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TEUCHAMAEDRIN C, A NEO-CLERODANE DITERPENOID FROM *TEUCRIUM CHAMAEDRYS*

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Key Word Index—*Teucrium chamaedrys*; Labiatae; new neo-clerodane derivative; teuchamaedrin C; 6α-hydroxyteuscordin; dihydroteugin.

Abstract—A new neo-clerodane diterpenoid, teuchamaedrin C, has been isolated from the aerial parts of *Teucrium chamaedrys*. Its structure, (12*S*,18*S*)-15,16-epoxy-neo-clerodane-13(16),14-dien-19,20-olide-18,6β-hemiacetal, was established by spectroscopic and chemical means. In addition, the previously known diterpenoids 6α-hydroxyteuscordin and dihydroteugin were isolated from the same source.

INTRODUCTION

Recently, we reported [1, 2] the isolation and structural elucidation of several furanoid diterpenes from an acetone extract of the aerial parts of *Teucrium chamaedrys* L. var. *chamaedrys*. Further investigation of the extract led to the isolation of three diterpenoids, two of which are the previously known 6α-hydroxyteuscordin, already found in *T. scordium* L. [3], and dihydroteugin, already found in Spanish *T. chamaedrys* [4], and a new diterpenoid, teuchamaedrin C (**1**), the structure of which was established by ^{1}H NMR and ^{13}C NMR spectroscopic studies and by chemical transformations.

RESULTS AND DISCUSSION

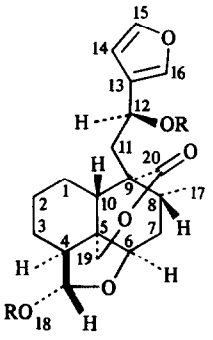
Teuchamaedrin C (**1**) had the molecular formula $C_{20}H_{26}O_6$ from high-resolution mass spectroscopy. Its IR spectrum was consistent with the presence of a furan ring (3140, 3120, 1505, 872 cm^{-1}), a δ-lactone group (1695 cm^{-1}) and two hydroxyl groups (3490, 3360 cm^{-1}). The presence of the two hydroxyl groups was confirmed by the formation of a diacetate (**2**), the IR spectrum of which showed no hydroxyl absorption. On the other hand, the absorption at 1695 cm^{-1} in **2** was shifted to 1740 cm^{-1} in **3**, suggesting that teuchamaedrin C had a hydrogen bond between a hydroxyl group and a δ-lactone. However, it was the ^{1}H NMR spectrum of teuchamaedrin C (**1**) that provided the most information. It showed (Table 1) signals for a secondary methyl group (δ0.91, 3H, *d*, J = 6.5 Hz) and a β-substituted furan ring (two α-furan protons at δ7.49 ad 7.47 and one β-furan proton at δ6.58). A double-doublet at δ5.12 (1H, J_1 = 10, J_2 = 4 Hz, H-12), a double-doublet at 4.26 (1H, J_1 = 4, J_2 = 1.5 Hz, H-6) and an AB quartet (4.58, 1H, *d*, J = 11.5 Hz; 4.02, 1H, *dd*, J_1 = 11.5 Hz; J_2 = 1 Hz, 2H-19) were also found. In addition, there was a one-proton doublet at δ5.28 which was assigned to a hemiacetalic function placed at a carbon atom with a vicinal proton. The closure of this hemiacetal group was revealed by a one-proton double-doublet at δ4.26, which must be vicinal to a methylene group. In agreement with all the above assignments, the ^{1}H NMR spectrum of the diacetyl derivative (**2**) showed the hemiacetalic and C-12 protons paramagnetically shifted (δ6.11, *d*, and 5.90, *dd*, respectively). Chromium trioxide–pyridine treatment of **1** gave a crystalline compound (**3**), which possessed a γ-lactone group (ν (CO)

Table 1. ^{1}H NMR spectral data and ^{13}C NMR chemical shifts of compound **1** (TMS as internal standard)

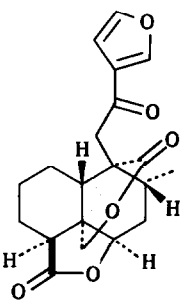
H	**1** (400 MHz, pyridine-d_5)	**1** (100 MHz, $CDCl_3$)	C	**1** (100.6 MHz, pyridine-d_5)
1α	2.51 *dddd*	—	1	21.2 *t*
1β	1.22 *ddd*	—	2	22.8 *t*
2α	1.12 *dddd*	—	3	23.3 *t*
4α	1.27 *t*	—		
6α	4.26 dd	4.05 *dd*	4	37.1 *d*
7β	1.25 *ddd*	—	5	42.6 *s*
7α	2.82 *dd*	2.62 *dd*	6	82.0 *d*
8β	2.11 *m*	—	7	34.1 *t**
10β	2.72 *dd*	2.55 *m*	8	39.3 *d*
11	2.38 *dd*	2.22 *d*	9	50.0 *s*
12	5.12 *dd*	5.10 *dd*	10	49.9 *d*
14	6.58 *dd*	6.52 *m*	11	34.4 *t**
15	7.47 *dd*	7.46 *m*	12	62.7 *d*
16	7.49 *dd*			
			13	123.5 *s*
Me-17	0.91 *d*	0.90 *d*	14	109.6 *d*
18	5.82 *d*	5.68 *d*	15	143.6 *d*
H_A-19	4.58 *d*	4.62 *d*	16	139.0 *d*
H_B-19	4.02 *dd*	4.08 *d*	17	16.7 *q*
			18	100.8 *d*
			19	70.4 *t*
			20	172.7 *s*

*These assignments may be interchanged.

J (Hz): 6α, 7β = 10β, 1β = 11_A, 12 = 4; 6α, 7α = 1.5; 7α, 8β = 7α, 7β = 15; 10β, 1α = 13; 11_A, 11_B, 12 = 10; 18, 4α = 6; 4α, 3β = 4α, 3α = 2.4; 19_A, 19_B = 11.5; 19_B, 6α = 1; 17, 8β = 6.5.



R
1 H
2 Ac



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1782 cm^{-1}) instead of the hemiacetalic function, and a keto group instead of the hydroxyl group at C-12, since its ^1H NMR spectrum lacked the signal assigned to the hemiacetalic proton; the signal (δ4.05, $CDCl_3$) attributed to the closure of the hemiacetalic group in teuchamaedrin C (**1**) was now shifted to δ4.25 (Table 1). From these facts it was evident that teuchamaedrin C had a hemiacetalic function placed between the C-18 and C-6 atoms. Moreover, the ^1H NMR spectrum of **3** showed the signals of the furan and C-11 methylene protons at δ6.66 (1H, *m*, H-14), 7.38 (1H, *m*, H-15), 7.99 (1H, *m*, H-16) and 3.23 (2H, *s* (*br*), H-11), respectively, showing unambiguously that the keto group in **3** was at the C-12 position [5, 6].

According to the small coupling constant, the protons at C-6 ($J_1 = 4$, $J_2 = 1.5$ Hz) and C-4 ($J_{H4,H3\beta} = J_{H4,H3\alpha} = 2.4$ Hz) were equatorial and the hemiacetalic group was axial [7–10]. The chemical shifts and coupling constants shown by the C-12 proton in compounds **2** and **3** were almost identical to those reported for some of the derivatives of montanin C, plaunal D and montanin E [2, 6, 10].

The presence of a C-20, C-19 δ-lactone group in **1** and the fact that the C-10 proton of **3** appeared at δ2.72 (*dd*, $J_{10,1\alpha} = 13$, $J_{10,1\beta} = 4$ Hz) established that the A/B ring junction of this diterpenoid was *trans* [2, 8], because it possessed a *trans* relationship between the H-10 proton and the lactone ring [8, 12, 13].

Structure **1** was confirmed by the ^{13}C NMR data (Table 1). The stereochemistry at the C-18 chiral centre was determined on the basis of the coupling value of H-4α and H-18β ($J = 6$ Hz), which showed that the H-18–H-4 dihedral angle was larger than 90°. According to these data, the C-18 hydroxyl group was of α-configuration, otherwise the dihedral angle would have been close to 0°. The Dreiding model of the molecule was in accordance with the ^1H NMR data. The stereochemistry at each of the other chiral centres was deduced by spin decoupling and by comparison of the ^{13}C NMR chemical shift data of **1** with those reported for related compounds [2, 6, 11]. Teuchamaedrin C is the first diterpenoid to be isolated from a *Teucrium* species which possesses a C-18,C-6β hemiacetalic function.

EXPERIMENTAL

Mps (Kofler apparatus) are uncorr.; ^1H NMR and ^{13}C NMR: 100 and 400 MHz and 100.6 MHz, respectively, in pyridine-d_5 or $CDCl_3$ soln with TMS as internal standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Plant material was collected in July 1982 near Pazardjik, Bulgaria.

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. chamaedrys* L. var. *chamaedrys* aerial parts (4.8 kg) were extracted with Me_2CO (50 l.) at room temp. for 1 week and after evapn of the solvent the residue was treated as in refs. [14, 15]. The $CHCl_3$ extract (32 g) was chromatographed on a silica gel (850 g, Merck, deactivated with 10% H_2O) column. Elution with $CHCl_3$–MeOH (99:1) gave crude 6α-hydroxyteuscordin (210 mg). Further elution with $CHCl_3$–MeOH (97:3) yielded crude teuchamaedrin C (200 mg), which was recrystallized from MeOH–Et_2O to yield pure **1** (185 mg). Elution with $CHCl_3$–MeOH (94:6) gave dihydroteugin (370 mg).

6α-Hydroxyteuscordin. Identical in all respects (mp, mmp, $[\alpha]_D$, IR, ^1H NMR, MS, combustion analysis and TLC) to the previously described compound [3].

Dihydroteugin. Mp 241–243° (MeOH–Et_2O); $[\alpha]_D^{28}$ −5.2° (Me_2CO; *c* 0.156) [lit. 250–252° (Me_2CO–Et_2O); $[\alpha]_D^{20}$ −9.8° (pyridine; *c* 0.37)]; IR, ^1H NMR and MS identical to the previously reported data [4].

Teuchamaedrin C (**1**). Mp 205–208°; $[\alpha]_D^{28}$ −37.5° (Me_2CO; *c* 0.149); IR ν_{max}^{KBr} cm^{-1}: 3490, 3360 (hydroxyl), 3140, 3120, 1505, 872 (furan ring), 1695 (δ-lactone), 1490, 1520, 1390, 1310, 1210, 1180, 1150, 1100, 1090, 1030, 980, 810, 690. MS (75 eV, direct inlet) *m/z* (rel. int.): 362 $[M]^+$ (37), 344 $[M-H_2O]^+$ (7), 296 (6), 266 (5), 176 (10), 161 (12), 147 (13), 145 (10), 133 (12), 131 (14), 119 (24), 117 (12), 111 (28), 107 (10), 105 (36), 97 (56), 95 (67), 94 (25), 91 (43), 81 (43), 79 (32), 77 (25), 69 (40), 67 (25), 55 (36), 41 (100). ^1H NMR and ^{13}C NMR: see Table 1. (Found: C, 65.92; H, 7.34. $C_{20}H_{26}O_6$ requires: C, 66.28; H, 7.23%.)

Acetylation of **1**. Acetylation of **1** (50 mg) with Ac_2O (0.7 ml) and pyridine (1–3 drops) yielded the diacetate **2** (40 mg), mp 158–161° (from Me_2CO–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3140, 3110, 1505, 875 (furan ring), 1740 (δ-lactone), 1725, 1236 (acetate), 2980, 2930, 2890, 1460, 1380, 1236, 1160, 1000, 950, 810, 740. ^1H NMR (100 MHz, $CDCl_3$): δ7.41 (1H, *m*, H-16), 7.30 (1H, *m*, H-15), 6.38 (1H, *m*, H-14), 6.10 (1H, *d*, $J = 5.5$ Hz, H-18), 5.89 (1H, *dd*, $J_1 = 10$, $J_2 = 4$ Hz, H-12), 4.05 (1H, *t*, $J = 3$ Hz, H-6), 4.55 (1H, *d*, $J = 12$ Hz, H_B-19), 3.90 (1H, *d*, $J = 12$ Hz, H_A-19), 2.70 (1H, *dd*, $J_1 = 15$, $J_2 = 4$ Hz, H-7 ax), 2.2 (3H, *s*, OAc), 2.0 (3H, *s*, OAc), 0.83 (3H, *d*, $J = 6.5$ Hz, H-17). (Found: C, 64.00; H, 6.80. $C_{24}H_{30}O_8$ requires: C, 64.56; H, 6.77%.)

Oxidation of **1**. Treatment of **1** (60 mg) in pyridine (2 ml) with CrO_3 (80 mg) in the usual manner yielded **3** (36 mg), mp 220–223° (from MeOH–Et_2O); IR ν_{max}^{KBr} cm^{-1}: 3140, 1505, 872 (furan ring), 1782 (γ-lactone), 1738 (δ-lactone), 1670 (ketone), 1580, 1510, 1420, 1390, 1280, 1150, 1010, 820, 750. ^1H NMR (100 MHz, $CDCl_3$): δ7.99 (1H, *m*, H-16), 7.38 (1H, *m*, H-15), 6.66 (1H, *m*, H-14), 4.25 (1H, *dd*, $J_1 = 4$, $J_2 = 1.5$ Hz, H-6), 4.72 (1H, *d*, $J = 12$ Hz, H_B-19), 4.16 (1H, *d*, $J = 12$ Hz, H_A-19), 3.22 (2H, *s* (*br*), H-11), 2.42 (1H, *m*, H-7 ax), 2.22 (1H, *m*, H-10), 0.94 (3H, *d*, $J = 6.5$ Hz, H-17). (Found: C, 66.87; H, 6.02. $C_{20}H_{22}O_6$ requires: C, 67.02; H, 6.19%.)

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