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6-PRENYLOXY-7-METHOXYCOUMARIN, A COUMARIN-HEMITERPENE ETHER FROM *CARDUUS TENUIFLORUS*

LUZ CARDONA, BEGOÑA GARCÍA, JOSÉ R. PEDRO* and JOSÉ PÉREZ

Departamento de Química Orgánica, Facultad de Química, Universidad de Valencia, E-46100 Burjassot (Valencia) Spain

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Key Word Index—*Carduus tenuiflorus*; Compositae; prenyloxycoumarins; isolation; synthesis; lignans; flavonoids.

Abstract—From the acetone extract of *Carduus tenuiflorus*, a new coumarin-hemiterpene ether was isolated, which was identified as 6-(3,3-dimethylallyloxy)-7-methoxycoumarin. The synthesis of this coumarin and that of its positional isomer 7-(3,3-dimethylallyloxy)-6-methoxycoumarin were carried out from esculetin. Two other coumarins, three lignans and three flavonoids were also isolated.

INTRODUCTION

In the family Compositae, the chemistry of *Carduus* species has received little attention [1, 2]. In a continuation of our investigation of the secondary metabolites from *Carduus* [3] we now report an analysis of the previously uninvestigated *C. tenuiflorus* [4]. This study has resulted in the isolation of the new natural product 6-(3,3-dimethylallyloxy)-7-methoxycoumarin (**1**), along with nine known compounds.

RESULTS AND DISCUSSION

Column chromatography of the ether-soluble portion of an acetone extract of the aerial parts of *C. tenuiflorus* afforded, in addition of coniferaldehyde, three lignans [5, 6], pinoresinol [3], syringaresinol [3] 1-hydroxypinoresinol [3], three flavonoids [7], apigenin, naringenin [8] and kaempferol-3-*O*-α-L-rhamnoside [3] and three coumarins, isoescopoletin [9], isofraxidin [10] and a new coumarin-hemiterpene ether. The mass spectrum of this compound showed a peak at *m/z* 260 $[M]^+$ which was consistent with a molecular formula $C_{15}H_{16}O_4$. The UV spectrum showed two maxima at 230 and 343 nm. The IR spectrum showed absorptions at 1715 (C=O), 1610 and 1560 (aromatic) cm^{-1}. The ^1H NMR spectrum showed a typical pair of doublets ($J=9.5$ Hz) for H-3 (δ 6.25) and H-4 (δ 7.58), and two uncoupled aromatic protons at δ 6.84 and 6.81, which are characteristic of a 6,7-disubstituted coumarin; two singlets at δ 1.77 and 1.73 corresponding to two methyl groups attached to a double bond of an isopentenil chain. A doublet ($J=6.7$ Hz) at δ 4.57 of methylene protons of the same moiety, coupled with an olefinic proton (broadened triplet at δ 5.50) indicated that 3,3-dimethylallyloxy was a substituent, the other being a methoxyl group (a singlet at δ 3.91) (Table 1).

From the above data, either structure **1** or **2** could be assigned to the coumarin-hemiterpene ether isolated from *C. tenuiflorus*. Compound **2** has been isolated from several plant species [11–14], whereas **1** had been described only once, as a synthetic material [15]. However, the ^1H NMR spectra are so similar that it was difficult to assign structure **1** or **2** to our product. The small amount of isolated product did not allow us to carry out a more complete characterization of the natural product, hence we have accomplished the synthesis of compounds **1** and **2** from 6,7-dihydroxycoumarin (esculetin, **3**).

The preparation of coumarin **1** was carried out by alkylation of isoscopoletin (**4**) with 3,3-dimethylallyl bromide–potassium carbonate–acetone at reflux for 1 hr [15]. Isoscopoletin (**4**) was obtained, in turn, by partial methylation of esculetin (**3**) in a system with methyl sulphate (1.2 eq.)–potassium carbonate (1.5 eq.)–acetone at room temperature for 2 hr [16]. Similarly by partial alkylation of **3** with 3,3-dimethylallyl bromide after Murray's method [14] and subsequent methylation, 7-(3,3-dimethylallyloxy)-6-methoxycoumarin **2** was obtained. From the ^1H NMR spectra of synthetic materials **1** and **2** (specially those registered in benzene-d_6), we assigned structure **1** to the product isolated from *C. tenuiflorus*. Thus, this constitutes the first report of 6-(3,3-dimethylallyloxy)-7-methoxycoumarin in nature.

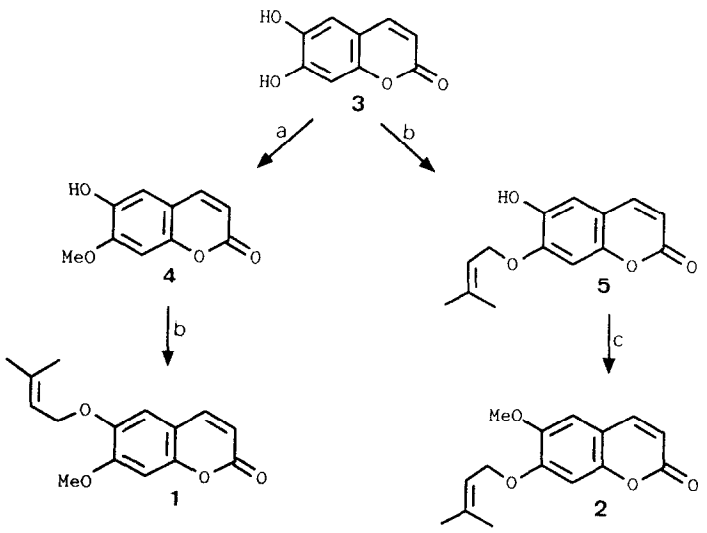
Further characterization of compounds **1** and **2** was carried out by ^{13}C NMR spectroscopy (Table 2). The assignments of the signals were made on the basis of a DEPT experiment, the additivity rules and previous work [17]. However, it is interesting to note that the best way to differentiate both isomers **1** and **2** is to use the ^1H NMR spectra registered in benzene-d_6. So, the signals for H-5 and H-8 are clearly different in both isomers (δ 6.37 and 6.40 for **1** and 6.24 and 6.60 for **2**) as well as the signals for H-1′ (δ 4.30 for **1** and 4.18 for **2**) and the methoxyl (δ 3.12 for **1** and 3.35 for **2**).

EXPERIMENTAL

Mass spectra were carried out on a Hewlett-Packard 5988-A spectrometer. The NMR spectra were obtained with a Bruker AC-200 (200 MHz for ^1H) and with a Varian Unity 300 spectrometer (75 MHz for ^{13}C).

Plant material. Aerial parts of *Carduus tenuiflorus* were collected at Burjassot (Valencia) and authenticated by Dr M.B. Crespo

*Author to whom correspondence should be addressed.



Reagents: (a) Me_2SO_4/ K_2CO_3; (b) $Me_2C=CHCH_2Br$/ K_2CO_3; (c) MeI/ K_2CO_3.

Table 1. ^{1}H NMR chemical shifts for compounds **1**, **2** and **5** [200 MHz, $CDCl_3$* and benzene-d_6† δ values]

H	1*	1†	2*	2†	5*	5†
3	6.25 *d*	5.98 *d*	6.24 *d*	6.03 *d*	6.25 *d*	5.88 *d*
4	7.58 *d*	6.70 *d*	7.59 *d*	6.75 *d*	7.56 *d*	6.50 *d*
5	6.81[a] *s*	6.37[a] *s*	6.81[a] *s*	6.24[a] *s*	6.80[a] *s*	6.43[a] *s*
8	6.84[a] *s*	6.40[a] *s*	6.82[a] *s*	6.60[a] *s*	6.93[a] *s*	6.58[a] *s*
1′	4.57 *d*	4.30 *d*	4.63 *d*	4.18 *d*	4.64 *d*	3.96 *d*
2′	5.50 *t*	5.53 *t*	5.46 *t*	5.41 *t*	5.45 *t*	5.12 *t*
4′	1.73[b] *s*	1.45[b] *s*	1.74[b] *s*	1.41[b] *s*	1.76[b] *s*	1.32[b] *s*
5′	1.77[b] *s*	1.54[b] *s*	1.76[b] *s*	1.51[b] *s*	1.80[b] *s*	1.49[b] *s*
OMe-6	—	—	3.87 *s*	3.35 *s*	—	—
OMe-7	3.91 *s*	3.12 *s*	—	—	—	—

$J_{3,4}=9.5$ Hz; $J_{1',2'}=6.7$ Hz.
[a,b]Assignments may be reversed.

(Departamento de Botánica, Facultad de Ciencias Biológicas, Universidad de Valencia). A voucher specimen is deposited in the herbarium of the above department.

Extraction and chromatography. The plant material (3.5 kg) was ground and extracted at room temp. with Me_2CO. This extract was concd *in vacuo* to *ca* 1 l, diluted with H_2O and re-extracted with Et_2O. Evapn of the solvent yielded a syrup which was chromatographed on a silica gel column using mixtures of hexane–Et_2O–EtOAc–MeOH of increasing polarity. Five main groups (A–E) of frs were obtained: A (hexane–Et_2O from 1:1 to 2:3), B (from hexane–Et_2O, 2:3 to Et_2O), C (from Et_2O to Et_2O–EtOAc, 4:1), D (Et_2O–EtOAc, from 3:2 to 3:7), E (from Et_2O–EtOAc, 3:7 to MeOH). Repeated chromatography on silica gel afforded 6-(3,3-dimethylallyloxy)-7-methoxycoumarin (**1**) (2 mg) and coniferaldehyde (2 mg) from group A; naringenin (13 mg) and *p*-hydroxybenzoic acid (8 mg) from group B; apigenin (10 mg), from group C; pinoresinol (3 mg) and vanillic acid (12 mg) from group D; isoscopoletin (2 mg), isofraxidin (7 mg), syringaresinol (3 mg), 1-hydroxypinoresinol (2 mg) and kaempferol 3-*O*-α-L-rhamnopyranoside (50 mg).

6-(3,3-*dimethylallyloxy*)-7-*Methoxycoumarin* (**1**). IR ν_{max} cm^{-1}: 1715, 1610, 1560, 1510, 1275, 1140 and 1000; UV λ_{max}^{MeOH} nm: 343, 293, 248sh and 230; MS *m/z* (rel. int.): 260 ([M]$^+$, 4), 192 (100), 177 (3), 164 (22), 149 (17).

6-*Hydroxy*-7-*methoxycoumarin or isoscopoletin* (**4**). A mixt. of esculetin (**3**) (50 mg, 0.28 mmol), methyl sulphate (0.032 ml, 0.33 mmol) and K_2CO_3 (57 mg, 0.41 mmol) in Me_2CO (6 ml) was stirred at room temp. for 2 hr and then diluted with H_2O. The Me_2CO was concd and the aq. soln was extracted with EtOAc. The combined organic layers were washed with 2 M HCl, saturated aq. $NaHCO_3$ and brine, dried with Na_2SO_4 and concd *in vacuo*. The obtained material was chromatographed on a silica gel column (hexane–EtOAc, 1:1) to give 19 mg (35% yield) of isoscopoletin (**4**) [9] and 23 mg of recovered starting product.

6-(3,3-*dimethylallyloxy*)-7-*Methoxycoumarin* (**1**). From isoscopoletin (**4**), **1** was obtained, after ref. [15]; mp 115–117° (hexane–EtOAc); identical by IR, UV and ^{1}H NMR with natural product (**1**).

6-*Hydroxy*-7-(3,3-*dimethylallyloxy*)*coumarin* (**5**). From escu-

Table 2. ^{13}C NMR chemical shifts for compounds **1**, **2** and **5** (75 MHz, $CDCl_3$, δ values)

C	1	2	5
2	161.4	161.5	161.5
3	113.3	113.2	113.6
4	143.3	143.3	143.4
4a	111.3	112.2	112.0
5	109.7	107.8	110.8
6	146.4	146.5	142.8
7	153.3	152.0	149.2[a]
8	99.9	101.0	100.2
8a	150.0	149.8	149.1[a]
1′	66.2	66.2	66.2
2′	119.1	118.5	118.4
3′	138.6	139.0	140.2
4′	25.8	25.8	25.8
5′	18.2	18.3	18.3
OMe-6	—	56.3	—
OMe-7	56.3	—	—

[a]Assignments may be reversed.

letin (**3**), **5** was obtained, after ref. [14], with the following properties: mp 142–144° (hexane–EtOAc); IR ν_{max} cm^{-1}: 3540, 1715, 1630, 1565, 1510 and 1285; UV λ_{max}^{MeOH} nm: 348, 296, 260, 254 and 230, λ_{max}^{NaOMe} nm: 395, 320, 274sh and 251; MS *m/z* (rel. int.): 246 ($[M]^+$, 3), 179 (8), 178 (69), 150 (26), 149 (16).

7-(3,3-*dimethylallyloxy*)-6-*Methoxycoumarin* (**2**). From **5** compound **2** was obtained, after ref. [14], with the following features: mp 80–82° (hexane–EtOAc); IR ν_{max} cm^{-1}: 1715, 1610, 1555, 1505, 1270 and 1140; UV λ_{max}^{MeOH} nm: 344, 293, 260sh, 251sh and 230; MS *m/z* (rel. int.): 260 ($[M]^+$, 0.9), 192 (100), 177 (30), 164 (24), 149 (18).

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