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LIPOPHILIC FLAVONOIDS FROM THE FERN *WOODSIA SCOPULINA*

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Key Word Index—*Woodsia scopulina*; Fern, Pteridophyta; Flavonol; Flavanonol; Chalcone; Dihydrochalcone; Sesquiterpene; Humulene.

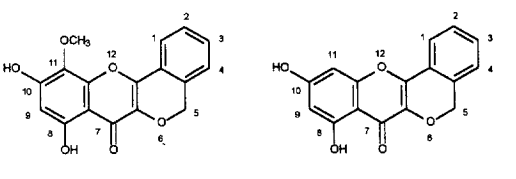
Abstract—Two new flavones with a hydroxymethyl substitution in the B-ring, 8,10-dihydroxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one and 8,10-dihydroxy-11-methoxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one and ten B-ring non-substituted dihydrochalcones, chalcones, flavonols including two new flavanonol stereoisomers, *cis*-3-acetoxy-5,7-dihydroxyflavanone and *cis*-3-hydroxy-5,7-dimethoxyflavanone, have been isolated from the dichloromethane extract of fronds of the North American fern *Woodsia scopulina*. Furthermore, two humulane-type sesquiterpenes, humulene-6,7-epoxide and the new compound 6,7-epoxy-5-hydroxyhumula-2,9-diene, were obtained from this plant. Their structures have been identified by spectroscopic analysis.

INTRODUCTION

The fern genus *Woodsia* contains about 25 species widespread in temperate zones of the northern and southern hemisphere [1]. Since there are no records on the chemistry of this fern genus we have analyzed the dichloromethane extract of the North American species *W. scopulina* D. C. Eaton [2].

RESULTS AND DISCUSSION

A combination of column chromatography (Sephadex LH-20), vacuum liquid chromatography and HPLC of the dichloromethane extract of fronds of *W. scopulina* afforded two new flavonol derivatives with a ring closure between rings B and C, 8,10-dihydroxy-11-methoxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one (**1**) and 8,10-dihydroxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one (**2**). Eight known flavonoids with unsubstituted B-rings, 4′-hydroxy-2′,6′-dimethoxydihydrochalcone (**3**) [3], 2′,4′,6′-trimethoxydihydrochalcone (**4**) [4], 4′,6′-dihydroxy-2′-methoxychalcone (cardamonin) (**5**) [5], 4′-hydroxy-2′,6′-dimethoxychalcone (**6**) [6], 3,5,7-trihydroxyflavone (galangin) (**7**) [7], 5,7-dihydroxy-3-methoxyflavone (galangin 3-methyl ether) (**8**) [8], 3,5,7-trihydroxy-8-methoxyflavone (**9**) [7], and 3,5-dihydroxy-7,8-dimethoxyflavone (gnaphaliin) (**10**) [9] and two new flavanonols, *cis*-3-acetoxy-5,7-dihydroxyflavanone (**11**) and *cis*-3-hydroxy-5,7-dimethoxyflavanone (**12**) were also isolated. This is the first report of **3**, **4** and **6** from a natural source although they have been previously from synthetis. Furthermore, two humulane-type sesquiterpenes, humulene-6,7-epoxide (humulenepoxide II) (**13**) [10–12] and the new compound 6,7-epoxy-5-hydroxyhumula-2,9-diene (**14**), were isolated.



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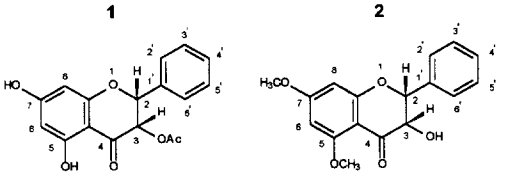

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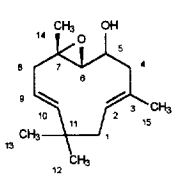

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8,10-dihydroxy-11-methoxy-5-H-isochromeno[4,3-b]chromen-7-one (**1**)

Compound **1** was obtained as a yellow amorphous powder with the molecular formula $C_{17}H_{12}O_6$ as indicated by the CI mass spectrum (*m/z* 321, $[M]^+$). The ^{13}C NMR spectrum showed the presence of 17 carbons in the molecule. The ^1H-NMR spectrum displayed the signal of a methoxyl group at δ_H 3.85 corresponding to the ^{13}C NMR signal at δ_C 60.9 The singlet at δ_H 12.26 was characteristic of a chelated hydroxyl proton and was assigned to an hydroxyl group in positon 8 of the A-ring. H-9 appeared as a singlet at δ_H 6.28, with the corresponding ^{13}C signal at δ_C 98.8. Furthermore, chemical shift and multiplicity of the four signals each integrating to one proton at δ_H 7.75 (m), δ_H 7.37 (m), δ_H 7.56 (m), and δ_H 7.54 (m) indicated the presence of a 1,2-substituted benzene ring. The singlet at δ_H 5.26 corresponding to two protons could be assigned to an methylene group with the respective ^{13}C signal at δ_C 67.3. The presence of a conjugated carbonyl group was indicated by the ^{13}C signal at δ_C 174.6 supported by the IR band at 1650 cm^{-1}. The substitution pattern was confirmed by the NOESY spectrum. The chelated proton (C-8-OH, δ_H 12.26) showed correlation to proton H-9 (δ_H 6.28). The position of the methoxyl group at C-11 of the A-ring has been proven by correlation of the methoxy signal to H-1 of the B-ring. The aromatic proton signal at δ_H 7.37 could be assigned to H-4 based on its correlation to the methylene group at δ_H 5.26. Thus, **1** is 8,10-dihydroxy-11-methoxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one, a flavonol derivative with ring closure between B-and C-ring *via* the methylene substituent of the B-ring.

8,10-dihydroxy-5-H-isochromeno[4,3-b]chromen-7-one (**2**)

The molecular formula $C_{16}H_{10}O_5$ of **2** which was obtained as a yellow amorphous powder was deduced from the CI mass spectrum (*m/z* 282, $[M]^+$). Chemical shifts and multiplicities of signals in the ^1H-NMR spectrum indicated a structure similar to the flavonol derivative **1**. The four signals of a 1,2-disubstituted benzene ring appeared as multiplets at δ_H 7.31 (*m*, H-4), δ_H 7.52 (*m*, H-3, H-4) and δ_H 7.83 (*m*, H-1). The two doublets at δ_H 6.22 and δ_H 6.47 with a coupling constant of 2.2 Hz each were assigned to a *meta*-substituted A-ring. The singlet at δ_H 5.25 corresponding to two protons was attributed to the methylene group substituent of the B-ring. The presence of a conjugated carbonyl group could be deduced from the IR absorption band at 1652 cm^{-1}. Thus, the structure of **2** could be established as 8,10-dihydroxy-5-*H*-isochromeno[4,3-*b*]chromen-7-one.

cis-3-acetoxy-5,7-dihydroxyflavanone (**11**)

Compound **11** consisted of a yellow amorphous powder with a molecular formula $C_{17}H_{14}O_6$, obtained from the CI mass spectrum (*m/z* 315, $[M+H]^+$). The ^{13}C-NMR-spectrum shows seven quaternary carbons, one of them corresponding to a carbonyl group (δ_C 189.1) and nine to tertiary carbons. The primary carbon at δ_C 20.8 was assigned to the methyl group of an acetate moiety corresponding to the signal at δ_H 1.88 in the ^1H-NMR-spectrum. Furthermore, the ^1H-NMR-spectrum shows two doublets at δ_H 5.97 and δ_H 6.02 ppm (H-6, H-8) with a coupling constant of 2.00 Hz each, that were attributed to *meta*-positioned protons of a flavonoid A-ring. The multiplet at δ_H 7.46 (H-2′, H-6′) and the multiplet in the range of δ_H 7.31-7.43 (H-3′, H-4′, H-5′) could be assigned to the five protons of an unsubstituted B-ring. The singlet at δ_H 11.59 corresponds to the chelated hydroxyl proton at C-5. The hydroxyl proton in position C-7 appeared as a singlet at δ_H 11.00. The coupling constant of 2.64 Hz of H-2 (δ_H 5.58, *d*) and H-3 (δ_H 5.86, *d*) indicated the *cis*-configuration of both protons. The acetyl group at C-3 explained the lowfield shift of H-3. The NOESY spectrum proved the location of the acetyl group by a correlation between the acetate methyl group and H-2′ and H-6′ of the B-ring. Furthermore, cross peaks between the signals of H-2 and H-3 confirmed the *cis*-configuration of these protons. Thus, compound **11** is *cis*-3-acetoxy-5,7-dihydroxyflavanone, a stereoisomer of the *trans* compound pinobanksin 3-O-acetate [13].

cis-3-hydroxy-5,7-dimethoxyflavanone (**12**)

Compound **12** was isolated as a yellow amorphous powder with a molecular formula $C_{17}H_{16}O_5$ calculated from the CI mass spectrum (*m/z* 301 $[M+H]^+$). The similarity of the ^1H-NMR data to data of **11** indicated that **12** is also a flavanonol derivative with unsubstituted B-ring. The two doublets at δ_H 6.02 and δ_H 6.14 with *meta* coupling contant (J = 1,83 Hz) were assigned to H-6 and H-8 of the A-ring, respectively. The five protons of the B-ring appeared as multiplets at δ_H 7.38 (H-2′,-6′) and at δ_H 7.17-7.24 (H-3′, H-4′, H-5′). The doublets at δ_H 4.81 and at δ_H 4.88 could be attributed to H-2 and H-3 of the C-ring. The coupling constant of 3.36 Hz of both signals indicated a *cis* configuration of H-2 and H-3. The singlets at δ_H 3.79 and δ_H 3.83, each integrating to three protons showed the presence of two methoxyl groups in the molecule. The positions of the methoxyl groups could be deduced from the NOESY spectrum. A correlation between the methoxy signal at δ_H 3.83 and the signal of H-6 showed the presence of a methoxyl group at C-5 and cross-peaks between the second methoxy signal (δ_H 3.79) and the signals of H-6 and H-8 proved this methoxyl group to be attached at C-7. Furthermore, the NOESY spectrum confirmed the *cis* configuration of protons H-2 and H-3. Therefore, **12** could be established as *cis*-3-hydroxy-5,7-dimethoxyflavanone. So far, only the *trans* isomer of **12** is known [14].

6,7-*epoxy*-5-*hydroxyhumula*-2,9-*diene* (**14**)

Compound **14** consisted of a colourless oil with a molecular formula $C_{15}H_{24}O_2$, obtained from the EI mass spectrum (*m/z* 236, $[M]^+$). The ^{1}H-NMR spectrum displayed signals corresponding to 24 protons. The three signals of olefinic protons at δ_H 5.02, δ_H 5.21 and δ_H 5.25 were assigned to two double bonds. The four singlets appearing at δ_H 0.64, 0.68, 0.87, and 1.12 corresponded to four methyl groups. The signals of two methine protons at δ_H 3.66 and δ_H 2.64 indicated the presence of an hydroxyl and an epoxy group. From the DEPT spectra, the 15 carbon signals could be assigned to four singlet methyls, three methylenes, two sp^3 methins with hydroxyl and epoxide shift, three olefinic methines and three quaternary carbons, one of the latter with olefinic shift (δ_C 130.0) and one with epoxide shift (δ_C 64.6). Based on the analysis of the ^{1}H-^{1}H-COSY, the HSQC and the HMBC spectra ^{1}H and ^{13}C signals could be assigned and the structure of **14** was established as 6,7-epoxy-5-hydroxyhumula-2,9-diene (Fig. 2). Compound **14** is the 5-hydroxy derivative of humulen-6,7-epoxide (humulenepoxide II) that has been also isolated from the plant. From the NOESY spectrum the stereochemistry at C-6 and C-7 could be deduced. The cross-peak between the signals of H-6 and H-8α proves the *cis* configuration of the methyl group (C-14) and the epoxide bond of the oxygen to C-6.

The structures of compounds **3-10** and **13** have been deduced from 1D and 2D NMR and mass spectral data in agreement with reported data in the literature.

The isolation of B-ring unsubstituted flavonoids from *W. scopulina* is not surprising since these compounds are commonly found in ferns. Particularly B-ring unsubstituted chalcone and dihydrochalcone derivatives are characteristic flavonoid constituents of the farina [15]. However, the presence of the 5-*H*-isochromeno[4,3-*b*]chromen-7-one derivatives **1**, and **2** in this plant is quite unusual. To date, only a few compounds with this structure are known from members of the family Caesalpiniaceae [16–19].

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$, Me_2CO-d_6, MeOH-d_4, DMSO-d_6 [^{1}H NMR: 400 MHz, ^{13}C NMR: 100.5 MHz for 1D spectra, 500 and 125 MHz, for 2D spectra, respectively] relative to $CDCl_3$ at δ_H 7.25, δ_C 77.0, Me_2CO-d_6 at δ_H 2.05, δ_C 206.18, MeOH-d_4 at δ_H 3.30, δ_C 49.05, DMSO-d_6 at δ_H 2.50, δ_C 39.43. ^{13}C multiplicities were determined using the DEPT pulse sequence. Optical rotations were measured in MeOH and $CHCl_3$.

Plant material. Woodsia scopulina D. C. Eaton was collected in the Schweitzer Mountains, Sandpoint, Idaho, USA in June 1994 and identified by K.-P. A. A voucher specimen (No. 24961) is deposited in the Herbarium Saar, Universität des Saarlandes, Saarbrücken.

Extraction and isolation: Powdered air dried plant material (860 g) was extracted with CH_2Cl_2. The CH_2Cl_2 extract (12.8 g) was chromatographed on Sephadex LH-20 (150 × 2.5 cm i.d.) with MeOH-CH_2Cl_2 (1:1) as eluent to give eight fractions (I-VIII). Fractions IV-VII were separated by vacuum liquid chromatography (VLC) (silica gel, 15 μm, stepwise with an *n*-hexane-EtOAc gradient) to give the fractions IV.1-IV.2, V.1-V.3, VI.1-VI.3, VII.1 (**8**, 9 mg), VII.2 (**11**, 139 mg) VII.3 (**1**, 12 mg) and VII.4. Mixtures were further separated yielding the following compounds: Fr. IV.1 (VLC, silica gel, 15 μm, CH_2Cl_2-HOAc (98:2)) 129 mg of sitosterol; fr. IV.2 (HPLC, diol, 5 μm, 4 × 250 mm, *n*-hexane-*t*-BME (70:30)) 40 mg of **4**; V.1 (HPLC, silica gel, 5 μm, 4 × 250 mm, *n*-hexane-EtOAc (95:5)), 6 mg of **13**; fr. V.2 (HPLC, silica gel, 5 μm, *n*-hexane-EtOAc (90:10), **14** (13 mg), **10** (10 mg), **11** (22 mg); fr. V.3 (HPLC, silica gel, 5 μm, *n*-hexane-EtOAc (70:30)), **3** (46 mg); fr. VI.1 (HPLC, silica gel, 5 μm, *n*-hexane-*t*-BME (80:20)), **8** (4 mg); fr. VI.2 (HPLC, silica gel, 5 μm, *n*-hexane-*t*-BME (60:40)), **3** (36 mg); fr. VI.3 (HPLC, silica gel, 5 μm, *n*-hexane-*t*-BME (80:20)), **6** (7 mg), **12** (1 mg); fr. VII.4 (HPLC, diol, 5 mm, *n*-hexane-EtOAc (75:25)), **2** (1 mg). Fr. VIII was separated by VLC (diol, 25 mm, stepwise with an *n*-hexane-EtOAc gradient) giving frs. VIII.1 and VIII.2. HPLC separation of VIII.1 and VIII.2 yielded **9** (5 mg) and **7** (11 mg), respectively.

8,10-*Dihydroxy*-11-*methoxy*-5-*H*-*isochromeno*[4,3-*b*]*chromen*-7-*one* (**1**) CI-MS *m/z*: 312 $[M]^+$; UV λ_{max}^{MeOH}: 279, 324, 380; IR ν_{max}^{KBr}: cm^{-1}: 3300, 1650, 1600, 1500, 1450, 1355, 1285, 1230, 1170, 1070, 1030, 1000, 825, 792, 761; ^{1}H NMR (DMSO-d_6): δ_H 3.26 (1H, *s*, OH (C-10)), 3.85 (3H, *s*, OCH_3), 5.26 (2H, *s* , H-5α, H-5*B*), 6.28 (1H, *s* , H-9), 7.37 (1H, *m* , H-4), 7.55 (2H, *m* , H-2, H-3), 7.75 (1H, *m* , H-1), 12.26 (1H, *s*, OH (C-8)); ^{13}C NMR (DMSO): δ_C 60.9 (*s*, OCH_3), 67.3 (*s*, C-5), 98.8 (*d*, C-9), 104.5 (*s*), 121.2 (*d*), 124.3 (*s*), 124.9 (*d*), 128.9 (*d*), 131.7 (*d*), 131.9 (*s*), 135.2 (*s*), 147.3 (*s*), 148.3 (*s*), 155.9 (*s*), 156.1 (*s*), 156.9 (*s*), 174.6 (s, C-7).

8,10-*Dihydroxy*-5-*H*-*isochromeno*[4,3-*b*]*chromen*-7-*one* (**2**). CI-MS *m/z*: 282 $[M]^+$; UV λ_{max}^{MeOH}: 273, 298, 322, 372; IR ν_{max}^{KBr}: cm^{-1}: 3150, 2970, 1652, 1600, 1500, 1450, 1415, 1363, 1310, 1280, 1225, 1190, 1175, 1089, 959, 800, 851, 879, 719, 770; ^{1}H NMR (MeOH-d_4): δ_H 5.25 (2H, *s* , H-5α, H-5*B*), 6.22 (1H, *d* , *J* = 2.2, H-9†), 6.47 (1H, *d*, *J* = 2.2, H-11†), 7.31 (1H, *m* , H-4), 7.52 (2H, *m* , H-2, H-3), 7.83 (1H, *m* , H-1); †: signals may be interchanged.

cis-3-*Acetoxy*-5,7-*dihydroxyflavanone* (**11**). $[\alpha]_D^{20}$ 198° (MeOH; c = 1.0); CI-MS *m/z*: 315 $[M+H]^+$; UV λ_{max}^{MeOH}: 282; ^{1}H NMR (DMSO-d_6): δ_H 1.88 (3H, *s*, CH_3), 5.58 (1H, *d* , *J* = 2.64, H-2)†, 5.86 (1H, *d*, *J* = 2.64, H-3)†, 5.97 (1H, *d*, *J* = 2.00, H-6)‡, 6.02 (1H, *d* , *J* = 2.00, H-8)‡, 7.31-7.43 (3H, *m* , C-3′, C-4′, C-5′), 7.46 (2H, *m* , C-2′, C6′), 11.00 (1H, *s* , OH (C-7)), 11.59 (1H, *s* , OH (C-5)); ^{1}H-NMR (Me_2CO-d_6): δ_H 1.90 (3H, *s*, CH_3), 5.70 (1H, *d* , *J* = 2.84, H-2)†, 5.82 (1H, *d* , *J* = 2.84, H-3)†, 6.03 (1H, *d*, *J* = 2.20, H-6)‡,

6.10 (1H, *d*, $J=2.20$, H-8)‡, 7.33-7.43 (3H, *m*, C-3′, C-4′, C-6′), 7.52 (2H, *m*, C-2′, C6′); ^{13}C-NMR (DMSO): δ_C 20.8 (*q*, CH_3), 70.2 (*d*, C-3)†, 79.4 (*d*, C-2)†, 95.4 (*d*, C-8)‡, 96.5 (*d*, C-6)‡, 100.9 (*s*), 126.6 (*d*), 128.2 (*d*), 128.4 (*d*), 134.9 (*s*), 131.7 (*d*), 162.3 (*s*), 163.9 (*s*), 167.6 (*s*), 168.5 (*s*), 189.1 (s, C-4); †,‡: signals may be interchanged.

cis-3-Hydroxy-5,7-dimethoxyflavanone (**12**). CI-MS *m/z*: 301 $[M+H]^+$; λ_{max}^{MeOH} : 284, 323 (*sh*); ^{1}H-NMR (Me_2CO-d_6): δ_H 3.79 (3H, *s*, CH_3 (C-7)), 3.83 (3H, *s*, CH_3 (C-5)), 4.81 (1H, *d*, $J=3.36$, H-2)†, 4.88 (1H, *d*, $J=3.36$, H-3)†, 6.02 (1H, *d*, $J=1.83$, H-6), 6.14 (1H, *d*, $J=1.83$, H-8), 7.17-7.24 (3H, *m*, C-3′, C-4′, C-6′), 7.38 (2H, *m*, C-2′, C-6′);†: signals may be interchanged.

Humulene-6,7-epoxide (**13**). ^{1}H-NMR ($CDCl_3$): δ_H 1.96 (1H, *m*, H-1a), 1.85 (1H, *m*, H-1β), 4.96 (1H, *m*, H-2), 2.19 (1H, *m*, H-4α), 2.09 (1H, *m*, H-4β), 2.14 (1H, *m*, H-5α), 1.32 (1H, *m*, H-5*B*), 2.50 (1H, *m*, H-6), 2.55 (1H, *m*, H-8α), 1.61 (1H, *m*, H-8β), 5.25 (1H, *ddd*, H-9), 5.12 (1H, *d*, $J=15.9$, H-10), 1.08 (3H, *s*, H-12), 1.05 (3H, *s*, H-13), 1.28 (3H, *s*, H-14), 1.56 (3H, *s*, H-15); ^{13}C-NMR ($CDCl_3$): δ_C 40.3 (*t*, C-1), 125.7 (*d*, C-2), 131.9 (*s*, C-3), 36.6 (*t*, C-4), 24.7 (*t*, C-5), 61.9 (*d*, C-6), 63.2 (*s*, C-7), 42.6 (*t*, C-8), 122.1 (*d*, C-9), 143.1 (*d*, C-10), 36.5 (*s*, C-11), 25.6 (*q*, C-12), 28.9 (*q*, C-13), 17.2 (*q*, C-14), 15.0 (*q*, C-15). Lit. data [12] were newly assigned according to ^{1}H-^{1}H-COSY, HSQC and HMBC spectra.

6,7-*Epoxy-5-hydroxyhumula-2,9-diene* (**14**). $[\alpha]_D^{20}$ -36.8° ($CHCl_3$; c=0.65), EI-MS *m/z*: 236 $[M]^+$; ^{1}H-NMR ($CDCl_3$): δ_H 1.96 (1H, *m*, H-1α), 1.94 (1H, *m*, H-1β), 5.02 (1H, *m*, H-2), 2.38 (1H, *m*, H-4α), 2.35 (1H, *m*, H-4β), 3.66 (1H, *m*, H-5), 2.64 (1H, *m*, H-6), 2.54 (1H, *m*, H-8α), 1.74 (1H, *m*, H-8β), 5.25 (1H, *m*, H-9), 5.21 (1H, *d*, $J=15.9$, H-10), 1.09 (3H, *s*, H-12), 1.08 (3H, *s*, H-13), 1.30 (3H, *s*, H-14), 1.62 (3H, *s*, H-15); ^{13}C-NMR ($CDCl_3$): δ_C 40.9 (*t*, C-1), 127.5 (*d*, C-2), 130.0 (*s*, C-3), 45.5 (*t*, C-4), 69.5 (*d*, C-5), 66.2 (*d*, C-6), 64.6 (*s*, C-7), 41.9 (*t*, C-8), 122.1 (*d*, C-9), 143.3 (*d*, C-10), 36.3 (*s*, C-11), 27.0 (*q*, C-12), 27.8 (*q*, C-13), 18.5 (*q*, C-14), 17.1 (*q*, C-15).

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