Zinc Reductions of Keto-Groups to Methylene Groups

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A new method is described for the reduction of keto-groups to methylene groups, and the scope and the optimum conditions for the conversion of keto-steroids into deoxy-derivatives, by use of active zinc powder in acetic anhydride saturated with hydrogen chloride, are also discussed.

DURING our studies of the transformation of isodaphniphylline into the other minor alkaloids isolated from the same plant, we discovered a useful method for the conversion of keto-groups into methylene groups in a Clemmensen-type reduction.[1] In the present work,[2] we have examined these reduction methods to establish the scope and the optimum conditions for the conversion of keto-groups into methylene groups by active zinc powder in acetic anhydride saturated with hydrogen chloride. Under the same conditions as were used in the case of isodaphniphylline,[1] cholestan-3-one, a typical keto-steroid, in acetic anhydride saturated with hydrogen chloride, was treated with a large amount of active zinc powder, at room temperature, to afford cholestane in 85% yield. However, in addition to zinc reduction of a keto-group at the 3-position to a methylene group, self-condensation reactions of acetic anhydride take place at room temperature. To prevent such undesirable reactions, the zinc reduction of cholestan-3-one was carried out, at 0° for 6 hours (or 2 hours), giving cholestane in 87% (or 18%) yield. Reductions were also effected with a mixture of zinc, acetic anhydride, and hydrogen bromide (instead of hydrogen chloride), to examine the effects of halide anions on the reduction. Thus, cholestan-3-one, in acetic anhydride saturated with hydrogen bromide, was treated with an excess of active zinc powder, to give cholestane in 66% (or 67%) yield. With this reduction system, however, the reactions become so vigorous that the temperature could not be controlled, which is very important for selective reductions of keto-groups, and undesirable side-reactions leading to low yields of reduction products also take place easily. Accordingly, zinc reductions of keto-steroids were carried out in the zinc–acetic anhydride–hydrochloride system. The results are summarized in the Table.

As reported previously,[1,2] this system seems to be very convenient for selective reductions of less-hindered keto-groups to methylene groups. For example, a mixture of androstan-17-one (II) (67% yield) and androstane (III) (15%) was obtained when androstane-3,17-dione (I) was treated with Zn–Ac_2O–HCl at 0°

[1] S. Yamamura, H. Irikawa, and Y. Hirata, *Tetrahedron Letters*, 1967, **35**, 3361.

[2] S. Yamamura, S. Ueda, and Y. Hirata, *Chem. Comm.*, 1967, 1049.

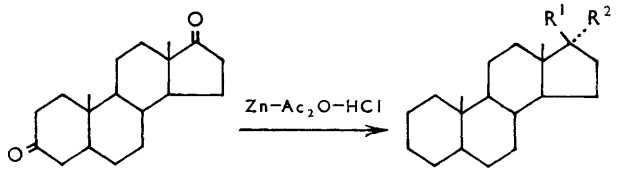
for 6 hr. In the above reaction, a carbonyl group at C-3 can be reduced easily, but that at C-17 is less reactive. Furthermore, an acetoxy-group can remain

Zinc reductions of keto-steroids

Ketone	Product	Yield (%)
Cholestan-3-one	Cholestane	85 [a]
		87 [b]
		18 [c]
		66 [d]
		67 [e]
3β-Acetoxycholestan-6-one	3β-Acetoxycholestane	54 [a]
		35 [b] *
17β-Acetoxyandrostan-3-one	17β-Acetoxyandrostane	79 [a]
3β-Acetoxy-5α-pregnan-20-one	3β-Acetoxy-5α-pregnane	70 [a]
Androstane-3,17-dione	Androstane	50 [a]
	Androstan-17-one	67 [b]
	17β-Acetoxyandrostane	6
	Androstane	15
	17β-Acetoxyandrostane	26 [f]
	Androstane	66

* Starting material recovered (60%).
[a] At room temperature for 10 hr. [b] At 0° for 6 hr. [c] At 0° for 2 hr.; starting material (68%) was recovered. [d] At 0° for 2 hr.; HBr used instead of HCl. [e] At 0° for 6 hr.; HBr used instead of HCl. [f] At 0° for 6 hr.; fresh active zinc powder used (see Experimental section).

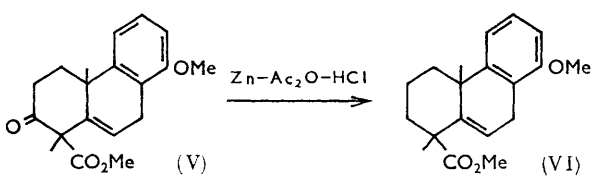
unaffected, as shown in the cases of acetoxy-keto-steroids (3β-acetoxycholestan-6-one, 17β-acetoxyandrostan-3-one, and 3β-acetoxy-5α-pregnan-20-one). We



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

can also expect selective conversions of keto-groups into methylene groups in compounds containing polyfunctional groups.

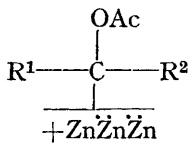
Studies are in progress to apply our reduction method to some compounds containing polyfunctional groups. Recently, Dr. H. Kakisawa and his co-workers at Tokyokyoiku University kindly informed us that the zinc reduction of (V), which contains a double bond as well as an ester group, afforded (VI) in high yield according to our procedure.



(V) (VI)

Less-hindered keto-groups are usually easily reduced to methylene groups, but with hindered keto-groups, the degree of activity of the zinc powder leads to different results. When the powder was used immediately after activation with 2% hydrochloric acid, androstane-3,17-dione (I) afforded a mixture of androstane (III) (66% yield) and 17β-acetoxyandrostane (IV) (26%). If the powder was not used immediately, selective reduction occurred, to give androstan-17-one (II) (67%) and androstane (III) (15%).

The mechanism of this reduction is probably similar to that of a Clemmensen reduction.[3] The formation of an acyl cation from acetic anhydride and hydrogen chloride is important in determining the ease of the former reduction, and the acetoxy-organozinc compound (VII) is a likely intermediate. Further electron-transfer from the metal to (VII) leads to the formation of a deoxy-product. Furthermore, we can also expect that an acetoxy-product is directly obtained from (VII); in the case of androstane-3,17-dione (I), 17β-acetoxyandrostane (IV) was isolated.



(VII)

EXPERIMENTAL

Melting points were determined on a micro hot-stage. The infrared spectra were recorded in both KBr and Nujol with a Jasco IR-S spectrometer.

Preparation of Active Zinc Powder.—Commercial zinc powder (Kishida Chemical Co.) was activated by washing well with 2% hydrochloric acid for 3—4 min., then successively with much water, ethyl alcohol, acetone, and dry ether. The powder thus obtained was warmed under reduced pressure at 90° for 10 min., and kept in a sealed flask at room temperature for 10—12 hr. for the selective reductions of less-hindered keto-groups. In the last experiment, of androstane-3,17-dione containing a hindered 17-keto-group, the powder was used immediately after its preparation.

General Procedure for the Zinc Reduction under Different Conditions.—(*a*) Cholestan-3-one (250 mg.) was dissolved, with stirring, in acetic anhydride (10 ml.) saturated with hydrogen chloride at 0°. Active zinc powder (2·5 g.) was slowly added to the resulting solution (15—20 min.), and then the temperature was gradually raised to room temperature. The mixture was stirred at room temperature for 10 hr.,* and then poured into a large quantity of ice–water. The aqueous solution was made basic with sodium carbonate, and thoroughly extracted with ether. The extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure, to give a brown oil, which was chromatographed on silica gel (20 g.) and eluted with benzene, to give colourless crystals (204 mg.), m.p. 77·5—78·5°. Recrystallization from acetone–methanol afforded cholestane, m.p. 79°.

(*b*) Cholestan-3-one (250 mg.) was dissolved, with stirring, in acetic anhydride (10 ml.) saturated with hydrogen chloride at 0°, and active zinc powder (2·5 g.) was slowly

* The reaction mixture turned brown when allowed to stand at room temperature.

[3] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 58.

added to the resulting solution, with stirring. After being stirred at 0° for 6 hr., the mixture was worked up according to the above-mentioned procedure, to afford cholestane (210 mg.), m.p. 77·5—79°.

According to procedure (*a*) or (*b*), zinc reductions of keto-steroids were carried out, and the reduction products were carefully separated by silica gel chromatography (Mallinckrodt; 100 mesh). All the products were identical (m.p., i.r. spectra) with known steroids (Table).

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