20.2 Arndt Eistert Synthesis (Rearrangement)

Arndt-Eistert synthesis consists in the conversion of a carboxylic acid into its next higher homologue or its derivative, i.e. the chain is lengthened by one carbon atom.

$$RCOOH \longrightarrow RCH_2COOH$$

The acid is first converted into its chloride which is then treated with excess* of diazomethane to give a diazoketone. The diazoketone, when heated with silver oxide in presence of water, gives the homologous acid. In presence of other reagents esters, acid amides and hydroxy ketones are formed as shown below.

$$RCOOH \xrightarrow{SOCl_2} RCOCl \xrightarrow{2CH_2N_2} \underset{\text{Diazoketone}}{RCOCHN_2}$$

$$RCOCHN_2 \xrightarrow{Ag_2O} \begin{cases} \xrightarrow{H_2O} RCH_2COOH \\ \xrightarrow{EtOH} RCH_2COOEt \\ \xrightarrow{NH_3} RCH_2CONH_2 \\ \xrightarrow{R'NH_2} RCH_2CONHR' \end{cases}$$

* Unless the diazomethane is in excess, halomethylketone is produced by the action of hydrogen chloride on the diazoketone.

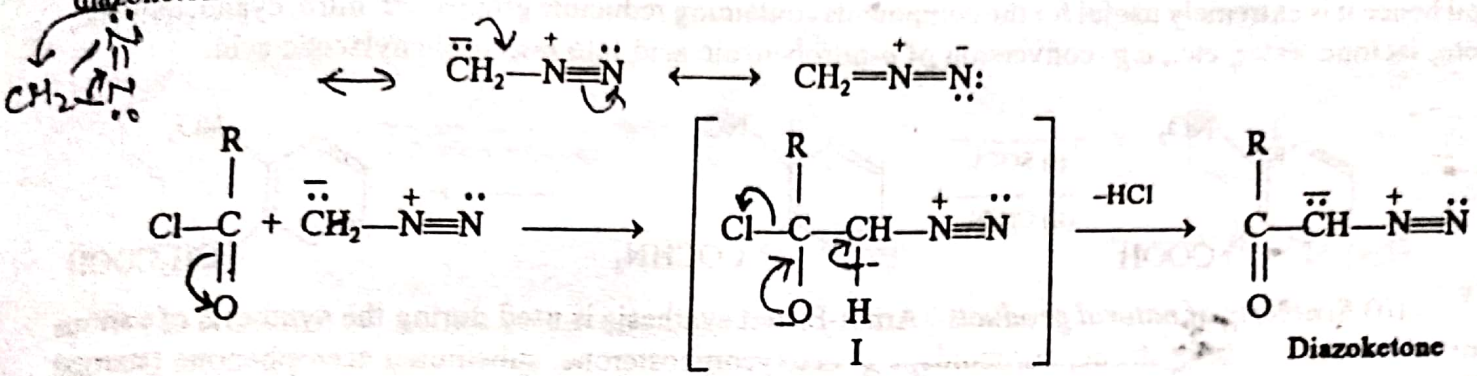
$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl$$
$$RCOCHN_2 + HCl \longrightarrow RCOCH_2Cl + N_2$$

$$RCOCHN_2 + H_2O \xrightarrow[\text{no catalyst}]{HCOOH} RCO.CH_2OH$$

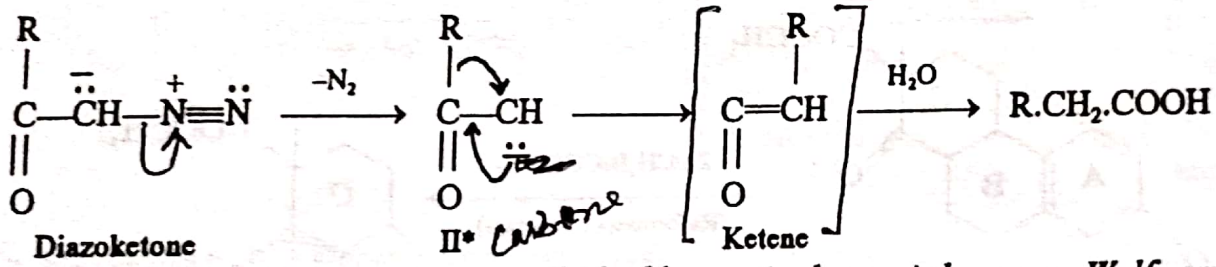
Diazoketone → Hydroxyketone

Colloidal silver, platinum and silver benzoate/triethylamine have also been used as efficient catalysts during Arndt Eistert synthesis.

Mechanism : It is assumed that the diazomethane attacks on carbon of carbonyl group of acid chloride (nucleophilic attack) to form an intermediate, I, which soon loses a molecule of HCl and gives the diazoketone.

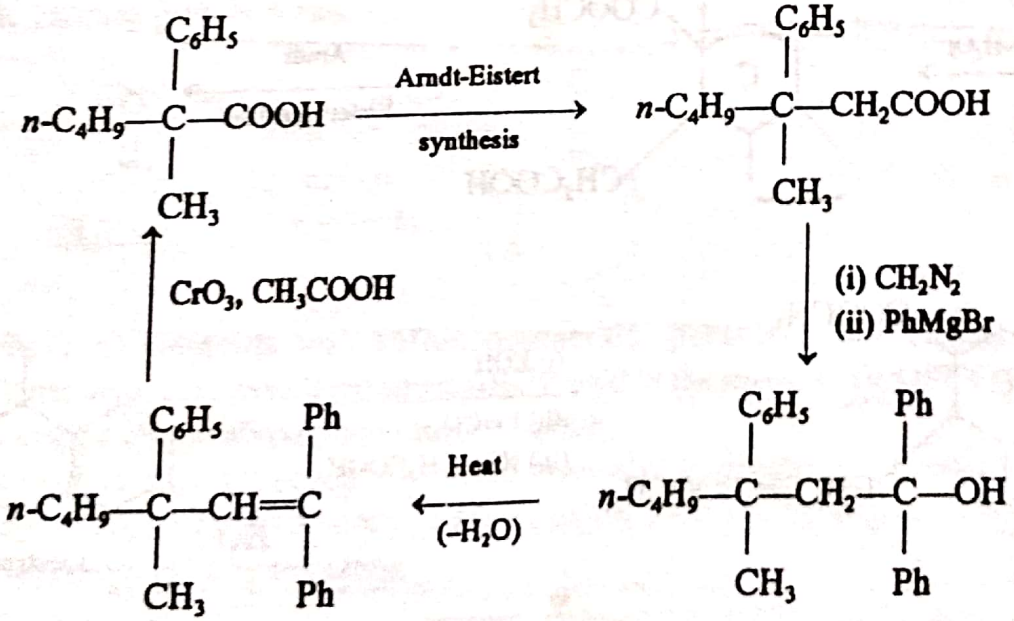


The diazoketone, so formed evolves a molecule of nitrogen with the simultaneous migration of R to form ketene. The ketene on hydrolysis with water forms the homologue acid.



The conversion of the diazoketone to the highly reactive ketene is known as Wolf rearrangement.

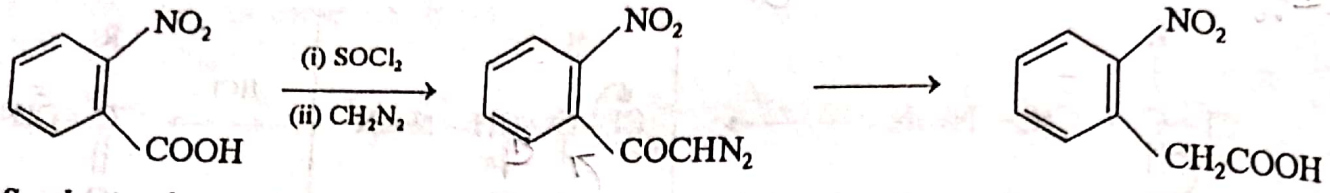
The alkyl group (R) migrates with retention of configuration. It can be proved by the following transformation involving an optically active acid.



* It must be noted that the intermediate, II, is not a carbonium ion, but an electron-deficient species, known as carbene.

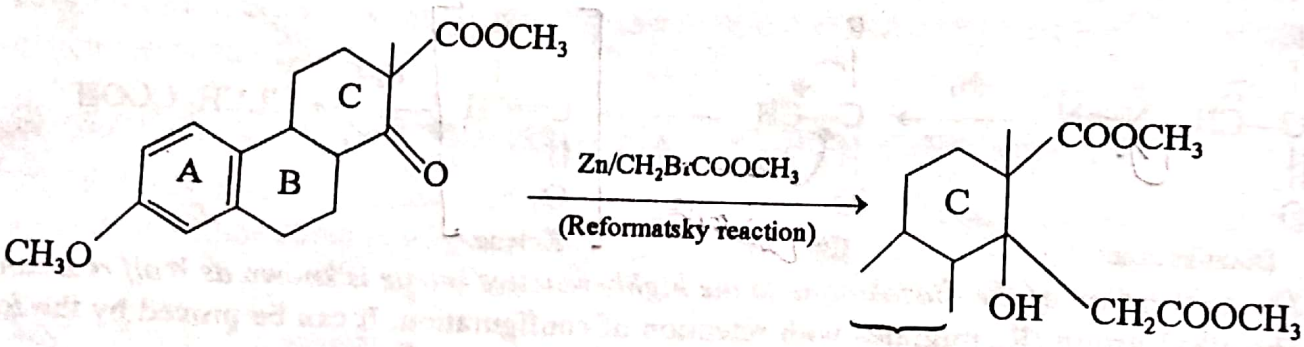
The acid obtained by the Arndt-Eistert synthesis was degraded to the original acid by Barbier--Wieland degradation. The acid thus obtained was found to have the same configuration as the original acid.

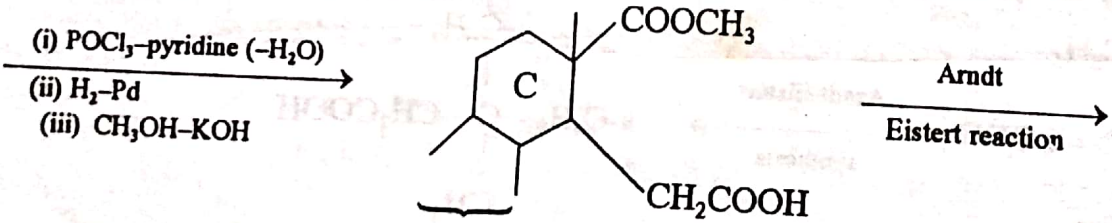
Synthetic applications : (*i*) *Synthesis of acids and their derivatives* : Arndt-Eistert method is used for the synthesis of higher acids from the lower ones. It is the method of choice when only a small amount of material is required ; the yields are generally 50 to 80% of the theoretical amount. Moreove, Arndt-Eistert synthesis of acids has an important advantage over other methods which is that this method does not require reduction and hence it is extremely useful for the compounds containing reducible groups, *viz,* nitro, cyano, quinone, keto, lactone, ester, etc., *e.g.* conversion of *o*-nitrobenzoic acid into *o*-nitrophenylacetic acid.

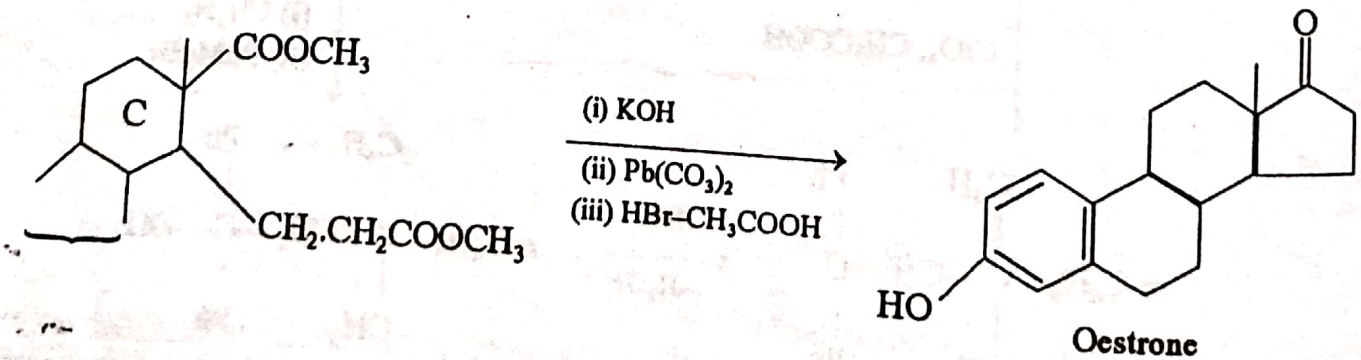


(*ii*) *Synthesis of natural products* : Arndt-Eistert synthesis is used during the synthesis of various natural products, *viz.* oestrone, corticoids, *e.g.* deoxycorticosterone, substituted acetophenone (starting material for the synthesis of anthocyanidins), mescaline (alkaloid), etc.

(a) Synthesis of oestrone.







Oestrone