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2,5-DIMETHYLCOUMARINS FROM LEAVES OF *JUNIPERUS SABINA*[*]

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The essential oil and extracts of *Juniperus sabina* L. were used in folk medicine as an abortive and a purgative, but its potency and hazardous effects prohibited its use. Some studies on the composition of this plant have been carried out [1–3], but no report on the existence of coumarins appears to have been made. In this paper we describe the identification of siderin (**1**) and the structure determination of coumarsabin (**2**) and 8-methoxycoumarsabin (**4**), two new coumarins with the previously undescribed 2,5-dimethyl substitution pattern.

Isolations were performed by chromatography and crystallization from a carefully defatted fraction of the hexane extract, which also contained some lignans and terpenoids. Siderin (**1**) showed MS, IR and UV spectra closely similar to those described [4, 5] and a ^{1}H NMR spectrum superimposable with that of an authentic sample.

Coumarsabin (**2**), mp 86–87°, showed MS with M^+ at m/z 234 ($C_{13}H_{14}O_4$). In the IR spectrum it presented the typical absorptions of methoxycoumarins at 1710, 1610, 1165, 1060 and 840 cm^{-1} and in the UV $\lambda_{\max}^{\mathrm{EtOH}} = 230$, 241 *sh*, 299 *sh* and 321 nm. The ^{1}H NMR spectrum contained singlets of two Me groups at δ 2.14 and 2.65, two aromatic OMe groups at δ 3.82 and 3.87 and a broad singlet of two aromatic protons at δ 6.66. The comparison with the spectrum of siderin has led us to propose the structure **2** for coumarsabin. The benzene and Eu(fod)$_3$-induced shifts in the ^{1}H NMR spectrum, which mostly agree with previous results in these fields [6, 7], are shown in Table 1. Degradation of **2** to the propiophenone derivative **3** [8] confirms the presence of the 3-Me group. The *m*-coupling constant of 3 Hz between the aromatic protons, the small *o*- and *p*-benzylic couplings observed in the ^{1}H NMR spectrum of **3**, its benzene-induced shifts (Table 1) and the IR and UV absorptions confirm structure **2** for coumarsabin.

Table 1. Benzene and Eu(fod)$_3$-induced shifts

2	3-Me	4-OMe	5-Me	6-H	7-OMe	8-H
$\Delta_{C_6D_6}^{CDCl_3}$ (ppm)	0.14	0.66	0.26	0.15	0.60	0.15
$\Delta_{Eu(fod)_3}^{*}$	1.00	0.31	0.23	0.17	0.03	0.17
3	α-CH$_2$	β-Me	3′-H	4′OMe	5′-H	6′-Me
$\Delta_{C_6D_6}^{CDCl_3}$ (ppm)	0.62	0.22	0.08	0.51	0.10	0.54

* Relative to 3-Me (shifted 2.31 ppm down-field).

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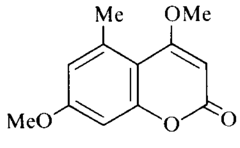
[*] For the preceding paper in this series see J. de Pascual *et al.* (1978) *An. Quim.* **74**, 1093.



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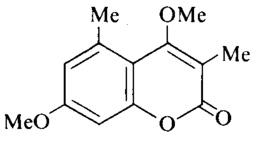

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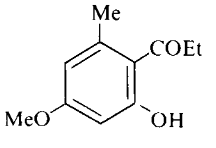

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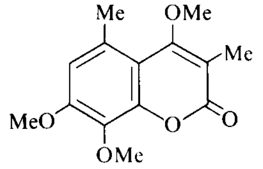

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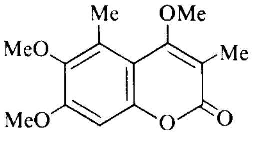

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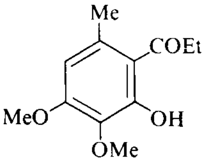

6

The last natural coumarin, mp 125–126°, showed MS with M^+ at m/z 264 (100%), ($C_{14}H_{16}O_5$) and IR absorptions at 1710, 1595, 1340, 1140 and 840 cm^{-1}. Its UV spectrum showed λ_{max}^{EtOH} = 227, 241, 250 *sh*, 257 *sh*, 311 *sh* and 317 nm. In the ^1H NMR spectrum the compound presented the typical signals of the 3-Me (δ 2.12), and 5-Me (δ 2.64), 3 OMe groups at δ 3.86 (3 H) and 3.93 (6 H) and only one aromatic proton at δ 6.64. These data suggest to us the possible structures **4** and **5**. The degradation product of the natural coumarin shows a benzene shielding shift $\Delta_{C_6D_6}^{CDCl_3} = 0.21$ ppm for its aromatic proton, that agrees with structure **6**. Finally, the identity of **6** with a synthetic sample obtained through Friedel–Crafts propionylation of 3,4,5-trimethoxytoluene with excess $AlCl_3$, confirms the structure of 8-methoxycoumarsabin (**4**) for the substance.

EXPERIMENTAL

IR: $CHCl_3$. UV: EtOH. ^1H NMR: 60 MHz, $CDCl_3$ with int. TMS. MS: 70 eV.

The plant was collected in April from the Zona de los lagos (Palencia, Spain). Dry leaves (2.4 kg) of *J. sabina*, extracted in a Soxhlet with hexane and soln maintained overnight at 0°, yielded 78.1 g of insoluble material, which successively defatted with MeOH and urea–MeOH gave 30.9 g of brownish resin. By CC on Si gel 0.35 g (C_6H_6–Et_2O, 9:1) of **2**, 2.4 g ($CHCl_3$–EtOAc, 9:1) of **4** and 0.85 g ($CHCl_3$–EtOAc, 7:3) of **1** were obtained.

Coumarsabin (**2**). Mp 86–87° (hexane–Et_2O). Found: C, 66.4; H, 6.0; $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%. IR ν_{max} cm^{-1}: 1710, 1630, 1610, 1520, 1460, 1366, 1350, 1340, 1240–1205, 1165, 1060 and 840. UV λ_{max} (ε): 230 (9600), 241 *sh* (7600), 251 *sh* (5040), 299 *sh* (1200) and 321 (16 300) nm. ^1H NMR δ: 2.14 (3 H, *s*, 3-Me), 2.65 (3 H, *br s*, 5-Me), 3.82 (3 H, *s*, 4-OMe), 3.87 (3 H, *s*, 7-OMe), 6.66 (2 H, *br s*, 6-H, 8-H). MS m/z (rel. int.): M^+ 234 (53), 219 (35), 206 (53), 191 (100), 177 (24), 165 (20). **2** (60 mg) in 6 ml of 10% KOH in MeOH, refluxed 2 hr and worked up as in [8] yielded 20 mg of 2′-hydroxy-4′-methoxy-6′-methyl-propiophenone (**3**), mp 82–83° (Me_2CO–hexane). IR: 1620, 1580, 1380, 1360, 1160 and 845 cm^{-1}. UV: 222 (3500) and 274 (2400) nm. ^1H NMR δ: 1.21 (3 H, *t*, J = 7 Hz, β-Me), 2.54 (3 H, *br s*, 6′-Me), 2.92 (2 H, *q*, J = 7 Hz, α-CH_2), 3.78 (3 H, *s*, 4′-OMe) and 6.62 (2 H, *br s*, 3′-H, 5′-H). ^1H NMR (C_6D_6): δ 0.99 (β-Me), 2.00 (6′-Me), 2.30 (α-CH_2), 3.17 (4′-OMe), 6.16 (1 H, *br d*, J_1 = 3 Hz, 5′-H) and 6.34 (1 H, *dq*, J_1 = 3 Hz, J_2 = 0.7 Hz, 5′-H).

8-*Methoxycoumarsabin* (**4**). Mp 125–126° (MeOH). Found: C, 64.2; H, 6.4; $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%. IR: 1710, 1595, 1505, 1460, 1340, 1140, 1100, 1040, 1015, 940 and 840 cm^{-1}. UV: 227 (11 200), 241 (8300), 250 *sh* (7800), 257 *sh* (7000), 311 *sh* (15 700) and 317 (16 000) nm. ^1H NMR: δ 2.12 (3 H, *s*, 3-Me), 2.64 (3 H, *s*, 5-Me), 3.86 (3 H, *s*, 4-OMe), 3.93 (6 H, *s*, 7-OMe, 8-OMe) and 6.64 (1 H, *br s*, 6-H). MS m/z (rel. int.): M^+ 264 (100), 259 (43), 246 (15), 221 (40), 189 (26), 161 (45). **4** (90 mg) in 10 ml of 10% KOH in MeOH, worked up as for **2** yielded 30 mg of **6**, mp 103–104°. IR: 1620, 1580, 1500, 1340, 1250, 1200, 1150, 1130 and 820 cm^{-1}. UV: 224 (6000) and 274 (3300) nm. ^1H NMR: δ 1.06 (3 H, *t*, J = 7 Hz, β-Me), 2.31 (3 H, *s*, 6′-Me), 2.80 (2 H, *q*, J = 7 Hz, α-CH_2), 3.75 (3 H, *s*, 4′-OMe), 3.77 (3 H, *s*, 3′-OMe), 6.21 (1 H, *s*, 5′-H) ppm.

Propionylation of 3,4,5-*trimethoxytoluene* (**7**). **7** (511 mg) in 14 ml CCl_4 was reacted at room temp. with 1.5 ml of EtCOCl and 0.9 g of dry $AlCl_3$. After 1.3 hr and usual work-up, the reaction product extrd with base yielded 190 mg of **6** and 368 mg of impure 2′,3′,4′-trimethoxy-6′-methyl-propiophenone.

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