Pergamon 0031–9422(94)00947–3

Phytochemistry, Vol. 39, No. 3, pp. 617–619, 1995

0031–9422/95 $9.50 + 0.00

NOR-SESQUITERPENES FROM *TEUCRIUM HETEROPHYLLUM*

BRAULIO M. FRAGA, MELCHOR G. HERNÁNDEZ, TERESA MESTRES, DAVID TERRERO and JOSÉ M. ARTEAGA*

Instituto de Productos Naturales y Agrobiología, CSIC, La Laguna, 38206-Tenerife, Canary Islands, Spain;
*Departmento de Quimica Orgánica, Universidad de La Laguna, Tenerife, Spain

(*Received* 21 *September* 1994)

Key Word Index—*Teucrium heterophyllum*; Labiatae; sesquiterpenes; eudesmane, nor-eudesmane; 7-epi-teucrenone; teuhetone; teuhetenone A; teuhetenone B; tephyllone; 9β-hydroxy-tephyllone; 9-oxo-tephyllone.

Abstract—A new sesquiterpene, 7-epi-teucrenone, and six novel nor-sesquiterpenes, teuhetone, teuhetenone A, teuhetenone B, tephyllone, 9β-hydroxy-tephyllone and 9-oxo-tephyllone, have been isolated from the aerial parts of *Teucrium heterophyllum*. This plant also contains the known terpene 3-oxo-α-ionol (3,4-dehydro-blumenol C)

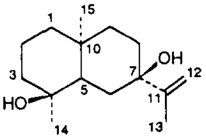
INTRODUCTION

During recent years we have been interested in the phytochemical study of species of the family Labiatae which are endemic to the Canary Islands [1, 2]. Continuing this work we have now studied *Teucrium heterophyllum* L'Her., a plant growing on the island of Tenerife, from which we have previously obtained the sesquiterpenes teucdiol A (**1**), teucdiol B (**2**) and teucrenone (**3**), the diterpene teuvidin, the triterpenes squalene, α-amyrin, β-amyrin, taraxerol, ursolic acid and oleanolic acids, the sterols sitosterol and ergosterol peroxide, and the flavones, salvigenin, circimaritin, 5,7-dihydroxy-3′,4′,5′-trimethoxy-flavone and 6,7,3′,4′-tetramethoxy-flavone (3′-*O*-methyl-eupatorin) [3].

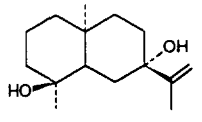
We have now isolated the new sesquiterpene 7-epi-teucrenone B (**4**) and the novel nor-sesquiterpenes teuhetone (**5**), teuhetenone A (**6**), teuhetenone B (**8**), tephyllone (**8**), 9β-hydroxy-tephyllone (**9**) and 9-oxo-tephyllone (**10**), and the known 3-oxo-α-ionol (**11**) from this species.

RESULTS AND DISCUSSION

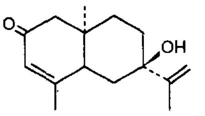
The structure **4** has been assigned to the new sesquiterpene, 7-epi-teucrenone, on the basis of the following considerations. In its mass spectrum the molecular ion appeared at m/z 234. The ^{1}H NMR spectrum showed the resonances of an angular methyl and of two methyls on double bonds. One of these double bonds must be conjugated with a carbonyl group because the α vinylic hydrogen resonated at δ5.88. The methylene of the isopropenyl group appeared as a singlet at δ5.10. The equatorial stereochemistry for the hydroxyl group at C-7 was determined by comparison with its epimer at this carbon, teucrenone, isolated previously from this species [3]. In the present case the H-5 appeared at higher field and the resonance of C-15 was at low field in agreement with the presence of an equatorial alcohol [4].



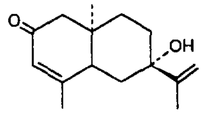
1



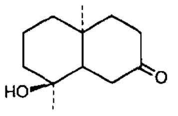
2



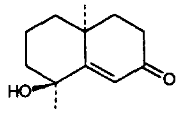
3



4

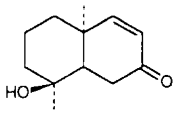


5

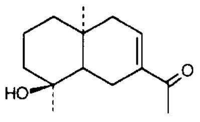


6

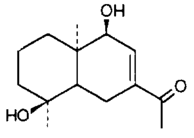
The mass spectrum of compound **5** was in accordance with the formula $C_{12}H_{20}O_2$. Its IR spectrum showed absorbances of hydroxyl and carbonyl groups and the ^{1}H NMR spectrum showed the resonances of two methyl groups. The ^{13}C NMR spectrum indicated that the twelve carbons of the molecule (Table 1) were in the form of two methyls, six methylenes, one methine, two tetrasubstituted carbons, one of which was joined to an oxygen, and a carbonyl group. Taking into consideration these data the structure **5** was assigned to this nor-sesquiterpene, which we have named teuhetone. The stereochemistry at C-4 was given on the basis of the ^{1}H NMR ROESY spectrum, which showed interactions between the C-14 and C-15 methyls.



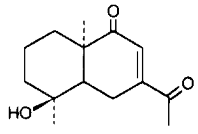
7



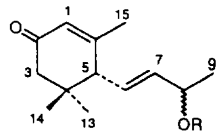
8



9



10



11 R = H

12 R = Ac

Table 1. ^{13}C NMR data of compounds **4–7** and **11** (50.3 MHz)

C	**4**	**5**	**6**	**7**	**11**
1	54.0	37.9[a]	40.6[a]	34.2	126.0
2	199.1	20.2	19.4	22.4	199.1
3	126.8	38.2[a]	40.8[a]	37.1	47.5
4	162.5	71.8	72.3	71.2	36.1
5	44.9	54.0	175.1	51.7	55.4[a]
6	33.0	43.5	122.4	42.4	129.2
7	74.7	212.1	200.5	200.8	133.8[a]
8	31.5	42.9	42.2	125.9	70.4
9	37.6	40.7[a]	33.9	161.2	20.4
10	37.4	34.5	36.1	37.3	161.3
11	145.9	—	—	—	—
12	114.1	—	—	—	—
13	18.6	—	—	—	26.9
14	16.9	17.3	24.5	17.9	27.9
15	22.0	22.0	29.6	19.6	23.4

[a]These values can be interchanged within the column.

Compound **6**, which we have named teuhetenone A, was obtained as a mixture with substance **5**. However, we can assign it the structure **6** on the basis of spectral data. The ^1H NMR spectrum showed the hydrogen of the double bond at $\delta 6.35$ and two angular methyl groups at $\delta 1.31$ and 1.42, whilst in the ^{13}C NMR spectrum there appeared signals of two methyls, five methylenes, one methine of a double bond ($\delta 122.4$), one carbonyl group ($\delta 200.5$), three tetrasubstituted carbons, one of these of a double bond ($\delta 175.1$) and another united to an oxygen function ($\delta 72.3$).

The third compound (**7**) was obtained in small quantities, also contaminated with **5**. The presence of the enone group was observed in the ^1H NMR spectrum where the characteristic pair of doublets appeared at $\delta 5.81$ and 6.68, with a coupling constant of 10 Hz. The H-8 hydrogen appeared broad, probably due to coupling with the equatorial H-6 proton. The ^{13}C NMR spectrum (Table 1) confirmed the structure **7** given to this new nor-sesquiterpene, which we have named teuhetenone B.

These two nor-sesquiterpenes, **6** and **7**, must be biosynthetically derived from **5**, and this nor-derivative can be formed from the eudesmane sesquiterpenes **1** and **2**, previously isolated from this species [3]. Thus, the same absolute configuration and the same relative stereochemistry at C-4 (and C-5 in **7**) was assigned to these compounds.

Another three new nor-eudesmane sesquiterpenes obtained in very low yield from this species were tephyllone (**8**), 9β-hydroxy-tephyllone (**9**) and 9-oxo-tephyllone (**10**).

The molecular ion of tephyllone (**8**) at m/z 222.1621 was in accordance with the formula $C_{14}H_{22}O_2$. Its ^1H NMR spectrum showed signals of two angular methyls at $\delta 0.81$ and 1.22, of a CH_3–CO– group at $\delta 2.29$ and of a vinylic proton at $\delta 6.80$. The chemical shift of this last hydrogen indicated that it must be in the β-position of the double bond, which must be conjugated with the carbonyl group. The pattern of the resonance of this proton points to a 7,8-double bond in a eudesmane skeleton.

The ^1H NMR spectrum of 9β-hydroxy-tephyllone (**9**) was very similar to that of **8**. In addition a geminal proton to a hydroxyl group appeared at $\delta 3.64$, which was coupled to the vinylic hydrogen indicating the C-9 position for this new alcoholic group. The coupling constant observed (6 Hz) indicated a β-stereochemistry for this hydroxyl group.

Finally, the third compound of this type was 9-oxo-tephyllone (**10**) with a molecular formula $C_{14}H_{20}O_3$ corresponding to a molecular ion of *m/z* 236.1419, two units fewer than that of **9**. Thus, taking into consideration its ^1H NMR spectrum, we assigned this new compound the structure **10**. In this spectrum a W-coupling was observed between H-8 and H-6. Thus, irradiation of the doublet at $\delta 6.51$, corresponding to the vinylic hydrogen, collapsed the *ddd* of H-6α at $\delta 2.26$ to a double doublet and sharpened the double doublet at $\delta 2.95$ of H-6β. This long-distance coupling was also observed in the spectra of **8** and **9**.

The absolute configuration and the same relative stereochemistry at C-4, C-5 and C-10 of **8–10** were given as those of teucdiols A (**1**) and B (**2**) from which these nor-sesquiterpenes must be biosynthetically derived.

The known compound 3-oxo-α-ionol (3,4-dehydro-blumenol C) (**11**) has also been isolated from this species and identified as the acetate derivative (**12**) by acetylation of the fraction containing it and on the basis of spectroscopic data (see Experimental). Hydrolysis of this acetate led to the alcohol **11**, which was identical with a substance previously obtained from *Nicotiana tabacum* [5]. Its dihydro-derivative, blumenol C, has been found in *Podocarpus blumei* [6].

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.

Plant material was collected in April, 1988, at El Caletón (La Matanza, Tenerife) and a voucher specimen has been deposited in the Herbarium of the Department of Botany, University of La Laguna (Tenerife).

The extraction and isolation of the chemical constituents of this plant have been described previously [3]. The mixt. of products obtained was rechromatographed, eluting with petrol–EtOAc, to give 7-epi-teucrenone (**4**) (7 mg), teuhetenone A (**6**) (12 mg), teuhetone (**5**) (21 mg), teuhetenone B (**7**) (5 mg) and tephyllone **8** (3 mg). Compounds **6**, **7** and **8** were isolated as mixt. with **5**. The products 9β-hydroxy-tephyllone (**9**) (1.5 mg) and 9-oxo-tephyllone (**10**) (1 mg) were separated by HPLC using a column of normal phase (1 × 25 cm) using hexane–*i*-PrOH (22:3) as eluent (3 ml min^{-1}).

7-Epi-teucrenone (**4**). $[M - H_2O]^+$ at *m/z* 216.1507. $C_{15}H_{20}O$ requires 216.1514; EIMS *m/z* (rel. int.): 234 $[M]^+$ (2), 216 (18), 201 (9), 161 (16), 149 (25), 135 (70), 123 (30). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3400, 1660, 1455, 1380, 915. ^1H NMR (200 MHz): δ 0.96 (3H, *s*), 1.85 and 1.92 (each 3H, *br s*), 2.35 (1H, *br d*, *J* = 12 Hz, H-5), 5.10 (2H, *br s*, H-12), 5.88 (1H, *br s*, H-3).

Teuhetone (**5**). Oil, $[M]^+$ at *m/z* 196.1451. $C_{12}H_{20}O_2$ requires 196.1463; EIMS *m/z* (rel. int.): 196 $[M]^+$ (68), 181 (13), 178 (19), 167 (41), 163 (26), 153 (71), 149 (20), 138 (55), 135 (22), 126 (26). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 1705, 1455, 1385, 930, 905. ^1H NMR (400 MHz): δ1.09 (3H, *s*, H-15), 1.14 (3H, *s*, H-14), 2.21 (1H, *d*, *J* = 15 Hz, H-5).

Teuhetenone A (**6**). ^1H NMR (200 MHz): δ1.31 and 1.42 (each 3H, *s*), 6.35 (1H, *s*, H-6).

Teuhetenone B (**7**). ^1H NMR (200 MHz): δ1.02 and 1.23 (each 3H, *s*), 2.36 (1H, *d*, *J* = 15 Hz, H-5), 5.81 (1H, *br d*, *J* = 10 Hz, H-8) and 6.68 (1H, *br d*, *J* = 10 Hz, H-9).

Tephyllone (**8**). $[M]^+$ at *m/z* 222.1621. $C_{14}H_{22}O_2$ requires 22.1619; EIMS *m/z* (rel. int.): 222 $[M]^+$ (10), 207 (11), 204 (41), 189 (23). ^1H NMR (200 MHz): δ0.81 and 1.22 (each 3H, s), 2.29 (3H, *s*), 6.80 (1H, *br s*, H-8).

9β-Hydroxy-tephyllone (**9**). $[M]^+$ at *m/z* 238.1575. $C_{14}H_{22}O_3$ requires 238.1568. EIMS *m/z* (rel. int.): 238 $[M]^+$ (25), 220, (15), 205 (18), 202 (22), 187 (50), 177 (26), 159 (56), 145 (29). ^1H NMR (200 MHz): δ0.77 and 1.28 (each 3H, *s*), 2.35 (3H, *s*), 2.68 (1H, *dd*, *J* = 18 and 4 Hz, H-6β), 3.64 (1H), *d*, *J* = 6 Hz, H-9), 6.72 (1H, *dd*, *J* = 6 and 2 Hz, H-8).

9-Oxo-tephyllone (**10**). $[M]^+$ at *m/z* 236.1419. $C_{14}H_{20}O_3$ requires 236.1412; EIMS *m/z* (rel. int.): 236 $[M]^+$ (57), 218 (24), 203 (10), 178 (22), 175 (44), 165 (37), 151 (77), 147 (24). ^1H NMR (200 MHz): δ1.02 and 1.33 (each 3H, *s*), 2.26 (1H, *ddd*, *J* = 18, 11 and 3 Hz, H-6α), 2.43 (3H, *s*), 2.95 (1H, *dd* *J* = 18 and 4 Hz, H-6β), 6.51 (1H, *d*, *J* = 3 Hz, H-8.

3-Oxo-α-ionol (*3,4-dehydro-blumenol C*) (**11**). This compound was obtained as the acetate (**12**) by acetylation of the fr. containing it. EIMS *m/z* (rel. int.): 250 $[M]^+$ (2), 175 (23), 163 (10), 159 (16), 134 (87), 123 (24), 108 (100), 91 (64). ^1H NMR (200 MHz): δ0.95 and 1.02 (each 3H, *s*), 1.31 (3H, *d*, *J* = 6 Hz), 1.88 (3H, *d*, *J* = 1.3 Hz), 2.06 (3H, *s*), 2.08 and 2.34 (each 1H, *d*, *J* = 16 Hz), 2.51 (1H, *t*), 5.34 (1H, *q*, *J* = 6 Hz), 5.59 (1H, *dd*, *J* = 2 and 3 Hz), 5.91 (1H, *br s*).

Alcohol (**11**). Obtained by hydrolysis of the acetate **12** with a methanolic saturated soln of Na_2CO_3, $[\alpha]_D$ + 168° ($CHCl_3$; *c* – 0.11), (lit. [5] + 177°); IR ν_{max} cm^{-1}: 3410, 1660, 1600. ^1H NMR (200 MHz): δ0.97 and 1.03 (each 3H, *s*), 1.29 (3H, *d*, *J* = 6 Hz), 1.89 (3H, *d*, *J* = 1.5 Hz), 2.07 and 2.33 (each 1H, *d*, *J* = 16 Hz), 2.52 (1H, *d*, *J* = 8 Hz), 4.34 (1H, *q*, *J* = 6 Hz), 5.60 (1H, *m*), 5.90 (1H, *br s*).

Acknowledgements—We thank Prof. P. Pérez de Paz (Department of Botany, University of La Laguna) for collecting and classifying the plant material, and the DGICYT, Ministry of Education and Science for financial support.

REFERENCES

1. Fraga, B. M., Guillermo, R., Hernández, M. G., Mestres, T. and Arteaga, J. M. (1991) *Phytochemistry* **30**, 3361.
2. Fraga, B. M., Diaz, C. E., Valdes, F. and Carmona, A. (1991) *Anal. Quim.* **87**, 929.
3. Fraga, B. M., Hernández, M. G., Mestres, T., Arteaga, J. M. and Perales, A. (1993) *Phytochemistry* **34**, 1083.
4. Eggert, H., Van Antwerp, C. L., Bhacca, N. S. and Djerassi, C. (1976) *J. Org. Chem.* **41**, 71.
5. Aasen, A. J., Kimland, B. and Enzell, C. R. (1971) *Acta Chim. Scand.* **25**, 1481.
6. Galbraith, M. N. and Horn, D. H. S. (1972) *J. Chem. Soc. Chem. Commun.* 113.