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STRUCTURE OF VINCAMINE

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VINCAMINE (minorine), an alkaloid constituent of Vinca minor L.[1-10] Vinca erecta Rgl. et Schmalh.[11-13], and Vinca difformis Pourr.[14], has the molecular formula $C_{21}H_{26}N_2O_3$, in satisfactory agreement with the experimentally determined molecular weight[1,5]. The ultra-violet spectrum shows it to be an indole derivative. Further structural information was obtained from the infra-red spectrum in Nujol, with bands at 747, 727 (1,2-

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disubstituted benzene ring[14]), 1756 (saturated ester[2]) and 1074 cm^{-1} (C-OH[4]). The band at 3320 cm^{-1} (characteristic for the NH-grouping) was absent. The infra-red spectrum in chloroform solution showed an additional band of medium intensity at 3520 cm^{-1}, characteristic for the O-H group. The titration equivalent[6] and salt formation,[2] indicate that vincamine is a monoacid base; the basic nitrogen atom $N_{(b)}$ is tertiary, as shown by the formation of a monomethiodide, m.p. 218-220° (Found: C, 53.38; H, 6.10. $C_{22}H_{29}N_2O_3I$ requires: C, 53.23; H, 5.89.). Schlittler and Furlenmeier[2] reported that vincamine has one active hydrogen atom, no $N\text{-}CH_3$ or $C\text{-}CH_3$ grouping and cannot be acetylated with acetic anhydride in pyridine.

From our own experiments, we propose the formula Ia for vincamine. Vincamine (Ia) takes up no hydrogen in the presence of Adams' catalyst in methanol or in acetic acid. With potassium hydroxide in boiling methanol it affords vincaminic acid (Ib), m.p. 262-263° (Found: C, 70.56; H, 7.29. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11.) (infra-red spectrum in Nujol: 1670 cm^{-1} - saturated carboxylic acid), which may be reconverted to the parent compound Ia by the action of diazomethane. On being heated to 220° or by reaction with acetic anhydride vincamine (Ia) loses one molecule of water forming apovincamine (II), m.p. 160-161° (Found: C, 74.64; H, 7.18. $C_{21}H_{24}N_2O_2$ requires: C. 74.97; H, 7.19.). The shift of the ester carbonyl band in the infra-red spectrum of II (in chloroform) to shorter frequencies (10 cm^{-1}) against Ia as well as the appearance of two new bands at 1618 and 1638 cm^{-1} suggests extended conjugation in II. The striking difference in the ultra-violet spectra of Ia and II (λ_{max} in mμ(log ε): 228 (4.45); 273 (4.04); 313 (3.82)) makes it probable that the newly formed double bond is conjugated with the indole nucleus. Dehydrogenation of Ia with lead tetra-acetate afforded py-tetradehydrovincamine chloride, m.p. 223-226° (Found: C, 64.31; H, 5.82. $C_{21}H_{23}N_2O_3Cl.1/4\ H_2O$ requires: C, 64.44; H, 6.05.)

as the main product; the ultra-violet spectrum of this compound, λ_{max} in mμ (log ε) : 255 (4.47); 308 (4.33); 370 (3.80), is practically identical with that of py-tetradehydroyohimbine chloride (λ_{max} in mμ (log ε) : 255 (4.47); 305 (4.31; 365 (3.65)). A byproduct of the dehydrogenation, not further characterized, showed an ultra-violet spectrum (λ_{max} in mμ (log ε) : 250 (4.06); 357 (4.14)), typical for a 3-dehydro-β-carboline. The β-carboline structure of Ia is also confirmed by the displacement of the ultra-violet absorption maxima of Ia to shorter wavelengths in acidic solution as against neutral or alkaline solution. This shift, characteristic for the protonation or quarternization of alkaloids of the β-carboline type on $N_{(b)}$,[15] was observed not only for Ia but also for Ia-methiodide and Ib.

Acid hydrolysis of Ia gave amphoteric products together with a base, m.p. 174°, (Found: C, 77.47; H, 7.72. $C_{19}H_{22}N_2O$ requires: C, 77.52; H, 7.53.), which was shown to be identical by both ultra-violet and infra-red spectra with eburnamonine (III),[16] an alkaloid of Hunteria eburnea Pichon[17-19]. The elemental formulae of vincamine (Ia) and eburnamonine (III) differ by $C_2H_4O_2$; of this CH_2 is evidently attributable to the methyl ester group of Ia leaving the elements of formic acid to be accounted for. The loss of these fragments on acid hydrolysis is best interpreted by primary hydrolysis of the methyl ester Ia to the acid Ib, followed by elimination of the elements of formic acid, behaviour typical of a α-hydroxyacid. These

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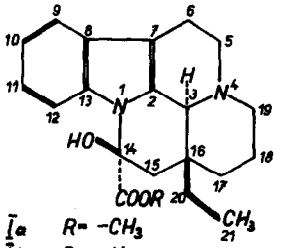
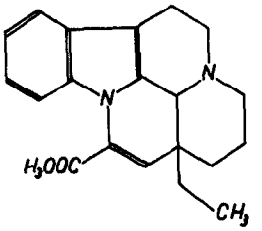
considerations lead to the formula Ia for vincamine.



Ia R= $-CH_3$
Ib R= -H



II

Further evidence for structure Ia was obtained from the chromic acid oxidation of Ia by the method of Garbers, Schmid and Karrer[20]. Unlike Schlittler and Furlenmeier[2], who were not able to establish the presence of C-methyl grouping, we have found both acetic and propionic acid among the oxidation products of Ia, proving the presence of a C-ethyl group.

The above transformations also give stereochemical information about all three centres of asymmetry in vińcamine (Ia), at $C_{(3)}$, $C_{(14)}$ and $C_{(16)}$. The trans-annelation of rings D and E, i.e. the relative configuration at $C_{(3)}$ and $C_{(16)}$, follows from the transformation of Ia to III, the stereochemistry of the latter already being well established.[19] The configuration of the remaining asymmetric centre at $C_{(14)}$ follows from the ready dehydration of vincamine (Ia) to apovincamine (II) under conditions characteristic for bimolecular trans-elimination. For a rigid structure such as Ia this requires the hydroxyl group to be cis to the ethyl group on $C_{(16)}$ and axial in conformation; the relatively bulky methoxycarbonyl group would then have the thermodynamically favoured equatorial orientation. The relative stereochemistry of vincamine is indicated in formula Ia.,

Interesting conclusions may be drawn about the absolute configuration of Ia. Bartlett, Taylor and Raymond-Hamet[17] consider eburnamonine (III)

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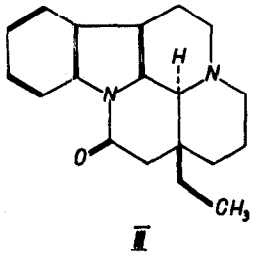
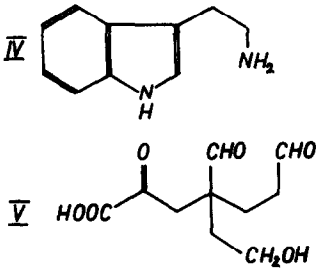
to have the same configuration of the ethyl group as aspidospermine and hence deduce the absolute configuration at $C_{(3)}$ and $C_{(16)}$ of III. Whereas native eburnamonine from Hunteria eburnea has $[\alpha]_D = +89^\circ$ (in chloroform)[17], the degradation product of vincamine (Ia) had a rotation of approximately the same value but of opposite sign ($[\alpha]_D = -105^\circ$ (c = 0.44, in chloroform)). Vincamine (Ia) thus evidently represents an antipode of the alkaloids of Hunteria eburnea. This finding affords a further example for existence in nature of antipodes with identical fundamental structures in addition to the known pairs (+) and (-) quebrachamine,[21] (+) and (-) akuammicine,[22] and pyrifolidine-aspidospermine.[23]

Structure Ia is also in full accord with biogenetic requirements. As in the biogenesis of eburnamonine (III),[24] tryptamine (IV) and diformyl-hydroxyketokarboxylic acid (V) are the most likely precursors. Closure of ring E may be interpreted as an addition of the indole nitrogen to the keto group giving rise to the rather unusual α-hydroxy-α-aminoacid grouping hitherto found only in the peptide moiety of the ergot alkaloids.



II



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