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TRITERPENOID SAPONINS FROM *ILEX INTEGRA**

ISSEI YANO, CHIKAGE NISHIIZUMI, KAZUKO YOSHIKAWA and SHIGENOBU ARIHARA

Faculty of Pharmaceutical Sciences, Tokushima-Bunri University, Tokushimashi, Tokushima 770, Japan

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Key Word Index—*Ilex integra*; Aquifoliaceae; pentacyclic triterpene; ilexoside; 23-hydroxyursolic acid; 23-hydroxytomentic acid; rotundic acid; bisdesmoside.

Abstract—Four new saponins named ilexosides XXV–XXVIII, respectively have been isolated from the fresh leaves of *Ilex integra*, together with the known saponins, ilexosides II and XIX. Their structures were established on the basis of spectral and chemical evidence.

INTRODUCTION

In a continuation of our chemical studies with Aquifoliaceous plants [1], we have now investigated *Ilex integra* THUNB., which is distributed in Eastern Asia. The bark of this plant has been used as a birdlime in Japan. In our previous studies with *Ilex crenata*, we isolated 31 saponins all of which were ursane-glycosides. The present paper reports the isolation and the structure of four new saponins along with two known saponins.

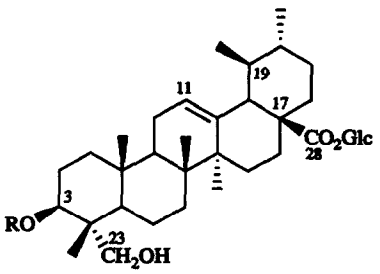
RESULTS AND DISCUSSION

Fresh leaves (5 kg) of *I. integra* furnished four new saponins, ilexoside XXV (**1**, 60 mg), XXVI (**2**, 60 mg), XXVII (**3**, 60 mg) and XXVIII (**4**, 80 mg), in addition to the known saponins, ilexosides II (**5**, 220 mg) and XIX (**6**, 340 mg).

Ilexoside XXV (**1**) was assigned a M_r of 796 (negative FAB-mass spectrum *m/z* 795 $[M-H]^-$). The elemental formula of this compound was confirmed as $C_{42}H_{68}O_{14}\cdot 3H_2O$ by elemental analysis. Its EI-mass spectrum showed fragment ion peaks at *m/z* 454, 248, 224, 206 and 203 and 175, which showed that the aglycone is an amyrin derivative having two hydroxyl groups in the A/B rings and one esterified carboxyl group in the D/E rings [2, 3]. Compound **1** afforded D-glucose on acid hydrolysis. The ^1H NMR spectrum of **1** indicated the presence of four tertiary methyl groups (δ 0.90, 0.97, 1.16 and 1.16), two secondary methyl groups [δ 0.94 (*d*, $J=6.0$ Hz), 0.96 (*d*, $J=6.0$ Hz)], one trisubstituted olefinic proton (δ 5.46 *br t*) and two β-glucosyl units [H-1: δ 5.15 (*d*, $J=7.5$ Hz) and 6.25 (*d*, $J=8.0$ Hz)].

Comparison of the ^{13}C NMR spectrum of **1** with that of ursolic acid showed that **1** is a glycoside of 23- or 24-hydroxyursolic acid. Further comparison with the ^{13}C NMR spectrum of cynarasaponin F (**7**) obtained from *Cynara cardunculus* [4, 5], showed that **1** was a glycoside of 23-hydroxyursolic acid, that varied structurally from **7** only its saccharide moieties, and that these sugar units were also affixed to the C-3 and C-28 positions. The EI-mass spectrum of **1** acetate showed the presence of a fragment ion peak due to a terminal hexosyl cation (*m/z* 331). The carbon signals due to sugar moieties in the ^{13}C NMR spectrum of **1** were superimposable on those of lucyoside E (**8**) obtained from *Luffa cylindrica* [6]. Therefore, **1** was formulated as 3-*O*-β-D-glucopyranosyl 23-hydroxyursolic acid 28-*O*-β-D-glucopyranoside.

Ilexoside XXVI (**2**), $C_{48}H_{78}O_{19}\cdot 4H_2O$, was obtained as a powder. Its FAB-mass spectrum revealed a quasi-molecular ion peak at *m/z* 957 $[M-H]^-$, i.e. 162 mass units higher than that of **1**. On acid hydrolysis, **2** afforded D-glucose. The ^1H NMR spectrum indicated the presence of three β-glucosyl units [H-1: δ 5.09 (*d*, $J=8.0$ Hz), 5.09 (*d*, $J=8.0$ Hz) and 6.25 (*d*, $J=8.0$ Hz)]. Comparison of the ^{13}C NMR spectrum of **2** with that of **1**, showed that **2** was also a glycoside of 23-hydroxyursolic acid, that varied



Ilexoside	R
XXV	1 - Glc
XXVI	2 - Glc $\xrightarrow{6}$ Glc
	7 - GlcA

Glc : β - D - Glucopyranosyl
GlcA: β - D - Glucuronopyranosyl

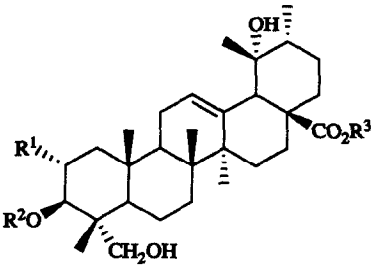
*Part VII in this series 'Triterpenoid Saponins of Aquifoliaceous Plants'. For Part VI see ref. [1].

structurally from **1** only in its saccharide moieties, and that these sugar units were also affixed to the C-3 and C-28 positions. The EI-mass spectrum of **2** acetate showed the characteristic fragment ion peaks due to a terminal hexosyl cation (*m/z* 331), and a hexosylhexosyl cation (*m/z* 619). The glucosy C-6 signal of the 3-*O*-glucosy unit in **2** appeared at lower field (+7.4 ppm) than in **1** because of the glycosylation shift [7] disclosing that a β-glucopyranosyl group was located at C-6 of the 3-*O*-glucose residue. Therefore, **2** was formulated as 3-*O*-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl 23-hydroxyursolic acid 28-*O*-β-D-glucopyranoside.

Ilexoside XXVII (**3**), $[\alpha]_D$+16.1° (MeOH) has the molecular formula, $C_{41}H_{66}O_{14}$ (quasi-molecular ion peak at *m/z* 781 in the FAB-mass spectrum and carbon counts in the ^{13}C NMR spectrum). On acid hydrolysis, compound **3** afforded L-arabinose and D-glucose in the ratio of 1:1. The ^1H NMR spectrum of **3** indicated the presence of five tertiary methyl groups (δ0.93, 1.10, 1.21, 1.40 and 1.65), one secondary methyl group [δ1.08 (*d*, *J* = 6.5 Hz), one trisubstituted olefinic proton (δ 5.57, *br t*), one α-arabinosyl unit [H-1: δ 5.01 (*d*, *J* = 7.0 Hz)] and one β-glucosyl unit [H-1: δ 6.35 (*d*, *J* = 8.5 Hz)].

Cellulase treatment of **3** gave rotundic acid (**9**) [8], mp >300°, $[\alpha]_D$+62.5° (MeOH), $C_{30}H_{48}O_5 \cdot 2H_2O$, which was converted to its methyl ester (**9'**) with CH_2N_2. The EI-mass spectrum of **3** acetate showed the fragment ion peaks due to a terminal deoxyhexosyl cation (*m/z* 259) and a hexosyl cation (*m/z* 331). By comparison of the ^{13}C NMR spectrum of **3** with that of pedunculoside (**10**) [9], obtained from *I. rotunda*, a glycosylation shift was observed for the C-3 signal (+8.3 ppm, from δ 73.7 to 82.0) of **3**, indicating that the arabinosyl unit is linked to the C-3-OH. The carbon signals due to the sugar moieties were superimposable on those of ziyu-glycoside I (**11**) [10], indicating the same sugar moieties. Therefore, **3** was formulated as 3-*O*-α-L-arabinopyranosyl rotundic acid 28-*O*-β-D-glucopyranoside.

Ilexoside XXVIII (**4**), $C_{41}H_{66}O_{15} \cdot 5/2H_2O$ was obtained as a powder. Its FAB-mass spectrum revealed a quasi-molecular ion peak at *m/z* 797 $[M-H]^-$, 16 mass units higher than that of **3**. Its EI-mass spectrum showed ion peaks at *m/z* 486, 264, 246, 222, 201 and 191, which showed that the aglycone was an amyrin derivative having three hydroxyl groups in the A/B rings, and one hydroxyl and one esterified carboxyl group in the D/E rings. Compound **4** afforded L-arabinose and D-glucose in the ratio of 1:1 on acid hydrolysis. The ^1H NMR spectrum indicated the presence of one α-arabinosyl unit [H-1: δ 4.98 (*d*, *J* = 7.5 Hz)], and one β-glucosyl unit [H-1: δ 6.29 (*d*, *J* = 8.0 Hz)]. Comparison of the ^{13}C NMR spectrum of **4** with that of niga-ichigoside F1 (28-*O*-glucoside of 23-hydroxytormentic acid, **12**) [11], showed a glycosylation shift of +10.2 for the C-3 signal (from δ 78.2 to 88.4) of genin, demonstrating that a α-arabinopyranosyl group is located at the C-3-OH. The carbon signals due to sugar moieties were superimposable on those of **3**. Therefore, **4** was formulated as 3-*O*-α-L-arabinopyranosyl 23-hydroxytormentic acid 28-*O*-β-D-glucopyranoside.



	R¹	R²	R³
Ilexoside XXVII **3**	-H	-Ara	-Glc
XXVIII **4**	-OH	-Ara	-Glc
9	-H	-H	-H
10	-H	-H	-Glc
12	-OH	-H	-Glc

Ara: α-L-Arabinopyranosyl

EXPERIMENTAL

Mp: uncorr. ^1H (400 MHz) and ^{13}C (100 MHz) NMR: pyridine-d_5 with TMS as an int standard. Chemical shifts are given in δ (ppm) and coupling constants (*J* values) are given in Hz. EI and FAB-MS: JEOL JMS-PX303 mass: spectrometer; CC: silica gel 60 (230–400 mesh, Merck) and silicic acid (100–200 mesh, Mallinckrodt); TLC: precoated silica gel 60F-254 (Merck).

Isolation of compounds **1**–**6**. The fresh leaves (5 kg) of *Ilex integra* were extracted with hot H_2O (3 hr). The H_2O extract was passed through an Amberlite XAD-2 column and eluated with MeOH. Crude saponins (110 g), obtained by evapn of the MeOH eluate, were chromatographed on a silica gel column with $CHCl_3$–MeOH–H_2O (25:2:0.1–65: 40:10) to give 10 frs, frs I–X in order to elution. Fr.VI (3 g) was chromatographed on Servachrome XAD-2 (eluated with 30–100% MeOH) to give 8 frs (frs VIa–VIj). Fr. VIf (0.3 g) was repeatedly chromatographed on silicic acid column with EtOAc–MEK–EtOH–H_2O (40:6:2:1) and on a silica gel column $CHCl_3$–BuOH–MeOH–H_2O (8:8:3:4) to afford ilexosides XXV (**1**, 0.06 g) and II (**5**, 0.1 g). Fr. VII (1.5 g) was chromatographed on Servachrome XAD-2 (eluated with 30–100% MeOH) to give 5 frs (frs VIIa–VIIe). Fr. VIIb (0.3 g) was subjected to silica gel CC with $CHCl_3$–MeOH–H_2O (25:4:0.1) to afford ilexosides XXVII (**3**, 0.06 g) and XXVIII (**4**, 0.08 g). Fr. VIII (3 g) was chromatographed on Servachrome XAD-2 (eluated with 30–100% MeOH) to give 5 frs (frs VIIIa–VIIIe). Fr. VIIIb (0.5 g) was repeatedly chromatographed on a silica gel column [$CHCl_3$–BuOH–MeOH–H_2O (16:8:3:4) and with $CHCl_3$–MeOH–H_2O (25:4:0.1)] to afford ilexosides XXVI (**2**, 0.06 g), II (**5**, 0.12 g) and XIX (**6**, 0.34 g).

Ilexoside XXV (**1**). Amorphous powder, $[\alpha]_D$+14.4° (MeOH; *c* 2.7). FAB-MS *m/z*: 795 $[M-H]^-$. (Found: C, 59.55; H, 8.58. $C_{42}H_{68}O_{14} \cdot 3H_2O$ requires: C, 59.28; H, 8.76.) EI-MS *m/z*: 454, 436, 424, 408, 248, 224, 206, 203 and 175; ^1H NMR δ: 0.90, 0.97, 1.16, 1.16 (3H × 4, *s*, Me-

24, Me-25, Me-26 and Me-27), 0.94, 0.96 (3H × 2, *d*, $J = 6.0$ Hz, Me-29 and Me-30), 3.70 (1H, *d*, $J = 10.5$ Hz, H-18), 5.15 (1H, *d*, $J = 7.5$ Hz, H-1′ of Glc), 5.46 (1H, *br t*, H-12), 6.25 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc); ^{13}C NMR: Tables 1 and 2.

Ilexoside XXVI (**2**). Amorphous powder, $[\alpha]_D - 0.4°$ (MeOH; *c* 2.6). FAB-MS *m/z*: 957 $[M-H]^-$. (Found: C, 55.97; H, 8.21. $C_{48}H_{78}O_{19}\cdot 4H_2O$ requires: C, 55.91; H, 8.41.) ^{1}H NMR δ: 0.90, 0.97, 1.12, 1.15 (3H × 4, *s*, Me-24, Me-25, Me-26 and Me-27), 0.93, 0.96 (3H × 2, *d*, $J = 6.0$ Hz, Me-29 and Me-30), 3.68 (1H, *d*, $J = 11.0$ Hz, H-18), 5.09 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc), 5.09 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc), 5.43 (1H, *br t*, H-12), 6.25 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc); ^{13}C NMR: Tables 1 and 2.

Ilexoside XXVI (**3**). Needles, mp 201–202°, $[\alpha]_D + 16.1°$ (MeOH; *c* 3.4). FAB-MS *m/z*: 781 $[M-H]^-$. (Found: C, 59.65; H, 8.46. $C_{41}H_{66}O_{14}\cdot 5/2H_2O$ requires: C, 59. 47; H, 8.64.) EI-MS *m/z*: 454, 436, 424, 408, 248, 224, 206, 203 and 175; ^{1}H NMR δ: 0.93, 1.10, 1.21, 1.40, 1.65 (3H × 5, *s*, Me-24, Me-25, Me-26, Me-27 and Me-29), 1.08 (3H, *d*, $J = 6.5$ Hz, Me-30), 2.92 (1H, *br s*, H-18), 5.01 (1H, *d*, $J = 7.0$ Hz, H-1′ of Ara), 5.57 (1H, *br t*, H-12), 6.35 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc); ^{13}C NMR: Tables 1 and 2.

Ilexoside XXVIII (**4**). Needles, mp 218–220°, $[\alpha]_D + 11.9°$ (MeOH; *c* 3.2). FAB-MS *m/z*: 797 $[M-H]^-$. (Found: C, 58.31; H, 8.27. $C_{41}H_{66}O_{15}\cdot 5/2H_2O$ requires: C, 58.35; H, 8.49.) EI-MS *m/z*: 486, 264, 246, 222, 201 and 191; ^{1}H NMR δ: 0.98, 1.08, 1.20, 1.39, 1.61 (3H × 5, *s*, Me-24, Me-25, Me-26, Me-27 and Me-29), 1.08 (3H, *d*, $J = 6.5$ Hz, Me-30), 2.91 (1H, *br s*, H-18), 4.98 (1H, *d*, $J = 7.5$ Hz, H-1′ of Ara), 5.53 (1H, *br t*, H-12), 6.29 (1H, *d*, $J = 8.0$ Hz, H-1′ of Glc); ^{13}C NMR: Tables 1 and 2.

Enzymatic hydrolysis of ilexoside XXII (**3**). Ilexoside XXVII (**3**) (40 mg) was dissolved in EtOH–H_2O (1:9) and 0.01 M NaH_2PO_4 buffer (pH 4.0) (3 ml each) and incubated with crude cellulase (40 mg, Sigma) for 2 weeks at 37°. After work-up as usual, the crude genin was chromatographed on a silica gel column with $CHCl_3$–MeOH–H_2O (25:6:0.1) giving rotundic acid (**9**, 15 mg), needles mp >300°, $[\alpha]_D + 62.5°$ (MeOH; *c* 1.6). (Found: C, 68.65; H, 9.67. $C_{30}H_{48}O_5\cdot 2H_2O$ requires: C 68.67; H, 9.99). IR ν_{max}^{KBr} cm^{-1}: 3450 (br, OH), 1690 (C=O), 1045, 1025; FAB-MS *m/z* 487 $(M-H)^-$; EI-MS *m/z*: 488 $[M]^+$, 470, 452, 442, 424, 264, 246, 224, 206, 201, and 175; ^{1}H NMR δ: 0.97, 1.03, 1.09, 1.44, 1.66 (3H × 5, *s*, Me-24, Me-25, Me-26, Me-27 and Me-29), 1.11 (3H, *d*, $J = 6.5$ Hz, Me-

Table 1. ^{13}C NMR spectral data for aglycone moeties of compounds **1**–**4**, **7**, **10** and **12** (pyridine-d_5, δ values)

C	1	2	3	4	7	10	12
1	39.0	38.9	39.0	47.3	39.0	39.0	47.9
2	26.0	26.1	26.2	67.8	28.8	27.8	68.8
3	82.3	82.8	82.0	88.4	82.4	73.7	78.2
4	43.5	43.4	43.5	44.8	43.5	42.9	43.5
5	47.7	47.7	47.6	47.3	47.6	48.7	48.5
6	18.3	18.3	18.4	18.5	18.2	18.9	18.7
7	33.0	33.2	33.2	33.4	33.3	33.3	33.1
8	40.2	40.2	40.7	40.7	40.3	40.6	40.6
9	47.6	48.1	47.9	47.9	48.2	47.9	47.9
10	36.8	36.9	37.0	37.9	36.8	37.3	38.3
11	23.7	23.7	24.7	24.3	23.9	24.2	24.2
12	126.1	126.2	128.5	128.4	126.2	128.5	128.3
13	138.4	138.4	139.4	139.3	138.4	139.3	139.2
14	42.5	42.5	42.2	42.2	42.6	42.2	42.1
15	28.7	28.7	29.3	29.2	26.1	29.3	29.1
16	24.6	24.7	26.2[a]	26.0[a]	24.7	26.2	26.0[a]
17	48.1	48.4	48.7	48.7	48.4	48.7	48.5
18	53.3	53.4	54.5	54.4	53.4	54.5	54.4
19	39.3[a]	39.4[a]	72.7	42.7	39.4	72.7	72.5
20	39.1[a]	39.2[a]	42.2	42.2	39.2	42.2	42.1
21	30.7	30.9	26.8[a]	26.8[a]	30.9	26.8	27.0[a]
22	36.8	36.9	37.8	37.9	36.8	37.8	37.7
23	64.7	65.0	64.5	63.7	64.4	68.0	66.6
24	13.6	13.7	13.7	14.7	13.7	13.2	14.2
25	16.3	16.4	16.4[b]	17.5[b]	16.4	16.2	17.5[b]
26	17.6[b]	17.5[b]	17.5	17.5[b]	17.4	17.6	17.5[b]
27	23.7	23.7	24.7	24.6	23.8	24.6	24.5
28	176.1	176.2	177.1	177.0	176.2	177.1	176.8
29	17.7[b]	17.8[b]	27.1	27.1	17.8	27.1	27.0
30	21.2	21.3	16.8[b]	16.8[b]	21.3	16.8	16.7[b]

[a,b]Values with the same symbol may be interchanged in the vertical column.

Table 2. ^{13}C NMR spectral data of sugar moeties of compounds **1–4**, **8** and **11** (pyridine-d_5, δ values)

	1	2	3	4	8	11
Inner Ara or Glc						
C-1	105.9	105.4	106.7	106.6	105.8	107.2
2	75.9	75.2	73.1	73.1	75.9	73.0
3-*O*-3	78.7	78.4	74.7	74.9	78.7	74.6
4	71.8	71.7	69.7	69.8	71.8	69.4
5	78.4	76.9	67.0	67.9	78.2	66.4
6	62.9	70.3			63.0	
Terminal Glc (1→6)						
C-1		106.1				
2		75.7				
3		78.6				
4		71.6				
5		78.5				
6		62.8				
Glc						
C-1	95.8	95.7	96.0	95.9	95.8	95.5
2	74.1	74.1	74.1	74.1	74.2	74.2
28-*O*-3	79.2	79.1	79.2	79.2	79.2	79.0
4	71.3	71.3	71.2	71.3	71.5	71.6
5	78.9	78.9	78.9	79.0	78.9	79.0
6	62.4	62.4	62.4	62.4	62.5	62.7

30), 2.59 (1H, *br s*, H-18), 3.68 and 4.12 (each, 1H, *d*, J = 11.0 Hz, H_2-23), 4.13 (1H, *dd*, J = 10.5, 5.5 Hz, H-3), 5.58 (1H, *br t*, H-12); ^{13}C NMR δ: 13.2, 16.1, 16.9, 17.4, 18.9, 24.2, 24.8, 26.5, 27.1, 27.3, 27.8, 29.5, 33.4, 37.3, 38.6, 40.0, 40.5, 42.3, 42.5, 43.0, 47.9, 48.1, 48.8, 54.7, 68.1, 73.0, 73.7, 128.2, 140.1, 180.8.

Methylation of rotundic acid (**9**). Compound **9** (20 mg) in Et_2O was treated with CH_2N_2–Et_2O to give the monomethylester **9′** (20 mg), needles mp 289–291°, $[\alpha]_D$ +43.3° ($CHCl_3$; *c* 1.7). (Found: C, 71.57; H, 10.07. $C_{31}H_{50}O_5 \cdot H_2O$ requires: C 71.50; H, 10.06.) IR ν_{max}^{KBr} cm^{-1}: 3350 (br, OH), 1720 (C=O), 1040, 1015; EI-MS *m/z*: 502 $[M]^+$, 484, 466, 442, 424, 278, 260, 224, 206, 201, and 175; ^1H NMR ($CDCl_3$) δ: 0.68, 0.88, 0.94, 1.20, 1.25 (3H × 5, *s*, Me-24, Me-25, Me-26, Me-27 and Me-29), 0.93 (3H, *d*, J = 7.0 Hz, Me-30), 3.01 (1H, *br s*, H-18), 3.58 (3H, *s*, *O*-Me), 3.39 and 3.69 (each, 1H, *d*, J = 10.0 Hz, H_2-23), 3.61 (1H, *dd*, J = 10.5, 7.0 Hz, H-3), 5.35 (1H, *br t*, H-12); ^{13}C NMR δ: 13.1, 16.0, 16.7, 17.1, 18.8, 24.0, 24.7, 26.1, 26.7, 26.9, 27.7, 29.1, 33.2, 37.2, 38.1, 38.9, 40.3, 42.0, 42.2, 42.9, 47.7, 48.6, 48.7, 51.5, 54.5, 68.1, 72.6, 73.6, 128.3, 139.4, 178.4.

Identification of component sugars. A soln of each compound (3–4 mg) in 5% H_2SO_4 in 50% EtOH was heated at 100° for 3 hr. The reaction mixt. was diluted with H_2O, neutralized with Amberlite IR-45 and evapd *in vacuo* to dryness. The mole ratio and D(L) of each sugar was determined by HPLC (Shodex RSpak DC-613, 75% MeCN, 1 ml min^{-1}, 70°) comparison with authentic sugars (10 mmol each of L-Ara and D-Glc) using RI (waters 410) and chiral (Shodex OR-I) detection. These sugars gave peaks as follows: L(+)-Ara; 6.2 min, D(+)-Glc; 7.38 min.

Acetylation of ilexosides XXV (**1**), XXVI (**2**) and XXVII (**3**). Each compound (1–2 mg) was acetylated with Ac_2O–pyridine (each 0.1 ml) at room temp. overnight. Work-up as usual gave acetylated **1**, **2** and **3**.

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