Neighbouring Group Participation in the Allylic Oxidation of a Δ^5-Steroid

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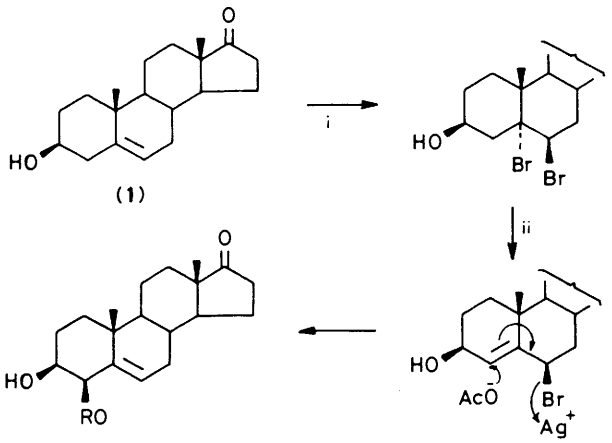
When 3β-acetoxy-Δ^5-steroids are treated with bromine and silver acetate, the product 3β-hydroxy-4β-acetate is formed by intramolecular acetoxy group migration via a 3β,4β-acetoxylinium ion.

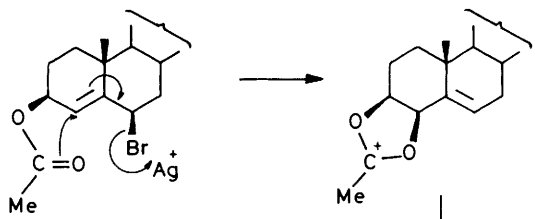
The allylic acetoxylation of Δ^5-steroids [*e.g.* (**1**)] by reaction with bromine in chloroform followed by treatment with silver acetate in pyridine at −60 °C provides a simple route to some 4β-acetoxy-Δ^5-steroids [*e.g.* (**2**)].[1] The reaction (see Scheme 1) is



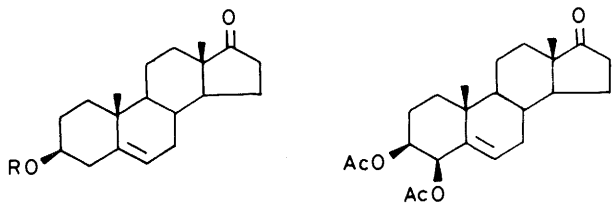
Scheme 1. *Reagents*: i, Br_2; ii, AgOAc, pyridine

limited to a certain extent by the nature of the 3β-substituent.[2] In the course of our studies on the scope and limitations of this reaction we observed that 3β-acetoxyandrost-5-en-17-one (**5**) gave the 4β-acetoxy-3β-hydroxy-Δ^5-steroid (**2**) rather than the 3β,4β-diacetate (**4**). The ^{1}H n.m.r. spectrum of this compound showed the 3α-H resonance as a multiplet (δ 3.65; $w_{\frac{1}{2}}$ 20 Hz) and the 4α-H resonance as a lower field doublet (δ 5.4; *J* 4 Hz). This contrasts with the isomeric 3β-acetoxy-4β-hydroxyandrost-5-en-17-one in which the 3α-H resonance was a multiplet (δ 4.65; $w_{\frac{1}{2}}$ 14 Hz) whilst the 4α-H resonance appeared at δ 4.2 as a doublet (*J* 4 Hz). In the 3β,4β-diacetate these signals appear at δ 4.73 and 5.53 respectively.[3] An interpretation of this result (see Scheme 2) is that the 3β-acetate is participating in the *syn* allylic displacement of the 6β-bromide intermediate in the reaction with the formation of a 3β,4β-acetoxylinium ion which then undergoes hydrolysis. In this paper we present some evidence to support this reaction scheme.[4]

The reaction (see Scheme 1) proceeds by the addition of bromine followed by the stepwise elimination and allylic substitution of the 5α- and 6β-bromine atoms. Treatment of both 3β-acetoxy-5α,6β-dibromoandrostan-17-one (**9**) and 3β-acetoxy-6β-bromoandrost-4-en-17-one (**11**) (obtained by dehydration *in situ* of the corresponding 5α-hydroxy-6β-bromo steroid with thionyl chloride) with silver acetate in pyridine gave the known 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (**2**).[1] The rearrangement of the 3β-ester was independent of the anion since treatment of the 3β-propionate (**6**) with bromine followed by silver acetate gave the 3β-hydroxy-4β-propionate (**3**) rather



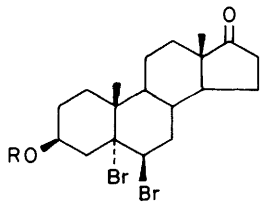
Scheme 2.



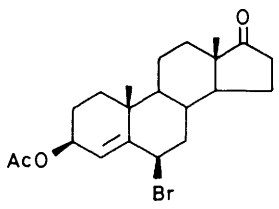
than the 4β-acetate (**2**). The authentic 4β-propionate (**3**) was obtained from the reaction of the 5α,6β-dibromide (**10**) of the 3β-alcohol, dehydroisoandrosterone, with silver propionate. Indeed, when silver oxide was used in place of the silver acetate, the 3β-acetate (**5**) still gave the 4β-acetoxy-3β-hydroxy steroid (**2**) although in lower yield.

The confirmation that an intramolecular acyl migration to C-4 had occurred was obtained when [1′-^{14}C]-3-acetoxyandrost-5-en-17-one (**7**) (specific activity, 11.4 kBq mmol^{-1}) was used as the substrate. The resultant 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (**2**) had a specific activity of 10.3 kBq mmol^{-1} having retained 89% of the radioactivity of the initial acetate (**7**). The intermediate acyloxonium ion was trapped by using 3β-ethoxycarbonylandrost-5-en-17-one (**8**) as a substrate. The product from this reaction was the cyclic 3β,4β-carbonate (**12**) which was identified by its i.r. ($\nu_{max.}$ 1 780 cm^{-1}) and ^{13}C n.m.r. (δ_C 155.0, O_2C=O) spectra.

The overall stereochemistry of the reaction followed from the fate of a 4β-deuterium label. [4β,17α-$^2H_2$]-3β,17β-Diacetoxyandrost-5-ene (**13**) was prepared by an adaption of a known



(9) R = Ac
(10) R = H



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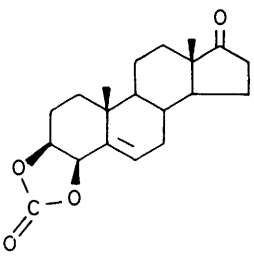

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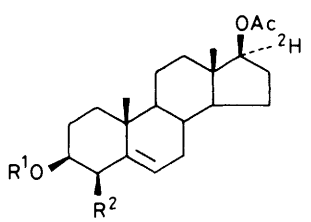
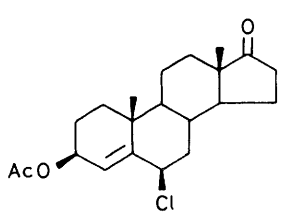


(13) R^1 = Ac, R^2 = ^2H
(15) R^1 = H, R^2 = OAc



(14)

procedure[5,6] involving the reduction of 3β-acetoxy-6β-chloroandrost-4-en-17-one (**14**) with lithium aluminium deuteride and subsequent acetylation of the product. The ^2H n.m.r. spectrum of the diacetate showed signals at δ(^2H) 2.29 (4β-^2H) and 4.59 (17α-^2H). The deuterium-labelled steroid was treated with bromine and subsequently silver acetate in pyridine. The ^2H n.m.r. spectrum of the resultant 4β,17β-diacetoxy-3β-hydroxyandrost-5-ene (**15**) showed only one signal at δ 4.58 which was attributed to the 17α-^2H. There was no signal at δ 5.37 which could be assigned to the 4α-^2H. This 4α-H signal remained in the ^1H n.m.r. spectrum of the product. Hence the 4β-acetate has replaced a 4β-deuterium label and the reaction has proceeded with an overall retention of configuration.

The reaction sequence can therefore be formulated as the addition of bromine to the Δ^5-double bond, the *trans* elimination of the 4β-proton and the 5α-bromine atom, followed by a *syn* intramolecular silver ion assisted substitution of the 6β-bromine atom by the 3β-acetoxy group to form a 3β,4β-acetoxylinium ion. This then collapses to afford the 4β-acetoxy-3β-hydroxy steroid. 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,[5] the opening of a 3β-acetoxy-4α,5α-epoxide,[7] and the addition of hypobromous acid to a 3β,17β-diacetoxyoestr-4-ene.[8] An interesting feature of each of these rearrangements is that the intermediate 3β,4β-acetoxylinium ion opens to give the less stable 4β-axial acetate, a feature which has recently been rationalized in terms of stereoelectronic effects.[9]

Experimental

Acetoxylation of 3β-*Acetoxyandrost*-5-*en*-17-*one* (**5**).—3β-Acetoxyandrost-5-en-17-one (4 g) in chloroform (30 ml) was cooled to −60 °C. Bromine (0.7 ml) was added with swirling followed by silver acetate (6 g) in pyridine (9 ml). The reaction mixture was stirred and allowed to attain room temperature in the dark during 24 h. The mixture was poured into dilute hydrochloric acid and the steroids were extracted into chloroform. The extract was washed with water and aqueous sodium hydrogen carbonate and dried. The solvent was evaporated and the residual gum was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (**2**) (2.5 g) which crystallized from acetone as needles, m.p. 198.5—200 °C, $[\alpha]_D$ −62°(*c* 0.3 in $CHCl_3$)(lit.,[1] m.p. 192—193 °C, $[\alpha]_D$ −60.7°). The product was identified by its i.r. and n.m.r. spectra. Under similar conditions 3β-acetoxy-5α,6β-dibromoandrostan-17-one (500 mg) gave 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (200 mg).

Preparation of 3β-*Acetoxy*-6β-*bromo*-5α-*hydroxyandrostan*-17-*one*.—A solution of 3β-acetoxy-5α,6α-epoxyandrostan-17-one (1 g) in chloroform (10 ml) was treated with an ice-cold solution of lithium bromide (1 g) in water (1 ml) and 48% hydrobromic acid (1 ml) for 12 h. Chloroform was added and the organic layer was separated, and washed with water and aqueous sodium hydrogen carbonate. The solvent was evaporated to afford 3β-*acetoxy*-6β-*bromo*-5α-*hydroxyandrostan*-17-*one* (1.1 g) which crystallized from acetone as small prisms, m.p. 180—183 °C, $[\alpha]_D$ −14.3° (Found: C, 60.5; H, 7.5. $C_{21}H_{31}BrO_4$ requires C, 59.0; H, 7.3%); $\nu_{max.}$ 3 540, 1 740, and 1 730 cm^{-1}; δ 0.90 (3 H, s, 18-H), 1.36 (3 H, s, 19-H), 2.03 (3 H, s, OAc), 4.0 (1 H, m, $w_{\frac{1}{2}}$ 4 Hz, 6-H), and 5.08 (1 H, m, $w_{\frac{1}{2}}$ 30 Hz, 3-H).

Dehydration of 3β-*Acetoxy*-6β-*bromo*-5α-*hydroxyandrostan*-17-*one and the Reaction with Pyridine and Silver Acetate*.—The bromo steroid (1 g) in dry pyridine (15 ml) was treated with thionyl chloride (0.5 ml) at 0 °C. The mixture was allowed to attain room temperature and then poured onto ice–water. The steroids were extracted with diethyl ether. The extract was washed thoroughly with aqueous copper sulphate and saturated sodium chloride solution. The extract was dried (Na_2SO_4) and the solvent was evaporated to give a gum which was redissolved in methylene dichloride and cooled to −60 °C. Silver acetate (1 g) in pyridine (2 ml) was added and the mixture was stirred at −60 °C for 1 h and then allowed to attain room temperature in the dark during 40 h. The mixture was diluted with methylene dichloride and filtered. The solution was washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The solvent was evaporated and the residue was chromatographed on silica. Elution with 50% ethyl acetate–light petroleum gave 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (290 mg) which was identified by its i.r. and n.m.r. spectra.[3]

Reaction of 3β-*Propionyloxyandrost*-5-*en*-17-*one with Bromine and Silver Acetate*.—3β-Propionyloxyandrost-5-en-17-one (2 g)[10] in chloroform (10 ml) was treated with bromine (0.4 ml) at −60 °C. Silver acetate (3 g) in pyridine (6 ml) was then added and the mixture was allowed to attain room temperature in the dark during 20 h, when poured into dilute hydrochloric acid and the steroid extracted with chloroform. The extract was washed with water and aqueous sodium hydrogen carbonate. The solvent was evaporated and the residue was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave 3β-hydroxy-4β-propionyloxyandrost-5-en-17-one (700 mg), m.p. 155—158 °C, identical (i.r. and n.m.r.) with the material prepared[2] by the action of silver propionate and bromine on dehydroisoandrosterone.

Reaction of 3β-*Acetoxyandrost-5-en*-17-*one with Bromine and Silver Oxide.*—Bromine (0.9 ml) was added to a solution of 3β-acetoxyandrost-5-en-17-one (500 mg) in chloroform (5 ml) at −60 °C. Moist silver oxide (1 g) in pyridine (1 ml) was added in two equal portions and the mixture was stirred at room temperature in the dark during 6 days. The mixture was poured into dilute hydrochloric acid and the steroids were recovered in ethyl acetate. The extract was washed with water and aqueous sodium hydrogen carbonate. The solvent was evaporated and the residue chromatographed on silica. Elution with 50% ethyl acetate–light petroleum gave 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (43 mg) which was identified by its i.r. and n.m.r. spectra.[3]

Reaction of [1′-^{14}C]-3β-*Acetoxyandrost-5-en*-17-*one with Bromine and Silver Acetate.*—[1′-^{14}C]-3β-Acetoxyandrost-5-en-17-one was prepared from [1′-^{14}C]acetic anhydride and pyridine. The labelled steroid (1 g, specific activity, 11.4 kBq mmol^{-1}) was treated with bromine (0.2 ml) in chloroform (10 ml) at −60 °C. Silver acetate (1 g) in pyridine (2 ml) was added and the mixture was stirred for 0.5 h. A further portion of silver acetate (0.5 g) in pyridine (1 ml) was then added and the solution was allowed to attain room temperature in the dark during 24 h. The products were recovered as above to afford 4β-[1′-^{14}C]acetoxy-3β-hydroxyandrost-5-en-17-one (500 mg) which was crystallized to constant radioactivity. It had specific activity 10.3 kBq mmol^{-1}.

3β-*Ethoxycarbonylandrost-5-en*-17-*one.*—3β-Hydroxyandrost-5-en-17-one (2 g) in pyridine (15 ml) was treated with ethyl chloroformate (5 ml) overnight. The solution was poured onto ice–water and the steroid was recovered in diethyl ether. The extract was washed thoroughly with aqueous copper sulphate, saturated sodium chloride solution, and dried. The solvent was evaporated to afford 3β-*ethoxycarbonylandrost-5-en*-17-*one* (2.4 g) which crystallized from acetone as prisms, m.p. 179—182 °C, $[\alpha]_D$ +1° (*c* 0.2) (Found: C, 73.3; H, 8.9. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95%); $\nu_{max.}$ 1 740, 1 665 cm^{-1}; δ 0.89 (3 H, s, 18-H), 1.04 (3 H, s, 19-H), 1.31 (3 H, t, *J* 7 Hz, OCH_2CH_3), 4.19 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.28 (1 H, m, 3-H), and 5.43 (1 H, m, 6-H).

Reaction of 3β-*Ethoxycarbonylandrost-5-en*-17-*one with Bromine and Silver Acetate.*—Bromine (0.4 ml) was added to a solution of 3β-ethoxycarbonylandrost-5-en-17-one (2 g) in methylene dichloride (15 ml) at −60 °C. Silver acetate (3 g) in pyridine (6 ml) was then added during 10 min and the mixture was allowed to attain room temperature during 3 days. The solution was filtered, diluted with methylene dichloride, washed with saturated copper sulphate solution, and water, dried and evaporated to give a residue which was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave the starting material (1.2 g). Further elution with 35% ethyl acetate–light petroleum gave the 3β,4β-cyclic carbonate of 3β,4β-dihydroxyandrost-5-en-17-one (550 mg) which crystallized from ethyl acetate–light petroleum as plates, m.p. 229—232 °C, and which was identified by its i.r. and n.m.r. spectra.[11]

Preparation of [4β,17α-$^2H_2$]-3β,17β-*Diacetoxyandrost-5-ene.*—3β-Acetoxy-4β-hydroxyandrost-5-en-17-one (2 g) (prepared by the partial acetylation of the 3,4-diol)[1] in dry diethyl ether (80 ml) and pyridine (0.4 ml) was treated with thionyl chloride (0.5 ml) in diethyl ether (8 ml). The suspension was stirred for 24 h. The mixture was washed with ice-cold dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The organic phase was dried and made up to 100 ml with diethyl ether. Lithium aluminium deuteride (500 mg) was added and the mixture was heated under reflux for 2.5 h. Ethyl acetate and water were then added. The ether was removed under reduced pressure, the residue was taken up in ethyl acetate, washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The solvent was evaporated and the residue dissolved in pyridine (9 ml) and treated with acetic anhydride (4 ml) for 24 h. The solution was poured into dilute hydrochloric acid and the steroids were extracted with ethyl acetate. The extract was washed with water and aqueous sodium hydrogen carbonate and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave [4β,17α-$^2H_2$]-3β,17β-diacetoxyandrost-5-ene (710 mg) which crystallized from ethyl acetate–light petroleum as plates, m.p. 158—160 °C, $[\alpha]_D$ −62° (*c* 0.4) (lit.,[12] 165—166 °C, $[\alpha]_D$ −69°); δ_H (360 MHz) 0.79 (3 H, s, 18-H), 1.02 (3 H, s, 19-H), 2.02 (3 H, s, OAc), 2.03 (3 H, s, OAc), 4.60 (1 H, m, $w_{\frac{1}{2}}$ 15 Hz, 3-H), and 5.36 (1 H, m, 6-H); δ (^{2}H) 2.29 (4β-H), 4.59 (17α-H).

Reaction of [4β,17α-$^2H_2$]-3β,17β-*Diacetoxyandrost-5-ene* (**13**) *with Bromine and Silver Acetate.*—Bromine (0.1 ml) was added to a solution of [4β,17α-$^2H_2$]3β,17β-diacetoxyandrost-5-ene (380 mg) in chloroform (10 ml) at −60 °C. Silver acetate (1 g) in pyridine (2 ml) was added in two portions. The mixture was allowed to warm to room temperature and stirred for 24 h in the dark. The mixture was poured into dilute hydrochloric acid and the steroids were extracted with chloroform. The extract was washed with water and aqueous sodium hydrogen carbonate, dried and the solvent was evaporated. The residue was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave [17α-^2H]-4β,17β-*diacetoxy*-3β-*hydroxy*-*androst*-5-*ene* (160 mg) which crystallized from acetone–light petroleum as needles, m.p. 125–128 °C, $[\alpha]_D$ −119° (*c* 0.3) (Found: C, 70.8; H, 8.8. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%); $\nu_{max.}$ 3 530, 3 490, 3 380, 1 740, and 1 700 cm^{-1}; δ_H (360 MHz) 0.79 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 2.03 (3 H, s, OAc), 2.07 (3 H, s, OAc), 3.64 (1 H, m, $w_{\frac{1}{2}}$ 15 Hz, 3-H) 5.37 (1 H, d, *J* 4 Hz, 4-H), and 5.82 (1 H, m, 6-H); δ(^{2}H) 4.58 (17-^{2}H).

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