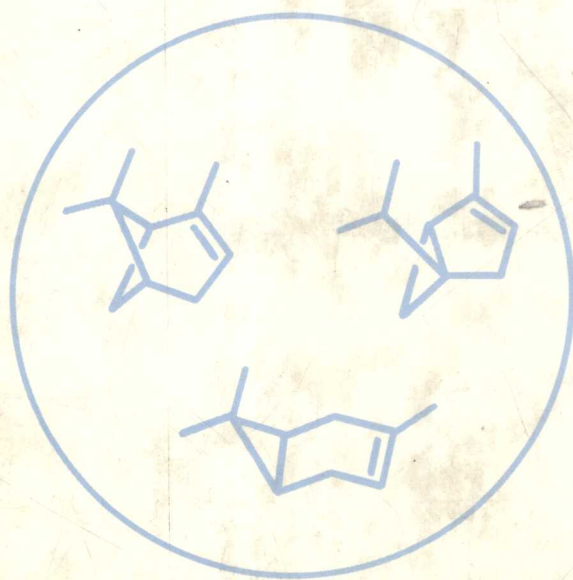


chemistry of the monoterpenes

an encyclopedic handbook

part A



WILLIAM F. ERMAN

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An Encyclopedic Handbook

Part A

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Preface

A new acquaintance on learning about my interest in terpene chemistry remarked that this area of chemistry seemed like a rather narrow field in which to conduct research. When I relayed this comment to my colleagues, they were predictably amused, for their explorations in terpene chemistry had led them into several disciplines of chemistry—organic, physical, analytical, and biological—and into a variety of intriguing fields where terpenes have been utilized—e.g., flavors, perfumes, insecticides, herbicides, and pharmaceuticals.

Terpene chemistry offers the chemist a variety of challenges: (1) isolation, structure elucidation, and determination of the absolute configuration of a group of exotically constructed natural products utilizing a multitude of analytical separation techniques, numerous spectral tools, and X-ray crystallography; (2) in vitro and in vivo tracer studies for the purpose of elucidating the often complex biogenetic pathways of these compounds; (3) intricate stereochemical problems including the effects of stereochemistry on the course of organic reactions; (4) a multitude of complex synthetic objectives; (5) the unraveling of the mechanisms of bizarre rearrangement reactions; and (6) a study of carbonium ion, carbanion, carbene, free radical, and concerted processes which may be acid-catalyzed, base-catalyzed, thermally induced, or photoinitiated and may involve oxidation, reduction, displacement, elimination and addition reactions, to name a few. Far from being narrow and limited, terpene chemistry includes almost all of the attractive aspects of organic and analytical chemistry.

Of the various classifications of terpenes—monoterpenes, sesquiterpenes, and the higher terpenes—the chemistry of the first class is perhaps the most interesting. Monoterpenes are more abundant in nature and are more easily synthesized in commercial quantities; therefore they are more readily available for

chemical studies. With a few exceptions, the sesqui- and higher terpenes have been isolated or synthesized only in small quantities; consequently, fewer chemical studies have been conducted on these terpenes.

The treatment of monoterpene chemistry in this treatise is not intended to be comprehensive. We have attempted to familiarize the reader with the most common monoterpene structural types encountered in nature, their biogenetic pathways, the nomenclature of the principle monoterpene skeletons, the reactions and techniques used to delineate the structures of some of the more common monoterpenes, the important stereochemical features of the terpene structures including their absolute configurations, and some of the general and/or most interesting synthetic approaches to the monoterpenes. However, in most instances we have placed greatest emphasis on chemical reactions of the monoterpenes. There are some exceptions. Like the sesqui- and higher terpenes, the geminate dimethylcyclohexanes (Chapter 5), the cyclopentanes (Chapter 6), and the monoterpene phenols (Chapter 12) have been isolated or synthesized only in small quantities, and, consequently, few studies of the chemical behavior of these classes of monoterpenes have been conducted. For this reason, the primary emphasis in these chapters (5, 6, 12) is on structure elaboration and synthesis.

A discussion of chemical reactions is incomplete without inclusion of some information about reaction mechanisms. Because of the speculative and controversial nature of many of the reaction pathways described here and the rapid rate at which ideas about the mechanisms of certain of these reactions are changing, the mechanistic hypotheses presented here are tentative. Nonetheless, we hope that the mechanistic reasoning offered here will clarify the otherwise nondescript chemical behavior of some of the monoterpenes.

Very little information about the spectral parameters and physical properties of the monoterpenes has been discussed here. Such data are described in a handbook by T. K. Devon and A. I. Scott (Handbook of Naturally Occurring Compounds, Vol. II, Terpenes, Academic Press, New York, 1972) and a handbook by S. Dev, J. S. Yadav, and A. Narula (Handbook of Terpenoids, Monoterpenoids, CRC Press, Inc., Boca Raton, Florida, 1982).

Special thanks are due to Dr. Paul Gassman, who read and critiqued the entire manuscript and suggested many excellent revisions. I am grateful to Charlotte Hutfles, Jacoba Atkins, Olga Carman, Barbara Beimesch and Rose Blanchet for reading and making corrections on portions of the manuscript. I particularly want to acknowledge those who typed and drew the structures for the several revisions of the manuscript--Beverly Nixon, Lucille Walsh, Loretta Hallbach, Charlene Wood, Mona Moore, Beverly Perkins, Jean Gullion, Ruth

Frankenstein, Rosemary Schlensker, Peggy Sehlhorst, and Sandra Galligan--and to those who skillfully and painstakingly completed the artwork for the camera-ready manuscript: Carol Dixon, Lisa Erman, Rosanne Erman, and Eileen Fletcher. I am especially indebted to Lucille Walsh who typed and drew the structures for the original manuscript and typed most of the camera-ready manuscript, to Loretta Hallbach who typed an entire revision of the manuscript and Beverly Nixon who coordinated the extensive work on the camera-ready manuscript. I would also like to thank the editors of Marcel Dekker, Inc. for their guidance in preparing the manuscript.

Some acknowledgement is due to our dining room table which served as a desk for the writing of the entire manuscript. That poor table has been covered with journals, books, papers, articles, etc., and hasn't enjoyed a normal life of Sunday dinners for several years. Today, at last, it is covered with a beautiful tablecloth, plates and silverware and is ready for the author's dinner with the loving, patient and understanding family to whom these volumes are dedicated: my wife, Rosemary, and our four children--Timothy, Lisa, Rosanne and Michael.

William F. Erman

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1

Introduction

1. THE ISOPRENE RULE

The biogenetic construction of the vast array of natural products produced by both plants and animals occurs via a limited number of general biosynthetic pathways. One of the pathways, which involves the coupling of two or more units of Δ^2 - and Δ^3 -isopentenyl pyrophosphates [Δ^2 -IPP (1) and Δ^3 -IPP (2)] (Fig. 1) by stereoregulated processes, leads to a classification of compounds termed terpenes [1,2]. The coupling of two of these units followed by a multitude of chemical processes, including complex cyclization and rearrangement reactions, affords the simplest compounds of the terpene class: the ten carbon-containing monoterpenes [3]. Although a limited number of monoterpenes are formed in nature by an anomalous coupling of the pyrophosphates (1) and (2) (see below), most are derived by "head-to-tail" [4] coupling of Δ^2 -IPP (2) and Δ^3 -IPP (1) as outlined in Fig. 1 [5a]. The resultant product of this coupling—geranyl pyrophosphate (3)—serves as a precursor to the monoterpenes. "Head-to-tail" coupling of Δ^3 -IPP (1) with geranyl pyrophosphate (3) affords farnesyl pyrophosphate (4), which is the progenitor of the 15 carbon-containing sesquiterpenes. Further condensation of (4) with (1) leads to geranylgeranyl pyrophosphate (5) which is converted in vivo to the 20 carbon-containing diterpenes. A limited number of terpenes which possess 25 carbon atoms have been isolated from natural sources. These compounds, which have been termed sesterterpenes, are formed by biochemical transformations from geranyl-farnesyl pyrophosphate (6); the latter compound is generated by condensation of Δ^3 -IPP with geranylgeranyl pyrophosphate (5). "Head-to-head" dimerization of farnesyl pyrophosphate (4) affords the 30 carbon triterpenes, while similar dimerization of geranylgeranyl pyrophosphate (5) provides the 40 carbon tetraterpenes and carotenoids.

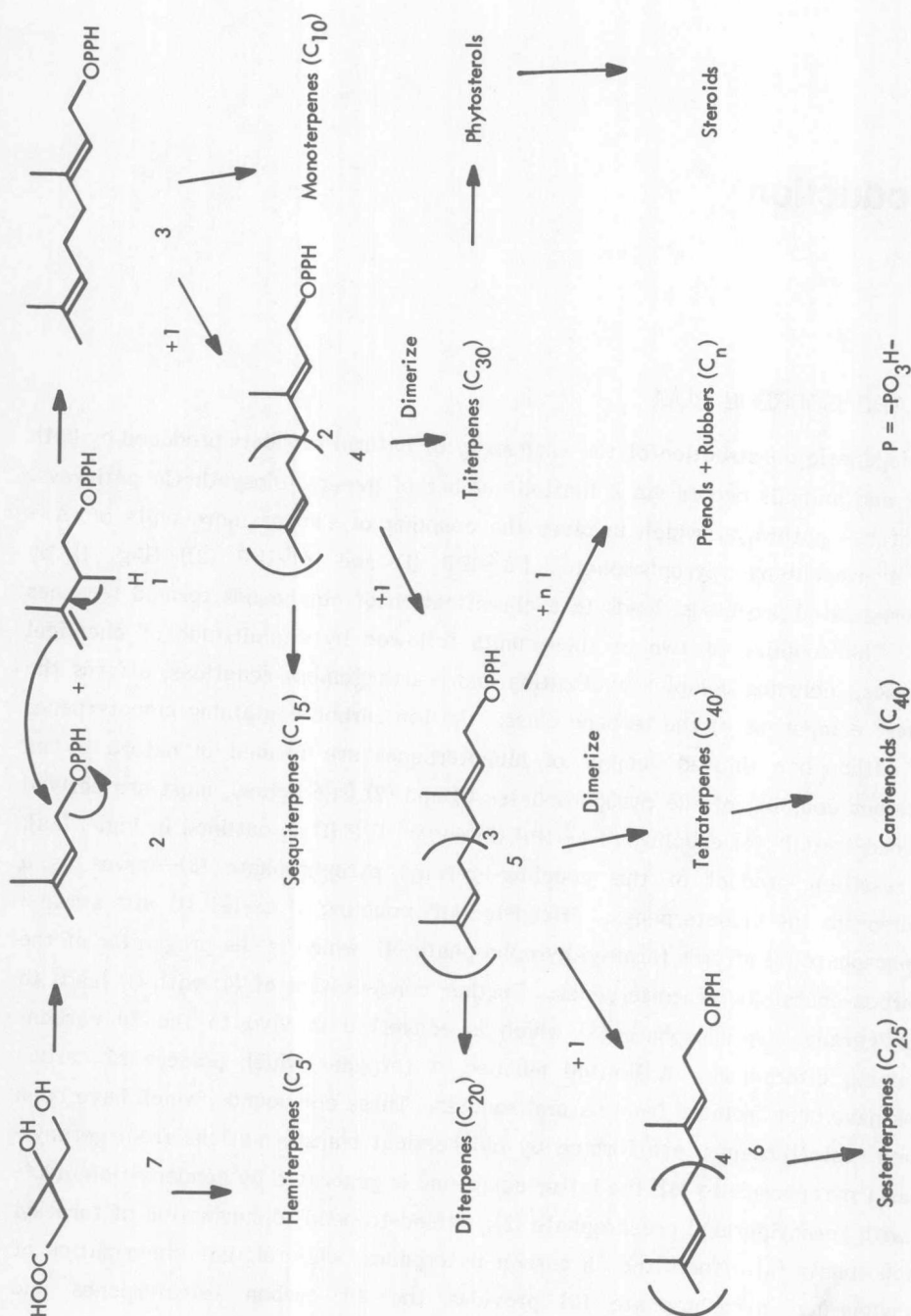


Figure 1

Several other types of compounds belong in the terpene class biogenetically: the C₅ hemiterpenes, the prenols, the rubbers, the phytosterols, and the steroids. The hemiterpenes probably are derived biogenetically from the IPP compounds (1) and (2) or from their precursor mevalonic acid (7), while rubber and the prenols are formed by enzymic-catalyzed head-to-tail addition of units of Δ^3 -IPP to geranylgeranyl pyrophosphate (5). The phytosterols and steroids are metabolites of the triterpenes. Although the hemiterpenes, prenols, rubbers, phytosterols and steroids are of the same biogenetic origin as the terpenes, they are commonly treated as separate chemical classes and will not be included in our discussion of terpenes in these volumes [5b].

A number of natural products contain units biogenetically constructed from both isoprenoid and nonisoprenoid biogenetic precursors. Such compounds in which the isoprenoid and nonisoprenoid units are connected via carbon-carbon bonds have been classified as meroterpenes [6a,b]. Examples of meroterpenes are the isoprenoid alkaloids, quinones, coumarins, acylphloroglucinols, flavoglucins, flavanoids, resorcinols and phenols. Because several recent treatise deal with the chemistry of terpene alkaloids adequately, this subject will not be reviewed in these volumes [6]. Treatment of the chemistry of most of the terpene hybrids of quinones, coumarins, acylphloroglucinols, and flavanoid type structures similarly is relegated to treatise on the chemistry of these compound classes [6d,e]. On the other hand, the most interesting aspects of the chemistry of certain terpene phenols, for example the cannabinoids, involve the terpene moiety of these compounds; consequently, the chemistry of these classes of natural products is discussed in this treatise.

Although the details of the pathways involved in the biosynthesis of the terpenes are still being elucidated [2], Wallach as early as 1887 recognized the commonality of the presence of isopentane units connected head-to-tail in a number of natural products isolated from the so-called "ethereal oils" [7]. The eventual recognition by Wallach that monoterpenes are elaborated by the head-to-tail joining of two isopentane units and sesquiterpenes are formed by the same joining of three such units became a general rule for defining terpenes as subsequent workers developed confirmatory evidence for Wallach's original observations and hypotheses.

Because early workers assumed that isoprene was the basic building block of the terpenes, this rule was defined as the "isoprene rule" [8a]. Subsequent recognition by numerous investigators that higher terpenes are not constructed by

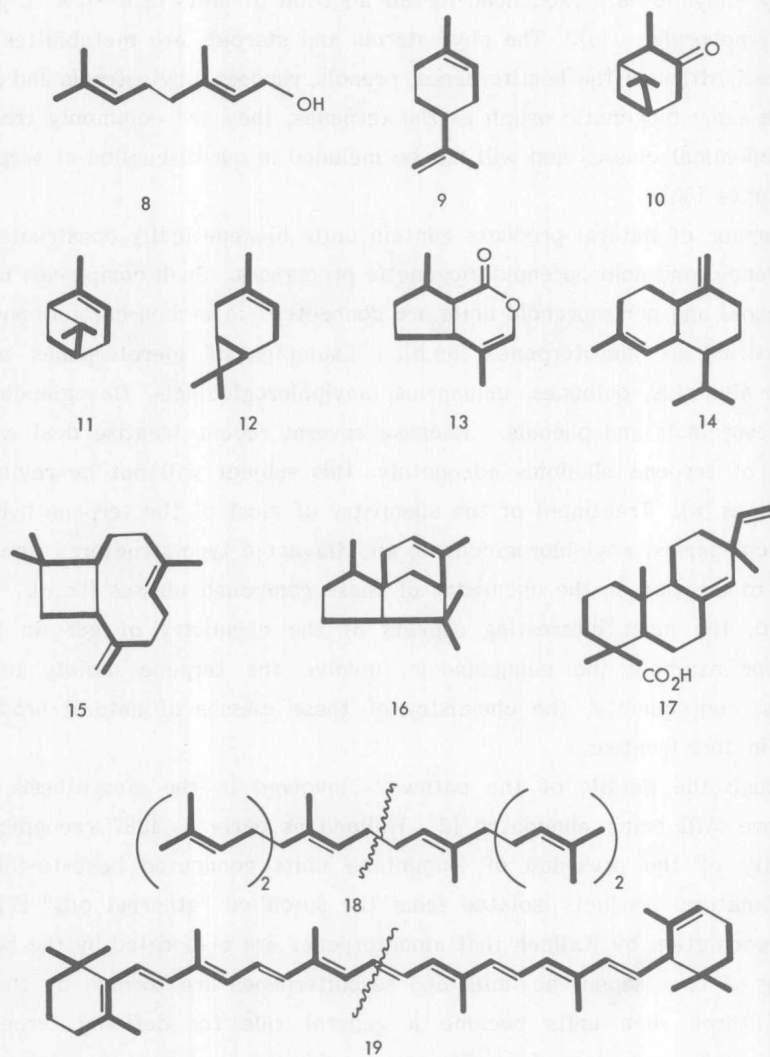


Figure 2

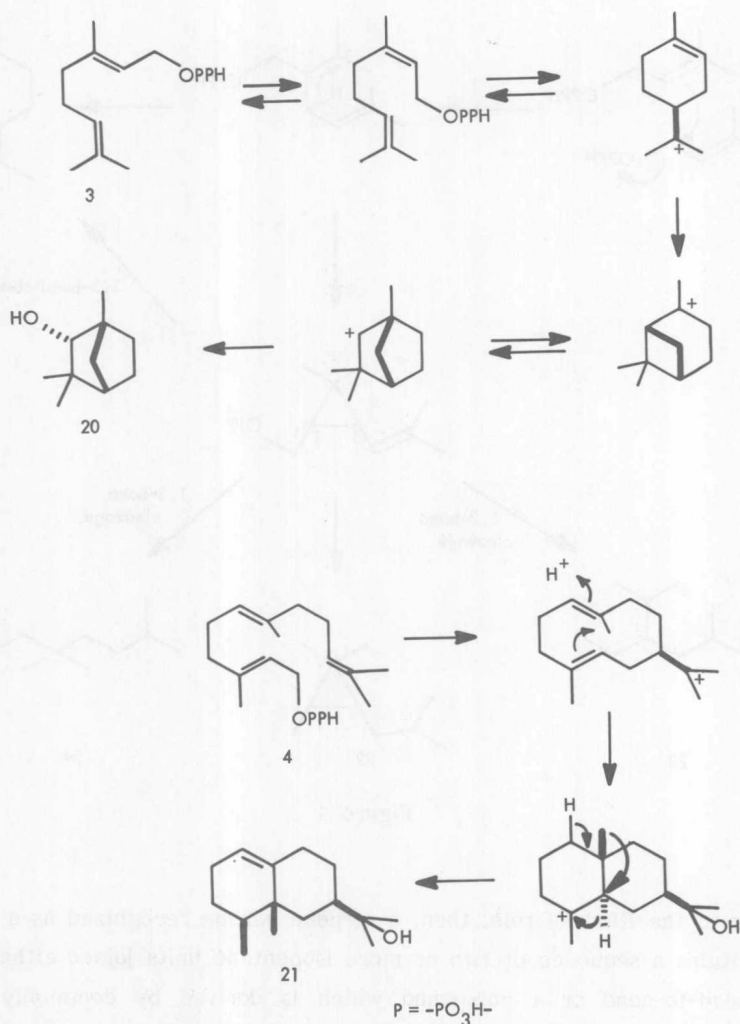


Figure 3

the simple head-to-tail coupling of isoprene units lead Ruzicka to propose that these higher terpenes are formed by head-to-head coupling of farnesyl or geranylgeranyl derivatives [8b]. He also proposed the theory that all terpenes are derived either directly or by cyclization, rearrangement or dimerization mechanisms from geraniol, farnesol, geranylgeraniol or similar isoprenoids [8b]. This hypothesis for the biogenetic construction of terpenes—which was in part prompted by the early development work on the elaboration of biosynthetic pathways to the steroids [9]—formed the basis for the presently accepted biogenetic theories (Fig. 1) and led to the formulation of a "biogenetic isoprene rule" for distinguishing terpenes.

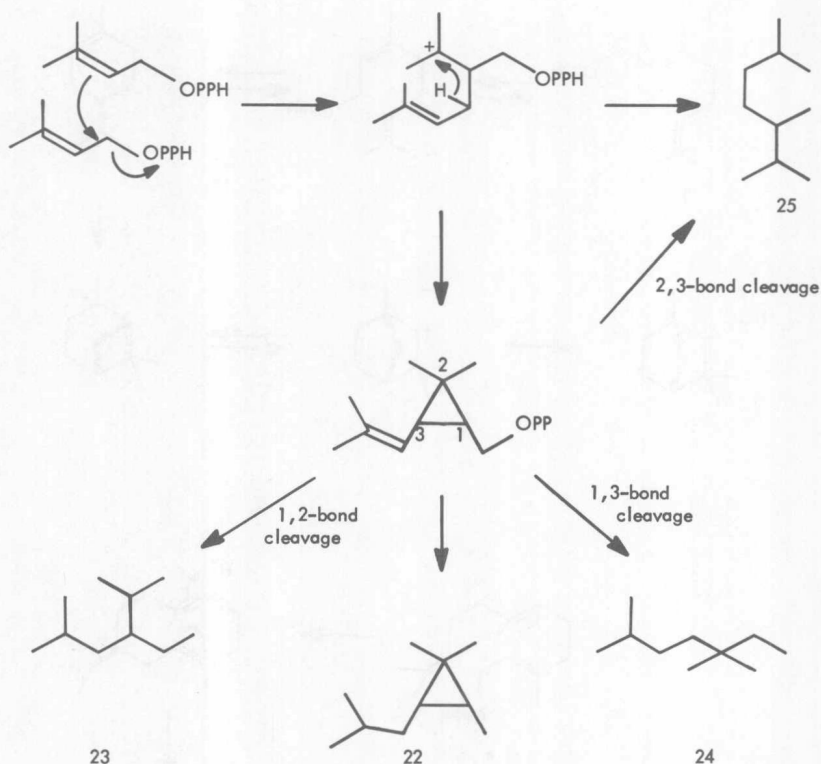


Figure 4

According to the Ruzicka rule, then, a terpene can be recognized as a compound which contains a sequence of two or more isopentane units joined either head-to-tail or head-to-head or a compound which is derived by commonly accepted chemical processes from one of the resultant products of the above condensations. To illustrate, each of the compounds (8)–(17) in Fig. 2 contains head-to-tail condensed IPP units, compounds (18) and (19) incorporate head-to-head coupled units of farnesyl pyrophosphate (4) and geranylgeranyl pyrophosphate (5), respectively, while compounds (20) and (21) must be derived by cyclizations and subsequent molecular rearrangements from geranyl pyrophosphate (3) and farnesyl pyrophosphate (4), respectively. Mechanisms for achieving (20) and (21) from logical precursors which are constructed of repeating isopentane units are outlined in cursory form in Fig. 3.

Several types of monoterpenes are not biogenetically constructed by the head-to-tail and head-to-head coupling of IPP units. Examples of such terpenes are the chrysanthemyl (22), santolinyll (23), artemisyl (24), and lavandulyl (25) monoterpenes

(shown in Fig. 4 in skeletal forms). Although the exact pathways by which these compounds are biosynthesized have not been established, they probably are formed via a common biogenetic pathway which involves an anomalous coupling of two molecules of Δ^2 -IPP as outlined in Fig. 4 [2].

2. OCCURRENCE AND ROLE OF TERPENES IN NATURE

The cells of a wide variety of plants and a limited number of insects manufacture terpenoid compounds. Until recent years, plant terpenes were viewed as irreversibly formed side- or end-products of plant metabolism with no specific purpose in the overall metabolic scheme. Terpenes were considered to be a form of wastage or "indifferent ballast that accumulates with age" [10-13]. This traditional view of the function of plant terpenes has been challenged by investigators whose plant feeding studies with radio-labelled carbon dioxide, mevalonic acid, and terpenes have shown that terpenes may provide a metabolic pool for synthesis of such plant essential components as pigments, sugars, amino acids [13,14,15], and certain respiratory coenzymes [16]. As discussed in section 1, specific mono- and sesquiterpene derivatives are direct intermediates in the biosynthesis of plant steroids (supra), the carotenoids, (which serve as photosensitizers in plant photosynthesis [14,17,18]), the phytol components of the important chlorophyll molecule [14,17,18], and the terpene alkaloids [19].

A number of terpenes play a specific role in plant physiology or in plant ecology. We already have mentioned that the carotenoids of the tetraterpene class play an important role in plant photosynthesis. Members of the giberellin class of diterpenes and the sesquiterpene abscissin (dormin) are plant growth stimulants [20a,b]. The sweet potato root responds to infection with black rot fungus by synthesizing the sesquiterpene ipomeamarone which shows potential antifungal action against this pathogen [20c]. The terpenoid quinones, plastoquinone and ubiquinone, play essential roles in photosynthetic or oxidative phosphorylation and electron transport [20d].

The pyrethrins and related anomalous terpenes, which are isolated from the blossoms of chrysanthemum cinerarianefolium [21], display insecticidal properties and undoubtedly serve to protect this plant from attack by insects. The mono-terpene citronellol, which is a constituent of a variety of plants [22], shows insect repellent properties which may serve to protect these plants from insect predators. β -Pinene, a constituent of the Douglas fir, repels the Douglas fir beetle [23,24]. Finally, the very pronounced and specific organoleptic properties of many of the terpene constituents of flowering plants may serve to attract specific insects for purposes of cross fertilization when the plant is in blossom [25].