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STEREOCHEMICALLY COMPLEMENTARY REDUCTIONS OF INDOLES

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Abstract: Indoles containing a 2, 3-fused bridged ring undergo highly stereoselective reduction to *cis*-fused derivatives with the *endo*-*exo* stereochemistry depending on choice of reducing agent.

The selective reduction of the 2,3-double bond of indoles has been accomplished by treatment with solutions of alkali metals in liquid ammonia followed by quenching with a source of protons[1], and by reduction in strongly acidic media. Reagents employed in the latter method have included hydrogen/catalyst, dissolving metal-acid combinations[2] acyloxyboranes[3], and amine-boranes[4]. In the case of indoles bearing a 2,3-fused ring, reduction by either method generally results in the formation of the *cis*-ring junction[5].

It was of interest to apply some of these techniques to compound **2**, since the presence of the ethano bridge restricts ring inversion, making possible a more detailed determination of the stereochemical course of the reduction.

Synthetic access to this previously unreported ring system was accomplished by deprotection of the hydrazone **1** followed by treatment *in situ* with HCl/isopropanol to afford **2**. Treatment of **2** with a solution of sodium in liquid ammonia-tetrahydrofuran, followed by quenching with NH_4Cl resulted in the formation of a single product, m.p. 111.5-112.5^0 isolated in 83% yield. The structure of this material was established as **3** by single crystal X-ray analysis[6]. The crystal structure was solved by direct methods[7]. Full matrix least-squares refinement of atomic positional[8] and thermal parameters (anisotropic C,N; isotropic H) converged to R=0.047 over 3463 reflections recorded on an Enraf-Nonius CAD-3 automated diffractometer[9] (Ni-filtered Cu-K $_\alpha$ radiation, γ =1.5418 Å; θ - 2θ scans, θ_{max}=67°). The conformations of the two crystallographically independent molecules defining the asymmetric crystal unit do not differ significantly. A view of the molecule is shown in the Figure.

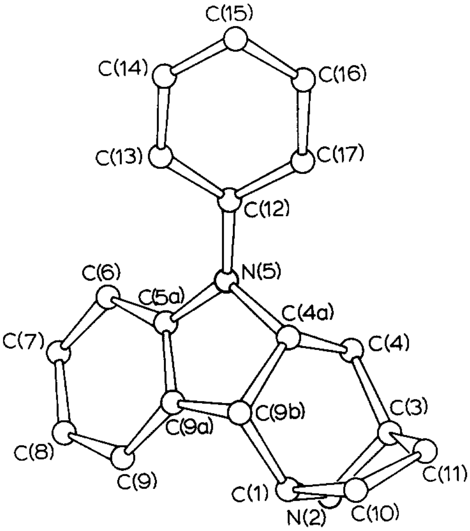
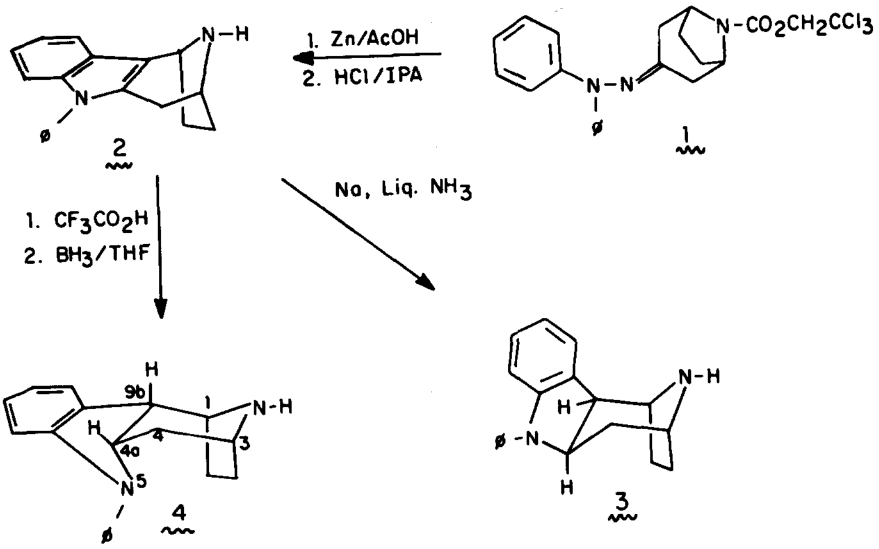
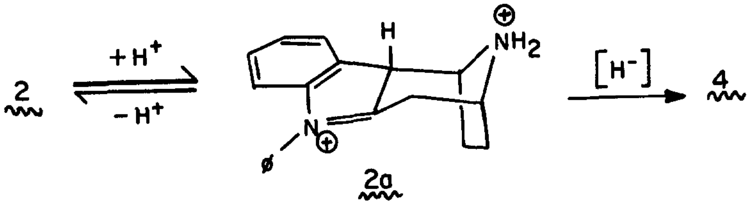


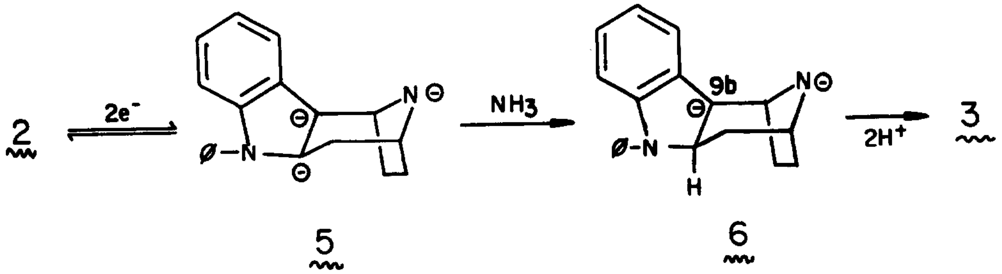
Figure. Structure and solid-state conformation of <u>3</u>.

Treatment of a trifluoroacetic acid solution of <u>2</u> with borane-tetrahydrofuran complex resulted in the isolation of 85% of a compound, m.p. 86-90°, isomeric with <u>3</u> (m/e*276). Thin-layer chromatographic examination of the total crude reaction product indicated the presence of only trace amounts of <u>3</u>. The assignment of the structure of this product as <u>4</u> is based on the PMR coupling constants: $J_{4a,9b}$=7.0 Hz., $J_{4a,4ax}$=5.0 Hz., $J_{4a,4eq}$=2.0 Hz. The magnitude of these constants precludes any axial-axial interactions, therefore excluding a <u>trans</u>-ring junction. These data also indicate considerable ring flattening in <u>4</u>, which is understandable in view of the considerable diaxial interaction between the 1, 3-ethano bridge and N_5.



Although the formation of these products may be rationalized on the basis of the respective reaction mechanism as follows, the high degree of stereoselectivity was unexpected. Thus, protonation of 2 in highly acidic media results in formation of the indolenium ion 2a. Attack of the iminium bond by the hydridic reducing species then takes place from the least hindered side to give 4. Treatment of 2 with sodium-liquid ammonia results in a stepwise reversible transfer of two electrons[1b] to give the thermodynamically most stable anionic species 5, which abstracts a proton from the solvent to yield 6. Final proton capture at the 9b-position during quenching occurs preferentially from the equatorial side, thus accounting for the formation of 3.





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5. An exception to this generalization results when *preformed* amineboranes of β- or γ-carbolines are treated with strong acids. See: J.G. Berger, S.R. Teller, C.D. Adams, and L.J. Guggenberger, Tetrahedron Lett., 1807 (1975); A.J. Elliott and H. Guzik, ibid., 1983 (1982). Open-chain aminoalkyl indoles may give *cis*-and/or *trans*-reduction products depending on structure of the substrate. See O. Repic and D.J. Long, Tetrahedron Lett., 115 (1983).
6. Crystal Data: 3 monoclinic, space group $P2_1/c$, a = 15.467(8), b = 9.454(5), c = 22.197 (10)Å, U = 2963.3 Å^3, Z =8, $D_{calc.}$ = 1.239 g cm^{-3}.
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8. Atomic co-ordinates for 3 have been deposited with the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.
9. For details, see: R.W. Miller and A.T. McPhail, J. Chem. Soc, Perkin Trans. 2, 1527 (1979).

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