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A GERMACRANOLIDE FROM *INULA INDICA**

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Key Word Index—*Inula indica*; Compositae; sesquiterpene lactones; new germacranolide.

Abstract—Chemical investigation of *Inula indica* has yielded a new germacranolide, 1β,10α-epoxy-2α,9β-dihydroxy-5β-acetoxy-6α(2-methylbutyryloxy)-germacran-8α,12-olide, whose structure and stereochemistry have been established from the spectral characteristics of the compound and its derivatives.

Inula species (Inuleae) have been reported to contain different types of sesquiterpene lactones such as guaianolides, pseudoguaianolides, eudesmanolides and germacranolides [1, 2]. We wish to report the isolation of a new germacranolide, 1β,10α-epoxy-2α,9β-dihydroxy-5β-acetoxy-6α(2-methylbutyryloxy)-germacran-8α,12-olide (**1**) from *Inula indica* L.

From the aerial parts of the above plant, **1** was isolated. On acetylation at room temperature and reflux temperature, it afforded the diacetate **2** and the triacetate **3**, respectively. Partial oxidation gave the ketone **4**, while reaction with HCl yielded the pentaol **5**, and catalytic hydrogenation yielded the dihydro compound **6**. The structures and the stereochemistry of **1–6** were deduced from their ^{1}H NMR spectral data (Table 1) and by careful spin decoupling which allowed the assignment of all signals.

The signals of H-6 and H-8 were assigned by irradiation of the four-fold doublet at δ 3.75 in the spectrum of **4**. The chemical shifts of H-6 and H-8 agreed with the presence of an 8,12-lactone as the signal of the proton over the lactone oxygen was always at higher fields. The observed couplings $J_{7,8}$ and $J_{8,9}$ were as required for the given stereochemistry at C-7, C-8 and C-9, while inspection of models indicated that the protons at C-4 and C-5 were most probably in α-positions whereas H-6 was in the β-position. The angle between H-4 and H-5 and H-6 and H-7 must be nearly 90° as the couplings were very small, while those between H-5 and H-6 had to be nearly 180° to explain the large coupling $J_{5,6}$. The β-orientation of the C-4 methyl followed from the couplings of H-3 in the spectrum of **4**.

The α-orientation of the hydroxyl group at C-2 was deduced from the small coupling $J_{1,2}$. In the spectrum of **3**, the H-1 signal was shifted downfield and a sharp singlet was observed, which supported the 2-position of the hydroxyl. The position of the second hydroxyl in **1** was deduced from the ^{1}H NMR spectral data, while the relative position of the two ester groups could not be determined. However, a small shift of the acetate methyl signal, observed in the spectrum of the ketone **4**, indicated that a 5-acetoxy compound was more probable. The ^{1}H NMR spectrum of **5** (Table 1) showed that on hydrolysis of **1** the epoxide ring had been opened and the acetate group lost. The observed shifts of the H-6 signal indicated that the methylbutyrate group was at C-6. Due to the flexibility of the ten-membered ring, the conformation had changed considerably as could be seen from the couplings. The stereochemistry of the C-11 methyl in the dihydro derivative **6** was assigned on the basis of the coupling $J_{7,11}$.

EXPERIMENTAL

IR: Nujol or CCl_4. Plant material, collected near NCL campus, Pune, during December 1978, was shade-dried, powdered and extracted (7 kg) with Me_2CO. The Me_2CO extract (300 g) was chromatographed over Si gel (grade II) to give **1** (0.25% of dry wt).

1β,10α-Epoxy-2α,9β-dihydroxy-5β-acetoxy-6α-(2-methylbutyryloxy)-germacran-8α,12-olide (**1**). Colourless crystals (C_6H_6–EtOAc), mp 205–208°. IR cm^{-1}: 3300 (OH), 1750, 1730 (carbonyl), 1650, 890 (unsaturation), 1240 (OAc); MS *m/z* (rel. int.): 440 (M^+, 0.2), 422 (M − H_2O, 0.2), 380 (422-ketone, 1) 320 (380 − HOAc, 2), 278 (380 − OCOR, 9), 260 (278 − H_2O, 6), 85 ($C_4H_9CO^+$, 47), 57 (85 − CO, 100). ^{13}C NMR: δ 174.52, 169.09, 167.64, 132.12, 123.13, 78.87, 75.30, 74.29, 70.05, 69.88, 65.30, 65.13, 41.72, 41.04, 31.21, 27.14, 26.46, 22.39, 21.03, 17.98, 16.28, 11.70.

Diacetate (**2**). 500 mg of **1** was treated with Ac_2O (5 ml) and pyridine (5 ml) at room temp. for 12 hr to yield 430 mg of **2** as a gum. IR cm^{-1}: 3300 (OH), 1760, 1740, 1730 (carbonyls), 1650, 890 (unsaturation), 1240 (OAc).

Triacetate (**3**). 500 mg of **1** was refluxed with pyridine (10 ml) and Ac_2O (10 ml) for 2 hr to afford after prep. TLC 490 mg of **3** as colourless crystals (MeOH), mp 170–171°. IR cm^{-1}: 1785 (γ-lactone), 1755, 1225 (OAc), 1740 (COOR).

$[\alpha]_{24°}^{\lambda}$ =	589	578	546	436 nm
	−99.8	−105.0	−119.5	−206.8

($CHCl_3$, $c = 0.4$).

MS *m/z* (rel. int.): 524.226 (M^+, 0.5), 465 (M − OAc, 2), 423 (M − OCOR, 2) 422 (M − RCOOH, 2), 380 (422 − ketone, 3), 320 (380 − HOAc, 4), 278 (320 − ketone, 3), 260 (320 − HOAc, 4), 242 (260 − H_2O, 2), 85 ($C_4H_9O^+$, 72), 57 (85 − CO, 100).

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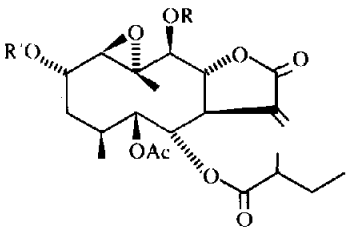
Table 1. ^{1}H NMR data of **1**–**6** (270 MHz, TMS as internal standard)

	1 ($CDCl_3$)	**2** ($CDCl_3$)	**3** (C_6D_6, 77°)	Δ*	**3** ($CDCl_3$)	**4** ($CDCl_3$)	**5** ($CDCl_3$)	**6** ($CDCl_3$)
1-H	2.93 *s* (*br*)	2.91 *s* (*br*)	2.64 *d*	0.21	3.00 *d*	3.91 *s*	3.87 *d*	2.95 *s* (*br*)
2-H	4.71 *d* (*br*)	4.70 *d* (*br*)	5.68 *d* (*br*)	0.49	5.76 *d* (*br*)	—	3.95 *m*	4.08 *d* (*br*)
3α-H	1.87 *dd*	1.88 *dd*	1.79 *dd*	0.23	2.02 *dd*	3.38 *dd*	2.62 *m*	2.13 *dd*
3β-H	2.11 *dd*	2.11 *dd*	1.97 *ddd*	0.17	2.18 *m*	2.08 *d*	1.67 *m*	1.85 *dd*
4-H	2.56 *ddq* (*br*)	2.57 *ddq* (*br*)	2.09 *ddq* (*br*)	0.32		2.55 *dq* (*br*)	2.62 *m*	
5-H	5.48 *d* (*br*)	5.48 *d* (*br*)	5.56 *dd*	0.27	5.47 *d* (*br*)	5.49 *d*	4.13 *dd*	5.46 *d* (*br*)
6-H	5.28 *d*	5.26 *d*	5.45 *d* (*br*)	0.25	5.36 *d*	5.28 *d*	4.96 *dd*	5.13 *d* (*br*)
7-H	3.95 *dddd*	4.03 *dddd*	3.76 *dddd*	0.34	3.66 *dddd*	3.75 *dddd*	3.29 *dddd*	3.34 *dd*
8-H	4.13 *dd*	4.19 *dd*	4.43 *dd*	0.27	4.23 *dd*	4.03 *dd*	4.48 *dd*	4.28 *dd*
9-H	4.40 *d*	5.72 *d*	6.00 *d*	0.46	5.69 *d*	3.83 *d*	4.55 *d*	4.23 *d*
11-H	—	—	—	—	—	—	—	2.96 *dq*
13-H	6.44 *d*	6.46 *d*	6.42 *d*	0.30	6.51 *d*	6.48 *d*	6.34 *d* }	1.50 *d*
13′-H	5.89 *d*	5.88 *d*	5.72 *d*	0.19	5.94 *d*	5.89 *d*	5.72 *d* }	
14-H	1.53 *s*	1.55 *s*	1.65 *s*	0.12	1.57 *s*	1.67 *s*	1.70 *s*	1.38 *s*
15-H	1.03 *d*	1.03 *d*	0.87 *d*	0.11	1.02 *d*	1.11 *d*	1.05 *d*	0.98 *d*
OMeBu	2.33 *tq*	2.33 *tq*	2.19 *tq*	0.09	2.34 *tq*	2.33 *tq*	2.33 *tq*	2.36 *tq*
	1.60 *tq*	1.59 *ddq*	1.54 *ddq*	0.06	1.60 *ddq*	1.60 *ddq*	1.67 *m*	1.67 *ddq*
	1.42 *ddq*	1.44 *ddq*	1.30 *ddq*	0.07	1.45 *ddq*	1.43 *ddq*	1.43 *ddq*	1.43 *ddq*
	0.87 *t*	0.85 *t*	0.75 *t*	0.05	0.86 *t*	0.85 *t*	0.90 *t*	0.92 *t*
	1.08 *d*	1.07 *d*	0.99 *d*	0.07	1.08 *d*	1.08 *d*	1.18 *d*	1.12 *d*
OAc	2.07 *s*	2.18 *s*	1.95 *s*	9.33	2.22 *s*	2.09 *s*		2.03 *s*
		2.06 *s*	1.79 *s*	0.11	2.16 *s*			
			1.78 *s*	0.09	2.08 *s*			

J (Hz): 1,2 = 1.5; 2,3α = 10; 2,3β ~ 1; 3,4 = 9; 4,15 = 7; 4,5 = 1.5; 5,6 = 10; 7,8 = 9; 7,13 = 3.3; 7,13′ = 2.8; 8,9 = 10; OCOR; 2′,3′ = 2′5′ = 3′,4′ = 7; $3'_1,3'_2$ = 14; **4**: 3,4 = 9.5; 3,3 = 14.5; 4,5 = 2.3; **5**: 1,2 = 9.5; 4,5 = 7; 5,6 = 9; 6,7 = 9; 7,8 = 6; 7,13 = 3.3; 7,13′ = 2.8; 8,9 = 3.
*Values after addition of $Eu(fod)_3$.



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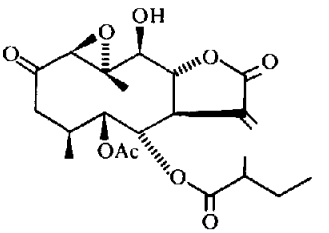

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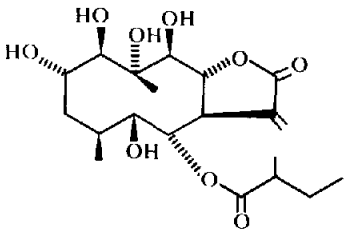

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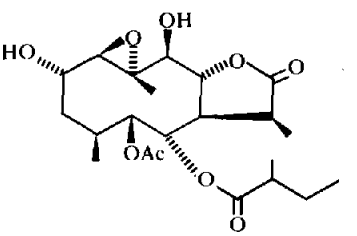

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Ketone (**4**). 500 mg of **1** in pyridine (8 ml) was treated with Sarrett's reagent (7 ml pyridine and 600 mg CrO_3), at room temp. for 16 hr to yield **4** as colourless crystals (C_6H_6), 390 mg, mp 190–192°. IR cm^{-1}: 3300 (OH), 1770, 1750, 1740, 1710 (carbonyl), 1660, 890 (unsaturation), 1240 (OAc), MS *m/z* (rel. int.): 438 (M^+, 0.5), 420 (M − H_2O, 0.25), 396 (M − ketone, 0.35), 378 (M − HOAc, 0.2), 276 (378 − RCOOH, 0.2), 85 ($C_4H_9CO^+$, 59), 57 (85 − CO, 100).

Pentaol (**5**). To **1** (450 mg) dissolved in Me_2CO (6 ml) was added conc. HCl (15 ml) and the mixture was left at room temp. for 48 hr. Usual work-up followed by prep. TLC afforded 120 mg of **5** as colourless crystals (C_6H_6), mp 156–158°, IR cm^{-1}: 3300 (OH), 1750, 1730 (carbonyl), 1650, 890 (unsaturation). MS *m/z* (rel. int.): 416 (M^+, 0.1, $C_{20}H_{32}O_9$), 398 (M − H_2O, 1), 380 (398 − H_2O, 1), 362 (380 − H_2O, 0.5), 260 (362 − RCOOH, 1), 85 ($C_4H_9O^+$, 42), 57 (85 − CO, 100).

Dihydro compound (**6**). 500 mg of **1** in 50 ml of EtOH was hydrogenated at atmos. pres. using Pd–C (10%) to yield 500 mg of **6** as colourless crystals (C_6H_6), mp 217–220°. IR cm^{-1}: 3300 (OH), 1760, 1750, 1740 (carbonyls), 1240 (OAc). MS *m/z* (rel. int.): M^+ −, 340 (M − RCOOH, 0.7), 322 (340 − H_2O, 0.2), 280 (322-ketone, 1.5), 85 ($C_4H_9CO^+$, 68), 57 (85 − CO, 100).

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