The Epoxidation of Androstane and Pregnane 2,4-Dienes

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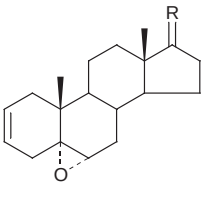
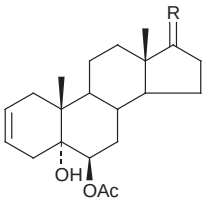
The epoxidation of 6β-acetoxyandrosta-2,4-diene-17-one, 6β-acetoxypregna-2,4-diene-20-one and the corresponding 6-ketones with *m*-chloroperbenzoic acid is shown to give, unexpectedly, the 4α,5α-monoepoxides.

The 2,3-enolization of a Δ^4-3-ketone is an important step in the conversion of a 19-oxygenated androst-4-ene-3,17-dione to estrone.[1] A glutamate residue in the aromatase enzyme system is believed to be responsible for abstracting the C-2β hydrogen atom. Some androsta-2,4-dien-17-ones have been shown[2] to be competitive inhibitors of this sequence. In the light of this, we have considered the possibility that 2α,3α-Δ^4- or Δ^2-4α,5α-epoxides might act as irreversible inhibitors by reacting with the glutamate residue. Furthermore the additional presence of an electron withdrawing functionality at C-6 might favourably influence the regiospecificity of opening of the epoxide to allow a nucleophile to attack C-2β. The epoxidation of 6β-acetoxy and 6-keto androstane and pregnane 2,4-dienes forms the subject of this paper. Prior work in the cholestane series with cholesta-2,4-diene[3] and cholesta-2,4-dien-6-one[4] has shown that these dienes were epoxidized preferentially at the 4,5-double bond. These results were unexpected since the 4,5-double bond is the more hindered double bond and, in the case of the 6-ketone, potentially less reactive towards electrophiles.



1 R = O
2 R = α-H, β-COMe



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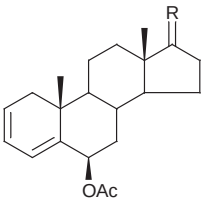

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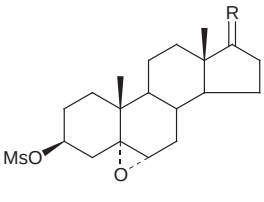
6 R = α-H, β-COMe



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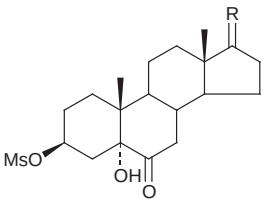
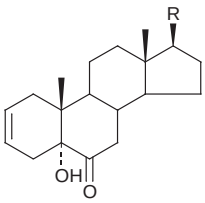
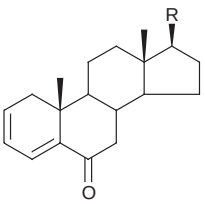
8 R = α-H, β-COMe



9 R = O
10 R = α-H, β-COMe



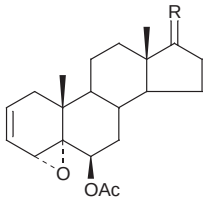
11 R = O
12 R = α-H, β-COMe



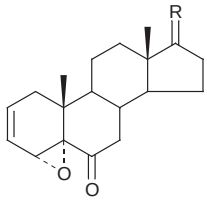
13 R = O
14 R = α-H, β-COMe

The substrates were prepared as follows. Acetolysis of 5α,6α-epoxyandrost-2-en-17-one **1** gave 6β-acetoxy-5α-hydroxyandrost-2-en-17-one **3**[5] which was dehydrated with thionyl chloride to afford 6β-acetoxyandrosta-2,4-diene-17-one **5**. 6β-Acetoxypregna-2,4-dien-20-one **6** was prepared in a similar manner from 5α,6α-epoxypregn-2-en-20-one **2** *via* the 6β-acetate **4**. Androsta-2,4-diene-6,17-dione **13** and pregna-2,4-diene-6,20-dione **14** were obtained[6] from dehydroisoandrosterone and pregnenolone respectively, by oxidation of their 5α,6α-epoxy-3β-methanesulfonates **7** and **8** with chromium trioxide.[7] This gave the 5α-hydroxy-6-ketones **9** and **10**. Elimination of the 3β-methanesulfonates in refluxing collidine afforded the 2-enes **11** and **12** and then elimination of the 5α-hydroxy groups with thionyl chloride gave the required 2,4-diene-6-ketones **13** and **14**.[8].

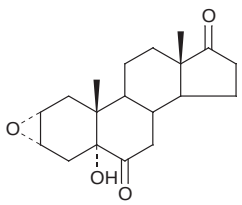
Epoxidation of both 6β-acetoxyandrosta-2,4-dien-17-one **5** and 6β-acetoxypregna-2,4-dien-20-one **6** with *m*-chloroperbenzoic acid in chloroform at room temperature overnight gave the 4α,5α-epoxides, **15** and **16** in 57% yield. Epoxidation of the dienones, androsta-2,4-diene-6,17-dione **13** and pregna-2,4-diene-6,20-dione **14** also gave the 4α,5α-epoxides **17** and **18** (33 and 57% yields, respectively). The structure and stereochemistry of the epoxides was established by analysis of their ^{1}H NMR spectra and by the reduction of the epoxide **17** to 5α-hydroxyandrostane-6.17-dione.[9] This was identical to a sample obtained by the chromium trioxide oxidation of 5α,6α-epoxyandrostan-17-one.[10] An attempt was made to prepare 2α,3α-epoxyandrost-4-ene-6,17-dione by dehydration



15 R = O
16 R = α-H, β-COMe



17 R = O
18 R = α-H, β-COMe



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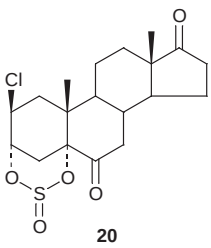

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of 2α,3α-epoxy-5α-hydroxyandrostane-6,17-dione[8] **19** with thionyl chloride but the product was the 2β-chloro-3α,5α-cyclic sulfite **20**.

There are several unusual features of these epoxidations. First, under these conditions the 2,4-dienes undergo mono-epoxidation at the more hindered 4,5-double bond rather than diepoxidation and secondly the 6-ketone appears to have little effect on the regiochemistry of epoxidation. A possible explanation is that the more electron-rich trisubstituted 4,5-double bond reacts from the less-hindered a-face more rapidly than the 2,3-double bond. A repulsive interaction between the lone pairs on the oxygen of the first epoxide and the π-electrons of the adjacent 2,3-alkene diminishes the electron density on the α-face and increases it on the opposite β-face. However attack of a reagent on the β-face is sterically hindered by diaxial interactions with the C-10β methyl group. Thus the overall effect is to diminish the reactivity of the Δ^2-double bond towards the second epoxidation. Molecular models of androsta-2,4-diene-6,17-dione show that there is a marked interaction between the C-6 carbonyl oxygen and C-4 which is relieved by twisting the carbonyl group out of planarity with the diene. The consequent diminution in conjugation between the carbonyl group and the diene is reflected both in this reactivity and in the UV spectrum. The absorption coefficient in the UV spectrum of the dieneone **13** is 8400 (λ_{max} 314 nm) which is somewhat less than that of a typical unsaturated ketone.

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Techniques used: ^{1}H NMR, IR, chromatography

References: 10

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References cited in this synopsis

1 S. S. Oh and C. H. Robinson, *J. Steroid Biochem. Mol. Biol.*, 1993, **44**, 389.
2 S. S. Oh and C. H. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2237.
3 W. Bergmann and E. L. Skau, *J. Org. Chem.*, 1940, **5**, 439.
4 V. Cerny, M. Hudesinsky, M. Ryba and F. Turecek, *Collect. Czech. Chem. Commun.*, 1988, **5**, 1549.
5 J. R. Hanson and I. Kiran, *J. Chem. Res.* 1999, (*S*) 594; (*M*) 2532.
6 J. R. Hanson and T. D. Organ, *J. Chem. Soc., Perkin Trans. 1*, 1970, 2473.
7 L. Knof, *Liebigs Ann. Chem.*, 1962, **657**, 171.
8 J. R. Hanson and H. J. Shapter, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1445.
9 S. Rakhit and N. Gut, *J. Org. Chem.*, 1968, **33**, 1196.
10 A. Crastes de Paulet and J. Bascoul, *Bull. Soc. Chim. Fr.*, 1966, 939.