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Stereochemistry of the Palladium-catalyzed Hydrogenation of 3-Oxo-4-ene Steroids. V.[1] A Kinetic Study in Basic and Acidic Media

Shigeo Nishimura,* Yasuhiro Momma, Hideo Kawamura, and Michio Shiota†
Department of Industrial Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184
† *Department of Chemistry, Ochanomizu University, Bunkyo-ku, Tokyo 112*

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Effects of the β-methyl group at C-10 and some oxygen functions (=O, OH, OAc) at C-11, C-17, and C-20 on the rates of hydrogenation of 3-oxo-4-ene steroids have been studied with palladium catalyst in pyridine or THF/HBr as solvent. In contrast to the hydrogenation in pyridine, the rate in THF/HBr was greatly depressed by the presence of 10β-methyl group. The reactivity of the steroids was enhanced by the oxygen functions, in particular, by 11, 17-dioxo group. The effects of the substituents are discussed from a mechanistic consideration based on the obtained results.

The stereochemistry of catalytic hydrogenation of cyclic α,β-unsaturated ketones to saturated ketones has been of wide interest from the viewpoint of stereoselective synthesis as well as from the mechanistic interpretation of the results.[2] Although a considerable body of studies has been described in literature, in particular, in the fields of 3-oxo-4-ene steroids and bicyclo[4.4.0]dec-1-en-3-one ($\Delta^{1(8a)}$-2-octalone), the mechanistic interpretations proposed do not appear to be sufficient to explain the stereochemical outcomes under various reaction conditions. This may be due to a rather complex nature of the reaction. The polar character of the unsaturated system is susceptible to a variety of factors which can influence the stereochemistry of hydrogenation, including the problem of 1,2- and 1,4-addition of hydrogen. Of these factors the most important is the effects of bases and acids.

As well known, 3-oxo-4-ene steroids are stereoselectively hydrogenated to 3-oxo-5β steroids in basic media.[3] The stereoselectivity, however, is not always satisfactory in these compounds with oxo and hydroxy functions at C-11, C-17, and C-20. The use of 4-methoxypyridine as a solvent has been found most effective for these compounds.[1] On the other hand, the addition of hydrobromic acid to acetic acid or, better, to tetrahydrofuran greatly increases the yields of 3-oxo-5β compounds from 19-nor-3-oxo-4-ene steroids.[1] The results on 19-nor steroids in acidic media are in line with those reported in the hydrogenation of 2-octalone where high yields of *cis*-2-decalone are obtained under acidic conditions.[4] In basic media, however, the results are not always consistent with those on 2-octalone in which the stereoselectivity is usually low under basic conditions.[2] Since 19-nor-3-oxo-4-ene steroids are very similar to 2-octalone in their A/B ring structures, a comparable study on 19-nor and 10β-methyl steroids allows an estimation of the effect of the angular methyl group more directly. Since the kinetic aspect of the hydrogenation of these steroids is little known, we have investigated the rates of hydrogenation of various steroids with or without 10β-methyl group in basic and acidic media in order to know the effect of the angular methyl group as well as the effect of some oxygen functions at C-11, C-17, and C-20.

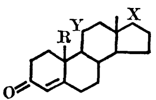
Results

Hydrogenation in Basic Medium. Seven 3-oxo-4-enes (**1a**—**g**) and three 19-nor-3-oxo-4-enes (**2c**—**e**) (see Table 1) have been hydrogenated in pyridine as a solvent at 25 °C and atmospheric pressure with palladium black as a catalyst. The hydrogenation was zero order in the concentration of the steroids and the zero-order kinetics held until the most portion of the steroids had been hydrogenated. The steroids have also been hydrogenated competitively in a 1:1 mixture of an appropriate pair of the compounds. The relative reactivity of a compound to cholest-4-en-3-one (**1a**), (R/R_{1a}), was obtained by employing the relationship of Eq. 1,

$$\log (C^\circ/C) = (R/R_{1a}) \log (C^\circ_{1a}/C_{1a}), \tag{1}$$

where C° and C represent the concentrations of the compound at the initiation and a given time, respectively, and the subscript 1a refers to cholest-4-en-3-one. Most of the values were obtained in competitive hydrogenation of a compound with **1a**, but in some cases, because of difficulty in analysis, the ratios were determined indirectly by competitive hydrogenation with another compound which was in turn hydrogenated competitively with **1a**. From the values obtained in individual and competitive hydrogenations, the ratios of adsorption coefficients, b/b_{1a}, were calculated from the relationship: $R/R_{1a}=(k/k_{1a})(b/b_{1a})$, where k/k_{1a} denotes the ratio of the rate of hydrogenation of a steroid to that of **1a** in individual hydrogenations. The results are summarized in Table 1. It is seen from the results that the rate of hydrogenation is generally enhanced by the oxygen functions at C-11, C-17, and C-20 which tend to lower the selectivity to 5β except the 17β-acetoxy group in **1c**. This trend is most prominently seen in the case of **1g** with 11,17-dioxo group where the rate of hydrogenation is 4 times as great as that of **1a** and the selectivity to 5β is as low as 32%. Since the relative reactivity of **1g** to **1a**, R_{1g}/R_{1a}, is 10, it results that the value for b_{1g}/b_{1a} is 2.5. Thus the compound **1g** is more strongly adsorbed to the catalyst than **1a**. With the compounds having the other oxygen functions, any tendency of strong adsorption over **1a** was not indicated. The reactivities of 19-nor steroids in individual hydrogenations are not much different from those of the corresponding 10β-methyl analogs, but the relative reac-

TABLE 1. HYDROGENATION OF 3-OXO-4-ENE AND 19-NOR-3-OXO-4-ENE STEROIDS IN PYRIDINE[a)]



1: R=Me
2: R=H

Compd	X	Y	10^4k / mol min^{-1} g-cat^{-1}	$k^{b)}/k_{1a}$	$R^{b)}/R_{1a}$	$b^{b)}/b_{1a}$	Selectivity to 5β/(%)
1a	β-C_8H_{17}	H	1.0	1.0	1.0	1.0	99
1b	H	H	1.2	1.2	1.3	1.1	95
1c	β-OAc	H	1.8	1.8	2.0	1.1	98.5
1d	β-OH	H	2.1	2.1	1.8	0.87	93
1e	=O	H	2.4	2.4	2.2	0.92	92.5
1f	β-Ac	H	2.6	2.6	1.8	0.72	86
1g	=O	=O	4.1	4.1	10[c)]	2.5	32
2c	β-OAc	H	1.8	1.8 (0.99)	1.9 (0.95)	1.1 (0.96)	95
2d	β-OH	H	2.4	2.4 (1.1)	2.7 (1.5)	1.1 (1.3)	85
2e	=O	H	2.8	2.8 (1.2)	4.2 (1.9)	1.5 (1.6)	89

a) The compound was hydrogenated in 0.0316 M solution (1.8 ml) with 3 mg of palladium catalyst at 25 °C and atmospheric pressure. In competitive hydrogenation an equimolar mixture of two compounds was hydrogenated in 0.0316 M solution. b) The figures in parentheses indicate the values for 19-nor steroids relative to the corresponding 10β-methyl analogs. c) Obtained from $R_{1g}/R_{2e}(2.4)$ and $R_{2e}/R_{1a}(4.2)$.

TABLE 2. HYDROGENATION OF 3-OXO-4-ENE AND 19-NOR-3-OXO-4-ENE STEROIDS IN TETRAHYDROFURAN AND HYDROBROMIC ACID[a)]

Compd[b)]	X	Y	10^4k / mol min^{-1} g-cat^{-1}	$k^{c)}/k_{1a}$	$R^{c)}/R_{1a}$	$b^{c)}/b_{1a}$	Selectivity to 5β/(%)
1a	β-C_8H_{17}	H	0.98	1.0	1.0	1.0	98.5
1b	H	H	0.98	1.0	1.0	1.0	94
1c	β-OAc	H	0.98	1.0	1.5	1.6	97
1d	β-OH	H	1.5	1.5	1.7	1.1	78
1e	=O	H	1.4	1.4	3.2	2.3	84
1f	β-Ac	H	1.8	1.8	2.1	1.2	79
1g	=O	=O	2.6	2.7	5.4	2.0	30
2c	β-OAc	H	13	13 (13)	26 (18)	2.1 (1.3)	99.9
2d	β-OH	H	12	12 (8.1)	24 (14)	2.0 (1.7)	98
2e	=O	H	13	13 (9.3)	66[d)] (21)	5.1 (2.3)	98

a) The compound was hydrogenated in 1.8 ml of THF containing 0.2 µl of concd HBr (48%). For the other conditions see the footnote a) in Table 1. b) For the compound structure, see Table 1. c) The figures in parentheses indicate the values for 19-nor steroids relative to the corresponding 10β-methyl analogs. d) Obtained from $R_{2e}/R_{1f}(31.5)$ and $R_{1f}/R_{1a}(2.1)$.

tivities in competitive hydrogenations are somewhat greater in the cases of **2d** and **2e**, indicating slightly stronger adsorption of these 19-nor steroids. The selectivity to 5β is always lower with 19-nor steroids than with the corresponding 10β-methyl analogs, although differences are not so great.

Hydrogenation in Acidic Medium. The results of the hydrogenation in tetrahydrofuran and hydrobromic acid are summarized in Table 2. The hydrogenation was zero order in concentration of steroids. Similar to the hydrogenation in pyridine, the oxygen functions enhance the reactivity of the steroids and lower the selectivity to 5β. As observed in pyridine, 11,17-dioxo steroid **1g** showed the greatest reactivity and afforded the lowest yield of 5β-product. High reactivities of **1g** and **1e** are more pronounced in competitive hydrogenation than in individual hydrogenation and this suggests that under acidic condition 11- and 17-oxo groups may contribute to adsorption to the catalyst probably at the α-face. In contrast to the hydrogenation in pyridine, the rates of hydrogenation of 19-nor steroids are all far greater than those of the corresponding 10β-methyl analogs. The selectivity to 5β is also much higher for the 19-nor steroids where the yields of 5β-products were almost quantitative.

Discussion

The Effect of 10β-Methyl Group. The course of catalytic hydrogenation of α,β-unsaturated ketones over palladium catalysts has been discussed in several papers with respect to product stereochemistry.[2,4–7] It appears likely that in basic or acidic conditions hydrogen adds *via* 1,4, rather than 1,2, to the unsaturated system. In the case of 3-oxo-4-ene steroids, the formation of 5β-compounds increases in both basic and acidic media, while with 2-octalone high stereoselectivity to the *cis* isomer was obtained only in acidic medium.[2]

As seen from the results in Table 1, the reactivities of 19-nor-steroids **2c**, **2d**, and **2e** are almost the same with or only slightly larger than those of the corresponding 10β-methyl analogs. The stereoselectivity to 5β always decreases with the 19-nor steroids, although the degree of the decrease is not great (98.5→95% with **2c**; 93→85% with **2d**; 92.5→89% with **2e**). In view of the rather small effects of 10β-methyl group on the rate and the product stereochemistry, it would be reasonable to assume that the transition state which may control the product is in an sp^3-like conformation at C-5. In this conformation, the formation of 5α isomer would be more favorable for 19-nor steroids than for 10β-methyl steroids, because in the transition state leading to 5α isomers the interaction between an axial 2β-hydrogen and 10β-methyl group lacks in 19-nor steroids (see Fig. 1). On the other hand, at the transition state leading to 5β isomers (Fig. 2), the energy difference between both series of the steroids would be rather small, because 10β-methyl group takes an equatorial conformation with respect to the ring A. Rather small differences in reactivities between 19-nor and 10β-methyl steroids would thus be plausible if we consider that the major products are 5β isomers for both series of the steroids. Accordingly, the increase in the formation of 5α isomers with 19-nor steroids is considered to be due to an increase in the rate of formation of 5α isomers.

In contrast to the results in pyridine, 19-nor steroids are hydrogenated much more rapidly in tetrahydrofuran/hydrobromic acid than the corresponding 10β-methyl steroids (Table 2). This result strongly suggests that in the presence of acid the product controlling transition state is in an sp^2-like conformation at C-5 and the attack of hydrogen from the β-face to C-5 is strongly hindered by 10β-methyl group. Almost exclusive formation of 5β isomers from 19-nor steroids in the presence of acid is thus considered to be a result of a great increase in the rate of β-addition of hydrogen. It is further noted that some favorable β-face adsorption in 19-nor steroids may also contribute to the increase of 5β-products.

The Effects of Functional Groups. It is well known that the stereochemistry of hydrogenation of 3-oxo-4-ene steroids is considerably influenced by the substituents which are located far from the reaction site.[8] The nature of the substituent effect, however, has not clearly been understood yet. Some models for explaining it have been discussed, *e.g.*, by Kirk and Hartshorn.[6] Henbest and coworkers have pointed out some similarities in the substituent effects between catalytic hydrogenation and alkaline epoxidation of 3-oxo-4-ene steroids.[9,10]

The results on the kinetic study (Tables 1 and 2) indicate that the compounds having the oxygen functions which may decrease the 5β/5α ratio of product are generally more reactive than those not carrying such functions (compare **1d**, **1e**, **1f**, and **1g** with **1a** and **1b**). The only exception to this is the case of **1c** in pyridine where the rate of hydrogenation is greater than that of **1a** or **1b** and the selectivity to 5β is very high. The compound **1g** with 11,17-dioxo group is noteworthy in that in both basic and acidic media it is definitely more reactive and affords considerably lower yields of 5β-product, than the other compounds investigated. In general, the effects of the oxygen functions are very similar in basic and acidic conditions, as shown in Fig. 3. Since the high stereoselectivity to 5β is obtained in both basic and acidic conditions which can assist polarized adsorption

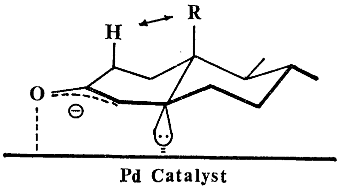


Fig. 1. The transition state leading to 5α-product in an sp^3-like conformation at C-5 (R=Me or H).

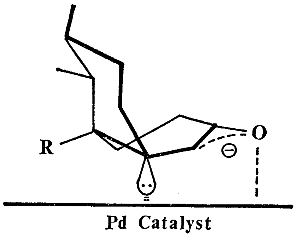


Fig. 2. The transition state leading to 5β-product in an sp^3-like conformation at C-5 (R=Me or H).

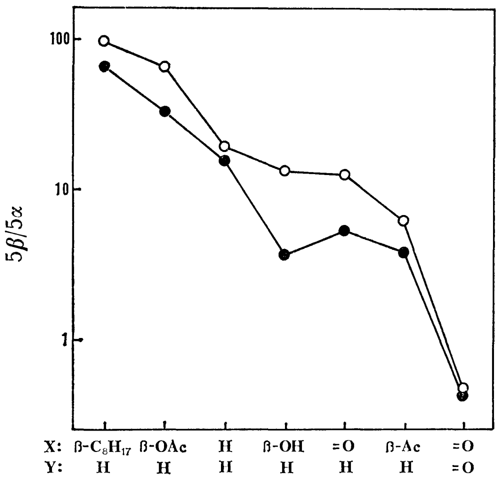


Fig. 3. Effects of substituents on 5β/5α ratio of product.

○: Hydrogenation in pyridine; ●: hydrogenation in THF/HBr.

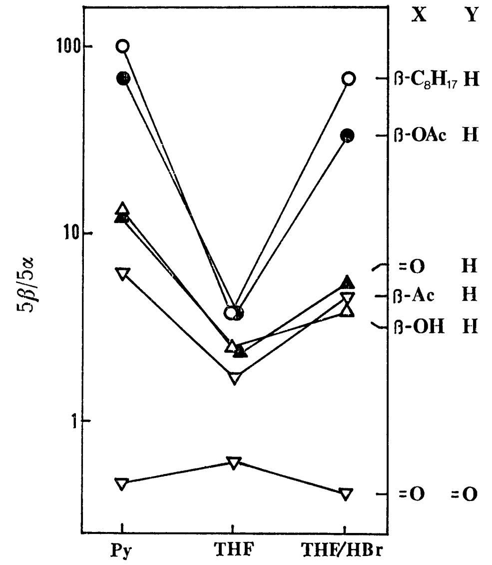


Fig. 4. Effects of media on 5β/5α ratio of product.

of the substrate onto the catalyst, it would be reasonable to consider that the electron-attractive oxygen functions may act in opposition to the π-electron polarization toward 3-oxo group, as suggested by Kirk and Hartshorn for the formation of a 4β,5β-bonded surface complex. Further, it is supposed that the interaction of the substrate with pyridine or hydrogen bromide would be stronger in a polarized state and under such circumstances the rate of hydrogenation would be depressed.[11] Hence the hydrogenation in a less polarized state would result in an increased rate as well as a decreased 5β/5α ratio of the product, as it is supposed to be the case with **1g**. This explanation is further supported by the fact that with **1g** the 5β/5α ratio of the product obtained in tetrahydrofuran was not much different from those observed in pyridine or in tetrahydrofuran and hydrobromic acid, while with other compounds the 5β/5α ratios distinctly increased in pyridine and tetrahydrofuran/hydrobromic acid, compared to those in tetrahydrofuran (see Fig. 4).

Experimental

General. All hydrogenations were carried out at 25 °C and atmospheric pressure in a small glass apparatus driven vibrationally. The compound to be hydrogenated (0.0569 mmol) was added in a solution after the catalyst (3 mg) had been shaken with hydrogen in the reaction medium for 20 min. The combined volume of the solution was 1.8 ml. In competitive hydrogenation an equimolar mixture of 0.0285 mmol of each compound was hydrogenated. Hydrogen bromide was added as a THF solution after the catalyst had been shaken with hydrogen for 20 min, and the mixture was further shaken with hydrogen for 30 min prior to the addition of the compound. The reaction mixture was taken into a microsyringe through a silicone rubber plug in the course of hydrogenation and analyzed by GLC using OV-17 as a stationary phase.

Solvent. Pyridine was treated with Raney nickel, dried over potassium hydroxide, and then distilled. THF was purified using $LiAlH_4$ as described previously.[1]

Catalyst. The palladium black used as the catalyst was prepared by reduction of palladium hydroxide in water.[12]

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References

1) Part IV: N. Tsuji, J. Suzuki, M. Shiota, I. Takahashi, and S. Nishimura, *J. Org. Chem.*, **45**, 2729 (1980).

2) For a review, see R. L. Augustine, *Adv. Catal.*, **25**, 56 (1976).

3) H. J. E. Loewenthal, *Tetrahedron*, **6**, 269 (1959).

4) R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, and M. J. Sisbarro, *J. Org. Chem.*, **34**, 1075 (1969).

5) M. G. Combe, H. B. Henbest, and W. R. Jackson, *J. Chem. Soc., C*, **1967**, 2467.

6) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier Publishing Co., New York (1968), p. 81.

7) T. Lolek, I. Malunowicz, and A. Mironowicz, *Polish J. Chem.* **53**, 453 (1979).

8) K. Mori, K. Abe, M. Washida, S. Nishimura, and M. Shiota, *J. Org. Chem.*, **36**, 231 (1971) and references cited therein.

9) H. B. Henbest and W. R. Jackson, *J. Chem. Soc., C*, **1967**, 2459.

10) H. B. Henbest, W. R. Jackson, and I. Malunowicz, *J. Chem. Soc., C*, **1967**, 2469.

11) Pyridine and hydrogen bromide are both catalyst poisons and may also contribute to the depression in the rate as such.

12) S. Nishimura, M. Ishige, and M. Shiota, *Chem. Lett.*, **1977**, 535.