Synthesis of Arene Oxide and *trans*-Dihydrodiol Metabolites of Quinoline

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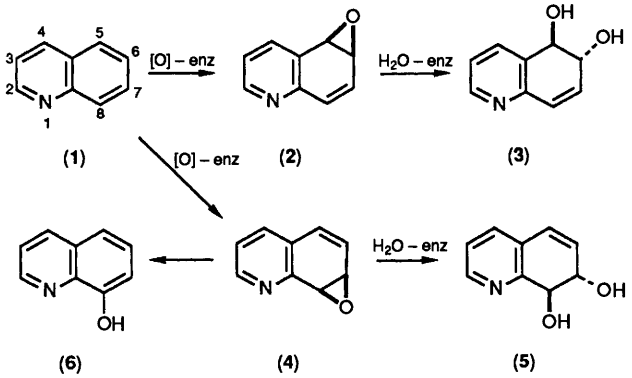
Racemic samples of 5,6-epoxy-5,6-dihydroquinoline (**2**) (quinoline 5,6-oxide) and 7,8-epoxy-7,8-dihydroquinoline (**4**) (quinoline 7,8-oxide) have been synthesised by two methods from the corresponding dihydroquinoline precursors. *trans*-5,6-Dihydroquinoline-5,6-diol (**3**) and *trans*-7,8-dihydroquinoline-7,8-diol (**5**) were obtained both by multi-step synthetic routes from the corresponding dihydroquinolines and by the direct base-catalysed hydration of the corresponding arene oxides (**2**) and (**4**).

Quinoline (**1**) is a major azapolycyclic aromatic hydrocarbon found in tobacco smoke,[1] urban particulates,[2] and automobile exhausts.[3] The prevalence of quinoline (**1**) in the environment,[1-3] allied to its mutagenic and carcinogenic[4] behaviour, has prompted the study of its metabolism in animal liver systems both from these[5] and other laboratories.[4] Prior to the preliminary report of the present study[5] the major metabolites were found to be the quinolin-2-, -3-, -6-, and -8-ols,[4,6,7] quinoline *N*-oxide,[4] and *trans*-5,6-dihydroquinoline-5,6-diol (**3**).[4,6] The initial formation of arene oxides of quinoline at the 5,6- and 7,8-positions could, in turn, account for the isolation of the *trans*-dihydro diol (**3**) and quinolin-8-ol (respectively) as metabolites (Scheme 1). In order to investigate further the formation of the dihydro diol (**3**) and the possible involvement of arene oxides (**2**) and (**4**), and the dihydro diol (**5**) in the metabolism of quinoline, and to determine the mechanism for the carcinogenicity of quinoline, a comprehensive synthetic programme has been undertaken. The initial phase of this programme to obtain authentic samples of the arene oxides (**2**) and (**4**), and the *trans*-dihydro diols (**3**) and (**5**) is presently reported.



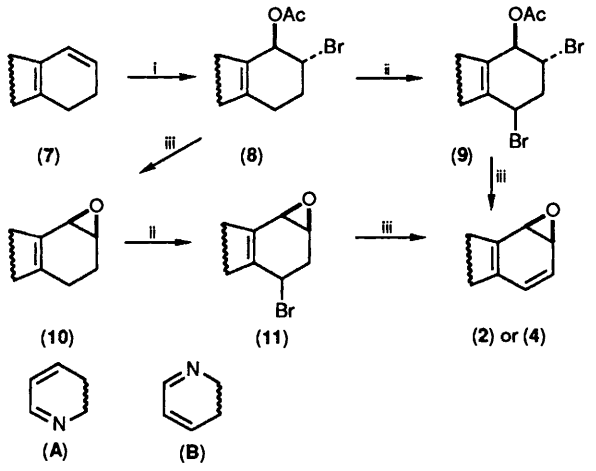
(1) (2) (3) (6) (4) (5)

Scheme 1.

Results and Discussion

The dihydroquinoline precursors (**7A**) and (**7B**) were each obtained by careful treatment of the corresponding alcohols with polyphosphoric acid (PPA).[8] Prolonged treatment of either alcohol with PPA yielded a mixtue of olefins (**7A**)/(**7B**) *via* an acid-catalysed isomerisation mechanism.

The oxides of quinoline (**2**) and (**4**) were obtained *via* the bromo acetate (**8**) and dibromo acetate (**9**) intermediates

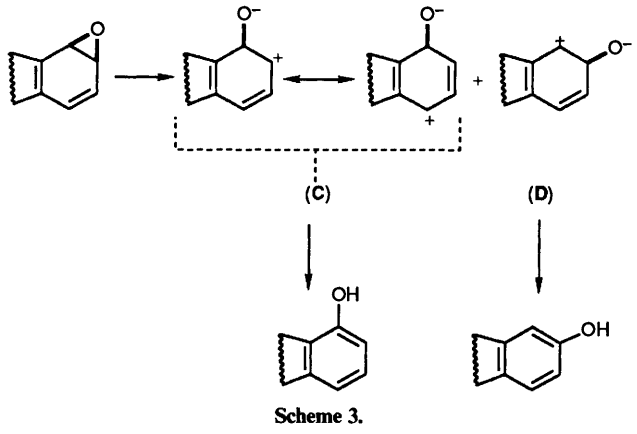


Scheme 2. *Reagents and conditions:* i, NBA/HOAc/LiOAC; ii, NBS/CCl_4; iii, NaOMe/THF.

(overall yield from (**7**), 56–74%) and *via* the tetrahydro epoxide (**10**) and bromo tetrahydro epoxide (**11**) intermediates (overall yield from (**7**), 59–65%) (Scheme 2). The latter synthetic routes to quinoline 5,6-oxide (**2**) and 7,8-oxide (**4**) were analogous to the methods previously reported for the synthesis of naphthalene 1,2-oxide and related arene oxides.[9]

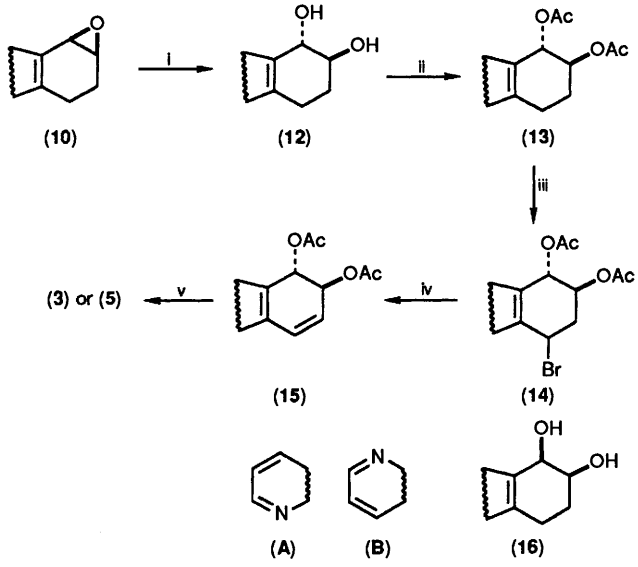
In contrast to most benzo-ring arene oxides of polycyclic aromatic hydrocarbons (PAHs), which are rather unstable compounds, the arene oxides (**2**) and (**4**) are remarkably stable, as much as 10^2–10^3 times less reactive than naphthalene 1,2-oxide under solvolytic conditions.[10] They withstand chromatographic purification on silica gel and are largely unchanged at ambient temperature in the crystalline state over a period of three weeks. The arene oxide (**2**) isomerized to a mixture of phenols at an elevated temperature (110 °C for 5 min). Capillary GLC–MS analysis of the trimethylsilyl ether derivatives indicated that quinolin-5-ol (86%) and quinolin-6-ol (14%) were formed. Similar thermal isomerisation of the arene oxide (**4**) yielded a mixture of quinolin-8-ol (95%) and quinolin-7-ol (5%).

The strong preference for the formation of quinolin-5- and -8-ols as aromatisation products of arene oxides (**2**) and (**4**) respectively can be rationalised in terms of the resonance stabilisation of dipole (**C**) relative to dipole (**D**) (Scheme 3) as



Scheme 3.

we have shown from HMO calculations of ΔE π/β.[10] A recent comprehensive kinetic study of the aromatisation of arene oxide (2) under aqueous acidic conditions also found a similar high proportion of quinolin-5-ol (93%) relative to quinolin-6-ol (7%). The arene oxide (4) gave quinolin-8-ol exclusively under these conditions.[10]



Scheme 4. *Reagents and conditions:* i, HCO_2H; ii, Ac_2O/pyridine; iii, NBS; iv, DBN/THF; v, NH_3/MeOH.

The tetrahydro epoxides (**10A**) and (**10B**) were hydrated using hot formic acid (70–80 °C) followed by base treatment, to yield mainly (≥95%) the desired *trans*-tetrahydro diols [(**12A**) and (**12B**) respectively]. ^{1}H NMR analysis of the crude product mixture also showed the presence of a very minor component (≤5%) which was identified as the *cis*-tetrahydro diol [(**16A**) and (**16B**) respectively] by comparison with authentic samples.[11] Recrystallisation of the product mixture of diols [(**12B**)/(**16B**)] yielded the pure *trans*-tetrahydro diol (**12B**). Purification of the *trans*-tetrahydro diol (**12A**) was carried out by a similar method, but was found to be more readily achieved by recrystallisation of the diacetate (**13A**). Both the tetrahydro diols (**12A**) and (**12B**) and tetrahydro diacetates (**13A**) and (**13B**) were stable compounds which could be readily purified and characterised. By contrast, the derived dihydro diacetates (**15A**) and (**15B**), and *trans*-dihydro diol (**5**) were all relatively unstable compounds which proved to be much more difficult to purify and characterise. The synthetic sequence from the tetrahydro epoxides (**10A**) and (**10B**) to the corresponding *trans*-dihydro diols (**3**) and (**5**) shown in Scheme 4 was similar to that previously used in other members of the PAH series, *e.g. trans*-8,9-dihydrobenz[*a*]anthracene-8,9-diol.[12]

trans-Dihydro diol (**3**) was more stable than the isomeric diol (**5**). Thus, the diol (**5**) was found to dehydrate to a mixture (*ca.* 9:1 respectively) of quinolin-8-ol and quinolin-7-ol over a period of several weeks at ambient temperature, while diol (**3**) remained unchanged under similar conditions.

A further synthetic route to the *trans*-dihydro diols (**3**) and (**5**) involved treatment of the corresponding arene oxides (**2**) and (**4**) with potassium hydroxide in t-butyl alcohol–water (1:1) at room temperature.[10,11] This reaction was monitored by ^{1}H NMR spectroscopy using KOD, Bu^{t}OD, and D_2O. The rate of hydration of arene oxide (**2**) was slower ($t_{\frac{1}{2}}$ 6 d) than that of the arene oxide (**4**), ($t_{\frac{1}{2}}$ 4 d). The less stable *trans*-dihydro diol (**5**) was found to undergo a significant degree (*ca.* 25%) of aromatisation during synthesis from the corresponding arene oxide (**4**) and could only be isolated in an overall yield of 26%. The greater stability of the *trans*-dihydro diol (**3**) allowed the base-catalysed hydration reaction to be completed at 40 °C (<48 h) or at 20 °C (<7 days) and in an isolated yield of (42–55%). Although the epoxide hydrolase-catalysed formation of *trans*-dihydro diol metabolites from arene oxides is well established (Scheme 1), the non-enzymatic hydration of non-K region arene oxides of similar general structure to arene oxides (**2**) and (**4**) has not previously been reported. The relative stability of the aza-arene oxides (**2**) and (**4**) may be an important factor in the success of these biomimetic hydrations. This stability can also account for the detection of arene oxide (**2**) as a metabolite of quinoline using a liver microsomal system in the presence of an epoxide hydrolase inhibitor.[5] The latter observation [5] is one of the few direct (by HPLC) detections of a non K-region arene oxide intermediate in the metabolism of an arene. Both arene oxides (**2**) and (**4**) were found to be acceptable substrates for the liver microsomal epoxide hydrolase enzyme and were converted into the corresponding *trans*-dihydro diols (**3**) and (**5**).[5] The rate of epoxide hydrolase-catalysed hydration of the arene oxide (**2**) was greater than that found for the arene oxide (**4**) by a factor of *ca.* 10.

The formation of quinolin-8-ol as the major (or exclusive [10]) isomerization product of quinoline 7,8-oxide (**4**), or dehydration product from the *trans*-dihydro diol (**5**) may provide a rationalisation for the observation that quinolin-8-ol is a metabolite of quinoline in rabbits.[7] Continuing metabolism studies from these laboratories using rat liver microsomes have indicated that not only the arene oxide (**4**) and the *trans*-dihydro diol (**5**), but also the arene oxide (**2**) and the *trans*-dihydro diol (**3**) are metabolites of quinoline. These results will be reported elsewhere.[13]

Experimental

^{1}H NMR spectra were obtained using either a 250 MHz Bruker WH250 or a 300 MHz General Electric QE300 instrument in the specified solvent with tetramethylsilane as reference. Mass spectra were recorded at 70 eV * on an AE1-MS902 instrument updated by V.G. Instruments. Accurate molecular weights were determined by the peak-matching method using perfluorokerosene as reference. GLC–MS analyses were carried out using a Hewlett-Packard Model 5790 gas chromatograph directly coupled to a VG analytical 12–250 mass instrument. Analyses of phenols were carried out using a 25 m SGE BP1 capillary column programmed from 100–200 °C at 2 °C min^{-1}. 5-Hydroxy-5,6,7,8-tetrahydroquinoline [14] and 5,6,7,8-tetrahydroquinolin-8-ol [15] were synthesised by the literature methods.

* 1 eV *ca.* 1.602 × 10^{-19} J.

7,8-*Dihydroquinoline* (**7A**).—5,6,7,8-Tetrahydroquinolin-5-ol (5 g, 0.03 mol) was heated with polyphosphoric acid (50 g) at 90–120 °C and the viscous solution was stirred and shaken. Reaction progress was monitored by TLC on silica gel using diethyl ether as eluant, and was found to be complete within 0.5 h. Higher temperatures (> 120 °C) and much longer reaction times must be avoided or isomerisation occurs giving a mixture of olefins (**7A**) and (**7B**). The reaction mixture was then poured into ice and basified (2M NaOH). The olefin product (**7A**) was extracted into diethyl ether. The solution was then dried ($MgSO_4$) and concentrated. The product was distilled to yield *compound* (**7A**) (4.0 g, 92%), b.p. 55–58 °C/0.2 mmHg (Found: C, 82.4; H, 6.6; N, 10.2. C_9H_9N requires C, 82.4; H, 6.9; N, 10.7%); δ_H(250 MHz; $CDCl_3$) 2.44 (2 H, m, 7-H), 2.98 (2 H, t, $J_{7,8}$ 8.4 Hz, 8-H), 6.05 (1 H, m, 6-H), 6.37 (1 H, m, 5-H), 7.04 (1 H, dd, $J_{2,3}$ 4.9, $J_{3,4}$ 7.6 Hz, 3-H), 7.22 (1 H, dd, $J_{2,4}$ 1.6, $J_{3,4}$ 7.6 Hz, 4-H), and 8.27 (1 H, dd, $J_{2,3}$ 4.9, $J_{2,4}$ 1.6 Hz, 2-H).

5,6-*Dihydroquinoline* (**7B**).—Using an identical procedure to that outlined for 7,8-dihydroquinoline (**7A**), 5,6,7,8-tetrahydroquinolin-8-ol (5 g, 0.03 mol) was converted into (**7B**) (2.9 g, 66%), b.p. 56–57 °C/0.4 mmHg (lit.,[8] b.p. 112–113 °C/17 mmHg); δ_H(250 MHz; $CDCl_3$) 2.32 (2 H, m, 6-H), 2.80 (2 H, t, $J_{5,6}$ 8.2 Hz, 5-H), 6.28 (1 H, m, 7-H), 6.62 (1 H, d, $J_{7,8}$ 9.9 Hz, 8-H), 6.97 (1 H, dd, $J_{3,4}$ 7.4, $J_{2,3}$ 4.9 Hz, 3-H), 7.31 (1 H, d, $J_{3,4}$ 7.4 Hz, 4-H), and 8.32 (1 H, d, $J_{2,3}$ 4.9 Hz, 2-H).

trans-6-*Bromo*-5,6,7,8-*tetrahydroquinolin*-5-*yl Acetate* (**8A**).—7,8-Dihydroquinoline (**7A**) (9.0 g, 0.07 mol) was treated at 0 °C with freshly recrystallised (dichloromethane–pentane) *N*-bromoacetamide (NBA) (10.5 g, 0.076 mol) in acetic acid (100 ml) containing lithium acetate and stirred at ambient temperature for 12 h. The resulting solution was concentrated under reduced pressure, basified (2M Na_2CO_3) and the bromoacetate product (**8A**) was extracted into chloroform. The latter solution was dried ($MgSO_4$) and after solvent evaporation the crude product was recrystallised from hexane to yield the *title compound* (**8A**) (17.0 g, 89%), m.p. 74–76 °C (Found: C, 48.6; H, 4.3; N, 5.3. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.4; N, 5.2%); δ_H(250 MHz; $CDCl_3$) 2.11 (3 H, s, OCH_3), 2.32 (1 H, m, 7-H), 2.58 (1 H, m, 7-H), 3.21 (2 H, m, 8-H), 4.47 (1 H, m, 6-H), 6.15 (1 H, d, $J_{5,6}$ 4.5 Hz, 5-H), 7.17 (1 H, dd, $J_{3,4}$ 7.7, $J_{3,2}$ 4.6 Hz, 3-H), 7.60 (1 H, dd, $J_{3,4}$ 7.7, $J_{2,4}$ 1.5 Hz, 4-H), and 8.54 (1 H, dd, $J_{2,3}$ 4.6, $J_{2,4}$ 1.5 Hz, 2-H).

trans-7-*Bromo*-5,6,7,8-*tetrahydroquinolin*-8-*yl Acetate* (**8B**).—5,6-Dihydroquinoline (**7B**) (12.0 g, 0.09 mol) was treated in a similar manner to olefin (**7A**) with NBA (14.0 g, 0.1 mol) to give the *title compound* (**8**) (22 g, 89%), m.p. 90–91 °C (hexane) (Found: C, 48.6; H, 4.4; N, 5.5. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.4; N, 5.2%); δ_H(250 MHz; $CDCl_3$) 2.13 (3 H, s, OCH_3), 2.24 (1 H, m, 6-H), 2.44 (1 H, m, 6-H), 2.90 (1 H, m, 5-H), 3.11 (1 H, m, 5-H), 4.61 (1 H, m, 7-H), 6.10 (1 H, d, $J_{7,8}$ 4.1 Hz, 8-H), 7.24 (1 H, dd, $J_{3,4}$ 7.8, $J_{2,3}$ 4.7 Hz, 3-H), 7.50 (1 H, d, $J_{3,4}$ 7.8 Hz, 4-H), and 8.52 (1 H, d, $J_{2,3}$ 4.7 Hz, 2-H).

6,8-*Dibromo*-5,6,7,8-*tetrahydroquinolin*-5-*yl Acetate* (**9A**).—The bromoacetate (**8A**) (5.0 g, 0.018 mol) and α,α′-azoisobutyronitrile (AIBN) (0.01 g) were dissolved in dry CCl_4 (100 ml) under an atmosphere of nitrogen. *N*-bromosuccinimide (NBS) (3.52 g, 0.02 mol) was added and the mixture was heated to *ca.* 60 °C with stirring and irradiation using a heating lamp for *ca.* 0.5 h. The solution was cooled to 0 °C, filtered through charcoal, and concentrated to yield the *dibromoacetate product* (**9A**). Recrystallisation from ethyl acetate gave (**9A**) (5.8 g, 92%); m.p. 105–108 °C (Found: C, 37.6; H, 3.3; N, 3.85. $C_{11}H_{11}Br_2NO_2$ requires C, 37.8; H, 3.2; N, 4.0%); δ_H(250 MHz; $CDCl_3$) 2.20 (3 H, s, OAc), 2.99 (2 H, m, 7-H), 4.76 (1 H, m, 6-H), 5.48 (1 H, t, $J_{7,8}$ 4.4 Hz, 8-H), 6.32 (1 H, d, $J_{5,6}$ 8.8 Hz, 5-H), 7.24 (1 H, m, 3-H), 7.52 (1 H, dd, $J_{4,3}$ 7.8, $J_{4,2}$ 1.8 Hz, 4-H), and 8.60 (1 H, dd, $J_{2,3}$ 4.9, $J_{2,4}$ 1.8 Hz, 2-H).

5,7-*Dibromo*-5,6,7,8-*tetrahydroquinolin*-8-*yl Acetate* (**9B**).—Using an identical procedure to that used in the synthesis of compound (**9A**), the bromoacetate (**8B**) (5.0 g, 0.018 mol) gave the *dibromoacetate* (**9B**) (6.0 g, 92%), m.p. 119–120 °C (hexane) (Found: C, 38.0; H, 3.5; N, 4.0. $C_{11}H_{11}Br_2NO_2$ requires C, 37.8; H, 3.2; N, 4.0%); δ_H(250 MHz; $CDCl_3$) 2.22 (3 H, s, OAc), 2.92 (2 H, m, 6-H), 4.74 (1 H, m, 7-H), 5.50 (1 H, dd, $J_{5,6} = J_{5,6'}$, 5.2 Hz, 5-H), 6.22 (1 H, d, $J_{7,8}$ 7.3 Hz, 8-H), 7.29 (1 H, dd, $J_{3,2}$ 4.8, $J_{3,4}$ 7.9 Hz, 3-H), 7.82 (1 H, dd, $J_{4,2}$ 1.5, $J_{3,4}$ 7.9 Hz, 4-H), and 8.57 (1 H, dd, $J_{2,4}$ 1.5, $J_{2,3}$ 4.7 Hz, 2-H).

5,6-*Epoxy*-5,6-*dihydroquinoline* (**2**).—The dibromoacetate (**9A**) (5.8 g, 0.016 mol) in dry THF was stirred with sodium methoxide (7.0 g) at 0 °C under nitrogen. The reaction mixture was maintained at 0 °C for 1 h followed by stirring at room temperature for a further 4 h. The solvent was removed under reduced pressure at room temperature. Water (20 ml) and dichloromethane were added to the residue (*ca.* 0 °C) and the organic phase was dried (K_2CO_3) and concentrated to give *arene oxide* (**2**) which was purified by flash chromatography on silica gel with diethyl ether as eluant and recrystallised from pentane at −70 °C, (1.6 g, 70%), m.p. 33–36 °C (Found: M^+, 145.06842. C_9H_7NO requires 145.068 40); δ_H(250 MHz; [$^2H_6$]-acetone) 4.20 (1 H, m, 6-H), 4.59 (1 H, d, $J_{5,6}$ 3.6 Hz, 5-H), 6.79 (1 H, dd, $J_{6,7}$ 3.8, $J_{7,8}$ 9.8 Hz, 7-H), 6.90 (1 H, dd, $J_{8,7}$ 9.8, $J_{8,6}$ 1.8 Hz, 8-H), 7.35 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 7.7 Hz, -H), 8.10 (1 H, dd, $J_{4,2}$ 1.5, $J_{3,4}$ 7.7 Hz, 4-H), and 8.60 (1 H, dd, $J_{2,3}$ 4.8, $J_{2,4}$ 1.5 Hz, 2-H).

7,8-*Epoxy*-7,8-*dihydroquinoline* (**4**).—Treatment of the dibromoacetate (**9B**) (5.0 g, 0.014 mol) with NaOMe (8 g) in a similar manner to that used for dibromoacetate (**9A**) gave *compound* (**4**) (1.9 g, 90%), m.p. 44–46 °C (pentane–diethyl ether) (Found: M^+, 145.068 42. C_9H_7NO requires 145.068 40); δ_H(250 MHz; $CDCl_3$) 4.19 (1 H, m, 7-H), 4.66 (1 H, d, $J_{7,8}$ 3.7 Hz, 8-H), 6.51 (1 H, dd, $J_{7,6}$ 3.7, $J_{5,6}$ 9.6 Hz, 6-H), 6.72 (1 H, dd, $J_{4,5}$ 1.7, $J_{5,6}$ 9.6 Hz, 5-H), 7.31 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 7.7 Hz, 3-H), 7.58 (1 H, dd, $J_{2,4}$ 1.3, $J_{3,4}$ 7.7 Hz, 4-H), and 8.53 (1 H, dd, $J_{2,4}$ 1.4, $J_{2,3}$ 4.8 Hz, 2-H).

5,6-*Epoxy*-5,6,7,8-*tetrahydroquinoline* (**10A**).—The bromoacetate (**8A**) (10.0 g, 0.037 mol) was dissolved in dry THF (100 ml) and was treated with sodium methoxide (10 g). The mixture was stirred under nitrogen for 4 h at ambient temperature. After removal of solvent under reduced pressure, water (50 ml), was added and the epoxide was extracted into diethyl ether which was dried (K_2CO_3) and concentrated to yield the crude epoxide (**10A**). Distillation yielded pure *title compound* (**10A**) (4.9 g, 91%), b.p. 53–57 °C/0.05 mmHg (Found: C, 74.0; H, 6.5; N, 9.5. C_9H_9NO requires C, 73.5; H, 6.1; N, 9.5%); δ_H(250 MHz; $CDCl_3$) 1.74 (1 H, m, 7-H), 2.38 (1 H, m, 7-H), 2.71 (2 H, m, 8-H), 3.68 (1 H, m, 6-H), 3.77 (1 H, d, $J_{5,6}$ 3.9 Hz, 5-H), 7.08 (1 H, dd, $J_{2,3}$ 4.9, $J_{3,4}$ 7.6 Hz, 3-H), 7.62 (1 H, dd, $J_{3,4}$ 7.6, $J_{2,4}$ 1.7 Hz, 4-H), and 8.38 (1 H, dd, $J_{2,4}$ 1.7, $J_{2,3}$ 4.9 Hz, 2-H).

7,8-*Epoxy*-5,6,7,8-*tetrahydroquinoline* (**10B**).—Using an identical method to that reported for epoxide (**10A**) the bromoacetate (**8B**) (10.0 g, 0.037 mol) gave the *title compound* (**10B**)(5.0 g, 90%), b.p. 82–83 °C/0.1 mmHg (Found: C, 73.75; H, 6.2; N, 9.4. C_9H_9NO requires C, 73.5; H, 6.1; N, 9.5%); δ_H(300 MHz; $CDCl_3$) 1.78 (1 H, m, 6-H), 2.49 (2 H, m, 5-H and 6-H), 2.80 (1 H, m, 5-H), 3.78 (1 H, m, 7-H), 4.05 (1 H, d, $J_{7,8}$ 4.1 Hz, 8-H), 7.17 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 7.6 Hz, 3-H), 7.39 (1 H, d, $J_{3,4}$ 7.6 Hz, 4-H), and 8.42 (1 H, dd, $J_{2,4}$ 0.9, $J_{2,3}$ 4.8 Hz, 2-H).

8-*Bromo*-5,6-*epoxy*-5,6,7,8-*tetrahydroquinoline* (**11A**).—The tetrahydroepoxide (**10A**) (0.390 g, 2.6 mmol) was brominated using NBS (0.520 g, 2.9 mmol) in a similar method to that reported for compounds (**8A**) and (**8B**). The crude product was found to be a liquid mixture of stereoisomers of compound (**11A**) (0.49 g, 82%) by ^{1}H NMR analysis. The major *isomer* (70%) of (**11A**) was isolated as a white crystalline solid by fractional crystallisation, m.p. 118–120 °C (light petroleum 40–60 °C) (Found: M^+, 224.9788. C_9H_8BrNO requires 224.9790); δ_H(300 MHz; $CDCl_3$) 2.64 (1 H, dd, $J_{7,8}$ 5.9, $J_{7,7'}$ 16.9 Hz, 7-H), 3.15 (1 H, d, $J_{7,7'}$ 16.9 Hz, 7′-H), 3.92 (1 H, m, 6-H), 3.97 (1 H, d, $J_{5,6}$ 3.9 Hz, 5-H), 5.38 (1 H, d, $J_{7,8}$ 5.8 Hz, 8-H), 7.27 (1 H, m, 3-H), 7.82 (1 H, d, $J_{3,4}$ 7.6 Hz, 4-H), and 8.60 (1 H, d, $J_{2,3}$ 4.8 Hz, 2-H). On chemical grounds *i.e.* benzylic bromination from the less hindered face, this major isomer is tentatively assigned as *trans*, which is also consistent with the ^{1}H NMR spectrum.

The minor *cis* isomer was only identified by the ^{1}H NMR spectrum of the mixture of isomers and was not separated.

Minor isomer: δ_H(300 MHz; $CDCl_3$), 2.54 (1 H, d, $J_{7,7'}$ 14.7 Hz, 7-H), 3.12 (1 H, d, $J_{7,7'}$ 14.8 Hz, 7′-H), 3.78 (1 H, m, 6-H), 3.94 (1 H, d, $J_{5,6}$ 4.0 Hz, 5-H), 5.16 (1 H, dd, $J_{7,8}$ 6.4, $J_{7',8}$ 10.2 Hz, 8-H), 7.27 (1 H, m, 3-H), 7.77 (1 H, d, $J_{3,4}$ 7.7 Hz, 4-H), and 8.63 (1 H, d, $J_{2,4}$ 5.0 Hz, 2-H).

5-*Bromo*-7,8-*epoxy*-5,6,7,8-*tetrahydroquinoline* (**11B**).—The tetrahydro epoxide (**10B**) (0.415 g, 2.8 mmol) was treated in a similar manner to the tetrahydro epoxide (**10A**) to yield the *title compound* (**11B**) as a mixture of stereoisomers (0.59 g, 92%). The major isomer (70%) of *compound* (**11B**) was isolated in pure form by fractional crystallisation; m.p. 101–108 °C (decomp.) (Found: M^+, 224.9781. C_9H_8BrNO requires 224.9790); δ_H(300 MHz; $CDCl_3$) 2.53 (1 H, dd, $J_{5,6}$ 5.9, $J_{6,6'}$ 16.9 Hz, 6-H), 3.07 (1 H, d, $J_{6,6'}$ 16.9 Hz, 6′-H), 3.94 (1 H, m, 7-H), 4.20 (1 H, d, $J_{7,8}$ 3.9 Hz, 8-H), 5.30 (1 H, d, $J_{5,6}$ 5.8 Hz, 5-H), 7.29 (1 H, m, 3-H), 7.61 (1 H, d, $J_{3,4}$ 7.7 Hz, 4-H), and 8.54 (1 H, d, $J_{2,3}$ 4.9 Hz, 2-H). Using similar arguments to those applied to compound (**11A**) the major bromo epoxide isomer (**11B**) is also tentatively assigned a *trans* configuration. The minor *cis* isomer was not separated but was identified from the ^{1}H NMR spectrum of the mixture of isomers.

Minor isomer: δ_H(300 MHz; $CDCl_3$) 2.35 (1 H, dd, $J_{5,6}$ 11.8, $J_{6,6'}$ 14.6 Hz, 6-H), 3.15 (1 H, m, 6′-H), 3.79 (1 H, m, 7-H), 4.16 (1 H, d, $J_{7,8}$ 4.2 Hz, 8-H), 5.16 (1 H, dd, $J_{5,6}$ 6.4, $J_{5,6}$ 11.7 Hz, 5-H), 7.33 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 7.9 Hz, 3-H), 8.02 (1 H, d, $J_{3,4}$ 8.0 Hz, 4-H), and 8.48 (1 H, d, $J_{2,3}$ 4.6 Hz, 2-H).

5,6-*Epoxy*-5,6-*dihydroquinoline* (**2**).—Treatment of the isomeric mixture of the bromo epoxides (**11A**) (0.42 g, 1.86 mmol) with NaOMe (1.0 g) in a similar manner to that used for the dibromo acetate (**9A**), gave *compound* (**2**) (0.240 g, 89%), m.p. 34–36 °C (pentane). This compound was found to be spectroscopically identical with that obtained *via* the dibromo acetate intermediate (**9A**).

7,8-*Epoxy*-7,8-*dihydroquinoline* (**4**).—Treatment of the isomeric mixture of the bromo epoxides (**11B**) (0.50 g, 2.21 mmol) with NaOMe (1.0 g) in a similar manner to that used for dibromo acetate (**9A**), gave *compound* (**4**) (0.28 g, 88%), m.p. 44–46 °C (pentane–diethyl ether). This compound was found to be spectroscopically identical with that obtained *via* the dibromo acetate intermediate (**9B**).

trans-5,6,7,8-*Tetrahydroquinoline*-5,6-*diol* (**12A**).—The tetrahydro epoxide (**10A**) (4.9 g, 0.03 mol) was heated in 90% formic acid (15 ml) at 85 °C for 5 h. The formic acid was removed under reduced pressure and the residue dissolved in water (50 ml) and basified (2M NaOH). The solution was saturated with K_2CO_3, extracted with ethyl acetate, and the extract dried ($MgSO_4$) and concentrated.

Recrystallisation of the residue yielded the *diol* (**12A**) (3.5 g, 70%), m.p. 160–162 °C (EtOAc) (Found: C, 65.7; H, 6.8; N, 8.5. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%); δ_H(250 MHz; $CDCl_3$) 2.38 (1 H, m, 7-H), 2.68 (1 H, m, 7-H), 3.45 (2 H, m, 8-H), 4.59 (1 H, m, 6-H), 5.27 (1 H, d, $J_{5,6}$ 7.0 Hz, 5-H), 7.41 (1 H, dd, $J_{3,4}$ 7.7, $J_{2,3}$ 4.7 Hz, 3-H), 8.45 (1 H, dd, $J_{2,4}$ 1.4, $J_{3,4}$ 7.7 Hz, 4-H), and 8.84 (1 H, dd, $J_{2,3}$ 4.7, $J_{2,4}$ 1.4 Hz, 2-H).

Prior to recrystallisation, ^{1}H NMR analysis of the crude product mixture showed the *trans*-diol (**12A**) to be the major (95%) component. A minor (5%) proportion of the *cis*-diol (**16A**) was also detected but not isolated.

trans-5,6,7,8-*Tetrahydroquinoline*-7,8-*diol* (**12B**).—The tetrahydro epoxide (**10B**) (5.0 g, 3.4 mmol) was converted into the *trans*-diol (**12B**) by the route used for diol (**12A**. ^{1}H NMR analysis showed both the *trans*-(**12B**) (95%) and the *cis*-(**16B**) (5%) diols to be present. Recrystallisation from ethyl acetate yielded the trans-*diol* (**12B**) (4.0 g, 71%), m.p. 97–98 °C (ethyl acetate) (Found: C, 65.5; H, 6.8; N, 8.4. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%); δ_H(300 MHz; $CDCl_3$) 1.93 (1 H, m, 6-H), 2.20 (1 H, m, 6-H), 2.91 (2 H, m, 5-H), 3.95 (3 H, m, 7-H and 2 × OH), 4.56 (1 H, d, $J_{7,8}$ 8.4 Hz, 8-H), 7.16 (1 H, dd, $J_{2,3}$ 4.7, $J_{3,4}$ 7.7 Hz, 3-H), 7.44 (1 H, d, $J_{3,4}$ 7.9 Hz, 4-H), and 8.45 (1 H, d, $J_{2,3}$ 4.5 Hz, 2-H).

trans-5,6,7,8-*Tetrahydroquinolin*-5,6-*diyl Diacetate* (**13A**).—The *trans* diol (**12A**) (1.15 g, 8 mmol) was dissolved in a mixture of pyridine (10 ml), triethylamine (5 ml), and acetic anhydride (4 ml). The mixture was stirred for 0.5 h at 0 °C, and for 20 h at ambient temperature. Water (10 ml) was added and the solution was concentrated under reduced pressure. The product was stirred with aqueous Na_2CO_3 (2M) and the aqueous solution was extracted with chloroform. The chloroform solution was dried ($MgSO_4$), passed through a short column of neutral alumina and concentrated to yield *title compound* (**13A**) which was recrystallised from diethyl ether–cyclohexane (yield 1.10 g, 57%); m.p. 85–88 °C (Found: C, 62.8; H, 6.1; N, 5.9. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.0; N, 5.6%); δ_H(250 MHz; $CDCl_3$) 2.04 (3 H, s, CH_3), 2.11 (3 H, s, CH_3), 2.25 (2 H, m, 7-H), 3.07 (2 H, t, $J_{7,8}$ 6.6 Hz, 8-H), 5.21 (1 H, m, 6-H), 6.05 (1 H, d, $J_{5,6}$ 5.5 Hz, 5-H), 7.28 (1 H, dd, $J_{3,4}$ 7.9, $J_{2,3}$ 4.8 Hz, 3-H), 7.61 (1 H, dd, $J_{2,4}$ 1.7, $J_{3,4}$ 7.9 Hz, 4-H), and 8.50 (1 H, dd, $J_{2,4}$ 1.7, $J_{2,3}$ 4.8 Hz, 2-H).

trans-5,6,7,8-*Tetrahydroquinolin*-7,8-*diyl Diacetate* (**13B**).—The *trans* diol (**12B**) (2.0 g, 0.012 mol) was treated with acetic anhydride in the same manner as diol (**12A**) to yield the trans-*diacetate* (**13B**) which was purified by flash column chromatography on silica gel (2% MeOH in $CHCl_3$ as eluant). Yield 2.45 g (82%), m.p. 82–83 °C (diethyl ether–hexane) (Found: C, 62.8; H, 5.8; N, 5.6. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.0; N, 5.6%); δ_H(300 MHz; $CDCl_3$) 2.06 (3 H, s, CH_3), 2.12 (2 H, m, 6-H), 2.14 (3 H, s, CH_3), 2.89 (1 H, t, $J_{5,6}$ 6.5 Hz, 5-H), 5.30 (1 H, m, 7-H), 6.01 (1 H, d, $J_{7,8}$ 5.8 Hz, 8-H), 7.20 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 7.8 Hz, 3-H), 7.47 (1 H, d, $J_{3,4}$ 7.8 Hz, 4-H), and 8.52 (1 H, d, $J_{2,3}$ 4.8 Hz, 2-H).

8-*Bromo*-5,6,7,8-*tetrahydroquinolin*-r-5,t-*diyl Diacetate* (**14A**).—The *trans*-diacetate (**13A**) (3.0 g, 0.011 mol) was brominated using NBS in a similar manner to that reported for compounds (**8A**), (**8B**), (**10A**), and (**10B**) to yield the *bromo diacetate* (**14A**) as a mixture of diastereoisomers (3.5 g, 91%). The major isomer (60% of mixture) was isolated by crystallisation from ethyl acetate–hexane, m.p. 119–120 °C (Found: C, 47.1; H, 4.6; N, 4.1. $C_{13}H_{14}BrNO_4$ requires C, 47.6; H, 4.3; N, 4.3%); δ_H(300 MHz; $CDCl_3$) 2.08 (3 H, s, CH_3), 2.18 (3 H, s, CH_3), 2.75 (2 H, m, 7-H), 5.48 (1 H, dd, $J_{7,8}$ 4.45 Hz, 8-H), 5.68 (1

H, m, 6-H), 6.22 (1 H, d, $J_{5,6}$ 7.9 Hz, 5-H), 7.25 (1 H, dd, $J_{3,4}$ 8.4, $J_{2,3}$ 4.6 Hz, 3-H), 7.56 (1 H, d, $J_{3,4}$ 8.45 Hz, 4-H), and 8.62 (1 H, d, $J_{2,3}$ 4.4 Hz, 2-H). From this spectrum, this major isomer is assigned the stereochemistry with the 5-acetoxy and 8-bromo-substituents *trans*.

^{1}H NMR data of the minor isomer was obtained from the spectrum of the mixture: δ_H(300 MHz; $CDCl_3$) 2.10 (3 H, s, CH_3), 2.17 (3 H, s, CH_3), 2.75 (2 H, m, 7-H), 5.20 (1 H, m, 6-H), 5.69 (1 H, m, 8-H), 6.12 (1 H, d, $J_{5,6}$ 4.9 Hz, 5-H), 7.29 (1 H, m, 3-H), 7.67 (1 H, dd, $J_{3,4}$ 7.7, $J_{2,4}$ 1.3 Hz, 4-H), and 8.69 (1 H, dd, $J_{2,3}$ 4.6, $J_{2,4}$ 1.4 Hz, 2-H).

This product was normally used immediately in the next stage [formation of (**15A**)] as either a mixture of diastereoisomers or the major isomer.

5-Bromo-5,6,7,8-tetrahydroquinolin-r-7,t-8-diyl Diacetate (**14B**).—Using the method reported for compound (**14A**), the *trans*-diacetate (**13B**) (2.0 g, 8 mmol) yielded the *bromo diacetate* (**14B**) (2.7 g, 90%), m.p. 51 °C (decomp.) (Found: M^+, 328.0186. $C_{13}H_{14}BrNO_4$ requires 328.018 48); δ_H(250 MHz; $CDCl_3$) 2.09 (3 H, s, CH_3), 2.13 (3 H, s, CH_3), 2.72 (2 H, m, 6-H), 5.26 (1 H, m, 7-H), 5.69 (1 H, m, 5-H), 6.12 (1 H, d, $J_{7,8}$ 7.6 Hz, 8-H), 7.28 (1 H, m, 3-H), 7.90 (1 H, d, $J_{3,4}$ 7.1 Hz, 4-H), and 8.58 (1 H, dd, $J_{2,3}$ 4.8, $J_{2,4}$ 1.5 Hz, 2-H). This product was also normally used directly (without further purification) in the synthesis of diacetate (**15B**).

trans-*5,6-Dihydroquinolin-5,6-diyl Diacetate* (**15A**).—The bromo diacetate (**14A**) (3.5 g, 0.01 mol) was dehydrobrominated using 1,5-diazabicyclo[4.3.0.]non-5-ene (DBN) (3.0 g, 0.025 mol) in dry THF (100 ml). The mixture was stirred at 0 °C for 1 h and then at 20 °C for 8 h. The THF was removed under reduced pressure and phosphate buffer (30 ml, pH 7.5) was added. The aqueous solution was extracted with dichloromethane and the extracts were dried (K_2CO_3) and concentrated to give the *diacetate* (**15A**) as an unstable product (1.52 g, 61%), m.p. 55 °C (decomp.) (Found: M^+, 247.0847. $C_{13}H_{13}NO_4$ requires 247.0844); δ_H(250 MHz; $CDCl_3$) 2.06 (3 H, s, CH_3), 2.11 (3 H, s, CH_3), 5.63 (1 H, m, 6-H), 6.18 (1 H, d, $J_{5,6}$ 6.1 Hz, 5-H), 6.26 (1 H, dd, $J_{6,7}$ 3.9 Hz, 7-H), 6.83 (1 H, d, $J_{7,8}$ 9.9 Hz, 8-H), 7.17 (1 H, dd, $J_{3,4}$ 7.7, $J_{2,3}$ 4.8 Hz, 3-H), 7.67 (1 H, dd, $J_{3,4}$ 7.7, $J_{2,4}$ 1.5 Hz, 4-H), and 8.52 (1 H, dd, $J_{2,4}$ 1.5, $J_{2,3}$ 4.8 Hz, 2-H). The product was used without purification in the next stage of the synthesis due to instability.

trans-*7,8-Dihydroquinolin-7,8-diyl Diacetate* (**15B**).—Using the method described for diacetate (**15A**) but with a reaction time of *ca.* 3 h the bromo diacetate precursor (**14B**) (0.86 g, 7 mmol), yielded the *diacetate* (**15B**) as a very unstable solid (0.9 g, 60%), m.p. 63 °C (decomp.) (Found: M^+, 247.0842. $C_{13}H_{13}NO_4$ requires 247.0844); δ_H(250 MHz; $CDCl_3$) 5.65 (1 H, m, 7-H), 6.06 (1 H, m, 6-H), 6.23 (1 H, d, $J_{7,8}$ 6.9 Hz, 8-H), 6.57 (1 H, d, $J_{5,6}$ 9.8 Hz, 5-H), 7.22 (1 H, dd, $J_{3,4}$ 6.3, $J_{2,3}$ 4.9 Hz, 3-H), 7.44 (1 H, d, $J_{3,4}$ 6.4 Hz, 4-H), and 8.47 (1 H, dd, $J_{2,4}$ 1.6, $J_{2,3}$ 4.9 Hz, 2-H).

trans-*5,6-Dihydroquinoline-5,6-diol* (**3**).—Dry ammonia was bubbled through a solution of the diacetate (**15A**) (1.5 g, 6 mmol) in dry methanol (20 ml) at 0 °C for 1 h. The methanol was evaporated under reduced pressure and the product was purified by preparative TLC on silica gel (6% MeOH in $CHCl_3$) to yield the trans-*dihydro diol* (**3**) (0.7 g, 77%), m.p. 185–188 °C (ethyl acetate) (Found: M^+, 163.063 37. $C_9H_9NO_2$ requires 163.063 32); δ_H(250 MHz; [$^2H_6$]acetone) 4.43 (1 H, dd, $J_{6,7}$ 2.4, $J_{5,6}$ 10.5 Hz, 6-H), 4.77 (1 H, d, $J_{5,6}$ 10.5 Hz, 5-H), 6.22 (1 H, dd, $J_{6,7}$ 2.4, $J_{7,8}$ 10.0 Hz, 7-H), 6.77 (1 H, d, $J_{7,8}$ 10.0 Hz, 8-H), 7.19 (1 H, dd, $J_{2,3}$ 5.0, $J_{3,4}$ 7.5 Hz, 3-H), 7.87 (1 H, dd, $J_{3,4}$ 7.5, $J_{2,4}$ 1.6 Hz, 4-H), and 8.35 (1 H, dd, $J_{2,3}$ 5.0, $J_{2,4}$ 1.6 Hz, 2-H).

trans-*7,8-Dihydroquinoline-7,8-diol* (**5**).—Treatment of the diacetate (**15B**) (0.9 g, 3.6 mmol) with dry ammonia in methanol in a similar manner to that described for diacetate (**15A**) yielded the trans-*dihydro diol* (**5**) (0.4 g, 67%), m.p. 186–187 °C (ethyl acetate) (Found: M^+, 163.063 37. $C_9H_9NO_2$ requires 163.063 32); δ_H(300 MHz; CD_3OD) 4.44 (1 H, m, 7-H), 4.71 (1 H, d, $J_{7,8}$ 7.8 Hz, 8-H), 6.09 (1 H, dd, $J_{5,6}$ 9.8, $J_{6,7}$ 3.3 Hz, 6-H), 6.53 (1 H, dd, $J_{5,6}$ 9.7, $J_{5,7}$ 0.9 Hz, 5-H), 7.30 (1 H, dd, $J_{3,4}$ 7.5, $J_{2,3}$ 4.9 Hz, 3-H), 7.55 (1 H, d, $J_{3,4}$ 7.6 Hz, 4-H), and 8.36 (1 H, d, $J_{2,3}$ 4.6 Hz, 2-H).

Base-catalysed Hydration of 5,6-*Epoxy*-5,6-*dihydroquinoline* (**2**) *to Yield* trans-5,6-*Dihydroquinoline*-5,6-*diol* (**3**).—5,6-Epoxy-5,6-dihydroquinoline (**2**) (0.104 g, 0.76 mmol) was dissolved in a solution of Bu^{t}OD (2.5 ml) and D_2O (2.5 ml) containing KOD (0.096 g) and was maintained at a temperature of 20 °C for 7 d. ^{1}H NMR analysis of this solution showed the presence of the diol (**3**) as the major product with the arene oxide precursor (**2**) as a minor component (25%) accompanied by a smaller proportion of aromatic products (presumably quinolinols). The sample was diluted with water (20 ml), saturated with K_2CO_3, and extracted with ethyl acetate. The latter extract was dried (K_2CO_3), filtered and concentrated to yield a crude product (0.111 g) which was purified by preparative TLC on silica gel (6% MeOH in $CHCl_3$ as eluant). The *trans*-dihydro diol (**3**) (0.065 g, 42%) was isolated and found to be spectroscopically indistinguishable from the sample prepared by the multi-step route. When this experiment was repeated using similar quantities, but using a temperature of 40 °C for 48 h, and an identical work-up procedure, the *trans*-dihydro diol (**3**) was isolated in 55% yield.

Base-catalysed Hydration of 7,8-*Epoxy*-7,8-*dihydroquinoline* (**4**) *to yield* trans-7,8-*Dihydroquinoline*-7,8-*diol* (**5**).—Treatment of the arene oxide (**4**) (0.224 g, 1.54 mmol) with KOD in Bu^{t}OD and D_2O under similar conditions (6 d at *ca.* 20 °C) to those used in the synthesis of the *trans*-diol (**3**), and a similar purification method yielded the *title compound* (**5**) (0.064 g, 26%). The latter product was identical with an authentic sample of (**5**) prepared earlier from the tetrahydro epoxide (**10B**).

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References

1 M. Dong, I. Schmeltz, E. Jacobs, and D. Hoffmann, *J. Anal. Toxicol*, 1978, **2**, 2.
2 M. Dong, I. Schmeltz, E. J. LaVoie, and D. Hoffmann, in 'Carcinogenesis, vol. 3: Polynuclear Aromatic Hydrocarbons,' Raven Press, New York, 1978, p. 97.
3 E. Sawicki, J. E. Meeker, and M. J. Morgan, *Arch. Environ. Health*, 1975, **11**, 773.
4 E. J. LaVoie, E. A. Adams, A. Shigematsu and D. Hoffmann, *Carcinogenesis*, 1983, **4**, 1169.
5 S. K. Agarwal, D. R. Boyd, H. P. Porter, W. B. Jennings, S. J. Grossman, and D. M. Jerina, *Tetrahedron Lett.*, 1986, **27**, 4253.
6 M. Tada, K. Takahashi, and Y. Kawazoe, *Chem. Pharm. Bull.*, 1982, **30**, 3834.
7 B. Scheunemann, *Arch. Exp. Pathol. Pharmacol.*, 1923, **100**, 51.
8 W. E. Hahn and J. Epstajn, *Rocz. Chem.*, 1964, **38**, 989.
9 D. R. Boyd and D. M. Jerina, in 'The Chemistry of Heterocyclic Compounds,' vol. 42, Part 3: 'Small Ring Heterocycles,' Wiley-Interscience, New York, 1985, p. 197.

10 D. R. Bushman, J. M. Sayer, D. R. Boyd, and D. M. Jerina, *J. Am. Chem. Soc.*, 1988, **111**, 2688.
11 D. R. Boyd, R. J. H. Davies, R. Dunlop, H. P. Porter, L. Hamilton, and J. J. McCullough, *J. Chem. Soc., Chem. Commun.*, 1989, 163.
12 D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malone, and N. D. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1981, 94.
13 D. R. Boyd, R. H. Davies, J. J. McCullough, L. Hamilton, D. R. Bushman, and D. M. Jerina, unpublished data.
14 F. Zymalowski and H. Rimek, *Arch. Pharm. (Weinheim, Ger.)*, 1961, **294**, 759.
15 W. E. Hahn and J. Epstajn, *Rocz. Chem.*, 1963, **37**, 395.

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