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

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, *Department of Chemistry, University of Glasgow*

Reporters
J. D. Connolly, *University of Glasgow*
J. R. Hanson, *University of Sussex*
D. N. Kirk, *Westfield College, University of London*
P. J. May, *Glaxo Research Ltd.*
G. P. Moss, *Queen Mary College, University of London*
J. S. Roberts, *University of Glasgow*
A. F. Thomas, *Firmenich et Cie.*

The Chemical Society
Burlington House, London, W1V 0BN

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.

J.D.C.	G.P.M.
J.R.H.	K.H.O.
D.N.K.	J.S.R.
P.J.M.	A.F.T.

Set in Times on Monophoto Filmsetter and printed offset by
J. W. Arrowsmith Ltd., Bristol, England

Made in Great Britain

Contents

Part I Terpenoids

Introduction — 3
By K. H. Overton

Chapter 1 Monoterpenoids
By A. F. Thomas

1 Physical Methods and Biogenesis — 7

2 Acyclic Monoterpenoids — 8
2,6-Dimethyl-octanes — 8
'Non-Isoprenoid' Monoterpenoids — 13
Telomerisation of Isoprene — 17

3 Monocyclic Monoterpenoids — 18
Cyclobutanes — 18
Cyclopentanes — 18
p-Menthanes — 23
(i) Hydrocarbons — 23
(ii) Oxygenated *p*-Menthanes — 29
m-Menthanes — 34
o-Menthanes — 35
Tetramethylcyclohexanes — 35
Cycloheptanes — 36

4 Bicyclic Monoterpenoids — 37
Bicyclo[3,2,0]heptanes — 37
Bicyclo[3,1,0]hexanes — 37
Bicyclo[2,2,1]heptanes — 39
Bicyclo[3,1,1]heptanes — 41
Bicyclo[4,1,0]heptanes — 47

5 Furanoid and Pyranoid Monoterpenoids — 48

Chapter 2 Sesquiterpenoids
By J. S. Roberts

1 Introduction — 51

2 Farnesane — 52

3 Monocyclo- and Bicyclo-farnesanes 56

4 Bisabolane, Curcumane, *etc.* 60

5 Carotane 62

6 Cadinane, Amorphane, Muurolane, Bulgarane, and related Tricyclic Sesquiterpenoids 62

7 Santalane and Bergamotane 69

8 Cuparane, Thujopsane, Cedrane, Acorane, Laurane, *etc.* 71

9 Caryophyllane and Humulane 77

10 Germacrane 82

11 Elemane 94

12 Eudesmane (Selinane) 96

13 Eremophilane, Valencane, Vetispirane, Tricyclovetivane, *etc.* 100

14 Guaiane 110

15 Aristolane, Aromadendrane, *etc.* 120

16 Non-farnesyl Sesquiterpenoids 122

Chapter 3 Diterpenoids
By J. R. Hanson

1 Introduction 124

2 Bicyclic Diterpenoids 124
The Labdane Series 124
The Clerodane Series 128

3 Tricyclic Diterpenoids 130
Pimaranes 130
Abietanes 131
Cassanes 133
Chemistry of Ring A 134
Chemistry of Ring B 135
Chemistry of Ring C 136

4 Tetracyclic Diterpenoids 141
The Kaurane–Phyllocladane Series 141
The Grayanotoxins 145
The Gibberellins 147
The Diterpene Alkaloids 148

5 Macrocyclic Diterpenoids and their Cyclisation Products 150
Phorbol and its Relatives 150
The Taxane Diterpenes 152

6 Synthesis of Diterpenoids 153

Chapter 4 Triterpenoids
By J. D. Connolly

1 Squalene 161

2 Fusidane–Lanostane Group 163

3 Dammarane–Euphane Group 171
Tetranortriterpenoids 174
Bicyclononanolides 176
Quassinoids 184

4 Lupane Group 185

5 Oleanane Group 188

6 Ursane Group 194

7 Hopane Group 195

8 Serratane Group 196

Chapter 5 Carotenoids and Polyterpenoids
By G. P. Moss

1 Introduction 198

2 Physical Methods 198

3 New Natural Carotenoids 201
Acyclic Carotenoids 201
Monocyclic Carotenoids 204
Bicyclic Carotenoids 204
Aromatic and Cyclopentanoid Carotenoids 206
Allenic and Acetylenic Carotenoids 207
Glycosides and Isoprenylated Carotenoids 209

4 Carotenoid Chemistry 211
Photochemistry 213

5 Degraded Carotenoids 213

6 Polyterpenoids 219

Chapter 6 Biosynthesis of Terpenoids and Steroids
By G. P. Moss

1 Introduction	221
2 Acyclic Precursors	221
3 Hemiterpenoids	224
Ergot Alkaloids	225
Furanocoumarin and Furanoquinoline Derivatives	226
4 Monoterpenoids	227
Cyclopentanoid Monoterpenoids and Indole Alkaloids	229
5 Sesquiterpenoids	231
6 Diterpenoids	233
Kauranes and Gibberellic Acids	234
7 Sesterterpenoids	237
8 Steroidal Trisnortriterpenoids	237
Cyclisation of Squalene	238
Loss of 4,4-Dimethyl Groups	241
Loss of 14α-Methyl Group	241
Isomerisation from Δ^8- to Δ^5-Double Bond	242
Reduction of Δ^{24}-Double Bond	243
Side-chain Alkylation	243
Δ^{22}-Double Bond	245
9 Cholesterol Metabolism	245
Spirostanols	246
Cardenolides and Bufatenolides	247
Side-chain Cleavage	247
Animal Steroid Metabolism	248
10 Triterpenoids	249
11 Carotenoids	251
12 Polyterpenoids	253
13 Taxonomy	255
Non-Arthropod Invertebrates	255
Arthropoda	256

Part II Steroids

Introduction 261
By K. H. Overton

Chapter 1 Steroid Properties and Reactions
By D. N. Kirk

Introduction 263

1 Structure, Stereochemistry, and Conformational Analysis 263
Spectroscopic Methods 269
Raman Spectroscopy 269
N.m.r. 269
Chiroptical Properties (O.r.d., C.d.) 272
Mass Spectrometry 276

2 Alcohols, their Derivatives, and Halides 276
Nucleophilic Substitution 276
Nucleophilic Opening of Epoxides 283
Solvolytic Reactions 287
Elimination Reactions 289
Esters, Ethers, and Related Derivatives of Alcohols 292
Oxidation 293
Reduction 295

3 Unsaturated Compounds 296
Electrophilic Addition 296
Other Addition Reactions 304
Reduction of Unsaturated Steroids 308
Oxidation and Dehydrogenation 311
Cyclopropanes 315
Miscellaneous 316

4 Carbonyl Compounds 317
Reduction of Ketones 317
Other Reactions at the Carbonyl Carbon Atom 320
Oxidation 324
Enolisation 327
Reactions of Enols and Enolate Anions 330
Reactions of Enol Ethers and Esters 336
Reactions of Enamines 339
Oximes 340
Hydrazones 343
Tosylhydrazones 344
Carboxylic Acids and their Derivatives 346

5 Compounds of Nitrogen and Sulphur 348
Deamination 348
Other Reactions 351

6 Molecular Rearrangements 353
The Contraction and Expansion of Steroid Rings 353
The 'Westphalen' and 'Backbone' Rearrangements 361
Epoxide Rearrangements 365
Aromatisation 376
Miscellaneous Rearrangements 380

7 Functionalisation of Non-activated Positions 386
Free-radical Reactions 386
Microbiological Hydroxylations 391

8 Photochemical Reactions 391
Unsaturated Steroids 392
Carbonyl Compounds 393
Miscellaneous Photochemical Reactions 397

9 Miscellaneous Reactions 401
Analytical Methods 401
Miscellaneous 402

Chapter 2 Steroid Synthesis
By P. J. May

1 Introduction 404

2 Steroid Lactones 405
Bufadienolides 405
Isobufadienolides 413
Cardenolides and Isocardenolides 414
Antheridiol 420
Withanolides 421

3 Insect Moulting Hormones 422

4 Oxa-steroids 427

5 Thia-steroids 429

6 Aza-steroids 430

7 Steroids Having Fused Heterocyclic Rings 433
Rings containing One Heteroatom 433
Oxygen Heterocycles 433
Sulphur Heterocycles 436
Nitrogen Heterocycles 437
Rings containing Two Different Heteroatoms 440

8 Fused Carbocyclic Rings 442

9 Steroids of Unnatural Configuration 446

10 Homo-steroids 449

11 Ring-nor Steroids 450

12 18-Nor Steroids 452

13 19-Nor Steroids 453

14 C-19-substituted Steroids 461

15 *Abeo*-steroids 463

16 Seco-steroids 466

17 Total Synthesis of Steroids 468
Carbocyclic Steroids 468
Aza-steroids 477
Miscellaneous Heterocyclic Steroids 480

18 Steroid Conjugates 481

19 Sapogenins 482

20 Amino-steroids and Steroidal Alkaloids 482

21 Anthra-steroids and 'Linear' Steroids 489

22 Syntheses of Miscellaneous Natural Products 490

23 Syntheses Involving the Steroid Side-chain 492

24 Photochemical Syntheses 499

25 Oxidation and Reduction 502

26 Syntheses Involving Reactions at Double Bonds 507

27 Miscellaneous Syntheses 509

28 Table of New Compounds Isolated from Natural Sources 517
Steroidal Alkaloids 517
Ecdysones 521
Withanolides 523
Cardenolides and Bufadienolides 527
Sapogenins 528
Glycosides 530
Miscellaneous 535

Author Index 539

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.