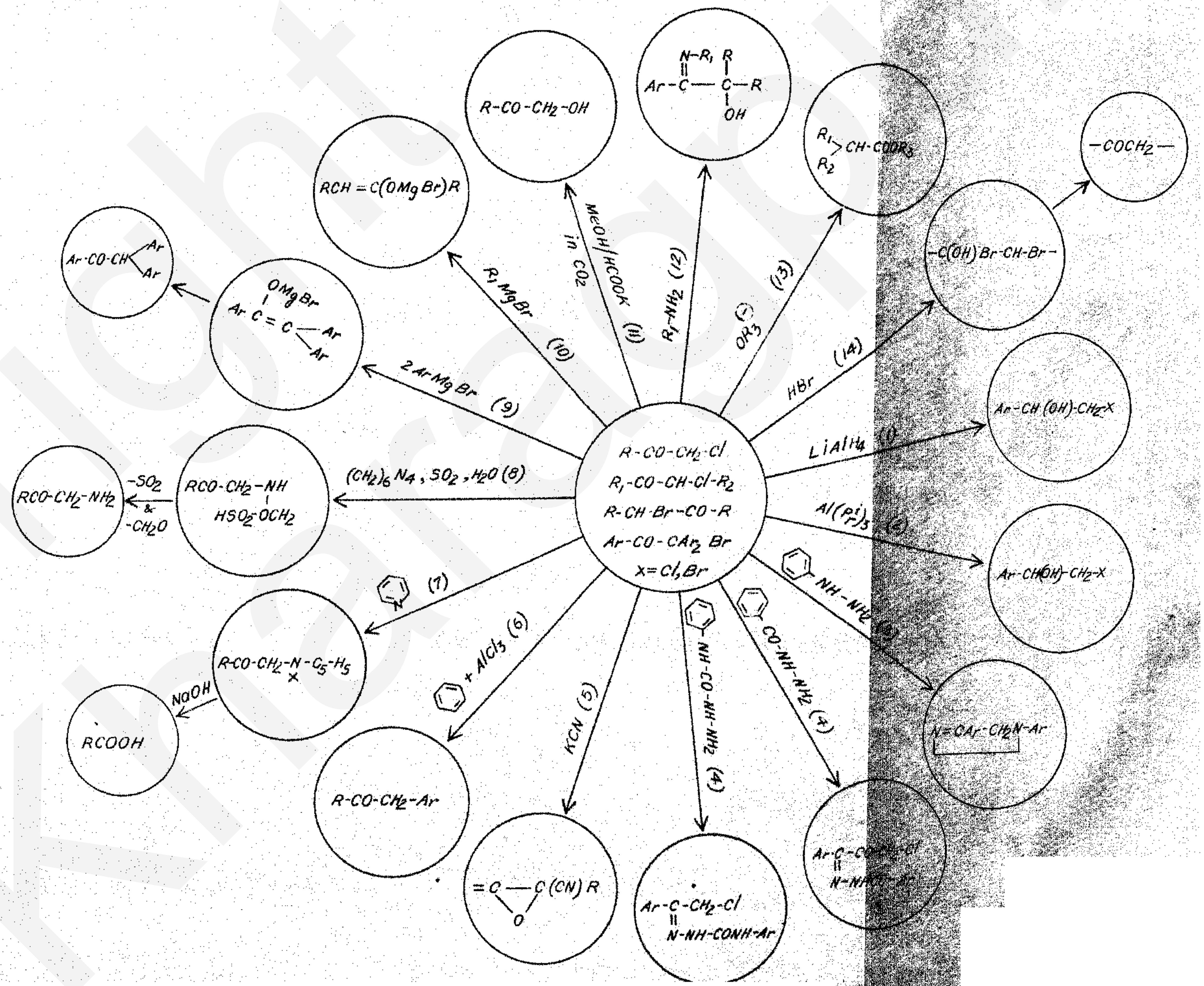
SECTION - A

INTRODUCTION

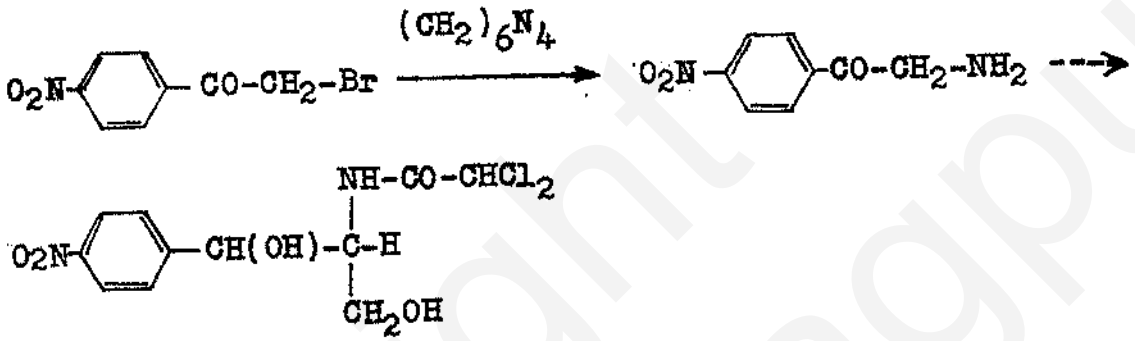
The ketones having the halogen atoms in the α-positions with respect to the keto group are known as α-haloketones. Depending on the number of halogen atoms present they could be mono-, di-, tri- and so on α-halogenated ketones. The author limits his discussion on the mono- α-halogenated ketones. Again, the halogen atom could be chlorine, bromine or iodine, but due attention has been given to study only the mono- α-chlorinated ketones. As α-haloketones possess two functional groups like the active halogen atom and the keto group, they may react in a great variety of ways involving either or both of their functional groups. Proper utilization of these characteristics of the α-haloketones leads to the syntheses of a number of important classes of compounds and thereby establishing the role of α-haloketones in synthetic organic chemistry. Without goining to the details some of the important reactions of α-haloketones have been assembled in the following table only to support the above statement.

TABLE-I

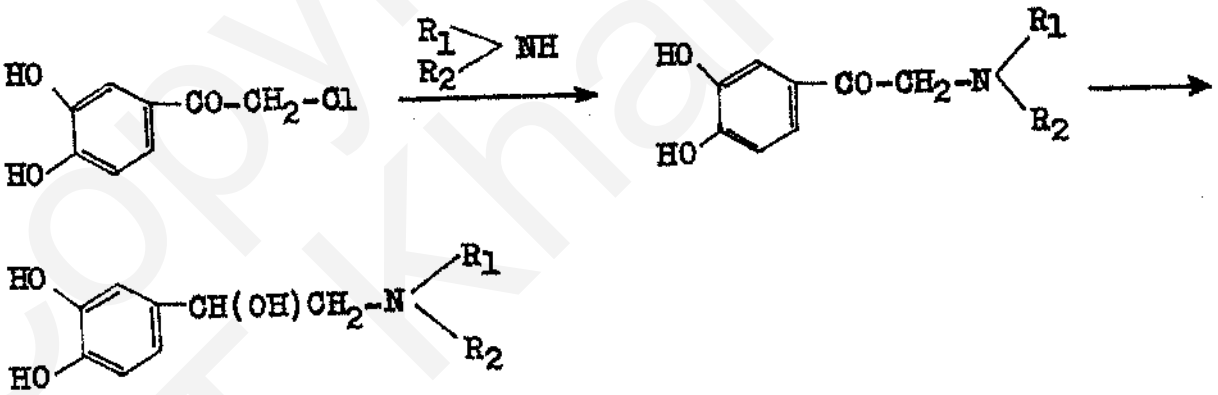


The importance of the ∝-haloketones as the key intermediate could easily be revealed by summarising a few of the many well-known syntheses.

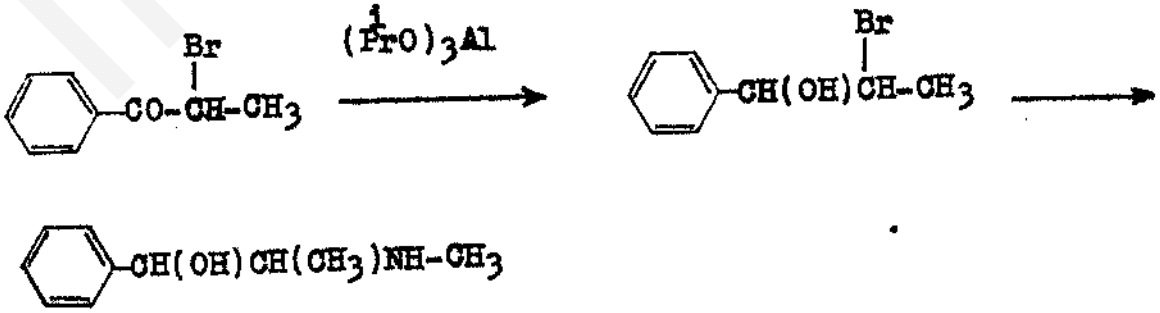
(a) Synthesis of chloramphenicol[15] :



(b) Synthesis of adrenergic drugs[16] :

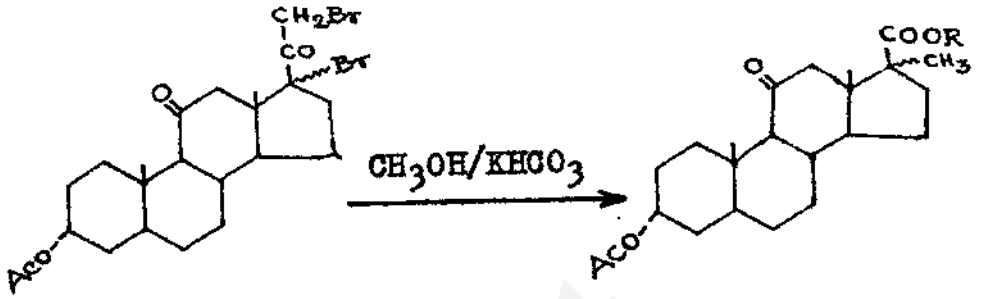


(c) Synthesis of dl-pseudoephedrine[17] :

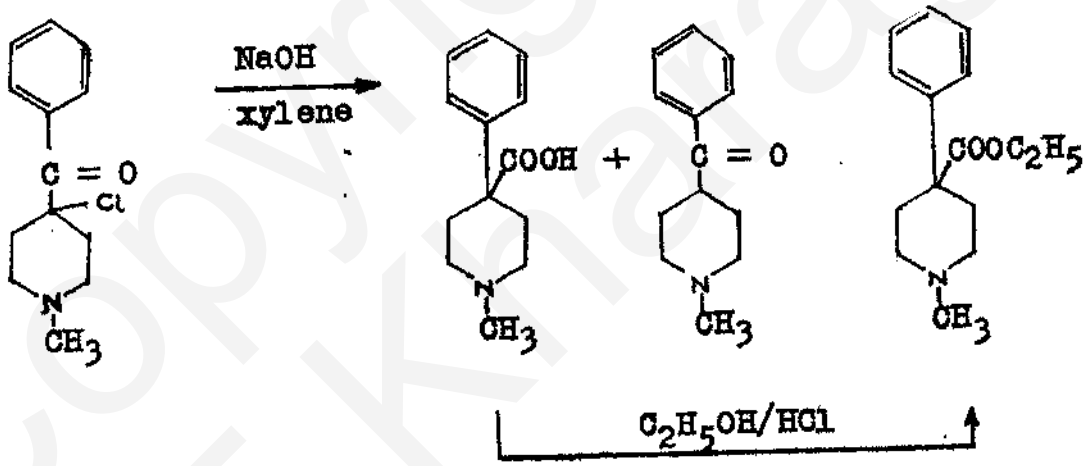


(d) Synthesis of cortical adrenal hormone [18]:

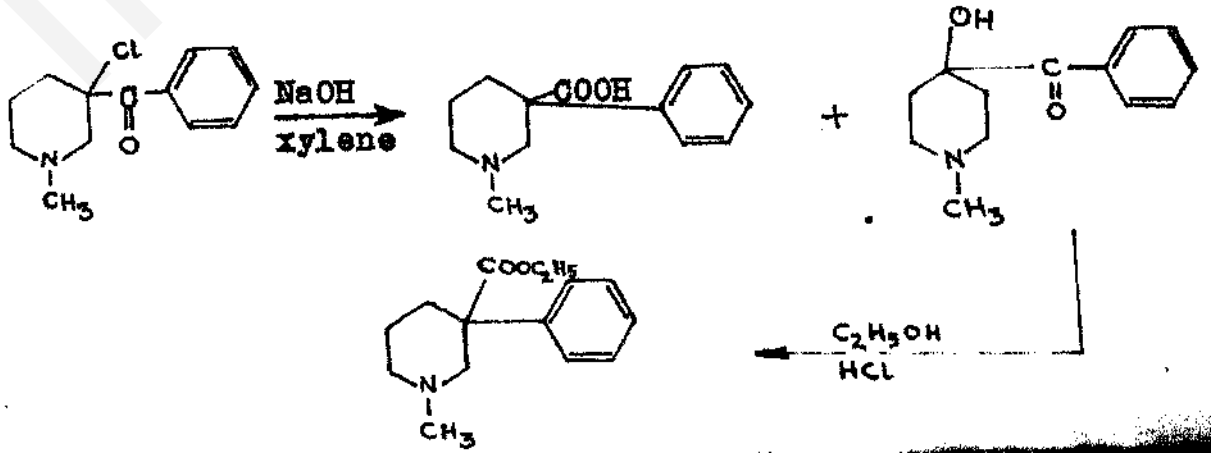
(by Favorskii rearrangement)



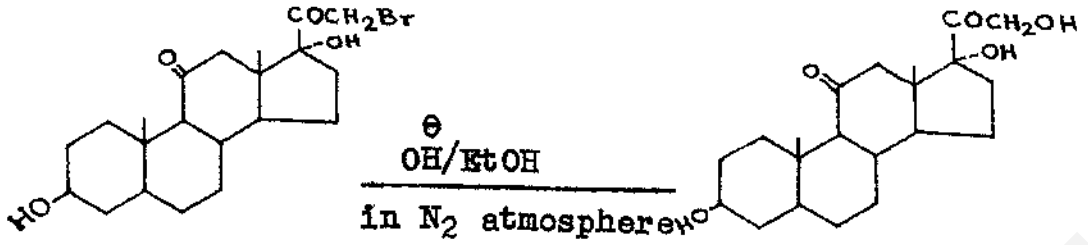
(e) Synthesis of demerol (ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate) [19]:



(f) Synthesis of β -pethidine (ethyl 1-methyl-3-phenyl-3-piperidinecarboxylate) [19]:

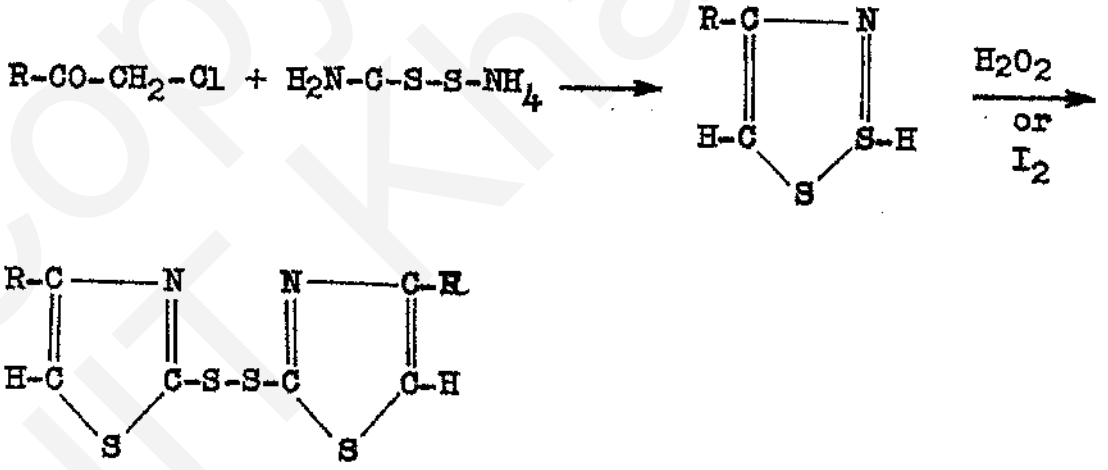


(g) Synthesis of steroid hormone[20] :

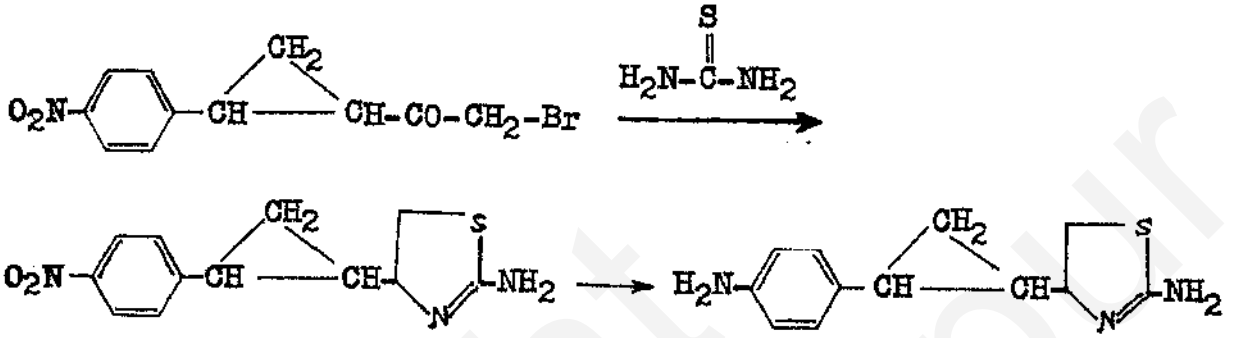


(h) Synthesis of thiazoles[21] :

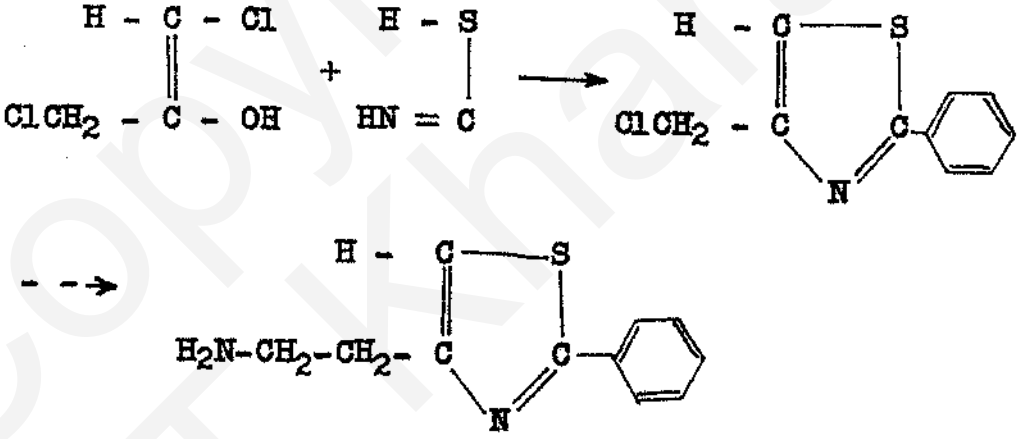
(i) Synthesis of mercaptothiazoles[22] :



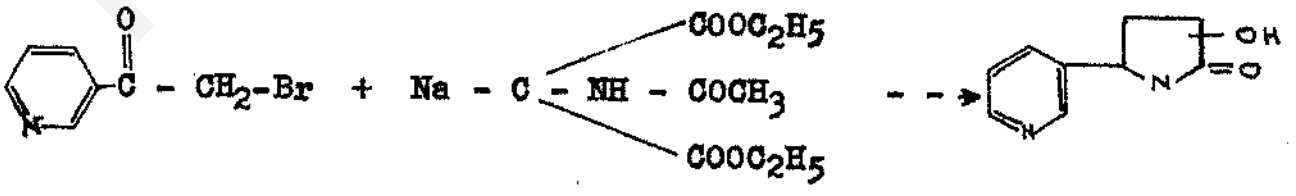
(j) Synthesis of 1-(2-amino-4-thiazolyl)-2-(4-aminophenyl)-cyclopropane, the antitubercular compound[23]:



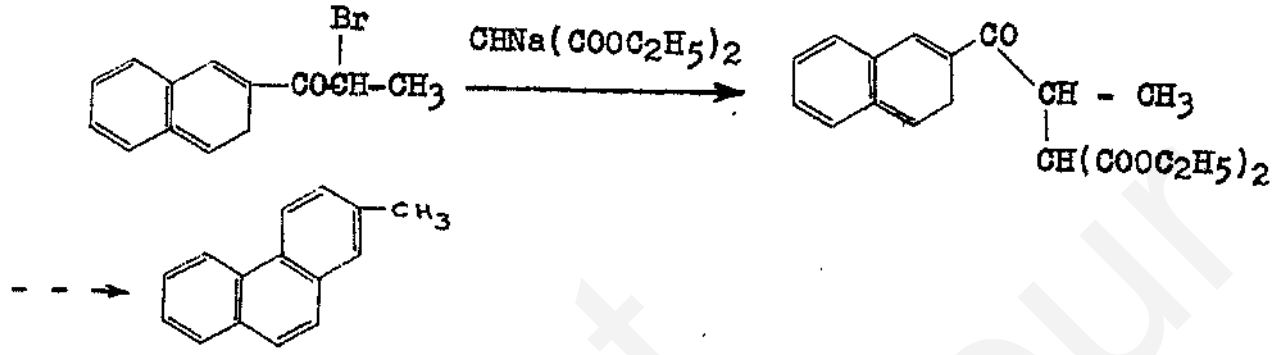
(k) Synthesis of thiazole amines possessing pharmacological interest[24]:



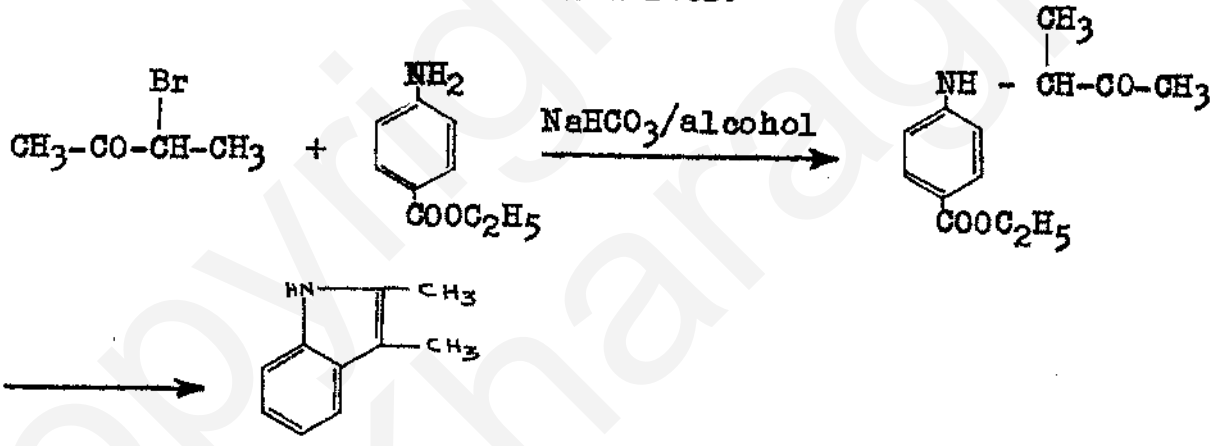
(l) Synthesis of hydrocotinine, an active metabolite[25]:



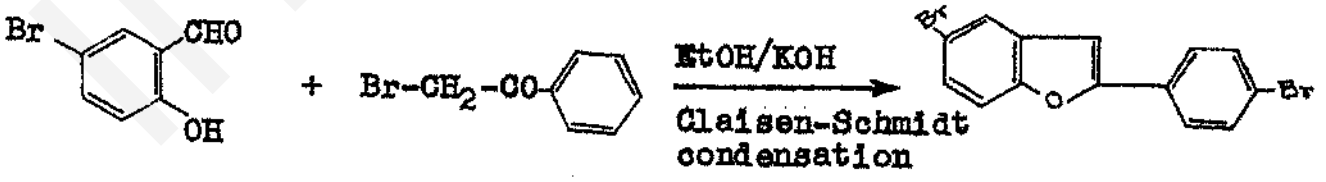
(m) Synthesis of polycyclic aromatic hydrocarbon[26]:



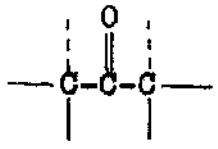
(n) Synthesis of indole derivatives:[27]



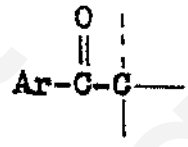
(o) Synthesis of substituted coumarone[28]:



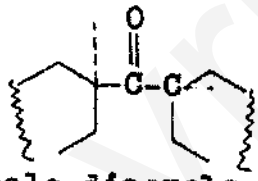
The mono- ∝ -halogenated ketones, as defined and established above, are, therefore, subjects of much interest and the study on their methods of preparation and properties would be highly interesting. But again even in the mono- ∝ -chlorinated ketones there could be a number of structural variations as shown below :

(a) 

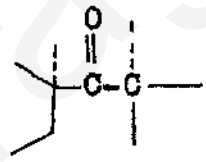
(∝ -halo-dialkyl ketone)

(b) 

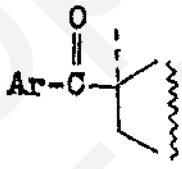
(∝ -halo-alkyl-aryl ketone)

(c) 

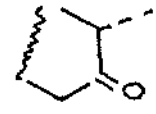
(∝ -halo-diacyclo-alkyl ketone)

(d) 

(∝ -halo-cyclo-alkyl-alkyl ketone)

(e) 

(∝ -halo-cyclo-alkyl-aryl ketone)

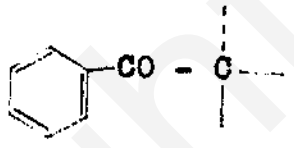
(f) 

(∝ -halo-cyclic ketone)

(halogen atom occupying any of the positions indicated by the (- - -) dotted lines). The author was interested only to study the method of preparations and properties of the class of mono- ∝ -haloketones as represented by the structure (b).

METHODS OF PREPARATION

On searching the literature the author finds a number of methods for the synthesis of mono- ∝ -haloketones of the type (b) by starting with widely different starting materials.



Type(b)

It would, therefore, not be out of the place to record some of these important synthetic routes to ∝ -haloketones and indicate their merits and demerits before he actually discusses the present method.

(a) Synthesis of ∝ -haloketones by direct halogenation of ketones [2,29,30] :

A large number of ∝ -haloketones have been prepared by the direct halogenation of the respective ketones

$$R\text{-}CO\text{-}CH_3 \xrightarrow{Cl_2} R\text{-}CO\text{-}CH_2\text{-}Cl$$

This method though gives ∝-haloketones in good yield, involves at least two major steps: (i) preparation of the desired ketones and (ii) halogenation. It is often difficult

to halogenate the ketone having other sensitive functional groups like - OH, - NH_2, - COOH etc.

(b) Synthesis of α-haloketones by reacting acid chloride with diazomethane followed by decomposition with dry HBr or dry HCl [31] :

Yield is generally very high.

$$R\text{-}CO\text{-}Cl + CH_2N_2 \xrightarrow{\text{dry HCl}} R\text{-}CO\text{-}CH_2\text{-}Cl$$

This method suffers from the following limitations :

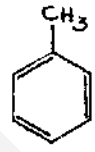
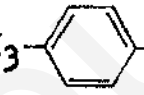
(i) The acid chloride will have to be prepared in the purest form ;

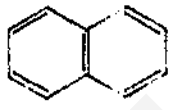
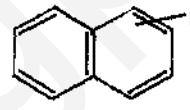
(ii) diazomethane is to be prepared fresh every time before it is used ;

(iii) the reaction cannot be carried out on a large scale;

and iv) suitably equipped laboratory and sufficiently trained hand are needed to work on this type of reaction.

(c) Synthesis of α-haloketones by the Friedel-Crafts reaction of α-haloacid chloride or its α-haloacid anhydride with aromatic nucleus like toluene, anisole, naphthalene and others in presence of anhydrous aluminium chloride [32,33] :

(i) $Cl\text{-}CH_2\text{-}COCl/(Cl\text{-}CH_2\text{-}CO)_2O$ +  $\xrightarrow{AlCl_3}$ CH_3-  -$CO\text{-}CH_2\text{-}Cl$

(ii)  + $Cl\text{-}CH_2\text{-}COCl$ $\xrightarrow{AlCl_3}$  -$CO\text{-}CH_2\text{-}Cl$

Largest number of mono- α-haloketones have been prepared by this method, but the yields are not always very high. In many cases a suitable inert solvent is needed for this reaction and that solvent plays important role towards the yield and the structure of the final product or products. Other defects like the preparation of pure acid chloride or anhydride, consumption of large quantities of pure anhydrous aluminium chloride, elaborate working-up of the reaction mixtures at the end are very common with this method.

(d) Synthesis of α-haloketones by the halogenation of the methylenic hydrogen containing ketone enol acetate with subsequent hydrolysis with methanol[34] :

$$C_4H_9\text{-}CH_2\text{-}CO\text{-}CH_3 + AC_2O \text{ (p-tol. sulf. acid)} \longrightarrow$$

$$C_4H_9\text{-}CH = \underset{\displaystyle OCOCH_3}{\overset{\displaystyle |}{C}}\text{-}CH_3 \xrightarrow[\text{in } CCl_4]{Br_2} C_4H_9\text{-}CHBr\text{-}\underset{\displaystyle OCOCH_3}{\overset{\displaystyle |}{C}}Br\text{-}CH_3 \xrightarrow{CH_3OH}$$

$$C_4H_9\text{-}CHBrCOCH_3 + CH_3OCOCH_3 + HBr$$

The chief disadvantages of this method are :

(i) preparation and isolation of the ketone enol acetate are essential before halogenation;

(ii) hydrolysis with methanol is to be done as a separate step ; and

(iii) the overall yields of the α-haloketone are not very good.

(e) Synthesis of α-haloketones by reacting α-chloroacid chloride with alkyl cadmium compounds[35] :

$$Cl\text{-}CH_2\text{-}COCl + CdR_2 \longrightarrow R\text{-}CO\text{-}CH_2\text{-}Cl$$

This method is applicable only to certain acid chlorides of suitable structures. The alkyl cadmium compound has to be prepared first which is generally very complicated. Here again the yields are not always satisfactory.