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FURTHER SESQUITERPENE LACTONES FROM THE GENUS *DITTRICHIA*

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Key Word Index—*Dittrichia graveolens*; *D. viscosa*; Compositae; sesquiterpene lactones; guaianolide; pseudoguaianolides; sesquiterpenes; benzoic acid derivatives.

Abstract—The aerial parts of *Dittrichia graveolens* afforded in addition to compounds isolated previously five new sesquiterpene lactones, two benzoic acid derivatives while *D. viscosa* gave two further derivatives of costic acid. The structures were elucidated by high field NMR spectroscopy.

INTRODUCTION

From the small genus *Dittrichia*, previously a section of *Inula*, one species, *D. viscosa* (L.) Greuter, has been investigated chemically. In addition to costic acid derivatives [1–4], the aerial parts of this very widespread species gave sesquiterpene lactones [2–4] as well as some flavanoids [5]. From the roots, in addition to a thymol derivative [3, 6], several rare germacranolides were isolated [6]. From *D. graveolens* (Desf.) Greuter, graveolide [7] and a pseudoguaianolide without assignment of stereochemistry were reported [8]. We have now reinvestigated a sample from Iran. In addition to known compounds several new sesquiterpene lactones and two unusual benzoic acid derivatives were isolated. From *D. viscosa* from Tenerife (Canary Islands) similar lactones but also a new costic acid derivative and a rearranged sesquiterpene were isolated. The structure elucidation will be discussed in this paper.

RESULTS AND DISCUSSION

The extract of the aerial parts of *D. graveolens* gave in addition to costic acid 10-isobutyryloxy-8,9-epoxythymol isobutyrate [9], confertin (3) [10], 8-epi-tomentosin [11], the benzoic acid derivatives 1 and 2, the pseudoguaianolides 4 and 5, the guaianolides 6, 6a and 6b as well as the diketone 7.

The structure of 2 followed from the molecular formula ($C_{12}H_{14}O_4$), the ^1H and the ^{13}C NMR spectra (see Experimental) and by the results of NOE difference spectroscopy. The presence of a vicinal disubstituted benzene derivative followed from the ^1H NMR data. The low field signal at δ7.85 required a neighbouring carbonyl group and the signals of the side chain indicated the presence of a hydroxyprenyl ester. Reaction of 2 with acetic anhydride afforded a monoacetate while prolonged reaction with diazomethane gave the phenolic ether. Saturation of the methoxy signal gave a clear NOE with H-3. The configuration of the double bond of the prenyl group followed from a clear NOE between H-4′ and H-2′. The mass spectrum of 2 showed typical fragments at *m/z* 138 $[M - C_5H_8O]^+$ and *m/z* 120 [base peak, $M - C_5H_{10}O_2]^+$. The ^{13}C NMR spectrum also supported the structure.

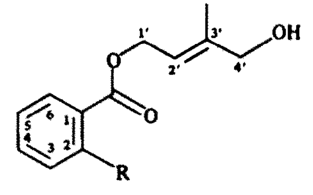
The ^1H NMR spectrum of 1 (see Experimental) was close to that of 2. However, the signals of the aromatic protons clearly showed that now a symmetric benzene derivative was present. As already followed from the molecular formula, 1 was the desoxy derivative of 2.

The ^1H NMR spectrum of 5 (Table 1) was close to that of 3. However, the signals of the exomethylene protons were replaced by a methyl doublet at δ1.00. Accordingly, a dihydro derivative of 3 was present. NOE difference spectroscopy allowed the assignment of the stereochemistry. Thus clear effects were obtained (always the first proton is the saturated one and the effect is given in parentheses; irradiation of H-14 and H-15 with low energy, $\gamma H_2 \sim 4$ Hz) between H-15, H-3 (2), H-6α (2), H-2β (4), H-9 (6) and H-6β (8), between H-14, H-9α (3), H-9β (5) and H-2β (3), between H-11, H-7 (6) and H-8 (2) as well as between H-8, H-11 (2) and H-7 (4).

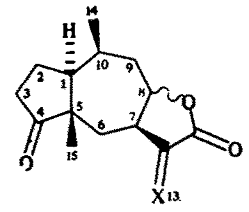
The ^1H NMR data of 4 (Table 1) were in part similar to those of 5. Clear differences were visible in the signals of H-8 indicating a changed stereochemistry. Clear NOEs were observed between H-15, H-14 (2), H-8 (4) and H-6β (7), between H-14, H-15 (3) and H-8 (5) as well as between H-13 and H-7 (3) which established the stereochemistry. The absence of a NOE between H-14 and H-1 indicated the configuration at C-1. A lactone with the same structure but without stereochemistry is reported from *Dittrichia graveolens* [8]. The data do not allow to decide whether 4 or 5 was isolated.

The structure of 6 followed from the ^1H NMR spectrum (Table 1) and NOE difference spectroscopy. The data differed slightly from those of the 1-epimer inuviscolide where the stereochemistry has been revised [12]. The configuration at C-1, C-4, C-5 and C-8 followed from the NOEs. Clear effects were observed between H-15, H-14 (3), H-2β (3) (not with H-5), between H-7, H-5 (4) and H-9α (4), between H-1 and H-5 (4) as well as between H-8, H-2β (5) and H-9β (6).

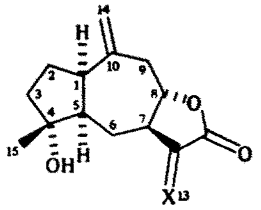
All data of 6a (Table 1) indicated that this lactone was the 11β,13-dihydro derivative of 6. This was further supported by the observed NOEs between H-7 and H-5 (7) as well as between H-11 and H-8 (4) while no effect was



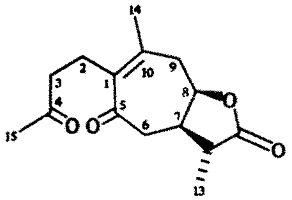
1 R = H
2 R = OH



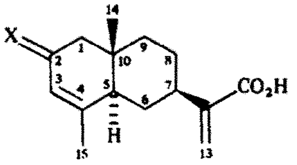
3 X = CH_2, 8αH
4 X = αMe,H,8βH
5 X = βMe,H,8αH



6 X = CH_2
6a X = αMe,H
6b X = αMe,H, 1*epi*



7



8a X = H_2
8b X = O
8c X = αOH, H
8d X = αO*i*Bu, H

9 **10**

observed between H-15 and H-5. The lactone **6b** was identical with a guaianolide from a *Geigeria* species [13]. A reinvestigation showed that the stereochemistry has to be revised to the 1β, 8βH-epimer as already established for inuviscolide [12]. Thus **6b** is 11β,13-dihydroinuviscolide.

The ^1H NMR spectrum of **7** (Table 1) again indicated the presence of a dihydrolactone. Furthermore, the chemical shift and the couplings of H-8 signal agreed with a 12,8β-olide. The downfield shifts of H-9 and H-15 required a conjugated 1(10)-double bond. This was supported by a broadened triplet (centre of an ABX system) for H-6 at δ2.41, a chemical shift which agreed with a keto group at C-5. The structure of **7** was further supported by the mass spectrum which showed a base peak at *m/z* 207, most likely due to loss of $MeCOCH_2$. Further loss of $C_5H_5O_2$ (lactone moiety) led to a strong fragment *m/z* 110. Obviously the lactone **7** was formed by degradation of *epi*-**6a** (elimination of water, followed by oxidative cleavage of the formed Δ^4-bond and isomerization of the $\Delta^{10(14)}$-bond).

Table 1. ^{1}H NMR spectral data of compounds **4**–**7** (400 MHz, $CDCl_3$, δ-values)

H	4	5	6	6a	7
1	1.81 *m*	2.11 *m*	3.13 *ddd*	3.03 *m*	—
2	2.01 *m*	1.94 *m*	1.90 *m*	1.89 *m*	2.58 *m*
2'	2.05 *m*	1.84 *m*	1.75 *m*	1.75 *m*	
3	2.20 *ddd*	2.14 *m*	1.83 *m*	1.73 *m*	2.39 *m*
3'	2.49 *ddd*	2.51 *ddd*			
5	—	—	2.18 *ddd*	2.13 *ddd*	—
6	2.57 *dd*	2.33 *dd*	2.08 *ddd*	1.80 *ddd*	2.41 *t*
6'	1.30 *dd*	1.25 *dd*	1.13 *ddd*	1.08 *ddd*	
7	1.85 *dddd*	2.57 *m*	2.64 *m*	1.71 *m*	2.07 *m*
8	4.29 *ddd*	4.64 *ddd*	3.84 *ddd*	3.79 *ddd*	4.44 *ddd*
9	2.29 *m*	2.25 *ddd*	3.11 *dd*	3.04 *dd*	2.78 (ABX)
9'	1.74 *ddd*	1.71 *ddd*	2.29 *dd*	2.17 *dd*	
10	2.31 *m*	2.16 *m*	—	—	—
11	2.33 *m*	2.87 *dq*	—	2.27 *dq*	2.25 *dq*
13	1.22 *d*	1.00 *d*	6.20 *d*	1.24 *d*	1.20 *d*
13'			5.50 *d*		
14	1.18 *d*	0.90 *d*	5.08 *br s*	5.09 *br s* 5.05 *br s*	2.10 *br s*
15	1.08 s	0.84 s	1.20 s	1.16 s	2.22 s

J [Hz]: Compound **4**; 2,3 = 2',3 = 2,3' = 9; 2',3' = 2; 3,3' = 19; 6,6' = 15; 6,7 = 5; 6',7 = 11.5; 7,8 = 9; 7,11 ~ 11; 8,9 = 3; 8,9' = 9,9' = 12; 9',10 = 6; 10,14 = 11,13 = 7; compound **5**: 2,3' = 9; 2',3' = 2; 3,3' = 19; 6,6' = 15; 6,7 = 2.5; 6',7 ~ 13; 7,8 = 6; 7,11 = 8; 8,9 = 5; 8,9' = 11; 9,9' = 13; 9,10 = 4; 9',10 = 10; 10,14 = 11,13 = 7; compound **6**: 1,2 = 1,2' ~ 9; 1,5 = 10; 5,6 = 5; 5,6' = 13; 6,6' = 14; 6',7 = 9; 7,8 = 8,9' = 10; 7,13 = 3.5; 7,13' = 3; 8,9 = 5; 9,9' = 12; compound **6a**: 1,5 = 10; 5,6 = 5; 5,6' = 6,6' = 13; 6,7 = 3; 6',7 = 10; 7,8 = 10; 7,11 = 11.5; 8,9 = 4.5; 8,9' = 10.5; 9,9' = 15; 11,13 = 7; compound **7**: 6,7 = 5; 7,8 = 9; 7,11 = 11; 8,9 = 3; 8,9' = 9; 11,13 = 7.

The aerial parts of *D. viscosa* (L.) Greuter collected in Tenerife gave the costic acid derivatives **8a**–**8c** [2, 4, 14] as well as the corresponding isobutyrate **8d**, the structure of which was easily deduced from its ^{1}H NMR spectrum which was close to that of **8c**. Furthermore the guaianolide **6**, its 8-epimer [15], carabrone [16], the corresponding alcohol [9] and the keto acid **9** were present. The structure of this compound which was isolated as its methyl ester followed from its ^{1}H NMR spectrum (see Experimental). All signals could be assigned by spin decoupling. They were in part very similar to those of related sesquiterpenes from an *Iphionia* species where the stereochemistry was established by NOE difference spectroscopy [17]. Most likely **9** is formed by oxidative cleavage of **8a** affording **10** which by aldol condensation would give the isolated ketone.

The chemistry of *Dittrichia* shows some differences to that of *Inula* which may support its separation from this genus. The constituents from the two species are similar but not identical.

EXPERIMENTAL

The air-dried aerial parts were extracted with MeOH–Et_2O–petrol (1:1:1) at room temp. and the extracts obtained were separated first by CC (silica gel) and further by PTLC (silica gel, PF 254) as reported previously [18]. The extract of the aerial parts of *D. graveolens* (300 g) collected 90 km north of Teheran (voucher deposited in the Dept. of Botany, Shahid Beheshty University, Teheran, Iran) gave by CC two main fractions (1; Et_2O–petrol, 3:1 and 2; Et_2O). PTLC (Et_2O–petrol, 3:1) of fraction 1 gave 40 mg 10-isobutyryloxy-8,9-epoxythymol isobutyrate, 80 mg costic acid, 30 mg **2** (R_f 0.75) and 3 mg **1** (R_f 0.68).

1. Colourless oil; MS *m/z* (rel. int.); 206 $[M]^+$ (1) ($C_{12}H_{14}O_3$), 188 $[M-H_2O]^+$ (2), 105 $[C_6H_5CO]^+$ (100), 77 $[105-CO]^+$ (22); ^{1}H NMR ($CDCl_3$); δ8.05 (*dd*, H-2, H-6), 7.44 (*dd*, H-3, H-5), 7.56 (*dd*, H-4), 4.92 (*br d*, H-1'), 5.67 (*tq*, H-2'), 4.10 (*br s*, H-4'), 1.81 (*br s*, H-5').

2. Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1680, 1620 (PhC=O); MS *m/z* (rel. int.); 222 $[M]^+$ (1) ($C_{12}H_{14}O_4$), 138 $[M-C_5H_8O]^+$ (54), 120 $[M-C_5H_{10}O_2]^+$ (100); ^{1}H NMR ($CDCl_3$, 400 MHz); δ6.98 (*ddd*, H-3), 7.46 (*ddd*, H-4), 6.88 (*ddd*, H-5), 7.85 (*dd*, H-6), 4.93 (*br d*, H-1'), 5.76 (*tq*, H-2'), 4.10 (*br s*, H-4'), 1.80 (*br s*, H-5'), 10.78 (*s*, OH) (*J* [*Hz*]; 3,4 = 4,5 = 5,6 = 8; 3,5 = 4,6 = 1.5; 1',2' = 7; 2',4' = 2',5' = 1); ^{13}C NMR ($CDCl_3$, C-1–C-7, C-1'–C-5'); δ105.5 *s*, 161.6 *s*, 117.6 *d*, 119.1 *d*, 117.8 *d*, 135.7 *d*, 170.1 *s*, 67.5 *t*, 130.0 *d*, 141.7 *s*, 61.6 *t*, 13.9 *q*. 5 mg **2** were heated with 0.1 ml Ac_2O for 2 hr at 70°. PTLC gave the monoacetate, ^{1}H NMR ($CDCl_3$); δ4.53 (*br s*, H-4'), 2.11 (*s*, OAc). To 5 mg **2** in 1 ml Et_2O 100 mg silica gel and excess of CH_2N_2 was added. After 12 hr, usual work-up gave the O-methyl ether, ^{1}H NMR ($CDCl_3$); δ3.91 (*s*, OMe), 6.98 (*d*, H-5).

Repeated PTLC of fraction 2 (Et_2O-petrol, 3:1) gave 5 mg 8-epitomentosin, 8 mg **3**, 10 mg **6b**, 3 mg **4** (purified by HPLC, RP 8, MeOH–H_2O, 1:1, R_t 14 min.), 12 mg **5** (R_f 0.5), 3 mg **6** (purified by PTLC, Et_2O–petrol, 17:3, R_f 0.85), 8 mg **6a** (purified by HPLC, RP 8, MeOH–H_2O, 13:7, R_t 6.5 min.) and 2 mg **7** (purified by PTLC, Et_2O, two developments, R_f 0.25).

11β,13-Dihydro-8-epi-confertin (**4**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1750 (C=O); MS *m/z* (rel. int.); 250.157 $[M]^+$ (18) (calc. for $C_{15}H_{22}O_3$: 250.157); $[\alpha]_D^{24°}+62$ ($CHCl_3$; *c*0.4).

11,13-Dihydroconfertin (**5**). Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 1780 (δ-lactone), 1750 (C=O); MS *m/z* (rel. int.); 250.157 $[\mathrm{M}]^+$ (100) (calc. for $C_{15}H_{22}O_3$: 250.157); $[\alpha]_D^{24°}$ + 17 ($CHCl_3$; *c*0.26).

1-epi-Inuviscolide (**6**). Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 3550 (OH), 1770 (γ-lactone): MS *m/z* (rel. int.): 248 $[\mathrm{M}]^+$ (1), 230.131 $[\mathrm{M}-H_2O]^+$ (100) (calc. for $C_{15}H_{18}O_2$: 230.131).

11β,13-Dihydro-1-epi-inuviscolide (**6a**). Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.); 250 $[\mathrm{M}]^+$ (3), 232.147 $[\mathrm{M}-H_2O]^+$ (100) (calc. for $C_{15}H_{20}O_2$: 232.147).

*4,5-Dioxo-11β-*H*-xanth-*1 (10)*-en-12,8β-olide* (**7**). Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 1780 (γ-lactone), 1700, 1660 (C=O); MS *m/z* (rel. int.): 264.136 $[\mathrm{M}]^+$ (24) (calc. for $C_{15}H_{20}O_4$: 264.136), 207 $[\mathrm{M}-CH_2COMe]^+$ (100), 206 $[\mathrm{M}-Me_2CO]^+$ (40), 110 $[207-C_5H_5O_2]^+$ (97); $[\alpha]_D^{24°}$ + 15 ($CHCl_3$; *c*0.1).

The extract of the aerial parts of *D. viscosa* (450 g) collected on Tenerife (voucher 3/78, deposited in the Inst. of Org. Chemistry, Technical University Berlin) gave by CC and PTLC 120 mg **8a**, 2 mg **8b**, 2 mg **8c**, 2 mg **8d** (purified by HPLC, RP 8, MeOH–H_2O, 9:1, R_t 7 min.), 4 mg **6**, 12 mg 8-epi **6**, 30 mg carabrone, 40 mg 4*H*-carabrone and 6 mg **9** (purified as its Me ester by PTLC, Et_2O–petrol, 3:7, R_f 0.75). **8d**: Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 1730 (C=CCO_2R, CO_2R); MS *m/z* (rel. int.); 334.214 $[\mathrm{M}]^+$ (1) (calc. for $C_{20}H_{30}O_4$: 334.214), 246 $[\mathrm{M}-RCO_2H]^+$ (100), 231 $[246-\mathrm{Me}]^+$ (12), 199 $[231-\mathrm{MeOH}]^+$ (68), 171 $[199-\mathrm{CO}]^+$ (64); ^{1}H NMR ($CDCl_3$); δ3.76 (*s*, OMe), 2.53 (*qq*, H-17). 1.16 (*d*, H-18, H-19), 5.43 (*br t*, H-2), 5.32 (*br s*, H-3), 2.12 (*br d*, H-5), 2.52 (*dddd*, H-7), 6.15 and 5.57 (*br s*, H-13), 0.92 (*s*, H-14), 1.66 (*br s*, H-15) (*J* [Hz]: 1,2 = 7; 1′,2 = 10; 2,3 = 2,15 = 3,15 ~ 1.5; 6,7 = 12; 6′,7 = 7,8 = 4; 7,8′ = 12); $[\alpha]_D^{24°}$ + 83 ($CHCl_3$; *c*0.14).

Me ester of **9**. Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 1730 (CO_2R, C=O); MS *m/z* (rel. int.): 280.167 $[\mathrm{M}]^+$ (10) (calc. for $C_{16}H_{24}O_4$: 280.167), 262 $[\mathrm{M}-H_2O]^+$ (8), 237 $[\mathrm{M}-\mathrm{COMe}]^+$ (6), 205 $[237-\mathrm{MeOH}]^+$ (62), 55 (100); ^{1}H NMR ($CDCl_3$); δ1.87 (*ddd*, H-1), 1.34 (*br dd*, H-1′), 2.34 (*dddd*, H-2), 1.78 (*dddd*, H-2′), 4.56 (*dd*, H-3), 2.11 (*ddd*, H-6), 1.84 (*dd*, H-6′), 2.75 (*br ddd*, H-7), 1.65 (*br d*, H-8), 1.40 (*m*, H-8′), 1.54 (*br ddd*, H-9), 1.40 (*m*, H-9′), 6.22 (*br s*, H-13), 5.62 (*br s*, H-13′), 0.99 (*br s*, H-14), 2.16 (*s*, H-15) (*J* [Hz]: 1,1′ = 1,2′ = 2,2′ = 6′7 = 7,8′ = 12; 1,2 = 7; 1′,2 = 2,3 = 10; 2′,3 = 6.5; 6,6′ = 13; 6,8 = 2; 6,7 = 3; 7,8 = 3; 8,8′ = 13; 8,9 = 3; 8′,9′ = 13; 9,9′ = 14).

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