STUDIES ON VINCA ALKALOIDS. THE STRUCTURE OF VINCARODINE

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The structure and stereochemistry of vincarodine (1) have been determined by an investigation of its spectroscopic properties, particularly NMR, electron impact and field ionization mass spectrometry and finally by X-ray analysis of the hydrobromide derivative.

Vincarodine, one of the minor alkaloids isolated from Vinca rosea, was tentatively proposed[2] as a dimer with a molecular formula, $C_{44}H_{52}N_4O_{10}$. More recent investigations by the British Columbia group employing electron impact mass spectrometry revealed that the alkaloid is a monomer, $C_{22}H_{26}N_2O_5$ (M^+ 398). The molecular ion was substantiated by means of field ionization mass spectrometry in which the base peak was observed at m/e 399 (M + 1). The NMR spectrum[3] of vincarodine indicated the presence of ethyl (1.12, triplet), methoxyl (3.87, singlet), carbomethoxy (4.14, singlet), a 1,2,4-H pattern in an aromatic system (7.39, doublet, J = 8.2 Hz; 6.87, doublet of doublets, J = 8.2 and 2.0 Hz; 6.61 doublet, J = 2.0 Hz) so characteristic of the alkaloid vindoline[4] and its derivatives studied extensively in our laboratories. One of the two remaining oxygen atoms could be ascribed to a secondary hydroxyl group when vincarodine was acetylated (Ac_2O, pyridine) to a monoacetate, $C_{24}H_{28}N_2O_6$, m.p. 219-221°. Comparison of the NMR spectra of the original alkaloid and the acetate derivative revealed the expected downfield shift of the proton adjacent to the hydroxyl group in vincarodine [$\geq$C<u>H</u>OH (3.85) $\longrightarrow$ $\geq$C<u>H</u>OAc (4.97)]. It was now clear that the remaining oxygen atom in the alkaloid is most likely part of a cyclic ether. Absence of an NH group in the IR and NMR spectra as well as the close similarity of the UV chromophore in vincarodine and its acetate with that of the known alkaloid vincine (9)[5] suggested that vincarodine may belong to the eburnamine-vincamine family of alkaloids[6].

Further investigations by mass spectrometry provided initially some confusion since the well-known fragmentation pattern of the eburnamine and related series as detailed by Djerassi[7] did not correspond entirely with those

observed in vincarodine and its acetate. Table I provides a summary of the significant fragments which were observed in the mass spectrum of vincarodine. The structural assignments for the observed fragments (column 1) could only be made with certainty after the X-ray determination.

TABLE I. Summary of Fragmentation Pattern of Vincarodine*

Fragment		Composition		Relative Intensity (%)
		Found	Calc.	
1.	$C_{22}H_{26}N_2O_5$	398.1823	398.1841	45
	$C_{20}H_{21}N_2O_5(M-C_2H_5)$	369.1416	369.1450	1
	$C_{20}H_{23}N_2O_3(M-CO_2CH_3)$	339.1698	339.1708	5
3.	$C_{18}H_{19}N\ O_3$	297.1341	297.1360	67
4.	$C_{18}H_{18}N\ O_3$	296.1268	296.1286	100
5.	$C_{17}H_{16}N\ O_3$	282.1096	282.1129	16
6.	$C_{16}H_{14}N\ O_3$	268.0941	268.0972	23
7.	$C_{13}H_{14}N_2O$	214.1070	214.1106	14
8.	$C_{12}H_{12}N_2O$	200.0923	200.0950	86

* Fragments 3 - 8 are also present in the spectrum of vincarodine acetate.

Critical analysis of the mass spectral data reveals a number of fragments which would be expected if a normal vincamine type fragmentation were to

prevail (fragments 3 - 6) but the fragment at m/e 200 (86% relative intensity) and apparently containing rings A, B and C is not normally observed in this series. It was thus clear that vincarodine was either not a member of this family or that the cyclic ether linkage suggested above is playing a significant role in altering the fragmentation pathway. The final solution to this problem came from the X-ray analysis of vincarodine hydrobromide.

Vincarodine hydrobromide ($C_{22}H_{26}N_2O_5$.HBr) crystallizes from isopropanol-ethanol, m.p. 206-209°, in the common orthorhombic system $P2_12_12_1$ with a = 7.088(7), b = 11.89(1) and c = 31.02(3)Å. The largest available single crystals were only 0.07 mm on an edge. Data were collected on a fully automated Hilger-Watts diffractometer using Ni-filtered Cu Kα (1.5418Å) radiation. No reflections were observed past 45° in θ. Of the 1242 reflections surveyed only 666 were judged to be observed ($F_o \geq 3\sigma(F_o)$).

The structure was solved by standard heavy atom methods and refined by full-matrix least-squares techniques. The final R-factor was 0.122 for the observed reflections. The final structure and relative stereochemistry is shown in 1 and 1a. Bond distances and angles, which were subject to the high standard deviations of 0.2Å and 3° because of the limited data, generally agreed well with accepted values. No intermolecular distances less than 3.4Å were found.

In conclusion, vincarodine represents a novel and biogenetically interesting variant of the eburnamine-vincamine family of alkaloids.

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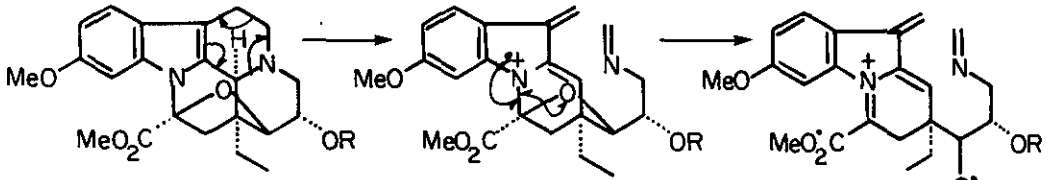
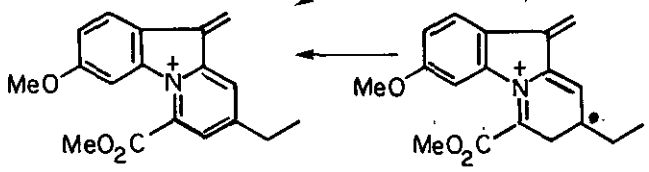


1, R = H (m/e 398)
2, R = Ac

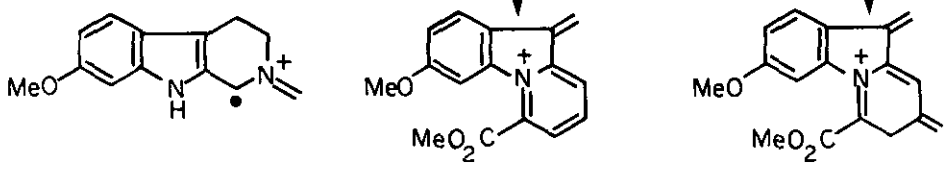
(m/e 398)

(m/e 398)



4, (m/e 296)

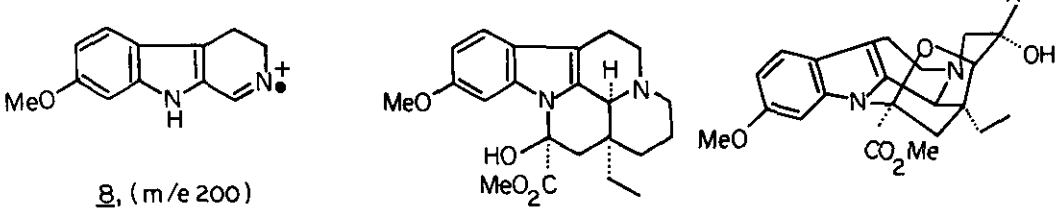
3, (m/e 297)



7, (m/e 214)

6, (m/e 268)

5, (m/e 282)



8, (m/e 200)

9

1a

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