The Formation and Structure of Some Androstane 4- and 6-Ketones

J. Chem. Research (S), 1999, 258–259
J. Chem. Research (M), 1999, 1257–1273

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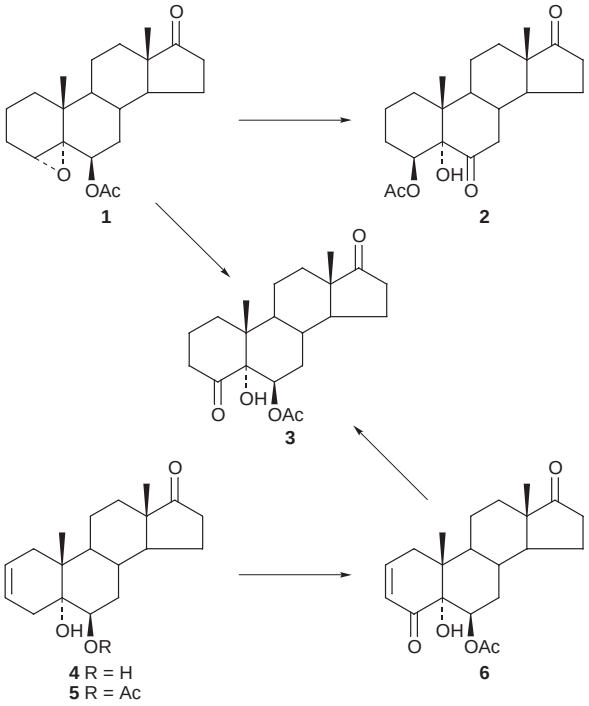
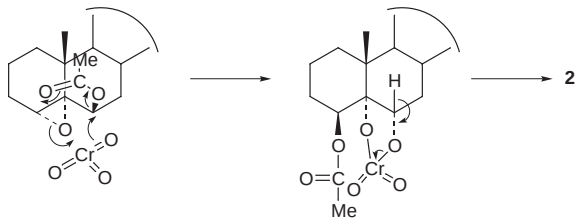
The preparation of some substituted androstane 4- and 6-ketones is described revealing further examples of neighbouring group participation between substituents at C-4 and C-6; the X-ray crystal structure of androstane-4,6,17-trione showed that it existed in a form that was a hybrid of the Δ^4- and Δ^6-enolates.

There are a number of examples of neighbouring group participation involving functional groups at C-4 and C-6 in the steroid series.[1] In previous work we have observed 1:3-rearrangements of steroid allylic 4β- and 6β-acetoxy groups during epoxidation of the Δ^5- and Δ^4-alkenes.[2] Acetylation of 4α,6α-diols leads to a substantial proportion of the 4- and 6-monoacetates through the intervention of a symmetrical and relatively persistant 1,3-dioxan-2-ol.[3] In this paper we report some further examples of this neighbouring group participation in the formation of 4- and 6-ketones.

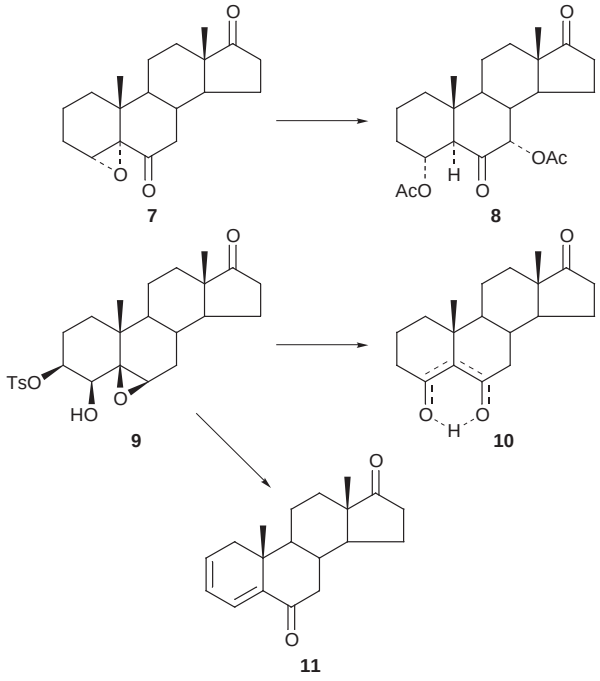
In connection with studies on the preparation of androst-5-ene-4,7,17-trione and some relatives,[4] we examined the chromium trioxide oxidation[5] of 6β-acetoxy-4α,5α-epoxyandrostan-17-one **1** with the object of obtaining a 4-ketone. This oxidation gave an inseparable mixture (1:2; based on the integral of the acetoxyl signals at δ_H 2.01 and 2.03) of 4β-acetoxy-5α-hydroxyandrostane-6,17-dione **2** and 6β-acetoxy-5α-hydroxyandrostane-4,17-dione **3**.



An authentic sample of 6β-acetoxy-5α-hydroxyandrostane-4,17-dione **3** was prepared from dehydroisoandrosterone *via* 5α,6α-epoxy-3β-methanesulfonoxyandrostan-17-one. Hydrolysis of the epoxide and elimination of the 3β-methanesulfonate with collidine gave 5α,6β-dihydroxyandrost-2-en-17-one **4**.[6] Mild acetylation with acetic anhydride in pyridine gave the 6β-acetate **5**. Allylic oxidation at C-4 with chromium trioxide[7] afforded 6β-acetoxy-5α-hydroxyandrost-2-ene-4,17-dione **6**. Catalytic reduction gave 6β-acetoxy-5α-hydroxyandrostane-4,17-dione **3**. The participation and rearrangement of the acetoxyl group during the oxidation may be rationalized as in Scheme 1.



Scheme 1



For comparison purposes we also attempted to prepare 4β-acetoxy-5α-hydroxyandrostane-6,17-dione **2** by acetolysis of 4α,5α-epoxyandrostane-6,17-dione **7**.[2] However the product was 4α,7α-diacetoxyandrostane-6,17-dione **8**. The formation of this product *via* the enol of the 6-ketone, may be rationalized as in Scheme 2.

An alternative route for the preparation of 4-ketones was explored using the 3β-toluene-*p*-sulfonate of 3β,4β-dihydroxy-5β,6β-epoxyandrostan-17-one **9**.[8] Treatment of this

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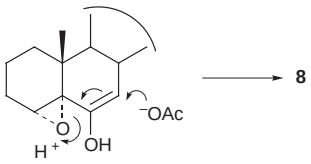
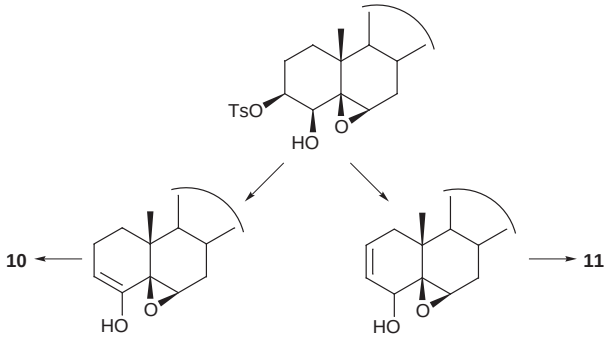


Scheme 2

with collidine gave two products which were identified from their ^{1}H NMR spectra as the enolate of androstane-4,6,17-trione **10** and androsta-2,4-diene-6,17-dione **11**.[9] The structure of **10** was established by X-ray crystallography (Fig. 1) which confirmed that it possessed the enolized β-diketone structure and that it was a hybrid of the two possible enolates. The formation of these two products may be rationalized (Scheme 3) in terms of the initial elimination of the 3β-toluene-*p*-sulfonate to give a Δ^2- or a Δ^3-alkene. Further elimination of the Δ^2-alkene would afford the 2,4-diene and thence by rearrangement of the epoxide, the 2,4-diene-6,17-dione **11**. On the other hand the Δ^3-alkene is the enol of a 4-ketone. Rearrangement of the epoxy-ketone would then afford the 4,6-dione **10**.



Scheme 3

Crystallographic Data and Structure Determination for Androstane-4,6,17-trione **10**.—$C_{19}H_{26}O_3$, $M_r = 302.4$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 7.144(5)$, $b = 13.505(3)$, $c = 16.904(5)$Å, $V = 1631(1)$ Å^3, $Z = 4$, $D_c = 1.23$ g cm^{-3}, $F(000) = 656$, $\lambda = 1.5418$ Å, $\mu = 0.65$ mm^{-1} Data were collected using a crystal of size *ca.* $0.3 \times 0.3 \times 0.2$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 2677 reflections were collected for $2 < \theta < 60^\circ$ and $0 < h < 7$, $0 < k < 15$, $-18 < l < 18$. There were 2368 independent reflections and 1807 reflections with $I > 2\sigma(I)$ that were used in the refinement. There was no crystal decay and no absorption correction was applied. The structure was solved by direct methods using SHELXS-86[11] and SHELXL-93.[12] The non-hydrogen atoms were refined anisotropically by full-matrix least squares on F^2. Hydrogen atoms were included in riding mode with $U_{iso} = 1.2U_{eq}$(C) or $1.5U_{eq}$(C) for methyl groups except that the hydroxyl hydrogen atom was located on a difference map and its position freely refined. The final R indices were $R_1 = 0.056$, $wR_2 = 0.139$ and (all data)

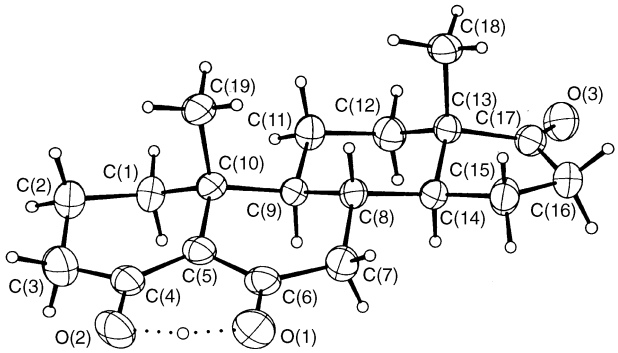


Fig. 1 X-Ray crystal structure of **10**

$R_1 = 0.076$, $wR_2 = 0.155$. The goodness of fit on F^2 was 1.033 and the maximum shift to esd was 0.004. Tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen atom co-ordinates, hydrogen bond distances and angles and selected torsion angles are given in the appendix.

I.K. wishes to thank the Turkish Government for financial support.

Techniques used: ^{1}H NMR, X-ray crystallography, IR, chromatography

References: 12

Appendix: Crystal data for 10

Received, 4th January 1999; Accepted, 15th January 1999
Paper E/9/00022D

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