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MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS.[1a] VINCADIFFORMINE (ALCALOÏDES DES PERVENCHES[1b])

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A RECENT investigation[2] of the leaves of Vinca difformis has led to an alkaloid mixture, which could be resolved upon chromatography. One of the new alkaloids, vincadifformine, forms the subject of the present communication since its biogenetically very interesting structure (I) was elucidated largely by means of mass spectrometry.

The empirical formula $C_{21}H_{26}N_2O_2$ (338) of vincadifformine (m.p. 124-125°; $[\alpha]_D$ 0°) was confirmed by the mass spectrometrically determined molecular weight (molecular ion at m/e 338), while its racemic nature was proved by the observation that the alkaloid exhibited zero rotation (c, 0.077 in methanol) in the region 700-370 mμ. The ultraviolet (λ_{max}^{EtOH} 225, 300 and 328 mμ, log ε 3.97, 4.03, 4.19) and infrared ($\lambda_{max}^{CHCl_3}$ 6.0 and 6.15 μ) spectra suggested the presence of the chromophoric system found in akuam-

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[1a] Part VII. For paper VI see L.D. Antonaccio, N.A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J.M. Wilson, L.J. Durham and C. Djerassi, J. Amer. Chem. Soc. 84, in press (1962).

[1b] Part XXI. For paper XX see ref. 2.

[2] J. Gosset, J. Le Men and M.-M. Janot, Ann. Pharm. Fr. 20, in press (1962).

micine (VII)[3] and this conclusion was confirmed by the NMR spectrum,[4] where the signals for the four aromatic protons (400-440 cps), the indolenine N-H (533 cps) and the three protons of the conjugated carbomethoxy group (225 cps) occurred in essentially the same locations as was observed in the NMR spectrum of akuammicine (VII). The most important difference between the NMR spectra of vincadifformine (I) and of akuammicine (VII) was the absence, in the former, of any signals attributable to olefinic protons and the presence of peaks associated with a C-ethyl grouping.

The most characteristic feature of the mass spectrum of vincadifformine was the peak at m/e 124, which was nearly ten times more intense than the next strongest one (molecular ion). Such a strong peak has been shown by Biemann and collaborators[5] to be characteristic of alkaloids with the aspidospermine (V) skeleton, irrespective of the aromatic substitution pattern (e.g. pyrifolidine[6]) and it has also been observed in our laboratory with C-3 substituted alkaloids, such as spegazzinine (VI).[7] This m/e 124 peak has been attributed[5] to species b and its genesis was visualized as involving expulsion of C-3 and C-4 (see arrows in V) followed by cleavage of the 10-11 bond.

If the presence of the intense m/e 124 peak in the mass spectrum of vincadifformine is assumed to be indicative of an aspidospermine-type

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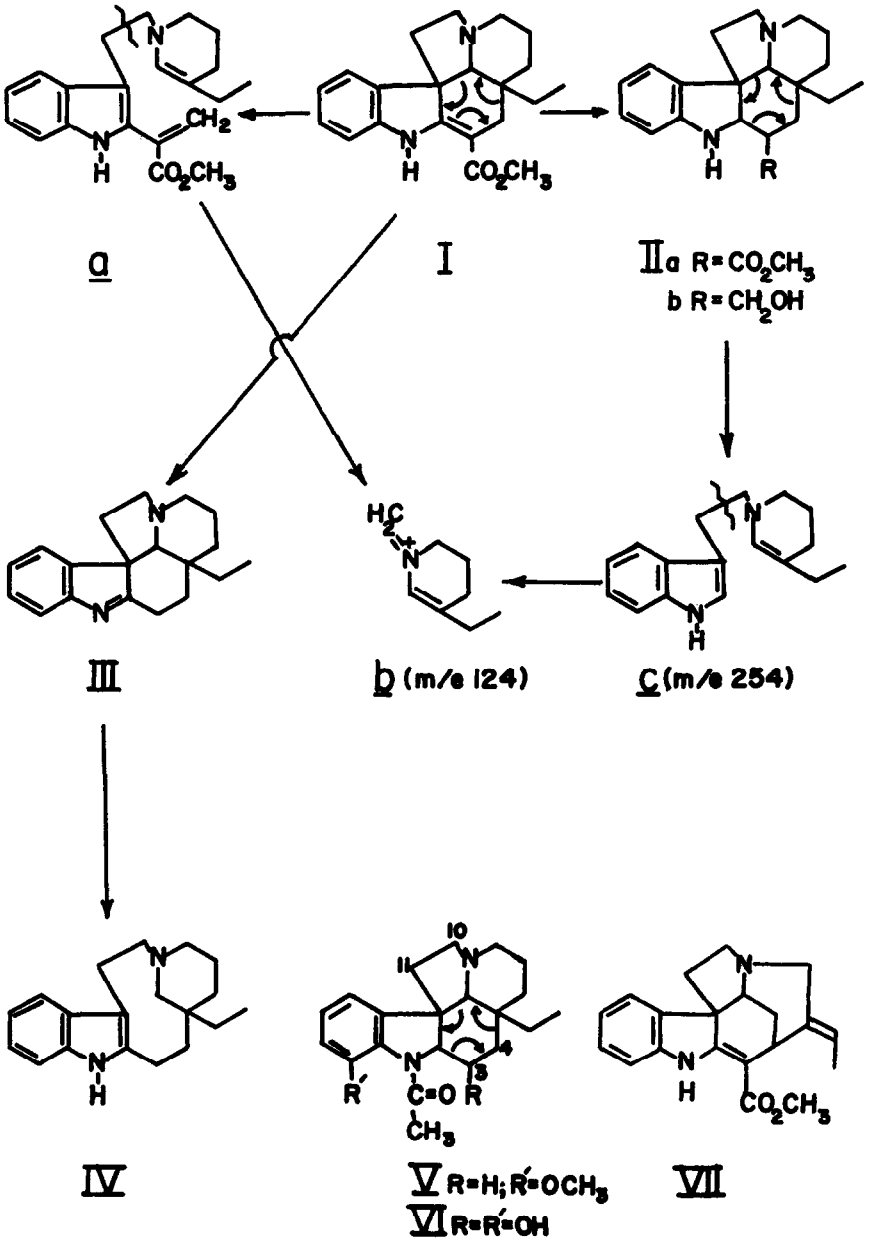
[3] K. Aghoramurthy and R. Robinson, Tetrahedron 1, 172 (1957); G.F. Smith and J.T. Wrobel, J. Chem. Soc. 793 (1960); K. Bernauer, W. Arnold, C. Weissmann, H. Schmid and P. Karrer, Helv. Chim. Acta 43, 717 (1960); J. Levy, J. Le Men and M.-M. Janot, Bull. Soc. Chim. Fr. 979 (1960).

[4] Measured by Dr. Lois J. Durham in deuteriochloroform solution (tetramethylsilane as internal standard) using a Varian A-60 spectrometer.

[5] K. Biemann, M. Friedmann-Spiteller and G. Spiteller, Tetrahedron Letters 485 (1961).

[6] C. Djerassi, B. Gilbert, J.N. Shoolery, L.F. Johnson and K. Biemann, Experientia 17, 162 (1961).

[7] C. Djerassi, H.W. Brewer, H. Budzikiewicz, O.O. Orazi and R.A. Corral, Experientia 18, March (1962).


a
I
IIa R=CO2CH3
b R=CH2OH
III
b (m/e 124)
c (m/e 254)
IV
V R=H; R'=OCH3
VI R=R'=OH
VII

skeleton, then the ultraviolet, infrared and nuclear magnetic resonance spectra coupled with the empirical formula $C_{21}H_{26}N_2O_2$ can only be accomodated in structure I, the formation of the m/e 124 ion (b) being rationalized readily through intermediate a (see arrows in I). Full confirmation for these views was adduced by zinc-sulfuric acid reduction of I, which provided oily dihydrovincadifformine (IIa) ($C_{21}H_{28}N_2O_2$ (340); found mass spectrometrically, 340) with spectral properties (λ_{max}^{EtOH} 250 and 300 mμ, $\lambda_{max}^{CHCl_3}$ 5.80 μ) typical of a dihydroindole. The most intense peak in the mass spectrum of dihydrovincadifformine (IIa) occurred again at m/e 124 (b), but the second most intense peak was now found at m/e 254 (c) due to the loss of the elements of methyl acrylate (see arrows in II). The direct loss of methyl acrylate (m/e 340 → m/e 254) was confirmed by the presence of a metastable peak at m/e 191, while the further decomposition of c (m/e 254) to b (m/e 124) was documented by a metastable peak at m/e 61. Similar mass spectrometric results were encountered with dihydrovincadifforminol (IIb; $C_{20}H_{28}N_2O$ (312); found mass spectrometrically, 312), which exhibited its most intense peak at m/e 124 (b) as well as a substantial one at m/e 254 (c) due to the loss of the elements of allyl alcohol. This expulsion of methyl acrylate or allyl alcohol with formation of the ion c (m/e 254) is completely analogous to the loss of ethylene (M-28) or vinyl alcohol (M-44) in the mass spectra of members of the aspidospermine (V)[5] or spegazzinine (VI)[7] groups.

Chemical verification for structure I could be provided by heating vincadifformine (I) in a sealed tube for 6 hr at 105° with 2N hydrochloric acid to yield the oily decarbomethoxyvincadifformine (III) (no infrared carbonyl band, ultraviolet indolenine-type spectrum with λ_{max}^{EtOH} 230 and 260 mμ; $C_{19}H_{24}N_2$ (280); found mass spectrometrically, 280), which was reduced with potassium borohydride in an alkaline medium under the conditions reported earlier[3] for decarbomethoxyakuammicine. The resulting

crystalline product (m.p. 114-116°) proved to be completely identical (mixture melting point, infrared spectrum, thin-layer chromatographic mobility, mass spectrum[8]), with an authentic sample of racemic quebrachamine (IV), which was prepared from an equimolar mixture of (-) and (+)-quebrachamine.[9] Since the structure of quebrachamine is known,[8] expression I for vincadifformine can now be considered to be established rigorously.

The structure elucidation of vincadifformine (I) is of considerable biogenetic interest, since this alkaloid forms an important connecting link between the aspidosperimine (V) and akuammicine (VII) type bases. The existence of this alkaloid and of the related Vinca alkaloid vindolinine[10] represents strong support for the recently proposed[11] biosynthetic scheme of the Aspidosperma alkaloids. The racemic nature of vincadifformine (I) and of ϕ-akuammicine (VII)[12] is also accomodated in Wenkert's hypothesis[11] through the postulated intervention of a non-asymmetric intermediate.

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[8] See K. Biemann and G. Spiteller, Tetrahedron Letters 299 (1961).

[9] F. Walls, O. Collera and A. Sandoval, Tetrahedron 2, 173 (1958).

[10] C. Djerassi, S.E. Flores, H. Budzikiewicz, J.M. Wilson, L.J. Durham, J. Le Men, M.-M. Janot, M. Plat, M. Gorman and N. Neuss, Proc. Natl. Acad. Sci. Wash. 48, 113 (1962).

[11] E. Wenkert, J. Amer. Chem. Soc. 84, 98 (1962).

[12] P.N. Edwards and G.F. Smith, Proc. Chem. Soc. 215 (1960).