A-Substituted 5β-Steroids. V.[1] Syntheses and Some Reactions of 1-Oxygenated 5β-Cholestanes

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1-Oxygenated 5β-cholestanes were synthesized in good yield from 3-oxygenated 5β-cholestane through 5β-cholest-1-en-3-one. The reaction of 1β,2β-epoxy-5β-cholestan-3-one with hydrogen halide occurs with a normal ring cleavage resulting in the formation of 2-halo-5β-cholest-1-en-3-one. The reaction of 1β-hydroxy-5β-cholest-2-ene with chromium trioxide gave the allylic rearrangement product, 5β-cholest-1-en-3-one. The oxidative acetylation and bromination of 5β-cholestan-1-one is described.

Although studies have been made on the syntheses of 1-oxygenated 5α-steroids,[2] only very little information can be found on 5β-steroids concerning the reactions of introducing oxygenated groups at the C_1 position.[3]

In a previous paper, we reported on the synthesis of 5β-cholest-1-en-3-one as a key intermediate for the synthetic pathway of 1-oxygenated 5β-cholestanes.[4] In the present paper, the synthesis of 1-oxygenated 5β-cholestanes is given in detail together with reactions of some of them.

Djerassi *et al.*[5] reported that 1-oxygenated 5α-cholestanes were synthesized from 5α-cholest-1-en-3-one derived from 3-oxygenated 5α-cholestane. Since the bromination of 3-oxo-5α-steroid gives a 2-brominated product, the 1-en-3-oxo derivative could easily be derived from the product by dehydrobromination. However, this procedure can be applied to 5β-steroid because the bromination of the 3-oxo derivative does not occur at C_2. Williamson and Johnson reported the synthesis of 4α-bromo-5α-cholestan-3-one, a compound that can be produced only with difficulty by the direct bromination of 5α-cholestan-3-one, or by the reductive monodebromination of the 2α,4α-dibromo-3-oxo derivative with chromous acetate.[6] We attempted the preparation of 2-bromo-5β-cholestan-3-one by the application of this method to 2β,4β-dibromo-5β-cholestan-3-one (**1**),[7] and achieved good results. The syntheses of 1-oxygenated 5β-cholestanes from 5β-cholest-1-en-3-one (**3**) were then carried out following the procedure of Djerassi *et al.*[5] for the synthesis of 1-oxygenated 5α-cholestanes. Some reactions have been examined for the 1-oxygenated derivatives thus obtained.

Results and Discussion

The α-bromoketone derived from 2β,4β-dibromo-5β-cholestan-3-one (**1**) by reductive monodebromination with chromous acetate was determined as 2β-bromo-5β-cholestan-3-one (**2**) from its NMR spectrum. The bromine susceptible to reductive elimination was found to be at C_4 rather than that at C_2 in the 5β-series, but at C_2 in the 5α-series.[6] By treating the product with calcium carbonate/dimethylformamide, 5β-cholest-1-en-3-one (**3**) was formed in good yield. Thus it seems that this pathway improves the insertion of the 1-en-3-oxo function in 5β-steroid.

The epoxy ketone derived from the 1-en-3-oxo derivative (**3**) with alkaline hydrogen peroxide was identified as 1β,2β-epoxy-5β-cholestan-3-one (**4**) from the fact that it shows a negative Cotton curve in its ORD spectrum.[8] The structure is also supported by the ring opening reaction of the epoxy ketone with hydrogen halide. If the epoxy ring has a β-orientation, it will be transformed into 2-halo-5β-cholest-1-en-3-one (**5**) in this reaction. In the present instance, the chemical shift of the C_1-vinyl proton in the presumed structure was calculated from the equation proposed by Matter *et al.*,[9] and the values (**5a**, τ 2.74; **5b**, 3.01) agreed very closely with the ones observed (τ 2.75 and 3.01, respectively) for the compound obtained. These results show that in the epoxydation of derivative (**3**) the attack of the reagent took place at the β-side of the molecule. The attack is the reverse of that in the epoxydation of 5α-cholest-1-en-3-one.[5] This is attritable to the environmental complexity of the α-side of 5β-steroids.

Reductive elimination of the 1β,2β-epoxy-3-oxo derivative (**4**) with 100% hydrazine hydrate gave an allylic alcohol (**6**). Catalytic hydrogenation of (**6**) followed by its acetylation gave 1β-acetoxy-5β-cholestane (**7b**). This shows that the hydrazine reduction product has a β-oriented hydroxy group at C_1. Oxidation of the catalytic hydrogenation product (**7a**) gave 5β-cholestan-1-one (**8**), which shows a negative Cotton curve having a shoulder near 310 nm similar to 5β-cholestan-2-one[10] in the ORD spectrum.

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In the synthetic pathway of 5β-cholestan-1-one from 5β-cholest-1-en-3-one (**3**), the synthesis from **3** to **7a** without purification of each product, followed by chromatographic separation of the oxidation product of **7a** in the last step, gave the 1-oxo derivative (**8**) in 55% yield based on the 1-en-3-oxo derivative.

Catalytic reduction of derivative (**8**) proceeds stereospecifically to give an equatorial hydroxy group. The configuration of the product (**9a**) was determined from the NMR spectrum of its acetate (**9b**). C_1-H of the acetate appeared in a higher field than that of the 1β-acetoxy epimer (**7b**), showing a triplet. This stereospecificity is attributable to preferential attack from the β-side rather than the α-side, which has a stereochemical complexity similar to the epoxy ketone (**4**). This catalytic reduction of the 1-oxo derivative is identical with that of Schlegel and Tamm on the catalytic reduction of methyl 1-oxo-etianate.[3a]

Oxidation of 2-en-1β-ol (**6**) with chromium trioxide gave predominantly 5β-cholest-1-en-3-one (**3**) along with a minor component, 5β-cholest-2-en-1-one (**10**). This may be attributed to the small interaction involved with respect to the 19-methyl group in the case of the reaction pathway through a six-membered transition state (A) between the 1β-chromic ester formed and the allylic position, as compared with that in the case of the pathway through a cyclic transition state (B) between the 1β-chromic ester and $C_{1\alpha}$-H (Fig. 1). We see that the properties of 1β-hydroxy-5β-cholest-2-ene (**6**) are similar to those of 1β-halo-5β-cholestan-2-one, which gave a 3-substituted product through various reactions.[11]

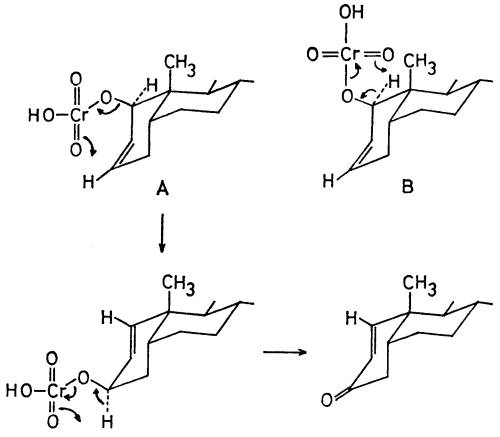
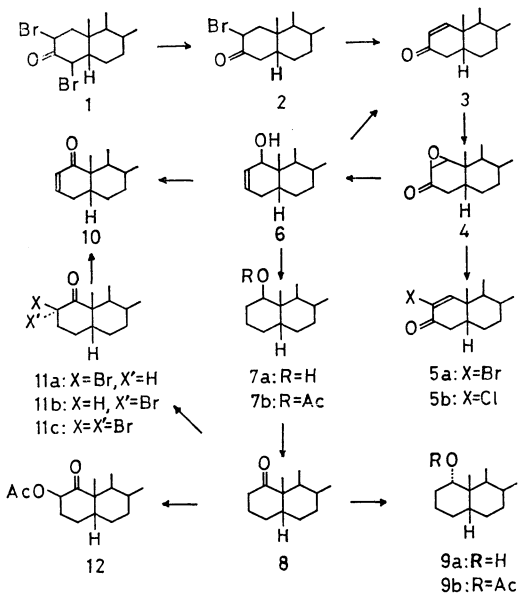


Fig. 1.

The reaction of 5β-cholestan-1-one (**8**) with bromine in acetic acid gave mainly a compound melting at 118—119 °C with two minor products: "A", mp 69—70.5 °C and "B", mp 141.5—143.5 °C. The main product was determined to be 2β-bromo-5β-cholestan-1-one (**11a**) from the fact that the ORD curve showed a negative Cotton effect and its λ_1 had a blue shift of 5 nm from that of the parent ketone (**8**), and from the coupling constant in the NMR spectrum. Dehydrobromination of bromoketone (**11a**) with $CaCO_3$/DMF gave an α,β-unsaturated ketone, identical with 5β-cholest-2-en-1-one (**10**) obtained from 1β-hydroxy-5β-cholest-2-ene (**6**) with chromium trioxide. The minor product "A" was determined to be the 2α-bromo epimer (**11b**) from the small half-height width of the peak at τ 5.69 in its NMR spectrum, as compared with that of the 2β-epimer (**11a**), and from the ORD curve showing a red shift of 28 nm from that of the parent ketone (**8**). The product could easily be converted into the 2β-epimer (**11a**) with HBr/AcOH. The NMR spectrum of the other product "B" did not reveal any peaks due to –CH(Br)–. Hence the product was concluded to be a 2,2-dibromo-1-oxo derivative (**11c**).



Oxidative acetylation of 5β-cholestan-1-one (**8**) with lead tetraacetate gave 2β-acetoxy-5β-cholestan-1-one (**12**). It was found from the NMR spectrum that the acetate was not deformed, as was the case with the other α-acyloxy-keto-5β-steroids having an equatorial acyloxy group in ring A.[12]

Experimental

All melting points are uncorrected. The IR spectra were measured on a Shimadzu model IR-27B infrared spectrometer, ORD spectra on a JASCO model ORD/UV-5 spectrometer, and NMR spectra on Hitachi-Perkin Elmer R-20A and JEOL model JNM-4H-100 instruments using TMS as an internal standard.

2β-Bromo-5β-cholestan-3-one (2). To a solution of **1** (31.7 g) in acetic acid (600 ml) and chloroform (240 ml) was added chromous acetate prepared from chromic chloride according to the method of Williamson and Johnson.[6] The end point of the reaction was confirmed by tlc. Ether extracts from the reaction mixture were neutralized, washed and evaporated. Crystallization of the residue from ethanol gave needles (22.2 g), mp 138—140 °C, IR (KBr): 1727 cm^{-1}; ORD (*c* 0.216, dioxane) at 16 °C: $[\alpha]_{311}$ −296° (trough) and $[\alpha]_{267}$ +494°; NMR (CCl_4) τ: 5.42 (dd, $J_{1\alpha,2}$=5 and

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$J_{1\beta,2}$=14 Hz, 1H).

Found: C, 69.45; H, 9.79%. Calcd for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74%.

*5β-Cholest-1-en-3-one (**3**).* A mixture of **2** (19.4 g), calcium carbonate (20 g), and DMF (300 ml) was refluxed for 2 hr. After the usual work-up, the resultant residue, on crystallization from ethanol, gave needles (12.8 g), mp 108—109 °C (lit,[3c] 105—106 °C).

*Synthesis of 5β-Cholestan-1-one (**8**) from 5β-Cholest-1-en-3-one (**3**).* The synthesis was carried out following the procedure of Djerassi *et al.*[5] for the synthesis of 5α-cholestan-1-one from 5α-cholest-1-en-3-one. Details are therefore omitted. Reaction of **3** (10 g) with 1 M sodium hydroxide solution (100 ml), dioxane (510 ml), and 30% hydrogen peroxide (35 ml) at room temperature for 15 hr gave **4** (7.4 g), mp 107—108.5 °C (lit,[3c] 107—109 °C), from ethanol. When the temperature was raised to 34—40 °C, the reaction was completed in 5 hr. By refluxing **4** (2.42 g) with 100% hydrazine hydrate (14.7 ml) for 15 min, **6** was obtained as a colorless amorphous substance (1.26 g), mp 95—96 °C (lit,[3c] 98—99 °C), from acetone. Hydrogenation of **6** (9.8 g) was carried out with 10% Pd-C (7 g) in cyclohexane (35 ml). Since crystallization of **7a** could not be accomplished from the residue (9.8 g, IR: 3330 cm^{-1}), the following procedure was used. A solution of **7a** (10 g) in acetic acid (605 ml) was treated with chromium trioxide (2.6 g) in acetic acid (242 ml) and water (12 ml) at room temperature. After being stirred for 5 hr, the reaction mixture was treated in the usual manner. The residue was chromatographed on silica gel. Elution with benzene-petroleum ether (1 : 1) gave needles of **8** (4.9 g), mp 101—102 °C (lit,[3c] 101—102 °C), from ethanol (Found: C, 83.79; H, 12.02%).

*Epoxy Ring Opening Reaction of 1β,2β-Epoxy-5β-cholestan-3-one (**4**).* A solution of **4** (200 mg) in chloroform (20 ml) was treated with 48% hydrobromic acid (2 ml) at room temperature for 24 hr. The reaction mixture was poured into water and the chloroform layer was worked up in the usual manner. Crystallization of the resulting oil from ethanol gave **5a** (156 mg), mp 137—139 °C; λ_{max}^{EtOH} 257 nm (ε 12500); IR (KBr): 1696 and 1600 cm^{-1}; ORD (*c* 0.611, dioxane) at 18.5 °C: $[\alpha]_{375.5}$ +200° (sh), $[\alpha]_{360}$ +237° (peak), $[\alpha]_{350}$ +193° (trough), $[\alpha]_{345.5}$ +198° (peak), $[\alpha]_{334}$ +148° (trough), $[\alpha]_{331}$ +149° (peak), $[\alpha]_{323}$ +136° (trough), and $[\alpha]_{300}$ +265°; NMR (CCl_4) τ: 2.75 (s, 1H) and 8.77 (s, 3H).

Found: C, 69.76; H, 9.43%. Calcd for $C_{27}H_{43}OBr$: C, 69.96; H, 9.36%.

When the epoxide was treated with 35% hydrochloric acid under the same conditions, **5b** (137 mg) mp 130—132.5 °C, was obtained from ethanol. λ_{max}^{EtOH} 249 nm (ε 10500); IR (KBr): 1703 and 1606 cm^{-1}; ORD (*c* 0.434, dioxane) at 18.5 °C: $[\alpha]_{373}$ +761° (sh), $[\alpha]_{359.5}$ +885° (peak), $[\alpha]_{350}$ +747° (trough), $[\alpha]_{344}$ +789° (peak), $[\alpha]_{334}$ +630° (trough), $[\alpha]_{328}$ +685° (peak), $[\alpha]_{323}$ +643° (trough), and $[\alpha]_{300}$ +1266°; NMR (CCl_4) τ: 3.01 (s, 1H), and 8.79 (s, 3H).

Found: C, 77.17; H, 10.27%. Calcd for $C_{27}H_{43}OCl$: C, 77.38; H, 10.34%.

*1β-Acetoxy-5β-cholestane (**7b**).* **7a** (2.3 g) was treated with acetic anhydride (55 ml) and pyridine (55 ml) for 10 hr at room temperature. After the usual work-up, the residue was chromatographed on silica gel. Benzene elution, on crystallization from ethanol, gave needles (1.48 g), mp 104—105.5 °C (lit,[3c] 100—101 °C).

*1α-Acetoxy-5β-cholestane(**9b**).* Sodium borohydride (500 mg) was gradually added to a solution consisting of **8** (1 g), ether (75 ml) and methanol (25 ml). After the usual work-up, an oily product (1.1 g; IR: 3400 cm^{-1}) was obtained. Attempts to crystallize it with several solvents were unsuccessful, and it was acetylated in the usual manner. **9b** was obtained as needles (783 mg) from ethanol. Mp 40—42 °C, IR (KBr): 1735 and 1242 cm^{-1}; NMR (CCl_4) τ: 5.57 (t, $J_{1,2}$=7.5 Hz, 1H) and 8.06 (s, 3H).

Found: C, 80.59; H, 11.72%. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.71%.

*Oxidation of 5β-Cholest-2-en-1β-ol (**6**).* A solution of **6** (900 mg) in acetone (7 ml) was treated with chromium trioxide (560 mg) and 40% H_2SO_4 solution (0.8 ml) at 10—15 °C. After 30 min, a small amount of methanol was added to the reaction mixture. The ether extracts from the solution were washed with sodium hydrogen carbonate solution and water, dried and evaporated. The residue was chromatographed on silica gel. From the first elution with benzene-petroleum ether (1 : 1), **10** (36 mg) was obtained from ethanol as needles, mp 100—101.5 °C (lit,[3c] 99—100 °C); IR (KBr): 1672 and 1631 cm^{-1}; λ_{max}^{EtOH} 223 nm (ε 7000); ORD (*c* 0.196, dioxane) at 23.5 °C: $[\alpha]_{400}$ −143°, $[\alpha]_{384}$ −250° (trough), $[\alpha]_{373}$ −89° (peak), $[\alpha]_{366}$ −189° (trough), $[\alpha]_{356}$ +92° (peak), $[\alpha]_{349}$ −59° (trough), $[\alpha]_{342}$ +120° (peak), $[\alpha]_{334}$ +20° (trough), $[\alpha]_{327}$ +112° (peak), $[\alpha]_{322}$ +94° (trough), and $[\alpha]_{280}$ +339°; NMR (CCl_4) τ: 3.40 (dq, $J_{3,4\alpha}$=2.1, $J_{3,4\beta}$=5.0 and $J_{2,3}$=10.2 Hz, 1H) and 4.32 (dd, $J_{2,4\beta}$=1.7 and $J_{2,3}$=10.2 Hz, 1H).

Found: C, 84.02; H, 11.46%. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53%.

The next fraction eluted with the same solvent, on crystallization from ethanol, gave needles of **3** (640 mg), mp 108—109 °C.

*Bromination of 5β-Cholestan-1-one (**8**).* To a solution of **8** (2.89 g) in acetic acid (200 ml) was added bromine (1.2 g) in acetic acid (50 ml). After being stirred for 30 min at room temperature, the reaction mixture was treated in the usual manner. The resulting oil (3.7 g) was chromatographed on silica gel. From the first elution with benzene-petroleum ether (1 : 9), **11c** was obtained as needles (184 mg), mp 141.5—143°C, IR (KBr): 1714 cm^{-1}; ORD (*c* 0.22, dioxane) at 21 °C: $[\alpha]_{350}$ +854° (peak) and $[\alpha]_{294}$ −1240° (trough); NMR ($CDCl_3$) τ: 8.70 (s, 3H).

Found: C, 59.65; H, 8.19%. Calcd for $C_{27}H_{44}OBr_2$: C, 59.56; H, 8.15%.

The second fraction, eluted with benzene-petroleum ether (2 : 8), on crystallization from ethanol gave plates of **11b** (494 mg), mp 69—70.5 °C, IR (KBr): 1699 cm^{-1}; ORD (*c* 0.66, dioxane) at 20 °C: $[\alpha]_{350}$ +555° (peak), $[\alpha]_{324}$ +350° (sh), and $[\alpha]_{304}$ −400° (trough); NMR ($CDCl_3$) τ: 5.67 m, $W_{h/2}$=6.5 Hz, 1H) and 8.85 (s, 3H).

Found: C, 69.76; H, 9.84%. Calcd for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74%.

The third fraction, eluted with the same solvent, on crystallization from ethanol, gave needles (1.22 g) of **11a**, mp 118—119 °C, IR (KBr): 1711 cm^{-1}; ORD (*c* 0.46, dioxane) at 30 °C: $[\alpha]_{317}$ −1150° (trough), $[\alpha]_{308}$ −1020° (sh), and $[\alpha]_{272}$ +1080° (peak); NMR ($CDCl_3$) τ: 5.04 (dd, $J_{2,3\alpha}$=6 and $J_{2.3\beta}$=12.5 Hz, 1H) and 8.76 (s, 3H).

Found: C, 69.58; H, 9.96%. Calcd for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74%.

Epimerization of **11b** with hydrogen bromide in acetic acid gave **11a**.

A solution of the 2β-bromo derivative (**11b**) (1.5 g) in DMF (25 ml) was refluxed with calcium carbonate (1.5 g). After 3 hr, the reaction mixture was treated in the usual manner. Crystallization of the product from ethanol gave needles (1.1 g), mp 99—101 °C. The compound was identical with 5β-cholest-2-en-1-one (**10**) in the IR and NMR spectra.

*2β-Acetoxy-5β-cholestan-1-one (**12**).* A mixture consisting of **8** (1 g), lead tetraacetate (1.2 g), boron trifluoride etherate (1.9 ml), and benzene (30 ml) was stirred at 30 °C in a nitrogen atmosphere. After 20 hr, the reaction mixture was poured into water and the benzene layer was taken up in ether. The ethereal solution was washed with water, dried and evaporated. Crystallization of the residue from ethanol gave needles (320 mg), mp 88—90 °C, IR (KBr): 1747 and 1711 cm^{-1}; ORD (*c* 0.23, dioxane) at 20 °C: $[\alpha]_{312}$ −1662° (trough), $[\alpha]_{304}$ −1386° (sh), and $[\alpha]_{264}$ +1586° (peak); NMR ($CDCl_3$) τ: 4.60 (dd, $J_{2,3\alpha}=5.8$ and $J_{2,3\beta}=12.7$ Hz, 1H) and 7.88 (s, 3H).

Found: C, 78.11; H, 11.02%. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88%.

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