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GLAUCOLIDE-LIKE SESQUITERPENE LACTONES FROM *COTULA CINEREA*

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Key Word Index—*Cotula cinerea*; Compositae; sesquiterpene lactones; germacranolides; glaucolides; guaianolide.

Abstract—The aerial parts of *Cotula cinerea* gave, in addition to widespread compounds, a characteristic diacetylenic spiroketal enolether and several sesquiterpene lactones, three of them being glaucolide-like lactones. The structures were elucidated by highfield ^{1}H NMR spectroscopy.

INTRODUCTION

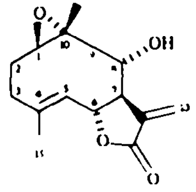
The genus *Cotula* (tribe Anthemideae) has been studied by several groups. Typical acetylenic compounds seem to be characteristic for this genus [1]; however, sesquiterpene lactones were reported from two species [2, 3]. As it is still not clear whether or not this genus should be placed into a separate tribe [4, 5], we have studied a further species. The results will be discussed in this paper.

RESULTS AND DISCUSSION

A reinvestigation of *Cotula cinerea* Del., from which only flavones had been isolated [6], gave β-farnesene, α- and γ-curcumene, camphor, taraxasteryl acetate, the spiro ketal enolether **6** [7], desacyl laurenobiolide angelate [8], 6α-angeloyloxy-1α-hydroxygermacra-4*E*, 9*Z*,11-trien-8α,12-olide [9], as well as five further sesquiterpene lactones, the germacranolides **1–4** and the guaianolide **5**. The structure of **1** followed from the characteristic ^{1}H NMR spectrum (Table 1). All the signals were assigned by spin decoupling which led to the sequence H-5–H-9 while the double doublet at δ 2.72 and a singlet at 1.46 indicated the presence of a 1,10-epoxide. Inspection of a model showed that the couplings observed agreed with the proposed stereochemistry.

The ^{1}H NMR spectrum of **2** and **3** (Table 1) indicated that these compounds were closely related, lactone **3** being the acetate of **2**. At elevated temperature all signals could be assigned by spin decoupling though a few were unresolved multiplets. The presence of glaucolide-like lactones was indicated by a pair of broadened doublets at δ 5.02 and 4.82 (H-13) and a pair of doublets at δ 5.64 and 4.69 (H-5 and H-6). A keto group at C-1 afforded a downfield shift of two exomethylene proton signals and a double doublet at δ 4.98 was due to H-8 as it was coupled with signals which only could be those of H-9. The relative position of the acetoxy group in **3** followed from the chemical shift.

The ^{1}H NMR spectrum of **4** (Table 1) showed that a further glaucolide-like lactone was present. When the spectrum of **4** was compared with that of **3** it was obvious that the exomethylene group was replaced by a trisubstituted double bond. The H-8 signal was now only a doublet and spin decoupling showed that it was coupled with a broadened doublet at δ 5.11. Accordingly, a Δ^9-double bond had to be assumed. The presence of a 1-hydroxy group was deduced from the broadened double doublet at δ 4.54 which on irradiation sharpened the doublet at



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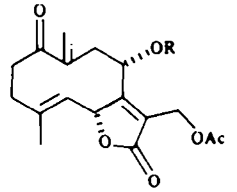
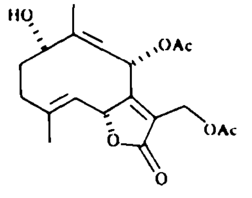


2 R = H
3 R = Ac



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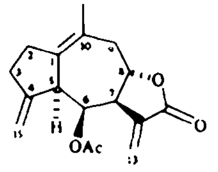

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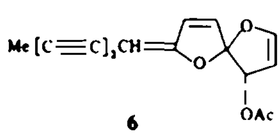

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Table 1. ^{1}H NMR spectral data of **1–5** (400 MHz, $CDCl_3$, TMS as int. standard)

H	**1** (60°)	**2**	**3** (60°)	**4**	**5**
1	2.72 *dd*	—	-	4.54 *br dd*	--
2	1.63 *m*	2.50 *m*	2.63 *m*	1.92 *m*	2.35 *m*
2′	2.15 *m*	3.15 *m*	3.23 *m*	2.06 *m*	
3	2.45 *m*	2.38 *m*	2.58 *m*	2.35 *m*	
3′	2.33 *m*	2.10 *m*	2.41 *m*		
5	5.29 *br d*	5.45 *d*	5.64 *d*	4.65 *d*	3.43 *br s*
6	4.29 *t*	4.64 *br d*	4.69 *br d*	5.56 *br d*	5.67 *dd*
7	2.99 *dddd*	–	—	—	3.03 *dddd*
8	4.13 *dt*	4.35 *br dd*	4.98 *dd*	5.90 *d*	4.68 *ddd*
9	2.08 *d*	2.64 *dd*	2.75 *t*	5.11 *br d*	2.35 *m*
9′		3.35 *br d*	3.29 *br d*		3.09 *br d*
13	6.40 *br d*	5.13 *br d*	5.02 *br d*	5.00 *br d*	6.25 *d*
13′	6.16 *br d*	5.00 *br d*	4.82 *br d*	4.94 *br d*	5.79 *d*
14	1.46 *s*	5.77 *d*	5.80 *br d*	1.91 *br s*	1.72 *br s*
14′		5.72 *d*	5.76 *d*		
15	1.88 *br s*	1.75 *br s*	1.78 *br s*	1.78 *br s*	4.99 *q* 4.83 *q*
OAc	—	2.13 *s*	2.09 *s* 2.02 *s*	2.08 *s* 2.11 *s*	2.04 *s*

J (Hz): Compound **1**: 1,2 = 10; 1,2′ = 3; 5,6 = 6,7 = 9.5; 7,8 = 5; 7,13 = 2.5; 7,13′ = 2; 8,9 = 8; compounds **2** and **3**: 5,6 = 10; 8,9 = 3; 8,9′ = 11; 9,9′ = 14; 13,13′ = 13; compound **4**: 1,2 = 11; 1,2′ = 4.5; 5,6 = 11; 8,9 = 10.5; 13,13′ = 12; compound **5**: 5,6 = 4.5; 6,7 = 7; 7,8 = 10; 7,13 = 3.5; 7,13′ = 3; 8,9 = 5; 8,9′ = 10; 9,9′ = 15.

δ5.11. Comparison with the data of a corresponding angelate with a 4,5-epoxy group, in which the stereochemistry had been established [Jakupovic, J., unpublished], indicated identical configuration. All the data, therefore, agreed best with the proposed structure. Compounds **3** and **4** are probably formed by oxygenation of 8α-acetoxycostunolide at C-7 followed by allylic rearrangement and acetylation. This diacetate then probably reacts with oxygen at C-1 and a hydrogen is abstracted at C-14 or C-9. This is supported by the occurrence of 7α-hydroxy derivatives and the corresponding $\Delta^{7(11)}$-13-acetoxy lactones in a *Podachaenium* species [10].

The ^{1}H NMR spectrum of **5** was close to that of chrysostamolide acetate [11]. However, the changed configuration at C-6 and the presence of a 1(10)-double bond was obvious. The coupling of H-6 was characteristically different and the exomethylene signals were missing. All signals were assigned by spin decoupling and only those of H-2, H-3 and H-9 overlapped.

The chemistry of this *Cotula* species may be an indication that this genus is related to the typical Anthemideae genera like *Artemisia*, *Chrysanthemum* and *Tanacetum*. Thus compounds like **6** have only been isolated from members of the tribe Anthemideae. Previous studies have shown that acetylenes of the dehydrofalcarinone type are also widespread [1]. They have, however, also been reported from other tribes. Sesquiterpene lactones which are highly oxygenated are present in many *Artemisia* species and related genera. So far glaucolide-like lactones have never been isolated from species outside the tribe Vernonieae and no lactones of type **2–4** have been reported. Further investigations may show whether these compounds are characteristic for *Cotula* or for a section of this problematic genus.

EXPERIMENTAL

The air dried aerial parts (150 g) (collected in the Red Sea coastal region near Hurgada in April 1984 voucher deposited in the department of Botany, University of Assiut, Egypt) were extracted with MeOH–Et_2O–petrol (1:1:1) and the extract was worked-up as reported previously [12]. The CC fraction (SiO_2) with petrol gave by TLC (SiO_2, $AgNO_3$-coated) 2 mg α- and 2 mg γ-curcumene as well as 4 mg β-farnesene. The fraction obtained with Et_2O–petrol (1:10) gave by TLC (SiO_2, PF 254, Et_2O–petrol, 1:10) 30 mg camphor and 15 mg taraxasteryl acetate. The fraction with Et_2O–petrol (1:3) gave by TLC (same solvent) 5 mg **6**. TLC of the fraction with Et_2O–petrol (1:1 and 2:3) gave 10 mg deacyllaurenobiolide angelate and 3 mg **5** (R_f 0.2). TLC ($CHCl_3$–MeOH, 10:1) of the fraction obtained with Et_2O gave 10 mg **3** (R_f 0.83), 2 mg 6α-angeloyloxy-1α-hydroxygermacra-4*E*,9*Z*,11-trien-8α,12-olide (R_f 0.63), 3 mg **1** (R_f 0.62) and 5 mg **2** (R_f 0.33). TLC (Et_2O) of the most polar CC fraction (Et_2O–MeOH, 10:1) gave 2 mg **4** (R_f 0.42) and 20 mg **2**. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material. All compounds were homogeneous by TLC in different solvent mixtures.

Deacetyl tulipinolide-1β,10α-*epoxide* (**1**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (2) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 $[M-H_2O]^+$ (3), 228 $[246-H_2O]^+$ (5), 213 $[228-Me]^+$ (4), 55 (100); CD (MeCN): $\Delta\varepsilon_{243} = -0.1$.

13-*Acetoxy*-8α-*hydroxy*-7,11-*dehydro*-11,13-*dihydroanhydroverlotorin* (**2**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone), 1745 (OAc); MS *m/z* (rel. int.): 320.126 $[M]^+$ (10) (calc. for $C_{17}H_{20}O_6$: 320.126), 260 $[M-HOAc]^+$ (100), 242 $[260-H_2O]^+$ (53), 214 $[242-CO]^+$ (40); CD (MeCN): $\Delta\varepsilon_{257} = +1.3$.

8α,13-*Diacetoxy*-7,11-*dehydro*-11,13-*dihydroanhydroverlotorin* (**3**). Colourless oil; IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1775 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 302.115 $[\mathrm{M}-\mathrm{HOAc}]^+$ (1.5) (calc. for $C_{17}H_{18}O_5$: 302.115), 287 $[302-\mathrm{Me}]^+$ (1), 260 $[302-\text{ketene}]^+$ (14), 242 $[302-\mathrm{HOAc}]^+$ (16), 55 (100).

8α,13-*Diacetoxy*-1α-*hydroxygermacra*-4E,7(11),9Z-*trien* 6α,12-*olide* (**4**). Colourless oil; IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1745 (OAc); MS *m/z* (rel. int.): 364.152 $[\mathrm{M}]^+$ (0.2) (calc. for $C_{19}H_{24}O_7$: 364.152), 304 $[\mathrm{M}-\mathrm{HOAc}]^+$ (0.6), 262 $[304-\text{ketene}]^+$ (3), 244 $[304-\mathrm{HOAc}]^+$ (6), 216 $[244-\mathrm{CO}]^+$ (4), 173 (36), 121 (58), 55 (100); CD (MeCN): $\Delta\varepsilon_{260} = -0.26$.

6-epi-1,10-*Dehydro*-10,14-*dihydrochrysostamolide acetate* (**5**). Colourless oil; IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1780 (γ-lactone), 1740 (OAc); MS *m/z* (rel. int.): 288.136 $[\mathrm{M}]^+$ (14) (calc. for $C_{17}H_{20}O_4$: 288.136), 228 $[\mathrm{M}-\mathrm{HOAc}]^+$ (34), 121 (71), 83 (100), 55 (84); CD (MeCN): $\Delta\varepsilon_{297} = -0.25$, $\Delta\varepsilon_{257} = +0.1$.

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