A Specialist Periodical Report

Terpenoids and Steroids

Volume 1

A Review of the Literature Published between September 1969 and August 1970

Senior Reporter
K. H. Overton

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General Introduction

We have attempted in this Report to provide a detailed coverage of the literature from September 1969 to August 1970, but for this first Report we have on occasion delved back into the preceding year to provide additional perspective.

In Part I the choice of the most suitable system of classification posed a problem. The two different solutions adopted, one based on structural relationships (monoterpenoids and carotenoids) and the other on biogenetic relationships (sesqui-, di- and tri-terpenoids) in part reflects current practice.

This Report does not include a section on the chemistry of the sesterterpenoids. The limited activity in this area has been on the biosynthetic side, and this is covered in Chapter 6.

Biogenetic theory and practice provide the stimulus and vehicle for an increasing proportion of significant researches in the terpenoid field. We have separated biogenetic practice, that is experiments with living systems, in Chapter 6. Biogenetic thinking, on the other hand, pervades the text. There is occasional overlap with Chapter 6; where the inclusion of *in vivo* experiments seemed particularly appropriate in other chapters, it seemed a mistake rigorously to exclude them.

Steroid researches account for a substantial fraction of the literature of organic chemistry each year. They continue to do so for two reasons: steroids have intrinsic biological and pharmacological interest and hence industrial importance; they also serve as readily accessible and very suitable substances for the study of reactions and reagents and physical methods of analysis. We have sought to separate these two aspects of steroid chemistry in Chapters 1 and 2 of Part II, but inevitably the two overlap to some extent. Steroid biosynthesis has been included in Chapter 6, because it logically belongs there, but also because the depth of enquiry applied to it is unequalled in other areas of terpenoid biosynthesis.

We would greatly welcome any suggestions that readers feel might improve the substance or presentation of future Reports in this series.

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Part I

TERPENOIDS

Introduction*

Monoterpenoids (Chapter 1).—*The study of monoterpenoid biosynthesis remains* experimentally difficult. Zavarin[4] has developed an interesting approach to biogenetic hypothesis based on statistical analysis of the occurrence and distribution of monoterpenoids. 'Non-isoprenoid' monoterpenoids might be formed in nature by sigmatropic rearrangement of suitable ylides and not, as previously supposed, by cyclopropyl cleavage of chrysanthemyl systems.[36,37] These speculations are encouraged by some successful laboratory syntheses.[31,32,38] Buchi and his colleagues[70] have synthesised loganin penta-acetate utilising a single photochemical step for assembly of the aglycone. A high-yield synthesis[156] of (racemic) camphor from (−)-dihydrocarvone enol acetate is notable for its simplicity. The sex attractant of the male boll weevil, whose formulation[55] and synthesis[56] followed in close succession, is of interest as the first monocyclic monoterpenoid containing a cyclobutane ring.

Sesquiterpenoids (Chapter 2).—In the sesquiterpenoid field there has been a veritable flood of synthetic activity, sometimes resulting in several syntheses of the same (usually biologically active) substance. Of the nine syntheses of juvenile hormone (11), that of Johnson's group,[16] employing the olefinic ketal Claisen reaction, is particularly notable. The need to construct small complex skeletons bearing multiple functionality has elicited many ingenious and felicitous solutions. Stork and Ficini's intramolecular cyclisation[1] of olefinic diazo-ketones stands out as a method of general utility, while de Mayo's synthesis[134] of methyl isomarasmate is remarkable for the inclusion of four photochemical steps. Our understanding of the conformational behaviour of germacranes has been enriched by exploitation of the Nuclear Overhauser Effect[6,136,137] and by *X*-ray analysis.[142,143] It appears, moreover, from n.m.r. and c.d. studies[138,140] that certain germacrane derivatives co-exist in solution in two conformations at room temperature. According to a recent report, urospermal (203) has even been isolated[141] as two stable (hydrogen-bonded) conformers. Insight into the conformations of germacranes in turn generates biogenetic speculation.[56,95,203] Thus, two conformations (277) and (279) of the same cyclodecadiene might lead respectively to eremophilone and valencane/vetispirane. Isolation[280] of the

* Reference and formula numbers are those of the relevant chapter.

bicyclogermacrene (384) makes it a plausible progenitor of sesquiterpenoids with a *gem*-dimethylated cyclopropane ring. Few advances have been recorded relevant to sesquiterpenoid biosynthesis. However, the *in vivo* formation of coriamyrtin and tutin has been convincingly clarified[75,76] in two laboratories and some progress has been made[105] in the trichothecane group. On the other hand, there has been a good deal of well-informed and potentially fruitful speculation based on co-occurrence of related sesquiterpenes and *in vitro* interconversion, supported by stereo-electronic interpretation. The work of Anderson,[56,72,204] Yoshikoshi,[71] Hirose,[144,145] and Zavarin[2] deserves mention.

Diterpenoids (Chapter 3).—Cyclisation *in vitro* of manool to 14α-hydroxybeyerane bears no resemblance to the *in vivo* formation of tetracyclic diterpenoids but proceeds instead through an 8-ring intermediate.[14–17] Cleistanthol[52] is the first example of an 'iso-cassane' formally derivable by migration of ethyl rather than methyl from C-13 to C-14 of a pimarane precursor. A group of plant growth inhibitors which includes the podolactones[47] and nagilactones[49] share a novel carbon skeleton which could arise from ring-C cleavage of a tricyclic diterpenoid. Among several *X*-ray structure analyses of C_{20} diterpene alkaloids which have brought rapid progress in this field those of denudatine,[124,126] a possible link between atisine and aconitine, stand out. Chemical studies[137–140] of the structurally fascinating co-carcinogen phorbol have been published in full and the structures of several cytotoxic relatives established by *X*-ray analysis[145,146] and correlation. Casbene,[133] a 14-ring triene related to cembrene, is clearly not far removed from a possible macrocyclic precursor of the phorbol group. There have been major synthetic advances in the gibberellin field, among them completion[162] of the total synthesis of gibberellin A_4.

Triterpenoids (Chapter 4).—Two notable syntheses of squalene[1,2] have been published, both utilising sulphur derivatives of farnesol. The 4α- and 4β-methyl groups of triterpenoids are distinguishable[5] as a result of the stereoselective abnormal Beckmann rearrangement of the 3-ketoximes. It can thus be shown that the 4α-methyl group derives from C-2 of mevalonic acid. Two dienes having the protostane skeleton of fusidic acid and corresponding to the long-postulated intermediate of lanosterol biosynthesis have been isolated together with helvolic acid.[9,10] Cyclonaolitsin[22] is an unusual 24,24-dimethyl derivative of cycloartenol. The cucurbitane and lanostane groups have been chemically interrelated.[31,32] A notable addition to the group of tetranortriterpenoids is utilin whose structure, established by *X*-ray analysis,[63] includes a novel and chemogenetically intriguing C-1—C-29 bond in a bicyclononanolide skeleton. The postulated β-diketone precursor of bicyclononanolides has been prepared by partial synthesis and cyclised[79] under very mild conditions to mexicanolide. β-Amyrin has been converted[119] into oleanolic acid and α-amyrin into ursolic acid, the key step involving functionalisation at C-28 by nitrite photolysis from C-13.

Carotenoids and Polyterpenoids (Chapter 5).—The absolute configuration of α-carotene has been established[53] as R. The list of acetylenic, allenic, and isoprenylated (C_{45} and C_{50}) carotenoids grows. A number of biologically important terpenoids of varying chain length appear to be degradation products of carotenoids. Notable among them is abscisic acid which has been chemically interrelated[108] with violaxanthin and efficiently synthesised[126] by oxidation of α-ionone.

Biosynthesis (Chapter 6).—Detailed studies have been reported with individual enzymes responsible for the early stages of terpenoid biosynthesis.[12–19] The mechanism whereby two molecules of farnesyl pyrophosphate couple to furnish squalene is still uncertain and the structure of the C_{30} pyrophosphate intermediate isolated by Rilling in 1966 remains elusive.[22,23] The genesis of the monoterpenoid portion of the indole alkaloids has been intensively studied.[42–51] Of special interest was the discovery of the bismonoterpenoid foliamenthin, which is a derivative of the indole alkaloid precursor secologanin. The biosynthesis of the gibberellins has received detailed attention on both sides of the Atlantic. *Ent*-kaurene, the parent, is formed[94,95] *via* geranylgeranyl pyrophosphate and *ent*-copalyl pyrophosphate and this seems to follow[102–104] a single pathway to 7β-hydroxy-*ent*-kaur-16-en-19-oic acid, the branch point to kaurenolides and gibberellins. The enzyme oxidosqualene cyclase has been isolated[114] and it has been shown[115,116] that, while it is sensitive to the environment of the epoxide, it is relatively indifferent to the other end of the polyene chain. The rather unexpected discovery has been made[131] that cycloartenol, not lanosterol, is the first-formed triterpenoid steroid intermediate in higher plants. Although the precise sequence of events in the conversion of lanosterol and cycloartenol into cholesterol is not established, it seems that the 4α-methyl group is lost before the 4β-methyl.[119,120,141–145] Also, a Δ^8-double bond is necessary for loss of the 14α-methyl group and both $\Delta^{8(14)}$- and $\Delta^{8,14}$-intermediates appear to be involved.[146,147,152,153] The transfer of the olefinic double bond from Δ^8 to Δ^5 has also received attention, as have the reduction of the Δ^{24} and introduction of the Δ^{22} double bonds and side-chain alkylation. Phytoene appears to be[243] the immediate biosynthetic precursor of carotenoids and is then progressively dehydrogenated. Incorporation of farnesyl pyrophosphate into polyprenols suggests[260] that they are formed by chain extension of farnesyl pyrophosphate with *cis*-C_5 units.