



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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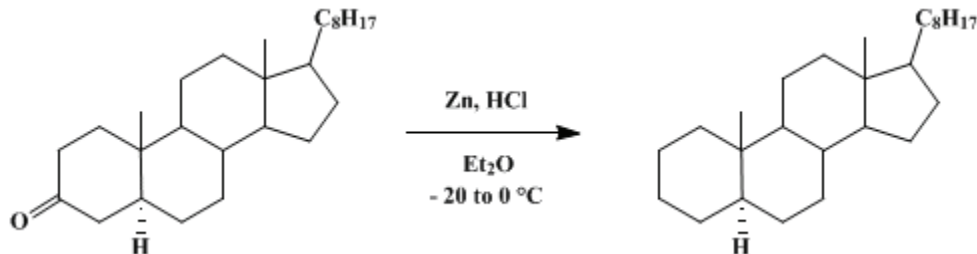
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.289 (1988); Vol. 53, p.86 (1973).

MODIFIED CLEMMENSEN REDUCTION: CHOLESTANE



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Checked by A. Laurenzano, L. A. Dolan, and A. Brossi.

1. Procedure

A 500-ml., four-necked, round-bottomed flask (Note 1) equipped with a sealed mechanical stirrer (Note 2), a gas-inlet tube, a low-temperature thermometer, and a calcium chloride tube is charged with 250 ml. of dry diethyl ether. With an acetone-dry ice bath the temperature of the ether is lowered to -10 to -15° and maintained within this range while a slow stream (Note 3) of hydrogen chloride is introduced, with slow stirring, for about 45 minutes. The gas-inlet tube is replaced with a glass stopper, and 10.0 g. (0.0259 mole) of cholestan-3-one (Note 4) is added while the temperature of the stirred solution (Note 5) is kept below -15° . The reaction mixture is cooled to -20° , and 12.3 g. (0.188 g.-atom) of activated zinc (Note 6) is added over a 2–3 minute period. The temperature of the reaction mixture is allowed to rise to -5° (Note 7), and it is maintained between -4° and 0° (Note 8) for 2 hours. Stirring is not interrupted for the duration of the reaction. The mixture is finally cooled to -15° and poured slowly onto about 130 g. of crushed ice. The ethereal layer is separated, and the aqueous layer is extracted with 100 ml. of ether that had been used to rinse the reaction vessel. The ethereal solutions are combined, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The ether is distilled under reduced pressure with a 50° water bath, leaving 9.3–9.5 g. of a colorless, liquid residue that solidifies on cooling. This solid is dissolved in 30–40 ml. of *n*-hexane (Note 9). The solution is poured onto a 3.5 cm. by 17 cm. column of silica gel (Note 10) and eluted with 80–90 ml. of *n*-hexane. Distillation of the solvent under reduced pressure with a 50° water bath leaves 8.0–8.2 g. (82–84%) of cholestane (Note 11), which, after recrystallization from ethanol-ether (Note 12), yields 7.3–7.5 g. (76–77%) of product as plates m.p. 78 – 79° (lit., m.p. 80°)³ (Note 13).

2. Notes

1. A standard, three-necked flask fitted with a Y-tube may be used.
2. An efficient magnetic stirrer may be substituted.
3. Approximately one bubble per second can be spot-checked periodically by connecting the calcium chloride tube to an oil-filled bubble counter.
4. Cholestan-3-one was prepared according to *Org. Synth., Coll. Vol. 2, 139 (1943)*; single spot on TLC with the system described in (Note 11).
5. The cholestanone does not dissolve completely at this low temperature, but the reaction is not affected.
6. The submitters prepared activated zinc by the following procedure. Commercial zinc powder (16 g.), special grade, *ca.* 300 mesh, obtained from either Kishida Chemical Company Ltd. or Hayashi Pure Chemical Company Ltd., is added with stirring to a 300-ml., round-bottomed flask containing 100 ml. of 2% hydrochloric acid. Vigorous stirring is continued until the surface of the zinc becomes bright (*ca.* 4 minutes). The aqueous solution is decanted, and the zinc powder in the flask is washed by decantation with four 200-ml. portions of distilled water. The activated zinc powder is transferred to a suction filter with 200 ml. of distilled water and washed successively with 50 ml. of ethanol, 100 ml. of acetone, and 50 ml. of dry ether. Filtration and washing should be done as rapidly as possible to minimize exposure of the activated zinc to air. The zinc is finally dried at 85 – 90° for 10 minutes in a vacuum oven (*ca.* 15

mm.), cooled, and used immediately; the yield is 13–14 g.

The checkers used this procedure with certified **zinc** powder, 325 mesh, obtained from Fisher Scientific Company.

7. This requires *ca.* 20 minutes.

8. The temperature is regulated by adding pieces of dry ice to the cooling bath as required. As the reduction proceeds, the solution separates into two phases.

9. The solution is decanted from any insoluble matter.

10. Silicic acid, 100 mesh (Mallinckrodt), was used.

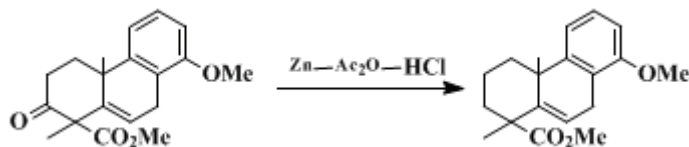
11. This material melts at 78–79°. On TLC [silica, development with *n*-hexane, visualization with **sulfuric acid-methanol** (1:1) and heating] the product had $R_f = 0.74$. An impurity, $R_f = 0.65$, was present.

12. The **cholestane** is dissolved in 50 ml. of **ether**. **Ether** is distilled until the volume is 25 ml., 200 ml. of **ethanol** is added, and the mixture is refrigerated.

13. Recovery is 92%. Recrystallization has no effect on the quality of the product as judged by m.p. and TLC (Note 11).

3. Discussion

The well-known Clemmensen reduction⁴ is a general method by which aralkyl ketones are readily converted to the corresponding hydrocarbons with amalgamated **zinc** and **hydrochloric acid**. It is not particularly effective, however, with alicyclic and aliphatic ketones. The procedure described herein provides a simple method of reducing a variety of ketones to their desoxy derivatives in high yields under much milder conditions (0°, 1–2 hours) than those normally used in the Clemmensen reaction.⁴ This permits selective deoxygenation of ketones in polyfunctional molecules⁵ containing groups such as cyano, amido, **acetoxy**, and carboalkoxy, which are stable under the mild reaction conditions. For example, the following reduction⁶ has been carried out successfully by the modification of our procedure, using **acetic anhydride** as the solvent.⁵



Wide latitude is permitted in choosing the solvent for the reaction. Several organic solvents (**tetrahydrofuran**, **benzene**, *n*-hexane)⁷ and particularly **acetic anhydride**^{5,8} may be used instead of dry ether. α -Halo- and α -acetoxycholestanone⁵ are converted to **cholestane** with Zn-HCl-Et₂O and also with Zn-HCl-Ac₂O.^{7,8} These reduction systems, however, have given different results with α,β -unsaturated ketones.⁹ With Zn-HCl-Et₂O, **cholest-1-en-3-one** gave **cholestane** in 88% yield, while **cholest-4-en-3-one** gave an 88% yield of a mixture of 1.2 parts of **cholestane** and 1 part of **coprostan**. By contrast, reaction of Zn-HCl-Ac₂O with **cholest-1-en-3-one** afforded a mixture of three compounds: **cholestane** (30–32%), **3-acetoxycholest-2-ene** (10–24%), and **cholestan-3-one** (30–40%). **Cholestan-3-one** appears to be formed from the corresponding **cyclopropanol acetate**¹⁰ during the work up. The mechanism of this reduction is probably similar to that of the Clemmensen reaction.¹¹

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

ethanol (64-17-5)

hydrogen chloride,
hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium chloride (7647-14-5)

acetone (67-64-1)

zinc (7440-66-6)

magnesium sulfate (7487-88-9)

Cholestanone,
cholestan-3-one (566-88-1)

Tetrahydrofuran (109-99-9)

n-hexane (110-54-3)

cholest-1-en-3-one

Cholest-4-en-3-one (601-57-0)

acetoxo

Cholestane,
coprostane (481-21-0)

sulfuric acid-methanol

3-acetoxycholest-2-ene

cyclopropanol acetate

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