

TABLE I

Mass found	Error ^a	Composition	Elements lost ^b
Vinblastine (I)			
838.4538	+2.4	C ₄₈ H ₆₂ N ₄ O ₉ ^c	
824.4372	+1.2	C ₄₇ H ₆₀ N ₄ O ₉ ^d	
811.4234	-0.3	C ₄₅ ¹³ CH ₅₈ N ₄ O ₉	
810.4219	+1.5	C ₄₆ H ₅₈ N ₄ O ₉	
752.4153	+0.4	C ₄₄ H ₅₆ N ₄ O ₇	C ₂ H ₂ O ₂
751.4080	+1.0	C ₄₄ H ₅₆ N ₄ O ₇	C ₂ H ₃ O ₂
750.4014	+2.2	C ₄₄ H ₅₄ N ₄ O ₇	C ₂ H ₄ O ₂
651.3906	-0.5	C ₄₀ H ₅₁ N ₄ O ₄	C ₆ H ₇ O ₅
650.3858	+2.6	C ₄₀ H ₅₀ N ₄ O ₄	C ₆ H ₈ O ₅
591.3723	+2.6	C ₃₈ H ₄₇ N ₄ O ₂	C ₈ H ₉ O ₇
154.1219	-1.3	C ₉ H ₁₆ NO	C ₃₇ H ₄₂ N ₃ O ₈
VLB hydrazide (II)			
711.4198	+1.1	C ₄₀ ¹³ CH ₅₄ N ₆ O ₅	
710.4126	-2.7	C ₄₁ H ₅₄ N ₆ O ₅	
651.3880	-2.8	C ₄₀ H ₅₁ N ₄ O ₄	CH ₃ N ₂ O
593.3841	-1.2	C ₃₈ H ₄₉ N ₄ O ₂	C ₂ H ₅ N ₂ O ₃
592.3775	-4.5	C ₃₈ H ₄₈ N ₄ O ₂	C ₂ H ₆ N ₂ O ₃
509.2711	+3.4	C ₃₂ H ₃₅ N ₃ O ₃	C ₉ H ₁₉ N ₃ O ₂
154.1232	+0.5	C ₉ H ₁₆ NO	C ₃₂ H ₃₆ N ₃ O ₄

^a Difference in millimass units between mass found and value calculated for the elemental composition in the third column (¹²C = 12.000000). ^b From mass 810 in case of I. ^c Dimethylation product. ^d Monomethylation product.

heating of compact sample) only mass 838 and no. 810 was observed.

Thus, the composition of VLB is C₄₆H₅₈N₄O₉ and the species of higher mass are most likely produced by methyl transfer from the CO₂CH₃ groups of one molecule to the nitrogen atom(s) of another followed by a Hofmann-type elimination,¹⁰ a hypothesis strengthened by the simultaneous increase of M - C₂H₂O₂ corresponding to the decarbomethoxylation product of one of the methylating molecules.

Aside from the expected elimination of CO₂CH₃ and/or OCOCH₃ and CH₃COOH, loss of C₆H₈O₅, *i.e.*, a highly oxygenated site in the molecule, is of interest. It represents the C-3, C-4 bridge analogous to the fragmentation observed with vindoline and its degradation products.¹¹ Without determining the elemental composition of the resulting ion, the loss of 160 mass units from VLB would also be compatible with many other processes.

Because of the thermal lability of VLB, we have determined also the masses of many peaks of the hydrazide II (which lacks the transmethylating carbomethoxy groups), some of which are listed in Table I. Particularly informative is the ion (592) which corresponds to the loss of C₃H₆N₂O₃, a unique combination that must contain the hydrazido group (CH₃N₂O) and two oxygen functions within two carbon atoms. This single piece of evidence requires that (i) the hydrazido group is in the highly oxygenated part, *i.e.*, at the C-3, C-4 bridge of the vindoline portion; (ii) the carbomethoxy group is thus lost from the velbanamine portion, only possible chemically if located at C-18' or C-8'; (iii) the acetoxy group is in fact located at C-4 rather than in the velbanamine moiety as VLB loses five oxygen atoms with this bridge (see discussion above). This corroborates the independent conclusions based on chemical evidence⁵ and n.m.r.⁷ and demonstrates that a high

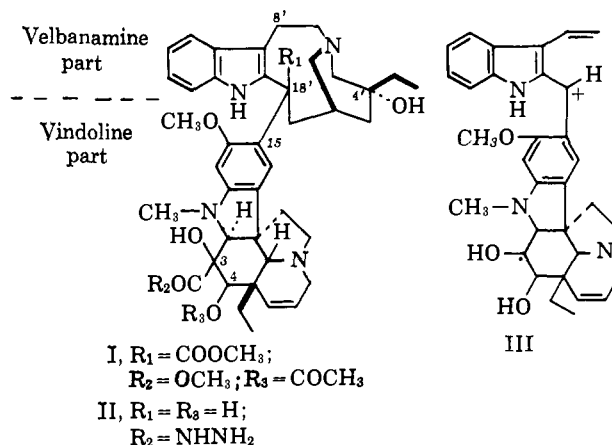
(11) M. Gorman, N. Neuss, and K. Biemann, *J. Am. Chem. Soc.*, **84**, 1058 (1962); K. Biemann, *Ind. Chim. Belge.*, 1319 (1962).

resolution mass spectrum requiring much less time and material leads to the same results.

Additional information regarding the attachment of the two parts of the VLB molecule requires fragments of medium size representing the aromatic moiety of vindoline and either the indole or the piperidine part of velbanamine. Such a peak is found at *m/e* = 509 in the spectrum of II and is in agreement with structure III for this ion as its high oxygen content requires the presence of part of the alicyclic moiety of vindoline with the exception of the hydrazido group (only three nitrogens), and its low hydrogen content eliminates the presence of the piperidine part of velbanamine.

The fragment of mass 154 (C₉H₁₆NO), most abundant in velbanamine and thought to represent the piperidine portion with C-1' and C-7',⁵ is present also in the spectra of I and II, making attachment of an aromatic ring to that region highly improbable, and agrees with a C-15, C-18' or C-15, C-8' bond.

The results demonstrate not only that masses in the region of mass 850 can be measured with high accuracy using *simultaneous* photographic recording⁸ and that such data are particularly useful in the interpretation of



the spectrum of a compound containing a large number of different heteroatoms, but, more importantly, that erroneous mass spectrometric molecular weights can be obtained with substances of low volatility containing within the molecule both potential alkylating and alkylatable groups. High resolution data, carefully obtained⁸ and interpreted, can eliminate this difficulty.

(12) Recipient of a fellowship from the Stiftung für Stipendien auf dem Gebiete der Chemie (Switzerland).

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RECEIVED OCTOBER 21, 1963

Vinca Alkaloids. XXI.¹ The Structures of the Oncolytic Alkaloids Vinblastine (VLB) and Vincristine (VCR)²

Sir:

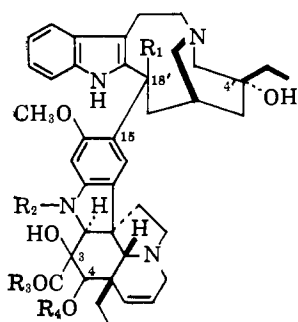
In an earlier communication³ partial formulas were suggested for VLB and VCR, two therapeutically use-

(1) Vinca XX: G. H. Svoboda, *Lloydia*, **26**, 243 (1963).

(2) These A.M.A. approved generic names refer to the alkaloids vincalubastine and leurocristine, respectively. VLB is supplied as VELBAN® (vinblastine sulfate, Lilly) and VCR as ONCOVIN® (vincristine sulfate, Lilly).

(3) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *J. Am. Chem. Soc.*, **84**, 1509 (1962).

ful antitumor alkaloids from *Vinca rosea* Linn. We wish to present further evidence which allows the assignment of structures I and II to these alkaloids.



- I, $R_1 = \text{COOCH}_3$; $R_2 = \text{CH}_3$;
 $R_3 = \text{OCH}_3$; $R_4 = \text{COCH}_3$;
 II, $R_1 = \text{COOCH}_3$; $R_2 = \text{CHO}$;
 $R_3 = \text{OCH}_3$; $R_4 = \text{COCH}_3$;
 III, $R_1 = R_4 = \text{H}$; $R_2 = \text{CH}_3$;
 $R_3 = \text{NHNH}_2$

Treatment of VLB with anhydrous hydrazine for 4 days at reflux temperature afforded a good yield of decarbomethoxydeacetyl-VLB monohydrazide (III), $\text{C}_{41}\text{H}_{54}\text{O}_5\text{N}_6$,⁴ m.p. 210–214°, $[\alpha]^{26\text{D}} + 40.8^\circ$ (CHCl_3). This transformation involved decarbomethoxylation⁶ at C-18', deacetylation at C-4, and acid hydrazide formation at C-3. As expected, the cleavage of the hydrazide III with aqueous hydrochloric acid in the presence of SnCl_2 and tin furnished velbanamine (IV)^{3,7} and deacetylvinoline hydrazide identical with an authentic specimen, m.p. 130–180° (solvate), $\text{C}_{22}\text{H}_{30}\text{O}_4\text{N}_4 \cdot 2\text{H}_2\text{O}$,⁴ $[\alpha]^{26\text{D}} + 18.6^\circ$ (CHCl_3), prepared from vindoline. The molecular formula of the hydrazide III and of VLB ($\text{C}_{46}\text{H}_{58}\text{O}_9\text{N}_4$)⁸ could not be rationalized with the previously proposed part structure but provided evidence for the tetracyclic nature of the indole moiety.

The indole portion of VLB contains a tertiary hydroxyl group which is retained in the degradation product velbanamine (IV).³ This function must occupy identical positions in both substances because upon cleavage in D_2O (*vide infra*) no deuterium was found to be present in the hydroxyl-bearing piperidine ring of deuteriovelbanamine prepared from VLB.

The mass spectrum of velbanamine (IV) had its most intense peak at $m/e = 154$ (VI)⁷ requiring the hydroxyl group to be situated in the alicyclic portion of the molecule but not at C-8 and C-18. Furthermore, the accurate mass of a characteristic fragment due to the loss of 57 mass units was determined⁹ to be 241.1709.

(4) Unless stated otherwise, satisfactory analyses and consistent mass spectral data were obtained for all compounds. Mass spectra were determined with a single focusing mass spectrometer (CEC 21-103C). We are indebted to Dr. B. Das and Mr. H. K. Schnoes for these spectra. The unequivocal elemental composition of III is described in the accompanying communication.⁵

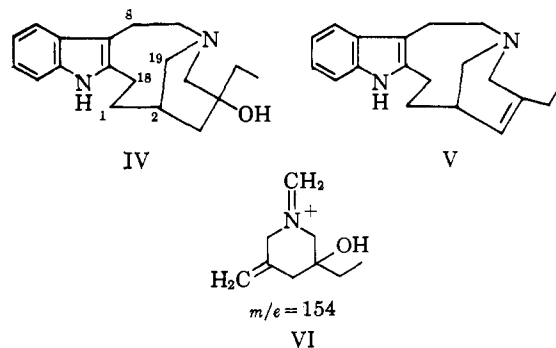
(5) P. Bommer, W. McMurray, and K. Biemann, *J. Am. Chem. Soc.*, **86**, 1439 (1964).

(6) U. Renner, D. A. Prins, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1572 (1959); N. Neuss and M. Gorman, *Tetrahedron Letters*, **6**, 206 (1961).

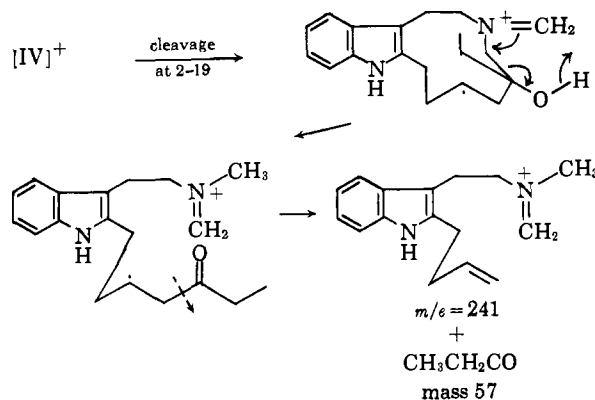
(7) M. Gorman and N. Neuss, *Ann. Chim. (Rome)*, **53**, 43 (1963). On further treatment under identical conditions, velbanamine (IV) gave a small amount of cleavamine (V) whose structure had been confirmed by X-ray analysis: J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind. (London)*, 648 (1963).

(8) This elemental composition was unequivocally established by high resolution mass spectrometry.⁵ The available analytical data (combustion and molecular weight determination from X-ray data) did not allow a differentiation between $\pm 2\text{H}$ or $\pm \text{CH}_2$.

(9) Determined with a double focusing mass spectrometer (CEC 21-110). The mass shown is that found for the monoisotopic species based on $^{12}\text{C} =$



This value corresponds to $\text{C}_{16}\text{H}_{21}\text{N}_2$ and indicates the elimination of $\text{C}_3\text{H}_5\text{O}$ which is in agreement with structure IV.

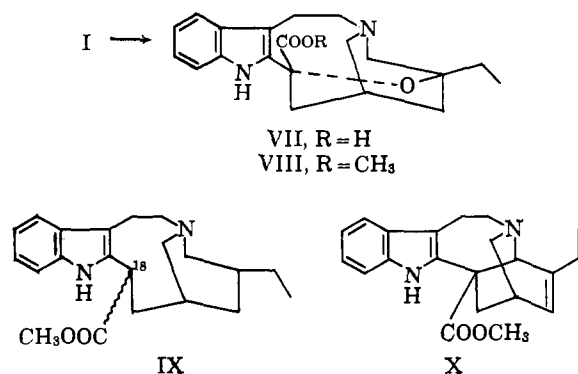


The shift of $m/e = 241$ in velbanamine to $m/e = 243$ in dideuteriovelbanamine ($\text{O}, \text{N}_a\text{-d}_2$, mol. wt. 300) corroborates this suggestion.

To establish finally the structure of VLB, the carbon-carbon bond linking C-15 of vindoline³ with the indole moiety had to be located. Cleavage of VLB in D_2O solution in the presence of DCl , SnCl_2 , and tin gave deuteriovelbanamine. Its mass spectrum⁴ (mol. wt. 304) showed absence of deuterium in the piperidine ring because the prominent peak remained at $m/e = 154$ as in undeuterated IV. Six deuterium atoms were located in a fragment of $m/e = 247$ corresponding to $m/e = 241$ in velbanamine itself. Four deuterium atoms are in the aromatic ring (n.m.r. evidence) while the remaining two must thus be at C-8 and/or C-18. Consequently, one of these two carbon atoms represents the vindoline terminus in VLB, and C-8 was eliminated as follows. Cleavage of VLB in boiling 40% aqueous sulfuric acid (2 hr.) in the absence of reducing agents afforded an amino acid VII which was esterified to the corresponding methyl ester VIII, $\text{C}_{21}\text{H}_{26}\text{O}_3\text{N}_2$ (mol. wt. 354),⁴ m.p. 129–132°, $[\alpha]^{26\text{D}} - 64.8^\circ$ (CHCl_3). The treatment of the ester with DCl in D_2O , SnCl_2 , and tin afforded deuteriovelbanamine whose mass spectrum was identical with that of a sample prepared analogously from VLB. Comparison of the n.m.r. spectrum of VIII with that of carbomethoxydihydrocleavamine (IX), $\text{C}_{21}\text{H}_{28}\text{O}_2\text{N}_2$ (mol. wt. 340),⁴ m.p. 164–166°, $[\alpha]^{26\text{D}} + 96^\circ$ (CHCl_3), obtained by the treatment of catharanthine (X) with Zn in acetic acid (4 hr., reflux) further supported structure VIII. The C-18 proton in the n.m.r. spectrum of the ester IX appeared as a multiplet centered at 4.0 δ which was absent in the spectrum of VIII.

12.0000. We are indebted to Drs. P. Bommer and W. McMurray for these determinations.

The formation of the ether VIII from VLB suggests that the C-4' ethyl group in VLB is β -oriented, and therefore the OH on the same carbon is *trans* to N_b of the indole moiety.



The stereochemistry at C-3, 4, and 18' is as yet uncertain. Our data are in agreement with structure I for VLB, and the known relationship³ between VLB and VCR requires the latter to be II. Another example of this type of alkaloid is provided by voacamine¹⁰ derived from *Voacanga* species (*Apocynaceae*).

(10) G. Büchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, **85**, 1893 (1963).

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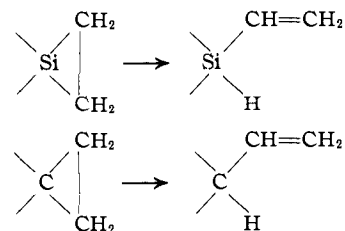
RECEIVED OCTOBER 21, 1963

Silacyclopropanes¹

Sir:

No successful synthesis of a three-ring compound with ring silicon has been reported.^{2,3} We have not succeeded in the isolation of a silacyclopropane. However, we have strong evidence that it was synthesized and that its thermal instability pre-empted success in isolation.

Silacyclopropanes appear to undergo rearrangement to vinylsilanes, analogous to the rearrangement of cyclopropane to propylene. The several routes employed for the synthesis of a silacyclopropane have

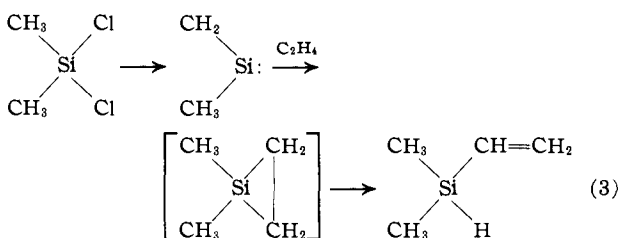
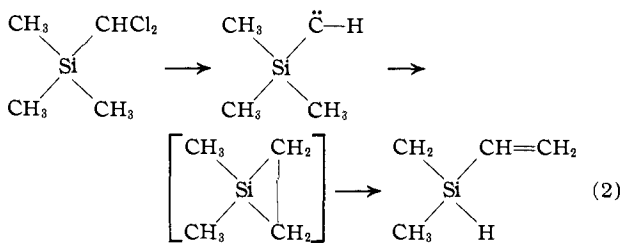
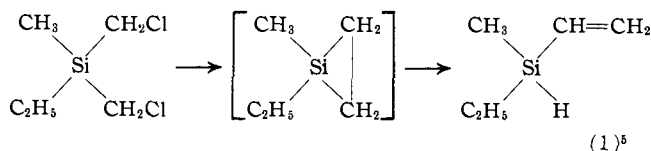


yielded vinylsilanes.⁴

All reactions were carried out by sweeping into an alkali metal vapor atmosphere (Na-K) a helium stream

(1) This work was supported by the National Science Foundation.
(2) F. Johnson and R. S. Gohlke, *Tetrahedron Letters*, 1291 (1962).
(3) R. West and R. E. Bailey, *J. Am. Chem. Soc.*, **85**, 2871 (1963).
(4) The assistance of Dr. A. Lee Smith, Dow Corning Corp., Midland, Mich., in providing authentic samples and infrared spectra for identification of the products isolated in this work is acknowledged with gratitude.

(200 mm.) carrying the organic halogen compound. Reaction temperatures of 260–280° were employed.



The first two reactions involve skeletal rearrangements which we can best rationalize by the assumption of a silacyclopropane intermediate. Although the third reaction can be rationalized as a dimethylsilene insertion on vinyl C-H, we prefer the mechanism as it is described above.

Unsuccessful efforts were made to trap the silacyclopropane intermediates by limiting residence time in the reaction zone to ~ 1 sec. and elapsed time in transference to the liquid nitrogen-cooled trap to ~ 10 sec. No vinylsilane precursor could be detected. A unimolecular decay of $t_{1/2} \leq 0.1$ sec. at 270° requires $E_{\text{act}} \leq 36$ kcal./mole (assuming $A = 10^{15.2}$ as observed for cyclopropane). This value approximates the E_{act} for a silacyclopropane thermolysis.

The large difference in thermal stability of cyclopropanes ($E_{\text{act}} \sim 60$ kcal./mole) and silacyclopropanes is attributed to strain, enhanced in the latter by the large size of the silicon atom, making the C-Si-C angle $\sim 48^\circ$.

(5) The analogous conversion of 1,3-dibromo-2,2-dimethylpropane to 1,1-dimethylcyclopropane occurs in good yield.

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Dimethylsilene: CH₃SiCH₃¹

Sir:

We wish to report the synthesis of dimethylsilene, CH₃SiCH₃, the silicon analog of a carbene, as a short-lived intermediate.

Dimethylsilene has been generated in the gas phase at temperatures between 260 and 280° by the reaction of sodium-potassium vapor with dimethyldichlorosilane. When the reaction is carried out in a helium atmosphere (200 mm.) most of the product is left in the reaction zone, probably as a polymer. However,

(1) This work was supported by the National Science Foundation.