

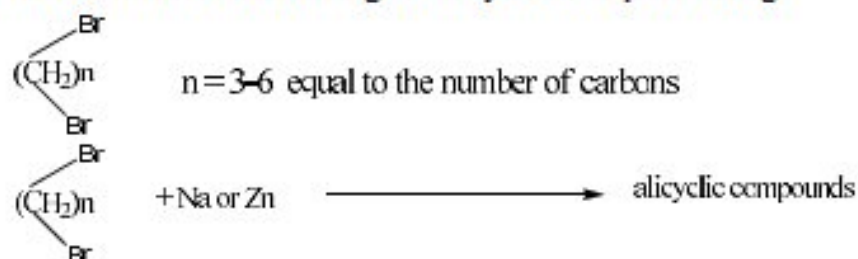
## *Chapter II*

**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.



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

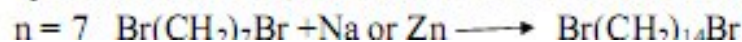
If  $n = 3$  means  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}$  cyclopropane is formed

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.



## ***2. Dry distillation of Ba or Ca salts of dicarboxylic acids(dibasic acids):***

The general formula of dicarboxylic acids as follows:



If  $n = 0$  it is oxalic acid ;

If  $n = 2$  it is succinic acid ;

If  $n = 4$  it is adipic acid ;

If  $n = 6$  it is sebacic acid ;

If  $n = 8$  it is sebacic acid

If  $n = 1$  it is malonic acid;

If  $n = 3$  it is glutaric acid ;

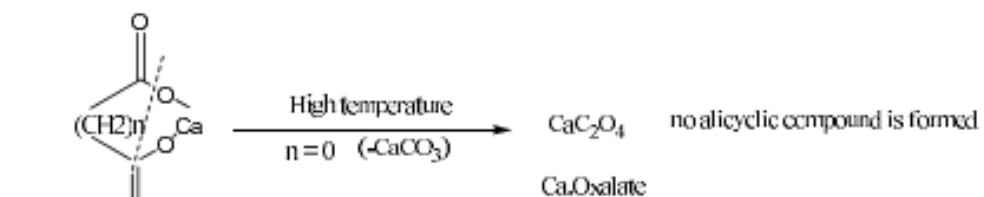
If  $n = 5$  it is pimelic acid;

If  $n = 7$  it is asylic acid ;

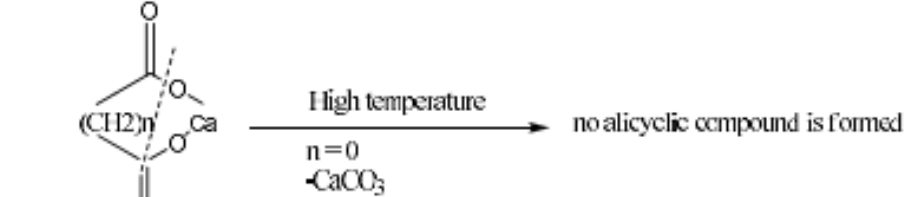
This method is used for preparation of five, six and seven membered rings .

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

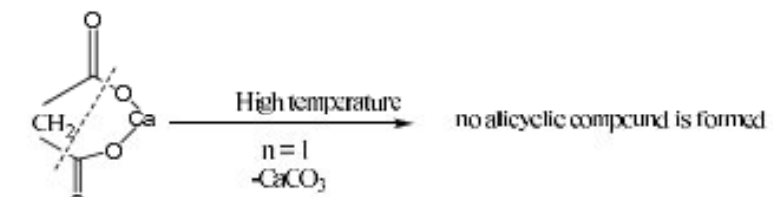
It is known that this is a good method for preparation of cyclopentane and cyclohexane ,but with large rings ,a low yield is obtained .This may be attributed to the stability of five and six membered rings according to Bayer-strain theory.



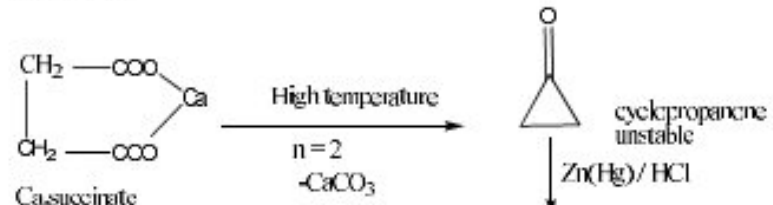
Ca salts of dicarboxylic acids



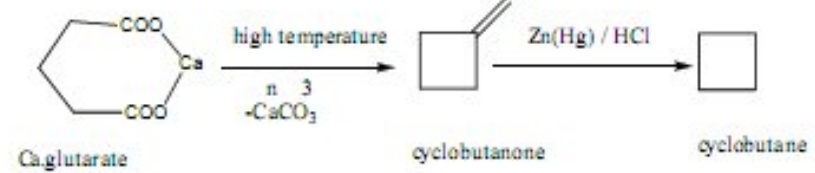
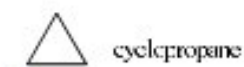
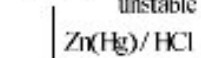
Ca salts of dicarboxylic acids



Ca.malonnate



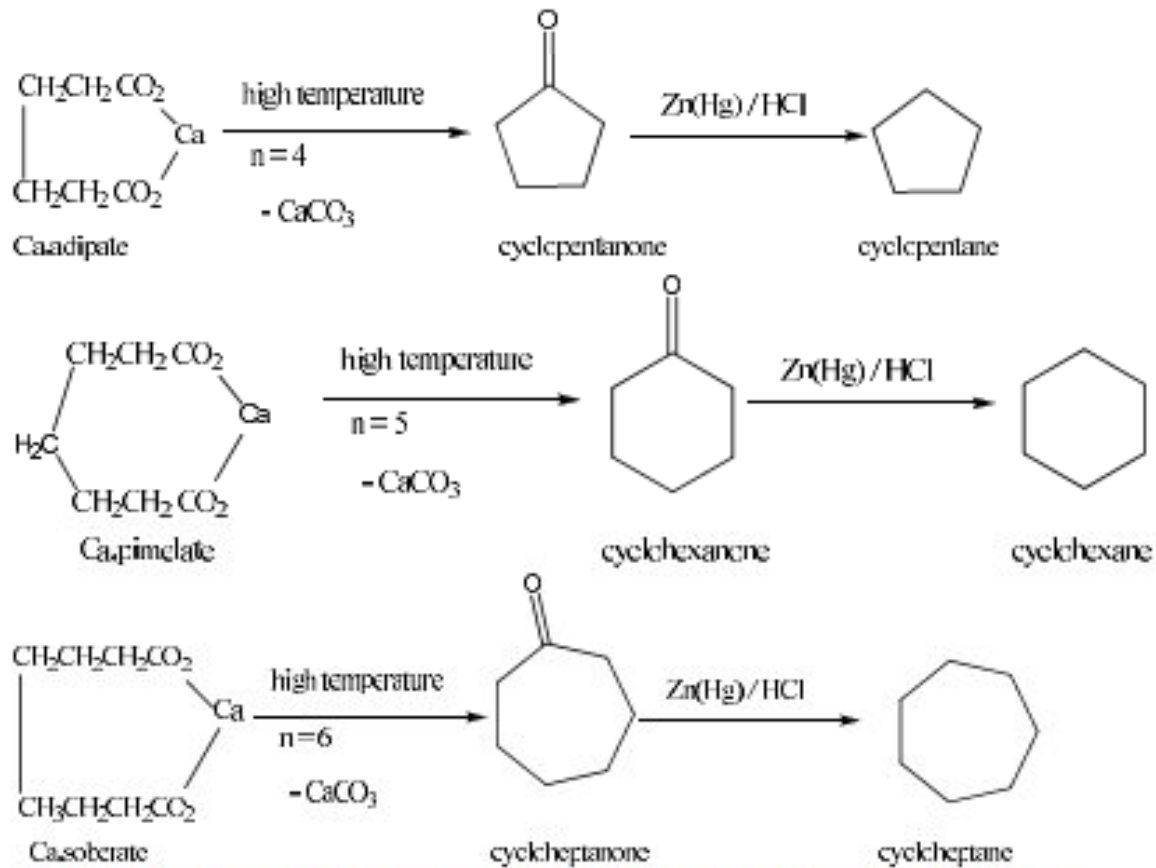
Ca.succinate



Ca.glutarate

cyclobutanone

cyclobutane

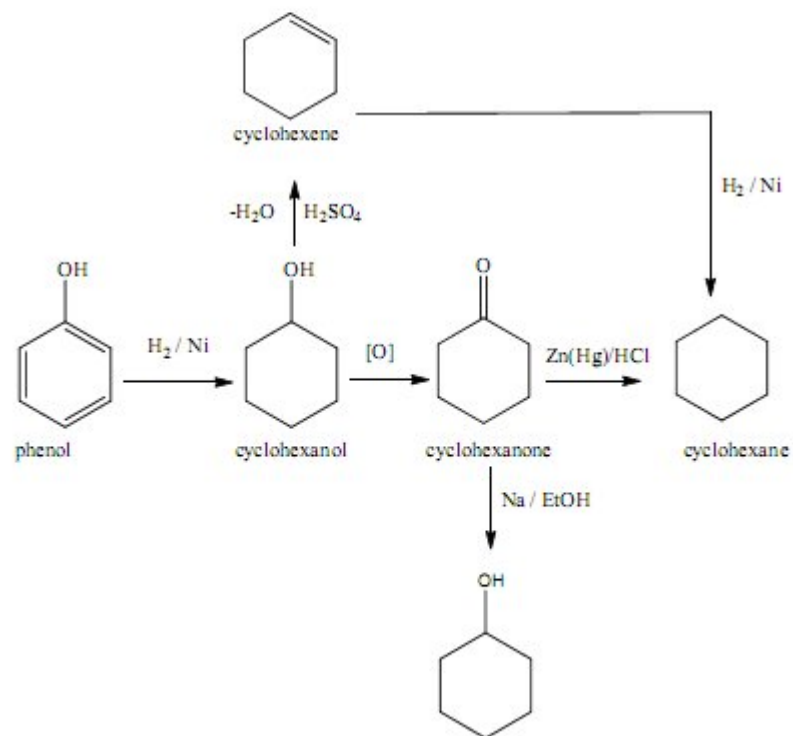
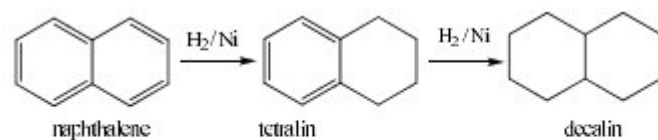
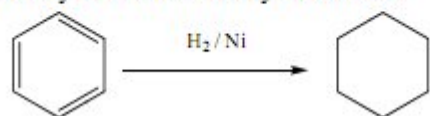


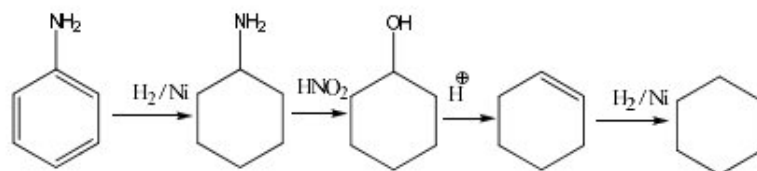
This method is used for preparation of only five, six and seven ring ketones .

### 3-Reduction of aromatic compounds :

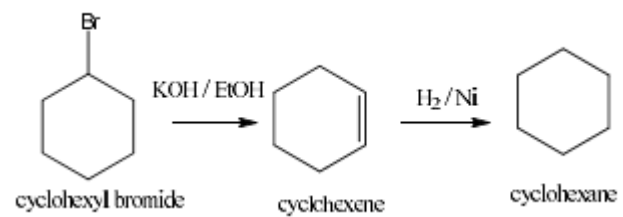
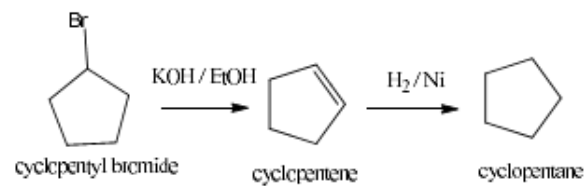
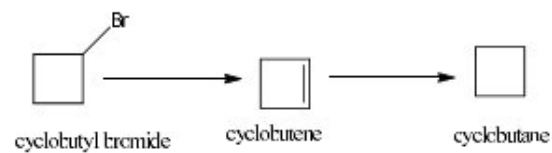
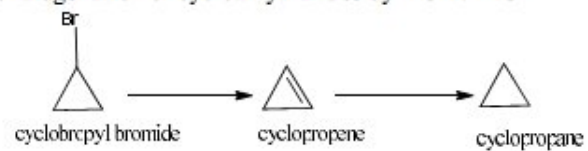
Six -membered alicyclic compounds may very conveniently be prepared by the reduction of benzene and its derivatives .

Catalytic under pressure using Nickel is the most satisfactory e.g.phenol is almost quantitatively converted into cyclohexanol.





Dehydrohalogenation of cycloalkylhalides by KOH / EtOH



#### 4-Condensation reactions :

i) Condensation reactions of diethyl malonate one or two molecules of it with dihaloalkanes

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

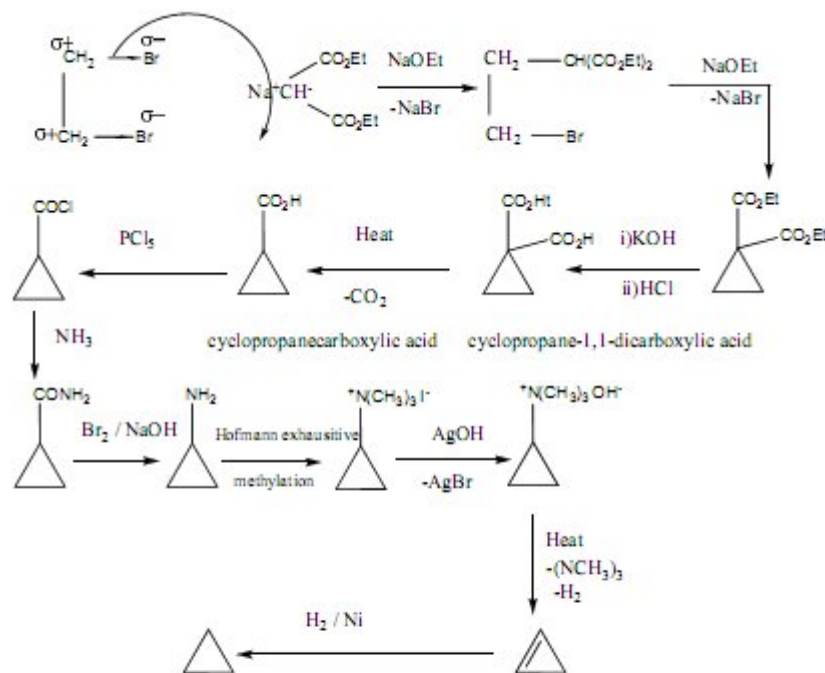
Dihaloalkanes  $X(CH_2)_nX$  e.g. dibromoalkanes  $Br(CH_2)_nBr$  ( $n = 2 - 6$ ) condense with *one* molecule of malonic ester in the presence of *two* molecules of sodium ethoxide to form cyclohexan-1,1-dicarboxylic ester. These may be converted into the monocarboxylic acid by the usual procedure used in malonic ester synthesis.

For  $Br(CH_2)_nBr$

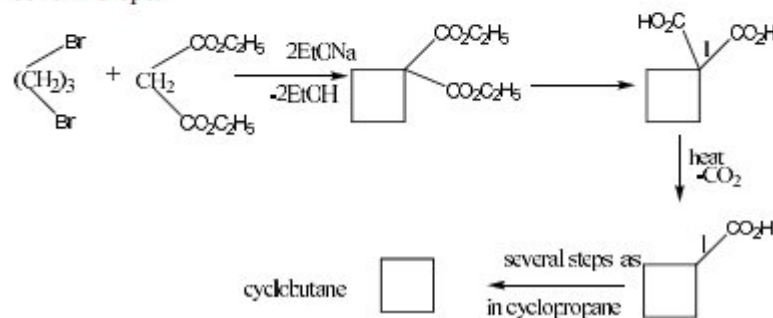
If  $n = 0$  means  $Br_2$  no alicyclic compound is formed

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.

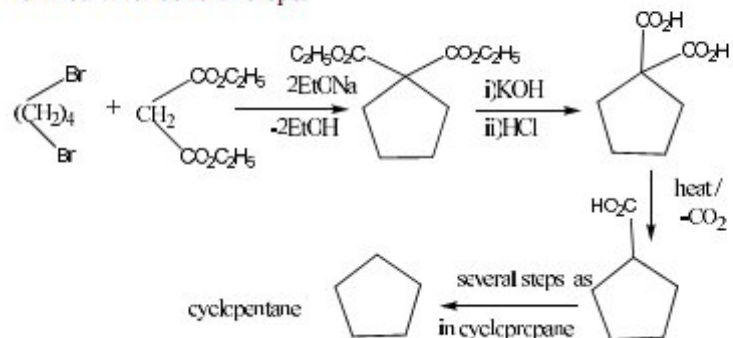


Similarly, If  $n = 2$  means  $Br(CH_2)_3Br$  cyclobutane is formed after several steps.

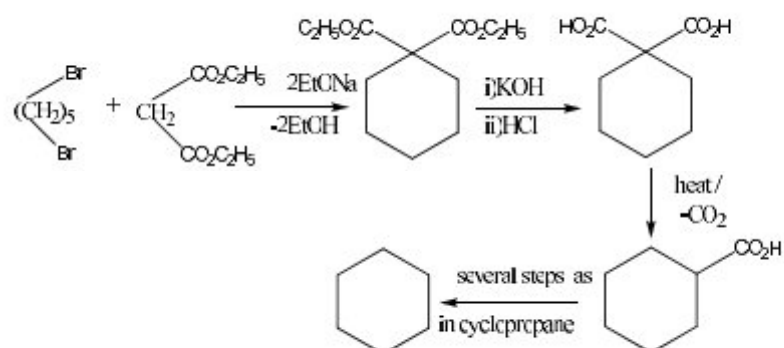




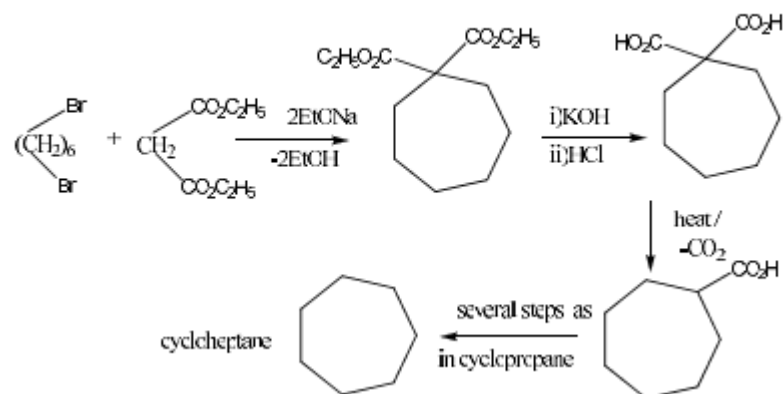
Similarly, If  $n = 4$  means  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$  cyclopentane is formed after several steps.



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

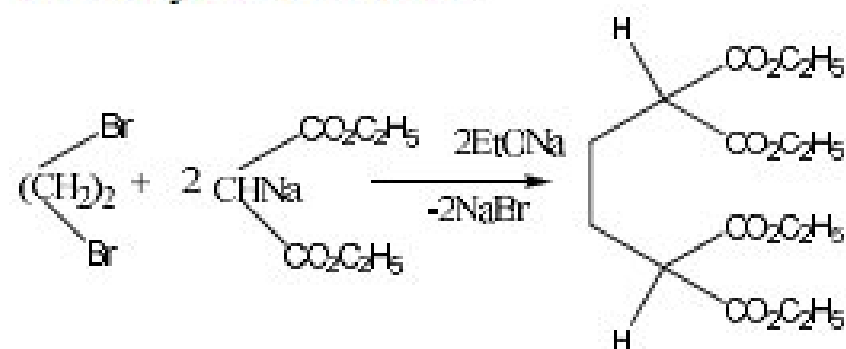


If  $n = 6$  means  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$  cycloheptane is formed after several steps.



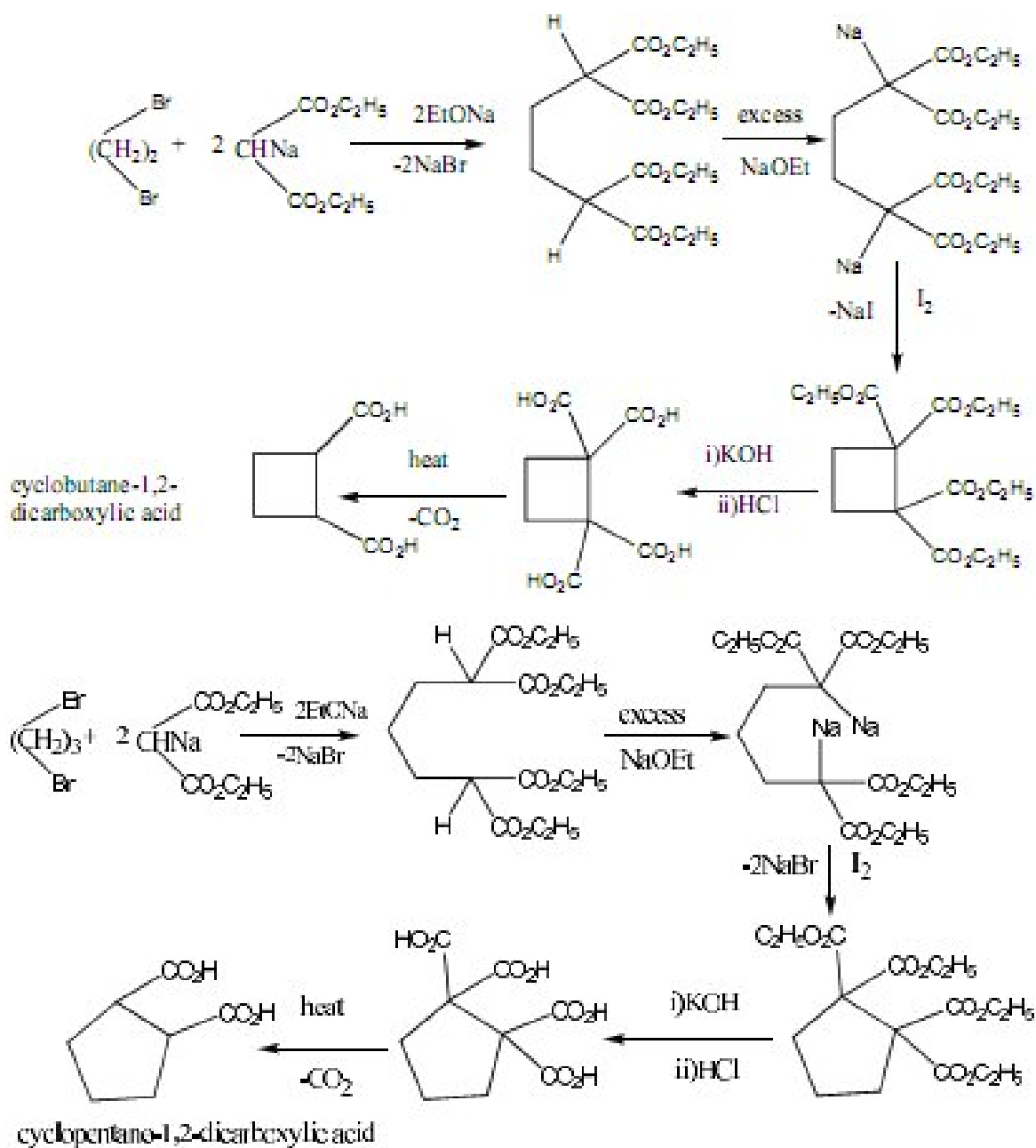
*b) Using one molecule of dihaloalkanes and two molecules of diethyl malonate :*

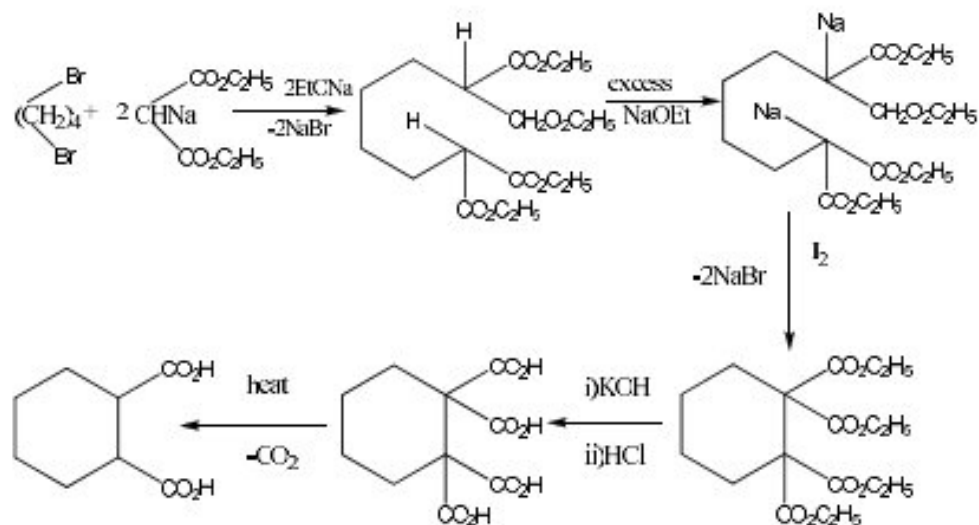
The above dihaloalkanes *one* molecule condense with *two* molecules of sodium malonic ester , butane-1,1,2,2-tetracarboxylic ester is formed from ethylene dibromide .



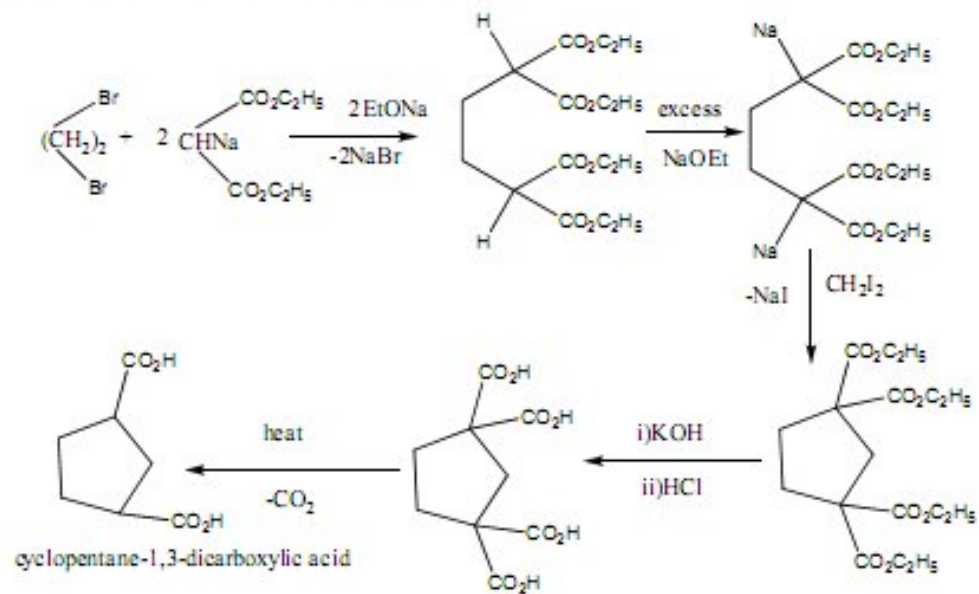
On treatment with an excess of  $\text{NaOC}_2\text{H}_5$  , this tetracarboxylic acid ester forms the disodium derivative which when treated with iodine is converted into cyclobutane-1,2-dicarboxylic acid derivative.

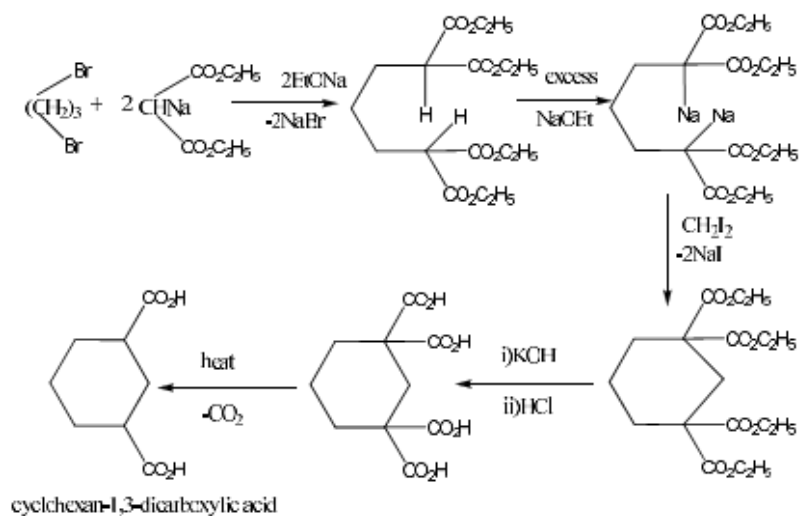
If methylene di-iodide is used instead of iodine , the cyclopentane derivative is formed.





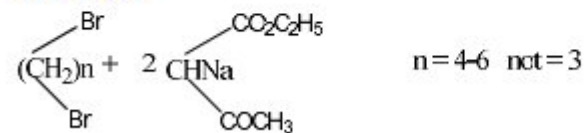
If methylene di-iodide is used instead of iodine, the cyclopentane-1,3-dicarboxylic acid derivative is formed.

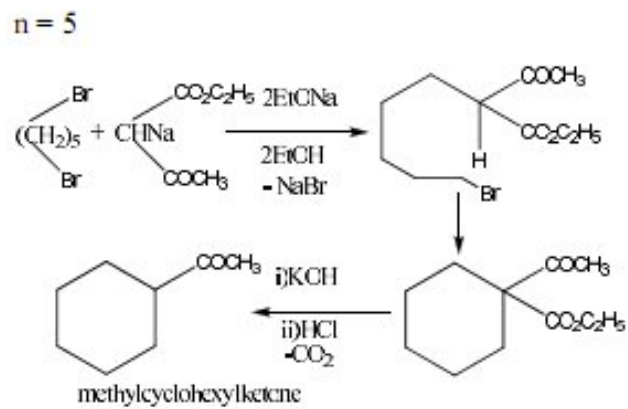
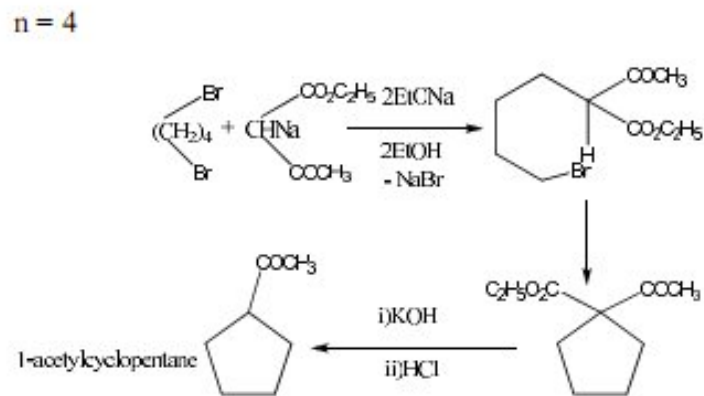
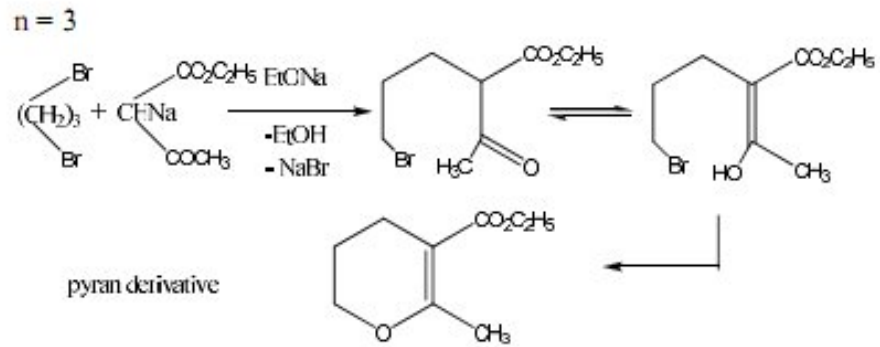




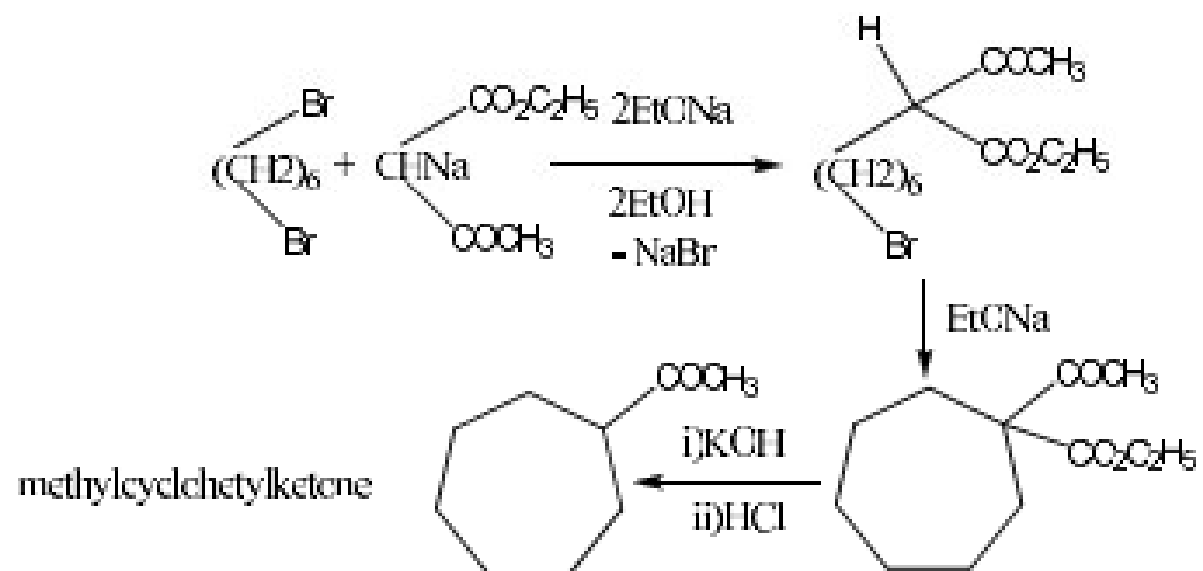
**ii) Condensation reactions of ethyl acetoacetate one molecule of it with one molecule of dihaloalkanes**

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.



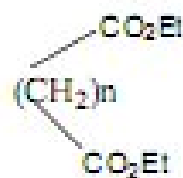


n = 6



iii) *Dieckmann condensation reaction* :

Claisen condensation: Is an intermolecular condensation of two molecules of ethyl acetate in presence of Na or NaOC<sub>2</sub>H<sub>5</sub> to give ethyl acetoacetate.



if n = 0 no ring formation ,because it is diethyl oxalate

if n = 1 no ring formation ,because it is diethyl malonate

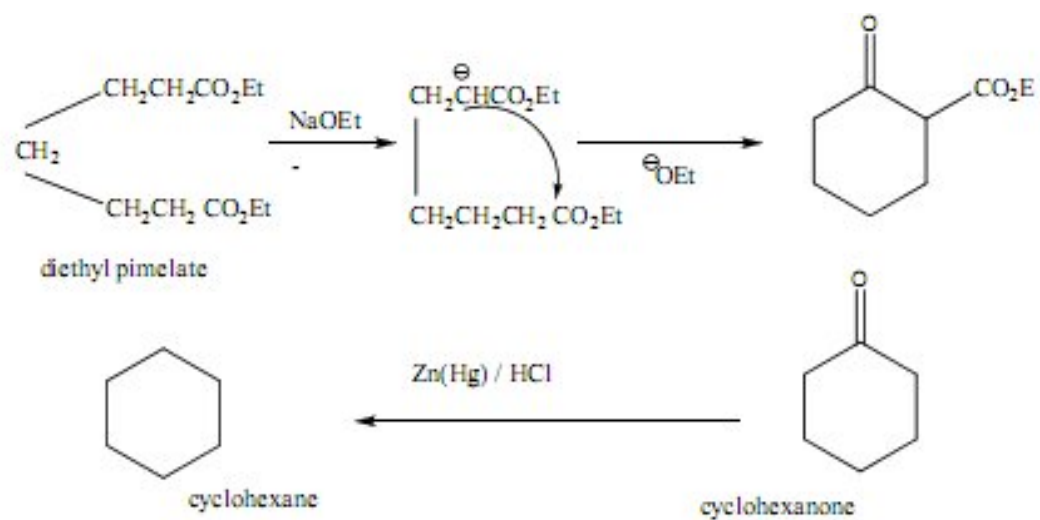
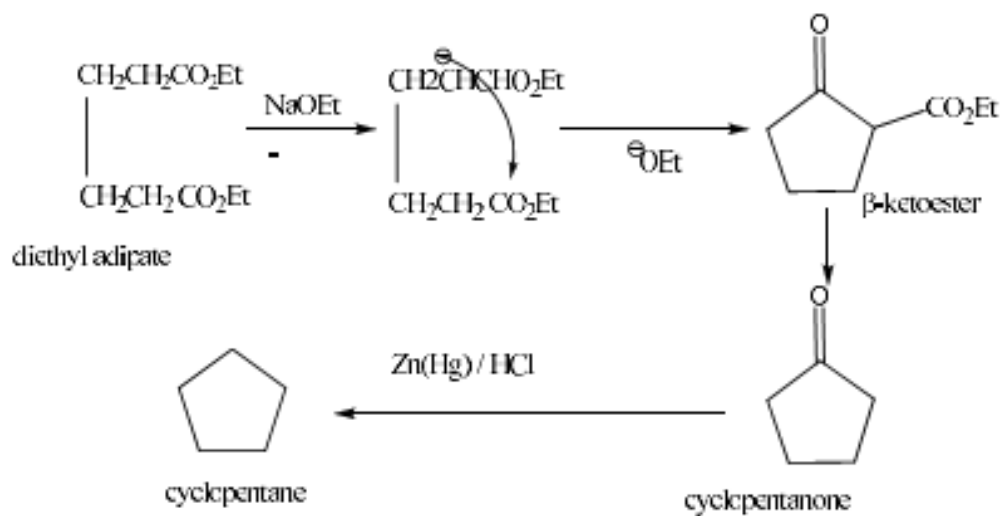
if n = 2 no ring formation ,because it is diethyl succinate

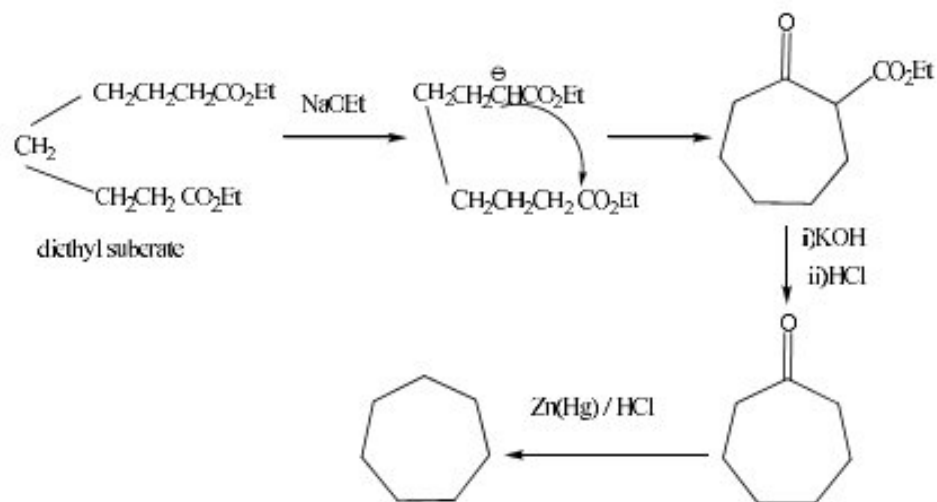
if n = 4 -6 rings are formed

2 ethyl acetate + Na or NaOC<sub>2</sub>H<sub>5</sub> → ethyl acetoacetate.

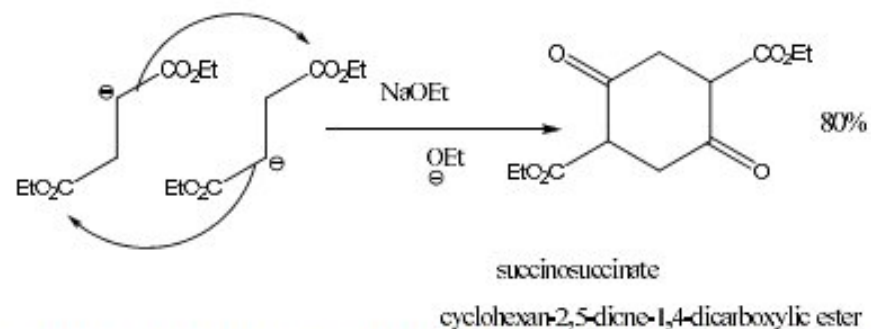
This reaction ,which is really *an intramolecular Claisen condensation*, is carried out by treating the esters of adipic acid , pimelic acid or suberic acid with sodium or better ,with sodium ethoxide whereupon five-, six-, or seven –membered rings respectively,are obtained.



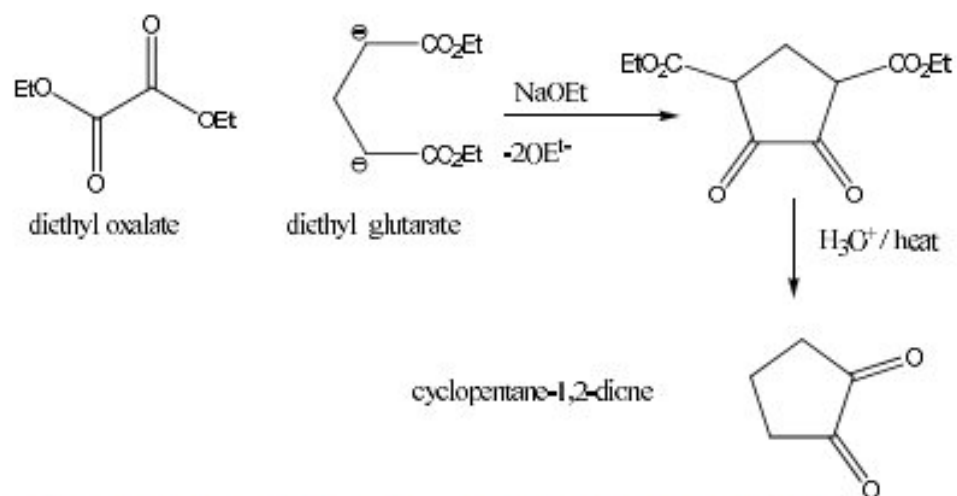




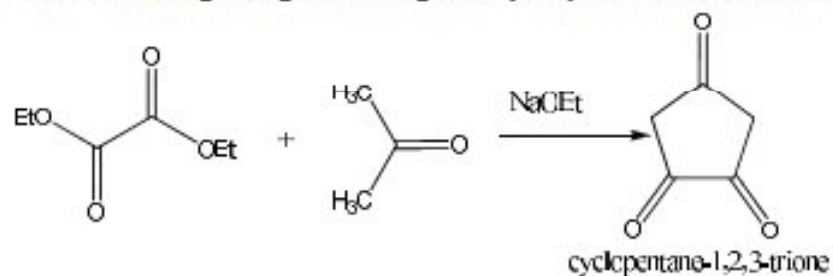
Esters lower than adipic ester may form products by *intermolecular* condensation and cyclization e.g. in the presence of sodium or sodium ethoxide, ethyl succinate forms succinosuccinic ester (cyclohexane-2,5-dione-1,4-dicarboxylic ester) ( $\beta$ -ketoester).



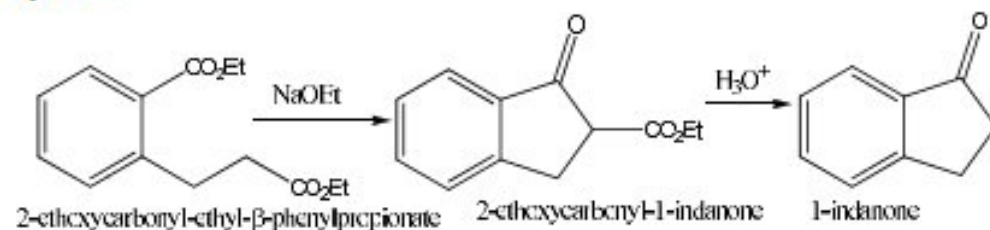
On the other hand, five-membered ring compounds may be prepared by the *intermolecular* condensation between diethyl oxalate and diethyl glutarate.



Certain ketones may be used with diethyl oxalate to give five-membered rings, e.g. acetone gives cyclopentane-1,2,4-trione.

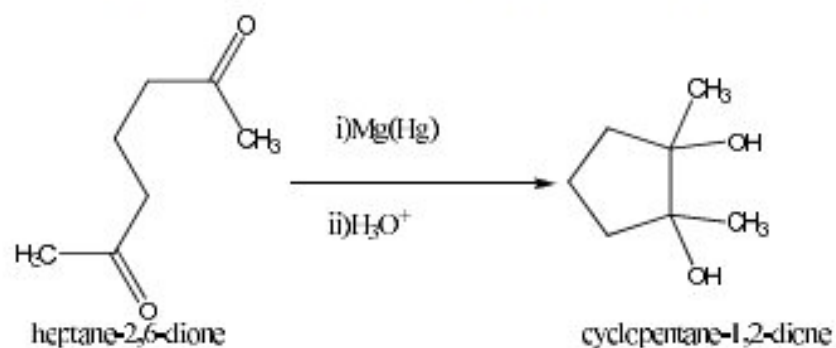


The Dieckmann condensation has been used for the synthesis of fused systems.

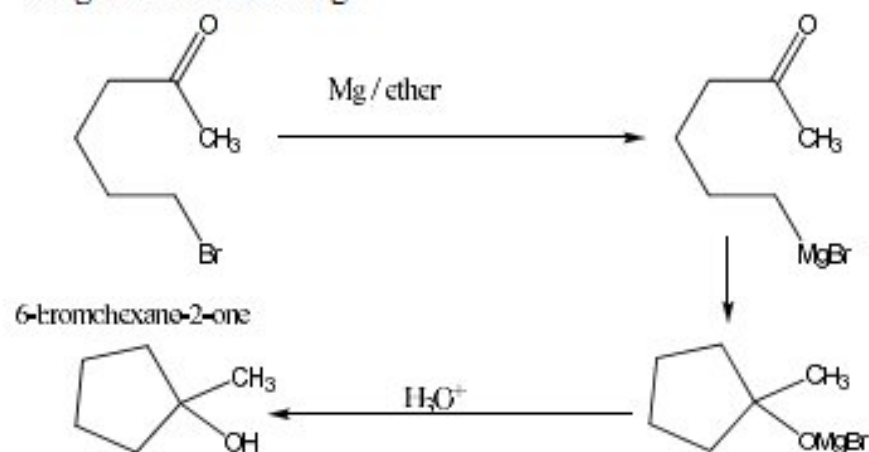


**6-Various types of bifunctional compounds** undergo *intramolecular* reactions under suitable conditions to form cyclic compounds, particularly when the product is a five or six membered rings e.g.

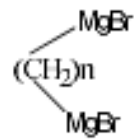
**a-Pinacol reduction** : Hydroxy-cyclic compounds may be prepared by reducing certain ketones with  $\text{Mg(Hg)} / \text{H}_3\text{O}^+$  e.g.



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



**c-** Reaction of monocarboxylic esters  $\text{RMgX}$  and di-Grignard reagent :e.g.

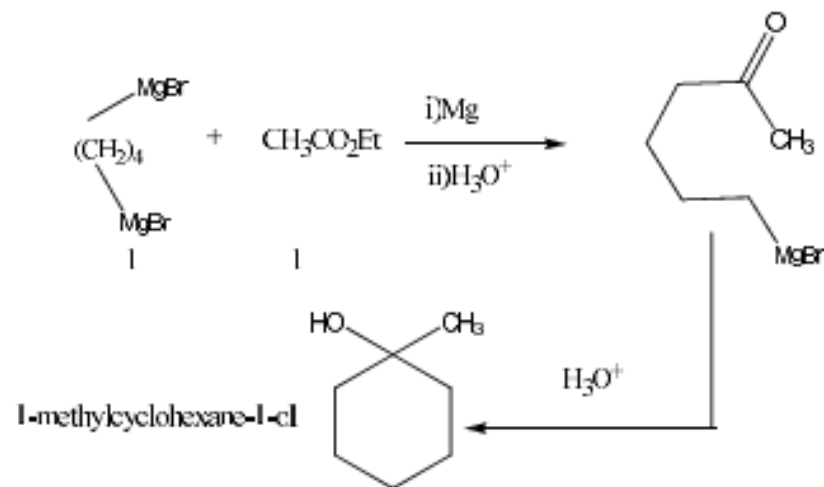
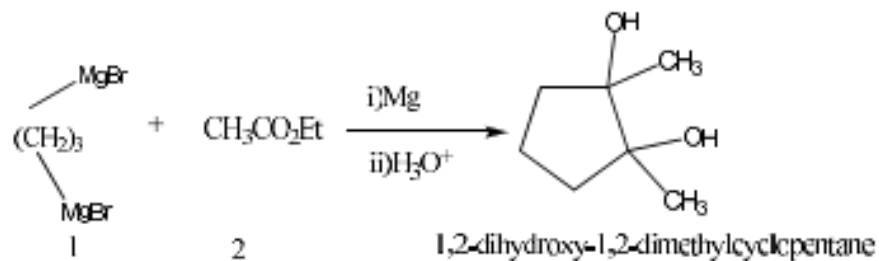


if  $n = 0$  no ring formation, because it is  $\text{MgBr}_2$

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

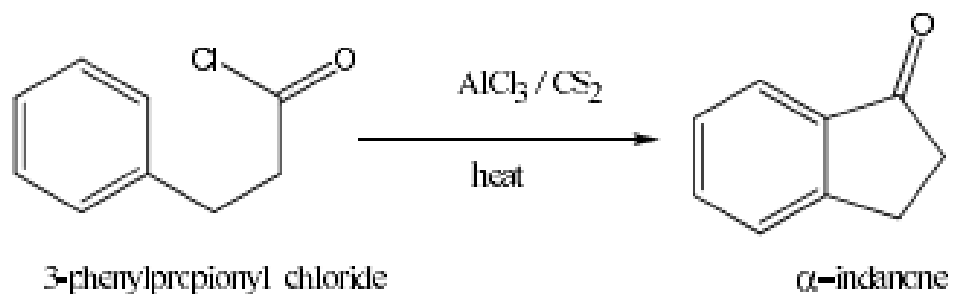
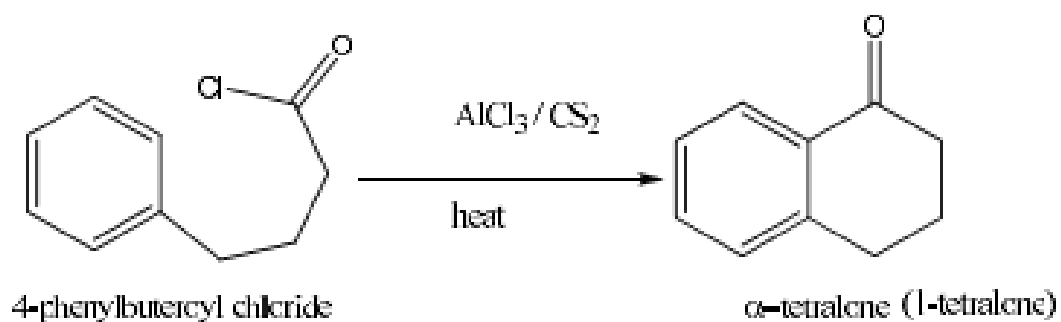
if  $n = 2$  no ring formation, because it is  $\text{BrMg}(\text{CH}_2)_2\text{MgBr}$

if  $n = 3-6$  rings are formed



**7-Friedel-Crafts reaction :**

This reaction has been used for the synthesis of fused alicyclic ketones as shown :

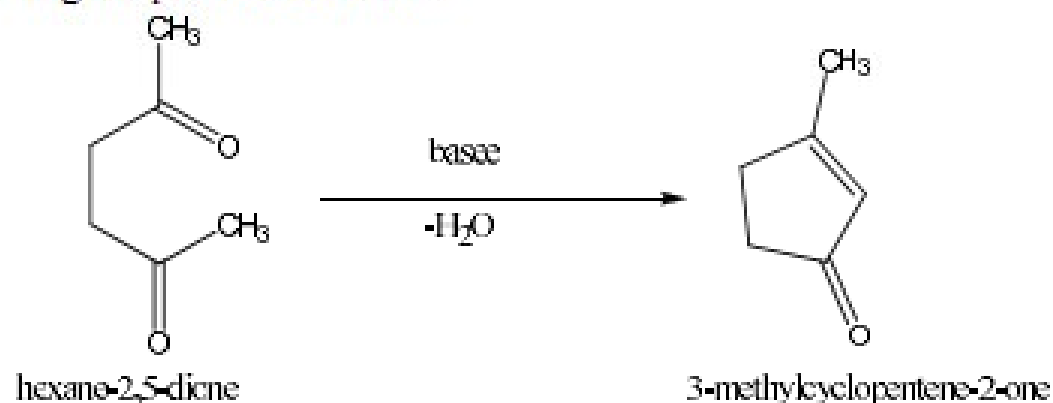


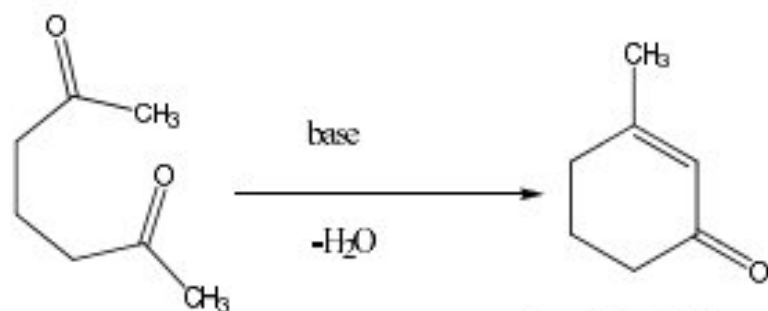
**8-Intramolecular elimination of water from diketones :**

In suitable diketones, the methyl or methylene group  $\alpha$ - 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.

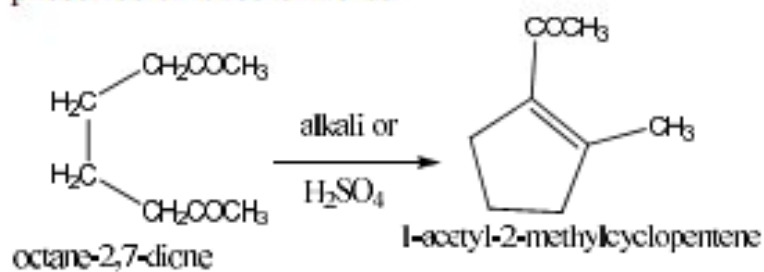




heptane-2,6-dione

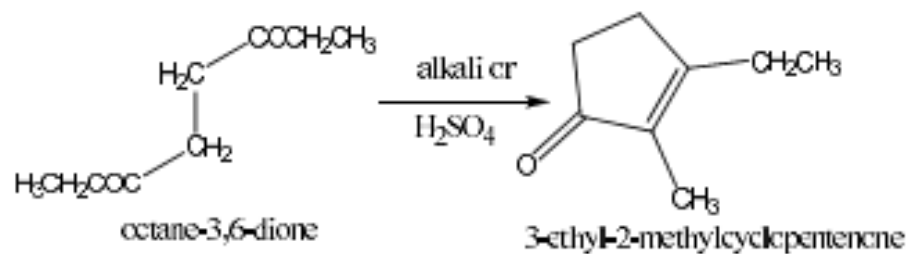
3-methylcyclohexenone

In case of 1,6-diketones were cyclized to five and six membered rings in presence of base or acid.



octane-2,7-dione

1-acetyl-2-methylcyclopentene



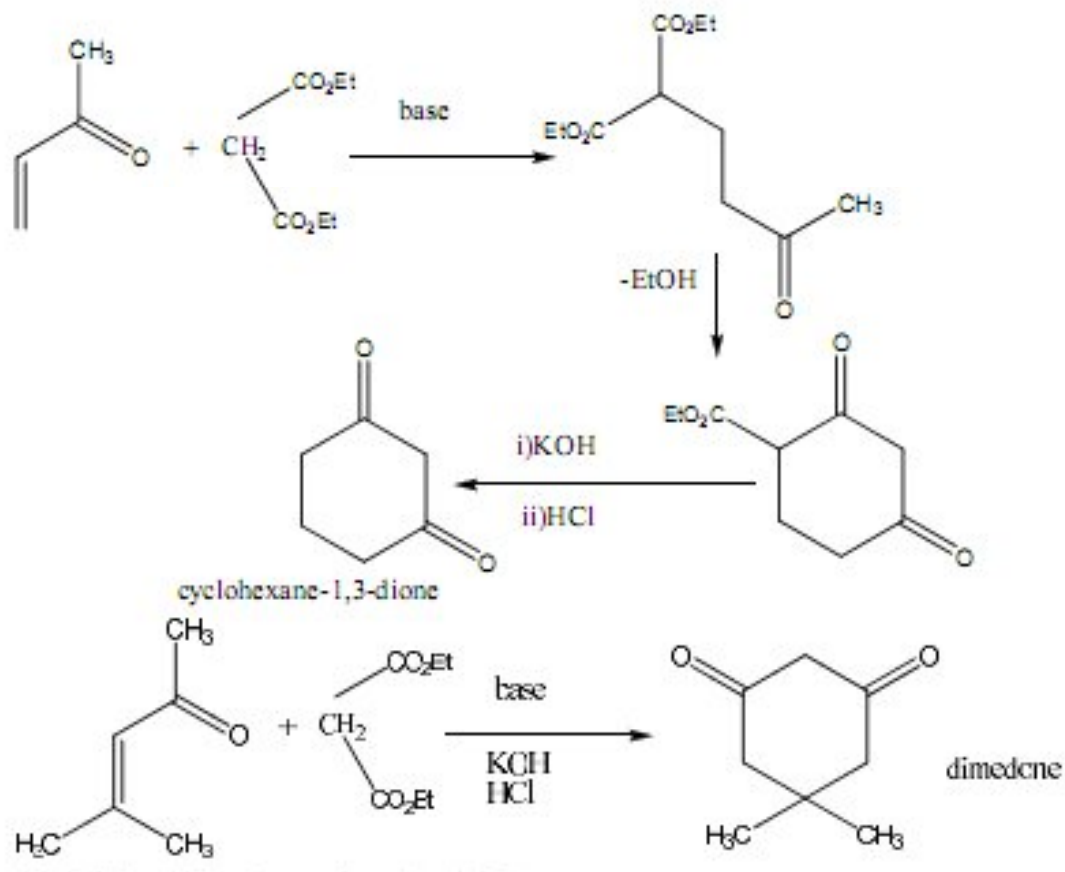
octane-3,6-dione

3-ethyl-2-methylcyclopentenone



**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.) :

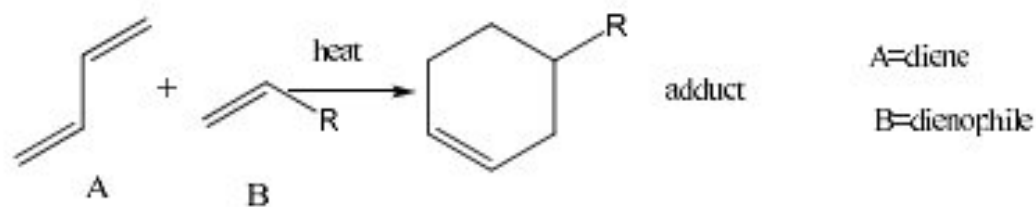
The D.A.R. is the addition of a conjugated diene to ethylenic compound in which the double bond is activated.

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

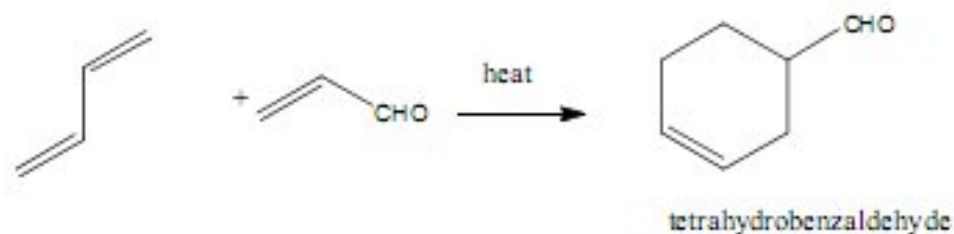
Diene :Contains two conjugated double bonds e.g. 1,3-butadiene , cyclopentadiene , anthracene ,furan.

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:



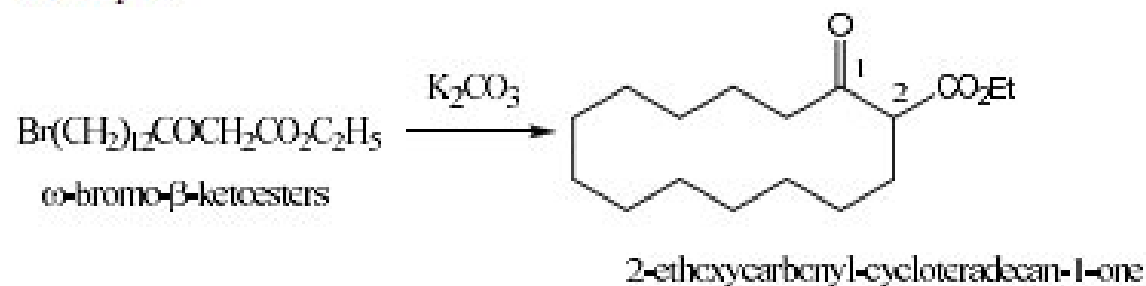
Example:



**11-Intramolecular alkylation:**

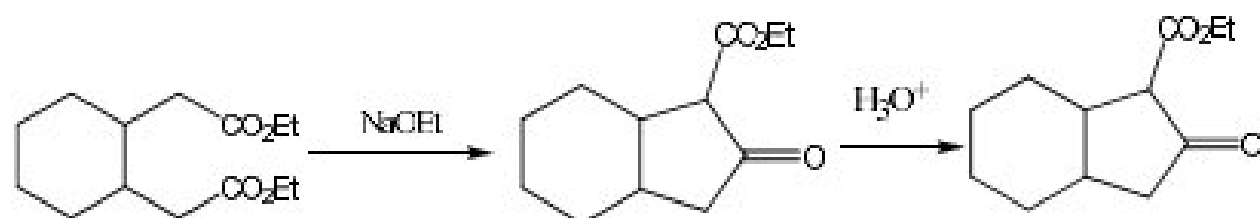
Under high-dilution conditions of  $\omega$ -bromo- $\beta$ -ketoesters with  $K_2CO_3$  produces C-14 - C-17 cyclic  $\beta$ -ketoesters (40-75%).

Example :

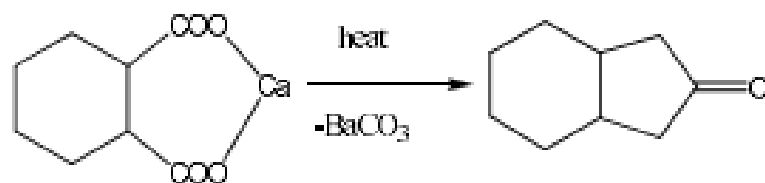


**12-Bicyclic systems may be obtained by :**

a-Dieckmann condensation :

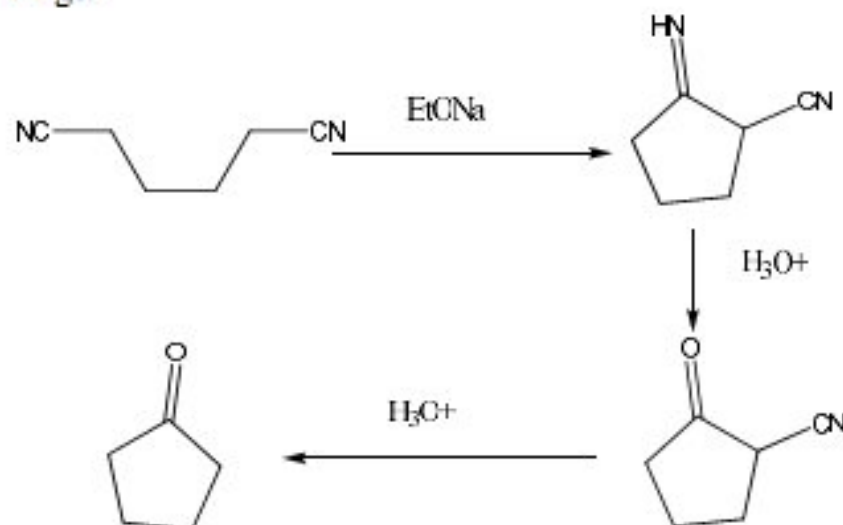


b-Pyrolysis of Ba or Ca salts of dicarboxylic acids:

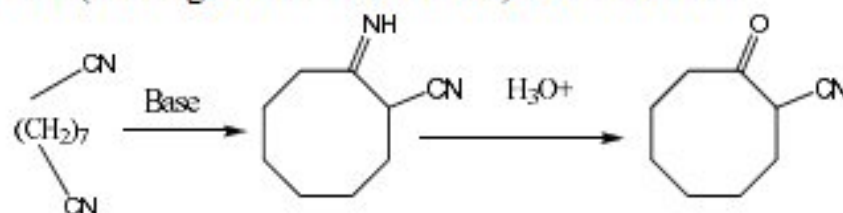


### 13-Thorpe-Ziegler reaction:

The cyclization of  $\alpha,\omega$ -dinitriles in the presence of base  $C_2H_5O^-$ . The initial product,  $\beta$ -iminonitrile is readily hydrolysed to  $\beta$ -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.

