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NEW MELAMPOLIDE SESQUITERPENE LACTONES FROM *MELAMPODIUM LEUCANTHUM*

NIKOLAUS H. FISCHER,* RUSSELL A. WILEY, JR., HUEI-NAN LIN, KHASHAYAR KARIMIAN and SAMUEL M. POLITZ

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, U.S.A.

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Abstract—The isolation of five germacranolide sesquiterpene lactones from *Melampodium leucanthum* Torrey and Gray (Compositae–Heliantheae) is reported. The structures of three new melampolides, melampodin-A acetate, leucanthin-A and leucanthin-B, have been determined by spectral methods and chemical correlations.

INTRODUCTION

Melampodium [1], the largest genus of the Melampodiinae (Compositae, Heliantheae), includes 37 species, three of which have flowering heads with white rays, the rest of the taxa having yellow–orange ligules. In connection with our biochemical systematic investigation of the white-rayed complex of *Melampodium*, we wished to learn about the chemistry and infraspecific variation of sesquiterpene lactones from *Melampodium leucanthum* Torrey and Gray. This paper describes the isolation and structure elucidation of new germacranolide type sesquiterpene lactones from populations of *M. leucanthum* from the south-central United States and northern Mexico.

RESULTS AND DISCUSSION

A. Melampodin-A [2] *and derivatives*

Collections of *M. leucanthum* from west Texas and neighbouring areas gave terpenoid containing syrup in about 4% yield from the dried plant material. Melampodin-A [3] and melampodin-B [4] were obtained by crystallization from the crude syrup. We have recently reported [3] on melampodin-A a novel germacranolide type sesquiterpene lactone which represents a 1(10)-*cis*, 4(5)-*trans* cyclodecadiene germacranolide (melampolide) [5]. The finding of this first documented 1(10)-*cis*, 4(5)-*trans*-germacradiene necessitated reclassification of the germacranolides into four subgroups [5, 6]. Most of the arguments concerning the structure assignments for melampodin-A (**1**) and its acetate (**2**) were presented previously [3, 6, 7]. The chemistry of melampodin-B and its analogs from *M. cinereum* will be described elsewhere.

Oxidation of melampodin-A. Oxidation of melampodin-A with CrO_3 in glacial acetic acid or with Jones' reagent produced the keto-compound (**5**). Comparison of the NMR spectrum of **5** in C_6H_6-d_6 with that of **1** showed significant changes: a characteristic doublet at 2·61 (J 6·0 Hz) corresponding to H-9 in **5** appeared and the most downfield H-1 signals at 6·92 in **1** were lost in the reaction. The assignments of the NMR signals of **5** are tabulated in Table 1. The data were verified by double irradiation experiments of **5** in C_6D_6: Irradiation of the center of the complex signal at 3·69 (H-7) caused a simplification of the following absorptions: the triplet at 4·75 (H-6) became a doublet and the doublets at 5·20 and 6·17 (H-13a and H-13b, respectively) collapsed to singlets. The doublet of a doublet at 6·12 (H-8) simplified to a doublet (J 6·0 Hz). In

*To whom inquires regarding this paper should be addressed.

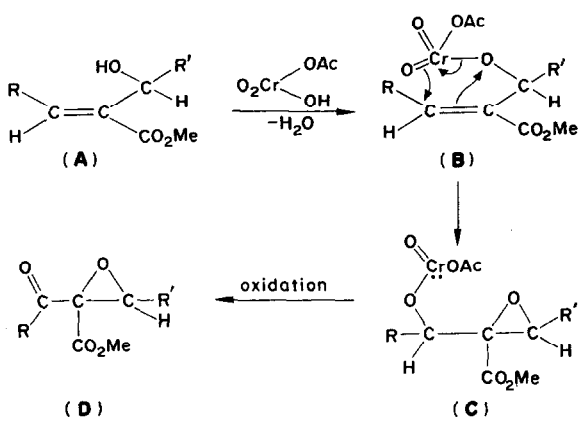
Table 1. NMR spectral parameters* of Leucanthin-A (**3**), Leucanthin-B (**4**), Epoxyketone **5** and Desacetylleucanthin-B (**6**)

Signal	Compound 3†	4†	5†	5‡	6§
H-1	7·23 *d* (5·5)	7·19 *d* (2·5)			6·94 *dd* (2·5; ~1·0)
H-2	6·03 *dd* (5·5; 12·0)	3·65 *m*	3·86 *m*	3·26 *d* (5·0)	3·71 *dd* (3·5; 2·5)
H-3	6·26 *d* (12·0)			2·79 *br* (5·0)	3·61 *br* (3·5)
H-5	3·16 *d* (10·0)	2·97 *d* (10·0)	5·85 *br* (10·0)	5·50 *br* (10·0)	3·04 *d* (9·8)
H-6	4·33 *t* (10·0)	4·28 *t* (10·0)	5·02 *t* (10·0)	4·75 *t* (10·0)	4·34 *t* (9·8)
H-7	~3·05 *m*	~2·9 *m*	3·90 *m*	3·69 *m*	3·23 *brt* (9·8; ~3·2)
H-8	6·81 *dd* (~1·5; 8·5)	6·78 *dd* (9·0)	5·88 *dd* (6·0; 4·0)	6·12 *dd* (4·2; 6·0)	6·56 *br* (8·8)
H-9	6·04 *d* (8·5)	5·74 *d* (9·0)	2·59 *d* (6·0)	2·61 *d* (6·0)	4·65 *br* (8·8)
H-13$_a$	5·82 *d* (3·0)	5·84 *d* (3·0)	5·51 *d* (3·3)	5·20 *d* (3·2)	5·75 *d* (3·1)
H-13$_b$	6·30 *d* (3·5)	6·31 *d* (3·0)	6·31 *d* (3·5)	6·17 *d* (3·5)	6·13 *d* (3·3)
H-3′	3·01 *q* (5·5)	3·03 *q* (5·0)	3·03 *q* (5·2)	2·45 *q* (5·2)	3·04 *q*
4-Me	1·82 *s*	1·85 *s*	1·75 *br*	0·95 *br*	1·52 *s*
2′-Me	1·45 *s*	1·46 *s*	1·52 *s*	1·18 *s*	1·35 *s*
3′-Me	1·18 *d* (5·5)	1·18 *d* (5·0)	1·27 *d* (5·2)	1·00 *d* (5·2)	1·22 *d* (5·5)
C-9-Ac	2·02 *s*	2·05 *s*			
CO_2Me	3·86 *s*	3·86 *s*	3·94 *s*	3·26 *s*	3·81 *s*

* Spectra were determined using TMS as an internal standard. Chemical shifts are in parts per million (δ). Figures in parentheses are coupling constants in Hertz. Spectrum run in: † $CDCl_3$, ‡ Benzene-d_6, § Acetone-d_6.

return, when the center of signals at 6·12 and 6·17 (H-8 and H-13b, respectively) was irradiated, the H-7 signal turned into a doublet of a doublet (J 10·0 and 3·2 Hz). Furthermore, the doublet at 2·61 collapsed to a singlet indicating that the upfield doublet at 2·61 must be due to H-9. Saturation of the triplet at 4·75 (H-6) simplified the H-7 multiplet by a loss of the large coupling; the broad doublet at 5·50 (H-5) changed to a broad singlet. Irradiation at the broadened singlet at 0·95 (C-4-Me) affected the broad doublets at 5·50 (H-5) and 2·79 (H-3) indicating a coupling not only between the C-4-methyl protons and H-5, but also C-4-Me and H-3. When the broadened H-3 doublet at 2·79 was saturated the H-2 signals flanking the carbomethoxy methyl singlet collapsed; irradiation at 3·26 resulted in the formation of a broad singlet at 2·79 (H-3). The decoupling experiments and the chemical shift data suggested that no change in the medium ring had occurred on the carbon atoms 2 through 8 or on the side chains. The empirical formula ($C_{21}H_{22}O_{10}$) of the oxidation product indicated an increase by one oxygen atom and the loss of two hydrogen atoms. The lack of a hydrogen atom at C-1 in **5** suggests the presence of a carbonyl group at C-1 and an epoxide function between C-9 and C-10, a structural arrangement which is in full agreement with the NMR spectral data. The stereochemistry of the 9,10-epoxide function was tentatively assigned by performing NMR solvent effect studies [8] in benzene-d_6 using $CDCl_3$ as a reference solvent (Table 1). The relatively upfield absorption of H-9 as well as its relatively low solvent dependence (2·61 in $CDCl_3$; 2·59 in C_6D_6) indicated that the hydrogen at C-9 must be situated in the shielding sphere of the C-4 methyl group and the 4,5-double bond, that is, it is oriented towards the center of the ten-membered ring as in **1** and **2** [3, 6]. Inspection of stereomodels revealed that an atomic arrangement as shown in **5** represents the best stereochemical relationship which is in agreement with the spectral data.

Chromate oxidations of allylic alcohols analogous to the conversion of **1**–**5**, have been described [9–11] and the mechanism formulated as an acid-catalyzed allylic rearrangement followed by an oxidation epoxidation reaction. When **1** was treated with glacial acetic acid under similar conditions without CrO_3, the starting material was recovered unchanged, indicating that allylic rearrangement could not have occurred previous to the involvement of CrO_3. Therefore, a different mechanism must govern the conversion of **1**–**5**, possibly involving several stepwise processes [10]. We suggest a further possible mechanism (Scheme 1). Initial formation of chromate ester **B** from the allylic alcohol **A** could follow an intramolecular, concerted rearrangement to give the chromate ester **C**, as indicated by the flow of arrows.



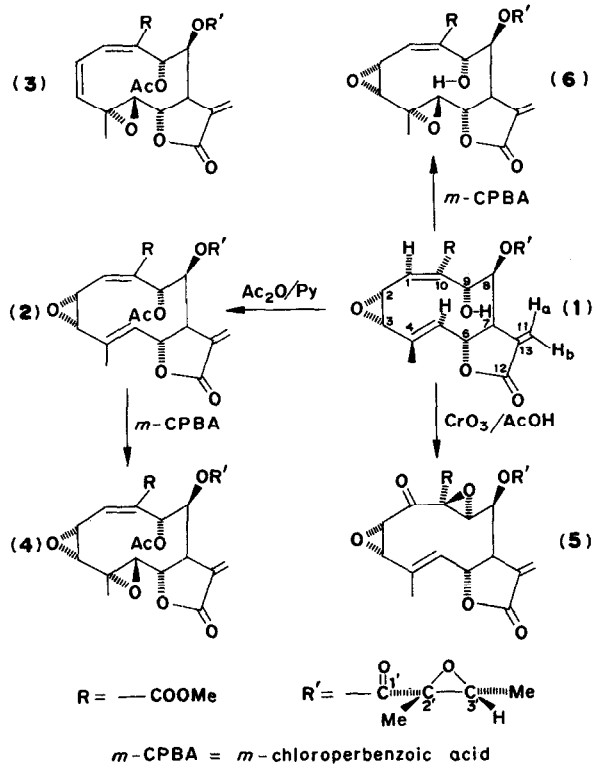
Scheme 1.

Further oxidation of the newly introduced oxygen function would lead to the epoxyketone **D**.

Two factors may play a major role in directing the oxidation process toward the epoxyketone (**5**). Firstly, the hydrogen atom at C-9 in **1** is oriented toward the center of the medium ring and is inaccessible to base as required for the "normal" oxidation reaction. Secondly, considerable relief of ring strain in the conversion of **1** into **5** can be deduced from inspection of stereomodels, whereas the introduction of a carbonyl group at C-9 would have represented a strong increase in ring strain.

Epoxidation of melampodin-A (**1**) *and the acetate* (**2**). Treatment of melampodin-A (**1**) and its acetate (**2**) with *m*-chloroperbenzoic acid in $CHCl_3$ gave high yields of the epoxides (**6**) and (**4**), respectively. Comparison of elemental analyses and NMR spectral parameters for **1** and **2** with **6** and **4**, respectively, indicated a conversion of the 4,5-double bonds in **1** and **2** into epoxide functions. In **1** and **2** the C-4 methyl doublets appear at 2·10 and 2·18, respectively, and the olefinic hydrogen at C-5 absorbs as complex multiplets at 5·1–5·4 and 5·1–5·42, respectively. Instead in **6** and **4** signals are observed at 1·52 and 1·85 (C-4 methyls), and 3·04 and 2·97 (H-5), respectively. The chemical shift data for H-5 in **4** and **6** are in good agreement with the parameters for related melampolides of similar structure, for instance the 4,5 epoxides of uvedalin [12] and enhydrin [13].

The stereochemistry of the epoxide in **4** and **6** was assigned 4-α, 5-β on the basis of the following arguments: (**a**) Melampodin-A (**1**) and the acetate (**2**) were shown to exist in a stable conformation with the C-4 methyl group oriented β and the olefinic hydrogen at C-5 α to the plane of the medium ring [3]. Therefore, stereospecific epoxidation would occur exclusively from the sterically accessible outer face of the C-4 double bond to give products with the stereochemistry as shown for **4** and **6**. (**b**) The observed large coupling constants of about 10·0 Hz between the protons at C-5 and C-6 in **4** and **6** indicate an *anti*-periplanar arrangement of these hydrogens. This requires an α-orientation of H-5 in **4** and **6**, since in both compounds H-6 is β-oriented.



B. Leucanthin-A (**3**) *and Leucanthin-B* (**4**).

Collections of *M. leucanthum* from Travis County, Texas afforded a syrup in about 0·4% yield from the dry plant material. Column chromatography over Si gel using ethyl acetate as an elutant resulted in a crystalline material which gave an elongated spot on TLC. NMR-spectral data indicated a mixture of one minor and two major sesquiterpene lactones. Repeated column chromatography followed by PLC led to enriched samples of each component. NMR spectral parameters of the minor, least polar constituent, were identical with those observed for melampodin-A

acetate (**2**) which had previously been synthesized from **1** by acetylation but had not before been observed as a natural product.

The two major constituents, which we named leucanthin-A and -B, exhibited NMR spectral parameters that were in many respects similar to melampodin-A acetate (Table 1 and Experimental). The NMR data for leucanthin-B were identical with those obtained for compound **4** which was synthesized from melampodin-A acetate (**2**) by epoxidation; this tentative structural assignment for leucanthin-B was verified by comparison of the IR and CD spectral data of **4** with leucanthin-B.

Leucanthin-A gave elemental analyses in good agreement with $C_{23}H_{26}O_{10}$ indicating that leucanthin-A must have the same empirical formula as **2** and must therefore be a structural isomer of **2**. Comparison of NMR spectra of leucanthin-A and **4** revealed that the H-2 and H-3 multiplets at 3·65 in compound **4** were not present in leucanthin-A. Instead proton absorptions typical for olefinic hydrogens, a doublet of doublets at 6·03 (J 5·5 & 12·0 Hz) and a doublet at 6·26 (J 12·0 Hz), were observed in leucanthin-A. The latter two signals were assigned by double irradiation studies. By comparison with the NMR data for compounds **1**, **2** and **4** (Table 1) the most downfield doublet at 7·23 (J 5·5 Hz) in leucanthin-A was assigned to the hydrogen at C-1, representing a β-unsaturated ester. Irradiation of the doublet at 7·23 simplified the doublet of doublets at 6·03 to a doublet (J 12·0). When the proton signals at 6·03 were saturated, the doublets at 7·23 and 6·26 collapsed to singlets, indicating that the proton signals at 6·03 and 6·26 are due to the hydrogens at C-2 and C-3, respectively. Further support for a 2,3-double bond in leucanthin-A was provided by the UV spectrum, which showed a strong $\pi \rightarrow \pi^*$ absorption at 258 nm typical for a doubly unsaturated ester. All the previous physical data are in full agreement with structure **3** for leucanthin-A, which contains a 2,3-double bond and an epoxide function at C-4 in the medium ring. On the basis of biogenetic considerations and the similarity of the NMR and CD parameters of leucanthin-A with **1**, **2** and **4**, it appears that the configurational and conformational relationships in compound **3** are the same as in the melampolides **1**, **2** and **4**.

EXPERIMENTAL

Mp's were performed in capillaries and are uncorrected. Elemental analyses were determined by Dr. Alfred Bernhardt, Max-Plank Institute für Kohlenforschung, Mülheim, West Germany and by Galbraith Laboratories, Inc., Knoxville, Tenn., U.S.A. IR spectra were taken in nujol. The voucher specimens marked with an asterisk are on deposit in the Herbarium of the University of Texas at Austin, Texas. All other vouchers are in the Louisiana State University Herbarium at Baton Rouge, Louisiana.

Isolation of Melampodin-A and -B from West Texas populations of M. leucanthum. Bulk collections of *Melampodium leucanthum* Torr and Gray were first made in 1967 (T. F. Stuessy 1122)* and on 26 July 1968 (A. S. Tomb 229)* 26 miles south of El Paso/Juarez on Routh 45 in the state of Chihuahua, Mexico, on 27 July 1968 (A. S. Tomb 231)* 25 miles east of El Paso on Highway 180 and on 15 October 1972 (N. H. Fischer No 28) 41 miles east of El Paso, Texas on Highway 180. NMR spectra of the crude extracts indicated the presence of the same constituents in the above collections.

Dried leaves (2·6 kg) were ground in a Waring blendor with cold $CHCl_3$. After filtration the combined $CHCl_3$ extracts and washings were evaporated *in vacuo* and the dark residue was dissolved in 2·6 l. EtOH. An aq 5% lead(II)acetate soln (2·6 l) was added. The gummy ppt was removed by filtration over celite and the filtrate evaporated *in vacuo* to remove most of the EtOH. Residual aq phase was extracted exhaustively with $CHCl_3$. From the combined $CHCl_3$ extracts, 105 g of a terpenoid-containing syrup was obtained. This was seeded with melampodin-A crystals (previously obtained by Si gel-chromatography with considerable loss of material due to decomposition) and left at −20° for 12 hr. Filtration and washing of the residual solid with EtOAc gave 6·6 g of a tan powder. Repeated trituration of this material with $CHCl_3$ left 1·34 g of melampodin-B [4]. From the $CHCl_3$ extracts, a final yield of 4·31 g of melampodin-A (**1**), mp 210–211°, was obtained by ppt with Et_2O. Recrystallization from EtOAc gave colourless orthorhombic crystals, mp 218–220° (dec.), $[\alpha]_D^{26}$ + 155° (*c* 0·7; MeOH); UV, λ_{max}^{MeOH} nm (log ϵ): 204 (4·38); CD (*c*, 5·26 × 10^{-5}, MeOH; *c*, 1·19 × 10^{-2}, dioxane), 25°, $[\theta]_{200}^{MeOH}$ + 25 × 10^3 (end absorption), $[\theta]_{214}^{MeOH}$ − 119 × 10^3, $[\theta]_{244}^{MeOH}$ + 37 × 10^3, $[\theta]_{208}^{dioxane}$ − 105 and $[\theta]_{310}^{dioxane}$ − 83 (shoulder); IR, ν_{max}^{nujol} cm^{-1}: 3405, 1755, 1712, 1675, 1635, 1305, 1260, 1145, 980 and 789. The NMR parameters of **1** are reported in Ref. [3]. (Found: C, 59·95; H, 5·74; O, 34·08; MW(MS), 420. $C_{21}H_{24}O_9$ required: C, 59·99; H, 5·75; O, 34·25%; MW, 420.)

Melampodin-A acetate (**2**). A soln of 500 mg **1** in 5 ml C_6H_5N and 5 ml Ac_2O was allowed to stand overnight at room temp. Evaporation under red. pres. gave a crystalline residue which was taken up in 15 ml $CHCl_3$ and washed 3× with 5 ml aq 5% $NaHCO_3$ soln. The $CHCl_3$ was dried over $MgSO_4$ and evaporated to yield 524 mg crystalline **2**. Recrystallization from *iso*-PrOH gave pure **2**, mp 182·5–183·5°; UV, λ_{max}^{MeOH} nm (log ϵ): 208 (4·30); CD (*c*, 5·4 × 10^{-4}, MeOH), $[\theta]_{200}$ + 8 × 10^3 (end absorption), $[\theta]_{214}$ − 153 × 10^3, $[\theta]_{245}$ + 23 × 10^3; IR, ν_{max}^{nujol} cm^{-1} 1780, 1755, 1712, 1675, 1640, 1270, 1220 and 1140. The NMR parameters of **2** are reported [3]. (Found: C, 59·48; H, 5·90; MW (MS), 462. $C_{23}H_{26}O_{10}$ required: C, 59·73; H, 5·67%; MW, 462.

Desacetylleucanthin-B (**6**). A soln of 150 mg **1** and 150 mg *m*-chloroperbenzoic acid (85%) in 2·5 ml $CHCl_3$ was left at room temp. for 22 hr. The soln was washed 3× with 5 ml aq 5% $NaHCO_3$ and then with H_2O. After drying with $MgSO_4$, the $CHCl_3$ phase was evaporated to yield 155 mg of colourless crystalline material. Recrystallization from EtOH

gave pure **6**, mp 250–253°; UV, λ_{max}^{MeOH} nm (log ϵ): 205 (4·50); CD (*c*, 8·6 × 10^{-4}, MeOH), $[\theta]_{200} - 31{\cdot}3 \times 10^3$ (end absorption), $[\theta]_{242} + 10{\cdot}2 \times 10^3$; IR, ν_{max}^{nujol} cm^{-1} 3490, 3420, 1782, 1760, 1710, 1695, 1650, 1260 and 1140. (Found: C, 57·79; H, 5·71; MW(MS), 436. $C_{21}H_{24}O_{10}$ required: C, 57·79; H, 5·54%; MW, 436.)

Epoxyketone **5.** (a) Oxidation of **1** with CrO_3 in glacial HOAc. Melampodin-A (200 mg) was dissolved in about 10 ml glacial HOAc and an excess of CrO_3 in glacial HOAc was added. The reaction mixture was diluted with the same vol of H_2O and extensively extracted with $CHCl_3$. The $CHCl_3$ layer was treated with a mixture of $NaHCO_3$ and $MgSO_4$. After filtration the $CHCl_3$ was partly evaporated and MeOH was added. Further evaporation *in vacuo* caused crystallization of **5**, 135 mg (65% yield), mp 219–222°. Recrystallization from MeOH gave pure **5**, mp 231–233°; UV, λ_{max}^{MeOH} nm (log ϵ): 208 (4·32); IR, ν_{max}^{nujol} cm^{-1}: 1760, 1723, 1675, 1260, 1160, 1132, 990. (Found: C, 57·99; H, 5·02; MW(MS), 434. $C_{21}H_{22}O_{10}$ required: C, 58·06; 5·11%; MW, 434.) When **1** was treated with glacial HOAc in the absence of CrO_3 **1** was recovered quantitatively. (b) Oxidation of **1** with Jones' reagent. 300 mg **1** were dissolved in 5 ml Me_2CO and Jones' reagent was added dropwise at 0°. The reaction mixture was poured into H_2O and the soln thoroughly extracted with $CHCl_3$. Combined $CHCl_3$ extracts were washed with aq 5% $NaHCO_3$ and then with H_2O. After drying ($MgSO_4$) and filtration the soln was evaporated to leave 289 mg of a gummy material. Crystallization from hot MeOH yielded pure **5**.

Epoxidation of **2**. A soln of 241 mg **2** and 200 mg *m*-chloroperbenzoic acid (85%) in 5 ml $CHCl_3$ was left at room temp. The progress of the reaction was checked by NMR. After 12 hr the reaction was complete. The $CHCl_3$ soln was washed with 5% aq $NaHCO_3$ then with H_2O and finally dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo* a syrup was obtained which after trituration with 3 ml Et_2O yielded 238 mg of colourless crystalline material. Recrystallization from *iso*-PrOH gave pure **4**, mp 217–219°; UV, λ_{max}^{MeOH} nm (log ϵ): 210 (4·18); CD, (*c*, 4·1 × 10^{-4}, MeOH), $[\theta]_{210} - 52 \times 10^3$, $[\theta]_{245} + 12 \times 10^3$; IR, ν_{max}^{nujol} cm^{-1}: 1780, 1760, 1720, 1270, 1230, 1155 and 1130. (Found: C, 57·60; H, 5·70; MW(MS), 478. $C_{23}H_{26}O_{11}$ required: C, 57·74; H, 5·48%; MW, 478.)

Isolation of Leucanthin-A, Leucanthin-B and Melampodin-A acetate from Central Texas populations of M. leucanthum. Bulk collections of *M. leucanthum* were made on 3 August 1968 (T. F. Stuessy 1405)* 7 miles west of Austin, Texas on Ranch Road 2244 (Sample 1) and on 4 August 1968 (T. F. Stuessy 1406°* 6 miles northwest of Austin, Texas on Ranch Road 2222.

Dried leaves of Sample 1 were extracted with $CHCl_3$ and worked up as described above. From 930 g plant material 40 g of a terpenoid-containing syrup was obtained. The crude syrup (6 g) was chromatographed over 200 g Sil gel (0·05–0·2 mesh) using EtOAc as elutant; 20 ml fractions were taken and monitored by TLC. Fractions 1–17 gave very small amounts of a yellow gum. From the combined fractions 18–29 a yellow syrup was obtained which crystallized when tritruated with Et_2O, 510 mg, mp 180–202°. Fractions 49–78 contained a yellow oil which distilled at 120–130°/0·01 Torr. The NMR spectrum indicated unsaturation and one acetyl group but no signals typical of a sesquiterpene lactone. Seeding of 31 g crude syrup with the previously obtained crystals gave, after storage at −20°, 2·3 g of crystalline material. In spite of repeated recrystallization from *iso*-PrOH and other solvents, crystals with a broad melting range of about 180–200° were obtained. NMR spectral data indicated a mixture of three sesquiterpene lactones in a 1:4:4 ratio. Repeated column chromatography and PLC on Si gel resulted in a considerable loss of material due to decomposition. This procedure provided samples of the different sesquiterpene lactones which were used for the structural assignments by spectroscopic methods. The minor, least polar compound showed NMR signals identical with melampodin-A acetate (**2**). The compound of intermediate polarity was leucanthin-A (**3**); mp 211–213° (dec); UV, $\lambda_{end.\ abs.}^{MeOH}$ nm (log ϵ): 205 (4·28), λ_{max}^{MeOH} nm (log ϵ); 258 (4·21); CD (*c*, 4·7 × 10^{-4}, MeOH), $[\theta]_{206} - 37{\cdot}5 \times 10^3$, $[\theta]_{262} + 8{\cdot}4 \times 10^3$: IR, ν_{max}^{nujol} cm^{-1}: 1760, 1740, 1718, 1260, 1220, 1142, 1118 and 1008. (Found: C, 59·76; H, 5·66; MW(MS), 462. $C_{23}H_{26}O_{10}$ requires: C, 59·73; H, 5·67%; MW 462.) Leucanthin-B (**4**) was obtained in 90% purity contaminated with about 10% leucanthin-A. Recrystallization from *iso*-PrOH gave colourless needles, mp 215–217°, which were identical by mmp, IR. CD and NMR with **4** obtained from **2.**

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