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NATURAL PRODUCTS FROM ACHILLEA LANULOSA

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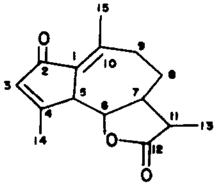
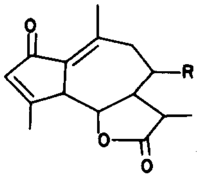
The wild flower *Achillea lanulosa* is found on waste land throughout the eastern part of the United States along with a closely related species, *Achillea millefolium*. The Achillea (referred to colloquially as Yarrow) have had a long history of use in folk medicine dating back, reputedly, to the use of the plant by Achilles.[1] *A. millefolium* has been extensively investigated and a large number of compounds have been isolated from the plant;[2] the active principles have not, however, been determined to date. *A. lanulosa*, on the other hand, has not been investigated previously and we chose to work with this species.[3] We have examined, in particular, one



Ia,b

a = Achillin series
b = Matricarin series



II a,b (R=OH)
III a,b (R=OAc)
IV a,b ($R=OSO_2C_6H_4NO_2$)
V a,b (R=I)

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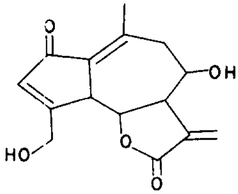
1. "Gray's Manual of Botany", 8th Ed., ed. M.L. Fernald, Amer. Book Co., New York, 1950, p. 1515.

2. R.E. Kremers, *J. Am. Pharm. Assoc.* **14**, 399 (1925); R.L. McMurray, *Am. J. Pharm.* **105**, 573 (1933); M. Pailer and W.G. Kump, *Arch. Pharm.* 646, (1960); J. Hochmanová, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.* **26**, 1826 (1961).

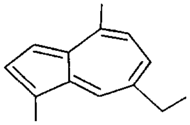
3. A. lanulosa is indistinguishable morphologically from A. millefolium, and consequently the identification of our plant material as A. lanulosa was achieved through a determination of the chromosome number (E.B. Ehrle, Rhodora, **60**, 7 (1958). We thank Dr. T. Merz for this measurement

of the subspecies of A. Lanulosa[4] and have isolated from it four sesquiterpene lactones, Ia, IIa, IIb, and IIIb; compounds IIIb and IIb were shown to be matricarin and desacetylmatricarin, respectively, and compounds Ia and IIa were shown to be new sesquiterpene lactones of the guaianolide type.

Compound Ia, m.p. 144-145°, $[\alpha]_D^{24}$ + 160° (C 1.20 in $CHCl_3$), to which we assign the name achillin, analyzed for $C_{15}H_{18}O_3$.[5] The absorption spectra (IR in CCl_4, UV in 95% EtOH) indicated the presence of a γ-lactone (5.57μ), two double bonds (6.05 and 6.16μ), and a cross-conjugated cyclopentadienone system (5.92μ; 255mμ, log ε 4.22); these values are practically identical to those reported for matricarin (IIIb)[6] and for lactucin (VI)[7], the two compounds of known structure most closely related to achillin. The gross structure of achillin was determined by its conversion into chamazulene (VII)[8] - by hydrogenation over platinum followed by dehydrogenation with selenium.



VI



VII

The presence of the double bonds was confirmed by hydrogenation to dihydroachillin (VIII) $C_{15}H_{20}O_3$, m.p. 173-174°, $[\alpha]_D^{24}$ + 265° (C 1.25 in $CHCl_3$), λ_{max}^{MeOH} 229mμ (log ε 4.18), λ_{max}^{CCl4} 5.60μ, 5.90μ 6.17μ, NMR, singlet at 3.78τ (H at C-3)

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[4] Part of the early work on locating and identifying the subspecies was carried out by Mr. Patrick Sullivan (deceased). The subspecies chosen was identified in particular by the strong absorption of its extracts in the infrared at 5.9μ.

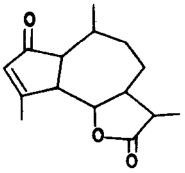
[5] Satisfactory analyses were obtained for the compounds listed in this report.

[6] (a) Z. Čekan, V. Procházka, V. Herout and F. Šorm, Collection Czech. Chem. Commun. 24, 1554 (1959). (b) W. Herz and K. Ueda, J. Am. Chem. Soc. 83, 1139 (1961).

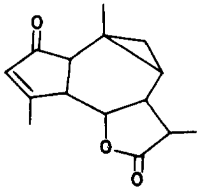
[7] D.H.R. Barton and C.R. Narayanan, J. Chem. Soc., 963 (1958); L. Dolejs, M. Souček, M. Horák, V. Herout and F. Šorm, Collection Czech. Chem. Commun. 23, 2195 (1958).

[8] A. Meisels and A. Weizmann, J. Am. Chem. Soc. 75, 3865 (1953); F. Sorm, J. Novak and V. Herout, Collection Czech. Chem. Commun. 18, 527 (1953).

and then to tetrahydroachillin ($C_{15}H_{22}O_3$), m.p. 146-147°, $[\alpha]_D^{23}$ + 92° (C 0.77 in $CHCl_3$), λ_{max}^{CCl4} 5.61 and 5.76μ. Treatment of VIII with base yielded the salt of a conjugated dieneone carboxylic acid (λ_{max}^{MeOH} 285mμ, log ε 4.18); this elimination reaction locates the lactone ether oxygen at C-6. The structure of achillin (Ia) was further confirmed by the NMR spectrum which showed a singlet at 3.84τ (H at 3), an unsymmetrical triplet at 6.16τ (H at 6, J = 9cps), a doublet at 6.60τ (H at 5, J = 10cps), a singlet at 7.57τ (H at 15), a singlet at 7.70τ (H at 14) and doublet at 8.87τ (H at 13, J = 8cps), all with the correct weighting, and by the cracking pattern in the mass spectrum.



VIII



IX

Compound IIb ($C_{15}H_{18}O_4 \cdot H_2O$), m.p. 130-132° (resolidifies and melts at 154°, the melting point of the anhydrous form), $[\alpha]_D^{23}$ + 9.7° (C 1.59 in CH_3OH), λ_{max} similar to the values given for achillin, on acetylation yielded compound IIIb which proved to be matricarin, a compound isolated recently from _Matricaria chamomila_[6a] and also from _Artemisia tilesii_[6b] and assigned structure IIIb.

Compound IIa ($C_{15}H_{18}O_4$), m.p. 161-162°, $[\alpha]_D^{22}$ + 110°, (C 1.59 in CH_3OH), λ_{max} similar to the values listed for achillin, on acetylation yielded the acetate IIIa ($C_{17}H_{20}O_5$) m.p. 193-194°, $[\alpha]_D^{22}$ + 116° (C 1.58 in $CHCl_3$) (also present in the extracts of _A. lanulosa_), which differed from matricarin (IIIb) and also from artilesin, an isomeric compound obtained from _Artemisia tilesii_.[6b]

Efforts were next directed to the correlation of the oxygenated compounds (II and III) and achillin (Ia). The oxygen function at C-8 was removed from compound IIa by the following reaction sequence:

$$\text{IIa} \longrightarrow \text{IVa} \longrightarrow \text{Va} \xrightarrow{Zn} \text{Ia}$$

The product proved to be achillin, and IIa is thus 8-hydroxyachillin.

The oxygen function was removed similarly from desacetylmatricarin (IIb), to yield Ib ($C_{15}H_{18}O_3$), m.p. 202-203°, $[\alpha]_D^{24}$ + 58° (C 1.31 in $CHCl_3$), λ_{max}

almost identical to the values given for achillin, which proved to be identical to leukodin, a compound isolated recently from Artemisia leukodia.[9] Leukodin is therefore desacetoxymatricarin. A by-product of the zinc reduction proved to be the cyclopropane derivative IX ($C_{15}H_{18}O_3$), m.p. 158-159°, λ_{max}^{MeOH}, 228mμ (log ε 4.10), $\lambda_{max}^{CCl_4}$ 5.59 and 5.88μ, NMR, singlet at 8.91 τ(H at C-15)[10]

This work establishes an achillin series of compounds (Ia, IIa, ...) and a matricarin series (Ib, IIb, ...) differing only in stereochemistry,[11] and further, it confirms the close botanic relationship of the Achillea, Artemisia, and Matricaria genera.

We thank Professor W. Herz for help in comparing our samples of matricarin, and Dr. V. Herout for samples of chamazulene and leukodin. We further thank the National Institutes of Health for its support of this work.

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[9] Private communication from Dr. V. Herout (Prague) who informs us that Mrs. Rybalko (Vilar, Moscow) has also isolated this compound.

[10] A similar reaction leading to a cyclopropane derivative has been reported by O. Gnoj, E.P. Oliveto, C.H. Robinson, and D.H.R. Barton, Proc. Chem. Soc. 207 (1961).

[11] It is of some interest that members of the matricarin series have a bitter taste whereas those of the achillin series are tasteless.