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Modified Clemmensen Reductions of Keto Groups to Methylene Groups

Masaaki Toda, Mikio Hayashi, Yoshimasa Hirata, and Shosuke Yamamura*
Chemical Institute, Nagoya University, Chikusa-ku, Nagoya
**Faculty of Pharmacy, Meijo University, Showa-ku, Nagoya*

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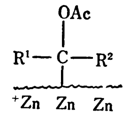
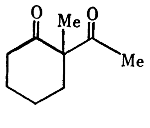
A modified Clemmensen reduction is described for the conversion of keto-groups into methylene groups by using active zinc powder in common organic solvents and acetic anhydride saturated with hydrogen chloride; the scope and limitations of these new reduction systems are also discussed.[1]

In a previous paper,[2] we reported a useful method for the conversion of isolated keto-groups into methylene groups using active zinc powder in acetic anhydride saturated with hydrogen chloride under very mild conditions (0°C, 2—6 hr). Furthermore, it has been suggested that the easy reductions of keto-groups to methylene groups are attributable to the formation of an acyl cation from acetic anhydride and hydrogen chloride, and that the acetoxyorganozinc compound is a likely intermediate (I). In fact, the treatment of the β-diketone (II) with Zn–Ac_2O–HCl has been known to afford the corresponding diacetoxycyclopropane (III) in a high yield.[3] However, attempts to reduce cholestan-3-one to cholestane with active zinc powder in Ac_2O-p-TsOH (or BF_3 etherate) under various conditions proved unsuccessful.


(I)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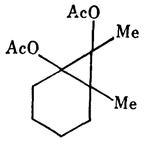
(III)

In the above experiments we were able to do such zinc reductions by using common organic solvents saturated with hydrogen chloride instead of acetic anhydride. When treated with active zinc powder in diethyl ether saturated with hydrogen chloride (0°C, 1 hr), cholestan-3-one afforded the corresponding reduction product, cholestane, in a high yield. Other solvents were also used; the results, summarized in Table 1, indicate that diethyl ether is much better for the modified Clemmensen reduction than the other solvents. These zinc reductions, which must be carried out under anhydrous conditions, take place more easily than the usual Clemmensen reduction. The mechanism of the former seems, however, to be essentially the same as that of the Clemmensen reduction.[4]

Table 1. Zinc reductions in common organic solvents saturated with hydrogen chloride

Ketone	Solvent	Product	Yield (%)
Cholestan-3-one	Ac_2O	Cholestane	87[a)]
	Et_2O	Cholestane	89[b)]
	Tetrahydrofuran	Cholestane	44[b)]
	Benzene	Cholestane 3-Chlorocholestane	64[b)] 21
	n-Hexane	Cholestane 3-Chlorocholestane	57[b)] 8
Androstan-3,17-dione	Ac_2O	Androstane 17β-Acetoxyandrostane	66[c)] 26
	Et_2O	Androstane	75[b)]

a) At 0°C for 2 hr. b) At 0°C for 1 hr. c) At 0°C for 6 hr.

In view of the high reactivity of these reduction systems (Zn–HCl–Ac_2O (or Et_2O)), zinc reductions of α-substituted, α,β-unsaturated, and aryl ketones were carried out (Table 2).

Table 2. Zinc reductions of α-substituted, α,β-unsaturated, and aryl ketones

Ketone	Product	Yield (%)
2α-Bromocholestan-3-one	Cholestane 3-Acetoxycholest-2-ene	86[a)], 85[b)] 8[a)]
α-Acetoxycholestan-3-one[c)]	Cholestane Enol acetates	90[a)], 79[b)] 2[a),d)]
3β,5α-Diacetoxy-7α-bromocholestan-6-one	3β-Acetoxycholestane	73[e)]
3β,17α-Diacetoxy-pregn-5-en-20-one	3β-Acetoxypregn-5-ene	62[e)]
Cholest-1-en-3-one	Cholestane 3-Acetoxycholest-2-ene Cholestan-3-one	30—32[a)], 88[b)] 24—10[a)] 30—40[a)]
Cholest-4-en-3-one	Cholestane Coprostane	48[b)] 40[b)]
Methyl β-benzoyl propionate	Methyl γ-phenyl butyrate	45[a)], 41[b)]
Indanone	Indane	22[a)], 42[b)]

a) In acetic anhydride saturated with HCl (0°C, 2 hr).
b) In diethyl ether saturated with HCl (0°C, 1 hr).
c) A mixture of 2α- and 4α-acetoxycholestan-3-ones (1:1).
d) A mixture of 3-acetoxycholest-2 and 3-enes.
e) In acetic anhydride saturated with HCl (0°C, 6 hr).

In particular, the reductions of α-halo- and α-acetoxy-oxo-steroids with active zinc powder in diethyl ether saturated with hydrogen chloride are expected to afford the following reduction products: an olefin (IV), an acetate (or halide) (V), and a completely reduced compound (VI). In the case of the (Zn–Ac_2O–HCl) reduction system, two more reduction products (VII and

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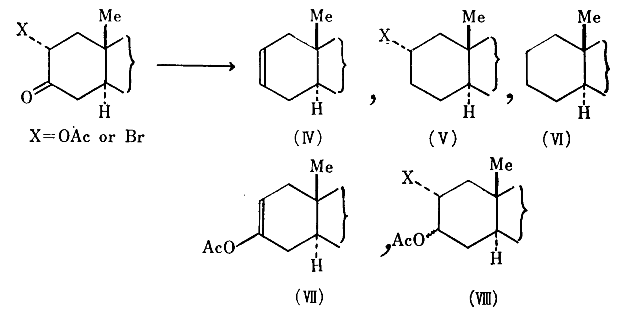
[1] Preliminary communications: S. Yamamura, *Chem. Commun.*, **1968**, 1494; M. Toda, Y. Hirata, and S. Yamamura, *ibid.*, **1969**, 919.

[2] S. Yamamura and Y. Hirata, *J. Chem. Soc., C*, **1968**, 2887.

[3] T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and J. H. Williams, *J. Amer. Chem. Soc.*, **91**. 2817 (1969).

[4] H. O. House, "Modern Synthetic Reactions," Benjamin, New York (1965), p. 58; J.G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev.* (London), **23**, 522 (1969).



X=OAc or Br (IV) (V) (VI)

(VII) (VIII)

VIII) are expected in addition to the three above compounds (IV, V, and VI). In our experiments, modified Clemmensen reductions of α-acetoxy and α-halo-cholestan-3-one afforded a mixture of cholestane (86—90%) and 3-acetoxycholest-2-ene (2—8%) with Zn–Ac_2O–HCl, and only cholestane (79—85%) with Zn–Et_2O–HCl. In these reactions, the first step is probably the same as in usual zinc reductions in acetic acid or aqueous mineral acid leading to the formation of an enolate anion. Therefore, the ketonization of the enolate anion and the subsequent protonation take place much faster than an attack of the acyl cation on the oxygen atom of the enolate anion.[5] The resulting cholestan-3-one is converted into cholestane as usual. In the cases of α,β-unsaturated ketones, results considerably different from those obtained with the α-substituted ketones were obtained. When treated with active zinc powder in acetic anhydride saturated with hydrogen chloride, cholest-1-en-3-one gave a mixture of three reduction products (cholestane (32—30%), 3-acetoxycholest-2-ene (24—10%) and cholestan-3-one (30—40%)). The completely reduced product, cholestane, is probably formed through the cyclopropoxide or enolate anion. Furthermore, both cholestan-3-one and 3-acetoxycholest-2-ene (VII) may be derived from an intermediate of the corresponding acetoxycyclopropane structure (IX), an intermediate which seems to be converted into cholestan-3-one in the course of isolation. Recently, Elphimoff-Felkin and Sarda[6] have reported that the α,β-unsaturated ketones with a phenyl group afford the corresponding acetoxycyclopropanes when treated with Zn–Ac_2O–HCl. Accordingly, it can be expected that the completely reduced product can be obtained in a high yield by using active zinc powder in diethyl ether saturated with hydrogen chloride. In fact, the reduction of cholest-1-en-3-one to cholestane was successfully achieved by the use of the above-mentioned reduction system under mild conditions. Cholest-4-en-3-one was also converted into a mixture of cholestane and coprostane in a high yield. Zinc reductions of aryl ketones were also carried out under the same conditions.[7] However, these reductions are not always better in yields than usual Clemmensen reductions of aryl ketones except under mild conditions (0°C, 1 hr), since undesirable dimerization reactions seem to take place between two anion radical intermediates, which are much more stabilized by the aryl group than is the anion radical from such an isolated ketone as cholestan-3-one.

Experimental

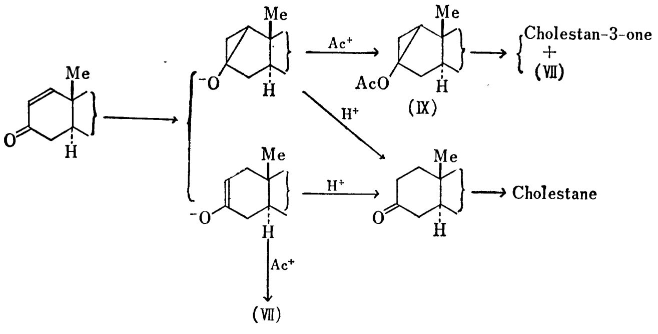
The melting points were determined on a micro hot-stage. The infrared spectra were recorded in KBr or film with a JASCO IR-S spectrophotometer.

Preparation of Active Zinc Powder. Commercial zinc powder (Kishida Chemical Co., *ca.* 300 mesh) was activated by washing it well with 2% hydrochloric acid according to a previously-described procedure (see Ref. 2). The zinc powder thus obtained was used immediately.

General Procedure for the Zinc Reduction. Cholestan-3-one was dissolved in diethyl ether saturated with hydrogen chloride at 0°C, and then active zinc powder was slowly stirred into the resulting solution. After being stirred at 0°C for 1 hr, the reaction mixture was poured into large amounts of ice water. Then, the aqueous solution was made basic with sodium carbonate and extracted thoroughly with diethyl ether. The extracts were dried over anhydrous Na_2SO_4; the solvent was then removed under reduced pressure to give a pale yellow oil, which was chromatographed on silica gel (Mallinckrodt, 100 mesh) (25 g) and eluted with benzene to afford colorless crystals of cholestane (mp 77.5—79°C). The yields of cholestane varied with the quantity of zinc powder, as the chart shows below.

Cholestan-3-one (mg)	Zn (g)	Et_2O (m*l*)	Yield (%)
500	5.0	75	89
500	1.25	12.5	84
500	0.50	10	85
500	0.25	10	56

According to the above-mentioned procedure or the previously-reported procedure,[2] zinc reductions of α-substituted, α,β-unsaturated and aryl ketones were carried out (see Tables 1 and 2); the reduction products were carefully separated by



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[5] The enol acetate (VII) is stable for the (Zn-Ac_2O-HCl) reduction system.

[6] M. I. Elphimoff-Felkin and P. Sarda, *Tetrahedron Lett.*, **1969**, 3045.

[7] The reaction mixture spontaneously turned brown when active zinc powder was added to the solution.

silica-gel chromatography (Mallinckrodt, 100 mesh), using benzene as the eluant, except for a mixture of cholestane and coprostane.[8] When experiments were carried out in a large scale, the reduction procedure was further modified as follows.

In a 500-m*l*, three-necked, round-bottomed flask fitted with a sealed mechanical stirrer, a gas inlet tube, and a Y-tube fitted with a low-temperature thermometer and a calcium chloride tube, we placed 250 m*l* of dry diethyl ether which had been cooled in a dry ice-acetone bath to −10—−15°C; then dry hydrogen chloride gas was bubbled in with slow stirring. After about 45 min, 10 g of cholestan-3-one were dissolved, with stirring, in the above solution below −15°C. To the ethereal solution we then added 12.3 g of activated zinc powder at about −20°C over a period of 2—3 min, and then the temperature of the reaction solution was elevated to −5°C. Stirring was continued for 2 hr, keeping the reaction temperature between 0—−4°C. Finally, the reaction mixture was cooled to −15°C, slowly poured into large amounts of ice, and then worked-up as usual to give 8.2—8.9 g of cholestane. mp 78—79°C.

All the reduction products were found to be identical with the known compounds by a study of their mps, IR, and mass spectra.

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[8] The relative ratio of the two reduction products was determined by studying their peak areas on a gas-liquid chromatogram (SE-30 (5%); 250°C, N_2; flame-ionized detector).