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SESQUITERPENE LACTONES FROM *CREPIS RHOEADIFOLIA*

W. KISIEL* and B. BARSZCZ

Department of Phytochemistry, Institute of Pharmacology, Polish Academy of Sciences, PL-31-343 Kraków, Poland

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Key Word Index—*Crepis rhoeadifolia*; Asteraceae; Lactuceae; sesquiterpene lactones; guaianolides, zaluzanin C derivatives; 9α-hydroxy-4β,11β,13,15-tetrahydrozaluzanin C; 9α-hydroxy-4α,11β,13,15-tetrahydrozaluzanin C.

Abstract—Four derivatives of the sesquiterpene lactone zaluzanin C were isolated from the roots of *Crepis rhoeadifolia*. Two of these were new epimeric guaianolides and their structures were determined by spectroscopic methods as 9α-hydroxy-4β,11β,13,15-tetrahydrozaluzanin C and 9α-hydroxy-4α,11β,13,15-tetrahydrozaluzanin C. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

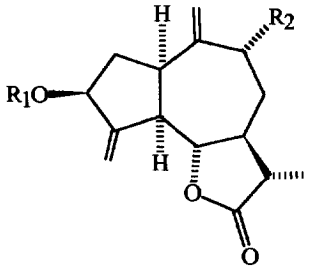
Representatives of the genus *Crepis* are being studied in several laboratories [1]. In our earlier paper, we reported the isolation of sesquiterpene lactone glycosides from *Crepis pyrenaica* (L.) W. Greuter [2]. The chemistry of *Crepis rhoeadifolia* M. B., a plant of medicinal interest [3], has not been examined so far. Recently we have obtained some phenolics from the root ethanolic extract of the plant [4] and now describe the results of our work on sesquiterpene lactone constituents present in the same extract. The known guaianolides isolated were β-D-glucopyranosides of 11β,13-dihydrozaluzanin C (**2**) [5] and its 9α-hydroxy derivative (ixerin F) (**3**) [6] and in addition two new epimeric derivatives of zaluzanin C (**4** and **5**) were characterized.

RESULTS AND DISCUSSION

The main sesquiterpene lactone constituent of the roots of *C. rhoeadifolia* was ixerin F (**3**); the other lactones were isolated in very small amounts only. The known guaianolide glucosides, identified by comparison of their ^{1}H NMR and mass spectra with spectra in our files, were reported previously from *Crepis species* [1, 7, 8].

Lactone **4** accompanied **5**, but could be separated by successive preparative TLC. The structures of the two compounds were evident from their ^{1}H NMR and mass spectra. Assignments of ^{1}H NMR signals were performed by spin decoupling and ^{1}H–^{1}H COSY correlations. The EI-mass spectrum of **4** and **5** showed M^+ ions at *m/z* 266 indicating the same molecular formula ($C_{15}H_{22}O_4$) and were both characterized by the presence of the same prominent fragments at *m/z* 248 and *m/z* 230, resulting from loss of two molecules of water. The ^{1}H NMR spectra were also similar and indicated that **4** and **5** are epimers at C-9 of the known guaianolides **6** and **7**, respectively. The latter lactone, which had originally been isolated from *Arctotis grandis* Thunb. and characterized by the formula **6** [9], was then revised in favour of the structure **7** [10]. Lactone **6** was obtained from *Liabum floribundum* Less. [10]. Later on, the compound was described as a constituent of *Vernonia angusticeps* Ekm. and its absolute configuration has been established [11]. Moreover, further evidence for the relative configuration of **7** was adduced by selective difference NOE experiments [11]. As regards the ^{1}H NMR spectra of **4** and **5** compared with those of **6** and **7**, respectively, the main differences were the coupling costants involving H-9 and the chemical shifts of H-1 and H-9 which resonated downfield by *ca* 0.6 ppm. The difference in the coupling constants of the H-9 signal (doublet of doublet, $J = 3.5$ and 3.5 Hz for **4** and **5** contrasted with doublet of doublet, $J = 11$ and 4 Hz, for **6** and **7**) demonstrated that the orientation of the C-9 hydroxyl group differed in the respective compounds. Consequently H-1 of **4** and **5** was deshielded relative to H-1 of **6** and **7** by the C-9 hydroxyl which is *cis* to H-1 and α-orientated. The frequencies of the diagnostic H-3 and H-15 signals of **4** and **5** were directly comparable with those of **6** and **7**, respectively [11]. Finally, the fact that the α-hydroxyl and the α-methyl were attached to C-9 and C-11, respectively, became obvious on comparison of the ^{1}H NMR spectra of **4** and **5** with that of their 4,15-dehydroderivative i.e. 9α-hydroxy-11β,13-dihydro-

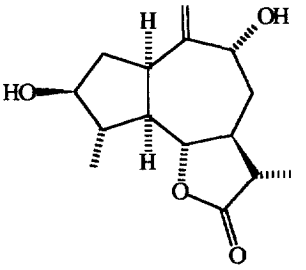
*Author to whom correspondence should be addressed.



1 R_1=H, R_2=OH

2 R_1=Glc, R_2=H

3 R_1=Glc, R_2=OH



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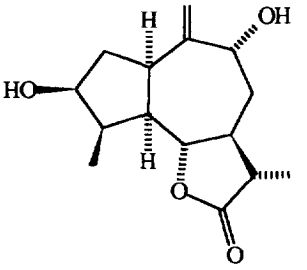

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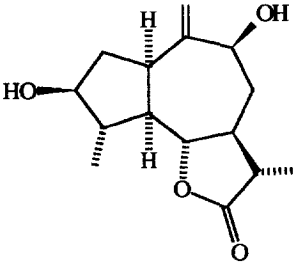

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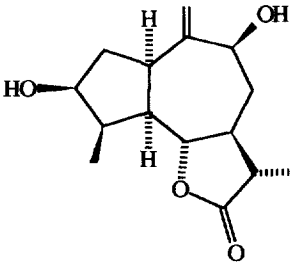

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zaluzanin C (**1**) which is also a constituent of *Crepis* species [8].

A survey of the phytochemical literature concerning *Crepis* species indicates that among the taxa containing guaianolides either 8-, or 9-hydroxyderivatives of zaluzanin C, often occurring together as in *C. pyrenaica* [2], are most common (9 out 10 taxa).

Table 1. ^{1}H NMR data of compounds **4** and **5** (500 MHz, $CDCl_3$, TMS as int. standard, δ values)

H	4	5
1	3.16 *br ddd*	3.28 *br ddd*
2	2.16 *br ddd*	1.98 *m*
2′	1.74 *br ddd*	1.98 *m*
3	3.76 *ddd*	4.28 *ddd*
4	1.83 *ddq*	2.35 *ddq*
5	1.94 *br ddd*	2.25 *m*
6	3.88 *br dd*	4.07 *dd*
7	2.19 *m*	2.23 *m*
8	2.26 *ddd*	2.25 *m*
8′	1.44 *ddd*	1.50 *ddd*
9	4.69 *br dd*	4.66 *dd*
11	2.19 *m*	2.23 *dq*
13	1.25 *d*	1.23 *d*
14	5.05 *s*	5.12 *s*
14′	4.99 *d*	5.09 *d*
15	1.21 *d*	0.97 *d*

J [Hz]: compound **4**: 1, 2 = 7.3; 1,2′ = 1, 5 = 5, 6 = 10.1; 1, 14′ = 1.5; 2, 2′ = 12.4; 2, 3 = 6.3; 2′, 3 = 3, 4 = 4, 5 = 9.1; 4, 15 = 6.6; 6, 7 = 9.6; 7, 8 = 3.0; 7, 8′ = 11.5; 8, 8′ = 13.0; 8, 9 = 8′, 9 = 3.5; 11, 13 = 7.0; compound **5**: 1, 2 = 1, 2′ = 10.0; 1, 5 = 10.8; 1, 14′ = 1.3; 2, 3 = 2′, 3 = 8.6; 3, 4 = 4, 5 = 6.0; 4, 15 = 7.2; 5, 6 = 11.0; 6, 7 = 9.0; 7, 8 = 11.5; 7, 8′ = 2.6; 7, 11 = 12.0; 8, 8′ = 13.0; 8, 9 = 8′, 9 = 3.4; 11, 13 = 6.6.

EXPERIMENTAL

General procedure. Merck silica gel was used for CC (Art. 7754) and TLC (Art. 5553). Semiprep. HPLC was performed on a Delta-Pak C-18 cartridge column (particle size 15 μm, 25 × 100 mm) coupled to a UV photodiode array detector. The column was eluted with MeOH–H_2O (1:1) at flow rate 3 ml min^{-1}.

Plant material. Roots of *C. rhoeadifolia* were collected in August 1993 from plants growing in the Garden of Medicinal Plants of the Institute of Pharmacology, Polish Academy of Sciences, Kraków, where a voucher specimen is deposited.

Extraction and isolation. The dried and powdered plant material (102 g) was exhaustively extracted with EtOH at room temp. The extract on evapn at red. pres. furnished a residue (7 g) which was chromatographed on silica gel using as eluents hexane–EtOAc (up to 50%), followed by EtOAc–MeOH (up to 10%). Elution of the column with hexane–EtOAc (1:1) afforded frs containing **4** and **5** which were combined according to their homogenity. The relevant frs after repeated separation by TLC (hexane–EtOAc, 1:1, two developments, and $CHCl_3$–MeOH, 9:1) gave **4** (6 mg), **5** (4 mg) and a mixture of **4** and **5** (8 mg). Elution with EtOAc–MeOH (19:1) and (9:1) furnished two crude sesquiterpene lactone glycoside frs, respectively. The less polar one was purified by TLC ($CHCl_3$–MeOH, 9:1), followed by RP HPLC giving **2** (7 mg). Sepn of the more polar fr. by TLC ($CHCl_3$–MeOH, 17:3) yielded **3** (92 mg).

9α-*Hydroxy*-4β,11β,13,15-*tetrahydrozaluzanin C* (**4**). Gum; EI-MS (15 eV) *m/z* (rel. int.): 266 [M^+]

(11), 248 $[M-18]^+$ (14), 230 $[M-2\times18]^+$ (8), 220 $[M-18-28]^+$ (11), 193 (38), 175 (19), 168 (100).

9α-*Hydroxy*-4α,11β,13,15-*tetrahydrozaluzanin C* (**5**). Gum; EI-MS (15 eV) *m/z* (rel. int.): 266 $[M^+]$ (4), 248 $[M-18]^+$ (8), 230 $[M-2\times18]^+$ (6), 220 $[M-18-28]^+$ (9), 193 (29), 175 (20), 168 (82), 44 (100).

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