ANTHEMIDIN, A NEW SESQUITERPENE LACTONE FROM *ARTEMISIA LUDOVICIANA*

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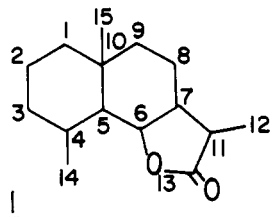
ABSTRACT.—A new sesquiterpene lactone, anthemidin (**4**), has been isolated from *Artemisia ludoviciana*, a member of the Composite family, Anthemideae tribe. The structure was determined by chemical and physical methods, and the stereochemistry was established by comparison to the known compound, tetrahydroalantolactone.

In the process of screening members of the Anthemideae tribe of the Compositae family for non-head-to-tail monoterpenes we isolated a compound from the pentane extracts of *Artemisia ludoviciana* which had chromatographic properties similar to pyrethrin II esters. This optically active compound, which we have given the trivial name anthemidin, proved to be a new sesquiterpene lactone of formula, $C_{15}H_{20}O_2$, as evidenced by its mass spectrum, elemental analysis, and spectral properties when compared to literature values for other sesquiterpene lactones (1–3).

The first consideration in the structure elucidation of anthemidin was the nature of the carbon skeleton. We made the later-justified assumption that anthemidin belonged to a known ring system. Of the six types of skeletons found in sesquiterpene lactones of the Compositae family, the following three are regularly found in plants of the Anthemideae tribe: the 6,6-fused ring eudesmanolides, the 7,5-fused ring guaianolides, and the ten-membered germacranolides. We also made the assumption that anthemidin belonged to one of these three groups. The cmr spectrum justified this assumption.

The molecular formula indicated six degrees of unsaturation, two carbon-carbon double bonds [δ 120.4 (d), δ 122.0 (d), δ 136.8 (s), δ 137.4 (d)]; one carbon-oxygen double bond [δ 179 (s)]; and a γ-lactone ring (1769 cm^{-1}) leaving two carbocycles. These data eliminate a normal monocyclic germacranolide skeleton. The presence of a quaternary carbon [δ 133.3 (s)] eliminates a normal guaianolide system since this skeleton has no quaternary carbon. The above data suggest the eudesmanolide system where there are two possible lactone attachments, **1**



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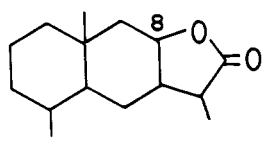

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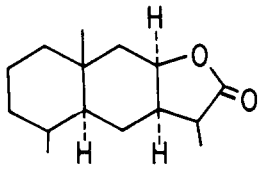

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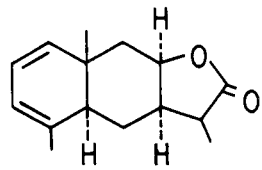

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and **2**. There are examples of the 6,13-(**1**) and 8,13-(**2**) eudesmanolides known in the Anthemideae tribe Arbotraum section of the *Artemisia* species to which *A. ludoviciana* belongs (1). Structure **2** was suggested by decoupling studies, i.e., irradiation of the C–8 proton [δ 4.3–4.5 (m)] simplified the 3H multiplet at δ 1.9–2.6. This assignment was confirmed by catalytic hydrogenation of anthemidin which gave the known compound tetrahydroalantolactone (4) **3**. A comparison of mp, mmp, ir, and optical rotation of known tetrahydroalantolactone with tetrahydroanthemidin definitely established the nature of the carbon skeleton of anthemidin including most stereochemical centers as well as absolute configuration.

The only remaining problem was the placement of the double bonds. The cmr indicated disubstituted and trisubstituted double bonds in agreement with the proton nmr. The presence of a 3H singlet at δ 1.8 suggested a 3,4-ene, while the uv spectra [λ max 263 nm (ϵ 6500)] indicated a homoannular diene. These facts can only be accommodated by the 1,3-diene structure **4**. Thus the complete stereochemical structure for anthemidin must be **4**.

Although the yield of **4** varied from less than 0.01% to 0.1% in collections from six different locations, it fits into a chemotaxonomic pattern which seems to be developing for the Compositae family (1).

EXPERIMENTAL[1]

ISOLATION OF ANTHEMIDIN (**4**).—*Artemisia ludoviciana* was collected while in bloom from six locations near Salt Lake City, primarily in August and September. The plant material was used fresh or stored frozen until needed. Ground flower heads (Waring blender) were extracted with pentane in a Soxhlet extractor for 5 to 7 days, then the solvent was removed *in vacuo*. The waxy solid was chromatographed on a short (6.8 cm length, 3 cm diameter) neutral Al_2O_3 column using a hexane to ethyl acetate gradient elution. The 10% ethyl acetate in hexane fractions were combined, and the solvent was removed *in vacuo*. The residue was taken up in 50 ml of pentane, filtered, and extracted with three 20 ml portions of nitromethane. The residue obtained from removal of the nitromethane was chromatographed using a silica gel (Woelm) medium pressure liquid chromatographic (mplc) system with a ethylacetate in hexane gradient elution. The 20% ethylacetate fractions were monitored by tlc (20% ethyl acetate in hexane, R_f 0.43), and **4** was visualized by a uv lamp. The combined anthemidin fractions were warmed *in vacuo* to remove the solvent, and the remaining white solid was recrystalized from 20% ethyl acetate in hexane to give crystalline **4**; mp 140–141°; [α]D+75° (c 1.45 $CHCl_3$); ir (Nujol) 3050, 1769 cm^{-1}; λ max (EtOH) 263 nm (ϵ 6840); ^1H nmr ($CDCl_3$) δ 0.9 (3H, s), 1.15 (3H, d, J=5 Hz), 1.1–1.3 (1H, m), 1.8 (3H, d, J=0.5), 1.5–1.9 (2H, m), 1.9–2.6 (3H, m), 2.6–2.9 (1H, m), 4.3 (1H, m), 5.3–5.8 (3H, m); cmr ($CDCl_3$), δ 9.3 (q), 16.4 (q), 20.0 (q), 20.2 (t), 33.8 (s), 38.7 (t), 41.0 (d), 41.5 (d), 43.4 (d), 78.5 (d), 120.4 (d), 122.0 (d), 136.8 (s), 137.4 (d), 179.0 (s); ms *m/e* 232 (molecular ion). Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.52; H, 8.85.

HYDROGENATION OF ANTHEMIDIN (**4**) TO TETRAHYDROALANTOLACTONE (**3**).—A solution of 115 mg of **4** in 10 ml of acetic acid was hydrogenated in the presence of 25 mg PtO_2 under 40 psi for 45 min. The catalyst was filtered off; the filtrate was diluted with 10 ml pentane and washed 3 times with water and once with sodium bicarbonate solution. The solvent was evaporated to yield a white solid. Chromatography on Al_2O_3 (5 cm long, 1 cm diameter) using chloroform gave, after recrystallization from chloroform-hexane, 91 mg of white crystals: mp 142–143°; [α]D+8.7° (c 2.4, $CHCl_3$); ir (CCl_4) 1755 cm^{-1}; nmr ($CDCl_3$) no olefinic peaks. A comparison with authentic **3** showed no depression on mmp and superimposable ir.

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[1]Melting points were taken on a Mel Temp. apparatus and are corrected. Uv spectra were obtained on a Cary 14 spectrophotometer. Ir spectra were obtained on a Beckman Beckman Acculab 3. ^1H nmr spectra were recorded on a Varian EM 390 (TMS standard). Cmr spectra were obtained on a Varian XL-100 (25 mHz) spectrometer in FT mode with $CDCl_3$ as internal standard. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter in a 1 dm cell at rt. Ms were obtained on a Varian MAT 112-S spectrometer. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. Tlc was run on pre-coated (0.2 cm) sheets of silica gel 60 F-254 and visualized with uv or anisaldehyde/H_2SO_4 spray. All solvents used for extraction and chromatography were redistilled before use. Voucher samples of the plant material are available in the University of Utah Herbarium.

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