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GRINDELANE DITERPENOIDS FROM *ISOCOMA TENUISECTA*

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Key Word Index—*Isocoma tenuisecta*; Asteraceae; Astereae; Solidagininae; diterpenoid acids; grindelanes; methyl 6β-hydroxy-18-acetoxygrindelate; methyl 17-acetoxy-19-hydroxygrindelate.

Abstract—Grindelic acid and eight of its derivatives including the new 6β-hydroxy-18-acetoxy- and 17-acetoxy-19-hydroxygrindelic acids were isolated as methyl esters from *Isocoma tenuisecta* and identified spectroscopically.

INTRODUCTION

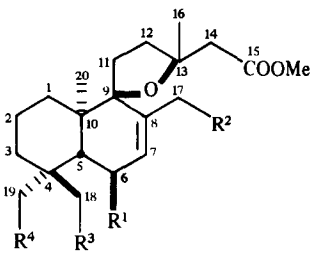
Isocoma tenuisecta Greene is a resinous shrub indigenous to the southwestern United States and northern Mexico that has been treated as part of the large genus *Haplopappus*. Only two species of *Isocoma* have so far been chemically investigated, *I. coronopifolia* and *I. wrightii*. The former was reported to contain grindelane diterpenoids and a eudesmane endoperoxide in addition to common constituents [1]. The latter species, studied by two groups, yielded eudesmane sesquiterpenoids [2], benzofurans, steroids, monoterpenoids and fatty acids [3], but no diterpenoids. As part of our phytochemical investigations of arid adapted Astereae in search of natural insecticides we decided to examine *I. tenuisecta*.

RESULTS AND DISCUSSION

From the ether-soluble portion of the dichloromethane extract of the aerial parts of *I. tenuisecta*, the sodium carbonate-soluble acidic fraction was separated and submitted to silica gel CC. Fractions eluted with *n*-hexane–ether (1:1) were methylated and the methylated product when subjected to silica gel CC and/or preparative TLC afforded seven known grindelane methyl esters [methyl grindelate (**1**), methyl 17-hydroxy-(**2**), 17-acetoxy-(**3**), 18-acetoxy-(**4**), 6-keto-17-hydroxy-(**5**), 6-keto-17-acetoxy-(**6**) and 6β-hydroxy-17-acetoxy-(**7**) grindelates] previously reported from *Grindelia acutifolia* [4], and two new isomeric grindelane methyl esters, methyl 6β-hydroxy-18-acetoxy-(**8**) and 17-acetoxy-19-hydroxy-(**9**) grindelates. All the known grindelanes (**1**–**7**) were identified by TLC, GC and ^{1}H NMR comparisons with authentic samples. The two new isomeric grindelanes (**8** and **9**) were not separated from one another due to their identical R_f values on chromatography but their structures were manifest from the NMR and mass spectra of the mixture (**8**:**9**::2:3).

The IR (neat) spectrum of the mixture of compounds **8** and **9** showed the presence of OH (3480 cm^{-1}), O ‖ –C–O– (1735, 1240 cm^{-1}), >C=CH– (3020, 1666, 865 cm^{-1}), Me (1380 cm^{-1}) groups but lacked geminal dimethyl absorptions. The ^{1}H NMR spectral parameters are shown in Table 1 with the spectra of related grindelanes **4**, **7** and **10** [5]. The similarity of spectral parameters for protons on carbons 18–20 of **9** with **10** and for protons on carbons 7, 17 and the acetate grouping of **9** with **7** define its structure. Compound **8** from comparison with **4** and **7** is methyl 6β-hydroxy-18-or-19-acetoxygrindelate, but since the other compounds were not sufficiently good models for making this distinction, we obtained a NOESY spectrum which defined the structure via a strong peak for the interaction of the Me-20 protons with a methyl (Me-19) and no peaks for the interaction of the Me-20 with the CH_2-18 protons.

The EIMS of the mixture of **8** and **9** conformed well with the above findings. The molecular ion peak and highly characteristic fragmentation peaks were identified

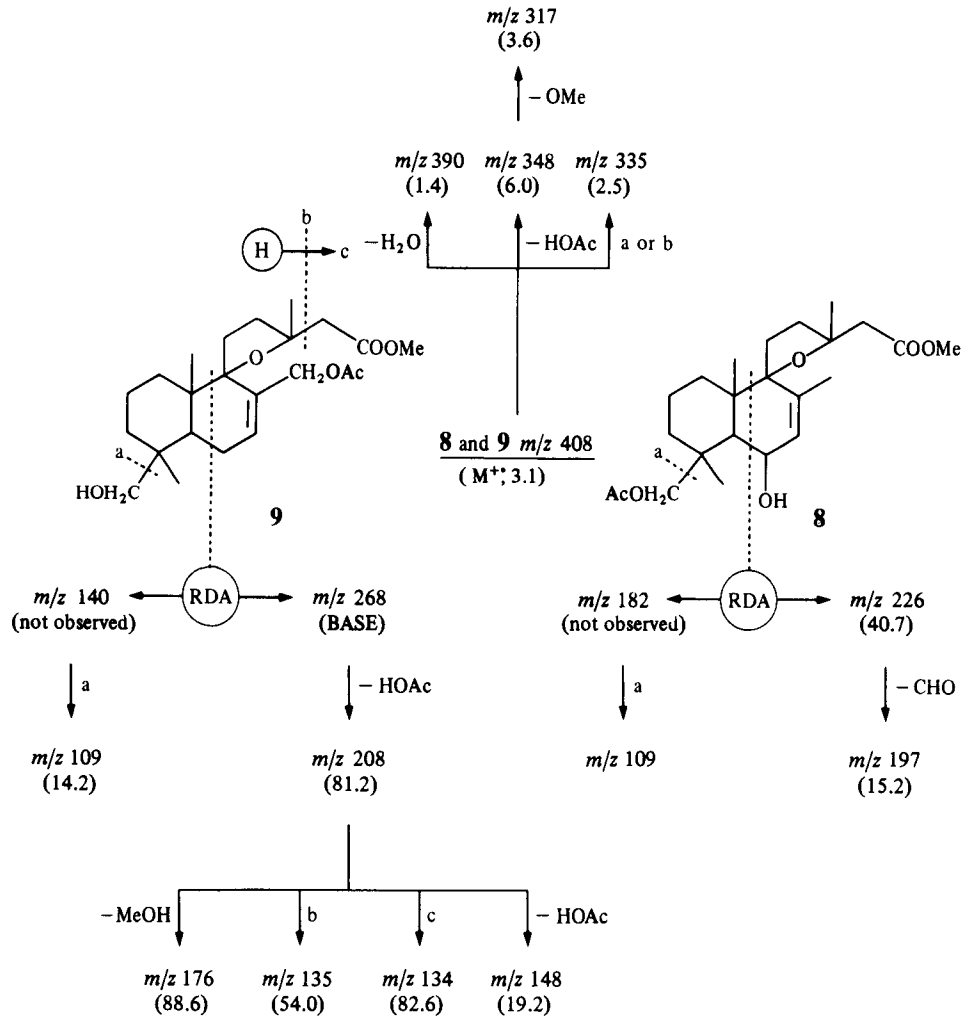


	R¹	R²	R³	R⁴
1	H	H	H	H
2	H	OH	H	H
3	H	OAc	H	H
4	H	H	OAc	H
5	6-keto	OH	H	H
6	6-keto	OAc	H	H
7	OH	OAc	H	H
8	OH	H	OAc	H
9	H	OAc	H	OH
10	H	H	H	OH

Table 1. ^{1}H NMR shifts (δ, $CDCl_3$) and coupling constants (Hz, in parentheses) for compounds **4** and **7–10**

H	4[5]	7[4]	8	9	10[5]
5	—	1.79 *d* (8.9)	1.93 *d* (9.9)	—	—
6	1.85 *m*	4.07 *td* (8.9, 3.5)	4.03 *d* (9.9)	—	1.85 *m*
7	5.46 *s* (*br*)	5.87 *d* (3.5)	5.47 *m*	5.90 *m*	5.47 *d* (*br*)
14	2.59 *d*	2.59 *d* (14.0)	2.57 *d* (13.6)	2.67 *d* (14.4)	2.59 *d* (*br*)
	2.70 *d*	2.64 *d* (14.0)	2.66 *d* (13.6)	2.68 *d* (14.4)	2.73 *d*
16	1.31 *s*	1.35 *s*	1.33 *s*	1.34 *s*	1.32 *s*
17	1.76 *s* (*br*)	4.58 *d* (13.2)	1.79 *t* (1.4)	4.53 *d* (12.3)	1.76 *s* (*br*)
		4.66 *d* (13.2)		4.63 *d* (12.3)	
18	3.73 *d* (10.5)	1.14 *s*	3.95 *d* (10.7)	0.88 *s*	0.88 *s*
	3.75* *d* (10.5)		4.33 *d* (10.7)		
19	0.91 *s*	1.01 *s*	1.06 *s*	3.17 *d* (10.8)	3.17 *d* (11)
				3.35 *d* (10.8)	3.35 *d* (11)
20	0.81 *s*	0.83 *s*	0.88 *s*	0.84 *s*	0.84 *s*
OMe	3.64 *s*	3.65 *s*	3.66 *s*	3.65 *s*	3.65 *s*
Ac	2.04 *s*	2.09 *s*	2.06 *s*	2.08 *s*	—

*Misprinted 2.75 in ref [5].



RDA = *retro*-Diels–Alder

Scheme 1. Diagnostic fragment ions (relative intensitites in parentheses) in the EIMS of the mixture of **8** and **9**.

and rationalized as shown in Scheme 1. The mass spectrum is more populated with fragments from the major component **9**. The presence of the *m/z* 124 ion and its daughter ion at *m/z* 109 in 7-en grindelanes/labdanes defines an unsubstituted ring A [6]. The EIMS of the mixture of **8** and **9** showed only the daughter ion (*m/z* 109). This clearly indicated that ring A was substituted in both molecules and that at least one was substituted only on either the 18-or 19-methyl group.

EXPERIMENTAL

Plant material. I. tenuisecta was collected by Timmermann and McLaughlin on 6 September 1985 in Pima County, Arizona, on Redington Pass Road, approximately 14 miles west of Cascabel junction. A voucher specimen (SPM 3041) is on deposit in the Herbarium of the University of Arizona. All plant material was air-dried, ground to 3 mm particle size and stored at 5° prior to extraction.

Extraction. The ground *I. tenuisecta* (aerial parts, 1.85 kg) was percolated with CH_2Cl_2 at room temp for 24 hr and the solvent removed. The CH_2Cl_2 extract (276 g) was stirred with Et_2O (2 l, 2 hr), left in the refrigerator overnight, filtered and the Et_2O-soluble filtrate extracted with 5% Aq. Na_2CO_3 (3 × 400 ml). The Na_2CO_3-soluble material was neutralized with 25% aq. HCl and the liberated acids were taken up in Et_2O, dried (dry Na_2SO_4) and the solvent removed. The resulting acid mixture (203 g) was separated by silica gel CC (2 kg, packed in *n*-hexane, eluted with *n*-hexane–EtOAc, 1:1) into four broad fractions (A, 17.3 g; B, 21.8 g; C, 19.3 g and D, 17.4 g) of increasing polarity. Each of these fractions was methylated with MeI [7] and a portion of each of the resulting methyl ester mixture was submitted to prep. TLC or CC on silica gel followed by prep TLC to isolate compounds **1**–**9** [compounds **1** and **3** from fraction A (prep TLC), **2**, **4** and **6** from fraction B (CC and prep TLC), **7** from fraction C (prep TLC) and **5**, **8** and **9** from fraction D (CC and prep TLC)].

Isolation of **8** *and* **9**. Fraction D (16.8 g) was separated by silica gel CC (500 g, packed in $CHCl_3$) into a number of fractions (1–17) by eluting with $CHCl_3$. The $CHCl_3$-soluble portion of fraction 17 (2.4 g) when submitted to prep. TLC on silica gel ($CHCl_3$–EtOAc–HOAc, 45:5:2) gave a TLC homogeneous mixture containing **8** and **9**: IR (see text), ^{1}H NMR (Table 1) and MS (Scheme 1).

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