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A VETISPIRANOLIDE AND OTHER SESQUITERPENE LACTONES FROM *PEYROUSEA UMBELLATA*

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Key Word Index—*Peyrousea umbellata*; Compositae; sesquiterpene lactones; guaianolides; vetispiranolide.

Abstract—The aerial parts of *Peyrousea umbellata* afforded, in addition to known sesquiterpene lactones, four new guaianolides and the first sesquiterpene lactone derived from vetispirane. The structures and the stereochemistry were determined by high field NMR techniques. The relationship of the genus *Peyrousea* is discussed briefly.

INTRODUCTION

The small South African genus *Peyrousea* with only two species is placed in the tribe Anthemideae, subtribe Chrysantheminae, but the separation of the tribe into the classical two subtribes is only useful for some genera [1]. A close relationship of *Peyrousea* to *Cotula* has been proposed [1]. A preliminary investigation of the aerial parts of *P. umbellata* gave, in addition to dehydrofalcarinone and related acetylenes dehydroleucodin, a guaianolide [2, 3] which has been isolated also from a *Lidbeckia* [3], a *Cotula* [4] and an *Artemisia* species [5]. Previously, a close relationship of *Peyrousea* to *Pentzia* was proposed [6]. We therefore have re-examined the *Peyrousea* species in order to obtain more information. The results are discussed in this paper.

RESULTS AND DISCUSSION

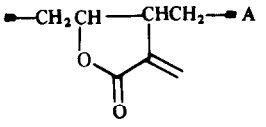
The extract of the aerial parts gave the known guaianolides **1** [3] and **3** [5] as well as the new ones, **2** and **4**–**6**. In addition, ridentin B [7], the germacranolide **7** [8], the *seco*-caryophyllene **10** [9] and the vetispiranolide **9** were isolated.

The structure of **2** followed from its ^{1}H NMR spectrum in deuteriobenzene (Table 1) where all signals could be assigned by spin decoupling. When the data were compared with those of **1**, it was obvious that H-5 was absent. In agreement with the MS therefore a 5-hydroxy derivative of **1** was very likely. The downfield shift of H-7 in the spectrum of **2** indicated a 5α-hydroxy group.

The ^{1}H NMR spectrum of **4** was in part similar to that of **5** and also to that of a guaianolide from a *Hymenothrix* species which has an additional hydroxy group at C-8 [10] (Table 1). However, a methoxy singlet in the spectrum of **5** and changed splitting of the signals of H-1–H-3 indicated that the configuration at C-2 was different in the lactones **4** and **5**, the latter being a 2-methoxy derivative. Inspection of models showed that the lactone **4** must be a 2β-hydroxy derivative as the coupling $J_{1,2}$ agreed with that of other guaianolides with the same configuration at C-2 [10, 11]. Accordingly, in the lactone **5** a 2α-methoxy group was very likely. It can not be excluded, however, that the latter was an artifact formed by reaction of **4** in methanol in the presence of traces of acid. Most likely the structure of a 2-hydroxyguaianolide from a *Kaunia* species, which was only isolated as its acetate, has to be revised to **4** as the observed coupling $J_{1,2}$ would support this assumption (compound **4** in ref. [12]).

The structure of **6** followed from the molecular formula ($C_{15}H_{18}O_3$) and its ^{1}H NMR spectrum (Table 1) which was similar to that of a 8β-acyloxy derivative from a *Helogyne* species [11]. As all signals could be assigned by spin decoupling, the only remaining problem was the determination of the stereochemistry. This was achieved by NOE difference spectroscopy. A clear effect between H-5, H-1 (5%) and H-15 (7%) required a 4β-hydroxy group and *cis*-orientation of H-1 and H-5. A NOE between H-15 and H-3 (7%) and between H-14′ and H-2 (5%) allowed the assignment of the olefinic signals which could not be deduced directly from the NMR data.

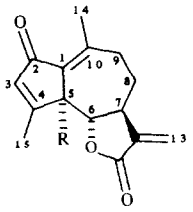
The structure of the lactone **9** caused somewhat more difficulties as the ^{1}H NMR data showed no similarities to known types. However, all signals could be assigned in the ^{1}H NMR spectrum in deuteriobenzene (Table 2). Saturation at δ2.66 clearly indicated that this signal was due to H-7 as both signals of H-13 collapsed to singlets. Furthermore, signals at δ4.29, 1.78 and 1.56 were altered. Accordingly, these signals were due to the proton under the lactone oxygen and to H-6 (1.78 *dd* and 1.56 *dd*). As the former was coupled with two double doublets at δ1.88 and 1.51 the sequence A was present:



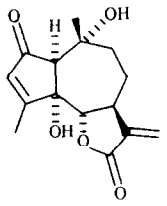
Furthermore, the lactone moiety must have two neighbouring blocked methylene groups, a situation not present in any known sesquiterpene lactone except those from *Wunderlichia* (see below). Spin decoupling further required the sequence B:

■–CH(Me)CH(OH)CH(OH)CH=C(CH_2OAng)–■ B

In agreement with the molecular formula, the two parts could only be combined by a quarternary carbon leading to a spirane. This proposal was confirmed by the



1 R = H
2 R = OH



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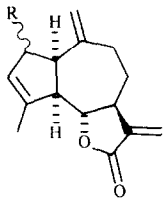
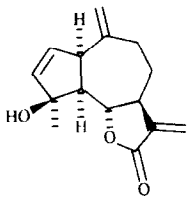


4 R = βOH
5 R = αOMe



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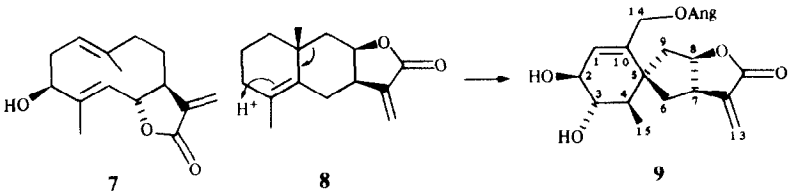
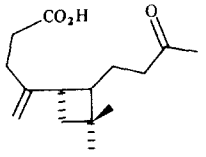


7 **8** **9**



10

^{13}C NMR spectrum (Table 2), as a singlet at δ53.3 could only be explained with the presence of a spiro compound. As six chiral centres were present the stereochemistry could only be determined by NOE difference spectroscopy. Clear effects between H-15, H-3 (4%), H-6α (4%), H-7 (6%), H-8 (4%) and H-9α (4%) established the configurations at C-3, C-4, C-7 and C-8, while effects between H-2, H-1 (4%) and H-4 (5%) together with the observed large coupling $J_{3,4}$ required the proposed configurations at C-2, C-3 and C-4 and a NOE between H-4 and H-9α (4%) that at C-5. The observed negative Cotton effect supports the presence of a 12,8β-olide if the Geissman rule is valid. All data agree with the presence of the first sesquiterpene lactone derived from vetispirane. We have named the lactone 14-angeloyloxy-2β,3α-vetispiranolide. Most likely this compound was formed biogenetically by a Wagner–Meerwein rearrangement of **8** (Scheme 1) of a corresponding eudesmanolide with a Δ^4 double bond. By attack of a proton it would give a cation which could rearrange to the spiro lactone. The stereochemistry is identical with that of hinesol. The only spiro lactones reported so far are those from a *Wunderlichia* species [13] which, however, have a different carbon skeleton. This is also the case in the bakkenolides [14] where the lactone ring is part of the spiro compound.

The new results on the chemistry of *Peyrousea* do not show close relationships to that of *Cotula* where sesquiterpene lactones are not very common. However, the proposed position next to *Pentzia* [6] may be supported by the chemistry as guaianolides are present in the latter genus [3, 15, 16], but in addition the C_{17}-acetylenes are replaced by others, especially spiroketal enol ether polynes, more typical for the *Chrysanthemum* complex [17]. However, the taxonomy of *Pentzia*, *Athanasia* and the South African '*Matricaria*' species is still not solved [1].

EXPERIMENTAL

The air-dried aerial parts (280 g) (voucher 86/88, deposited in the Compton Herbarium at Kirstenbosch, R.S.A., collected near Humansdorp, R.S.A.) were extracted with Et_2O–MeOH–petrol (1:1:1). The extract obtained was treated with MeOH to remove long chain saturated compounds. After CC (silica gel) the polar fractions (1: Et_2O and 2: Et_2O–MeOH, 9:1) were separated

Table 1. ^{1}H NMR spectral data of compounds **2** and **4–6** ($CDCl_3$, 400 MHz, δ-values)

H	2	C_6D_6*	4	5†	6
1	—	—	3.15 *br dd*	2.95 *dd*	3.36 *br d*
2	—	—	4.73 *br d*	4.43 *br s*	5.75 *dd*
3	6.15 *q*	5.92 *q*	5.72 *dq*	5.78 *dq*	5.92 *dd*
5	—	—	2.68 *br t*	3.09 *br t*	2.40 *dd*
6	3.89 *d*	2.99 *d*	4.23 *dd*	3.94 *dd*	4.42 *dd*
7	3.70 *dddd*	3.30 *dddd*	2.84 *ddddd*	2.85 *ddddd*	2.92 *ddddd*
8α	2.24 *m*	1.33 *dddd*	2.21 *dddd*	2.27 *dddd*	2.27 *dddd*
8β	1.49 *m*	0.67 *dddd*	1.50 *dddd*	1.43 *dddd*	1.44 *dddd*
9α	2.95 *br t*	2.44 *dt*	2.29 *ddd*	2.20 *ddd*	2.07 *ddd*
9β	2.24 *m*	1.54 *ddd*	2.63 *ddd*	2.54 *ddd*	2.67 *ddd*
13	6.17 *d*	6.03 *d*	6.20 *d*	6.23 *d*	6.27 *d*
13′	5.45 *d*	4.80 *d*	5.48 *d*	5.50 *d*	5.54 *d*
14	2.42 *br s*	2.35 *s*	5.08 *br s*	4.90 *br s*	4.97 *br s*
14′			5.01 *br s*	4.78 *br s*	4.80 *br s*
15	2.30 *d*	2.04 *d*	1.95 *d*	1.92 *q*	1.54 *s*

*OH 1.96 *d*;

†OMe 3.33 *s*.

J [Hz]: Compound **2**: 3,15 = 1.5; 6, OH = 1; 6,7 = 10; 7,8α = 3; 7,8β = 11; 7,13 = 3; 7,13′ = 2.5; 8α,9α = 1.5; 8α,9β = 6; 8α,8β = 13.5; 8β,9α = 9α, 9β = 13; compound **4**: 1,2 = 6; 1,5 = 9; 2,3 = 2; 2,15 = 3,15 = 5,15 = 1; 5,6 = 9; 6,7 = 7,8β = 10; 7,8α = 5; 7,13 = 3.5; 7,13′ = 3; 8α,8β = 13; 8α,9α = 8α, 9β ~ 5; 8β,9α = 11; 8β,9β = 5; 9α,9β = 12; compound **5**: 1,2 = 2.5; 1.5 = 8; 2,3 = 2,15 = 3,15 = 5,15 ~ 1.5; 5,6 = 10; 6,7 = 7,8β = 10; 7,8α = 7,13 = 3.5; 7,13′ = 3; 8α,8β = 8β, 9α = 12; 8α,9α = 5; 8β,9α = 9α, 9β ~ 12; 8β,9β ~ 5; compound **6**: 1,2 = 2.5; 1,3 = 1.5; 1,5 = 9; 2,3 = 5.5; 5,6 = 10; 6,7 = 7,8β = 9; 7,8α = 7,13 = 3.5; 7,13′ = 3; 8α,8β = 13; 8α,9α = 5; 8α,9β ~ 4; 8β,9α = 9α, 9β = 13; 8β,9β = 2.5.

Table 2. ^{1}H NMR spectral data of compound **9** (400 and 100.6 MHz, δ-values)

H	9 (^{1}H NMR) $CDCl_3$	C_6D_6*	C	9 (^{13}C NMR)† $CDCl_3$
1	5.62 *dt*	5.57 *dt*	1	127.8 *d*
2	4.04 *br d*	3.75 *br d*	2	73.6 *d*
3	3.35 *dd*	3.04 *br dd*	3	75.1 *d*
4	1.72 *m*	1.32 *dq*	4	44.6 *d*
6α	2.31 *dd*	1.78 *dd*	5	53.3 *s*
6β	1.72 *m*	1.56 *dd*	6	42.3 *t*
7	3.43 *tq*	2.66 *tq*	7	45.9 *d*
8	5.02 *dt*	4.29 *dt*	8	84.8 *d*
9α	2.12 *dd*	1.51 *dd*	9	40.2 *t*
9β	2.42 *dd*	2.15 *dd*	10	140.0 *s*
13	6.19 *d*	6.14 *d*	11	139.2 *d*
13′	5.61 *d*	5.04 *d*	12	169.9 *s*
14	4.61 *dt*	4.62 *dt*	13	122.2 *t*
14′	4.55 *dt*	4.42 *dt*	14	63.2 *t*
15	1.03 *d*	0.68 *d*	15	11.6 *q*
OAng	6.08 *qq*	5.75 *qq*	OCOR	167.3 *s*
	1.96 *dq*	2.00 *dq*		127.4 *s*
	1.87 *dq*	1.88 *dq*		138.9 *d*
				20.6 *q*
				15.8 *q*

*OH 1.93 *br s*.

†Assigned by 2D-techniques.

J [Hz]: 1,2 = 1,15 = 1.5; 2,3 = 7.5; 3,4 = 11; 4,15 = 7; 6α,6β = 15; 6α,7 = 9; 6β,7 = 7; 7,8 = 8,9α = 7; 7,13 = 2; 7,13′ = 1.7; 8,9β = 2.5; 9α,9β = 16; 14,14′ = 15.

again by medium pressure chromatography (MPLC) (silica gel, Φ 30–60 μ). Fraction 1 gave 400 mg **2**, 100 mg **10**, 30 mg **3** and two mixtures (1/4 and 1/5). TLC of fraction 1/4 (Et_2O) gave 100 mg **1** and a mixture which gave by HPLC (MeOH–H_2O, 3:1) two fractions (R_t 1.7 min and R_t 3.2 min). The first one gave by TLC ($CHCl_3$–C_6H_6–Et_2O, 2:2:1) 20 mg **4** (R_f 0.65) and 2 mg **6** (R_f 0.50). The second one gave by TLC (same solvent) 1 mg **5** (R_f 0.75). TLC of fraction 1/5 ($CHCl_3$–C_6H_6–Et_2O–MeOH, 30:30:30:1) afforded 50 mg **1**, 100 mg **2** and 5 mg **7**. CC fraction 2 gave three fractions by MPLC. Fraction 2/1 gave 50 mg **2**, 2/2 10 mg **3** and fraction 2/3 afforded by HPLC (RP 8, MeOH–H_2O, 1:1, flow rate 3 ml/min) 2 mg ridentin B and 25 mg **9** (R_t 9.7 min). Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectrum with those of authentic material.

5α-Hydroxydehydroleucodin (**2**). Colourless crystals, mp 173°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1780 (γ-lactone), 1695, 1650, 1630 (C=CC=O); MS *m/z* (rel. int.): 260.105 $[M]^+$ (100) (calc. for $C_{15}H_{16}O_4$: 260.105), 242 $[M-H_2O]^+$ (36), 227 $[242-Me]^+$ (17), 214 $[242-CO]^+$ (24), 199 $[214-Me]^+$ (36), 161 (24), 151 (28), 150 (29); $[\alpha]_D^{24°}$ −8 ($CHCl_3$; *c* 2.95).

2β-Hydroxyguaia-3,10(14),11(13)-trien-12,6α-olide (**4**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590 (OH), 1775 (γ-lactone); MS *m/z* (rel. int.): 246.126 $[M]^+$ (45) (calc. for $C_{15}H_{18}O_3$: 246.126), 228 $[M-H_2O]^+$ (100).

2α-Methoxyguaia-3,10(14),11(13)-trien-12,6α-olide (**5**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 260.141 $[M]^+$ (81) (calc. for $C_{16}H_{20}O_3$: 260.141), 245 $[M-Me]^+$ (91), 228 $[M-MeOH]^+$ (100), 215 $[245-CH_2O]^+$ (97).

4β-Hydroxyguaia-2,10(14),11(13)-trien-12,6α-olide (**6**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580 (OH), 1775 (γ-lactone); MS *m/z*

(rel. int.): 246.126 $[M]^+$ (42) (calc. for $C_{15}H_{18}O_3$: 246.126), 231 $[M-Me]^+$ 100, 228 $[M-H_2O]^+$ (27), 213 $[228-Me]^+$ (17), 185 (31), 164 (32), 91 (70).

14-*Angeloyloxy-2β,3α-dihydroxyvetispiranolide* (**9**). Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1770 (γ-lactone); 1720, 1650 (C $=CCO_2R$); MS *m/z* (rel. int.): 362.173 $[M]^+$ (0.5) (calc. for $C_{20}H_{26}O_6$: 362.173), 344 $[M-H_2O]^+$ (0.7), 263 $[M-OAng]^+$ (5), 262 $[M-AngOH]^+$ (3), 245 $[263-H_2O]^+$ (5), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (45); CD (MeCN): $\Delta\varepsilon_{255}$ −0.36

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REFERENCES

1. Heywood, V. H. and Humphries, C. J. (1977) in *The Biology and Chemistry of the Compositae* (Heywood, V. H., Harborne, J. B. and Turner, B. L., eds), pp. 856, 870. Academic Press, London.
2. Bohlmann, F. and Zdero, C. (1974) *Chem. Ber.* **107**, 1044.
3. Bohlmann, F. and Zdero, C. (1972) *Tetrahedron Letters* 621.
4. Bohlmann, F. and Zdero, C. (1979) *Phytochemistry* **18**, 336.
5. Huneck, S., Zdero, C. and Bohlmann, F. (1986) *Phytochemistry* **25**, 883.
6. Hoffmann, O. (1899) in *Die natürlichen Pflanzenfamilien* (Engler, A. and Prantl, K., eds) Vol. IV/5, p. 283. W. Engelmann, Leipzig.
7. Irwin, M. A. and Geissman, T. A. (1973) *Phytochemistry* **12**, 871.
8. Zakirov, S. K., Kasymov, S. Z., Rakhmankulov, V. and Sidyakin, G. P. (1976) *Khim. Prir. Soedin.* 397.
9. Jakupovic, J., Pathak, V. P., Bohlmann, F., King, R. M. and Robinson, H. (1987) *Phytochemistry* **26**, 803.
10. Jakupovic, J., Schuster, A., Bohlmann, F., Sanchez, V. and Dominguez, X. A. (1987) *Phytochemistry* **26**, 2543.
11. Zdero, C., Bohlmann, F. and Dillon, M. O. (1988) *Phytochemistry* **27**, 616.
12. Bohlmann, F., Kramp, W., Gupta, R. K., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 2375.
13. Bohlmann, F., Ludwig, G. W., Jakupovic, J., King, R. M. and Robinson, H. (1984) *Liebigs Ann. Chem.* 228.
14. Harmatha, J., Samek, Z., Synackova, M., Novotny, L., Herout, V. and Sorm, F. (1976) *Coll. Czech. Chem. Commun.* **41**, 2047.
15. Cekan, Z., Prochazka, V., Herout, V. and Sorm, F. (1960) *Coll. Czech. Chem. Commun.* **25**, 2553.
16. Jakupovic, J., Boeker, R., Grenz, M., Paredes, L., Bohlmann, F. and Seif El-Din, A. (1988) *Phytochemistry* **27**, 1135.
17. Bohlmann, F., Burkhardt, T. and Zdero, C. (1973) *Naturally Occurring Acetylenes*, pp. 398, 404. Academic Press, London.