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CATALYTIC REDUCTION OF SOME 4-PIPERIDONES

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Abstract—The catalytic reduction of four different 4-piperidones was investigated in neutral and acidic media. The stereochemistry of these reductions was found to be different from that of cyclohexanones.

THE reduction of a number of 4-piperidones with sodium–n-butanol, aluminium isopropoxide–isopropanol and LAH has been reported.[1,2] Each piperidone afforded two epimeric piperidin-4-ols, the α-form with an equatorial OH and the β-form with an axial OH. The stereochemistry of these piperidinols was established[1,2] and the kinetics of acetylation,[3] as well as IR[3] and NMR spectra[4] confirmed the configurational assignments. We now report the catalytic reduction of these piperidones using Adams' platinum oxide catalyst.

The hydrogenations were carried out in neutral, weakly acidic and strongly acidic media. When strongly acidic conditions were used, any acetate that may have been formed was hydrolyzed during preliminary treatment (Experimental). When treated under identical conditions, the piperidinols did not undergo epimerization. The composition of the reduction product was determined by column chromatography on alumina. The results recorded in Table 1 show that: (1) 1,2,2-Trimethyl-6-phenyl-4-piperidone affords only the β-piperidinol (axial OH) irrespective of the medium of hydrogenation. (2) Other piperidones give the β-forms only in neutral medium. (3) Maximum yields of the α-piperidinol (equatorial OH) are obtained under acidic conditions. (4) In strongly acidic medium, the yield of the reduction product is significantly low, much of the unreacted ketone being recovered. (5) The presence of Me groups α to the CO increases the yield of the β-form (compare entries 1,4 and 7). The observations (2) to (4) are contrary to results of analogous studies on substituted cyclohexanones. Hydrogenation of hindered and unhindered cyclohexanones in strongly acidic media affords cyclohexanols with an axial OH and in neutral media yields the equatorial alcohol, if the CO is not hindered and the axial alcohol, if it is strongly hindered.[5] It is generally accepted that catalytic hydrogenation occurs through the *cis* addition of hydrogen to that side of a molecule which presents least steric hindrance to adsorption on the catalyst surface.[6,7] Accordingly, the least hindered arrangement of the chair form of the piperidone ring over the catalyst surface would lead to the addition of hydrogen from the equatorial side resulting in the formation of an axial OH group.[8] For example, 1-methyl-2,6-diphenyl-4-piperidone (I) should yield the axial alcohol (II, β-epimer). The unexpected results obtained in the reduction of the 4-piperidones are even more significant when

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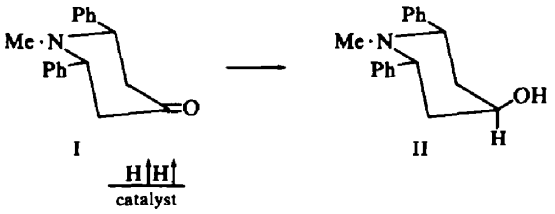
TABLE 1. CATALYTIC REDUCTION OF 4-PIPERIDONES

No.	4-Piperidone	Medium	Time (hr)	Total recovery %	Composition of the product		
					α-Piperidinol %	β-Piperidinol %	Unreacted piperidone %
1	1-Methyl-2,6-diphenyl	MeOH	4	85	75	25	—
2	1-Methyl-2,6-diphenyl	AcOH	3	84	100	—	—
3	1-Methyl-2,6-diphenyl	AcOH–HCl	2	81	54	—	46
4	1,3-Dimethyl-2,6-diphenyl	MeOH	4	100	27	73	—
5	1,3-Dimethyl-2,6-diphenyl	AcOH	3	99	100	—	—
6	1,3-Dimethyl-2,6-diphenyl	AcOH–HCl	2	94	30	—	70
7	1,3,5-Trimethyl-2,6-diphenyl	MeOH	4	97	32	68	—
8	1,3,5-Trimethyl-2,6-diphenyl	AcOH	3	96	100	—	—
9	1,3,5-Trimethyl-2,6-diphenyl	AcOH–HCl	2	91	13	—	87
10	1,3,5-Trimethyl-2,6-diphenyl	AcOH–HCl	6	78	15	—	85
11	1,2,2-Trimethyl-6-phenyl	MeOH	4	97	—	100	—
12	1,2,2-Trimethyl-6-phenyl	AcOH	3	91	—	100	—
13	1,2,2-Trimethyl-6-phenyl	AcOH–HCl	2	88	—	19	81

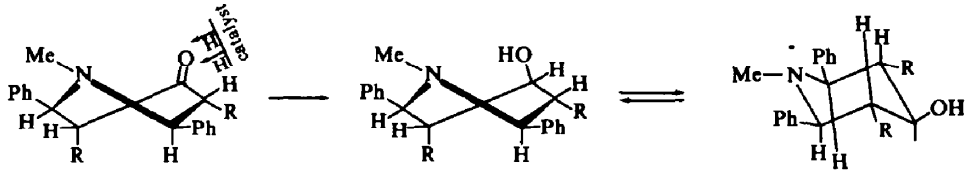


compared to the hydrogenation of *cis*-3,5-diphenylcyclohexanone (configurationally analogous to I) which gives the axial *trans*-cyclohexanol irrespective of the medium.[9]

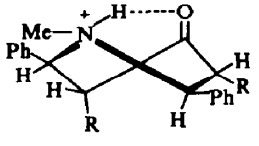
It is considered that the more stable equatorial alcohols are formed in neutral or weakly acidic media through an equilibration of the following type:

Axial alcohol ⇄ ketone ⇄ Equatorial alcohol

Studies by Wicker[8] have shown that such dehydrogenation–hydrogenation equilibria are possible in the presence of Adams' Platinum oxide at higher temperatures, higher catalyst concentration and in the absence of acids. Since the equatorial α-piperidinols are exclusively formed under acidic conditions (entries 2,3,5,6,8,9 and 10 in Table 1), it may be concluded that equilibria of the type shown are not involved in the reduction of the piperidones. Furthermore, the β-piperidinols have been recovered unchanged after subjecting them to the conditions of hydrogenation. Since hydrogenation from the axial side of the chair form of a piperidone is hindered by the β-axial H atoms, the only possibility for the formation of the equatorial alcohol is adsorption of the flexible form (III) on the catalyst surface and addition of hydrogen from the less hindered equatorial side. Ring flip to the chair form should result in the equatorial

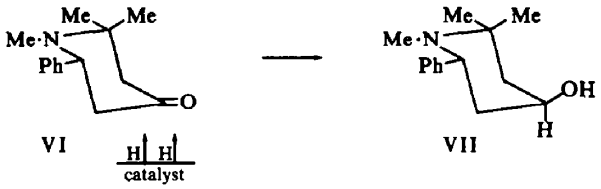


α-piperidinol (IV). In acidic media, the piperidones would exist largely in the protonated form. The exclusive formation of the equatorial alcohols from the 2,6-diphenylpiperidones in acidic media suggests that these react in the flexible form in such media. It is possible that the flexible form is favoured by interaction of the type V.



V, R = Me or H

Since only the β-piperidinol (VII; axial OH) results from 1,2,2-trimethyl-6-phenyl-4-piperidone (VI), this should react only in the chair conformation:



EXPERIMENTAL

Catalytic reduction of 4-piperidones

Neutral medium. The 4-piperidone (500 mg) was dissolved in anhyd MeOH (10 ml) and mixed with Adams' PtO_2 (75 mg). Hydrogenation was carried out at a H_2 press of 50 lb/sq inch using a low pressure Parr hydrogenation apparatus. After 4 hr the catalyst was filtered off and washed successively with MeOH and water. The filtrate free from MeOH was diluted with water and the ppt collected, after washing with water. The product after drying was subjected to chromatography.

Weakly acidic medium. The reduction was carried out as above using glacial AcOH (10 ml) in place of MeOH as the solvent. After 3 hr, the catalyst was removed and the product was isolated by neutralizing the acid with NH_4OH. In the case of 1,2,2-trimethyl-6-phenyl-4-piperidone, after removal of the catalyst, most of the AcOH was removed under reduced press and the residue worked up as in the previous case.

Strongly acidic medium. The hydrogenation was carried out using a soln of the piperidone (500 mg) in AcOH (10 ml) containing HCl (2 ml) and the PtO_2 (75 mg). A shorter duration (2 hr) avoided any possibility of equilibration. However, even longer duration (6 hr, entry 10 in Table 1) had no effect on the composition of the product. The product, a semi-solid, obtained after neutralization with NH_4OH, was dissolved in MeOH (10 ml) containing KOH (300 mg) and the soln was heated under reflux (7 hr), allowed to cool, diluted with water and extracted with ether. The ethereal soln was dried (Na_2SO_4), the solvent stripped off and the residue subjected to chromatography. E. Merck's Brockmann grade alumina was used and the details are given elsewhere.[2]

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