Two New Cyclopentenone Derivatives and a New Cyclooctadienone Derivative from *Erigeron annuus* (L.) PERS., *Erigeron philadelphicus* L., and *Erigeron sumatrensis* RETZ.

Takeyoshi IJIMA, Yasunori YAOITA, and Masao KIKUCHI*

Tohoku Pharmaceutical University; 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan.

Received March 6, 2003; accepted March 30, 2003

Two new cyclopentenone derivatives, erigerenones A (**1**) and B (**2**), and a new cyclooctadienone derivative, erigerenone C (**3**), were isolated from the aerial parts of *Erigeron philadelphicus* L. Compound **2** was also isolated from the aerial parts of *Erigeron annuus* (L.) PERS. and *Erigeron sumatrensis* RETZ. The structures of **1**–**3** were elucidated on the basis of their spectral data.

Key words *Erigeron annuus*; *Erigeron philadelphicus*; *Erigeron sumatrensis*; Compositae; cyclopentenone derivative; cyclooctadienone derivative

The genus *Erigeron* is a common group of Compositae plants, and *Erigeron annuus* (L.) PERS. (*himejyon* in Japanese), *Erigeron philadelphicus* L. (*harujion* in Japanese) and *Erigeron sumatrensis* RETZ. (*oarechinogiku* in Japanese) are now, as naturalized weeds, widely distributed throughout urban and rural areas of Japan.¹⁾ Among these, *E. annuus* has been used as an hypoglycemic drug in China.²⁾ The constituents of *E. annuus*, *E. philadelphicus*, and *E. sumatrensis* have been previously investigated and shown to contain monoterpenoids,³⁾ sesquiterpenoids,³⁾ diterpenoid,⁴⁾ polyacetylenic compounds,⁵⁾ and γ -pyrone derivatives.¹⁾ Recently we reported the isolation and structural elucidation of norisoprenoids,⁶⁾ sesquiterpenoids,⁷⁾ diterpenoids,⁷⁾ triterpenoids,⁸⁾ and sterols⁸⁾ from the aerial parts and roots of *E. annuus*, *E. philadelphicus*, and *E. sumatrensis*. As part of our continuing study of the constituents of the genus *Erigeron* plants, we now report the isolation and structural elucidation of two new cyclopentenone derivatives, erigerenones A (**1**) and B (**2**), and a new cyclooctadienone derivative, erigerenone C (**3**), from the aerial parts of *E. annuus*, *E. philadelphicus*, and *E. sumatrensis*.

Compound **1** was isolated as a colorless oil, $[\alpha]_D +7.3^\circ$. The molecular formula was determined to be $C_{12}H_{16}O_4$ by high-resolution (HR)-electron ionization (EI)-MS. The IR spectrum showed the presence of ester (1735 cm^{-1}) and α,β -unsaturated ketone ($1691, 1596\text{ cm}^{-1}$) functionalities. The UV spectrum also suggested the presence of an α,β -unsaturated ketone ($\lambda_{\text{max}}=237\text{ nm}$). The ^1H - (Table 1) and ^{13}C -NMR spectra (Table 2), obtained with the aid of distortionless enhancement by polarization transfer (DEPT) and ^1H -detected heteronuclear multiple quantum coherence (HMQC) spectra, showed signals due to a methyl [δ_{H} 1.70 (3H, H_3 -10); δ_{C} 13.1 (C-10)], a methylene [δ_{H} 2.58 (1H, H_a -2), 2.77 (1H, H_b -2); δ_{C} 33.8 (C-2)], two methines [δ_{H} 2.56 (1H, H-3), 3.68 (1H, H-7); δ_{C} 44.8 (C-7), 49.9 (C-3)], two methoxyl groups [δ_{H} 3.67 (3H, CH_3O -1), 3.84 (3H, CH_3O -6); δ_{C} 51.7 (CH_3O -1), 59.0 (CH_3O -6)], a trisubstituted double bond [δ_{H} 5.32 (1H, H-5); δ_{C} 102.9 (C-5), 190.3 (C-6)], a disubstituted double bond [δ_{H} 5.24 (1H, H-8), 5.74 (1H, H-9); δ_{C} 127.6 (C-8), 128.5 (C-9)], and two carbonyl carbons [δ_{C} 172.3 (C-1), 204.2 (C-4)]. The gross structure of **1** was elucidated by analyses of two-dimensional (2D) NMR data including ^1H - ^1H shift correlation spectroscopy (^1H - ^1H COSY) and ^1H -

detected heteronuclear multiple bond connectivity (HMBC) spectra (Fig. 1). The ^1H - ^1H COSY spectrum of **1** implied connectivities for H_2 -2—H-3, H-3—H-7, H-7—H-8, H-8—H-9, and H-9—H-10. Interpretation of the HMBC spectrum revealed correlations from H_2 -2 to C-1 and C-4; H-5 to C-3 and C-7; H-7 to C-6; CH_3O -1 to C-1; and CH_3O -6 to C-6. Thus the gross structure of **1** was deduced to be as shown in Fig. 1. The relative stereochemistry at C-3 and C-7 was established by comparing the proton coupling constant between H-3 and H-7 with analogous couplings observed for other cyclopentenones.^{9,10)} In cyclopentene rings, a vicinal coupling constant of 5–6 Hz normally indicates a *cis* relationship, while a coupling constant of *ca.* 2 Hz suggests a *trans* relationship.¹¹⁾ These observations have been extended to cyclopentenone rings and a similar correlation has been observed.^{9,10)} Thus, in the case of **1**, the small coupling constant of 2.2 Hz is suggestive of a *trans* relationship between H-3 and H-7. The geometry of the Δ^8 -double bond was deduced to be *Z* from ^1H - ^1H coupling constant ($J=11.0\text{ Hz}$) between H-8 and H-9. On the basis of the above data, the structure of **1** was represented as shown in the formula.

Compound **2** was isolated as a colorless oil, $[\alpha]_D +7.9^\circ$. The molecular formula was determined to be $C_{12}H_{18}O_4$ by HR-EI-MS. The ^1H - and ^{13}C -NMR spectra of **2** resembled those of **1**, except for the presence of two methylene groups [δ_{H} 1.51 (1H, H_a -8), 1.75 (1H, H_b -8), 1.33 (2H, H_2 -9); δ_{C} 19.5 (C-9), 33.8 (C-8)] instead of a disubstituted double bond in **1**. The molecular formula of **2** suggested that **2** was a dihydro derivative of **1**. The ^1H - ^1H COSY spectrum of **2** implied

Chart 1

* To whom correspondence should be addressed. e-mail: mkikuchi@tohoku-pharm.ac.jp

Table 1. ^1H -NMR Chemical Shifts of Compounds **1**–**3** (CDCl_3 , 400 MHz)

Proton	1 ^{a)}	2	3
2	a 2.58 dd (20.5, 8.1) ^{b)} b 2.77 dd (20.5, 8.8)	a 2.53 dd (20.2, 8.1) b 2.75 dd (20.2, 8.8)	3.16 ddd (13.2, 5.6, 3.9)
3	2.56 m	2.51 m	α 3.30 dd (13.2, 11.0) β 2.40 ddd (11.0, 3.9, 1.5)
5	5.32 d (1.1)	5.27 d (0.7)	5.49 br s
7	3.68 ddd (9.9, 2.2, 1.1)	2.64 ddd (5.4, 5.1, 2.4)	6.19 dd (11.7, 0.7)
8	5.24 ddq (11.0, 9.9, 1.8)	a 1.51 m b 1.75 m	6.16 dd (12.7, 11.7)
9	5.74 ddq (11.0, 7.0, 1.1)	1.33 ^{c)} m	2.92 m
10	1.70 dd (7.0, 1.8)	0.93 t (7.3)	1.11 d (6.6)
$\text{CH}_3\text{O-1}$	3.67 s	3.68 s	3.69 s
$\text{CH}_3\text{O-6}$	3.84 s	3.84 s	3.66 s

a) Measured at 600 MHz. b) Coupling constants (J in Hz) are given in parentheses. c) 2H.

Table 2. ^{13}C -NMR Chemical Shifts of Compounds **1**–**3** (CDCl_3 , 100 MHz)

Carbon	1 ^{a)}	2	3
1	172.3	172.4	172.8
2	33.8	35.3	54.0
3	49.9	48.0	41.9
4	204.2	204.9	199.9
5	102.9	102.8	107.2
6	190.3	192.0	166.6
7	44.8	46.3	125.4
8	127.6	33.8	145.0
9	128.5	19.5	34.6
10	13.1	14.2	17.6
$\text{CH}_3\text{O-1}$	51.7	51.7	51.6
$\text{CH}_3\text{O-6}$	59.0	58.7	56.0

a) Measured at 150 MHz.

connectivities for H-7—H-8, H-8—H-9, and H-9—H-10. The relative stereochemistry at C-3 and C-7 was deduced to be *trans* from the ^1H – ^1H coupling constant ($J=2.4\text{ Hz}$) between H-3 and H-7.^{9–11} Thus compound **2** was an 8,9-dihydro derivative of **1**. From the above data, the structure of **2** was represented as shown in the formula.

Compound **3** was isolated as a colorless oil, $[\alpha]_{\text{D}} +4.2^\circ$. The molecular formula was determined to be $\text{C}_{12}\text{H}_{16}\text{O}_4$ by HR-EI-MS. The IR spectrum showed the presence of ester (1731 cm^{-1}) and $\alpha,\beta,\gamma,\delta$ -unsaturated ketone (1627 , 1592 cm^{-1}) functionalities. The UV spectrum also suggested the presence of an $\alpha,\beta,\gamma,\delta$ -unsaturated ketone ($\lambda_{\text{max}}=279\text{ nm}$). The ^1H - and ^{13}C -NMR spectra showed signals due to a secondary methyl [δ_{H} 1.11 (3H, H-10); δ_{C} 17.6 (C-10)], a methylene [δ_{H} 2.40 (1H, H- β -3), 3.30 (1H, H- α -3); δ_{C} 41.9 (C-3)], two methines [δ_{H} 2.92 (1H, H-9), 3.16 (1H, H-2); δ_{C} 34.6 (C-9), 54.0 (C-2)], two methoxyl groups [δ_{H} 3.66 (3H, $\text{CH}_3\text{O-6}$), 3.69 (3H, $\text{CH}_3\text{O-1}$); δ_{C} 51.6 ($\text{CH}_3\text{O-1}$), 56.0 ($\text{CH}_3\text{O-6}$)], a trisubstituted double bond [δ_{H} 5.49 (1H, H-5); δ_{C} 107.2 (C-5), 166.6 (C-6)], a disubstituted double bond [δ_{H}

Fig. 1. ^1H – ^1H COSY (Bold Lines) and HMBC (Arrows) Correlations for **1** Fig. 2. ^1H – ^1H COSY (Bold Lines) and HMBC (Arrows) Correlations for **3** Fig. 3. Selected J -Values (Dotted-Line Arrows) and Significant NOEs (Full-Line Arrows) in **3**

6.16 (1H, H-8), 6.19 (1H, H-7); δ_{C} 125.4 (C-7), 145.0 (C-8)], and two carbonyl carbons [δ_{C} 172.8 (C-1), 199.9 (C-4)]. The gross structure of **3** was elucidated by analyses of 2D NMR data including ^1H – ^1H COSY and HMBC spectra (Fig. 2). The ^1H – ^1H COSY spectrum of **3** implied connectivities for H-2—H-3, H-2—H-9, H-7—H-8, H-8—H-9, and H-9—H-10. Interpretation of the HMBC spectrum revealed correlations from H-2-3 to C-1 and C-4; H-5 to C-3, C-4, C-6 and C-7; $\text{CH}_3\text{O-1}$ to C-1; and $\text{CH}_3\text{O-6}$ to C-6. Thus the gross structure of **3** was deduced to be as shown in Fig. 2. The relative stereochemistry at C-2 and C-9 was established as follows (Fig. 3). In the ^1H -NMR spectrum, the long-range coupling observed between H- β -3 and H-5 ($J=1.5\text{ Hz}$) indicated that the bonds between them are W-shaped. The magnitude of $J_{2,3\alpha}=13.2$ and $J_{2,3\beta}=3.9\text{ Hz}$ suggested that H-2 and H- α -3, H-2 and H- β -3 were located in *anti* and *gauche* arrangements, respectively. Thus the relative stereochemistry at C-2 was determined to be R^* . The magnitude of $J_{8,9}=12.7\text{ Hz}$ suggested that H-8 and H-9 were located in an *anti* arrangement. In the difference nuclear Overhauser effect (NOE) experiments, irradiation at δ 1.11 (H-10) caused NOE enhancement in the signals of the H-2, H-8, and H-9. The ^1H – ^1H coupling constant ($J=12.7\text{ Hz}$) between H-8 and H-9, and the observation of NOE from the H-10 methyl group to H-8 implied that the relative stereochemistry at C-9 was S^* . The geometry of the Δ^5 -double bond was shown to be *E*. Accordingly, irradiation at δ 5.49 (H-5) caused NOE enhancement in the signal of the $\text{CH}_3\text{O-6}$. The *Z* configuration of the Δ^7 -double bond was shown by the ^1H – ^1H coupling constant ($J=11.7\text{ Hz}$) between

H-7 and H-8. On the basis of the above data, the structure of **3** was represented as shown in the formula.

In conclusion, we described here the isolation and structure elucidation of erigerenones A (**1**), B (**2**), and C (**3**) from the aerial parts of *E. annuus*, *E. philadelphicus*, and *E. sumatrensis*. Although dibenzocyclooctadienone lignans such as steganone¹²⁾ and benzocyclooctadienone sesquiterpenes such as isoparvifolinone¹³⁾ are known, compound **3** is, to the best of our knowledge, the first example of a naturally occurring cyclooctadienone derivative without the fused phenyl system.

The framework of compounds **1**–**3** resembles that of (5-butyl-3-oxo-2,3-dihydrofuran-2-yl)-acetic acid (**4**), which was recently isolated from *E. annuus*.¹⁴⁾ This implies that compounds **1**–**4** may be formed by similar biosynthetic processes.

Experimental

General Procedures Optical rotations were determined using a JASCO DIP-360 digital polarimeter. IR spectra were recorded with a Perkin-Elmer FT-IR 1725X IR spectrophotometer and UV spectra on a Beckman DU-64 spectrophotometer. ¹H- and ¹³C-NMR spectra were recorded using JEOL JNM-LA 600 (600 and 150 MHz, respectively) and JEOL JNM-LA 400 (400 and 100 MHz, respectively) spectrometers. Chemical shifts are given on a δ (ppm) scale, with tetramethylsilane as an internal standard. The HR-EI-MS were recorded on a JEOL JMS-DX 303 mass spectrometer. Column chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck). Preparative HPLC was carried out on a Tosoh HPLC system (pump, CCPM; detector, RI-8020 and UV-8020) using TSKgel ODS-120T (7.8 mm i.d. $\times$ 30 cm) column (Tosoh).

Plant Material The aerial parts of *E. annuus* were collected in Sendai City, Miyagi Prefecture, Japan, in July 2001; those of *E. philadelphicus* in Sendai City in April 2002; and those of *E. sumatrensis* in Sendai City in October 2000.

Extraction and Isolation *E. annuus*: The aerial parts of *E. annuus* (5.3 kg) were extracted with MeOH at room temperature for 2 weeks. The MeOH extract was concentrated under reduced pressure and the residue was suspended in a small excess of water. This suspension was extracted with CHCl₃. The CHCl₃-soluble fraction was concentrated under reduced pressure to afford a residue (79.4 g). A part of this residue (67.0 g) was chromatographed on a silica gel column using hexane–EtOAc (7:1–1:7) and CHCl₃–MeOH (9:1–1:1) to afford 62 fractions. Fraction 19 was purified by preparative HPLC [column temperature, 40 °C; mobile phase, MeOH–H₂O (1:1); flow rate, 1.5 ml/min; RI detector] to give **2** (0.5 mg).

E. philadelphicus: The aerial parts of *E. philadelphicus* (2.5 kg) were extracted with MeOH at room temperature for 2 weeks. The MeOH extract was concentrated under reduced pressure and the residue was suspended in a small excess of water. This suspension was extracted with CHCl₃. The CHCl₃-soluble fraction was concentrated under reduced pressure to afford a residue (24.0 g). This residue was chromatographed on a silica gel column using hexane–EtOAc (7:1–1:7) and CHCl₃–MeOH (9:1–1:1) to afford 47 fractions. Fraction 11 was purified by preparative HPLC [column temperature, 40 °C; mobile phase, MeOH–H₂O (1:1); flow rate, 1.5 ml/min; RI detector] to give **3** (2.4 mg). Fraction 17 was purified by preparative

HPLC [column temperature, 40 °C; mobile phase, MeOH–H₂O (1:1); flow rate, 1.5 ml/min; UV detector, 230 nm] to give **1** (1.5 mg) and **2** (0.4 mg).

E. sumatrensis: The aerial parts of *E. sumatrensis* (4.0 kg) were extracted with MeOH at room temperature for 2 weeks. The MeOH extract was concentrated under reduced pressure and the residue was suspended in a small excess of water. This suspension was extracted with CHCl₃. The CHCl₃-soluble fraction was concentrated under reduced pressure to afford a residue (80.7 g). A part of this residue (50.0 g) was chromatographed on a silica gel column using hexane–EtOAc (7:1–1:7) and CHCl₃–MeOH (9:1–1:1) to afford 60 fractions. Fraction 18 was purified by preparative HPLC [column temperature, 40 °C; mobile phase, MeOH–H₂O (1:1); flow rate, 1.5 ml/min; RI detector] to give **2** (2.5 mg).

Erigerenone A (**1**): Colorless oil. $[\alpha]_D^{24} + 7.3^\circ$ ($c=0.14$, MeOH). UV $\lambda_{\max}$ MeOH nm (log ϵ): 237 (4.2). IR $\nu_{\max}$ CHCl₃ cm^{−1}: 1735, 1691, 1596. HR-EI-MS m/z : 224.1063 (M^+ , Calcd for C₁₂H₁₆O₄: 224.1049). ¹H-NMR (600 MHz, CDCl₃): see Table 1. ¹³C-NMR (150 MHz, CDCl₃): see Table 2.

Erigerenone B (**2**): Colorless oil. $[\alpha]_D^{26} + 7.9^\circ$ ($c=0.25$, MeOH). UV $\lambda_{\max}$ MeOH nm (log ϵ): 238 (4.1). IR $\nu_{\max}$ CHCl₃ cm^{−1}: 1735, 1688, 1593. HR-EI-MS m/z : 226.1178 (M^+ , Calcd for C₁₂H₁₈O₄: 226.1205). ¹H-NMR (400 MHz, CDCl₃): see Table 1. ¹³C-NMR (100 MHz, CDCl₃): see Table 2.

Erigerenone C (**3**): Colorless oil. $[\alpha]_D^{22} + 4.2^\circ$ ($c=0.24$, MeOH). UV $\lambda_{\max}$ MeOH nm (log ϵ): 279 (3.8). IR $\nu_{\max}$ CHCl₃ cm^{−1}: 1731, 1627, 1592. HR-EI-MS m/z : 224.1055 (M^+ , Calcd for C₁₂H₁₆O₄: 224.1049). ¹H-NMR (400 MHz, CDCl₃): see Table 1. ¹³C-NMR (100 MHz, CDCl₃): see Table 2.

Acknowledgments We are grateful to Mr. S. Sato and Mr. T. Matsuki of this university for providing the mass and NMR spectra.

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