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New terpenoids from *Haplopappus multifolius*

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The chemical investigation of the aerial parts of *Haplopappus multifolius* afforded the new monoterpene 2,9-epoxy-*p*-menth-6-en-8-ol (**7**, haplopappol), the new monoterpenoid ester 9-*cis*-*p*-coumaroyloxy-α-terpineol (**8**, haplofolin), the new diterpene 18-hydroxylabda-7,13*Z*-dien-15-oic acid (**6**) and its known *E*-isomer (**5**). In addition, the known dihydroflavones 3′,5-dihydroxy-4′,7-dimethoxydihydroflavone and 3′,4′,5-trihydroxy-7-methoxydihydroflavone and the known dihydroflavonols 3′,5-dihydroxy-4′,7-dimethoxydihydroflavonol and 3′,4′,5-trihydroxy-3-acetyl-7-methoxydihydroflavonol were also obtained. The structural assignments of these compounds were made possible by the different spectroscopic measurements.

1. Introduction

The genus *Haplopappus*, Asteraceae, is common in North and South America. The chemical investigation of *Haplopappus* species revealed different chemical profiles [1]. Clerodanes [2–7], labdanes [4, 8–10], flavonoids [8, 11–15], umbelliferone derivatives [1], sesquiterpenes, monoterpenes [8, 9] and other wide spread compounds [8] were reported. In this communication the isolation and identification of some flavonoids and terpenoides from *Haplopappus multifolius* are discribed.

2. Investigations, results and discussion

The dihydroflavones 3′,5-dihydroxy-4′,7-dimethoxydihydroflavone (**1**) and 3′,4′,5-trihydroxy-7-methoxydihydroflavone (**3**) and the dihydroflavonols 3′,5-dihydroxy-4′,7-dimethoxydihydroflavonol (**2**) and 3′,4′,5-trihydroxy-3-acetyl-7-methoxydihydroflavonol (**4**) were isolated and characterized by direct comparison of their spectroscopic data with those reported in the literature [16–22]. The detection of these flavonoids is valuable from the chemotaxonomic point of view, since they are comparable with those isolated before from other *Haplopappus* species [8].

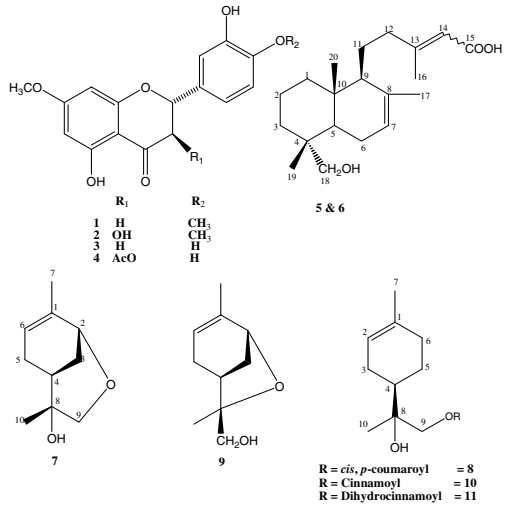
The ^{1}H NMR and ^{13}C NMR data of **5** (Table 1) and its mass spectral data are similar to those reported for 18-hydroxylabda-7,13*E*-dien-15-oic acid isolated from *Haplopappus remyanus* Wedd. [8].

The spectroscopic data of **6** are very similar to those of **5** [8] with few differences. The methyl protons signals of positions-19 and 20 of compound **5** were found at δ 0.85 and 0.81 ppm, respectively [8] while in compound **6** one singlet at δ 1.10 ppm was integrated for the two methyl groups. The hydroxylation at position-19 was excluded because the observed chemical shifts for the carbinol methylene group are the same in both **5** and **6**, furthermore, a *gem* dimethyl group at position-4 will be asymmetric and will give separate signals with a W-coupling [8]. The hydroxylation at position-20 was excluded based on the observed δ 14.8 ppm ^{13}C-chemical shift value assigned to this position and the insignificant chemical shifts deviations around this vicinity [23]. This suggested that **6** should be an isomer of **5** and the variation in the chemical shift values may be attributed to the effect of the side chain through space, which became evident by the Dridling model.

The observed δ 71.9 ppm carbon signal assigned to 18-position in **5** and **6** is a relatively high value [23], which infers its possible estrification. This was excluded by acetylation (Ac_2O/pyridine) followed by TLC comparison where **5** and **6** were converted into less polar spots, which supported the likely presence of a free CH_2OH group in these compounds. For these reasons **6** was suggested to be the *Z*-isomer of **5;** 18-hydroxylabda-7,13*Z*-dien-15-oic acid.

The EI-MS of **7** gave *m/z* of 168 analyzed for $C_{10}H_{16}O_2$. The ion peaks at *m/z* 153 $[M\text{-}CH_3]^+$, 150 $[M\text{-}H_2O]^+$, 138 $[M\text{-}2CH_3]^+$ and 135 $[M\text{-}H_2O\text{-}CH_3]^+$ were also detected. The ^{13}C NMR spectrum of **7** displayed ten carbon resonances. The multiplicities of these signals were discriminated by DEPT experiment into two methyl groups at δ 23.8 and 25.6 ppm, three methylene groups at δ 19.9, 28.9 and 75.4 ppm, three methine groups at δ 45.9, 78.2 and 120.3 ppm and two quaternary carbon signals at δ 79.2 and 140.3 ppm. From these results **7** is likely a C-10 monoterpene with two methyl groups, a double bond, three oxygenated carbon atoms, two methylene, one methine and a quaternary carbon atom (DEPT). Based on the NMR data, the postulated molecular formula for **7** is $C_{10}H_{18}O_3$, which is inconsistent with the observed parent peak of *m/z* 168. This suggested the possible presence of an epoxide ring by losing a H_2O molecule to get $C_{10}H_{16}O_2$. This formula requires three unsaturation equivalents, which were analyzed for a double bond and two rings. The *p*-menthene skeleton was found to be the best fit with one more exoskeleton epoxid ring. The presence of only two methyl groups suggested the likely oxidation of the third one of the *p*-menthane. This was confirmed by the appearance of a carbinol methylene signal at δ 75.4 ppm which was correlated with the proton doublets at δ 3.60 and 3.78 ppm (J = 11 Hz, each). The location of the oxidized methyl group could be either at positions-7 or 9. On the other hand, the quaternary carbon signal at δ 79.2 ppm has to be at either position-1, 4 or 8. The appearance of one methyl group protons signal as a singlet at δ 1.41 ppm, while the second methyl group protons signal appeared as a singlet at δ 1.67 ppm, indicated that position-7 has to be a methyl group attached to a double bond, while position-10 has to be the second methyl group attached to a hydroxylated carbon (C-8). This indicated that the oxygenated quaternary carbon signal at δ 79.2 ppm has to be assigned for position-8 rather than position-1 or 4 and hence position-9 has to be assigned for the oxygenated methylene group at δ 75.4 ppm. Moreover, the olefinic methine carbon signal at δ 120.3 ppm and the quaternary carbon signal at δ 140.3 ppm were assigned to a double bond at position-1.

The carbon signal at δ 78.2 ppm is correlated to the proton signal at δ 4.28 ppm assigned to an oxygenated methine group forming the other side of the epoxide bridge. The location of this signal was assigned to be at position-2, rather than position-3 or 5, to give a tetrahydropyran ring. A tetrahydrofuran ring was excluded through the observed chemical shift values of δ 78.2 and 75.4 ppm which are consistent with a tetrahydropyran ring rather than THF ring [23]. Moreover, the spectroscopic data of **7** were found to be comparable to those reported for 2,8-epoxy-*p*-menth-6-en-9-ol (**9**) (bottrospicatol), isolated from the microbial transformation reaction of carveol by *Streptomyces bottropensis* [24] and the terpenoid moieties of 9-cinnamoyloxy-α-terpineol (**10**) and 9-dihydrocinnamoyloxy-α-terpineol (**11**), isolated from different *Haplopappus* species [8]. Dridling model indicated that the bonds at 2–3, 3–4 and the methyl group at position-10 are β-equatorial. For these clues the structure of **7** was established as 2,9-epoxy-*p*-menth-6-en-8-ol (haplopappol).



The ^{1}H and ^{13}C NMR spectra of **8** proved the presence of a *p*-coumarat as a partial structure. In the ^{1}H NMR spectrum, a pair of doublets (J = 7.0 Hz each) at δ 6.83 and 7.34 ppm, each integrated for two protons, were assigned to the *para*-disubsitiuted aromatic ring protons. Another pair of doublets (J = 11.5 Hz each) at δ 6.24 and 7.60 ppm, each integrated for one proton, were assigned to the H-2′ and H-3′ of the *p*-coumarate, respectively. The relatively small coupling constant of these two protons (J = 11.5 Hz) indicated that these protons are occurring in a *cis* configuration [25]. The DEPT and HETCOR indicated that the carbon signals at δ 114.1 and 145.7 ppm are linked to both C-2′ and C-3′, respectively. Meanwhile, the carbon signals at δ 130.2 and 116.2 ppm were assigned to (5′ and 9′) and (6′ and 8′) positions of the aromatic ring, respectively. The three quaternary carbon signals at δ 159.1, 126.1 and 168.1 ppm were assigned to the hydroxylated C-7, position-4′ and the carbonyl ester group at position-1′, respectively. These partial structure findings were supported by the appearance of a base peak at *m/z* 165 in CI-MS (CH_4) for [*p*-coumaric acid +1]$^+$ and *m/z* 147 [*p*-coumaroyl]$^+$ (90%). The ^{13}C NMR spectrum of **8** showed ten carbon signals more. These signals were discriminated by DEPT into two methyl groups at δ 21.0 and 23.3 ppm, four methylene groups at δ 24.2, 25.8, 30.8 and 69.7 ppm, two methine groups at δ 41.2 and 120.3 ppm and two quaternary carbon signals at δ 74.4 and 133.9 ppm. The ^{1}H NMR data (Table) and the H-C correlation and the aforementioned results are partially close to those of **7**, which suggested the likely presence of a *p*-menthene skeleton. This conclusion is also based on a consistency of the data with those reported for several hydroxylated *p*-menthene derivatives [26] and the ^{13}C NMR data reported for α-terpineol [27]. Moreover, the whole NMR data of **8** are comparable to those reported for 9-cinnamoyloxy-α-terpineol (**10**) and 9-dihydrocinnamoyloxy-α-terpineol (**11**), isolated from different *Haplopappus* species [8]. For these reasons the structure of **8** should be 9-*cis*-*p*-coumaroyloxy-α-terpineol (haplofolin).

In conclusion, four dihydroflavones and dihydroflavonols were isolated from *H. multifolius*, which are comparable with those reported before from a different *Haplopappus* species [8, 11–15]. The *E* and *Z* isomers of 18-hydroxy-labda-7,13-dien-15-oic acid were also isolated. The newly reported monoterpene, haplopappol, and the monoterpene ester, haplofolin, were found to be comparable with some monoterpenes isolated from *H. remyanus* [8].

3. Experimental

3.1. Instrumentation

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a Bruker WM 250 NMR spectrometer, at 250 MHz and 62.5 MHz, respectively, with $CDCl_3$ as a solvent and TMS as the internal standard. The chemical shift values were expressed in δ ppm. DEPT, HETCOR and HMBC were measured on a Bruker WM. 300 NMR spectrometer, at 300 MHz. CI-MS (CH_4) and EI-MS (70 eV) was conducted on a Hewlett Packard 5988A spectrometer, equipped with a Hewlett Packard RTE-6/VM data system. IR was conducted on Beckman Acculab I IR spectrometer. UV data was obtained from Beckman Model 26 spectrophotometer. The optical rotations were measured on an Autopole III, automatic polarimeter (Rudolph Scientific).

3.2. Plant material, extraction and chromatographic isolation

The aerial part of *Haplopappus multifolius*, Asteraceae, was collected from northern Chile, 1996, air dried and a voucher sample was kept at the Bioresources Research Facility. The powdered aerial part (930 g) was extracted with 6.0 l CH_2Cl_2-MeOH (1 : 1) followed by 4.0 l of MeOH. The combined extract afforded 204.1 g dry extract, after solvent evaporation under reduced pressure. A sample (3.0 g) of *H. multiflius* extract was column chromatographed by flash method, 200 g Si gel, 63–200 m, 2.5 × 55 cm. The eluting solvent was 500 ml each of CH_2Cl_2, 1% Me_2CO/CH_2Cl_2, 2%, …, 6%, 8%, 10%, 15%, 20% then 50% MeOH/CH_2Cl_2. Twenty-eight fractions were generated.

Fr. 2 eluted with 1% Me_2CO/CH_2Cl_2 (180 mg) gave 90 mg of **1** as needles. Compound **1** gave orange color changed to reddish brown after spraying with vanillin/H_2SO_4 spray reagent followed by heating for 5–10 s with a heat gun (R_f, 0.78, Si gel, 2% MeOH/CH_2Cl_2).

Frs. 3–5 eluted with 2–3% Me_2CO/CH_2Cl_2 (927 mg) were subjected to MPLC, 50 g Si gel, 15–25 m, 15 × 460 mm. The eluting solvent was 250 ml of C_6H_{14}-CH_2Cl_2 (1 : 1) + 0.5% H_2CO_2, 250 ml CH_2Cl_2 + 0.5% H_2CO_2, 250 ml 0.2% MeOH/CH_2Cl_2 + 0.5% H_2CO_2, 1000 ml 0.5% MeOH/CH_2Cl_2 + 0.5% H_2CO_2, 375 ml 0.75% MeOH/CH_2Cl_2 + 0.5% H_2CO_2, 500 ml 2% MeOH/CH_2Cl_2 + 0.5% H_2CO_2, 250 ml 5% MeOH/CH_2Cl_2 + 0.5% H_2CO_2 and 250 ml 50% MeOH/CH_2Cl_2. Seven groups of frs. were generated based on TLC results. Groups 3 (211 mg) and 4 (175 mg) eluted with 0.5% MeOH/CH_2Cl_2 + 0.5% H_2CO_2 afforded **2** (23 mg) and **3** (150 mg) as needles. Both **2** and **3** gave yellow color which changed to orange red after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f, 0.53 (**2**) and 0.48 (**3**), Si gel, 3% MeOH/CH_2Cl_2). Group 5 (110 mg) gave **4** (46 mg) as needles after purification on 1 mm-thick prep TLC plates using 3% MeOH/CH_2Cl_2 + 0.5% H_2CO_2 as the solvent. Compound **4** gave an orange color after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f, 0.50, Si gel, 3% MeOH/CH_2Cl_2).

Frs. 6–8 eluted with 4–5% MeOH/CH_2Cl_2 (302 mg) displayed two minor spots (R_f, 0.41 and 0.55, Si gel, C_6H_{14}-EtOAc; 1 : 1). An equivalent fr. (35.0 g) was generated using 200 g of the crude extract (2 kg Si gel, 63–200 m, 8.5 × 50 cm). The eluting solvent was 8.0 l of CH_2Cl_2 then Me_2CO/CH_2Cl_2, 4.0 l each of 2%, 4%, 6%, 8%, 10%, 15% and then 100%. The frs. eluted with 2–4% Me_2CO/CH_2Cl_2 (35 g) were fractionated by cc 1 kg Si gel, 63–200 m, 5 × 50 cm, the eluting solvent was 1.0 l each

Table: ^{1}H and ^{13}C NMR data of *Haplopappus multifolius* compounds 5–8*

C#	5		6		C#	8		7	
	^{13}C	^{1}H	^{13}C	^{1}H		^{13}C	^{1}H	^{13}C	^{1}H
1	35.5	–	37.8	–	1	133.9	–	140.3	–
2	18.0	–	18.8	–	2	120.3	5.40, br s	78.2	4.28 br s
3	37.5	–	40.1	–	3	25.8	1.98, m	19.9	1.56, ddd, 1.90, ddd
4	36.5	–	36.9	–	4	41.2	1.85, m	45.9	1.79 m
5	43.6	–	44.5	–	5	24.2	1.25, 1.74, ddd, ddd	28.9	2.10 m
6	25.2	1.87 m	26.7	1.96 m	6	30.8	1.82, m	120.3	5.58 br s
7	122.3	5.38 br s	123.7	5.47 br s	7	23.3	1.65 br s	23.8	1.76 br s
8	134.8	–	135.9	–	8	74.4	–	79.2	–
9	54.2	–	55.6	–	9	69.7	4.15, 4.28, d, d, (J = 11 each)	75.4	3.60, 3.78, d, d (J = 11, each)
10	38.7	–	38.7	–	10	21.0	1.22, s	25.6	1.41 s
11	23.6	–	24.7	–	1′	168.1	–		
12	43.4	2.13, 2.39 ddd, ddd (J = 13, 5)	44.5	2.16, 2.33 ddd, ddd (J = 13, 5)	2′	114.1	6.24, d (J = 11.5)		
13	163.4	–	161.9	–	3′	145.7	7.60, d, (J = 11.5)		
14	115.1	5.72 br s	117.1	5.74 br s	4′	126.1	–		
15	171.8	–	170.4	–	5′, 9′	130.2	7.34, d (J = 7)		
16	19.3	2.20 br s	19.3	2.24 br s	6′, 8′	116.2	6.83, d (J = 7)		
17	22.1	1.68 br s	22.7	1.78 br s	7′	159.1	–		
18	71.9	3.13, 3.37 d, d (J = 11, each)	71.9	3.10, 3.38 d, d (J = 11, each)					
19	17.7	0.85 s	19.2	1.10 s					
20	14.1	0.81 s	14.8	1.10 s					

At 250 MHz (^{1}H) and 62.5 MHz (^{13}C), using $CDCl_3$ as a solvent, TMS is the internal standard and the chemical shifts (δ) are expressed in ppm, J = coupling constant in Hz, br s = broad singlet, d = doublet, dd, double doublet, ddd = triple doublets.

of C_6H_{14}, 5% EtOAc/C_6H_{14}, 10% then 5.0 l of 20% EtOAc/C_6H_{14} and 3.0 l Me_2CO. The frs eluted with 10% EtOAc/C_6H_{14} gave **7** (85 mg) as needles. Compound **7** gave a brown color after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f, 0.41, Si gel, EtOAc/C_6H_{14}; 1 : 1). The frs. eluted with the early 20% EtOAc/C_6H_{14} (4.5 g) displayed one major spot which gave a brownish blue color after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f, 0.55, Si gel, C_6H_{14}-EtOAc; 1 : 1). This fraction was subjected to MPLC, 150 g Si gel, 15–25 m, 26 × 460 mm. The eluting solvent was EtOAc/C_6H_{14}, 500 ml 5%, 500 ml 10% and one liter each of 15%, 20%, 25%, 35%, …, 50%. Frs. eluted with 20% EtOAc/C_6H_{14} (350 mg) were subjected to MPLC, 50 g Rp-C18, 15–25 m, 15 × 460 mm. The elution was isocratic using 1500 ml of 50% MeCN/H_2O. This afforded 150 mg of **5** and 125 mg of **8** (needles). Final purification of **5** on 1 mm-thick prep TLC using 50% EtOAc/C_6H_{14} afforded 110 mg of pure **5** as needles. Compound **5** gave a yellow color changing to red, brown then blue, while **8** gave a reddish violet color which changed to brown after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f = 0.51 and 0.37, Rp-C-18, 75% MeCN/H_2O, respectively).

Frs. 9–27 (597 mg) eluted with 6–20% Me_2CO/CH_2Cl_2 were subjected to MPLC, 50 g Si gel, 15–25 m, 15–460 mm. The eluting solvent was *iso*-PrOH/ CH_2Cl_2, 1 l each of 0.5%, 1% and 500 ml each of 1.5%, 2%, 5% then 25% MeOH/CH_2Cl_2. The frs. eluted with 1.5% *iso*-PrOH/CH_2Cl_2 (50 mg) gave **6** as crystals after purification on Si gel 1 mm-thick prep TLC plates using 5% *iso*-PrOH/CH_2Cl_2 as a solvent (R_f, 0.61). Compound **6** gave a yellow color which changed to reddish brown then blue after spraying with vanillin/H_2SO_4 followed by heating for 5–10 s with a heat gun (R_f, 0.28, Si gel, C_6H_{14}-EtOAc; 1 : 1).

3.2.1. Compound **6***; 18-hydroxylabda-7, 13Z-dien-15-oic acid*

Needles, m.p. 128–130 °C, α[D]^{25}, +75.0 (CH_2Cl_2; c. 2.0). IR υ_{max} cm^{-1}; 3610, 2950, 1720, 1620, 1410, 1350 and 1180. UV λ_{max} nm; 304 sh, 292. EI-MS, 70 eV, *m/z* (rel. int.); 320 $[M]^+$ (1), 305 $[M\text{-}CH_3]^+$ (2), 302 $[M\text{-}H_2O]^+$ (2), 276 $[M\text{-}CO_2]^+$ (2), 220 $[M\text{-}Me_2C{=}CHCO_2H]^+$ (33), 187 (10), 135 (18), 109 (100), 81 (55), 55 (30), 43 (32) and 42 (32).

3.2.2. Compound **7***; haplopappol; 2, 9-epoxy-p-menth-6-en-8-ol*

Needles, m.p. 72–73 °C, α[D]^{25}, +13.3 (CH_2Cl_2; c. 2.5). IR υ_{max} cm^{-1}; 3420, 2940,1615, 1510, 1320, 1210, 930 and 820. UV λ_{max} nm; 265, 242 sh. EI-MS, 70 eV, *m/z* (rel. int.); 168 $[M]^+$ (8), 153 $[M\text{-}CH_3]^+$ (100), 150 $[M\text{-}H_2O]^+$ (3), 138 $[M\text{-}2CH_3]^+$ (10), 135 $[M\text{-}H_2O\text{-}CH_3]^+$ (11), 123 (22), 95 (40), 94 (50), 93 (35), 84 (40), 79 (43) and 43 (85).

3.2.3. Compound **8***; haplofolin; 9-cis-p-coumaroyloxy-α-terpineol*

Needles, m.p. 124–126 °C, α[D]^{25}, + 13.25 (CH_2Cl_2; c. 2.0). IR υ_{max} cm^{-1}; 3550, 2960, 2860, 1725, 1640, 1585, 1415, 1360, 1260, 1130 and 890. UV λ_{max} nm; 244, 290. CI-MS (CH_4), *m/z* (rel. int.); 315 $[M + 14 + 1]^+$ (4), 301 $[M + 1]^+$ (4), 300 $[M]^+$ (10), 299 $[M\text{-}H_2O + 14 + 2]^+$ or $[M\text{-}CH_3 + 14]^+$ (50), 298 (10), 297 (7), 257 (3), 221 (3), 205 (3), 193 (15), 175 (5), 165 [*p*-coumaric acid + 1]$^+$ (100), 147 [*p*-coumaroyl]$^+$ (90), 135 (70), 123 (10), 107 (30), 95 (40), 93 (50) and 69 (10).

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