87. The Hydroxylation of Cholest-5-en-3-one with Osmium Tetroxide

By Fumikazu Mukawa*1
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Setagaya, Tokyo
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The hydroxylation of unsaturated steroids with osmium tetroxide has been the subject of extensive study, but there is no report that this reaction was conducted on cholest-5-en-3-one. In a previous paper, it was reported that \(3_1^2\) or \(3\alpha^2\)-substituted \(\delta^2\)-steroids give the corresponding \(5\alpha\)-chloro-6\(\beta\)-hydroxy-compounds on treatment with hypochlorous acid (isocyanuric chlorid-acetic acid). Reaction of cholest-5-en-3-one or its ethyleneketal, however, has been found to be exceptional and 6\(\beta\)-chloro-3-oxo-5\(\alpha\)-cholestan-5-ol has been thus obtained. Similar observations were reported by S. Bernstein et al.3 who found that 3-ethyleneketal group plays an important role in stereochemistry of osmylation of \(\delta^2\)-double bond, because, in oxidation with osmium tetroxide, \(3\beta\) or \(3\alpha\)-hydroxysteroids gave mainly \(5\alpha,6\alpha\)-diol, while 3-ethyleneketal-\(\delta^2\)-steroids gave mainly \(5(\xi),6\beta\)-diol.

Now, the present author found that the oxidation of cholest-5-en-3-one (I) with osmium tetroxide gave mainly 5,6\(\delta\)-dihydroxy-5\(\alpha\)-cholestan-3-one and 5,6\(\alpha\)-diol compound could not be isolated.

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\begin{align*}
\text{(I)} & \quad \rightarrow \\
\text{(II)} & \quad \text{C}_{2}H_{17} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{OH} \\
\end{align*}
\]

The structure of II was proved by the following reactions: Treatment of II with acetic acid afforded, in 60% yield, the known 6\(\beta\)-acetoxy-cholesterol-4-en-3-one. Oxidation of II with chromium trioxide in pyridine gave the known 5-hydroxy-5\(\alpha\)-cholestan-3,6-dione; and reduction of II with sodium borohydride gave the known 5\(\alpha\)-cholestan-3,5\(\alpha\),5,6,9-triol. Hydrolysis of II in methanol with sulfuric acid (8%) resulted in the known 5\(\alpha\)-cholestan-3,6-dione.

*1 Present address: Tsurumi Research Laboratory of Chemistry, Tsurumi-ku, Yokohama.
Comparison of the optical rotatory dispersion curve (see the figure) of II with that of 17α-methyl-5,17β-dihydroxy-5α-androstan-3-one\(^9\) (III) showed such striking similarities of the two that the configuration of 5-hydroxy in both compounds is thought to be identical.

Its infrared absorption for free hydroxyl group is shown at 3600 cm\(^{-1}\) and the absorption for bonded hydroxyl groups\(^5\) was not observed. Also, it shows maximum at 1710 cm\(^{-1}\), clearly indicative of a normal carbonyl.

Satisfactory explanation, however, has not been found for these interesting facts that the 3-oxo and 3-ethyleneketal groups have an important influence on the stereochemistry of osmylation or the addition of hypohalorous acid of a \(\Delta^5\) double bond.

Experimental.\(^6\) 5,6β-Dihydroxy-5α-cholestan-3-one (II; \(\cdots\cdots\)) in methanol (\(c=0.0545\)) and 17a-Methyl-5,17β-dihydroxy-5α-androstan-3-one (III; \(\cdots\cdots\)) in dioxane (\(c=0.1,320\) – 700 \(\mu\); \(c=0.05,300\) – 315 \(\mu\))

A solution of cholest-5-en-3-one (0.3 g) in ether (60 ml) and pyridine (0.3 ml) was treated with osmium tetroxide (0.3 g) and the mixture was allowed to stand at room temperature (17°C) for five days. The osmate ester was then decomposed by stirring for 4 hours in addition of sodium sulfite (1 g), potassium bicarbonate (1 g), water (12 ml), and methanol (10 ml). The precipitate was separated by filtration, and washed with ether. The ether layer was washed with saturated saline water, dried, and evaporated. The residue was recrystallized from methanol to furnish 0.15 g of the diol, m.p. 215–218°, \([\alpha]_D^{20}=+37.8\) (c 1.05, CHCl\(_3\)), \(\nu_{\text{max}}^{\text{KBr}} 3450\) cm\(^{-1}\) (OH), and 1710 cm\(^{-1}\) (C=O), \(\nu_{\text{max}}^\text{CHCl}_3\) 3600 cm\(^{-1}\) (OH). Anal. Calcd for C\(_{27}\)H\(_{46}\)O\(_3\): C, 77.46; H, 11.08; O, 11.47. Found: C, 77.30; H, 11.08; O, 10.50.

i) Treatment of II with acetic acid. A solution of II (0.1 g) in acetic acid was heated on a steam-bath for 3 hours. Cold water was added, and the mixture was neutralized with a saturated sodium bicarbonate solution, and extracted with ether. This afforded 0.06 g of crude 6β-acetoxy-cholest-4-en-3-one, m.p. 95–97°. Recrystallization from aqueous acetone raised the m.p. to 102–103°, \(\delta_{\text{max}}^{\text{D}} 237\) m\(\mu\) (E 4.13). The compound did not depress the m.p. on admixture with the authentic sample.
ii) Oxidation of II with chromium trioxide. A pyridine (20 ml) solution of II (0.1 g) was mixed with a solution of chromium trioxide (50 mg) in pyridine (5 ml). The mixture was kept at room temperature for 24 hours, poured into water, and extracted with ether. The etheral layer was washed with dilute hydrochloric acid solution and water, and then evaporated. The residue was recrystallized from methanol-chloroform, yielded 5-hydroxy-5α-cholestan-3,6-dione, m.p. 229–230°. Yield 0.06 g. Mixed melting point with authentic sample did not depress.

iii) Reduction of II with sodium borohydride. A solution of II (0.1 g) in methanol (20 ml) was treated with sodium borohydride (50 mg), and kept at room temperature for 3 hours. The product, isolated by dilution with water and extracted with benzene, was refluxed with acetic acid anhydride for 45 minutes. 3β,6β-Diacetoxy-5α-cholestan-5-one, m.p. 165°, 0.05 g, was obtained. It was identified by mixed melting point with authentic sample.

iv) Treatment of II with acid. A mixture of II (0.1 g), a few drops of sulfuric acid (8%) and 10 ml of methanol was heated under reflux for two hours. After cooling the concentrate was diluted with water until faint turbidity appeared and allowed to stand. The crystals were, then crystallized from aqueous acetone, melted at 170°. Yield 0.05 g. The compound did not depress the melting point with authentic sample of 5α-cholestan-3,6-dione.

Ultraviolet and infrared absorption spectra. The spectral measurements were made by use of Hitachi Photoelectric Spectrophotometer Model EPU-2 and Perkin-Elmer Model 21 doublebeam instrument.

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References
4) Pure sample of these substances was kindly donated by Mr. M. Sawai (Tsurumi Research Laboratory of Chemistry), to whom the author's thanks are due.
6) All melting points are uncorrected.