Unusual Enolizations in 19-Nor-3-ketosteroids

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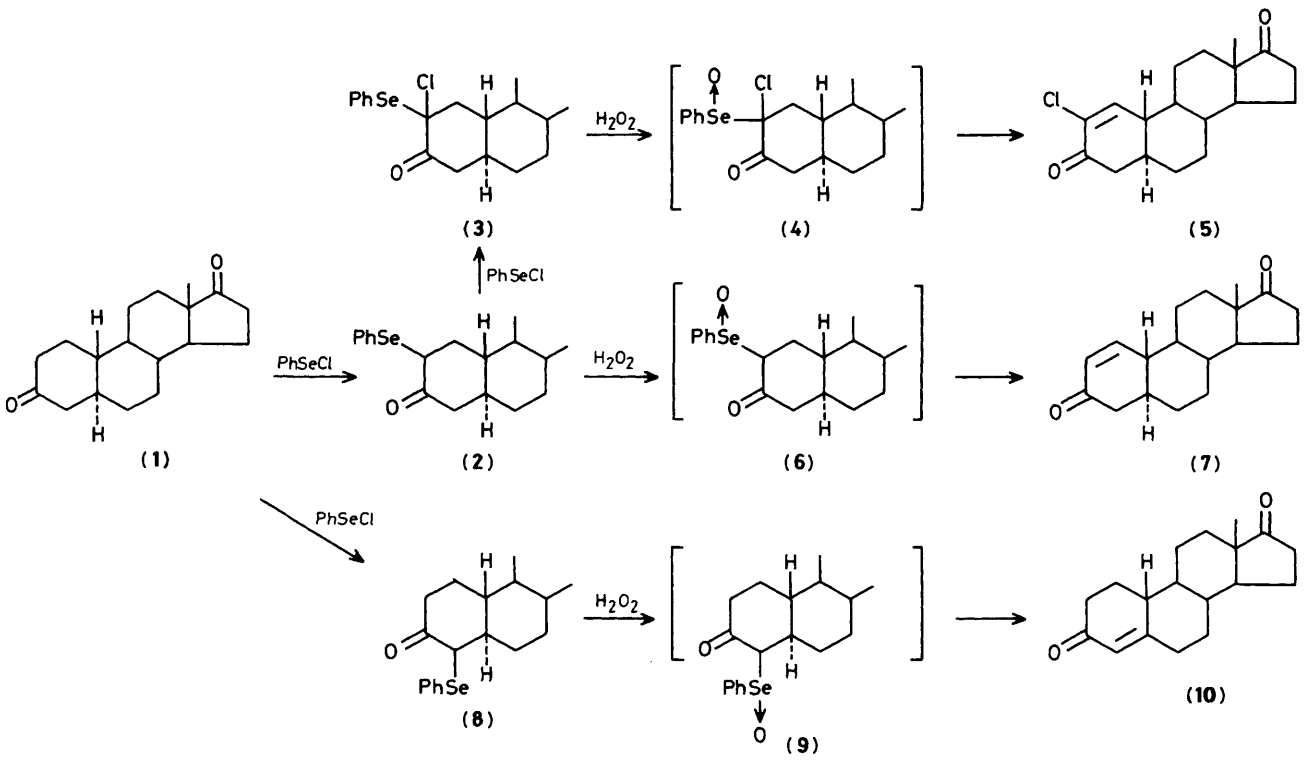
The direction of enolization of 19-nor-3-ketosteroids was found to proceed predominantly towards C-2 irrespective of the ring junction at C-5.

In a study dealing with the mechanism of estrogen binding to macromolecules, we wished to prepare 5α-estr-1-ene-3,17-dione (**7**) as an intermediate in our synthetic scheme. Our efforts in this research have uncovered some interesting observations on the enolization of 5α- and 5β-3-ketoestranes. The synthesis of enone (**7**) was carried out as shown in Scheme 1. Thus, treatment of 5α-estrane-3,17-dione (**1**) with phenylselenenyl chloride by the general procedure of Sharpless *et al.*[1] gave the corresponding α-phenylselenenyl derivatives (**2**), (**3**), (**8**) presumably *via* the enol form of the 3-ketone. Treatment of the seleno compounds with 30% H_2O_2 led to the formation of the selenoxides (**4**), (**6**), (**9**) which eliminate at room



Scheme 1

temperature to yield 15% of 2-chloro-5α-estr-1-ene-3,17-dione (**5**), 55% of 5α-estr-1-ene-3,17-dione (**7**), and 24% of estr-4-ene-3,17-dione (**10**).† The selenoxide intermediates have not been isolated but are presumed to be formed and undergo 1,4-elimination as described by Sharpless *et al.*[1]

It is interesting to note that the formation of compound (**5**) is unusual and would constitute the first observation in which a chloro group is introduced using PhSeCl. While the exact mechanism for formation of compound (**5**) is speculative at this time, it is possible that compound (**2**) reacts with another molecule of PhSeCl in which the chloro group acts as an electrophile leading to the formation of compound (**3**). Studies will be carried out to elucidate this mechanism.

The yield of Δ^4-3-one from the 5α-3-one in the estrane series is not altogether unexpected. For the 19-methyl series, Corey *et al.*[2] have calculated that a Δ^3-double bond forces the 6β-H and 19-Me group closer together and hence, for the 19-methyl series, a 5α-3-one preferentially enolizes to give the Δ^2-double bond. Furthermore, Djerassi[3] has shown that non-bonding interactions and hyperconjugation contribute to the direction of enolization of 5α-3-ones, although certainly the steric interactions are the major factors. However, in the estrane series, this steric interaction is not a factor. The results obtained by Sharpless *et al.*[1] using 5α-cholestan-3-one as starting material further support the predominant direction of enolization in the 5α-series (Table 1). Essentially similar results were obtained using 5α-androstane-3,17-dione (**14**), giving (**15**), (**16**), and (**17**).‡

Thus our initial studies suggest that enolization of 5α-3-ketosteroids in the 19-nor series is substantially different from that in the 19-methyl series which led us to investigate the dehydrogenation of 5β-estrane-3,17-dione (**11**). Unlike the 5α-3-ketosteroids, enolization of 5β-3-ketosteroids is directed predominantly towards C-4.[2] The results obtained from our studies on the dehydrogenation of 5β-androstane-3,17-dione (**18**) using PhSeCl showed the predominant formation of Δ^4-3-ketone (**20**).§ However, when 5β-estrane-3,17-dione (**11**) was dehydrogenated similarly, the predominant product was 5β-estr-1-ene-3,17-dione (**12**) (Table 1).¶ These studies indicate that the direction of enolization in the 19-nor steroids is towards C-2 irrespective of the ring junction at C-5.

† *Physical data:* (**5**): m.p. 176—178 °C; i.r. (KBr) 1730 (17-ketone), 1690 cm^{-1} (3-ketone); u.v. (EtOH) 249 nm (ε 16 100); ^1H n.m.r. ($CDCl_3$) 0.92 (s, 3H, C-18 Me), 7.24 (d, 1H, *J* 5.7 Hz, C-1 H); the electron impact spectrum shows a parent ion *m/z* 306 and a significant *M* + 2 (308, 1/3 as high as 306 peak height) which is common to chloro compounds owing to chlorine 37. Satisfactory elemental analyses were obtained.

(**7**): m.p. 135—136 °C; i.r. (KBr) 1730 (17-ketone), 1685 cm^{-1} (3-ketone); ^1H n.m.r. ($CDCl_3$) 0.93 (s, 3H, C-18 Me), 6.08 (d, 1H, *J* 10 Hz, C-2 H), 7.16 (dd, 1H, *J* 10, 5.7 Hz, C-1 H); *m/z* 272 (M^+). Satisfactory elemental analyses were obtained.

(**10**): m.p. 171—173 °C; this compound was found to be identical in all respects to an authentic sample.

‡ *Physical data:* (**15**): m.p. 139—140 °C; ^1H n.m.r. 0.91 (s, 3H), 1.05 (s, 3H), 5.86 (d, 1H, *J* 10 Hz), 7.12 (d, 1H, *J* 10 Hz); i.r. is identical to authentic sample.

(**16**): m.p. 170—172 °C; identical in all respects to an authentic sample of androst-4-enedione.

(**17**): m.p. 141—142 °C; identical to an authentic sample of androsta-1,4-dienedione.

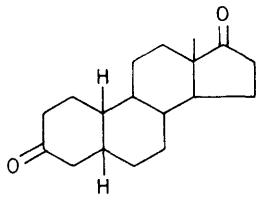
§ *Physical data:* (**19**): m.p. 168—169 °C, ^1H n.m.r. 0.90 (s, 3H), 1.23 (s, 3H), 5.90 (d, 1H, *J* 10 Hz, C-2 H), 6.81 (d, 1H, *J* 10 Hz, C-1 H).

(**20**): m.p. 170—172 °C; n.m.r. and i.r. identical to androst-4-enedione.

(**21**): m.p. 140—142 °C; n.m.r. and i.r. identical to androsta-1,4-dienedione.

¶ *Physical data:* (**12**): m.p. 185—187 °C; *m/z* 272 (M^+); ^1H n.m.r. 0.93 (s, 3H), 5.99 (d, 1H, *J* 10 Hz, C-2 H); 7.08 (dd, 1H, *J* 10, 2 Hz, C-1 H). Satisfactory elemental analyses were obtained.

(**13**): m.p. 171—173 °C; *m/z* 272 (M^+); ^1H n.m.r. 0.93 (s, 3H), 5.85 (s, 1H); i.r. identical to Δ^4-estrene-3,17-dione.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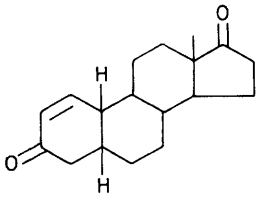
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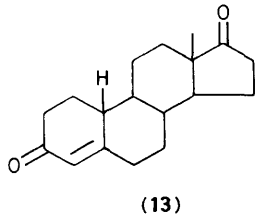
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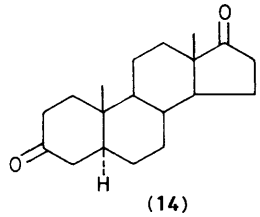
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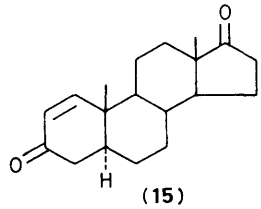
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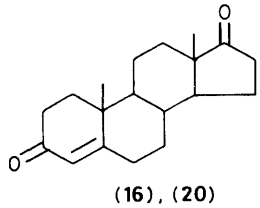
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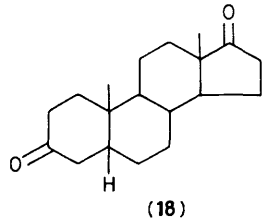
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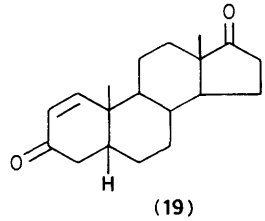
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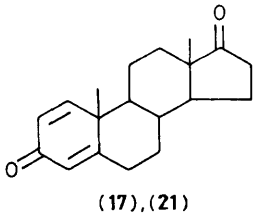
(17), (21)

In view of the fact that the synthesis of Δ^1-5β-3-ketosteroids involves several steps and is normally difficult to obtain,[4—6] the use of PhSeCl seems to provide a simple, convenient and the most efficient method yet reported for the synthesis of Δ^1-5β-19-nor-3-ketosteroids.

Table 1. Dehydrogenation of 5α- and 5β-3-ketosteroids with phenylselenenyl chloride/H_2O_2.

Starting Material	Products	Yield,[a] %
19-Norsteroids		
5α-Estrane-3,17-dione (**1**)	2-Chloro-5α-estr-1-enedione (**5**)	15
	5α-Estr-1-enedione (**7**)	55
	Estr-4-enedione (**10**)	24
5β-Estrane-3,17-dione (**11**)	5β-Estr-1-enedione (**12**)	88
	Estr-4-enedione (**13**)	4
19-Methylsteroids		
5α-Cholestan-3-one[b]	5α-Cholest-1-enone	84
	Cholest-4-enone	2
	Cholesta-1,4-dienone	4
5α-Androstane-3,17-dione (**14**)	5α-Androst-1-enedione (**15**)	89
	Androst-4-enedione (**16**)	2
	Androsta-1,4-dienedione (**17**)	4
5β-Androstane-3,17-dione (**18**)	5β-Androst-1-enedione (**19**)	16
	Androst-4-enedione (**20**)	74
	Androsta-1,4-dienedione (**21**)	4

[a] Yields are based on isolated products. [b] Results reported in ref. 1.

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