A ^{2}H N.M.R. study of the Steroidal Dienone–Phenol Rearrangement

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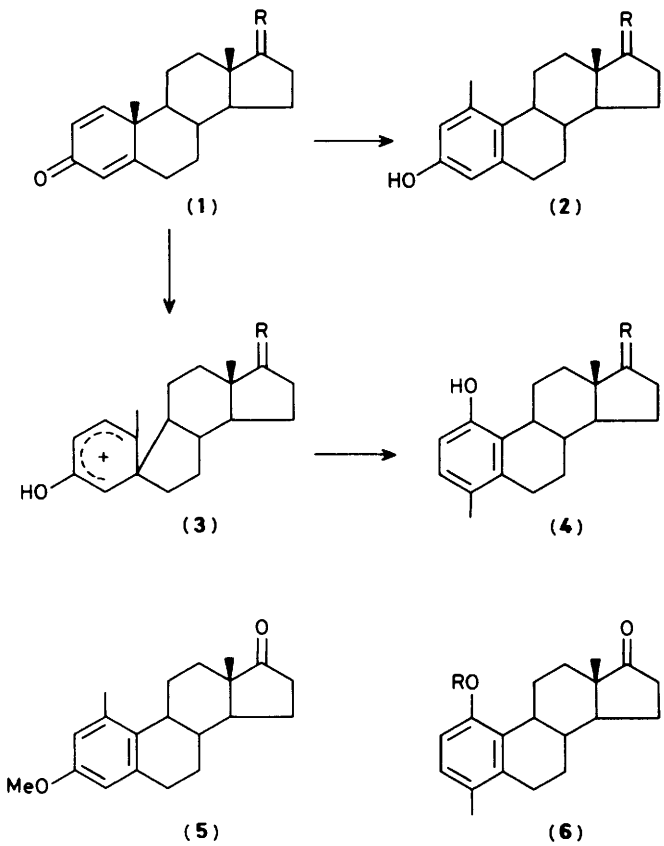
The extent of deuteriation is reported for the products of the dienone–phenol rearrangement of androsta-1,4-dien-3-ones using as catalysts (i) deuteriated acetic anhydride, acetic acid, and zinc chloride; (ii) deuterium bromide; and (iii) methan[^{2}H]ol, ethyl orthoformate, and [$^2H_2$]sulphuric acid. The stereochemistry of the acid-catalysed enolization of 1-dehydrotestosterone is also reported.

The mechanism of the steroidal dienone–phenol rearrangement has been examined on a number of occasions.[1] When a steroidal 1,4-dien-3-one (**1**) is treated with acid two sets of products are formed,[2] a '*meta*'-phenol (**2**) arising by the 1,2-shift of the C-19 methyl group from C-10 to C-1 and a *para*-phenol (**4**) arising *via* a spiranic intermediate (**3**). With mineral acid, the '*meta*'-phenol is the major product whilst the '*para*'-phenol predominates when zinc chloride is used as a catalyst.[3,4] Under hyperacid conditions, *e.g.* HF–SbF_5, products of further deep-seated rearrangements are observed.[5] Since the ratio of '*meta*' (**2**) to '*para*' (**4**) phenols which are formed by the dienone–phenol rearrangement is very dependent upon the reagents used, we considered the possibility that the formation of one phenol might lie through protonation of the 1,3,5(6)-trienol whilst the other phenol might be formed directly without the intervention of C-6. Hence it was the object of this ^{2}H n.m.r. study to identify those centres which might be involved either in the dienone–phenol reactions leading to both types of phenol or in competing equilibria such as the enolization of the dienone. We have recently examined the dienol–benzene reaction in this way.[6] Three sets of reaction conditions were examined: (i) zinc chloride, acetic anhydride, and acetic acid;[3] (ii) hydrobromic acid;[2] (iii) ethyl orthoformate, methanol, and sulphuric acid.[7] In each case deuteriated reagents (≥98%) were used and the products were examined by ^{1}H (360 MHz) and ^{2}H (55.2 MHz) n.m.r. spectroscopy.

A prerequisite to this work was the assignment of the proton resonances that lie within the complex methylene envelope of the dienones (**1**; R = OH and R = O) and the phenols (**2**; R = O) and (**4**; R = O). The ^{1}H n.m.r. spectrum of 1-dehydrotestosterone (**1**; R = OH) has already been completely assigned[8] by a combination of one- and two-dimensional n.m.r. techniques. In particular, signals at δ 2.36 and 2.47 had been assigned to the 6α-H and 6β-H resonances respectively. The same signals appeared in the 360 MHz ^{1}H n.m.r. spectrum of androsta-1,4-diene-3,17-dione (**1**; R = O). The ^{13}C n.m.r. spectra of a number of oestratrienes have been assigned,[9,10] permitting the analysis of the spectra of (**2**; R = O) and (**4**; R = O). Consequently, using two-dimensional ^{1}H–^{13}C n.m.r. correlated spectroscopy, it was then possible to identify all the proton resonances (see Table 1). The 6α-H resonances appeared as a doublet (*J* 17 Hz) of double-doublets (*J* 2 and 5 Hz) at δ 2.70 and 2.71 in (**2**; R = O) and (**4**; R = O) whilst the 6β-H resonances appeared as a partly overlapped octet (*J* 5, 12, and 17 Hz) at δ 2.88 in (**2**; R = O) and δ 2.62 in (**4**; R = O).

Since enolization is likely to be a competitive reaction, the stereochemistry of enolization of 1-dehydrotestosterone (**1**; R = OH) in deuterium bromide was examined. The exchange reaction was carried out at 55 °C for 6 h. Mass spectral analysis of the recovered 1-dehydrotestosterone (20%) showed that it contained 77.8% $^2H_0$, 11.6% $^2H_1$, 8.5% $^2H_2$, and 2.2% $^2H_3$ species whilst the ^{1}H and ^{2}H n.m.r. spectra showed that the label was at 4-H (0.11 atom), 6α-H (0.04 atom), and 6β-H (0.15 atom). The amount of deuterium at each centre was determined by the decrease in the ^{1}H integral compared to the 17-H integral. In contrast, the acid-catalysed enolization of testosterone has been shown[11] to involve preferentially the 2- and 6β-positions and there was no observable exchange at C-4 under acidic conditions.



The acid-catalysed deuteriation of the phenolic products was also examined. The '*para*'-phenol (**4**; R = OH) was treated with deuterium chloride in acetic [^{2}H]acid for 1.5 h under reflux. The ^{1}H and ^{2}H n.m.r. spectra showed that the product possessed, as expected, 0.77 atom deuterium at C-2. Treatment of the '*meta*'-phenol methyl ether (**5**) with methan [^{2}H]ol and [$^2H_2$]sulphuric acid in ethyl orthoformate for 1.5 h under reflux led to a substantial incorporation of deuterium: 0.85 atom at C-2, 0.65 atom at C-4, and 1.0 and 0.9 atom at C-16.

Table 1. ^{13}C and ^{1}H N.m.r. signals of the phenols (**2**; R = O) and (**4**; R = O) (determined at 90.55 and 360 MHz in $CDCl_3$)

Carbon atom	Phenol (**2**; R = O)		Phenol (**4**; R = O)	
	^{13}C	^{1}H	^{13}C	^{1}H
1	138.7		153.3	
2	113.5	6.4	113.3	6.48
3	153.2		127.9	6.84
4	116.4	6.49	126.7	
5	139.8		138.3	
6	32.3	(α), 2.70; (β), 2.88	29.1	(α), 2.71; (β), 2.62
7	27.6	(α), 1.30; (β), 2.47	25.4	(α), 1.3; (β), 1.94
8	41.5	1.65	40.1	1.6
9	46.6	2.38	45.5	2.47
10	130.6		128.7	
11	24.9	1.25, 1.85	26.0	1.3, 3.19
12	32.4	1.7, 1.82	32.6	1.6, 1.84
13	48.8		48.7	
14	50.8	1.54	50.8	1.55
15	21.7	1.7, 2.01	21.8	1.71, 2.04
16	35.9	2.14, 2.46	35.9	2.15, 2.53
17	220.6		220.7	
18	14.7	0.95	14.6	0.95
19	22.3	2.29	19.1	2.15

Coupling constants for rings A and B: (**2**; R = O) *J* 2,4 2.7 Hz; 6α, 6β 17 Hz; 6α, 7α 5 Hz; 6α, 7β 2 Hz; 6β, 7α 12 Hz; 6β, 7β 5 Hz. (**4**; R = O) *J* 2,3 8 Hz; 6α, 6β 17 Hz; 6α, 7α 5 Hz; 6α, 7β 2 Hz; 6β, 7α 12 Hz; 6β, 7β 5 Hz.

Table 2. Deuterium labels in the products of the dienone–phenol reactions

Compd.	Site of deuteriation						
	2-H	3-H	4-H	6α-H	6β-H	16-H	
Reaction of (1; R = O) with deuterium bromide							
(**1**; R = O)			0.32	0.4	0.6	1.0	1.0
(**2**; R = O)	0.06		0.06	0.03	0.06	0.35	0.65
(**4**; R = O)	0.4	0.6		0.03	0.06	0.4	0.72
Reaction of (1; R = O) with methan[^{2}H]ol, ethyl orthoformate, and [$^{2}H_2$]sulphuric acid							
(**5**)	0.82		0.39	0.64	0.89	0.89	0.93
(**6**; R = Me)	0.13			0.63	1.0	1.0	1.0
(**6**; R = Et)	0.14			0.64	1.0	1.0	1.0

The extent of deuteriation was calculated by taking the integral in the ^{1}H n.m.r. spectrum (determined at 360 MHz) for H-18 = 3 protons and then calculating the decrease in the relevant ^{1}H n.m.r. integral at the deuteriated centre. The ^{2}H n.m.r. spectrum (determined at 55.28 MHz) was superimposed on the ^{1}H spectrum to facilitate the calculation.

Treatment of androsta-1,4-diene-3,17-dione (**1**; R = O) with deuteriated acetic anhydride–acetic acid–zinc chloride gave 1-hydroxy-4-methyloestra-1,3,5(10)-trien-17-one (**4**; R = O) (86% yield) and 1-methyl-3-hydroxyoestra-1,3,5(10)-trien-17-one (**2**; R = O) (6% yield). Previous workers[3] had only isolated the '*para*'-phenol. The phenols were treated with methanolic potassium hydroxide to remove any label from C-16. They then contained no deuterium. A control experiment in which both phenols were treated with 5% methanolic sodium deuteroxide showed that exchange occured only at C-16 and that no exchange took place on the aromatic ring. Under more vigorous conditions (3 days reflux in deuterium oxide containing sodium deuterioxide), the '*para*' phenol (**4**; R = O) exchanged 0.17 atom at C-2 and the '*meta*'-phenol (**5**) exchanged 0.67 atom at C-2 and 1.0 atom at C-4. Djerassi observed[12] exchange only at C-4 with oestrone under these conditions.

Treatment of androsta-1,4-diene-3,17-dione (**1**; R = O) with deuterium bromide in deuterium oxide gave a higher yield (59.3%) yield of the '*meta*'-phenol (**2**; R = O) and only 11% of the '*para*'-phenol (**4**; R = O) together with recovered starting material (5%). ^{1}H and ^{2}H N.m.r. (see Table 2) showed that the '*meta*'-phenol contained small amounts of deuterium at C-2, C-4, and C-6β with rather less at C-6α and substantial amounts of deuterium at C-16. The '*para*'-phenol was labelled at C-2, C-3, and C-16 and again to a small extent at C-6β and to a lesser extent at C-6α. The recovered starting material showed labels at C-4, C-6, and C-16.

The reaction of androsta-1,4-diene-3,17-dione (**1**; R = O) with ethyl orthoformate in methanol containing sulphuric acid, was originally examined in the context of enol–ether formation.[7] The original paper only described the isolation of the ether corresponding to the alcoholic solvent and the formation of some '*meta*'-product. In our study we were able to isolate both the ethyl (**6**; R = Et) and the methyl ether (**6**; R = Me) together with the '*meta*'-methyl ether (**5**). As would be expected from conditions designed to stabilize enol–ether formation, the ^{1}H and ^{2}H n.m.r. spectra (see Table 2) showed a substantial incorporation of deuterium at both the C-6α and C-6β positions as well as at C-16. However the '*para*'-phenol ethers showed a relatively small amount of deuterium (0.13 and 0.14 atom) at C-2 whilst the '*meta*'-phenol ether showed a larger amount of deuterium at both C-2 (0.82 atom) and C-4 (0.39 atom). This may arise by exchange after the aromatization since the '*meta*'-ether (**5**) readily incorporated deuterium under these reaction conditions.

The following conclusions can be drawn from this work. Firstly, the absence of deuterium from centres elsewhere in the steroid molecule such as C-8, C-9, and C-14 precludes their involvement in the aromatization reaction. Secondly, the absence of deuterium on the aromatic ring in the case of the zinc chloride–acetic acid–acetic anhydride system and its presence in non-integral amounts that can be accounted for by post-aromatization exchange in the products from the other systems, precludes C-protonation steps from the mechanism of the reaction. Thirdy, the presence of deuterium at C-6, particularly at the β-position, suggests that in some circumstances enolization is a competing reaction. However the presence of deuterium at this centre in comparable amounts in both the '*meta*'- and '*para*'-phenols suggests that these are formed *via* a common cation rather than one being formed *via* the enol and the other directly from a carbonyl protonated species.

Experimental

The ^{1}H, ^{2}H and ^{13}C n.m.r. spectra were obtained on a Bruker WH 360 spectrometer for solutions in chloroform. Light petroleum refers to the fraction of b.p. (60—80 °C).

Acid-catalysed Exchange Reactions.—(a) 17β-Hydroxyandrosta-1,4,-dien-3-one (400 mg) was suspended in 47% aqueous deuterium bromide (5 ml) and heated at 55 °C for 6 h. The solution was cooled and the precipitate (400 mg) was subjected to flash chromatography on silica in 30% ethyl acetate–light petroleum to give 17β-hydroxyandrosta-1,4-dien-3-one (55 mg) which was examined by mass spectroscopy and by ^{1}H and ^{2}H n.m.r. spectroscopy (see below).

(6) 1,17β-Dihydroxy-4-methyloestra-1,3,5(10)-triene (100 mg) was heated under reflux for 15 min in a mixture of deuterioacetic acid (1 ml) and deuterium chloride (20% DCl in D_2O)(0.3 ml). The solution was poured into ice–water and the precipitate was collected and treated with sodium methoxide (50 mg) in methanol (5 ml) at room temperature overnight to

hydrolyse the acetates. The solution was then poured into water, acidified, and the product was recovered and crystallized as needles (58 mg), m.p. 238—240 °C. The ratio of the integrals of the ^1H signal at δ 6.50 (2-H) δ 6.87 (3-H), and δ 0.85 (18-H_3) was 0.32:1:3.

(c) 3-Methoxy-1-methyloestra-1,3,5(10)-trien-17-one (137 mg) was heated under reflux for 1.5 h in methan[^{2}H]ol (3 ml), ethyl orthoformate (1.5 ml), and sulphuric acid (0.01 ml). The solution was poured into water (10 ml) and the mixture stirred for 2 h; the precipitate was then recrystallized from acetone–light petroleum to give needles (50 mg) of the [^{2}H]-3-methoxy-1-methyloestra-1,3,5(10)-trien-17-one, m.p. 129—130 °C, δ_{2H} 2.10, 2.47, 6.54, and 6.60 (1.0:0.90:0.85:0.65).

Aromatization Reactions.—(a) Androsta-1,4-diene-3,17-dione (500 mg)[13] was dissolved in glacial acetic [^{2}H]acid (1.0 ml) containing freshly fused zinc chloride (50 mg) and [$^2H_6$]acetic anhydride (5 ml) and left at room temperature for 4 days by which time t.l.c. showed that the reaction was complete. The solution was poured into cold 10% aqueous sodium hydroxide (60 ml) and the products were recovered in ethyl acetate. The solvent was evaporated and the residue (500 mg) was heated under reflux in 5% methanolic potassium hydroxide (25 ml) for 1 h. Most of the methanol was evaporated and the residue was poured into dilute hydrochloric acid. The steroids were recovered in ethyl acetate. The solvent was evaporated and 1-hydroxy-4-methyloestra-1,3,5(10)-trien-17-one (**4**; R = O) (320 mg) was crystallized from acetone as prisms, m.p. 250—254 °C (lit.,[2] 247—249 °C). Chromatography of the mother liquors on silica and elution with 10% ethyl acetate–light petroleum gave a further quantity of (**4**; R = O) (108 mg) and 3-hydroxy-1-methyloestra-1,3,5(10)-trien-17-one (**2**; R = O) (30 mg) which crystallized from methanol as prisms, m.p. 250—254 °C (lit.,[2] 248—250 °C). No deuterium label was detected by ^{2}H n.m.r. analysis.

(b) Androsta-1,4-diene-3,17-dione (1 g) was left in 47% aqueous deuterium bromide (10 ml) at room temperature for 2 days and then heated in an oil bath at 55 °C for 1 day. The precipitate was collected and recrystallized from methanol to afford 3-hydroxy-1-methyloestra-1,3,5(10)-trien-17-one (**2**; R = O) (240 mg), m.p. 250—254 °C. The mother liquors were evaporated and the residue was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 1-hydroxy-4-methyloestra-1,3,5(10)-trien-17-one (**4**; R = O) (124 mg) which recrystallized from methanol as needles, m.p. 254—257 °C; continued elution gave a mixture of the two phenols (**2**; R = O) (**4**; R = O) (288 mg) followed by 3-hydroxy-1-methyloestra-1,3,5(10)-trien-17-one (**2**; R = O) (110 mg), m.p. 250—254 °C. Further elution with 40% ethyl acetate–light petroleum gave androsta-1,4-diene-3,17-dione (**1**; R = O) (50 mg) which crystallized from ethyl acetate–light petroleum as plates, m.p. 142—144 °C.

(c) Androsta-1,4-diene-3,17-dione (1 g) was heated under reflux for 1.5 h in methan[^{2}H]ol (20 ml), ethyl orthoformate (10 ml) containing [$^2H_2$]sulphuric acid (0.14 ml). The solution was poured into water (50 ml), stirred for 2 h, neutralized with saturated sodium hydrogen carbonate, and the products recovered in ethyl acetate. Chromatography on silica gave in the fractions eluted with 5% ethyl acetate–light petroleum, 1-ethoxy-4-methyloestra-1,3,5(10)-trien-17-one (**6**; R = Et) (114 mg) as a gum, $\nu_{max.}$ 1 740, 1 582, 1 260, 1 220, 1 115, 1 060, and 800 cm^{-1}; δ 0.91 (3 H, s, 18-H_3), 2.18 (3 H, s, 4-Me), 3.96 (2 H, q, *J* 7 Hz, OCH_2Me), 6.5 (1 H, d, *J* 8 Hz, 2-H), and 6.92 (1 H, d, *J* 8 Hz, 3-H). Further elution gave 1-methoxy-4-methyloestra-1,3,5(10)-trien-17-one (**6**; R = Me) (210 mg) which crystallized from methanol as plates, m.p. 118—119 °C (lit.,[2] 117—118 °C), $\nu_{max.}$ 1 740, 1 595, 1 580, 1 255, 1 220, 1 080, 1 060, 800 cm^{-1}; δ 0.92 (3 H, s, 18-H_3), 2.13 (3 H, s, 4-Me), 3.72 (3 H, s, OMe), 6.52 (1 H, d, *J* 8 Hz, 2-H), and 6.9 (1 H, d, *J* 8 Hz, 3-H). Further elution then gave1-methyl-3-methoxyoestra-1,3,5(10)-trien-17-one (**5**) which was purified by further chromatography to afford needles (62 mg), m.p. 125—127 °C (lit.,[14] 125—126 °C), $\nu_{max.}$ 1 735, 1 595, 1 585, 1 220, 1 060, and 850 cm^{-1}; δ 0.98 (3 H, s, 18-H_3), 2.35 (3 H, s, 1-Me), 3.72 (3 H, s, OMe), and 6.5 (2 H, br s, $\frac{w}{2}$ 2-,4-H).

Base-catalysed Exchange Reactions.—(a) 1-Hydroxy-4-methyloestra-1,3,5(10)-trien-17-one (50 mg) was heated under reflux for 1 h in methan[^{2}H]ol (5 ml) containing sodium methoxide (from 23 mg sodium). The solution was concentrated, poured into water (10 ml), acidified, and the phenol (**4**; R = O) recovered and crystallized from methanol to give prisms (37 mg), m.p. 250—254 °C; δ_{2H} 2.11 and 2.47.

(b) The phenol (**4**; R = O) (100 mg) was heated under reflux in deuterium oxide (30 ml) containing sodium (100 mg) for 3 days. The solution was acidified and the product recovered to afford 1-hydroxy-4-methyloestra-1,3,5(10)-trien-17-one (20 mg); δ_{2H} 2.11, 2.47, and 6.54 (1:1:0.17) p.p.m.

(c) 3-Hydroxy-1-methyloestra-1,3,5(10)-trien-17-one (**2**; R = O) (50 mg) in methan[^{2}H]ol (5 ml) and sodium (23 mg) was heated under reflux for 1 h. The product (31 mg), m.p. 250—254 °C showed (mass spectroscopy) 4.6% $^2H_1$, 93.2% $^2H_2$, and 2.2% $^2H_3$. Repetition of the more vigorous conditions (expt. b) gave material showing δ_{2H} n.m.r. signals at 2.10, 2.46, 6.47, and 6.51 (1:1:1.0:0.67) p.p.m.

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