

APRESSIN, A GUAIANOLIDE OF THE ENDOPEROXIDE TYPE FROM *ACHILLEA DEPRESSA*

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INTRODUCTION

As a part of our research on the sesquiterpene lactones from Compositae, especially from the genus *Achillea*, we have begun a study of *Achillea depressa* L. We now wish to report the isolation and structural elucidation of a new guaianolide from the flowers of this species. We have named this compound apressin, to which structure **1** has been assigned.

RESULTS AND DISCUSSION

Following the method described in the Experimental we obtained a crystalline product with a bitter taste, mp 182–184°, $[\alpha]_D -46.6^\circ$, which had the molecular formula $C_{17}H_{20}O_7$ ($M^+ 336$). The presence of an α -methylene- γ -lactone moiety was indicated by the appearance of IR bands at 1768 and 1652 cm^{-1} and this was substantiated by the presence, in the 1H NMR spectrum, of characteristic pairs of low field doublets at δ 5.81 and 6.19 as well as a triplet at 119.7 in the ^{13}C NMR spectrum (off

Table 2. ^{13}C NMR spectral data of compound **1**

Carbons	Chem. shift
C-1	74.1* (s)
C-2	133.3 (d)
C-3	137.6 (d)
C-4	78.5* (s)
C-5	41.7 (d)
C-6	72.1 (d)
C-7	69.7 (d)
C-8	30.4 (t)
C-9	98.4 (d)
C-10	93.7 (s)
C-11	139.3 (s)
C-12	169.2 (s)
C-13	119.7 (t)
C-14	21.6* (q)
C-15	13.6 (q)
OAc	20.8* (q)
	170.1 (s)

*These signals may be interchanged.

Table 1. 1H NMR spectral data of compounds **1** and **2**

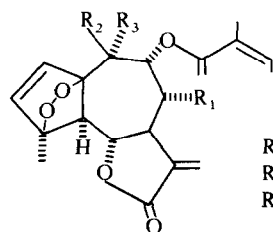
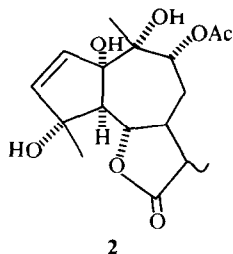
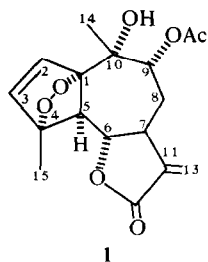
Protons	1	2
H-2	6.41 dd	5.94 d
H-3	6.37 dd	5.88 d
H-5	2.67 dbr	2.75 d
H-6	3.78 t	4.25 t
H-7	3.44 m	2.25 m
H-8 α	2.31 ddd	2.25 m
H-8 β	1.95 ddd	1.75 m
H-9	5.03 dd	5.17 dd
H-11	—	2.25 m
H-13	5.45 d	1.26 d
H-13'	6.19 d	
H-14	1.36 s	1.12 s
H-15	1.72 s	1.45 s
OAc	2.16 s	2.17 s
OH	2.33 s	2.20 s br 3.20 s br 3.42 s br

J (Hz) for **1**: 2, 3 = 5.9; 2, 5 = 3, 5 = 0.7; 5, 6 = 6, 7 = 7, 8 β = 10.3; 7, 8 α = 9, 8 β = 7.8; 7, 13 = 3.2; 7, 13' = 3.7; 8 α , 8 β = 13.1; 8 α , 9 = 9.2.

resonance). All 1H NMR spectral data are summarized in Table 1. They are in accordance with the proposed structure and the assignments were confirmed by decoupling experiments. The data of the ^{13}C NMR spectrum are given in Table 2.

The IR spectrum of **1** exhibited one strong carbonyl band at 1740 cm^{-1} due to an acetoxy group, which was also indicated by the 1H NMR signal at δ 2.12 and by the mass spectral fragmentation ($M^+ - 42$ and $M^+ - 60$). Similarly the presence of a hydroxyl group was verified by IR and MS data (ν_{max} 3450 cm^{-1} and $M^+ - 18$). The lack of a signal due to a proton geminal to the hydroxyl group in the 1H NMR spectrum of **1**, as well as the resistance of the hydroxyl group towards acetylation with acetic anhydride in pyridine at room temperature, supports its assignment to a tertiary position.

The 1H and ^{13}C NMR spectra of **1** also revealed the presence of a double bond (δ 6.37, 6.41 and 133.3, 137.6, respectively). The position of this double bond between C-2 and C-3 was substantiated by the fact that apart from



	3	4	5
R ₁	H	H	OH
R ₂	Me	OH	Me
R ₃	OH	Me	OH

the long-range coupling between the olefinic protons and H-5 (see below) no other coupling was observed, i.e. irradiation of all other signals present in the ^1H NMR spectrum did not have any influence on the pattern of the signals due to the olefinic protons.

The lactone moiety, the acetoxyl and hydroxyl groups account for five of the seven oxygen atoms present in the molecule. Since there are no ^1H NMR signals characteristic of protons on an oxirane it became evident that both the remaining oxygen atoms must form an endoperoxide ring attached to the tertiary carbons C-1 and C-4. This suggestion was supported by the ^{13}C NMR resonance in the region characteristic of sp^3 -hybridized carbons carrying oxygen atoms. The singlets at 74.1 and 78.5 ppm (off-resonance) were assigned to C-4 and C-1 (or vice versa). The presence and location of the endoperoxide ring were also confirmed by the ^1H NMR spectral data of the 11,13-dihydro-1,4,10-triol **2**, obtained by catalytic hydrogenation of **1**. The signals due to the methyl protons at C-4 and C-10 as well as those of the olefinic protons at C-2 and C-3 were shifted significantly upfield in the ^1H NMR spectrum of the triol **2** compared with the endoperoxide **1** (Table 1). The mass spectrum of the triol **2** showed the molecular formula $\text{C}_{17}\text{H}_{24}\text{O}_7$ (M^+ at m/z 340) and the elimination of three molecules of water ($M^+ - 18$, $M^+ - 36$ and $M^+ - 54$).

The relative configuration of the seven chiral centres present in apressin **1** at C-1, C-4, C-6, C-7, C-9 and C-10 was established on the basis of the following data. The *trans*-junction of the lactone ring was deduced from the coupling pattern of the H-6 signal ($J_{5,6} = J_{6,7} = 10.3$ Hz). The significant upfield shift (0.47 ppm) of the H-6 signal of **1** relative to the H-6 signal of **2** is due to the characteristic anisotropic effect of the C-2/C-3 double bond. This allowed us to assign the β -orientation of the olefinic bridge. This assignment was confirmed by NOE experiments.* Irradiation of the H-2 and H-3 signals caused enhancement of the signals due to H-6, H-9 and H-8 β . Furthermore, the observed long-range coupling

(0.7 Hz) between the olefinic protons and H-5 provided additional evidence for the β -position of the olefinic bridge. A similar homoallylic coupling is reported to be present in a norbornene system between the bridge hydrogen and the olefinic protons only when they are in the *anti*-position [1]. The large NOE between H-6 and H-9 shows that they are in a *syn*- β -relationship to each other. This is also consistent with the coupling pattern of the H-9 ^1H NMR signal. The *syn*-relationship of H-9 and the methyl group at C-10 was also established by the observation of a significant NOE.

From the foregoing data we deduced that apressin (**1**) is 9 α -acetoxyl-1 α ,4 α -endoperoxy-10 α -hydroxy-6 β ,7 α -guaiano-2,3-en-6,12-olide.

Recently Bohlmann and Knoll [2] reported the isolation of three guaianolides, **3**, **4** and **5**, from two South African *Athanasia* species. The novel endoperoxide structure and the stereochemistry of these lactones were tentatively assigned on the basis of the ^1H NMR and ^{13}C NMR data. Apart from the ester side chain at C-9, there are no structural differences between **3**, **4** and **1**. The ^1H NMR data of compounds **1** and **3** also correlate very well. However, the assignment of the signals due to the C-4 and C-10 methyl groups of lactones **3** and **4** contradict our interpretation. There is no doubt that the singlet at δ 1.36 in the spectrum of apressin (**1**) must be due to the C-10 methyl group, since irradiation at this frequency leads to a large increase of the area of the H-9 signal. The comparatively low field resonance of the C-4 methyl group might be due to the anisotropic effects of the neighbouring double bond and oxygen atoms. Apressin (**1**) and the lactones **3**–**5** differ only in their stereochemistry, in particular in the orientation of the endoperoxide bridge. Bohlmann and Knoll [2] suggested the β -position of the endoperoxide ring and they claimed that the compounds **3** and **4** are epimeric at C-10. They concluded that the C-10 hydroxyl group in **4** is β -orientated on the basis of the downfield shift of the signals of H-2, H-6 and H-9 when compared with these signals in **3**. By comparing the ^1H NMR data of **1** with that of **3** and **4** we do not believe that the hydroxyl group located on a flexible cycloheptane ring is likely to lead to the observed differences in the chemical shifts of certain ^1H NMR signals. This fact might be better explained by an epimeric relationship of the endoperoxide ring in **3** and **4**. Hence, we suggest that the stereochemistry of the lactone **3** is the same as that of apressin (**1**). The lactone **4** is most probably epimeric at C-1 and C-4.

The guaianolides represent a large group among the sesquiterpene lactones [3]. A number of different oxygen functions and substitution patterns of the guaianolide skeleton have been recorded. However, guaianolides of endoperoxide nature have previously not been described. The occurrence of 1,4-endoperoxide is not unexpected in view of their close chemical relationship to the corresponding 1,2,3,4-diepoxy, a few of which are already known.

EXPERIMENTAL

Mps are uncorr. All spectra were recorded under the following conditions: IR in KBr, ^1H NMR and ^{13}C NMR at 200 MHz in CDCl_3 with TMS as internal standard, MS at 70 eV direct inlet.

Plant material. The flowers of *Achillea depressa* L. were collected near Kostenez (Bulgaria) in June 1976.

*NOE values referred to in the text are $>10\%$.

Isolation of apressin (1). Air-dried flowers (2.8 kg) were extracted at room temp. $3 \times$ with 10l. CHCl_3 . The extracts were evapd *in vacuo* yielding a viscous liquid (210 g) which was dissolved in hot aq. EtOH (1:1) containing $\text{Pb}(\text{OAc})_4$. This was left for 24 hr, thereafter filtered and extracted with petrol. The aq. ethanolic layers were concd *in vacuo*, most of the EtOH being eliminated, and the residue was extracted with CHCl_3 . After evaporating the solvent the resulting viscous liquid (23 g) was chromatographed on Si gel (1 kg) and the column was eluted with C_6H_6 and mixtures of C_6H_6 - Me_2CO .

Apressin (1). The product obtained in 0.1% yield from the C_6H_6 - Me_2CO (7:1) elution crystallized in petrol-EtOAc (1:1), mp 182 – 184° , $\text{C}_{17}\text{H}_{26}\text{O}_7$ (M^+ 336), $[\alpha]_D - 46.6^\circ$ (c 0.27, EtOH), IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450, 1768, 1740, 1652, 920, ^1H NMR and ^{13}C NMR: Tables 1 and 2.

Attempted acetylation of 1. Compound **1** (10 mg) was kept in Ac_2O (0.3 ml) and pyridine (0.3 ml) for 20 hr at room temp. Work-up in the usual way yielded the starting compound **1** (TLC, IR, mp).

Hydrogenation of 1. Compound **1** (12 mg) in EtOAc was hydrogenated in the presence of Pd/C at room temp. and 4 mol of H_2 was consumed in 2 hr. The filtered soln was evapd *in vacuo* and the crude product (11 mg) was purified by prep. TLC to give colourless crystals of **2** (5 mg), mp 205 – 207° , $\text{C}_{17}\text{H}_{24}\text{O}_7$ (M^+ 340), IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3520, 3370, 1762, 1745, ^1H NMR: Table 1.

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REFERENCES

1. Snyder, E. I. and Franzus, B. (1964) *J. Am. Chem. Soc.* **86**, 1166.
2. Bohlmann, F. and Knoll, K.-H. (1979) *Phytochemistry* **18**, 995.
3. Fischer, N. H., Olivier, E. J. and Fischer, H. D. (1979) *Prog. Chem. Nat. Prod.* **38**, 166.