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NEO-CLERODANE DITERPENOIDS FROM *SCUTELLARIA CYPRIA*

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Key Word Index—*Scutellaria cypria* var. *cypria*; Labiatae; neo-clerodane diterpenes; scutecyprin; scutecyprols A and B.

Abstract—Two pairs of diastereomeric hemiacetals, scutecyprols A and B, have been detected in the aerial parts of *Scutellaria cypria* var. *cypria*. They were isolated, after oxidation, as their γ-lactone derivatives, along with the known scutecyprin.

INTRODUCTION

In a continuation of our systematic studies of neo-clerodane diterpenoids within the genus *Scutellaria* [1–5], we have investigated the aerial parts of *S. cypria* Rech. fil. var. *cypria*. We report here on the occurrence of two pairs of diastereomeric hemiacetals, besides the already known scutecyprin [4] isolated from *S. cypria* var. *elatior*.

RESULTS AND DISCUSSION

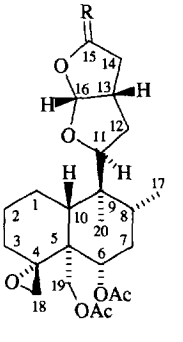
The acetone extract of the aerial parts yielded scutecyprin [4] and an apparently homogeneous fraction on TLC. However, the ^{1}H NMR spectrum of the latter showed four doublets in the δ 5.70–5.85 range, assignable to the 16β-H of a furofuranic fragment, thus suggesting the occurrence of four products. As all attempts to separate the mixture failed, it was carefully oxidized, yielding two easily separated derivatives.

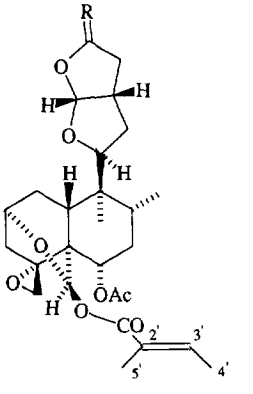
The first product was identified with the γ-lactone **1** obtained by Barton *et al.* [6] on oxidizing the 'clerodin hemiacetal' isolated (together with clerodin) from *Clerodendron infortunatum* (family Verbenaceae). Whereas the absolute configuration of **1** is well known, the stereochemistry at C-15 of the hemiacetal was not ascertained at that time, but suggested [6] to be *exo* as this was the much less hindered orientation.

In our opinion, the original product occurring in the extract should be the pair of hemiacetals diastereomeric at C-15, i.e. **1a** and **1b**, and involved in a tautomeric equilibrium through the common open chain form. We named the product scutecyprol A: it differs from clerodin by having the 14, 15 double bond converted into a 14-H, 15-OH derivative. Similar pairs of coexisting diastereomers are known [7–11].

The second product, **2**, had the molecular formula $C_{27}H_{36}O_9$. Its ^{1}H NMR spectrum was almost identical with that of scutecyprin (**3**), the only differences being related to the protons H-13, H-14, H-15 and H-16. Thus, the lactone **2** differs from scutecyprin only in the occurrence of C-15 as a carbonyl instead of a methylene. For the placement of the two ester groups at C-6 (acetate) and C-19 (tiglate) and for the assignment of the stereochemistry to the chiral centres, the same reasonings used for scutecyprin and other neo-clerodanes from *Scutellaria* were employed. Therefore, the original product (named scutecyprol B) occurring in the extract should be the pair of hemiacetals diastereomeric at C-15, i.e. **2a** and **2b**.

It is known that the 14, 15 double bond of clerodin can undergo an addition reaction with either H_2O or acetic acid to form the hemiacetal or its acetate. The hypothesis that such products could be artefacts of the





1 R = O
1a R = β-OH, α-H
1b R = α-OH, β-H

2 R = O
2a R = β-OH, α-H
2b R = α-OH, β-H
3 R = H_2

extraction or processing procedures had been rejected by Barton *et al.* [6]. In support of Barton's opinion, we have never observed the co-occurrence of unsaturated and hydrated products in *Scutellaria* species investigated prior to this study. Indeed, either unsaturated or hydrated products were found. Also, in *S. cypria* var. *cypria*, no trace of clerodin was found to co-occur with scutecyprol A.

EXPERIMENTAL

Plant materials were collected at Chionistra, Cyprus, at 1870 msl on June 1992, and voucher specimens were deposited in the Herbarium of Dipartimento Bontanica e Ecologia, Università Camerino.

Extraction and isolation. Dried and powdered aerial parts of *S. cypria* Rech. fil. var. *cypria* (690 g) were extracted with Me_2CO (3 × 5 l) at room temp. for 5 days. The extract (60 g) was subjected to CC on silica gel Merck No. 7734, deactivated with 15% H_2O, 800 g; hexane, hexane-EtOAc mixts and EtOAc–MeOH mixts as eluents, yielding in the hexane–EtOAc (3:7) eluate a mixt. that was rechromatographed (CC, eluent hexane–EtOAc, and radial chromatography on Chromatotron, eluent $CHCl_3$–MeOH 49:1), to give two distinct frs. The first fr. (8 mg) contained a single product identified as **3** [4] by conventional methods and comparison with an authentic sample. The second fr. (100 mg) gave a single spot on TLC with different mixts of eluents, but the ^{1}H NMR spectrum was indicative of a mixt. This mixt. was dissolved in pyridine (2 ml) and oxidized with a soln of pyridinium chromate (200 mg) in pyridine (2 ml) at room temp. for 24 hr. After dilution with H_2O (10 ml) and extraction with Et_2O (8 × 25 ml), the extract was washed with H_2O, dried and the solvent evapd. The residue was purified by CC (eluent: hexane–EtOAc, 1:1) to give **1** (9 mg) and **2** (60 mg).

Lactone **1**. Mp 191–193° (from hexane–EtOAc), $[\alpha]_D$ − 22.3° ($CHCl_3$; *c* 0.200); lit. [6] mp 192–193°, $[\alpha]_D$–23° ($CHCl_3$; *c* 1.04). EIMS (70 eV, direct inlet) *m/z* 464 $[M]^+$. $C_{24}H_{32}O_9$ M_r 464. IR and ^{1}H NMR in agreement with previous data [6].

Lactone **2**. Mp 245–248° (from hexane-EtOAc); $[\alpha]_D$ + 18° ($CHCl_3$; *c* 0.205). EIMS (70 eV, direct inlet) *m/z* 504 $[M]^+$. $C_{27}H_{36}O_9$ M_r 504. IR ν_{max}^{KBr} 1780, 1740, 1705, 1240. ^{1}H NMR ($CDCl_3$, 250 MHz): Table 1.

Table 1. ^{1}H NMR spectral data for compounds **1**–**3*** (250 MHz, $CDCl_3$, TMS as standard)

H	1	2	3
2β	n.o.	4.18 *m*	4.18 *m*
6β	4.67 *dd*	4.61 *dd*	4.62 *dd*
11α	4.11 *dd*	4.08 *dd*	4.08 *dd*
13β	3.18 *m*	3.13 *m*	2.85 *m*
14A	2.39 *dd*	2.40 *dd*	n.o.
14B	2.89 *dd*	2.87 *dd*	n.o.
15 (2)	—	—	3.88 *m*
16β	6.04 *d*	6.00 *d*	5.64*d*
Me-17	0.86 *d*	0.90 *d*	0.90 *d*
18A	2.20 *d*	2.43 *d*	2.43 *d*
18B	2.97 *d*	2.98 *d*	3.00 *d*
19α	—	6.79 *s*	6.80 *s*
19A	4.36 *d*	—	—
19B	4.97 *d*	—	—
Me-20	0.94 *s*	1.15 *s*	1.16 *s*
H-3′	—	7.08 *qq*	7.08 *qq*
Me-4′	—	1.79 *d*	1.81 *d*
Me-5′	—	1.88 *s*	1.89 *s*
OAc	1.93 *s*	1.78 *s*	1.80 *s*
OAc	2.09 *s*	—	—

	J(Hz)		
	1	2	3
2β,3α	n.o.	2.7	2.0
6β,7α	11.7	11.4	11.3
6β,7β	4.4	4.6	4.6
11α,12A	11.5	11.3	10.9
11α,12B	5.1	6.5	5.8
13β,14A	3.9	3.7	n.o.
13β,14B	10.7	10.5	n.o
14A,14B	18.7	18.6	n.o.
13β,16β	5.7	5.5	5.1
17,8β	6.4	6.2	7.0
18A,18B	3.9	4.3	4.3
19A,19B	12.2	—	—
3′,4′	—	7.1	7.1
3′,5′	—	1.4	1.3

*Taken from ref. [4].
n.o. = not observed.

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