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HELENANOLIDES FROM *GAILLARDIA POWELLII*

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Key Word Index—*Gaillardia powellii*; Compositae; sesquiterpene lactones; helenanolides; flavones.

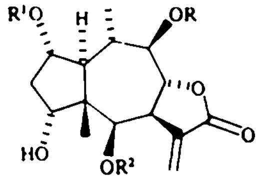
Abstract—The chloroform extract of the aerial parts of *Gaillardia powellii* afforded four known and four new helenanolides, the latter all oxygenated on C-15, as well as the flavones hispidulin and eupafolin.

INTRODUCTION

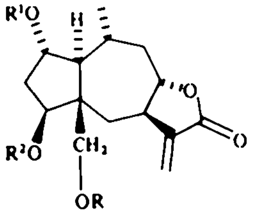
About a dozen representatives of the North American genus *Gaillardia* (tribe Heliantheae, subtribe Gaillardiinae) have been investigated chemically [1–4]. Characteristic constituents are sesquiterpene lactones of the helenanolide class exemplified by spathulin (**1**). We have now studied the aerial parts of the recently described gypsophilous species *Gaillardia powellii* Turner [5]. In addition to lactones **2–5** [2, 4–6] previously obtained from *G. aristata*, *G. grandiflora* and *G. pulchella*, four new helenanolides, **6a**, **7a**, **8** and **9a**, all oxygenated on C-15, were isolated. The flavones hispidulin (**10**) and eupafolin (**11**) were also found.

RESULTS AND DISCUSSION

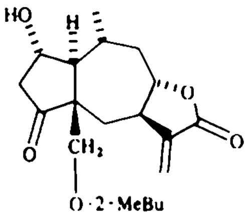
The entire carbon skeleton of lactone **6**, $C_{20}H_{30}O_6$, mp 171°, could be deduced by spin decoupling of its ^1H NMR spectrum (Table 1), beginning with irradiation at the frequencies of H-13a,b (narrowly split doublets at δ6.15 and 5.60) which collapsed the signal of H-7 to a *ddd*. Irradiation at the frequency of H-7 identified the signals of H-6a,b (*dds* at δ2.05 and 1.52) as well as that of H-8 (*ddd* at δ4.18). Irradiation at the frequency of H-8 simplified the mutually coupled signals of H-9α (*t* at δ1.40) and H-9β (*dt* at δ2.38); each of these was further coupled to H-10, which was in turn coupled to the protons of a methyl doublet (H-14), as well as to H-1 (*dd* at δ1.78). H-1 was also coupled to



1 R = Ac, R^1, R^2 = H
2 R = H, R^1 = 2-MeBu, R^2 = Ac
3 R = H, R^1 = iVal, R^2 = Ac
4 R, R^2 = H, R^1 = 2-MeBu
5 R, R^2 = H, R^1 = iVal



6 R, R^1 = H, R^2 = 2-MeBu
7a R = 2-MeBu, R^1, R^2 = H
7b R = 2-MeBu, R^1, R^2 = Ac



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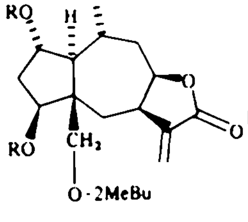
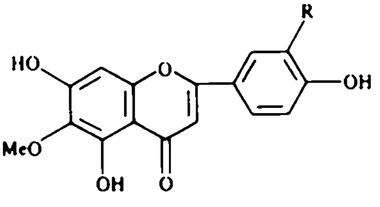


9a R = H
9b R = Ac



10 R = H
11 R = OH

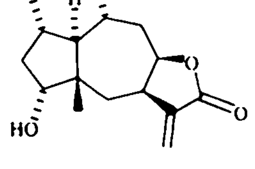


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Table 1. ^{1}H NMR spectral data of **6**, **7a**, **7b**, **8**, **9a** and **9b** ($CDCl_3$, 270 MHz)

	6	**7a**	**7b**	**7b***	**8**	**9a**	**9b**	**9b***
H-1	1.78 *dd* (10, 7.5)	1.76 *dd* (11.7)	2.11 *dd* (11.9)	1.62 *dd*	2.08 *dd* (10, 8)	1.33 *dd* (12, 8)	1.68 *dd* (12, 9.5)	1.20 *dd*
H-2	4.35 *dt* (7.5, 6)	4.28 *ddd* (10, 7, 3)	5.20 *ddd* (10, 9, 3)	5.28 *ddd*	4.60 *ddd* (9, 8, 7)	4.13 *ddd* (9.5, 8, 3)	5.07 *td* (9.5, 3)	5.16 *td*
H-3a	2.16 *dd* (9.5.6)†	2.02 *m*†	2.24 *ddd* (14, 10, 9.5)	2.37 *ddd*	3.00 *dd* (19, 9)	2.21 *dt* (15, 9.5)	2.36 *dt* (15, 9.5)	2.48 *dt*
H-3b			2.04 *ddd* (14, 9.5, 3)	2.14 *ddd*	2.32 *dd* (19, 7)	2.05 *ddd* (15, 9.5, 3)	2.06 *ddd* (15, 9.5, 3)	2.15 *ddd*
H-4	5.23 *t* (9.5)	4.24 *t*	5.16 *t*	5.00 *t*		4.14 *t*	5.13 *t*	4.99 *t*
H-6α	2.05 *dd* (14.5, 5)	2.27 *dd* (15, 5.5)	2.22 *dd*	1.68 *dd*	2.46 *dd* (15, 5)	1.93 *dd* (15, 4)	1.71 *dd*	1.28 *dd*
H-6β	1.52 *dd* (14.5, 12)	1.38 *dd* (15, 12)	1.26 *dd*	0.69 *dd*	1.46 *dd*	1.59 *dd* (15, 14.5)	1.54 *dd*	0.95 *dd*
H-7	2.85 *ddddd* (12, 10, 5, 3, 3)	2.87 *ddddd* (12, 11, 5.5, 3.2, 3.2)	2.90 *ddddd*	1.92 *ddddd*	2.88 *ddddd* (12, 10, 5, 3, 3)	3.22 *ddddd* (14.5, 8, 4, 2.3, 2.2)	3.27 *ddddd*	2.14 *ddddd*
H-8	4.18 *ddd* (12, 10, 3)	4.20 *ddd* (12, 11, 3)	4.15 *ddd*	3.34 *ddd*	4.16 *ddd* (12, 10, 3)	4.77 *ddd* (12, 8, 3)	4.78 *ddd*	4.05 *ddd*
H-9α	1.40 *q* (12)	1.38 *q*	1.42 *q*	0.85 *q*	1.48 *q*	1.83 *ddbr* (14,3)	1.83 *ddbr*	1.45*oldbr*
H-9β	2.38 *dt* (12, 3)	2.38 *dt*	2.38 *dt*	1.86 *dt*	2.44 *dt*	2.15 *m*	2.10 *m*	2.65 *m*
H-10	2.03 *ddqd* (12, 10, 7, 3)	1.89 *ddqd*	1.90 *ddqd* (12, 11, 7, 3)	1.41 *m*	2.00 *m*	1.96 *m*	2.00 *m*	1.65 *m*
H-13a	6.15 *d* (3)	6.18 *d* (3.2)	6.18 *d*	6.02 *d*	6.21 *d*	6.29 *d* (2.3)	6.30 *d*	6.19 *d*
H-13b	5.40 *d* (3)	5.47 *d* (3.2)	5.44 *d*	4.74 *d*	5.52 *d*	5.64 *d* (2.2)	5.62 *d*	5.01 *d*
H-14‡	1.20 *d* (7)	1.18 *d*	1.01 *d*	0.78 *d*	1.31 *d*	1.21 *d*	1.07*d*	0.79 *d*
H-15a	3.66 *br*†	4.22 *d* (12)	4.13 *d*	4.07 *d*	4.25 *d*	4.19 *d*	4.13 *d*	4.05 *d*
H-15b		3.95 *d* (12)	3.98 *d*	3.72 *d*	3.89 *d*	4.03 *d*	4.03 *d*	3.84 *d*
H-2′	2.40 *tq* (7.7)	2.34 *tq*	2.40 *tq*	2.27 *tq*	2.35 *tq*	2.35 *tq*	2.41 *tq*	2.29 *tq*
H-3′a	1.70 *m*	1.67 *m*	1.68 *m*	1.64 *m*	1.65 *m*	1.65 *m*	1.70 *m*	1.67 *m*
H-3′b	1.40 *m*	1.48 *m*	1.53 *m*	1.34 *m*	1.45 *m*	1.48 *m*	1.53 *m*	1.38 *m*
H-4′‡	0.92 *t* (7)	0.91 *t*	0.91 *t*	0.80 *t*	0.88 *t*	0.94 *t*	0.93 *t*	0.84 *t*
H-5′‡	1.16 *d* (7)	1.14 *d*	1.18 *d*	1.07 *d*	1.13 *d*	1.15 *d*	1.17 *d*	1.11 *d*
OH	2.05 *br*, 1.88 *br*	2.05 *br*		—	1.95 *br*	2.15 *br*, 2.10 *br*	—	—
Ac‡	-		2.09, 2.01	1.64, 1.63	-		2.08, 2.03	1.65, 1.62

*Run in C_6D_6.

†Intensity two protons.

‡Intensity three protons.

H-2 (*dt* at δ4.35) which adjoined H-3a,b and whose chemical shift indicated that it was geminally coupled to one of the two hydroxyl groups present in the molecule. Finally, the two-proton signal of H-3a,b was also coupled to a triplet at δ5.23 (H-4), whose chemical shift showed that it was geminal to the 2-methylbutanoyl residue whose presence was evident from NMR and mass spectrometry. The multiplicities of H-1, H-4 and H-6a,b required that the remaining two carbon atoms of the empirical formula—one quaternary (carbon singlet at δ50.1—Table 2), the second a $-CH_2OH$ residue (carbon triplet at δ64.8, two-proton singlet at δ3.66) -be inserted as shown in formula **6**.

The stereochemistry of the lactone ring could be inferred from the coupling constants involving H-6, H-7, H-8, H-9 and H-13, which parallel those of helenanolides with authenticated stereochemistry. That the lactone ring is *trans*-fused is also evident from the positive Cotton effect in the 250 nm region.* The remaining questions, in particular the stereochemistries at C-2 and C-4, were settled by NOE difference spectrometry (Table 3) and consideration of models. Since H-2, H-8, H-10 and H-15 are *cis* and since H-8 is β, H-2, H-10 and H-15 are β as well. H-1 and H-4 are *cis*; the absence of an interaction between H-4 and H-15 shows that H-4 is *trans* to C-15, hence H-1 and H-4 are α.

Lactone **7a** was an isomer of **6**; comparison of the ^{1}H NMR and ^{13}C NMR spectra of the two compounds (Tables 1 and 2) showed that the stereochemistry was identical but that the 2-methylbutanoyl residue of **7a** esterified the primary hydroxyl group on C-15. This was confirmed by the paramagnetic shift exhibited by H-2 and H-4 on conversion of **7a** to a diacetate, **7b**. Lactone **8** was the corresponding 4-keto derivative; noteworthy is the characteristically large germinal coupling constant between the protons on C-3, the carbons alpha to the new carbonyl group.

Table 3. NOE difference spectral data of compound **6**

Saturation	Observed NOE (%)
H-2	H-3a, b (5), H-10 (8)
H-4	H-1 (11), H-3a, b (12), H-6a (13.5), H-15 (0)
H-14	H-2 (16), H-9β (25)
H-15	H-3a, b (16), H-4 (0), H-6β (15), H-8 (16), H-10 (18)

Table 2. ^{13}C NMR spectral data of compounds **6**, **7a** and **9a** (67.89 MHz, $CDCl_3$)

C	**6**	**7a**	**9a**
1	56.3 *d*	56.5 *d*	55.9 *d*
2	72.7 *d*	72.6 *d*	72.9 *d**
3	39.2 *t*	41.9 *t*	42.6 *t*
4	81.8 *d*	80.5 *d*	75.4 *d**
5	50.1 *s*	49.5 *s*	49.0 *s*
6	32.3 *t*	33.4 *t*	35.1 *t*
7	44.6 *d*	44.6 *d*	37.9 *d*
8	81.7 *d*	81.6 *d*	76.7 *d*
9	44.1 *t*	44.1 *t*	34.2 *t*
10	28.5 *d*	28.8 *d*	29.3 *d*
11	140.2 *s*	140.1 *s*	139.2 *s*
12	169.8 *s*	169.6 *s*	169.4 *s*
13	119.8 *t*	119.9 *t*	123.3 *t*
14	20.7 *q*	20.6 *q*	21.0 *q*
15	64.8 *t*	65.1 *t*	64.8 *t*
1'	175.8 *s*	176.4 *s*	176.7 *s*
2'	41.2 *d*	41.3 *d*	41.2 *d*
3'	26.8 *t*	26.6 *t*	26.5 *t*
4'	16.6 *q*	16.5 *q*	16.4 *q*
5'	11.5 *q*	11.6 *q*	11.6 *q*

*Assignments may be interchanged.

Spin decoupling in the manner described for **6** and conversion to the diacetate **9b** established the gross structure of lactone **9a** as a stereoisomer of **7a**. While the coupling constants involving the protons of the five-membered ring did not differ significantly from those exhibited by **7a** and **7b**, the characteristically small values of $J_{7,13}$ and the *negative* lactone Cotton effect showed that the lactone ring of **9a** was *cis*-fused. In fact, the coupling constants involving the protons in the seven-membered ring parallel those of neopulchellin (**12**) whose structure has been established by X-ray crystallography [8].

EXPERIMENTAL

Extraction of G. powellii. Above-ground parts of *G. powellii* Turner (0.4 kg), collected by Prof. B. L. Turner on 11 April 1970, 0.5 m S. of Estación Hermanas along Highway 57, Coahuila, Mexico (voucher B. L. Turner No. 6035 deposited at the herbarium of the University of Texas), were extracted with $CHCl_3$. Work-up in the usual fashion [9] gave 14 g of crude gum which was absorbed on 30 g of silicic acid (Mallinckrodt, 100 mesh) and chromatographed over 500 g of the same adsorbent packed in heptane, 375 ml fractions being collected as follows: fractions 1–4 (heptane), 5–8 (heptane–EtOAc, 9:1), 9–12 (heptane–EtOAc, 4:1), 13–16 (heptane–EtOAc, 2:1), 17–20 (heptane–EtOAc, 7:7), 21–24 (heptane–EtOAc, 2:3), 25–28 (heptane–EtOAc, 1:4), 29–32 (EtOAc), 33–36 (EtOAc–MeOH, 9:1). Fraction 17 (0.5 g) dissolved in $CHCl_3$ on refrigeration (−20°) deposited 40 mg of hispidulin (**10**), identified by comparison with authentic material. Fraction 18 (1 g) was purified by CC (hexane–Et_2O, 3:7) to give three fractions. The first fraction contained a 7:3 mixture of **2** [2] and **3** [6], which were not separated but identified by comparison of the ^{1}H NMR spectrum of the mixture with data in the literature. The second fraction was purified by CC (hexane–EtOAc, 7:3) and crystallization (hexane–EtOAc, 7:3, −20°) to give 40 mg of **6**, mp 171°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1760, 1730; CD curve (MeOH) $[\theta]_{253}$ + 1820, $[\theta]_{223}$ 0, $[\theta]_{212}$ − 2910; ^{1}H NMR and ^{13}C NMR spectra: see Tables 1 and 2. The low resolution EIMS did not exhibit the molecular ion; significant peaks were at *m/z* (rel. int.): 348 (0.1), 264 (3.1), 246 (2.9), 228 (2.5), 192 (3.6), 147 (5), 107 (14.6), 103 (9.7), 91 (8.3), 85 (37.7), 57 (100). The positive CIMS exhibited peaks at *m/z* (rel. int.): 367 $[M + H]^+$ (100), 349 (26), 265 (18), 47 (20.2), 229 (6.1), 103 (37.1) and 85 (34.7).

Purification of the third fraction by CC (C_6H_6–EtOAc, 3:2) gave 10 mg of **8** as a gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1771, 1752, 1735; CD curve (MeOH) $[\theta]_{246}$ + 6700 (max) $[\theta]_{263}$ + 1800 (sh),

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*That the empirical rule of Stöcklin *et al.* [7], which relates the sign of the lactone Cotton effect to the direction and nature of the ring closure, is applicable to compounds of this type has been shown in a number of instances.

$[\theta]_{244}$ + 770 (min), $[\theta]_{215}$ + 6180 (max); ^{1}H NMR spectrum: see Table 1. The low resolution EIMS did not exhibit the molecular ion; significant peaks were at *m/z* (rel. int.): 346 (0.5), 276 (8), 262 (6.9), 244 (4), 192 (7.9), 173 (7), 136 (11.2), 107 (11.2), 85 (100) and 57 (99.2). The positive CIMS exhibited peaks at *m/z* (rel. int.): 365 $[M + H]^+$ (9.7), 347 (7.7), 263 (5.5), 245 (13.1), 210 (6.4), 169 (6.4), 141 (11.6), 113 (18), 103 (48.8), 95 (23), 85 (90), 83 (68.6) and 81 (100).

Fraction 19 (0.3 g) dissolved in $CHCl_3$ on refrigeration deposited 20 mg of eupafolin (**11**), identified by comparison with authentic material. Fraction 20 (1 g) was purified by CC (hexane EtOAc, 1:1) to give 150 mg of **7a** (gum); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1760, 1730; CD curve (MeOH) $[\theta]_{253}$ + 1590 (max), $[\theta]_{236}$ + 1135 (min), $[\theta]_{216}$ + 4770 (max); ^{1}H NMR and ^{13}C NMR spectra: see Tables 1 and 2. The low resolution EIMS did not exhibit the molecular ion; significant peaks were at *m/z* (rel. int.): 264 (6.9), 246 (8.4), 220 (6.7), 192 (30.9), 175 (10.8), 163 (10.4), 159 (12.3), 147 (20), 136 (38.1), 107 (70), 103 (37), 95 (14), 85 (38.1), 73 (21.7), 57 (100). The positive CIMS exhibited peaks at *m/z* (rel. int.): 367 $[M + H]^+$ (51.4), 349 (9.3), 283 (8.1), 265 (100), 247 (10.1), 229 (5.5), 145 (4.0), 127 (6.6), 107 (6.4), 103 (5.3), 91 (23.5) and 85 (32.6). Acetylation of 10 mg of **7a** (Ac_2O pyridine followed by the usual work-up gave 9 mg of **7b** whose ^{1}H NMR spectral data are listed in Table 1.

Fractions 21 and 22 (4 g) were purified by CC (Et_2O–Me_2CO, 9:1). The initial fractions furnished 1.2 g of a 4:1 mixture of **4** and **5** [4], which were not separated but identified by comparison of the ^{1}H NMR spectrum with data in the literature. The latter fractions on further purification by radial chromatography (hexane–Et_2O, 1:4) furnished 70 mg of **9a** as a gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1760, 1735; CD curve (MeOH) $[\theta]_{253}$ −2660, $[\theta]_{234}$ 0, $[\theta]_{217}$ +27600; ^{1}H NMR and ^{13}C NMR spectra: see Tables 1 and 2. The positive CIMS exhibited peaks at *m/z* (rel. int): 367 $[M + H]^+$ (100), 349 (1.1), 283 (1.5), 265 (7.6), 247 (3.6), 192 (20), 147 (1), 103 (10.5) and 85 (8.0). Acetylation of 15 mg of **9a** followed by the usual work-up gave 13 mg of **9b** whose ^{1}H NMR spectrum is listed in Table 1. Purification of fractions 23–25 (2.5 g) by CC (Et_2O–Me_2CO, 4:1) gave an additional 0.5 g of the mixture of **4** and **5** and 0.2 g of **9a**.

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