Selective Homogeneous Hydrogenation of 3-Oxo-1,4-diene Steroids. III.[1] On the Formation of Saturated 5α-Ketone in the Hydrogenation Catalyzed by Dichlorotris(triphenylphosphine)ruthenium

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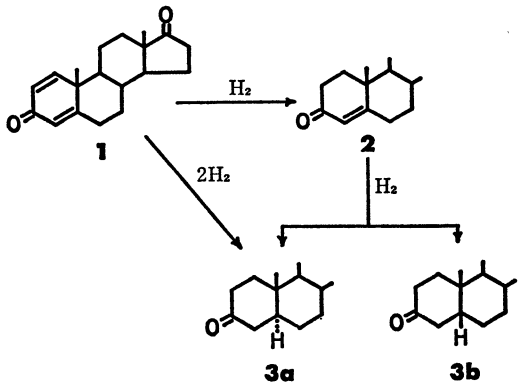
Hydrogenation of 1,4-androstadiene-2,17-dione (**1**) with $RuCl_2(Ph_3P)_3$ gives some saturated 5α-ketone together with 4-androstene-3,17-dione (**2**). The ratio of **2** to the saturated ketone formed increases almost in proportion to hydrogen pressure. The rate dependence upon hydrogen pressure has been shown to be first-order for formation of **2** and zero-order for formation of the saturated ketone. A mechanism which involves a 1,5-hydride shift at an intermediate species is proposed for the stereoselective formation of the 5α-ketone.

In previous papers,[1,2] it was shown that 1,4-androstadiene-3,17-dione (**1**) is hydrogenated selectively to 4-androstene-3,17-dione (**2**) with dichlorotris(triarylphosphine)rutheniums as catalysts. Although hydrogenation of **2** to saturated ketones (**3a** and **3b**) was very slow with the ruthenium complex some saturated 5α-ketone was found to arise directly from **1**.[2] This was in contrast to the hydrogenation catalyzed by chlorotris(triphenylphosphine)rhodium[3,4] where saturated ketones were all produced consecutively through **2**.[2]



Scheme 1. Hydrogenation pathways of 1,4-androstadiene-3,17-dione (**1**).

This paper describes further studies which were undertaken to get an insight into the mechanism of formation of the saturated 5α-ketone in the ruthenium complex catalyzed hydrogenation.

Experimental

Material. 1,4-Androstadiene-3,17-dione (**1**) was obtained from the Kikkoman Shoyu Co. and used without further purification, mp 138—139 °C.

Catalyst. Dichlorotris(triphenylphosphine)ruthenium was prepared as described previously.[1]

Hydrogenation and Analysis of the Products. The hydrogenation apparatus and the method of analysis of the products were the same as those described previously.[1] **1** (500 mg) was hydrogenated with 50 mg of the ruthenium complex in 10 ml benzene at 50 °C under various hydrogen pressures. During each hydrogenation the hydrogen pressure was kept almost constant. The reaction time was varied from 505 min for the hydrogenation at the lowest pressure (2.2 kg/cm²) to 60 min for that at the highest pressure (101 kg/cm²). The conversion of **1** ranged from 16% to 42% by hydrogenations. The pseudo-first-order rate constants were calculated from the compositions of reaction mixtures employing the integrated form of Eq. (1).

Results

Figure 1 shows the effect of hydrogen pressure on the ratio of **2** to saturated ketone formed in the hydrogenation of **1** in benzene at 50 °C. Hydrogenation of **2** to saturated ketones **3a** and **3b** was extremely slow under these conditions and this ratio was, therefore, practically independent of the conversion of **1** at a given hydrogen pressure. As described previously,[2] the saturated ketone formed here is predominantly 5α-androstane-3,17-dione (**3a**) and this is also indicative that the saturated ketone was not formed through **2**, because hydrogenation of **2** gave an about 2 : 1 mixture of **3a** and **3b**. As is seen from Fig. 1, the ratio of **2** to the saturated ketone increases

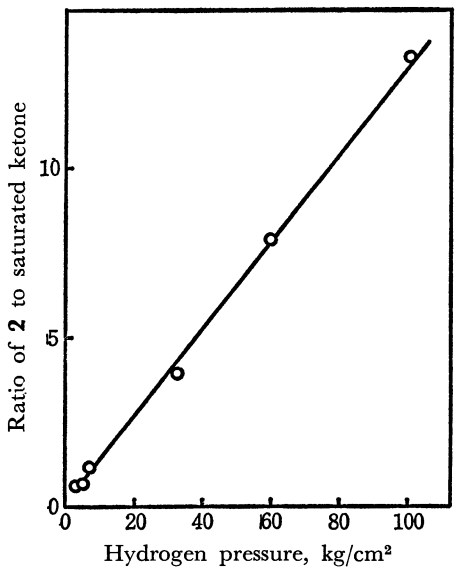


Fig. 1. Effect of hydrogen pressure on the ratio of 4-androstene-3,17-dione (**2**) to the saturated ketone formed in the hydrogenation of **1**. **1** (500 mg) was hydrogenated with 50 mg of $RuCl_2(Ph_3P)_3$ in 10 ml benzene at 50 °C. Each hydrogenation was performed at nearly constant pressure.

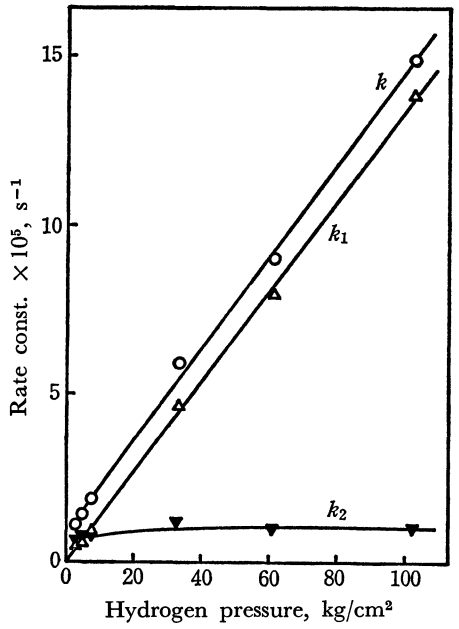


Fig. 2. Effects of hydrogen pressure on the conversion of **1**, the formation of **2** and the formation of saturated ketone. k, k_1, and k_2 are pseudo-first-order rate constants defined by Eq. (1). For experimental conditions, see the footnote of Fig. 1.

almost in proportion to the hydrogen pressure in a wide range of 2 to more than 100 kg/cm².

Figure 2 shows the effect of hydrogen pressure on a pseudo-first-order rate constant k defined by Eq. (1).[5] The rate constant k can be separated into the

$$-\frac{d[\mathbf{1}]}{dt} = k[\mathbf{1}] = (k_1+k_2)[\mathbf{1}] \quad (1)$$

two rate constants k_1 and k_2 for formation of **2** and the saturated ketone, respectively, from the results shown in Fig. 1. From the effects of hydrogen pressure on k_1 and k_2 thus obtained (Fig. 2), it is concluded that the rate of formation of **2** is first-order in hydrogen pressure while that of the saturated ketone is independent of hydrogen pressure. At low pressures, however, k_2 appears to decrease with decreasing hydrogen pressure.

From the plots of the log of the ratio **2**: saturated ketone *vs.* the reciprocal of reaction temperature (Fig. 3), we know that the apparent activation energy for formation of saturated ketone is 3.8 kcal/mol higher than for formation of **2**. Thus a better selectivity for **2** is obtained in the hydrogenation at a low temperature.

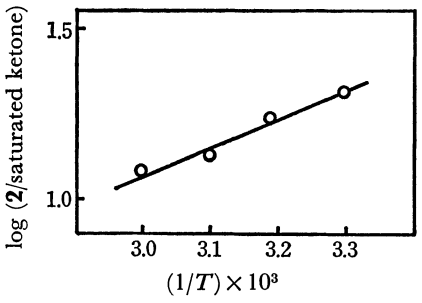
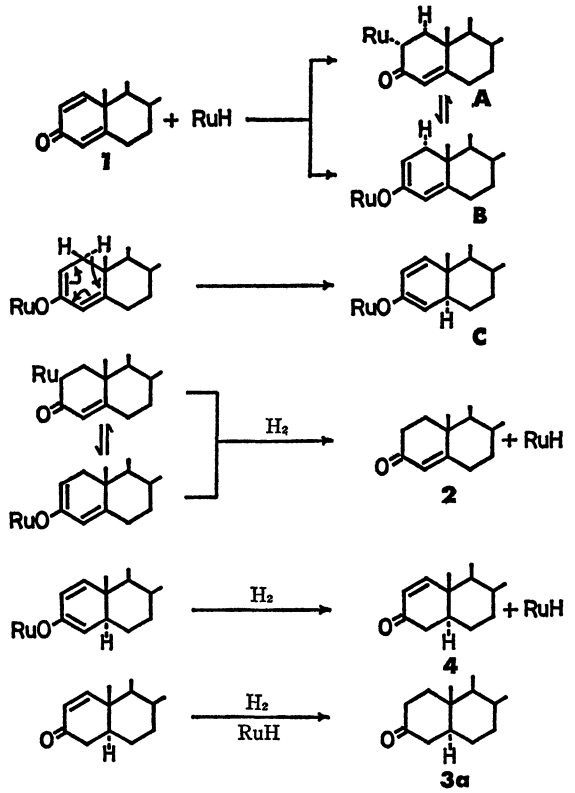


Fig. 3. Effect of reaction temperature on the ratio of **2** to the saturated ketone formed in the hydrogenation of **1**. **1** (500 mg) was hydrogenated with 50 mg of $RuCl_2(Ph_3P)_3$ in 10 ml benzene at 100 kg/cm² hydrogen pressure.

Discussion

The active species in the hydrogenation catalyzed by dichlorotris(triphenylphosphine)ruthenium is considered to be the hydrido complex $RuClH(Ph_3P)_3$ formed by the hydrogenolysis of the dichloro complex.[6,7] The first step of the hydrogenation of **1**, therefore, will be the addition of the hydrido complex (abbreviated as RuH) to **1**, probably from the α-face.[4] Although the mode of addition of RuH to an α,β-unsaturated ketone is not certain, it might be presumed to occur in the following ways: *1,2* to the C_1–C_2 double bond to give **A** or *1,4* to give **B** as shown in Scheme 2.[8] If we assume that isomerization of **B** to **C** by a 1,5-hydride shift at the cyclic conjugated diene system would occur during the hydrogenation of **A** or **B**,[9] the stereoselective formation of saturated 5α-ketone **3a** could be accounted for because such hydride shifts would be expected to occur without difficulty between quasi-axial 1α and axial 5α positions, assisted by the cyclic conjugated system.[10] The observed zero-order dependence of the rate of formation of **3a** upon hydrogen pressure will not be in conflict with this mechanism if we assume that the hydride shift is rate-controlling in the course of hydrogenation leading to the formation of **3a**. The driving



Scheme 2. A mechanism for formation of 4-androstene-3,17-dione (**2**) and saturated 5α-ketone (**3a**) in the ruthenium complex catalyzed hydrogenation of 1,4-androstadiene-3,17-dione (**1**).

force for the isomerization of **B** is presumed to be the decrease of electron density at the C-5 carbon atom, which would be caused by the coordination of the enolate anion to ruthenium.[11] The hydrogen chloride liberated by the hydrogenolysis of the dichloro ruthenium complex may contribute to this decrease of electron density by interacting with the triphenylphosphine ligand. The effect of the addition of triethylamine to depress the formation of the saturated ketone[1] may give a support for this consideration, because the degree of the depression caused by the addition of triethylamine was so great (from 10.5% to 1.7%), and such a great effect would be difficult to explain by an only twofold increase in the rate of hydrogenation with addition of the amine alone.

From the observed dependencies of the rates on hydrogen pressure, it seems that **C** and **4** are hydrogenated faster than those species which afford **2** on hydrogenation. It is suggested that **C** and **4**, which both have the 5α configuration, will be less hindered than **A** and **B** for the hydrogenation from the α-face, because the 5α species are in a flatter conformation regarding the rings A and B than the Δ^4 species such as **A** and **B**. This is supported by the fact that 5α-1-androstene-3,17-dione (**4**) is hydrogenated more easily than **1** with the ruthenium complex under comparable conditions.[12]

The authors are grateful to Professor J. A. Marshall of Northwestern University for his valuable suggestion concerning the 1,5-hydride shift.

References

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2) S. Nishimura and K. Tsuneda, *ibid.*, **42**, 852 (1969).

3) A. J. Birch and K. A. M. Walker, *J. Chem. Soc., C*, **1966**, 1894.

4) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4357 (1966).

5) The first-order kinetics in concentration of **1** which was obtained in the hydrogenation with added triethylamine[1] was confirmed to hold for the hydrogenation without the amine (unpublished results).

6) P. S. Hallman, B. R. McGarvey, and G. Wilkinson, *J. Chem. Soc., A*, **1968**, 3143.

7) D. Rose, J. O Gilbert, R. P. Richardson, and G. Wilkinson, *ibid.*, **1969**, 2610.

8) A similar mode of addition to α,β-unsaturated carbonyl compounds has been suggested by Goetz and Orchin in the cobalt hydrocarbonyl catalyzed hydrogenation [*J. Amer. Chem. Soc.*, **85**, 2782 (1963)]. Alternative reverse addition of RuH would be less probable because of an increased steric interaction between the Ru moiety and 9α-hydrogen in the resulting species.

9) For the preference of 1,5- over 1,3-hydrogen shift, see R. T. Morrison and R. N. Boyd, "Organic Chemistry," 3rd ed., Allyn and Bacon, Inc., New York (1973), p. 954.

10) The saturated 5α-ketone formed in the deuteration of **1** at about 40% conversion, on treatment with methanolic sodium hydroxide, gave 5α-ketone-d_2 as the predominant product. This result suggests that no exchange occurred at the C-6 carbon during the deuteration and excludes the mechanism involving the C-6 hydrogen, e.g., enolization of **1** prior to hydrogenation, which may well explain the stereospecific 5α-ketone formation.

11) For a coordination of a similar type, see H. W. Thompson and E. McPherson, *J. Amer. Chem. Soc.*, **96**, 6232 (1974).

12) **4** was completely hydrogenated to **3a**, compared with only 84% conversion of **1** under the same conditions (unpublished results; see also Ref. 2)