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THE STRUCTURE OF EVOZINE, AN ALKALOID ISOLATED FROM EVONYMUS EUROPAEA L.

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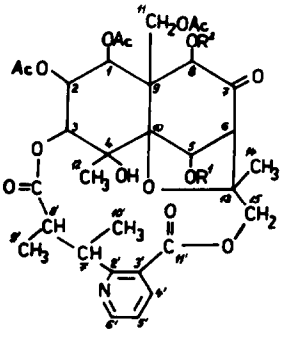
The first published account on the isolation of alkaloids from E. europaea L. was by Doebel and Reichstein (1). The three alkaloids obtained by them were referred to as A, B, and C. We have reported (2) the isolation of the same alkaloids and their empirical formulae. We called the alkaloid A ($C_{34}H_{41}NO_{16}$) evorine, the alkaloid B ($C_{32}H_{39}NO_{15}$) evozine, and the alkaloid C ($C_{36}H_{43}NO_{17}$) was found to be identical with evonine which was isolated from E. europaea L. by Pailer and Libiseller (3).

Recently, Japanese authors (4,5) have reported the isolation of the alkaloid evonine from E. Sieboldiana Blume. Its PMR spectrum is identical with that of our evonine. They assigned to it structure 1 on the basis of PMR spectroscopy, some chemical reactions and of the biogenetic relationship with the sesquiterpenoid alkaloids maytine and maytoline. The structures of the latter two alkaloids were elucidated by Kupchan and co-workers (6). The same molecular structure of the sesquiterpenoid nucleus of evonine as that found by the Japanese authors was achieved by us independently on the basis of our PMR spectra and the mentioned biogenetic premises. Therefore, we accept the structure 1 as the most probable structure of evonine.

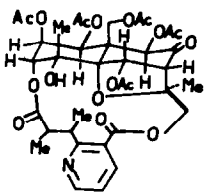
A comparison of the PMR data and the physical constants revealed the identity of our evorine with neo-evonine which was also isolated from E. Sieboldiana Blume. It was assigned (7) the structure 2. The position of the free secondary hydroxyl of evorine at C-5 was evident from the upfield shift of the

signal H-5 from 6.76 ppm in evonine to 5.36 ppm in evorine and from the simultaneous downfield shift of the signal H-12 from 1.60 ppm in evonine to 1.89 ppm in evorine. An unequivocal assignment of $CH_3-\overset{|}{C}-OH$ and $-\overset{|}{C}H-OH$ was made on the basis of the nonzero interactions ^4J (CH_3-OH) and ^3J (CH-OH), and confirmed by decoupling and exchange experiments.

The PMR spectrum of evozine ($C_{32}H_{39}NO_{15}$) exhibited signals of the protons H-5 at 5.20 ppm ($J_{5,6}$ = 1.2 Hz, $J_{5,OH} \neq 0$), H-8 at 4.49 ppm ($J_{8,OH} \neq 0$), and H-12 at 1.84 ppm ($J_{12,OH} \neq 0$). The other aspects of the PMR spectrum were similar to those of evonine (1) and evorine (2) (Table 1). Consequently, the structure 3 is attributable to the alkaloid evozine.



1 $R^1 = R^2$ = Acetyl
2 R^1 = H, R^2 = Acetyl
3 $R^1 = R^2$ = H



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More recently, the relative stereostructure 4 of evonine was inferred (8) from considerations of vicinal couplings and NOE observations. The stereostructure of the sesquiterpenoid nucleus differs from that of maytoline (6) only in the configuration of the center at C-8. In principal, the proposed stereostructure 4 is acceptable. The different sterical relationship of H-8 and H-6 in evonine is supported by the absence of the significant "trough carbonyl" long-range coupling $^4J_{6,8}$ found by us in the PMR spectra of 1 - 3. However, the PMR arguments (8) for the structure 4 are still ambiguous. Questionable is the relative configuration of the centers C-4 and C-5. The

Table 1. NMR Spectral Data (9)

	Evonine (1)	Evorine (2)	Evozine (3)
H-1	5.69 (d ~3.5)	5.69 (d ~3.5)	5.87 (d 3.4)
H-2	5.28 (t, $\sum J$ ~6.5)	5.31 (t, $\sum J$ ~6.5)	5.22 (dd 3.4, 3.0)
H-3	4.77 (d ~3.0)	4.77 (d ~3.0)	4.80 (d 3.0)	
H-5	6.76 (d 1.0)	5.36 (dd 1.0, 3.5)	~5.20
H-6	3.02 (d 1.0)	3.16 (d 1.0)	3.22 (d 1.2)
H-8	5.56 (s)	5.56 (s)	4.49 (s, $J_{8,OH} \neq 0$)
H-11	4.55, 4.81 (AB q 13.0)	4.42, 4.89 (AB q 13.0)	4.62 (s)
H-12	1.60 (s, $J_{12,OH} \neq 0$)	1.89 (d, $J_{12,OH} = 1.5$)	1.84 (s, $J_{12,OH} \neq 0$)
H-14	1.60 (s)	1.60 (s)	1.51 (s, $J_{14,15} \neq 0$)
H-15	3.71 (d 11.5) 6.03 (d 11.5)	3.73 (d 11.5) 6.07 (d 11.5)	3.74 (d 11.5) 6.09 (d 11.5)
H-4'	8.07 (dd 8.0, 2.0)	8.14 (dd 8.0, 2.0)	8.12 (dd 8.0, 2.0)
H-5'	7.25 (dd 8.0, 4.5)	7.27 (dd 8.0, 4.5)	7.27 (dd 8.0, 4.5)
H-6'	8.69 (dd 4.5, 2.0)	8.69 (dd 4.5, 2.0)	8.70 (dd 4.5, 2.0)
H-7'	~4.69 ($J_{7',8'} \neq 0$)	~4.85 ($J_{7',8'} \neq 0$)	~4.75 ($J_{7',8'} \neq 0$)
H-8'	2.58 (q 7.0)	2.54 (q 7.0)	2.54 (q 7.0)
H-9'	1.22 (d 7.0)	1.17 (d 7.0)	1.17 (d 7.0)
H-10'	1.41 (d 7.0)	1.40 (d 7.0)	1.40 (d 7.0)
OH-4	~4.63 ($J_{12,OH} \neq 0$)	5.87 (q 1.5)	5.71 (q 1.5)
R^1	Acetyl	OH, 6.17 (d, $J_{5,OH} = 3.5$)	OH, OH } 5.62, 6.15
R^2	Acetyl	Acetyl	
Acetyls	1.88, 2.04, 2.09, 2.14, 2.22	1.88, 1.96, 2.06, 2.15	1.94, 1.99, 2.17

reported NOE 15% between H-3 and H-12 (8) does not make a differentiation between the axial and the equatorial position of the methyl at C-4 possible because both positions are synclinal with the C-H bond at C-3 in chair form of the ring A. The NOE 8% between H-5 and H-12 (8) fails to indicate unequivocally the 1,3-diaxial position of H-5 and of the methyl at C-4. Our interpretation of the chemical shifts of the methyl protons H-12 of evonine (1) and evorine (2) (Table 1) on the basis of the Van der Waals effect might indicate a 1,3-diaxial position of the methyl at C-4 and RO- at C-5 in the structure 4.

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9. Spectra were recorded in $CDCl_3$ solutions on Varian HA-100 Spectrometer using hexamethyldisiloxane (HMDS) as internal standard. All couplings were confirmed by double resonance experiment. Multiplicities and coupling constants are given in parentheses; chemical shifts are given as δ(TMS)-values (δ_{HMDS} = 0.06 ppm).