Reductions of Oxo-steroids with Activated Zinc Powder

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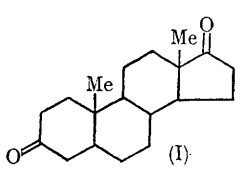
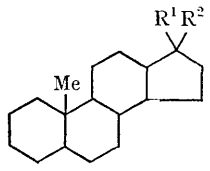
WE have reported[1] a useful method for the reduction of oxo-groups to methylene groups under mild conditions.

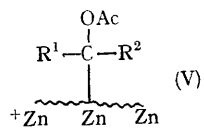
Cholestan-3-one was stirred in acetic anhydride (saturated with hydrogen chloride gas at 0°) for 2 hr. (or 6 hr.) with zinc powder (which had been kept in a sealed flask for more than 10 hr. at room temperature after activation with 2% hydrochloric acid) to give cholestane, in 18% (or 87%) yield.[1],† However, when active zinc powder was used immediately after its preparation, an otherwise identical reduction gave cholestane in 90% yield in only 2 hr. Generally, less hindered oxo-groups of other oxo-steroids were also readily reduced when active zinc powder was used immediately after its preparation. With hindered oxo-groups, however, the grade of activity of the zinc powder leads to different results: when the zinc powder was used immediately after activation, androstan-3,17-dione (I) gave androstane (II) (66%) and 17β-acetoxyandrostane (III) (26%), at 0° for 6 hr.§ The expected products, an enol acetate (VI), an olefin (VII), an acetate (or halide)



(I)

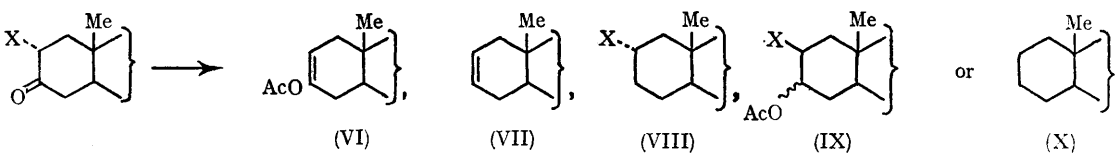


(II) $R^1=R^2=H$
(III) $R^1=OAc$, $R^2=H$
(IV) $R^1,R^2=O$



(V)

(VIII), a diacetate (IX), or a completely reduced compound (X), are shown.



(VI) (VII) (VIII) (IX) (X)

otherwise, androstan-17-one (IV) (67%) was isolated in addition to androstane (15%).[1] Thus, activated zinc powder should be used immediately after its preparation for the reduction of a sterically hindered oxo-group, although less active zinc powder will cause selective reduction of a less hindered oxo-group. Furthermore, with androstan-3,17-dione, 17β-acetoxyandrostane (III) is probably formed *via* an acetoxy organozinc compound (V), which, on further electron-transfer, would lead to the formation of androstane (II).

In view of the high reactivity of this reduction system (Zn–HCl–Ac_2O),‡ zinc reductions of α-halogeno- and α-acetoxy-oxo-steroids were carried out

Generally, zinc reductions of α-halogeno- and α-acetoxy-ketones in aqueous mineral acid or acetic acid (or acetic anhydride) give the corresponding ketones (or enol acetates).[2] However, when treated with activated zinc powder in acetic anhydride saturated with hydrogen chloride gas at 0° for 6 hr.,¶ 2α-bromocholestan-3-one afforded cholestane (X) (86%) as a main product and a small amount of an enol acetate (VI) 8%.

A mixture of 2α- and 4α-acetoxycholestan-3-one (1 : 1) was similarly reduced to give cholestane (X) (90%) and a mixture of acetates (2% >).[3] Zinc reduction of 3β,5α-diacetoxy-7α-bromocholestan-6-one and 3β,17α-diacetoxypregn-5-en-20-one gave

† Commercial zinc powder (Kishida Chemical Co. Ltd.) was activated by washing well with 2% hydrochloric acid for 3–4 min., then successively with water, ethanol, acetone, and dry ether. Active zinc powder thus obtained was then warmed under reduced pressure at 90° for 10 min.

‡ These results will be reported soon in detail.

§ Zinc powder was used immediately after activation with 2% hydrochloric acid.

¶ Cholestane was also obtained in high yield (86%), when the reaction mixture was stirred at 0° for only 8 hr.

3β-acetoxycholestane (73%) and 3β-acetoxypregn-5-ene (62%), respectively.

In these reactions, the first step is probably the same as that of the usual zinc reduction in acetic acid or aqueous mineral acid leading to the formation of an enolate anion. Then oxidation of the enolate anion followed by protonation takes place much faster than an attack of the acyl cation [leading to the enol acetate (VI)] on the oxygen atom of the enolate anion.** Finally, the oxo-group thus formed is reduced to the methylene group, in a Clemmensen-type reduction.

The author thanks Professor T. Goto, Nagoya University, for provision of some α-acetoxy-oxo-steroids.

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** The enol acetate (VI) has been proved to be stable for the reduction system (Zn–Ac_2O–HCl) in our laboratory.

[1] S. Yamamura, S. Ueda, and U. Hirata, *Chem. Comm.*, 1967, 1049.
[2] H. O. House, "Modern Synthetic Reactions," Benjamin, New York, 1965, p. 56.
[3] L. F. Fieser and M. A. Romero, *J. Amer. Chem. Soc.*, 1953, **75**, 4716; K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, 1961, **26**, 4563.