Azepinoindoles. II. 1,2,3,4,5,6-Hexahydroazepino[3,2-*b*]indole and 1,2,3,4,5,6-Hexahydroazepino[4,3-*b*]indole

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3,4,5,6-Tetrahydroazepino[4,3-*b*]indol-1(2H)-one and 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one were selectively prepared by Beckmann rearrangements of the oxime and tosyloxy oxime of 1,2,3,4-tetrahydrocarbazol-4-one with polyphosphoric acid and alumina, respectively. The chemistry of these compounds and some of their derivatives was investigated.

Because of our interest in the biological activity of azepinoindoles,[1] we studied the Beckmann rearrangement of 1,2,3,4-tetrahydrocarbazol-4-one oxime (**1**) as a possible route to the 1,2,3,4,5,6-hexahydroazepino-[4,3-*b*]indole (**2**) and 1,2,3,4,5,6-hexahydroazepino-[3,2-*b*]indole (**3**) ring systems. An application of this approach to the preparation of 3,4,5,6-tetrahydroazepino[4,3-*b*]indol-1(2H)-one (**4**) has recently been reported.[2] Preparation of oxime **1** from 1,2,3,4-tetrahydrocarbazol-4-one[3] (**5**) (Scheme I) proceeded to give a good yield of a single, sharp melting product.[4] The nmr spectrum[5a] of this compound had a singlet at 672 cps for the NH, a sharp singlet at 616 cps for the OH, a complex multiplet at 481–419 cps assigned to the aromatic protons, a pair of partially superimposed triplets centered at 169.5 and 164 cps (apparent J = 5.5 cps) assigned to the two sets of methylene protons at C-1 and C-3, respectively, and a poorly resolved quintet centered at 115 cps (apparent J = 5.5 cps) for the C-2 protons. In addition to supporting structure **1**, this spectrum demonstrates that only one of the two possible oxime isomers was obtained. Rearrangement of oxime **1** was initially accomplished by the use of polyphosphoric acid[6] under carefully controlled conditions. By silica gel chromatography of the crude product from this reaction, we obtained one lactam to which structure **4** was assigned based on spectral and chemical evidence. The ultraviolet spectrum (*vide infra*) reflected the influence of the amide carbonyl on the indole chromophore.[7] The infrared spectrum had an amide carbonyl band at 1625 cm^{-1} and the expected NH absorption. The nmr spectrum[5a] was in complete agreement with structure **4**. In particular the amide NH was represented by a triplet centered at 450 cps (apparent J = 5 cps) which was erased by the addition of hydrogen chloride to the sample tube.[8] This absorption distinguishes structure **4** from the isomeric lactam (**6**) since only in the former case can the amide NH be coupled with the hydrogens of an adjacent methylene. Lithium aluminum hydride reduction of **4** proceeded with difficulty when the reaction was carried out in refluxing tetrahydrofuran; the yield of product (**2**) after 15 hr was 7%. When the reaction was carried out in dioxane at 100°, however, a 70% yield of 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indole (**2**) was obtained. The ultraviolet spectrum of **2** was that of a simple 2,3-disubstituted indole and the nmr spectrum[5b] had a singlet at 238 cps for the newly formed methylene at C-1. Methylation of the basic nitrogen to give **7** was achieved, in two steps, by lithium aluminum hydride reduction of the formamide prepared *via* reaction of **2** with formic acetic anhydride.[9]

At the outset of this study we had expected to obtain 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one (**6**) from the rearrangement of oxime **1** which we assumed would have the sterically preferred *anti* configuration[10] by analogy with the α-tetralone and 1-indanone cases.[6,11-13] If the oxime configuration were *anti* as assigned, the seemingly abnormal Beckmann rearrangement of **1** in polyphosphoric acid could be accommodated by postulating an acid-catalyzed rearrangement of the oxime configuration prior to carbon migration (*viz.* A–C, Scheme II) which might be favored over the sterically strained intermediate (D) required for aryl migration.[10] To determine if this were the case we investigated the method of Craig and Naik[14] which had been shown to give good yields of Beckmann products with preservation of the configurational integrity of the oxime during the rearrangement. Thus the *p*-toluenesulfonate of **1** was prepared in pyridine and adsorbed on a column of neutral alumina (Brockmann[15] activity grade I) which had been deactivated by the addition of 1% water. Elution of the column with chloroform gave a moderate yield of one product, 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one (**6**). The infrared spectrum of **6** had a normal amide carbonyl band at 1650 cm^{-1}, a somewhat higher frequency than that observed for **4**.[16] The ultraviolet spectrum (*vide infra*) appeared to be reasonable for **6** although no close analogs are available. The nmr spectrum had two singlets at 638 and 566 cps for the indole NH and the amide proton, respectively, two complex multiplets at 468–459 and 439–408 cps for the aromatic protons, a triplet centered at 179 cps (apparent J = 6.5 cps) assigned to the C-5 protons, and two broad peaks

(1) J. B. Hester, A. H. Tang, H. H. Keasling, and W. Veldkamp, *J. Med. Chem.*, in press.

(2) H.-J. Teuber, D. Cornelius, and U. Wolcke, *Ann.*, **696**, 116 (1966).

(3) G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951).

(4) H.-J. Teuber and D. Cornelius, *Ann.*, **671**, 127 (1964).

(5) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) deuteriodimethyl sulfoxide or (b) deuteriodimethylformamide. The chemical shifts were recorded in cycles per second downfield from tetramethylsilane.

(6) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

(7) J. Szmuszkovicz, *ibid.*, **82**, 1180 (1960).

(8) G. Slomp and J. G. Lindberg, *Anal. Chem.*, **39**, 60 (1967).

(9) E. Shaw, *J. Am. Chem. Soc.*, **76**, 1384 (1954).

(10) Excellent reviews of the Beckmann rearrangement have been presented by P. A. S. Smith in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 457, and by L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(11) R. Huisgen, I. Ugi, H. Brade, and E. Rauenbusch, *Ann.*, **586**, 30 (1954).

(12) P. T. Lansbury and N. R. Mancuso, *J. Am. Chem. Soc.*, **88**, 1205 (1966).

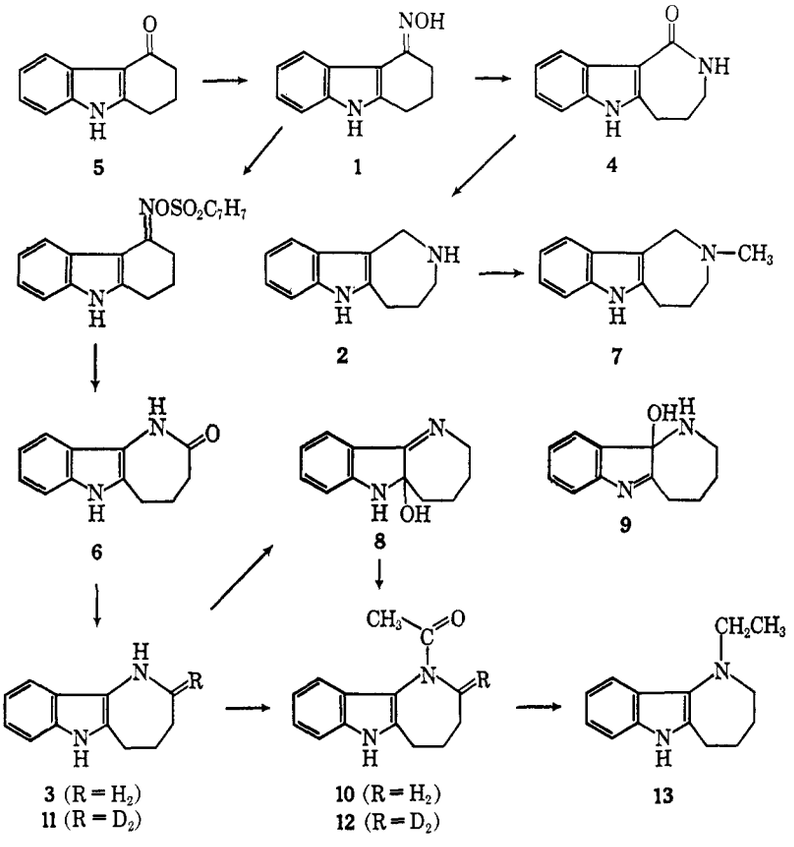
(13) R. T. Conley and L. J. Frainier, *J. Org. Chem.*, **27**, 3844 (1962).

(14) J. C. Craig and A. R. Naik, *J. Am. Chem. Soc.*, **84**, 3410 (1962).

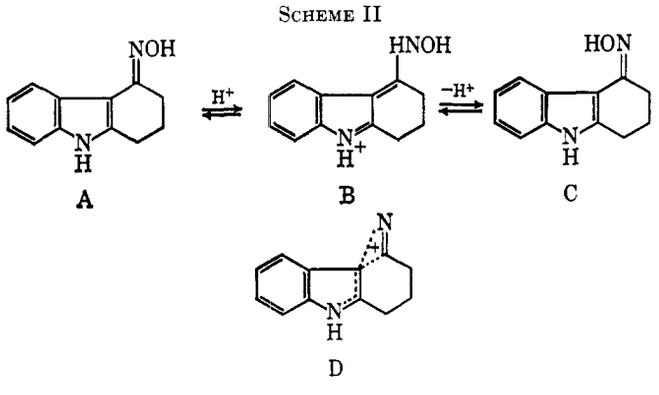
(15) H. Brockmann and H. Schodder, *Chem. Ber.*, **74**, 73 (1941).

(16) *Cf.* D. R. Liljegren and K. T. Potts, *J. Org. Chem.*, **27**, 377 (1962).

SCHEME I



SCHEME II



centered at about 150 and 125 cps for the C-3 and C-4 protons, respectively. Lithium aluminum hydride reduction of **6** followed by careful work-up under nitrogen gave the white crystalline amine (**3**) in 61% yield. The nmr spectrum[5b] of **3** had a broad multiplet at 458–410 cps assigned to four aromatic protons and broad peaks centered at about 602, 274, 185, and 104 cps assigned to one proton on N-6, one proton on N-1, four protons on C-2 and C-5, and four protons on C-3 and C-4, respectively.

In ethyl acetate solution air oxidation of this amine (**3**) occurred rapidly at ambient temperature to give a compound to which we have assigned structure **8**. This structure is analogous to structures proposed for similar oxidation products of 1-substituted 2-phenyl-3-aminoindoles.[17,18] Compound **8** is a bright yellow, highly insoluble material which has an ultraviolet spectrum [λ_{max}^{EtOH} 234 and 380 mμ (ε 20,000 and 3365, respectively)] that is compatible with its pseudo-indoxyl-like structure and precludes the alternate possibility (**9**).[19] Compare, for example, the ultraviolet spectrum of spiro(cyclopentane-1,2′-indoxyl) [λ_{max}^{EtOH} 233 and 395 mμ (ε 26,900 and 4680, respectively)][20] with that of 1,2,3,4-tetrahydro-11-methylcarbazoline [λ_{max} 255 mμ (ε 7030)].[21] The infrared spectrum of **8** had NH–OH absorption at 3310, 2700, and 2540 cm^{-1} and an imine band at 1650 cm^{-1}. The mass spectrum had a molecular ion *m/e* 202 with a primary fragmentation peak at *m/e* 184, indicating loss of water from the molecular ion. Owing to solubility problems, the nmr spectrum was of little value. If structure **8** is correct, catalytic reduction should regenerate the original amine (**3**) either by reduction of the imine followed by elimination of water or by hydrogenolysis of the carbinol amine followed by double-bond tautomerization. When such a reduction was carried out in acetic anhydride using a platinum oxide catalyst, the acetamide (**10**) obtained was identical with that obtained by treating a pyridine solution of **3** with acetic anhydride. The infrared spectrum of **10** had an amide carbonyl band at 1620 cm^{-1} and the expected NH absorption at 3150 and 3100 cm^{-1}. The ultraviolet spectrum was similar to that of **6**. The nmr spectrum[5a] had a singlet at 662 cps for the indole NH, a complex multiplet at 418–447 cps for the four aromatic protons, a triplet centered at 171 cps (apparent J = 5 cps) as-

(17) Huang-Hsinmin and F. G. Mann, *J. Chem. Soc.*, 2903 (1949).
(18) C. W. Bird, *ibid.*, 3490 (1965).
(19) Since the ultraviolet spectrum of **8** (*vide infra*) is essentially the same in both polar (ethanol) and nonpolar (methylene chloride, dioxane) solvents, it is not likely that the observed spectrum is due to the dehydration of **9**, in solution, prior to the spectral determination.
(20) E. E. van Tamelen, K. V. Siebrasse, and J. B. Hester, *Chem. Ind.* (London), 1145 (1956).
(21) G. F. Smith and J. T. Wróbel, *J. Chem. Soc.*, 792 (1960).

signed to the two C-5 hydrogens, a sharp singlet at 112 cps for the C-methyl protons of the acetamide, and a broad absorption under the C-methyl peak at about 120–71 cps assigned to the four hydrogens of C-3 and C-4. The remaining methylene protons (C-2) formed the MX portion of an A_2MX pattern. One of these protons was represented by a pair of triplets centered at 282.5 cps (apparent J_{MX} = 13 cps; apparent J_{A_2X} = 3 cps) and the other by a broad absorption under the solvent peak which was centered at 151 cps. The suggested coupling was verified by a spin decoupling experiment.[5a] Thus, irradiation of the sample at a frequency 128 cps upfield from the 282.5-cps absorption resulted in a collapse of the hextet to a broad singlet indicating that the second C-2 proton absorption was centered at about 154 cps. Irradiation at 169 cps upfield from the 282.5-cps absorption eliminated the A_2 coupling and gave a doublet; thus the C-3 proton absorption which must form the A_2 portion of the A_2MX system is centered 169 cps upfield from that of the X proton or 113.5 cps downfield from tetramethylsilane. To confirm our interpretation of this spectrum, lactam **6** was reduced with lithium aluminum deuteride and without isolation the resulting amine (**11**) was acylated to give **12**. The nmr spectrum[5b] of **12** was essentially the same as that[5b] of **10** except the peaks assigned to the C-2 protons of **10** were absent.

Dreiding models of **10**, assuming a trigonal amide nitrogen (owing to electron delocalization between the nitrogen and carbonyl oxygen) show that the azepine ring may assume either a rigid chair or a flexible boat conformation.[22] In this case the boat conformation appears to be of somewhat higher energy than the chair conformation by approximately one eclipsed interaction. The C-2 protons in the boat conformation are not equivalent and could be equilibrated only by a rapid conformational flip involving serious steric interactions between the axial C-2 and C-5 protons as well as between the acetamide moiety and the C-10 hydrogen. For the chair conformation the C-2 protons are also nonequivalent and could be equilibrated only by conversion of the chair to the boat conformation with the concomitant steric interactions and angle strain. In this rigid conformation the equatorial C-2 hydrogen forms an angle of about 30° with the acetamide moiety and an angle of about 60° with each of the C-3 hydrogens. This conformation could thus explain the observed 282.5-cps absorption assuming a deshielding of the equitorial C-2 proton by the anisotropy cone of the amide carbonyl, a 13-cps coupling with the geminal C-2 axial proton, and a 3-cps coupling with each of the C-3 protons. From the above discussion we would conclude that the azepine ring of **10** would offer considerable resistance to conformational equilibration; this has been verified experimentally. Thus it was found that the nmr spectrum[5a] of **10** was only slightly different at 94° from that observed at ambient temperature; however, when the spectrum[5b] was run at 120° the 292.5-cps absorption appeared as a broad singlet centered at about 283 cps. At 140° this singlet had disappeared although the integral still showed absorption in this region. Evidently complete equilibration of the C-2 protons had not occurred even at this temperature. Recently[23] the nmr study of a series of N-acyl-N-alkylanilines demonstrated the nonequivalence of methylene hydrogens adjacent to nitrogen in molecules with one *ortho* substituent on the benzene ring. In this case the authors proposed that the observed nonequivalence was due to restricted rotation about the phenyl–nitrogen bond. A situation completely analogous to ours has been reported for 4-substituted 1-acetylpiperidines. For 1-acetyl-4-methylpiperidine the equatorial proton *cis* to the amide carbonyl had a chemical shift of 274 cps and the equatorial proton *trans* to the amide carbonyl had a chemical shift of 230 cps. The corresponding axial protons had chemical shifts of 154 and 182 cps, respectively.[24] In this case the chemical shifts for the protons *cis* to the amide carbonyl are in remarkable agreement with those obtained for the C-2 protons of **10** and thus support our conclusions.

Lithium aluminum hydride reduction of **10** gave the amine (**13**) in good yield. The physical properties of this compound were in complete agreement with the proposed structure. In particular the nmr spectrum[5b] had a triplet centered at 67 cps (apparent J = 7 cps) for the C-methyl, a broad peak centered at 109 cps for the four protons on C-3 and C-4, and a broad absorption under the solvent peaks at about 197–161 cps for the remaining aliphatic hydrogens.

Mechanistically the oxidation of **3** may be viewed as the reaction of the amine with oxygen to form hydroperoxide E (Scheme III), a reaction which has many precedents in the literature.[25] Reduction of this hydroperoxide by a second molecule of **3** might then give two molecules of the observed alcohol (**8**). In this regard, it is of interest that the tertiary amine (**13**) is relatively resistant to air oxidation.

Experimental Section[26]

1,2,3,4-Tetrahydrocarbazol-4-one Oxime (1).—A mixture of 1,2,3,4-tetrahydrocarbazol-4-one[3] (4.50 g, 0.0243 mole), hydroxylamine hydrochloride (2.53 g, 0.364 mole), sodium acetate (2.98 g, 0.0364 mole), ethanol (48 ml), and water (21 ml) was refluxed under nitrogen for 4 hr. The cooled mixture was concentrated under reduced pressure and the residue was suspended in water. The crystalline material was collected by filtration, washed with water, and dried under reduced pressure to yield 4.70 g, mp 196° dec, of crude product. This was chromatographed on silica gel (200 g) with 50% ethyl acetate–Skellysolve B. The product was obtained in the first band eluted from the column. It was crystallized from ethyl acetate to yield 3.47 g (71.3%) of 1,2,3,4-tetrahydrocarbazol-4-one oxime, mp 205–209° dec. The analytical sample, mp 208.5–210° dec (lit.[4] mp 208° dec), was prepared by recrystallizing this material several times from ethyl acetate. The ultraviolet spectrum had λ_{max} 226, 262, and 283 mμ (ϵ 22,200, 18,800 and 11,450, respectively).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.19; H, 6.08; N, 14.24.

(22) For conformational analyses of cycloheptane and cycloheptene, see R. Pauncz and D. Ginsburg, *Tetrahedron*, **9**, 40 (1960), and N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

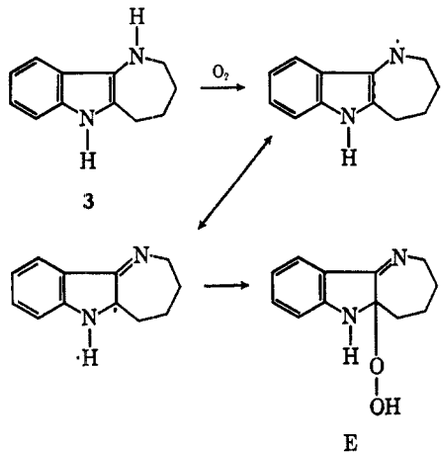
(23) T. H. Siddall, III, and C. A. Prohaska, *ibid.*, **88**, 1172 (1966).

(24) D. M. Lynch and W. Cole, *J. Org. Chem.*, **31**, 3337 (1966).

(25) For a review of autoxidations of this type, see A. G. Davies, "Organic Perioxides," Butterworth and Co. Ltd., London, 1961, pp 27–31.

(26) Melting points were taken in capillary tubes and are corrected. Unless otherwise indicated, ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer. Infrared spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Mass spectra were obtained on an Atlas CH4 spectrometer. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Darco G60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck AG, Darmstadt, Germany.

SCHEME III



3,4,5,6-Tetrahydroazepino[4,3-*b*]indol-1(2H)-one (4).—A stirred mixture of powdered 1,2,3,4-tetrahydrocarbazol-4-one oxime (2.21 g, 11.0 mmoles) and polyphosphoric acid (70 g) was heated, under nitrogen, in an oil bath, maintained at 102–112°, for 10 min. It was then cooled and poured into a stirred mixture of ice and water. The polyphosphoric acid was hydrolyzed as rapidly as possible and the resulting solid was collected by filtration and washed with water and dilute ammonium hydroxide. A methanolic solution of this material was decolorized with Darco G 60 and the product was crystallized from methanol–ethyl acetate to yield 0.889 g (40.3%) of 3,4,5,6-tetrahydroazepino[4,3-*b*]indol-1-(2H)-one, mp 200–217° dec. This material was chromatographed on silica gel (50 g) with 20% methanol–ethyl acetate. The product thus obtained was crystallized several times from methanol for analysis. The sample had mp 219–220° with sintering at 100° (lit.[2] mp 210°). For analysis the sample was finely ground and dried at 80°. The ultraviolet spectrum had λ_{max} 216, 230, 253, 281, and 288 mμ (ε 37,050, 18,050, 8200, 10,000, and 9600, respectively). The infrared spectrum showed NH 3320 and 3280 cm^{-1} and C=O 1625 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.25; H, 6.14; N, 13.76.

1,2,3,4,5,6-Hexahydroazepino[4,3-*b*]indole (2). A.—3,4,5,6-Tetrahydroazepino[4,3-*b*]indol-1(2H)-one (1.0 g, 5.0 mmoles) was added to a stirred, ice-cold suspension of lithium aluminum hydride (1.5 g) in dry tetrahydrofuran (150 ml) and the resulting mixture was refluxed, under nitrogen, for 15 hr. It was then cooled in an ice bath and treated successively with water (1.5 ml), 15% sodium hydroxide (1.5 ml), and water (4.5 ml). The solid was collected by filtration and washed with tetrahydrofuran. Concentration of the combined filtrates yielded an oil which was stirred with dilute acetic acid. The resulting solid was collected by filtration, washed with water, and recrystallized from methanol to yield 460 mg of the starting material, mp 218.5–220°. The acetic acid filtrate was cooled in an ice bath, made ammoniacal, and saturated with sodium chloride. The solid which precipitated was collected by filtration, washed with water, dried, and recrystallized from methanol to yield 65 mg (7.0%) of 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indole, mp 193–195°. The analytical sample, mp 200–202.5°, was prepared by recrystallizing this material several times from methanol. The ultraviolet spectrum had λ_{max} 221, 282, and 289 mμ (ε 33,650, 7300, and 6500, respectively) with an inflection at 274 mμ (ε 6600).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.16; H, 7.88; N, 14.95.

B.—3,4,5,6-Tetrahydroazepino[4,3-*b*]indol-1(2H)-one (1.0 g, 5.0 mmoles) was added, under nitrogen, to a stirred, ice-cold suspension of lithium aluminum hydride (1.0 g) in dioxane. The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (1 ml), 15% aqueous sodium hydroxide (1 ml), and water (3 ml). This mixture was stirred for about 1 hr and filtered. Concentration of the filtrate *in vacuo* gave a solid residue which was dissolved in dilute acetic acid. This solution was extracted with ether, cooled in an ice bath, and made alkaline with dilute sodium hydroxide. The solid which formed was collected by filtration, washed with water, and dried to give 0.732 g of crude product. Crystallization of this material from methanol yielded 0.652 g (70.1%) of 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indole, mp 197.5–200°.

1,2,3,4,5,6-Hexahydroazepino[4,3-*b*]indol-2-carboxaldehyde.—1,2,3,4,5,6-Hexahydroazepino[4,3-*b*]indole (4.00 g, 0.0215 mole) was added to an ice-cold solution of acetic anhydride (6.43 ml) and 97% formic acid (2.72 ml) and the resulting mixture was allowed to stand at 25°, under nitrogen, for 18 hr. It was then poured into water. The gum which initially separated from this mixture crystallized. It was collected by filtration, washed with water, and dried to give 4.56 g of crude product. This was recrystallized from methylene chloride–methanol to give 2.79 g (60.6%) of 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indol-2-carboxaldehyde, mp 158–160°. The analytical sample, mp 160–161°, was prepared by recrystallizing some of this material from methanol–methylene chloride. The ultraviolet spectrum had λ_{max} 223, 283, and 289 mμ (ε 26,650, 7500, and 6650, respectively) with an inflection at 274 mμ (ε 6950). The infrared spectrum showed NH 3260 cm^{-1} and C=O, 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.27; H, 6.36; N, 13.41.

1,2,3,4,5,6-Hexahydro-2-methylazepino[4,3-*b*]indole (7).—1,2,3,4,5,6-Hexahydroazepino[4,3-*b*]indol-2-carboxaldehyde (2.38 g, 0.0110 mole) was added, under nitrogen, to a stirred, ice-cold suspension of lithium aluminum hydride (2.5 g) in dry tetrahydrofuran (250 ml), and the resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (2.5 ml), 15% aqueous sodium hydride (2.5 ml), and water (7.5 ml). This mixture was filtered and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethyl acetate–Skellysolve B gave 1.71 g, mp 167–168.5°, and 0.147 g, mp 165.5–167°, of 1,2,3,4,5,6-hexahydro-2-methylazepino[4,3-*b*]indole (83.8% yield). The analytical sample, mp 168.5–170°, was prepared by recrystallizing some of this material from ethyl acetate. The ultraviolet spectrum had λ_{max} 224, 283, and 289 mμ (33,700, 7250, and 6600, respectively, with an inflection at 274 mμ (ε 6600).

Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 78.01; H, 8.23; H, 14.25.

1,2,3,4-Tetrahydrocarbazol-4-one Oxime *p*-Toluenesulfonate.—A stirred solution of 1,2,3,4-tetrahydrocarbazol-4-one oxime (100 g, 0.500 mole) in dry pyridine (2 l.) was cooled in an ice bath and treated with *p*-toluenesulfonyl chloride (105 g, 0.550 mole). The resulting mixture was allowed to warm to room temperature and stand for 18 hr under nitrogen. It was then poured into ice water (6 l.) and extracted with methylene chloride. The methylene chloride extract was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was treated successively with toluene and benzene with concentration after each addition. It was then dissolved in ethyl acetate, decolorized with Darco G 60, and crystallized by evaporating the solvent under reduced pressure on the rotating evaporator to yield 124.8 g, mp 135–138° dec, and 10.6 g, mp 158–160° dec, of 1,2,3,4-tetrahydrocarbazol-4-one oxime tosylate. The analytical sample, mp 122.5–123° dec, was prepared by recrystallizing some of the lower melting material from ethyl acetate–Skellysolve B. The ultraviolet spectrum had λ_{max} 222, 246, 266, and 296 mμ (ε 33,000, 10,750, 14,950, and 14,200, respectively) with inflections at 273 and 300 mμ (ε 13,300 and 12,100, respectively).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.38; H, 5.12; N, 7.91; S, 9.05. Found: C, 64.34; H, 5.25; N, 7.88; S, 8.86.

3,4,5,6-Tetrahydroazepino[3,2-*b*]indol-2(1H)-one (6).—A solution of crude 1,2,3,4-tetrahydrocarbazol-4-one oxime tosylate (135.4 g) in benzene (8 l.) was adsorbed on a column of neutral alumina (5.3 kg) which had been deactivated with 1% water. (The column was prepared by pouring the dry alumina into a chromatographic column filled with Skellysolve B). The column was developed with 10 l. of benzene, and the product was eluted with chloroform (25 l.) and crystallized from methanol–ethyl acetate to yield 31.1 g of 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one, mp 243–244°. The analytical sample, mp 243.5–246°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum (ethanol) had end absorption, λ_{max} 232, 278, and 281 mμ (ε 33,950, 9250, and 9250, respectively) with inflections at 265 and 291 mμ (ε 8500 and 8050, respectively). The infrared spectrum showed NH 3190, 3260, 3230, 3120, and 3100 cm^{-1} and C=O 1650 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.78; H, 6.13; N, 13.83.

1,2,3,4,5,6-Hexahydroazepino[3,2-*b*]indole (3).—To a stirred, ice-cold suspension of lithium aluminum hydride (1.0 g) in dry tetrahydrofuran (100 ml) was added, under nitrogen, 1.00 g

(0.00500 mole) of 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one. The mixture was refluxed for 8 hr, cooled in an ice bath, and treated successively with water (1 ml), 15% aqueous sodium hydroxide (1 ml), and water (3 ml). This mixture was stirred for 1 hr and filtered. Concentration of the filtrate under reduced pressure gave a white, crystalline residue which was recrystallized from ethyl acetate to yield 0.569 g (61.2%) of 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole, mp 175–178° dec, with sintering at 167°. (This compound is very sensitive to air. It should be rapidly crystallized under nitrogen and stored in the freezer.) The analytical sample, mp 153–180° dec, was prepared by recrystallizing this material from ether. The ultraviolet spectrum (ethanol) had end absorption, λ_{max} 239 and 286 mμ (ε 25,850 and 4100, respectively) with an inflection at 310 mμ (ε 3150).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.08; H, 7.33; N, 15.28.

1-Acetyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (10).—1,2,3,4,5,6-Hexahydroazepino[3,2-*b*]indole (1.00 g, 5.38 mmoles) was added to a stirred, ice-cold solution of acetic anhydride (2 ml) in pyridine (50 ml). The resulting solution was allowed to warm to room temperature and stand for 18 hr. It was then poured into cold water and concentrated under reduced pressure at 20–30°. The solid product was collected by filtration, washed with water, dried, and recrystallized from methanol–ethyl acetate to give 1.14 g (93%) of 1-acetyl-1,2,3,4,5,6-hexahydroazepino-[3,2-*b*]indole, mp 217.5–218.5°. The analytical sample, mp 217.5–218.5°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had λ_{max} 224, 281, and 288 mμ (ε 38,950, 8250, and 7850, respectively) with inflections at 273 and 278 mμ (ε 7350 and 8000, respectively). The infrared spectrum showed C=O 1620 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.53; H, 7.14; N, 11.99.

1-Ethyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (13).—A solution of 1-acetyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (1.00 g, 4.38 mmoles) in tetrahydrofuran (25 ml) was added, under nitrogen, to a refluxing suspension of lithium aluminum hydride (1.0 g) in tetrahydrofuran (75 ml), and the mixture was refluxed for an additional 18 hr. It was then cooled in an ice bath and treated successively with water (1 ml), 15% aqueous sodium hydroxide (1 ml), and water (3 ml). The solid was collected by filtration and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethyl acetate–Skellysolve B gave 0.675 g (72%) of 1-ethyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole, mp 124–128°. The analytical sample, mp 128–129.5°, was prepared by recrystallizing some of this material from ether–Skellysolve B. The ultraviolet spectrum had λ_{max} 226, 283, and 289 mμ (ε 25,600, 6000, and 5700, respectively).

Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.07; H, 8.68; N, 13.17.

1-Acetyl-2,2-dideuterio-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]-indole (12).—3,4,5,6-Tetrahydroazepino[3,2-*b*]indol-2(1H)-one (0.500 g, 2.5 mmoles) was added, under nitrogen, to a stirred, ice-cold suspension of lithium aluminum deuteride (0.500 g) in 100 ml of tetrahydrofuran which had been freshly distilled from lithium aluminum hydride. The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (0.5 ml), 15% aqueous sodium hydroxide (0.5 ml), and water (1.5 ml). The solid was collected by filtration and the filtrate was concentrated under reduced pressure. A stirred solution of the residue in dry pyridine (25 ml) was cooled in an ice bath, treated with acetic anhydride (1 ml), and allowed to stand at room temperature, under nitrogen for 18 hr. It was then diluted with ice water and concentrated *in vacuo* at 20–30°. The solid which crystallized during the concentration was collected by filtration, washed with water, and dried to give 0.502 g of crude product. Recrystallization of this material from methanol–ethyl acetate gave 0.387 g (67.3%) of 1-acetyl-2,2-dideuterio-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole, mp 217.5–218.5°. The analytical sample, mp 217–218°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had λ_{max} 223, 282, and 288 mμ (ε 38,100, 8250, and 7850, respectively). The mass spectrum had a molecular ion at *m/e* 230.

Anal. Calcd for $C_{14}H_{14}D_2N_2O$: C, 73.01; H (D), 7.88; N, 12.17. Found: C, 72.97; H (D), 7.33; N, 12.33.

2,3,4,5-Tetrahydroazepino[3,2-*b*]indol-5a(6H)-ol (8).—A solution of 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (1.00 g, 5.38 mmoles) in ethyl acetate (150 ml) was stirred at room temperature for 18 hr. The yellow solid was collected by filtration and dried to give 0.766 g (70.3%) of 2,3,4,5-tetrahydroazepino[3,2-*b*]-indol-5a(6H)-ol, mp 166–167° dec. The analytical sample, mp 170.5–176° dec, was prepared by recrystallizing some of this material from methylene chloride–methanol. The ultraviolet spectrum was run in three different solvents. In ethanol it had end absorption, λ_{max} 234 and 380 mμ (ε 20,000 and 3365, respectively) with an inflection at 263 mμ (ε 5920); in dioxane it had λ_{max} 233 and 369 mμ (ε 20,200 and 3750, respectively) with inflections at 260 and 308 mμ (ε 6650 and 1000, respectively); in methylene chloride it had λ_{max} 318 and 356 mμ (ε 2300 and 2700, respectively) with inflections at 265 and 305 mμ (ε 6700 and 2400, respectively). The infrared spectrum showed NH–OH 3310, 2700, and 2540 cm^{-1} and C=N 1650 and 1615 $cm.^{-1}$

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.78; H, 7.00; N, 13.86.

Hydrogenation of 2,3,4,5-Tetrahydroazepino[3,2-*b*]indol-5a-(6H)-ol with Platinum Oxide in Acetic Anhydride.—A mixture of 2,3,4,5-tetrahydroazepino[3,2-*b*]indol-5a(6H)-ol (500 mg, 2.47 mmoles), acetic anhydride (50 ml), sodium acetate (1.0 g), and platinum oxide (200 mg) was hydrogenated on a Parr apparatus at an initial pressure of 29 psi for 5.75 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was suspended in water and the solid was collected by filtration and dried. The solid obtained by filtering the reaction mixture was extracted with hot methanol. The extract was concentrated under reduced pressure. This residue was combined with the solid product obtained from the filtrate and crystallized from methanol–ethyl acetate to give 0.310 g of 1-acetyl-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole, mp 216.5–218.5°. The mother liquor, which contained acetic acid, was concentrated. The residue was diluted with water and filtered. The solid was washed with water, dried, and crystallized from methanol–ethyl acetate to give additional product: yield, 130 mg (mp 217–218.5°) and 18 mg (mp 216–217°) (81.3% yield). This material was identical with the authentic sample by infrared, ultraviolet, and nmr comparison; the mixture melting point was undepressed.

Registry No—**1**, 14362-50-6; **1** *p*-toluenesulfonate, 14296-27-6; **2**, 14362-51-7; **3**, 14296-20-9; **4**, 14482-89-4; **6**, 14296-21-0; **7**, 14296-22-1; **8**, 14296-23-2; **10**, 14362-52-8; **12**, 14296-24-3; **13**, 14296-25-4; 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indol-2-carboxaldehyde, 14296-26-5.

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