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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM LEPICEPHALUM* AND *TEUCRIUM BUXIFOLIUM*

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Key Word Index—*Teucrium lepicephalum*; *Teucrium buxifolium*; Labiatae; diterpenoids; neo-clerodane derivatives; teulepicin; 19-acetylteulepicin; teulepicephin.

Abstract—Three new neo-clerodane diterpenoids, teulepicin, 19-acetylteulepicin and teulepicephin, have been isolated, together with the previously known flavone cirsiliol from the aerial parts of *Teucrium lepicephalum*. The structures of the diterpenoids were established by chemical and spectroscopic means and by correlation with known substances. In addition, 19-acetylteulepicin and the already known neo-clerodane diterpenoid 19-acetylgnaphalin have been isolated from the species *T. buxifolium*.

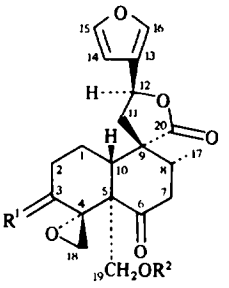
INTRODUCTION

In continuation of our studies on diterpenoid compounds from *Teucrium* species [1–4], we have now investigated the aerial parts of *T. buxifolium* Schreber and *T. lepicephalum* Pau, two species which grow in Spain. From the first material, the already known diterpenoid 19-acetylgnaphalin (**1**) [5–7] and a new neo-clerodane derivative, 19-acetylteulepicin (**3**) were isolated. The second species also yielded 19-acetylteulepicin (**3**) in addition to other neo-clerodane diterpenoids not previously described: teulepicin (**2**) and teulepicephin (**4**). The already known flavone cirsiliol (5,3′,4′-trihydroxy-6,7-dimethoxyflavone) [8] was also found in *T. lepicephalum*.

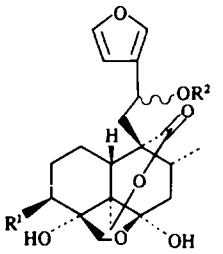
The structures of the new diterpenoids, 4α,18;15,16-diepoxy-3β,19-dihydroxy-6-keto-neo-clerodane-13(16),14-dien-20,12*S*-olide (**2**, teulepicin), 19-acetoxy-4α,18;15,16-diepoxy-3β-hydroxy-6-keto-neo-clerodane-13(16),14-dien-20,12*S*-olide (**3**, 19-acetylteulepicin) and 6β,18;15,16-diepoxy-3β,4α,12ξ-tetrahydroxy-neo-clerodane-13(16),14-dien-20,19-olide (**4**, teulepicephin), were established by chemical and spectroscopic means and, in the case of 19-acetylteulepicin, by correlation with a previously described compound.

RESULTS AND DISCUSSION

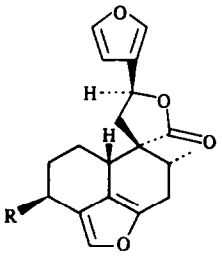
Teulepicin (**2**, $C_{20}H_{24}O_7$) and 19-acetylteulepicin (**3**, $C_{22}H_{26}O_8$) yielded the same derivative (**5**, $C_{24}H_{28}O_9$) after treatment with acetic anhydride–pyridine, thus establishing that compound **3** was a monoacetyl-derivative of teulepicin (**2**). The ^{1}H NMR spectrum of 19-acetylteulepicin (**3**, Table 1) suggested a structure closely related to 19-acetylgnaphalin (**1**), a neo-clerodane diterpenoid previously isolated from *T. gnaphalodes* [5] and *T. hyrcanicum* [6]. The structure of **1** was established by an X-ray diffraction analysis [7]. In fact, the only difference was the presence, in the ^{1}H NMR spectrum of compound **3**, of an additional secondary hydroxyl group equatorially oriented, whose geminal proton appeared at δ4.33 as a double-doublet ($J_{a,a'}$ = 11.7 Hz, $J_{a,e'}$ = 4.8 Hz). This equatorial hydroxyl group must be attached [2,9,10] to the C-3 carbon atom of a 19-acetoxy-4α,18;15,16-



	R^1	R^2
1	H_2	Ac
2	αH,βOH	H
3	αH,βOH	Ac
5	αH,βOAc	Ac
6	H_2	H
9	O	Ac



	R^1	R^2
4	OH	H
10	OAc	Ac
11	H	Ac (12*S*)
12	H	H (12*S*)



7 R = OH
8 R = H

diepoxy-6-keto-neo-clerodane-13(16),14-dien-20,12-olide structure.

Comparison of the ^{13}C NMR spectra of 19-acetylteulepicin (3, Table 2) and 19-acetylgnaphalin (1) [6, 11] firmly established structure 3 for the new diterpenoid, since the C-6–C-9, C-11–C-17, C-19 and C-20 carbon atom resonances were identical in both compounds, and the observed differences in the C-1–C-5, C-10 and C-18 carbon atoms were due [2, 9] to the presence in 19-acetylteulepicin (3) of an equatorial hydroxyl group on C-3 [compare the *γ-trans* effect on C-1 ($\Delta\delta - 1.5$) and C-5 ($\Delta\delta$ −0.3) with the *γ-gauche* effect on C-18 ($\Delta\delta$ −6.3)].

Table 1. ^1H NMR spectral data of compounds 2, 3, 5, 7 and 10 (300 MHz, TMS as internal standard)*

	2†	3‡	5‡	7‡	10†
H-1α	1.92 *br qd*	1.88 *br qd*	~1.9 §	1.35 *br qd*	§
H-1β	2.46 §	2.17 §	~2.1 §	~2.80 §	§
H-2α	2.46 §	2.33 *dddd*	2.30 *dddd*	2.39 *dddd*	§
H-2β	1.71 *br qd*	1.42 *br qd*	1.53 *br qd*	1.59 *dddd*	~1.65 §
H-3α	4.75 *dd*	4.33 *dd*	5.44 *ddd*	4.80 *ddd*	5.63 *dd*
H-7α	3.66 *t*	3.54 *t*	3.55 *t*	~2.80 §	§
H-7β	2.27 *dd*	2.17 *dd*	2.15 *dd*	~2.80 §	§
H-8β	2.14 *ddq*	2.03 *ddq*	2.02 *ddq*	2.26 *ddq*	~2.4 §
H-10β	2.10 §	2.00 §	2.18 *dd*	2.14 *br dd*	2.23 *br dd*
H_A-11	2.57 *dd*	2.45 *dd*	2.44 *dd*	2.50 *dd*	2.60 *dd*
H_B-11	2.65 *dd*	2.49 *dd*	2.48 *dd*	2.63 *dd*	3.05 *dd*
H-12	5.73 *t*	5.47 *t*	5.45 *t*	5.43 *t*	6.37 *dd*
H-14	6.65 *dd*	6.39 *dd*	6.38 *dd*	6.40 *dd*	6.69 *dd*
H-15	7.74 *t*	7.46 *t*	7.45 *t*	7.44 *t*	7.63 *t*
H-16	7.90 *m*	7.47*m*	7.46 *m*	7.47 *m*	7.86 *m*
Me-17	1.07 *d*	1.09 *d*	1.08 *d*	1.16 *d*	0.94 *d*
H_A-18‖	3.28 *d*	2.79 *d*	2.62 *d*	7.35 *d* **	4.47 *d*
H_B-18 ¶	3.69 *d*	3.40 *d*	3.35 *dd*	—	4.75 *d*
H_A-19	4.70 *d*	4.85 *d*	4.76 *d*	—	5.02 *d*
H_B-19	5.46 *d*	5.47 *d*	5.46 *d*	—	5.18 *d*
OAc	—	2.07 *s*	2.07 *s*	—	2.13 *s*
	—	—	2.01 *s*	—	1.94 *s*
J(Hz)					
1α,1β	13.1	13.4	§	13.0	§
1α,2α	3.6	4.1	2.5	2.0	§
1α,2β	13.1	13.4	12.5	13.0	§
1β,2α	§	§	3.9	6.5	§
1β,2β	4.4	5.2	5.6	2.4	§
2α,2β	13.0	12.0	12.5	13.0	§
2α,3α	5.3	4.8	5.1	6.0	6.0
2β,3α	11.7	11.7	12.5	10.0	11.3
7α,7β	13.6	13.8	13.7	§	§
7α,8β	13.6	13.8	13.7	6.8	§
7β,8β	4.0	3.8	4.0	5.6	§
8β,17	6.7	6.7	6.6	6.6	6.6
10β,1α	13.1	13.4	12.7	13.0	11.7
10β,1β	§	§	3.3	3.6	3.0
11A,11B	14.2	14.1	14.3	13.6	16.0
11A,12	8.6	8.6	8.6	8.1	10.3
11B,12	8.6	8.6	8.6	8.9	2.9
14,15	1.5	1.8	1.8	1.7	1.7
14,16	0.8	0.9	0.9	0.8	0.7
15,16	1.5	1.8	1.8	1.7	1.7
18A,18B	6.5	5.5	5.9	—	10.6
18B,3α	0	0	0.8	0.4 **	0
19A,19B	12.5	12.9	13.1	—	12.2

*Spectral parameters were obtained by first order approximation. All these assignments have been confirmed by double resonance experiments.

†In pyridine-d_5 solution.

‡In $CDCl_3$ solution.

§Overlapped signal.

‖Exo hydrogen with respect to ring B.

¶Endo hydrogen with respect to ring B.

**Furanic proton at C-18.

Table 2. ^{13}C NMR chemical shifts of compounds **3** and **10** (δ values from TMS)

Carbon	3*	10†
1	22.0 *t*‡	21.7 *t*
2	31.8 *t*	29.7 *t*
3	64.8 *d*	75.4 *d*
4	63.7 *s*	82.9 *s*
5	53.9 *s*	49.9 *s*§
6	206.0 *s*	107.1 *s*
7	43.3 *t*§	40.9 *t*
8	41.2 *d*	36.0 *d*
9	51.5 *s*	49.0 *s*§
10	54.9 *d*	42.7 *d*
11	43.1 *t*§	34.9 *t*
12	72.0 *d*	65.1 *d*
13	124.6 *s*	126.6 *s*
14	107.8 *d*	109.3 *d*
15	144.4 *d*	144.1 *d*
16	139.5 *d*	140.9 *d*
17	16.9 *q*	16.4 *q*
18	42.2 *t*	75.4 *t*
19	61.9 *t*	67.2 *t*
20	176.4 *s*	171.4 *s*
OAc	170.8 *s*	170.3 *s*
	—	170.0 *s*
	20.7 *q*	21.2 *q*
	—	20.9 *q*

*In $CDCl_3$ solution.
†In pyridine-d_5 solution.
‡SFORD multiplicity.
§These assignments may be reversed, but those given here are considered to be the most likely.

Thus, 19-acetylteulepicin (**3**) differs from compound **1** [5–7, 9, 11] only in an additional 3β-hydroxyl group.

In addition to the above conclusions, the neo-clerodane absolute configuration of compound **3** was inferred from its CD curve, which showed a negative Cotton effect ($\Delta\varepsilon_{301}$ −0.52) as does 19-acetylgnaphalin (**1**, $\Delta\varepsilon_{298.5}$ −0.48) [5, 7]. The 12*S*-configuration of the new diterpenoid (**3**) was consistent with NOE experiments, since irradiation of the Me-17 protons (δ1.09) produced NOE enhancements of the H-14 (δ6.39, 4%) and H-16 (δ7.47, 1%) signals, whereas no effect was observed on the signal of the H-12 proton (δ5.47). This indicated an exo relationship between the Me-17 and the H-12 proton [12, 13].

Thus, it was evident that 19-acetylteulepicin (**3**) is the 3β-hydroxy derivative of 19-acetylgnaphalin (**1**) [5–7] and teulepicin (**2**) is the 3β-hydroxy derivative of gnaphalin (**6**) [5, 7], because compounds **2** and **3** were correlated by acetylation yielding the same peracetyl derivative (**5**, see above). Furthermore, the easy transformation of teulepicin (**2**, see Experimental) into the furanoid 19-nor-neoclerodane derivative **7** (3β-hydroxy derivative of montanin A, **8** [14]) was also consistent [5, 7] with the structure depicted in formula **2** for this new diterpenoid.

In complete agreement with all the above conclusions, chromium trioxide–pyridine treatment of 19-acetylteulepicin (**3**) yielded a compound (**9**) identical in all respects with the epoxy derivative of tafricanin A [15, 16], a neo-clerodane diterpenoid previously isolated from *T. africanum*, the structure and absolute configuration of which were firmly established by X-ray diffraction analysis [15].

Teulepicephin (**4**) was isolated as an impure amorphous powder, the ^{1}H NMR spectrum of which was devoid of acetoxyl signals. It was purified by transformation into its diacetyl derivative **10** ($C_{24}H_{30}O_{10}$), whose IR spectrum showed hydroxyl (3460, 3340 cm^{-1}) absorptions. The ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) spectra of compound **10** were almost identical with those of the monoacetyl derivative (**11**) of teugnaphalodin (**12**), a neo-clerodane diterpenoid recently isolated by us from *T. gnaphalodes* [1]. In fact, the only differences were consistent with the presence in the derivative **10** of a 3β-acetoxyl group (δ5.63, 1H, *dd*, $J_{a,a'}$ = 11.3 Hz, $J_{a,c}$ = 6.0 Hz, H-3α proton; δ1.94, 3H, *s*, OAc) instead of the C-3 methylene grouping of compound **11** [1]. The identical chemical shift values of the C-6–C-9, C-11–C-17, C-19 and C-20 carbon atoms of compounds **10** (Table 2) and **11** [1], and the observed differences in the chemical shifts of the C-1 ($\Delta\delta$ −0.7), C-2 ($\Delta\delta$ +5.8), C-3 ($\Delta\delta$ +45.3), C-4 ($\Delta\delta$ +1.5), C-5 ($\Delta\delta$ +1.9), C-10 ($\Delta\delta$ −0.2) and C-18 ($\Delta\delta$ −1.6) carbons of the former (**10**) with respect to the latter (**11**) [1], clearly established that the diacetyl derivative of teulepicephin possessed a structure and relative stereochemistry such as those depicted in formula **10**. Thus, teulepicephin possessed structure **4**.

The configuration at the C-12 centre and the absolute configuration of teulepicephin (**4**) were not ascertained. However, compound **4** is believed to belong to the neo-clerodane series like teulepicin (**2**) and 19-acetylteulepicin (**3**), co-occurring in the same species. Moreover, all the diterpenoids previously isolated from *Teucrium* species [1–7, 9–16 and references therein] belong to the neo-clerodane series.

EXPERIMENTAL

Mps are uncorr. For general details on methods, see refs [1–4, 7, 9, 11–13, 16]. Plant materials of *T. lepicephalum* and *T. buxifolium* were collected in July 1985, near Altea (Alicante, Spain) and at Orihuela (Alicante, Spain), respectively, and voucher specimens of both species were deposited in the Herbarium of the 'Dipartimento di Biologia' of the University of Milan, Italy.

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. lepicephalum* Pau aerial parts (390 g) were extracted with Me_2CO (1.5 l.) at room temp. for 1 week. The extract (19 g) was chromatographed on a silica gel column (Merck No. 7734, deactivated with 15% H_2O, 300 g), eluted with petrol (alkanes, fats and waxes), then petrol–EtOAc mixtures, yielding the following compounds in order of elution: cirsiliol (1.2 g) [8], 19-acetylteulepicin (**3**, 900 mg), impure teulepicephin (**4**, 700 mg) and teulepicin (**2**, 1 g).

Identical treatment of the aerial parts of *T. buxifolium* Schreber (126 g) yielded 7 g of an extract from which 19-acetylgnaphalin (**1**, 16 mg) [5–7] and 19-acetylteulepicin (**3**, 10 mg) were isolated.

The previously known compounds, cirsiliol [8] and 19-acetylgnaphalin (**1**) [5–7], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

Teulepicin (**2**). Mp 174–176° (decomp., EtOAc); $[\alpha]_D^{20}$ +59.5° (MeOH; *c* 0.441); CD nm ($\Delta\varepsilon$): 245 (0), 302 (−0.87), 345 (0) (MeOH; *c* 0.032); IR ν_{max}^{KBr} cm^{-1}: 3560, 3510, 3420, 3200, 3160,

3115, 3020, 2950, 2880, 1760, 1715, 1503, 1450, 1345, 1320, 1175, 1040, 1025, 905, 875, 815, 745, 675; ^{1}H NMR (300 MHz, pyridine-d_5): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): $[M]^+$ absent, 328 $[M-CH_2O-H_2O]^+$ (19), 310 (3), 234 (15), 201 (45), 132 (50), 105 (31), 96 (100), 95 (52), 91 (36), 81 (46), 77 (37), 55 (19), 43 (69). (Found: C, 63.69; H, 6.36. $C_{20}H_{24}O_7$ requires: C, 63.82; H, 6.43%.)

19-*Acetylteulepicin* (**3**). 204–206° (EtOAc–*n*-hexane); $[\alpha]_D^{20}$ +73.4° ($CHCl_3$; *c* 0.496); CD nm ($\Delta\varepsilon$): 250 (0), 301 (−0.52), 350 (0) (MeOH; *c* 0.077); IR ν_{max}^{KBr} cm^{-1}: 3570, 3480, 3140, 3130, 3110, 3010, 2970, 2940, 2870, 1760, 1740, 1720, 1503, 1435, 1385, 1265, 1240, 1175, 1035, 900, 875, 805, 735; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (75.4 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 418 $[M]^+$ (0.2), 370 (1.2), 345 (2.4), 327 (68), 201 (8), 178 (12), 161 (13), 133 (12), 121 (14), 105 (15), 95 (51), 94 (23), 91 (22), 81 (34), 69 (23), 55 (17), 43 (100). (Found: C, 63.08; H, 6.32. $C_{22}H_{26}O_8$ requires: C, 63.15; H, 6.26%.)

Peracetate **5** *from compounds* **2** *and* **3**. Ac_2O–pyridine treatment of compounds **2** and **3** gave the same derivative **5**: mp 189–190.5° (EtOAc–*n*-hexane); $[\alpha]_D^{18}$ +36.6° ($CHCl_3$; *c* 0.172); IR ν_{max}^{KBr} cm^{-1}: 3125, 3020, 2970, 2885, 1760, 1740 (br), 1715, 1505, 1475, 1385, 1365, 1250, 1230, 1180, 1040, 910, 875, 785, 735; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 460 $[M]^+$ (0.2), 369 (4), 328 (28), 309 (10), 300 (10), 201 (9), 179 (16), 149 (16), 133 (13), 132 (15), 121 (13), 105 (12), 95 (36), 94 (18), 91 (16), 81 (24), 69 (19), 43 (100). (Found: C, 62.76; H, 6.21. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13%.)

Compound **7** *from teulepicin* (**2**). Treatment of teulepicin (**2**) with methanolic KOH at room temp. [5] or slow chromatography through silica gel quantitatively yielded compound **7**: mp 179–182° (decomp., EtOAc–*n*-hexane); $[\alpha]_D^{20}$ +136.3° ($CHCl_3$; *c* 0.364); IR ν_{max}^{KBr} cm^{-1}: 3400, 3150, 3130, 3120, 2920, 2860, 1760, 1730, 1670, 1565, 1550, 1507, 1440, 1345, 1185, 1165, 1050, 1020, 975, 925, 875, 810, 740, 720; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 328 $[M]^+$ (26), 310 (3), 234 (18), 201 (52), 132 (41), 105 (13), 96 (100), 95 (44), 91 (25), 81 (39), 77 (23), 43 (12). (Found: C, 69.62; H, 6.19. $C_{19}H_{20}O_5$ requires: C, 69.50; H, 6.14%.)

Compound **9** *from* 19-*acetylteulepicin* (**3**). CrO_3–pyridine oxidation of compound **3** (44 mg) in the usual manner gave a substance [30 mg, mp 212–214° (Me_2CO–*n*-hexane); $[\alpha]_D^{18}$ +115.1° ($CHCl_3$; *c* 0.194)] identical in all respects (IR, ^{1}H NMR, MS, TLC) with the previously described compound **9** [lit. [15]: mp 200°; $[\alpha]_D^{20}$ +112° ($CHCl_3$; *c* 0.7); [16]: mp 210–212° (Me_2CO–*n*-hexane); $[\alpha]_D^{19}$ +110.1° ($CHCl_3$; *c* 0.218)].

Teulepicephin (**4**) *and its* 3β, 12ξ-*diacetyl-derivative* (**10**). Impure teulepicephin (**4**) was an amorphous powder which showed a ^{1}H NMR spectrum without acetoxyl signals. Ac_2O–pyridine treatment of this material (200 mg) in the usual manner, followed by crystallization (EtOAc) of the crude product of the reaction gave pure **10** (170 mg), mp 217–220°; $[\alpha]_D^{18}$ −63.7° (pyridine; *c* 0.157); IR ν_{max}^{KBr} cm^{-1}: 3460, 3340, 3150, 3140, 3120, 2990, 2950, 2900, 1735 (br), 1710, 1505, 1415, 1380, 1370, 1250, 1160, 1025, 960, 875, 805, 790, 740; ^{1}H NMR (300 MHz, pyridine-d_5): see Table 1; ^{13}C NMR (75.4 MHz, pyridine-d_5): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): $[M]^+$ absent, 436 $[M-C_2H_2O]^+$ (15), 418 $[M-AcOH]^+$ (13), 400 (4), 375 (0.5), 349 (1), 328 (1), 137 (7), 95 (17), 94 (13), 91 (10), 81 (13), 69 (14), 43 (100). (Found: C, 60.03; H, 6.18. $C_{24}H_{30}O_{10}$ requires: C, 60.24; H, 6.32%.)

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