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Phytochemistry, Vol. 21, No. 6, pp. 1443–1445, 1982.
Printed in Great Britain.
0031-9422/82/061443-03$03.00/0

INEUPATOROLIDE-LIKE SESQUITERPENE LACTONES FROM *DITTRICHIA VISCOSA*[*]

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(*Received* 20 *October* 1981)

Key Word Index—*Dittrichia viscosa*; Compositae; Inuleae; sesquiterpene lactones; germacranolides.

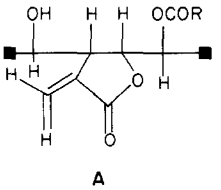
Abstract—*Dittrichia viscosa* afforded, in addition to known compounds, minute amounts of nine sesquiterpene lactones, all closely related to ineupatorolide B, some of which could not be separated from each other. The structures could be elucidated by high field ^{1}H NMR spectroscopy. The chemotaxonomic importance of these compounds is discussed briefly.

INTRODUCTION

The small Mediterranean genus *Dittrichia*, in the subtribe Inulinae [1] has not been investigated chemically. We now have studied the constituents of *D. viscosa* (L.) Greuter. The results are discussed here.

RESULTS AND DISCUSSION

The roots gave the thymol derivative **1** [2] and a mixture of sesquiterpenes, the germacranolides **3a** (main constituent), **3c–3f** and **4a–4c**. The ^{1}H NMR spectrum (Table 1) of **3a** clearly showed that a methyl senecioate was present, which in addition to the keto and methylene lactone group contained two hydroxyl groups. While one of these groups was indicated by the double doublet at δ 3.86, the presence of the second one followed indirectly from the molecular formula and from the IR spectrum of the monoacetate obtained by acetylation. Spin decoupling in the usual way starting with the H-7 signal allowed the assignment of the sequence A:



A

As the hydroxyl at C-6 showed a hydrogen bond, a keto group at C-5 was very likely. The doublet doublet quartet at δ 3.16 was coupled with the methyl doublet at δ 1.18. The chemical shift of the former signal indicated a neighbouring keto group, thus indicating that the secondary methyl group was at C-4. Therefore, the tertiary hydroxyl had to be placed at C-10 leading to the structure **3a**, a lactone closely related to ineupatorolide B (**2**) [3], where, however, the 6-hydroxy group is missing and the ester group is replaced by an angelate residue. Accordingly, the ^{1}H NMR spectral data of **3a** and **2** were in part similar. In particular, the coupling of H-4, H-8 and H-9 were the same, indicating identical stereochemistry at C-4 and C-7 through C-9. The α-orientation of the hydroxyl at C-6 followed from the coupling $J_{6,7}$ while the chemical shift of H-14 indicated the same stereochemistry at C-10 as that of ineupatorolide B, the stereochemistry of which had been established by X-ray analysis [3]. Furthermore, **3a** was closely related to similar lactones isolated from *Inula cuspidata* [4].

In addition to **3a** minute amounts of four other esters were isolated, which could not be separated. The mass spectrum as well as the ^{1}H NMR spectral data, however, indicated the presence of **3c–3f**. Furthermore, three lactones were isolated, the germacranolides **4a–4c**, as followed from the ^{1}H NMR spectrum (Table 1) and the molecular formula. Again **4b** and **4c**, which differed in the ester groups only, could not be separated completely from the isobutyrate **4a**, which was the main constituent of the mixture. Spin decoupling allowed the assignment of the sequence H-4 through H-9. As the molecular

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[*] Part 434 in the series "Naturally Occurring Terpene Derivatives". For Part 433 see Bohlmann, F. and Zdero, C. (1982) *Phytochemistry* **21**, (in press).

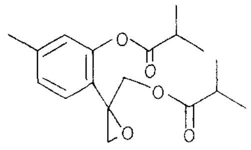
Table 1. ^{1}H NMR spectral data of compounds **3a–3c** and **4a** (400 MHz, $CDCl_3$, TMS as int. standard)

	3a*	**3a** (C_6D_6)	**3b**	**3c**	**4a**†
H-4	3.16*ddq*	2.74*ddq*	3.06*ddq*	3.16*ddq*	1.9*m*
H-5	—	—	—	—	3.79*ddd*
H-6	3.86*dd*	3.81*dd*	4.89*d*	3.85*dd*	α2.18*ddd* β1.68*ddd*
H-7	3.33*dddd*	3.08*dddd*	3.47*dddd*	3.35*dddd*	3.03*ddddd*
H-8	4.54*dd*	4.75*dd*	4.65*dd*	4.56*dd*	4.27*dd*
H-9	4.65*d*	4.68*d*	4.67*d*	4.71*d*	5.54*d*
H-13	6.42*d*	6.41*d*	6.38*d*	6.43*d*	6.18*d*
H-13′	6.04*d*	5.70*d*	5.92*d*	6.04*d*	5.45*d*
H-14	1.14*s*	0.98*s*	1.16*s*	1.18*s*	1.27*s*
H-15	1.18*d*	1.07*d*	1.05*d*	1.18*d*	0.95*d*
OCOR	5.74*tq*	5.80*tq*	5.74*tq*	6.17*qq*	2.65*qq*
	2.20*q*(*br*)	1.82*q*(*br*)	2.20*q*(*br*)	1.97*dq*	1.21*d*
	1.08*t*	0.81*t*	1.08*t*	1.94*dq*	1.22*d*
	2.11*d*	2.23*d*	2.11*d*	—	—
OH	2.52*d*	—	—	2.75*d*	—
OAc	—	—	2.14*s*	—	—

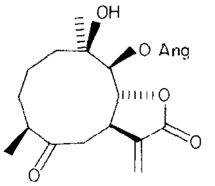
*Data of **3d–3f** nearly the same.

†Data of **4b** and **4c** nearly the same.

J(Hz): Compounds **3a–3f**: 3, 4 = 3; 3′, 4 = 11; 4, 15 = 7; 6, 7 = 11; 6, OH = 5; 7, 8 = 6.5; 7, 13 = 2; 7, 13′ = 1.5; 8, 9 = 6.5; OMeSen: 2′, 4′ = 2′, 6′ = 1; 4′, 5′ = 7.5; OAng: 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5; *i*Bu: 2.48 (*qq*, *J* = 7 Hz); 1.19 (*d*, *J* = 7 Hz); Mebu: 2.52 (*tq*, *J* = 7, 7 Hz), 0.92 (*t*, *J* = 7 Hz), 1.20 (*d*, *J* = 7 Hz), *i*Val: 2.19(*d*, *J* = 6 Hz), 0.97 (*d*, *J* = 7 Hz); compounds **4a–4c**: 4, 5 = 1.5; 5, 6 = 4; 5, 6′ = 10; 6, 6′ = 13; 6, 7 = 3; 6′, 7 = 10; 7, 8 = 10; 7, 13 = 3.5; 7, 13′ = 3; 8, 9 = 10; *i*Bu: 2′,3′ = 2′,4′ = 7; MeBu: 2.35 (*tq*, *J* = 7, 7 Hz); 0.95 (*t*, *J* = 7 Hz); 1, 20 (*d*, *J* = 7 Hz); *i*Val: 0.99 (*d*, *J* = 7 Hz).



1



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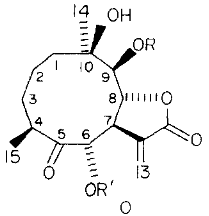
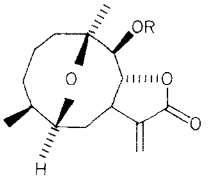
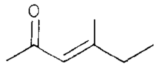
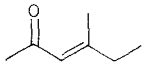




3a R =  , R′= H

3b R =  , R′= Ac

3c R = Ang, R′= H

3d R = *i*Bu, R′= H

3e R = Mebu, R′= H

3f R = *i*Val, R′= H

4a R = *i*Bu

4b R = *i*Val

4c R = Mebu

formula was $C_{19}H_{28}O_5$ the nature of the fifth oxygen had to be clarified. Obviously this oxygen function was at C-5 as followed from the threefold doublet at δ 3.79, which indicated an ether ring, as the IR spectrum showed no hydroxyl band. Furthermore, the number of the hydrogens required three rings, as no double bond except the exomethylene group was present. The stereochemistry at C-4 through C-9 was deduced from the couplings observed, if a model was inspected. Although a 6, 12-lactone was possible by analogy to **3a** an 8, 12-lactone was more likely. The ^{1}H NMR spectrum of **4b** and **4c** clearly showed that the ester group at C-9 was isovalerate and methylbutyrate respectively. The corresponding 9-hydroxy compound we have named dittrichiolide. The chemistry of this species shows close relationships to parts of the genus *Inula* by the occurrence of high concentrations of a thymol derivative and the in-eupatorolide-like lactones. Taxonomic studies may be of interest to determine whether *Dittrichia*, which has been classified as a section of *Inula* [1], is closely related to those *Inula* species which also contain these lactones.

EXPERIMENTAL

The air-dried roots (150 g), collected in Sept. 1980 on Tenerife (voucher Ten 3, deposited in the Herbarium of the Botanic Museum Berlin–Dahlem) were extracted with Et_2O–

petrol (1:2) and the resulting extracts were separated by CC (Si gel) and further by repeated TLC (Si gel). The less polar fractions afforded 500 mg γ-humulene and 200 mg **1**, while the polar fractions (Et_2O–MeOH, 20:1) gave 200 mg **3a**, 5 mg **3c**–**3f**, 5 mg **4a** as well as 3 mg **4b** and **4c**. Separation of the lactones was achieved by TLC (C_6H_6–CH_2Cl_2–Et_2O, 10:10:1, several times). However, **3c**–**3f** and **4b**/**4c** could not be separated.

6α-Hydroxy-9-desacylineupatorolide-9-O-(3-methyl-pent-3c-enoate) (**3a**). Colourless crystals, mp 191–192° (Et_2O–petrol), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1720, 1650 (C=CCO$_2$R, C=O); MS *m/z* (rel. int.): 394.199 [M]$^+$ (0.5) ($C_{21}H_{30}O_7$), 376 [M − H$_2$O]$^+$ (2.5), 97 [C$_5$H$_9$CO]$^+$ (100), 69 [97 − CO]$^+$ (11).

10 mg **3a** was heated for 1 hr with 0.1 ml Ac$_2$O at 70°. Usual work-up afforded 8 mg **3b**, colourless crystals, mp 168–169° (Et_2O–petrol), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1730 (OAc, C=O, C=CCO$_2$R); MS *m/z* (rel. int.): 436.210 [M]$^+$ (0.5) ($C_{23}H_{32}O_8$), 418 [M − H$_2$O]$^+$ (3), 358 [418 − HOAc]$^+$ (1), 245 [358 − OCOR]$^+$ (1), 97 [C$_5$H$_9$CO]$^+$ (100), 69 [97 − CO]$^+$ (9);

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+44 \quad +46 \quad +56 \quad +146}\,(CHCl_3;\ c = 0.5).$$

The mixture of **3c**–**3f** was a colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1730 (CO$_2$R, C=CCO$_2$R, C=O); MS *m/z* (rel. int.): 382, 380, 368 [M]$^+$ (0.1, 0.2, 0.1), 280 [M − RCO$_2$H]$^+$ (1), 85 [C$_4$H$_9$CO]$^+$ (40), 83 [C$_4$H$_7$CO]$^+$ (60), 71 [C$_3$H$_7$CO]$^+$ (33), 57 [85 − CO]$^+$ (100), 55 [83 − CO]$^+$ (61).

Dittrichiolide-isobutyrate (**4a**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775 (γ-lactone 1720 (C=CCO$_2$R); MS *m/z* (rel. int.): 336.294 [M]$^+$ (0.5) ($C_{19}H_{28}O_5$), 248 [M − RCO$_2$H]$^+$ (18), 71 [C$_3$H$_7$CO]$^+$ (100); CD (MeCN) $\Delta\varepsilon_{256}$ − 1.4.

Dittrichiolide-isovalerate and (*2-methylbutyrate*) (**4b** and **4c**). Colourless gum, not free from **4a**, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775 (γ-lactone), 1730 (CO$_2$R); MS *m/z* (rel. int.): 350 [M]$^+$ ($C_{20}H_{30}O_5$), 248 [M − RCO$_2$H]$^+$ (20), 85 [C$_4$H$_9$CO]$^+$ (95), 57 [85 − CO]$^+$ (100).

Acknowledgements— We thank Dr. H. W. Lack, Botanical Museum, Berlin-Dahlem, for identification of the plant material and the Deutsche Forschungsgemeinschaft for financial support.

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Phytochemistry, Vol. 21, No. 6, pp. 1445–1447, 1982.
Printed in Great Britain.
0031-9422/82/061445-03$03.00/0

GLAUCOLIDE FROM *VERNONIA STAEHELINOIDES**

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(*Received* 27 *October* 1981)

Key Word Index—*Vernonia staehelinoides*; Compositae; sesquiterpene lactone; glaucolide.

Abstract—*Vernonia staehelinoides* afforded a new glaucolide.

In a continuation of our investigations of representatives of the tribe Vernonieae, we now have studied the constituents of the South African *Vernonia* species, *V. staehelinoides* Harv. The roots afforded squalene, stigmasterol and sitosterol, while the aerial parts gave caryophyllene, α-humulene, germacrene D and the glaucolide **1**. Acetylation of **1** gave the acetate **2**, while treatment with slightly acidic Si gel afforded **3**. The structures were elucidated by ^{1}H and ^{13}C NMR spectroscopy (Table 1). The nature of the ester group followed from the ^{1}H NMR signals. A triplet quartet was coupled with broadened singlets at δ 1.94 and 5.14. The chemical shifts of these signals indicated an acetoxy derivative of a senecioate, where the CH$_2$OAc group was *cis* to the carbonyl group. The typical pair of doublets around δ 4.9 were assigned to H-13 and the double doublet at δ 4.79 to H-8 as spin decoupling showed that the latter was coupled with

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*Part 436 in the series "Naturally Occurring Terpene Derivatives". For Part 435 see Bohlmann, F., Wallmeyer, M. and Jakupovic, J. (1982) *Phytochemistry* **21** (in press).