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THE STRUCTURAL AND BIOGENETICAL RELATIONSHIP OF VINCAMINE, VINCANORINE AND EBURNAMONINE

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BY investigation of the structure of vincamine (Ia), the main alkaloid of Vinca minor L.,[1] vincamone by oxydation of vincaminic acid (Ib) with the amoniacal solution $Ag^{\bullet}$ and by oxydation of vincaminole (Ic) with periodic acid respectively has been obtained. Vincamone has also been obtained from vincamine in a different manner.[2] Its infra-red and ultra-violet spectra and its melting point, thus its fundamental structure are identical with those of eburnamonine (II), isolated by Bartlett and Taylor from Hunteria eburnea Pichon.[3]

From Vinca minor L. another alkaloid - vincanorine[4] the infra-red and ultra-violet spectrum (λ_{max} 242 mμ, log ε 4.33; λ_{max} 268 mμ, log ε 4.03; λ_{max} 296 mμ, log ε 3.71; λ_{max} 304 mμ, log ε 3.71) of which is identical with that of vincamone and eburnamonine[5] has been isolated.

[1] J. Mokrý, I. Kompiš, J. Suchý, P. Šefčovič and Z. Votický, Chem. Zvesti 16, 140 (1962).

[2] J. Trojánek, O. Štrouf, J. Holubek and Z. Čekan, Tetrahedron Letters 702 (1961).

[3a] M.F. Bartlett and W.I. Taylor, J. Amer. Chem. Soc. 82, 5941 (1960);
[b] M.F. Bartlett, W.I. Taylor and Raymond-Hamet, C.R. Acad. Sci., Paris 249, 1259 (1959).

[4] J. Mokrý, I. Kompiš, O. Bauerová, J. Tomko and Š. Bauer, Experientia 17, 354 (1961).

[5] Physical Data of Indole and Dihydroindole Alkaloids (4th Ed.). Eli Lilly (1960).

These three compounds differ in the values of their optical rotation: while the specific rotation of eburnamonine is given as $[\alpha]_D = +89^\circ$ (chloroform),[3b] that of vincamone as $[\alpha]_D = -94^\circ$ (chloroform),[1] vincanorine is optically inactive.[4] These facts indicate vincanorine probably to be the equimolar mixture of two optical antipodes - vincamone and eburnamonine. In agreement with this assumption the melting point of vincanorine differs from that of the optically active substances and is identic with the melting point of the synthetically prepared rac-eburnamonine.[3a] Resolving vincanorine by crystallization of its dibenzoyltartaric acid salt we confirmed this supposition.

The direct proof of the fact that vincanorine is racemized at the carbon C_{16}, while vincamone and eburnamonine are corresponding optical antipodes, is the rac-4-ethyl-4-propyl-4,5-dihydrocantin-6-one (IV) obtained from the selenium dehydrogenization of vincanorine and the corresponding (+)- and (-)-cantinones respectively from the selenium dehydrogenization of eburnamonine[3a] and vincamone. Since in such a rigid pentacyclic skeleton racemization cannot be assumed, we excluded, in agreement with the experiments of racemization, the possibility of vincanorine to be the artefact resulting during the isolation by racemization either from vincamone or from vincamine and we are of the opinion that vincanorine is a native racemic alkaloid.

The existence of antipodal alkaloids or their racemates respectively in the group of indole,[6] dihydroindole,[7,8] and oxindole[9] alkaloids is rare but not exclusive.

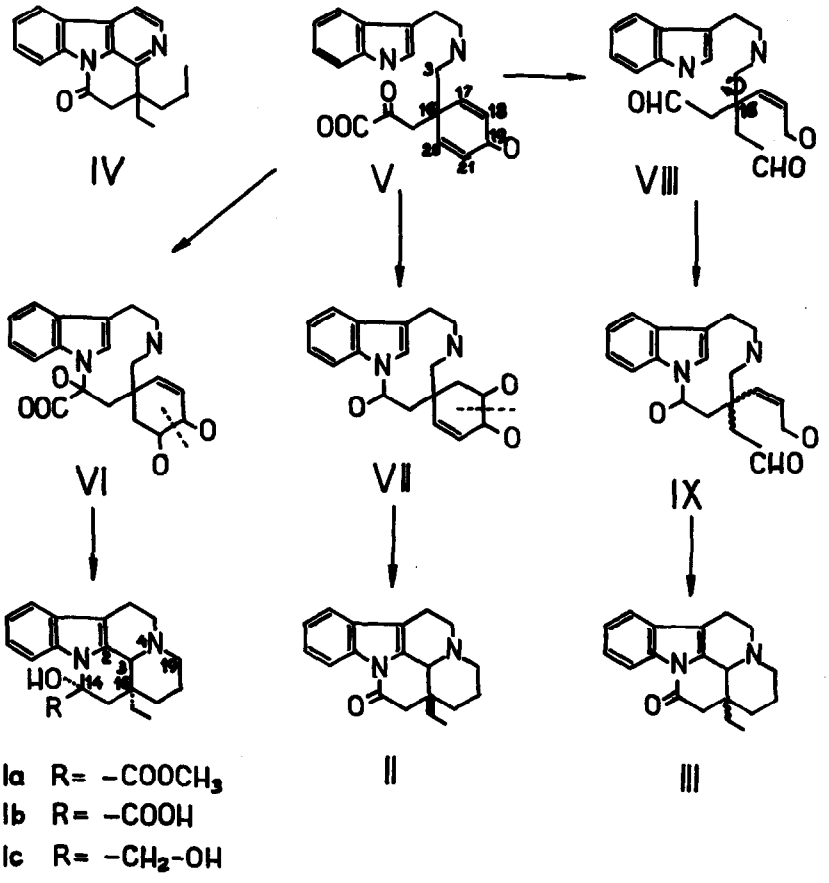
6a T.H. Henry, The Plant Alkaloids (4th Ed.) p. 511
b F. Walls, O. Collers and A. Sandoval, Tetrahedron 2, 173 (1958).

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

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

9 G.M. Badger, J.W. Cook and P.A. Ongley, J. Chem. Soc. 867 (1950).

The recent state of the theory of the indole alkaloids biogenesis represented by the works of Wenkert[10] is the starting point for our conception of the biogenesis of vincamine (Ia), eburnamonine (II) and vincanorine (III). The basic biogenetical progenitor of the three mentioned



alkaloids is probably the product of the initial interaction of the reduced unrearranged form of prephenate and aminogroup of tryptamine (V), of which at biogenesis of vincamine (Ia) by addition of the keto-group to indole

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10a E. Wenkert and N.V. Bringi, J. Amer. Chem. Soc. 81, 1474 (1959);
b E. Wenkert, Experientia 15, 165 (1959).

nitrogene and by the hydratation of the bond C_{20}-C_{21} arises VI. The product which have arisen from Woodward's fission[11] of diole VI has a defined configuration at the carbon C_{16}, that determines after ring closure C and D also the configuration at the second centre of asymmetry C_3.

By the biogenesis of eburnamonine (II) we assume decarboxylation, hydratation of the second of two equivalent double bonds and thus the ring cleavage between the carbon atoms C_{18}-C_{19} (VII). The antipodal configuration at C_{16} presents under analogical conditions as in the previous scheme the antipodal configuration at C_3 and gives origin to the antipodal skeleton of vincamine - to eburnamonine (II).

For the formation of vincanorine (III) the intermediate V might be expected to create VIII by hydratation, by the ring cleavage in the rest of prephenic acid at the same place as we assumed by vincamine (VI) and by the subsequent oxydation. Two acetaldehyde rests of this crucial intermediate (VIII) temporary destroy the asymmetry of carbon C_{16} and render possible two different manners of addition at nitrogen $N_{(a)}$ (IX). So the configuration at the repeated asymmetrical centre C_{16} is determined and the native racemate (III) explicitly results from both intermediates by the same reactions.

The suggested biogenetical scheme of the genesis of vincamine, eburnamonine and vincanorine from the intermediates VI, VII and IX does not determine the stereochemistry of this pentacyclic skeleton. Even when the theoretical possibilities of ring closures by linkage of $N_{(a)}$ -C_{19} and C_2 - C_3 do not exclude C/D/E ring juncture trans-trans or trans-cis, we take the trend of Wickberg's conclusion, who in agreement with Wenkert's theory of cis-anelation of the perhydroisoquinoline system of the aspidosperma-like skeleton, considers for eburnamonine C/D cis ring juncture and syn-confor-

[11] R.B. Woodward, Nature 162, 155 (1948).

mation C_3-H and C_{16}-CH_2CH_3,[12] which explicitely supposes D/E cis ring juncture. On the contrary to this there are authors[3] who assume for eburnamonine D/E trans-anelation and for C_3-H and C_{16}-CH_2CH_3 anti-conformation.

The pathway of genesis of the optically active alkaloid and its racemate in the same plant can occur parallel as in the case of Vinca minor L. (vincamine-vincamone - vincanorine) or in Picralima klaineana (nitida) (Stapf) T. et H. Durand (akuammicine - ϕ-akuammicine).[13] The optically active alkaloid with the configuration at the asymmetric centre corresponding to that in prephenic acid, and the racemate that has arisen by the temporary destruction of the centre of asymmetry after the formation of two equal acetaldehydic rests are always the final results. Therewith the suggested theory differs from the up to date theories suggested for some concrete alkaloids[7,12,14] on the biogenesis of antipodale alkaloids and their racemates respectively and allows the acceptable explanation on the origin of all hitherto extant indole antipodal alkaloids.

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

[13] T.A. Henry, J. Chem. Soc. 2259 (1932).

[14a] A. Chatterjee, S. Ghosal, Sci. & Cult. 27, 359 (1961); [b] A. Chatterjee, N. Adityachandhury and S. Ghosal, Ibid. 27, 405 (1961).