Tetrahedron Letters,Vol.23,No.17,pp 1851-1854,1982 0040-4039/82/171851-04$03.00/0
Printed in Creat Britain

NEIGHBOURING GROUP PARTICIPATION IN THE ALLYLIC OXIDATION OF A Δ^5-STEROID

James R. Hanson and Paul B. Reese

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

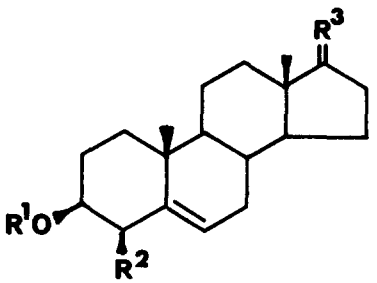
Ian H. Sadler

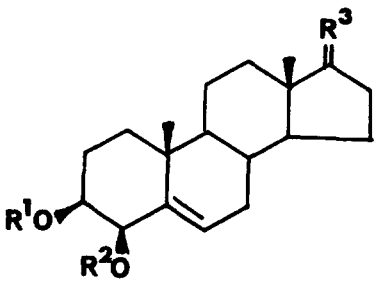
Department of Chemistry, University of Edinburgh, West Mains Road,Edinburgh, EH9 3JJ.

Abstract: The allylic oxidation of 3β-acetoxyandrost-5-en-17-one by bromine and silver acetate affords 4β-acetoxy-3β-hydroxyandrost-5-en-17-one rather than the 3β,4β-diacetate. Labelling studies show that this involves the migration of the 3β-acetoxyl group and an overall retention of configuration at C-4.

Treatment of dehydroisoandrosterone (1) and related 3β-hydroxy-Δ^5-steroids with bromine in chloroform at -60° followed by reaction with silver acetate in pyridine at room temperature, provides a simple route to 4β-acetoxy-3β-hydroxy-Δ^5-steroids (e.g.2).[1] Suprisingly when the corresponding 3β-acetate (3) or its 5α,6β-dibromide were subjected to the same sequence, the 4β-acetoxy-3β-hydroxy-Δ^5-steroid (2) rather than the 3β,4β-diacetate (4) was formed. The intermediate 5α,6β-dibromide was also obtained from the 3β-acetate (3). Furthermore when the corresponding 3β-propionate (5) was treated with bromine followed by silver acetate, the product was the 4β-propionate (6) rather than the 4β-acetate (2). The authentic sample of the 4β-propionate (6) was prepared by treatment of dehydroisoandrosterone (1) with bromine and silver propionate.

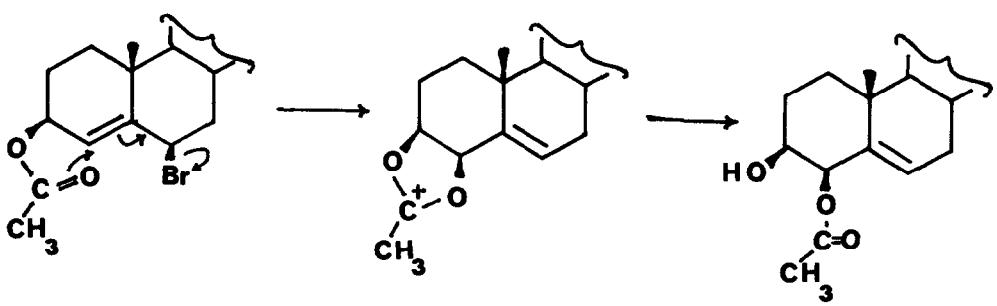
Confirmation that an acyl migration to C-4 had occurred was obtained when [1-^{14}C]-3β-acetoxyandrost-5-en-17-one (3) (specific activity, $6.86.10^5$ dpm/mmol.) was used as the substrate. The resultant 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (2) had a specific activity of $6.2.10^5$ dpm/mmol. having retained 89% of the radioactivity of the initial acetate (3).





1 $R^1 = R^2 = H$, $R^3 = O$.
3 $R^1 = Ac$, $R^2 = H$, $R^3 = O$.
5 $R^1 = COEt$, $R^2 = H$, $R^3 = O$.
7 $R^1 = Ac$, $R^2 = {}^2H$, $R^3 = \alpha\text{-}{}^2H, \beta\text{-}OAc$.
9 $R^1 = R^2 = H$, $R^3 = \alpha\text{-}H, \beta\text{-}OAc$.

2 $R^1 = H$, $R^2 = Ac$, $R^3 = O$.
4 $R^1 = R^2 = Ac$, $R^3 = O$.
6 $R^1 = H$, $R^2 = COEt$, $R^3 = O$.
8 $R^1 = H$, $R^2 = Ac$, $R^3 = \alpha\text{-}{}^2H, \beta\text{-}OAc$



The overall stereochemistry of the reaction followed from the fate of a 4-deuterium label. [4β,17α-$^2H_2$]-3β,17β-Diacetoxyandrost-5-ene (7) was prepared by reduction of 3β-acetoxy-6β-chloroandrost-4-en-17-one with lithium aluminium deuteride[2] and subsequent acetylation. The ^2H NMR spectrum, determined in chloroform at 55.28 MHz, showed signals at δ 2.29 (4β-^2H) and 4.59 (17α-^2H). The ^2H labelled steroid (7) was treated with bromine and subsequently with silver acetate in pyridine. The ^2H NMR spectrum of the resultant 4β,17β-diacetoxy-3β-hydroxyandrost-5-ene (8) showed a ^2H signal at δ 4.58 assigned to the 17α-^2H but no signal at δ 5.37 assigned to a 4α-H. This 4α-H signal remained in the ^1H NMR spectrum. Hence the 4β-acetate has replaced a 4β-deuterium label and thus the reaction has proceeded with an overall retention of configuration.

When silver oxide was used in place of the silver acetate, the acetate (3) still gave the hydroxy-acetate (2) albeit in lower yield, showing that the reaction was independent of the anion.

The reaction sequence can be formulated as an addition of bromine to the Δ^5-double bond, a trans elimination of the 4β-proton, followed by a syn S_n2' substitution of the 6β-bromine atom by the 3β-acetoxyl group to form an acetoxylinium ion which then affords the 3β-hydroxy-4β-acetoxy steroid (see scheme). The intervention of a 3β,4β-acetoxylinium ion has been invoked in a number of previous studies including the allylic displacement of a Δ^4-6-chloride[3] and the opening of a 3β-acetoxy-4α,5α-epoxide.[4]

Partial hydrolysis of the [4β,17α-$^2H_2$]-3β,17β-diacetoxyandrost-5-ene (7) with methanolic potassium carbonate gave [4β,17α-$^2H_2$]-17β-acetoxy-3β-hydroxyandrost-5-ene (9). When this was treated with bromine and then with silver acetate in pyridine, the resultant 4β,17β-diacetoxy-3β-hydroxyandrost-5-ene (8) also lacked a δ 5.37 signal in the ^2H NMR spectrum but retained this signal in the ^1H NMR spectrum. Hence the 4β-acetate has again replaced a 4β-deuterium label. Therefore the bromination and silver acetate reaction has also proceeded with an overall retention of configuration at this centre which is consistent with an addition of bromine followed by a trans elimination of hydrogen bromide and a syn S_N2' substitution of a 6β-bromine by the incoming 4β-acetoxyl group.

REFERENCES

1. V.A.Petrow, J.C.S., 1937, 1077; V.A.Petrow, O.Rosenheim and W.W.Starling, J.C.S., 1943, 135.

2. W.J.S.Lockley, H.H.Rees, and T.J.Goodwin, J.Labelled Compounds, 1978, 15, 413.

3. R.E.Ireland, T.I.Wrigley and J.G.Young, J.Amer. Chem.Soc., 1959, 81, 2818.

4. S.Julia and B.Furer, Bull.Soc. Chim. (France)., 1966, 1106.

(Received in UK 18 February 1982)