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IRIDOID AND EUGENOL GLYCOSIDES FROM *NEPETA CADMEA*

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Key Word Index—*Nepeta cadmea*; Labiatae; 1,8,9-epideoxyloganic acid glucosyl ester; iridoid glucoside; eugenyl apiofuranosylglucopyranoside.

Abstract—From the aerial parts of *Nepeta cadmea*, a new iridiod glucoside, 1,5,9-epideoxyloganic acid glucosyl ester, and a new eugenyl glucoside were isolated, together with the known compounds, 1,5,9-epideoxyloganic acid, eugenyl-*O*-*β*-D-glucoside, icarisides B_1 and B_2, (6*S*,9*S*)-roseoside, lariciresinol-4′-*O*-*β*-D-glucoside and rosmarinic acid. Sodium and potassium salts of 1,5,9-epideoxyloganic acid were also isolated. The structures of newly isolated compounds were elucidated by spectral and chemical analyses.

INTRODUCTION

Nepetalactone which has a peculiar physiological activity to cats has been known as a constituent of plants belonging to the genus *Nepeta* [1]. Species in this genus are also known to contain iridoid glucosides having a novel stereochemistry [2–6]. In the course of studies on the constituents of Turkish medicinal and related plants, we examined the glycosidic constituents of *Nepeta cadmea* collected in central Anatolia and isolated a new iridoid glucoside, 1,5,9-epideoxyloganic acid glucosyl ester (**1**), and a new phenylpropanoid glycoside, eugenyl-*O*-*β*-apiofuranosyl-(1″-6′)-*O*-*β*-glucopyranoside (**5**), together with the known compounds, 1,5,9-epideoxyloganic acid (**2**) [2], eugenyl-*O*-*β*-D-glucopyranoside (**6**) [7], icarisides B_1 and B_2[8],(6*S*,9*S*)-roseoside(= corchoionoside C)[9, 10], lariciresinol-4′-*O*-*β*-D-glucoside [11] and rosmarinic acid [12]. The sodium (**3**) and potassium (**4**) salts of 1,5,9-epideoxyloganic acid were also isolated for the first time. This paper describes the isolation and characterization of these compounds.

RESULTS AND DISCUSSION

Methanolic extract of the aerial parts of *N. cadmea* was fractionated as described in the Experimental section. The *n*-BuOH-soluble fraction was separated by a combination of several types of chromatography to give 11 compounds, seven of which were known compounds and identified by comparison of their physicochemical data with reported values.

1,5,9-Epideoxyloganic acid glucosyl ester (**1**), $[\alpha]_D$ +37.2°, was obtained as an amorphous powder and the molecular formula was determined as $C_{22}H_{34}O_{14}$ based on its negative ion HR-FAB mass spectrum. The ^1H and ^{13}C NMR spectra were almost identical to 1,5,9-epideoxyloganic acid (**2**), except for the appearance of signals due to a *β*-glucopyranosyl ester moiety [δ_H 5.53 (1H, *d*, J = 7.6 Hz); ^{13}C NMR: see Table 1] and an upfield shift (3.4 ppm) of the C-11 signal. These facts strongly suggested that compound **1** is the *β*-glucopyranosyl ester of 1,5,9-epideoxyloganic acid (**2**). Thus, alkaline hydrolysis of **1** gave 1,5,9-epideoxyloganic acid (**2**), confirming the above mentioned presumption.

Compound **3** $[\alpha]_D$ +63.1° and Compound **4** $[\alpha]_D$ +67.4° were obtained as amorphous powders and the elemental compositions were determined as $C_{16}H_{24}O_9$ Na and $C_{16}H_{24}O_9$ K, respectively. The ^1H and ^{13}C NMR spectra were similar to those of **2** and the following discrepancies were observed. The ^1H signals due to H-3 resonated at upper field by 0.27 ppm in **3** and 0.13 ppm in **4**, and the ^{13}C signals due to C-3, C-4 and C-11 shifted (see Table 1). Such shift changes have been reported when a carboxylic function changed to its anion [13]. Thus, compounds **3** and **4** were suggested to be sodium and potassium salts of 1,5,9-epideoxyloganic acid (**2**). The presumption was con-

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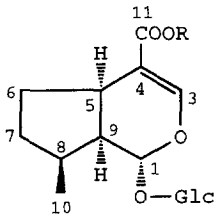
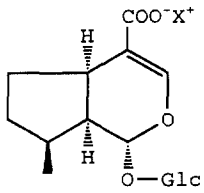
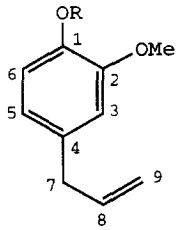


(**1**) R=Glc
(**2**) R=H



(**3**) X=Na
(**4**) X=K



(**5**) R=Glc(6'-1")-Api
(**6**) R=Glc

Glc : β-D-Glucopyranose
Api : β-D-Apiofuranose

Table 1. ^{13}C NMR data for 1,5,9-epideoxyloganic acid glucosyl ester (**1**), 1,5,9-epideoxyloganic acid (**2**), and sodium (**3**) and potassium (**4**) salts of **2** (CD_3OD)

C	1	2	3	4
1	100.9	100.7	100.6	100.6
3	154.9	153.2	148.5	150.0
4	112.7	113.4	119.0	117.9
5	33.9	34.0	35.2	34.9
6	32.2	32.3	32.7	32.8
7	33.7	33.6	33.8	33.9
8	37.1	37.2	37.4	37.4
9	44.3	44.3	44.5	44.5
10	16.7	16.8	16.9	16.9
11	167.6	171.0	175.9	177.3
1′	103.9	103.9	103.9	103.9
2′	75.2	75.2	75.2	75.3
3′	78.3 [(a)]	78.3	78.3	78.3
4′	71.1 [(b)]	71.1	71.2	71.3
5′	78.0 [(a)]	78.0	78.1	78.2
6′	62.6 [(c)]	62.5	62.5	62.7
1″	95.4	—	—	—
2″	73.9	—	—	—
3″	78.7[a]	—	—	—
4″	71.2[b]	—	—	—
5″	78.2[a]	—	—	—
6″	62.4[c]	—	—	—

(a)–(c):Assignments may be reversed.

firmed when both compounds gave **2** on treatment with ion-exchange resin.

Compound **5** was obtained as an amorphous powder, $[\alpha]_D$ −95.9° and the molecular formula was determined as $C_{21}H_{30}O_{11}$ based on its negative ion HR-FAB mass spectrum. The ^1H and ^{13}C NMR spectra showed the presence of a eugenol moiety as the structure of the aglycone portion, since both spectra were superimposable on those of eugenyl-*O*-β-D-glucopyranoside (**6**) [7], except for the signals due to the sugar moiety. The ^{13}C NMR spectrum (see Table 2) also showed the presence of a terminal β-apiofuranosyl moiety [14]. The structure of the sugar moiety was finally deduced as β-apiofuranosyl-(1″-6′)-β-glucopyranoside by comparison of the ^{13}C NMR spectral data with those reported [14]. Thus, the structure of compounds **5** was elucidated as eugenyl-*O*-β-apiofuranosyl-(1″-6′)-*O*-β-glucopyranoside.

EXPERIMENTAL

General

Mps: uncorr.. NMR: ^1H (400 MHz) and ^{13}C (100 MHz), TMS as int. standard. FAB-MS matrix, PEG-400. CC: silica gel 60 (230–400 mesh, Merck). TLC: precoated silica gel 60 F_{254}. HPLC: column, cosmosil $10C_{18}$, detection, 230 nm, solvent, MeOH–H_2O (6 ml min^{-1}).

Plant material

Plant material was collected near Kovad Lake park in July, 1995, and identified as *N. cadmea* Boiss. by the authors (G.H. and E.S.). Voucher specimens (95

Table 2. ^{13}C NMR data of eugenyl-*O*-*β*-apiofuranosyl-(1″-6′)-*O*-*β*-glucopyranoside (**5**) and eugenyl-*O*-*β*-glucopyranoside (**6**) (CD_3OD)

C	5	6
1	146.3	146.3
2	150.8	150.7
3	118.4	118.2
4	136.5	136.4
5	122.2	122.1
6	114.1	114.1
7	40.8	40.8
8	139.0	139.0
9	115.9	115.9
OMe	56.7	56.7
1′	103.1	103.0
2′	74.9	74.9
3′	78.0	78.1
4′	71.6	71.3
5′	77.8	77.8
6′	68.7	62.5
1″	111.0	—
2″	77.0	—
3″	80.5	—
4″	75.0	—
5″	65.6	—

E 013) are deposited in the Herbaria of the Faculty of Pharmaceutical Sciences, Kyoto University, and the Faculty of Pharmacy, Gazi University.

Isolation

Dried aerial parts (1.25 kg) were extracted (×2) with MeOH (18 l) at room temp. for a month. The combined MeOH exts were concd *in vacuo*. The residue was dissolved in 90% MeOH (1 l) and the soln washed with *n*-hexane (1 l × 3). The 90% MeOH layer was concd *in vacuo* and the resultant residue suspended in H_2O (1 l). After the suspension was washed with EtOAc (1 l × 3), the aq. layer was extracted with *n*-BuOH (1 l × 3). The *n*-BuOH layer was concd *in vacuo* to give a residue (20 g). The *n*-BuOH-soluble fr. was sepd by CC on the highly porous synthetic resin, Dianion HP-20 (Φ = 70 mm, L = 420 mm) with stepwise increases of MeOH in H_2O [0 (3 l), 20 (3 l) and 50 (4 l)% aq. MeOH and MeOH (3 l)], frs of 1 l being collected. The residue (2.96 g) from frs 3–10 was subjected to silica gel CC (200 g) with increasing amounts of MeOH in $CHCl_3$. $CHCl_3$, $CHCl_3$–MeOH (97:3), $CHCl_3$–MeOH (19:1), $CHCl_3$–MeOH (93:7), $CHCl_3$–MeOH (9:1), $CHCl_3$–MeOH (17:3), $CHCl_3$–MeOH (4:1), $CHCl_3$–MeOH (7:3), $CHCl_3$–MeOH (1:1) (each 1 l) and MeOH (500 ml) were passed successively. From the $CHCl_3$–MeOH (17:3) eluant, 12 ml fr were collected. Frs 179–256 gave a residue (281 mg) on evap which was separated by HPLC (MeOH:H_2O, 2:3) to give 1,5,9-epideoxyloganic acid (**2**) [2] (64 mg) and 1,5,9-epideoxyloganic acid glucosyl ester (**1**) (19.6 mg). Frs 312–358 gave a residue (1.68 g), which was separated on an ODS column (Φ = 40 mm, L = 350 mm) with a linear increase of MeOH in H_2O [20% MeOH (500 ml)→70% MeOH (500 ml)], collecting 5 ml frs. Frs 20–64 gave a residue (800 mg) on evapn, an aliquot of which (400 mg) was separated by repeated HPLC (MeOH–H_2O, 2:3, then MeOH–H_2O, 1:4) to give 1,5,9-epideoxyloganic acid Na salt (3)(30.4 mg) and 1,5,9-epideoxyloganic acid K salt (**4**) (192 mg).

The residue (5.88 g) from frs 11–13 was subjected to silica gel CC (300 g) with increasing amount of MeOH in $CHCl_3$. $CHCl_3$ (1 l), $CHCl_3$–MeOH (9:1, 1 l), $CHCl_3$–MeOH (17:3, 2 l), $CHCl_3$–MeOH (4:1, 1.5 l) and $CHCl_3$–MeOH (7:3, 1.5 l) were passed successively. The 10–15% MeOH eluate gave a residue (646 mg) which was separated by repeated HPLC (MeOH–H_2O (2:3) and then MeOH–H_2O (3:7)] to give icariside B_2 [8] (18.2 mg). The 15% MeOH eluate gave a residue (325 mg) which was separated by HPLC (MeOH–H_2O, 1:1) to give eugenyl-*O*-*β*-D-glucoside (6)(42.2 mg). The 15% MeOH eluate gave a residue (167 mg) which was separated by HPLC (MeOH–H_2O, 2:3) to give (6*S*, 9*S*)-roseoside [9] (68 mg). The 15–20% eluate gave a residue (271 mg) which was separated by HPLC (MeOH–H_2O,3:7) to give icariside B_1 [8] (37.7 mg). The 20% eluate and the 30% MeOH eluate gave residues (831 and 878 mg, respectively) which were separated by HPLC (MeOH–H_2O, 2:3) to give 1,5,9-epideoxyloganic acid (**2**) (122 mg from the former and 273 mg from the latter).

The residue (4.2 g) from frs 14–15 was subjected to silica gel CC (220 g) with increasing amounts of MeOH in $CHCl_3$. $CHCl_3$ (1 l) and $CHCl_3$–MeOH [(19:1, 1 l), (9:1, 1 l), (17:3, 1.5 l), (4:1, 1 l), (9:1, 1 l), (17:3, 1.5 l), (4:1, 1 l) and (7:3, 500 ml)] were passed successively. The 5–10% MeOH eluate gave a residue (489 mg) which were separated by HPLC (MeOH–H_2O, l = 1) to give eugenyl-*O*-*β*-D-glucoside (**6**) (42.2 mg). The 15% MeOH eluate gave a residue (167 mg) which was separated by HPLC (MeOH–H_2O, 2:3) to give lariciresinel-4′-*O*-*β*-D-glucopyranoside [11] (18.7 mg). The 10–15% MeOH eluate gave a residue (370 mg) which was separated by HPLC (MeOH–H_2O, 7:13) to give the new eugenyl-*O*-*β*-apiofuranosyl(1″-6′)-*O*-*β*-glucopyranoside (**5**) (10.7 mg). The 20–30% MeOH eluate gave a residue (1.22 g), an aliquot (420 mg) of which was separated by HPLC (MeOH–H_2O, 3:7) to give rosmarinic acid [12] (29.8 mg).

Known compounds isolated. 1,5,9-*Epideoxyloganic acid* (**2**). Needles, mp 122–123°, $[\alpha]_D^{27}$ +91.6° (MeOH, *c* 2.87) [2]. *Icariside* B_1. Amorphous powder, $[\alpha]_D^{27}$ −41.5° (MeOH, *c* 1.86) [8]. *Icariside* B_2. Amorphous powder, $[\alpha]_D^{27}$ −77.0° (MeOH, *c* 0.96) [8]. (6*S*,9*S*)-*Roseoside*. Amorphous powder, $[\alpha]_D^{27}$ +50.2° (MeOH, *c* 3.23) [9, 10]. *Eugenyl-O-β*-D-glucopyranoside. Amorphous powder, $[\alpha]_D^{27}$ −48.3° (MeOH, *c* 0.99) [7]. *Lariciresinol*-4′-*O*-*β*-D-glucopyranoside. Amorphous powder, $[\alpha]_D^{27}$ −30.9° (MeOH, *c* 0.93) [11]. *Rosmarinic*

acid. Amorphous powder, $[\alpha]_D^{27}+64.4°$ (MeOH, *c* 1.31) [12].

1,5,9-*Epideoxyloganic acid glucosyl ester* (**1**). Amorphous powder, $[\alpha]_D^{27}+37.2°$ (MeOH, *c* 0.98). IR ν_{max} (KBr) cm^{-1}: 3349, 1704, 1637. UV λ_{max} (MeOH); 240 nm (log ε 4.01). CD Δ $\varepsilon_{233}+2.17$ (MeOH, *c* 1.88×10^{-4} M). ^1H NMR (CD_3OD): δ 1.07 (3H, *d*, *J* = 7.6 Hz, 10-H_3), 1.30 (1H, *m*, Ha-7) 1.65 (1H, *m*, Ha-6), 1.78 (1H, *m*, Hb-7), 2.01 (1H, *m*, Hb-6) 2.30 (1H, *m*, H-8), 2.44 (1H, *dt*, *J* = 8.8 and 4.0 Hz, H-9), 2.96 (1H, *m*, H-5), 3.22 (1H, *dd*, *J* = 8.4 and 8.0 Hz, H-2′), 4.58 (1H, *d*, *J* = 8.0 Hz, H-1′), 5.34 (1H, *d*, *J* = 4.0 Hz, H-1), 5.53 (1H, *d*, *J* = 7.6 Hz, H-1″), 7.55 (1H, *s*, H-3). ^{13}C NMR: Table 1. HR-FABMS (negative) *m/z* 521.1883 $[M-H]^-$ ($C_{22}H_{33}O_{14}$ requires 521.1871).

1,5,9-*Epideoxyloganic acid Na salt* (**3**). Amorphous powder, $[\alpha]_D^{27}+63.1°$ (MeOH, *c* 1.16). IR ν_{max} (KBr) cm^{-1}: 3317, 1651, 1524. UV λ_{max} (MeOH) 230 nm (log ε 3.88). CD Δ $\varepsilon_{222}+3.69$, Δ $\varepsilon_{247}-1.48$ (MeOH, *c* 3.02×10^{-4} M). ^1H NMR (CD_3OD): δ 1.08 (3H, *d*, *J* = 7.3 Hz, H_3-10), 1.31 (1H, *m*, Ha-7) 1.63 (1H, *m*, Ha-6), 1.73 (1H, *m*, Hb-7), 2.00 (1H, *m*, Hb-6) 2.25 (1H, *m*, H-8), 2.35 (1H, *dt*, *J* = 8.4 and 4.0 Hz, H-9), 2.97 (1H, *m*, H-5), 3.22 (1H, *dd*, *J* = 8.0 and 8.0 Hz, H-2′), 3.67 (1H, *dd*, *J* = 11.8 and 4.4 Hz, Ha-6′), 3.83 (1H, *dd*, *J* = 11.8 and 1.6 Hz, Hb-6′), 4.55 (1H, *d*, *J* = 8.0 Hz, H-1′), 5.19 (1H, *d*, *J* = 4.4 Hz, H-1), 7.14 (1H, *s*, H-3). ^{13}C NMR: Table 1. HR-FABMS (negative) *m/z* 381.1154 $[M-H]^-$ ($C_{16}H_{22}O_9$ requires 381.1162).

1,5,9-*Epideoxyloganic acid K salt* (**4**). Amorphous powder, $[\alpha]_D^{27}+67.4°$ (MeOH, *c* 1.08). IR ν_{max} (KBr) cm^{-1}: 3333, 1651, 1539. UV λ_{max} (MeOH) 230 nm (log ε 3.87). CD Δ $\varepsilon_{224}+3.64$, Δ $\varepsilon_{245}-1.27$ (MeOH, *c* 2.71×10^{-4} M). ^1H NMR (CD_3OD): δ 1.08 (3H, *d*, *J* = 7.2 Hz, H_3-10), 1.29 (1H, *m*, Ha-7) 1.67 (1H, *m*, Ha-6), 1.73 (1H, *m*, Hb-7), 2.00 (1H, *m*, Hb-6) 2.26 (1H, *m*, H-8), 2.36 (1H, *dt*, *J* = 8.4 and 4.0 Hz, H-9), 2.97 (1H, *m*, H-5), 3.23 (1H, *dd*, *J* = 8.4 and 8.0 Hz, H-2′), 3.69 (1H, *dd*, *J* = 11.5 and 0.8 Hz, Ha-6′), 3.85 (1H, *brd*, *J* = 11.5 Hz, Hb-6′), 4.57 (1H, *d*, *J* = 8.0 Hz, H-1′), 5.22 (1H, *d*, *J* = 4.0 Hz, H-1), 7.28 (1H, *s*, H-3). ^{13}C NMR: Table 1. HR-FABMS (negative) *m/z* 397.0868 $[M-H]^-$ ($C_{16}H_{22}O_9$ requires 397.0901).

Alkaline hydrolysis of 1,5,9-*epideoxyloganic acid glucosyl ester* (**1**). Compound **1** was dissolved in 0.5 N aq. NaOH (2 ml) and the soln stirred at room temp. for 2 h. The soln was treated with Amberlite IR-120 B (H-form). After removal of ion-exchange resin, the filtrate was concd *in vacuo* to give **2** (5.4 mg) as needles, mp 122–123°, which was identical to an authentic sample of 1,5,9-epideoxyloganic acid, based on mmp and comparisons of ^1H and ^{13}C NMR spectra. HR-FABMS (negative) *m/z*: 359.1336 $[M-H]^-$ (calcd for $C_{16}H_{23}O_9$: 359.1342).

Ion-exchange resin treatments of **3** *and* **4**. Compounds **3** (10.8 mg) and **4** (16.5 mg) were separately treated with Amberlite IR-120 B (H-form) in H_2O (3 ml). After removal of ion-exchange resin by filtration, the filtrate was concd, *in vacuo* to give 8.3 mg and 10.9 mg of 1,5,9-epideoxyloganic acid (**2**), respectively, as colourless needles. Sample from 3: mp 123–124°, $[\alpha]_D^{27}+84.7°$ (MeOH, *c* 0.42); HR-FABMS (negative) *m/z* 359.1359 $[M-H]^-$ (calcd for $C_{16}H_{23}O_9$: 359.1342). Sample from **4**: mp 122–124°, $[\alpha]_D^{27}+90.6°$ (MeOH, *c* 0.50); HR-FABMS (negative) *m/z* 359.1326 $[M-H]^-$ (calcd for $C_{16}H_{23}O_9$: 359.1342). Both samples were identical to an authentic sample of 1,5,9-epideoxyloganic acid (**2**) based on mmp and comparisons of ^1H and ^{13}C NMR spectra.

Eugenyl-O-β-apiofuranosyl (1″-6′)-*O-β-glucopyranoside* (**5**). Amorphous powder, $[\alpha]_D^{27}-95.9°$ (MeOH, *c* 0.54). IR ν_{max} (KBr) cm^{-1}: 3365.1594. UV λ_{max} (MeOH) nm (log ε): 226 (3.94), 278 (3.44). ^1H NMR (CD_3OD): δ 3.56 (2H, *s*, H_2-5″), 3.73 (1H, *d*, *J* = 9.5 Hz, Ha-4″), 3.84 (3H, *s*, OMe), 3.89 (1H, *d*, *J* = 2.4 Hz, H-2″), 3.94 (1H, *d*, *J* = 9.5 Hz, Hb-4″), 3.99 (1H, *dd*, *J* = 11.2 and 2.0 Hz, H_1-6′), 4.79 (1H, *d*, *J* = 7.2 Hz, H-1′), 4.96 (1H, *d*, *J* = 2.4 Hz, H-1″), 5.03 (1H, *dd*, *J* = 10.0 and 2.0 Hz, Ha-9), 5.06 (1H, *dd*, *J* = 16.9 and 2.0 Hz, Hb-9), 5.95 (1H, *ddt*, *J* = 16.9, 10.0 and 6.8 Hz, H-8), 6.74 (1H, *dd*, *J* = 8.3 and 1.7 Hz, H-5), 6.82 (1H, *d*, *J* = 1.7 Hz, H-3), 7.07 (1H, *d*, *J* = 8.3 Hz, H-6). ^{13}C NMR: Table 2. HR-FABMS (negative) *m/z* 457.1715 $[M-H]^-$ ($C_{22}H_{29}O_{11}$ requires 457.1710).

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