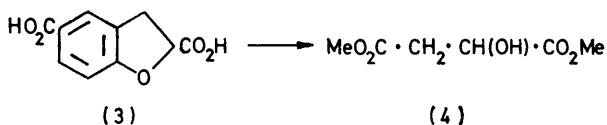
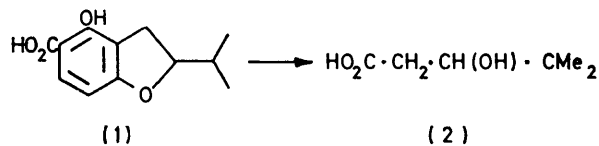


Absolute Configuration of Aromatic Oxygenated Isoprenoid Derivatives: Formation of 3-Hydroxy-4,4-dimethyl-4-butyrolactone by Ozonolysis and a Study of its Stereochemistry¹

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Ozonolysis of the hydroxyisopropylfuroquinoline alkaloid, platydesminium metho-salt, afforded (+)-3-hydroxy-4,4-dimethyl-4-butyrolactone. The structure of the lactone was established by asymmetric synthesis of its formate ester and its absolute configuration by correlation with (-)-4-methylpentane-1,3-diol.

THERE has been considerable recent interest in the establishment of the absolute configuration of isopropylidihydrofuro-derivatives and related compounds of isoprenoid origin. Of particular significance is the work of Büchi *et al.*² with rotenone, which was converted into dihydrotubaic acid (1). Ozonolysis of the acid afforded the hydroxy-acid (2) which was reduced to



4-methylpentane-1,3-diol (10) of known configuration. Another approach³ involves oxidation to a dihydrofuran-2-carboxylic acid (3) followed by ozonolysis to a derivative of malic acid (4). The stereochemistry of hydroxyisopropylfuro-compounds has been investigated by the malic acid method⁴ and by correlation with hydroxydihydrotubaic acid.⁵

Because of our interest in correlating the stereochemistry of oxygenated isoprenoids,⁶ we sought a more

general method, involving direct ozonolysis of hydroxyisopropylfuro-derivatives and related compounds. The process is illustrated by application to an isoprenoid quinoline alkaloid.

The quaternary alkaloid, platydesminium metho-salt (5), $[\alpha]_D +33^\circ$ was isolated from *Skimmia japonica*; its constitution has been established.⁷ Ozonolysis of the alkaloid in chloroform at 0° and oxidation of the ozonide with alkaline hydrogen peroxide afforded the (+)-hydroxy-lactone (7; R = H) (50% yield). The structure of the lactone was indicated by its n.m.r. spectrum [τ 8.60 and 8.64 (CMe₂) and an ABX system at 5.8, 7.53, and 7.05 (>CH-CH₂-)]. Treatment of the lactone with 90% formic acid afforded the monoformate (7; R = HCO), τ 8.6 (CMe₂) and 1.9 (CHO) and an ABX system at 6.8—7.5 and 4.75 (>CH-CH₂-). It is apparent that the diol acid (6), the expected primary product of ozonolysis, readily lactonises.

The constitution of the hydroxy-lactone (7; R = H) was confirmed by synthesis of its monoformate ester; in order to investigate its stereochemistry a method of asymmetric synthesis was employed. Methyl 4-methylpent-3-enoate (8), prepared by a known method,⁸ was shown by n.m.r. spectroscopy to contain ca. 5% of the 2-ene isomer. The structure of the corresponding (+)-epoxide (9) (72%), obtained by treatment of the unsaturated ester with (+)-peroxycamphoric acid in chloroform, was indicated by the n.m.r. spectrum

¹ Preliminary communication, J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 1078.

² G. Büchi, L. Crombie, P. J. Godin, J. S. Kaltenbronn, K. S. Siddalingaiah, and D. A. Whiting, *J. Chem. Soc.*, 1961, 2843.

³ W. A. Bonner, N. I. Burke, W. E. Fleck, R. K. Hill, J. A. Joule, B. Sjobert, and J. H. Zalkow, *Tetrahedron*, 1964, **20**, 1419.

⁴ I. Harada, K. Naemura, and M. Nakazaki, *Tetrahedron Letters*, 1968, 5463.

⁵ B. E. Nielsen and J. Lemmich, *Acta Chem. Scand.*, 1964, **18**, 2111.

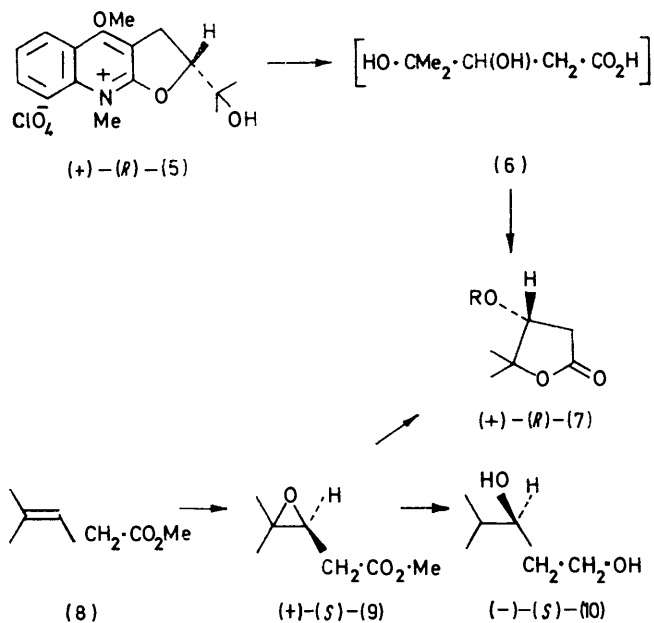
⁶ R. M. Bowman, J. F. Collins, and M. F. Grundon, *Chem. Comm.*, 1967, 1131.

⁷ D. R. Boyd and M. F. Grundon, *J. Chem. Soc. (C)*, 1970, 556.

⁸ J. B. Rogan, *J. Org. Chem.*, 1962, **27**, 3910.

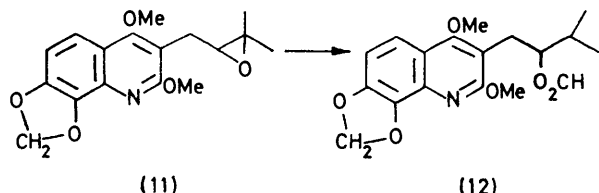
[τ 8.7 (6H, CMe_2), 6.9 (1H, t, CH), 7.45 (2H, d, CH_2), and 6.2 (3H, s, CO_2Me)]. Reaction of the epoxide with 90% formic acid at 20° afforded the (+)-monoformate ester (7; R = HCO) (92%), identical with the ester obtained from the hydroxy-lactone (7; R = H).

In an attempt to establish the absolute configuration of the hydroxy-lactone (7; R = H), the (+)-epoxide (9) was treated with diborane and lithium borohydride



SCHEME

to give (-)-4-methylpentane-1,3-diol, shown previously² to have the *S*-configuration (10). On the basis of these transformations and by application of the sequence rules we suggest the assignments of configuration given in the Scheme. These assignments, however, rest on certain assumptions of mechanism; it is probable that configurations are retained in the Brown-Yoon reaction (9) \longrightarrow (10),⁹ and in the esterification of the lactone (7; R = H) \longrightarrow (7; R = HCO), but the mechanism of the reaction of the epoxide with formic acid (9) \longrightarrow (7; R = CHO) is less clear. It has been shown¹⁰ that the epoxide (11) reacts rapidly with formic acid exclusively



at the secondary carbon atom of the epoxide ring to give the formate ester (12), and we conclude that the epoxide (9) behaves similarly to give a hydroxy-formate ester that subsequently affords the lactone (7; R = HCO). This process will result in inversion of configuration as indicated in the Scheme, but an alternative

⁹ H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, 1968, **90**, 2686.

sequence, namely lactonisation followed by esterification with formic acid, results in retention of configuration and cannot be excluded.

After the completion of this work Lemmich and Nielsen¹¹ showed that ozonolysis of hydroxyisopropyl-dihydrofurocoumarins also gave the hydroxy-lactone (7; R = H). In particular, (+)-8,9-dihydro-oreselol of known configuration gave the (-)-lactone, thereby establishing the absolute stereochemistry of the latter compound as *S*. These results agree with our own, confirm the assignments given in the Scheme and establish the *R*-configuration for the (+)-quaternary quinoline alkaloid (5).

Ozonolysis of related compounds, for example hydroxypyran-derivatives and isoprenyl diols, also affords the hydroxy-lactone (7; R = H).¹ It is clearly a convenient general method for establishing the absolute configuration of compounds containing oxygenated isoprenyl groups attached directly to aryl systems.

EXPERIMENTAL

The n.m.r. spectra were determined with a Varian HR-100 spectrometer (tetramethylsilane as internal standard). G.l.c. was performed on a Perkin-Elmer F11 instrument (versamid 930 column). Optical rotations were determined with a Perkin-Elmer 121 electronic polarimeter capable of measurement to $\pm 1 \times 10^{-3}$ degrees.

(+)-3-Hydroxy-4,4-dimethyl-4-butyrolactone from Ozonolysis of *Platydesminium Methoperchlorate* (5).—Ozone-oxygen was passed into a solution of platydesminium methoperchlorate (0.71 g) in chloroform-methanol (7 : 3) at 0° for 2 h. The yellow oil obtained by evaporation was boiled with water (25 ml) for 30 min, and aqueous 2*N*-potassium hydroxide (10 ml) and 30% hydrogen peroxide were added. After 1 h, the solution was heated at 50° for 15 min, water (20 ml) was added, and an excess of sulphur dioxide was passed through. The solution was extracted continuously with chloroform for 1 week. Evaporation of the solvent, chromatography on silica gel, and elution with ether gave the hydroxy-lactone (0.18 g, 51%), $[\alpha]_D +7.1^\circ$ (CHCl_3); (Found: C, 55.2; H, 7.8. Calc. for $\text{C}_6\text{H}_{10}\text{O}_3$: C, 55.4; H, 7.8%); it was homogeneous by g.l.c., and was identical (i.r. and g.l.c.) with an authentic sample.¹¹

Methyl 4-Methylpent-3-enoate.—The ester was obtained by the method of Rogan⁸ as an oil, b.p. 156–160° at 760 mmHg (lit.,⁸ 160–164° at 640 mmHg), τ (CDCl_3) 4.8 (1H, t), 6.35 (3H, s), 6.95 (2H, d), and 8.3 (6H, d). The n.m.r. spectrum showed that the compound contained ca. 5% of methyl 4-methylpent-2-enoate.

4-Formyloxy-4,4-dimethyl-4-butyrolactone.—A solution of (+)-peroxycamphoric acid (7 g) in chloroform (50 ml) was added to methyl 4-methylpent-3-enoate (5 g) in chloroform (100 ml). After 3 days at 20° the solution was extracted with 2*N*-sodium carbonate (4 \times 50 ml) and evaporated to give the epoxide (9) (4.03 g, 72%), $\alpha_D +0.2^\circ$ (neat). Attempts to purify the epoxide by chromatography or by distillation led to decomposition. The epoxide (1 g) in 90% formic acid (5 ml) was kept for 4 h, added to 2*N*-sodium carbonate, and extracted with methylene chloride. Evaporation of the solvent and chromatography on alumina gave the formate as an oil (1.01 g), $\alpha_D +0.18^\circ$

¹⁰ R. M. Bowman and M. F. Grundon, *J. Chem. Soc. (C)*, 1967, 2368.

¹¹ J. Lemmich and B. E. Nielsen, *Tetrahedron Letters*, 1969, 3.

(neat), identical (i.r. and n.m.r.) with a sample prepared by treatment of the hydroxy-lactone (7; R = H) with formic acid.

4-Methylpentane-1,3-diol.—The (+)-epoxide (9) (1.0 g) in dry tetrahydrofuran (5 ml) was added slowly to an excess of an equimolar mixture of diborane in tetrahydrofuran and lithium borohydride. After being stirred at 0° for 24 h, the mixture was treated with a 1 : 1 mixture of 2N-sulphuric acid and tetrahydrofuran (25 ml). The aqueous phase was saturated with potassium carbonate and the tetrahydrofuran layer was evaporated. The residue was shown by

g.l.c. to contain five components, one of which predominated. Chromatography on silica gel and elution with ether-light petroleum (b.p. 40–60°) (9 : 1) gave the diol (0.42 g, 56%), $[\alpha]_D -0.1^\circ$ (CHCl₃), identical with a sample of the (±)-diol prepared by the method of Büchi *et al.*²

We thank Professor B. E. Nielsen for a sample of the hydroxy-lactone (7; R = H) and the Ministry of Education for Northern Ireland for a postgraduate studentship (to J. F. C.).

[2/1784 Received, 28th July, 1972]
