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Stereochemistry of the Palladium-Catalyzed Hydrogenation of 3-Oxo-4-ene Steroids[1]

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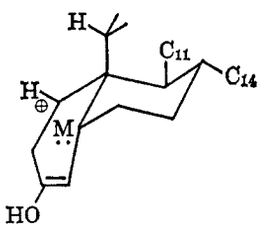
Recently, the effect of solvents on the stereochemistry of the catalytic hydrogenation of α,β-unsaturated ketones has been reported with two series of ketones.[3,4] Augustine has shown that under acidic conditions $\Delta^{1,9}$-2-octalone and 2-benzoyl-1,2,3,4,8,8a-hexahydro-6-isoquinolone give the corresponding saturated *cis* ketones predominantly in the hydrogenation with a 10% palladium–charcoal as a catalyst.[3] On the other hand, McQuillin, Ord, and Simpson have reported that the use of less polar solvents or the presence of acid causes the decrease of the formation of 5β ketones, the ring A/B-*cis* isomers, in the hydrogenation of cholest-4-en-3-one and testosterone with a palladium–charcoal catalyst.[4] Thus, the effect of acid on the stereochemistry of the hydrogenation led to completely different results with the two series of ketones. Apparently the main difference in these studies seems to come from the fact that the former deals with the ketones having no angular methyl group, while the latter with those having such a group at C-10 position. In order to obtain more comparable data and to clarify the cause of this difference in results, three steroid ketones with and without the C-19 angular methyl group, cholest-4-en-3-one (I), testosterone (II), and 19-nortestosterone (III), have been hydrogenated using prereduced palladium oxide and palladium hydroxide as catalysts. Unsupported catalysts were used in this study, because supported catalysts seemed to be more difficult to be prepared in a state free from alkaline or acidic substances. The acetates of II and III have also been subjected to hydrogenation in order to know the effect of the 17-hydroxyl group on the stereochemistry of the hydrogenation.

Table I summarizes the ratio of saturated 5β to 5α ketone formed in the hydrogenation of I, II, III, and the acetates of II and III with palladium black catalysts at 25° and atmospheric pressure of hydrogen. The hydrogenation in ethanol was complicated by an unexpected reaction: the resulting saturated ketones are easily liable to further reduction to give the corresponding ethoxy compounds along with slight amounts of saturated alcohols.[5] This reaction is strongly depressed with addition of alkali or hydrochloric acid. Because of an extensive occurrence of this reaction, the results obtained in ethanol will not be reliable ones, although the hydrogenations were carried out under the conditions to minimize the formation of the ethoxy compounds by using a smaller ratio of catalyst to substrate and a shorter reaction time. Palladium hydroxide was used preferentially in the hydrogenations in neutral alcoholic solutions, because palladium oxide of the Adams type probably contains a small amount of alkaline substances,[6] which may affect the formation of 5β ketone to increase.[4,7]



M = Catalyst metal

Figure 1.

TABLE I

RATIO OF 5β TO 5α KETONE FORMED IN THE HYDROGENATION OF 3-OXO-4-ENE STEROIDS WITH PALLADIUM CATALYSTS

	Compd				
Solvent	I	II	III	Acetate of II	Acetate of III
EtOH + 20% NaOH, 0.1 ml	11.5	6.3[a]	2.09	...	...
t-BuOH	1.35[a]	...	...	...	...
i-PrOH	1.38[a]	0.74[a]	1.68[a]	0.80[a]	1.10[a]
EtOH	1.34[a]	0.52[a]	1.25[a]	1.43[a]	2.04[a]
EtOH + 3 *N* HCl, 0.1 ml	1.44	0.46	1.18	1.95[a]	3.93[a]
AcOH	2.85	0.52	2.02	1.48[a]	4.44[a]
CF_3COOH	3.12	...	...	...	...
AcOH + 3 *N* HCl, 0.1 ml	4.56	0.95	3.17	2.70[a]	12.1[a]

[a] Palladium hydroxide was used as the catalyst. In other cases palladium oxide catalyst was used.

From the results of Table I it is obvious that the formation of 5β-ketone increases under acidic conditions irrespective to the ketones investigated. These results are in line with those reported by Augustine,[3] but not with those reported by McQuillin and his coworkers that the presence of acid decreased the yield of 5β-ketone in the hydrogenation of I and II.[4] For the predominant formation of *cis* ketones in acidic medium, Augustine[3] has proposed a mechanism which involves a 1,4 addition of hydrogen *via* the protonated ketone as an intermediate. When his explanation is applied to the steroid ketones having the C-19 methyl

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(3) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); R. L. Augustine and A. D. Broom, *ibid.*, **25**, 802 (1960); R. L. Augustine, *ibid.*, **28**, 152 (1963).

(4) F. J. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

(5) A direct formation of the ethoxy compounds from the starting unsaturated ketones may also be possible, since such compounds were found in the products at the intermediate stages of the hydrogenation. Details of this reaction will be published elsewhere.

(6) The palladium hydroxide used in this study probably contains a smaller amount of alkali than the palladium oxide of Adams type, since the resulting catalyst catalyzes the formation of ethoxy compounds from ketones in ethanol more efficiently than the catalyst from the oxide, the reaction being depressed by the presence of alkali. *Cf.* C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.*, **76**, 229 (1954).

(7) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *ibid.*, **72**, 5524 (1950).

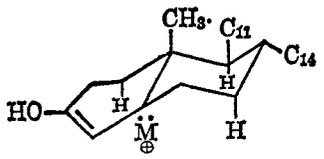

Figure 2.

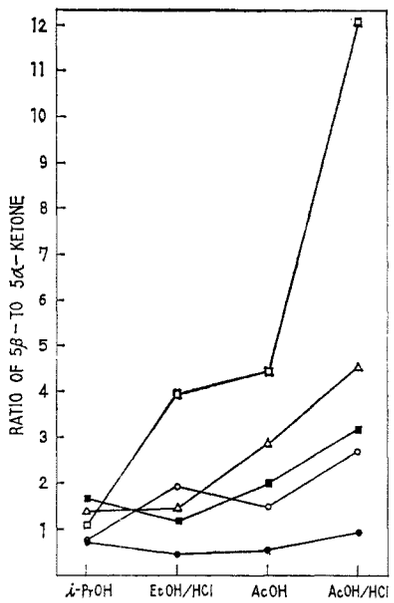

Figure 3.—Effect of acidic solvents on the $5\beta/5\alpha$ ratio of ketones formed in hydrogenation of 3-oxo-4-ene steroids with palladium catalyst: △, cholest-en-3-one; ●, testerone; ○, testerone acetate; ■, 19-nortesterone; □, 19-nortesterone acetate.

group, there exist two 1,3 interactions between two hydrogen atoms, one axial and one methyl hydrogen, and the catalyst surface at the position of the methyl group giving the greatest interaction in the intermediate leading to the 5β isomer as shown in Figure 1. On the other hand, there are three such interactions in the structure leading to the 5α isomer (Figure 2). Thus, the formation of 5β ketone will be more favored sterically even in the ketones having the angular methyl group.[8] The hydrogenation in the absence of alkali or acid will proceed with a less stereospecificity because the species hydrogenated may be a less polarized ketone in which the $5\beta/5\alpha$ ratio of the product will be controlled by an interaction of the π electrons of the unsaturated ketone and the catalyst surface. The fact that I gives much greater yields of 5β ketone than II and even than III in acidic media suggests that the 17-hydroxyl group may have some effect to decrease the formation of 5β ketone probably in combination with acids. This may be presumed further by the finding that in acidic media the acetates of II and III give much greater yields of 5β ketone than II and III, respectively (see Figure 3).

Experimental Section

Materials.—The substances hydrogenated are all known compounds of the following melting points:[9] cholest-4-en-3-one, 80.0–80.5° (lit.[10] 82°); testosterone, 155–156° (lit.[10] 155°); testosterone acetate, 140–140.5° (lit.[11] 140–141°); 19-nortestosterone, 124–125° (lit.[10] 124°); 19-nortestosterone acetate, 62–67° (lit.[12] 91–93°). Purity of these compounds was further ascertained by gas–liquid partition chromatography.

Catalysts.—Palladium oxide was prepared by the method of Shriner and Adams.[13] Palladium hydroxide was prepared by adding a slight excess of lithium hydroxide solution to a hot aqueous solution of palladium chloride, the precipitate being washed with hot distilled water thoroughly until the filtrate became neutral to thymol blue.

Hydrogenation.—The substrate (30–100 mg) dissolved in 10–15 ml of a solvent was shaken in a glass bottle with 10–30 mg of prereduced palladium oxide or palladium hydroxide at 25° and atmospheric pressure of hydrogen until hydrogen uptake ceased. In the hydrogenation using ethanol as the solvent, the absorption of hydrogen did not cease with the uptake of 1 mole, and so when 1 mole of hydrogen was absorbed, the reaction was stopped to examine the products at that stage.

Analysis of Products.—The products were analyzed by means of gas–liquid partition chromatography using a column of 1% SE-52 silicone on Chromosorb W (30–60 mesh). The following conditions were used for the analyses: for the products from cholestenone, column length 1.5 m, column temperature 238°; for the products from testosterone, 19-nortestosterone and its acetate, column length 2.25 m, column temperature 218°; for the products from testosterone acetate, column length 2.25 m, column temperature 228°. Small amounts of hydrogenolyzed products (1–5%) were formed in all the hydrogenations, but the products contained saturated alcohols in only slight amounts. This, if necessary, was confirmed by the analysis of the products treated with acetic anhydride and pyridine, since the retention times of the saturated 5α alcohols obtained from I and II were nearly the same with those of the corresponding saturated 5β ketones.

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(8) The same conclusion may also be deduced in hydrogenation of 4,5-unsaturated steroids in neutral media [H. I. Hadler, *Experientia*, **11**, 175 (1955)]. However, it may be suggested that the steric control will be more pronounced in the formation of the intermediates as shown in Figures 1 and 2, since the adsorption between a carbonium ion and the catalyst surface is involved.

(9) All melting points were measured on a hot-stage apparatus and were not corrected.

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

(11) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1275 (1935).

(12) J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955). The acetate was prepared from the 19-nortestosterone of mp 124–125°. Although the melting point of the resulting acetate was considerably lower than that reported in the literature, it was confirmed by gas chromatography that the acetate contained only a trace of impurities.

(13) R. L. Shriner and R. Adams, *ibid.*, **46**, 1683 (1924).

Steroids. CCXCV. A Novel Ring A Aromatization Reaction[1]

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The aromatization of ring A in steroids containing a CH_3 group at C-10 has been mainly accomplished starting either from $\Delta^{1,4}$-3 ketones[2] or more recently through microbiological transformation of 19-oxygenated steroids.[3] The reactions involved in these trans-

(1) Steroids. CCXCIV: C. Beard, I. Harrison, L. Kivkham, and J. Fried, *J. Am. Chem. Soc.*, in press.

(2) L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p 479.

(3) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **83**, 4627, 4631 (1961). C. J. Sih, S. S. Lee, Y. Y. Tsong, K. C. Wang, and F. N. Chang, *ibid.*, **87**, 2765 (1965), and earlier papers.