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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM BOTRYS*

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Key Word Index—*Teucrium botrys*; Labiatae; new neo-clerodane diterpenoids; 19-deacetylteuscorodol; teubotrin; teucvidin; montanin D; teuchamaedrin C; 6β-hydroxyteuscordin.

Abstract—From the aerial parts of *Teucrium botrys* two new neo-clerodane diterpenoids, 19-deacetylteuscorodol and teubotrin, have been isolated, together with the previously known diterpenes teucvidin, montanin D, teuchamaedrin C and 6β-hydroxyteuscordin. The structures of 19-deacetylteuscorodol [15,16-epoxy-6β,18,19-trihydroxy-neo-cleroda-3,13(16),14-trien-20,12*S*-olide] and teubotrin [15,16-epoxy-6β,12ξ,18-trihydroxy-neo-cleroda-3,13(16),14-trien-20,19-olide] were established by chemical and spectroscopic means and, in the case of 19-deacetylteuscorodol, by correlation with a previously known compound.

INTRODUCTION

In continuation of our studies on diterpenoid compounds from the *Teucrium* species [1–4], we have now investigated *T. botrys* L., a species which grows all over Europe. From the aerial parts of a sample of this plant collected at Beceite (Teruel, Spain) the previously known diterpenoid 6β-hydroxyteuscordin [5, 6] has been isolated as the sole detectable diterpenoid constituent. However, from another sample of the same species collected at Cervera del Maestre (Castellón, Spain) five diterpenoid compounds have been isolated, three of which are the previously known teucvidin [7], montanin D [8] and teuchamaedrin C [9], and the other two are new substances, whose structures were established as 15,16-epoxy-6β,18,19-trihydroxy-neo-cleroda-3,13(16),14-trien-20,12*S*-olide (**1**, 19-deacetylteuscorodol) and 15,16-epoxy-6β,12ξ,18-trihydroxy-neo-cleroda-3,13(16),14-trien-20,19-olide (**2**, teubotrin).

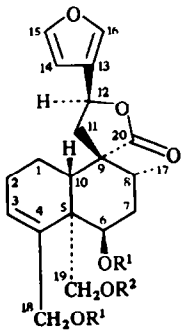
From a chemotaxonomic point of view it is important to note that the above result clearly suggests that the neo-clerodanes found in *Teucrium* are not adequate as chemical characters for taxonomic purposes.

RESULTS AND DISCUSSION

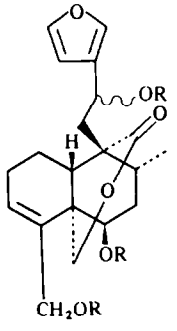
19-Deacetylteuscorodol (**1**, $C_{20}H_{26}O_6$) showed an IR spectrum with hydroxyl (3440, 3350, 3270 cm^{-1}), furanoid (3140, 3120, 1506, 875 cm^{-1}) and γ-lactone (1762 cm^{-1}) absorptions. Its ^1H NMR spectrum (Table 1) was almost identical with that of teuscorodol (**3**), a diterpenoid previously isolated from *T. scorodonia* [10]. In fact, the small differences between the ^1H NMR spectra of teuscorodol (**3**) [10] and compound **1** (Table 1) would seem to be due merely to the absence in the latter of the 19-acetyl group present in the former. In agreement with this assumption, acetic anhydride–pyridine treatment of compound **1** gave a triacetyl derivative (**4**) identical in all respects ($[\alpha]_D$, IR, ^1H NMR, MS, TLC) with the peracetyl derivative of teuscorodol [10].

In addition to the chemical correlation of diterpenoid **1** with compound **4** [10], its 12*S*-configuration was in agreement with NOE experiments, since irradiation of the Me-17 protons (δ1.13) produced NOE enhancements of the H-14 (δ6.62, 4%) and H-16 (δ7.83, 1.5%) proton signals, and no effect was observed in the signal of the H-12 proton (δ5.59) [11, 12]. Moreover, the ^{13}C NMR spectrum of the new diterpenoid (**1**, Table 2) was in complete agreement with all the above conclusions. Thus, the new diterpenoid (**1**) is the 19-deacetyl derivative of teuscorodol (**3**) [10] and the 12-epimer of teusalvin C, a neo-clerodane derivative recently isolated by us from *T. salviastrum* [4].

The other new diterpenoid isolated from *T. botrys*, teubotrin ($C_{20}H_{26}O_6$), possesses structure **2**, which was established from its ^1H NMR and ^{13}C NMR data given in Tables 1 and 2, respectively. Comparison of the ^1H NMR spectra of compounds **1** and **2** (Table 1) shows a close similarity between them. The difference in the chemical



1 $R^1 = R^2 = H$
3 $R^1 = H$, $R^2 = Ac$
4 $R^1 = R^2 = Ac$



2 R = H
5 R = Ac

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Table 1. ^{1}H NMR spectral data of compounds 1, 2 and 5 (TMS as internal standard)*

	1†	2‡	5‡
H-3	6.02 *br t*	5.97 *br t*	5.95 *br dd*
H-6α	5.06 *dd*	4.27 *t*	5.17 *t*
H-7α	2.63 *td*	1.69 *ddd*	1.65 *ddd*
H-7β	1.93 §	1.92 *ddd*	1.98 §
H-10β	2.77 *dd*	2.75 *dd*	§
H_A-11	2.50 *d*	2.21 *dd*	2.42 *dd*
H_B-11	2.50 *d*	2.42 *dd*	2.63 *dd*
H-12	5.59 *t*	4.88 *dd*	6.05 *dd*
H-14	6.62 *dd*	6.43 *dd*	6.43 *dd*
H-15	7.69 *t*	7.38 *t*	7.39 *t*
H-16	7.83 *m*	7.41 *m*	7.45 *m*
Me-17	1.13 *d*	0.86 *d*	0.87 *d*
H_A-18	4.78 *br d*	4.04 *br d*	4.24 *br d*
H_B-18	4.94 *br d*	4.09 *br d*	4.52 *br d*
H_A-19	4.42 *d*	4.20 *d*	4.31 *d*
H_B-19	5.05 *d*	4.38 *d*	4.44 *d*
OAc	—	—	2.07 *s*
	—	—	2.04 *s*
	—	—	2.04 *s*
J (Hz)			
1α,10β	13.6	13.0	§
1β,10β	2.7	2.6	§
2α,3	3.5	3.6	4.5
2β,3	3.5	3.6	2.3
6α,7α	1.9	2.6	2.8
6α,7β	3.4	2.6	2.8
7α,7β	12.5	14.8	15.0
7α,8β	12.5	13.4	13.1
7β,8β	§	4.1	§
8β,17	6.2	6.6	6.8
11A,11B	0.0	15.9	16.2
11A,12	8.7	9.7	9.8
11B,12	8.7	2.2	3.4
14,15	1.7	1.7	1.8
14,16	0.9	0.9	0.6
15,16	1.7	1.7	1.8
18A,18B	11.5	11.6	12.6
19A,19B	11.1	12.2	12.8
18,3	<0.3	<0.3	<0.3

*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.

shifts of the C-12 protons (δ5.59 in **1** and 4.88 in **2**) can be attributed to the fact that compound **2** has a C-12 hydroxyl group and a C-20–C-19 δ-lactone (IR spectrum: ν_{CO} 1715 cm^{-1}) instead of the C-19 hydroxyl group and the C-20–C-12 γ-lactone (IR spectrum: ν_{CO} 1762 cm^{-1}) functions of compound **1** [4, 9, 13, 14]. Moreover, acetic anhydride–pyridine treatment of teubotrin (**2**) yielded the triacetyl derivative **5**, the ^{1}H NMR spectrum of which (Table 1) showed the signal of the C-12 proton at δ6.05, which is characteristic of an acetylated C-12 hydroxyl group in neo-clerodane diterpenoids [4, 9, 13–15]. These structural differences between compounds **1** and **2** were clearly reflected in their ^{13}C NMR spectra (Table 2). In particular, the chemical shifts of the C-12, C-19 and C-20 carbon atoms of compound **2** (δ62.6 *d*, 74.7 *t* and 173.3 *s*), as compared with those of **1** (δ72.0 *d*, 65.6 *t* and 178.3 *s*), rigorously established [4, 9, 13] that teubotrin (**2**) differs from 19-deacetylteuscorodol (**1**) in the lactone arrangement.

The stereochemistry at the C-12 centre and the absolute configuration of teubotrin were not ascertained. However, the decalin moiety of compound **2** is believed to belong to the neo-clerodane series like the other diterpenoids co-occurring in the same species. Moreover, all the diterpenoids until now isolated from *Teucrium* [1–15 and references therein], and whose structures have been rigorously established, belong to the neo-clerodane series.

EXPERIMENTAL

Mps are uncorr. For general details on methods, see refs [1–4, 10–15]. Plant materials were collected in June 1985 at Beceite (Teruel, Spain) and near Cervera del Maestre (Castellón, Spain), and voucher specimens were deposited in the Herbarium of the Royal Botanic Garden of Madrid, Spain.

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. botrys* L. aerial parts (280 g, collected near Cervera del Maestre) were extracted with Me_2CO (2 l.) at room temp. for a week. The extract (11 g) was chromatographed on a silica gel column (Merck, No. 7734, deactivated with 15% H_2O, 300 g) eluted with *n*-hexane, *n*-hexane–EtOAc mixtures, EtOAc, $CHCl_3$ and $CHCl_3$–MeOH mixtures, yielding the following compounds in order of elution: teucvidin (150 mg) [7], montanin D (60 mg) [8], teuchamaedrin C (5 mg) [9], 19-deacetylteuscorodol (**1**, 20 mg) and teubotrin (**2**, 25 mg).

Plant materials of the same species collected at Beceite (60 g) yielded an extract (5 g) from which only β-hydroxyteuscordin (7 mg) [5, 6] was isolated.

The previously known diterpenoids, teucvidin [7], montanin D [8], teuchamaedrin C [9] and β-hydroxyteuscordin [5, 6], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data and by comparison (TLC, mmp) with authentic samples.

19-Deacetylteuscorodol (**1**). Mp 200–202° (EtOAc–*n*-hexane); $[\alpha]_D^{24}$ −46.2° (pyridine; *c* 0.197); IR ν_{max}^{KBr} cm^{-1}: 3440, 3350, 3270, 3140, 3120, 3010, 2980, 2940, 2880, 1762, 1506, 1475, 1380, 1325, 1200, 1180, 1160, 1120, 1050, 1035, 1000, 975, 875, 785; ^{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.): 362 [M]$^+$ (15), 344 (2), 314 (5), 296 (15), 269 (2), 216 (12), 171 (24), 143 (26), 129 (27), 118 (30), 111 (39), 97 (36), 95 (100), 91 (85), 81 (55), 77 (49), 55 (38), 41 (72). (Found: C, 66.37; H, 7.15. $C_{20}H_{26}O_6$ requires: C, 66.28; H, 7.23%.)

Triacetate **4** *from* 19-*deacetylteuscorodol* (**1**). Ac_2O–pyridine treatment of **1** (10 mg) in the usual manner yielded a substance [12 mg, a syrup, $[\alpha]_D^{25}$ −34.9° ($CHCl_3$; *c* 0.533)] identical in all respects (IR, ^{1}H NMR, MS, TLC) with the previously described compound **4** [lit. [10]: $[\alpha]_D^{20}$ −36.9° ($CHCl_3$; *c* 0.979)].

Teubotrin (**2**). An amorphous powder which melted at 110–114°; $[\alpha]_D^{24}$ −39.4° ($CHCl_3$; *c* 0.241); IR ν_{max}^{KBr} cm^{-1}: 3430 (br), 3160, 3050, 2980, 2940, 1715, 1505, 1480, 1450, 1405, 1160, 1120, 1025, 875; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (75.4 MHz, pyridine-d_5): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 362 [M]$^+$ (7), 344 (2), 314 (5), 296 (4), 277 (100), 262 (4), 239 (67), 201 (20), 183 (26), 149 (17), 128 (17), 105 (24), 97 (17), 95 (45), 91 (37), 81 (27), 77 (57), 55 (22), 51 (23), 43 (26), 41 (36). (Found: C, 66.07; H, 7.41. $C_{20}H_{26}O_6$ requires: C, 66.28; H, 7.23%.)

Table 2. ^{13}C NMR chemical shifts of compounds 1 and 2 (pyridine-d_5, TMS as internal standard)

Carbon	1	2	Carbon	1	2
1	20.0 *t**	20.5 *t*	11	44.8 *t*	36.4 *t*†
2	26.4 *t*	25.4 *t*	12	72.0 *d*	62.6 *d*
3	129.5 *d*	132.8 *d*	13	126.7 *s*	131.1 *s*
4	145.2 *s*	138.8 *s*	14	109.0 *d*	108.8 *d*
5	48.9 *s*	41.9 *s*	15	144.7 *d*	143.3 *d*
6	66.8 *d*	70.0 *d*	16	140.5 *d*	138.4 *d*
7	34.5 *t*	36.6 *t*†	17	16.9 *q*	16.4 *q*
8	33.1 *d*	31.0 *d*	18	65.3 *t*†	63.9 *t*
9	52.5 *s*	50.1 *s*	19	65.6 *t*†	74.7 *t*
10	45.9 *d*	37.0 *d*	20	178.3 *s*	173.3 *s*

*SFORD multiplicity.
†These assignments may be interchanged.

Teubotrin triacetate (5). Ac_2O–pyridine treatment of 2 (12 mg) in the usual manner gave compound 5 (15 mg): an amorphous solid which melted at 73–79°; $[\alpha]_D^{24}$ −56.3° ($CHCl_3$; *c* 0.215); IR ν_{max}^{KBr} cm^{-1}: 3150, 3120, 2970, 2930, 1735 (br), 1505, 1450, 1370, 1240, 1165, 1125, 1025, 875, 800; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 488 $[M]^+$ (0.1), 446 (21), 428 (27), 368 (2), 326 (10), 325 (5), 197 (5), 171 (12), 169 (11), 143 (10), 129 (11), 105 (12), 97 (11), 95 (21), 91 (17), 81 (15), 43 (100). (Found: C, 64.07; H, 6.34. $C_{26}H_{32}O_9$ requires: C, 63.92; H, 6.60%.)

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