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CONSTITUENTS OF *HELENIUM AMARUM*, IV. DESACETYL-1-EPIISOTENULIN

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In previous communications from our laboratories (1-4), we reported isolation of the sesquiterpene lactones tenulin, heleniamarin, isoheleniamarin, aromaticin, mexicanin I, and amarilin from leaves of *Helenium amarum* (Rafin.) H. Rock (bitterweed). Chromatography of the tenulin mother liquors also yielded, in addition to amarilin, a very small amount (ca. 20 mg) of an unknown compound, mp 101-105° (3). We now describe identification of this substance as the previously unreported desacetyl-1-epiisotenulin (**1a**).

Structure and stereochemistry of the new lactone, $C_{15}H_{20}O_4$ (high resolution mass spectrum), were deduced on the basis of the 270 MHz pmr spectrum in $CDCl_3$ (**1a** in Table 1); extensive spin decoupling and the cd curve, which exhibited a very weak negative maximum at 325 nm ($\theta = -349$); and a positive maximum at 227 m ($\theta = +18900$). The value of $J_{1,10}$ (2.5 Hz) was quite inappropriate for the usual 1αH-helenanolide stereochemistry found, for example in aromaticin and mexicanin I as was the cd curve, with isotenulin (**2b**) and similarly constituted compounds exhibiting a very strongly negative maximum near 320 nm. β-Orientation of the C-10 methyl group as in ambrosanolides could be dismissed because of the plant source and because of the chemical shifts of H-8 and H-7. The resonance of H-8 was upfield and that of H-7 was unusually far upfield from that ordinarily found in cyclopentenones of the helenanolide and ambrosanolide series. However, our observations could be accommodated by a model of **1a** in which H-7 appeared to be in the shielding zone of the 2,3-double bond (but see below). This model also places H-1 and H-9a in a W-relationship, which accounts for the long-range coupling between these protons. The large value of $J_{7,11}$ (12 Hz) shows that the C-11 methyl group is α, as in isotenulin.

TABLE 1. Pmr Spectra (270 MHZ, $CDCl_3$

	1a	**1b**	**3**
H-1	2.76brq	2.80qd	2.74qd
2	7.83dd	7.85dd	7.83dd
3	6.29dd	6.34dd	6.35dd
6	4.00br	5.47br	5.61br
7	1.33brdd	1.35m	1.90brdd
8	4.44ddd	4.17ddd	4.16ddd
9a	2.04tdd	2.04ddbr	1.12brdd
9b	1.38q	1.39q	1.42q
10	2.47m	2.44m	2.37m
11	2.59dq	2.27dq	2.57dq
13	1.12d	1.19d	1.10d
14	1.28d	1.33d	1.32d
15	1.26br	1.13br	1.09br
Ac	—	2.19	2.16

J's (Hz) for **1a,1b**: 1,2=1,3=1,10=2.5; 1,9a=9a,10=6,7=1; 2,3=6; 7,8=10.5; 7,11=8,9b=9a,9b=9b,10=12; 8,9a=4; 10,14=11, 13=7. For **3**: 7,11=9.

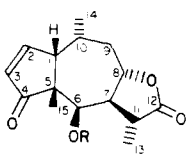
While 1βH-helenanolides have so far not been encountered as natural products,[1] 1-epiisotenulin (**1b**) has been known since 1966, when its synthesis by isomerization of isotenulin (**2b**) *via*

[1]Recent compilations (5,6) list linifolin A as a 1βH-helenanolide. In fact, 1βH-stereochemistry, advanced earlier (7) as a tentative hypothesis for this substance, was refuted in a later publication (8).

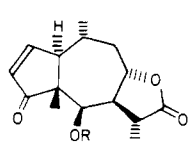
isoheleniamarin was reported (7). Its C-11 epimer Δ^2-anhydrodihydrogaillardilone (**3**) is also known, having been prepared by isomerization of Δ^1-anhydrodihydrogaillardilone (11-epimer of isoheleniamarin) which was in turn obtained from gaillardilin (**4**) in several steps (9). High resolution pmr spectra of **1b** and **3**, which have not been reported previously, are listed in Table 1; it is seen that the coupling constants and chemical shifts of **1a** compare very well with those of **1b**, except for the shift of the proton attached to the acylation site C-6. The shifts of H-7 and the values of $J_{7,11}$ for **1a** and **1b**, on the one hand, and **3**, on the other, differ markedly, as would be expected for substances that are epimeric at C-11. Final confirmation for the deduction that the minor lactone from *H. amarum* was desacetyl-1-epiisotenulin was provided by its acetylation. This gave material whose nmr spectrum was superimposable on that of **1b**.

shift of H-7 in **1a** and **1b**, to which reference was made in an earlier paragraph, cannot be due to shielding by the 2,3-double bond as its saturation produces little change in the frequency of H-7.

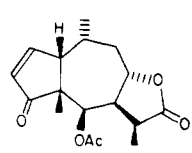
Isolation of the lactones, tenulin, heleniamarin, isoheleniamarin, and **1a** from a single collection of *H. amarum* provides the complete array of lactone types previously obtained in the laboratory by sequential isomerization of tenulin. Whether **1a** is a genuine natural product or an artifact arising from desacetylisotenulin in the process of isola-



1a R=H
1b R=Ac



2a R=H
2b R=Ac



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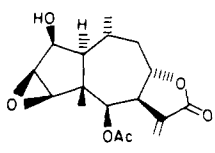

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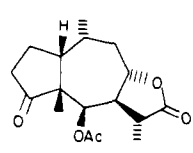

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Cmr spectra of **1a** and **1b** are listed in Table 2 and are compared with the spectrum of 1-epidihydroisotenulin **5**) (7), a comparison which facilitated some of the assignments. Surprisingly, the conversion of **1a** to **1b** produces only small changes in chemical shifts of C-6 and its neighbors. A comparison of the pmr spectrum of **1b** with the spectra of **5** and its C-11 epimer in our files (7,9) also shows that the unusual diamagnetic

TABLE 2. Cmr Spectra (67.89 MHz, $CDCl_3$)[a]

	1a	1b	5
C-1	59.89d	59.76d	52.43d
2	165.02d	164.72d	20.18t
3	133.41d	133.26d	36.45t
4	[b]	210.42	219.12
5	54.91	54.08	54.20
6	72.62d	72.76d[c]	71.95d[c]
7	53.08d	52.23d	52.55d[c]
8	77.32d	77.72d[c]	77.22d[c]
9	36.90t	36.54t	34.91t[c]
10	28.31d	29.17d	27.93d
11	39.24d	39.35d	39.41d
12	178.06	177.19	177.36
13	23.58q	23.60q	23.35q
14	22.98q	22.83q[c]	26.04q
15	12.07q	11.83q	12.00q
1′	—	170.20	170.23
2′	—	20.59q	20.58q

[a]Unmarked signals are singlets.
[b]Not detected.
[c]Assignments established by selective decoupling.

tion and purification *via* the Δ^1-isomer of desacetylisoheleniamarin is not known.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.— Pmr spectra were recorded in $CDCl_3$ at 270 MHz and cmr spectra at 67.89 MHz on a Bruker HX-270 spectrometer with TMS as internal standard. Low resolution mass spectra were determined on a Finnigan 3200 mass spectrometer at 70 eV, high resolution mass spectra on an AEI MS-902 instrument. Ir spectra were determined on a Beckman IR-33 recording spectrophotometer in KBr pellets.

The isolation of lactone **1a** has been described previously (3); ir 3510 (non-bonded-OH), 3350 (broad, bonded-OH), 1770 (γ-lactone), 1690 and 1595 cm^{-1} (cyclopentenone); cd curve (MeOH, c 0.45mg/5ml) $[\theta]_{235}$-349 (neg. max), $[\theta]_{227}$ +18900 (max); ms *m/z* (%) 264 (M^+, 6.5), 249 (5.4), 231 (3.7), 218 (2.8), 203 (4.0), 191 (3.8), 190 (4.2), 177 (2.5), 176 (2.0), 175 (5.9), 166 (3.8), 163 (5.9), 162 (3.2), 161 (3.6), 159 (2.1), 151 (37.3), 149 (7.4), 148 (5.5), 147 (5.3), 145 (3.0), 137 (15.4), 135 (8.2), 133 (7.2), 124 (100), 123 (98). Calcd for $C_{15}H_{20}O_4$: mol wt 264.1361. Found: mol wt (ms), 264.1365. Acetylation of **1a** recovered from the pmr spectrum (approx. 9 mg) with Ac_2O-pyridine in the customary fashion followed by the usual work-up but without chromatographic purification gave material whose pmr spectrum indicated the absence of impurities and was superimposable on the nmr spectrum of authentic **1b** (7). Lactones **3** and **5** were also available from earlier work (7,9).

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LITERATURE CITED

1. W. Herz and R.P. Sharma, *J. Organ. Chem.*, **40**, 2557 (1975) and references cited therein.
2. T. Ottersen, U. Sorensen, M. ElSohly, and C.E. Turner, *Acta Chem. Scand.*, **B32**, 79 (1978).
3. M. ElSohly, J.C. Craig, C.E. Turner, and A.S. Sharma, *J. Nat. Prod.*, **42**, 450 (1979).
4. M. ElSohly, A.S. Sharma, and C.E. Turner, *J. Nat. Prod.*, **44**, 618 (1981).
5. N.H. Fischer, E.J. Olivier, and H.D. Fischer, *Progr. Chem. Organ. Nat. Prod.* (W. Herz, H. Grisebach, and G.W. Kirby, eds.), **38**, 47 (1979).
6. F.C. Seaman, *Botan. Rev.*, **48**, 123 (1982).
7. W. Herz, M.V. Lakshmikantham, and R.N. Mirrington, *Tetrahedron*, **22**, 1709 (1966).
8. W. Herz, C.M. Gast, and P.S. Subramaniam, *J. Organ. Chem.*, **33**, 2780 (1968).
9. W. Herz, S. Rajappa, M.V. Lakshmikantham, and J.J. Schmid, *Tetrahedron*, **22**, 693 (1966); see also reference 7, footnote 12.

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