Biomimetic Radical Ring Expansion and Aromatisation; a Model for the Biogenesis of Natural Ring-D Aromatic Steroids

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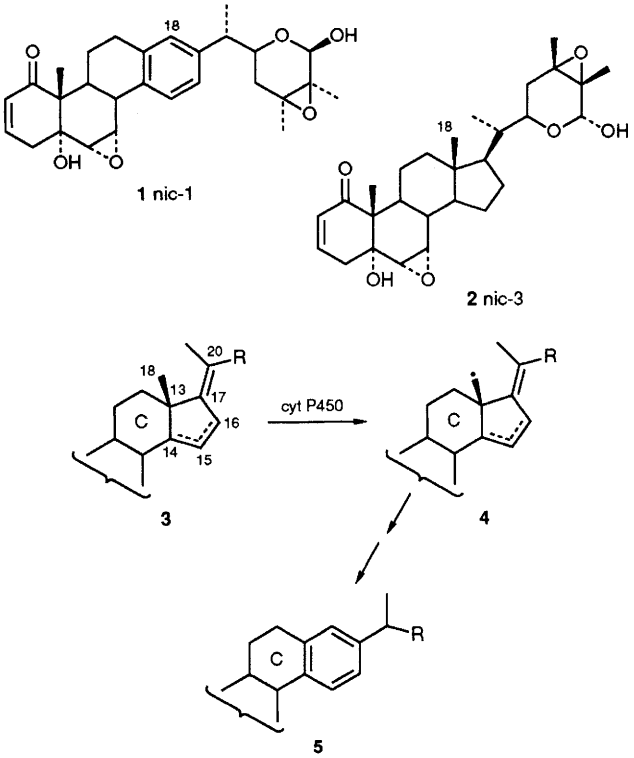
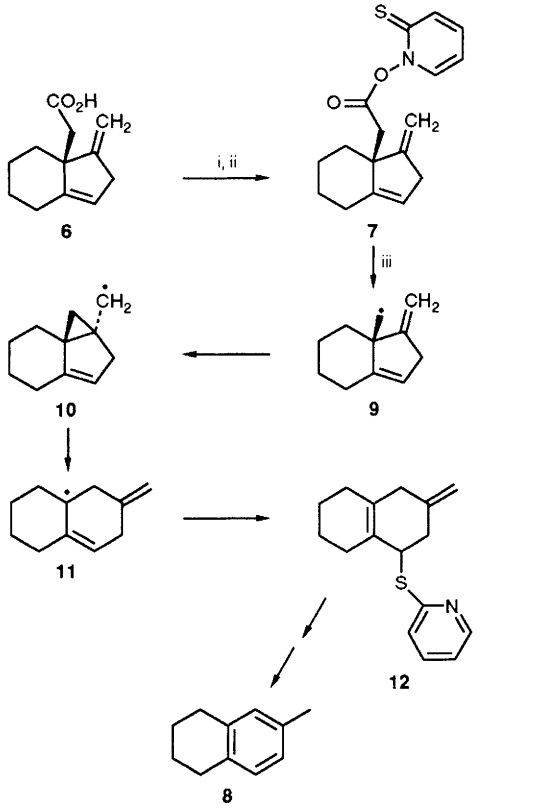
Photolysis of the thiohydroxamate **7** generated the carbon radical **9**, which rearranged and aromatised to the methyltetralin **8**, providing a model for the biogenesis of the insect antifeedant steroid nic-1 **1** from the conventional C/D precursor nic-3 **2**: photolysis of the isomeric thiohydroxamate **13** gave both methyltetralins **8** and **14**, through an unusual rearrangement sequence, possibly involving the benzvalene related radical **17**.

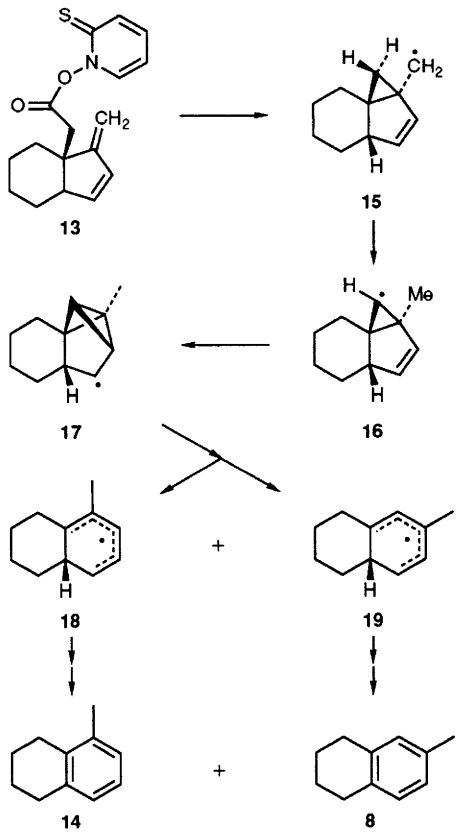
The withanolides[1] are an important group of plant steroids, which contain a 24-methyl cholestane skeleton modified by heavy oxidation, especially in the A/B rings and in the side chain, leading to a wide range of varied and complex structures. The nicandrenoides[1] comprise a small sub-group, from *Nicandra physaloides*, which includes the insect antifeedant nic-1 **1** and some derived relatives, which contain the unique feature of an aromatic ring-D which has incorporated the C/D angular methyl (C-18).[2] The biogenesis of nic-1 is most likely to involve the co-metabolite nic-3 **2** as its immediate precursor, with a late stage rearrangement–aromatisation sequence. Among various reasonable mechanisms for this sequence, that shown in Scheme 1 seemed to us to require serious consideration. In this hypothesis, two double bonds would be introduced into ring D **3** before rearrangement to facilitate subsequent aromatisation, which would be triggered by cytochrome P450 oxidation of the angular methyl to the corresponding radical **4**, the normal intermediate for hydroxylation. In the presence of a C-17(20) double bond and another at C-14(15) or C-15(16) radical ring expansion might ensue leading finally to the aromatic system **5**. Although



Scheme 1 Postulated biogenesis of nic-1



Scheme 2 Ring expansion and aromatisation *Reagents and conditions*: i, $(COCl)_2$, dimethylformamide (DMF), CH_2Cl_2; ii, 2-mercaptopyridine *N*-oxide sodium salt, 4-dimethylaminopyridine (DMAP), PhH, reflux, dark; iii, tungsten lamp, reflux, 1 h



Scheme 3 Ring expansion and rearrangement

'recoil' oxygenation of carbon radicals in cytochrome P450 hydroxylation is usually considered very fast,[3] we consider that a wide range of rates must be exhibited in secondary metabolism, where low substrate specificity prevails and substrates with relatively poor enyme 'fit' are processed. This view is supported by our results from investigations of biomimetic radical cyclisations to *O*-hererocycles.[4]

To test this postulate we have synthesised[1] two C/D model bicyclic structures, which allow specific generation of the required carbon radicals, using Barton decarboxylation methodology.[5] Scheme 2 displays the results obtained with the unconjugated diene acid **6**. This acid (22 mg) was converted into the corresponding thiohydroxamic ester **7** *via* treatment of the acid chloride with 2-mercaptopyridine *N*-oxide sodium salt, and **7** was irradiated in refluxing benzene with a tungsten lamp for 1 h. A major hydrocarbon product proved to be 6-methyltetralin **8**, by mass and ^{1}H NMR spectroscopy, and GLC comparison with authentic material.† The yield was 2–5% from **6**, in a process which must involve at least five distinct steps, mean yield *ca.* 50% per step. The likely mechanism is illustrated and involves photolysis to radical **9**, which rearranges to radical **11** by way of **10**. Trapping of **11** with 2-pyridinethiyl yields **12** or a regioisomer, and **12** aromatises by thermal elimination of 2-mercaptopyridine and prototropic shift(s).

These results show that the carbon radical based Scheme 1 is chemically feasible and is a plausible mechanism for biogenesis. In the chemical model the final double bond for aromaticity, after ring expansion, is introduced by capture of the 2-pyridinethiyl radical followed by elimination; in nature, this could be achieved by radical hydroxylation and elimination, or other means *e.g.* oxidation to a carbocation and deprotonation.

We also examined the photolysis of the conjugated diene thiohydroxamate **13**. A hydrocarbon product (23%, from the corresponding acid, over five steps) composed of a *ca*: 1:1 mixture of 6-methyltetralin **8** and the isomeric 5-methyltetralin **14** was obtained; the latter was also identified by spectroscopic and chromatographic comparisons with an authentic sample.† Currently, we interpret this result as shown in Scheme 3; formation of radical **15** is envisaged, followed by 1,3-hydrogen shift to form **16**, which is set up to generate the benzvalene-like radical **17**, collapse of which leads to both **18** and **19** and hence to the observed products. Further mechanistic studies of this process are in hand.

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