A New Synthesis of 2,2-Dimethylchromenoquinolines from Epoxides: Synthesis of the Alkaloid Flindersine

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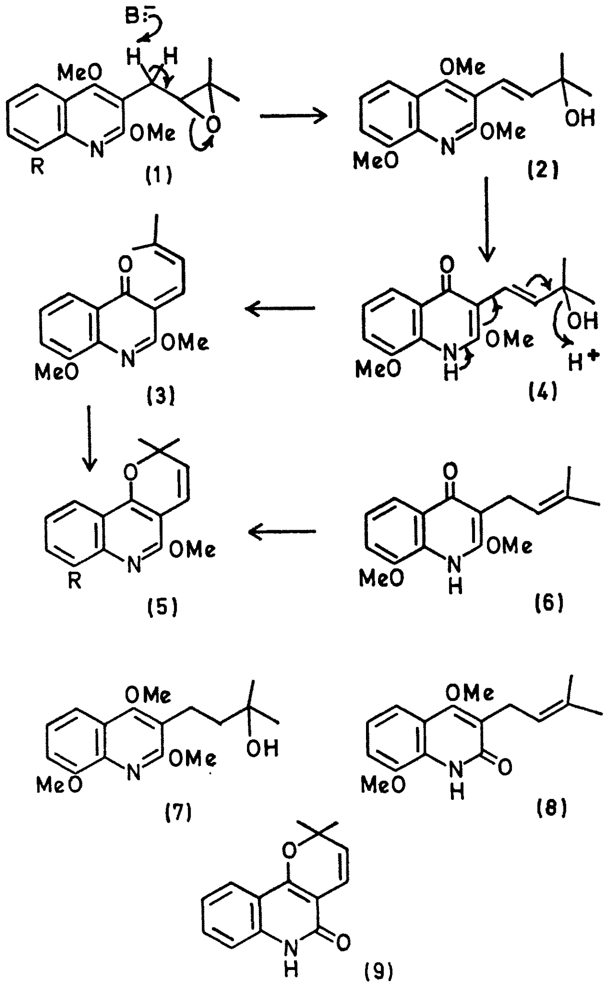
Summary Treatment of isopentenylquinoline epoxides with sodium hydroxide in dimethyl sulphoxide gave chromenoquinolines *via* allylic alcohol intermediates; this led to a new synthesis of the alkaloid, flindersine.

REACTION of the epoxide (**1**; R = OMe) with sodium hydroxide in aqueous dimethyl sulphoxide at 100°, followed by dilution with water gave a clear solution; neutralisation then afforded a precipitate of the 2,2-dimethylchromenoquinoline (**5**; R = OMe) in 74% yield. Spectroscopic data indicated the general structure of the compound but did not distinguish between the angular and linear tricyclic isomers. The product was shown to have the angular formulation (**5**; R = OMe) by an independent synthesis involving the reaction of the 4-quinolone (**6**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Since the chromene (**5**; R = OMe) is insoluble in aqueous sodium hydroxide it is not the initial product of the epoxide reaction but is only obtained in work-up. In fact, three steps in the formation of the chromene were revealed when the base-catalysed reaction of epoxide (**1**; R = OMe) was conducted in deuteriated solvents and followed by n.m.r. spectroscopy. The epoxide was converted rapidly into the allylic alcohol (**2**), which was isolated. Its constitution was indicated by comparison of the n.m.r. spectrum with that of similar alcohols,[1] and was supported by hydrogenation to the tertiary alcohol (**7**).[2] The mechanism shown for formation of the allylic alcohol (**2**) is similar to that described by Burness[3] for analogous reactions. Alcohol (**2**) was converted slowly into a base-soluble intermediate (**4**), which could not be isolated. The n.m.r. spectrum of the new compound was similar to that of alcohol (**2**), except that one less methoxyl resonance was present; resonance of the proton at C-5 indicated deshielding by a 4-quinolone carbonyl group. The structure of this intermediate was verified by heating the alkaline solution with dimethyl sulphate, thereby regenerating the 4-methoxyquinoline (**2**).



Cardillo *et al.*[4] obtained 2,2-dimethylchromenes by reaction of *o*-dimethylallylphenols with DDQ and suggested that quinone methides were intermediates. A similar quinone methide (**3**) is probably involved in the reaction of the 2-methoxy-4-quinolone (**6**) with DDQ and in the formation of chromene (**5**; R = OMe) that occurs on neutralisation of the alkaline solution of allylic alcohol (**4**). In our quinoline series, corresponding reactions leading to linear chromenoquinolines seem less likely to occur since formation of the requisite quinone methide involves disruption of the conjugated system. We find, indeed, that the 4-methoxy-2-quinolone (**8**) fails to react with DDQ.

The chromene (**5**; R = H) was obtained analogously from epoxide (**1**; R = H). Reaction of the chromene with aqueous hydrobromic acid gave the alkaloid, flindersine (**9**) in good yield.

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[2] G. A. Gray and M. F. Grundon, unpublished work.

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[4] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.