Synthesis of 2β-Hydroxy-3,17-dioxoandrost-4-en-19-al and its Facile Aromatisation into Estrone

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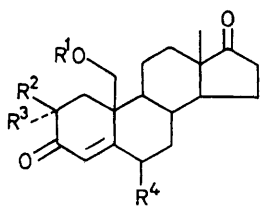
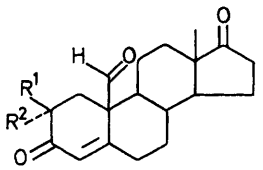
Summary 2β-Hydroxy-3,17-dioxoandrost-4-en-19-al was synthesised and was shown to aromatise rapidly into estrone in the presence of water at neutral pH.

THE stoicheiometry of the biosynthesis of estrogens requires 3 moles each of oxygen and NADPH per mole of estrogen formed.[1] This is consistent with the participation of three enzymatic hydroxylations in the aromatisation process. Two of these have been identified to take place on the C-19 methyl group as the initial steps in the biotransformation of androgens into estrogens leading successively to the 19-hydroxy- and 19-aldehyde-intermediates.[2] The nature and site of the third hydroxylation is presently unknown and the possibility that the C-2 position might be involved suggested the synthesis of the isomeric 2-hydroxy derivatives of the 19-hydroxy- and 19-oxo-androst-4-ene-3,17-diones as potential intermediates in the biosynthesis of estrone.

Reaction of 19-acetoxyandrost-4-ene-3,17-dione (**1b**) with *N*-bromosuccinimide provided 19-acetoxy-6β-bromo-androst-4-ene-3,17-dione (**2**). When (**2**) was refluxed in glacial acetic acid for 12 min in the presence of potassium acetate,[3] 2β,19-dihydroxyandrost-4-ene-3,17-dione diacetate (**3b**) and 2α,19-dihydroxyandrost-4-ene-3,17-dione diacetate (**4b**) were obtained. The 2α-isomer (**4b**) was also obtained in superior yield by another independent route. Sulphuric





(**1**) **a**; $R^1=R^2=R^3=R^4=H$
b; $R^1=Ac$, $R^2=R^3=R^4=H$
(**2**) $R^1=Ac$, $R^2=R^3=H$, $R^4=Br$
(**3**) **a**; $R^1=R^3=R^4=H$, $R^2=OH$
b; $R^1=Ac$, $R^2=OAc$, $R^3=R^4=H$
c; $R^1=R^3=R^4=H$, $R^2=OSiMe_2Bu^t$
(**4**) **a**; $R^1=R^2=R^4=H$, $R^3=OH$
b; $R^1=Ac$, $R^2=R^4=H$, $R^3=OAc$

(**5**) **a**; $R^1=H$, $R^2=OH$
b; $R^1=OH$, $R^2=H$
c; $R^1=OSiMe_2Bu^t$, $R^2=H$

acid rearrangement[4] of 4β,5β-epoxy-19-hydroxyandrost-3,17-dione which in turn was obtained from the alkaline hydrogen peroxide oxidation of 19-hydroxyandrost-4-ene-

3,17-dione (**1a**) gave 2α,19-dihydroxyandrost-4-ene-3,17-dione (**4a**). Acetylation of (**4a**) gave the diacetate (**4b**) identical in all respects with that obtained from the 6-bromo-compound (**2**). Brief alkaline hydrolysis of the other diacetate (**3b**) yielded 2β,19-dihydroxyandrost-4-ene-3,17-dione (**3a**). The hydrolysis proceeded without rearrangement since reacetylation regenerated the diacetate (**3b**).

Oxidation of the 2α,19-dihydroxy compound (**4a**) with the chromic oxide–pyridine complex gave 2α-hydroxy-3,17-dioxoandrost-4-en-19-al (**5a**). Similar oxidation of the epimeric (**3a**) failed to stop at the aldehyde stage and yielded a 2,19-lactone product. Since anchimeric assistance of the 2β-hydroxy group was clearly involved in the facile oxidation of the 19-hydroxy, access to the desired 19-aldehyde required masking of the 2β-hydroxy function in (**3a**). Reaction of (**3a**) with dimethyl-t-butylsilyl chloride in the presence of imidazole[5] proceeded selectively to give 2β,19-dihydroxyandrost-4-ene-3,17-dione 2-dimethyl-t-butylsilyl ether (**3c**). Oxidation of (**3c**) with the chromic oxide–pyridine complex provided 2β-hydroxy-3,17-dioxoandrost-4-en-19-al dimethyl-t-butylsilyl ether (**5c**). Removal of the masking silyl ether was achieved with acetic acid in tetrahydrofuran[5] to give the desired 2β-hydroxy-3,17-dioxoandrost-4-en-19-al (**5b**).

The 2β-hydroxy-19-aldehyde derivative (**5b**) in phosphate buffer pH 7 at room temperature was rapidly and quantitatively converted into estrone. In contrast the other 2-hydroxy derivatives (**3a**), (**4a**), and (**5a**) remained unchanged under these conditions. The known facts of estrogen biosynthesis including the β stereochemistry of C-2 hydrogen loss[6] are accommodated by the 2β-hydroxy-Δ^4-3 keto-19-aldehyde structure (**5b**). The uniquely facile aromatisation of (**5b**) under physiological conditions suggests that it may be the enzymatic end product in estrogen biosynthesis with its nonenzymatic collapse to estrone as the final step in the pathway.

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