

A NEW APPROACH TO Δ^{16} -ANDROSTENES

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THE synthesis of Δ^{16} derivatives of androstane starting from easily available 17 oxy or oxo derivatives has been largely investigated¹. Sondheimer *et al.*² developed a convenient way, involving a four steps synthesis from 17 keto derivatives of androstane.

Recently in our laboratory we achieved the synthesis³ of Δ^{16} androstenes through hydroboration of enolderivatives of 17 keto compounds, followed by treatment of the reaction mixture with acetic anhydride, and Barton reported⁴ a three steps synthesis from 17 ketones, involving oxidation with iodine of hydrazones of 17 ketones, and reduction of the resulting vinyl iodide with sodium and ethanol.

In the course of a research on the reduction of tosylhydrazones of ketones and aldehydes with LiAlH_4 , we remarked that tosylhydrazones of 17 keto steroids, by treating with LiAlH_4 in tetrahydrofurane, give a 60-70% yield of the corresponding Δ^{16} unsaturated derivatives.⁵

¹ L.F. Fieser, M. Fieser, Steroids p. 528 Reinhold (1959).

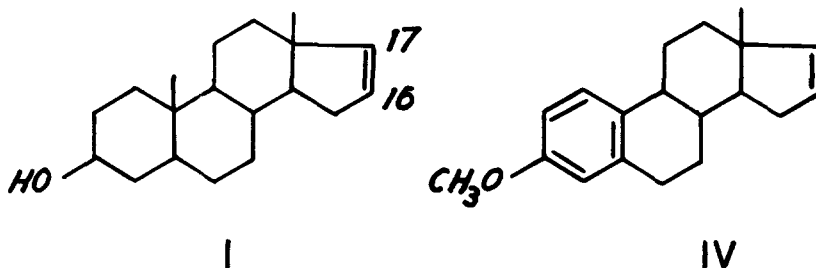
² F. Sondheimer, O. Mancera, M. Urquiza, G. Rosenkrans, J. Amer. Chem. Soc. **77**, 4145 (1955).

³ L. Caglioti, G. Cainelli, G. Maina, A. Selva, Gazz. Chim. Ital. **92**, 309 (1962).

⁴ D.H.R. Barton, R.E. O'Brien, S. Sternhell, J.Chem.Soc. 470 (1962).

⁵ In other cases the reaction follows another route: for instance, cholestan-3 one and coprostan-3 one tosylhydrazones are reduced by LiAlH_4 to cholestane and coprostane (L.Caglioti, M.Magi, unpublished).

The tosylhydrazone of 17-keto-3 β -acetoxy-5 α -androstane (m.p. 175°)⁶ refluxed overnight in dry tetrahydrofuran with an excess of LiAlH_4 , after careful destruction of excess hydride and extraction with ether, gave a 70% yield of Δ^{16} -5 α androsten-3 β ol (I) (m.p. 123°, $[\alpha]_D^{20} + 16^\circ$; found: C, 83,22; H, 11,28. $\text{C}_{19}\text{H}_{30}\text{O}$ requires C, 83,15; H, 11,02%), identified with an authentic specimen. Reduction of (I) with Pd charcoal, after adsorption of 1 mol H_2 , gave a product (II) (m.p. 148°, $[\alpha]_D^{20} = -1^\circ$; found: C, 82,79; H, 11,88. $\text{C}_{19}\text{H}_{32}\text{O}$ requires C, 82,54; H, 11,66%) identical to an authentic specimen of 3 β -hydroxy-5- α -androstane.



The reaction was extended to the tosylhydrazone of estrone methylether⁷ (III). Treatment of (III) in the above mentioned conditions, after working up with ether, gave a 60-70% yield of a compound (IV) (m.p. 63°, $[\alpha]_D^{20} + 113^\circ$; found: C, 84,93; H, 9,05. $\text{C}_{19}\text{H}_{24}\text{O}$ requires C, 85,02; H, 9,01%), the 3-methoxy-1,3,5(10), 16-estratetraene. (IV), after treatment with OsO_4 in ether - pyridine and working

⁶ In general tosylhydrazones are nicely crystalline compounds, rapidly available from ketones by boiling them in a methanolic solution with an excess of *p*-toluensulphonyl hydrazine. As a result of cooling, the tosylhydrazones crystallize out in an almost pure form.

⁷ W.F. Johns, J. Org. Chem. **26**, 4583 (1961).

up of osmate ester with mannite in alkali, gave a nicely crystalline diol (V) (m.p. 158-160°, $[\alpha]_D^{20} + 48^\circ$; found; C, 75,52; H, 8,68. $C_{19}H_{26}O_3$ requires C, 75,46; H, 8,67%), the 16 α -17 α dihydroxy-3 methoxy-1,3,5(10) estratriene.

Reduction of (IV) with Pd charcoal in ethanol, after adsorption of 1,1 mol, H₂, furnished a product (VI) (m.p. 75-76°, $[\alpha]_D^{20} + 87^\circ$; found: C, 84,54; H, 9,89. $C_{19}H_{26}O$ requires C, 84,39; H, 9,69% which was identified with an authentic specimen of 3 methoxy-1,3,5(10)-estratriene.

Also in this case the reaction of a 17 keto tosylhydrazone with $LiAlH_4$ leads to the formation of a Δ^{16-17} double bond,⁸ without rearrangement of the adjacent methyl group. This is noteworthy, if we consider that treatment of (III) with Na in ethylenglycol leads⁷, through migration of the methyl group, to the 17 β -methyl-3 methoxy-18 norestra-1,3,5(10), 13(14)-tetraene and other isomers.

The above described reaction constitutes a rapid way to Δ^{16} androstenes from the easily available 17 keto androstanes, and seems to have some convenience over the methods used hitherto.

Full details of this work will be published elsewhere.

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⁸ An attempted conversion of 3 β -hydroxyandrost-5en-17one into androsta-5-16-dien-3 β ol by reaction of its toluen *p*-sulphonylhydrazone with sodium in ethylene glycol furnished after acetylation 3 β -17 β -diacetoxyandrost-5ene. (W.J. Adams, D.K. Patel, V. Petrov, J. A. Stuart Webb, *J. Chem. Soc.* 297 (1956).