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ABIETANE DITERPENES FROM *NEPETA TEYDEA*

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Key Word Index—*Nepeta teydea*; Labiatae; diterpenes; netidiol A; netidiol A 7α-monoacetate; netidiol A 18-monoacetate; netidiol A 7α-propyl ether; 8α,14α-epoxy-netidiol A; netidiol B; netidiol B 14α-monoacetate; netidiol B 18-monoacetate; netiol.

Abstract—The structures of two abietane diterpenes previously isolated from *Nepeta teydea* have been corrected and they have now been named netidiol A and netidiol B. The new diterpenes netidiol A 7α-monoacetate, netidiol A 18-monoacetate, 8α,14α-epoxy-netidiol A, netidiol A 7α-propyl ether, netidiol B 14α-monoacetate, netidiol B 18-monoacetate and netiol have also been isolated from this species. © 1997 Published by Elsevier Science Ltd

INTRODUCTION

The phytochemical study of the Canarian species of the Labiatae family has been the object of our attention over the last 20 years. We have now re-examined *Nepeta teydea* W.B., a species endemic to the higher parts of Tenerife. In previous studies several dehydroabietane diterpenes such as teideadiol [1–3] and teidic acid [3], abietane diterpenes such as 13α-isopropyl-8(14)-podocarpen-7α,18-diol (**17**) [4, 5] and 13α-isopropyl-7(8)-podocarpen-14α,18-diol (**18**) [5, 6], two spirostan compounds [7] and the triterpenes oleanolic, ursolic, 2α,3β-dihydroxy-ursolic and 2α,3β, 19α-trihydroxy-ursolic acids have been isolated from this plant [2]. The essential oils of this species have also been studied [8–10].

We have assigned compounds **17** and **18** the new structures **1** and **8**, respectively, and named them netidiol A and B. We also report on the isolation of the novel diterpenes netidiol A 7α-monoacetate (**2**), netidiol A 18-monoacetate (**3**), netidiol A 7α-propyl ether, 8α,14α-epoxy-netidiol A (**13**), netidiol B 14α-monoacetate (**9**), netidiol B 18-monoacetate (**10**) and netiol (**14**).

RESULTS AND DISCUSSION

To two abietane diterpenes previously obtained from this plant had been assigned the structures **17** and **18** [4–6]. We have now named them netidiol A and netidiol B and assigned the structures **1** and **8**, respectively, correcting the stereochemistry of the isopropyl group from α to β in both cases. The basis of these structural changes is as follows: (a) The observed coupling constant between H-13 and H-14 in the ^{1}H NMR spectrum of **8** was 2 Hz, which is more in accordance with that calculated for the minimum energy conformation of **8** (2.0 Hz) than with that calculated for its C-13 α-epimer **18** (4.9 Hz), a chair being the most favourable conformation of ring C in **8**; (b) a NOE effect was observed between H-14 and the methyls of the isopropyl group in the ROESY spectrum of **8**. On the other hand, the stereochemistry of H-14(β) was confirmed because another NOE interaction was observed between this proton and H-7. (c) Both compounds **1** and **8** in acid medium gave the same product, **14** (see below).

Compounds **15** and **16**, also with a β-stereochemistry of the isopropyl group, have been isolated from *Aeollanthus buchnerianus* [11] and *Hyptis suaveolens* [12], respectively, both these species also belonging to the Labiatae family.

The 7α- and 18-monoacetate of netidiol A, **2** and **3**, were obtained for the first time as natural compounds. Both show a similar ^{1}H NMR spectrum and the differences observed between them were mainly the chemical shifts of the geminal proton at C-7 and the methylene at C-18, δ 5.37 for the former and δ 3.07 and 3.36 (each 1H) for the latter in **2** and δ 4.19, for the former, and δ 3.54 and 4.04 (each 1H), for the latter, in **3**. The mass spectrum of this 18-monoacetate showed the $[M]^+$ at *m/z* 348, but in the case of the 7α-monoacetate (**2**) only the peak produced by the loss of ketene at *m/z* 306 was observed.

An unstable epoxide of netidiol A was also isolated

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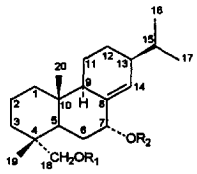
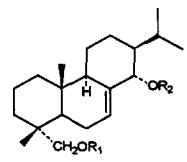
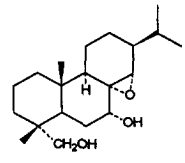


1 $R_1 = R_2 = H$
2 $R_1 = H$ $R_2 = Ac$
3 $R_1 = Ac$ $R_2 = H$
4 $R_1 = R_2 = Ac$
5 $R_1 = H$ $R_2 = CH_2\text{-}CH_2\text{-}CH_3$
6 $R_1 = Ac$ $R_2 = CH_2\text{-}CH_2\text{-}CH_3$
7 $R_1 = (CO)CH_2CO_2Et$ $R_2 = Ac$



8 $R_1 = R_2 = H$
9 $R_1 = H$ $R_2 = Ac$
10 $R_1 = Ac$ $R_2 = H$
11 $R_1 = R_2 = Ac$
12 $R_1 = (CO)CH_2CO_2Et$ $R_2 = Ac$



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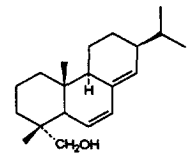

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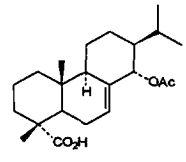

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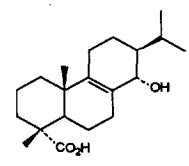

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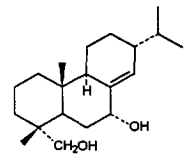

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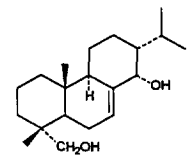

18

and assigned the structure **13**. Its ^1H NMR spectrum showed the resonance of the geminal proton of the hydroxyl group at C-7 as a broad singlet at δ 3.37. The geminal hydrogen to the oxyrane ring appears as a sharp singlet at δ 2.79. This form of resonance enabled us to assign the position and the α-stereochemistry of this epoxidic function.

Another derivative of netidiol A, its 7-propyl ether **5**, was also obtained from this species. Its ^1H NMR showed the resonances of the methyl group at C-4 and C-10 (δ 0.76 and 0.79), those of the isopropyl group at C-13 (δ 0.87 and 0.90, each *d*, $J = 3.2$ Hz) and that of the propyl ether (δ 1.11, *t*, $J = 7$ Hz; δ 3.40, *m*). The hydrogen geminal to this last group at C-7 appears as a triplet at δ 3.67 ($J = 2.8$ Hz) and the proton at C-14 of the double bond resonates at δ 5.53 as a doublet ($J = 1.2$ Hz).

The 14α- and 18-monoacetates of netidiol B, **9** and **10**, have been obtained and characterised on the basis of their ^1H NMR spectra, in a similar way to the identification of the corresponding monoacetates of netidiol A (see above). But we must remark here that the spectra of the 7α-monoacetate of netidiol A (**2**) and 14α-monoacetate of netidol B (**9**) were very similar, and their identification was based on their comparison with the diacetates, **4** and **11**, which were obtained by acetylation of the corresponding alcohols, netidiol A (**1**) and netidiol B (**8**), respectively.

The least polar substance isolated was named netiol. We assigned to this compound the structure **14** based on the following spectroscopic data. Its $[M]^+$ at *m/z* 288 was in accordance with the molecular formula $C_{20}H_{32}O$. The presence in the molecule of two angular methyls, an isopropyl group, a hydroxymethylene group, and two double bonds was deduced from its NMR spectra. The two vinylic functions were assigned to C-6, C-7 and C-8, C-14, because in the ^1H NMR spectrum there was a broad singlet at δ 5.45 (H-14), a broad doublet at δ 5.54 with a coupling constant of 10 Hz (H-6) and a double doublet at δ 6.04 ($J = 10$ and 4 Hz), assigned to H-7. The minor *J* of this last signal was due to allylic coupling with H-5, which appears as a broad singlet at δ 2.21. Irradiation of this proton transformed the H-6 and

Table 1. ^{13}C NMR data of compounds **1**, **3**, **4**, **8**, **11** and **14**

C	1	3	4	8*	11	14
1	38.3	38.4	38.4	40.7	39.1	36.9
2	16.2	18.0	18.0	19.2	17.9	18.2
3	34.9	35.9	35.9	36.8	36.1	34.6
4	37.6	36.5	36.4	35.8	34.8	37.0
5	39.2	40.8	41.7	44.2	44.6	48.8
6	28.4	29.6	27.7	26.5	24.8	125.8
7	73.4	73.0	75.3	125.4	127.6	131.2
8	140.7	140.2	141.6	141.8	135.8	137.4
9	47.0	47.0	47.9	49.3	48.2[a]	50.8
10	38.1	38.1	37.9	38.4	36.1	35.6
11	22.2	22.2	22.2	24.1[a]	23.4[b]	22.3
12	25.3	25.3	24.8	24.2[a]	23.6[b]	25.2
13	41.6	41.7	42.1	51.0	48.3[a]	42.6
14	131.1	131.2	134.3	75.1	76.0	129.6
15	32.0	32.0	31.7	29.6	28.7	32.3
16	19.2[a]	19.3[a]	19.0[a]	21.0[b]	20.9[c]	19.2[a]
17	19.5[a]	19.6[a]	19.4[a]	21.6[b]	21.5[c]	19.5[a]
18	70.3	72.3	72.4	72.2	73.7	71.5
19	16.1	17.7	17.6	18.6	17.9	17.5
20	14.3	14.3	14.4	16.1	15.3	13.8

[a,b,c] These values can be interchanged.
* Solvent: CD_3OD.

H-7 signals into two sharp doublets. The form of the signal of H-14 also confirmed the β-stereochemistry assigned to the isopropyl group (see above). The carbon methines at δ 125.81, 129.63 and 131.21 were assigned to C-6, C-14 and C-7, respectively, and that at δ 137.40 to the tetrasubstituted C-8. Other carbon resonances are in accordance with this structure **14** and are described in Table 1. Their assignments were made utilizing HMQC and HMBC 2D-NMR experiments. This compound could be an artefact, because when both netidiol A (**1**) and netidiol B (**8**) were left separately in $CDCl_3$, for several days in the NMR tube, they were transformed into netiol (**14**).

A small amount of mixture of the ethyl ester of the 7α-monoacetate-18-malonate of netidiol A (**7**) and the ethyl ester of the 14α-monoacetate-18-malonate of netidiol B (**12**) was also isolated from this plant. From this mixture, the diterpene **12** was obtained in pure form by rechromatography. The structures were assigned by considering the ^1H NMR spectra and comparing them with those of the diacetates **4** and **11**. These ethyl esters are artefacts produced during the extraction of the plant with ethanol. The natural diterpenes must be the corresponding acids. Other known compounds such as the diterpene, phytol epoxide, and the flavone, apigenin (5,6,7,4′-tetrahydroxyflavone), have also been obtained from this species.

EXPERIMENTAL

General. Mps: uncorr. IR: $CHCl_3$. ^1H NMR: $CDCl_3$, except were otherwise stated; MS: 70 eV (probe); CC: silica gel 0.063–0.2 mm. The substances were crystallised from petrol–EtOAc except where otherwise indicated. Conformations of minimum energy and calcd coupling constants were determined by computational methods employing the Chem X program.

Plant material. Collected in June at the highest part of 'Barranco de Erques' near the Teide National Park (Tenerife) and a voucher specimen (TFC 40.657) has been deposited in the Herbarium of the Department of Botany, University of La Laguna (Tenerife).

Extraction and isolation of the chemical constituents. The finely cut aerial parts (5 kg) were extracted and treated as previously described [3] to give several mixts of substances, which were re-chromatographed on silica gel dry columns eluted with petrol–EtOAc mixts to afford **1** (45 mg), **2** (120 mg), **3** (55 mg), **5** (5 mg), **13** (3 mg), **8** (140 mg), **9** (80 mg), **10** (7 mg), **14** (11 mg), **12** (3 mg), (**7**) impurified with **12** (6 mg), phytol epoxide (20 mg) and apigenin (55 mg).

Netidiol A (**1**). ^1H NMR (200 MHz): δ 0.71 and 0.74 (each 3H, s), 0.85 and 0.88 (each 3H, *d*, $J = 7$ Hz), 2.86 and 3.50 (each 1H, *d*, $J = 11$ Hz, H-18), 4.19 (1H, *t*, $J = 2.6$ Hz, H-7), 5.63 (1H, *br s*, H-14); EIMS *m/z* (rel. int.): 306 $[M]^+$ (8), 288 (4), 257 (15), 245 (14), 227 (6), 215 (9), 201 (4), 166 (71), 151 (40). Diacetate (**4**) ^1H NMR (200 MHz): δ 0.77 and 0.86 (each 3H, *s*), 0.83 (6H, *t*, $J = 7$ Hz), 1.98 and 2.06 (each 3H, *s*), 3.58 and 3.86 (each 1H, *d*, $J = 11$ Hz, H-18), 5.32 (1H, *t*, H-7), 5.74 (1H, *br s*, H-14).

Netidiol A 7α-monoacetate (**2**). ^1H NMR (200 MHz): δ 0.78 (6H, *s*), 0.84 (6H, *t*, $J = 7$ Hz), 2.00 (3H, *s*), 3.07 and 3.36 (each 1H, *d*, $J = 11$ Hz, H-18), 5.32 (1H, *t*, $J = 3$ Hz, H-7), 5.74 (1H, *d*, $J = 1.3$ Hz, H-14); EIMS *m/z* (rel. int.): 306 $[M-42]^+$ (7), 288 (13), 267 (11), 261 (15), 257 (10), 245 (53).

Netidiol A 18-*monoacetate* (**3**). ^{1}H NMR (200 MHz): δ 0.76 and 0.86 (each 3H, *s*), 0.87 (6H, *t*, $J = 6$ Hz), 3.54 and 4.04 (each 1H, *d*, $J = 11$ Hz, H-18), 4.19 (1H, *t*, $J = 2.4$ Hz, H-7), 5.63 (1H, *d*, $J = 1.2$ Hz); EIMS *m/z* (rel. int.): 348 $[M]^+$ (18), 288 (8), 270 (9), 257 (20), 245 (27), 227 (36), 201 (12), 185 (11), 170 (10), 166 (100).

Netidiol A 7α-*propyl ether* (**5**). ^{1}H NMR (200 MHz): δ 0.76 and 0.79 (each 3H, *s*), 0.87 and 0.89 (each 3H, *d*, $J = 6$ Hz), 1.11 (3H, *t*, $J = 7$ Hz, propyl ether), 2.97 and 3.49 (each 1H, *d*, $J = 11$ Hz, H-18), 3.17 and 3.40 (each 1H, *m*, propyl ether), 3.67 (1H, *t*, $J = 2.8$ Hz, H-7), 5.53 (1H, *d*, $J = 1.2$ Hz, H-14). Acetate (**6**), 0.78 and 0.85 (each 3H, *s*), 0.87 and 0.89 (each 3H, *d*, $J = 6.4$ Hz), 1.32 (3H, *t*, $J = 7$ Hz, propyl ether), 3.14 and 3.31 (each 1H, *m*, propyl ether), 3.56 and 3.98 (each 1H, *d*, $J = 11$ Hz, H-18), 3.62 (1H, *t*, $J = 2.7$ Hz, H-7), 5.51 (1H, *d*, $J = 1.2$ Hz, H-14); EIMS *m/z* (rel. int.): 348 $[M-42]^+$ (7), 305 (7), 245 (10), 229 (18).

8α,14α-*Epoxy-netidiol A* (**13**). ^{1}H NMR (200 MHz): δ 0.74 and 0.97 (each 3H, *s*), 0.97 (6H, *t*, $J = 7$ Hz), 2.53 (1H, *m*, H-15), 2.79 (1H, *s*, H-14), 3.02 and 3.46 (each 1H, *d*, $J = 11$ Hz, H-18), 3.37 (1H, *br s*, H-7).

Netidiol B (**8**). Mp 185–188° (Lit. 195–196° [4]); $[M]^+$ at *m/z* 306.2575. $C_{20}H_{34}O_2$ requires 306.2558; ^{1}H NMR (200 MHz): δ 0.82 and 0.88 (each 3H, *s*), 0.93 and 0.98 (each 3H, *d*, $J = 7$ Hz), 3.10 and 3.37 (each 1H, *d*, $J = 11$ Hz, H-18), 4.19 (1H, *d*, $J = 2$ Hz, H-14), 5.66 (1H, *dd*, $J = 4.4$ and 2 Hz, H-7); EIMS *m/z* (rel. int.): 306 $[M]^+$ (4), 288 (6), 275 (8), 257 (7), 245 (11), 227 (6), 166 (11), 153 (30). Diacetate (**11**), ^{1}H NMR (200 MHz): δ 0.81 and 0.92 (each 3H, *s*), 0.88 and 0.90 (each 3H, *d*, $J = 7$ Hz), 2.00 and 2.04 (each 3H, *s*), 3.73 (2H, *s*, H-18), 5.50 (1H, *br s*, H-14), 5.80 (1H, *t*, $J = 2$ Hz, H-7); EIMS *m/z* (rel. int.): 348 $[M-C_2H_2O]^+$ (5), 330 (9), 315 (10), 287 (31), 270 (33), 255 (20), 241 (7), 227 (100), 199 (15).

Netidiol B 14α-*monacetate* (**9**). $[M]^+$ at *m/z* 348.2667. $C_{22}H_{36}O_3$ requires 348.2664; ^{1}H NMR (200 MHz): δ 0.82 and 0.87 (each 3H, *s*), 0.88 and 0.90 (each 3H, *d*, $J = 7$ Hz), 2.01 (3H, *s*), 3.13 and 3.37 (each 1H, *d*, $J = 11$ Hz, H-18), 5.50 (1H, *br s*, H-14), 5.82 (1H, *t*, $J = 2$ Hz, H-7); EIMS *m/z* (rel. int.): 348 $[M]^+$ (1), 306 (3), 288 (7), 273 (11), 259 (13), 257 (11), 255 (12), 245 (24), 243 (17), 229 (16), 227 (15), 215 (11), 213 (13), 201 (15), 199 (13).

Netidiol B 18-*monacetate* (**10**). ^{1}H NMR (200 MHz): δ 0.81 and 0.88 (each 3H, *s*), 0.93 and 0.99 (each 3H, *d*, $J = 7$ Hz), 2.33 (1H, *m*), 3.74 and 3.79 (each 1H, *d*, $J = 11$ Hz, H-18), 4.19 (1H, *br s*, H-14), 5.66 (1H, *t*, H-7).

Netiol (**14**). $[M]^+$ at *m/z* 288.2454. $C_{20}H_{32}O$ requires 288.2453; ^{1}H NMR (500 MHz): δ 0.75 (3H, *s*, H-20), 0.83 (3H, *s*, H-19), 0.83 and 0.84 (each 3H, *d*, $J = 7$ Hz, H-16 and H-17), 2.07 (1H, *m*, H-9), 2.21 (1H, *br s*, H-5), 3.21 and 3.48 (each 1H, *d*, $J = 11$ Hz, H-18), 5.45 (1H, *br s*, H-14), 5.54 (1H, *br d*, $J = 10$ Hz, H-6), 6.04 (1H, *dd*, $J = 10$ and 4 Hz, H-7); EIMS *m/z* (rel. int.): 288 $[M]^+$ (27), 255 (17), 245 (23), 227 (16), 201 (11), 187 (10), 185 (14), 171 (13).

Ethyl ester of 14-*monoacetate*-18-*malonate of netidiol B* (**12**). ^{1}H NMR (200 MHz): δ 0.81 and 0.96 (each 3H, *s*), 0.88 and 0.90 (each 3H, *d*, $J = 7$ Hz), 1.29 (3H, *t*, $J = 7$ Hz), 2.02 (3H, *s*), 4.16 and 4.23 (each 1H, *d*, $J = 7$ Hz, OEt), 3.37 (2H, *s*, malonate), 3.80 (2H, *br s*, H-18), 5.50 (1H, *br s*, H-14), 5.80 (1H, *br s*, H-7); EIMS *m/z* (rel. int.): 420 $[M-CH_2{=}CO]^+$ (11), 402 (4), 387 (3), 270 (53), 255 (20), 227 (100), 186 (23).

Ethyl ester of 7-*monoacetate*-18-*malonate of netidiol A* (**7**). This compound was obtained in a mixt. with the isomer **12**. The following signals in the ^{1}H NMR (200 MHz) could be assigned as belonging to the ester **7**: δ 0.79 and 0.88 (each 3H, *s*), 0.82 (6H, *d*, $J = 7$ Hz), δ 1.29 (3H, *t*, $J = 7$ Hz), 2.01 (3H, *s*), 3.39 (1H, *s*, malonate), 3.73 and 3.92 (each 1H, *d*, $J = 11$ Hz, H-18), 4.17 and 4.25 (each 1H, *d*, $J = 7$ Hz, OEt), 5.35 (1H, *t*, $J = 3$ Hz), 5.76 (1H, *s*).

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