# Quinoline Alkaloids. Part XIV.[1] Asymmetric Synthesis by the Peroxy-acid–Olefin Reaction. The Absolute Stereochemistry of Balfourodine, Isobalfourodine, and Related Compounds, and the Biosynthesis of Isomeric Dihydrofuro- and Dihydropyrano-derivatives [2]

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Reactions of 3-(3-methylbut-2-enyl)-2.4-dihydroxyquinoline derivatives with (+)- and (−)-peroxycamphoric acid. with (+)- and (−)-peroxyhydratropic acid. and with (+) and (−)-norbornane-2-*endo*-peroxycarboxylic acid furnished optically active dihydrofuroquinoline alkaloids. balfourodine and *O*-methylbalfourodinium salt. and the dihydropyranoquinoline. isobalfourodine (2—10% optical induction). The absolute stereochemistry of the alkaloids was determined by ozonolysis to 3-hydroxy-4.4-dimethyl-γ-butyrolactone. The stereochemical results are discussed in relation to the peroxy-acid–olefin reaction. to the balfourodine–isobalfourodine rearrangement. and to the biosynthesis of coumarins and quinolines containing hydroxyisopropyldihydrofuran and hydroxy-dimethyldihydropyran rings.

THE first group of isoprenoid quinoline alkaloids to be recognised were isolated from the rutaceous plants *Balfourodendron riedelianum* Engl. and *Lunasia* species.[3,4] *B. riedelianum* contains the hydroxyisopropyl derivative,

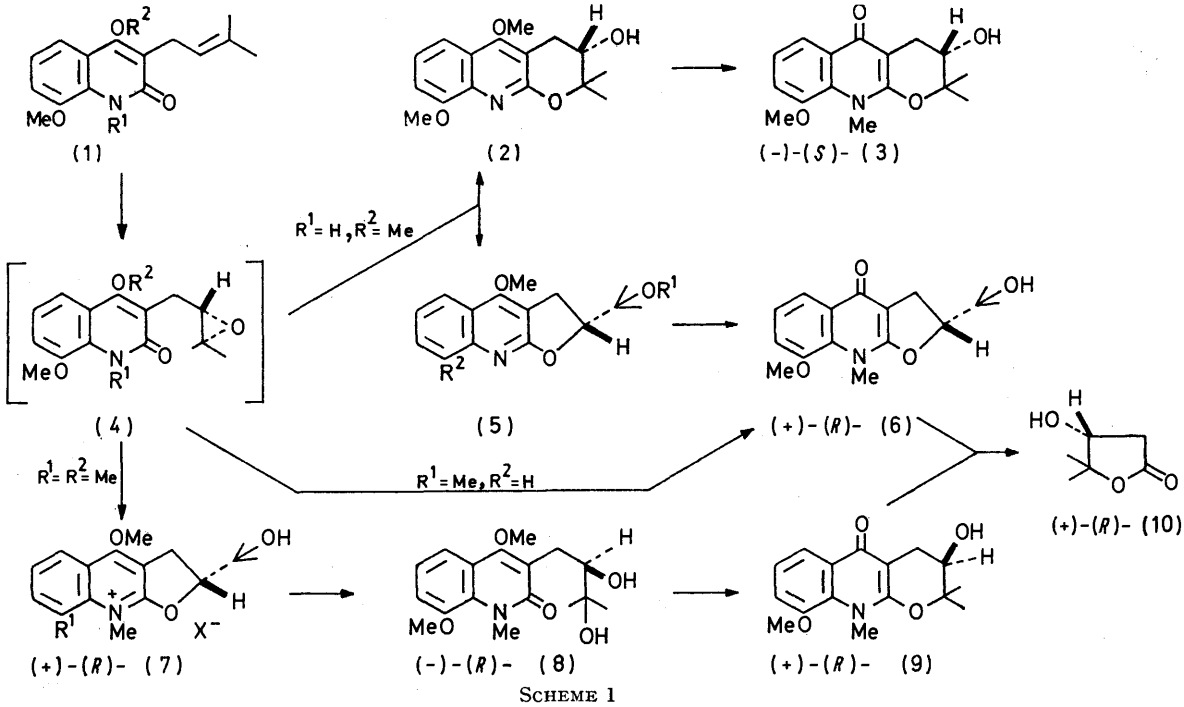
[1] Part XIII, J. F. Collins, G. A. Gray, M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J.C.S. Perkin I*, 1973, 94.

[2] Preliminary reports (*a*) R. M. Bowman, J. F. Collins, and M. F. Grundon, *Chem. Comm.*, 1967, 1131; (*b*) J. F. Collins and M. F. Grundon, *ibid.*, 1969, 1078.

[3] H. C. Beyerman and R. W. Rooda, *Proc. k. ned. Akad. Wetenschap.*, 1959, **62**, *B*, 187; 1960, **63**, *B*, 427; S. Goodwin, A. F. Smith, A. A. Velasquez, and E. C. Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 6209.

[4] H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, 1959, **81**, 3738; 1960, **82**, 4395.

(+)-balfourodine (6) and the hydroxy-dimethylpyran isomer, (+)-isobalfourodine (9); the corresponding enantiomers (−)-hydroxylunacrine and (−)-Lunasia II (3) occur in *Lunasia amara*. The related alkaloids, *O*-methylbalfourodinium salt (7; $R^1$ = OMe) and balfourolone (8) were also obtained, but the latter compound was shown [4] to be an artefact arising by hydrolysis of the quaternary salt (7; $R^1$ = OMe) during isolation. The structures of these alkaloids were confirmed by syntheses (Scheme 1) involving the reactions of isoprenylquinolines (1) with peroxy-acids. The *N*-methyl derivative (1; $R^1$ = Me, $R^2$ = H) gave balfourodine (6) almost quantitatively [5] and the *NO*-dimethylquinolone




SCHEME 1

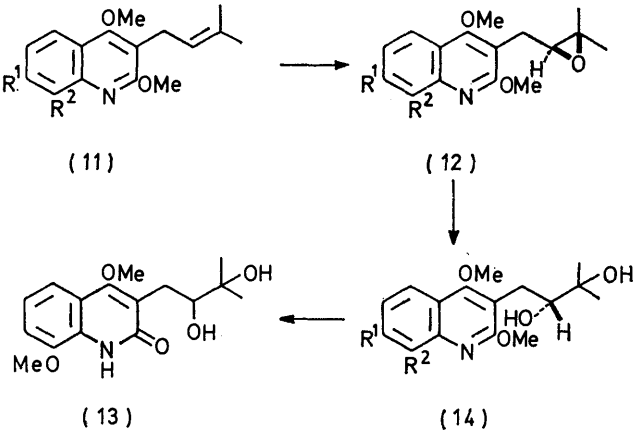
(1; $R^1 = R^2$ = Me) afforded *O*-methylbalfourodinium salt (7; $R^1$ = OMe).[5] The quinolone (1; $R^1$ = H, $R^2$ = Me), however, yielded a mixture of furo- and pyrano-isomers (5; $R^1$ = H, $R^2$ = OMe), and (2), readily converted, respectively, into balfourodine (6) and isobalfourodine (3).[6] The reactions presumably occur *via* epoxides (4) that cyclise readily. The biosynthesis of the furan and the pyran alkaloids may follow a similar route, involving a common epoxide intermediate; in order to examine this possibility further we decided to study the stereochemistry of the alkaloids. The method of choice was direct ozonolysis, and since sufficient of the natural alkaloids was not available, we explored their asymmetric synthesis.

*Asymmetric Synthesis.*—Preliminary work had already been carried out.[7] Thus, following the observations that treatment of mono- and di-substituted olefins with (+)-peroxycamphoric acid afforded optically active epoxides,[8] we applied the reaction to the 3-isoprenyl-2,4-dimethoxyquinoline (11; $R^1R^2 = O{\cdot}CH_2{\cdot}O$) and obtained the (−)-epoxide (12; $R^1R^2 = O{\cdot}CH_2{\cdot}O$). Conversion into the alkaloid orixine (14; $R^1R^2 = O{\cdot}CH_2{\cdot}O$) of known specific rotation indicated that optical induction during epoxidation was at least 2·4%.

The syntheses of balfourodine, isobalfourodine, and related alkaloids already mentioned and previously described fully [5,6] were repeated, using optically active peroxy-acids in the oxidative steps. The quinoline (1; $R^1$ = Me, $R^2$ = H) in chloroform at 0° was treated with an excess of (+)-peroxycamphoric acid, and balfourodine (6), $[\alpha]_D$ +4·6° (9·3% optical induction), was obtained. Crystallisation from ethyl acetate afforded optically inactive balfourodine, but (+)-balfourodine, $[\alpha]_D$ +19·5°, was isolated from the mother liquors. It appears that the racemate separates preferentially from ethyl acetate solution, and in subsequent work with partially optically active balfourodine, crystallisation was not used for purification. Further investigation of the oxidation of the isoprenylquinolone (1; $R^1$ = Me, $R^2$ = H) was undertaken with a range of peroxy-acids, and the results are summarised in the Table. (+)- and (−)-Peroxycamphoric acid, (+)- and (−)-peroxyhydratropic acid, and (+)- and (−)-norbornane-2-*endo*-peroxycarboxylic acid, all of known configuration,[9] were

[5] E. A. Clarke and M. F. Grundon, *J. Chem. Soc.*, 1964, 4196.
[6] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1966, 1504.
[7] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1967, 2368.
[8] H. B. Henbest, *Chem. Soc. Special Publ.*, No. 19, 1965, 83; R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Comm.*, 1967, 1085; F. Montanari, I. Moretti, and G. Torre, *ibid.*, 1969, 135.
[9] J. F. Collins and M. A. McKervey, *J. Org. Chem.*, 1969, **34**, 4172.

employed under standard conditions and afforded balfourodine (6) (2·1—6·1% optical yield) in each case. The results are stereochemically consistent, in the sense that (*S*)-peroxy-acids gave (+)-balfourodine and (−)-balfouro-dine was formed from (*R*)-acids.



(11) (12) (13) (14)

Optically active *O*-methylbalfourodinium salt (7; $R^1$ = OMe) was prepared by two methods. Thus, treatment of the isoprenyl-*N*-methylquinolone (1; $R^1$ = $R^2$ = OMe) with (+)-peroxycamphoric acid gave *O*-methylbalfourodinium salt (7; $R^1$ = OMe), isolated as the perchlorate. Because of the sparing solubility of the product, the specific rotation could not be determined accurately by direct measurement, but the optical activity of the quaternary salt was indicated by mild alkaline hydrolysis to the diol, (−)-balfourolone (8). Conversion of the quaternary perchlorate into the chloride and heating the latter briefly at 100° furnished (+)-balfourodine (6). The quaternary salt (7; $R^1$ = OMe) was also prepared by reaction of (+)-balfourodine with methyl iodide, and again gave (−)-balfourolone (8) on alkaline hydrolysis.

The asymmetric oxidation was also applied to the isoprenyl-4-methoxyquinolone (1; $R^1$ = H, $R^2$ = Me). (+)-Peroxycamphoric acid afforded the furoquinoline (5; $R^1$ = H, $R^2$ = OMe), $[\alpha]_D$ +1·83°, and the pyrano-isomer (2), $[\alpha]_D$ −1·48°. By the procedure described previously,[6] the furo-compound (5) was converted into (+)-balfourodine (6) (4·7% optical purity) and the pyrano-derivative (2) afforded (−)-isobalfourodine (3) (9·3% optical purity). The enantiomeric (+)-iso-balfourodine (9) was obtained by two routes, rearrangement of (+)-balfourodine (see later) and cyclisation of (−)-balfourolone (8) by refluxing in aqueous 20% hydrochloric acid.

Since the products obtained by asymmetric synthesis were used to establish the absolute configurations of quinoline alkaloids (see later), it was important to ensure that the observed optical rotations, and particularly the *signs* of the rotations, were not affected by contamination with optically active impurities derived from the peroxy-acids. The evidence for genuine optical induction in these reactions is summarised as follows. (*a*) All optically active samples were purified rigorously to eliminate contaminants, particularly traces of carboxylic acids formed from the reagents. Balfourodine (6), obtained from (+)-peroxycamphoric acid, was the starting point for most transformations, and was afforded special study; purification was performed by repeated washing with aqueous base, extraction into acid, and final chromatography. The value of the rotation, $[\alpha]_D$ +4·6°, after this treatment is itself convincing. The procedure was also applied to balfourodine derived from other peroxy-acids (Table). The norbornane peroxy-acids are of particular interest, since the (+)-enantiomer has the (*R*)-configuration and gives (−)-balfourodine and the (−)-(*S*)-enantiomer yields (+)-balfourodine; in these cases the isolation of optically active balfourodine cannot be due to contamination by the peroxy-acid or by the corresponding carboxylic acid. (*b*) Reaction of the quinoline (1; $R^1$ = H, $R^2$ = OMe) with (+)-peroxycamphoric acid furnished isomeric products with opposite signs of optical rotation, a result not explicable by the presence of impurities derived from the peroxy-acid. (*c*) The reactions of partially optically active balfourodine were carried out with purification at each stage, for example, (+)-balfourodine (6) ⟶ *O*-methylbalfourodinium iodide (7; $R^1$ = OMe, X = I) ⟶ (−)-(8) (extracted from basic solution, and crystallised) ⟶ (+)-(9) (extracted from a basic solution and chromatographed) ⟶ (+)-(10). This sequence involves two changes in the sign of rotation and thereby further substantiates the induction observed during reaction of olefins with chiral peroxy-acids in our work and in previous studies.[7,8] Thus, the *signs* of the optical rotations of compounds described here are regarded as established; the rotation values of the primary products, (6), (5; $R^1$ = H, $R^2$ = OMe), (2), and (12; $R^1$ = H, $R^2$ = OMe), obtained in the olefin–peroxy-acid reactions represent the optical yields, but the latter are not necessarily reflected in the values of optical rotations of transformation products, since in these cases some racemisation may have occurred during their formation.

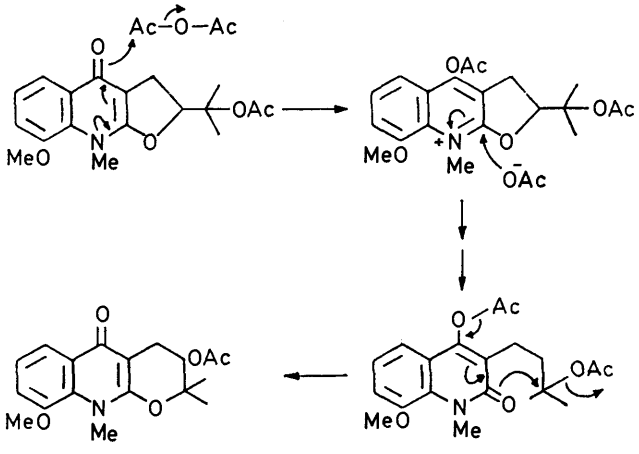
*Absolute Stereochemistry.*—We described earlier a new method for establishing the configuration of hydroxyisopentyl derivatives.[2b,10] Ozonolysis of the alkaloid, (+)-platydesminium metho-salt (7; $R^1$ = H), for example, followed by oxidation with hydrogen peroxide gave the (+)-hydroxy-lactone (10). The absolute stereochemistry of the hydroxy-lactone was determined by two methods, and application of the selection rules indicated that the quaternary alkaloid had the (*R*)-configuration (7; $R^1$ = H). The method was applied to the optically active alkaloids obtained as just described by asymmetric synthesis. In this way (+)-balfourodine (6), (+)-isobalfourodine (9), and (−)-balfourolone (8) each gave the hydroxy-lactone containing a preponderance of the (+)-enantiomer (10). Thus, three alkaloids, which were isolated as (+)-, (+)-, and (−)-enantiomers, respectively, from *Balfourodendron riedelianum*, have the (*R*)-configuration, with the stereoformulae shown. It is

[10] J. F. Collins and M. F. Grundon, *J.C.S. Perkin I*, 1973, 161.

assumed that *O*-methylbalfourodinium salt found naturally as the (+)-enantiomer also has the (*R*)-configuration (7; $R^1$ = OMe), since it can be obtained from (+)-balfourodine by reaction with methyl iodide, presumably without affecting the chiral centre.

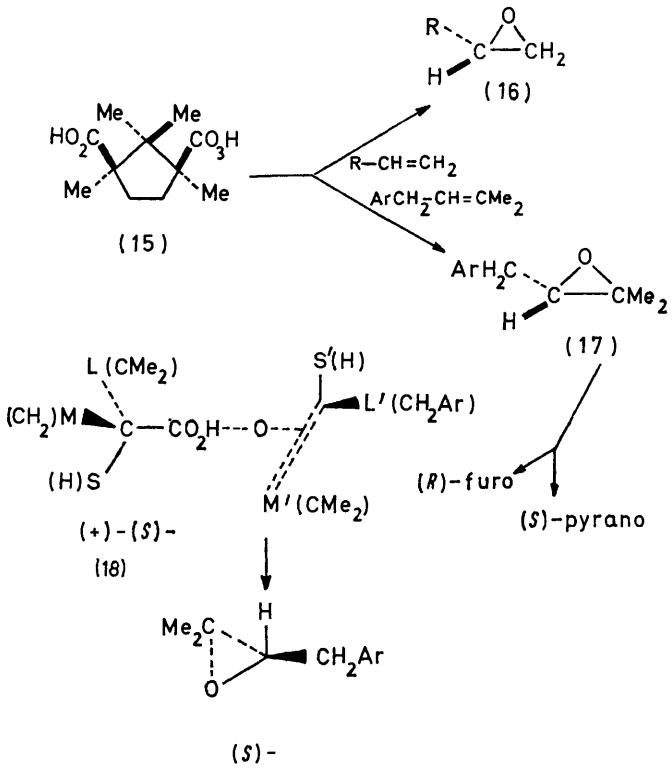
The assignment of configuration to the alkaloids assists in the understanding of some reactions described earlier. Thus, it was suggested [4] that the formation of (−)-balfourolone (8) by treatment of (+)-*O*-methylbalfourodinium perchlorate (7; $R^1$ = OMe, X = $ClO_4$) with aqueous base occurs with retention of configuration by nucleophilic reaction at the 2-position of the quinoline ring; the knowledge that both compounds have the (*R*)-configuration is consistent with this mechanism. Conversion of (−)-(*R*)-balfourolone (8) into (+)-(*R*)-isobalfourodine (9) by reaction with aqueous acid (see before) apparently occurs at the tertiary carbon atom without affecting the chiral centre.

*The Balfourodine–Isobalfourodine Rearrangement.*—Rapoport and Holden [4] reported that reaction of (−)-balfourodine with acetic anhydride furnished (+)-isobalfourodine acetate, which was hydrolysed to (+)-isobalfourodine. The rearrangement was accompanied by 48% racemisation. Alternative mechanisms were proposed involving inversion of configuration. We repeated the rearrangement but obtained a different stereochemical result. Using synthetic (+)-balfourodine, (+)-isobalfourodine acetate with some racemisation was obtained and hydrolysis afforded (+)-isobalfourodine. Since (+)-balfourodine and (+)-isobalfourodine have the (*R*)-configuration we propose a mechanism for the rearrangement (Scheme 2) involving partial retention of configuration. The presence of a 4-carbonyl group appears to be necessary for rearrangement (*cf.* first step in Scheme 2), because the 4-methoxyquinoline (5; $R^1$ = H, $R^2$ = OMe) affords the tertiary acetate (5; $R^1$ = Ac, $R^2$ = OMe), which resists rearrangement.




SCHEME 2

*Asymmetric Synthesis with Peroxy-acids.*—Henbest and McKervey [8] studied the reaction of (+)-(*S*)-peroxycamphoric acid (15) with a series of monosubstituted ethylenes and showed that an epoxide containing a preponderance of (*S*)-enantiomer (16) was obtained in each case. Our results with trisubstituted olefins of




type $ArCH_2{\cdot}CH{=}CMe_2$ (Ar = substituted quinolyl) indicate that reaction with (+)-peroxycamphoric acid also yields predominantly the (*S*)-enantiomer (17), which by intramolecular cyclisation is transformed into a mixture of (*S*)-pyrano-derivative without affecting the chiral centre and (*R*)-furo-derivative by inversion. The two sets of results are not readily reconciled by consideration of preferred transition states based on a Cram-Prelog model (18). In the diagram the symbols L, M, and S represent substituents at the requisite chiral centre of the peroxy-acid and L′, M′, and S′ indicate substituents in the olefin. This approach has been discussed in relation to the reaction of peroxy-acids with sulphides [11] as well as with olefins, and has been criticised in principle by Mislow.[12] One problem is to identify the relative size of groups, and this is apparent in the present comparison of the mono- and tri-substituted olefins in which it is necessary to postulate that $=CH_2$ and $=CMe_2$ are both ' medium-sized ' groups M′ in (18). The more important conclusion is that the reactions of the trisubstituted olefins with peroxy-acids are stereochemically consistent within the compounds (1; $R^1$ = Me, $R^2$ = H), (1; $R^1$ = H, $R^2$ = Me), and (1; R = $R^1$ = Me) and for the range of peroxy-acids employed (Table). We suggest, therefore, that the results can be used empirically to predict the stereochemistry of analogous products. Thus, the (−)-epoxide obtained by reaction of

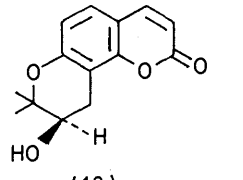
[11] U. Folli, D. Larossi, F. Montanari, and G. Torre, *J. Chem. Soc.* (*C*), 1968, 1372.

[12] K. Mislow, M. M. Green, P. Laucz, J. T. Melillo, T. Simmons, and A. L. Terray, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

the methylenedioxy-isoprenylquinoline (11; $R^1R^2$ = O·$CH_2$·O) with (+)-peroxycamphoric acid [7] is likely to have the (*S*)-configuration as indicated in formula (12), and the alkaloid (+)-orixine, derived from the epoxide by reaction with formic acid (inversion) followed by hydrolysis (retention) is presumably the (*R*)-enantiomer (14; $R^1R^2$ = O·$CH_2$·O). Application of the same reaction sequence to the trimethoxy-derivative (11; $R^1$ = H, $R^2$ = OMe) furnished the epoxide (12; $R^1$ = H, $R^2$ = OMe) and the diol (14; $R^1$ = H, $R^2$ = OMe), which by analogy, respectively contain a preponderance of (*S*)-(−)- and (*R*)-(+)-enantiomers as shown. Treatment of the (+)-trimethoxy-diol (14; $R^1$ = H, $R^2$ = OMe) with hydrogen chloride in dry ether gave the (+)-dimethoxy-diol (13), presumably without affecting the chiral centre. This method was shown previously [13] to cleave 2-methoxy-groups in 2,4-dimethoxyquinoline derivatives, and in our case i.r. absorption at 1630 $cm^{-1}$ indicated a 2-quinolone structure (13).

*Biosynthesis of Balfourodine and Isobalfourodine and Related Furo- and Pyrano-derivatives.*—In a recent biosynthetic study [14] involving use of precursors specifically labelled with $^{14}C$ we showed that the pathway to the furo-derivative (7; $R^1$ = H) in *Skimmia japonica* involves the sequence 2,4-dihydroxyquinoline ⟶ isoprenylquinoline (1) ⟶ platydesmine (5; $R^1 = R^2$ = H) ⟶ (7; $R^1$ = H). The biosynthesis of (+)-balfourodine (6) in *Balfourodendron riedelianum* probably follows a similar route involving oxidative cyclisation of an isoprenylquinoline (1); as in the asymmetric synthesis (Scheme 1) the (*S*)-epoxide (4; $R^1$ = Me, $R^2$ = H) is the presumed biological intermediate. It appears however, that the pyrano-derivative isobalfourodine does not arise by direct oxidative cyclisation of the methylbutenylquinoline (1), because the (+)-(*R*)-enantiomer (9) is found in *B. riedelianum* rather than the (−)-(*S*)-enantiomer (3) that would be expected if a common epoxide intermediate were involved in the biosynthesis of the two alkaloids. We suggest that the biosynthesis of isobalfourodine occurs by rearrangement of balfourodine (6); the (*R*)-configurations of the natural alkaloids (+)-balfourodine and (+)-isobalfourodine are consistent with this pathway, since the *in vitro* rearrangement occurs with retention of configuration (see before).

It is of interest to consider the origin of similar pyrano- and furo-isomers isolated from the same species. The angular dihydropyranocoumarin, (+)-lomatin (19), and the isomeric dihydrofurocoumarin, (+)-8,9-dihydroreselol (20) (present as a glycoside) occurring in *Lomatium nuttalii* [15] have been shown to have (*R*)- and (*S*)-configurations, respectively.[16] The corresponding linear isomers, (+)-(*S*)-decursinol (21) and (−)-(*R*)-nodakenetin (22) are found in *Angelica decursiva*.[16,17] For these coumarins the observed 'opposite' configuration of pyrano- and furo-isomers occurring in the same plant is consistent with a biosynthetic pathway involving stereospecific biological oxidation of 3-methylbut-2-enyl groups through a common epoxide intermediate. This is in contrast to the structurally analogous quinolines in which (+)-(*R*)-isobalfourodine (9) and (+)-(*R*)-balfourodine (6), with the 'same' configuration at the chiral centre, occur in *Balfourodendron riedelianum* and the respective enantiomers, (−)-(*S*)-Lunasia II and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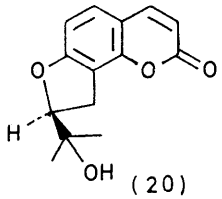
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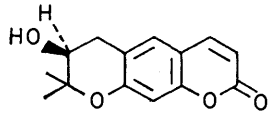
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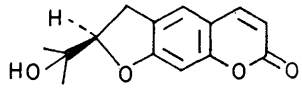
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(−)-(*S*)-hydroxylunacrine are found in *Lunasia amara*. The results described here emphasise the need to relate stereochemistry to biosynthetic theories, even when only a simple chiral centre is present. The different stereochemical situation with the coumarins and quinolines indicates, however, that in considering detailed biosynthetic pathways there is a danger in applying too widely conclusions based on a study of particular compounds.

## EXPERIMENTAL

The n.m.r. spectra were determined with a Varian HR-100 spectrometer, with tetramethylsilane as an internal standard. Optical rotations were measured on a Bendix-Ericsson automatic polarimeter (type 143A, fitted with a precision control unit capable of measurement to $\pm 2 \times 10^{-4}$ degrees) or with a Perkin-Elmer 121 electronic polarimeter capable of measurement to $\pm 1 \times 10^{-3}$ degrees. The following peroxy-acids, prepared as described previously,[9] were used: (+)-peroxycamphoric acid, m.p. 51°, $[\alpha]_D$ +54° (EtOH) (optically pure), 85—90% active oxygen content; (−)-peroxycamphoric acid (optical purity 89%); (+)-peroxyhydratropic acid, m.p. 44—47°, $[\alpha]_D$ +38° ($CHCl_3$) (optical purity 31%), 97—98% active oxygen content; (−)-peroxyhydratropic acid (optical purity 30%); (−)-norbornane-2-*endo*-peroxycarboxylic acid, m.p. 64—65°, $[\alpha]_D$ −12·3° ($CHCl_3$) (optical purity 49%), 98% active oxygen content; (+)-norbornane-2-*endo*-peroxycarboxylic acid (optical purity 33%).

(+)- and (−)-*Balfourodine*.—The 4-hydroxyquinolone (1; $R^1$ = Me, $R^2$ = H) [18] (2·6 g) in chloroform (30 ml) was treated with (+)-peroxycamphoric acid (5·0 g) in chloroform (20 ml). The solution was kept at 25° for 3 days, diluted with chloroform (20 ml) and extracted with 2N-

[13] M. Terasaka, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 523.
[14] J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621; M. F. Grundon and K. J. James, *ibid.*, 1971, 1311.
[15] T. O. Soine and F. H. Jawad, *J. Pharm. Sci.*, 1964, **53**, 990; K. H. Lee and T. O. Soine, *ibid.*, 1968, **51**, 865.
[16] J. Lemmich and B. E. Nielsen, *Tetrahedron Letters*, 1969, 3.
[17] K. Hata and K. Sano, *Tetrahedron Letters*, 1966, 1461.
[18] E. A. Clarke and M. F. Grundon, *J. Chem. Soc.*, 1964, 438.

sodium hydroxide (6 × 20 ml). The chloroform solution was extracted with 2N-hydrochloric acid (4 × 20 ml) and the aqueous solution was washed with chloroform and made alkaline. The alkaline solution was immediately extracted with chloroform (3 × 30 ml). Evaporation of the solvent, chromatography of the residue on alumina, and elution with ethanol–chloroform (5 : 95) gave balfourodine (1·44 g, 41%), m.p. 178—183°, $[\alpha]_D$ +4·6° (EtOH) (9·3% optical induction) {lit.,[5] m.p. 187—189° for racemate; lit.,[4] m.p. 191—192° and $[\alpha]_D$ +49° (EtOH) for (+)-balfourodine; lit.,[3] m.p. 201—203° and $[\alpha]_D$ −14·6° for hydroxylunacrine perchlorate}. The i.r. spectrum was identical with that of (±)-balfourodine.

Crystallisation of a sample (1·3 g) from ethyl acetate gave (±)-balfourodine in needles (1·1 g), m.p. 184—186°. The filtrate was evaporated and the residue was chromatographed on alumina as before to give (+)-balfourodine (0·1 g), m.p. 178—182°, $[\alpha]_D$ +19·5° (EtOH).

Balfourodine containing an excess of the (+)-enantiomer or of the (−)-enantiomer was prepared by use of a variety of optically active peroxy-acids. The results are given in the Table. The quinoline (1; $R^1$ = Me, $R^2$ = H) (200 mg) was epoxidised at 24·8° with a two-fold excess of peroxy-acid. Each % optical induction quoted in the Table is the mean of two experiments, and allowance is made for the degree of optical purity of the peroxy-acid.

| Peroxy-acid | Sign of rotation of balfourodine | % Induction of balfourodine |
|---|---|---|
| (+)-(*S*)-Peroxycamphoric acid | + | 6·1 |
| (−)-(*R*)-Peroxycamphoric acid | − | 5·8 |
| (+)-(*S*)-Peroxyhydratropic acid | + | 3·2 |
| (−)-(*R*)-Peroxyhydratropic acid | − | 2·1 |
| (+)-(*R*)-Norbornane-2-*endo*-peroxy-carboxylic acid | − | 4·9 |
| (−)-(*S*)-Norbornane-2-*endo*-peroxy-carboxylic acid | + | 5·3 |

*O-Methylbalfourodinium Salts and (−)-Balfourolone.*—(*a*) (+)-Balfourodine (1·0 g), $[\alpha]_D$ +4·6°, in methyl iodide (20 ml) was refluxed for 4 h. Evaporation gave *O*-methylbalfourodinium iodide (1·5 g), m.p. 152—153° (lit.,[5] 152—153°), identical (mixed m.p. and i.r. spectrum) with an authentic sample. Sparing solubility prevented determination of its optical activity. Treatment of the methiodide (0·3 g) with 2N-sodium hydroxide at 25° furnished balfourolone in prisms (from hexane), m.p. and mixed m.p. 96—98°, $[\alpha]_D$ −0·95° ($CHCl_3$) {lit.,[4] for (−)-balfourolone, m.p. 99—100°, $[\alpha]_D$ −36° (EtOH); lit.,[19] for (±)-balfourolone, m.p. 97—98°}.

(*b*) The *N*-methyl-4-methoxyquinolone (1; $R^1$ = $R^2$ = Me) [18] (1·55 g) in ether (15 ml) and (+)-peroxycamphoric acid (2·8 g) in ether (15 ml) were mixed and kept at −18° for 2 weeks. Work-up as described for the (±)-compound gave *O*-methylbalfourodinium perchlorate (0·87 g), m.p. 204—205°. Reaction of the perchlorate with base, as described for the methiodide, afforded balfourolone in prisms (from hexane), m.p. 96—98°, $[\alpha]_D$ −0·28° (0·8% optical purity).

The perchlorate (425 mg) in acetone–methanol (1 : 1) was passed through an ion-exchange column [Amberlite IRA 400 ($Cl^-$)] to give the crude chloride, m.p. 115—150° (decomp.). Brief heating of the chloride at 150° gave balfourodine, m.p. 181—184°, $[\alpha]_D$ +0·43° (EtOH) (0·9% optical purity).

(−)-*Isobalfourodine* (3).—(*a*) The 4-methoxyquinolone (1; $R^1$ = N, $R^2$ = Me) [18] was treated with (+)-peroxycamphoric acid in ether–dichloromethane (3 : 1) at −18° for 2 weeks or in chloroform at 25° for 3 days; by the method described previously [6] there were obtained the pyrano-derivative (2), m.p. 147—149°, $[\alpha]_D$ −1·48° ($CHCl_3$) and the furo-compound (5; $R^1$ = H, $R^2$ = OMe), m.p. 166—169°, $[\alpha]_D$ +1·83° ($CHCl_3$). The products were converted, respectively, into (−)-isobalfourodine, m.p. 182—184° (from ethyl acetate), $[\alpha]_D$ −1·45° (EtOH) (9·7% optical purity), and (+)-balfourodine, m.p. 184—186°, $[\alpha]_D$ +2·34° (EtOH) (4·7% optical purity).

(+)-*Isobalfourodine* (9).—(*a*) By the method of Rapoport and Holden,[4] (+)-balfourodine, $[\alpha]_D$ +2·19° (4·5% optically pure) was converted into isobalfourodine acetate, $[\alpha]_D$ +0·7° (EtOH). Saponification, chromatography of the product on alumina, and elution with chloroform–methanol (3 : 1) afforded isobalfourodine, m.p. 183—185° (from ethyl acetate), $[\alpha]_D$ +0·41° (EtOH) (2·8% optically pure).

(*b*) A solution of balfourolone (8) (0·32 g), $[\alpha]_D$ −1·15°, in 20% hydrochloric acid (10 ml) was refluxed for 5 h and made alkaline with sodium hydroxide. The product obtained with dichloromethane was chromatographed on alumina and afforded isobalfourodine (0·057 g), m.p. 182—183° (from ethyl acetate), $[\alpha]_D$ +0·37° (EtOH), identical (mixed m.p. and i.r. spectrum) with an authentic sample.

2-(1-*Acetoxy*-1-*methylethyl*)-2,3-*dihydro*-4,8-*dimethoxyfuro*-[2,3-b]*quinoline* (5; $R^1$ = Ac, $R^2$ = OMe).—A solution of the tertiary alcohol (5; $R^1$ = H, $R^2$ = OMe) (100 mg) in pyridine (0·8 ml) and acetic anhydride (3·5 ml) was refluxed for 3 h and then added to water (20 ml). The aqueous solution was brought to pH 8 by addition of sodium carbonate. Extraction with dichloromethane afforded the *acetate* (112 mg), separating from ethyl acetate–light petroleum (b.p. 60—80°) in needles, m.p. 160—165° (decomp.), $\nu_{max.}$ (KBr) 1745 $cm^{-1}$ (OAc), τ ($CDCl_3$) 5·76 (3H, s), 5·99 (3H, s), 6·38 (1H, q, $J_{AX}$ 9, $J_{AB}$ 17 Hz), 6·42 (1H, q, $J_{BX}$ 7 Hz), 5·02 (1H, t), 8·04 (3H, s), 8·36 (3H, s), and 8·43 (3H, s) (Found: C, 65·2; H, 6·6; N, 4·4. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4; N, 4·2%).

Hydrolysis with aqueous methanolic sodium hydroxide furnished the tertiary alcohol (5; $R^1$ = H, $R^2$ = OMe), m.p. and mixed m.p. 166—169°.

*Ozonolysis of (+)-Balfourodine, (+)-Isobalfourodine, and (−)-Balfourolone.*—By the procedure described previously for (+)-platydesminium metho-salt,[10] the three alkaloids were converted by ozonolysis into the hydroxy-lactone (10), shown to be homogeneous by g.l.c. and to be identical with an authentic sample [16] (n.m.r. and i.r. spectra and g.l.c.). (+)-Balfourodine, $[\alpha]_D$ +4·6°, gave the (+)-hydroxy-lactone (10), $[\alpha]_D$ +0·6° ($CHCl_3$), (+)-isobalfourodine, $[\alpha]_D$ +0·41°, gave the (+)-hydroxy-lactone, $[\alpha]_D$ +0·32°, and (−)-balfourolone, $[\alpha]_D$ −0·95°, gave the (+)-hydroxy-lactone, $[\alpha]_D$ +0·47°.

(−)-3-(3,3-*Dimethyloxiran*-2-*ylmethyl*)-2,4,8-*trimethoxy*-*quinoline* (12; $R^1$ = H, $R^2$ = OMe).—The trimethoxyquinoline (11; $R^1$ = H, $R^2$ = OMe) (1·05 g) [18] was treated with (+)-peroxycamphoric acid essentially as described [7] for the corresponding 7,8-methylenedioxy-derivative to give the *epoxide* (815 mg, 74%) in needles (from pentane), m.p. 78—80°, $[\alpha]_D$ −0·63° ($CHCl_3$), τ ($CDCl_3$) 2·46 (1H, q), 2·61—3·04 (2H, m), 5·82 (3H, s), 5·94 (3H, s), 6·01 (3H, s), 6·79—7·18 (2H, m), *ca.* 6·95 (1H), 8·55 (3H, s), and 8·69 (3H, s), (Found: C, 66·9; H, 7·2; N, 4·7. $C_{17}H_{21}NO_4$ requires C, 67·3; H, 7·0; N, 4·6%).

[19] E. A. Clarke, Ph.D. Thesis, Queen's University of Belfast, 1963.

(−)-3-(2-*Formyloxy*-3-*hydroxy*-3-*methylbutyl*)-2,4,8-*trimethoxyquinoline*.—As described for the corresponding 7,8-methylenedioxy-derivative,[7] the epoxide (12; $R^1$ = H, $R^2$ = OMe) (325 mg) was converted into the *monoformate* (209 mg, 60%), prisms [from ether–light petroleum (b.p. 40—60°)], m.p. 131—132°, $[\alpha]_D$ −0·17° ($CHCl_3$), $\nu_{max.}$ (KBr) 1720 $cm^{-1}$ (HCO·O), τ ($CDCl_3$) 2·11 (1H, s, HCO·O), 5·99 (3H, s), 6·72 (1H, q, $J_{AX}$ 10, $J_{AB}$ 14·5 Hz), 6·95 (1H, q, $J_{BX}$ 3 Hz), 4·65 (1H, q), 8·00 (1H, s, OH), 8·62 (3H, s), and 8·66 (3H, s) (Found: C, 61·5; H, 6·7; N, 4·1. $C_{18}H_{23}NO_6$ requires C, 61·9; H, 6·7; N, 4·0%).

(+)-3-(2,3-*Dihydroxy*-3-*methylbutyl*)-2,4,8-*trimethoxyquinoline* (14; $R^1$ = H, $R^2$ = OMe).—As described for the corresponding methylenedioxy-derivative,[7] the monoformate was converted quantitatively into the diol, needles (from di-isopropyl ether), m.p. 135—136°, $[\alpha]_D$ +0·68° ($CHCl_3$), τ ($CDCl_3$) 2·47 (1H, q), 2·58—3·04 (2H, m), 5·82 (3H, s), 5·94 (3H, s), 5·99 (3H, s), 6·29 (1H, q), 6·97 (1H, q, $J_{AX}$ 9, $J_{AB}$ 14·5 Hz), 7·08 (1H, q, $J_{BX}$ 3 Hz), 7·27 (1H, s, OH), 7·65 (1H, s, OH), and 8·66 (s, 6H).

(+)-3-(2,3-*Dihydroxy*-3-*methylbutyl*)-4,8-*dimethoxy*-2-*quinolone* (13).—A solution of the diol (14; $R^1$ = H, $R^2$ = OMe) (260 mg) ($[\alpha]_D$ +0·95°) in ether (100 ml) was saturated with dry hydrogen chloride and kept for 12 h at 25°. After evaporation of the solution, the residue in dichloromethane was washed with N-sodium carbonate, and the solvent was evaporated. The product, after heating with ether and filtration, gave the 2-*quinolone* as a solid (155 mg, 62%), $[\alpha]_D$ +0·43° (EtOH), separating from methanol–ether in needles, m.p. 182—183°, $\nu_{max.}$ (KBr) 1635 $cm^{-1}$ (Found: C, 62·4; H, 6·7. $C_{16}H_{21}NO_5$ requires C, 62·5; H, 6·9%).

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