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## Trans Hydrindanes by Dimide Reduction: Synthesis of Dihydro-B-nortestosterone and its $17\alpha$ -Methyl Derivative

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Abstract. Reductive hydroboration of  $\Delta^5$ -B-norsteroids (e.g., 1) affords  $5\alpha$ -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 - 17*B*-hydroxy-B-nor- $5\alpha$ -androstan-3-one (8) and its  $17\alpha$ -methyl derivative (9). Copyright © 1996 Elsevier Science Ltd

In the formation of hydrindanes from unsaturated derivatives (e.g., by hydrogenation), cis hydrindanes are known<sup>1,2</sup> to be the preferred products. E.g., on addition,  $\Delta^{14}$ -unsaturated steroids as well as  $\Delta^{5}$ -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<sup>3</sup>.



R = cholestane side chain

## Scheme 1

The major hindrance to the 5ß-approach of a reagent was recently<sup>4,5</sup> attributed to the presence of an angular methyl group. If relative yields of formation of  $5\alpha,6\alpha$ - and  $5\beta,6\beta$ -epoxides indicate the relative steric hindrance of the double bonds involved, the  $\Delta^5$ -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  $\alpha$ -side leading to substituted trans hydrindanes<sup>6</sup>. 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  $5\alpha$ -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-5 $\alpha$ -steroids are presented here.

Hydroboration, followed by oxidation, of  $\Delta^{14}$ -olefins was<sup>7</sup> successfully utilized in the synthesis of 15 $\alpha$ -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-5 $\alpha$ -cholestan-3B-ol (3, 9%). <sup>1</sup>H NMR spectrum of the product confirms an axial character of the 3 $\alpha$ -proton (triplet of triplets, J=11.0 and 8.9 Hz). No 5B-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  $\Delta^5$ -B-norsteroids to A/B trans products was found to be diimide<sup>8,9</sup>. Treatment of olefins (e.g., 1,4,5) with p-toluenesulfonyl hydrazine in collidine at 150 °C yielded 5 $\alpha$ -dihydro derivatives (3,6,7) in good yields (85-95 %).

On oxidation, compounds 6 and 7 afforded ketones 8 and 9. The latter<sup>10</sup> represents the sought-for  $5\alpha$ -dihydro derivative of 17-methyl-B-nor-testosterone, the former was hydrolyzed to the  $5\alpha$ -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<sup>11</sup>. The biological activity of 9 and 10 will be reported elsewhere.



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## **References and Notes:**

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- 6. On oxidation with MPA, compound yields 1  $5\alpha, 6\alpha$ -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 %), [α]<sub>D</sub> -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.<sup>12</sup> 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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