Quinoline Alkaloids. Part 17.[1] Mechanism of Base-catalysed Rearrangement of Hydroxyisopropyldihydrofuroquinolones and of Dihydrodimethylpyranoquinolones [2]

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A re-investigation of the stereospecific base-catalysed rearrangement of (+)-(*R*)-balfourodine (1) and of (+)-(*R*)-isobalfourodine (8) has resulted in improved methods of preparing (+)- and (−)-*ψ*-balfourodine, in establishing the absolute stereochemistry of the rearrangement products, and in trapping an epoxide intermediate as its methyl ether (9); a new mechanism for rearrangement is proposed.

THE hydroxyisopropyldihydrofuroquinoline alkaloid (+)-balfourodine (1) and its dihydropyrano-isomer (+)-isobalfourodine (8) were isolated from *Balfourodendron riedelianum* Engl. by Rapoport and Holden,[3,4] These authors studied the stereospecific base-catalysed rearrangements of the alkaloids,[4] and showed that (+)-balfourodine (1) † was converted into a mixture of the angular isomers, (+)-*ψ*-balfourodine (4) and (−)-*ψ*-isobalfourodine (7), while (+)-isobalfourodine (8) on refluxing in concentrated alkali gave (+)-*ψ*-isobalfourodine (14). A mechanism was proposed involving substitution by hydroxy-ion at the carbon atom adjacent to nitrogen (*cf.* Scheme 1). According to this mechanism the chiral centres are not affected; since optically antipodal *ψ*-isobalfourodines were obtained from (+)-balfourodine and (+)-isobalfourodine, it was concluded that the alkaloids had ' opposite ' absolute configurations. The establishing of (*R*)-configurations for (+)-balfourodine (1) and (+)-isobalfourodine (8) [5] means that the proposed mechanism (Scheme 1) is no longer tenable; this has prompted us to re-examine the rearrangement reactions.

Rearrangements of dihydrofuro- and dihydropyrano-quinolines

Reactant	Reagent [a]	Product	Reference
(+)-(*R*)-Balfourodine	A or B	(+)-(*R*)-*ψ*-balfourodine	This work
(+)-(*R*)-Balfourodine	C	(−)-(*S*)-*ψ*-isobalfourodine	This work
(+)-(*R*)-*ψ*-Balfourodine	C	(−)-(*S*)-*ψ*-isobalfourodine	This work
(−)-*N*-Methylorixidinine (19)	C	iso-*N*-methylorixidinine (20)	10
(+)-(*R*)-Isobalfourodine	B	(−)-(*S*)-*ψ*-balfourodine	This work
(+)-(*R*)-Isobalfourodine	C	(+)-(*R*)-*ψ*-isobalfourodine	4
(*R*)-Isobalfourodine methosulphate	D	(−)-(*S*)-*ψ*-balfourodine	4
Dubinine acetate (22)	C	dihydropyrano-2-quinolone (24)	11

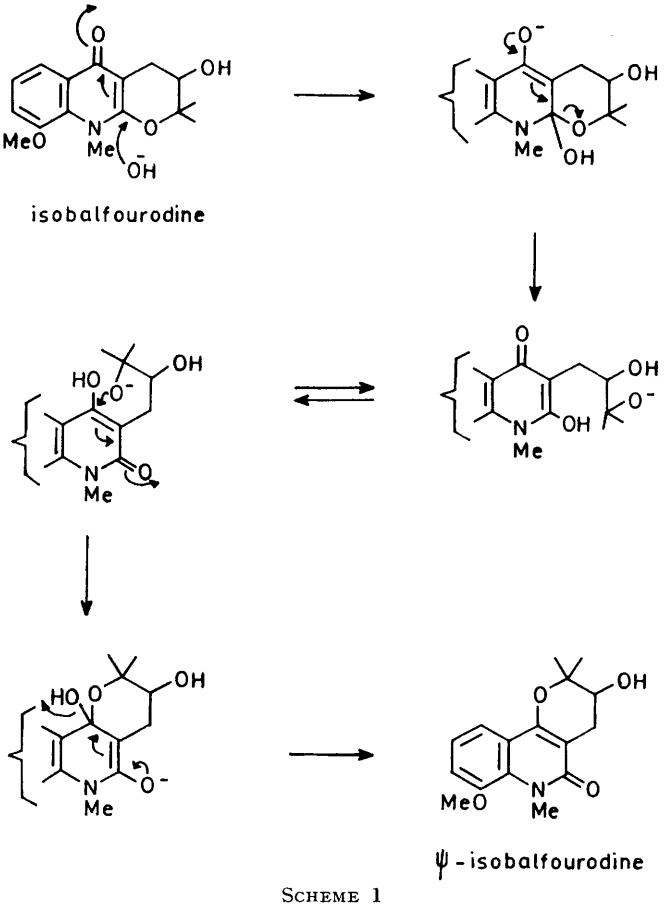
[a] A, NaH in DMF at 50°; B, NaOMe in DMF at 20°; C, reflux in 20—30% NaOH or KOH in methanol, ethanol, or aqueous ethanol; D, warm NaOH in aqueous methanol.

(+)-Balfourodine (1) (8.1% optical purity) and (+)-isobalfourodine (8) (4.8% optical purity) were prepared by asymmetric synthesis as described previously.[5] We have developed improved methods of preparing the angular compounds (Table). Thus, treatment of (+)-balfourodine (1) with sodium hydride or with sodium methoxide in dimethylformamide at 50 and 15 °C, respectively, furnished (+)-*ψ*-balfourodine (4) (96%). When (+)-balfourodine was heated with 2N-methanolic sodium hydroxide for 4 h, *ψ*-balfourodine (37%) was again formed but (−)-*ψ*-isobalfourodine (7) (32%) was also isolated. Prolonged reflux of (+)-balfourodine or of (+)-*ψ*-balfourodine with more concentrated alkali afforded (−)-*ψ*-isobalfourodine (7) quantitatively. It thus appears that the primary rearrangement product is (+)-*ψ*-balfourodine (4), which is then converted into (−)-*ψ*-isobalfourodine (7). The rearrangement of (+)-isobalfourodine (8) was also studied; it is already known that rigorous treatment with ethanolic potassium hydroxide yields (+)-*ψ*-isobalfourodine (14) [4] and we now find that (+)-isobalfourodine is converted into (−)-*ψ*-balfourodine (10) (80%) by reaction with sodium methoxide in dimethylformamide at 20 °C. (−)-*ψ*-Isobalfourodine is unaffected by treatment with sodium methoxide. These results (Scheme 2) indicate that starting with either balfourodine or isobalfourodine, *ψ*-balfourodine is formed at 20 °C under kinetic control and that the thermodynamically more stable *ψ*-isobalfourodine results from an equilibrium-controlled reaction at elevated temperatures.

ψ-Balfourodine and *ψ*-isobalfourodine were previously assigned structures (4) and (7), respectively, on the basis of their u.v. and i.r. spectra and of their formation from balfourodine.[4] We have now confirmed the structures of the angular compounds by n.m.r. spectroscopy. Neither compound shows low-field aromatic resonances typical of 4-quinolones containing a proton at C-5. In the spectrum of *ψ*-balfourodine, the doublet at τ 6.80 (J_{AX} = J_{BX} = 9.5 Hz) and the triplet at τ 5.10 (J 9.5 Hz) are characteristic of the ABX system ($ArCH_2$–CH–O–)

† Chart 1 in ref. 4, summarising the rearrangements of balfourodine, refers to the (−)-enantiomer; it is now known, however, that the products formed with acetic anhydride in pyridine [5] and with base (see below) are derived from (+)-balfourodine, and in any case there is no indication that (−)-balfourodine was available to the original investigators. Discussion with Professor Rapoport failed to resolve this inconsistency, but it seems probable that (−)-balfourodine in ref. 4 is a misprint for the (+)-balfourodine that is a constituent of *B. riedelianum*.

present in hydroxyisopropyldihydrofuroquinolines.[6] ψ-Balfourodine, in contrast to balfourodine (1),[4] did not react with acetic anhydride. The n.m.r. spectrum of ψ-isobalfourodine (7) (see Experimental section) was less informative due to the overlap of signals, but the spectrum of the acetate showed doublets at τ 7.10 and 7.19 (Ar–CH_2–) and a triplet at τ 4.80 (>C*H*–OAc), thus confirming that ψ-isobalfourodine contains a secondary alcohol function.



SCHEME 1

In relation to the mechanism of rearrangement it was clearly important to establish the absolute stereochemistry of ψ-balfourodine and ψ-isobalfourodine. It was shown previously that ozonolysis of hydroxyisopropyldihydrofuroquinoline alkaloids, *e.g.* balfourodine (1), and of hydroxydihydrodimethylpyranoquinoline alkaloids, *e.g.* isobalfourodine (8), afforded the (*R*)-hydroxylactone (3) or its (*S*)-enantiomer (6) with retention of configuration at the chiral centre;[5,7a] the same lactones are obtained from related hemiterpenoid coumarins.[7b] The procedure has been widely used to determine the configuration of quinoline alkaloids and of natural coumarins, and has now been applied to ψ-balfourodine and to ψ-isobalfourodine. ψ-Balfourodine containing an excess of the (+)-enantiomer was ozonised at 0 °C; oxidative decomposition of the ozonide furnished the (+)-(*R*)-hydroxylactone (3), thus establishing (*R*)-configuration (4) for (+)-ψ-balfourodine. (−)-ψ-Isobalfourodine was similarly shown to have (*S*)-configuration (7) by ozonolysis to the (−)-(*S*)-hydroxylactone (6).

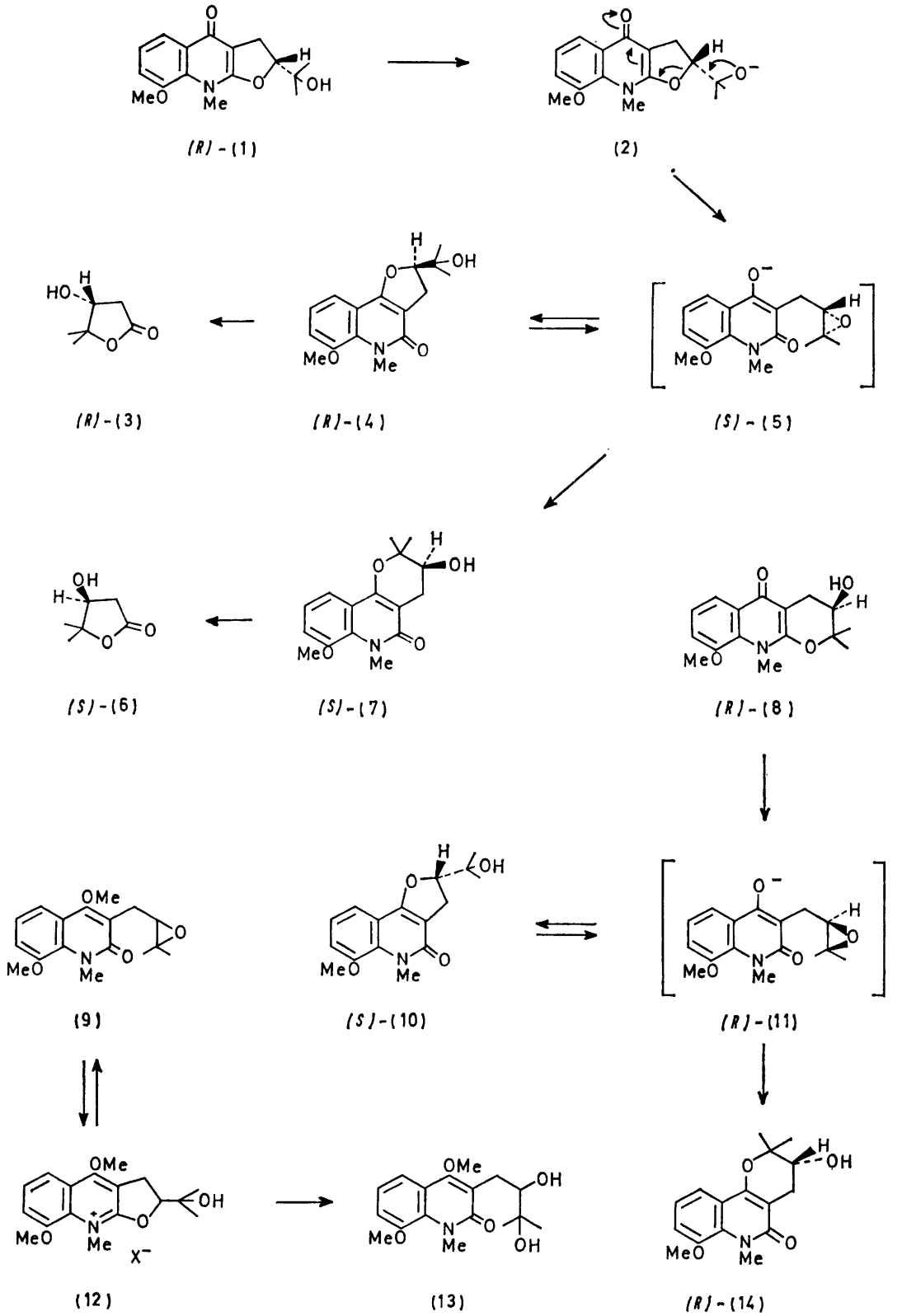
On the basis of the stereochemical relationships of the isomeric compounds (1), (4), (7), (8), (10), and (14) mechanisms for the base-catalysed rearrangements are now proposed (Scheme 2) in which reaction of (+)-(*R*)-balfourodine with base occurs with inversion of configuration to give an (*S*)-epoxide (5). Two possible reactions follow; an internal nucleophilic attack at the secondary carbon atom of the side-chain in (5), also occurring with inversion of configuration, giving (+)-(*R*)-ψ-balfourodine (4), or reaction at the tertiary carbon atom of epoxide (5) leading to (−)-(*S*)-ψ-isobalfourodine (7), without affecting the chiral centres. A similar argument applied to the rearrangement of (+)-(*R*)-isobalfourodine (8) accounts for the formation of (−)-(*S*)-ψ-balfourodine (10) and (+)-(*R*)-ψ-isobalfourodine (14) *via* an (*R*)-epoxide (11). Thus, intramolecular reaction of the oxygen anion of (8) at the tertiary carbon atom leads to cleavage of the pyran ring and formation of epoxide (11) with retention of configuration. Ring closure of (*R*)-epoxide (11) then occurs by a kinetically-controlled internal nucleophilic attack at the secondary carbon atom of the epoxide ring, resulting in the formation of (*S*)-ψ-balfourodine (10) with inversion of configuration; alternatively, reaction under equilibrium control at the tertiary carbon atom of epoxide (11) affords (*R*)-ψ-isobalfourodine (14) without affecting the chiral centre. In fact, this epoxide mechanism correctly predicts the stereochemistry of each product obtained (Table).

In order to trap the proposed epoxide intermediate (5), (+)-balfourodine (1) in dimethylformamide at 20 °C was treated with sodium hydride in the presence of methyl iodide. The 4-methoxy-2-quinoline epoxide (9), contaminated with balfourolone (13), was obtained from this reaction; it was extremely sensitive to mild acid or basic conditions and was purified by chromatography on cellulose. Insufficient pure epoxide was obtained to carry out a reliable determination of optical rotation. The i.r. spectrum of epoxide (9) showed that hydroxy-groups were absent but a strong absorption at 1 646 cm^{-1} was consistent with the presence of a 2-quinolone function. The n.m.r. spectrum was similar to that of other prenyl epoxides, for example compound (15),[5] in showing well separated signals at τ 8.59 and 8.75 corresponding to non-equivalent methyl groups; the other three protons of the side-chain occurred as a multiplet at τ 6.70—7.18.

Corral and Orazi [8] prepared epoxide (17) by reaction of *O*-methylribalinium chloride (16) with sodium hydride, and we find that application of this procedure to *O*-methylbalfourodinium iodide, *cf.* (12), gives epoxide (9), identical with the compound obtained from balfourodine in the trapping experiment.

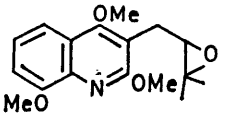
Two reactions of epoxide (9) provide further evidence for its structure. Thus, treatment with 2N-sodium hydroxide at ambient temperature gave balfourolone

(13) in high yield. A mechanism suggested for a similar reaction of epoxide (17) involved nucleophilic ring opening of the oxiran ring by hydroxide,[8] but the mild conditions of the reaction militates against this proposal



SCHEME 2

and the failure of 2,4-dimethoxyquinoline epoxides, *e.g.* compound (15), to react in this way suggests that the 2-quinolone oxygen atom participates. A reasonable

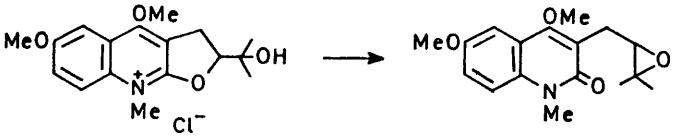


(15)

alternative mechanism (Scheme 2) involves *O*-methylbalfourodinium cation (12), which is known to give balfourolone (13) under the reaction conditions.[3] Addition of hydrogen iodide to a solution of epoxide (9) resulted in trapping of the intermediate *O*-methylbalfourodinium cation (12) as its iodide; this reaction supports the proposal that epoxide (9) is an intermediate in the oxidative cyclisation of the prenylquinoline (18) to the quaternary salt (12) by means of a peracid.[9]

Reaction of ψ-balfourodine (4) with sodium hydride in the presence of methyl iodide gave the epoxide (9), thus demonstrating the reversibility of the transformation, (5) ⟶ (4) and supporting the proposed mechanism (Scheme 2) for the conversion of ψ-balfourodine (4) into ψ-isobalfourodine (7).

The mechanism given in Scheme 2 is probably applicable to reactions related to the balfourodine-isobalfourodine rearrangements (Table). Thus, isobalfourodine



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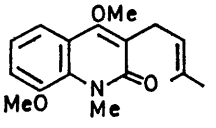
methosulphate on warming with 1M-sodium hydroxide in aqueous methanol was reported to give (+)-isobalfourodine (8) (73%) and (−)-ψ-balfourodine (10);[4] our



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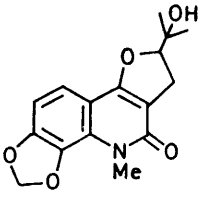
results suggest that the latter compound is formed from (+)-isobalfourodine in this reaction. In the 7,8-methylenedioxy series, *N*-methylorixidinine (19) is converted into the angular dihydropyrano-derivative (20).[10] The presence of 2- or 4-quinolone carbonyl groups is apparently a prerequisite for rearrangement, since the 4-methoxydihydrofuroquinoline (21) is unaffected by refluxing 20% methanolic potassium hydroxide. On the other hand, the 4-methoxyquinoline, dubinine acetate (22), on heating with base is reported to give the *N*-methyldihydropyranoquinolone (24);[11] a partial explanation of this result is that an intermediate *N*-methyl-4-quinolone (23) is converted into the product in a reaction similar to the balfourodine-ψ-isobalfourodine rearrangement, but the formation of the *N*-methylquinolone from a 4-methoxyquinoline precursor is less easily rationalised.



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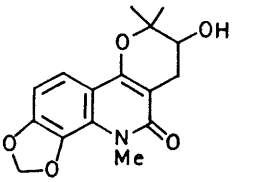

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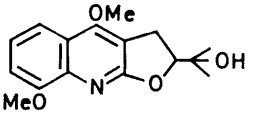

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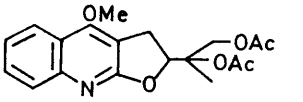

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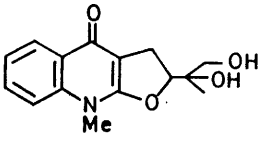

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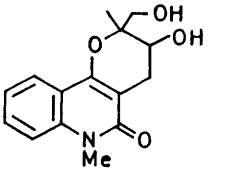

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EXPERIMENTAL

N.m.r. spectra were determined with Perkin-Elmer 60 MHz R 12 and R 10A spectrometers, with tetramethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer 121 electronic polarimeter.

(+)-*ψ-Balfourodine* (4).—A solution of (+)-balfourodine (1.1 g), $[\alpha]_D$ +4.0° (EtOH), and sodium methoxide (2.0 g) in dimethylformamide (30 ml) was stirred at room temperature for 4 h and diluted with water. Extraction with chloroform and chromatography on alumina [ether–chloroform (1 : 1) as solvent] gave ψ-balfourodine (1.04 g, 95%), as prisms, $[\alpha]_D$ +3.2° (EtOH), m.p. 171° [from chloroform–light petroleum (b.p. 40—60°)] {lit.,[4] m.p. 144—145° for ψ-balforodine, $[\alpha]_D$ +52°, mixed m.p. of (+)- and (−)-ψ-balfourodine, 165—168°}, $\nu_{max.}$ (KBr) 1 665 cm^{-1} [–(NMe)CO–], τ($CDCl_3$) 3.00—3.58 (3 H, m, aromatic), 5.10 (1 H, t, *J* 9.5 Hz, >C*H*–CH_2–), 6.05 (3 H, s, OMe or NMe), 6.08 (3 H, s, OMe or NMe), 6.80 [2 H, d, $\frac{1}{2}(J_{AX} + J_{BX})$ 9.5 Hz, >CH–CH_2–], 7.48br (1 H, s, OH), 8.60 (3 H, s), and 8.70 (3 H, s).

(+)-ψ-Balfourodine was also prepared by reaction of (+)-balfourodine with sodium methoxide in methanol at 15 °C for 20 h or with sodium hydride in dimethylformamide at 50 °C for 1.5 h.

(−)-*ψ-Balfourodine* (10).—(+)-Isobalfourodine (0.15 g), $[\alpha]_D$ +0.71° (EtOH) and sodium methoxide (0.35 g) in dimethylformamide (10 ml) was kept at 20 °C for 16 h. Usual work-up gave (−)-ψ-balfourodine (0.12 g, 80%), $[\alpha]_D$ −2.3° (EtOH).

(−)-*ψ-Isobalfourodine* (7).—(*a*) A solution of balfourodine (0.15 g), $[\alpha]_D$ +4.0° (EtOH), in methanol (8 ml) and 2N-

sodium hydroxide (28 ml) was refluxed for 4 h, and allowed to cool. Crystallisation of the precipitate from chloroform–hexane gave ψ-isobalfourodine (0.48 g, 32%), $[\alpha]_D$ −2.3° (EtOH), m.p. 189° [lit.,[4] m.p. 198° for (−)-ψ-isobalfourodine; mixed m.p. of (+)- and (−)-ψ-isobalfourodine, 190—191°], $\nu_{max.}$ 1 643 cm^{-1} [−(Me)CO−], τ($CDCl_3$) 2.28—2.97 (3 H, m, aromatic), 6.1 (4 H, >C*H*−CH_2− and OMe or NMe), 6.12 (3 H, s, OMe or NMe), 7.20 (3 H, >CH−CH_2− and OH), 8.59 (3 H, s), and 8.62 (3 H, s). The *acetate*, prepared by reaction of ψ-isobalfourodine with acetic anhydride and pyridine at 20 °C, separated from ether–hexane in prisms, m.p. 125—126°, $\nu_{max.}$ 1 737 (−OCOMe) and 1 638 cm^{-1} [−N(Me)CO−], τ($CDCl_3$) 2.17—2.98 (3 H, m, aromatic), 4.80 [1 H, t, *J* 5 Hz, −C*H*(OAc)−CH_2−], 6.02 (3 H, s, OMe or NMe), 6.08 (3 H, s, OMe or NMe), 7.10 and 7.19 [2 H, two d, ½(J_{AX} + J_{BX} 5 Hz], 7.95 (3 H, s, OAc), 8.47 (3 H, s), and 8.53 (3 H, s) (Found: C, 65.4; H, 6.5; N, 4.3. $C_{18}H_{21}NO_5$ requires C, 65.5; H, 6.4; N, 4.2%).

Neutralisation of the original filtrate, extraction with chloroform, and chromatography of the product on alumina gave ψ-balfourodine (0.055 g, 37%), m.p. 170°.

When balfourodine (1.3 g) was refluxed (15 h) with 20% methanolic potassium hydroxide (50 ml) under nitrogen, ψ-isobalfourodine (1.15 g, 88%), $[\alpha]_D$ −2.3°, m.p. 187—188°, was the only product obtained.

(*b*) Refluxing a solution of ψ-balfourodine (0.22 g), $[\alpha]_D$ +3.2° in 20% methanolic potassium hydroxide under nitrogen for 18 h gave ψ-isobalfourodine (0.204 g, 93%), $[\alpha]_D$ −2.2°.

Ozonolysis of ψ-Balfourodine and ψ-Isobalfourodine.—Ozonolysis of ψ-balfourodine (1.00 g), $[\alpha]_D$ +2.2°, by the method described previously [7] gave the hydroxylactone (3) (0.165 g, 37%), $[\alpha]_D$ +0.39° ($CHCl_3$), identical (i.r. and n.m.r.) with an authentic sample. A similar degradation of ψ-isobalfourodine, $[\alpha]_D$ −2.3°, gave the hydroxylactone (6), $[\alpha]_D$ −0.35° ($CHCl_3$).

Preparation and Reactions of Epoxide (9).—(*a*) Sodium hydride (0.055 g) was added to a solution of *O*-methylbalfourodinium iodide (0.36 g) in dimethylformamide (10 ml). After 1 h, the solution was evaporated and the residue was extracted repeatedly with hexane and ether; t.l.c. of the solution with chloroform–ethyl acetate (4 : 1) on alumina showed two spots, R_F 0.55 (balfourolone) and 0.70. Chromatography of the products on cellulose gave the epoxide (9) as an oil, R_F 0.70, $\nu_{max.}$ 1 646, 1 474, and 1 069 cm^{-1}, τ($CDCl_3$) 2.42—3.10 (3 H, m, aromatic), 6.07 (6 H, s, OMe and NMe), 6.70—7.18 (3 H, m, CH_2 and >CH−), 8.59 (3 H, s), and 8.75 (3 H, s).

(*b*) A mixture of balfourodine (0.3 g), methyl iodide (20 ml), sodium hydride (0.15 g), and dimethylformamide (20 ml) was kept for 2 h, filtered, and worked-up as in (*a*) to give epoxide (9). Similarly, ψ-balfourodine was converted into the epoxide.

(*c*) Epoxide (9) (0.028 g) in ether (2 ml) was treated dropwise with hydriodic acid. Crystallisation of the yellow precipitate from ethanol–ether gave *O*-methylbalfourodinium iodide (0.018 g, 43%), m.p. 150—151°, identical (mixed m.p. and i.r.) with an authentic sample.

(*d*) A solution of epoxide (9) (0.028 g) in methanol (2 ml) containing 2N-sodium hydroxide (1 ml) was kept for 20 h. Addition of water and extraction with ether gave balfourolone (13) (0.019 g, 64%), m.p. and mixed m.p. 95—96°.

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