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METAL SALT OXIDATIONS OF STEROID OLEFINS

REACTION OF 17-METHYLENE-5α-ANDROSTAN-3β-YL ACETATE WITH LEAD(IV), THALLIUM(III) AND MERCURY(II) ACETATES IN METHANOL

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Abstract—Oxidative rearrangements during the title reaction give **2**, **3** and **4** when lead(IV) acetate is used. The major products from thallium(III) oxidation are the allylic ethers **5**, **6** and **7**. Oxymercuration-demercuration followed by acetylation gives **8** and **10** in addition to the 'normal' compound **9**. The general rules previously developed for the metal salt oxidation of simple olefins depend on the nature of the substrate.

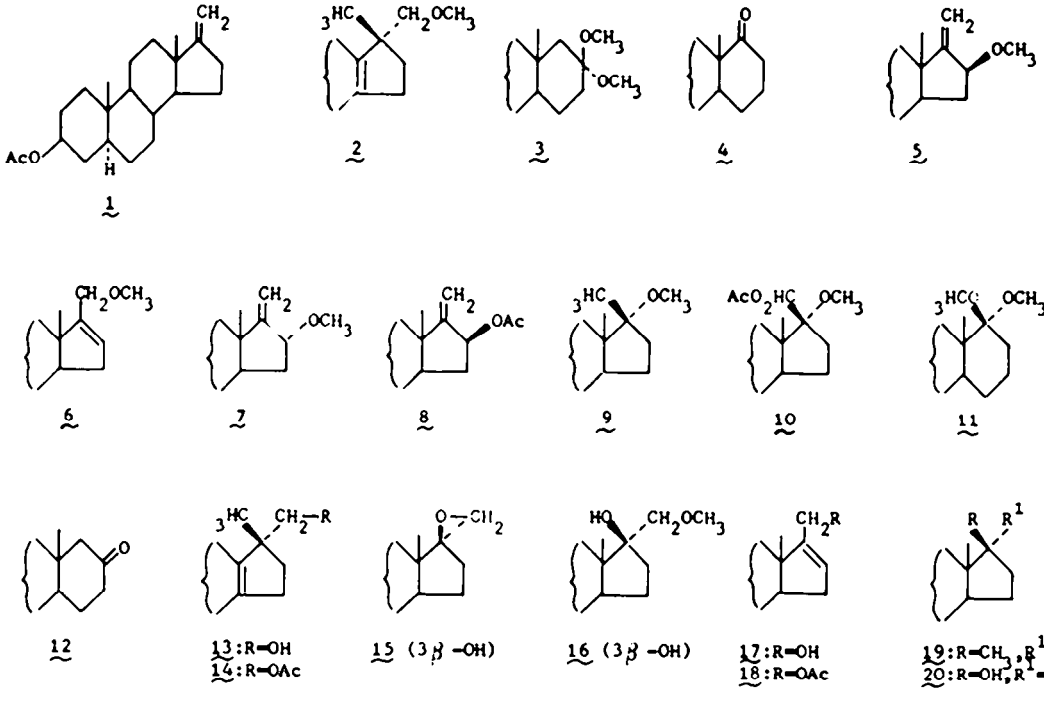
Recent reports by Lethbridge, Norman and Thomas on the reactions of simple olefins with lead(IV), thallium(III) and mercury(II) acetates[1] have prompted us to extend their study to the oxidation of a steroidal exocyclic olefin, as part of our work on the applications of oxymetalation reactions in the steroid field.[2] The 17-methylene-5α-androstan-3β-yl acetate **1**[3] was employed as model substrate, since rearranged products should be obtained (e.g. 13-Me shifts, ring enlargements) and this would provide more mechanistic information.

†This was found to be the optimum ratio in order to avoid incomplete oxidation without increasing substantially over-oxidation. To the same end was the amount of MeOH reduced to a third in the case of Tl(III) oxidation. Disappearance of starting material was monitored by TLC.

RESULTS AND DISCUSSION

The reactions were carried out in methanol at 60° in a steroid-metal ratio 1:3.† The lead(IV) and thallium(III) oxidations were worked up in the usual way (see Experimental) while in the case of the mercury(II), the crude product obtained was reduced with alkaline sodium borohydride and then acetylated before analysis.

$Pb(OAc)_4$ oxidation of **1** gave 17α - methoxymethyl - 17β - methyl - 18 - nor - 5α - androst - 13 - en - 3β - yl acetate **2**, D - homo - 17,17 - dimethoxy - 5α - androstan - 3β - yl acetate **3**, and D - homo - 17a - oxo - 5α - androstan - 3β - yl acetate **4**.[4] Compound **3** surprisingly survived work-up suggesting it to be more resistant to hydrolysis than **11** (which may be assumed as the precursor of **4**) was converted to the corresponding ketone **12** by shaking for an extended time with aqueous acetic acid. The structure



of the ether **2** was inferred from analytical data, the presence of a tetrasubstituted double bond (no vinyl proton in the NMR spectrum), and the appearance of a two proton singlet due to the methylene protons of the methoxymethyl group.† Attempts to cleave the ether function of **2** with BF_3 etherate $-Ac_2O$' to give the diacetate **14**[6] failed and resulted both in recovery of starting material and in formation of olefins. On the other hand methylation of the alcohol **13** in all cases gave complex mixtures. Finally the reaction of the 17β-spiro oxiran **15**[6] with sodium methoxide in refluxing methanol gave the C-20 methoxy-derivative **16** which by treatment with formic acid (and then hydrolysis) was converted to the C-3 hydroxyderivative of **2** in good yield.

Tl(OAc)$_3$ oxidation of **1** gave 17 - methylene - 16β - methoxy - 5α - androstan - 3β - yl acetate **5**, 17 - methoxymethyl - 5α - androst - 16 - en - 3β - yl acetate **6**, and 17 - methylene - 16α - methoxy - 5α - androstan - 3β - yl acetate **7** together with minor amounts of 17 - methylene - 3β,16β - dihydroxy - 5α - androstane 3,16-diacetate **8**[2d] and of D-homoderivative **4**. The structure of the epimers **5** and **7** was deduced on the basis of analytical and spectral data. In addition, both **5** and **7** afforded, on treatment with BF_3 etherate and Ac_2O' and then ozonolysis,[2d] a mixture of the two epimeric 16-acetoxyderivatives of epiandrosterone acetate.[7] The relative orientation of the 16-OMe group was assigned from the examination of the position of 13-Me and of both the position and pattern of 16-proton in the NMR spectra according to the observations of MacKellar and Slomp.[8] An authentic sample of **6** was prepared by methylation[9] of the corresponding alcohol **17** obtained in turn by selective hydrolysis of the diacetate **18**[2d] at C-20.

Finally, oxymercuration of **1**, followed by $NaBH_4$ reduction in alkaline medium and acetylation resulted, in addition to the regeneration of the starting olefin, in the formation of 17α - methoxy - 17β - methyl - 5α - androstan - 3β - yl acetate **9**, 16β-acetoxyderivative **8**,[2d] and 17β - acetoxymethyl - 17α - methoxy - 5α - androstan - 3β - yl acetate **10**. The ether **9** was oxidised with ruthenium tetroxide in carbon tetrachloride.[9] The crude formate obtained was hydrolysed and then re-acetylated at C-3 to give 17β - methyl - 5α - androstan - 3β,17α - diol 3-acetate **19**, distinctly different from the C-17 epimer **20**.[10] This proved the stereochemistry at the C-17 position of **9**. Structure assignment for **10** was made on the basis of elemental analysis and the appearance of an AB quartet centred at δ 4.19 (J = 13 Hz), due to the 17-$\underline{CH_2}$OAc group isolated from spin-spin interaction with other protons. The configuration at C-17 was expected to be the same as in **9** according to the proposed reaction mechanism (see below).

The results of the three oxidations are summarised in the Table 1.

The same order of reactivity as noted in Table 1 has been observed for oct-1-ene[4] and similar explanations may be given to account for it.

Turning next to the products of reaction, the Hg(II) oxidation offers no simple situation. The regeneration of such a large amount of the starting olefin **1** according to the scheme proposed by German workers[11] is unusual, in view especially of the low MeO- leaving-group ability, but we are unable to offer an alternative explanation. Compounds **8** and **10** which occur in addition to the 'normal' product **9** could have resulted from solvolysis of mercurial adducts or from oxygen trapping of intermediate radicals,[12] during the reduction step. Since no appreciable amount of **10** was observed on carrying out the reduction step in the absence of oxygen while the other products were still present, the latter process should be the more effective for **10**. Additional support for this seems to be provided by the fact that the product ratio of **9**:**10** was significantly affected by substituting $NaBD_4$ for $NaBH_4$, as shown in Table 1. A control experiment involving stirring the mercurial adducts without $NaBH_4$ in basic medium open to the air did not produce any detectable amount of mercury or metal-free steroids. The most plausible mechanism for **8** should be therefore an electrophilically-promoted decomposition by attack on the mercury atom of a suitable allylic mercurial before the reduction step (Treibs reaction;[13] see later). Since only mercurial adducts are shown on TLC before $NaBH_4$ treatment, we assume that **8** undergoes further electrophilic attack by Hg(II). In fact, when **8** was reacted with $Hg(OAc)_2$ in MeOH for 10 min the NMR spectrum of the residue showed no 17-methylene proton signals, but reduction with alkaline $NaBH_4$ and then acetylation regenerated **8** quantitatively.

†Methylene protons of the C-CH_2OR type are known to appear as quartets, doublets, or even singlets, depending on their conformation and on the nature of substituents and neighbouring groups (e.g. A. Gaudemer, J. Polonsky and E. Wenkert, *Bull. Soc. Chim. Fr* 407 (1964)).

Table 1. Oxidation of **1** by Pb(IV), Tl(III) and Hg(II) acetates in MeOH

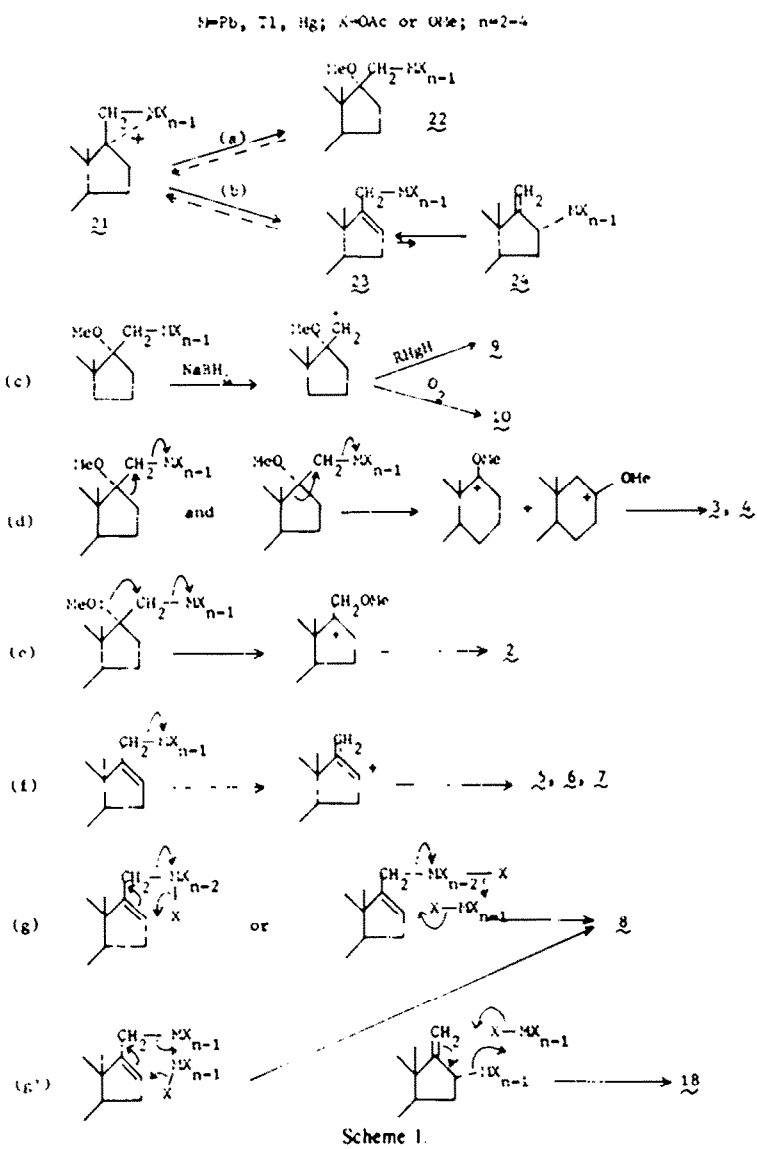
Oxidant	Reaction time (h) [a]		Products (%) [b]										
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Pb(IV)	0.15		-	10	7	50	-	-	-	-	-	-	
Tl(III)	2		-	-	-	2	9	17	14.5	6	-	-	29[c]
Hg(II)	0.15	Reduction with $NaBH_4$	17.5	-	-	-	-	-	-	19	27	14.5	
		Reduction with $NaBD_4$	12	-	-	-	-	-	-	16[d]	8[d]	38	

[a] The time required for the disappearance of **1** (TLC) was 1 min and 4 min for Hg and Pb, respectively; the two oxidations were therefore allowed to proceed for the same time period (10 min).

[b] Percentages calculated from weights of pure chromatographic fractions. Although conversion of **1** is quantitative, the isolated yields of pure compounds are in most cases low. Careful chromatography was required at the expense of yield in order to obtain pure fractions.

[c] Over-oxidised polar material. Longer reaction time caused in fact the yields of **5**, **6** and **7** to fall to the advantage of this material, which appeared on TLC to be a complex mixture and was therefore not further examined.

[d] Yields of deuterated products.



Scheme 1.

The oxidation of **1** by the three metal acetates can be best summarised by Scheme 1.

Whether electrophilic attack by metal on the double bond takes place from the α-side and then *cis*-opening by a MeOH molecule or, alternatively, from the β-side and then *trans*-opening is a moot point. In fact the "rule of α-attack" has been shown need not apply to exocyclic double bonds.[14] From inspection of Dreiding models it appears that 17-methylenes are not subject to considerable steric interference by 13-Me with β-attack.† Solvent attack at the β-carbon atom of the cationic intermediate **21** competes with the abstraction of a proton. The former is the major process for lead. Decomposition of the adduct occurs via paths (d) and (e). The ratio of **4** to **3** is near to that found for the Tiffeneau-Demyanov homologation procedure on epiandrosterone acetate,[1] providing another instance of preferred migration of C-16, reasons for which are still not clear. Anchimeric assistance by the methoxy substituent leads to **2**. In the case of thallium the olefin reacts mainly by loss of a proton. The allylic organothallium derivative **23** undergoes the dethallation reaction via a mesomeric carbonium ion (route f) together with an S_Ni'-type Tl-promoted decomposition (route g). This situation has analogy in the oxidation of some diterpenic exocyclic olefins by thallium(III) nitrate.[15] Finally, an intermediate behaviour is exhibited by Hg(II), resulting in the conversion of **21**, to a small extent, into **22**, **23**, and **24**.‡ Reduction of **22** according to route (c) gives **9** and **10**, while S_Ni'-type decomposition of **23** (and **24**) affords **8** (and **18**) [route (g')].

The relative importance of the two processes (a) and (b) is more difficult to unravel. One outstanding point is the discrepancy with Winstein's report[19] that the tendency toward allylic oxidation of cyclohexene in acetic acid solvent increases in the series Tl(III), Pb(IV), Hg(II). Marked effects of change of the substrate on the course of the oxidation are evident. We can only suggest that both the extent and the stabilisation[20] of the positive charge on the 17-carbon atom of the carbonium-like ion **21** should be of critical importance in affecting the balance between the nucleophilic attack by solvent and the abstraction by base of a C-16 proton.

†On the other hand both epoxidation with peracids[11] and hydroxylation with OsO_4[18] of 17-methylenederivatives occur from the α-direction.

‡Compound **8** is, in fact, contaminated by some **18**,[24] see Ref. 13.

EXPERIMENTAL

M.ps are uncorrected. Optical rotations were measured in $CHCl_3$. IR spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer in $CHCl_3$ soln. NMR spectra were measured for $CDCl_3$ soln. with a Jeol C-60 HL spectrometer (using TMS as internal standard); chemical shifts are given in δ values. Preparative layer chromatography (PLC) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick). Neutral Woelm alumina (grade II) was used for column chromatography. Thallium triacetate was prepared by the method of Kochi and Bethea.[21] Lead tetra-acetate and mercuric acetate were purchased from Merck AG.

General procedure for oxidation of **1**

A solution of **1** (1.10 g, 3.3 mmol) and of the metal oxidant (10 mmol) in methanol [60 ml for Pb(IV) and Hg(II), 20 ml for Tl(III)] was heated with stirring at 60°. The products of the lead and thallium oxidations were poured into water, the mixture was extracted with ether,† and the extracts were washed to neutrality, dried (Na_2SO_4), and evaporated. In the case of mercury oxidation the crude mercuration product was stripped of solvent and to the residue, suspended in 200 ml of dioxan, 10% NaOH (66 ml) was added followed by 1.26 g of solid $NaBH_4$ portionwise. The reduction mixture was stirred at room temperature for 48 h, filtered and the filtrate acidified with dilute hydrochloric acid and extracted with ethyl acetate. Work-up of the extract afforded a residue (0.99 g) which was directly acetylated (Ac_2O-pyridine).

$Pb(OAc)_4$ oxidation of **1**

The residue from the ethereal extract (1.18 g) was chromatographed on alumina (60 g). Elution with benzene-n. hexane (1:1) gave: (i) 0.11 g [after further purification on silica (PLC) (elution with benzene-ether 95:5)] of 17α - methoxymethyl - 17β - methyl - 18 - nor - 5α - androst - 13 - en - 3β - yl acetate **2** as an oil, NMR: 0.81 (3H, s, 10-Me), 0.97 (3H, s, 17β-Me), 2.00 (3H, s, 3β-OAc), 3.11 (2H, s, CH_2OCH_3), 3.29 (3H, s, OMe), and 4.7 (1H, m, 3α-H). Saponification of **2** with 5% methanolic NaOH afforded the 3β-hydroxyderivative, m.p. 99.5–101° (from light-petroleum, b.p. 40–60°); $[\alpha]_D$ -19° (c 1.0); NMR 0.79 (3H, s, 10-Me), 0.97 (3H, s, 17β-Me), 3.13 (2H, s, CH_2OCH_3), 3.31 (3H, s, OMe) and 3.6 (1H, m, 3α-H). (Found: C, 79.09; H, 10.73. Calcd. for $C_{21}H_{36}O_2$: C, 79.19; H, 10.76%). (ii) 65 mg [after further purification on silica (PLC) (elution with benzene-ether 95:5)] of D - homo - 17,17 - dimethoxy - 5α - androstan - 3β - yl acetate **3**, m.p. 162.5–164.5° (from n-hexane).‡ $[\alpha]_D$ -5° (c 1.0); NMR: 0.82 (3H, s, 10-Me), 0.94 (3H, s, 13-Me), 2.02 (3H, s, 3β-OAc), 3.12 and 3.15 (6H, 2s, gem OCH_3) and 4.7 (1H, m, 3α-H). (Found: C, 73.43; H, 10.27. Calcd. for $C_{24}H_{40}O_4$: C, 73.18; H, 10.16%). By shaking an ethereal solution of **3** with dilute acetic acid (1:1), the D - homo - 17 - oxo - 5α - androstan - 3β - yl acetate **12** was obtained, m.p. 152–4° (from n-hexane); $[\alpha]_D$ -67.5° (c 1.0) identical with a sample obtained in a classical fashion from epiandrosterone acetate, according to Engel and Ruest.[4]§

Elution with benzene gave 0.55 g of D - homo - 17a - oxo - 5α - androstan - 3β - yl acetate **4**, m.p. 127–127.5° (from MeOH); $[\alpha]_D$ -48° (c 1.0), identical with an authentic sample.[4]

17α-methoxymethyl-5α-androstan-3β,17β diol **16**

0.43 g of 17β-spiro oxiran **15**[5] was refluxed with 15 ml of a 0.87M methanolic sodium methoxide solution for 5 h. Usual work-up gave 0.44 g of **16**, m.p. 155–156° (from acetone-n-hexane); $[\alpha]_D$ +14° (c 1.3); NMR: 0.82 (3H, s, 10-Me), 0.88 (3H, s, 13-Me), 3.10, 3.25, 3.42 and 3.57 (2H, ABq, J = 9 Hz, CH_2OMe), 3.38 (3H, s, OMe) and 3.6 (1H, m, 3α-H). (Found: C, 74.78; H, 10.63. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78%).

Reaction of **16** *with formic acid*

0.25 g of **16** were stirred overnight with 10 ml of HCO_2H at room temperature. A solution of the residue from the ethereal extract (0.24 g) in methanol (10 ml) was refluxed for 45 min with 10 N NaOH (1 ml). The crude product from CH_2Cl_2 extraction (0.20 g) was chromatographed on silica (PLC) [elution with benzene-ethyl acetate (7:3)] giving 92 mg of 3β-hydroxy derivative of **2** in addition to 84 mg of starting material **16**.

$Tl(OAc)_3$ oxidation of **1**

The residue from the ethereal extraction (1.16 g) was chromatographed on alumina (60 g). Elution with benzene-n-hexane (1:1) gave: (i) 96 mg (after further purification by PLC, benzene-ether 95:5 as eluent) of 17 - methylene - 16β - methoxy - 5α - androstan - 3β - yl acetate **5**, m.p. 113.5–114° (from MeOH); $[\alpha]_D$ +37° (c 1.0); NMR: 0.84 (3H, s, 10-Me), 0.90 (3H, s, 13-Me), 2.00 (3H, s, 3β-OAc), 3.32 (3H, s, 16β-OMe), 4.01 (1H, apparent triplet, 16α-H, $J_{16\alpha H,15\alpha H} - J_{16\alpha H,15\beta H} = 6.5$ Hz), 4.7 (1H, m, 3α-H) and 4.86 and 4.96 (2H, broad signals, $C{=}CH_2$). (Found: C, 76.70; H, 9.93. Calcd. for $C_{21}H_{36}O_3$: C, 76.62; H, 10.07%). (ii) 185 mg of 17 - methoxymethyl - 5α - androst - 16 - en - 3β - yl acetate **6**, m.p. 132–134° (from MeOH); $[\alpha]_D$ 0° (c 1.0); NMR: 0.82 (3H, s, 10-Me), 0.87 (3H, s, 13-Me), 2.03 (3H, s, 3β-OAc), 3.31 (3H, s, OMe), 3.95 (2H, broad signal, CH_2OMe), 4.7 (1H, m, 3α-H), and 5.6 (1H, m, C=CH). (Found: C, 76.20; H, 9.99. Calcd. for $C_{21}H_{36}O_3$: C, 76.62; H, 10.07%). (iii) 160 mg of 17 - methylene - 16α - methoxy - 5α - androstan - 3β - yl acetate **7**, m.p. 104–110° (from MeOH); $[\alpha]_D$ -64° (c 1.0); NMR: 0.78 (3H, s, 13-Me), 0.84 (3H, s, 10-Me), 2.00 (3H, s, 3β-OAc), 3.33 (3H, s, 16α-OMe), 4.22 (1H, m, 16β-H, $J_{16\beta H,15\alpha H} = 7$ Hz, $J_{16\beta H,15\beta H} = 2$ Hz), 4.7 (1H, m, 3α-H) and 4.85 and 5.07 (2H, broad signals, $C{=}CH_2$). (Found: C, 76.35; H, 9.91. Calcd. for $C_{21}H_{36}O_3$: C, 76.62; H, 10.07%).

Elution with benzene gave (i) 65 mg [after purification by PLC; benzene-ether (95:5) as eluent] of 17 - methylene - 3β,16β - dihydroxy - 5α - androstane 3,16-diacetate **8**, m.p. 123.5–125° (from MeOH); $[\alpha]_D$ +10° (1.0) identical with an authentic sample;[24] (ii) 25 mg of **4**. Elution with benzene-methanol (9:1) gave 0.32 g of more polar complex mixture.

17 - hydroxymethyl - 5α - androst - 16 - en - 3β - yl acetate **17**

0.22 g of 17 - acetoxymethyl - 5α - androst - 16 - en - 3β - yl acetate **18**[24] in 28 ml of MeOH were stirred at room temp. with a solution of 52 mg of $KHCO_3$ in 2.4 ml of MeOH-H_2O (1:1) for 16 h. The reaction mixture was poured into water and ether extracted. Chromatography of the residue (0.19 g) on silica (PLC) [elution with benzene-ether (9:1)] and extraction of the major band gave **17** (73 mg), m.p. 114–116° (from di-isopropyl ether-n-hexane); $[\alpha]_D$ 0° (c 1.30); NMR: 0.83 (3H, s, 10-Me), 0.87 (3H, s, 13-Me), 2.01 (3H, s, 3β-OAc), 4.20 (2H, broad signal, CH_2OH), 4.7 (1H, m, 3α-H) and 5.7 (1H, m, C=CH). (Found: C, 76.27; H, 10.00. Calcd. for $C_{22}H_{36}O_3$: C, 76.26; H, 9.89%).

Methylation of **17** (70 mg) with potassium metal (35 mg) and methyl iodide (1.2 ml) in refluxing dry benzene (10 ml) according to Narayanan and Iyer[3] gave a residue (70 mg) which by chromatography on silica (PLC) [elution with benzene-ether (99:1)] gave the methoxyderivative **6** (16 mg) as the major component.

$Hg(OAc)_2$ oxidation of **1**

The residue from the acetylation procedure (1.10 g) was chromatographed on silica (PLC) [elution with benzene-ether (95:5)] to give four main bands.

Band I was identified as the starting material **1** (0.19 g). Band II: 17α - methoxy - 17β - methyl - 5α - androstan - 3β - yl acetate **9** (0.29 g), m.p. 94–94.5° (from MeOH); $[\alpha]_D$ -24° (c 1.0); NMR: 0.67 (3H, s, 13-Me), 0.83 (3H, s, 10-Me), 1.08 (3H, s, 17β-Me), 2.01 (3H, s, 3β-OAc), 3.13 (3H, s, 17α-OCH_3) and 4.7 (1H, m, 3α-H). (Found: C, 76.08; H, 10.56. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%). Band III: was identified as the 16β-acetoxyderivative **8**[24] (0.21 g). Band IV: 17β - acetoxymethyl - 17α - methoxy - 5α - androstan - 3β - yl acetate **10** (0.16 g), m.p. 178–179° (from MeOH); $[\alpha]_D$ -19° (c 1.0); NMR 0.77 (3H, s, 13-Me), 0.83 (3H, s, 10-Me), 2.02 (3H, s, 3β-OAc), 2.07 (3H, s, CH_2OAc), 3.17 (3H, s, 17α-OMe), 3.85, 4.06, 4.32 and 4.52 (2H, ABq, J = 13 Hz,

†In the case of Tl, the extraction was troublesome owing to the large amount of Tl_2O_3 precipitated. Alternatively MeOH was evaporated to dryness, and the residue extracted with ether.

‡Sample inserted into oil-bath at 155°.

§These authors report quite different values for m.p. and $[\alpha]_D$ of **12**; spectral data (NMR and IR values) agree with ours.

CH_2OAc) and 4.7 (3α-H). (Found: C, 71.39; H, 9.60. Calcd. for $C_{23}H_{36}O_3$: C, 71.39; H, 9.59%).

Oxidation of **9** *with ruthenium tetroxide*

Ether **9** (89 mg) in 18 ml CCl_4 was oxidised with 123 mg of RuO_4 (molar ratio 3:1) at room temperature, according to the procedure of Berkowitz and Rylander.[22] The reaction product (71 mg) was directly saponified with 5% methanolic KOH and then re-acetylated (Ac_2O-pyridine) to give, after PLC [benzene–ether (9:1)], 63 mg of 17β - methyl - 3β,17α - dihydroxy - 5α - androstane 3-acetate **19**, m.p. 152.5–153° (from MeOH); $[\alpha]_D$ −18.6° (c 1.76); NMR: 0.67 (3H, s, 13-Me), 0.84 (3H, s, 10-Me), 1.18 (3H, s, 17β-Me), 2.02 (3H, s, 3β-OAc) and 4.7 (1H, m, 3α-H). (Found: C, 75.73; H, 10.32. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41%). 17-Epimer **20**: m.p. 146–147° (from n-hexane), $[\alpha]_D$ −19.3° (c 1.75); NMR: 0.85 (6H, s, 13-Me and 10-Me), 1.21 (3H, s, 17α-Me), 2.01 (3H, s, 3β-OAc) and 4.7 (1H, m, 3α-H).

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