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TERPENOIDS FROM *SIDERITIS VAROI* SUBSP. *ORIENSIS**

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Key Word Index—*Sideritis varoi* subsp. *oriensis*; Labiatae; eudesmanes.

Abstract—From the aerial parts of *Sideritis varoi* subsp. *oriensis* the previously known 1β-hydroxy-6β-acetoxyeudesm-4(15)-ene, 1β-hydroxy-6β-acetoxyeudesm-3-ene, 1β-hydroxy-6β-acetoxyeudesm-4-ene, 1β,4β-dihydroxy-6β-acetoxyeudesmane and the new 1β,4α-dihydroxy-6β-acetoxyeudesmane, as well as the *ent*-8α-hydroxylabda-13(16),14-dienes 6-deoxyandalusoic acid, 6-deoxyandalusal, 6-deoxyandalusol, 18-deoxyandalusol, andalusol, the *ent*-13-epi-manoyl oxide varodiol and the *ent*-kaur-15-ene sideridiol were isolated. The stereochemistry at C-4 of the isolated eudesmanes, which has been under discussion for other similar compounds, was elucidated by chemical and spectroscopic means.

INTRODUCTION

Sideritis varoi Soc. is a plant which grows over extensive areas of gypsum-rich soils. At the moment this species is under botanical study and some subspecies are now being proposed. The phytochemistry of these plants [1–3] is an aid for their botanical classification. We report now a study of *S. varoi* subsp. *oriensis* which identified a series of diterpenoids and sesquiterpenoids and a new natural eudesmane.

RESULTS AND DISCUSSION

Sideritis varoi subsp. *oriensis* contained several sesquiterpenes and diterpenes previously isolated from *S. varoi* [1, 2] and *S. varoi* subsp. *cuatrecasasii* [2, 3]: 1β-hydroxy-6β-acetoxyeudesm-4(15)-ene (**1**), 1β-hydroxy-6β-acetoxyeudesm-3-ene (**2**), 1β-hydroxy-6β-acetoxyeudesm-4-ene (**3**), 1β,4β-dihydroxy-6β-acetoxyeudesmane (**4**), *ent*-8α-hydroxylabda-13(16),14-dien-19-oic acid (**5**), *ent*-8α-hydroxylabda-13(16),14-dien-19-al (**6**), *ent*-6α,8α-dihydroxylabda-13(16),14-diene (**7**), *ent*-6α,8α,18-trihydroxylabda-13(16),14-diene (**8**), *ent*-3β,12α-dihydroxy-13-epi-manoyl oxide (**9**) and *ent*-7α,18-dihydroxykaur-15-ene (**10**) and the *ent*-8α,18-dihydroxylabda-13(16),14-diene (**11**) isolated from *S. arborescens* subsp. *paulii* [4].

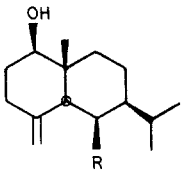
Another compound (**12**) isolated from this plant was a sesquiterpene which contained hydroxyl and acetoxyl groups (IR) and it had the same molecular formula as compound **4**. The ^{1}H NMR spectrum of compound **12** also showed similar signals to those found for **4** [2] but with different chemical shifts (see Experimental). Hence, compound **12** must be an isomer of **4** and the difference between these compounds could be in the position of the secondary hydroxyl group (i.e. at C-9) and/or the configuration at C-4. The application of Horeau's method [5] to **12** gave a positive enantiomeric excess, which was compatible with either C-1 hydroxylation in a normal series or C-9 hydroxylation in an *ent*-series. The oxidation of **12** yielded a keto compound **13** which showed a Cotton effect very similar to that found in the corresponding ketone (**14**) [2] obtained from **4**. Elsewhere, this Cotton effect was not conclusive for the structure because it is compatible with both the C-1 location in the normal series or C-9 in the enantio series.

As previously reported [2] saponification of **4** can be easily performed in basic media, presumably due to the assistance of the axial hydroxyl group at C-4. In the case of compound **12** cleavage of the acetoxy group was unsuccessful in basic media but it was achieved by lithium aluminium hydride (to give **15**), which suggested an equatorial disposition of the hydroxyl group at C-4. To confirm this hypothesis we attempted the formation of a 4,6-isopropylidene derivative by treatment with 2,2-dimethoxypropane, in a similar form to that described for product **16** (obtained by saponification of **4** [2]). In the case of compound **15** the reaction was unsuccessful. Thus, no isopropylidenedioxy derivative was obtained, while the acidic and dehydrating conditions of the reaction gave a series of compounds, one of which was identical to another one (**17**) whose structure was correlated [2] to compound **1**. Thus, we confirmed the position of the secondary hydroxyl group at C-1 and the absolute configuration of compound **12**, as well as the epimeric character at C-4 for both compounds **4** and **12**. Another compound (**18**) which was also isolated from the treatment of **15** with 2,2-dimethoxypropane was later correlated with compound **2**.

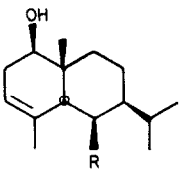
On the other hand, the ^{1}H NMR spectra of ketones **13** and **14** were also in accord with the epimeric character at C-4 of both compounds because in the spectrum of ketone **13**, any clear signal (80 MHz) can be observed downfield of δ3.0. The ketone **14**, with the hydroxyl group situated axially at C-4, gave an isolated signal at δ3.05 (*ddd*, $J_1 = J_2 = 12$, $J_3 = 7$ Hz) for its 2β-proton.

The configuration at C-4 of these seemingly simple eudesmanes has been discussed previously and subsequently reassigned following the isolation of some products from *Verbesina* species [6–10]. Table 1 shows

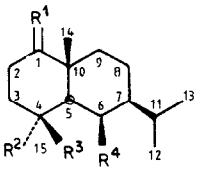
*Part 21 in the series "Terpenic Components of Spanish Labiatae". For Part 20 see ref. [4].



R	
1	OAc
17	OH



R	
2	OAc
18	OH



	R^1	R^2	R^3	R^4
4	αH, βOH	Me	OH	OAc
12	αH, βOH	OH	Me	OAc
13	O	OH	Me	OAc
14	O	Me	OH	OAc
15	αH, βOH	OH	Me	OH
16	αH, βOH	Me	OH	OH

the ^{13}C NMR assignments for both products **4** and **12**. As can be observed, chemical shifts of C-4 are not indicative of the assignment of the configuration at this carbon. Elsewhere, the chemical shifts of C-15 for compounds **4** and **12** are conclusive evidence for the configuration at C-4, as was pointed out before [7], but in agreement with the configuration recently proposed [10].

EXPERIMENTAL

Mps were determined in a Kofler apparatus and are uncorr. ^1H NMR spectra were measured at 80 MHz ($CDCl_3$ soln with TMS as internal standard). ^{13}C NMR spectra were determined at 20.13 MHz in a Bruker WP80SY spectrometer also in $CDCl_3$ (which also provided the lock signal) with TMS added as internal reference. Assignments were made with the aid of distortionless enhancement by polarization transfer (DEPT) using a 'flip angle' of 135°. IR spectra were recorded on a Pye Varian SP-1000 grating IR spectrometer. The rotatory powers were measured on a Perkin–Elmer 240 polarimeter. Silica gel, Merck 7729 (less than 0.08 mm) was used for flash chromatography. The eluents used were CH_2Cl_2 containing increasing amounts of Me_2CO. Plant material was collected in June 1984 near Oria (Almería) and voucher specimens have been deposited at the Herbarium of the Faculty of Pharmacy (University of Granada).

Extraction and isolation of the terpenoids. Dried and finely powdered aerial parts of *Sideritis varoi* subsp. *oriensis* (2 kg) were extracted with hexane (4 l.) in a Soxhlet and processed as described in ref. [1] to give 28 g of a terpenoid fraction. This material in CH_2Cl_2 was washed with aq. $NaHCO_3$. The neutral fraction (20 g) was chromatographed on a silica gel column. The homogeneous fractions were repeatedly chromatographed on a 10% $AgNO_3$–silica gel column, yielding the following compounds in order of elution: 1β-hydroxy-6β-acetoxyeudesm-4(15)-ene (**1**, 875 mg) [2], 1β-hydroxy-6β-acetoxyeudesm-3-ene (**2**, 630 mg) [2], 1β-hydroxy-6β-acetoxyeudesm-4-ene (**3**, 40 mg) [2], 1β,4β-dihydroxy-6β-acetoxyeudesmane (**4**, 700 mg) [2], *ent*-8α-hydroxylabda-13(16),14-dien-19-al (**6**, 35 mg) [1], *ent*-8α,18-dihydroxylabda-13(16),14-diene (**11**, 380 mg) [11], ent-6α,8α-dihydroxylabda-13(16),14-diene (**7**, 95 mg) [4], *ent*-7α,18-dihydroxykaur-15-ene (**10**, 50 mg) [12], 1β,4α-dihydroxy-6β-acetoxyeudesmane (**12**, 140 mg), *ent*-3β,12α-dihydroxy-13-epimanoyl oxide (**9**, 850 mg) [1] and *ent*-6α,8α,18-trihydroxylabda-13(16),14-diene (**8**, 1 g) [13]. From the acidic fraction, 5 g of *ent*-8α-hydroxylabda-13(16),14-dien-18-oic acid (**5**) [3] was isolated.

Table 1. ^{13}C NMR spectral data for compounds **4** and **12**

Carbon	**4** [2]	**12**
1	80.34	80.25
2	28.82	28.52
3	40.78	41.34
4	71.70	71.10
5	52.98	55.08
6	70.43	69.70
7	49.57	49.55
8	21.19	20.59
9	39.55	41.45
10	39.42	39.08
11	29.65	28.75
12	21.63	21.24
13	20.85	20.59
14	13.51	14.67
15	20.51	24.56
MeCO	21.79	21.76
MeCO	171.34	172.28

1β,4α-Dihydroxy-6β-acetoxyeudesmane (**12**). Colourless gum; $[\alpha]_D^{20} = +21.4°$ (*c* 1; $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3500, 1740 and 1260; ^1H NMR (80 MHz): δ 5.75 (1H, *m*, $W_{1/2}$ = 4 Hz, H-6), 3.26 (1H, *m*, $W_{1/2}$ = 16 Hz, H-1), 2.10 (3H, *s*, AcO group), 1.21 and 1.12 (3H each, *s*, C-14 and C-15 Me groups) and 0.90 (6H, *d*, *J* = 6 Hz, C-12 and C-13 Me groups). ^{13}C NMR: See Table 1. (Calc. for $C_{17}H_{30}O_4$: C, 68.43; H, 10.12. Found: C, 68.51; H, 10.20%.)

Determination of absolute configuration at C-1 *of compound* **12**. Compound **12** (25 mg) was treated with 100 mg (±)-α-phenylbutyric anhydride in pyridine (1 ml) as described in ref. [5]. $[\alpha]_D^{20} = +0.262°$ (*c* 6; benzene).

Saponification of compound **12**. Compound **12** (40 mg) in Et_2O (10 ml) was treated with $LiAlH_4$ (15 mg) and the mixture refluxed for 4 hr. After CC 28 mg of 1β,4α,6β-trihydroxyeudesmane (**15**) was isolated. Colourless gum; $[\alpha]_D^{20} = -20.6°$ (*c* 1; $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3500; ^1H NMR (80 MHz): δ 4.55 (1H, *m*, $W_{1/2}$ = 5 Hz, H-6), 3.20 (1H, *m*, $W_{1/2}$ = 16 Hz, H-1), 1.52 and 1.18 (3H each, *s*, C-14 and C-15 Me groups), 0.96 and 0.97 (3H each, *d*, *J* = 6 Hz, C-12 and C-13 Me groups).

Treatment of **15** *with* 2,2-*dimethoxypropane*. Compound **15** (28 mg) was dissolved in 2,2-dimethoxypropane (10 ml) and refluxed for 3 hr with *p*-toluenesulphonate of pyridine (5 mg). The mixture was concd under vacuum, washed with H_2O, extracted with CH_2Cl_2 and dried with $MgSO_4$, yielding 8 mg of starting product **15**, 7 mg of 1β,6β-dihydroxyeudesm-4(15)-ene (**17**) [2] and 3 mg of 1β,6β-dihydroxyeudesm-3-ene (**18**). Colourless gum: $[\alpha]_{436}^{20} = +3.4$ (*c* 0.5; $CHCl_3$); IR ν_{max}^{neat} cm^{-1}:

3450 and 3050; ^{1}H NMR (80 MHz): δ5.42 (1H, *m*, $W_{1/2}$ = 8 Hz, H-3), 4.27 (1H, *m*, $W_{1/2}$ = 6 Hz, H-6), 3.50 (1H, *m*, $W_{1/2}$ = 16 Hz, H-1), 1.82 (3H, *d*, *J* = 1.5 Hz, C-15 Me), 1.02 (3H, *s*, C-14 Me), 1.00 and 0.98 (3H each, *d*, *J* = 6 Hz C-12 and C-13 Me groups).

Saponification of compound **2**. Compound **2** (15 mg) was dissolved in Et_2O (5 ml) and 5 mg of $LiAlH_4$ were added and the mixture refluxed for 3 hr. After CC 10 mg of product **17** were isolated.

Oxidation of **12**. Compound **12** (40 mg) was dissolved in Me_2CO (5 ml) and oxidized with Jones' reagent [14]. After CC 4α,6β-dihydroxyeudesm-1-one (**13**, 36 mg) was isolated. Mp 108–110°; $[\alpha]_D^{20} = +18°$ (*c* 1; $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 3400, 1730, 1680 and 1260; ^{1}H NMR (80 MHz): δ5.77 (1H, *m*, $W_{1/2}$ = 4 Hz, H-6), 2.10 (3H, *s*, AcO group), 1.42 and 1.34 (3H each, *s*, C-14 and C-15 Me groups), 0.92 and 0.90 (3H each, *d*, *J* = 6 Hz, C-12 and C-13 Me groups).

$$[\alpha]_\lambda^{20} = \frac{\begin{array}{cccc}589 & 578 & 546 & 436\end{array}}{\begin{array}{cccc}+18.0 & +20.0 & +22.8 & +38.8\end{array}} (c\ 1;\ CHCl_3).$$

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