Hydrolysis of Steroidal Esters Catalysed by Tetracyanoethylene†

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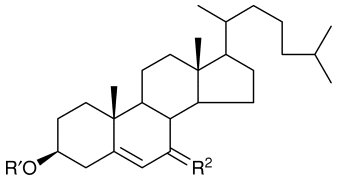
James R. Hanson,* Cavit Uyanik and Kudret Yildirim

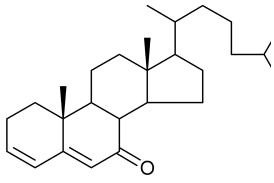
School of Chemistry, Physics and Environmental Science, University of Sussex, Brighton, Sussex BN1 9QJ, UK

Tetracyanoethylene has been shown to be a mild catalyst which possesses some stereoselectivity, for the hydrolysis of the esters of steroidal alcohols.

Tetracyanoethylene (TCNE) is well-known as a dienophile in Diels–Alder reactions.[1] Recently it has attracted interest as a π-acid and it has been shown to act as a catalyst for the cleavage of epoxides.[2,3] We have studied the stereochemistry of the methanolysis of steroidal epoxides catalysed by TCNE[4] and we have shown that the reaction may be affected by the neighbouring group participation of hydroxy groups.[5] We have also used the reagent to catalyse some cyclization and rearrangement reactions of sesquiterpene epoxides.[6,7] In the course of these studies we have observed



1 R^1 = Ac, R^2 = H_2
2 R^1 = H, R^2 = H_2
3 R^1 = Ac, R^2 = O
4 R^1 = H, R^2 = O



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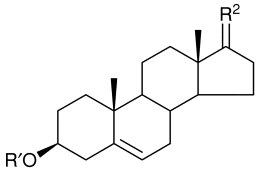
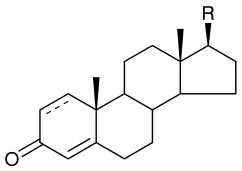
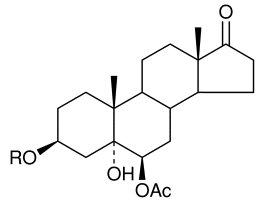


6 R^1 = Ac, R^2 = O
7 R^1 = H, R^2 = O
8 R^1 = Pr, R^2 = O
9 R^1 = H, R^2 = H, OAc
10 R^1 = H, R^2 = H, OAc
11 R^1 = H, R^2 = H, OH



12 R = Ac, no 1, 2-double bond
13 R = H, no 1, 2-double bond
14 R = Ac $\Delta^{1,2}$
15 R = H $\Delta^{1,2}$
16 R = Pr
17 R = Pv



18 R = Ac
19 R = H

Pr = EtCO Pv = Me_3CCO

the hydrolysis of some steroidal acetates through what is probably a π-acid catalysed ester exchange. As a bulky reagent, unlike the proton, we considered that TCNE might afford some steric control over the acid catalysed hydrolysis allowing differentiation between various esters. Furthermore TCNE is a relatively mild reagent and hence other acid-catalysed reactions might be less likely to occur.

The optimum conditions for the hydrolysis were established with cholesteryl acetate **1** as the substrate. Since this was not sufficiently soluble in methanol, toluene was used as a co-solvent. A temperature of 50 °C and a reaction period of eight hours gave a satisfactory yield. There was no detectable hydrolysis in the absence of the catalyst. The hydrolysis of a range of steroidal esters were then investigated. The extent of hydrolysis in an eight hour period is given in Table 1. The C-3β, C-6β and C-17β positions represent sites of differing steric hindrance in which the axial C-6β position is the most hindered. The esters were varied from acetate through propionate to trimethylacetate (pivaloate). The alcohols were identified by their ^{1}H NMR spectra in particular by the change in the chemical shift of the CH(OAc) resonance when it was replaced by a CH(OH) group.

Comparison of the results of hydrolysis of the C-3β, C-6β and C-17β-acetates in **6**, **9** and **18** and of the 17-acetate, 17β-propionate and 17β-pivaloate, **12**, **16** and **17** shows that the reaction is susceptible to steric hindrance from both the alcohol and acid components. Furthermore when the hydrolysis of the 3β-acetate **6** was carried out in the sterically more hindered solvent isopropanol at 50 °C, the reaction was very slow and only 8.5% hydrolysis occurred. Consequently TCNE may be used as an alternative to mildly basic conditions for differentiating between esters at various centres on the steroid framework.

The hydrolysis of 3β-acetoxycholest-5-en-7-one **3** led to a substantial amount of the acid-catalysed elimination product, cholesta-3,5-dien-7-one **5** identified by its ^{1}H NMR spectrum. On the other hand the conditions were not sufficiently vigorous to bring about the dienone:phenol rearrangement of **14** or of the elimination and backbone rearrangement of the tertiary 5α-hydroxy group in **18**.[8]

In conclusion we have shown that tetracyanoethylene may be used as a mild catalyst for the hydrolysis of steroidal esters with the potential to distinguish between sites and esters of different steric hindrance. It may have more general application as a reagent for the catalysis of ester hydrolysis.

Experimental

General experimental details have been described previously.[4]

General Procedure for the Hydrolysis of Esters.—The steroid (500 mg) was dissolved in methanol (10 cm^3) or toluene–methanol (1:1) (10 cm^3) and treated with tetracyanoethylene (100 mg) and warmed to 50 °C for 8 h. The reaction was monitored by TLC (the reaction time may be varied depending on the ester). The solvent was evaporated under reduced pressure. The residue was absorbed on silica and chromatographed in an increasing gradient of ethyl acetate in light petroleum. The steroids were identified by comparison of their ^{1}H NMR spectra with known samples and in particular by the change of the CH(OAc) resonance (δ_H 4.5–5.0) to a CH(OH) resonance (δ_H 3.5–4.0) and by the loss of a $COCH_3$ signal (δ_H *ca.* 2.0). The % yields for the standard reaction time of 8 h are given in Table 1.

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Hydrolysis of esters of steroidal alcohols by TCNE

Substrate	Product	Yield (%)
Cholesteryl acetate (**1**)	cholesterol (**2**)	93
3β-Acetoxyandrost-5-en-17-one (**6**)	3β-hydroxyandrost-5-en-17-one (**7**)	88
in isopropanol–recovered starting material		86
	3β-hydroxyandrost-5-en-17-one (**7**)	8.5
3β-Propionyloxyandrost-5-en-17-one (**8**)		
recovered starting material		38
	3β-hydroxyandrost-5-en-17-one (**7**)	57
3β,17β-Diacetoxyandrost-5-ene (**9**)		
recovered starting material		26
	17β-acetoxy-3β-hydroxyandrost-5-ene (**10**)	22
	3β,17β-dihydroxyandrost-5-ene (**11**)	49
17β-Acetoxyandrost-4-en-3-one (**12**)	17β-hydroxyandrost-4-en-3-one (**13**)	73
17β-Acetoxyandrosta-1,4-diene-3-one (**14**)		
recovered starting material		6
	17β-hydroxyandrosta-1,4-diene-3-one (**15**)	65
17β-Propionyloxyandrost-4-en-3-one (**16**)	17β-hydroxyandrost-4-en-3-one (**13**)	56
17β-Pivaloyloxyandrost-4-en-3-one (**17**) no reaction		
3β,6β-Diacetoxy-5α-hydroxyandrostan-17-one (**18**)	6β-acetoxy-3β,5α-dihydroxyandrostan-17-one (**19**)	95
3β-Acetoxycholest-5-en-7-one (**3**)	cholesta-3,5-dien-7-one (**5**)	45
	3-hydroxycholest-5-en-7-one (**4**)	10

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8 For a review, see D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, Elsevier, Amsterdam, 1968, ch. 5.