Cadinene Derivatives from *Eupatorium adenophorum*

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A new norsesquiterpene named eupatorone (=(4*S*,4*aR*,6*R*)-1-acetyl-6-(acetyloxy)-4,4a,5,6-tetrahydro-4,7-dimethylnaphthalen-2(3*H*)-one; **1**) and a new sesquiterpene derivative named 2-deoxo-2-(acetyloxy)-9-oxoageraphorone (=(1*R*,4*S*,4a*R*,6*R*,8a*S*)-6-(acetyloxy)-3,4,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)naphthalen-2(1*H*)-one; **2**), together with the five known cadinene derivatives **3**–**7** were isolated from the flower of *Eupatorium adenophorum* (SPRENG.). Their structures were established by extensive NMR experiments, including 1D and 2D NMR.

Introduction. – *Eupatorium adenophorum* (SPRENG.), originating from Mexico, has invaded Yunnan Province from Burma since the 1950s. It has resulted in much harm to agriculture and environment [1]. To study the influences that *E. adenophorum* imposes on environment concerning chemical aspects, we explored the chemical constituents of the *adenophorum* species. Many cadinene derivatives were isolated both from *E. adenophorum* (SPRENG.) and *Ageratina adenophorum* (SPRENG.) [1][2]. In our present research, a rare norsesquiterpene, namely eupatorone (**1**), and another, new sesquiterpene, namely 2-deoxo-2-(acetyloxy)-9-oxoageraphorone (**2**), along with five known cadinene derivatives, 9-oxoageraphorone (**3**) [2], muurol-4-en-7-ol (**4**) [3], 8β-hydroxy-9,12-dehydroverbocciolenten (**5**) [4], eupatoranolide (**6**) [5], and 3-hydroxymuurola-4,7(11)-dien-8-one (**7**) [6] were isolated from the flower of *E. adenophorum* (*Fig. 1*)[1]). In this paper, we report the isolation and the structure elucidation of the two novel compounds.

Results and Discussion. – The air-dried and powdered flower (10 kg) was extracted with MeOH (4x25 l) at room temperature to give a crude extract (800 g), which was suspended in H_2O and extracted with petroleum ether and AcOEt. The AcOEt (178 g), and petroleum ether extracts (170 g) were both chromatographed over silica gel to give **1** (3 mg) and **2** (100 mg), respectively.

The molecular formula of compound **1** was $C_{16}H_{20}O_4$ as revealed by HR-ESI-MS ($C_{16}H_{20}O_4Na^+$ at *m/z* 299.1257), which was supported by the ^{13}C-NMR (DEPT) spectra.

Based on the ^{1}H- and ^{13}C-NMR spectra (*Table*), HMQC, HMBC and ROESY experiments, and IR data, the structure of eupatorone (**1**) was established as

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[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*

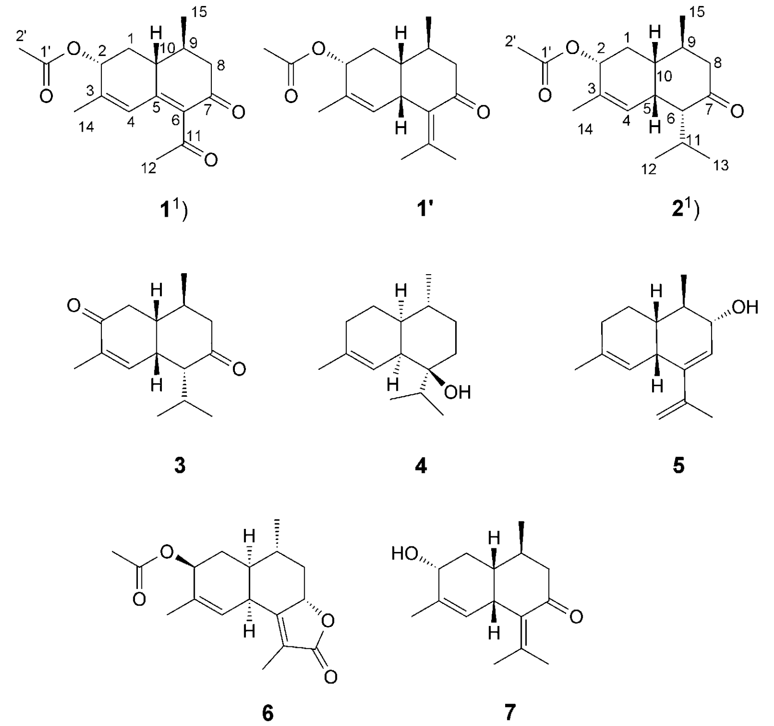

Fig. 1. *Compounds* **1**–**7** *isolated from* E. adenophorum

(4*S*,4a*R*,6*R*)-1-acetyl-6-(acetyloxy)-4,4a,5,6-tetrahydro-4,7-dimethylnaphthalen-2(3*H*)-one. In accord with the biosynthesis of the cadinene skeleton and the configuration of the known compounds isolated from *E. adenophorum*, the absolute configuration of **1** was assumed as (4*S*,4a*R*,6*R*) [1–7]. The NMR spectral data and the relative configuration of **1** were further confirmed by comparing them with those of the reported compounds **1**′ and **3** [3][6]. To the best of our knowledge, **1** is an unusual degraded cadinene derivative.

The ^{1}H- and ^{13}C-NMR spectra of **1** showed the signals of six quaternary C-atoms and, four OH, two CH_2, and four Me groups. In the ^{13}C-DEPT spectra, two carbonyl groups were evident from the signals at δ(C) 204.3 (*s*) and 196.8 (*s*), and the signals at δ(C) 150.9 (*s*), 123.7 (*d*), 152.4 (*s*), and 135.7 (*s*) were typical of a C=C- and a CH=C moiety in **1**, which was also supported by its IR spectra. In the latter, absorption bands for C=O (1732, 1695 cm^{-1}) groups and C=C bonds (1650, 1619 cm^{-1}) appeared. The comparison of the ^{1}H- and ^{13}C-NMR spectra of **1** with those of the known compounds **3**–**7** suggested that **1** should have a cadinene skeleton missing a C-atom (*Table*) [2–6].

In the HMQC and HMBC (*Fig. 2,a*), the ^{1}H,^{13}C long-rang correlations between δ(H) 2.13 (Me(2′)) and δ(C) 170.4 (C(1′)) and between δ(H) 5.59 (H–C(2)) and δ(C) 170.4 (C(1′)) suggested that an AcO group was at C(2). The ^{1}H,^{13}C long-rang correlations between δ(H) 1.44 and 2.52 (CH_2(1)) and δ(C) 71.3 (C(2)) and 150.9 (C(3)), together with the correlations between δ(H) 5.59 (H–C(2)) and δ(C) 150.9 (C(3)) and 123.7(C(4)) and between δ(H) 1.87 (Me(1)) and δ(C) 150.9 (C(3)) and 123.7 (C(4)) suggested the presence of partial structure **A** in **1** (*Fig. 2,a*). Comparison of the 1D and 2D NMR spectra of **1** with those of **3**–**7** revealed that H–C(5), H–C(6), and a Me group were missing in partial structure **B** of **1**

Table. *^{1}H- and ^{13}C-NMR Data (*$CDCl_3$*) of Compound* **1** *and* **2**[1]). δ in ppm, J in Hz

	1		**2**	
	δ(C) (DEPT)	δ(H)	δ(C) (DEPT)	δ(H)
CH_2(1)	32.6 (CH_2)	1.42–1.45 (*m*, H_α), 2.49–2.52 (*m*, H_β)	30.5 (CH_2)	1.85–1.86 (*m*, H_α), 2.20–2.22 (*m*, H_β)
H–C(2)	71.3 (CH)	5.59 (*dd*, J=3.5, 6)	69.1 (CH)	5.17 (*dd*, J=3.6, 6)
C(3)	150.9 (C)		132.3 (C)	
H–C(4)	123.7 (CH)	6.24 (*s*)	130.2 (CH)	5.34 (*s*)
C(5) or H–C(5)	152.4 (C)		41.5 (CH)	2.71 (*s*)
C(6) or H–C(6)	135.7 (C)		64.2 (CH)	1.88 (br.)
C(7)	196.8 (C)		214.2 (C)	
CH_2(8)	46.0 (CH_2)	2.21–2.22 (*m*, H_α), 2.51–2.53 (*m*, H_β)	46.4 (CH_2)	2.10–2.12 (*m*, H_α), 2.12–2.14 (*m*, H_β)
H–C(9)	34.0 (CH)	1.90–1.95 (*m*)	32.0(CH)	2.26–2.28 (*m*)
H–C(10)	41.3 (CH)	2.21–2.24 (*m*)	35.1 (CH)	1.83–1.84 (*m*)
C(11) or H–C(11)	204.3 (C)		28.3 (CH)	2.01–2.03 (*m*)
Me(12)	32.0 (Me)	2.37 (*s*)	20.3 (Me)	0.83 (*d*, J=6.5)
Me(13)			21.1 (Me)	0.99 (*d*, J=6.5)
Me(14)	19.7 (Me)	1.87 (*s*)	20.0 (Me)	1.61 (*s*)
Me(15)	19.2 (Me)	1.11 (*d*, J=7.5)	20.2 (Me)	0.95 (*d*, J=6.5)
C(1′)	170.4 (C)		170.7 (C)	
Me(2′)	20.9 (Me)	2.13 (*s*)	21.2 (Me)	2.02 (*s*)

(*Fig. 2,b*). In the HMBC spectra, the ^{1}H,^{13}C long-rang correlations between δ(H) 2.21 and 2.53 (CH_2(8)) and δ(C) 196.8 (C(7)), between δ(H) 2.53 and 2.21 (CH_2(8)) and δ(C) 135.7 (C(6)) and 152.4 (C(5)), and between δ(H) 2.22 (H–C(10)) and δ(C) 152.4 (C(5)) and 135.7 (C(6)) suggested that a C=C bond should be placed between C(5) and C(6). The correlations between δ(H) 2.37 (Me(12)) and δ(C) 204.3 (C(11)) and 135.7 (C(6)) indicated that an Ac group was at C(6), and the correlations between δ(H) 1.11 (Me(15)) and δ(C) 41.3 (C(10)) and 46.2 (C(8)), and between δ(H) 1.44 and 2.52 (CH_2(1)) and δ(C) 41.3 (C(10)) confirmed the presence of the partial structure **B** in **1** (*Fig. 2,b*). In the ROESY experiment (*Fig. 2,b*), the correlations between δ(H) 5.59 (H–C(2)) and δ(H) 2.22 (H–C(10)), and between δ(H) 2.22 (H–C(10)) and δ(H) 1.11 (Me(15)) suggested that H–C(2), H–C(10), and Me(15) are positioned on the same side of the rings A/B. The J values of H–C(2) (J=3.5, 6 Hz) implied that H–C(2) and the 2 H–C(1) are in an ax/ax and ax/eq position, so the AcO group should is α-oriented. The correlations between δ(H) 6.24 (H–C(4)) and δ(H) 2.37 (Me(12)) established that H–C(4) and Me(12) are close to each other (*Fig. 2,b*).

The molecular formula of **2** was $C_{17}H_{26}O_3$ as revealed by HR-ESI-MS ($C_{17}H_{26}O_3Na^+$ at *m*/*z* 301.1784), which was further confirmed by its ^{13}C-NMR (DEPT) spectra. The ^{1}H- and ^{13}C-NMR spectra (*Table*), the HMQC, HMBC, ROESY, and IR data, and comparison with those of **3**–**7** established the structure of **2** as (1*R*,4*S*,4a*R*,6*R*,8a*S*)-6-(acetyloxy)-3,4,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)naphthalen-2(1*H*)-one. As for compound **1,** the absolute configuration of compound **2** was assumed as (1*R*,4*S*,4a*R*,6*R*,8a*S*).

The ^{1}H- and ^{13}C-NMR spectra of **2** suggested that **2** has three quaternary C-atoms and seven CH, two CH_2, and five Me groups. The IR spectra showed absorption bands for C=O (1725, 1702 cm^{-1}) groups and C=C bonds (1658 cm^{-1}). The comparison of the above data with those of **3**–**7** suggested that **2** should also possess a cadinene skeleton. In the HMQC and HMBC (*Fig. 3,a*), the ^{1}H,^{13}C long-rang correlations

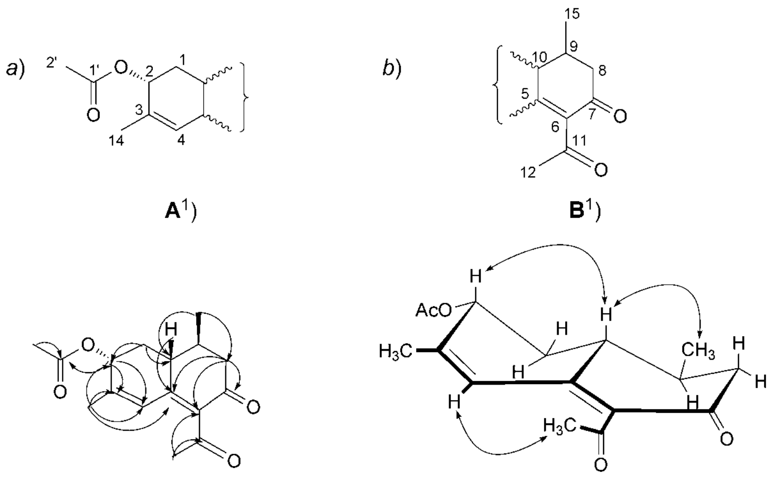

Fig. 2. a) *Partial structure* **A** *and key HMBC correlations and* b) *partial structure* **B** *and key ROESY correlations of* **1**

between δ(H) 2.02 (Me(2′)) and δ(C) 170.7 (C (1′)) and between δ(H) 5.17 (H−C(2)) and δ(C) 170.7 (C(1′)) suggested that an AcO group should be at C(2). The comparison of 1D and 2D NMR and IR spectra of **2** with those of **3** indicated that **2** may be directly derived from **3** (Fig. 3). In the ROESY experiment (*Fig 3,b*), the correlations between δ(H) 5.17 (H−C(2)) and δ(H) 1.83 (H−C(10)), between δ(H) 1.83 (H−C(10)) and δ(H) 0.99 (Me(13)) and 2.71 (H−C(5)), and between δ(H) 2.71 (H−C(5)) and δ(H) 1.88 (H−C(6)) suggested that H−C(2), H−C(10), Me(13), H−C(5), and H−C(6) were all on the same side. The *J* values of H−C(2) ($J = 3.6$, 6 Hz) indicated that H−C(2) and the 2 H−C(1) are in an ax/ax and ax/eq position. Therefore, the AcO group is α-oriented, as in compound **1** (*Fig. 3*).

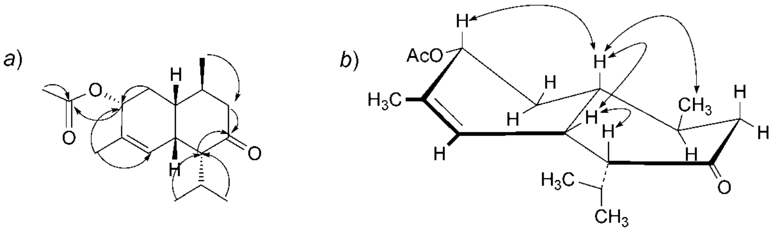

Fig. 3. a) *Key HMBC correlations and* b) *key ROESY correlations of* **2**

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Experimental Part

General. Column chromatography (CC): silica gel (200–300 mesh) from *Qingdao Marine Chemical Factory*, Qingdao, P. R. China. Optical rotation: *Horiba-SEAP-300* spectropolarimeter. M.p.: *YuHua-X-4* apparatus. UV: *Shimadzu-210A* double-beam spectrophotometer; λ_{max} in nm. IR Spectra: *Bruker-Tensor-27* spectrometer; with KBr pellets; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AV-400* and *DRX-500*; $SiMe_4$ as internal standard; δ in ppm, J in Hz. MS: *VG-Auto-Spec-3000* spectrometer; in m/z (rel.%).

Plant Material. The whole flower of *E. adenophorum* was collected in June 2005 in Kunming Yunnan Province, P. R. China, and identified by Prof. *XiaoDong Luo*. A voucher specimen was deposited in the herbarium of the Department of Taxonomy, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, P. R. China.

Extraction and Isolation. The air-dried and powered flowers (10 kg) were extracted with MeOH (4×25 l) at r.t., and the MeOH soln. was concentrated to give a crude extract (800 g) which was partitioned in H_2O and extracted with petroleum ether (3×) and AcOEt (3×). The petroleum ether extract (170 g) was subjected to CC (silica gel (1.7 kg), petroleum ether/Me_2CO 10:0 → 0:10) *Fractions 1.1–1.7*. *Fr. 1.2* (30 g) was repeatedly subjected to CC (silica gel (400 g), petroleum ether/Me_2CO 20:1 → 10:1)): *Fr. 1.2.1–1.2.4*. *Fr. 1.2.1* (3.3 g) was subjected to reversed-phase CC (*RP-18,* MeOH/H_2O 3:2). *Fr. 1.2.1.1* (500 mg) was repeatedly subjected to CC (silica gel (15 g), petroleum ether/AcOEt 20:1): **5** (7 mg) and **3** (10 mg). *Fr. 1.2.4* (10 g) was repeatedly subjected to the same process as described for *Fr. 1.2.1*: **4** (50 mg). *Fr. 1.2.3* (8 g) was directly subjected to CC (silica gel (160 g), petroleum ether/Me_2CO 20:1): **2** (100 mg). The AcOEt extract (178 g) was subjected to CC (silica gel, petroleum ether/Me_2CO 10:1 → 0:1): *Fr. 2.1–2.9*. *Fr. 2.1* contained **6** (100 mg). *Fr. 2.2* (35 g) was subjected to CC (silica gel, petroleum ether/Me_2CO 20:1 → 10:1): *Fr. 2.2.1–2.2.5*. *Fr. 2.2.4* (4 g) was subjected to reversed-phase CC (*RP-18,* MeOH/H_2O 4:1): *Fr. 2.2.4.1–2.2.4.4*. *Fr. 2.2.4.1* (600 mg) was again subjected to CC (silica gel (18 g), petroleum ether/Me_2CO 30:1): **7** (10 mg) and **1** (3 mg).

Eupatorone (= *(4*S*,4a*R*,6*R*)-1-Acetyl-6-(acetyloxy)-4,4a,5,6-tetrahydro-4,7-dimethylnaphthalen-2(3*H*)-one*; **1**): Light yellow oil. $[\alpha]_D^{28} = +193.7$ ($c = 0.6$, $CHCl_3$). UV ($CHCl_3$): 293.4, 229.4. IR (KBr): 2959, 2926, 2854, 1732, 1695, 1650, 1619, 1573, 1460, 1379, 1369, 1237. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 276 (5), 234 (100), 217 (69), 216 (70), 201 (65), 191 (55), 173 (66), 163 (30), 159 (60), 132 (35), 91 (45). HR-ESI-MS: 299.1257 ($C_{16}H_{20}O_4Na^+$; calc. 299.1259).

2-Deoxo-2-(acetyloxy)-9-oxoageraphorone (= *(1*R*,4*S*,4a*R*,6*R*,8a*S*)-6-(Acetyloxy)-3,4,4a,5,6,8a-hexahydro-4,7-dimethyl-(1-methylethyl)naphthalen-2(1*H*)-one*; **2**): Colorless needles from Me_2CO. M.p. 118–120°. $[\alpha]_D^{28} = -111.6$ ($c = 0.5$, $CHCl_3$). IR (KBr): 2963, 2926, 2890, 1725, 1702, 1658, 1368, 1241, 1013. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 278 (3), 218 (18), 178 (20), 176 (26), 161 (25), 136 (81), 119 (100). HR-ESI-MS: 301.1784 ($C_{17}H_{26}O_3Na^+$; calc. 301.1779).

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