THE PREPARATION OF SOME 13α-ANDROSTANES

James R. HANSON[1], A. Christy HUNTER and Sandrine ROQUIER

School of Chemistry, Physics and Environmental Science, University of Sussex, Brighton, Sussex, BN1 9QJ, England; e-mail: [1] j.r.hanson@sussex.ac.uk

Received April 14, 1998
Accepted May 18, 1998

Dedicated to Dr Jan Fajkos on the occasion of his 75th birthday and in recognition of his outstanding contributions to steroid chemistry.

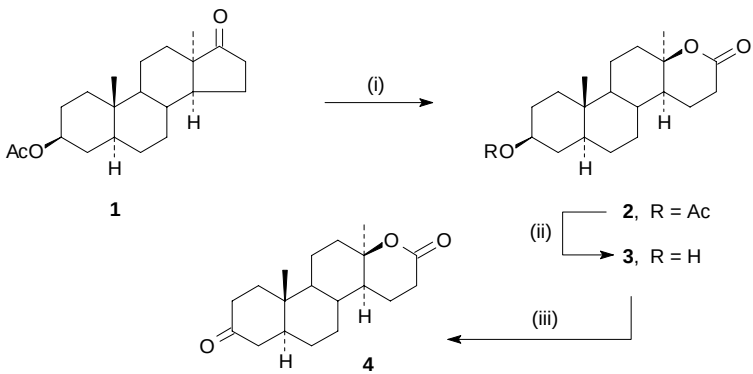
The preparation of 17a-oxa-5α,13α-androstane-3,17-dione, 5α,13α-androstane-3,7,17-trione, 4-chloro- and 4-hydroxy-13α-androst-4-ene-3,17-dione and 13α-androst-4-ene-3,6,17-trione is described.
Key words: Steroids; Steroidal lactones; 13α-Androstanes; ^{13}C NMR spectroscopy; Aromatase inhibitors.

The isomerization of steroids at C-13 to form the 13α-androstanes[1] has the effect of substantially distorting the relatively planar steroidal geometry of the 5α,13β-androstanes and of altering the relative position of the 17-carbonyl compared to the 3-oxygen function. Receptor-binding studies have suggested that for androgenic activity, a ring D binding/ring A acting model encompasses many structure–activity relationships[2]. Not suprisingly therefore isomerization at C-13 can alter the pharmacological profile[3] and metabolism of these compounds[4]. Thus microbiological hydroxylation of 5α,13α-androstane-3,17-dione by *Cephalosporium aphidicola* took place at the C-1α and C-7α positions whereas the corresponding compounds in the normal 13β-androstane series were hydroxylated at the C-11α and C-14α positions[4]. The chemical aspects of this biotransformation study in the 13α-androstane series and some related work to prepare compounds for evaluation of their biological activity, form the subject of this paper.

The 13α-androstanes required for this work were prepared by treatment of the 17-oximes with refluxing acetic anhydride in pyridine[5]. This afforded the 17-acetylamino-16-enes with the more stable *cis* C/D ring junction. Hydrolysis of the enamides afforded the 17-ketones. Thus 3β-hydroxy-5α-androstan-17-one and 3β-hydroxyandrost-5-en-17-one were converted *via* 17-acetylamino-5α,13α-androst-16-en-3β-yl acetate and 17-acetylamino-13α-androsta-5,16-dien-3β-yl acetate to 17-oxo-5α,13α-androstan-3β-yl acetate (**1**) and 17-oxo-13α-androst-5-en-3β-yl acetate[6] (**6**) which formed the starting materials for these studies.

Ring D δ-lactones are known metabolites[7] of androstane 17-ketones and consequently we prepared the 13α-androstane analogues in order to obtain authentic samples

for our biotransformation studies[4]. The effect of the inversion at C-13 was revealed by the rate of the Baeyer–Villiger oxidation of the C-17 ketone, 17-oxo-5α,13α-androstan-3β-yl acetate (**1**). This reaction (see Scheme 1) proceeded more slowly and in much poorer yield when compared to the normal series, to give 17-oxo-17a-oxa-17a-homo-5α,13α-androstan-3β-yl acetate (**2**). In the 13α-androstanes, C-17 becomes an axial substituent on ring C and consequently the tetrahedral intermediate in the Baeyer–Villiger oxidation suffers more severe diaxial steric interactions than would be the case in the normal 13β-androstane series. However the rearrangement had proceeded as in the normal series[8,9] to give the 17a-oxa steroid. The ^{1}H NMR signal assigned to the 13α-methyl group showed a significant downfield shift to δ 1.38 whilst the ^{13}C NMR signal assigned to C-13 had shifted downfield to 82.4 ppm (see Table I). The 3β-acetate **2** was selectively hydrolyzed with aqueous methanolic potassium carbonate and the resultant 3-alcohol **3** was oxidized with chromium trioxide to form the 3-ketone **4**.



(i) 3-ClC$_6$H$_4$CO$_3$H, TosOH.H$_2$O/CH$_2$Cl$_2$; (ii) K$_2$CO$_3$/H$_2$O, MeOH; (iii) Jones reagent/acetone

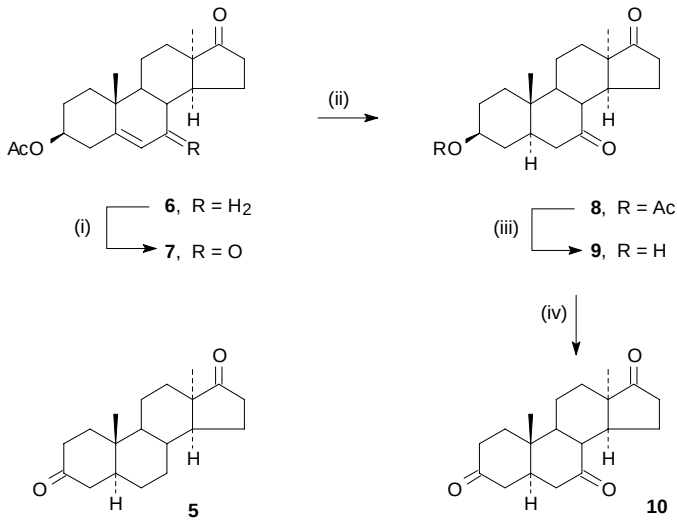
SCHEME 1

In the course of the biotransformation experiments with 5α,13α-androstane-3,17-dione[4] (**5**), oxidation took place at C-7 and consequently authentic 5α,13α-androstane-3,7,17-trione (**10**) was required for comparison purposes. Allylic oxidation (see Scheme 2) of 17-oxo-13α-androst-5-en-3β-yl acetate (**6**) with *tert*-butyl chromate afforded the 7-ketone **7** [^{13}C NMR: 164.3 (C-5); 126.1 (C-6); 199.7 (C-7)]. Hydrogenation of this unsaturated ketone over palladium on charcoal proceeded from the α-face to give 7,17-dioxo-5α,13α-androstan-3β-yl acetate (**8**). The *trans* A/B stereochemistry followed from the multiplicity of the 3α-hydrogen resonance (δ 4.67) which was a triplet (J = 11.2 Hz) of triplets (J = 4.7 Hz) characteristic of an axial proton at C-3. Hydrolysis of the 3β-acetate and oxidation of the resultant 3β-alcohol **9** with chromium trioxide afforded 5α,13α-androstane-3,7,17-trione (**10**). This was identical to the material that had been obtained previously in the biotransformation[4].

TABLE I
^{13}C NMR data for 13α-androstanes (in $CDCl_3$)

Carbon	**2**	**7**	**8**	**9**	**10**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	33.7	35.7	33.5	33.5	36.6	35.4	34.1	32.6	34.4	34.1	31.6	35.3
2	27.3	27.0	26.8	30.8	37.2	33.7	33.6	25.8	31.7	30.8	37.1	33.4
3	72.5	77.5	72.6	70.5	208.5	199.5	190.6	206.7	193.6	69.2	210.6	199.1
4	36.6	38.3	33.6	37.7	43.7	123.9	127.3	62.6	141.1	41.8	44.2	125.6
5	43.3	164.3	42.2	42.1	41.8	170.4	163.9	70.0	139.1	62.5	82.3	159.8
6	28.2	126.1	45.6	45.8	45.2	32.8	29.0	29.6	23.1	63.3	211.4	201.1
7	30.8	199.7	207.5	209.9	209.2	32.7	31.8	31.2	31.8	36.7	42.3	46.8
8	33.0	42.5	45.2	45.6	46.5	38.0	37.6	37.2	37.7	31.8	39.5	36.2
9	52.2	45.7	53.1	53.3	52.2	51.4	51.7	43.9	51.9	49.0	42.9	48.7
10	35.6	37.7	35.8	35.9	35.7	38.6	41.4	37.4	37.8	35.2	41.9	39.6
11	17.3	23.0	23.5	23.5	23.3	21.5	21.4	21.3	21.5	21.9	20.8	21.2
12	38.7	31.1	31.3	31.4	31.1	31.7	31.7	31.7	31.6	31.7	31.7	31.2
13	82.4	48.4	49.5	49.5	49.3	49.9	49.9	50.0	49.9	49.8	50.7	50.0
14	43.8	49.7	51.3	51.3	50.8	49.8	49.8	50.0	50.0	49.3	50.5	50.7
15	20.4	24.2	23.6	23.7	23.9	22.6	22.7	22.8	22.6	23.6	22.9	22.3
16	24.9	33.7	35.6	35.9	33.3	33.8	33.8	33.5	33.8	33.8	33.4	33.8
17	172.1	222.4	222.0	222.0	221.6	221.3	221.5	221.4	221.3	222.0	221.4	220.4
18	28.8	24.8	24.8	24.8	24.6	25.0	25.0	25.1	25.1	25.2	24.9	24.8
19	12.1	17.0	11.5	11.6	10.7	17.5	17.9	18.6	17.3	16.6	13.6	17.6
OAc (**C**H_3)	21.4	21.2	21.3	–	–	–	–	–	–	–	–	–
OAc(**C**=O)	170.7	170.2	170.5	–	–	–	–	–	–	–	–	–

The enzyme system, aromatase, mediates the conversion of androgens such as androst-4-ene-3,17-dione to estrogens such as estrone. The inhibition of aromatase is an important target in the chemotherapy of estrogen-dependent breast cancers[10]. Some analogues of the natural substrate such as 4-hydroxyandrost-4-ene-3,17-dione (Formestane®) are in clinical use as aromatase inhibitors[11–13]. An aspect of the design of novel inhibitors involves distinguishing between the factors that contribute to the action of aromatase and those structural features that are responsible for particular steroid effects. Studies on the inhibition of aromatase have shown that provided the ring remained intact, deletion of the C-17 substituent had relatively little effect on the inhibition of aromatase[14]. Consequently the preparation of 13α-androstanes incorporating the functionality of known aromatase inhibitors but possessing a different orientation of ring D relative to ring A was an attractive target.



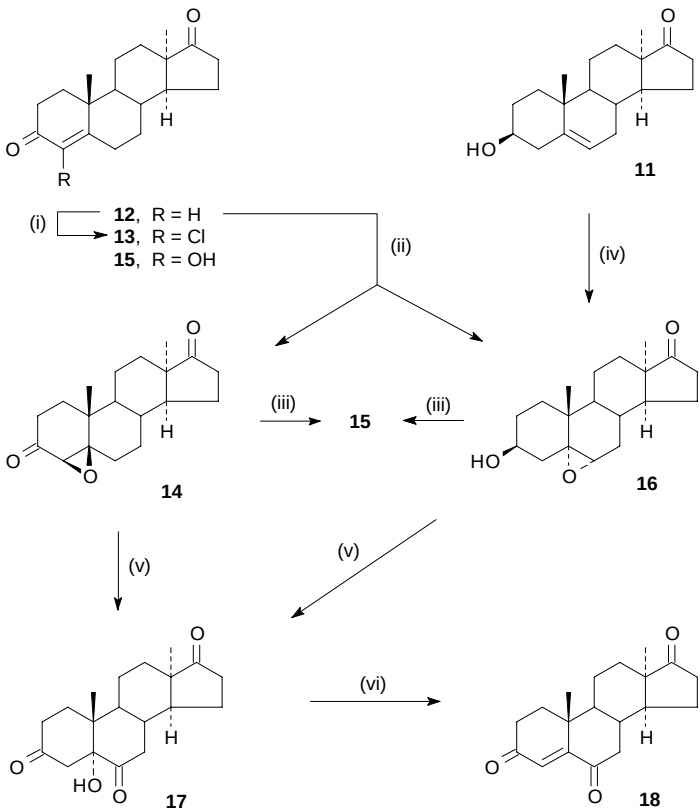
(i) *tert*-butyl chromate/AcOH, Ac_2O; (ii) H_2, Pd-C/ethyl acetate;
(iii) K_2CO_3/H_2O, MeOH; (iv) Jones reagent/acetone

SCHEME 2

13α-Androst-4-ene-3,17-dione (**12**) was obtained by the Oppenauer oxidation[6] of 3β-hydroxy-13α-androst-5-en-17-one (**11**). Treatment of this unsaturated ketone with sulfuryl chloride in pyridine (see Scheme 3) gave 4-chloro-13α-androst-4-ene-3,17-dione (**13**). This was characterized by the loss of the H-4 resonance in the ^1H NMR spectrum. Epoxidation of 13α-androst-4-ene-3,17-dione (**12**) with alkaline hydrogen peroxide gave a 1 : 3.5 mixture of the 4α,5α- and 4β,5β-epoxides. The major epoxide **14**, which was assigned the 4β,5β-stereochemistry by analogy with the normal series[15], was obtained pure by recrystallization. The mixture of epoxides underwent rearrangement

with formic acid to afford the 13α-androstane analogue of Formestane®, 4-hydroxy-13α-androst-4-ene-3,17-dione (**15**).

Epoxidation of 3β-hydroxy-13α-androst-5-en-17-one (**11**) with 3-chloroperoxybenzoic acid gave a 5 : 1 mixture of 5α,6α- and 5β,6β-epoxides from which the major epoxide **16** was readily isolated. The stereochemistry of the epoxides were assigned by comparison of the positions of the H-6 ^{1}H NMR signals (δ 2.92, 5α,6α-epoxide; δ 3.07, 5β,6β-epoxide) with those of the normal series[16] (δ 2.87, 5α,6α-epoxide; δ 3.07, 5β,6β-epoxide). Oxidation of the mixture of epoxides gave ketol **17** which was dehydrated with thionyl chloride in pyridine to give 13α-androst-4-ene-3,6,17-trione (**18**). This is a 13α-androstane analogue of a known aromatase inhibitor[17]. As expected the H-4 resonance showed a significant downfield shift (δ 5.81 to 6.19) compared to the 6-deoxy series.



(i) $SOCl_2$/pyridine; (ii) H_2O_2, NaOH/H_2O, MeOH; (iii) HCOOH, reflux;
(iv) 3-$ClC_6H_4CO_3H$/$CHCl_3$; (v) CrO_3/H_2O, butan-2-one; (vi) $SOCl_2$/pyridine

SCHEME 3

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Extracts were dried over anhydrous sodium sulfate. The purity of products and the course of reactions were followed by thin layer chromatography (TLC) on silica followed by spraying with methanolic sulfuric acid. Column chromatography was performed on silica (Merck 9385). Elution was with increasing concentrations of ethyl acetate in light petroleum (b.p. 60–80 °C). Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Perkin–Elmer 1710 spectrometer as Nujol mulls. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker 300 MHz spectrometer for solutions in deuteriochloroform. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz.

17-Oxo-17a-oxa-17a-homo-5α,13α-androstan-3β-yl Acetate (**2**) and 3β-Hydroxy-17a-oxa-17a-homo-5α,13α-androstan-17-one (**3**)

17-Oxo-5α,13α-androstan-3β-yl acetate[5] (**1**) (1.8 g, 5.4 mmol) in dichloromethane (100 ml) was treated with 3-chloroperoxybenzoic acid (1.2 g, 4.9 mmol) and 4-toluenesulfonic acid monohydrate (300 mg, 1.6 mmol) at room temperature for 5 days (TLC control). The mixture was diluted with dichloromethane (150 ml) and washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave the starting material **1** (649 mg). Further elution with ethyl acetate–light petroleum (15 : 85) gave the lactone **2** (371 mg, 20%) which crystallized from ethyl acetate–light petroleum as needles, m.p. 144–145 °C. IR spectrum: 1 726, 1 709 (C=O). ^1H NMR spectrum: 0.76 s, 3 H (3 × H-19); 1.38 s, 3 H (3 × H-18); 2.02 s, 3 H (OAc); 4.69 tt, 1 H, J = 5, J' = 11 (H-3α). For $C_{21}H_{32}O_4$ (348.5) calculated: 72.38% C, 9.26% H; found: 72.3% C, 9.2% H.

Elution with ethyl acetate–light petroleum (40 : 60) gave lactone **3** (150 mg, 9%) which crystallized from ethyl acetate–light petroleum as fine needles, m.p. 150–151 °C. IR spectrum: 3 222 (O–H); 1 708 (C=O). ^1H NMR spectrum: 0.75 s, 3 H (3 × H-19); 1.37 s, 3 H (3 × H-18); 3.60 tt, 1 H, J = 5, J' = 11 (H-3α). For $C_{19}H_{30}O_3 \cdot H_2O$ (324.5) calculated: 70.33% C, 9.94% H; found: 70.5% C, 9.8% H.

3β-Hydroxy-17a-oxa-17a-homo-5α,13α-androstan-17-one (**3**)

The above acetate **2** (360 mg, 1.1 mmol) in methanol (20 ml) was treated with potassium carbonate (0.4 g, 2.9 mmol) in water (2 ml) for 3 h at room temperature. Acetic acid (0.5 ml) was added and the solution was concentrated *in vacuo*. The concentrate was extracted with ethyl acetate. This extract was washed with aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated to give the compound **3** (270 mg, 81%), m.p. 150–151 °C, identical (IR and NMR) to the material described above.

17a-Oxa-17a-homo-5α,13α-androstane-3,17-dione (**4**)

Hydroxy derivative **3** (400 mg, 1.2 mmol) in acetone (30 ml) was treated with the Jones reagent (2.7 M chromium trioxide in diluted sulfuric acid) until the orange colour persisted. The mixture was stirred for a further 30 min. Methanol was added to destroy the excess reagent and the solution was concentrated *in vacuo* and poured into water. The mixture was extracted with ethyl acetate. The extract was washed with water, aqueous sodium hydrogen carbonate, brine and dried. The solvent was evaporated to give the ketone **4** (370 mg, 99%) which crystallized from ethyl acetate as cubes, m.p. 198–199 °C.

IR spectrum: 1 723, 1 714 (C=O). ^{1}H NMR spectrum: 0.89 s, 3 H (3 × H-19); 1.33 s, 3 H (3 × H-18). For $C_{19}H_{28}O_3$ (304.4) calculated: 74.96% C, 9.27% H; found: 74.8% C, 9.0% H.

7,17-Dioxo-13α-androst-5-en-3β-yl Acetate (**7**)

tert-Butyl chromate was prepared by adding chromium trioxide (3.7 g, 37 mmol) to *tert*-butyl alcohol (9.5 ml) in portions. The solution was diluted with carbon tetrachloride (30 ml). An aqueous phase was separated and the organic phase was dried over sodium sulfate and concentrated to half its volume.

A mixture of the above *tert*-butyl chromate solution (12.5 ml), glacial acetic acid (3 ml) and acetic anhydride (1 ml) was added to a solution of 17-oxo-13α-androst-5-en-3β-yl acetate[6] (**6**) (850 mg, 2.6 mmol) in carbon tetrachloride (8 ml) over 30 min. The mixture was heated under reflux for 6 h and then left to stand overnight. Oxalic acid (2.5 g) in water (20 ml) was added and the mixture was stirred for 4 h. The mixture was then extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (10 : 90) gave the unsaturated ketone **7** (675 mg, 76%) which crystallized from ethyl acetate–light petroleum as needles, m.p. 152–154 °C. IR spectrum: 1 732, 1 713, 1 654 (C=O), 1 626 (C=C). ^{1}H NMR spectrum: 1.03 s, 3 H (3 × H-18); 1.09 s, 3 H (3 × H-19); 2.07 s, 3 H (OAc); 4.72 tt, 1 H, J = 4.9, J' = 11.5 (H-3α); 5.79 d, 1 H, J = 1.6 (H-6). For $C_{21}H_{28}O_4$ (344.5) calculated: 73.23% C, 8.19% H; found: 73.3% C, 8.2% H.

7,17-Dioxo-5α,13α-androst-3β-yl Acetate (**8**)

Compound **7** (590 mg, 1.7 mmol) and 10% palladium on charcoal (300 mg) in ethyl acetate (20 ml) were stirred under an atmosphere of hydrogen for 4 h. The catalyst was filtered off and the solvent evaporated to give the saturated ketone **8** (575 mg, 97%) which crystallized from methanol as needles, m.p. 164–165 °C. IR spectrum: 1 738, 1 704 (C=O). ^{1}H NMR spectrum: 0.96 s, 3 H (3 × H-18); 1.02 s, 3 H (3 × H-19); 2.03 s, 3 H (OAc); 4.67 tt, 1 H, J = 4.7, J' = 11.2 (H-3α). For $C_{21}H_{30}O_4$ (346.5) calculated: 72.80% C, 8.73% H; found: 72.7% C, 8.7% H.

3β-Hydroxy-5α,13α-androstane-7,17-dione (**9**)

The above acetate **8** (500 mg, 1.4 mmol) in methanol (20 ml) was treated with potassium carbonate (1.5 g, 10.8 mmol) in water (7.5 ml) for 1 h at room temperature. Acetic acid (3 ml) was added and the solution was then concentrated before being poured into water. The solution was extracted with ethyl acetate and the extract was washed with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated to give alcohol **9** (330 mg, 71%) which crystallized from ethyl acetate–light petroleum as needles, m.p. 119 °C. IR spectrum: 3 387 (O–H); 1 733, 1 703 (C=O). ^{1}H NMR spectrum: 0.95 s, 3 H (3 × H-18); 1.01 s, 3 H (3 × H-19); 3.64 tt, 1 H, J = 5.0, J' = 11.1 (H-3α). For $C_{19}H_{28}O_3 \cdot H_2O$ (322.4) calculated: 70.77% C, 9.38% H; found: 71.1% C, 9.5% H.

5α,13α-Androstane-3,7,17-trione (**10**)

The alcohol **9** (200 mg, 0.6 mmol) in acetone (10 ml) was treated with the Jones reagent (1 ml) for 30 min. Methanol was added and the solution was concentrated and then diluted with water. The product was recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated to give the trione **10** (120 mg) which crystallized from ethyl acetate–light petroleum as plates, m.p. 163–164 °C. IR spectrum: 1 737, 1 716, 1 697 (C=O). ^{1}H NMR spectrum: 0.96 s, 3 H (3 × H-18); 1.09 s, 3 H (3 × H-19). For $C_{19}H_{26}O_3$ (302.4) calculated: 75.46% C, 8.67% H; found: 74.9% C, 8.7% H.

4-Chloro-13α-androst-4-ene-3,17-dione (**13**)

13α-Androst-4-ene-3,17-dione[6] (**12**; 375 mg, 1.3 mmol) in dry pyridine (4 ml) was treated with sulfuryl chloride (0.4 ml, 5.0 mmol) dropwise. The mixture was stirred at room temperature for 1 h and then poured into dilute hydrochloric acid (75 ml). The product was recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid, water, aqueous potassium carbonate and dried. The solvent was evaporated to afford the chloroketone **13** (214 mg, 51%) which crystallized from ethyl acetate–light petroleum as needles, m.p. 191–194 °C. IR spectrum: 1 725, 1 692 (C=O); 1 580 (C=C). ^{1}H NMR spectrum: 1.00 s, 3 H (3 × H-18); 1.09 s, 3 H (3 × H-19); 3.53 d, 1 H, J = 1.5 (H-6). For $C_{19}H_{25}ClO_2$ (320.9) calculated: 71.12% C, 7.85% H; found: 70.9% C, 7.9% H.

4β,5β-Epoxy-13α-androstane-3,17-dione (**14**)

13α-Androst-4-ene-3,17-dione[6] (**12**; 655 mg, 2.3 mmol) in methanol (20 ml) was cooled in ice and treated dropwise with 4 M aqueous sodium hydroxide (1.6 ml) and 30% hydrogen peroxide (2.6 ml). The mixture was kept overnight in a refrigerator and then poured onto crushed ice (35 ml). The suspension was allowed to attain room temperature and filtered to give a mixture of 4α,5α- and 4β,5β-epoxides (517 mg, 75%; 1 : 3.5 based on NMR signals at 3.0 ppm). Recrystallization of a portion from ethyl acetate–light petroleum gave the 4β,5β-epoxide **14** as needles, m.p. 182–185 °C. IR spectrum: 1 728, 1 703 (C=O). ^{1}H NMR spectrum: 1.00 s, 6 H (3 × H-18 and 3 × H-19); 3.02 s, 1 H (H-4). For $C_{19}H_{26}O_3$ (302.4) calculated: 75.46% C, 8.67% H; found: 75.3% C, 8.7% H.

4-Hydroxy-13α-androst-4-ene-3,17-dione (**15**)

The above mixture of epoxides (168 mg, 0.6 mmol) in formic acid (7 ml) was heated under reflux for 1.5 h and then poured into warm water (50 ml). The solution was cooled and left overnight. The product was recovered in ethyl acetate and the solvent evaporated to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (15 : 85) gave the hydroxyketone **15** (112 mg, 67%) which crystallized from ethyl acetate–light petroleum as needles, m.p. 200–203 °C. IR spectrum: 3 427 (O–H); 1 726, 1 633 (C=O). ^{1}H NMR spectrum: 1.00 s, 3 H (3 × H-18); 1.03 s, 3 H (3 × H-19); 3.0 d, 1 H, J = 14 (H-6); 6.09 s, 1 H (OH). For $C_{19}H_{26}O_3$ (302.4) calculated: 75.46% C, 8.67% H; found: 75.2% C, 8.7% H.

5α,6α-Epoxy-3β-hydroxy-13α-androstan-17-one (**16**)

3β-Hydroxy-13α-androst-5-en-17-one[6] (**11**; 1.5 g, 5.2 mmol) dissolved in chloroform (50 ml) was treated with 3-chloroperoxybenzoic acid (70%; 2.25 g, 9.1 mmol) in portions at 0 °C. The mixture was left to attain room temperature for 3 h. The solution was diluted with chlorofoem, washed with 10% aqueous sodium sulfite, saturated aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated to give a mixture of 5α,6α- and 5β,6β-epoxides (1.5 g, 95%) [5 : 1 based on the ^{1}H NMR signals at δ 2.92 (α-isomer) and 3.10 (β-isomer)]. The 5α,6α-epoxide **16** crystallized from ethyl acetate as needles, m.p. 177–181 °C. IR spectrum: 3 448 (O–H); 1 724 (C=O). ^{1}H NMR spectrum: 0.88 s, 3 H (3 × H-18); 0.93 s, 3 H (3 × H-19); 2.92 d, 1 H, J = 3.5 (H-6); 3.87 tt, 1 H, J = 5, J' = 11 (H-3α).

5α-Hydroxy-13α-androstane-3,6,17-trione (**17**)

Aqueous chromium trioxide (75%, 1.5 ml) was added dropwise to a solution of the above epoxides (1.2 g, 4.0 mmol) in butan-2-one (20 ml) at 35–40 °C. After 40 min the solution was poured into water and the steroids were recovered in ethyl acetate. The extract was washed with aqueous sodium

hydrogen carbonate, water and dried. The solvent was evaporated to afford the hydroxytrione **17** (750 mg, 59%) which crystallized from ethyl acetate as needles, m.p. 235–236 °C. IR spectrum: 3 466 (O–H); 1 734, 1703 (C=O). ^{1}H NMR spectrum: 0.86 s, 3 H (3 × H-18); 1.02 s, 3 H (3 × H-19); 3.67 s, 1 H (OH). For $C_{19}H_{26}O_4$ (318.4) calculated: 71.67% C, 8.23% H; found: 71.4% C, 8.2% H.

13α-Androst-4-ene-3,6,17-trione (**18**)

Thionyl chloride (0.3 ml, 4.1 mmol) was added to dry pyridine (3.75 ml) and the solution was cooled to –20 °C. This solution was added to a solution of the above hydroxytrione **17** (280 mg, 0.9 mmol) in dry pyridine (15 ml) at –20 °C. After 30 min the solution was allowed to warm to room temperature. It was then cooled again to 0 °C and poured into water (50 ml). The product was extracted with ethyl acetate and the extract was washed with dilute hydrochloric acid, water and dried. The solvent was evaporated to afford the unsaturated ketone **18** (170 mg, 64%) which crystallized from ethyl acetate as needles, m.p. 181–182 °C. IR spectrum: 1 729, 1 715, 1 687 (C=O), 1 614 (C=C). ^{1}H NMR spectrum: 1.02 s, 3 H (3 × H-18); 1.05 s, 3 H (3 × H-19); 6.19 s, 1 H (H-4). For $C_{19}H_{24}O_3$ (300.4) calculated: 75.97% C, 8.05% H; found: 75.9% C, 8.0% H.

REFERENCES

1. Butenandt A., Poschmann L.: *Ber. Dtsch. Chem. Ges*. **1944**, *77*, 394.
2. Daux W. L., Ghosh D., Pletner V., Griffin J. F.: *Pure Appl. Chem*. **1996**, *68*, 1297.
3. Neef G., Sauer G., Seeger A., Wiechert R.: *Tetrahedron Lett*. **1984**, *25*, 3425.
4. Boynton J., Hanson J. R., Hunter A. C.: *Phytochemistry* **1997**, *45*, 951.
5. Boar R. B., Jetuah F. K., McGhie J. F., Robinson M. S., Barton D. H. R.: *J. Chem. Soc., Perkin Trans. 1* **1977**, 2163.
6. Bots J. P. L.: *Rec. Trav. Chim. Pays-Bas* **1958**, *77*, 1010.
7. Fried J., Thoma R. W., Klingsberg A.: *J. Am. Chem. Soc*. **1953**, *75*, 5764.
8. Levy H., Jacobsen R. P.: *J. Biol. Chem*. **1947**, *171*, 71.
9. Wendler N. L., Taub D., Slates H. L.: *J. Am. Chem. Soc*. **1955**, *77*, 3559.
10. Brodie A. M., Santen J.: *Breast Cancer Res. Treat*. **1994**, *30*, 1.
11. Dowsett M., Coombes R. C.: *Breast Cancer Res. Treat*. **1994**, *30*, 81.
12. Mann J., Pietrzak B.: *J. Chem. Soc., Perkin Trans. 1* **1983**, 2681.
13. Tavares da Silva E. J., Sae Malo M. L., Campos Neves A. S.: *J. Chem. Soc., Perkin Trans 1* **1996**, 1649.
14. Sherwin P. F., McMullan P. C., Covey D. F.: *J. Med. Chem*. **1989**, *32*, 651.
15. Henbest H. B., Jackson W. R.: *J. Chem. Soc. C* **1967**, 2459.
16. Cross A. D.: *J. Am. Chem. Soc*. **1962**, *84*, 3206.
17. Marsh D. A., Brodie H. J., Garrett W., Tsai-Morris C. H., Brodie A. M. H.: *J. Med. Chem*. **1985**, *28*, 788.