Zinc–Acetic Acid Reduction of the Steroid 4-En-3-one: Novel Conversion of the 4-En-3-one into the 2-En-4-one *via* a Vinyl Chloride

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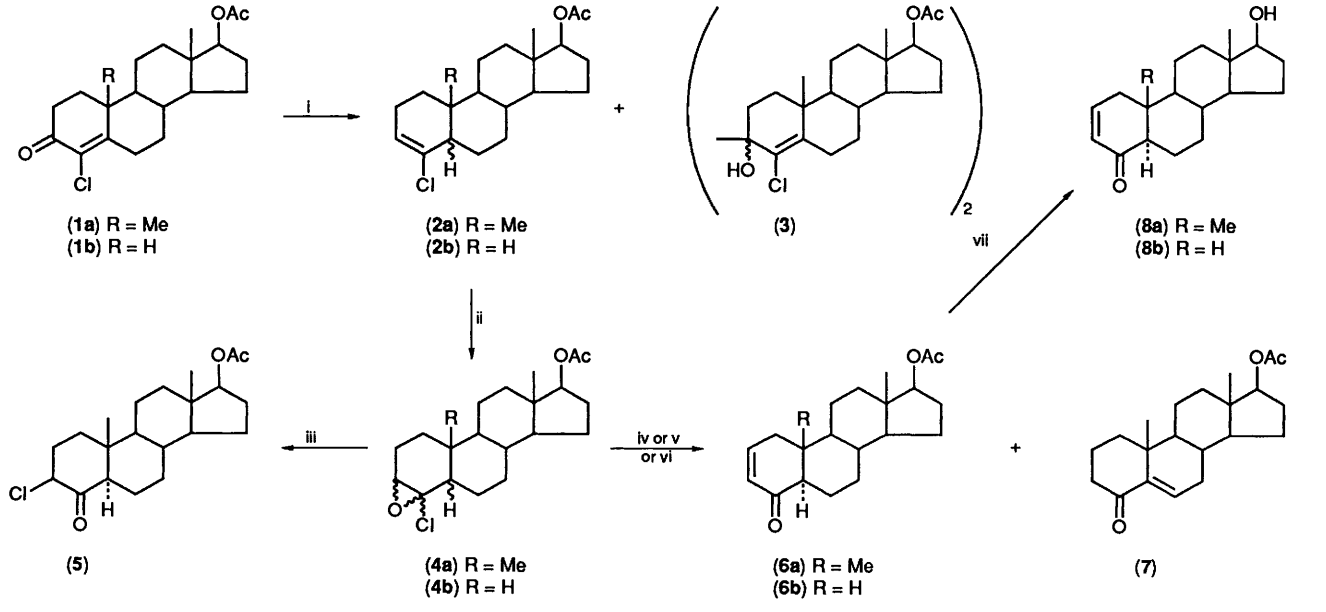
Transposition of a steroid 4-en-3-one to the 2-en-4-one has been carried out. 4-Chlorotestosterone acetate on Zn–HOAc reduction yields a mixture of the C-5 epimers of the 4-chloro-3-ene together with a C-3 dimer. The vinyl chlorides, after epoxidation followed by rearrangement and elimination, give the 2-en-4-one. A synthesis of 17β-hydroxy-5α-androst-2-en-4-one and 17β-hydroxy-5α-estr-2-en-4-one is described.

As part of a metabolic study we were interested in the synthesis of steroidal C-2 and C-4 ketones.[1] The C-2, 5α ketone was prepared from the C-3, 5α ketone *via* a vinyl chloride[2] and we now report a short conversion of the 4-en-3-one into the 2-en-4-one by means of a vinyl chloride intermediate as shown in Scheme 1. This transposition of an unsaturated ketone may be of general synthetic value.

McKenna *et al.*[3] showed that Zn–HOAc reduction of the steroid 4-en-3-one gave a mixture of the 5α and 5β, C-3 olefin [5α–5β (1.7:1) by ^{1}H NMR]. Similar reduction of 4-chlorotestosterone acetate (**1a**) gave the 5α- and 5β-vinyl chlorides (**2a**) [5α–5β (2:1)] as shown by two 10-Me chemical shifts and the two vinyl protons (see Table 1). Treatment of the vinyl chlorides (**2a**) with concentrated sulphuric acid gave a mixture of intractable products which may have resulted from rearrangement and elimination products of the C-5 carbocation formed from the protonated olefin through hydrogen migration from C-5 to C-3.[4]

Epoxidation of the vinyl chlorides (**2a**) with *m*-chloroperbenzoic acid (*m*CPBA) was expected to give an epimeric mixture of the chloro epoxides (**4a**), resulting from addition to the least hindered face of the double bond. The presence of a NOE between the 3β-H and the 10-Me clearly identifies the 4β-chloro-3α,4α-epoxy-5α isomer as the major product. ^{1}H NMR showed a ratio of 4β-chloro-5α–4α-chloro-5β (2:1). Reflux in dimethylacetamide (DMA)–$CaCO_3$ gave an epimeric mixture of 3-chloro-4-ketones from which the major product, the thermodynamically more stable 3β-chloro ketone (**5**), was isolated. On reflux in s-collidine, chloro epoxides (**4a**) gave a mixture of the 2-en-4-one (**6a**) and 5-en-4-one (**7**) [(**6a**)–(**7**) (1:2.5)] from which (**7**) was isolated. Thermal rearrangement of the chloro epoxides (**4a**) gave a similar mixture from which the 5-en-4-one (**7**) was separated. Reflux with Li_2CO_3–LiBr–dimethylformamide (DMF) gave the 2-en-4-one (**6a**) containing only a trace of (**7**) by ^{1}H NMR. Alkaline hydrolysis gave the 17-alcohol (**8a**).

A major by-product in the Zn–HOAc reaction was identified as the dimer (**3**) based on the following evidence. The ^{1}H NMR spectrum showed signals for the 17α-H at δ 4.46 and the 13-Me at δ 0.82. Furthermore, the 6α-H at δ 3.00 showed appropriate coupling to three protons (6β-H, 7α-H, and 7β-H) consistent with that seen in 4-chlorotestosterone acetate (**1a**), indicating



(**1a**) R = Me
(**1b**) R = H

(**2a**) R = Me
(**2b**) R = H

(**3**)

(**8a**) R = Me
(**8b**) R = H

(**5**)

(**4a**) R = Me
(**4b**) R = H

(**6a**) R = Me
(**6b**) R = H

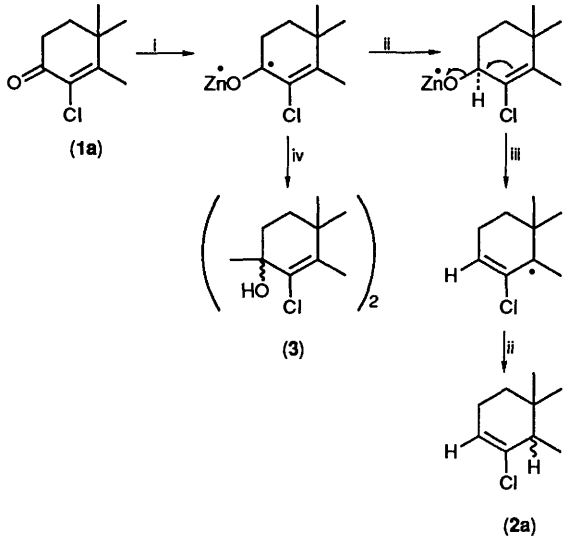
(**7**)

Scheme 1. *Reagents and conditions:* i, Zn-HOAc; ii, *m*CPBA; iii, DMA–$CaCO_3$; iv, Li_2CO_3–LiBr–DMF; v, s-collidine; vi, 203–216 °C, 10 min; vii, KOH–MeOH

Table 1. ^{1}H Chemical shifts (J in Hz)[a]

Compound	10-Me	13-Me	17-OAc	17-H	Other
(1a)	1.23	0.84	2.04	4.60dd (J 7.7 and 9.1)	3.25ddd (J 2.6, 4.1, 14.9) (6α H)
(1b)		0.87	2.04	4.62dd (J 7.8 and 9.1)	3.36ddd (J 2.6, 4.0, 15.1) (6α H)
(2a) (5α)[b]	0.85	0.80[c]	2.03[d]	4.60dd (J 7.8 and 9.1)	5.75m (3 H)
(5β)	1.03[c]	0.79[c]	2.04[d]	4.59dd (J 7.8 and 9.1)	5.88m (3 H)
(3)	1.10	0.82	2.03	4.46dd (J 7.8 and 9.2)	3.00ddd (J 13, 3.6, 3.6) (6α H); 3.48br s (R_3OH)
(4a) (5α)[b,e]	0.86	0.78	2.04	4.58dd (J 7.8 and 9.0)	3.44br s (3β H)
(5β)	0.94	0.78	2.04	4.59dd (J 7.8 and 9.0)	3.50br s (3β H)
(5)	0.77	0.79	2.03	4.60dd (J 7.8 and 9.1)	4.49ddd (J 1,6. 8, 12.6) (3α H)
(6a)	0.87	0.79	2.04	4.61dd (J 7.8 and 9.1)	2.41dd (J 6.0, 18.7) (1β H); 5.99dd (J 2.5, 10) (3 H); 6.78ddd (J 2.3, 6.0, 8.3) (2 H)
(6b)		0.80	2.04	4.62dd (J 7.8 and 9.1)	2.28dq (J 3.5, 14.0) (6α H); 2.59dt (J 5.3, 18.7) (1β H); 6.00dd (J 2.3, 10.0) (3 H); 6.92ddd (J 2.1, 6.1, 8.3) (2 H)
(7)	0.96	0.81	2.04	4.62dd (J 7.8 and 9.1)	6.40dd (J 2.7, 5.0) (6 H)
(8a)	0.87	0.75		3.65t (J 8.3)	2.42dd (J 6.0, 18.6) (1β H); 5.99dd (J 2.5, 10); (3 H); 6.79ddd (J 2.3, 6.0, 8.3) (2 H)
(8b)		0.76		3.66m	2.28dq (J 3.5, 14.0) (6α H); 2.60dt (J 5.3, 18.6); (1β H); 6.00dd (J 2.2, 10.0) (3 H); 6.92ddd (J 2.1, 6.1, 10.0) (2 H)

[a] For solutions in $CDCl_3$ ($SiMe_4$ internal standard) on a Bruker AM300 instrument. [b] Mixture 5α-5β (2:1) based on integration of the 3 H. [c,d] Chemical shift values are interchangeable. [e] NOE between 3β H and 10-Me.



Scheme 2. *Reagents:* i, Zn–HOAc; ii, H$^+$; iii, $-$ZnO; iv, $-$2Zn, 2H$^+$

the presence of the C-4 double bond. The 10-Me had undergone an upfield shift consistent with the removal of the C-3 ketone. A signal at δ 3.49 is in agreement with a tertiary hydroxy group attached at C-3. The IR spectrum confirmed the presence of a hydroxy group. ^{13}C NMR showed loss of the C-3 ketone and the formation of a quaternary C at δ 50.78 in agreement with the formation of a tertiary alcohol at C-3. A ^{13}C T_1 measurement gave an average T_1 value of *ca.* 250 ms for the CH_2 carbon atoms compared with the more usual value of 600 ms under the same conditions.[5] For a given class of molecules in the same solvent and temperature, the ^{13}C T_1 is inversely proportional to the molecular weight.[6] The T_1 value is therefore consistent with a dimeric product. The MS (EI) spectrum was complex with no clearly definable signal consistent with a molecular ion and not that expected from a single steroid molecule. There was no TLC evidence of a similar product formed in the absence of a C-4 chlorine atom. The products (**2a**) and (**3**) may have been formed as outlined in Scheme 2 where the initially formed diradical at C-3 can undergo a coupling reaction to give (**3**) instead of proton abstraction to give the olefin (**2a**). As there was no evidence from TLC for dimer formation with testosterone acetate, the relative stability of the C-3 radical appears to be significantly altered by the presence of the C-4 chlorine.

The same series of reactions have been carried out on 17β-acetoxy-4-chloroestr-4-en-3-one (**1b**). Reaction of (**1b**) with Zn–HOAc gave the vinyl chlorides (**2b**) which after epoxidation gave a mixture of chloro epoxides (**4b**). Treatment of the chloro epoxides (**4b**) with LiBr–Li_2CO_3–DMF afforded 17β-acetoxy-5α-estr-2-en-4-one (**6b**) which after alkaline hydrolysis gave the 17-alcohol (**8b**).

All of the above structures are consistent with their ^{1}H and ^{13}C NMR spectra (see Tables 1 and 2), based on internal consistency, published data[7], C, H correlation[8] and COSY[9] spectra.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ (TMS internal standard) on a Bruker AM 300 instrument. The MS (EI) spectrum was recorded on a VG 7070-EHF mass spectrometer and the IR spectrum on a Perkin-Elmer 267 instrument. TLC refers to precoated silica gel plates (Merck type 60) run in 10–25% ethyl acetate–hexane unless otherwise stated. The method described by Kihara *et al.*[10] was used for column chromatography on silica (Merck type 60H for TLC). M.p.s are uncorrected.

4-Chlorotestosterone Acetate (**1**).—The acetate (**1**), m.p. 228–231 °C (lit.,[11] 228–230 °C) was prepared from testosterone acetate by the method of Mori.[12]

17β-Acetoxy-4-chloro-5α- and 5β-androst-3-ene (**2a**) *and Dimer* (**3**).—To 4-chlorotestosterone acetate (**1a**) (5.84 g), prepared by the method of Mori,[12] in acetic acid (300 ml) was added zinc dust (120 g). The mixture was shaken for 5.5 h at room temperature. When no starting material remained (by TLC), the solution was filtered and evaporated at reduced pressure. The residue was diluted with water and extracted with ether. The ether layer was washed successively with water and excess of aqueous sodium hydrogen carbonate to give a product which was dissolved in dichloromethane and placed on

Table 2. ^{13}C Chemical shifts.[a,b]

Carbon No.	Compound (1a)	(1b)	(2a) (5α)	(2a) (5β)	(3)	(4a) (5α)	(4a) (5β)	(5)	(6a)	(6b)	(7)
1	34.98	25.93	33.43	33.62	32.34	30.12	28.97	37.92	40.74	31.09	36.68
2	34.01	36.56	23.62[c]	22.89[c]	32.08	20.98[c]	20.49[c]	34.59	128.85	129.16	19.29
3	190.54	191.05	123.60	126.34	50.78	61.95	63.41	64.03	146.50	148.55	40.10
4	127.38	127.49	135.11	135.57	127.49	80.40	81.27	203.05	201.23	201.23	203.10
5	164.38	160.00	50.70	48.49	146.33	52.58[d]	49.15	58.49	55.75	49.75	145.47
6	28.92	31.98	23.96[c]	23.74[c]	31.50	25.85	24.76	20.83	20.26[b]	24.97[b]	131.90
7	30.70	29.96	31.13	27.57	27.77	31.02	27.71[d]	29.86	30.24	24.47	31.21
8	34.48	39.94	34.96	35.22	35.46	34.80	34.36	34.68	34.72	39.81	30.95
9	53.93	49.46	53.10	41.70	53.02	52.46[d]	42.56	54.17	54.10	48.81	49.15
10	41.42	44.79	37.47	36.33	40.60	35.52	34.19	42.98	40.29	43.97	36.68
11	20.68	25.37	20.89	21.17	21.13	20.92[c]	20.62[c]	21.23	20.61[b]	25.20[b]	20.76
12	36.63	36.56	36.92	37.14	36.90	36.85	36.97	36.80	36.79	36.74	36.68
13	42.50	42.66	42.66	42.69	42.56	42.58	42.65	42.61	42.62	42.71	42.44
14	50.24	49.17	50.26	50.47	50.78	50.51	50.70	50.46	50.60	50.79	50.99
15	23.44	23.26	23.43[c]	23.50[c]	23.45	23.41	23.46	23.42	23.46	23.24	23.43
16	27.54	27.46	27.56	27.56	27.54	27.55	27.57[d]	27.48	27.51	27.43	27.47
17	82.37	82.39	82.73	82.77	82.43	82.64	82.69	82.56	82.69	82.70	82.51
18	12.08	12.04	12.41[d]	12.05	12.12	12.17	12.02	12.11	12.13	12.06	12.05
19	17.85		12.41[d]	23.14	20.98	13.12	22.96	13.80	13.23		21.30
$OCOCH_3$	21.18	21.13	21.17	21.17	21.07	21.17	171.09	21.17	21.22	21.17	21.15
$OCOCH_3$	171.05	171.03	171.10	171.06	171.02	171.09	21.17	171.13	171.18	171.11	171.12

[a] For solutions in $CDCl_3$ ($SiMe_4$ internal standard) on a Bruker AM300 instrument. [b] Assignments are based on C, H correlation (**1a**) and COSY spectra (**6a**) and (**6b**). [c,d] Chemical shifts are interchangeable or overlapping within a column.

silica. Elution with 10–15% dichloromethane–hexane gave fractions (3.1 g) of the vinyl chlorides (**2a**). Elution with 1% acetone–dichloromethane gave fractions (858 mg) which after recrystallization from dichloromethane–methanol gave the *dimer* (**3**) (233 mg), m.p. 218–222 °C (Found: C, 68.6; H, 8.6; Cl, 9.4. $C_{42}H_{62}Cl_2O_6$ requires C, 68.7; H, 8.5; Cl, 9.7%). Analogous reduction of testosterone acetate gave a crude product showing one component on TLC corresponding to the 5α (δ 5.54, m, 3 H) and 5β (δ 5.66, m, 3 H) C-3 olefin (1.7:1) by ^1H NMR.

17β-*Acetoxy*-4-*chloroestr*-4-*en*-3-*one* (**1b**).—To a stirred solution of 17β-acetoxyestr-4-en-3-one (2 g) in dry pyridine (20 ml) cooled in an ice-bath was added dropwise sulphonyl chloride (10.4 ml) as described by Mori.[12] Dilution with water followed by ether extraction gave, after recrystallization from dichloromethane–methanol, the 4-*chloro ketone* (**1b**) (1g), m.p. 175–180 °C (Found: C, 71.5; H, 8.3; Cl, 10.3. $C_{20}H_{27}ClO_2$ requires C, 71.7; H, 8.1; Cl, 10.6%).

17β-*Acetoxy*-4ξ-chloro-3,4-*epoxy*-5ξ-*androstane* (**4a**).—A mixture of 5α- and 5β-vinyl chlorides (**2a**) (2.93 g) was dissolved in dichloromethane (225 ml) and 85% *m*CPBA (5.10 g) added and the solution set aside at room temperature for 18 h. TLC (10% dichloromethane–hexane) showed no starting material and a more polar product. The mixture was stirred with an excess of 10% aqueous sodium sulphite for 0.5 h. The organic layer was separated and washed thoroughly with sodium sulphite solution and excess of aqueous 10% sodium carbonate to yield the chloro epoxides (**4a**) (3.15 g).

17β-*Acetoxy*-3β-*chloro*-5α-*androstan*-4-*one* (**5**).—To the chloro epoxides (**4a**) (340.5 mg) in DMA (23 ml) was added calcium carbonate powder (1.8 g) and the mixture heated to reflux for 35 min, by which time TLC indicated no starting material remained. Ether and water were added and the ether layer was washed with dilute HCl, to give a product which was chromatographed over silica. Elution with 15% dichloromethane–hexane gave a mixture of 3-chloro-5ξ-4-ketone isomers (55 mg); δ 0.74—0.7 (13-Me in isomers), 1.23, 1.25 (10-Me), 2.00, 2.02, 2.03 (17β-OAc), 4.17 (br s, C-3 equatorial H), and 4.38-4.63 (C-3 axial H and 17α-H). Elution with 20–45% dichloromethane–hexane gave the 3β-*chloro ketone* (**5**) (160 mg), m.p. 221–225 °C; recrystallization from dichloromethane–methanol gave m.p. 224–227 °C (Found: C, 68.6; H, 8.6; Cl, 9.4. $C_{21}H_{31}ClO_3$ requires C, 68.7; H, 8.5; Cl, 9.7%).

17β-*Acetoxy*-5α-*androst*-2-*en*-4-*one* (**6a**).—The chloro epoxides (**4a**) (3.15 g) were stirred and heated to reflux in DMF (83 ml) with lithium carbonate (4.0 g) and lithium bromide (4.65 g) for 1.5 h. Water and ether were added and the ether layer washed with water and dilute HCl to give a product which, when eluted from silica in 10% dichloromethane–hexane, gave the 2-*en*-4-*one* (1.12 g), m.p. 181–186 °C (lit.,[13] 182–184 °C). Further recrystallization from dichloromethane–methanol gave m.p. 184–186 °C (Found: C, 76.1; H, 9.1. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%).

17β-*Hydroxy*-5α-*androst*-2-*en*-4-*one* (**8a**).—The 17-acetate (**6a**) (600 mg) was allowed to stand at room temperature overnight in 0.5M methanolic KOH (36 ml) under N_2. The mixture was acidified with dilute HCl, concentrated at reduced pressure, and extracted with ether to give a product which was passed through silica. Elution with 17% ether–hexane afforded the 17-*alcohol* (**8a**) (200 mg), m.p. 177–181 °C from dichloromethane–ethyl acetate (Found: C, 79.2; H, 9.7. $C_{19}H_{28}O_2$ requires C, 79.1; H 9.8%).

17β-*Acetoxyandrost*-5-*en*-4-*one* (**7**).—(*a*) *By s-collidine reflux.* The chloro epoxides (**4a**) (340.5 mg) were heated to reflux in s-collidine (10 ml) for 4 h. The mixture was poured into water, extracted with ether, and the ether layer washed with excess dilute HCl. The residue was passed through silica in dichloromethane to yield a crystalline mixture of (**6a**)–(**7**) (1:2) (144 mg) based upon the downfield ^1H NMR spectrum

{5.99 (dd), 6.78 [ddd, C-1 and -2 of (**6**)] 6.41 [dd, C-6 of (**7**)]} from which the 5-en-4-one (**7**) was crystallized from dichloromethane–methanol, m.p. 114–117 °C (lit.,[14] 115–117 °C).

(*b*) *By thermolysis.* The chloro epoxides (**4a**) (781 mg) were heated at reduced pressure on an oil bath at 203–216 °C for 10 min and the product placed on silica. After elution with hexane and increasing concentrations of dichloromethane in hexane, crystalline fractions (285 mg) were obtained, which on recrystallization from dichloromethane–methanol yielded the 5-en-4-one (**7**) (145 mg), m.p. 110–112 °C (lit.,[14] 115–117 °C).

17β-*Acetoxy*-5α-*estr*-2-*en*-4-*one* (**6b**).—17β-Acetoxy-4-chloro-estr-4-en-one (**1b**) (1.56 g) was treated with zinc (32 g) and acetic acid (80 ml) as described for (**1a**) and the product chromatographed to give fractions corresponding to the vinyl chlorides (**2b**) (1.21 g) which were treated with 85% *m*CPBA (2.1 g) in dichloromethane (92 ml) as described for (**2a**). The chloro epoxides (**4b**) (1.43 g) were treated with lithium bromide (2.2 g) and lithium carbonate (1.9 g) in DMF (40 ml) as for (**4a**) to give the 2-*en*-4-*one* (**6b**) (135 mg), m.p. 184–186 °C from dichloromethane–acetone (Found: C, 76.1; H, 9.2. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%).

17β-*Hydroxy*-5α-*estr*-2-*en*-4-*one* (**8b**).—The 17-acetate (**6b**) (300 mg) was treated with 0.5M methanolic KPH (30 ml) as described for (**6a**) to give after elution with 8% ether–hexane the 17-*alcohol* (**8b**) (100 mg), m.p. 165–169 °C from dichloromethane–ethyl acetate (Found: C, 78.9; H, 9.4. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%).

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