A Formal Synthesis of (±)-Ibogamine

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A formal synthesis of the indole alkaloid (±)-ibogamine (2) from a mixture of methyl *cis*- and *trans*-5-ethyl-3-cyclohexenecarboxylate is described. This mixture of esters was prepared by reaction of the lactone of 3-hydroxycyclohexenecarboxylic acid (14) with ethylmagnesium bromide–cuprous iodide–dimethyl sulfide to give, after esterification, trans ester 8. Epimerization gave a 3:2 mixture of esters 4 and 8, epoxidation of which, followed by reaction with tryptamine, gave an inseparable mixture of lactams 5 and 15. This mixture selectively afforded tosylate 3, a known synthetic precursor to (±)-ibogamine. Attempted preparation of esters 4 and 8 by elimination reactions of various derivatives of 2-ethyl-4-carboxycyclohexanone afforded mixtures containing significant amounts of methyl 3-ethyl-3-cyclohexenecarboxylate (10).

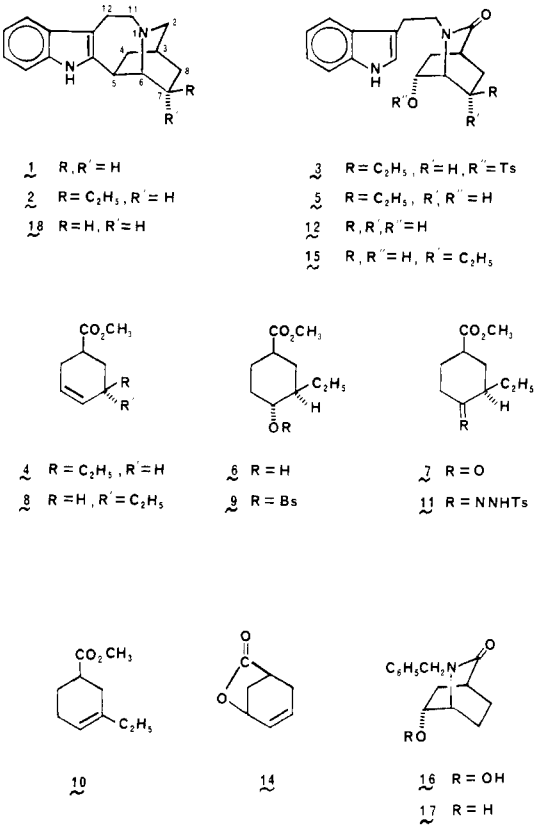
Several years ago we reported a short efficient synthesis of desethylibogamine (1), which constituted one of the first successful syntheses of the pentacyclic nucleus of the iboga alkaloids.[1] A number of syntheses of ibogamine (2) have been reported subsequently,[2] however our approach remains an attractive one due to its brevity and inherent simplicity. We wish to report at this time the preparation of lactam tosylate 3, which constitutes a formal synthesis of (±)-ibogamine.[3]

Our original synthesis of desethylibogamine (1) was effected in five steps and an overall yield of 15% from methyl 3-cyclohexene-1-carboxylate with chromatography needed only in the final step.[1] Extension of this route to the natural product (2) required only the preparation of methyl *cis*-5-ethyl-3-cyclohexene-1-carboxylate (4), which on epoxidation and reaction with tryptamine would afford lactam 5, the precursor of (±)-ibogamine (2).

Initially it was envisioned that ester 4 would be prepared regio- and stereoselectively by an elimination reaction carried out on an appropriate derivative or conversion product of hydroxy ester 6, which in turn would be prepared by reduction of 2-ethyl-4-carboxycyclohexanone (7),[4] followed by esterification. It was assumed, on the basis of standard conformational arguments, that cis ester 4 would be considerably more stable than the trans epimer 8 in which one substituent would, of necessity, be axial or quasi-axial. Lithium–ammonia reduction of keto acid 7 was predicted, by analogy with other cyclohexanones, to be an efficient stereoselective route to 6,[5] however, reduction of 7 followed by esterification afforded a mixture containing 65% of 6 and 35% of its axial epimer. The stereochemical assignments are based on standard NMR considerations (see Experimental Section) and the relative amounts of each isomer were determined by GLC. A mixture of similar composition was obtained on reduction of 7 with $NaBH_4$ in aqueous $NaHCO_3$, while reductions with borohydride in alcohols were even less stereoselective.

Attempted separation of 6 and its epimer by preparative GLC was not entirely successful, however, the mixture of isomers reacted selectively with *p*-bromobenzenesulfonyl chloride to give equatorial brosylate 9. This derivative is sterically oriented to undergo normal trans elimination to afford 4, however, it was recovered unchanged on heating in 0.5 M potassium *tert*-butoxide in *tert*-butyl alcohol for 24 h. Potassium *tert*-amyloxide in refluxing *tert*-amyl alcohol under similar conditions gave a complex mixture which contained little, if any, of the expected elimination product (NMR). Elimination could be effected by heating brosylate 9 in γ-collidine, however, the major product was the undesired trisubstituted isomer of 4 (10). Dehydration of hydroxy ester 6 with $POCl_3$–pyridine gave in poor yield (21%) a mixture of 4 and 10 in which 10 predominated.[6]

Chart I



(1) Huffman, J. W.; Rao, C. B. S.; Kamiya, T. *J. Am. Chem. Soc.* **1965**, *87*, 2288; *J. Org. Chem.* **1967**, *32*, 697.

(2) (a) Kutney, J. P. "The Total Synthesis of Natural Products"; Ap Simon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. III, pp 402–422 reviews those syntheses reported through 1971, with supplemental references through 1976. (b) Trost, B. M.; Godelski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (c) Atta-ur-Rahman; Beisler, J. A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063. (d) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382.

(3) Kuehne, M. E.; Reider, P. J. *J. Org. Chem.* **1985**, following article in this issue. They describe an alternative preparation of tosylate 3 and its conversion to (±)-ibogamine by a method similar to that described for the preparation of 1 from the desethyl analogue of 3 (ref 1).

(4) (a) Huffman, J. W.; Sawdaye, R. *Synth. Commun.* **1981**, *11*, 979. (b) Rosemund, P.; Haase, W. H.; Bauer, J.; Fische, R. *Chem. Ber.* **1975**, *108*, 1871.

(5) (a) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486. (b) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 399.

0022-3263/85/1950-1460$01.50/0

Table I. ^{13}C NMR Spectra[a] (δ)

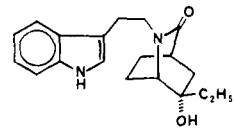
C	11	12	13	15	16	17
3	38.2	38.0	38.8	38.0	38.1	37.9
4	32.5	33.3	38.8	34.1	33.6	26.6
5	67.1	66.6	73.0	68.9	66.4	23.8
6	61.5	57.5	60.9	59.7	56.5	52.1
7	40.2	19.1	21.5[b]	40.3	19.1	26.6
8	31.2	23.7	22.6[b]	31.6	23.9	23.6
9	27.0		32.7	27.0		
10	11.4		6.8	12.6		
11	45.4	44.5	45.8	44.2	46.8	46.7
12	24.4	24.2	24.2	24.2		

[a] All spectra were recorded using Me_2SO-d_6 as solvent. No attempt was made to assign resonances of aromatic carbons. [b] These values may be interchanged.

For the purpose of spectral and chromatographic characterization, a small sample of a homogeneous (GLC) ester, assumed originally to be **4**, but undoubtedly a mixture of **4** and **8** (see below) was obtained as a minor component (30%) from the Diels–Alder reaction of 1,3-hexadiene and methyl acrylate, followed by base-catalyzed epimerization. As anticipated, the major product of this sequence was methyl 2-ethyl-3-cyclohexenecarboxylate, which was also homogeneous to GLC and which is assumed to be predominantly the trans isomer.

A final approach to ester **4** from keto acid **7** was based on Shapiro's modification of the Bamford–Stevens reaction.[7] Although this reaction usually affords high yields of the less substituted olefin on reaction of the tosylhydrazone of an unsymmetrical cyclohexanone with strong base under aprotic conditions, reaction of tosylhydrazone **11** with *n*-butyllithium in hexane under controlled conditions followed by esterification gave a mixture of **10** and **4** plus **8** in which **10** predominated (**10**/**4** and **8** = 69/31).[8] Tosylhydrazone **11** under standard Bamford–Stevens conditions[9] followed by esterification of the crude reaction product gave mixtures of esters **4** (plus **8**) and **10**, the exact composition of which varied from run to run but which always contained approximately equal amounts of di- and trisubstituted olefins.

Although the regioselectivity of the Bamford–Stevens reaction was not satisfactory, this mixture of esters was carried through the isoquinuclidone synthesis with the expectation that it would be possible to isolate hydroxy lactam **5** from the reaction mixture. Epoxidation of the mixture of esters **4** and **10**, followed by reaction with tryptamine afforded material which on the basis of analytical and ^1H NMR spectral data was tentatively assigned structure **5**.[10] However, this material did not afford a tosylate under normal conditions, nor could it be oxidized to the corresponding ketone under a variety of conditions. The ^{13}C NMR spectrum (Table I) revealed a carbinol carbon at lower field than that of desethyl lactam **12**, and the off-resonance decoupled spectrum clearly showed that this carbon was quaternary indicating a tertiary alcohol. This hydroxy lactam must have structure **13**, which arises from ester **10**, and the synthetic approach employing keto acid **7** was abandoned.



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It was ultimately found that reaction of the readily available allylic, bicyclic lactone **14**[11] with ethylmagnesium bromide–CuI–dimethyl sulfide[12] afforded a carboxylic acid, the ester of which was homogeneous to GLC and which had spectral properties identical with those of the ester obtained from the Diels–Alder reaction of 1,3-hexadiene and methyl acrylate described above. However, it has been established that the reaction of allylic esters with organocuprates proceeds with net inversion,[13] strongly suggesting that this ester is *trans*-3-ethyl-5-carbomethoxycyclohexene (**8**). The ester originally assigned structure **4** had been obtained via base-catalyzed isomerization of a mixture of **4** and **8** and was assumed on the basis of careful GLC to be homogeneous. This apparent dilemma was resolved when it was learned that esters **4** and **8** are not separated under normal GLC conditions and that capillary GLC indicated that the equilibrium mixture of **4** and **8** contains approximately 55% of **8**.[14] Capillary GLC of the ester obtained from lactone **14** indicated that it is homogeneous and is identical with the major component of the equilibrium mixture of esters **4** and **8**.[14] ^{13}C NMR of ester **8** also indicated that it is homogeneous (see Experimental Section). On reaction with *m*-chloroperoxybenzoic acid, ester **8** gave a mixture of stereoisomeric epoxides in a ratio of 6:4.

Based on the expectation that the basic conditions of the initial stages of the isoquinuclidone synthesis would effect equilibration adjacent to the ester in the epoxides derived from **8** and lead to ibogamine precursor **5**, the epoxide mixture was treated with tryptamine as described previously.[1] From this reaction there was obtained a lactam, mp 163–164 °C, which was homogeneous to TLC. At this stage we learned that Kuehne and Reider[3,14] had prepared lactam **5** from the mixture of epoxides derived from an equilibrium mixture of esters **4** and **8**. This lactam, mp 145–146 °C, which was also homogeneous to TLC and appeared homogeneous when examined by 100-MHz ^1H NMR (but not 250 MHz) was actually a mixture of lactam **5** and the epiibogamine precursor (**15**).[3,14] This mixture had been converted to tosylate **3** and then to (±)-ibogamine, thus assuring the correct stereochemistry about the ethyl group.[3,14] Although there was a possibility that the lactam which we had obtained was a pure (or less heterogeneous) sample of ibogamine precursor **5**, it seemed more probable that it was actually the epimeric iso-

(6) The major product of the attempted dehydration of **4** appeared to be a phosphate ester. The failure of brosylate **7** to undergo elimination is undoubtedly due to the fact that the conformation in which all three substituent groups on the cyclohexane are equatorial is far more favorable than either the alternative chair conformer with all groups axial or a twist conformer in which the brosylate is antiperiplanar with respect to hydrogen.

(7) (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (b) Shapiro, R. H. *Org. React.* **1976**, *23*, 405.

(8) Subsequent to the time this experiment was carried out, strong bases other than alkyllithium were introduced as reagents for this transformation (Kolonko, K. J.; Shapiro, R. H. *J. Org. Chem.* **1978**, *43*, 1404). The anomalous regiochemistry which we observe is probably caused by the carboxylate α-hydrogen serving as the proton in a traditional protic variation of the Bamford–Stevens reaction.

(9) Bamford, W. S.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. For a concise review of this reaction see: March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp. 932–933.

(10) In both the 60- and 90-MHz ^1H NMR spectra of compounds in this series, the carbinol proton is obscured by the signals due to the protons adjacent to the amide nitrogen.

(11) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.

(12) Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Tetrahedron Lett.* **1982**, *23*, 3583 and references therein.

(13) (a) Goering, H. L.; Singleton, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (b) Kreft, A. *Tetrahedron Lett.* **1977**, 1035. (c) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035.

(14) Kuehne, M. E., private communication.

quinuclidone (15). ^{13}C NMR indicated the material was homogeneous and attempted formation of the tosylate under standard conditions gave only an unstable oil, from which small quantities of starting material could be obtained on attempted crystallization.[15]

Equilibration of ester 8 with methanolic sodium methoxide gave a mixture (^{13}C NMR) of 4 (60%) and 8 (40%) which appeared to be homogeneous to GLC and which had a mass spectrum very similar to that of pure 8. This mixture was converted to a mixture of epoxides, which appeared by GLC to contain the same two epoxides which were obtained from ester 8, but in a ratio of 3:7. This apparent binary mixture is in actuality a mixture of the four possible epoxides derived from esters 4 and 8. Assuming that the starting material consisted of 60% ester 4 and 40% of ester 8, it may be concluded that ester 4 gives a mixture of two epoxides in a ratio of 5:1. The mixture of esters 4 and 8 and the derived mixture of epoxides correspond to the material prepared by Kuehne and Reider; however, in order to confirm their identity this mixture was subjected to the isoquinuclidone synthesis to afford an inseparable mixture of lactams 5 and 15, mp 138–144 °C. The ^{13}C NMR spectrum indicated that this material contained 54% of lactam 5 and 46% of 15. This mixture gave selectively tosylate 2, the ^{13}C and 250-MHz ^1H NMR of which indicated that it was homogeneous and which had physical and spectral properties in agreement with those described by Kuehne and Reider.[3,14] Since these workers have described the conversion of tosylate 3 to (±)-ibogamine (2), the preparation of 3 constitutes a formal synthesis of the natural product. Also, since the conversion of the mixture of esters 4 and 8 to lactam 5 has been described by Kuehne and Reider,[3] no effort was made to optimize the yields in the isoquinuclidone synthesis nor in the preparation of tosylate 3.

During the course of this work it became very apparent that neither TLC nor ^1H NMR at 60 or 90 MHz[10] were particularly useful for determining the homogeneity or structures of indolylethylisoquinuclidones 5, 13, and 15. ^{13}C NMR, however, proved very useful in both assigning structures and stereochemistry in this series and in determining the homogeneity of these compounds. The ^{13}C data for lactams 5, 13, 15, and three model lactams (12,[1] 16,[16] 17[17]) are summarized in Table I.[18] These assignments were made by comparison with the ^{13}C assignments of ibogamine (2) and epiibogamine (18),[19] combined with off-resonance decoupling experiments. The usual assumptions regarding deshielding β-effects were also employed; however, γ-shielding effects appear to be considerably less than in chair cyclohexyl systems.[20] ^{13}C data were also most useful in the analysis of mixtures of esters 4 and 8 (see Experimental Section); however, off-resonance decoupling experiments were not carried out.

Experimental Section

Melting points were determined with a Kofler hot stage and are uncorrected. IR spectra were obtained as neat films or KBr disks with a Perkin-Elmer Model 137 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}); ^1H NMR spectra were obtained on JEOL FX-90Q, Hitachi-Perkin-Elmer Model R-24, or Varian A-60A spectrometers with deuteriochloroform as a solvent for all compounds with the exception of lactams 3, 5, 12, 13, and 15 for which Me_2SO-d_6 was used. ^{13}C NMR spectra were obtained on a JEOL FX-90Q spectrometer operating at 22.5 MHz by using, unless noted otherwise, Me_2SO-d_6 as solvent. NMR data are reported in parts per million relative to tetramethylsilane (δ). Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, or Galbraith Laboratories, Knoxville, TN. Mass spectra were obtained at 70 ev by using a Hewlett-Packard 5985 mass spectrometer.

Reduction of 2-Ethyl-4-carboxycyclohexanone (7). A. With Lithium–Ammonia. To 500 mL of liquid ammonia was added a solution of 3.39 g of acid 7 in 100 mL of a 1:1 mixture of anhydrous ether and dry methanol. There was then added, with stirring, over a period of 1.5 h, 5.50 g of lithium metal and the reaction mixture was stirred at reflux (−33 °C) for 15 min. The excess reducing agent was destroyed by the addition of 25 mL of methanol and the ammonia allowed to evaporate. The residue was taken up in water, acidified with 10% aqueous HCl and extracted with CH_2Cl_2. The extracts were dried and the solvent removed at reduced pressure to afford 2.90 g (85%) of hydroxy acid as a viscous liquid: IR 3310, 2898, 1709 cm^{-1}; NMR 0.92 (t, J = 7 Hz, 3 H, CH_3CH_2), 3.32 (m, $W_{1/2}$ = 25 Hz, 0.67 H, CHOH), 3.90 (m, $W_{1/2}$ = 11 Hz, 0.33 H, CHOH). From 3.70 g of acids there was obtained 3.40 g (85%) of a mixture of epimeric methyl esters, bp 96–97 °C (0.6 mm). Analysis by GLC indicated 35% axial alcohol and 65% of the equatorial isomer. Repeated preparative GLC gave material containing 80% of the equatorial alcohol.

Reaction of 0.225 g of a sample of the mixture of epimeric hydroxy esters containing 80% of the equatorial alcohol with 0.700 g of *p*-bromobenzenesulfonyl chloride in 5 mL of dry pyridine at ambient temperature for one week gave 0.230 g (58%) of brosylate 9, mp 84–87 °C, after crystallization from hexanes–ethyl acetate. Recrystallization from hexanes gave white needles: mp 89–90 °C; NMR δ 0.85 (t, J = 7 Hz, 3 H, CH_3CH_2), 3.71 (s, 3 H, CH_3O), 4.79 (m, $W_{1/2}$ = 22 Hz, 1 H, CHO), 7.79 (br s, 4 H, ArH) Anal. Calcd for $C_{16}H_{21}BrO_5S$: C, 47.39; H, 5.22. Found: C, 47.50; H, 5.21. The brosylate could also be obtained in somewhat lower yield from the unchromatographed mixture of epimeric hydroxy esters.

(B) With Sodium Borohydride. To a solution of 0.34 g of keto acid 6 in 10 mL of 5% aqueous $NaHCO_3$ was added 2.72 g of $NaBH_4$ and the reaction mixture allowed to stand at room temperature for 18 h, then acidified with 10% aqueous HCl, and extracted with CH_2Cl_2. After drying, the solvent was removed to afford 0.33 g (97%) of epimeric hydroxy acids as a colorless oil, the spectral properties of which were identical with those of material prepared as described in part A. GLC analysis of the methyl esters showed that the mixture contained 65% of the equatorial isomer and 35% of its axial epimer.

Reduction of the acid with $NaBH_4$ in methanol, ethanol, or 2-propanol gave mixtures (GLC and/or ^1H NMR) containing 40–50% of the equatorial alcohol.

Methyl 5-Ethyl-3-cyclohexenecarboxylate and Methyl 2-Ethyl-3-cyclohexenecarboxylate. A mixture of 1.64 g of 1,3-hexadiene (mixture of cis and trans), 1.72 g of methyl acrylate, and 0.02 g of hydroquinone was heated in a sealed tube at 170–180 °C for 17 h. After cooling to 0 °C, the tube was opened to give 3.33 g (99%) of a colorless liquid, bp 41 °C (0.60 mm). This material was dissolved in 60 mL of 15% methanolic sodium methoxide and heated at reflux under N_2 for 144 h. The solvent was evaporated at reduced pressure and the residue acidified with 4 N HCl. After extraction with ether and drying, the solvent was removed leaving a pale yellow oil which was reesterified with

(15) It is probable that the tosylate of 15 is being formed, but that it reacts rapidly with nucleophiles due to steric acceleration created by interactions with the *syn*-ethyl group. In one experiment, the crude tosylate was treated with sodium acetate–acetic acid to give in 76% yield the acetate of alcohol 15. This reaction probably proceeds via an intermediate acylaziridinium ion, for which precedent exists in the isoquinuclidone series.[16]

(16) Huffman, J. W.; Kamiya, T.; Rao, C. B. S. *J. Org. Chem.* **1967**, *32*, 700.

(17) Werner, L. H.; Ricca, S. *J. Am. Chem. Soc.* **1958**, *80*, 2733. The authors thank Dr. Neville Finch of Ciba Pharmaceutical Company for a sample of this material which was provided some years ago.

(18) All compounds listed in Table I are numbered using the same system as the natural products (cf. 2) in which the ethyl group contains carbons 9 and 10.

(19) Wenkert, E.; Cochran, D. W.; Gottlieb, H. E.; Hagaman, E. W.; Filho, R. B.; de Abreu Matos, F. J.; Madruga, M. I. L. M. *Helv. Chim. Acta* **1976**, *59*, 2437. The data obtained by these authors for *N*-methylisoquinuclidine were used to assign the ^{13}C chemical shifts for 17.

(20) Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley Interscience: New York, 1980; pp 50–57.

ethereal diazomethane. GLC analysis indicated that this material consisted of two components in a ratio of 7:3 and a portion of the mixture was separated by preparative GLC to give as the major component methyl 2-ethyl-3-cyclohexenecarboxylate as a colorless liquid: NMR δ 0.92 (t, J = 7 Hz, CH_3CH_2), 2.37 (m, 1 H, $CHCO_2CH_3$), 3.72 (s, 3 H, CH_3O), 5.69 (br S, 2 H, HC=CH). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.22; H, 9.48.

The minor component of the mixture, methyl 5-ethyl-3-cyclohexenecarboxylate (mixture of **4** and **8**) was also obtained as a colorless liquid: NMR δ 0.94 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.64 (m, 1 H, $CHCO_2CH_3$), 3.68 (s, 3 H, CH_3O), 5.66 (br s, 2 H, HC=CH). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.34; H, 9.50.

p-Toluenesulfonylhydrazone of 2-Ethyl-4-carboxycyclohexanone (11). To a solution of 8.50 g of keto acid **7** in 130 mL of glacial acetic acid was added 11.30 g of *p*-toluenesulfonylhydrazine. The reaction mixture was stirred at room temperature for 18 h and poured into water, and the precipitated solid filtered off. Recrystallization from methanol gave 11.40 g (68%) of tosylhydrazone **11**, mp 150–153 °C. Repeated recrystallization from methanol gave the analytical sample: mp 164–165 °C. Anal. Calcd for $C_{16}H_{22}N_2SO_4$: C, 56.80; H, 6.55. Found: C, 57.08; H, 6.52.

Bamford–Stevens Reaction of the p-Toluenesulfonylhydrazone of 2-Ethyl-4-carboxycyclohexanone. To a cooled solution of 1.73 g of sodium in 106 mL of diethylene glycol was added 1.11 g of tosylhydrazone **11** and the reaction mixture heated at 150–160 °C for 5 h in a N_2 atmosphere. The reaction mixture was cooled, poured into ice water, and acidified with dilute aqueous HCl. After extraction with three portions of ether, the acidic reaction products were isolated by extraction with aqueous $NaHCO_3$ followed by acidification and extraction with ether. After drying, removal of the solvent afforded a mixture of acids which was converted to their methyl esters (diazomethane).

For characterization and purification, the crude mixture of esters was dissolved in cyclohexane and chromatographed on silica gel. Elution with cyclohexane–benzene (3:1) followed by distillation gave 0.296 g (67%) of a mixture of esters **4**, **8**, and **10**: bp 41–44 °C (1.5 mm); NMR 0.95 (t, J = Hz, 3 H, CH_3CH_2), 3.69, (s, 3 H, OCH_3), 5.44 (m, CH=C of **9**), 5.65 (br s, HC=CH of **4** and **7**). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.56; H, 9.49.

GLC analysis of the products from several runs in which the temperature, concentration, and stoichiometry were varied gave mixtures of esters containing from 37% to 48% of the mixture of esters **4** and **8**. GC/MS of a sample of this mixture which was several years old showed 29% of **4** and **8**, MS identical with that of the mixture prepared by other methods, and 71% of **10**: MS, m/e (relative intensity) 168 (43), 137 (11), 136 (29), 109 (100), 108 (35).

Epoxidation of Methyl 5-Ethyl-3-cyclohexenecarboxylate and Methyl 3-Ethylcyclohexenecarboxylate. To a cooled (5 °C) solution of 0.500 g of the mixture of esters **4**, **8**, and **10** obtained from the Bamford–Stevens reaction in 10 mL of $CHCl_3$ was added 0.70 g of *m*-chloroperoxybenzoic acid. The reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The excess peracid was decomposed with 10% aqueous $NaHSO_3$. After washing with water and drying the solvent was removed to leave a pale yellow oil: bp 76–81 °C (1.5 mm); NMR 0.95 (t, J = 7 Hz, CH_3CH_2), 2.97 (m, $CHCO_2$, $\overline{HCCHO}$ and $\overline{CCHO}$), 3.60 (s, 3 H, OCH_3). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.87.

2-(2-Indol-3-ylethyl)-3-oxo-6-*endo*-hydroxy-6-*exo*-ethyl-2-azabicyclo[2.2.2]octane (13). To a solution of 4.40 g of the above mixture of epoxides in 12 mL of ethanol was added 4.06 g of tryptamine and the solution heated at reflux under N_2 for 12 h. After stirring at ambient temperature for 9 h, the solvent was removed and the residue heated under N_2 at 150–160 °C for 4 h and then at 190 °C for an additional 1 h. The residue was taken up in 15 mL of methanol and 10 mL of 10% aqueous NaOH and heated at reflux under N_2 for 4 h. The reaction mixture was cooled and diluted with H_2O, the material which separated was taken up in methanol–CH_2Cl_2 (1:1) and dried, and the solvents removed to afford a yellow gum. Trituration with hexanes afforded off-white crystals which on recrystallization from CH_2Cl_2–hexanes gave 0.75 g (37% based on the epoxide of ester **10**) of lactam **13**, mp 185–187 °C. The mother liquors were evaporated, and the residue taken up in CH_2Cl_2 and chromatographed on Merck acid washed alumina. Elution with $CHCl_3$ and crystallization gave an additional 0.825 g (40% based on epoxide **10**) of lactam **13**: mp 184–186 °C; NMR 0.84 (t, J = 7 Hz, CH_3CH_2), 2.29 (m, 1 H, CHCO), 2.93 (m, 2 H, $ArCH_2$), 3.21 (br s, 2 H, NCH_2), 3.74 (m, 1 H, NCH), 4.15 (s, 1 H, OH), 7.30 (m, 5 H, ArH). Recrystallization from CH_2Cl_2–hexanes gave white crystals: mp 187–188 °C. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.75; H, 7.56; N, 9.05.

Methyl *trans*-5-Ethyl-3-cyclohexenecarboxylate (8). To a chilled (−30 °C) solution of 5.73 g of cuprous iodide and 18.0 mL of dimethylsulfide in 150 mL of dry THF in a N_2 atmosphere was added 30.0 mL of 2 M ethylmagnesium bromide. The mixture was stirred at −30 °C for 0.5 h and a solution of 7.44 g of lactone **14**[11] in 45 mL of dry THF was added dropwise. The reaction mixture was stirred for 1 h at 30 °C, warmed to 0 °C (ice bath), and stirred at 0 °C for 1 h. TLC of an aliquot indicted that lactone **14** had not been completely consumed, and the reaction was warmed to ambient temperature and stirred for an additional 1 h. After quenching with 150 mL of 3 N HCl, the product was isolated by extraction with ether. The ethereal extracts were extracted with three portions of 3 N NaOH, the combined alkaline extracts were acidified with dilute HCl, extracted with ether, and dried, and the solvent removed to afford 9.50 g of crude acid as a pale brown oil: NMR δ 0.94 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.69 (m, 1 H, $CHCO_2H$), 5.67 (br s, 2 H, HC=CH); MS, m/e (relative intensity) 154 (8), 136 (20), 125 (7), 109 (100), 97 (16), 93 (18), 79 (95). Without further purification this material was esterified by dissolution in 200 mL of methanol, cooling to 0 °C, and the addition of 4 mL of acetyl chloride. After standing at ambient temperature for 24 h, the reaction mixture was concentrated, the residue was taken up in ether, washed with water, and dried, and the solvent removed to give 7.60 g (75%) of ester **8** which was homogeneous to both GLC and TLC. The IR and ^1H NMR (60 MHz) spectra were identical with that of the mixture of esters **4** and **8** obtained by the Diels–Alder reaction route described above: ^{13}C NMR ($CDCl_3$) δ 11.4, 27.2, 28.1, 29.5, 34.7, 35.9, 51.2, 124.2, 130.8, 175.9; MS, m/e (relative intensity) 168 (27), 137 (19), 136 (53), 109 (100), 108 (46).

A solution of 7.55 g of ester **8** was dissolved in 150 mL of methonolic sodium methoxide, prepared by using 1.50 g of sodium, and heated at reflux under N_2 for 76 h. The reaction mixture was concentrated at reduced pressure, diluted with water, and acidified with 10% aqueous HCl. The aqueous suspension was extracted with three portions of ether, the combined extracts washed with water and brine and dried, and the solvent removed to give 6.00 g of crude material which was reesterified with methanol–acetyl chloride to give 5.22 g (69%) of a mixture of esters **4** and **8**. The IR and 60-MHz NMR spectra of this mixture were virtually identical with those of ester **8** and the mixture appeared to be homogeneous to GLC. The ^{13}C NMR ($CDCl_3$) showed the peaks characteristic of ester **8**, (see above) with additional peaks at δ 10.8, 27.8, 28.6, 31.6, 37.1, 39.7, 124.5, 131.5. The relative peak heights indicated that the mixture contained 60% of ester **4** and 40% of ester **8**: mass spectrum, m/e (relative intensity) 168 (7), 137 (7), 136 (24), 109 (72), 93 (19), 79 (100), 77 (21).

3-Carbomethoxy-5-ethyl-7-oxabicyclo[4.1.0]heptane. The epoxidation of ester **8** was effected in the manner described above for the oxidation of the mixture of esters **4**, **8**, and **10**. From 1.12 g of ester **8** there was obtained 1.22 g (99%) of a pale yellow oil which was homogeneous to TLC: NMR δ 1.05 (t, J = 7, 3 H, CH_3CH_2), 3.12 (m, 2 H, $\overline{HCCHO}$), 3.63 (s, 3 H, OCH_3); GC/MS indicated the presence of two stereoisomers A (61%) MS, m/e (relative intensity) 184 (1), 169 (32), 155 (83), 153 (28), 137 (21), 128 (14), 125 (100), 124 (77) and B (39%) MS, m/e (relative intensity) 169 (27), 155 (98), 137 (18), 128 (15), 125 (100), 124 (71).

Epoxidation of 0.698 g of the equilibrium mixture of esters **4** (60%) and **8** (40%) afforded 0.631 g (83%) of a mixture of four epoxides, which on GC/MS gave rise to two peaks, the retention times and mass spectra of which corresponded to those of A and B above in a ratio of 32:68.

2-(2-Indol-3-ylethyl)-3-oxo-6-*endo*-hydroxy-7-*endo*-ethyl-2-azabicyclo[2.2.2]octane (15). A solution of 7.50 g of

the isomeric mixture of epoxides of ester 8 and 7.25 g of tryptamine in 20 mL of ethanol was heated at reflux for 7 h under N_2. After removing the ethanol, the isoquinuclidone synthesis was completed in the usual manner (see above).[1] The crude product was taken up in ethyl acetate–methylene chloride (1:4) and chromatographed on Woelm silica gel to give 2.87 (23%) of lactam **15** as an off-white solid which was homogeneous to TLC.[21] Recrystallization from a small volume of methanol gave white crystals: mp 163–164 °C; NMR 0.84 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.26 (m, 1 H, CHCO), 2.85 (m, 2 H, $ArCH_2$), 3.30–3.64 (br m, 3 H, $CHOH$, NCH_2), 3.91 (m, 1 H, NCH), 5.00 (d, J = 2.7 Hz, 1 H, $CHOH$), 7.29, (br m, 5 H, ArH). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.86; H, 7.78; N, 8.92.

2-(2-Indol-3-ylethyl)-3-oxo-6-*endo*-hydroxy-7-*endo*-ethyl-2-azabicyclo[2.2.2]octane (15) and 2-(2-Indol-3-ylethyl)-3-oxo-6-*endo*-hydroxy-7-*exo*-ethyl-2-azabicyclo[2.2.2]octane (5). The reaction of the mixture of epoxides derived from esters 4 and 8 with tryptamine was carried out as described above for the preparation of lactam **15**. From 1.52 g of epoxides and 1.45 g of tryptamine there was obtained a dark brown viscous gum which was taken up in CH_2Cl_2, and the dark brown solution washed with water, dilute HCl, and water. After drying the solvent was removed to leave a brown gum which partially crystallized on tritration with ethyl acetate. Recrystallization from ethyl acetate gave 0.405 g (16%) of a mixture, which from the relative heights of the ^{13}C NMR peaks contained 53% of **5** and 47% of **15**. The brown gum obtained on evaporation of the mother liquors was dissolved in ethyl acetate and chromatographed on Woelm silica gel. Elution with the same solvent gave an additional 0.238 g (9%) of the lactam mixture. Recrystallization from ethyl acetate gave a mixture of lactams, mp 126–128 °C, which appeared homogeneous to TLC, the composition of which was unchanged on repeated recrystallization from ethyl acetate, methanol, or aqueous methanol. In another run, using an incompletely equilibrated mixture of epoxides, a mixture containing 63% of **15** and 37% of **5** was obtained which had mp 143–147 °C after recrystallization from ethyl acetate, followed by aqueous methanol. Kuehne and Reider report mp 144–145 °C for a mixture of these lactams of unspecified composition. The ^1H NMR spectra (90 MHz) of these mixtures were indistunguishable from those of pure lactam **15**. The ^{13}C NMR spectra are reported in Table I.

2-(2-Indol-3-ylethyl)-3-oxo-6-*endo*-(tosyloxy)-7-*exo*-ethyl-2-azabicyclo[2.2.2]octane (3). To a chilled solution of 0.120 g of a mixture of lactams **5** (53%) and **15** (47%) in 1 mL of dry pyridine was added 0.08 g of freshly recrystallized *p*-toluenesulfonyl chloride. The mixture was stored at 7 °C for 25 h, poured into ice water, and extracted with three portions of CH_2Cl_2. The combined extracts were washed successively with water, ice cold dilute HCl, and brine and the solvent removed in vacuo at 25 °C to leave a pale tan solid. Recrystallization from methanol gave 0.048 g (54% based on lactam **5**) of off-white crystals: mp 155–157 °C (reported[3] mp 156–157 °C) which were homogeneous to TLC: ^1H NMR ($CDCl_3$) 0.82 (t, J = 6.6 Hz, 3 H, CH_3CH_2), 2.38 (s, 3 H, $ArCH_3$), 2.91–3.47 (m, 4 H, $ArCH_2CH_2N$), 4.20 (m, 2 H, NCH, CHOTs), 7.08–8.34 (m, 9 H, ArH); ^{13}C NMR ($CDCl_3$), 11.2, 21.6, 24.3, 27.0, 30.4, 30.8, 32.3, 38.0, 46.4, 59.6, 76.3, 111.4, 112.3, 118.6, 119.4, 121.9, 122.0, 127.4, 127.6, 129.9, 133.5, 136.5, 145.0, 174.2.

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(21) Since it was determined that this material was not a precursor to ibogamine, no effort was made to improve the yield of this preparation.

A Synthesis of Ibogamine

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A synthesis of ibogamine was developed by elaboration of 5-carbomethoxy-3-ethylcyclohexene. The latter was obtained as a 1:1 epimeric mixture from condensation of diethyl (2-ethyl-3-oxopropyl)malonate with triphenylvinylphosphonium bromide, followed by hydrolysis, decarboxylation, and esterification.

The iboga alkaloids, with a characteristic fused indoloazepine–isoquinuclidine ring system, exemplified by ibogamine (**1**), have offered a synthetic challenge to organic chemists since their structure elucidation.[1] While chemically intriguing, this class of alkaloids is also of interest because of an inherent pharmacological activity.[2] Thus the central nervous activity of ibogamine (**1**) parallels that of ibogaine (10-methoxy-**1**), which is utilized by African natives for alerting and sleep and hunger combating effects, and for relief of fatique under stress, as well as for generation of a euphoric or wild state in ritual ceremonies, as documented since the last century.[3] The role of catharanthine (16-carbomethoxy-Δ^{15-20}-**1**) as a synthetic and biosynthetic precursor of anhydrovinblastine and the clinically valuable antineoplastic vinblastine[4-8] provided further attraction to this class of alkaloids in the context of our research program, which is directed at indole alkaloids of pharmacologic and medicinal interest.

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