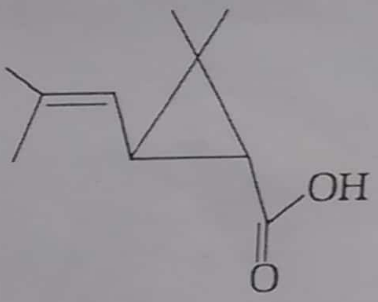
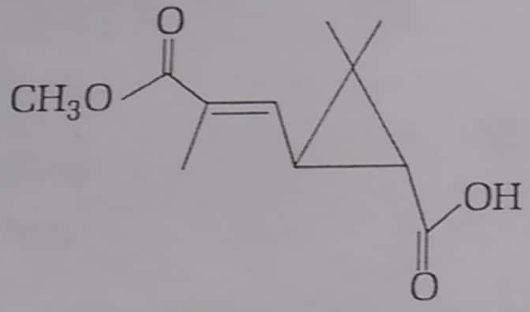
8.1. PYRETHRINS AND PYRETHROIDS

The insecticidal properties of pyrethrum daisy flower, *Tanacetum* or *Chrysenthemum Cineriaefoleum* (Asteraceae) are known for centuries. In the early 1800's, pyrethrum flowers were used to control body lice. Before World War II, powdered pyrethrum flowers and their extracts were used to control agricultural pest insects in the household, in barns and in stored products.

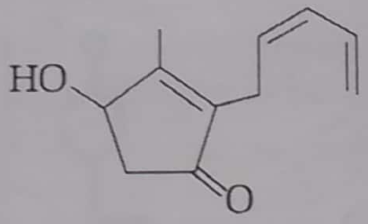
Pyrethrum extract contains six closely related esters which are collectively known as pyrethrins which are non-persistent insecticides of low mammalian toxicity. They knock down houseflies, mosquitoes and other flying insects rapidly and at appropriate doses kill the insects, but their use in the field is limited as they decompose in light. Pyrethrins differ structurally only in the terminal substituents in the side chains of the acid and alcohol components. The acid is a substituted cyclopropanecarboxylic acid and alcohol a substituted cyclopentenolone. The two carboxylic acids are chrysanthemic acid (Series I) and pyrethric acid (Series II). Three alcohols are pyrethrolone, cinerolone and jasmolone for pyrethrins, cinerins and jasmolins, respectively.



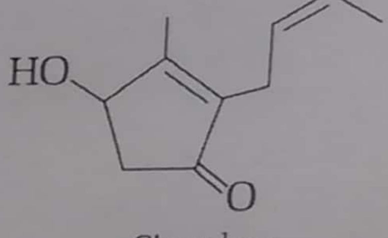
Chrysanthemic acid



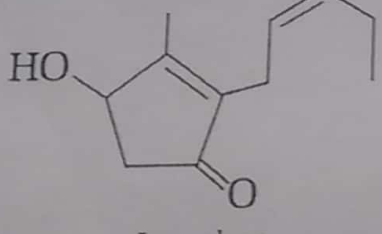
Pyrethric acid



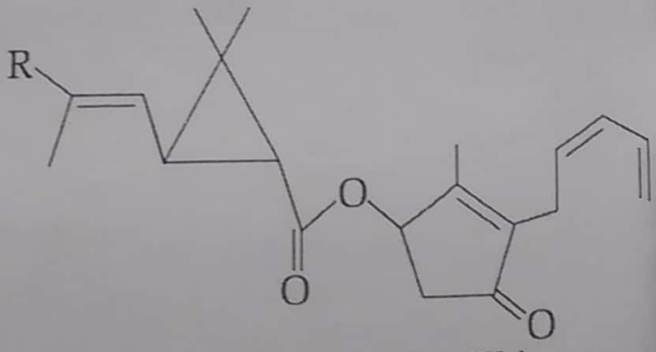
Pyrethrolone



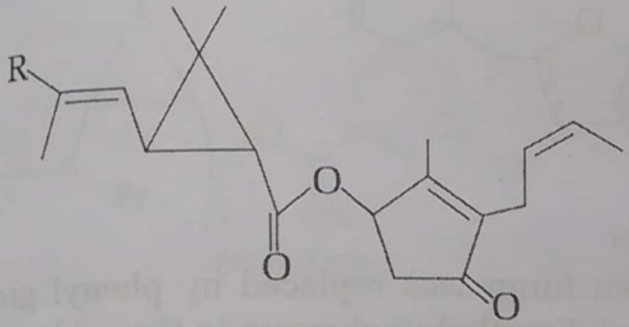
Cinerolone



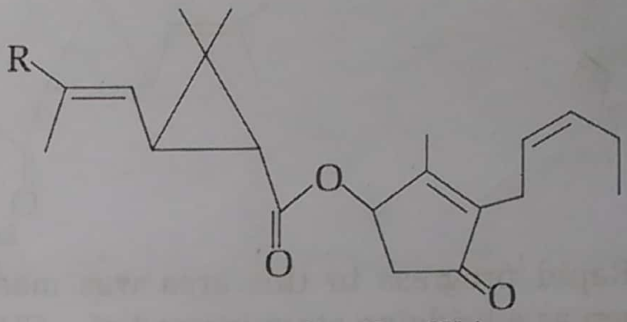
Jasmolone



Pyrethrin I (R = CH_3)
Pyrethrin II (R = – $COOCH_3$)



Cinerin I (R = $-CH_3$)
Cinerin II (R = $-COOCH_3$)



Jasmolin I (R = CH_3)
Jasmolin II (R = $-COOCH_3$)

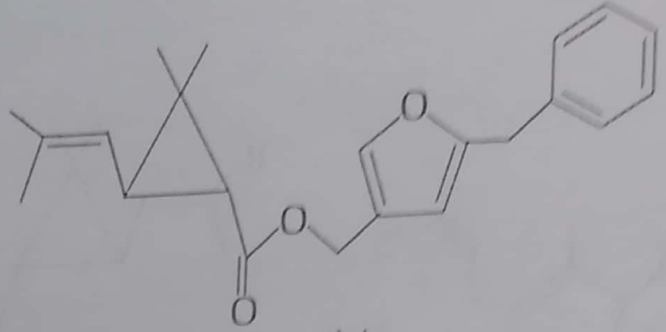
Pyrethrins have three chiral centres and therefore eight optically active forms are possible. There is also geomatrical isomerism in the side chain of the alcohol (chrysanthemates) and in the carboxylic acid and alcohol (Pyrethrates) increasing the number of possible isomers to 16 for chrysanthemates and 32 for pyrethrates. Although these isomers have not all been tested, there is evidence which suggests that naturally occurring configuration is likely to be most potent.

The biological activities of pyrethrum constituents depend on their structure and stereochemical characteristics of both the carboxylic acid and alcohol components. Pyrethrin I and II are most potent while chrysanthemates are generally more potent for kill and pyrethrates for knock down.

Pyrethroids are synthetic analogues of natural pyrethrins. They are more potent and more stable in light and comprise a new important class of crop protection chemicals. They now account for about a fifth of total insecticide market.

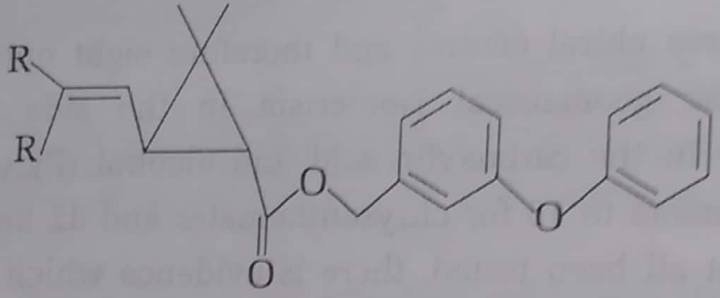
Schechter (1949) synthesized the first non-natural pyrethroid called allethrin which was commercialized. It was a simpler synthetic analogue of Pyrethrin I which contained an allyl group in place of, pentadienyl side chain of alcohol moiety but it was more effective against houseflies than pyrethrim I. He also showed the importance of the 1R-stereochemistry in acid moiety which led to the development of S-bioallethrin.

Elliott and coworkers later showed that allethrin was only superior to pyrethrin I against houseflies and pyrethrin I was more potent against a variety of other insects. This led him to consider the replacement of diene side chain with a phenyl group and a 3, 5-disubstituted furan ring as a replacement for cyclopentenone moiety in alcohol which led to the discovery of resmethrin which was found 50-fold more effective than pyrethrin I against houseflies and a range of other insects.



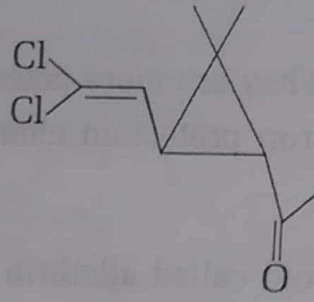
Resmethrin

Rapid progress in this area was made when furan was replaced by phenyl grou oxygen as a bridging atom instead of $-CH_2-$ and dimethylvinyl group in the acid mole was changed with dichloro (or dibromo-) vinyl moiety which led to the developmen compounds such as phenothrin and permethrin.

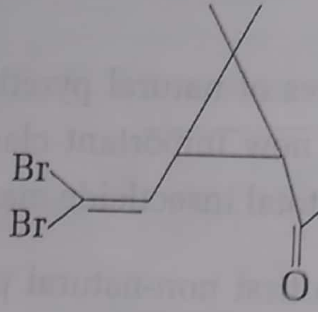


Phenothrin (R = $-CH_3$)
Permethrin (R = $-Cl$)

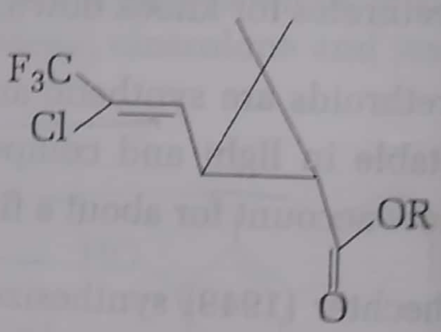
The enhancement of insecticidal activity by introduction of a α-cyano group in the phenoxybenzyl moiety was observed which led to the development of several pyrethroi such as cypermethrin, deltamethrin and cyhalothrin etc. which were more potent tha natural pyrethrins and had low toxicity against mammals.



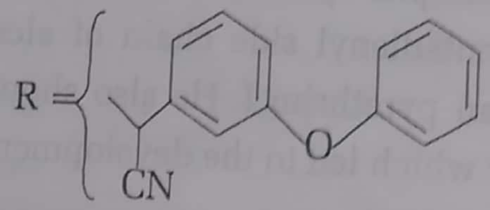
Cypermethrin



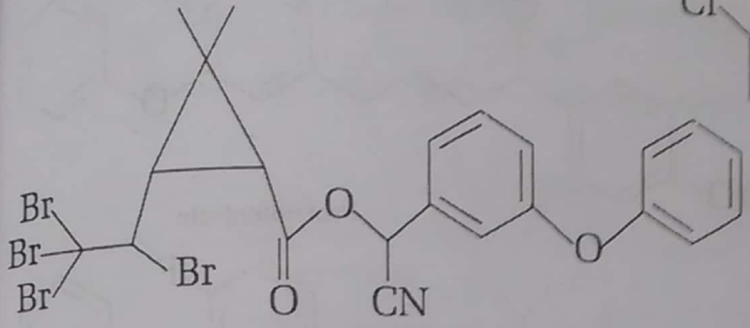
Deltamethrin



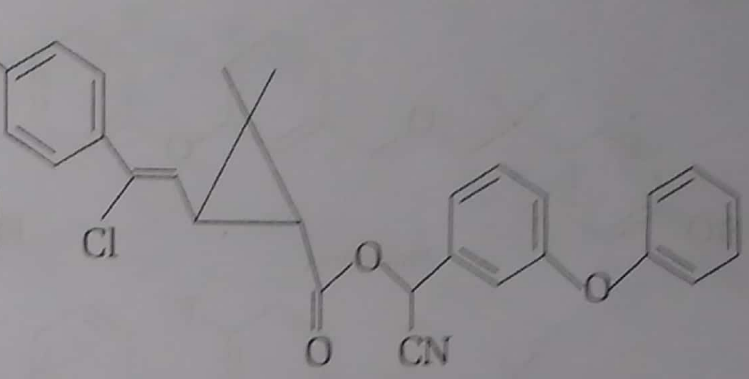
Cyhalothrin



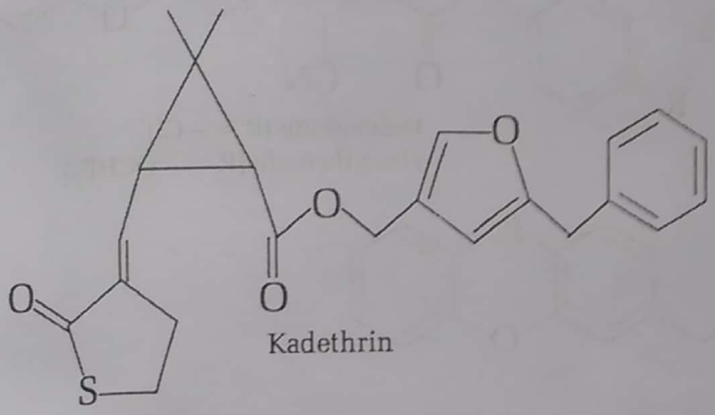
Some examples of commercial pyrethroids with variations in the acid moiety are tralomethrin, obtained from deltamethrin by addition of bromine. Flumethrin is an effective tickicide which is obtained by incorporating a phenyl group in the side chain of acid moiety. Kadethrin contains a thiolactone group and exhibits high knockdown activity against flying insects. Bifenthrin has a broad spectrum of activity.



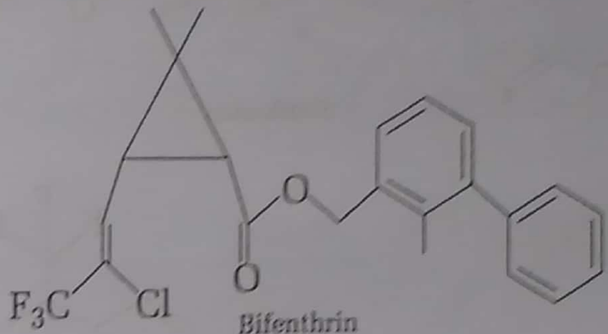
Tralomethrin



Flumethrin

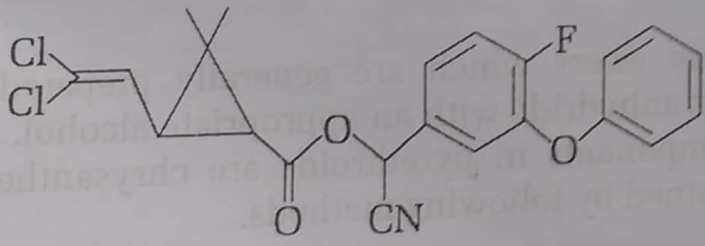


Kadethrin

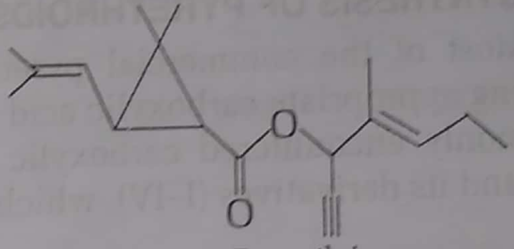


Bifenthrin

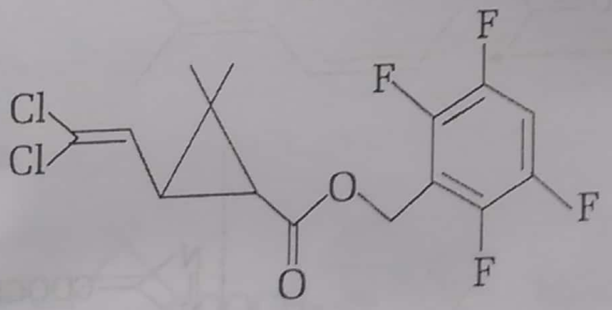
Large number of pyrethroids have been prepared by variation in the alcohol moiety. Introduction of a fluorine atom at position 4 in cypermethrin gave cyfluthrin which was found more active than cypermethrin against some insects. Low molecular weight alcohols or polyfluorinated alcohol groups have been employed for increasing volatility of pyrethroids, *e.g.* empenthrin, transfluthrin and tefluthrin.



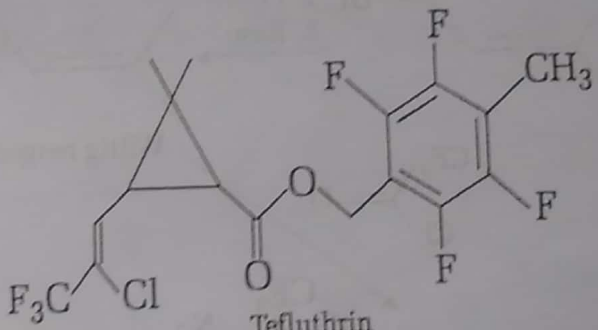
Cyfluthrin



Empenthrin

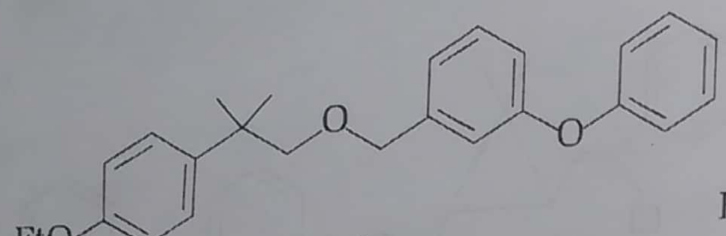


Transfluthrin

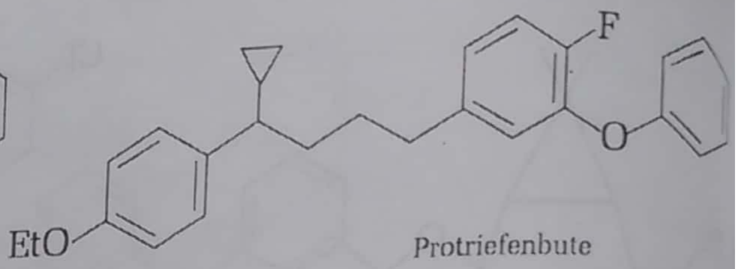


Tefluthrin

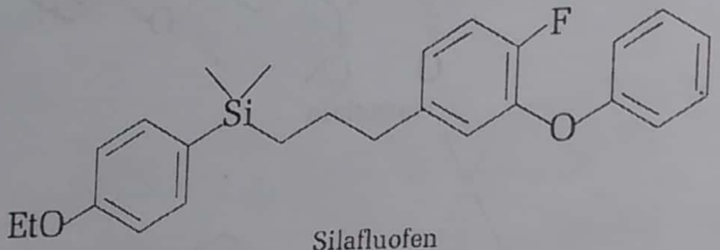
Toatsu (1981) developed first pyrethroid (etofenprox) lacking the ester group because absence of ester group was expected to result in higher metabolic stability. The discovery prompted major interest in this area and several useful compounds have been discovered, e.g., protriefenbute and silafluofen. Several pyrethroids having an ester moiety but lacking a cyclopropane ring were also developed, e.g. fenvalerate, flucythrinate and flufenprox.



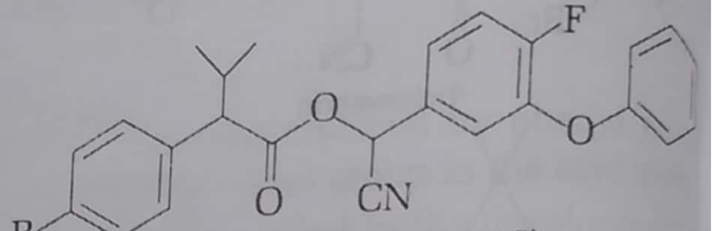
Etofenprox



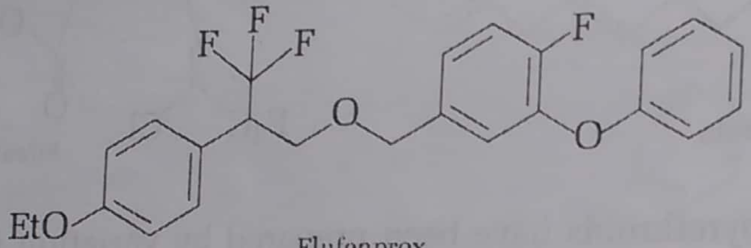
Protriefenbute



Silafluofen



Fenvalerate (R = – Cl)
Flucythrinate (R = – $OCHF_2$)

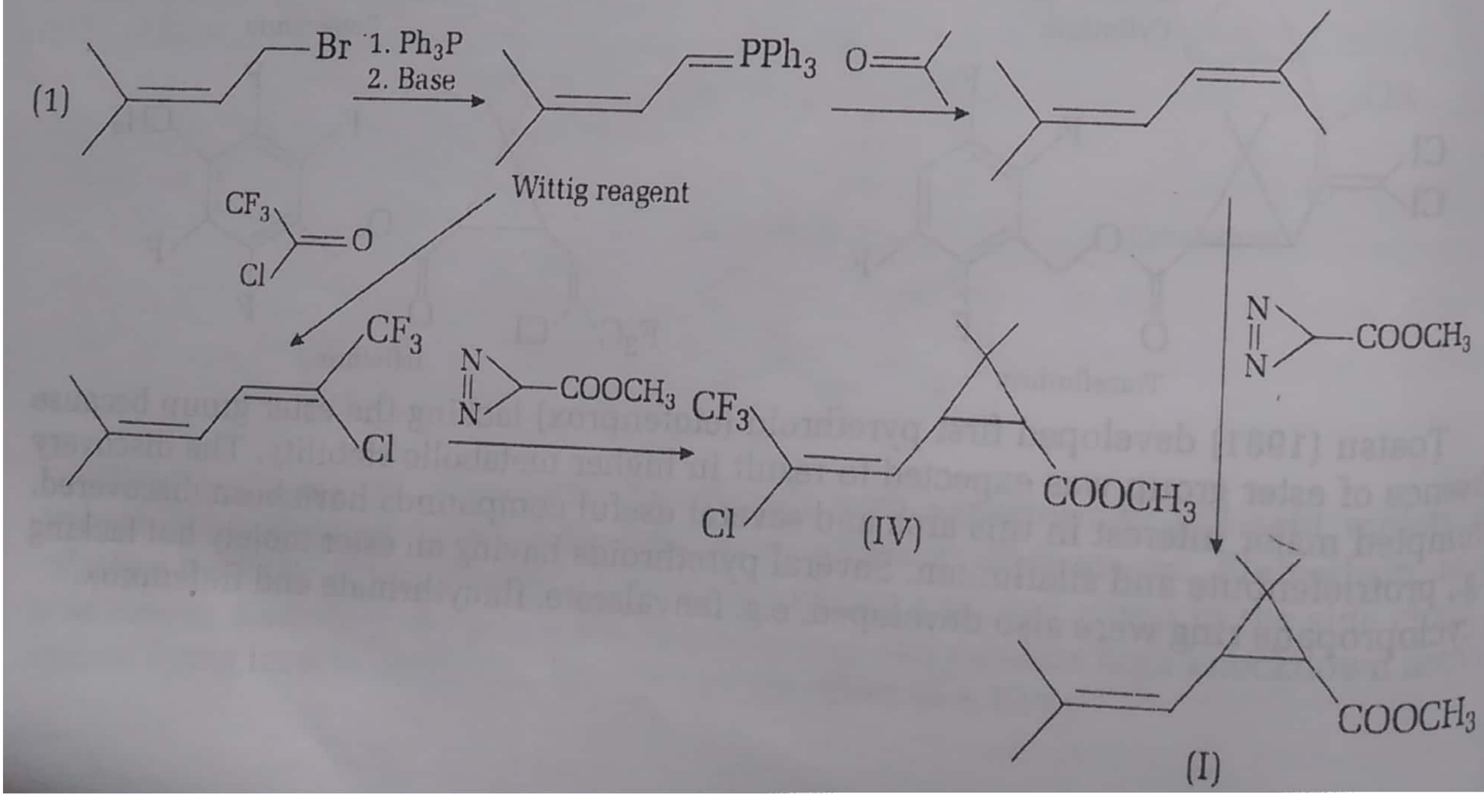


Flufenprox

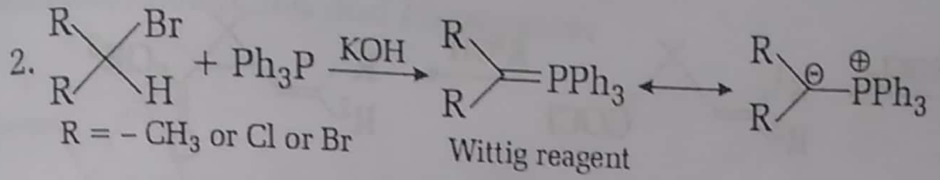
It is sometimes difficult to decide whether a synthetic insecticide is a pyrethroid o not but a compound may be considered a pyrethroid if its biological properties depend o stereochemical features similar to those of pyrethroids.

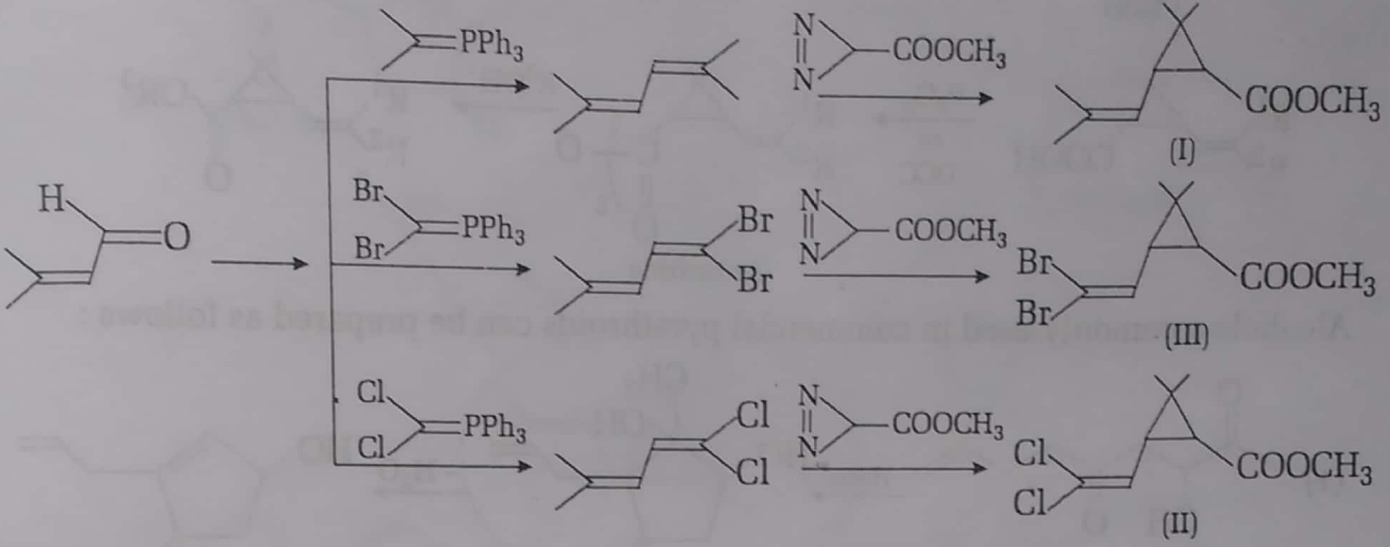
8.2. SYNTHESIS OF PYRETHROIDS

Most of the commercial pyrethroids are esters which are generally prepared b treating appropriate carboxylic acid halide or anhydride with an appropriate alcohol. Th commonly encountered carboxylic acid components in pyrethroids are chrysanthemi acid and its derivatives (I–IV), which are obtained by following methods.

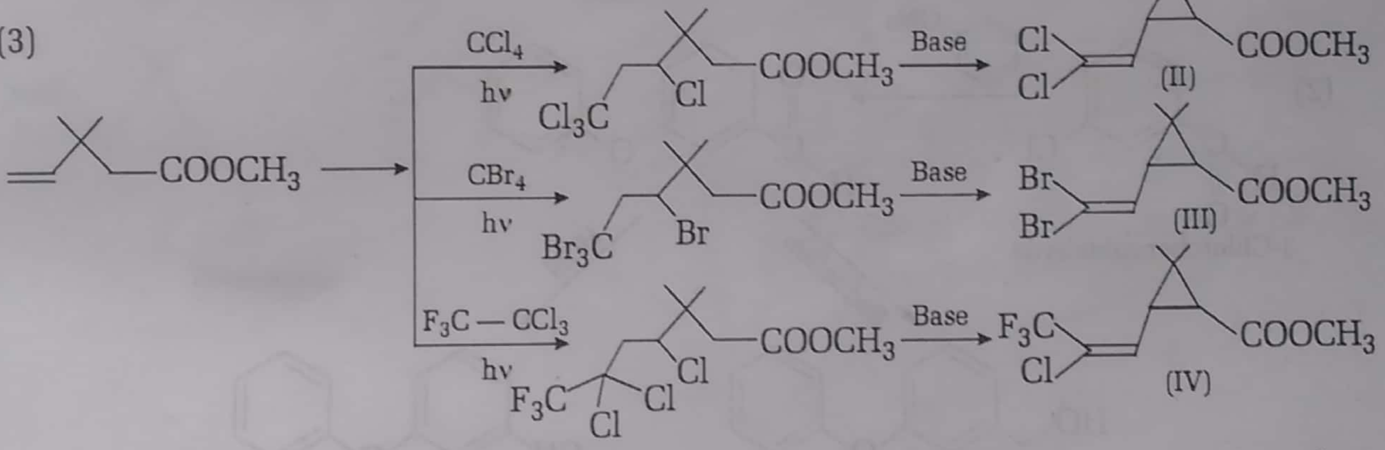


2.

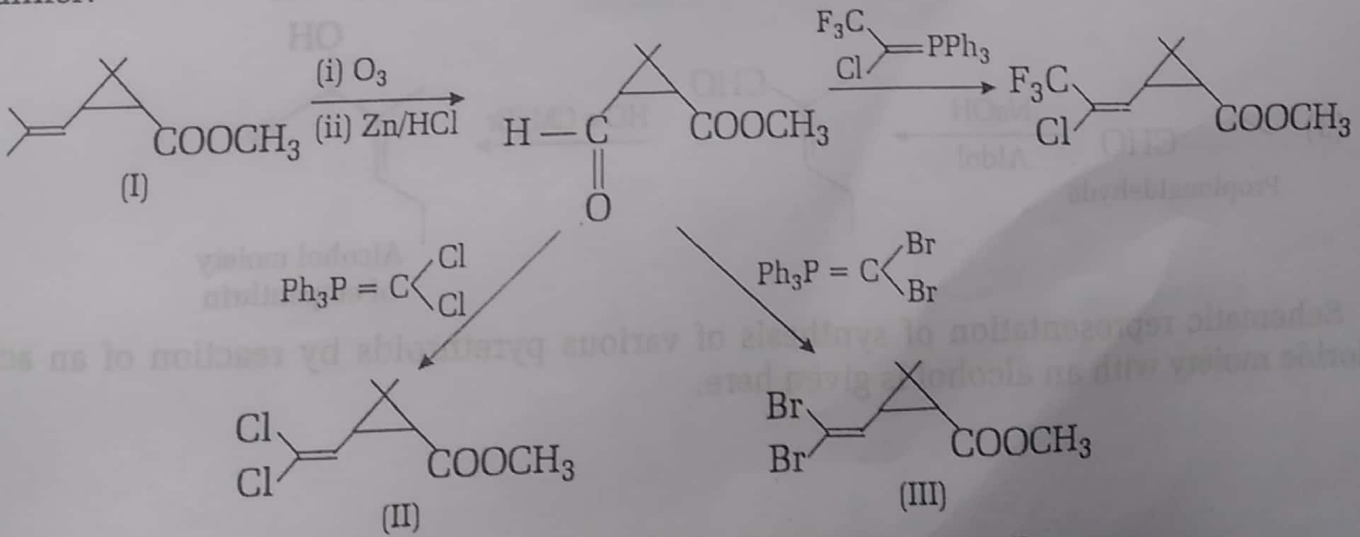




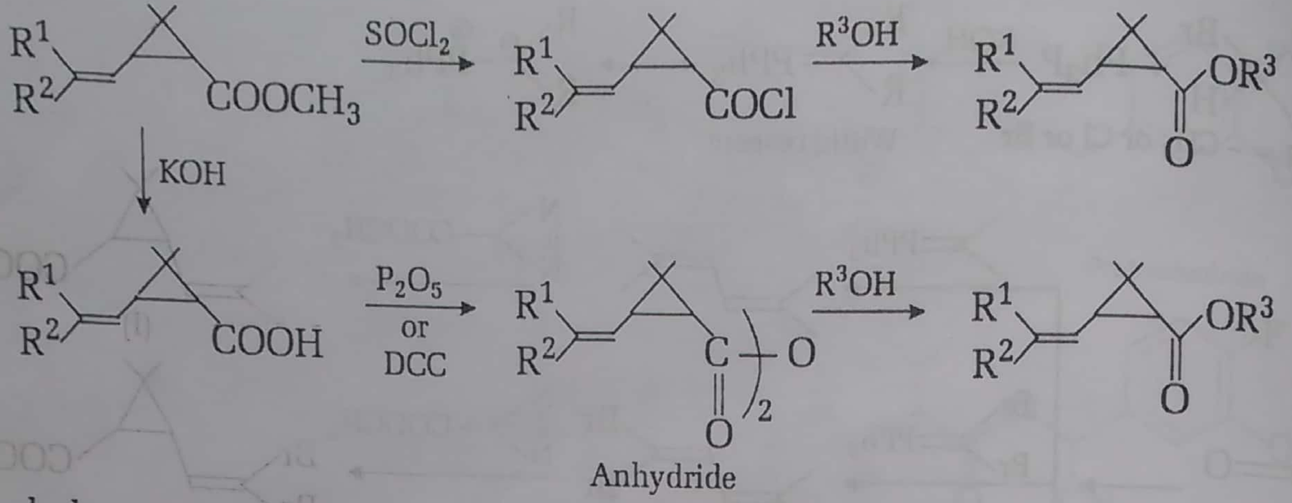
(3)



All the above methods yield mixture of stereoisomers which can be isolated to obtain pure isomers. These esters can be interconverted, e.g. chrysanthemic acid ester can be converted to dichlorovinyl or dibromovinyl substituted derivatives in the following manner.

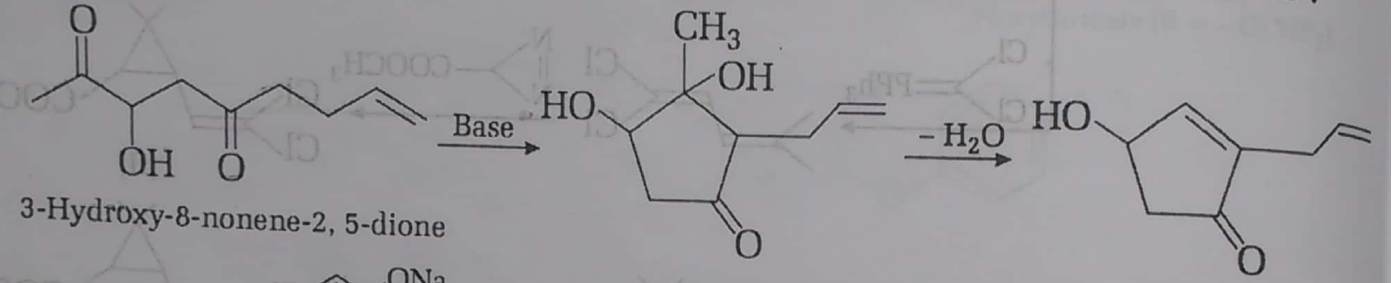


The desired pyrethroids are prepared in the following manner.

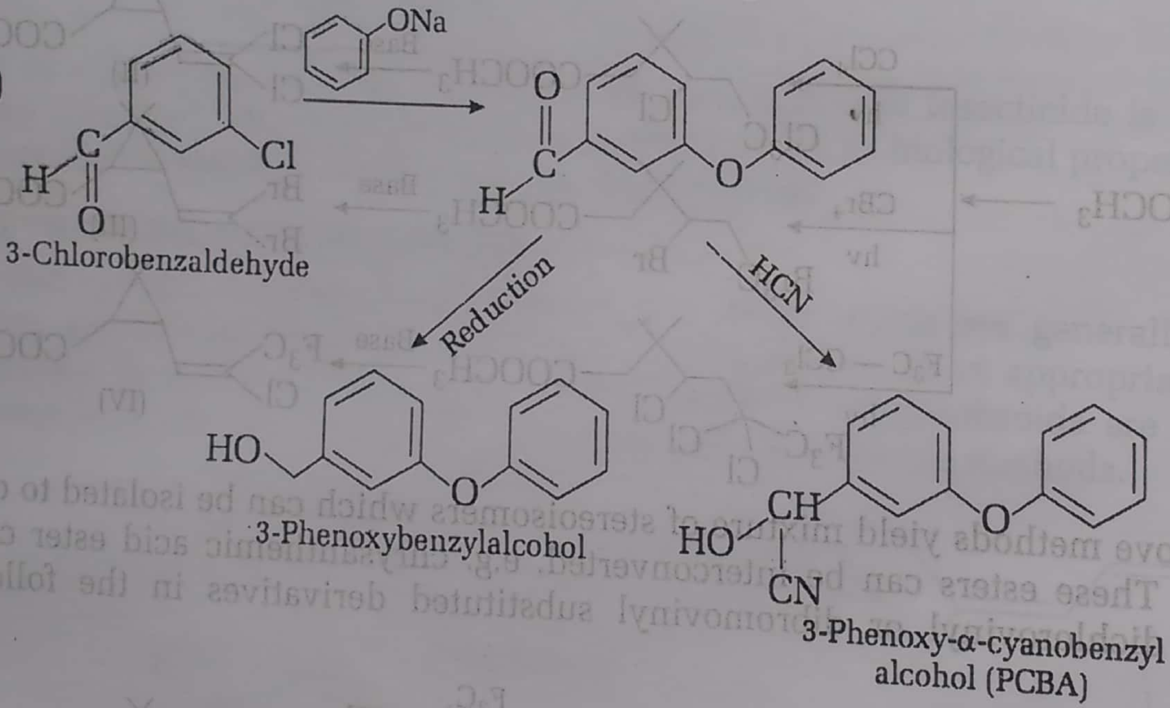


Alcohols commonly used in commercial pyrethroids can be prepared as follows :

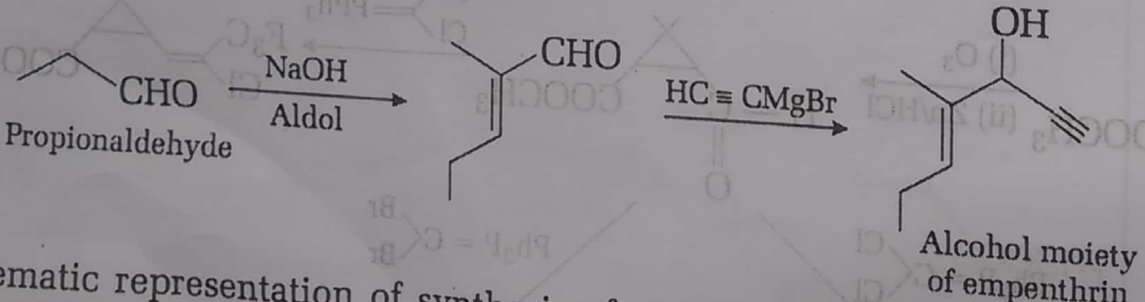
(1)



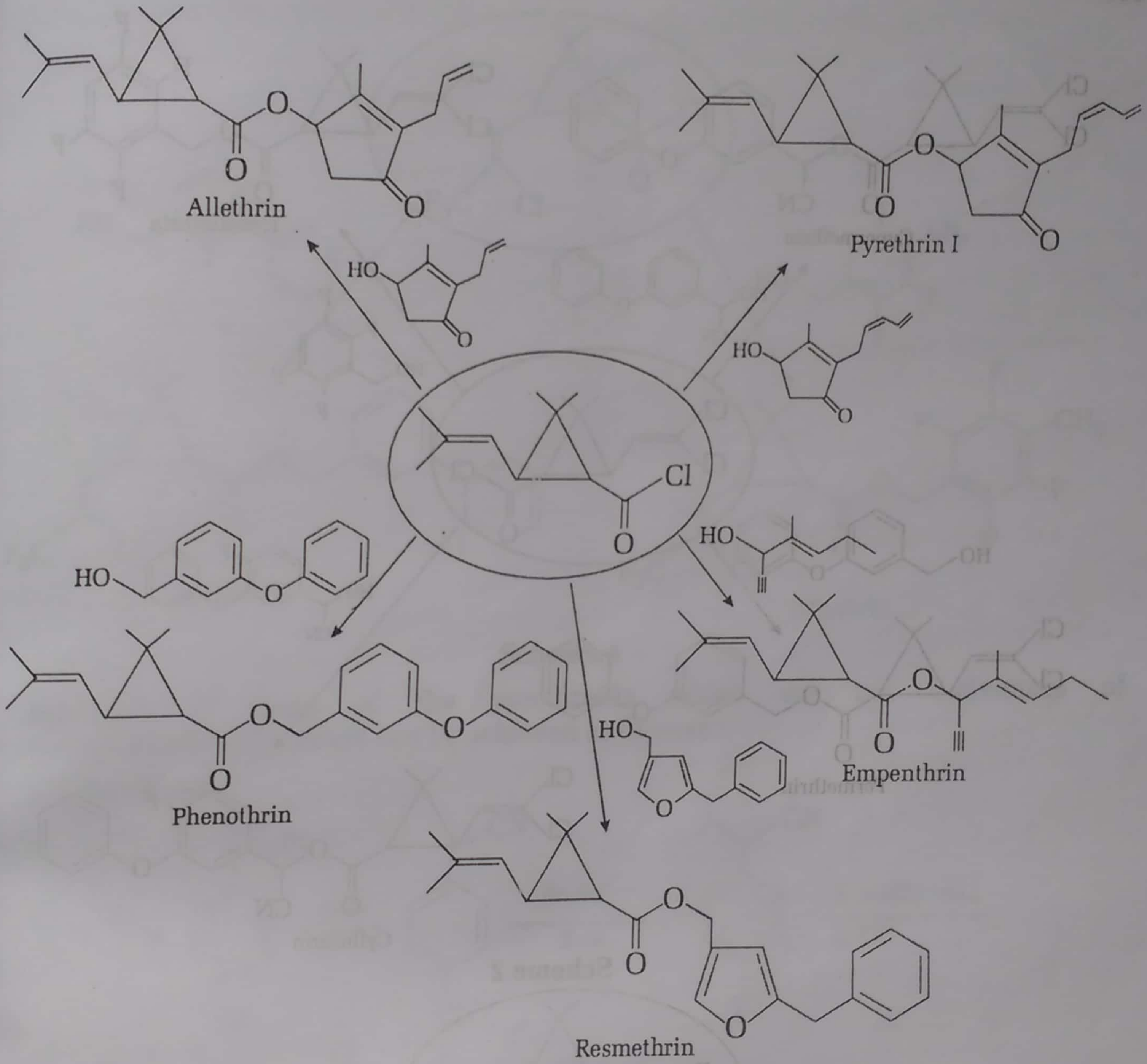
(2)



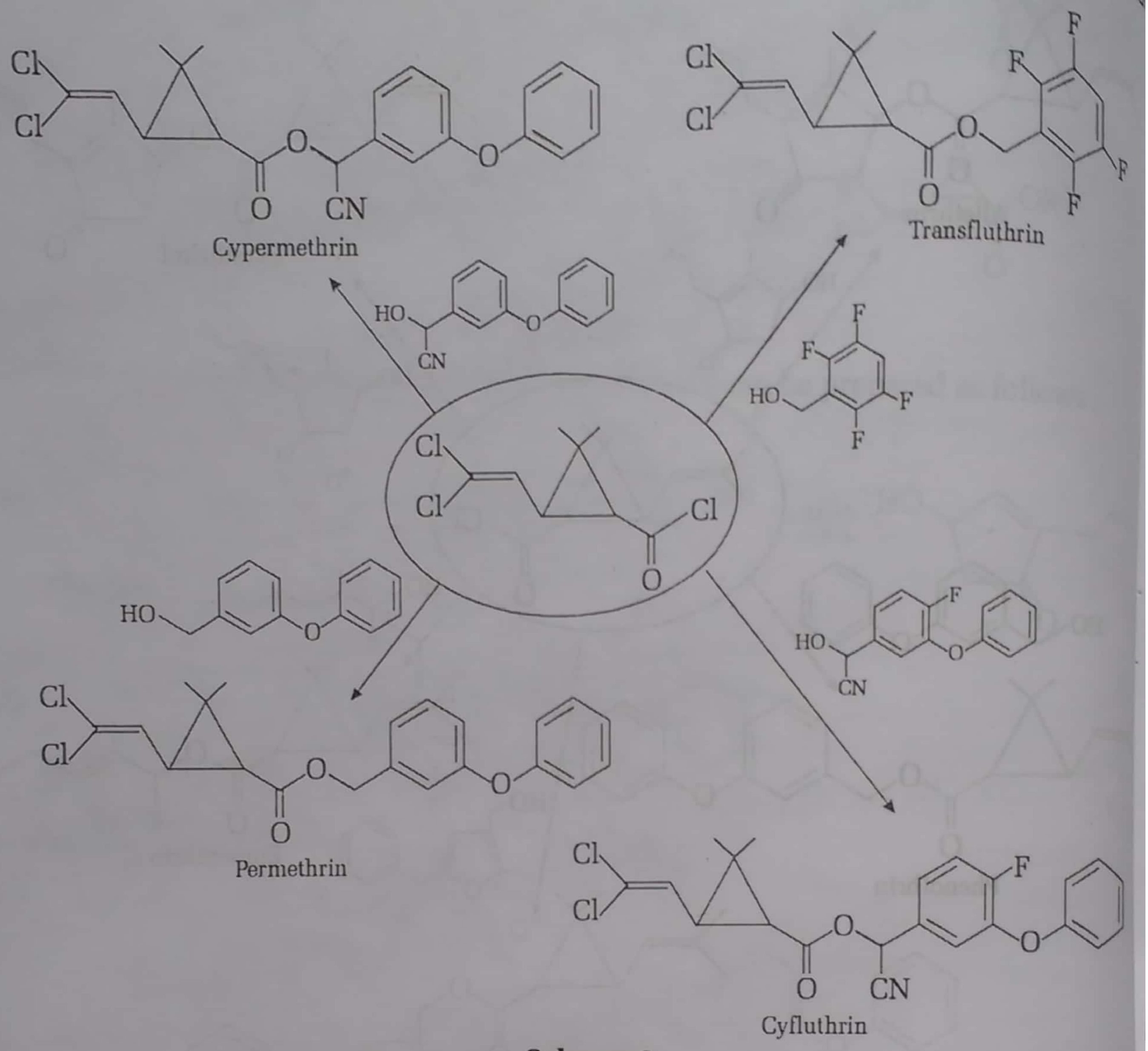
(3)



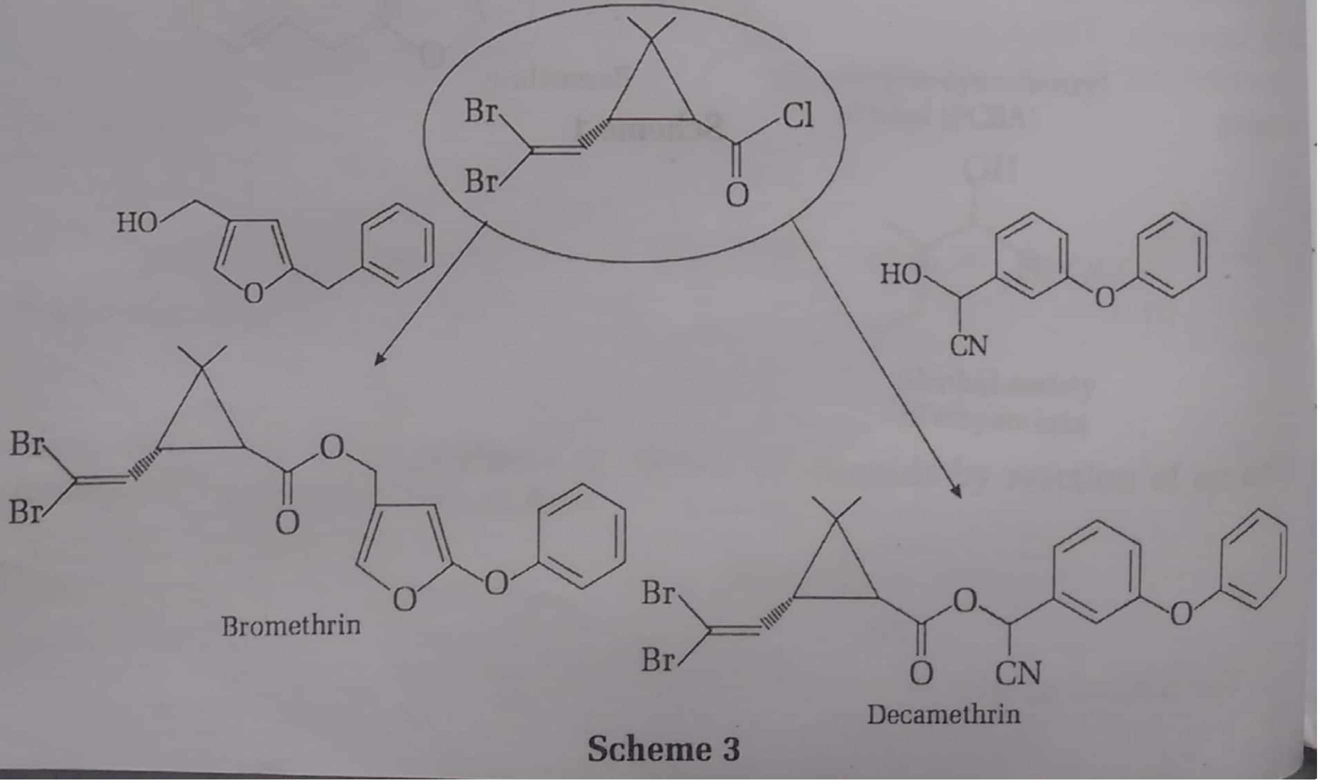
Schematic representation of synthesis of various pyrethroids by reaction of an acid chloride moiety with an alcohol is given here.


Allethrin
Pyrethrin I
HO
O
Cl
Phenothrin
Empenthrin
Resmethrin

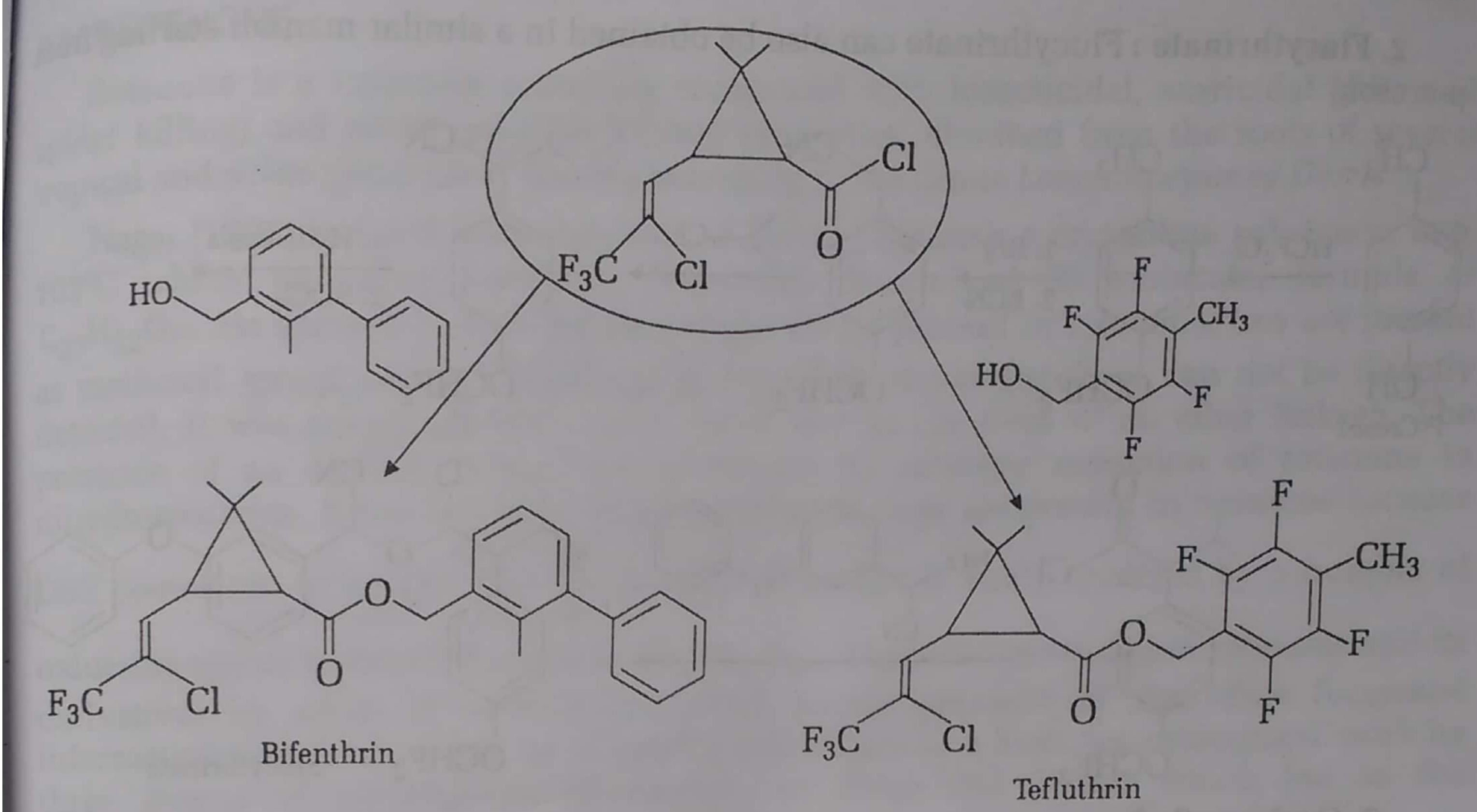
Scheme 1



Scheme 2



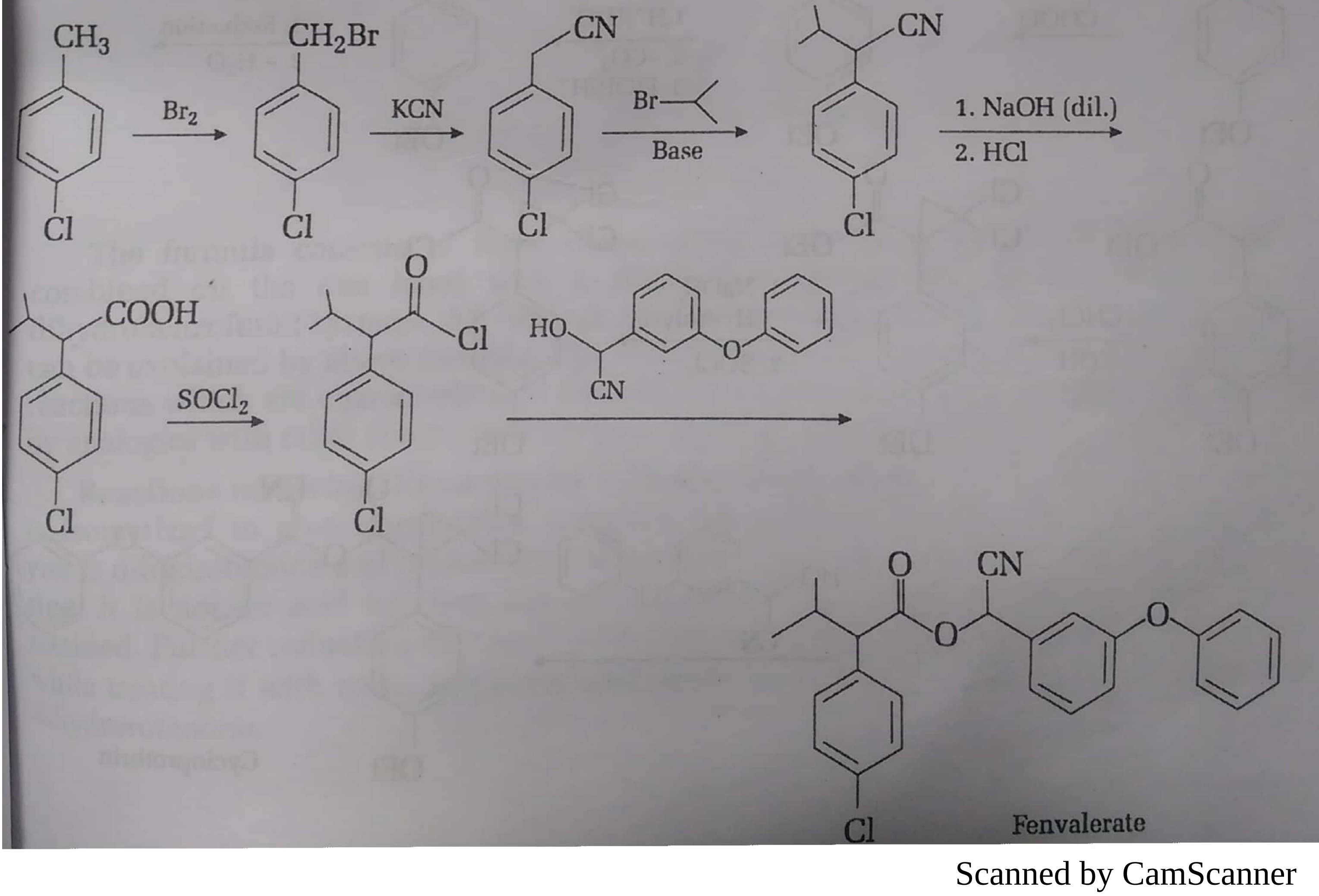
Scheme 3



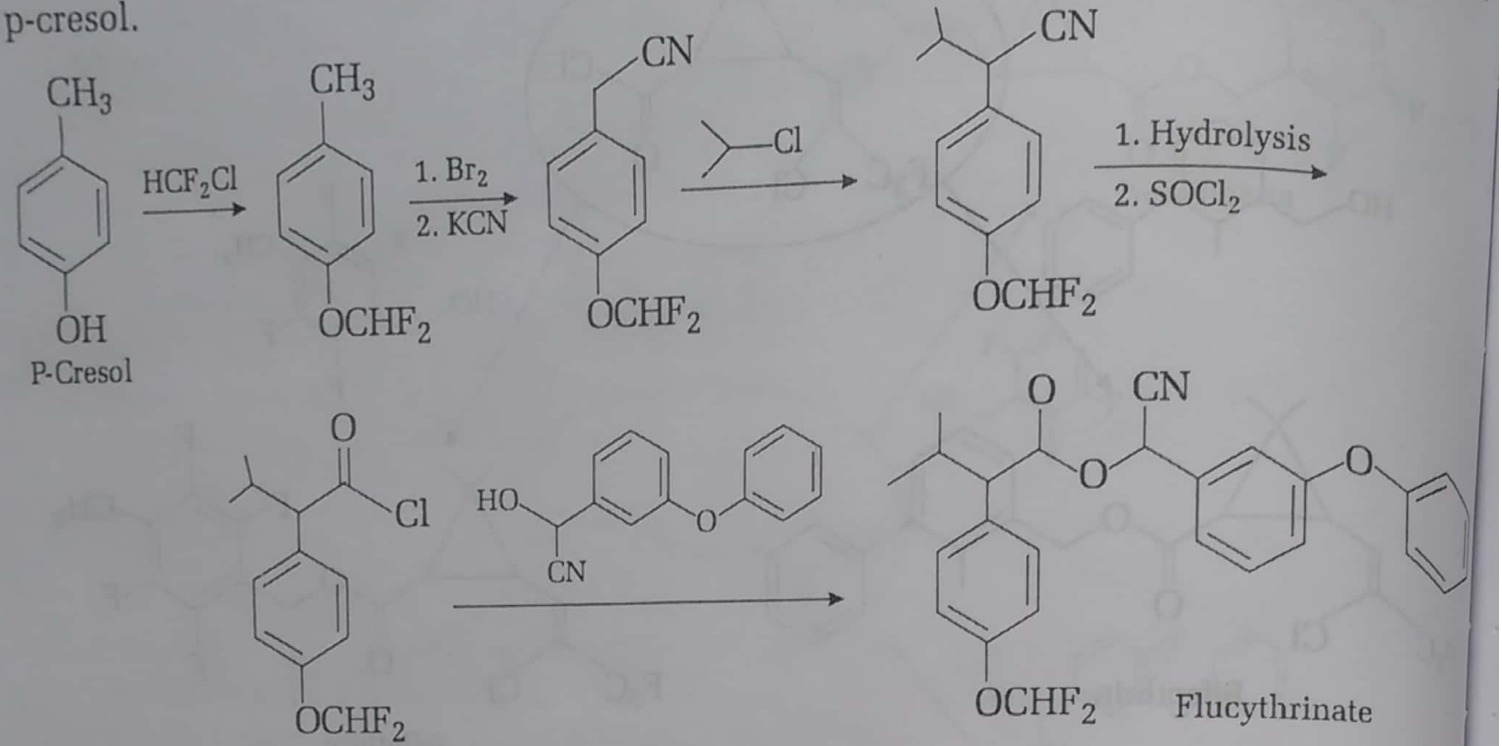
Scheme 4

Synthesis of some of the pyrethroids which are not derivatives of cyclopropanecarboxylic esters can be achieved as follows :

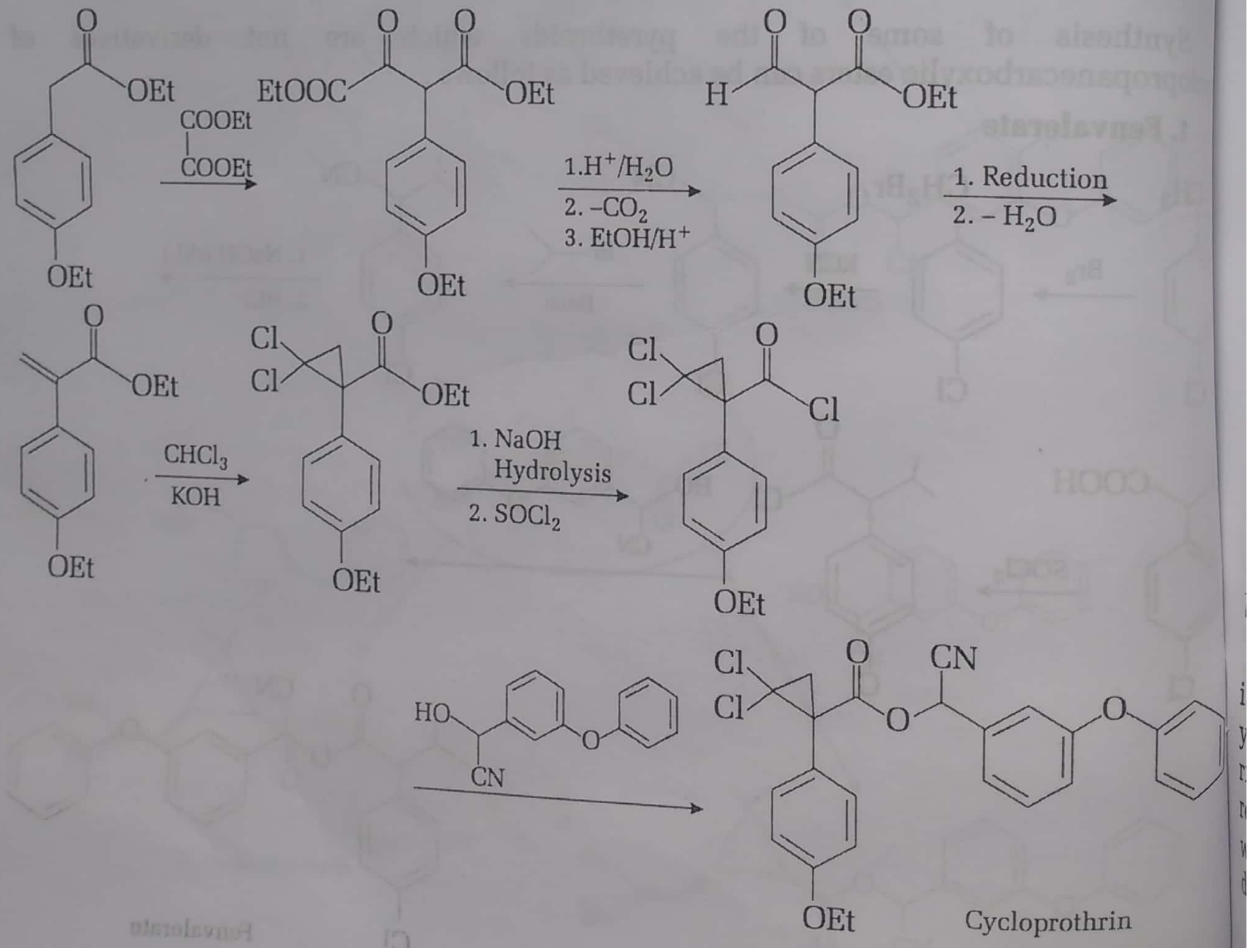
1. Fenvalerate



2. Flucythrinate : Flucythrinate can also be obtained in a similar manner starting from p-cresol.



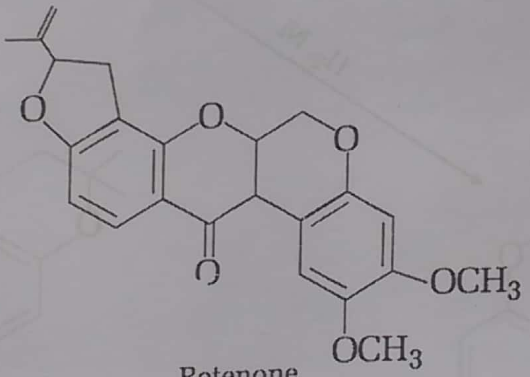
3. Cycloprothrin



8.3. ROTENONE

Rotenone is a naturally occurring compound with insecticidal, acaricidal (mite and spider killing) and piscicidal (fish killing) properties, obtained from the roots of several tropical and subtropical plant species belonging to the genus *Lonchocarpus* or *Derris*.

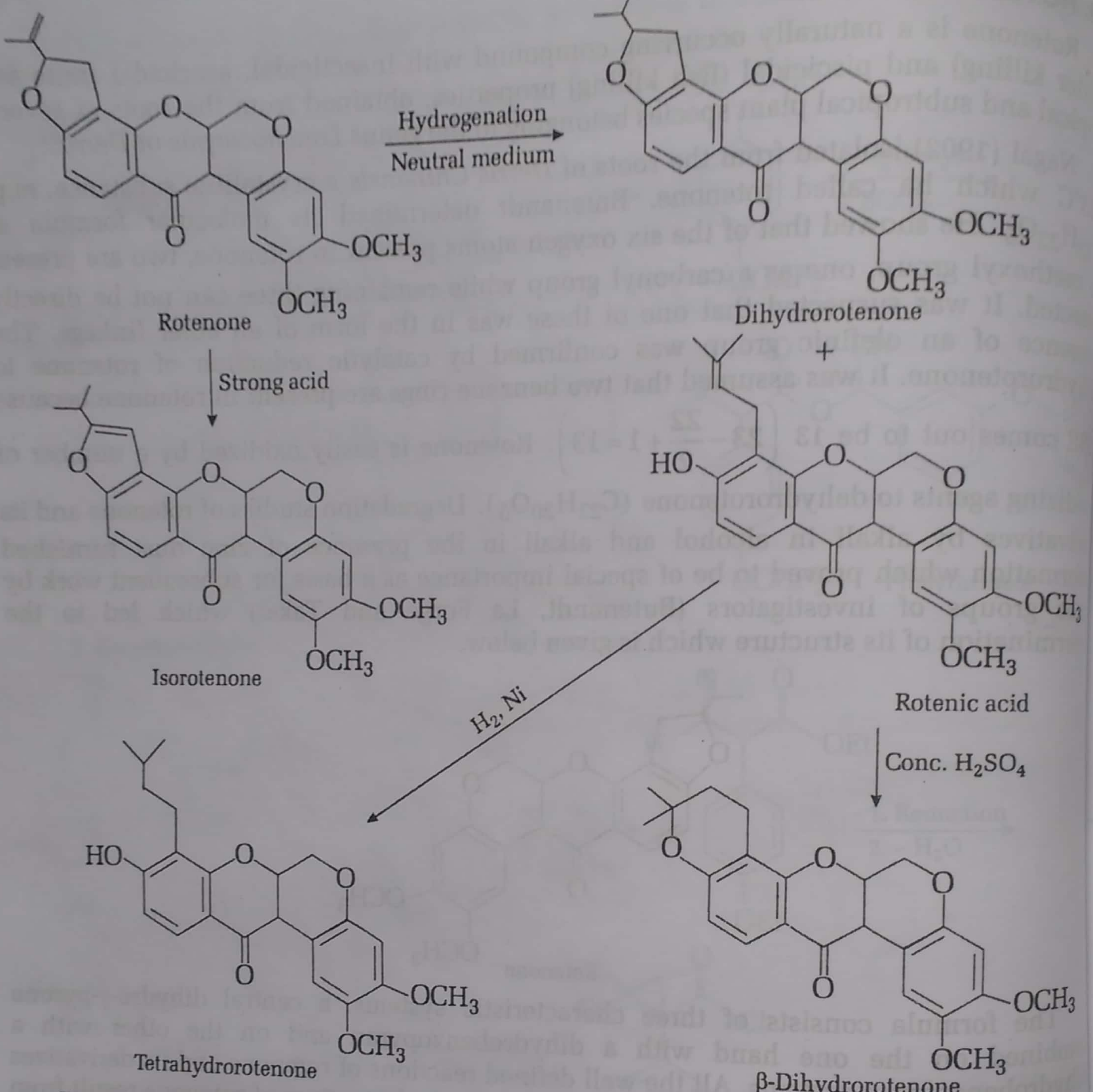
Nagai (1902) isolated from the roots of *Derris Chinensis* a crystalline substance, m.p. 163°C which he called rotenone. Butenandt determined its molecular formula as $C_{23}H_{22}O_6$. He showed that of the six oxygen atoms present in rotenone, two are present as methoxyl group, one as a carbonyl group while remaining three can not be directly detected. It was suspected that one of these was in the form of an ether linkage. The presence of an olefinic group was confirmed by catalytic reduction of rotenone to dihydrorotenone. It was assumed that two benzene rings are present in rotenone because DBE comes out to be 13 $\left(23-\frac{22}{2}+1=13\right)$. Rotenone is easily oxidized by a number of oxidizing agents to dehydrorotenone ($C_{23}H_{20}O_6$). Degradation studies of rotenone and its derivatives by alkali in alcohol and alkali in the presence of zinc dust furnished information which proved to be of special importance as a basis for subsequent work by three groups of investigators (Butenandt, La Forge and Takei) which led to the determination of its structure which is given below.



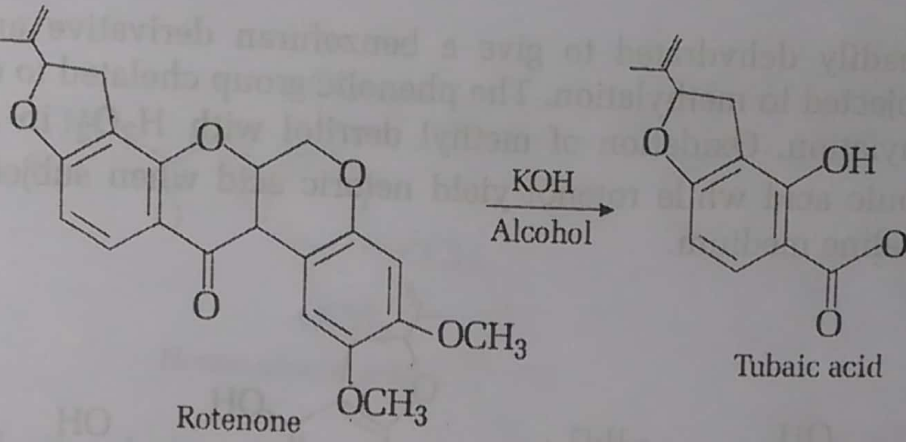
Rotenone

The formula consists of three characteristic systems, a central dihydro-γ-pyrone combined on the one hand with a dihydrobenzopyran and on the other with a dihydrobenzofuran systems. All the well defined reactions of rotenone and its derivatives can be explained by above formula. The characteristic derivatives of rotenone result from reactions which are characteristic of the one or other of three systems, and are supported by analogies with other compounds containing same system.

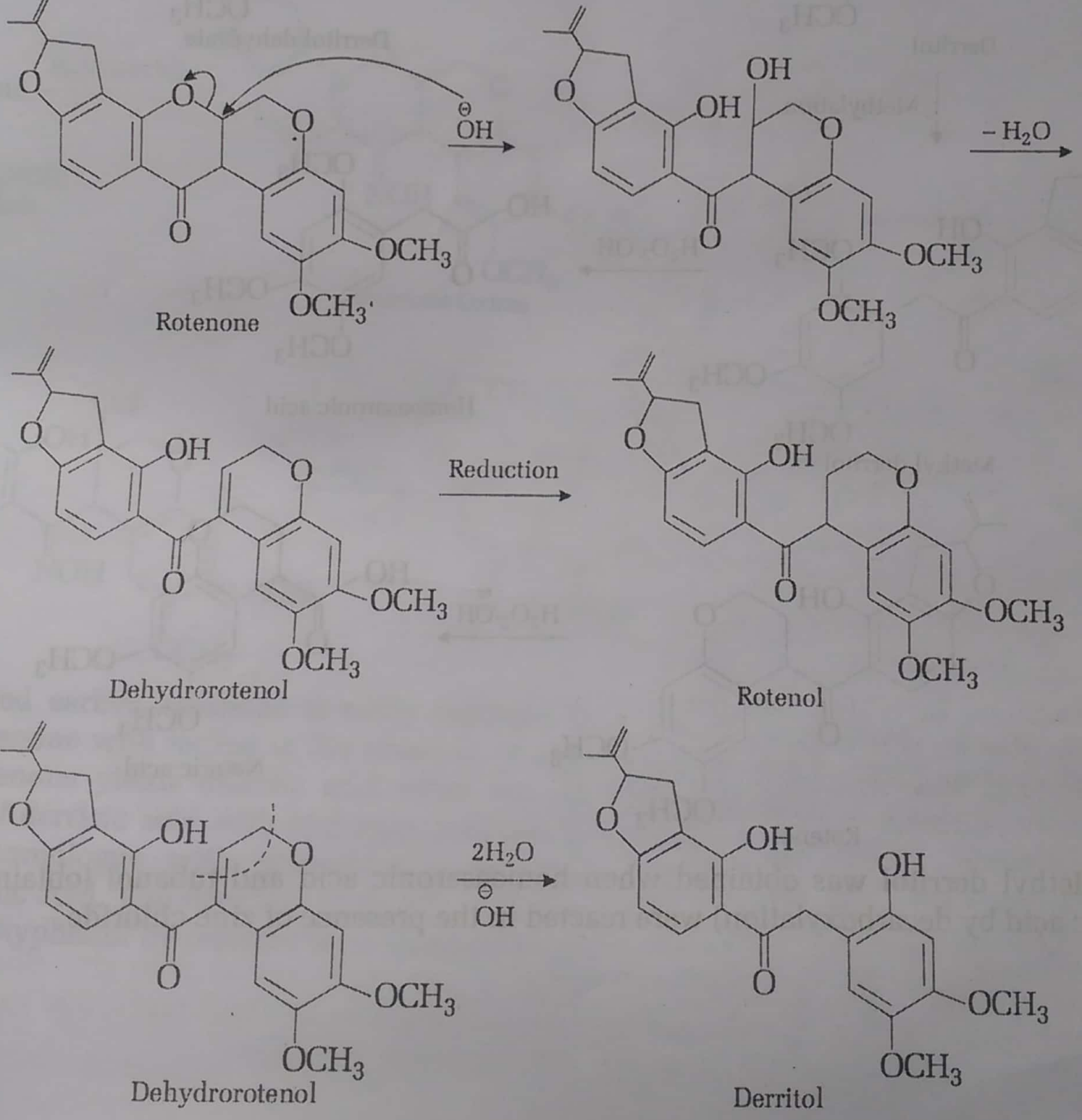
Reactions Involving Dihydrofuran System : When treated with strong acid, rotenone is isomerized to give isorotenone. Catalytic reduction of rotenone in neutral medium yields dihydrotenone and rotenic acid. Rotenic acid is formed by opening of dihydrofuran ring. It is not an acid but was initially assumed to be an acid and this name is still retained. Further reduction of rotenic acid gives tetrahydrorotenone (dihydrorotenic acid) while treating it with conc. sulphuric acid yields an isomeric dihydrorotenone named β-dihydrorotenone.



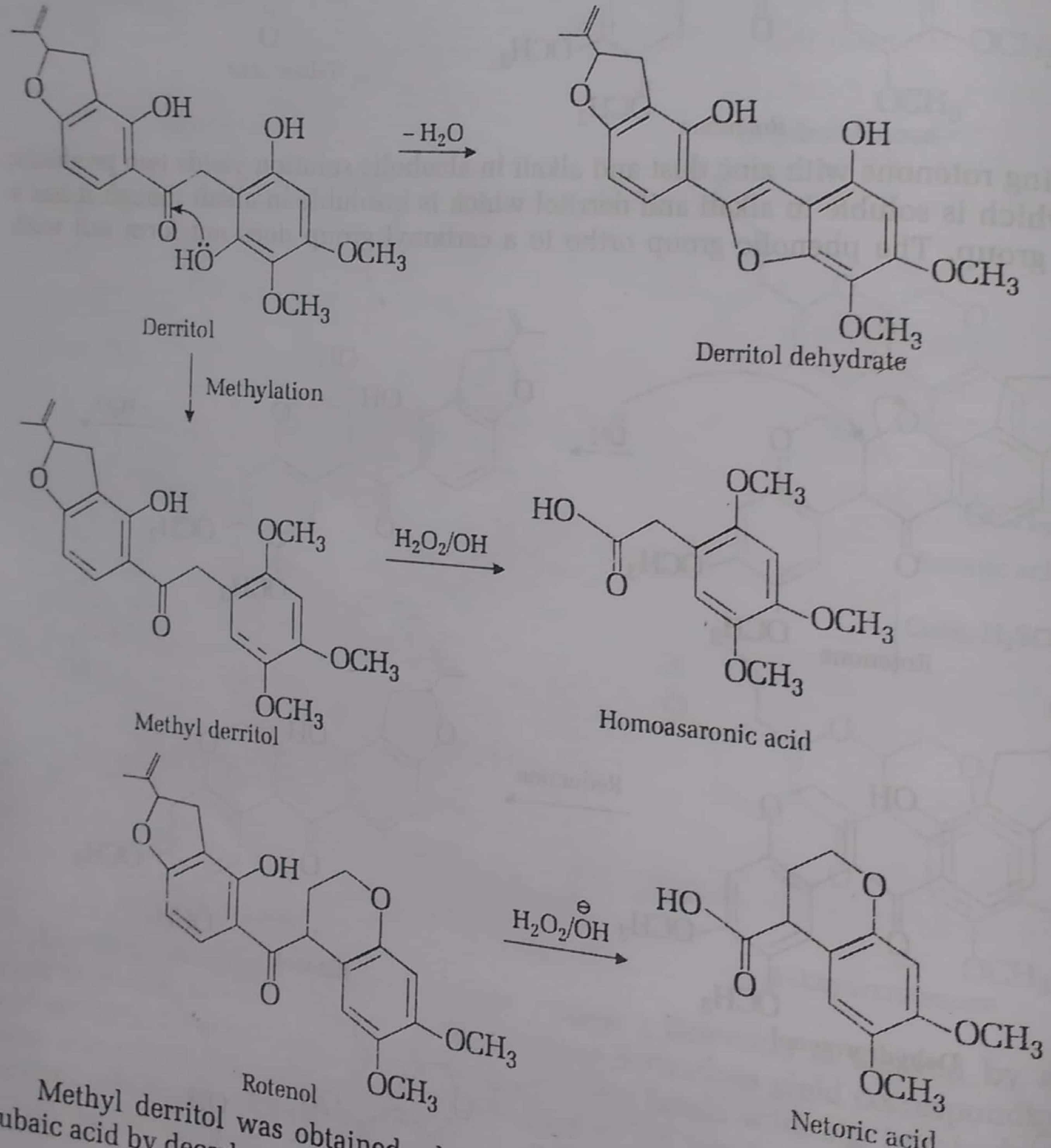
Reactions Involving Dihydro-γ-pyrone System : Retenone is cleaved by alcoholic alkali to give an acid called tubaic acid. Rotenone derivatives yield corresponding tubaic acid derivatives which could also be prepared from tubaic acid, *e.g.* tetrahydrorotenone gives tetrahydrotubaic acid which was identical to the tetrahydrotubaic acid formed by catatylic reductions of tubaic acid.



Treating rotenone with zinc dust and alkali in alcoholic solution yields two products; rotenol which is soluble in alkali and derritol which is insoluble in alkali though it has a phenolic group. The phenolic group ortho to a carbonyl group does not form salt with alkali.



Derritol is readily dehydrated to give a benzofuran derivative and forms methyl derritol when subjected to methylation. The phenolic group chelated to carbonyl group is resistant to methylation. Oxidation of methyl derritol with H_2O_2 in alkaline medium forms homoasaronic acid while rotenol yield netoric acid when subjected to oxidation with H_2O_2 in alkaline medium.



Derritol

Derritol dehydrate

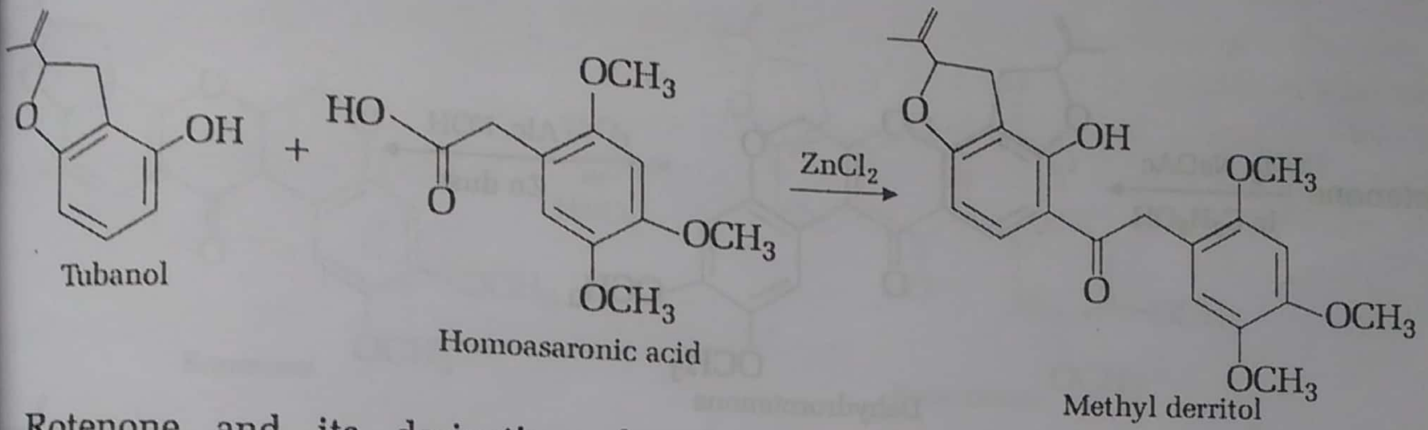
Methyl derritol

Homoasaronic acid

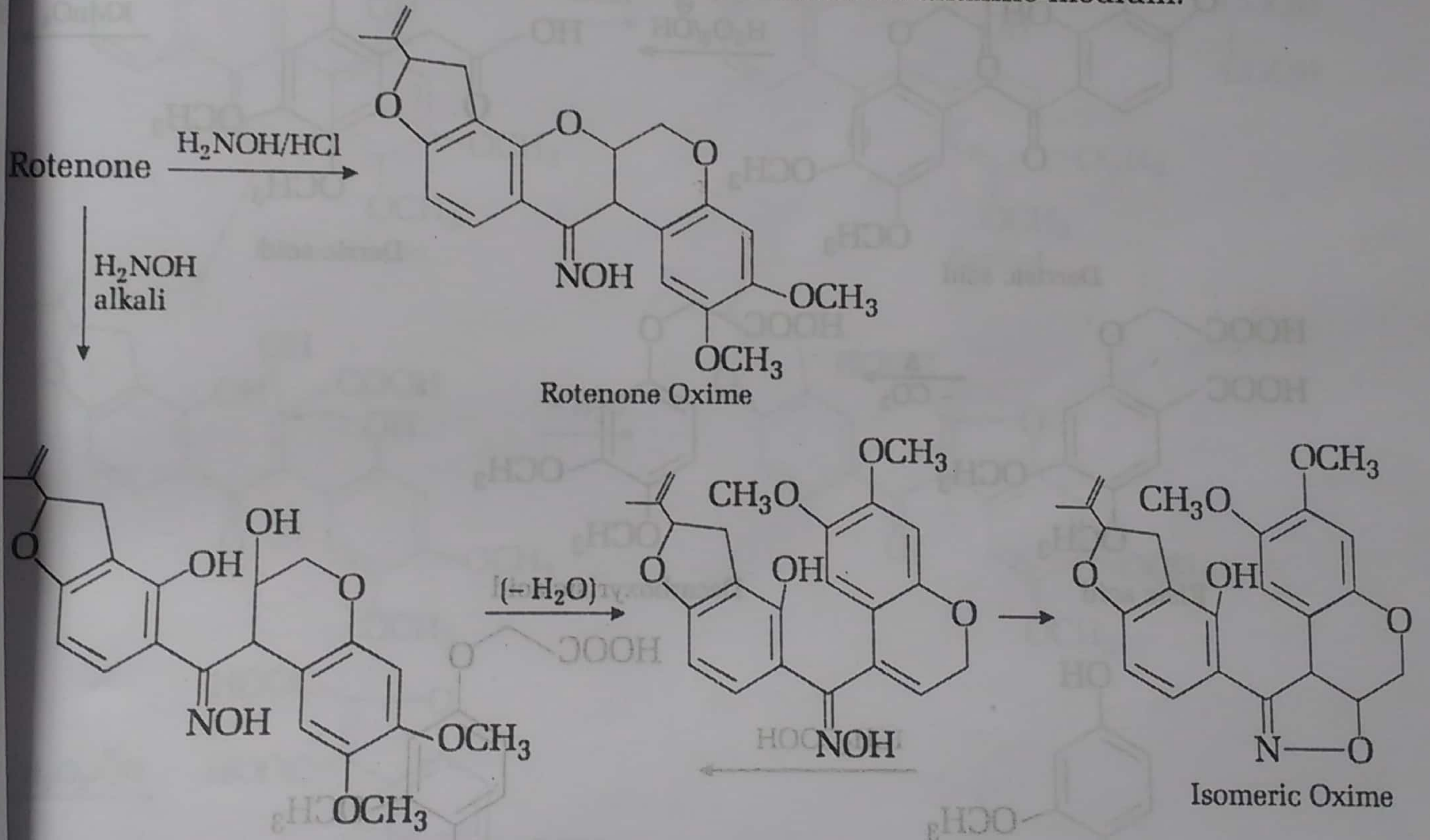
Rotenol

Netoric acid

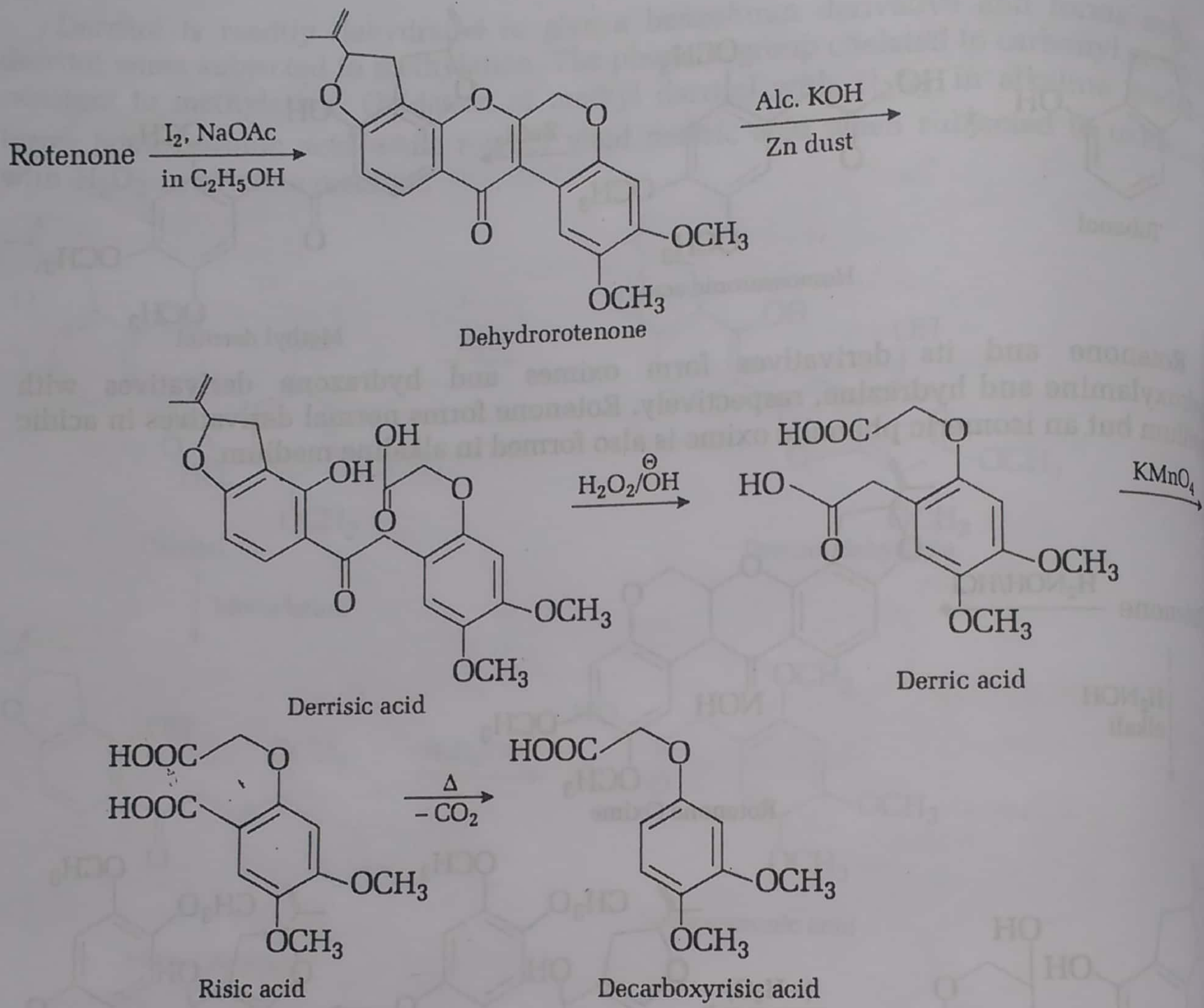
Methyl derritol was obtained when homoasaronic acid and tubanol (obtained from tubaic acid by decarboxylation) were reacted in the presence of zinc chloride.

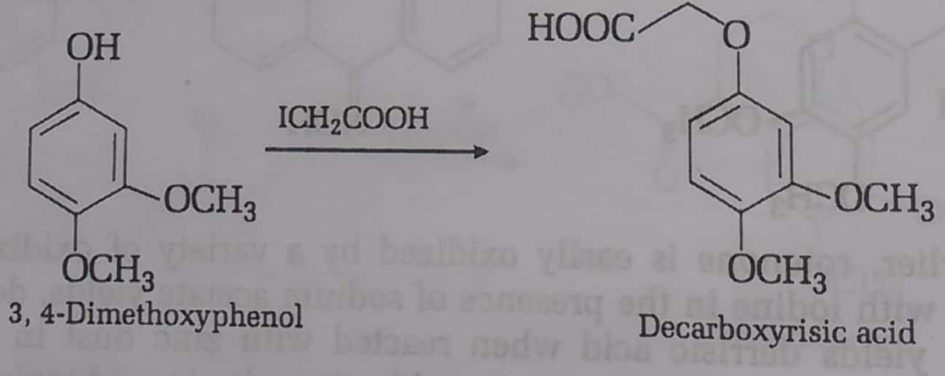


Rotenone and its derivatives form oximes and hydrazone derivatives with ydroxylamine and hydrazine, respectively. Rotenone forms normal derivatives in acidic nedium but an isomeric phenolic oxime is also formed in alkaline medium.



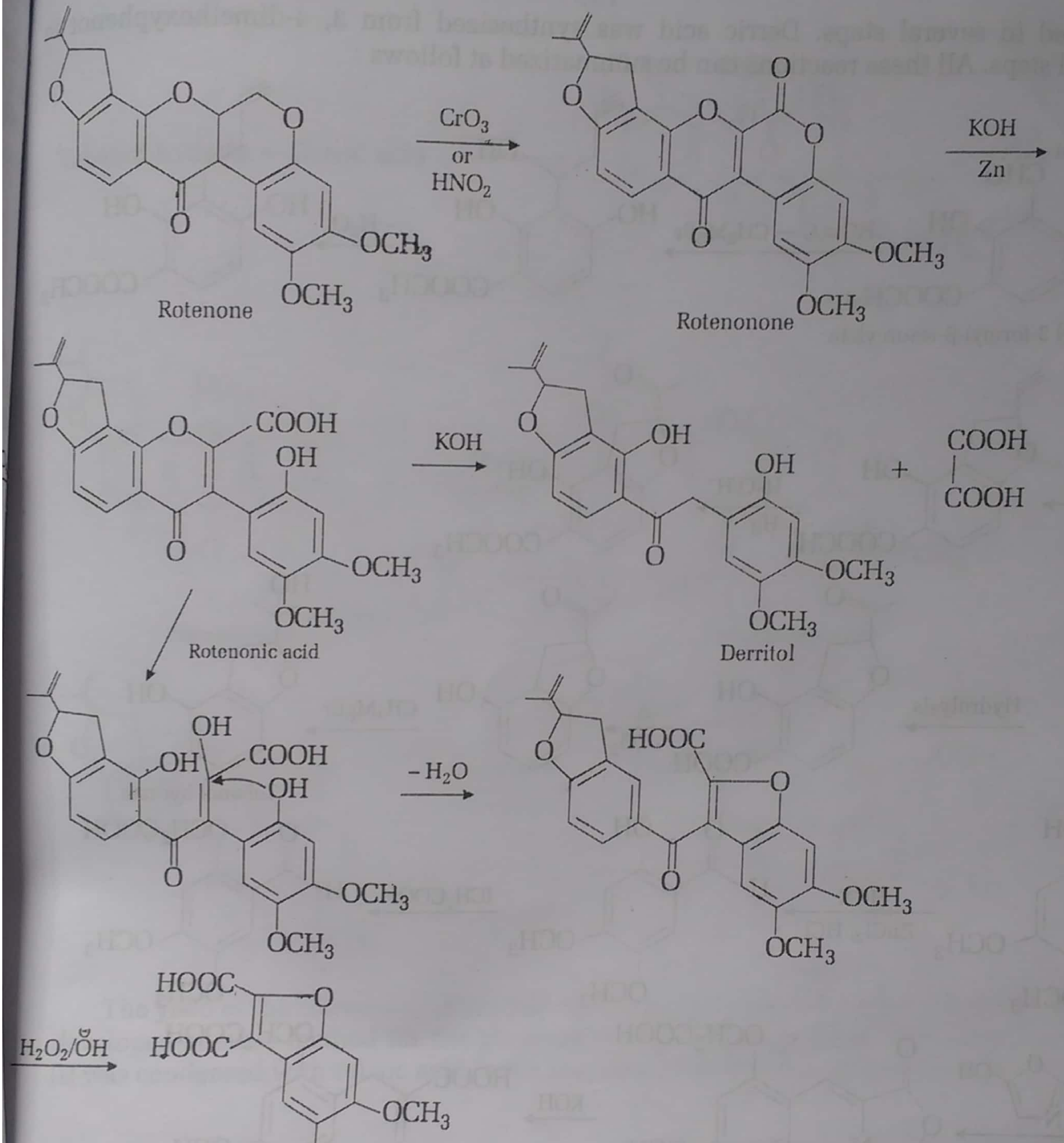
As stated earlier, rotenone is easily oxidized by a variety of oxidizing agents, e.g. ating rotenone with iodine in the presence of sodium acetate yields, dehydrorotenone. hydrorotenone yields derrisic acid when reacted with zinc dust in alcoholic KOH. idation of derrisic acid with hydrogen peroxide gives derric acid which is oxidized to lower homologue with potassium permanganate. Risic acid so obtained gives arboxyrisic acid. The structure of decarboxyrisic acid was confirmed by synthesis from -dimethoxyphenol by reaction with iodoacetic acid.





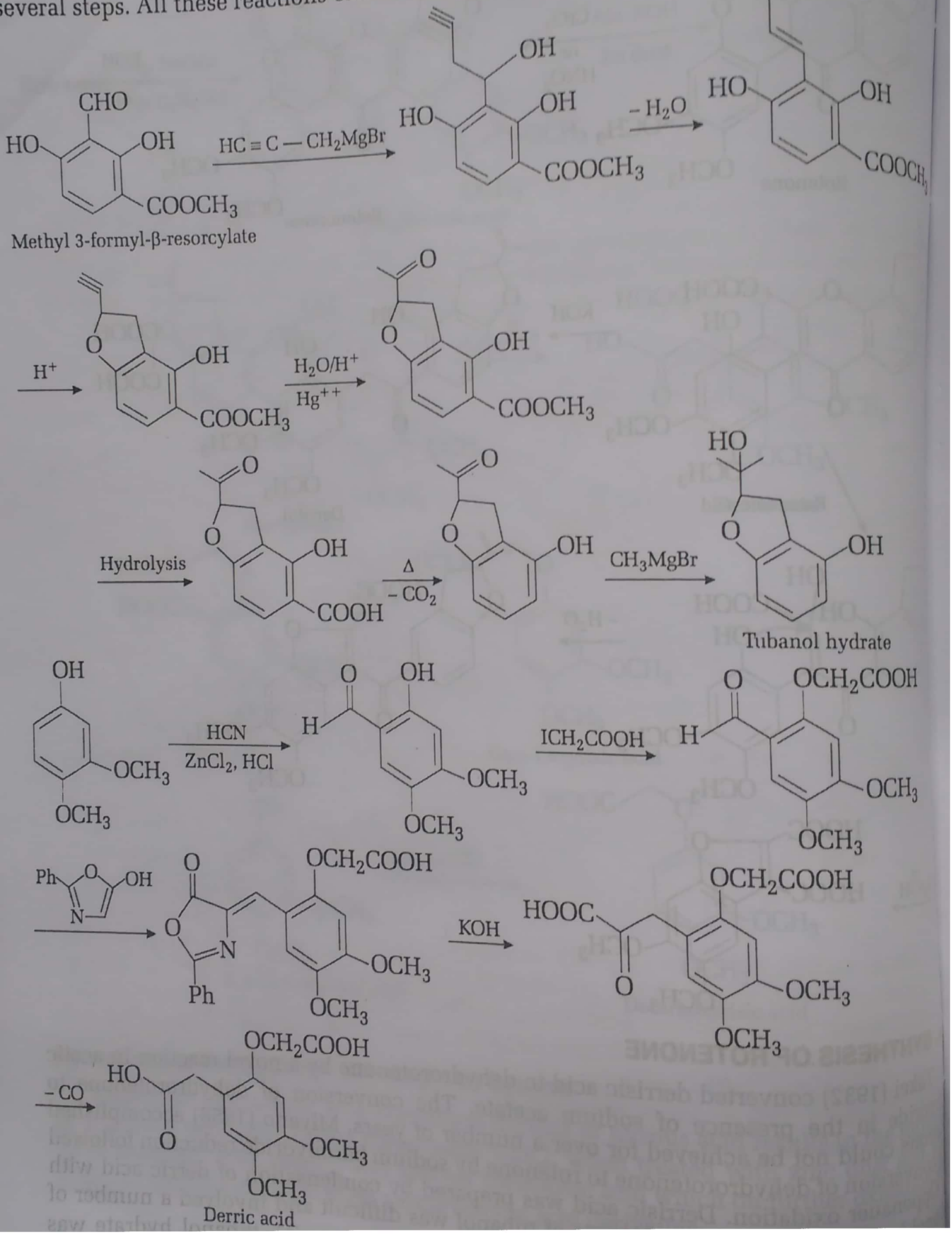
Reactions Involving Dihydrobenzopyran System

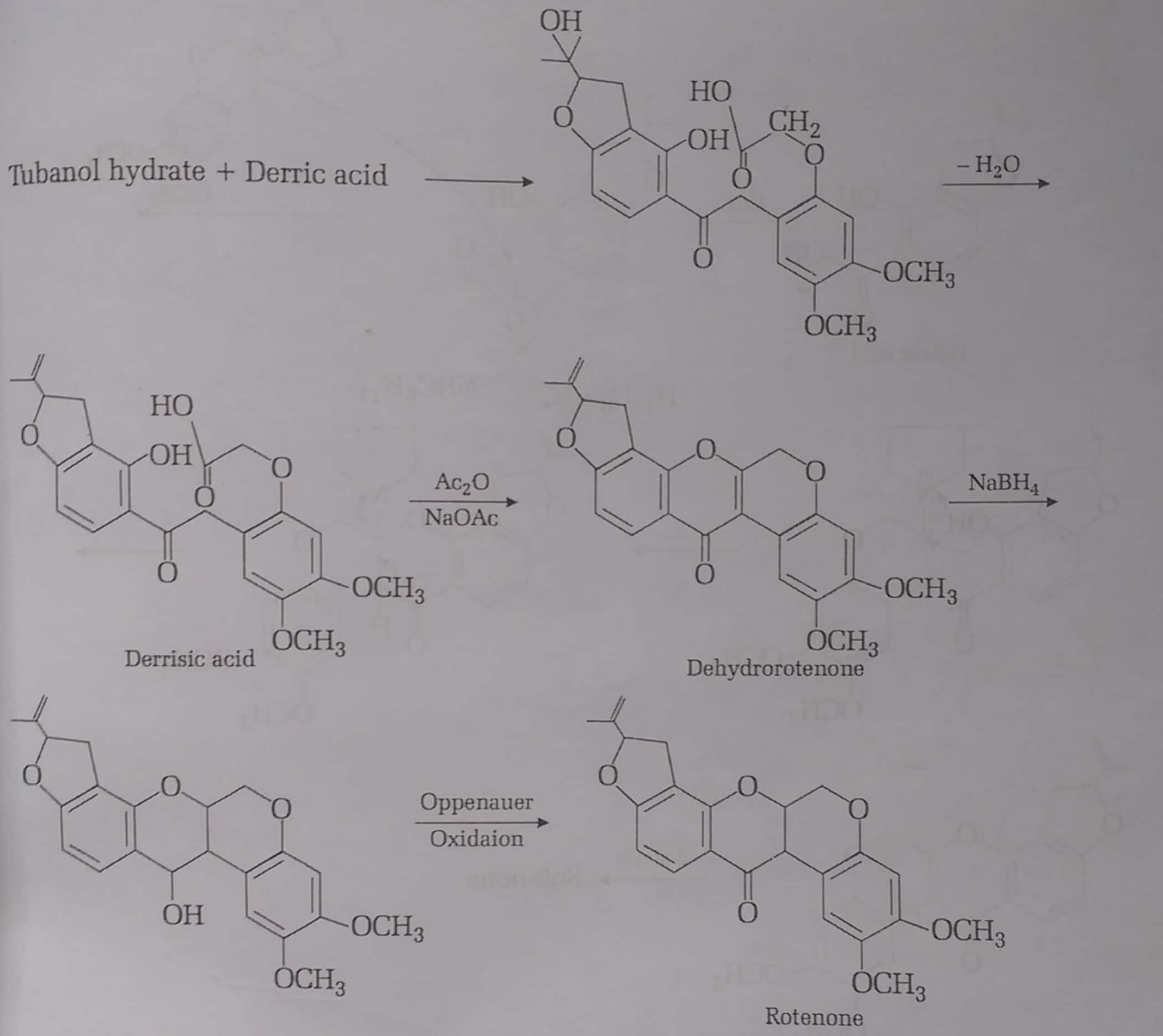
Oxidation of rotenone with chromium trioxide or nitrous acid results in the format of a lactone derivative called rotenonone which when treated with zinc dust and alk gives rotenonic acid, derritol and another carboxylic acid which on further oxidation w H_2O_2 in alkaline medium gives a dicarboxylic acid derivative.



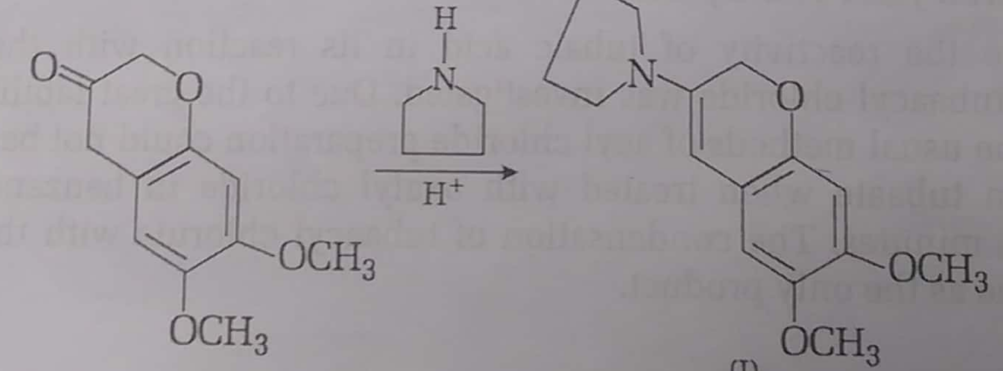
.4. SYNTHESIS OF ROTENONE

Takei (1932) converted derrisic acid to dehydrorotenone by a novel reaction in acetic nhydride in the presence of sodium acetate. The conversion of dehydrorotenone to otenone could not be achieved for over a number of years. Miyano (1958) accomplished he conversion of dehydrorotenone to rotenone by sodium borohydride reduction followed y Oppenauer oxidation. Derrisic acid was prepared by condensation of derric acid with ubanol by Hoesch reaction. Synthesis of tubanol was difficult and involved a number of eps. Using methyl 3-formyl-β-resorcylate as the starting material, tubanol hydrate was obtained in several steps. Derric acid was synthesized from 3, 4-dimethoxyphenol in several steps. All these reactions can be summarized at follows :

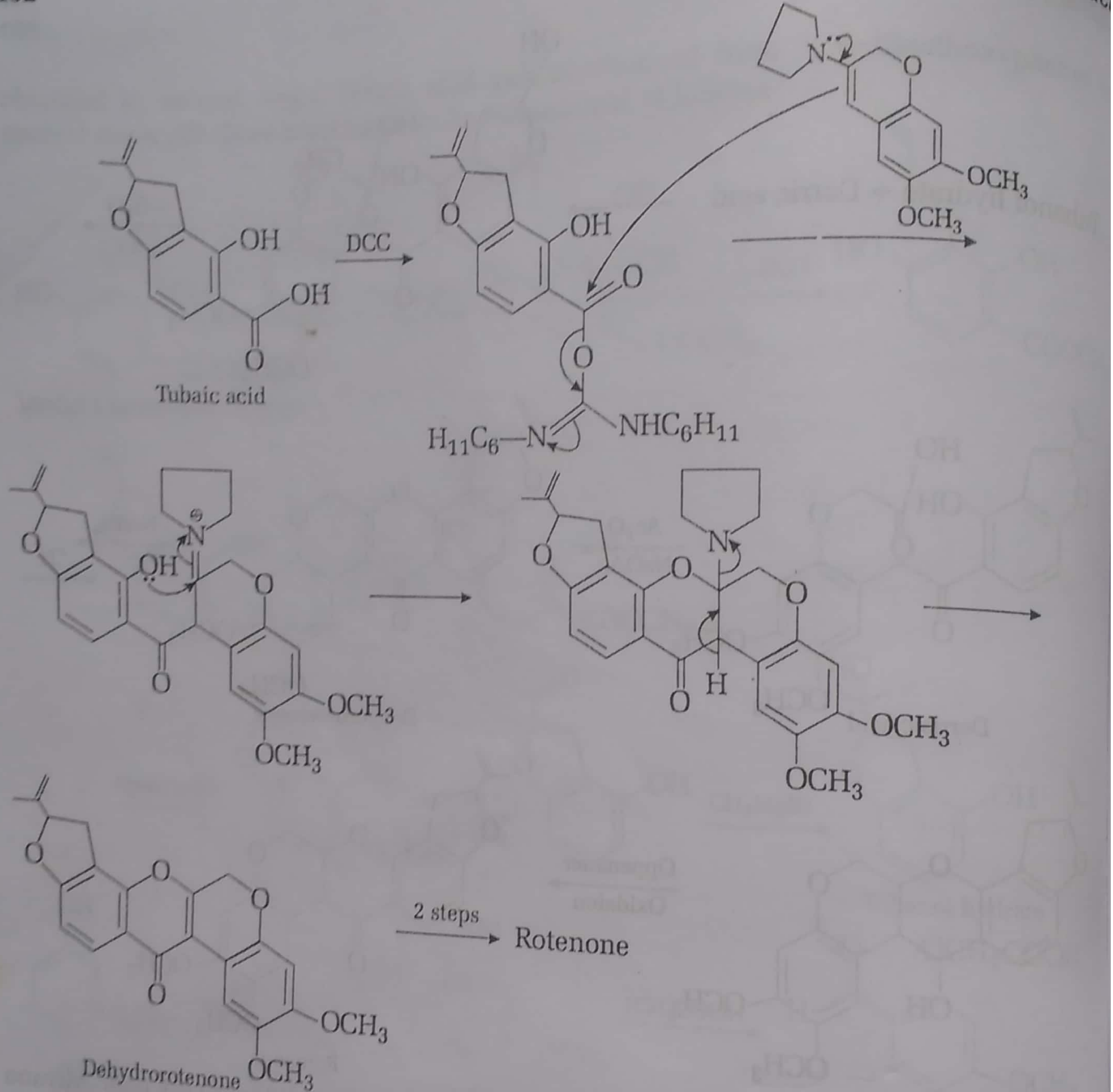




The yield of the conversion of derrisic acid to dehydrorotenone was very poor. Miyano developed another method for the preparation of dehydrorotenone. Pyrrolidine enamine (I) was condensed with tubaic acid in the presence of dicyclohexylcarbodiimide (DCC).

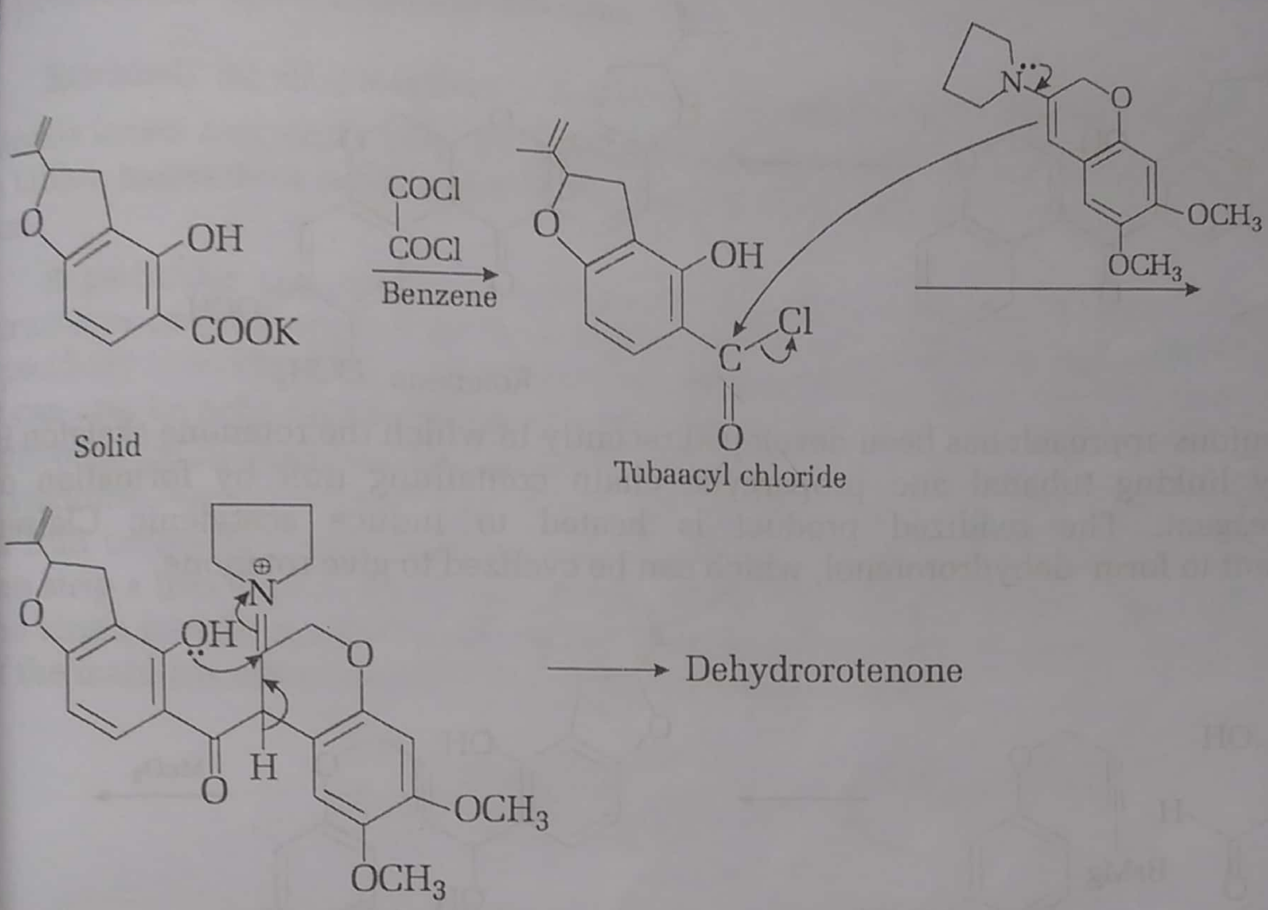


(I)

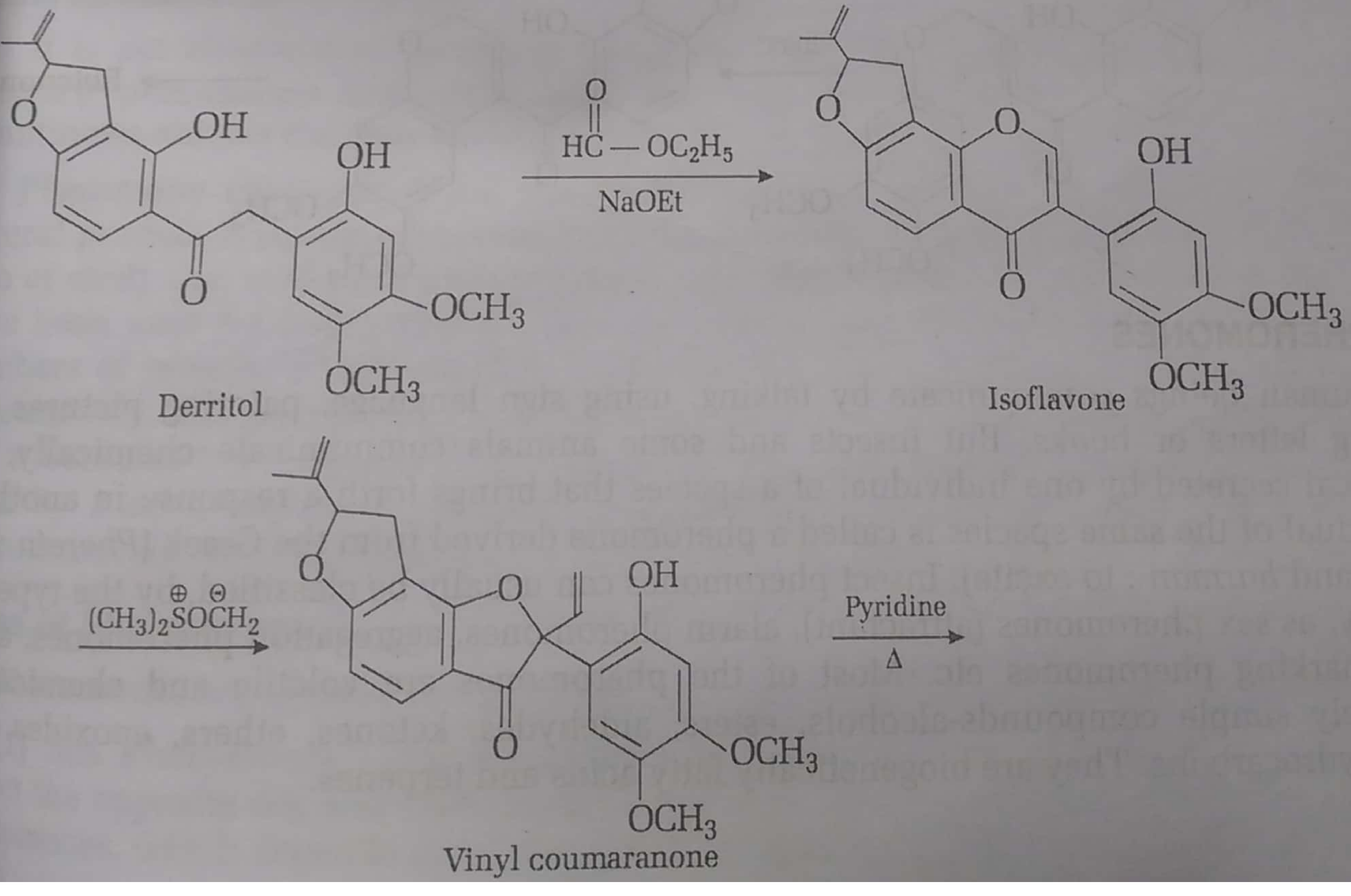


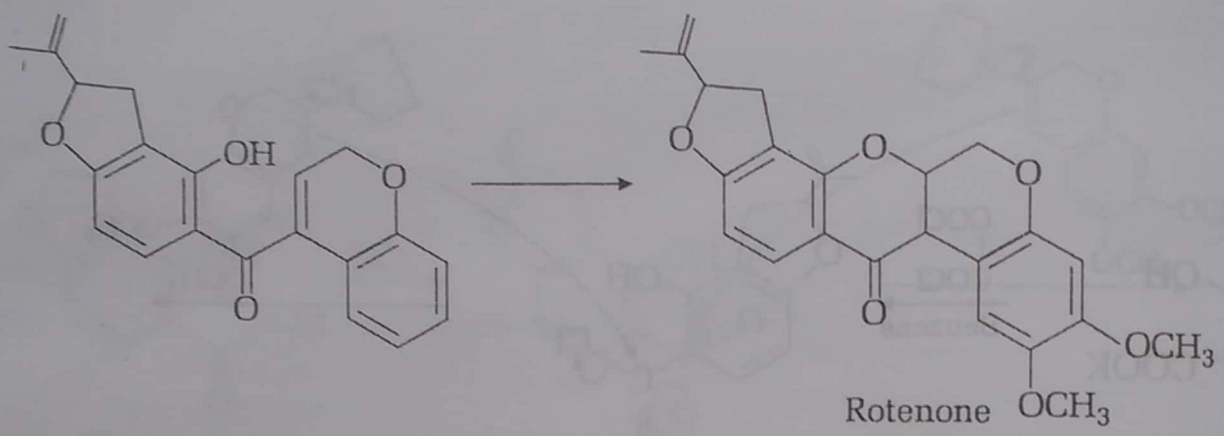
The yield of dehydrorotenone improved a lot but the intermediate formed by the reaction of tubaic acid and DCC decomposes to give a side product in equal amount which affected the overall yield of dehydrorotenone.

To enhance the reactivity of tubaic acid in its reaction with the enamine, the preparation of tubaacyl chloride was investigated. Due to the great lability of side-chain double bond, the usual methods of acyl chloride preparation could not be used. However, dried potassium tubaate when treated with oxalyl chloride in benzene gave tubaacyl chloride within minutes. The condensation of tubaacyl chloride with the enamine gave dehydrorotenone as the only product.



Another approach to the synthesis of rotenone involves reaction of 2′-hydroxyisoflavone with dimethyl sulphoxonium methylide to afford a vinyl coumaranone which when heated in pyridine gives rotenone skeleton via a dehydrorotenol intermediate. Derritol can be converted to isoflavone by reaction with ethyl formate in the presence of a base.





Rotenone

An ingenious approach has been developed recently in which the rotenone skeleton is obtained by linking tubanal and propargylic chain containing unit by formation of Grignard reagent. The oxidized product is heated to induce acetylenic Claisen rearrangement to form dehydrorotenol, which can be cyclized to give rotenone.