Stereochemistry and Mechanism of Base-catalysed Rearrangement of Hydroxyisopropyldihydrofuranoquinolines. Trapping of an Epoxide Intermediate

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Summary The absolute stereochemistry of products from stereospecific base-catalysed rearrangement of (+)-*R*-balfourodine has been established and a suggested epoxide intermediate has been trapped as its methyl ether.

RAPOPORT AND HOLDEN[1] showed that when the quinoline alkaloids balfourodine and isobalfourodine were heated with aqueous ethanolic sodium hydroxide stereospecific rearrangement to angular isomers occurred. For example, balfourodine (**1**) afforded (−)-ψ-isobalfourodine (**7**). A

mechanism was suggested[1] involving nucleophilic reaction of hydroxide ion at the 2-position of the quinoline nucleus followed by cyclisations in which the chiral centres were not affected. It was concluded on the basis of these and other arrangements that balfourodine and isobalfourodine had "opposite absolute configurations". Since we have now shown that this is not the case,[2,3] it was of interest to re-examine the stereochemistry and mechanism of the base-catalysed rearrangements.

(+)-Balfourodine (**1**), obtained by asymmetric synthesis,[2] was converted at 20° with sodium hydride or with sodium methoxide into (+)-ψ-balfourodine (**4**) almost quantitatively. Prolonged reflux with ethanolic potassium hydroxide, however, resulted in formation of (−)-ψ-isobalfourodine (**7**); this was also the product of a similar reaction with (+)-ψ-balfourodine (**4**).

(+)-Balfourodine (**1**) is known to possess the *R*-configuration,[3] but in order to clarify the stereochemistry of the rearrangement it was necessary to establish the absolute configuration of the two angular isomers. This was accomplished by ozonolysis, whereby (+)-ψ-balfourodine (**4**) like (+)-(*R*)-balfourodine (**1**) was converted into the (+)-(*R*)-lactone (**5**)[3,4] and (−)-ψ-isobalfourodine (**7**) into the (−)-(*S*)-lactone (**10**). These results are consistent with the epoxide mechanism (**1**) → (**2**) → (**3**) → (**4**) or (**7**) shown in the scheme; according to this route, formation of ψ-balfourodine (**4**) involves two inversions and production of the pyrano-isomer (**7**) only one. It appears that reaction (**3**) → (**4**) is reversible, ψ-balfourodine (**4**) being formed at 20° under kinetic control and the more stable pyrano-compound (**7**) resulting from an equilibrium controlled reaction at the elevated temperature.

The suggested mechanism was supported by trapping the epoxide intermediate (**3**). Thus, reaction of (+)-balfourodine with sodium hydride at 20° in the presence of methyl iodide furnished the 4-methoxy-epoxide (**6**; R^1 = OMe, R^2 = H). Its structure was established first by the n.m.r. spectrum which resembled that of the 2,4-dimethoxy-epoxide (**8**)[5] and of the 4-methoxy-epoxide (**6**; R^1 = H, R^2 = OMe)[6] and secondly by its synthesis from *O*-methyl-balfourodinium iodide (**9**) by the method devised by Corral and Orazi[6] for the analogous epoxide (**6**; R^1 = H, R^2 = OMe). Treatment of ψ-balfourodine (**4**) with sodium hydride and methyl iodide resulted in partial conversion into the 4-methoxy-epoxide (**6**; R^1 = OMe, R^2 = H), thus demonstrating the reversibility of the transformation (**3**) → (**4**) and supporting the suggested mechanism for the ψ-balfourodine–ψ-isobalfourodine conversion.

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