bromide was obtained. The gold benzene solution was evaporated and the yellow oil, 2.28 g., chromatographed over 75 g. of neutral alumina (Merck 71707). Elution with 20% carbon tetrachloride in petroleum ether (b.p. 30–60°) gave 0.65 g. (32.5%) of a crystalline material: m.p. 158–162°, raised to 165.0–166° dec. on recrystallization from hexane; $\lambda_{max}^{isooctane}$ (log ϵ values in parentheses) 258 sh, (3.47), 262 sh (3.64), 269.7 (3.77), 275.5 (3.72), 279 sh, (3.56), 292 sh (2.53), and 299.3 mμ (2.39).

Anal. Found: C, 93.63, 93.50; H, 6.48, 6.42; mol. wt. (Rast), 388.

Further elution of the column with 30–40% carbon tetrachloride in petroleum ether (b.p. 30–60°) gave 0.90 g. (45%) of a halogen-free solid. From 95% ethanol the latter crystallized into a tan powder.

Anal. Found: C, 89.62; H, 6.27; mol. wt. (Rast), 364.

Final elution of the column with ether gave 0.70 g. of a halogen-free glass which could not be obtained crystalline on attempted crystallization from either polar or nonpolar solvents. At room temperature no reaction occurred between the dibromide VII and nickel carbonyl in either benzene or ether.

Vinca Alkaloids. XVII. Chemistry of Catharanthine[2,3]

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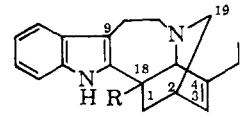
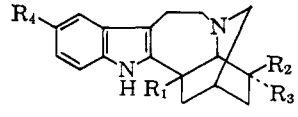
Contribution from the Lilly Research Laboratories, Indianapolis 6, Indiana.
Received August 26, 1964

Catharanthine (I), a major alkaloid of the isoquinuclidine type in the leaves of Vinca rosea Linn. (Catharanthus roseus G. Don.), undergoes a number of interesting transformations under acidic conditions. These reactions appear to proceed via tetracyclic immonium intermediates of the type XVI or XXVI. The products of these transformations are related to the naturally occurring alkaloid quebrachamine (XIII) and are represented by cleavamine (XI) and its derivatives.

Catharanthine (I), $C_{21}H_{24}O_2N_2$, one of the major alkaloids in the leaves of *Vinca rosea* Linn., has been shown to be closely related to the indole moiety of the dimeric oncolytic alkaloids, vinblastine and vincristine, also found in this plant.[4] Spectral data indicate that the alkaloid is a simple 2,3-substituted pentacyclic indole containing an ester group and closely related to the isoquinuclidine alkaloid coronaridine (II), $C_{21}H_{26}O_2N_2$.[5,6] The n.m.r. spectra (Figure 1) confirm the above assignments and indicate that the alkaloid contains a double bond with one vinyl proton at δ 5.3, a C-ethyl group characterized by a methyl triplet at δ 1.1, and an allylic methylene quartet at δ 1.9. These data clearly suggested structure I for catharanthine. Supporting evidence for the position of the double bond was obtained from decoupling experiments performed on the vinyl proton of the alkaloid.[7] Saturation of this proton led to changes in the shape of the C-2 proton at δ 2.62, and, in addition, small decoupling effects were seen on the protons at δ 4.18 (C-5 proton) and 1.9 (methylene of ethyl group). As expected, dehydrogenation of catharanthine with palladium on carbon yielded 3-ethylpyridine by the cleavage of the allylic C-1–C-2 bond. In the isoquinuclidine Iboga alkaloids which do not have a double bond at C-3–C-4 (*viz.*, voacangine (III) and dihydrocatharanthine (IV) (*vide supra*)), the C-1–C-18 bond is broken to afford 3-methyl-5-ethylpyridine.[8]



I, R = $COOCH_3$
X, R = H



II, R_1 = $COOCH_3$; R_2 = C_2H_5; R_3 = H; R_4 = H; coronaridine
III, R_1 = $COOCH_3$; R_2 = C_2H_5; R_3 = H; R_4 = OCH_3; voacangine
IV, R_1 = $COOCH_3$; R_2 = H; R_3 = C_2H_5; R_4 = H; dihydrocatharanthine
VII, R_1 = H; R_2 = H; R_3 = C_2H_5; R_4 = H; epi-ibogamine
VIII, R_1 = H; R_2 = C_2H_5; R_3 = H; R_4 H; ibogamine

Hydrogenation of I afforded only one isomer, dihydrocatharanthine (IV). Its infrared spectrum is strikingly similar to that of coronaridine (II). The differences in these compounds could be explained by examining Dreiding models which showed that the hydrogens most likely entered the molecule from the side nearest to N_b to give an axial ethyl group in dihydrocatharanthine. The ethyl group in the Iboga

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1–4, 1963, Abstracts, p. 38M.

(2) Vinca Alkaloids. XVI: M. Gorman, G. H. Svoboda, I. S. Johnson, H. F. Wright, and N. Neuss, ref. 1, p. 40L.

(3) N. Neuss and M. Gorman, *Tetrahedron Letters*, 206 (1961).

(4) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.*, **86**, 1440 (1964).

(5) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *ibid.*, **82**, 1142 (1960).

(6) The correlation of isoquinuclidine alkaloids (with no aromatic methoxyl groups) is readily found by the observance of a triplet centered at 6.8 μ in the infrared spectrum: N. Neuss, "Lilly Collection of Physical Data on Indole and Dihydroindole Alkaloids," Eli Lilly and Co., Indianapolis, Ind., 1964.

(7) The decoupling experiments described herein were carried out by Mr. P. Landis from these laboratories on a proton–proton decoupler patterned after that described by Mr. L. F. Johnson, Varian Associates, Palo Alto, Calif.

(8) F. Walls, O. Collera, and A. Sandoval, *Tetrahedron*, **2**, 173 (1958).

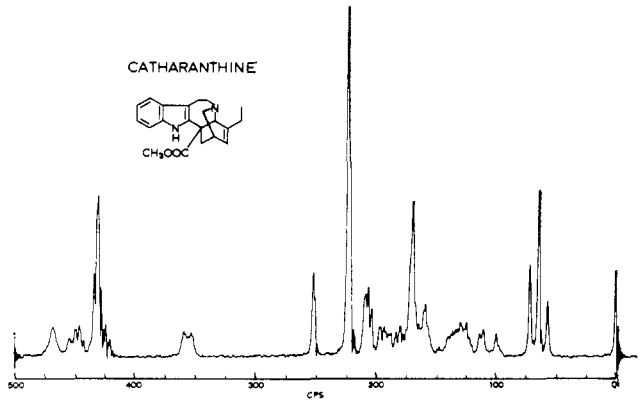
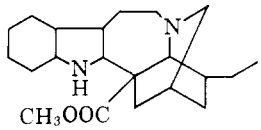
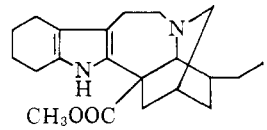


Figure 1. N.m.r. spectrum of catharanthine.

alkaloids has been shown to be equatorial.[9,10] More vigorous hydrogenation conditions (3.5 hr., 60°, concentrated hydrochloric acid, ethanol) afforded two compounds. One is a decahydro derivative (V), and the other is a hexahydrocatharanthine (VI).



V

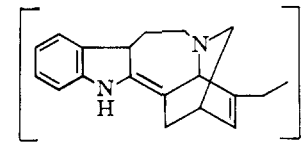


VI

The reduction of catharanthine and dihydrocatharanthine with $LiAlH_4$ afforded corresponding alcohols. The formation of the tetrahydro-1,3-oxazine derivative[11] from catharanthinol gave additional evidence for the position of carbomethoxyl at C-18.[3]

The Iboga alkaloids possessing a carbomethoxy function at C-18 are known to decarboxylate smoothly on saponification,[5] followed by mild acid treatment, or alternately after prolonged refluxing of the ester with hydrazine[12] in ethanol. Analogously, dihydrocatharanthine afforded the corresponding decarbomethoxy base epiibogamine (VII), differing from the known ibogamine (VIII) only in the orientation of the C-4 ethyl group as previously mentioned.[3] The final confirmation of the nature of the ring system was given by the isolation of 4-ethyl-2,6-dimethyl-11H-indolo-[2,3-*c*]quinoline from selenium dehydrogenation of epiibogamine. The identical compound has been obtained earlier by the same treatment of ibogamine (VIII).[13]

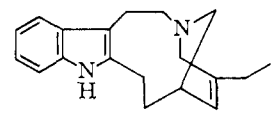
In contrast to facile decarboxylation of dihydrocatharanthine, catharanthine did not undergo an analogous transformation. Consideration of the accepted decarboxylation mechanisms[12,13] for these compounds leads in the case of catharanthine to a highly strained intermediate of the type IX which appears to account for the failure of this reaction.



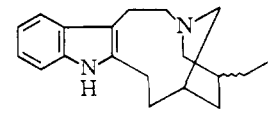
IX

When catharanthine, however, was treated with concentrated hydrochloric acid at reflux, two products were obtained in low yield. One of these was shown to be decarbomethoxycatharanthine (X), $C_{19}H_{22}N_2$ (hydrochloride, m.p. 150–154°, $[\alpha]^{26}D$ +90° [$CHCl_3$]), since its catalytic reduction yielded epiibogamine (VII). The second product, named cleavamine, was found to be a $C_{19}H_{24}N_2$ (XI) compound (mass = 280, mass spectra; m.p. 112–113°, $[\alpha]^{26}D$ +68.4).

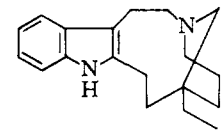
The ultraviolet spectrum of cleavamine indicates that the indole moiety is similar to that of catharanthine. From the n.m.r. spectrum it is apparent that the double bond in the C-ethyl containing portion of the molecule is unchanged. Therefore, cleavamine has to be tetracyclic. Hydrogenation of cleavamine in platinum oxide–ethanol afforded a dihydrocleavamine (XII), $C_{19}H_{26}N_2$ (mass = 282, m.p. 136–138°), isomeric with the known Aspidosperma alkaloid quebrachamine (XIII).[14] Cleavamine, dihydrocleavamine, and quebrachamine have many bands in common in their infrared spectra. Of particular significance is the presence of long wave-length C–H bands at 3.8 μ which are absent in the spectra of more rigid corresponding pentacyclic compounds[15] (*e.g.*, dihydrocatharanthine). On the basis of this evidence, structures XI and XII have been proposed for cleavamine and dihydrocleavamine, respectively.[16]



XI



XII



XIII

Structures XI, XII, and XIII are well corroborated by mass spectral data[17] (Figure 2: mass spectra of cleavamine, dihydrocleavamine, and quebrachamine). Of particular interest are two groups of fragments. The first group includes those which are common for all three compounds, *m/e* = 143 and 156. The second group represents fragments of different mass, presumably formed by the same fragmentation mechanism in each of the three compounds.[18] The fragmentation

(9) G. A. Jeffrey, G. Arai, and J. Coppola, *Acta Cryst.*, **13**, 553 (1960).

(10) The following evidence can also be correlated with this assignment: (a) The pK_a' values of the axial series are higher than those in the equatorial series: dihydrocatharanthine, pK_a' = 6.4; coronaridine, pK_a' = 6.1 (33% DMF). (b) The rate of methiodide formation has been found to be a sensitive indicator of the configuration of the C-ethyl group, the rate being much faster in the axial series [M. Shamma and H. E. Soyster, *Experientia*, **20**, 36 (1964)]. (c) The R_f values of these compounds vary when they are run by thin layer chromatography on silica gel plates (R_f: dihydrocatharanthine, 0.2; coronaridine, 0.8; solvent ethyl acetate–chloroform, 1:1). This difference may be ascribed to the acidity of the silica.

(11) O. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **41**, 169 (1959).

(12) U. Renner, D. A. Prins, and W. G. Stoll, *ibid.*, **42**, 1572 (1959).

(13) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958). We thank Dr. Taylor for specific details concerning this reaction and an authentic sample of the indoloquinoline.

(14) K. Biemann and G. Spiteller, *ibid.*, **84**, 4578 (1962).

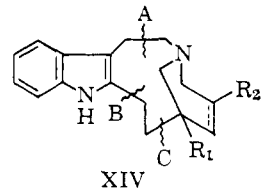
(15) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

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

(17) M. Gorman and N. Neuss, *Ann. Chim.* (Rome), **53**, 43 (1963).

(18) Dehydroquebrachamine, obtained by degradation of the alka-

mechanisms for quebrachamine and its analogs, which give rise to ions mentioned above, can be visualized as shown in XIV. Fragments of *m/e* = 143,

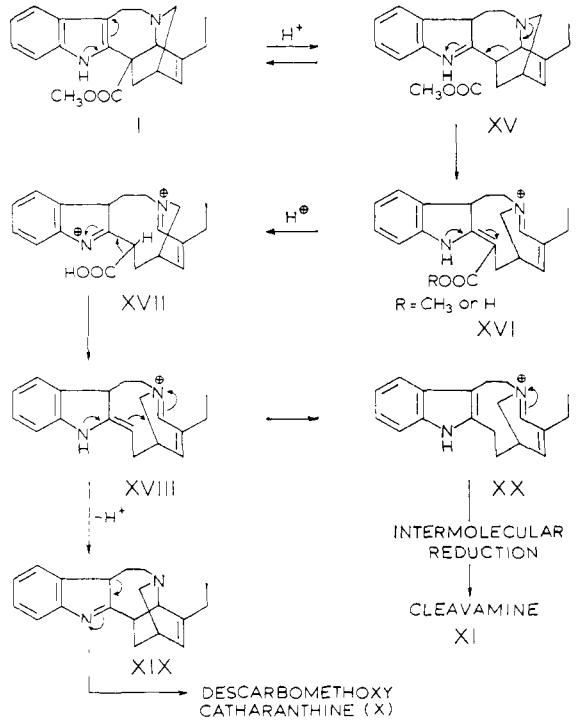


XIV

110 (XIII), 136 (XI), and 138 (XII) arise from cleavage at "A" and "B", while *m/e* = 156, 124 (XIII), 122 (XI), and 124 (XII) are formed by cleavage at "A" and "C".[14,19] The X-ray analysis of cleavamine methiodide[20] confirmed the proposed structure of cleavamine[16] and established its absolute configuration.

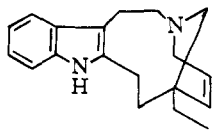
The formation of cleavamine and decarbomethoxycatharanthine from catharanthine in the presence of acid cannot be explained by the conventional mechanism proposed for decarboxylation of isoquinuclidine alkaloids.[12,13] Therefore, we would like to propose an alternate mechanism involving formation

Chart I



of an immonium salt with concomitant cleavage of the C-5–C-18 bond as outlined in Chart I. It will be shown (*vide infra*) that the intermediate similar to XVI

loid tabersonine, exhibits a similar fragmentation pattern with major peaks occurring at *m/e* = 143, 156, 122, and 108 [M. Plat, J. LeMen, M. M. Janot, J. M. Wilson, H. Budzikiewicz, L. Durham, V. Nakagawa, and C. Djerassi, *Tetrahedron Letters*, 271 (1962)]. We thank



Professor Djerassi, Stanford University, Palo Alto, Calif., for a copy of the mass spectrum of this compound.

(19) The cleavage of dehydroquebrachamine leading to the formation of *m/e* = 122 and 108 proceeds also *via* A,C and A,B, respectively.[14]

(20) J. P. Kutney, J. Tratter, T. Tabata, A. Kerigan, and V. Cameman, *Chem. Ind.* (London), 648 (1963).

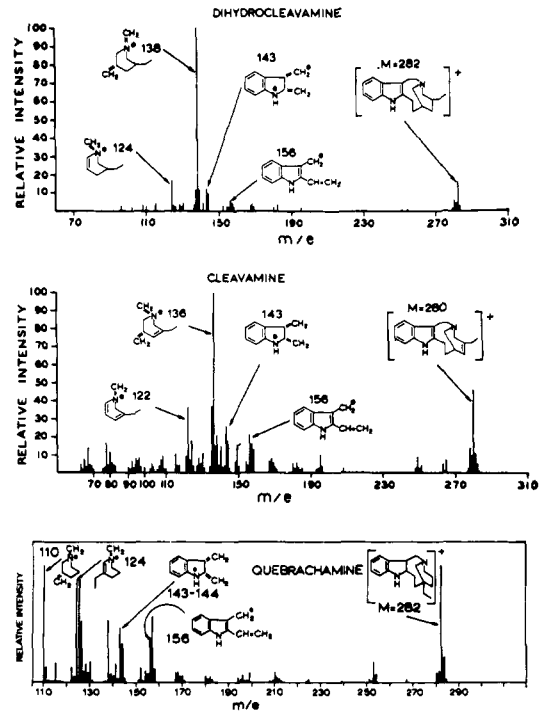


Figure 2. Mass spectra of dihydrocleavamine, cleavamine, and quebrachamine.

is also the common species leading to the formation of other products in acid solution in the case of coronaridine and dihydrocatharanthine.

Since cleavamine is at a lower oxidation state than catharanthine, it is necessary to postulate the reduction of a carbonium ion or an intermolecular hydride shift in going from XX to cleavamine.[21] As expected, the ease of the reduction step was facilitated by the addition of an agent capable of reducing a carbonium ion[22] which led to an increase in the yield of cleavamine.[23] A mixture of stannous chloride and tin metal in concentrated hydrochloric acid was found to give the best yield. We cannot as yet determine in what sequence these reactions occur following the formation of intermediate XVI.

When dihydrocatharanthine was subjected to a prolonged refluxing in concentrated hydrochloric acid, two products, ibogamine (VIII) and epiibogamine (VII), were obtained. Since we have shown that ibogamine and epiibogamine differ only in the orientation of the C-4 ethyl group, equilibration of this saturated carbon would have taken place only *via* an immonium salt–enamine equilibrium as shown by the mechanism in Chart II for dihydrocatharanthine. Again, this mechanism is visualized as proceeding through an intermediate of the type XVI without a double bond at C-3–C-4 (XXI).

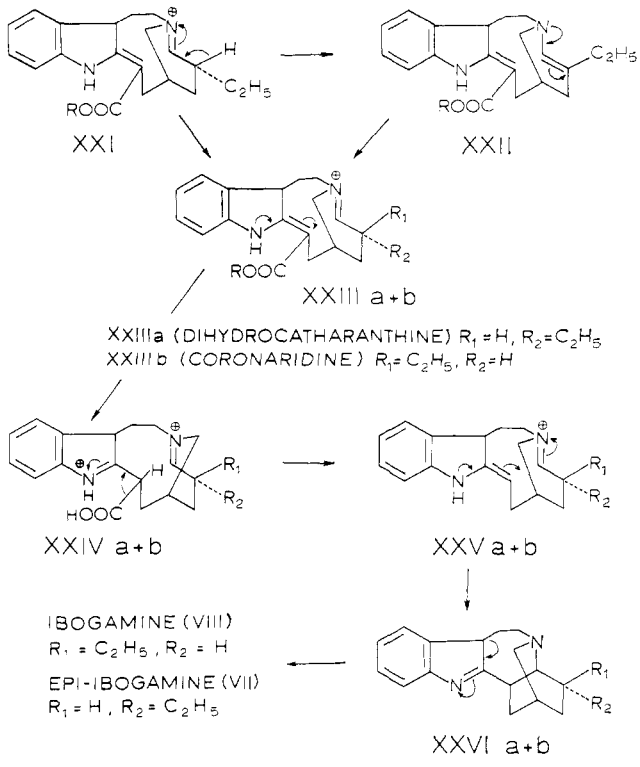
Identical equilibration conditions (hydrochloric acid, heat) were attempted on the decarbomethoxy bases (epiibogamine or ibogamine); however, only unchanged starting materials were recovered. It would appear, therefore, that the presence of carbomethoxyl

(21) One could visualize the dihydropyridinium intermediate XVI serving as a hydrogen donor in this reaction.

(22) D. Ginsburg, "The Opium Alkaloids," Interscience Publishers, Inc., New York, N. Y., 1962, pp. 40–42.

(23) We wish to thank Professor E. Wenkert of Indiana University for a stimulating discussion of this mechanism.

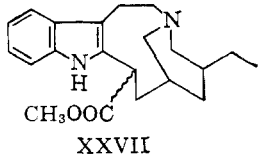
Chart II



is essential for the generation of the intermediate XXI. The formation of the immonium salt without cleavage of the C-5–C-18 bond would seriously violate Bredt's rule; however, in XXI the resulting nine-membered ring is large enough to overcome this hindrance.[24]

An interesting observation was made when dihydrocatharanthine was treated with glacial acetic acid at reflux. No decarboxylation could be observed under these anhydrous conditions. Instead, a mixture of starting material and coronaridine (II) was obtained. Undoubtedly, under these conditions hydrolysis of the methyl ester in XXIIIa and b cannot take place, and the reaction is reversed to afford the equilibrated products.[25]

Additional evidence for the formation of the tetracyclic intermediate XVI was furnished from the reaction of pentacyclic alkaloids with glacial acetic acid in the presence of zinc dust. Büchi and co-workers have observed the formation of carbomethoxydihydrocleavamine XXVII[4,26] from catharanthine under these conditions.



XXVII

(24) An analogous immonium compound obtained by mercuric acetate oxidation of dihydrocleavamine (XII) leads to the formation of a new rigid pentacyclic system through transannular bonding of C-9 and C-19: J. P. Kutney and E. Piers, *J. Am. Chem. Soc.*, **86**, 953 (1964).

(25) By carrying out this reaction over long (>3 days) periods of time and following its course by t.l.c.,[10c] it was found that up to 95% of dihydrocatharanthine was converted to coronaridine. When coronaridine was heated under reflux in glacial acetic acid for 3 days, one could detect in the reaction mixture by t.l.c. small quantities of dihydrocatharanthine.

(26) We thank Professor Büchi of M.I.T. for advanced information on this phase of his work as well as for an authentic sample of this substance.

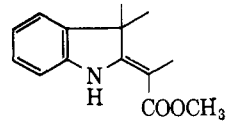
Decarboxylation of carbomethoxydihydrocleavamine with alkali followed by acid gave rise to dihydrocleavamine different from that obtained by catalytic hydrogenation of cleavamine.[17] The n.m.r. spectra of the two isomers are consistent, with the only difference being in the configuration of the C-4 ethyl group. At present, we cannot assign a definite configuration to these tetracyclic epimers. It should be pointed out that the reduction of the double bond in the course of formation of XXVII and its epimer is not surprising and most probably arises by a 1,4-reduction of the conjugated immonium intermediate XVI.

The final confirmation of the existence of the reactive tetracyclic intermediate of the type represented by XVI or XXIII was afforded by the preparation of carbomethoxydihydrocleavamine XXVII directly from the reaction of dihydrocatharanthine with acetic acid and zinc dust.

The reaction of catharanthine in glacial acetic acid alone was more complex. After 16 hr. at reflux, the reaction mixture was chromatographed on silica and two compounds obtained.

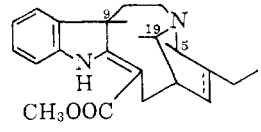
The ultraviolet spectra of both substances are no longer those of a simple indole derivative, but now exhibit a spectrum typical of the chromophore shown in XXVIII and found in alkaloids such as lochnericine[27] or tabersonine.[16]

Accordingly, the infrared spectra were virtually superimposable in the region of 2–7 μ with those of the above-mentioned alkaloids.



XXVIII

One of the compounds (XXIXa), $C_{21}H_{24}O_2N_2$, m.p. 114–116°, was isomeric with catharanthine while the other (XXIXb), m.p. 126–128°, contained two more hydrogens. The n.m.r. spectra of the two substances substantiated these findings and suggested that the difference between XXIXa and b rested in the presence of the $\Delta^{3,4}$-double bond in the former and its absence in the latter (*vide supra*). Therefore, these substances must be pentacyclic and derived by further reaction of intermediate XVI.



XXIXa and b

Decarboxylation and alkaline borohydride reduction[16,28] of XXIXa afforded cleavamine.

Our results allow only partial structures XXIXa and b for the new compounds. The data at hand do not differentiate between the position of the new bond as being between C-9–C-19 or C-9–C-5.[29]

(27) M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, and N. J. Cone, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 256 (1959).

(28) G. F. Smith and J. T. Wrobel, *J. Chem, Soc.*, 793 (1960).

(29) The infrared spectrum and t.l.c.[10c] of XXIXb are identical with those of isovincadifformine prepared by Kutney from dihydrocarbomethoxycleavamine: J. P. Kutney, R. T. Brown, and E. Piers, *J. Am. Chem. Soc.*, **86**, 2286 (1964).

The conversion of a tetracyclic indole immonium salt (XVI) into alkaloids of the Iboga and Aspidosperma types has been postulated by Wenkert.[30] In fact, the rearrangements described herein closely parallel the later steps of his suggested biosynthetic pathways. In the Aspidosperma series (tertiary C-ethyl groups) the corresponding alkaloids quebrachamine[14] and tabersonine[16] occur naturally. In the Iboga series (secondary C-ethyl) only the pentacyclic indole bases have been found. It will be of interest to see if compounds related to cleavamine are eventually found in nature.

Experimental

General. All reactions were run in a nitrogen atmosphere except when using reducing conditions. Melting points were taken on a Kofler micro hot stage; rotations are in chloroform ($c \sim 1$) unless mentioned otherwise. Analyses are in agreement with molecular weights from the mass spectra. The ultraviolet spectra in ethanol were recorded on a Cary Model 14 recording spectrophotometer. The infrared spectra in chloroform solution were recorded on a Beckman IR-7 double beam instrument. Nuclear magnetic resonance spectra were recorded on a Varian HR-60 instrument in deuteriochloroform with tetramethylsilane as an internal standard. pK_a' values are in 33% dimethylformamide unless otherwise mentioned. Thin layer chromatography was performed on 5 × 20 cm. or 20 × 20 cm. plates uniformly covered with a 0.25-mm. layer of silica gel G or alumina. Detection was accomplished with 1% ceric ammonium sulfate in sirupy phosphoric acid.[31] Chromatographic separations were carried out on neutral Woelm alumina activity II.

Isolation of Catharanthine (I). The base was prepared according to the procedure described earlier[32] and crystallized as monohydrate from aqueous methanol, m.p. 126–128°, pK_a' = 6.9, $[\alpha]^{27}D$ +29.8°. Analytical data and physical constants of base, hemisulfate, and methiodide have been reported earlier.[33] In addition to these salts, the hemitartrate was also prepared for its better solubility in water since the hemisulfate is quite insoluble. It was recrystallized from ethanol, m.p. 148–150° dec.

Anal. Calcd. for $C_{21}H_{24}N_2O_2 \cdot 0.5C_4H_6O_6 \cdot H_2O$: C, 64.32; H, 6.81; N, 6.52. Found: C, 64.46; H, 6.93; N, 6.31.

Dihydrocatharanthine (IV). Anhydrous catharanthine base was hydrogenated with platinum oxide in alcohol for 2 days at atmospheric pressure. After the usual work-up and evaporation *in vacuo*, the residue was treated with charcoal in ether, evaporated *in vacuo*, crystallized from aqueous methanol, and recrystallized from methanol. The yield varied from 65–89%, m.p. 63–65° (recrystallizes and melts at 150° dec.); $[\alpha]^{25}D$ +33°; λ_{max}^{EtOH} 202 mμ (ε 18,400) (the intensity of the corresponding band in catharanthine is 26,000).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; O, 9.46; N, 8.28. Found: C, 74.38; H, 7.63; O, 9.96; N, 7.98.

The hydrochloride salt was prepared in ether. The amorphous salt was recrystallized from acetone–methanol (5:1); m.p. 216–221° dec., $[\alpha]^{26}D$ +44° (CH_3OH).

Anal. Calcd. for $C_{21}H_{26}N_2O_2 \cdot HCl$: C, 67.27; H, 7.26; N, 7.47. Found: C, 67.25; H, 7.47; N, 7.40.

Catalytic Reduction of Catharanthine in Acid. Preparation of Decahydrocatharanthine (V) and Hexahydrocatharanthine (VI). To a solution of 2 g. of catharanthine hydrochloride in 60 ml. of alcohol, containing 2 ml. of concentrated hydrochloric acid, was added 0.5 g. of platinum oxide. Hydrogenation proceeded at 48 p.s.i. and was continued for 6 hr. at 65°. After this time the mixture was worked up and the free base liberated to afford 1.58 g. This material was chromatographed (A) on 50 g. of alumina using benzene as eluent. Fractions of 50 ml. were collected. Fraction 1 gave 740 mg. and was rechromatographed as above using petroleum ether–benzene as eluent. Recrystallization of the first three fractions from methanol gave 260 mg. of hexahydrocatharanthine, m.p. 71–75°; λ_{max}^{EtOH} 240 mμ (ε 2870), consistent with a tetrasubstituted pyrrole; [M] = 342.

Anal. Calcd. for $C_{21}H_{30}N_2O_2 \cdot H_2O$: C, 69.77; H, 8.95; N, 7.77. Found: C, 70.18; H, 8.96; N, 7.53.

Fractions 2 and 3 (chromatography A) afforded 420 mg. which upon crystallization from acetone gave 65 mg. of decahydrocatharanthine, m.p. 83–90°; [M] = 346; ultraviolet transparent; n.m.r. transparent below δ 3.7.

$LiAlH_4$ Reduction of Catharanthine. Preparation of Catharanthinol. A suspension of 500 mg. of lithium aluminum hydride in 40 ml. of tetrahydrofuran was stirred under reflux for 1 hr. To this suspension was added a solution of 1.3 g. of amorphous, anhydrous catharanthine in 25 ml. of tetrahydrofuran. After 3 hr. of refluxing and standing overnight, the reaction mixture was decomposed with 3.1 ml. of water (cooling); the suspension was refluxed for 1 hr. and filtered. The clear filtrate was evaporated *in vacuo* and afforded, after crystallization from methanol, 1.0 g. of carbinol, m.p. 227–228° dec., pK_a' 8.5.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.03; mol. wt., 308.4. Found: C, 77.73; H, 7.85; N, 8.85; mol. wt., 309.3 (X-ray).

Catharanthinol hydrochloride was prepared in methanol and recrystallized from acetone, m.p. 225–228° dec.

Anal. Calcd. for $C_{20}H_{24}N_2O \cdot HCl$: C, 69.64; H, 7.30; N, 8.10; Cl, 10.28. Found: C, 69.21; H, 7.44; N, 7.89; Cl, 10.10.

Catharanthinol Acetonide. Through a solution of 250 mg. of the carbinol in 25 ml. of absolute acetone, dry hydrogen chloride was bubbled very slowly for 15 min. The reaction mixture was allowed to stand for an additional 15 min. and worked up as described for voacangarine alcohol,[11] m.p. 188–191° dec.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.22; H, 8.19; N, 8.26.

$LiAlH_4$ Reduction of Dihydrocatharanthine. Dihydrocatharanthinol. A solution of 2.1 g. of dihydro-

(30) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).
(31) N. J. Cone, R. Miller, and N. Neuss, *J. Pharm. Sci.*, **52**, 688 (1963).
(32) G. H. Svoboda, N. Neuss, and M. Gorman, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 659 (1959).
(33) M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, Jr., and N. J. Cone, *ibid.*, **48**, 256 (1959).

catharanthine in 60 ml. of tetrahydrofuran was added to a suspension of 1.0 g. of lithium aluminum hydride in 90 ml. of redistilled tetrahydrofuran as described for the reduction of catharanthine. After refluxing for 5 hr. and standing overnight, the reaction mixture was treated with 6.2 ml. of water, decomposed by boiling for 1 hr., and filtered. After the evaporation *in vacuo*, the amorphous residue was crystallized from ether to afford 1.3 g. of crystals, m.p. 132–133°.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.65; H, 8.70; N, 9.19.

The material was identical with a sample of catharanthinol reduced catalytically using platinum oxide in ethanol at atmospheric pressure.

Decarboxylation of Dihydrocatharanthine. Preparation of Epiibogamine (VII). Dihydrocatharanthine was decarboxylated as described for voacangine[12] and afforded crystalline epiibogamine from ethyl acetate; m.p. 162–164°.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.98. Found: C, 81.63; H, 8.41; N, 9.94.

The hydrochloride salt was prepared in ether and recrystallized from acetone, m.p. 183–188°, $[\alpha]^{25}D$ +86° (CH_3OH).

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot HCl$: C, 72.02; H, 7.95; N, 8.84; Cl, 11.19. Found: C, 71.76; H, 8.19; N, 8.99; Cl, 11.09.

Selenium Dehydrogenation of Epiibogamine. This reaction was carried out according to the procedure of Taylor described in the dehydrogenation of ibogamine. The 4-ethyl-2,6-dimethyl-11H-indolo[2,3-*c*]-quinoline obtained from epiibogamine was identical in each respect with an authentic specimen (ultraviolet, infrared, X-ray powder patterns, and mass spectra).

Palladium on Carbon Dehydrogenation of Catharanthine. Amorphous catharanthine (1.0 g.) was thoroughly mixed with 2.0 g. of palladium (10%) on carbon and slowly heated. At 160–180° over a period of 10–15 min., a distillate was collected and shown by v.p.c. to be 3-ethylpyridine.[34] The picrate was prepared and recrystallized from methanol; m.p. 119–123°. It was identical with that prepared from an authentic sample[34] of the base (X-ray powder data, ultraviolet, and infrared).

Palladium on Carbon Dehydrogenation of Dihydrocatharanthine. The reaction was carried out as described for catharanthine. In this case, however, the reaction mixture had to be heated to about 230° before a distillate was obtained. This base was shown to be 3-methyl-5-ethylpyridine by v.p.c., and the picrate was prepared, m.p. 181–184°. It was identical with that prepared from an authentic sample[34] of the base (X-ray powder data, ultraviolet, and infrared).

Acid Treatment of Catharanthine. A. Hydrochloric Acid. Preparation of Cleavamine (XI) and Decarbomethoxycatharanthine (X). A suspension of 50 g. of amorphous catharanthine hydrochloride in 350 ml. of concentrated hydrochloric acid, 50 g. of stannous chloride, and 5 g. of tin metal was refluxed for 45 min. A red-orange oil formed the upper layer. The yellow acid layer was decanted, thoroughly extracted with methylene chloride after cooling, and combined with the methylene chloride solution of the red-orange oil. The combined methylene chloride solutions were thoroughly washed with cold 1 *N* sodium hydroxide and water. The organic phase was dried over anhydrous sodium sulfate, evaporated *in vacuo*, and extracted with three 100-ml. portions of ether. The ether extract was filtered, dried, and evaporated *in vacuo* to yield 30 g. of solids. The residue was chromatographed on 700 g. of alumina using petroleum ether–benzene mixture (1:1) as eluent. Fractions of 150 ml. were collected. Fractions 4–14 gave cleavamine after crystallization from methanol (15% yield). Fractions 20–35, obtained by elution with benzene–chloroform (5:1), crystallized from hexane to give decarbomethoxycatharanthine (10% yield); cleavamine m.p. 102–113° (after change at 82°), pK_a' 8.2, $[\alpha]^{26}D$ +68.4°.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.34; H, 8.54; N, 9.65.

Decarbomethoxycatharanthine had m.p. 92–94°.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 82.21; H, 8.04; N, 9.99.

The hydrochloride salt was prepared in ether and recrystallized from water, m.p. 150–154° dec., $[\alpha]^{26}D$ +90° (CH_3OH).

Anal. Calcd. for $C_{19}H_{22}N_2 \cdot HCl$: C, 73.77; H, 8.12; Cl, 11.26; N, 7.47. Found: C, 73.79; H, 8.08; Cl, 10.97; N, 7.73.

B. Acetic Acid. Preparation of Indolines XXIXa and b. A solution of amorphous, dried catharanthine (5.5 g.) in glacial acetic acid (50 ml.) was refluxed under nitrogen for 16 hr., evaporated *in vacuo*, taken up in diluted sulfuric acid, and filtered. The filtrate was adjusted to pH 5 with diluted ammonia and extracted three times with ether. Ether was dried over sodium sulfate and evaporated to give 2.41 g. of the bases; t.l.c. examination indicated that this residue contained both XXIXa and b. In a similar experiment run only 2.5 hr. and extracted at pH 5, the residue (0.23 g. from 0.50 g.) contained little of XXIXb.

Silicic acid (dried 1 hr. at 110° *in vacuo*) chromatography in benzene gave a 20% yield of each of the two new indolines: XXIXa, m.p. 114–116° (crystallized from methanol); λ_{max}^{EtOH} 225, 297, and 329 mμ log ε 4.07, 4.12, and 4.24); $\lambda_{max}^{CHCl_3}$ 5.8, 6.2, and 2.9 μ; [M] = 336; n.m.r., methyl triplet centered at δ 1, methylene quartet at δ 2, single vinyl proton at δ 5.9 (reminiscent of that in catharanthine).

The hydrochloride salt was recrystallized from acetone; m.p. 173–179°.

Anal. Calcd. for $C_{21}H_{24}N_2O_2 \cdot HCl$: C, 66.88; H, 7.25; N, 6.50; Cl, 8.23. Found: C, 66.77; H, 7.31; N, 6.37; Cl, 8.42.

The second compound, XXIXb, crystallized from methanol, m.p. 132–134°, [M] = 338; n.m.r., methyl at δ 0.73 and methylene at δ 1.12. The difference of the relative position of methylene protons is consistent with an isolated double bond between C-3 and C-4.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.59; H, 7.75; N, 7.99.

The hydrochloride salt crystallized from methanol–ether; m.p. 178–182°

C. Acetic Acid and Zn Dust: Preparation of Carbomethoxydihydrocleavamine (XXVII). Two grams of amorphous catharanthine base was dissolved in 25 ml.

(34) We wish to thank Dr. S. E. Cislak of Reilly Tar and Chemical Corp., Indianapolis, Ind., for samples of the above bases.

of glacial acetic acid and 10 g. of zinc dust. The mixture was refluxed under nitrogen for 3 hr. After the usual work-up, bases were extracted with ether. The resulting mixture was crystallized from methanol to give 510 mg. of carbomethoxydihydrocleavamine.[4,26] The hydrochloride was recrystallized from acetone, m.p. 220–224° dec.

Anal. Calcd. for $C_{21}H_{28}N_2O_2 \cdot HCl$; C, 66.91; H, 7.78; N, 7.43. Found: C, 66.97; H, 7.84; N, 7.97.

Dihydrocleavamine (XII). Cleavamine base was hydrogenated using platinum oxide in ethanol at atmospheric pressure for 2 days. After the usual work-up, the base was recrystallized from aqueous methanol, m.p. 136–138°, $pK_a' = 8.8$, $[\alpha]^{26}D$ −67.6°.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.56; H, 9.27; N, 9.87.

Epimerization of Dihydrocatharanthine. A. Hydrochloric Acid. A mixture of 100 mg. of dihydrocatharanthine hydrochloride in 10 ml. of concentrated hydrochloric acid was refluxed under nitrogen for 16 hr. after which time the solution was homogeneous. The reaction mixture was evaporated *in vacuo* to dryness and worked up as usual for the free base. Chromatography on alumina using 1:1 petroleum ether–benzene as eluent afforded 37 mg. of ibogamine and 32 mg. of epiibogamine (infrared and X-ray diffraction patterns).

B. Acetic Acid. Dihydrocatharanthine (180 g.) was refluxed with 3240 ml. of glacial acetic acid for 42 hr., evaporated *in vacuo* to a sirup, taken up in 2 l. of water, filtered, made alkaline, and extracted with ether. After evaporation, the residue (90 g.) contained about equal amounts of the starting material and coronaridine (t.l.c.). Chromatography on Mallinckrodt silicic acid (ratio 10:1) in benzene afforded, after elution with 40 l. of benzene, 34 g. of coronaridine. Continued elution with chloroform–benzene (25:75) gave 25 g. of dihydrocatharanthine.

C. Zinc and Acetic Acid.[26] Zinc dust (15 g.) was added to a solution of amorphous dihydrocatharanthine (0.45 g.) in glacial acetic acid (30 ml.). The solution was refluxed 3 days, removing aliquots after 4 hr. and after 1 day; t.l.c. of the aliquots and of the product indicated the presence of a trace of coronaridine and a slower moving material which increased with time. After 3 days, two other products, moving in the same area as dihydrocatharanthine, were evident with less than 20% dihydrocatharanthine remaining. The residue was chromatographed on alumina (10 g.), using benzene as an eluent. The second fraction (175 mg.) contained several components on t.l.c. and was rechromatographed on silicic acid (4 g.) in chloroform. The first two fractions afforded 53 mg. of material which crystallized from methanol and was shown to be carbomethoxydihydrocleavamine.[4]

Decarboxylation of Carbomethoxydihydrocleavamine. Preparation of Epidihydrocleavamine. A solution of 3.2 g. of carbomethoxydihydrocleavamine in 100 ml. of ethanol containing 15 g. of potassium hydroxide in 20 ml. of water was boiled under reflux for 4 hr. After dilution with water, concentrated hydrochloric acid was added to pH 2.2, and the solution was boiled under reflux for 50 min. After cooling and addition of ammonium hydroxide followed by extraction with methylene dichloride, 2.8 g. of base was obtained. Chromatography on 90 g. of alumina (activity III) using benzene as eluent afforded 1.94 g. of material in the first fraction. It crystallized from methanol and afforded 1.2 g. of epidihydrocleavamine, m.p. 109–111°, [M] = 282, $[\alpha]^{26}D$ +94.3, $pK_a' = 9.0$.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.75; H, 9.61; N, 10.05.

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New Methods in Peptide Synthesis. II. Further Examples of the Use of the *o*-Nitrophenylsulfenyl Group for the Protection of Amino Groups[1,2]

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Further examples are presented of the usefulness of the N-o-nitrophenylsulfenyl (NPS) group as an N-protecting group for α-amino acids or α-amino acids bearing a protected side-chain functional group. The wide applicability of the new method is demonstrated by the synthesis of various peptides, e.g., L-*phenylalanyl-*L-*glutaminyl-*L-*glutamyl-*L-*glutamine, which normally present great difficulties in their synthesis by conventional methods.*

(1) A summary of this paper was presented at the 6th European Peptide Symposium, Athens, Greece, Sept. 1963; E. Gazis, D. Borovas, C. Hamalidis, G. C. Stelakatos, and L. Zervas in "Peptides: Proceedings of the Sixth European Peptide Symposium, Athens, 1963," Pergamon Press, Oxford, 1964, in press.

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