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BORANE REDUCTION OF INDOLES WITH SECONDARY AMINE SUBSTITUENTS IN A 2,3-FUSED SIDE-CHAIN

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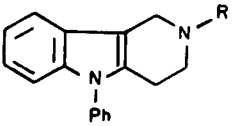
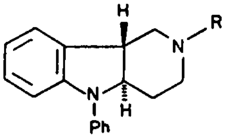
ABSTRACT: *Trifluoroacetic acid treatment of the borane adducts of indoles with 2,3-fused side-chains containing secondary amines leads to the trans-indolines via intramolecular hydride transfer.*

The reduction of indoles in acidic media by boron hydrides to give the cis-indolines is well documented.[1,2,3] A particularly interesting and useful variation concerns indoles bearing a tertiary amine in a side-chain The preformed amine-borane complex in refluxing aqueous HCl gives a product in which the hydrogen atoms have been introduced from opposite sides.[4] Thus with tricyclic compounds such as 1, the trans-indoline, 3, is obtained. The amine·BH_3 complex is thought to deliver hydride intramolecularly to the 3H-indolenium salt [4]



1, R = CH_3
2, R = H

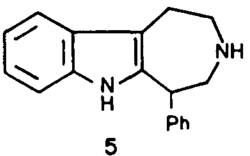


3 R = CH_3
4 R = H

The synthetic utility of this reaction is limited by the fact that a tertiary amine is required Treatment of the BH_3 adduct of the secondary amine, 2, with aqueous HCl gives starting material[4], presumably because secondary amine BH_3 adducts are much more rapidly hydrolyzed.[5] To obtain the trans-reduced secondary amine it has been necessary to introduce and remove a methyl or a benzyl group.[6,7,8]

We reasoned that an acid sufficiently strong to produce the 3H-indolenium ion but not nucleophilic enough to hydrolyze the amine·BH_3 complex might allow the use of secondary amines in this procedure The required BH_3 adduct was obtained by adding 2 to an excess of BH_3·THF followed by careful dilution with water. Addition of 1 3 mmoles of this adduct to 15 mL of trifluoroacetic acid at 0°, stirring for 20 minutes and dilution with 100 mL of water gave a high yield (>80%) of 4 after basic work-up. Only traces of the cis-indoline could be detected by tlc. The m p and spectral characteristics of 4 were identical with an authentic sample obtained by demethylation of 3.[8,9]

Similar treatment of the borane complex of the azepinoindole 5[10] gave the two *trans*-indolines, 6 and 7, as a 1 1 mixture [9] The identities of 6 and 7 were established by comparison with authentic materials and by x-ray analysis.[11]



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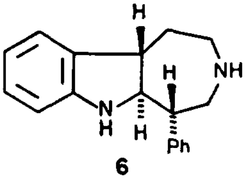

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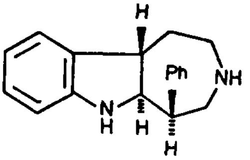

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It should be noted that this procedure differs from the recently reported[2] synthesis of *cis*-indolines by treatment with $BH_3 \cdot TFA$ In this case the amine·BH_3 complex is not preformed and hydride transfer cannot take place intramolecularly and stereospecifically.

Acknowledgement We wish to thank Dr. J. G Berger for helpful discussions.

References

1 J G Berger, *Synthesis*, 508 (1974)

2. B E Maryanoff and D F McComsey, *J Org. Chem* , 43, 2733 (1978).

3. G. W. Gribble, P D Lord, J Skotnicki, S. E. Dietz, J E Eaton and J. L. Johnson, *J Amer Chem Soc* , *96*, 7812 (1974)

4 J G Berger, S R Teller, C D. Adams and L. F Guggenberger, *Tetrahedron Lett.*, 1807 (1975)

5 G. E. Ryschkewitsch, *Advances in Chemistry*, Vol 42, American Chemical Society, Washington, D. C , 1964, pp 53-58

6 Y Nagai, A. Irie, Y Masuda, M Oka and H Uno, *J Med Chem.*, *22*, 677 (1979).

7 A J Elliott and H Guzik, Unpublished Results.

8 U S. Patent 3,991,199, November 9, 1976.

9. Although only one enantiomer is shown the compounds were obtained as racemic mixtures.

10 A J Elliott, E H Gold and H. Guzik, *J. Med. Chem* , *23*, 1268 (1980).

11 A. J Elliott, H. Guzik, M. Puar and A T. McPhail, Unpublished Results

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