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ISOLATION OF THREE NEW ALKALOIDS FROM EUONYMUS SIEBOLDIANA BLUME AND THEIR STRUCTURES

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We have recently established the structure of evonine, the principal alkaloid of *Euonymus Sieboldiana* Blume (Japanese name, Mayumi).[1,2] Three new alkaloids were further obtained from the same source.

Isolation of alkaloids. From the hexane extract of dried fruits of the plant, resinous basic material was obtained by the procedure reported,[3] which was taken up in EtOH. After evonine crystallized out, the residue from the mother liquor was repeatedly chromatographed on silicic acid with $CHCl_3$ and $CHCl_3$-MeOH (10:1), affording, in addition to evonine, three new alkaloids, neo-evonine **2**, euonymine **3**, and neo-euonymine **4**.[4]

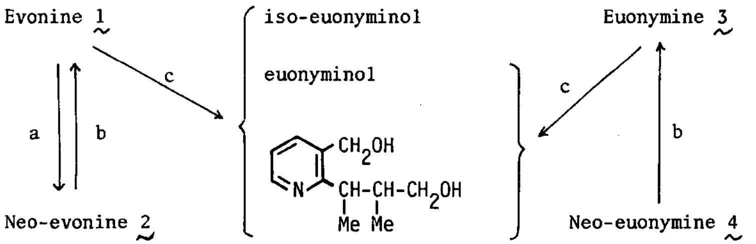
Table 1

	evonine **1**	neo-evonine **2**	euonymine **3**	neo-euonymine **4**
mp	184-190° (EtOH)	264-265° (EtOH)	picrate 140-146° (benzene)	259-262° (MeOH)
Molecular formula[a)]	$C_{36}H_{43}NO_{17}$	$C_{34}H_{41}NO_{16}$	$C_{38}H_{47}NO_{18}$	$C_{36}H_{45}NO_{17}$
$[\alpha]_D^{CHCl_3}$	+8.4° (c 1.50)	+24.9° (c 1.27)	-20° (c 0.32)	-11° (c 0.49)
λ_{max}^{EtOH}, nm (ε)	227 (6200) 267 (3200)	224 (5500) 265 (3200)	230 266	228 (4800) 266 (3500)
$\nu_{max}^{CHCl_3}$, cm^{-1}	3500 1755 (broad) 1725 1585, 1565	3400 1760 (broad) 1720 1585, 1565	3550 1750-1730 1585, 1565	3440 1755 (broad) 1725 (shoulder) 1585, 1565
M^+	761	719	805	763
Number of AcO group[b)]	5	4	6	5

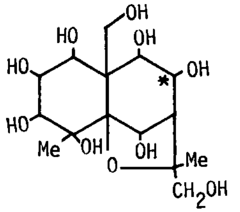
a) Established by mass spectral and elemental analyses
b) Determined by NMR spectral analysis ($CDCl_3$; 100 MHz and 60 MHz).

Relation of evonine and three new alkaloids. Physical and spectral data of the three alkaloids together with those of evonine are listed in Table 1, which suggest that they are closely related to evonine 1. Evonine and the three alkaloids were correlated and the result is illustrated in Chart. The structures of the three products (cf. Chart) obtained by $LiAlH_4$ reduction of evonine were already established.[1,2,3]

Chart



[a: NaOMe-MeOH, -5°; b: Ac_2O-pyridine, 60°; c: $LiAlH_4$/ether-THF]



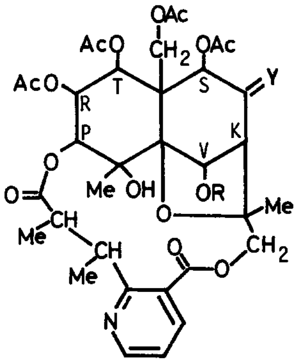
euonyminol, iso-euonyminol (diastereoisomers at a starred carbon)

Structure of neo-evonine 2. Neo-evonine 2 was proved to be a desacetyl derivative of evonine 1 (cf. Chart). Comparison of the NMR spectra of 1 and 2 made it possible to determine the positions of four acetate groups in 2; whereas chemical shifts of protons on carbons carrying the primary hydroxyl (H_M, H_Q) and the three secondary hydroxyls (H_R, H_S, H_T) were essentially same in both 1 and 2, the signal H_V which appeared at δ 6.72 in 1 was observed at 5.41 in 2 (Table 2). The structure of neo-evonine was therefore established as 2. Oxidation of neo-evonine 2 with CrO_3-pyridine gave neo-evoninone [mp 308°; $C_{34}H_{39}NO_{16}$; IR ($CHCl_3$) 1780, 1740 cm^{-1}; mass 717 (M^+)].

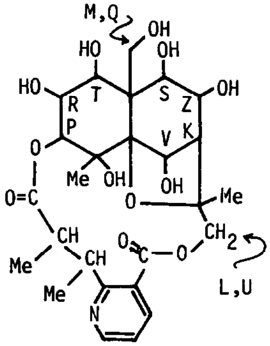
Structures of euonymine 3 and neo-euonymine 4. On reduction with $LiAlH_4$ in ether-THF euonymine 3 afforded euonyminol[2,3] and the diol[1] derived from evoninic acid. Considering the molecular formula and the presence of six acetate groups in euonymine, it is deduced that a keto group of the C_{15}-part of evonine 1 exists as a secondary hydroxyl, which is acetylated, in euonymine. This inference was confirmed by the NMR spectra of evonine and euonymine. In addition to the signals corresponding to those of evonine 1, signals of an ABX type (H_S, H_Z, and H_K at 5.34, 5.51, and 2.33 respectively) were observed in euonymine (see Table 2). Methanolysis (MeONa-MeOH, 30-35°, 6 hr) of euonymine afforded two products, hexadesacetyl euonymine 3a [mp 257-261°; $C_{26}H_{35}NO_{12}$; mass 553 (M^+)] and hexadesacetyl euonymine methyl ester

3b [amorphous powder; $C_{27}H_{39}NO_{13}$; mass 567 (M^{+}-18)]. Based on the NMR spectra of euonymine **3** and the hexadesacetyl derivative **3a**, the positions of six acetate groups in the sesquiterpene part were determined (Table 2): whereas signals due to protons (H_M, H_Q and H_R, H_T, H_S, H_Z, H_V) carrying one primary hydroxyl and five secondary hydroxyls shifted to a higher field region by the methanolysis of **3**, essentially no change in the chemical shifts was observed regarding protons, H_P, H_L, H_U of **3** and **3a**. This finding also indicated the location of evoninic acid residue in the sesquiterpene part: evoninic acid is connected through two ester linkages to a secondary hydroxyl (H_P) and a primary one (H_L, H_U). Of the two ester linkages between evoninic acid and the sesquiterpene moiety, the ester involved in methanolysis leading to **3b** was shown to be the one formed between the aromatic carboxyl group and the primary hydroxyl (H_L, H_U): while no significant shift of the signal due to H_P was observed in the NMR spectra of **3a** and **3b**, the signal due to a proton (H_U) of primary hydroxyl showed a up-field shift in **3b** in comparison with the one in **3a**; and the signal due to the methyl ester of **3b** appeared at δ 3.99 (acetone-d_6), indicating the presence of the aromatic methyl ester in **3b**.[5] From these findings the structure of euonymine is represented by **3**.[6]

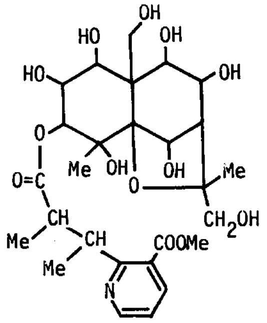
Neo-euonymine **4** was a desacetyl derivative of euonymine **3** (cf. Chart). Since the signal corresponding to H_V (δ 7.02) of **3** was absent around the δ 6 - 7 region in the NMR spectrum of neo-euonymine, the structure **4** was assigned to this alkaloid.



1: evonine R=Ac, Y=O
2: neo-evonine R=H, Y=O
3: euonymine R=Ac, Y=H,OAc
4: neo-euonymine R=H, Y=H,OAc



3a



3b

Table 2. NMR Spectral Data[a)]

	H_K	H_M, H_Q	H_P	H_R	H_S	H_T	H_V	H_Z	H_U
1	3.04 (d 1.0)	4.58, 4.82 (AB q 13.0)	4.78 (d 3.2)	5.29 (t 3.2)	5.57 (s)	5.71 (d 3.2)	6.72 (d 1.0)		6.04 (br.d 12)
2	3.20 (d 1.5)	4.47, 4.92 (AB q 13.0)	4.82 (d 3.2)	5.34 (t 3.2)	5.59 (s)	5.72 (d 3.2)	5.41 (d 1.5)		6.10 (br.d 12)
3[b)]	2.33 (dd 3.8, 1.0)	4.50, 5.13 (AB q 13.5)	4.72 (d 2.5)	5.23 (dd 4.0, 2.5)	5.34 (d 6.2)	5.55 (d 4.0)	7.02 (d 1.0)	5.51 (dd 6.2, 3.8)	5.94 (br.d 12)
3a[c)]		*	4.81 (d 3.0)	*	*	*	5.41 (d ~ 1)	*	6.00 (br.d 12)
3b[c)]		*	4.73 (d 3.0)	*	*	*	5.20 (d ~ 1)	*	*

a) The spectra were taken in $CDCl_3$ (**1**, **2**, **3**) and acetone-d_6 (**3a**, **3b**) at 100 MHz (**1**, **3**) and 60 MHz (**2**, **3a**, **3b**). Multiplicities and coupling constants are given in parentheses.

b) All the couplings were confirmed by the double resonance experiment.

c) Since it was shown that the differences in chemical shifts caused by using two solvents were small (less than 0.1 ppm), comparison of chemical shifts in different solvents was made.

* Signals due to these protons appeared in the region of δ 3.5 - 4.5 as a complex pattern.

REFERENCES AND FOOTNOTES

1) M. Pailer and R. Libiseller, Monatsh. Chem., **93**, 405, 511 (1962).

2) H. Wada, Y. Shizuri, K. Yamada, and Y. Hirata, Tetrahedron Letters, this issue.

3) Y. Shizuri, H. Wada, K. Sugiura, K. Yamada, and Y. Hirata, Tetrahedron Letters, this issue.

4) Molecular formulas of new compounds were obtained by elemental analyses and/or high resolution mass spectrometry.

5) Distinction of two monomethyl esters of evoninic acid can be made as follows:
dimethyl evoninate showed two singlets due to an aromatic methyl ester and an aliphatic methyl ester at δ 3.92, and 3.39, respectively (acetone-d_6, 60 MHz).
The methyl signal of methyl nicotinate was also observed at δ 3.93 (acetone-d_6, 60 MHz).

6) Attempts were made to correlate euonymine **3** to evonine **1** more directly: e.g., reduction of evonine with $NaBH_4$-EtOH, followed by acetylation with Ac_2O-pyridine afforded almost exclusively a diastereoisomer of euonymine, and euonymine could not be obtained so far.