The Role of Asymmetric Epoxidation in the Biosynthesis of Oxygenated Isoprenoides

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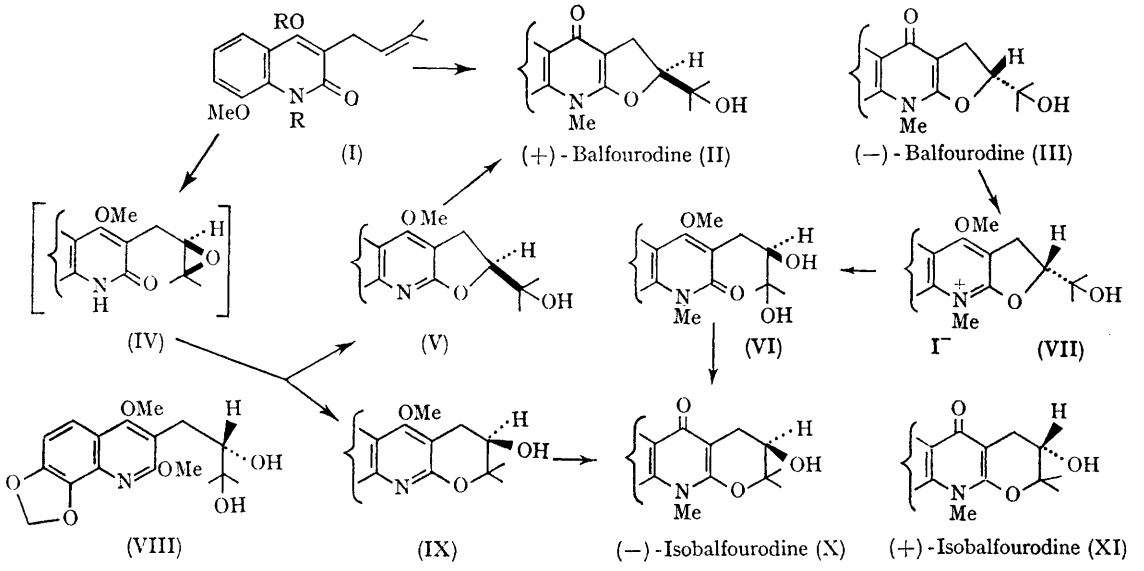
A wide range of natural products containing oxygenated isoprenoid units apparently arise by stereospecific biological oxidation of 3,3-dimethylallyl groups.[1] This may occur by epoxidation (*cf.*, sterol biosynthesis[2]) followed by hydrolysis, reduction, or cyclisation. We have now simulated this process in a representative group of isoprenoid alkaloids.

Balfourodine was obtained by asymmetric oxidation of the 3,3-dimethylallylquinoline (I; R = H, R^1 = Me); (+)-peroxycamphoric acid, (+)-peroxyhydratropic acid, or (−)-peroxy-*endo*-norbornane-2-carboxylic acid (all of the *S*-configuration) furnished (+)-balfourodine (II)† of 4—10% optical purity, while the (−)-enantiomer (III) was prepared from (−)-peroxycamphoric acid or (−)-peroxyhydratropic acid. A 3-(3,3-dimethylallyl)-2,4-dimethoxyquinoline was converted similarly into the diol, (+)-orixine (VIII) (2·4% optical purity),[3] but in this case the intermediate optically-active epoxide was isolated, and then hydrolysed.

Another group of experiments was concerned with the relative stereochemistry of isobalfourodine, (X) or (XI), and balfourodine. Thus, reaction of (−)-balfourodine (III) with methyl iodide furnished the quaternary salt (VII) which with aqueous alkali yielded (+)-balfourolone (VI),

† The absolute configurations of the products are unknown and formulae (II)–(XI) represent only the relative stereochemistry of the enantiomers.

probably by an addition–elimination mechanism resulting in cleavage of the quinoline–heterocyclic oxygen bond.[4] On heating with aqueous acid balfourolone (VI) then gave (−)-isobalfourodine (X), presumably by an $S1_N$ reaction at the tertiary carbon.[5] Assumption of these mechanisms implies that the rearrangement proceeds without affecting the asymmetric centres and that the relative configurations of (−)-balfourodine and (−)-isobalfourodine are indeed represented by formulae (III) and (X), respectively. This result was confirmed independently in the following way. Asymmetric oxidation of the quinolone (I; R = Me, R′ = H) with (+)-peroxycamphoric acid afforded the optically-active pyranoquinoline (IX) and its furano-isomer (V). These products were converted by reactions not affecting the asymmetric centres[6] into (−)-isobalfourodine (X) (9·3% optical purity) and (+)-balfourodine (II) (4·7% optical purity), respectively. If it is assumed that the isomers (V) and (IX) arise by attack of 2-quinolone oxygen at secondary or at tertiary carbon atoms, respectively, of an epoxide intermediate (IV), then the products in this reaction sequence have the configurations indicated in the chart. Our conclusions are contrary to those of Rapoport and Holden[7] who suggested that (+)-balfourodine and (+)-isobalfourodine have 'opposite absolute configurations', *i.e.*, could be represented by formulae (II) and (X).



It is interesting to note that (+)-balfourodine and (−)-isobalfourodine were the products from the 'simulated' biological oxidation described above whereas the (+)-enantiomers occur together in *Balfourodendron riedelianum* Engl.,[7] and the (−)-enantiomers in *Lunasia amara* Blanco.[8] Although synthetic results cannot provide firm evidence for biosynthetic schemes, it appears unlikely that *both* alkaloids arise *in vivo* by direct biological epoxidation of a dimethylallylquinoline.

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[1] W. D. Ollis and I. O. Sutherland in "Recent Developments in the Chemistry of Natural Phenolic Compounds", Pergamon, Oxford, 1961, p. 88.
[2] E. A. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *J. Amer. Chem. Soc.*, 1966, **88**, 4752; E. J. Corey and W. E. Russey, *ibid.*, p. 4750.
[3] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.*, (*C*), 1967, 2368.
[4] *Cf.*, J. R. Price, *Austral. J. Chem.*, 1959, **12**, 458; R. A. Corral and O. O. Orazi, *Tetrahedron*, 1966, **22**, 1153.
[5] E. A. Clarke and M. F. Grundon, *J. Chem. Soc.*, 1964, 4190.
[6] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1966, 1504.
[7] H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, 1959, **81**, 3738; *ibid.*, 1960, **82**, 4395.
[8] S. Goodwin, A. F. Smith, A. A. Velasquez, and E. C. Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 6209; H. C. Beyerman and R. W. Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1959, **62**, *B*, 187, *ibid.*, 1960, **63**, *B*, 427.