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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM RACEMOSUM*

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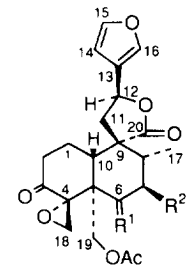
Key Word Index— *Teucrium racemosum*; Labiatae; diterpenoids; chlorine-containing *neo*-clerodane derivative; teuracemin.

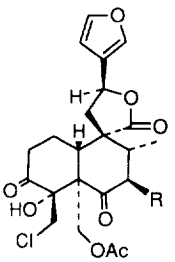
Abstract—A novel chlorine-containing *neo*-clerodane diterpene, teuracemin, (19-acetoxy-18-chloro-15,16-epoxy-4α,7β-dihydroxy-3,6-dioxo-*neo*-cleroda-13(16),14-dien-20,12*S*-olide), and three known compounds, teutrifidin, 4α,18-epoxytafricanin A and 20-oxo-teuflavin, were isolated from the aerial parts of *Teucrium racemosum*.

INTRODUCTION

The genus *Teucrium* (Labiatae) is the most abundant natural source of *neo*-clerodane diterpenoids identified so far [1–3]. Interest in these compounds has been stimulated by their biological activity as antifeedants against some economically important lepidopterous pests [1, 4–8]. In continuation of our search for new insect antifeedants from natural sources [9–12], we have studied *Teucrium racemosum*, a species which grows in Australia. We report here, the isolation and structure determination of a novel chlorine-containing *neo*-clerodane, teuracemin, which was found in *T. racemosum* together with other already known compounds.



	R^1	R^2
1	O	OH
2	O	H
3	αH, βOH	H



4 R = OH
5 R = H

RESULTS AND DISCUSSION

Repeated chromatography of the acetone extract of the aerial parts of *T. racemosum* (see Experimental) led to the isolation of the previously known *neo*-clerodane diterpenoids teutrifidin (**1**, recently isolated from *T. trifidum* [13]), 4α,18-epoxytafricanin A, **2**, already known as a natural [14] and synthetic [15–17] compound and 20-oxo-teuflavin, **3**, previously found in *T. pestalozzae* [14] and obtained by partial oxidation of teuflavin [16], together with a new substance, teuracemin, whose structure (**4**) was established as follows.

Teuracemin (**4**, $C_{22}H_{25}O_9Cl$) showed ^1H and ^{13}C NMR spectra (Table 1) almost identical with those of teutrifidin (**1**) [13] and the observed differences were consistent with the existence in **4** of a 4α-hydroxy-18-chloro structural moiety [C-18 methylene protons as an AB system at δ3.90 and 4.59, J_{gem} = 11.7 Hz, δ_C 81.3 *s* (C-4) and 46.6 *t* (C-18); Table 1] instead of the 4α,18-oxirane of **1** (C-18 methylene protons as an AB system at δ2.46 and 4.01, J_{gem} = 6.7 Hz, $\delta_{C\text{-}4}$ 63.8 *s*, $\delta_{C\text{-}18}$ 50.6 *t*; [13]). The 4α-hydroxy-18-chloro arrangement of the chlorohydrin grouping of teuracemin (**4**) was firmly supported by its ^{13}C NMR spectrum (Table 1) which showed identical chemical shift for the C-1–C-5, C-10 and C-18 carbons as those reported [15] for tafricanin A, a naturally occurring *neo*-clerodane derivative whose structure (**5**) is well known from an X-ray diffraction analysis [15].

Final proof of the structure of teuracemin (**4**) was achieved by treating teutrifidin (**1**) with hydrochloric acid, which yielded a compound identical in all respects ($[\alpha]_D$, ^1H NMR, MS) with the natural diterpenoid (**4**), as a consequence of the attack of the nucleophile on the primary centre of the epoxide [5].

Neo-Clerodane natural products containing chlorine are relatively rare among the diterpenoids isolated from *Teucrium* species [15, 18, 19] and all of them are chlorohydrins. Therefore, it is just conceivable that these chloroderivatives are artefacts. However, in all the cases

Table 1. ^1H and ^{13}C NMR spectral data of compound **4***

H	δ	C	δ
7α	4.75 *dd*†	1	24.1 *t*
8β	1.79 *dq*	2	36.6 *t*
11A	2.57 *dd*	3	206.5 *s*
11B	2.65 *dd*	4	81.3 *s*
12	5.53 *t*	5	60.8 *s*
14	6.43 *dd*	6	204.6 *s*
15	7.50‡	7	73.8 *d*
16	7.50‡	8	48.2 *d*
Me-17	1.33 *d*	9	52.7 *s*
18A	3.90 *d*	10	50.6 *d*
18B	4.59 *d*	11	43.9 *t*
19A	4.82 *d*	12	72.5 *d*
19B	4.94 *d*	13	124.2 *s*
OAc	1.95 *s*	14	107.7 *d*
OH-4	4.44 *s*§	15	144.6 *d*
OH-7β	3.53 *d*§	16	139.8 *d*
		17	13.4 *q*
		18	46.6 *t*
		19	61.3 *t*
		20	175.8 *s*
		OAc	169.0 *s*
			20.6 *q*

J_{H-H} (Hz): 7α,8β = 11.7; 7α,OH-7β = 4.3; 8β,17 = 6.6; 11A,11B = 13.7; 11,12 = 8.6; 14,15 = 1.9; 14,16 = 1.1; 18A,18B = 11.7; 19A,19B = 11.7.

*At 250 MHz (^1H) and 63 MHz (^{13}C), in $CDCl_3$ solution. TMS as internal standard.

†Collapsed into a *d* (J = 11.7 Hz) after addition of D_2O.

‡Overlapped signal.

§Disappeared after addition of D_2O.

including this one, these chlorohydrins have been detected in the acetone extract of the fresh plant material, thus showing that they are not artefacts of the isolation procedure. The existence in the same extract [18, 19] of several 4α,18-epoxy-*neo*-clerodanes together with only one chlorohydrin derivative, also supported the natural origin of the latter, because it is known that the oxirane-opening process of 4α,18-epoxy-*neo*-clerodanes by hydrochloric acid is a general, easy and very fast reaction [5, 7, 15, 18, 20].

EXPERIMENTAL

Mp: uncorr. Plant materials were collected in December 1993 at Ilparpa Swamp, near Alice Springs, Australia, and voucher specimens were deposited in the Herbarium of the 'Dipartimento di Chimica Organica', University of Palermo, Italy.

Extraction and isolation of the diterpenoids. Dried and powdered *Teucrium racemosum* R. Br. aerial parts (1.1 kg) were extracted (× 3) with Me_2CO (10 l) at room temp. for 1 week. The extract (58 g) was subjected to CC (silica gel Merck No. 7734, deactivated with 15% H_2O, w/v, 500 g) with petrol–EtOAc gradient as eluent. Elution with EtOAc–petrol (4:1) successively yielded 20-oxo-teuflavin (**3**, 30 mg) [14, 16] and 4α,18-epoxytafricanin A (**2**, 800 mg) [14–17]. Elution with EtOAc gave teuracemin (**4**, 8 mg) and teutrifidin (**1**, 15 mg, most polar constituent) [13].

The previously known compounds (**1**–**3**) were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (^1H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

Teuracemin (**4**). Amorphous solid, mp 80–95°; $[\alpha]_D^{18}$ + 21.4° ($CHCl_3$; *c* 0.042). IR ν_{max}^{KBr} cm^{-1}: 3460 (OH), 3140, 3130, 1505, 875 (furan), 1755 (γ-lactone), 1735, 1235 (OAc), 1720 (ketone), 2960, 2930, 1370, 1145, 1065, 1040, 1020, 985, 910, 800, 725. ^1H and ^{13}C NMR: Table 1. EI-MS (70 eV, direct inlet) *m/z* (rel. int.): 470 (0.1) and 468 (0.3) $[M]^+$, 450 (0.1), 432 (3), 414 (0.6), 372 (2), 338 (3), 153 (19), 127 (12), 107 (10), 105 (12), 97 (27), 95 (35), 94 (46), 91 (13), 85 (10), 81 (23), 71 (22), 69 (23), 57 (30), 55 (38), 43 (100), 41 (26). $C_{22}H_{25}O_9Cl$ M_r 468 and 470.

Teuracemin (**4**) *from teutrifidin* (**1**). A soln of **1** (6 mg) in $CHCl_3$ (5 ml) at room temp. was treated with aq. conc. HCl (0.2 ml) for 15 min with stirring. The reaction mixt. was dild with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 10 ml). The extract was dried (Na_2SO_4), filtered and evaporated to dryness giving a residue from which 4 mg of **4** were obtained after CC (silica gel, EtOAc–petrol, 4:1, as eluent). This compound showed identical $[\alpha]_D$, ^1H NMR and MS to that of natural teuracemin. TLC confirmed this identity.

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