Tetrahedron Letters No. 22 + 23, pp 1807 - 1810, 1975. Pergamon Press. Printed in Great Britain.

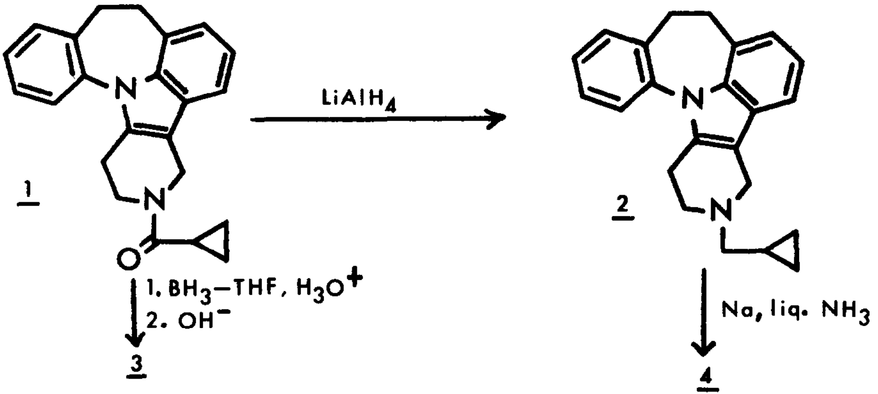
AN UNUSUAL STEREOSPECIFIC REDUCTION OF SOME BASIC SIDE-CHAIN SUBSTITUTED INDOLES.[1]

J.G. Berger* and S.R. Teller
Endo Laboratories, Inc., Garden City, NY 11530

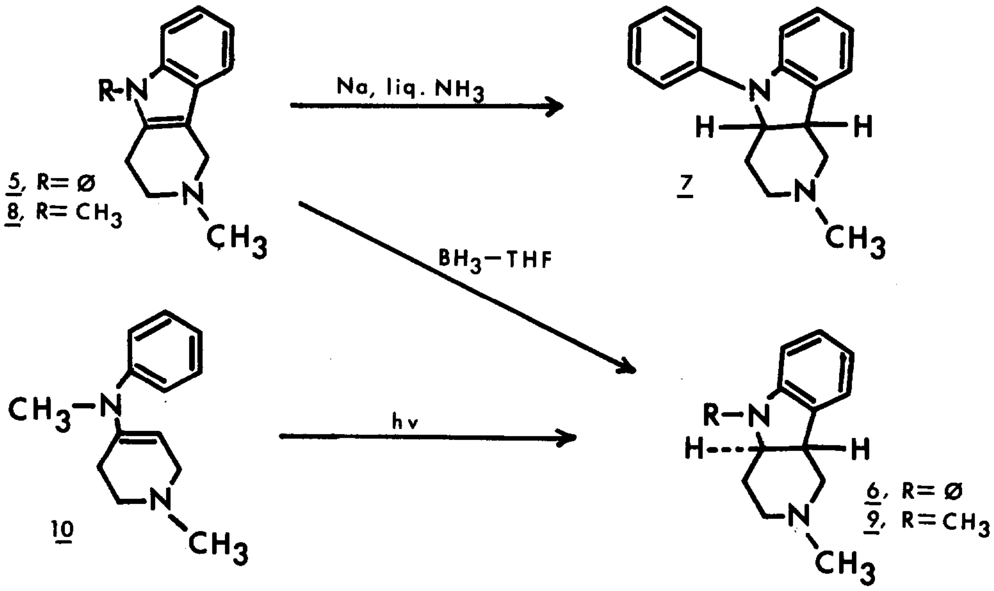
C.D. Adams[+] and L.J. Guggenberger[++]
Biochemicals[+] and Central Research Depts.,[++] E.I. du Pont de Nemours & Co.
Wilmington, Delaware 19898

(Received in U.S.A. 28 January 1975; received in UK for publication 16 April 1975)

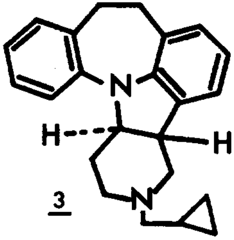
Although the amide function of the pentacyclic indole derivative 1 was reduced uneventfully to 2 (λ_{max}^{MeOH} 307(4.18), 297(4.06), 261(4.16)) with $LiAlH_4$, treatment with BH_3-THF followed by acid hydrolysis and subsequent workup gave an indoline 3 (λ_{max}^{MeOH} 281 (4.10)) which was isomeric with indoline 4 obtained by treatment of 2 with Na in liquid NH_3[2].

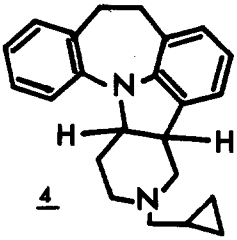


The related compound 5 gave the known 7[2] on treatment with Na/liq. NH_3, but, as above, gave the isomeric 6 on treatment with BH_3-THF. The structure of 6 was determined as its methiodide by X-ray analysis: Crystals monoclinic, space group $P2_1/c$, a=10.776(10), b=19.411(8), c=9.675(6)Å, β=115.60(6)°, four molecules per cell. The structure was solved by Patterson and Fourier techniques and refined by least squares to a conventional R of 0.038 for 1534 observed data.



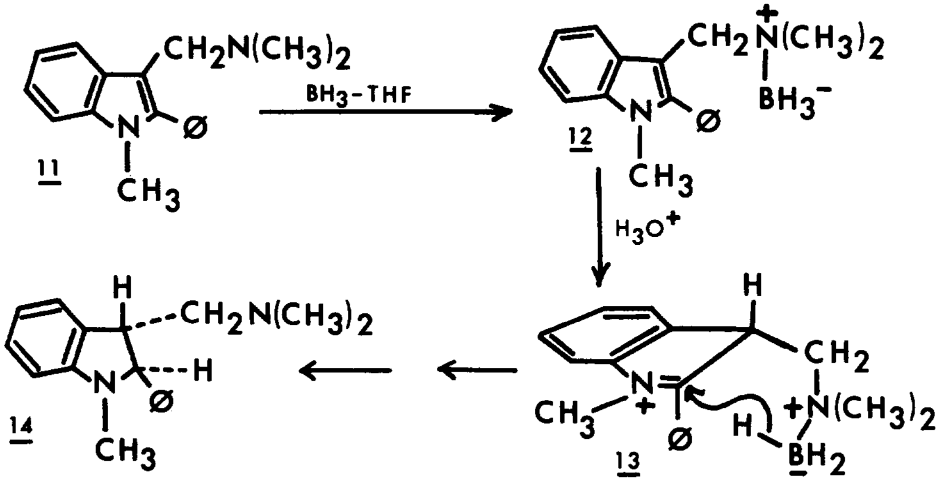
Based on this result, 3 and 4 are assigned the structures below:


3


4

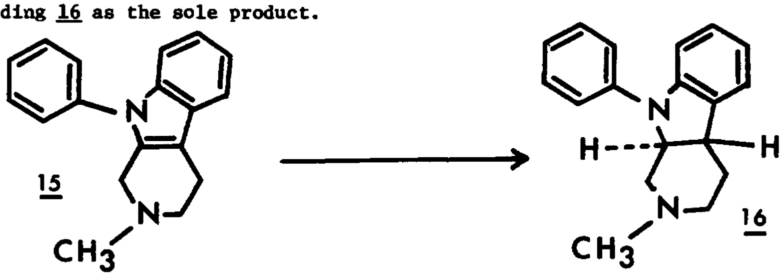
Both 3 and 6 were obtained in 65-75% yield. In view of the fact that indoles are not generally reduced by BH_3[3], the facility of this reduction was not anticipated. In addition, the unfavorable angle strain associated with trans-fused 6-5-6 ring systems of this type[4] makes the observed stereospecificity of the reduction most surprising. Recently, however, it was shown that certain N-arylenamines could be non-oxidatively photocyclized to trans-hexahydrocarbazoles in accord with the rules concerning conservation of orbital symmetry[5]. As further confirmation of the stereochemical course of the reaction, it was shown that both BH_3-THF reduction of 8 and irradiation of 10 yielded 9 as the sole reaction product.

Our studies on a related open-chain model compound 11[6] indicate the reaction mechanism as outlined below:



The trans-indoline 14 was the sole reaction product[7]. Treatment of the isolable 12 with DCl/D_2O resulted in incorporation of deuterium only at position 3, and treatment of the BD_3-12 with HCl/H_2O gave deuterium only at position 2 as determined by NMR. The observed stereospecificity is accomodated by this mechanism in view of the constraints imposed by a short chain (as in 13) or fused 6-membered ring system in the hydride transfer step.

With regard to the scope of the reaction, it was found that compounds such as 15, in which the basic center in the fused pyrido ring is shifted, also undergo the reduction, yielding 16 as the sole product.



Interestingly, the derivatives of 5 and 2 unsubstituted at the basic nitrogen atom do not undergo the reduction. Although a BH_3-adduct is formed, and is isolable, treatment with acid results only in reversion to the starting material. This behavior is probably due to the fact that secondary amine-BH_3 adducts are much more rapidly hydrolyzed by acid than tertiary amine adducts[8], and the hydrolysis in this case proceeds faster than protonation of the indole nucleus and subsequent hydride transfer.

References and Footnotes

1. Contribution No. 102 from Endo Laboratories, Inc. (Subsidiary of E.I. du Pont de Nemours and Co.)
2. B. Heath-Brown, Chem. and Ind., 1595 (1969).
3. S.A. Monti and R.R. Schmidt, III, Tetrahedron, 27, 3331 (1971) and references cited therein. However, see R. Littell and G.R. Allen, Jr., J. Org. Chem. 38, 1504 (1973).
4. J. Gurney, W.H. Perkin, and S.G.P. Plant, J. Chem. Soc., 2676 (1927); A. Smith and J.H.P. Utley, ibid., Sec. C, 2302 (1970).
5. O.L. Chapman, G.L. Eian, A. Bloom, and J. Clardy, J. Amer. Chem. Soc., 92, 2918 (1971).
6. V.I. Shvedov, G.N. Kurilo, and A.N. Grinev, Khim. Farm. Zh., 4, 11 (1970).
7. Reduction of 11 with trimethylamine-borane under acidic conditions (J.G. Berger, Synthesis, 508 (1974)) gave both 14 (2-H, δ 4.18(d)) and its cis-isomer (2-H, δ 4.61(d)). The paramagnetic shift to lower field is characteristic of cis-oriented substituents in the indoline series (F.A.L. Anet and J. Muchowski, Chem. & Ind., 81 (1963)).
8. G.E. Ryschkewitsch, Advances in Chemistry, vol. 42, American Chemical Society, Washington, D.C., 1964, pp. 53-58.