Synthesis of 1-Oxygenated 5β-Cholestanes

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Although the synthesis of 1-oxygenated 5α-steroids has been studied by several groups,[1] little has been found in literature concerning the synthesis of 1-oxygenated 5β-steroids except for the preparation of 1-oxoetianic acid from acovenosigenin A, which has two hydroxy groups in C-1 and -3.[2]

The present communication deals with a study on the synthesis of 1-oxygenated 5β-cholestanes from 4β-bromo-3-oxo-5β-cholestane. As a key intermediate in this synthesis, we chose 3-oxo-5β-cholest-1-ene. The synthesis of this derivative in circuitous route or in the method using a special reagent has already been reported by a few groups.[3] We wish to present a more practical method for the synthesis of 3-oxo-5β-cholest-1-ene.

In a previous paper, it was reported that the substitution reaction of 4β-Br in 3-oxo-5β-steroids with AcOK/AcOH is accompanied by a new rearrangement of the substituent from C_4 to C_2 resulting in the formation of the 2β-acetoxy-3-oxo derivative in good yield.[4] In the reaction using piperidine/piperidine hydrobromide/dioxane as reagents instead of AcOK/AcOH, we have found that the 1-en- and 4-en-3-oxo derivatives were formed in the ratio of 1 : 1. Chromatographical separation and recrystallization of the product from methanol gave needles of 3-oxo-5β-cholest-1-ene, mp 103°C, in over 35% yield.

When the 4β-bromo-3-oxo derivative was refluxed with pyridine, 1-[2-(3-oxo-5β-cholestanyl)]pyridinium bromide was formed. Needles, mp 266—268°C (decomp.), $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1725 (C=O), 1633, 1493 (C=C, C=N), 789, 763 (=C–H), $\lambda_{\max}^{\mathrm{EtOH}}$ 261 mμ (ε 3700). On the pyrolysis of the pyridinium bromide at 480—500°C, 3-oxo-5β-cholest-1-ene was also obtained. The total yield of this α,β-unsaturated ketone from the 4β-bromo-3-oxo-5β-cholestane was 43%.

The synthesis of 1-oxygenated 5β-cholestane from this derivative was carried out using the procedure of Djerassi *et al.*[5] for the syntehsis of 1-oxygenated 5α-steroids. The physical constants of the products in this synthetic pathway are as follows:

Epoxidation of the 1-en-3-oxo derivative gave needles of 1β,2β-epoxide, mp 107—108.5°C, from methanol. $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1702 (C=O), 856, 844 (C–O), ORD (c 0.19, Di) at 22°C: $[\alpha]_{589}$ $-5°$, $[\alpha]_{333}$ $-697°$ (trough), $[\alpha]_{329}$ $-678°$ (peak), $[\alpha]_{325}$ $-687°$ (trough), $[\alpha]_{280}$ $+1355°$ (peak), NMR (CDCl$_3$) τ: 6.57 (d., J=4.5 cps, 1H), 6.72 (d., J=4.5 cps, 1H). Configuration of this product was established by analysis, IR, ORD and NMR spectra, conversion to 1β,3α-dihydroxy-5β-cholestane with lithium aluminum hydride, and conversion to the 2-halo-3-oxo-1-ene derivatives by cleavage of the epoxy ring with hydrogen halides.[*1] The result of this epoxidation of 3-oxo-5β-cholest-1-ene is contrary to that reported for 5α-series which gives the α-epoxide from the 1-en-3-oxo derivative.[1]

1β-Hydroxy-5β-cholest-2-ene: mp 95—96°C, $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3320 (O–H), 1655 (C=C), 740, 724 (=C–H), NMR (CDCl$_3$) τ: 4.16 (b.d., 2H), 6.16 (m., $W_{h/2}$=7 cps, 1H).

1β-Hydroxy-5β-cholestane: oil, $\nu_{\max}^{\mathrm{Film}}$ cm^{-1}: 3330 (O–H).

1β-Acetoxy-5β-cholestane: needles, mp 104—105.5°, $\nu_{\mathrm{KBr}}^{\max}$ cm^{-1}: 1720 (C=O), 1240 (C–O), $[\alpha]_{\mathrm{D}}^{25}$ $-10.0°$ (c 1.01, CHCl$_3$), NMR (CDCl$_3$) τ: 5.00 (b.s., $W_{h/2}$=6 cps, 1H), 7.98 (s., 3H).

1-Oxo-5β-cholestane: needles, mp 101—102°C, $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1702 (C=O), ORD (c 0.43, Di) at 25°C: $[\alpha]_{589}$ $-69°$, $[\alpha]_{322}$ $-1681°$ (trough), $[\alpha]_{313}$ $-1290°$ (sh.), $[\alpha]_{280}$ $+1470°$ (peak). This derivative showed a negative Cotton effect curve having a shoulder at near 310 mμ similar to 2-oxo-5β-cholestane[6] in ORD spectrum. This 1-oxo derivative was obtained in 55% over-all yield from 3-oxo-5β-cholest-1-ene.

Further details will be published later.

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[*1] Our report concerning these conversions has hitherto been unpublished.

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