

## DITERPENES FROM *SIDERITIS SVENTENII* AND *S. CYSTOSIPHON*

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**Key Word Index.**—*Sideritis sventenii*; *S. cystosiphon*; Lamiaceae; diterpenes; sventenic acid; episinfernal; sideritriol; epicandicandiol.

**Abstract**—The new diterpenes,  $7\beta$ -monoacetate of episinfernal,  $7\beta$ -monoacetate of sideritriol, and sventenic acid, have been isolated from *Sideritis sventenii*. From *S. cystosiphon*, three new diterpenic esters, the  $7\beta$ -acetate, 18-palmitate of epicandicandiol, the 18-acetate of epicandicandiol, and the  $7\beta,17$ -diacetate of sideritriol, have been obtained.

### INTRODUCTION

Phytochemically, the genus *Sideritis* is characterized by containing diterpenic compounds. For the past few years we have been interested in the chemical study of these species endemic to the Canary Islands [1-5]. In continuation of this work we have now investigated the aerial parts of *S. sventenii* (Kunk) Mend. Heu., and completed an earlier study of *S. cystosiphon* Svent [5].

### RESULTS AND DISCUSSION

The most polar diterpene to be isolated from *S. sventenii* was a new natural compound, sventenic acid, characterized in methyl ester form, to which the structure 1 was assigned on the basis of the following considerations. High resolution mass spectrometry of the methyl ester 2 was in accordance with the formula  $C_{21}H_{32}O_3$ . Its  $^1H$ NMR spectrum showed signals of the two methyl groups at  $\delta$ 1.04 and 1.15 of the geminal hydrogen to the hydroxyl group at C-7 ( $\delta$ 3.52, *br s*), and of the two protons of the exocyclic double bond ( $\delta$ 4.77 and 4.79, *br s*). The carboxylate group was assigned at C-18 for biogenetic reasons. This is the methyl normally oxidized in the *ent*-kaur-16-ene diterpenes found in the *Sideritis* genus. It was confirmed by assignment of the  $^{13}C$ NMR spectrum of 2 (Table 1) together with that of candol A (5) for comparison purposes. Finally, the structure of the compound was confirmed by preparing it from epicandicandiol  $7\beta$ -monoacetate (11) [2]. Oxidation of 11 with Jones reagent gave a mixture of the aldehyde 3 and the acid 4, which were separated by chromatography. Hydrolysis of 4 with methanolic potassium hydroxide afforded the acid 1, which was methylated with diazomethane to give 2, identical with the substance obtained by methylation of the natural product 1.

Another new diterpene obtained from *S. sventenii* was an aldehyde 6 related to episinfernal (7). This substance 7 was isolated previously from *S. infernalis* and characterized as its diacetate [4], and now has also been obtained from *S. sventenii* (see Experimental). The difference between these two compounds was that in 6 the  $7\beta$ -

hydroxyl was acetylated. Its  $^1H$ NMR spectrum showed the geminal hydrogen to the  $7\beta$ -acetate at  $\delta$ 4.76. Thus, this compound is the  $7\beta$ -monoacetate of episinfernal (6).

The third new diterpene isolated, sideritriol  $7\beta$ -monoacetate (8), was a compound related to 6. In its  $^1H$ NMR spectrum the aldehydic proton had disappeared, being replaced by a pair of doublets typical of a hydroxymethylene group, and the hydrogen of the double bond was now at a higher field than in 6. Reduction of 6 with sodium borohydride in the presence of cerium trichloride [6] afforded 8, identical with the natural compound.

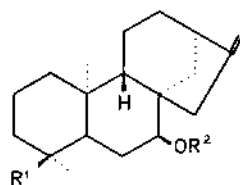
Other known compounds isolated from this species were the diterpenes candol B (16) [2],  $7\beta$ -monoacetate of epicandicandiol (11) [2], epicandicandiol (15) [7], episinfernal (7) [4], and sideritriol (10) [8], the flavone cirsimaritin [9], and the flavanone, 5,4'-dihydroxy-6,7-dimethoxyflavanone [10].

The three new diterpenic esters isolated from *S. cystosiphon* were the  $7\beta$ -acetate, 18-palmitate of epicandicandiol (12), the 18-acetate of epicandicandiol (13) and the  $7\beta,17$ -diacetate of sideritriol (9).

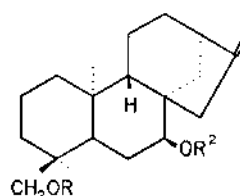
Compound 12 showed a  $^1H$ NMR spectrum similar to that of the 18-palmitate of epicandicandiol (14), also obtained from this plant [5]. The difference was that in 12 the  $7\beta$ -hydroxyl is also esterified, with the geminal hydrogen to a second ester group at  $\delta$ 4.77 (*br s*). Acetylation of 14, in the usual way, afforded 12, identical with the natural compound. The structure of substance 13 was determined by comparison of its spectral data with those of a synthetic sample obtained by partial acetylation of epicandicandiol (15) [2].

The last compound obtained,  $7\beta,17$ -diacetate of sideritriol (9), showed a  $^1H$ NMR spectrum similar to that of compound 8, with a new acetoxy group that was assigned at C-17, because the two hydrogens of this carbon and that of C-15 now appear at a lower field. The  $7\beta$ -monoacetate of episinfernal (6) and the  $7\beta$ -monoacetate of sideritriol (8) were also obtained from this plant.

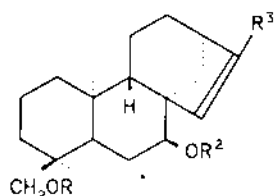
The similar results obtained in the phytochemical study of *S. infernalis* [4], *S. cystosiphon* and *S. sventenii* indicate that the latter species must be included in the same group of the three in which the *Sideritis* genus, endemic to the Canary Islands, has been divided [3].



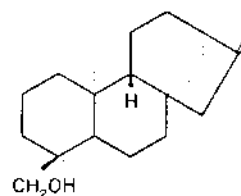
- 1  $R^1 = \text{CO}_2\text{H}$   $R^2 = \text{H}$   
 2  $R^1 = \text{CO}_2\text{Me}$   $R^2 = \text{H}$   
 3  $R^1 = \text{CHO}$   $R^2 = \text{Ac}$   
 4  $R^1 = \text{CO}_2\text{H}$   $R^2 = \text{Ac}$   
 5  $R^1 = \text{Me}$   $R^2 = \text{H}$



- 11  $R^1 = \text{H}$   $R^2 = \text{Ac}$   
 12  $R^1 = \text{Palm}$   $R^2 = \text{Ac}$   
 13  $R^1 = \text{Ac}$   $R^2 = \text{H}$   
 14  $R^1 = \text{Palm}$   $R^2 = \text{H}$   
 15  $R^1 = R^2 = \text{H}$



- 6  $R^1 = \text{H}$   $R^2 = \text{Ac}$   $R^3 = \text{CHO}$   
 7  $R^1 = R^2 = \text{H}$   $R^3 = \text{CHO}$   
 8  $R^1 = \text{H}$   $R^2 = \text{Ac}$   $R^3 = \text{CH}_2\text{OH}$   
 9  $R^1 = \text{H}$   $R^2 = \text{Ac}$   $R^3 = \text{CH}_2\text{OAc}$   
 10  $R^1 = R^2 = \text{H}$   $R^3 = \text{CH}_2\text{OH}$



16

Table 1.  $^{13}\text{C}$  NMR spectral data of compounds **2** and **5** ( $\text{CDCl}_3$ , 50.32 MHz)

C	2	5	C	2	5
1	39.50	40.26	11	17.63	17.76
2	17.81	18.70	12	33.59	33.69
3	37.05	42.05	13	43.79	43.90
4	47.23	32.75	14	38.53	38.63
5	41.23	46.34	15	45.25	45.40
6	30.70	27.72	16	155.12	155.17
7	77.00	77.32	17	103.47	77.32
8	48.62	48.37	18	179.10	33.47
9	50.86	50.57	19	16.45	21.72
10	38.73	39.22	20	17.63	17.49

#### EXPERIMENTAL

Mps: uncorr. IR:  $\text{CHCl}_3$ . NMR:  $\text{CDCl}_3$ . MS: 70 eV (probe). CC was performed on silica gel 0.063–0.2 mm. The substances were crystallized from petrol–EtOAc except where otherwise indicated.

*Isolation of compounds from S. sventenii.* The air-dried aerial parts (1 kg) were collected at Presa de la Gambuesa (Gran Canaria Island) in May. A voucher specimen has been deposited at the Herbarium of the 'Centro de Investigación y Tecnología Agraria' (Tenerife) (ORT 29301). A general description of the procedure to isolate the substances of species of the genus *Sideritis* has been published previously [3]. Thus, candol B (**16**) (200 mg), 7 $\beta$ -monoacetate of epicandiciol (**11**) (380 mg), circimaritin (45 mg), 5,4'-dihydroxy-6,7-dimethoxyflavanone (30 mg), 7 $\beta$ -monoacetate of episinferral (**6**) (150 mg), epicandiciol (**15**) (700 mg), 7 $\beta$ -monoacetate of sideritriol (**8**) (250 mg), episinferral (**7**) (20 mg), sideritriol (**10**) (20 mg), and sventenic acid (**1**) (80 mg) were obtained.

*Episinferral 7 $\beta$ -monoacetate (6).* Gum,  $[\text{M} - \text{C}_2\text{H}_4\text{O}_2]^+$  at  $m/z$  300.2111.  $\text{C}_{20}\text{H}_{28}\text{O}_2$  requires 300.2090;  $^1\text{H}$  NMR (200 MHz):  $\delta$ 0.71 and 1.10 (each 3H, s), 2.12 (3H, s), 2.99 and 3.34 (each 1H, d,  $J = 10$  Hz, H-18), 4.76 (1H, br s, H-7), 6.76 (1H, s, H-15), 9.73 (1H, s, H-17); EIMS  $m/z$  (rel. int.): 300  $[\text{M} - \text{C}_2\text{H}_4]^+$  (4), 269 (26), 213 (5), 187 (4), 185 (5), 173 (6), 171 (6).

*Sideritriol 7 $\beta$ -monoacetate (8).* Gum, 300  $[\text{M} - \text{C}_2\text{H}_2\text{O}]^+$  at  $m/z$  320.2352.  $\text{C}_{20}\text{H}_{32}\text{O}_3$  requires 320.2351;  $^1\text{H}$  NMR (200 MHz):  $\delta$ 0.71 and 1.09 (each 3H, s), 2.08 (3H, s), 2.99 and 3.34 (each 1H, d,  $J = 10$  Hz, H-18), 4.20 (2H, d, H-17), 4.71 (1H, br s, H-

7), 5.57 (1H, s, H-15); EIMS  $m/z$  (rel. int.): 320 [ $M - C_2H_2O$ ] $^+$  (1), 302 (14), 284 (22), 271 (20), 269 (6), 253 (22).

*Episinferral* (7). Gum,  $[M]^+$  at  $m/z$  318.2192.  $C_{20}H_{30}O_3$  requires 318.2194;  $^1H$  NMR (200 MHz):  $\delta$  0.72 and 1.09 (each 3H, s), 3.02 and 3.46 (each 1H,  $d$ ,  $J = 11$  Hz, H-18), 3.72 (1H, *br s*, H-7), 7.07 (1H, s, H-15), 9.74 (1H, s, H-17); EIMS  $m/z$  (rel. int.): 318 [ $M$ ] $^+$  (1), 300 (6), 287 (9), 269 (30), 255 (3), 241 (7), 227 (3).

*Sventenic acid* (1). This compound was characterized as its Me ester following treatment with  $CH_2N_2$  and chromatography of some frs containing it. *Me ester* (2), mp 182–184 $^\circ$ ;  $[M]^+$  at  $m/z$  332.2314.  $C_{21}H_{32}O_3$  requires 332.2314;  $^1H$  NMR (200 MHz):  $\delta$  1.04 and 1.15 (each 3H, s), 3.52 (H, *br s*, H-7), 3.64 (3H, s), 4.77 and 4.79 (each 1H, *br s*, H-17); EIMS  $m/z$  (rel. int.): 332 [ $M$ ] $^+$  (3), 314 (34), 299 (22), 255 (49), 239 (42), 211 (16).

*Reduction of 6*. Compound 6 (30 mg) was added to a soln of  $NaBH_4$  (30 mg) and  $CeCl_3$  (170 mg) in MeOH (4 ml). The mixt was stirred at room temp for 90 min, dil. with  $H_2O$  and extd with EtOAc as usual. Evapn of solvent and chromatography of the residue afforded 8 (20 mg).

*Oxidation of 11*. Epicandicandiol 7 $\beta$ -monoacetate (11) (200 mg) in  $Me_2CO$  was treated dropwise with Jones reagent and left at room temp for 24 hr, after which MeOH was added to destroy excess reagent. The mixt. was poured into  $H_2O$  and extd as usual. Dry CC of the resulting product, with petrol–EtOAc (40%) as eluent, gave the aldehyde 3 (22 mg) [11]. Further elution afforded the acid 4 (160 mg), mp 194–196 $^\circ$ , [ $M - C_2H_4O_2$ ] $^+$  at  $m/z$  300.2092.  $C_{20}H_{28}O_2$  requires 300.2089;  $^1H$  NMR (200 MHz):  $\delta$  1.07 and 1.14 (each 3H, s), 2.04 (3H, s), 4.64 (1H, *br s*, H-7), 4.76 and 4.81 (each 1H, s, H-17); EIMS  $m/z$  (rel. int.): 300 [ $M - C_2H_4O_2$ ] $^+$  (48), 285 (17), 271 (6), 255 (11), 254 (11), 239 (16), 220 (11), 199 (15), 185 (25).

*Hydrolysis of 4*. A soln of 4 (150 mg) in MeOH was saponified with 3% KOH in MeOH (15 ml), leaving the mixt at room temp for 24 hr. Usual work-up and chromatography of the residue afforded 1, mp 232–233 $^\circ$ ,  $[M]^+$  at  $m/z$  318.2162.  $C_{20}H_{30}O_3$  requires 318.2195;  $^1H$  NMR (200 MHz):  $\delta$  0.99 and 1.09 (each 3H, s), 3.56 (1H, *br s*, H-7), 4.73 (2H, *br s*, H-17); EIMS  $m/z$  (rel. int.): 318 [ $M$ ] $^+$  (1), 300 (38), 285 (20), 255 (17), 239 (14), 292 (11), 211 (10), 199 (12), 185 (20). Methylation with  $CH_2N_2$  gave 2, identical with the Me ester, of the natural compound.

*Isolation of compounds from S. cystosiphon*. Several diterpenes obtained from this plant have been described previously [5]. From some frs of the same extract, 7 $\beta$ -acetate-18-palmitate of epicandicandiol (12) (6 mg), 18-monoacetate of epicandicandiol (13) (43 mg), 7 $\beta$ -monoacetate of episinferral (6) (40 mg), 7 $\beta$ -monoacetate of sideritriol (8) (3 mg), and 7 $\beta$ ,17-diacetate of sideritriol (9) (11 mg), have now been obtained.

*7 $\beta$ -Acetate-18-palmitate of epicandicandiol* (12). Gum,  $[M - C_2H_4O_2]^+$  at  $m/z$  524.4608.  $C_{36}H_{60}O_2$  requires 524.4593;

$^1H$  NMR (200 MHz):  $\delta$  0.83 and 1.08 (each 3H, s), 1.25 (s,  $n-CH_2$ ), 2.04 (3H, s), 3.62 and 3.76 (each 1H,  $d$ ,  $J = 11$  Hz, H-18), 4.75 and 4.80 (each 1H, s, H-17), 4.77 (1H, *br s*, H-7); EIMS  $m/z$  (rel. int.): 524 [ $M - C_2H_4O_2$ ] $^+$  (4), 509 (1), 328 (1), 286 (1), 268 (91), 253 (32), 239 (21), 255 (11).

*18-Monoacetate of epicandicandiol* (13). Mp 124–125 $^\circ$ ;  $[M]^+$  at  $m/z$  346.2510.  $C_{22}H_{34}O_3$  requires 346.2506;  $^1H$  NMR (80 MHz):  $\delta$  0.80 and 1.05 (each 3H, s), 2.05 (3H, s), 3.46 and 4.06 (each 1H,  $d$ ,  $J = 11$  Hz, H-18), 3.56 (1H, *br s*, H-7), 4.78 and 4.80 (each 1H, s, H-17); EIMS  $m/z$  (rel. int.): 346 [ $M$ ] $^+$  (1), 328 (7), 313 (3), 286 (2), 268 (31), 255 (37), 239 (8), 225 (7), 199 (12).

*7 $\beta$ ,17-Diacetate of sideritriol* (9).  $[M - C_2H_4O_2 - C_2H_2O - Me]^+$  at  $m/z$  287.1995.  $C_{19}H_{27}O_2$  requires 287.1979;  $^1H$  NMR (200 MHz):  $\delta$  0.70 and 1.08 (each 3H, s), 2.07 (6H, s), 3.00 and 3.33 (each 1H,  $d$ ,  $J = 11$  Hz, H-18), 4.56 (2H, s, H-17), 4.70 (1H, *br s*, H-7), 5.70 (1H, s, H-15); EIMS  $m/z$  (rel. int.): 302 [ $M - C_2H_2O - C_2H_4O_2$ ] $^+$  (4), 287 (6), 284 (5), 270 (12), 269 (29), 237 (2), 233 (2), 213 (7), 199 (6).

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