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DITERPENOIDS FROM *TEUCRIUM SCORODONIA*, THREE NEO-CLERODANE DERIVATIVES

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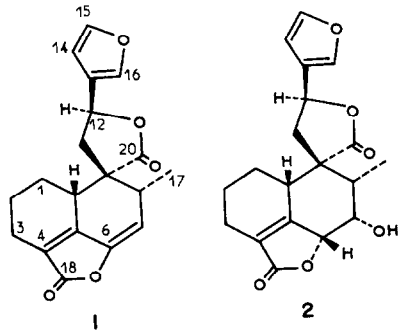
Key Word Index—*Teucrium scorodonia*; Labiatae; new neo-clerodane diterpenoids; teuscorolide; teuscorodal; teuscorodol.

Abstract—From the aerial parts of *Teucrium scorodonia* the previously known diterpenoid teupolin I and the flavone luteolin have been isolated. In addition, three new neo-clerodane derivatives have also been obtained from the same source. The structures of these new natural diterpenoids have been established by chemical and spectroscopic means and by correlation with known products.

INTRODUCTION

In a continuation of our studies on diterpenic compounds from the *Teucrium* species [1–4], we have now investigated *T. scorodonia* L., a species which grows all over Europe. From the aerial parts of this plant four diterpenic compounds have been isolated, one of which is the previously known teupolin I (19-acetoxy-6α-hydroxy-4α, 18:15, 16-diepoxy-neo-clerodane-13(16), 14-dien-20, 12*S*-olide) [5, 6] and the other three are new substances, whose structures are established as 15,16-epoxy-19-nor-neo-clerodane-4,6,13(16),14-tetraene-18,6:20,12*S*-diolide (**1**, teuscorolide), 19-acetoxy-6β-hydroxy-15,16-epoxy-neo-clerodane-3,13(16),14-trien-20,12*S*-olid-18-al (**3**, teuscorodal), and 19-acetoxy-6β,18-dihydroxy-15,16-epoxy-neo-clerodane-3,13(16),14-trien-20,12*S*-olide (**4**, teuscorodol). In addition, the known flavone luteolin has also been isolated from the same source.



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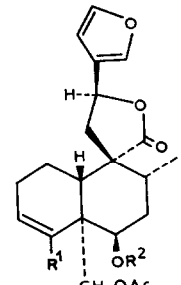

	R^1	R^2
3	CHO	H
4	CH_2OH	H
5	CH_2OAc	Ac

RESULTS AND DISCUSSION

The first of the new diterpenoids (teuscorolide, **1**), $C_{19}H_{18}O_5$, showed physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^1H NMR and MS) data identical with those previously reported [7–9] for a synthetic derivative of teucrin A (see Table 1 and Experimental). As the structure and absolute configuration of teucrin A (**2**) have been firmly established [8, 9], and acetic anhydride–sodium acetate treatment of it yielded teuscorolide (see ref. [7] and Experimental), it is evident that the structure and absolute configuration of this new diterpenoid are represented by formula **1**.

The second new diterpenoid, teuscorodal (**3**), had a molecular formula $C_{22}H_{26}O_7$ and its IR spectrum showed hydroxyl (3500 cm^{-1}), furanic (3160, 1505, 880 cm^{-1}), α,β-unsaturated aldehyde (2730, 1685, 1630 cm^{-1}), γ-lactone (1760 cm^{-1}) and acetate (1740, 1240 cm^{-1}) absorptions. The presence of an α,β-unsaturated aldehyde grouping was supported by UV absorption at λ_{max} 225.5 nm (ϵ 10 400) [10] and then confirmed by sodium borohydride reduction of **3** to give a $C_{22}H_{28}O_7$ derivative (**4**), the UV spectrum of which showed only furanic absorption at λ_{max} 211 nm (ϵ 5100). The ^1H NMR spectrum of teuscorodal (**3**, Table 1) suggested a structure with a β-substituted furan ring, a C-20–C-12 γ-lactone group and a C-17 secondary methyl group identical with those found in teuscorolide (**1**). In addition, the ^1H NMR spectrum showed signals for an α,β-unsaturated aldehyde grouping [δ 9.40 (1H, *s*) and 6.83 (1H, *t*, J = 3.5 Hz)] [10], an acetylated hydroxy methylene group attached to a fully substituted carbon atom (an AB system at δ

Table 1. ^{1}H NMR data of compounds **1** and **3–5** (90 MHz, $CDCl_3$, TMS as int. standard)

	1	3	4	5
H-3	*	6.83 *t* (J = 3.5 Hz)	5.88 *br t* (J = 3 Hz)	5.76 *br t* (J = 3 Hz)
H-6	—	4.97 *m* ($W_{1/2}$ = 6 Hz)	4.65 *m* ($W_{1/2}$ = 6 Hz_2)	5.30 *m* ($W_{1/2}$ = 6 Hz)
H-7	5.28 *d* (J = 1.5 Hz)	*	*	*
2H-11	2.50 *dd*, 2.43 *dd* ($J_{11A,11B}$ = 11 Hz) ($J_{11,12}$ = 8.5 Hz)	*	*	*
H-12	5.40 *t* (J = 8.5 Hz)	5.39 *t* (J = 8.5 Hz)	5.40 *t* (J = 8.5 Hz)	5.41 *t* (J = 8.5 Hz)
H-14	6.38 *m* ($W_{1/2}$ = 4 Hz)	6.40 *m* ($W_{1/2}$ = 4.5 Hz)	6.38 *m* ($W_{1/2}$ = 4.5 Hz)	6.40 *m* ($W_{1/2}$ = 4 Hz)
H-15	7.47 *m* ($W_{1/2}$ = 5 Hz)	7.42 *m* ($W_{1/2}$ = 4 Hz)	7.43 *m* ($W_{1/2}$ = 5 Hz)	7.43 *m* ($W_{1/2}$ = 4.5 Hz)
H-16	7.47 *m*	7.42 *m*	7.43 *m*	7.43 *m*
3H-17	1.23 *d* (J = 7.5 Hz)	1.02 *d* (J = 6.5 Hz)	1.00 *d* (J = 6.5 Hz)	1.00 *d* (J = 6.5 Hz)
H-18†	—	9.40 *s*	4.20 *br s* ($W_{1/2}$ = 5 Hz)	4.48 *br s* ($W_{1/2}$ = 4.5 Hz)
2H-19	—	4.82 *d*, 4.38 *d* (J = 11.5 Hz)	4.33 *d*, 3.90 *d* (J = 11.5 Hz)	4.80 *d*, 4.53 *d* (J = 11.5 Hz)
-OAc	—	1.96 *s*	1.97 *s*	2.10 *s*, 2.05 *s* 2.01 *s*

*Could not be identified.
†One proton signal in **3**, two proton signal in **4** and **5**.

4.82 and 4.38 (J_{AB} = 11.5 Hz) and a 3H singlet at 1.96) [6, 11] and, finally, an equatorial proton geminal to an axial hydroxyl group (δ 4.97, *m*, $W_{1/2}$ = 6 Hz). Moreover, the ^{1}H NMR spectrum of the sodium borohydride reduction product of teuscorodal (compound **4**, Table 1) confirmed all the above conclusions, since it showed a diamagnetically shifted olefinic proton ($\Delta\delta$ − 0.95) and the signal of the aldehydric proton of compound **3** was substituted by a two proton broadened singlet ($W_{1/2}$ = 5 Hz) at δ 4.20. On the other hand, the ^{1}H NMR spectrum of compound **4** showed a strong diamagnetic shift in the AB system of the C-19 protons ($\Delta\delta$ − 0.49), which may be due to a transacetylation reaction from the C-19 to the C-18 hydroxyl groups.

However, selective oxidation of compound **4** with chromate in HMPA [12, 13], quantitatively yielded natural teuscorodal (**3**); thus, the allylic alcohol in compound **4** is not acetylated and the unexpected [10] upfield shift of the C-19 protons of this compound must be due to the C-6 hydroxyl, C-18 hydroxyl and C-19 acetate interactions [14]. Furthermore, acetic anhydride–pyridine treatment of compound **4** yielded the triacetyl derivative **5**, the ^{1}H NMR spectrum of which showed C-18 and C-19 proton resonances (Table 1) in agreement with the previously reported values for 3-dehydro-6β,18,19-triacetoxy-neoclerodanes [11].

All the above data must be accomodated on a structure as **3** for teuscorodal, in which the secondary hydroxyl group is placed at the C-6 axial position on the basis of the following considerations. (1) The ^{1}H NMR signal of the geminal proton of the secondary hydroxyl group appeared as a multiplet with a $W_{1/2}$ = 6 Hz, thus it is equatorial. (2) This equatorial proton was shifted upfield ($\Delta\delta$ − 0.32) when the C-18 aldehyde group was reduced (compounds **3** and **4**). Thus, it must be near to the C-18 function, and as C-2 is a methylene grouping (H-3 appeared as a triplet in the ^{1}H NMR spectra of compounds **3–5**, see above), only the axial C-6 position is likely for the secondary hydroxyl group. (3) This conclusion was also supported by the fact that neither of the two protons at C-19 in **3–5** (Table 1) showed any long-range coupling in their ^{1}H NMR spectra. The requirement for the existence of such a long-range coupling is the presence of an axial proton at C-6 [10, 2].

Finally, the absolute neo-clerodane configuration [15] depicted in **3** for teuscorodal was established by application of Horeau's method [16], which defined as 6*R* the absolute configuration of its axial alcohol.

The last diterpenoid was named teuscorodol. It possesses the structure and absolute configuration depicted in **4**, since it was correlated with teuscorodal (**3**) by selective allylic oxidation, and also yielded compound **5** by acetic anhydride–pyridine treatment. Teuscorodol (**4**) is thus the 7-deoxy-derivative of lolin [11], a neo-clerodane diterpenoid isolated from *T. capitatum* and whose structure was established by X-ray analysis.

EXPERIMENTAL

Mps (Kofler apparatus) are uncorr. Plant materials were collected in July 1981, near Rodiezmo (León, Spain), and voucher specimens were deposited in the Herbarium of the Faculty of Biology, Oviedo University, Spain.

Isolation of the diterpenoids. Dried and finely powdered *T. scorodonia* L. aerial parts, (1.5 kg) were extracted with

Me_2CO (15 l.) at room temp. for 1 week. After filtration the solvent was evaporated yielding a gum (120 g) which was repeatedly chromatographed over Si gel (Merck, No. 7734, deactivated with 15% H_2O) dry columns with *n*-hexane–EtOAc and $CHCl_3$–MeOH mixtures as eluents, yielding the following compounds in order of elution: teuscorolide (**1**, 60 mg), teuscorodal (**3**, 276 mg), teuscorodol (**4**, 81 mg), teupolin I (19 mg) [5, 6] and the flavone luteolin (7 mg). The previously known products (teupolin I and luteolin) were identified by their physical (mp $[\alpha]_D$) and spectroscopic (IR, UV, ^1H NMR, MS) data and by comparison with authentic samples.

Teuscorolide (**1**). Mp 198–200° (from Me_2CO–*n*-hexane); $[\alpha]_D^{20}$ +13.5° ($CHCl_3$; *c* 0.31); IR ν_{max}^{KBr} cm^{-1} 3160, 3130, 1508, 880 (furan ring); 1775 (γ-lactone); 3075, 1755, 1670, 1600 (α,β-unsatd enol-γ-lactone); 2995, 2960, 2850, 1440, 1360, 1220, 1185, 1165, 1145, 1030, 975, 955, 850, 795, 745; UV λ_{max}^{EtOH} nm (log ε): 210 (3.80) (furan ring); 281.5 (4.24) (α,β-unsatd enol-γ-lactone); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV *m/z* (rel. int.): 326 $[M]^+$ (56), 311 (4), 267 (7), 232 (77), 187 (100), 173 (24), 160 (38), 115 (28), 95 (56), 94 (28), 91 (35), 81 (37), 77 (56), 69 (60). (Found: C, 69.86; H, 5.60. Calc. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56%.) Identical in all respects to the product previously described [7–9]: mp 198–200°; $[\alpha]_D$ +18° ($CHCl_3$; *c* 3.4).

Teuscorolide (**1**) *fom teucrin A* (**2**). A mixture of 100 mg teucrin A- (**2**) [3, 7–9], 2 ml Ac_2O and 260 mg fused NaOAc was boiled under reflux for 5 hr. Work-up in the usual manner yielded 70 mg of a compound identical (mp, mmp, $[\alpha]_D$, IR, UV, ^1H NMR and MS) in all respects with natural teuscorolide (**1**).

Teuscorodal (**3**). Mp 60–63° (*n*-hexane); $[\alpha]_D^{20}$ −51.4° ($CHCl_3$; *c* 0.36); IR ν_{max}^{KBr} cm^{-1}: 3500 (OH); 3160, 1505, 880 (furan ring); 2730, 1685, 1630 (α,β-unsatd aldehyde); 1760 (γ-lactone); 1740, 1240 (acetate); 2980, 1460, 1390, 1370, 1155, 1030, 935, 810, 725; UV λ_{max}^{EtOH} nm (log ε): 210 sh. (3.83) (furan ring); 225.5 (4.02) (α,β-unsatd aldehyde); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 402 $[M]^+$ (1), 384 (3), 372 (4), 354 (1), 342 (2), 330 (7), 329 (3), 324 (6), 311 (9), 248 (4), 145 (7), 133 (8), 121 (8), 105 (13), 96 (18), 95 (43), 94 (16), 91 (23), 81 (31), 79 (16), 77 (20), 53 (16), 43 (100). (Found: C, 65.41; H, 6.36. $C_{22}H_{26}O_7$ requires: C, 65.66; H, 6.51%.)

Teuscorodol (**4**). An amorphous powder which melts at 65–70°; $[\alpha]_D^{20}$ −55.8° ($CHCl_3$; *c* 0.807); IR ν_{max}^{KBr} cm^{-1}: 3380 *br* (OH); 3160, 3120, 1505, 880 (furan ring); 3050, 1660 (olefinic double bond); 1760 (γ-lactone); 1740, 1240 (acetate); 2980, 2900, 2850 1460, 1390, 1370, 1180, 1155, 1030, 1005, 960, 925, 800, 735; UV λ_{max}^{EtOH} nm (log ε): 211 (3.70) (furan ring); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 404 $[M]^+$ (1), 386 (2), 344 (3), 326 (11), 313 (11), 281 (4), 179 (7), 149 (12), 105 (19), 96 (17), 95 (50), 91 (27), 81 (33), 43 (100). (Found: C, 65.26; H, 6.83. $C_{22}H_{28}O_7$ requires: C 65.33; H, 6.98%.)

Teuscorodol (**4**) *from teuscorodal* (**3**). A MeOH–dioxane (1:1) soln of compound **3** (100 mg) was treated with excess $NaBH_4$ for 10 min yielding a compound identical (TLC, $[\alpha]_D$, IR, UV, ^1H NMR and MS) in all respects with natural teuscorodol (**4**).

Teuscorodal (**3**) *from teuscorodol* (**4**). A soln of **4** (30 mg) in HMPA (1 ml) was added to an stirred soln of CrO_3 (30 mg) in HMPA (1 ml) and left at room temp. for 36 hr. The soln was then diluted with H_2O and extracted with Et_2O. Evaporation of the solvent left a residue of a compound which was crystallized from *n*-hexane (19 mg). This compound was identical (mp, mmp, TLC, $[\alpha]_D$, IR, UV, ^1H NMR and MS) in all respects with natural teuscorodal (**3**).

Compound **5**. Ac_2O–C_5H_5N treatment of both teuscorodol (**4**) and the $NaBH_4$ reduction product of teuscorodal, yielded the same derivative (**5**) as a syrup, $[\alpha]_D^{20}$ −36.9° ($CHCl_3$; *c* 0.97); IR ν_{max}^{NaCl} cm^{-1}; 3160, 3150, 1505, 880 (furan ring); 3040, 1665 (olefinic double bond); 1770 (γ-lactone); 1740 *br*, 1250 (acetates); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): $[M]^+$ absent, 428 $[M-60]^+$ (7), 386 (3), 368 (3), 338 (3), 326 (27), 296 (6), 251 (5), 232 (6), 199 (7), 168 (10), 156 (14), 96 (26), 95 (42), 91 (16), 81 (24), 43 (100). (Found: C, 64.09; H, 6.48. $C_{26}H_{32}O_9$ requires: C, 63.92; H, 6.60%.)

Application of Horeau's method to compound **3**. Performed in the usual manner [16]. Compound **3** (0.051 mmol); (±)-α-phenylbutyric anhydride (0.293 mol); $\alpha_1 = -0.262$; $\alpha_2 = -0.300$; $\alpha_1 - 1.1\alpha_2 = +0.068$; configuration 6*R*.

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