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Studies on the Constituents of *Acanthopanax koreanum*

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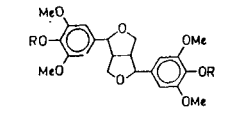
Abstract—*Acanthopanax koreanum* Nakai (Araliaceae) is a indigenous medicinal plant growing throughout Jeju-Do in Korea. The plant extract is used in rheumatism, tonic, paralysis and sedative agent. From the roots of *A. koreanum*, lignan compounds, a diterpenoid, and a polyacetylene compound were isolated and their structures were elucidated by using IR, PMR, CMR and MS spectral data.

Keywords—*Acanthopanax koreanum* · Araliaceae · Eleutheroside E · ariensin · Eleutheroside B · isopimara-9(11), 15-diene-19-ol · falcarindiol

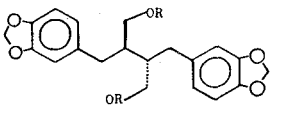
Out of the many species of the Araliaceae family only Panax ginseng has been used in medicine up to now. Ccomparative chemical and pharmacological studies of *Eleutherococcus senticosus* Rupr. et Maxim by Russian scientists have brought out a new valuable medicinal plant *Eleutherococcus* species.[1,2] Korea is one of important areas favorable to distribution of *Acanthopanax* species. *Acanthopanax koreanum* Nakai is an indigenous plant and distributes only in Jeju-Do. It is used in medicine for people in their dotage, for paralysis, arthritis, rheumatism, lameness, high blood pressure and as a tonic[3].

From the MeOH extract of the root bark of *Acanthopanax koreanum* we have isolated five compounds; three are lignan compounds, one is anew diterpenoid and the other is a polyacetylene compound. (Fig. 1)

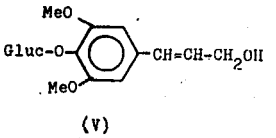
(I) is crystalline with molecular formula $C_{34}H_{46}O_{18}$, mp 257-259° and gives a positive mäule test and anthrone test. The ir spectrum of (I) suggested the presence of a β-glucose moiety (890 cm^{-1}, β-sugar) with a broad hydroxyl band centered at 3400 cm^{-1}, a phenyl ring (1595, 1500, 1460 and 805 cm^{-1}), a $-CH_2-O-$ linkage (1416 cm^{-1}) and methyl (1365 cm^{-1}) groups. The H^1-nmr spectrum of the aglycone indicated a generally symmetrical structure with four aromatic protons (δ 6.66), and four methoxyls (δ 3.76). In the comparison of the chemical shifts of (I) and various lignan compounds[4] (Table I), the signals due to protons at C-2 and C-6 at



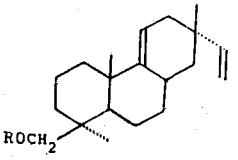
(I) R = $C_6H_7O(OH)_4$
(II) R = $C_6H_7O(OAc)_4$



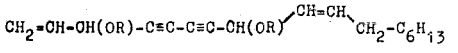
(III) R = Ac
(IV) R = H



(V)



(VI) R = H
(VII) R = Ac



(VIII) R = H
(IX) R = Ac

Fig. 1.

Table I. Chemical shifts of comp. I compared with various lignan compounds

compound	Form	1-H, 5-H	2-H, 6-H	4-H, 8-H
Comp. I		3.19	4.67	4.20, 4.32
Lirioresinol B	IIIb	3.11	4.73 d(J=4)	4.15~4.45 m(2H), 3.90~4.04 m(2H)
Lirioresinol A	IIb	2.9, 3.3	4.83 d(J=5)	4.08 m(1H), 3.88m(2H)
			4.41 d(J=7.5)	3.2~3.5 m(1H)
Lirioresinol dimethylether	Ia	3.25	4.98 (J=5)	3.63 m(2H), 3.72 m(2H)
Eudesmin	IIIc	3.15	4.73 d(J=4)	4.2~4.4 m(2H), 3.8~4.0 m(2H)
Epieudesmin	IIc	2.9, 3.3	4.85 d(J=5.5)	4.1~4.4 m(1H), 3.7~3.9 m(2H)
			4.45 (J=7)	3.87~3.90 m(1H)
Dieudesmin	Ic	3.15	4.90 d(J=5)	3.65~4.0 m(2H), 3.3~3.65 m(2H)

a : Ar=3, 4, 5-trimethoxypenyl

b : Ar=4-hydroxy-3, 5-dimethoxyphenyl

c : Ar=3, 4-dimethoxyphenyl

δ 4.66 in the H^1-nmr spectrum strongly suggests that it is one of the diequatorial type.

(I) did not display a recognizable molecular ion peak but did exhibit an intense peak at m/e 418 (aglycone peak). The mass spectrum of the aglycone gives rise to all the principal fragment ions at m/z 388, 236, 235, 210, 193, 181, 167 and 154 by a breakdown pattern characteristic of aryl-substituted furofuranoid lignans.[5] (Fig. 2)

(I) by acetylation under mild conditions gives the eight acetate signals and indicates that it has two glucose moiety. All reported data clearly support the structure and absolute configuration of it.

(III) is a colourless viscous liquid, showing aromatic ring absorption at λ max (EtOH) 287

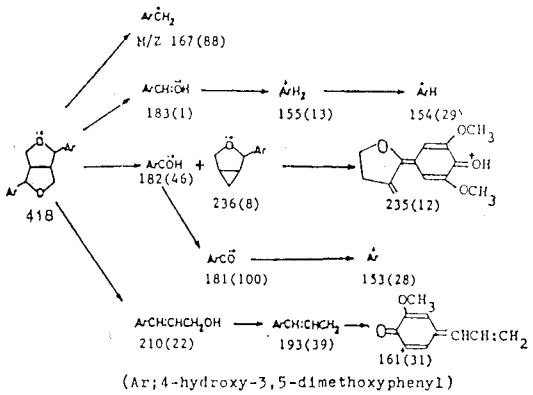
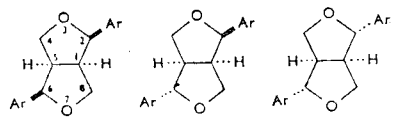


Fig. 2. MS Fragmentation pattern of compound I



(I) (II) (III)

nm in the uv spectrum and ester carbonyl absorption at 1730 cm^{-1} in the ir spectrum. The apparent odd number of protons displayed in the H^1-nmr spectrum showed the dimeric nature of the molecule,[6] since for a methylenedioxy group at δ 5.91, there are one acetate singlet at δ 2.05, three aromatic protons at δ 6.5-6.7, one methylene of an esterified primary alcohol at δ 4.03, one benzylic methylene at δ 2.60 and one methine proton at δ 2.10. These data show that (III) is a neolignan that belongs to the group of austrobailignans.[7] In the ms spectrum of comp. III, the molecular ion peak appeared at m/z 442 and fragmentation pattern showed that (III) is symmetrical configuration. Hydrolysis of ariensin gave the corresponding solid diol (IV), mp, 79-81°C. Its spectral data, given in the experimental section, are in full agreement with those corresponding to its structure. This compound is first isolated in *Acanthopanax* species.

(V) is white needle crystal with molecular formula $C_{17}H_{24}O_9$, mp 186-188°, and is shown to be identical with syringin by its spectral data; 4′-O-β-D-glucosyl sinapyl alcohol, which is widely distributed in the plant kingdom.[8]

(VI) is a new diterpene compound and is

white needle crystal with molecular formula $C_{20}H_{32}O$, mp 73°C. In the ir spectrum, it showed hydroxyl (3340 cm^{-1}) and olefinic (1645, 812 cm^{-1}) absorptions and no CO bands. The H^1-nmr spectrum contains three tertiary methyl signals at δ 0.96 and 1.02, and an AB pattern (δ_A 4.25, δ_B 3.37, J=10.8 Hz) attributed to the methylene protons of a primary alcohol. A broadened doublet at δ 5.35 was attributed to the proton (apparently coupled to two adjacent protons) of a trisubstituted olefin. The olefinic proton region (δ 4.8-5.8) of the spectrum also showed an ABC pattern which was assigned to a monosubstituted double bond and closely resembled the vinyl spectrum of methyl isopimarate. The ms spectra of the dienes show molecular ion peak at m/e 288, intense peaks for M-CH_2OH, M-C_5H_8 and

Table II. CMR spectrum of compound VI

C-Number	Chemical shifts	C-Number	Chemical shifts
1	41.05(t)	11	115.70(d)
2	19.08(t)	12	35.41(t)
3	37.53(t)	13	34.79(s)
4	38.33(s)	14	41.57(t)
5	46.25(s)	15	150.19(d)
6	17.98(t)	16	109.00(t)
7	26.83(t)	17	22.43(q)
8	28.94(d)	18	26.49(q)
9	151.17(s)	19	64.77(t)
10	37.69(s)	20	25.97(q)

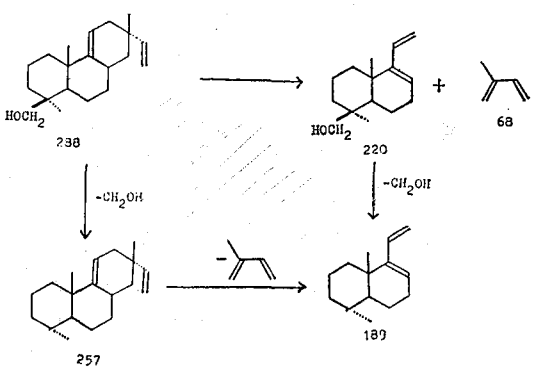


Fig. 3. MS fragmentation pattern of compound VI

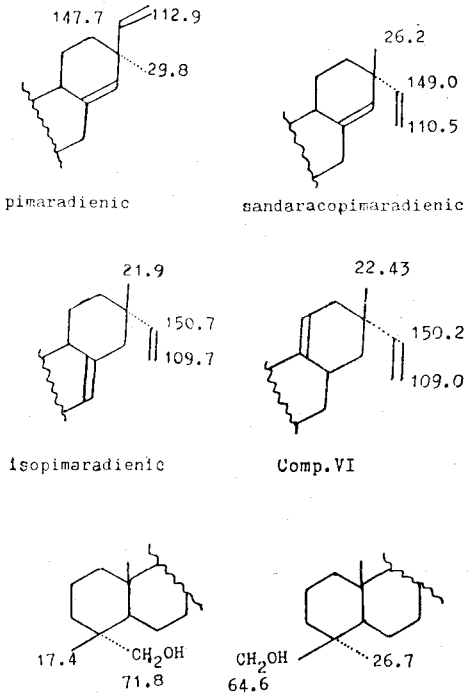


Fig. 4. *Comparison of the carbon shifts of diterpenic substances*

M-CH_2OH-C_5H_8, the latter pair corresponding to elimination of 2-methylbutadiene by a retro Diels-Alder process with and without loss of a —CH_2OH group. from A-ring.[9] (Fig. 3)

The C^{13}-nmr spectrum of (VI) (Table II) was assigned by off-resonace test and APT and it was consistent with structure (VI).

Comparison of the olefinic carbon shifts of (VI) with those of pimaradienic, sandaracopimaradienic, and isopimaradienic systems shows the compound to be of the isopimaradienic type and comparison of the oxymethylene shift of 18-hydroxy and 19-hydroxy diterpenic substances with that of (VI) classifies this compound as an 19-hydroxy diterpene.[10] (Fig. 4)

The spectral data of acetate (VII) was also in good agreement of its structure.

(VIII) was characterized as falcarindiol by analysis of the uv, ir, H^1-nmr and C^{13}-nmr spectra of it and its diacetate.[11] This compound

was also first isolated in the *Acanthopanax* species.

Experimental

A. koreanum was collected in September at Halla-Mt. (Jeju-Do). Dried root bark (8 kg) was extracted with MeOH (10 $l \times 3$). The MeOH extract was evaporated in vacuo and fractionated with ethylether and n-BuOH. The ethylether fraction was evaporated in vacuo and chromatographed silica gel column with benzene: ethylacetate: aceton (60:20:8) as eluent to give ariensin (III), isopimara-9(11), 15-diene 19-ol (VI) and falcarindiol (VIII). The n-BuOH fraction was chromatographed silica gel column with $CHCl_3$: MeOH: H_2O (70:30:4) as eluent to give Eleutheroside E and Eleutheroside B.

Eleutheroside E(I): colorless needles (from dil. MeOH) $C_{34}H_{46}O_{18}$, mp 257-259°, $[\alpha]_D^{25}$ −5.6 (c=9×10^{-2}, H_2O); uv, λ_{max} (MeOH) 270 nm; ir, ν_{max} (KBr) 3400 (−OH), 1595, 1505, 1465, 810 (phenyl ring), 1420 (−CH_2—O—), 1365 (methyl) and 890 (β-glucose moiety); H^1-nmr (360 MHz, DMSO-d6) δ 3.19 (2H, m, 1,5-H) 3.0-3.9 (4H, glucose-H), 3.76 (12H, s, 4 OCH_3) 4.20 (2H, m, 4,8-Ha), 4.32 (2H, m, 4,8-He), 4.66 (2H, m, 2, 6-H) 6.66 (4H, s, aromatic proton); C^{13}-nmr (20 MHz, DMSO-d_6) δ 53.6 (1,5-C), 56.6 (−OCH_3), 61.1 (6-C, glucose), 70.1 (4-C, glucose), 71.4 (4, 8-C), 74.2 (2-C, glucose), 76.6 (3-C, glucose), 77.1 (5-C, glucose), 85.1 (2, 6-C), 102.9 (1-C, glucose), 104.6 (2-C, Ar), 134.1 (1-C, Ar), 137.2 (4-C, Ar), 152.7 (3-C, Ar); EI-ms, *m/z* (rel. int. %), 418(100), 388(1.98), 387(6.63) 236 (9.88), 235 (11.46), 210(20.43), 193(35.23); CI-ms (70 eV, CH_4) *m/z*, 419, 235, 163, 145, 127, 115.

Eleutheroside E octaacetate (II): (I) (50 mg) was acetylated with acetic anhydride (2 ml) and pyridine (2 ml) at room temperature overnight and gave Eleutheroside Eoctaacetate (II). H^1-nmr, δ 3.15 (2H, m, 1,5-H), 3.85 (12H, s, -OCH_3), 4.05 (4H, m, 4,9-H), 4.15 (6H, m, 5,6-H, glucose), 4.77 (2H, m, 2,6-H), 5.15 (8H, m, 1,2,3,4-H, glucose), 6.56 (4H, s, Ar-H).

ariensin (III): colourless viscous liquid, $C_{24}H_{26}O_8$, uv, λ_{max} (EtOH) 287 nm; ir, ν_{max} (neat), 1730, 1610, 1043 and 930 cm^{-1}; H^1-nmr, (80 MHz, $CDCl_3$) δ 2.05 (6H, s, 2 × -OCH_3), 2.10 (2H, m, 8,8-H), 2.60 (4H, m, 7,7-H), 4.03 (4H, m, 9,9-H), 5.91 (4H, s, 2 × -O-CH_2-O-), 6.51-6.68 (6H, m, Ar-H); ms, *m/z*. 442 (M^+), 220, 182, 174, 161, 148 and 135.

Hydrolysis of ariensin (III)

A solution of 80 mg of (III) in 10 ml of MeOH was mixed with a solution of 1g of KOH in 1ml of H_2O and 10 ml of MeOH. The mixture was refluxed for 6hr, concentrated, poured over ice water and extracted with ethyacetate. The ethylacetate layer was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed over 15 g of silica gel and eluted hexane: ethylacetate (8:1). The crystalline fractions were combined and recrystallized from choroform-hexane, yielding 50 mg of white crystrals (IV), mp, 79~81°, uv, λ_{max} (KBr), 3040 (-OH), 1045 and 930 cm^{-1}; H^1-nmr, (80 MHz, $CDCl_3$), δ 1.85 (2H, m, 8,8-H), 2.67 (4H, m, 7,7-H), 3.63 (4H, m, 9,9-H), 5.85 (4H, s, 2× -O-CH_2-O-), 6.52~6.70 (6H, m, Ar-H); ms, *m/z*; 358(M^+), 187, 173, 161, 149, 135.

Eleutheroside B(syringin) (V); white needle crystal, $C_{17}H_{24}O_9$, mp, 186~188°C, uv, λ_{max} (EtOH) 265 nm; ir, ν_{max} (KBr) 3320, 1650, 1595, 1510 and 980 cm^{-1}; H^1-nmr, (80 MHz, DMSO-d6) δ 3.78 (6H, s, 2× -OCH_3), 4.11 (2H, d, 1-H), 4.84~4.92 (1H, m, glucose 1-H), 6.36~6.41 (2H, m, 2,3-H) 6.70 (6H, s, 2× -OCH_3); ms, *m/e*, 210, 182, 167, 154, 149.

Isopimara-9 (11), 15-diene-19-ol (VI); white

needle crystal $C_{20}H_{32}O$, mol. wt. 288, mp, 73°C, $[\alpha]_D^{20}$ +15.09 ($CHCl_3$, c, 0.053), ir, ν_{max} (KBr), 3340 (-OH), 3090, 1645, 910 and 815(C=C) cm^{-1}; H^1-nmr ($CDCl_3$, 200MHz) δ 0.96 (s, 2× tertiary methyl) 1.02 (s, tertiary methyl), 3.50, 3.82 (2H, AB pair of d, 1 each J=10.8, 19-H_2), 4.84 (1H, dd, J=10.5, 1.4, 16-H), 4.90 (1H, dd, J=17.3, 1.4, 16-H), 5.35 (1H, m, 11-H), 5.79 (1H, dd, J=17.3, 10.5, 15-H); C^{13}-nmr, see Table 2; ms, m/z, 288(M^+), 257 (M-CH_2OH), 220 (M-C_5H_{10}), 189 (M-CH_2OH-C_5H_{10}).

Acetylation of Isopimara-9(11), 15-diene-19-ol (VI); Treatment of (VI) (70 mg) with Ac_2O-Py. in the usual manner gave the monoacetate (VII), a white crystal, ir, ν_{max} (KBr), 2910, 1740, 1642, 910, 842 and 818 cm^{-1}; H^1-nmr, ($CDCl_3$, 80 MHz) δ 0.97, 1.09 (tertiary methyl), 2.04 (s, 3H, -OAc), 4.01, 4.33 (2H, d, 19-H), 4.86 (1H, dd, 16-H), 4.92 (1H, dd, 16-H), 5.38 (1H, m, 11-H), 5.84 (1H, dd, 15-H); ms, m/e, 330(M^+), 315, 257, 202, 187. falcarindiol (VIII): colorless viscous oil. uv, λ_{max} (ethylether) 238.7, 250.9, 264.6 and 281.6 nm; ir, ν_{max} (neat), 3365(OH), 2250, 2115(C≡C) and 1650 (C=C) cm^{-1}; H^1-nmr ($CDCl_3$, 200 MHz) δ 5.98 (1H, m, J=17.0, 10.0 and 5.5, 2-H), 5.62~5.40 (3H, m, 1,9, 10-H), 5.23 (1H, d, J=10, 1-H), 5.19 (1H, d, J=7.5, 8-H), 4.92 (1H, d, J=5.5, 3-H), 3.54 (2H, brs, -OH), 2.10 (2H, m, J=7.5, 11-H), 1.29 (10H, s, -$(CH_2)_5$-), 0.90 (3H, t, J=6.5, 17-H); C^{13}-nmr (20 MHz, $CDCl_3$) 136.4 (2-C), 134.0 (10-C), 128.3 (9-C), 116.8 (1-C), 80.3 (4-C), 78.3 (7-C), 70.4 (5-C), 68.5 (6-C), 63.2 (3-C), 58.4 (8-C), 31.8 (12-C), 29.4 (15-C), 29.2 (13,14-C), 27.7 (11-C), 22.7 (16-C), 14.1 (17-C)

Acetylation of falcarindiol (VIII);

A solution of VIII (110 mg) in a mixture of acetic anhydride (4 ml) and pyridine (3 ml) was allowed to stand at room temperature for 24 hour. The reaction mixture was treated in the usual manner and chromatographed on silica gel with hexane: ethyacetate (8:1) to give the diacetate (IX) (90 mg), colourless viscous liquid, uv, λ_{max} (ethylether) 232.0, 245.0, 258.5 nm; ir, ν_{max} (neat) 2145 (C≡C), 1740, (C=O), 1640 (C=C) cm^{-1}; H^1-nmr ($CDCl_3$, 80 MHz) δ 2.04, 2.06 (2×-OAc); ms, m/z, 259, 233, 175, 161, 157 and 115.

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