required for an optical density of 0.70 to 1.00. A 1-ml aliquot of this solution was transferred to a 5-ml volumetric flask and diluted to the mark with previously prepared pyridine–2,6 lutidine solutions. This enabled us to work at constant porphyrin concentration and known pyridine concentration. The point in pure 2,6-lutidine was obtained by evaporating the 1 ml of pyridine–porphyrin stock solution to dryness with a stream of dry nitrogen and dissolving the magnesium porphyrin remaining in 2,6-lutidine.

In the case of the stability constant determinations using 4-substituted pyridines as ligands a slightly different method was used. A solution of magnesium deuteroporphyrin IX dimethyl ester in 2,6-lutidine was made up to such a concentration that it was *ca.* five times that required to obtain an optical density of 1.00 to 1.25. One-milliliter aliquots of this solution were then placed in 5-ml flasks and measured amounts of the 4-substituted pyridine added. The 5-ml flask was then filled to the mark with 2,6-lutidine.

The two peaks in the Soret (OD_I and OD_{II}) are close enough together so that neither one is completely resolved. The OD_{II} peak must be corrected for the residual absorption by OD_I. The spectrum in 2,6-lutidine was taken and the ratio of the peak height at the λ_{max} to the place where the OD_{II} falls was determined. This ratio was then used to determine the residual OD_I absorption in OD_{II} at the different ligand concentrations. This was accomplished by multiplying the observed OD_I by the earlier determined ratio and subtracting the result from the observed OD_{II}.

The Soret region of the solutions was recorded using a Beckman DK-2 Ratio recording spectrophotometer equipped with a constant-temperature cuvette holder. One-centimeter glass-stoppered matched quartz cuvettes were used. The temperature was held at 30 ± 0.5°. The thermodynamic data were obtained on 12.36 *M* pyridine solutions by varying the temperature of the cuvette holder. All spectra were run twice at 5-min intervals to ensure temperature equilibration. The magnesium porphyrin solutions were made up fresh before each stability constant determination. The magnesium porphyrins are unstable so it is not possible to use the same solution even 24 hr later. All determinations were made in duplicate and the two sets of points were treated together in the statistical analysis.

The pyridine used was Baker Analyzed reagent grade. It was distilled from potassium hydroxide at atmospheric pressure through a Vigreux column. A center cut was taken (bp 115–116°) and stored over Linde 5A molecular sieve. The presence of any water in the reagents caused nonlinearity of the plots and nonreproducible results.

The 2,6-lutidine was purified from Eastman practical grade. It was first stored in a freezer at *ca.* −15°. The unfrozen portion was rapidly decanted off and discarded. The remainder was allowed to thaw completely and then recrystallized twice more, discarding the liquid phase each time. The remainder from the crystallization was then distilled at atmospheric pressure from potassium hydroxide and a center cut was taken (bp 143–144°). This was then stored over Linde 5A molecular sieve. The nmr spectrum of the 2,6-lutidine prepared in this way showed no spurious peaks when compared to the literature spectrum.[28]

The 4-substituted pyridines were obtained from the Reilly Tar and Chemical Co. All were quite brown when first opened. Passage over alumina and vacuum distillation from potassium hydroxide gave water white material. The distilled materials were stored over Linde 5A molecular sieve. The nmr spectra were in all cases consistent with the structure of the ligand and showed no spurious peaks.

(28) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalogue," Varian Associates, Palo Alto, Calif., 1962.

Chemical Transformations of Ibogaine

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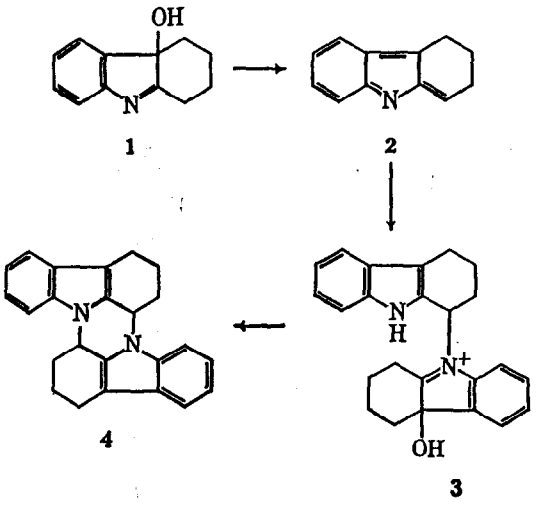
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received February 19, 1966*

Abstract: Ibogaine has been converted to the naturally occurring ester alkaloid voacangine by a four-step sequence. Treatment of ibogaine with *t*-butyl hypochlorite yielded the chloroindolenine which combined with potassium cyanide to give 18-cyanoibogaine and an isomeric nitrile resulting from an amusing rearrangement. Vigorous base hydrolysis of the former nitrile followed by esterification with diazomethane furnished voacangine. The chloroindolenine served also as a convenient intermediate for the preparation of 18-methoxy- and 18-hydroxyibogaine.

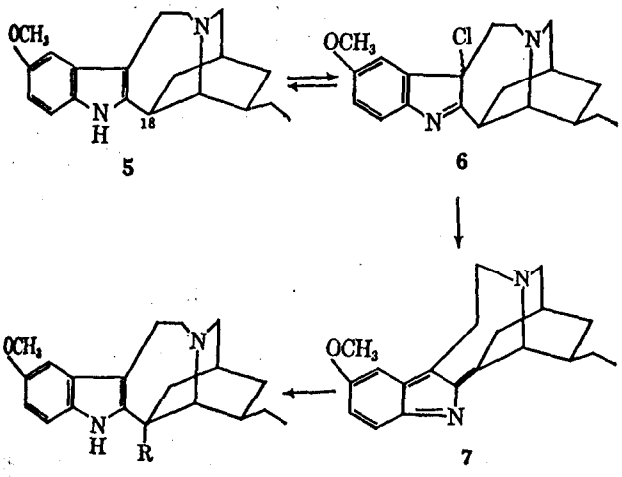
The molecular structures of a number of Iboga alkaloids[1] contain a carbomethoxy group and in the course of structural studies it was found that the carboxylic acids derived from the esters suffer ready decarboxylation to the parent Iboga bases.[2,3] This evidence strongly suggested that the carbomethoxy groups were located at C_{18} in the ester alkaloids. We have recently completed total syntheses of racemic ibogamine and ibogaine and planned from the outset to use the two bases as relays for the synthesis of the corresponding ester alkaloids.[4]

The starting material chosen for such transformations was ibogaine (5)[5,6] which is readily available from natural sources. It was suspected that the hypothetical imine (7) would be highly electrophilic and combine with cyanide ion to yield the nitrile (8) which in turn could be transformed to voacangine (9) by standard operations. The method chosen for the genesis of the unstable imine (7) was suggested by the acid-catalyzed conversion of 11-hydroxytetrahydrocarbazolenine (1) to the dimer (4) which probably proceeds through the imine (2) and further intermediates, *e.g.*, 3.[7] Initiation of imine formation clearly requires a suitable leaving group and in practice we employed chloroindolenines which are easily prepared from indoles and *t*-butyl hypochlorite.[8,9] Treatment of ibogaine (5)[10] with

(1) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, 1964.
(2) M. M. Janot and R. Goutarel, *Compt. Rend.*, 241, 986 (1955).
(3) U. Renner, D. A. Prins, and W. G. Stoll, *Helv. Chim. Acta*, 42, 1572 (1959).
(4) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, 87, 2073 (1965).
(5) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *ibid.*, 80, 126 (1958).
(6) G. A. Jeffrey, G. Arai, and J. Coppola, *Acta Cryst.*, 13, 553 (1960).
(7) J. B. Patrick and B. Witkop, *J. Am. Chem. Soc.*, 72, 633 (1950).
(8) W. O. Godfredsen and S. Vangedal, *Acta Chem. Scand.*, 10, 1414 (1956).
(9) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, 84, 3871 (1962).

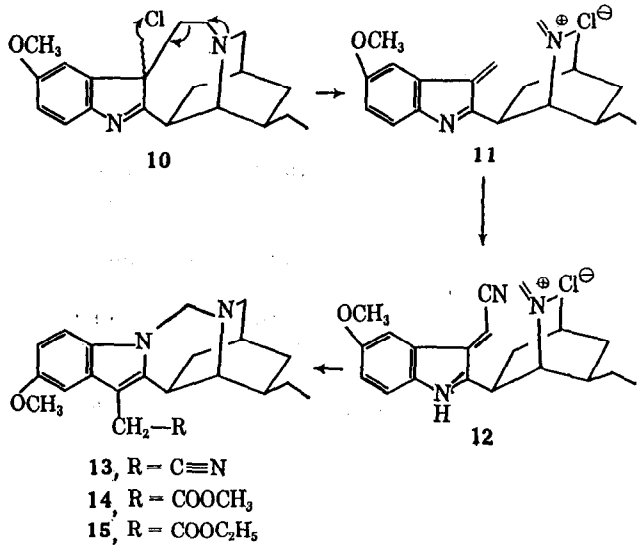


this reagent gave the crystalline chloroindolenine with the anticipated spectral properties.[14] Reduction with lithium aluminum hydride regenerated ibogaine (**5**) whereas exposure to a hot solution of potassium cyanide in methanol yielded two products in approximately equal amounts. Their separation was made easier when it was found that at room temperature the reaction furnished mostly one substance shown to be the desired 18-cyanoibogaine (**8**). When the latter was heated for 3 days in methanolic hydrochloric acid it was recovered unchanged and we were unable to find conditions allowing the one-step conversion of this highly hindered nitrile to voacangine (**9**). Hydrolysis with potassium hydroxide in diethylene glycol at 140° followed by careful acidification at low temperatures and esterification with diazomethane furnished voacangine (**9**) identical in melting point, mixture melting point, chromatographic behavior, and infrared spectrum with natural material.



8, R = C≡N
9, R = $COOCH_3$

The second substance formed in the reaction of the chloroindolenine (**6**) with potassium cyanide was not isolated in pure form. Spectral analysis of the crude reaction mixture suggested the presence of a second nitrile and exposure to hot methanolic hydrogen chloride followed by base hydrolysis yielded a readily separable mixture containing unchanged 18-cyanoibogaine (**8**) and a carboxylic acid fully characterized in the form of its methyl ester. This ester had typical indole absorption in its ultraviolet spectrum and the infrared spectrum indicated the absence of an indole N–H grouping. The second compound formed in the reaction of the chloroindolenine (**6**) with cyanide consequently is an unhindered nitrile containing an N-substituted indole ring, and the formation of a product (**13**) meeting these requirements can be rationalized by the sequence **10** (arrows) → **11** → **12** → **13**.



13, R = C≡N
14, R = $COOCH_3$
15, R = $COOC_2H_5$

An nmr spectrum of the methyl ester (**14**) is seen to be in good agreement with the structure proposed. A low-field eight-line ABX pattern centered at 7 ppm is assigned to the three aromatic protons. A broad, two-proton "singlet" at 4.88 ppm is attributed to the aminoacetal protons, the three proton singlet at 3.90 ppm to the aromatic methoxy group, and the five-proton singlet at 3.70 ppm to the superposed signals due to the carbomethoxy group and the methylene group attached to it. The methyl function of the ethyl side chain appears as an unsymmetrical triplet at 0.95 ppm. This interpretation is substantiated by the spectrum of the corresponding ethyl ester (**15**) which exhibits a two-hydrogen singlet at 3.66 ppm for the methylene group bearing the carboethoxy function.

We have also investigated the possibility of introducing a hydroxyl group on the carbon atom adjacent to the α position of indole alkaloids. Such compounds are key intermediates in the partial syntheses of bisindole alkaloids and in analogy to the synthesis of voacamine[11,15] it should be possible to effect a partial

(10) The molecular structures used in this paper indicate the absolute configuration of the Iboga alkaloids. Assignments presented in earlier papers[11-13] were based on erroneous interpretation of a two-dimensional representation of cleavamine in an article by J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind.* (London), 648 (1963). Dr. J. P. Kutney, University of British Columbia, has independently reached the same conclusion: J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, in press.

(11) G. Büchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, 86, 4631 (1964).

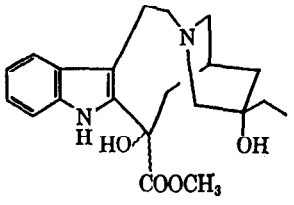
(12) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *ibid.*, 86, 1440 (1964); P. Bommer, W. McMurray, and K. Biemann, *ibid.*, 86, 1439 (1964).

(13) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 43, 1545 (1965).

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

(15) G. Büchi, *Pure Appl. Chem.*, 9, 21 (1964), and other references cited.

synthesis of vinblastine (18)[12,16] from the unknown hydroxyindole (16) and vindoline (17)[16,17] in the presence of acidic reagents.



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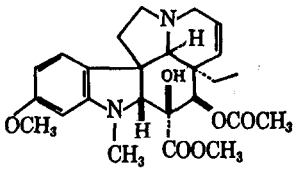

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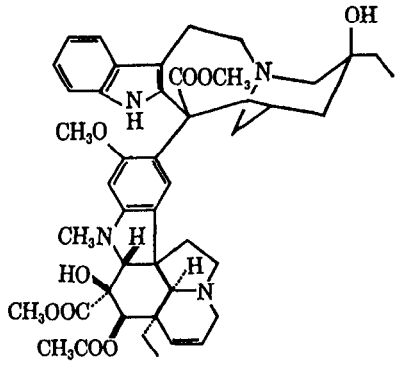


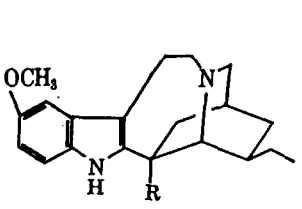
18

A method for introducing the hydroxy group at the desired position has now been tested successfully in the pentacyclic series. When the chloroindolenine (6) was warmed in methanol solution containing some hydrochloric acid 18-methoxyibogaine (19) was formed. An nmr spectrum contains two three-proton singlets at 3.77 and 3.09 ppm attributable to the aromatic and aliphatic methoxy groups, respectively. The absence of any signal in the region from δ 3.9 to 6.5 excludes the alternate structure (22). The structural assignment was confirmed further by reduction to ibogaine (5) with lithium aluminum hydride. When performed with lithium aluminum deuteride, a monodeuterioibogaine was produced whose nmr spectrum differs markedly from that of ibogaine (5) in the 2–3.5-ppm region but which is identical with that of 18-deuterioibogaine (21) obtained by decarbomethoxylation of voacangine (9) in a deuterated medium.[18] The methoxy group in 18-methoxyibogaine (19) could easily be replaced by other functionalities and on exposure to aqueous mineral acid it is transformed to 18-hydroxyibogaine (20). When the latter in turn was heated in methanol in the presence of acidic agents it was reconverted to the methoxy derivative (19). These exchange reactions as well as the reduction of 18-methoxyibogaine (19) with lithium aluminum hydride seem to involve the ubiquitous imine (7) or its conjugate acid. A Dreiding stereomodel of this molecule however reveals much angle strain and yet all reactions seemingly proceeding through this intermediate proceed with exceptional ease. It is tempting to suggest that the reactive intermediate has actually the geometry of the less strained nonclassical carbonium ion (23).

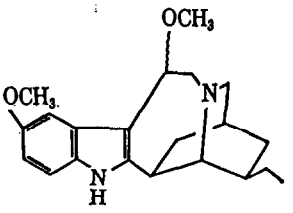
(16) J. W. Moncrief and W. N. Lipscomb, *J. Am. Chem. Soc.*, 87, 4963 (1965).

(17) M. Gorman, N. Neuss, and K. Biemann, *ibid.*, 84, 1058 (1962).

(18) 18-Deuterioibogaine was prepared previously by a different method: K. Biemann and M. Friedmann-Spiteller, *ibid.*, 83, 4805 (1961).



19, R=OCH_3
20, R=OH
21, R=D



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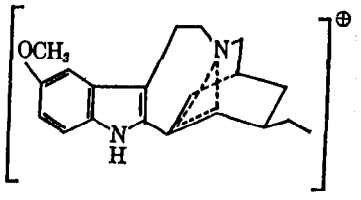
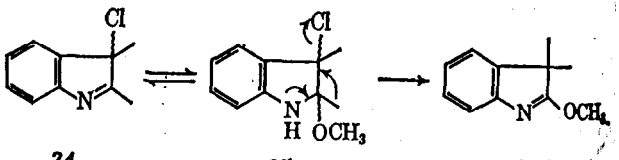


23

Finally it should be noted that by no means do all 3-chloroindolenines follow the reaction path just outlined when allowed to react with methanol. The diastereomeric chloroindolenines derived from yohimbine, for example, on treatment with methanol in the presence of acid[19] or base[20] are converted to imido ethers. This transformation can only proceed in the sense indicated (24 → 25 → 26) when the chlorine atom to be displaced and the migrating carbon–carbon are properly oriented in space to allow inversion. This demands *cis* disposition of the chlorine atom and the methoxy group in the intermediate indoline (25). Of the two theoretically possible diastereomers the isomer with the two substituents above the plane of the benzene ring is excessively crowded in the Iboga series and this adverse factor might prohibit the formation of such an intermediate and the transformation takes a different course. Consequently we tentatively propose that the chlorine atom in the chloroindolenine (6) is β oriented.



24 25 26

Experimental Section[21]

Oxidation of Ibogaine (5) with *t*-Butyl Hypochlorite. *t*-Butyl hypochlorite (1.40 g, 13 mmoles) in carbon tetrachloride (80 ml) was added dropwise over 20 min to a stirred solution of ibogaine (3.72 g, 12 mmoles) in methylene chloride (160 ml) containing triethylamine (1.21 g, 12 mmoles) cooled in an ice–salt mixture. After the addition was completed, stirring was continued for 40 min. The

(19) J. Shavel, Jr., and H. Zinnes, *ibid.*, 84, 1320 (1962).

(20) N. Finch and W. I. Taylor, *ibid.*, 84, 3871 (1962); 84, 1311 (1962).

(21) Melting points were observed on a Kofler micro hot stage and are corrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model 14, and infrared spectra were recorded on a Perkin-Elmer Model 237 grating infrared spectrophotometer. Optical rotations were determined on a Zeiss photoelectric polarimeter and $[\alpha]D$ was calculated from the observed $\alpha_{546\ m\mu}$ and $\alpha_{578\ m\mu}$ by means of the first approximation of Drude's formula for normal rotational dispersion. The nmr spectra were taken in deuteriochloroform on a Varian Associates Model A-60 nmr spectrometer and the chemical shifts are reported in ppm (δ) downfield from an internal tetramethylsilane reference. Woelm alumina was used as a chromatographic adsorbent. Microanalyses were performed by the Midwest Microlab, Inc., Indianapolis, Ind.

reaction mixture was washed with ice water, dried (sodium sulfate), and evaporated under vacuum to yield the crude chloro derivative as a light brown, viscous oil. A solution of a portion of the material in benzene and hexane was filtered through alumina (activity III) and crystallized from hexane containing a little benzene to give the pure product: mp 90–92°; $\lambda_{max}^{isooctane}$ 230 mμ (ε 16,100), 280 (6000), and 310 (2480); $\nu_{max}^{CHCl_3}$ 2950, 2850, 1600, 1550, 1475, 1435, 1360, 1315, 1275, 1180, 1155, 1100, 1080, 1030, 985, 900, 865, 840, and 825 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}N_2OCl$: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.16; H, 7.38; N, 8.64.

Lithium Aluminum Hydride Reduction of Chloroindolenine (6) Prepared from Ibogaine. A solution of lithium aluminum hydride in ether was added to an ether solution of pure chloro compound (100 mg). After 5 min, ethyl acetate and water were added and the reaction mixture was filtered. Evaporation of the filtrate gave 90 mg of crude crystals, which gave only one spot with the same R_f value as ibogaine when analyzed by thin layer chromatography. Crystallization from methanol gave a pure product, identical by melting point, mixture melting point, and infrared spectrum with authentic ibogaine.

18-Methoxyibogaine (19). A solution of crude chloroindolenine (from 3.7 g of ibogaine) in 1% hydrochloric acid in methanol solution (100 ml) was heated under reflux for 1 hr. The brown reaction mixture was treated with sodium carbonate solution and methylene chloride. The organic layer was washed with water, dried (sodium sulfate), and evaporated. A solution of the residue in benzene was filtered through alumina (activity III) and the material obtained by evaporation was crystallized from methanol. Recrystallization from methanol afforded the product: 2.7 g; mp 107–108°; [α]D +51° (*c* 3.91, chloroform); λ_{max}^{EtOH} 225 mμ (ε 28,000), 284 (9850), and 298 (8080); $\nu_{max}^{CHCl_3}$ 3450, 3300, 2995, 2920, 2850, 1620, 1580, 1480, 1450, 1375, 1280, 1230, 1185, 1175, 1150, 1120, 1080, 1060, 1030, 1000, 980, 960, 945, 865, and 835 cm^{-1}; mol wt 340 (mass spectrum).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.12; H, 8.33; N, 8.25.

18-Hydroxyibogaine (20) from 18-Methoxyibogaine (19). 18-Methoxyibogaine (3 g) was heated at 70° for 1 hr in 1.5% hydrochloric acid (120 ml). The cooled solution was treated with sodium carbonate solution and methylene chloride. The organic phase was washed with water, dried (sodium sulfate), and evaporated. A solution of residue in benzene was filtered through alumina (activity III) and the material obtained by evaporation was crystallized from methanol–water to give a pure product: mp 117–119°; [α]D +4° (*c* 2.14, chloroform); λ_{max}^{EtOH} 228 mμ (ε 24,600) and 294 mμ (ε 9050); $\nu_{max}^{CHCl_3}$ 3550, 3450, 3000, 2920, 2850, 1625, 1580, 1480, 1450, 1435, 1375, 1360, 1310, 1290, 1230, 1175, 1150, 1120, 1030, 1000, 985, 960, and 835 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.58; H, 8.20; N, 8.60.

Lithium Aluminum Hydride Reduction of 18-Methoxyibogaine (19). 18-Methoxyibogaine (150 mg) dissolved in ether was added to a solution of lithium aluminum hydride in ether and heated under reflux overnight. The reaction mixture was treated successively with ethyl acetate and water, and subsequently filtered. Evaporation of the filtrate gave 150 mg of crude crystals. Analysis by thin layer chromatography indicated only one product with the same R_f value as ibogaine. Crystallization of the crude material from methanol afforded ibogaine, mp 152–154°, pure and mixed with authentic ibogaine, mp 152–154°. The infrared spectrum of the product was identical with that of authentic ibogaine.

Lithium Aluminum Deuteride Reduction by 18-Methoxyibogaine (19). Using the procedure described above 18-methoxyibogaine (90 mg) was reduced with lithium aluminum deuteride to give, after crystallization of the crude product from methanol, 60 mg of 18-deuterioibogaine, mp 153–154°. The nmr spectrum of this material was identical with that of the 18-deuterioibogaine described below.

Preparation of 18-Deuterioibogaine (21). Voacangine (180 mg) was added to a solution of sodium (0.8 g) in methanol-O-*d* (11 ml) and deuterium oxide (0.8 ml) and the resultant mixture was heated under reflux for 12 hr. After cooling, the reaction mixture was diluted with deuterium oxide (5 ml) and adjusted to pH 2 by the addition of a portion of a solution prepared by reacting phosphorus oxychloride (2 ml) with deuterium oxide (15 ml). After heating for 5 min, sodium carbonate solution and methylene chloride were added. The organic phase was dried (sodium sulfate) and evaporated to give a crude residue (160 mg). A benzene solution of this material was filtered through alumina (activity III) and the residue obtained by evaporation was crystallized from methanol to give 18-deuterioibogaine (70 mg), mp 153–154°, pure and mixed with authentic ibogaine: mp 153–154°; mol wt 311 (mass spectrum).

18-Cyanoibogaine (8). A solution of crude chloroindolenine (from 3.7 g ibogaine) and potassium cyanide (7 g) in methanol (90 ml), water (10 ml), and ether (20 ml) was stirred at room temperature for 2 days. The reaction mixture was treated with sodium carbonate solution and methylene chloride and the organic phase was successively washed with water, dried (sodium sulfate), and evaporated. A solution of the residue in benzene was filtered through alumina (activity III) and the material obtained by evaporation was recrystallized from methanol to give 1.2 g of pure 18-cyanoibogaine: mp 171–173°; [α]D +28° (*c* 2.39, chloroform); λ_{max}^{EtOH} 213 mμ (ε 34,500), 282 (9620), and 295 (7820); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2930, 2855, 2220, 1620, 1590, 1480, 1450, 1370, 1320, 1290, 1210, 1170, 1150, 1130, 1110, 1090, 1030, 990, 955, 925, and 830 cm^{-1}; mol wt 335 (mass spectrum).

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.20; H, 7.45; N, 12.44.

Methyl Ester 14 Derived from the Isomeric Nitrile 13. The mother liquors from the preparation of 18-cyanoibogaine were heated under reflux overnight in methanol saturated with hydrogen chloride. The reaction mixture was treated with excess sodium carbonate solution and methylene chloride and the organic phase was dried (sodium sulfate) and evaporated. A solution of the residue in 12% potassium hydroxide in methanol solution was heated under reflux overnight, diluted with an equal amount of water, extracted with ether, acidified with hydrogen chloride in methanol, and heated under reflux for 1 hr. After treatment with excess sodium carbonate solution, the mixture was extracted with methylene chloride and the organic phase was washed with water, dried (sodium sulfate), and evaporated. A solution of the residue in benzene was filtered through alumina (activity III) and the material obtained by evaporation was crystallized from methanol to give a pure product: mp 78–80°; λ_{max}^{EtOH} 226 mμ (ε 24,900), 282 (8150), and 295 (6800); $\nu_{max}^{CHCl_3}$ 3000, 2950, 2930, 2860, 1730, 1650, 1590, 1490, 1460, 1445, 1335, 1325, 1275, 1230, 1170, 1150, 1120, 1105, 1060, 1030, 985, 890, and 825 cm^{-1}; mol wt 368 (mass spectrum).

Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.95; H, 7.78; N, 7.97.

Conversion of 18-Cyanoibogaine (8) to Voacangine (9). A solution of 18-cyanoibogaine (150 mg) in 20% potassium hydroxide in diethylene glycol solution (1.5 ml) was heated at 150° under nitrogen for 11 hr. The reaction mixture was diluted with methanol, cooled to 0°, neutralized with methanolic hydrogen chloride, and treated with excess diazomethane in ether solution. After 15 min, sufficient methanol–hydrogen chloride was added to destroy the excess diazomethane and the resultant solution was again treated with excess ethereal diazomethane. The reaction mixture was subsequently partially evaporated, basified with sodium carbonate solution, and extracted with ether. The ether solution was dried (sodium sulfate) and evaporated to give 165 mg of crude material which was dissolved in benzene and filtered through alumina (activity III) to give 80 mg of crude voacangine. Crystallization from methanol gave pure voacangine, mp 137–138°; pure and mixed with authentic voacangine, mp 137–138°. The infrared spectrum of this material was identical with that of authentic voacangine.

Acknowledgments. We wish to thank the National Institutes of Health (GM 09686) for financial support and Professor K. Biemann, Massachusetts Institute of Technology, for mass spectra.