

A Specialist Periodical Report

Terpenoids and Steroids

Volume 2

A Review of the Literature Published
between September 1970 and August 1971

Senior Reporter

K. H. Overton

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K. H. Overton, *Department of Chemistry,
University of Glasgow*

Reporters

J. D. Connolly, *University of Glasgow*

P. Crabbé, *National University of Mexico*

J. R. Hanson, *University of Sussex*

D. N. Kirk, *Westfield College, University of London*

G. P. Moss, *Queen Mary College, University of London*

J. S. Roberts, *University of Stirling*

A. F. Thomas, *Firmenich et Cie., Geneva, Switzerland*

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General Introduction

The period covered by this Report is September 1970 to August 1971.

The aims of our survey and our presentation of it remain as set out in the General Introduction to last year's Report.

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

Contents

Part I Terpenoids

Introduction	3
 Chapter 1 Monoterpenoids	
<i>By A. F. Thomas</i>	
1 Analytical Methods and General Chemistry	5
2 Biogenesis and Biological Activity	6
3 Acyclic Monoterpenoids	8
Telomerization of Isoprene	8
2,6-Dimethyloctanes	8
Artemisyl, Santoliny, Lavandulyl, and Chrysanthemyl Derivatives	13
4 Monocyclic Monoterpenoids	16
Cyclopentanes, including Iridoids	16
<i>p</i> -Menthanes	21
General Chemistry and Hydrocarbons	21
Oxygenated <i>p</i> -Menthanes	23
<i>o</i> -Menthanes	34
Tetramethylcyclohexanes	35
Cycloheptanes	35
5 Bicyclic Monoterpenoids	36
Bicyclo[3,1,0]hexanes	36
Bicyclo[2,2,1]heptanes	38
Bicyclo[3,1,1]heptanes	48
Bicyclo[4,1,0]heptanes	56
6 Furanoid Monoterpenoids	58
7 Cannabinoids and other Phenolic Monoterpenoids	60
 Chapter 2 Sesquiterpenoids	
<i>By J. S. Roberts</i>	
1 Farnesane	65

2 Monocyclo- and Bicyclo-Farnesanes	71
3 Bisabolane and Sesquicarane	73
4 Daucane	75
5 Cadinane and Related Tricyclic Sesquiterpenoids	76
6 Campherane and Santalane	79
7 Thujopsane, Acorane, Chamigrane, Bazzanane, and Trichothecane	82
8 Longifolane	86
9 Caryophyllane, Humulane, and Related Compounds	88
10 Germacrane	92
11 Elemene	98
12 Eudesmane	100
13 Eremophilane, Valencane, Vetispirane, Tricyclovetivane, etc.	103
14 Guaiane	113
15 Aristolane	121
16 General	123

Chapter 3 Diterpenoids

By J. R. Hanson

1 Introduction	124
2 Physical Methods	124
3 Bicyclic Diterpenoids	126
The Labdane Series	126
The Clerodane Series	128
4 Tricyclic Diterpenoids	129
Pimaranes	129
Abietanes	130
Rosanes	133
Cassane and Miscellaneous Tricyclic Diterpenoids	134
The Chemistry of Ring A	135
The Chemistry of Ring B	136
The Chemistry of Ring C	137

5 Tetracyclic Diterpenoids	140
The Kaurene Series	140
Trachylobanes	145
Gibberellins	145
Grayanotoxins	147
6 Diterpene Alkaloids	148
7 Macrocyclic Diterpenoids and their Cyclization Products	149
Phorbol and its Relatives	149
Taxane Diterpenes	151
8 Diterpenoid Synthesis	152

Chapter 4 Triterpenoids
By J. D. Connolly

1 Squalene Group	155
2 Fusidane-Lanostane Group	159
3 Dammarane-Euphane Group	163
Quassinoids	167
Baccharis Oxide	168
4 Lupane Group	169
5 Oleanane Group	170
6 Hopane Group	176
7 Onocerane Group	179

Chapter 5 Carotenoids and Polyterpenoids
By G. P. Moss

1 Introduction	180
2 Physical Methods	180
3 Carotenoids	183
Acyclic Carotenoids	183
Cyclic Carotenoids	184
Allenic and Acetylenic Carotenoids	188
Isoprenylated Carotenoids	190
Carotenoid Reactions	191
4 Degraded Carotenoids	192
5 Polyterpenoids	195

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

1 Introduction	197
2 Acyclic Precursors	198
3 Hemiterpenoids	201
4 Monoterpenoids	202
Cyclopentanoid Monoterpenoids	203
5 Sesquiterpenoids	204
6 Diterpenoids	208
7 Steroidal Triterpenoids	210
Cyclization of Squalene	210
Steroidal Trianortriterpenoids	211
Loss of the 4,4-Dimethyl Groups	213
Loss of the 14 α -Methyl Group and Isomerization of the Double Bond	213
Side-chain Alkylation	214
Δ^{22} -Double Bond	215
8 Cholesterol Metabolism	216
Spirostanols, Cardenolides, and Related Compounds	217
Side-chain Cleavage	218
Metabolism of the Steroid Nucleus	219
9 Triterpenoids	219
10 Carotenoids	221
11 Taxonomy	223
Arthropod Sterols	224

Part II Steroids

Introduction	227
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Chapter 1 Steroid Properties and Reactions*By D. N. Kirk*

1 Structure, Stereochemistry, and Conformational Analysis	229
Spectroscopic Methods	231
Chiroptical Properties (O.R.D. and C.D.)	232
N.M.R. Spectroscopy	237
Mass Spectrometry	240

2 Alcohols, their Derivatives, Halides, and Epoxides	242
Nucleophilic Substitution	242
Solvolytic and Elimination Reactions	243
Ring-opening of Epoxides	245
Esters, Ethers, and Related Derivatives of Alcohols	246
Oxidation	247
Reduction	249
Miscellaneous	251
3 Unsaturated Compounds	253
Electrophilic Addition	253
Other Addition Reactions	258
Reduction of Unsaturated Steroids	264
Oxidation and Dehydrogenation	265
Miscellaneous Reactions	268
4 Carbonyl Compounds	269
Reduction of Ketones	269
Other Reactions at the Carbonyl Carbon Atom	272
Oxidation and Dehydrogenation	273
Enolization and Related Reactions	274
Reactions of Enolate Anions	276
Reactions of Enol Derivatives and Enamines	278
Oximes	280
Other Nitrogen-containing Derivatives of Ketones	281
Sapogenins: Reactions of the Spiro-acetal System	283
Reactions of Aldehydes, Carboxylic Acids, and their Derivatives	286
Miscellaneous	289
5 Compounds of Nitrogen and Sulphur	290
6 Molecular Rearrangements	298
Contraction and Expansion of Steroid Rings	298
The 'Westphalen' and 'Backbone' Rearrangements	301
Epoxide Rearrangements	306
Aromatization	309
Miscellaneous Rearrangements	313
7 Functionalization of Non-activated Positions	316
8 Photochemical Reactions	319
Unsaturated Steroids	319
Carbonyl Compounds	321
Miscellaneous Photochemical Reactions	323
9 Miscellaneous Reactions	326
Analytical Methods	326

Chapter 2 Steroid Synthesis*By P. Crabbé**In collaboration with G. A. Garcia, J. Haro,
L. A. Maldonado, C. Rius, and E. Santos*

1 Introduction	329
2 Total Synthesis	329
3 Photochemical Reactions	338
4 Halogeno-steroids	343
5 Oestrane	348
6 Androstane	363
7 Pregnane and Corticoids	372
8 Seco-steroids	388
9 Cholestane and Vitamin D₃ and its Analogues	398
10 Steroidal Insect and Plant Hormones	406
11 Steroidal Alkaloids	412
12 Sapogenins	424
13 Bufadienolides	427
14 Cardenolides	430
Errata	435
Author Index	436

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Part I

TERPENOIDS

Introduction*

Unexpected results have come to light bearing on monoterpenoid biosynthesis (Chapter 1). Banthorpe's group have shown^{11,13} that in the formation of the thujane and camphor skeletons, activity from labelled mevalonic acid can appear predominantly in the C₅ unit supposedly derived from isopentenyl pyrophosphate and only to a minor extent in the dimethylallyl pyrophosphate-derived portion. Banthorpe has also presented⁵² evidence for a chrysanthemyl intermediate, analogous to presqualene alcohol, in the biosynthesis of artemesia ketone.

Laboratory synthesis again dominates the year's activity in the sesquiterpenoid field (Chapter 2) and continues to elicit much ingenuity. Notable are the routes developed⁵ by Corey's group to the C₁₇ and C₁₈ *Cecropia* juvenile hormones, the synthesis⁵⁶ of trichodermin, the first member of the trichothecane group to be synthesized, syntheses⁴⁰ of copacamphor, copacamphene, and cyclocopacamphene, and extension⁴² of Money's camphor synthesis to campherenone and campherenol with potential for further elaboration to *e.g.* longifoline and sativine. Routes to nootkatone and α -vetivone,^{119,120} zizanoic acid,¹²⁶ and patchoulone¹³⁸ also merit mention among a long list of synthetic achievements. The structure²² of bilobalide, a highly oxygenated sesquiterpenoid containing the unusual *t*-butyl group, is of special interest. It could be derived from the structurally related C₂₀ ginkgolides, whose biosynthesis has been clarified.²³

X-Ray analysis, increasingly by the direct method, is coming into routine use for structure determination. A notable concentration of effort is evident in the phorbol,^{132-134,136} grayanotoxin¹¹⁷ and taxane¹⁴³ series of diterpenoids (Chapter 3), where novel skeletons and complex functionality make pre-X-ray methods quite unsuitable. But the relatively ready access to X-ray facilities is underlined by analyses (*e.g.* grayanotoxin-1,¹¹⁷ and taxinine¹⁴³) undertaken to establish doubtful points of stereochemistry.

The structure of presqualene alcohol^{1,2} has been established beyond reasonable doubt by three independent rational syntheses (Chapter 4).^{3,4,5} As the last isolable intermediate between acetate and squalene to be formulated, its structure has been a subject of controversy since its isolation in 1966. Its formulation therefore represents a major advance which makes it possible to consider its mode of formation from farnesol and its transformation into squalene. Enzymic

* Reference numbers are those of the relevant chapter.

and non-enzymic cyclizations of oxidosqualene and related substances continue with vigour. (\pm)-Malabaricanediol is the first natural product to be formed⁸ *in vitro* by cyclization of a squalene derivative. On the basis of numerous *in vivo* and *in vitro* experiments, van Tamelen has delineated¹² the minimum substrate requirements of the enzyme 2,3-oxidosqualene sterol cyclase. New skeletal types of triterpenoids now appear only rarely. Baccharis oxide⁵⁶ is such a type, but its structure is readily derivable from an intermediate cation, the result of squalene cyclization, which is assumed to lead to the lupane, oleanane, and ursane families of triterpenoids. The total synthesis of unsymmetrical triterpenoids has represented a major challenge for many years: this year has seen the completion of total syntheses of germanicol¹² and alnusenone.⁹³

The unusual structure of the carotenoid pigment peridinin required for its solution¹⁵ the collaboration of four laboratories and a combination of all available physical techniques (Chapter 5).

The problem of whether *cis*- or *trans*-olefinic double bonds are involved in any particular polyisoprenoid biosynthesis has been brought into prominence this year (Chapter 6). Thus the sesquiterpenoid dimer gossypol is biosynthesized³¹ from *cis*,*cis*-farnesyl pyrophosphate. However, it is not clear whether the central *cis*-unit is incorporated as such (as in the case of rubber) or whether geranyl pyrophosphate is isomerized to neryl pyrophosphate before the third C₅ unit is added. Nerol itself is formed, like geraniol, initially from all-*trans* units and must therefore include an isomerization step in its genesis. These results raise the interesting possibility that any of the appropriate geometrically isomeric open-chain polyenes may be involved in a particular polyisoprenoid biosynthesis. The long-postulated 1,2-hydrogen shift from C-13 to C-17 in the biosynthesis of lanosterol and β -amyrin has been demonstrated directly⁷⁷ by incorporation of the appropriately tritiated oxidosqualene. Euphol is excluded¹⁴² as a biosynthetic precursor of the quassinoid bitter principle glaucaroubolone by incorporation experiments with the appropriately tritiated mevalonic acid, and lanosterol has been similarly excluded⁷⁹ from curcubitacin biosynthesis. An interesting result to emerge from biosynthetic studies⁵⁹ with mycophenolic acid is that the side chain represents a degraded farnesyl rather than geranyl unit. Nakanishi and his colleagues have proposed a most ingenious biogenetic derivation⁶⁷ for ginkgolide B from a pimarane; the unusual t-butyl group is formed from an isopropylidene group (ex C-4) and methionine.

Although this report covers the period from September 1970 to August 1971, certain earlier publications that came too late for inclusion in the previous Specialist Report in this series will be mentioned. It is depressing to find, among the papers reviewed, several reporting works that had been previously published.

1 Analytical Methods and General Chemistry

The problems associated with lability of double bonds during the mass spectrometric examination of monoterpenes have been discussed.¹ The mass spectra of ketones are not as easy to interpret as those of thioketones, the latter having a higher proportion of heteroatom-containing fragments. They are readily available by reaction of the ketones either with phosphorus pentasulphide, or with hydrogen sulphide and dry hydrogen chloride, and are recommended for the study of bicyclic ketones in the norbornane series.²

The mass spectra of many monoterpenoids have been published.³ Analysis by gas chromatography of the mixture which constitutes the sex pheromone of the boll weevil (*Anthonomus grandis* Boheman) has been described.⁴ It consists of a cyclobutane monoterpenoid (Vol. 1, p. 18), and three 3,3-dimethyl- $\Delta^{1,2}$ -cyclohexane-ethanols and -acetaldehydes.

Scott and Wrixon have developed a quadrant rule for the c.d. of platinum(II)-olefin complexes that depends on $d-d$ orbital transitions. Application of the rule to monoterpenes was considered, and generally conformed to expectations based on known absolute configurations, but in some cases (notably β -pinene) the results were not satisfactory.⁵ The complex measured may be that of α -pinene, for which a Cotton curve of the opposite sign is predicted. Further work on the use

¹ H. Rapoport and U. T. Bhalerao, *J. Amer. Chem. Soc.*, 1971, **93**, 105.

² M. M. Campbell, G. M. Anthony, and C. J. W. Brooks, *Org. Mass Spectrometry*, 1971, **5**, 297.

³ E. Von Sydow, K. Anjou, and G. Karlsson, *Arch. Mass Spectral Data*, 1970, **1**, 392, and subsequent papers.

⁴ D. L. Bull, R. A. Stokes, D. D. Hardee, and R. C. Gueldner, *J. Agric. Food Chem.*, 1971, **19**, 202.

⁵ A. I. Scott and A. D. Wrixon, *Tetrahedron*, 1971, **27**, 2339.

of ^{19}F n.m.r. spectra of terpene alcohol derivatives has appeared.⁶ The interaction of epoxide with the hydroxy-group in the epoxypulegols has been examined by following the i.r. frequency of the OH band.⁷

In the course of an examination of the autoxidation of terpene hydrocarbons, Bardyshev and Shavyrin have found, predictably, that those containing conjugated double bonds (e.g. allo-ocimene, myrcene) are oxidized most rapidly, those with isolated double bonds or cyclopropane rings more slowly (e.g. limonene, carene), and those with a single double bond slowest (e.g. pinene). The effect of light, heat, and inhibitors was studied.⁸

The rearrangement of monoterpenoid epoxides on alumina⁹ and silica gel¹⁰ surfaces has been studied. On the latter support, the rearrangements are typical of carbonium ions.

2 Biogenesis and Biological Activity

The main advances in monoterpenoid biogenesis have been achieved by Banthorpe's group, who have extended their work (published earlier in note form) on the thujane derivatives obtained from *Thuja*, *Tanacetum*, and *Juniperus* species. More than 90% of the label from $[2-^{14}\text{C}]$ mevalonic acid is incorporated in that part of the skeleton derived from isopentenyl pyrophosphate, the part supposedly derived from 3,3-dimethylallyl pyrophosphate being essentially unlabelled.¹¹ These results are not consistent with the accepted view that both isopentenyl and 3,3-dimethylallyl pyrophosphates are directly derived from mevalonic acid. However, in a second experiment concerned with the incorporation of $[2-^{14}\text{C}]$ mevalonic acid into the petals of rose flower heads, the results accorded with the accepted pattern, geraniol being labelled as in (1), with a similar distribution being found in nerol.¹² The anomaly in the thujane experiments could be explained by the existence of a metabolic pool of dimethylallyl pyrophosphate, by compartmentation effects, or by a non-mevaloid source for the compound. In this connection it is possibly significant that the leaf and stem tissues employed in the thujane work contain discrete oil glands not seen in petal tissue. In the biosynthesis of (+) and (–) camphor in *Artemisia*, *Salvia*, and *Chrysanthemum* species, 73–83% of the label is incorporated from $[2-^{14}\text{C}]$ mevalonic acid at C(6) as shown in (2); again, that part of the skeleton supposedly derived from 3,3-dimethylallyl pyrophosphate was not equivalently labelled.¹³ The biogenesis

⁶ W. Ebbinghausen, E. Breitmaier, G. Jung, and W. Voelter, *Z. Naturforsch.*, 1970, **25b**, 1239; H.-J. Schneider, G. Jung, E. Breitmaier, and W. Voelter, *Tetrahedron*, 1970, **26**, 5369.

⁷ T. Suga, S. Watanabe, T. Shishibori, and T. Matsuura, *Bull. Chem. Soc. Japan*, 1971, **44**, 204.

⁸ I. I. Bardyshev and V. S. Shavyrin, *Sbornik. Trudy. Tsentr. Nauch. Issled. Proekt. Inst. Lesokhim. Prom.*, 1969, **15**, 23 (*Chem. Abs.*, 1971, **75**, 20 647, 20 639).

⁹ V. S. Joshi, N. P. Damodaran, and Sukh Dev, *Tetrahedron*, 1971, **27**, 459.

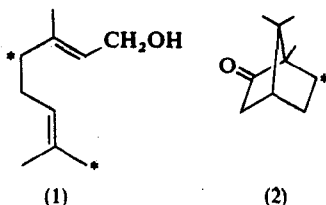
¹⁰ V. S. Joshi, N. P. Damodaran, and Sukh Dev, *Tetrahedron*, 1971, **27**, 475.

¹¹ D. V. Banthorpe, J. Mann, and K. W. Turnbull, *J. Chem. Soc. (C)*, 1970, 2689.

¹² M. J. O. Francis, D. V. Banthorpe, and G. N. J. Le Patourel, *Nature*, 1970, **228**, 1005.

¹³ D. V. Banthorpe and D. Baxendale, *J. Chem. Soc. (C)*, 1970, 2694.

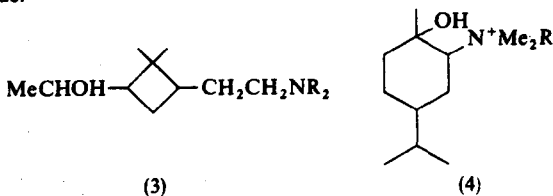
of the artemisia monoterpenoids is mentioned later.



Zavarin has continued his chemotaxonomic approach to biogenetic problems with a study of the leaf monoterpenes of some *Cupressus* species.¹⁴

Tidd has clarified the role of pyrophosphates in terpene biogenesis by measuring the hydrolysis rate of isopentenyl pyrophosphate and related pyrophosphates over the physiological pH range.¹⁵ Potty and Bruemmer, continuing their search for enzymes causing transformations of terpenes in citrus fruits, have discovered a system that reduces (+)-limonene [but not (-)-limonene] in the orange.¹⁶

Because of their ready availability, there is a constant search for possible uses for the more common naturally occurring terpenes and their simple derivatives. This year has seen the claim of insecticidal^{17,18} and juvenile hormone¹⁸ activity for esters of geraniol and its epoxide (see below). Pharmacological (hypoglycaemic) activity was found in the piperidinesulphonamide of D-camphor *endo*-3-carbonic acid,¹⁹ but less successful were the esters of guaiacol, thymol, and carvacrol, which were almost non-toxic.²⁰ Some of the 1-(1'-hydroxyethyl)-2,2-dimethyl-3-(2'-dialkylaminoethyl)cyclobutanes (3), obtained from the reduction of pinonic acid amides, are reported to show antiparkinson activity.²¹ Quaternized 2-dimethylaminomenth-8-en-1-ols (4) are claimed to be growth regulants, nematocides, and fungicides,²² and β -pinene resins are said to potentiate a herbicide.²³



¹⁴ E. Zavarin, L. Lawrence, and M. C. Thomas, *Phytochemistry* 1971, 10, 379.

¹⁵ B. K. Tidd, *J. Chem. Soc. (B)*, 1971, 1168.

¹⁶ V. H. Potty and J. H. Bruemmer, *Phytochemistry*, 1970, 9, 2319.

¹⁷ H. Lee, J. J. Menn, and F. M. Pallos, Ger. Offen. 2 023 791 (*Chem. Abs.*, 1971, 74, 31 868); Ger. Offen. 1 932 062 (*Chem. Abs.*, 1971, 74, 22 682).

¹⁸ J. Ratusky and F. Šorm, Ger. Offen. 2 022 363 (Nov. 19, 1970).

¹⁹ H. Bretschneider, K. Hohenlohe-Oehringen, A. Grüssner, and K. zur Nedden, Ger. Offen. 2 004 327 (*Chem. Abs.*, 1971, 74, 13 301).

²⁰ F. De Marchi, M. V. Torrielli, and G. Tamagone, *Chim. Ther.*, 1968, 3, 433.

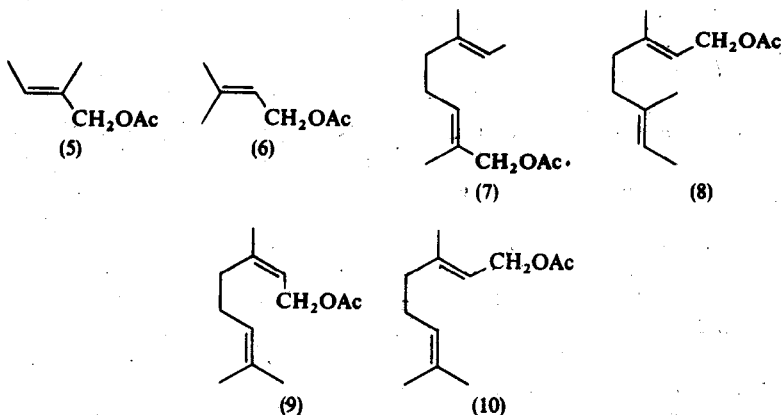
²¹ P. Schenone, G. Minardi, and M. Longobardi, *Farmaco, Ed. Sci.*, 1970, 25, 533.

²² W. F. Newhall, U.S. P. 3 564 046 (*Chem. Abs.*, 1971, 74, 100 237).

²³ W. Hurtt and A. R. Templeton, *Chem. and Eng. News*, 1971, 49, No. 2, 25.

3 Acyclic Monoterpenoids

Telomerization of Isoprene.—Reviews have appeared on isoprene²⁴ and chloroprene,²⁵ and on the complex reactions of isoprene to form terpenoids²⁶ (in Japanese). Isoprene reacts with magnesium, especially in the presence of Lewis acids, and the resulting complex gives adducts with aldehydes. As usual in this type of reaction, a very complex mixture is obtained.²⁷ The palladium-chloride-catalysed reaction of isoprene with acetic acid gives different products in different solvents. Monomers predominate in benzene [2-methylbut-2-enyl acetate (5) and 3-methylbut-2-enyl acetate (6)] while dimers [(7), (8), neryl (9), and geranyl (10) acetates] tend to be formed in tetrahydrofuran.²⁸ Further details of the synthesis of C₁₀ alcohols from isoprene and naphthyl-lithium are available,²⁹ as well as of the *in situ* oxidation,³⁰ but there is little of novelty (see Vol. 1, p. 17).



2,6-Dimethyloctanes.—The full account of the synthetic work on achillene (see Vol. 1, p. 9) includes a technique for improvement of the yield of natural *cis*-achillene (12) by irradiation of the *trans*-compound (11), in the presence of benzophenone, the equilibrium mixture containing 45% *cis*-achillene.³¹ Thermal isomerization of *cis*- β -ocimene (13) [= (16)] yields 6-*cis*-allo-ocimene (14) without any *trans*-isomer (15); this is presumably because the preferred conformer (16) has the bulky isobutenyl group in a pseudo-equatorial position (the 6-*trans*-

²⁴ W. J. Bailey, *High Polymers*, 1971, 24, part 2, 997.

²⁵ P. S. Baughwitz, J. B. Finlay, and C. A. Stewart, jun., *High Polymers*, 1971, 24, part 2, 1149.

²⁶ K. Suga and S. Watanabe, *Yukagaku*, 1970, 19, 1061.

²⁷ M. Yang, K. Yamamoto, N. Otake, M. Ando, and K. Takase, *Tetrahedron Letters*, 1970, 3843.

²⁸ K. Suga, S. Watanabe, and K. Hijikata, *Austral. J. Chem.*, 1971, 24, 197.

²⁹ S. Watanabe and K. Suga, *Austral. J. Chem.*, 1971, 24, 1301.

³⁰ K. Suga, S. Watanabe, T. Watanabe, and M. Yonemitsu, *Yukagaku*, 1971, 20, 82 (*Chem. Abs.*, 1971, 75, 20 652).

³¹ K. H. Schulte-Elte and M. Gadola, *Helv. Chim. Acta*, 1971, 54, 1095.