061 g, 72%) as a white solid: mp 38−40 °C; IR ν 3111, 1693 cm^{-1}; ^1H NMR (90 MHz) δ 1.0 (tr, J = 7.6 Hz, 3H), 1.71 (br sex, J = 7.6 Hz, 2H), 2.47 (tr, J = 7.6 Hz, 2H), 6.25 (s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 7.54 (tr, J = 8.8 Hz, 1H), 10.94 (s, 1H, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.30; H, 6.12.

8-Hydroxy-3-methylisocoumarin (7a). The phthalide **10a** (0.104 g, 0.5 mmol) provided the isocoumarin **7a** (0.072 g, 82%) as a white solid: mp 99−100 °C (lit.[2i] mp 99−100 °C); IR ν 3105, 1680 cm^{-1}; ^1H NMR (90 MHz) δ 2.28 (s, 3H), 6.31 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.60 (tr, J = 8.0 Hz, 1H).

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.37; H, 4.85.

6,8-Dimethoxy-3-methylisocoumarin (8b). The phthalide **10b** (0.120 g, 0.5 mmol) furnished the isocoumarin **8b** (0.083 g, 76%) as a solid: mp 156 °C (lit.[10k] mp 154−156 °C); IR ν 1713 cm^{-1}; ^1H NMR (200 MHz) δ 2.22 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.14 (s, 1H), 6.35 (d, J = 2.5 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 69.19; H, 5.64.

8-Hydroxy-6,7-dimethoxy-3-methylisocoumarin (7c). The phthalide (0.134 g, 0.5 mmol) provided the isocoumarin **7c** (0.083 g, 71%) as a white solid: mp 196−200 °C (lit.[2j] mp 199 °C); IR ν 3111,1693 cm^{-1}; ^1H NMR (200 MHz) δ 2.26 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 6.20 (s, 1H), 6.34 (s, 1H).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.18; H, 5.15.

8-Hydroxy-7-methoxy-3-methylisocoumarin (7f). The phthalide **10d** (0.08 g, 0.334 mmol) provided the isocoumarin **7f** (0.06 g, 86%) as a white solid: mp 134 °C; IR ν 1685 cm^{-1}; ^1H NMR (90 MHz) δ 2.24 (s, 3H), 3.93 (s, 3H), 6.21 (s, 1H), 6.41 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 10.75 (s, 1H, exchangeable with D_2O).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.23; H, 5.11.

Reaction of the Hydroxyphthalides 10a−e with *p*-TsOH in the Absence of Solvent. General Procedure. A mixture of the hydroxyphthalides **10a−e** (0.5 mmol) and *p*-TsOH (0.237 g, 1.25 mmol) was heated at 110 °C for varying periods (until the starting compound disappeared as monitored by TLC). Water was added to it and the reaction mixture extracted three times with CH_2Cl_2. The residue, obtained on usual workup, was chromatographed on silica gel using 3% EtOAc/hexane as eluent to give the isocoumarins **7a**,**c**,**f** and **8a−c**.

8-Hydroxy-3-methylisocoumarin (7a) and 8-Methoxy-3-methylisocoumarin (8a). The phthalide **10a** (0.104 g) on heating for 1.5 h provided two compounds: 8-hydroxy-3-methylisocoumarin **7a** (0.054 g, 62%) as a white solid, mp 99−100 °C, identical with authentic sample (co-TLC and IR) and the isocoumarin **8a** (0.021 g, 22%) as a solid: mp 110 °C (lit.[10a] mp 109.5−110.5 °C); IR ν 1734, 1693 cm^{-1}; ^1H NMR (90 MHz) δ 2.25 (s, 3H), 3.98 (s, 3H), 6.24 (s, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.68 (tr, J = 9.0 Hz, 1H).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.62; H, 5.55.

6,8-Dimethoxy-3-methylisocoumarin (8b). The phthalide **10b** (0.120 g) on heating for 4 h provided the isocoumarin **8b** (0.079 g, 72%) as a solid: mp 156 °C, identical with authentic sample (co-TLC and IR).

8-Hydroxy-6,7-dimethoxy-3-methylisocoumarin (7c) and 6,7,8-Trimethoxy-3-methylisocoumarin (8c). The phthalide **10c** (0.135 g) on heating for 2.5 h provided two compounds: 8-hydroxy-6,8-dimethxoyisocoumarin **7c** (0.070 g, 59%) as a solid, mp 196 °C, identical with authentic sample (co-TLC and IR) and isocoumarin **8c** (0.035 g, 28%) as a solid:

mp 120 °C (lit.[10b] mp 118 °C); IR ν 1724, 1693 cm^{-1}; ^1H NMR (200 MHz) δ 2.27 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.0 (s, 3H), 6.22 (s, 1H), 6.39 (s, 1H).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.25; H, 5.77.

8-Hydroxy-7-methoxy-3-methylisocoumarin (7f). The phthalide **10d** (0.08 g, 0.334 mmol) on heating for 0.5 h provided the isocoumarin **7f** (0.057 g, 82%) as a white solid: mp 134 °C, identical with authentic sample (co-TLC and IR).

8-Hydroxy-3-butylisocoumarin 7g (Dihydro-8-hydroxyartemidin). The phthalide **10e** (0.250 g, 1 mmol) on heating for 2 h provided dihydro-8-hydroxyartemidin **7g** (0.194 g, 89%) as a solid: mp 58−60 °C; IR ν 1680 cm^{-1}; ^1H NMR (200 MHz) δ 1.0 (tr, J = 6.4 Hz, 3H), 1.22−1.51 (m, 2H), 1.58−1.80 (m, 2H), 2.53 (tr, J = 6.4 Hz, 3H), 6.30 (s, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 7.62 (tr, J = 9.0 Hz, 1H), 11.10 (s, 1H, exchangeable with D_2O)

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.29; H, 6.67.

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