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EVONINE, AN ALKALOID OBTAINED FROM EUONYMUS SIEBOLDIANA BLUME. I.
RELATIONSHIP OF FUNCTIONAL GROUPS AND PARTIAL STRUCTURE

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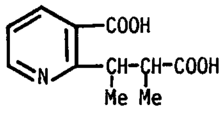
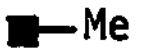
In 1962 Pailer and Libiseller reported the isolation of an ester alkaloid, evonine $C_{36}H_{43-45}NO_{17}$ from Evonymus europaea L.[1,2] The alkaloid was shown to contain seven ester linkages: five acetate groups and two others due to a dicarboxylic acid, evoninic acid, whose structure was elucidated as (I).[1] Recently the structure of maytoline, a nicotinoyl sesquiterpene alkaloid obtained from Maytenus ovatus Loes. was determined by X-ray crystallography and the close relationship between maytoline and complex alkaloids in the Celastraceae family was suggested.[3]

We have isolated several alkaloids from Euonymus Sieboldiana Blume (Japanese name, Mayumi), among which the pricipal alkaloid was found to be evonine:[4] mp 184-190° (EtOH); $C_{36}H_{43}NO_{17}$; $[\alpha]_D^{CHCl_3}$ +8.4° (c 1.5); UV(EtOH) 227 (ε 6200), 267 nm (ε 3200); IR($CHCl_3$) 3500(OH), 1755(broad), 1725(shoulder), 1585, 1565 cm^{-1}; NMR (see Figure); mass 761 (M^+).

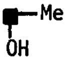
Extensive studies have been carried out on the structure of the polyhydroxy component ($C_{15}H_{24}O_{10}$) of evonine, which was regarded as a highly oxygenated sesquiterpene. From the NMR spectrum of evonine **1** the presence of the following groups (A, B, C, D) is evident: two tertiary methyls (H_C and H_D in Fig.); five acetate methyls (H_E, H_F, H_G, H_H, H_I); an acetoxymethyl (H_M, H_Q; cf. the signals of **4** and **5** in Table); one hydroxyl (H_N, disappeared on addition of D_2O) which was shown to be attached to carbon bearing the tertiary methyl by the double resonace (NMDR) experiment. Further the presence of a 1,2,3-triol grouping as in (D) was indicated by NMDR experiment. Methanolysis of **1** with NaOMe-MeOH (5°, 5 hr, under nitrogen) afforded pentadesacetylevonine **2**[5] [mp 257°(dec.); $C_{26}H_{33}NO_{12}$; mass 551 (M^+); IO_4^- consumption, 2 molar equiv.], which lacked signals due to five acetate groups in the NMR spectrum. The derivative **2** formed an acetonide **4** [mp 194-197°; $C_{29}H_{37}NO_{12}$; mass 591 (M^+); IO_4^- consumption, 1 molar equiv.] on treatment with 2,2-dimethoxypropane - p-TsOH in DMF. From the NMR spectra of evonine **1** and **4** (cf. Table)



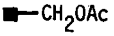
(I)



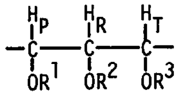
(A)



(B)

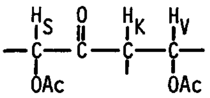


(C)



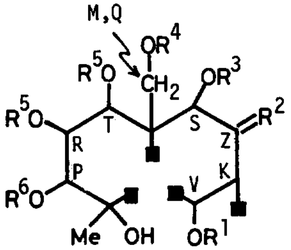
(D): $R^1 = R^2 = R^3 =$ Acyl

(D'): $R^1 =$ Acyl, $R^2 = R^3 =$ Ac

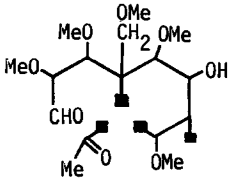


(E)

nature of five acetoxy groups was disclosed: one primary (H_M, H_Q) and four secondary (H_R, H_S, H_T, H_V) hydroxyls exist as acetates in 1, respectively. Thus the partial structure (D) is expressed by (D'). Reduction of 1 with $LiAlH_4$ in ether-THF afforded a mixture of two products (8a, 8b), which was acetylated with Ac_2O-pyridine at 60°, to give dihydrooctaacetate-A, 9a [mp 192-193°; $C_{31}H_{42}O_{18}$; mass 702 (M^+)] and -B, 9b [mp 206-207°; $C_{31}H_{42}O_{18}$; mass 685 (M^+-17)]. Both 9a and 9b on treatment with NaOMe-MeOH gave two polyols, euonyminol,[6] 8a [mp 250°(dec.); $C_{15}H_{26}O_{10}$] and iso-euonyminol, 8b (amorphous powder). Formation of diastereoisomeric 8a and 8b from 1 implies that a keto group is present in 1, which underwent reduction together with reductive cleavage of seven ester linkages. The NMR spectra of 9a and 9b, confirming this view, further indicated the relation of two protons, H_K and H_S as shown in (E): while H_K and H_S appeared as a doublet and a singlet, respectively in 1 (cf. Fig. and Table), the corresponding protons in 9a (and 9b) were observed as a double doublet and a doublet, and in addition, a new signal (H_Z) appeared at 5.50 (dd, J = 6.0, 4.0 Hz) in 9a.[7]



	R^1	R^2	R^3	R^4	R^5	R^6
1 :	Ac	O	Ac	Ac	Ac	Acyl
2 :	H	O	H	H	H	Acyl
3 :	Me	O	Me	Me	Me	Acyl
4 :	H	O	isopropylidene		H	Acyl
5 :	Ac	O	isopropylidene		Ac	Acyl
6 :	Ac	O	H	H	Ac	Acyl
8 :	H	H,OH	H	H	H	H
9 :	Ac	H,OAc	Ac	Ac	Ac	Ac



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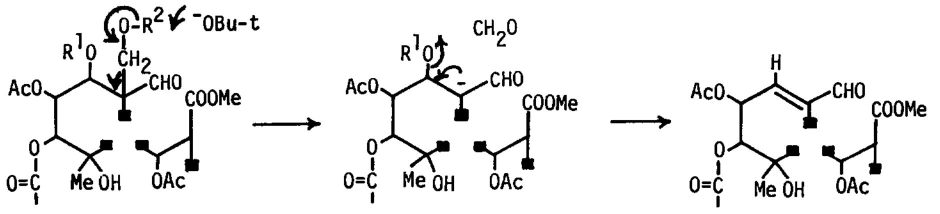

10: R^1=Ac, R^2=H
11: R^1=H, R^2=Ac

12

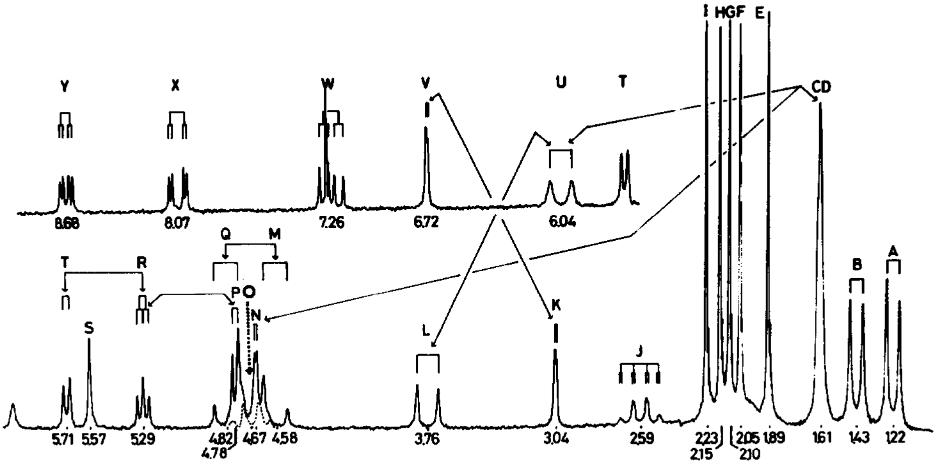

Figure. NMR Spectrum of Evonine 1 in $CDCl_3$ at 100 MHz (δ in ppm).
Couplings confirmed by double resonace experiment are indicated by lines with arrows. Signals due to evoninic acid part are A, B, J, O, W, X, and Y.

Table. NMR Spectral Data (δ in ppm)[a)]

	H_K	H_M,H_Q	H_P	H_R	H_S	H_T	H_V	H_Z
1[b)]:	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)	
4 :		4.24 (m)	4.85 (d 3.0)	4.06 (t 3.0)	4.45 (s)	4.24 (m)	5.12 (s)	
5 :	2.99 (br.s)	4.25 (s)	4.75 (d 3.0)	5.20 (dd 3.0,3.8)	4.25 (s)	5.76 (d 3.8)	6.36 (br.s)	
9a[b)]:	2.34 (dd 4.0,0.8)	4.42, 5.23 (AB q 13.7)	4.81 (d 2.8)	5.27 (dd 3.8,2.8)	5.34 (d 6.0)	5.60 (d 3.8)	6.76 (d 0.8)	5.50 (dd 6.0,4.0)
9b[b)]:	2.45 (dd 2.6,1.0)	4.46 (s)	4.79 (d 2.7)	5.27 (dd 3.6,2.7)	5.69 (d 10.0)	5.59 (d 3.6)	6.51 (d 1.0)	5.57 (dd 2.6,10.0)
10 :			4.63 (d 4.5)	5.30 (dd 4.5,3.8)	9.73 (s)	5.93 (d 3.8)	6.39 (d 10.5)	

a)Multiplicities and coupling constants are given in parentheses. Spectra were taken in $CDCl_3$ at 100 MHz (1, 9a, 9b) and at 60 MHz (4, 5, 10).
b)All the couplings were confirmed by double resonace experiment.

Acetylation of the acetonide 4 (Ac_2O-pyridine, 60°) afforded an acetonide triacetate 5 [mp 175-178°; $C_{35}H_{43}NO_{15}$; mass 717 (M^+)], which was further converted by treatment with aqueous AcOH (1:1) (80°, 4 hr) to a triacetate 6 (mp 187-192°; $C_{32}H_{39}NO_{15}$). The primary hydroxyl (H_M, H_Q) and the secondary one (H_S) of the α-ketol moiety were shown to be involved in the formation of the acetonide in 4 from the NMR spectra of 4 and 5 (cf. Table), and these two hydroxyls were deduced to be situated in 1,3-relationship.

The triacetate 6 was reacted with $Pb(OAc)_4$ in MeOH-AcOH, giving an aldehyde-ester triacetate 10 [mp 163-167°; $C_{33}H_{41}NO_{16}$] together with the isomer 11 [mp 220-223° (dec.); $C_{33}H_{41}NO_{16}$; mass 707 (M^+)].[8] The coupling constant between H_K and H_V, which is small (1.0 Hz) in 1 was found to be 10.5 Hz in 10, indicating clearly that the protons (H_K, H_V) are located on the two adjacent carbons, respectively. Thus the partial structure (E) in 1 was established.

On treatment with t-BuOK in t-BuOH - DME (75°, 3 hr), 10 afforded an α,β-unsaturated aldehyde ester, 12 [mp 224-225°; $C_{30}H_{35}NO_{13}$; UV(EtOH) 223 (ε 7700), 265 nm (ε 3100); NMR($CDCl_3$) δ 9.73 (s); mass 617 (M^+)] and formaldehyde.[9] This reaction, illustrated above, is retro-aldolization of the hydroxymethyl group with concomitant loss of 1 mole of AcOH, and made it possible to correlate three partial structures, (C), (D'), and (E), as shown in 1.

Pentamethyl ether 3 [mp 245-248°; $C_{31}H_{43}NO_{12}$; mass 621 (M^+)] was obtained by treating 2 with CH_3I - NaH in DMF (50°, 18 hr). Reduction of 3 with $LiAlH_4$ in THF afforded an alcohol, which on oxidation with $NaIO_4$ gave an aldehyde-methyl ketone 7 [amorphous powder; $C_{20}H_{34}O_{10}$; IR($CHCl_3$) 1735, 1708 cm^{-1}; NMR($CDCl_3$) δ 2.19 (s, Me-CO-), 9.61 (d, J = 2.3 Hz, CHO); mass 433 (M^+-1)]. Formation of 7 indicates that the group (B) is adjacent to the terminal carbon (H_P) of the 1,2,3-triol grouping (D').

Based on the results so far obtained, the C_{15} component of evonine is represented by the partial structure 1.

REFERENCES AND FOOTNOTES

1) M. Pailer and R. Libiseller, Monatsh. Chem., 93, 403, 511 (1962).

2) Though *Evonymus europaea* L. was used in the Pailer's papers, *Euonymus europaea* L. is generally recorded in the recent literatures.

3) S. M. Kupchan, R. M. Smith, and R. F. Bryan, J. Amer. Chem. Soc., 92, 6667 (1970).

4) The identity of our alkaloid with evonine was proved by mixed melting points and spectral comparison (solution IR and mass). We express our sincere thanks to Prof. Pailer for providing us with evonine.

5) Satisfactory elemental analyses were obtained for all crystalline compounds. Molecular formulas of some compounds were secured by high-resolution mass spectrometry.

6) Since one of the polyols was proved to be identical with the one derived from euonymine, a minor alkaloid of *Euonymus Sieboldiana* Blume, a name euonyminol was given to the polyol.

7) Protons, H_K and H_S of 9a and 9b obtained by reduction of 1 with $LiAlD_4$ appeared as a doublet and a singlet, respectively.

8) The isomer 11 was formed by acetyl migration from the secondary hydroxyl to the primary one, which was revealed by NMR spectral data.

9) Formaldehyde was obtained as 2,4-dinitrophenylhydrazone (46%).