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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, 7β-monoacetate of episinfernal, 7β-monoacetate of sideritriol, and sventenic acid, have been isolated from *Sideritis sventenii*. From *S. cystosiphon*, three new diterpenic esters, the 7β-acetate, 18-palmitate of epicandicandiol, the 18-acetate of epicandicandiol, and the 7β,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 ^{1}H NMR spectrum showed signals of the two methyl groups at δ1.04 and 1.15 of the geminal hydrogen to the hydroxyl group at C-7 (δ3.52, *br s*), and of the two protons of the exocyclic double bond (δ4.77 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 7β-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 7β-hydroxyl was acetylated. Its ^{1}H NMR spectrum showed the geminal hydrogen to the 7β-acetate at δ4.76. Thus, this compound is the 7β-monoacetate of episinfernal (**6**).

The third new diterpene isolated, sideritriol 7β-monoacetate (**8**), was a compound related to **6**. In its ^{1}H 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.

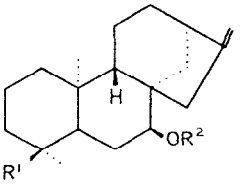
Other known compounds isolated from this species were the diterpenes candol B (**16**) [2], 7β-monoacetate of epicandicandiol (**11**) [2], epicandicandiol (**15**) [7], episinfernal (**7**) [4], and sideritriol (**10**) [8], the flavone cirsimaritin [9], and the flavanone, 5,4′-dihydroxy-6,7-dimethoxyflavanone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

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

Compound **12** showed a ^{1}H 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 7β-hydroxyl is also esterified, with the geminal hydrogen to a second ester group at δ4.77 (*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, 7β,17-diacetate of sideritriol (**9**), showed a ^{1}H 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 7β-monoacetate of episinfernal (**6**) and the 7β-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].



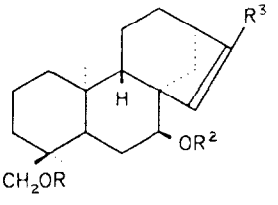
1 $R^1 = CO_2H$ $R^2 = H$

2 $R^1 = CO_2Me$ $R^2 = H$

3 $R^1 = CHO$ $R^2 = Ac$

4 $R^1 = CO_2H$ $R^2 = Ac$

5 $R^1 = Me$ $R^2 = H$



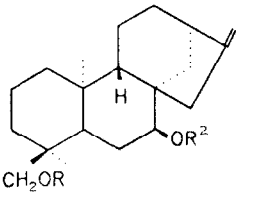
6 $R^1 = H$ $R^2 = Ac$ $R^3 = CHO$

7 $R^1 = R^2 = H$ $R^3 = CHO$

8 $R^1 = H$ $R^2 = Ac$ $R^3 = CH_2OH$

9 $R^1 = H$ $R^2 = Ac$ $R^3 = CH_2OAc$

10 $R^1 = R^2 = H$ $R^3 = CH_2OH$



11 $R^1 = H$ $R^2 = Ac$

12 $R^1 = Palm$ $R^2 = Ac$

13 $R^1 = Ac$ $R^2 = H$

14 $R^1 = Palm$ $R^2 = H$

15 $R^1 = R^2 = H$

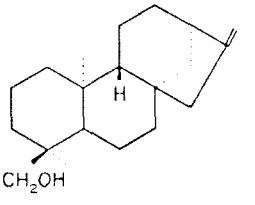


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Table 1. ^{13}C NMR spectral data of compounds **2** and **5** ($CDCl_3$, 50.32 MHz)

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: $CHCl_3$. NMR: $CDCl_3$. 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), 7β-monoacetate of epicandicandiol (**11**) (380 mg), cirsimaritin (45 mg), 5,4′-dihydroxy-6,7-dimethoxyflavanone (30 mg), 7β-monoacetate of episinfernal (**6**) (150 mg), epicandicandiol (**15**) (700 mg), 7β-monoacetate of sideritriol (**8**) (250 mg), episinfernal (**7**) (20 mg), sideritriol (**10**) (20 mg), and sventenic acid (**1**) (80 mg) were obtained.

Episinfernal 7β-monoacetate (**6**). Gum, $[M-C_2H_4O_2]^+$ at *m/z* 300.2111. $C_{20}H_{28}O_2$ requires 300.2090; ^1H NMR (200 MHz): δ0.71 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$[M-C_2H_4]^+$ (4), 269 (26), 213 (5), 187 (4), 185 (5), 173 (6), 171 (6).

Sideritriol 7β-monoacetate (**8**). Gum, 300 $[M-C_2H_2O]^+$ at *m/z* 320.2352. $C_{20}H_{32}O_3$ requires 320.2351; ^1H NMR (200 MHz): δ0.71 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).

Episinfernal (**7**). Gum, $[M]^+$ at *m/z* 318.2192. $C_{20}H_{30}O_3$ requires 318.2194; ^{1}H NMR (200 MHZ): δ0.72 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°; $[M]^+$ at *m/z* 332.2314. $C_{21}H_{32}O_3$ requires 332.2314; ^{1}H NMR (200 MHz): δ1.04 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 7β-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°, $[M-C_2H_4O_2]^+$ at *m/z* 300.2092. $C_{20}H_{28}O_2$ requires 300.2089; ^{1}H NMR (200 MHz): δ1.07 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°, $[M]^+$ at *m/z* 318.2162. $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (200 MHz): δ0.99 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, 7β-acetate-18-palmitate of epicandicandiol (**12**) (6 mg), 18-monoacetate of epicandicandiol (**13**) (43 mg), 7β-monoacetate of episinfernal (**6**) (40 mg), 7β-monoacetate of sideritriol (**8**) (3 mg), and 7β,17-diacetate of sideritriol (**9**) (11 mg), have now been obtained.

7β-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; ^{1}H NMR (200 MHz): δ0.83 and 1.08 (each 3H, *s*), 1.25 (*s*, *n*-CH_2–), 2.04 (3H, *s*), 3.62 and 3.76 (each 1H, *d*, $J\simeq11$ 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°; $[M]^+$ at *m/z* 346.2510. $C_{22}H_{34}O_3$ requires 346.2506; ^{1}H NMR (80 MHz): δ0.80 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).

7β,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; ^{1}H NMR (200 MHz): δ0.70 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 $[M-C_2H_2O-C_2H_2O]^+$ (4), 287 (6), 284 (5), 270 (12), 269 (29), 237 (2), 233 (2), 213 (7), 199 (6).

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REFERENCES

1. González, A. G., Bretón, J. L., Fraga, B. M. and Luis, J. G. (1971) *Tetrahedron Letters* 3097.
2. González, A. G., Fraga, B. M., Hernández, M. G. and Luis, J. G. (1973) *Phytochemistry* **12**, 2721.
3. González, A. G., Fraga, B. M., Hernández, M. G., Luis, J. G. and Larruga, F. (1979) *Biochem. Syst. Ecol.* **7**, 115.
4. Fernández, C., Fraga, B. M., and Hernández, M. G. (1986) *Phytochemistry* **25**, 2573.
5. Fraga, B. M., Hernández, M. G., Fernández, C. and Arteaga, J. M. (1987) *Phytochemistry* **26**, 775.
6. Luche, J. L., Rodriguez-Hahn and Crabbe, P. (1978) *J. Chem. Soc., Chem. Commun.* 601.
7. Piozzi, F., Venturella, P., Bellino, A., Paternostro, M. P., Rodriguez, B. and Valverde, S. (1971) *Chem. Ind.* 962.
8. Piozzi, F., Venturella, P., Bellino, A. and Selva, A. (1969) *Gazz. Chim. Ital.* **99**, 582.
9. González, A. G., Fraga, B. M., Hernández, M. G., Larruga, F., Luis, J. G. and Ravelo, A. G. (1978) *Lloydia* **41**, 279.
10. Fernández, C., Fraga, B. M., Hernández, M. G. and Arteaga, J. M. (1988) *J. Nat. Prod.* **51**, 591.
11. González, A. G., Fraga, B. M., Hernández, M. G. and Luis, J. G. (1973) *Tetrahedron* **29**, 561.