A General Synthesis of Bis[coumarinyl] Ethers: Synthesis of Daphnoretin Methyl Ether

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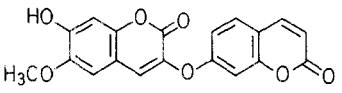
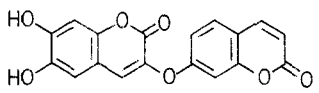
A general synthesis of 3,7′-bis[coumarinyl] ethers is given. The key step involves a reaction of the preformed complex of *N,N*-diethylcoumarin-7-oxyacetamide and phosphoryl chloride, with substituted salicylaldehydes. A new synthesis of daphnoretin methyl ether using this method is also described.

Daphnoretin (**1**)[1], its methyl ether (**8aa**)[2], and edgeworthin (**2**)[3] are the only three hitherto known naturally occurring 3,7′-bis[coumarinyl] ethers. The antineoplastic activity[4] and inhibition of DNA producing enzymes[5] or protein and nucleic acid synthesis *in vivo*[6] shown by **1** attracted our attention towards this class of compounds. In spite of these interesting properties no general synthesis of this class has been reported. We report here a new synthesis of daphnoretin methyl ether (**8aa**), using easily available starting compounds. The generality of the present method is illustrated by the synthesis of four previously unknown bis[coumarinyl] ethers (**8ab–8bc**).



1 daphnoretin



2 edgeworthin

Three synthesis of daphnoretin derivatives are known. Tschesche[7] condensed 3-bromo-6,7-dimethoxycoumarin and 7-hydroxycoumarin with copper powder to get 21% yield of daphnoretin methyl ether. Mentzer[8] reacted 3,4-dimethoxyphenol and 7-coumarinyloxymalonate in veratrol as solvent to get 52% yield of the same compound. Daphnoretin tosylate was synthesised by Mentzer[9] starting from 2,4-dihydroxyanisole and 7-coumarinyloxymalonate in three steps. Our method gives the required compounds in moderate to good yield.

The key step in the present synthesis of daphnoretin methyl ether (**8aa**) involves reaction of the preformed complex of *N,N*-diethylamide **6a** and phosphoryl chloride, with substituted salicylaldehydes. The amide **6a** was obtained in 60% yield from the phenol **3a** in three steps. The phenol was converted to the ester **4a**[10] by reaction with ethyl bromoacetate and potassium carbonate. The ester **4a** was then hydrolysed to the acid **5a** which was then converted to the amide **6a** by the usual method. This three step sequence was needed since direct conversion[11] of phenol **3a** to the acid **5a** or amide **6a** and also direct conversion of ester **4a** to the amide **6a** were unsuccessful.

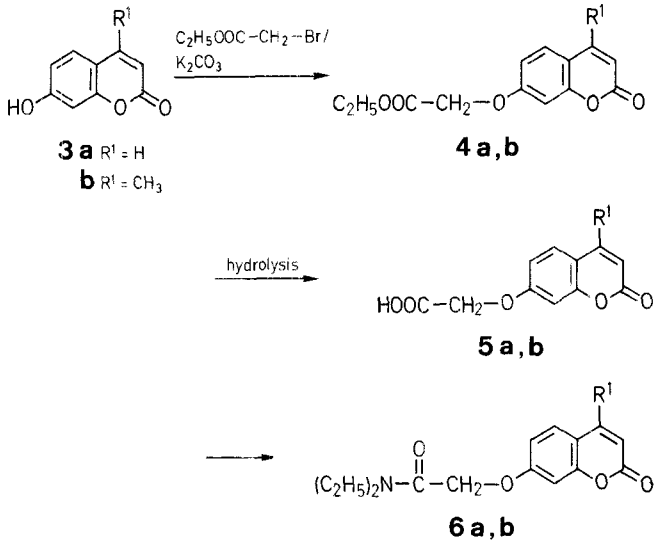
The new amide **6b** was prepared in 60% yield from the phenol **3b** in three steps. The phenol **3b** was converted to the ester **4b**[14] which was then converted to the acid **4h**[14]. This acid was then converted to the amide **6b**. Here also direct conversion of phenol **3b** to the acid **5b** or amide **6b** and direct conversion of ester **4b** to amide **6b** were unsuccessful.

A solution of 2-hydroxy-4,5-dimethoxybenzaldehyde[12] (**7a**) [prepared from 4,5-dimethoxy-β-methyl β-nitrostyrene], was added to a preformed complex of **6a** with phosphoryl chloride in refluxing dichloromethane. The reaction mixture was poured on ice and hydrolysed by sodium carbonate

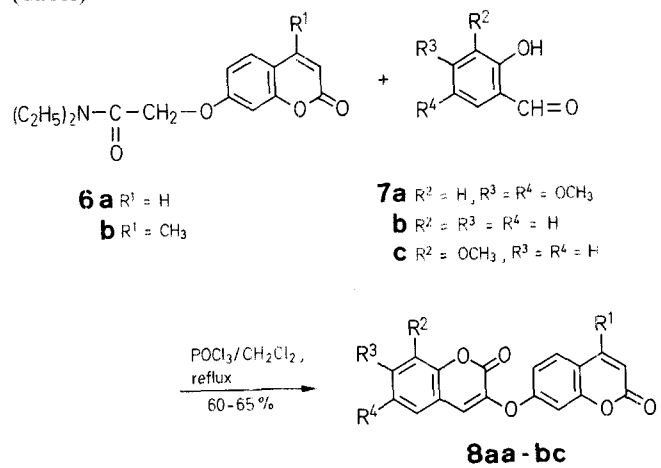
Table. 3,7′-Bis[coumarinyl] Ethers **8** prepared

Product	Yield[a] [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R.[c] ($CDCl_3$ + TFA/TMS) δ [ppm]				
					C4—H	C3′—H	C4′—H	OCH_3	CH_3
8aa	60	230°	231–232°[7]	1720	7.56	6.52	7.92	4.02, 3.99	–
8ab	60	201°	$C_{18}H_{10}O_5$ (306.3)	1720	7.67	6.60	8.01	–	–
8ac	61	222°	$C_{19}H_{12}O_6$ (336.3)	1720	7.59	6.55	7.95	4.02	–
8bb	65	241°	$C_{19}H_{12}O_5$ (320.3)	1720	7.60	6.45	–	–	2.55
8bc	60	222°	$C_{20}H_{14}O_6$ (350.3)	1720	7.59	6.46	–	4.04	2.58

[a] Yield of isolated pure product.
[b] Satisfactory microanalysis obtained for all products (C ±0.30, H ±0.17).
[c] N.M.R. recorded on Perkin Elmer R 32 90 MHz instrument.



solution, to yield a compound in 60% yield. The spectral properties and m.p. are in good agreement with those reported for **8aa**[2]. In a similar manner the amide **6a** on condensation with **7b** and **7c** was converted to the bis-coumarinylethers **8ab** and **8ac**, respectively. These were characterised by their physical and spectral properties (Table).



As substituted salicylaldehydes are known to condense with the preformed complex of *N,N*-diethylamides and phosphoryl chloride[13] it could be expected that reaction of amide **6b** with **7b** and **7c** should furnish **8bb** and **8bc**, respectively. The products obtained from these reaction were identified as **8bb** and **8bc** from their spectral properties (Table). In all cases **8ab–8bc**, the final condensation step proceeds in 60–65% yield.

***N,N*-Diethylcoumarin-7-oxyacetamides (6a, b); General Procedure:** A mixture of coumarin-7-oxyacetic acid[14] (**4a, b**; 7 mmol) and thionyl chloride (17 mmol) is refluxed for 2 h in dry chloroform (25 ml). Excess thionyl chloride is removed under reduced pressure. The chloroform solution of the residue is added dropwise at 0 °C to diethylamine taken up in chloroform (25 ml) and water (25 ml). The mixture is stirred for 30 min. The chloroform layer is separated, washed with sodium carbonate solution, then with water, and dried with sodium sulfate. After removal of chloroform, the pure amides **6a, b** are obtained by crystallisation.

Product **6a**; yield: 80%; m.p. 84 °C.

$C_{15}H_{17}NO_4$ (275.3) calc. C 65.44 H 6.22 found 65.43 6.18

I.R. (Nujol): ν = 1710, 1610 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS) δ = 1.13 (t, 3 H, J = 8 Hz); 1.22 (t, 3 H, J = 8 Hz); 3.39 (br.q, 4H, J = 8 Hz); 4.75 (s, 2 H); 6.23 (d, 1 H, J = 9 Hz); 6.79 (d, 1 H, J = 2 Hz); 6.91 (dd, 1 H, J = 2 Hz, 8 Hz); 7.37 (d, 1 H, J = 8 Hz); 7.63 ppm (d, 1 H, J = 9 Hz).

Product **6b**; yield: 80%; m.p. 151 °C.

$C_{16}H_{19}NO_4$ (289.3) calc. C 66.42 H 6.62 found 66.43 6.58

I.R. (Nujol): ν = 1700, 1620 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.13 (t, 3 H, J = 8 Hz), 1.22 (t, 3 H, J = 8 Hz), 2.37 (br. s, 3 H), 3.39 (br. q, 4 H, J = 8 Hz), 4.72 (s, 2 H), 6.09 (br. s, 1 H), 6.78 (d, 1 H, J = 3 Hz), 6.93 (dd, 1 H, J = 3 Hz, 9 Hz), 7.47 ppm (d, 1 H, J = 9 Hz).

3,7′-Bis[coumarinyl] Ethers 8aa–8bc; General Procedure: *N,N*-Diethylcoumarin-7-oxyacetamide **6a, b** (0.25 mmol) and phosphoryl chloride (0.25 mmol) are mixed at 0 °C in dichloromethane (25 ml). The mixture is refluxed for 30 min to get a yellow complex. The aldehyde **7a–c** (0.25 mmol) is added in one lot. The mixture is heated in oil bath at 100 °C, for 3 h, cooled, and poured in cold 10% solution of sodium carbonate. This is warmed on water bath (60 °C) for 5 min, cooled, and acidified. The solid obtained is passed through a short column (silica, 10 g), eluting with chloroform to give the pure 3,7′-bis[coumarinyl] ether **8** as a fluorescent white solid in the reported yields (Table).

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