Vinca ALKALOIDS

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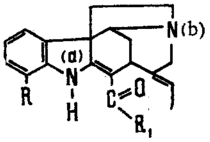
UDC 547.944/1

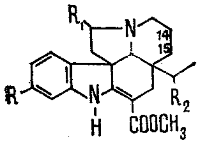
The plant Vinca (from the latin vincere – to conquer) is so called because of the evergreen leaves in many of its species [1]. Plants of the genus Vinca (periwinkle), belonging to the family Apocynaceae, are represented by 28 species [2], of which V. rosea, V. lanceus, and V. pusillus are assigned to the independent genus Catharanthus. A total of eight species of Vinca has been investigated; 45 alkaloids were isolated from V. minor, 21 from V. major, 61 from V. erecta, 22 from V. herbacea, 11 from V. libanotica, 7 from V. elegantissima, 5 from V. pubescens, and 9 from V. difformis. It must be mentioned that 32 bases are found in several species of Vinca, the most widespread proving to be vincamine, vincamajine, reserpinine, majdine, and isomajdine, these being found in 5 species, while eight bases appear in 3 species.

In sum, from the 28 species of Vinca that have been studied 117 alkaloids have been isolated (the structures of 13 bases have not yet been determined and they are therefore not given):

I. INDOLINE DERIVATIVES. α-METHYLENEINDOLINE ALKALOIDS



1. Vincanine	$R=R_1=H$	V. erecta [6], V. herbacea [2, 16]
2. (±)-Vincanine	$R=R_1=H$	V. erecta [35]
3. Vincanine N-oxide	$N_{(b)}\to O$	V. erecta [88]
4. Vincanidine	$R=OH;\ R_1=H$	V. erecta [34]
5. Vincanicine	$R=OCH_3;\ R_1=H$	V. erecta [35]
6. Akuammicine	$R=H;\ R_1=OCH_3$	V. erecta [87], V. major [11], V. herbacea [21]
7. Vinervine	$R=OH;\ R_1=OCH_3$	V. erecta [87]
8. Vinervinine	$R=R_1=OCH_3$	V. erecta [36]



9. (−)-Vincadifformine	$R=R_1=R_2=H$	V. erecta [89], V. minor [2]
10. Ervinidinine	$R=R_2=H;\ R_1=O$	V. erecta [43]
11. Methoxyvincadifformine	$R=OCH_3;\ R_1=R_2=H$	V. erecta [44], V. minor [101]
12. Methoxyvincadifformine N-oxide	$R=OCH_3;\ R_1=R_2=H;\ N_{(b)}\to O$	V. erecta [80]
13. Minovincinine	$R=R_1=H;\ R_2=OH$	V. minor [2]
14. Tabersonine	$R=R_1=R_2=H;\ \Delta^{14,\ 15}$	V. herbacea [2], V. libanotica [71]
15. Methoxytabersonine	$R=OCH_3;\ R_1=R_2=H_2;\ \Delta^{14,\ 15}$	V. erecta [90], V. herbacea [2]
16. Ervincinine	$R=OCH_3;\ R_1=O;\ R_2=H$	V. erecta [90]
17. (±)-Vincadifformine	$R=R_1=R_2=H$	V. minor [2], V. difformis [2]
18. Minovincine	$R=R_1=H;\ R_2=O$	V. minor [2]
19. Methoxyminovincine	$R=OCH_3;\ R_1=H;\ R_2=O$	V. minor [2]
20. N-Methylvincadifformine	$R=R_1=R_2=H;\ N_{(a)}-CH_3$	V. minor [2]
21. Methoxyminovincinine	$R=OCH_3;\ R_1=H;\ R_2=OH$	V. minor [2]
22. 5-Oxominovincine	$R=H;\ R_1=R_2=O$	V. minor [2]
23. Lochnerinine	$R=R_1=R_2=H;\ C_{14,\ 15}-O-$	V. herbacea [2]

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 597-617, September-October, 1977. Original article submitted May 6, 1977.

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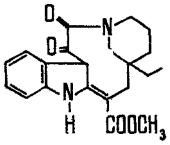
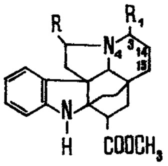
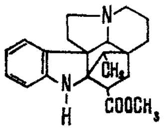
24. Ervinidine		V. erecta [43]

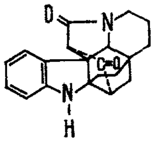
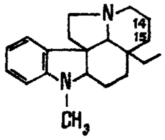
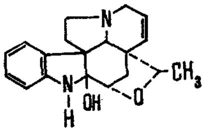
Indoline alkaloids

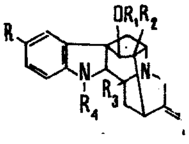


25. Kopsinine	$R=R_1=H$	V. erecta [93]
26. Kopsinine N-oxide	$R=R_1=H$, $N_{(b)}\rightarrow O$	V. erecta [94]
27. Kopsinilam	$R=O$; $R_1=H$	V. erecta [90]
28. 14,15-Epoxykopsinine	$R=R_1=H$; $C_{14,15}-O-$	V. erecta [91]
29. Venalstonine	$R=R_1=H$; $\Delta^{14,15}$	V. erecta [88], V. libanotica [71] V. herbacea [21]
30. 3-Oxodehydrokopsinine	$R=H$; $R_1=O$; $\Delta^{14,15}$	V. erecta [88]
31. 3-Oxodehydrokopsinine N-oxide	$R=H$; $R_1=O$; $N_{(b)}\rightarrow O$; $\Delta^{14,15}$	V. erecta [77]
32. Kopsinilamine	$R=O$; $R_1=H$; $N_{(b)}-OH$; $\Delta^{3,4}$ or $R=O$; $R_1=OH$.	V. erecta [92]



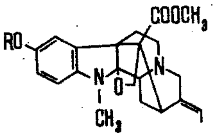
33. Pseudokopsinine		V. erecta [12]
34. Pseudokopsinine N-oxide	$N_{(b)}\rightarrow O$	V. erecta [94]
35. Pseudokopsinine hydroxymethylate	$N_{(b)}<^{CH_3}_{OH}$	V. erecta [95]

36. Kopsanone lactone 5		V. erecta [90]
37. N-Methylaspidospermidine 38. N-Methyl-$\Delta^{14,15}$-dehydroaspidospermidine		V. minor [2] V. herbacea [22]
39. Vincoline		V. libanotica [103]

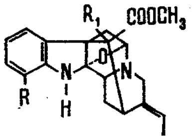


40. Vincarine	$R-R_1=R_3=R_4=H$; $R_2=COOCH_3$;	V. erecta [55] V. herbacea [19]
41. Majoridine	$R=OCH_3$; $R_1=Ac$; $R_2=R_3=H$; $R_4=CH_3$	V. major [13] V. pubescens [5], V. erecta [77]
42. Vincamajoreine	$R=OCH_3$; $R_1=R_2=R_3=H$; $R_4=CH_3$	V. major [15], V. elegantissima [102]

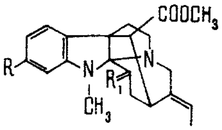
43. Vincamajine	$R=R_1=R_3=H$; $R_2=COOCH_3$; $R_4=CH_3$	V. major [15], V. difformis [2], V. pubescens [5], V. erecta, V. herbacea
44. Herbaline	$R=R_1=R_4=H$; $R_2=COOCH_3$; $R_3=OH$	V. herbacea [20], V. libanotica [57]
45. Herbamine	$R=R_1=H$; $R_2=COOCH_3$; $R_3=OH$; $R_4=CH_3$	V. herbacae [20], V. libanotica [58]
46. Quebrachidine	$R=R_1=R_3=R_4=H$; $R_2=COOCH_3$	V. libanotica [71]
47. Vincamedine	$R=R_3=H$; $R_1=Ac$; $R_2=COOCH_3$; $R_4=CH_3$	V. difformis [2], V. major [2], V. erecta



48. Akuammine	$R=H$	V. erecta [96], V. major [11], V. herbacea [16]
49. O-Methylakuammine	$R=CH_3$	V. erecta [91]

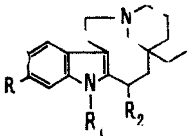


50. Picrinine	$R=R_1=H$	V. erecta [60], V. minor [107], V. libanotica [71]
51. Vincaricine	$R=OCH_3$; $R_1=H$	V. erecta [61]
52. Vincarinine	$R=OCH_3$; $R_1=CHO$	V. erecta [62]

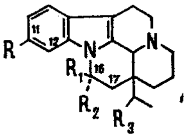


53. Vincoridine	$R=H$; $R_1=O$	V. minor [2]
54. Vincovine	$R=OCH_3$; $R_1=H$	V. minor [106]

II. Indole Derivatives

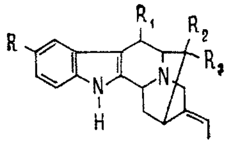


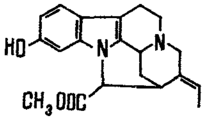
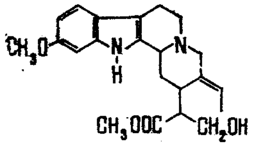
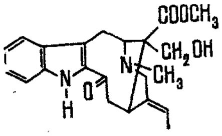
55. Quebrachamine	$R=R_1=R_2=H$	V, minor [2] V. erecta [90]
56. N-Methylquebrachamine	$R=R_2=H$; $R_1=CH_3$	V. minor [2]
57. Vincadine	$R=R_1=H$; $R_2=COOCH_3$	V. minor [2]
58. Vincaminoreine	$R=H$; $R_1=CH_3$; $R_2=COOCH_3$	V. minor [2]
59. Vincaminorine	$R=H$; $R_1=CH_3$; $R_2=COOCH_3$	V. minor [2]
60. Vincaminoridine	$R=OCH_3$; $R_1=CH_3$; $R_2=COOCH_3$	V. minor [2]

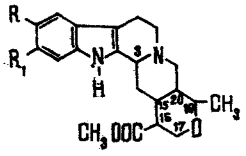


61. Vincamine	$R=R_3=H$; $R_1=OH$; $R_2=COOCH_3$	V. minor [66], V. erecta [93], V. difformis [2], V. major [2], V. herbacea [21]

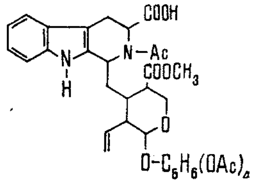
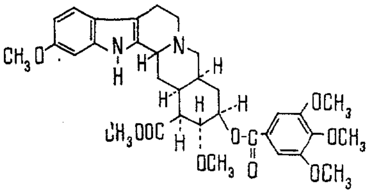
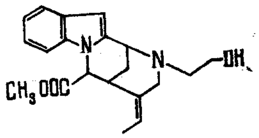
62. 16-Epivincamine	$R=R_3=H$; $R_1=COOCH_3$; $R_2=OH$	V. minor [2]
63. (±)-Eburnamonine	$R=R_3=H$; R_1, $R_2=O$	V. erecta [90], V. minor [2]
64. Vincine	$R=OCH_3$; $R_1=OH$; $R_2=COOCH_3$; $R_3=H$	V. erecta [79], V. minor [2]
65. (—)-Eburnamine	$R=R_1=R_3=H$; $R_2=OH$	V. erecta [90], V. minor [2]
66. (±)-Eburnamine	$R=R_1=R_3=H$; $R_2=OH$	V. erecta [90]
67. Apovincamine	$R=R_3=H$; $R_2=COOCH_3$; $\Delta^{16,17}$	V. erecta [90]
68. Eburnamenine	$R=R_3=H$; $R_1=H$; $\Delta^{16,17}$	V. minor [2]
69. (—)-Eburnamenine	$R=R_3=H$; R_1, $R_2=O$	V. minor [2]
70. (+)-Isoeburnamine	$R=R_2=R_3=H$; $R_1=OH$	V. minor [2]
71. 11-Methoxyburnamonine	$R=OCH_3$; R_1, $R_2=O$; $R_3=H$	V. minor [2]
72. 11, 12-Dimethyloxyeburnamonine	$R=OCH_3$; R_1, $R_2=O$; $R_3=H$	V. minor [2]
73. Vincaminine	$R=H$; $R_1=OH$; $R_2=COOCH_3$; $R_3=O$	V. minor [2]
74. Vincinine	$R=OCH_3$; R_1—OH; $R_2=COOCH_3$; $R_3=O$	V. minor [2]
75. Hydroxyvincamine	$R=H$; $R_1=R_3=OH$; $R_2=COOCH_3$	V. minor [2]



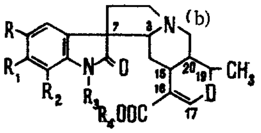
76. Tombozine	$R=R_1=R_2=H$; $R_3=CH_2OH$	V. erecta [90]
77. O-Benzoltombozine	$R=R_1=R_2=H$; $R_3=CH_2\ OCOC_6H_5$	V. erecta [94]
78. Ervincidine	$R_1=OH$; $R=R_2=H$; $R_3=CH_2OH$	V. erecta [97]
79. Akuammidine	$R_2=COOCH_3$; $R=R_1=H$; $R_3=CH_2OH$	V. erecta [90], V. difformis [2]
80. Lochnerine	$R=OCH_3$; $R_1=R_2=H$; $R_3=CH_2OH$	V. elegantissima [102]
81. Lochvinerine	$R=OCH_3$; $R_1=R_2=H$; $R_3=CH_2OH$	V. major [108]
82. Vellosimine	$R=OCH_3$; $R_1=R_2=H$; $R_3=CHO$	V. difformis [2]
83. 10-Methoxyvellosimine	$R=OCH_3$; $R_1=R_2=H$; $R_3=CHO$	V. minor [2], V. erecta
84. Sarpagine	$R=OH$; $R_1=R_2=H$; $R_3=CH_2OH$	V. difformis [2]
85. 11-Hydroxypleiocarpamine		V. erecta [73]
86. Hervine		V. herbacea [2, 72]
87. Vincadiffine		V. difformis [2]



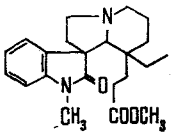
88. Reserpinine	$R=H$; $R_1=OCH_3$; $\Delta^{16,17}$	V. erecta [98], V. major [14], V. pubescens [3, 4], V. herbacea [2, 16, 17], V. libanotica [71]

89. Isoreserpiline	$R=R_1=OCH_3$; $\Delta^{16,17}$	V. erecta [30]
90. Ervine (rauniticine)	$R=R_1=H$; $\Delta^{16,17}$	V. erecta [67], V. major [15], V. libanotica [71]
91. Herbaine	$R=H$; $R_1=OCH_3$	V. herbacea [2, 99]
92. Herbaceine	$R=R_1=OCH_3$	V. herbacea [2, 99]
93. 5α-Carboxystrictosidine		V. elegantissima [109]
94. Reserpine		V. minor [9, 10]
95. Vinoxine		V. minor [2]

III. OXINDOLE DERIVATIVES

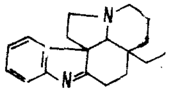


96. Carapanaubine	$R=R_1=OCH_3$; $R_2=R_3=H$; $R_4=CH_3$	V. pubescens [3, 4]
97. Vinerine	$R=R_2=R_3=H$; $R_1=OCH_3$; $R_4=CH_3$	V. erecta [74]
98. Vinerine N-oxide	$R=R_2=R_3=H$; $R_1=OCH_3$; $R_4=CH_3$; $N_{(b)}\rightarrow O$	V. erecta [77]
99. N-Acetylvinerine	$R=R_2=H$; $R_1=OCH_3$; $R_3=Ac$; $R_4=CH_3$	V. erecta [79]
100. Vineridine	$R=R_2=R_3=H$; $R_1=OCH_3$; $R_4=CH_3$	V. erecta [74]
101. Vineridine N-oxide	$R=R_2=R_3=H$; $R_1=OCH_3$; $R_4=CH_3$ $N_{(b)}\rightarrow O$	V. erecta [80]
102. Vinerine	$R=R_3=H$; $R_1=OCH_3$; $R_2=OH$; $R_4=CH_3$	V. erecta [83]
or	$R=R_3=H$; $R_1=OH$; $R_2=OCH_3$; $R_4=CH_3$	
103. Majdine	$R=R_3=H$; $R_1=R_2=OCH_3$; $R_4=CH_3$	V. major [11], V. herbacea [2, 18], V. erecta [80], V. pubescens [6], V. elegantissima [102]
104. Isomajdine	$R=R_3=H$; $R_1=R_2=OCH_3$; $R_4=CH_3$	V. major [14], V. pubescens [6], V. herbacea [2, 17], V. elegantissima [102]
105. Herboxine (elegantissine)	$R=R_3=H$; $R_1=R_2=OCH_3$; $R_4=CH_3$	V. herbacea [27], V. elegantissima [102]
106. 16-Carboxyherbavine	$R=R_3=H$; $R_1=R_2=OCH_3$; $R_4=H$	V. herbacea [100]
107. Isoelegantissine	$R=R_3=H$; $R_1=R_2=OCH_3$; $R_4=CH_3$	V. elegantissima [102]
107a. Herbaline	$R=R_1=OCH_3$; $R_2=R_3=H$; $R_4=CH_3$ (16, 17-dihydro)	V. herbacea [2]

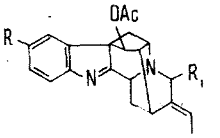


108. Vincatine		V. minor [2]

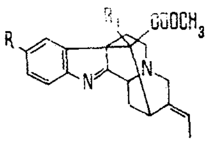
IV. 3H-INDOLE DERIVATIVES



109. Dehydroaspidospermide		V. erecta [90], V. minor [2]

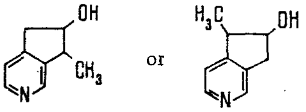


110. Vinorine	$R=R_1=H$	V. minor [104]
111. 10-Methoxyvinorine	$R=OCH_3$; $R_1=H$	V. erecta [85]
112. Majorinine	$R=OCH_3$; $R_1=OH$	V. major [15]

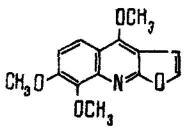


113. 10-Methoxydeacetylakuammiline	$R=OCH_3$; $R_1=CH_2OH$	V. minor [105]
114. Deacetylakuammiline	$R=H$; $R_1=CH_2OH$	V. minor [105]
115. Vincamidine	$R=R_1=H$	V. minor [2], V. libanotica [71]

OTHER ALKALOIDS



116. Monoterpenoid alkaloid		V. major [32]



117. Skimmianine		V. erecta [31], V. herbacea [31]

Five species of Vinca grow on the territory of the USSR. The chemical study of these plants was begun by A. B. Orekhov and his colleagues in the 1930's. They showed that the plant V. minor collected at the Lubenskaya Experimental Station (Ukraine) contains a considerable amount of alkaloids and from the epigeal part of V. pubescens growing in the region of Gagra they isolated reserpine and carapanaubine [3, 4]. Subsequently, majoridine, majdine, and isomajdine were isolated from the epigeal part of the plant cultivated in Tbilisi [5, 6].

Only two alkaloids – vincamine [7, 8] and reserpine [9, 10] – have been isolated from V. minor growing in the Ukraine and in the environs of Moscow.

V. major is an evergreen decorative plant. Its epigeal part collected in Tashkent at Tbilisi has been studied chemically. Akumamine, reserpinine, ervine, majdine, isomajdine, vincamajine, vincamajoreine, majorinine, majoridine, and akuammicine were isolated [11-15].

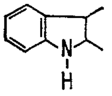
Intensive investigations of the alkaloids of the roots and epigeal part of *V. herbacea* growing in Georgia and Azerbaidzhan are being performed: 20 bases have been isolated [16-27].

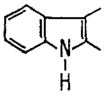
Vinca erecta Rgl. et Schmalh. is a perennial plant which is widely distributed in the mountain and foothill regions of Central Asia [28]. Investigations have shown that while the qualitative composition of the combined alkaloids of its roots (vincanine, vincanidine) does not vary appreciably with a change in its growth site and with the vegetation period, the pattern is different in the epigeal part of the plant. The alkaloids isolated in greatest amount from *V. erecta* collected in the Fergana oblast (kopsinine, *l*-vincadifformine), the Osh oblast of the KirgSSR (pseudokopsinine), the Tashkent oblast (the hydroxyindole bases vinerine and vineridine), and the Surkhandar'ya oblast of the UzbekSSR (the phenolic alkaloid vinervine), and at Sagir-Dashte, TadzhSSR (11-hydroxypleiocarpamine, vincamine) proved to be different and with different structures. In this respect, *V. erecta* is a clear example confirming the law pronounced by S. Yu. Yunusov previously that each plant organ may contain qualitatively and quantitatively different alkaloids according to the growth site and the vegatation period and may be considered as an independent object of investigation [29].

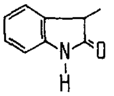
From this plant alone, with the aid of modern methods of separation (different solubilities of the bases and their salts, countercurrent distribution according to basicity, ion-exchange resins, and column, thin-layer, and paper chromatography), 30 known and 31 new alkaloids have been obtained, including 7 oxides, d,*l*-vincanine, d,*l*-eburnamonine, and d,*l*-eburnamine [30].

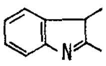
Thus, 75 alkaloids have been isolated from plants of the genus *Vinca* growing in the territory of the USSR.

The *Vinca* alkaloids are derivatives of indoline, indole, hydroxyindole, and 3H-indole.









The indole derivatives include the nucleus of ajmaline – 8 alkaloids; that of akuammine-picrinine – 7 alkaloids; that of aspidospermine-kopsinine – 31 alkaloids; and that of akuammicine – 8 alkaloids. The last two groups are subdivided according to their chromophoric system into derivatives of indole (30 alkaloids) and of α-methyleneindoline (24 alkaloids).

The indole derivatives are the most diverse in structure and contain the heterocyclic rings of quebrachamine – 6 alkaloids; of vincamine – 15 alkaloids; of tombozine-pleiocarpamine – 12 alkaloids; of heteryohimbane – 6 alkaloids; and of yohimbane (reserpine). 5α-Carboxystrictosidine and vinoxine are somewhat unusual and have no structural analogs.

Except for vincatine, all 12 hydroxyindole alkaloids are structural analogs of carapanaubine. Vincatine is the only hydroxyindole alkaloid containing the heterocyclic skeleton of aspidospermidine.

3H-Indole derivatives are few in number and are represented by bases containing the nuclei of aspidospermidine, ajmaline, and picrinine.

Skimmianine (117) and another, unnamed, monoterpenoid alkaloid (116) are the first representatives of the furanoquinoline and pyridine bases detected in plants of the genus *Vinca.* Both physical (IR, UV, NMR, and mass spectra, ORD, X-ray structural analysis, etc.) and also chemical methods of investigation have been used to identify and prove the structure of the alkaloids found.

Indole Derivatives

α-Methyleneindoline Alkaloids. Alkaloids of this type have, in the α position to the indoline nitrogen atom, N_a, a double bond conjugated with a carbonyl group: in vincanine (1) [33], vincanidine (4) [34], and vincanicine (5) [35] the double bond is conjugated with an aldehydic carbonyl group and in vinervine (7) [34] and vinervinine (8) [36] it is conjugated with an ester carbonyl group. While the UV spectra of compounds containing an aldehyde group absorb at 240-245, 290-300, and 365-375 nm, the UV spectra of bases having $COOCH_3$ in place of CHO show absorption maxima in the 225-235, 290-300, and 330-335 nm regions. All the compounds mentioned are derivatives of akuammicine (6) and contain a heterocyclic skeleton which includes 18 carbon atoms.

Another group of α-methyleneindole alkaloids contains the heterocyclic skeleton of vincadifformine (9) (including 19 carbon atoms).

The conjugated double bond at C_2-C_{16} is readily reduced by zinc in sulfuric acid and by sodium tetrahydroborate with the formation of the corresponding indoline basis – 2,16-dihydro derivatives. The ethylidine double bond characteristic for the akuammicine group is not affected under these conditions.

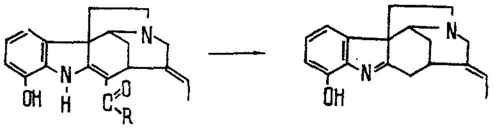
On being heated with hydrochloric acid in a sealed tube [34], vincanidine and vinervine form one and the same 3H-indole base (I).

To prove the structure of vinervine, passage through akuammicine was effected by eliminating the phenolic hydroxyl of vinervine.

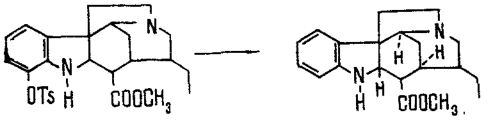
Reduction of the tosyl ester of tetrahydrovinervine (II) in the presence of Raney nickel catalyst gave tetrahydroakuammicine (III) [37].

Vincanine (1), on reduction with sodium in ethanol, forms two products [33]; tetrahydrovincanine $C_{19}H_{24}N_2O$ and deoxytetrahydrovincanine $C_{19}H_{24}N_2$. Tetrahydrovincanine proved to be identical with the 18-deoxy derivative of the Wieland–Gumlich glycol (IV), which is a product of the decomposition of strychnine [38]. On this basis, the structure of norfluorocurarine has been proposed for this base [39].

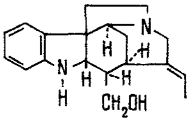
By performing mutual transitions it has been shown that the OH and OCH_3 groups of vincanidine, vincanicine, vinervine, and vinervinine occupy the same positions. As the result of a study of the chemical shifts and spin–spin coupling constants of the signals of the aromatic protons in the NMR spectra of vinervinine and its dihydro and N-acetyldihydro derivatives it has been established tha the OCH_3 group in it is located at C_{12}. Consequently, in vinervine, vincanidine, and vincanicine the OH and OCH_3 groups likewise occupy the C_{12} position in the aromatic ring [40].



(4) R=H (7) R=OCH$_3$ I



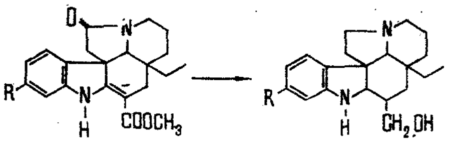
II III



IV

The chemical properties and spectral methods of proving the structure of the α-methyleneindoline alkaloids of the vincadifformine type are similar to those for the akuammicine group. Ervinidinine (10) and ervincinine (16) are new vincadifformine derivatives [41].

The mass spectrum of ervinidinine has the peaks of ions with m/e 352 (M^+), 320 $(M - CH_3OH)^+$, 214 $(M - 138)^+$, and 138. The maximum peak with m/e 214 shows that (10) belongs to alkaloids of the vincadifformine type and the third oxygen in the base may be present in the piperidine or the pyrrolidine ring. The IR spectra of (10) and its 2,16-dihydro derivative contain a band that is characteristic for a lactam carbonyl group and, consequently, it may be present at C_3 or C_5. The magnitude of the absorption of the –N–CO group in dihydroervinidinine (1675 cm^{-1}) showed that the CO group is present at C_5 of the pyrrolidine ring [42], and ervinidine has the structure of 5-oxovincadifformine. This was confirmed by the formation of vincadifforminol (V) when (10) was reduced with lithium tetrahydroaluminate [43].



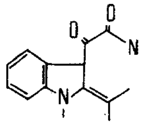
(10) R=H; (16)R=OCH$_3$ V R=H

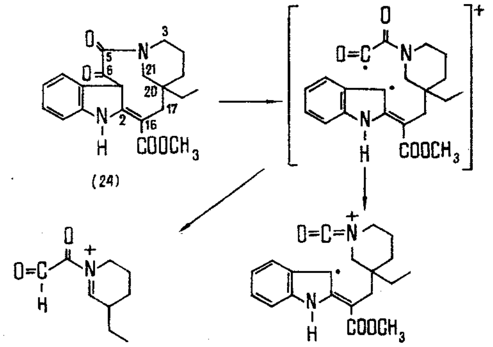
Ervincinine is a methoxy derivative of ervinidinine and, since the IR spectrum of the base shows the presence of a 1,2,4-substituted benzene ring, the methoxy group may be in the C_{10} or C_{11} position.

According to its NMR spectrum, the methoxy group is located at C_{11} [44] and, thus, ervincinine has the structure of 11-methoxyervinidinine [45].

The UV spectrum of ervinidine (24) is similar to those of vincadifformine and ervinidinine, and the IR spectrum differs from the spectrum of (10) by the presence of the absorption band of a ketonic carbonyl group.

The mass spectrum of the base contains the peaks with m/e 368 (M^+) 340 $(M-28)^+$, 228, 214, 168, and 154. The appearance of a strong peak with m/e 340 $(M-28)^+$ shows that in the base the ketonic carbonyl group is possibly attached directly to a lactam carbonyl, i.e., ervinidine contains the grouping (a). Then ervinidine will have a structure very close to that of ervinidinine. In the mass spectrometry of ervinidine, the C_6-C_7 bond is first cleaved, and then carbon monoxide is split out and an ion with m/e 340 is formed, and a strong peak of an ion with m/e 168 apparently arises as the result of the cleavage of the $C_{17}-C_{20}$ bond.


(a)


(24)

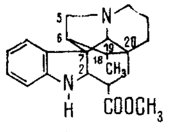
m/e 168

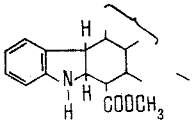
m/e 340

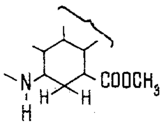
The reduction of ervinidine with lithium tetrahydroaluminate forms a mixture of substances with mol. wt. 326, 324, and 312 (mass spectrometrically). The substance with mol. wt. 312 is identical with (V) according to its R_f values and mass spectrum [43]. The results given show that ervinidine has the structure (24) which is very close, on the one hand, to vincadine [47] and, on the other hand, to ervinidinine [43].

Indoline Alkaloids. For the indoline bases, in which the conjugated double bond at C_2-C_{16} is lacking, the presence of two absorption maxima in the UV spectra in the 245-250 and 295-310 nm regions is characteristic. One of the indoline alkaloids present in V. erecta – pseudokopsinine (33) – contains the heterocyclic skeleton of kopsinine. Its IR spectrum has the absorption bands of a secondary nitrogen atom, an ester carbonyl, and a disubstituted benzene ring. The NMR spectra of kopsinine and pseudokopsinine differ mainly by the presence in the latter of the signal of a $-CH-CH_3$ methyl group (0.82 ppm, doublet).

Chemical properties, and also NMR and mass spectra, have shown that pseudokopsinine belongs to alkaloids having a hexacyclic structure of the type of vindolinine [48] and tuboxenine [49], and structure (VI) in which the C_{19} methylene bridge connectes carbon atoms C_6 and C_{20} has been proposed for it [12]. However, in the spectrum of its N-acetyl derivatives, unlike that of pseudokopsinine, there is a one-proton quartet at 5.34 ppm, $J_1 = 12.0$ Hz, $J_2 = 6.0$ Hz, the nature of the splitting of which shows that it belongs to a proton interacting with two neighboring vicinal protons. From its chemical shift, the quartet may be assigned either to the signal of C_2H, when formulas VII and VIII are possible or to the signal of $C_{16}H$, when structure (33) is possible.


VI

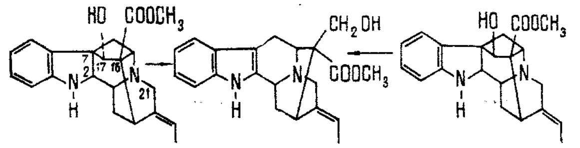

VII


VIII

The results of an x-ray structural investigation have shown the (−)-pseudokopsinine has formula (33) in which the C_{19} methylene bridge connects the C_2 and C_{20} atoms [50].

It must be mentioned that, in spite of the analogous absolute configuration for vindolinine [51, 52], the question of the stereochemical interrelationship of pseudokopsinine and 14,15-dihydrovindolinine remains open, since the chemical properties of these compounds differ considerably [48].

Continuing an investigation of the alkaloids of V. erecta, for various organs of the plant a number of bases have been isolated which consist of dehydro, oxo, hydroxy, epoxy, N-oxide, and quaternary derivatives of kopsinine and of pseudokopsinine. The detection of such structural analogs of the indoline bases is appparently the consequence of the participation of the alkaloids in redox processes taking place in the plant organism [53, 54]. According to chemical properties and spectral results, vincarine (40) [55] is a stereoisomer of quebrachidine (46) [56]. On oxidation with lead tetraacetate followed by reduction with sodium tetrahydroborate these two bases give one and the same product, polyneuridine (IX).



(40) IX (46)

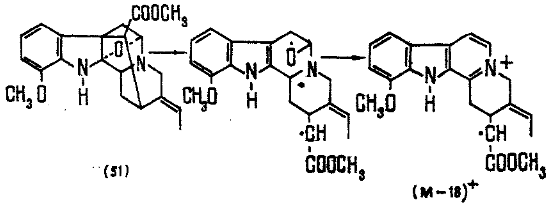
Consequently, (40) and (46) differ from one another by the mutual positions of the functional groups at C_{16} or C_{17}.

In quebrachidine the methoxycarbonyl and hydroxy groups are in the cis position [56]. If it is borne in mind that on passing from (40) and (46) to polyneuridine only the cleavage of the C_7-C_{17} bond takes place, vincarine must differ from quebrachidine by the configuration at C_{17} and have the structure of 17-epiquebrachidine.

In the structure of herbadine (44) and herbamine (45) proposed previously, the positions of the two hydroxy groups (C_2 and C_{21}) were shown only provisionally [20]. Subsequently, these bases were also found in the plant V. libanotica. Comparative investigations of the NMR and high-resolution mass spectra have shown that in (44) and (45) the OH groups occupy the C_3 and C_{17} positions [57, 58].

Vincaricine and vincarinine are structural analogs of picrinine. The main heterocyclic nucleus of these compounds, like that of the alkaloids vincanine and akuammicine, includes 18 carbon atoms.

The mass spectrum of vincaricine (51) has strong peaks of ions with m/e 366 (M^+), 350 $(M-18)^+$, and 269. The peak of the ion with m/e 269 is formed by the elimination of CO plus a $C-COOCH_3$ group [59], and the probable mechanism of the formation of the maximum peak of the ion with m/e 350 can be represented in the following way:



(51) $(M-18)^+$

Since the absorption band of a 1,2,3-trisubstituted benzene ring was observed in the IR spectrum of vincaricine and the NMR and mass spectra showed the presence of an OCH_3 group, the hypothesis has been put forward that the base has the structure of C_9-OCH_3- or $C_{12}-OCH_3$-picrinine. The features of the NMR spectrum of vincaricine in the region of aromatic protons showed that position 12 is the most probable, and therefore the structure of 12-methoxypicrinine has been proposed for it [60, 61].

A comparative investigation has shown that another indoline alkaloid – vincarinine (52) – has the structure of 16-formylvincaricine [62].

Thus, picrinine, vincaricine, and vincarinine, which have been found in V. erecta, are tetrahydrofuranoindoline bases.

On the basis of transitions from picrinine to nor-C-fluorocurarine (vincanine) [63] and from deacetylakuammiline to akuammicine [64], and also of the isolation from V. erecta of the alkaloids picrinine, vincaricine, and vincarinine, together with alkaloids of the vincanine and akuammicine group, it has been concluded that the latter are possibly formed from their biogenetic precursors picrinine and vincadinine [65]. In view of this, we considered it desirable to check the position of substitution of the HO and OCH_3 groups in the aromatic rings of vincanidine [34], vincanidine [35], vinervine [34], and vinervinine [36]. As was found, in actual fact in these alkaloids the substituting groups occupy position C_{12} [40] as in vincaricine and vincarinine.

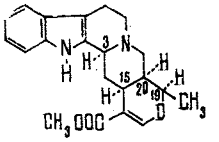
Indole Derivatives

The alkaloids quebrechinine and vincamine are the parents of the corresponding group of indole derivatives, which were first isolated from V. minor, while vincamine was one of the first alkaloids found in plants of the genus Vinca [66]. Reserpine is the single alkaloid of the yohimbane derivatives and has been isolated only from V. minor [9, 10].

While alkaloids of the quebrachamine and vincamine type contain a C-ethyl side chain, the main tombozine-pleiocarpamine group contains an ethylidene side chain. The heteroyohimbane bases contain the pyran ring E with a $C-CH_3$ side chain.

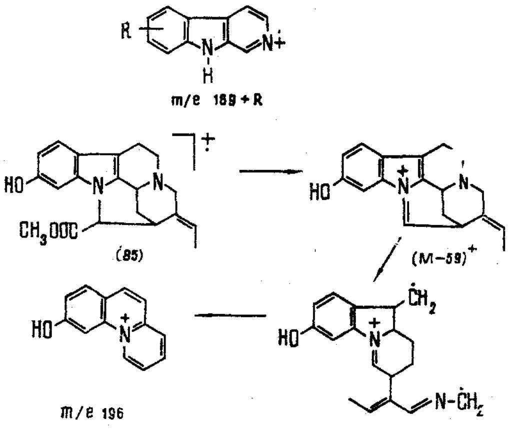
Indole derivatives show absorption maxima in the UV region at about 224-226, 240-245, and 280-290 nm.

Spectral characteristics and chemical properties show that ervine (90) belongs to the alkaloids of the heteroyohimbane group and is possibly a stereoisomer of ajmalicine or of tetrahydroalstonine, and therefore the determination of the structure of ervine reduces to determining the absolute configuration of the substituents at C_3, C_{15}, C_{19}, and C_{20}.



(90)

The results of a comparative investigation of the NMR and mass spectra and some chemical properties of ervine have shown that in the base rings C/D are trans-linked and D/E cis-linked, and the $C_{19}-CH_3$ group has the βaxial configuration [67]. It must be observed that a similar structure has also been proposed for raumiticine [68], but the melting points and specific rotations of raumiticine [69] and ervine [70] differed strongly, which did not permit the identity of these substances to be assumed.



Recently, corrections have been made in the constants of raunitiçine given above [71] and they now coincide with those for ervine. Another indole alkaloid – hervine (86) – has been isolated only from V. herbacea [72], and it may be considered as a biogenetic precursor of several groups of bases. This alkaloid will apparently be found in other species of Vinca, as well. 11-Hydroxypleiocarpamine (85) is also similar in structure to hervine.

Its structure has been shown on the basis of spectral characteristics and chemical transformations. A characteristic feature of 11-hydroxypleiocarpamine is its peculiar mechanism of fragmentation on mass spectrometry. Together with a β-carbonyl ion having m/e 169 + R, stable ions corresponding to $(M - COOCH_3)^+$ and to m/e 196 are formed. The probable mechanism for the fragmentation of hydroxypleiocarpamine is shown above [73].

Oxindole Derivatives

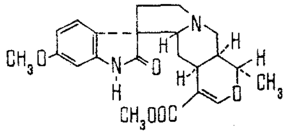
The oxindole alkaloids contain the heterocyclic system of spiro[pyrrolidine-7,7'-oxindole] and are structurally close to the alkaloids of the heteroyohimbane group.

The chemical properties and many of the transformations of the oxindole alkaloids are explained by the high reactivity of the substituent at C_7. Their UV spectra show one characteristic absorption maximum in the range of 220-230 nm and a small inflexion at 275-290 nm.

The oxindole bases found in plants of the genus Vinca are structural analogs of carapanaubine and differ by the nature and positions of the substituents and also by the configurations at the C_3, C_{15}, C_{19}, and C_{20} asymmetric centers. In addition, depending on the spatial position of the substituents at C_7, they may be found in the form of two pairs of spiroisomers, such as majdine-isomajdine [12, 14, 17], vinerine–vineridine [74], etc.

Spectral characteristics have shown that vinerine and vineridine are isomeric compounds, and on being heated in pryidine or acid solution they may be converted into one another. In the process of the mutual transformations of these compounds the β-aminolactam group is involved, with the opening and rearrangement of the C_3-C_7 bond, which is characteristic for pairs of spiroisomeric oxindole alkaloids [75].

The combination of chemical properties and the characteristics of the circular dichroism and NMR spectra have permitted the conclusion that vinerine (97) and vineridine (100) are oxindole derivatives of heteroyohimbane. Their absolute configurations have been established [76]: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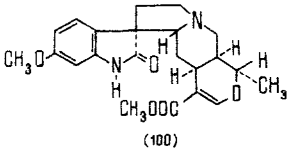
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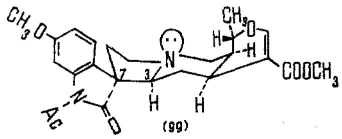

(99)

When vinerine is heated in 10% acetic acid, isomerization takes place at the C_3 and C_7 asymmetric centers [77] and a mixture of four substances is formed: vinerine, vineridine, and two iso compounds. One of the latter resembles caboxine [78], and the other is isomeric with vineridine at C_3.

When an alkaloid with a trans-D/E linkage of the rings is isomerized, one of the asymmetric centers – C_3 or C_7 – is involved, a consequence of which is the formation of two isomeric compounds. This fact can be used to determine the absolute configurations of the oxindole alkaloids.

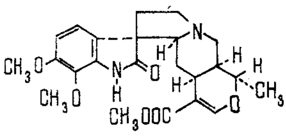
The acetylation of vinerine with acetic anhydride formed a N-acetyl derivative (99) which was subsequently found in nature [79]. In the circular dichroism (CD) spectrum of (99) as compared with that of (97) the signs of the maxima have changed and they have shifted in the short-wave direction [76]. Consequently, when vinerine is acetylated not only does the introduction of an acetyl group take place but also isomerization at the C_3 and C_7 carbon atoms and the inversion of the unshared electron pair on the N_b nitrogen atom. On the basis of the signs of the maxima in the CD spectra of N-acetylvinerine it is possible to establish for it the 3S, 7S configuration with the C=O of the lactam group located beneath the plane of rings C, D, and E.

The IR and NMR spectra of vinerine and vineridine N-oxides are basically similar [77, 80], and in the mass spectrum of vinerine N-oxide the peak of the molecular ion is twice as strong as the peak of the molecular ion of vineridine N-oxide.

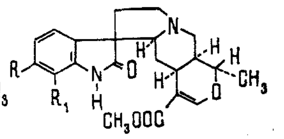
It is known that in the NMR spectra of the N-oxides of oxindole alkaloids having the anti form of the lactam carbonyl with respect to the free pair of electrons of the nitrogen atom there is a characteristic downfield shift of the C_9H aromatic proton, and in the mass spectra the intensity of the peak of the molecular ion usually exceeds 10%.

The new oxindole alkaloid majdine (103) was first isolated from V. major [11], and then from V. herbacea [2, 17]. After a preliminary study of chemical properties and spectral characteristics, the hypothesis was put forward that majdine is possibly an isomer of the oxindole alkaloid carapanaubine [12], but subsequently, in a study of the NMR spectrum, two one-proton doublets were found corresponding to the ortho protons of an aromatic ring. This showed that in majdine the two methoxy groups may be present in positions 9, 10 or 11, 12 [81]. Consequently, for an unambiguous answer to this question the method of measuring the intramolecular nuclear Overhauser effect was used, and this showed that the two methoxy groups in majdine and isomajdine are located at C_{11} and C_{12} [82].

Vinerinine (102) is a new phenolic oxindole alkaloid. Its structure and interrelationship with vinerine and majdine were established as the result of comparative investigations of chemical properties and spectral characteristics [83].



(103)



(102)

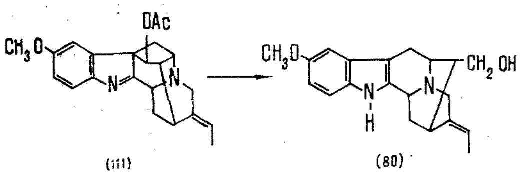
In the investigation of the structure and stereochemistry of the oxindole alkaloids, two new isomers of majdine have been obtained [80]. It was established that the latter are spiroisomers at C_7 and the epiallo forms of majdine and isomajdine. One of these isomers – herboxine – has recently been found in two species of plants [27, 102]. Thus, the possibility of the existence and mutual transitions of pairs of spiroisomeric oxindole alkaloids has been conformed.

3H-Indole Derivatives

Bases forming derivatives of 3H-indole are few and they can be considered as desmotropic forms [84] of the indole alkaloids in which the substituents at C_7 possess an increased reactivity.

The region of adsorption maxima of 3H-indole bases in the UV spectrum is close to that of the spectra of indole derivatives, but they differ substantially in the intensity of their absorption maxima. The IR spectra of these compounds show absorption bands in the 1630-1640 cm^{-1} region due to the stretching vibrations of a N=C double bond.

The specificity of the properties of the 3H-indole derivatives of vinorine (110) and of 10-methoxyvinorine (111) is shown in the performance of the transition to tombozine and lochnerine (80) in lithium tetrahydroaluminate reduction [85].



(111) (80)

The presence in the spectrum of (111) of strong peaks with m/e 198, 199, 212, and 213 [73], which are characteristic for β-carboline fragments of indole derivatives [86] shows that, apparently, under the conditions of mass spectrometric fragmentation there is a preliminary transformation of the 3H-indole base into a 1H-indole base.

Thus, plants of the genus Vinca contain indoline, indole, oxindole, and 3H-indole alkaloids. Each of these groups of alkaloids has its characteristic reactions and spectral properties and, moreover, a number of functional groups are diagnostic for definite groups of alkaloids. Consequently, the identification of compounds belonging to the above-mentioned groups or the determination of their structure can be effected comparatively readily with the aid of the combined use of chemical and physical methods of investigation. In spite of the great structural differences between these compounds, a definite interrelationship and mutual transitions exist which depend on the vegetation period and the organ of the plant, i.e., the alkaloids take part in the redox processes occurring in the plant organism. The isolation of the corresponding intermediate structural analogs in nature (see above) and the observed change in the quantitative relationships between certain alkaloids is evidence in favor of this hypothesis.

In this connection, it is interesting to observe that in the plants V. erecta, V. major, V. herbacea, and V. pubescens a heteroyohimbane alkaloid (reserpinine) is accompanied by oxindole bases (majdine, isomajdine, carapanaubine, etc.), but in V. minor and V. difformis these groups of compounds are not found. While in V. minor in place of the heteroyohimbane oxindole alkaloids the new oxindole alkaloids vincatine with the aspidospermidine skeleton has been detected, in V. difformis the 2-acylindole base vincadiffine is found. Thus, it may be assumed that in the plant V. elegantissima heteroyohimbane derivatives of indole should be found, and in V. libanotica oxindole derivatives. Furthermore, taking into account the hypothesis that picrinine and deacetylakuammiline are biogenetic precursors of the α-methyleneindole alkaloids of the vincanine and akuammicine group, it may be expected that in the plants V. minor and V. libanotica akuammicine and vincamine or new derivatives of these compounds will be found in addition to those isolated previously.

Many alkaloids and their derivatives found in plants of the genus Vinca have shown a high physiological activity as hypotensive and sedative compounds and agents stimulating the central nervous system and the uterus. However, some of these compounds cannot be widely used because of their limited natural sources and, consequently, to perform comparative investigations and to expand the raw materials bases of these alkaloids the study of methods for cultivating all species of Vinca must be intensified. Attention is also merited by the development of methods for industrial synthesis of natural compounds, especially alkaloids, by the cultivation of tissues of the alkaloid-bearing plants.

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