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Trans Hydrindanes by Dimide Reduction: Synthesis of Dihydro-B-nortestosterone and its 17α-Methyl Derivative

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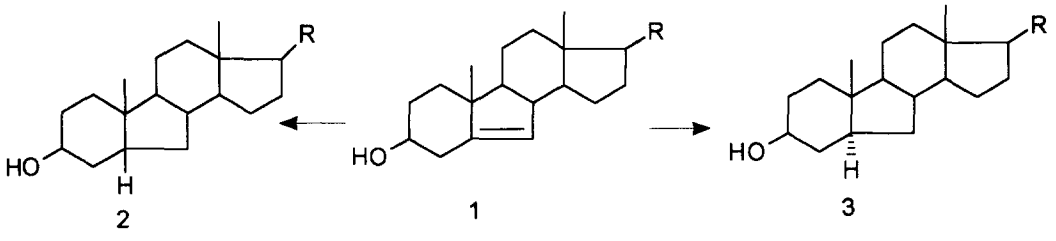
Abstract. Reductive hydroboration of Δ^5-B-norsteroids (e.g., **1**) affords 5α-dihydro products (e.g., **3**) in a low yield. Better yields, however, were obtained by reduction with diimide. The method was employed in the synthesis of potential antiandrogens - 17ß-hydroxy-B-nor-5α-androstan-3-one (**8**) and its 17α-methyl derivative (**9**). Copyright © 1996 Elsevier Science Ltd

In the formation of hydrindanes from unsaturated derivatives (e.g., by hydrogenation), cis hydrindanes are known[1,2] to be the preferred products. E.g., on addition, Δ^{14}-unsaturated steroids as well as Δ^5-unsaturated B-norsteroids yield mainly C/D and cis A/B cis products (e.g., **2**), respectively. This preference affected the total synthesis of steroids even 40 years ago[3].



2 1 3

R = cholestane side chain

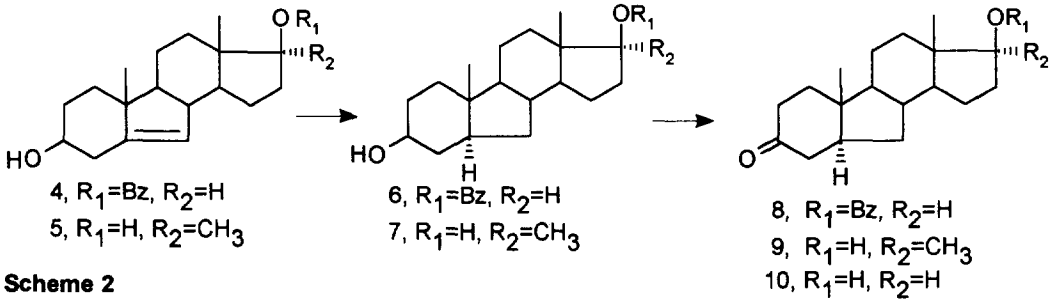
Scheme 1

The major hindrance to the 5ß-approach of a reagent was recently[4,5] attributed to the presence of an angular methyl group. If relative yields of formation of 5α,6α- and 5ß,6ß-epoxides indicate the relative steric hindrance of the double bonds involved, the Δ^5-double bond in B-norsteroids is much more accessible, than the same double bond in normal steroids, to an electrophilic attack of reagents from the α-side leading to substituted trans hydrindanes[6]. This steric factor was not manifest in reversible reactions, however, stereospecific addition reactions proceeding in a four-centre mechanism (e.g., hydroboration, reduction with diimide), which does not allow for internal rotation or inversion of intermediates, should produce even better yields of 5α-adducts (i.e., A/B trans products) than corresponding classical steroids with six-membered rings A and B. Recent results of this more direct approach to such B-nor-5α-steroids are presented here.

Hydroboration, followed by oxidation, of Δ^{14}-olefins was[7] successfully utilized in the synthesis of 15α-hydroxy steroids. Now we used a similar sequence in the transformation of B-norcholesterol (**1**). Hydroboration and treatment of borane formed with propionic acid yielded B-nor-5α-cholestan-3ß-ol (**3**, 9 %). ^{1}H NMR spectrum of the product confirms an axial character of the 3α-proton (triplet of triplets, J=11.0 and 8.9 Hz). No 5ß-isomer **2** was found in the mixture either by NMR spectroscopy of the crude reaction product, or by TLC analysis.

The best reagent for the desired reduction of Δ^5-B-norsteroids to A/B trans products was found to be diimide[8,9]. Treatment of olefins (e.g., **1**,**4**,**5**) with p-toluenesulfonyl hydrazine in collidine at 150 °C yielded 5α-dihydro derivatives (**3**,**6**,**7**) in good yields (85-95 %).

On oxidation, compounds **6** and **7** afforded ketones **8** and **9**. The latter[10] represents the sought-for 5α-dihydro derivative of 17-methyl-B-nor-testosterone, the former was hydrolyzed to the 5α-dihydro derivative of B-nor-testosterone (**10**). Because of the difficulties in their synthesis, their biological activity has not been thoroughly tested. However, it is of great interest since B-nortestosterone and its derivatives act as antiandrogens[11]. The biological activity of **9** and **10** will be reported elsewhere.



Scheme 2

References and Notes:

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6. On oxidation with MPA, compound yields **1** 5α,6α-epoxide only.
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9. E.g., compound **5** (200 mg, 0.69 mmol) and p-toluenesulfonhyl hydrazide (600 mg, 3.22 mmol) in collidine (3 ml) was heated to 150 °C for 3 h. The solvent was evaporated in a vaccum, the residue was dissolved in chloroform and washed with aqueous hydrochloric acid (5%), water, potassium carbonate (7%) and water, and dried. After evaporation compound **7** crystallized from acetone. M.p. 159-160 °C (186 mg, 92.5 %), $[\alpha]_D$ -33° (methanol).
10. Compound **9**: m.p. 168-168.5 °C, $[\alpha]_D$ +5° (c 1.4). Compound **10**: m.p. 176.5-177 °C (acetone-heptane), $[\alpha]_D$ +27.4° (lit.[12] records 173-174 °C and +38 °). $\Delta\varepsilon_{291}$ +1.63 (methanol). The 5ß-isomer exerts a negative Cotton effect ($\Delta\varepsilon_{288}$ -1.50, methanol).
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