The Synthesis of Desethylibogamine[1]

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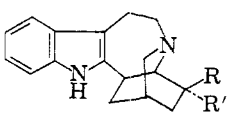
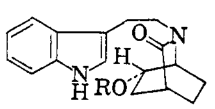
The synthesis of desethylibogamine (Ia) in several steps from the epoxide of methyl 3-cyclohexene-1-carboxylate has been carried out as follows. The epoxide with tryptamine, followed by pyrolysis, gives the isoquinuclidone (IIa). The tosylate of IIa with aluminum chloride gives desethylibogamine lactam (IX), which affords the title compound on lithium aluminum hydride reduction. Various reactions, and the spectral properties of these compounds are discussed.

Although several years have passed since the elucidation of the structures of the iboga alkaloids,[2] there have been relatively few reports of work directed toward the total synthesis of these polycyclic indole alkaloids. Sallay has reported the synthesis of a tetracyclic compound related to desethylibogamine, but lacking the isoquinuclidine system,[3] Cava has developed a new isoquinuclidine synthesis and pointed out its potential utility in the synthesis of the iboga alkaloids,[4] and the synthesis of 3-(2-indolyl)piperidine has been accomplished.[5]

We have now carried out the synthesis of desethylibogamine (Ia), a totally synthetic compound containing the full carbon skeleton of the iboga alkaloids.[6] Although at the time this work was completed, it appeared that this was the first total synthesis of the iboga nucleus, Büchi and co-workers almost simultaneously completed the total synthesis of (±)-ibogamine (Ib) and (±)-epiibogamine (Ic).[7]



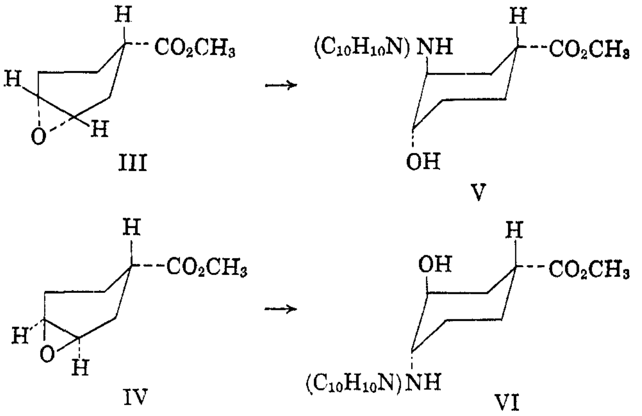
Ia, R = H; R' = H
b, R = C_2H_5; R' = H
c, R = H, R' = C_2H_5



IIa, R = H
b, R = $C_7H_7SO_2$

The initial goal of our synthesis was an isoquinuclidine bearing substituents such that it might be cyclized to form the seven-membered C ring of the iboga nucleus. The indolylethylisoquinuclidone (IIa) appeared to be such a compound and it was synthesized in three steps from methyl 3-cyclohexene-1-carboxylate in an over-all yield of 68%.

Oxidation of methyl 3-cyclohexene-1-carboxylate with *m*-chloroperbenzoic acid gave a mixture of *cis* and *trans* epoxides (III and IV), with the latter predominating.[8] If it be assumed that the major contributing conformations of the *cis* and *trans* epoxides are those where the carbomethoxy group is equatorial (III and IV), then normal *trans*-diaxial opening[9] of the epoxide ring with an appropriate nucleophile (in this case tryptamine), will give the 3- and 4-substituted carbomethoxyaminocyclohexanols (V and VI) with the substituent in the 4 position *cis* to the carbomethoxy group. Treatment of the mixture of epoxy esters with tryptamine in boiling ethanol did, in fact, give a mixture of amino alcohols which was, without purification, heated to effect cyclization. Under these conditions the amino alcohol (VI) derived from *trans* epoxide gave the desired isoquinuclidone (IIa), while the other amino alcohol afforded either a bicyclic lactone or a polymeric amide. In order to effect a separation of these compounds advantage was taken of the known stability of ibogaine lactam to base.[2a] Treatment of the pyrolysate with mild base effected hydrolysis of the lactone (and/or amide) and IIa was obtained in 68% yield based on tryptamine. The infrared spectrum of IIa showed the carbonyl absorption (6.05 μ) expected for a 2-aza-3-oxobicyclo[2.2.2]octane,[10] and was consistent with that of other similar isoquinuclidones.[11]



III → V

IV → VI

Treatment of the indolylethylisoquinuclidone (IIa) with tosyl chloride in pyridine gave the expected tosylate (IIb); however, when excess tosyl chloride and longer reaction times were used, a second compound ($C_{31}H_{32}N_2S_2O_6$), was obtained. This substance, which corresponds to the addition of 2 equiv of tosyl chloride and the elimination of two molecules of hydrochloric acid, shows no carbonyl absorption in the infrared, but does show a band at 6.20 μ corresponding to a carbon–nitrogen double bond. The ultraviolet spectrum is

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[1] A preliminary communication discussing a portion of this work appeared in *J. Am. Chem. Soc.*, **87**, 2288 (1965).

[2] (a) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *ibid.*, **80**, 126 (1958); (b) G. A. Jeffrey, G. Arai, and J. Coppola, *Acta. Cryst.*, **13**, 553 (1960).

[3] S. I. Sallay, *Tetrahedron Letters*, 2443 (1964).

[4] M. P. Cava, C. K. Wilkins, D. R. Dalton, and K. Bessho, *J. Org. Chem.*, **30**, 3772 (1965).

[5] J. W. Huffman, *ibid.*, **27**, 503 (1962).

[6] J. P. Kutney, R. T. Brown, and E. Piers [*J. Am. Chem. Soc.*, **86**, 2287 (1964)] have obtained a compound containing the ibogamine ring system from the mercuric acetate oxidation of carbomethoxydihydrocleavamine.

[7] G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **87**, 2073 (1965); **88**, 3099 (1966). We would like to thank Professor Büchi for sending us a copy of the manuscript of the communication in advance of the publication date.

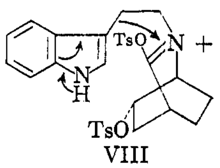
[8] H. B. Henbest and B. Nicholls [*J. Chem. Soc.*, 221 (1959)] report that the oxidation of methyl 3-cyclohexene-1-carboxylate with perbenzoic acid gives exclusively the *trans* epoxide.

[9] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 230, and references cited.

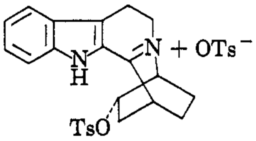
[10] C. M. Lee and W. D. Kumber, *J. Am. Chem. Soc.*, **83**, 4593 (1961), and references therein.

[11] (a) J. W. Huffman and T. Kamiya, *Tetrahedron Letters*, 1857 (1966); (b) J. W. Huffman and T. R. Nasser, unpublished work.

similar to that of dehydroyohimbine[12] and sodium borohydride reduction gave an unstable monotosylate ($C_{24}H_{26}SO_3$) which gave a normal indole ultraviolet spectrum. On the basis of this data and mechanistic considerations, the bistosylate must be the pentacyclic compound (VII), formed from the normal tosylate (IIb), presumably *via* the imino tosylate (VIII).[13]



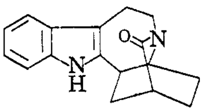
VIII



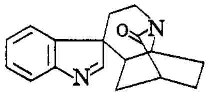
VII

The nmr spectrum of VII, although very poorly resolved owing to low solubility, was consistent with the assigned structure. The borohydride reduction product was too unstable to characterize properly, but is undoubtedly either the dihydro free base from the reduction of VII, or an aziridinium salt derived from it. The normal monotosylate (IIb) shows the expected spectral characteristics with carbonyl absorption at 6.05 μ and the nmr is consistent with the assigned structure (see the Experimental Section).

A number of attempts to effect the cyclization of the isoquinuclidone tosylate (IIb) with various protic acids (toluenesulfonic acid–acetic acid, trifluoroacetic acid, etc.) afforded no material giving a negative Ehrlich test.[14] Reaction of the tosylate with mild Lewis acids gave either recovered starting material or various decomposition products; however aluminum chloride or bromide in toluene gave the desired desethylibogamine lactam (IX).[15] The spectral data were in agreement with those predicted for a compound of this structure, and were quite similar, with the exception of the expected deviations, to those of ibogaine lactam (see the Experimental Section).



IX



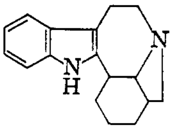
X

This pentacyclic lactam could also be obtained from the isoquinulidone tosylate by base-catalyzed cyclization. Treatment of IIb with potassium *t*-butoxide in either *t*-butyl alcohol or DMSO gave a substance isomeric with IX, but which did not have the ultraviolet spectrum characteristic of an indole.[16] By analogy with the base-catalyzed cyclization of various ajmaline deriviative,[17] a consideration of its spectral properties (see the Experimental Section and ref 16) and its facile rearrangement to an indole derivative (see below), this compound must be the indolenine (X) corresponding to desethylibogamine lactam.

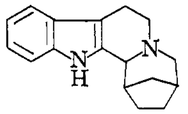
Although X was formed in quite low yield from the tosylate, there were no other identifiable products from this reaction, with the exception of recovered starting material. In view of the known course of reaction of tosylates with potassium *t*-butoxide,[18] it is most unlikely that any profound rearrangement has occurred in this cyclization. The principal side reactions are probably elimination to the bicyclooctene derivative and N-alkylation to form polymeric materials. Isomerization of X with dilute acid gave the corresponding indole, which was identical with the compound obtained from the aluminum halide catalyzed cyclization.[19]

The reduction of the lactam to desethylibogamine (Ia) was straightforward, and again the analytical and spectral data were consistent with the assigned structure.

Although the cyclization of IIb to X and the subsequent rearrangement to the lactam obtained by direct cyclization of IIb would seem to preclude any structures other than Ia for the reduction product, there are two mechanistically plausible alternative structures for this compound which could result from rearrangement during the aluminum chloride cyclization. One of these (XI) would arise from the migration of the amide nitrogen during cyclization,[11] and the other (XII) from a Wagner–Meerwein rearrangement. Structure XI may be excluded on the basis of the carbonyl absorption of the lactam actually obtained (6.12 μ); the five-membered lactam derived from XI would be expected to absorb at lower wavelength (*ca.* 5.9 to 6.0 μ).[11]



XI



XII

Compounds of gross structure XII (either isomer at C-3) may be excluded on the basis of the nmr spectrum of desethylibogamine and its resistance to mercuric acetate oxidation. It has been found that indole alkaloids having an equatorial proton at C-3 show an nmr signal near δ 4.45,[20] while compounds with an axial

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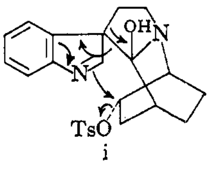
(12) F. A. Weisenborn and P. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).

(13) This reaction is in reality a variation of the Bischler–Napieralski isoquinoline synthesis.

(14) Although the products of these reactions have not been studied in detail in this case, similar reactions in the N-benzyl series afford a mixture of products with skeletal rearrangement.[11]

(15) Since no trace to this compound could be detected (thin layer chromatography) in those reactions where a carbonium ion has almost certainly been formed from the tosylate (*i.e.*, treatment with protic acids), it is probable that the Lewis acid catalyzed cyclization proceeds *via* a completely different mechanism. For instance, an initial cyclization at C-3 to give i followed by rearrangement to the product.



→ desethylibogamine lactam

i

(16) This compound had λ_{max} 243 mμ with tailing to *ca.* 300 mμ, shifted in acid to a shoulder at 238 mμ and a broad shoulder at 278 mμ. A. H. Jackson and A. E. Smith [*Tetrahedron*, **21**, 989 (1965)] report that a series of 3,3-dialkylindolenines have λ_{max} between 253 and 256 mμ in neutral solution, shifted to a shoulder at 236 to 238 mμ with a second maxima at 273–280 mμ in dilute acid. These authors discuss in some detail the problems associated with trimerization and solvation of indolenines in neutral solution, which appear to make it quite difficult to *a priori* predict the exact position of the maximum of a given indolinine.

(17) M. F. Bartlett, B. F. Lanbert, H. M. Werblood, and W. I. Taylor, *J. Am. Chem. Soc.*, **85**, 475 (1963).

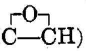
(18) H. C. Brown and L. Klimisch, *ibid.*, **88**, 1430 (1966).

(19) M. F. Bartlett, D. F. Dickel, R. C. Maxfield, L. E. Paszek, and A. F. Smith [*ibid.*, **81**, 1932 (1959)] have reported the reduction and rearrangement of iboluteine lactam. Since this reaction occurs with exclusive migration of the most substituted carbon, it seems certain that the rearrangement of indolenine X follows the same path. Also, since ibogaine lactam is stable to aluminum chloride, (see the Experimental Section) it seems unlikely that rearrangement of the carbon skeleton of desethylibogamine lactam is occurring after cyclization of the tosylate.

(20) W. E. Rosen and J. N. Shoolery, *ibid.*, **83**, 4816 (1961).

proton at C-3 are rather easily oxidized by mercuric acetate.[12] The final product of our synthetic sequence was inert to mercuric acetate and showed no nmr signal between the aromatic multiplet and δ 3.45, thus excluding XII as a possible structure for this compound.

Experimental Section[21]

3-Carbomethoxy-7-oxabicyclo[4.1.0]heptane.—To a solution of 30.0 g of methyl 3-cyclohexene-1-carboxylate in 200 ml of chloroform was added, with cooling, 47.0 g of *m*-chloroperbenzoic acid. The reaction mixture was stirred at room temperature for 2 hr, sodium sulfite was added to destroy the excess peracid, and the mixture was extracted with aqueous sodium bicarbonate. The chloroform solution was washed with water and dried, and the solvent was removed at reduced pressure to give a pale yellow oil. Distillation at oil-pump pressure gave 30.5 g (91%) of a mixture of the *cis* and *trans* epoxides, bp 58–59° (0.9 mm). Vapor phase chromatography (0.25 × 6 ft column of silicone grease on diatomaceous earth, 122°) showed that the mixture contained 71% of the *trans* isomer, the balance being the *cis* epoxide. All attempts to separate these isomers failed, and the relative precents composition were based on the assumption that the major component was the *trans* epoxy ester.[8] The infrared spectrum of this mixture showed a carbonyl band at 5.79 μ and absorption at 12.12 which may be assigned to the epoxide group.[22] The nmr spectrum showed peaks at 3.08 (multiplet, two protons  $\overset{\ulcorner O \urcorner}{HC—CH}$); 3.61 (singlet, three protons, CH_3O), and a high field envelope from 1.5 to 2.5.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.53; H, 7.74.

2-(3-Indolylethyl)-3-oxo-6-*endo*-hydroxy-2-azabicyclo[2.2.2]octane.—A mixture of 8.0 g of tryptamine and 8.0 g of the mixture of epoxy esters in 20 ml of ethanol was heated at reflux for 7 hr. The solvent was removed at reduced pressure, and the resulting red oil was heated at 150–160° for 2 hr and at 190–200° for 1.5 hr. The reaction mixture was dissolved in 30 ml of methanol, and 20 ml of 10% aqueous sodium hydroxide was added. The mixture was heated at reflux for 1.5 hr, methanol was distilled off, and water was added. On cooling the lactam separated as a pale brown powder, mp 170–173° (9.65 g, 68%). Recrystallization from methanol gave the analytical sample, mp 180–181°. The infrared spectrum of this compound showed carbonyl absorption at 6.05 μ (δ-lactam), and in the ultraviolet had $\lambda_{\max}$ 275 mμ (log ε 3.72), 281 (3.76), and 290 (ε 3.68), plus intense absorption below 230 mμ. The nmr spectrum, (run in DMSO-d_6 owing to the insolubility of this compound in chloroform) in addition to an aromatic multiplet and high-field aliphatic protons, showed the following peaks: 2.29 (multiplet, one proton, CHCO), 3.00 and 3.48 (multiplets, four protons, CH_2CH_2NCO; the low-field portion of these peaks is partially obscured by the water present in the solvent), 3.80 (multiplet, one proton, C*H*OH), and 5.08 (doublet, J = 4 cps, one proton CHO*H*).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.59; H, 6.85; N, 9.83.

2-(3-Indolylethyl)-3-oxo-6-*endo*-tosyloxy-2-azabicyclo[2.2.2]octane.—To a suspension of 3.0 g of the above alcohol in 10 ml of dry pyridine at 5–10° was added 2.56 g of *p*-toluenesulfonyl chloride. The mixture was stirred with cooling for 5 hr, and then allowed to warm to room temperature and stirred for 2 hr. Upon pouring into water, a pale yellow solid was obtained. Recrystallization from methanol gave 3.58 g (77%) of white crystals, mp 149–150°; infrared, 6.05 (C=O), 7.30, and 8.45 μ (tosylate). The nmr spectrum, in addition to the aromatic multiplet, and high-field envelope, showed the following peaks: 2.30 (singlet, three protons, CH_3Ar), 2.92 and 3.59 (A_2B_2, four protons, ind-CH_2CH_2NCO), 3.80 (multiplet, one proton, CHNCO), 4.32 (multiplet, CHOTs). The ultraviolet spectrum showed $\lambda_{\max}$ 274 mμ (log ε 3.93), 281 (3.93), and 290 (3.86), plus intense absorption below 230 mμ.

Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.90; H, 6.10; N, 6.50.

When this reaction was carried out with 2.00 g of alcohol and 2.00 g of tosyl chloride in 15 ml of pyridine at room temperature for 24 hr, in addition to 0.72 g of material, mp 147–149°, identical with that obtained above, concentration of the mother liquors gave 0.14 g of yellow crystals, mp 230–232° dec. Recrystallization from methanol gave the analytical sample, mp 245–246° dec. This material showed infrared absorption at 6.20 μ (C=N) and had $\lambda_{\max}$ 249 mμ (log ε 4.09) and 360 mμ (log ε 4.52). The nmr spectrum, although poorly defined owing to insolubility, showed peaks at 2.40 (singlet, CH_3Ar), a series of peaks between 2.90 and 4.0 (ind-$CH_2CH_2N^+$= and =NCH), and 4.29 (multiplet, CHOTs), plus an aromatic multiplet and high-field envelope.

Anal. Calcd for $C_{31}H_{32}N_2O_6S_2$: C, 62.81; H, 5.44; N, 4.73. Found: C, 62.52; H, 5.41; N, 4.56.

A solution of 0.30 g of this material in 30 ml of methanol was treated with 0.20 g of sodium borohydride at room temperature until the reaction mixture was colorless, and the solvent was removed *in vacuo* to give a white semisolid. This material was taken up in methylene chloride, washed with water, and dried, and the solvent was removed giving 0.25 g of yellow oil. Trituration with acetone gave 0.05 g of white powder which decomposed slowly in air and also on heating. The infrared spectrum showed strong absorption in the 8.2- to 8.7-μ region, indicative of a sulfonate salt, aromatic absorption at 6.23 μ, and the aromatic substitution peak for the tosylate group at 12.20 μ. The ultraviolet spectrum showed $\lambda_{\max}$ 277 sh mμ (log ε 3.92), 283 (3.93), and 291 (3.85), plus high end absorption below 235 mμ.

Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.23; H, 6.20; N, 6.60; S, 7.56. Found: C, 67.68; H, 6.45; N, 6.43; S, 7.60.

Desethylibogamine Lactam. A.—To a suspension of 2.00 g of the isoquinuclidone tosylate in 100 ml of dry toluene was added 1.00 g of aluminum chloride, and the reaction mixture was heated on the steam bath overnight. The toluene was removed at reduced pressure and water was added. After standing for 2 hr at room temperature, the aqueous layer was decanted and the remaining pasty solid was stirred with ethanol. The precipitated solid (0.37 g) was collected and the filtrates were combined and evaporated to dryness. The brown residue was taken up in methylene chloride, and chromatographed on Merck alumina. Elution with the same solvent gave an additional 0.09 g of product. Total yield of crude material was 0.46 g (38%). This material showed a negative Ehrlich test, and had infrared absorption at 6.12 μ (C=O). The nmr spectrum, although poorly resolved owing to the insolubility of the material in suitable solvents showed peaks at 2.54 (multiplet, CHCO), 3.12 (multiplet, ind-CH_2- and ind-CH), 3.79 (multiplet, CHNCO), and two one proton multiplets at 4.19 and 4.65 (CH_2NCO) plus aromatic and high-field aliphatic peaks.

The infrared spectrum of ibogaine lactam shows a carbonyl peak at 6.12 μ and the nmr spectrum has peaks at 0.95 (triplet, CH_3CH_2), 2.48 (multiplet, one proton, CHCO), 3.05 (multiplet, three protons, ind-CH_2- and ind-CH), 3.70 (unsymmetrical triplet, J = 4 cps and J = 2 cps, CHNCO), 3.81 (singlet, $ArOCH_3$), 4.50 and 5.02 (one-proton multiplets, CH_2NCO), plus aromatic and saturated aliphatic protons.

Recrystallization of the crude lactam from ethanol gave white crystals, mp 313–315° dec; $\lambda_{\max}$ 225 mμ (log ε 4.50), 283 (3.81), 291 (3.78).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.65; H, 7.01; N, 10.53.

When this reaction was carried out with smaller quantities of aluminum chloride, or at lower temperatures (boiling benzene) the tosylate was recovered unchanged. Shorter reaction times, or increased temperature (toluene at reflux) gave diminished yields (16 to 30%) of the lactam. In one experiment aluminum bromide was substituted for the chloride, and from 0.18 g of tosylate, 0.02 g of lactam was obtained. The use of other Lewis acids (boron trifluoride, stannic chloride, or ferric chloride) under various conditions gave either recovered starting material or various products of gross decomposition. Treatment of the tosylate with acetic acid–sodium acetate gave a mixture of two compounds, which on the basis of thin layer chromatography and infrared spectroscopy consisted of the acetate of the

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[21] Melting points were determined on a Fisher-Johns melting point block and are uncorrected. Infrared spectra were carried out as liquid films or in potassium bromide pellets on a Perkin-Elmer 137 spectrophotometer. Ultraviolet spectra were carried out in 95% ethanol, employing a Perkin-Elmer 4000A spectrophotometer. Nmr spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer and are reported in parts per million (ppm) relative to tetramethylsilane. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn.

[22] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p 103.

indolyl isoquinuclidinol and the bicyclo[3.2.1]octane derivative. No material giving a negative Ehrlich test was obtained.[23]

B.—A solution of 0.48 g of tosylate in 15 ml of dry *t*-butyl alcohol in which 0.06 g of potassium had been dissolved was heated at reflux for 25 hr under nitrogen. The solvent was removed at reduced pressure, water was added, and the mixture was extracted with methylene chloride. After washing with water and drying, the solvent was removed at reduced pressure to give 0.17 g of waxy solid. This solid was dissolved in methylene chloride and chromatographed on 4 g of Merck alumina. The first fractions eluted with methylene chloride gave 0.01 g (3.8%) of the indolenine as a white solid. The infrared spectrum showed a carbonyl maximum at 6.03 μ and the nmr showed the following peaks: 2.73 (multiplet, CHCO), 3.82 (multiplet, CHNCO), 4.40 (multiplet, CH_2NCO), and the aromatic multiplet at *ca.* 7.3. The analytical sample, mp 249–251°, was obtained by recrystallization from benzene; λ_{max} 243 mμ (log ϵ 3.83), shifted in acid to λ_{max} 238 sh mμ (log ϵ 3.79) and λ_{max} 278 sh mμ (log ϵ 3.53).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.70; H, 6.99; N, 10.37.

Further elution of the column with methylene chloride gave 0.12 g of recovered tosylate.

When the reaction was carried out using 0.88 g of tosylate and 0.38 g of potassium *t*-butoxide in 10 ml of dimethyl sulfoxide at room temperature for 15 hr, followed by warming on the steam bath for 1.5 hr, there was obtained after chromatography and recrystallization from benzene 0.025 g (5%) of material, mp 249–251°.

A solution of 0.03 g of the indoleneine in 5 ml of methanol and 10 ml of 10% hydrochloric acid was allowed to stand at room temperature overnight. The mixture was evaporated to dryness at reduced pressure, and the residue was triturated with water. The solid material was collected, washed with water, and recrystallized from ethanol to give 0.01 g (33%)[24] of desethylibogamine lactam, mp 313–315° dec, identical with that of the material obtained in part A above.

Reaction of Ibogaine Lactam with Aluminum Chloride.—A solution of 0.2 g of ibogaine lactam[2a] was treated with 0.10 g of aluminum chloride in 0.10 ml of toluene under the reaction conditions described above for the cyclization. Upon isolation of the product there was obtained 0.18 g (90%) of recovered lactam, identical in all respects with the starting material.

Desethylibogamine.—To a suspension of 0.30 g of desethylibogamine lactam in 50 ml of dry tetrahydrofuran was added 0.60 g of lithium aluminum hydride. The reaction mixture was heated at reflux 8 hr and cooled, the excess hydride was decomposed with ethyl acetate, and 0.8 ml of water was added. The aluminum salts were filtered off and washed with tetrahydrofuran, and the combined filtrates were concentrated *in vacuo*. The oily residue was taken up in methylene chloride and filtered through a column of 4 g of neutral alumina. After evaporation of the solvent and recrystallization from methanol 0.23 g (81%) of material, mp 186–187°, was obtained. The nmr spectrum showed a high-field envelope centered about 1.8 and a complex series of peaks between 2.70 and 3.39 for the various protons adjacent to the aliphatic nitrogen and the indole nucleus. There was also an aromatic multiplet centered about 7.15. Electronic integration indicated the ratio of the three types of protons was 7:8:4. The nmr spectrum of ibogamine shows peaks at 0.93 (triplet CH_3CH_2), an envelope centered about 1.6, and a complex series of peaks between 2.55 and 3.60, plus the aromatic multiplet. The ultraviolet spectrum showed λ_{max} 226 mμ (log ϵ 3.41), 283 (3.89), and 293 (3.80).

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.65; H, 7.90; N, 11.32.

Mercuric Acetate Oxidation of Desethylibogamine.—A solution of 0.03 g of desethylibogamine in 4 ml of 5% aqueous acetic acid containing 0.12 g of mercuric acetate was heated on the steam bath for 2 hr; the solution was saturated with hydrogen sulfide. The reaction mixture was filtered, made basic with sodium bicarbonate, and extracted with methylene chloride. Evaporation of the solvent and recrystallization from methanol gave 0.01 g of recovered desethylibogamine. Evaporation of the mother liquors gave a brown oil which by tlc consisted largely of starting material. The same reaction conditions applied to ibogamine gave similar results, while yohimbine gives an instantaneous precipitate of mercurous acetate.

Registry No.—Ia, 1630-03-1; III, 1630-02-0; IV, 1630-01-9; IIa, 10039-12-0; IIb, 10027-77-7; VII, 10043-41-1; IX, 1747-98-4; X, 10043-42-2.

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[23] In view of the results obtained in model systems under similar conditions,[11] this reaction was not investigated in detail.

[24] Owing to the low yields in the cyclization step, no efforts were made to find the optimum conditions for this reaction.

The Synthesis and Reactions of Some Isoquinuclidones[1,2]

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In the course of work directed at the total synthesis of the iboga alkaloids, the isoquinuclidones, 3-oxo-6-*endo*-hydroxy-2-azabicyclo[2.2.2]octane (Ia) and the corresponding N-benzyl compound (Ic), have been prepared. Acetolysis of the tosylate of the latter affords 2-benzyl-3-oxo-6-*endo*-acetoxy-2-azabicyclo[2.2.2]octane and 2-benzyl-3-oxo-7-*endo*-acetoxy-2-azabicyclo[3.2.1]octane with the latter predominating. Similarly, acetolysis of the bicyclo[3.2.1]octyl tosylate affords the same two products in the same ratio. This rearrangement proceeds with migration of a carboxamido group, apparently with participation of the amide nitrogen, a reaction for which there are few precedents.

In the course of work directed at the synthesis of compounds related to the iboga alkaloids a new general synthesis of substituted isoquinuclidones was developed.[3] In the early phases of this work it was planned that a rather simple N-unsubstituted hydroxyisoquinuclidone (Ia) would be employed in the synthesis of desethylibogamine, with the indolyl ethyl moiety being added at a later stage.[4] Consequently, Ia was synthesized from the reaction of ammonia and 3-carbomethoxy-7-oxabicyclo[4.1.0]heptane, using the conditions described earlier.[3] Although the yields of

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[1] A preliminary communication describing a portion of this work has been published by J. W. Huffman and T. Kamiya, *Tetrahedron Letters*, 1857 (1966).

[2] This work was supported in part by Grant NB-04589 from the National Institute of Neurological Diseases and Blindness and in part by Public Health Service Career Program Award 1-K3-GM-5433.

[3] (a) J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Am. Chem. Soc.*, **87**, 2288 (1965); (b) J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Org. Chem.*, **32**, 697 (1967).

[4] This approach, and the one using the N-benzylisoquinuclidone, were explored initially, since it was felt that the conditions used in the isoquinuclidone synthesis would result in extensive decomposition of tryptamine. This is, however, not the case (see ref 3).