# Synthesis and Characterization of Some Coumarins with Two Hydroxy or Methoxy Substituents 

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The first synthesis of the 6-hydroxy-4-methoxycoumarin (5) was carried out in $25 \%$ overall yield from 6-methoxy-4-hydroxycoumarin (1) by hydrolysis of the methoxy group and subsequent selective methylation of the hydroxyl group at position 4 . The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of compounds 1-6 are reported.
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Though long known, coumarins have in recent years attracted growing interest, some having been found to possess properties of considerable pharmacological or industrial significance [1-5]. In the course of our previous work in this field [5-7] we realized that several very simple coumarins of apparent interest have not yet been synthesized, and that others have been characterized only incompletely. In particular, this is true of coumarins with hydroxy or methoxy groups in positions 4, 6 and/or 7 (the usual substitution positions in both natural and synthetic coumarins), which have great synthetic potential. For example, in spite of abundant references in the literature to 4,7-disubstituted coumarins of this type
(compounds 2, 4 and 6) [8-12], only the 4-hydroxy-7methoxy derivative $\mathbf{4}$ has been totally characterized [12], while the 4-methoxy-6-hydroxy compound 5 appears not to have been synthesized and its precursors in Scheme 1 (1 and 3 ) have been only very incompletely characterized $[8,9]$. Here we describe the first synthesis of compound $\mathbf{5}$, and present ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data for this compound and for the other disubstituted coumarins shown in Scheme 1.

Compound 3 was obtained from 1 [9] in $45 \%$ yield by hydrolysis of the methoxy group with HI in acetic acid [10], and selective methylation of the $4-\mathrm{OH}$ group by a mixture of hydrochloric acid and methanol [11] then

Scheme 1


Reagentes: (i) $\mathrm{IH} /(\mathrm{AcO})_{2} \mathrm{O} / \mathrm{AcOH}$; (ii) conc. $\mathrm{HCl} / \mathrm{MeOH}$.

Table 1
${ }^{1} \mathrm{H}$ NMR Spectra of Coumarins $\mathbf{1 - 6}$ in DMSO- $d_{6}$ : Chemical Shifts and Coupling Constants


| Compoumd | H 3 | H 5 | H 6 | H 7 | H 8 | $\mathrm{OH}-4$ | $\mathrm{OH}-6$ | $\mathrm{OH}-7$ | CH 3 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{1}$ | $5.59, \mathrm{~s}$ | 7.22 |  | 7.19 | 7.30 | $12.56, \mathrm{~s}$ |  |  |  |
| $\mathbf{2}$ | 5.43 | $\mathrm{~d}, J=2.40$ | 7.71 |  | 6.93 | $\mathrm{dd}, J=8.33,2.40$ | $\mathrm{~d}, J=8.33$ |  |  |

Table 2
${ }^{13} \mathrm{C}$ NMR Spectra of Coumarins 1-6 in DMSO- $d_{6}$

| Compound | C 2 | C 3 | C 4 | C 4 a | C 5 | C 6 | C 7 | C 8 | C 8 a | $\mathrm{CH}_{3}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathbf{1}$ | 162.42 | 91.54 | 165.78 | 120.71 | 105.29 | 155.61 | 116.58 | 117.92 | 148.19 | 55.97 |
| $\mathbf{2}$ | 162.82 | 87.46 | 167.05 | 108.03 | 124.75 | 114.53 | 163.14 | 100.79 | 155.79 | 56.18 |
| $\mathbf{3}$ | 162.50 | 91.60 | 165.83 | 123.12 | 110.40 | 154.72 | 121.03 | 119.89 | 145.73 |  |
| $\mathbf{4}$ | 162.40 | 87.75 | 166.00 | 107.50 | 124.45 | 112.48 | 161.50 | 101.93 | 156.03 |  |
| $\mathbf{5}$ | 162.29 | 90.62 | 165.99 | 115.94 | 107.08 | 153.99 | 117.87 | 121.31 | 146.311 | 57.30 |
| $\mathbf{6}$ | 162.53 | 87.20 | 166.79 | 107.40 | 124.47 | 113.18 | 162.02 | 102.37 | 154.96 | 57.33 |

afforded compound 5 in 55\% yield. Compound $\mathbf{6}$ was prepared analogously from 2 via $\mathbf{4}$ [9], with an overall yield of $48 \% .{ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data for compounds 1-6 are listed in Tables 1 and 2, respectively.

## EXPERIMENTAL

Melting points were determined in a Reichert Kofler thermopan, and are uncorrected. IR spectra were recorded in a Perkin-Elmer 1640FT spectrometer ( $v$ in $\mathrm{cm}^{-1}$ ). ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded in a Bruker AMX spectrometer at 300 and 75.47 MHz , respectively, using TMS as internal standard (chemical shifts in $\delta$ values, $J$ in Hz ). Mass spectrometry was carried out in a Hewlett Packard 5988A spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B microanalyser. Flash chromatography (FC) was performed on silica gel (Merck 60, 230-400 mesh).

## 4,6-Dihydroxycoumarin (3).

Compound $\mathbf{1}(1 \mathrm{~g}, 5.2 \mathrm{mmol})$ was added to a mixture of hydriodic acid ( 25 ml ), acetic anhydride ( 10 ml ) and acetic acid (10 ml ), and the mixture was heated at $80^{\circ} \mathrm{C}$ for 1 hour. After cooling to room temperature, 100 ml of water was added. The resulting precipitate was isolated by filtration and purified by flash chromatography ( FC ) using $4: 1 \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ as eluent. Yield 0.4 g . ( $45 \%$ ), mp 286-288 ${ }^{\circ} \mathrm{C}(\mathrm{MeOH})$; RF: 0.22 ( $\left.4: 1 \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}\right)$; ir: v 3100-2800, 1663, 1567, 1462, 1325, 1153, 1097, $1002 \mathrm{~cm}^{-1}$; MS $m / z(\%): 178\left(\mathrm{M}^{+}, 96\right), 150\left(\mathrm{M}^{+}-\mathrm{CO}, 30\right), 136\left(\mathrm{M}^{+}-\mathrm{CO}_{2}\right.$, 100), 108 (47), 78 (64).

Anal. Calcd. for $\mathrm{C}_{9} \mathrm{H}_{6} \mathrm{O}_{4}$ : C, 62.5; H, 4.20. Found: C, 62.38; H, 4.43.

6-Hydroxy-4-methoxycoumarin (5).
A mixture of $\mathbf{3}(1 \mathrm{~g}, 5.6 \mathrm{mmol})$, $\mathrm{MeOH}(40 \mathrm{ml})$ and concentrated $\mathrm{HCl}(5 \mathrm{ml})$ was refluxed for 1.5 hours. The solvent was removed in vacuo and the residue was purified by FC using 9:1
$\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$, yielding the desired compound $5(0.6 \mathrm{~g} \mathrm{55} \mathrm{\%})$, and $0.16 \mathrm{~g}(15 \%)$ of the starting coumarin 3; mp 283-285 ${ }^{\circ} \mathrm{C}$ (EtOH); RF: 0.43 (9:1 CH2 $\left.\mathrm{Cl}_{2} / \mathrm{MeOH}\right)$; ir: v 3186, 1664, 1571, 1468, 1398, 1243, $1092 \mathrm{~cm}^{-1}$; MS m/z (\%): 192 ( $\mathrm{M}^{+}, 100$ ), 164 $\left(\mathrm{M}^{+}-\mathrm{CO}, 41\right), 149\left(\mathrm{M}^{+}-\mathrm{CO}_{2}, 46\right), 134$ (27), 121 (14), 78 (25).

Anal. Calcd. for $\mathrm{C}_{10} \mathrm{H}_{8} \mathrm{O}_{4}$ : C, 60.68; H, 3.39. Found: C, 60.51 ; H, 3.55.

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