Chapter II
General methods for preparation of alicyclic compounds:
1-Freund method:

a- This is similar to Wurtz method for preparation of alkanes
b- It is an internal cyclization of dihalogen derivatives of alkanes when treated with Na or Zn to give alicyclic compounds e.g.

\[
\begin{align*}
\text{Br} \\
\text{Br} \\
(\text{CH}_2)_n \\
\text{Br} \\
\text{Br}
\end{align*}
\]

\[n = 3-6 \text{ equal to the number of carbons}\]

\[
\begin{align*}
\text{Br} \\
\text{Br} \\
(\text{CH}_2)_n \\
\text{Br} \\
+ \text{Na or Zn} & \quad \text{ Alicyclic compounds}
\end{align*}
\]

If \(n = 0\) means \(\text{Br}_2\) no alicyclic compound is formed (no ring formation)
If \(n = 1\) means \(\text{CH}_2\text{Br}_2\) no alicyclic compound is formed
If \(n = 2\) means \(\text{BrCH}_2\text{CH}_2\text{Br}\) no alicyclic compound is formed
If \(n = 3\) means \(\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}\) cyclopropane is formed
If \(n = 4\) means \(\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}\) cyclobutane is formed
If \(n = 5\) means \(\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}\) cyclopentane is formed
If \(n = 6\) means \(\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}\) cyclohexane is formed

If \(n > 6\) the two halogen atoms will be further apart, at which no cyclization occurs, but usual Wurtz reaction takes place.

\(n = 7\) \(\text{Br(CH}_2\text{)}_7\text{Br} + \text{Na or Zn} \rightarrow \text{Br(Ch}_2\text{)}_7\text{Br}\)
2. **Dry distillation of Ba or Ca salts of dicarboxylic acids (dibasic acids):**

The general formula of dicarboxylic acids as follows:

\[ \text{HO}_2\text{C} \text{(CH}_2\text{)}\text{nCO}_2\text{H} \]

If \( n = 0 \) it is oxalic acid;  
If \( n = 1 \) it is malonic acid;  
If \( n = 2 \) it is succinic acid;  
If \( n = 3 \) it is glutaric acid;  
If \( n = 4 \) it is adipic acid;  
If \( n = 5 \) it is pimelic acid;  
If \( n = 6 \) it is sebacic acid  
If \( n = 7 \) it is asylic acid.

This method is used for preparation of five, six and seven membered rings.

This is resulted in the formation of cyclic aliphatic ketones, cyclopentanone and cyclohexanone which could be reduced to cyclopentane and cyclohexane respectively.

It is known that this is a good method for preparation of cyclopentane and cyclohexane, but with large rings, a low yield is obtained. This may be attributed to the stability of five and six membered rings according to Bayer-strain theory.
Ca salts of dicarboxylic acids

\[ \text{CaC}_2\text{O}_4 \rightarrow \text{Ca(OH)}_2 \]

Ca salts of dicarboxylic acids

\[ \text{CaC}_2\text{O}_4 \rightarrow \text{Ca(OH)}_2 \]

Ca malonate

\[ \text{CaC}_2\text{O}_4 \rightarrow \text{Ca(OH)}_2 \]

Ca succinate

\[ \text{CaC}_2\text{O}_4 \rightarrow \text{Ca(OH)}_2 \]

Ca glutarate

\[ \text{CaC}_2\text{O}_4 \rightarrow \text{Ca(OH)}_2 \]
This method is used for preparation of only five, six and seven ring ketones.
3-Retduction of aromatic compounds:

Six-membered alicyclic compounds may very conveniently be prepared by the reduction of benzene and its derivatives. Catalytic under pressure using nickel is the most satisfactory e.g. phenol is almost quantitatively converted into cyclohexanol.
Dehydrohalogenation of cycloalkylhalides by KOH / EtOH

- Cyclopropyl bromide $\rightarrow$ Cyclopropane $\rightarrow$ Cyclopropane
- Cyclobutyl bromide $\rightarrow$ Cyclobutene $\rightarrow$ Cyclobutane
- Cyclopentyl bromide $\rightarrow$ Cyclopentene $\rightarrow$ Cyclopentane
- Cyclohexyl bromide $\rightarrow$ Cyclohexene $\rightarrow$ Cyclohexane
4-Condensation reactions:
i) Condensation reactions of diethyl malonate one or two molecules of it with dihaloalkanes

Using one molecule of dihaloalkanes and one molecule of diethyl malonate:

Dihaloalkanes \( X(CH_2)_nX \) e.g. dibromoalkanes \( Br(CH_2)_nBr \) \( n = 2 \cdot 6 \)
condense with one molecule of malonic ester in the presence of two molecules of sodium ethoxide to form cyclohexan-1,1-dicarboxylic ester.

These may be converted into the monocarboxylic acid by the usual procedure used in malonic ester synthesis.

For \( Br(CH_2)_nBr \)

If \( n = 0 \) means \( Br_2 \) no alicyclic compound is formed
If \( n = 1 \) means \( CH_2Br_2 \) no alicyclic compound is formed
If \( n = 2 \) means \( BrCH_2CH_2Br \) cyclopropane is formed after several steps.

Similarly, if \( n = 2 \) means \( Br(CH_2)_3Br \) cyclobutane is formed after several steps.
Similarly, If $n = 4$ means BrCH$_2$CH$_2$ CH$_2$CH$_2$ Br cyclopentane is formed after several steps.

Similarly, If $n = 5$ means BrCH$_2$CH$_2$ CH$_2$CH$_2$ Br cyclohexane is formed after several steps.

If $n = 6$ means BrCH$_2$CH$_2$ CH$_2$CH$_2$CH$_2$ Br cycloheptane is formed after several steps.
b) Using one molecule of dihaloalkanes and two molecules of diethyl malonate:

The above dihaloalkanes one molecule condense with two molecules of sodium malonic ester, butane-1,1,2,2-tetracarboxylic ester is formed from ethylene dibromide.

On treatment with an excess of NaOC\(\textsubscript{2}H\textsubscript{5}\), this tetracarboxylic acid ester forms the disodium derivative which when treated with iodine is converted into cyclobutane-1,2-dicarboxylic acid derivative. If methylene di-iodide is used instead of iodine, the cyclopentane derivative is formed.
If methylene di-iodide is used instead of iodine, the cyclopentane-1,3-dicarboxylic acid derivative is formed.
ii) Condensation reactions of ethyl acetoacetate one molecule of it with one molecule of dihaloalkanes

Acetoacetic ester may also be used to prepare rings containing three, five, six and seven carbon atoms, not four; all attempts to prepare a four-membered ring resulted in the formation of a dihydroxyran derivatives.

\[
\text{(CH}_2\text{n + 2 CH}_3\text{Na)} \rightarrow \text{CO}_2\text{CH}_3
\]

\[
\text{Br} \quad \text{Br}
\]

\[
n = 4-6 \quad \text{not = 3}
\]
n = 6

\[
\text{Br} \quad (\text{CH}_2)_6 \quad \text{Br} \quad + \quad \text{CO}_2\text{C}_2\text{H}_5 \quad \text{CH}_3 \quad \text{CO}_2\text{C}_2\text{H}_5 \quad 2\text{EtCNa} \quad 2\text{EtOH} \quad \text{EtCNa} \quad \text{NaBr}
\]

methylcyclhexylketone

[i] KCl

[ii] HCl
iii) Dieckmann condensation reaction:

Claisen condensation: Is an intermolecular condensation of two molecules of ethyl acetate in presence of Na or NaOC₂H₅ to give ethyl acetoacetate.

\[
\begin{align*}
\text{CO₂Et} & \quad \text{(CH₂)ₙ} & \quad \text{CO₂Et} \\
\text{if } n = 0 \text{ no ring formation, because it is diethyl oxalate} \\
\text{if } n = 1 \text{ no ring formation, because it is diethyl malonate} \\
\text{if } n = 2 \text{ no ring formation, because it is diethyl succinate}
\end{align*}
\]

If \( n = 4 \) - 6 rings are formed

2 ethyl acetate + Na or NaOC₂H₅ \[\text{ethyl acetoacetate.} \]

This reaction, which is really an intramolecular Claisen condensation, is carried out by treating the esters of adipic acid, pimelic acid or suberic acid with sodium or better, with sodium ethoxide whereupon five-, six-, or seven-membered rings respectively, are obtained.
Reaction scheme:

- **Diethyl adipate**
  - Reaction with NaOEt
  - Result: \( \text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \rightarrow \text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \text{NaOEt} \rightarrow \beta\text{-ketoester} \)

- **Cyclopentane**
  - Reaction with \( \text{Zn(Hg)} / \text{HCl} \)

- **Diethyl pimelate**
  - Reaction with NaOEt
  - Result: \( \text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \rightarrow \text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \text{NaOEt} \rightarrow \text{ketoester} \)

- **Cyclohexanone**
  - Reaction with \( \text{Zn(Hg)} / \text{HCl} \)

**Chemical Structures:**
- **Diethyl adipate**
- **Cyclopentane**
- **Diethyl pimelate**
- **Cyclohexanone**
Esters lower than adipic ester may form products by intermolecular condensation and cyclization e.g. in the presence of sodium or sodium ethoxide, ethyl succinate forms succinosuccinic ester (cyclohexane-2,5-dione-1,4-dicarboxylic ester) (β-ketoester).

On the other hand, five-membered ring compounds may be prepared by the intermolecular condensation between diethyl oxalate and diethyl glutarate.
Certain ketones may be used with diethyl oxalate to give five-membered rings, e.g., acetone gives cyclopentane-1,2,4-trione.

The Dieckmann condensation has been used for the synthesis of fused systems.
Various types of bifunctional compounds undergo intramolecular reactions under suitable conditions to form cyclic compounds, particularly when the product is a five or six membered rings e.g.

a- **Pinacol reduction**: Hydroxy-cyclic compounds may be prepared by reducing certain ketones with Mg(Hg) / H₃O⁺ e.g.

\[
\text{heptane-2,6-dione} \xrightarrow{i) \text{Mg(Hg)}} \xrightarrow{ii) \text{H}_3\text{O}^+} \text{cyclopentane-1,2-diene}
\]

b- Hydroxy-cyclic compounds may be also prepared by intramolecular -Grignard reaction e.g.

\[
\text{6-bromoheptane-2-one} \xrightarrow{\text{Mg/ether}} \xrightarrow{\text{H}_3\text{O}^+} \text{cyclopentanone-1,2-diene}
\]

c- Reaction of monocarboxylic esters RMgX and di-Grignard reagent : e.g.
if \( n = 0 \) no ring formation, because it is \( \text{MgBr}_2 \)

if \( n = 1 \) no ring formation, because it is \( \text{BrMgCH}_2\text{MgBr} \)

if \( n = 2 \) no ring formation, because it is \( \text{BrMg(CH}_2\text{)}_2\text{MgBr} \)

if \( n = 3 - 6 \) rings are formed

\[
\begin{align*}
\text{MgBr} & \quad \text{(CH}_2\text{)}_n & \quad \text{CH}_3\text{CO}_2\text{Et} & \quad \text{i)Mg} & \quad \text{ii)H}_3\text{O}^+ \\
\text{MgBr} & \quad \text{I} & \quad 2 & \quad \text{I} & \quad \text{I} & \quad \text{OH} & \quad \text{CH}_3 & \quad \text{OH} & \quad \text{CH}_3 & \quad \text{1,2-dihydroxy-1,2-dimethylcyclopentane}
\end{align*}
\]

\[
\begin{align*}
\text{MgBr} & \quad \text{(CH}_2\text{)}_4 & \quad \text{CH}_3\text{CO}_2\text{Et} & \quad \text{i)Mg} & \quad \text{ii)H}_3\text{O}^+ \\
\text{MgBr} & \quad \text{I} & \quad \text{I} & \quad \text{HO} & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{MgBr} & \quad \text{1-methylcyclohexane-1-chloride} & \quad \text{H}_2\text{O}^+ & \quad \text{H}_2\text{O}^+ & \quad \text{H}_2\text{O}^+
\end{align*}
\]
7-Friedel-Crafts reaction:
This reaction has been used for the synthesis of fused alicyclic ketones as shown:

4-phenylbuteryl chloride → \( \text{AlCl}_3/\text{CS}_2 \) → heat → \( \alpha \)-tetralene (1-tetralene)

3-phenylpropionyl chloride → \( \text{AlCl}_3/\text{CS}_2 \) → heat → \( \alpha \)-indane
8-Intramolecular elimination of water from diketones:

In suitable diketones, the methyl or methylene group α- to the keto group, will condense with the other carbonyl group in the molecule (in acid or base catalysed reaction of aldol type). This method is only applicable to the formation of five and six membered rings. In case of 1,4- or 1,5-diketones were cyclized to five and six membered rings in presence of base.
In case of 1,6-diketones were cyclized to five and six membered rings in presence of base or acid.
9-Michael addition reaction:
Addition of diethyl malonate to \( \alpha,\beta \)-unsaturated aldehydes or \( \alpha,\beta \)-unsaturated ketones.
**10-Diels Alder Reaction (D.A.R.)**

The D.A.R. is the addition of a conjugated diene to ethylenic compound in which the double bond is activated.

It is cycloaddition reaction between Diene and Dienophile to form a six-membered ring.

Diene: Contains two conjugated double bonds e.g., 1,3-butadiene, cyclopentadiene, anthracene, furan.

Dienophile: Compounds contain double bond attached to unsaturated aldehydes, ketones, acids, esters, maleic anhydride. The compound formed by the condensation of A and B is known as the adduct which is usually six-membered ring.

In general, the diene synthesis is the following type of reaction:

![Chemical Reaction Diagram]

**Example:**

![Example Reaction Diagram]
11- Intramolecular alkylation:
Under high-dilution conditions of ω-bromo-β-ketoesters with K₂CO₃ produces C-14 - C-17 cyclic β-ketoesters (40-75%).
Example:

\[
\text{Br(CH₂)₁₂COCH₂CO₂C₂H₅} \xrightarrow{\text{K₂CO₃}} \text{2-ethoxycarbonyl-cyclohexadecan-1-one}
\]

12- Bicyclic systems may be obtained by:
a- Dieckmann condensation:

b- Pyrolysis of Ba or Ca salts of dicarboxylic acids:
13-Thorpe-Ziegker reaction:

The cyclization of α,ω-dinitriles in the presence of base C2H5O-. The initial product, β-iminonitrile is readily hydrolysed to β-ketonitrile, which can be converted into a cyclic ketone by hydrolysis. The reaction is used for synthesis of five and six membered rings.

Large rings can be obtained by this reaction when carried out in very dilute solutions, using Li or Na N-maleimide as a basic catalyst. In this way yields of 95% for 7-membered, 88% for 8-membered rings and 60-80% (for rings with C-14 or more) were obtained.
**14-Spiro-cyclic systems:**
May be obtained by Dieckmann type or Thorpe-Ziegler reaction.

```
CN
CN
\[ \text{BOH} / \text{HCl} \] \hspace{1cm} \text{EtONa} \\
\text{Base} \hspace{1cm} \text{Dieckmann reaction}
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```
\text{H}_3\text{O}^+ \hspace{1cm} \text{H}_3\text{O}^+
```

1-tetralone-2-spiro-4'-cyclohexanone