

The Oxidation of Some Steroidal Dienes and Trienes with Chromic Acid

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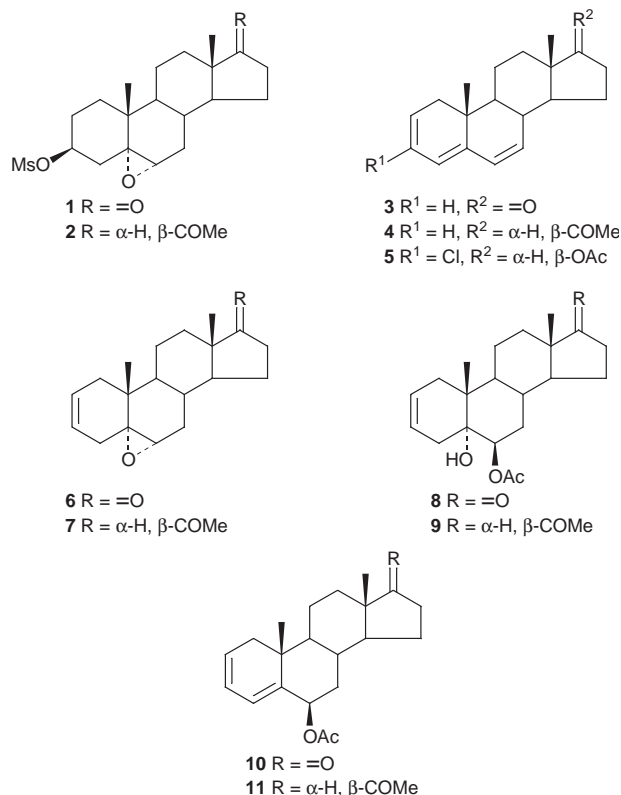
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J. Chem. Research (S),
1999, 594–595
J. Chem. Research (M),
1999, 2532–2545

The chromic acid oxidation of steroidal 2,4- and 3,5-dienes and 2,4,6-trienes is shown to take place at the secondary termini of the alkenes rather than at the allylic positions and is rationalized in terms of a sequence of 1:4-additions of chromic acid.

The oxidation of steroidal alkenes by chromic acid¹ or by reagents derived from chromium trioxide such as chromyl diacetate,² di-*tert*-butoxychromate,³ pyridinium chlorochromate,^{4,5} pyridinium dichromate⁶ or the chromium trioxide-pyrazole complex⁷ may yield products arising from addition to the alkene such as epoxides and their cleavage products or from allylic oxidation. However the oxidation of steroidal dienes has been less widely investigated.

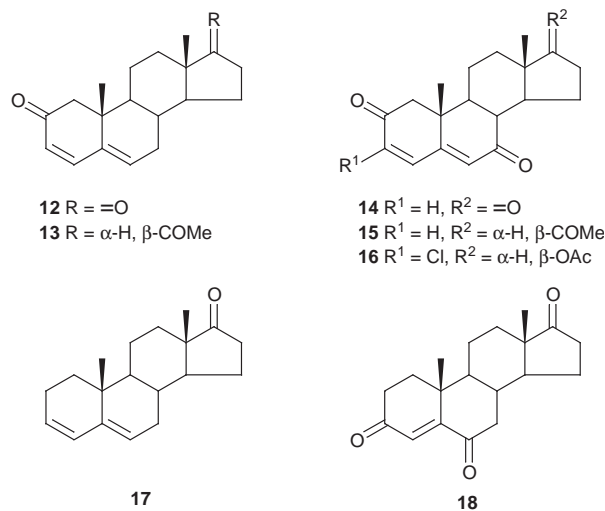
Oxidation of cholesta-3,5-diene with pyridinium chlorochromate has been reported⁸ to give cholest-4-ene-3,6-dione whilst oxidation of 17 β -acetoxyandrosta-3,5-diene with di-*tert*-butoxychromate was shown⁹ to give firstly the 7-ketone and then the androsta-3,5-diene-2,7-dione. Here we describe the oxidation of some steroidal 2,4- and 3,5-dienes and 2,4,6-trienes with chromic acid (chromium trioxide in sulfuric acid).¹⁰ This not only gave access to the relatively inaccessible 2-ketones from 2,4-dienes, but it also shed some light on the possible mechanism of these oxidations with chromium trioxide.



The substrates **3**, **4**, **10** and **11** were prepared as follows. Treatment of the 3 β -methanesulfonate of 5 α ,6 α -epoxy-3 β -hydroxyandrostan-17-one **1**¹¹ with collidine gave androsta-2,4,6-trien-17-one **3**¹² and androst-4-ene-6,17-dione whilst

treatment with lithium carbonate in dimethylformamide¹¹ gave 5 α ,6 α -epoxyandrosta-2-en-17-one **6**. Acetylation of **6** in refluxing acetic acid gave 6 β -acetoxy-5 α -hydroxyandrosta-2-en-17-one **8** which was dehydrated with thionyl chloride to give 6 β -acetoxyandrosta-2,4-dien-17-one **10**. A similar set of reactions utilizing the 3 β -methanesulfonate of 5 α ,6 α -epoxy-3 β -hydroxypregnan-20-one **2** gave, on the one hand prena-2,4,6-trien-20-one **4** and on the other hand, 6 β -acetoxypregna-2,4-dien-20-one **11** via **7** and **9**.

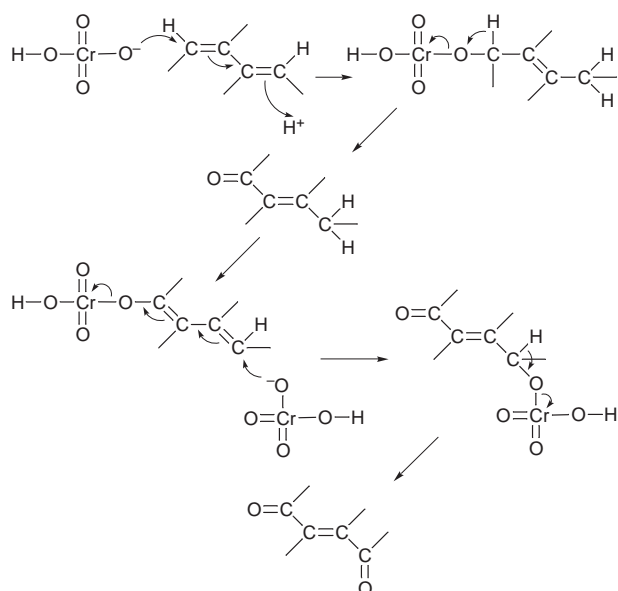
Oxidation of 6 β -acetoxyandrosta-2,4-dien-17-one **10** with chromic acid gave androsta-3,5-diene-2,17-dione **12** whilst 6 β -acetoxypregna-2,4-dien-20-one **11** gave prena-3,5-diene-2,20-dione **13** in 35 and 34% yields respectively. Oxidation of androsta-2,4,6-trien-17-one **3**, prena-2,4,6-trien-20-one **4** and 17 β -acetoxy-3-chloroandrosta-2,4,6-triene **5**¹³ gave the corresponding 3,5-diene-2,7-diones **14**, **15** and **16** in 34, 25 and 32% yields respectively, whilst androsta-3,5-dien-17-one **17**¹⁴ gave androst-4-ene-3,6,17-trione **18**¹⁵ in 20% yield. Hence the oxidation of these steroidal dienes and trienes with chromic acid to form ketones has taken place albeit in rather low yield, at the secondary termini of the diene or triene rather than at an allylic position.



The formation of these different products may be rationalized in the following manner. There are two groups of chromium(vi) reagent, one in which the proton is the dominant electrophile and the chromium oxidant is present as the chromate anion, and the other in which the chromium(vi) oxidant is present as an electron-deficient Lewis acid. Oxidation of a diene by chromic acid (see Scheme 1) may involve the initial acid-catalysed 1,4-addition of chromic acid followed by oxidation to the unsaturated ketone.

The second step then involves the formation of an enol-chromate in which the chromium(vi) may again act as an oxidant facilitating the addition of a further chromate

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Scheme 1 Oxidation of dienes with chromic acid

ion and thus the final oxidation leading to the enedione. The formation of androsta-3,5-diene-2,17-dione may arise through the acid-catalysed elimination of the 6β -acetate taking precedence over the formation of an enol-chromate.

I.K. thanks the Turkish Government for financial assistance.

Techniques used: IR, ^1H NMR, chromatography

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Received, 25th May 1999; Accepted, 22nd June 1999
Paper E/9/04215F

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