Oxidation of Secondary Allylic Acetates with Chromium(VI) Reagents

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Steroidal allylic acetates which can form strongly resonance stabilized allylic cations are oxidized smoothly by chromic acid in acidic medium to the corresponding αβ-unsaturated ketones. Axial acetates are more reactive than the equatorial counterparts. Oxidation of the *quasi* axial 3α-acetoxycholest-4-ene is 2.7 times faster than that of the *quasi* equatorial 3β-acetoxycholest-4-ene. The difference is very sharp when the allylic system is in ring B which has less conformational flexibility than ring A. Thus, 3β,6β-diacetoxy-5α-cholest-7-ene is oxidized smoothly to the corresponding 7-en-6-one, whereas the stereoisomeric 3β,6α-diacetoxy-5α-cholest-7-ene remains unchanged. A similar difference was observed with α-substituted cyclopropanes such as 6β-acetoxy-3α-5-cyclo-5α-cholestane and 6α-acetoxy-3α,5-cyclo-5α-cholestane.

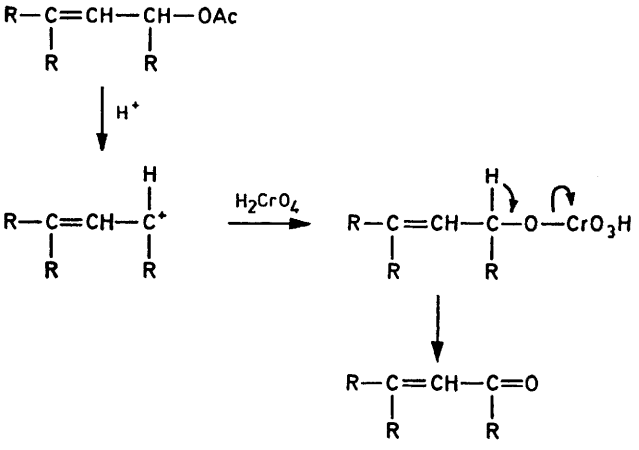
SECONDARY allylic alcohols are oxidized by Cr^{VI} reagents much faster than the corresponding saturated alcohols;[1] however, the rate of oxidation of saturated axial alcohols is significantly larger than that of their equatorial stereoisomers,[2] whereas the oxidation of the related αβ-unsaturated *quasi* axial alcohols is slower than that of the corresponding *quasi* equatorial counterparts.[3] The first two steps of the mechanism of such oxidations involve the fast equilibrium formation of a chromate ester, followed by the rate-limiting cleavage of the adjacent C–H bond.[4] Based on a deuterium isotope effect, Burstein and Ringold [3] concluded that removal of this hydrogen is rate limiting in the oxidation of allylic alcohols as well; the faster rate of oxidation of the equatorial isomers was attributed to the axial configuration of the hydrogen being removed, which permits continuous overlap with the π-electrons of the adjacent double bond.

If the prior formation of a chromate ester is impossible, for instance due to transformation of the αβ-unsaturated alcohol into an ester, an unsaturated ketone would be obtained only by oxidation of an intermediate allylic carbonium ion which could eventually be generated under the conditions of the reaction. Transformation of allylic alcohols into the corresponding acetates afforded simple systems for checking such an hypothesis.

Treatment of 3β-acetoxy- (1) and 3α-acetoxycholest-4-ene (2) with Jones reagent (CrO_3 in 8N-H_2SO_4) in acetone solution, for 1 h at room temperature, afforded quantitatively cholest-4-en-3-one (3). The oxidation of (1) proceeded at a much slower rate with chromium trioxide in 90% acetic acid (it reached completion only after *ca.* 20 h), whereas in acetic acid–sodium acetate, less than 10% conversion was attained after 20 h. Compound (1) remained unchanged on attempted oxidation with pyridinium chlorochromate in dichloromethane (Corey's reagent) and with chromium trioxide complex in pyridine solution (Sarret's reagent). These experiments lead to the conclusion that chromium trioxide should operate in acidic conditions in order to oxidize the allylic acetate.

The reaction can be explained by assuming the prior cleavage of the C–OAc bond, leading to the formation of a strongly resonance-stabilized allylic cation. Indeed, in acidic conditions (a few drops of 8N-H_2SO_4 in acetone solution), but in the absence of the oxidizing agent, cholesta-3,5-diene is quantitatively obtained from either compound (1) or (2). In the presence of chromic acid, nucleophilic attack of the intermediate cation leads to the formation of a chromate ester which is subsequently transformed into the unsaturated ketone.

A competitive oxidation of allylic acetates (1) and (2) with chromium trioxide in 90% acetic acid showed that the *quasi* axial acetate (2) is oxidized 2.7 times faster than the *quasi* equatorial stereoisomer,† thus suggesting that



cleavage of an axial C–OAc bond is favoured because it facilitates orbital overlap with the π-electrons of the adjacent double bond. If the formation of an allylic cation is more difficult, the oxidation would require more drastic conditions, or it would not take place at all. In aliphatic systems, γγ-dialkyl substituted allyl halides are solvolysed *ca.* 10^3 times faster than γ-monoalkyl substituted analogues.[5] The behaviour towards chromium trioxide of several steroidal γ-monoalkyl allylic acetates was therefore investigated. The stereoisomeric 3β-acetoxy (4) [6] and 3α-acetoxy-5α-cholest-2-ene (5),[7] as well as 4β-acetoxy- (6) and 4α-acetoxy-5α-cholest-2-ene (7) remained unchanged in the presence of Jones reagent. The only reaction which took place with 1β-acetoxy- (10) and 1α-acetoxy-5α-cholest-2-ene (11) was allylic oxid-

† By integration of the n.m.r. signals of 3-H and 4-H at 270 MHz.

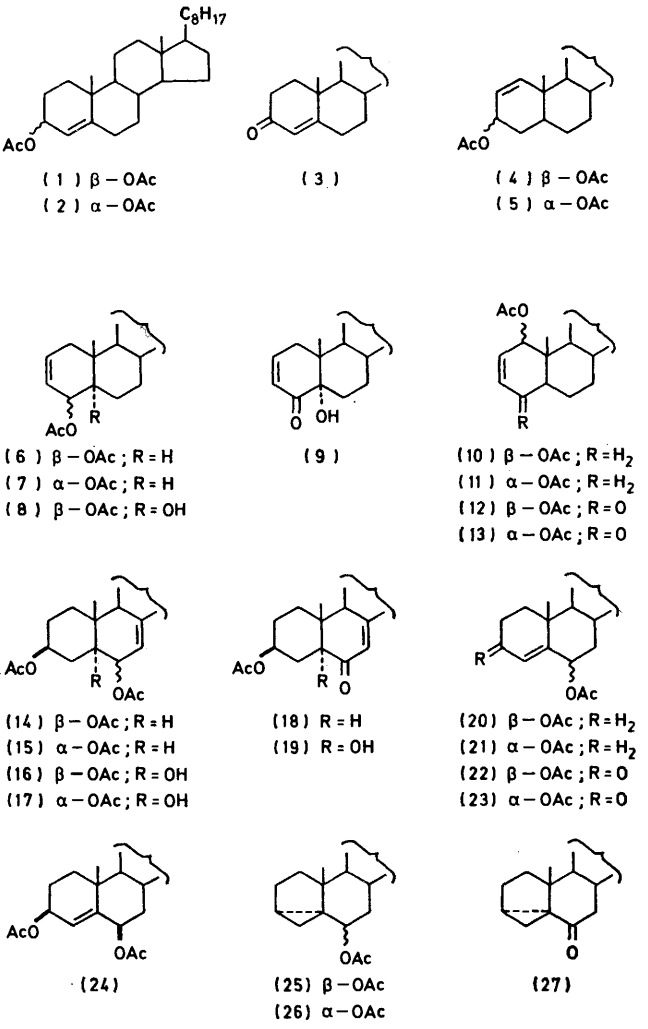
ation to give the corresponding 4-ones (12) and (13), respectively;[8] the reaction proceeded in low yield (*ca.* 5%) with Jones reagent and in moderate yield (30—40%) with Na_2CrO_4 in acetic acid–acetic anhydride.

A tremendous difference in reactivity between axial and equatorial allylic acetates was observed with 3β,6β-diacetoxy- (14)[9] and 3β,6α-diacetoxy-5α-cholest-7-ene (15);[3] whereas the former (6β-OAc axial) was quantitatively transformed into the corresponding enone (18) (Jones reagent, 1 h), the latter (6α-OAc equatorial) remained unchanged even after 6 h. The difference in reactivity between the two γγ-dialkyl substituted allylic systems (1) and (15), both with equatorial acetoxy-groups, can be attributed to the lack of conformational flexibility in the latter, leading to a drastic decrease in the possibility of orbital overlap between the π-electrons of the double bond and the σ-electrons of the 6α-OAc bond.

A similar behaviour was encountered in systems in which an α-cyclopropyl cation can easily be generated. Although 6β-hydroxy- and 6α-hydroxy-3α,5-cyclo-5α-cholestane rearrange in the presence of acid catalysts to give cholesterol, the rate of solvolysis of the former is *ca.* 500 times faster than that of the latter, and is attributed to orbital overlap between the 6β-OH bond and the electron cloud of the cyclopropane system.[10] We took advantage of this difference in reactivity in order to study the behaviour of the corresponding acetates (25) and (26)[11] in the presence of Jones reagent; whereas the former is rapidly and quantitatively oxidized to 3α,5-cyclo-5α-cholestan-6-one (27), the latter remains unchanged. Although either 6β-acetoxy-3α,5-cyclo-5α-cholestane or 6β-methoxy-3α,5-cyclo-5α-cholestane are oxidized with chromium trioxide in acetic acid at room temperature to 3α,5-cyclo-5α-cholestanone (27), the oxidation of the latter is significantly slower than that of the former. It is noteworthy, however, that oxidation of the methyl ether with the same reagent, but at 97 °C, afforded *ca.* 20% of 3β-acetoxycholest-5-en-7-one.[12]

The only reaction which took place when 6β-acetoxy-(20)[13] and 6α-acetoxy-cholest-4-ene (21)[13] were treated with Na_2CrO_4 in acetic acid–acetic anhydride, was allylic oxidation to the corresponding enones (22)[1,14] and (23).[15] The compounds remained unchanged in the presence of Jones reagent over short periods of time (up to 2 h), but gave mixtures of unchanged material and unidentified overoxidized products on prolonged contact with the reagent (20—24 h). The different behaviour of compound (1) (a γγ-dialkyl substituted allylic acetate) and (21) (a βγ-dialkyl substituted system) prompted us to investigate the behaviour of the allylic diacetate (24) in the presence of Jones reagent. The compound was indeed oxidized to the enone (22), however, in contrast to the oxidation of (1) which was complete after 1 h, the oxidation of (24) proceeded only in *ca.* 12% yield after 8 h, and *ca.* 25% yield after 15 h. A reasonable explanation of the slow oxidation of (24) as compared to (1) is the inductive electron-withdrawal effect of the C-6 substituent, which decreases the polarization of the 3β-OAc bond.

To our knowledge, there are only two reactions which are related to the above oxidations. (*a*) Oxidation of allyl halides with potassium chromate in the presence of a crown ether leads to the formation of the corresponding aldehyde.[16] It is noteworthy that best results are obtained with γγ-dialkyl substituted allyl halides. The reaction with octyl chloride proceeds in low yield because the formation of the intermediate chromate



ester is not assisted by resonance. (*b*) Oxidation of alkyl and allyl halides with dimethyl sulphoxide in the presence of $AgBF_4$ affords the corresponding aldehydes or ketones; the reaction proceeds faster with allyl than with alkyl halides.[17]

Contradictory results were obtained on attempted oxidation with chromium trioxide of αβ-unsaturated glycol acetates. 3β,6β-Diacetoxy-5-hydroxy-5α-cholest-7-ene (16)[9] was oxidized with Jones reagent to the corresponding 6-one (19),[9,18] however, the reaction was *ca.* 2 times slower than that of the 5-deoxy-analogue (12). Conversely, 4β-acetoxy-5-hydroxy-5α-cholest-2-ene (8) was oxidized by Na_2CrO_4 to the 4-one (9), although the corresponding 5-deoxy-analogue (6) could

not be oxidized. As expected, 3β,6α-diacetoxy-5-hydroxy-5α-cholest-7-ene (17) remained unchanged in the presence of the above oxidizing agents, the same as the deoxy-analogue (15).

EXPERIMENTAL

Oxidations.—(*a*) *With Jones reagent.* To a stirred solution of allylic acetate (0.1 mmol) in pure acetone (10—20 ml), a slight excess of Jones reagent [19a] (0.2—0.3 ml) was added and stirring was continued at room temperature, as stated. Excess of reagent was then destroyed with a few drops of methanol, most of the solvent was removed under reduced pressure, water was added, and the product was isolated by filtration or by extraction with ether.

(*b*) *With sodium chromate.* Sodium chromate (60 mg) was added to a stirred solution of allylic acetate (0.1 mmol) in acetic acid (3 ml) and acetic anhydride (1.5 ml). The mixture was stirred overnight at room temperature, water was then added, and the product was isolated by extraction with ether.

(*c*) *With chromium trioxide in acetic acid.* The oxidizing solution was prepared by dissolving chromium troxide (1 g) in 90% acetic acid (100 ml). To a solution of allylic acetate (0.1 mmol) in pure acetone (5 ml) the oxidizing solution (5 ml) was added, and stirring was continued for the specified time, at room temperature. Excess of reagent was destroyed with methanol, the solution was concentrated to a small volume under reduced pressure, and the product was extracted with ether.

(*d*) *With chromium trioxide in acetic acid–sodium acetate.* The oxidizing solution was prepared by adding a solution of sodium acetate (1 g) in water (10 ml) to a solution of chromium trioxide (1 g) in acetic acid (90 ml). The reaction was carried out as described above.

(*e*) *With pyridinium chlorochromate.*[20] To a stirred solution of allylic acetate (0.1 mmol) in dichloromethane (1 ml), a solution of pyridinium chlorochromate (0.2 mmol) in dichloromethane (2 ml) was added. Stirring was continued overnight at room temperature, and the product was isolated by dilution with the same solvent and filtration through a Pasteur pipette containing 1—2 g of silica gel 60 (70—230 mesh; Merck).

(*f*) *With chromium trioxide in pyridine.*[19b] A solution of allylic acetate (0.1 mmol) in dry pyridine (1 ml) was added to the reagent prepared by adding chromium trioxide (50 mg), in several portions, to pyridine (1 ml), at 0 °C. The mixture was kept overnight at room temperature and the product was isolated by extraction with ether.

Preparation of 4β-*Acetoxy-* (6) *and* 4α-*Acetoxy-*5α-*cholest-*2-*ene* (7).—3α,4α-Epoxy-5α-cholestan-2-one was prepared according to the procedure developed in the androstane series.[21] The crude product was chromatographed on silica gel 60; elution with hexane–ethyl acetate (9 : 1) afforded the epoxy-ketone, which showed one spot on a chromatoplate. N.m.r.: δ 0.64 s (18-H), 0.69 s (19-H), 0.86 (d, 21-H), 3.09 (dd, *J* 4 and 10 Hz, 4β-H), and 3.13 (d, *J* 4 Hz, 3β-H). To a solution of this compound (200 mg) in methanol (70 ml), a 10% methanolic solution of 100% hydrazine hydrate (4.5 ml) was added under nitrogen. The yellow colour which appears on addition of the reagent gradually fades away. After 3 h at room temperature, most of the solvent was evaporated under reduced pressure at *ca.* 30 °C, ice–water was added and the precipitate was collected by filtration. The crude product was dissolved in dichloromethane, dried (Na_2SO_4), and filtered through a short column of silica gel 60 (10 g) to give 4α-hydroxy-5α-cholest-2-ene (170 mg), m.p. 138—140 °C (from methanol), $[\alpha]_D$ +21° (*c* 0.37) (Found: C, 83.9; H, 12.0. $C_{27}H_{46}O$ requires C, 83.9; H, 12.0%). Acetylation with acetic anhydride and pyridine, overnight at room temperature, afforded 4α-acetoxy-5α-cholest-2-ene (7), n.m.r.: δ 0.66 (s, 18-H), 0.86 (s, 19-H), 0.86 (d, 21-H), 2.06 ($OCOCH_3$), 4.9br (m, 4β-H), 5.5 (m, 2- and 3-H).

Oxidation of 4α-hydroxy-5α-cholest-2-ene (100 mg) with Jones reagent (1 h at 15 °C) afforded 5α-cholest-2-en-4-one which was isolated by extraction with dichloromethane. The product showed one spot on a chromatoplate. N.m.r.: δ 0.66 (s, 18-H), 0.85 (s, 19-H), 0.86 (d, 21-H), 5.96 (dq, 3-H), and 6.75 (dq, 2-H). This ketone (70 mg) in methanol (30 ml), was reduced with sodium borohydride (70 mg) for 2 h at room temperature. The solution was neutralized with dilute hydrochloric acid, most of the solvent was removed, water was added, and the crude alcohol was collected by filtration. Acetylation afforded 4β-acetoxy-5α-cholest-2-ene (6), n.m.r. δ 0.66 (s, 18-H), 0.94 (s, 19-H), 0.86 (d, 21-H), 2.01 ($OCOCH_3$), 5.1 (narrow m, 4α-H), and 5.7 (m, 2-H and 3-H).

Preparation of 3β,6α-*Diacetoxy-*5-*hydroxy-*5α-*cholest-*7-*ene* (17).—This reaction was carried out according to the procedure developed for the corresponding derivative in the ergostane series.[22] To a solution of 7-dehydrocholesteryl benzoate [23] (3 g) in dry chloroform (90 ml), a solution of perbenzoic acid in benzene (40 mg/ml; 20% excess) was added. After 20 h at 4 °C the solution was washed with 5% aqueous Na_2CO_3, then with water, and then finally dried (Na_2SO_4). After removal of the solvent, the residue was crystallized from hot light petroleum (b.p. 60—80 °C). The crude crystalline product (1.5 g) was chromatographed through silica gel 60 (100 g). Impurities were eluted with light petroleum–dichloromethane (4 : 1). 3β,6α-Dibenzoyloxy-5-hydroxy-5α-cholest-7-ene (1.3 g) was eluted with light petroleum–dichloromethane (1 : 1), m.p. 223—225 °C (from ethyl acetate–ethanol). A solution of the dibenzoate (2 g) in 5% methanolic KOH (100 ml) was heated to reflux for 3 h. After cooling, ice water was added, and the product was filtered, dried, and acetylated with acetic anhydride (7 ml) and pyridine (8 ml), overnight at room temperature. After addition of ice water, the diacetate (17) was isolated by filtration and purified by chromatography over silica gel 60 (elution with dichloromethane), m.p. 198—200 °C (from ethanol), $[\alpha]_D$ +54° (*c* 0.27) (Found: C, 73.9; H, 10.0. $C_{31}H_{50}O_5$ requires C, 74.05; H, 10.05%).

Preparation of 4β-*Acetoxy-*5-*hydroxy-*5α-*cholest-*2-*ene* (8).—To a solution of 5-hydroxy-5α-cholest-2-ene [24] (2 g) in acetic acid (40 ml) and acetic anhydride (20 ml), sodium chromate (2.4 g) was added. The solution was stirred for 20 h at room temperature, ice–water was then added, and the product was extracted with ether. The ethereal solution was washed consecutively with water, aqueous $NaHCO_3$, and water, and then dried (Na_2SO_4). The residue after evaporation of the solvent was chromatographed over silica gel 60 (100 g). Elution with hexane–ether (9 : 1) afforded 5-hydroxy-5α-cholest-2-en-4-one (9) (480 mg) which showed one spot on a chromatoplate. The product could not be crystallized; n.m.r.: δ 0.66 (s, 18-H), 0.86 (d, 21-H), 0.92 (s, 19-H), 5.95 (dq, 3-H), and 6.85 (dq, 2-H). A similar oxidation, but with Jones reagent, was done previously [25] in the androstane series. To the above hydroxy-enone (700 mg), in methanol (100 ml), sodium borohydride (350 mg) was added portionwise. Work-up was done as for the

reduction of 5α-cholest-2-en-4-one. The crude diol (630 mg) was acetylated with acetic anhydride and pyridine overnight at room temperature. The acetate precipitated on addition of ice–water and was collected by filtration. Crystallization from methanol afforded pure 4β-acetoxy-5-hydroxy-5α-cholest-2-ene (8), m.p. 162—163 °C (lit.,[26] 159—160 °C). The structure of (8) was confirmed by catalytic hydrogenation in ethanol solution over 5% Pd–C to 4β-acetoxy-5-hydroxy-5α-cholestane, m.p. 178—180 °C (from acetone) (lit.,[27] 175—176 °C; mixed m.p. undepressed).

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