

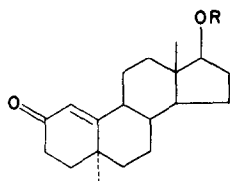
10 α -SUBSTITUTED STEROIDS

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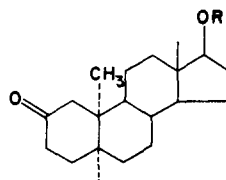
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Despite the great variety of steroid derivatives which have been synthesized, compounds with the unnatural 10 α -configuration have received relatively little attention. Only very recently has the synthesis of 10 α -testosterone by a photochemical isomerization reaction been recorded.^{2,3} The present communication describes three different procedures for the preparation of 10 α -substituted steroids. These methods offer the distinct advantage in that they permit the introduction of a large variety of substituents into the 10 α position.

The starting material in each instance was the 17 β hydroxy-1(10)-estren-2-one (Ia) previously prepared in these laboratories.⁴ Reaction of Ia with methyl magnesium bromide in the presence of cuprous chloride resulted in 1,4-addition^{5,6} to give 17 β hydroxy-5 α ,10 α -androstan-2-one (IIa)



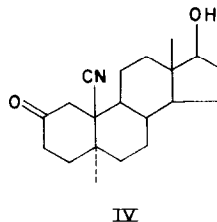
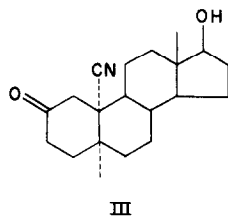
Ia R=H
b R=CH₃CO



IIa R=H
b R=CH₃CO

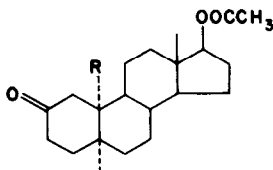
m.p. 162-165 $[\alpha]_D^{23} + 49$.⁷ Only the cis compound was obtained and the 10 α -stereochemistry was evident from the optical rotatory dispersion curve which corresponded to that of a 5 β -3-ketone which has the same bicyclic environment.

Another procedure for introducing a substituent into the C-10 position involved application of the cyanation reaction^{8,9} to the Δ 1(10)-2 ketone (Ia). Reaction of Ia with potassium cyanide and ammonium chloride¹⁰ gave a 50% yield of the 10 α cyano compound III m.p. 187 $[\alpha]_D^{23} + 38$ and a 20% yield of the 10 β cyano isomer IV m.p. 215-216 $[\alpha]_D^{23} + 40$. Optical rotatory dispersion served to identify the stereochemistry of the cyano groups in III and IV, the O.R.D. curve of III corresponding to that of 5 β -3 ketone and the curve of IV to that of a 5 α -3 ketone.



In addition, the 10 α -cyano compound III was converted to the 10 α methyl compound II by the following sequence. With ethylene glycol compound III gave a noncrystalline ketal which on acetylation gave the crystalline 2-ethylene ketal 17-acetate (Va) m.p. 192-194/205-207 $[\alpha]_D^{23} + 20$. Lithium aluminum hydride reduction of Va followed by alkaline hydrolysis¹¹ and reacetylation gave the 19 aldehyde Vb

m.p. 194-197 $[\alpha]_D^{24} + 3$. Huang-Minlon reduction of the aldehyde Vb



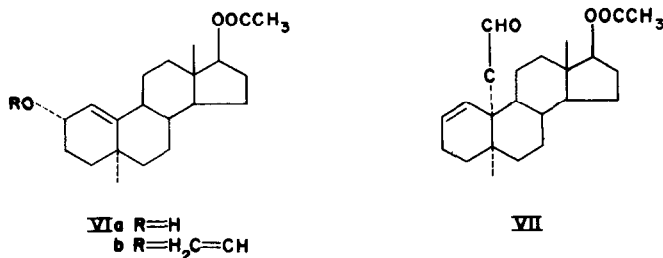
Va R=CN
 b R=CHO
 c R=CH₃

and reacylation yielded the 10 α -methyl ethylene ketal Vc m.p. 166-167 $[\alpha]_D^{24} + 31$, which on deketalization with hydrochloric acid in acetone gave 17 β acetoxy-5 α ,10 α -androstan-2-one (IIb) m.p. 196-198, identical in all respects with the acetate of the compound II obtained from the Grignard reaction. Lithium aluminum hydride reduction of the aldehyde Vb gave the 2,2-ethylenedioxy-5 α ,10 α -androstan-17 β ,19-diol m.p. 192-194 $[\alpha]_D^{23} + 23$.

The recently described method¹² of angular alkylation via the Claisen rearrangement of allyl vinyl ethers suggested yet another route leading to 10 α -substitution.

17 β acetoxy-1(10)-estren-2-one (Ib) was reduced with lithium tri t-butoxyaluminum hydride to give as the main product the 2 α -hydroxy compound VIa m.p. 141-145 $[\alpha]_D^{23} - 5$. The orientation of the hydroxy group at C-2 is assigned as α , in view of the known stereoselectivity of the reagent to yield equatorial products.^{13,14} The compound VIa was then converted to the 2 vinyl ether VIb m.p. 72-74 in good yield by the procedure of Watanabe and Conlon.¹⁵ The satisfactory

yield of vinyl ether further supports the equatorial orientation of the hydroxy group since axial hydroxy groups give poor yields of ether by this procedure.¹² Rearrangement of the vinyl ether VIb in decalin at 195°C gave



in low yield an aldehyde which was homogeneous but which could not be crystallized. The infrared spectrum of the compound in carbon tetrachloride showed aldehyde bands at 2715 cm^{-1} and 1719 cm^{-1} , acetate band at 1738 cm^{-1} and double bond absorption at 1643 cm^{-1} . The α stereochemistry at C-10 follows from the stereospecific nature of the rearrangement.¹² The major product of the rearrangement lacked aldehyde absorption in the infrared and is being further investigated.

Each of the 10 α -substituted products obtained by the above procedures retains a functional group in ring A which permits the introduction of oxygen at C-3 to give 3 oxygenated 10 α steroids. These and other aspects of the chemistry of these compounds will be described in the near future.

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