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ISOLATION AND SYNTHESIS OF TWO COUMARINS FROM *MELAMPODIUM DIVARICATUM**

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Key Word Index—*Melampodium divaricatum*; Heliantheae; Compositae; new coumarins; NMR; synthesis.

Abstract—Two new coumarin isomers have been isolated from *Melampodium divaricatum* and identified by spectral procedures as 8-hydroxy-7-(3′-methyl-2′-butenyloxy)coumarin (**1**) and 7-hydroxy-8-(3′-methyl-2′-butenyloxy)coumarin (**2**). The regioselective synthesis of each isomer was made by two different alkylation pathways confirming their structures.

INTRODUCTION

In continuation of our phytochemical studies of Salvadorian Compositae we report in this paper the isolation and synthesis of two coumarins from *Melampodium divaricatum*.

From an ethanolic extract of the aerial parts of this species two coumarin isomers **1** and **2** were isolated. The structural assignment of both isomers was made by ^{1}H NMR solvent shifts and confirmed by unequivocal synthesis. The methylation of **1** and **2** enabled a comparison to be made with 7-isopentenyloxy-8-methoxycoumarin, a coumarin isolated from *Artemisia apiacea* [1].

RESULTS AND DISCUSSION

The coumarin **1** was found to correspond to $C_{14}H_{14}O_4$ by elemental analysis and mass spectrometry. The UV spectrum showed two maxima at 263 nm (log ε 4.29) and 322 nm (log ε 4.47). The IR spectrum showed absorptions at 1712 (C=O), 1628 and 1575 (C=C) cm^{-1}. The ^{1}H NMR spectrum taken in deuteriochloroform showed a pair of doublets with an allylic coupling of 1 Hz, centred at δ 1.75 and 1.80 that correspond to two methyl groups attached to a double bond of an isopentenyl chain, a doublet of δ 4.66 of methylene protons of the same moiety coupled with an olefinic proton (broadened triplet at δ 5.50), two *ortho*-coupled aromatic protons at δ 6.83 and 6.98, and a pair of doublets, J = 9.5 Hz, centred at 6.24 and 7.60 characteristic signals of the H-3 and H-4 protons, respectively. A signal at δ 5.77 which disappears with D_2O indicates a phenolic hydroxyl group. These data indicate a 7,8 oxygenation pattern as confirmed by the UV spectra.

Compound **2** was assigned the formula $C_{14}H_{14}O_4$ by elemental analysis and mass spectrometry. The UV spectrum showed maxima at 260 nm (log ε 4) and 327 nm (log ε 4.33). The IR spectrum had absorptions at 1700, 1618 and 1575 cm^{-1}. The ^{1}H NMR spectrum showed similar signals to those found in **1** for an isopentenyl chain with shifts at δ 1.68 and 1.75 of methyl groups, a 4.80 doublet due to methylene and olefinic proton at δ 5.50. The coumarin ring protons appear at δ 7.60 and 6.21 for H-4 and H-3, and 7.09 and 6.86 ppm for aromatic protons H-5 and H-6, respectively. At 6.33 a singlet which disappeared with D_2O indicates a phenolic proton.

The UV and ^{1}H NMR spectra of both compounds are very similar, being positional isomers of a 7,8-dihydroxycoumarin with an isopentenyl group joined by an ether linkage.

The addition of sodium ethoxide to the ethanolic solutions of **1** and **2** shift the absorption band of the pyrone ring at 332 nm (4.33) and 388 nm (4.47), respectively. Electron delocalization of the phenoxide ion by the pyrone-carbonyl group is possible for salts of 7-hydroxycoumarins but not for those of 8-hydroxycoumarins. Consequently when UV spectra are recorded in an alkaline medium the intensities of the maxima of the first increase with 7-hydroxycoumarins showing marked bathochromic shifts while in the second group bathochromic shifts also occur but with a simultaneous fall in log ε of the long-wavelength band [2].

The benzene-d_6 induced shifts in coumarins have a marked positional effect according to the indicated reference plane (**3**) [3]. Consequently the methoxyl substituents are shielded 0.60 to 0.77 ppm except when these are located at C-3 or C-8 in which case only small changes of *ca* 0.20 ppm are shown which are readily distinguished from other isomers. If assimilated the methylene protons to those of the methoxyl group, these would also show similar behaviour as can be seen in Table 1 where these increments are smaller. We can observe that while **1** has a shift of 0.03 ppm for the methylene group, **2** has 0.58 ppm for this group. These data suggest that **1** and **2**

* Part 6 in the series "Salvadorian Compositae". For Part 5 see Arriaga-Giner, F. J., Borges-del-Castillo, J., Manresa-Ferrero, M. T., Vazquez-Bueno, P., Rodríguez-Luis, F. and Valdés-Iraheta, S. (1983) *Phytochemistry* **22**, 1767.

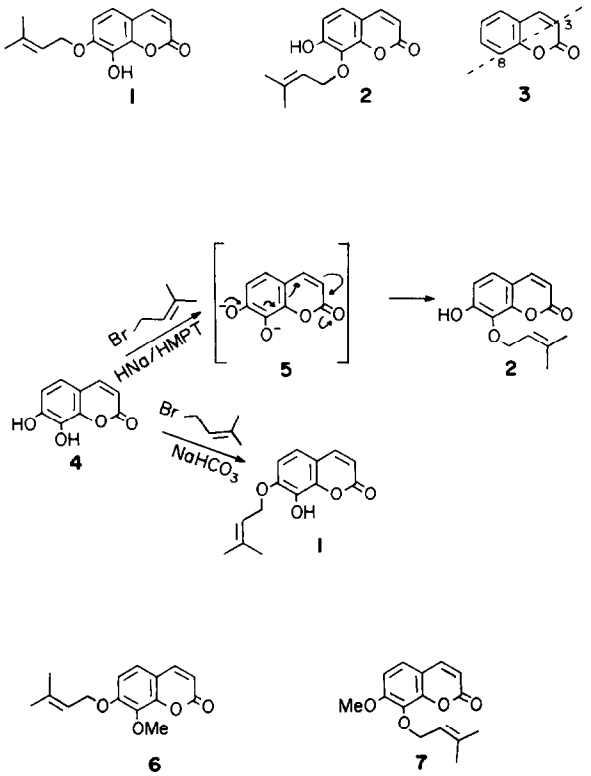

Fig. 1.

are respectively 8-hydroxy-7-isopentenyloxy- and 7-hydroxy-8-isopentenyloxycoumarin.

To confirm these structures the synthesis of both isomers was performed. Alkylation of 7,8-dihydroxycoumarin **4** goes regioselectively at C-7 in the phenol [4], when the reaction is made with isopentenyl bromide and $NaHCO_3$ in acetone to give mainly regioisomer **1**. However with this base the reaction is very slow. Recently we have developed a method for hydroxycoumarin alkylation using hexamethylphosphoric triamide (HMPT) [F. Rodríguez-Luis and J. C. Rodríguez-Ubis, unpublished results]. With this solvent the solvation of the phenoxide ion is low whereas the reaction with alkyl halide is very quick at room temperature using sodium hydride as base. When alkylation was made under these conditions we found that the regioisomer **2** is the main product. This change in the regiochemistry of alkylation may be explained from the formation of the diphenoxide ion **5** in the medium. In this, the charge density on the oxygen atom at C-8 would appear to be greater than that on the oxygen atom at C-7, in which conjugation with the carbonyl group of the pyrone is possible. This would lead to preferential alkylation of the oxygen atom at C-8, (see Fig. 1).

Finally we made the methyl derivatives of both isomers. The similarity of the chemical shifts of **6** and **7** permitted the unequivocal identification of one of these with the natural sample of 7-isopentenyloxy-8-methoxycoumarin. The chemical shifts of **6** and **7** in hexadeuteriobenzene (Table 2) showed increments of -0.08 and 0.35 ppm for methylene, 0.63 and 0.21 ppm for methoxy groups compared with those in deuteriochloroform, data that are consistent with the proposed structures.

EXPERIMENTAL

Mps are uncorr. UV spectra were recorded in EtOH and IR spectra in KBr. ^{1}H NMR spectra were recorded at 100 MHz.

Extraction and isolation. M. divaricatum (Rich in Pers.) D.C. was collected in 1979 at El Salvador. Leaves (500 g) were extracted with EtOH. The residue (38 g) was chromatographed on a silica gel (Merck Kieselgel 60) column and eluted with $CHCl_3$–EtOAc mixtures. With $CHCl_3$–EtOAc (3:2) was isolated compounds **1** and **2**. The separation of these compounds was achieved by prep. TLC using toluene–EtOAc (4:1).

8-Hydroxy-7-(3'-methyl-2'-butenyloxy)coumarin (**1**). $C_{14}H_{14}O_4$, mp 166–167° (toluene–petrol); UV λ_{max}^{EtOH} nm: 322 (log ε 4.47) and 263 (log ε 4.29); λ_{max}^{EtONa} nm: 332 (log ε 4.33) and 283 (log ε 4.59); IR ν_{max}^{KBr} cm^{-1}: 3390, 1712, 1268 and 1575; MS *m/z* (rel. int.): 246 $[M]^+$, (1.9), 178 (100), 150 (27.7), 122 (3.7) and 69 (35.4); (Found: C, 68.25; H, 5.70. Calc. for $C_{14}H_{14}O_4$: C, 68.29; H, 5, 69%.)

7-Hydroxy-8-(3'-methyl-2'-butenyloxy)coumarin (**2**). $C_{14}H_{14}O_4$,

Table 1. ^{1}H NMR data of compounds **1** and **2** (100 MHz, TMS internal standard)

	1			**2**		
	$CDCl_3$	C_6D_6	Δ	$CDCl_3$	C_6D_6	Δ
H-3	6.24 *d*	5.79 *d*	0.45	6.21 *d*	5.84 *d*	0.37
H-4	7.60 *d*	6.55 *d*	1.05	7.60 *d*	6.63 *d*	0.97
H-5	6.98 *d*	6.68 *d*	0.30	7.09 *d*	6.35 *s*	0.74
H-6	6.83 *d*	6.35 *d*	0.48	6.86 *d*	6.34 *s*	0.52
O–CH_2	4.66 *d* (*br*)	4.63 *d* (*br*)	0.03	4.80 *d* (*br*)	4.22 *d* (*br*)	0.58
CH	5.50 *t* (*br*)	5.27 *t* (*br*)	0.23	5.50 *t* (*br*)	5.30 *t* (*br*)	0.20
	1.75 *d* (*br*)		0.35	1.68 *d* (*br*)	1.38 *d* (*br*)	0.32
gem-Me		1.40 *s* (*br*)				
	1.80 *d* (*br*)		0.40	1.75 *d* (*br*)	1.52 *d* (*br*)	0.23

J (Hz): **1** ($CDCl_3$): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2',3' = 7, 3',4' = 3', 5' = 1; **1** (C_6D_6): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2',3' = 7; **2** ($CDCl_3$): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2',3' = 7.5; 3',4' = 0.5 and 3',5' = 1; **2** (C_6D_6): 3,4 = 9.5; *O*-isopent: 2', 3' = 7; 3', 4' = 0.5 and 3',5' = 1.

Table 2. ^{1}H NMR data of compounds **6** and **7** (100 MHz, TMS internal standard)

	6			**7**		
	$CDCl_3$	C_6D_6	Δ	$CDCl_3$	C_6D_6	Δ
H-3	6.23 *d*	5.86 *d*	0.37	6.21 *d*	5.85 *d*	0.36
H-3	7.60 *d*	6.66 *d*	0.94	7.59 *d*	6.65 *d*	0.94
H-5	7.04 *d*	6.52 *d*	0.52	7.15 *d*	6.49 *d*	0.66
H-6	6.93 *d*	6.41 *s*	0.52	6.83 *d*	6.27 *d*	0.56
O–CH_2	4.65 *d* (*br*)	4.30 *d* (*br*)	0.35	4.63 *d* (*br*)	4.71 *d* (*br*)	0.08
CH	5.68 *t* (*br*)	5.40 *t* (*br*)	0.28	5.57 *t* (*br*)	5.72 *t* (*br*)	0.15
OMe	3.97 *s*	3.76 *s*	0.21	3.92 *s*	3.29 *s*	0.63
gem-OMe	1.78 *d* (*br*)	1.42 *d* (*br*)	0.36	1.67 *d* (*br*)	1.52 *d* (*br*)	0.15
	1.80 *d* (*br*)	1.53 *d* (*br*)	0.27	1.72 *d* (*br*)	1.56 *s* (*br*)	0.16

J (Hz): **6** ($CDCl_3$): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2′,3′ = 7; 3′,4′ = 3′,5′ = 1; **6** (C_6D_6): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2′,3′ = 7; 3′,4′ = 1; 3′,5′ = 0.5; **7** ($CDCl_3$): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2′,3′ = 7.5; 3′,4′ = 3′,5′ = 1; **7** (C_6D_6): 3,4 = 9.5; 5,6 = 8.5; *O*-isopent: 2′,3′ = 7.5; 3′,4′ = 3′,5′ = 1.

mp 115–117° (toluene–petrol); UV λ_{max}^{EtOH} nm: 327 (log ε 4.33) and 260 (log ε 4); λ_{max}^{EtONa} nm: 388 (log ε 4.47) and 280 (log ε 3.97); IR ν_{max}^{KBr} cm^{-1}: 3200, 1700, 1618 and 1575; MS *m/z* (rel. int.): 246 $[M]^+$, (1), 178 (100), 150 (18), 122 (2.4) and 69 (34); (Found: C, 68.10; H, 5.75. Calc. for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69%.)

Synthesis of **1**. $NaHCO_3$ (1.25 g) was added to a soln of 7,8-dihydroxycoumarin **3** (1 g) in Me_2CO (100 ml) and the mixture stirred at room temp for 1 hr. 1-Bromo-3-methyl-2-butene (2 g) was then added and the mixture refluxed for 24 hr. On cooling, $NaHCO_3$ (2 g) and 1-bromo-3-methyl-2-butene (2 g) were added and refluxing continued for a further 24 hr. The mixture was allowed to cool and, after filtration, it was evaporated. Separation of the residue by silica gel CC (toluene–EtOAc, 9:1) gave 8-hydroxy-7-isopentenyloxycoumarin (**1**), mp 165–167° (0.93 g, 67%). (Found: C, 68.40, H, 5.65%. Calc. for $C_{14}H_{14}O_4$: C, 68.29, H, 5.69%.)

Synthesis of **2**. 7,8-Hydroxycoumarin (5 g) in HMPT (10 ml) were added to a suspension of NaH (0.85 g, ~ 80%) in HMPT (20 ml) and the mixture stirred at room temp for 1 hr. 1-Bromo-3-methyl-2-butene (4.15 g) was added and after 30 min the mixture was poured into ice H_2O. The solid was filtered and 7-hydroxy-8-isopentenyloxycoumarin (**2**) was separated by CC after eluting with toluene–EtOAc (9:1), mp 115–117° (5.45 g, 79%). (Found: C, 68.15, H, 5.60. Calc. for $C_{14}H_{14}O_4$: C, 68.29, H, 5.69.)

Methylation of **1** *and* **2**. Treatment of **1** and **2** in K_2CO_3 in Me_2CO with MeI gave 8-methoxy-7-isopentenyloxycoumarin (**6**) and 7-methoxy-8-isopentenyloxycoumarin (**7**) in quantitative yields.

8-Methoxy-7-isopentenyloxycoumarin (**6**). Mp 99–100° (EtOH) (lit [2], 101°) (Found: C, 69.30, H, 6.05. Calc. for $C_{15}H_{16}O_4$: C, 69.23, H, 6.15%); UV λ_{max}^{EtOH} nm: 320 (log ε 4.12) and 260 (log ε 3.51); IR ν_{max} cm^{-1}: 1735, 1610 and 1567.

7-Methoxy-8-isopentenyloxycoumarin (**7**). Mp 60–65° (EtOH) (Found: C, 69.25, H, 6.00. Calc. for $C_{15}H_{16}O_4$: C, 69.23, H, 6.15%); UV λ_{max}^{EtOH} nm: 320 (log ε 4.41) and 260 (log ε 4.17), IR ν_{max} cm^{-1}: 1725, 1615 and 1567.

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