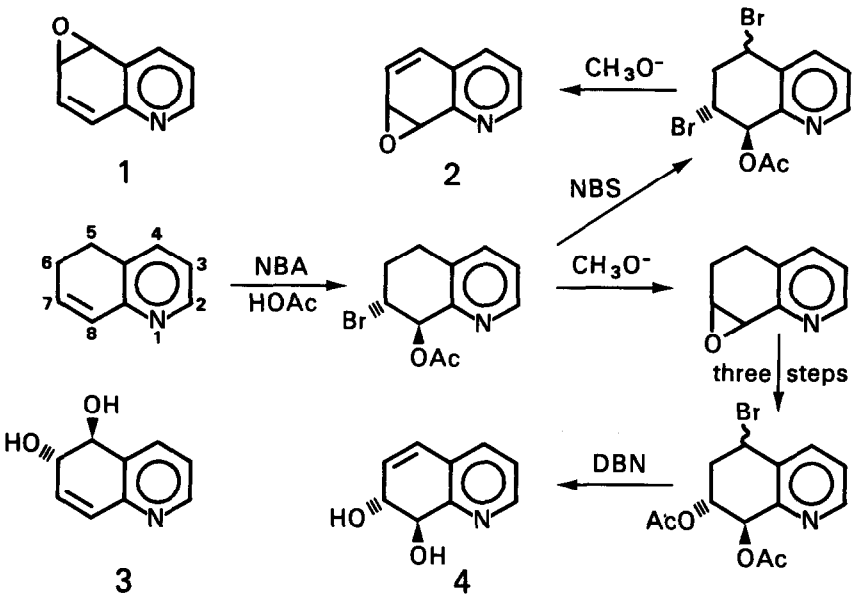


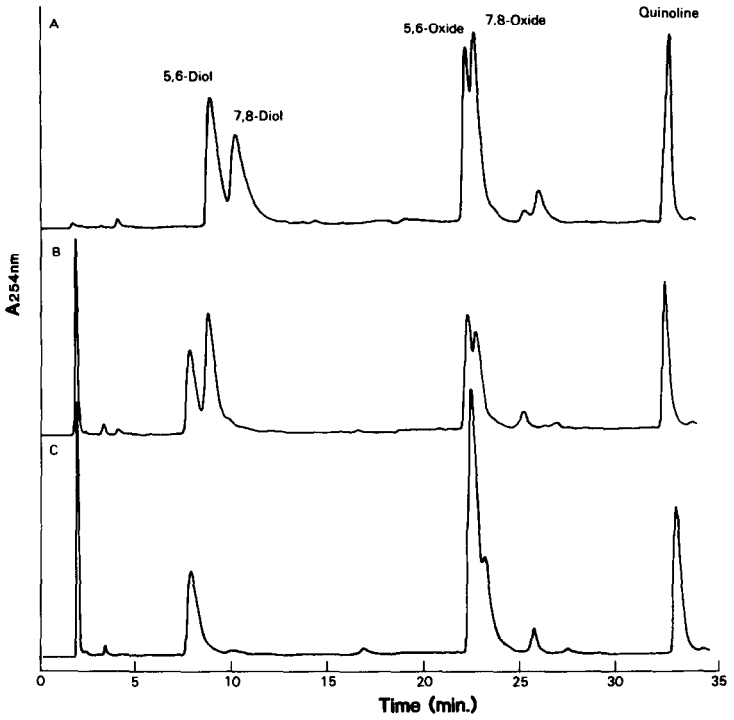
NMR Spectra (300 MHz, acetone-d_6) of Arene Oxides and *trans*-Dihydrodiols (DHD) After Exchange With CD_3OD. Chemical Shifts Are In δ And Coupling Constants In Hertz.

Compound	Oxygen Bearing		Vinyl		Aromatic[a]		
	benzylic	nonbenzylic	benzylic	nonbenzylic	H_2	H_3	H_4
1 5,6-Oxide	H_5 4.59	H_6 4.20	H_8 6.90	H_7 6.79	8.60	7.35	8.10
	($J_{5,6}$ = 3.6, $J_{6,7}$ = 3.8, $J_{6,8}$ = 1.8, $J_{7,8}$ = 9.8)						
2 7,8-Oxide	H_8 4.53	H_7 4.20	H_5 6.83	H_6 6.56	8.51	7.42	7.76
	($J_{7,8}$ = 3.6, $J_{6,7}$ = 3.7, $J_{5,7}$ = 1.8, $J_{5,6}$ = 9.7)						
3 5,6-DHD	H_5 4.77	H_6 4.43	H_8 6.47	H_7 6.22	8.35	7.19	7.87
	($J_{5,6}$ = 10.5, $J_{6,7}$ = 2.2, $J_{7,8}$ = 10.0)						
4 7,8-DHD	H_8 4.67	H_7 4.48	H_5 6.46	H_6 6.02	8.36	7.26	7.53
	($J_{7,8}$ = 10.0, $J_{6,7}$ = 2.3, $J_{5,6}$ = 10.0)						

[a]Coupling constants of $J_{2,3}$ = 4.8, $J_{3,4}$ = 7.7 and $J_{2,4}$ = 1.5 were typical in the aromatic region of the four compounds.

as HPLC on silica and ODS columns, but do isomerize to phenols with heat (110 °C, 15 min). Analysis of the trimethylsilyl ethers of these phenols by capillary GC-MS (25 m SGE BPI, 100 to 200 °C at 2°/min), indicated that 1 isomerized to 5-hydroxy (25.01 min, 86%) and 6-hydroxyquinoline (26.01 min, 14%) while 2 isomerized to 8-hydroxy (21.01 min, 95%) and 7-hydroxyquinoline (26.15 min, 5%).[6]

Quinoline 5,6- (1) and 7,8-oxide (2) are stable in aqueous buffer. Very efficient (>95%) recovery of the arene oxides was observed after incubation (pH 8.0, 37 °C for 20 min) and



extraction. Both arene oxides (1 and 2) and dihydrodiols (3 and 4) were separable by analytical HPLC (Figure A: Vydac ODS column, 4.6 x 250 mm, eluted for 5 min with 2.5% MeOH in 25 mM Tris-acetate buffer [pH 8] followed by a linear gradient to 45% MeOH in buffer over 25 min and a further gradient to 90% MeOH in buffer over 5 min). Both quinoline oxides were found to be substrates for microsomal epoxide hydrolase and were converted to the corresponding *trans*-dihydrodiols. Incubations of the 5,6-oxide (0.25 mg protein/ml) and 7,8-oxide (1.0 mg protein/ml) were carried out with liver microsomes in 50 mM Tris-HCl buffer, pH 8.0, at 37 °C (0.2 mM arene oxides). Aliquots were removed and analyzed at various intervals up to 30 min. Rates of metabolism (nmol dihydrodiol/mg protein/min) were estimated at 23.0 for the 5,6-oxide and 2.1 for the 7,8-oxide. Thus, while the 5,6-oxide was metabolized at a rate comparable to that observed for naphthalene 1,2-oxide (15 nmol/mg/min),[7] the 7,8-oxide proved to be a relatively poor substrate for epoxide hydrolase.

The traces shown in Figures B and C were obtained when quinoline (1 μmol in 0.1 ml acetone) was incubated (20 minutes, 37 °C) with liver microsomes (10 mg of protein) from 3-methylcholanthrene-treated, mature male rats of the Long-Evans strain in 10 ml of 0.1 M phosphate buffer (pH 7.4) containing 5 μmol of NADPH. Reaction solutions were salt saturated and extracted twice with 20 ml of ethyl acetate/acetone (2/1). Residues from the concentrated

extracts were dissolved in MeOH/water (1/1) for analysis by HPLC. The early eluting peak (7.8 min) observed with the microsomal extracts is present in the blank (boiled microsomes) and derives from the sample of NADPH used. Incubation of quinoline with these liver microsomes established the 5,6-dihydrodiol (3) as a major metabolite in accord with previous studies[2] (Figure B). The pair of peaks at 22-24 min appeared to consist mainly of phenols (*vide* UV spectra). There was no evidence for the formation of 7,8-dihydrodiol 4. When 1 mM 3,3,3-trichloroproprene 1,2-oxide, a potent microsomal epoxide hydrolase inhibitor,[8] was present in the incubation (Figure C), the 5,6-oxide (1) was detected spectrally in the earlier member of this pair of peaks, and practically none of the 5,6-dihydrodiol (3) was formed. This result contrasts with a previous report[1] which claimed that 3,3,3-trichloropropene 1,2-oxide did not alter the profile of metabolites formed from quinoline.

The possibility that the 7,8-oxide was present in the incubation medium, but had not been hydrated, was examined by an incubation in which 0.1 M cyanide was added after 20 minutes in order to block further oxidation of the quinoline[9] without affecting epoxide hydrolase. Incubation was continued for an additional 1.5 hr but no significant formation of the 7,8-dihydrodiol was detected. Since 0.1 M cyanide did not significantly inhibit the microsomal epoxide hydrolase catalyzed hydration of racemic quinoline 7,8-oxide, these microsomes may not have the capacity to form one or possibly both enantiomers of arene oxide 2.

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