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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Burlington House, London, W1V 0BN

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.

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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 C_5 unit supposedly derived from isopentenyl pyrophosphate and only to a minor extent in the dimethylallyl pyrophosphate-derived portion. Banthorpe has also presented[52] 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 developed[5] by Corey's group to the C_{17} and C_{18} Cecropia juvenile hormones, the synthesis[56] of trichodermin, the first member of the trichothecane group to be synthesized, syntheses[40] of copacamphor, copacamphene, and cyclocopacamphene, and extension[42] 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 patchoulenone[138] also merit mention among a long list of synthetic achievements. The structure[22] of bilobalide, a highly oxygenated sesquiterpenoid containing the unusual t-butyl group, is of special interest. It could be derived from the structurally related C_{20} gingkolides, 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] grayanotoxin[117] and taxane[143] 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 taxinine[143]) 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. (±)-Malabaricanediol is the first natural product to be formed[8] *in vitro* by cyclization of a squalene derivative. On the basis of numerous *in vivo* and *in vitro* experiments, van Tamelen has delineated[12] the minimum substrate requirements of the enzyme 2,3-oxidosqualene sterol cyclase. New skeletal types of triterpenoids now appear only rarely. Baccharis oxide[56] 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 germanicol[92] and alnusenone.[93]

The unusual structure of the carotenoid pigment peridinin required for its solution[15] 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 biosynthesized[31] 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 C_5 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 directly[77] by incorporation of the appropriately tritiated oxidosqualene. Euphol is excluded[142] as a biosynthetic precursor of the quassinoid bitter principle glaucaroubolone by incorporation experiments with the appropriately tritiated mevalonic acid, and lanosterol has been similarly excluded[79] from curcurbitacin biosynthesis. An interesting result to emerge from biosynthetic studies[59] 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 derivation[67] for gingkolide B from a pimarane; the unusual t-butyl group is formed from an isopropylidine group (ex C-4) and methionine.

1
Monoterpenoids

BY A. F. THOMAS

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-$\Delta^{1,\alpha}$-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 alumina[9] and silica gel[10] 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}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}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}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., Tsent, 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.

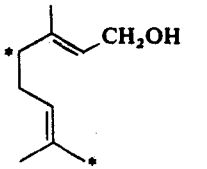
[10] V. S. Joshi, N. P. Damodaran, and Sukh Dev, *Tetrahedron*, 1971, **27**, 475.

[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.



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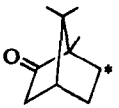
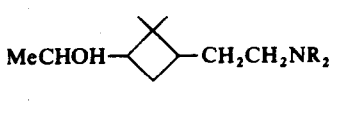


(2)

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 hormone[18] 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, nematicides, and fungicides,[22] and β-pinene resins are said to potentiate a herbicide.[23]



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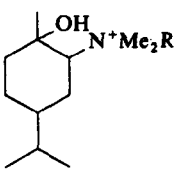
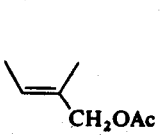


(4)

[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 isoprene[24] and chloroprene,[25] and on the complex reactions of isoprene to form terpenoids[26] (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 C_{10} 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).



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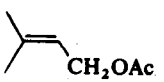

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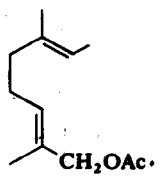

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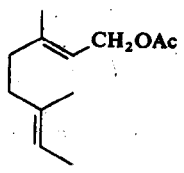

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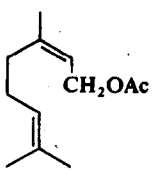

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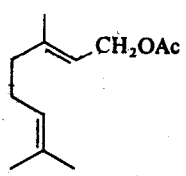

(10)

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. Bauchwitz, 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. Watanals, 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.