Hydrogenolysis of steroid 3β-acetoxy-5-ene systems[1]

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Palladium catalyzed hydrogenation of 3β-acetoxy (or hydroxy)-5-ene-type steroids was shown to afford small amounts (5–10%) of the corresponding 3-deoxy derivatives. The hydrogenolysis reaction appeared general in scope and offers a one-step method for converting, e.g., cholesteryl acetate to 5α-cholestane.

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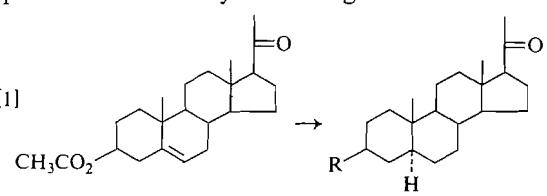
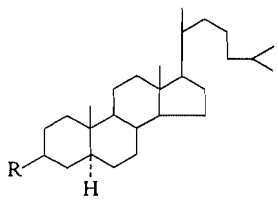
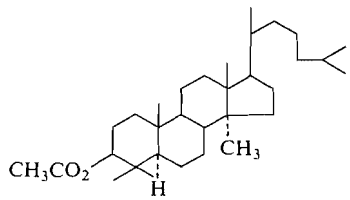
Catalytic hydrogenation of 3β-acetoxy- or 3β-hydroxy-5-ene substituted steroids is one of the most commonly encountered reactions in steroid chemistry. The small amount of side product generally accompanying hydrogenation had been known to us for some time and with adoption of thin-layer chromatography (t.l.c.) in our laboratory (1959), it became apparent that such reactions were generally accompanied by approximately 5% of a relatively nonpolar component readily identified as the 3-deoxy hydrogenolysis product.[2] In a typical hydrogenation, pregnenolone acetate (**1**) was treated with hydrogen under a slight positive pressure for three days in the presence of 10% palladium-on-carbon to yield primarily 3β-acetoxy-20-oxo-5α-pregnane (**2***a*) accompanied by 20-oxa-5α-pregnane (**2***b*) (eq. [1]). Using small amounts of 70% perchloric acid, reduction was complete in 4 h and led to a 10% yield of hydrogenolysis product **2***b*. In each instance, evidence for any significant formation of the 5β-isomers was not detected. Similarly, 5α-cholestane (**3***a*) was obtained from cholesteryl acetate. Repeating the reduction reaction with saturated 3β-acetates **2***a*, **3***b*, or **4** gave only quantitative recovery of starting material.

[1] 

1 **2**
a, R = $OCOCH_3$
b, R = H

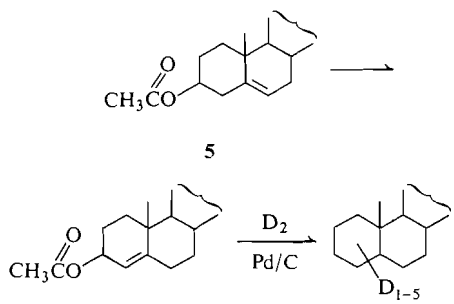


3
a, R = H
b, R = $OCOCH_3$



4

Resistance of the 3β-acetoxy-5α-steroids implicated a partial isomerization of the Δ^5-olefin to the Δ^4-position.[3] In order to explore this possibility (**5** → **6**), reduction of cholesteryl acetate was repeated employing deuterium gas (eq. [2]). As previously observed (4) during

[2] 

5 **6** **7**

[1]Steroids and Related Natural Products. 61. For Part 60, see ref. 1.

[2]We earlier reported (2) reduction of 3β-hydroxy-17-oxo-androst-5-ene to 17-oxo-5α-androstane (ca. 6% yields) by this means.

[3]Hydrogenolysis of allylic acetates readily occurs: see, e.g., ref. 3.

analogous reduction of cholesterol, excessive introduction of deuterium occurred. Extensive scrambling (see **7**) was illustrated by a mass spectrum of the product which exhibited molecular ions of gradually decreasing relative abundance from M^+ to M + 5. Doubtlessly, future efforts concerned with the mechanism of such hydrogenolysis reactions will profit from employing one of the recently introduced homogeneous solution catalysts which are referred to in an important review (5) of selective deuteration in steroid chemistry.

In summary, palladium catalyzed reductive removal of 3β-acetoxy or 3β-hydroxyl groups from Δ^5-steroids appears general in scope and offers a one-step, albeit low yield, procedure for obtaining certain saturated A/B ring steroids.

Experimental

Silica gel (0.05–0.20 mm) used for column chromatography and silica gel G employed for t.l.c. were obtained from E. Merck, Darmstadt. The thin-layer chromatograms were developed with concentrated sulfuric acid. Melting points were determined using a Kofler apparatus.

*Hydrogenation of 3β-Acetoxy-20-oxo-5-pregnane (**1**)*

Method A

An ethyl acetate (50 ml) solution of pregnenolone acetate (1.0 g) was shaken under a slightly positive pressure of hydrogen (72 h) with 10% palladium-on-carbon (0.20 g). Following filtration and concentration, the residue in 3:1 hexane–benzene was chromatographed on silica gel (30 g). Elution with 1:1 hexane–benzene gave 54 mg of 20-oxo-5α-pregnane (**2***b*). Recrystallization from methanol gave 40 mg of platelets (**2***b*) melting at 133–134° (lit., ref. 6, m.p. 133–135°); ν 1700 (20-ketone) cm^{-1}; proton magnetic resonance δ 0.6 (18-methyl), 0.77 (19-methyl), and 2.06 ($COCH_3$). Continued elution with benzene and benzene-chloroform mixtures gave 0.91 g of 3β-acetoxy-20-oxo-5α-pregnane (**2***a*).[4]

A solution of 3β-acetate **2***b* (0.63 g) in ethyl acetate (40 ml) was subjected to hydrogenation in the presence of 10% palladium-on-carbon (0.12 g) during 120 h as described above. A t.l.c. examination of the product indicated presence of only starting material (**2***b*).

Method B

The hydrogenation experiment described above in method *A* was repeated using ethyl acetate (100 ml), pregnenolone acetate (2.0 g), 10% palladium-on-carbon (0.4 g) and 2 ml of 70% perchloric acid. After 4 h the solution was passed through a bed of filter aid and washed with saturated aqueous sodium bicarbonate and water. Removal of solvent gave a residue which was chromatographed on silica gel (60 g) as noted above. By this means, 0.20 g of 20-oxo-5α-pregnane (10% yield, pure by t.l.c.) was isolated. Two recrystallizations from methanol gave a specimen melting at 137–138.5°.

Hydrogenation of 3β-acetoxy-5-Cholestene

The hydrogenation reaction described in method *A*, above, was repeated employing ethyl acetate (100 ml), cholesteryl acetate (2.0 g), and 10% palladium-on-carbon (0.4 g). Reaction was followed by t.l.c. and seemed complete after 6 h. A solution of the product in hexane was chromatographed on silica gel (50 g) and elution with the same solvent gave 0.11 g of 5α-cholestane (**11***a*).The hydrocarbon was shown to be pure by t.l.c. and recrystallization from isopropyl ether – methanol gave plates melting at 77–80°.[4] Elution with benzene gave 1.6 g of 3β-acetoxy-5α-cholestane[4] which recrystallized from chloroform–methanol as needles melting at 108°.

Reduction of cholesteryl acetate (4.0 g) in ethyl acetate (200 ml) was repeated in the presence of 10% palladium-on-carbon (0.8 g) as summarized in the preceding paragraph except that deuterium was substituted for hydrogen and catalyst was removed by filtering the solution through a layer of activated alumina. Following chromatography on silica gel (75 g) a hexane fraction provided 0.27 g of extensively deuterated 5α-cholestane. Three recrystallizations from isopropyl ether – methanol gave plates melting at 78–80°. The benzene fractions provided 3.7 g of deuterated 3β-acetoxy-5α-cholestane.

Repeating the hydrogenation experiment over a 20 h period with 3β-acetoxy-5α-cholestane or with 3β-acetoxy-5α-lanostane (**4**) over 48 h gave, in each case, only starting material. Examination of both products by t.l.c. revealed no trace of 3-deoxy derivatives.

[4]Identification was confirmed by mixture melting point determination and infrared spectral comparison with an authentic sample.

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