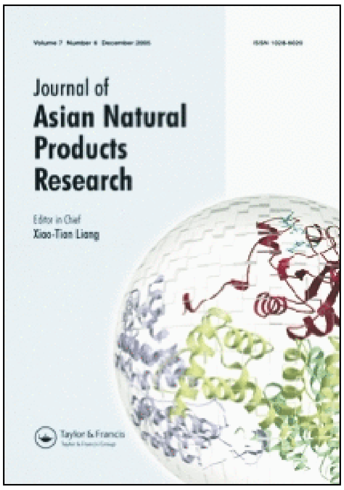

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TWO NEW CAFFEOYL CONJUGATION FROM *ERIGERON BREVISCAPUS*

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Two new constituents with a novel basic skeleton were isolated from *Erigeron breviscapus*. On the basis of chemical and spectroscopic evidences, the structures of the new compounds were elucidated as 1R,3R-dihydroxy-4S,5R-dicaffeoyloxy cyclohexane carboxylic acid methyl ester (V), 1,4-dihydroxy-3R,5R-dicaffeoyloxy cyclohexane carboxylic acid methyl ester (VI).

Keywords: Erigeron breviscapus; Compositae; Caffeoyl conjugation

INTRODUCTION

Erigeron breviscapus (Vant.) Hand-Mazz is a Chinese traditional medicine. The whole herb is used as a drug to treat a variety of paralysis and its sequelae [1]. Many erigerosides have been isolated previously in this plant [2–4]. Previous research works indicated that scutellarin in this plant was the bioactive constituent for treating apoplexy of the brain [1]. This paper reports the isolation and structural elucidation of two new caffeoyl conjugates (V, VI) from the ethyl acetate soluble fraction of the ethanolic extract of *Erigeron breviscapus*.

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RESULTS AND DISCUSSION

The EtOH extract of the powdered whole plant was partitioned with petroleum ether, $CHCl_3$, EtOAC and *n*-BuOH. The EtOAc fraction was further subjected to silica gel chromatography to afford compounds V and VI (Figs. 1 and 2).

Compound V was isolated as a yellow amorphous powder with chemical composition $C_{26}H_{26}O_{12}$ deduced from ^{13}CNMR, DEPT and MS (FAB and EI). Its IR spectrum indicated the presence of hydroxyl groups (IR 3000–3600 cm^{-1}) and ester groups (IR 1690, 1700, 1720 cm^{-1}). The ^{13}CNMR spectrum also gave the evidence of three carbonyl groups (175.14, 168.45, 167.93 ppm). The ^{1}HNMR and ^{13}CNMR spectra (Table I) indicated the presence of two caffeoyls [5]. Based on the ^{13}CNMR and DEPT spectra, the remaining carbons showed a methoxy (53.09 ppm), a carbonyl (175.14 ppm), two methylene carbons (38.29, 38.59 ppm), three tertiary carbon atoms (78.67, 74.95, 69.01 ppm) and a quaternary carbon (75.83 ppm). The spectral data mentioned above suggested that compound V is most likely composed of one nucleus of subunit A bearing two caffeoyl groups B and C. The structure of subunit A was elucidated by DEPT, ^{1}H–^{1}H COSY, ^{1}H–^{13}C

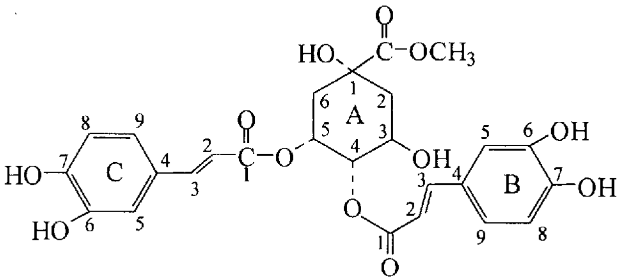

FIGURE 1 Structure of compound V.

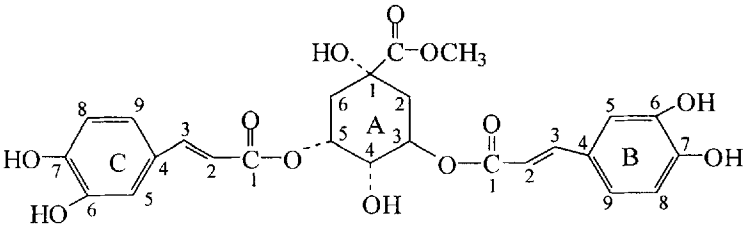

FIGURE 2 Structure of compound VI.

TABLE I ^{1}HNMR, ^{13}CNMR chemical shifts of compound V in CD_3OD

H/C	δ_A			δ_B			δ_C		
	^{1}H	J (Hz)	^{13}C	^{1}H	J (Hz)	^{13}C	^{1}H	J (Hz)	^{13}C
1			75.83			168.45			167.93
2	Ha 2.08(dd)	13.84, 6.23	38.29	6.26(d)	15.82	114.70	6.14(d)	15.53	114.56
	He 2.3(dd)	13.84, 1.45							
3	4.35(m)		78.67	7.85(d)	15.82	149.64	7.57(d)	15.53	149.58
4	5.11(dd)	8.19, 3.02	74.95			127.66			127.52
5	5.53(m)		69.0	7.01(d)	1.71	115.17	7.00(d)	1.6	115.17
6	2.24(m)		38.59			146.68			146.68
7						149.64			149.58
8				6.88(d)	8.15	116.47	6.86(d)	8.21	116.47
9				6.91(dd)	8.15, 1.71	123.11	6.89(dd)	8.21, 1.6	123.11
CO			175.14						
OCH_3			53.09						

correlation and COLOC techniques. The ^{1}H–^{13}CNMR correlation revealed the direct attachment between protons and carbons. It afforded an initial assignment of the protons in the subunits A, B and C. According to the chemical shifts of carbons and protons, the oxygen-bearing and non-oxygen-bearing could be distinguished. In the subunit A, three tertiary carbons (78.67, 74.95, 69.01 ppm) and one quaternary carbon (75.83 ppm) were connected with oxygen. The ^{1}H–^{1}H COSY showed the coupling correlation in subunit A. In the ^{1}H–^{1}H COSY, the H-2β (2.08 ppm, dd, $J = 13.84$, $J = 6.23$ Hz) and H-2α (2.3 ppm, dd, $J = 13.84$, $J = 1.45$ Hz) proton signals correlating with the H-3 (4.35 ppm, m, $J = 6.23$, 1.45, 8.19 Hz) signals indicated that C-2(–CH_2–) is connected with the C-3(–CH–). That the H-3 had a very strong contour with H-4 (5.11 ppm, dd, $J = 8.19$, 3.02 Hz) suggested that C-3(–CH–) connected with C-4(–CH–), which in turn gave a cross-peak with H-5 at δ 5.53. H-5 revealed the coupling correlation with H-6 (2.24 ppm, m, 2H). But H-6 had no coupling contours with H-2. So the subunit A consisted of six carbons with partial structure –CH_2–CH–CH–CH–CH_2–C–. The COLOC spectrum showed that two methylene carbons connected with a quaternary carbon (75.83 ppm) and two caffeoyl attached to C-5 and C-4. The quaternary carbon at δ 175.14 and the methoxy group at δ 53.09 were assigned to be a methoxycarbonyl (CH_3OOC–), which was attached to the C-1. This was supported by the COLOC spectrum. In the COLOC spectrum, carbonyl at δ 175.14 had strong cross-peak with H-2 and H-6. The planar structure of compound V was thus elucidated.

The relative stereochemistry of compound V has been assigned based on the analysis of coupling constants and NOESY spectrum. In the ^{1}HNMR spectrum the coupling constants between H-4 and H-3 ($J_{aa} = 8.19$ Hz), H-4 and H-5 ($J_{ae} = 3.02$ Hz), H-2 and H-3 ($J_{aa} = 6.23$ Hz, $J_{ae} = 1.45$ Hz) revealed that in the subunit A the protons were H-3α, H-4β, H-5β. On the basis of the proton coupling constants and the NOESY spectrum, that hydroxy connected with C-1 was α configuration. The structure of compound V was thus assigned to be 1R,3R-dihydroxy-4S,5R-dicaffeoyloxy cyclohexane carboxylic acid methyl ester.

Compound VI was isolated as a yellow amorphous powder with chemical composition $C_{26}H_{26}O_{12}$ deduced from ^{13}CNMR, DEPT and MS (FAB and EI). Its IR, ^{1}HNMR and ^{13}CNMR spectra were remarkably reminiscent of compound V. IR spectrum showed the presence of hydroxyl groups (IR 3000–3600 cm^{-1}) and three ester groups (IR 1690, 1700, 1725 cm^{-1}). The ^{1}HNMR and ^{13}CNMR spectra indicated the presence of two caffeoyls [5]. On the basis of ^{1}HNMR, ^{13}CNMR and DEPT spectra, subunit A of compound VI bore two caffeoyl, two hydroxy and one methoxycarbonyl. These were just like compound V. Comparing with compound V, chemical shifts of H-2 (δ 2.19) and H-6 (δ 2.21) revealed that they had almost identical values. By the ^{1}H–^{1}H COSY, subunit A of compound VI was also elucidated to be composed of the structure of $-CH_2-CH-CH-CH-CH_2-C-$. In the COLOC spectrum, H-3 at δ 4.35 showed the coupling correlation with a carbonyl of caffeoyl (δ 168.45), H-5 (δ 5.53) correlated to the other carbonyl of caffeoyl (δ 167.93). This was the reason why the chemical shifts of H-2 and H-6 were identical, thus the hydroxy connected with C-4. On the basis of ^{1}H–^{1}H COSY, ^{1}H–^{13}C correlation spectra and COLOC techniques, all the chemical shifts of carbons and protons were assigned (Table II). The NOESY spectrum and the proton coupling constants revealed that the relative configuration of compound VI was the same as

TABLE II ^{1}HNMR, ^{13}CNMR chemical shifts of compound VI in CD_3OD

H/C	δ_A			δ_B			δ_C		
	^{1}H	J(Hz)	^{13}C	^{1}H	J(Hz)	^{13}C	^{1}H	J(Hz)	^{13}C
1			74.64			167.98			168.73
2	2.19(m)		36.78	6.21(d)	15.92	114.81	6.33(d)	15.89	115.38
3	5.35(m)		72.08	7.54(d)	15.92	147.37	7.62(d)	15.89	147.09
4	3.98(dd)	3.17, 6.77	69.81			127.56			127.81
5	5.41(m)		71.98	7.06(d)	2.0	115.14	7.06(d)	2.0	115.14
6	2.21(m)		35.63			146.65			146.65
7						149.56			149.40
8				6.79(d)	8.17	116.46	6.76(d)	8.12	116.45
9				6.96(dd)	8.17, 2.0	123.05	6.93(dd)	8.12, 2.0	122.99
–CO–			175.59						
–OCH_3			53.03						

that of compound V. The structure of compound VI was elucidated as 1,4-dihydroxy-3R,5R-dicaffeoyloxy cyclohexane carboxylic acid methyl ester.

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were measured on a ZMD 83-1 electric hot-stage and are uncorrected. IR was tested by Hitachi 275-50. NMR spectra were acquired on Bruker AC-300, TMS as internal standard. EI-MS and FAB-MS data were obtained on a Varian MAT 212, direct inlet method. Chromatographic column: silica gel H (10–40 µ, made in Qing Dao Oceanic Chemical Industry). TLC: silica gel H (10–40 µ), spots were visualized by spraying with 10% H_2SO_4 followed by heating.

Plant Material

Erigeron breviscapus (Vant.) Hand-Mazz was collected at Yunnan province, China. The species was identified by Dr. Qin Lu-Ping, Department of Pharmacognosy, School of Pharmacy, Second Military Medical University, Shanghai, where a voucher specimen is deposited.

Extraction and Isolation

Air-dried and powdered whole plant (50 kg) was extracted three times with 85% EtOH at room temperature. The extract was evaporated to dryness under reduced pressure to get 1801 g of residue. After adding 2000 ml H_2O to the residue, the mixture was extracted with petroleum ether, $CHCl_3$, EtOAc and *n*-BuOH to give fractions P (132 g), C (200 g), E (398 g) and N (280 g) respectively. Fraction E (198 g) was chromatographed on a column of silica gel (2000 g) eluting with petroleum ether containing gradually increasing amounts of EtOAc to give fractions 1–24. Fraction 16 was chromatographed on a column of silica gel with $CHCl_3$–CH_3OH (10 : 1) as eluent to yield two fractions 1 (550 mg), 2 (700 mg). These fractions were further chromatographed on silica gel with $CHCl_3$–CH_3OH (12 : 1) to yield compound V (130 mg), compound VI (140 mg).

Structure and Identification

Compound V, $C_{26}H_{26}O_{12}$ yellow amorphous powder, m.p. 121–122°C. $[\alpha]_D^{25} = -135.6$ ($c = 1$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3000–3600 cm^{-1} (OH), 1690, 1700, 1720 cm^{-1}(C=O), FAB-MS *m/z*: 531[M+1]$^+$, 553[M+Na]$^+$. ^{1}HNMR and ^{13}CNMR see Table I. EI-MS *m/z*: 163[caffeoyl–OH]$^+$(100), 180[caffeoyl]$^+$(27), 350[M – caffeoyl]$^+$(4), 153[M – 2caffeoyl–OH]$^+$(4).

Compound VI, $C_{26}H_{26}O_{12}$ yellow amorphous powder, m.p. 116–117°C. $[\alpha]_D^{25} = -81$ ($c = 1$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3000–3600 cm^{-1}(OH), 1690, 1700, 1725 cm^{-1}(C=O). FAB-MS *m/z*: 531[M+1]$^+$, 569[M+K]$^+$. ^{1}HNMR and ^{13}CNMR see Table II. EI-MS *m/z*: 163[caffeoyl–OH]$^+$(100), 350[M – caffeoyl]$^+$(6), 180[caffeoyl]$^+$(41), 153[M – 2caffeoyl–OH]$^+$(13).

Acknowledgments

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