Synthesis of 4-hydroxyestrogens from steroid 4,5-epoxides: thermal rearrangement of 4-chloro-4,5-epoxides

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The synthesis of 4-hydroxyestrone and 4-hydroxyestradiol from estr-4-ene-3,17-dione through the 4,5-epoxyestra-3,17-diones is described. Thermolysis of 4-chloro-4,5-epoxyestra-3,17-diones also gives 4-hydroxyestrone, but in lower yield, together with 4-hydroxyestra-4,6-diene-3,17-dione and the B ring aromatic product, estra-5,7,9-triene-4,17-dione. Structures have been established by NMR methods except for the structure of 4β-chloro-4,5-epoxy-5α-estra-3,17-dione which has been determined by X-ray crystallographic analysis.

Introduction

4-Hydroxyestrone and 4-hydroxyestradiol are metabolites of the female hormones, estrone and estradiol. Studies on the physiological role played by these compounds requires their availability through synthesis. Both compounds have been the subjects of successful chemical syntheses.[1a–g] Treatment of 19-methyl steroid 4-en-3-ones with alkaline hydrogen peroxide is known to yield the β-epoxide as the major isomer with the α : β ratio dependent on long range effects from the C-17 substituent.[2] Similar treatment of estr-4-ene-3,17-dione **1a** also yields the β-epoxide as the major product (α : β = 1 : 9).[3–6] Treatment of progesterone with dimethyldioxirane gave a mixture of the epoxides, however, with this reagent the α-epoxide predominated.[7] This report describes the synthesis of 4-hydroxyestrone and 4-hydroxyestradiol from the 4,5-epoxides of estr-4-ene-3,17-dione and from the thermal rearrangement of the 4-chloro-4,5-epoxyestra-3,17-diones.

Results and discussion

In the present work, treatment of estr-4-ene-3,17-dione **1a** with 1,1,1-trifluoromethyl(methyl)dioxirane gave the α-epoxide **2a** as the major product in a higher ratio (α : β = 9 : 1, by comparison of H-4 in the ^{1}H NMR spectrum) than for treatment of the 10-methyl analogue with dimethyldioxirane (α : β = 4 : 1)[7] (Scheme 1). The β-epoxide **2b** was prepared from the dione **1a** with alkaline hydrogen peroxide (**2a** : **2b**; α : β = 1 : 9 by comparison of H-4 in the NMR spectrum of the reaction product).[3,6,8]

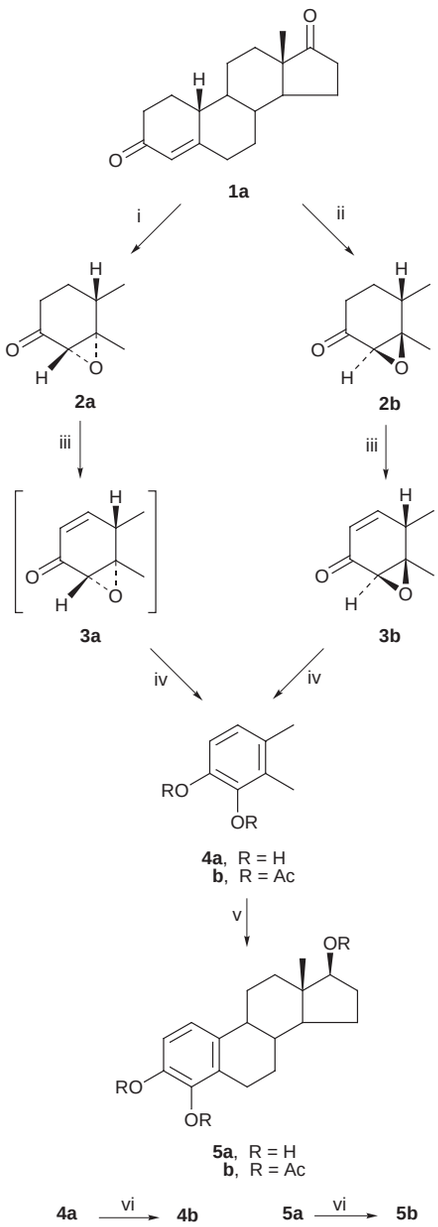
The α-stereochemistry of the epoxide **2a** was confirmed by irradiation of the H-4 proton which showed an NOE to H-6α, but no NOEs to other protons on the α-face of the steroid. A model confirms that the H-4 to H-6 NOE is reasonable even though H-4 is nominally β. Furthermore the C-10 proton signal (observed in the HSQC experiment) shows two large splittings (*J* 10 Hz) indicative of diaxial coupling to H-1α and H-9(α). These results are consistent with 5α-stereochemistry with a normal half-chair conformation for ring A. The β-stereochemistry of the epoxide **2b** was confirmed by irradiation of H-4 which showed NOEs to H-6α, H-7α and H-9(α). The C-10 proton signal (observed in the HSQC experiment) shows only one large splitting (*J* 10 Hz), from diaxial coupling to H-9. These results are in agreement with an inverted half-chair conformation for ring A.

Treatment of the β-epoxide **2b** with diphenyl diselenide, 3-iodylbenzoic acid and 10-camphorsulfonic acid in tetrahydrofuran[9] introduced a double bond at C-1–C-2 to give the unsaturated β-epoxide **3b**.[3,8] The β-epoxide **3b**, on reflux with *p*-toluenesulfonic acid in benzene, rearranged to 4-hydroxyestrone **4a**.[8] The overall yield of **4a** from **1a** (*via* the β-epoxides **2b** and **3b**) was 42%.

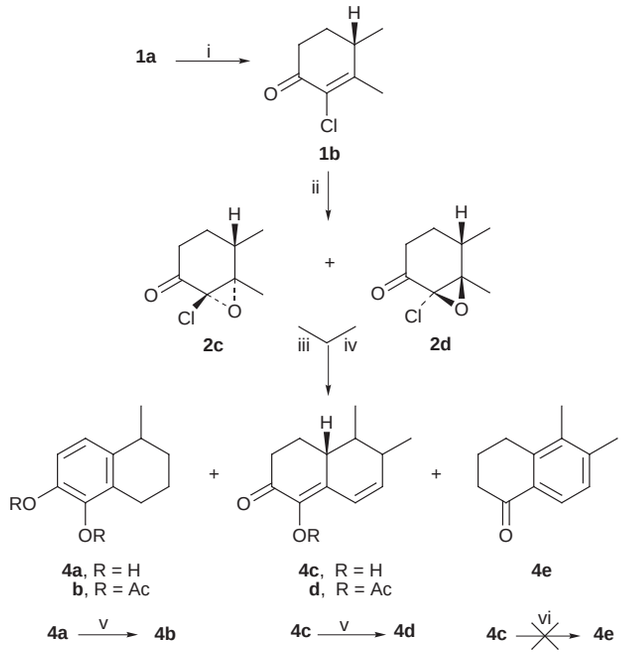
When the α-epoxide **2a** was treated with Ph_2Se_2 in the same manner as the β-epoxide **2b**, a component corresponding to the unsaturated α-epoxide **3a**, together with a more polar component corresponding to **4a**, was observed on TLC. ^{1}H NMR spectroscopy of the mixture showed the presence of both compounds **3a** and **4a**. When the starting material had been consumed, the product was extracted and chromatographed, to give only a low yield (5%) of 4-hydroxyestrone **4a**, and none of the unstable α-epoxide **3a**. A low yield (12%) of **4a** was also obtained when the product was isolated as the diacetate **4b**. Syntheses of the C-17 alcohol analogues of **2a**, **2b**, **3a** and **3b** have been reported and the NMR data given is in agreement with the data presented in Table 1.[3–5]

Lithium aluminium hydride reduction of 4-hydroxyestrone **4a** gave 4-hydroxyestradiol **5a**. The ^{1}H NMR spectra of compounds **4a**, **4b**, **5a** and **5b** show a pair of downfield doublets consistent with H-1 and H-2 of an aromatic ring (Table 1). Their ^{13}C NMR spectra were assigned by COSY and HSQC methods (Table 2).[10]

In an alternative approach to the synthesis of 4-hydroxyestrone **4a** through the 4-chloro-4,5-epoxides **2c** and **2d**, estr-4-ene-3,17-dione **1a** was treated with sulfuryl chloride in pyridine, as used for the 10-methyl analogue,[11] to give 4-chloroestr-4-ene-3,17-dione **1b** (Scheme 2). Epoxidation of the chloro ketone **1b** with excess dimethyldioxirane proceeded very slowly and the more reactive 1,1,1-trifluoromethyl(methyl)dioxirane[12] was employed; generation of this reagent *in situ*[13] proved the most convenient preparative method. Treatment of the chloro ketone **1b** with 1,1,1-trifluoromethyl(methyl)dioxirane gave the chloro-α- **2c** and chloro-β-epoxide **2d**. Epoxidation of the chloro ketone **1b**, in which the double bond is deactivated both by conjugation with the 3-oxo substituent and by chlorine substitution, required excess reagent and longer reaction time when compared with the non-halogenated conjugated C-4 double bond. The chloro-α-epoxide **2c** was the major product but in a smaller ratio (**2c** : **2d**; α : β = 7 : 3) than for the non-chlorinated compound **1a**. The **2c** : **2d** ratio was determined by comparison of their 6β-H proton in the NMR spectrum of the total reaction product. The structure of the chloro-α-epoxide **2c** was determined by X-ray crystallographic analysis (see Fig. 1)



Scheme 1 *Reagents and conditions*: i, trifluoromethyl(methyl)dioxirane; ii, H_2O_2–NaOH; iii, Ph_2Se_2–3-iodylbenzoic acid–10-camphorsulfonic acid; iv, *p*-TsOH–benzene; v, $LiAlH_4$–Et_2O; vi, Ac_2O–DMAP–CH_2Cl_2



Scheme 2 *Reagents and conditions*: i, SO_2Cl_2–pyridine; ii, trifluoromethyl(methyl)dioxirane; iii, 180 °C; iv, 162 °C; v, Ac_2O–DMAP–CH_2Cl_2; vi, 248 °C

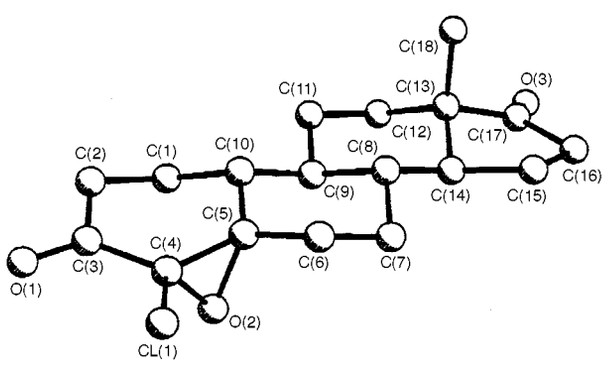


Fig. 1 PLUTO view of the 4β-chloro-4α,5α-epoxyandrostane-3,17-dione **2c**

establishing the stereochemistry of both isomers **2c** and **2d**. Treatment of the chloro ketone **1b** with alkaline hydrogen peroxide gave an intractable mixture of products from which no epoxides were isolated.

Thermolysis of the chloro-α-epoxide **2c** at 180 °C gave three products, 4-hydroxyestrone **4a**, 4-hydroxyestra-4,6-diene-3,17-dione **4c** and estra-5,7,9-triene-4,17-dione **4e** which were separated by flash column chromatography. The NMR spectra (^{1}H and ^{13}C) of 4-hydroxyestrone **4a** were in agreement with the sample reported above. 4-Hydroxyestra-4,6-diene-3,17-dione **4c** was identified by comparison of its ^{1}H NMR spectrum with that of the 10-Me analogue previously reported.[14] The structure of **4e** was based upon EI–MS, elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy as follows. EI–MS showed a strong signal corresponding to the molecular ion in agreement with elemental analysis. The IR spectrum showed both a saturated five membered ring carbonyl and a conjugated carbonyl group together with aromatic bands consistent with the proposed conjugated ketone **4e**. The ^{1}H and ^{13}C NMR spectra were assigned by COSY and HSQC analysis which showed signals corresponding to two carbonyl groups and an aromatic ring in agreement with the assigned structure.

In a separate thermolysis reaction of **2c** at 180 °C, followed by acetylation of the crude product, three compounds (**4b**:**4d**:**4e** = 1.5:1.8:1) were isolated. The polarity of compound **4e** on TLC was unchanged during the acetylation reaction indicating that it did not contain a hydroxy group.

Thermolysis of the chloro-β-epoxide **2d** at 162 °C gave the same three products, **4a**, **4c** and **4e** (2:2:1), as were obtained from the chloro-α-epoxide **2c**.

It has been generally accepted that thermal rearrangement of chloro epoxides first forms an α-oxocarbenium ion–chloride ion pair.[15] In this example the oxo group may be stabilized by conjugation with the C-3 enol and hydrogen bonding (Scheme 3). As the reaction proceeds, enolization and tautomerism may be promoted by the HCl formed. The C-5 tertiary carbocation intermediate obtained from **2c** or **2d** can be neutralized by either loss of the axial 6β-H (route a) or the axial 10β-H (route b). Loss of the 6β-H followed by a 7ξ-H and tautomerism gives the conjugated diene **4c** whereas loss of the 10β-H and tautomeric ring A aromatization yields the catechol **4a** (route c). Alternatively, following loss of 10β-H, loss of the 9α-H (route d), followed by stepwise tautomerism and loss of the 8β-H, 7ξ-H and 6ξ-H, leads to the conjugated aromatic B ring derivative **4e**. The 4,6-diene **4c**, on thermolysis, remained unchanged indicating that it is not an intermediate in the formation of the

Table 1 ^{1}H NMR Chemical shifts[a] (δ/ppm)

Compound	13-Me	Others
1b	0.94	2.50 (dd, *J* 8.7, 19.0, 16β-H), 2.65 (ddd, *J* 4.3, 4.6, 16.2, 2α-H), 3.41 (dq, *J* 2.5, 4.6, 15.1, 6α-H)
2a	0.92	2.41–2.52 (m, 16β-H plus 2H), 3.03 (s, 4-H)
2b	0.92	2.48 (dd, *J* 8.7, 19.1, 16β-H), 3.05 (s, 4-H)
2c	0.93	2.49 (dd, *J* 8.8, 18.7, 16β-H), 2.66 (ddd, *J* 2.2, 4.4, 18.3, 6α-H)
2d	0.92	2.49 (3H, m, 16β-H plus 2H)
3a	0.88	2.71 (dd, *J* 5.3, 10.9, 10-H), 3.28 (t, *J* 1.6, 4β-H), 5.98 (dt, *J* 1.4, 1.9, 10.5, 2-H), 6.74 (dd, *J* 5.3, 10.3, 1-H)
3b	0.95	2.48 (dd, *J* 8.7, 19.0, 16β-H), 2.63 (dd, *J* 5.3, 10.9, 10-H), 3.26 (t, *J* 1.5, 4α-H), 5.96 (ddd, *J* 1.3, 1.6, 10.8, 2-H), 6.72 (dd, *J* 5.3, 10.6, 1-H)
4a[b]	0.87	2.68 (ddd, *J* 6.6, 11.4, 18.0, 6β-H), 2.91 (dd, *J* 5.5, 17.7, 6α-H), 6.61 (d, *J* 8.6, 1-H), 6.65 (d, *J* 8.6, 2-H)
4b[c]	0.89	2.28 and 2.31 (2s, 3- and 4-OAc), 2.49 (dd, *J* 8.8, 18.7, 16β-H), 2.60 (ddd, *J* 6.8, 11.9, 18.6, 6β-H), 2.79 (dd, *J* 5.4, 17.5, 6α-H), 6.98 (d, *J* 8.6, 1-H), 7.20 (d, *J* 8.6, 2-H)
4c	0.96	2.96 (ddd, *J* 2.5, 4.3, 17.4, 2α-H), 6.15 (dd, *J* 2.1, 9.8, 6-H), 6.23 (s, 4-OH), 6.78 (dd, *J* 2.8, 9.9, 7-H)
4d[c]	0.93	2.45 (s, OAc), 6.29 (d, *J* 5.9, 6-H), 6.46 (dd, *J* 1.4, 5.9, 7-H)
4e[c]	0.75	3.01 (dd, *J* 5.8, 12.3, 14-H), 7.11 (d, *J* 8.0, 7-H), 7.94 (d, *J* 8.0, 6-H)
5a[b,c]	0.78	2.60 (ddd, *J* 6.8, 11.9, 18.6, 6β-H), 2.90 (q, *J* 5.4, 17.4, 6α-H), 3.68 (t, *J* 8.5, 17α-H), 6.63 (d, *J* 8.4, 1-H), 6.69 (d, *J* 8.4, 2-H)
5b	0.82	2.06 (s, 17β-OAc), 2.27 and 2.30 (2s, 3- and 4-OAc), 2.57 (m, 6β-H), 2.75 (dd, *J* 5.5, 17.3, 6α-H), 4.69 (dd, *J* 7.8, 9.0, 17α-H), 6.97 (d, *J* 8.6, 1-H), 7.20 (d, *J* 8.6, 2-H)

[a] For solutions in $CDCl_3$ ($CHCl_3$ internal standard) on a Bruker AM300 instrument unless otherwise indicated, *J* values are given in Hz. [b] CD_3OD–$CDCl_3$ (1 : 1). [c] Determined by 2D analysis (COSY AND HSQC) on a Bruker AMX500 instrument.

Table 2 ^{13}C NMR Chemical shifts[a] (δ/ppm)

	Compound												
Carbon	**1b**	**2a**	**2b**	**2c**	**2d**	**3b**	**4a**[b]	**4b**[c,d]	**4c**	**4d**[c,d]	**4e**[d]	**5a**[b,d]	**5b**[e]
1	25.63	20.78	16.95	20.61	16.91	125.25	116.67	120.05	24.55	24.41	38.39	116.64	123.51
2	35.71	35.74	31.60	35.71	30.36	147.58	112.73	123.42	35.47[f]	35.47	22.48	112.49	119.93
3	190.89	205.62	206.24	195.89	196.39	195.66	142.02	130.67	194.22	191.02	24.17	142.02	140.03[f]
4	127.73	61.72	61.75	82.56	82.11	61.87	142.39	138.98	129.11	140.61	198.40	142.39	140.73[f]
5	159.39	64.49	67.18	69.65	71.68	63.63	132.45	140.10	141.17	143.71	131.36[f]	133.19	133.19
6	31.81	32.98	33.17	29.56	31.86	32.25	23.83	23.50	122.93	122.17	123.45[g]	23.83	23.24
7	31.26	31.38	31.11	31.29	31.08	31.10	26.46[f]	25.51[f]	136.13	138.84	125.08[g]	27.28	26.00[g]
8	39.63	39.97	40.16	39.48	40.15	39.99	38.45	37.24	39.64	45.96	142.36[h]	38.81	37.52
9	44.32	40.54	40.65	41.27	41.10	44.82	44.67	44.09	40.29	40.36	134.16[f]	44.57	44.01
10	49.32	46.49	44.01	46.18	44.17	49.75	124.37	140.15	46.42	40.41	143.35[h]	124.37	130.82
11	29.24	27.26	28.89	27.27	28.31	28.25	26.69[f]	25.62[f]	31.29	31.08	26.20	26.82	26.28[g]
12	25.40	25.63	25.66	25.50	25.62	26.22	32.04	31.41	26.51	26.51	28.85	37.14	36.80
13	47.63	47.74	47.79	47.67	47.74	47.64	47.66	47.74	48.36	48.17	46.82	43.49	42.79
14	50.06	50.09	50.11	49.96	50.03	51.12	51.01	50.22	48.61	48.17	47.19	50.48	49.72
15	21.60	21.68	21.72	21.62	21.69	21.65	22.04	21.46	21.40	21.17	21.40	23.42	23.68
16	36.52	36.30	35.66	36.25	35.65	35.48	36.42	35.71	35.64[f]	36.94	36.38	30.12	27.55
17	219.99	220.38	220.05	220.15	219.78	219.73	220.22	220.41	219.70	219.18	219.26	81.79	82.57
18	13.79	13.79	13.80	13.78	13.80	13.81	14.15	13.70	13.69	13.51	13.51	11.28	12.00

[a] For solutions in $CDCl_3$ ($CDCl_3$ internal standard) on a Bruker AM300 instrument unless otherwise indicated. [b] CD_3OD–$CDCl_3$. [c] The acetyl group signals in **4b** occur at δ_C 20.22, 20.57 ($CO\mathit{C}H_3$) and 168.04, 168.53 ($\mathit{C}OCH_3$); in **4d** at δ_C 20.22 and 168.43. [d] Determined by 2D analysis (HSQC and COSY) on a Bruker AMX500 instrument. [e] δ_C 20.32, 20.68, 168.10, 168.61 (3- and 4-$COCH_3$), 21.17, 171.11 (17-$COCH_3$). [f–h] Numbers in columns are interchangeable.

ring B aromatic product **4e**. The proposed mechanism for formation of **4e** *via* the 4,9-dien-3-one is consistent with this observation.

The three-step synthesis of 4-hydroxyestrone by way of the 4-chloro-4,5-epoxides **2c** and **2d** gave a low yield and is not suitable as a preparative method, whereas the three step synthesis through rearrangement of the unsaturated β-epoxide **3b** is a convenient, efficient, procedure.

Experimental

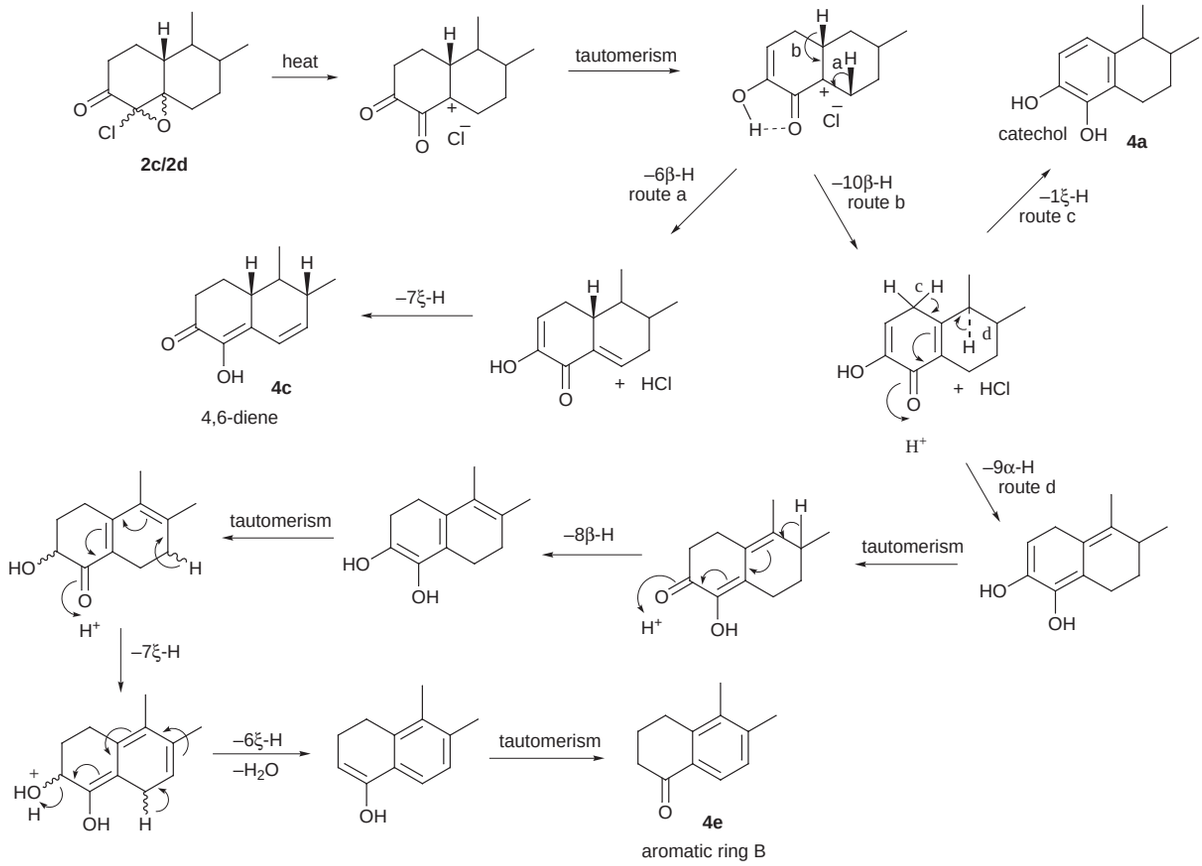
Compounds were run on TLC (silica gel, Merck type 60H) in 20% acetone–light petroleum 35–60 °C (LP). Flash column chromatography (FCC) was carried out on silica gel (Merck type 60 for column chromatography). Mps were measured on a Kofler-type hot stage apparatus and are uncorrected. Elemental analyses were performed by W. Baldeo, School of Pharmacy, University of London, England, UK.

^{1}H and ^{13}C NMR spectra are reported in Tables 1 and 2. Survey spectra were obtained on a Bruker AM300 instrument while homonuclear correlation (COSY) and heteronuclear correlation (HSQC) spectra were recorded on a Bruker AMX500 spectrometer as described previously.[16] Samples were measured as ~50 mmol dm^{-3} solutions in $CDCl_3$ in 5 mm sample tubes. The residual $CHCl_3$ peak in the solvent (δ_H 7.26 ppm, δ_C 77.0 ppm) was used as the internal reference for both proton and carbon spectra, respectively. *J* Values are given in Hz. Sample temperature was controlled at 300 K for all spectra. Carbon spectra were classified as to multiplicity with the DEPT technique.[17]

The infrared spectrum of compound **4e** was recorded on a Perkin Elmer 881 instrument. The mass spectrum of compound **4e** was recorded on a VG-7070E instrument at 70 eV.

X-ray crystallographic data collection for compound **2c** was measured on a Rigaku AFC6S diffractometer with a graphite monochromator Mo-Kα (λ = 0.710 69 Å) radiation.† Crystallo-

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/214.



Scheme 3 Thermal rearrangement products of steroid 3-oxo-4-chloro-4,5-epoxides

Table 3 Crystallographic data

	2c
Formula	$C_{18}H_{23}O_3Cl$
Formula wt.	322.83
T/K	299
Crystal system	orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Cell dimensions (Å) *a*	11.953(2)[a]
b	18.644(2)
c	7.252(2)
Z	4
Cell volume/Å^3	1616.1(6)
F(000)	688
D_c/g cm^{-3}	1.327
μ/cm^{-1}	2.43 (Mo-Kα)
Crystal dimensions/mm	0.450 × 0.300 × 0.250
2θ max./°	50.2
Independent reflections	1699
Observed reflections [$I > 2.00\sigma(I)$]	1344

[a] Estimated standard deviations in parentheses refer to the last digit.

graphic data are summarised in Table 3. Cell constants and an orientation matrix for data collection were obtained by least-squares using a setting angle of 18 reflections in the 2θ ranges 9.08–23.39°. Data collection used the ω–2θ scan technique. Omega scans of several intense reflections, made before data collection, had an average scan width at half-height of 0.36° with a take off angle of 6°. Scans of (1.47 + 0.35 tan θ)° were made at a speed of 4° min^{-1} (in ω). The weak reflections $1 < 10.0\sigma(1)$ were rescanned (maximum of four rescans), and the counts accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. Three reference reflections, measured every 150 reflections, remained constant and no decay correction was applied. Intensities were corrected for Lorentz and polarization effects; a correction for absorption was applied based on azimuthal scans of several reflections. The structure was solved using direct methods. Full-matrix least-squares refinement with anisotropic factors given to all non-H atoms converged ($R = 0.042$, $Rw = 0.038$, $S = 2.22$). The weighting scheme was based on counting statistics. The maximum shift/error in the final cycle was 0.00. The largest peaks in the final difference map were 0.21 and −0.25 e Å^{-3}. Atomic scattering factors were taken from International Tables for X-ray crystallography;[18] anomalous dispersion effects were included in *F*.[18] All calculations were made with the TEXSAN crystallographic software package.[19] Fig. 1 was prepared using PLUTO.[20]

4,5-Epoxy-5α-estra-3,17-dione 2a

To a stirred solution of estr-4-ene-3,17-dione **1a** (2.0 g, 7.3 mmol) in acetonitrile (80 cm^3), cooled in an ice-bath, was added aqueous disodium edetate (30 cm^3, 4×10^{-14} M) followed by 1,1,1-trifluoroacetone (7 cm^3). To the vigorously stirred mixture was added in portions a solid mixture of $NaHCO_3$ (4.7 g, 0.057 mmol) and Oxone (11.3 g, 0.037 mmol) over 25 min. After a further 35 min no starting material remained as determined by TLC. Water was added and the reaction mixture extracted with CH_2Cl_2 to yield a product which on recrystallization gave the α-epoxide **2a** (1.5 g, 71%), mp 215–220 °C (from CH_2Cl_2–MeOH), further recrystallization gave mp 220–221 °C (Found: C, 75.1; H, 8.5. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%).

4,5-Epoxy-5β-estra-3,17-dione 2b

To estr-4-ene-3,17-dione **1a** (1.0 g, 3.7 mmol) in MeOH (100 cm^3) containing 4 M NaOH (5 cm^3), cooled in an ice-bath, was added 30% H_2O_2 (5.5 cm^3). After 20 min the reaction mixture was diluted with water and extracted with Et_2O to give a crude product which showed two components on TLC. Recrystallization gave the β-epoxide **2b** (830 mg, 78%), mp 166–172 °C

(from CH_2Cl_2–MeOH), further recrystallization gave mp 170–173 °C (Found: C, 75.1; H, 8.4. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%).

4,5-Epoxy-5β-estr-1-ene-3,17-dione 3b

A stirred mixture of diphenyl diselenide (34 mg, 0.11 mmol), 3-iodylbenzoic acid (1.0 g, 3.6 mmol) and 10-camphorsulfonic acid (128 mg, 0.55 mmol) in tetrahydrofuran was refluxed for 10 min until the yellow colour disappeared. A solution of the β-epoxide **2b** (280 mg, 0.97 mmol) in THF (2 cm^3) was then added and reflux continued for 4 h when no starting material remained by TLC. Aqueous $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2 to give **3b** (220 mg, 79%), mp 213.5–216 °C (from CH_2Cl_2–EtOAc) (lit.,[8] 205 °C).

4-Hydroxyestrone 4a

(a) From 3b. A solution of the estr-1-ene **3b** (130 mg, 0.454 mmol) and *p*-toluenesulfonic acid (10 mg) in benzene (15 cm^3) was refluxed under Ar for 18 h, diluted with Et_2O and washed with aqueous $NaHCO_3$ to give 4-hydroxyestrone **4a** (75 mg, 57%) mp 261–263 °C (from 2% HOAc–benzene–EtOAc) (lit.,[1e] 266–270 °C).

(b) From 2a *via* 3a. Treatment of the α-epoxide **2a** (300 mg, 1.03 mmol) with Ph_2Se_2 (36 mg, 0.11 mmol), 3-iodylbenzoic acid (950 mg, 3.4 mmol) and 10-camphorsulfonic acid (116 mg, 0.5 mmol) as described for **2b** on reflux gave two major products (R_f 0.34 and R_f 0.18, 20% acetone–LP). On further reflux the less polar component **3a** was converted into the more polar component **4a** on TLC. After 6 h no starting material remained and the reaction mixture was diluted with diethyl ether, the ether layer was washed with water, brine and aqueous $NaHCO_3$ to give a residue which on FCC gave fractions of 4-hydroxyestrone **4a** (16 mg, 5%), mp 261–263 °C, the ^{1}H NMR spectrum of which was identical with the material prepared above.

4-Hydroxyestrone 3,4-diacetate 4b

(a) From 2a *via* 3a. Treatment of the α-epoxide **2a** (800 mg, 2.75 mmol) with Ph_2Se_2 (94 mg, 0.30 mmol), 3-iodylbenzoic acid (2.80 g, 11.1 mmol) and 10-camphorsulfonic acid (348 mg, 1.49 mmol) in dry THF (15 cm^3) as described for **2b** was followed by reflux for 18 h, dilution with water and extraction with CH_2Cl_2 to give a residue. To the residue (430 mg) in benzene (3 cm^3) was added *p*-TsOH (250 mg, 1.31 mmol) and acetic anhydride (3 cm^3, 32 mmol) and the mixture refluxed for 18 h and then quenched with MeOH (3 cm^3). The solvents were evaporated and the residue taken up in CH_2Cl_2 to give on FCC, on elution with 13% acetone–LP, fractions of the diacetate **4b** (120 mg, 12%), mp 218–220 °C (from EtOAc–LP) (lit.,[1a] 212.5–215.5 °C).

(b) From 4a. To a solution of 4-hydroxyestrone **4a** (30 mg, 0.10 mmol) in CH_2Cl_2 (3 cm^3) was added Ac_2O (0.35 mmol) and dimethylaminopyridine (DMAP) (15 mg). After 2 h, MeOH (2 cm^3) was added and the mixture stirred for 0.5 h and washed with water and aqueous $NaHCO_3$ to give the diacetate **4b** (35 mg, 94%), mp 217–220 °C (from EtOAc–LP) (lit.,[1a] 212.5–215.5 °C).

4-Hydroxyestradiol 5a

(a) From 4a. To a stirred solution of 4-hydroxyestrone **4a** (45 mg, 0.16 mmol) in dry THF (3 cm^3) was added $LiAlH_4$ (8 mg, 0.2 mmol). After 30 min, TLC showed no starting material and the mixture was washed with 5% HCl, to give a white residue, which rapidly became pale yellow. Crystallization gave the triol **5a** (35 mg, 77%) mp 235–237 °C which resolidified mp 257–260 °C (decomp.) (from 2% HOAc–benzene–EtOAc) (lit.,[1e] 214–216 °C) [lit.,[1e] δ_H(300 MHz; C_6D_5N) 7.1 (d, H-1), 6.8 (d, H-2)].

(b) From 4b. 4-Hydroxyestrone 3,4-diacetate **4b** (59 mg, 0.17 mmol) was treated with $LiAlH_4$ (20 mg, 0.53 mmol) in THF (3 cm^3) as above to give the triol **5a** (33 mg, 65%).

4-Hydroxyestradiol 3,4,17-triacetate 5b

(a) Acetylation of 5a. (35 mg, 0.12 mmol), obtained from LAH reduction of 4-hydroxyestrone **4a**, as described for **4b**, gave the triacetate **5b** (42 mg, 84%), mp 204–207 °C (from CH_2Cl_2–MeOH) (lit.,[1g] 192–196 °C, no solvent reported).

(b) Acetylation of 5a. (33 mg, 0.11 mmol), obtained from LAH reduction of 4-hydroxyestrone 3,4-diacetate **4b**, as described for **4b** gave the triacetate **5b** (40 mg, 88%), mp 204–207 °C (from CH_2Cl_2–MeOH) (lit.,[1f] 192–196 °C, no solvent reported).

4-Chloroestr-4-ene-3,17-dione 1b

To a stirred, cooled (ice-bath), solution of estr-4-ene-3,17-dione **1a** (2.0 g, 7.4 mmol) in dry pyridine (20 cm^3) was added, over 15 min, 1 M SO_2Cl_2 in CH_2Cl_2 (15 cm^3, 15 mmol, 2 equiv.). After 1 h at 0 °C followed by 2 h at 20 °C no starting material remained on TLC and the mixture was poured into excess cold dilute HCl and extracted with Et_2O. The Et_2O layer was washed with water, aqueous $NaHCO_3$ and brine to give a residue which on FCC, on elution with 20% EtOAc–LP, gave fractions of the 4-chloroketone **1b** (1.74 g, 81%), mp 181–183 °C (from CH_2Cl_2–MeOH) (Found: C, 70.2; H, 7.5; Cl, 11.7. $C_{18}H_{23}ClO_2$ requires C, 70.5; H, 7.55; Cl, 11.55%).

4β-Chloro-4,5-epoxy-5α-estra-3,17-dione 2c and 4α-chloro-4,5-epoxy-5β-estra-3,17-dione 2d

To a stirred, cooled (ice-bath), solution of the 4-chloroketone **1b** (1.0 g, 3.26 mmol) in acetonitrile (50 cm^3) was added aqueous disodium edetate (20 cm^3, 4×10^{-14} M). To the cooled solution was added 1,1,1-trifluoroacetone (25 cm^3) followed by a solid mixture of $NaHCO_3$ (15 g, 0.18 mmol) and Oxone (25 g, 0.081 mmol) over 1 h. After 24 h reaction was not complete by TLC and an equal amount of 1,1,1-trifluoroacetone followed by $NaHCO_3$ and Oxone was again added. After a further 24 h, although some starting material remained, the reaction mixture was poured into water and extracted with CH_2Cl_2 to give on FCC, on elution with 15–25% EtOAc–LP, fractions of the chloro β-epoxide **2d** (60 mg, 5.7%) mp 147–149 and 184–187 °C from (CH_2Cl_2–MeOH) (Found: C, 67.1; H, 7.2; Cl, 10.8. $C_{18}H_{23}ClO_3$ requires C, 67.0; H, 7.2; Cl, 11.0%) and the chloro α-epoxide **2c** (360 mg, 34%) mp 155–159 °C (from CH_2Cl_2–MeOH) (Found: C, 67.0; H, 7.2; Cl, 10.8. $C_{18}H_{23}ClO_3$ requires C, 67.0; H, 7.2; Cl, 11.0%).

Thermolysis of the 4-chloro-4,5-epoxyestra-3,17-diones 2c and 2d: formation of compounds 4a, 4c and 4e

The chloro epoxide reaction mixture of **2c** and **2d** (570 mg, 1.77 mmol), obtained from **1b** as described above, in a sealed tube was immersed in an oil bath preheated to 165 °C until effervescence ceased (5 min). Separation of the brown residue on FCC by elution with 10% EtOAc–LP gave fractions (i) estra-5,7,9-triene-4,17-dione **4e** (60 mg, 13%), mp 128–130 °C (from CH_2Cl_2) (Found: C, 80.3; H, 7.8. $C_{18}H_{23}O_2$ requires C, 80.6; H, 7.5%); ν_{max}/cm^{-1} 1739 (C=O), 1660 (conj. C=O), 1658, 1591 (aromatic C=C); *m/z* 268 (M^+, 100%), 253 (10), 250 (5), 240 (15), 211 (85), (ii) 4-hydroxyestra-4,6-diene-3,17-dione **4c** (170 mg, 33%), mp 234–235 °C (from CH_2Cl_2–EtOAc) (Found: C, 75.5; H, 7.8. $C_{19}H_{24}O_3$ requires C, 75.5; H, 7.7%) and (iii) 4-hydroxyestrone **4a** (110 mg, 23%), mp 263–265 °C (from 2% HOAc–EtOAc–$CHCl_3$) (lit.,[1d] 268–271 °C).

Thermolysis of 4α-chloro-4,5-epoxy-5β-estra-3,17-dione 2d: formation of compounds 4a, 4c and 4e

The chloro β-epoxide **2d** (10 mg, 0.031 mmol) in a sealed melting point tube was heated in an oil bath maintained at 162 °C for 4 min. The crude product showed the presence of three components on TLC corresponding to **4a**, **4c** and **4e** (ratio 2:2:1 by ^{1}H NMR spectroscopy).

Acetylation of the products from thermolysis of 4β-chloro-4,5-epoxy-5α-estra-3,17-dione 2c: formation of compounds 4b, 4d and 4e

The chloro α-epoxide **2c** (220 mg, 0.35 mmol) in a sealed tube was immersed in an oil bath preheated to 180 °C until effervescence ceased (*ca.* 4 min). The residue dissolved in CH_2Cl_2 (20 cm^3) was treated with Ac_2O (1.8 cm^3) and DMAP (10 mg) for 2 h. MeOH was added to remove excess reagent and the mixture washed with water to give a residue which on separation by FCC, by elution with 30–50% EtOAc–LP, gave fractions (i) estra-5,7,9-triene-4,17-dione **4e** (20 mg, 20%), mp 128–130 °C (from CH_2Cl_2), (ii) 4-hydroxyestrone 3,4-diacetate **4b** (40 mg, 16%), mp 217–220 °C (from EtOAc–LP) (Found: C, 71.3; H, 7.1. $C_{22}H_{26}O_5$ requires C, 71.3; H, 7.1%), and (iii) 4-acetoxyestra-4,6-diene-3,17-dione **4d** (44 mg, 20%), mp 216–218 °C (from CH_2Cl_2–EtOAc) (Found: C, 73.1; H, 7.5. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.4%).

Thermolysis of 4-hydroxyestra-4,6-diene-3,17-dione 4c

Thermolysis of **4c** at 248 °C in a sealed tube for 4 min gave only starting material as identified by TLC and ^1H NMR spectroscopy of the crude product.

Acknowledgements

We thank the Medical Research Council of Canada for financial assistance. H. Majgier-Baranowska was the recipient of a Duff Roblin Graduate Fellowship, University of Manitoba. NMR spectra were recorded by T. Foniok, Department of Chemistry, University of Manitoba. We thank Dr N. Hunter, Department of Chemistry, University of Manitoba, for helpful discussions.

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Paper 7/09186I
Received 22*nd December* 1997
Accepted 9*th April* 1998