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EUDESMANOLIDES FROM *PLUCHEA DIOSCORIDIS*

FERDINAND BOHLMANN, MOHAMED A. METWALLY and JASMIN JAKUPOVIC

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, West Germany

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Key Word Index—*Pluchea dioscoridis*; Compositae; sesquiterpene lactones; eudesmanolides; thiophene derivatives.

Abstract—Reinvestigation of the aerial parts of *Pluchea dioscoridis* afforded, in addition to known compounds, five new eudesmanolides and a new thiophene derivative. The stereochemistry of one of the eudesmanolides isolated previously has been corrected. The structures were elucidated by spectroscopic methods.

INTRODUCTION

The genus *Pluchea* (Compositae, tribe Inuleae) is placed in the subtribe Inulinae [1]. So far nine of the 40 species of this genus have been studied chemically. In addition to typical thiophenacetylenes [2], eudesmane derivatives such as the plucheines [3–9] as well as a few eudesmanolides [9–11] were reported and may be of chemotaxonomic importance. We now have reinvestigated the aerial parts of *P. dioscoridis* (L.) DC. [= *Conyza dioscoridis* (L.) Desf.] and the results are discussed in this paper.

RESULTS AND DISCUSSION

From the aerial parts of *P. dioscoridis*, two eudesmanolides [10, 11] and some thiophenacetylenes [2] have so far been isolated. A more detailed investigation of material, collected in the desert near Geza in Egypt, gave in addition to the thiophenacetylene **8** [2] and the eudesmanolides **1** [11] and **4** [10] five new eudesmolides, 9α-hydroxysantamarin (**2**), the corresponding 11β,13-dihydroderivative **3**, 9α-angeloyloxy ludovicin A (**5**), the corresponding isovalerate **6** as well as the 3-methylvalerate **7**.

The structure of the diol **2** followed from the molecular formula ($C_{15}H_{20}O_4$) and the ^{1}H NMR spectrum (Table 1) which was close to that of **1**. The absence of an ester group caused the expected shift differences while the stereochemistry followed from the couplings observed. The flexibility of the cyclohexene ring did not allow a clear assignment of the configuration at C-1 if models were inspected. However, NOE difference spectroscopy clearly established the proposed stereochemistry. Irradiation of the H-5 signal gave a clear effect of H-1 and vice versa, while irradiation of the H-14 signal caused NOE of H-2β, H-6, H-8β and H-9.

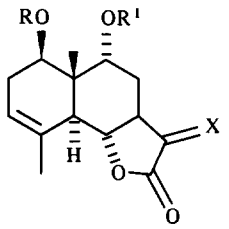
The dihydro derivative **3** could not be separated completely from **2** even by HPLC. However, after addition of diazomethane, **2** was transformed to the corresponding pyrazoline and **3** could then be separated easily by TLC. The structure of **3** followed from the ^{1}H NMR spectrum (Table 1) and was of course similar to that of **2**. Spin decoupling allowed the assignment of all signals. The stereochemistry at C-11 was deduced from the large $J_{7,11}$ coupling.

The ^{1}H NMR spectral data of **5** (Table 1) were close to those of **4**. The different position of the angelate residue clearly followed from the results of spin decouplings and the altered shifts of H-1 and H-9. Also the stereochemistry at C-1, C-5, C-6, C-7 and C-9 could easily be deduced from the couplings observed while that at C-3 and C-4 could not be elucidated directly. Preliminary assignment of the configuration of **4** was achieved from inspection of models [10]. We have now studied the problem again using NOE difference spectroscopy. As expected, irradiation of the H-14 signals gave NOE of H-1, H-2β, H-6 and H-8β, while irradiation of the H-15 signal first led to some confusion as clear NOE were observed only for H-3, H-5 and H-6. Careful inspection of the ^{1}H NMR spectrum, however, showed that together with the methyl group a small water signal was present at δ1.56. As in other cases, a rapid exchange with the proton of the 1-hydroxy group caused the observed NOE with H-5. After exchange with deuterium oxide, only NOE with H-3 and H-6 could be observed, thus clearly establishing the β-orientation of the 4-methyl group. As the couplings and the chemical shifts of **4** were the same as in the spectrum of **5** the configuration of **4** and **5** at C-4 obviously were the same. Accordingly, the configuration of **4** previously proposed [10] is in error and has to be changed at C-3 and C-4 (α-epoxide).

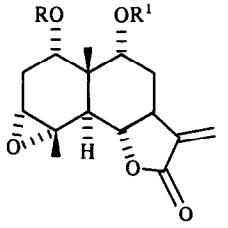
The ^{1}H NMR spectrum of **6** (Table 1) was very close to that of **5**, only the signals of the angelate residue were replaced by those of an isovalerate and the chemical shift of H-9 was slightly influenced as α, β-unsaturated esters always lead to a small downfield shift of the signal of the proton at the carbon bearing the ester group.

The ^{1}H NMR spectrum of **7** (Table 1), molecular formula $C_{21}H_{30}O_6$, was very close to that of **6**, but the signals from the ester were replaced by those of 3-methylvalerate. The mass spectrum also showed that the acyl cation (*m/z* 85) in the spectrum of **6** was replaced by *m/z* 99 [$C_5H_{11}CO$] in **7**. The position of the methyl group in the C-6 ester followed from the ^{1}H NMR spectrum by the chemical shift of the methyl doublet and the signal of one of the H-2′ signals. This was overlapped by the H-8 multiplet as followed from spin decoupling.

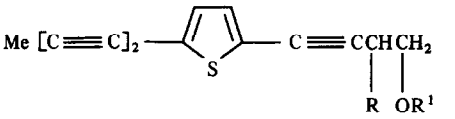
From a second sample of *P. dioscoridis*, collected near Mansoura, the less polar parts gave in addition to **9** [2] a second ester, the isovalerate **10**. The ^{1}H NMR spectral data (see Experimental), the UV maxima and the molecu-



	1	2	3
R	Ang	H	H
R^1	H	H	H
X	CH_2	CH_2	αMe.H



	4	5	6	7
R	Ang	H	H	H
R^1	H	Ang	iVal	$COCH_2CH(Me)Et$



	8	9	10
R	OH	Cl	Cl
R^1	H	Ac	iVal

Table 1. ^1H NMR spectral data of 2, 3 and 5–7 (400 MHz, $CDCl_3$, TMS as internal standard)

	2	3	5	6	7
H-1	4.14 *dd*	4.07 *dd*	3.67 *br d*	3.61 *br d*	3.63 *br d*
H-2α	2.39 *dddq*	2.35 *br d*	2.23 *ddd*	2.19 *m*	2.23 *ddd*
H-2β	1.91 *m*	1.90 *m*	2.15 *br d*		2.16 *br d*
H-3	5.30 *br s*	5.23 *br s*	3.04 *br s*	3.04 *br s*	3.04 *br s*
H-5	2.77 *br d*	2.57 *br d*	2.92 *d*	2.91 *d*	2.92 *d*
H-6	3.96 *dd*	3.91 *dd*	4.05 *dd*	4.03 *dd*	4.04 *dd*
H-7	3.09 *ddddd*	2.10 *m*	3.04 *m*	3.04 *m*	3.04 *m*
H-8α	2.16 *ddd*	1.82 *ddd*	2.08 *m*	2.05 *m*	2.05 *m*
H-8β	1.85 *br dd*	1.91 *br dd*			
H-9	4.10 *dd*	4.00 *dd*	5.22 *dd*	5.12 *dd*	5.13 *dd*
H-11	—	2.20 *dq*	—	—	—
H-13	6.06 *d*	1.13 *d*	6.13 *d*	6.13 *d*	6.14 *d*
H-13′	5.37 *d*		5.41 *d*	5.40 *d*	5.41 *d*
H-14	0.86 *s*	0.82 *s*	0.96 *s*	0.93 *s*	0.94 *s*
H-15	1.84 *br s*	1.76 *s*	1.56 *s*	1.55 *s*	1.56 *s*
OH	—	—	2.64 *d*	2.64 *d*	2.65 *d*
OCOR	—	—	6.10 *qq*	2.19 *br d*	2.33 *dd*
			2.01 *dq*	2.10 *m*	2.05 *m*
			1.89 *dq*	0.94 *d*	1.30 *m*
					0.88 *t*, 0.92 *d*

J (Hz): Compounds 2/3: 1, 2α = 6; 1, 2β = 10; 2α, 2β = 18; 2α, 3 = 2β, 3 = 2, 5 = 3, 15 ~ 2; 5, 6 = 11; 6, 7 = 11; 7, 8α = 3; 7, 8β = 11; 7, 13 = 3.5; 7, 13′ = 3; 8α, 8β = 13; 8α, 9 = 2.5; 8β, 9 = 2.5 (compound 3: 7, 11 = 12.5; 11, 13 = 7); compounds 5–7: 1, OH = 8.5; 1, 2α = 4; 1, 2β = 1.5; 2α, 2β = 17; 2α, 3 = 2; 2β, 3 = 1.5; 5, 6 = 12; 6, 7 = 11; 7, 13 = 3; 7, 13′ = 3; 8α, 9 = 2.5; 8β, 9 = 2.5; OAng: 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5; iVal: 2′, 3′ = 3′, 4′ = 3′, 5′ = 7; $OCOCH_2CH(Me)Et$: 2′, 2′ = 14; 2′, 3′ = 3′, 6′ = 4′, 5′ = 7.

lar formula clearly showed that we were dealing with the corresponding isovalerate **10**. Thus surprisingly all epoxides differ in the configuration at C-1 from that of the corresponding Δ^3 lactones.

The isolation of these further five eudesmanolides clearly supports the placement of *Pluchea* in the Inulinae since this type of sesquiterpene lactone is widespread among other genera of this subtribe.

EXPERIMENTAL

The air dried aerial parts (470 g, collected in the desert near Geza, Egypt, in March 1982) was extracted with MeOH–Et_2O–petrol, 1:1:1, and worked-up in the usual fashion [12]. The polar CC-fractions (Et_2O–petrol, 1:1 and Et_2O–MeOH, 10:1) were further separated by TLC. TLC (Et_2O) of the first fraction gave 50 mg **1** (identical with authentic material by ^1H NMR, mp and TLC). TLC of the second fraction (Et_2O–MeOH, 50:1) gave 60 mg 9-hydroxycostunolide (R_f 0.62) (identical with authentic material by ^1H NMR and TLC), a mixture (R_f 0.55) which gave by repeated TLC (Et_2O–MeOH, 100:1) further 40 mg 9-hydroxycostunolide and again a mixture (A) and second mixture (R_f 0.45) (B). HPLC (RP 8, MeOH–H_2O, 3:2) of mixture A gave 5 mg **4** (R_t = 2.0 min), 2.1 mg **5** (R_t = 2.7 min), 3 mg **6** (R_t = 3.2 min) 1.8 mg **7** (R_t = 5.5 min) and 6 mg **8** (R_t = 9.0 min). HPLC (RP 8, MeOH–H_2O, 3:2) of mixture B afforded 9 mg of a mixture of **2** and **3** (R_t = 2.4 min) as well as 2.1 mg **2** (R_t = 3.2 min). To the mixture of **2** and **3** in Et_2O excess of CH_2N_2 was added. TLC (Et_2O–MeOH, 50:1) gave 7.5 mg **3** (R_f 0.45). The extract of a second collection (550 g) (obtained near Mansoura, Egypt, in August 1983) afforded by CC (Et_2O–petrol, 1:3) and TLC (Et_2O–petrol, 1:6) 5 mg **10** (R_f 0.55) and 20 mg **9** (R_f 0.50). Probably due to the small amounts **3**, **5**–**7** and **10** could not be induced to crystallize though they were homogeneous by TLC, HPLC and by ^1H NMR.

9α-Hydroxysantamarin (**2**). Colourless crystals, mp 149°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3605 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (6) (calc. for $C_{15}H_{20}O_4$:264.136), 246 $[M-H_2O]^+$ (7.4), 228 $[246-H_2O]^+$ (8.5), 55 (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+56.7 \quad +57.6 \quad +66.2 \quad +117.1} (CHCl_3,\ c\ 0.2).$$

9α-Hydroxy-11β,13-dihydrosantamarin (**3**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 266.152 $[M]^+$ (8) (calc. for $C_{15}H_{22}O_4$: 266.152), 248 $[M-H_2O]^+$ (26), 233 $[248-Me]^+$ (5), 230 $[248-H_2O]^+$ (3), 173 (66), 55 (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+20 \quad +21 \quad +24 \quad +49} (CHCl_3;\ c\ 0.5).$$

9α-Angeloyloxyludovicin A (**5**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1775 (γ-lactone), 1715, 1640 (C=CCO_2R); MS *m/z* (rel. int.): 362.173 $[M]^+$ (0.2) (calc. for $C_{20}H_{26}O_6$: 362.173), 344 $[M-H_2O]^+$ (0.4), 263 $[M-OCOR]^+$ (8), 262 $[M-RCO_2H]^+$ (9), 245 $[263-H_2O]^+$ (4), 83 $[C_4H_7CO]^+$ (83), 55 $[83-CO]^+$ (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 58 \quad 546 \quad 436\,nm}{+68 \quad +72 \quad +76 \quad +142} (CHCl_3;\ c\ 0.9).$$

9α-Isovaleryloxyludovicin A (**6**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 1765 (γ-lactone), 1725 (CO_2R); MS *m/z* (rel. int.): 364.189 $[M]^+$ (0.1) (calc. for $C_{20}H_{28}O_6$: 364.189), 346 $[M-H_2O]^+$ (0.3), 320 $[M-C_2H_4O]^+$ (3.3), 262 $[M-RCO_2H]^+$ (41), 85 $[C_4H_9CO]^+$ (74), 57 $[85-CO]^+$ (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+73 \quad +77 \quad +87 \quad +148} (CHCl_3;\ c\ 0.6).$$

9α-[3'-Methyl valeryloxy]-ludovicin A (**7**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 1770 (γ-lactone), 1725 (CO_2R); MS *m/z* (rel. int.): 378.204 $[M]^+$ (0.2) (calc. for $C_{21}H_{30}O_6$: 378.204), 334 $[M-C_2H_4O]^+$ (5), 262 $[M-RCO_2H]^+$ (58), 99 $[C_5H_{11}CO]^+$ (58), 71 $[99-CO]^+$ (69), 55 (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+71 \quad +73 \quad +106 \quad +178} (CHCl_3;\ c\ 0.18).$$

2-[Penta-1,3-diin-1-yl]-5-[4-isovaleryloxy-3-chloro-but-1-in-1-yl]-thiophene (**10**). Yellow oil; UV (Et_2O): 341, 321 nm; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2215 (C≡C), 1740 (CO_2R); MS *m/z* (rel. int.): 332.064 $[M]^+$ (6) (calc. for $C_{18}H_{17}SO_2Cl$: 332.064), 230 $[M-RCO_2H]^+$ (100), 195 $[230-Cl]^+$ (32), 85 $[C_4H_9CO]^+$ (20), 57 $[85-CO]^+$ (89); ^1H NMR ($CDCl_3$): δ4.43 *dd* and 4.39 *dd* (H-1), 4.96 *ddd* (H-2), 7.07 *d* and 7.11 *d* (H-6 and H-7), 2.04 *s* (H-13), 2.27 *d* (H-2'), 2.14 *tqq* (H-3'), 0.97 *d* (H-4', H-5') [*J* (Hz): 1, 1 = 11; 1, 2 = 5.5; 1', 2 = 7; 6, 7 = 4; 2', 3' = 3', 4' = 3', 5' = 7].

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