Peracid Oxidation of 16-Arylidene- and 16-Alkylidene-17-oxo-steroids

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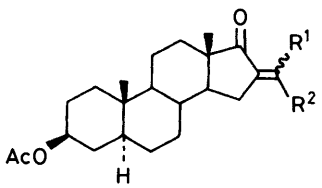
Peracid oxidation of 16-arylidene- and 16-alkylidene-5α-androstan-17-ones (**1**)—(**6**) gave no α,β-unsaturated δ-lactones, but resulted mainly in products of direct oxidation of the olefinic double bond.

Steroidal α-methylene lactones[1-3] have been found to be cytotoxic to certain cancer cell lines and may have potential as anti-tumour agents.† We have reported[2,3] the synthesis of some α-methylene lactones by methylenation of preformed lactones. The primary products of peracid oxidation of α,β-unsaturated ketones[4-10] may be enol lactones, α,β-unsaturated lactones, and epoxy ketones. The usual major product is the enol lactone, but changes in substitution may be expected to modify the migratory aptitudes of the alkyl *versus* the vinyl group.[6] We report here an investigation of the Baeyer–Villiger oxidation of 16-arylidene- and 16-alkylidene-17-oxo-steroids as a potential route to α,β-unsaturated δ-lactones.

The 16-arylidene-5α-androstan-17-ones (**1**)—(**4**) were prepared from 3β-acetoxy-5α-androstan-17-one by base-catalysed condensation with the appropriate benzaldehyde[11] followed by acetylation with acetic anhydride and pyridine. It is presumed that the 16-arylidene-5α-androstan-17-ones (**1**)—(**4**) have the *E*-configuration since a singlet at low field (δ 7.30—7.50) is present in each of the ^{1}H n.m.r. spectra. The 16-alkylidene-5α-androstan-17-ones (**5**) and (**6**) were similarly prepared *via*



(**1**) R^1 = H, R^2 = Ph, *E*
(**2**) R^1 = H, R^2 = *p*-ClC_6H_4, *E*
(**3**) R^1 = H, R^2 = *p*-$NO_2C_6H_4$, *E*
(**4**) R^1 = H, R^2 = *p*-$MeOC_6H_4$, *E*
(**5**) R^1 = R^2 = Me
(**6**) R^1 = Me, R^2 = Et, *E* and *Z*

condensation[12] of 3β-hydroxy-5α-androstan-17-one with acetone and methyl ether ketone (MEK). Two singlets (δ 2.2 and 1.83) in the ^{1}H n.m.r. spectrum of compound (**6**), assigned to the olefinic methyl groups, confirmed the presence of *E*- and *Z*-isomers.

Oxidation of the 16-arylidene ketones (**1**)—(**3**) with trifluoroperacetic acid in the presence of disodium hydrogen phosphate[13] in CH_2Cl_2 at 0 °C afforded the epoxy ketones (**7**)—(**9**) respectively. That these products were mixtures of α- and β-isomers was evident from the ^{1}H n.m.r. spectra in which the epoxide methine proton signals were duplicated; integration of these signals afforded the isomer ratios (Table). The signals (δ 215.0 p.p.m.) of the carbonyl carbons in the ^{13}C n.m.r. spectra of compounds (**7a**) and (**7b**), which were separated by preparative t.l.c., confirmed that the products were epoxy ketones rather than lactones. It would be expected that the major product of oxidation would, in each case, be the α-

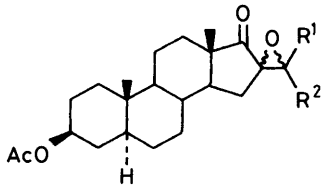
† For a recent review of α-methylene-γ-butyrolactones, see H. M. R. Hoffman and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 94.

Table. Stereoselectivity of oxidation of the arylidene ketones (**1**)—(**3**)

Arylidene ketone	^{1}H N.m.r. (δ)		Epoxide composition (%)	
	α-epoxide	β-epoxide	α	β
(**1**)	4.15	4.34	65	35
(**2**)	4.10	4.30	72	28
(**3**)	4.25	4.45	55	45

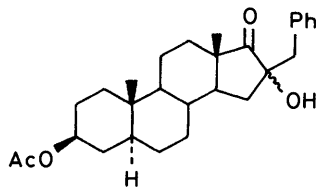
epoxide. This was confirmed by the 13-methyl group signals (δ 0.54 and 1.0) in the ^{1}H n.m.r. spectra of the α-ketols (**12a**) and (**12b**), which were prepared by Pd-catalysed hydrogenolysis of the epoxy ketones (**7a**) and (**7b**), respectively. The 13-methyl group of compound (**12a**) is believed to be significantly shielded by the phenyl group, as shown in conformation (**13**).

A mixture of the α-ketols (**12a**) and (**12b**) was obtained by Pd-catalysed hydrogenolysis of the mixed chlorophenylepoxy ketones (**8**). The nitrophenylepoxy ketones (**9**) were resistant to

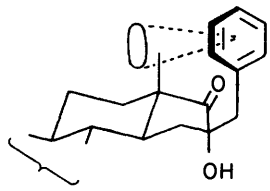


(**7a**) R^1 = H, R^2 = Ph, 16α
(**7b**) R^1 = H, R^2 = Ph, 16β
(**8**) R^1 = H, R^2 = *p*-ClC_6H_4
(**9**) R^1 = H, R^2 = *p*-$NO_2C_6H_4$
(**10**) R^1 = R^2 = Me, 16α
(**11a**) R^1 = Me, Et; R^2 = Et, Me, 16α
(**11b**) R^1 = Me, Et; R^2 = Et, Me, 16β

hydrogenolysis. Further confirmation of the structures of the α-ketols (**12a**) and (**12b**) was afforded by their dehydration ($SOCl_2$–pyridine) to give the *E*-benzylidene ketone (**1**).

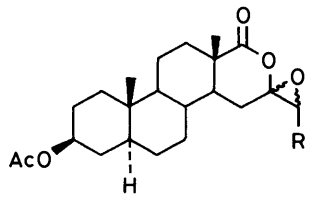


(**12a**) 16α
(**12b**) 16β



(**13**)

Oxidation of the methoxybenzylidene ketone (**4**) with trifluoroperacetic acid gave the epoxy enol lactone (**14**) and rearrangement products identified as the β-diketones (**15**) and



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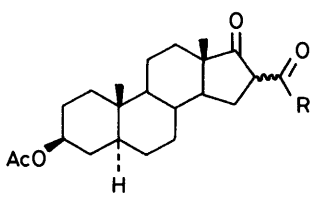

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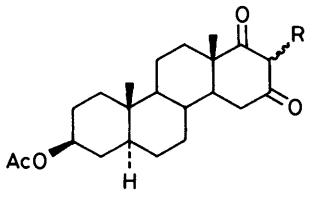
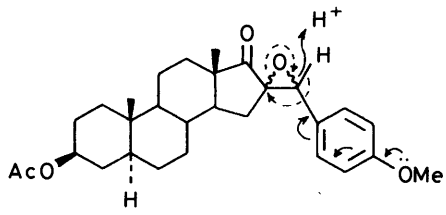


(16)

R = C_6H_4OMe-*p*



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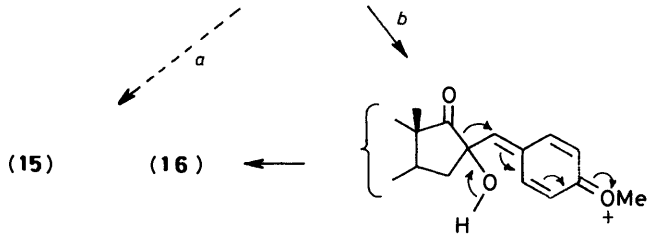


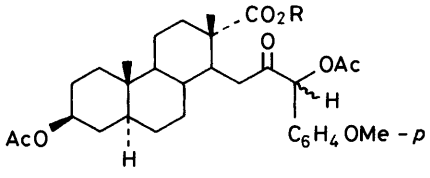
Scheme 1.

(**16**). T.l.c. of the crude reaction mixture suggests that the β-diketones arise from rearrangment of a primary product during work-up. Characterisation of the epoxy enol lactone (**14**) was afforded by its i.r. ($\nu_{max.}$ 1 730 cm^{-1} RCO_2) and ^1H n.m.r. [δ 4.2, s, $ArC\overline{H-O-C}(R)OCO-$] spectra and by a molecular ion at *m/z* 482 in the mass spectrum. It is likely that the epoxide oxygen has the α-configuration, but this was not rigorously established. The β-diketone (**15**) gave a characteristic u.v. spectrum ($\lambda_{max.}$ 239 and 272 nm in ethanol and 291 nm in the presence of NaOH) and i.r. spectrum [$\nu_{max.}$ 3 550—3 400 cm^{-1}, OH; and 1 630 cm^{-1}, RCO–CH=C(OH)–]. The ^1H n.m.r. spectrum confirmed the assignment of structure, showing aromatic proton doublets (*J* 9 Hz) at δ 7.1 and 6.9 and a broad singlet at δ 6.1, exchangeable with D_2O, assigned to the enolic OH group. The mass spectrum showed a molecular ion at *m/z* 466. The β-diketone (**16**), which was always contaminated with compound (**14**) or an isomer, was tentatively identified from its i.r. spectrum ($\nu_{max.}$ 3 600—3 000 cm^{-1}, OH; and 1 690 cm^{-1}, enolised cyclohexane-1,3-dione) and its mass spectrum which showed a molecular ion at *m/z* 466. The aromatic proton doublets (*J* 9 Hz) at δ 7.98 and 6.93 in the ^1H n.m.r. spectrum are consistent with the proposed structure since the protons *ortho* to the attached enolised β-diketone would be expected to be significantly deshielded.

Oxidation of the isopropylidene ketone (**5**) with trifluoroperacetic acid afforded the epoxy ketone (**10**) which appeared to be a single isomer and is assumed to have the α-configuration. The structural assignment is supported by the i.r. spectrum ($\nu_{max.}$ 1 740 cm^{-1}, cyclopentanone) and the ^1H n.m.r. spectrum in which the epoxide methyl group singlets appear at δ 1.35 and 1.38 and the 13-methyl group singlet at δ 0.96, is close to that (δ 0.93) of the α-epoxide (**7a**). Similar oxidation of the 2-butylidene ketone (**6**) afforded a mixture (76:24 respectively) of *cis*- and *trans*-α-epoxides (**11a**) and the *cis*- and *trans*-β-epoxides (**11b**) which were separated by preparative t.l.c. The ^1H n.m.r. spectrum of compound (**11a**) showed two singlets at δ 1.32 and 1.35 for the epoxide methyl groups and a singlet for the 13-methyl group at δ 0.98, whereas that of the minor isomer (**11b**) showed corresponding singlets at δ 1.38 and 1.52 for the epoxide methyl groups and δ 0.99 for the 13-methyl group. Integration of the epoxide methyl signals indicated that the *cis*:*trans* ratio for (**11a**) and (**11b**) was *ca.* 1:1.

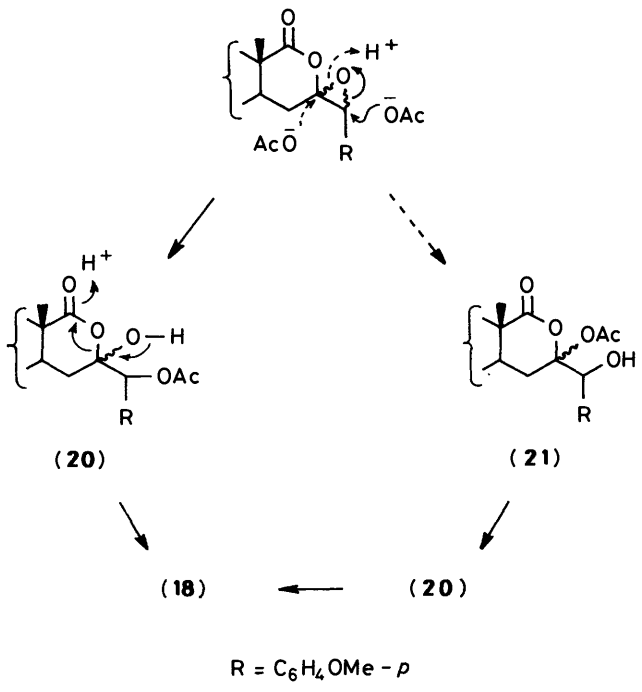
Although the electron availability in the olefinic double bond in the arylidene ketones (**1**)—(**4**) and the alkylidene ketones (**5**) and (**6**) would be expected to be significantly different, the compounds reacted mainly by direct oxidation of the double bond to afford the epoxides. Some difference in the stereoselectivities of the oxidations of compounds (**1**)—(**3**) was observed but this was not dramatic. The major primary product of oxidation of the methoxybenzylidene ketone (**4**) is probably the epoxide (**17**). Rearrangement of compound (**17**) as indicated in Scheme 1 could account for the occurrence of the β-diketones (**15**) and (**16**). Path *a* involves a hydride shift and epoxide cleavage, whereas path *b* involves proton initiated epoxide cleavage followed by the 1,2-shift of an acyl group (C-17). The formation of the epoxy enol lactone (**14**) indicates that the C-13 has a lower migratory aptitude than C-16 which presumably is electron rich because of the electron donation from the methoxy group.

As the methoxybenzylidene ketone (**4**) would be expected to be the most reactive of the series examined, its reaction with KOAc–peracetic acid[9] rather than with trifluoroperacetic acid was investigated. Preparative t.l.c. of the crude product afforded two isomeric acids (**18**) which were converted into the methyl esters (**19**) by reaction with diazomethane. The structural



(**18**) R = H
(**19**) R = Me

assignments of the esters (**19**) were supported by the presence of the ester carbonyl ($\nu_{max.}$ 1 735 cm^{-1}) and ketone carbonyl ($\nu_{max.}$ 1 720 cm^{-1}) bands in the i.r. spectra. The ester derived from the more polar acid showed a singlet in the ^1H n.m.r. spectrum at δ 5.83 which was assigned to the benzylic proton at C-17. A similar singlet at δ 5.94 was present in the parent acid and the equivalent proton in the less polar acid and its methyl ester gave singlets at δ 5.95 and 5.87 respectively. The mass spectra of the isomeric acids (**18**) did not show molecular ions but did show ions at *m/z* 482 corresponding to $[M - CH_3CO_2H]^+$. The mass spectra of the methyl ester (**19**) each showed ions at *m/z* 377 corresponding to the loss of the acetoxybenzyl moiety ($C_{10}H_{11}O_3$). It is possible that the isomeric carboxylic acids (**18**) are derived from the epoxyenol lactone (**14**) (Scheme 2). Cleavage of the epoxide by acetate ion may afford the regio-isomeric hydroxy acetates (**20**) and (**21**), of which the former



Scheme 2.

would ring open to give the acids (**18**), while the latter may undergo acetyl transfer to afford compound (**20**) and thence (**18**).

It has been established that the direct formation of α,β-unsaturated δ-lactones by oxidation of 16-arylidiene- and 16-alkylidene-17-oxo-steroids is not a practicable route even though the electron availability in the olefinic double bond has been varied significantly. In no case did C-13 appear to migrate to any significant extent.

Experimental

^{1}H N.m.r. spectra were routinely recorded (unless otherwise stated) at 60 and 90 MHz in deuteriochloroform using Varian EM360A and Perkin-Elmer R32 spectrometers. ^{13}C N.m.r. spectra were recorded at 20.1 MHz in deuteriochloroform using a Bruker WP80 spectrometer. I.r. spectra were recorded for Nujol mulls (unless otherwise stated) using a Perkin-Elmer 177 spectrophotometer, and u.v. spectra were obtained for ethanol solutions using a Pye-Unicam SP8-100 spectrophotometer. Mass spectra were recorded using Kratos MS 50 and MS 80 spectrometers and optical rotations were measured for chloroform solutions (unless otherwise stated) at ambient temperature with an Optical Activity AA-10 digital polarimeter. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Preparative t.l.c. was performed on silica gel (Merck 60PF254) on 1-m plates at a thickness of 0.75 mm. Solutions were dried over magnesium sulphate and evaporated under reduced pressure on a rotatory evaporator. Ether refers to diethyl ether.

General Procedure[11] *for the Preparation of the* 16-*Arylidene Ketones* (**1**)—(**4**).—A solution of 3β-acetoxy-5α-androstan-17-one in aqueous ethanol containing an excess of potassium hydroxide and the appropriate freshly distilled benzaldehyde was heated briefly under reflux and stirred at room temperature overnight. The mixture was cooled and filtered to afford the 3β-hydroxy-16-arylidene ketone which was recrystallised and acetylated with acetic anhydride to give the 3β-acetoxy-16-arylidene ketone.

This procedure afforded 3β-acetoxy-16-benzylidene-5α-androstan-17-one (**1**) (60%), m.p. 238—240 °C (chloroform–methanol) (lit.,[11a] m.p. 237—238 °C), $\nu_{max.}$ 1 730 (AcO) and 1 720 cm^{-1} (17-C=O); δ 7.45 (m, C_6H_5CH=), 4.65 (m, 3-H), 2.02 (s, $MeCO_2$), 0.96 (s, 13-Me), and 0.89 (s, 10-Me); 3β-hydroxy-16-*p*-chlorobenzylidene-5α-androstan-17-one, m.p. 219—221 °C (ethanol–water); 3β-*acetoxy*-16-p-*chlorobenzylidene*-5α-*androstan*-17-*one* (**2**) (69%), m.p. 217—219 °C (ethanol), $[\alpha]_D$ −11° (*c*, 2.0), $\nu_{max.}$ 1 730 (AcO) and 1 720 cm^{-1} (17-C=O); δ 7.51 and 7.36 (d, *J ca.* 7 Hz, ClC_6H_4), 7.31 (s, C_6H_5CH=), 4.65 (m, 3-H), 1.99 (s, $MeCO_2$), 0.90 (s, 13-Me), and 0.86 (s, 10-Me) (Found: C, 73.9; H, 8.0; Cl, 7.7. $C_{28}H_{35}ClO_3$ requires C, 73.9; H, 7.75; Cl, 7.8%); 3β-hydroxy-16-*p*-nitrobenzylidene-5α-androstan-17-one, m.p. 268.5—269.5 °C (ethanol), 3β-*acetoxy*-16-p-*nitrobenzylidene*-5α-*androstan*-17-*one* (**3**) (90%), m.p. 254—256 °C (ethyl acetate), $[\alpha]_D$ −13° (c, 1.2), $\nu_{max.}$ 1 732 (AcO) and 1 725 (17-C=O), 1 520 and 1 345 cm^{-1} ($ArNO_2$); δ 8.25 and 7.65 (d, *J* 9 Hz, $NO_2C_6H_4$), 7.45 (s, $NO_2C_6H_4CH$=), 4.65 (m, 3-H), 2.02 (s, $MeCO_2$), 0.98 (s, 13-Me), and 0.90 (s, 10-Me) (Found: C, 72.1; H, 7.6; N, 3.0. $C_{28}H_{35}NO_5$ requires C, 72.25; H, 7.6; N, 3.0%); and 3β-acetoxy-16-*p*-methoxybenzylidene-5α-androstan-17-one (**4**) (88%), m.p. 191—193 °C (methanol) (lit.,[11b] m.p. 190.5—192 °C), $\nu_{max.}$ 1 730 (AcO) and 1 715 cm^{-1} (17-C=O); δ 7.51 and 6.92 (d, *J ca.* 9 Hz, $MeOC_6H_4$), 7.31 (s, $MeOC_6H_4CH$=), 4.6 (m, 3-H), 3.83 (s, $MeOC_6H_4$), 2.0 (s, $MeCO_2$), and 0.90 and 0.89 (s, 10-Me and 13-Me).

General Procedure[12] *for the Preparation of* 16-*Alkylidene Ketones* (**5**) *and* (**6**).—A solution of 3β-hydroxy-5α-androstan-17-one in the ketone–methanol (1:1) containing an excess of potassium hydroxide was heated under reflux for 24 h using acetone, 48 h using MEK. The reaction mixture was diluted with ether, washed with water and dried and the crude product was acetylated with acetic anhydride in pyridine. In the preparation of compound (**6**) the intermediate hydroxy derivative was purified by chromatography on silica gel eluting with toluene–ethyl acetate (8:2). This procedure afforded 3β-*acetoxy*-16-*isopropylidene*-5α-*androstan*-17-*one* (**5**) (86%), m.p. 165—167 °C (methanol), $[\alpha]_D$ −40° (*c*, 1.0), $\lambda_{max.}$ 250 nm (ε 7 000); $\nu_{max.}$ 1 735 (AcO) and 1 705 cm^{-1} (17-C=O); δ 4.65 (m, 3 H), 2.22 (s, isopropylidene Me *cis* to C=O), 2.03 (s, $MeCO_2$), 1.85 (s, isopropylidene Me *trans* to C=O), and 0.87 (s, 10-Me and 13-Me) (Found: C, 77.2; H, 9.9. $C_{24}H_{36}O_3$ requires C, 77.35; H, 9.75%); and 3β-*acetoxy*-16-(*s-butylidene*)-5α-*androstan*-17-*one* (**6**) (88%), m.p. 123—126 °C (methanol–water), $\lambda_{max.}$ 252 nm (ε 6 185); $\nu_{max.}$ 1 740 (AcO) and 1 712 cm^{-1} (17-C=O); δ 4.7 (m, 3-H), 2.2 (s, s-butylidene Me *cis* to C=O), 2.03 (s, $MeCO_2$), 1.83 (s, s-butylidene Me *trans* to C=O), 1.01 and 1.03 [t, *J ca.* 7 Hz, $CH_3CH_2C(Me)$=], and 0.86 (s, 10-Me and 13-Me) (Found: C, 77.8; H, 10.1. $C_{25}H_{38}O_3$ requires C, 77.7; H, 9.9%).

Oxidation of 16-*Arylidene- and* 16-*Alkylidene-ketones with Trifluoroperacetic Acid.*[13]—(*a*) *Benzylidene ketone* (**1**). Cold trifluoroacetic anhydride (0.85 g) was added to a cold and stirred solution of hydrogen peroxide (0.17 g, 86.6%) in dichloromethane (8 ml) during 20 min. After 0.5 h, the resulting solution was added to a vigorously stirred suspension of disodium hydrogen phosphate (0.5 g) and the benzylidene ketone (**1**) in dichloromethane (30 ml) at 0 °C during 0.5 h. The mixture was stirred for 3 h at 0 °C and at room temperature overnight and filtered. The organic layer was washed with water, dried and evaporated to afford a crude product comprised mainly of the epoxides (**7a**) and (**7b**) (65:35, Table). Preparative t.l.c., eluting with light petroleum (b.p. 60—80 °C)–methanol (95:5) gave (3′R,16S)-3β-*acetoxy*-3′-*phenyl*-5α-*androstan*-16-*spiro*-2′-*oxiran*-17-*one* (**7a**) (0.09 g), m.p. 208—210 °C (ethyl acetate–hexane), $[\alpha]_D$ +190° (CH_2Cl_2; *c*, 0.2); $\nu_{max.}$(CH_2Cl_2) 1 752 (17-C=O) and 1 730 cm^{-1} (AcO); δ(^{1}H) 7.35 (m, C_6H_5), 4.65 (m,

3-H), 4.15 (s, C_6H_5CH), 2.02 (s, $MeCO_2$), 0.92 (s, 13-Me), and 0.82 (s, 10-Me); δ(^{13}C) 215.0 (17-C=O) and 14.3 (13-Me) (Found: $M^{+\cdot}$, 436.2610; C, 76.7; H, 8.4. $C_{28}H_{36}O_4$ requires *M*, 436.2614; C, 77.05; H, 8.3%); and (3'S,16R)-3β-*acetoxy*-3'-*phenyl*-5α-*androstane*-16-*spiro*-2'-*oxiran*-17-*one* (**7b**) (0.05 g), m.p. 194—196 °C (ethyl acetate–ethanol) $[\alpha]_D$ −121° (CH_2Cl_2; *c*, 0.14), $\nu_{max.}$($CHCl_2$) 1 750 (17-C=O) and 1 730 cm^{-1} (AcO); δ(^{1}H) 7.31 (m, C_6H_5), 4.6 (m, 3-H), 4.34 (s, C_6H_5CH), 2.01 (s, $MeCO_2$), 1.08 (s, 14-Me), and 0.86 (s, 10-Me); δ(^{13}C) 215.0 (17-C=O) and 14.4 (13-Me) (Found: M^+, 436.2609. $C_{28}H_{36}O_4$ requires *M*, 436.2614).

(*b*) p-*Chlorobenzylidene ketone* (**2**). Under similar conditions the *p*-chlorobenzylidene ketone (**2**) (0.3 g), without chromatography, afforded the mixture of *epoxides* (**8a**) and (**8b**) (72:28; Table) (0.27 g), m.p. 72—82 °C (ethyl acetate–ethanol), $\nu_{max.}$(CH_2Cl_2) 1 755 (17-C=O) and 1 735 cm^{-1} (AcO); δ 7.4 and 7.2 (d, *J ca.* 8 Hz, ClC_6H_4), 4.65 (m, 3-H), 4.3 and 4.1 (s, ClC_6H_4CH), 2.01 (s, $MeCO_2$), 1.06, 0.91, 0.84, and 0.80 (s, 13-Me and 10-Me) (Found: $M^{+\cdot}$, 470.2223. $C_{28}H_{35}ClO_4$ requires *M*, 470.2224).

(*c*) p-*Nitrobenzylidene ketone* (**3**). Under similar conditions the *p*-nitrobenzylidene ketone (**3**) (0.2 g) gave, after preparative t.l.c., eluting with light petroleum (b.p. 60—80 °C)–ether (50:50), the mixture of *epoxides* (**9a**) and (**9b**) (55:45; Table) (0.1 g), m.p. 107—114 °C (ethyl acetate–ethanol), $\nu_{max.}$(CH_2Cl_2) 1 750 (17-C=O) and 1 725 cm^{-1} (AcO); δ 8.24 and 7.45 (d, *J ca.* 8 Hz, $NO_2C_6H_4$), 4.65 (m, 3-H), 4.45 and 4.25 (s, $NO_2C_6H_4CH$), 2.02 (s, AcO), 1.1, 0.94, 0.86, and 0.82 (s, 13-Me and 10-Me) (Found: $M^{+\cdot}$, 481.2462. $C_{28}H_{35}NO_6$ requires *M*, 481.2464), and starting material (**3**) (0.04 g).

(*d*) p-*Methoxybenzylidene ketone* (**4**). Reaction of the *p*-methoxybenzylidene ketone (**4**) (0.4 g) with trifluoroperacetic acid as above, at 0 °C for 4 h, afforded a crude product which on crystallisation and recrystallisation from ethyl acetate gave 3β-*acetoxy*-3'-*p-methoxyphenyl*-17-*oxa*-D-*homo*-5α-*androstane*-16-*spiro*-2'-*oxiran*-17-*one* (**14**) (0.06 g), m.p. 143—145 °C, $[\alpha]_D$ +2° (*c*, 2.0), $\nu_{max.}$(CH_2Cl_2) 1 730 cm^{-1} (RCO_2); δ(CD_2Cl_2; 220 MHz) 7.05 and 6.9 (d, *J ca.* 8 Hz, $MeOC_6H_4$), 4.65 (m, 3-H), 4.2 (s, $MeOC_6H_4CH$), 3.8 (s, MeO), 3.0 (dd, *J ca.* 15 and 3 Hz, 15α-H), 2.69 (t, *J ca.* 15 Hz, 15β-H), 1.98 (s, $MeCO_2$), 0.80 and 0.78 (s, 10-Me and 13-Me) (Found: $M^{+\cdot}$, 428.2661; C, 71.9; H, 7.9. $C_{29}H_{38}O_6$ requires *M*, 482.2668; C, 72.15; H, 7.95%). Preparative t.l.c. of the mother liquor, eluting with toluene–ethyl acetate (8:2), gave 3β-*acetoxy*-16ξ-p-*methoxybenzoyl*-5α-*androstan*-17-*one* (**15**) (0.2 g), m.p. 238—240 °C, $[\alpha]_D$ −24° (CH_2Cl_2; *c*, 0.5), $\nu_{max.}$(CH_2Cl_2) 3 550—3 400 (enolic OH), 1 730 (AcO), 1 685 and 1 630 (enolised β-diketone); $\lambda_{max.}$ 239 (ε 9 440) and 272 nm (ε 7 515); $\lambda_{max.}$(NaOH) 291 nm (ε 7 455); δ 7.1 and 6.9 (d, *J ca.* 9 Hz, $MeOC_6H_4$), 6.1 (br s, enolic OH, exchangeable with D_2O), 4.65 (m, 3-H), 3.82 (s, MeO), 2.02 (s, $MeCO_2$), 1.1 (s, 13-Me) and 0.84 (s, 10-Me) (Found: $M^{+\cdot}$, 466.2706. $C_{29}H_{38}O_5$ requires *M*, 466.2719) and an impure fraction (0.1 g), m.p. 179—182 °C (ethanol–water) containing the β-diketone (**16**), $\nu_{max.}$(CH_2Cl_2) 3 600—3 000 (OH), 1 730 (AcO), and 1 690 cm^{-1} (enolised cyclohexanedione); δ 7.98 and 6.93 (d, *J ca.* 9 Hz, $MeOC_6H_4$), 4.7 (m, 3-H), 3.91 (s, MeO), 2.02 (s, $MeCO_2$), 1.22 (s, 13-Me), and 0.81 (s, 10-Me) (Found: M^+, 466.2743. $C_{29}H_{38}O_5$ requires *M*, 466.2719).

(*e*) *Isopropylidene ketone* (**5**). Reaction of the isopropylidene ketone (**5**) (0.11 g) as in (*d*) for 5 h afforded (16S)-3β-*acetoxy*-3',3'-*dimethyl*-5α-*androstane*-16-*spiro*-2'-*oxirane*-17-*one* (**10**) (0.1 g), m.p. 214—216 °C $[\alpha]_D$ +60° (CCl_4; *c*, 0.5); $\nu_{max.}$(CH_2Cl_2) 1 740 (17-C=O), 1 730 (AcO); δ 4.65 (m, 3-H), 2.03 (s, $MeCO_2$), 1.38 and 1.35 (s, Me_2C), 0.96 (s, 13-Me), and 0.89 (s, 10-Me) (Found: $M^{+\cdot}$, 388.2612; C, 74.5; H, 9.5. $C_{24}H_{36}O_4$ requires *M*, 388.2613; C, 74.2; H, 9.35%).

(*f*) 2-*Butylidene ketone* (**6**). Reaction of the 2-butylidene ketone (**6**) (0.2 g) as above for 6.5 h followed by preparative t.l.c., eluting with light petroleum (b.p. 60—80 °C)– ether (8:2), gave (3'RS,16S)-3β-*acetoxy*-3'-*ethyl*-3'-*methyl*-5α-*androstane*-16-*spiro*-2'-*oxiran*-17-*one* (**11a**) (0.097 g), m.p. 150—155 °C [ethyl acetate–light petroleum (b.p. 40—60 °C)]; $\nu_{max.}$(CCl_4) 1 750 (17-C=O) and 1 732 cm^{-1} (AcO); δ 4.7 (m, 3-H), 2.04 (s, $MeCO_2$), 1.35 and 1.32 [s, *Me*C(Et)<], 0.98 (s, 13-Me), and 0.88 (s, 10-Me) (Found: $M^{+\cdot}$, 402. $C_{25}H_{38}O_4$ requires *M*, 402), and the (3'*RS*,16*R*)-isomer (0.03 g), $\nu_{max.}$(CCl_4) 1 750 (17-C=O) and 1 732 cm^{-1} (AcO); δ 4.7 (m, 3-H), 2.02 (s, $MeCO_2$), 1.52 and 1.38 [s, *Me*C(Et)], 0.99 (s, 13-Me), and 0.91 (s, 10-Me).

Hydrogenolysis of the Epoxy Ketones (**7**) *and* (**8**).—(*a*) α-*Epoxy ketone* (**7a**). A solution of the α-epoxy ketone (**7a**) (0.095 g) in ethyl acetate (80 ml) containing 10% Pd/C catalyst was stirred under hydrogen for 26 h. Filtration and removal of the solvent gave a quantitative yield of 3β-*acetoxy*-16β-*benzyl*-16α-*hydroxy*-5α-*androstan*-17-*one* (**12a**), m.p. 180—182 °C (ethyl acetate–hexane), $[\alpha]_D$ +92° (CH_2Cl_2; *c*, 1.0); $\nu_{max.}$ 3 520 (OH), 1 740 (17-C=O), and 1 730 cm^{-1} (AcO); δ 7.24 (m, C_6H_5), 4.65 (m, 3-H), 2.95 (s, $C_6H_5CH_2$), 2.21 (br s, 16-OH, exchangeable with D_2O), 2.03 (s, $MeCO_2$), 0.81 (s, 10-Me), and 0.54 (s, 13-Me) (Found: $M^{+\cdot}$, 438.2767; C, 76.5; H, 8.7. $C_{28}H_{38}O_4$ *M*, 438.2770; C, 76.65; H, 8.75%).

(*b*) β-*Epoxy ketone* (**7b**). As above, the β-epoxy ketone (**7b**) gave 3β-*acetoxy*-16α-*benzyl*-16β-*hydroxy*-5α-*androstan*-17-*one* (**12b**), m.p. 176—178 °C [ethyl acetate–light petroleum (b.p. 40—60 °C], $[\alpha]_D$ −20° (CH_2Cl_2; *c*, 0.8); $\nu_{max.}$ 3 565 (OH), 1 740 (17-C=O), and 1 730 cm^{-1} (AcO); δ 7.22 (m, C_6H_5), 4.65 (m, 3-H), 2.88 (s, $C_6H_5CH_2$), 2.45 (br s, 16-OH, exchangeable with D_2O), 2.02 (s, $MeCO_2$), 1.0 (s, 13-Me), and 0.81 (s, 10-Me) (Found: $M^{+\cdot}$, 438.2789. $C_{28}H_{38}O_4$ requires *M*, 438.2770).

(*c*) *Epoxy ketones* (**8**). As above, but over a period of 5 days, the epoxy ketones (**8**) (0.5 g) gave a crude product (0.3 g) which, on preparative t.l.c., eluting with light petroleum (b.p. 60—80 °C)–chloroform–ether (45:5:50), gave a mixture (0.13 g) of (**12a**) and (**12b**) from which the 16β-benzyl-16α-hydroxyketone (**12a**), m.p. 180—182 °C, was isolated after several crystallisations from ethyl acetate–hexane.

Dehydration of the α-Ketols (**12a**) *and* (**12b**).—Treatment of the α-ketols (**12a**) and (**12b**) with thionyl chloride in pyridine solution at 0 °C afforded the benzylidene ketone (**1**), m.p. 239—241 °C.

Peracetic Acid Oxidation[9] *of the* p-*Methoxybenzylidene Ketone* (**4**).—A solution of the methoxybenzylidene ketone (**4**) (0.4 g) in glacial acetic acid (20 ml) saturated with potassium acetate was stirred with an excess of 45% peracetic acid solution at room temperature until t.l.c. showed that no starting material was present (24 h). Ether (200 ml) and water (100 ml) were added and the aqueous layer was extracted with ether (×2). The combined ether solutions were washed with water (×2), aqueous sodium carbonate (×2), and water (×3) and dried and evaporated to give the crude product (0.435 g). Preparative t.l.c., eluting with toluene–ethyl acetate (65:35), gave the isomeric 3β,17ξ-*diacetoxy*-17ξ-p-*methoxyphenyl*-16-*oxo*-17,17a-*seco*-D-*homo*-5α-*androstan*-17-*oic acids* (**18**). The more polar acid (0.11 g), gave the following, m.p. 83—85 °C, $\nu_{max.}$ 3 600—2 500 (CO_2H), 1 730 (AcO), 1 715 (16-C=O), and 1 700 cm^{-1} (CO_2H); δ 7.32 and 6.9 (d, *J ca.* 8 Hz, $MeOC_6H_4$), 6.3 (br s, CO_2H, exchangeable with D_2O), 5.94 (s, $MeOC_6H_4CH$) 4.65 (m, 3-H), 3.82 (s, MeO), 2.35 (br s, 15-CH_2), 2.15 (s, 17-$MeCO_2$), 2.02 (s, 3-$MeCO_2$), 1.07 (s, 13-Me), and 0.72 (s, 10-Me) (Found: $M^{+\cdot}$ − CH_3CO_2H 482.2657. $C_{31}H_{42}O_8$ requires *M* − CH_3CO_2H 482.2668). It reacted with diazomethane to afford the *methyl ester* (**19**), m.p. 137—139 °C (ethanol), $[\alpha]_D$ −137° (*c*, 2.0); $\nu_{max.}$ 1 735 (AcO and CO_2Me) and 1 720 cm^{-1} (16-C=O); δ 7.31 and 6.9 (d, *J ca.* 9 Hz, $MeOC_6H_4$), 5.83 (s, $MeOC_6H_4CH$),

4.6 (m, 3-H), 3.8 (s, $MeOC_6H_4$), 3.56 (s, CO_2Me), 2.3 (br s, 15-CH_2), 2.15 (s, 17-$MeCO_2$), 1.99 (s, 3-$MeCO_2$), 1.05 (s, 13-Me), and 0.71 (s, 10-Me) (Found: $M^{+\bullet} - C_{10}H_{11}O_3$, 377.2323; C, 68.9; H, 8.0. $C_{32}H_{44}O_8$ requires $M - C_{10}H_{11}O_3$; 377.2328; C, 69.05; H, 7.95%).

The less polar acid (0.12 g), m.p. 75—80 °C; $\nu_{max.}$ 3 600—2 500 (CO_2H), 1 730 (AcO), 1 710 (16-C=O) and 1 700 cm^{-1} (CO_2H); δ 8.5 (br s, CO_2H, exchangeable with D_2O), 7.3 and 6.9 (d, *J ca.* 8 Hz, $MeOC_6H_4$), 5.95 (s, $MeOC_6H_4CH$), 4.65 (m, 3-H), 3.8 (s, MeO), 2.3 (br s, 15-CH_2), 2.14 (s, 17-$MeCO_2$), 2.00 (s, 3-$MeCO_2$), 1.0 (s, 13-Me), and 0.76 (s, 10-Me) (Found: $M^+ - CH_3CO_2H$, 482.2660. $C_{31}H_{42}O_8$ requires $M - CH_3CO_2H$, 482.2668). It reacted with diazomethane to give an oil which was purified by preparative t.l.c., eluting with light petroleum (b.p. 60—80 °C)–ether (1:1), and gave the *methyl ester* (**19**), a low melting solid, $[\alpha]_D$ + 52° (*c*, 2.0); $\nu_{max.}$ 1 735 (AcO and CO_2Me) and 1 720 (16-C=O), δ 7.3 and 6.89 (d, *J ca.* 8 Hz, $MeOC_6H_4$), 5.87 (s, $MeOC_6H_4CH$), 4.65 (m, 3-H), 3.81 (s, $MeOC_6H_5$), 3.38 (s, CO_2Me), 2.3 (br s, 15-CH_2), 2.15 (s, 17-$MeCO_2$), 2.01 (s, 3-$MeCO_2$), 1.0 (s, 13-Me), and 0.76 (s, 10-Me) (Found: $M^{+\bullet} - C_{10}H_{11}O_3$, 377.2336. $C_{32}H_{44}O_8$ requires $M - C_{10}H_{11}O_3$, 371.2328).

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