The Stereochemistry of Oxidation of Some B-Norsteroids

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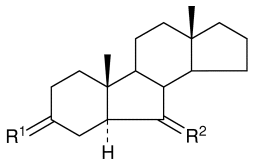
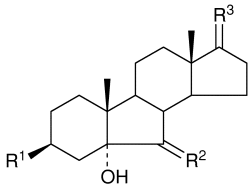
The oxidation of ring B of some B-norsteroids is shown to have a different stereochemistry when compared to the same reactions in the normal six-membered series and it is suggested that caution should be exercised in drawing general stereochemical conclusions solely on evidence from the six-membered series.

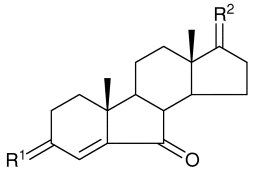
The stereochemistry of many reactions of the five-membered ring B norsteroids differs from that of the normal six-membered ring B series[1,2] and it is important that these differences are recognized because the six-membered steroids such as cholesterol are often used as specific examples on which general stereochemical conclusions are based. Not only is the stereochemistry of addition to a 5-ene different but in some instances the products in the B-nor series also undergo rearrangements that are not found under comparable conditions in the normal series.[3–7] A difference that has been noted[6] is the epoxidation of 5-enes with potassium permanganate:copper sulfate which affords the 5α,6α-epoxide in the B-nor series and the 5β,6β-epoxide in the normal series. Further differences in oxidation reactions are discussed here.



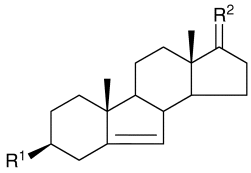
1 R^1 = α-H, β-OAc, R^2 = α-OH, β-H
2 R^1 = α-H, β-OAc, R^2 = O
3 R^1 = α-H, β-OH, R^2 = α-OH, β-H
4 R^1 = R^2 = O



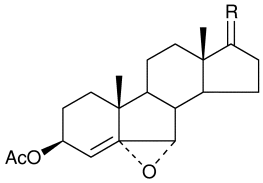
5 R^1 = OAc, R^2 = O, R^3 = H_2
6 R^1 = H, R^2 = O, R^3 = α-H, β-OAc
7 R^1 = OAc, R^2 = α-OH, β-H, R^3 = α-H, β-OAc
8 R^1 = OAc, R^2 = O, R^3 = α-H, β-OAc



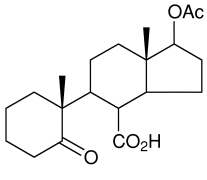
9 R^1 = O, R^2 = H_2
10 R^1 = R^2 = O
11 R^1 = H_2, R^2 = α-H, β-OAc
12 R^1 = O, R^2 = α-H, β-OAc



13 R^1 = OH, R^2 = O
14 R^1 = OAc, R^2 = O
15 R^1 = H, R^2 = α-H, β-OAc



16 R = O
17 R = α-H, β=OAc



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Oxidation of 3β-acetoxy-6α-hydroxy-B-norandrostane **1**[8] with chromium trioxide at 0 °C gave the anticipated 6-ketone **2** together with the 5α-hydroxy-6-ketone **5** whilst oxidation of the 3β,6α-diol **3** gave the dione **4** and the ene-dione **9**. Oxidation of 3-hydroxy-B-norandrost-5-en-17-one **13** with chromium trioxide at 0 °C gave a good yield of B-norandrost-4-ene-3,6,17-trione **10**. This facile further oxidation does not take place so readily in the normal six-membered series. Oxidation of 3-acetoxy-B-norandrost-5-en-17-one **14** with chromyl acetate[9] gave the 5α,6α-epoxide **16** in 91% yield in contrast to the normal series in which the 5β,6β-epoxide was obtained in 71% yield.

In the normal series under more vigorous conditions, allylic oxidation of a 5-ene with *tert*-butyl chromate[10] takes place at C-7 to give the androst-5-en-7-one. In the B-nor series oxidation of **15** was complex and a low yield of the products, **6**, **11**, **12** and **18** were obtained. These were probably based on the oxidative cleavage of a 5,6-epoxide. Over-oxidation of B-nor steroids was also observed during glycol formation with osmium tetraoxide as a catalyst and *tert*-butyl hydroperoxide as the co-oxidant[11–13] leading to the glycol **7**, the 5α-hydroxy-6-ketone **8** and the 5α,6α-epoxide **17** whereas in the normal series the 5β,6β-epoxide was found amongst the minor products rather than the 5α,6α-epoxide.[13]

There are several features of the B-norsteroids which contribute to these differences in their reactivity towards oxidation when compared to the normal series. Firstly in the A/B *trans* series, the 6-ketones may enolize to give the 5(6)-enol relieving the unfavourable ring junction and facilitating both the oxidation at C-5 and the formation of the 4-ene-3,6-dione. Secondly a C-6α substituent is a pseudo-axial substituent on a B-norsteroid unlike the normal six-membered series. Those reactions which involve axial attack on the π-system of an alkene, will be favoured by attack from the less-hindered α-face. Finally the absence of C-7 and the fact that the axial hydrogen at C-4 lies on the more hindered β-face of the molecule reduces the tendency of the B-nor-5-enes to undergo allylic oxidative reactions involving bulky reagents that may initially coordinate to the double bond.

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Techniques used: IR, ^{1}H and ^{13}C NMR spectroscopy

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Table 1: ^{13}C NMR data for B-norsteroids

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