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DIOXIRANE MEDIATED STEROIDAL ALKENE EPOXIDATIONS AND OXYGEN INSERTION INTO CARBON-HYDROGEN BONDS

Brian A. Marples* and James P. Muxworthy
Department of Chemistry, The University of Technology
Loughborough, Leics., LE11 3TU

Keith H. Baggaley
SmithKline Beecham Pharmaceuticals
Brockham Park, Betchworth, Surrey, RH3 7AJ

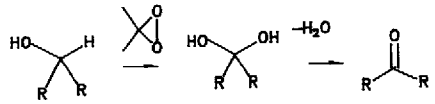
Abstract Dioxiranes generated *in situ* from a range of ketones afforded the 5,6-epoxides in high yield from cholesterol or its acetate. The α:β ratio was close to 1 in contrast to that observed for peroxyacids (*ca.* 4). 4,4-Dimethylcholesterol and its acetate were not epoxidised but were oxidised respectively to the 3,7-dioxo- and the 7-oxo-derivative respectively with dimethyldioxirane. Oxidations of steroidal alcohols were shown to proceed *via* an oxygen insertion mechanism by use of ^{18}O-labelled substrates and 5α-cholestan-3α-ol was oxidised more quickly (>1.5 x) than its 3β-epimer.

Dioxiranes have recently been shown to be important and versatile oxidants which may be isolated or generated *in situ*.[1,2] Among the many uses described are epoxidation of alkenes, oxygen insertion into C-H bonds and oxidation of secondary alcohols to ketones. The electrophilic nature of the epoxidations has been established and it has been suggested that a spiro transition state is involved.[3] However, there are few examples of epoxidations of relatively complex alkenes and little is reported about the detailed mechanism of the C-H oxygen insertion reactions and the oxidation of secondary alcohols to ketones. We report here some further insight into the mechanistic aspects through a study of steroidal epoxidations and C-H oxygen insertions.

Table 1 shows the result of biphasic oxidations of Δ^5-steroids (1) with a range of dioxiranes generated from simple ketones *in situ*. In all cases except the 4,4-dimethyl derivatives, the 5,6-epoxides were obtained in high yield and the α:β ratio, which was obtained by integration of the signals for the C6-H in the ^1H n.m.r. spectra,[4] was *ca* 1. This contrasts markedly with that observed for epoxidation of Δ^5-steroids with peroxyacids where the α:β ratio is *ca* 4. Furthermore, peroxyacid epoxidation of 4,4-dimethyl Δ^5-steroids is straightforward[5] in contrast to the use of dimethyldioxirane where the double bond was not attacked. Instead, with somewhat longer reaction times the 3,7-diketone (2)[6] (36%) and the 7-ketone (3)[6] (44%) were obtained from 4,4-dimethylcholesterol and its acetate respectively (Table 1, entries 7 and 8). The results are best explained by the requirement for spiro transition states (4) for epoxidations.

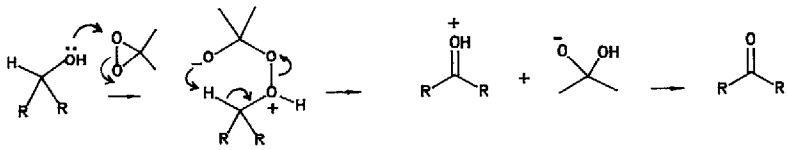
In the absence of substitutent at C4 the steric interaction between the 4β-H or the 3α-H and the α-substituent group of the dioxirane appear to be more or less equivalent. The bulkier α-substituent of the dioxirane would take up the less congested position near to C6, hence the lack of sensitivity of the α:β ratio to the dioxirane used. The dioxirane derived from 2-hydroxy-2-methylcyclohexanone[7] (Table 1, entry 4) gave relatively low yields owing to its cleavage to 6-ketoheptanoic acid which was purified as its methyl ester. It is presumed that the cleavage is similar to that proposed for α-hydroxy diketones with alkaline hydrogen peroxide[8] and is *via* the intermediate (5) (Cf other 1,4-eliminations[9]). If transition states (4) are involved then in the 4,4-dimethyl derivatives both the α- and β-faces of the double bond would be significantly hindered. The likely distortation of the A-ring arising from steric interaction between the 10β-methyl and the 4β-methyl groups[10] would enhance the α-face hindrance to attack. Interestingly, the possible change from a spiro to a planar transition state[3] is not apparently preferred over the alternative allylic C-H oxygen insertion since such a transition state leading to α-face attack would not be expected to be seriously hindered.

The most obvious mechanism for the oxidation of secondary alcohols would involve oxygen insertion followed by elimination of water (Equn 1). However, there are no reports of the detailed



Equn 1.

mechanism and an alternative which does not involve inclusion in the product of any of the dioxirane oxygen is shown in Equn 2. We report here that ^{18}O labelled (48%)† 5α-cholestan-3β-ol, prepared by



Equn 2

$H_3{}^{18}O^+$-catalysed hydrolysis of the ethylene acetal (6) and $NaBH_4$ reduction of the resultant ketone, is converted with dimethyldioxirane (0.05M) in acetone to 5α-cholestanone with a reduced ^{18}O content (29%)†, consistent with the oxygen insertion mechanism (Equn 1). Furthermore, there is a significant difference in the reaction rate of axial versus equatorial alcohols since partial oxidation (ca 60%) of an equimolar mixture of 5α-cholestan-3α-ol and its 3β-epimer resulted in an α:β ratio of 0.54 to 1, as

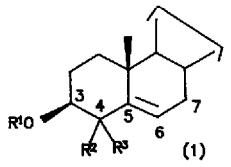
†determined by EI mass spectrometry

Table 1: Reactions of Dioxiranes with Δ^5-Steroids

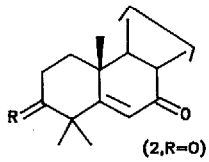
Steroid(1)	Ketone[a]	α:β epoxide ratio	Yield %
1. R^1=R^2=R^3=H	acetone	50:50	90
2. R^1=R^2=R^3=H	cyclohexanone	55:45	59
3. R^1=R^2=R^3=H	2-methylcyclohexanone	35:65	70
4. R^1=R^2=R^3=H	2-hydroxy-2-methylcyclohexanone	40:60	37[b]
5. R^1=R^2=R^3=H	ethyl pyruvate	64:36	83
6. R^1Ac,R^2=R^3=H	acetone	40:60	86
7. R^1=H,R^2=R^3=Me	acetone	---	---
8. R^1=Ac,R^2=R^3=Me	acetone	---	---

a Dioxirane generated *in situ* from reaction of ketone with $KHSO_5$ at 0-5°C in aqueous phosphate buffer/methylene chloride containing Bu_4NHSO_4 - pH maintained at 7.5 by pH stat controlled addition of 5M KOH.

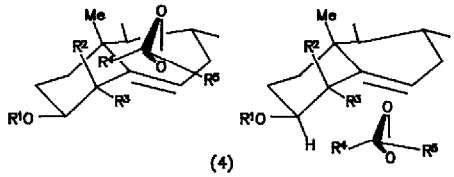
b. low owing to cleavage of ketone (see text)



(1)



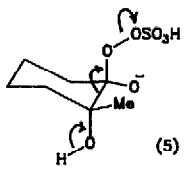
(2,R=O)
(3,R=β-OAc,H)



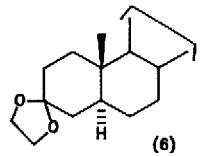
(4)

spiro transition states

determined by g.l.c. of the TMS ethers. Conceivably, the greater reactivity (>1.5 x) of the axial alcohol may be rationalised assuming butterfly transition states (7) for the oxygen insertion[1] and some intramolecular hydrogen bonding between the second oxygen of the dioxirane and the OH group. A simple explanation using this model would be that the transition states are close to the *gem*-diol on the reaction coordinate so that the higher ground state energy of the 3α-epimer is largely responsible for its enhanced reactivity. However, more work will be required to establish the detailed mechanism.



(5)



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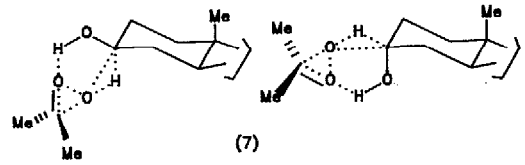

(7)

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