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A NEO-CLERODANE DITERPENOID FROM *TEUCRIUM ASIATICUM*

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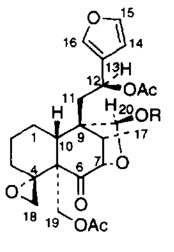
Key Word Index—*Teucrium asiaticum*; Labiatae; *neo*-clerodane derivative; teucrasiolide.

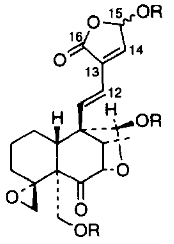
Abstract—A novel neo-clerodane diterpene, teucrasiolide, was isolated from the aerial parts of *Teucrium asiaticum* as a mixture of C-15 epimers. Its structure, (15*R* and 15*S*, 20*R*)-15,19-diacetoxy-4α, 18-epoxy-6-oxo-20, 7α-(20-*O*-acetyl)-hemicetal-neo-cleroda-11*E*, 13*Z*-dien-16,15-olide, was established by spectroscopic means. © 1977 Elsevier Science Ltd. All rights reserved

INTRODUCTION

In a previous communication [1], we reported on the isolation of a new diterpenoid, teucrasiatin, and a known substance, auropolin (**1**) [2, 3] from an acetone extract of the aerial parts of *Teucrium asiaticum*. A further study on the same extract allowed the isolation of another neo-clerodane derivative, teucrasiolide. We report here on the structural elucidation of this compound.



1 R=H
3 R=Ac



2 R=Ac
4 R=H

RESULTS AND DISCUSSION

The more polar chromatographic fractions of the acetone extract of *Teucrium asiaticum* [1] (see Experimental) contained a compound, more polar than auropolin (**1**), contaminated with other products. Attempts at obtaining a pure sample of this substance were unsuccessful because it was extremely unstable and decomposed on storage, chromatography through silica gel or alumina or when its solutions (MeOH, EtOAc, $CHCl_3$, etc.) were left at room temperature for 1 hour. The ^1H NMR spectrum of the impure compound revealed the absence of acetoxyl groups and we decided to obtain its acetyl derivative in order to avoid decomposition.

Treatment of the crude compound with acetic anhydride–pyridine for 24 hours at room temperature, followed by column chromatography, allowed the isolation of a stable derivative (**2**, teucrasiolide), which was apparently homogeneous on TLC. Compound **2** had the molecular formula $C_{26}H_{30}O_{11}$ and its IR spectrum was devoid of hydroxyl absorptions. However, its ^1H and ^{13}C NMR spectra showed some protons and carbons as pairs of signals (Table 1), thus suggesting that **2** was a 1:1 mixture of two epimers.

The ^1H and ^{13}C NMR spectra of **2** were very similar to those of acetylauropolin (**3**) [2], showing almost identical signals for the decalin moiety and its 4α,18-oxirane, 19-acetoxymethylene, 6-oxo, 17-methyl and 20, 7α-(20-*O*-acetyl)-hemiacetal substituents. In addition, **2** possessed a *trans* C-11, C-12 olefinic double bond (δ_H 6.90 *d* and 6.15 *d*, $J_{trans} = 16.9$ Hz; δ_C 136.3 *d* and 120.8 *d*) conjugated (UV λ_{max}^{MeOH} at 251 nm, log ε 3.86) with an α,β-unsaturated γ-lactone (IR ν_{max} 1780 cm^{-1}) involving the C-13, C-14, C-15 and C-16 carbons and having an acetoxyl substituent at its γ-position [δ_H 7.00 *br s*, $W_{1/2} = 5$ Hz (olefinic proton), 6.94 *br s*, $W_{1/2} = 2$ Hz (γ-proton), 2.11 *s* and 2.10 *s*, 1.5H each (γ-acetoxyl group); δ_C 131.8 *s* and 140.7 *d* (olefinic carbons), 168.4 *s* (lactone carbonyl) and 92.05 *d* and 92.02 *d* (double signal, γ-carbon bearing the acetoxyl group)].

The double signals observed for the γ-acetoxyl protons and the γ-carbon atom, together with the

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Table 1. ^1H and ^{13}C NMR spectral data for compound **2***

H	**2**	$J_{H,H}$(Hz)	**2**	C	**2**	C	**2**
1α	1.66 *qd*	1α,1β	12.7	1	21.9 *t*	OAc	170.6 *s*
1β	1.83 *m* ($W_{1/2}$ = 20 Hz)	1α,2α	3.4	2	24.8 *t*		169.6 *s*
2α	1.93 *m* ($W_{1/2}$ = 24 Hz)	1α,2β	12.7	3	31.5 *t*		168.8 *s*
2β	1.38 *m* ($W_{1/2}$ = 40 Hz)	1α,10β	12.7	4	62.1 *s*		21.1 *q*
3α	2.43 *dddd*	1β,2α	†	5	53.1 *s*		20.9 *q*
3β	1.04 *ddd*	1β,2β	†	6	202.6 *s*		20.6 *q*
7β	4.28 *br s* ($W_{1/2}$ = 2 Hz)	1β,10β	1.4	7	90.5 *d*		
8β	2.25 *qd*	2α,2β	†	8‡	48.92 *d*, 48.87 *d*		
10β	2.00 *dd*	2α,3α	4.7	9‡	57.3 *s*, 57.2 *s*		
11‡§	6.90 *d*, 6.89 *d*	2α,3β	3.4	10‡	55.8 *d*, 55.7 *d*		
12	6.15 *d*	2β,3α	13.0	11	136.3 *d*		
14	7.00 *br s* ($W_{1/2}$ = 5 Hz)	2β,3β	2.1	12	120.8 *d*		
15	6.94 *br s* ($W_{1/2}$ = 2 Hz)	3α,3β	13.6	13	131.8 *s*		
Me-17‡‖	1.25 *d*, 1.24 *d*	7β,8β	0.5	14	140.7 *d*		
18A¶	2.35 *d*	8β,17	7.1	15‡	92.05 *d*, 92.02 *d*		
18B**	3.06 *dd*	11,12	16.9	16	168.4 *s*		
19A	4.81 *d*	18A,18B	5.1	17	15.0 *q*		
19B	5.23 *d*	18B,3α	2.1	18	49.0 *t*		
20	6.31 *s*	19A,19B	11.4	19	62.3 *t*		
OAc	2.15 *s*			20	96.3 *d*		
	2.11 *s*, 2.10 *s*‡Π						
	2.07 *s*						

* At 500 MHz (^1H) and 125.7 MHz (^{13}C), $CDCl_3$. Chemical shifts (δ values) are relative to residual $CHCl_3$ for ^1H (δ_{CHCl_3} 7.25) and to the solvent for ^{13}C (δ_{CDCl_3} 77.00). The multiplicity of the carbons was assigned from the HMQC spectrum.

† Not determined.

‡ Double signals.

§ 0.5 H each signal.

‖ 1.5 H each signal.

¶ *Exo* hydrogen with respect to ring B.

** *Endo* hydrogen with respect to ring B.

duplicity of the H-11 and Me-17 proton signals and those of the C-8, C-9 and C-10 carbons (Table 1), indicated that **2** was a mixture of epimers at the γ-position of a γ-acetoxy-α,β-unsaturated γ-lactone [4].

A 15-acetoxy-16,15-γ-lactone regiochemistry for **2** was evident after comparing its ^1H and ^{13}C NMR data with those of other diterpenoids previously described. In the 15-hydroxy (or acetoxy)-16,15-γ-lactone regioisomers, like teuponin [5] and others [4], the H-14 and H-15 protons resonate between δ 6.96 and 7.67 (or δ 6.20 and 6.61), and the C-13–C-16 resonances appear at δ 135.8, 147.7, 100.5 and 169.4, respectively, for the 15-hydroxy derivative [5]. These values are in agreement with those of **2** [$\delta_{H\text{-}14}$ 7.00, $\delta_{H\text{-}15}$ 6.94, δ_C 131.8 (C-13), 140.7 (C-14), 92.0 (C-15) and 168.4 (C-16)], and they are very different from those observed in the 16-acetoxy-15,16-γ-lactone regioisomer [$\delta_{H\text{-}14}$ 5.73, $\delta_{H\text{-}16}$ 6.84; δ_C 169.2 (C-13), 118.3 (C-14), 165.0 (C-15) and 94.0 (C-16)] [6]. Moreover, the UV absorption at λ_{max} 251 nm also supported [7] the existence of an 11,12-ene-α,β-unsaturated-16,15-γ-lactone cross-chromophore in this compound.

The stereochemistry of the C-20 stereogenic centre of **2** was suggested as *R* because of the absence of a long-range coupling in its H-20 proton (δ 6.31 *s*); the existence of such coupling ($^4J_{20,10\beta}$) has been observed in the corresponding 20*S* epimers [8, 9]. This assumption was strongly supported by NOE experiments, because irradiation at δ 6.31 (H-20 proton) caused NOE enhancement in the signals of the H-1α and H_A-19 protons, thus establishing that H-20 and H-1α are on the same side of the plane defined by the C-20, C-7α hemicetal ring. Moreover, irradiation at δ 1.25 (Me-17 protons) only caused NOE enhancement in the signals of the C-11 and C-12 olefinic and H-7β and H-8β protons, and not in the H-20 proton signal [8, 9].

The absolute configuration of **2** was not ascertained. However, on biogenetic grounds, it is reasonable to assume that it belongs to the neo-clerodane series [10], like all the diterpenoids previously isolated from *Teucrium* species [1–5, 8, 9, 11–13], including auropolin (**1**) and teucrasiatin [1–3], co-occurring with **2** in the same plant.

Teucrasiolide (**2**) is the first neo-clerod-11-ene derivative isolated from *Teucrium* species, although this structural feature has previously been found in some clerodanes isolated from *Scutellaria* species [12, 14], which also belong to the Labiatae family.

In the light of the structure of **2**, it is possible that its natural precursor could possess structure **4**. This explains the instability of the natural substance, because it is known that the neo-clerodane-20,7α-hemiacetal derivatives are extremely unstable compounds under mild conditions such as chromatography through silica gel [15, 16], and also because the 19-hydroxy-6-oxo-neo-clerodanes are unstable and easily transformed into their corresponding 19-nor derivatives [17], even by chromatography through silica gel [18].

From a biogenetic point of view, compound **4** could be formed from auropolin (**1**) by oxidation of the furan ring [4], a 1,2-*trans*-elimination reaction of the 12-acetoxyl group and a hydrolysis of the C-19 acetate.

EXPERIMENTAL

For general details on the collection and extraction of *Teucrium asiaticum* L. aerial parts, see ref [1].

Isolation of the diterpenoid and its transformation into **2** (*teucrasiolide*). The chromatographic frs eluted with EtOAc–petrol (2:1) and pure EtOAc, showed one spot on TLC (EtOAc as eluent), more polar than auropolin [1–3], accompanied by other compounds. Purification by chromatography was unsuccessful and the mixture (38 mg) was treated with Ac_2O–pyridine (1:1, 6 ml) for 24 hr at room temp. Work-up in the usual manner yielded a residue (37 mg), which was subjected to CC (silica gel Merck no. 7734, deactivated with 15% H_2O, w/v, 30 g; EtOAc–petrol 3:2 as eluent) giving 26 mg of **2** as a white solid.

Teucrasiolide (**2**). Mp 95–100° (amorphous solid); $[\alpha]_D^{26}+20.6°$ ($CHCl_3$; *c* 0.189). IR ν_{max}^{KBr} cm^{-1}: 3090, 1780, 1660, 970 (1,2-disubstituted *trans*-olefin and α,β-unsaturated γ-lactone), 1750, 1230 (OAc), 1730 (ketone), 2950, 1450, 1380, 1020, 1000, 910, 730; UV λ_{max}^{MeOH} nm (log ε): 201 (4.02), 251 (3.86); ^1H NMR: Table 1; ^{13}C NMR: Table 1; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 518 $[M]^+$ (0.1), 458 $[M\text{-}HOAc]^+$ (0.2), 445 $[M\text{-}CH_2OAc]^+$ (9.5), 357 (1), 281 (3), 205 (10), 137 (5), 121 (11), 95 (4), 91 (4), 79 (10), 69 (5), 55 (6), 43 (100). (Found: C, 60.39; H, 5.69. $C_{26}H_{30}O_{11}$ requires: C, 60.22; H. 5.83%.)

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