CHEMISTRY LETTERS, pp. 535-538, 1977. Published by the Chemical Society of Japan

STEREOCHEMISTRY OF THE HYDROGENATION OF 5α- AND 5β-CHOLESTAN-3-ONES OVER PLATINUM METALS. AN UNUSUAL ASPECT WITH PALLADIUM AND PLATINUM

Shigeo NISHIMURA,* Masayoshi ISHIGE,** and Michio SHIOTA**

*Department of Industrial Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184

**Chemical Laboratory, Ochanomizu University, Bunkyo-ku, Tokyo 112

Hydrogenation of 5α-cholestan-3-one with palladium gives an equatorial 3β-ol while hydrogenation of 5β-cholestan-3-one under the same condition affords an axial 3β-ol with high stereoselectivities in alcohols and tetrahydrofuran. This unusual hydrogenation stereochemistry is also seen with platinum in alcohols, but not with platinum in tetrahydrofuran nor with ruthenium, osmium and iridium in t-butyl alcohol. With rhodium in ethanol, the both ketones afford the axial alcohols in high selectivities.

During our studies on the stereochemistry of hydrogenation of cycloalkanones over transition metals, we have found an unusual aspect in the stereochemistry of hydrogenation of 5α- and 5β-cholestan-3-ones (1 and 2) over palladium and platinum. Hydrogenation of 1 with palladium in t-butyl alcohol at 26°C and atmospheric pressure gave an equatorial 3β-ol in a selectivity of 98%, while hydrogenation of 2 under the same conditions resulted in the formation of an axial 3β-ol in a selectivity of 95%. The high selectivities to the equatorial and axial alcohols were also obtained with isopropyl alcohol and tetrahydrofuran as solvents. Basing simply on the chair conformations of steroids, the stereochemistry of hydrogenation is expected to be similar for 1 and 2 whether the medium is neutral or acidic.[1,2] It is, therefore, not usual that the equatorial alcohol is produced predominantly from 1 and the axial alcohol from 2 under the same conditions. This unusual hydrogenation stereochemistry has also been observed with platinum in alcohols, with less stereoselectivities than with palladium. But in contrast to palladium, it was not observed with platinum in tetrahydrofuran, nor with ruthenium, osmium and iridium

in t-butyl alcohol. In these cases the equatorial alcohols were formed in excess from the both ketones. The unusual aspect has also become not prominent with cyclohexane as solvent. The results with rhodium were greatly dependent on the solvents used. Thus in ethanol both 1 and 2 gave the corresponding axial alcohols in high selectivities (95 and 93%, respectively), while in t-butyl alcohol the selectivities to the axial alcohols were only 17 and 42%, respectively. The results are summarized in Table 1, together with those obtained with 4-t-butylcyclohexanone (3) for comparison.

In contrast to the results with the steroid ketones, hydrogenation of 3 with palladium in isopropyl or t-butyl alcohol is not stereoselective, the cis- and trans-alcohols being formed in almost equal amounts. Although hydrogenation of 3 was carried out in a considerably higher concentration than in the case of the steroid ketones, decreasing the concentration to one-tenth has been found not to affect the stereochemical composition of the resulting alcohols in an experiment with palladium and isopropyl alcohol (see footnote b, Table 1). The formation of the equatorial alcohols in larger amounts with 1 and 2 than with 3 over ruthenium, osmium and iridium is plausible if we consider that the β-methyl at C-10 in 1 and the C-9 group in 2 oriented axially with respect ring A may interfere with the adsorption on the equatorial side of the 3-keto groups. With rhodium in ethanol, 3 gave rise to the cis-alcohol in a high selectivity of 97%[3] in line with the results on the steroid ketones.

Major formation of 3β-methoxycholestanes has previously been observed in the hydrogenation of both 1 and 2 with palladium in methanol[4] and with platinum in methanol and hydrobromic acid.[5] 19-Nor-5α-cholestan-3-one also afforded a 3β-methoxy derivative with palladium in methanol.[6] It has also been reported that biohydrogenation of 1 and 2 with a bacterium gave the corresponding 3β-ols.[7]

The mechanism of the unusual hydrogenation stereochemistry remains uncertain. Since 1 and 2, both unhindered ketones, were hydrogenated under the same conditions, it would not be probable that the unusual results are accompanied by a drastic change in the mechanism or product-controlling step between 1 and 2. The fact that the unusual aspect was observed with an alcohol or ether (in the case of palladium) as solvent and was not prominent in cyclohexane suggests that the solvents which can function as Lewis bases play an important role, probably coupled with the ionized hydrogen on the catalyst surface.[4,8] This consideration comes from the fact that the unusual results were obtained over the metals which can catalyze an acetal formation in hydrogenation of a ketone or enol ether in alcohols such as palladium and

Table 1. % Unstable Isomer in Alcohol Products from Hydrogenation of 5α- and 5β-Cholestan-3-ones (1 and 2) and 4-t-Butylcyclohexanone (3)[a)]

Catalyst	Solvent	Ketone hydrogenated		
		1	2	3
Pd	t-BuOH	2.0	95	47
Pd	i-PrOH	1.1	98.5	55[b)]
Pd	Tetrahydrofuran	1.3	92	80
Pd	Cyclohexane	48	80	49
Pt	t-BuOH	15[c)]	77[d)]	80[e)]
Pt	i-PrOH	17[f)]	78[g)]	76[h)]
Pt	Tetrahydrofuran	28[i)]	33[j)]	62[k)]
Pt	Cyclohexane	54[l)]	43[m)]	58[n)]
Ru	t-BuOH	44	44	62
Os	t-BuOH	33	37	60
Ir	t-BuOH	26	24	34
Rh	t-BuOH	17	42	41
Rh	EtOH	95[o)]	93[p)]	97[q)]

a) Cholestan-3-one (10 mg) or 4-t-butylcyclohexanone (100 mg) was hydrogenated with 3-5 mg of the catalyst in 2-3 ml of the solvent at 25 or 26°C (for t-BuOH) and atmospheric pressure. The products were analyzed, with a few exceptions, after complete hydrogenation by glpc using the columns of OV-17 for 1 and 2 with trimethylsilylation and PEG 20M for 3. It was confirmed that the isomerization of the axial to equatorial alcohols does not occur under the conditions employed and that the composition of the products does not change to any appreciable extents during the course of hydrogenation. The products other than alcohols are given below in percent. b) 4-t-Butyl-1-isopropoxycyclohexanes, 55. With 10 mg of 3 in 2 ml of the solvent, the selectivity to the cis-alcohol was 54%. c) 5α-Cholestane, 5. d) 5β-Cholestane, 15. e) t-Butylcyclohexane, 24. f) 5α-Cholestane, 9. g) 5β-Cholestane, 24. h) t-Butylcyclohexane, 36. i) 5α-Cholestane, 10. j) 5β-Cholestane, 8. k) t-Butylcyclohexane, 19. l) 5α-Cholestane, 6. m) 5β-Cholestane, 3. n) t-Butylcyclohexane, 27. o) 3-Ethoxy-5α-cholestanes, 16. p) 3-Ethoxy-5β-cholestanes, 9. q) 1-Ethoxy-4-t-butylcyclohexanes, 7.

platinum[9)] and not with the metals which are not active in the acetal formation such as ruthenium, osmium and iridium.[4,8)] The different results with platinum between in alcohols and in tetrahydrofuran suggest that a change in the product-controlling step has occurred with the change of the solvents.

The stereochemistry of hydrogenation of alicyclic ketones in neutral solvents has been found very sensitive to the methods of preparation of the catalysts. The unsupported metals used in this study were prepared by hydrogen reduction of the

corresponding hydroxides (Pd, Pt, Rh, Ru, Ir) or oxide (Os) in water at atmospheric or high pressure. The water usually became acidic or slightly acidic after the reduction. After decanting off the water and washing the precipitates with water, the reduction process was repeated further with addition of new portions of water, until the water became no more acidic after the reduction. The metals were dried over silica gel and, before adding the ketones, were shaken with hydrogen in the solvent.

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9) Rhodium is one of the metals which can catalyze the acetal formation.[4,8] Although in ethanol the stereochemistry of hydrogenation with this metal is quite different from those with palladium and platinum, the favorable formation of the equatorial alcohol from 1 over from 2 is seen with the metal in t-butyl alcohol (see Table 1).

(Received March 3, 1977)