The Westphalen rearrangement of 5α, 6α-epoxy-3β-methanesulfonyloxy-androstan-17-one

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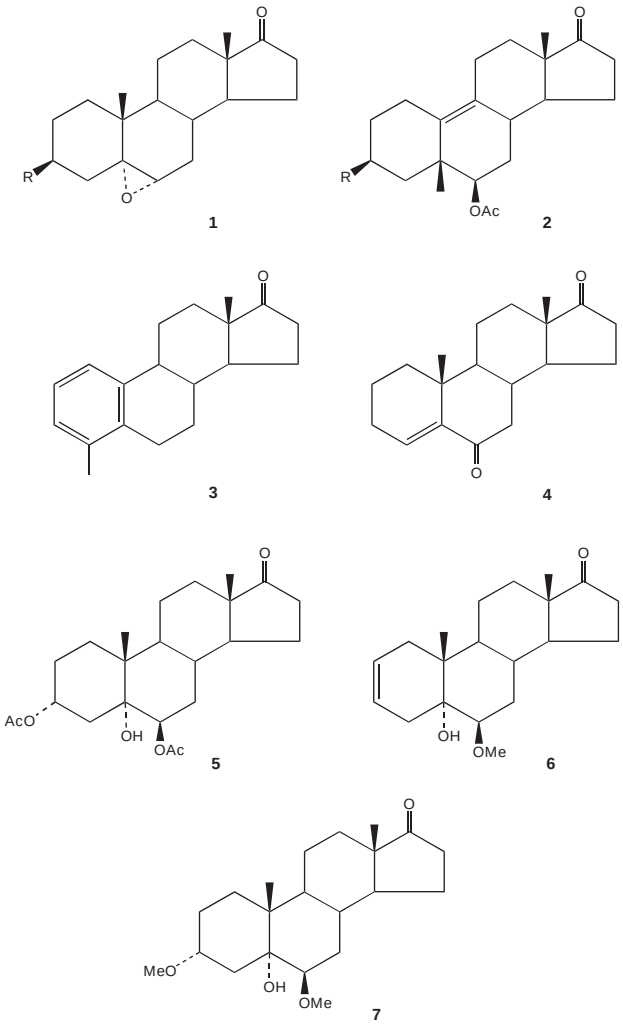
5α,6α-Epoxy-3β-methanesulfonyloxyandrostan-17-one undergoes a Westphalen backbone rearrangement rather than an aromatisation in acetic acid : acetic anhydride containing sulfuric acid catalyst, suggesting that under these conditions the formation of a 5α-sulfate from the epoxide and its ionisation takes precedence over the elimination of the 3β-methanesulfonate.

Keywords: epoxyandrostane, steroids, Westphalen rearrangement

There are three general reactions which occur on treatment of 3β-acetoxy-5α,6α-epoxyandrostan-17-one (**1**, R = OAc) with acid. Treatment with sulfuric acid in an acetic acid : acetic anhydride mixture gives, *via* acetolysis of the epoxide, the products of the Westphalen rearrangement[1] in which the 10β-methyl group has migrated to C-5β, affording a 19-nor-androst-9(10)-ene **2**. This reaction takes place *via* the formation and ionization of a 5α-acetylsulfate.[2] In contrast, treatment with hydrobromic acid in glacial acetic acid gives 4-methylestra-1,3,5(10)-trien-17-one **3** via a spiranic dienol : benzene rearrangement pathway.[3] The aromatisation reactions are accompanied by the formation of variable amounts of androst-4-ene-6,17-dione **4** and trace amounts of anthra-steroids. 5α,6α-Epoxy-3β-methanesulfonyloxyandrostan-17-one (**1**, R = OSO_2Me), has played an important part in the study of the aromatisation reaction.[4] In the presence of hydrobromic acid in glacial acetic acid, it gives the aromatic steroid **3**, a small amount of the 4-ene-6,17-dione **4** and a trace of a 17-oxoanthrasteroid. Treatment of **1** with lithium bromide and lithium carbonate in dimethylformamide afforded mainly androst-4-ene-6,17-dione **4** and a smaller amount of the aromatic steroid **3**.[5] We have now examined the reaction of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one (**1**, R = OSO_2Me) under conditions that might lead to a Westphalen backbone rearrangement to see whether or not reactions that depend on the elimination of the methanesulfonate might take precedence over the formation and ionisation of the 5α-acetylsulfate.

Treatment of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one (**1**, R = OSO_2Me) with a mixture of acetic acid and acetic anhydride containing a catalytic amount of sulfuric acid gave 6β-acetoxy-3β-methanesulfonyloxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OSO_2Me). We did not detect any aromatic products The structure of the rearrangement product was established by the partial hydrolysis of authentic 3β,6β-diacetoxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OAc)[6] with methanolic potassium carbonate to the 3β-alcohol (**2**, R = OH) followed by treatment with methanesulfonyl chloride in pyridine.

The requirement for the sulfuric acid catalyst was apparent when treatment of the methanesulfonate (**1**, R = OSO_2Me) with acetic acid/anhydride containing perchloric acid catalyst, gave 3α,6β-diacetoxy-5α-hydroxyandrostan-17-one **5**. The importance of the solvent was revealed by treatment with methanol containing a trace of sulfuric acid, which gave a separable mixture of 5α-hydroxy-6β-methoxyandrost-2-en-17-one **6** and 3α,6β-dimethoxy-5α-hydroxyandrostan-17-one **7**. Treatment of the methanesulfonate **1** with collidine gave a small amount of 4-methylestra-1,3,5(10)-trien-17-one **3** and a large amount of androst-4-ene-6,17-dione **4**.



In an attempt to observe a 'switch-over' between the pathways, the Westphalen product, 3β,6β-diacetoxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OAc) was heated with hydrobromic acid in glacial acetic acid. However this gave a complex mixture which we were unable to resolve. In earlier work[4] a large scale reaction of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one (**1**, R = OSO_2Me) with hydrobromic acid in glacial acetic acid gave no sign of Westphalen products.

In conclusion, the conditions for the Westphalen backbone rearrangement appear to be more stringent than those for aromatisation. The mechanism of the Westphalen rearrangement is believed[7] to involve the formation of a 5α-acetylsulfate and the slower rate-determining ionisation of the 5α-acetylsulfate to form a C-5 carbocation which leads to the rearrangement of the 10β-methyl group to C-5. In acetic acid:

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acetic anhydride containing sulfuric acid, this would appear to take precedence over the cleavage of the 3β-methanesulfonate which is necessary for the aromatisation reaction.

Experimental

Light petroleum refers to the fraction b.p.60–80 °C. Extracts were dried over sodium sulfate. Silica for chromatography was Merck 9385. IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined at 300 MHz in deuteriochloroform. Mass spectra were determined on a Fisons Autospec mass spectrometer.

Reaction of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one with acetic acid, acetic anhydride and sulfuric acid: The steroid **1** (R = OSO_2Me)[5] (200 mg) in glacial acetic acid (2 cm^3) and acetic anhydride (1 cm^3) was treated with conc.sulfuric acid (2 drops) and the mixture was stirred at 50 °C for 5 min. The mixture was poured into brine and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, and dried. The solvent was evaporated to give a residue (140 mg). This was purified by preparative layer chromatography on silica in 50% ethyl acetate:light petroleum to give 6β-acetoxy-3β-methanesulfonyloxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OSO_2Me) (70 mg) as an oil. IR: ν_{max}/cm^{-1} 1735; NMR: δ_H 1.00 (3H, s, 18-H), 1.29 (3H, s, 5β-Me), 2.05 (3H, s, OAc), 1.0 - 2.5 (18H, overlapping multiplets), 3.04 (3H, s, 3-Ms), 4.73 (1H, dd, *J* = 2.5 and 12 Hz, 6-H), 5.04 (1H, br.s. 3H). Found: $[M - CH_3SO_3H]^+$, 328.203, $C_{21}H_{28}O_3$ requires 328.204.

Preparation of 6β-acetoxy-3β-methanesulfonyloxy-5β-methyl-19-norandrost-9(10)-en-17-one: 3β,6β-Diacetoxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OAc)[6] (1 g) in methanol (30 cm^3) and water (5 cm^3) was treated with potassium carbonate (1 g) at room temperature for 5 h. The solution was concentrated, water was added and the product was recovered in ethyl acetate. The extract was dried and the solvent evaporated to give a residue (840 mg) which was chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave 6β-acetoxy-3β-hydroxy-5β-methyl-19-norandrost-9(10)-en-17-one (**2**, R = OH) (260 mg) which crystallised from acetone:light petroleum as needles, m.p. 225–226 °C. IR: ν_{max}/cm^{-1} 3500, 1745; NMR: δ_H 1.01 (3H, s, 18-H), 1.23 (3H, s, 5β-Me), 2.03 (3H, s, OAc), 1.0 - 2.5 (18H, overlapping multiplets), 4.09 (1H, br.s, 3-H), 4.76 (1H, dd, *J* 2.5 and 12 Hz, 6-H). Found: C, 72.9; H, 8.7; $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7 %. The methanesulfonate, prepared with methanesulfonyl chloride in pyridine at room temperature for 1 h, was an oil, identical (IR and NMR) to the sample described above.

Reaction of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one with acetic acid, acetic anhydride and perchloric acid: The steroid (**1**, R = OSO_2Me) (200 mg) in glacial acetic acid (2 cm^3) and acetic anhydride (1 cm^3) was treated with perchloric acid (four drops) and the mixture was stirred at 50 °C for 5 mins. The mixture was poured into brine and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, brine and dried. The solvent was evaporated to give a residue. This was purified by preparative layer chromatography on silica in 50% ethyl acetate:light petroleum to give 3α,6β-diacetoxy-5α-hydroxyandrostan-17-one (**5**) which crystallised from light petroleum as needles, m.p.178–180 °C. IR: ν_{max}/cm^{-1} 3500, 1735; NMR: δ_H 0.90 (3H, s, 18-H), 1.12 (3H, s, 19-H), 2.05 (6H, s, OAc), 1.0–2.2 (19H, overlapping multiplets), 3.38 (1H, s, disappears on shaking with ^2H_2O, OH), 4.78 (1H, br.s, 6-H), 5.28 (1H, br.s, 3-H). Found: C, 68.1; H, 8.4; $C_{23}H_{34}O_6$ requires C, 68.0; H, 8.4 %.

Methanolysis of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one: The steroid (**1**, R = OSO_2Me) (1.0 g) in methanol (30 cm^3) containing conc.sulfuric acid (2 drops) was heated at 50 °C for 5 h. The solution was concentrated *in vacuo*, poured into water and the product was recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, then brine, and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 5% ethyl acetate : light petroleum gave 5α-hydroxy-6β-methoxyandrost-2-en-17-one **6** (450 mg) as needles, m.p. 162-164 °C. IR: ν_{max}/cm^{-1} 3570, 1730; NMR: δ_H 0.90 (3H, s, 18-H), 1.02 (3H, s,19-H), 1.0 - 2.4 (17H, overlapping multiplets), 3.16 (1H, s, 6-H), 3.36 (3H, s, OMe), 5.68 (2H, m, 2- and 3-H). Found: C, 75.5; H, 9.5; $C_{20}H_{30}O_3$ requires C, 75.4; H, 9.5 %. Further elution with 10% ethyl acetate:light petroleum gave 3α,6β-dimethoxy-5α-hydroxyandrostan-17-one **7** (210 mg) as needles, m.p.165-167 °C. IR: ν_{max}/cm^{-1} 3435, 1730; NMR: δ_H 0.88 (3H, s, 18 H), 1.08 (3H, s, 19-H), 1.0 - 2.2 (18H, overlapping multiplets), 3.05 (2H, m, 3- and 6-H), 3.32 (6H, s, 2 × OMe), 4.66 (1H, s, disappears on shaking with ^2H_2O, OH, 5-OH). Found: C, 72.2; H, 9.8; $C_{21}H_{34}O_4$ requires C, 72.0; H, 9.8 %

Reaction of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one with collidine: A solution of 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one (**1**, R = OSO_2Me) (650 mg) in freshly distilled collidine (10 cm^3) was heated under reflux for 1 h. The solution was cooled, poured into dil. hydrochloric acid and the product was recovered in ethyl acetate. The extract was washed with dilute. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated to give a residue which was chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave 4-methylestra-1,3,5(10)-trien-17-one **3** (80 mg) which crystallised from acetone as needles, m.p. 180–182 °C (lit.,[5] 180–181°C), identified by its ^{1}H NMR spectrum. Elution with 20% ethyl acetate:light petroleum gave androst-4-ene-6,17-dione **4** (260 mg), m.p. 190–192 °C (lit.,[5] 189–191°C), identified by its ^{1}H NMR spectrum.

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