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Terpenoids and Steroids

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Introduction

The terpenoids and steroids have continued to provide a fascinating wealth of chemistry. Over the past few years the availability of spectroscopic instrumentation has led to many structures being proposed utilizing plausible analogies based partly on potential biogenetic relationships with compounds of known structure but without a firm inter-relationship. However, each year new skeletal types of terpenoid are discovered. There are many examples now of terpenoids with differing carbon skeleta co-occurring or at least occurring in related plants. Thus, although biogenetic analogy forms a powerful tool for focusing attention on likely structures, the need for either a definitive *X*-ray analysis or an unambiguous chemical correlation is an ever-present one. A substantial amount of ^{13}C n.m.r. data has now been obtained for the various major groups of terpenoid and this method has now taken its place alongside ^{1}H n.m.r. as a structural tool. It has found considerable application in biosynthesis in determining the origin of carbon skeleta. Stereochemical studies in biosynthesis have also been a major area of interest during the year. The steroids have remained valuable substrates for studying the scope of physical methods and of new reactions. The number of highly oxygenated plant steroids, such as the withanolides and the *Nicandra* products, has continued to increase. In this Report, we have included the section on the partial synthesis of steroids within the chapter on steroid properties and reactions in an effort to reduce the overlap between the steroid reactions and steroid synthesis chapters.

July 1977

J. R. HANSON

Contents

Part I Terpenoids

Chapter 1 Monoterpenoids

Part II Steroids

Section A: Steroid Properties and Reactions

Section B: Partial Synthesis of Steroids

Part I

TERPENOIDS

1

Monoterpenoids

BY R. B. YEATS

This Report covers the primary literature from August 1975 up to August 1976; literature available only as a *Chemical Abstract* after September 1st 1976 is not included.

Two useful supplementary volumes[1a,2a] update the corresponding chapters in the second edition of Rodd[3] on acyclic and monocyclic monoterpenoids,[1b] on bicyclic monoterpenoids,[2b] and on the biogenesis of mevalonate, hemiterpenoids, and monoterpenoids.[2c] A useful textbook on natural plant constituents includes some biochemistry and chemistry of monoterpenoids.[4]

1 Physical Measurements: Spectra *etc.*; Chirality

^{13}C N.m.r. assignments for campholenic aldehyde, car-3-ene, β-cyclocitral, three lavandulyl derivatives, and nerol oxide, as well as for 24 acyclic, 39 *p*-methane, six bicyclo[3,1,0]hexane, twelve bicyclo[2,2,1]heptane, and eight bicyclo[3,1,1]heptane monoterpenoids are recorded.[5]

The use of trichloroacetyl isocyanate to generate carbamates *in situ* can be used to identify methyl groups adjacent to a tertiary alcohol (downfield shift of 0.29—0.44 p.p.m.) and to assign the geometry of double bonds in allylic alcohols.[6] Similarities in the ^{1}H n.m.r. and infrared spectra of monoterpenoids may be valuable in identifying new sesquiterpenoid analogues.[7]

Mass spectral papers include another compilation of monoterpenoid alcohol spectra,[8] a comparison of fragmentation patterns for camphor and menthone with their oxime, semicarbazone, and nitrophenylhydrazone derivatives,[9] and a comparison of collisional activation mass spectra of ten related acyclic, monocyclic, and bicyclic monoterpenoid hydrocarbons together with derived $C_7H_9^+$ ions.[10]

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[1] (*a*) 'Rodd's Chemistry of Carbon Compounds', Second Edition Supplement, Vol. II, Parts A and B, ed. M. F. Ansell, Elsevier, Amsterdam, 1974; (*b*) S. H. Harper, *ibid.*, Chapter 6, p. 175.

[2] (*a*) 'Rodd's Chemistry of Carbon Compounds', Second Edition Supplement, Vol. II, Parts C, D, and E, ed. M. F. Ansell, Elsevier, Amsterdam, 1974; (*b*) R. T. Brown, *ibid.*, Chapter 12, p. 53; (*c*) T. W. Goodwin, *ibid.*, Chapter 19, pp. 237—247.

[3] 'Rodd's Chemistry of Carbon Compounds', Second Edition, Vol. II, Part B and Vol. II, Part C, ed. S. Coffey, Elsevier, Amsterdam, 1968 and 1969.

[4] T. Robinson, 'The Organic Constituents of Higher Plants', 3rd edn., Cordus Press, North Amherst, Massachusetts, 1975.

[5] F. Bohlmann, R. Zeisberg, and E. Klein, *Org. Magn. Resonance*, 1975, **7**, 426.

[6] D. R. Taylor, *Canad. J. Chem.*, 1976, **54**, 189.

[7] S. J. Terhune, J. W. Hogg, A. C. Bromstein, and B. M. Lawrence, *Canad. J. Chem.*, 1975, **53**, 3285.

[8] J. Iwamura, K. Beppu, and N. Hirao, *Bunseki Kiki*, 1976, **14**, 162 (*Chem. Abs.*, 1976, **85**, 63 172).

[9] J. Cassan, R. Camain, and M. Azzaro, *Analysis*, 1975, **3**, 323.

[10] H. Schwarz, F. Borchers, and K. Levsen, *Z. Naturforsch.*, 1976, **31b**, 935.

The c.d. spectra of *N*-salicylidene derivatives of *p*-menthane, thujane, and fenchane amines correlate with known absolute configurations,[11] and a new octant rule for nitramines is illustrated with *N*-nitrocamphidine.[12] In measuring the fluorescent-detected c.d. spectrum of camphor, differences in the fluorescence intensity of the chromophore may result from restricted Brownian rotation during the lifetime of the excited state rather than from the circular dichroism of the chromophore.[13] Differences in the absorption and fluorescence c.d. spectra of a number of bicyclo[2,2,1]heptanones have been explained.[14] The greater sensitivity of vibrational c.d. to structural changes than absorption spectra should make it a valuable tool for determining molecular stereochemistry; some C—H data are provided for borneol, camphor, menthol, and the pinenes.[15]

Alkylation of the Schiff base derived from (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one and glycine t-butyl ester has yielded D-amino-acids in high optical purity (*e.g.* D-alanine, 83%),[16] and asymmetric hydrogenolysis of the chiral hydrazone derived from (2*S*)-bornylamine and ethyl pyruvate yields L-alanine in 46.5% optical purity.[17] In another model system for the action of NAD(P)H, (−)-menthyl benzoylformate is reduced with (−)-menthyl Hantzsch ester, catalysed by Zn^{2+} under Reformatsky-type conditions, in 77% optical yield to (−)-menthyl (2*R*)-mandelate (*cf.* Vol. 6, p. 6).[18] (+)-8-Phenylmenthyl acrylate is dramatically superior to (−)-menthyl acrylate in chiral directing ability in Diels–Alder cycloaddition reactions.[19] The substituted caprolactam available from (−)-menthone oxime by Beckmann rearrangement is used to oxidize sulphides in low optical yields.[20] Other syntheses of chiral sulphur compounds based upon (−)-menthol include the synthesis of *O*-substituted diaryl sulphilimines, sulphonium ylides, and sulphoxides from the corresponding (*O*)-(−)-menthoxydiarylsulphonium salts,[21] the synthesis of thiirans in low optical yield using *S*-lithiomethyl *O*-(−)-menthyl dithiocarbonate,[22] and the straightforward diastereomeric preparation of chiral benzyl thiols from sodium *O*-(−)-menthyl dithiocarbonate.[23] Other asymmetric induction reactions involving monoterpenoids include the synthesis of a chiral Dewar-benzene,[24] a one-step synthesis of *S*-(+)-2,2,2-trifluorophenylethanol of sufficient purity for direct use as a chiral n.m.r. solvent,[25] two routine investigations using chiral lithium aluminium hydride

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[11] H. E. Smith, E. P. Burrows, E. H. Massey, and F.-M. Chen, *J. Org. Chem.*, 1975, **40**, 2897.

[12] T. Polonski and K. Prajer, *Tetrahedron Letters*, 1975, 3539; *N*-camphidine is structure 3 and not 2 as reported.

[13] D. Ehrenberg and I. Z. Steinberg, *J. Amer. Chem. Soc.*, 1976, **98**, 1293.

[14] H. P. J. M. Dekkers and L. E. Closs, *J. Amer. Chem. Soc.*, 1976, **98**, 2210.

[15] L. A. Nafie, T. A. Keiderling, and P. J. Stephens, *J. Amer. Chem. Soc.*, 1976, **98**, 2715.

[16] S.-I. Yamada, T. Oguri, and T. Shioiri, *J.C.S. Chem. Comm.*, 1976, 136.

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[18] K. Nishiyama, N. Baba, J. Oda, and Y. Inouye, *J.C.S. Chem. Comm.*, 1976, 101.

[19] E. J. Corey and H. E. Ensley, *J. Amer. Chem. Soc.*, 1975, **97**, 6908.

[20] Y. Sato, N. Kunieda, and M. Kinoshita, *Chem. Letters*, 1976, 563.

[21] M. Moriyama, S. Oae, T. Numata, and N. Furukawa, *Chem. and Ind.*, 1976, 163.

[22] C. R. Johnson and K. Tanaka, *Synthesis*, 1976, 413; formula 2 is incorrect.

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[24] J. H. Dopper, B. Greijdanus, D. Oudman, and H. Wynberg, *J.C.S. Chem. Comm.*, 1975, 972.

[25] D. Nasipuri and P. K. Bhattacharya, *Synthesis*, 1975, 701.

complexes,[26,27] and a report of acetophenone reduction with monoterpenoid glycol–lithium aluminium hydride complexes.[28]

Chromatography of radiochemically homogeneous terpenoids has been reviewed;[29] useful gas-chromatographic techniques reported include the use of polyphenyl ether in g.c.–m.s. of 23 monoterpenoid hydrocarbons,[30] the use of 3,4,5-trimethoxybenzylhydrazine for pre-column removal of aldehydes and ketones,[31] and the resolution of some bicyclic alcohols and ketones by co-injection with a volatile chiral resolving agent.[32]

2 General Synthetic Reactions

Some useful reviews which discuss applications from, or are of value to, monoterpenoid chemistry include applications of singlet oxygen,[33] manganese dioxide,[34] di-isobutylaluminium and tri-isobutylaluminium hydrides,[35] catecholborane,[36] and chlorosulphonyl isocyanate,[37] discussions of functional group selectivity of complex hydride reducing agents,[38] hydrozirconation,[39] selenium reagents,[40] and the photochemistry and spectroscopy of $\beta\gamma$-unsaturated carbonyl compounds;[41] an interesting, but non-novel, account of industrial terpenoid synthesis has also appeared.[42]

Epoxidation of tetrahydropyranyl ethers (*e.g.* isopentenyl tetrahydropyranyl ether) produces readily detonatable peroxides which are stable to many commonly used methods of destruction.[43]

Thermal[44,45] and mercury(II)-catalysed[44] [3,3]sigmatropic rearangement of allylic trichloroacetimidates[44] and allylic pseudo-ureas[45] (*e.g.* geraniol, linalool) are useful for the 1,3-transposition of hydroxy- and amino-groups; the former is synthetically preferred. The [2,3]sigmatropic rearrangement of allylic sulphoxides has been used to effect an alkylative 1,3-carbonyl transposition of enones (*e.g.* carvone).[46]

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[26] U. Valcavi, P. Balzano, and V. Monterosso, *Ann. Chim. (Italy)*, 1975, **65**, 91.

[27] U. Valcavi, P. Balzano, and V. Monterosso, *Ann. Chim. (Italy)*, 1975, **65**, 543.

[28] E. D. Lund and P. E. Shaw, 172nd A.C.S. Meeting, San Francisco, August 1976, Abstracts ORGN, No. 169.

[29] C. J. Coscia, in 'Chromatography', ed. E. Heftmann, 3rd. edn., Van Nostrand-Reinhold, New York, 1975, p. 571.

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[32] P. D. Maestas and C. J. Morrow, *Tetrahedron Letters*, 1976, 1047.

[33] G. Ohloff, *Pure Appl. Chem.*, 1975, **43**, 481.

[34] J. J. Fatiadi, *Synthesis*, 1976, **65**, 133.

[35] E. Winterfeldt, *Synthesis*, 1975, 617.

[36] C. F. Lane and G. W. Kabalka, *Tetrahedron*, 1976, **32**, 981.

[37] J. K. Rasmussen and A. Hassner, *Chem. Rev.*, 1976, **76**, 389.

[38] E. R. H. Walker, *Chem. Soc. Rev.*, 1976, **5**, 23.

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[40] K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scripta*, 1975, **8A**, 9.

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[43] A. I. Meyers, S. Schwartzman, G. L. Olson, and H.-C. Cheung, *Tetrahedron Letters*, 1976, 2417.

[44] L. E. Overman, *J. Amer. Chem. Soc.*, 1976, **98**, 2901; an earlier communication, *ibid.*, 1974, **96**, 597, was omitted from these Reports.

[45] S. Tsuboi, P. Stromquist, and L. E. Overman, *Tetrahedron Letters*, 1976, 1145.

[46] B. M. Trost and J. L. Stanton, *J. Amer. Chem. Soc.*, 1975, **97**, 4018; this paper was inadvertently omitted from last year's Report.

A 1,3-hydroxy-transposition [*e.g.* geraniol to linalool, (+)-*cis*-carveol to (−)-*cis*-carveol] has been accomplished *via* the previously reported (Vol. 5, p. 6) metal-catalysed epoxidation and sodium–ammonia reduction of the corresponding α-epoxymesylate.[47] The full paper (Vol. 6, p. 7) on bromine–trialkyltin alkoxide oxidation of alcohols has appeared and includes a one-step procedure using bromine–bis(tributyltin) oxide;[48] related work using *N*-bromosuccinimide reports oxidation of primary allylic alcohols (*e.g.* geraniol) to aldehydes, but in the presence of aldehydes, non-allylic alcohols yield esters.[49] Chromyl chloride oxidation of alcohols (citronellol, geraniol, pinocarveol) to aldehydes is difficult to control and led to a new method of preparing pure di-t-butyl chromate,[50] the use of which is also reviewed (with only four references post-1969!);[51] oxidation of allylic alcohols is less satisfactory than with Collins oxidation because of double-bond isomerization and allylic oxidation.[50] Chromium trioxide in hexamethylphosphoramide (HMPA) readily oxidizes geraniol to geranial although menthol oxidation proceeds only in moderate yield;[52] geranial is also obtained in high yield from geranyl bromide by the use of chromate ion as a nucleophile in HMPA in the presence of dicyclohexyl-18-crown-6.[53] Corey has used potassium superoxide as a nucleophile in DMSO–DMF in the presence of polyether-18-crown-6 to convert geranyl bromide directly into geraniol;[54] in benzene, potassium superoxide–18-crown-6 readily cleaves α-keto-(*e.g.* camphorquinone), α-hydroxy-, and α-halogeno-ketones (*e.g.* 3-bromocamphor), -esters, and -carboxylic acids to the corresponding carboxylic acids.[55]

In connection with atmospheric pollution by monoterpenoids, α-pinene, β-pinene, and (+)-limonene have been shown to be extremely reactive towards $O(^3P)$ atoms, with rate constants an order of magnitude higher than that for the reaction of $O(^3P)$ with propylene;[56] a second paper reports the Arrhenius expressions.[57] Acid-catalysed oxidation of borneol to camphor using *m*-chloroperbenzoic acid[58] is less efficient than the corresponding nitroxide-catalysed oxidation.[59] Two very mild methods for oxidizing alcohols to aldehydes or ketones without double-bond isomerization or epimerization are the use of *N*-methylmorpholine *N*-oxide, catalysed by $[RuCl_2(PPh_3)_3]$,[60] and photochemical cleavage of pyruvate esters.[61] The 'forbidden' insertion of triplet oxygen into *cis*-1,3-dienes by photochemical irradiation in the presence of trityl cation gives 1,4-peroxido-*cis*-2-enes (*e.g.* α-terpinene to

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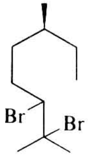
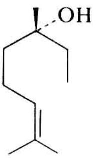
[47] A. Yasuda, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1976, 2621.
[48] K. Saigo, A. Morikawa, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1976, **49**, 1656.
[49] T. Ogawa and M. Matsui, *J. Amer. Chem. Soc.*, 1976, **98**, 1629.
[50] K. B. Sharpless and K. Akashi, *J. Amer. Chem. Soc.*, 1975, **97**, 5927.
[51] A. K. Lala and A. B. Kulkarni, *J. Sci. Ind. Res., India*, 1975, **34**, 605.
[52] G. Cardillo, M. Orena, and S. Sandri, *Synthesis*, 1976, 394.
[53] G. Cardillo, M. Orena, and S. Sandri, *J.C.S. Chem. Comm.*, 1976, 190.
[54] E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Letters*, 1975, 3183; see J. San Filippo, C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, 1975, **40**, 1678, and R. A. Johnson and E. G. Nidy, *ibid.*, 1975, **40**, 1680 for earlier reports of this reaction.
[55] J. San Filippo, C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, 1976, **41**, 1077.
[56] J. S. Gaffney, R. Atkinson, and J. N. Pitts, *J. Amer. Chem. Soc.*, 1975, **97**, 5049.
[57] J. S. Gaffney, R. Atkinson, and J. N. Pitts, *J. Amer. Chem. Soc.*, 1975, **97**, 6481.
[58] J. A. Cella, J. P. McGrath, and S. L. Regen, *Tetrahedron Letters*, 1975, 4115.
[59] J. A. Cella, J. A. Kelley, and E. F. Kenehan, *J. Org. Chem.*, 1975, **40**, 1860.
[60] K. B. Sharpless, K. Akashi, and K. Oshima, *Tetrahedron Letters*, 1976, 2503.
[61] R. W. Binkley, *Synth. Comm.*, 1976, **6**, 281.

ascaridole) in high yield.[62] Hydroxylation of (1) with ozone on silica gel proceeds in low yield but with high retention of configuration to yield dihydrolinalool (2) after debromination.[63]

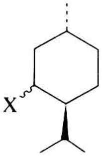


(1)



(2)

Further investigations of selective reductions include 1,4-reduction of enones (*e.g.* carvone) as well as reductive alkylation, using Li- and K-Selectrides,[64] and the use of 9-borabicyclo[3,3,1]nonane, which in the case of camphor yields only 75% of the *exo*-isoborneol[65] compared with 99.3% using the very sterically hindered lithium trisiamylborohydride;[66] bornan-2-*exo*-yloxyaluminium dichloride reduces (−)-menthone to a 95:5 mixture of (+)-neomenthol (3; X = *S*-OH) and (−)-menthol (3; X = *R*-OH).[67] Silver-ion-induced oxidation of acyclic and cyclic organoboranes is a useful method for cyclizing dienes; geranyl acetate, after *cis*-elimination, yields (4; X = *cis*-H), and linalyl acetate yields (4; X = *cis*-OH) and (4; X = *trans*-OH).[68] Non-rearranged allylic ethers [*e.g.* (5)] are formed in good yield on treating the *p*-tosylhydrazones of $\alpha\beta$-unsaturated aldehydes and ketones with sodium borohydride–methanol owing to decreased C=N reactivity favouring base-catalysed elimination.[69] Only the olefinic bond in $\alpha\beta$-unsaturated carbonyl compounds (*e.g.* carvone) is reduced in high yield using $Na[HFe_2(CO)_8]$,[70] whereas only the carbonyl group in citral (the formula is incorrect in this paper) is reduced using propan-2-ol on dehydrated alumina.[71]



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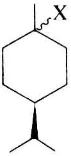

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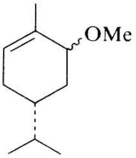

(5)

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[62] D. H. R. Barton, R. K. Haynes, G. Leclerc, P. D. Magnus, and I. D. Menzies, *J.C.S. Perkin I*, 1975, 2055; D. H. R. Barton, P. D. Magnus, and I. D. Menzies, Brit. P. 1 410 483 (*Chem. Abs.*, 1976, **84**, 16 917); an earlier report of this reaction, D. H. R. Barton, G. Leclerc, P. D. Magnus, and I. D. Menzies, *J.C.S. Chem. Comm.*, 1972, 447, was omitted from these Reports.

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[64] J. M. Fortunato and B. Ganem, *J. Org. Chem.*, 1976, **41**, 2194.

[65] H. C. Brown, S. Krishnamurthy, and N. M. Yoon, *J. Org. Chem.*, 1976, **41**, 1778.

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