Non-Enzymatic Hydration, Amine Addition, and Oxidation Reactions of Aza-arene Oxides

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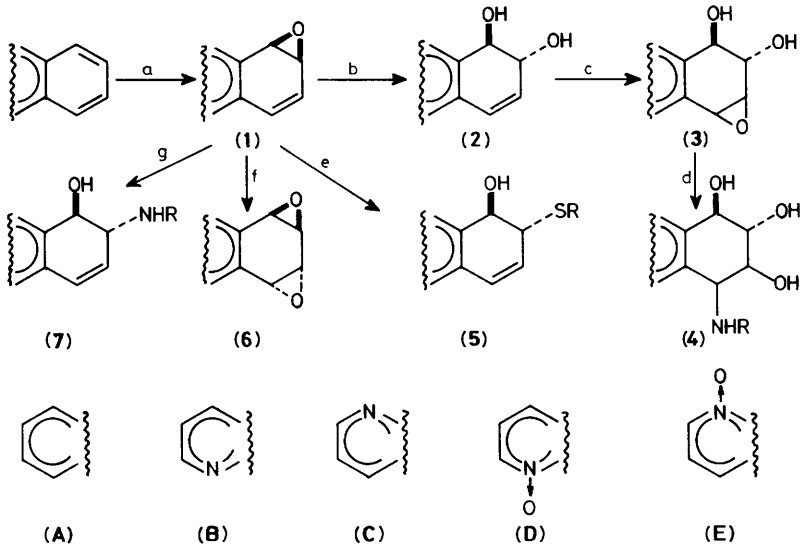
The 5,6- and 7,8-arene oxides of quinoline were found to undergo unusual addition reactions with water and primary amines at ambient temperature to yield *trans*-dihydrodiol and *trans*-hydroxyamine adducts respectively; oxygen atom addition yielded *N*-oxide and *trans*-5,6,7,8-dioxide derivatives.

Quinoline is a common environmental pollutant which is known to be both mutagenic and carcinogenic,[1] and to yield a range of mammalian metabolites including quinoline *N*-oxide,[1,2] quinoline 5,6-oxide (**1B**),[3] *trans*-5,6-dihydroxy-5,6-dihydroquinoline (**2B**),[1—3] and several quinolinols (2-, 3-, 6-, 8-hydroxyquinolines).[1,2,4]

Members of the polycyclic aromatic hydrocarbon (PAH) and azapolycyclic aromatic hydrocarbon (APAH) series have been found to follow common metabolic pathways in mammalian systems (Scheme 1).[5—7] All the isolated metabolites emanate from the initially formed arene oxide metabolite (**1**, step a). Arene oxides (**1**) in the PAH series [exemplified by naphthalene 1,2-oxide, (**1A**)] have previously been found to yield *trans*-hydroxy-thioether adducts by both enzymatic [(**5A**), *e.g.* R = glutathione] and non-enzymatic [(**5A**), *e.g.* R = Et] methods[6] (step e). Similarly, in the present study, the quinoline arene oxides (**1B**) and (**1C**) were rapidly converted into the *trans*-hydroxy-thioether adducts [(**5B**, **5C**) R = Bu^t, Bu^{t}SH–H_2O–NaOH, 70% yield] at ambient temperature. To date, however, no reports on the formation of *trans*-dihydrodiols [*e.g.* (**2A**)] by non-enzymatic reactions of arene oxides of type (**1**) are available. Similarly, although diol epoxides (**3**)



Scheme 1

formed in step c may undergo non-enzymatic addition reactions with amines,[5] to form amino-triols (**4**) (step d), the uncatalysed addition of amines to type (**1**) arene oxides has not previously been observed (Al_2O_3-catalysed addition of primary amines to non-K region arene oxides has been observed).[8]

The present communication reports on the non-enzymatic hydration (step b), amine addition (step g), and epoxidation (step f) or *N*-oxidation (**1B** → **1D**, **1C** → **1E**) reactions of arene oxides (**1**) in the polycyclic aza-arene series [exemplified by the 5,6-(**1B**) and 7,8-arene oxides (**1C**) of quinoline].

The base-catalysed addition of water to arene oxides (**1B**) and (**1C**) at *ca.* 20 °C was monitored by ^{1}H n.m.r. spectroscopy [300 MHz, 0.24 M KOH–D_2O –Bu^{t}OD (1 : 1)] and yielded the *trans*-dihydrodiols [(**2B**), $t_{\frac{1}{2}}$ 6 days] and [(**2C**), $t_{\frac{1}{2}}$ 4 days] respectively.† The lower stability of the *trans*-dihydrodiol (**2C**) led to some aromatization during isolation. This hydration reaction may be run at higher temperatures (40 °C) and thus provides a synthetically useful biomimetic route to the *trans*-dihydrodiol metabolite (**2B**) in isolated yields of *ca.* 50—55% after p.l.c. purification. These *trans*-dihydrodiols [(**2B**) and (**2C**)] have previously only been available by a synthetic route involving three additional steps.[3]

The addition of n-butylamine (pK_a 10.61) and aniline (pK_a 4.62) to arene oxides (**1B**) and (**1C**) at ambient temperature was found to yield mainly (>95%) the *trans*-hydroxyamine adducts [(**7B**), R = Bu or Ph] and [(**7C**), R = Bu or Ph] respectively. This addition reaction was found to be accelerated by using the amine as both solvent and nucleophile [*e.g.* $t_{\frac{1}{2}}$ = 6 h for addition of n-butylamine to quinoline 7,8-oxide (**1C**) at 40 °C]. The major product hydroxy amines [(**7B**), R = Bu or Ph; (**7C**), R = Bu or Ph] were isolated by p.l.c. (20—30% yield). Cellular amines including the nucleobases adenine and guanine which have been found to undergo non-enzymatic nucleophilic addition reactions with diol epoxide metabolites[5] (step d) may thus in principle also be capable of reacting directly with the arene oxide metabolites of quinoline (**1B**). The presence of a very small proportion (<5%) of the minor amine (or thiol) adducts formed by nucleophilic attack at the benzylic position of arene oxides (**1B**) and (**1C**) suggests that non-enzymatic hydration reactions also occur by preferential (>95%) attack of the hydroxide anion at the allylic position as found during enzyme catalysed hydration.

A common feature of nucleophilic attack by hydroxide anion or amines on arene oxides (**1B**) and (**2B**) is the faster reactivity with the epoxide moiety at the 7,8-position compared with the 5,6-position. This is presumably due to the stronger electron withdrawing effect of the pyridine ring on the epoxide at the 7,8-position. The electronegativity of the nitrogen atom in aza-arene oxides (**1B**) and (**1C**) can account for this enhanced reactivity toward nucleophiles and their stability in the presence of acids compared with normal arene oxides, *e.g.* (**1A**). The latter stability is reflected in the direct (h.p.l.c.) detection of an arene oxide metabolite of type (**1**), *i.e.* quinoline 5,6-oxide (**1B**).[3]

While naphthalene 1,2-oxide (**1A**)[9] and naphthalene *trans*-1,2;3,4-dioxide (**6A**)[7] have been found as enzymatically formed mammalian metabolites of naphthalene, and as chemical oxidation products of naphthalene,[10,11] the use of naphthalene 1,2-oxide (**1A**) as substrate for metachloroperoxybenzoic acid (MCPBA) oxidation results in acid-catalysed aromatization rather than epoxidation to yield the arene dioxide (**6A**). Using sodium hypochlorite[12] (NaOCl–CH_2Cl_2–Bu_4NHSO_4, 2 days, room temp.) as oxidant, the quinoline arene oxides [(**1B**) and (**1C**)] gave the *trans*-dioxide [(**6B**)/(**6C**), 56% yield] without *N*-oxidation. In contrast, MCPBA oxidation of the arene oxides (**1B**) and (**1C**) yielded regioselectively the arene oxide-*N*-oxide derivatives [(**1D**), 82% yield] and [(**1E**), 51% yield] respectively with the *trans*-diepoxide [(**6B**), (**6C**)] as a very minor product only. Further MCPBA oxidation of these arene oxide-*N*-oxide products [(**1D**), (**1E**)] yielded the *trans*-dioxide-*N*-oxide [(**6D**)/(**6E**)]. Preliminary results on the regioselective acid catalysed hydration of the arene dioxide (**6**) indicate that this compound is a convenient diol epoxide (**3**) precursor.

It is widely accepted[5] that bay region epoxy diol metabolites of polycyclic aromatic hydrocarbons play a prominent role in the covalent modification of nucleic acids and that this is ultimately responsible for the mutagenic and carcinogenic activity. Since quinoline does not possess a bay region its mutagenic/carcinogenic activity relative to naphthalene may reflect the formation of other types of metabolites or may be

† A detailed kinetic and product analysis study[13] has recently shown that this hydration reaction can occur under both basic [compounds (**1B**) and (**1C**)] and acidic [compound (**1B**)] conditions.

due to enhanced reactivity of the epoxydiol metabolites of quinoline. Following our characterization of the presently reported new adducts arising from nucleophilic addition of water and amines, and the *trans*-dioxide or *N*-oxide oxidation products, formed from the arene oxides of quinoline [(**1B**), (**1C**)] it will be of considerable interest to evaluate their biological activity and to establish whether they constitute minor metabolites of quinoline *in vivo*.

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