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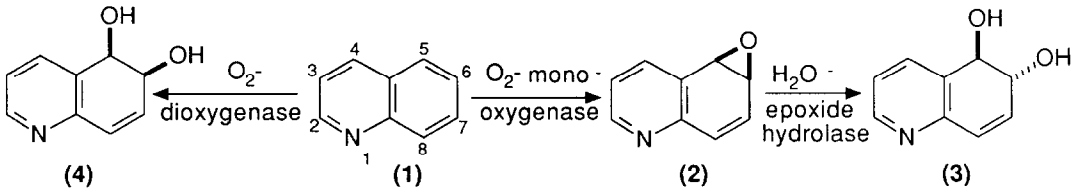
ABSOLUTE CONFIGURATIONS OF THE ARENE OXIDE, *TRANS*-DIHYDRODIOL AND *CIS*-DIHYDRODIOL PRODUCTS RESULTING FROM METABOLISM OF QUINOLINE AT THE 5,6-BOND

Derek R. Boyd*[a], Daniel R. Bushman[c], R. Jeremy H. Davies[b], Michael R.J. Dorrity[a], Lynne Hamilton[a], Donald M. Jerina[c], Wayne Levin[d], John J. McCullough[a], R. Austin S. McMordie[a], John F. Malone[a], and H. Patricia Porter[a]

Departments of Chemistry[a] and Biochemistry[b], The Queen's University of Belfast, Belfast BT9 5AG, UK.
[c]Laboratory of Bioorganic Chemistry, NIDDK, The National Institutes of Health, Bethesda, Md. 20892, USA.
[d]Department of Protein Biochemistry, Hoffmann-La Roche Inc. Nutley, NJ 07110, USA.

Summary: *Trans*-6-bromo-5-hydroxy-5,6,7,8-tetrahydroquinoline enantiomers have been resolved *via* their dibenzoyltartrate salt diastereoisomers. X-ray crystallographic analysis of the (+)-dibenzoyltartrate salt obtained from reaction of (+)-dibenzoyltartaric acid and (-)-*trans*-6-bromo-5-hydroxy-5,6,7,8-tetrahydro-quinoline, when allied to a stereochemical correlation sequence linking the arene oxide, *trans*-dihydrodiol and *cis*-dihydrodiol enantiomers, provides an unequivocal assignment of absolute configuration for these quinoline metabolites.

Quinoline, **1**, known to be both mutagenic[1] and carcinogenic[2], is found at relatively high concentrations in tobacco smoke.[3] The metabolism of quinoline has thus been studied[2,4,5] in order to identify metabolites and to investigate their mutagenic-carcinogenic properties. Quinoline 5,6-oxide, **2**[4], and *trans*-5,6-dihydroquinoline-5,6-diol **3**[2,4,5], have previously been identified as major liver microsomal metabolites of quinoline. Similarly, *cis*-5,6-dihydroquinoline-5,6-diol, **4**, has been isolated as a major quinoline metabolite from growing cultures of a mutant strain of the soil bacterium *Pseudomonas putida* (UV4).[6] To date, neither the enantiomeric excess (% e.e.) nor the absolute configuration of any of the chiral metabolites (**2-4**) has been determined. This letter outlines a new approach to the resolution and absolute configuration assignment of the enantiomers of arene oxide, **2**, *trans*-dihydrodiol, **3**, and *cis*-dihydrodiol, **4**, which are obtained by monooxygenase (**2** and **3**)- or by dioxygenase-catalysed (**4**)-oxidation at the 5,6-bond.



Racemic *trans*-6-bromo-5-hydroxy-5,6,7,8-tetrahydroquinoline, **5**, (obtained by treatment of 7,8-dihydroquinoline with N-bromoacetamide in aqueous THF) was resolved into enantiomers *via* the diastereoisomeric salts formed from (+) and (-)-dibenzoyltartaric acid. Thus, using (-)-dibenzoyltartaric acid as resolving agent, fractional crystallization from ethanol yielded the less soluble dibenzoyltartrate salt, (-)-**6**, as a pure diastereoisomer which upon treatment with base ($NaHCO_3$) gave the pure dextrorotatory enantiomer of the bromohydrin, (+)-**5**. Separation of the more soluble dibenzoyltartrate salt diastereoisomer proved to be much

more difficult. This problem was however circumvented by treatment of the residual enantiomerically enriched bromohydrin (recovered by base treatment of the ethanol mother liquors) with (+)-dibenzoyltartaric acid, by separation of the less soluble diastereoisomeric salt, **(+)-6**, and by isolation of the laevorotatory enantiomer of the bromohydrin, **(-)-5**, after basification.

X-ray structure analysis of a crystal of the dibenzoyltartrate salt, **(+)-6** (less soluble diastereoisomer obtained using [+]-[S,S]-dibenzoyltartaric acid) allowed confirmation of the [5R,6R] absolute configuration of the salt **(+)-6** and the parent bromohydrin, **(-)-5**. (Figure 1). Thus, a correlation of absolute configuration between the (+)-[5S, 6S]-bromohydrin, **5**, the (+)-[5S,6R]-arene oxide, **2**, the (-)-[5S,6R]-tetrahydroepoxide, **7**, and the (-)-[5R,6R]-*trans*-dihydrodiol, **3**, is evident from the synthetic sequence shown in Scheme 1 (previously reported[7] for the racemic metabolites **2** and **3**). Base-catalysed hydration of (-)-[5R,6S]-arene oxide, **2**, (derived from the (-)-[5R,6R]-enantiomer of bromohydrin **5**) yielded the (-)-[5R,6R]-*trans*-dihydrodiol, **3**. The latter sample of diol, **3** ($[\alpha]_D$ -100°) had a slightly lower $[\alpha]_D$ value than that obtained *via* the sequence **5 --> 7 --> 9 --> 10 --> 11 --> 12 --> 3** ($[\alpha]_D$ -107°) due to preferential rather than exclusive nucleophilic attack of hydroxide anion at the allylic (C-6) rather than the benzylic (C-5) centre.

The enantiomeric excess of arene oxide **2** was determined by chiral stationary phase HPLC analysis (Chiralcel OB, α 2.0, isopropanol [20%]: hexane [80%]) where the (+)-[5S,6R]-enantiomer was eluted early. Using the latter HPLC method the samples of arene oxide **2** (+22° and -23°) obtained from the corresponding dibenzoyltartrate salts **6** (-76° and +76°) were found to be enantiomerically homogeneous.

Chemical interconversion of the bromohydrin enantiomer (+)-[5S,6S]-**5** to the (+)-[5S,6R]-*cis*-tetrahydrodiol, **16**, was carried out using the bromoester, **13**, dioxolane, **14**, and hydroxy ester, **15**, intermediates shown in Scheme 1. Optical rotations were not recorded for compounds **8, 13, 14** and **15** since mixtures of tautomers **(13)**, structural isomers **(15)** and stereoisomers **(8)** and **(14)** were formed. Catalytic hydrogenation of *cis*-5,6-dihydroquinoline-5,6-diol, **4** ($[\alpha]_D$ +220°), which was isolated as a metabolite of quinoline from growing cultures of *P.putida* (UV4),[6,8] yielded the pure (-)-[5R,6S] enantiomer of the *cis*-tetrahydrodiol, **16** ($[\alpha]_D$ -7°). Thus, the dioxygenase enzyme in *P.putida* has an exclusive preference for the [5R,6S] enantiomer of the *cis*-dihydrodiol **4**.

On incubation of quinoline with liver microsomes from 3-methylcholanthrene-treated, immature male rats of the Long Evans strain in the presence of an epoxide hydrolase inhibitor (3,3,3-trichloropropene-1,2-oxide), the 5,6-arene oxide **2,** was shown to constitute 50-60% of the total metabolites and was found to have an excess of the [5R,6S]enantiomer (50% e.e.). In separate microsomal incubations, the metabolically predominant [5R,6S]arene oxide enantiomer **2** was shown to be the better epoxide hydrolase substrate and was converted (> 98% attack of water at C-6) to the [5R,6R]-enantiomer of the 5,6-dihydrodiol, **3**.

Treatment of the (-)-[5R,6R]-bromohydrin, **5**, with Ac_2O to yield the (-)-[5R,6R]-bromoacetate, **17**, followed by reductive dehalogenation using tributyltin hydride yielded (+)-[5S]-5-hydroxy-5,6,7,8-tetrahydroquinoline, **18**. The measured specific rotation for this enantiomer ($[\alpha]_D$ + 44°) was comparable in magnitude but opposite in sign to the value of $[\alpha]_D$ -44° previously assigned[9,10] to the [5S] enantiomer. The latter assignment thus appears to be incorrect.

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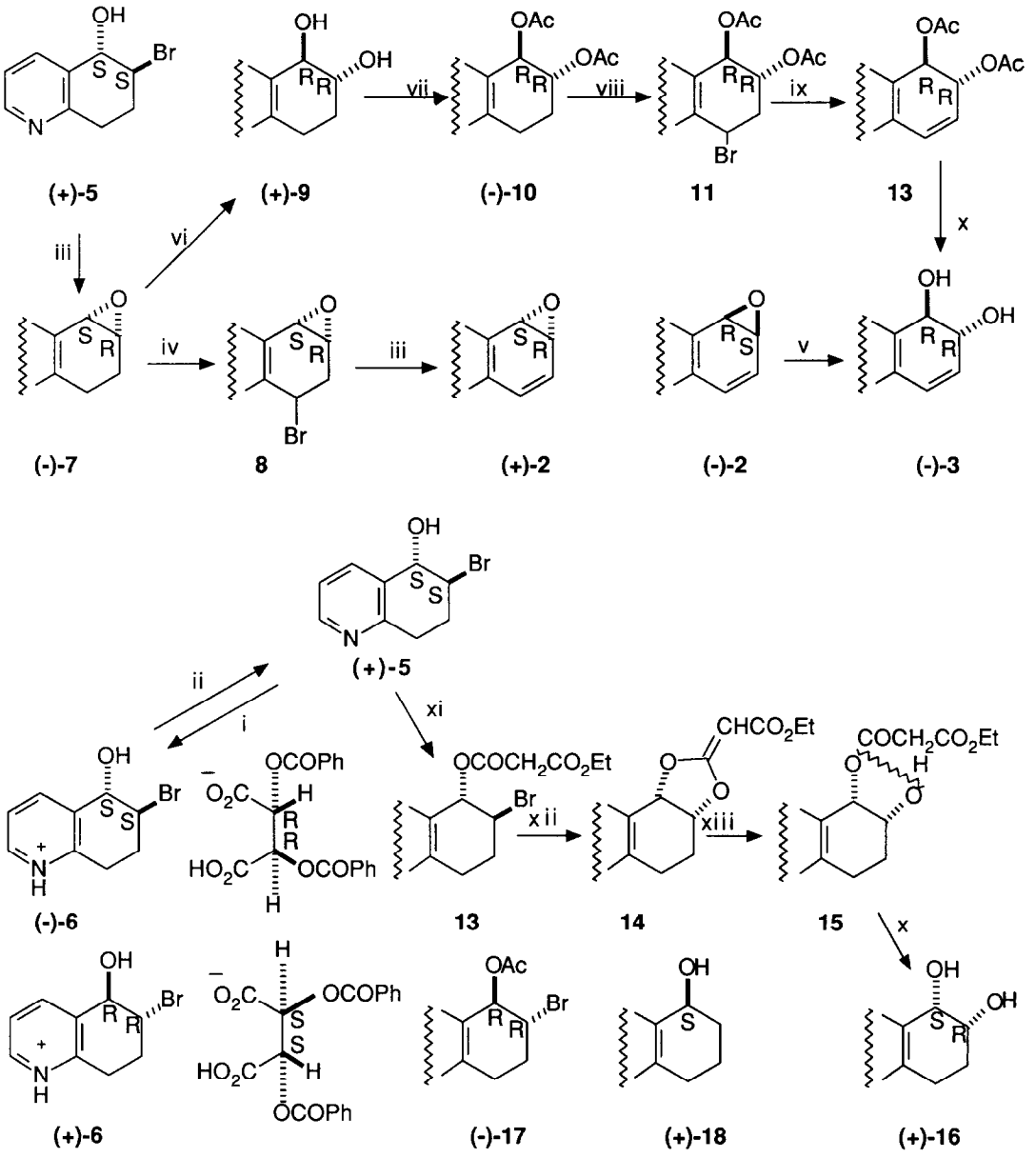

Reagents (% yields):

i Dibenzoyl tartaric acid(98) ii $NaHCO_3$ (98) iii NaOMe-THF (85 - 89)
iv NBS- CCl_4(83) v ^tBuOH- H_2O- KOH vi HCO_2H (70) vii Ac_2O-pyridine(91)
viii NBS-CCl_4 (91) ix DBN-THF (61) x NH_3-MeOH (77-83) xi $ClCOCH_2CO_2Et$ (93)
xii NaH-THF (83) xiii HCl-THF-H_2O

Scheme 1

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Table 1. Specific rotations and absolute configurations of chiral compounds related to quinoline metabolites

Compound	$[\alpha]_D$	Absolute Configuration	Compound	$[\alpha]_D$	Absolute Configuration
6	-76[a]	[5S,6S][b]	**9**	+97[e]	[5R,6R]
	+76[a]	[5R,6R][c]	**10**	-118[e]	[5R,6R]
5	+14[a]	[5S,6S]	**16**	+7[e]	[5S,6R]
7	-96[d]	[5S,6R]		-7[e,g]	[5R,6S]
2	+22[d]	[5S,6R]	**18**	+44[e]	[5S]
3	-107[e]	[5R,6R]			
	-100[e,f]	[5R,6R]			

(a) EtOH; (b) Salt from (-)-[R,R]-dibenzoyltartaric acid; (c) Salt from (+)-[S,S]-dibenzoyltartaric acid; (d) $CHCl_3$; (e) MeOH; (f) From (-)-[5R,6S] arene oxide, **2**; (g) Obtained by catalytic (Pd/C) hydrogenation of the metabolite from *P.putida*.

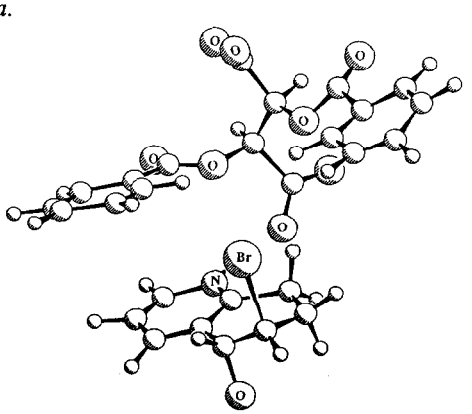

Figure 1

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