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Selective Homogeneous Hydrogenation of 3-Oxo-1,4-diene Steroids. II.[1] Effects of Basic Additives and of *para* Substituents on the Hydrogenation with Dichlorotris(triphenylphosphine)ruthenium

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The catalytic homogeneous hydrogenation of 1,4-androstadiene-3,17-dione (I) with dichlorotris(triphenylphosphine)ruthenium has been investigated in the presence of basic additives. The rate of hydrogenation increased with respect to added amines in the order pyridine<none<butylamine<aniline<diethylamine≅triethylamine. The hydrogenation was also promoted by the addition of calcium carbonate, but slightly retarded by that of sodium carbonate. The amount of triethylamine required for obtaining the maximum rate of hydrogenation has been determined. Addition of triethylamine also reduced the formation of 5α-androstane-3,17-dione produced by a different pathway from that for the formation of 4-androstene-3,17-dione (II), resulting in an increased selectivity for the formation of II. I was also hydrogenated with the ruthenium complexes having *p*-methoxy-, *p*-methyl-, and *p*-fluoro-substituted triphenylphosphines as ligands. The catalytic activity of the ruthenium complex was greatly enhanced by *p*-methoxyl and *p*-methyl groups and reduced by *p*-fluoro group when the catalyst was used in the presence of triethylamine.

In a previous paper[1] we showed that 3-oxo-1,4-diene steroids are selectively hydrogenated to the corresponding 3-oxo-4-enes with dichlorotris(triphenylphosphine)-ruthenium as a catalyst. Hydrogenation with the ruthenium complex also yielded small amounts of saturated 5α-ketones which were formed by a different pathway from that for the formation of 3-oxo-4-enes.

1) Part I: S. Nishimura and K. Tsuneda, This Bulletin, **42**, 852 (1969).

This was in contrast to the hydrogenation with chlorotris(triphenylphosphine)rhodium,[2,3] where saturated ketones were all formed consecutively *via* the intermediate 3-oxo-4-enes. It was also shown that the ratio of 3-oxo-4-ene to the saturated 5α-ketone formed increases with increasing hydrogen pressure and decreasing reaction temperature. Thus, with the ruthenium complex catalyst, high yields of 3-oxo-4-enes were obtained by hydrogenating the corresponding 3-oxo-1,4-dienes at a relatively low temperature and under a high hydrogen pressure.

In this study we have investigated the effects of added basic substances and of *para* substituents in the triphenylphosphine ligand on the hydrogenation of 1,4-androstadiene-3,17-dione (I) with the ruthenium complex as catalyst.

The Effects of Basic Additives. It is known that bases promote the formation of the hydrido complex of ruthenium, the active species in hydrogenation, according to the equation[4]

$$RuCl_2(PPh_3)_3 + H_2 + \text{base} = RuClH(PPh_3)_3 + \text{base}\cdot HCl \quad (1)$$

We have therefore studied the effect of the addition of various basic substances in the hydrogenation of I in benzene. We see from Table 1 that the rate of hydrogenation increased with respect to the added amines in the order pyridine<none<butylamine<aniline< diethylamine≅triethylamine. The hydrogenation was also effectively promoted by the addition of calcium carbonate, but retarded slightly by the addition of sodium carbonate. Figure 1 shows the effect of the varying amount of added triethylamine on the rate of hydrogenation of I. It is seen that the maximum rate is obtained when triethylamine is added in a slightly greater amount than that required by Eq. (1) and addition of the amine in further excess ureslts in the decrease in rate.

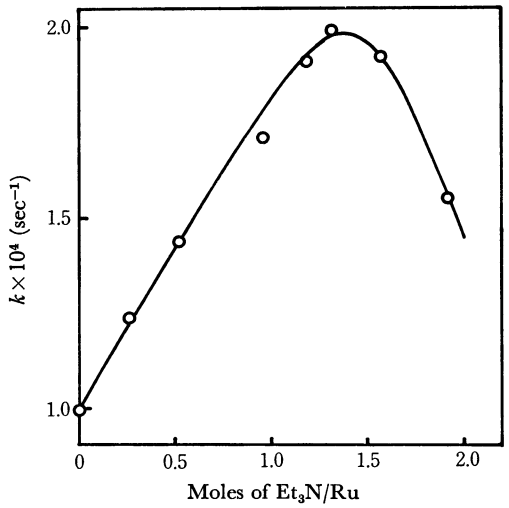


Fig. 1. Effect of the varying amount of added triethylamine on the rate of hydrogenation of I. I (500 mg) was hydrogenated with 50 mg of $RuCl_2(PPh_3)_3$ in 10 ml benzene at 50°C and 100 kg/cm² H_2.

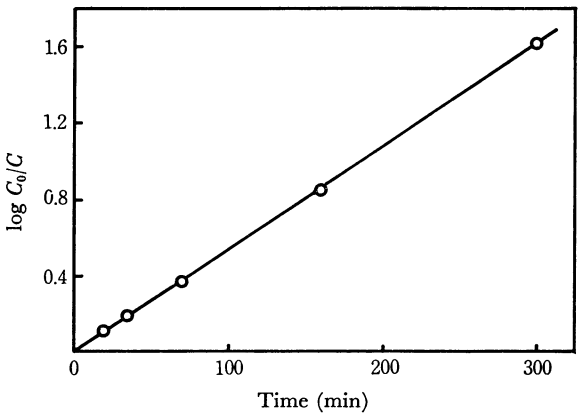


Fig. 2. First-order dependence of the rate of hydrogenation on the concentration of I. I (500 mg) was hydrogenated with 50 mg (0.052 mmol) of $RuCl_2(PPh_3)_3$ and 6.9 mg (0.068 mmol) of triethylamine in 10 ml benzene at 50°C and 100 kg/cm² H_2.

Table 1. Effect of basic additives on the hydrogenation of 1,4-androstadiene-3,17-dione (I) with dichlorotris-(triphenylphosphine)ruthenium[a]

Additive[b]	Conversion of I, %
Triethylamine	95.4
Diethylamine	95.4
Butylamine	86.5
Aniline	88.1
Pyridine	62.7
Calcium carbonate	95.2
Sodium carbonate	73.0
None	76.0

a) I(500 mg) was hydrogenated with 50 mg of $RuCl_2(PPh_3)_3$ in 10 ml benzene at 40°C under a hydrogen pressure of 130—135 kg/cm² for 6 hr.

b) The amines were added in the stoichiometric amounts required by Eq. (1). Calcium and sodium carbonates were added in the amounts 21 and 22 mg (four times of the amounts required by Eq. (1)), respectively.

The rate of hydrogenation is strictly of first order in the concentration of I as shown in Fig. 2. This kinetic dependence of the rate on concentration is also in contrast to the hydrogenation of I with the rhodium complex where the rate obeys the Langmuir type equation in the same region of the concentration of I.[5]

Variations in the amounts of products during hydrogenation are shown in Fig. 3. Since the reaction pathways for the formation of saturated ketones (IIIα and IIIβ) are considered to be as shown in Scheme 1, the variation in concentration of 4-androstene-3,17-dione (II) can be expressed as a function of the concentration of I by the equation[6]

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

3) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966).

4) P. S. Hallman, D. Evans, J. A. Osborn, and G. Wilkinson, *Chem. Commun.*, **1967**, 305; P. S. Hallman, B. R. McGarvey, and G. Wilkinson, *J. Chem. Soc. A*, **1968**, 3143.

5) S. Nishimura and S. Kamihara, unpublished results.

6) J. H. de Boer and R. J. A. M. van der Borg, "Actes Congr. Intern. Catal.", 2e, Paris, 1960, p. 919 (Editions Technip, Paris, 1961).

Table 2. Hydrogenation of 1,4-androstadiene-3,17-dione (I) with dichlorotris(triarylphosphine)ruthenium[a)]

Catalyst X in $RuCl_2[(p\text{-}XC_6H_4)_3P]_3$	Composition of reac. mixture (mol%) I	II	III	10^4k_X[b)] (sec^{-1})	k_X/k_H[b)]	k_X/k_H[b)] with no added Et_3N	r_X/r_H[c)] for $RhCl[(p\text{-}XC_6H_4)_3P]_2$
MeO	2.1	93.7	4.2	10.8	5.6	0.96	2.4
Me	3.9	93.3	2.8	9.0	4.6	1.8	2.1
H	49.8	48.4	1.8	1.9	1.0	1.0	1.0
F	91.5	8.5	trace	0.24	0.12	0.21	0.14

a) I (500 mg) was hydrogenated in the presence of 0.026 mmol of the ruthenium catalyst and 0.034 mmol of triethylamine in 10 ml benzene at 50°C under a hydrogen pressure of 100 kg/cm² for 1 hr.
b) k_X and k_H denote the first-order rate constants for the hydrogenation catalyzed by the ruthenium complex with *para* substituent X and not with substituent, respectively.
c) The ratio of rates of hydrogenation of cyclohexene catalyzed by the rhodium complex with *para* substituent X and with no substituent [Data from C. O'Connor and G. Wilkinson, *Tetrahedron Lett.*, **1969** 1375].

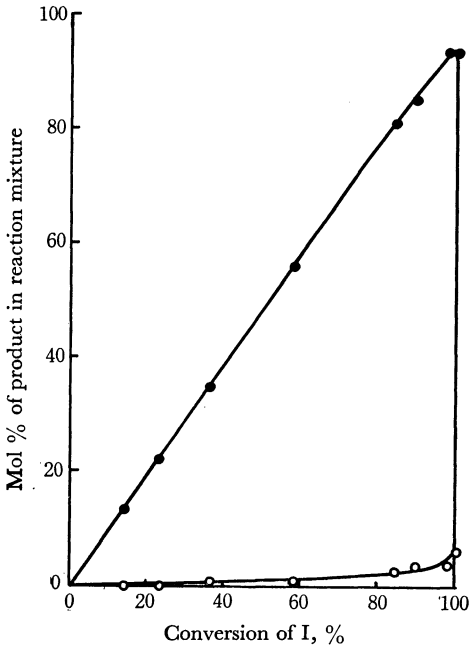
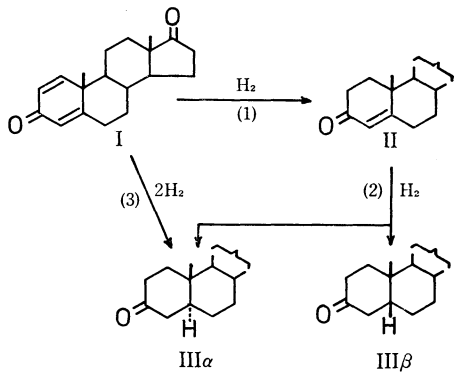


Fig. 3. Variations in the amounts of II (●) and III (○) in the reaction mixture as a function of the conversion of I. The points indicate individual experiments. Full lines give theoretical curves showing the variations in the amounts of II and III when $f=0.983$ and $K=1/90$ in Eq. (2). The reaction conditions are the same as in Fig. 2.

$$C_{II} = \frac{f}{K-1}(C_I - C_I^K) \qquad (2)$$

where $f=k_1/(k_1+k_3)$, $K=k_2/(k_1+k_3)$, and k_i's are the first-order rate constants for the corresponding reaction paths shown in Scheme 1. C_I and C_{II} are the concentrations of I and II, respectively, when the initial concentration of I is taken as unity. It follows from Eq. (2) that the variation in concentration of added IIIα and IIIβ is given by $1-C_I-f(C_I-C_I^K)/(K-1)$. By applying this relation to the observed change in the amount of IIIα and IIIβ, we obtain $f=0.983$ and $K=1/90$ as a most satisfactory set of values. This implies that the amount of IIIα formed by the reaction path (3) was depressed to the extent of only 1.7% in the presence of added triethylamine as compared with 10.5% for that in the absence of the amine.[1)] On the other hand, the result indicates that hydroganetion of



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

II to IIIα and IIIβ, which practically did not take place in the absence of base,[1)] occurs very slowly in the presence of triethylamine. The ratio of IIIα to IIIβ formed decreases toward the end of hydrogenation, indicating increasing contribution of the saturated ketones formed *via* II with the extent of hydrogenation.[7)] The maximum yield of II is given by $f\times K^{K/(1-K)}$ and calculated to be 93.5% at 98.9% conversion of I from the obtained values of f and K.

The Effect of para *Substituents in the Triphenylphosphine Ligand.* It has been reported that the catalytic activity of chlorobis(triphenylphosphine)rhodium is enhanced by electron-releasing *para* substituents in the triphenylphosphine ligand, as observed in the hydrogenation of olefins.[8)] As regards the ruthenium complex, the use of tri-*p*-tolyl- and tri-*p*-fluorophenylphosphines as ligands has recently been described in a patent.[9)] We prepared the ruthenium complexes

7) Small amounts of IIIβ and an alcohol, possibly 3-hydroxy-5α-androstan-17-one, appear to be formed also by the reaction path (3). The ratio of IIIβ to IIIα, however, was much smaller than that in the products formed through II.

8) S. Montelatici, A. van der Ent, A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, **1968**, 1054; C. O'Connor and G. Wilkinson, *Tetrahedron Lett.*, **1969**, 1375.

9) J. P. Candlin, J. R. Jennings, and P. F. Todd, Brit. Pat. 1246123 (1971); *Chem. Abstr.*, **75**, 129935 m (1971).

9a) Note Added in Proof. After this manuscript was submitted to publication, preparations of *para*-substituted triphenylphosphineruthenium complexes and their use in an isomerization reaction have been described by Blum and Becker [*J. Chem. Soc. Perkin II*, **1972**, 982].

with tri-*p*-methoxyphenyl-, tri-*p*-tolyl-, and tri-*p*-fluorophenylphosphines as ligands and compared their catalytic activities in the hydrogenation of I.[9a] The results are summarized in Table 2. It is seen that the activity of the ruthenium complex is also enhanced by the electron-releasing *p*-methoxyl and *p*-methyl groups and decreased by the electron-withdrawing *p*-fluoro group. The effects of the *para* substituents seem to be more pronounced than in the case of the rhodium complex (see Table 2). It is to be noted that their electronic effects are observed in a proper order only in the presence of triethylamine.

The results show that the activity as well as the selectivity of dichlorotris(triphenylphosphine)ruthenium in the hydrogenation of I are greatly improved by the addition of an optimal amount of triethylamine. The activity of the ruthenium complex is further enhanced by the electron-releasing *p*-methoxyl and *p*-methyl groups in the triphenylphosphine ligand. Thus the hydrogenation of 3-oxo-1,4-diene steroids under these conditions might be useful for the preparation of the corresponding 3-oxo-4-enes. Typical examples of the preparation of II using the ruthenium complexes are given (see Experimental).

Experimental

Material. 1,4-Androstadiene-3,17-dione (I) was obtained from the Kikkoman Shoyu Co., Ltd., and used without further purification. Mp 142.5—143.5°C.[10]

Catalysts. Dichlorotris(triarylphosphine)ruthenium was prepared by refluxing ruthenium chloride trihydrate with six-fold excess of the triarylphosphine in ethanol for about 1 hr (for 2.5 hr in the case of tri-*p*-fluorophenylphosphine).

Dichlorotris(triphenylphosphine)ruthenium. Found: C, 66.93; H, 4.92%. Calcd for $C_{54}H_{45}Cl_2P_3Ru$: C, 67.64; H, 4.74%.

Dichlorotris(tri-*p*-methoxyphenylphosphine)ruthenium. Found: C, 60.92; H, 5.26%. Calcd for $C_{63}H_{63}Cl_2O_9P_3Ru$: C, 61.56; H, 5.18%.

Dichlorotris(tri-*p*-tolylphosphine)ruthenium. Found: C, 69.47; H, 5.38%. Calcd for $C_{63}H_{63}Cl_2P_3Ru$: C, 69.72; H, 5.86%.

Dichlorotris(tri-*p*-fluorophenylphosphine)ruthenium. Found: C, 57.94; H, 3.93%. Calcd for $C_{54}H_{36}Cl_2F_9P_3Ru$: C, 57.87; H, 3.24%.

Hydrogenation. The hydrogenation was performed in a 30 ml bomb equipped with a magnetic stirrer. The bomb was immersed in an oil bath maintained at a constant temperature.

Analysis of Product. The product was analyzed by gas chromatography (2% OV-17 at 250°C or 1.5% QF-1 at 220°C) after evaporation of the solvent followed by extraction with methylcyclohexane.

Examples of the Preparation of 4-Androstene-3,17-dione (II).

a) By Hydrogenation of I with Dichlorotris(triphenylphosphine)ruthenium. I (500 mg) was hydrogenated with 50 mg (0.052 mmol) of the ruthenium catalyst and 5.3 mg (0.052 mmol) of triethylamine in 10 ml benzene at 40°C under a hydrogen pressure of 130 kg/cm² for 8 hr. The benzene solution was passed through alumina followed by elution with benzene–ether. Evaporation of the solvent gave 498 mg of a solid residue. Recrystallization from acetone–hexane gave 447 mg of colorless needles (89% yield). Mp 169.5—171°C (98% purity by glpc analysis) (reported mp: 173—174°C[11]).

*b) By Hydrogenation of I with Dichlorotris(tri-*p*-tolylphosphine)ruthenium.* I (500 mg) was hydrogenated with 28 mg (0.026 mmol) of the ruthenium catalyst and 3.4 mg (0.034 mmol) of triethylamine in 10 ml benzene at 50°C under a hydrogen pressure of 100 kg/cm² for 2 hr. Treatment of the benzene solution in the same way as above gave 506 mg of a solid residue. Recrystallization from acetone–hexane gave 452 mg of light brown needles (90% yield). Mp 168.5—171°C (97.5% purity by glpc analysis).

*c) By Hydrogenation of I with Dichlorotris(tri-*p*-methoxyphenylphosphine)ruthenium.* I (2.0 g, recrystallized from ethanol–hexane, mp 144—145°C) was hydrogenated with 32 mg (0.026 mmol) of the ruthenium catalyst and 3.4 mg (0.034 mmol) of triethylamine in 10 ml benzene at 50°C under a hydrogen pressure of 100 kg/cm² for 2.5 hr. Treatment of the benzene solution in the same way as above gave 2.02 g of a solid residue. Recrystallization from acetone–hexane gave 1.82 g of colorless needles (90% yield). Mp 170—171°C (98.5% purity by glpc analysis).

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10) All melting points were measured by an instrument for measurement of micromelting point, Mettler FP-2.

11) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 986 (1935).