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STUDIES ON THE STRUCTURE OF VINCAMINE

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VINCAMINE is the major alkaloid of Vinca minor L. (family of Apocynaeceae). The alkaloid was first isolated in 1953[1], and its structure together with that of some accompanying minor alkaloids, has been investigated by several workers[2-10]. Attention to the therapeutic value of the alkaloid was called first by A. Orechov[11] and A. Quevauviller[12], recently by K. Szász et al.[13], the latter workers developed a method of producing the drug on industrial scale. The first data concerning the structure of the alkaloid were

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offered by Trojanek[14] and later by Mokry[15-16] and Janot[17].

Our studies on the structure of vincamine[18-19] were carried out simultaneously with those of Trojanek et al.[14], and essentially the same results have been achieved in an entirely different way.

Vincamine contains comparatively few substituents, and has a highly condensed ring system. Thus, the main task has been the elucidation of the structure of the multinuclear core. Characteristic evidence for the structure of the vincamine ring system was obtained by Trojanek et al.[14], when the acid hydrolysis of the alkaloid gave a well crystallized product which had the characteristic u.v. spectrum of eburnamonine[20]. However, the direction of optical rotatory power indicated that the compound was the antipode of the naturally occurring alkaloid.

The same compound has been prepared by us in a high yield by the Curtius reaction of the hydrazide of the alkaloid. This method has the advantage of mild reaction conditions which leave the optical centres unchanged, thus it is suitable for investigating anellations and stating the absolute configuration in the ring system.

The empirical formula and molecular weight of the alkaloid have been determined by combustion analysis, titration in non-aqueous medium and the M. Sobotka-Rast method[21], resp., and gave - in agreement with Schlittler's

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data - the following results: (Found: C, 71,02; H, 7,42; N, 7,88; Calc. for $C_{21}H_{26}O_3N_2$ C, 71,18; H, 7,40; N, 7,90; O, 13,72).

An investigation of the substituents of the alkaloid skeleton showed by paper chromatography method of P. Karrer[22] the presence of a C-ethyl group. Further investigations revealed the presence of an ester-group as an oxygen-containing function. The hydrolysis of vincamine by shortly refluxing the compound in alcoholic aqueous sodium[18] or potassium hydroxyde[6] gave vincaminic acid which after evaporating the alcohol could be isolated at p_H 7 in crystalline form, m.p. 254-256°. (Found: C, 70,46; H, 7,19; N, 8,22. Calc. for $C_{20}H_{24}O_3N_2$ C, 70,54; H, 7,11; N, 8,23; O, 14,12.) Vincaminic acid was successfully re-esterified with ethereal diazomethane solution in anhydrous acetone medium to give back the vincamine in 85% yield, m.p. 230-232°. The identity of this product with vincamine was further proved by optical rotation measurement, paper chromatography, and combustion analysis. Thus, vincamine is an ester-alkaloid of methanol.

No methoxy content was found in the vincaminic acid.

When vincamine was treated with acetyl chloride, chlorovincamine was obtained. Boiling for 1 hour in acetic anhydride produced practically no change; reflux times of 3 to 8 hours resulted in dehydration to give apovincamine in yields of 15 to 36%. Other dehydrating agents, such as formic acid, dehydrated the compound more readily to yield, e.g. 64% apovincamine in 1 hour, m.p. 162-164°; $[\alpha]_D^{25}$ + 121° (in $CHCl_3$). (Found: C, 74,90; H, 7,19; N, 8,38; Calc. for $C_{21}H_{24}O_2N_2$ C, 75,00; H, 7,14; N, 8,33; O, 9,53.)

The u.v. spectrum of the apovincamine is characteristic, and differs from the pure indole ring by the appearance of a third maximum. ($\lambda_{max.}$ in mμ(log ε): 228 (4,48); 274 (3,98); 315 (3,50); $\lambda_{min.}$ in mμ

[22] C.F. Garber, H. Schmidt, P. Karrer, Helv. Chim. A. 37, 1336 (1957).

(log ε): 245 (3,50); 305 (3,52).

Concluded from the above results, two of the three oxygen atoms of vincamine is contained in the methyl ester grouping of the carboxylic function, and the third is in a tertiary hydroxyl group.

From among the two nitrogen atoms, $N_{(a)}$ is contained in an indole ring. The u.v. measurement showed the characteristic spectrum of 2,3-dimethylindole, as it had been found also by Schlittler[1]. The Zerewitinoff determination indicated the presence of one active-hydrogen group. As it follows from the above considerations, it may be attributed to the tertiary alcohol group. The nitrogen atom in the indole ring may contain no active hydrogen, and since there was found no $N\text{-}CH_3$ grouping in the compound either, the third substituent of the indole nitrogen atom must also be a member of the ring system.

The $N_{(b)}$ nitrogen atom could not be acylated. Acids gave monobasic salts with the base picrate, m.p. 216-217°.

Treatment of the alkaloid with methyl iodide gave vincaminium iodide in the form of crystalline needles, m.p. 219-220°. (Found: C, 52,71; H, 6,50; N, 5,63; Calc. for $C_{21}H_{26}O_3N_2.CH_3J$ C, 53,23; H, 5,89; N, 5,64; J, 25, 59.)

The Emde and Braun degradation reactions were found to be negative. Thus, $N_{(b)}$ must be a tertiary nitrogen atom contained in a ring.

Vincamine contains no double bond except that contained in the indole ring. The compound could not be hydrogenated in the presence of Adams catalyst or palladium on charcoal or Raney nickel.

Starting with the ratio of carbon to hydrogen as present in vincamine, and calculating with the unsaturation due to the indole ring, it could be concluded that the alkaloid has a system of five condensed rings.

Since all indole alkaloids can be derived biogenetically from tryptophane or tryptamine, this fact determines the positions of the two nitrogen atoms and the structure and anellation of the ring system.

Based on biogenetical considerations and pharmacological data, the third ring was thought to have the constitution of β-carboline. For chemical proof, dehydration of the ring system was attempted: if a β-carboline skeleton is present, this reaction is decisive, its result being dependent upon the saturated or aromatic character of the carbocyclic ring. Applying the principle of the method of Hahn et al.[23], vincamine was reacted with lead tetraacetate at 80° in acetic acid medium to give py-tetradehydro-vincamine. The product showed the pale yellow colour of an anhydronium base, m.p. 176-178°, $[\alpha]_D^{25}$+ 129° (in $CHCl_3$). The u.v. spectrum of this compound showed the same maxima as py-tetradehydroyohimbine. (Py-tetra-dehydrohimbine $\lambda_{max.}$ in mμ (log ε): 258 (4,50); 310 (4,35); 362 (4,00); py-tetradehydrovincamine $\lambda_{max.}$ in mμ (log ε): 255 (4,25); 310 (4,05); 360 (4,00).

This change of the u.v. spectrum indicated the tetrahydroharman character of the first three rings. Since the anellation in this type of alkaloids is angular when the number of the rings is increased, an indolo-quinolizidine structure of the next ring was inferred. This assumption was proved also by the negative results of the Emde and Braun degradations.

Conclusive evidence for the character of the fifth ring in vincamine (I) was afforded by the Curtius degradation of its hydrazide (II), and the vincaminic acid hydrazide was prepared with 80% aqueous hydrazin hydrate, to give a compound of the empirical formula $C_{20}H_{26}O_2N_4$ (assay 100,8%, by iodometric titration). This hydrazide was treated at 0° in acetic acid-benzene solution with sodium nitrite to yield the azide, then

[23] G. Hahn, E. Kappes, H. Ludewig, Ann. d. Chem. 67, 686 (1935).

it was gently warmed and decomposed with dilute aqueous sodium carbonate solution (IV), resulting in the formation of the antipode of eburnamonine, called vincamone (V) by Mokry[16], m.p. 168-170°, $[\alpha]_D^{25}$ -102° (in $CHCl_3$). The product is identical with the compound described by Trojanek[14] and with eburnamonine[20](IX). ($\lambda_{max.}$ in mμ (log ε): 205 (4,28); 240 (4,16); 265 (3,90); 290 (3,59); 300 (3,57); $\lambda_{min.}$ 220 (3,87); 255 (3,88); 285 (3,55); 295 (3,56).) (Found: C, 76,75; H, 7,47; N, 9,80; Calc. for $C_{19}H_{22}ON_2$; C, 77,5; H, 7,70; N, 9,53; O, 5,44.)

The same reaction was carried out also with apovincamine (VI). Apovincaminic acid hydrazide (VII) was prepared with concentrated hydrazine hydrate (assay: 95%, by iodometric titration), it was converted into the azide (VIII), and the latter decomposed to afford vincamone as indicated in Fig. 1.

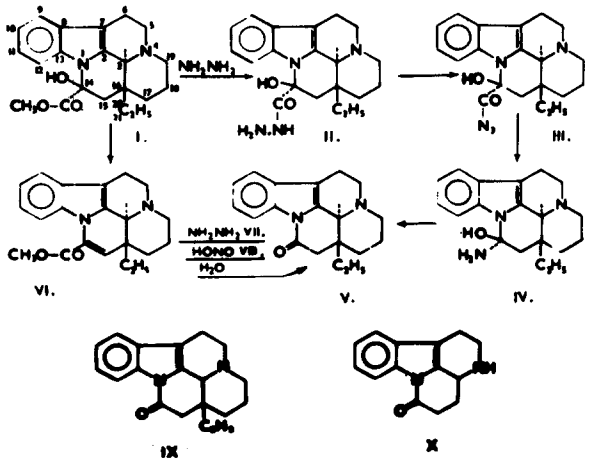

FIG. 1

In order to prove the structure of vincamone by the aid of its u.v. spectrum, hexahydrocanthinone[24] (X) was synthesized. This compound

[24] Hahn and Hansel, Ber. d. Deutsch. Ges. 71, 2163 (1938).

completely contains the ring system which determines the character of the u.v. spectrum. The maxima in the spectra of both compounds were at the same wavelengths, the only difference being in that the maxima of the former compound were a little higher (hexahydrocanthinone $\lambda_{max.}$ in mμ (log ε): 205 (4,36); 240 (4,39); 290 (3,75); 300 (3,76); $\lambda_{min.}$ 220 (4,02); 255 (3,88); 285 (3,67); 295 (3,72).

Concerning the configuration of vincamine, Trojanek et al.[14] stated that as indicated by the optical rotation of the product of the acid hydrolysis, it may be regarded as the antipode of eburnamonine.

Calculations have been made in this laboratory on the analogy of published methods[25] in order to determine the relative configuration of the $C_{(3)}$ carbon atom of vincamine, py-tetradehydrovincamine and vincamone, based on data of molecular rotatory power. In the case of vincamine, if the stable conformation of the two nitrogen atoms is provisionally left out of consideration, three asymmetric centres are found, namely $C_{(3)}$, $C_{(14)}$ and $C_{(16)}$. The optical rotation was determined in each case in chloroform. The following values were found:

Vincamine	$C_3 + C_{14} + C_{16}$	$M_D = -22^o$
Py-tetradehydrovincamine	$C_{14} + C_{16}$	$M_D = +452^o$
	$- C_3$	$\Delta = -375^o$

During an investigation of the absolute configuration of alkaloids having the yohimbine ring system, Klyne[26] always found laevorotatory power when the configuration of the $C_{(3)}$ atom was determined from the rotation of the alkaloid and the corresponding tetradehydro-derivative, e.g. yohimbane -606° (in $CHCl_3$); yohimbine -636° (in EtOH-AcOH), alloyohimbine -690° (in $CHCl_3$); accordingly, the above results indicate that the configuration of the C_3

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26 W. Klyne, Chem. Industry, 1198 (1954).

atom of vincamine and thus the anellation of its ring system here belongs to the type of yohimbane skeleton.

In vincamone, the asymmetric centre C_{14} is missing, $M_D = -299^o$. Since the Curtius degradation leaves the configuration of the optically active centres unaffected, and no racemization is caused by the reaction, the optical behaviour of this compound is again an indication of the high laevorotatory power of the asymmetric centre at C_3 which also supports our above suggestions concerning the configuration.

Based on the above result, the following stereochemical formula is suggested for vincamine:

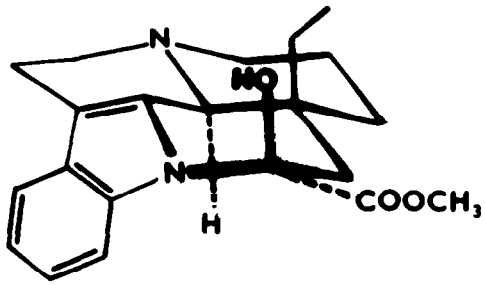

FIG. 2.

The high dextrorotatory power of apovincamine is intended to be dealt with in a later paper.