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2-METHYL-2-HYDROXYMETHYLCHROMENES FROM *ARTEMISIA CAMPESTRIS* SUBSP. *GLUTINOSA*

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Key Word Index—*Artemisia campestris* subsp. *glutinosa*; Compositae; neutral fraction; chromanones; chromenes.

ıct—From the non volatile neutral part of a hexane extract from *Artemisia campestris* subsp. *glutinosa*, two new 2-l-2-hydroxymethyl chromenes have been isolated. The structures were assigned by spectral methods and ned by partial synthesis.

INTRODUCTION

vious papers, we reported the composition of the ial oil [1] and the weakly acidic fraction [2, 3] of a e extract from the aerial parts of *Artemisia campes-*, subsp. *glutinosa* (Gay ex Besser), Batt.

v, we report the results of a study of the neutral n of a previously steam-distilled hexane extract, ne isolation of two new chromenes, named artemi- **1**, and acetyl artemisenol, **2**, as the first examples of l optically active 2-hydroxymethylchromenes, be- he already known sesquiterpenes phytol, spatulenol, smol, criptomeridiol, oplopanone [4–8], the chro- nes 6-acetyl-2,2-dimethylchromanone, **3**, and 6(1'-xyethyl)-2,2-dimethylchromanone, **4** [9, 10] and the nes dehydrofalcarinol, **5** and dehydrofalcarindiol, 12] not previously reported as components as *A. stris*.

RESULTS AND DISCUSSION

misenol was isolated as a semi-solid mass, with an at $m/z = 218$ ($C_{13}H_{14}O_3$) which by acetylation anhydride–pyridine), gave the monoacetate **2**, spectral data are identical with the natural product. t spectrum of **1**, shows characteristic absorptions of ry OH (3400, 1050 cm^{-1}) and conjugated (C=O, m^{-1}) groups and that of an aromatic ring (1600, m^{-1}). The ^1H NMR spectrum was the expected one structure **1**, showing singlet signals (δ, ppm) at 1.38 1.45 (3H) and 3.50 (2H), which suggest the presence e–C–O, Me–CO and CH_2OH groups in the ene skeleton. The protons at C-3 and C-4 occurred symmetrical AB system at δ 5.58 (1H, *d*, $J = 10$ Hz) 32 (1H, *d*, $J = 10$ Hz); these signals were not present ^1H NMR of the dihydro derivative **7**, obtained by genation of **1** (hydrogen–platinum dioxide). In the tic proton region, signals at 6.60 (1H, *d*, $J = 8$ Hz, 7.35 (1H, *d*, $J = 2$ Hz, H-5) and 7.50 (1H, *dd*, $J = 8$ Hz, H-7), were observed indicating that the MeCO s must be situated at C-6.

stereochemistry at C-2 has not been determined, suggest the (*S*) configuration by comparison of the l rotations of **1**, $[\alpha]_D = +4.5°$ (*c* 0.87, $CHCl_3$) and ıydroderivative **7**, $[\alpha]_D = +2.6°$ (*c* 0.62, $CHCl_3$) with those of the chromane **8** and other analogous compounds [13]. The proposed structure was confirmed by synthesis from **9** [3], (the major component of the weakly acidic fraction of *A. campestris*), by two different methods, A and B. By procedure A, **9** was treated with *m*-chloroperbenzoic acid, giving two racemic products, the chromane **10** (40%) and **11** (60%) which were separated by CC, as acetyl derivatives, **10a** and **11a**. Dehydration of **10**, with $POCl_3$, gave (±) artemisenol, **1**.

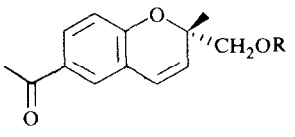
In procedure B, **9** was treated with an acidified mercury acetate–dichloromethane–tetrahydrofuran mixture [14] and then with calcium oxide, to give (±) **7** (yield, 100%). Dehydrogenation of the acetyl derivative (±) **7a** with DDQ gave (±) **2** (yield, 60%).

EXPERIMENTAL

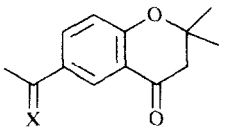
Mps are uncorr. UV spectra were recorded in EtOH. ^1H NMR spectra were recorded at 60 MHz using TMS as an int standard. Analytical TLC was performed on silica gel G (Merck 7748), prep. TLC on silica gel $PF_{234-336}$ and CC on silica gel 60. The plant was identified by Prof. B. Casaseca Mena, Department of Botany, Salamanca University, where a specimen is held (Herbarium No 7362). The aerial parts of the plant (2.64 kg) collected near La Flecha (Salamanca) were finely ground and extracted with hot hexane. The hexane extract, previously steam distilled, consists of 65% (78 g) neutral fraction, 15% acidic fraction and 20% weak acids. The neutral fraction (29 g) was chromatographed on silica gel and eluted with C_6H_6–Et_2O mixtures and Et_2O, giving **5** (41 mg), **6** (1.19 g), phytol (350 mg), spatulenol (194 mg), β-eudesmol (144 mg), criptomeridiol (152 mg), oplopanone (112 mg), **2** (75 mg), **3** (147 mg), **4** (253 mg) and **1** (215 mg).

Artemisenol (*6-acetyl-2-methyl-2-hydroxymethylchromene*) (**1**). Chromatographic fractions eluted with C_6H_6–Et_2O (1:1) (2.5 g) after purification by prep. TLC, afforded 253 mg of **4** and 215 mg of **1**. Compound **1** was obtained as a semi-solid mass. UV λ_{max}^{EtOH} at 250 nm ($\varepsilon = 8.115$), 280 nm ($\varepsilon = 5.500$) and 330 nm ($\varepsilon = 1060$). IR ν cm^{-1}: 3400 (OH), 1680 (C=O), 1600, 1500 (aromatic), 1340, 1180, 1060, 840, 730. ^1H NMR ($CDCl_3$): δ 1.38 (3H, *s*), 2.45 (3H, *s*), 3.50 (2H, *s*), 5.58 (1H, *d*, $J = 10$ Hz), 6.32 (1H, *d*, $J = 10$ Hz), 6.60 (1H, *d*, $J = 8$ Hz), 7.35 (1H, *d*, $J = 2$ Hz), 7.50 (1H, *dd*, $J = 10$ and 2 Hz). MS *m/z* (rel. int.): 218 $[M]^+$ (5), 203 (11), 187 (41), 175 (12), 149 (24), 119 (11), 91 (25), 77 (32), 55 (35), 43 (100).

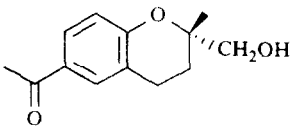
Acetylation of **1**. Acetylation of **1** (40 mg) gave an oily acetate,



1 R = H
2 R = Ac



3 X = O
4 X = H,OH



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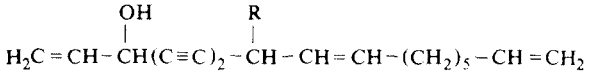
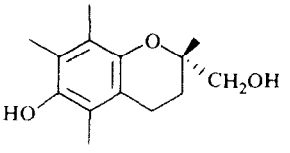


5 R = H
6 R = OH



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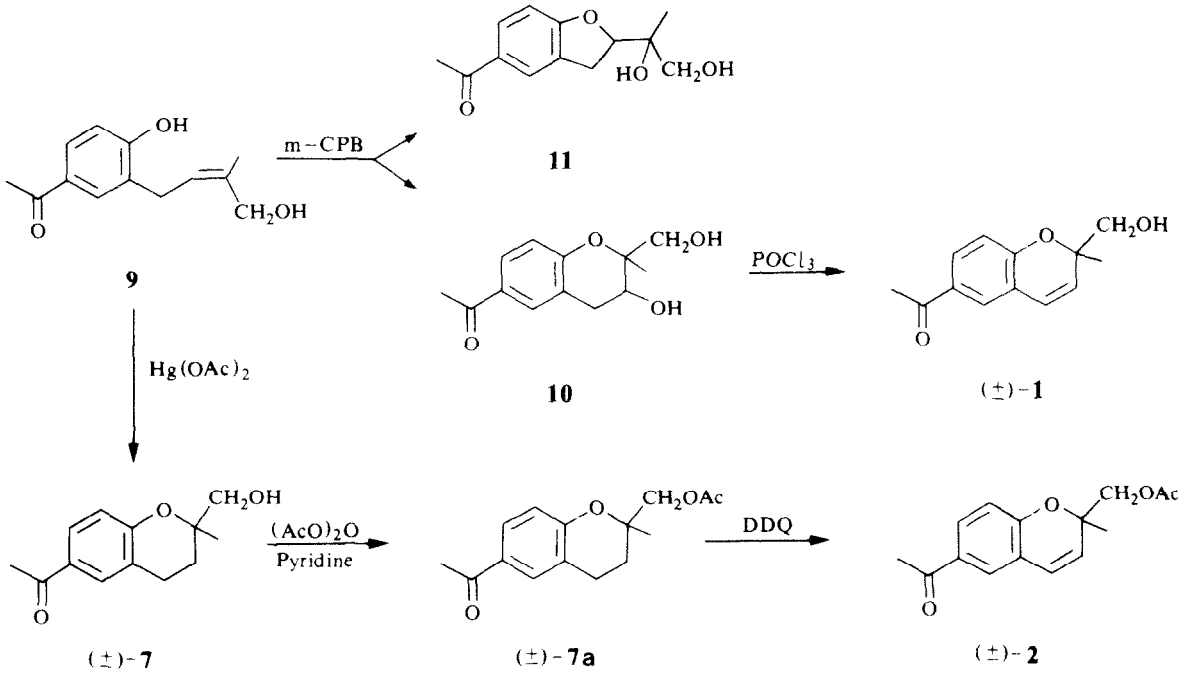

9

11

10

(±)-**1**

(±)-**7**

(±)-**7a**

(±)-**2**

identical in all respects with the natural product **2**. IR ν cm^{-1}: 1730, 1680, 1620, 1580, 1500, 1360, 1260, 1230, 1100, 832, 750. ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, *s*), 2.04 (3H, *s*), 2.54 (3H, *s*), 4.16 (2H, *s*), 5.63 (1H, *d*, J = 10 Hz), 6.50 (1H, *d*, J = 10 Hz), 6.80 (1H, *d*, J = 8 Hz), 7.70 (1H, *d*, J = 2 Hz), 7.80 (1H, *dd*, J = 8 and 2 Hz). MS *m/z* (rel. int.): 260 $[M]^+$ (6), 217 (7), 201 (12), 187 (56), 163 (16), 149 (38), 121 (12), 79 (23), 59 (67), 43 (100).

Hydrogenation of **1**. Compound **1** (50 mg) was hydrogenated (PtO_2-H_2) to give 35 mg of the dihydro derivative **7**. $[\alpha]_D$ = + 2.6° (*c* 0.62, $CHCl_3$). IR ν cm^{-1}: 3400, 1670, 1600, 1500, 1440, 1370, 1265, 1050, 900, 830. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, *s*), 1.90 (2H, *m*), 2.50 (3H, *s*), 3.25 (2H, *m*), 3.80 (2H, *s*), 6.78 (1H, *d*, J = 8 Hz), 7.62 (1H, *d*, J = 2 Hz), 7.70 (1H, *dd*, J = 8 and 2 Hz). MS *m/z* (rel. int.): 220 $[M]^+$ (4), 189 (14), 162 (18), 149 (20), 137 (26), 95 (38), 81 (46), 71 (54), 43 (65), 31 (100).

Synthesis of (±) *artemisenol* (*procedure A*). To a stirred soln of 3-[4-hydroxyisopent-2(*Z*)-enyl]-4-hydroxyacetophenone, **9** (1.186 g), in $CHCl_3$ (18 ml) was added with stirring for 1 hr, a soln of *m*-chloroperbenzoic acid (0.93 g) in $CHCl_3$ (15 ml). A 10% soln of Na_2SO_3 was then added dropwise and the $CHCl_3$ soln was washed × 3 with 5% aq. $NaHCO_3$, dried and evaporated. The residue (968 mg), was acetylated and gave a crude mixture of acetates, which were chromatographed on silica gel to afford 417 mg of (±) **10a** and 588 mg of (±) **11a**.

(±)6-*Acetyl*-3-*acetoxy*-2-*methyl*-2-*acetoxymethylchroman* **10a**. A semi-solid mass mp 115–116°. IR ν cm^{-1}: 1730, 1740, 1680, 1620, 1580, 1500, 1435, 1380, 1360, 1250, 1050, 1030, 950, 840. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, *s*), 2.00 (3H, *s*), 2.08 (3H, *s*), 2.52 (3H, *s*), 3.00 and 3.10 (2H, 2*d*, J = 4 Hz), 4.10 and 4.30 (2H, 2*d* AB system, J = 12 Hz) 5.15 (1H, *t*, J = 4 Hz), 6.85 (1H, *d*, J

58 (1H, *d*, $J = 2$ Hz), 7.75 (1H, *dd*, $J = 8$ and 2 Hz). *etyl-2,3-dihydro-2(1-hydroxy-2-acetoxy-1-methyl-furan* **11a**. A semi-solid mass. IR ν cm^{-1}: 3410, 1740, 1510, 1380, 1260, 1150, 1030, 900, 840. ^{1}H NMR 1.25 (3H, *s*), 2.10 (3H, *s*), 2.50 (3H, *s*), 3.20 (2H, *d*, *J* 40 (1H, *s*, D_2O exchangeable), 4.10 and 4.30 (2H, 2*d* $J = 12$ Hz), 4.85 (1H, *t*, $J = 9$ Hz), 6.70 (1H, *d*, *J* 70 (1H, *dd*, $J = 8$ and 2 Hz), 7.73 (1H, *d*, $J = 8$ Hz). *Hydrolysis of* **10a** *and* **11a**. Alkaline hydrolysis of **10a** d **11a** (190 mg), with aq. KOH (10%, 20 ml) gave the ompounds **10** (180 mg) and **11** (176 mg), respectively. **10** was a solid, mp 82–84°. IR ν cm^{-1}: 3400, 1680, 1500, 1370, 1280, 1130, 1060, 900, 830. ^{1}H NMR 1.15 (3H, *s*), 2.47 (3H, *s*), 2.90 (2H, *t*, $J = 4$ Hz), 3.80 .05 (1H, *t*, $J = 4$ Hz), 6.72 (1H, *d*, $J = 8$ Hz), 7.60 (1H,), 7.63 (1H, *dd*, $J = 8$ and 2 Hz). Compound **11** was a 2–74°. IR ν cm^{-1}: 3400, 1690, 1600, 1500, 1380, 1150, 40. ^{1}H NMR ($CDCl_3$): δ1.17 (3H, *s*), 2.48 (3H, *s*), 3.10 $)_2O$ exchangeable), 3.20 (2H, *d*, $J = 9$ Hz), 3.60 and *l*, AB system, $J = 12$ Hz), 4.85 (1H, *t*, $J = 9$ Hz), 6.72 8 Hz), 7.70 (1H, *dd*, $J = 8$ and 2 Hz), 7.75 (1H, *d*, *J*

ion of **10**. Dehydration of **10** (90 mg) with idine gave a semi-solid compound whose spectral identical with the natural product (±)artemisenol **1**. *of* (±) *artemisenol acetate* (**2**) (*procedure B*). A soln of in CH_2Cl_2–THF–H_2SO_4 (30:1:3 drops, 2 ml) was stirring for 15 hr to $Hg(OAc)_2$ (320 mg). The reaction s decomposed with CaO (3 M, 1 ml), acidified with racted with CH_2Cl_2, giving (±) **7** (98 mg) identical to nation product of **1**. Acetylation of (±) **7** gave (±) **7a**. *of* (±) **7a** *with DDQ*. A soln of chroman (±) **7a** lry C_6H_6 (8 ml) was refluxed with DDQ (80 mg) for 23 hr (the progress of reaction was checked by TLC on silica gel in C_6H_6). The soln was filtered, the filtrate washed succesively with $NaHCO_3$ (5%, 10 ml), H_2O and distilled. The crude product, thus obtained, was purified by CC on silica gel, giving (±) **2**; yield 50 mg.

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