Abbreviated Ibogaine Congeners. Synthesis and Reactions of Tropan-3-yl-2- and -3-indoles. Investigation of an Unusual Isomerization of 2-Substituted Indoles Using Computational and Spectroscopic Techniques†

David B. Repke,*,‡ Dean R. Artis,*,§ Janis T. Nelson,§ and Erik H. F. Wong⊥

Syntex Discovery Research, 3401 Hillview Avenue, Palo Alto, California 94303

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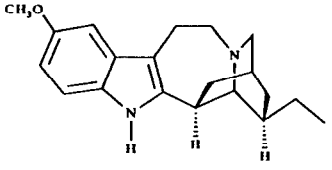
The syntheses of several *N*-methyltropan-3-ylindoles, designed as congeners of ibogaine, are described. The synthetic approach to *N*-methyltropan-3-yl-2-indole revealed that the tropanyl 3′-center was quite sensitive to acid-catalyzed epimerization. The carbocyclic analog, *N*-methyl-2-[bicyclo[3.2.1]-oct-3-anyl]indole, also underwent this rearrangement. However, *N*-methyltropan-3-yl-3-indole was insensitive to acid or base, even under more vigorous conditions. This simple isomerization is quite rare for 2-substituted indoles, especially for cases where the center of reaction is not additionally activated, and normally only takes place under extreme reaction conditions. The mechanism of this reaction was investigated using *ab initio* molecular orbital calculations, NMR spectroscopy, and deuterium labeling studies. These results indicate that, in contrast to those previously obtained for more reactive 2-substituted indoles, the reaction can best be explained using a simple exchange mechanism involving the exocyclic enamine tautomer of the indole ring as an intermediate. The difference in reactivity is suggested to arise from a decrease in the relative energy of the exocyclic enamine tautomer due to the presence of increased strain in the endo bicyclic 2-substituent. The title compounds displayed modest pharmacological activity in a variety of biological assays.

Introduction

Ibogaine (1) represents not only a challenge to synthetic chemists but also the starting point for intriguing pharmacological adventures. As a molecule which combines



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the structural features of tryptamine, tetrahydroharmine, and the indoloazepines,[1,2] medicinal chemical efforts centered around ibogaine have been surprisingly lacking. Although total syntheses of this structural class have been reported,[3-5] there has been little pharmacological afterthought. Recently, ibogaine has been studied as a possible agent for the treatment of opiate addiction,[6] and a thorough survey of receptor affinity for ibogaine has been reported.[7] Perhaps the inclusion of ibogaine in Schedule I of the Controlled Substances Act,[8] despite the lack of its appearance in "underground" circles, has tainted research with ibogaine or its congeners.

Our initial interest in ibogaine centered around its possible 5-HT receptor activity. With this in mind we turned our investigations to the indolotropanes, a chemical class which represents an abbreviated view of the ibogaine skeleton. An examination of molecular models showed that the basic structural features of ibogaine could be approximated by linking the indole-2- or -3-carbon with the tropanyl-3-carbon. Such compounds were predicted to result in ibogaine congeners in which both structural parameters and lipophilic character were preserved.

Results and Discussion

The synthesis of **4a** was thus pursued in the manner shown in Scheme 1. The 2-lithio species of *N*-methylindole was reacted with tropinone at low temperature. The resulting amino alcohol **2a** was dehydrated to the olefin **3a** by treatment with ethanolic hydrogen chloride at 60 °C. The structure of the olefin **3a** was clearly indicated by the appearance of a doublet at 6.0 ppm in the ^{1}H-NMR spectrum. Upon catalytic hydrogenation of **3a** the downfield doublet disappeared with the concomitant appearance of multiplets at 2.07 and 2.50 ppm characteristic of the C-2′ and C-4′ methylene protons of the saturated tropane system. The "narrow", or simplified, multiplet for the C-3′ proton of **4a**[9] indicated that it was the kinetic endo product, as expected.[10] Treatment of **4a** with warm ethanolic hydrogen chloride was expected to result in the routine production of a pharmacologically acceptable salt. However, thin-layer chromatographic examination indi-

† Dedicated to Dr. John Edwards on the occasion of his retirement after more than 30 years with Syntex. Contribution no. 885.

‡ Institute of Organic Chemistry.

§ Institute of Analytical Research. Current address: Genentech, Inc., Bio-organic Chemistry Dept., 460 Pt. San Bruno Blvd., So. San Francisco, CA 94080.

⊥ Institute of Pharmacology.

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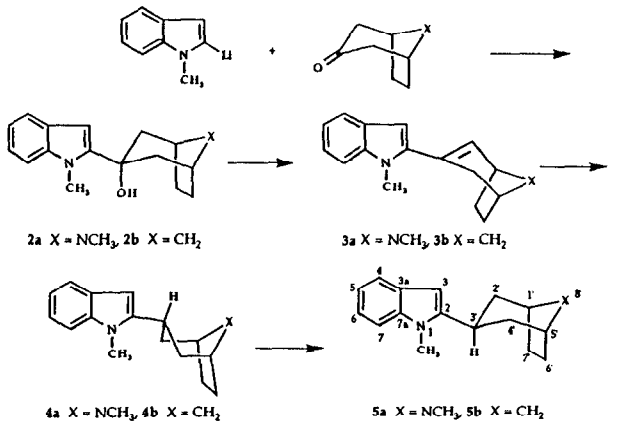
Scheme 1



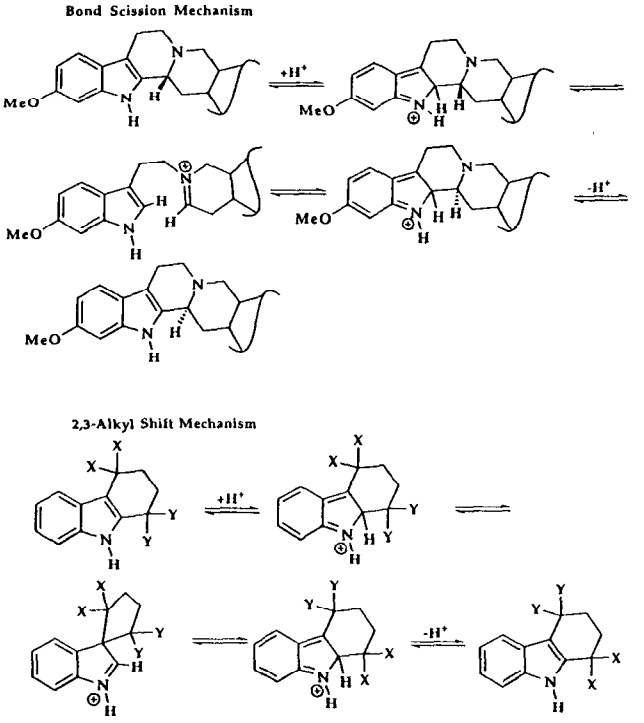
cated the presence of a compound that was completely different from the free base of **4a**. Examination of the ^{1}H-NMR spectrum of this new product (as the base) confirmed its chemical nonidentity with **4a**. Comparison of the ^{1}H-NMR spectra of the new product and of **4a** showed clear chemical shift differences for the *N*-methyl and C-3-H of the indole ring and the tropanyl C-3′ protons. These changes, especially the clearly defined and upfield-shifted seven-line multiplet of the C-3′ proton, indicated that the new compound was the "exo" isomer, **5a**.[9]

A number of interesting particulars of this epimerization shortly became apparent. The reaction of the free base of **4a** did not proceed thermally in refluxing ethanol or toluene. When the carefully prepared HCl salt of **4a** was subjected to these reaction conditions, **5a** began to appear quite slowly, only detectable after several hours. However, upon addition of a further 0.1 mol equiv of HCl, the conversion to **5a** proceeded to completion within 30 min. Furthermore, **5a** was isolated and subjected to a variety of acidic and basic reaction conditions, none of which produced **4a** in any detectable amount.

This isomerization, and the facility with which it proceeded under quite mild conditions, was extremely surprising. Epimerization at the center attached to the 2-position of indoles rarely occurs unless, as in the case of reserpine[11,12] or other tetrahydrocarboline-based systems,[13,14] there is an activating functionality immediately adjacent. These systems require significantly more vigorous reaction conditions, such as refluxing acetic acid or concentrated mineral acids, in order for the epimerization to take place. Exchange at the center attached to the 2-position can, however, be driven for nonactivated systems, such as tetrahydrocarbazole, by prolonged reaction in refluxing concentrated DCl.[15] In addition, a study of the methanolysis reaction of 3-bromoindolenines[16] provided some indication that this type of exchange may occur for a related system under the conditions of stoichiometric toluenesulfonic acid in methanol.

These latter reports are significant in that they implicate an exocyclic enamine tautomer of the indole system as an intermediate. Most mechanistic studies of these systems

Scheme 2



have provided evidence indicating that the reactivity at the 2-position usually follows one of two pathways, representative examples of which are shown in Scheme 2. The generally accepted mechanism for epimerization or incorporation of the substituent at the 2-position of tetrahydrocarboline-type systems involves protonation at the indole 2-position, followed by scission of the bond to the original 2-substituent.[17] The thorough work of Gaskell and Joule[11] on the reserpine–isoreserpine equilibrium indicated specifically that the mechanistic pathway did not include the enamine tautomer for these systems and was proceeding through the bond scission mechanism. However, this same study concluded that for the slower isomerization of deserpidine, which lacks a methoxyl group on the indole aromatic ring, a small contribution from the enamine pathway may have been in effect. In another study, scrambling of the substituents at the 2- and 3-positions of tetrahydrocarbazoles has been described as occurring through a 2,3-alkyl shift.[18]

Given the unusual facility of this epimerization, we decided to investigate this transformation in more detail. The aforementioned studies suggested three mechanistic pathways that might be operative. The bond scission mechanism, which is dominant for reserpine-type systems, appeared unlikely for the indole tropanes for two reasons. First, the only stabilizing group present on the tropane is the bridging nitrogen, the involvement of which would result in a highly strained tricyclic intermediate. Second, such a mechanism would be expected to yield products resulting from the reaction of this transient species with solvent, since the only connection between the tropanyl and indole rings would have been severed. Thus, the bond scission mechanism did not seem plausible. However, the possibility that the nitrogen played some role in facilitating the isomerization remained distinct.

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(12) MacPhillamy, H. B.; Huebner, C. F.; Schlittler, E.; St. Andre', A. F.; Ulshafer, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 4335.
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In an attempt to resolve some of the mechanistic issues raised above, the synthesis of several compounds was undertaken. In order to examine the role of the tropanyl nitrogen in this isomerization, **4b**, the carbocyclic analog of **4a**, was prepared. The synthesis of **4b**, from *N*-methylindole and bicyclo[3.2.1]octan-3-one, was carried out in an analogous fashion to that of **4a**. In addition, **11**, an analog of **4a** with the tropanyl substituent at the 3-position of the indole, already of interest from the initial impetus of the project, was examined as a probe for involvement of the 2,3-alkyl shift mechanism. The intermediate alcohol, **8**, was prepared from the reaction of 1-(phenylsulfonyl)-3-iodoindole and *tert*-butyllithium at −100 °C, to which a solution of tropinone in THF was slowly added. The elimination to the olefin **9** and subsequent hydrogenation to the saturated tropanyl system **10** were carried out as in the synthesis of **4a**.

Compound **4b** was treated with 0.1 mol equiv of HCl in methanol for 30 min. While no change in the reaction mixture was observed when followed by TLC, subsequent analysis of the products of the reaction by NMR indicated that complete conversion to a new compound had taken place. In contrast, compound **11** was stable to a variety of acidic and basic reaction conditions and could be recovered unchanged. Thus, the epimerization reaction appeared specific for groups at the 2-position of the indole. This would appear to discount the possibility of an alkyl shift mechanism between the 2- and 3-positions. In addition, the bridging nitrogen of the tropanyl system did not appear to be essential for facile isomerization under catalytic conditions.

To further investigate the details of the reaction, we turned to NMR spectroscopy and *ab initio* molecular orbital theory. The former technique would afford on opportunity to follow the progress of the reaction under deuterium labeling conditions and potentially might allow for direct spectroscopic observation of reaction intermediates. From the latter we hoped to obtain information on the structure and energetics of minima on the reaction potential energy surface as well as insight into the factors influencing the increased facility of the epimerization.

Compound **4a** was subsequently placed in an NMR tube containing CD_3OD and treated with substoichiometric DCl. This prolonged the time-course of the reaction and permitted easy monitoring of the extent of conversion to products. The progress of the reaction could be conveniently followed by monitoring the integrated values for the indole NMe peaks of **4a** and **5a**. Analysis of the ^1H- and ^{13}C-NMR indicated rapid exchange of the indole 3-H. This occurred much faster than conversion of **4a** to **5a**. While most of the peaks attributable to **5a** could be seen increasing over time, the multiplet corresponding to the proton at the epimeric center did not appear, indicating complete deuterium incorporation at this position. Interestingly, at a time point where the reaction was approximately two-thirds complete, the proton at the epimeric center of **4a** had also almost completely disappeared. This indicated that exchange of the 3′-H of **4a** with solvent was occurring to some extent as well.

A number of auxiliary and control experiments were then run on a preparative scale to corroborate some of these results. The conversion of **4a** to **5a**-*3′-d* in DCl/CD_3OD was confirmed. Surprisingly, when **5a**-*3′-d* was treated with HCl/CH_3OH, the proton at the 3′-epimeric center failed to reappear in the subsequent NMR of the product mixture. Similarly, **5a** was also found not to incorporate deuterium at the 3′-center on treatment with DCl/CD_3OD, via analysis of the mass spectrum of the isolated product. The deuterium incorporation at the indole 3-position, observed in the reactions monitored by NMR, was not present in any of the isolated products due to rapid exchange with solvent during workup.

Table 1. Relative Energies (kcal/mol) for the Different Species Involved in the Transformation of 4 to 5

	conformation			
starting compd	endo-boat	endo-chair	exocyclic olefin	exo-chair
neutral **4a**	−1.827	[0.000][a]	7.910	−6.369
protonated **4a**	2.930	[0.000][b]	3.527	−5.339
4b	−0.385	[0.000][c]	7.631	−7.019

[a] Reference energy (hartrees) = −761.205 013 926. [b] Reference energy (hartrees) = −761.615 202 291. [c] Reference energy (hartrees) = −706.500 339 815.

These experiments produced fairly similar results when applied to the conversion of **4b** to **5b**. However, one notable difference was found in the time course of the exchange reaction as observed by NMR. Under conditions of catalytic acid concentration at room temperature, the time required appeared to be somewhat longer for the conversion of **4b** to **5b** than for the conversion of **4a** to **5a**. The indole 3-H position also appeared more resistant to exchange in **4b** than in **4a**. However, it was unclear whether or not this was simply due to slight differences in the acid concentration.

Since the issue of relative rates of reaction of **4a** and **4b** was important to establishing the role of the tropanyl nitrogen in the epimerization, a competitive rate experiment in a single tube was carried out. An equimolar mixture of compounds **4a** and **4b** was treated with 1.1 equiv of DCl/D_2O in CD_3OD at 55 °C. Under these conditions, the rates of conversion of **4a** to **5a** and **4b** to **5b** were very similar. However, the rate of deuteration at the indole 3-position of **4a** was significantly faster than that for **4b**. Thus, while the tropanyl nitrogen did not appear to be essential for the epimerization, the simplest interpretation of this data implied some involvement of this group in the exchange of the indole 3-H.

The reactants, products, and some potential intermediates in these transformations were subjected to study using *ab initio* molecular orbital techniques. The observations to this point had provided evidence for the involvement of an intermediate enamine tautomer in this reaction, and this point in particular was explored. The boat and chair conformations of the tropanyl and bicyclo[3.2.1]octanyl systems were examined for the various reactants and intermediates. It was assumed that the chair conformation of the exo-substituted products would be substantially lower in energy than the boat conformation. The fully optimized structures and energies of these species were determined using the 3-21G basis set[19] as implemented within the Gaussian series of programs.[20] The relative energies for the species involved in the conversion of **4b** to **5b**, neutral **4a** to **5a**, and protonated **4a** to **5a** are shown in Table 1. Relaxed stereoviews of the four structures on the path from neutral **4a** to **5a** are shown in Figure 1. A stereoview of the overlap of the endo-chair conformation of protonated **4a**, neutral **4a**, and **4b** is shown in Figure 2.

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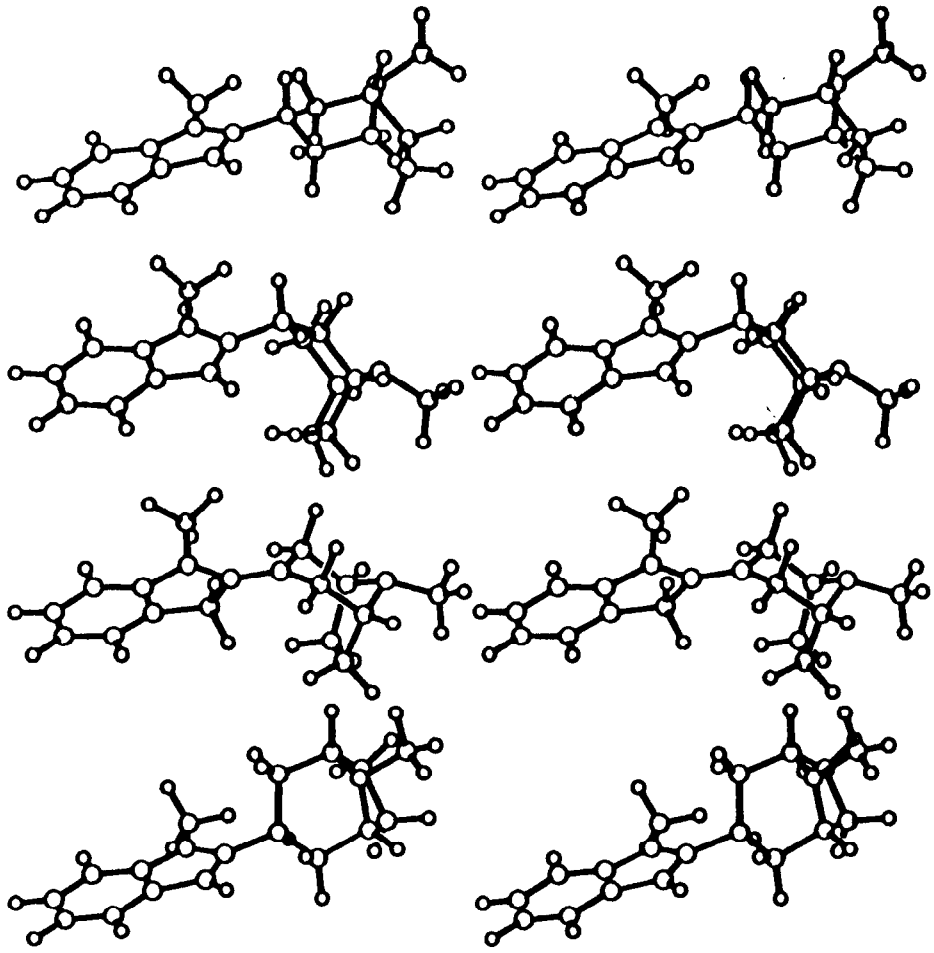


Figure 1. From top to bottom, relaxed stereoviews of the calculated structures for the endo-boat, endo-chair, exocyclic olefin, and exo-chair species from the transformation of neutral **4a** into **5a**.

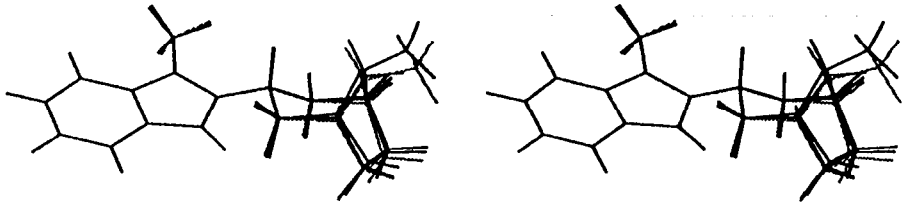


Figure 2. Relaxed stereoview of the overlap of the endo-chair conformations of neutral **4a** (black), **4b** (dark gray), and protonated **4a** (light gray).

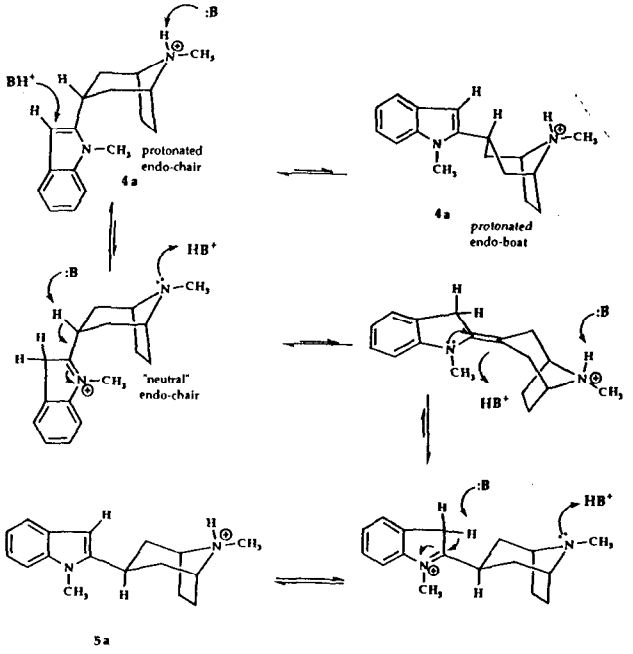
Some remarkable differences in the relative energetics of these structures can be seen in Table 1. There is a shift in preference from boat conformation to the chair conformation of the tropanyl ring system on protonation of **4a**, a swing of 4.75 kcal/mol. The energy of the intermediate enamine tautomer, relative to the lower energy conformation of **4a**, drops dramatically on protonation, by over 6 kcal/mol. The relative energy of the product, **5a**, also decreases by about 0.8 kcal/mol.

One feature of the calculated potential energy surfaces of these compounds was quite notable. In no case could a stable region of the surface be found for a conformation that would correspond to the boat form of the exocyclic olefin. Minimization started from several different "boat-like" initial geometries for these systems inevitably resulted in a descent into "chairlike" local minima. In general, the energies for those intermediate structures with reasonable bond lengths and angles were 10–15 kcal/mol above the energies for the chair form of the exocyclic olefin. Given the large change in geometry from the boat forms of **4a** and **4b** to the chair forms, this result implied that the conversion of the endo form of these two compounds to the forms containing the exocyclic olefin occurred exclusively from and to the chair conformations.

Close examination of the calculated structures for the conformations of neutral and protonated **4a** revealed clear differences in the dihedral orientation of the protons at the 2′- and 4′-positions of the tropanyl ring relative to the proton at the 3′-position. For neutral **4a** in the boat conformation, the dihedral angles fall roughly at ±55°

(20) (a) Gaussian 88, VAX Rev. C: Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian, Inc. Pittsburgh, PA. Gaussian 90, SGI Rev. J: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA.

Scheme 3



and ±173° for the pseudoequatorial and pseudoaxial positions, respectively. For protonated **4a** in the chair conformation, these dihedral angles are about ±29° and ±87°, respectively. Thus, if the preferred conformation were to actually change on protonation, it should be possible to observe this change as a difference in the appearance of the multiplet for the C-3′ proton. In fact, the fairly even multiplet for this proton in the NMR of neutral **4a** was found on protonation to change to a notably distinct triplet of triplets, with one coupling constant quite small.

Thus, the behavior of compound **4a** appeared to follow the conformational profile determined computationally for the neutral and protonated species. However, it remained unlikely that the reaction would proceed through a doubly protonated species, which would be required if **4a** were to remain continuously protonated at the tropanyl nitrogen throughout the reaction sequence. In addition, the energetics of the protonated system, shown in Table 1, imply that, insofar as the relative energies of the enamine intermediates are related to the overall rate of the epimerization, the reaction of the tropanyl system **4a** should be significantly faster than the carbocyclic analog **4b**. The competition study clearly indicates that this is not correct.

A possible reconciliation of these observations is shown in Scheme 3. The dominant conformation of **4a** in acidic solution is clearly the chair form. This species would be expected to be in rapid equilibrium with the unprotonated chair form and in a slower equilibrium with the protonated boat form. If the requisite sequence of deprotonation–protonation steps, fast on the time scale of ring conformational changes, proceeds transiently through a neutral chair form of **4a**, then the relative energetics of the reaction may well be more reflective of those for the neutral species rather than the protonated form. In this light, it is interesting to note that the calculated relative energy difference between the neutral chair form of **4a** and its exocyclic tautomer (7.9 kcal/mol) is quite similar to the difference for the chair form of the carbocyclic system **4b** and its corresponding enamine (7.6 kcal/mol). However, such a simple explanation does not address such critical kinetic factors as the relative concentrations of the reactants at the rate-limiting step for the conversion of **4a** and **4b** or how the energetics of the transformation would be affected by synchronous protonation/deprotonation steps.

Nevertheless, a number of observations are in line with a general mechanistic hypothesis involving the indole exocyclic enamine tautomer. As might be expected, the calculated energies of the exo-chair conformations of **5a** and **5b** are lower than for either conformation of **4a** or **4b** and much lower than for the exocyclic olefin intermediates. Both **5a** and **5a**-*3′-d* are stable to exchange at the 3′-position under the reaction conditions, and **5a** is not converted back into **4a** in any detectable measure. These facts, coupled with the exchange of the C-3′ proton in the reaction of **4a** at a rate faster than the conversion of **4a** to **5a**, is consistent with the presence of a higher energy intermediate which generally proceeds to product, but can occasionally return to starting material. Conversion from product to this intermediate (thus enabling exchange or reversal of the epimerization) would not occur at a significant rate due to the large energy difference between the two species.

The fundamental issue of why these species display enhanced reactivity over most 2-substituted indoles had not been addressed to this point. To further explore this issue, calculated structure and energies for *N*-methyl-2-methylindole, *N*-methyl-2-isopropylindole, and their corresponding enamine tautomers were determined (structures not shown). The relative energy of the enamine tautomer increases to 11.39 kcal/mol for the 2-methyl-substituted system and to 16.26 kcal/mol for the 2-isopropyl compound. This latter energy difference is over twice that for any of the endo-substituted bicyclic systems but is comparable to the change if measured from the corresponding exo-substituted systems.

This observation leads directly to a simple explanation for the facility of the epimerization for these systems. The endo-substituted compounds are significantly strained due to the bulkiness of the *N*-methylindole ring and its interaction with the two-carbon bridge of the bicyclic substituent. This strain is largely alleviated in the enamine tautomer. Where the 2-substituent is isopropyl or one of the bicyclic moieties, the steric issues in the enamine tautomer are similar and related to those inherent in a tetrasubstituted olefin. Thus, the additional strain in **4a** and **4b** would destabilize these compounds relative to their enamine tautomers, as compared to the values for simple alkyl analogs, and increase the reactivity of these systems.

A key element of this explanation is the prediction that the 2-isopropyl compound would be essentially kinetically inert to this transformation. This could be readily tested by evaluating the ability of the 2-isopropyl compound to incorporate deuterium at the analogous 2′-position under the reaction conditions. Treatment of this compound under the standard reaction conditions of catalytic DCl and refluxing methanol produced no evidence of deuterium incorporation at the 2′-position after 30 min. The difference in reactivity was more obviously demonstrated by subjecting this compound to much more extreme conditions. After treatment for 1 h in refluxing concentrated DCl, there was still no evidence for exchange at the 2′-position. In both cases, the integrated area of the peak in the ^{1}H-NMR spectrum of the reaction product corre-

Table 2. Receptor Binding Properties of Ibogaine and Congeners[a]

	ibogaine (1)		4		5		11	
receptor (^{3}H ligand)	pK_i (SEM)	*n*H(SEM)	pK_i(SEM)	*n*H(SEM)	pK_i(SEM)	*n*H(SEM)	pK_i(SEM)	*n*H(SEM)
muscarinic M_1 (pirenzepine)	4.5	0.75	6.2 (0.1)	1.13 (0.28)	5.5 (0.3)	1.34 (0.36)	6.5 (0.1)	0.92 (0.08)
muscarinic M_2 (*N*-methylscopolamine)	4.3	0.75	5.7 (0.1)	0.91 (0.03)	6.1 (0.2)	1.32 (0.24)	5.8 (0.1)	0.93 (0.06)
muscarinic M_3 (*N*-methylscopolamine)	4.9	0.80	6.2 (0.2)	0.96 (0.05)	5.2 (0.1)	1.16 (0.11)	6.5 (0.1)	1.09 (0.08)
5-HT_{1A} (8-hydroxy-DPAT)	<4.0		5.4 (0.1)	1.06 (0.21)	4.2 (0.1)	0.79 (0.05)	5.3 (0.1)	0.95 (0.09)
5-HT_{2A} (ketanserin)	4.9	1.09	5.5 (0.1)	1.00 (0.10)	5.0 (0.1)	1.01 (0.06)	4.5 (0.1)	0.82 (0.17)
5-HT_3 (quipazine)	<4.0		6.2 (0.1)	1.24 (0.28)	5.4 (0.1)	1.16 (0.1)	6.7 (0.2)	1.40 (0.20)
κ-opiate (U69593)	5.5	0.09	<5.0		<5.0		<5.0	

[a] Affinity (pK_i) and Hill Coefficient (*n*H) values are means (standard error of the means) of three separate determinations.

sponding to the hydrogen at the 2′-center was determined to have a relative value unchanged from that in pure starting material. By comparison, almost complete exchange of the aryl protons had taken place under the more extreme conditions. The experimental and computational results are thus in agreement, and the increase in reactivity of **4a** and **4b** relative to the simple alkyl-substituted indoles can be reasonably attributed to the increased strain inherent in the endo-substituted bicyclic systems.

The only difference in the reactivity of **4a** as compared to **4b** was seen in the rate of protonation at the indole 3-position. In the single-tube experiment, exchange at the 3-position occurred significantly faster for the tropanyl system. Measurements for different conformations of the calculated structures indicate that the closest approach of the tropanyl nitrogen to the 3-position of the indole is roughly 5.0 Å and that there is considerable steric interference between the two points. Thus, a direct, intramolecular delivery of the proton on the tropanyl nitrogen to the 3-position would seem unlikely. However, since **4a** and **4b** exchange at different rates under identical conditions in a single tube, the effect would appear likely to be due to a simple increase in the localized concentration of the proton or deuteron due to the rapid exchange off of the tropanyl nitrogen.

The results of preliminary pharmacological testing in muscarinic, 5-HT, and κ-opiate radioligand binding assays are shown in Table 2. Ibogaine belongs to a family of indole alkaloids which have CNS activity, e.g., possibly hallucinogenic and tremorigenic effects. Early mechanistic investigations seem to have ruled out adrenergic, serotonin, cannabinoid, dopamine, GABA, nicotine, and muscarinic receptors as the target (or targets) for its action. Ibogaine (**1**) has been shown to exhibit moderate activity for the κ-opiate receptor.[7] As shown in Table 1, **1** has weak affinity in all the 5-HT and muscarinic receptor binding assays, except at the κ-opiod receptor where an affinity of 3.0 μM was observed, consistent with that reported.[7] It is interesting that the congeners tested (**4a**, **5a**, and **11**) show improved affinity over **1** in some of the binding assays. There is a selective improvement in affinity of these compounds for muscarinic receptors when compared to **1**. The most striking is that of **11** with increases of 100, 30, and 40-fold affinity at M_1, M_2, and M_3 sites, respectively. There was a slight improvement in affinity for compounds **4a** and **5a** at the 5-HT_{1A} and 5-HT_{2A} receptors. Compounds **4a**, **5a**, and **11** showed less affinity than **1** at the κ-opiod site.

Experimental Section

Thin-layer chromatography was performed using silica gel GF on glass plates supplied by Analtech, Inc. Column chromatography was performed under medium pressure with 230–400-mesh Merck Kieselgel. Melting points are uncorrected. Microanalyses were performed by the Syntex Analytical department. ^{13}C NMR resonances of the tropane ring were assigned following the work of Lounasmaa et al.[21] and Hanisch et al.[22] APT,[23] ^{1}H–^{1}H homonuclear correlation,[24] and ^{1}H–^{13}C heteronuclear correlation were used to confirm assignments where necessary. Computed structures and energies were determined using Gaussian 88 and 90[20] at the 3-21G level of theory. Initial structures for neutral **4a** and **5a** were generated using the MNDO Hamiltonian in MOPAC 5.0. The starting structures for other species were modified from the *ab initio* results for **4a**. Vibrational frequency calculations were carried out for the endo-boat conformation of protonated **4a** and the enamine tautomers of neutral **4a** and of **4b** to ensure that the structures corresponded to local minima on the potental energy surface.

3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (2a). To a solution of 5.0 g (38.2 mmol) of *N*-methylindole in 40 mL of THF at 0 °C under N_2 was added 23 mL (57 mmol) of 2.5 M n-BuLi/hexane. The cooling bath was removed, and the mixture was stirred for 1 h. The mixture was cooled to 0 °C, and a solution of 5.0 g (36 mmol) tropinone in 20 mL of THF was added slowly. After 0.5 h, 100 mL of H_2O was added, and the mixture was extracted with 100 mL of ethyl acetate. The organic phase was dried with Na_2SO_4, and the solution was concentrated under reduced pressure. The residue was recrystallized from Et_2O to give 3.0 g (29%) of **2a**: mp 178–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (m, 2H), 2.01 (bd, 2H, J = 14.3 Hz), 2.20 (m, 2H), 2.22 (s, 3H), 2.40 (dd, 2H, J = 14.3, 3.4 Hz), 2.88(s, 1H, OH), 3.15 (m, 2H), 3.88 (s, 3H), 6.29 (s, 1H), 7.01 (ddd, 1H, J = 7.6, 6.7, 1.0 Hz), 7.13 (ddd, 1H, J = 8.0, 6.7, 0.9 Hz), 7.19 (bd, 1H, J = 8.0 Hz), 7.47 (bd, 1H, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.7 (t), 32.0 (q), 39.8 (q), 42.4 (t), 60.3 (d), 69.6 (s, 97.6 (d), 108.9 (d), 119.2 (d), 120.5 (d), 121.4 (d), 126.7 (s), 138.6 (s), 147.0 (s); EIMS *m/z* (relative intensity) 270 (100, M^+), 252 (22), 223 (58), 125 (15), 96 926), 83 (34), 82 (28).

Anal. Calcd: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.65; H, 8.02; N, 9.95.

3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]oct-3-ene (3a). Compound **2a** (1.0 g, 3.69 mmol) was dissolved in 10 mL of 10% HCl in ethanol, and the solution was warmed on a steam bath for 10 min. The solvent was removed under reduced pressure, and the residue was partitioned between 25 mL of 10% NH_4OH and 100 mL of ethyl acetate. The organic layer was

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dried with Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from ether/hexane, 0.78 g (84%): mp 94–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (ddd, 1H, J = 12.8, 9.4, 6.1 Hz), 1.95 (ddd, 1H, J = 11.7, 9.8, 2.6 Hz), 2.05 (d, 1H, J = 17.5 Hz), 2.13 (m, 1H), 2.25 (m, 1H), 2.47 (s, 3H), 2.85 (bd, 1H, J = 17.5 Hz), 3.39 (bdd, 1H, J = 6.4, 4.8 Hz), 3.47 (dd, 1H, J = 5.5, 5.4 Hz), 3.74 (s, 3H), 6.01 (ddd, 1H, J = 5.4, 1.7, 1.7 Hz), 6.38 (s, 1H), 7.07 (ddd, 1H, J = 7.9, 7.0, 1.1 Hz), 7.19 (ddd, 1H, J = 8.2, 7.0, 1.2 Hz), 7.27 (dd, 1H, J = 8.2, 0.8 Hz), 7.54 (ddd, 1H, J = 7.9, 1.0, 1.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$ δ 29.7 (t), 31.5 (q), 33.8 (t), 35.1 (t), 36.8 (q), 57.9 (d), 59.4 (d), 100.2 (d), 109.4 (d), 119.6 (d), 120.3 (d), 121.6 (d), 125.8 (s), 127.6 (s), 131.2 (d), 138.4 (s), 141.0 (s).

Anal. Calcd: C, 80.91; H, 7.99; N, 11.10. Found: C, 79.86; H, 8.24; N, 10.86.

***endo*-3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]-octane Hydrochloride (4a).** A mixture of 500 mg (1.98 mmol) of **3a** and 100 mg of 10% Pd/C in 50 mL of ethanol was shaken under 20 psi of hydrogen for 2 h. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up in 5.0 mL of ethanol and 5.0 mL of Et_2O, and the solution was stirred at 0 °C while 0.72 mL of 10% HCl/EtOH (1.98 mmol) was added. The crystalline solid was collected and dried *in vacuo* to give 430 mg of **4a** (75%): mp 281–282 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.05–2.30 (m, 4H), 2.35 (bd, 2H, J = 15.9 Hz), 2.70–2.90 (m, 2H), 2.79 (s, 3H), 3.49 (bt, 1H, J = 8.7 Hz), 3.65 (s, 3H), 3.92 (nm, 2H), 6.53 (d, 1H, J = 0.9 Hz), 7.03 (ddd, 1H, J = 8.2, 7.1, 1.1 Hz), 7.14 (ddd, 1H, J = 8.2, 7.1, 1.2 Hz), 7.30 (bd, 1H, J = 8.2 Hz), 7.49 (ddd, 1H, J = 8.2, 1.1, 0.9 Hz); ^{13}C NMR (125.8 MHz, CD_3OD) δ 24.6 (d), 24.9 (t), 30.8 (q), 34.5 (t), 39.4 (q), 64.1 (d), 98.3 (d), 110.0 (d), 120.5 (d), 120.9 (d), 122.3 (d), 128.6 (s), 139.8 (s), 144.7 (s).

Anal. Calcd: C, 69.14; H, 8.02; N, 9.49. Found: C, 69.31; H, 7.91; N, 9.34.

4a free base: mp 73–74 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, CD_3OD) δ 1.65 (m, 2H), 1.88 (ddd, 2H, J = 13.7, 4.0, 2.1 Hz), 1.98 (m, 2H), 2.2 (s, 3H), 2.43 (ddd, 2H, J = 13.7, 9.0, 5.6 Hz), 3.12 (nm, 2H), 3.21 (ddddd, 1H, J = 9.0, 9.0, 4.0, 4.0, 0.3 Hz), 3.52 (s, 3H), 6.32 (d, 1H, J = 0.3 Hz), 6.97 (ddd, 1H, J = 7.9, 7.7, 0.09 Hz), 7.08 (ddd, 1H, J = 8.0, 7.7, 0.09 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 7.9 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (m, 4H), 2.10 (m, 2H), 2.38 (s, 3H), 2.66 (m, 2H), 3.34 (m, 3H), 3.68 (s, 3H), 6.39 (s), 7.09 (ddd, 1H, J = 8.0, 7.6, 0.9 Hz), 7.19 (ddd, 1H, J = 8.0, 7.9, 1.3 Hz), 7.28 (bd, 1H, J = 7.9 Hz), 7.55 (bd, 1H, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.4 (d), 27.2 (t), 30.1 (q), 36.3 (t), 40.3 (q), 60.0 (d), 97.4 (d), 108.8 (d), 119.3 (d), 119.8 (d), 120.8 (d), 127.6 (s), 137.8 (s), 146.3 (s).

***exo*-3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]-octane Hydrochloride (5a).** To a solution of 180 mg (0.71 mmol) of **4a** free base in 5.0 mL of EtOH was added 1.3 mL (3.56 mmol) of 2.74 M HCl/EtOH. The reaction mixture was heated under reflux for 0.5 h. The solvent was removed under reduced pressure at 40 °C, and the residue was recrystallized from EtOH to afford 172 mg of **5a** (83%): mp 286–287 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.10–2.50 (m, 8H), 2.82 (s, 3H), 3.42 (m, 1H), 3.72 (s, 3H), 3.97 (nm, 2H), 6.33 (s, 1H), 7.00 (ddd, 1H, J = 7.8, 7.1, 1.1 Hz), 7.13 (ddd, 1H, J = 8.2, 7.1, 1.2 Hz), 7.32 (dd, 1H, J = 8.2, 0.7 Hz), 7.46 (d, 1H, J = 7.8 Hz); ^{13}C NMR (125.8 MHz, CD_3OD) δ 25.1 (t), 25.6 (d), 29.8 (q), 37.3 (t), 39.6 (q), 65.3 (d), 98.7 (d), 109.9 (d), 120.3 (d), 120.9 (d), 122.2 (d), 129.0 (s), 138.9 (s), 142.7 (s).

Anal. Calcd: C, 68.10; H, 8.07; N, 9.34. Found: C, 68.53; H, 7.89; N, 9.19.

5a free base: mp 114–115 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (m, 4H), 2.00 (ddd, 2H, J = 13.4, 13.4, 2.4 Hz), 2.15 (m, 2H), 2.35 (s, 3H), 3.07 (dddd, 1H, J = 13.4, 13.4, 5.0, 5.0 Hz), 3.28 (nm, 2H), 3.68 (s, 3H), 6.30 (s, 1H), 7.04 (ddd, 1H, J = 7.8, 7.0, 1.0 Hz), 7.14 (ddd, 1H, J = 8.2, 7.0, 1.2 Hz), 7.24 (bd, 1H, J = 8.2 Hz), 7.51 (bd, 1H, J = 7.8 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 26.4 (t), 26.5 (d), 29.4 (q), 37.6 (t), 40.3 (q), 61.4 (d), 97.6 (d), 108.7 (d), 119.3 (d), 120.0 (d), 120.7 (d), 128.0 (s), 137.4 (s), 144.8 (s).

3-[(1-Phenylsulfonyl)indol-3-yl]-8-methyl-8-azabicyclo-[3.2.1]octan-3-ol (8). Under an N_2 atmosphere a solution of 3 g (7.86 mmol) of 1-(phenylsulfonyl)-3-iodoindole[26] (**6**) in 60 mL of THF was cooled to −100 °C. To this mixture was added 9.2 mL (15.64 mmol) of 1.7 M *tert*-butyllithium/pentane. After 5 min, a solution of 1.1 g (7.91 mmol) of tropinone in 20 mL of THF was added slowly. The cooling bath was removed, and the reaction mixture was stirred until the temperature was 0 °C. Then 50 mL of H_2O was added, and the mixture was extracted with 100 mL of EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from MeOH to give 1.12 g (36%) of **8**: mp 243–244 °C; ^{1}H NMR (300 MHz, DMSO d-6) δ 1.78 (bd, 2H, J = 14.2 Hz), 1.90 (m, 2H), 2.18 (m, 2H), 2.22 (s, 3H), 2.30 (m, 2H), 3.09 (nm, 2H), 4.89 (s, 1H), 7.20–7.35 (m, 2H), 7.45 (s, 1H), 7.58 (dd, 2H, J = 7.5, 7.4 Hz), 7.68 (dd, 1H, J = 7.4, 7.4 Hz) 7.80 (d, 1H, J = 8.2 Hz), 7.91 (d, 1H, J = 8.2 Hz), 7.93 (d, 2H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, DMSO d-6) δ 24.9 (t), 40.8 (q), 44.0 (t), 60.4 (d), 68.4 (s), 113.2 (d), 121.4 (d), 121.6 (d), 124.2 (d), 126.4 (d), 128.1 (s), 129.6 (d), 133.4 (s), 134.3 (d), 135.2 (s), 137.1 (s).

Anal. Calcd: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.27; H, 6.03; N, 6.90.

3-[(1-Phenylsulfonyl)indol-3-yl)]-8-methyl-8-azabicyclo-[3.2.1]oct-3-ene (9). Compound **9** was prepared from compound **8** following the method for compound **3a** in 68% yield: mp 147–148 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.93 (m, 1H), 2.03 (d, 1H, J = 16.9 Hz), 2.12 (m, 1H), 2.20 (m, 1H), 2.44 (s, 3H), 2.90 (bdd, 1H, J = 16.9, 4.6 Hz), 3.41 (dd, 1H, J = 4.6, 4.6 Hz), 3.46 (dd, 1H, J = 5.5, 5.5 Hz), 6.39 (dt, 1H, J = 5.5, 1.4 Hz), 7.24 (ddd, 1H, J = 7.3, 7.2, 1.2 Hz), 7.31 (ddd, 1H, J = 7.7, 7.3, 1.5 Hz), 7.42 (bt, 2H, J = 7.2 Hz), 7.46 (s, 1H), 7.52 (m, 1H), 7.77 (bd, 1H, J = 7.2 Hz), 7.87 (bd, 2H, J = 8.3 Hz), 7.99 (bd, 1H, J = 7.7 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 29.6 (t), 33.5 (t), 34.4 (t), 36.8 (q), 57.9 (d), 59.4 (d), 113.8 (d), 121.3 (d), 122.5 (d), 123.2 (s), 123.5 (d), 124.8 (d), 126.5 (s), 126.8 (d), 128.7 (d), 128.8 (s), 129.3 (d), 133.8 (d), 135.6 (s), 138.2 (s).

***endo*-3-[(1-Phenylsulfonyl)indol-3-yl]-8-methyl-8-azabicyclo[3.2.1]octane Hydrochloride (10).** Compound **9** was reduced following the procedure for compound **3a** to give compound **10** in 26% yield after column chromatography eluting with 5% methanol in CH_2Cl_2 containing 1% ammonium hydroxide. The hydrochloride salt was recrystallized from MeOH/Et_2O: mp 177 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.78 (m, 2H), 2.15 (m, 2H), 2.49 (d, 2H, J = 15.9 Hz), 2.70 (m, 2H), 2.78 (s, 3H), 3.43 (bt, 1H, J = 8.3 Hz), 3.90 (nm, 2H), 7.28 (dd, 1H, J = 7.5, 7.5 Hz), 7.38 (dd, 1H, J = 8.3, 7.5 Hz), 7.4–7.6 (m, 4H), 7.74 (d, 1H, J = 1.5 Hz), 7.89 (bd, 1H, J = 7.3 Hz), 8.07 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 24.6 (d), 24.7 (t), 33.6 (t), 39.4 (q), 64.3 (d), 115.3 (d), 121.3 (d), 124.7 (d), 126.3 (d), 127.7 (d), 128.3 (s), 130.4 (d), 131.2, 135.2 (d), 137.2 (s), 139.1 (s).

Anal. Calcd: C, 63.37; H, 6.04; N, 6.72. Found: C, 63.54; H, 5.93; N, 6.67.

***endo*-3-(Indol-3-yl)-8-methyl-8-azabicyclo[3.2.1]octane Hydrochloride (11).** A mixture of 1.3 g (3.125 mmol) of **10** in 100 mL of 5% KOH in MeOH containing 1% H_2O was heated under reflux for 20 h. The reaction mixture was concentrated under reduced pressure at 40 °C. The residue was partitioned between 10 mL of H_2O and 100 mL of EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was converted to the hydrochloride salt using 10% HCl/EtOH and recrystallized from EtOH/Et_2O to give 0.3 g (35%) of compound **11**: mp 216–217 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.02–2.19 (m, 4H), 2.63–2.67 (m, 4H), 2.78 (s, 3H), 3.54–3.57 (m, 1H), 3.91 (M, 2H), 7.00–7.05 (m, 1H), 7.09–7.15 (m, 1H), 7.31 (d, 1H, J = 1.4 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 7.9 Hz).

11 free base: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.90 (ddd, 2H, J = 14.1, 4.8, 2.0 Hz), 2.01 (ddd, 2H, J = 7.1, 7.1, 3.3 Hz), 2.31 (s, 3H), 2.52 (ddd, 2H, J = 14.1, 8.3, 6.0 Hz), 3.22 (m), 3.39 (m, 1H), 7.02 (dd, 1H, J = 2.1, 1.2 Hz), 7.08 (ddd, 1H, J = 7.9, 7.8, 0.9 Hz), 7.17 (ddd, 1H, J = 8.0, 7.8, 1.1 Hz), 7.32 (bd, 1H, J = 8.0 Hz), 7.62 (bd, 1H, J = 7.9 Hz), 8.25 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 24.3 (d), 27.0 (t), 36.3 (t), 40.4 (q), 60.1 (d), 111.1 (d), 118.8 (d), 119.5 (d), 119.7 (d), 121.7 (d), 122.4 (s), 127.0 (s), 136.8 (s).

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Anal. Calcd: C, 68.31; H, 7.71; N, 9.96. Found: C, 68.75; H, 7.56; N, 9.58.

3-(1-Methylindol-2-yl)bicyclo[3.2.1]octan-3-ol (2b). The alcohol **2b** was prepared from 1-methylindole and bicyclo[3.2.1]-octan-3-one[27] following the procedure for **2a**. Compounds**2b** was obtained in 20% yield after column chromatography over silica gel using 5% Et_2O in hexane: mp 124–125 °C (Et_2O/hexane); ^1H NMR (300 MHz, CD_3OD) δ 1.55 (m, 2H), 1.66 (m, 2H), 2.20 (m, 2H), 2.20 (m, 4H), 2.35 (m, 2H), 3.94 (s, 3H), 6.31 (s, 1H), 6.96 (ddd, 1H, J = 8.0, 8.0, 1.0 Hz), 7.09 (ddd, 1H, J = 8.2, 8.0, 1.1 Hz), 7.27 (bd, 1H, J = 8.2 Hz), 7.43 (bd, 1H, J = 8.0 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 29.3 (t), 32.5 (q), 36.2 (d), 39.5 (t), 45.2 (t), 72.2 (s), 98.3 (d), 109.6 (d), 119.9 (d), 121.1 (d), 122.0 (d), 128.2 (s), 140.1 (s), 149.4 (s). Anal. Calcd: C, 79.65; H, 8.65; N, 5.46. Found: C, 79.62; H, 8.55; N, 5.51.

3-(1-Methylindol-2-yl)bicyclo[3.2.1]oct-3-ene (3b). A solution of 0.15 g (0.6 mmol) of alcohol **2b** in 5.0 mL of 10% HCl/EtOH was stirred at 22 °C for 5 min. The solvent was removed under reduced pressure. The residue was partitioned between 25 mL of Et_2O and 10 mL of 10% $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from hexane to give compound **3b**, 0.135 g (94%): mp 56 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.76 (m, 2H), 1.94 (m, 2H), 2.23 (bd, 1H, J = 17.2 Hz), 2.51 (m, 1H), 2.62 (m, 1H), 2.72 (bd, 1H, J = 17.2 Hz), 3.71 (s, 3H), 6.12 (bd, 1H, J = 6.0 Hz), 6.32 (s, 1H), 7.07 (ddd, 1H, J = 8.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.5 (t), 31.3 (q), 33.4 (d), 35.2 (t), 35.4 (t), 35.7 (d), 41.3 (t), 99.6 (d), 109.3 (d), 119.5 (d), 120.2 (d), 121.2 (d), 126.8, 136.1 (d), 138.2 (s), 142.4 (s).

Anal. Calcd: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.06; H, 8.40; N, 6.31.

***endo*-3-(1-Methylindol-2-yl)bicyclo[3.2.1]octane (4b).** Following the procedure for **4a** the olefin **3b** was reduced to **4b** in 91% yield: mp 82–83 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (m, 1H), 1.45–1.80 (m, 7H), 2.30 (m, 4H), 3.00 (m, 1H), 3.64 (s, 3H), 6.30 (s, 1H), 7.05 (ddd, 1H, J = 8.1, 7.7, 1.0 Hz), 7.13 (ddd, 1H, J = 8.1, 8.1, 1.4 Hz), 7.24 (dd, 1H, J = 8.1, 1.3 Hz), 7.52 (bd, 1H, J = 7.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9 (d), 29.7 (q), 32.3 (t), 32.5 (d), 32.6 (t), 39.2 (t), 97.2 (d), 108.7 (d), 119.2 (d), 119.8 (d), 120.5 (d), 127.9 (s), 137.5 (s), 147.0 (s).

Anal. Calcd: C, 85.31; H, 8.84; N, 5.85. Found: C, 84.94; H, 9.17; N, 5.80.

***exo*-3-(1-Methylindol-2-yl)bicyclo[3.2.1]octane (5b).** Treatment of **4b** with ethanolic HCl as described for the preparation of **5a** gave compound **5b** in 90% yield: mp 86–87 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.5–1.9 (m, 10H), 2.38 (nm, 2H), 3.10 (dddd, 1H, J = 12.0, 12.0, 5.1, 5.1 Hz), 3.74 (s, 3H), 6.29 (s, 1H), 7.09 (ddd, 1H, J = 8.1, 7.7, 1.1 Hz), 7.18 (ddd, 1H, J = 8.2, 8.1, 1.2 Hz), 7.30 (d, 1H, J = 8.2 Hz), 7.56 (d, 1H, J = 7.7 Hz).

Anal. Calcd: C, 85.31; H, 8.84; N, 5.85. Found: C, 85.54; H, 8.68; N, 5.48.

***exo*-3-Deuterio-3-(1-methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (5b).** To a solution of 0.08 g (0.315 mmol) of *endo*-amine free base compound **4a** in 1.0 mL of 99.8% CD_3OD under N_2 was added 30 μL (0.352 mmol) of 35% DCl/D_2O. The reaction mixture was heated under reflux for 0.5 h. The solvent was removed under reduced pressure at 40 °C. The aryl deuteriums were exchanged by dissolving the residue in 2.9 mL of EtOH, adding two drops of 10% HCl in EtOH, and heating under reflux for 0.5 h. The solvent was removed under reduced pressure, and the residue was partitioned between 5.0 mL of 10% NH_4OH and 25 mL of EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from EtOAc/hexane to give compound **5b**, 0.065 g in 74% yield: mp 112 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 4H), 2.00 (bd, 2H, J = 13.0 Hz), 2.15 (m, 2H), 2.35 (s, 3H), 3.28 (nm, 2H), 3.68 (s, 3H), 6.30 (s, 1H), 7.04 (ddd, 1H, J = 7.7, 7.0, 1.0 Hz), 7.14 (ddd, 1H, J = 8.2, 7.0, 1.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.0 (d, $J_{C,D}$ = 18.6 Hz), 26.3 (t), 29.5 (q), 37.5 (t), 40.3 (q), 61.4 (d), 97.5 (d), 108.7 (d), 119.2 (d), 119.8 (d), 120.5 (d), 127.7 (s), 137.1 (s), 144.6 (s); EIMS m/z (relative intensity) 255 (78, M^+), 225 (8), 160 (31), 132 (41), 96 (40), 83 (100). Anal. Calcd: C, 79.96; H, 8.29; N, 10.97. Found: C, 79.45; H, 8.21; N, 10.44.

1-Methyl-2-isopropylindole. To a solution of 0.5 g (2.65 mmol) of 1-(1-methyl-2-indolyl)-1-methylethanol[28] in 25 mL of ethyl acetate was added 0.1 g of 10% Pd/C. The reaction was stirred under hydrogen, and 0.3 mL (0.84 mmol) of 2.78 M HCl in ethanol was added. The reaction mixture was stirred at room temperature for 15 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by medium-pressure column chromatography over silica gel 230–400 mesh eluting with hexane. Product fractions were combined and concentrated under reduced pressure to give 1-methyl-2-isopropylindole[29] as an oil in 59% yield: ^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, 6H), 3.14 (m, 1H), 3.69 (s, 3H), 6.20 (s, 1H), 6.96 (ddd, 1H, J = 7.6, 7.1, 1.1 Hz), 7.06 (ddd, 1H, 8.1, 7.1, 1.3 Hz), 7.36 (bdd, 1H, J = 8.1, 1.1 Hz), 7.44 (bdd, 1H, J = 7.6, 1.3 Hz).

Anal. Calcd: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.19; H, 8.76; N, 8.03.

Competitive Reaction of 4a and 4b. In an NMR tube 1.91 mg (0.00752 mmol) of free base **4a** and 1.8 mg (0.00752 mmol) of **4b** were dissolved in 0.5 mL of 99.8% CD_3OD. A base-line spectrum was recorded. Subsequently, 70 μL of 0.12 M DCl/D_2O in CD_3OD was added to the NMR tube. The tube was inserted into the probe and heated to 328 K (55 °C). After 30 min the only notable change was the complete deuteration of the aryl C-3 of **4a**. The rates of conversion of **4a** to **5a** and **4b** to **5b**, followed by monitoring the presence of the distinct indole *N*-methyl peaks in the ^1H-NMR for the four compounds, were comparable. The conversion was monitored over the course of 50 h, at which time the reaction had proceeded to 50% completion.

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Supplementary Material Available: Experimental data for **2a**, **3a**, **4a**, **4a** (free base), **5a**, **5a** (free base), **8–11**, **11** (free base), **2b**, **3b**, **4b**, and **5b** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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