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SESQUITERPENE LACTONES OF *BALTIMORA RECTA**

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Key Word Index—*Baltimora recta*; Compositae; Heliantheae; sesquiterpene lactones; alantolides.

Baltimora L. (Compositae, Heliantheae), a small American genus of two species [1], has been customarily placed in subtribe Melampodiinae [2], but has recently been moved to the new subtribal segregate Ecliptinae [3]. We now report the isolation of a number of alantolides from a large scale extraction of the central American species *Baltimora recta*.

INTRODUCTION

The major sesquiterpene lactone of *B. recta* was the alantolide encelin (**1**) previously isolated from *Encelia farinosa* (Helianthinae) [4]. ^{1}H and ^{13}C NMR spectra of encelin are included in Tables 1 and 2; in accordance with our earlier revision [5] of the structure of farinosin (**5**), the original assignments for H-13 and H-14 of encelin [4] must be interchanged. The previously unreported CD curve of **1** (see Experimental) exhibited multiple Cotton effects due to the presence of α,β-unsaturated lactone and *cis* and *trans* α,β-unsaturated ketone functions. Two minor constituents were **3** and **4** of known structure which had been obtained earlier [5] as transformation products of 3-epiisotelekin (**6**). ^{1}H NMR at 270 MHz and ^{13}C NMR spectra of these substances are also included in Tables 1 and 2. The C-11 stereochemistry of **4**, while firmly established through correlation and with tetrahydroalantolactone, was corroborated by the solvent shift method ($\Delta\delta$ 0.25 ppm) [6] and the chemical shift of C-13 [7, 8]. In the santonin series, pseudoaxial methyl groups attached to C-11 give rise to signals near δ 9.5, which are shielded by 2 ppm or more relative to the pseudoequatorial isomer.

Two new alantolides were **2a** and its acetate **2b** whose structure was established by oxidation of **2a** to **1**. The stereochemistry at C-3 was evident from the ^{1}H NMR spectra (Table 1). The chemical shift changes of H-3 and H-15 in going from **2a** to **2b** parallel those in the epiisotelekin series (3β-hydroxyl), but not those in the isotelekin series (3α-hydroxyl) [5]. Likewise the chemical shift changes experienced by H-14 and H-15 on oxidation of **6** to **1** parallel those taking place on oxidation of **4** to **3** [5].

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Table 1. ^{1}H NMR spectra of compounds from *Baltimora recta**

	1	2a	2b	3	4a
H-1	6.82 *d* (10)	5.53 *dd* (9.5, 2.5)	5.42 *dd* (10, 2)	†	†
H-2	6.00 *d*	5.60 *dd* (9.5, 2.5)	5.70 *dd* (10, 2)	†	†
H-3	—	4.68 *ddbr* (2.5, 2)	5.88 *ddbr* (2.5, 2)	—	4.00 *ddbr* (12, 3.5)
H-5	2.61 *dd* (14, 2.5)	2.17 *dd* (14, 2.5)	2.28 *dd* (14, 2.5)	2.25 *dd* (14, 2.5)	†
H-6a	2.03 *ddd* (14, 7, 2.5)	1.82 *ddd* (14, 7, 2.5)	1.82 *ddd* (14, 7, 2.5)	1.98 *ddd* (14, 7, 2.5)	†
H-6b	1.54 *q* (14)	1.55 *q* (14)	1.54 *q* (14)	1.39 *q* (14)	†
H-7	3.09 *m*	3.04 *m*	3.03 *m*	3.02 *m*	†
H-8	4.50 *ddd* (5, 4.5, 2)	4.53 *ddd* (5, 4.5, 2)	4.50 *ddd* (5, 4.5, 2)	4.55 *ddd* (5, 4.5, 2)	4.48 *ddd* (5, 4.5, 2)
H-9a	2.39 *dd* (15, 2)	2.28 *dd* (15, 2)	2.25 *dd* (15, 2)	2.33 *dd* (15, 2)	2.20 *dd* (15, 2)
H-9b	1.80 *dd* (15, 4.5)	1.64 *dd* (15, 4.5)	1.65 *dd* (15, 4.5)	1.57 *dd* (15, 4.5)	1.45 *dd* (15, 4.5)
H-13a	6.19 *d*(1)	6.16 *d*(1)	6.16 *d*(1)	6.18 *d*(1)	1.23 *d*(7)‡
H-13b	5.69 *d*(1)	5.63 *d*(1)	5.55 *d*(1)	5.60 *d*(1)	
H-14†‡	1.04	0.92	0.97	0.99	0.80
H-15a	6.11 *br*	5.27 *br*	5.00 *br*	5.90 *dd*(2, 1)	5.15 *br*
H-15b	5.20 *br*	4.73 *br*	4.68 *br*	5.12 *dd*(2, 1)	4.65 *br*
Miscellaneous			2.14 (Ac)‡		2.84 *m* (H-11)

* Run in $CDCl_3$ at 270 MHz. Unmarked signals are singlets. Frequencies in ppm downfield from TMS as internal standard. Coupling constants (in parentheses) in hertz.
† In envelope or obscured.
‡ Intensity three protons.

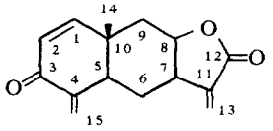
Table 2. ^{13}C NMR spectra of compounds from *Baltimora recta**

	1	2a	2b	3	4
C-1	160.31 *d*	127.47 *d*	123.23 *d*	40.42 *t*	40.09 *t*†
C-2	127.17 *d*	139.88 *d*	141.49 *d*	36.04 *t*	32.14 *t*
C-3	189.13 *d*	70.35 *d*	71.68 *d*	201.23	73.02 *d*
C-4	145.04	148.59	143.15	147.32	151.51
C-5	45.25 *d*	44.07 *d*	44.19 *d*	44.80 *d*	44.91 *d*
C-6	27.35 *t*	27.07 *t*	26.90 *t*	27.31 *t*	21.30 *t*
C-7	40.18 *d*	40.37 *d*	40.30 *d*	39.63 *d*	41.71 *d*‡
C-8	78.06 *d*	76.43 *d*	76.17 *d*	76.07 *d*	76.65 *d*
C-9	37.95 *t*	38.39 *t*	38.26 *t*	38.86 *t*	40.09 *t*†
C-10	36.71	36.63	36.54	32.06	34.55
C-11	141.85	141.61	141.49	141.60	41.21 *d*‡
C-12	170.53 *t*	170.31	170.44	170.04	179.30
C-13	121.85 *t*	120.69 *t*	120.67 *t*	120.71 *t*	9.20 *q*
C-14	20.02 *q*	20.59 *q*	20.31 *q*	17.16 *q*	17.7 *q*
C-15	119.62 *t*	105.34 *t*	105.92 *t*	118.95 *t*	103.33 *t*
C-1′			170.01		
C-2′			21.02 *q*		

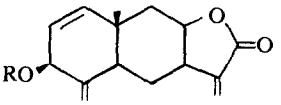
* Run in $CDCl_3$ at 67.9 MHz. Unmarked signals are singlets. Assignments are tentative and not established by single frequency off-resonance decoupling.

† Superimposed signals.

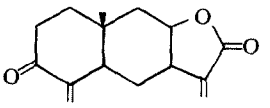
‡ Assignments may be interchanged.



1



2a R = H
2b R = Ac



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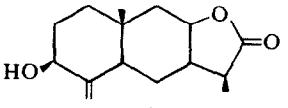

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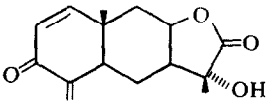

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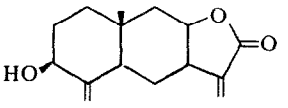

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Although most Melampodiinae studied so far have yielded melampolide-type sesquiterpene lactones, it would be premature to conclude on the basis of these results that the chemical evidence justifies the removal of *Baltimora* from Melampodiinae to Ecliptinae. Ivalin, an alantolide, has been isolated [9] from *Polymnia laevigata* (Melampodiinae) and *Wedelia rugosa* (Ecliptinae) [10], while *Enhydra fluctuans*, the only other member of Ecliptinae for which results are available, is a source of melampolides [11].

EXPERIMENTAL

Above ground parts of *Baltimora recta* L. (Tyson #6283) collected by Dr. E. L. Tyson on 28 June, 1970 near the Pacific Saddle Club, Pedro Miguel, Canal Zone, Panama, 11.6 kg, were extracted with $CHCl_3$ and worked up in the usual manner. The crude gum (25 g) was chromatographed over 0.4 kg of Si gel (Baker, 60–200 mesh), 500 ml fractions being collected in the following order; 1–12 (C_6H_6), 13–20 (C_6H_6–$CHCl_3$, 1:1), 21–25 ($CHCl_3$), 26–31 ($CHCl_3$–MeOH, 9:1), 32–38 ($CHCl_3$–MeOH, 3:1). Fractions 13–20 (semicrystalline) were combined and recrystallized from $CHCl_3$–hexane as colorless flakes (**2b**), 0.1 g, mp 166–7°; $[\alpha]$ +120° (*c*, 1.5, $CHCl_3$; IR ν_{max}^{KBr} cm^{-1}: 1752, 1730, 1735, 1650, 1645, 1238, 970, 910 and 810; UV λ_{max}^{MeOH} nm: 211 (ε 13000). MW(MS), 288. (Calc. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99; O, 22.22. Found: C, 69.42; H, 6.71; O, 22.19%).

Fractions 21–25 which contained one major constituent were combined and recrystallized from C_6H_6, yield of encelin (**1**) 4.0 g, mp 196–7°; $[\alpha]_D$ −20.5° (*c* 3.5, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 1765, 1670, 1620 (very intense, *cis* db), 955 and 854; UV λ_{max}^{MeOH} nm: 239 and 213 (ε 10600, 15200), CD curve $[\theta]_{310}$ 7250, $[\theta]_{300}$ 3200, $[\theta]_{288}$ 9660, $[\theta]_{278}$ 9180, $[\theta]_{228}$ −9180, $[\theta]_{213}$ +37200 (last reading); MS *m/e*: 244 (M^+), 229 (M^+ − Me), 216 (M^+ − COO), 200 (M^+ − CO_2), 185 (M^+ − CO_2 − Me).

Rechromatography of fractions 26–31 which contained one major constituent and recrystallization from $CHCl_3$–hexane gave **3** (0.09 g) as needles, mp 144–5°; $[\alpha]_D$ +151.5° (*c* 2.0, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 1690, 1672, 1612, (very intense, *cis* db), 948, 920 and 875; UV λ_{max}^{MeOH} nm: 209 (ε 39100). The substance was identical with material prepared from 3-epiisotelekin [5].

TLC of fractions 32–40 (3 g) showed 2 spots of very similar R_f which were separated by PLC (Si gel Merck 60 PF-254 + 366) using the hexane–EtOAc (1:1) solvent system. The upper band yielded **2a** which was recrystallized from $CHCl_3$–hexane as needles (0·15 g), mp 146–7°; $[\alpha]_D$ +160° (*c* 2.5, $CHCl_3$); IR

ν_{max}^{KBr} cm^{-1}: 3490, 1752, 1660, 1640, 975, 940, 900 and 830; UV λ_{max}^{MeOH} nm: 213 (ε 12500). (Calc. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.51; MW, 246.1251. Found: C, 72.58; H, 7.08; O, 19.49%; MW(MS) 246.1266).

Acetylation of 20 mg **2a** (Py–Ac_2O) furnished 20 mg **2b** identical in all respects with material isolated directly from the plant. Oxidation of 25 mg **2a** in 2 ml Me_2CO with 0.5 ml Jones' reagent for 20 min at 0° and 15 min at room temp. gave 20 mg of material, mp 198°, identical in all respects with encelin.

The lower band from PLC gave solid material (**4a**) which crystallized from $CHCl_3$–hexane as needles (0.12 g), mp 178–80°; $[\alpha]_D$ +24.5° (*c* 2.1, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 3575, 1765, 1649, 973, 918 and 878; UV end absorption only: MS *m/e*: 250 (M^+), 235 (M – Me), 220, 107 (base peak), 93. The substance was identical with material prepared from 3-epiisotelekin [5].

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REVISION OF THE STRUCTURES OF CALEINE A AND B, GERMACRANOLIDE SESQUITERPENES FROM *CALEA ZACATECHICHI**

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Key Word Index—*Calea zacatechichi*; Compositae; Heliantheae; new germacranolide-type sesquiterpene lactones; caleine A; caleine B.

In a previous paper [1] we assigned the structures **1a** and **1b** to caleine A and B rather than the alternative structures **2a** and **2b**. Based on chemical transformations and spectroscopical data, mainly of the ^{1}H NMR, structures **2a** and **2b** were discarded based on the chemical shift parameters of H-2 and H-3. Since H-2 appears as a doublet at δ 6.61 (J = 11 Hz) and H-3 as a doublet of doublets at 6.01 (J = 11 Hz, J = 12 Hz) these chemical shifts are in disagreement with common α,β-unsaturated ketones, in which the β-protons generally absorb further downfield than the α-protons.

Most recently, the isolation and structure determination of neurolenins A and B by X-ray diffraction have been reported [2]. The structure of neurolenin B (**5e**) is very similar to the alternative structures **2a** and **2b** of the caleines. Comparison of the reported ^{1}H NMR spectral parameters with those of the caleines indicated close similarities (Table 1). These new findings led to a re-investigation of caleine A and B. Based on the following new results, we propose the revised structures **2a** and **2b** for the caleines but without assigning the stereochemistry. Reduction of caleine with sodium borohydride gave the diol **3** which, in the ^{1}H NMR spectrum, lacked the C-13 α-methylene signals and showed a new secondary methyl absorption. Oxidation of the diol **3** with periodic acid produced the α,β-unsaturated aldehyde **4** which exhibited chemical shifts expected for an α,β-unsaturated aldehyde in the ^{1}H NMR spectrum; a doublet of doublets at δ 5.9 (J = 11 Hz, J = 7.5 Hz) and a doublet of doublets at 6.39 (J = 11.5 Hz, J = 11.5 Hz), respectively were observed. Formation of the aldehyde **4** from caleine A and B provided unambiguous evidence for their structures **2a** and **2b** but without stereochemistry. The stereochemistry of **2a** and **2b** was assigned by comparison of the ^{1}H NMR data of **2a** and **2b** with neurolenin B whose structure had been determined by X-ray work [2]. Based on the newly obtained chemical data and the great similarities of the ^{1}H NMR spectral parameters of **2a** and **2b** with neurolenin B, we propose the stereostructures **5a** and **5b** for caleine A and B, respectively.

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