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Neighbouring Group Participation in the Methanolysis of a Vicinal Diepoxide

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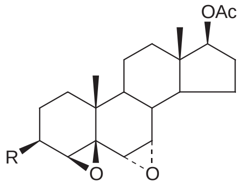
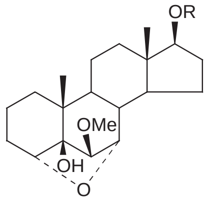
The tetracyanoethylene catalysed methanolysis of 17β-acetoxy-4β,5β:6α,7α-diepoxyandrostane afforded 17β-acetoxy-4α,7α-oxido-5β-hydroxy-6β-methoxyandrostane in which the methanolysis product of the 6α,7α-epoxide has participated in the cleavage of the 4β,5β-epoxide; the reaction is modified however by an adjacent 3β-hydroxy group.

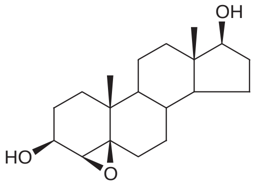
Tetracyanoethylene (TCNE) is a mild π-acid catalyst which will facilitate the methanolysis of epoxides.[1] The stereochemistry of the reaction involves the *trans*-diaxial cleavage of the epoxide.[2] However the presence of an adjacent hydroxy group can modify the stereochemistry of the methanolysis leading, in certain situations, to the formation of diequatorial products.[3] The neighbouring hydroxyl group, possibly by hydrogen bonding to the reagent, can direct the regiochemistry of opening of the epoxide favouring the formation of a vicinal glycol. Here, we report the stereochemistry of the TCNE catalysed methanolysis of a vicinal diepoxide and the influence of neighbouring group participation on the structure of the products.



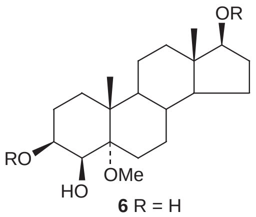
1 R = H
2 R = OH



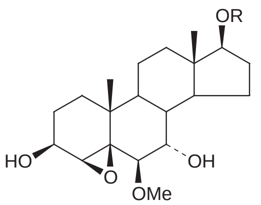
3 R = Ac
4 R = H



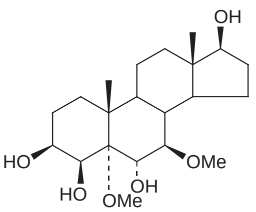
5



6 R = H
7 R = Ac



8 R = H
9 R = Ac



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Treatment of 17β-acetoxy-4β,5β:6α,7α-diepoxyandrostane **1**[4] with TCNE in methanol gave the 17β-acetoxy-6β-methyl ether **3** and the corresponding 17β-alcohol **4**. TCNE is known[5] to catalyse the methanolysis of esters. The structure of the ether **4** was established by a combination of ^{1}H NMR and X-ray crystallographic studies (Fig. 1). The effect of a neighbouring 3β-hydroxy group was then examined. When 3β,17β-dihydroxy-4β,5β-epoxyandrostane **5**[6] was treated with TCNE in methanol, the reaction proceeded relatively slowly to afford 5α-methoxy-3β,4β,17β-trihydroxyandrostane **6** which was purified as its diacetate **7**. Methanolysis of 17β-acetoxy-4β,5β:6α,7α-diepoxy-3β-hydroxyandrostane **2**[4] gave 4β,5β-epoxy-6β-methoxy-3β,7α,17β-trihydroxyandrostane **8** and its corresponding 17β-acetate **9** as the major products. A small amount of a tetraol, 5α,7β-dimethoxy-3β,4β,7α,17β-tetrahydroxyandrostane **10** was also formed. The structures of these products were established from their ^{1}H NMR spectra.

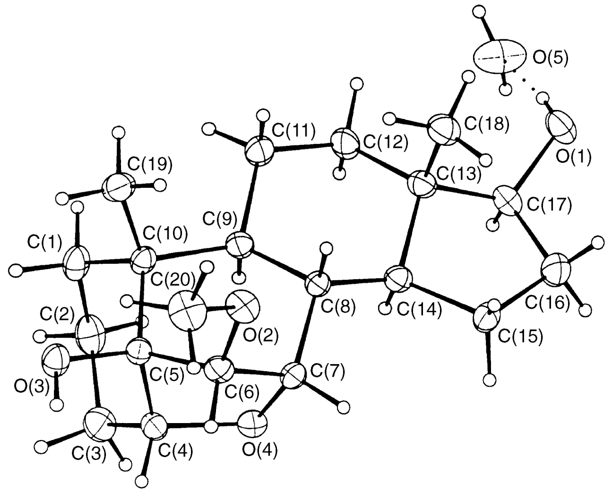

Fig. 1 X-Ray crystal structure of **4**

These results can be rationalized in terms of the initial diaxial cleavage of the disubstituted 6α,7α-epoxide. The axial 7α-hydroxy group then participates in the cleavage of the 4β,5β-epoxide with the formation of the ethers **3** and **4**. However the presence of the 3β-hydroxy group slows the cleavage of the 4β,5β-epoxide and the major products **8** and **9** were those of simple methanolysis of the 6α,7α-epoxide. The minor product **10** may arise from a small amount of methanolysis of the 4β,5β-epoxide taking place first affording the stereochemistry found in **6**. This then directed the opening of the 6α,7α-epoxide in a diequatorial manner to give **10**.

Crystallographic Data and Structure Determination for 5β,17β-Dihydroxy-4α,7α-oxido-6β-methoxyandrostane **4**.—$C_{20}H_{32}O_4 \cdot H_2O$, $M_r = 354.47$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 7.328(2)$, $b = 13.161(4)$, $c = 19.933(3)$ Å, $V = 1922.4(8)$ Å^3, $Z = 4$, $D_c = 1.225$ g cm^{-3}, $F(000) = 776$, $\lambda = 0.71073$ Å, $\mu = 0.086$ mm^{-1}. Data were collected using a crystal of size *ca.* 0.3 × 0.3 × 0.2 mm on an Enraf-Nonius CAD4 diffractometer. A total of 3805 reflections were collected for $2 < \theta < 25°$ and $0 < h < 8$, $0 < k < 15$, $-23 < l < 23$. There were 3386 independent reflections and 2879 reflections with $I > 2\sigma(I)$ that were used in the refinement. There was no crystal decay and no absorption correction was applied. The structure was solved by direct methods using SHELXL-97[7] and interactive graphics and final drawings using CAMERON.[8] The non-hydrogen atoms were refined anisotropically by full matrix least squares on F^2. Hydrogen atoms bonded to oxygen were freely refined

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isotropically. Other hydrogen atoms were included in riding mode with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C)$ for methyl groups. The final R indices were $R_1 = 0.043$, $wR_2 = 0.096$ and R indices (all data) $R_1 = 0.054$, $wR_2 = 0.103$. The goodness of fit on F^2 was 1.039 and the maximum shift to esd was 0.002. Tables of atomic co-ordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen atom coordinates, hydrogen bond distances and angles and selected torsion angles are given in the appendix.

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Techniques used: ^{1}H NMR, X-ray crystallography, IR, chromatography

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Appendix: Crystal data for **4**

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