Pergamon

PII: S0031-9422(96)00694-2

Phytochemistry, Vol. 44, No. 6, pp. 1175–1177, 1997

0031-9422/97 $17.00+0.00

CHROMENES FROM *EVODIA LEPTA*

GUO-LIN LI, JIA-FENG ZENG, CHUN-QING SONG and DA-YUAN ZHU*

State Key Laboratory of Drug Research of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, People's Republic of China

(*Received in revised form* 16 *September* 1996)

Key Word Index—*Evodia lepta*; chromenes; leptol A; ethylleptol A; leptene A.

Abstract—Three new chromenes, leptol A, ethylleptol A and leptene A, along with the two known chromenes, isoevodionol and evodione, were isolated from the traditional Chinese herb *Evodia lepta*. The structures were elucidated by spectroscopic analysis and chemical techniques. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

Evodia lepta, a traditional Chinese herb, is widely used as an antipyretic, anti-inflammatory and analgesic; externally it is used to treat trauma, abscesses, wound infections, eczema, dermatitis and haemorrhoids [1]. Its chemical constituents have only been investigated cursorily [2]. In the present paper, we report the isolation and identification of three new chromenes (**3**–**5**) and the known ones, isoevodionol (**1**) [3] and evodione (**2**) [4].

RESULTS AND DISCUSSION

Compound **2** was obtained as prisms, $C_{16}H_{20}O_5$ ($[M]^+ m/z$ 292). Its IR spectrum exhibited the presence of a *gem*-dimethyl group (1380 and 1360 cm^{-1}) and a benzene ring (1590 and 1470 cm^{-1}). The electron impact (EI) mass spectrum and melting point were identical to those of evodione, a known compound the structure of which has been elucidated by total synthesis [5] and chemical decomposition [4] in a previous study. Owing to absence of ^1H NMR and IR spectra of evodione in published articles, without further work we could not be sure that **2** and evodione were same compounds. Therefore, we synthesized evodione from isoevodionol and found that the ^1H NMR and IR spectra of evodione were identical to those of **2**. Thus, the structure of **2** was determined and its ^1H NMR and IR spectra are reported for the first time.

Leptol A (**3**) ($C_{16}H_{22}O_5[M]^+ m/z$ 294) was also shown to be a chromene by comparing its spectral data with those of evodione. Its IR and mass spectra showed the presence of a hydroxyl group (broad band at 3500 cm^{-1} in IR spectrum, and fragment at $[M-15-18]^+$, 22% in the EI-mass spectrum). The ^1H NMR spectrum showed the presence of a $-CH(OH)CH_3$ group. Oxidation of **3** using CrO_3–pyridine [6] gave evodione (**2**) and led to its structure as 6-(1′-hydroxyethyl)-5,7,8-trimethoxy-2,2-dimethyl-2*H*-[1]-benzopyran.

Ethylleptol A (**4**) and leptene A (**5**) were identified as 6-(1′-ethoxyethyl)-5,7,8-trimethoxy-2,2-dimethyl-2*H*-[1]-benzopyran and 6-vinyl-5,7,8-trimethoxy-2,2-dimethyl-2*H*-[1]-benzopyran, respectively, by comparison of their spectral data with those of leptol A (**3**) and chemical reactions. Compound **4** was obtained by ethylation of **3** using the EtOH–HCO_2H method. Dehydrolysis of **3** with formic acid in chloroform (refluxed for two hours) afforded **5**, the ^1H NMR, IR and mass spectra of which were identical to those of the natural product.

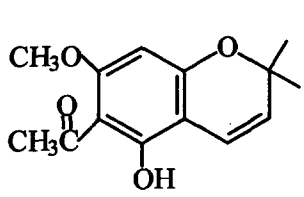
EXPERIMENTAL

General. Mps: uncorr. EI-MS: 70 eV, direct inlet. ^1H NMR: 400 MHz, $CDCl_3$, chemical shifts are given in δ and refer to $CDCl_3$ in the residual $CHCl_3$ (δ 7.24). ^{13}C NMR: 100 MHz, CD_3COCD_3. Chemical shifts are given in δ and refer to CD_3COCD_3 in the residual Me_2CO (δ 29.8).

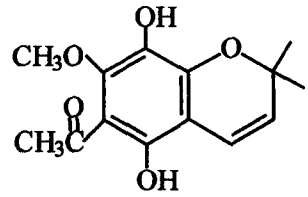
Plant material. Aerial parts of *E. lepta* (Spr.) Merr. were collected from Hainan province, P.R. China, in July 1992. A voucher sample is deposited in the Herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and isolation. Dried and powdered plant material (10 kg) was extracted × 2 with 95% EtOH at

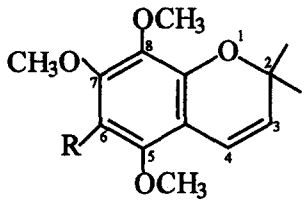
*Author to whom correspondence should be addressed.

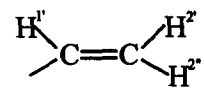


1



6



	R
2	—$COCH_3$
3	—$CH(OH)CH_3$
4	—$CH(OCH_2CH_3)CH_3$
5	

room temp. over 2 weeks. The combined extracts were evapd to dryness under red. pres. (35°) and the residue (250 g) obtained subjected to CC over silica gel, eluting with petrol–EtOAc (10:1) to give an orange oil (80 g). Part of this oil (20 g) was fractionated by silica gel CC eluting with a petrol–EtOAc gradient. The frs obtained were repeatedly chromatographed by silica gel CC using petrol–EtOAc mixts to give the following chromenes (in increasing order of chromatographic polarity): **5** (37 mg), **1** (1504 mg), **4** (327 mg), **2** (1390 mg), **3** (2517 mg).

Evodione (**2**). $C_{16}H_{20}O_5$. Prisms, mp 57° (in EtOAc). IR ν_{max}^{KBr} cm^{-1}: 3040, 2970, 2940, 2840, 1710, 1590, 1470, 1378, 1364, 1240, 1060. ^1H NMR: δ 6.47 (1H, *d*, J = 10.0 Hz, H-4), 5.59 (1H, *d*, J = 10.0 Hz, H-3), 3.86 (3H, *s*, $-OCH_3$), 3.82 (3H, *s*, $-OCH_3$), 3.70 (3H, *s*, $-OCH_3$), 2.48 (1H, *s*, $-COCH_3$), 1.46 (6H, *s*, *gem*-dimethyl). EI-MS *m/z* (rel. int.): 292 $[M]^+$ (17), 277 (100), 247 (18).

Leptol A (**3**). $C_{16}H_{22}O_5$. Orange oil. $[a]_D^{26} = +1.18°$ ($CHCl_3$; *c* 0.398). IR ν_{max}^{KBr} cm^{-1}: 3500, 3040, 2960, 2930, 2830, 1740, 1590, 1465, 1374, 1360, 1230. ^1H NMR: δ 6.46 (1H, *d*, J = 10.0 Hz, H-4), 5.57 (1H, *d*, J = 10.0 Hz, H-3), 5.08 (1H, *q*, J = 6.6 Hz, H-1′), 3.97 (3H, *s*, $-OCH_3$), 3.81 (3H, *s*, $-OCH_3$), 3.73 (3H, *s*, $-OCH_3$), 1.52 (3H, *d*, J = 6.6 Hz, H-2′), 1.48 (3H, *s*, CH_3-2), 1.42 (3H, *s*, CH_3-2). ^{13}C NMR: δ 152.9, 150.2, 146.9, 139.6, 130.0 (C-3), 124.6, 117.9 (C-4), 112.5, 76.9 (C-2), 63.9 (C-1′), 63.5 ($-OCH_3$), 62.0 ($-OCH_3$), 61.0 ($-OCH_3$), 27.9 (*gem*-dimethyl), 24.7 (C-2′). EI-MS *m/z* (rel. int): 294 $[M]^+$ (16), 279 (100), 261 (21), 249 (28), 231 (9).

Ethylleptol A (**4**). $C_{18}H_{26}O_5$. Oil. $[a]_D^{26} = -1.21°$ ($CHCl_3$; *c* 0.347). IR ν_{max}^{KBr} cm^{-1}: 3040, 2970, 2930, 2840, 1590, 1465, 1375, 1360, 1232, 1030. ^1H NMR: δ 6.47 (1H, *d*, J = 10.0 Hz, H-4), 5.54 (1H, *d*, J = 10.0 Hz, H-3), 4.81 (H, *q*, J = 6.6 Hz, H-1′); 3.82 (3H, *s*, $-OCH_3$), 3.81 (3H, *s*, $-OCH_3$), 3.68 (3H, *s*, $-OCH_3$), 3.36 (2H, *m*, H-1″), 1.57 (3H, *d*, J = 6.6 Hz, H-2′), 1.45 (3H, *s*, CH_3-2), 1.42 (3H, *s*, CH_3-2), 1.14 (3H, *t*, J = 7.0 Hz, H-2″). EI-MS *m/z* (rel. int.): 322 $[M]^+$ (18), 307 (100), 277 (16), 263 (16), 247 (10), 217 (6).

Leptene A (**5**). $C_{16}H_{20}O_4$. Pale yellow oil. IR ν_{max}^{KBr} cm^{-1}: 3010, 2960, 2920, 2860, 1585, 1465, 1385, 1366, 1230, 1050, 980, 910. ^1H NMR: δ 6.72 (1H, *dd*, J_1 = 18.1 Hz, J_2 = 11.8 Hz H-1′), 6.54 (1H, *d*, J = 10.1 Hz, H-4), 6.00 (1H, *dd*, J_1 = 18.1 Hz, J_2 = 2.3 Hz, H-2″), 5.57 (1H, *d*, J = 10.1 Hz, H-3), 5.35 (1H, *dd*, J_1 = 11.8 Hz, J_2 = 2.3 Hz, H-2′), 3.83 (3H, *s*, $-OCH_3$), 3.82 (3H, *s*, $-OCH_3$), 3.66 (3H, *s*, $-OCH_3$), 1.45 (6H, *s*, *gem*-dimethyl). EI-MS *m/z* (rel. int.): 276 $[M]^+$ (83), 261 (100), 245 (23), 231 (43), 213 (9).

5,8-*Dihydroxy*-7-*methoxy*-6-*acetyl*-2,2-*dimethyl*-2H-[1]-*benzopyran* (**6**). Emerald prisms, mp 112° (petrol–EtOAc). IR ν_{max}^{KBr} cm^{-1}: 3400, 2970, 2920, 1599, 1460, 1380, 1365, 1243, 1090. ^1H NMR: δ 13.5 (1H, *s*, OH-5), 6.67 (1H, *d*, J = 10.0 Hz, H-4), 5.50 (1H, *d*, J = 10.0 Hz, H-3), 3.96 (3H, *s*, $-OCH_3$), 2.64 (3H, *s*, $-COCH_3$), 1.47 (6H, *s*, *gem*-dimethyl). HR-MS: $[M]^+$ *m/z* 264.0980 (calcd for $C_{14}H_{16}O_5$ 264.0997). EI-MS *m/z* (rel. int.): 264 $[M]^+$ (28), 249 (100), 234 (22), 216 (9), 140 (9).

Synthesis of evodione from isoevodionol. 1. *Preparation of* 5,8-*dihydroxy*-7-*methoxy*-6-*acetyl*-2,2-*dimethyl*-2H-[1]-*benzopyran* (**6**) [7]. Isoevodionol (140 mg, 0.56 mmol) was added to 2 ml aq. soln of KOH (158 mg, 2.82 mmol) and a small quantity of pyridine added to the soln until the material dissolved completely. Then, 3 ml aq. soln of $K_2S_2O_8$ (305 mg, 1.13 mmol) was slowly added over 2 hr at 0°. The mixt. was stirred continuously overnight at room temp., Et_2O (3 ml) added the next day and the mixt. acidified with excess

3 N HCl with stirring for 10 min. The aq. layer was extracted $\times 2$ with Et_2O. The combined Et_2O layers were washed with 5% $NaHCO_3$ soln, dried (Na_2SO_4), evapd *in vacuo* and subjected to CC over silica gel to obtain **6**. 2. *Methylation of* **6** *to give evodione* [8]. Compound **6** (12 mg) in dry Me_2CO (2 ml) was refluxed with Me_2SO_4 (50 μl) in the presence of dry K_2CO_3 (200 mg) for 5 hr, then filtered, inorganic salts washed out with hot Me_2CO and combined, filtered and concd. The residue was subjected to CC eluting with petrol–EtOAc (10:1) to give evodione (**2**) (5 mg). HR-MS: $[M]^+$ *m/z* 292.1313 (calcd for $C_{16}H_{20}O_5$, 292.1311). IR, MS and ^1H NMR data identical to natural product.

Synthesis of **4** *from* **3.** Compound **3** (30 mg) was dissolved in EtOH (3 ml) and HCO_2H (0.5 ml) added to the soln. The mixt. was stirred continuously for 5 hr at room temp., neutralized with satd $NaHCO_3$ soln, 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 using petrol–EtOAc (8:1) to furnish **4**, whose IR, ^1H NMR and EI-MS were identical to those of natural product.

REFERENCES

1. Jiangsu New Medical College, *The Dictionary of Chinese Herb*, Vol. 1. China, 1986, p. 68.
2. Gunawardana, Y. A. G. P. and Cordell, G. A., *Journal of the Science Society of Thailand*, 1987, **13**, 107.
3. Allan, R. D., Correll, R. L. and Well, R. J., *Tetrahedron Letters*, 1969, **53**, 4673.
4. Wright, S. E., *Journal of the Chemical Society*, 1948, 2005.
5. Huls, R. and Brunelle, S., *Bulletin de la Societe Chimique, Belgique*, 1959, **68**, 325.
6. Ratcliffe, R. and Rodehorst, R., *Journal of Organic Chemistry*, 1970, **35**, 4000.
7. Sethna, S. M., *Chemical Reviews*, 1951, **49**, 91.
8. Ahluwalia, V. K., Arora, K. K. and Manchanda, S., *Indian Journal of Chemistry*, 1982, **21B**, 1093.