trans-S_N2' Reaction in Acylolysis of 4β-Halogeno-5β-cholestan-3-ones

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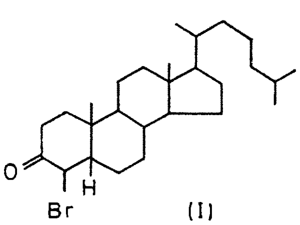
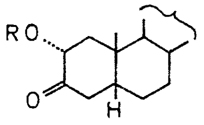
Summary A new type of S_N2' reaction in which the nucleophile enters *trans* to the leaving group occurs in the acylolysis of a 4β-halogeno-5β-cholestan-3-one to give a 2α-acyloxy-5β-cholestan-3-one as a product.

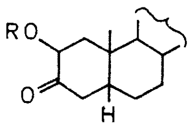
MANY studies have been reported on the S_N2' reactions of allyl halides.[1] In these reactions the nucleophile has a *cis*-relationship to the leaving group when it attacks a γ-carbon (allylic position).[1] The same behaviour has been observed for steroidal α-bromo-ketones. For example, on acetolysis of 2α-bromo-5α-cholestan-3-one, Fieser and Romero[2] obtained 2α-acetoxy- and 4α-acetoxy-5α-cholestan-3-one in a 1 to 1 ratio. Under the same conditions, Clarke *et al.*[3] obtained a 2β-acetoxy-Δ^4-3-keto-derivative from 6β-bromotestosterone acetate.



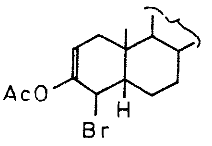
(I)



(II)



(III)



(IV)

[R = Ac or $Me_3C\cdot CO$]

We report a new type of S_N2' reaction in which the nucleophile enters *trans* to the leaving group. Previously, we reported that on acetolysis of 4β-bromo-5β-cholestan-3-one (I) under Fieser's conditions, the 2β-acetoxy-3-keto-derivative (III) was produced in good yield.[4] We have now treated the α-bromo-ketone (I) with (a) AcOK–AcOH, (b) AcOK–dioxan, (c) Et_3N–AcOH at 90—95°, (d) potassium pivalate–dioxan at 70°, and (e) $AcO^-N^+Me_4$–dioxan at room temperature. Samples were taken from each reaction mixture at intervals and the progress of the reaction was followed by t.l.c. and by using a Varian HR-220 n.m.r. spectrometer to observe the change in the signals due to the methyl protons of the 2α- and 2β-acetoxy-groups. One of the n.m.r. spectra is shown in Figure 1. It was found that, in each case, 2α-acyloxy-5β-cholestan-3-one (II) was produced first. Since the isomerization of the 2α-acyloxy- to the 2β-acyloxy-derivative is relatively fast for the cases (a) and (c), it was impossible to isolate the initial product, 2α-acyloxy-5β-cholestan-3-one. In cases (b), (d), and (e), however, this product was easily obtained. The 2α-acyloxy-derivative was produced almost stereospecifically in 2·5 h for method (d) and in 5 days for method (e), and it gradually isomerized to the 2β-acyloxy-derivative when the reaction was continued for any longer.

The fact that the 2α-acyloxy-derivative (II) is produced initially from the acylolysis of (I) indicates that the reaction proceeds in a *trans*-S_N2' manner in which the leaving group is *trans* to the entering group, unlike the ordinary S_N2' reaction, where a *cis*-relationship obtains.

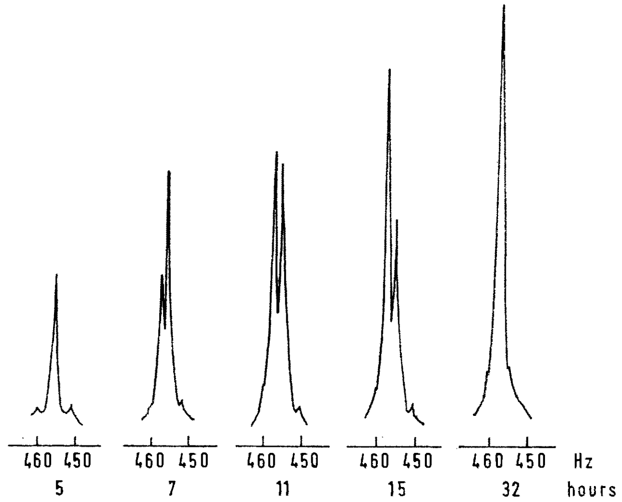


FIGURE 1. *220 MHz n.m.r. signals due to the methyl protons of the acetoxy-groups in the case of* (I)–AcOK–*dioxan*–H_2O (100 *mg*/ 500 *mg*/7 *ml*/0·5 *ml*) *at intervals. α-Isomer*: 455 *Hz, β-Isomer*: 458 *Hz* (*from* Me_4Si *as internal standard*).

Dihedral angles (*degrees*) *for three possible conformers*

	1α-H–2-H	1β-H–2-H	4-H–5-H
Half chair ..	43	77	174
Boat-A	10	110	94
Boat-B	110	10	175

Experimental dihedral angles of the enol acetate (IV)

1α-H–2-H	1β-H–2-H	4-H–5-H
123	27	172

Although the α-side of ring A of a 5β-steroid is less favoured than the β-side for nucleophilic attack, the attack did take place at the α-face. We consider that the conformation of the intermediate must be responsible for this unexpected behaviour. Fieser[2] and Clarke[3] reported that enolisation took place during the acetolysis of 2α-bromo- and 6β-bromo-derivatives. If (I) undergoes enolisation, it is possible that a conformation will result in which ring A is relatively flat with respect to ring B, and hence nucleophiles may attack at the α-face. To test this possibility, 4β-bromo-5β-cholest-2-en-3-ol acetate (IV) was synthesized through enol acetylation of the 4β-bromo-3-ketone (I), since the enol derivative (2-en-3-ol) was not stable enough to isolate. The projections of three possible conformers for the compound are shown in Figure 2. In each case, the dihedral angles (Table), one between vinyl-H at C-2 and *gem*-H at C-1, and the others between 4-H and 5-H were derived from Dreiding models. From the n.m.r. spectrum of the enol acetate (IV), coupling constants, $J_{1\alpha,2}$, $J_{1\beta,2}$, and $J_{4,5}$ were measured and dihedral angles were calculated using the Karplus equation.† These values are also listed in the Table. Comparing these values with those of three possible conformers listed above, it was assumed that the enol acetate (IV) has the boat-B conformation shown in Figure 2. On the acylolysis of (I), therefore, the enolisation of the 3-oxo-group allows ring A to be relatively flat with respect to ring B, shown as boat-B. This conformation provides a favourable environment for the nucleophile to attack at C-2. Furthermore, α-attack occurs more readily than β-attack at this position, resulting from the steric effect of the 10-methyl group. The 2α-acyloxy-derivative (II) was, therefore, formed as the product of *trans*-S_N2' reaction and then isomerized to the more stable 2β-isomer.

Such reaction has also been found to occur in the case of the acylolysis of 4β-chloro-5β-cholestan-3-one under the same conditions, the initial product being 2α-acyloxy-5β-cholestan-3-one (II).

On the basis of these results, we conclude that in the S_N2' reaction of the α-halogeno-ketone, the entering group is not always *cis* to the leaving group. Whether the nucleophile enters *trans* or *cis* to the leaving group depends on the stereochemistry of the reactant.

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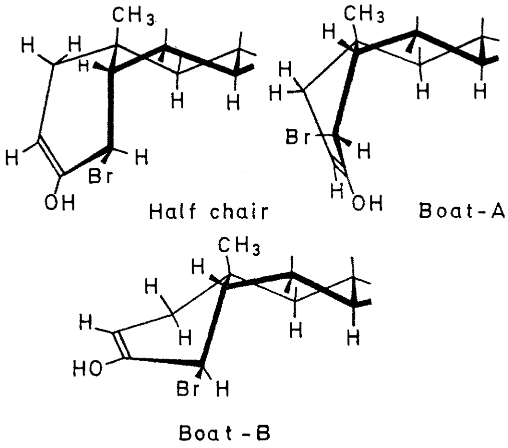

FIGURE 2. *Three possible conformers of the enol.*

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† L. D. Hall (*J. Org. Chem.*, 1964, **29**, 297) used the equation to determine the conformation of shikimic acid by calculating dihedral angles. Although C-2 of the acid has sp^2 hybridization, the result gave good agreement with the model.

[1] P. de Mayo, "Molecular Rearrangement," Interscience, London, 1963, p. 27.
[2] L. F. Fieser and M. Romero, *J. Amer. Chem. Soc.*, 1953, **75**, 4716.
[3] R. L. Clarke, K. Dobriner, A. Mooradian, and M. Martini, *J. Amer. Chem. Soc.*, 1955, **77**, 661.
[4] Y. Satoh, M. Mukoh, Y. Ogaki, T. Takahashi, T. Kimura, H. Aoki, and A. Hagitani, *Bull. Chem. Soc. Japan*, 1966, **39**, 855.