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.

Acknowledgment. The early stages of this work were supported in part by Grant NB-04589 from the National Institutes of Health. We thank Fred J. Matthews and William H. Balke for assistance in obtaining the 90-MHz ^1H and ^{13}C NMR spectra. The JEOL FX-90Q NMR spectrometer was obtained through an NSF Support of Research Equipment Grant. We also thank Dr. Martin E. Keuhne and Dr. Paul J. Reider for an open exchange of information concerning their work and for determining the 250-MHz NMR spectra of lactams **3** and **15**.

(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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Received October 30, 1984

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.

(1) Taylor, W. I. *J. Am. Chem. Soc.* **1957**, *79*, 3298.
(2) (a) Raymond-Hamet, *C.R. Seances Soc. Biol.* **1940**, *133*, 426. (b) Raymond-Hamet *Arch. Intern. Pharmacodyn.*, **1939**, *63*, 27. (c) Schneider, J. A.; Sigg, E. B. *Ann. N.Y. Acad. Sci.* **1957**, *66*, 765.
(3) (a) Baillou, H. *Bull. Mens. Soc. Linn. Lyon* **1869**, *1*, 782. (b) Dybowski, J.; Landrin, A. *C. R. Acad. Sci.* **1901**, *133*, 748. (c) Landrin, A. *Bull. Sci. Pharmacol.* **1905**, *11*, 319.
(4) (a) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670. (b) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.
(5) (a) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639. (b) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858.
(6) (a) Atta-ur-Rahman; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2651. (b) Atta-ur-Rahman *J. Chem. Soc. Pak.* **1979**, *1*, 81.
(7) (a) Scott, A. I.; Gueritte, F.; Lee, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 6253. (b) Baxter, R. L.; Dorschel, C. A.; Lee, S. L.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1979**, 257.
(8) Stuart, K. L.; Kutney, J. P.; Honda, T.; Worth, R. B. *Heterocycles* **1978**, *9*, 1391, 1419.

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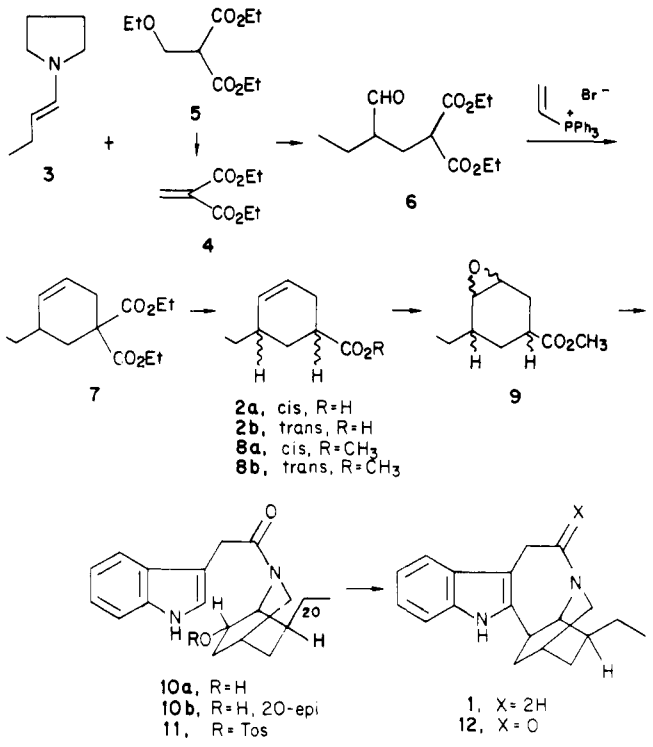
Scheme I



In the most frequently used fundamental strategy of otherwise very diverse syntheses of the iboga alkaloid skeleton, *N*-β-[3[1]-indolylethyl]isoquinuclidines were generated first and followed by cyclization of those intermediates with formation of the hydroazepine ring. This strategy was used by Huffman in a synthesis of desethylibogamine,[9] and by Büchi in syntheses of ibogamine and 20-epiibogamine,[10] as well as in later syntheses by Nagata and Trost.[11,12] An isoquinuclidine is also the initial intermediate of the Ban synthesis,[13] which proceeds by subsequent elaboration to a tricyclic hydroazepinone and a final Fischer indole synthesis.[14] In these syntheses, the isoquinuclidine moiety was generated either by bridging of 4-substituted cyclohexenes or by Diels–Alder additions to dihydropyridines.[15] Since others[10,13,20,21] and we had found the latter approach to be burdened by poor yields (a problem only recently solved)[19,22] we also explored the apparent simplicity of conversion of cyclohexene precursors to ibogamine (**1**).

The clarity of the Huffman route from 3-cyclohexenecarboxylic acid to desethylibogamine[9] was hazed only by a lack of the required *cis*-5-ethylcyclohex-3-enecarboxylic acid (**2a**) starting material. A Diels–Alder reaction of 1,3-hexadiene with methyl acrylate typically results in an undesired 4:21 ratio of 3,5:3,4-substituted cyclohexene products. Although, we found that when *tert*-butyl acrylate was used, a 4:6 ratio of these isomeric products could be obtained;[23] this improvement still seemed inadequate.

We therefore decided to synthesize a cyclohexenecarboxylic acid **2** by the reaction sequence shown in Scheme I. Alkylation of 1-pyrrolidinobutene (**3**) with diethyl methylenemalonate (**4**), which was introduced directly, or more simply as its less sensitive synthetic precursor, the diethyl (ethoxymethyl)malonate (**5**), provided the aldehyde diester **6**. A following condensation of the anion of this malonyl aldehyde **6** with triphenylvinylphosphonium bromide was optimized by addition of the diester to a mixture of sodium hydride and the vinylphosphonium salt. The resulting cyclohexenyl diester **7** could then be decarboethoxylated by its reaction with potassium cyanide in dimethyl sulfoxide (76%) and the consequent monoester product hydrolyzed (97%) to a corresponding carboxylic acid **2**. Alternatively, this acid was obtained from hydrolysis of the diester **7** (98%), followed by thermal monodecarboxylation (100%). A methyl ester product **8** was prepared by esterification of the acid **2** with methanol and BF_3.

While initial 100-MHz NMR spectra and GLC analysis of the cyclohexenecarboxylic ester product **8** did not allow recognition of a stereoisomeric mixture, this was revealed by subsequent availability of better instrumentation. The presence of two distinguishable ethyl substituents in a 1:1 ratio could be seen in a 250-MHz spectrum and capillary gas chromatography, coupled with mass spectrometry, confirmed a 1:1 mixture of stereoisomeric esters. While this isomeric mixture was not altered by sodium methoxide in methanol for two days at 20 °C nor on treatment with 0.3 equiv of lithium diisopropylamide in tetrahydrofuran for 2 days at 20 °C, a small increase of the trans vs. cis isomer (1.2:1.0) of this ester product **8** was found after one week of reflux with 1% sodium methoxide in methanol (with some destruction of the compounds).

Epoxidation of the, preparatively inseparable, 1:1 mixture of 5-carbomethoxy-3-ethylcyclohexenes **8** with *m*-chloroperbenzoic acid furnished, in 80% yield, a mixture of stereoisomeric epoxides **9**. Three isomeric fractions could be seen by GC-mass spectrometry, in a ratio of 34:28:38.

Epoxidation of 4-carbomethoxycyclohexene had been found to give predominantly a trans ester epoxide product.[9] Assuming that π interaction of the axial carbomethoxy and olefin functionalities in 4-carbomethoxycyclohexene is responsible for this selective trans epoxidation, one might expect that such an interaction and its directive effect would be diminished with 1,3-*cis*-carbomethoxy and ethyl substituents in **8a**.[24] With superposition of some stereo-

(9) Huffman, J. W.; Rao, C. B. S.; Kamiya, T. *J. Am. Chem. Soc.* **1965**, *87*, 2288; *J. Org. Chem.* **1967**, *32*, 697.
(10) Büchi, G.; Coffen, D.; Koesis, K.; Sonnet, P.; Ziegler, F. E. *J. Am. Chem. Soc.* **1965**, *87*, 2073.
(11) Nagata, W.; Hirai, S.; Kawata, K.; Aoki, T. *J. Am. Chem. Soc.* **1967**, *89*, 5046. Nagata, W.; Hirai, S.; Kawata, K. *Ibid.* **1968**, *90*, 1650; *Chem. Commun.* **1968**, 1016.
(12) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.
(13) Ban, Y.; Wakamatsu, T.; Fugimoto, Y.; Oishi, T. *Tetrahedron Lett.* **1968**, 3383.
(14) The same tricyclic hydroazepinone intermediate was generated in an alternative route: Sallay, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 6762.
(15) An alternative route to isoquinuclidines, by elaboration of dihydropyridines, was reported [Imanishi, T.; Yagi, N.; Shin, H.; Hanaoka, M. *Tetrahedron Lett.* **1981**, *22*, 4001] in a recent ibogamine synthesis. Other synthetic schemes for the iboga alkaloid skeleton were also also developed.[16-22]
(16) Rosenmund, P.; Haase, W. H.; Bauer, J.; Frische, R. *Chem. Ber.* **1975**, *108*, 1871.
(17) (a) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1964**, *86*, 2286, 2287. (b) *Ibid.* **1970**, *92*, 1708. (c) Kutney, J. P.; Brown, R. T.; Piers, E. *Can. J. Chem.* **1963**, *43*, 1545.
(18) Atta-ur-Rahman; Beisler, J. A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063.
(19) Sundberg, R. J.; Bloom, J. D. *Tetrahedron Lett.* **1978**, 5157.
(20) Marazano, C.; LeGoff, M.-T.; Fourney, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Comun.* **1981**, 389.
(21) Kutney, J. P.; Karton, Y.; Kawamura, W.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 1269.
(22) Studies in this group by W. G. Bornmann and W. G. Earley.
(23) Saavedra, J. E. Ph.D. Thesis, 1974.
(24) π-Interaction of a carbonyl substituent and the olefinic function in 4-substituted cyclohexenes has been noted to result in decreased chemical reactivity of both functionalities. Such interaction requires an axial carbonyl group substituent: (a) Kugatova-Shemyakina, G. P.; Ovchinnikov, Yu, A. *Tetrahedron* **1962**, *18*, 697. (b) Kugatova-Shemyakina, G. P.; Nikolaev, G. M.; Andreev, V. M. *Ibid.* **1967**, *23*, 2721.

direction of this epoxidation by the ethyl substituent, specific assignment of the three detectable epoxide fractions to any of the four possible epoxide structures of **9** would then be very speculative.

When the mixture of epoxides **9** was heated in ethanol with tryptamine and when the uncharacterized amino alcohol products were subsequently heated at 210–220 °C, a crystalline hydroxy lactam product (**10**) was obtained in 48% yield (mp 140 °C, recrystallized mp 145–146 °C). While this product again initially appeared to be homogeneous (TLC, and 100-MHz NMR spectrum), a later 250-MHz spectrum indicated that it was also an ethyl epimeric mixture with a product ratio of about 1.2:1.0 (at mp 140 °C), as seen from two corresponding ethyl CH_3 triplets.

On reaction of the initial crystalline alcohol mixture **10** with tosyl chloride in pyridine, a crystalline tosylate product **11** was obtained in 85% yield. Even after recrystallization this product still contained about 25% of a minor isomeric component, resulting again in a duality of NMR ethyl signals, which could barely be seen in an unexpanded 250-MHz spectrum, but was nicely analyzed on spectrum expansion.

Cyclization of this β-ethyl enriched tosylate **11** with aluminum chloride in toluene at 100 °C now provided 5-oxoibogamine **12** in 42% yield. In the isolated crystalline product none of the C20 epimeric ethyl product could be seen by 250-MHz NMR nor by HPLC analysis. For comparison, one enantiomer of this racemic compound was prepared by oxidation of natural ibogamine.[25] Reduction of the synthetic ibogamine lactam **12** with lithium aluminum hydride then provided racemic ibogamine in 72% yield.

While this ibogamine synthesis was completed in 1978,[26] its report at that time would have indicated a completely stereoselective synthetic pathway, based on the evidence collected then. The available analytical instrumental methods did not resolve the isomeric products, which were actually obtained. Prudent reserve, prompted by lack of high yields in the final stages of the synthesis, however, let us delay publication until the present use of more high powered instrumentation became possible.

Experimental Section

Diethyl (2-Ethyl-3-oxopropyl)malonate (6). Method 1. A solution of 8.00 g (46.5 mmol) of diethyl methylenemalonate[27,28] in 12 mL of acetonitrile was added to a solution of 7.50 g (60.0 mmol) of 1-pyrrolidino-1-butene[29] in 38 mL of acetonitrile at 5 °C. The reaction mixture was stirred overnight at room temperature and then a solution of 3.5 mL of acetic acid in 20 mL of water was added. After stirring at 25 °C for 6 h, the two-phase system was saturated with sodium chloride and the layers were separated. The aqueous phase was extracted with 3 × 50 mL of ether and the combined organic solutions were washed with 2 × 40 mL of saturated brine, dried over $MgSO_4$, and concentrated to provide 14 g of crude product, which was purified by filtration through Florasil with ether and distillation at 110 °C (0.01 mm).

Method 2. A solution of 0.40 mL (2.7 mmol) of diethyl (ethoxymethyl)malonate[28] in 1.5 mL of acetonitrile was added to 1-pyrrolidino-1-butene (0.50 mL, 2.50 mmol) in 1.5 mL of acetonitrile. The reaction mixture was stirred at 25 °C for 17 h, then 1 mL of 30% aqueous acetic acid was added, and stirring continued for 5 h. The mixture was partitioned between water and ether and the ether extract dried ($MgSO_4$), concentrated, and distilled (120 °C Kugelrohr, 0.01 mm) to give 411 mg (67%) of product: 100-MHz NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.29 (t, 6 H), 1.68 (q, 2 H), 1.88–2.48 (m, 3 H), 3.48 (dd, 1 H), 4.28 (q, 4 H), 9.83 (m, 1 H); IR (neat) ν_{max} 2985, 2948, 2880, 2815, 2700, 1740, 1470, 1450, 1375, 1305, 1230, 1160, 1100, 1040 cm^{-1}.

Diethyl 5-Ethylcyclohex-3-ene-1,1-dicarboxylate (7). To a suspension of 16.4 g (44.5 mmol) of triphenylvinylphosphonium bromide in 50 mL of dry tetrahydrofuran was added 1.10 g (45.7 mmol) of sodium hydride (from a 50% in oil suspension, washed with petroleum ether). After stirring for 15 min at 20 °C, 10.0 g (41.0 mmol) of the malonate **6** in 50 mL of dry tetrahydrofuran was added dropwise, over 2 h. The resulting suspension was heated at reflux for 1 h, cooled, and filtered through Celite. Concentration and trituration of the residue with ether allowed removal of crystallized triphenylphosphine oxide by filtration. After concentration of the filtrate and repetition of this process, the residue was distilled to give 6.38 g (61%) of diester **7**: bp 88–90 °C (0.01 mm); 100-MHz NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.24 (t, 6 H), 1.12–1.72 (m, 4 H), 244 (m, 3 H), 4.26 (q, 4 H), 5.72 (brd s, 2 H); IR (film) ν_{max} 3010 (w), 2950 (m), 1732 (s), 1465 (m), 1445 (w), 1245 (s), 1182 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.38; H, 8.74.

***cis*- and *trans*-Ethyl 5-Ethylcyclohex-3-ene-1-carboxylates.** A solution of 300 mg (1.18 mmol) of the diester **7**, 77 mg (1.18 mmol) of potassium cyanide, and two drops of water in 5 mL of dimethyl sulfoxide was heated at reflux for 6 h. The cooled reaction mixture was diluted with water and extracted with dichloromethane. The extract was concentrated under vacuum (15 mm), mixed with hexane, and washed with water and saturated brine. The dried ($MgSO_4$) hexane solution was concentrated and distilled at a heating block temperature of 96–98 °C (15 mm) or 119–121 °C (40 mm) to give 164 mg (76%) of an ethyl ester: mass spectrum, m/z 182; 100-MHz NMR ($CDCl_3$) 0.95 (t, 3 H), 125 (t, 3 H), 4.15 (q, 2 H), 5.67 (m, 2 H); IR (film) ν_{max} 3020 (w), 2970 (m), 2940 (m), 2875 (w), 1735 (s), 1660 (w), 1160 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.25; H, 9.78.

***cis*- and *trans*-5-Ethylcyclohex-3-ene-1-carboxylic Acids (2a,b). Method A.** The diester **7** (3.00 g, 25.4 mmol) and 2.00 g (35.7 mmol) of potassium hydroxide in 10 mL of water were heated at reflux for 8 h. The cooled solution was acidified to below pH 4 and partitioned between water and ether. The organic extract was washed with saturated brine, dried ($MgSO_4$), and concentrated to 2.30 g (98%) of a crystalline diacid, mp 115 °C. When this product was heated to 165 °C (10 mm) smooth decarboxylation gave a quantitative yield of distilled epimeric monoacids, identical with the product described below.

Method B. A mixture of the epimeric ethyl 5-ethylcyclohex-3-enecarboxylates (260 mg, 1.43 mmol) and 500 mg (1.59 mmol) of barium hydroxide octahydrate, in 15 mL of water, was heated at reflux for 3 h, then cooled, and acidified. Partitioning between water and ether, concentration of the organic extracts, and distillation at 64 °C (Kugelrohr, 0.005 mm) gave 215 mg (97%): 100-MHz NMR ($CDCl_3$) 0.90 (t, 3 H), 1.25 (q, 2 H), 5.57 (m, 2 H), 11.90 (s, 1 H); IR (film) ν_{max} 3018, 2965, 2910, 2845, 1700, 1655, 1455, 1420 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.37; H, 9.05.

***cis*- and *trans*-Methyl 5-Ethylcyclohex-3-ene-1-carboxylates (8a,b).** A solution of 1.69 g (11.0 mmol) of the corresponding epimeric acids obtained above and 2 mL of 50% boron trifluoride methanol complex in 18 mL of methanol was heated at reflux for 18 h.

The cooled mixture was partitioned between water and ether and the extracts were washed with saturated $NaHCO_3$ solution and brine. The dried (Na_2SO_4) solution was concentrated and distilled at 45 °C (0.003 mm) to give 1.58 g (86%) of esters **8**. GC–mass spectrum, m/z (relative abundance) 168 (M^+, 15), 137 (9), 136 (23), 110 (5), 109 (65), 108 (46), 107 (7), 93 (17), 81 (8), 80 (14), 79 (100), 78 (12), 77 (27), 67 (46), 65 (6), 59 (13), 55 (12), 53 (10), 51 (7) for both epimeric fractions, which showed relative retentions of 12 and 13 min for the trans and cis epimers and a respective ratio of 0.95 on a 30-m SE 54 silica capillary column at 90 °C: 250-MHz NMR ($CDCl_3$) δ 0.93 (t, 0.51 × 3 H), 0.94 (t, 0.49 × 3 H), 1.22–1.44 (m, 2.5 H), 1.74–1.94 (m, 1.5 H), 2.04–2.19 (m, 2 H), 2.22–2.27 (m, 1 H), 2.57–2.66 (m, 1 H), 3.70 (s, 3 H), 5.59–5.68 (m, 2 H); IR (film) ν_{max} 3015, 2955, 2920, 2870, 2850,

(25) Bartlett, M. F.; Dickel, D. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1958**, *80*, 126.
(26) Reider, P. J. Ph.D. Thesis, 1978.
(27) Bachman, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 500.
(28) Feely, W.; Boekelheide, V. "Organic Syntheses"; Wiley: New York, 1963; Vol. IV, p 298.
(29) Stork, G.; Brizzolara, A.; Landesman, H. K.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

1730, 1645, 1450, 1435, 1185 cm^{-1}. When a sample of this epimeric mixture was stirred with 0.3 equiv of lithium diisopropylamide in dry tetrahydrofuran or with 1 equiv of sodium methoxide in methanol, each at 20 °C for 2 days, the epimeric ratio was not changed. However, a sample kept at reflux for 7 days in a 1% sodium methoxide in methanol solution showed an epimeric ratio of 1.2:1.0 of the GC faster moving trans to the cis epimer.

Methyl 3,4-Epoxy-5-ethylcyclohexanecarboxylates (9). To 1.523 g (9.06 mmol) of the epimeric esters **8**, dissolved in 10 mL of dichloromethane, was added 2.00 g (14.4 mmol) of *m*-chloroperbenzoic acid at 0 °C.

After 20 h at 20 °C a saturated solution of Na_2SO_3 was added and the mixture was poured into chloroform. The separated organic phase was washed with saturated $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated under vacuum. Tube distillation (oven 50–60 °C) at 0.001 mm gave 1.337 g (80%) of a mixture of stereoisomeric epoxides; 100-MHz NMR ($CDCl_3$) δ 1.00 (t, 3 H), 3.20 (d, 2 H), 3.70 (s, 3 H); GC–mass spectrum with a 30-m SE 54 silica capillary column, showed three fractions in a ratio of 34:28:38, with relative retention times of 39, 43.5, and 45 min at 60 °C or 8.5, 10.3, and 11.0 min at 120 °C, which had identical fragmentation patterns except for a somewhat reduced fragment peak at 107 for the later fractions: *m/z* (relative intensity) 184 (M^+, 0.6), 169 (7), 155 (20), 125 (35), 124 (41), 115 (13), 109 (15), 107 (31 or 17) 100 (22), 97 (10), 96 (17), 95 (34), 91 (10), 87 (17), 83 (29), 81 (38), 79 (32), 77 (12), 71 (17), 70 (15), 69 (35), 68 (24), 67 (54), 65 (11), 59 (38), 57 (22), 56 (10), 55 (100), 54 (17), 53 (32). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.44; H, 8.67.

2-(2-Indol-3-yl-1-oxoethyl)-6-*endo*-hydroxy-7-ethyl-2-azabicyclo[2.2.2]octanes (10a,b). A solution of 390 mg (3.06 mmol) of tryptamine and 564 mg (3.06 mmol) of the stereoisomeric epoxides **9** in 3 mL of ethanol was heated at reflux for 12 h and then concentrated under vacuum. The residue was heated at 210–220 °C for 3.5 h, then cooled, and heated at reflux with 5 mL of methanol and 3 mL of 10% aqueous NaOH for 1 h. Concentration and partitioning of the residue between dichloromethane and successive portions of water, 5% HCl, and brine and concentration of the dried (Na_2SO_4) extract gave 444 mg (48%) of a white foam with TLC (silica, 1:1 $CHCl_3$:acetonitrile) R_f 0.41 for a major component and R_f 0.58 for a minor component. Crystallization from ethyl acetate and hexane gave a sample with mp ≈140 °C, recrystallized to 145–146 °C: mass spectrum, *m/z* (relative intensity) 312 (M^+, 23), 182 (13), 144 (47), 143 (100), 130 (48), 57 (21), 55 (22), 43 (48); IR (KBr) ν_{max} 3320, 2960, 2930, 2875, 1625, 1480, 1455, 1432, 1091, 1073, 745 cm^{-1}; 250-MHz NMR ($CDCl_3$ on sample mp 140 °C) δ 0.85 and 0.91 (two t, 1:1.3, 3 H), 1.21–1.45 (m, 3 H), 1.60–1.80 (m, 2 H), 1.93–2.36 (m, 3 H), 2.45–2.55 (m, 1 H), 3.03 (t, 2 H), 3.27–3.33 (m, 1.5 H), 3.62–3.88 (m, 1.5 H), 3.95–4.15 (m, 1 H), 7.06–7.25 (m, 3 H), 7.37 (d, 1 H), 7.64 (d, 1 H), 8.02 (s, 1 H). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.19; H, 7.63; N, 8.80.

2-(2-Indol-3-yl-1-oxoethyl)-6-*endo*-(tosyloxy)-7-*exo*-ethyl-2-azabicyclo[2.2.2]octane (11a). A solution of 222 mg (0.71 mmol) of the hydroxide **10** in 1 mL of pyridine was cooled to 0 °C and 135 mg (0.71 mmol) of *p*-toluenesulfonyl chloride added. After 2 h at 0 °C, 60 h at −25 °C, and 2 h at 20 °C, the reaction mixture was poured into 15 mL of iced water and extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), and concentrated to 291 mg (85%) of crude tosylate. Crystallization from methanol gave a sample with mp ≈148 °C which showed about 25% contamination by the 7-*endo*-ethyl epimer by NMR δ 0.86 (t, 0.25 × 3 H). A recrystallized sample had mp 156–157 °C: TLC (silica, 1.4:1 chloroform:acetonitrile) R_f 0.8; IR (KBr) ν_{max} 3260, 3060, 2960, 2920, 2873, 1655, 1579, 1455, 1350, 1196, 1185, 963, 866, 740 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.83 (t, 3 H), 1.0–1.50 (m, 4 H), 1.80–2.15 (m, 3 H), 2.39 (s, 3 H), 2.42–2.50 (m, 1 H), 3.00 (t, 2 H), 3.08–3.21 (m, 1 H), 3.43–3.50 (m, 1 H), 4.15–4.28 (m, 2 H), 7.09–7.29 (m, 5 H), 7.36–7.55 (m, 3 H), 7.63 (d, 1 H), 8.09 (s, 1 H). Anal. Calcd for $C_{26}H_{31}N_2O_4S$: C, 66.78; H, 6.68; N, 5.99; S, 6.86. Found: C, 66.71; H, 6.53; N, 5.84; S, 6.98.

5-Oxoibogamine (12). A suspension of 200 mg (0.43 mmol) of the tosylate **11** and 75 mg (0.64 mmol) of aluminum chloride in 20 mL of toluene was heated at 100 °C for 10 h. The cooled mixture was concentrated under vacuum and 25 mL of water was added to the residue. After 2 h the water was decanted and the residue triturated with ethanol to give 52 mg (42%) of the racemic lactam **12**. A sample recrystallized from methanol had mp 265–267 °C. HPLC: Micro Porasil 1 ft column, chloroform:acetonitrile 1.4:1, flow rate 1.5 mL/min, R_t 3.75 min; 250-MHz NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.35–1.56 (m, 3 H), 1.70–2.02 (m, 3 H), 2.19 (dt, 1 H), 2.65 (brd s, 1 H), 2.93–3.06 (m, 1 H), 3.10–3.38 (m, 3 H), 3.98 (s, 1 H at C21), 4.57 (p, 1 H), 7.04–7.19 (m, 2 H), 7.25 (d, 1 H), 7.45 (d, 1 H), 7.75 (s, 1 H). IR (KBr) ν_{max} 3240, 2960, 2935, 2875, 1644, 1618, 1462, 1369, 1330, 1248, 1161 cm^{-1}; IR (film) ν_{max} 3280 (NH), 1655 (CO) cm^{-1}. For comparison, a sample of natural ibogamine was oxidized to the corresponding lactam.[25] The racemic and nonracemic samples showed identical IR and 250-MHz NMR solution spectra and the same HPLC retention times.

***dl*-Ibogamine (1).** A solution of 22 mg (0.070 mmol) of the racemic lactam **12** was dissolved in 1 mL of dry tetrahydrofuran and added dropwise to 0.5 mL (0.5 mmol) of a 1 M solution of lithium aluminum hydride. The mixture was heated at reflux for 6 h and cooled, and 0.02 mL of water was added, followed by 0.02 mL of 15% NaOH and 0.06 mL of water. Filtration and concentration gave 15 mg (72%) of an oily product which corresponded by TLC (silica, 1% methanol in dichloromethane) R_f 0.35 to natural ibogamine. Preparative TLC and crystallization from aqueous ethanol provided a sample with mp 127–129 °C (lit.[10,12,14] mp 126–131 °C).

Acknowledgment. We thank Dr. John W. Huffman for exchange of information and for allowing us to examine his synthetic intermediates, particularly his *trans*-carbomethoxyethylcyclohexene, with our instrumental facilities. We also thank Tim Spitzer of our group for GC–mass spectrometric analyses and we thank the National Cancer Institute for support under Grant CA R01 12010.

Monochlorination of *n*-Alkyl Phenyl Ethers in Micellar Sodium Dodecyl Sulfate

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Received August 28, 1984

The effect of chain length on the regioselectivity and rate of monochlorination of C_6H_5OR (1: **a**, R = *n*-C_5H_{11}; **b**, R = *n*-C_9H_{19}; **c**, R = *n*-$C_{12}H_{25}$) with Cl_2 in micellar sodium dodecyl sulfate was determined. On going from **1a** to **1b** to **1c**, only modest changes were observed in the para/ortho product ratio and in relative rate. These results were interpreted to indicate that the hydrophilic character of C_6H_5O dominates the lipophilic character of R in the micellar reactivity of the ethers.

The ability of dynamic multimolecular surfactant aggregates to control the selectivity of organic reactions has been investigated with several systems.[2] Previously, we reported[3] that for monohalogenation of $C_6H_5OC_5H_{11}$-*n* with

0022-3263/85/1950-1467$01.50/0