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The stereochemistry of epoxidation of 5β-methyl-19-norsteroidal 9,10-alkenes

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Crystallographic studies have shown that the oxidation of 3β,6β-dihydroxy-5β-methyl-19-norsteroidal 9(10)-alkenes with chromium trioxide leads to 9α,10α-epoxides as minor products.

Keywords chromium trioxide, epoxidation, steroidal 9(10)-alkenes, Westphalen rearrangement, oxidations

The epoxidation of alkenes during oxidation with chromium trioxide and its derivatives has been observed on a number of occasions.[1,2] In the steroid series the stereochemistry of the epoxides may differ from that of epoxidation with per-acid. Thus treatment of acetylated Δ^5-steroids with chromyl diacetate, prepared from chromium trioxide and acetic anhydride at low temperatures, afforded[3] the 5β,6β-epoxides with a stereoselectivity that was greater than 90%. On the other hand epoxidation with per-acid gave predominantly the 5α,6α-epoxide.[4]

The 9(10)-alkene of a 5β-methyl-19-nor-steroidal-9(10)-ene bears the same relationship to the 5β-methyl group as does the 5(6)-ene to the 10β-methyl group of the normal steroid. Oxidation of the Westphalen rearrangement product,[5] 3β,6β-dihydroxy-5β-methylestr-9-en-17-one **1** with chromium trioxide gave the 3,6,17-trione **2** together with a small amount of the 9(10)-epoxide. In the ^{13}C NMR spectrum the alkene resonances of the starting material had been replaced by two quaternary carbon resonances at δ_C 65.10 and 64.77. The stereochemistry of this epoxidation might be directed to the β–face by the presence of the 3β or 6β-hydroxyl groups or to the α–face by the steric hindrance arising from the 5β-methyl group. Consequently the structure and stereochemistry of the epoxide was established by X-ray crystallography (see Fig. 1). This shows that the epoxide had the 9α,10α-stereochemistry. The same epoxide **3** was obtained by treatment of 5-methylestr-9-ene-3,6,17-trione **2** with *m*-chloroperbenzoic acid.

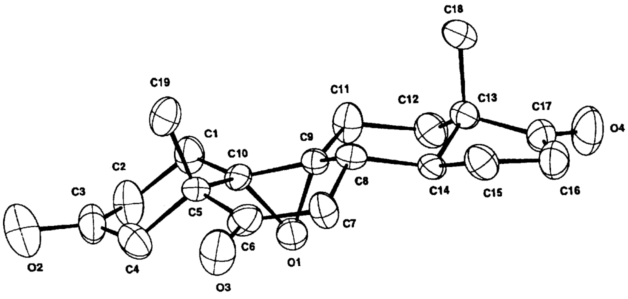
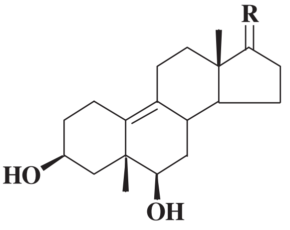
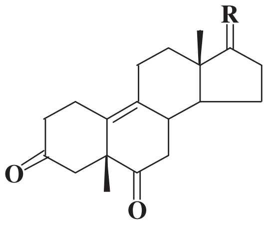


Fig. 1 X-ray structure of **3**.

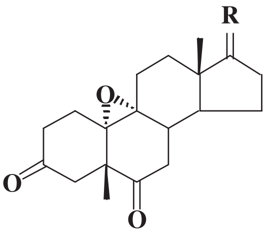
Oxidation of 3β,6β-dihydroxy-5β-methyl-19-norpregn-9-en-20-one[6] **4** with chromium trioxide gave 5β-methyl-19-norpregn-9-ene-3,6,20-trione **5** and an epoxide which was assigned the same 9α,10α-stereochemistry **6**. The same epoxide **6** was obtained by treatment of 5β-methyl-19-norpregn-9-ene-3,6,20-trione with chromium trioxide.



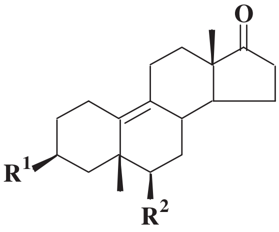
1 R= O
4 R= α-H, β-COCH3



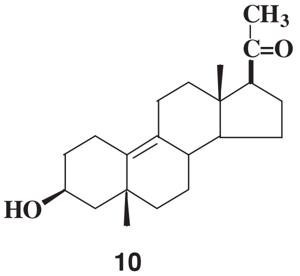
2 R= O
5 R= α-H, β-COCH3



3 R= O
6 R= α-H, β-COCH3



7 $R^1 = R^2 =$ OAc
8 $R^1 =$ OH, $R^2 =$ Cl
9 $R^1 =$ OH, $R^2 =$ H



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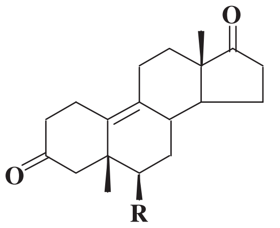
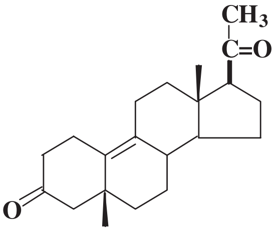


11 R= Cl
12 R= H



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The formation of the 9(10)-epoxide appeared to be limited to compounds that also possessed a 6β-hydroxyl group or a 6-ketone. No epoxide was detected on oxidation of 3β,6β-diacetoxy-5β-methylestr-9-en-17-one **7**, 6β-chloro-3β-hydroxy-5β-methylestr-9-en-17-one **8** or on repetition of the previously described[6-8] oxidations of 3β-hydroxy-5β-methylestr-9-en-17-one **9** and 3β-hydroxy-5β-methy-19-norpregn-9-en-20-one **10**. The oxidation of the 3β-alcohols only gave the corresponding 3-ketones **11**–**13**.

In conclusion we have shown that epoxidation of the 9(10)-ene of a 5β-methyl steroid by both chromium trioxide and per-acid takes place from the α–face. In the case of chromium trioxide the formation of this side product appears to require the presence of a 6-ketone. A possible explanation of this is that in this particular case the "spectator" oxygen of the chromium trioxide is loosely attached to the electron-deficient carbon of the carbonyl group to provide some stabilisation of the intermediate in the oxidation. The adjacent 5β-methyl group would direct this to the α–face.

Experimental

General experimental details: Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. ^{1}H and ^{13}C NMR spectra were determined at 300 and 75 MHz respectively using a Bruker AMX 300 spectrometer for solutions in deuteriochloroform. IR spectra were determined as nujol mulls on a Perkin-Elmer 1710 FTIR. High-resolution mass spectra were determined on a Bruker Daltonics Apex III electrospray mass spectrometer. Extracts were dried over anhydrous sodium sulfate. The chromium trioxide reagent[9] was prepared by dissolving chromium trioxide (26.7 g) in the minimum of water. Conc. sulfuric acid (23 ml) was carefully added to the solution which was then diluted to 100 ml with water.

Oxidation of 5β-methyl-19-norsteroidal 9,10-alkenes; general procedure: The diol **1**[5] (1.0 g) in acetone (50 ml) was treated with the chromium trioxide reagent (5 ml) at room temperature for 30 min. The reaction was quenched with methanol and the solution was concentrated *in vacuo*. The residue was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 20% ethyl acetate: light petroleum gave 5β-methylestr-9-ene-3,6,17-trione **2** (0.67 g, 67.9%) which crystallised from acetone as needles, m.p. 173–175 °C (lit.,[6] 175–177 °C), ν_{max}/cm^{-1} 1740, 1710, 1696, 1636; δ_H 0.99 (3H, s, 18-H), 1.24 (3H, s, 5β-Me), 1.00–2.30 (18H, overlapping multiplets). Further elution with 20% ethyl acetate light petroleum gave 9α,10α-epoxy-5β-methylestra-3,6,17-trione **3** (20 mg, 2.0%), m.p.195 °C (decomp.), (Found: C, 72.0, H, 7.6. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%), ν_{max} / cm^{-1} 1740, 1718, 1700; δ_H 1.01 (3H, s, 18-H), 1.18 (3H, s, 5β-Me), 0.70–2.75 (18H, overlapping multiplets); δ_C 12.82, 21.63, 21.66, 25.39, 25.93, 28.98, 33.24, 35.57, 37.94, 37.97, 46.52, 47.16, 48.96, 50.43, 64.77, 65.10, 208.56, 208.76, 218.69.

Under similar conditions 3β,6β-dihydroxy-5β-methyl-19-norpregn-9-en-20-one **4** (1.0 g) gave, after chromatography, in 10% ethyl acetate in light petroleum, 5β-methyl-19-norpregn-9-en-3,6,20-trione **5** (590 mg, 59.7%), m.p.144–146 ° C (decomp.), (lit.,[8] 148–149 °C), ν_{max}/cm^{-1} 1731, 1717, 1642; (Found: M$^+$ 351.19 $C_{21}H_{28}O_3$ + Na requires 351.19), ν_{max} / cm^{-1} 1731, 1717, 1642; δ_H 0.74 (3H, s, 18-H), 1.00 (3H, s, 5β-Me), 2.12 (3H, s, 21-H), 0.77–2.95 (19H, overlapping multiplets). Further elution with 15% ethyl acetate in light petroleum gave 9α,10α-epoxy-5β-methylpregna-3,6,20-trione **6** (38 mg, 3.6%), m.p.178–180 °C (decomp.), (Found: M$^+$ 367.187 $C_{21}H_{28}O_4$ + Na requires 367.189); ν_{max}/cm^{-1} 3381, 1716, 1700; δ_H 0.76 (3H, s, 18-H), 1.41 (3H, s, 5β-Me), 2.16 (3H, s, 21-H), 0.90–2.60 (19H, overlapping multiplets); δ_C 12.80, 21.98, 23.32, 24.66, 26.38 (2 × C), 31.86,33.80, 36.30, 38.42, 39.32, 43.79, 46.95, 50.87, 54.30, 63.25, 65.12, 65.54, 209.03, 209.14, 209.64.

Under similar conditions 5β-methyl-19-norpregn-9-en-3,6,20-trione **5** (500 mg) gave 9α,10α-epoxy-5β-methylpregna-3,6,20-trione **6** (86 mg, 16%) identified by its ^{1}H NMR spectrum.

Under similar conditions 6β-chloro-3β-hydroxy-5β-methylestr-9-en-17-one **8**$^{1\circ}$ (500 mg) gave 6β-chloro-5β-methylestr-9-ene-3,17-dione **11** (355 mg, 71.7%), m.p. 181–183 °C (decomp.): (Found: M$^+$ $C_{19}H_{25}ClO_2$ + Na requires 343, 144), ν_{max}/cm^{-1} 3585, 1735; δ_H 1.00 (3H, s, 18-H), 1.17 (3H, s, 5β-Me), 4.01 (1H, dd, *J* 3.5 and 11.8 Hz, 6α-H), 1.01–2.88 (18H, overlapping multiplets).

Epoxidation with m-chloroperbenzoic acid: 5β-Methylestr-9-ene-3,6,17-trione **2** (50 mg) was treated with *m*-chloroperbenzoic acid (50 mg) in chloroform (5 cm^3) at 0 °C and then allowed to attain room temperature over 1 h. The solution was washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate, water and brine. The solution was dried and the solvent was evaporated to give 9α, 10α-epoxy-5β-methylestra-3,6,17-trione **3** (40 mg, 76%) identified by its ^{13}C NMR spectrum.

X-ray crystallographic data and structure determination: 9α,10α-Epoxy-5β-methylestra-3,6,17-trione **3**, $C_{19}H_{24}O_4$, M_r 316.4, orthorhombic, space group $P2_12_12_1$ (No.19), a = 7.177(2), b = 12.081(3), c = 19.051(7) Å, $\alpha = \beta = \gamma = 90°$, V = 1651.8(9) Å^3, Z = 4, D_{calc} = 1.27 g cm^{-3}, μ = 0.71 mm^{-1}, F(OOO) = 680. Data were collected using a crystal of size 0.20 × 0.10 × 0.10 mm^3. A total of 1947 reflections were collected on an Enraf Nonius CAD4 diffractometer for $2<\theta<50°$ and $0 \le h \le 7$; $0 \le k \le 11$, $-18 \le l \le 18$. There were 1691 independent reflections and 1091 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods using SHELXS-97and refined using SHELXL-97. The final R indices were [$I > 2\sigma(I)$], R_1 = 0.066, wR_2 = 0.179 and (all data), R_1 = 0.117, and wR_2 = 0.230. The largest difference peak and hole was 0.16 and –0.16 eÅ^{-3}.

CCDC250707 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.

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