Azabicyclo Chemistry. 7. Ultra-High Field (600 MHz) NMR Spectroscopy in Solving Conformational Problems: *cis*-Octahydroindoles [1]

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Studies using ultra-high field (600 MHz) nmr spectroscopy has allowed us to assign the conformational preference of *cis*-octahydroindoles, including the position of their nitrogen lone-pair electrons. Lithium aluminum hydride reduction of *cis*-octahydroindol-2-one (**4**) gave *cis*-octahydroindole (**5a**) which showed three distinct nmr resonances, the C7a proton at δ 3.04 (apparent q, J = 5.3 Hz) and the two C2 protons at δ 3.10 and 2.94. The latter two resonances were absent in the C2 deuterated compound **5b**. Deuteromethylation of **5a**, *via* a urethane intermediate, gave 1-deuteromethyl-*cis*-octahydroindole (**8a**) which showed resonances at δ 3.12 for the α-faced C2 proton, the β-faced C2 proton at δ 2.17, and the C7a proton at δ 2.15. The resonances at δ 3.12 and 2.17 are absent in the corresponding C2 deuterated compound **8b**, and the C7a remains as a doublet of triplets (d, J = 5.5 Hz; t, J = 3.8 Hz). Interpretation of the above data led us to assign **8a** as the *cis* compound with nitrogen axial, and the lone pair electrons in a pseudo-axial position and antiperiplanar to the C7a and β-faced C2 protons. The amine **5a** is also *cis* and has the nitrogen axial, but the lone pair electrons are pseudo-equatorial. Inspection of the Bohlmann band region in the ir of **5a** and **8a** supports the above assignments. These investigations thus suggest, in *cis*-octahydroindoles, the following steric order: methyl > lone pair > H.

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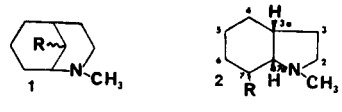
Since the initial report of Aroney and LeFevre [3] that the proton on the nitrogen in piperidine was axial, there has been considerable discussion in the literature relative to the conformational rivalry of the lone pair electrons and the proton on nitrogen [4]. However, in the case of *N*-methylpiperidine, there is a general consensus that the alkyl group has a decided preference for the equatorial position [5,6]. Booth and Bostock [7] have shown that in *cis*-decahydroquinolines, the N-H bond preferentially assumes the equatorial position, while Vierhapper and coworkers [8] have found this same preference in *trans*-decahydroquinolines.

It is known that the addition of a methyl or other alkyl substituent to cyclohexane compounds causes a shielding effect on the alpha protons which is seen as an upfield shift of these protons in the ^{1}H nmr spectra [9]. This shielding affects both the adjacent axial and equatorial hydrogens. In the case of piperidine, *N*-alkylation also produces a shielding effect, causing an upfield shift of the alpha protons relative to piperidine [10]. However, in this case the shielding effect on the axial proton is accentuated, resulting in a chemical shift difference of greater than 0.4 ppm. This difference in chemical shifts was first reported by Hamlow, *et al.* [11,12] during their nmr study of *trans* fused quinolizidine. They attributed this selective shielding to the specific *trans*-coplanar relationship of the nitrogen lone pair electrons and the axial proton on the alpha carbon.

Fewer studies have been done with pyrrolidines and other five-membered nitrogen containing heterocycles in regards to the position of the lone pair electrons and its shielding effect on the *cis* and *trans* alpha protons. Breuer and Melumad [13] have concluded from their experiments that the alpha protons of a pyrrolidine are shielded when they are *trans* to the lone pair and *cis* to an *N*-methyl group. Most nmr studies concerning the pyrrolidine ring alpha protons have been in structural studies of alkaloids that contain a pyrrolidine nucleus [14,15].

Our interest in the effects of nitrogen lone-pair electrons on nmr chemical shifts dates back to a study [16] aimed at preparing 2-azabicyclo[3.3.1]nonanes (**1**). At that time it was necessary to synthesize the isomeric *cis*-octahydroindoles **2** for comparison. This was accomplished [17] by catalytic hydrogenation of 1-methyl-7-methoxyindole, in which the products of the reaction were identified as 1-methyl-7(*e*)-methoxy-*cis*-octahydroindole and 1-methyl-*cis*-octahydroindole (**2**, R = H). The latter compound has been reported by King and co-workers [18]



simply as the *cis* compound, while Mertes, *et al.* [19] assigned compound **2** (R = H) as the *cis* structure with the nitrogen axial based on the observation of a low-field multiplet at δ 3.13 in the nmr, assigned to the equatorial C7a proton. We have examined this compound at 600 MHz and observed a one proton signal at δ 3.12 as a triplet (J = 9.3 Hz), each part being further split into a

doublet (J = 4.0 Hz). We have observed similar chemical shifts in other oxygenated octahydroindoles **2** (R = OCH_3, ONO_2, OH) and identified [16] those resonances as one of the C2 protons by replacement of both C2 hydrogens with deuterons. Therefore, we felt that the reported [19] assignment of δ 3.13 for the C7a proton in **2** (R = H) was erroneous. In order to prove this and correctly establish the conformational preference of **2** (R = H), we chose an unambiguous route that would afford us the desired compound with C2 either deuterated or not.

Commercially available oxindole (**3**) was reduced, by a modification of a method used for the oxindole alkaloid rhyncophylline, [20] to the known [21] *cis*-octahydroindol-2-one (**4**) in an 86% yield. Examination of the nmr spectrum of **4** at 600 MHz enabled us to assign it as the *cis* conformation which has the nitrogen axial. The C7a proton was observed as an apparent quartet centered at δ 3.69 with a coupling constant of 5.1 Hz. This implies that H3a, H7(a) and H7(e) all couple to H7a by a 5.1 Hz coupling; most likely a doublet in which each line is further split into a triplet which then fortuitously overlaps to form a quartet. The lack of any large coupling indicates the equatorial nature of the C7a proton. Jeffs and Molina [22,23] have previously reported that the corresponding 1-methyl-*cis*-octahydroindol-2-one also has an equatorial C7a proton (δ 3.48, Japp = 5.0 Hz), and thus the *cis* conformation in which the nitrogen is axial. This type of *cis* conformation has been found to be characteristic of *cis*-octahydroindoles [23] and related systems, [22] such as seen in the *Sceletium* and *Amarylidaceae* alkaloids. The upfield shift of the C7a proton in going from N-H to *N*-methyl is no doubt due to the known [9,10] shielding effect of methyl groups on adjacent protons.

The reduction of the lactam, **4**, was accomplished using lithium aluminum hydride (LAH) and afforded the amine, **5a**, the gross structure being identified by mass spectrometry and comparison of its picrate salt with that in the literature [21]. The amine **5a** when observed in the nmr at 600 MHz showed three distinct downfield resonances (see Figure 1). We have assigned the C7a proton as that resonance which is observed at δ 3.04, as an apparent quartet with coupling constants of 5.3 Hz. The other two discrete multiplets at δ 2.94 and 3.10 were assigned to the two C2 protons. The splitting observed is due to coupling with the two C3 protons and to geminal coupling, resulting in a doublet of doublets of doublets. The signal at δ 3.10 has coupling constants of 6.2, 8.8, and 11.0 Hz while the signal at δ 2.94 has coupling constants of 5.3, 9.9, and 11.0 Hz [24]. The 11.0 Hz was assigned as the geminal coupling. Proof for these assignments was easily accomplished by preparing the identical compound but with C2 deuterated. Thus, the reduction of lactam **4** with lithium aluminum deuteride (LAD) gave the deuterated amine **5b**. The latter compound, at 600 MHz, showed only one resonance downfield at δ 3.05, as an apparent quartet with coupling constants of 5.3 Hz. Therefore, the preferred conformation of amines **5a** and **5b** is also *cis* with the nitrogen axial, as indicated by the small coupling constant of the equatorial C7a proton.

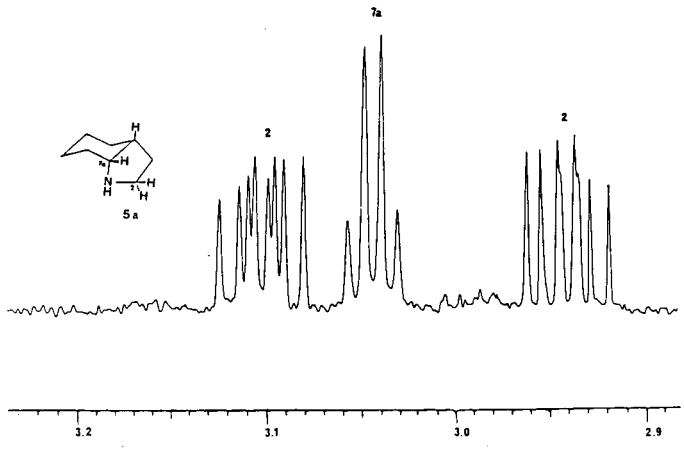
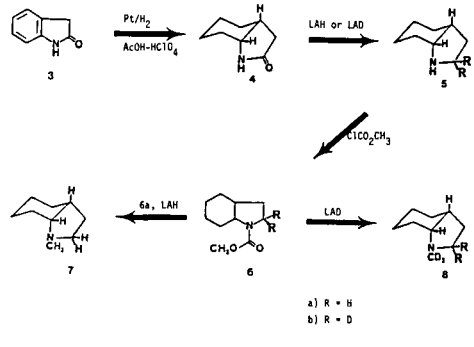


Figure 1. Expanded view of the δ 2.9-3.1 region, *cis*-octahydroindole (**5a**).

Methylation of **5a** was accomplished by lithium aluminum hydride reduction of the intermediate methyl urethane **6a**, thus yielding the desired 1-methyl-*cis*-octahydroindole (**7**) (see Scheme I). This latter compound **7**, as its picrate salt, was identical in the infrared with 2-picrate (R = H) obtained by catalytic hydrogenation of 1-methyl-7-methoxyindole. Therefore, both routes afford the same stereochemical compound which, as will be described below, has the *cis* conformation with the nitrogen axial.

SCHEME I



Examination of the nmr spectrum of **7** at 600 MHz indicated two key resonances, a low-field resonance at δ 3.12 which we assigned as one of the C2 protons, and a broad multiple resonance upfield at δ 2.13-2.19 assigned to two protons, namely the one at C7a and the other C2 proton. In order to remove the *N*-methyl resonance, which appears close (δ 2.26) to the resonance of the C7a proton, we prepared the deuteromethyl amine **8a** by lithium

aluminum deuteride reduction of urethane **6a**. The nmr spectrum of **8a** at 600 MHz was virtually identical to that of **7** except for the absence of the methyl resonance. An expanded nmr spectrum of the key resonances of **8a** is shown in Figure 2.

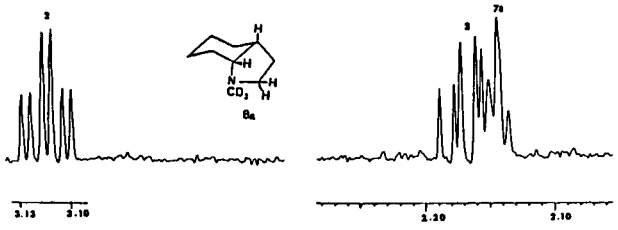


Figure 2. Expanded view of the C7a and C2 protons in the spectrum of 1-methyl-d_3-*cis*-octahydroindole (**8a**).

The above nmr assignments for **7** were confirmed *via* the preparation of the C2 deuterated analog **8b**, the latter being synthesized from **5b** *via* **6b** as shown in Scheme I.

Observation of **8b** at 600 MHz revealed the absence of any low field resonance in the δ 3.1 area and only a resonance for the C7a proton centered at δ 2.15. The C7a proton of **8b**, when expanded, was observed as a doublet of triplets with a doublet coupling of 5.5 Hz and a triplet coupling of 3.8 Hz. These coupling constants are consistent with gauche couplings, [16] indicating that the C7a proton is again in the equatorial position.

The penta-deuterated compound **8b** was subjected to decoupling experiments which has allowed us to locate several of the other resonances in this molecule. As seen in Figure 3, irradiation at the position of the C7a proton (δ 2.15) caused perturbations in both the irradiated and difference spectra which were centered at δ 1.98, 1.73, and 1.48. These resonances were assigned to the C3a proton and the two C7 protons, respectively. In a subsequent experiment, irradiation at the position of the C3a proton (δ 1.98) revealed changes centered at δ 2.15, 1.83, 1.53, and 1.33. We have assigned these resonances as the C7a proton, one of the C3 protons, tentatively one of the C4 pro-

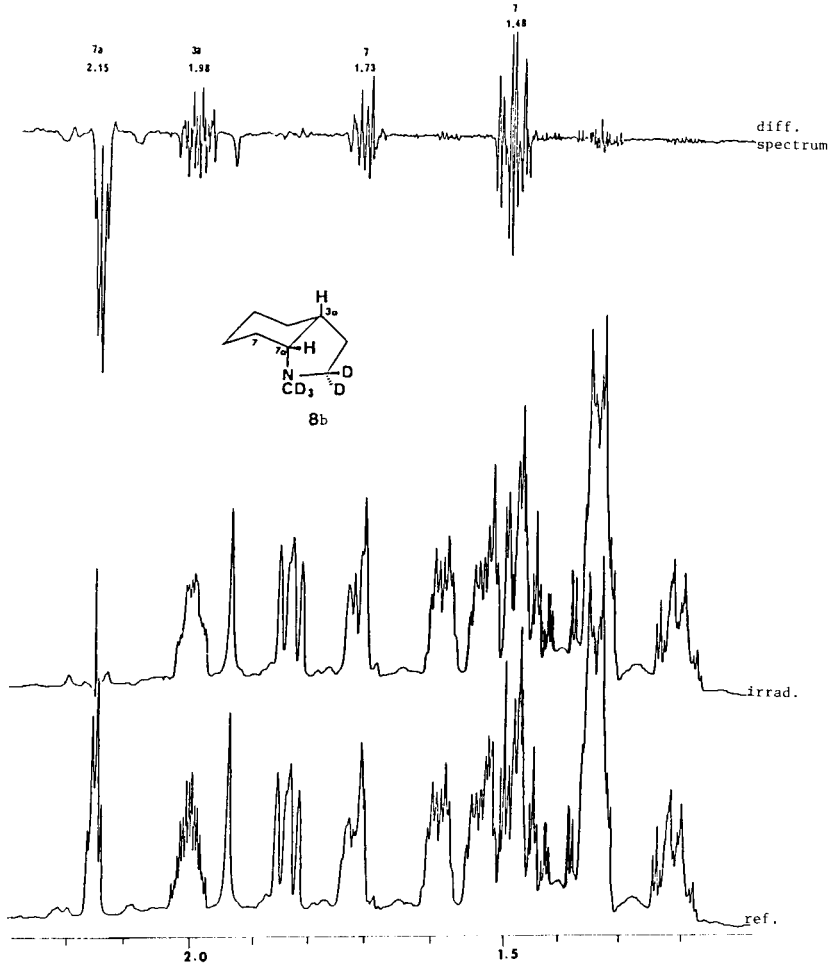


Figure 3. Spin decoupled and difference spectra of 1-methyl-d_3-*cis*-octahydroindole-$2d_2$ with irradiation at δ 2.15. The lower tracing is the reference spectrum and above it is the irradiated spectrum. The uppermost tracing is the difference spectrum showing the position of the perturbed resonances and their assignments.

tons, and the second C3 proton, respectively (see Figure 4). Furthermore this latter experiment caused the pair of doublets centered at δ 1.83 to collapse to a doublet, thus allowing us to assign the geminal C3 proton coupling constant as 12.4 Hz and the coupling constant between H3 and H3a as 8.4 Hz. The position of the C3 protons was confirmed in another irradiation experiment on compound **8a** wherein the difference spectrum due to irradiation at δ 3.12, the position of one of the C2 protons, indicated that the signals affected were at δ 2.17, 1.85, and 1.35. The signal at δ 2.17 is the other C2 proton, as this disappears in the nmr spectrum of **8b**, and the latter two are due to the C3 protons. Corroboration for the C3 proton assignments is based on the decrease in complexity at these positions in the nmr spectrum of deuterated **8b**.

Several of the observations we have made need to be interpreted; for example, why in the case of the N-H compound **5a** are both C2 protons found downfield whereas in the *N*-methylated compounds **7** and **8a** only one of the C2 protons is downfield while the other one is found almost a full ppm upfield? Furthermore, when comparing the chemical shifts for the C7a proton of **5a** and **7** or **5b** and **8b**, why does one see an upfield shift of nearly 0.9 ppm in going from NH to *N*-methyl, more than one would expect for just methyl shielding [9,10]? We believe these questions can be answered by considering the steric location of the nitrogen lone pair electrons.

By way of nitrogen inversion two possible conformations, **I** and **II** (R = H, CH_3) can exist for either **5a** or **7** (see Scheme II). As was previously discussed above, [8, 11-15] there is a body of literature which supports the large shielding effect of axial protons by lone pair electrons situated *trans*-coplanar on adjacent nitrogen atoms. In the equilibrium **I** $\rightleftharpoons$ **II** (R = CH_3), as concerns **7**, we believe the data indicates that **II** is the preferred conformer wherein the methyl group is pseudo-equatorial and

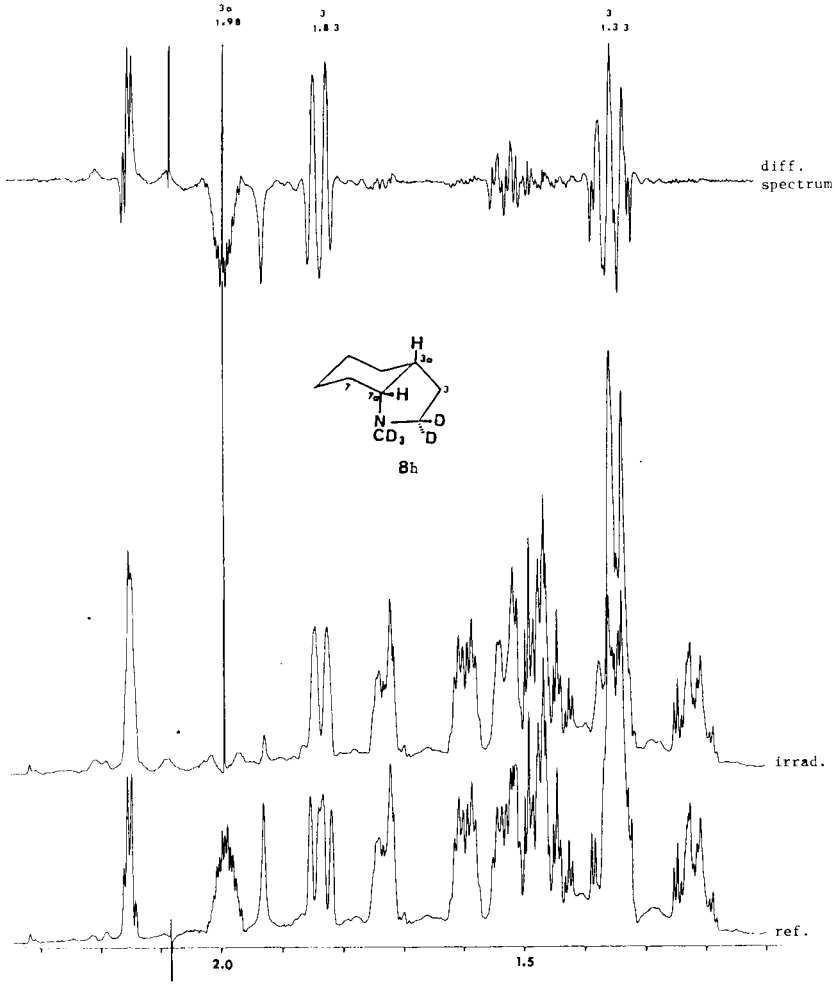
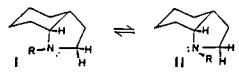


Figure 4. Spin decoupled and difference spectra of 1-methyl-d_3-*cis*-octahydroindole-$2d_2$ with irradiation at δ 1.98. The lower tracing is the reference spectrum and above it is the irradiated spectrum. The uppermost tracing is the difference spectrum showing the position of the perturbed resonances and their assignments.

the lone pair electrons pseudo-axial and thus roughly *trans*-coplanar to the β-faced C7a and C2 protons. In addition to this is the additive shielding by the methyl group, and one sees an upfield shift of the C7a proton relative to **5a** of 0.89 ppm, and an upfield shift of the β-faced C2 proton to δ 2.17. The α-faced C2 proton is *cis* to the lone pair electrons and thus remains downfield at δ 3.12. In the equilibrium **I** ⇌ **II** (R = H) as concerns **5a**, we believe that the nmr data indicates that **I** is the preferred conformer, that is the H is pseudo-axial and the lone pair electrons pseudo-equatorial. In this conformation there is no shielding by the lone pair electrons and there is no methyl to cause shielding and therefore all three protons, the C7a and both C2 protons, appear downfield.

SCHEME II



However, as we pointed out above, Vierhapper and Eliel [8] observed that there is no upfield shifting effect by the antiperiplanar lone pair in piperidine containing NH compounds. Even though the octahydroindoles studied contain a pyrrolidine rather than a piperidine ring, we considered it was possible that our interpretation of the nmr data for **5a** was erroneous, as concerns the position of the lone pair electrons. Thus, another interpretation is that the H on nitrogen is in the pseudo-equatorial position and the pseudo-axial lone pair electrons have no upfield shifting effect on the β-faced H2 and H7a protons.

In an attempt to settle this question we chose the method Vierhapper and Eliel [8] used in their study of the position of the nitrogen lone pair, namely the presence or absence of Bohlmann bands [25] in the ir spectra of compounds **5a** and **8a**. The ir spectra were recorded as 0.03*M* solutions in carbon tetrachloride and the pertinent regions of **5a** and **8a** are shown in Figure 5. The ir spectrum of **8a** is as expected for a compound with an equatorial N-CD_3; positive Bohlmann bands in the region between 2800 and 2500 cm^{-1}, due to the pseudo-axial lone pair on nitrogen which is anti to the β-faced C2 and C7a protons. This substantiates the conformation assigned to **8a** based on the observed nmr data. The ir of **5a** (which also has β-faced C2 and C7a protons) reveals little absorption of significance in the region between 2800 and 2500 cm^{-1}. This signifies an absence of Bohlmann bands and indicates that the nitrogen lone pair electrons are in the pseudo-equatorial position. Since the lone pair is not anti positioned to the α-protons in **5a**, an exchange of the protons at C2 by deuteriums, as in **5b**, should not change the intensities in the 2800-2500 cm^{-1} region. When the ir of **5b** was recorded, the absorption in the 2800-2500 cm^{-1} region was virtually identical to that of **5a**. Thus, the ir study substantiates the conformation assigned to **5a** based on the nmr data. In conclusion, it appears that in the *cis*-octahydroindole molecule, at least in the solvents used (deuterochloroform, carbon tetrachloride), the predominant species in solution possesses a hydrogen bound to nitrogen which is in the somewhat more hindered "inside" or pseudo-axial position and the lone pair electrons in the less sterically hindered pseudo-equatorial position. However, in the *N*-methyl-*cis*-octahydroindole molecule, the methyl is sterically more demanding and is found in the pseudo-equatorial position. These investigations thus suggest the following steric order: methyl > lone pair > H.

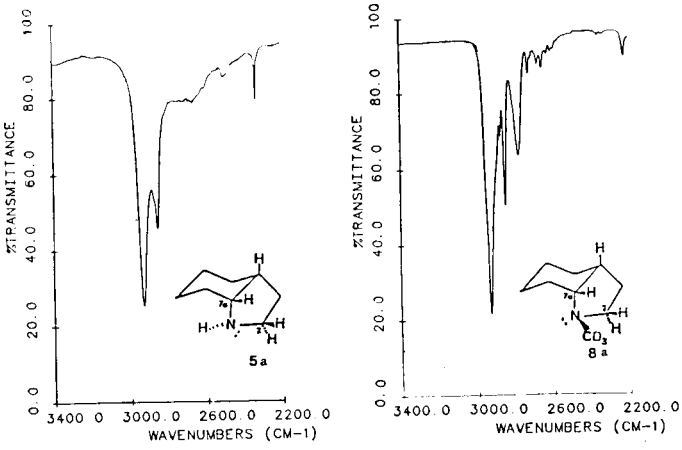


Figure 5. Infrared spectra in the 3400-2200 cm^{-1} region of *cis*-octahydroindole (left trace) and 1-methyl-d_3-*cis*-octahydroindole (right trace).

EXPERIMENTAL

The ^1H nmr (89.55 MHz) and ^{13}C nmr (22.5 MHz) spectra were recorded on a JEOL FX-90Q using deuterochloroform as a solvent and TMS as an internal standard. The ^{13}C nmr assignments were based on changes in the spectra upon specific deuteration, off-resonance proton decoupling, and empirical relationships of substituent effects [26]. High field ^1H nmr were recorded on a 600 MHz instrument at the NMR Facility for Biomedical Studies at Carnegie Mellon University. The 600 MHz data were collected, for most spectra, in the FT mode with the following usual parameters: accumulated at 32K using a 90° pulse width of 12 microseconds, a sweepwidth of either 2500 or 6024 Hz, an acquisition time of 6.5 seconds and digitized at either 0.15 or 0.4 Hz per point. Normal processing using Bruker software was performed with Lorentzian broadening of -2.0 to -3.0 Hz and a GB parameter of 0.15 to 0.20. Decoupling difference spectra were obtained by direct subtraction of spectra recorded with the decoupling power centered on the signal of interest, and displaced to a nearby vacant area of the spectrum. For these spectra more moderate resolution enhancement (LB -1.0, GB 0.2) was used. Low resolution mass spectra were obtained on a Finnigan 3200 GC mass spectrometer. Routine ir spectra were recorded on a Perkin-Elmer model 267 spectrometer, as solutions in chloroform. The ir spectra for the Bohlmann band studies were recorded on a Nicolet 5DXB Fourier transform spectrometer using 0.532 mm path length sodium chloride cells, as 0.03 *M* solutions in Fisher Spectra-analyzed carbon tetrachloride; 500 scans were accumulated at a resolution of 2 cm^{-1}. The purity of the volatile amines was determined by gc analysis using a Gow-Mac Series 150 Chromatograph with thermal conductivity detector and OV-1 col-

umn at 135°. Micro analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Tetrahydrofuran (THF) was distilled from potassium metal or from Na-benzophenone ketyl. All concentrations were performed *in vacuo* on a rotary evaporator. Organic solutions that had been previously extracted with aqueous solutions were dried over magnesium sulfate prior to concentration. The LAH and LAD used was obtained from Aldrich Chemical Co.

cis-Octahydroindol-2-one (**4**).

Oxindole (**3**) (Aldrich, 5.01 g, 37.67 mmoles) and platinum oxide (Strem, 84.1% Pt, 0.25 g, 1.07 mmoles) were placed into a 500 ml Parr bottle to which glacial acetic acid (200 ml) and 70% perchloric acid (0.29 ml) was added. Catalytic hydrogenation (initial pressure of 45 psi) was then carried out with a total pressure change of 156 psi occurring over a 19 hour period (calcd. 145 psi). After removal of the catalyst the resulting filtrate was concentrated. The remaining acid was neutralized with solid sodium bicarbonate and then water added. The resulting mixture was then extracted with three portions of dichloromethane. The combined organic extracts were washed with saturated sodium chloride and then dried. After concentration, the resulting viscous liquid was purified by Kugelrohr distillation (120°, 0.4 torr) to give **4** as a clear liquid (refractive index 1.5086, lit [21] 1.5095) which solidified to a low melting solid on standing (4.52 g, 86% yield, mp 39.5-40.5°, lit [21] mp 30°); ir: 1680 cm^{-1} (C=O); ^{13}C nmr: δ 179.3 (C2), 53.5 (C7a), 38.3 (C3a), 34.4, 28.5 (C4, C7), 27.4 (C3), 22.8, 20.6 (C5, C6); ms: m/z (ion, relative intensity) 139 (M^+, 33), 96 (M-43, 100).

cis-Octahydroindole (**5a**).

LAH (1.49 g, 39.12 mmoles) was placed in a flask with dry THF (40 ml). The mixture in the flask was kept under a nitrogen atmosphere by means of a nitrogen balloon apparatus. An ice bath was used to chill the mixture prior to the dropwise addition of lactam **4** (2.94 g, 21.13 mmoles) in dry THF (20 ml). After 20 minutes the addition was complete and the ice bath was removed. The reaction mixture was then brought to reflux overnight with a nitrogen atmosphere being maintained throughout. After 16 hours, the reaction mixture was cooled and 10% sodium hydroxide solution (about 7.5 ml) was added dropwise to neutralize the remaining LAH. The THF was then removed by evaporation. The aluminum hydroxide residue was washed with dichloromethane to recover the free amine. The dichloromethane washings were combined and extracted with 10% hydrochloric acid (3 x 12 ml). The combined acid extracts were then neutralized with 6.25 *N* sodium hydroxide and extracted with five portions of dichloromethane. The organic extracts were combined and dried. Evaporation of the solvent gave 2.19 g of a viscous liquid, which upon purification by Kugelrohr distillation (90°, 27 torr) afforded 1.43 g of **5a** as a clear liquid (54% yield). A portion of **5a** was converted to its picrate salt and recrystallized from benzene, mp 135-137° (lit [21] mp 136-137°); ^{13}C nmr: δ 57.6 (C7a), 44.3 (C2), 38.4 (C3a), 31.0 (C3), 28.1, 27.5 (C4, C7), 23.7 (C5), 21.8 (C6); ms: m/z (ion, relative intensity), 125 (M^+, 13), 82 (M-43, 100), 69 (M-56, 12), 68 (M-56-H, 15).

cis-Octahydroindole-2-d_2 (**5b**).

A slurry of LAD (1.48 g, 35.25 mmoles) in dry THF (40 ml) was cooled in an ice bath under a nitrogen atmosphere. Lactam **4** (3.09 g, 22.23 mmoles) in dry THF (20 ml) was dripped into the LAD solution over a 15 minute period. After the addition was complete, the reaction mixture was brought to reflux overnight. The mixture was then cooled prior to the addition of 10% sodium hydroxide (approximately 7 ml) to neutralize the remaining LAD. The THF was removed by evaporation and the resulting aluminum hydroxide residue was washed with dichloromethane (5 x 10 ml). The combined dichloromethane washes were extracted with 10% hydrochloric acid (4 x 10 ml). These acid extracts were then neutralized with 6.25 *N* sodium hydroxide (approximately 8 ml) and the free amine then extracted with five portions of dichloromethane. The organic layer was dried and concentration yielded **5b** as a crude oil (2.03 g, 16.0 mmoles), a small portion of which was distilled using the Kugelrohr apparatus (90°, 27 torr); ^{13}C nmr: δ 57.5 (C7a), 43 (1:3:4:3:1 pentant, C2), 38.2 (C3a), 30.7 (C3), 27.8, 27.4 (C4, C7), 23.7 (C5), 21.6 (C6); ms: m/z (ion, relative intensity), 127 (M^+, 2), 84 (M-43, 100), 71 (M-56, 18), 70 (M-56-H, 24). A portion of **5b** was converted to its picrate salt, recrystallized from benzene, and then sublimed, mp 137-139°.

Anal. Calcd. for $C_{14}H_{16}D_2N_4O_7$: C, 47.18; H,D, 5.65; N, 15.73. Found: C, 47.16; H,D, 5.51; N, 15.83.

Methyl *cis*-Octahydroindole-1-carboxylate (**6a**).

Amine **5a** (1.23 g, 9.86 mmoles) was dissolved in THF (20 ml) and then water (36 ml) added. The solution was cooled in ice while stirring. Methyl chloroformate (Aldrich, 0.84 ml, 10.84 mmoles) was diluted with THF (16 ml) and placed into a dropping funnel. Aqueous 1.43 *N* sodium hydroxide (6.9 ml) was placed in a second dropping funnel. A Claisen head was attached to the reaction flask such that the two solutions could be added simultaneously. Initially, approximately half of the chloroformate solution was added, then the remainder of the chloroformate solution and the base were added simultaneously, in a dropwise fashion. After the addition was complete, the solution was stirred for 5 hours as 5°. The THF was removed by evaporation and the resulting solution was made acidic with 1 *N* hydrochloric acid and then extracted with three portions of diethyl ether. The combined etheral extracts were dried and concentrated, thus affording 1.60 g of crude oil. This oil was further purified by Kugelrohr distillation (135°, 35 torr) to give **6a** as a clear oil (1.49 g, 83% yield); ir: 1680 cm^{-1} (urethane C=O); ^1H nmr: δ 3.62 (s, 3, H, CH_3OCO), 3.45 (m, 3 H, C7aH, $C2H_2$), 1.7 m, 11 H; ^{13}C nmr: δ 155.5 (CH_3OCO), 56.7 (C7a), 51.9 (CH_3OCO), 45.2 (C2), 37.3 (C3a), 27.7, 26.9, 26.3 (C3, C4, C7), 23.6, 21.1 (C5, C6); ms: m/z (ion, relative intensity), 183 (M^+, 23), 140 (M-43, 100).

Methyl *cis*-Octahydroindole-2-d_2-1-carboxylate (**6b**).

Deuterated amine **5b** (1.90 g, 15.0 mmoles) was converted to its corresponding urethane **6b** as described above for **6a**, affording 1.84 g of a clear liquid (67% yield); ms: m/z (ion, relative intensity), 185 (M^+, 20), 142 (M-43, 100).

1-Methyl *cis*-Octahydroindole (**7**).

A slurry of LAH (0.41 g, 10.80 mmoles) in dry THF (13.5 ml) was cooled using an ice bath prior to the dropwise addition of freshly distilled urethane **6a** (1.41 g, 7.70 mmoles) in dry THF (7.7 ml) under an atmosphere of nitrogen. After the addition was complete, the mixture was brought to a reflux and continued for 13 hours. Water was added to neutralize the excess LAH and the aluminum hydroxide precipitate was extracted with dichloromethane. The organic extracts were combined, washed with saturated sodium chloride and dried. Concentration yielded a crude oil that was further purified by Kugelrohr distillation (95°, 40 torr) to give 0.42 g of the desired product **7** (40% yield); ^{13}C nmr: δ 65.1 (C7a), 55.2 (C2), 40.3 (NCH_3), 38.1 (C3a), 30.0, 29.1, 25.4 (C3, C4, C7), 24.9 (C6), 20.7 (C5); ms: m/z (ion, relative intensity), 139 (M^+, 12), 96 (M-43, 100), 83 (M-56, 18), 82 (M-56-H, 28).

1-Methyl-d_3-*cis*-Octahydroindole (**8a**).

Urethane **6a** (2.00 g, 10.93 mmoles) was converted to the deuterated N-methyl compound **8a** as described above for **7**, except that LAD (0.64 g, 15.24 mmoles) was used. Distillation of the initial product by Kugelrohr (95°, 40 torr) gave **8a** as a colorless liquid (1.12 g, 72% yield); ^{13}C nmr: δ 65.0 (C7a), 55.1 (C2), 40 (multiplet, NCD_3), 38.1 (C3a), 30.0, 29.1, 25.4 (C3, C4, C7), 24.8 (C6), 20.7 (C5); ms: m/z (ion, relative intensity) 142 (M^+, 15), 99 (M-43, 100), 86 (M-56, 8), 85 (M-56-H, 15).

Anal. Calcd. for $C_9H_{14}D_3N$: C, 75.99; H,D, 12.05; N, 9.85. Found: C, 75.70; H,D, 11.96; N, 9.74.

1-Methyl-d_3-*cis*-Octahydroindole-2-d_2 (**8b**).

Urethane **6b** (1.84 g, 9.97 mmoles) was converted to the pentadeuterated compound **8b** using LAD (0.59 g, 14.05 mmoles) as described above for **7**. Distillation of the crude product by Kugelrohr (95°, 40 torr) gave **8b** as a clear liquid (0.86 g, 60% yield); ms: m/z (ion, relative intensi-

ty) 144 (M^+, 20), 101 (M-43, 100), 88 (M-56, 12), 87 (M-56-H, 12).

Anal. Calcd. for $C_9H_{12}D_5N$: C, 74.93; H,D, 11.88; N, 9.71. Found: C, 74.68; H,D, 11.56; N, 9.71.

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