Herticins A and B, New Sesquiterpenes from *Hertia intermedia*

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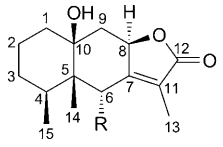
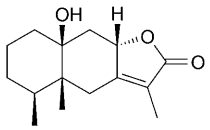
Herticins A (=(8αH)-10β-hydroxyeremophilenolide; **1**) and B (=(8αH)-6α,10β-dihydroxyeremophilenolide; **2**), two new sesquiterpenes, have been isolated from the AcOEt-soluble fraction of the MeOH extract of *Hertia intermedia* (whole plant). Their structures were assigned from ^{1}H- and ^{13}C-NMR spectra (DEPT) and 2D-NMR analyses (COSY, NOESY, and HMBC experiments) in combination with HR-MS experiments and comparison with literature data of related compounds.

Introduction. – The genus *Hertia* belongs to the family Compositae, tribe Senecioneae. The twelve species of *Hertia* are distributed all over South and North Africa and South West Asia [1]. *Hertia intermedia* is also known as *Othonnopsis intermedia*. It is found in Baluchistan commonly in Quetta, Koeie, Chaman, Kanozai-Moorga, and Wazir. It is also found in Kurram and regions below Parachinar. These are small shrubs with pretty yellow flowers [2]. A literature survey revealed that no phytochemical or biological studies have so far been carried out on this plant. The methanolic extract of the whole plant of *H. intermedia* showed significant toxicity in the brine shrimp lethality test [3][4]. On further fractionation, major toxicity was observed in the AcOEt-soluble fraction which prompted us to investigate the chemical constituents of this fraction. As a result, we have isolated two new sesquiterpenes named herticins A (=(8αH)-10β-hydroxyeremophilenolide; **1**) and B (=(8αH)-6α,10β-dihydroxyeremophilenolide; **2**), respectively.



1 R = H
2 R = OH

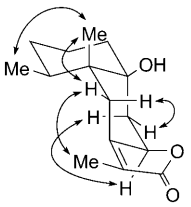


10β-Hydroxyeremophilenolide

Results and Discussion. – The MeOH extract of the whole plant was divided into fractions soluble in hexane, AcOEt, BuOH, and H_2O. Column chromatography of the

AcOEt-soluble fraction provided two new eremophilenolide type sesquiterpenes named as herticins A (=(8αH)-10β-hydroxyeremophilenolide; **1**) and B (=(8αH)-6α,10β-dihydroxyeremophilenolide; **2**), respectively.

Herticin A (**1**) was obtained as a white solid. The IR spectrum exhibited the OH group (3607 and 3468 cm^{-1}) and α,β-unsaturated γ-lactone bands (1756 and 1645 cm^{-1}). The molecular formula of **1** was established as $C_{15}H_{22}O_3$ on the basis of HR-EI-MS showing an M^+ peak at m/z 250.3334 (calc. 250.3378). The molecular formula was confirmed by the ^{13}C-NMR (BB and DEPT) spectra (*Table 1*), which showed 15 signals: three Me, five CH_2, two CH, and five quaternary C-atoms. The fragment peak at m/z 232 ($[M-H_2O]^+$) in the EI-MS spectrum revealed the presence of one OH group, which was confirmed by a quaternary C-atom at δ(C) 75.0. The H-atom appearing at δ(H) 5.07 (*ddq*, J = 10.5, 4.8, 1.5, 1 H) showed coupling to the C-atom at δ(C) 77.2 in the HMQC experiment, and was assigned to the secondary OH group integrated in a lactone ring. Three Me groups appeared in the ^{1}H-NMR spectrum at δ(H) 1.79 (*d*, J = 1.5), 0.98 (*s*), and 0.81 (*d*, J = 6.4). The Me group at δ(H) 1.79 showed interaction in the HMBC with C(11) (δ(C) 120.6), C(7) (δ(C) 161.2), and C(12) (δ(C) 175.1) suggesting a Me-substituted α,β-unsaturated lactone. One of the CH_2 groups appeared at δ(H) 2.13 (*dd*, J = 13.0, 4.8, 1 H) and 1.94 (*dd*, J = 13.0, 10.5, 1 H). Another CH_2 group gave rise to two *doublet*s at δ(H) 2.64 (*d*, J = 13.8, 1 H) and 2.42 (*d*, J = 13.8, 1 H). In the HMBC, significant correlations were observed between the CH_2 group appearing at δ(H) 1.94 and 2.13 with the C-atoms C(5) (δ(C) 44.9), C(10) (δ(C) 75.0), C(8) (δ(C) 77.2), and C(7) (δ(C) 161.2); the Me group appearing at δ(H) 0.98 correlated with the C-atoms C(4) (δ(C) 33.5), C(6) (δ(C) 31.7), C(5) (δ(C) 44.9), and C(10) (δ(C) 75.0). The ^{1}H- and ^{13}C-NMR data were comparable to the eremophilenolide class of sesquiterpenes [5–7]. A literature search revealed that the data is almost superimposible to 10β-hydroxyeremophilenolide [8]. The optical rotation observed for **1** ($[\alpha]_D$ = +165 (c = 0.470, $CHCl_3$)) was, however, different from that of 10β-hydroxyeremophilenolide ($[\alpha]_D$ = −169 (c = 0.470, $CHCl_3$)), indicating that herticin A (**1**) is a stereoisomer of 10β-hydroxyeremophilenolide. The signal for Me attached to C(5) was shifted downfield, which indicated that the *A*/*B* ring system could not be *trans* fused, thus confirming a 10β-OH group [9]. The absence of a NOESY correlation between H–C(8) and the Me group attached to C(5) and the coupling constant of H–C(8) and H–C(9) [1] provided evidence for their relative *trans*-orientation (*Fig.*). Hence, herticin A (**1**) was assigned the structure (8αH)-10β-hydroxyeremophilenolide, *i.e.*, compound **1** ist the *C(8)*-epimer of the known natural product 10β-hydroxyeremophilenolide (see *Formulae*).



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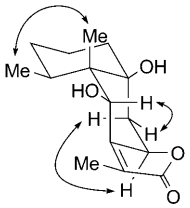

2

Figure. *Key NOESY correlations for* **1** *and* **2**

Table 1. *^{1}H- and ^{13}C-NMR Data, and HMBC Correlations of Compound* **1** (in $CDCl_3$; δ in ppm, J in Hz)

	δ(H)	δ(C)	HMBC (H → C)
CH_2(1)	1.47–1.51 (*m*), 1.71–1.74 (*m*)	36.5	C(3), C(5), C(9)
CH_2(2)	1.30–1.36 (*m*), 1.57–1.61 (*m*)	22.3	C(10), C(4)
CH_2(3)	1.17–1.21 (*m*), 1.38–1.41 (*m*)	29.7	C(1), C(4), C(5)
H–C(4)	1.42–1.45 (*m*)	33.5	C(2), C(10), C(6), C(15)
C(5)		44.9	
CH_2(6)	2.64 (*d*, J = 13.8), 2.42 (*d*, J = 13.8)	31.7	C(4), C(5), C(7), C(8), C(10), C(11)
C(7)		161.2	
H–C(8)	5.07 (*ddq*, J = 10.5, 4.8, 1.5)	77.2	C(9), C(7), C(10)
CH_2(9)	2.13 (*dd*, J = 13.0, 4.8), 1.94 (*dd*, J = 13.0, 10.5)	40.9	C(5), C(7), C(8), C(10)
C(10)		75.0	
C(11)		120.6	
C(12)		175.1	
Me(13)	1.79 (*d*, J = 1.5)	8.3	C(7), C(11), C(12)
Me(14)	0.98 (*s*)	14.7	C(4), C(5), C(6), C(10)
Me(15)	0.81 (*d*, J = 6.4)	16.0	C(3), C(4), C(5)

Herticin B (**2**) was also obtained as a white solid and exhibited bonds for OH (3529, 3419, and 3214 cm^{-1}) and an α,β-unsaturated γ-lactone (1756 and 1645 cm^{-1}). The broad band and DEPT ^{13}C-NMR spectra displayed 15 signals: three Me, four CH_2, three CH, five quaternary C-atoms (*Table 2*). The molecular formula of **2** was established as $C_{15}H_{22}O_4$ from its HR-EI-MS showing an M^+ peak at m/z 266.3326 (calc. 266.3372). In the EI-MS, strong peaks at m/z 266 (M^+), 248 ($[M - H_2O]^+$), and 230 ($[M - 2\,H_2O]^+$) were observed, suggesting the presence of two OH groups in the molecule. Beside the signal for an additional oxygenated C-atom appearing at δ(C) 71.3, the ^{1}H- and ^{13}C-NMR spectra were nearly identical with those of compound **1**, which disclosed that compound **2** is a hydroxylated derivative of compound **1**. The H-

Table 2. *^{1}H- and ^{13}C-NMR Data, and HMBC Correlations of Compound* **2** (in $CDCl_3$; δ in ppm, J in Hz)

	δ(H)	δ(C)	HMBC (H → C)
CH_2(1)	1.33–1.36 (*m*), 1.73–1.77 (*m*)	35.9	C(3), C(5), C(10), C(9)
CH_2(2)	1.21–1.24 (*m*), 1.57–1.61 (*m*)	22.1	C(10), C(4)
CH_2(3)	1.16–1.20 (*m*), 1.29–1.31 (*m*)	29.5	C(1), C(4), C(5)
H–C(4)	1.26–1.28 (*m*)	33.3	C(2), C(10), C(6), C(15)
C(5)		46.3	
H–C(6)	4.60 (*s*)	71.3	C(4), C(5), C(7), C(8), C(10), C(11), C(14)
C(7)		160.7	
H–C(8)	5.31 (*ddq*, J = 10.5, 4.7, 1.4)	76.1	C(7), C(9),C(10)
CH_2(9)	2.25 (*dd*, J = 13.2, 4.7), 1.98 (*dd*, J = 13.2, 10.5)	41.4	C(5), C(7), C(8), C(10)
C(10)		76.0	
C(11)		122.0	
C(12)		174.6	
Me(13)	1.85 (*d*, J = 1.4)	8.6	C(7), C(11), C(12)
Me(14)	1.20 (*s*)	10.5	C(4), C(5), C(6), C(10)
Me(15)	0.81 (*d*, J = 5.6)	16.0	C(3), C(5)

atom appearing as a *ddq* at δ(H) 5.31 ($J = 10.5$, 4.7, 1.4, 1 H) was assigned to the H-atom α to the lactone O-atom. The H-atom of a secondary OH group at δ(H) 4.60 appeared as a *singlet* in the ^{1}H-NMR spectrum. In the HMBC, it showed correlations with C(11) (δ(C) 122.0), C(7) (δ(C) 160.7), C(8) (δ(C) 76.1), C(5) (δ(C) 46.3), and C(14) (δ(C) 10.5), allowing us to place this OH group at C(6). The ^{1}H- and ^{13}C-NMR data of compound **2** showed similarity to that of 6β,10β-dihydroxyeremophilenolide [10]. The two compounds differ in their melting point and optical rotation. Thus, the two compounds differ in their configuration. The absence of a NOESY correlation between H–C(8) and the Me group attached to C(5) and the coupling constant of H–C(8) and H–C(9) [1] confirmed that this compound has the same configuration at C(8) as compound **1**. The downfield chemical shift (δ(H) 1.20) of the Me group attached to C(5) confirmed a *cis*-fused *A*/*B* ring system. The absence of a NOESY interaction between H–C(6) and H–C(8) allowed us to assign α orientation for the OH group at C(6). Thus herticin B (**2**) was assigned to be (8αH)-6α,10β-dihydroxyeremophilenolide.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 230–400 mesh; *Merck*). Thin-layer chromatography (TLC): SiO_2 *60* F_{254} plates (*Merck*). Optical rotations: *Jasco DIP-360* digital polarimeter. IR spectra: *Jasco 302-A* spectrophotometer, in $CHCl_3$ or MeOH solns.; in cm^{-1}. NMR spectra: *Bruker* instrument; δ in ppm, J in Hz. EI- and HR-EI-MS: *Jeol JMS-DA-500* mass spectrometers; in *m*/*z* (rel. %).

Plant Material. The whole plant material of *H. intermedia* BOISS was collected from Baluchistan (Pakistan) in May 2006 and identified by *R. B. T.*, Plant Taxonomist, Department of Botany, University of Baluchistan, where a voucher specimen (HI-36-06) has been deposited.

Extraction and Isolation. The air dried whole plant (28 kg) was exhaustively extracted with MeOH (3×50 l) at r.t. The combined MeOH extracts were concentrated, and the residue (750 g) was divided into hexane (135 g), AcOEt (150 g), BuOH (68 g), and H_2O (38 g) soluble fractions. The AcOEt soluble fraction was subjected to CC (SiO_2; hexane/AcOEt, AcOEt, AcOEt/MeOH, of increasing polarity). The fractions from hexane/AcOEt 75 : 25 were combined and subjected to CC (SiO_2; hexane/AcOEt 85 : 15) to yield **1** (13 mg) and (**2**) (9 mg) from the top and tail fractions, resp.

Herticin A (=*(8αH)-10β-Hydroxyeremophilenolide*; *(4a*R,5S,*8a*S,*9a*R*)-4a,5,6,7,8,8a,9,9a-Octahydro-8a-hydroxy-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one*; **1**). White solid. M.p. 184–186°. $[\alpha]_D^{26} = +165$ ($c = 0.470$, $CHCl_3$). IR (KBr): 3607, 3468, 1756, 1645. ^{1}H- and ^{13}C- NMR: *Table 1*. EI-MS: 250 (3, M^+), 232 (39, $[M - H_2O]^+$), 126 (34), 125 (72), 97 (70). HR-EI-MS: 250.3334 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.3378).

Herticin B (=*(8αH)-6α,10β-Dihydroxyeremophilenolide*; *(4*S,*4a*S,*5*S,*8a*S,*9a*R*)-4a,5,6,7,8,8a,9,9a-Octahydro-4,8a-dihydroxy-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one*; **2**). White solid. M.p. 79–83°. $[\alpha]_D^{26} = +104$ ($c = 0.06$, MeOH). IR (KBr): 3529, 3419, 3214, 1756, 1645. ^{1}H- and ^{13}C- NMR: *Table 1*. EI-MS: 266 (3, M^+), 248 (6, $[M - H_2O]^+$), 230 (3, $[M - 2\,H_2O]^+$), 141 (25), 123 (55), 97 (100), 55 (80). HR-EI-MS: 266.3326 (M^+, $C_{15}H_{22}O_3^+$; calc. 266.3372).

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