Phytochemistry, Vol. 21, No. 3, pp. 721–723, 1982.
Printed in Great Britain.

0031-9422/82/030721-03$03.00/0
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DIHYDROTEUGIN, A NEO-CLERODANE DITERPENOID FROM *TEUCRIUM CHAMAEDRYS**

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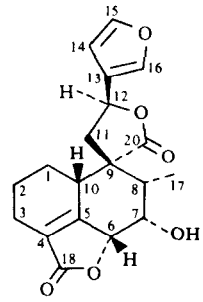
(*Received* 30 *June* 1981)

Key Word Index—*Teucrium chamaedrys*; Labiatae; diterpenoids; teucrin A; teugin; new neo-clerodane derivative; dihydroteugin; ^{13}C NMR data.

Abstract—From the aerial part of *Teucrium chamaedrys* a new neo-clerodane diterpenoid, dihydroteugin, has been isolated, besides the previously known diterpenoids teucrin A and teugin. The structure of dihydroteugin, (12*S*)-15,16-epoxy-2β,6β-dihydroxy-neo-cleroda-13(16),14-diene-18,19:20,12-diolide, was established by chemical and spectroscopic means and by partial synthesis from teugin.

INTRODUCTION

In a continuation of our studies on the diterpenic compounds from *Teucrium* spp. [1–4], we have now investigated *T. chamaedrys*, a species from which several new neo-clerodane diterpenoids have previously been isolated [5–7]. However, as we have observed in the case of other *Teucrium* spp. collected in different countries [4], the nature of the diterpenic fraction isolated from Spanish *T. chamaedrys* is not the same as the fractions from *T. chamaedrys* samples collected in eastern Europe [5–7]. From the Spanish sample, we have now isolated three neo-clerodane diterpenoids: teucrin A (**1**), already found in eastern European samples [5–10], teugin (**2**), not previously described as a constituent of *T. chamaedrys* but found in *T. fragile* [3], and a new diterpenoid, dihydroteugin (**3**), the structure and absolute configuration of which has been established.



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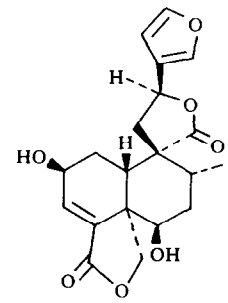

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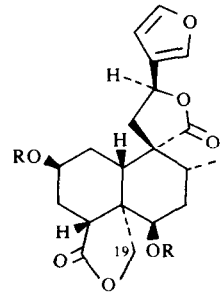

3 R = H
4 R = Ac

RESULTS AND DISCUSSION

Elemental analysis and mass spectrometry gave the molecular formula of dihydroteugin (**3**) as $C_{20}H_{24}O_7$. Its IR spectrum was consistent with the presence of a furan ring (3155, 1510, 880 cm^{-1}), two lactone groups (1755, 1745 cm^{-1}) and two hydroxyl groups (3660, 3430 cm^{-1}). The presence of the two hydroxyl groups was confirmed by the formation, on treatment with acetic anhydride–pyridine, of a diacetate (**4**), the IR spectrum of which showed no hydroxyl absorption. The ^1H NMR spectrum (pyridine-d_5) of the natural diterpenoid (**3**) showed signals for a β-substituted furan ring (ABX system, two α-furan protons at δ 7.73 and 7.62, and one β-furan proton at δ 6.53), and for a secondary methyl group (δ 1.03, 3H, *d*, J = 6 Hz). The following signals due to five protons on carbons bearing oxygen atoms were also seen: δ 5.49 (1H, *t*, J = 8.5 Hz), 4.78 and 4.70 (AB system, J = 11.5 Hz), 4.47 (1H, *m*, $W_{1/2}$ = 10 Hz) and 4.08 (1H, *m*, $W_{1/2}$ = 8 Hz). The signals at δ 4.47 and 4.08 were assigned to the two protons at the carbon atoms bearing hydroxyl groups, as these signals were shifted downfield in the ^1H NMR spectrum of the diacetyl derivative (**4**), appearing at δ 5.21 and 4.96, respectively. In addition, the ^1H NMR spectrum of dihydroteugin (**3**) showed four one proton signals at δ 6.94 (*d*, J = 4 Hz) 6.40 (*m*, $W_{1/2}$ = 7 Hz), 3.76 (*dd*, J_1 = 12 Hz, J_2 = 6.5 Hz) and 3.42 (*dd*, J_1 = 13 Hz, J_2 = 4 Hz). The signals at δ 6.94 and 6.40 were lost after addition of D_2O to the sample, which also caused a

*Dedicated to Professor F. Martín-Panizo, Instituto de Quimica Orgánica, CSIC, on the occasion of his 70th birthday.

narrowing of those at δ 4.47 (now $W_{1/2} = 8$ Hz) and 4.08 (now a clear triplet, $J = 3$ Hz). On the basis of these results, the following assignments for the protons could be made, which are in agreement with structure **3** for dihydroteugin. The signal at δ 5.49 was assigned to the lactonic C-12 proton, the signals at δ 4.78 and 4.70 to the C-19 lactonic protons, the multiplet at δ 4.47 to the 2α-equatorial proton, the triplet at δ 4.08 to the equatorial 6α-proton, whilst the double doublets at δ 3.76 and 3.42 were assigned to the C-4β and C-10β axial protons, respectively, which are strongly deshielded by the 1,3-diaxial interactions with the two secondary hydroxyl groups at C-2 and C-6. Finally, the 3H doublet at δ 1.03 was assigned to the secondary C-17 methyl group and the three low field signals (δ 7.73, 7.62 and 6.53) to the β-substituted furan ring.

These deductions were confirmed and the equatorial 8α-configuration of the C-17 secondary methyl group, the *trans*-junction of rings A and B and the 12*S* configuration established by comparing the ^{13}C NMR chemical shift data of dihydroteugin (**3**) (see Experimental) with those reported for related compounds[2, 3, 11, 12]. Final proof that dihydroteugin has the structure and absolute configuration depicted in formula **3** was obtained by sodium borohydride treatment [13] of teugin (**2**) [3], which yielded a compound identical in all respects (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR and MS) with natural dihydroteugin (**3**).

As a result of the above data, and in accordance with the terminology suggested by Rogers *et al.*[14], dihydroteugin can be assigned as (12*S*) - 15,16 - epoxy - 2β,6β - dihydroxy - neo - cleroda - 13(16),14 - diene - 18,19:20,12 - diolide (**3**), but from a biogenetic point of view [2–4] we would prefer to consider dihydroteugin (**3**) as (12*S*) - ent - 15,16 - epoxy - 2α,6α - dihydroxy - cleroda - 13(16),14 - diene - 18,19:20,12 - diolide.

EXPERIMENTAL

Mps are uncorr. Elemental analyses were carried out in Madrid with the help of an automatic analyser. 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 1980, near Ciruelos del Pinar (Guadalajara, Spain) and voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy (Madrid 'Complutense' University).

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. Chamaedrys* L. aerial parts (770 g) were extracted with Me_2CO (7 l.) at room temp. for 1 week. After filtration the solvent was evaporated yielding a gum (54 g) which was subjected to dry-CC over Si gel (600 g, Merck No. 7734, deactivated with 15% H_2O). Elution with EtOAc–*n*-hexane (4:1) gave a mixture (1.05 g) of teugin (**2**) and dihydroteugin (**3**), and elution with EtOAc–*n*-hexane (9:1) yielded teucrin A (**1**, 1 g). The mixture of **2** and **3** was easily separated on a Si gel (300 g, Merck No. 7734, deactivated with 10% H_2O) column eluted with $CHCl_3$–MeOH (9:1), to give teugin (**2**, 390 mg) and dihydroteugin (**3**, 516 mg).

Teucrin A (**1**). Mp 249–250° (Me_2CO–Et_2O); $[\alpha]_D^{20}$ + 190.0° (pyridine; *c* 0.38) (lit. [5]: mp 251–253°; $[\alpha]_D^{20}$ + 190°). IR UV, ^{1}H NMR and MS identical with the previously reported data[5, 8, 9]. ^{13}C NMR (25.2 MHz, pyridine-d_5): δ 21.8 (*t*, C-1), 19.8 (*t*, C-2), 24.8 (*t*, C-3), 128.1 (*s*, C-4), 158.7 (*s*, C-5), 81.1 (*d*, C-6), 74.9 (*d*, C-7), 38.6 (*d*, C-8), 56.9 (*s*, C-9), 41.9 (*d*, C-10), 42.2 (*t*, C-11), 72.4 (*d*, C-12), 124.6 (*s*, C-13), 108.6 (*d*, C-14), 144.8 (*d*, C-15), 141.0 (*d*, C-16), 13.8 (*q*, C-17), 173.4 (*s*, C-18) and 180.8 (*s*, C-20). (Found: C, 66.25; H, 6.01. Calc. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%.)

Teugin (**2**). Identical in all respect (mp, mmp, $[\alpha]_D$, IR, UV, ^{1}H NMR, MS, combustion analysis and TLC) with the previously described compound[3].

Dihydroteugin (**3**). Mp 250–252° (Me_2CO–Et_2O); $[\alpha]_D^{20}$ − 9.8° (pyridine; *c* 0.37); IR ν_{max}^{KBr} cm^{-1}: 3660, 3430, 3155, 3050, 2980, 2955, 2920, 2900, 1755, 1745, 1625, 1600, 1510, 1475, 1370, 1330, 1285, 1250, 1195, 1170, 1150, 1110, 1075, 1025, 990, 910, 880, 805, 715; UV λ_{max}^{EtOH} nm (ϵ): 215 (6000); ^{1}H NMR (100 MHz, pyridine-d_5 and pyridine-d_5 plus D_2O): see Results and Discussion. ^{13}C NMR (25.2 MHz, pyridine-d_5): δ 30.5 (*t*, C-1), 64.1 (*d*, C-2), 32.4 (*t*, C-3), 41.3 (*d*, C-4), 48.1 (*s*, C-5), 67.7 (*d*, C-6), 35.0 (*t*, C-7), 33.1 (*d*, C-8), 51.3 (*s*, C-9), 35.0 (*d*, C-10), 41.8 (*t*, C-11), 72.0 (*d*, C-12), 126.0 (*s*, C-13), 108.7 (*d*, C-14), 144.4 (*d*, C-15), 140.2 (*d*, C-16), 17.0 (*q*, C-17), 179.1 (*s*, C-18), 70.7 (*t*, C-19) and 177.9 (*s*, C-20); EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 376 [M]$^+$ (41), 358 (6), 340 (5), 282 (12), 264 (9), 246 (7), 218 (5), 190 (21), 178 (8), 161 (9), 157 (7), 105 (15), 95 (100), 94 (60), 91 (25), 82 (29), 81 (34). (Found: C, 63.50; H, 6.39. $C_{20}H_{24}O_7$ requires: C, 63.82; H, 6.43%.)

Dihydroteugin (**3**). Mp 250–252° (Me_2CO–Et_2O); $[\alpha]_D^{20}$ −9.8° (pyridine; *c* 0.37); IR ν_{max}^{KBr} cm^{-1}: 3660, 3430, 3155, 3050. crystallization from MeOH): mp 195–196°; $[\alpha]_D^{19}$ + 6.4° ($CHCl_3$; *c* 0.98); IR ν_{max}^{KBr} cm^{-1}: 3160, 3130, 3120, 3010, 2990, 2970, 2940, 1770, 1755, 1735, 1610, 1585, 1505, 1445, 1380, 1340, 1240, 1200, 1180, 1150, 1075, 1030, 1010, 990, 940, 880, 820, 755, 725; ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.46 (2H, *m*, H-15 and H-16), 6.39 (1H, *m*, H-14), 5.35 (1H, *t*, $J = 8.5$ Hz, H-12), 5.21 (1H, *m*, $W_{1/2} = 12$ Hz, H-2), 4.96 (1H, *t*, $J = 3$ Hz, H-6), 4.56 and 4.37 (AB system, $J = 11.5$ Hz, 2H-19), 2.11 and 2.10 (3H each, *s,s*, 2 × OAc), and 1.00 (3H, *d*, $J = 6.5$ Hz, 3H-17); EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 460 [M]$^+$ (18), 432 (2), 400 (8), 399 (2), 366 (4), 340 (10), 324 (6), 312 (4), 282 (5), 264 (4), 246 (8), 218 (5), 190 (8), 183 (6), 178 (6), 176 (6), 172 (7), 157 (9), 144 (8), 143 (10), 133 (6), 129 (10), 119 (6), 117 (7), 115 (6), 105 (10), 95 (41), 94 (37), 91 (16), 82 (10), 81 (20), 53 (8), 43 (100). (Found: C, 62.90; H, 6.29. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13%.)

Dihydroteugin (**3**) *from teugin* (**2**). To a soln of teugin (**2**, 60 mg) in dioxane–MeOH (1:1, 10 ml) excess $NaBH_4$ was added and the soln stirred at room temp. for 10 min. The excess of reagent was then destroyed by addion of Me_2CO. Work-up in the usual manner yielded a compound (58 mg) identical in all respects (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR and MS) with natural dihydroteugin (**3**).

Acknowledgements—We thank Dr. J. Borja, Botany Department, Faculty of Pharmacy, Madrid, for the botanical classification of the plant material, Miss M. D. Casado and Miss M. Plaza for recording the ^{1}H and ^{13}C NMR spectra and Mr. J. Prieto for elemental analyses. This work was supported in part by the National Research Council (CNR), Rome.

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