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ALKALOIDS OF *VINCA MINOR* L.

THE STRUCTURE OF VINCADINE AND VINCAMINOREINE

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VINCADINE (I) a new alkaloid isolated from *Vinca minor* L. and described in our previous communication[1] has the molecular formula $C_{21}H_{28}N_2O_2$. The ultra-violet spectrum shows it to be an indole derivate. The infra-red spectra in KBr and in CCl_4 indicated the presence of an unconjugated ester group (1730 cm^{-1}), free NH group (3450 cm^{-1}) and disubstituted benzene ring (740 cm^{-1}). The titration equivalent and the formation of the monopicrate indicate the $N_{(b)}$-nitrogen atom as basic.

The quoted facts suggested the fundamental skeleton of vincadine (I) not to be a pentacyclic as is in the case of vincamine, vincanorine respectively[2], but that a tetracyclic skeleton with an unsubstituted *ind*-N-nitrogen atom can be assumed.

The acid hydrolysis was the deciding experiment to propose the structure of vincadine (I). Heated with 5N hydrochloric acid on water-bath vincadine (I) undergoes hydrolysis and decarboxylation and yields in cca 90% decarbomethoxyvincadine (II)(m.p. 146-147°; found: C, 80.67; H, 9.33; N, 9.98; $C_{19}H_{26}N_2$ requires: C, 80.80; H, 9.28; N, 9.92; $[\alpha]_D^{EtOH}$-121°).

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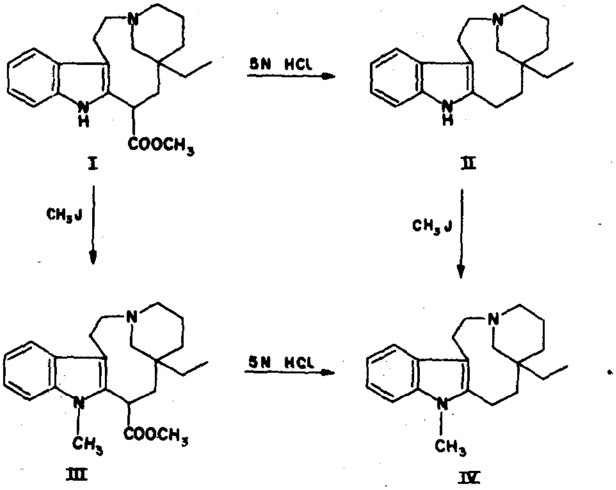
[1] J. Mokrý, L. Dúbravková and P. Šefčovič, *Experientia* **18**, in press (1962).
[2] J. Mokrý, I. Kompiš and P. Šefčovič, *Tetrahedron Letters* No. **10**, 433 (1962)

The ultra-violet spectrum (λ_{max}^{EtOH} 230, 286 and 292 mμ, log ε 4.60, 3.87, 3.85) possesses a typically indole character. All these values agree with those reported for the alkaloid (+)-quebrachamine[3] isolated from *Stemmadenia donnell-smithii*. Their infra-red spectra[4] are superimposable. These facts allow to suggest for vincadine (I) the carbomethoxy-(+)-quebrachamine structure. The carbomethoxy group we propose locate at position C_3 as Wenkert[5] according to biogenetic aspects forsaw for the alkaloids of this type and as *e.g.* it is found in vindoline[6], vindolinine[7], vincadifformine[8] or in kopsinine[9].



I II III IV

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[3] a) F. Walls, O. Collera and A. Sandoval, *Tetrahedron* **2**, 173 (1958).
b) H. Kny and B. Witkop, *J. Org. Chem.* **25**, 635 (1960).

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

[5] E. Wenkert, *J. Am. Chem. Soc.* **84**, 98 (1962).

[6] M. Gorman, N. Neuss and K. Biemann, *J. Amer Chem. Soc.* **84**, 1058 (1962).

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

[8] C. Djerassi, H. Budzikiewicz, J.M. Wilson, J. Gosset, J. LeMen and M.-M. Janot, *Tetrahedron Letters* No. **6**, 235 (1962)

[9] W.G. Kump, D.J. LeCount, A.R. Battersby and H. Schmid, *Helv. Chim. Acta* **45**, 854 (1962).

From the fraction T[10] of the alkaloids of Vinca minor L. we isolated by chromatography on alumina (akt. II, light petrolether-benzene 1:1) a further alkaloid, the values (m.p. 138-139°; found: C, 74.47; H, 8.52; N, 7.86; OMe, 9.03; (N)Me, 4.52; m.w. 344,8 (perchloric acid titration); $C_{22}H_{30}N_2O_2$ requires: C, 74,54; H, 8.53; N, 7.90; OMe, 8.75; (N)Me, 4.24; m.w. 354,5; ultra-violet spectrum: λ_{max}^{EtOH} 230, 288 and 296 mμ, log ε 4.59, 3.93, 3.91; infra-red spectrum: ν_{max}^{KBr} 741 and 1740 cm^{-1}) of which agree with those reported for vincaminoreine[11]. Its specific rotation is $[\alpha]_D^{CHCl_3}$ +26, 5°. The ultra-violet spectrum of vincaminoreine proves it to be an indole alkaloid, the molecular formula of which indicates again a tetracyclic skeleton. According to the infra-red spectrum (no NH-free band) and the presence of a methylimino group vincaminoreine (III) could possibly be the ind-N-methyl-derivate of vincadine (I). In fact vincadine (I) methylated in liquid ammonia with methyliodide afforded a product identical with vincaminoreine (III) in all respects. This structure relationship was proved by further reactions, where through decarbomethoxylation of vincaminoreine (III) in 5N hydrochloric acid ind-N-methyl-(+)-quebrachamine (IV) was obtained. Its values (m.p. 86-87°; found: C, 80.96; H, 9.47; N, 9.53; (N)Me, 5.45; $C_{20}H_{28}N_2$ requires: C, 81.03; H, 9.52; N, 9.45; (N)Me, 5.07; $[\alpha]_D^{CHCl_3}$ +110°; ultra-violet spectrum λ_{max}^{EtOH} 233, 290 and 296 mμ, log ε 4.48, 3.82, 3.82) and infra-red spectrum were identical with the product obtained by methylation of (+)-quebrachamine in all respects.

Vincadine (I) and vincaminoreine (III) are the first alkaloids isolated from the gender Vinca having a quebrachamine-like structure. In last time Wenkert[5] proposed a hypothesis of biogenesis of such a skeleton following

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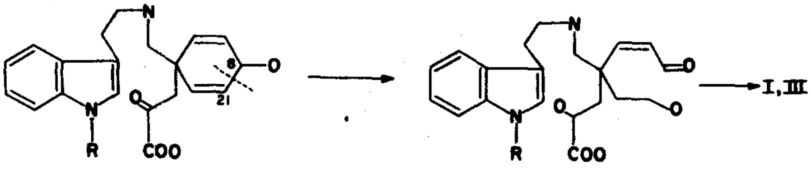
[10] J. Mokrý, I. Kompiš, P. Šefčovič and Š. Bauer, Coll. Czech. Chem. Communs. 27, in press (1962).

[11] J. Trojánek, O. Štrouf, K. Kavková and Z. Čekan, Coll. Czech. Chem. Communs. 25, 2045 (1960).

the *seco*-prephenate-formaldehyde line. With regard to recently reported works on structures of the native racemate vincadifformine[8] and (-)-tabersonine[12] we incline to the opinion that vincadine (I) and vincaminoreine (III) are created from the intermediate VI. This can arise either from simple compounds, taking into consideration Leete's work[13] or in the same pathway as we explain the origin of vincamine, ebernamonine and the native racemate vincanorine[2], *i.e.* by the prephenate line.



V VI

According to this hypothesis the intermediate V, arisen by condensation of tryptamine and the reduced unrearranged form of the prephenate leads after Woodward's fission at the position C_8 - C_{21} through the already indicated reactions[2] to vincadine (I), vincaminoreine (III) respectively.

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[12] M. Plat, J. LeMen, M.-M. Janot, J.M. Wilson, H. Budzikiewicz, L.H. Durham, Y. Nakagawa and C. Djerassi, *Tetrahedron Letters*, No. *6*, 271 (1962)

[13] E. Leete, S. Ghosal and P.N. Edwards, *J. Amer. Chem. Soc.* *84*, 1068 (1962).