SHORT PAPER

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The role of metal salts in a solid phase β-selective epoxidation of Δ^5-steroids with potassium permanganate†

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Epoxidation of Δ^5-steroids with a potassium permanganate and a range of metal salts in the solid phase gives the 5β, 6β-epoxides. The results have been rationalised in terms of the oxophilic metal ions favouring epoxide formation in the collapse of a manganate intermediate.

Keywords: solid phase β-selective epoxidation, Δ^5-steroids, potassium pemanganate

The synthesis of steroidal 5β, 6β-epoxides from Δ^5-steroids is of interest not only because a 5β, 6β-epoxide is found in a number of biologically-active steroids[1] but also because the stereochemistry of the epoxide can shed some light on the mechanism of various epoxidation reactions. The β-oriented C-10 methyl group directs the epoxidation of Δ^5-steroids by per-acids[2] and dioxirans[3] to the α-face of the molecule leading to the predominant formation of the 5α, 6α-epoxide. A different stereochemical feature must be considered to rationalise those epoxidations of Δ^5-steroids which give the 5β, 6β-epoxide. If the initial step in the reaction of the alkene with the epoxidising reagent takes place in a Markownikoff sense, *i.e.* at C-6, and from an axial direction$_7$ then the initial intermediate will, in most situations, contain a C-6β oxygen atom. When the reaction is under kinetic control and this oxygen atom forms the epoxide$_1$ this will lead to a 5β, 6β-epoxide.

Steroidal 5β, 6β-epoxides can be obtained from Δ^5-steroids by oxidation using a biphasic system involving potassium permanganate, various metal sulfates and nitrates and a trace of water.[4–10] In contrast to our previous rationalisation,[5] Parish has suggested[9] that the facial selectivity resulted from the metal ion co-ordinating to the less-hindered α-face of the double bond forming a π-complex which directed subsequent attack by the permanganate to the β-face. It was reported[9] that the reaction did not occur with main group metal ions which do not form a π-complex with the double bond.

We have now examined the reaction again with 3β-acetoxyandrost-5-en-17-one **1** as the substrate and with a range of metal salts including a number of main group metals which had not worked in Parish's hands but which we have found work (see Table 1). The rate of the reaction was also increased by the presence of sodium dihydrogen phosphate as a buffer. The reaction was also successful with a number of other steroids (see Table 2), including some bearing substituents which might react in the presence of the metal salts.

These results may be rationalised in the following way. Mechanistic studies on the oxidation of alkenes to vicinal diols with potassium permanganate have implicated[11,12] the formation of a cyclic manganate ester via the intermediate A (see Scheme 1). In the biphasic system the role of the metal

Table 1 Effect of metal salts on the epoxidation of 3β-acetoxyandrost-5-en-l7-one **1**

Metal salt	Weight of $KMnO_4$/g	Reaction time/h	Yield/%	Ratio of isomers β:α
$FeSO_4$ $7H_2O$	1	1.5	92	94:6
$FeSO_4$ $7H_2O$[a]	1	0.75	86	93:7
Ag_2SO_4	1	48	79	90:10
Ag_2SO_4[b]	1	24	73	88:12
$(NH_4)_2Fe(S0_4)_2$ $6H_2O$	1.5	12	90	97:3
$KAl(SO_4)_2$ $12H_2O$	2	18	89	91:9
$BeSO_4$ $4H_2O$	2	2	91	95:5
$Fe(NO_3)_3$ $9H_2O$	0.5	4	92	94:6
$La(NO_3)_3$ $6H_2O$	1	4	86	92:8
$Ca(NO_3)_2$ $4H_2O$	2	48	80	82:18
$Ca(NO_3)_2$ $4H_2O$*	2	4	90	97:3
$Mg(ClO_4)_2$ H_2O	2	1	88	90:10
$Ba(ClO_4)_2$ $3H_2O$	2	24	87	90:10
$Mn(ClO_4)_2$ $6H_2O$	2	0.25	81	84:16
ZrOCl $8H_2O$	2	1	90	92:8
$VOSO_4$ H_2O	2	0.5	87	96:4
$CuWO_4$ xH_2O	2	36	52	88:12
$CuWO_4$ xH_2O	2	36	88	94:6

[a]In the presence of $NaH_2PO_4.2H_2O$ (1 g); [b]with 200 μl H_2O. No reaction was observed with $Cu(OAc)_2.H_2O$, $Zn(OAc)_2.H_2O$, $MgCO_3Mg(OH)_2.3H_2O$ or $K_4Fe(CN)_6.3H_2O$.

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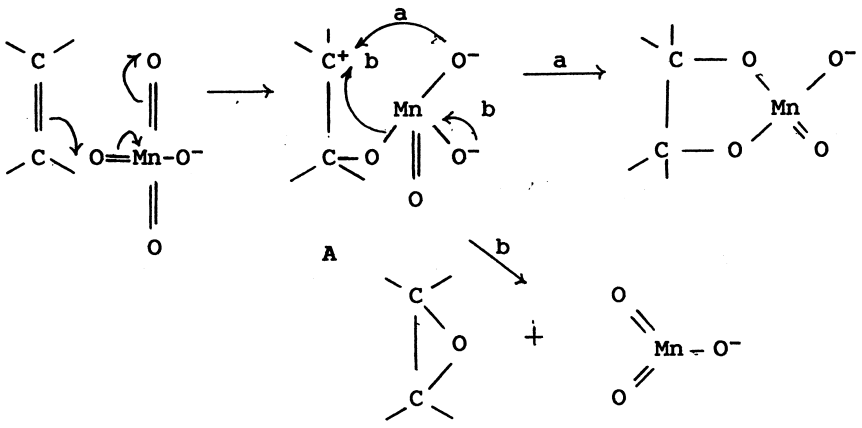
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 2 Oxidations with $KMnO_4$:$Fe_2(SO_4)_3$ $5H_2O$ (2:1 w/w)

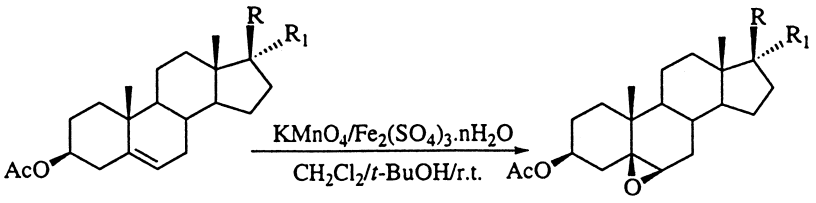
Substrate	Time/h	Yield/%	Ratio of isomers β:α	Product
1	0.3	93	98:2	2
3	4	92	88:12	4
3[a]	16	89	90:10	4
5	4	91	91:9	6
5[a]	4	84	84:16	6
7	3.5	85	90:10	8
9	4	86	92:8	10
11	3	90	90:10	12

[a]Using $Fe(NO_3).9H_2O$ in place of $Fe_2(SO_4)_3.9H_2O$.

ion is to co-ordinate with the oxygen anions of the intermediate **A** and favour the decomposition through pathway (b). The effectiveness of the metal ions in terms of the rates of the reactions (see Table 1) is a reflection of their oxophilicity. This rationalisation would account for the failure of the reaction with metal salts containing co-ordinating anions because the metal ions are already complexed. Since potassium permanganate oxidations become alkaline, the role of the sodium dihydrogen phosphate buffer is to prevent the formation of insoluble metal hydroxides. The facial selectivity of the reac-



Scheme 1

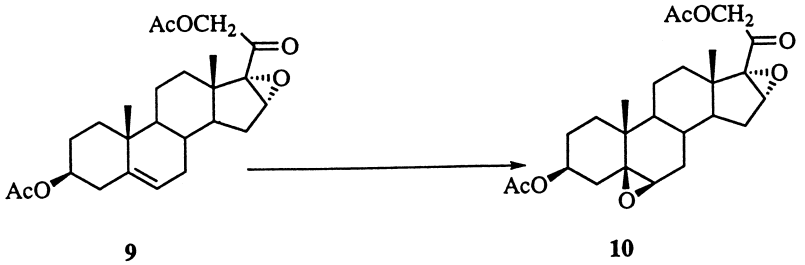


1.....R;R_1=O.....**2**

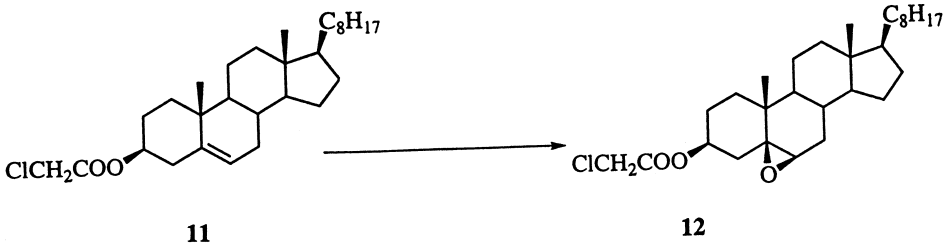
3.....R=C_8H_{17};R_1=H.....**4**

5.....R=$COCH_3$;R_1=H.....**6**

7.....R=OAc;R_1=H.....**8**



9 **10**



11 **12**

tion is determined by kinetic control. The irreversible decomposition of intermediate **A** via pathway (b) to form the epoxide leads to kinetic control and hence the facial selectivity which arises from axial attack at C-6.

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 in deuteriochloroform. IR spectra were determined as nujol mulls.

General procedure for the oxidation: A mixture of potassium permanganate (2 g) and the metal salt (1 g) (or as given in Tables 1 and 2) was ground to a fine powder, water (100 μ1) was added and the mixture transferred to the reaction vessel. The substrate, (*e.g.* 3β-acetoxyandrost-5-en-l7-one, 0.33 g, 1 mmole) in dichloromethane (5 cm^3) and *t*-butanol (0.5 cm^3) was added to a stirred suspension. The reaction was followed by TLC. When the reaction was complete, ether (10 cm^3) was added and the inorganic residue was removed by filtration through a Celite pad. The filtrate was washed with water, dried over sodium sulfate and the solvent evaporated. The residue was crystallised from methanol. The ratio of α:β-epoxides was determined from the integral of the 6-H signals. Known steroids were identified by their m.p. and ^{1}H NMR spectra.

3β-Acetoxy-5β, 6β-epoxyandrostan-17-one 2 had m.p. l88–190°C, (lit.,[13] 188–189°C).

3β-Acetoxy-5β, 6β-epoxyandrostan **4** had m.p. 110–112°C (lit.,[14] 110–1l2°C).

3β-Acetoxy-5β, 6β-epoxyandrostan-20-one **6** had m.p. 129–131°C (lit.,[15] l3l–l32°C).

3β-Acetoxy-5β, 6β-epoxyandrostan **8** had m.p. l30–l31°C (from acetone-hexane) (lit.,[15] 139–l4l°C from dichloromethane: methanol).

3β, 2l-Diacetoxy-5β, 6β; 16α, 17α-diepoxypregnan-20-one **10** had m.p. 151–152°C, (Found: M$^+$ 446.230 $C_{25}H_{34}O_7$ requires M$^+$ 446.230) ν_{max}/cm^{-1} 1754, 1731; δ_H 1.01(3H, 5, H-18), 1.06 (3H, 5, H-19), 2.02 and 2.14 (each 3H, s, OAc), 3.09(1H, m, H-6), 3.78 (IH, m, H-16)$_1$, 4.58 and 4.68 (each lH, d, *J* 17.3 Hz, H-21), 4.76(1H, m, H-3).

3β-Chloroacetoxy-5β, 6β-epoxycholestane 12 had m.p. 82–84°C (Found: M$^+$ 478.323 $C_{29}H_{47}ClO_3$ requires 478.321),ν_{max}/cm^{-1} 1750; δ_H 0.63(3H, 5, H-18), 0.84(3H, d, *J* 6 Hz, H-21) 0.87(6H, d, *J* 7 Hz, H-26, 27), 1.08 (3H, s, H-19), 3.08(1H, m, H-6), 4.03(2H, 5, CH_2Cl), 4.86(1H, m, H-3).

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