A ^{2}H N.M.R. Study of the Dienol–Benzene and Related Steroid Aromatization Reactions†

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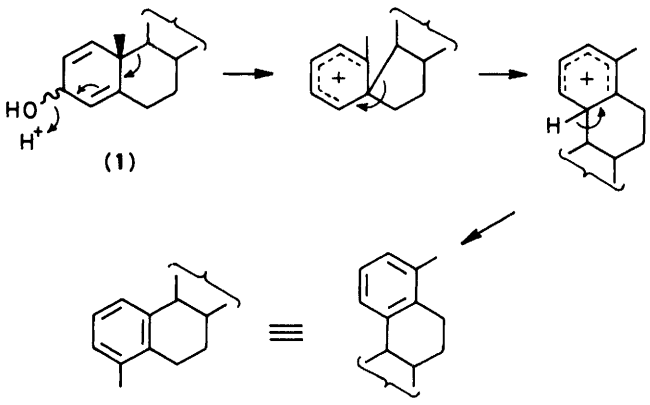
^{2}H N.m.r. studies have shown that when the dienol–benzene rearrangements of 5α,6β-epoxy-3β-mesyloxyandrostan-17-one, the corresponding 5α,6β-bromohydrin, 4β-acetoxy-3β-mesyloxyandrost-5-en-17-one, 17β-acetoxy-4β,5β-epoxy-3α-mesyloxyandrostane, and 17β-acetoxy-3β,4β-epoxy-5β-hydroxyandrostane are carried out in ^{2}HBr–$CH_3CO_2{}^2$H, deuterium labels are introduced at predominantly the 6β position and at both 7 positions in the resultant 4-methyloestratriene. However the 4-methyloestratriene arising from a 3-hydroxyandrosta-1,4-diene only bears deuterium labels on the aromatic ring.

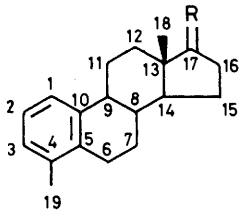
The dienol–benzene aromatization reaction of ring A of the steroids (see Scheme 1)[1] is one example of a more general class of steroid aromatization reaction which requires two double bond equivalents and a carbonium ion source in order to proceed.[2] In our previous work[3-11] we have shown that although the final product may possess an aromatic ring A, some of the double bond equivalents may be associated with ring B. Furthermore, the aromatization reaction utilizes reaction conditions (HBr–glacial CH_3CO_2H) that are similar to those [H_2SO_4–glacial CH_3CO_2H–$(CH_3CO)_2O$] of 'backbone' rearrangements (*e.g.* the Westphalen rearrangement).[1] Other parallel reactions include the formation of α,β-unsaturated ketones from some hydroxyepoxides. Consequently we have undertaken† a ^{2}H n.m.r. analysis of the 4-methyloestratriene obtained from a series of substrates using deuterium bromide in deuterioacetic acid (^{2}HBr–$CH_3CO_2{}^2$H) with the object of defining the centres involved in the reaction.

The assignment of the proton resonances of the 4-methyloestratrienes is a necessary prerequisite to this study. The ^{13}C n.m.r. signals of the 4-methyloestratrienes have been assigned and used in a previous mechanistic study.[12] By carrying out a two-dimensional ^{13}C–^{1}H n.m.r. experiment with 4-methyloestratrien-17-one (**2**) it was possible to correlate the ^{13}C and ^{1}H resonances (see Table 1) and thereby assign the proton signals within the complex aliphatic region of the spectrum. This enabled the 6-H resonances to be identified as a double doublet at δ 2.83 (*J* 6 and 17 Hz) and an overlapping octet at δ 2.67 (*J* 6, 12, and 17 Hz). The latter was assigned to the 6β-axial proton and the former to the 6α-equatorial proton on the basis of these coupling constants. The 7-H resonances appeared within a complex group of multiplets at δ 2.12 and at δ 1.45 (partially obscured octet, *J* 6, 12, 12, and 12 Hz). The magnitude of these coupling constants showed that the latter was the 7α-H_{ax} resonance and hence the former was the 7β-H_{eq} resonance which appeared, as expected, at lower field.

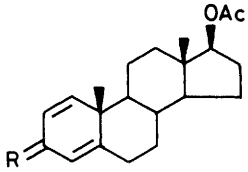
17β-Acetoxyandrosta-1,4-dien-3-one (**3**) was reduced[13] with sodium borohydride and the crude 3-alcohol (**4**) treated with deuterium bromide in deuterioacetic acid. The resultant 17β-acetoxy-4-methyloestratriene (**5**) was hydrolysed with methanolic sodium hydroxide and oxidized to the 17-ketone (**2**).[5] The ^{1}H and ^{2}H n.m.r. spectra (determined at 360 and 55.2 MHz) showed that the product contained deuterium (*ca.* 0.7 atom at C-1, 0.2 atom at C-2, and 0.5 atom at C-3 with *ca.* 0.01 atom at 6β-H). The absence of aliphatic deuterium labels suggested that



Scheme 1.



(**2**) R = O
(**5**) R = α-H, β-OAc



(**3**) R = O
(**4**) R = H, OH

the rearrangement occurred directly as a result of cleavage of the C(3)–O bond rather than *via* prior dehydration to a 1,3,5(6)-triene and then reprotonation. This is in contrast to the results obtained with other substrates. The presence of aromatic deuterium labels is consistent with exchange occurring on the aromatic ring with differing rates at each site.

Treatment of the methanesulphonate of 5α,6β-epoxy-3β-hydroxyandrostan-17-one (**6**)[13] with hydrobromic acid in glacial acetic acid affords 4-methyloestratrien-17-one (**2**). This aromatization reaction probably proceeds *via* a dienol–benzene type pathway, with or without the intervention of a Δ^6-ene (see Scheme 2). Examination of the ^{13}C n.m.r. spectrum of the labelled 4-methyloestratrien-17-one (**2**) produced by the action of deuterium bromide in deuterioacetic acid on compound (**6**), revealed the presence of deuterium on the aromatic ring, at C-6, C-7, and C-16. Comparison of the ^{2}H n.m.r. spectrum with the

† For a preliminary communication of part of this work see: J. R. Hanson and P. B. Reese, *Tetrahedron Lett.*, 1983, 3405.

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

Carbon atom	δ_C/p.p.m.	δ_H/p.p.m. (*J* in Hz)
1	120.08	7.20 (d), 7.5
2	125.48	7.10 (t), 7.5
3	127.51	7.03 (d), 7.5
4	134.93	
5	136.45	
6	26.98	2.83 (dd, *J* 6, 17), 2.67 (oct. *J* 6.5, 12, 17),
7	26.63	2.12 (m), 1.45 (oct. *J* 6.5, 12, 12, 12)
8	37.51	1.58 (m)
9	44.71	2.35 (m)
10	139.68	
11	26.01	2.45 (m), 1.52 (m)
12	31.67	197 (dd, *J* 3, 9), 1.50 (m)
13	47.83	
14	50.62	1.53 (m)
15	21.58	2.1 (m), 1.62 (m)
16	35.88	2.51 (dd, *J* 9 and 19), 2.15 (*J* 9 and 19)
17	220.80	
18	13.79	0.90
19	19.79	2.23

Table 2. Deuterium labels in compound (**2**)*

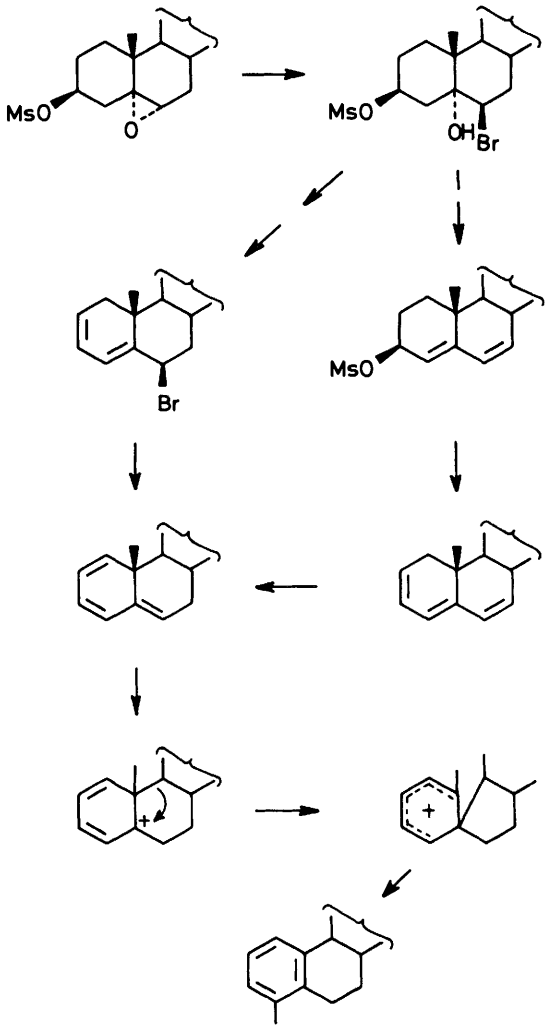
Substrate	1-H	2-H	3-H	6α-H	6β-H	7α-H	7β-H
(**4**)	0.7	0.2	0.5		0.01		
(**6**)	0.8	0.7	0.8	0.2	0.8	0.5	0.5
(**7**)	0.9	0.7	0.9	0.2	0.75	0.6	0.6
(**8**)	0.9	0.9	0.8	0.2	0.75	0.7	0.6
(**9**)	0.9	0.8	0.9	0.3	0.8	0.8	0.7
(**10**)	0.9	0.8	0.9	0.3	0.7	0.6	0.5

* The extent of deuterium labelling was calculated by taking the integral in the ^{1}H n.m.r. spectrum at δ 0.90 (18-H) = 3 protons and then calculating the decrease in ^{1}H integral at δ 2.67 and 2.81. Since the 7-H ^{1}H n.m.r. signals overlap with other resonances, the extent of deuteriation at these centres was calculated from the ^{2}H integral using the 6β-H value as an internal standard. The extent of the aromatic deuteriation was calculated directly from the changes in the ^{1}H integrals.

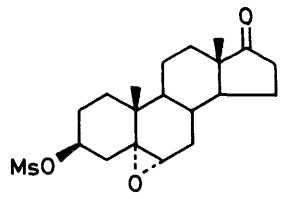
^{1}H n.m.r. spectrum (see Table 2) confirmed the presence of deuterium at 7α-H (δ 1.45), 16-H (δ 2.15 and 2.51) and 6β-H (δ 2.67). The 6α-H resonance at δ 2.8 in the ^{1}H n.m.r. spectrum appeared as a broad singlet (relative integral, 0.8 H). Since one of the 16-H resonances (δ 2.15) overlaps the signal which was assigned to 7β-H (δ 2.12), the sample was treated with methanolic sodium hydroxide to exchange out the labels at C-16. The resultant sample of compound (**2**) contained ^{2}H n.m.r. signals at δ 1.45, 2.1, and 2.65 suggesting that although the C-7 label was almost evenly distributed between 7α-H and 7β-H, the C-6 label was predominantly located at 6β-H.

The bromohydrin (**7**)[6] is a potential intermediate in this rearrangement and, with a 5α-hydroxy group, it might also be a progenitor of any 'backbone' rearrangement. However the ^{1}H and ^{2}H n.m.r. spectra of the resultant 4-methyloestratrien-17-one (determined after exchange of the 16-H label) revealed the incorporation of deuterium at both 7α-H and 7β-H and again predominantly, at 6β-H. 4β-Acetoxy-3β-mesyloxyandrost-5-en-17-one (**8**)[14,15] might aromatize by eliminating directly to give a 1,3,5-triene which could then protonate at C-6 to generate the spiranic intermediate of the dienol–benzene rearrangement. Alternatively a $\Delta^{2,4,6}$-triene might be involved which would then isomerize to the $\Delta^{1,3,5}$-triene prior to aromatization. When the reaction was carried out with deuterium bromide in deuterioacetic acid and followed by base-catalysed exchange to remove the 16-H labels, the resultant 4-methyloestratrien-17-one (**2**) had again incorporated deuterium, at 7α-H and 7β-H as well as at 6β-H. This requires the formation of a 6-ene during the reaction sequence.

17β-Acetoxy-4β,5β-epoxy-3α-mesyloxyandrostane (**9**) and 17-acetoxy-3β,4β-epoxy-5β-hydroxyandrostane (**10**) both possess potential leaving groups that are *trans* to the migrating C(9)–C(10) bond whilst the remaining double bond equivalents are on ring A. Hence it was of interest to see if the reaction was, like that of 17β-acetoxyandrosta-1,4-dien-3-ol (**4**), confined to ring A. The rearrangements were carried out in deuterium bromide–deuterioacetic acid and the resultant 17-acetoxy-4-methyloestratriene was hydrolysed and oxidized to afford 4-methyloestratrien-17-one (**2**). In each case comparison of the ^{1}H and ^{2}H n.m.r. spectra (see Table 2) revealed the presence of deuterium at both 7α-H and 7β-H as well as at 6β-H, with a smaller amount of label at 6α-H. The presence of deuterium at C-7 requires the elimination of the ring A substituents and the formation of a $\Delta^{2,4,6}$-triene with a subsequent double bond migration to form a $\Delta^{1,3,5}$-triene prior to the formation of the spiranic intermediate of the dienol–benzene rearrangement. The predominance of 6β-H (axial) deuteriation is compatible with the migration of the C(9)–C(10) bond. The absence of significant amounts of deuterium at C-8, C-9, and C-14 implies that the



Scheme 2.



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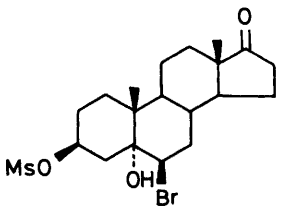

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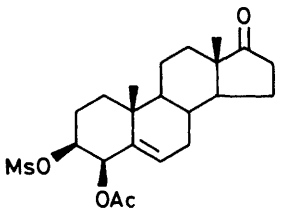

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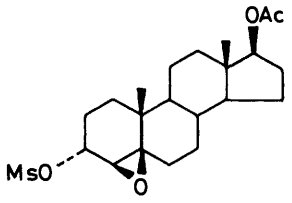

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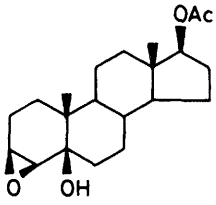

(10)

intermediates in the dienol–benzene pathway are not in equilibrium with those involved in the backbone rearrangement of steroids.

Experimental

The ^1H, ^2H, and ^{13}C n.m.r. spectra were obtained on a Bruker WH 360 spectrometer, for solutions in chloroform.

Aromatization of 17β-*Acetoxy*-3-*hydroxyandrosta*-1,4-*diene* (4).—Sodium borohydride (500 mg) in methanol (10 ml) was added to a solution of 17β-acetoxyandrosta-1,4-dien-3-one (2 g) in methanol (40 ml) at 0 °C. The mixture was stirred for 2 h and then acetic acid (1 ml) was added. The solvent was evaporated, saturated sodium chloride solution was added, and the steroid was recovered in ethyl acetate. The solvent was evaporated and the residue was heated in deuterioacetic acid (10 ml) and 48% deuterium bromide (3 ml) under reflux for 10 min. The solution was cooled and carefully neutralised with aqueous sodium hydrogen carbonate. The steroid was recovered in ethyl acetate. The solvent was evaporated to give a gum which was then dissolved in methanol (150 ml) and stirred with a solution of sodium hydroxide (2 g) in water (5 ml) at 40 °C for 3 h. Acetic acid (4 ml) was added and the solution was concentrated and poured into water. The steroid was recovered in ethyl acetate. Evaporation of the solvent gave a gum which was dissolved in acetone (200 ml). The solution was cooled to −10 °C and the 8N-chromium trioxide reagent (3.5 ml) was added. The mixture was stirred at room temperature for 45 min. Methanol (10 ml) was added and the solvents were evaporated. Water was added and the steroid was recovered in ethyl acetate. The solvent was evaporated to give a gum which was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave [^2H]-4-methyloestra-1,3,5(10)-trien-17-one [^2H]-(2) (320 mg) which crystallized as plates, m.p. 188—191 °C, $[\alpha]_D$ +150° (*c* 0.3) (lit.,[16] m.p. 190—192 °C, $[\alpha]_D$ +144°), identified by its i.r. and n.m.r. spectra.

General Aromatization Procedure.—The steroid (1 g) in deuterioacetic acid (6 ml) was treated with 48% deuterium bromide (2 ml) and heated under reflux for 30 min. The solution was cooled and neutralised with aqueous sodium hydrogen carbonate. The steroid was recovered in ethyl acetate. The solvent was evaporated and the residue dissolved in methanol (50 ml) and heated under reflux with sodium hydroxide (200 mg) in water (2 ml) for 2 h. The solution was cooled, neutralised with acetic acid and the solvents were evaporated. The product was recovered in ethyl acetate and chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave 4-methyloestratrien-17-one (2) (*ca.* 200 mg) which was crystallized from ethyl acetate–light petroleum and identified by its i.r. and n.m.r. spectra.

Acknowledgements

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