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# THE STRUCTURES OF EVONIMINE AND EUONINE, TWO MINOR ALKALOIDS OBTAINED FROM EUONYMUS SIEBOLDIANA BLUME.

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Previously we reported the isolation and structural elucidation of four alkaloids including the principal alkaloid evonine 1 from the seeds of Euonymus Sieblodiana Blume (Japanese name, Mayumi).[1,2,3,4] In further scrutiny of the alkaloidal components of the same source, we have obtained two new alkaloids, evonimine 3 and euonine 4. The physical and spectral properties of both alkaloids are summarized in Table 1.

Table 1.

| | mp | molecular formula[5] | $[\alpha]_D^{CHCl_3}$ | UV (EtOH) nm (ε) | IR ($CHCl_3$) $cm^{-1}$ | $M^+$ |
|---|---|---|---|---|---|---|
| evonimine | amorphous | $C_{36}H_{43}O_{17}N$ | + 21° (c 1.5) | 229<br>269 | 3460<br>1755-1725<br>1588, 1570 | 761 |
| euonine | 149-153° | $C_{38}H_{47}O_{18}N$ | - 2.5° (c 6.4) | 230 (7600)<br>270 (3300) | 3440<br>1750-1730<br>1588, 1572 | 805 |

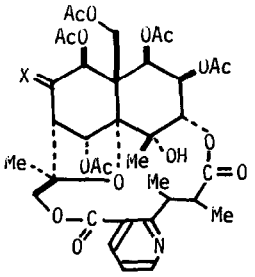
Structure of evonimine 3. Evonimine 3 possesses the same molecular formula as that of evonine 1.[1,2,4] Partial methanolysis [NaOMe (0.3 molar equiv) - MeOH, 20°] of evonimine afforded pentadesacetyl evonimine 5[5] [mp 184° (dec), $C_{26}H_{33}O_{12}N$] and pentadesacetyl evonimine methyl ester 8[6] (amorphous); on acetylation[7] the former regenerated 3. The presence of five acetate groups in 3 was also indicated by the NMR spectrum [δ 1.93, 2.05, 2.12, 2.16, 2.21 (3H each)]. Extensive methanolysis [NaOMe (5.5 molar equiv) - MeOH, 20°] of evonimine yielded a dimethyl ester 20[5] [liquid, $C_{12}H_{15}O_4N$, 251 ($M^+$)], which on hydrolysis (10% KOH - $H_2O$, 20°) gave wilfordic acid 19[5,8,9,10] [mp 194-196° (lit.[9] 195-196°), $C_{11}H_{13}O_4N$]. Evonimine was thus shown to be a $C_{15}$-polyhydroxy compound esterified with wilfordic acid 19 and five moles of acetic acid. This $C_{15}$-component of evonimine was expected to be identical with the sesquiterpene part [evoninol 7[11] ($C_{15}H_{24}O_{10}$)] of evonine 1 by the NMR spectral comparison of 1 and 3. This inference was confirmed by obtaining a common derivative, evoninol hexaacetate 11 from both

Table 2. NMR Spectral Data (δ in ppm, 60 MHz)

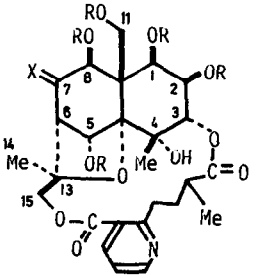
| | H-1 | H-2 | H-3 | H-5 | H-6 | H-8 | H-11 | H-15 |
|---|---|---|---|---|---|---|---|---|
| 1 [a,d] | 5.71<br>d 3.2 | 5.29<br>dd 3.2, 3.2 | 4.78<br>d 3.2 | 6.72<br>d 1.0 | 3.04<br>d 1.0 | 5.57<br>s | 4.58, 4.82<br>AB q 13.0 | 3.78, 6.00<br>AB q 13.0 |
| 3 [b] | 5.73<br>d 3.0 | 5.10<br>dd 3.0, 3.0 | 4.97<br>d 3.0 | 6.71<br>d 1.0 | 3.05<br>d 1.0 | 5.55<br>s | 4.50, 4.86<br>AB q 12.0 | 3.82, 5.81<br>AB q 11.0 |
| 5 [b] | 4.35<br>d 3.0 | 3.70<br>dd 3.0, 3.0 | 5.00<br>d 3.0 | 5.61<br>d 1.0 | 3.00<br>d 1.0 | 4.53<br>s | 4.20<br>br.s | 3.92, 5.90<br>AB q 11.0 |
| 8 [b] | 4.42<br>d 3.0 | ca. 3.9<br>m | 4.88<br>d 3.0 | 5.55<br>d ~1 | 3.00<br>d ~1 | 4.56<br>s | 4.18<br>br.s | 3.12, *<br>AB q 11.0 |
| 9 [b] | 5.60<br>d 3.0 | 5.19<br>dd 3.0, 3.0 | 4.59<br>d 3.0 | 6.45<br>br.s | 3.15<br>br.s | 5.50<br>s | 4.68<br>br.s | 4.23, 4.79<br>AB q 13.0 |
| 9 [a] | 5.70<br>d 3.0 | 5.32<br>dd 3.0, 3.0 | 4.82<br>d 3.0 | 6.60<br>br.s | 3.10<br>br.s | 5.58<br>s | 4.45<br>br.s | 4.42, 4.88<br>AB q 13.0 |
| 11 [a] | 5.83<br>d 3.2 | 5.43<br>dd 3.2, 3.2 | 3.67<br>d 3.2 | 6.58<br>br.s | 3.10<br>br.s | 5.60<br>s | 4.50<br>s | 4.42, 4.90<br>AB q 12.0 |
| 4 [c,e] | 5.64<br>d 3.2 | 5.15<br>dd 3.2, 3.0 | 4.93<br>d 3.0 | 6.90<br>br.s | 2.62<br>br.d 3.0 | 5.20<br>d 6.7 | 4.43, 5.42<br>AB q 13.0 | 4.10, 5.77<br>AB q 12.0 |
| 6 [c,f] | * | * | 4.97<br>d 3.0 | 5.26<br>br.s | 2.40<br>br.d 3.0 | * | * | 3.92, 5.80<br>AB q 12.0 |
| 17 [c,f] | * | * | 4.85<br>d 3.0 | 5.15<br>br.s | * | * | * | * |

a) $CDCl_3$. b) $CD_3OD$. c) $CD_3COCD_3$. d) Taken at 100 MHz.
e) The signal of H-7 was observed at δ 5.48 (dd, J = 3.0, 6.7 Hz).
f) The signal of H-7 appeared in the region of δ 3.0 - 4.5.
* This signal appeared in the region of δ 3.0 - 4.5.

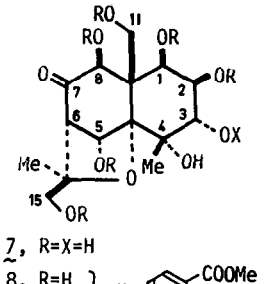
1 and 3 (vide post) and by the following result; reduction of evonimine with $LiAlH_4$ in ether - THF followed by acetylation[7] gave, in addition to a diol 21[5] [liquid, $C_{11}H_{17}O_2$, 195 ($M^+$)], euonyminol octaacetate 14[1,3] and the isomer 16[1,3] (ratio 1:2), which were obtained in the same ratio from evonine 1 by the same sequence of reactions.[1,3] The positions of the ester linkages due to acetic acid (five moles) in 3 were disclosed by comparison of the NMR spectra of 3 and its pentadesacetyl derivative 5 (Table 2); five acetate groups were found to be located at C-1, C-2, C-5, C-8, and C-11. Since the tertiary hydroxyl group at C-4 of evonimine was not involved in the ester formation,[12] a large ring bis-lactone must be formed between wilfordic acid 19 and the two hydroxyls at C-3 and C-15 of evoninol nucleus 7. The sequence of the following reactions coupled with the NMR spectral findings provided the rigorous proof that the aliphatic carboxyl group of wilfordic acid 19 was connected with the hydroxyl group at C-3 of 7. Comparison of the NMR spectra of 5 and 8 clearly indicated that one of the two ester linkages due to wilfordic acid 19 was attached at C-15 (Table 2). On acetylation[7] the methyl ester 8 afforded the hexaacetate 9[5] [mp 113-116°, $C_{39}H_{49}O_{19}N$, 835 ($M^+$); as to the sites of acetylation, cf. Table 2]. Catalytic hydrogenation ($PtO_2$/AcOH) of 9 afforded the piperidine derivative 10, which, on intramolecular aminolysis effected by heating in dioxane was cleaved into the δ-lactam methyl ester 22[5] [two stereoisomers,[13] 225 ($M^+$): 22a, mp 88.5-90°; 22b, oil] and



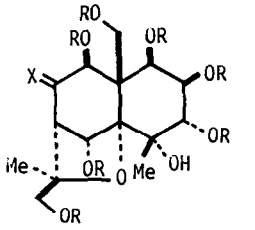
1, X=O (evonine)
2, X= (euonymine)



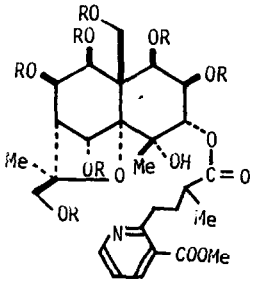
3, R=Ac, X=O (evonimine)
4, R=Ac, X= (euonine)
5, R=H, X=O
6, R=H, X=



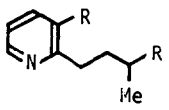
7, R=X=H
8, R=H } , X=
9, R=Ac }
10, R=Ac, X=
11, R=Ac, X=H
12, R=H } , X=
13, R=Ac }



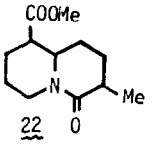
14, R=Ac, X=
15, R=H, X=
16, R=Ac, X=



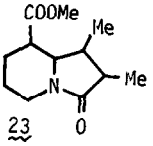
17, R=H
18, R=Ac



19, R=COOH
20, R=COOMe
21, R=$CH_2OH$



22 0



23 0

evoninol hexaacetate 11[5] [amorphous, $C_{27}H_{36}O_{16}$, 616 ($M^+$)] identical in all respcts (IR, NMR, mass, tlc) with the specimen prepared from evonine 1 as follows: acetylation of a derivative 12[2] of evonine 1 afforded the hexaacetate 13[5] [amorphous, $C_{39}H_{49}O_{19}N$, 835 ($M^+$)], which on catalytic hydrogenation ($PtO_2$/AcOH) yielded evoninol hexaacetate 11 and the γ-lactam methyl ester 23[5] [three oily stereoisomers,[13] 225 ($M^+$)]. The NMR spectral change of H-3 in the reactions, 9 → 10 → 11 + 22, (δ 4.82 in 9 and 3.67 in 11; see Table 2) and the formation of the δ-lactam methyl esters (22a, 22b) clearly established that the aliphatic carboxyl group of wilfordic acid 19 was connected to the hydroxyl at C-3 of evoninol nucleus 7.[14] Thus the structure of evonimine was determined and is represented by 3.

Structure of euonine 4. Euonine 4 and euonymine 2[3] possess the same molecular formula. Extensive methanolysis [NaOMe (20 molar equiv) - MeOH, 20°] of euonine followed by acetylation[7] afforded euonyminol octaacetate 14[1,3] and dimethyl wilfordate 20. Partial methanolysis [NaOMe (0.3 molar equiv) - MeOH, 20°] of euonine gave hexadesacetyl euonine 6[5] (mp 237-239°,

$C_{26}H_{35}O_{12}N$) and hexadesacetyl euonine methyl ester 17[5] [amorphous, $C_{27}H_{39}O_{13}N$, 585 ($M^+$)]; the former on acetylation[7] was converted to euonine 4 and the latter 17 to the heptaacetate 18[5] [amorphous, $C_{41}H_{53}O_{20}N$, 879 ($M^+$)]. From these results of methanolysis, euonine was shown to be euonyminol 15[3] esterified with wilfordic acid 19 and six moles of acetic acid. Comparison of the NMR spectra of euonine and its hexadesacetyl derivative 6 revealed the positions of six acetate groups to be at C-1, C-2, C-5, C-7, C-8, and C-11, and the location[15] of wilfordic acid 19 to be at C-3 and C-15 (Table 2). Further it was shown that the aromatic carboxyl group of wilfordic acid 19 formed the ester linkage with the hydroxyl at C-15; the signal due to H-15 showed the up-field shift in 17 in comparison with the one in 6 (Table 2), and the signal due to the methyl ester of 17 appeared at δ 3.93, indicating the presence of the aromatic methyl ester in 17.[16] Based on these findings the structure of euonine is represented by 4.[17]

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## REFERENCES AND FOOTNOTES

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3) K. Sugiura, Y. Shizuri, H. Wada, K. Yamada, and Y. Hirata, Tetrahedron Lett., 2733 (1971).
4) H. Wada, Y. Shizuri, K. Sugiura, K. Yamada, and Y. Hirata, Tetrahedron Lett., 3131 (1971).
5) Elemental analysis and/or high resolution mass spectral data on the molecular ion for this compound are in accord with theory.
6) The molecular formula ($C_{27}H_{37}O_{13}N$) of this amorphous compound lacking the $M^+$ peak in the mass spectrum was deduced by the NMR spectral analysis and by conversion to crystalline 9.
7) By acetic anhydride and pyridine at 60° overnight.
8) M. Beroza, J. Amer. Chem. Soc., 75, 44 (1953).
9) M. Beroza, J. Org. Chem., 28, 3562 (1963).
10) Identified by the NMR spectral comparison.
11) Although the $C_{15}$-octahydroxy nucleus of evonine 1 itself was not obtained so far, the trivial name "evoninol" was given to this highly oxygenated sesquiterpene.
12) There was observed a long range coupling between the tertiary hydroxyl and the methyl group both attached at C-4; on addition of deuterium oxide the doublet (J = 1 Hz) due to the methyl protons at C-4 became a singlet in the NMR spectrum of evonimine 3.
13) The planar structure of each compound was established by spectral (IR, NMR, mass) data.
14) This chemical method of determining unambiguously the positions of the ester linkages of wilfordic acid 19 is a much simpler one than that employed previously,[2] and is particularly useful in the structure elucidation of this type of alkaloids obtained in a small amount.
15) The long range coupling was observed between the tertiary hydroxyl and the methyl group both attached at C-4 in the NMR spectrum of euonine 4, as in the case of evonimine 3 (cf. ref. 12).
16) Dimethyl wilfordate 20 showed two singlets due to aromatic and aliphatic methyl esters at δ 3.90 and 3.62, respectively. The methyl signal of methyl nicotinate was also observed at δ 3.93 (The spectra were taken in acetone-$d_6$ at 60 MHz).
17) For direct correlation of evonimine 3 and euonine 4, reduction of 3 with $NaBH_4$ - DMF (or THF) followed by acetylation was carried out, but the C-7 epimer of 4 was the sole product.