SHORT PAPER

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The oxidation of 3-hydroxy-3-methyl-Δ^4-steroids by chromium trioxide†

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Oxidation of the allylic tertiary alcohols of 3-hydroxy-3-methyl-Δ^4-steroids by chromium trioxide in sulfuric acid leads to C–C bond fission together with the formation of a 3-methylestra-1,3,5(10)-triene from a 19-nor steroid and a 3β,4β-epoxy-5β-hydroxy compound from an androstane; the structure of the hydroxy-epoxide was established by X-ray crystallography.

Keywords: tertiary allylic alcohols, 3-hydroxy-3-methyl-Δ^4-steroids, chromium trioxide, oxidation, epoxidation

The initial step in the oxidation of an alcohol by chromium trioxide is the formation of a chromate ester.[1] Although a tertiary alcohol itself is usually inert to oxidation, the alcohol may act as a tether for a chromate ester to participate in another intramolecular oxidation. For example, some years ago we showed[2] that the oxidation of the homoallylic alcohol, 5α-hydroxyandrost-2-en-17-one by chromium trioxide took place readily at C–4. The oxidation did not take place under the same conditions in the absence of the 5α-alcohol.

The oxidation of steroidal secondary allylic alcohols by chromium trioxide under acidic conditions was originally studied as a consequence of structural work on the withanolides. These studies[3] employing isomeric Δ^5-4-ols and Δ^4-6-ols showed that oxidation of equatorial allylic secondary alcohols gave the enones whilst oxidation of the axial alcohols led either to the enone or to epoxidation of the double bond and then to the formation of the epoxy ketone. The epoxidation of the double bond was stereospecific and took place on the same face as the hydroxyl group. The epimeric 5-hydroxycholest-3-enes both gave cholest-4-en-3-one possibly by rearrangement and oxidation.

We have now examined the oxidation of some allylic 3-alkyl-3-hydroxy-Δ^4-steroids. These tertiary, as opposed to secondary 3α- and 3β- alcohols have given some unexpected and potentially useful results. 3α,17β-Dihydroxy-3β-methylestra-4-ene **1** was obtained by a Grignard reaction between 17β-acetoxyestra-4-en-3-one and methylmagnesium iodide.[4] Oxidation with chromium trioxide in sulfuric acid (Jones' reagent) gave 3-methylestra-1,3,5(10)-trien-17-one **2**[5] and estra-4-ene-3,17-dione **3**.[6] The ^{1}H NMR spectrum of **2** contained aromatic C–H resonances at δ_H 6.92 (singlet) and 6.97 and 7.18 (each doublets, *J* 8 Hz) together with an aromatic C-methyl resonance at δ_H 2.29. This oxidation has therefore provided a conveniently simple route to 3-methylestratrienes which have been investigated for their effect on plasma cholesterol levels.[5]

17β-Acetoxy-3β-hydroxy-3α-methylandrost-4-ene **4** is epimeric at C–3 to the estr-4-ene derivative.[4] Oxidation of this allylic alcohol gave 17β-acetoxyandrost-4-en-3-one 5[7] and a hydroxy epoxide (δ_H 2.78, 4-H)[6]. This hydroxy epoxide differed from the product **7** of epoxidation of **4** with *m*-chloroperbenzoic acid. The stereochemistry of the epoxide in **7** was assigned the 4β, 5β-configuration on the basis of the known[8] directing effect of an allylic hydroxyl group on the stereochemistry of epoxidation by per-acids. The structure of the chromium trioxide oxidation product **6** was therefore established by X-ray crystallography (see Fig. 1). This showed that the product was 17β-acetoxy-3β, 4β-epoxy-5β-hydroxyandrostane and that an allylic rearrangement had taken place in the course of the epoxidation with chromium trioxide. Oxidation of 3β,17β-dihydroxy-3α-ethylandrost-4-ene **8** gave predominantly androst-4-ene-3,17-dione **9**.[9] We were unable to isolate any of the hydroxy epoxide corresponding to **6**.

The contrast between the reactivity of an allylic tertiary alcohol and an isolated tertiary alcohol under these conditions was shown by the oxidation of 3β, 20-dihydroxy-3α, 20-dimethylpregn-4-ene[10]. This was obtained by treatment of progesterone with methylmagnesium bromide. Its stereochemistry at C–3 was assigned by analogy with the reaction in the androstene series.[4] Oxidation of this diol with chromium trioxide gave 20-hydroxy-20-methylpregn-4-en-3-one **11**[10] in reasonable overall yield from progesterone and by a simpler method to that described previously.[10]

These reactions can be rationalised in the following manner. In the formation of the 3β, 4β-epoxy-5β-alcohol, the 3β-chromate ester undergoes an allylic rearrangement to a 5β-chromate ester which epoxidises the Δ^3-double bond (Scheme 1). This 5β-ester possesses an axial relationship to the 3(4)-ene. In the case of the 19-nor steroid either the intermediate (A) or the final hydroxy epoxide can undergo a series of elimination reactions to generate the estratriene. The formation of estratrienes from hydroxy epoxides has been reported previously.[11] The formation of the unsaturated ketones probably involves elimination of the allylic tertiary alcohol to form a diene followed by cleavage of the diene.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80°C. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls, High-resolution mass spectra measurements were obtained using electrospray ionisation on a Bruker Daltonics Apex III mass spectrometer. The chromium trioxide reagent was prepared by dissolving chromium trioxide (26.7 g) in distilled water (25 cm^3), carefully adding concentrated sulfuric acid (23 cm^3) and making the solution up to 100 cm^3 with distilled water.

Oxidation reactions: (**a**) 3α, 17β-Dihydroxy-3β-methylestra-4-ene **1** (500 mg) was dissolved in acetone (25 cm^3) and treated with the chromium trioxide reagent at room temperature until the orange colour persisted (*ca* 2 cm^3). The solution was left to stand for 30 minutes. Methanol was added to destroy the excess reagent. The solution was concentrated *in vacuo*, diluted with water and the products were extracted with ethyl acetate. The extract was washed with water, brine and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica. Elution with 5% ethyl acetate:light petroleum gave 3-methylestra-1,3,5(10)-trien-17-one **2**

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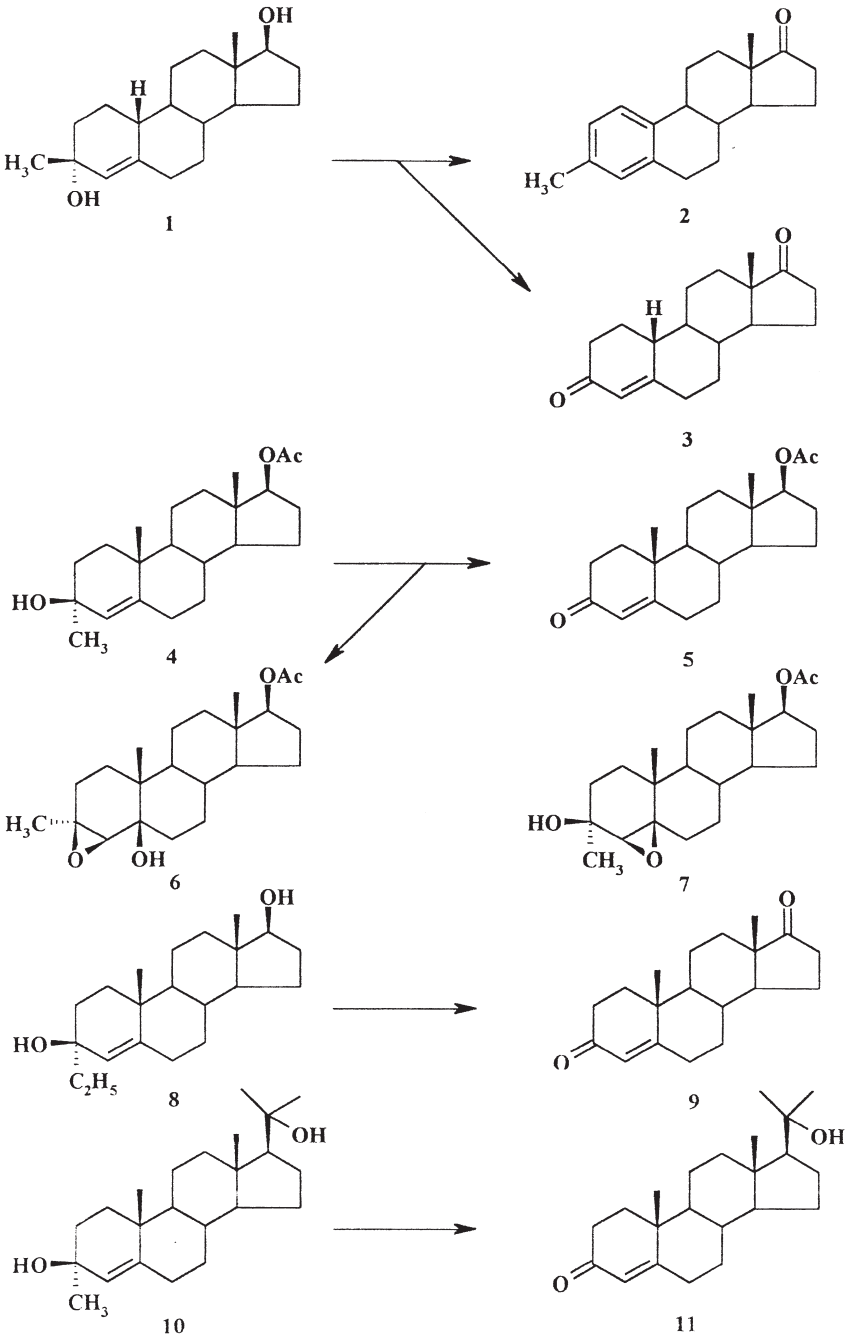

(120 mg) which crystallised from acetone as plates, m.p. 176–178°C (lit.,[5] 174–181°C); ν_{max}cm^{-1} 1737, 1609; δ_H 0.90 (3H, s, 18-H), 1.1–2.4 (15H, overlapping multiplets), 2.29 (3H, s, Ar-Me), 6.92 (1H, s, 4-H), 6.97 and 7.18 (each 1H, d, *J* 8 Hz, 1- and 2-H). Further elution with 10% ethyl acetate:light petroleum gave estra-4-ene-3,17-dione 3 (295 mg) which crystallised from acetone as plates, m.p. 162–164°C (lit.,[6] 160–162°C), ν_{max}cm^{-1} 1738, 1669, 1625; δ_H 0.93 (3H, s, 18-H), 1.1–2.4 (20H, overlapping multiplets), 5.85 (1H, s, 4-H).

(b) Under similar conditions 17β-acetoxy-3β-hydroxy-3α-methylandrost-4-ene (500 mg) gave 17β-acetoxyandrost-4-en-3-one[7] (50 mg) identified by comparison of its ^{1}H NMR spectrum with that of an authentic sample, and 17β-acetoxy-3β, 4β-epoxy-5β-hydroxy-3α-methylandrostane (290 mg) which crystallised from acetone as needles, m.p. 128-131°C, (Found: M$^+$ 385.237 $C_{22}H_{34}O_4Na^+$ requires 385.235); ν_{max}cm^{-1} 3557, 1739; δ_H 0.76 (3H,s, 18-H), 0.85 (3H,s, 19-H), 1.35 (3H, s, 3-Me), 1.0–2.2 (22H, overlapping multiplets), 2.02 (3H, s, 17β-OAc), 2.78 (lH, s, 4α-H), 4.59 (1H, t, *J* 8.6 Hz, 17α-H).

(c) Under similar conditions 3β, 17β-dihydroxy-3α-ethylandrost-4-ene **8** (250 mg) gave androst-4-ene-3,17-dione **9** (159 mg), m.p. 170–173°C (lit.,[9] 173–176°C); ν_{max}cm^{-1} 1735, 1686; δ_H 0.87 (3H, s, 18-H), 1.17 (3H,s, 19-H), 1.0–2.4 (19H overlapping multiplets), 5.70 (1H, s, 4-H).

(d) Under similar conditions 3β,20-dihydroxy-3α, 20-dimethylpregn-4-ene **10** (500 mg) gave 20-hydroxy-20-methylpregn-4-en-3-one **11** (320 mg), m.p.219–220°C, (lit.,[10] 220–222°C); ν_{max}^{cm-1} 3518. 1663, 1605; δ_H 0.85 (3H,s, 18-H), 1.16 and 1.17 (each 3H, s, 21- and 22-H), 1.29 (3H, s, 19-H), 0.90-2.40 (20H, overlapping multiplets), 5.70 (1H,s, 4-H).

Preparation of 3β, 20-dihydroxy-3α, 20-dimethylpregn-4-ene **10** A solution of progesterone (1 g) in tetrahydrofuran (50 cm^3) was treated with methylmagnesium bromide in tetrahydrofuran (3M, 5cm^3) at room temperature overnight. Aqueous ammonium chloride (100 cm^3) was added and the products were recovered in dichloromethane. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica. Elution with light petroleum gave 3β, 20-dihydroxy-3α, 20-dimethylpregn-4-ene **10** (760 mg), m.p. 145–147°C, (Found: M$^+$ 369.278 $C_{23}H_{38}O_2Na^+$ requires 369.277); ν_{max}cm^{-1} 3306; δ_H 0.82 (3H, s,18-H), 1.16 (3H, s 3-Me), 1.23 (3H, s, 19-H); 1.28 and 1.29 (each 3H, s, 21- and 22-H), 0.90–2.20 (20H, overlapping multiplets), 5.17 (1H, s, 4-H).

Epoxidation of 17β-acetoxy-3β-hydroxy-3α-methylandrost-4-ene **4** The steroid **4** (500 mg) in dichloromethane (50 cm^3) was treated with *m*-chloroperbenzoic acid (750 mg) at 0°C for 20 h. The mixture was

diluted with dichloromethane and then washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate, brine and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica. Elution with 25% ethyl acetate: light petroleum gave 17β-acetoxy-4β, 5β-epoxy-3β-hydroxy-3α-methylandrostane **7** (230 mg) as an oil, (Found: M^+ 385.237 $C_{22}H_{34}O_4Na^+$ requires 385.235); $\nu_{max}cm^{-1}$ 3450, 1737; δ_H 0.78 (3H, s, 18-H3, 1.01 (3H, s, 19-H), 1.31 (3H, s, 3-Me), 2.02 (3H, s, OAc), 0.85–2.15 (20H, overlapping multiplets), 2.79 (1H,s, 4-H), 4.57 (1H, t, *J* 8.5 Hz, 17-H).

X-Ray crystallographic data and structure determination of 17β-acetoxy-3β, 4β-epaxy-5β-hydroxyandrostane. Compound **6**, $C_{22}H_{34}O_4$, M_r 362.49, monoclinic, space group $P2_1$ (No.4), a = 9.3794(3), b = 7.5896(3), c = 14.0395(5)Å, α = γ = 90°, β = 101.200(2)°, V = 980.38(6)Å^3 Z = 2, D_{calc} = 1.23 g cm^{-3} μ = 0.08mm^{-1}, F(OOO) = 396. Data were collected using a crystal of size 0.4 × 0.3 × 0.2 mm^3 on a KappaCCD diffractometer. A total of 5149 reflections were collected for $3.95 < \theta < 25.09$ and $-11 \le h \le 11$, $-7 \le k \le 8$, $-15 \le l \le 16$. There were 2868 independent reflections and 2690 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined using SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.079 wR_2 = 0.212 and (all data) R_1 = 0.083, wR_2 = 0.214. The goodness-of-fit on F^2 was 1.093 and the largest difference peak and hole was 0.40 and –0.26 e.Å^{-3}. The crystallographic data will be deposited with the Cambridge Crystallographic Data Centre.

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