

P A R T I

REDUCTIVE ACTION OF KETONES WITH POTASSIUM HYDROXIDE
IN DIETHYLENE GLYCOL TO ALCOHOLS

CHAPTER I

PART - I

A short review on the reduction of ketones to alcohols in presence of bases and alcohols

The reduction of ketones by alcohols is well known. In Meerwein Ponndorf reduction with aluminium isopropoxide¹, there are a number of references in which sodium alkoxides effect reduction of ketones². The possibility of reducing quinone in the proposed manner had been realized in several experiments. It had been found that many alcohols in the presence of their corresponding alkoxides were capable of carrying out the reduction of quinone to a mixture of the four stereoisomers. The rates of reduction vary widely depending on the structure of the alcohol effecting reduction. Isopropanol, n-butanol, pentanol-3 and cyclo hexanol reduced quinone at reasonable rates but di-isopropyl - carbinol effected reduction at a barely observable rate. These results paralleled the observations of Baker and Adkins³ in their study of the establishment of equilibrium between pairs of alcohol-ketone systems by aluminium alkoxides (Oppenauer Oxidation - Meerwein Ponndorf reduction). They observed that di-isopropyl ketone and benzophenone were among the most slowly reacting ketones clarifies the failure. It was found that, ketones should be incapable of reduction by tertiary alcohols, the latter being incapable of oxidation by the ketones. In accord with this conclusion, quinone had been found to be completely stable in a boiling solution of potassium tertiary-

butoxide in tertiary-butyl alcohol under nitrogen. In fact when quinine was boiled with a solution of potassium in triethyl-carbinol, a reaction product was obtained in which no epiquinine, quinidine or epiquinidine could be detected.

It had been found that quinine should be stable and remain unequilibrated in primary and secondary alcohols free of carbonyl compounds. In such an experiment it was important to exclude air since alkoxides were oxidized by air to the corresponding carbonyl compounds. It was found that quinine was converted to quinone in a purely base catalyzed reaction when quinine was boiled with a solution of potassium in carefully purified triethyl carbinol under nitrogen, the main insoluble product (41.2%) was quinone. It had been demonstrated experimentally that quinine was convertible to quinone in the absence of oxidising agent by a type of disproportionation reaction that was apparently catalyzed by strong base. In pure ketone-free solvent, the equilibration might not, in fact, be initiated but the formation of quinone by the base catalyzed disproportionation proceeded at a slow rate. Therefore at the beginning of the reaction in ketone-free alcohol, quinine was being converted gradually to quinone. Quinone is, however, a carbonyl compound capable of catalyzing the equilibration reaction so that this reaction proceeded at an increasing rate as the concentration of carbonyl compound increased, until finally the reaction was identical to a normal equilibration reaction initiated by carbonyl impurities in the alcohol solvent. When quinine was treated with the potassium salt of triethyl carbinol, the oxidation-reduction mechanism of equilibration might not operate. Since no epibases are

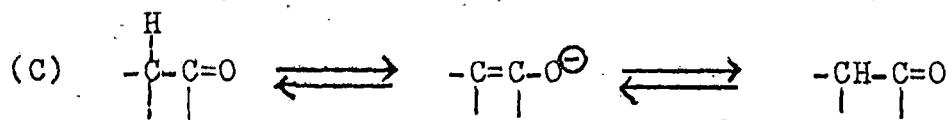
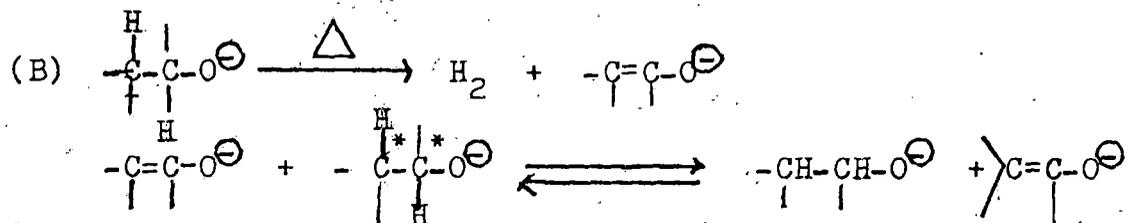
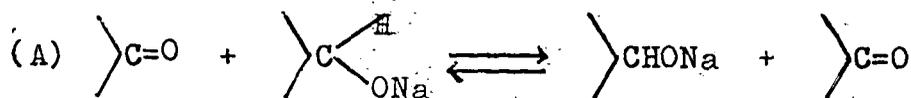
formed, the possibility of converting quinine to the epibases by a purely base catalyzed reaction was excluded. Therefore with a high degree of probability, the epibases formed only by the reduction of quinone.

An interesting difference in rate of reaction was observed when sodium was compared with lithium. The half life of quinine when boiled with sodium heptoxide in heptanol-2 containing 4.7 equivalents of benzo-phenone was 0.7 hr. On replacing the sodium by lithium heptoxide, the half life increased to 3.0 hrs. Since the equilibration required the catalytic action of strong bases, the decreased rate in the presence of lithium ion might be ascribed to the greater acidity of Li^+ in comparison with the more metallic Na^+ .

Huckel et al had failed to effect the epimerization of the fenchyl alcohols by using conditions which should accelerate dehydrogenation (sodium metal in boiling decahydronaphthalene). It was probable that the reaction failed not for want of the formation of fenchone, but rather because of the sluggish nature of the fenchone-fenchyl alcohol system.

Doering et al⁵ reported the equilibration of ketones and alcohols in presence of their respective alkoxides. They carried out reactions under nitrogen in a wholly glass apparatus specially designed to permit the withdrawal of aliquot portions without opening the system to air or interrupting the heating. Wagner Jauregg⁶ and Huckel⁷ suggested that equilibration was initiated by the dehydrogenation of alkali-alkoxides to aldehyde or ketone which then takes part in a Meerwein-Ponndorf Verley reduction and Oppenauer oxidation. Wagner

Jauregg had formulated the following scheme.



Doering, Cortes and Knox⁸ had presented considerable evidence in support of the mechanism (A & C) but had been unable to demonstrate (in case of quinine) the consequence of the mechanism, that optically active alcohols should not be racemized in the absence of oxidants.

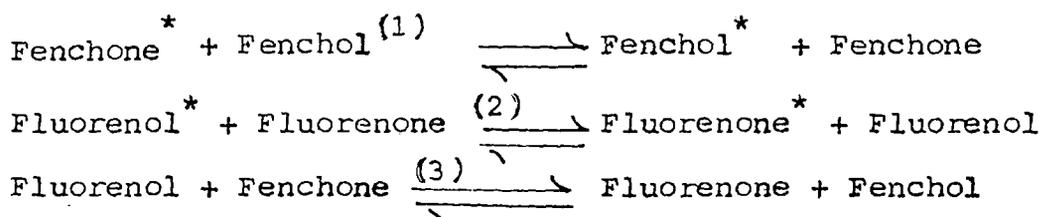
The racemization of (-) phenyl methyl carbinol by potassium tertiary butoxide at 100° was completely inhibited by excluding oxygen, K-peroxides and carbonyl compounds and that, other non racemizing conditions. The addition of the rapid oxidation-reduction system⁹, fluorenone (3 moles %) fluorenol (6 mole %) caused 56% racemization.

(-) 2 methyl butanol-1 stable to boiling for twenty hrs with 5 mole % of sodium but racemized in a few hrs by adding 5 mole % of benzophenone. Aluminium isopropoxide as catalyst no racemization occurred until an oxidant benzophenone was added. It shows that the

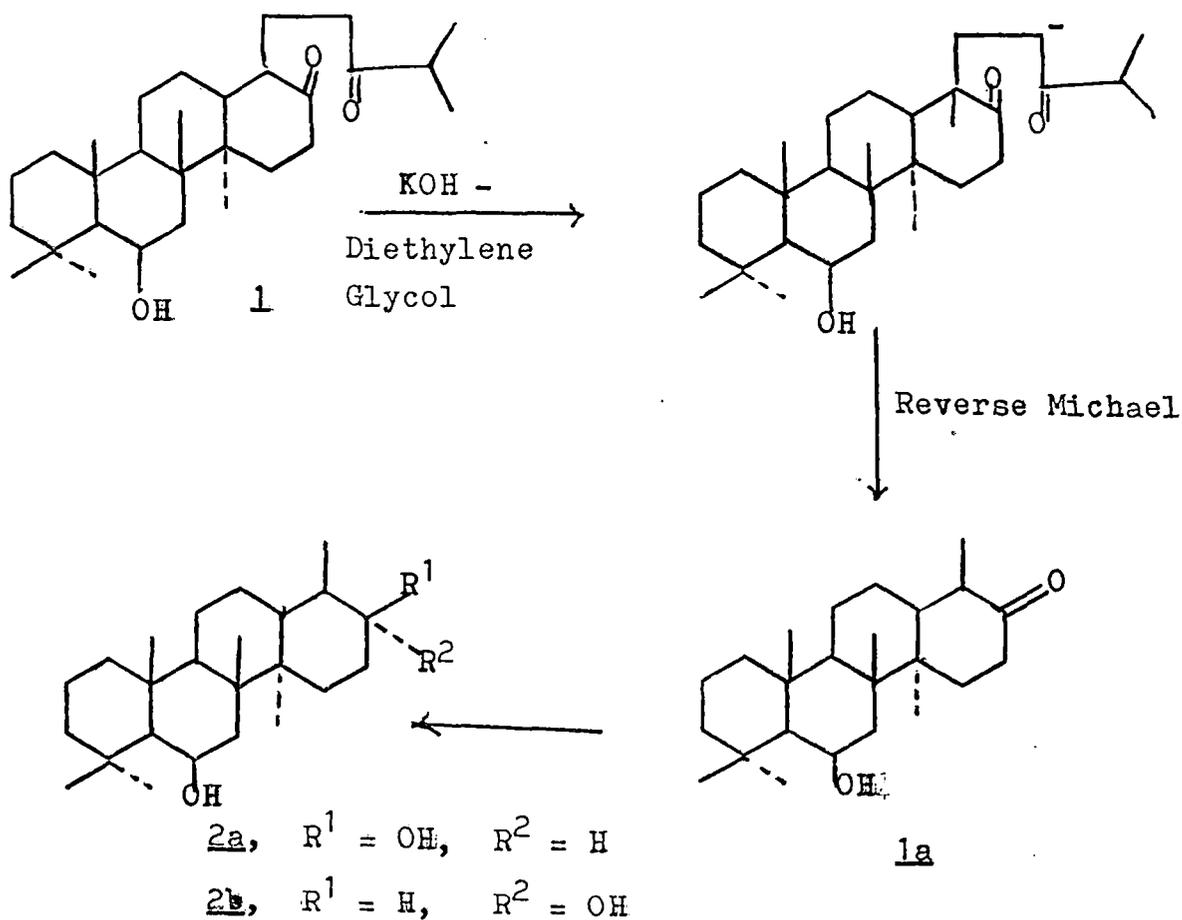
presence of carbonyl compound is necessary condition for effecting the stereochemical equilibration of alcohols and it means that a reversible oxidation-reduction process is the essential mechanism of the equilibration.

The structural consequence of mechanism (B), that it should be impossible stereochemically to equilibrate those secondary alcohols in which lack of α -hydrogen prohibits dehydrogenation to a related enolate ion. It had been given temporary confirmation in the negative observation that α and β fenchol could not be epimerized even under enough drastic conditions to form the corresponding ketone, fenchone¹⁰. But both α and β -fenchol could be epimerized when the rapid oxidation reduction system fluorenol fluorenone was added.

The failure to epimerized the fenchols in the presence of fenchone and the vain attempt to effect the partial racemization of quinine in the presence of quinone indicated that excessively slow rates of oxidation-reduction conspired to make the necessary presence of carbonyl compound an insufficient condition for stereochemical equilibration. The stereochemical equilibration was catalyzed by adding a much more rapid oxidation - reduction system, e.g. in the very slow reacting fenchol-fenchone system (1) the addition of fluorenol and fluorenone, which interact very rapidly (2) introduced a cross reaction (3) of intermediate rate that caused in the more rapid establishment of equilibrium (1)



From literature it has been found that Barton et al¹¹ when refluxed compound 1 with diethylene glycol in potassium hydroxide and a stream of nitrogen passed through the mixture the compound 1 was converted to 2a and 2b. In this case keto compound was first converted to ketone 2a by reverse Michael reaction and the 1a reduced to epimeric alcohols.



Similar observation was made by Halsall et al¹², they refluxed 3,5-dioxo-4,5-secolupane 3 in diethylene glycol with potassium hydroxide in nitrogen and found that 3 was converted to 4.

