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

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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 methods2,3d,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 (NaBH4) in trifluoroacetic acid (CF3CO2H) has been used to reduce several indole[2,3-a]quinolizidines and other indole alkaloids (i.e., yohimbine,7 reserpine,7b ibogaine,7b tetrahylline,7b raubasine7b). 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 available8 alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1)9 with NaBH4/CF3CO2H.10,11

Treating a solution of 1 in neat CF3CO2H at -5° to 0° with NaBH4 (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 1H-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 $H_A$.\textsuperscript{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$_3$CO$_2$H produced 4 in 66% yield whose $^1$H-nmr spectrum showed a greatly diminished signal at 3.5 ppm, confirming this as arising from $H_A$.

Treating 1 with NaBH$_4$/CF$_3$CO$_2$D produced 5 in 88% yield which displayed $H_A$ as a
doublet (2.1 Hz), and treating \( \text{2}^{15} \) with NaBH\(_4/\text{CF}_3\text{CO}_2\text{H} \) produced \( \text{6} \) in 65\% yield which displayed \( \text{H}_A \) as a doublet (6.6 Hz). Thus, the two couplings involving \( \text{H}_A \) are assigned \( J_{\text{AC}}=2.1 \text{ Hz} \) and \( J_{\text{AB}}=6.6 \text{ Hz} \).

Using Dreiding stereomodels\(^{16} \) we have examined all of the reasonable conformations of the four diastereomers of \( \text{2} \), and measured the appropriate dihedral angles in each with a Dreiding torsimeter\(^{16} \) to estimate \( J_{\text{AB}} \) and \( J_{\text{AC}} \) from the Karplus equation.\(^{17-19} \) The only pair of dihedral angles (\( \text{H}_B\text{C}_7\text{aC}_12\text{aH}_A \) and \( \text{H}_A\text{C}_12\text{aC}_12\text{bH}_C \)) that gives reasonable agreement between the predicted and observed coupling constants \( J_{\text{AB}} \) and \( J_{\text{AC}} \) belongs to a conformation having the **cis-cis** configuration for \( \text{2} \) (shown below). The value \( J_{\text{AB}}=6.6 \text{ Hz} \) (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), 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 \(^{13}\text{C} \) chemical shifts for \( \text{C}-7\text{a} \) (40.3 ppm) and \( \text{C}-12\text{a} \) (63.9 ppm) in \( \text{2} \) (signals which respectively disappear in the \(^{13}\text{C} \) spectra of \( \text{5} \) and \( \text{4} \)) 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 \( J_{\text{AC}}=2.1 \text{ Hz} \) (dihedral angle 40-45°) is smaller than the Karplus equation would generally predict, and most likely is a consequence of the two electro-negative nitrogens attached to the coupling fragments, since this is known to decrease vicinal coupling, sometimes substantially.\(^{18,19} \) A **trans**-stereochemistry of \( \text{H}_A\text{H}_C \), regardless of the \( \text{H}_A\text{H}_B \) stereochemistry, would have given rise to a large \( J_{\text{AC}} \) (8-12 Hz)\(^{20} \). Therefore, we assign the **cis-cis** configuration to \( \text{2} \).

![Diagram](image_url)
This stereochemistry is reasonable mechanistically since one anticipates stereo-electronic axial protonation\textsuperscript{21} of 1 giving cis-indolium ion 2, followed by hydride delivery by the bulky bis- or tris(trifluoroacetoxy)borohydride species\textsuperscript{10} from an equatorial direction\textsuperscript{22} giving the generally presumed\textsuperscript{2a,3b,6,14} more stable five-six cis-fused indoline ring.\textsuperscript{23} Indeed, treating a solution of 1 and NaBH\textsubscript{4} in tetrahydrofuran with CF\textsubscript{3}CO\textsubscript{2}H, conditions which produce the more reactive and less selective reducing agent sodium mono(trifluoroacetoxy) borohydride,\textsuperscript{10} gives 2 in only 20% yield along with at least two of the other diastereomers.

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References and Notes

1. This paper is Part X in the series "Reactions of Sodium Borohydride in Acidic Media." For Part IX, see G. W. Gribble, W. J. Kelly, and M. P. Sibi, Synthesis, submitted.


12. 2: $^1$H NMR (CDCl$_3$) $\delta$ 1.1-2.2 (m, 11H), 2.6-3.1 (m, 3H), 3.55 (dd, 1H), 6.5-7.2 (m, 4H); $^{13}$C NMR (CDCl$_3$) $\delta$ 24.9 (C-2), 25.6 (C-3), 29.6 (C-1), 29.8 (C-7), 40.3 (C-7a), 54.6 (C-6), 56.7 (C-4), 62.8 (C-12b), 63.9 (C-12a), 110.5 (C-11), 118.6 (C-9), 122.9 (C-10), 127.0 (C-8), 134.7 (C-7b), 149.6 (C-11a); mass spectrum, m/e 228.1620 (M$^+$, calcd 228.1626), 144, 111, 98 (100%), 83, 69, 55. IR (CHCl$_3$) 3390, 2940, 2855, 2805, 2765, 1610, 1485, 1465, 1355, 1245, 1125, 1105 cm$^{-1}$. Anal. calcd for C$_{15}$H$_{20}$N$_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.74; H, 8.85; N, 12.21.

13. There was also isolated 5% of 1 (flash chromatography); two minor reaction components (tlc) have not been identified but are probably diastereomers.

14. For comparison, the corresponding proton (H-9a) in cis-hexahydrocarbazole resonates at 3.67 ppm: S. A. Monte and R. R. Schmidt, Tetrahedron, 1971, 27, 3331.


16. Brinkmann Instruments, Inc. Cantiague Road, Westbury, N.Y. 11590, USA.

18. Although vicinal proton coupling depends also on substituent electronegativity, bond angles, and bond lengths, dihedral angle measurements give a good approximation to the relative magnitude ("large", "medium", or "small") of vicinal couplings: M. Karplus, J. Am. Chem. Soc., 1963, 85, 2870.


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