which had been dissolved in 5 ml of absolute ethanol. The solution was allowed to remain at room temperature for 5 hr. The precipitate which had formed was filtered and recrystallized from 95% ethanol, yielding 360 mg (36%) of *endo*-4-chloro-*anti*-8-phenylsulfonyldibenzobicyclo[3.2.1]octadiene (XI), mp 244–245°.

The pmr spectrum in deuteriochloroform showed a sharp doublet (1 H) at τ 4.51 (J_{45} = 4.5 cps),[10] a series of complex overlapping multiplets (3 H) between 5.6 and 6.2, and two distinct sets of aromatic protons (2 H and 11 H) at 2.1–2.4 and 2.5–3.1.

Anal. Calcd for $C_{22}H_{17}ClO_2S$: C, 69.37; H, 4.50. Found: C, 69.17; H, 4.49.

Preparation of 8-Phenylsulfonyldibenzotricyclo[3.2.1.0^{2,8}]-3,6-octadiene (XVIII). The preparation of XVIII was performed in exactly the same manner as V was prepared from III, 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 τ 6.00 and 5.20, respectively, and two distinct sets of aromatic protons (2 H and 11 H) at 2.1–2.3 and 2.6–3.1.

Anal. Calcd for $C_{22}H_{16}O_2S$: C, 76.71; H, 4.68. Found: C, 76.70; H, 4.59.

Hydrogenolysis of V with Raney Nickel to Give XVIII. About 5 g of Raney nickel W-2[27] was added to a solution of 1.05 g (2.53 mmoles) of V in 75 ml of ethyl ether. The mixture was stirred for 2 hr at room temperature. The Raney nickel was removed by filtration, 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 amount of V left. Crystallization from carbon tetrachloride gave 810 mg (80%) of XVIII, mp and mmp 179–180°

Attempted Elimination from the *exo*-Chloro Sulfones in Ethanol–Dioxane. To a solution containing 1.30 g (3.41 mmoles) of *exo*-chloro sulfones X or XII in 25 ml of dry dioxane and 10 ml of absolute ethanol was added 15 ml of absolute ethanol in which 1.20 g (52 mg-atoms) of sodium metal had been dissolved. This mixture was held at reflux for 5 days and worked up in the usual manner. A pmr spectrum of the crude reaction mixture showed only X present. Crystallization from carbon tetrachloride gave 1.20 g (92%) of X, mp and mmp 150–151°.

Elimination of Hydrogen Chloride from *exo*-Chloro Sulfones X and XII in Dimethyl Sulfoxide with Potassium *t*-Butoxide. To a solution containing 500 mg (1.31 mmoles) of either of the *exo*-chloro sulfones X and XII dissolved in 25 ml of dry dimethyl sulfoxide was added 700 mg (6.25 mmoles) of potassium *t*-butoxide. The mixture was allowed to stand at room temperature for 10 min. The mixture was poured into 150 ml of water which was extracted with 100 ml of ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and decolorized with activated charcoal. The ether was removed by rotary evaporation. A pmr spectrum of the crude reaction mixture showed XVIII as the only compound present. Recrystallization from carbon tetrachloride gave 375 mg (83%) of XVIII.

Preparation of Dibenzotricyclo[3.2.1.0^{2,8}]-3,6-octadiene-8-carboxylic Acid (XXII). To a solution containing 1.20 g (4.28 mmoles) of *anti*-8-carbomethoxydibenzobicyclo[3.2.1]octadien-*exo*-4-ol[28] in 30 ml of anhydrous ether was added 2 ml of thionyl chloride. This mixture stood for 15 hr at room temperature and was then poured into 100 ml of water, after the excess thionyl chloride had been carefully destroyed by dropwise addition of water. The mixture was extracted with 100 ml of ether; the ethereal solution was washed with water and dried over magnesium sulfate and the ether removed by rotary evaporation. A pmr spectrum of the resulting yellow oil showed that oil to be nearly all *exo*-4-chloro-*anti*-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°. (*Anal.* Calcd for $C_{18}H_{15}ClO_2$: C, 72.36: H, 5.06. Found: C, 72.29; H, 5.11.) The remainder of the oil was dried under vacuum and used without further purification. The dried oil was dissolved in 30 ml of dry dimethyl sulfoxide, and 4.0 (36 mmoles) of potassium *t*-butoxide was added. This mixture stood for 10 min at room temperature and was then poured into a 5% sodium hydroxide solution. The sodium hydroxide solution was washed with 100 ml of ether and was then acidified with 5% hydrochloric acid. This was extracted with 100 ml of ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and decolorized with activated charcoal, and the ether was removed by rotary evaporation. The oil was crystallized from carbon tetrachloride, yielding 750 mg (70%) of acid XXII, mp 230–231° (sublimes).

The pmr spectrum in deuteriochloroform showed two sharp singlets (2 H:1 H) at τ 6.29 and 5.20, respectively, and aromatic protons (8 H) centered at 2.99.

Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; neut equiv, 248. Found: C, 82.05; H, 4.66; neut equiv, 248.

Acknowledgments. This work was supported in part by Public Health Service Grant GM-12139, from the Institute of General Medical Sciences. One of us (B. B. J.) also wishes to acknowledge, with thanks, fellowship support from the Shell Companies Foundation, Inc.

(27) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(28) W. R. Vaughan and A. C. Schoenthaler, *J. Am. Chem. Soc.*, **80**, 1956 (1958).

The Total Synthesis of Iboga Alkaloids[1]

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received March 7, 1966*

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

Through common usage the term "iboga alkaloids" has come to include all of the bases from diverse *Apocyanaceae*[5] species having the ibogamine (**1**) skeleton, or simple variations of it as catharanthine[6] (**3**), iboluteine[7] (**4**), and kisantine[8] (**5**).

(1) The synthesis of ibogamine was announced previously by G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, **87**, 2073 (1965).

(2) Woodrow Wilson Fellow, 1961–1962.

(3) National Institutes of Health Postdoctoral Fellow, 1963–1964.

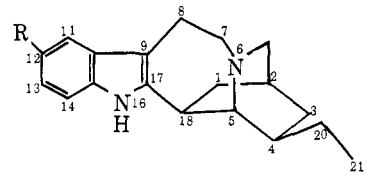
(4) National Science Foundation Postdoctoral Fellow, 1964–1965.

(5) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, 1964.

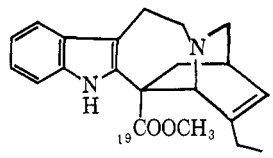
(6) M. Gorman, N. Neuss, and N. J. Cone, *J. Am. Chem. Soc.*, **87**, 93 (1965).

(7) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *ibid.*, **80**, 123 (1958).

(8) W. I. Taylor, *J. Org. Chem.*, **30**, 309 (1965).



1, R = H
2, R = OCH_3



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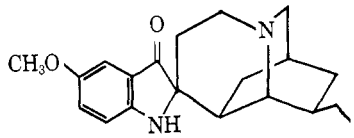

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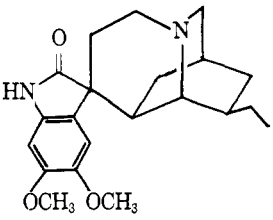

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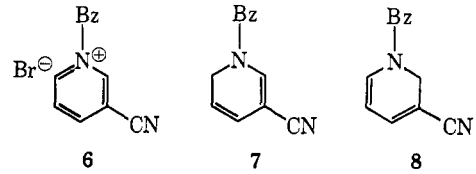
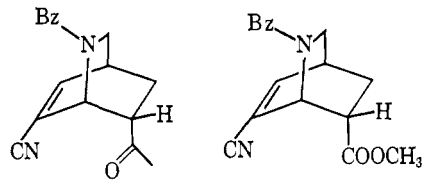
Ibogaine (**2**) appears to be the most abundant of the naturally occurring members of this class of alkaloids and was the first target of serious structural studies. The correct gross structure was established in 1957[9] through chemical studies, and an X-ray crystallographic investigation[10] provided firm evidence for the configuration of the ethyl group.[11] Until now none of the iboga alkaloids have been synthesized although progress toward this objective has been achieved in other laboratories.[12,13] 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[14] 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 α-acetoxyacrylonitrile, ethoxyacetylene, and nitroethylene did not yield isolable amounts of the anticipated isoquinuclidines, and subsequent efforts were directed toward the acquisition of an α,β-unsaturated primary amide which could be transformed to an isoquinuclidone by Hofmann degradation. Thus, reduction of N-benzyl-3-cyanopyridinium bromide (**6**) with sodium borohydride[15] 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

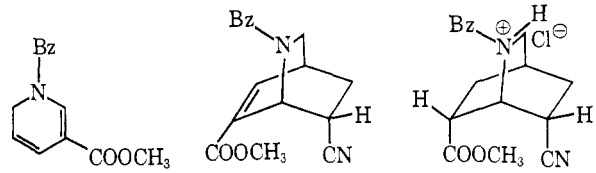


6 7 8



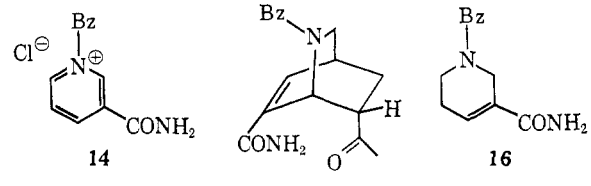
9 10

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



11 12 13

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-car-



14 15 16

boxamidopyridinium chloride (**14**) followed by condensation of the crude mixture of reduced pyridines with methyl vinyl ketone. In larger scale preparations of

(9) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958).

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

(11) The absolute configuration of the iboga alkaloids is that shown throughout this paper. It is based on chemical correlation with cleavamine and vinblastine 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.

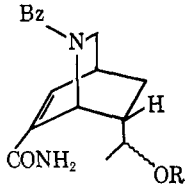
(12) S. I. Sallay, *Tetrahedron Letters*, 2443 (1964).

(13) J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Am. Chem. Soc.*, **87**, 2288 (1965).

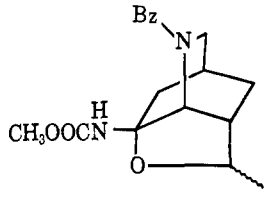
(14) O. Mumm and J. Diedrichsen, *Ann.*, **538**, 195 (1939); K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960, 1971 (1959); M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962); T. Agawa and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 449 (1961).

(15) H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964); P. S. Anderson and R. E. Lyle, *Tetrahedron Letters*, 153 (1964), and much other literature cited.

the amide **15** 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 tetrahydropyridine **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 isoquinuclidone. 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 asymmetry 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

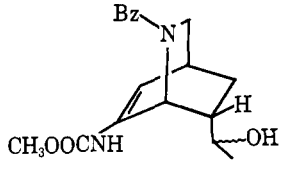


17, R = H
18, R = $COCH_3$



19

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**.



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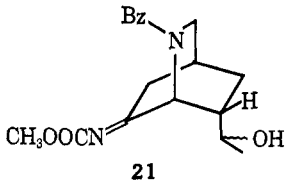
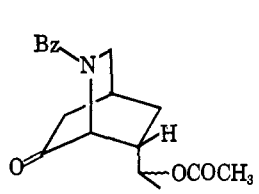


21

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 acetoxy 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 acetoxy 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.



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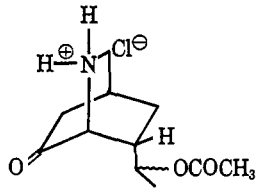
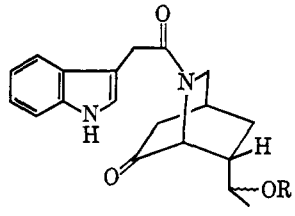
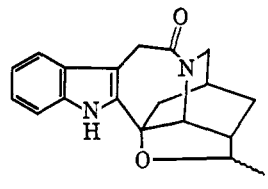


23

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 isoquinuclidine 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}.[16] 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



24, R = $COCH_3$
25, R = H



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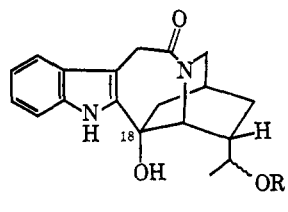
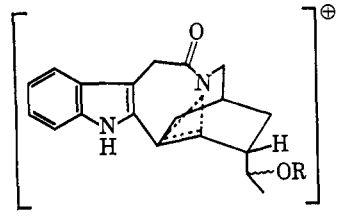


27, R = H
28, R = $COCH_3$



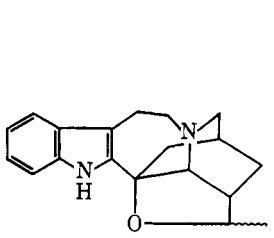
29, R = H
30, R = $COCH_3$

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.[17] Although 18-methoxyibogaine is rapidly reduced to ibogaine (**2**) with lithium aluminum hydride, reduction of the lactam **26** did not proceed to the desired pentacyclic 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).
(17) G. Büchi and R. E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966).

24. Treatment with *p*-toluenesulfonic 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



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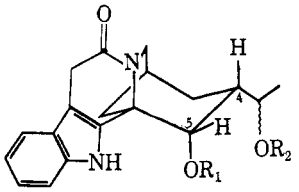
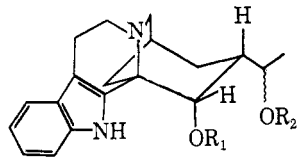
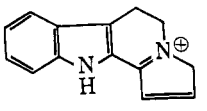


32, $R_1 = H$; $R_2 = COCH_3$
33, $R_1 = R_2 = COCH_3$
34, $R_1 = R_2 = H$

provided by the nuclear magnetic resonance spectrum measured in d_6-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 a secondary alcohol.[18] 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 disecondary 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 dihydroxyamine **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, $R_1 = R_2 = H$
36, $R_1 = H$; $R_2 = COCH_3$
37, $R_1 = R_2 = COCH_3$



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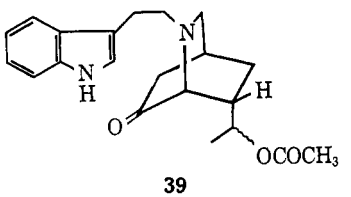

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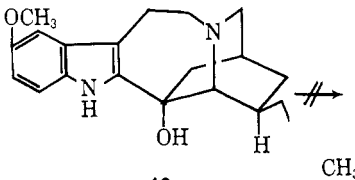
As already mentioned we were initially suspicious of any attempts at acid-catalyzed cyclization of the amino ketone **39** because we believed that the positively charged nitrogen atom would suppress protonation of the neighboring carbonyl group requisite for bond formation to the indole ring. After realizing that the cyclization of the ketoamide **24** to the lactam **32** 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 isoquinuclidine or again an azabicyclo[1.2.3]octane. Alkylation of the secondary amine **23** with tryptyl bromide produced the tertiary amine **39** which without purification was subjected to the action of *p*-toluenesulfonic acid in acetic acid solution. The salt of the cyclized product **36** crystallized from the crude reaction mixture and, after conversion to the corresponding amines, 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]octane series[19] 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. In 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 cinchona halides to hetero ethers in the presence of silver salts in alcoholic solutions.[20,21] Stereomodels of the two monoacetates **28** and **32** leave no doubt that the latter represents the less crowded and consequently more stable isomer. Interestingly, 18-hydroxyibogaine (**40**) with the side chain in the opposite configuration is stable in relation to its isomer **41**. Although no



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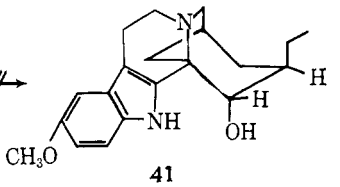


41

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

(18) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

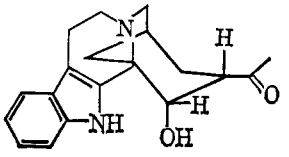
(19) J. A. Berson in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 111.

(20) R. B. Turner and R. B. Woodward in "The Alkaloids," Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1953, p 17.

(21) E. W. Warnhoff in "Molecular Rearrangements," Vol. II, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 877.

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*-toluenesulfonic acid, the acetoxytosylate (**32** $R_1 = SO_2C_7H_7$) 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 dicyclohexylcarbodiimide[22,23] to the hydroxy ketone **42** whose mass spectrum again shows an intense fragment peak at *m/e* 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 (d_6-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 β-hydroxy ketone **42** to basic catalysts caused dehydration to the α,β-unsaturated ketone **43**, ν_{max}^{Nujol} 1670, 1640 cm^{-1}, and one vinyl proton in the nmr spectrum (singlet at 7.20 ppm). As anticipated the α,β-unsaturated ketone grouping had a marked effect on the ultraviolet light absorption properties also and caused a raise of the extinction at 226 mμ to 48,500.



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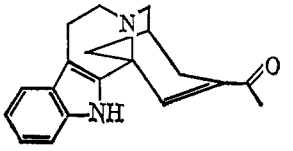
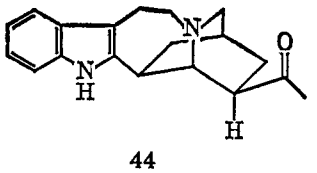


43

To complete the synthesis of ibogamine (**1**) three further changes are necessary. The oxidation stage of the alicyclic moiety has to be adjusted, the azabicyclo-[1.2.3]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 α,β-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



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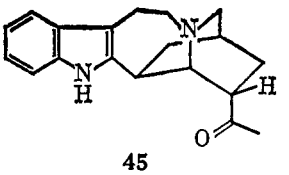

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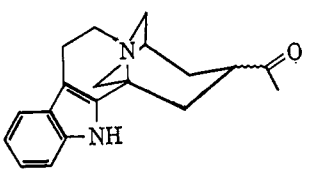
the epimeric ketones **46** produced by catalytic reduction of the unsaturated ketone **43** and they consequently must have different skeletons. The mechanism of reduction of the unsaturated ketone by zinc undoubtedly



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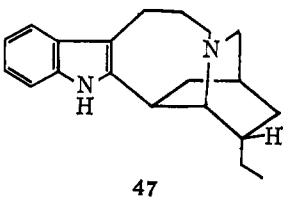

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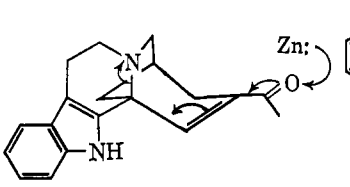
involves cleavage of the carbon nitrogen bond (**48**, arrows) to yield the tetracyclic compound **49** and subsequent internal Michael addition (**49**, arrows) to an enol and thence to the epimeric ketones **44** and **45**.



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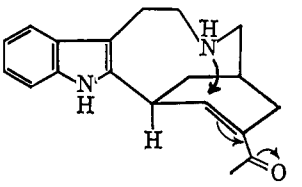
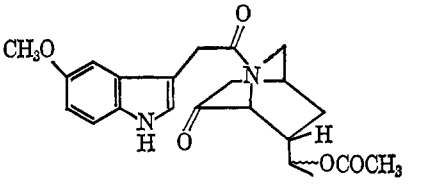


49

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 epiibogamine (**47**) readily separable by chromatography. Comparison of infrared and mass spectra and of R_f values on thin layer chromatograms established the identity of racemic ibogamine with a sample of natural origin. Identical criteria were used to ascertain the identity of racemic epiibogamine (**47**) with material prepared by degradation of catharanthine (**3**).[6,24]

Analogous procedures were used to synthesize ibogaine (**2**). Condensation of 3-(5-methoxyindolyl)-acetyl chloride[25] with the secondary amine **23** furnished the amorphous amide **50**. Cyclization to the lactam **51** was again effected in acetic acid solution containing



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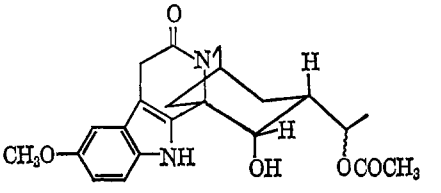


51

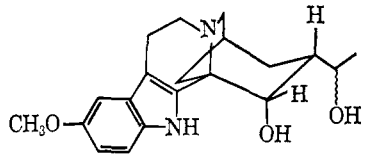
p-toluenesulfonic acid. Reduction with lithium aluminum hydride afforded the diol **52** which was subsequently oxidized to the hydroxy ketone and dehydrated to the α,β-unsaturated ketone **53**. Reduction with zinc in acetic acid followed by Wolff–Kishner reduction yielded a readily separable mixture of ibogaine (**2**) and its C_4 epimer (**54**). Infrared and mass

(22) K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.*, **85**, 3027 (1963); *ibid.*, **87**, 5661, 5670 (1965).

(23) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

(24) We wish to thank Dr. N. Neuss, Eli Lilly and Co., Indianapolis, Ind., for an authentic sample of epiibogamine.

(25) E. Shaw and D. W. Wolley, *J. Biol. Chem.*, **203**, 979 (1953).



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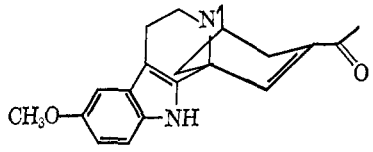
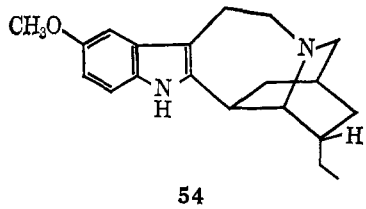


53

spectra of racemic ibogaine were identical with those of the natural material. The mass spectra of epiibogamine (**47**) and epiibogaine (**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 epiibogaine.[26]



54

Unfortunately the two total syntheses just described do not corroborate the configuration of the ethyl group in iboga alkaloids but both crystallographic[10] and chemical[27] evidence is already available on this point. We have previously developed a method for the introduction of a carbomethoxy group at C_{18} 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 Infracords; 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; the strongest peaks only are listed. Thin layer chromatograms (tlc) were made with Woelm Silica Gel G and developed with 7 or 25% methanol in benzene. Merck acid-washed alumina was used in preparing column chromatograms unless otherwise indicated. Anhydrous sodium sulfate was used as drying agent in working up reactions.

N-Benzyl-3-cyanopyridinium Bromide (6). A solution of 3-cyanopyridine (260 g, 2.5 moles) and benzyl bromide (462 g, 2.7 moles) in ethyl acetate (750 ml) was allowed to reflux for 1 hr. The salt was obtained in four separate crops, 594 g (86%), mp 146–151°. An analytical sample was recrystallized from methanol–ethyl acetate as colorless needles, mp 153–155°.

Anal. Calcd for $C_{13}H_{11}BrN_2$: C, 56.74; H, 4.03; N, 10.18. Found: C, 56.96; H, 4.15; N, 10.10.

Adduct 9 from N-Benzyl-3-cyano-1,6-dihydropyridine and Methyl Vinyl Ketone. A solution of N-benzyl-3-cyanopyridinium bromide (200 g, 0.73 mole) in water (850 ml) was cooled in an ice–salt bath and treated slowly while stirring with a solution of sodium carbonate (17 g) and sodium borohydride (34 g, 0.90 mole) in water (350 ml). The mixture was stirred for 10 min, then extracted three times with chloroform. Hydroquinone (1 g) was added to the extract which was dried and concentrated giving 123 g of a red oil, $\nu_{max}^{CHCl_3}$ 2200, 1680, 1650, 1620, 1590, and 1530 cm^{-1}. The mixture of dihydropyridines was dissolved in chloroform (200 ml) and treated with methyl vinyl ketone (120 g, 1.7 moles) and hydroquinone (1 g). This solution was heated under reflux in an atmosphere of nitrogen for 70 hr and then evaporated to a dark oil. This oil in hot methanol (200 ml) was treated with picric acid (180 g, 0.79 mole) in hot methanol (700 ml), and the resulting solution was stored in the cold for 2 days. The methanol was decanted from the picrate which had separated as a dark, viscous oil and the picrate was then dissolved in methylene chloride (300 ml) and decomposed by shaking with 1 *N* sodium hydroxide solution (1.5 l.). The aqueous phase was extracted twice with methylene chloride, and the extracts were combined with the organic phase, dried, and evaporated. The residue in benzene solution was filtered through Florisil (1 kg) and the yellow oil recovered from the eluate was taken up in ether (150 ml) and stored on Dry Ice. The precipitate was filtered and washed with very cold ether giving 32.6 g (16.8%) of colorless needles, mp 105–108°. An analytical sample recrystallized from ether had mp 109–110°; $\nu_{max}^{CHCl_3}$ 2210, 1705, 1610, and 1495 cm^{-1}; nmr ($CDCl_3$) 1.6–2.2 (m, 3 H), 2.09 (s, 3 H), 2.6–3.4 (m, 3 H), 3.55 (AB quartet, J = 13 cps), 3.94 (unsymmetrical q, 1 H), and 7.35 (s, 6 H) ppm. The vinyl proton signal is partially obscured by the five aromatic protons. In the cyanamide obtained by von Braun degradation of the benzylamine (not described here), the vinyl proton appears as a doublet of doublets, J = 7 and 2 cps.

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.68; H, 6.73; N, 10.48.

N-Benzyl-3-carboxamidopyridinium Chloride (14). A solution of benzyl chloride (100 g, 0.79 mole) and nicotinamide (95.5 g, 0.78 mole) in methanol (250 ml) was heated under reflux overnight. The resulting suspension was cooled and filtered and the crystals were washed with acetone. Both filtrate and washings were evaporated and the residue was taken up in acetone giving an additional crop of product. The salt was obtained as a colorless powder: mp 258°, in quantitative yield; ν_{max}^{Nujol} 3200, 1705, 1660, 1600, and 1520 cm^{-1}.

Adduct 15 from N-Benzyl-3-carboxamido-1,6-dihydropyridine and Methyl Vinyl Ketone. A solution of N-benzyl-3-carboxamidopyridinium chloride (100 g, 0.40 mole) in water (600 ml) was cooled to 0° in an ice–methanol bath and treated with vigorous stirring, first with a saturated aqueous sodium carbonate solution (60 ml) and then dropwise with a solution of sodium borohydride (12.0 g, 0.316 mole) in dilute, aqueous sodium carbonate (100 ml). The mixture was allowed to stand without stirring for 5 min; then the aqueous phase was decanted off. The red oil was washed three times with water then taken up in chloroform (200 ml) and washed again with water and then dried. The solution showed three spots on tlc, ν_{max}^{film} 1530–1700 cm^{-1} (unresolved).

The solution was treated with hydroquinone (0.5 g) and methyl vinyl ketone (40 g, 0.57 mole) and was then 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 hydrochloric acid (50 ml in 500 ml of water). The organic phase was washed with water and discarded. The combined aqueous parts were washed with ether, neutralized with sodium carbonate, and extracted with methylene chloride giving 79 g of an oil. This was chromatographed on a column of alumina (800 g) packed in pentane. Fractions eluted with ethyl acetate and 5% methanol–ethyl acetate were solid or solidified on seeding. Recrystallization from chloroform–ethyl acetate afforded 15.2 g (13.4%) of colorless crystals: mp 173–175°; ν_{max}^{Nujol} 3500, 3250, 1710, 1675, 1635, 1610, 1500, and 700 cm^{-1}, nmr (d_6-DMSO) 1.3–2.0 (m, 2 H), 2.06 (s, 3 H), 2.3–3.9 (m, 6 H), 3.46 (s, 2 H), 4.36 (broad s, 1 H), 7.2 (m, 1 H), and 7.30 (s, 5 H) ppm.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.08; N, 9.85. Found: C, 71.91; H, 7.18; N, 9.50.

In some experiments small quantities of N-benzyl-3-carboxamido-1,2,5,6-tetrahydropyridine (**16**) were obtained from later fractions of the chromatogram. This substance crystallized from benzene in colorless crystals, mp 118–120°; ν_{max}^{Nujol} 3500, 3200, 1670, 1600, 1500, 750, and 700 cm^{-1}.

(26) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 310.

(27) K. Biemann and M. Friedmann-Spiteller, *J. Am. Chem. Soc.*, **83**, 4805 (1961); U. Renner and D. A. Prins, *Experientia*, **15**, 456 (1959).

Hydrolysis of Adduct 9 to Adduct 15. A solution of nitrile **9** (2.0 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 resulting extracts 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 samples were identical.

Adduct 10 from N-Benzyl-3-cyano-1,6-dihydropyridine 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 5 g of Na_2CO_3 and 10 g of $NaBH_4$ in 100 ml of water. The mixture was stirred for 10 min and then extracted three times with $CHCl_3$. The dried extracts were evaporated to give 36.5 g of light red oil. This mixture of dihydropyridines was taken up in 100 ml of dimethylformamide, treated with 50 ml of methyl acrylate and 0.50 g of hydroquinone, and then allowed to reflux under N_2 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 H_2O and 90 ml of CH_2Cl_2 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 Na_2CO_3. The slightly basic mixture was extracted twice with CH_2Cl_2 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 8.42 g (13.8%) of yellowish white prisms, mp 107–110°. Recrystallization from CH_2Cl_2–ether on Dry Ice gave white needles: mp 111–113°; ν_{max} 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): λ_{max}^{EtOH} 258, 264 mμ (ε 700).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.35; 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 188–189°.

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.09; H, 5.08; N, 7.39.

Transformation of the Unsaturated Amine 10 to the Saturated Amine Hydrochloride 13. A solution of the amine **10** (1.0 g) in methanol was hydrogenated over prereduced 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 residued was issolved in tetrahydrofuran. Upon addition of hydrogen chloride gas a precipitate formed which on recrystallization from ethanol gave small colorless crystals (0.41 g): mp 177–183°; ν_{max}^{Nujol} 2270 (w), 1740 (s), and 1600 cm^{-1} (w).

Anal. Calcd for $C_{17}H_{21}O_2N_2Cl$: C, 63.64; H, 6.60; N, 8.74. Found: C, 63.41; H, 6.72; N, 8.48.

N-Benzyl-3-carbomethoxypyridinium Bromide. A solution of methyl nicotinate (32 g) and benzyl bromide (40 g) in acetone (250 ml) was allowed to reflux for 4 hr. The solution was then cooled; the precipitate formed was collected on a filter and washed with cold acetone. The salt (50.6 g) was obtained as colorless crystals, mp 143°.

Adduct 12 from N-Benzyl-3-carbomethoxy-1,6-dihydropyridine and Acrylonitrile. This adduct was prepared from N-benzyl-3-carbomethoxypyridinium bromide and acrylonitrile by the method described for the preparation of the adducts **9** and **10**. It was obtained as a colorless oil which could not be induced to crystallize in 11% yield based on pyridinium salt used. The material appeared homogeneous on thin layer chromatograms and had ν_{max}^{film} 2260 (w), 1710 (s), and 1630 (m) cm^{-1}.

Catalytic Reduction of the Unsaturated Amine 12 to the Saturated Amine Hydrochloride 13. The adduct **12** (1 g) in methanol solution was hydrogenated over a Pd–C catalyst (0.1 g). After hydrogen uptake was complete (80 ml) the catalyst was removed by filtration and gaseous hydrogen chloride was then added to the filtrate until solution was acidic. Evaporation of the solvent gave a foam which could be crystallized from tetrahydrofuran. Recrystallization from ethanol gave the hydrochloride **13** (0.12 g), mp 177–181°. A mixture melting point with the compound obtained from adduct **10** showed no depression. The infrared spectra of samples from the two sources were superimposable.

Reduction of the Ketoamide 15 to the Hydroxyamide 17. A solution of ketoamide **15** (5.0 g, 0.0176 mole) and sodium borohydride (2.0 g, 0.0525 mole) in methanol (50 ml) was maintained at 0°. After 1 hr, a clear solution had formed which was then diluted with water (50 ml) and chloroform (100 ml). After shaking, the organic phase was separated and the aqueous phase was extracted twice with chloroform. The combined chloroform parts were dried and evaporated. The oily residue crystallized from ether giving 4.02 g (80%) of colorless crystals, mp 135–150°.

A sample of this alcohol obtained by base hydrolysis of the acetoxyamide (**18**) had mp 157–162°; ν_{max}^{Nujol} 3400, 3200, 1675, 1650, 1600, 1500, 740, and 695 cm^{-1}. The infrared spectra of samples obtained by the two routes were essentially identical but not superimposable.

Acetylation of the Hydroxyamide 17 to the Acetoxyamide 18. A crude mixture of epimeric alcohols from reduction of the ketoamide (**15**, 5 g) was taken up in acetic anhydride (15 ml) and pyridine (15 ml) and left overnight at room temperature. The solution was diluted with water, neutralized with aqueous sodium carbonate, and extracted with methylene chloride. The partially crystalline residue from the dried extract was triturated with ether, filtered, and washed with more ether giving 2.83 g (49%) of colorless crystals, mp 172–179°. Recrystallization from chloroform–ether yielded needles: mp 178–180°; ν_{max}^{Nujol} 3500, 3250, 1730, 1680, 1635, 1610, 1500, 1260, 730, and 700 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.36; N, 8.53. Found: C, 69.12; H, 7.40; N, 8.37.

Hofmann Rearrangement of the Hydroxyamide 17 to the Tricyclic Urethan 19. The crystalline mixture of hydroxyamide **17** and its epimer (2.30 g, 8.05 mmoles) in methanol (65 ml) solution was treated with potassium hydroxide (0.85 g, 15.2 mmoles) in aqueous sodium hypochlorite (15.7 ml of 5.25% solution, 11.0 mmoles). The resulting solution turned yellow and warmed spontaneously to about 50°. After 1 hr it was poured into saturated aqueous sodium chloride (300 ml) and the resulting mixture was extracted five times with chloroform. The dried extracts were evaporated to an oil which crystallized from ether in colorless needles, 1.51 g (53%), mp 140–147°. An analytical sample recrystallized from methylene chloride–ether had mp 147.5–149°; ν_{max}^{Nujol} 3300, 1750, 1545, 1500, 1255, 1060, 925, 735, and 700 cm^{-1}; nmr ($CDCl_3$) 1.18 (d, J = 7 cps, 3 H) 1.4–3.6 (m, 10 H), 3.64 (s, 3 H), 3.78 (s, 2 H), 5.3 (broad s, 1 H, exchanged by Na_2CO_3–D_2O), and 7.28 (s, 5H) ppm; mass spectrum m/e 316 (M^+), 301, 284, 269, 225, 200, 198, 158, and 91.

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.86. Found: C, 68.48; H, 7.93; N, 8.82.

Hydrolysis of the Urethan 19 and Acetylation to the Isoquinuclidone 22. A solution of the urethan **19** (4.0 g, 12.7 mmoles) in 6 *N* sulfuric acid (40 ml) was heated on a steam bath overnight. The solution was then cooled, neutralized with saturated aqueous sodium carbonate, and then extracted five times with methylene chloride. The extracts were dried and evaporated giving 3.71 g of hydroxy ketone as a colorless oil, ν_{max}^{film} 3500, 1715, 1500, 1405, and 700 cm^{-1}. A solution of this oil in acetic anhydride (15 ml) and pyridine (5 ml) was allowed to stand at room temperature for 44 hr. It was then diluted by adding ice. When the product began to crystallize, aqueous sodium carbonate and ice were added in small portions until the mixture was neutral. The product was filtered, washed with water, and then dried under vacuum giving 3.54 g (93%) of colorless plates, mp 108–112°. A sample recrystallized from ether–hexane had mp 111.5–112.5°; ν_{max}^{Nujol} 1740, 1720, 1500, 1400, 1250, 750, 740, and 700 cm^{-1}; nmr ($CDCl_3$) 1.0–1.5 (m, 1 H), 1.24 (d, J = 7 cps, 3 H), 2.02 (s, 3 H), 2.27 (broad s, 4 H), 2.3–2.7 (m, 2 H), 2.9–3.2 (m, 2 H), 3.76 (AB q, J = 14 cps), 4.79 (quintet, J = 7 cps, 1 H), and 7.54 (s, 5 H) ppm; mass spectrum m/e 301 (M^+), 273, 258, 242, 230, 214, 158, and 91.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.66. Found: C, 71.63; H, 7.65; N, 4.71.

Debenzylation of Tertiary Amine 22 to the Secondary Amine Hydrochloride 23. Concentrated hydrochloric acid was added dropwise to a solution of the isoquinuclidone **22** (2.00 g, 6.64 mmoles) in methanol (60 ml) until the solution was acidic. This solution was added to a slurry of 10% palladium on charcoal (100 mg) in methanol (5 ml) and the mixture was stirred under hydrogen until absorption ceased (uptake 150 ml, 1 equiv). The catalyst was removed by filtration and the filtrate was evaporated to a small volume. Addition of tetrahydrofuran induced crystallization. The solvent was then evaporated completely leaving 1.65 g (100%) of colorless needles, mp 207–212°. An analytical sample recrystallized

from methanol–tetrahydrofuran had the same melting point; ν_{max}^{Nujol} 2700, 2500, 1750, 1595, 1440, 1250, and 1100 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}ClNO_3$: C, 53.33; H, 7.32; Cl, 14.32; N, 5.66. Found: C, 53.24; H, 7.54; Cl, 14.17; N, 5.47.

Acylation 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 indole-3-acetyl chloride[25,28] (2.00 g, 10.3 mmoles) 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 methylene chloride (100 ml), washed with dilute hydrochloric acid and then with dilute aqueous sodium carbonate, dried, and evaporated leaving 2.5 g (100%) of a pale brown foam. Chromatography on alumina afforded a pure (tlc), colorless sample which could not be crystallized; ν_{max}^{film} 3400, 1745, 1640, 1250, and 750 cm^{-1}.

Hydrolysis of the Acetoxyketoamide 24 to the Hydroxyketoamide 25. A solution of the amide **24** (368 mg, 1 mmole) in methanolic potassium hydroxide (4 pellets in 5 ml) was left at room temperature for 1.5 hr. It was then diluted with water and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid, dried, and evaporated to give 150 mg of a foam. Crystallization from chloroform–benzene afforded 94 mg (29%) of small colorless crystals: mp 167–173°; ν_{max}^{Nujol} 3400, 1740, 1600, 745, and 688 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.30; H, 6.63; N, 7.63.

Cyclization of Amide 25 to the Hexacyclic Ether 26. A solution of the hydroxyketoamide **25** (65 mg, 0.20 mmole) and *p*-toluenesulfonic acid dihydrate (15 mg, 0.072 mmole) in ethylene chloride (2 ml) was allowed to reflux under nitrogen gas for 18 hr. The solution was cooled, washed with dilute aqueous sodium bicarbonate, dried, and evaporated. The colorless residue was chromatographed on alumina and the fraction eluted with ether–benzene (2:1) crystallized from ethanol to give 53 mg (86%) of colorless, needles: mp 257–260°; ν_{max}^{Nujol} 3300, 1640, 1420, 1160, 1140, 1015, 994, 900, 810, 745, 740, 717, and 703 cm^{-1}; λ_{max}^{EtOH} 222 mμ (ε 36,600) 275 (7400), 282 (7750), and 290 (6600); nmr ($CDCl_3$) 1.22 (d, J = 7 cps, 3 H) 1.5–2.7 (m, 6 H), 3.0 (d, J = 13 cps, 1 H), 3.5–4.3 (m, 4 H), 4.45 (d, 1 H) 6.9–7.6 (m, 4 H), and 8.8 (broad s, 1 H) ppm; mass spectrum *m/e* 308 (M^+), 279, 265, 237, 223, 210, 154, 129, and 108.

Cyclization of Amide 24 to the Lactam 32. A solution of crude acetoxyketoamide **24** (2.45 g, 6.66 mmoles) and *p*-toluenesulfonic acid dihydrate (0.30 g, 1.44 mmoles) in glacial acetic acid (25 ml) was allowed to reflux under nitrogen for 1.5 hr. Zinc dust (5 g) was added to the dark solution, and the mixture was stirred and heated for 1 additional hr leaving a light yellow solution. The mixture was cooled, diluted with water (100 ml), and decanted from the zinc which was then washed several times with chloroform. The washings were used to extract the aqueous phase. Three chloroform extracts were combined, washed with dilute aqueous sodium carbonate until neutral, dried, and concentrated under reduced pressure until the product commenced to crystallize. After being stored in the cold, the product was filtered and washed with a small amount of cold chloroform giving 1.59 g (65%) of yellowish white crystals, mp 268–275°. An analytical sample recrystallized from ethanol in colorless needles: mp 280–283°; $\nu_{max}^{CHCl_3}$ 3550, 1720, 1640, 1415, 1260, 1140, and 1050 cm^{-1}; λ_{max}^{EtOH} 222 mμ (ε 36,400) 281 (7180), and 288 mμ (5820); nmr (d_6-DMSO) 1.11 (d, J = 7 cps, 3 H), 1.4–1.7 (m, 3 H), 1.84 (s, 3 H), 2.3–2.7 (m, 2 H), 3.2–3.7 (m, 6 H), 4.5–4.9 (m, 1 H), 5.23 (d, J = 6 cps, 1 H), 6.8–7.5 (m, 4 H), and 10.91 (broad s, 1 H) ppm; mass spectrum *m/e* 368 (M^+), 325, 309, 281, 279, 253, 236, 223, 195, 129, 115, and 97.

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.07; H, 6.72; N, 7.77.

The mother liquors were evaporated and the residue hydrolyzed with methanolic potassium hydroxide (1 g in 20 ml) at room temperature. After 1 hr the solution was diluted with water and extracted with methylene chloride. The dried extract was evaporated and the residue taken up in hot ethyl acetate. On cooling, tan crystals of the dihydroxylactam **34** separated, 0.61 g (28%, total yield of cyclized products 93%), mp 265–275°; ν_{max}^{Nujol} 3400 1640, 1140, 1070, 1010, and 740 cm^{-1}.

Diacetoxylactam 33. Treatment of acetoxyhydroxylactam **32** (30 mg) with pyridine (0.5 ml) and acetic anhydride (1 ml) for 16 hr gave, on adding ice, 29 mg (87%) of crystalline diacetate: mp 298–302°; ν_{max}^{Nujol} 3400, 1750, 1635, 1240, 1210, 1060, and 755 cm^{-1}; nmr ($CDCl_3$) 1.20 (d, J = 6 cps, 3 H), 1.93 (s, 3 H), 2.15 (s, 3 H), 4.9 (m, 1 H), 5.4 (d, J = 4 cps, 1 H), 7.2–7.7 (m, 4 H), and 9.15 (s, 1 H) ppm. Similar treatment of the dihydroxylactam **34** gave the same product.

Cyclization of Amide 24 to the Acetoxytosylate. A solution of acetoxyketoamide **24** (1.00 g, 2.72 mmoles) and *p*-toluenesulfonic acid dihydrate (1 g) in chlorobenzene (10 ml) was refluxed under nitrogen for 1 hr. The solution was cooled, diluted with chloroform (50 ml), and washed with dilute aqueous sodium carbonate. The dried solution was concentrated to a small volume under reduced pressure and chilled, causing the product to crystallize. The first crop was filtered and washed with ether giving 220 mg of the tosylate, yellowish white crystals: mp 270–274°; ν_{max}^{Nujol} 3200, 1755, 1620, 1230, 1195, 1185, 1030, 910, 890, 820, 810, 790, 750, and 670 cm^{-1}. The second crop (225 mg) was a mixture, mp 200–207°, containing two acetate carbonyl bands in the infrared spectrum. Recrystallization from ethanol gave in one crop, an additional 120 mg of the tosylate, and 15 mg of large, thick needles which were separated mechanically from the smaller crystals of the tosylate. This second product, mp 265–280°, was identified by its infrared spectrum as the acetoxyhydroxylactam **32**.

Conversion of the Acetoxytosylate to the Diacetate 33. Exposure of the tosylate (110 mg) to hot glacial acetic acid (2 ml) for 1 hr caused conversion to the diacetate **33** (100 mg). After crystallization from ethanol the sample had mp 297–302°. An infrared spectrum measured in a Nujol mull was identical with that of a sample obtained by acetylation of the monoacetate **32** or the diol **34**.

Reduction of the Hexacyclic Lactam 26 to the Hexacyclic Ether 31. The lactam **26** (5 mg) was allowed to reflux in tetrahydrofuran solution in the presence of excess $LiAlH_4$ for 4 hr. The product isolated in the conventional manner had mp 226–234° after recrystallization from ethanol. Its infrared spectrum was superimposable on that of a sample prepared by cyclization of the amino alcohol corresponding to the amino ketone **39** and the samples were indistinguishable by thin layer chromatography.

Reduction of the Hydroxyacetoxylactam 32 to the Dihydroxyamine 35. A solution of the hydroxyacetoxylactam **32** (2.00 g, 5.44 mmoles) in tetrahydrofuran (40 ml) was cooled in ice water and treated with lithium aluminum hydride (1.00 g, 26.3 mmoles) in small portions with stirring. The mixture was stirred for 1 hr at 30°. Excess lithium aluminum hydride was destroyed by dropwise addition of saturated aqueous sodium sulfate and the mixture was then diluted with chloroform, and the organic layer was dried, filtered, and evaporated. The residue after evaporation was filtered through Florisil (20 g, in hexane), eluting with ethyl acetate. Evaporation of the eluate left 1.42 g (83%) of crude product in yellowish white crystals, mp 125–147° (partly solvated, one spot on tlc). An analytical sample recrystallized from methylene chloride was obtained in long, colorless needles, mp 124–140°. After drying at 80° (0.02 mm) for 18 hr it had mp 189–191°; ν_{max}^{Nujol} 3500, 3200, 1100, 1045, 995, 955, 735, and 695 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ε 38,000), 282 (7800), and 289 (7230); nmr (d_6-DMSO) 1.09 (d, J = 6 cps, 3 H), 1.2–3.8 (m, 14 H), 4.36 (m, 1 H), 4.75 (d, J = 5 cps, 1 H), 6.8–7.5 (m, 4 H), and 10.16 (broad s, 1 H); mass spectrum *m/e* 312 (M^+) and 209.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 71.66; H, 7.68; N, 8.61.

Acetylation of the Dihydroxyamine 35 to the Diacetate 37. The dihydroxyamine **35** (290 mg, 0.93 mmole) in pyridine (2 ml) was treated with acetic anhydride (3 ml) and the solution was left at room temperature for 11 hr. The solution was diluted with ice water, neutralized with aqueous sodium carbonate, and extracted with chloroform. The extract was dried and evaporated leaving a dark oil which crystallized from methylene chloride–ether to give 145 mg (40%) of tan crystals, mp 224–230°. An analytical sample recrystallized from methanol in the form of colorless prisms had mp 237–240°; ν_{max}^{Nujol} 3500, 1750, 1725, 1280, 1260, 745, 730, and 715 cm^{-1}; nmr (d_6-DMSO) 1.06 (d, J = 6 cps, 3 H), 1.70 (s, 3 H), 1.97 (s, 3 H), and 6.7–7.4 (m, 4 H) ppm.

Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.13; H, 6.75; N, 7.15.

Alkylation of the Secondary Amine 23 and Cyclization of the Tertiary Amine 39. A mixture of tryptyl bromide[29] (mp 96–100°, 0.85 g, 3.8 mmoles), secondary amine hydrochloride (0.80 g, 3.2

(28) The acid was prepared by the method of H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 1246 (1963).

(29) T. Hoshino and K. Shimodaira, *Ann.*, **520**, 19 (1935).

mmoles), and sodium carbonate (1.5 g) in dimethylformamide (20 ml) was stirred at room temperature for 24 hr. It was then diluted with water and extracted with ether twice. The combined ether layers were extracted with dilute HCl and the combined acid extracts were neutralized by adding 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 mmoles) in glacial acetic acid (5 ml) for 1.5 hr under nitrogen. The solution was then cooled and diluted 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 276–280° dec; ν_{max}^{Nujol} 3400, 2700, 1745, 1240, 1170, 1125, 1080, 1055, 1040, 1010, 955, 815, 758, and 685 cm^{-1}.

The free base 36 was obtained by shaking the toluenesulfonate (50 mg) with chloroform and dilute aqueous sodium carbonate. The amine, recovered from the chloroform phase, crystallized from ethanol as a solvate (42 mg): mp 83–90°; ν_{max}^{Nujol} 3400, 1720, 1260, 1140, 1045, 1000, 750, and 730 cm^{-1}.

In another preparation of **36**, the mother liquor from the basic work-up of the cyclization reaction was chromatographed on Florisil. Eluting with ethyl acetate gave first a small amount (*ca.* 5 mg) of the diacetate **37** which crystallized from ethanol, mp 228–232°, identified by comparison of its infrared spectrum with that of an authentic sample. Further elution with ethyl acetate afforded a small amount (*ca.* 10 mg) of the ether **31** which also crystallized from ethanol: mp 226–234°; ν_{max}^{Nujol} 1135, 1015, and 740 cm^{-1}; λ_{max}^{EtOH} 227 mμ (ε 34,000), 284 (7000), and 290 (6800). This substance was identical with that obtained by reducing the lactam ether **26** with excess $LiAlH_4$.

Conversion of the Diol Monoacetate 36 to the Diol 35. The toluenesulfonate of the amine **36** (223 mg) was shaken with chloroform and dilute aqueous sodium carbonate. The chloroform phase was dried and evaporated and the residue was reduced with excess $LiAlH_4$ in tetrahydrofuran solution for 1 hr. Under vigorous stirring an aqueous solution of sodium sulfate was added and the emulsion was subsequently extracted with chloroform. The organic phase was dried and evaporated furnishing, after crystallization from methylene chloride, a product (128 mg, 97%), mp 188–191° after drying at 80° under high vacuum. A mixture melting point with a sample of the diol **35** obtained from the lactam **32** showed no depression and the infrared spectra were superimposable.

Oxidation of the Diol 35 to the Hydroxy Ketone 42. A solution of the diol **35** (1.32 g, 4.23 mmoles) and trifluoroacetic acid (0.725 g, 6.35 mmoles) in dry dimethyl sulfoxide (25 ml) was treated with dicyclohexylcarbodiimide (5.20 g, 25.2 mmoles) and left at room temperature. After 18 hr the mixture was diluted with ethyl acetate (150 ml) and water (100 ml), shaken, and made slightly basic with aqueous sodium carbonate. The aqueous phase was discarded and the ethyl acetate phase was extracted twice with dilute hydrochloric acid. During the first extraction, a precipitate of dicyclohexylurea was filtered off and washed with water, the washings being added to the acid extract. The combined aqueous phases were then neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried and evaporated leaving 1.14 g of a red solid. This was recrystallized from ether to give, in three crops, 0.865 g (66%) of brownish-white crystals, mp 169–174°. An analytical sample was recrystallized from methylene chloride–ether to give colorless needles: mp 175–176°; ν_{max}^{Nujol} 3450, 1710, 755, and 748 cm^{-1}; λ_{max}^{EtOH} 224 mμ (ε 38,200), 282 (8300), and 290 (7130); mass spectrum *m/e* 310 (M^+) and 209; nmr ($CDCl_3$) 2.26 (s, 3 H), 4.05 (d, J = 3 cps, 1 H), 7.4–8.1 (m, 4 H), and 9.3 (s, 1 H, disappears after shaking with D_2O) ppm; nmr (d_6-DMSO) 2.05 (s, 3 H), 3.7 (unresolved multiplet, 1 H), 5.20 (d, J = 6 cps, 1H), 6.8–7.5 (m, 4 H), and 10.4 (s, 1 H) ppm. On adding D_2O to the solution, the signals at 5.20 (*sec*-OH) and 10.4 ppm (NH) vanish.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.26; H, 7.07; N, 9.23.

Acetylation of the Hydroxy Ketone 42 to the Corresponding Acetate. A solution of the hydroxy ketone **42** (50 mg) in acetic anhydride (2 ml) and pyridine (1 ml) was kept at room temperature for 4 hr. It was then diluted by adding ice, neutralized with aqueous sodium carbonate, and extracted with chloroform. The residue from the extract contained three products (tlc). One product crystallized from methylene chloride was shown by tlc and infrared spectrum to be the pentacyclic unsaturated ketone **43**. The mother liquor was evaporated and the residue taken up in methanol from which the acetoxy ketone crystallized as colorless needles, mp 118–125° dec; ν_{max}^{Nujol} 3500, 3400, 1750, 1710, 1260, 1240, 1130, 750, and 735 cm^{-1}.

Dehydration of the Hydroxy Ketone 42 to the Unsaturated Ketone 43. A solution of the hydroxy ketone **42** (0.888 g, 2.84 mmoles) and sodium methoxide (0.100 g, 1.85 mmoles) in methanol (25 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), eluting with ethyl acetate. The residue from the eluate crystallized from benzene to give 0.778 g (93%) of colorless crystals. An analytical sample recrystallized from methylene chloride–ether had mp 90–120° before drying. When dried at 80° (0.02 mm) for 30 hr, it had mp 193–195°; ν_{max}^{Nujol} 3500, 3350, 1670, 1640, 1330, 1280, 745, and 735 cm^{-1}; λ_{max}^{EtOH} 226 mμ (ε 48,500), 272 (9950), 280 (9500), and 288 (7400); λ_{max}^{HCl} 267 mμ (ε 9700), 283 (8600), and 288 (5600); nmr (d_6-DMSO) 2.18 (s, 3 H), 6.77 (s, 1 H), 6.9–7.5 (m, 4 H), and 11.0 (s, 1 H) ppm; nmr ($CDCl_3$) 2.40 (s, 3 H), 7.20 (s, 1 H), 7.4–8.0 (m, 4 H), and 8.9 (s, 1 H) ppm; mass spectrum *m/e* 292 (M^+) and 209.

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.42; H, 6.54; N, 9.06.

Hydrogenation of the Unsaturated Ketone 43 to the Saturated Ketone 46. Catalytic reduction of the unsaturated ketone **43** in methanol solution over a 10% Pd–C catalyst afforded an oily saturated ketone: ν_{max}^{film} 1710 cm^{-1}; nmr ($CDCl_3$) 2.15 (s, 3 H), 3.7 (m, 1 H), 7.0–7.7 (m, 4 H), and 8.9 (s, 1 H) ppm. On tlc this ketone was cleanly separable from ketones **44** and **45**.

Reduction of the Unsaturated Ketone 43 to a Mixture of the Two Saturated Ketones 44 and 45. A solution of the unsaturated ketone **43** (0.600 g, 2.05 mmoles) in glacial acetic acid (15 ml) was treated with zinc dust (2 g, 30 mg-atoms) and stirred at reflux for 1 hr. The mixture was evaporated to 5 ml, diluted with water (50 ml), and decanted from the unreacted zinc. The zinc was washed with water and chloroform and the washings were added to the dilute acetic acid solution. This mixture was neutralized with aqueous sodium carbonate and extracted three times with chloroform giving, when dried and evaporated, 0.527 g of a pale yellow gum. Chromatography of this material on Florisil (15 g) yielded a total of 0.357 g (59%) of a mixture of the two ketones (tlc) in the chloroform and ethyl acetate eluates. A sample richer in the more polar ketone was changed to a mixture of equal amounts of each (tlc) by sodium methoxide in methanol. Methanolic hydrochloric acid had no further effect on this mixture. An analytical sample of the mixture crystallized from methanol in large, colorless prisms: mp 201–207°; ν_{max}^{Nujol} 3450, 1710, 1360, 1180, 768, and 758 cm^{-1}; λ_{max}^{EtOH} 228 mμ (ε 34,500), 283 (7600), and 291 (7200).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.78; H, 7.65; N, 9.30.

Wolff–Kishner Reduction of the Ketones 44 and 45 to (±)-Ibogamine and (±)-Epiibogamine. The mixture of epimeric ketones **44** and **45** (229 mg) in ethylene glycol (10 ml) was treated with 95% hydrazine (0.50 ml) and left overnight at room temperature. Potassium hydroxide (2 g) was added and the solution was allowed to reflux for 3 hr. The cooled mixture was diluted with water (50 ml) and the crystalline precipitate of crude alkaloids was filtered, washed with water, and dried giving 184 mg (84%) of a pale yellow solid showing two spots on tlc. This material was chromatographed on Florisil (10 g) in a column packed in hexane. Benzene–ether (3:1) eluted 58 mg (26%) of (±)-ibogamine which crystallized from methanol in colorless crystals, mp 129–132°. Ethyl acetate eluted 72 mg (33%) of (±)-epiibogamine which also crystallized from methanol in colorless crystals, mp 193–197°.

The infrared spectra in chloroform solution and the mass spectra of the products were superimposable on those of natural ibogamine (mp 162–163°) and of epiibogamine (mp 175–179°) derived from catharanthine (**3**), respectively. The R_f values of the synthetic products on tlc were identical with those of the materials of natural origin, using the solvent systems methanol–benzene (1:4) and cyclohexane–chloroform–diethylamine (5:4:1).

Preparation of the Amide 50. To a solution of 5.3 g (0.05 mole) of anhydrous sodium carbonate in 40 ml of water at 0° was added 2.71 g (0.011 mole) of the isoquinuclidone hydrochloride **23** and 60 ml of methylene chloride. To this vigorously stirred two-phase system was added 2.7 g (0.012 mole) of 3-(5-methoxyindolyl)acetyl chloride in small portions over a period of 3 to 4 min. After the addition had been completed, the mixture was stirred for an additional 15 min. The layers were separated, the aqueous phase was extracted thoroughly with methylene chloride, and the organic fractions were combined. The organic extracts were washed in

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, ν_{max}^{film} 1730 and 1630 cm^{-1}.

Cyclization of Amide 50 to Lactam 51. To 3.8 g (0.0095 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 then allowed to reflux under 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 10% sodium carbonate to remove residual acetic acid, dried over anhydrous magnesium sulfate, filtered, and concentrated affording 2.87 g (65.5%, based on isoquinuclidone hydrochloride) of **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°; ν_{max}^{Nujol} 1625 and 1730 cm^{-1}; λ_{max}^{EtOH} 223 mμ (ε 28,900), 275 (8480), and 295 (6560); nmr (d_6-DMSO) 1.15 (d, J = 7 cps, 3 H), 1.90 (s, 3 H), 3.88 (s, 3 H), 4.90 (m, 1 H), 5.45 (d, J = 7 cps, 1H), 6.95 (q, J = 9 and 3 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 D_2O, the signals at 5.45 and 11.25 ppm vanished, showing them to arise from a secondary OH and the indolic NH, respectively.

Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.70; H, 6.76; N, 6.72.

Reduction of the Lactam 51 to the Diol 52. To a solution of 1 g (0.026 mole) of lithium aluminum hydride in 50 ml of tetrahydrofuran was added 2.87 g (0.0072 mole) of lactam **51**. After boiling at reflux for 1 hr the reaction mixture was cooled to room temperature and decomposed with saturated sodium sulfate. The mixture was filtered *in vacuo* and the filtrate was diluted with chloroform, dried over anhydrous magnesium sulfate, filtered, and concentrated. Trituration of the residue with ether–methylene chloride afforded 1.24 g of crystalline diol, 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 methylene chloride had mp 204–207°; ν_{max}^{Nujol} 3450, 1220, 1100, and 1040 cm^{-1}; λ_{max}^{EtOH} 227 mμ (ε 28,600), 280 (9240), and 294 (8070).

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.92; H, 7.31; N, 8.12.

Oxidation of the Diol 52 to the Ketone. To a solution of 1.50 g (0.0044 mole) of the diol **52** in 60 ml of dry dimethyl sulfoxide was added 5.43 g (0.0264 mole) of dicyclohexylcarbodiimide and 750 mg (6.57 mmoles) of trifluoroacetic acid. The mixture was stirred for 18 hr under a nitrogen atmosphere, at which time ice and 15 ml of 10% hydrochloric acid were added and stirring was continued for 15 min. The mixture was filtered *in vacuo* and washed with water. The filtrate was diluted with water and extracted seven times with chloroform. Ice was added to the aqueous layer which was neutralized with solid sodium carbonate, followed by thorough extraction with methylene chloride, backwashing with water, drying over anhydrous magnesium sulfate, filtering, and concentrating. Trituration of the residue with ether afforded 1.03 g (70%) of crystalline hydroxy ketone. A sample recrystallized from methylene chloride–ether had mp 164–166°; ν_{max}^{Nujol} 3450 and 1715 cm^{-1}; λ_{max}^{EtOH} 227 mμ (ε 27,100), 270 (9040), and 286 (7950).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.89; H, 7.21; N, 7.95.

Preparation of the Unsaturated Ketone 53 from the Hydroxy Ketone. To a solution of 100 mg (4.35 mg-atoms) of sodium dissolved in 30 ml of methanol under nitrogen was added 1.03 g (0.003 mole) of hydroxy ketone. The mixture was heated under reflux for 1 hr, cooled, poured into water, extracted thoroughly with chloroform, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue afforded two crops of white crystals, 400 and 300 mg (73%), respectively. A sample, crystallized from ether–methylene chloride, had mp 109-111° after drying 6 hr at 80° and 0.05 mm; ν_{max}^{Nujol} 1670 and 1635 cm^{-1}; $\nu_{max}^{CH_3CN}$ 3600, 3400, 1670, 1630, and 1610 cm^{-1}; λ_{max}^{EtOH} 229 mμ (ε 39,600) 281 (11,950), and 295 (8180); nmr (d_6-DMSO) 2.24 (s, 3 H), 3.78 (s, 3 H), 6.75 (q, J = 9 and 2 cps, 1 H); 6.8 (a singlet superimposed on a quartet, 1 H); 6.95 (d, J = 2 cps, 1 H), 7.25 (d, J = 9, 1 H), and 10.8 (s, 1 H) ppm.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 73.65; H, 7.18; N, 8.80.

Reduction of the Unsaturated Ketone 48 to a Mixture of Epimeric Saturated Ketones and Transformation to a Mixture of Ibogaine 2 and Epiibogaine 54. Method A. To a solution of 570 mg (1.78 mmoles) of unsaturated ketone **43** in 30 ml of acetic acid was added 3 g (0.044 g-atom) of zinc dust. The resulting suspension was boiled at reflux for 1 hr. The cooled reaction mixture was poured into water, neutralized with sodium carbonate, extracted thoroughly with chloroform, dried over anhydrous magnesium sulfate, filtered, and concentrated affording 550 mg of an oil. The ether eluate of a chromatogram on Florisil gave a mixture of crystalline amino ketones showing infared absorption at 1710 cm^{-1}. A thin layer chromatogram (25% methanol–benzene) showed the early ether 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 1 pellet of KOH. Upon dilution with water, 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 310 mg (54.4%). The mixture of amino ketones was dissolved in 30 ml of ethylene glycol, treated with excess 95% hydrazine, and allowed to stand overnight at room temperature. To this mixture was added 8 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–ether eluates from a chromatogram of the residue (225 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, mp 178–180°, after crystallization from methanol. The substance was identified as epiibogaine **54**; ν_{max}^{Nujol} 1220, 1140, and 1040 cm^{-1}; λ_{max}^{EtOH} 288 mμ (ε 8750), 295 (8950), and 307 (6280).

Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.30; H, 8.63; 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 2.4 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, filtered, and concentrated affording 660 mg of semicrystalline material (1710 cm^{-1}, film). This residue was taken up in 10 ml of methanol, treated with excess 95% hydrazine, 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 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 epiibogaine **54** and which gave the same color reactions with ceric sulfate–phosphoric acid spray. This crude product was then chromatographed on Florisil (10 g) packed in benzene. The fractions eluted with benzene–ether (3:1) contained (±)-ibogaine (tlc), 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 crystalline (±)-ibogaine hydrochloride (76 g, 18% of the crude) precipitated. The salt was recrystallized from methanol giving 58 mg of colorless prisms, mp 267–274° dec; infrared spectrum (Nujol) similar to that of natural ibogaine hydrochloride; mp 287–299° dec (lit. mp 299°). A 30-mg sample of the hydrochloride was shaken with dilute aqueous sodium bicarbonate and methylene chloride. The organic phase was combined with a methylene chloride washing of the aqueous phase, dried, and evaporated. The residual oil was taken up in a few drops of ethanol and the mixture was cooled. After being stored overnight in the cold, the crystals were washed with ethanol and dried leaving crystalline (±)-ibogaine, mp 112–114°. Infrared ($CHCl_3$) and mass spectra were identical with those of natural ibogaine (mp 152°). Synthetic and natural materials were indistinguishable on tlc in two solvent systems, benzene–methanol (4:1) and cyclohexane–chloroform–diethylamine (5:4:1).

Elution of the chromatogram with benzene–ether (1:1) gave (±)-epiibogaine **54** which crystallized on removal of solvent. This product (151 mg, 41% of the crude) recrystallized from ethyl acetate in colorless prisms, mp 180–182°; one spot on tlc, more polar than ibogaine; $\nu_{max}^{CHCl_3}$ 3450, 1620, 1560, 1475, 1450, 1425, 1355, 1290, 1275, 1170, 1140, 1105, 1030, and 830 cm^{-1}; nmr ($CDCl_3$) 1.05 (t, J = 7 cps, 3 H), 4.05 (s, 3 H), 7.0–7.7 (m, 3 H), and 8.4 (s, 1 H) ppm. A mass spectrum was the same as that of epiibogamine with peaks from fragments containing aromatic moiety raised by 30 mass units.

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The Structures of Two Alkaloids from Patchouli Oil

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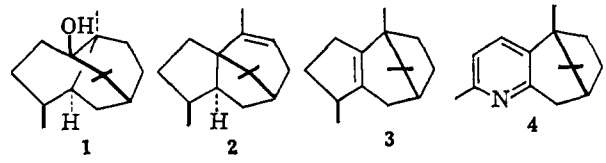
Abstract: Two new alkaloids, for which the names patchoulipyridine and epiguaipyridine are suggested, have been isolated from the essential oil of *Pogostemon patchouli* Pellet. Spectral evidence was used to derive structures which were confirmed by total synthesis of patchoulipyridine and by conversion 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.[2-4] 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 $C_{15}H_{21}N$ and this was reinforced by a mass spectrum. Patchoulipyridine exhibits ultraviolet light absorption typical of alkyl-substituted pyridines[5] 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.[6] 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**),[7] α-patchoulene (**2**)[8] and β-patchoulene (**3**)[8] in the essential oil structure (**4**) for patchoulipyridine seemed most reasonable on biogenetic grounds. In agreement with this assignment ozonization yielded, *inter alia*, a



1 2 3 4

dicarboxylic acid which chromatographically was indistinguishable from homocamphoric 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-patchoulene (**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 muscopyridine.[9] Exposure of β-patchoulene (**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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