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STUDY OF STEROIDAL KETOL ACETATES

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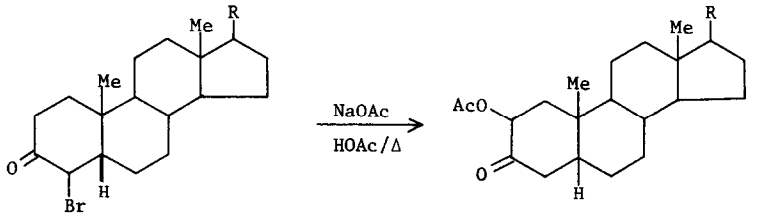
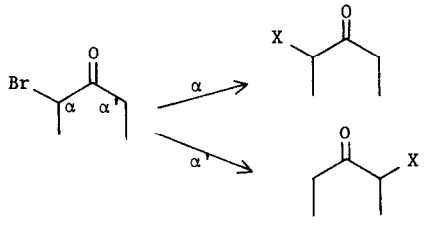
The steroidal nucleus has provided the template on which a wealth of molecular rearrangements have been forged.[2] Recently, we[3] and others[4] have found that 3-keto-4-bromo-5β-steroids are converted into 2-acetoxy steroids, eq 1, on treatment with sodium acetate in refluxing



(1)

1, R = OAc 2, R = OAc

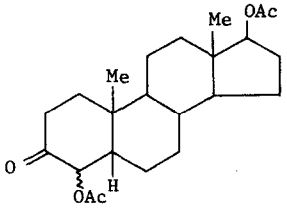
acetic acid. In the case of 1 we have found this rearrangement to occur in excellent yield and we cannot find any trace of isomeric ketol acetate in the crude product 2 either spectroscopically or chromatographically. There are many examples of cine substitutions in steroidal chemistry,[2,5] however this reaction (eq 1) is notable for the high yield (>85%) and purity of product. There are several possible mechanisms for this type of transformation. Fieser[6] and Cox[7] have found that α-bromoketones can undergo substitution at the α- or α'-position, eq 2.



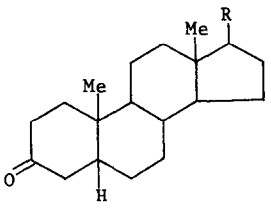
(2)

Thus one should consider the intermediacy of the 4α- or 4β-acetoxy compound in reaction 1. Warnhoff[8] has found that α-acetoxycyclohexanone transfers the acetate group to the α'-carbon above 220°, and similar rearrangements have been found to occur at lower temperatures.[9,10] This further enhances the possibility that the 4-acetoxy isomer may be an intermediate in reaction 1. Recently, Satoh and Takahashi[11] have isolated an intermediate in this reaction

and they suggest that this is the 2α-acetoxy isomer. From this they conclude that reaction 1 involves an unusual trans-S_N2' displacement on the 4β-bromo compound 1. Our aim was to determine if the 4β- or 4α-acetoxy compounds, 3 and 4, were intermediates in reaction 1 and to determine if either 3 or 4 was related to the intermediate isolated by Satoh and Takahashi.[11] Since these workers started with 5β-cholestan-3-one (5) and we start with 17β-acetoxy-5β-androstan-3-one (6) direct comparisons could not be made.

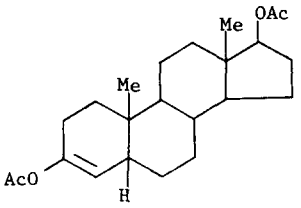


3, 4α-OAc
4, 4β-OAc



5, R = C_8H_{17}
6, R = OAc

A sample of 6 was converted into the enol acetate 7 in excellent yield following minor modifications of Liston's procedure[12] to prevent oxidation of the product. The enol acetate 7 was epoxidized with m-chloroperbenzoic acid - sodium bicarbonate[13] to give the β-epoxide 8.



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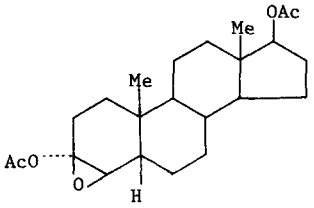


8

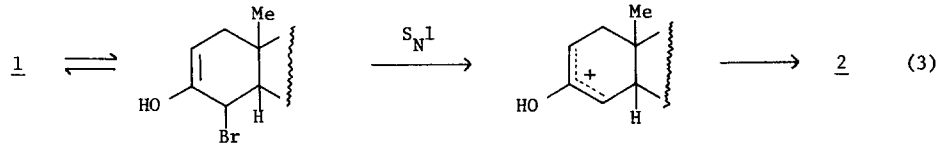
We assign the β-configuration to the epoxidation product on the following bases. The β-face appears to be the sterically more accessible direction for peracid attack.[14] The nmr spectrum of 8 has a singlet at δ 3.07 due to the proton on C-4. An examination of the Dreiding model of 8 indicates that the dihedral angle between the hydrogens on C-4 and C-5 is ca. 100°. The dihedral angle between the hydrogens on C-4 and C-5 in the isomeric α-epoxide is estimated to be ca. 50°. In an extensive study of steroidal epoxides and episulfides it was found that the coupling constant could approach zero only for dihedral angles of 70-100° while a dihedral angle of 50° is expected to yield a coupling constant of at least 2 Hz.[15] Also, the chemical shift of the C-19 methyl protons in 8, δ 0.87_5, agrees closely with that of the C-19 protons of 3β,4β-oxido-5β-cholestane, δ 0.86_8.[16]

Pyrolysis of 8 at 160° for 5 min gave 4β,17β-diacetoxy-5β-androstan-3-one (3) in ca.

80% yield. The salient feature of the nmr spectrum of 3 which suggested its structure was a one-proton doublet (J= 8 Hz) at δ 5.41. This is assigned to the 4β-hydrogen of 3 which probably is in a boat conformation due to the severe interaction of the 4α-acetoxy group with C-7 and C-9 in the chair conformation. On refluxing in acetic acid - sodium acetate, which are conditions for reaction 1, 3 is converted cleanly to the 4β-acetoxy isomer 4. The 4β-isomer 4 was also obtained by treating 8 with HCl in ether. The 4β-acetoxy compound 4 has in its nmr spectrum a one-proton doublet (J = 12 Hz) at δ 5.52 which is assigned to the 4α-hydrogen. These epoxide rearrangements parallel those of 2α,3α-oxido-3β-acetoxycholestane.[17] When 4 was subjected to the conditions for reaction 1 it was recovered unchanged.

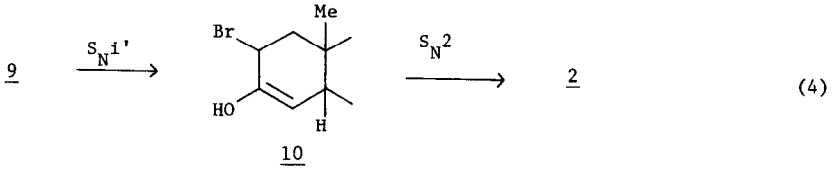
These experiments would indicate that neither 3 nor 4 can be an intermediate in reaction 1. In fact, 3 and 4 did not rearrange to either 2-acetoxy isomer on thermolysis at 160°. Hence the intermediate isolated by Satoh and Takahashi[11] must be the 2α-acetoxy compound and it does not arise *via* the 4α- or 4β-acetoxy isomer.

Bordwell[18] has catalogued some of the possible pathways by which a *cine* substitution such as reaction 1 can occur. The first possibility, a S_N2 substitution at C-4 followed by a S_Ni' rearrangement *via* the enol is discarded by the above results. An S_N1 pathway, eq 3, is



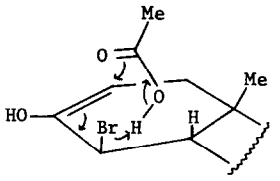
(3)

a possibility. A S_Ni' rearrangement of the bromo enol 9 to 10 followed by a S_N2 reaction as outlined in eq 4 is also a possibility. However, Liston has found that the bromoketone 1 and 17β-acetoxy-2β-bromo-5β-androstan-3-one are not interchanged or equilibrated even in HBr-HOAc[12].



(4)

This would suggest that the rearrangement of 9 to 10 does not occur under our conditions. A second type of S_Ni' reaction is shown in eq 5; but, this does not require the intermediacy of the 2α-isomer. A final possibility is a S_N2' reaction of 9.[11,18] We have synthesized 17β-acetoxy-2β-bromo-5β-androstan-3-one[12] and it is cleanly converted to 2 in refluxing acetic



9 ⟶ ⟶ 2 (5)

acid - sodium acetate at a rate comparable to 1. This would suggest that the mechanism shown in eq 3 is operating; namely both bromoketones give the same intermediate 11.[19]

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