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A CAROTANE DERIVATIVE AND A EUDESMANOLIDE FROM *INULA CRITHMOIDES**

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Key Word Index—*Inula crithmoides*; Compositae; carotane derivative; sesquiterpene lactone; eudesmanolide.

Abstract—The aerial parts of *Inula crithmoides* afforded a new carotane derivative and a eudesmanolide, inucrithmolide. The most probable structures were elucidated by the spectroscopic data and by some chemical transformations.

INTRODUCTION

About 25 species (including unpublished results) of the large genus *Inula* (Compositae, tribe Inuleae) have already been investigated chemically. Most widespread are eudesmanolides [1–4], but other types of sesquiterpene lactones were also isolated [1, 4]. We have now investigated *Inula crithmoides* L. for the first time.

RESULTS AND DISCUSSION

From the aerial parts, in addition to friedelin, α-amyrin, sitosterol, its β-D-glucoside and fatty acids, a sesquiterpene of molecular formula $C_{20}H_{30}O_4$ was isolated. The spectral data indicated the presence of an angelate, a keto and a hydroxy group. The ^1H NMR spectrum (Table 1) displayed signals typical of an olefinic methyl and an

Table 1. ^1H NMR spectral data of compounds **1** and **2** ($CDCl_3$)

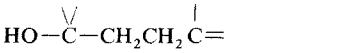
	1	**1** + $Eu(fod)_3$, 65°	**2**		**1** ^{13}C
1-H	5.26 *d*	8.64 *d* (*br.*)	5.58 *d*	C-1	75.8 *d*
2-H	5.69 *d* (*br.*)	6.39 *d* (*br.*)	5.63 *d* (*br.*)	C-2	119.9 *d*
4α-H		3.32 *dd*	2.2 *m*	C-3	145.1 *s*
4β-H		2.71 *dd*		C-4	37.2 *t*
5α-H	2.4–2.0 *m*	2.98 *d* (*br.*)	2.0 *m*	C-5	29.2 *t*
5β-H		2.93 *dd*	1.8 *m*	C-6	82.4 *s*
7-H	2.15 *m*	3.48 *ddd*	2.15 *m*	C-7	50.9 *d*
8α-H	2.1 *m*	3.62 *dd*	1.95 *m*	C-8	38.6 *t*
8β-H	2.4 *m*	4.02 *dd*	1.55 *ddd*	C-9	220.0 *s*
9-H	—	—	4.03 *dd*	C-10	60.3 *s*
11-H	2.09 *dqq*	2.57 *m*	1.84 *dqq*	C-11	26.4 *d*
12-H	1.07 *d*	1.34 *d*	1.02 *d*	C-12	21.1 *q*
13-H	0.99 *d*	1.19 *d*	0.95 *d*	C-13	18.3 *q*
14-H	1.07 *s*	2.18 *s*	1.06 *s*	C-14	26.4 *q*
15-H	1.76 *s* (*br.*)	1.98 *s* (*br.*)	1.74 *s* (*br.*)	C-15	24.6 *q*
OAng	6.03 *qq*	6.31 *q* (*br.*)	6.21 *qq*	C-1′	166.2 *s*
	1.98 *dq*	2.48 *d* (*br.*)	2.03 *dq*	C-2′	127.2 *s*
	1.84 *dq*	2.38 *s* (*br.*)	1.93 *dq*	C-3′	138.9 *d*
				C-4′	20.7 *q*
				C-5′	15.7 *q*

J (Hz): compound **1**: 1, 2 = 7.5; 4α, 4β = 13; 4α, 5β = 12; 5α, 5β = 13; 7, 8α = 7; 7, 8β = 11; 7, 11 = 5; 8α, 8β = 15; 11, 12 = 13, 13 = 7; 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5; compound **2**: 8α, 9 = 7; 8β, 9 = 6.

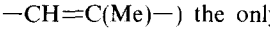
* Part 309 in the series 'Naturally Occurring Terpene Derivatives'. For Part 308 see Bohlmann, F., Zdero, C., Robinson, H. and King, R. M. (1981) *Phytochemistry* **20**, 522.

olefinic proton. The latter was coupled with a hydrogen which must be placed at the ester-group bearing carbon (5.26 *d*, $J = 7.5$ Hz). Additional methyl signals, two doublets and a singlet, were visible, indicating the presence of an isopropyl group. This was confirmed by spin decoupling as irradiation at 2.15 collapsed the methyl doublets to singlets. The other signals could be assigned only by adding $Eu(fod)_3$ and by further spin decoupling. Two additional sequences **A** and **B** could be established.

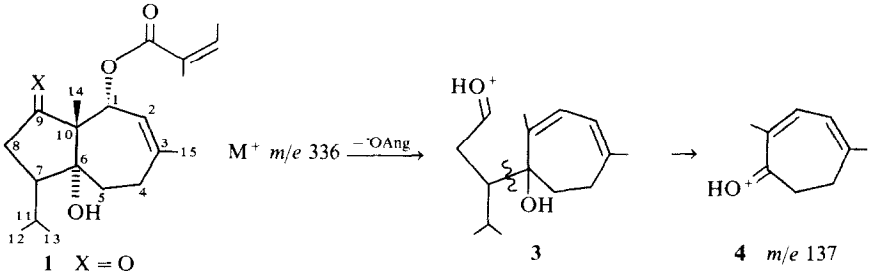
A



B

However, the presence of a hydroxyl at C-6 followed from the observed strong $Eu(fod)_3$ induced shifts of 7-H and of two of the protons in **B** only. Together with the already discussed part () the only possible structure seems to be that of the carotane derivative **1**. Inspection of Dreiding models in connection with the observed $Eu(fod)_3$ induced shifts led to the stereochemistry at C-6 and C-7, while that at C-1 could be deduced from the observed coupling $J_{1,2}$, which should be much smaller with a β-acyloxy group. Borohydride reduction afforded the epimer **2** only. Its ^{1}H NMR data and the ^{13}C NMR data (Table 1) of the ketone supported the proposed structure. The chemical shift of C-7 could be explained only if this carbon is deshielded by a neighbouring hydroxyl, while the upfield shift of the C-5 signal obviously must be due to the γ-effects of the 10-methyl and the isopropyl group, which should not be present in a compound with a 6β-hydroxyl group. Also the downfield shift of the C-10 signal required deshielding effects of several groups. The mass spectrum supported the structure. Especially the base peak **4** (*m/e* 137, $C_9H_{13}O$) in the spectrum of **2**, most probably formed via **3** as shown in the scheme, is important.

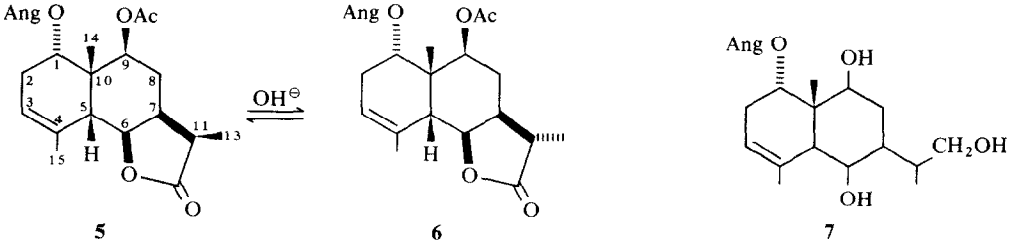
The isolation of **1** seems to be the first example of a carotane derivative from Composites. So far carotanes have been isolated only from Umbelliferae. A sesquiterpene lactone was also isolated, which was probably the eudesmanolide **5** and which we have named inucrithmolide. The structure followed from the ^{1}H NMR data (Table 2). The nature of the two ester residues followed from the characteristic signals, while the presence of a 11,13-dihydro lactone was indicated by the doublet at δ 1.21 and the absence of typical signals for methylene protons. Careful spin decouplings allowed assignment of all signals. The proposed *cis*-6,12-lactone was indicated by the observed coupling $J_{6,7} = 6.3$ Hz. Inspection of a Dreiding model further showed that the observed couplings indicated a *cis*-decalin system ($J_{5,6} = 9$ Hz) with oxygen functions at C-1 and C-9. In conformation with this assignment irradiation of the signals of the allylic protons (2-H) resulted in sharpening of both 1-H and the 3-H signals, while irradiation at 5.02 (*dd*, 9-H) collapsed the three-fold doublets at 1.83 and 1.65 to double doublets. The latter were further coupled with a four-fold doublet at 2.69, obviously the 7-H signal, as spin decoupling allowed the assignment of the sequence 5-H through 7-H and 7-H through 13-H. The stereochemistry at C-1, C-9 and C-11, as well as the relative position of the ester residues, was still unsolved. All attempts at partial saponification were unsuccessful. Only isomerisation was observed on treatment with potassium hydroxide in methanol–water at room temperature. The only possible epimerization centre seems to be C-11. The changes in the ^{1}H NMR data (Table 2) clearly indicated different conformations for both isomers. The observed couplings of 9-H in both isomers could be explained only if one isomer is present in a chair and the other in a boat conformation. A boat conformation should be preferred in an isomer with a 11-β-methyl group and a 9β-ester residue, which would lead to strong steric interactions in a chair conformation. However, isomerisation at C-11 would lead to an isomer with a chair conformation, where steric effects between the ester and the C-11-methyl group are negligible. Dreiding models of these two conformations agree with the observed couplings. Therefore the natural compound most probably had the proposed stereochemistry with the B ring



1 X = O
2 X = β-OH, H

3

4 *m/e* 137



5

6

7

Table 2. ^{1}H NMR spectral data of compounds **5**, **6** and **7** ($CDCl_3$)

	5	6	7*
1β-H	4.80 *dd* (*br.*)	4.85 *s* (*br.*)	4.78 *s* (*br.*)
2α-H	2.30 *d* (*br.*)	2.35 *m*	
2β-H	2.06 *d* (*br.*)		
3-H	5.33 *s* (*br.*)	5.37 *s* (*br.*)	5.28 *s* (*br.*)
5β-H	2.95 *d* (*br.*)	2.95 *m*	
6α-H	4.60 *dd*	4.68 *dd*	
7α-H	2.96 *dddd*	2.92 *m*	
8α-H	1.65 *ddd*	2.1–1.8 *m*	
8β-H	1.83 *ddd*		
9α-H	5.02 *dd*	5.21 *dd*	
11-H	2.95 *dq*	3.03 *dq*	
13-H	1.21 *d*	1.23 *d*	1.04 *d*
14-H	1.08 *s*	1.00 *s*	1.04 *s*
15-H	1.89 *s* (*br.*)	1.89 *s* (*br.*)	1.97 *s* (*br.*)
OAc	1.97 *s*	1.87 *s*	—
OAng	6.03 *qq*	6.16 *qq*	6.00 *qq*
	1.94 *dq*	2.03 *dq*	1.95 *dq*
	1.85 *dq*	1.93 *dq*	1.85 *dq*

* Other signals very broad.

J (Hz): compound **5**: 1β, 2 ~ 2; 2α, 2β = 18; 5β, 6α = 9; 6α, 7α = 6.3; 7α, 8α = 3; 7, 8β = 11; 7, 11 = 8; 8α, 9 = 6.5; 8β, 9α = 11.5; 11, 13 = 7; compound **6**: 5β, 6α = 11; 6α, 7α = 7; 7α, 11 = 11.5; 8α, 9α = 4; 8β, 9α = 3.

in a boat form. Finally the relative position of the ester groups could be established by partial reduction with lithium aluminium hydride, which resulted in the formation of a triol **7**. Though this compound was not obtained in a pure state, the absence of the acetate signal and the presence of the angelate signals together with an unchanged 1-H signal in the ^{1}H NMR spectrum allowed the assignment of the relative positions of the two ester groups.

The presence of a 6,12-eudesmanolide and of a carotane derivative is remarkable, as most lactone-containing *Inula* species investigated so far have afforded 7,12-eudesmanolides [1–4]. However, there are some species, from which no lactones have been isolated [1, 6]. Further investigations may show whether separation of this genus is indicated.

EXPERIMENTAL

^{1}H NMR: 270 MHz, TMS as internal standard; MS: 70 eV, direct inlet. The air-dried plant material (5 kg), collected in the flowering state in January 1979 from the Mediterranean coastal region near Alexandria (Egypt), was extracted with Et_2O–petrol (1:2). The resulting extract was treated with EtOH–H_2O (3:2) and the soluble part was extracted first with petrol (A) and then with $CHCl_3$ (B). Fraction A (60 g) afforded on chromatography (Si gel) friedelin, sitosterol and its β-D-glucoside, α-amyrin and fatty acid. Fraction B (8 g) was fractionated on Si gel with $CHCl_3$–(2–8%)MeOH. After rechromatography (Si gel, $CHCl_3$) 60 mg **5** and 20 mg **1** (TLC: CCl_4–EtOAc, 4:1) were obtained.

1α-*Angeloyloxy*-6α-*hydroxy*-9-*oxo*-*carot*-2-*ene* (**1**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1750 (five-membered ring ketone); 1725, 1650 (C=CCO$_2$R), 855 (—CH=C<); MS *m/e* (rel. int.): 334,214 (M^+, 1) ($C_{20}H_{30}O_4$), 316 (M – H_2O, 1), 291 (M – $CHMe_2$, 1), 251 (M – COC_4H_7, 33), 234 (M – AngOH, 5), 233 (316 – COC_4H_7, 5), 137 ($C_9H_{13}O$, 18), 119 (137 – H_2O, 15), 83 ($C_4H_7O^+$, 100), 55 (83 – CO, 55).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-212.8 \quad -222.8 \quad -256.5 \quad -466.8}$$

(c = 3.69, $CHCl_3$).

To 10 mg **1** in 1 ml MeOH 10 mg $NaBH_4$ were added at room temp. After 10 min dil. H_2SO_4 was added. Usual work-up and TLC (Et_2O–petrol, 1:1) afforded 7 mg **2**, colourless oil, MS *m/e* (rel. int.): 336.230 (M^+, 0.5) ($C_{20}H_{32}O_4$), 318 (M – H_2O, 0.5), 300 (318 – H_2O, 0.2), 253 (M – COC_4H_7, 17), 236 (M – AngOH, 28), 218 (236 – H_2O, 9), 203 (218 – Me, 3), 193 (236 – $CHMe_2$, 7),, 175 (218 – $CHMe_2$, 26), 137.097 ($C_9H_{13}O$, 100), 119 (137 – H_2O, 20), 83 ($C_4H_7CO^+$, 64), 55 (83 – CO, 59).

Inucrithmolide (**5**). Colourless crystals, mp 162–4°. IR ν_{max}^{KBr} cm^{-1}: 1765 (lactone), 1720, 1250 (OAc), 1700, 1645 (C=CCO$_2$R); MS *m/e* (rel. int.): 330.183 (2) (M – AcOH) ($C_{20}H_{26}O_4$), 230 (330 – AngOH, 5), 215 (230 – Me, 3), 204 (42), 83 ($C_4H_7CO^+$, 100), 55 (83 – CO, 52).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-122.0 \quad -127.3 \quad -145.1 \quad -246.8} \quad (c = 0.41).$$

To 5 mg **5** in 1 ml MeOH were added 200 mg KOH in 0.5 ml H_2O at room temp. for 1 hr. TLC (Et_2O–petrol, 1:1) afforded a mixture of 4 mg **5** and **6**, which could not be separated (*ca* 1:1). Reaction at 70° (30 min) changes only the relation of **5** and **6** to 2:3, while no saponification product could be obtained.

To 3 mg **5** in 2 ml absolute Et_2O 5 mg $LiAlH_4$ in 0.1 ml Et_2O were added at room temp., directly followed by addition of dil.

H_2SO_4. The crude product obtained by extraction with Et_2O was analysed by ^1H NMR only.

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