Novel Synthesis of 5α-Androstane-3α,17α-diol

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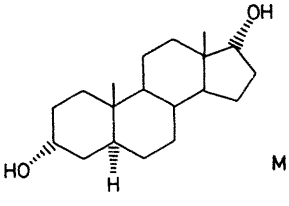
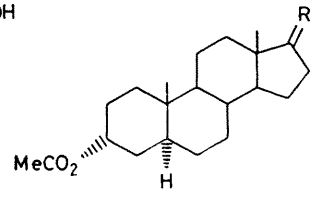
Summary A novel synthesis of the pharmacologically interesting 5α-androstane-3α,17α-diol is described involving the stereospecific cleavage of an oxadiazoline.

THERE has been considerable interest recently in 5α-androstane-3α,17α-diol (**1**) as a possible canine androgen.[1] The lack of a convenient published procedure for the preparation of 5α-androstane-3α,17α-diol prompted us to develop a new synthetic route involving the base-induced decomposition of a steroidal oxadiazoline. Using the readily available 3α-hydroxy-5α-androstan-17-one as the starting material, this novel route furnishes (**1**) in 63% overall yield. Thus lead tetra-acetate (LTA) oxidation (CH_2Cl_2, 0 °C) of the acetylhydrazone (**2**), m.p. 229—231 °C (lit.,[2] 230—231 °C), ν_{max} (KBr) 3220, 1730, 1665, and 1255 cm^{-1} (*cf.* refs. 3 and 4), gave a mixture of the oxadiazolines (**3**) and (**4**) (2:1) which was readily separated by high-performance liquid chromatography. Subsequent base-catalysed decomposition (10% KOH–MeOH, heat) of the major isomer (**3**),† m.p. 131—132 °C, ν_{max} (KBr) 1763, 1728, 1240, and 1210 cm^{-1}, δ ($CDCl_3$) 5·00 (1H,m,3β-H), 2·05 (3H,s,3α-MeCO), 2·03 (3H,s,MeCO), 1·93 (3H,s,Me), 1·22 (3H,s,13-Me), and



(1)



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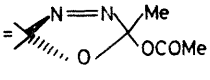
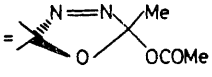
(3) R = 

(4) R = 

† N.m.r. assignments were simplified by reference to the corresponding 3-deoxy-compounds. Satisfactory C, H, and N analyses were obtained for all new compounds.

0·80 (3H,s,10-Me), was found to yield exclusively 5α-androstane-3α,17α-diol, m.p. 225—226 °C (lit.,[5] 228 °C), $[\alpha]_D$ −10·3° (EtOH). Moreover, base-catalysed cleavage of the minor isomer, (**4**), m.p. 134—136 °C, ν_{max} (KBr) 1765, 1732, 1235, and 1210 cm^{-1}, δ ($CDCl_3$) 5·00 (1H,m,3β-H), 2·05 (3H,s,3α-MeCO), 2·01 (3H,s,MeCO), 1·87 (3H,s,Me), 0·93 (3H,s,13-Me), and 0·80 (3H,s,10-Me), furnished solely 5α-androstane-3α,17β-diol, m.p. 222—224 °C (lit.,[6] 223 °C), $[\alpha]_D$ + 16° (EtOH) [lit.,[6] + 13° (EtOH)]. On the basis of the established preference for attack upon the less-hindered α-face at C-17, *e.g.* in the LTA oxidation of steroidal 20-acetylamino-17(20)-ene derivatives,[7] the major product (**3**) is expected to have the stereochemistry shown. A plausible explanation for the observed stereospecific base-cleavage involves collapse of the oxadiazoline (**3**) to a 17β-carbanionic species which rapidly protonates before equilibration can occur. Similar considerations involving a 17α-carbanionic species apply to oxadiazoline (**4**). It is interesting that the barrier to inversion has been predicted to be large for pyramidal carbanion centres bearing oxygen substituents.[8] Although base-induced decomposition of Δ^3-1,3,4-oxadiazolines has been reported,[9] there is no report of its use in the generation of a chiral centre.

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