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STEREOSELECTIVE REDUCTION OF 1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO-[2,3-a]QUINOLIZINE WITH SODIUM BOROHYDRIDE IN TRIFLUOROACETIC ACID[1]

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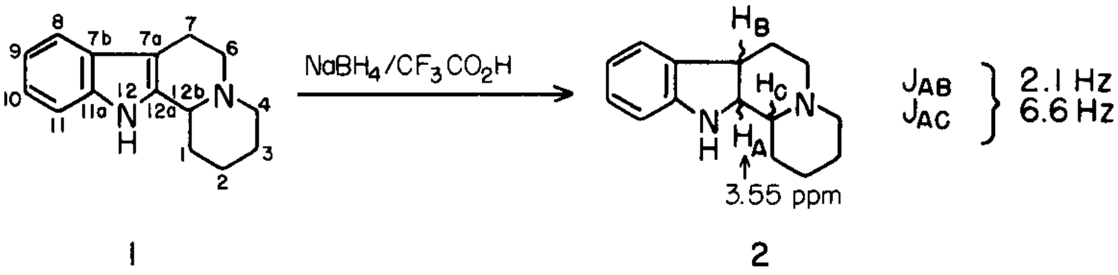
Abstract - The sodium borohydride/trifluoroacetic acid reduction of the title alkaloid (1) is highly stereoselective, giving the all-cis product 2 in excellent yield.

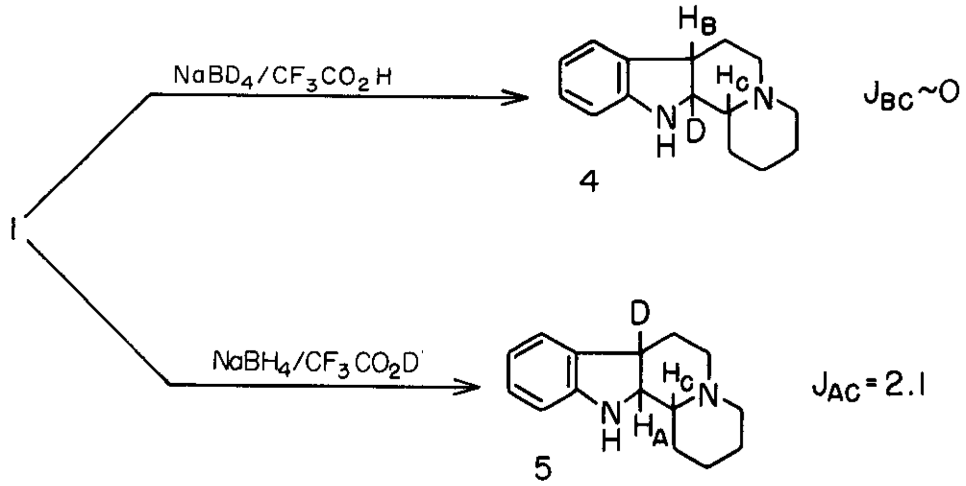
Recent years have seen great improvements in the methodology for reducing indoles to dihydroindoles (indolines). These newer methods, generally under acidic conditions, with borane,[2] amine-boranes,[3] boron hydrides,[4] and trialkylsilanes,[5] supersede the older methods (i.e., metals in mineral acid, catalytic hydrogenation)[6] for generality, convenience, and efficiency. Furthermore, the use of trifluoroacetic acid in several of these methods[2,3d,4b,4c,4e,5b] allows one to reduce 1,2,3,4-tetrahydro-β-(and γ-)-carbolines and other indoles containing a second, basic nitrogen. These particular indoles can be difficult to reduce under weaker acid conditions because protonation of the basic nitrogen suppresses protonation of the indole double bond, which is presumed necessary for successful reduction.

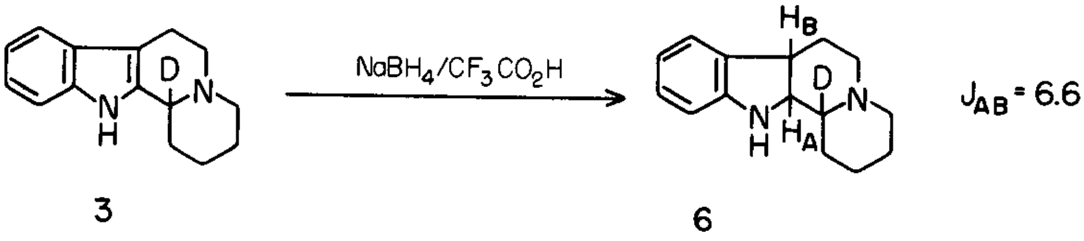
For example, sodium borohydride ($NaBH_4$) in trifluoroacetic acid (CF_3CO_2H) has been used to reduce several indole[2,3-a]quinolizidines and other indole alkaloids (i.e., yohimbine,[7] reserpiline,[7b] ibogaine,[7b] tetraphylline,[7b] raubasine[7b]). Although these reductions were reported to be stereoselective, no attempt was made to ascertain the stereochemistry of the major product.[7b] To answer this question we have studied the reaction of the readily available[8] alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1)[9] with $NaBH_4/CF_3CO_2H$.[10,11]

Treating a solution of 1 in neat CF_3CO_2H at -5° to 0° with $NaBH_4$ (pellets) gave 1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizine (2) as one major stereoisomer, mp 75-75.5°, in 90% purified yield.[12,13] The ^{1}H-nmr spectrum of 2 reveals one distinguishing feature: a one-proton doublet of doublets at 3.55 ppm



(J=2.1 and 6.6 Hz), suggestive of H_A.[14] To identify this signal unambiguously and to assign the two associated coupling constants, we prepared the deuterated derivatives 4-6 as shown below.

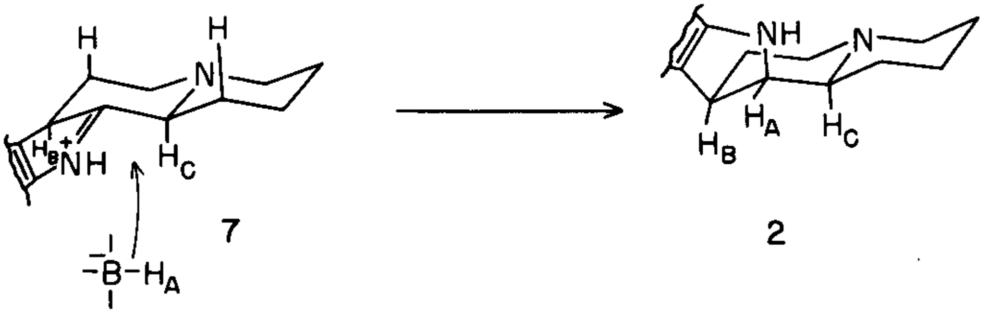




Treating 1 with $NaBD_4/CF_3CO_2H$ produced 4 in 66% yield whose ^1H-nmr spectrum showed a greatly diminished signal at 3.5 ppm, confirming this as arising from H_A. Treating 1 with $NaBH_4/CF_3CO_2D$ produced 5 in 88% yield which displayed H_A as a doublet (2.1 Hz), and treating $\underline{3}^{15}$ with $NaBH_4/CF_3CO_2H$ produced $\underline{6}$ in 65% yield which displayed H_A as a doublet (6.6 Hz). Thus, the two couplings involving H_A are assigned J_{AC}=2.1 Hz and J_{AB}=6.6 Hz.

Using Dreiding stereomodels[16] we have examined all of the reasonable conformations of the four diastereomers of $\underline{2}$, and measured the appropriate dihedral angles in each with a Dreiding torsiometer[16] to estimate J_{AB} and J_{AC} from the Karplus equation.[17-19] The only pair of dihedral angles ($H_BC_{7a}C_{12a}H_A$ and $H_AC_{12a}C_{12b}H_C$) that gives reasonable agreement between the predicted and observed coupling constants J_{AB} and J_{AC} belongs to a conformation having the cis-cis configuration for $\underline{2}$ (shown below). The value J_{AB}=6.6 Hz (dihedral angle 25-30°) is in excellent agreement with the comparable couplings reported for cis-1,2,3,4,4a,9a-hexahydrocarbazole (6 Hz)[20] and for a cis-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole derivative (6.6 Hz),[4c] both of which have a cis-fused five-six ring system. In contrast, a five-six trans-ring fusion is known to produce larger coupling (e.g., 11.8 Hz in trans-hexahydrocarbazole[20]). Similarly, the ^{13}C chemical shifts for C-7a (40.3 ppm) and C-12a (63.9 ppm) in $\underline{2}$ (signals which respectively disappear in the ^{13}C spectra of $\underline{5}$ and $\underline{4}$) match well with the corresponding chemical shifts reported for the cis-fused pyrido[4,3-b]indole derivative cited above (41.1 and 57.5 ppm) but not for the trans-fused isomer (47.3 and 68.4 ppm).

The value J_{AC}=2.1 Hz (dihedral angle 40-45°) is smaller than the Karplus equation would generally predict, and most likely is a consequence of the two electronegative nitrogens attached to the coupling fragments, since this is known to decrease vicinal coupling, sometimes substantially.[18,19] A trans-stereochemistry of H_AH_C, regardless of the H_AH_B stereochemistry, would have given rise to a large J_{AC} (8-12 Hz[20]). Therefore, we assign the cis-cis configuration to $\underline{2}$.



This stereochemistry is reasonable mechanistically since one anticipates stereoelectronic axial protonation[21] of **1** giving *cis*-indolenium ion **7**, followed by hydride delivery by the bulky *bis*- or *tris*(trifluoroacetoxy)borohydride species[10] from an equatorial direction[22] giving the generally presumed[2a,3b,6,14] more stable five-six *cis*-fused indoline ring.[23] Indeed, treating a solution of **1** and $NaBH_4$ in tetrahydrofuran with CF_3CO_2H, conditions which produce the more reactive and less selective reducing agent sodium mono(trifluoroacetoxy) borohydride,[10] gives **2** in only 20% yield along with at least two of the other diastereomers.

Acknowledgments

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References and Notes

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