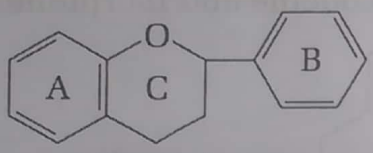
1.9. BIOSYNTHESIS OF ACETOGENINS

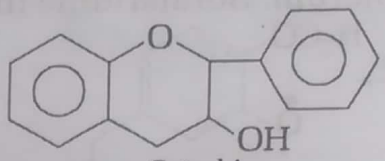
The compounds which originate from poly-β-keto acids are known as acetogenins. The main examples of acetogenins include fatty acids, flavonoids, anthraquinones, linear polyacetylenes etc.

1.9.1. Biosynthesis of flavonoid compounds

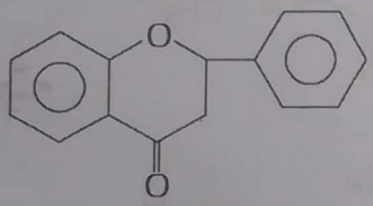
Substances derived from 2-phenyl chromane are termed flavonoid compounds (or flavans). The most important types of naturally occurring flavonoid derivatives are given below (**Scheme-13**). The substitutents in ring A and B are not considered here.



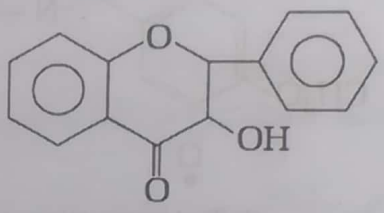
2-Phenyl chromane



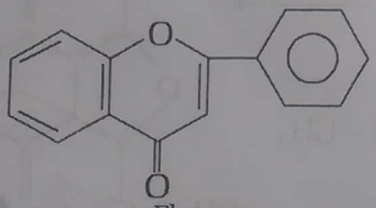
Catechin



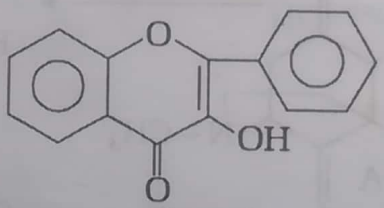
Flavanone



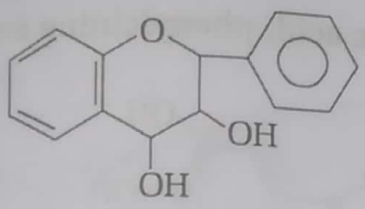
3-Hydroxy flavanone



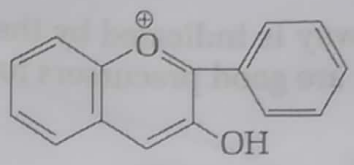
Flavone



Flavonol



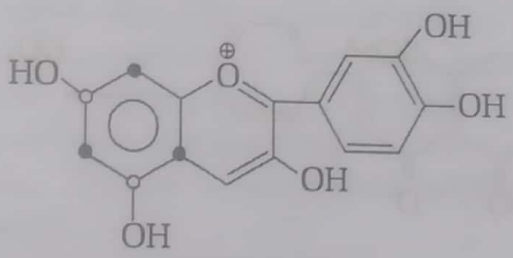
Flavan-3, 4-diol
(Leucoanthocyanidine)



Anthocyanidine

Scheme 13 : Various types of naturally occurring flavonoid compounds

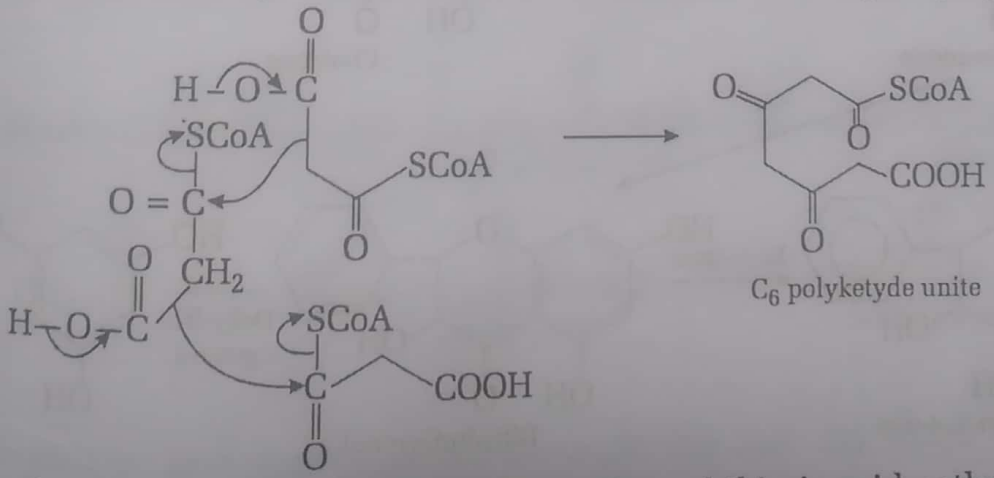
Ring A of the flavoniod compounds are generally oxygenated. With few expectations, the oxygen containing substituents are arranged at the *m*-positions. Similarly it has been found that the substitution pattern in ring B resembles that of the cinnamic acid derivatives. These substitution patterns of ring-A and ring-B is due to the fact that ring-A originate from three molecule of acetate by head to tail condensation, while the rest of the carbons originate from a cinnamic acid. It is now well established that rings A and B are formed by different routes. Ring A is produced by the acetate pathway. This was proposed by Birch and was confirmed by feeding experiments with labelled acetate. Grisebach fed $^{14}CH_3COOH$ (°C) and $CH_3 - {}^{14}COOH$ (C•) to red cabbage plant and obtained cyanidine chloride labelled as shown.



Cyanidine chloride

The actual mechanism for the formation of ring-A is, however, still unknown. Now it is supposed that the CoA derivatives of the acids react with each other by head to tail condensation. Acetyl CoA is probably first converted to malonyl CoA as in the case of biosynthesis of fatty acids.

Three molecules of malonyl CoA condensed with each other to give polyketyde.

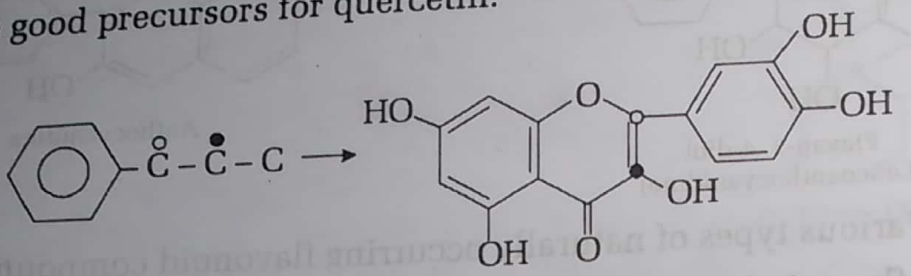


C_6 polyketyde unite

Ring-B, *i.e.*, the $C_6 - C_3$ unit (or C_9 unit) arise from shikimic acid pathway :

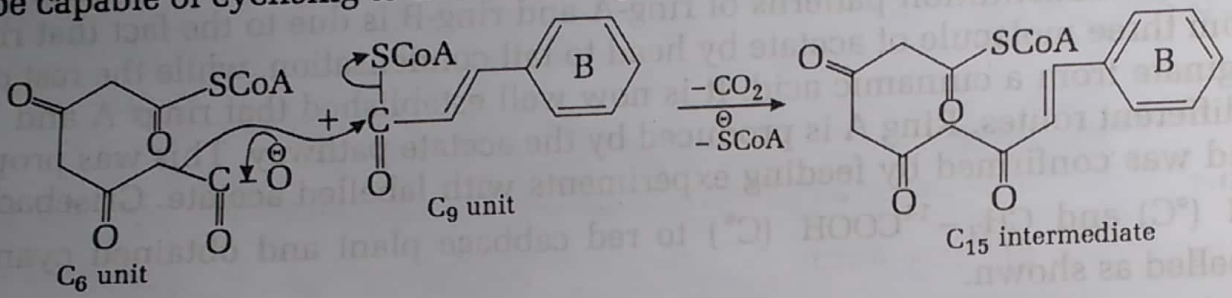
Shikimic acid → Prepheric acid → Phenyl pyruvic acid
→ Phenyl alanine → Cinnamic acid

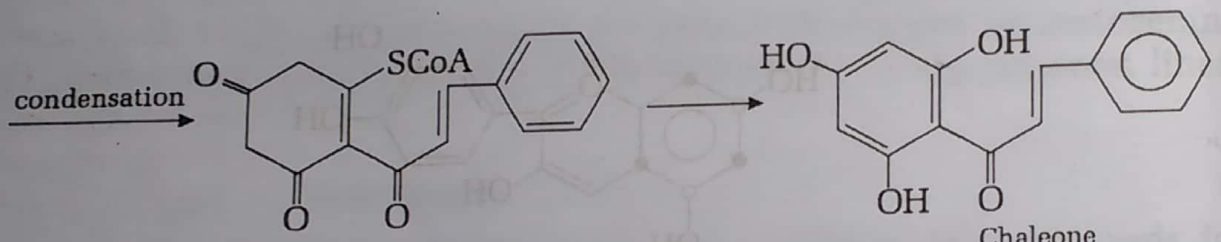
This pathway is indicated by the fact that shikimic acid, phenylalnine and p-hydroxy cinnamic acid are good precursors for quercetin.



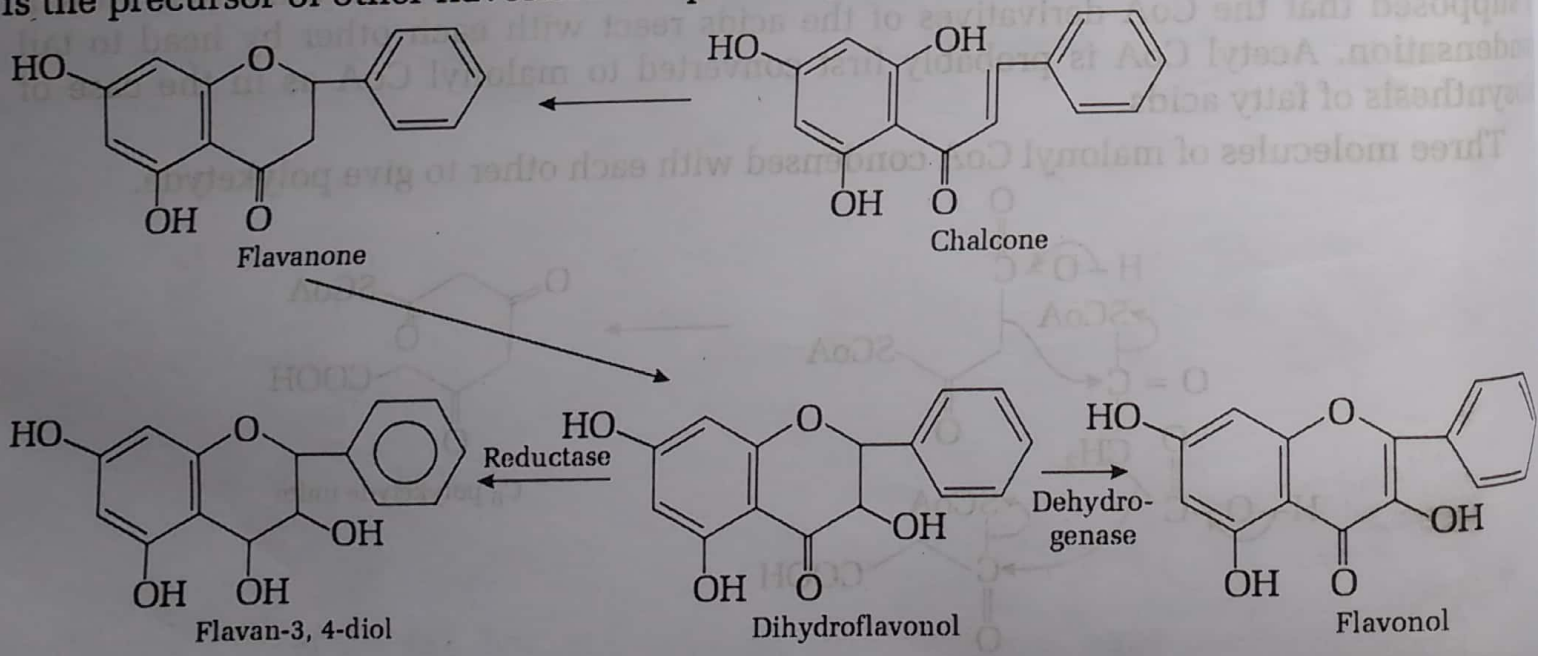
Quercetin

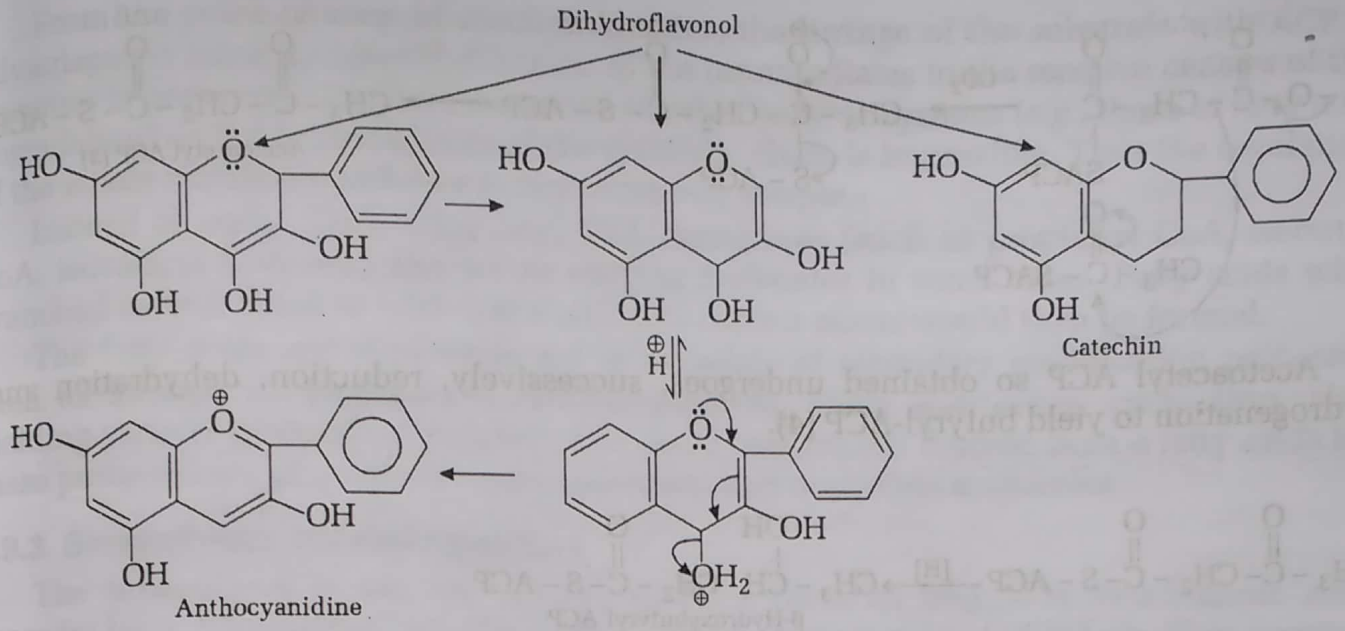
C_6 and C_9 unites then join together to form a C_{15} intermediate. This intermediate may be capable of cyclising to a chalcone by forming bond between carbon-1 and –6.





This chalcone then converts into flavanone in the presence of enzyme. This flavanone is the precursor of other flavonoid compounds (**Scheme 14**)





Scheme 14 : Possible pathway of formation of various flavonoid compounds.

1.9.2. Biosynthesis of Fatty Acids

Saturated and unsaturated aliphatic monocarboxylic acids (fatty acids) occur in all living organisms. They are components of oils, fats, lipids and waxes. Fatty acids with even number of carbon atoms preponderate, in contrast to those having an odd number of carbons in nature. Fatty acids having sixteen and eighteen carbon atoms are most common fatty acids found in nature. This is because they originate from a precursor with two carbon atoms (*i.e.*, acetic acid).

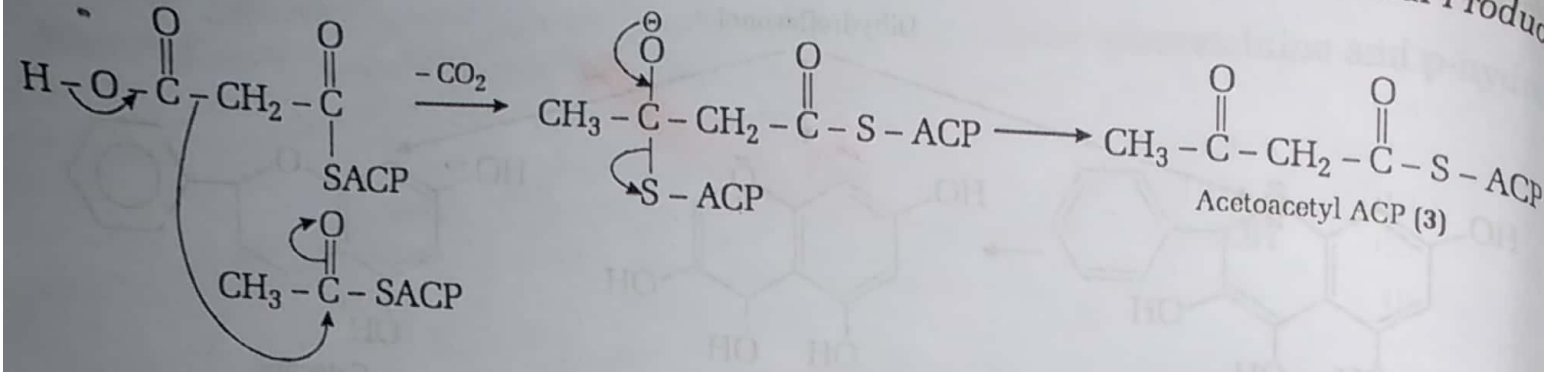
The synthesis of fatty acids begins as follows :

First of all acetyl CoA converts into malonyl CoA in the presence of biotin and CO_2. A malonyl residue is then transferred to acyl carrier protein (ACP) to give malonyl ACP **(1)**. An acetyl residue is also transferred from CoA to acyl carrier protein and them to an enzyme **(2)**.

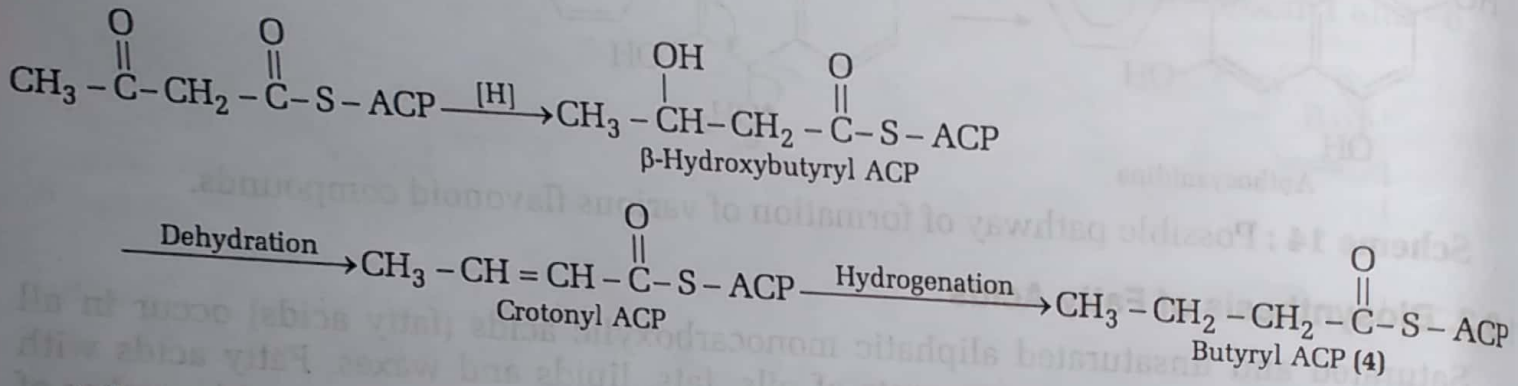
$$CH_3-\overset{O}{\overset{\|}{C}}-SCoA + CO_2 \xrightarrow{\text{biotin}} \underset{\text{Malonyl CoA}}{HO-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-SCoA} \xrightarrow{ACP} \underset{\text{Malonyl ACP (1)}}{HO-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-S-ACP}$$

$$CH_3-\overset{O}{\overset{\|}{C}}-SCoA \xrightarrow{ACP} \underset{\text{Acetyl ACP}}{CH_3-\overset{O}{\overset{\|}{C}}-S-ACP} \xrightarrow{\text{Enzyme}} \underset{\text{Acetyl protein (2)}}{CH_3-\overset{O}{\overset{\|}{C}}-S-Enz}$$

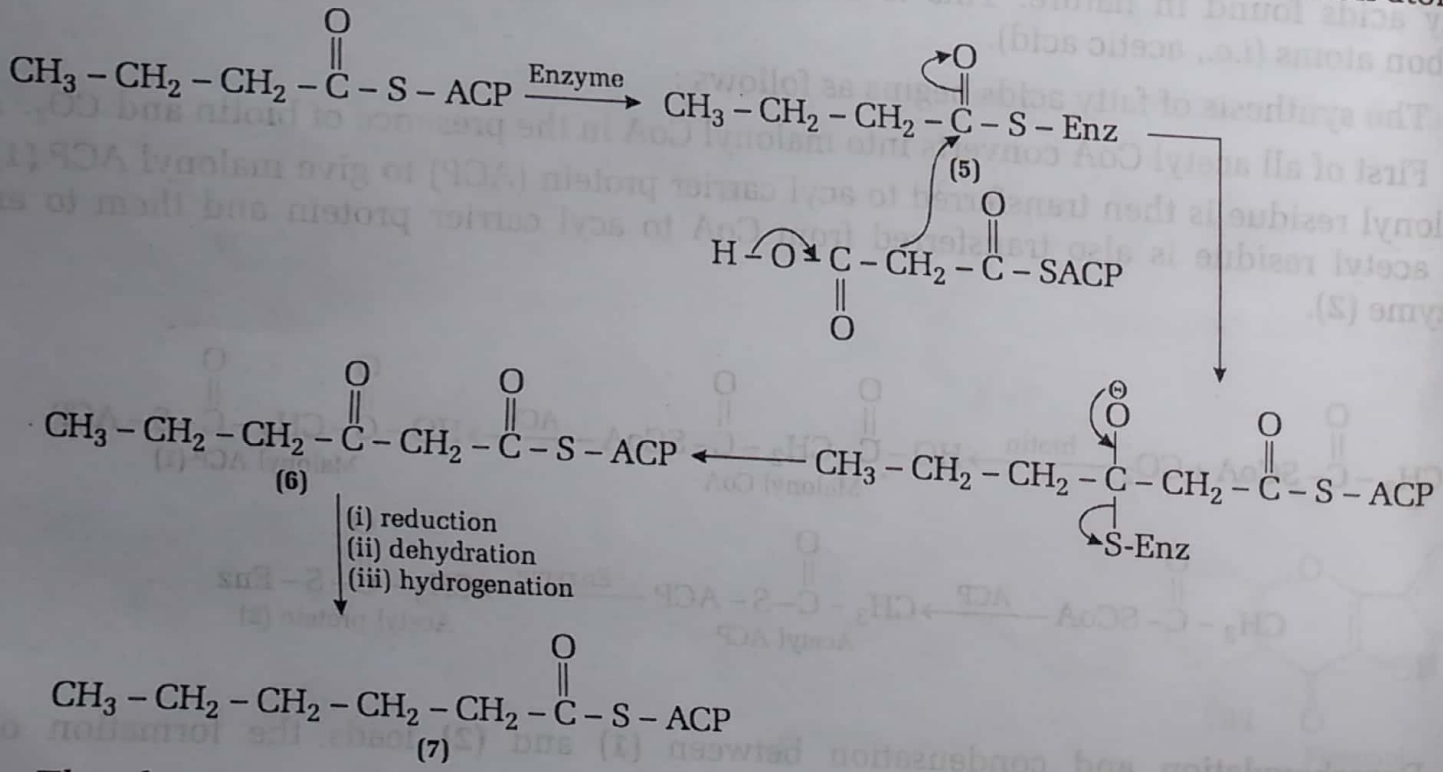
Decarboxylation and condensation between **(1)** and **(2)** leads the formation of acetoacetyl ACP **(3)**.



Acetoacetyl ACP so obtained undergoes, successively, reduction, dehydration and hydrogenation to yield butyryl-ACP **(4)**.



Like acetyl ACP, butyryl ACP can be attached to the enzyme protein and enter the cycle again. In this manner a stepwise elongation of the carbon chain by two carbon atoms is possible.



The above process of chain elongation is repeated until C_{16}, C_{18} or C_{20} fatty acid is formed. Why chain elongation stops after the formation of acids with about sixteen to twenty carbon atoms is still unknown.

From the point of view of reaction kinetics, the linkage of the substrate with ACP is advantageous since accidental diffusion of the intermediates to the reactive centers of the enzymes is prevented. Further, the action of other enzyme systems (*e.g.*, those of fatty acid degradation) on the intermediates of the synthetic chain is impossible. Thus the regulation of the whole metabolic pathway is comparatively simple.

Instead of acetyl CoA, other acyl CoA derivatives (such as propionyl CoA, isobutyl CoA, isovaleryl CoA etc.) can act as starting molecules in some cases. Fatty acids with branched carbon chain or with odd number of carbon atoms would then be formed.

The fatty acids are then subjected to a variety of secondary modification processes such as alkylation, oxygenation, dehydrogenation, chain shortening, cyclisation, etc., yielding various types of compounds. The main compounds derived from a fatty acids by these processes are pheromones, prostaglandins and macrolide antibiotics.