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CHROMANS FROM *EVODIA LEPTA*

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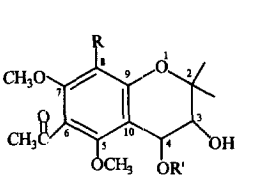
Key Word Index—*Evodia lepta*; Rutaceae; 2,2-dimethylchromans; leptins D–H.

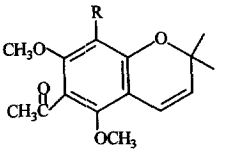
Abstract—Five new compounds, leptins D–H, along with one known chromene, methylevodionol, were isolated from the aerial parts of *Evodia lepta*. Their structures were determined by spectroscopic analysis and chemical techniques as (*trans*)-3,4-dihydroxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman, 3-hydroxy-4-ethoxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman, 3-hydroxy-4-butoxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman, (*trans*)-3,4-dihydroxy-5,7,8-trimethoxy-6-acetyl-2,2-dimethylchroman and 3-hydroxy-4-ethoxy-5,7,8-trimethoxy-6-acetyl-2,2-dimethylchroman, respectively. © 1997 Elsevier Science Ltd

INTRODUCTION

Previous papers reported the isolation and identification of three chromenes, leptol A, ethylleptol A, leptene A and evodione (**7**) [1], and three new 2,2-dimethylchromans, leptins A–C [2] from *Evodia lepta*. As a continuing chemical investigation of the same species, we wish to report the isolation and identification of five new 2,2-dimethylchromans (leptins D–H).



	R	R'
1,1a	H	H
2	H	CH_2CH_3
3	H	$CH_2CH_2CH_2CH_3$
4,4a	OCH_3	H
5	OCH_3	CH_2CH_3



	R
6	H
7	OCH_3

RESULTS AND DISCUSSION

Leptin D (**1**) was obtained as colourless gum. Its ^1H NMR spectrum was very similar to that of compound **6** [3], except that the ^1H resonances at positions 3 and 4 were shifted upfield to δ 3.66 and 4.71, respectively; the coupling constant between these two protons also became smaller (J = 5.2 Hz). Its EI mass spectrum showed the $[M]^+$ at m/z 296, and 34 mu more than that of **6** (M_r 262). The IR spectrum demonstrated the presence of hydroxyl groups (broad band at 3442 cm^{-1}). From above evidence, we could assume that compound **1** was the dihydroxy derivative of **6** at positions 3 and 4. Oxidation of **6** using $KMnO_4$–NaOH gave **1a**, the *cis*-3,4-dihydroxy product; the coupling constant between the protons 3 and 4 was 4.7 Hz. Oxidation of olefins using H_2O_2–HCOOH usually affords the *trans*-dihydroxy product, but we found that oxidation of **6** using this method gave compounds **1** and **1a**, a mixture of *trans*- and *cis*-isomers. **1a** was probably the isomerized product of **1** because the hydroxyl at position 4 was unstable under acidic condition and easily changed its configuration. This inference was confirmed by the following experiment. Compound **1** was dissolved in chloroform containing formic acid and the mixture stirred continuously overnight. By TLC analysis, we found that part of compound **1** was transformed to **1a**. From the above results, compounds **1** and **1a** were established as (*trans*)-3,4-dihydroxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman, and (*cis*)-3,4-dihydroxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman, respectively.

The ^1H and ^{13}C NMR spectra of leptin E (**2**) showed the presence of one ethoxyl group [^1H NMR: δ 3.86–3.64 (2H, *m*, H-1′), δ 1.17 (3H, *t*, J = 7.0 Hz); ^{13}C NMR: δ 65.07 (*t*), 15.92 (*q*)]; the other signals were very similar to those of compound **1**. Its IR spectrum exhibited one hydroxyl absorption at 3437 cm^{-1}. Based on the above evidence, we could infer that compound **2** should be the product of ethylation of **1** at

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Table 1. ^{1}H NMR spectral data for compounds **1–5**, **1a** and **4a**

H	1	1a	2	3	4	4a	5
3	3.66 *d* (5.2)	3.69 *d* (4.7)	3.88 *d* (2.8)	3.88 *d* (2.5)	3.69 *d* (5.0)	3.71 *d* (4.8)	3.91 *d* (2.9)
4	4.71 *d* (5.2)	4.87 *d* (4.7)	4.35 *d* (2.8)	4.34 *d* (2.5)	4.75 *d* (5.0)	4.89 *d* (4.8)	4.39 *d* (2.9)
8	6.21 *s*	6.21 *s*	6.19 *s*	6.19 *s*	—	—	—
CH_3-2	1.42 *s*	1.39 *s*	1.42 *s*	1.42 *s*	1.47 *s*	1.43 *s*	1.47 *s*
	1.30 *s*	1.38 *s*	1.39 *s*	1.39 *s*	1.35 *s*	1.43 *s*	1.43 *s*
CH_3CO-6	2.42 *s*	2.41 *s*	2.41 *s*	2.41 *s*	2.44 *s*	2.43 *s*	2.44 *s*
CH_3O-5	3.81 *s*	3.83 *s*[a]	3.80 *s*	3.79 *s*	3.78 *s*[b]	3.78 *s*[c]	3.76 *s*[d]
CH_3O-7	3.80 *s*	3.81 *s*[a]	3.79 *s*	3.79 *s*	3.86 *s*[b]	3.86 *s*[c]	3.85 *s*[d]
CH_3O-8	—	—	—	—	3.78 *s*[b]	3.80 *s*[c]	3.78 *s*[d]
1′	—	—	3.86–3.64 *m*	3.84–3.62 *m*	—	—	3.85–3.63 *m*
2′	—	—	1.17 *t* (7.0)	1.56 *m*	—	—	1.18 *t* (7.0)
3′	—	—	—	1.41 *m*	—	—	—
4′	—	—	—	0.90 *t* (7.4)	—	—	—

Coupling constants (Hz) in parenthesis.
[a–d] Interchangeable assignments.

Table 2. ^{13}C NMR spectral data for compounds **1–5**

C	1	2	3	4	5
2	78.8	78.1	78.0	79.0	78.3
3	75.3	70.2	69.9	74.9	69.7
4	66.9	73.8	73.8	67.0	73.8
5	158.8	159.6	159.6	152.8	153.5
6	119.2	119.4	119.2	123.4	123.2
7	158.4	158.6	158.5	150.6	150.7[b]
8	96.5	96.5	96.4	138.6[b]	138.5
9	156.2	156.7	156.6	149.3	149.7
10	111.0	108.7	108.5	115.4	113.0
CH_3-2	25.6	25.3	25.3	25.4	25.2
	21.9	24.2	24.0	22.0	24.0
CH_3CO-6	32.6	32.6	32.6	32.6	32.6
C=O	201.3	201.4	201.4	201.2	201.2
CH_3O-5	56.1	56.1	56.1	63.4[c]	63.7[d]
CH_3O-7	63.2	63.7	63.6	62.0[c]	62.0[d]
CH_3O-8	—	—	—	60.8[c]	60.7[d]
1′	—	65.1	69.5	—	65.2
2′	—	15.9	33.0	—	15.8
3′	—	—	20.0	—	—
4′	—	—	14.1	—	—

[a–d] Interchangeable assignments.

position 3 or 4. In its HMBC spectrum, H-4 correlated with C-2, 3, 5, 9, 10, 1′, and H-1′ correlated with C-4; therefore, the ethoxyl group should be assigned to position 4. Thus, leptin E (**2**) was identified as 3-hydroxy-4-ethoxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman. The EI mass spectrum (*m/z* 324 $[M]^+$) confirmed the proposed structure.

Leptin F (**3**) was obtained as colourless oil. Its EI mass spectrum showed the $[M]^+$ at *m/z* 352. The ^{1}H and ^{13}C NMR spectra suggested the presence of a *n*-butoxyl group (Tables 1 and 2). Using the methods described above, we established the structure of **3** as 3-hydroxy-4-butoxy-5,7-dimethoxy-6-acetyl-2,2-dimethylchroman.

Because leptin G (**4**) could be correlated with **7**, using the same methods as the structural elucidation of compounds **1**, **1a** and **2**, we determined the structures of compounds **4**, **4a** and leptin H (**5**) as (*trans*)-3,4-dihydroxy-5,7,8-trimethoxy-6-acetyl-2,2-dimethylchroman, (*cis*)-3,4-dihydroxy-5,7,8-trimethoxy-6-acetyl-2,2-dimethylchroman and 3-hydroxy-4-ethoxy-5,7,8-trimethoxy-6-acetyl-2,2-dimethylchroman, respectively.

The assignment of the ^{1}H and ^{13}C resonances of leptins D–H were performed by analysing their HMBC spectra (Table 3). The ^{13}C resonances of the two methoxyl groups in leptin F were differentiated by analysing its HMQC spectrum. Because leptins D–F shared structural and spectral similarity, the ^{13}C resonances of the methoxyl groups in leptins D and E were differentiated using reasoning similar to that for leptin F. The ^{1}H and ^{13}C signals of methoxyl groups in leptins G and H were assigned interchangeably because we did not carry out further experiments.

EXPERIMENTAL

General. Mps: uncorr. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz): CD_3COCD_3. Chemical shifts are given in δ and refer to CD_3COCD_3 in residual Me_2CO (δ 2.05 for ^{1}H NMR, δ 29.8 for ^{13}C NMR).

Plant material. Aerial parts of *E. lepta* (Spr.) Merr. were collected from Hainan province, Peoples Republic of China, in July, 1992. A voucher sample is deposited in the herbarium of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and isolation. Dried and powdered aerial

Table 3. ^{1}H-^{13}C long-range correlation by HMBC of compounds **1–5** (two or three bond correlation)

	Correlated C				
H	**1**	**2**	**3**	**4**	**5**
3	4, 10	4, 10	4, 10	2, CH_3-2, 4, 10	2, CH_3-2, 4, 10
4	2, 3, 5, 9, 10	2, 3, 5, 9, 10, 1′	2, 3, 5, 9, 10, 1′	2, 3, 5, 9, 10	2, 3, 5, 9, 10, 1′
8	6, 7, 9, 10	6, 7, 9, 10	6, 7, 9, 10	—	—
CH_3-2	CH_3-2*, 2, 3	CH_3-2*, 2, 3	CH_3-2*, 2, 3	CH_3-2*, 2, 3	CH_3-2*, 2, 3
CH_3CO-6	C=O	C=O	C=O	C=O	C=O
CH_3O-5	5	5	5	5	5
CH_3O-7	7	7	7	7	7
CH_3O-8	—	—	—	8	8
1′	—	2′, 4	2′, 3′, 4	—	2′, 4
2′	—	1′	1′, 3′, 4′	—	1′
3′	—	—	1′, 2′	—	—
4′	—	—	2′, 3′	—	—

* The protons of one methyl group at position 2 correlated with carbons of another methyl group at the same position.

parts (10 kg) were extracted ×2 with 95% EtOH at room temp. over 2 weeks. The combined extracts were evapd to dryness under red. pres. (35°) and the residue (250 g) obtained was subjected to CC over silica gel, eluting with petrol–EtOAc (10:1) and $CHCl_3$. Compound **6** was obtained from the petrol–EtOAc eluate by CC over silica gel eluting with a petrol–EtOAc gradient. The $CHCl_3$ eluate (65 g) was fractionated by silica gel CC eluting with a CH_2Cl_2–EtOAc gradient. Fr. 3 was subjected to repeated CC over silica gel, eluting with CH_2Cl_2–EtOAc (10:1) to give compound **3** (30 mg). Compounds **2** (298 mg) and **5** (224 mg) were isolated from fr. 4 by silica gel CC eluting with $CHCl_3$–Me_2CO (15:1). Compounds **1** (60 mg) and **4** (60 mg) were obtained from fr. 6 by silica gel CC eluting with $CHCl_3$–Me_2CO (5:1).

Leptin D (trans-3,4-*dihydroxy*-5,7-*dimethoxy*-6-*acetyl*-2,2-*dimethylchroman*, **1**). $C_{15}H_{20}O_6$. Gum $[\alpha]_D^{15}$ +1.07° (EtOH; *c* 0.420). IR ν_{max}^{film} cm^{-1}: 3442, 2982, 2941, 1695, 1606, 1581, 1468, 1199, 1138, 1103. EI-MS *m/z* (rel. int.): 296 $[M]^+$ (14), 281 (8), 225 (100), 209 (67). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Compound **1a**. $C_{15}H_{20}O_6$. Prisms (EtOAc), mp 133.5–134.5°. IR ν_{max}^{KBr} cm^{-1}: 3525, 3396, 2940, 1664, 1605, 1578, 1257, 1140, 1105. EI-MS *m/z* (rel. int.): 296 $[M]^+$ (13), 225 (100), 209 (78). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Leptin E (3-*hydroxy*-4-*ethoxy*-5,7-*dimethoxy*-6-*acetyl*-2,2-*dimethylchroman*, **2**). $C_{17}H_{24}O_6$. White solid, mp 114.0–116.0°. $[\alpha]_D^{15}$ +9.18° (EtOH; *c* 0.806). IR ν_{max}^{KBr} cm^{-1}: 3437, 2978, 1691, 1606, 1581, 1471, 1246, 1199, 1146, 1107, 1067. EI-MS *m/z* (rel. int.): 324 $[M]^+$ (14), 253 (38), 237 (25), 209 (100). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Leptin F (3-*hydroxy*-4-*butoxy*-5,7-*dimethoxy*-6-*acetyl*-2,2-*dimethylchroman*, **3**). $C_{19}H_{28}O_6$. Oil $[\alpha]_D^{15}$ +0.85° (EtOH; *c* 0412). IR ν_{max}^{film} cm^{-1}: 3450, 2922, 1695, 1605, 1466, 1352, 1244, 1198, 1142, 1105. EI-MS *m/z* (rel. int.): 352 $[M]^+$ (15), 280 (32), 225 (24), 209 (100). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Leptin G (trans-3,4-*dihydroxy*-5,7,8-*trimethoxy*-6-*acetyl*-2,2-*dimethylchroman*, **4**). $C_{16}H_{22}O_7$. Needles (EtOAc), mp 101.0–102.0°. $[\alpha]_D^{18}$ +1.24° (EtOH; *c* 0.403). IR ν_{max}^{KBr} cm^{-1}: 3516, 3415, 2990, 2950, 1693, 1589, 1475, 1292, 1194, 1065. EI-MS *m/z* (rel. int.): 326 $[M]^+$ (46), 254 (71), 239 (100), 211 (45). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Compound **4a**. $C_{16}H_{22}O_7$. Needles (EtOAc), mp 111.0–111.5°. IR ν_{max}^{KBr} cm^{-1}: 3500, 2990, 2930, 1701, 1595, 1292, 1100. EI-MS *m/z* (rel. int.): 326 $[M]^+$ (100), 254 (76), 239 (71), 211 (31). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Leptin H (3-*hydroxy*-4-*ethoxy*-5,7,8-*trimethoxy*-6-*acetyl*-2,2-*dimethylchroman*, **5**). $C_{18}H_{26}O_7$. Prisms (EtOAc), mp 138.0–138.5°. $[\alpha]_D^{26}$ +1.44° (EtOH; *c* 0.265). IR ν_{max}^{KBr} cm^{-1}: 3504, 2998, 2937, 1697, 1606, 1473, 1292, 1199, 1103. EI-MS *m/z* (rel. int.): 354 $[M]^+$ (69), 282 (100), 267 (19), 254 (45), 239 (51). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Oxidation of evodione (**7**) *using* $KMnO_4$-*NaOH to give* **4a** [4]. To a cold mixt. of NaOH (25 mg) and $KMnO_4$ (100 mg) in 2 ml of H_2O was added a soln of evodione (122 mg) in 1 ml *t*-BuOH under stirring. The reaction mixt. was stirred continuously at 0° for 15 min and then extracted with Et_2O, the organic layer washed with brine and dried (Na_2SO_4). Removal of solvent gave a residue which was subjected to CC over silica gel using petrol–EtOAc (1:1) to furnish **4a** (38 mg); yield 30%.

Oxidation of evodione (**7**) *using* H_2O_2-HCO_2H *to give* **4** *and* **4a** [5]. A soln of evodione (305 mg) in CH_2Cl_2 (0.5 ml) was added slowly to a mixt. of HCO_2H (725 μl) and H_2O_2 (180 μl) under stirring. The reaction mixt. was stirred continuously overnight at room temp. HCO_2H and H_2O were removed by distillation under red. pres., then EtOAc (2 ml) was added

to the residue. The soln was neutralized with diluted NaOH soln, the EtOAc layer sepd and the aq. layer extracted with EtOAc (2 ml × 2). The EtOAc layers were combined, washed with brine and dried (Na_2SO_4). Removal of Na_2SO_4 and solvent gave a residue which was subjected to CC over silica gel using petrol–EtOAc (1:1) to afford **4a** (81 mg) and **4** (112 mg).

Oxidation of methylevodionol (**6**) *using* $KMnO_4$-*NaOH to give* **1a** *and using* H_2O_2-HCO_2H *to give* **1** *and* **1a**. The procedures described above were used except that evodione (**7**) was replaced with methylevodionol (**6**).

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