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A DEUTERIUM NMR STUDY OF 4-METHYLOESTRATRIENE FORMATION

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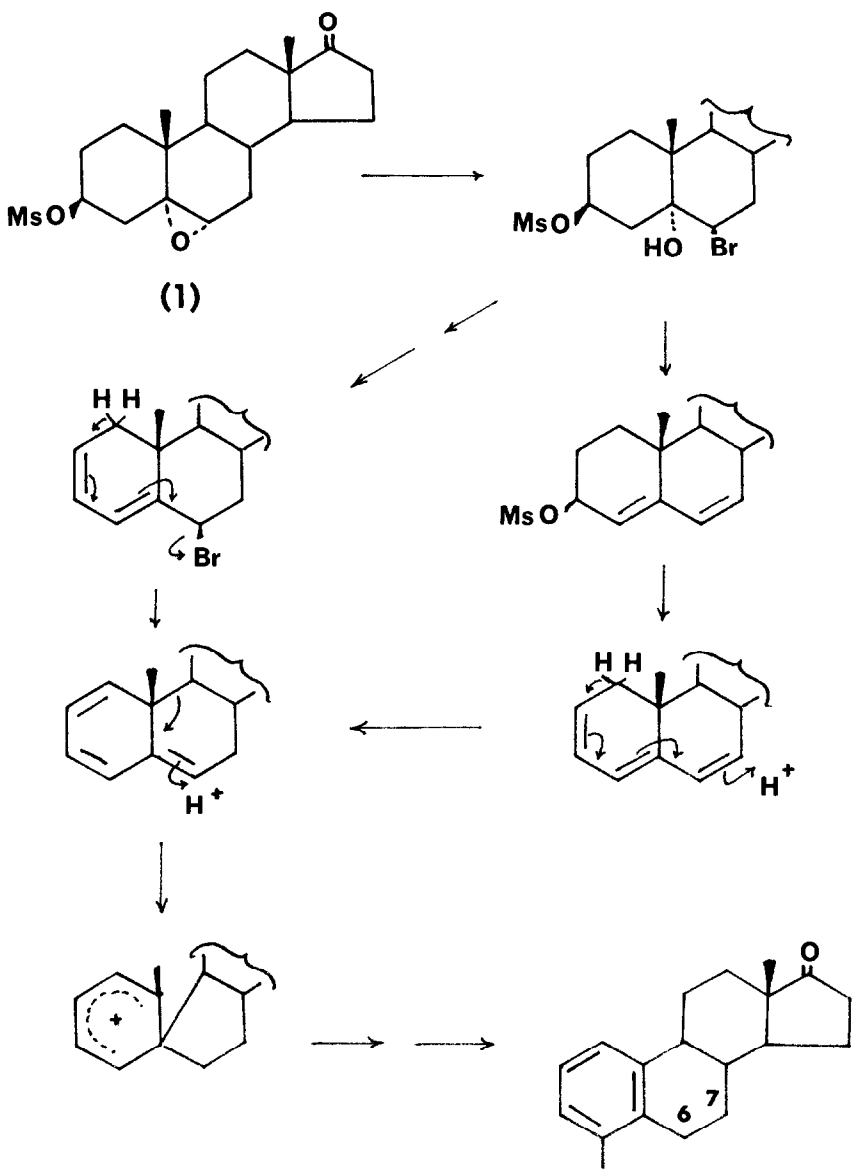
Abstract: Nmr studies have shown that the dienol:benzene rearrangement of 5α,6α-epoxy-3β-methanesulphonoxyandrostan-17-one involves the addition of a proton at H-6β ,trans to the migrating 9:10-bond together with a non-stereospecific hydrogen exchange at C-7.

Treatment of the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (1) with hydrobromic acid in glacial acetic acid, affords 4-methyloestratriene-17-one (2).[1] This aromatization reaction probably proceeds via a dienol:benzene type of pathway (see scheme 1) with or without the intervention of a Δ^6-ene. By carrying out the reaction with deuterium bromide in deuterioacetic acid, we have been able to demonstrate the involvement of C-7 in the reaction and to establish the stereochemistry of protonation at C-6.

The ^{13}C nmr resonances of the 4-methyloestratrienes have been assigned.[2] By carrying out a two-dimensional $^{13}C:^{1}H$ nmr experiment, it was possible to correlate the carbon-13 and proton resonances (see table) and thereby assign the proton signals within the complex aliphatic region of the spectrum. In particular the H-6 proton resonances were identified as a double doublet at δ 2.85,J 6 and 17 Hz, and an overlapping octet, δ 2.67, J 6.5, 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 H-7 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-(axial) proton resonance and hence the former was the 7β-(equatorial) proton appearing, as anticipated, at lower field.



(1)

(2)

Table

^{13}C and ^{1}H NMR Signals of (2)

(determined at 90.55 and 360 MHz in $CDCl_3$)

Carbon atom	^{13}C Signal	^{1}H Signal (δ, J in Hz)
1	123.08	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,6 and 17; 2.67,oct. 6.5,12 and 17
7	26.63	2.12, m; 1.45,oct. 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	1.97, dd, 3 and 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, 9 and 19; 2.15, 9 and 19.
17	220.80	
18	13.79	0.90
19	19.79	2.23

Examination of the ^{13}C nmr spectrum of deuteriated 4-methyloestratrien-17-one (2) produced by the action of deuterium bromide on (1), revealed the presence of deuterium on the aromatic ring, at C-6, C-7 and C-16. Comparison of the ^{2}H nmr spectrum (determined at 55.2 MHz) with the ^{1}H nmr spectrum (determined at 360 MHz) confirmed the presence of deuterium at H-7α (δ 1.45), H-16 (δ 2.15 and 2.51) and H-6β (δ 2.67). There was no observable deuterium signal at δ 2.8 whilst in the ^{1}H nmr spectrum this resonance appeared as a broad singlet (relative integral 0.9H). Although the ^{2}H nmr spectrum established the presence of a label at H-7 , one of the H-16 resonances (δ 2.15) overlaps the signal assigned to H-7β (δ 2.12). Hence the sample was treated with methanolic sodium hydroxide to exchange out the labels at C-16. The resultant sample contained ^{2}H signals at δ 1.45, 2.1 and 2.65 in the ratio 0.63:0.63: 1 suggesting that the label was almost evenly distributed between H-7α and H-7β . However the deuteriation at C-6 is much more stereoselective with the label appearing at H-6β which is trans to the migrating 9:10 bond. The presence of deuterium at C-7 is compatible with the hydrolysis of the epoxide and elimination of the methanesulphonate to form a $\Delta^{2,4,6}$-triene with a subsequent double bond migration prior to the formation of the spiranic intermediate in the dienol:benzene rearrangement. The absence of significant amounts of deuterium from C-8, C-9 and C-14 suggests that the intermediates in the dienol:benzene pathway are not in equilibrium with those involved in the backbone rearrangements of steroids.[3]

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