The Total Synthesis of Iboga Alkaloids

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Abstract: The two alkaloids, ibogamine and ibogaine, have been prepared in the form of their racemates from nicotine by a 13-step sequence.

Through common usage the term "iboga alkaloids" has come to include all of the bases from diverse species having the ibogamine (1) skeleton, or simple variations of it as catharanthine (3), iboluteine (4), and kisantine (5).


(8) National Science Foundation Postdoctoral Fellow, 1964–1965.

The preparation of XVIII was performed in exactly the same manner as V was prepared from XIII, starting either with XIII or XI. The product XVIII was obtained essentially quantitatively and was recrystallized from carbon tetrachloride, mp 179–180°.

The pmr spectrum of a deuteriochloroform solution showed two sharp singlets (2 H: 1 H) at δ 6.00 and 5.20, respectively, and two doublets of aromatic protons (2 H and 11 H) at 2.1–2.3 and 3.4–3.5.

Found: C, 70.74; H, 4.49.

Hydrogenolysis of V with Raney Nickel to Give XVIII. About 3 g of Raney nickel W-2 was added to a solution of 1.05 g (2.53 mmole) of V in 75 ml of ethyl ether. The mixture was stirred for 1 hr at room temperature. The Raney nickel was removed by filtration, and the ethereal solution was washed with 100 ml of water. The ethereal solution was washed with activated charcoal, and the ether was removed by rotary evaporation.

A comparison of the pmr spectrum of the crude reaction mixture with that for XVIII showed them to be identical with no observable impurity of V left. Crystallization from carbon tetrachloride gave yellow oil showing that oil to be nearly all exo-4-chloro-8-carbomethoxydibenzobicyclo[3.2.1]octadiene (XXI). A small portion of the oil (ca. 100 mg) was crystallized from absolute methanol giving colorless needles of XXI, mp 108–109°.

Ibogaine (2) appears to be the most abundant of the naturally occurring members of this class of alkaloids and was the first target of serious structural studies. The correct gross structure was established in 1957 through chemical studies, and an X-ray crystallographic investigation provided firm evidence for the configuration of the ethyl group. Until now none of the iboga alkaloids have been synthesized although progress toward this objective has been achieved in other laboratories. In the present paper we describe the total synthesis of two naturally occurring alkaloids in their racemic modifications.

Some isoquinuclidone was an obvious intermediate in the synthesis of ibogamine (1) and our plan was to first prepare a polyfunctional isoquinuclidine by Diels-Alder condensation of a dihydropyridine with a dienophile and to subsequently replace one of the functionalities in the resulting adduct by a cyclic carbonyl group. Attempts to condense 1-benzyl-3-cyano-1,6-dihydropyridine (7) with a-acetoxyacrylonitrile, ethoxyacetylene, and nitroethylene did not yield isolable amounts of the anticipated isoquinuclidines, and subsequent efforts were directed toward the acquisition of an a,b-unsaturated primary amide which could be transformed to an isoquinuclidine by Hofmann degradation. Thus, reduction of N-benzyl-3-cyanopyridinium bromide (6) with sodium borohydride in aqueous solution containing sodium carbonate gave an oily mixture of the yellow 1,2-dihydropyridine 8 and the colorless 1,6-dihydropyridine 7 separable only by thin layer chromatography. Condensation of the crude mixture of reduced pyridines with methyl vinyl ketone yielded the crystalline isoquinuclidine 9 in 16% yield based on the pyridinium salt 6. Molecular composition and infrared and nuclear magnetic resonance spectra agreed with those anticipated for structure 9. The configuration of the acetyl group follows from subsequent transformations but the position of this functionality on the isoquinuclidine ring was not proven for this particular compound. It follows however from analogy with two similar Diels-Alder adducts 10 and 12 of established structure. Condensation of the dihydropyridine 7 with methyl acrylate yielded the adduct 10 while analogous combination of 1-benzyl-3-carbomethoxy-1,6-dihydropyridine (11) with acrylonitrile gave the isomeric compound 12. On catalytic hydrogenation both adducts furnished the same isoquinuclidine 13 characterized in the form of its crystalline hydrochloride. Since either substituent in the final product 13 can be derived from a 3-substituted pyridine, the functionality introduced by the dienophile and the basic nitrogen atom must be located on vicinal carbon atoms. Before leaving this discussion of the various Diels-Alder reactions it should be mentioned that isoquinuclidines originating from 1,2-dihydropyridines were never observed. This difference in behavior of the two isomeric dihydropyridines seems to reflect the greater electron delocalization in the more extensively conjugated 1,2 isomers (e.g., 8). Hydrolysis of the nitrile 9 with cold concentrated hydrochloric acid afforded the amide 15, identical with the adduct prepared by reduction of 1 benzyl-3-cyanopyridinium chloride (14) followed by condensation of the crude mixture of reduced pyridines with methyl vinyl ketone. In larger scale preparations of

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(11) The absolute configuration of the iboga alkaloids is that shown throughout this paper. It is based on chemical correlation with cleavamine and vindoline whose absolute configurations have been ascertained by the X-ray method: N. Camerman and J. Trotter, ibid., 17, 384 (1964); J. W. Moncrief and W. N. Lipscomb, J. Am. Chem. Soc., 87, 4963 (1965). All substances of synthetic origin are actually racemates.

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We made the useful observation that the yield of dihydropyridines and consequently of adducts was increased considerably if the aqueous layer of the sodium borohydride reduction was decanted from the water-insoluble reduced pyridines before the reaction mixture was extracted with chloroform. A plausible explanation of this finding involves further reduction of one or both dihydropyridines to the isolable tetracyclodione 16 by diborane in the chloroform layer. Diborane is being produced and transferred to the organic phase as long as excess sodium borohydride is present in the aqueous layer. With a three-step conversion of nicotinamide to the isoquinuclidine 15 in hand, the next operations were concerned with transformation to an isoquinuclidione. Before proceeding with the Hofmann degradation, the ketone 15 was reduced with sodium borohydride to a crystalline mixture of epimeric alcohols 17. The major component further characterized by its acetate 18 could be separated from the minor epimer by crystallization, but no configurations were determined because the symmetry introduced here is destined to be eliminated at a later stage. Oxidation of either the alcohol 17 or its acetate 18 with sodium hypochlorite in methanol afforded the tricyclic urethan 19. In practice it was found to be advantageous to perform the Hofmann reaction on the mixture of epimeric alcohols 17 because separation of the major isomer was more complete in the case of the highly crystalline urethans 19. Urethan formation undoubtedly proceeds through an initially formed vinyl isocyanate and thence to the enamine 20 or directly to the conjugated imine 21 which is expected to be more stable than its nonconjugated tautomer 20.

Somewhat contrary to expectation, the tricyclic urethan 19 proved to be exceptionally inert to hydrolytic conditions and was recovered unchanged after exposure to cold concentrated hydrochloric acid as well as to hot potassium hydroxide. It was, however, convertible in essentially quantitative yield to the acetoxyl ketone 22 by hydrolysis with 6 N sulfuric acid followed by acetylation. The vigorous reaction conditions necessary did not preclude molecular rearrangements but the infrared, nuclear magnetic resonance, and mass spectra of the acetoxyl ketone 22 were in perfect agreement with those anticipated. The benzyl group was now removed in quantitative yield by catalytic reduction of the tertiary amine 22 in the presence of excess hydrochloric acid.

At this stage the remaining carbon atoms had to be introduced into the ibogamine (1) molecule and the secondary amine 23 permitted this to be done in at least two ways. For reasons to be discussed later, the tryptyl moiety was initially introduced by acylation rather than alkylation. Treatment of the secondary amine 23 with β-indolylacetyl chloride yielded the amorphous amide 24, hydrolyzed with alkali to the crystalline alcohol 25. When the latter substance was subjected to the action of p-toluenesulfonic acid in boiling ethylene chloride solution it was converted to the hexacyclic lactam 26. This reaction proceeds in high yield and it is undoubtedly the rigidity of the isoquinuclidione ring which facilitates the formation of the seven-membered ring. A second point of interest concerns the geometry of the amide bond in the lactam 26. Although the nitrogen atom is at a bridgehead position the rings involved are large enough to allow the essentially planar amide grouping indicated by infrared absorption at 1640 cm\(^{-1}\). It is clear that the formation of the hexacyclic compound 26 must proceed through several stages and if the hypothetical intermediate 27 proceeds to a carbonium ion 29 (or less likely, the corresponding planar iminium ion) the final cyclization is unexceptional. Evidence in favor of such a suggestion is provided by the facile interconversion of 18-hydroxy- and 18-methoxyibogaine. Although 18-methoxyibogaine is rapidly reduced to ibogaine (2) with lithium aluminum hydride, reduction of the lactam 26 did not proceed to the desired penta cyclic amino alcohol but only to the hexacyclic amino ether 31.

To avoid the formation of the tetrahydrofuran ring, we investigated the cyclization of the acetoxylactam (16) 2,2-Dimethylquinuclidone-(6) absorbs at 1733 cm\(^{-1}\). H. Pracejus, Ber., 92, 988 (1959).

24. Treatment with p-toluensulfonic acid in hot acetic acid solution furnished a diol monoacetate to which we originally assigned structure 28,1 but it became clear that expression 28 does not represent the structure of the product but that of an elusive intermediate. The first evidence against 28 but in favor of 32 was provided by the nuclear magnetic resonance spectrum measured in d6-DMSO solution. A one-proton multiplet centered at 4.7 ppm is attributed to the proton attached to the side-chain carbon atom carrying the acetate grouping, and a one-proton doublet (J = 6 cps) at 5.23 ppm to a hydroxyl proton of an elusive intermediate. Again in support of structure 33 the spectrum of the corresponding diacetate has singlets at 1.93 and 2.15 ppm due to two acetate methyl groups, a one-proton multiplet at 4.9 ppm due to the proton adjacent to the side-chain acetate function, and a doublet at 5.40 ppm caused by the analogously situated cyclohexane proton. It is thus clear that the original product is a disaccharide diol monoacetate. This monoacetate 32 could be hydrolyzed to the corresponding diol 34 by means of alkali. Attempts to dehydrate the diol to the hexacyclic ether 26 in the presence of acidic catalysts failed and this situation again cannot be reconciled with structure 27. It should be recalled that a compound with this structure plays the role of an intermediate in the conversion of 25 to 26. When the lactam 32 was reduced with lithium aluminum hydride in tetrahydrofuran it was smoothly transformed to the dihydroxylamine 35. A very intense peak at m/e 209 in the mass spectrum of the diol 35 and its derivatives is attributed to the ion 38. Before describing the conversion of this diol to ibogamine (1), we wish to discuss an alternate synthesis.

35, R1 - R2 = -H
36, R1 = H, R2 = -COCH3
37, R1 = R2 = -COCH3

As already mentioned we were initially suspicious of any attempts at acid-catalyzed cyclization of the amino ketone 39 because we believed that the positively charged nitrogen atom would suppress protonation of the neighboring carbonyl group requisite for bond formation to the indole ring. After realizing that the cyclization of the ketoamide 24 to the lactam 31 is followed by a rearrangement, it became of interest to inquire whether the amine 39 could indeed be cyclized and whether the resulting product would be an inquinclidine or again a azabicyclo[1.2.3]octane. Alkylolation of the secondary amine 23 with trityl bromide produced the tertiary amine 39 which without purification was subjected to the action of p-toluensulfonic acid in acetic acid solution. The salt of the cyclized product 36 crystallized from the crude reaction mixture and, after conversion to the corresponding amine, the mother liquors yielded minor amounts of the previously described ether 31 and the diacetate 37. Reduction of the monoacetate 36 with lithium aluminum hydride to the diol 35 completed an alternate synthesis of this crucial intermediate. These experiments showed that our fears concerning the cyclization of the amine 39 were not justified and that the hypothetical tertiary alcohol is again unstable in relation to its rearranged secondary isomer 36. Although analogous Wagner-Meerwein rearrangements in the bicyclo[2.2.2]octane25 series are well known, the changes observed here involve 1,2 shifts of amine and amide nitrogen. Such transformations of amines are fairly common whenever an ethylenimine can function as an intermediate. If the present cases, however, such intermediates are very severely strained and the unshared electron pair on the nitrogen atom is not available for displacement of the leaving group. The only analogy for a direct 1,2 shift of nitrogen we are aware of is the rearrangement of cinchonine halides to hetero ethers in the presence of silver salts in alcoholic solutions.25,26 Stereomodels of the two monoacetates 28 and 32 leave no doubt that the latter represents the less crowded and consequently most stable isomer. Interestingly, 18-hydroxyibogamine (40) with the side chain in the opposite configuration is stable in relation to its isomer 41. Although no rigorous evidence is available concerning the configurations of the hydroxy groups in 32 and 36, they are most probably axially oriented. It should be remembered that the cyclizations of the ketones 24 and 39 give mainly the monoacetates 32 and 36 rather than the diacetates 33 and 37, although the reactions are performed in acetic acid solution. This seems to result from internal return within ion pairs derived from the

References:
hypothetical cation 30 and the corresponding desoxo analog demanding that leaving and entering hydroxyl groups be located on the same face of the molecule. Under more vigorous conditions the cation 30 does combine with external anions and when the cyclization of the acetoxy ketone 24 was performed in boiling chlorobenzene in the presence of 1 molar equiv of p-toluene-sulfonic acid, the acetoxysaltate (32 R1 = SO3C6H5) was obtained. Solvolysis in refluxing acetic acid gave the diacetate 33 presumably with retention of configuration. A second argument in favor of an axially oriented hydroxyl group in 32 was provided by the coupling constant for the two vicinal hydrogen atoms attached to C-4 and C-5 in the diacetate 33. The observed value of 4 cps agrees with an axial-equatorial relationship.

Returning to the synthesis of ibogamine (1) the diol 35 was oxidized with dimethyl sulfoxide and cyclohexylcarbodiimide\(^\text{25,26}\) to the hydroxy ketone 42 whose mass spectrum again shows an intense fragment peak at \(m/z\) 209 (38). In association with this change the methyl group in the hydroxy ketone now appears as a singlet at 2.05 ppm in the nmr spectrum (DMSO) and a one-proton doublet at 5.20 ppm (\(J = 6\) cps) which disappears on exchange with deuterium oxide again demands the presence of a secondary alcohol. Exposure of the \(\beta\)-hydroxy ketone 42 to basic catalysts caused dehydration to the \(\alpha,\beta\)-unsaturated ketone 43, \(\nu_{\text{C=O}} = 1670, 1640\) cm\(^{-1}\), and one vinyl proton in the nmr spectrum (singlet at 7.20 ppm). As anticipated the \(\alpha,\beta\)-unsaturated ketone grouping had a marked effect on the ultraviolet light absorption properties also and caused a raise of the extinction at 226 \(\text{nm}\) to 48,500.

To complete the synthesis of ibogamine (1) three further changes are necessary. The oxidation stage of the bicyclic moiety has to be adjusted, the azabicyclo[3.3.1]octane has to be reconverted to an isoquinuclidine, and the acetyl side chain needs transformation to an ethyl group. The first two objectives were achieved in a single operation when it was found that reduction of the \(\alpha,\beta\)-unsaturated ketone 43 with zinc in acetic acid yielded a mixture of the two epimeric ketones 44 and 45. Neither one of the two was identical with the epimeric ketones 46 produced by catalytic reduction of the unsaturated ketone 43 and they consequently must have different skeletons. The mechanism of reduction of the unsaturated ketone by zinc undoubtedly involves cleavage of the carbon-nitrogen bond (48, arrows) to yield the tetracyclic compound 49 and subsequent internal Michael addition (49, arrows) to an enol and thence to the epimeric ketones 44 and 45.

The two methyl ketones 44 and 45 were partly separable by chromatography on Florisil but it was not possible to convert the mixture of ketones to a single isomer by either acid or base catalysis, suggesting that they differ little in thermodynamic stability. Wolff-Kishner reduction of this mixture yielded ibogamine (1) and epibogamine (47) readily separable by chromatography. Comparison of infrared and mass spectra and of \(R_f\) values on thin layer chromatograms established the identity of racemie ibogamine with a sample of natural origin. Identical criteria were used to ascertain the identity of racemic epibogamine (47) with material prepared by degradation of catharanthine (3).\(^\text{24}\)

Analogous procedures were used to synthesize ibogaine (2). Condensation of 3-(5-methoxyindolyl)-acetyl chloride\(^\text{26}\) with the secondary amine 23 furnished the amorphous amide 50. Cyclization to the lactam 51 was again effected in acetic acid solution containing p-toluenesulfonic acid. Reduction with lithium aluminum hydride afforded the diol 52 which was subsequently oxidized to the hydroxy ketone and dehydrated to the \(\alpha,\beta\)-unsaturated ketone 53. Reduction with zinc in acetic acid followed by Wolff-Kishner reduction yielded a readily separable mixture of ibogaine (2) and its C\(_4\) epimer (54). Infrared and mass
spectra of racemic ibogaine were identical with those of the natural material. The mass spectra of epibogaine (47) and epibogaine (54) were identical in the lower mass region, but peaks due to fragments containing the indole ring appeared 30 mass units higher in the case of epibogaine.26

Unfortunately the two total syntheses just described do not corroborate the configuration of the ethyl group in iboga alkaloids but both crystallographic10 and chemical evidence is already available on this point. We have previously developed a method for the introduction of a carbomethoxy group at C5 in iboga alkaloids and used it for the conversion of ibogaine to voacangine.17

Experimental Section

Microanalyses were performed by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology microchemical laboratories, and by Midwest Microlabs, Inc., Indianapolis, Ind. Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Models 137 and 237 Infraordie; in general only bands characteristic of the functional groups present are listed. Ultraviolet spectra were recorded on a Cary, Model 14, recording spectrophotometer. The nmr spectra were obtained with a Varian A-60 instrument and are given in ppm from an internal tetramethylsilane standard; coupling constants (J) are given in cps. Complete spectra are quoted when deemed appropriate and when adequately resolved; otherwise the pertinent and salient features only are given. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were determined on a CEC 103 instrument using a direct inlet system; in general only bands characterizing the functional groups present are listed. Ultraviolet spectra are quoted when deemed appropriate and when adequately resolved; otherwise the pertinent and salient features only are listed. Mass spectra were determined on a CEC 103 instrument using a direct inlet system; in general only bands characterizing the functional groups present are listed. Ultraviolet spectra are quoted when deemed appropriate and when adequately resolved; otherwise the pertinent and salient features only are listed.

N-Benzyl-3-carboxamidopyridinium Chloride (14). A solution of benzyl chloride (100 g, 0.79 mole) and nicotinamide (95 g, 0.78 mole) in methanol (250 ml) was heated under reflux overnight. After cooling, the precipitate was collected and washed with acetone. The residue was recrystallized from ethanol and dried. The crude products were recrystallized from benzene to give a colorless oil (1 g). This solution was heated under reflux in an ice-methanol bath and treated with picric acid (1 g). This slurry was filtered and washed with acetone. The yellow oil recovered from the filtrate and washings was washed with acetone. The resulting suspension was cooled and filtered and the colorless powder was taken up in methanol giving an additional 15% of product. The salt was obtained as a colorless powder. The yield was 72%, mp 153-155°. 

Adduct 19 from N-Benzyl-3-carboxamido-1,6-dihydropryidine and Methyl Vinyl Ketone. A solution of N-benzyl-3-carboxamido-1,6-dihydropyridine in methanol (200 ml) was treated with picric acid (1 g). The mixture was allowed to stand without stirring for 5 min; the precipitate was collected and washed again with water and then dried. The solution showed three spots on tlc, y: 1530-1700 cm−1 (unresolved). 

The solution was treated with hydroquinone (0.5 g) and methyI vinyl ketone (40 g, 0.57 mole) and then was allowed to reflux under nitrogen for 18 hr. Evaporation left a dark red oil which was taken up in ethyl acetate (300 ml) and extracted with hydrobromic acid (30 ml in 500 ml of water). The organic phase was washed with water and discarded. The combined aqueous parts were put through Florisil (1 kg) and the yellow oil recovered from the eluate was dissolved in a mixture of dihydropyridines was dissolved in chloroform (200 ml) and treated with methyl vinyl ketone (120 g, 1.72 moles) and hydroquinone (1 g). This solution was heated under reflux in an ice-methanol bath and treated with picric acid (1 g). This slurry was filtered and washed with acetone. Both filtrate and washings were evaporated and the residue was taken up in acetone giving an additional 15% of product. The salt was obtained as a colorless powder. The yield was 72%, mp 153-155°. 

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Hydrolysis of Adduct 9 to Adduct 15. A solution of nitrile 9 (10 g) in concentrated hydrochloric acid (15 ml) was allowed to stand at room temperature for 18 hr. The solution was diluted with water, neutralized with sodium carbonate, and extracted with chloroform. The organic layers were dried and evaporated to an oil which crystallized from isopropyl alcohol giving 1.55 g (75%) of colorless plates, mp 167-170°. A mixture melting point with adduct 15 showed no depression and the infrared spectra of the two were identical.

Adduct 10 from N-Benzyl-3-cyanoo-1,6-diacydropyridine and Methyl Acrylate. A solution of 50 g of N-benzyl-3-cyanopyridinium chloride in 250 ml of water was cooled in an ice-salt bath and treated slowly while stirring with a solution of 3 g of Na2CO3 in 100 ml of water. The mixture was stirred for 10 min and then extracted three times with CHCl3. The dried extracts were evaporated to give 36.5 g of light red oil. This mixture of diacydropyridines was taken up in 100 ml of dimethylformamide, treated with 50 ml of methyl acrylate and 0.5 g of hydroquinone, and then allowed to reflux under N2 for 3 days. The solution was cooled and evaporated to a red oil under reduced pressure. This oil was shaken with 75 ml of concentrated HCl in 500 ml of H2O and 90 ml of CH2Cl2 in 250 ml of ether. The organic phase was washed twice with water and discarded. The combined washings and the acid phase were washed with ether and slowly neutralized with Na2CO3. The slightly basic mixture was extracted twice with CH2Cl2 giving, when dried and evaporated, a dark oil. This oil in benzene solution was filtered through Florisil giving a yellow oil which crystallized from 50 ml of ether on Dry Ice. The crystals were filtered and washed with Dry Ice-cold ether giving 41.3 g (13.84%) of yellowish white prisms, mp 107-110°. Recrystallization from CH2Cl2-water on Dry Ice gave white needles: mp 111-113°; vmax 2210 (m), 1730 (s), 1600 (w), and 1595 cm-1 (w). The nmr spectrum is consistent with structure 10 and as observed with other adducts in the N-benzyl series, the benzylic protons appear as a quartet (3.48 ppm) and the vinyl proton as a doublet (7.12 ppm): δ 2.58, 2.64 (m, 2 H), 3.76 (AB'q, J = 14 cps), 7.42 ppm (w, 2 H). Anal. Calcd for C22H20N3O3: C, 69.49; H, 7.36; N, 8.53. Found: C, 69.25; H, 6.42; N, 10.39.

When treated with oxalic acid in ethanol the amine formed a crystalline oxalate. An analytical sample recrystallized from ethanol had mp 175-176°.


Transformation of the Unsatminated Amine 10 to the Saturated Amines Hydrochloride 13. A solution of the amine 10 (1.0 g) in methanol was hydrogenated over pre-reduced 10% Pd-C catalyst (0.1 g). The solution absorbed 92 ml of hydrogen in 86 min. The catalyst was removed by filtration, the filtrate was evaporated to dryness, and the residue was isolated in tetrahydrofuran. Upon addition of hydrochloric acid it gave a precipitate which on recrystallization from methanol gave small colorless crystals (0.41 g): mp 177-178°; vmax 2270 (w), 1740 (s), 1600 (w), and 1595 cm-1 (w). The nmr spectrum is consistent with structure 13 and as observed with other adducts in the benzylic series, the benzylic protons appear as a quartet (3.48 ppm) and the vinyl proton as a doublet (7.12 ppm): δ 2.58, 2.64 (m, 2 H), 3.76 (AB'q, J = 14 cps), 7.42 ppm (w, 2 H). Anal. Calcd for C16H20N3O3.HCl: C, 58.36; H, 5.08; N, 8.74. Found: C, 56.41; H, 5.72; N, 8.48.

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from methanol-tetrahydrofuran had the same melting point; anal. Caled for C10H16N2O2: C, 52.28; H, 6.50; N, 8.30; O, 22.92; Found: C, 52.24; H, 6.57; N, 8.29; O, 22.91.

Acetylation of the Secondary Amine 23 to the Amide 24. The secondary amine hydrochloride 23 (1.65 g, 6.66 mmoles) was dissolved in a mixture of methylene chloride (25 ml) and triethylamine (2 ml) and treated, with stirring and cooling in ice, with a solution of iodine-3-acyl chloride in methylene chloride (10 ml). Additional triethylamine (2 ml) was added and the solution was left at room temperature for 1 hr. It was then diluted with dilute aqueous sodium carbonate, dried, and evaporated to give 1.5 g of a light yellow solid. This solid was recrystallized from methanol-tetrahydrofuran to give 150 mg of a colorless sample which could not be crystallized; mp 298-302°.

Reduction of the Hexacyclic Ether 26 to the Hexacyclic Ester 31. The lactam 26 (5 mg) was allowed to reflux in tetrahydrofuran (5 ml) for 1 hr, and then treated with acetic anhydride (3 ml) and the solution was left at room temperature for 1 hr. The residue after evaporation was dissolved in a mixture of methylene chloride (25 ml) and triethylamine (2 ml) and treated, with stirring and cooling in ice, with a solution of iodine-3-acyl chloride in methylene chloride (10 ml). Additional triethylamine (2 ml) was added and the solution was left at room temperature for 1 hr. It was then diluted with dilute aqueous sodium carbonate, dried, and evaporated to give 1.5 g of a light yellow solid. This solid was recrystallized from methanol-tetrahydrofuran to give 150 mg of a colorless sample which could not be crystallized; mp 298-302°.

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Reduction of the Hexacyclic Ether 26 to the Hexacyclic Ester 31. The lactam 26 (5 mg) was allowed to reflux in tetrahydrofuran (5 ml) for 1 hr, and then treated with acetic anhydride (3 ml) and the solution was left at room temperature for 1 hr. The residue after evaporation was dissolved in a mixture of methylene chloride (25 ml) and triethylamine (2 ml) and treated, with stirring and cooling in ice, with a solution of iodine-3-acyl chloride in methylene chloride (10 ml). Additional triethylamine (2 ml) was added and the solution was left at room temperature for 1 hr. It was then diluted with dilute aqueous sodium carbonate, dried, and evaporated to give 1.5 g of a light yellow solid. This solid was recrystallized from methanol-tetrahydrofuran to give 150 mg of a colorless sample which could not be crystallized; mp 298-302°.
nmol), and sodium carbonate (1.5 g) in dimethylformamide (20 ml) was stirred at room temperature for 24 hr. It was then filtered with water and extracted with ether twice. The combined ether layers were extracted with dilute HCI and the combined acid extracts were neutralized with sodium bicarbonate. The aqueous sodium bicarbonate extraction with methylene chloride gave 0.478 g of an oil whose infrared spectrum showed the presence of some dimethylformamide. Without further purification this material was allowed to reflux with toluenesulfonic acid (0.50 g, 2.6 mmol) in glacial acetic acid (20 ml) and cooled with ethyl acetate. The residue after being washed with water (50 ml) was extracted with water (50 ml). The toluenesulfonate of the amine 36 separated in brownish white crystals. These were filtered, washed with water, and dried giving 0.194 g (11%) of material: mp 118-125° dec; $^{13}$C NMR 3500, 3400, 1750, 1710, 1260, 1240, 1130, 750, and 735 cm$^{-1}$. 

Dehydration of the Hydroxy Ketone 42 to the Unsatuated Ketone 43. A solution of the hydroxy ketone 42 (0.888 g, 2.84 mmol) and potassium carbonate (0.750 g, 5.6 mmol) in methanol (35 ml) was allowed to reflux for 1 hr. It was then evaporated to a small volume, diluted with water, and extracted with chloroform twice. The combined extracts were dried and evaporated leaving a brown gum which was filtered through a column of Florisil (10 g). The residue from this column was then eluted with benzene to give 0.778 g (93%) of colorless crystals. An analytical sample recrystallized from methylene chloride ether other had mp 90-120° before drying. When dried at 80° (0.02 mm) for 30 hr, it had mp 193-195°; $^{13}$C NMR 3500, 3350, 1670, 1640, 1330, 1250, 745, and 735 cm$^{-1}$; $^{1}$H NMR (4,800, 272 (9950), 280 (9400), and 288 (3400); $^{13}$C NMR (3500, 2090 (3400), 1840 (2000), and 1350 (7000); $^{1}$H NMR (4,800, 272 (9950), 280 (9400), and 288 (3400); $^{13}$C NMR (3500, 2090 (3400), 1840 (2000), and 1350 (7000).
turn with 10% sodium carbonate, water, 10% hydrochloric acid, and water. The solution was dried over anhydrous magnesium sulfate, filtered, and concentrated affording 3.8 g of an oil in 86.4% yield, $\text{C}_{21} \text{H}_{13} \text{O}_2 \text{N}$.

Cyclization of Amide 50 to Lactam 51. To 3.8 g (0.0093 mole) of oily amide 50 was added 40 ml of acetic acid and 800 mg (4.21 mmoles) of p-toluenesulfonic acid and the mixture was refluxed with nitrogen for 1 hr. To the refluxing solution was added 6.5 g (0.1 g-atom) of zinc dust and stirring was continued for 10 min followed by cooling to room temperature. The reaction mixture was poured into an excess of water, extracted thoroughly with chloroform, and filtered, to remove any zinc. The organic phase was washed with saturated aqueous sodium carbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated affording 2.87 g (65.5%, based on the theoretical yield) of lactam 51 upon trituration with methylene chloride.

A sample prepared for analysis by chromatography on Florisil followed by crystallization from 95% ethanol (dried for 3 hr at 100°) had mp 157-160°; $\nu_{\text{KBr}}$ 3400-3200, 1625 and 1730 cm$^{-1}$; $\delta_{\text{NMR}}$ 223 (2H); 6.95 (d, $J = 7$ cps, 1 H), 7.2 (d, $J = 3$ cps, 1 H), 7.55 (d, $J = 9$ cps, 1 H), and 11.25 (s, 1 H) ppm. On adding 30% hydrochloric acid, the resulting precipitate was filtered and the filtrate was diluted with chloroform, dried over anhydrous magnesium sulfate, filtered, and concentrated. The mixture of amino ketones showed infrared absorption at 1710 cm$^{-1}$. A thin layer chromatogram (25% methanol-benzene) showed the earlier eluates to be rich in the amino ketone having the larger $R_f$ value. The later fractions containing the material having the smaller $R_f$ value were combined and allowed to stand overnight in 20 ml of methanol containing 0.1% methanol-benzene. After extraction with chloroform, drying over anhydrous magnesium sulfate, filtration, and concentration, a mixture of amino ketones richer in the material with larger $R_f$ was obtained. The combined fractions containing saturated ketones weighed 510 mg (54.3%). The mixture of amino ketones was dissolved in 20 ml of ethylene glycol, treated with excess 95% hydrochloric acid, and allowed to stand overnight at room temperature. To this mixture was added 6 g of potassium hydroxide and the solution was then allowed to reflux for 4 hr under nitrogen. The cooled reaction mixture was diluted with water, extracted with chloroform, dried over anhydrous magnesium sulfate, filtered, and concentrated. The benzene-ethyl acetate eluates from a chromatogram of the residue (275 mg) on Florisil gave an oil having the same $R_f$ value as ibogaine and gave the same color reaction with ceric sulfate-phosphoric acid spray. The ether eluates yielded 40 mg of a crystalline material, $\text{mp}$ 178-180°, after crystallization from methanol. The substance was identified as epibogaine 54; $\nu_{\text{KBr}}$ 3450, 1140, and 1040 cm$^{-1}$; $\delta_{\text{NMR}}$ (CDCl$_3$) 1.24 g of crystalline dial, while the mother liquors afforded an additional 310 mg (63% over-all) after filtration in ether solution through a column of Florisil. A sample crystallized from methylbenzene afforded 660 mg of semicrystalline material.

Anal. Calcd for $\text{C}_{26} \text{H}_{24} \text{NO}_2$: $\text{C}$, 77.30; $\text{H}$, 8.63; $\text{N}$, 8.41. Found: $\text{C}$, 77.30; $\text{H}$, 8.63; $\text{N}$, 8.41.

Method B. To a boiling solution of 675 mg (2.11 mmoles) of unsaturated ketone 48 in 20 ml of acetic acid was added 24 g (0.037 g-atom) of zinc dust. After 1 hr the mixture was cooled, poured into water, neutralized with sodium carbonate, extracted with chloroform, dried over anhydrous magnesium sulfate, and concentrated affording 600 mg of acetylated material (1710 cm$^{-1}$, film). This residue was taken up in 10 ml of methanol, treated with excess 95% hydrochloric acid, and allowed to stand overnight. The solution was subsequently concentrated; the residue was dissolved in 20 ml of ethylene glycol containing 5 g of potassium hydroxide and allowed to re reflux for 4 hr under nitrogen. After cooling the mixture was poured into water and the precipitate was filtered in vacuo and washed with water, yielding 370 mg (57%) of a solid mixture which had $R_f$ values identical with those of ibogaine 2 and epibogaine 54 and which gave the same color reactions with ceric sulfate-phosphoric acid spray. This crude product was chromatographed on Florisil (1710 cm$^{-1}$), and the benzene-ethyl acetate eluates fracciones were identified as epibogaine (11), which however could not be induced to crystallize.

The oil was taken up in a little acetone and when treated with a few drops of concentrated HCl a crystalline (f)-ibogaine (11), which however could not be induced to crystallize. The solution was subsequently concentrated; the residue was dissolved in 20 ml of ethylene glycol containing 5 g of potassium hydroxide and allowed to reflux for 4 hr under nitrogen. After cooling the mixture was poured into water and the precipitate was filtered in vacuo and washed with water, yielding 370 mg (57%) of a solid mixture which had $R_f$ values identical with those of ibogaine 2 and epibogaine 54 and which gave the same color reactions with ceric sulfate-phosphoric acid spray. This crude product was chromatographed on Florisil (1710 cm$^{-1}$), and the benzene-ethyl acetate eluates fracciones were identified as epibogaine (11), which however could not be induced to crystallize.

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The Structures of Two Alkaloids from Patchouli Oil

G. Büchi, I. M. Goldman, and Dana W. Mayo

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Abstract: Two new alkaloids, for which the names patchoulipyridine and epiguaipyridine are suggested, have been isolated from the essential oil of Pogostemon patchouli Pellet. Spectral evidence was used to derive structures which were confirmed by total synthesis of patchoulipyridine and by conversion of guaiol to dihydroepiguaipyridine.

The voluminous literature on essential oil components refers to an enormous number of lower terpenes but to essentially no mono- and sesquiterpene alkaloids. By contrast alkaloids derived from diterpenes and steroids are widespread in plants. Furthermore, most recent investigations have shown the varied group of indole alkaloids to be biogenetically derived from monoterpenes. This situation then raises the question of whether low molecular weight alkaloids derived from mono- and sesquiterpenes are indeed rare in nature or not sufficiently volatile to show up in essential oils or simply escaped detection.

In the course of structural studies on patchouli alcohol we had an opportunity to examine the oil of Pogostemon patchouli Pellet for alkaloidal constituents. Extraction of the essential oil with aqueous hydrochloric acid removed the basic constituents and chromatography of the regenerated bases yielded two pure substances which, for reasons to become clear in the sequel, we have named patchoulipyridine and epiguaipyridine. The former was obtained as colorless crystals and is optically active. Combustion analysis revealed a molecular composition of C_{13}H_{16}N and this was reinforced by a mass spectrum. Patchoulipyridine exhibits ultraviolet light absorption typical of alkyl-substituted pyridines and the substitution pattern became clear from the proton magnetic resonance spectrum. A low-field AB pattern (J = 8 cps) with chemical shifts of 7.38 and 6.88 ppm is attributed to the γ and β protons on the pyridine ring and a three-proton singlet at 2.48 ppm is assigned to a methyl group attached to the α position of this ring. The two remaining locations on the pyridine nucleus are occupied by alkyl groups other than methyl. Two protons situated on carbon atoms adjacent to the aromatic ring give rise to two broad absorptions centered at 3.12 and 2.9 ppm, respectively. Singlets at 0.80, 1.03, and 1.26 ppm are assigned to three methyl groups and the remaining five protons appear as a very broad multiplet in the region of 1.7 ppm. Vinylic hydrogen atoms are clearly absent and the compound was indeed found to be resistant to catalytic reduction. The empirical formula dictates the presence of three rings and considering the coexistence of the alkaloid with patchouli alcohol (1), α-patchoulen (2) and β-patchoulen (3)* in the essential oil structure (4) for patchoulipyridine seemed most reasonable on biogenetic grounds. In agreement with this assignment ozonization yielded, inter alia, a dicarboxylic acid which chromatographically was indistinguishable from homocamphoronic acid (5) but positive identification was thwarted by lack of material.

More convincing evidence in favor of structure 4 was provided by synthesis. The acid-stable β-patchoulen (3) was selected as starting material and for nitrogen insertion we chose treatment with hydrazoic acid, a reaction which served previously in the synthesis of muscopolpyridine. Exposure of β-patchoulen (3) to the action of hydrazoic acid in the presence of sulfuric acid furnished an unstable mixture of unsaturated amines which, after rapid distillation, was dehydrogenated in hot 1-methylnaphthalene over a carbon-supported palladium catalyst. Thin layer chromatographic analysis of the resulting basic products revealed the presence of two major, and at least one minor, components which were separated on a preparative scale by chromatography on silica gel. Both major constituents

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