CHAPTER–I

INTRODUCTION
Pest control is an important aspect of agricultural development. The success of any insect control programme depends ultimately upon a combination of methods. The most efficient and dependable single means of control has been that of poisoning by chemical pesticides. Although this approach to insect control has been highly successful, it is not free from negative effects. The principle drawback of the use of classical insecticides consists in the lack of their specificity; the useful insects being also killed with the insect pests. Furthermore, the large scale application of insecticides for many years had led to the formation of more resistant insect strains requiring higher and higher doses of insecticides, resulting in increased disturbance of the local ecology and pollution of the environment. The residues of the commonly used chlorinated compounds (e.g. D.D.T.) accumulate in human and animal foods and thereby produce harmful effects. Under these circumstances, it is quite natural that more fundamental methods of insect control must be developed which take advantage of the biological, biochemical and behavioral differences which set insects apart from other animals.

Plants have evolved highly elaborate chemical defences against insect attack and these have provided us with a rich source of biologically active molecules having
insecticidal, antifeedant, attractant, repellent and insect growth regulating properties.

A number of insecticidal isobutylamides of straight chain, aliphatic, unsaturated, C\textsubscript{10-18} acids have been isolated from plants of the families Compositae and Rutaceae. Although most of these compounds have been completely identified, and in some cases synthesised, others as yet have been only partially characterised. Some examples of insecticides of the above type are pellitorine, spilanthol, heliopsin etc. The presumptive advantage of these insecticides was that they break down quickly into harmless compounds on exposure. Moreover, these compounds proved to be less of health hazard to human beings compared to synthetic insecticides. But the commercialisation of these natural plant insecticides is hampered by their high production costs.

Insect antifeedants\textsuperscript{1} are attracting the research interest owing to their effect on a range of major crop pests. An antifeedant is a chemical which inhibits feeding but does not kill the insect directly. The insect often remains near the antifeedant source and possibly dies through starvation. Synthetic work in the antifeedant area has been active\textsuperscript{2}, the terpenoid drimane and the diterpenoid clerodane antifeedants being popular targets. Two important examples of sesquiterpene drimanes are polygodial and
warburganal, which are potent antifeedants for African army worms. With antifeedants, only surface feeding insects are prevented from feeding, but sucking insects are not affected.

Recently, attention has been directed to put sex pheromones to practical use for the field control of pests. Insect attractants are the chemical substances which elicit oriented movements by insects towards their source. Female gypsy moth releases a potent pheromone, disparlure, that attracts the male for mating. Attractants help to lure pests to the sites of destruction by poison, electrocution or trapping. Repellents have also played a very important role in the protection of man against blood sucking insects and vectors of diseases. These are the chemicals causing insects to move away from their source. Oil of citronella and oil of camphor are widely used as mosquito repellents.

Another method of insect control is by radiation inducing sterility as also chemosterilisation methods. But these become valuable only when the population density of the pest is low. For the insect control, attention has also been paid especially to the insect endocrinology and insect hormones.

Insect hormones are a physiologically active class of organic compounds which regulate the specific development of the insects from the egg to the adult stage. Exhaustive reviews and books on the chemistry and biochemistry
of juvenile hormones show the significance of hormonal control in insect growth.

Wigglesworth\textsuperscript{22,23} was the pioneer in establishing the existence of insect hormones as brain hormone (BH), prothoracic gland hormone or moulting hormone (MH) and juvenile hormone (JH). Neurosecretory cells secrete the brain hormone, whose action on the prothoracic glands initiates the synthesis and release of moulting hormone, i.e. ecdysone, which induces the events associated with each moult, which have been shown diagramatically below.

\begin{center}
\begin{tikzpicture}
  \node (brain) {Brain};
  \node (nc) [below of=brain] {Neurosecretory cells};
  \node (cc) [below of=nc] {Corpora Cardiaca};
  \node (ca) [below of=cc] {Corpora allata};
  \node (j) [right of=ca] {JH \to Ecdysone \quad (Maintains juvenile character)};
  \node (mh) [left of=ca] {Brain hormone \to Corpora allata};
  \node (bg) [right of=cc] {Moulting gland};
  \node (ec) [right of=bg] {Ecdysone \to JH \quad (Stimulates moulting)};

  \draw[->] (brain) -- (nc);
  \draw[->] (nc) -- (cc);
  \draw[->] (cc) -- (ca);
  \draw[->] (ca) -- (j);
  \draw[->] (ca) -- (mh);
  \draw[->] (cc) -- (bg);
  \draw[->] (bg) -- (ec);
\end{tikzpicture}
\end{center}

Corpora allata are the endocrine glands associated with the corpora cardiaca and are under the influence of the
brain hormone secreted by the corpora cardiaca. These glands secrete juvenile hormone as it maintains the juvenile character of the developing stage and then control the amount of JH which enters the bloodstream of the insect. If high concentrations circulate in the bloodstream, the insect will remain sexually immature. The flow of the juvenile hormone into the bloodstream must stop if the larva is to metamorphose into a mature adult. During the adult hood of the insects, the JH also performs other functions, such as controlling the sexual development, the production of sex attractants, the ability to reproduce and the ripening of the eggs from which the insects are born. This hormone is activated when the titre of ecdysone is low after moulting of the developing stage. When ecdysone is activated, the juvenile hormone suppresses. Thus there is a titre between ecdysone and juvenile hormone for regulation of moulting or metamorphosis.

When the synthetic juvenile hormone analogues (JHA's) are applied on the developing stages at a critical period when ecdysiotropin secreted by neurosecretory cells is very low, these disturb the titre in the hemolymph and do not allow the ecdysone to overpower the juvenile hormone with the result moulting is inhibited as this moult must take place in the relative absence of juvenile hormone. It has been found that the treatment of the last stage larva with juvenile hormone causes it to moult to a larval-pupal
monster retaining a mixture of larval and pupal features, or it may moult into a supernumerary larva which can continue feeding. If the exogenous supply of hormone is stopped, it may eventually moult to a giant pupa and subsequently to a giant adult. In actual practice most of these monsters and supersized larvae die shortly after or during moulting. The juvenile hormone must likewise be absent during pupal-adult transformation. Treatment of a pupa with juvenile hormone results in the formation of a pupal-adult intermediate or the pupa may simply moult to a second pupa. The result in either case is a deformed insect which lives but a few days and is unable to reproduce.

So juvenile hormone analogues can provide another method for controlling insect population because of their insecticidal, morphogenetic and chemosterilant effects not only on the adults but also on the eggs and various larval stages of insects. Juvenile hormone analogues (JHA's) or juvenoids encompass a wide range of synthetic compounds with a relatively smaller amount of natural products isolated from plants and animals. The only criterion for classification of a compound as a JHA is its property to exhibit or mimic some morphological or physiological effects of the hormone secreted by the corpora allata.

The main advantage of juvenoids lies in their low or practically zero toxicity which also applies to their
breakdown products. Moreover, whole series of juvenoids act selectively on certain species of insect pests which may enable to achieve selective control with minimum disturbances of natural zoocenoses, including normal development of the pest's natural enemies such as parasites and predators. Further advantage is enormously high biological activity of certain juvenoids which make it possible to use considerably smaller amounts of the active compounds and thus minimize contamination of the environment. However, insecticides can be used in emergency situations whereas juvenoid action is less immediate and most efficient in preventing gradations and reproduction of the pest populations.

There are two categories of juvenoids with respect to their suitability for insect control. First of them is represented by compounds with relatively low selectivity, which act on many unrelated insect species and the second category includes compounds with selective action on some insect species. The choice to produce juvenoids for commercial use are in favour of the universal juvenoids. Juvenoids must also persist for considerably longer periods in order to achieve a complete control.

The idea of using chemicals with insect juvenile hormone activity as pesticides was known since 1956. William was the first to obtain juvenile hormone effects on metamorphosis using lipid extracts prepared from abdomens.
of adult male Cecropia moths and the presence of juvenile hormone activity in these extracts was confirmed by Wigglesworth\textsuperscript{25} on Rhodnius. William and coworkers\textsuperscript{26} found juvenile hormone activity in lipid extracts prepared from Thymus and human placenta. Lipid extracts prepared from adrenal cortex of vertebrates\textsuperscript{27}, from crustaceans and also from microorganisms and plants\textsuperscript{28} were found to possess juvenile hormone activity by Schneiderman and Gilbert. Juvenile active compounds were also found to be produced by insect parasite Nosema\textsuperscript{29}.

The primary action of a hormone cannot be revealed unless the chemical nature of that hormone is known. For many years intensive efforts were made to purify and analyse the Cecropia extract\textsuperscript{30-32}. After a series of biological and chemical investigations, the structure of the juvenile hormone isolated from the giant silkworm moth Hyalophora cecropia was determined to be methyl 10,11-epoxy-3,11-dimethyl-7-ethyl-trans-2,6-tridecadienoate\textsuperscript{33-35} (A\textsubscript{1}) i.e. Cecropia C\textsubscript{18}-JH.

\[\text{A}_1\]
The stereochemistry of the Cecropia C18-juvenile hormone was finally elucidated on the basis of synthesis. Sidall et al. has reported a stereospecific synthesis of A1 based on sequential fragmentation of the bicyclic precursor (I). The control of olefin geometry therefore, being transposed to a control of relative stereochemistry in cyclic systems. The reaction sequence is shown in the scheme:

\[ \text{reaction sequence shown in the scheme} \]
Another stereospecific total synthesis of the racemic Cecropia C₁₈-juvenile hormone was given by Corey et al. Corey's synthetic route comprised several novel synthetic processes of general application as shown below:

(i) Propylvinyl ketone, (ii) H⁺, (iii) NaBH₄, (iv) Dihydropyran, H⁺ (V) MeI, (vi) LiAl(0. t Bu)₃H, (vii) m-chloroperbenzoic acid (viii) LiAlH₄, (ix) p-CH₃C₆H₄SO₂Cl, (x) NaH, (xi) MeLi
In the course of investigations on the Cecropia extract, Meyer et al. reported the isolation and identification of another juvenile hormone (A2) which was shown to be identical with (A1) except for the presence of a methyl group instead of an ethyl group at C7-position. The structure of (A2) was found to be methyl cis-10,11-epoxy-
3,7,11-trimethyl-trans-2,6-tridecadienoate (A2) (Cecropia C17-JH).

The structure of the C17-JH was confirmed by a stereospecific synthesis\textsuperscript{42} of the racemic form. The reaction sequence leading to (A2) is depicted below:

\begin{align*}
\text{R} & \quad \text{OH} \\
\text{IV} & \quad \text{COOCH}_{3} \\
\text{COOCH}_{3} \\
\end{align*}
The Cecropia juvenile hormones (A₁) and (A₂) showed immense biological activity on Lepidoptera. Corey and associates synthesized these compounds through simple routes which are given below:

(i) Methyl trans-4-bromosenecionate,
(ii) decarboxylation, (iii) NaBH₄,
(iv) PBr₃, LiBr, ZnBr₂, (v) NaI,
(vi) Li-enolate of heptane-3,5-dione,
(vii) CuCl₂-LiCl, (viii) Ba(OH)₂,
(ix) MeMgCl, (x) K₂CO₃
The third juvenile hormone ($A_3$) was reported by Judy\textsuperscript{44} which is now considered to be the most abundant of the three juvenile hormones known so far\textsuperscript{45}. The total synthesis of methyl juvenate ($A_3$) was devised by Cavill and Williams\textsuperscript{46}.
A number of synthesis of third juvenile hormone have been reported including three chiral synthesis\textsuperscript{47-49}. Yamamoto and associates\textsuperscript{50} synthesised (A\textsubscript{3}) through another convenient process which can provide a powerful route to the useful building block of chiral terpenes. The reaction sequence is depicted below:

(i) Ph\textsubscript{3}P=CH\textsubscript{3}

(ii) H\textsuperscript{+}, (iii) (CH\textsubscript{3}O\textsubscript{3})\textsubscript{2}POCH\textsubscript{2}COOCH\textsubscript{3},

(iv) Mesyl chloride (v) MeONa

\begin{align*}
\text{(ii) } & \text{H}^+ , \text{(iii) (CH}_3\text{O}_3)\text{POCH}_2\text{COOCH}_3, \\
\text{(iv) Mesyl chloride (v) MeONa}
\end{align*}

\textbf{A number of synthesis of third juvenile hormone have been reported including three chiral synthesis}^{47-49}. Yamamoto and associates\textsuperscript{50} synthesised (A\textsubscript{3}) through another convenient process which can provide a powerful route to the useful building block of chiral terpenes. The reaction sequence is depicted below:

\begin{align*}
\text{(i) } & \text{Ph}_3\text{P} \equiv \text{CH}_3 \\
\text{(ii) } & \text{H}^+, \text{(iii) (CH}_3\text{O}_3)\text{POCH}_2\text{COOCH}_3, \\
\text{(iv) Mesyl chloride (v) MeONa}
\end{align*}
(i) 4-t-BuC_{6}H_{4}NTf_{2}, LDA/THF-HMPA, -78°– -20°, 80%,
(ii) PdCl_{2} (CH_{3}CN)_{2}, PPh_{3}/CHCl_{3}, 80°, 76%,
(iii) Pd (PPh_{3})_{4}, CsF/THF, reflux, 58%,
(iv) Cr(CO)_{3} Np, H_{2} (80 atm), THF, 45°, 66%

The juvenile hormone activity was found not only in insects but also in wood and bark extracts of some forest trees. Slama and Williams\(^{51-53}\) observed the inability of certain insect species to reproduce in contact with an ordinary paper. When reared on 'active paper' the fifth stage larvae of *Pyrrhocoris apterus* undergo one or more supernumerary larval moults and finally die without completing metamorphosis or attaining sexual maturity. Even the eggs could not be hatched in contact with active paper. However, it has no detectable effect on eggs of many other species. The active compound in the paper, (+) juvabione (A_{4}) was independently isolated by Bowers et al\(^{54}\) and Cerny et al\(^{55}\) and identified as the methyl ester of todomataic acid. In addition to juvabione, the Czech authors isolated another biologically active compound as dehydrojuvabione (A_{5}) from slovak fir.
Both juvabione and dehydrojuvabione were shown to exhibit a highly specific juvenile hormone activity.

The first synthesis of racemic (+)-juvabione was reported by Mori and Matsui\textsuperscript{56,57} using \(p\)-methoxy acetophenone as the starting material.
The absolute configuration of naturally occurring (+)-juvabione, originally proposed as R,R at both the optically active centres was proved wrong by Pawson et al, who in connection with the stereospecific synthesis of all the four theoretically possible isomers of juvabione, proved the absolute configuration to be R at position 4 of the menthane skeleton and S at the 8th position of the same system. The reaction sequence used in the synthesis is described below:

(i) BrCH₂COOR, (ii) H₂, Ni, (iii) SOCl₂, (iv) NH (CH₃)₂, (v) (C₂H₅O)₃ LiAlH, (vi) MgBr₂, (vii) Li, liq. NH₃, (viii) H⁺, (ix) H₂, Pd, (x) Ac₂O, (xi) HCN, (xii) POCl₃, (xiii) KOH, (xiv) Cr₂O₃, (xv) CH₂N₂
Bis-3-methyl-2-butylborane, TsCl, NaCN, Li, O₂ (hv), H₂CrO₄, Ag₂O, CH₂N₂

Juabione served as a model substance in the synthesis of numerous compounds of potential insect juvenile hormone activity. The history of synthetic juvenoids started with the discovery of Schmialek⁶¹-⁶³ who found that the active component in Tenebrio excrements and yeasts were farnesol (B₁) and farnesal (B₂). These results interested many terpene chemists and soon numerous acyclic terpenes were tested for their juvenile hormone activity. It was found that alkyl farnesyl ester (B₃), farnesyl methyl ether (B₄) and N, N-diethyl farnesyl amine (B₅)⁶⁴-⁶⁷ were among the most active compounds.

\[ B₁, \ X = -\text{CH}_2\text{OH} \]
\[ B₂, \ X = -\text{CHO} \]
\[ B₃, \ X = -\text{COOR} \]
\[ B₄, \ X = -\text{CH}_2\text{OCH}_3 \]
\[ B₅, \ X = -\text{CH}_2\text{N(Et)}₂ \]
Epoxidation of farnesol and farnesyl methyl ether was carried out by Bowers et al. and the activity of the resulting compounds was tested. It was observed that epoxidation affords an efficient route to increase the morphogenetic activity of parent unsaturated compounds.

The esters (C) of farnesoic acid prepared by its esterification or by the reaction of geranyl acetone with Werner-Wittig reagent or Wadsworth-Emmons reagent were found to be considerably more active as compared to the parent acid whose activity for all practical purpose is nil.

Both the above reactions have been frequently used in the preparation of juvenoids because of their simplicity and good yields. Further, the \( \alpha, \beta \)-unsaturated ester grouping in the synthetic acyclic juvenoids seems to be of great significance for the JH activity. Thus, hexahydropseudoionone yielded methyl 3,7,11-trimethyl-2-dodecenoate \((D_1)\), citronellyl acetone gave methyl 3,7,11-trimethyl-2,10-dodecadienoate \((D_2)\) using Werner-Wittig reaction.
Law and coworkers\textsuperscript{77} reported the preparation of a mixture of chlorinated farnesyl ester by bubbling gaseous hydrogen chloride into a solution of farnesoic acid in lower aliphatic alcohols. The crude reaction mixture showed morphogenetic activity on butterflies, beetles as well as on the bugs of family pyrrhocoridae reported by Romanuk et al\textsuperscript{78} as alkyl 3,7,11-trimethyl-7,11-dichloro-2-dodecenoate (E).

Among the various farnesolic acid amide derivatives\textsuperscript{79}, N-ethyl-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoic acid amide (F) was found to be very active against the last instar larvae of Musca domestica, Aedes aegypti and Tenebrio molitor. 10,11-epoxy-3-methyl-7,11-diethyl-trans-2,6-dodecadienoic acid amide also exhibited fairly good potency.
Soon after, numerous acyclic terpenes were also tested for their JH activities. Encouraged by the presence of juvenile hormone activity in terpenic compounds, many more acyclic juvenoids \(^{75,80-88}\) which may be represented by a carbon skeleton of the general formula as illustrated below were prepared.

Where, \(R_1-R_4 = \text{H or alkyl group (C}_1\text{-C}_6\)\)

\(X = \text{alkoxy, carbonyl, alkoxy methylene, amino carbonyl, amino methylene, phosphono methylene or cyano group.}\)

\(Z_1\) and \(Z_2\)  May together represent: a carbon-carbon bond, an oxygen, sulphur, methylene,

\(Z_3\) and \(Z_4\)  dichloromethylene or a difluoromethylene bridge.

\(Z_1 = \text{-H or -OH}\)

\(Z_3\) & \(Z_5 = \text{-H or -OH}\)

\(Z_2, Z_4 & Z_6 = \text{-H, -OH, alkoxy or halogen}\)
Extending the interest in juvabione chemistry, Slama et al\textsuperscript{89} and Suchy et al\textsuperscript{90} have prepared the synthetic analogues (G\textsubscript{1}-G\textsubscript{6}) of juvabione and dehydrojuvabione in which the cyclic ring is replaced by an aromatic ring. Some of these synthetic derivatives are more active than natural (+)-juvabione.
Some geranyl phenyl ethers and their epoxides have been reported by Bowers\textsuperscript{91,92}. They were found to show high juvenile hormone activity. All these compounds were prepared by alkylation of different phenols with geranyl bromide in dimethoxy ethane and in the presence of powdered potassium hydroxide. Introduction of the epoxy group into position 6,7 of the geranyl residue was accomplished by the reaction of m-chloroperbenzoic acid with parent compounds in CH\textsubscript{2}Cl\textsubscript{2} at 0\textdegree.

The following compounds were also reported by Bowers\textsuperscript{91,92}.

H\textsubscript{4}, \hspace{1em} R =

H\textsubscript{5}, \hspace{1em} R =

H\textsubscript{6}, \hspace{1em} R =
It was found that the presence of the methylene-dioxy group markedly potentiates the juvenile hormone activity and has a great influence on the specificity of action. All these compounds have been found to exhibit morphogenetic properties as well as ovicidal activity on eggs of some Coleoptera e.g., the Mexican bean beetle, the cigarette beetle.

Similar to the oxirane derivatives certain carbene derivatives have also been reported\(^9\) in which the terminal double bond of geranyl p-chlorophenyl ether (I\(_1\)) has been replaced by a carbene, dichlorocarbene and ethoxycarbonyl carbene to yield I\(_2\), I\(_3\) and I\(_4\) respectively. The JH activity of the compounds I\(_2\) and I\(_3\) on the hemipterans, Pyrrhocoris apterus and Dysdercus cingulatus was practically equal to that of the analogous epoxides, but very low on Tenebrio molitor.
Relatively small number of geranyl phenyl thioethers have been reported. Sorm and coworkers\textsuperscript{94} prepared thioethers $(J_1)$ and $(J_2)$ by the alkylation of 3,4-methylenedioxythiophenol with geranyl bromide and citronellyl bromide respectively. Various derivatives of these compounds have also been reported.

![Derivative structures](image)

Derivatives of p-nitroaniline\textsuperscript{95} and also of p-nitrophenol with geranyl bromide showed very high JH activity, but exclusively on hemipterans of the family Pyrrhocordiae. It may be appropriate to mention that the numerous hybrids of geranyl bromide and p-aminobenzoate also exhibit remarkable biological activity on some otherwise resistant hemipteran species. The highest biological activity was shown by the compounds $(K_1)$ and $(K_2)$.

![Additional derivative structures](image)
The very high biological activity of some terpenic derivatives of \( \varepsilon \)-aminobenzoic acid led Zaoral and Slama\(^{96} \) to report the preparation of some peptide derivatives of alkyl-\( \varepsilon \)-aminobenzoate. The compound (L), a close analogue of ethyl \( n \)-geranyl-\( \varepsilon \)-aminobenzoate was very active on \textit{Pyrrhocoris apterus} and \textit{Dysdercus cingulatus}.

![Chemical structure of L]

\[ \text{L} \]

JH analogues containing two or three heteroatoms have also been reported\(^{97-99} \) (\( M_1-M_3 \)). Several terpenoid ethers as JH analogues (\( M_3 \)) reported by G. Brieger et al\(^{99} \) showed JH activity on \textit{O. fasciatus} and \textit{Autographia californica}.

![Chemical structures of \( M_1, M_2, \) and \( M_3 \)]

\[ \text{M}_1 \]

\[ \text{M}_2 \]

\[ \text{M}_3 \]
A large number of geranyl alkyl ethers and epoxides have been reported by Deshpande et al\textsuperscript{100}. Vig et al\textsuperscript{101-110} also prepared quite a large number of geranyl alkyl ethers, long chain substituted aromatic hydrocarbons and their derivatives. The ethers and the derivatives of hydrocarbons were screened for their JH activity against common Indian red cotton bug in order to establish the structure-activity relationship.

Some silicon-containing JHA's ($N_1,N_2$) were synthesised by Ujvary et al\textsuperscript{111}. The topical application of $N_1$ and $N_2$ on yellow mealworm, housefly, fleshfly and cabbage white butterfly have shown that these compounds are quite active.

\begin{equation}
\begin{aligned}
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{Si} & \quad \text{(CH}_2\text{)}_3 & \quad \text{-CH} & \quad \text{-CH}_2 & \quad \text{-CH} & \quad \text{=CH} & \quad \text{C} & \quad \text{=CHCOOR} \\
& \quad \text{CH}_3 & \quad & \text{N}_1 \\
& \quad \text{CH}_3
\end{aligned}
\end{equation}

\begin{equation}
\begin{aligned}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{Si} & \quad \text{(CH}_2\text{)}_3 & \quad \text{-CH} & \quad \text{-CH}_2 & \quad \text{-CH}_2 & \quad \text{-O} & \quad \text{R} \\
& \quad \text{CH}_3 & \quad & \text{N}_2 \\
& \quad \text{CH}_3
\end{aligned}
\end{equation}

A number of synthetic juvenoids containing $\alpha,\beta$-unsaturated ester grouping have also been synthesised\textsuperscript{112-114}. 

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Compounds containing oxime ether function have been reported to possess JH activity against *Culex pipiens pallens* larvae\textsuperscript{115-118}. Recently a series of propionaldoxime (Oa-h) and acetoxime (Pa-h) ethers have been synthesised by Patwardhan and Coworkers\textsuperscript{119}, all these compounds exhibited complete adult emergence in mosquitoes at 1ppm, while some are active at 0.1 ppm.

\begin{align*}
\text{RO} & \text{O} \text{N} \\
0 & \text{(a–h)}
\end{align*}

\begin{align*}
\text{RO} & \text{O} \text{N} \\
P & \text{(a–h)}
\end{align*}

\begin{array}{l}
a, \text{CH}_3^- \\
b, \text{C}_2\text{H}_5^- \\
c, \text{C}_6\text{H}_5\text{CH}_2^- \\
d, \text{C}_6\text{H}_5 \\
e, 4-\text{CH}_3\text{C}_6\text{H}_4^- \\
f, 4-\text{C}_2\text{H}_5\text{C}_6\text{H}_4^- \\
g, 4-(\text{CH}_3)_2\text{CHC}_6\text{H}_4^- \\
h, 4-\text{Cl}\text{C}_6\text{H}_4^- \\
\end{array}
Currently four juvenile hormones have been practically applied\textsuperscript{120}. Kinoprene (Enstar) is used to control Homoptera on ornamental plants in the greenhouse. Various formulations of methoprene are used for control of mosquitoes, ants, fleas and stored product insects. The juvenile hormone hydroprene is used to control cockroaches. Phenoxy carb, a juvenile hormone with a wide spectrum of action is used against caterpillars of fruit moth, as well as against aphids and scale insect orchards.

\begin{align*}
\text{Kinoprene} & : & \begin{array}{c}
\text{\includegraphics[width=0.4\textwidth]{kinoprene.png}}
\end{array} \\
\text{Methoprene} & : & \begin{array}{c}
\text{\includegraphics[width=0.4\textwidth]{methoprene.png}}
\end{array} \\
\text{Hydroprene} & : & \begin{array}{c}
\text{\includegraphics[width=0.4\textwidth]{hydroprene.png}}
\end{array} \\
\text{Phenoxy carb} & : & \begin{array}{c}
\text{\includegraphics[width=0.4\textwidth]{phenoxy Carb.png}}
\end{array}
\end{align*}
Methoprene is a metabolically and environmentally stable analogue of the insect juvenile hormone JH (III) i.e. A₃. It was developed by Zoecon for fly and mosquito control and was the first insect growth regulator to be registered for use in pest control. A radio iodinated juvenoid, (iodovinyl) methoprene (S) having both high biological activity and high specific activity has also been synthesised by Prestwich and coworkers.

\[ S, R = CH_3 \]

The present investigations were aimed at preparing a few prototype of active juvenoids which would be more stable and more accessible for practical use in the control of insects.

During the present synthetic endeavours, two principle reactions namely coupling of Grignard reagents with suitable alkyl halides in the presence of catalytic amounts of Li₂CuCl₄ for carbon chain elongation and the modified Wittig reaction for introducing a conjugated ester with known geometry of the double bond in an appropriate alkyl chain have been made use of in addition to many other well-established organic reactions. The coupling
reaction in presence of Li$_2$CuCl$_4$ is free of any structural limitations on the Grignard reagent component and is very versatile whereas the Wittig reaction ensures stereospecific fixation of conjugated ester moiety in a large variety of substrates.

In the following pages, synthesis of various juvenile hormone analogues having different functional groups (ethers, esters, amides) have been described. The second chapter has been subdivided into two sections A and B. Section A incorporates the synthesis of 1-[(2-pinen-10-yl) oxy] 3,7-dimethyl 2(E),6-octadiene (II) and 1-(2'-isopropyl-5'-methylcyclohexyloxy)-3,7-dimethyl 2(E), 6-octadiene (III), which have been transformed into mono oxirane derivatives (IV,V), mono thirane derivatives (VI,VII), bis-dichloromethylene derivatives (VIII,IX), bis-dibromomethylene derivatives (X,XI) and carbethoxymethylene derivatives (XII,XIII). Section B describes the synthesis of two long chain hydrocarbons (XVI,XVII) using dilithium tetrachlorocuprante catalysed coupling reaction. In order to study the effect of different substituents present at the terminal double bond on its juvenile hormone activity, hydrocarbon (XVI,XVII) were also converted to mono oxirane derivatives (XVIII,XIX), mono-thirane (XX,XXI), bis-dichloromethylene derivatives (XXII,XXIII), bis-dibromomethylene derivatives (XXIV,XXV) and carbethoxymethylene derivatives (XXVI,XXVII).
Chapter III (section A) deals with synthesis of various \(\alpha,\beta\)-unsaturated esters (XXIX-XXXIII) using Horner-Wittig reaction. Amides (XXXV-XXXIX) have also been synthesised from 3,9,13-trimethyl-6-oxa-2(\(E\)),8(\(E\)),12-tetradecatrienoic acid (XXXIV) and different anilines. Epoxidation of (XXIX-XXXIII) and (XXXV-XXXIX) with \(m\)-chloroperbenzoic acid at 0\(^\circ\) resulted in the formation of mono-oxirane derivatives (XL-XLIX) which on further reaction with KSCN in ethanol gave mono-thirane derivatives (L-LIX).

Section B comprises the synthesis of different long chain alkoxy alkyl phenyl ethers (LXII-LXVI). To evaluate the effect of presence of different moieties at the terminal double bond on activity, diether (LXII-LXVI) were converted to epoxides (LXVII-LXXI) and thirane derivatives (LXXII-LXXVI).

All these synthesised compounds have been screened against *Culex pipiens quinquefasciatus* Say/Aedes albopictus (skuse). The laboratory screening results at different concentrations have been summarized in the form of tables reported in Chapter IV.