Synthesis of Arene Oxide and *trans*-Dihydro Diol Metabolites of Isoquinoline

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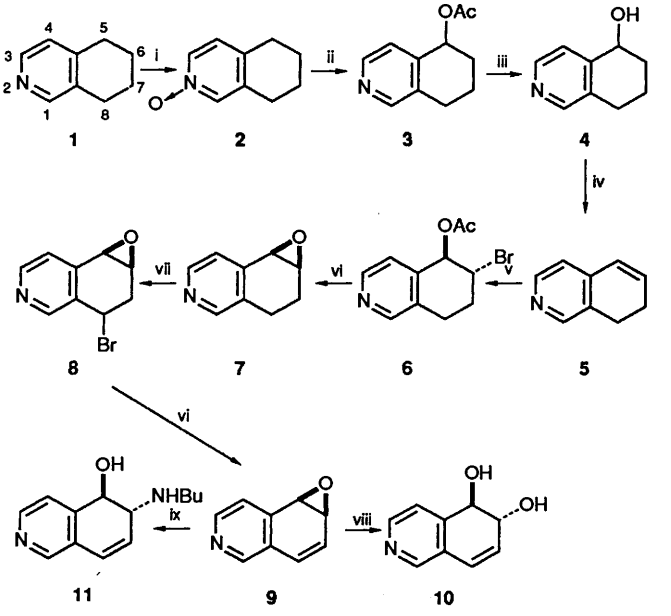
5,6-Epoxy-5,6-dihydroisoquinoline **9** and 7,8-epoxy-7,8-dihydroisoquinoline **21** were each obtained by multi-step synthetic sequences from 5,6,7,8-tetrahydroisoquinoline **1**. The mammalian metabolite, *trans*-5,6-dihydroisoquinoline-5,6-diol **10** was chemically synthesised by base-catalysed hydration of the isoquinoline arene oxide **9**.

The isomeric aza-arenes quinoline and isoquinoline are both prevalent in the respiratory environment (urban particulates and cigarette smoke).[1] Despite their close structural similarity, only quinoline has been found to be carcinogenic[2] and mutagenic.[3] Metabolism studies on quinoline, using either animal liver enzymes[4,5] (*in vitro*) or growing cultures of a soil bacterium (*in vivo*),[6] indicate preferential reactivity at the 5,6-bond. Thus, major liver microsomal metabolites include an arene oxide (5,6-epoxy-5,6-dihydroquinoline[5]) and a *trans*-dihydro diol (*trans*-5,6-dihydroquinoline-5,6-diol[5]). The *cis*-5,6-dihydro diol (*cis*-5,6-dihydroquinoline-5,6-diol) has been identified[6] as the major product when quinoline undergoes biotransformation by a mutant strain of *Pseudomonas putida* (UV4). In contrast, the metabolism of isoquinoline does not show a specific preference for the 5,6-bond. Although the action of liver enzymes[4] is reported to give *trans*-5,6-dihydroisoquinoline-5,6-diol **10** as one of the metabolites, *P. putida*[6] converts it mainly into *cis*-7,8-dihydroisoquinoline-7,8-diol.

By using chemically synthesised samples of the arene oxides and *trans*-dihydro diols of quinoline it has been possible to: (i) confirm the formation of *trans*-5,6-dihydroquinoline-5,6-diol as a major mammalian metabolite of quinoline,[5] (ii) detect 5,6-epoxy-5,6-dihydroquinoline as an initial metabolite when quinoline is treated with liver microsomal fractions,[5] (iii) establish that metabolism of quinoline at the 7,8-bond can occur as a very minor metabolic pathway[5] in mammals, and (iv) prove that hydrolysis of non-K-region arene oxides to yield *trans*-dihydro diols can occur by both enzymatic (epoxide hydrolase) and non-enzymatic routes in the quinoline series.[7,8] As a prelude to more detailed metabolism studies on isoquinoline, this paper describes chemical syntheses of its arene oxides, 5,6-epoxy-5,6-dihydroisoquinoline **9** and 7,8-epoxy-7,8-dihydroisoquinoline **21**, and of the *trans*-dihydro diol, *trans*-5,6-dihydroisoquinoline-5,6-diol **10**.

Results and Discussion

The synthetic route to the isoquinoline arene oxide 5,6-epoxy-5,6-dihydroisoquinoline **9** is outlined in Scheme 1. Peroxyacetic acid oxidation of commercially available 5,6,7,8-tetrahydroisoquinoline **1** gave 5,6,7,8-tetrahydroisoquinoline 2-oxide **2** (63%). Treatment of the *N*-oxide **2** with acetic anhydride yielded 5-acetoxy-5,6,7,8-tetrahydroisoquinoline **3** (58%). The yields of the *N*-oxide **2** and acetate **3** were lower than those previously reported[5] for the synthesis of the corresponding derivatives from 5,6,7,8-tetrahydroquinoline (77 and 72% respectively). This typically reflects the lower stability of many synthetic intermediates and the greater tendency to form side products (*e.g.* by deoxygenation of the *N*-oxide **2**) in the isoquinoline series as compared with their quinoline counterparts.



Scheme 1 *Reagents and conditions:* i, H_2O_2, AcOH; ii, Ac_2O; iii, HCl; iv, PPA; v, NBA, LiOAc, AcOH; vi, NaOMe, THF; vii, NBS, CCl_4; viii, KOH, Bu'OH; ix, $BuNH_2$

Acid-catalysed hydrolysis of the acetate **3** yielded the alcohol **4** (72%) which was dehydrated, with polyphosphoric acid (PPA) at 90–100 °C, to give 7,8-dihydroisoquinoline **5** (51%). Careful temperature control was essential during this dehydration step because isomerization of 7,8-dihydroisoquinoline **5** to 5,6-dihydroisoquinoline **17** occurred readily at ≥ 120 °C. Separation of the mixture of olefins **5** and **17** resulting from thermal isomerization, proved to be extremely difficult. Treatment of 7,8-dihydroisoquinoline **5** with *N*-bromoacetamide (NBA) and lithium acetate in acetic acid yielded a red oil which was identified as *trans*-5-acetoxy-6-bromo-5,6,7,8-tetrahydroisoquinoline **6** (crude yield 94%). Attempted purification of this material by flash chromatography on silica gel (using 4% methanol, 1% triethylamine in chloroform as eluent) resulted in decomposition but treatment with decolorizing charcoal in dichloromethane solution, followed by rapid filtration and recrystallization, gave the required pure bromoacetate **6** in a very low yield.

The crude bromoacetate **6** was therefore used in preparing 5,6-epoxy-5,6,7,8-tetrahydroisoquinoline **7** by the action of sodium methoxide in anhydrous tetrahydrofuran (THF). Distillation of the epoxide **7** under reduced pressure gave a colourless oil (79% yield) which became dark upon exposure to air as a result of autoxidation. Consequently, the epoxide **7** was

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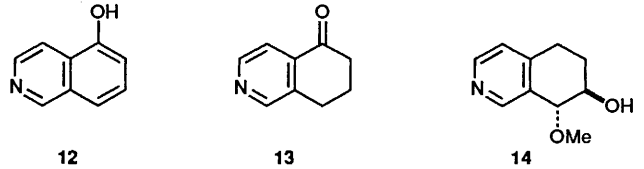
distilled immediately before use or stored at −70 °C in the absence of air. In view of the aerial instability of the epoxide **7**, the bulk of the bromo epoxide **8** (obtained by treatment of freshly distilled tetrahydro epoxide **7** with *N*-bromosuccinimide, NBS) was used without purification. ^{1}H NMR analysis of the crude product mixture containing **8** indicated the presence of two stereoisomers which were not separated. Treatment of crude 8-bromo-5,6-epoxy-5,6,7,8-tetrahydroisoquinoline **8** with sodium methoxide in THF gave the required arene oxide **9** which was purified by recrystallisation (diethyl ether–pentane at −70 °C). The overall yield of the arene oxide **9** from the alcohol precursor **4** was *ca.* 21% and contrasts with a yield of *ca.* 50% for a comparable sequence of reactions in the quinoline series.[5]

In common with many of the isoquinoline derivatives synthesised (**2**–**8**), colourless crystals of 5,6-epoxy-5,6-dihydroisoquinoline **9** rapidly became dark when stored in contact with air, even at 0 °C. Although susceptible to aerial oxidation, the arene oxide **9** was stable up to 100 °C in the neat state when kept under an atmosphere of nitrogen. It aromatized, under acid conditions, when two drops of trifluoroacetic acid were added to an NMR sample of **9** in $CDCl_3$ solution. The major (>95%) product of aromatization was identified as isoquinolin-5-ol **12** by GLC–MS and ^{1}H NMR analysis in comparison with an authentic sample. The reported formation of isoquinolin-5-ol **12** as a metabolite of isoquinoline[4] could thus result from aromatization of the arene oxide **9** or from dehydration of the *trans*-dihydro diol **10** during either metabolism or the work-up procedure.

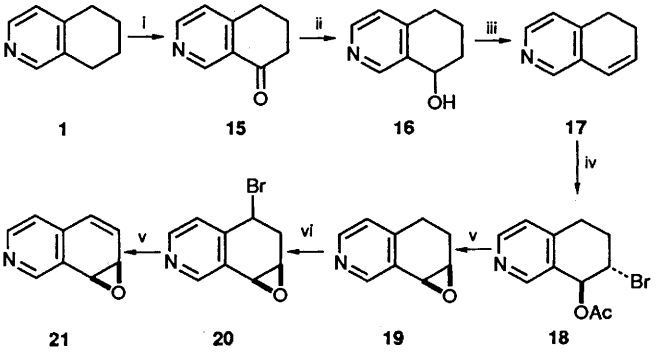


12 **13** **14**

Previous work with 5,6-epoxy-5,6-dihydroquinoline had indicated[10] that (in contrast to all non-K-region and bay-region arene oxides in the polycyclic aromatic hydrocarbon series[9]) this arene oxide from the azapolycyclic aromatic hydrocarbon series was sufficiently stable toward aromatization that it could undergo hydrolysis by aqueous alkali to yield the corresponding *trans*-dihydro diol. In order to determine if other epoxide derivatives of aza-arenes could be similarly hydrolysed, the isoquinoline arene oxide **9** was stirred with potassium hydroxide in an aqueous solution of *tert*-butyl alcohol. *trans*-5,6-Dihydroisoquinoline-5,6-diol **10** was isolated (40% yield) by preparative TLC from a mixture containing mainly aromatized products. Upon storage at *ca.* 0 °C over an extended period, a pure sample of the *trans*-diol **10** dehydrated spontaneously to give isoquinolin-5-ol **12**. The *trans*-diol **10** is the expected product of epoxide hydrolase catalysed hydrolysis of the arene oxide **9** during liver microsomal metabolism of isoquinoline. LaVoie *et al.*[4] detected an isomer of 5,6-dihydroisoquinoline-5,6-diol as a minor mammalian metabolite of isoquinoline by GLC–MS analysis, but did not assign its stereochemistry. This metabolite can now be identified as the *trans*-diol **10** because the reported mass spectral fragmentation pattern of its bis silylated (TMS) derivative[4] closely resembles that of silylated compound **10** and is quite different from the pattern observed for the corresponding bis silylated *cis*-diol, *cis*-5,6-dihydroisoquinoline-5,6-diol.[11] The ready dehydration of **10** to give isoquinolin-5-ol is also in agreement with the observations of LaVoie *et al.*[4]

Nucleophilic attack of butylamine (40 °C, 24 h) on 5,6-epoxy-5,6-dihydroisoquinoline **9** occurred preferentially (90%) at the C-6 position. The product **11** was separated by preparative TLC and identified as *trans*-6-butylamino-5,6-dihydroisoquinolin-5-ol. Nucleophilic attack at the allylic position of compound **9** is consistent with previously reported[10] results for the 5,6- and 7,8-arene oxides of quinoline which suggests that hydrolysis of the arene oxide **9** also proceeds by attack of hydroxide ion at C-6.

Synthesis of the isomeric arene oxide of isoquinoline, 7,8-epoxy-7,8-dihydroisoquinoline, **21** (Scheme 2), proved to be more difficult than for the arene oxide **9** since the ketone precursor **15** was not readily available. A literature method[12] for its preparation involves oxidation of 5,6,7,8-tetrahydroisoquinoline **1** using chromium trioxide in a solution of acetic acid–sulfuric acid and separation of the ketone products **15** and **13** by fractional crystallization of the hydrochloride salts. However, this procedure was found to be very tedious and resulted in a very low yield of the desired ketone **15**. An improved separation of the ketone **15** was achieved by fractional distillation using a spinning band column. By this method, a mixture of 5,6,7,8-tetrahydroisoquinoline **1** (30%) and 7,8-dihydroisoquinolin-5(6*H*)-one **13** (30%) was separated leaving 5,6-dihydroisoquinolin-7(8*H*)-one **15** (40%) as a residual fraction. This material was purified by flash chromatography on silica gel and recrystallised from diethyl ether–pentane to give a pure sample in low yield (25%) which was reduced with sodium borohydride to the alcohol **16** (89%). Similar conditions to those used in the synthesis of the arene oxide **9** (careful control of temperature during dehydration of alcohol **16**, minimal exposure of products to air and, where possible, utilization of intermediates in the crude form) were employed in the synthesis of 7,8-epoxy-7,8-dihydroisoquinoline **19**. The base-catalysed cyclization of the bromoacetate **18** was less efficient than the analogous step between compounds **6** and **7** owing to the susceptibility of the tetrahydro epoxide **19** to nucleophilic attack by methoxide ion. Thus, compound **19** was formed in equal proportion with *trans*-8-methoxy-5,6,7,8-tetrahydroisoquinolin-7-ol **14** and had to be separated by preparative TLC. Following benzylic bromination to yield an isomeric mixture of compound **20**, and treatment of the crude product with sodium methoxide, the overall yield of arene oxide **21** from alcohol **16** was *ca.* 18%.



Scheme 2 *Reagents and conditions:* i, CrO_3. H_2SO_4, AcOH; ii, $NaBH_4$, MeOH; iii, PPA; iv, NBA, LiOAc, AcOH; v, NaOMe; vi, NBS, CCl_4

Both the arene oxides of isoquinoline, **9** and **21**, were unstable in air and rapidly underwent autoxidation. However, like their quinoline analogues, the arene oxides **9** and **21** could be heated to a temperature of *ca.* 100 °C in the neat state under a nitrogen atmosphere before undergoing decomposition. This high thermal stability confirms that the presence of the nitrogen heteroatom is a stabilizing feature in the arene oxide derivatives of aza-arenes.

In conclusion, the first chemical syntheses of 5,6-epoxy-5,6-dihydroisoquinoline **9** and 7,8-epoxy-7,8-dihydroisoquinoline **21** have been achieved. An interesting property of these compounds is their relative resistance towards aromatization in the presence of nucleophiles which contrasts with the behaviour

of their polycyclic aromatic hydrocarbon analogues. This is exemplified by the ability of aza-arene oxide **9** to undergo nucleophilic attack to form a *trans*-dihydro diol **10** and a *trans*-hydroxyamino adduct **11**. The chemical synthesis of the *trans*-dihydro diol **10** allows its identity as a minor metabolite of isoquinoline to be confirmed.

Experimental

^{1}H NMR spectra were recorded at 300 MHz with a General Electric QE300 instrument. Tetramethylsilane was used as an internal reference and deuteriochloroform as solvent unless otherwise stated. Coupling constants are recorded as Hz. Mass spectra were recorded at 70 eV on an AEI-MS902 instrument updated by VG instruments. Accurate molecular masses were determined by the peak matching method using perfluorokerosene as reference. GLC–MS analyses were carried out using a VG 12-250 instrument linked to a PDP11/23 PLUS data system and a 25 m BP1 column. 5,6,7,8-Tetrahydroisoquinoline was purchased from the Aldrich Chemical Company.

5,6,7,8-*Tetrahydroisoquinoline 2-Oxide* **2**.—5,6,7,8-Tetrahydroisoquinoline (25 g, 0.19 mol) was treated with hydrogen peroxide (20 ml, 60%) in acetic acid (75 ml), and heated at 90 °C for 8 h. A second portion of hydrogen peroxide (20 ml) was added and the solution was heated for a further 12 h. The reaction mixture was concentrated under reduced pressure, cooled, basified (saturated aqueous sodium carbonate) and extracted with chloroform (3 × 150 ml). The combined extracts were dried ($MgSO_4$), evaporated under reduced pressure and the crude product recrystallized from diethyl ether to give colourless crystals of the title compound **2** (17.5 g, 63%), m.p. 36–38 °C (lit.,[13] b.p. 170–173 °C at 3 mmHg); δ_H 1.84 (4 H, m, 6-H and 7-H), 2.76 (4 H, m, 5-H and 8-H), 7.06 (1 H, d, $J_{3,4}$ 6.5, 4-H), 8.11 (1 H, d, $J_{3,4}$ 6.5, 3-H) and 8.14 (1 H, s, 1-H).

5-*Acetoxy*-5,6,7,8-*tetrahydroisoquinoline* **3**.—A cold solution of 5,6,7,8-tetrahydroisoquinoline 2-oxide **2** (17.5 g, 0.12 mol) in acetic anhydride (40 ml) was added dropwise over 0.5 h to refluxing acetic anhydride (60 ml). The solution was heated under reflux for 3 h after which the acetic anhydride was removed under reduced pressure and the crude product distilled *in vacuo* to yield the title compound **3** (13.1 g, 58%), b.p. 100–104 °C at 0.6 mmHg (lit.,[14] b.p. 112–115 °C at 0.8 mmHg); δ_H 1.95 (4 H, m, 6-H and 7-H), 2.12 (3 H, s, OCOMe), 2.79 (2 H, m, 8-H), 5.93 (1 H, t, $J_{5,6}$ 5.1, 5-H), 7.16 (1 H, d, $J_{3,4}$ 5.1, 4-H) and 8.39 (2 H, m, 3-H and 1-H).

5,6,7,8-*Tetrahydroisoquinolin*-5-*ol* **4**.—5-Acetoxy-5,6,7,8-tetrahydroisoquinoline **3** (13 g, 68 mmol) was heated under reflux overnight with 10% hydrochloric acid (100 ml) after which it was basified with sodium hydroxide and extracted with dichloromethane (4 × 100 ml). The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the residue recrystallized from hexane to yield the title compound **4** (7.5 g, 72%), m.p. 89–91 °C (lit.,[14] 90–91 °C); δ_H 1.82 (2 H, m, 7-H), 2.00 (1 H, m, 6-H), 2.09 (1 H, m, 6′-H), 2.75 (2 H, m, 8-H), 2.99 (1 H, br s, OH), 4.73 (1 H, m, 5-H), 7.39 (1 H, d, $J_{3,4}$ 5.1, 4-H), 8.31 (1 H, s, 1-H) and 8.36 (1 H, d, $J_{3,4}$ 5.1, 3-H).

7,8-*Dihydroisoquinoline* **5**.—5,6,7,8-Tetrahydroisoquinolin-5-ol **4** (5 g, 34 mmol) was heated and stirred with polyphosphoric acid (50 g) at 90–100 °C. The reaction, the progress of which was monitored by TLC analysis (silica gel, using diethyl ether as eluent), was complete within 40 min. The mixture was diluted with water (100 ml), cooled to 0 °C, basified with sodium hydroxide and extracted with diethyl ether (4 × 150 ml). The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the product, the title compound **5**, was distilled (1.8 g, 51%), b.p. 46–48 °C at 0.25 mmHg (Found: C, 82.5; H, 7.0; N, 10.9. C_9H_9N requires C, 82.4; H, 6.9; N, 10.7%); δ_H 2.36 (2 H, m, 7-H), 2.76 (2 H, m, 8-H), 6.24 (1 H, m, 6-H), 6.41 (1 H, dd, $J_{5,6}$ 9.6, $J_{5,7}$ 1.6, 5-H), 6.87 (1 H, d, $J_{3,4}$ 4.9, 4-H), 8.31 (1 H, s, 1-H) and 8.37 (1 H, d, $J_{3,4}$ 4.9, 3-H).

trans-5-*Acetoxy*-6-*bromo*-5,6,7,8-*tetrahydroisoquinoline* **6**.—*N*-Bromoacetamide (1.36 g, 9.8 mmol) was added to a solution of 7,8-dihydroisoquinoline **5** (1.17 g, 8.9 mmol) and lithium acetate (1.26 g, 19.1 mmol) in acetic acid (20 ml) and the mixture was stirred at room temperature for 3 h. It was then concentrated under reduced pressure, cooled to 5 °C and basified using saturated aqueous sodium carbonate. The product was extracted with dichloromethane (3 × 40 ml) and the extracts were dried (K_2CO_3) and evaporated to yield the crude title compound **6** (2.26 g, 94%) as a red oil. A small portion was heated in dichloromethane in the presence of decolourizing charcoal and the solution filtered and evaporated to give the bromoacetate **6** which crystallized from dichloromethane–pentane as colourless crystals, m.p. 207–209 °C (Found: C, 48.6; H, 4.2; N, 5.0. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.4; N, 5.2%); δ_H 2.14 (3 H, s, OCOMe), 2.32 (1 H, m, 7-H), 2.48 (1 H, m, 7′-H), 2.92 (1 H, m, 8-H), 3.03 (1 H, m, 8′-H), 4.42 (1 H, m, 6-H), 6.10 (1 H, d, $J_{5,6}$ 5.3, 5-H), 7.14 (1 H, d, $J_{3,4}$ 5.2, 4-H), 8.44 (1 H, d, $J_{3,4}$ 5.3, 3-H) and 8.47 (1 H, s, 1-H). Owing to its instability, the bulk of the bromoacetate **6** was used immediately without purification.

5,6-*Epoxy*-5,6,7,8-*tetrahydroisoquinoline* **7**.—To a solution of the crude tetrahydroisoquinoline **6** (2.1 g, 7.8 mmol) in dry THF (50 ml) was added sodium methoxide (2.1 g) and the solution was stirred at room temperature for 4 h. It was then evaporated under reduced pressure, diluted with water (20 ml) and extracted with dichloromethane (3 × 40 ml). The extract was dried ($MgSO_4$), concentrated under reduced pressure, and distilled under reduced pressure to yield the pure *title compound* **7** (0.9 g, 79%), b.p. 61–66 °C at 0.05 mmHg (Found: C, 73.1; H, 6.6; N, 9.6. C_9H_9NO requires C, 73.5; H, 6.1; N, 9.5%); δ_H 1.76 (1 H, m, 7-H), 2.54 (1 H, m, 7′-H), 2.70 (2 H, m, 8-H), 3.78 (2 H, m, 5-H and 6-H), 7.33 (1 H, d, $J_{3,4}$ 4.8, 4-H), 8.34 (1 H, s, 1-H) and 8.45 (1 H, d, $J_{3,4}$ 4.8, 3-H).

8-*Bromo*-5,6-*epoxy*-5,6,7,8-*tetrahydroisoquinoline* **8**.—The freshly distilled tetrahydroisoquinoline **7** (0.2 g, 1.36 mmol) was brominated with *N*-bromosuccinimide (0.266 g, 1.5 mmol) in carbon tetrachloride (60 ml) at 60–70 °C for *ca.* 40 min under nitrogen in the presence of azoisobutyronitrile as initiator. The succinimide by-product was filtered off and the filtrate was evaporated to give the *title compound* **8** as an oil (0.28 g, 91%); ^{1}H NMR analysis showed the presence of two isomers but owing to their instability these were not purified further or separated (Found: M^+, 226.9779. $C_9H_8{}^{81}BrNO$ requires *M*, 226.9770); δ_H(major isomer) 2.51 (1 H, dd, $J_{7,7'}$ 16.8, $J_{7,8}$ 5.6, 7-H), 3.10 (1 H, d, $J_{7,7'}$ 16.8, 7′-H), 3.78 (1 H, m, 6-H), 3.88 (1 H, d, $J_{5,6}$ 4.2, 5-H), 5.37 (1 H, d, $J_{7,8}$ 5.5, 8-H), 7.43 (1 H, d, $J_{3,4}$ 4.9, 4-H), 8.56 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.58 (1 H, s, 1-H).

5,6-*Epoxy*-5,6-*dihydroisoquinoline* **9**.—Sodium methoxide (0.28 g) was added to a solution of the bromo epoxide isomers **8** (0.28 g, 1.24 mmol) in dry THF (100 ml) under nitrogen and the mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. It was then evaporated under reduced pressure and the residue dissolved in water (25 ml) and the product extracted into dichloromethane (4 × 40 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give a yellow oil which when crystallized from diethyl ether–pentane at −70 °C yielded colourless crystals of the title compound **9**

(0.11 g, 62%), m.p. 60–62 °C (Found: M^+, 145.0528. C_9H_7NO requires *M*, 145.0528); δ_H 4.16 (1 H, m, 6-H), 4.43 (1 H, d, $J_{5,6}$ 3.7, 5-H), 6.56 (1 H, dd, $J_{7,8}$ 9.6, $J_{6,7}$ 3.7, 7-H), 6.82 (1 H, dd, $J_{7,8}$ 9.6, $J_{6,8}$ 0.9, 8-H), 7.55 (1 H, d, $J_{3,4}$ 5.0, 4-H), 8.56 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.60 (1 H, s, 1-H). Addition of trifluoroacetic acid (2 drops) to an NMR sample of the arene oxide **9** (5 mg in 1 ml $CDCl_3$) yielded isoquinolin-5-ol **12**, whose ^1H NMR and GLC-MS characteristics were identical with those of a reference sample.

trans-5,6-*Dihydroisoquinoline*-5,6-*diol* **10**.—The dihydroisoquinoline **9** (0.04 g, 0.28 mmol) dissolved in *tert*-butyl alcohol (1 ml) and water (1 ml) containing potassium hydroxide (0.023 g, 0.41 mmol) was stirred at room temperature for 7 days. The solution was diluted with water (4 ml), saturated with sodium carbonate and extracted with ethyl acetate (5 × 10 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude product. ^1H NMR spectral analysis indicated that no starting material remained and that the *trans*-dihydro diol **10** had been formed in a yield of *ca.* 40% with the residual portion being aromatized. Purification of the *trans*-diol **10** by preparative TLC on silica gel (6% MeOH in $CHCl_3$ as eluent) followed by crystallization from ethyl acetate yielded the *title compound* (0.012 g, 27%), m.p. 170–190 °C (decomp.) (Found: M^+, 163.0636. $C_9H_9NO_2$ requires M^+, 163.0633); δ_H 4.41 (2 H, br s, 2 × OH), 4.59 (1 H, d, $J_{5,6}$ 11.7, 6-H), 4.86 (1 H, d, $J_{5,6}$ 11.6, 5-H), 6.06 (1 H, d, $J_{7,8}$ 9.8, 7-H), 6.42 (1 H, d, $J_{7,8}$ 9.8, 8-H), 7.54 (1 H, d, $J_{3,4}$ 4.7, 4-H), 8.28 (1 H, s, 1-H) and 8.46 (1 H, d, $J_{3,4}$ 4.8, 3-H). The *trans*-diol **10** upon treatment with bis-trimethylsilylacetamide yielded the bis-trimethylsilyl ether which showed a characteristic MS pattern: *m/z* 307 (M^+, 34), 147 (48), 75 (14) and 73 (100). The *trans*-diol **10** was found to decompose to isoquinolin-5-ol **12**, after prolonged storage at *ca.* 0 °C.

trans-6-*Butylamino*-5,6-*dihydroisoquinolin*-5-*ol* **11**.—The dihydroisoquinoline **9** (0.04 g, 0.28 mmol) was heated in butylamine (0.5 ml) at *ca.* 40 °C for 24 h after which excess of butylamine was removed under reduced pressure to give the crude product. This was shown by ^1H NMR analysis to be a mixture of two isomers in a ratio of 10:1. Preparative TLC on silica gel (1% triethylamine and 8% methanol in dichloromethane) followed by crystallization from dichloromethane–diethyl ether yielded the major isomer which was identified as the *title compound* **11** (0.038 g, 63%), m.p. 114–116 °C (Found: M^+, 218.1419. $C_{13}H_{18}N_2O$ requires *M*, 218.1419); δ_H 0.93 (3 H, t, *J* 7.1, Me), 1.40 (2 H, m, CH_2Me), 1.53 (2 H, m, CH_2Et), 2.60 (1 H, m, NCH_2), 2.91 (1 H, m, NCH_2), 3.46 (1 H, m, 6-H), 4.65 (1 H, d, $J_{5,6}$ 12.5, 5-H), 6.13 (1 H, dd, $J_{7,8}$ 9.8, $J_{6,7}$ 1.9, 7-H), 6.48 (1 H, dd, $J_{7,8}$ 9.9, $J_{6,8}$ 2.4, 8-H), 7.51 (1 H, d, $J_{3,4}$ 4.8, 4-H), 8.28 (1 H, s, 1-H) and 8.46 (1 H, d, $J_{3,4}$ 4.9, 3-H).

5,6-*Dihydroisoquinolin*-8(7H)-*one* **15**.—To a mechanically stirred solution of the tetrahydroisoquinoline **1** (15.5 g, 0.116 mol) in acetic acid (80 ml) and sulphuric acid (30 ml) at 15–20 °C, was added a solution of chromium trioxide (21.6 g, 0.216 mol) in acetic acid (45 ml) and water (13 ml) over a 2 h period. The solution was stirred for a further 3 h before being concentrated under reduced pressure and basified with aqueous sodium hydroxide. The product was extracted with diethyl ether (4 × 200 ml) and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure. ^1H NMR analysis showed the presence of unchanged starting compound **1** (30%), 7,8-dihydroisoquinolin-5(6*H*)-*one* **13** (30%) and 5,6-dihydroisoquinolin-8(7*H*)-*one* **15** (40%). Separation of this mixture was achieved using a spinning band column (Perkin-Elmer Microstill M-131T) to yield compounds **1** (65–75 °C at 3.0–3.5 mmHg), **13** (87–90 °C at 2.5–3.0 mmHg) and a residue of compound **15**. After flash chromatography on silica gel, using 6% methanol in dichloromethane as eluent, the latter ketone was crystallized from diethyl ether–pentane to yield the title compound **15** (4.2 g, 25%), m.p. 42–44 °C (lit.,[12] b.p. 123–124 °C at 12 mmHg) (Found: C, 73.6; H, 6.2; N, 9.7. Calc. for C_9H_9NO: C, 73.5; H, 6.1; N, 9.5%); δ_H 2.18 (2 H, m, 6-H), 2.70 (2 H, t, $J_{6,7}$ 6.5, 7-H), 2.97 (2 H, t, $J_{5,6}$ 5.8, 5-H), 7.18 (1 H, d, $J_{3,4}$ 5.1, 4-H), 8.61 (1 H, d, $J_{3,4}$ 5.1, 3-H) and 9.16 (1 H, s, 1-H).

5,6,7,8-*Tetrahydroisoquinolin*-8-*ol* **16**.—Sodium borohydride (4.0 g, 10.4 mmol) was added portionwise to a solution of compound **15** (4.0 g, 27.2 mmol) in methanol (120 ml) at 0 °C over 1 h. Stirring was then continued at 0 °C for 1 h and at room temperature overnight. The solvent was evaporated and the residue diluted with water and extracted with dichloromethane (4 × 150 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Recrystallization of the residue from diethyl ether–pentane gave the *title compound* **16** (3.6 g, 89%), m.p. 70–72 °C (Found: C, 72.8; H, 7.7; N, 9.3. $C_9H_{11}NO$ requires C, 72.5; H, 7.4; N, 9.4%); δ_H 1.82 (1 H, m, 6-H), 1.99 (3 H, m, 6′-H and 7-H), 2.75 (3 H, m, 5-H and OH), 4.86 (1 H, m, 8-H), 7.01 (1 H, d, $J_{3,4}$ 5.1, 4-H), 8.33 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.60 (1 H, s, 1-H).

5,6-*Dihydroisoquinoline* **17**.—5,6,7,8-Tetrahydroisoquinolin-8-ol **16** (3.5 g, 23.5 mmol) was dehydrated with polyphosphoric acid (35 g) using a similar procedure (90 °C for 40 min) to that described for the alkene **5**. The *title compound* **17** (2.7 g, 88%) was obtained after distillation, b.p. 46–47 °C at 0.5 mmHg (Found: C, 82.2; H, 6.8; N, 11.0. C_9H_9N requires C, 82.4; H, 6.9; N, 10.7%); δ_H 2.37 (2 H, m, 6-H), 2.80 (2 H, t, $J_{5,6}$ 8.3, 5-H), 6.12 (1 H, m, 7-H), 6.48 (1 H, d, $J_{7,8}$ 9.6, 8-H), 7.02 (1 H, d, $J_{3,4}$ 5.0, 4-H), 8.22 (1 H, s, 1-H) and 8.31 (1 H, d, $J_{3,4}$ 4.9, 3-H).

trans-8-*Acetoxy*-7-*bromo*-5,6,7,8-*tetrahydroisoquinoline* **18**.—The dihydroisoquinoline **17** (1.6 g, 12.2 mmol) was treated with *N*-bromoacetamide (1.9 g, 13.8 mmol) and lithium acetate (1.5 g) in acetic acid (30 ml) in a similar manner to that described for compound **6** to yield the crude bromoacetate **18** as a red solid (2.8 g, 85%). Purification of a small portion by charcoal decolorization and crystallization from dichloromethane–pentane gave the *title compound* **18**, m.p. 84–86 °C (Found: C, 48.6; H, 4.4; N, 4.95. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.4; N, 5.2%); δ_H 2.10 (3 H, s, OCOMe), 2.23 (1 H, m, 6-H), 2.45 (1 H, m, 6′-H), 2.87 (1 H, m, 5-H), 3.08 (1 H, m, 5′-H), 4.51 (1 H, m, 7-H), 6.14 (1 H, d, $J_{7,8}$ 4.0, 8-H), 7.10 (1 H, d, $J_{3,4}$ 5.1, 4-H), 7.45 (1 H, d, $J_{3,4}$ 5.1, 3-H) and 8.50 (1 H, s, 1-H). The crude bromoacetate **18** was used immediately without purification owing to its instability.

7,8-*Epoxy*-5,6,7,8-*tetrahydroisoquinoline* **19**.—The crude tetrahydro isoquinoline **18** (2.7 g, 0.01 mol) was treated with sodium methoxide (2.7 g) in THF (100 ml) using the method described for compound **7**. ^1H NMR analysis of the crude product showed that it comprised equal amounts of two components. Separation was achieved by preparative TLC on silica gel (1% triethylamine in diethyl ether as eluent). On distillation under reduced pressure, the component with higher R_f gave pure *title compound* **19** (0.62 g, 42%), b.p. 90–100 °C at 0.1 mmHg (Found: C, 73.1; H, 6.3; N, 9.2. C_9H_9NO requires C, 73.5; H, 6.1; N, 9.5%); δ_H 1.77 (1 H, m, 6-H), 2.51 (2 H, m, 6′-H and 5-H), 2.77 (1 H, m, 5′-H), 3.79 (1 H, m, 7-H), 3.91 (1 H, d, $J_{7,8}$ 4.2, 8-H), 7.02 (1 H, d, $J_{3,4}$ 4.9, 4-H), 8.47 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.59 (1 H, s, 1-H).

The second component was identified as trans-8-*methoxy*-5,6,7,8-*tetrahydroisoquinolin*-7-*ol* **14** (0.72 g, 40%), m.p. 100–106 °C (decomp.) (diethyl ether–pentane) (Found: M^+, 179.0940. $C_{10}H_{13}NO_2$ requires *M*, 179.0946); δ_H 1.91 (1 H, m,

6-H), 2.15 (1 H, m, 6′-H), 2.73 (1 H, m, 5-H), 2.90 (1 H, br s, OH), 3.04 (1 H, m, 5′-H), 3.55 (3 H, s, OMe), 4.14 (1 H, m, 7-H), 4.28 (1 H, d, $J_{7,8}$ 3.4, 8-H), 7.06 (1 H, d, $J_{3,4}$ 5.1, 4-H), 8.40 (1 H, d, $J_{3,4}$ 5.1, 3-H) and 8.57 (1 H, s, 1-H).

5-Bromo-7,8-epoxy-5,6,7,8-tetrahydroisoquinoline **20**.—Freshly distilled 7,8-epoxy-5,6,7,8-tetrahydroisoquinoline **19** (0.20 g, 1.36 mmol) was brominated with *N*-bromosuccinimide (0.266 g, 1.5 mmol) in carbon tetrachloride (60 ml) to give the *product* **20** (0.26 g, 85%) using the procedure described in the synthesis of the bromo epoxide **8**. ^{1}H NMR analysis showed that the reaction had gone to completion yielding two stereoisomers (1:2). Recrystallization from hexane–dichloromethane gave the major isomer of the title compound **20**, m.p. 162–172 °C (decomp.) (Found: M^+, 224.9790. $C_9H_8{}^{79}BrNO$ requires *M*, 224.9790); δ_H 2.53 (1 H, dd, $J_{6,6'}$ 16.9, $J_{5,6}$ 5.5, 6-H), 3.10 (1 H, m, 6′-H), 3.93 (1 H, m, 7-H), 4.04 (1 H, d, $J_{7,8}$ 3.9, 8-H), 5.21 (1 H, d, $J_{5,6}$ 5.6, 5-H), 7.21 (1 H, d, $J_{3,4}$ 5.0, 4-H), 8.60 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.73 (1 H, s, 1-H).

7,8-Epoxy-7,8-dihydroisoquinoline **21**.—5-Bromo-7,8-epoxy-5,6,7,8-tetrahydroisoquinoline **20** (0.25 g, 1.11 mmol) was treated with sodium methoxide (0.25 g) in THF (100 ml) in the manner described for the bromo epoxide **8**. The *title compound* **21** (0.11 g, 69%) was obtained after recrystallization from diethyl ether–pentane at −70 °C, m.p. 56–60 °C (decomp.) (Found: M^+, 145.0528. C_9H_7NO requires *M*, 145.0528); δ_H 4.17 (1 H, m, 7-H), 4.54 (1 H, d, $J_{7,8}$ 3.8, 8-H), 6.73 (2 H, m, 5-H and 6-H), 7.20 (1 H, d, $J_{3,4}$ 5.0, 4-H), 8.62 (1 H, d, $J_{3,4}$ 5.0, 3-H) and 8.85 (1 H, s, 1-H).

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