[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF CIBA PHARMACEUTICAL PRODUCTS, INC.]

# The Alkaloids of *Tabernanthe iboga*. Part IV.[1] The Structures of Ibogamine, Ibogaine, Tabernanthine and Voacangine

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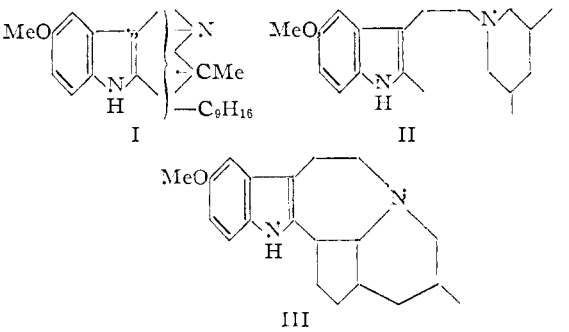
The alkaloids named in the title are shown each to have a C-ethyl group. Dehydrogenation of ibogaine with selenium gave 4-ethyl-5,6,7,12-tetrahydro-9-methoxy-2-methylindolo[3,2-d][1]benzazepine (VIII) and 4-ethyl-8-methoxy-2,6-dimethyl-11H-indolo[3,2-*c*]quinoline (IX). Similarly ibogamine furnished the corresponding demethoxy compounds From this knowledge the structures VIa and VI were derived for ibogaine and ibogamine, respectively, which have two unusual features for indole alkaloids—a seven-membered ring and an isoquinuclidine residue. A new method for the degradation of indole alkaloids was also developed and is illustrated by the fission of 6-methoxy-2,2-tetramethylene-pseudoindoxyl oxime into 4-methoxyanthranilonitrile and cyclopentanone. Since the respective pseudoindoxyl oximes of the first three alkaloids afforded the same tricyclic ketone (XX) and their corresponding anthranilonitriles, tabernanthine must be VIb. The ketone was further degraded into 8-ethyl-6-methylquinoline providing a second proof for the proposed formulas. A third proof for the structures is furnished by the conversion of a von Braun degradation product of ibogaine into a derivative of a β-carboline. For the first time lactams of these alkaloids were prepared. As a corollary to this work a new structure (XXXVI) is proposed for voacangine.

Although ibogaine, the principal alkaloid of *Tabernanthe iboga* Baillon, was first described by French authors[2] almost fifty years ago, it has only been the subject of a more detailed investigation within the last five years. Raymond-Hamet[3] first showed by means of color reactions that ibogaine was probably an indole and also that it had a methoxy group. In 1944, Delourme-Houdé[4] attributed to ibogaine the now accepted formula $C_{20}H_{26}N_2O$. Although the ultraviolet absorption spectrum was measured several times[4-6] and was recognized to be indolic, its exact nature was not established as a derivative of 5-methoxyindole until permanganate oxidation was found to afford 5-methoxy-N-oxalylanthranilic acid.[7] At that time all the information concerning the pentacyclic base could be summarized by the expression I. Later from the neutral products formed in a potash fusion of ibogaine Schlittler, *et al.*,[8] isolated 1,2-dimethyl-3-ethyl-5-hydroxyindole (IV) which they also synthesized. Since this was a rather unusual product that work has now been repeated and found to be correct. Although Schlittler, *et al.*, have argued that the isolation of IV might imply that ibogaine was a methoxytetrahydro-β-carboline, compounds of this type have not previously been recorded as yielding 2-alkyl substituted indoles under the described conditions. As far as the hydroaromatic portion of the molecule was concerned the first clue was provided by the isolation of 3-ethyl-5-methylpyridine (VII) from the basic fraction formed during the above fusion experiment.[9] These two fragments, assuming no overlap of atoms, accounted for all the carbons, both nitrogens and the oxygen of ibogaine and if these are put together with the further proviso that a tryptamine residue be present then the partial structure II for the molecule could be inferred. There remained two rings to be elaborated and it is clear that on the basis of II that ring C cannot be six membered since the basic nitrogen would have to be quaternary, but it could be five, seven or more. In agreement with this it should be noted that neither β-carbolines nor their derivatives have been isolated from the dehydrogenation products of ibogaine.[10,11]




A β-carboline moiety was also excluded on the grounds that in the present work no extension of conjugation was observed spectroscopically when ibogaine was treated with either lead tetraacetate, mercuric acetate or *t*-butyl hypochlorite. A five-membered ring C for the base could also be excluded because it was already known that autoxidized ibogaine could be converted into a pseudoindoxyl (iboluteine)[12,13] and a 4-quinolinol (iboquine),[11,12] rearrangements which involve a ring C

(1) (a) Paper III, D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek and W. I. Taylor, THIS JOURNAL, **80**, 123 (1958). (b) Presented at the Gordon Conference on Steroids and Related Natural Products, New Hampton, N. H., August 7, 1957.

(2) J. Dybowski and A. Landrin, *Compt. rend.*, **133**, 748 (1901); A. Haller and E. Heckel, *ibid.*, **133**, 850 (1901).

(3) Raymond-Hamet, *Bull. sci. pharmacol.*, **33**, 518 (1926); *Bull. soc. chim. biol.*, **25**, 205 (1943).

(4) J. Delourme-Houdé, Thèse doc. pharm., Paris, 1944. This thesis summarized very well the then known botanical, chemical and pharmacological material. More recently the neuropharmacological properties of ibogaine have been studied in detail; J. A. Schneider and E. B. Sigg, *Ann. New York Acad. Sci.*, **66**, 765 (1957).

(5) I. Sero, Thèse, doc. pharm., Toulouse, 1944.

(6) Raymond-Hamet, *Compt. rend.*, **229**, 1359 (1949).

(7) M.-M. Janot, R. Goutarel and R. P. A. Sneedon, *Helv. Chim. Acta*, **34**, 1205 (1951).

(8) E. Schlittler, C. A. Burckhardt and E. Gellért, *ibid.*, **36**, 1337 (1953).

(9) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Compt. rend.*, **237**, 1718 (1953).

(10) C. A. Burckhardt, Dissertation, Basle, 1953.

(11) R. Goutarel, Thèse doc. sci. Paris, 1954.

(12) R. Goutarel and M.-M. Janot, *Ann. pharm. franc.*, **11**, 272 (1953). No proofs are given in this note. In the case of iboquine no satisfactory spectral comparison has been published. Goutarel has compared iboquine with quinine. In the Experimental we have shown the close correspondence between ultraviolet of iboquine and 3-ethyl-6-methoxy-2-methyl-4-quinolinol.

(13) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Helv. Chim. Acta*, **39**, 742 (1956).

contraction.[14] Incidentally the formation of iboquine established a methylene group attached to the $\beta$-position of the indole residue.

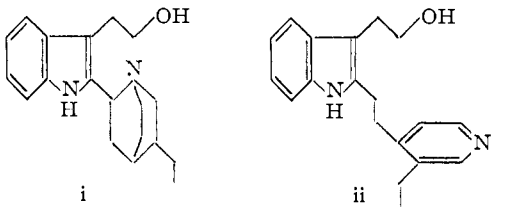
Goutarel[11] has proposed the structure III for ibogaine with a seven-membered ring C. It seemed surprising, however, if this formula should be correct, that expected dehydrogenation products such as indole–pyridine derivatives have not been readily formed and isolated.[15] There was also the implicit assumption that the C-alkyl determined by the Kuhn–Roth procedure was a C–Me which was unwarranted in view of the number of indole alkaloids[16] known to have a C–Et or its equivalent. We have found, through the use of paper chromatography, that the volatile acids formed in the chromic acid oxidation of ibogaine consisted of propionic and acetic acids; therefore the base must have had a C-ethyl[17] which eliminated III from further discussion.

In the potash fusion of ibogaine[8] besides the two compounds already mentioned, two isomeric bases, $C_{20}H_{26}N_2O$, were isolated and named compounds B and C whose properties suggested that the O-methyl had migrated to the indole nitrogen. Goutarel[11] who repeated this work showed that compound C was in reality somewhat impure compound B which he renamed alloibogaine. The present reinvestigation of this compound was motivated by the thought that an alteration might have occurred also in the hydroaromatic portion of the molecule which would shed new light on the constitution of ibogaine. That the skeleton was unaltered, however, was shown by the preparation of N-methylibogaine and its subsequent O-demethylation to give the allo compound.[18]

Attempted dehydrogenation of ibogaine using palladium–charcoal either at 230–300° or in refluxing Dowtherm yielded no characteristic products in our hands. With selenium, however, after a short period at 300° it was possible to isolate two crystalline products, examination of which enabled the structure VIa to be put forward for ibogaine[19] (see Chart I). Although these compounds had characteristic ultraviolet spectra this was not discernible in the crude dehydrogenation mixture and it was only after a careful work up that they were discovered. The very weakly basic compound $C_{20}H_{22}N_2O$ (VIII) isolated from the neutral fraction was shown to have a methoxyl, no N-methyl and two C-alkyls at least one of which was a C-ethyl. The basic nitrogen was secondary since it formed an N-nitroso derivative and it was also hindered because its acetyl derivative could not be hydrolyzed under normal conditions.[20] Its ultraviolet absorption spectrum measured in acidic solution closely resembled 2,2′-aminophenylindole which defined the nature of three of the four rings. Inspection of the infrared spectrum of the dehydrogenation product in the 700–900 cm.$^{-1}$ region[21] supported the positioning of the substituents as shown in VIII, but naturally did not determine their type. In considering the nature of the remaining ring in this compound it should be remembered that there are only one or two carbons unaccounted for depending on whether there are two or one C-ethyls, and also that its nature should be such that it would be expected to survive the conditions of its formation. This would eliminate, for example, 3,4-dihydro-$\gamma$-carbolines and indolines. The only satisfactory formula which could be derived was VIII which had the merit that the structure for ibogaine (VIa) deduced from it was consistent with the results of the potash fusion (see Chart I). Alloibogaine could now be represented by V.

The basic product, $C_{20}H_{20}N_2O$, had an ultraviolet absorption spectrum similar to indolo[3,2-c]quinoline, and had a methoxy group and probably three C-alkyls. The structure IX suggested for this compound was in agreement with the prediction that it would be expected to be formed by a ring contraction and aromatization of ring C in VIII. Experimentally evidence was found for a conversion of VIII into IX with selenium at 300°, but the yield was very low and the compound was only detected among the dehydrogenation products because of its ultraviolet absorption spectrum. From the weakly basic fractions a third base was isolated in very small yield and characterized as its picrate. It was not further examined but is probably the methoxy derivative of the base obtained in a similar fashion from ibogamine (*vide infra*).

Besides ibogaine and iboluteine two other indole alkaloids have been recorded as occurring in *Tabernanthe iboga*. One of them, ibogamine,[22] $C_{19}H_{24}N_2$, was considered to be demethoxyibogaine, and the




(14) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2196 (1951), have shown that autoxidized dihydropentindole gave only a ring-opened product instead of the four-membered ring possibilities.

(15) *Cf.* cinchonamine (i) which yielded dehydrocinchonamine (ii); R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

(16) *Inter alia*, corynantheine, ajmaline and cinchonamine.

(17) This method was first used by H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955); in the course of their elegant studies on the curare alkaloids. More recently in the same way a C-ethyl has been shown to be present in both aspidospermine (A. J. Everett, H. T. Openshaw and G. F. Smith, *J. Chem. Soc.*, 1120 (1957)) and dihydrogelsemine (L. Marion and K. Sargeant, *Can. J. Chem.*, **35**, 301 (1957)); see also ref. 19.

(18) That the skeleton of the base was also unaffected by acid under demethylating conditions was shown by the preparation of noribogaine lactam and its remethylation to the starting material (see Experimental).

(19) W. I. Taylor, Paper II, THIS JOURNAL, **79**, 3298 (1957). In this note the m.p. of the weakly basic compound obtained from ibogamine should read 187° instead of 214°.

(20) For example, quantitative estimation of N-acetyl by the conventional method gave only 10% of the theoretical.

(21) The bands studied were the out-of-plane aromatic CH deformation vibrations; see L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, pp. 64–69. We are grateful to Mr. L. Dorfman who pointed this out to us.

(22) C. A. Burckhardt, R. Goutarel, M.-M. Janot and E. Schlittler, *Helv. Chim. Acta*, **35**, 642 (1952).

other, tabernanthine,[23] $C_{20}H_{26}N_2O$, was thought[12] to be isomeric with ibogaine. That the methoxy group was in the same position as in tetrahydroharmine was observed spectroscopically by Raymond-Hamet[24] in 1949. The similarity in the optical rotations of the three alkaloids would seem to support these ideas. The experimental evidence available was by analogy, *viz.*, that ibogamine could be converted into a pseudoindoxyl[13] analogous to iboluteine and that tabernanthine after potash fusion[11,25] afforded allotabernanthine and 3-ethyl-5-methylpyridine. Goutarel[11] has, however, recorded a $pK_a$ 6.04 (80% methyl-Cellosolve–water) for tabernanthine, markedly different from the identical $pK_a$'s, 8.1 for ibogaine and ibogamine which would indicate a real difference in the vicinity of the basic nitrogen. We have not been able to confirm this result and find a value 8.1 consistent with expectation.

Ibogamine has now been found on selenium dehydrogenation to furnish the two compounds (VIII, MeO = H; IX, MeO = H) whose properties were very similar to the corresponding degradation products derived from ibogaine. The correctness of these structures has been established by synthetic methods.[26]

From the 0.5 *N* sulfuric acid extract of the dehydrogenation products of ibogamine a base characterized as its crystalline picrate was isolated. The amount was too small for further investigation, but there was some evidence that it contains both an indole and a pyridine moiety.

In both the dehydrogenation of ibogaine and ibogamine the bulk of the isolated material was a neutral oil which could not be purified and did not yield any crystalline derivatives; the absorption spectrum showed that it was still indolic and the ultimate analyses indicated that the basic nitrogen had been eliminated,[27] and it would seem that irrespective of the detailed nature of this product, it ought to contain derivatives of 3-ethylindole. This was confirmed by the isolation of *o*-aminopropiophenone from the products of the peracid oxidation of the oil from ibogamine.

The stepwise oxidative degradation of ibogaine was now investigated as a potential route to simpler compounds. It was possible to prepare an ibogaine lactam XVa by the use of either iodine in a weakly basic medium or chromic oxide in pyridine. Reduction with lithium aluminum hydride regenerated the alkaloid so that it was certain that no other changes had occurred. The position of the carbonyl was in agreement with its infrared spectrum, its non-reactivity to benzaldehyde in a basic medium and the product XIX of its further oxidation. This was obtained after vigorous ozonolysis followed by digestion with performic acid. If the lactam had had the alternative constitution, further oxidation would have afforded a half amide of malonic acid which would not have survived the acidic conditions of the performic acid treatment. Because of the poor yield the degradation of the diacid XIX was not continued.

In the chromic oxide oxidation along with ibogaine lactam, a second compound, oxoibogaine lactam[28] (XVIII) was isolated. Its constitution followed from its analysis, infrared spectrum and its ultraviolet absorption spectrum which closely resembled 3-formyl-5-methoxyindole in both neutral and alkaline solution.[29] The formation of this compound provided another proof for the presence of a methylenic group attached to the $\beta$-carbon atom of the indole moiety. The possible use of this derivative for further transformations should be noted. The addition of water to the pyridine in the above oxidation of ibogaine resulted in the isolation of the hydroperoxy indolenine derivative XIa. In all probability the basic nitrogen in the more polar medium was protected from attack of the oxidizing agent due to salt formation. Both iboquine (X) and iboluteine (XIIIa) were subjected to oxidation by chromic oxide in pyridine and an attempt was made to relate the resulting lactams XIV and XVI to ibogaine lactam by conversion of the latter into the former two by autoxidation and rearrangement. Iboquine lactam (XIV) was prepared from the hydroperoxy indolenine derivative of XVa, but all attempts to prepare iboluteine lactam from this by reduction followed by base treatment gave either XVI or XVa. No evidence was found for the formation of the alternative ibogaine lactam with the carbonyl in ring C which would have provided a direct proof for a second methylene group attached to nitrogen.[30] As expected both ibogamine and tabernanthine furnished lactams with properties analogous to those of ibogaine lactam.

Attention turned to the use of the autoxidation products of ibogaine as starting points for systematic degradation. It was known,[31] for example, that 11-hydroxycarbazolenine (XXII) could be diazotized and coupled with $\beta$-naphthol and the resulting compound XXIII contained an $\alpha$-ketol moiety suitable for ring cleavage. However, the one attempt to duplicate this reaction in the ibogaine series gave a crude product which showed no carbonyl in the infrared. Another route of potential interest lay in the preparation and alkaline

(23) Tabernanthine may have been discovered originally by Haller and Heckel (ref. 2) who determined only its m.p. It was isolated by Delourme-Houdé (ref. 4) who named it and ascribed to it the formula $C_{21}H_{28-30}N_2O$, which was revised more recently by Goutarel and Janot (ref. 12).

(24) Raymond-Hamet, *Compt. rend.*, **229**, 1359 (1949).

(25) Goutarel also claimed the isolation of 1,2-dimethyl-3-ethyl-6-hydroxyindole as its picrate, m.p. 137–138°, but no analyses were given and the compound was not synthesized; however, the published ultraviolet spectrum of the crude compound measured in neutral and alkaline media lend support to his conclusion.

(26) Paper VI, to be published.

(27) The nitrogen was probably eliminated as ammonia; *cf.* dehydrogenation of quebrachamine, B. Witkop, THIS JOURNAL, **79**, 3193 (1957).

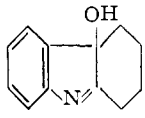
(28) By the same method 1,2,3,4-tetrahydrocarbazole was found to furnish the corresponding 1-oxo derivative (see Experimental).

(29) The spectral data of the 2- and 3-acylindoles recorded in this paper are in agreement with those recently published for other derivatives by J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings and A. Robertson, *J. Chem. Soc.*, 2227 (1957). These workers did not make use of the characteristic bathochromic shift of 3-acylindoles in alkaline solution for diagnostic purposes.

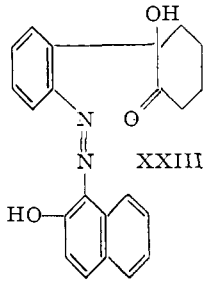
(30) The nuclear magnetic resonance spectrum of ibogamine, measured through the courtesy of Dr. H. Conroy, provided direct physical evidence for the presence of two methylene groups attached to this nitrogen.

(31) S. G. P. Plant and M. L. Tomlinson, *J. Chem. Soc.*, 298 (1933); R. J. S. Beer, J. McGrath and A. Robertson, *ibid.*, 3283 (1950).

fission of an 11-dichloromethylcarbazolenine, *e.g.*, XXIV, which by analogy with the corresponding

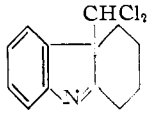


XXII

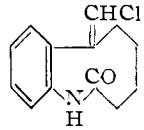


XXIII

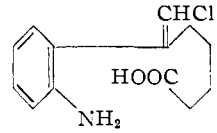
11-hydroperoxy derivative[32] should furnish the lactam XXV and the amino acid XXVI. Prolonged reflux of XXIV in the presence of alkali did in fact yield the desired compounds. Although the corresponding dichloromethyl derivative of ibogamine was prepared, the low yield precluded further steps. Iboquine did not look very useful, lactam formation did not take place in ring C which might have made possible the oxidative removal of three rings and a preliminary selenium dehydrogenation showed that products with characteristic ultra-



XXIV



XXV

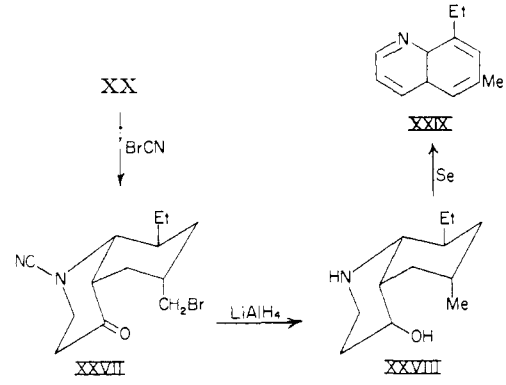


XXVI

violet spectra were formed in very low yield. Iboluteine, on the other hand, looked promising and the scheme conceived is illustrated by the sequence XIIIa → XVIIa → XX + XXIa which was expected to provide an elegant method for interrelating the three alkaloids (see Chart II).

An analogous reaction was already on record, namely, the conversion of isatinoxime into 2-cyanophenyl isocyanate by phosphorus pentachloride.[33] As a closer model, 2,2-tetramethylene-pseudoindoxyl oxime was heated in polyphosphoric acid and furnished cyclopentanone and anthranilamide.[34] The best method for carrying out this abnormal Beckmann rearrangement was to form the O-tosylate of the oxime in pyridine, then to continue to reflux after the addition of water; thus 6-methoxy-2,2-tetramethylene pseudoindoxyl oxime gave cyclopentanone and 4-methoxyanthranilonitrile (XXIb).[35] The three alkaloids, ibogaine, ibogamine and tabernanthine were thus interrelated through conversion of their pseudoindoxyls into the corresponding anthranilonitriles and the same tricyclic ketone XX (in which the original ring C was contracted by one carbon atom). The position of the carbonyl band in the infrared spectrum of this ketone indicated that the ring was not five membered but six or more, unambiguous proof that in the original bases ring C must be at least seven membered. In further agreement with its structure, the ketone formed only a monobenzylidene derivative, the infrared spectrum of which, as expected, showed no band at *ca.* 1434 cm.$^{-1}$ which would have been characteristic of a methylene group adjacent to the carbonyl.[36]

The tricyclic ketone reacted smoothly with cyanogen bromide to furnish the crystalline N-cyano bromo derivative XXVII which after vigorous treatment with lithium aluminum hydride gave the amino alcohol XVIII. Dehydrogenation of this amine afforded the expected product 8-ethyl-6-methylquinoline (XXIX) which established unequivocally the structure of the ketone and therefore that of ibogaine and its relatives.



Iboluteine was used as the starting material for the degradation of the tricyclic ketone. It was prepared by the alkaline rearrangement of the products of the aerial oxidation of ibogaine in benzene. Since iboluteine crystallized out of the reaction mixture in good yield, this route was preferred to the catalytic oxidation method.[13] The facile aerial oxidation of ibogaine and its congeners has been noted previously[4,12] and it has been found now that the rate of autoxidation is solvent dependent. In ethanol, at least for relatively short periods of time, *e.g.*, several hours, ibogaine can be recovered unaltered. On the other hand in cyclohexane or benzene, ibogaine was destroyed rapidly and after 1.5 hours none of the original alkaloid remained. In the same solvents ibogamine was oxidized rather more slowly. The hydroxyindolenine derivative XIIc of ibogamine could be crystallized from the products of the reaction, but the ibogaine analog was isolated only after chromatography. The oxidation of ibogaine in chloroform gave appreciable amounts of iboluteine and, in contrast to the hydrocarbon solvents, ibogaine disappeared more slowly. Neither the catalytic nor the autoxidation of tabernanthine were investigated in detail and the pure hydroperoxy (XIb) and hydroxy (XIIb) indolenine derivatives were not isolated. However, during the work-up of the pseudoindoxyl derivative of tabernanthine a new compound probably an oxindole was obtained, but up till now the

(32) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2196 (1951). The referee has pointed out a closer analogy to us, *viz.*, in footnote 17 of a paper by E. Wenkert and T. E. Stevens, *ibid.*, **78**, 5629 (1956). These elimination reactions fall into a single group which has recently been discussed in a generalized fashion by C. A. Grob, *Experientia*, **13**, 126 (1957).

(33) W. Borsche and W. Sander, *Ber.*, **47**, 2815 (1914).

(34) This experiment was carried out by Dr. R. K. Hill, Princeton, who participated in the early phase of this work.

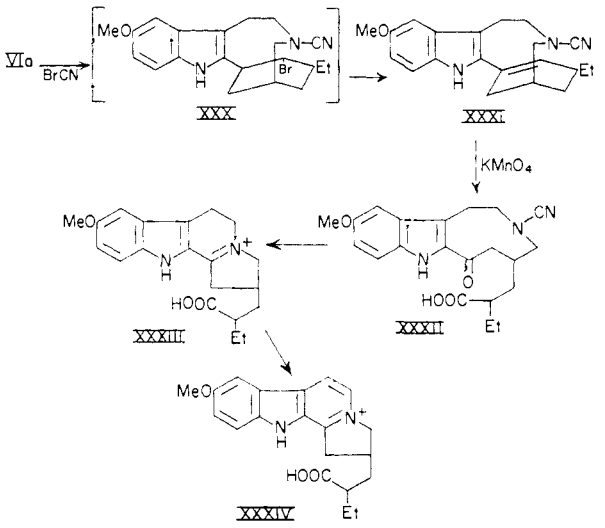
(35) It would be interesting to know whether this reaction can be applied to N-alkylated pseudoindoxyls, *e.g.*, Calabash alkaloids such as fluorocurinine and fluorocurine.

(36) R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952).

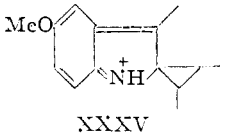
analogous substances derivable from ibogaine and ibogamine have not been observed.

Besides the conversion of iboluteine into the tricyclic ketone discussed above, another way also was found to contract ring C, in fact to turn ibogaine into a derivative of a β-carboline. Ibogaine reacted readily with cyanogen bromide at room temperature in non-polar solvents. The major product, in which fission had probably taken place between the nitrogen and the bridge methylene group of the isoquinuclidine residue, could neither be characterized nor converted into products amenable to further study. The sole crystalline product was N-cyano apoibogaine (XXXI) which contained a double bond conjugated with the indole nucleus. Oxidation of the apo-base with potassium permanganate gave the keto acid XXXII which in turn was converted successively into the dehydro base XXXIII and the tetradehydro compound XXXIV. Exact spectral models for the latter two compounds were prepared readily from aricine.[37,38]

A synthesis of either XXXIII or XXXIV would complete a third proof for the structure of the unusual ring system of ibogaine.




The isolation of N-cyanoapoibogaine from ibogaine requires some comment. Possibly the initial step lies in the formation of the normal von Braun product XXX. The introduced bromine is axial and *trans* to the vicinally substituted axial indolic moiety which readily can participate by a neighboring group reaction in the elimination of the halogen by an intermediate such as XXXV.

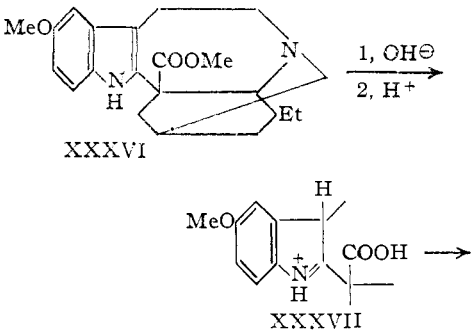



XXXV

Up till now no information has been presented which would in any way assist us in determining the configuration of the ethyl group. It would seem, however, that for steric reasons formation of a methiodide at room temperature can be cited as evidence against the ethyl group being *cis* to the nitrogen-containing bridge of the isoquinuclidine moiety. It also might be argued on a less firm basis that if the ethyl group were *cis*, the $pK_a$ of the alkaloids ought to have been much less than 8.1. It is proposed therefore as a working hypothesis that the ethyl group is *trans* to the bridge as indicated by formula VIa.

Since the constitution of ibogaine was now known with certainty it was possible to consider the structure of voacangine first isolated from *Voacanga africana* and *V. obtusa*[39] and more recently from *Tabernanthe iboga*.[1]

Janot and Goutarel[40] have shown that voacangic acid suffered ready decarboxylation on heating in acid media to furnish ibogaine. The problem now was to insert the carbomethoxy group. The only place, assuming no rearrangements had occurred, was on the 18-position in VI, *i.e.*, voacangine must be XXXVI. Some analogous examples had already been reported, *viz.*, the facile decarboxylation of 2-substituted 2-carboxy-β-carbolines under conditions of acid-catalyzed esterification.[41] A mechanism readily could be envisioned which involved the addition of a proton to the β-position of the indolic nucleus to form a carbazolinium ion (XXXVII) which then underwent decarboxylation in a manner analogous to β-keto acids.




A possible biogenesis for these alkaloids has been considered elsewhere.[42]

We are grateful to Dr. E. Schlittler for his constant interest and encouragement. We are also indebted to Mr. Louis Dorfman for invaluable aid in the interpretation of the spectral data and to his staff for the microanalyses, and to Dr. E. Wenkert for discussions concerning some of the theoretical points raised during this work. We wish also to acknowledge the capable assistance of Mmes. Helen Petriti, Ann F. Smith and Mrs. Nina Raab.

## Experimental

All melting points were uncorrected. Unless otherwise noted the optical rotations were recorded in ethanol at 26°, the ultraviolet spectra were measured in ethanol, the infrared taken in Nujol mulls and the alumina used in chroma-

(37) A. Stoll, A. Hofmann and R. Brunner, *Helv. Chim. Acta*, **38**, 270 (1955); R. Goutarel, M.-M. Janot, A. Le Hir, H. Corrodi and V. Prelog, *ibid.*, **37**, 1805 (1954).

(38) In this connection it would appear from the spectral data that the dehydroaricine described by Djerassi and co-workers is seriously contaminated with the tetradehydro compound; C. Djerassi, F. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi, THIS JOURNAL, **79**, 1217 (1957).

(39) M.-M. Janot and R. Goutarel, *Compt. rend.*, **240**, 1800 (1955).

(40) M.-M. Janot and R. Goutarel, *ibid.*, **241**, 986 (1955).

(41) G. Hahn, L. Bärwald, O. Schales and M. Werner, *Ann.*, **520**, 102 (1935).

(42) W. I. Taylor, *Experientia*, in press.

CHART I

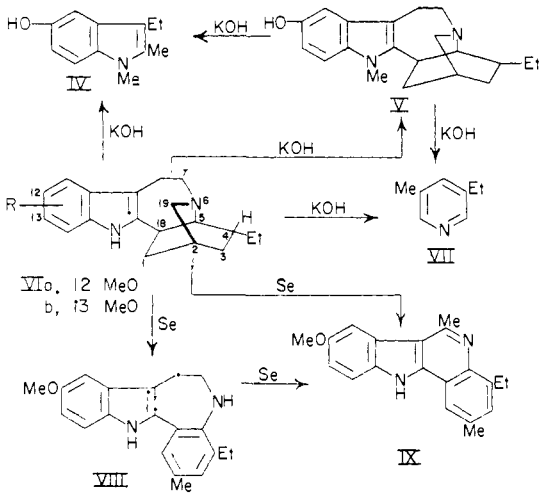
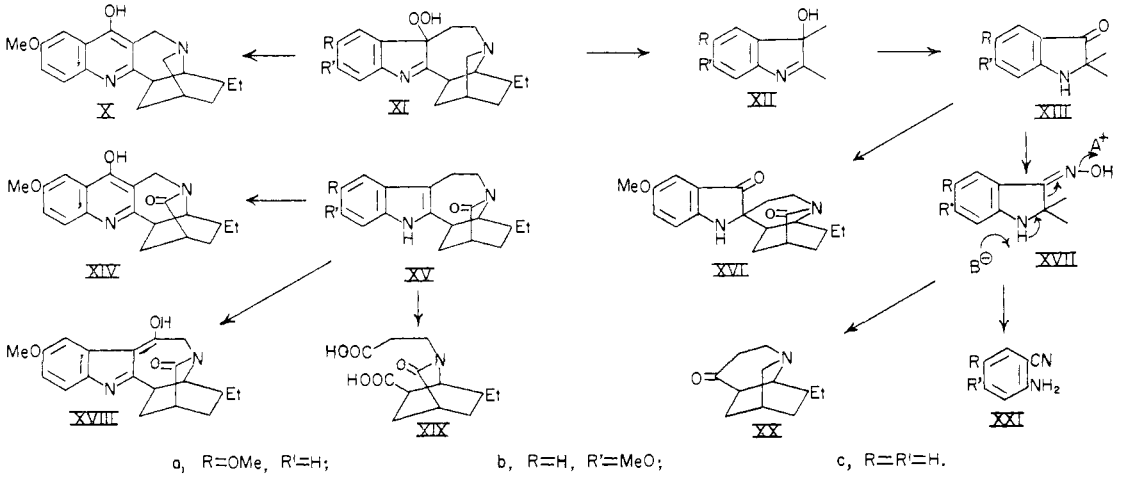


CHART II



a, R=OMe, R'=H; b, R=H, R'=MeO; c, R=R'=H.

tography was Woelm, neutral activity I. Analytical samples normally were dried between 25–100° and 0.02 mm. for 12 hours depending on circumstances.

**Noribogaine.**—Ibogaine (0.5 g.) was refluxed for 3.5 hours under nitrogen in acetic acid (7.5 ml.) and 49% hydrobromic acid (1.5 ml.). The reaction mixture was diluted with water, basified and the crude amorphous demethylated base was filtered off and converted into its crystalline hydrochloride for characterization. The product crystallized from water had m.p. 310° dec., $[\alpha]D$ −36.5° (water); $\lambda_{max}$ 225 mμ (24000) and 277 mμ (8000), and shoulders at 292 mμ (6500) and 307 mμ (4600).

*Anal.* Calcd. for $C_{19}H_{24}N_2O \cdot HCl$: C, 68.5; H, 7.6; OMe, 0.0. Found: C, 68.2; H, 7.7; OMe, 0.25.

**N-Methylibogaine.**—Sodium (0.37 g.) was dissolved in dry liquid ammonia (100 ml.) and after the blue color was discharged, powdered ibogaine (5 g.) was added with stirring, followed 20 minutes later by the dropwise addition of methyl iodide (1.03 ml.) in ether (40 ml.). After the ammonia had been allowed to evaporate the residue was triturated with methylene chloride. The extract was concentrated to dryness, taken up in benzene and passed through alumina (25 g.). The benzene eluate yielded 4.1 g. of the N-methyl derivative which was crystallized from ethanol to m.p. 104–106°, $[\alpha]D$ −33° ($CHCl_3$), $\lambda_{max}$ 226 mμ (24300) and 289 mμ (8600).

*Anal.* Calcd. for $C_{21}H_{28}N_2O$: C, 77.8; H, 8.7. Found: C, 77.5; H, 8.6.

**Alloibogaine (V).**—(a) N-Methylibogaine (500 mg.) was demethylated in acetic acid–hydrobromic acid as described above for ibogaine. The demethylated product was amorphous but could be purified through its oxalate, m.p. 200°. The free base generated from the oxalate was sublimed as a glass at 180° at 0.03 mm.; $\lambda_{max}$ 228–230 mμ (24400) and 289 mμ (8800), with a shoulder at 305 mμ (7400).

*Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.4. Found: C, 77.3; H, 8.4.

The base was also characterized as its hydrochloride, m.p. 294–296° dec. from ethanol, $[\alpha]D$ −58° (MeOH).

*Anal.* Calcd. for $C_{20}H_{26}N_2O \cdot HCl \cdot 0.5H_2O$: C, 67.4; H, 7.9. Found: C, 67.7; H, 8.0.

(b) Ibogaine was subjected to a potassium hydroxide fusion as described in Part I[8] and compound B was isolated and purified *via* its oxalate, m.p. 200°. The free base generated from the oxalate and sublimed at 180° at 0.04 mm. had an infrared spectrum superimposable with the allo compound prepared under a.

*Anal.* Found: C, 77.7; H, 8.6.

Its hydrochloride from ethanol had m.p. 294–296° dec., $[\alpha]D$ −58° (MeOH) and an undepressed mixed m.p. with the sample prepared under a.

*Anal.* Found: C, 67.6; H, 7.8.

**Ibogaine Lactam (XVa).**—(a) Iodine (2.48 g.) in tetrahydrofuran (40 ml.) was added dropwise to a stirred solution of ibogaine (2 g.) in a mixture of tetrahydrofuran (50 ml.) and water (40 ml.) containing 2.7 g. of sodium bicarbonate. After the addition was complete, water and methylene chloride were added to the cooled reaction mixture. The methylene chloride layer was washed successively with sodium thiosulfate, 2 *N* sulfuric acid and water, dried and concentrated. The residue crystallized from alcohol gave 2.1 g. of the lactam, m.p. 203° raised to 218–220° after two further crystallizations, $[\alpha]D$ −9°; $\lambda_{max}$ 222–224 mμ (26700) and 282 mμ (9000) with a shoulder at 298 mμ (7400); $\nu_{C=O}$ 1650 cm.$^{-1}$.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.0; H, 7.5; N, 8.6; OMe, 9.3; CMe, 4.5. Found: C, 74.0, 74.2; H, 7.8, 7.7; N, 8.6; OMe, 9.3; CMe, 3.3.

The lactam was isolated unchanged after reflux with 2 *N* hydrochloric acid or 25% potassium hydroxide and was unaffected by benzaldehyde in the presence of sodium ethoxide.

(b) Ibogaine (1 g.) in pyridine (10 ml.) was added slowly to chromic oxide (1 g.) in pyridine (17 ml.) with cooling. The solution was allowed to stand 20 hours at room temperature. Part of the pyridine was then removed under reduced pressure. The resulting solution was filtered and both the precipitate and the filtrate extracted with methylene chloride. The combined extracts were washed twice with dilute sodium hydroxide, then with water, dried ($Na_2SO_4$) and concentrated to dryness. The residue after crystallization with methanol gave ibogaine lactam (0.44 g.), m.p. 212–224° raised after recrystallization to m.p. 221°, $[\alpha]D$ −16°.

*Anal.* Found: C, 74.2; H, 7.6; N, 8.9.

**Ibogaine from Ibogaine Lactam.**—Ibogaine lactam (100

mg.) in tetrahydrofuran (20 ml.) was refluxed for four hours with lithium aluminum hydride (150 mg.). A few drops of water was added, the filtered solution was concentrated to dryness and the residue crystallized from alcohol. This gave ibogaine (60 mg.), m.p. 146–148°, $[\alpha]D$ −48°.

**Oxoibogaine Lactam (XVIII).**—The crude oxidation product obtained from the chromic oxide oxidation of ibogaine (5.0 g.) was chromatographed over 100 g. of alumina (activity II). Elution with methylene chloride gave ibogaine lactam (1.86 g.), m.p. 220–221°. Further elution with methylene chloride containing 0.5% methanol furnished oxoibogaine lactam (0.21 g.), m.p. 310–315° raised to 318–320° dec. after recrystallization from methanol–ether, $[\alpha]D$ −49°; $\lambda_{max}$ 212 mμ (29500), 252 mμ (17200), 278 mμ (10600), 304 mμ (10500); $\lambda_{max}^{0.1\,N\,KOH}$ 279 mμ (15200), 331 mμ (11700), with plateau at 254–256 mμ (8600), 274–276 mμ (15000), 327–329 mμ (11700) and shoulders at 272 mμ (15000) and 291 mμ (13500); $\nu_{max}$ 1670 and 1634 cm.$^{-1}$ (lactam carbonyl and enolized carbonyl, respectively).

*Anal.* Calcd. for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.6; N, 8.3. Found: C, 70.7; H, 6.8; N, 8.2.

**3-Formyl-5-methoxyindole**[43] had m.p. 186° and $\lambda_{max}$ 251 mμ (17500), 270 mμ (13600), 297 mμ (9600); the ultraviolet spectrum was unaffected by 0.1 *N* acid in alkali[44]; it had $\lambda_{max}^{0.1\,N\,KOH}$ 252 mμ (7500), 275 mμ (17000), 317 mμ (11100), with a shoulder at 283 mμ (16300); $\nu_{C=O}$ 1641 cm.$^{-1}$ (probably enolized).

*Anal.* Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.2. Found: C, 68.5; H, 5.3.

**4-Oxo-1,2,3,4-tetrahydrocarbazole.**—Tetrahydrocarbazole (5 g.) in pyridine (50 ml.) was added to chromic oxide (5 g.) dissolved in pyridine (85 ml.). After 20 hours the solid was filtered off, triturated with methylene chloride followed by thorough washing on a filter. The methylene chloride extracts were washed successively with two portions of dilute sodium hydroxide, dilute sulfuric acid and water, dried and concentrated to furnish starting material (3.75 g.). The acidic extracts were combined, made slightly basic with alkali and extracted with methylene chloride. The dried extract after concentration furnished a dark brown residue (0.63 g.) which afforded a crystalline sublimate of the ketone at 200° at 0.03 mm. For analysis it was recrystallized from methanol–ether to m.p. 225°[45] then resublimed at 145° at 0.04 mm.; $\lambda_{max}$ 212 mμ (26000), 241 mμ (15900), 263 mμ (12900), 294 mμ (10700); $\lambda_{max}^{0.1\,N\,KOH}$ 242 mμ (9900), 266 mμ (13900), 301 mμ (8200), 323–326 plateau (8000).

*Anal.* Calcd. for $C_{12}H_{11}NO$: N, 7.6. Found: N, 7.5.

**Hydroperoxyindolenine Derivative of Ibogaine (XIa).**—Ibogaine (1.0 g.) in pyridine (10 ml.) and water (5 ml.) was added to chromic oxide (1.0 g.) in pyridine (17 ml.). After 20 hours at room temperature the filtered solution was basified and extracted with methylene chloride, dried and concentrated. The residue (1.18 g.) was chromatographed over alumina (20 g.) and the product (600 mg.) of the chloroform eluate after several weeks at 0° in ether furnished XIa in low yield. For analysis it was crystallized from acetone–ether and had m.p. 228–229°.

*Anal.* Calcd. for $C_{20}H_{26}N_2O_3$: C, 70.2; H, 7.7; N, 8.2. Found: C, 70.5; H, 7.3; N, 8.6.

**Noribogaine Lactam.**–Ibogaine lactam (0.5 g.) was refluxed with acetic acid (7.5 ml.) and 49% hydrobromic acid (1.5 ml.) for 3.5 hours under nitrogen. After cooling and basifying the solution the precipitate was crystallized from ethanol to give the product, m.p. 184–188° (foaming) raised to 275° after drying in high vacuum at 100°, $\nu_{C=O}$ 1630 cm.$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.5; H, 7.1; N, 9.0. Found: C, 72.9; H, 7.3; N, 8.7.

Noribogaine lactam on treatment with potassium hydroxide and dimethyl sulfate in acetone was reconverted into ibogaine lactam.

**Ozonolysis of Ibogaine Lactam.**—A stream of ozonized oxygen was passed into a solution of ibogaine lactam (1 g.) in chloroform (50 ml.) at 0° until a permanent blue color appeared (about 40 minutes). Formic acid (15 ml.) and perhydrol (3.5 ml.) were then added and the whole refluxed for three hours. After the addition of water the aqueous acidic layer was separated and evaporated to dryness and the residue treated with excess diazomethane, followed by distillation. At 100° at 17 mm. an oily, partially crystalline, distillate was obtained which after crystallization from methylene chloride had a m.p. 118° undepressed in mixed m.p. with methyl oxanate and showed an identical infrared spectrum. The yield was variable amounting to only a few milligrams in some cases and up to one hundred in others.

Further distillation at 130° at 0.01 mm. gave a liquid (190 mg.). This was dissolved in water and after the addition a little hydrochloric acid was extracted exhaustively with ether. The ethereal solution was concentrated to dryness, treated with excess diazomethane and distilled as above to furnish a neutral liquid methyl ester of XIX, $[\alpha]D$ +14°, transparent in the ultraviolet, $\nu_{C=O}$ 1742 and 1678 cm.$^{-1}$.

*Anal.* Calcd. for $C_{15}H_{23}O_5N$: C, 60.6; H, 7.8; N, 4.7; 2OMe, 20.9. Found: C, 60.5; H, 7.7; N, 4.7; OMe, 19.0.

**Ibogamine Lactam (XVc).**—Oxidation of ibogamine with iodine and bicarbonate gave the lactam in a manner analogous to that of ibogaine. Chromic acid oxidation of ibogamine (1.0 g.) gave the lactam (0.31 g.), m.p. 329–331° dec. after crystallization from methanol; $\lambda_{max}$ 223 mμ (34500), 283 mμ (7600) and 291 mμ (6650); $\nu_{C=O}$ 1650 cm.$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{22}N_2O$: C, 77.5; H, 7.5; N, 9.5. Found: C, 77.6; H, 7.2; N, 9.5.

Reduction of the lactam as described for ibogaine lactam regenerated ibogamine.

**Tabernanthine lactam (XVb)** prepared from tabernanthine by the methods described for ibogaine crystallized from methylene chloride–ether, m.p. 312–315° dec.; $\lambda_{max}$ 224 mμ (33700), 272 mμ (4870) and 298 mμ (6570); $\nu_{C=O}$ 1661 cm.$^{-1}$.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.0; H, 7.5; N, 8.6. Found: C, 74.4; H, 7.8; N, 8.5.

Reduction of the lactam as described for ibogaine lactam regenerated tabernanthine.

**Iboluteine Lactam (XVI).**—Iboluteine (3.0 g.) in pyridine (30 ml.) was added slowly to chromic oxide (3.0 g.) in pyridine (50 ml.) and allowed to stand at room temperature for 18 hours. The pyridine was removed and the residue was triturated with methylene chloride and filtered. The filtrate was washed with small portions of saturated sodium chloride, dried and evaporated to dryness. The product (2.29 g.) was chromatographed over alumina yielding from the 0.1% methanol-in-methylene chloride eluate the lactam (0.89 g.) which was crystallized from methanol–ether, m.p. 171–172°; $\lambda_{max}$ 224 mμ (28000), 418 mμ (3560) and a shoulder at 253 mμ (8830); $\nu_{C=O}$ 1661, 1678 cm.$^{-1}$.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.3; H, 7.3; N, 8.0. Found: C, 70.6; H, 7.1; N, 8.2.

**Iboquine Lactam (XIV).**—(a) Iboquine (290 mg.) in pyridine (10 ml.) was added to chromic oxide (290 mg.) in pyridine (3 ml.) and the whole allowed to stand at room temperature for 22 hours. The solution was filtered, diluted with methylene chloride then washed successively with two portions each of dilute sodium hydroxide, dilute sulfuric acid and water. The neutralized basic and acidic extracts yielded 80 and 60 mg., respectively, of the crude lactam; crystallization from methanol–ether gave the pure compound, m.p. 334–347° dec., $\nu_{C=O}$ 1694 cm.$^{-1}$.

*Anal.* Calcd. for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.6; N, 8.3. Found: C, 70.6; H, 6.7; N, 7.6.

(b) Ibogaine lactam (2.0 g.) in benzene (150 ml.) and ethanol (20 ml.) was heated and aerated for one day, being illuminated at the same time with a long wave length ultraviolet light. During the course of the reaction the hydroperoxyindolenine derivative of ibogaine lactam (0.8 g.) precipitated out and was purified by crystallization from ethanol; m.p. 246°.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; H, 7.9. Found: C, 66.8; H, 7.2; N, 7.6.

The hydroperoxy compound was refluxed in 87% aqueous ethanol (40 ml.) containing sodium hydroxide (2.5 g.) for two hours, concentrated and the acidified residue was extracted with methylene chloride from which iboquine lactam

(43) K. G. Blaikie and W. H. Perkin, *J. Chem. Soc.*, **125**, 324 (1924).

(44) The shift in base is analogous to that observed for 3-formyl indole, G. F. Smith, *ibid.*, 3842 (1954).

(45) For the compound prepared by a Fischer indole synthesis G. R. Clemo and D. G. I. Felton, *ibid.*, 700 (1951), give m.p. 223°.

(0.32 g.) was obtained. It was crystallized for analysis from methanol and had m.p. 343–346°.

*Anal.* Found: C, 69.9; H, 6.6; N, 8.3.

**Selenium Dehydrogenation of Ibogaine.**—A finely powdered mixture of ibogaine (4 g.) and selenium (6 g.) were heated from 180 to 300° over 12 minutes, then maintained at 300–317° for a further 18 minutes. The cooled powdered reaction mixture was extracted exhaustively with benzene overnight. The product was divided into alkali-soluble (a trace), 2% acetic acid-soluble (see below), 0.5 *N* sulfuric acid-soluble (see below) and neutral fractions.

**4-Ethyl-5,6,7,12-tetrahydro-9-methoxy-2-methylindolo-[3,2-d][1]benzazepine (VIII).**—The neutral fraction (1.5 g.) was chromatographed over basic alumina (25 g.) and gave the following fractions: (i) petroleum ether:benzene (1:1), 100 ml., 675 mg. of oil; (ii) petroleum ether:benzene (1:1), 100 ml., 100 mg. of oil; (iii) petroleum ether:benzene (1:3), 100 ml., 60 mg.; (iv) benzene, 100 ml., 56 mg., crystalline; (v) methylene chloride, 150 ml., 223 mg.; (vi) methanol, 400 ml., 395 mg. Rechromatography of fractions ii and iii over alumina (5 g.) furnished from the benzene eluate a further 97 mg. of crystalline material.

The combined crystalline fractions after several crystallizations from methanol gave the pure compound VIII (35 mg.), m.p. 208°; $\lambda_{max}$ 226–228 mμ (34600), 308 mμ (16100) and 340 mμ (20400); $\lambda_{max}^{0.1\ N\ HCl}$ 232 mμ (21500) and 317 mμ (25300).

*Anal.* Calcd. for $C_{20}H_{22}N_2O$: C, 78.4; H, 7.2; N, 9.2; OMe, 10.1; 2CMe, 9.8. Found: C, 78.4; H, 7.5; N, 9.0; OMe, 10.1; NMe, 0.0; CMe, 6.7.

The N-nitroso derivative was prepared by reaction with sodium nitrite in acetic acid as fine needles from ethanol, m.p. 204–205°.

*Anal.* Calcd. for $C_{21}H_{21}N_3O_2$: N, 12.2. Found: N, 11.8.

The original base was regenerated after treatment of the N-nitroso derivative with cuprous chloride and concentrated hydrochloric acid.[46]

Treatment of the base with sodium acetate and acetic anhydride at 110° for 2.5 hours furnished the N-acetyl derivative, stout needles from ethanol, m.p. 246°; $\lambda_{max}$ 216 mμ (34600) and 321–322 mμ (27200) with shoulders at 243 mμ (17700) and 336 mμ (21900); $\nu_{C=O}$ 1640 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.9; H, 6.9; N, 8.0; NAc, 12.3. Found: C, 75.6; H, 6.9; N, 8.0; NAc, 1.0.

This compound was recovered unchanged after treatment with sodium nitrite in acetic acid.

**4-Ethyl-8-methoxy-2,6-dimethyl-11H-indolo[3,2-c]quinoline (IX).**—The 2% acetic acid-soluble material (9.68 g. from 79.5 g. of ibogaine), chromatographed over 70 g. of alumina gave the following fractions: (i) benzene, 100 ml., 2.28 g.; (ii) benzene, 40 ml., 2.25 g.; (iii) benzene, 300 ml., 0.91 g., crystalline; (iv) methylene chloride, 400 ml., 2.49 g. Ibogaine (1.13 g.) was obtained from fraction ii after crystallization from ethanol. Fraction iii, crystallized from methanol, gave a mixture of plates, m.p. 100° and 156°, and needles, m.p. 100° and 176°, which were shown to be dimorphic by recrystallization of the hand-separated forms and by comparison of their respective infrared spectra in chloroform solution. Sublimation of both forms at 140° at 0.01 mm. gave identical material, m.p. 178°, which was also occasionally obtained by direct crystallization; $\lambda_{max}$ 237 mμ (39000), 276 mμ (43900), 298 mμ (22800), 333 mμ (5800), 349 mμ (2850), and shoulders at 245 mμ (32400), 265 mμ (31500), 281 mμ (41400); $\lambda_{max}^{0.1\ N\ HCl}$ 219 mμ (27700), 230 mμ (28100), 269–271 mμ (43100), 296 mμ (27800), 310 mμ (19900), plateau at 327–335 mμ (9450) and shoulders at 249 mμ (29000), 256 mμ (33800), 263 mμ (37100), 284 mμ (22900).

*Anal.* Calcd. for $C_{20}H_{20}N_2O\cdot H_2O$: C, 74.5; H, 6.9; N, 8.7. $C_{20}H_{20}N_2O$: C, 78.9; H, 6.6; 3CMe, 14.7. Found, Plate form: C, 74.4; H, 7.0; N, 8.3. Needle form: C, 73.8; H, 7.0; N, 8.7. Sublimed: C, 78.4; H, 6.8; CMe, 8.8.

**4-Ethyl-8-methoxy-2,6-dimethyl-11H-[3,2-c]quinoline Methiodide.**—The base (30 mg.) was heated to 130° in a sealed tube with excess methyl iodide for 2.5 hours. The product was crystallized from methanol and had m.p. >300°.

*Anal.* Calcd. for $C_{20}H_{20}N_2O\cdot CH_3I\cdot H_2O$: C, 54.3; H, 5.4. Found: C, 54.6; H, 5.1.

**The Sulfuric Acid Extract.**—The crude 0.5 *N* sulfuric acid-soluble material (2.5 g.) was chromatographed over alumina (30 g.), and the benzene eluate (0.586 g.) was treated with picric acid (400 mg.) to furnish a crude picrate (210 mg.) obtained pure after six recrystallizations from ethanol; m.p. 165–167°.

*Anal.* Calcd. for $C_{20}H_{24}N_2O\cdot C_6H_3N_3O_7$: C, 58.1; H, 5.1; N, 13.0. Found: C, 57.9, 57.8; H, 5.1, 5.1; N, 12.8.

**Dehydrogenation of Ibogamine.**—A powdered mixture of ibogamine (4.3 g.) and selenium (6 g.) was heated over 35 minutes from 180 to 315°. The benzene extract was divided into base-soluble (trace of material), 2% acetic acid-soluble (280 mg.), 0.5 *N* sulfuric acid-soluble (110 mg.) and neutral portion (2.28 g.).

**4-Ethyl-5,6,7,12-tetrahydro-2-methylindolo[3,2-d][1]-benzazepine (VIII, MeO = H).**—The neutral portion was chromatographed over 30 g. of basic alumina and gave the following fractions: (i) petroleum ether:benzene (1:3), 100 ml., 1.04 g.; (ii) petroleum ether:benzene (1:3), 200 ml., 70 mg.; (iii) benzene, 200 ml., 150 mg.; (iv) methylene chloride, 100 ml., and methanol, 300 ml., 1.24 g. Crystallization of fraction iii from ethanol gave the indolobenzazepine, m.p. 187°; $\lambda_{max}$ 230 mμ (31700), 310 mμ (16800), 337 mμ (16200), with inflection at 247 mμ (21200); $\lambda_{max}^{0.1\ N\ HCl}$ 313–315 mμ (24200).

*Anal.* Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3. Found: C, 82.4; H, 7.4.

**4-Ethyl-2,6-dimethyl-11H-indolo[3,2-c]quinoline (IX, MeO = H).**—The 2% acetic acid-soluble material was chromatographed over 10 g. of alumina and furnished the following fractions: (i) benzene, 250 ml., crystals, 59 mg.; (ii) methylene chloride, 150 ml., crystals, 42 mg.; (iii) methanol, 50 ml., resin, 130 mg. Crystallization of fractions i and ii gave the indoloquinoline which melted at 110°, resolidified and remelted at 192–193°. Very slow crystallization, on the other hand, afforded the base, m.p. 196–197°; $\lambda_{max}$ 244 mμ (38500), 272 mμ (69300), 289 mμ (24100), 327 mμ (5050), 341 mμ (1280), with shoulders at 238 mμ (34900) and 313 mμ (8570) and inflections at 264 mμ (40800) and 303 mμ (14500).

*Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.3; H, 6.6. Found: C, 83.2; H, 6.6.

The base hydrochloride had m.p. >320° from ethanol–water.

*Anal.* Calcd. for $C_{19}H_{18}N_2\cdot HCl$: C, 73.4; H, 6.2. Found: C, 73.3; H, 6.2.

**The Sulfuric Acid-Soluble Material.**—The crude 0.5 *N* sulfuric acid-soluble material (110 mg.) was distilled at 0.02 mm. to furnish an oil (78.9 mg.) which with picric acid (50 mg.) gave a picrate, m.p. 179° from ethanol.

*Anal.* Calcd. for $C_{19}H_{22}N_2\cdot C_6H_3N_3O_7$: C, 59.2; H, 5.0; N, 13.8. Found: C, 58.9; H, 4.7; N, 14.4.

The base regenerated from the picrate (20 mg.) and distilled had the following spectrum $\lambda_{max}$ 224 mμ (32200), 274 mμ (9700) with plateaus at 268–272 mμ (7550) and 290–291 mμ (7150) and a shoulder at 285 mμ (8300).

***o*-Aminopropiophenone from Ibogamine.**—The oily material (800 mg.), fraction i in the chromatography of the neutral selenium degradation products of ibogamine (see above), was allowed to stand 24 hours in acetic acid (50 ml.) containing perhydrol (11 ml.) and 1% ammonium molybdate solution (0.2 ml.). The basified solution was extracted with methylene chloride to afford an oil (0.54 g.) which was heated on a steam-bath for 40 minutes in methanol (5 ml.) and 50% hydrochloric acid (10 ml.). After the acidic solution was extracted with methylene chloride it was basified and re-extracted with methylene chloride. This extract afforded, after concentration and sublimation, *o*-aminopropiophenone (26 mg.), m.p. 44–45°, which gave an identical infrared spectrum and an undepressed mixed m.p. with an authentic sample.

**Iboluteine (XIIIa).**—Ibogaine (99 g.) in benzene (1.5 l.) was slowly aerated for 40 hours under an ultraviolet lamp. The benzene was distilled off and the dark brown residue refluxed for 3 hours in 80% ethanol (1.75 l.) containing sodium hydroxide (280 g.). After standing at room temperature overnight the solution deposited iboluteine (33.3 g.), m.p. 128–135° raised after recrystallization from methanol to

(46) E. C. S. Jones and J. Kenner, *J. Chem. Soc.*, 713 (1932).

m.p. 140–142°. A further quantity of iboluteine (3.3 g.) was obtained by working up the mother liquors. The final yield of iboluteine, m.p. >140° was 31 g., with less pure material (4.3 g.) of m.p. 125–134°.

**Iboluteine Oxime (XVIIa).**—Iboluteine (2 g.) and hydroxylamine hydrochloride (2 g.) were taken up in carefully dried ethanol (40 ml.) containing sodium (1.8 g.). After 24 hours in a sealed tube at 140° under nitrogen the solution was poured onto cracked ice and thoroughly extracted with methylene chloride. The washed and dried extract after evaporation and crystallization from 95% ethanol gave the oxime (1.44 g.), m.p. 293–294°, $[\alpha]_D$ −151° (Py); $\lambda_{max}$ 216 mμ (28900), 322 mμ (3500) with a shoulder at 232 mμ (12900).

*Anal.* Calcd. for $C_{20}H_{27}N_3O_2$: C, 70.4; H, 8.0; N, 12.1. Found: C, 70.8; H, 8.3; N, 12.7, 11.8.

**Demethoxyiboluteine Oxime (XVIIc).**—In a manner analogous to that described for iboluteine oxime, demethoxyiboluteine (1.21 g.) gave the oxime (0.6 g.), m.p. 273–276°, $[\alpha]_D$ −183° (Py.), from 95% ethanol; $\lambda_{max}$ 226 mμ (19500), 247 mμ (10100), 263 mμ (7800), 358 mμ (4040).

*Anal.* Calcd. for $C_{19}H_{25}N_3O$: C, 73.3; H, 8.1; N, 13.5. Found: C, 73.7; H, 8.1; N, 13.5.

**Fission of Iboluteine Oxime.**—Iboluteine oxime (5.0 g.) and *p*-toluenesulfonyl chloride (5.0 g.) in pyridine (150 ml.) were refluxed under nitrogen for two hours. The solution was refluxed for an additional hour after the slow addition of water. Two such reaction mixtures were combined and the water and pyridine removed at 17 mm. by distillation through column packed with stainless steel helices. The residue was diluted with water and brought to *p*H 10 with dilute sodium hydroxide followed by thorough extraction with methylene chloride. The dried extract was evaporated carefully under reduced pressure in the same apparatus as used above, and the product in benzene was chromatographed over alumina (activity II). The benzene:methylene chloride (1:1) eluate (6 l.) afforded a light yellow oil which was dissolved in acetic anhydride (10 ml.) and allowed to stand at 0° overnight. The crystals of N-acetyl-5-methoxyanthranilonitrile (1.82 g.), m.p. 177–180°, were filtered off and crystallized for analysis from pure tetrahydrofuran, m.p. 179–180°; $\lambda_{max}$ 239 mμ (8090), 306 mμ (3250); $\nu_{C=O}$ 1664 cm.$^{-1}$, $\nu_{C\equiv N}$ 2240 cm.$^{-1}$. This compound was identical in all respects with the synthetic sample whose preparation is given below.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.3; H, 5.3; N, 14.6.

The acetic anhydride mother liquors obtained above were diluted with methylene chloride and extracted several times with 5% sulfuric acid which in turn was washed twice with methylene chloride. The aqueous acidic solution was made strongly basic and extracted well with methylene chloride, dried, concentrated to dryness using the same column as above, the resulting oil distilled, had b.p. 92° at 0.3 mm. The crude tricyclic ketone XX (1.82 g., 32%) had $\nu_{C=O}$ 1695 cm.$^{-1}$. It could not be induced to crystallize and was best characterized through its monobenzylidene derivative, prepared as follows. The ketone (190 mg.) and benzaldehyde (0.44 ml.) were dissolved in 95% ethanol (25 ml.) and 5 *N* sodium hydroxide (1.0 ml.) was added. After an hour at room temperature it was diluted with water and the precipitate taken up in ether. The dried extract evaporated to dryness gave the benzylidene derivative which was crystallized from hexane–ether (110 mg.), m.p. 115°, $[\alpha]_D$ −208°; $\lambda_{max}$ 222 mμ (7040), 289–291 mμ (17400); $\nu_{C=O}$ 1672 cm.$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{23}NO$: C, 81.1; H, 8.2; N, 5.0. Found: C, 81.5; H, 8.1; N, 4.8.

**Fission of Demethoxyiboluteine Oxime (XVIIc).**—Demethoxyiboluteine oxime (360 mg.) was refluxed with *p*-toluenesulfonyl chloride (360 mg.) in pyridine (10 ml.) for two hours and worked up in a manner analogous to that described for iboluteine oxime. After acetylation N-acetylanthranilonitrile (50 mg.), m.p. 134–135°,[47] was obtained; $\lambda_{max}$ 237 mμ (8300), 291 mμ (2260) and shoulder at 216 mμ (27100); $\nu_{C=O}$ 1717 cm.$^{-1}$.

*Anal.* Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.0. Found: C, 67.8; H, 5.1.

(47) J. Pinnow and C. Sämann, *Ber.*, **29**, 623 (1896), record m.p. 133°.

From the acetylation mother liquors the crude tricyclic ketone (70 mg.) was obtained which was converted into its monobenzylidene derivative, m.p. 113–114°, $[\alpha]_D$ −204°, identical in all respects with the corresponding derivative of the tricyclic ketone derived from ibogaine.

*Anal.* Calcd. for $C_{19}H_{23}NO$: C, 81.1; H, 8.2. Found: C, 81.2; H, 8.3.

**Pseudoindoxyl Derivative of Tabernanthine (XIIIb).**—Tabernanthine (500 mg.) was oxidized in ethyl acetate (50 ml.) in the presence of prereduced platinum oxide (300 mg.). After 4.5 hours 44 ml. of oxygen was taken up. The solution was filtered, evaporated to dryness and the residue in ethanol (20 ml.) was hydrogenated in the presence of freshly reduced platinum oxide (100 mg.). The hydrogenation was stopped 30 minutes later when 22 ml. was taken up. After removal of the catalyst, 50% sodium hydroxide (2 ml.) was added and the solution refluxed for 3 hours. Extraction with methylene chloride gave a material which after chromatography over alumina (activity III) gave tabernanthine (50 mg.) from the benzene eluate and its pseudoindoxyl derivative (280 mg.) from the benzene–ether (1:1) eluate. Only a small amount of the latter compound was obtained crystalline, m.p. 168–170°, in spite of the fact that the ultraviolet spectrum of the crude substance and the crystals were the same; $\lambda_{max}$ 228 mμ (19100), 248 mμ (20700), 279 mμ (10100) and 381 mμ (4300).

The crude indoxyl (900 mg.) and hydroxylamine hydrochloride (900 mg.) in pyridine (30 ml.) were refluxed for 40 hours under nitrogen and then the solvent was removed *in vacuo*. Chromatography of the residue over alumina (activity III) furnished starting pseudoindoxyl (700 mg.) from the methylene chloride eluate, and the oxime (100 mg.) from the methylene chloride containing 1% methanol eluate. This oxime, crystallized from methanol–ether, had m.p. 268–275° raised to m.p. 279–281°, $[\alpha]_D$ −149° (Py.), after recrystallization from acetone; $\lambda_{max}$ 225 mμ (23900), 245 mμ (14800) and 346 mμ (5530) with a plateau at 266–269 mμ (8410) and a shoulder at 271 mμ (5530).

*Anal.* Calcd. for $C_{20}H_{27}N_3O_2$: C, 70.4; H, 8.0; N, 12.1. Found: C, 70.5; H, 8.1; N, 11.9.

The recovered pseudoindoxyl was recycled several times until enough of the oxime for the next step was accumulated.

**Fission of the Oxime XVIIb of the Pseudoindoxyl Derivative of Tabernanthine.**—The oxime (310 mg.) and *p*-toluenesulfonyl chloride (310 mg.) in pyridine (10 ml.) were refluxed under nitrogen for two hours. After the addition of water (10 ml.) the refluxing was continued for one hour. The reaction mixture was worked up as described under the fission of iboluteine oxime. In this way N-acetyl-4-methoxyanthranilonitrile (20 mg.) was obtained, m.p. 155–156°; $\lambda_{max}$ 228 mμ (27700), 253 mμ (14900), with a shoulder at 296 mμ (870); $\nu_{C\equiv N}$ 2230 cm.$^{-1}$, $\nu_{C=O}$ 1717 cm.$^{-1}$.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3. Found: C, 63.3; H, 5.4.

From the neutral fraction the tricyclic ketone (70 mg.) was isolated after distillation at bath temperature 110–130° at 0.2 mm. The ketone was characterized as its benzylidene derivative (50 mg.), m.p. 115–116°, $[\alpha]_D$ −216° identical in all respects with the corresponding derivative prepared from iboluteine oxime.

**The Oxindole Derived from Tabernanthine.**—In the above isolation of the pseudoindoxyl derivative of tabernanthine by chromatography a crystalline substance was obtained from the 2% methanol in methylene chloride eluate. It was further purified by crystallization from acetone to m.p. 191–197°, $\lambda_{max}$ 214 mμ (31800), 255–258 mμ (3650), 283 mμ (2890) and 292 mμ (2340); $\nu_{C=O}$ 1695 cm.$^{-1}$. For analysis it was dried for a prolonged period at 78° in high vacuum and appeared even then to retain tenaciously a small amount of water.

*Anal.* Calcd. for $C_{20}H_{26}N_2O_2 \cdot 0.25H_2O$: C, 72.6; H, 7.9; N, 8.5. $C_{20}H_{26}N_2O_2$: C, 73.6; H, 8.0; N, 8.6. Found: C, 72.9, 72.7, 73.0; H, 8.2, 8.1, 8.4; N, 8.5, 8.5.

**The von Braun Degradation of the Tricyclic Ketone.**—The tricyclic ketone (255 mg.) was allowed to stand overnight in methylene chloride with an excess of cyanogen bromide. The solution was evaporated to dryness and taken up in benzene which was washed several times with dilute sulfuric acid. Concentration of the dried benzene solution to a small volume gave, after the addition of ether, the crystalline N-cyanobromo derivative XXVII, m.p.

96–97° which was sublimed for analysis, $[\alpha]_D$ −76°, $\nu_{C\equiv N}$ 2202 cm.$^{-1}$ and $\nu_{C=O}$ 1719 cm.$^{-1}$.

*Anal.* Calcd. for $C_{13}H_{19}N_2OBr$: C, 52.2; H, 6.4; N, 9.4. Found: C, 52.3; H, 6.5; N, 9.4.

**8-Ethyl-6-methylquinoline from the von Braun Product.**—The above N-cyano bromo compound (380 mg.) and lithium aluminum hydride (300 mg.) were refluxed in tetrahydrofuran (10 ml.) for 12 hours. Water was added, the resulting precipitate was removed and the filtrate was concentrated to dryness and the residue distilled to furnish a solid (280 mg.) which melted just above room temperature. Although it could not be successfully crystallized it was essentially 8-ethyl-6-methyl-4-hydroxydecahydroquinoline as shown by the analysis. (Calcd. for $C_{12}H_{23}NO$: C, 73.0; H, 11.8. Found: C, 71.7; H, 11.7). The decahydroquinoline (260 mg.) was heated with selenium (260 mg.) for six hours at 330° in a sealed evacuated tube. The basic portion was isolated and distilled to afford 8-ethyl-6-methylquinoline (63 mg.) which formed the picrate quantitatively on admixture with picric acid (80 mg.) in ether. On recrystallization from ethanol, the picrate had m.p. 154–155° and an undepressed mixed m.p. with a synthetic sample. The infrared spectra of the picrate and the regenerated base were identical with the synthetic samples.

*Anal.* Calcd. for $C_{18}H_{16}N_4O_7$: C, 54.0; H, 4.0. Found: C, 54.1; H, 4.2.

**8-Ethyl-6-methylquinoline (XXIX).**—2-Ethyl-4-methylaniline (1.31 g.), glycerol (2.4 ml.), arsenic pentoxide (1.39 g.) and concentrated sulfuric acid (1.5 ml.) were heated at 140–150° for four hours. The reaction mixture was diluted with water, made strongly basic and extracted with ether. The crude quinoline was purified through its picrate, m.p. 156–158°.

*Anal.* Calcd. for $C_{18}H_{16}N_4O_7$: C, 54.0; H, 4.0. Found: C, 54.0; H, 4.0.

**N-Cyanoapoibogaine (XXXI).**—Ibogaine (1.0 g.) and cyanogen bromide (400 mg.) were dissolved in dry benzene (30 ml.) and after several hours the precipitated ibogaine hydrobromide (600 mg.) was filtered off. The benzene solution was washed several times with 0.5 *N* sulfuric acid, water, dried and evaporated to dryness. The residue in ethanol slowly deposited needles of the N-cyano compound (30 mg.), m.p. 203° raised on recrystallization to m.p. 208–209°, $[\alpha]_D$ −165° ($CHCl_3$); $\lambda_{max}$ 218 mμ (20000), 311 mμ (24000); $\nu_{C\equiv N}$ 2228 cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{25}N_3O$: C, 75.2; H, 7.5; N, 12.5. Found: C, 75.2; H, 7.7; N, 12.8.

The amorphous solid from the mother liquors of the crystalline apo compound could not be induced to crystallize. It contained bromine (13.32%) and its ultraviolet spectrum was essentially that of a 5-methoxyindole [$\lambda_{max}$ ($\epsilon^{1\%}_{1cm.}$) 225 mμ (608.2), 284–291 mμ (217.4); 296 mμ (216.4)]. Neither chromatography nor lithium aluminum hydride reduction followed by chromatography led to a crystalline product or apparently homogeneous materials.

**Permanganate Oxidation of N-Cyanoapoibogaine.**—Potassium permanganate (840 mg.) in acetone (15 ml.) was added slowly at room temperature over four hours to the apo compound (203 mg.) in acetone (15 ml.). After decolorization of the permanganate was complete the precipitate was filtered off and treated with a saturated aqueous solution of sulfur dioxide. The resulting yellow solid was filtered off to furnish the crude acid (100 mg.) which was soluble in bicarbonate solution. Crystallization from ethanol with a trace of water gave the crystalline acid XXXII (50 mg.), m.p. 196°; $\lambda_{max}$ 319 mμ (20800) with shoulder at 229 mμ (14400); $\nu_{C\equiv N}$ 2220 cm.$^{-1}$, $\nu_{C=O}$ 1710 and 1630 cm.$^{-1}$ (enolized).

*Anal.* Calcd. for $C_{21}H_{23}N_3O_4 \cdot 0.5H_2O$: C, 64.3; H, 6.7. Found: C, 64.6, 64.7; H, 6.6, 6.5.

Treatment with diazomethane gave a highly crystalline methyl ester, m.p. 186° from methanol, $[\alpha]_D$ +112° ($CHCl_3$); $\lambda_{max}$ 319 mμ (21500) with shoulder at 231 mμ (13300) unaffected by acid or base; $\nu_{C\equiv N}$ 2225 cm.$^{-1}$, $\nu_{C=O}$ 1738 (ester) and 1616 cm.$^{-1}$ (enolized carbonyl).

*Anal.* Calcd. for $C_{22}H_{27}N_3O_4$: C, 66.5; H, 6.9; 2MeO, 15.6. Found: C, 66.0, 66.4; H, 6.9, 6.9; MeO, 15.0.

**Formation of the Dehydro Compound XXXIII.**—The ester (50 mg.) of the keto acid XXXII and 2 *N* hydrochloric acid (1 ml.) were heated in a sealed tube at 100° for 12 hours. On cooling, the dehydro compound crystallized out; it sinters from 90–100°. For analysis it was crystallized either from 2 *N* hydrochloric acid as a hydrate or from methanol–ethyl acetate in an anhydrous form, m.p. 201° dec.; $\lambda_{max}$ 366 mμ (19000) with a shoulder at 374 mμ (18200); $\nu_{C=O}$ 1730 cm.$^{-1}$ and a strong band at 1620 cm.$^{-1}$ (C=N$^+$< and MeO-aromatic).

*Anal.* Calcd. for $C_{21}H_{27}N_2O_3Cl$: C, 64.5; H, 7.0; N, 7.2. Calcd. for $C_{21}H_{27}N_2O_3Cl \cdot 1.5H_2O$: C, 60.4; H, 7.2. Found: C, 64.6; H, 7.0; N, 7.5, and C, 60.6; H, 6.7.

When the dehydro compound was refluxed in aqueous acetic acid containing maleic acid and palladium the typical spectrum for the tetradehydro compound XXXIV with the strong maximum at 313 mμ was found.

**Dehydroaricine Hydrochloride.**—A solution of *t*-butyl hypochlorite[48] in carbon tetrachloride (2.33 ml. of 0.27 molar) was added slowly to aricine (200 mg.) in cold methylene chloride (10 ml.) containing one drop of triethylamine. Two minutes later it was allowed to warm up to room temperature, then was washed twice with water (5 ml.), dried, concentrated to dryness and the residue crystallized from ethanol–ether after the addition of a few drops of alcoholic hydrochloric acid to m.p. 201° dec., $\lambda_{max}$ 372 mμ (15100).

*Anal.* Calcd. for $C_{22}H_{25}N_2O_4Cl \cdot H_2O$: C, 60.7; H, 6.3. Found: C, 60.3; H, 6.5.

**Tetradehydroaricine Hydrochloride.**—Aricine (100 mg.), maleic acid (30 mg.) and palladium black (40 mg.) were refluxed in 50% acetic acid for two hours, then cooled and filtered. After concentration and treatment with a few drops of alcoholic hydrogen chloride, tetradehydroaricine chloride was obtained and was further purified by crystallization from ethanol–ethyl acetate, m.p. 185° dec.; $\lambda_{max}$ 233 mμ (32700), 262–273 mμ (19600), 313 mμ (20100) and 387–393 (3910) with a shoulder at 303 mμ (15900). For analysis the sample was dried *in vacuo* at room temperature.

*Anal.* Calcd. for $C_{22}H_{23}N_2O_4Cl \cdot 2.5H_2O$: C, 57.6; H, 5.9. Found: C, 57.6; H, 6.2.

**Action of Chloroform on Ibogamine.**—Chloroform (2 ml.) was added slowly to a well stirred solution of ibogamine (2 g.) in *t*-butyl alcohol (100 ml.) containing dissolved potassium (0.55 g.). After one hour the solvent was distilled off and water added. Extraction with methylene chloride gave a product (1.72 g.) which on crystallization from ethanol afforded unchanged ibogamine (0.67 g.). No further crystals could be obtained from the mother liquors which were therefore evaporated to dryness and the residue chromatographed and the benzene eluate (0.64 g.) crystallized from ethanol to furnish the dichloromethylindolenine derivative, m.p. 140°; $\lambda_{max}$ 222 mμ (14300), 261–263 mμ (5440) with a shoulder at 229 mμ (10500); infrared showed the absence of band characteristic of an NH group.

*Anal.* Calcd. for $C_{20}H_{24}N_2Cl$: C, 66.1; H, 6.7. Found: C, 66.3, 65.9; H, 6.9, 6.6.

**11-Dichloromethylcarbazolenine (XXIV).**—Chloroform (17 ml.) was added slowly with efficient stirring to a solution of tetrahydrocarbazole (10 g.) and potassium (4.7 g.) in dry *t*-butyl alcohol (250 ml.). After two hours most of the solvent was removed by distillation and the residue extracted into methylene chloride. The product was crystallized from benzene and gave 11-dichloromethylcarbazolenine (3.4 g.), m.p. 158–159°[49]; $\lambda_{max}$ 219 mμ (17100), 260 mμ (5540), with a shoulder 225 mμ (12600) and inflections at 284 mμ (2630) and 292 mμ (1580).

*Anal.* Calcd. for $C_{13}H_{13}NCl_2$: C, 61.5; H, 5.2. Found: C, 61.3; H, 5.0.

**Alkaline Hydrolysis of 11-Dichloromethylcarbazolenine.**—11-Dichloromethylcarbazolenine (2.04 g.) was refluxed under nitrogen for 16 hours in ethanol (100 ml.) containing 5 *N* potassium hydroxide (20 ml.). The ethanol was distilled off and the alkaline concentrate was extracted with methylene chloride. The product (1.1 g.), m.p. 130–170°, was chromatographed over alumina (23 g.) and yielded from the benzene eluate starting material 0.44 g., m.p. 156–159°. From the benzene containing 20% methanol the lactam XXV (0.51 g.) was obtained, which when crystallized from

(48) W. O. Godfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

(49) G. Plancher and G. Testoni, *Atti reale accad. nas. Lincei*, [5] **10**, 304 (1901), record m.p. 158–159°.

ethanol–water had m.p. 194–195°; $\lambda_{max}$ 212 mμ (17400) with inflection at 263 mμ (705); $\nu_{C=O}$ 1667 cm.$^{-1}$.

*Anal.* Calcd. for $C_{13}H_{14}NOCl$: C, 66.3; H, 6.0; N, 6.0; Cl, 15.0. Found: C, 66.1; H, 6.0; N, 6.3; Cl, 15.0.

The above alkaline concentrate was brought to *p*H 6 and extracted for 48 hours with ether to furnish the oily acid XXVI (0.7 g.). Treatment of this with ethereal diazomethane followed by distillation at 0.01 mm., bath temperature 110–120°, gave the ester; $\lambda_{max}$ 292–295 mμ (2440) with inflections at 217 mμ (15600) and 237 mμ (7330); in 0.1 *N* hydrochloric acid the spectrum showed only a shoulder at 229 mμ (10950).

*Anal.* Calcd. for $C_{14}H_{13}NO_2Cl$: C, 62.9; H, 6.7; N, 5.3. Found: C, 63.2; H, 7.0; N, 5.4.

**11-Hydroperoxy-7-methoxycarbazolenine.**—7-Methoxy-1,2,3,4-tetrahydrocarbazole[50] (1.5 g.) was maintained for 2.5 hours at 40° in petroleum ether (1.5 l.). At the end of this time there was a copious crystalline precipitate of the hydroperoxy compound, which was filtered off and recrystallized from ethyl acetate, m.p. 104° dec.; $\lambda_{max}$ 231 mμ (24200), 274 mμ (2900) and shoulders at 223 mμ (19400), 238 mμ (20200) and 323 mμ (770).

*Anal.* Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5. Found: C, 67.0; H, 6.7.

**11-Hydroxy-7-methoxycarbazolenine.**—The above hydroperoxyindolenine (1 g.) in ethyl acetate (15 ml.) was reduced in the presence of hydrogen with a platinum catalyst. The product (yield 800 mg.) was crystallized from acetone to m.p. 145°; $\lambda_{max}$ 230 mμ (21000), 280 mμ (2280), with shoulders at 236 mμ (19900) and 307 mμ (1400).

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0. Found: C, 72.0; H, 7.0.

**7-Methoxy-2,2-tetramethylene-pseudoindoxyl.**—The above hydroxyindolenine (0.66 g.) was refluxed for 30 minutes in 50% aqueous ethanol (12 ml.) containing potassium hydroxide (0.5 g.). The dilute solution was extracted with ether which was washed several times with water, dried and concentrated. The residue gave the indoxyl from ethanol–water, m.p. 137.5–139°; $\lambda_{max}$ 230 mμ (19200), 248 mμ (22000), 280 mμ (11700) and 379 mμ (5140).

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0. Found: C, 71.7; H, 7.0.

The oxime was prepared by refluxing the ketone in pyridine with excess hydroxylamine hydrochloride for four hours. It had m.p. 204–205° from ethanol; $\lambda_{max}$ 226 mμ (21800), 247 mμ (14100), 269 mμ (8900) and 351 mμ (5860).

*Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.3; H, 7.0. Found: C, 67.5; H, 6.9.

**Fission of 6-Methoxy-2,2-tetramethylene-pseudoindoxyl Oxime.**—The oxime (100 mg.) in pyridine (3 ml.) was refluxed for two hours under nitrogen in the presence of toluenesulfonyl chloride (100 mg.). After the addition of water (3 ml.) refluxing was continued for a further hour. Most of the solvent was removed under reduced pressure and the residue taken up in dilute sodium hydroxide and extracted with methylene chloride which was washed three times with saturated sodium chloride. The residue obtained by evaporation of the dried methylene chloride solution was dissolved in a mixture of acetic anhydride (1 ml.) and pyridine (2 ml.). After 48 hours at room temperature the solution was concentrated and the residue sublimed at 120° (0.01 mm.) to furnish N-acetyl-4-methoxyanthranilonitrile, m.p. 155–156° from tetrahydrofuran.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3. Found: C, 63.3; H, 5.3.

No attempt was made to isolate the cyclopentanone because of its comparative volatility, although its presence was readily shown by its characteristic odor.

**5-Methoxyisatin.**—2-Hydroxyimino-4′-methoxyacetanilide[51] (3 g.) was added with stirring to 90% sulfuric acid[52] at such a rate that the temperature was maintained at 50–70°. After the addition was complete the solution was heated to 80° for 10 minutes then cooled and poured onto cracked ice (250 ml.). The reddish product (1.9 g.) was filtered off and crystallized from water, m.p. 201–203°; $\lambda_{max}$ 235 mμ (19900), 299 mμ (2320), 476 mμ (720) with a shoulder at 262 mμ (15400); $\nu_{C=O}$ 1730 and 1746 cm.$^{-1}$.

*Anal.* Calcd. for $C_9H_7NO_3$: C, 61.0; H, 4.0; N, 7.9. Found: C, 60.6; H, 4.1; N, 8.3.

The oxime was prepared by refluxing the isatin in pyridine in the presence of excess hydroxylamine hydrochloride, m.p. 236°; $\lambda_{max}$ 257 mμ (23200), 404 mμ (1070) and a shoulder at 261 mμ (22900); $\nu_{C=O}$ 1732 cm.$^{-1}$.

*Anal.* Calcd. for $C_9H_8N_2O_3$: N, 14.6. Found: N, 14.7.

**5-Methoxyanthranilonitrile (XXIa).**—5-Methoxyisatin oxime (9 g.) and phosphorus pentachloride (10 g.) were mixed thoroughly under ether (100 ml.), then the solvent removed and the residue heated to 90–100° in a vacuum. The sublimate 3.5 g., m.p. 98°, $\lambda_{max}$ 2305 and 2245 cm.$^{-1}$ (C≡N and C=N=O), was crude 2-cyano-4-methoxyphenyl isocyanate.

*Anal.* Calcd. for $C_9H_6N_2O_2$: N, 16.1. Found: N, 16.2.

The isocyanate was dissolved in excess dilute alkali, followed by acidification to furnish a semi-solid precipitate of the nitrile XXIa (2.1 g.). This was collected, dried in methylene chloride over sodium sulfate, concentrated and sublimed. The pure nitrile had m.p. 40°; $\lambda_{max}$ 250 mμ (7800), 347 mμ (4560); $\nu_{C\equiv N}$ 2234 cm.$^{-1}$.

*Anal.* Calcd. for $C_8H_8N_2O$: N, 18.9. Found: N, 19.1.

The nitrile in acetic anhydride slowly deposited needles of the N-acetyl derivative, m.p. 179–180°.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.2; H, 5.4; N, 15.1.

**Iboquine (X)** was isolated from autoxidized ibogaine as described by Goutarel.[11] It had m.p. 284–288° dec. and $\lambda_{max}$ 217 mμ (18600), 244 mμ (35600), 248 mμ (35500), 284 mμ (3160), 296 mμ (3030), 333 mμ (9020) and 347 mμ (9200) with shoulders at 253 mμ (31000), 275 mμ (2570) and 320 mμ (5430).

**3-Ethyl-6-methoxy-2-methyl-4-quinolinol** was prepared from *p*-anisidine and ethyl C-ethylacetoacetate according to published directions,[53] and had m.p. 293–295° dec.; $\lambda_{max}$ 215 mμ (20500), 246 mμ (31300), 255 mμ (29600), 276 mμ (2170), 287 mμ (3020), 298 mμ (3210), 332 mμ (9300), 346 mμ (9000) with an inflection at 319 mμ (5700).

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0. Found: C, 71.8; H, 6.7.

NOTE ADDED IN PROOF.—There are a number of ways in which a clue as to the absolute stereochemistry of this group of alkaloids might be provided. Dr. C. Djerassi of Wayne State University has made the suggestion that a comparison of the rotatory dispersion curve of the ketone (XXVII) with similarly constituted compounds of known absolute configurations would yield useful information. He has found that the curve obtained for (XXVII) closely resembled that of 1-*cis*-9-methyl-4-decalone, whose absolute configuration has been determined unequivocally. Assuming that a piperidone ring can be equated with a cyclohexanone ring, and assuming also that the absence of an angular methyl group does not make much difference, then the above comparison is valid, which means that the absolute stereochemistry of this group of alkaloids is as illustrated in VI.

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(50) J. R. Chambers, H. T. Openshaw and G. F. Smith, *J. Chem. Soc.*, 1115 (1937).

(51) T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(52) If concentrated sulfuric acid is used, in agreement with J. Halberkann, *Ber.*, **54**, 3079 (1921), and Sandmeyer, the methoxy isatin could not be isolated from the reaction mixture, see however, G. B. Bachmann and G. M. Picha, THIS JOURNAL, **68**, 1601 (1946).

(53) J. M. L. Stephen, I. M. Tonkin and D. J. Walker, *J. Chem. Soc.*, 1034, (1947).