250.157); $-H_2O$ 232 (7); $-CH_2OH$ 219 (17); $C_6H_9^+$ 81 (100).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436 \quad 365\,nm}{+84 \quad +87 \quad +103 \quad +211 \quad +426°}$$

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ERIOFERTOPIN AND 2-*O*-ACETYLERIOFERTOPIN, NEW TUMOR INHIBITORY GERMACRADIENOLIDES FROM *ERIOPHYLLUM CONFERTIFLORUM**

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Key Word Index—*Eriophyllum confertiflorum*; Asteraceae; new germacranolides; eriofertopin and 2-*O*-acetyleriofertopin; confertiphyllide.

During the course of our continuing search for tumor inhibitors, we have isolated two new significantly active tumor inhibitory germacradienolides, eriofertopin, **1a**, and 2-*O*-acetyleriofertopin, **1b**, from *Eriophyllum confertiflorum* Gray (Asteraceae).

Activity guided fractionation (KB) [1] of a 95% EtOH (Soxhlet) extract of the twigs, leaves and flowers showed the activity to be successively concentrated in the $CHCl_3$ phase of a $CHCl_3$–H_2O partition, 10% aq. MeOH phase of a 10% aq. MeOH–Skellysolve B partition, 20% aq. MeOH phase of a 20% aq. MeOH–CCl_4 partiton and finally in the $CHCl_3$ phase of a $CHCl_3$–40% aq. MeOH partition. The final $CHCl_3$ phase was chromatographed on Si gel. Elution with 2% MeOH–$CHCl_3$ yielded 2-*O*-acetyleriofertopin, **1b**, as a colorless, air sensitive foam. Elution with 5% MeOH–$CHCl_3$ afforded eriofertopin (**1a**) as a highly air sensitive colorless foam. The structures of **1a** and **1b** were assigned on the basis of their spectral data (Table 1). The stereochemistry at C-2 and C-8 was determined by comparison

Table 1. PMR data for eriofertopin (**1a**), 2-*O*-acetyleriofertopin (**1b**) and eriofertopin diacetate (**1c**) Chemical shifts are given as δ-values, coupling constants (Hz) are quoted in parenthesis

	1a	1b	1c
H-1	5.06 *m*	5.10 *obsc*	5.09 *obsc*
H-2	4.84 *dt* (5.9, 10)	5.81 *obsc*	5.78 *obsc*
H-5	5.05 *m*	5.10 *obsc*	5.09 *obsc*
H-6	5.05 *m*	5.10 *obsc*	5. 24 *d* (10)
H-7	2.98 *m*	2.95 *m*	2.98 *m*
H-8	5.82 *brd* (5)	5.81 *obsc*	5.78 *obsc*
H-9	3.37 *dd* (5.3, 14.5)	3.18 *dd* (5.6, 14.2)	3.33 *dd* (5.6, 14.6)
	2.16 *obsc*	2.39 *obsc*	2.23 *obsc*
H-13A, B	5.63 *obsc*	5.65 *obsc*	5.62 *obsc*
	6.32 *d* (3.5)	6.33 *d* (3.4)	6.33 *d* (3.4)
H-14	3.74 *d*	3.74 *d*	4.21 *d*
	4.28 *d* (AB *q* 12.7)	4.41 *d* (AB *q* 13.8)	4.82 *d* (AB *q* 12.7)
H-15	1.72 *brs*	1.78 *brs*	1.81 *brs*
H-3′	6.02 *brs*	6.03 *brs*	6.03 *brs*
	5.62 *brs*	5.68 *obsc*	5.62 *obsc*
H-4′	1.94 *brs*	1.94 *brs*	1.91 *brs*
-COMe		2.08	1.96
			2.07

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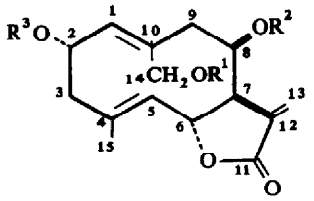
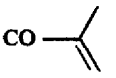
of the PMR spectra of **1a** and **1b** to the PMR spectra of eupasserin [2] and dihydrotamaulipin A [3]. Both eriofertopin (**1a**) and 2-*O*-acetyleriofertopin (**1b**) are among a select group of sesquiterpene lactones that demonstrate both *in vitro* (KB) and *in vivo* (PS) activity.

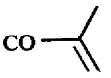
We have also isolated confertiphyllide (**2**) which had previously been suggested as a possible artifact of the isolation procedure [4]. Confertiphyllide was isolated from both Soxhlet and room temp. 95% EtOH extracts and was found not to be formed to any perceptible extent (TLC) at room temperature from eriofertin (**1d**). Since the temperatures used during the isolation procedure (25–35°) are far below those necessary for the Cope rearrangement of eriofertin [4], confertiphyllide indeed appears to be a natural constituent of *E. confertiflorum*.



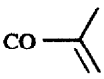
1a $R^1 = R^3 = H$, $R^2 = CO$



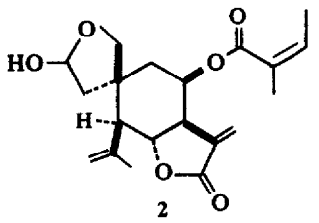
1b $R^1 = H$, $R^3 = Ac$, $R^2 = CO$



1c $R^1 = R^3 = Ac$, $R^2 = CO$



1d $R^1 = R^3 = H$, $R^2 = CO$



2

EXPERIMENTAL

General procedure. Mp's were uncorr. PMR spectra were recorded at 100 MHz in $CDCl_3$ using TMS as internal standard. PLC was on Si gel 60 plates (0.5 mm) eluting with either *iso*-PrOH–C_6H_6 (1:9) or EtOH–Et_2O (7:93). Stems, leaves and flowers of *E. confertiflorum* were collected in California in April, 1973. We thank Dr. Robert E. Perdue, Jr., U.S.D.A., Beltsville, Md., for supplying the dried plant material in accordance with the program developed by the National Cancer Institute. Biological testing was conducted under the auspices of the National Cancer Institute [1]. Eriofertopin and 2-*O*-acetyleriofertopin showed significant tumor inhibitory activity against P-388 lymphocytic leukemia in the mouse (PS), T/C 167 and T/C 130 at 20 mg/kg and 30 mg/kg, respectively and cytotoxicity against KB cell culture (ED_{50} = 1.2 and 1.75 μg/ml, respectively).

Extraction and isolation. Dried and ground stems, leaves and flowers (1 kg) of *E. confertiflorum* were extracted with 95% EtOH (Soxhlet) for 22 hr. The extract was concd *in vacuo* and the residue partitioned as above. The final $CHCl_3$ partition phase was chromatographed on 1 kg Si gel 60 eluting successively with $CHCl_3$, 1% MeOH–$CHCl_3$, 2% MeOH–$CHCl_3$ and finally 5% MeOH–$CHCl_3$. The 2% MeOH–$CHCl_3$ eluate, after PLC (30 mg/plate) eluting with *iso*-PrOH–C_6H_6 (1:9) × 2, yielded 2-*O*-acetyleriofertopin (**1b**). The 5% MeOH–$CHCl_3$ eluate, after repeated PLC (30 mg/plate) eluting with EtOH–Et_2O (7:93) × 4, yielded eriofertopin (**1a**).

Eriofertopin. (**1a**). ν_{max}^{KBr} cm^{-1}: 3430, 1765, 1725, 1660, 1637. λ_{max}^{MeOH} strong end absorption. MS (probe, C.I.-CH_4) high resolution *m/e* 349.1666 ($M^+ + 1$) calc. for $C_{19}H_{25}O_6$ *m/e* 349.1651 $[\alpha]_D^{21} = +89°$ (c = 0.9, $CHCl_3$).

2-O-Acetyleriofertopin (**1b**). $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1765, 1733, 1725, 1660, 1637. λ_{max}^{MeOH} strong end absorption. MS (probe, C.I.-CH_4) *m/e* 391 ($M^+ + 1$). $[\alpha]_D^{21} = +29°$ (c = 0.83, $CHCl_3$).

Eriofertopin diacetate (**1c**). Acetylation of eriofertopin (**1a**) with C_6H_5N–Ac_2O gave the diacetate in 73.5% yield (recrystallized from $CHCl_3$–hexanes) Mp 132–3°. ν_{max}^{KBr} cm^{-1}: 1770, 1740, 1725, 1675, 1637. MS (probe, C.I.-CH_4) high resolution *m/e* 433.1880, calc. for $C_{23}H_{29}O_8$ *m/e* 433.1862.

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