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6-METHOXYFLAVONOIDS FROM *BRICKELLIA CALIFORNICA*

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Key Word Index—*Brickellia californica*; Compositae; Eupatorieae; Alomiinae; 6-methoxyflavonol methyl ethers, glycosides and sulfates; 6-methoxyflavone methyl ethers.

Abstract—Two new and eleven known 6-methoxyflavonoids were identified in leaf tissue of *Brickellia californica*. The new flavonols are eupatin 3-SO_3 $Ca_{1/2}$ and patuletin 3-SO_3K. The known compounds include the flavones hispidulin and eupafolin and their respective 7- and 4′-monomethyl ethers and the flavonols; spinacetin, eupatin, patuletin 3-glucoside and 3-galactoside, and eupatolitin 3-galactoside.

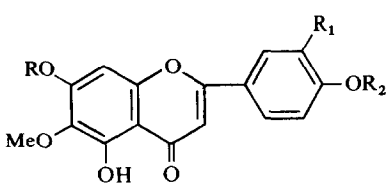
INTRODUCTION

The New World genus *Brickellia*, with *ca* 100 species, is one of the largest taxa in the tribe Alomiinae (Eupatorieae) of the Compositae. Although the species are distributed from the Canadian border, southward through the western US and Mexico and sparingly into Central and South America, the greatest concentration is in the southwestern US and Mexico. This report is the first of a series on the flavonoid chemistry of *Brickellia* and describes the isolation and characterization of 13 6-methoxyflavonoids including two new sulfated flavonols from *Brickellia californica* (T. & G.) Gray.

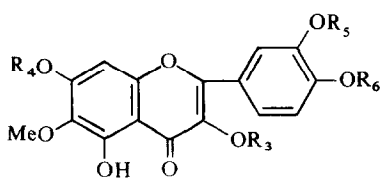
RESULTS

Leaves of *Brickellia californica* were extracted with aqueous methanol and the concentrated extract partitioned between water–chloroform and water–ethyl acetate. The $CHCl_3$ and EtOAc layers yielded 6-methoxyapigenin (**1**) [1–4] (hispidulin); 6-methoxyapigenin 7-methyl ether (**2**) [4–7] (cirsimaritin); 6-methoxyapigenin 4′-methyl ether (**3**) [3, 8–11] (pectolinarigenin); 6-methoxyluteolin (**4**) [3, 12–14] (eupafolin); 6-methoxyluteolin 7-methyl ether (**5**) [15, 16] (cirsiliol); 6-methoxyluteolin 4′-methyl ether (**6**) [17] (desmethoxycentaureidin); 6-methoxyquercetin 3′-methyl ether (**7**) [18, 19] (spinacetin); and 6-methoxyquercetin 7,4′-dimethyl ether (**8**) [20] (eupatin). Three glycosides were isolated from the EtOAc and water layers: patuletin (6-methoxyquercetin) 3-glucoside (**9**) and patuletin 3-galactoside (**10**) [18, 21, 22], and eupatolitin (6-methoxyquercetin 7-methyl ether) 3-galactoside (**11**) [21, 23]. Glycosides **9** and **10** were isolated as a mixture and determined by MS of their permethyl ethers.

Two new sulfated flavonols were isolated from the water layer: eupatin 3-$SO_3Ca_{1/2}$ (**12**) and patuletin 3-SO_3K (**13**). The ^1H NMR spectrum of **12** in DMSO exhibited three methoxyl signals at δ 3.81, 3.89 and 3.93, in addition to a broad singlet at δ 6.4 (H-8), a doublet (J = 9 Hz) at 7.04 (H-5′), a double doublet (J = 2.5 and 9 Hz) at 7.82 (H-6′) and a doublet (J = 2.5 Hz) at 7.68 (H-2′). When **12** and **13** were hydrolysed with either 0.1 N TFA or sulfatase, they yielded, respectively, eupatin and patuletin. The sulfate group in the hydrolysate gave a precipitate with $BaCl_2$ and the cations in the same solution were determined to be Ca and K, respectively, by atomic absorption spectroscopy. Since both **12** and **13** were purple when viewed on paper over UV light and hydrolysed to known aglycones with free 3-hydroxyl groups, at least one sulfate group could be assigned to C_3 in both compounds. Moreover electrophoretic migrations on paper for both **12** and **13** were in



Hispidulin (**1**) R, R_1, R_2 = H
Cirsimaritin (**2**) R = Me; R_1, R_2 = H
Pectolinarigenin (**3**) R, R_1 = H; R_2 = Me
Eupafolin (**4**) R, R_2 = H; R_1 = OH
Cirsiliol (**5**) R = Me; R_1 = OH; R_2 = H
Desmethoxycentaureidin (**6**) R = H; R_1 = OH; R_2 = Me



Spinacetin (**7**) R_3, R_4, R_6 = H; R_5 = Me
Eupatin (**8**) R_3, R_5 = H; R_4, R_6 = Me
Patuletin 3-glc (**9**) R_3 = glc; R_4, R_5, R_6 = H
Patuletin 3-gal (**10**) R_3 = gal; R_4, R_5, R_6 = H
Patuletin R_3, R_4, R_5, R_6 = H
Eupatolitin 3-gal (**11**) R_3 = gal; R_4 = Me; R_5, R_6 = H
Eupatolitin R_3, R_5, R_6 = H; R_4 = Me
Eupatin 3-$SO_3Ca_{1/2}$ (**12**) R_3 = $SO_3Ca_{1/2}$; R_4, R_6 = Me; R_5 = H
Patuletin 3-SO_3K (**13**) R_3 = SO_3K; R_4, R_5, R_6 = H

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accord with monosulfates. That only one sulfate group was present in **12** was confirmed when methylation with diazomethane followed by hydrolysis of the sulfate group gave 3-hydroxy-5,6,7,3′,4′-pentamethoxyflavone: methoxyl ^{1}H NMR signals at δ 3.94, 3.98, 4.00, 4.01 and 4.06, H-8 at 6.82 (*s(br)*), H-2′ at 7.86 (*d*, J = 2 Hz), H-5′ at 7.04 (*d*, J = 9 Hz) and H-6′ at 7.86 (*dd*, J = 2 and 9 Hz); MS: $M^{+\cdot}$ *m/z* 388 (80%) for $C_{20}H_{20}O_6$, M − Me *m/z* 373 (100%) and B_2 *m/z* 165 (85%). The latter B_2 ion, $[C_6H_3(OMe)_2CO]$, requires two methoxyl groups in the B-ring. Since compound **13** exhibited the same electrophoretic mobility as did **12**, it must also contain only one sulfate group and must therefore be patuletin 3-sulfate.

EXPERIMENTAL

Plant material. Leaves and vouchers of *B. californica* were collected in Fort Davis, Chisos Mountains, Texas (A. M. Powell 3177, 3228, 916). Voucher specimens are deposited in the Herbarium, Sul Ross University, Alpine, Texas. All plant material was air-dried prior to extraction.

General techniques. Column chromatography employed polyamide, Polyclar AT (GAF Corp) and Sephadex LH-20 (Pharmacia); PC and electrophoresis were carried out on Whatman 3MM paper. Precoated cellulose plates (E. Merck); polyamide, Polygram, Polyamid-6 (Macherey-Nagel and Co.) and Si gel 60 GF-254 (E. Merck) were used for TLC. PLC was carried out with microcrystalline cellulose (E. Merck) and polyamide MN-Polyamid-DC 11 (Macherey-Nagel and Co.). The solvent systems were: BPMM$_1$, (C_6H_6–petrol (65–110°)–MeCOEt–MeOH, 60:26:3.5:3.5); BPMM$_2$ (C_6H_6–petrol (65–110°)–MeCOEt–MeOH, 60:26:7:7); BMM (C_6H_6–MeCOEt–MeOH, 4:3:3); CAA ($CHCl_3$–Me_2CO–HCO_2H, 9:2:1); BPA (C_6H_6–Py–HCO_2H, 36:9:5); TBA (*t*-BuOH–HOAc–H_2O, 3:1:1) and *n*-BAW, upper layer (*n*-BuOH–HOAc–H_2O, 4:1:5). Visualization of the flavonoids on paper and TLC plates was either by UV light + NH_3 or by spraying with NA (Naturstoffreagenz-A, Carl Roth, Germany) in MeOH. Hydrolyses were carried out with 0.1 N TFA on a steam cone for 30 min for the sulfated flavonoids and 50 min for the flavonoid glycosides. Mps were not corr. The analysis of Ca and K was carried out on a Perkin Elmer 306 spectrophotometer. All the flavonoids were purified over Sephadex LH-20 using MeOH or 80% aq. MeOH prior to spectral analyses (see Tables 1–5) by standard procedures [24, 25].

Extraction, purification and identification of flavonoids from Brickellia californica. Ground leaf material of *Brickellia californica* (65 g) was extracted × 5 with 1 l. aq. MeOH (80 and 50%) until the extract was colorless. The extracts were combined and evapd under red. pres. until only H_2O remained. The aq. layer was extracted with (1) 1 l. $CHCl_3$ and (2) 1.2 l. EtOAc.

The $CHCl_3$ extract (1) was chromatographed over a polyamide column (7.5 × 100 cm; 560 g) packed in the elution solvent. The column was eluted with (1) $CHCl_3$–MeOH–MeCOEt–2,4-pentanedione (20:10:5:1) and (2) $CHCl_3$–MeOH–MeCOEt–2,4-pentanedione (1:1:0.5:0.1). Cirsimaritin (**2**) and pectolinarigenin (**3**) eluted together and were further sep. on a small polyamide column with BPMM$_1$. Cirsiliol (**5**) and desmethoxycentaureidin (**6**), found in low concn (8 mg of each), were separated by PLC on polyamide with BPMM$_2$ while 40 mg of yellow needles of hispidulin (**1**), mp 235° (dec.), were obtained.

The EtOAc extract (2) was chromatographed on a polyamide column using the same conditions as above. Eupatin (**8**), 15 mg, was isolated from a polyamide column using $CHCl_3$–MeOH–MeCOEt–2,4-pentanedione (20:10:5:1), as yellow needles, mp 245°. Eupafolin (**4**) and spinacetin (**7**) were further separated on a polyamide column with MeCOEt–MeOH–2,4-pentanedione (10:5:1). Eupatolitin 3-galactoside (**11**) eluted separately from patuletin 3-glucoside (**9**) and 3-galactoside (**10**). The latter two compounds (6 mg) could not be separated by PC, TLC or column chromatography. UV spectra clearly indicated a patuletin 3-glycoside and after hydrolysis of the mixture, the aglycone was identified as patuletin and the sugars as glucose and galactose. MS of the permethyl ethers and mobility of the natural products on TLC established the presence of two monoglycosides rather than a diglycoside.

Table 1. Chromatographic data (R_fs × 100 and colours) for flavonoids of *Brickellia californica**

Compound	Cellulose HOAc 15%	Cellulose HOAc 40%	Cellulose TBA	Cellulose *n*-BAW	Polyamide BMM	Polyamide BPMM$_2$	Silica gel CAA	Silica gel BPA	Colours UV (350)†	Colours UV/NH$_3$ (350)†	Colours UV/NA (254)†
Hispidulin (**1**)	8	43	92	91	61	10	48	42	p	w-y	w-ol-y
Cirsimaritin (**2**)	13	56	96	95	81	53	82		p	w-y	w-o
Pectolinarigenin (**3**)	13	56	96	95	80	44			p	p	p
Eupafolin (**4**)	2	23	70	75	36	3		21	p	y	or-y
Cirsiliol (**5**)	5	38	83	86	42	75			p	y	or-y
Desmethoxycentaureidin (**6**)	5	39		86	71		49	39	p	p	w-ol
Spinacetin (**7**)	3	26	67	77	58	6			y	y	ol-g
Eupatin (**8**)	5	37	75	84	76	39	57	48	y	y	g
Patuletin 3-glc (**9**)	39	65	60	61	27	0	3		p	y	or-y
Patuletin 3-gal (**10**)	39	65	60	61	27	0	3		p	y	or-y
Patuletin	2	18	55	69	33	1	28	15	ol-y	ol-y	or-y
Eupatolitin 3-gal (**11**)	46	79	60	66	43	10	1	4	p	y	or-y
Eupatolitin	2	28	52	71	60	8	37	30	y	y	or-y
Eupatin 3-SO_3 $Ca_{1/2}$ (**12**)	60	85	44	56	2	0	3	2	p	p	p
Patuletin 3-SO_3K (**13**)	36	67	28	48	0	1	10	0	p	y	or-y

* The chromatograms (TLC) were developed in one dimension with: cellulose microcrystalline Merck; polyamide MN (polygram) and Si gel GF 254 Merck; all solvent systems are described in the Experimental.

† UV, long wavelength 350 nm; short wavelength 254 nm. Colours are indicated as follows: p = purple; y = yellow; ol = olive; or = orange; g = green; w = weak. NA refers to Naturstoffreagenz A in MeOH.

Table 2. UV-data for flavonoids from *Brickellia californica**

Compound	MeOH + HCl† (λ max, nm)		MeOH (λ max, nm)		NaOMe (λ max, nm)		$AlCl_3$ (λ max, nm)		$AlCl_3$–HCl (λ max, nm)		NaOAc (λ max, nm)		NaOAc–H_3BO_3 (λ max, nm)	
Hispidulin (1)	—		334	274	390	326	358	296	352	296	382	326*sh*	338	276
					274		280*sh*		260*sh*		302	274		
Cirsimaritin (2)	—		330	274	380	290*sh*	358	296	352	294	378	272	332	274
					272		258*sh*		260*sh*					
Pectolinarigenin (3)	—		330	274	366	290*sh*	354	300*sh*	370	300*sh*	370	300*sh*	334	274
					274		292	258*sh*	274		274			
Eupafolin (4)	—		344	272	396	330*sh*	416	335*sh*	362	280	394	330*sh*	366	262
			252		264		298*sh*	272	260		268			
Cirsiliol (5)	—		340	272	400	338*sh*	374	276	366	282	394	270	356	272
			235*sh*		262		258*sh*		258					
Desmethoxycentaureidin (6)	—		340	272	380	298*sh*	370	292*sh*	362	286	372	272	342	274
			238*sh*		268	238*sh*	280	260	258					
Spinacetin (7)	—		364	274*sh*	394	330*sh*	420	300*sh*	420	365*sh*	380	266	364	256
			254		270		266		304*sh*	266				
Eupatin (8)	—		362	256	408	335*sh*	416	365*sh*	416	366*sh*	392	256	362	256
					266	230*sh*	306*sh*	266	302*sh*	266				
Patuletin 3-glc (9)	—		354	266*sh*	412	324	428	302*sh*	378	300*sh*	396	330*sh*	376	260
Patuletin 3-gal (10)	—		254		272		272		266		270			
Patuletin	—		368	272*sh*	420	334*sh*	458	270	430	378*sh*	400	336*sh*	390	262
			256		242				264		272			
Eupatolitin 3-gal (11)	—		358	268*sh*	410	278	440	278	376	284*sh*	430	267	378	262
			258						270					
Eupatolitin	—		368	276*sh*	434	284	450	326*sh*	432	378*sh*	394	258	386	262
			256				274		268					
Eupatin 3-$SO_3Ca_{1/2}$ (12)	362	272*sh*	336	286	394	326	376	300*sh*	370	300*sh*	342	270	346	268*sh*
	266		250*sh*		276		276	268	278	266	256		256	
Patuletin 3-SO_3K (13)	368	256	348	268*sh*	404	336	434	334*sh*	372	274*sh*	386	326*sh*	378	262
			256		270		304*sh*	276	266		270			

* All UV spectra were recorded using standard procedures [24, 25].

† The UV spectra of sulfated flavonoids with added reagents are best compared with the spectrum of the compound in MeOH–HCl not MeOH. Rules for the UV spectral analysis of sulfated flavonoids are presently being formulated.

The H_2O remaining after the $CHCl_3$ and EtOAc extractions yielded the following flavonoids when chromatographed over Sephadex LH-20 using 80% aq. MeOH and MeOH: additional 10 mg of eupatolitin 3-galactoside (**11**), 5 mg of a mixture of patuletin 3-glucoside (**9**) and 3-galactoside (**10**), eupatin 3-$SO_3Ca_{1/2}$ (**12**) (6 mg) and patuletin 3-SO_3K (**13**) (4 mg). Additional material of **12** and **13** was obtained from another *Brickellia* species (*B. laciniata*) in order to complete the structure studies described here. All the flavonoids of *B. laciniata* will be reported later.

The presence of a sulfate group in both **12** and **13** was indicated by high voltage electrophoresis (1.5 kv) on Whatman 3 MM paper (27 × 46 cm) for 1.5 hr at pH 1.9 (HCO_2H–HOAc–H_2O, 33:147:1820). **12** and **13** both migrated 3.5 cm from the origin, typical for monosulfates.

Hydrolysis of **12**. 5 mg of **12** were hydrolysed in 5 ml of 0.1 N TFA on a steam cone for 30 min. 1.5 mg of **12** was hydrolysed with 20 mg of sulfatase from limpets, type V, 1000 units (Sigma—8629) at 37° for 3 hr. EtOAc extraction of both hydrolysates yielded eupatin. The H_2O layer yielded a white ppt. of $BaSO_4$ upon addition of $BaCl_2$.

Methylation of eupatin 3-$SO_3Ca_{1/2}$ (**12**). **12** (20 mg) in 5 ml of ice-cooled DMSO was treated with 20 ml of an Et_2O soln containing a 30-molar excess CH_2N_2. The stoppered reaction flask was covered with aluminium foil and stirred at room temp. for 24 hr. The reaction soln was checked for permethylation by spot-paper testing with $FeCl_3$ after removal of Et_2O with N_2. The reaction was repeated ×5 before methylation was complete. Then the Et_2O was removed under a stream of N_2 and the DMSO evapd under high vacuum. The methylated derivative, on hydrolysis with 0.1 N TFA in a steam cone for 30 min, gave (after purification over Sephadex LH-20) 3-hydroxy-5,6,7,3′,4′-pentamethoxyflavone and sulfate.

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Table 3. MS-data for flavonoid aglycones from *Brickellia californica**

Compound	M^+	$[M-H]^+$	$[M-Me]^+$	$[M-18]^+$	$[M-HCO]^+$	$[M-COMe]^+$	$[A_1-Me]^+$	$[A_1-MeCO]^+$	$[A_1-MeCO-CO]^+$	$[B_1]^+$	$[B_2]^+$
Hispidulin (1)	300	299	285	282	271	257	167	139	111	118	121
	(100)	(24)	(76)	(60)	(25)	(73)	(33)	(44)	(12)	(40)	(26)
PDM-Hispidulin (1)	351	350	336	333	322	308	201	173	145	135	138
	(64)	(20)	(100)	(12)	(24)	(10)	(23)	(50)	(31)	(32)	(25)
PDM-Cirsimaritin (2)	348	347	333	330	319	305	198	170	142	135	138
	(48)	(7)	(100)	(3)	(3)	(3)	(9)	(27)	(8)	(21)	(11)
Pectolinarigenin (3)	314	313	299	296	285	271	167	139	111	132	135
	(100)	(11)	(93)	(15)	(22)	(69)	(19)	(21)	(10)	(45)	(12)
PDM-Cirsiliol (5)	381	380	366	363	352	338	198	170	142	168	171
	(26)	(4)	(100)	(2)	(2)	(1)	(2)	(10)	(2)	(4)	(2)
Desmethoxycentaureidin (6)	330	329	315	312	301	287	167	139	--	148	151
	(100)	(18)	(85)	(26)	(32)	(66)	(25)	(32)		(11)	(8)
PDM-Spinacetin (7)	414	413	399	396	385	---	201	173	145	---	168
	(78)	(45)	(100)	(29)	(1)		(9)	(17)	(11)		(12)
PDM-Eupatin (8)	411	410	396	393	382	368	198	170	142	165	168
	(87)	(49)	(100)	(35)	(2)	(2)	(4)	(7)	(1)	(2)	(6)
Patuletin	332	331	317	314	303	289	167	139	111	134	137
	(100)	(20)	(24)	(59)	(18)	(98)	(6)	(6)	(2)	(4)	(36)
Eupatolitin	346	345	331	328	317	303	181	153	125		137
	(100)	(18)	(13)	(42)	(14)	(96)	(3)	(11)	(2)		(40)

* MS were recorded at 70 eV, source temp. 200° and probe temp. from 50 to 425°. Values are given in *m/z* and in parentheses the % abundance relative to the base peak. The A_1, B_1 and B_2 terminology for the fragments is given in ref. [26].

Table 4. MS-data for flavonoid glycosides from *Brickellia californica**

Compound	M^+	$[Agly\dagger+2]^+$	$[Agly\dagger+H]^+$	$[Agly\dagger]^+$	$[Agly\dagger+2-Me]^+$	$[Agly\dagger+H-Me]^+$	$[Agly\dagger-Me]^+$	$[A_1]^+$	$[A_1-15]^+$	$[A_1-43]^+$	$[B_2]^+$
Mixture of PDM-Patuletin 3-glc(9)	630	401	400	399	386	385	384	216	201	173	171
and PDM-Patuletin 3-gal (10)	(<1)	(15)	(45)	(100)	(5)	(14)	(44)	(3)	(10)	(15)	(23)
Mixture of PM-Patuletin 3-glu (9)	606	389	388	387	374	373	372	210	195	167	165
and PM-Patuletin 3-gal (10)	(4)	(50)	(100)	(10)	(21)	(57)	(5)	(2)	(7)	(10)	(25)
PDM-Eupatolitin 3-gal (11)	627	398	397	396	383	382	381	213	198	170	171
	(<1)	(46)	(100)	(31)	(19)	(37)	(15)	(3)	(12)	(17)	(20)
Hexose-fragment peaks											
PDM-glycosides:	230	196	161	149	133	122	114	107	95		
	(20)	(21)	(15)	(13)	(19)	(20)	(46)	(75)	(28)		
PM-glycoside:	218	187	155	143	127	116	111	101	89		
	(18)	(22)	(14)	(13)	(20)	(21)	(41)	(70)	(25)		

* Spectra were recorded under the same conditions as described in Table 3.
† Agly: Aglycone fragment.

Table 5. NMR spectra of *Brickellia californica* flavonoids*

Compound	H-2′	H-6′	H-5′	H-3′	H-8	H-3	Sugar H_1'	Sugar H_2''-H_6''	4′	CCl_4 6	CCl_4 7	−OMe† 4′	−OMe† C_6D_6 6	−OMe† 7
(1)	7.46 *d*	7.46 *d*	6.58 *d*	6.58 *d*	6.26	6.04				3.46				
	(9.0)	(9.0)	(9.0)	(9.0)										
(8)	7.60 *d*	7.64 *dd*	6.86 *d*		6.52				3.88	3.94	3.72	3.32	3.90	3.24
	(2.5)	(2.5, 9.0)	(9.0)									Δ = +0.56	Δ = +0.04	Δ = +0.48
(11)	7.32 *d*	7.72 *dd*	6.82 *d*		6.52									
	(2.5)	(2.5, 9.0)	(9.0)				5.62 *d* (7)	3.4–3.9 *m*		3.92	3.74		3.70	3.16
													Δ = +0.22	Δ = +0.58

* Spectra were recorded in CCl_4 and C_6D_6 (only OMe signals are recorded for this solvent) on a Varian HA 100 spectrometer. Values are given in ppm (δ-scale) relative to TMS as an internal standard. Numbers in parentheses denote coupling constants in Hz. Signals are singlets unless otherwise stated: *d* = doublet; *dd* = double doublet; *m* = multiplet.

† Some OMe signal assignments may need to be interchanged especially in CCl_4. Additional material to record the spectra of these compounds was obtained from *B. laciniata*, a species still under investigation.

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