Ethanolysis of steroidal epoxides catalysed by tetracyanoethylene

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Ethanolysis of the epimeric androstane 4,5- and 5,6- epoxides catalysed by tetracyanoethylene is reported. In contrast to other reagents, these reactions involve the mild room temperature *trans* diaxial opening of the epoxides. The stereochemistry of three of the products was established by X-ray crystallography.

Keywords: steroids, androstanes, ethanolysis, epoxides, X-ray crystallography

Tetracyanoethylene (TCNE) has recently been reported to be a mild catalyst for the alcoholysis of epoxides.[1] It has been widely used for the methanolysis of steroidal epoxides. The stereochemistry of the reaction of simple polycyclic epoxides including those of the steroids follows a normal epoxide hydrolysis pathway in which there is a *trans*-anti-periplanar relationship between, in this case, the resultant methoxy and hydroxy groups.[2] The effect of 3β-acetoxyl and 3β-hydroxyl group on the cleavage of the epimeric 4,5-epoxides in which the 3-substituent modifies the course of the reaction has been studied.[3,4]

In our previous studies we had unsuccessfully attempted the ethanolysis of steroidal epoxides. We now report the TCNE catalysed ethanolysis of the pairs of epimeric steroidal epoxides **1**, **4**, **5**, and **6** using thoroughly dried ethanol. We have examined the region- and stereochemistry of these reactions by X-ray crystallography.

Treatment of 3β,17β-diacetoxy-5α,6α-epoxyandrostane **1** with TCNE in ethanol gave 3β,5α,17β-trihydroxy-6β-ethoxyandrostane **2**. The [1]H NMR spectrum of **2** established the presence of a CH-OEt group [δ_H 1.15 (3 H, t, *J* = 7.4 Hz, 6-$OCH_2\underline{CH_3}$), δ_H 3.06 (1 H, br s, 6α-H)δ_H 3.29–3.57 (each 1 H, q, *J* = 7.4 Hz , 6-$O\underline{CH_2}CH_3$),]. The narrow C*H*–O signal indicated that H-6 was an equatorial resonance whilst the downfield shift of the 3α-H resonance was consistent with a diaxial interaction with the 5α-hydroxy group. The structure and stereochemistry of this product was established by X-ray crystallography (see Fig. 1).

Ethanolysis of 3β-acetoxy-5β,6β-epoxyandrostan-17-one **3** gave 3β-acetoxy-5α-ethoxy-6β-hydroxyandrostan-17-one **4** in which there was the anticipated downfield shift at δ_H 3.92 (1 H, t, *J* = 2.9 Hz) of the C*H*–O resonance. The tertiary ethyl ether proton resonances were obtained at δ_H 1.12 (3H, t, *J* = 7.8 Hz) and at 3.26 and 3.52 (each 1H, q, *J* = 7.8 Hz). The separate resonances reveal the hindered rotation of the ethoxyl group. The structure and stereochemistry of this product was established by X-ray crystallography (see Fig. 2).

Ethanolysis of 17β-acetoxy-4α,5α-epoxy-3β-hydroxyandrostane **5** gave 17β-acetoxy-3β,5α-hydroxy-4β-ethoxyandrostane **6**. The structure and stereochemistry of this product was established by X-ray crystallography (see Fig. 3). The 4-H NMR signal (δ_H 3.18) was a doublet (*J* = 4 Hz) whilst the 3-H resonance (δ_H 4.03) was a doublet (*J* = 11 Hz) of triplets (*J* = 4 Hz).

3β,17β-Diacetoxy-4β,5β-epoxyandrostane **7** gave the diacetoxy compound which was assigned the structure of 3β, 17β-diacetoxy-5α-ethoxy-4β-hydroxyandrostane **8** since the C-3 proton resonance (δ_H 5.08) was a doublet (*J* = 10 Hz) of triplets (*J* = 3.2 Hz) whilst the C-4 proton resonance at δ_H 3.96 was a doublet (*J* = 3.2 Hz) which was a narrow signal and hence this proton was equatorial. 2D-NOESY spectra showed that there was no correlation between signals at δ_H 0,75 (18-H), δ_H 1,14 (19-H), and δ_H 3,96 (4-H) showing that the proton at δ_H 3,96 was α–oriented. In order for this proton to be equatorial, the tertiary ethyl ether at C-5 must be α–oriented.

In conclusion we report ethanolysis of steroidal epoxides catalysed by teteracyanoethylene. These reactions involve the mild room temperature trans-diaxial opening of the epoxides. The geometrical relationship outweighs the electronic features which led to the more highly substituted alkoxy products in the simpler molecules, like all other bimolecular cleavage reactions of steroidal epoxides.[5,6]

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. [1]H and [13]C NMR spectra were determined at 500 and 125 MHz respectively using a Varian-INOVA spectrometer for solutions in deuteriochloroform. IR spectra were determined as nujol mulls on a Perkin-Elmer 1710 FTIR. Microanalyses were obtained using a Thermo Finnigan Elementary Analyser Flash EA 1112 at TUBITAK-MAM (The Scientific and Technical Research Council of Turkey-Marmara Research Centre). Extracts were dried over anhydrous sodium sulfate. Absolute ethanol was purified and dried according to the procedure prior to use.[7]

The 3β-substituted epimeric 4,5- and 5,6-epoxides that were used were obtained by orevious synthetic studies, in the laboratory.[3]

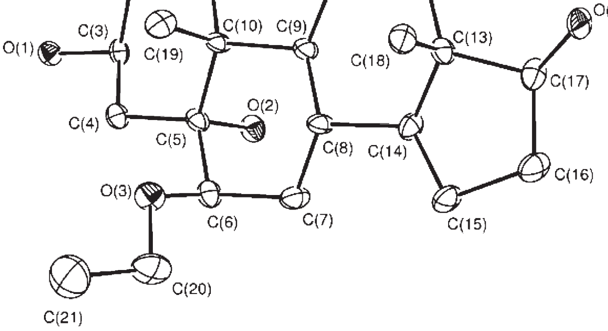

Fig. 1 X-ray structure of **2**.

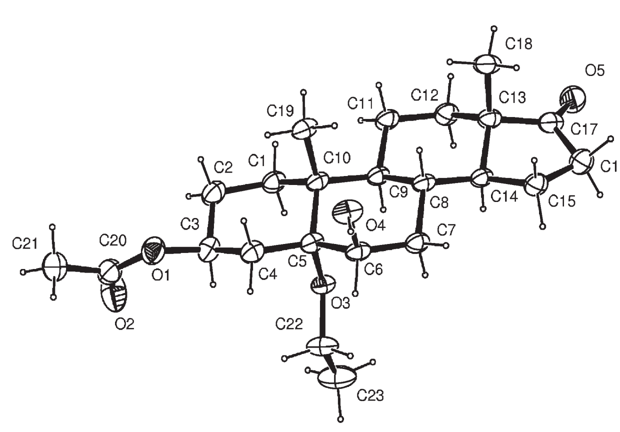

Fig. 2 X-ray structure of **4**.

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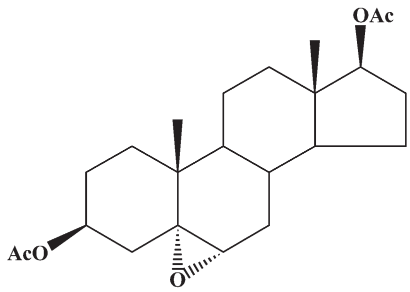
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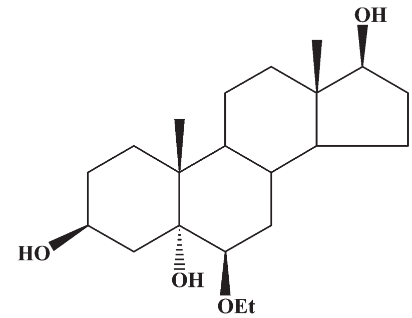
AcO
O

1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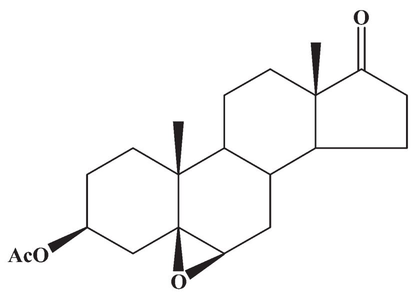
HO
OH
OEt

2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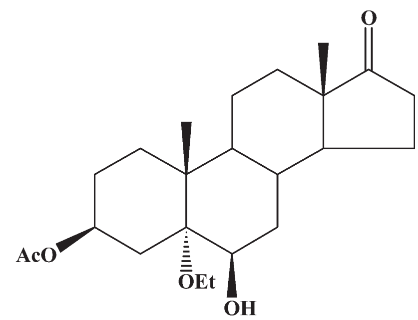
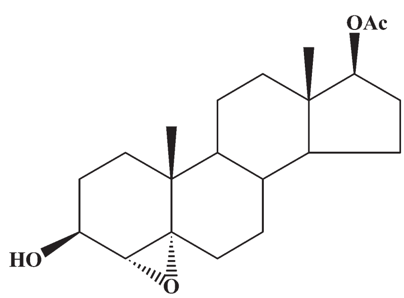
AcO
O

3


O
AcO
OEt
OH

4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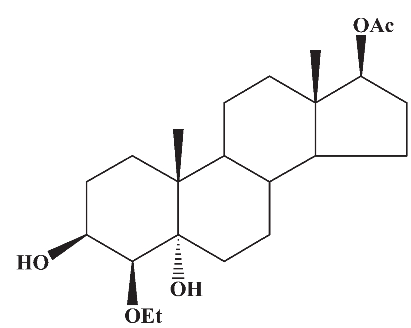
HO
O

5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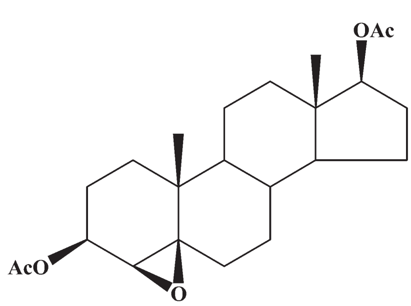
HO
OH
OEt

6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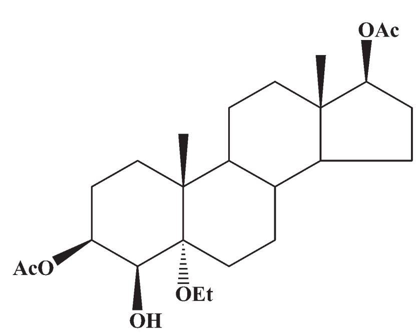
AcO
O

7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8

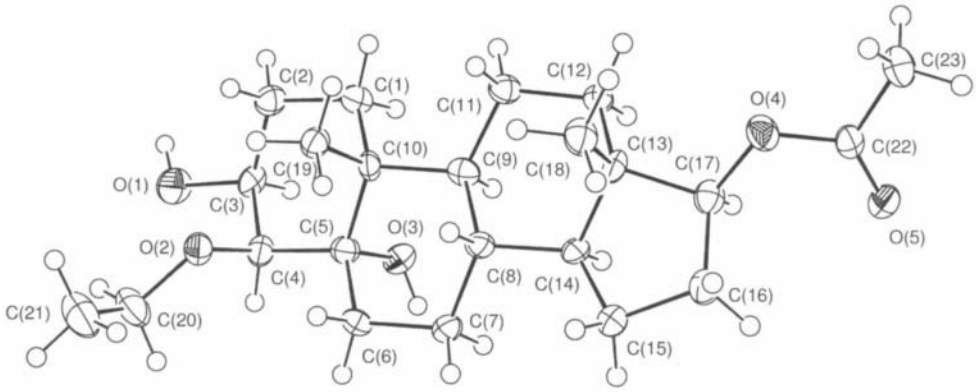

Fig. 3 X-ray structure of **6**.

Reaction of epoxides with tetracyanoethylene
The epoxide (250 mg) in dry ethanol (15 cm^3) was treated with TCNE (25 mg) at room temperature. The reaction was monitored by TLC after 5 h, the solvent was evaporated *in vacuo* and the residue chromatographed on silica. The products were eluted with increasing concentrations (10–20%) of ethyl acetate in n-hexane.

3β,17β-Diacetoxy-5α,6α-epoxyandrostane **1** gave *3β,5α,17β-trihydroxy-6β-ethoxyandrostane* **2** (140 mg, 62%), m.p.183–185 °C(decomp.), (Found: C, 71.18, H, 9.95. $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29%), ν_{max} / cm^{-1} 3450, 3300, 1738; δ_H (500 MHz, $CDCl_3$) 0.76 (3H, s, 18-H), 1.14 (3H, s, 19-H), 1.15 (3H, t, *J* = 7.4 Hz, 6-OCH$_2$<u>CH$_3$</u>), 0.90–2.20 (19H, overlapping multiplets), 3.06 (1H, br s, 6α-H), 3.29–3.57 (each 1H, q, *J* = 7.4 Hz , 6-O<u>CH$_2$</u>CH$_3$), 3.64 (1H, t, *J* = 8.5 Hz, 17α-H), 4.06 (1H, tt, *J* = 5.2 and 9,7 Hz, 3α-H).).

3β-Acetoxy-5β,6β-epoxyandrostan-17-one **3** gave *3β-acetoxy-5α-ethoxy-6β-hydroxyandrostan-17-one* **4** (116 mg, 41%), m.p.199–201 °C (decomp.), (Found: C, 70.39, H, 9.28. $C_{23}H_{36}O_5$ requires C, 70.38; H, 9.24%), ν_{max} / cm^{-1} 3450, 1722, 1721; δ_H (500 MHz, $CDCl_3$) 0.86 (3H, s, 18-H), 1.12 (3H, t, *J* = 7.8 Hz, 5-OCH$_2$<u>CH$_3$</u>), 1.18 (3H, s, 19-H), 2,02 (3H, s, 3-OAc), 0.90–2.50 (19H, overlapping multiplets), 3.26–3.52 (each 1H, q, *J* = 7.8 Hz , 5-O<u>CH$_2$</u>CH$_3$), 3.92 (1H, t, *J* = 2.9 Hz, 6α-H), 4.84 (1H, t, *J* = 5.3 and 12 Hz, 3α-H).).

17β-Acetoxy-4α,5α-epoxy-3β-hydroxyandrostane **5** gave *17β-acetoxy-3β,5α-hydroxy-4β-ethoxyandrostane* **6** (69 mg, 24%), m.p. 162–164 °C (decomp.), (Found: C, 70.37, H, 9.74. $C_{23}H_{38}O_5$ requires C, 70.02; H, 9.71%), ν_{max} / cm^{-1} 3557, 1702; δ_H (500 MHz, $CDCl_3$) 0.78 (3H, s, 18-H), 1.12 (3H, s, 19-H), 1.22 (3H, t, *J* = 7.7 Hz, 4-OCH$_2$<u>CH$_3$</u>), 2.14 (3H, s, 17-OAc), 0.80-2.30 (19H, overlapping multiplets), 3.18 (1H, d, *J* = 4.0 Hz, 4α-H), 3.61–3.67 (each 1H, q, *J* = 7.7 Hz , 4-O<u>CH$_2$</u>CH$_3$), 4.03 (1H, dt, *J* = 11.0 and 4.0 Hz, 3α-H), 4.59 (1H, t, *J* = 8.4 Hz, 17α-H).

3β,17β-Diacetoxy-4β,5β-epoxyandrostane **7** gave *3β,17β-diacetoxy-5α-ethoxy-4β-hydroxyandrostane* **8** (98 mg, 35%), m.p.125–127 °C (decomp.), (Found: C, 68.40, H, 9.30. $C_{25}H_{40}O_6$ requires C, 68.78; H, 9.23%), ν_{max} / cm^{-1} 3481, 1732, 1709; δ_H (500 MHz, $CDCl_3$) 0.75 (3H, s, 18-H), 1.11 (3H, t, *J* = 7.6 Hz, 5-OCH$_2$<u>CH$_3$</u>), 1.14 (3H, s, 19-H), 2.00 and 2.04 (each 3H, s, 3-OAc and 17-OAc), 0.80–2.30 (19H, overlapping multiplets), 3.30 (2H, q, *J* = 7.6 Hz , 5-O<u>CH$_2$</u>CH$_3$), 3.96 (1H, d, *J* = 3.2 Hz, 4α-H), 4.56 (1H, t, *J* = 8.5 Hz, 17α-H), 5.08 (1H, dt, *J* = 10.0 and 3.2 Hz, 3α-H).

X-ray crystallographic data and structure determination of 3β,5α,17β-trihydroxy-6β-ethoxyandrostane (**2**)**:** CCDC deposition no. 785109, $C_{21}H_{36}O_4$, M_r 352.51, orthorhombic, $P2_1/n$ (no.3), *a* = 15.7273(4), *b* = 16.2206(4), *c* = 18.1338(5) Å, α = β= γ = 90°, *V* = 4626.0(2) Å^3, *Z* = 8, D_{cal} = 1.162 g cm^{-3}, μ = 0.631 mm^{-1}, F(OOO) = 1782.4. Data were collected on a crystal of size 0.32 × 0.20 × 0.20 mm^3 on a KappaCCD diffractometer operating for 5.45<θ<70.07. 37052 Reflections were collected for –19≤ *h* ≤ 19, –19≤ *k* ≤19, –22 ≤ *l* ≤22. There were 4458 independent reflections. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.141. The final R indices were [I > 2σ(*I*)] R^1 = 0.093, wR^2 = 0.228 and the R indices (all data) were R^1 = 0.104 and wR^2 = 0.252. The largest difference peak and hole were 0.53 and –0.51 e Å^{-3}.

X-ray crystallographic data and structure determination of 3β-acetoxy-5α-ethoxy-6β-hydroxyandrostan-17-one (**4**)**:** CCDC deposition no. 785110, $C_{23}H_{36}O_5$, M_r 392.52, monoclinic, $P\bar{1}$ (no.4), *a* = 8.4954(3), *b* = 9.4100(3), *c* = 14.1582(4) Å, α = γ = 90°, β = 104.103(2)°, *V* = 1097.72(6) Å^3, *Z* = 2, D_{cal} = 1.19 g cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) = 428. Data were collected on a crystal of size 0.4 × 0.4 × 0.2 mm^3 on a KappaCCD diffractometer operating for 3.67<θ<26.01°. 10379 Reflections were collected for –10≤ *h* ≤8, –11≤ *k* ≤11, –17≤ *l* ≤17 There were 2287 independent reflections with 2124 possessing I > 2σ(*I*). The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 0.940. The final R indices were [I > 2σ(*I*)] R_1 = 0.047, wR_2 = 0.121 and the R indices (all data) were R^1 = 0.053 and wR^2 = 0.126. The largest difference peak and hole were 0.22 and –0.33 e. Å^{-3}.

X-ray crystallographic data and structure determination of 17β-acetoxy-3β,5α-hydroxy-4β-ethoxyandrostane (**6**)**:** CCDC deposition no. 785108, $C_{23}H_{38}O_5$, M_r 394.53, orthorhombic, $P\bar{1}$ (no.3), *a* = 7.3130(3), *b* = 14.4646(10), *c* = 20.0815(14) Å, α = β= γ = 90°, *V* = 2124.2(2) Å^3, *Z* = 4, D_{cal} = 1.234 Mg m^{-3}, μ = 0.085 mm^{-1}, *F*(OOO) = 864. Data were collected on a crystal of size 0.34 × 0.04 × 0.02 mm^3 on a KappaCCD diffractometer operating for 2.96<θ<25.02°. 14383 Reflections were collected for –8≤ *h* ≤8, –17≤ *k* ≤17, –23≤ *l* ≤23. There were 2166 independent reflections. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.218. The final R indices were [I > 2σ(*I*)] R^1 = 0.079, wR^2 = 0.138 and the R indices (all data) were R^1 = 0.129 and wR^2 = 0.162. The largest difference peak and hole were 0.307 and –0.306 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers as above. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or E-mail: deposit@ccdc.cam.ac.uk].

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