Chapter-1

INTRODUCTION

The terpenoids form a group of compounds the majority of which occur in the plant kingdom. The classical unity of this group of compounds as shown by their simple molecular formulae (composed of three organogenic elements, viz., carbon, hydrogen and oxygen) together with their great structural diversity and ubiquity of occurrence has made the terpenes one of the most explored group of compounds. Inspite of the long history of these compounds, the field is not emptied and remains a rich source of new findings.

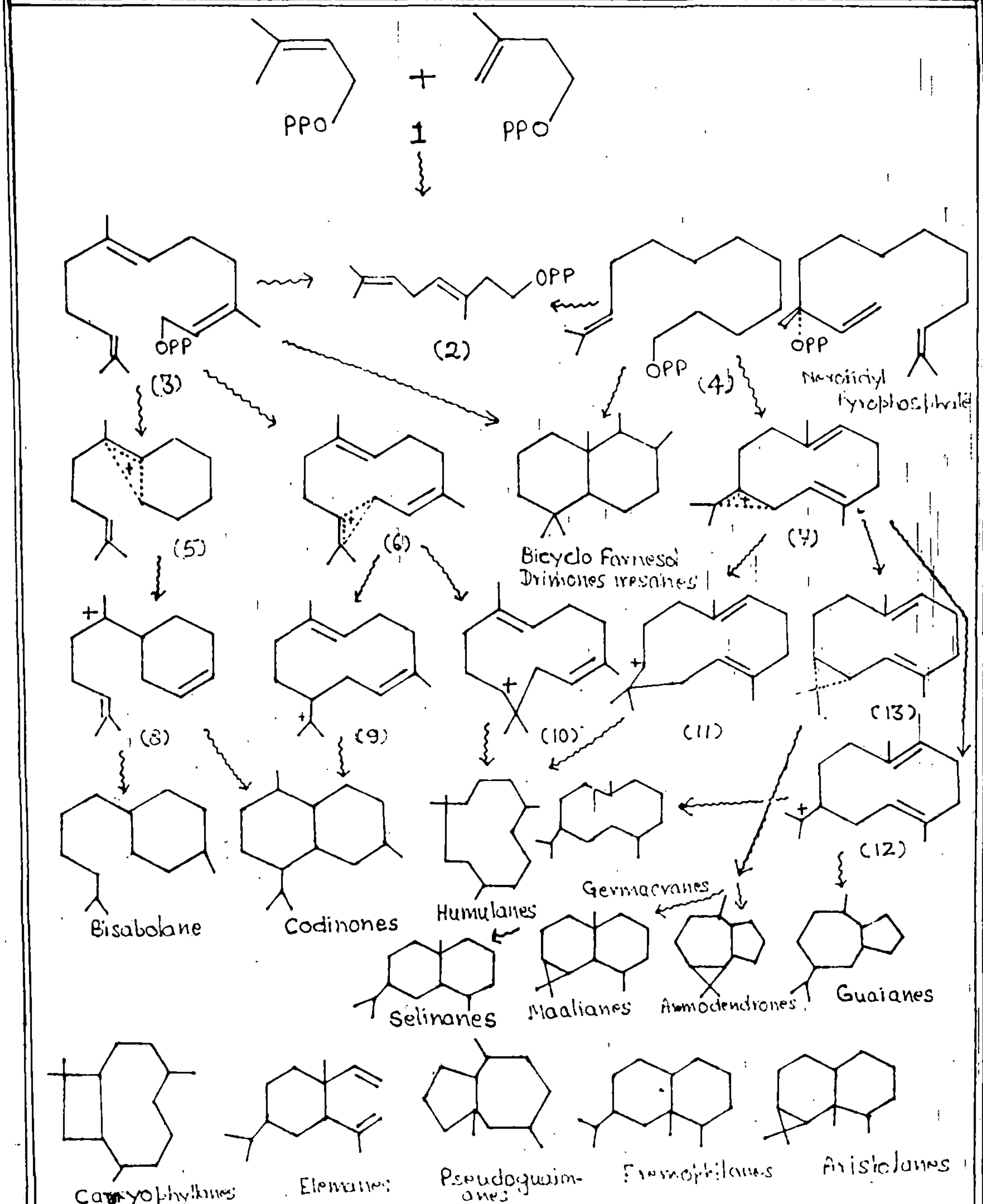
Of a large number of terpenoid natural products known to-day the sesquiterpenes represent the largest single class consisting of different and perverse structural types. The structural elucidation of these compounds by classical chemical and modern instrumental methods is definitely an achievement on the part of an organic chemist. The historical background to sesquiterpenoids can be traced back to the early nineteenth century, but the real impetus to the study of these compounds was due to the pioneering efforts of **Wallach, Semmler and Ruzicka. Wallach** was the first, to suggest that the sesquiterpenoid structure is built up of three isoprene units to form a partially hydrogenated napthalene type of skeleton for sesquiterpenes. But now it is known that this class of compounds may have open chain, azulene type, spiro and other different frame works. The sesquiterpenoids which occur primarily in higher plants, less frequently in lower plants and in the animal kingdom , comprise not only unsaturated hydrocarbons (including alkynes) but also alcohols, ketones, aldehydes and carboxylic acids. They may also contain three to seven membered rings, spiro systems and furan rings. Chlorine and bromine substituted sesquiterpenoids as well as nitrogen containing compounds with fifteen carbon atoms isolated from Nymphacaceae deserve mention. Compounds with only twelve or fourteen carbon atoms (nor-sesquiterpenes) can also be derived from certain sesquiterpenes.

The sesquiterpene lactones occuring in composite and also in other plant families have attracted particular interest. The first compound of this class, α-santonin[1] which was isolated in crystalline form in 1830, is still the object of intensive investigations[2]. Of a large number of sesquiterpene lactones known, worthy of particular mention are the germacrenolides[3,4], guaianolides[3,4,5], pseudoguaianolides[1,6,7], selinanolides (Syn: eudesmanolides)[8] and cremophinolides[4]. Most of them are α,β unsaturated γ-lactones. Apart from a delta-lactone, only two β-lactones (anisatin and neoanisatin)[9] have been found. A trilactone, lilabolide[10], is also known alongside about a good number of dilactones.

The large number of sesquiterpene skeleton known to-day, corresponding to a large number of presently known compounds which is in order of magnitude greater than twenty years ago, requires their systematization so that they may be surveyed in a comprehensive manner.

BIOGENESIS:- According to the well founded concepts developed in recent years for biogenesis of their highly diverse carbon skeletons, the sesquiterpenes have been divided into nine sections dealing respectively with farnesenes, bicyclo farnesols (drimanes, iresanes), bisabolanes, cadinanes, humulanes and caryophyllanes, germacranes, hydroazulenes, selenanes and eremophilanes and maalianes and aristolanes. Further groups of sesquiterpenes can be derived from each of these structural types[11]. Sesquiterpenes having the same carbon skeleton are classified as a single group. At the first sight sesquiterpenoid structures present a bewildering collection of acyclic, monocyclic, bicyclic and tetracyclic systems and is within the framework of original "Isoprene Rule"[12,13] and later extensions[14,15] that semblance of relationship can be achieved.

The focal point of this conceptual biogenetic scheme is the utilization of 2-cis,6-trans - farnesyl pyrophosphate(3) the corresponding 2-trans,6-cis-farnesyl or 2-cis,6-cis farnesyl or nerolidyl pyrophosphate can also be a crucial building blocks of a few sesquiterpenoids.The farnesyl pyrophosphate,the biological precursor of almost all sesquiterpenoids is formed from acetyl Co-enzyme-A via mevalonic acid isopentenyl pyrophosphate(**1**) and geranyl pyrophosphate(**2**). Removal of the pyrophosphate group from(**3**) or(**4**) yields the non classical cations(**5**) and (**6**) or (**7**) each of which can cyclise to two cyclic cations e.g.,(**9**) and (**10**)from (**6**) ;(**11**) and (**12**) from (**7**). These can afford most of the sesquiterpenes by processes such as 1,2 or 1,3-hydro shifts, electronically and sterically controlled cyclisation with two remaining double bonds (Markownikoff and anti Markownikoff cyclisations) ,**Wagner-Meerwein** rearrangements,and 1,2-methyl shifts. It must however be mentioned that many hypothesis based on structure,stereochemistry and reactivity regarding the biosynthesis of sesquiterpenes still require experimental proof in vivo[15,16].



Biogenesis of the sesquiterpenes. Wavy Lines signify biogenetic transformation. The basic skeleton are shown without multiple bonds.

CONTRIBUTION OF THE RESEARCH ON TERPENOIDS TO THE WORLD OF CHEMISTRY

Studies on the sesquiterpenoids have contributed significantly to the advancement of spectroscopic techniques, mechanistic insight and synthetic methodology and the trend along these lines shows no sign of letup, as new and increasingly complex structures join the list of known members.

The future of the terpenes research will still be concerned primarily with the isolation and structural elucidiation of new compounds which could be important as missing biosynthetic links , as biologically active substances or as reactants for the study of chemical problems. The sesquiterpenes throw up problems largely of stereochemical nature.The course of their numerous rearrangements provides information about relationship between stereochemical and electronic factors and the reactivity of the compounds. The chemistry of nonclassical carbonium ions has also profited much from work on sesquiterpenoids.The photochemistry of the sesquiterpenes is still in its infancy.Knowledge of reactivity, photochemistry and synthesis stimulate research into sesquiterpene biogenesis , a field that will become increasingly important in the future. The aim is to elucidate the formation of numerous carbon skeletons and to obtain information about the reasons behind the frequently complex stereospecific biosynthetic pathways that could also be of interest for biogenesis of other natural products.The biological properties of some sesquiterpenes show that they are not merely metabolic waste products. For instance, they are of significance as plant growth substances,growth regulators and sex attractants of fungi.This area of sesquiterpene research is of potential interest e.g.,for solution of practical problems of influencing the growth of cultivated plants and in plant protection.

Sesquiterpenes can provide impetus to drug research too. The starting point of such work is the pharmacological effects, determined so far for relatively small number of compounds. They include cytotoxic, antibiotic, fungistatic, virostatic, antiphlogistic,and sedative properties,thus covering a fairly broad spectrum. Sesquiterpene research is also of importance in the chemistry of essences and of aromas and flavours.

The major high light of recent years has been the dramatic eruption of outstanding and elegant synthesis.In the solution of the inherently different problems of skeletal construction and stereochemical control associated with some of these synthesis which have endowed the synthetic organic chemist with a rich new array of armaments for future use.In particular the work of **Buchi,Corey and Marshall** and their respective research teams deserves a special mention.In this connection one must have to mention the case of "Vetivanes" which were formerely regarded as hydroazulenes but now proved to be spirocyclic agarospiranes or eremophilanes with decalin skeleton[17].The detection of sesquiterpenes with toxic and interesting biological properties e.g.,cytotoxic activity [18] also deserves mention[18,19,20].

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