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NEIGHBOURING GROUP PARTICIPATION IN THE REARRANGEMENT OF 4β-ACETOXY-Δ^5-STEROIDS TO 6β-ACETOXY-Δ^4-STEROIDS

James R. Hanson* and Paul B. Reese

School of Molecular Sciences, University of Sussex, Brighton, BN1 9QJ.

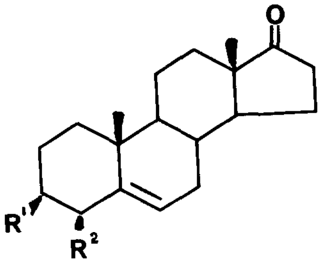
Abstract: ^{2}H, ^{13}C and ^{14}C-Labelling studies are presented as evidence for the intervention of the 3β-hydroxyl group, possibly via a 3β,4β-acetoxylinium ion in the rearrangement and acetylation of 3β-hydroxy-4β-acetoxy-Δ^5-steroids by glacial acetic acid to form 3β,6β-diacetoxy-Δ^4-steroids.

The allylic rearrangement and acetylation of 4β-acetoxy-3β-hydroxycholest-5-ene in refluxing acetic acid to form 3β,6β-diacetoxycholest-4-ene has been known for many years.[1] Although several reaction pathways can be envisaged for the rearrangement much of the discussion has centred on the probable intervention of a 3β,4β-acetoxylinium ion.[1 - 3] Related to this is the epimerization at C-3 and acetolysis at C-6 of 6β-substituted 3β-acetoxycholest-4-enes.[3] In this note we present some experimental evidence which supports the intervention of this intermediate in the rearrangement reaction.

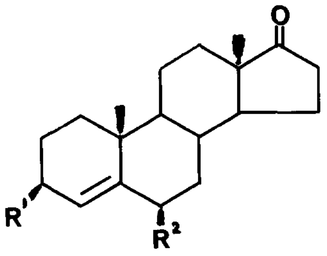
Whilst both 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (1) and 3β-acetoxy-4β-hydroxyandrost-5-en-17-one (2) both yield 3β,6β-diacetoxyandrost-4-en-17-one (3) after reaction with refluxing acetic acid for 15 minutes, the corresponding 3β,4β-diacetate (4) was recovered unchanged after 2 hours. In the presence of hydrobromic acid and glacial acetic acid aromatization of ring A occurs.[4] Thus a free hydroxyl group is required for the facile rearrangement to proceed. Secondly when 4β-[1'-^{14}C]-acetoxy-3β-hydroxyandrost-5-en-17-one (5)($2.29.10^{6}$ dpm.m.mol.$^{-1}$) was subjected to the rearrangement, the resultant 3β,6β-diacetoxyandrost-4-en-17-one ($2.01.10^{6}$ dpm. m.mol.$^{-1}$) retained 87.8%

of the radioactivity. Mild hydrolysis of the diacetate with methanolic potassium carbonate afforded 6β-acetoxy-3β-hydroxyandrost-4-en-17-one (6) which had lost most of the radioactivity. Hence the 4β-acetoxyl group had migrated to C-3. To establish that only the 3β-acetoxyl group was hydrolysed, the mono-hydroxy compound (6) was acetylated with $[^{2}H_{6}]$-acetic anhydride to afford 3β-$[2'-^{2}H_{3}]$-acetoxy-6β-acetoxy-androst-4-en-17-one (7). The 1' and 2' -^{13}C NMR resonances of the 3β- and 6β-acetates were assigned by acetolysis of 3β-acetoxy-5α,6α-epoxyandrostan-17-one with $[1-^{13}C]$-acetic acid (8.3% ^{13}C) to afford 3β-acetoxy-6β-$[1'-^{13}C]$-acetoxy-5α-hydroxy-androstan-17-one (8). The corresponding 6β-$[2'-^{2}H_{3}]$-acetate (9) was prepared by acetylation of 3β-acetoxy-5α,6β-dihydroxyandrostan-17-one with $[^{2}H_{6}]$ - acetic anhydride. Dehydration of these with thionyl chloride gave the corresponding 4-enes. This showed that the ^{13}C NMR signals at 169.81 and 21.64 ppm belonged to the 6β-acetate whilst those at 170.77 and 21.31 ppm were assigned to the 3β-acetate. The rearrangement of 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (1) was carried out in the presence of $[1-^{13}C]$- and $[2-^{2}H_{3}]$ -acetic acids. In the first case the signal at 169.81 ppm in the resultant 3β,6β-diacetate was enriched whilst in the second case the signal at 21.64 ppm was absent. Hence the 6β-acetate arises from the acetic acid. Finally when 3β-carboethoxy-4β-hydroxyandrost-5-en-17-one (10) was treated with glacial acetic acid at 80° for 6 hours, the intermediate acyloxylinium ion was trapped as the 3β, 4β-cyclic carbonate (11). This evidence strongly supports the intervention of a 3β,4β-acetoxylinium ion in the allylic rearrangement (see scheme) and excludes pathways involving the intramolecular migration of the 4β-acetate to the 6β-position.

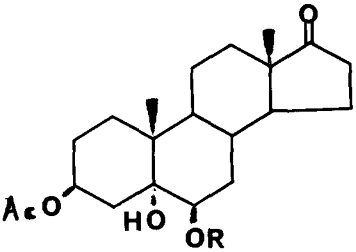
The intervention of a 3β,4β-acetoxylinium ion has also been proposed[5] in the allylic substitution of a 3β-acetoxy-Δ^{5} -steroid at C-4 with bromine and silver acetate.[6] The intermediate ion in this case has also been trapped by using 3β-carboethoxyandrost-5-en-17-one (12) as the substrate. Reaction of this with bromine and silver acetate gave the 3β,4β-cyclic carbonate (11) identical to the material obtained above.



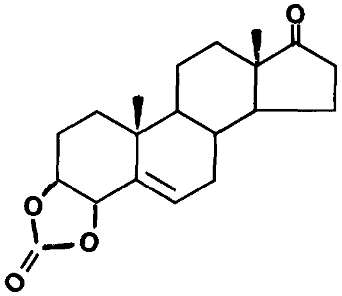
1 R^1 = OH, R^2 = OAc
2 R^1 = OAc, R^2 = OH
4 R^1 = R^2 = OAc
5 R^1 = OH, R^2 = $O^{14}CO.CH_3$
10 R^1 = $O.CO.OC_2H_5$, R^2 = OH
12 R^1 = $O.CO.OC_2H_5$, R^2 = H



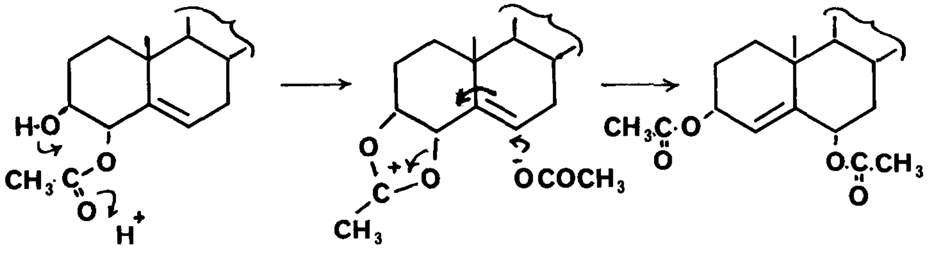
3 R^1 = R^2 = OAc
6 R^1 = OH, R^2 = OAc
7 R^1 = $O.CO.C^2H_3$, R^2 = OAc



8 R = $^{13}CO.CH_3$
9 R = $CO.C^2H_3$



11



Scheme

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