—CHAPTER 9—

THE IBOGA AND *VOACANGA* ALKALOIDS

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I. The Iboga Alkaloids

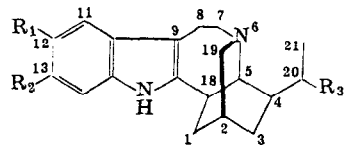
The iboga alkaloids (Table I) presently number twelve, if their oxidation products are excluded, all from apocynaceous plants of the genera *Conopharyngia* (*Plumeria*), *Ervatamia*, *Gabunea*, *Stemmadenia*, *Tabernaemontana*, *Voacanga*, *Vinca* (*Lochnera*, *Catharanthus*), and *Tabernanthe*. It was from the last genus that the parent pentacyclic heterocycle, ibogamine, was first obtained. The structures of these compounds depend entirely upon their interrelationships with ibogaine, whose structure was derived by degradation (illustrated schematically in Charts I to IV) and X-ray analysis. The absolute stereochemistry has not been rigorously determined, and none of the bases, at the time of writing, had been synthesized.

The alkaloids can be conveniently grouped as shown in Table I, and it should be noted that the trivial names currently used obscure their similarities.

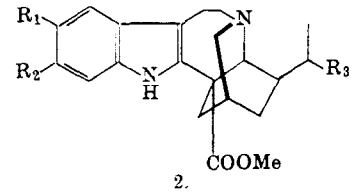
Many of the alkaloids suffer facile autoxidation to yield hydroperoxy- and hydroxyindolenines, whose further degradation products are 4-hydroxyquinolines and pseudoindoxyls (Table I). Therefore, the

TABLE I

IBOGA ALKALOIDS OF KNOWN STRUCTURE



1.



2.

Alkaloid	Melting point (° C)	$[\alpha]_D$ (Solvent)	R_1	R_2	Source[a]
A. Ethyl side chain; $R_3 = H$					
Ibogamine	162–164	−36° ($CHCl_3$)	H	H	n(2), l(10), i(11)
Ibogaine	152–153	−53° ($CHCl_3$)	MeO	H	n(1)
Tabernanthine	211–212	−35° ($CHCl_3$)	H	MeO	n(3), h(11)
Ibogaline	141–143	−43° ($CHCl_3$)	MeO	MeO	n(4)
B. Hydroxyethyl side chain; $R_3 = OH$					
Iboxygaine	234	−5° ($CHCl_3$)	MeO	H	n(5)

Alkaloid	Melting point (° C)	$[\alpha]_D$ (Solvent)	R_1	R_2	Source[a, b]
A. Ethyl side chain; $R_3 = H$					
Coronaridine	238 (B.HCl)	−8° (MeOH)	H	H	e(10), f(10), l(10), m(10)
Catharanthine (Δ^3-coronaridine)	126–128	+30° ($CHCl_3$)	H	H	u(12)
Voacangine	137–138	−42° ($CHCl_3$)	MeO	H	n(6), o(8, 9), l(10), i(11), g(18), h(11), t(8), r(13), m(10), j(10)
Isovoacangine	156–157	−52° ($CHCl_3$)	H	MeO	d(14), h(11)
Conopharyngine	141–143	−40° ($CHCl_3$)	MeO	MeO	d(14)
B. Hydroxyethyl side chain; $R_3 = OH$					
Voacristine (voacangarine)			MeO	H	

211–212	Tabernanthine $-35°$ ($CHCl_3$)	H	MeO	n(3), h(11)
141–143	Ibogaline $-43°$ ($CHCl_3$)	MeO	MeO	n(4)
156–157	Isovoacangine $-52°$ ($CHCl_3$)	H	MeO	d(14), h(11)
141–143	Conopharyngine $-40°$ ($CHCl_3$)	MeO	MeO	d(14)

B. Hydroxyethyl side chain; $R_3 = OH$

234	Iboxygaine $-5°$ ($CHCl_3$)	MeO	H	n(5)
231–232	(Kimvuline) $+4°$ ($CHCl_3$)			n(6)
112–114 or 166–167	Voacristine (voacangarine) $-25°$ ($CHCl_3$)	MeO	H	o(15, 16)

D. Oxidation and rearrangement products of parent bases

168–172	9-Hydroxy-9*H*-ibogamine $+82°$ (alc.)	H	H	n(6)
141	Demethoxyiboluteine (ibogamine-ψ-indoxyl)	H	H	n(6)
123–124	9-Hydroxy-9*H*-ibogaine $+74°$ (EtOH)	MeO	H	n(6)
142	Iboluteine (ibogaine-ψ-indoxyl) $-114°$ ($CHCl_3$)	MeO	H	n(7)
284–285	Iboquine (ibogaine-4-quinolinol)	MeO	H	n(7)

C. Acetyl side chain; $R_3 = O$

175–176	Voacryptine $+25°$ ($CHCl_3$)	MeO	H	o(17)

[a]Sources: a, *Callichilia barteri* Stapf; b, *C. stenosepala* Stapf; c, *C. subsessilis* Stapf; d, *Conopharyngia durissima* Stapf; e, *Ervatamia coronaria* Stapf; f, *E. divaricata* Burkill; g, *Gabunia eglandulosa* Stapf; h, *Stemmadenia donnell-smithii* R. E. Woodson; i, *S. galeottiana* Miers; j, *Tabernaemontana australis* Muell. Arg.; k, *T. coronaria* Willd.; l, *T. oppositifolia* Urb.; m, *T. psychotrifolia* H.B. and K.; n, *Tabernanthe iboga* Baill.; o, *Voacanga africana* Stapf ex S. Elliot; p, *V. bracteata* Stapf; q, *V. chalotiana* Pierre ex Stapf; r, *V. dregei* E. Mey.; s, *V. schweinfurthii* Stapf; t, *V. thouarsii* Roem. et Schult. var. *obtusa* Pichon; u, *Vinca rosea* Linn.

Parenthetical numbers refer to reference list.

isolation of these products from the plant cannot by itself be taken as proof of their natural occurrence. This situation is similar to that which exists for several of the tertiary bases obtained from *Hunteria eburnea* Pichon and possibly for some of the dimeric curare alkaloids derived from the Wieland-Gumlich aldehyde.

A. The Structures of Ibogaine and Iboxygaine

Although the isolation of the principal alkaloid, ibogaine, of *Tabernanthe iboga* was described at the turn of the present century (1), it was not until the early 1950's that serious work on its structure was begun. It had been shown to contain a methoxy group and, by means of color reactions (19) and by measurement of its UV-spectrum, to be an indole (20), but it was not recognized to be a methoxyindole until permanganate oxidation was found to afford 5-methoxy-*N*-oxalylanthranilic acid (21).

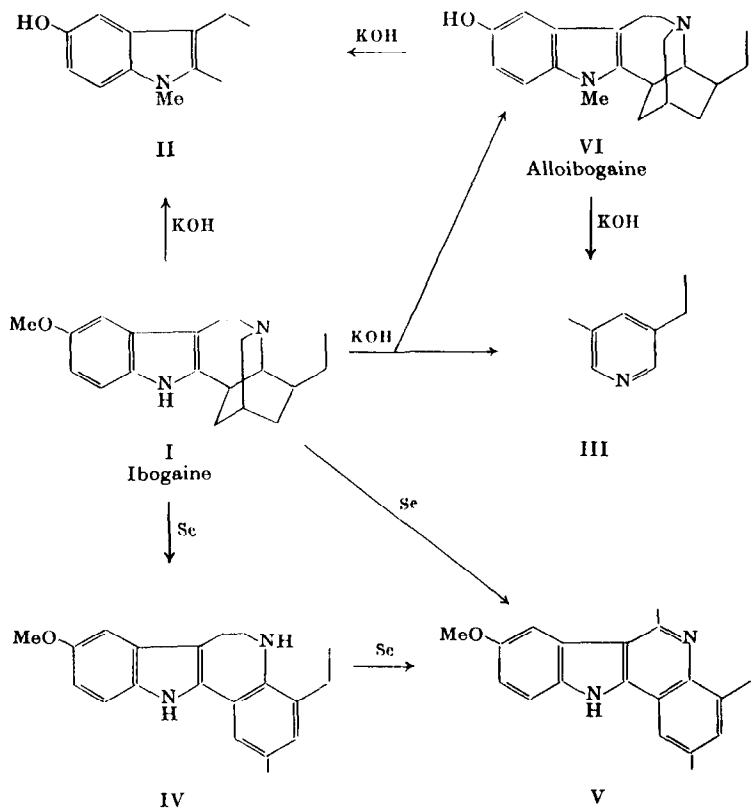
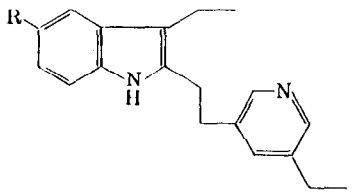
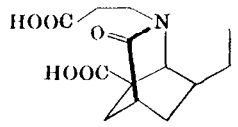


Chart I. KOH and Se degradation of ibogaine.

A complete structure (22) for ibogaine (I) was derivable from a consideration of its potash fusion products (23, 24), 1,2-dimethyl-3-ethyl-5-hydroxyindole (II) and 3-ethyl-5-methylpyridine (III) on the one hand, and its selenium dehydrogenation products (22, 25), the cyclic 2,2′-aminophenylindole (IV), mp 208°, and the indolo[3,2-*c*]quinoline (V), mp 178°, on the other hand. In each case all the carbons, both nitrogens, and the oxygen were accounted for. Alloibogaine (VI), amorphous, oxalate, mp 200° [readily prepared from ibogaine by a more conventional route (25)] was an intermediate in the potash fusion (23, 24). The structures of the degradation products were confirmed by synthetic studies, and the routes which led to successful synthesis of the selenium degradation products (IV and V; MeO = H) of ibogamine are given in Chart V. A third product (25) of the selenium dehydrogenation of ibogaine (ibogamine gave a similar product), characterized as its picrate, mp 165–167°, may be VII (R = MeO), but it has not been further examined (cf. the analogous dehydrogenation product of cinchonamine, p. 239).



VII



VIII

In an attempt to confirm the formula for ibogaine derived from the foregoing results, rings A and B of ibogaine lactam (XI), mp 221°, $[\alpha]_D$ −16° (EtOH), were removed oxidatively to furnish a dibasic acid, believed to be VIII, in an amount unsuitable for further degradation (25).

The chemistry of the (auto)oxidation products of ibogaine can now be considered (Chart II). Ibogaine in air with or without catalytic assistance (25, 26) was readily convertible into the indolenines, 9-hydroperoxy-9*H*-ibogaine[1] (IX), mp 218°—220°, and 9-hydroxy-9*H*-ibogaine[1] (X). This is a well-understood process which requires no comment except that in

[1] The names are derived systematically from the hypothetical tautomer of ibogaine, 9*H*-ibogaine:

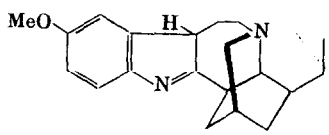
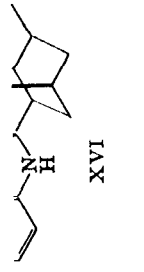


CHART II. Oxidative transformations of ibogaine.

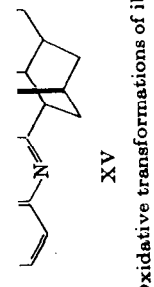
this case it is unusually facile as compared with other indoles. The derivation of iboquine (XII) and iboluteine (XIII) from these indolenines was in agreement with the work on model compounds. With other oxidizing agents, especially chromic oxide in pyridine, ibogaine gave ibogaine lactam (XI) along with 8,19-dioxoibogaine (XIV), mp 318°–320°, $[\alpha]_D$ −49° (EtOH) (25). The facile formation of a lactam, in contrast to the behavior of other indole alkaloids, e.g., yohimbine, was a consequence of a suitable stereochemistry about the nitrogen. The formation of the 8-oxo compound may be a result of an initial attack of the reagent at C-9 followed by rearrangement to the C-8 hydroxy derivative which undergoes further oxidation. In the case of the chromic acid oxidation of yohimbine, an alternate pathway is preferred (27), which leads to $\Delta^{3,14}$-yohimbine (28). The chromic acid oxidation of iboquine and iboluteine gave the analogous lactams XV and XVI, respectively (25). In none of the work were any 7-oxo compounds detected.

Lithium aluminum hydride reduction of ibogaine lactam regenerated ibogaine as expected (25). The same reduction of iboluteine, which also was claimed (26) to give back ibogaine, in actual fact produced dihydrodeoxyiboluteine, mp 78°–79° (29, 30). If iboluteine was reduced by sodium borohydride, two dihydroiboluteines (XVII) were obtained: A, mp 150°–152° $[\alpha]_D$ +28° (EtOH); and B, mp 184°–186°, $[\alpha]_D$ −63° (EtOH). Both A and B upon treatment with acid afforded the inverted ibogaine derivative (XVIII), picrate, mp 201°–202° (30). This was the expected result, since in a Wagner-Meerwein rearrangement the more nucleophilic group generally migrates.

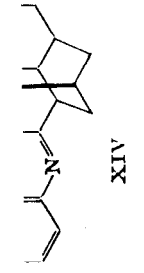
The availability of iboluteine (XIII) made possible work which provided a second proof of the structure of ibogaine (Chart III), along with its unequivocal correlation with ibogamine and tabernanthine (25). When *O*-tosyliboluteine oxime (XIX) was refluxed in pyridine, it underwent an abnormal Beckmann rearrangement to provide 4-methoxyanthranilonitrile (XX) and the ring C contracted ketone (XXI). The same ketone and the corresponding anthranilonitriles were obtained analogously from the pseudoindoxyls of ibogamine and tabernanthine. The amino ketone (XXI) subjected to a von Braun cyanogen bromide reaction (25) gave the *N*-cyano ketone (XXII) which, after reduction ($LiAlH_4$) to XXIII and dehydrogenation (Se), gave 6-methyl-8-ethylquinoline (XXIV). The rotatory dispersion of the ketone (XXII) was compared with a number of decalones and found to resemble most closely that of 1-*cis*-9-methyl-4-decalone, whose absolute configuration is known. Assuming that a decahydroquinolone can be equated with a



XVI



XV



XIV

CHART II. Oxidative transformations of ibogaine.

XIII Iboluteine

XVII

XVIII "Invert" ibogaine

XIX

XXI

XXII

XXIII

XX

XXIV

CHART III. Degradation of iboluteine.

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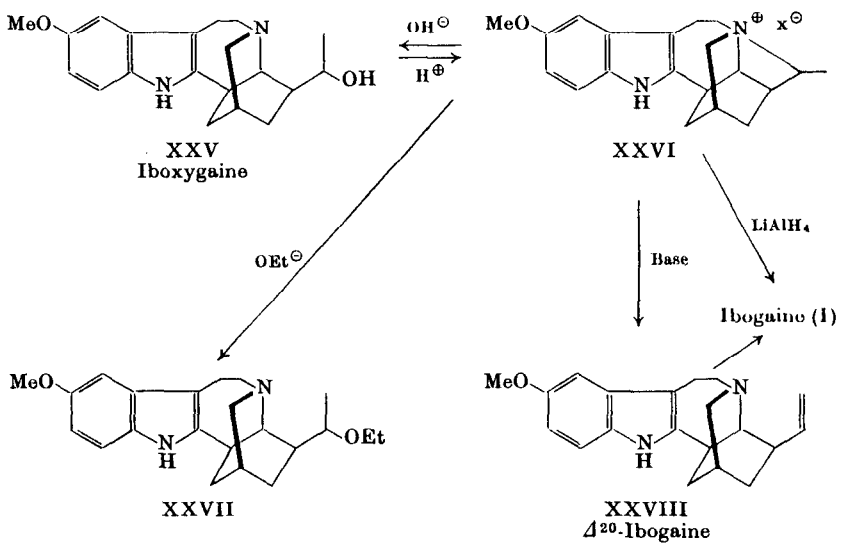
decalone and that the angular methyl group does not make much difference, then the foregoing comparison is valid. This means that the stereochemistry of ibogaine is that pictured in I, with the exception of the configuration of the ethyl group.

The configuration of the ethyl group, as well as an independent proof of the thus developed structure of ibogaine, came from a three-dimensional X-ray analysis of its hydrobromide (31).

On the chemical side, the stereochemistry of the ethyl group of ibogaine was a consequence of the properties of 20-hydroxyibogaine [iboxygaine, kimvuline (XXV)]. Iboxygaine gave a positive iodoform reaction, formed an amorphous ketone, and furnished acetic acid upon chromic acid oxidation (5). Borohydride reduction of the ketone gave an amorphous alcohol, also obtainable by Wolff-Kishner reduction, but the relationship of this product to the starting alcohol is not known (32).



Upon treatment with tosyl chloride in pyridine, a quaternary salt (XXVI) was produced (5). The quaternary base was reconverted into iboxygaine by aqueous sodium hydroxide (33). With sodium ethylate, on the other hand, 20-ethoxyibogaine [XXVII, iboxygaine ethyl ether, γ-isomer of Stauffacher and Seebeck (16)], mp 194°–196°, $[\alpha]_D$ −16° (EtOH), was the major product (33). In both the preceding reactions, Δ^{20}-ibogaine (XXVIII), mp 155°–156°, $[\alpha]_D$ −80° (EtOH), was also

isolated, hydrogenation of which gave ibogaine. If the crude Hofmann products were reduced before work-up, ibogaine along with an unidentified isomer, mp 119°–120°, $[\alpha]_D$ +95° (EtOH), was obtained (33). Treatment of XXVI under Emde conditions (Na/EtOH) was reported to yield ibogaine, a β-isomer, mp 185°–187°, $[\alpha]_D$ −114° (EtOH), and 20-ethoxyibogaine (16), but a repetition of this experiment by another group gave only the last two substances (33). By far the most efficient

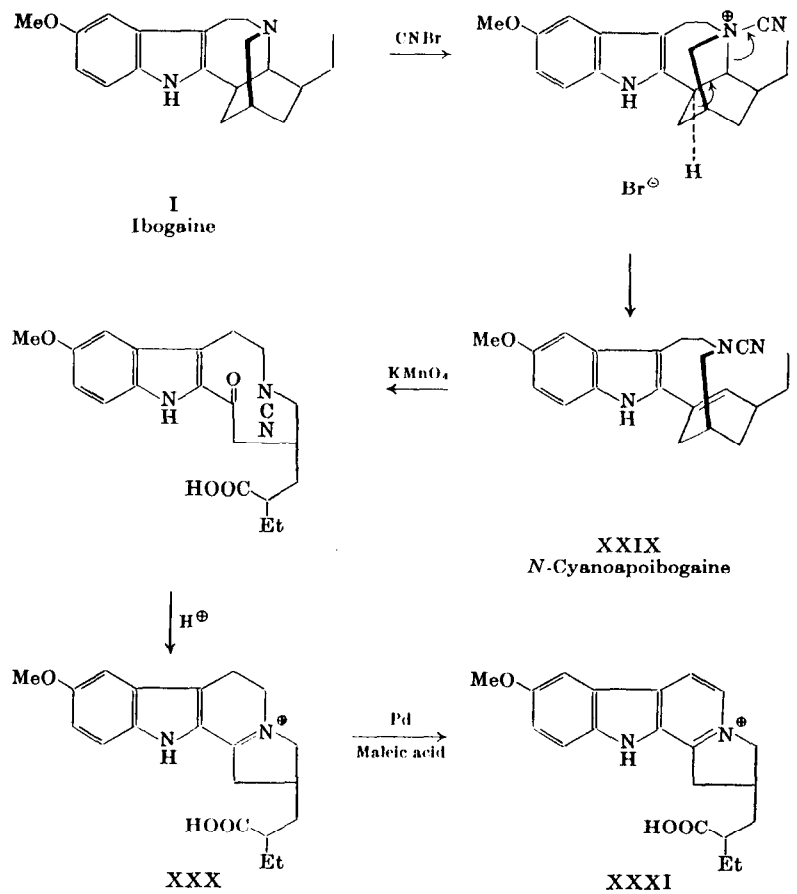


CHART IV. Von Braun degradation of ibogaine.

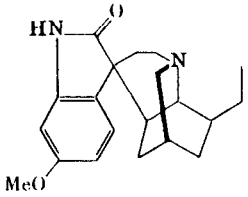
agent for the conversion of XXVI to ibogaine was lithium aluminum hydride (34).

A third degradation (Chart IV) of ibogaine, not carried as far as a known compound, was complementary to the above results and is of

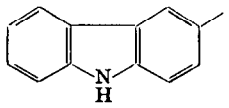
interest because it is a conversion of the indoloazepine rings A, B, C into a derivative of a β-carboline (25). The first step leading to *N*-cyanoapoibogaine (XXIX) may be a Hofmann-type elimination. The subsequent reactions require little comment, except to point out that either XXX or XXXI may be suitable for correlation with substances of known absolute stereochemistry.

B. Ibogamine and Tabernanthine

Both ibogamine and tabernanthine (formulas, Table I) have been related to ibogaine via fission of their respective pseudoindoxyls in the manner indicated in Chart III (XIX → XX + XXI). In general, their chemical reactions were very similar to those of ibogaine, although tabernanthine, during the preparation of its pseudoindoxyl, gave rise to an oxindole (XXXII), mp 191°–197°, a class of compound which was not picked up in the more exhaustive study of ibogaine (25). Both ibogamine lactam, mp 329°–331°, and tabernanthine lactam, mp 312°–315°, were also prepared (25).



XXXII



XXXIII

Selenium dehydrogenation (25) of ibogamine gave products completely analogous to ibogaine, viz., IV, V, and VII (MeO = H in all three), the two major products being synthesized according to the procedures outlined in Chart V (35). Zinc dust distillation (36) of ibogamine yielded 3-methyl-5-ethylpyridine along with an unexpected compound, 3-methylcarbazole (XXXIII). The formation of the latter, although it was of no value in the elucidation of the structure of ibogamine, may be a characteristic pyrolytic product for this heterocyclic system under such reaction conditions.

C. 18-Carbomethoxy Alkaloids

The structures of these compounds (see Table I) have been established almost entirely by decarbomethoxylation to the parent heterocycle.

CHART V. Synthesis of the selenium degradation products of ibogamine.

The
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boxyl
indole
metho

MeO

LiAl
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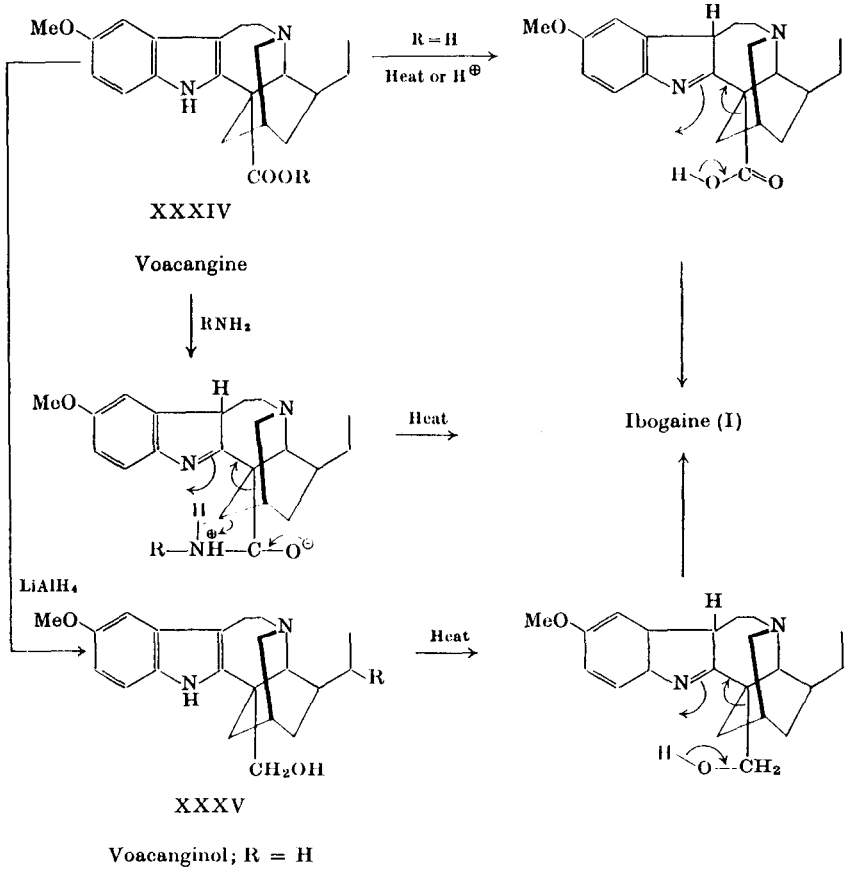
The properties of voacangine (XXXIV, 18-carbomethoxy-12-methoxyibogamine) are characteristic of this group. Voacangine is about 2 pK_a units less basic than ibogaine. Voacangic acid was readily decarboxylated thermally or by reflux in mineral acid (37), and resembled indole-2-acetic acid (38) in this property. The ester also suffered decarbomethoxylation when refluxed with suitable amines such as hydrazine or



ethanolamine (14). Voacanginol ($LiAlH_4$ reduction product of voacangine), mp 203°, $[\alpha]_D$ +38°, ($CHCl_3$), eliminated formaldehyde above its melting point to furnish ibogaine (39). The ease with which these eliminations proceed is facilitated by the almost planar geometry of the

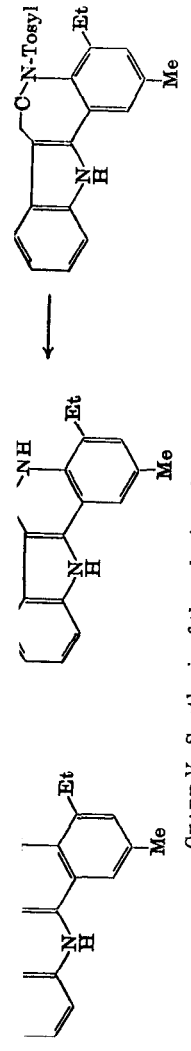
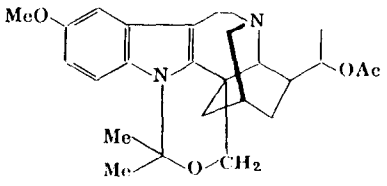


CHART V. Synthesis of the selenium degradation products of ibogamine.

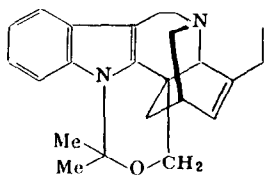
aromatic rings, C_{18}, and its substituent. The reactions are believed to proceed by the illustrated mechanisms, which involve the intermediacy of the 9*H*-tautomer, the indolenine (25, 14, 39).

Voacanginol could be tosylated without quaternization occurring (cf. iboxygaine, Section I, A), and the resulting sulfonate with lithium aluminum hydride afforded 18-methylibogaine, mp 189°–190° (32).

The site of the carboxyl in voacangine was confirmed by treating 20-hydroxyvoacanginol (XXXV; R = OH) with acetone containing hydrogen chloride to yield the acetonyl derivative, which was characterized as its *O*-acetate (XXXVI) (16). A similar reaction, starting from Δ^3-coronaridine (see Table I), led analogously to XXXVII (40).

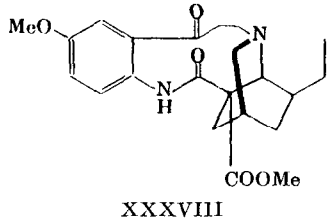


XXXVI

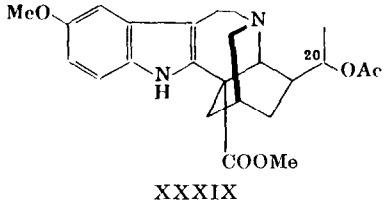


XXXVII

With palladium charcoal, voacangine gave the expected 3-methyl-5-ethylpyridine along with an as yet unidentified 5-methoxyindole (or indolenine), $C_{11}H_{13}NO_2$ (?), mp 80°–81°. In the same paper, isovoacangine (see Table I) was shown to furnish, along with the pyridine, a product, mp 81°–82°, which was assumed to be 6-methoxy-2-methyl-3-ethylindole (11). When selenium was used, ibogaine was the only isolable product. Ozonolysis of voacangine has given a yellow compound,



XXXVIII



XXXIX

mp 186°–187°, $[\alpha]_D$ +136° ($CHCl_3$), for which the structure XXXVIII was suggested (11). This formula might be in agreement with the recorded UV-spectrum (λ_{max} 270, 386 mμ), but its stability to base is more difficult to understand, since it furnished an acid reconvertible into the ester with

diazomethane rather than a carbomethoxyiboquine. Voacanginol gave an analogous product (XXXVIII; COOMe = CH_2OH).

Voacangine has been subjected to the action of cyanogen bromide (11) and has yielded three compounds: the major product, an indole, $C_{23}H_{28}N_3O_3Br$, mp 203°–204°, $[\alpha]_D$ −92°; minor products, an indole, $C_{23}H_{28}N_3O_3Br$, mp 238°–240°, $[\alpha]_D$ +46°, and an indolenine (?), $C_{23}H_{27}N_3O_3$, mp 175°–176°, $[\alpha]_D$ −34°. The first two compounds were probably normal von Braun products, one of which may be convertible into *N*-cyanoapoibogaine (XXIX). The formation of the indolenine would be a consequence of the nucleophilic reactivity of the indole at C-9 and another example (quebrachamine and cyanogen bromide) is reported in the same paper.

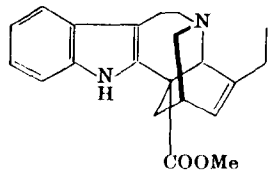
The catalytic oxidation of voacangine has been studied (32). After reduction of the "hydroperoxide," a compound, mp 249°, $[\alpha]_D$ −45° ($CHCl_3$), was isolated that was suggested to be 18-carbomethoxyibogaine lactam but, in the absence of proof of its nonbasic character, UV-absorption data, or decomposition into ibogaine lactam, its reformulation as an oxindole [cf. formation of tabernanthine oxindole (XXIII)] is a possibility.

D. Voacryptine

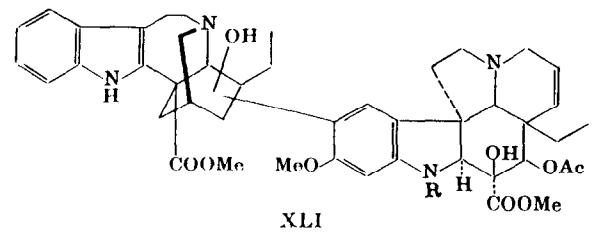
Voacryptine (see Table I) was recognized to be an oxovoacangine on the basis of its impirical formula and physical properties (41). The carbonyl group was placed on the side chain, since only acetic acid was produced after chromic acid oxidation and by its positive iodoform reaction. Voacryptine formed an oxime, mp 114°–116°, and under Wolff-Kishner conditions it generated ibogaine. Because of the basic conditions of the last experiment, it was not possible to deduce the configuration of the acetyl side chain. However, reduction of voacryptine with potassium borohydride gave a mixture of diastereoisomeric dihydro compounds which was acetylated and resulted in the isolation of voacristine *O*-acetate (XXXIX), mp 191°–193°, $[\alpha]_D$ −27° ($CHCl_3$), and a second compound, mp 180°, which, it was suggested, may have been slightly impure 20-epivoacristine-*O*-acetate (41). Therefore, unless it can be shown that an epimerization at C-4 preceded the borohydride reduction of voacryptine, its stereochemistry can be considered as established. It can also be deduced that the β-configuration of the ethyl is preferred over the α-configuration; some support for this can be adduced by a conformational argument, based on the skewed nature of the isoquinuclidine moiety (cf. catharanthine and the related quinuclidine system in ajmaline, Chapter 22).

E. Catharanthine, Cleavamine, and Velbanamine

The occurrence of catharanthine (XL) is presently confined to *Vinca rosea* L., and it is the only known iboga alkaloid to contain an olefinic double bond (40). A derivative of this compound makes up the indolic portion of the clinically useful antileukemic drug, vincaleukoblastine



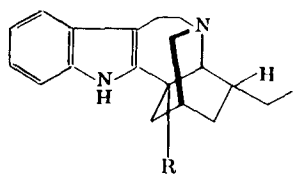
XL



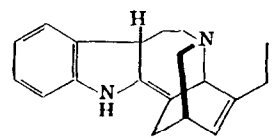
XLI

(XLI; R = CH_3). Hydrogenation (12) of catharanthine led to only one isomer, dihydrocatharanthine (XLII, 18-carbomethoxy-4-epi-ibogamine), mp 63°–65°, $[\alpha]_D$ +35° ($CHCl_3$), the hydrogen coming in on the less hindered side of the isoquinuclidine residue (40).

The alkaloid behaved similarly to voacangine, since on the one hand its dihydro derivative was readily decarbomethoxylated to 4-epi-ibogamine (XLIII), mp 162°–164°, $[\alpha]_D$ +86° (hydrochloride in MeOH), and on the other its lithium aluminum hydride reduction product, catharanthinol, afforded an acetonide (XXXVII), mp 188°–191°. To account for the difficulty with which catharanthine eliminated the carbomethoxy group, it has been suggested that an intermediate in this reaction (XLIV) is highly strained (40). Since XLIV can be readily constructed from Dreiding Atomic Models, this explanation may not be correct. In actual fact, it is probable that the acid-catalyzed decomposition of catharanthine takes a different course. It has more recently



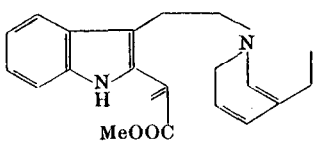
XLII; R = COOMe
XLIII; R = H



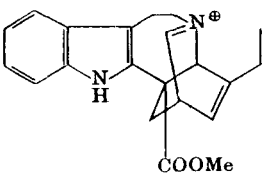
XLIV

been shown that catharanthine is converted in concentrated hydrochloric acid under reflux into Δ^3-ibogamine (hydrochloride, mp 150°–154°, $[\alpha]_D$ +90°) and cleavamine (XLVII), the low yield being higher if a

reducing agent (e.g., stannous chloride) was present (42, 42a). This point is discussed further at the end of this section. The structure of catharanthine was completely established by the isolation of the indoloquinoline (Chart I, V; MeO = H) from the selenium dehydrogenation products of XLIII (40). Whereas XLII required a temperature of 230°–250° in the presence of palladium on carbon to generate 3-methyl-5-ethylpyridine, catharanthine with the same catalyst at 150°–160° gave a good yield of 3-ethylpyridine. The latter reaction may proceed via the retro Diels-Alder product, XLV, or, even better, via XLVI, whose fragmentation would be even more facile than that of XLII.

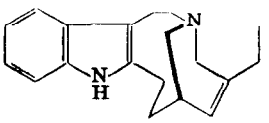


XLV

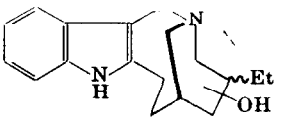


XLVI

The structures of cleavamine and velbanamine are considered here since they are probably derived from precursors with the iboga skeleton. Cleavamine (XLVII), mp 109°–113°, $[\alpha]_D$ +56° ($CHCl_3$), was obtained along with deacetylvindoline when leurosine (structure unknown but closely related to XLI) was refluxed with concentrated hydrochloric acid, stannous chloride, and tin (42). Velbanamine (XLVIII), mp 139°–141°, $[\alpha]_D$ +56° ($CHCl_3$), was the indolic product when vincaleukoblastine (XLI; R = Me) or leurocristine (XLI; R = CHO) were treated in the same way (42). Aside from the question of the mode of fission of the dimers (XLI), the production of the new tetracyclic systems in XLVII and XLVIII can be regarded as proceeding via a reverse Mannich



XLVII

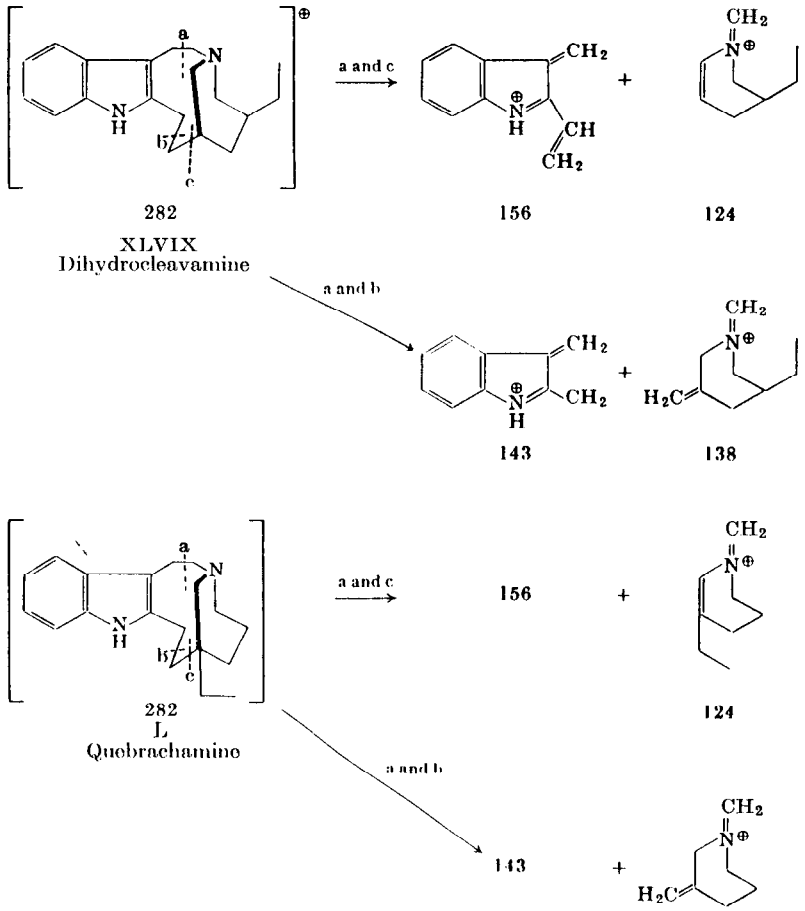


XLVIII

reaction, reduction of the resulting iminium salt, and decarbomethoxylation. If the pentacyclic iboga system does not pre-exist in the dimer, a reverse Mannich reaction would not have to be invoked.

Reduction of cleavamine gave a dihydro derivative, mp 136°–138°, which is a *C*-ethyl isomer of quebrachamine, and, in fact, their IR-spectra

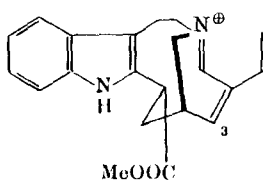
are very similar. Of particular interest was a comparison of the mass spectra of dihydrocleavamine (XLVIX) and quebrachamine (L), which showed the expected similarities, viz., aromatic residues m/e 156 and 143, hydroaromatic residue m/e 124 (42a, 42b). This developed structure



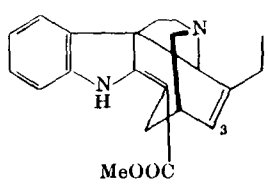
for cleavamine has been confirmed in all respects by the determination of its structure by X-ray crystallographic analysis (42c).

In a recent paper, the formation of cleavamine and Δ^3-ibogamine from catharanthine (XL) under strongly acidic reducing conditions has been discussed in greater detail (42a). It is regarded as proceeding via the

retro Mannich or equivalent product (LI) which after decarboxylation could either be reduced to furnish cleavamine or ring closed again to generate Δ^3-ibogamine. An analogous intermediate (LI; Δ^3 double bond reduced) has to be invoked if the production of ibogamine along with



LI



LII
LIII (Δ^3-reduced)

4-epi-ibogamine by the prolonged reflux of either 18-carbomethoxy-ibogamine or its C-4 epimer in concentrated hydrochloric acid is to be understood (42a). The carbomethoxy group is essential for the ring opening since, under identical acidic conditions, the C-4 epimeric ibogamines were recovered unchanged.

LI as its equivalent indole has also to be invoked to explain the formation of two new bases, pseudocatharanthine (LII), mp 114°–116°, $[\alpha]_D$ ± 0° (solvent unspecified), and pseudodihydrocantharanthine (LIII), by refluxing catharanthine for 16 hours in acetic acid. The absence of water must be an important contributor to the success of this reaction because, in aqueous acid, it is the free acid which decarboxylates to drive the reaction in the direction of cleavamine (42a).

F. Mass Spectra of Iboga Alkaloids

Just as UV-, IR-, and NMR-spectra are used to identify structural elements, to fingerprint, and to elucidate the structures of molecules, so very recently has mass spectroscopy been applied to the problems of the organic chemist with very useful results in the case of indole alkaloids, of which the iboga group is but one class. When the mass spectra (34) of ibogamine, ibogaine, tabernanthine, and ibogaline are compared, they show a group of peaks m/e 122, 124, 135, 136, and 149 owing to fragments of the molecule originating from a part which does not contain the additional substituents in the benzene ring. A second group of peaks in the case of ibogamine, at m/e 156, 175, 251, 265, and 280, appear with almost the same intensity but 30 mass units higher for ibogaine and tabernanthine and 60 mass units higher for ibogaline. These results

The asterisked structure becomes a positive ion if the alternate fission takes place; then, M = 122 is a radical.

CHART VI. Principal electron-impact fragmentation products of ibogaine.

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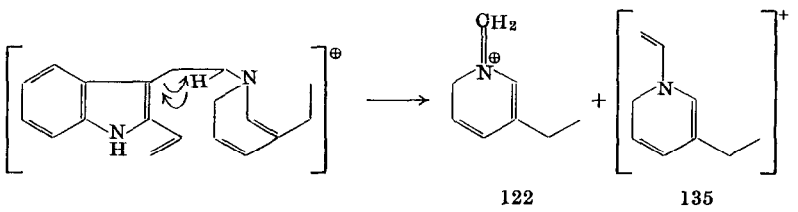
at 253,
$C_{21}H_{28}$

alone, accumulated on a few micrograms of material, show (stereochemistry excepted) that they differ only in the nature of the methoxyl substituent(s). In this way, the structure of ibogaline was proved to be 12,13-dimethoxyibogamine, which is in agreement with an earlier suggestion. The course of the fragmentation has been deduced (Chart VI) and was supported by the examination of deuterio compounds, e.g., ibogaine-20-*d* from XXVI and lithium aluminum deuteride; ibogaine-18-*d* from the decarbomethoxylation of voacangine by deuterated hydrazine; and ibogaine-19-d_2 by reduction of ibogaine lactam with lithium aluminum deuteride.

In the case of the carbomethoxy alkaloids, the fragmentation peaks which contain the aromatic nucleus are 58 mass units higher, and the typical iboga pattern in the range 120–150 mass units is retained without alteration.

The pattern changes for Δ^3-ibogamine (XL; COOMe = H; decarbomethoxycatharanthine) and fissions "d" and "e" (Chart VI) are negligible, since the ethyl group is no longer close to N_b, which stabilizes the charge in the saturated bases. The presence of the double bond facilitates a retro Diels-Alder cleavage, the product of which directly yields m/e 122 or, by hydrogen rearrangement, m/e 135, along with m/e 136, 143, and 156 analogous to those of dihydrocleavamine (XLVIX) (42a, 42b).



122 135

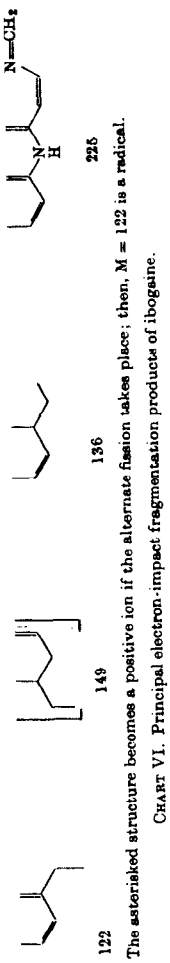


CHART VI. Principal electron-impact fragmentation products of ibogaine.
The asterisked structure becomes a positive ion if the alternate fission takes place; then, M = 122 is a radical.

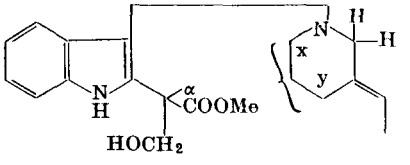
G. OTHER ALKALOIDS

Under this heading are collected the alkaloids from the plants given in Table I, with the exception of the iboga bases already considered and those dealt with under *Voacanga* alkaloids.

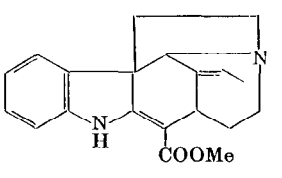
There were two bases isolated from *Tabernanthe iboga*, gabonine and kisantine, by only one group of workers (6). Gabonine, $C_{21}H_{28}N_2O_4$, mp 223°–226°, $[\alpha]_D$ + 65° ($CHCl_3$), had bands in the carbonyl region at 1672 cm^{-1} (medium) and 1620 cm^{-1} (strong); its UV-spectrum with maxima at 253, 287, and 355 mμ is indicative of extended conjugation. Kisantine, $C_{21}H_{28}N_2O_3$, mp 236°–238°, $[\alpha]_D$ − 15° ($CHCl_3$), had a medium-strength

band at 1670 cm^{-1} and an indole-like UV-spectrum. It has recently been recognized that kisantine is an oxindole, i.e., the 12-methoxy derivative of XXXII, and that gabonine may be the 13-methoxy equivalent of XXXVIII (COOMe=H). Both these alkaloids may be artifacts obtained instead of ibogaline in the original isolation procedure (6).

From *Stemmadenia donnell-smithii*, besides iboga alkaloids and voacamine, the indole (+)-quebrachamine (L), mp 147°–149°, $[\alpha]_D$ +111° ($CHCl_3$), and the indole stemmadenine (LIV, $\alpha \rightarrow x$ or $\alpha \rightarrow y$ bond), mp 199°–200° (dec.), $[\alpha]_D$ +324° (pyridine), were isolated (11). The latter alkaloid also occurs in *Diplorrhynchus condylocarpon* (43) along with condylocarpine, shown (43a), to be LV (rather than LVI), and into which it was converted by potassium permanganate oxidation (44). Stem-

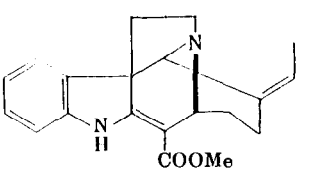


LIV



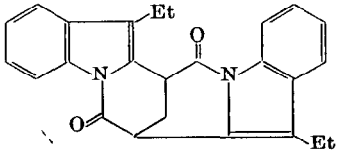
LV

or

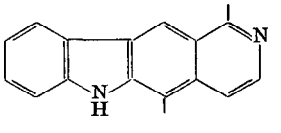


LVI

madenine is therefore LIV (α—y bond). These results were derived largely from a comparison of the physical properties (UV-, IR-, NMR-spectra) and mass spectra of a number of derivatives, among which were the palladium dehydrogenation products of stemmadenine, the dimer (LVII), and 3-ethylpyridine, which accounted for all the carbons of the original molecule (44). In the NMR-spectrum, the ethyl signals in dihydrocondylocarpine were at abnormally high field which was



LVII



LVIII

compatible with either structure, since the ethyl group would lie either above the aromatic ring [this is true for the *C*-ethyl of vindoline (42)] or above the acrylic ester system (44).

From *Ervatamia*, besides coronaridine, the 2-acylindoles tabernaemontanine and dregamine (*vide infra*) were obtained; from various *Tabernaemontana* species, iboga bases, voacamine, and olivacine (LVIII), mp 318°, were identified (10).

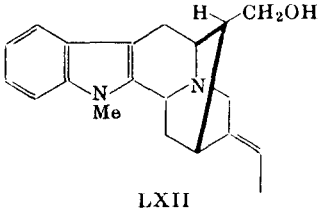
Conopharyngia durissima has afforded iboga bases, two dimeric alkaloids discussed under *Voacanga* alkaloids, and a trace of a base, alkaloid E, mp 191°–193°, pK'_a 7.26, UV-maxima at 210 and 305 mμ, which differed from the other isolates in having no carbonyl absorption in the IR-spectrum (14). *Conopharyngia pachysiphon*, in contrast to *C. durissima*, has yielded only steroidal bases (45).

II. The *Voacanga* Alkaloids

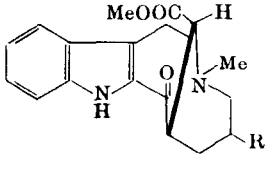
Plants of the *Voacanga* genus have given rise so far to four groups of bases, apart from the iboga type represented by voacangine, voacristine, and voacryptine (Table I); these are the sarpagine, 2-acylindole secosarpagine (derivatives), carbomethoxymethyleneindoline, and dimer types (Table II). The terms "bisindoles" or "dimers" were used to indicate the belief that the last group is probably derived by a doubling-up of monomeric systems. The reported production of voacangine from voacamine supports this view. The genus *Callichilia* is included here, since vobtusine is a constituent of the three species examined.

A. Voachalotine

This alkaloid is a member of the sarpagine group, and its structure was readily derived by simple transformations (58) which, among others, enabled it to be correlated with N_a-methyldeoxysarpagine (LXII). Its



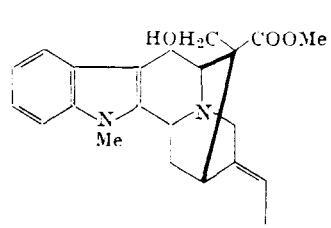
LXII



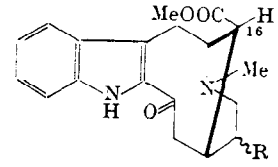
LXIII

TABLE II

Voacanga AND RELATED ALKALOIDS[a]



LIX



LX; R = $CHCH_3$
LXI; R = Et

Name	Melting point (° C)	$[\alpha]_D$ ($CHCl_3$)	Observations	Source[b]
A. Sarpagine type				
Voachalotine (LIX)	223–224	−3°		q(46)
B. 2-Acylindoles				
Vobasine (LX)	111–113	−158°		o(17)
Tabernaemontanine (LXI)	208–210 217–219	−57°	Dihydrovobasine	k(47)
Dregamine (LXI)	106–109 186–205	−93°	Dihydrovobasine	r(48), e(10)
Voacafrine ($C_{22}H_{26}N_2O_4$)	135–137	−107° (B.HCl in MeOH)	Structure unknown	o(49)
Voacafricine ($C_{22}H_{24\text{-}26}N_2O_4$)	196–198	—	Structure unknown	o(49)

Voacafrine ($C_{22}H_{26}N_2O_4$)	135–137	−107° (B.HCl in MeOH)	Structure unknown	o(49)
Voacafricine ($C_{22}H_{24\text{-}26}N_2O_4$)	196–198	—	Structure unknown	o(49)
C. Carbomethoxymethyleneindoline type				
Callichiline ($C_{22}H_{24}N_2O_3$)	235	−460°	UV ≈ β-anilinoacrylate	c(50)
D. Bisindoles: structures unknown (tentative formulas)				
Voacamine (voacanginine) ($C_{45}H_{56}N_4O_6$)	223	−52°	2 COOMe, OMe, NMe; UV ≈ 5 MeO-indole; acid yields voacangine (61)	o(51, 9), t(51), s(52), h(11)
Voacorine [voacaline ? (54)] $C_{45\text{-}46}H_{54\text{-}56}N_4O_7$	273	−42°	2 COOMe, OMe, NMe; UV ≈ 5 MeO-indole; acid yields no voacangine (61)	o(53), p(56)
Vobtusine ($C_{42}H_{48}N_2O_6$)	305	−321°	2 COOMe, 1 NMe; UV ≈ β-anilinoacrylate	o(51), r(13), t(51), s(52), c(50), b(55), a(55)
Voacamidine ($C_{45}H_{56}N_4O_6$)	128	−174°	2 COOMe, OMe, NMe; UV ≈ voacamine	o(15)
Voacaminine	242	−45°	Mixgure of voacamine and voacarine (32)	o(8, 57), t(8, 57)
Conodurine ($C_{41\text{-}42}H_{50\text{-}52}N_4O_5$)	222–225	−101°	2 COOMe, OMe, no NMe; UV ≈ voacamine	d(14)
Conoduramine ($C_{41\text{-}42}H_{50\text{-}52}N_4O_6$)	215–217 (foaming)	−77°	2 COOMe, OMe, no NMe; UV ≈ voacorine	d(14)

[a] Co-occurring iboga alkaloids and plant key are given in Table I, page 204.

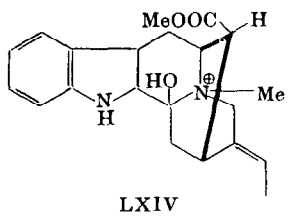
[b] Parenthetical numbers refer to reference list.

chemistry and relationship to other members of the ajmaline-sarpagine group is discussed in Chapter 22. The presence of a methyl substituent on N_a is for the present of rare occurrence among indole alkaloids.

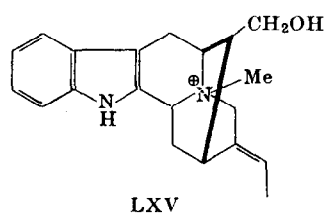
B. Vobasine, Dregamine, Tabernaemontanine, and Callichiline

Dregamine and tabernaemontanine were recognized (10) to possess a 2-acylindole chromophore, and vobasine has been correlated to them by showing that the first two alkaloids were diasteroisomeric dihydrovobasines (59). On the basis of degradation work, which has not been reported in full, the structures LX and LXI (see Table II) have been deduced for these alkaloids, although the experimental results do no uniquely establish the heterocyclic system shown. Biogenetic considerations may have influenced the authors since, among others, LXIII also fits the published data.

Vobasine, by either the action of strong base or hydrolysis followed by re-esterification, gave isovobasine (LX; C-16 epimer), mp 175°–178°, $[\alpha]_D$ −191° ($CHCl_3$) (17). Vobasine methiodide, subjected to a Hofmann degradation under mild conditions, furnished vobasine methine, $[\alpha]_D$ −103° (UV-spectrum = 3-vinyl-2-acylindole). From isovobasine, an analogous methine ($[\alpha]_D$ +45°; UV-spectrum = 3-vinyl-2-acylindole) was obtained. Both methines, upon treatment with sodium methoxide, formed the same optically inactive vobasineisomethine (no change in the UV-spectra). It should be noted that two optically active centers are involved in this "racemization." Vobasine methine subjected to a second Hofmann degradation eliminated trimethylamine to yield deazavobasine, which retained the 3-vinyl-2-acylindole moiety and had, in addition, an isolated 1,3-diene function. Hexahydrodeazavobasine,



LXIV



LXV

upon oxidation with chromic acid, formed α-methylbutyric acid (60). If the structure LX for vobasine is correct, then LXIV may exist in acidic solution. Such an observation could be made the basis of a trivial solution

for the structure of this class of compound, viz., the quaternary salt macusine B (LXV) should be the product of the acid treatment of the lithium aluminum hydride reduction product of either vobasine or isovobasine. Borohydride reduction (59) of vobasine gave vobasinol, mp 100°–102° (solvate) (*O*-acetate, mp 160°–162°) upon which the action of acid could also be tried.

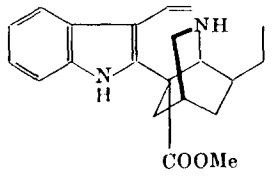
The structure of callichiline, apart from recognition of its chromophoric moiety which must include the carbonyl and methoxy groups, is practically unknown; it has no *N*-methyl and is apparently not identical with any of the other indole alkaloids (about a dozen) with the same UV-spectra. If the functional group analyses are correct, biogenetic considerations would suggest that the formula be revised to $C_{21}H_{22-24}N_2O_3$.

C. Bisindoles

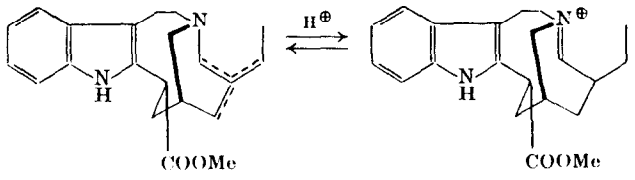
The known members of this group can be divided into three classes on the basis of their UV-spectra and base strengths. First, vobtusine with a UV-$\approx$two β-anilinoacrylates and pK_a 6.95 may be built up of two identical monomeric units (two callichilines ?). Second, voacorine with pK_a 6.40 and a chromophoric moiety approximately equal to two isolated 5-oxyindoles may also be constructed from identical units. Third, voacamine and conduramine, also with 5-oxyindole chromophores, with two dissociation constants pK'_a $\sim$5.4 (note similarity to voacangine, pK'_a 5.6) and $\sim$7.0 may be derived from two dissimilar units. Voacamidine and condurine remain unplaced, since their dissociation constants are unknown.

In all cases where a *C*-methyl determination has been made and where the resulting acids have been analyzed, they have been found to have formed acetic acid which, although excluding methyls attached to methylene, in these alkaloids cannot distinguish between an ethylidene (resistant to hydrogenation ?) and/or a —CHOR—CH_3 residue (R unspecified). The nature of the fusion in these bisindoles is still unknown, and it does not appear to involve an aldehyde function, as it does in certain curare and *Geissosperma* alkaloids. Among other possibilities are ether bonds, involvement of N_a (*vide infra*), or a linkage similar to that in the indole-indoline alkaloids represented by vincaleukoblastine (XLI). The isolation (61) of voacangine from voacamine (but not from voacorine), after reflux of the latter in 3 *N* hydrochloric acid or alcoholic hydrochloric acid, may indicate that voacangine is present as such in the dimer and is linked via N_a to the second unit. This would be in

agreement with the pK'_a data, the isolation of 3-methyl-5-ethylpyridine after potash fusion of voacamine (other products were trimethylamine, acetic acid, propionic acid, and perhaps isobutyric acid), and those properties of the alkaloid which showed that one of its carbomethoxyl groups could be removed under the same conditions as were successful with voacangine (32). There are, however, other possibilities to consider; thus, in the foregoing fission with hydrochloric acid, an intermediate such as LXVI, LXVII, or LXVIII could have been formed, all of which could collapse into the isolated monomer, voacangine. The suggestion (17) that vobasine is a precursor of voacamine and that the latter compound undergoes an inversion of one of its carbomethoxyl functions upon hydrolysis (cf. vobasine, Section II, B) cannot be decided on the



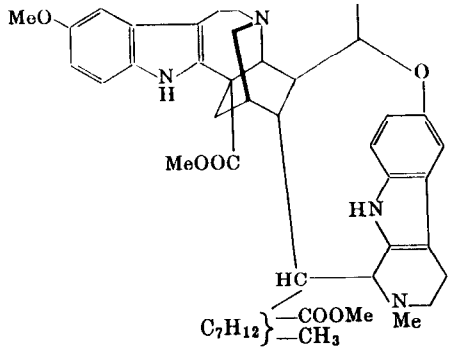
LXVI



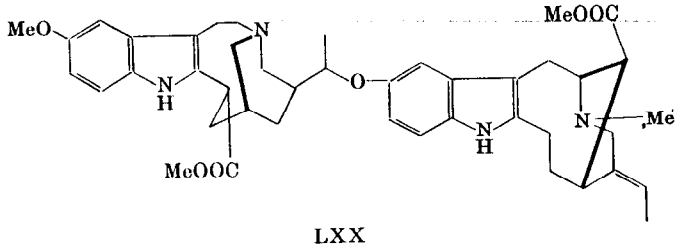
LXVII LXVIII

basis of published work. Saponification of voacamine gave a dipotassium salt which, upon esterification in methanolic hydrogen chloride, resulted in a decarbomethoxyvoacamine (32). The same product was also produced upon lithium aluminum hydride reduction of voacamine in refluxing tetrahydrofuran. Selenium dehydrogenation of voacamine produced 4-methyl-3-ethylpyridine (β-collidine) and β-carboline (32). This result could be interpreted as indicating that a voacangine nucleus does not pre-exist in voacamine, since voacangine with selenium has given the expected 3-methyl-5-ethylpyridine (13). Voacorine, like voacamine, furnished 3-methyl-5-ethylpyridine (56) upon potash fission, and vobtusine with selenium formed quinoline (13). A final property of significance is concerned with the behavior of both voacamine (62) and voacorine (56) upon pyrolysis *in vacuo* when trimethylamine and carbon dioxide (one mole equivalent of each) were given off. This has been

interpreted as occurring via a double betainization of the *N*-methyl and elimination via a retro Michael or fragmentation of a β-amino ester and/or extrusion of nitrogen from a γ or δ-dialkyl amino acid ester in which the corresponding lactone could be formed (56). Structure LXIX for voacamine has been put forward as a working hypothesis (32), although on the basis of the published information LXX is equally as attractive.



LXIX

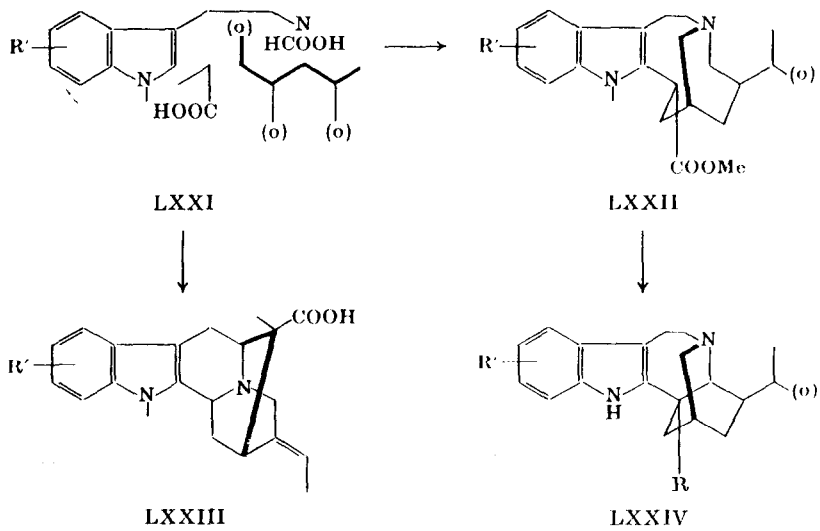


LXX

III. Miscellaneous

The mode of biosynthesis of none of these alkaloids is known but, in the case of the iboga group, some guesses have been made (39, 63, 64), all of which start from the amino acids, tryptophan and dihydroxyphenylalanine, and involve a fission of the latter's aromatic ring. A more sophisticated approach (65), starting from precursors of the aromatic amino acids, namely shikimic and prephenic acids, is apparently not in agreement with recent work on other indole alkaloids (66). The genesis of most indole alkaloids appears to stem from tryptophan and three

formal fragments, 6C + 1C + 3C (67), whose exact nature remains to be elucidated but are now thought to involve 3-acetates + formic acid + malonic acid. Thus, the origin of the iboga and related bases is depicted formally as LXXIII ← LXXI → LXXII → LXXIV, in which LXXII and LXXIV may be proximate precursors of the *Voacanga* alkaloids.



From a pharmacological point of view, the *Voacanga* alkaloids are relatively nontoxic, rapidly eliminated, and of no great interest (68). The reported potent cardiotonic properties (9, 54, 69) of some of these alkaloids have apparently not withstood the test of time (52).

The physiological actions of *Tabernanthe iboga* are very interesting. Its roots have been reported to exhibit sleep-combating and alerting effects (70). When chewed during stress, they are also said to prevent fatigue and hunger and have been used by natives in the Congo for this purpose (71). The roots have also been used in larger quantity by the same natives in fetishism. Modern research has traced this activity to the alkaloid portion and, in particular, to ibogaine (72). This alkaloid was shown to have distinct stimulating properties with weak anticonvulsant effects accompanied by reactions of apprehension and fear. Insertion of the carbomethoxyl group, i.e., voacangine, gave a product with only weak central nervous stimulating properties (73). Other papers have been published on pharmacological aspects which are beyond the scope of this article (74).

A particularly good summary of the early botany and pharmacology

of *Tabernanthe iboga* has been written (3), and a more recent paper has dealt with the former aspect in relation to the genus *Daturicarpa* (75).

A paper has appeared on some aspects of the physiological properties of the alkaloids of *Stemmadenia donnell-smithii* (76).

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