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VISCIDIC ACID A AND B, TWO *ENT*-LABDANE DERIVATIVES FROM *CHRYSOTHAMNUS VISCIDIFLORUS*

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Key Word Index—*Chrysothamnus viscidiflorus*; Astereae; Compositae; diterpenes; new *ent*-labdane derivatives; viscidic acids A and B; *ent*-labd-8(17),13*E*-dien-15-ol-18-oic acid; *ent*-labd-8(17),13*E*-dien-15-acetoxy-18-oic acid.

Abstract—The chemical investigation of *Chrysothamnus viscidiflorus* afforded, in addition to known bisabolene derivatives, elemicin and *p*-hydroxyacetophenone, two new diterpene acids. Their structures were determined, by spectroscopic methods and some chemical transformations, as *ent*-labd-8(17),13*E*-dien-15-ol-18-oic acid (viscidic acid A) and *ent*-labd-8(17),13*E*-dien-15-acetoxy-18-oic acid (visidic acid B).

INTRODUCTION

Chrysothamnus is a North American genus with 14 species (tribe Astereae) [1]. The latex of several species contains rubber of fair quality, that of *C. nauseosus* being reported to yield 2.8–6.5% [2, 3]; only one species has been investigated for flavonoids, *C. viscidiflorus* [4], whereas *C. parryi* afforded many matricaria ester derivatives [5]. Many labdane derivatives as well as a bisabolene, a germacrene and a flavanone derivative were found as constituents of *C. nauseosus* [6].

We now wish to report herein the isolation and structure elucidation of two new diterpene acids, named viscidic acid A and B, as well as other constituents of *C. viscidiflorus*.

RESULTS AND DISCUSSION

The aerial parts of *C. viscidiflorus* afforded the known bisabolene derivatives **1** [5, 7] and **2** [5, 8], *p*-hydroxyacetophenone (**3**) and elemicin (**4**) [7, 9], together with two new diterpene acids which were isolated pure after repeated TLC and transformation to their methyl esters.

Viscidic acid A (**5**)

The IR spectrum of the more polar acid **5**, $C_{20}H_{32}O_3$, showed the presence of an exomethylene group (3100, 895 cm^{-1}), a carboxylic acid (3480–2800 cm^{-1}) and probably an alcohol (3610 cm^{-1}) which were confirmed by conversion of **5** into the corresponding methyl ester **6** (δ 3.65, *s*, 3 H) and into the acetate **7** (2.07, *s*, 3 H).

The ^{13}C NMR of **5** indicated the presence of one carboxyl group (*s* 183.9) and two double bonds, one disubstituted (*s* 147.8 and *t* 106.9) and the other trisubstituted (*s* 140.3 and *d* 123.0, see Table 2). The ^{13}C NMR data taken in combination with the MS lead to the conclusion that the diterpene acid must be bicyclic.

In the ^1H NMR spectrum of **5** the vinylidene protons absorbed as broadened singlets at δ 4.86 and 4.54, whereas the other olefinic proton on a trisubstituted double bond appeared as a broadened triplet at 5.35 (J = 7 Hz), which coupled with one two-proton doublet at 4.16 (J = 7 Hz) and one broadened methyl singlet at 1.67 as shown by double irradiation experiments at 270 MHz. The two-proton doublet at 4.16 was assigned to the allylic primary

Table 1. ^1H NMR spectral data of diterpenes **5**–**12***

Proton	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
14-H	5.39 *t*(*br*) (7)	5.39 *t*(*br*) (7)	5.33 *t*(*br*) (7)	5.32 *t*(*br*) (7.5)	5.89 *d*(*br*) (8)	5.88 *d*(*br*) (8)	5.40 *t*(*br*) (7)	5.33 *t*(*br*) (7)
15-H	4.16 *d* (7)	4.15 *d* (7)	4.60 *d* (7)	4.59 *d* (7.5)	10.99 *d* (8)	10.00 *d* (8)	4.16 *d* (7)	4.57 *d* (7)
16-H	1.67 *s*(*br*)	1.67 *s*(*br*)	1.71 *s*(*br*)	1.70 *s*(*br*)	2.17 *d* (1)	2.17 *d* (1)	1.67 *s*(*br*)	1.70 *s*(*br*)
17-H	4.86 *s*(*br*)	4.83 *s*(*br*)	4.85 *s*(*br*)	4.84 *s*(*br*)	4.87 *s*(*br*)	4.86 *s*(*br*)	4.84 *s*(*br*)	4.84 *s*(*br*)
17′-H	4.54 *s*(*br*)	4.53 *s*(*br*)	4.54 *s*(*br*)	4.53 *s*(*br*)	4.51 *s*(*br*)	4.50 *s*(*br*)	4.53 *s*(*br*)	4.53 *s*(*br*)
19-H	1.15 *s*	1.14 *s*	1.16 *s*	1.14 *s*	1.15 *s*	1.14 *s*	0.76 *s*	0.82 *s*
18-H	—	—	—	—	—	—	3.10 *d*†	3.63 *d*†
18′-H	—	—	—	—	—	—	3.44 *d*†	3.87 *d*†
20-H	0.72 *s*	0.70 *s*	0.73 *s*	0.71 *s*	0.73 *s*	0.71 *s*	0.72 *s*	0.72 *s*
COOMe	—	3.65 *s*	—	3.67 *s*	—	3.66 *s*	—	—
COOH	3.70 *m*	—	—	—	4.23 *m*	—	—	—
OAc	—	—	2.07 *s*	2.07 *s*	—	—	—	2.05 *s* 2.04 *s*

* Spectra were run in $CDCl_3$, at 270 MHz (**5**, **7**, **8**) or 80 MHz (**6**, **9**–**12**) and TMS was used as internal standard. Chemical shifts are in ppm relative to TMS. Figures in parentheses are coupling constants in hertz.

† J (18–18′) = 11 Hz.

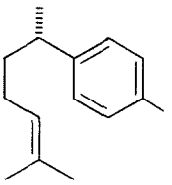
alcohol group which could be oxidized with MnO_2 to give the α,β-unsaturated aldehyde **9** (δ 10.0, *d* and 5.89, *br d*, J = 10 Hz, Table 1). In the acetate **7** this doublet (4.16) moved downfield to 4.60 (*d*, J = 7 Hz). The nature of the side chain was also deduced and the *E*-configuration of the double bond at C-13, C-14 was clearly shown by comparison of the 16-H chemical shift of **5** and **9** or **6** and **10**, respectively. The broadened singlet at δ 1.67 due to the C-13 methyl group of the alcohols **5** and **6** moved downfield to 2.17 after conversion into the α,β-unsaturated aldehydes **9** and **10** (Table 1). The ^{1}H NMR spectrum of **5** showed further the presence of two methyl groups at quaternary positions (δ 0.72 and 1.15, *s*, 3 H). The chemical shift of the C-10 methyl group of **6** (0.70) [10–12], together with the strong IR absorption at 1240 cm^{-1} [10, 13] indicated that the C-4 carboxyl group was equatorial. The signals due to the CH_2-group of the C-4 hydroxymethylene function in the diol **11** appeared at δ 3.10 and 3.44 characteristic of an equatorial CH_2OH at C-4, whereas the axial system of the agathadiol **14** appeared at 3.38 and 3.72 [14–16]. Thus, there is no doubt about the equatorial configuration of the C-4 carboxyl group in viscidic acid A (**5**) and B (**7** see below). The negative values of the optical rotations of **7** and **8**, as well as the diol **11**, lead to the proposed *ent*-labdane derivatives for viscidic acid A and B. The structural assignment was confirmed by oxidation of the alcohol ester **6** with excess chromium trioxide followed by esterification with diazomethane whereupon the diester **13** was obtained. The IR and NMR spectra as well as the optical rotation of **13** were identical with those of the known *ent*-labdane derivative, dimethyl guamaate [12]. Therefore, the structure of viscidic acid A (**5**) is *ent*-labd-8(17),13-*E*-dien-15-ol-18-oic acid.

Table 2. ^{13}C NMR spectral data of viscidic acid A(**5**) and B(**7**)*

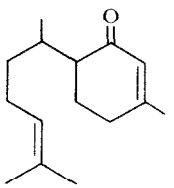
	5	**7**
C(1)	38.2 *t* †	38.2 *t* †
C(2)	18.4 *t*	18.4 *t*
C(3)	38.0 *t* †	38.0 *t* †
C(4)	47.4 *s*	47.5 *s*
C(5)	56.2 *d*	56.1 *d*
C(6)	26.8 *t*	26.8 *t*
C(7)	37.0 *t* †	37.1 *t* †
C(8)	147.8 *s*	147.7 *s*
C(9)	49.5 *d*	49.5 *d*
C(10)	38.3 *s*	38.8 *s*
C(11)	21.6 *t*	21.4 *t*
C(12)	37.8 *t* †	37.8 *t* †
C(13)	140.3 *s*	142.8 *s*
C(14)	123.0 *d*	118.1 *d*
C(15)	59.3 *t*	61.4 *t*
C(16)	16.3 *q*	16.5 *q*
C(17)	106.9 *t*	107.0 *t*
C(18)	183.9 *s*	185.1 *s*
C(19)	29.6 *q*	29.7 *q*
C(20)	14.7 *q*	14.7 *q*
OAc	----	21.0 *q*
		171.2 *s*

* The δ values are in ppm relative to the solvent $CDCl_3$ (δ 77.0 downfield from TMS).

† Signals in the vertical column may be reversed.



1



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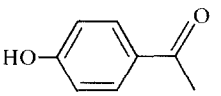

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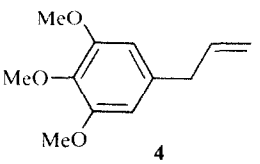

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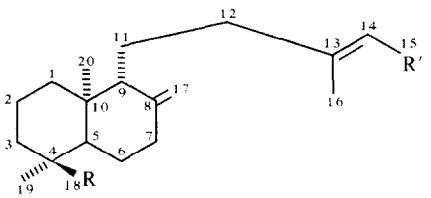
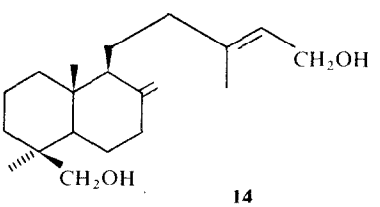




14

5 R = COOH, R′ = CH_2OH
6 R = COOMe, R′ = CH_2OH
7 R = COOH, R′ = CH_2OAc
8 R = COOMe, R′ = CH_2OAc
9 R = COOH, R′ = CHO
10 R = COOMe, R′ = CHO
11 R = R′ = CH_2OH
12 R = R′ = CH_2OAc
13 R = R′ = COOMe

Viscidic acid B (**7**)

Compound **7**, $C_{22}H_{34}O_4$, which was less polar than **5**, exhibited a ^{1}H NMR spectrum, which indicated the presence of an acetate group (δ 2.07, *s*). The two-proton doublet at δ 4.60 was assigned to the CH_2OAc. Acetylation of **5** with acetic anhydride in pyridine gave an acetate which was identical with the natural compound **7**. The structure of viscidic acid B is therefore *ent*-labd-8(17),13*E*-dien-15-acetoxy-18-oic acid.

EXPERIMENTAL

IR spectra were run in CCl_4 or $CHCl_3$; ^{1}H NMR spectra were recorded in $CDCl_3$; ^{13}C NMR were in $CDCl_3$; MS were at 70 eV, direct probe; optical rotations in $CHCl_3$. The air-dried plant material was collected on 8 August 1973 in Colorado: Lake Co.: 1 mile from the junction of 82 and 24, along 82, road side (Urbatch No. 1302, voucher deposited at Louisiana State University Herbarium at Baton Rouge), was extracted with Et_2O–petrol (1:1) at room temp. The crude extract was first separated by CC (Si gel, grade II activity), using petrol–Et_2O and Et_2O–MeOH mixtures as eluants and further purified by TLC (Si gel, GF 254), which was repeated several times. Known compounds were identified by comparison of IR and ^{1}H NMR spectra with those of authentic material. The aerial part (490 g) of *C. viscidiflorus* ssp. lanceolatus afforded 10 mg **1**, 42 mg **2**, 20 mg **3**, 50 mg **4**, 260 mg **7** (2 runs in Et_2O–petrol *ca* 1:1) and *ca* 600 mg **5** [2 runs in Et_2O, then 3 runs in EtOAc–CH_2Cl_2 (1:6)].

Viscidic acid A (**5**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: OH 3610, COOH 3480–2800, 1710; C=CH_2 3100, 895, C=CH 850. MS *m/e* (rel. int.): 320 (M^+, 13.3); 305.212 (M − Me, 20) (calc. for $C_{19}H_{29}O_3$ 305.212); 302.223 (M − H_2O, 15) (calc. for $C_{20}H_{30}O_2$ 302.224); 287 (302 − Me, 26.6); 257 (302 − COOH, 18.3); 221 (M − $CH_2CH_2C(Me)$=$CHCH_2OH$, 13.3); 234 (**A**, 16.6); 189 (**A** − COOH, 33.3); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 96.6).

Esterification of **5**. To 30 mg **5** in 2 ml Et_2O an excess of an etheral CH_2N_2 soln was added. After 10 min the soln was evapd and the residue purified by TLC to give 29 mg **6**, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: OH 3620; COOMe 1745, 1240; C=CH_2 3090, 890; C=CH 850. MS *m/e* (rel. int.): 334 (M^+, 1.8); 319.228 (M − Me, 7.4) (calc. for $C_{20}H_{31}O_3$ 319.227); 316 (M − H_2O, 3.7); 301 (316 − Me, 5.6); 257 (316 − COOMe, 9.3); 235 (M − $CH_2CH_2C(Me)$=$CHCH_2OH$, 2.8); 248 (**B**, 3.7); 189 (**B** − COOMe, 21.3); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 37).

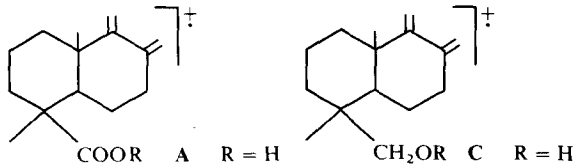
Acetylation of **5**. Compound **5** (10 mg) in 0.5 ml Ac_2O and 10 mg 4-pyrrolidino-pyridine [17] were stirred overnight at room temp. After TLC (Et_2O–petrol, *ca* 3:2) 8 mg **7** were obtained, identical with the natural product (**7**), colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: COOH 3500–2800, 1705; OAc 1750, 1240; C=CH_2 3100, 900, MS *m/e* (rel. int.): 362 (M^+, 0.6); 347 (M − Me, 2.3); 302.223 (M − HOAc, 44) (calc. for $C_{20}H_{30}O_2$ 302.224); 287 (302 − Me, 50); 221 (M − $CH_2CH_2C(Me)$=$CHCH_2OAc$, 7.3); 234 (**A**, 14.7); 189 (**A** − COOH, 26.5); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 63.2); 43 ($C_3H_7^+$, 82.3).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{-31 \quad -33 \quad -37 \quad -62} \quad (c = 0.24, CHCl_3).$$

Esterification of **7**. Compound **7** (20 mg) was esterified as above. After TLC 19 mg **8** were obtained, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: OAc 1740; COOMe 1740, 1250; C=CH_2 3100, 900. MS *m/e* (rel. int.): 376 (M^+, 0.6%); 361 (M − Me, 1.2); 316.239 (M − HOAc, 17.1) (calc. for $C_{21}H_{32}O_2$ 316.240); 301 (316 − Me, 12.3); 235 (M − $CH_2CH_2C(Me)$=$CHCH_2OAc$, 2.6); 257 (316 − COOMe, 19.4); 248 (**B**, 4.2); 189 (**B** − COOMe, 18.8); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 34.2).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{-24.2 \quad -25.3 \quad -28.6 \quad -47.3} \quad (c = 2.73, CHCl_3).$$

MnO_2 *oxidation of* **5**. Compound **5** (10 mg) in 2 ml Et_2O was stirred at room temp. with 100 mg MnO_2 overnight. After TLC



(Et_2O–CH_2Cl_2, 1:1) 8 mg **9** were obtained, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: COOH 3500–2800, 1705; C=CCHO 1690; C=CH_2 3080; C=CH 855. MS *m/e* (rel. int.): 318 (M^+, 4.8); 303.195 (M − Me, 29) (calc. for $C_{19}H_{27}O_3$ 303.196); 274 (303 − CHO, 22.6); 235 (M − $CH_2C(Me)$=$CHCHO$, 17.7); 221 (M − CH_2CH_2-C(Me)=CHCHO, 6.4); 234 (**A**, 12.9); 84 (H_2C=$C(Me)CH_2$-CHO, 90.3); 55 (84 − CHO, 96.7); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 90).

Esterification of **9**. Compound **9** (5 mg) was esterified as above. After TLC 5 mg **10** were obtained, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: COOMe 1730, 1260; C=CCHO 1680; C=CH_2 3100, 880;. MS *m/e* (rel. int.): 332 (M^+, 2.7); 317.210 (M − Me, 21.8) (calc. for $C_{20}H_{29}O_3$ 317.211): 288 (317 − CHO, 8.9): 249 (M − CH_2-C(Me)=CHCHO, 13.7); 248 (**B**, 2.7); 189 (**B**−COOMe, 28.8); 121 ($C_9H_{13}^+$, 100); 81 ($C_6H_9^+$, 39.7); 84 (H_2C=$C(Me)CH_2$-CHO, 27.4); 55 (84 − CHO, 30.1).

Reduction of **5** *or* **7**. To 15 mg **5** or **7** in 2 ml abs Et_2O an excess of $LiAlH_4$ was added. After 30 min the excess reagent was destroyed with 2 N H_2SO_4 and the diol **11** (12 mg) extracted with Et_2O, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: OH 3640; C=CH_2 3100, 850. MS *m/e* (rel. int.): 306 (M^+, 3.1); 291.232 (M − Me, 9.4) (calc. for $C_{19}H_{31}O_2$ 291.232); 288 (M − H_2O, 4.2); 273 (M − H_2O − Me, 6.2); 257 (288 − CH_2OH, 18.7); 207 (M − CH_2CH_2C(Me) =$CHCH_2OH$, 4.2); 220 (**C**, 3.1); 189 (**C** − CH_2OH, 27.1); 121 ($C_9H_{13}^+$, 56.2); 81 ($C_6H_9^+$, 100); 67 (81 − CH_2, 43.7).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{-32 \quad -34 \quad -36 \quad -54} \quad (c = 0.5, CHCl_3).$$

Acetylation of **11**. Compound **11** (10 mg) was acetylated as above to give 7 mg **12**, colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: OAc 1745, 1235; C=CH_2 3090, 895. MS *m/e* (rel. int.): 390 (M^+, 1.0); 375 (M − Me, 1.3); 330.255 (M − HOAc, 25) (calc. for $C_{22}H_{34}O_2$ 330.256); 315 (330 − Me, 19); 270 (330 − HOAc, 19); 255 (270 − Me, 32); 257 (330 − CH_2OAc, 54); 249 (M − CH_2CH_2C(Me) =$CHCH_2OAc$, 4); 262 (**D**, 4); 202 (**D** − HOAc, 42); 189 (D − CH_2OAc, 47); 175 (189 − CH_2, 22); 161 (175 − CH_2, 22); 147 (161 − CH_2, 33); 121 ($C_9H_{13}^+$, 70); 81 ($C_6H_9^+$, 100).

Oxidation of **6**. Compound **6** (15 mg) in 2 ml Py was stirred at room temp. with 300 mg CrO_3 for 24 hr. After usual work-up the residue was esterified with etheral CH_2N_2 soln. After TLC (Et_2O–petrol, *ca* 1:1) 8 mg **13** were obtained, colourless oil, IR NMR, and optical rotation were identical with those of the known dimethyl guamaate [12].

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