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FURANOID DITERPENES FROM *TEUCRIUM POLIUM*

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Key Word Index—*Teucrium polium* L. var. *polium*, Labiatae; furanoid diterpenes; clerodane derivatives; teupolin IV; teupolin V.

Abstract—From the aerial part of *Teucrium polium* L. var. *polium* two new clerodane diterpenoids, teupolin IV and teupolin V, have been isolated. Their structures were established by spectroscopic and chemical means and for teupolin V by partial synthesis from teucrin P_1.

INTRODUCTION

Recently, we reported [1,2] the isolation and structure elucidation of several furanoid diterpenes from the acetone extract of the aerial part of *Teucrium polium* L. var. *polium*. Further investigation of the acetone extract of this plant led to the isolation of two new clerodane diterpenes for which we propose the names teupolin IV and teupolin V. Their structures and stereochemistry have been established by detailed studies of the ^1H NMR and ^{13}C NMR spectra and by chemical transformations.

RESULTS AND DISCUSSION

Teupolin IV (**1**) $C_{22}H_{26}O_8$ had mp 196–198°, $[\alpha]_D^{28}$ +90.9° (*c* 0.154; acetone), MS *m/z* 418, and it gave a positive Ehrlich test. Its IR spectrum showed characteristic absorptions for a furan ring (3150, 3130, 1505, 870 cm^{-1}), a ketone (1705 cm^{-1}), an ester group (1730, 1250 cm^{-1}), a hydroxyl group (3500, 1040 cm^{-1}) and a γ-lactone (1750 cm^{-1}). The ^1H NMR spectrum of **1** (Table 1) revealed a secondary methyl group at δ 1.41 (3H, *d*, J = 6.5 Hz), an acetoxyl group at 1.81 (3H, *s*) and three protons for a β-substituted furan ring at 7.63 and 7.79 (1H, each, *dd*, H-15, H-16) and 6.55 (1H, *dd*, H-14). In addition, this spectrum showed signals of a methyne proton at δ 5.40 (1H, *d*, J = 11.5 Hz), two epoxide protons at 3.69 (1H, *dd*, J_1 = 6.0 Hz, J_2 = 2.5 Hz) and 2.18 (1H, *d*, J = 6.0 Hz) and a signal at 5.61 (1H, *t*, J = 8.5 Hz) for a proton attached to a carbon atom bearing a lactonic oxygen atom. Moreover, the ^1H NMR spectrum of **1** showed signals due to two protons attached to carbon atoms having an oxygen atom at 5.89 (1H, *d*, J = 13.0 Hz) and 5.21 (1H, *dd*, J_{gem} = 13.0 Hz and $J_{19\beta,10\beta}$ = 2.5 Hz).

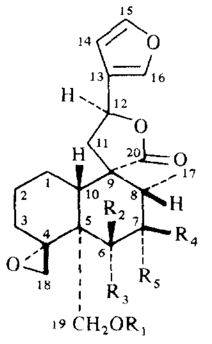
Table 1. ^1H NMR spectral data and ^{13}C NMR chemical shifts (ppm from internal TMS) of **1** and capitatin (**3**) [5]

1 (Pyridine-d_5)	**1**	**3**
1α-H 1.48 *dddd*	C-1 23.58 *t*	C-1 21.5 *t*
1β-H 1.73 *br d*	C-2 24.87 *t*	C-2 24.9 *t*
3α-H 1.42 *ddd*	C-3 33.11 *t*	C-3 30.6 *t*
3β-H —	C-4 61.71 *s*	C-4 61.0 *s*
7α-H 5.40 *d*	C-5 54.92 *s*	C-5 52.8 *s*
—	C-6 207.94 *s*	C-6 198.3 *s*
10β-H 2.32 *dd*	C-7 73.06 *d*	C-7 74.6 *d*
11α-H 1.96 *dd*	C-8 48.67 *d*	C-8 40.9 *d*
11β-H 1.88 *d′*	C-9 54.40 *s*	C-9 49.3 *s*
12-H 5.61 *dd*	C-10 53.40 *d*	C-10 46.4 *d*
14-H 6.55 *dd*	C-11 43.51 *t*	C-11 49.3 *t*
15-H 7.63 *dd*	C-12 72.80 *d*	C-12 71.6 *d*
16-H 7.79 *dd*	C-13 125.83 *s*	C-13 125.9 *s*
17-H_3 1.41 *d*	C-14 108.91 *d*	C-14 107.4 *d*
18α-H 3.69 *dd*	C-15 144.90 *d*	C-15 144.3 *d*
18β-H 2.18 *d*	C-16 140.73 *d*	C-16 138.2 *d*
19α-H 5.87 *d*	C-17 14.09 *q*	C-17 13.0 *q*
19β-H 5.21 *dd*	C-18 48.93 *t*	C-18 48.2 *t*
OH —	C-19 63.07 *t*	C-19 61.7 *t*
OAc 1.81 *s*	C-20 177.73 *s*	C-20 174.4 *s*
	Ac–CO–170.64 *s*	
	Ac–Me–20.67 *q*	

J (Hz): 1α, 1β = 10α, 10β = 13; 1β, 10β = 10β, 19β = 18β, 3 = 2.5; 7α, 8β = 11.5; 11, 12 = 11′, 12 = 8.5; 18, 18′ = 6; 19, 19′ = 13; 8β, 17 = 6.5.

As shown in Table 1 the H-7 of **1** was observed at lower field (δ 5.40), which showed unambiguously that the keto group was at C-6 [3, 4]. The presence of a keto group was confirmed by reduction of **1** with excess of $NaBH_4$ in MeOH, yielding the derivative **2**, mp 154–157°. The ^1H NMR spectrum of **2** showed one proton double doublet at δ 3.32 ($J_{7\alpha,6\beta}$ = 10 Hz, $J_{7\alpha,8\beta}$ = 11 Hz) and one proton doublet at δ 3.97 (J = 10 Hz), which were assigned to the H-7 and H-6 protons, respectively. According to the value of $J_{7,8}$ = 11.5 Hz the H-7 in **1** is axial and consequently the ester group is equatorial. The presence of a primary hydroxyl group at C-19 in compound **1** was established by addition of trichloroacetylisocyanate, the ^1H NMR spectrum of which showed the >NH signal as a singlet at δ 8.5 (1H), whereas the signals of the C-19 protons at 5.30 and 4.90 shifted to lower field at 5.37 and 5.82. Finally, the one proton signals at δ 3.69 (1H, *dd*, J_{gem} = 6.0 Hz, $J_{18,3ax}$ = 2.5 Hz) and 2.18 (1H, *d*, J_{gem} = 6.0 Hz) were assigned to the 4α,18-oxirane ring [3, 4] of teupolin IV (**1**).

The stereochemistry at the other chiral centres and the *trans*-junction of rings A and B was deduced from spin decoupling experiments and by comparing the ^{13}C NMR chemical shift data of **1** (Table 1) with those reported for capitatin (**3**) [5] and related compounds [6, 7]. Based on the above results, the structure and stereochemistry of teupolin IV was assigned as **1**.



1 $R_1 = R_5 = H$, $R_2 = R_3 = O$, $R_4 = OAc$
2 $R_1 = R_5 = H$, $R_2 = H$, $R_3 = OH$, $R_4 = OAc$
3 $R_1 = Ac$, $R_2 = R_3 = O$, $R_4 = H$, $R_5 = OAc$

When the ^{13}C NMR chemical shifts of C-6, C-8 and C-10 of compounds **1** and **3** are compared (Table 1) the shielding effect undergone by the latter compound is apparent. This effect must be due to the β-equatorial configuration of the C-7 ester group in **1**. The Dreiding model of teupolin IV showed that the bonds C-7–OAc, C-6 = O and C-4–C-18 lie in one and the same plane, which is in accordance with ^{1}H NMR and ^{13}C NMR data.

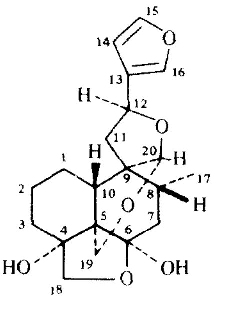
Elemental analysis and mass spectrometry of teupolin V (**4**) gave the molecular formula as $C_{20}H_{26}O_6$. Its IR spectrum was consistent with the presence of a furan ring (3125, 1600, 1510 and 870 cm^{-1}) and tertiary and pseudo-tertiary hydroxyl groups (3440, 3360 and 1150 cm^{-1}). The ^{1}H NMR spectrum of **4** (Table 2) showed signals for a β-substituted furan ring (two α-furan protons at δ 7.69, *dd*, and 7.56, *dd*, and one β-furan proton at 6.52, *dd*) and for a secondary methyl group at δ 0.78 (3H, *d*, $J = 6.5$ Hz). Two singlets at δ 4.92 and 6.32 were assigned to the two protons of the hydroxyl groups at C-4 and C-6, because these signals disappeared after addition of D_2O.

In addition, the ^{1}H NMR spectrum of teupolin V (**4**) showed two AB quartets at δ 4.43 and 4.28 ($J = 12$ Hz) and 4.20 and 4.11 ($J = 10$ Hz), which were assigned to the C-19 and C-18 methylene groupings. A double doublet signal at δ 5.13 (1H, $J = 8$ Hz) and a singlet at 5.32 (1H) were assigned to the H-12 and H-20 protons, respectively. The protons of the two hydroxyl groups appeared as singlets, which indicated that these groups are equatorial, hence the C-18/C-6 epoxide bridge must be diaxial [2, 8]. Even under drastic conditions, no dehydration of **4** was observed, thus confirming that the tertiary and pseudo-tertiary hydroxyl groups are equatorial. All these data suggested structure **4** for teupolin V, and this was also supported by its ^{13}C NMR spectral data (Table 2).

Table 2. ^{1}H NMR spectral data and ^{13}C NMR chemical shifts (ppm from internal TMS) of **4**

4 (Pyridine-d_5)	**4** (Pyridine-d_5)
1α-H 1.96 *dddd*	C-1 23.96 *t*
2α-H 1.19 *dddd*	C-2 24.47 *t*
7α-H 2.38 *dd*	C-3 30.89 *t*
7β-H —	C-4 81.46 *s*
10β-H 1.32 *dd*	C-5 48.03 *s*
11-H 2.03 *d*	C-6 108.27 *s*
12-H 5.13 *dd*	C-7 38.33 *t*
14-H 6.52 *dd*	C-8 35.56 *d*
15-H 7.56 *dd*	C-9 49.49 *s*
16-H 7.69 *dd*	C-10 44.68 *d*
17-H$_3$ 0.78 *d*	C-11 41.39 *t*
18α-H 4.20 *d*	C-12 71.95 *d*
18β-H 4.11 *d*	C-13 128.21 *s*
19α-H 4.42 *d*	C-14 109.51 *d*
19β-H 4.28 *d*	C-15 143.95 *d*
20-H 5.32 *s*	C-16 139.80 *d*
OH 4.81 *s* (C-4α)	C-17 16.37 *q*
OH 6.28 *s* (C-6α)	C-18 76.23 *t*
	C-19 59.61 *t*
	C-20 101.70 *d*

J (Hz): 7α, 7β = 14; 8β, 17 = 6.5; 10β, 1α = 13; 12, 11′ = 11, 12 = 8: 8, 18′ = 10; 19, 19′ = 12.



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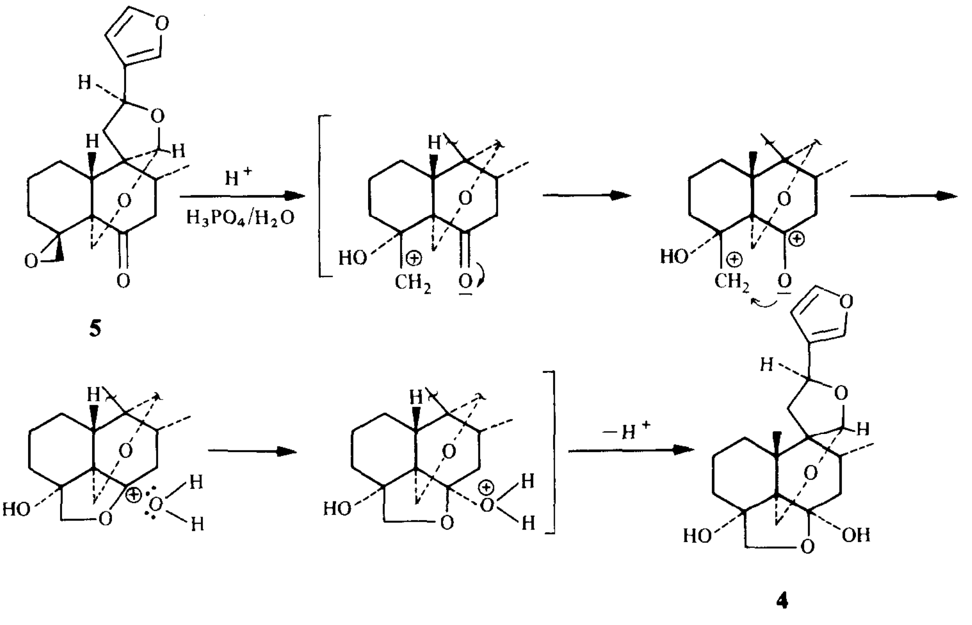
Final proof that teupolin V has the structure and stereochemistry depicted in formula **4** was obtained by treating teucrin P$_1$ (**5**) [9–11] with phosphonic acid, yielding a main compound identical in all respects with natural teupolin V. This transformation is explained in Scheme 1.

EXPERIMENTAL

Mps were determined on a Kofler apparatus and are uncorr. ^{1}H NMR and ^{13}C NMR spectra were measured at 100, 400 and 100.6 MHz respectively, in pyridine-d_5 or $CDCl_3$ soln with TMS as int. standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Plant materials were collected in July (1981) near Plovdiv, Bulgaria.

Extraction and isolation of the diterpenoids. Dried and finely powered *T. polium* L. var. *polium* aerial parts (5 kg) were extracted with Me_2CO (50 l.) at room temp. for 1 week, and after evaporation of the solvent the residue was treated as in ref. [12]. The $CHCl_3$ extract (40 g) was chromatographed on a silica gel



Scheme 1.

(800 g, Merck, deactivated with 10% H_2O) column. Elution with C_6H_6–Me_2CO (94 : 6) gave crude crystals (120 mg), which were recrystallized from Me_2CO–Et_2O to yield pure teupolin IV (105 mg). Further elution with $CHCl_3$ leads to the isolation of crude crystals (140 mg), which were recrystallized from MeOH–Et_2O to yield pure teupolin V (120 mg).

Teupolin IV (**1**). IR ν_{max}^{KBr} cm^{-1}: 3500, 3140, 3120, 3080, 2990, 2950, 2880, 1750, 1730, 1705, 1600, 1505, 1490, 1440, 1380, 1250, 1230, 1180, 1140, 1130, 1040, 1020, 980, 905, 870, 840 and 740. MS (75 eV, direct inlet) *m/z* (rel. int.): 418 $[M]^+$ (1), 416 (0.4), 400 $[M - H_2O]^+$ (0.2), 376 (0.4), 370 (0.4), 360 (2.5), 358 $[M - AcOH]^+$ (4.8), 346 (2.8), 345 (5.5), 343 (3.6), 340 (0.9), 328 (50), 327 (20), 315 (3.3), 300 (2.0), 285 (3.6), 283 (4.2), 219 (12), 201 (13), 189 (15), 179 (20), 161 (15), 133 (13), 121 (20), 105 (20), 95 (73), 94 (53), 91 (32), 81 (60), 79 (28), 77 (25) and 43 (100). ^{1}H NMR and ^{13}C NMR (100.6 MHz): see Table 1. ^{1}H NMR (100 MHz), $CDCl_3$ plus trichloroacetylisocyanate: δ 8.5 (1H, *s*, >NH), 7.38 (2H, *m*, H-15 and H-16), 6.24 (1H, *m*, H-14), 5.82 and 5.39 (2H, AB system, J = 12 Hz, 2H-19), 5.42 (1H, *t*, J = 8 Hz, H-12), 4.90 (1H, *d*, J = 11.5 Hz, H-7), 3.43 (1H, *dd*, J_1 = 6 Hz; J_2 = 2.5 Hz, H-18), 2.43 (1H, *d*, J = 8 Hz, H-11), 1.98 (3H, *s*, OAc) and 1.12 (3H, *d*, J = 6.5 Hz, H-17).

$NaBH_4$ *reduction of teupolin IV* (**1**). To a soln of teupolin IV (50 mg) in MeOH, excess $NaBH_4$ was added and the soln stirred at room temp. for 20 min. Work-up in the usual manner yielded a product (40 mg), which was recrystallized from Me_2CO–Et_2O to give **2** (30 mg); mp 154–157°. IR ν_{max}^{KBr} cm^{-1}: 3500, 3130, 2950, 1745, 1725, 1600, 1505, 1480, 1460, 1390, 1250, 1170, 1160, 1100, 1040, 1030, 910, 872 and 800. ^{1}H NMR (100 MHz, $CDCl_3$): 1.11 (3H, *d*, J = 6.5 Hz, H-17), 2.01 (3H, *s*, OAc on C-7), 2.40 (2H, *d*, J = 8.5 Hz, H-11), 3.32 (1H, *dd*, $J_{7\alpha,6\beta}$ = 10 Hz, $J_{7\alpha,8\beta}$ = 1 Hz, H-7), 3.97 (1H, *d*, J = 10 Hz, H-6), 4.64 and 4.92 (AB_q, J = 12 Hz, H-19), 5.37 (1H, *t*, J = 8 Hz, H-12); 6.38 (1H, *m*, H-14) and 7.42 (2H, *m*, H-15 and H-16).

Teupolin V (**4**). Mp 194–197° (MeOH–Et_2O); $[\alpha]_D^{28}$ −24.4° (Me_2CO; *c* 0.164). IR ν_{max}^{KBr} cm^{-1}: 3440, 3360, 2950, 2910, 2880, 1600, 1500, 1460, 1410, 1320, 1210, 1160, 1140, 1120, 1050, 1000, 940, 900, 885, 870, 790 and 730. MS (75 eV, direct inlet) *m/z* (rel. int.): 362 $[M]^+$ (3.5), 344 $[M - H_2O]^+$ (21.4), 284 (10.7), 262 (5.3), 250 (7.1), 248 (7.1), 230 (5.3), 191 (23.2), 172 (12.5), 162 (14.2), 147 (12.5), 145 (14.2), 105 (21.4), 95 (39.2), 94 (100), 91 (39.2), 81 (51.7), 69 (17.8) and 55 (46.4). ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz): see Table 2.

Preparation of teupolin V (**4**) *from teucrin P_1* (**5**). Teucrin P_1 (100 mg) was added to a soln of 0.1 N H_3PO_4 (20 ml) and the reaction mixture was stirred and refluxed at 105° for 5 hr. The mixture was then extracted with $CHCl_3$. The extract was washed with H_2O dried over dry Na_2SO_4, filtered and concd. The residue (90 mg) was chromatographed on a silica gel (10 g) column with $CHCl_3$ as eluent to give a compound (50 mg), which was identical in all respects (mp mmp, $[\alpha]_D$, IR, ^{1}H NMR and MS) with natural teupolin V.

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