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GUAIANOLIDES AND HELIANGOLIDES FROM *HYMENOPAPPUS NEWBERRYI*

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Key Word Index—*Hymenopappus newberryi*; Compositae; sesquiterpene lactones; guaianolides; heliangolides; *ent*-kaurene derivative; chemotaxonomy.

Abstract—The aerial parts of *Hymenopappus newberryi* afforded two heliangolides, two thymol derivatives, as well as two new guaianolides and a *trans,trans*-germacranolide closely related to hiyodorilactone A. Furthermore, the *ent*-kaurene derivative abbeokutone was present. These results are of chemotaxonomic interest.

INTRODUCTION

So far only the roots of one species of the genus *Hymenopappus* have been investigated chemically [1]. In addition to the widespread tridecapentaynene, the thymol derivative **7** was isolated. As the relationship of this genus, previously regarded as a member of the tribe Helenieae, is not really clear, further information was desirable. Prior to new investigations [2–5] *H. newberryi* was treated as the sole member of a genus (*Leucampyx*) belonging to the tribe Anthemideae, while the rest of *Hymenopappus* was placed in the tribe Helenieae. Even if recombined, there still remains the problem of the proper tribal position: Helenieae (Heliantheae) or Anthemideae? The possibility of an anthemoid relationship [3, 4] is still held by Cronquist [5]. The results of our studies on the chemistry of *H. newberryi* (Gray) T. M. Johnst., which is a primitive member of the genus [3], are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of the plant afforded the thymol derivatives **7** and **8** [6], and a complex mixture of sesquiterpene lactones. Separation by TLC and HPLC afforded eucannabinolide (**2**) as the main compound [7], as well as the corresponding 5′-desoxy derivative **1** [8] and three new lactones, the *trans, trans*-germacradienolide **3** and the guaianolides **4** and **6**.

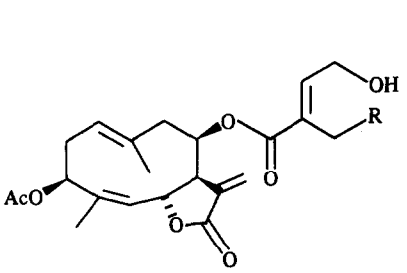
The structure of **3** was elucidated by comparing the ^{1}H NMR data (Table 1) with those of hiyodorilactone A [9], which is the corresponding 5′-desacetyl-3-*O*-acetate. Accordingly, all signals were similar, only the chemical shifts of H-3 and H-4′ being characteristically different. Spin decoupling allowed the assignment of all signals and established again the structure. The stereochemistry followed from the couplings observed.

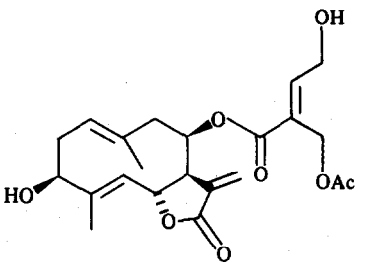
The structure of **4**, molecular formula $C_{25}H_{30}O_8$, also followed from the ^{1}H NMR spectrum (Table 1). While a few signals were overlapped in $CDCl_3$, addition of deuteriobenzene allowed the assignment of all signals by spin decoupling. The nature of the ester side chain was deduced from the characteristic signals [δ6.88 *t* (H-3′), 4.20 and 4.15 *dd* (H-4′), 4.78 and 4.73 *d* (H-5′), 6.75 *q* (H-8′), 1.69 *d* (H-9′) and 4.16 *s* (H-10′)], which were influenced in their chemical shift by transforming to the diacetate **5** in the expected way (Table 1). The remaining signals were close to those of a ligustrin 4′,5′-dihydroxytiglate [10]. The coupling of H-8 further showed that a β-orientated C-8 ester group was present. Irradiation of the H-15 signal changed the H-3 signal to a three-fold doublet and sharpened the signals of H-2. By irradiating the signals of H-1 and H-3, the multiplicity of the H-2 signal was determined. The stereochemistry at C-1 and C-5–C-7 followed from the couplings observed.

The ^{1}H NMR data of **6** (Table 1), which we have named hymenopappolide, clearly showed that this lactone had the same ester side chain as **4**, while the position of the double bond was changed. The typical couplings indicated a 2,3-double bond. Spin decoupling showed that again a guainolide was present. The observed chemical shift of H-15 and the absence of a 3,4-coupling showed that a 4-hydroxy derivative of **4** was most likely. Accordingly, the H-5 signal was now a sharp double-doublet. Its chemical shift indicated a 4α-hydroxyl group, especially when the shifts were compared with those of the C-4 epimers of a corresponding 1(10),2-diene [11].

A small amount of **9** was isolated along with **4**. After acetylation, the corresponding acetates **5** and **10** could be easily separated. The ^{1}H NMR data of **10** (see Experimental) agreed with the structure shown, especially when compared with those of diterpenes with a 3-keto group or kauranes with oxygen functions at C-16 and C-17. Also the ^{13}C NMR spectrum agreed well with the proposed structure, especially when compared with the data of a diketone derived from **9** by periodate cleavage [12, 13]. Compound **10** was therefore the acetate of abbeokutone [12]. Accordingly, reduction of **10** with lithium alanate afforded **11**, which showed a mp reported for this triol [12]. Saponification of **10** afforded **9**, its data agreeing with those of abbeokutone [12].

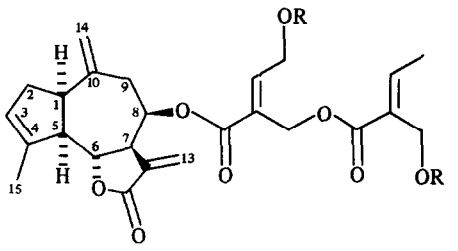
The occurrence of heliangolides in *Hymenopappus* indicates a close relationship of the genus with *Villanova* [14], *Schkuhria* [15] and *Picradeniopsis* [16], which also contain **1** and **2**. Similar heliangolides are also present in



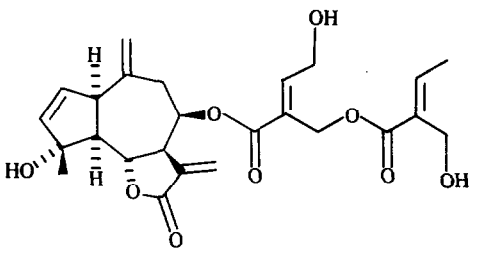


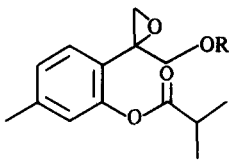
R
1 H
2 OH

3



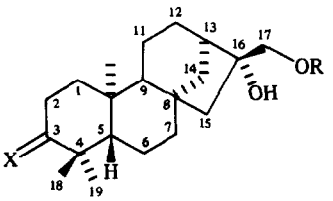
R
4 H
5 Ac





6

R
7 iBu
8 MeBu



	9	**10**	**11**
X	O	O	αOH,H
R	H	OAc	H

the related taxa *Bahia* [17] and *Peucephyllum* [18], while *Chaenactis* species contain the germacranolide eupatoriopicrin [19], which is closely related to **3**. From *Bahia* [20] and *Picradeniopsis* species [16], the guaianolides related to **4** are also reported. Thymol derivatives are present in a *Schkuhria* [21] and in a *Hymenopappus* species [1]. The co-occurrence of the red-coloured dithioacetylenes in *Schkuhria*, *Picradeniopsis*, *Villanova* and *Chaenactis* species may also be of chemotaxonomic interest.

The above data clearly suggest that *Hymenopappus* is properly aligned with the helenoid genera centring about the subtribe Bahiinae of Rydberg [22]. In his survey of the subtribal limits of the Heliantheae, Robinson [23] recognized *Hymenopappus*, along with *Galeana*, *Loxothysanus*, *Trichocorye* and *Villanova*, as constituting the subtribe Hymenopappinae: he placed *Schkuhria* and *Picradeniopsis* in the subtribe Chaenactidinae. It would appear, on chemical grounds, that the genera discussed above make up an interrelated 'core-group' which might be best treated within a single subtribe; for example, the Bahiineae of Stuessy [24]. Whatever the treatment, the rich diversity of compounds revealed in *Hymenopappus*

Table 1. ^{1}H NMR spectral data of compounds **3–6** (400 MHz, $CDCl_3$, TMS as internal standard)

	3	4	$CDCl_3/C_6D_6$	5	6
H-1	4.93 *dd br*	3.18 *m*	2.84 *ddd br*	3.18 *m*	3.60 *ddd*
H-2	2.52 *ddd br*	2.51 *dddq*	2.33 *dddq*	2.50 *dd br*	5.80 *dd*
H-2′	2.33 *ddd*	2.42 *dddq*	2.26 *dddq*	2.41 *d br*	
H-3	4.36 *dd*	5.57 *dddq*	5.41 *dddq*	5.57 *dddq*	6.01 *dd*
H-5	4.84 *d br*	2.85 *dd br*	2.57 *dd br*	2.84 *dd br*	2.96 *dd*
H-6	5.21 *dd*	4.51 *dd*	4.37 *dd*	4.47 *dd*	4.71 *dd*
H-7	2.92 *ddd br*	3.18 *m*	2.75 *dddd*	3.18 *m*	3.12 *dddd*
H-8	5.81 *ddd*	5.67 *ddd*	5.44 *ddd*	5.66 *ddd*	5.75 *ddd*
H-9	2.85 *dd br*	2.59 *dd*	2.41 *dd*	2.59 *dd*	2.81 *dd*
H-9′	2.33 *dd*	2.54 *dd*	2.22 *dd*	2.54 *dd*	2.42 *dd br*
H-13	6.33 *d*	6.24 *d*	6.12 *d*	6.25 *d*	6.29 *d*
H-13′	5.63 *d*	5.55 *d*	5.34 *d*	5.54 *d*	5.65 *d*
H-14	1.52 *s br*	5.01 *s br*	4.85 *s br*	5.00 *s br*	4.92 *s*
H-14′		4.87 *s br*	4.71 *s br*	4.85 *s br*	
H-15	1.81 *d*	1.87 *s br*	1.80 *s br*	1.87 *s br*	1.45 *s*
H-3′	6.72 *t*	7.02 *t*	6.88 *t*	6.90 *t*	7.05 *t*
H-4′	4.85 *dd*	4.50 *dd*	4.20 *dd*	4.88 *d*	5.01 *d*
		4.45 *dd*	4.15 *dd*		4.89 *d*
H-5′	4.38 *s br*	4.97 *d*	4.78 *d*	4.89 *d*	4.53 *dd*
		4.91 *d*	4.73 *d*	4.85 *d*	4.48 *dd*
H-8′	—	6.89 *q*	6.75 *q*	7.04 *q*	6.89 *q*
H-9′	—	1.90 *d*	1.69 *d*	1.93 *d*	1.92 *d*
H-10′	—	4.30 *s*	4.16 *s*	4.80 *s*	4.32 *s*
OAc	2.10 *s*	—	—		

J [Hz]: compounds **4–6**: 1, 2 = 8.5; 1, 2′ = 5; 1, 5 = 8.5; 2, 2′ = 17; 2, 3 = 2, 3′ = 3, 5 = 3, 15 ~ 1.5; 5, 6 = 10.5; 6, 7 = 9; 7, 8 = 2.5; 7, 13 = 3.5; 7, 13′ = 3; 8, 9 = 5; 8, 9′ = 5; 9, 9′ = 14; 3′, 4′ = 6; $4_1'$, $4_2'$ = 16; $5_1'$, $5_2'$ = 12; 8′, 9′ = 7.5 (compound **6**: 1, 2 = 2.5; 1, 3 = 1.5; 1, 5 = 10; 2, 3 = 6; 5, 6 = 11; 6, 7 = 9). Compound **3**: 1, 2 = 3.5; 1, 2′ = 11.5; 2, 2′ = 14; 2, 3 = 6; 2′, 3 = 10; 5, 6 = 10; 5, 15 = 1.5; 6, 7 = 9; 7, 8 ~ 1; 7, 13 = 3.5; 7, 13′ = 3; 8, 9 = 5; 8, 9′ = 2; 9, 9′ = 14; 3′, 4′ = 6.5; 4′, 5′ = 1.5.

newberryi, especially the lactones, which are close to those of some genera of the tribe Eupatorieae, makes it a strong candidate as a likely primitive species in this 'core-group'.

EXPERIMENTAL

The air-dried aerial parts (480 g) (collected in south central Colorado, U.S.A.; voucher Turner *s.n.* TEX) were extracted at room temp. with Et_2O–petrol–MeOH, 1:1:1, for 12 hr. The extract obtained was treated with MeOH to remove saturated long-chain hydrocarbons and was first separated by CC (SiO_2) into five fractions (each 100 ml): 1 (petrol), 2 (Et_2O–petrol, 1:10), 3 (Et_2O–petrol, 1:1), 4 (Et_2O) and 5 (Et_2O–MeOH, 10:1). TLC (SiO_2 PF 254) of fractions 1 and 2 gave no characteristic compounds. TLC of fraction 3 (Et_2O–petrol, 1:3, detection by UV light) afforded 4 mg **7** and 3 mg **8** [R_f 0.46 and 0.49 respectively: identical with authentic material (400 MHz ^{1}H NMR)], while TLC of fraction 4 gave no characteristic compounds. Repeated TLC of fraction 5 (Et_2O, followed by $CHCl_3$–MeOH, 10:1, detection by UV light) gave 200 mg **2** (R_f 0.07), a mixture of **3** and **4** and **6** (R_f 0.23), as well as 10 mg **1** (R_f 0.7). **1** and **2** were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material, and by systematic spin decoupling. The mixture of **2–4**, **6** and **9** was separated by HPLC (RP 8, MeOH–H_2O, 3:2). The main fraction (R_t 8.1 min) gave 28 mg **4**, while the others (R_t 2.0 and 3.8 min) were still impure. HPLC (RP 8, MeOH–H_2O, 11:9) of these fractions gave 10 mg of a mixture of **4** and **9**, 5 mg **3** (R_t 2.7 min) and 2 mg **6** (R_t 1.8 min). The mixture of **4** and **9** was separated after acetylation (Ac_2O, 1 hr, 70°). TLC (Et_2O) afforded 3 mg **5** and 5 mg **10** (R_f 0.52). **3–6** could not be induced to crystallize, but their ^{1}H NMR spectra showed no apparent impurities and they were homogeneous by TLC ($CHCl_3$–MeOH, 30:1 and $CHCl_3$–C_6H_6–Et_2O, 1:1:1).

3β-Hydroxy-8β-(4′-acetoxy-5′-hydroxytigloyloxy)-costunolide (**3**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 3420 (OH), 1770 (γ-lactone), 1745, 1240 (OAc), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 246.125 [M − RCO_2H]$^+$ (8) (calc. for $C_{15}H_{18}O_3$: 246.125), 228 [246 − H_2O]$^+$ (7), 115 [RCO − ketene]$^+$ (40), 97 [115 − H_2O]$^+$ (54), 69 [97 − CO]$^+$ (100); CI (isobutane): 421 [M + 1]$^+$ (80), 247 [M − RCO_2H]$^+$ (100).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ \text{nm}}{+64 \quad +68 \quad +79 \quad +156} \ (CHCl_3;\ c\ 0.4).$$

Ligustrin-[4′-hydroxy-5′-(5′-hydroxytigloyloxy)-tiglate] (**4**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3430 (OH), 1765 (γ-lactone), 1710 (C=CCO_2R); MS *m/z* (rel. int.): 458.194 [M]$^+$ (2) (calc. for $C_{25}H_{30}O_8$: 458.194), 440 [M − H_2O]$^+$ (1), 422 [440 − H_2O]$^+$ (0.6), 360 [M − $C_5H_6O_2$]$^+$ (3), 342 [M − RCO_2H]$^+$ (3), 246 [M − $C_{10}H_{12}O_5$]$^+$ (5), 228 [M − RCO_2H]$^+$ (41), 213 [RCO]$^+$ (10), 99 [RCO]$^+$ (67), 69 [99 − CHO]$^+$ (100).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ \text{nm}}{+18 \quad +19 \quad +22 \quad +71} \ (CHCl_3;\ c\ 2.6).$$

5 mg **4** was heated for 1 hr with 0.2 ml Ac_2O at 70°. TLC (Et_2O, R_f 0.35) afforded 5 mg **5**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1750, 1240 (OAc), 1720, 1655 (C=CCO_2R); MS *m/z* (rel. int.): 542.115 $[M]^+$ (1.3) (calc. for $C_{29}H_{34}O_{10}$: 542.115), 482 $[M-HOAc]^+$ (5), 422 $[482-HOAc]^+$ (2), 383 $[M-RCO_2]^+$ (4.7), 228 $[M-RCO_2H]^+$ (48), 141 $[RCO]^+$ (82), 99 $[141-ketene]^+$ (59), 81 $[99-H_2O]^+$ (100).

Hymenopappolide (**6**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 3440 (OH), 1770 (γ-lactone), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 244.110 $[M-RCO_2H]^+$ (5) (calc. for $C_{15}H_{16}O_3$: 244.110), 98 $[C_5H_6O_2]^+$ (71), 69 $[98-CHO]^+$ (100).

$$[\alpha]_{24}^{\lambda\,\circ} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{-124 \quad -117 \quad -134 \quad -239} \ (CHCl_3;\ c\ 0.18).$$

Abbeokutone 17-O-*acetate* (**10**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745 (OAc), 1710 (C=O); MS *m/z* (rel. int.): 362.246 $[M]^+$ (5.5), 347 $[M-Me]^+$ (4.5), 344 $[M-H_2O]^+$ (3.5), 289 $[M-CH_2OAc]^+$ (100), 271 $[289-H_2O]^+$ (18); ^1H NMR ($CDCl_3$): δ1.98 *dt* (H-1, *J* = 13, 7 Hz), 1.38 *dt* (H-1′, *J* = 13, 8 Hz), 2.47 *dd* (H-2, *J* = 8, 7 Hz), 2.07 *s br* (H-13), 1.90 *d br* (H-15), 4.23 *s* (H-17), 1.08 *s* (6H), 1.03 *s* (H-18, 19, 20), 2.11 *s* (OAc); ^{13}C NMR ($CDCl_3$, C-1–C-20): δ39.2 *t*, 34.0 *t*, 217.5 *s*, 47.1 *s*, 54.4 *d*, 21.7 *t*, 40.8 *t*, 44.6 *s*, 55.4 *d*, 18.8 *t*, 26.1 *t*, 46.0 *d*, 36.8 *t*, 52.8 *t*, 79.9 *s*, 68.5 *t*, 27.3 *q*, 20.9 *q*, 17.7 *q* (OAc: 171.1 *s*, 20.9 *q*).

To 3 mg **10** in 1 ml Et_2O, 20 mg $LiAlH_4$ was added at room temp. After 5 min, dil. H_2SO_4 was added. Extraction with Et_2O afforded **11**, colourless crystals, mp 217° (lit. mp 218°); ^1H NMR ($CDCl_3$): δ3.18 *dd* (H-3, *J* = 11, 6 Hz), 2.04 *s br* (H-13), 1.94 *d br* (H-15), 3.77 and 3.65 *d* (H-17, *J* = 11 Hz), 1.02, 0.97, 0.77 *s* (H-18, 19, 20).

2 mg **10** was heated in 1 ml MeOH with 0.5 ml 2 M KOH. TLC (Et_2O) afforded **9**, colourless crystals, mp 190° (lit. mp 190–192°); $[\alpha]_D$ −68° ($CHCl_3$, *c* 0.15) (lit. −73°).

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