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DITERPENES FROM *SIDERITIS NUTANS*

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Key Word Index—*Sideritis nutans*; Labiatae; diterpenes; oxides of *ent*-labdane; sidnutol; gomerol; 13-epi-gomerol; *ent*-2α-hydroxy-13-epi-manoyl oxide; gomeric acid; 13-epi-gomeric acid, 3α-hydroxy-gomeric acid.

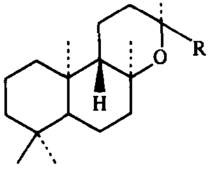
Abstract—Four new *ent*-labdane oxide diterpenes, sidnutol, gomerol, 13-epi-gomerol and 3α-hydroxy-gomeric acid, and the previously known gomeraldehyde, 13-epi-gomeraldehyde, *ent*-norambreinolide, *ent*-2α-hydroxy-13-epi-manoyloxide, gomeric acid and 13-epi-gomeric acid, have been isolated from the aerial parts of *Sideritis nutans*.

INTRODUCTION

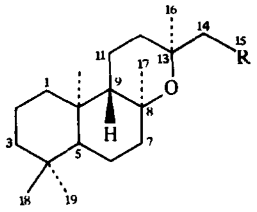
Continuing our work on the phytochemical study of species of the genus *Sideritis* which are endemic to the Canary Islands [1–4], we have studied *S. nutans* Svent., a plant found on the island of Gomera, from which we have previously isolated the norditerpene *ent*-norambreinolide [3]. From this species we have now isolated four new diterpenes: sidnutol (**1**), gomerol (**4**), 13-epi-gomerol (**9**) and 3α-hydroxy-gomeric acid (**14**).

RESULTS AND DISCUSSION

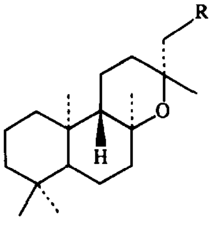
Sidnutol is a norditerpene ($C_{19}H_{34}O_2$) to which was assigned structure **1** in accordance with the following considerations. Its IR spectrum showed a band indicative of an alcoholic function (3540 cm^{-1}). In the ^1H NMR spectrum signals of one hydroxymethylene and five methyl groups were observed. The two oxygens of the molecule must form part of an alcoholic group and an ether bridge. Two methyl groups, which appeared in the



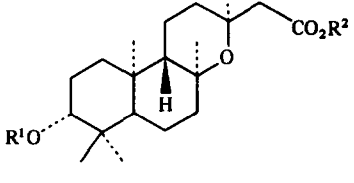
1 R = CH_2OH
2 R = CH_2OAc
3 R = CO_2H



4 R = CH_2OH
5 R = CH_2OAc
6 R = CHO
7 R = CO_2H
8 R = CO_2Me



9 R = CH_2OH
10 R = CH_2OAc
11 R = CHO
12 R = CO_2H
13 R = CO_2Me



14 R^1 = R^2 = H
15 R^1 = H R^2 = Me
16 R^1 = Ac R^2 = Me

^{1}H NMR spectrum as two singlets at δ 1.16 and 1.29, must be attached to carbon atoms bearing the oxygen atom of the ether function.

Acetylation of sidnutol in the usual way afforded the acetate **2**. When the ^{13}C NMR spectrum of **2** was compared with that of compound **4** (Table 1), it was deduced that the A, B and C rings were identical in both substances. Thus, sidnutol possesses a hydroxymethylene group geminal to a methyl group at C-13. The stereochemistry at this centre can be deduced from comparison of the methyl resonances in the ^{1}H NMR spectrum, where it can be observed that only the methyl at C-13, was shifted from **1** to **4** or **9**. Thus the hydroxymethylene group is equatorial. If this group were axial, the methyl at C-8 should also be shifted. Chemical proof of the structure **1** was obtained as follows. Chromic oxidation of **1** gave the nor-acid **3**, identical with a compound obtained by chemical degradation of barbatol [5] and also an enantiomer of a borjatriol [6] and of a manoyl oxide [7, 8] derivative.

Two isomeric diterpenes ($C_{20}H_{36}O_2$) were also isolated from this species. Both compounds have a labdane oxide skeleton with a $-CH_2-CH_2OH$ side chain and five methyl groups. Their ^{13}C NMR data are given in Table 1. On the basis of the above data structures **4** and **9** were assigned to these substances, which were named gomerol and 13-epi-gomerol, respectively. These two compounds (**4** and **9**) were identical with the reduction products of gomeric acid (**7**) and 13-epi-gomeric acid (**12**), respectively, both isolated from *S. gomerae* [9]. Their enantiomers have also been obtained from a manoyl oxide derivative [10].

The most polar of the new compounds isolated from *S. nutans* was 3α-hydroxygomeric acid (**14**). Its structure was established on the basis of the following considerations. High resolution mass spectrometry was in accordance with a molecular formula $C_{20}H_{34}O_4$ and its IR spectrum showed characteristic bands of hydroxyl and acid groups (see Experimental). The ^{1}H NMR spectrum showed signals of five tertiary methyl groups, the two protons of a $-CH_2CO_2H$ group and a hydrogen atom geminal to a secondary hydroxyl group at δ 3.21. This last signal appeared as a double doublet with coupling constants of 11 and 5 Hz, indicating that this alcoholic group is equatorial and placed between a methylene group and a tetrasubstituted carbon atom. Thus this hydroxylic function can be placed only at carbons, 1, 3, 7 or 12. The ^{13}C NMR data of the methyl ester **15**, compared with those of gomeric acid methyl ester (**8**) (Table 1), established that this alcoholic group must be located at C-3, with an α-stereochemistry.

Other known diterpenes isolated from this species were the labdane oxides gomeraldehyde (**6**) [9], 13-epi-gomeraldehyde (**11**) [9], *ent*-norambreinolide [3], *ent*-2α-hydroxy-13-epi-manoyl oxide [11], gomeric acid (**7**) [9] and 13-epi-gomeric acid (**12**) [9] and a trachilobanic diterpene, trachinodiol 7β-monoacetate [12]. All these compounds were previously isolated from species of *Sideritis* genus.

EXPERIMENTAL

Mps are uncorr.; NMR: $CDCl_3$, except where otherwise indicated; IR: $CHCl_3$; UV: EtOH; MS: 70 eV (probe); optical activities: $CHCl_3$; column and dry column chromatography: silica gel 0.063–0.2 mm.

Isolation of the diterpenoids. Air-dried aerial parts of the plant *Sideritis nutans* Svent. (0.7 kg), collected above Taguluche (island of Gomera) in May, were used for this work. A voucher specimen was deposited in the Herbarium of the Instituto Canario de Investigaciones Agrarias (ORT 78778).

A general description of the procedure to isolate the terpenoid substances of species of the genus *Sideritis* has been published

Table 1. ^{13}C NMR data ($CDCl_3$, 50.32 MHz)

Carbon	2	3	4	8	9	13	15
1	39.45	39.01	39.83	39.14	39.11	39.26	37.45
2	18.79	18.56	19.32	18.71	18.64	18.69	27.39
3	42.42	42.09	42.87	42.25	42.25	42.27	78.98
4	33.47	33.43	34.02	33.43	33.35	33.44	38.99
5	56.77	55.71	57.09	56.46	54.32	56.56	55.28
6	20.08	20.04	20.55	19.95	20.10	20.05	19.60
7	43.43	43.37	43.91	43.04	43.91	43.39	42.98
8	75.26	75.82	76.68	75.51	74.53	75.65	75.28
9	57.69	56.52	58.95	57.50	56.69	57.49	57.35
10	37.21	37.30	37.63	36.98	37.30	37.06	36.73
11	15.15	14.80	15.94	15.36	15.03	15.33	15.50
12	33.78	32.82	37.75	35.81	35.06	36.61	35.78
13	71.95	78.09	78.43	72.49	75.17	72.27	72.66
14	73.00	176.77	46.52	49.58	44.26	46.00	49.54
15	—	—	60.34	171.72	60.14	171.18	†
16	25.28*	26.40	28.37	28.33	28.91	30.70	28.31
17	24.95*	24.79	25.28	24.76	25.44	24.69	24.66
18	33.47	33.43	34.02	33.43	33.51	33.44	28.11
19	21.02	21.47	21.99	21.41	21.53	21.39	15.34
20	15.74	15.48	16.51	15.84	15.26	15.78	15.89

*These assignments may be reversed.

†Not recorded.

previously [2]. In this way, an unidentified substance (20 mg), gomeraldehyde (**6**, 75 mg) [9], 13-epi-gomeraldehyde (**11**, 15 mg) [9], *ent*-norambreinolide (15 mg) [3], sidnutol (**1**, 200 mg), gomerol (**4**, 210 mg), gomeric acid (**7**, 100 mg) [9], *ent*-2α-hydroxy-13-epi-manoyl oxide (15 mg) [11], trachinodiol monoacetate (150 mg) [12], 13-epi-gomerol (**9**, 160 mg), 13-epi-gomeric acid (**12**, 50 mg) [9], and 3α-hydroxy-gomeric acid (**14**, 190 mg) were obtained.

Sidnutol (**1**). Mp 99–102°, $[\alpha]_D$ −7° (*c* 0.10), $[M-Me]^+$ at 279.2310, $C_{18}H_{31}O_2$ requires 279.2324; IR ν_{max} cm^{-1}: 3540, 2980, 2930, 2860, 1460, 1385, 1375, 1260, 1240, 1170, 1140, 1115, 1095, 1075, 1045, 1035, 995, 960, 830; ^1H NMR (200 MHz): δ0.77, 0.79, 0.85, 1.16 and 1.29 (each 3H, *s*), 3.07 and 3.36 (each 1H, *d*, *J* = 10 Hz, H-14); EIMS *m/z* (rel. int.): 279 $[M-Me]^+$ (3), 263 (38), 261 (2), 246 (27), 245 (100), 235 (4), 207 (3), 205 (5), 193 (5). Sidnutyl acetate (**2**), mp 57–59°, $[M-Me]^+$ at 321.2439, $C_{20}H_{33}O_3$ requires 321.2430; ^1H NMR (200 MHz): δ0.77, 0.79, 0.86, 1.23 and 1.28 (each 3H, *s*), 2.07 (3H, *s*), 3.74 and 3.92 (each 1H, *d*, *J* = 11 Hz, H-14); EIMS *m/z* (rel int.): 321 $[M-15]^+$ (2), 263 (41), 246 (31), 245 (100), 205 (5), 163 (9), 149 (25), 139 (13), 137 (61), 135 (11).

Gomerol (**4**). $[M-Me]^+$ at 293.2467. $C_{19}H_{33}O_2$ requires 293.2480; ^1H NMR (200 MHz): δ0.76, 0.78, 0.83, 1.27 and 1.29 (each 3H, *s*), 3.77 and 3.80 (each 1H, *d*, *J* = 4 Hz, H-15); EIMS *m/z* (rel. int.): 293 $[M-Me]^+$ (13), 275 (14), 263 (29), 245 (92), 205 (15), 192 (10), 191 (8), 177 (17), 163 (9), 149 (52), 137 (71), 135 (18). Gomeryl acetate (**5**). $[M-Me]^+$ at 335.2549, $C_{21}H_{35}O_3$ requires 335.2586; ^1H NMR (60 MHz): δ0.75, 0.78 and 0.84 (each 3H, *s*), 1.24 (6H, *s*), 2.01 (3H, *s*), 4.22 (2H, *m*, $W_{1/2}$ = 16 Hz, H-16); EIMS *m/z* (rel. int.): 335 $[M-Me]^+$ (5), 317 (1), 275 (7), 263 (11), 257 (6), 245 (40), 192 (4), 177 (5), 163 (3), 153 (2), 149 (4), 137 (17).

13-*Epi-gomerol* (**9**). ^1H NMR (90 MHz): δ0.79 (6H, *s*), 0.85, 1.21 and 1.28 (each 3H, *s*), 3.83 (2H, *m*, $W_{1/2}$ = 23 Hz, H-15); EIMS (rel. int.): 293 $[M-Me]^+$ (6), 275 (8), 263 (14), 257 (9), 245 (54), 192 (9), 177 (17), 137 (31). 13-Epi-gomeryl acetate (**10**). ^1H NMR: δ0.74, 0.76, 0.83, 1.12 and 1.24 (each 3H, *s*), 2.00 (3H, *s*), 4.16 (2H, *br s*, $W_{1/2}$ = 15 Hz, H-15); EIMS *m/z* (rel. int.): 335 $[M-Me]^+$ (8); 275 (12), 263 (19), 257 (10), 245 (82), 137 (26).

3α-*Hydroxy-gomeric acid* (**14**). $[M-15]^+$ at 323.2205, $C_{19}H_{31}O_4$ requires 323.2223; ^1H NMR (200 MHz): δ0.74, 0.77, 0.96, 1.22 and 1.34 (each 3H, *s*), 2.36 and 2.54 (each 1H, *d*, *J* = 15 Hz, H-14), 3.21 (1H, *dd*, *J* = 5 and 11 Hz, H-3); EIMS *m/z* (rel. int.): 3.23 $[M-Me]^+$ (49), 305 (8), 287 (8), 279 (3), 277 (6), 261 (6), 243 (15), 189 (7), 187 (8), 175 (11), 161 (7), 159 (10), 147 (11), 135 (30). Methyl ester (**15**). $[M-Me]^+$ at 337.2382, $C_{20}H_{33}O_4$ requires 337.2379; ^1H NMR (60 MHz): 0.76 (6H, *s*), 0.97, 1.27 and 1.32 (each 3H, *s*), 2.42 (2H, *br*, H-14), 3.21 (1H, *t*, $W_{1/2}$ = 16 Hz, H-3), 3.64 (3H, *s*); EIMS *m/z* (rel. int.): 337 $[M-Me]^+$ (74), 319 (5), 301 (9), 287 (4), 279 (9), 243 (19). Methyl ester acetate (**16**). $[M-Me]^+$ at 379.2481, $C_{22}H_{35}O_5$ requires 379.2482; ^1H NMR (60 MHz): δ0.80 (3H, *s*), 0.85 (6H, *s*), 1.28 and 1.34 (each 3H, *s*), 2.04 (3H, *s*), 2.43 (2H, *s*, H-14), 3.66 (3H, *s*), 4.49 (1H, *t*, $W_{1/2}$ = 16 Hz, H-3); EIMS *m/z* (rel. int.): 379 $[M-Me]^+$ (47), 319 (13), 301 (10), 287 (6), 201 (9), 135 (30).

Oxidation of compound **1**. Sinutol (**1**) (49 mg) in Me_2CO (minimum quantity) was treated dropwise with a slight excess of Jones reagent and left at room temp. for 5 min, MeOH was then added to destroy the excess of reagent. The mixture was poured into H_2O and worked up, yielding the acid **3** (40 mg); $[\alpha]_D$ −30° (*c* 0.10); $[M-Me]^+$ at 293.2103, $C_{18}H_{29}O_3$ requires 293.2116; ^1H NMR (200 MHz): δ0.74, 0.75, 0.82, 1.27 and 1.43 (each 3H, *s*); EIMS *m/z* (rel. int.): 293 $[M-Me]^+$ (4), 263 (19), 245 (94), 206 (3), 205 (4), 175 (5), 167 (4), 163 (8), 149 (34), 137 (43), 135 (11).

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