Phytochemistry, Vol. 28, No. 12, pp. 3528 3530, 1989.
Printed in Great Britain.

0031 9422/89 $3.00 + 0.00

GLAUCOLIDES FROM *ACHILLEA FRAGRANTISSIMA*

M. ABDEL-MOGIB, J. JAKUPOVIC, A. M. DAWIDAR, M. A. METWALLY* and M. ABOU-ELZAHAB*

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, F.R.G.; *Department of Chemistry, Faculty of Science, University of Mansoura, Mansoura, Egypt

(*Received in revised form* 28 *April* 1989)

Key Word Index—*Achillea fragrantissima*; Compositae; sesquiterpene lactones; glaucolides.

Abstract—*Achillea fragrantissima* afforded, in addition to several known glaucolides, five new compounds whose structures were elucidated by high field ^{1}H NMR spectroscopy.

INTRODUCTION

The mainly Mediterranean genus *Achillea* (Compositae, tribe Anthemideae) with about 85 species contains a wide variety of constituents. In addition to flavones and highly unsaturated amides many other compounds have been reported. *Achillea fragrantissima* (Forssk.) Sch. Bip. has been studied for flavanoids [1, 2], essential oil [3], sesquiterpene lactones [4] and the roots for unsaturated amides [5]. The aerial parts, collected from Sinai, gave several sesquiterpene lactones, all belonging to the glaucolide type, closely related to two lactones from a collection from Israel [4]. The results are discussed in this paper.

RESULTS AND DISCUSSION

The extract of the aerial parts of *A. fragrantissima* gave in addition to known glaucolides **1**–**6**, **12** and **13** [6–8], five new ones, **7**–**11**. The glaucolide **7** has already been prepared by the oxidation of **3** and **4** respectively [7]. The comparison of the ^{1}H NMR data of the natural product with that of the synthetic product showed their identity.

The ^{1}H NMR spectra of **8** and **9** differed from that of **7** (Table 1) by the lack of one and two acetate signals, respectively, and the expected upfield shift of the protons at the acetoxy group-bearing carbons. By acetylation both lactones gave **7**. The results of the NOE experiments with **8** confirmed the proposed stereochemistry. Saturation of H-15 enhanced the signal of H-6 (10%). Similar intensity enhancement was observed for H-5 (12%) on irradiation of H-3. The ^{13}C NMR spectrum (Experimental) further supported the structure.

The ^{1}H NMR spectra of **10** and **11** (Table 1) again differed in the number of the acetate signals and the chemical shifts of H-13. The upfield shift of the methyl group signals and of H-5 indicated the presence of eudesmanolides. The NOE experiments with **11** solved the stereochemical problems and the relative position of the acetate group in the A ring. Effects were observed between H-14, H-15, H-2β, H-6 and H-8β, as well as between H-1, H-3, H-5 and H-9.

The chemistry of this species differed from that found previously with other *Achillea* species. The isolation of glaucolides, usually only found in Vernonieae but recently also observed in representatives of the tribe Anthemideae (*Artemisia* [6, 7], *Brocchia* [8]) and *Cotula* [9], could be of chemotaxonomical importance. Further investigations may show the relevance of these compounds.

EXPERIMENTAL

The air-dried plant material (550 g, collected from Wadi Elarbaeen, Saint Katherine, Sinai on 2 April 1987) was extracted with Et_2O–petrol–MeOH (1:1:1) for 24 hr at room temp. After defatting, the extract was separated by CC into four fractions (1, Et_2O–petrol 1:9; 2, Et_2O–petrol 1:3 and Et_2O–petrol 1:1; 3, Et_2O and Et_2O–MeOH 9:1 and 4, Et_2O–MeOH, 3:1). TLC of fr. 1 gave 25 mg cycloartenyl acetate and 20 mg taraxasteryl acetate and of fr. 2 gave 12 mg santolinadiol. One-sixth of fr. 3 was separated by HPLC (MeOH–H_2O, 1:1, always RP 8) affording 16 mg **8** (R_t 9.5 min), 8 mg **13** and 6 mg **7** (R_t 18.0 min). One-half of fr. 4 was reseparated by flash chromatography. Three crude fractions were collected. HPLC of the fr. 1 (MeOH–H_2O, 11:9) gave 25 mg of the mixture of **3** and **4** (4:1). HPLC of the fr. 2 (MeOH–H_2O, 1:1) afforded 15 mg **9** (R_t 4.4 min), 18 mg **11** (R_t 6 min) and 25 mg **2**. Fraction 3 gave by HPLC (MeOH–H_2O, 9:11) 45 mg **10**, 60 mg **5** and **6** (4:1), 45 mg **1** and 40 mg **12**.

1-*Oxo-afraglaucolide* (**7**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755 (γ-lactone, OAc), 1680 (C=C–C=O); MS reported in ref. [7].

13-*O-Desacetyl*-1-*oxo-afraglaucolide* (**8**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1755 (γ-lactone, OAc), 1685 (C=C–C=O); MS *m/z* (rel. int.): 320.126 [M]$^+$ (6) (calc. for $C_{17}H_{20}O_6$: 320.126), 260 [M−HOAc]$^+$ (100), 242 [260 −H_2O]$^+$ (46), 232 [260−CO]$^+$ (42), 214 (50), 109 (90); ^{13}C NMR ($CDCl_3$, C-1–C-15): 198.4 *s*, 44.2 *t*, 75.5 *d*, 136.3 *s*, 127.0 *d*, 79.5 *d*, 164.9 *s*, 23.4 *t*, 33.6 *t*, 148.2 *s*, 127.5 *s*, 169.9 *s*, 55.0 *t*, 125.2 *t*, 10.8 *q*; OAc: 173.9 *s*, 21.0 *q*.

1,13-*Bis*-O-*desacetyl*-1-*oxo-afraglaucolide* (**9**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1750 (γ-lactone), 1675 (C=C–C=O); MS *m/z* (rel. int.): 278 [M]$^+$ (0.5), 260.105 [M−H_2O]$^+$ (8) (calc. for $C_{15}H_{16}O_4$: 260.105), 85 (100).

3β-*Acetoxy*-1β, 4α, 13-*trihydroxyeudesm*-7(11)-*en*-6α,12-*olide* (**10**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1765 (γ-lactone),

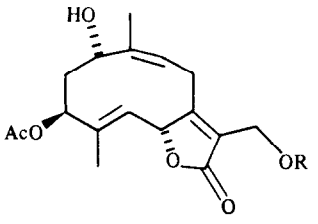
Table 1. ^{1}H NMR spectral data of compounds **7**–**11** ($CDCl_3$, 400 MHz, δ-values)

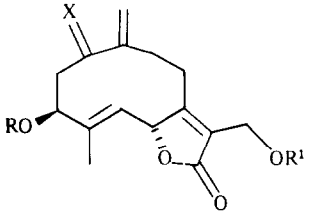
H	7	8	9	10†	11
1	—	—	—	3.35 *dd*	3.53 *dd*
2	3.74 *dd*	3.74 *dd*	3.46 *br dd*	1.89 *ddd*	2.02 *ddd*
2′	2.63 *dd*	2.63 *dd*	2.68 *br dd*	1.62 *ddd*	1.71 *ddd*
3	5.55 *dd*	5.55 *br dd*	4.60 *br dd*	4.65 *dd*	4.80 *ddd*
5	4.88 *br d*	4.87 *br d*	4.70 *br d*	1.38 *d*	1.51 *d*
6	5.33 *br d*	5.33 *br d*	5.32 *br d*	5.06 *br d*	5.14 *br d*
8	2.85 *dd*	2.78 *ddd*	2.83 *ddd*	2.94 *ddd*	3.07 *ddd*
8′	2.16 *br dd*	2.15 *ddd*	2.09 *br dd*	2.35 *br ddd*	2.44 *br ddd*
9	3.10 *br dd*	3.09 *ddddd*	2.99 *ddd*	2.12 *ddd*	2.23 *ddd*
9′	2.23 *br dd*	2.25 *ddd*	2.29 *br dd*	1.17 *br ddd*	1.27 *br ddd*
13	4.88 *d*	4.42 *	4.33 *	4.23 *br s*	4.82 *br d*
13′	4.80 *d*				4.75 *br d*
14	5.83 *br s*	5.83 *d*	5.73 *br s*	0.99 *br s*	1.10 *s*
14′	5.70 *d*	5.74 *d*	5.69 *d*		
15	1.78 *d*	1.78 *d*	1.74 *br s*	1.36 *br s*	1.45 *s*
15′					
OAc	2.10 s	2.10 s		2.02 s	2.10 s
	2.11 s				2.08 s

*Centre of AB system.

†In $CDCl_3$–CD_3OD (2:1).

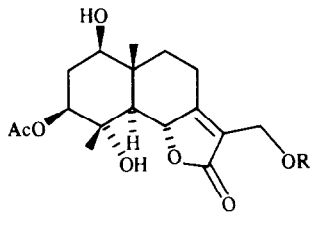
J[Hz]: Compounds **7**–**9**: 2, 2′ = 14; 2, 3 = 2′, 3 = 9; 5, 6 = 10; 5, 15′ = 1.5; 8, 8′ = 14; 8, 9 = 6.5; 8, 9′ = 8′, 9 = 9, 14 = 9, 14′ = 2; 8′, 9′ = 9, 9′ = 13; compounds **10** and **11**: 1,2 = 2, 3 = 4; 1, 2′ = 2, 2′ = 2′, 3 = 12.5; 5, 6 = 11.5; 8, 8′ = 15; 8, 9 = 2; 8, 9′ = 4; 8′, 9 = 5.5; 8′, 9′ = 9, 9′ = 13.

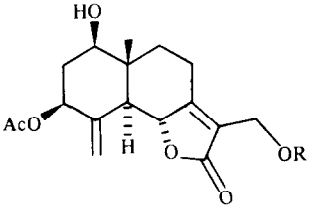




	1	2
R	H	Ac

	3	4	5	6	7	8	9
R	Ac	Ac	Ac	Ac	Ac	Ac	H
R¹	Ac	Ac	H	H	Ac	H	H
X	β-OH,H	α-OH,H	β-OH,H	α-OH,H	O	O	O





	10	11
R	H	Ac

	12	13
R	H	Ac

1745, 1240 (OAc); MS *m/z* (rel. int.): 322.142 $[M-H_2O]^+$ (4) (calc. for $C_{17}H_{22}O_6$: 322.142), 307 $[322-Me]^+$ (7), 304 $[322-H_2O]^+$ (3), 262 $[322-HOAc]^+$ (12), 223 (36), 221 (32), 205 (80), 191 (100), 164 (56).

3β,13-Diacetoxy-1β,4α-dihydroxyeudesm-7(11)-en-6α,12-olide (**11**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1770 (γ-lactone), 1740, 1240 (OAc); MS *m/z* (rel. int.): 364.153 $[M-H_2O]^+$ (7) (calc. for $C_{19}H_{24}O_7$: 364.153), 349 $[364-Me]^+$ (6), 304 $[364-HOAc]^+$ (9), 244 $[304-HOAc]^+$ (32), 206 (90), 205 (81), 191 (100), 164 (63).

REFERENCES

1. Valent-Vetschera, K. (1978) *Naturwissenschaften* 437.
2. Valent-Vetschera, K. (1985) *Biochem. Syst. Ecol.* **13**, 119.
3. Aboubabl, E. A., Soliman, F. M., El-Zalani, S. M., Brunke, E. J. and El. Karsh, T. A. (1986) *Egypt J. Pharm. Sci.* **27**, 215.
4. Segal, R., Dov, A., Duddek, N., Snatzke, G., Rosenbaum, D. and Kajtar, M. (1987) *Tetrahedron* **43**, 4125.
5. Greger, H. (1964) *Planta Med.* 366.
6. Khafagy, S. M., Seif El-Din, A. A., Jakupovic, J., Zdero, C. and Bohlmann, F. (1988) *Phytochemistry* **27**, 1125.
7. Jakupovic, J., Klemeyer, H., Bohlmann, F. and Graven, E. H. (1988) *Phytochemistry* **27**, 1129.
8. Jakupovic, J., Abdel Aal, M., Eid, F., Bohlmann, F., El-Dahmy, S. and Sarg, T. (1988) *Phytochemistry* **27**, 2219.
9. Metwally, M. A., El-Dahmy, S., Jakupovic, J., Bohlmann, F., Dawidar, A. M. and Metwally, S. A. (1986) *Phytochemistry* **25**, 255.

Phytochemistry, Vol. 28, No. 12, pp. 3530–3531, 1989.
Printed in Great Britain.

0031 9422/89 $3.00 + 0.00

SYNTHESIS OF *EPI*-DEOXY- AND DEOXYARTEANNUIN B

NANCY ACTON and RONALD J. ROTH*

Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100. U.S.A.; *Department of Chemistry, George Mason University, Fairfax, VA 22030, U.S.A.

(*Received* 7 *March* 1989)

Key Word Index—*Artemisia annua*; Compositae; sesquiterpene lactones; photooxidation.

Abstract—Arteannuic acid has been converted into *epi*-deoxy- and deoxyarteannuin B in a rational synthesis and in good yield via a hydroperoxide.

INTRODUCTION

Artemisinin (qinghaosu, **1**) is an antimalarial drug isolated from *Artemisia annua* [1]. Other constituents of *A. annua* are of interest because they may be on a common biosynthetic pathway to artemisinin [2] and because they may be synthetic precursors to artemisinin in the laboratory. One such compound is arteannuic acid, **2**, a relatively abundant and easily isolable plant constituent [3]. Others have reported the chemical conversion of **2** into **1** by a seven step route in *ca* 7% overall yield [4].

epi-Deoxyarteannuin B (**3a**) and arteannuin B (α-epoxide of deoxyarteannuin B, **3b**), both known constituents of *A. annua* [5, 6], have been produced in the laboratory upon photooxidation of arteannuic acid [7–10]. The relative yield of each of these compounds varies considerably with photolysis conditions, and the reported yield of **3a** has been low. The photooxidation is presumed to occur via the hydroperoxide **4a**, but this compound was not isolated.

RESULTS AND DISCUSSION

We find that low temperature photooxidation of **2** (−78°, CH_2Cl_2, Methylene Blue) affords hydroperoxide **4a** with only trace amounts of either arteannuin B or **3a** evident by liquid chromatography. On standing in chloroform-d_1 hydroperoxide **4a** produces arteannuin B in 28% yield. More interesting, however, is that **4a** can be converted into either **3a** or **3b** uncontaminated with arteannuin B as follows.

Treatment of the photooxidation reaction mixture with one equivalent of triphenylphosphine or triethyl phosphite effected deoxygenation of the hydroperoxide to the corresponding alcohol **4b**. To prepare **3a**, this alcohol acid was not isolated, but was extracted into aqueous sodium carbonate. Heating the carbonate solution (100°, 2 hr), then acidifying, afforded, after extraction and bulb-to-bulb distillation, a 72% yield (from arteannuic acid) of **3a**. Thus **3a** can be obtained from *A. annua* via **2** with no chromatographic separations required.

On treatment with trifluoroacetic acid, **4b** rapidly dehydrates to the conjugated 1,8a-dehydroarteannuic acid (Acton, N., unpublished results). However, allowing **4b** to stand at 30–40° in $CDCl_3$ resulted in conversion to **3b**, a labile compound which was reported as the last intermediate in the synthesis of (racemic) arteannuin B [11]. The identity of **3b** was confirmed by epoxidation to give arteannuin B which was identical with the natural product by ^1H NMR, IR, HPLC, TLC, and optical rotation.