The Stereochemistry of Epoxidation of Δ^5-Steroids with Sodium Perborate and Potassium Permanganate†

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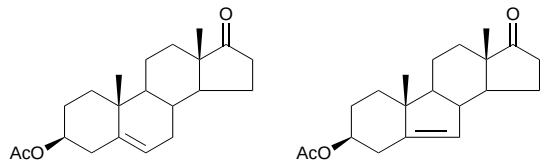
Sodium perborate, with potassium permanganate as a catalyst, has been shown to be a novel reagent for the epoxidation of steroidal 5-enes with the attack occurring predominantly on the β-face.

The epoxidation of steroidal 5-enes with peracids takes place predominantly from the α-face of the molecule to afford the 5α,6α-epoxides.[1] Recently there has been an effort to prepare[2,3] the biologically interesting but relatively inaccessible 5β,6β-epoxides. A number of groups[4–9] have shown that these epoxides can be obtained from the 5-enes using the biphasic systems involving potassium permanganate and transition metal nitrates or sulfates. Many years ago, it was shown[10] that potassium permanganate in acetic acid would epoxidize 3β-acetoxyandrost-5-en-17-one (**1**) although at the time the stereochemistry of the epoxides was unknown. We have now repeated this work and shown that the major product was the 5β,6β-epoxide (2:1; β-epoxide:α-epoxide). The epoxides may be clearly distinguished by the position of the 6-H resonance in the ^{1}H NMR spectrum (δ_H 2.87, α-epoxide; δ_H 3.07 β-epoxide).[11] In this paper we report the catalytic use of potassium permanganate in forming the β-epoxides.

Sodium perborate in glacial acetic acid provides an epoxidizing agent for alkenes.[12] With **1** it slowly gave a mixture of the 5α,6α- and 5β,6β-epoxides, containing predominantly the 5α,6α-epoxides (*ca*. 4:1; α:β-epoxides) paralleling the stereochemical results obtained with other peracids.[1] However, in the presence of catalytic amounts of potassium permanganate, the reaction was much faster and the stereoselectivity was reversed with the β-epoxide now predominating. A number of steroidal 5-enes were examined, including some with β-substituents at C-4. The ratios of the epoxides that were formed are given in Table 1. In the case of **1** some cleavage of the epoxide and allylic oxidation also took place. A similar oxidation has been reported with the permanganate–periodate reagent in pyridine.[13] Interestingly, the 5α,6α-epoxide, identical to the product of peracid oxidation, was obtained from the B-nor steroid, 3β-acetoxy-7-norandrost-5-en-17-one (**2**).



1 **2**

These results confirm the earlier observations[10] that the epoxidation on the β-face of a steroidal 5-ene occurs with potassium permanganate and show that the β-epoxidation does not have an absolute requirement for a metal sulfate. We have suggested previously that the stereochemical-determining feature of the potassium permanganate–metal sulfate epoxidation is the kinetically preferred pseudo-axial attack of the electron-deficient manganese, in a Markownikov sense, on the alkene to form a manganate, the collapse of which to form an epoxide in the second step was facilitated by the metal sulfate.[5,7] In the six-membered ring B of the steroids, the axial position at C-6 is β-oriented whilst in the five-membered 7-nor series the pseudo-axial position is α-oriented. This interpretation has been challenged[8] and the alternative view has been proposed that prior complexation by the metal sulfate on the less hindered face of the alkene occurs, directly the permanganate to the more hindered face of the molecule. Although we also considered this[7] it has difficulty in explaining why the 7-nor steroid affords the same epoxide with both peracid and permanganate. In the case of the perborate system the role of the perborate/acetic acid (peracetic acid) is to re-oxidize the manganese. This reaction is faster than the peracetic acid epoxidation.

In conclusion the potassium permanganate/sodium perborate/glacial acetic acid reagent is a novel, cheap epoxidizing system that in this instance has afforded epoxides, albeit in moderate yield, that differ in their stereochemistry from those formed by conventional peracids.

Table 1 Epoxidation of steoridal Δ^5-alkenes

Compound	Ratio α:β-epoxide
Cholesteryl acetate	1:5
3β-Acetoxyandrost-5-en-17-one (**1**)	1:4
3β-Acetoxyandrost-5-ene	β-Epoxide only
3β,17β-Diacetoxyandrost-5-ene	β-Epoxide only
3β-Acetoxy-4β-hydroxyandrost-5-en-17-one	1:4
4β-Acetoxy-3β-hydroxyandrost-5-en-17-one	1:6.5
3β-Acetoxy-7-norandrost-5-en-17-one (**2**)	α-Epoxide only

Experimental

Experimental details have been described previously.[5]

General Experimental Procedure. • Sodium perborate (1.1 g) was dissolved in glacial acetic acid (15 cm^3) with gentle warming $<$50 °C. Potassium permanganate (80 mg) in water (1 cm^3) was added to a solution of the steroid (900 mg) in glacial acetic acid (10 cm^3). The sodium perborate solution was then added in portions (2.5 cm^3) over a period of 1 h. The mixture was left to stand at room temperature overnight. It was poured into aqueous sodium hydrogen carbonate and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate and water, and dried over sodium sulfate. The solvent was evaporated to give a gum, which was assayed by ^{1}H NMR for its epoxide content [ratio of signals at δ_H 2.87 (α) to 3.07 ppm (β)] and separated by chromatography on silica by elution with increasing concentrations of ethyl acetate in light petroleum (bp 60–80°C). The epoxides were identified by their mps and ^{1}H NMR spectra.

3β-Acetoxycholest-5-ene (900 mg) gave the starting material (85 mg), 3β-acetoxy-5β,6β-epoxycholestane (295 mg)[14] and 3β-acetoxy-5α,6α-epoxycholestane (62 mg).[14]

3β-Acetoxyandrost-5-en-17-one (**1**) (900 mg) gave the starting material (79 mg), 3β-acetoxy-5β,6β-epoxyandrostan-17-one (292 mg),[15] 3β-acetoxy-5α,6α-epoxyandrostan-17-one (67 mg),[15] 3β-acetoxyandrost-5-ene-7,17-dione (30 mg)[16] and 3β,6β-diacetoxy-5α-hydroxyandrostan-17-one (73 mg).[10]

3β-Acetoxyandrost-5-ene (900 mg) gave the starting material (105 mg) and 3β-acetoxy-5β,6β-epoxyandrostane (345 mg).

3β,17β-Diacetoxyandrost-5-ene (500 mg) gave the starting material (53 mg) and 3β,17β-diacetoxy-5β,6β-epoxyandrostane (104 mg).[17]

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3β-Acetoxy-4β-hydroxyandrost-5-en-17-one (500 mg) gave the starting mterial (45 mg) and 3β-acetoxy-5β,6β-epoxy-4β-hydroxy-androstan-17-one (98 mg).

4β-Acetoxy-3β-hydroxyandrost-5-en-17-one (500 mg) gave the starting material (32 mg) and 4β-acetoxy-5β,6β-epoxy-3β-hydroxy-androstan-17-one (99 mg).

3β-Acetoxy-7-norandrost-5-en-17-one (**2**) (500 mg) gave the starting material 913 mg) and 3β-acetoxy-5α-6α-epoxy-7-norandro-stan-17-one (223 mg).[18]

3β-Acetoxy-5β,6β-epoxyandrostane: mp 98–100 °C; δ_H ($CDCl_3$) 0.68 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 2.03 (3 H, s, OAc), 3.08 (1 H, s, 6α-H), 4.76 (1 H, tt, *J* 11.3 and 5.5 Hz, 3α-H) (Found: C, 76.1; H, 9.9. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%).

3β-Acetoxy-5β,6β-epoxy-4β-hydroxyandrostan-17-one had mp 182–185 °C; δ_H ($CDCl_3$) 0.81 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.08 (3 H, s, OAc), 3.25 (1 H, d, *J* 2 Hz, 6α-H), 3.44 (1 H, dd, *J* 3.5 and 1 Hz, 4α-H), 4.79 (1 H, ddd, *J* 3.5, 4.5 and 11.5 Hz, 3α-H) (Found: C, 69.3; H, 8.4. $C_{21}H_{30}O_5$ requires C, 69.6; H, 8.3%).

4β-Acetoxy-5β,6β-epoxy-3β-hydroxyandrostan-17-one had mp 181–184 °C; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 2.07 (3 H, s, OAc), 3.20 (1 H, d, *J* 4 Hz, 6α-H), 3.89 (1 H, ddd, *J* 3.5, 5 and 11.5 Hz, 3α-H), 4.32 (1 H, dd, *J* 3.5 and 1.1 Hz, 4α-H) (Found: C, 65.7; H, 8.0. $C_{21}H_{30}O_5 \cdot H_2O$ requires C, 66.3; H, 8.5%).

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