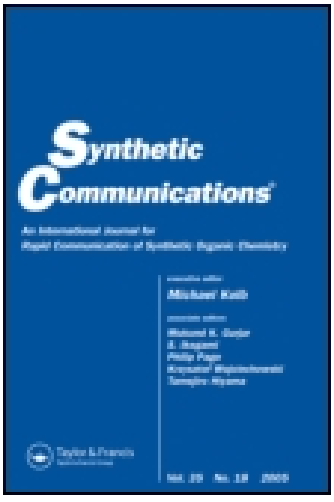

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New Total Synthesis of O-Methyledgeworin and Edgeworin

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New Total Synthesis of O-Methyledgeworin and Edgeworin

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Abstract: Upon thermal condensation of diethyl (coumarinyl-7-oxy)malonate with O-methyl-resorcine, the corresponding bis[coumarinyl]ether, 4-hydroxy-O-methyl-edgeworin is obtained in good yield. This leads to 4-bromo-O-methyledgeworin, O-methyledgeworin, and edgeworin.

Keywords: Bis[coumarinyl]ethers, edgeworin, O-methyledgeworin

INTRODUCTION

The 3,7′-bis[coumarinyl]ethers constitute a group of naturally occurring oxygen heterocyclic compounds, isolated principally in the *Thymeliaceae* but also in the *Leguminosae* and *Rutacea* families: edgeworin **1** and daphnoretin **2** from *Edgeworthia chrysantha*;[1] daphnoretin **2** and O-methyl-daphnoretin **3** from *Daphne mezereum*, various other plants,[2,3] and more recently from *Artemisia keiskeanea*;[4] and edgeworthin **4** from *Edgeworthia gardneri*[5] (Figure 1). Besides their phytochemical interest, the 3,7′-bis[coumarinyl]ethers present interesting biological properties. Daphnoretin inhibits the growth of Ehrlich ascites carcinoma in mice,[6] DNA-producing enzymes,[7] and nucleic acid synthesis,[8] whereas edgeworin, edgeworthin, and daphnoretin inhibit the lyase activity of DNA polymerase β, providing useful agents for adjuvant cancer therapy.[9]

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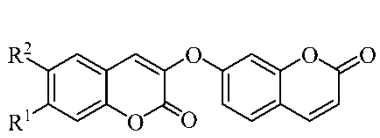
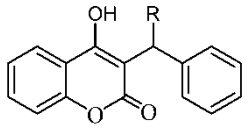


1 : $R^1 = OH$; $R^2 = H$: Edgeworin
2 : $R^1 = OCH_3$; $R^2 = H$: O-Methyledgeworin
3 : $R^1 = OH$; $R^2 = OCH_3$: Daphnoretin
4 : $R^1 = R^2 = OCH_3$: O-Methyldaphnoretin
5 : $R^1 = R^2 = OH$: Edgeworthin



6 : $R = C_2H_5$: Phenprocoumon
7 : $R = CH_2COCH_3$: Warfarin

Figure 1. Reference structures.

However, the discovery of phenprocoumon **6** and warfarin **7** as lead templates to the human immunodeficiency virus protease (HIV-PR) led to the identification of various 3-substituted 4-hydroxy-coumarins as active nonpeptide HIV-PR inhibitors,[10,11] opening up a new therapeutic possibility (Figure 1).

During the course of a research program in connexion with the preparation of potential HIV-1 PR inhibitors, we investigated the structure–activity relationships of various 3-substituted-4-hydroxycoumarins.[12] Therefore, we synthesized 4-hydroxy-O-methyledgeworin, which led us also to the synthesis of the natural compounds O-methyledgeworin and edgeworin.

There are some available routes for the synthesis 3,7′-bis[coumarinyl] ethers:

O-Methyldaphnoretin **4** was prepared by the Williamson condensation of 3-bromo-6,7-dimethoxycoumarin and 7-hydroxycoumarin using copper powder with a low yield.[2]

O-Methyldaphnoretin **4** and some 3,7′-bis[coumarinyl]ethers were prepared by Perkin reactions of N,N-diethylcoumarin-7-oxyacetamide[13] or (coumarinyl-7-oxy)acetic acid[14] with conveniently substituted salicylaldehydes.

Daphnoretin 2 derivatives were obtained via the corresponding 4-hydroxy-3,7′-bis[coumarinyl]ethers prepared by thermal condensation of diethyl (coumarinyl-7-oxy)malonate with conveniently substituted phenols.[15]

Among the previously reported procedures leading to 3,7′-bis[coumarinyl]ethers, the last one is more satisfactory for the following reasons:

It leads to derivatives substituted by a 4-hydroxy group, which is necessary as much for their bonding to the HIV-PR as for their inhibitory potency.[16]

Besides their antithrombotic activity, the 3-substituted 4-hydroxycoumarins present interesting free-radical scavenging properties.[17]

The synthesis of O-methyledgeworin and edgeworin could be performed starting from the corresponding 4-hydroxy-7-methoxy-3,7′-bis[coumarinyl] ether **10a**.

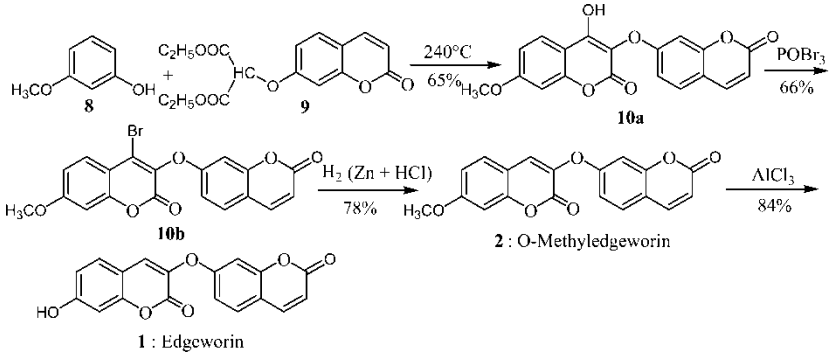
RESULTS

The thermal condensation was therefore selected and performed by reaction of O-methyl-resorcine **8** and diethyl (coumarinyl-7-oxy)malonate **9**. The expected 4-hydroxy-O-methyledgeworin **10a** was obtained with good yield. The synthesis of O-methyledgeworin **2** was achieved in two steps by removing the 4-hydroxy group after formation of 4-bromo-O-methyledgeworin **10b** using phosphorus oxybromide followed by the reductive debromination. Edgeworin **1** was finally obtained from compound **2** by demethylation with aluminium chloride (Scheme 1).

The structure of the compounds **10a**, **10b**, **2**, and **1** was established by elemental analysis, IR, and ^{1}H NMR spectroscopy. The chemical shifts of the NMR spectra are in agreement with those already reported for various 3-substituted 4-hydroxycoumarins[18] and for O-methyledgeworin and edgeworin.[1,14]

EXPERIMENTAL

The purity of all the compounds was routinely checked on 'Merck' 60 F_{254} silica-gel plates, and the spots were located by UV lamp. Melting points (mp) were taken on a Kofler bench and are uncorrected. IR spectra were recorded on a Perkin-Elmer 177 spectrophotometer and ^{1}H spectra on a Bruker AC 200 spectrometer. Glass equipment was dried at 100°C in an oven prior to use when anhydrous conditions were required.



Scheme 1. Total synthesis of O-methyledgeworin and edgeworin.

Synthesis of Compounds 10a, 10b, 2, and 1

3-(7-Coumarinyloxy)-4-hydroxy-7-methoxycoumarin 10a (4-hydroxy-O-methyledge-worin, $C_{19}H_{12}O_7$). In a dry, round-bottom flask equipped with an argon bubbler and a Vigreux distillation column, a mixture of O-methyl-resorcine (2.48 g, 2.0 mmol), diethyl coumarinyl-7-oxy)malonate[19] (7.44 g, 2.2 mmol), and diphenylether (5.0 mL) is heated at 250°C for 5 h (the progress of the reaction is monitored by TLC). The reaction mixture is evaporated under reduced pressure on a rotary evaporator. The cooled mixture is then triturated with diethylether (5 mL), giving a white solid, which is filtered and washed with a small portion of diethylether (5.0 mL). The solid is crystallized in acetic acid and in an ethanol–THF–water mixture (7/2/1), Yield 4.55 g (65%); mp 325°C.

IR (cm^{-1}): 3078, 1688, 1610, 1236, 1129, 1076, 834. ^{1}H NMR (DMSO-d_6): 3.88 (s, 3H, OCH_3), 6.33 (d, $J = 9.4$ Hz, 1H), 7.0–7.06 (m, 4H), 7.66 (d, $J = 9.4$ Hz, 1H), 7.82 (d, $J = 9.6$ Hz, 1H), 8.02 (d, $J = 9.6$ Hz, 1H). Anal. calcd. for $C_{19}H_{12}O_7$: C, 64.78; H, 3.43. Found: C, 64.43; H, 3.36.

Acetate ($C_{21}H_{14}O_8$): mp: 283°C. IR (cm^{-1}): 3422, 1719, 1612, 1274, 1256, 1123, 849. ^{1}H NMR (DMSO-d_6): 2.36 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.30 (d, $J = 9.4$ Hz, 1H), 6.93–7.00 (m, 4H), 7.39–7.48 (m, 2H), 7.64 (d, $J = 9.8$ Hz, 1H).

Tosylate ($C_{26}H_{18}O_9S$): mp: 238°C. IR (cm^{-1}): 3087, 1722, 1614, 1392, 1371, 1254, 1132, 1058, 731. ^{1}H NMR (DMSO-d_6): 2.39 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.30 (d, $J = 9.4$ Hz, 1H), 6.85 (dd, $J = 8.6$ Hz and 2.6 Hz, 1H), 6.96 (d, $J = 2.2$ Hz, 1H), 7.07 (d, $J = 2.2$ Hz, 1H), 7.10 (dd, $J = 8.8$ Hz and 2.2 Hz, 1H), 7.19 (d, $J = 2.2$ Hz, 1H), 7.42 (d, $J = 8.2$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.59 (d, 8.6 Hz, 1H), 7.85 (d, 8.4 Hz, 1H), 8.00 (d, $J = 9.6$ Hz, 1H).

3-(7-Coumarinyloxy)-4-bromo-7-methoxycoumarin 10b (4-bromo-O-methyledgeworin, $C_{19}H_{11}BrO_6$). In a dry, 100 mL, double-necked, round-bottom flask fitted with a magnetic stirring bar and a reflux condenser protected with a $CaCl_2$ drying tube, 1.0 g (2.8 mmol) of 4-hydroxy-O-methyl-edgeworin **10**, 0.9 g (31 mmol) of phosphorus oxybromide, and 1,2-dichloro-benzene (40 mL) are introduced. The mixture is heated under reflux for 8 h (the progress of the reaction is monitored by TLC). The solvent is concentrated to 10 mL under reduced pressure, and the crude mixture is purified by column chromatography over silica gel (solvent: $CHCl_3$) to give 0.767 g (yield: 66%) of pure product. Mp: 230°C. IR (cm^{-1}): 3074, 2918, 2850, 1714, 1611, 1249, 1120, 835. ^{1}H NMR (DMSO-d_6): 3.91 (s, 3H, OCH_3), 6.37 (d, $J = 9.6$ Hz, 1H), 7.08–7.21 (m, 3H), 7.29 (d, $J = 2.4$ Hz, 1H), 7.71 (d, $J = 8.6$ Hz, 1H), 7.76 (d, $J = 8.6$ Hz, 1H), 8.02 (dd, $J = 9.4$ Hz, 1H). Anal. calcd. for $C_{19}H_{11}BrO_6$: C, 54.96; H, 2.67. Found: C, 54.43; H, 2.46.

3-(7-Coumarinyloxy)-7-methoxycoumarin 2 (O-methyledgeworin $C_{19}H_{12}O_6$). In a 200 mL, double-necked, round-bottom flask fitted with a magnetic stirring

bar and a reflux condenser, 3-(7-coumarinyloxy)-4-bromo-7-methoxycoumarin **10b** (0.400 g, 0.964 mmol), zinc powder (1.4 g), ethanol (100 mL), and concentrated hydrochloric acid (2.0 mL) are introduced. The mixture refluxed for 1.0 h. Another portion of zinc powder (1.4 g) and hydrochloric acid (2.0 mL) are added, and the mixture refluxed again for 30 min (the TLC showed the end of the reaction). The mixture was filtered, ethanol distilled, and crushed ice added to the residue. The separated solid was filtered, washed with water, and dried to yield 0.252 g (78%), Mp: 220°C, lit. 215°C.[14] IR (cm^{-1}): 3085, 2920, 2850, 1714, 1611, 1249, 1120. ^{1}H NMR (DMSO-d_6): 3.91 (s, 3H, OCH_3); 6.37 (d, $J = 9.6$ Hz, 1H); 7.08–7.21 (m, 3H); 7.29 (d, $J = 2.4$ Hz, 1H); 7.71 (d, $J = 8.6$ Hz, 1H); 7.76 (d, $J = 8.6$ Hz, 1H); 8.02 (dd, $J = 9.4$ Hz, 1H).

3-(7-Coumarinyloxy)-7-hydroxycoumarin 1 (edgeworin, $C_{18}H_{10}O_6$). O-Methyledgeworin (0.10 g) and aluminium chloride (1.0 g) in dichloromethane (40 mL) are stirred at room temperature for 48 h. The solvent is evaporated, 50 mL of 10% hydrochloric acid is added, and the mixture is stirred for 1 h. A brown solid is recovered by filtration. The recovered solid is purified by column chromatography over silica gel (solvent ethyl acetate–toluene, 5/7), giving 0.080 g of edgeworin (yield: 84%). Mp 283°C, lit. 284–296°C,[1] 283°C.[14] IR (cm^{-1}): 3352, 2917, 1707, 1610, 1391, 1262, 1235, 1132, 1081, 847. ^{1}H NMR (DMSO-d_6): 6.37 (d, $J = 9.6$ Hz); 6.81 (dd, $J = 5$ Hz and 2.2 Hz, 1H); 6.87 (d, $J = 2.2$ Hz, 1H); 7.11 (dd, $J = 8.6$ Hz and 2.4 Hz); 7.18 (d, $J = 2.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H); 7.70 (d, 8.6 Hz, 1H); 7.92 (s, 1H), 8.03 (d, $J = 9.6$ Hz, 1H); 12.9 (s b, 1H).

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