# The Mechanism of Biological C–C Bond Formation to Methoxy Groups; Biomimetic Cyclisation *via* Alkyloxyl Radicals

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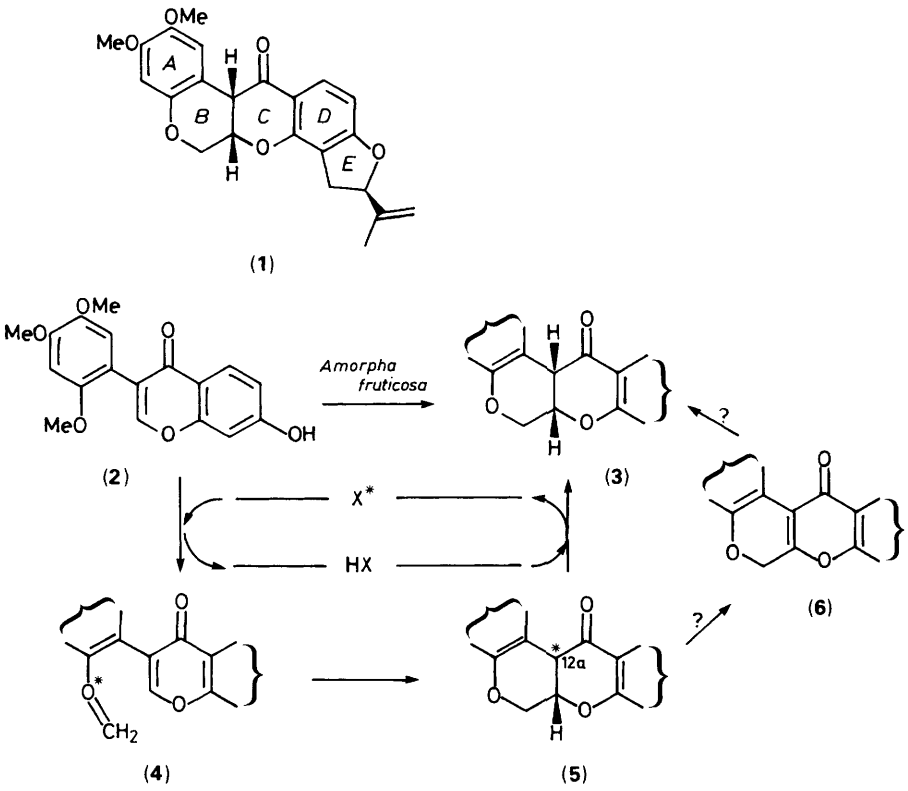
Aryl(methylene)oxyl radicals generated by decarboxylation of the thiohydroxamate ester (**8**) undergo 6-*endo* cyclisation, yielding ketones (**9**) and (**11**), mimicking an unusual biosynthetic conversion.

Extensive investigations into the biosynthesis[1] of rotenone (**1**) and its congeners in leguminous plants have revealed a remarkable enzyme-mediated reaction (Scheme 1) in which an *O*-methyl group of a precursor isoflavone (**2**) becomes the ring-*B* methylene of the rotenoid (**3**) by addition to a double bond in a net non-oxidative process. The favoured mechanism, on current information, requires abstraction of hydrogen to generate an intermediate cation or radical (**4**) whose



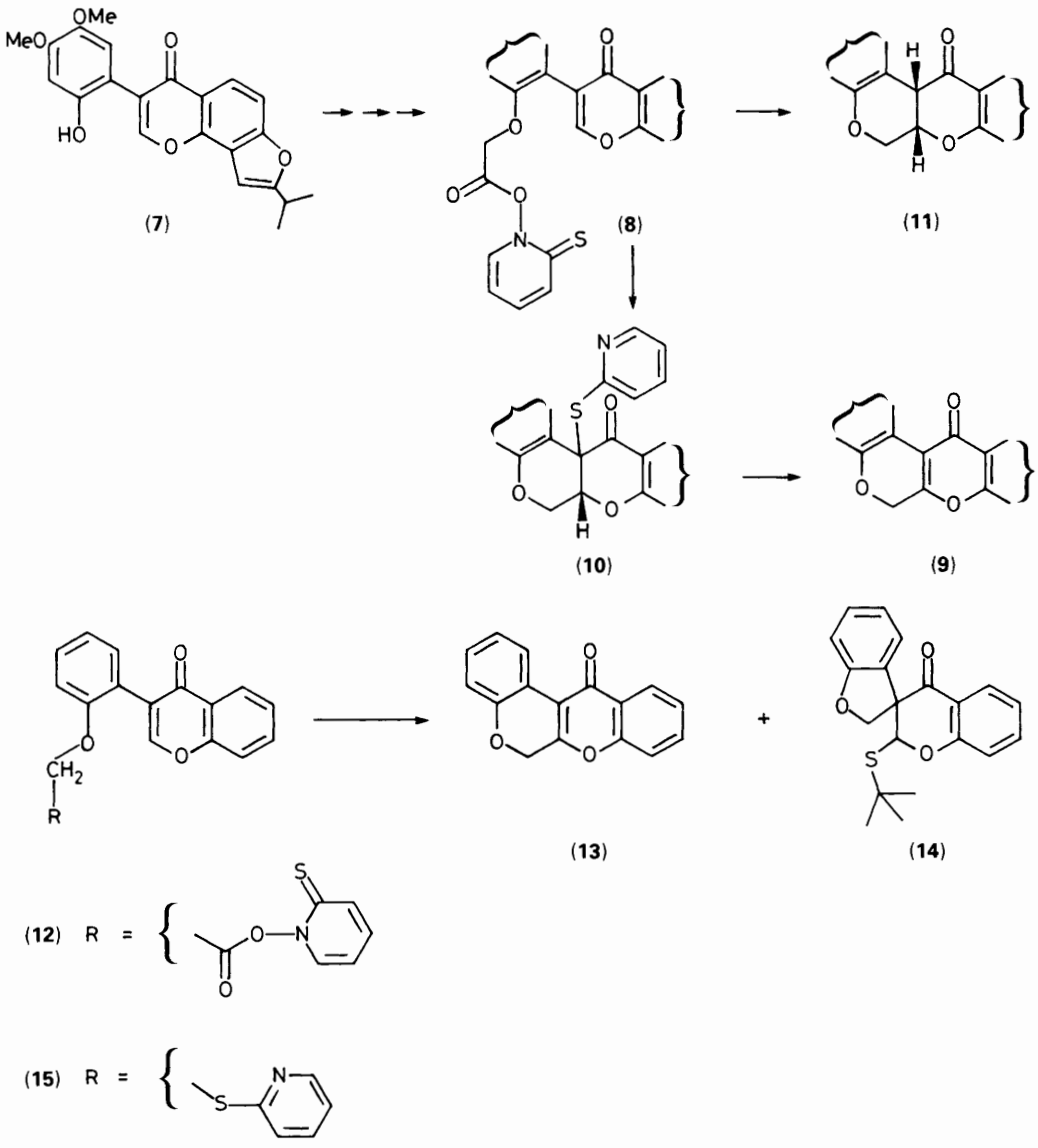

**Scheme 1**

cyclisation is followed by hydrogen return to C-12a. However the possibility cannot be rigorously excluded that intermediate (**5**) loses hydrogen to give a 6a,12a-didehydro species (**6**), reduced *in situ* to (**3**).

A similar sequence has been supported experimentally for the biosynthesis of eucomin[2] and related homoisoflavonoids, and circumstantial evidence (co-occurrence of metabolites) suggests that similar processes operate in the formation of stachyoidin,[3] scabequinone,[4] peltogynol,[5] cathedulin E3,[5] and interiorin.[7] The formation of the methylenedioxy function is a well known related reaction.[8] Some of these examples, at face value, involve a net non-oxidative process, while others require overall loss of hydrogen.

The nature of the intermediate (**4**) is central to the mechanism. It occurred to us that some light could be shed on this problem through an investigation of the viability of cyclisation of radicals and cations generated *in vitro*. In this Communication we address the radical aspect of the problem and report the fate of aryl(methylene)oxyl radicals (**4**; * = ·), showing that they can cyclise *via* a 6-*endo* pathway in a biomimetic fashion.

We chose to employ the methodology of Barton and collaborators[9] and to work, for convenience, in the isorotenone series as represented by isoflavone (**7**); this group contains the furan rather than the dihydrofuran ring *E*. Derritol isoflavone (**7**) was prepared by literature methods[10] and converted to the corresponding aryloxyacetic acid. The thioxopyridyl ester (**8**) was prepared *in situ*[9] and irradiated (tungsten lamp) in refluxing tetrahydrofuran solution (0.022 M) with t-butyl thiol (0.033 M) to afford a mixture containing one major product. This proved to be dehydroisorotenone (**9**), identified by comparison with authentic material; in further experiments the yield was raised to 60%. Under some conditions a little isorotenone (**11**) was also detected, with (**9**):(**11**) *ca.* 11:2. Under our experimental conditions it appears that the initially formed radical cyclises, *cf.* (**4**) → (**5**), and abstracts a pyridinethio moiety to form (**10**) which undergoes thermal elimination to the major product (**9**); a minor pathway can involve hydrogen abstraction from thiol to yield isorotenone (**11**). It is clear from this experiment that radicals of type (**4**) do undergo the desired biomimetic 6-*endo* cyclisation to form the rotenoid ring-*B*.



The synthetic isoflavone hydroxamate (**12**) was also investigated; it decomposed on irradiating a refluxing tetrahydrofuran solution (0.011 M) with t-butyl thiol (0.016 M) to produce two major compounds, 6a,12a-didehydrorotoxen-12-one (**13**)[11] (25%), and the thioacetal (**14**) (11%). The best explanation for this observation may be that the initial methyleneoxyl radical cyclised inefficiently (perhaps unaided by ring-*A* methoxy groups) and was also trapped to yield the sulphide (**15**). The latter then reacted with the thiol *via* polar conjugate addition with subsequent anionic displacement of 2-mercaptopyridine.

The formation of dehydrorotenoids in this chemistry may have further biosynthetic significance if it proves that these products, which have been isolated from natural sources, are formed in enzyme-mediated reactions and are not artefacts; their present status is equivocal.

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