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METHOXYLATED FLAVONOIDS FROM *ARTEMISIA*

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Key Word Index—*Artemisia*; Compositae; flavonoids; methyl ethers of apigenin, kaempferol, quercetin and quercetagetin; dihydroquercetin 7,3′-dimethyl ether.

Abstract—One new and six known flavonoid methyl ethers were isolated variously from seven *Artemisia* taxa. The new natural product, dihydroquercetin 7,3′-dimethyl ether, was obtained from *A. pygmaea.* The known compounds were apigenin 4′-methyl ether, kaempferol 6-methyl and 3,6,7-trimethyl ethers, quercetin 7,3′-dimethyl ether and the 3,6-dimethyl and 3,6,7-trimethyl ethers of quercetagetin.

INTRODUCTION

IN CONTINUATION of the intensive biochemical investigation of the genus *Artemisia*[1–11] we report the isolation of seven flavonoid methyl ethers from seven *Artemisia* taxa. One of the natural products, dihydroquercetin 7,3′-dimethyl ether (I), isolated from *A. pygmaea*, is a new dihydroflavonol. The previously known constituents, quercetin 7,3′-dimethyl ether (rhamnazin) (II)[12–14] and apigenin 4′-methyl ether (acacetin) (III),[15–17] were also present in *A. pygmaea* Gray. *A. tridentata* Nutt. ssp. *tridentata* f. *parishii* (Gray) Beetle, *A. tridentata* Nutt. ssp. *vaseyana* (Rydb.) Beetle f. *spiciformis* (Osterhout) Beetle and *A. rothrockii* Gray yielded the known flavonols quercetagetin 3,6-dimethyl ether (axillarin) (IV)[18,19] and quercetagetin 3,6,7-trimethyl ether (V).[20] In addition, *A. tridentata* Nutt. ssp. *vaseyana*

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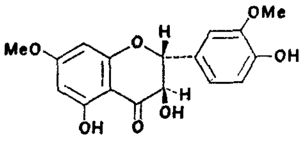
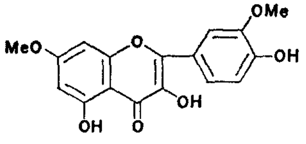
(Rydb.) Beetle afforded kaempferol 3,6,7-trimethyl ether (penduletin) (VI).[21,22] *Artemisia longiloba* (Osterhout) Beetle and *A. arbuscula* Nutt. ssp. *arbuscula* both contained penduletin as the major constituent; the latter species also contained V and kaempferol 6-methyl ether (VII)[23] (see Table 1).



(I)



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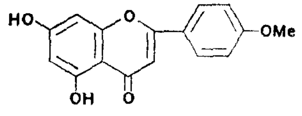

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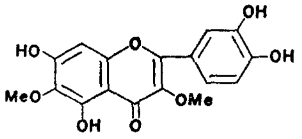

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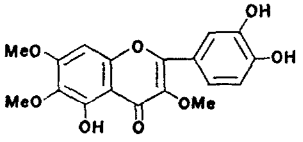

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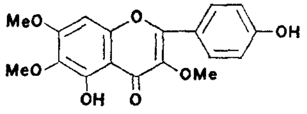

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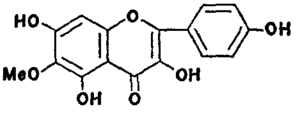

(VII)

TABLE 1. DISTRIBUTION OF METHOXYLATED FLAVONOIDS IN *Artemisia*

Compound	*Artemisia pygmaea*	*A. tridentata* ssp. *parishii*	*A. tridentata* ssp. *vaseyana* f. *spiciformis*	*A. tridentata* ssp. *vaseyana*	*A. arbuscula* ssp. *arbuscula*	*A. longiloba*	*A. rothrockii*
I	+						
II	+						
III	+						
IV		+	+	+			+
V		+	+	+	+		+
VI				+	+	+	
VII					+		

Dihydroquercetin 7,3′-*dimethyl ether* (I)

The NMR spectrum of the trimethylsilyl ether of the new flavonoid indicated that it was a dimethyl ether of dihydroquercetin: 2 methoxyl groups at 3·75* and 3·85; aromatic protons at 6·85–7·0 (H-2′, H-5′ and H-6′); doublets at 6·10 ($J = 2{\cdot}5$) and 5·97 ($J = 2{\cdot}5$), characteristic for H-6 and H-8. The H-2 and H-3 protons exhibited doublets at 4·95 and 4·15, respectively, with a coupling constant of 11 Hz, characteristic for trans diaxial protons.[24,30] In benzene-d_6[25] one observes upfield shifts to 3·45 (+0·40 ppm) and 3·14 (+0·60 ppm) for methoxyl functions at either the 7,3′ or 4′ positions in flavones and flavonols;

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* Values are given in ppm (δ-scale) relative to TMS as an internal standard.

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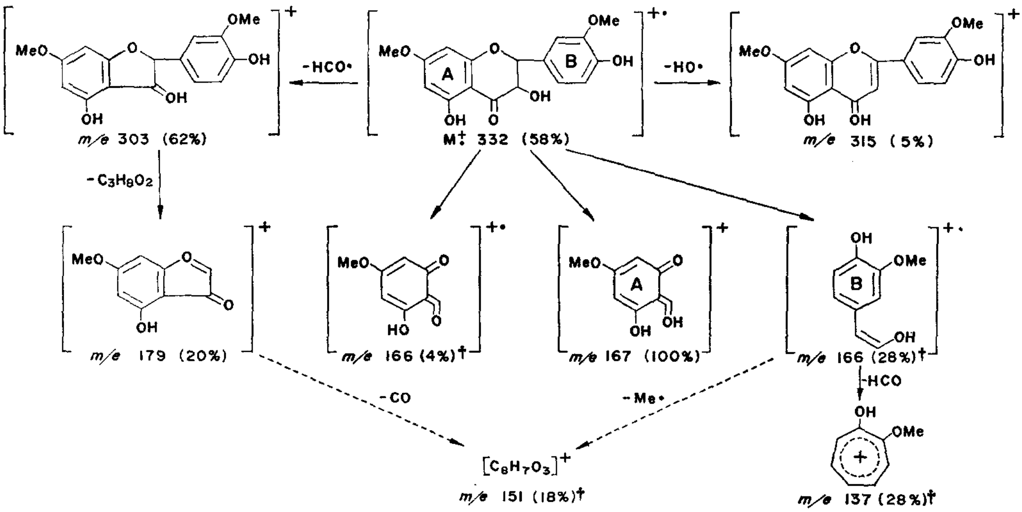
that the 7 and 3′ positions were methoxylated became evident when the natural product was oxidized with bismuth tetra-acetate[26] to quercetin 7,3′-dimethyl ether (rhamnazin) (II).

Mass spectral data supported structure I: parent peak at *m/e* 332 (MW for $C_{17}H_{16}O_7$) and a base peak at *m/e* 167 corresponding to the A-ring fragment formed by retro-Diels–Alder fission of the heterocyclic nucleus accompanied by a hydrogen transfer[27,28] (see Scheme 1).



SCHEME 1. MASS SPECTRAL FRAGMENTATIONS OF DIHYDROQUERCETIN 7,3′-DIMETHYL ETHER*

* Spectra taken at increasing sample temperatures showed increases in the relative intensities of ions at *m/e* 330, 314 and 164 are probably due to thermal loss of H_2, H_2O, and loss of H_2 followed by retro-Diels–Alder fission with charge retention on the *B* ring fragment, respectively.

† The elemental compositions of these ions and the relative intensities of the two *m/e* 166 species were determined by high resolution MS. No structure is given for the *m/e* 151 fragment since the two possible pathways shown cannot be distinguished by MS measurements alone.

TABLE 2. PRINCIPAL IONS (RELATIVE INTENSITIES) IN THE MS OF THREE *Artemisia* FLAVONOLS*

Compound	$M^{+\cdot}$ (%)†	$(M-1)^+$	$(M-Me)^+$	$(M-OH)^+$	$(M-H_2O)^{+\cdot}$	$(M-H_3O)^+$	$(M-CO)^{+\cdot}$	$(M-CHO)^+$	$(M-MeO)^+$	$(M-MeCO)^+$	$(M-CH_2O_2)^{+\cdot}$
IV	346	345 (35)	331 (42)	329 (3)	328 (12)	327 (9)	318 (3)	317 (5)	315 (3)	303 (22)	300 (3)
V	360	359 (40)	345 (55)	343 (10)	342 (10)	341 (20)	332 (2)	331 (7)	329 (8)	317 (12)	314 (5)
VI	344	343 (30)	329 (56)	327 (6)	326 (10)	325 (24)	316 (2)	315 (8)	313 (5)	301 (16)	298 (7)

* MS data for compounds II, III and VII have been reported (see Ref. 17, 12 and 23, respectively).
† All at 100%.

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TABLE 3. NMR SPECTRA OF TRIMETHYLSILYL ETHERS OF METHOXYLATED FLAVONOIDS FROM *Artemisia**

Compound†,‡	H-2′	H-6′	H-3′	H-5′	H-3	H-6	H-8
III	7·80d (*J* 9·0)	7·80d (*J* 9·0)	6·95d (*J* 9·0)	6·95d (*J* 9·0)	6·37	6·55d (*J* 2·5)	6·20d (*J* 2·5)
IV	7·60d (*J* 2·5)	7·65dd (*J* 2·5) (*J* 9·0)	—	6·8d (*J* 9·0)	—	—	6·52
V	7·57d (*J* 2·5)	7·63dd (*J* 2·5) (*J* 9·0)	—	6·90d (*J* 9·0)	—	—	6·50
VI	8·0d (*J* 9·0)	8·0d (*J* 9·0)	6·90d (*J* 9·0)	6·90d (*J* 9·0)	—	—	6·53

* Spectra recorded in CCl_4 on a Varian A-60 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).

† Data for compound I (including C_6D_6 spectrum) are given in the text.

‡ NMR assignments for compounds II and VII in CCl_4 and C_6D_6 have been reported.[12,23]

TABLE 4. NMR SOLVENT SHIFT DATA FOR THE METHOXYL GROUPS OF TRIMETHYLSILYLATED FLAVONOID METHYL ETHERS FROM *Artemisia*

	δ for OMe			
Compound*	CCl_4† (TMS)	C_6D_6 (TMS)	Δ ppm	Position of OMe
III	3·85	3·25	+0·60	C-4′
IV	3·75	3·65	+0·10	C-3
	3·90	3·87	+0·03	C-6
V	3·85	3·82	+0·03	C-3
	3·72	3·73	+0·01	C-6
	3·92	3·30	+0·62	C-7
VI	3·72	3·75	−0·03	C-3
	3·85	3·84	+0·01	C-6
	3·92	3·30	+0·62	C-7

* All compounds with a 5–0 TMS gave the expected downfield shift for this group (−0·10 to −0·17 ppm) in benzene-d_6 (see Ref. 25).

† When more than one methoxyl is present the chemical shift assignments for methoxyls in CCl_4 may be interchanged.

The absolute configuration at C-2 and C-3 in I was determined as $2R{:}3R$ by comparison of the ORD data for I with those for (+)-taxifolin (whose absolute stereochemistry has been shown to be $2R{:}\,3R$);[29] it is known[30] that all simple polyoxygenated dihydroflavonols (and their 3-*O*-glycosides) that possess the *trans* $2R{:}3R$ absolute configuration give CD and ORD curves which exhibit four Cotton effects, in the order (+), (−), (+), (+), from 400 to 220 nm. UV, MS, and NMR data are presented in Tables 2–6 for those compounds for which these spectral data have not been previously reported.

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[30] K. R. MARKHAM and T. J. MABRY, *Tetrahedron* **24**, 823 (1968).

TABLE 5. UV SPECTRA OF *Artemisia* METHOXYLATED FLAVONOIDS*

Compound	MeOH	$AlCl_3$	$AlCl_3$–HCl	NaOMe	NaOAc	NaOAc–H_3BO_3
I	272 350sh	270, 310 380sh	275, 308 375sh	246, 272 357sh	264 385sh	275 355sh
II	252 273sh 302sh 326sh 370	263, 300sh 365sh 425	260, 298sh 359sh 423	270, 304sh 363sh, 450†	252, 273sh 305sh 365†	252, 275sh 305sh 370
III	267 306sh 325	275, 302 342, 380	274, 300 336, 380	275, 295sh 365	275, 296sh 364	268, 329
IV	254 266sh 350	277, 301sh 433	272, 281sh 304sh, 371 410sh	273, 335sh 409†	268, 330sh 380†	263, 378
V	260 273sh 351	277, 308sh 345sh 444	267, 280sh 296sh 373, 400sh	268, 310sh 404†	263, 310sh 405†	262, 375
VI	268 340	280, 303sh 365 400sh	280, 300sh 360, 390sh	274, 302sh 390†	268, 338†	270, 340
VII	255sh 269 294sh 344sh 367	271 306sh 375sh 426	271, 305sh 367, 425	280, 316sh 423†	272, 298 312sh 378†	270, 344sh 368

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

† After 5–10 min one observes 10–30% decomposition.

TABLE 6. CHROMATOGRAPHIC DATA*

Compound	TBA R_f	HOAc R_f	Colors†	
			UV	UV/NH_4OH
I	0·85	0·09	P	P
II	0·79	0·06	Y	Y
III	0·89	0·06	P	P
IV	0·85	0·14	P	Y
V	0·76	0·29	P	Y
VI	0·86	0·27	P	Y
VII	0·81	0·19	Y	Y

* Two-dimensional chromatographs on Whatman 3MM paper were developed first in TBA (*t*-BuOH–HOAc–H_2O, 3:1:1) and then in 15% HOAc.

† P = purple, Y = yellow.

EXPERIMENTAL

All of the methoxylated flavonoids from *Artemisia* were encountered during an investigation of sesquiterpene lactones in this genus.[1]

Isolation of dihydroquercetin 7,3′-dimethyl ether from A. pygmaea. The dry plant (4·67 kg; Voucher specimens deposited in U.C.L.A. Herbarium, No. RJB-81568) consisting mainly of stems and leaves, was milled and extracted with $CHCl_3$ (10 l.). A slurry of the concentrated extract in 75% aq. MeOH (3 l.) was extracted with hexane (3 l.). The hexane phase was extracted with MeOH–H_2O (1:1) and the combined MeOH–H_2O phases were extracted with hexane and concentrated to a gum. The gum was chromatographed over a silica gel column (8 × 45 cm) and eluted in benzene–$CHCl_3$ (1:1). Fractions 3–9 concentrated and taken up in Et_2O yielded dihydroquercetin 7,3′-dimethyl ether (400 mg); m.p. 182–184° (uncorrected). Purification of fractions (3–9) by PC yielded a second compound, rhamnazin (II). On standing the mother liquor yielded 100 mg of acacetin (III), m.p. 245–254°. The sesquiterpene lactones cryptomeridiol and pygmol were also isolated.[1] All other flavonoids were isolated in the same manner with the compounds from each species described in Table 1.

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