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Terpenoids and Steroids

VOLUME 3

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A Specialist Periodical Report

Terpenoids and Steroids

Volume 3

A Review of the Literature Published
between September 1971 and August 1972

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General Introduction

The period covered by this Report is September 1971 to August 1972.
The aims and presentation follow those of Volumes 1 and 2.

J.D.C.	G.P.M.
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Contents

Part I Terpenoids

Introduction

Chapter 1 Monoterpenoids

By A. F. Thomas

1 Analytical Methods and General Chemistry	5
2 Biogenesis, Occurrence, and Biological Activity	7
3 Acyclic Monoterpenoids	11
Terpene Synthesis from Isoprene	11
2,6-Dimethyloctanes	12
Artemisyl, Santolinyl, Lavandulyl, and Chrysanthemyl Derivatives	20
4 Monocyclic Monoterpenoids	24
Cyclobutane	24
Cyclopentanes, including Iridoids	26
<i>p</i> -Menthanes	31
General Chemistry and Hydrocarbons	31
Oxygenated <i>p</i> -Menthanes	37
<i>m</i> -Menthanes	51
Tetramethylcyclohexanes	51
1,4-Dimethyl-1-ethylcyclohexanes	53
Cycloheptanes	53
5 Bicyclic Monoterpenoids	56
Bicyclo[2,1,1]hexane	56
Bicyclo[3,1,0]hexanes	57
Bicyclo[2,2,1]heptanes	58
Bicyclo[3,1,1]heptanes	71
Bicyclo[4,1,0]heptanes	80
6 Furanoid and Pyranoid Monoterpenoids	84
7 Cannabinoids and other Phenolic Monoterpenoids	86

Chapter 2 Sesquiterpenoids

By J. S. Roberts

1 Farnesane	92
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2 Mono- and Bi-cyclofarnesanes	101
3 Bisabolane, Bergamotane, Campherane, Santalane, and Related Tricyclic Sesquiterpenoids	104
4 Cadinane, Copaane, Ylangane, and Cubebane	111
5 Cuparane, Thujopsane, Chamigrane, Acorane, Alaskane, Cedrane, Zizaane, and Trichothecane	115
6 Daucane	127
7 Longifolane and Longipinane	130
8 Caryophyllane, Humulane, and Related Tricyclic Sesquiterpenoids	132
9 Germacrane	137
10 Elemene	144
11 Eudesmane	145
12 Eremophilane, Valencane, and Valerane	152
13 Guaiane	154
14 Maaliane and Aromadendrane	160
15 General	161

Chapter 3 Diterpenoids

By J. R. Hanson

1 Introduction	163
2 Bicyclic Diterpenoids	163
The Labdane Series	163
The Clerodane Series	166
3 Tricyclic Diterpenoids	168
The Pimarane Series	168
Abietanes	169
Cassane and Miscellaneous Tricyclic Diterpenoids	171
The Chemistry of Ring A	172
The Chemistry of Ring B	173
The Chemistry of Ring C	173
4 Tetracyclic Diterpenoids	175
The Kaurane Series	175
Trachylobane Series	180
Gibberellins	180

<i>Contents</i>	vii
Grayanotoxins	183
5 Diterpene Alkaloids	184
6 Macrocyclic Diterpenoids and their Cyclization Products	185
Taxanes	186
7 Miscellaneous Diterpenoids	186
8 Diterpenoid Synthesis	187
Chapter 4 Sesterterpenoids <i>By J. D. Connolly</i>	193
Chapter 5 Triterpenoids <i>By J. D. Connolly</i>	
1 Reviews	196
2 Squalene Group	196
3 Fusidane–Lanostane Group	198
4 Dammarane–Euphane Group	205
Tetanortriterpenoids	206
Quassinoids	210
5 Baccharis Oxide	211
6 Lupane Group	212
7 Oleanane Group	216
8 Ursane Group	225
9 Hopane Group	227
10 Serratane Group	228
Chapter 6 Carotenoids and Polyterpenoids <i>By G. P. Moss</i>	
1 Introduction	230
2 Physical Methods	230

3 Carotenoids	234
Acyclic Carotenoids	234
Monocyclic Carotenoids	235
Bicyclic Carotenoids	236
Acetylenic and Allenic Carotenoids	238
Isoprenylated Carotenoids	239
Carotenoid Chemistry	239
4 Degraded Carotenoids	240
5 Polyterpenoids	244

Chapter 7 Biosynthesis of Terpenoids and Steroids

By G. P. Moss

1 Introduction	245
2 Acyclic Precursors	246
3 Hemiterpenoids	251
4 Monoterpenoids	252
Cyclopentanoid Monoterpenoids	254
5 Sesquiterpenoids	255
6 Diterpenoids	258
7 Sesterterpenoids	260
8 Steroidal Triterpenoids	260
Squalene Cyclization	261
Loss of the 4,4-Dimethyl Groups	262
Loss of the 14 α -Methyl Group	263
Formation of the Δ^5 -Double Bond	264
Reduction of the Δ^{24} -Double Bond	264
Formation of the Δ^{22} -Double Bond	265
Side-chain Alkylation	265
9 Cholesterol Metabolism	266
Spirostanols and Related Compounds	267
Side-chain Cleavage	268
Modification of Ring A	269
10 Triterpenoids	270
11 Carotenoids	270
Degraded Carotenoids	272
12 Polyterpenoids	273
13 Taxonomy	273

Part II Steroids

Introduction	275
Chapter 1 Steroid Properties and Reactions <i>By D. N. Kirk</i>	
1 Structure, Stereochemistry, and Conformational Analysis	279
Spectroscopic Methods	284
I.r. spectra	284
U.v. Spectra and Chiroptical Properties (O.R.D. and C.D.)	285
N.M.R. Spectroscopy	295
Mass Spectrometry	298
2 Alcohols and their Derivatives, Halides, and Epoxides	300
Substitution and Elimination	300
Ring-opening of Epoxides	303
Esters, Ethers, and Related Derivatives of Alcohols	309
Miscellaneous Reactions	314
3 Unsaturated Compounds	315
Addition Reactions	315
Reduction of Unsaturated Steroids	327
Oxidation and Dehydrogenation	328
Alkynes and Allenes	332
Miscellaneous	335
4 Carbonyl Compounds	336
Reduction of Ketones	336
Other Reactions at the Carbonyl Carbon Atom	338
Reactions Involving Enols or Enolate Anions	342
Reactions of Enol Esters, Ethers, and Enamines	352
Reactions of Oximes, Hydrazones, and Related Derivatives	356
Reactions of Carboxylic Acids and their Derivatives	361
5 Compounds of Nitrogen and Sulphur	365
Amines and their Derivatives	365
Miscellaneous Nitrogen Compounds	368
Sulphur Compounds	371
6 Molecular Rearrangements	373
Contraction and Expansion of Steroid Rings	373
'Backbone' and Related Rearrangements	378
Epoxide Rearrangements	387
Miscellaneous Rearrangements	391

7 Functionalization of Non-activated Positions	393
8 Photochemical Reactions	397
Unsaturated Steroids	397
Carbonyl Compounds	401
Esters	404
Miscellaneous	405
9 Miscellaneous Properties and Reactions	407
Chapter 2 Steroid Synthesis	
<i>By P. Crabbé</i>	
<i>in collaboration with G. A. García, A. Guzmán, L. A. Maldonado, G. Pérez, C. Rius, and E. Santos</i>	
1 Introduction	409
2 Total Synthesis	409
3 Halogeno-steroids	417
4 Oestrans	419
5 Androstanes	432
6 Pregnanes and Corticoids	445
7 Seco-steroids	463
8 Cholestane and Analogues	467
9 Steroidal Insect and Plant Hormones	487
10 Steroidal Alkaloids	490
11 Sapogenins	502
12 Bufadienolides	504
13 Cardenolides	506
Errata	510
Author Index	511

Part I

TERPENOIDS

Introduction*

The interesting formal parallel that exists between the rearrangements of the chrysanthemyl cation and the conversion of presqualene alcohol into squalene (and now of prephytoene alcohol into phytoene) has been further explored. Solvolyses¹⁰⁹ of the cyclopropyl (65) and cyclobutyl (63) esters both afford head-to-head coupled C₁₀ chains analogous to squalene. A versatile new method provides access to 9-substituted *p*-menthanes. This starts with natural limonene and proceeds *via* the anion (135) which retains chirality and leads to chiral products (see below). Skeletal rearrangements in the bicycloheptane series, an historic field in the study of organic reaction mechanisms, has received a fresh impetus from the extended work of Kirmse and his colleagues,^{265,266} which is of preparative and mechanistic significance.

Excellence and diversity in the synthetic field again characterize the year's work on sesquiterpenoids, with some notable examples of sophisticated methodology on the industrial scale. The production of C₁₇ and C₁₈ juvenile hormones^{11,12} and the conversion of the C₁₇ into the C₁₈ hormone are cases in point. The metallation of limonene referred to above has been turned to good account²⁸ in stereospecific routes to bisabolane sesquiterpenoids. The unique antibiotic fumagillin has been synthesized³⁶ by an imaginative route. Two notable syntheses of zizaene^{81,82} have been reported. Wiesner's approach utilized a synthetic route to bicyclo[3,2,1]octanes developed in the course of an approach to diterpene alkaloids. The labile *trans,trans*-1,5-cyclodecadiene system of hedycaryol has been successfully generated by Marshall fragmentation of the appropriate cyclo-octyl tosylate.¹⁰⁸ Ourisson has described^{152,153} a simple two-stage procedure whereby the α -methylene- γ -butyrolactone function so widespread among natural sesquiterpenoids can be obtained from the more readily available α -methyl- γ -lactones. The method succeeds only with *cis*-fused lactones. The *in vitro* interconversion of acyclic, mono-, bi-, and tri-cyclic sesquiterpenes and their potential relevance to biosynthesis continue to attract widespread experimental attention⁷⁰⁻⁷⁶ and the complex acid-catalysed rearrangements of thujopsene have been subjected to penetrating study.⁶³⁻⁶⁶ An attempt¹¹⁶ to systematize the nomenclature of germacranolides should be noted by workers in the field.

Much effort in the diterpenoid field is concentrated on substances having biological activity. Thus the coleons,^{35,36} inumakilactones,³⁹ and

* Reference and structure numbers are those of the appropriate chapter.

podolactones^{40,41} control the expansion and division of cells. Combined g.l.c. and mass spectrometry has played an important part in the detection and characterization of new gibberellins⁹⁹⁻¹⁰¹ and there have been important advances in gibberellin synthesis.^{134,135,140,141} The antheridium-inducing factor of ferns¹⁰⁶ has a gibberellin-like structure. Cyathin A₃, isolated from the 'bird's nest' fungus, represents a novel mode of cyclization of geranylgeraniol. Notable synthetic successes in the diterpene alkaloid field have come from Wiesner's laboratory in the total synthesis¹⁴⁴ of the delphinine degradation product (158) and the intermediate (159)¹⁴⁵ for a synthesis of songorine.

Cheilanthatriol¹ represents a new type of sesterterpenoid whose carbon skeleton resembles that of triterpenoids.

The structure of Baccharis oxide has been revised;⁶⁶ biosynthetically this is close to the previous structure (Vol. 2, p. 168) and therefore of comparable interest. The total laboratory synthesis of lupeol⁶⁸ is a notable further achievement in the synthesis of unsymmetrical triterpenoids.

Cornforth and his colleagues have investigated²³ the stereochemistry of isomerization of isopentenyl to dimethylallyl pyrophosphate in isoprenoid biosynthesis. They find that the prototropic change involved is stereochemically different from the superficially analogous association of C₅ units. Bisabolene appears to be excluded as an intermediate in the biosynthesis of helicobasidin and trichothecin by recent labelling studies⁵⁹⁻⁶¹ (see also Vol. 1, p. 232, ref. 81) and a 1,4-hydride shift in the initially formed intermediate is indicated. The loss of the C-14 methyl group in cholesterol biosynthesis differs⁹⁷ from loss of the C-4 methyl groups. The 32-carbon atom is released at the aldehyde oxidation level as formic acid.

In the carotenoid and polyterpenoid field a number of important stereochemical studies have appeared. These include assignments of the complete stereochemistry of phytoene¹¹ and lutein⁴⁰ and the absolute configurations of abscisic acid⁵⁸⁻⁶⁰ and the natural irones.¹⁶

1

Monoterpenoids

BY A. F. THOMAS

The volume of work published on monoterpenoids is increasing, not only in the absolute sense, but relative to that on other natural products (including other terpenoids). There are at least three possible causes: many monoterpenoids are plentiful, further exploitation is desired, and recent refinements of analytical techniques have made possible the examination of reaction detail that was previously inaccessible. Monoterpenoids lend themselves especially well to such studies because of their suitability for gas chromatography, and also provide examples of a wide variety of structural types. Chemotaxonomy is also increasingly moving toward the use of monoterpenes because of the simplicity of analysis.

Duplication of previously published work (see Vol. 2, p. 5) is reaching new levels. It is incomprehensible that reputable journals (in some cases) with a good refereeing policy still do not detect earlier work—even when it has appeared in this and other reviews—and this year an attempt has been made to quote the earlier reference (this is rarely done by the later authors) in order to highlight the problem.

1 Analytical Methods and General Chemistry

The first of two books with monoterpenoid sections is of the 'dictionary' type.¹ It would be useful were it not for the incredible number of errors. Space will not permit a full criticism, but they include incorrect formulae (carquejyl acetate, artemisia and isoartemisia ketones, linalool, linalool oxide, lippione), double bonds of incorrect geometry (yomogi alcohol, cosmene), the inclusion of many discredited or doubtful compounds (santolinenones, osmane, hymenetherene, *etc.*), and a very unusual biogenetic scheme. The other book purports to give a brief introduction to the chemistry, but terpenoids related to chrysanthemic acid, iridoids, *ortho*-menthanes, and heterocyclic terpenoids are omitted, and there are only 236 references, eight of which are post-1969 and twenty post-1968.² Omission of recent literature also spoils a review of photochemistry in the field of monoterpenes:³ although this has a large literature collection, it is mostly only up to 1969.

¹ T. K. Devon and A. I. Scott, 'Handbook of Naturally Occurring Compounds, Vol. 2, Terpenes', Academic Press, New York, 1971.

² D. Whittaker, in 'Chemistry of Terpenes and Terpenoids', ed. A. A. Newman, Academic Press, London, 1972, p. 11.

³ M. Pfau, *Flavour Ind.*, 1972, 3, 89. The Specialist Periodical Reports are not quoted among the several reviews listed here.

A method for purifying saturated monoterpene hydrocarbons by multistage extractive crystallization with thiourea has been used for menthane, pinane, carane, and 1,1,4-trimethylcycloheptane purification.⁴ The results are analogous to distillation or liquid-liquid extraction with greatly increased volatility between components in the two phases in the adduct-formation process. A more specific crystallization process concerns the isolation of 98% pure (–)-menthol by crystallizing the mixture with wintergreen oil or limonene at 5°C.⁵ Monoterpenes are also used in a discussion about physical (especially crystallographic) properties of racemates susceptible to spontaneous or induced resolution by crystallization,⁶ and a later paper from the same laboratory gives details of the carvoximes and camphoroximes.⁷ Gas chromatography of monoterpenoids is included in a paper concerned with an improved calculation of Kováts indices in gas chromatography⁸ and the use of various columns is discussed.⁹ Retention index data of various substituted cyclohexanes have been used to establish the stereochemistry of various *p*-menthanediols.¹⁰

A microtechnique for the analysis of monoterpenoids consists of hydrogenolysis in the inlet port of a gas chromatograph and analysis of the saturated hydrocarbons. Certain ring cleavages occur, and *p*-alcohols lose their CH₂OH group. The products obtained are identified by mass and i.r. spectrometry.¹¹ The mass spectrometry of some monoterpene semicarbazones is reported; many mechanisms are described, but without labelling evidence.^{11a}

Terpenoids are frequently used to introduce asymmetry into molecules (a classic example is isopinocampheylborane), and the use of camphor to introduce chirality into lanthanide shift reagents is now established¹² (see also the section on bicyclo[2.2.1]heptanes below). The difference in geminal non-equivalence of methylene hydrogens of diastereomeric (–)-menthoxyacetamides has been used as a monitor for the optical resolution of amines,¹³ this being a development of earlier work using menthoxyacetates for diastereomeric alcohols. The optical purity of chiral amines can also be checked from the n.m.r. spectrum of the amides obtained with (+)-(1*R*,4*R*)-camphor-10-sulphonic acid.¹⁴ Use of a menthol ester to separate pseudoasymmetric ferrocenes has been described.¹⁵

(–)-Menthyl glyoxylate has been used in an attempt to induce asymmetry during a Diels-Alder reaction between the aldehyde group of the glyoxylate and a

⁴ F. P. McCandless, *Ind. and Eng. Chem., Product Res. and Development*, 1971, **10**, 406.

⁵ Y. Matsubara, H. Hashimoto, J. Katsuhara, and H. Watanabe, *Jap. P.*, 26 933/1971 (*Chem. Abs.*, 1971, **75**, 141 018).

⁶ A. Collet, M.-J. Brienne, and J. Jacques, *Bull. Soc. chim. France*, 1972, 127.

⁷ J. Jacques and J. Gabard, *Bull. Soc. chim. France*, 1972, 342.

⁸ R. U. Luisetti and R. A. Yunes, *J. Chromatog. Sci.*, 1971, **9**, 624.

⁹ I. I. Bardyshev and V. I. Kulikov, *Zhur. analit. Khim.*, 1971, **26**, 1857 (*Chem. Abs.*, 1971, **75**, 15 192); T. J. Betts, *Australas. J. Pharm.*, 1971, **52**, S57.

¹⁰ C. Paris and P. Alexandre, *J. Chromatog. Sci.*, 1972, **10**, 402.

¹¹ R. E. Kepner and H. Maarse, *J. Chromatog.*, 1972, **66**, 229.

^{11a} J. Cassan, M. Azarro, and R. I. Reed, *Org. Mass Spectrometry*, 1972, **6**, 1023.

¹² G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, 1971, **93**, 5914; H. L. Goering, J. N. Eikenberry, and G. S. Koerner, *ibid.*, p. 5913.

¹³ T. G. Cochrane and A. C. Huitric, *J. Org. Chem.*, 1971, **36**, 3046.

¹⁴ G.-A. Hoyer, D. Rosenberg, C. Rufér, and A. Seeger, *Tetrahedron Letters*, 1972, 985.

¹⁵ S. I. Goldberg and W. D. Bailey, *Tetrahedron Letters*, 1971, 4087.

1-alkoxybutadiene. In the simple case the optical yield was very low,¹⁶ but it rose to 25% when the reaction was effected in the presence of Lewis acids at low temperatures.¹⁷ Another attempt at inducing asymmetry in a Diels-Alder reaction used (–)-dimenthyl fumarate and isoprene. The optical yield rose from 0% at atmospheric pressure to 4.7% at 5000 atmospheres.¹⁸

The preferred rotational conformations of acetyl and formyl groups can be predicted by temperature-dependent c.d. measurements, and the technique has been applied to some monoterpene aldehydes.¹⁹ The sign of the Cotton effect has been related to the chirality of a series of π -molecular complexes of monoterpene (and other) hydrocarbons with tetracyanoethylene. Inconclusive results found with (+)-sabinene were ascribed to complexation with the cyclopropane ring.²⁰

2 Biogenesis, Occurrence, and Biological Activity

An excellent review, particularly where it concerns his own work, has been published by Banthorpe²¹ which covers the whole field of monoterpene biogenesis. The same author has examined the biosynthesis of (+)-pulegone in *Mentha pulegium*, in which [2-¹⁴C]mevalonic acid gave unequal labelling, almost all the tracer being associated with the isopentenyl pyrophosphate part of the molecule, in agreement with earlier work (Vol. 2, p. 6). 3,3-Dimethyl[1-¹⁴C]acrylic acid, on the other hand, appeared to be incorporated after degradation to acetate units.²² The conversion of monoterpenes into carotenoids in *Tanacetum vulgare* and *Artemisia annua* has been found to occur in whole plants either as undegraded C₁₀ units or as 3,3-dimethylallyl pyrophosphate equivalents.²³ Some studies on *in vitro* tissue cultures of *T. vulgare* were also made.²⁴

In this plant the petals contain β -D-glucosides of isothujol, neoisothujol, and other compounds, and it is observed that [2-¹⁴C]mevalonate incorporation into the glucose portion is ten times more than into the terpenoid portion.²⁵ Results not in agreement with Banthorpe's unequal labelling have been obtained by Suga *et al.*, who fed [2-¹⁴C]mevalonic acid to twigs of *Cinnamomum camphora* Sieb. var. *linalooliferum* and found the linalool to be equally labelled.²⁶ When [2-¹⁴C]mevalonate is fed through cut stems of *Mentha piperita* in the presence of sucrose, the incorporation into the monoterpenes is markedly increased. This was interpreted as support for the compartmentation of sites of monoterpene

¹⁶ J. Jurczak and A. Zamojski, *Tetrahedron*, 1972, **28**, 1505.

¹⁷ O. Achamatowicz, jun. and B. Szechner, *J. Org. Chem.*, 1972, **37**, 964.

¹⁸ B. S. El'yanov, E. I. Klabunovskii, M. G. Gronikberg, G. M. Parfenova, and L. F. Godunova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 1658.

¹⁹ T. Suga, K. Imamura, and T. Shishibori, *Bull. Chem. Soc. Japan*, 1972, **45**, 545.

²⁰ A. I. Scott and A. D. Wrixton, *Tetrahedron*, 1972, **28**, 933.

²¹ D. V. Banthorpe, B. V. Charlwood, and M. J. O. Francis, *Chem. Rev.*, 1972, **72**, 101. The carquejol formula is incorrect in this review (see Vol. 1, p. 35 of these Reports).

²² D. V. Banthorpe, B. V. Charlwood, and M. R. Young, *J.C.S. Perkin I*, 1972, 1532.

²³ D. V. Banthorpe, H. J. Doonan, and A. Wirz-Justice, *J.C.S. Perkin I*, 1972, 1764.

²⁴ D. V. Banthorpe and A. Wirz-Justice, *J.C.S. Perkin I*, 1972, 1769.

²⁵ D. V. Banthorpe and J. Mann, *Phytochemistry*, 1972, **11**, 2589.

²⁶ T. Suga, T. Shishibori, and M. Bukeo, *Phytochemistry*, 1971, **10**, 2725.