120 °C for 24 h. A similar workup as described in the general procedure for the reduction of aromatic ketones and purification by column chromatography on silica gel resulted in the recovery of 1-phenylethanol (94%).

Registry No. **1a**, 98-86-2; **1b**, 99-91-2; **1c**, 709-63-7; **1d**, 93-55-0; **1e**, 611-70-1; **1f**, 938-16-9; **1g**, 529-34-0; **1h**, 83-33-0; **1i**, 93-08-3; **1j**, 941-98-0; **1k**, 1122-62-9; **1l**, 1192-62-7; **1m**, 88-15-3; **2**, 100-41-4; **7**, 98-85-1; **8**, 109445-64-9; DBU, 6674-22-2; *p*-ClC_6H_4Et, 622-98-0; *p*-$CF_3C_6H_4Et$, 27190-69-8; $Ph(CH_2)_2CH_3$, 103-65-1; $PhCH_2CH(CH_3)_2$, 538-93-2; $PhCH_2C(CH_3)_3$, 1007-26-7; Se, 7782-49-2; H_2O, 7732-18-5; CO, 630-08-0; *p*-MeC_6H_4Ac, 122-00-9; NaSeH, 12195-50-5; *p*-MeC_6H_4Et, 622-96-8; 1,2,3,4-tetrahydronaphthalene, 119-64-2; 2,3-dihydro-1*H*-indene, 496-11-7; 2-ethylnaphthalene, 939-27-5; 1-ethylnaphthalene, 1127-76-0; 2-ethylpyridine, 100-71-0; 2-ethylfuran, 3208-16-0; 2-ethylthiophene, 872-55-9; (1-bromoethyl)benzene, 585-71-7.

Synthesis of Bay-Region Diol Epoxides and Other Derivatives of Benzo[*h*]quinoline

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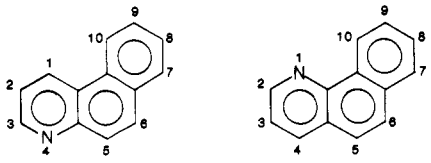
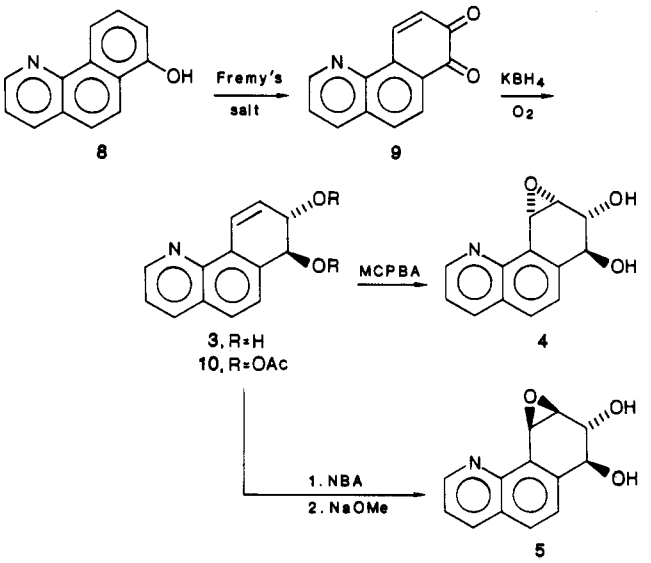
The azaphenanthrenes, benzo[*f*]quinoline (BfQ, **1**) and benzo[*h*]quinoline (BhQ, **2**), are environmental contaminants that have been detected in automobile exhaust, urban air particulates, and cigarette smoke.[2-4] BfQ and BhQ have been shown to be metabolically activated to products mutagenic to *Salmonella typhimurium*.[5-8] In contrast to BfQ and BhQ, their carbon analogue phenanthrene is nonmutagenic.[9] In a previous paper,[10] we have described the synthesis of dihydrodiol and diol epoxide derivatives of benzo[*f*]quinoline. Since we are interested in understanding (i) the mechanism by which the presence and position of aza substitution influence the biological activity of azaphenanthrenes and (ii) the metabolism of these chemicals, we require dihydrodiol and diol epoxide derivatives of benzo[*h*]quinoline. The present paper describes the synthesis of dihydro diol **3**, diol epoxides **4** and **5**, and tetrahydro epoxides **6** and **7**.



Scheme I



Treatment of 7-hydroxy-BhQ (**8**)[11] with Fremy's salt readily afforded BhQ-7,8-dione (**9**) (see Scheme I) in 76% yield. The ^1H NMR and mass spectra of the dione were consistent with its structure. The potassium borohydride reduction of dione **8** in ethanol bubbled with air produced the crude dihydro diol **3** which was purified as dihydro diacetate **10** in an overall yield of 20%. The significant shift of H_{10} in the ^1H NMR spectra (δ 8.01) of **10** compared to that of H_4 in the ^1H NMR spectra (δ 6.29)[12] of *trans*-1,2-diacetoxy-1,2-dihydrophenanthrene is due to the presence of the nitrogen in the bay region of **10**. A similar observation has been made with the analogous dihydro diol diacetates of benz[*c*]acridine,[13] dibenz[*c*,*h*]acridine,[14] and dibenz[*a*,*h*]acridine.[15] The hydrolysis of diester **10** with methanol–ammonia afforded 78% yield of the required dihydro diol **3**. The large coupling constant ($J_{7,8}$ = 10.8) between carbinol protons of **3** compared to that ($J_{7,8}$ = 5.7) of the corresponding protons of diacetate **10** suggested that the trans hydroxyl groups of **3** occupy quasi-diequatorial conformation.

The epoxidation of the dihydro diol **3** with an excess of *m*-chloroperoxybenzoic acid yielded anti diol epoxide **4**. A large coupling constant ($J_{7,8}$ = 9.4) between carbinol protons and small coupling constant ($J_{9,10}$ = 4.4) between H_9 and H_{10} confirmed the structure of **4** and indicated that vicinal hydroxyl groups are in quasi-diequatorial conformations. There was no evidence for the presence of an *N*-oxide based on UV, mass, and ^1H NMR spectra. The mass spectrum showed a molecular ion only at *m*/*e* 229 and the expected upfield shift of the H_2 and H_4 for an *N*-oxide was not observed in the ^1H NMR spectrum of **4**.[10] This observation was in contrast to the previous observation[10] that indicated that the similar oxidation of *trans*-7,8-dihydroxy-7,8-dihydro-BfQ with *m*-chloroperoxybenzoic acid produced only N-oxidation products. The

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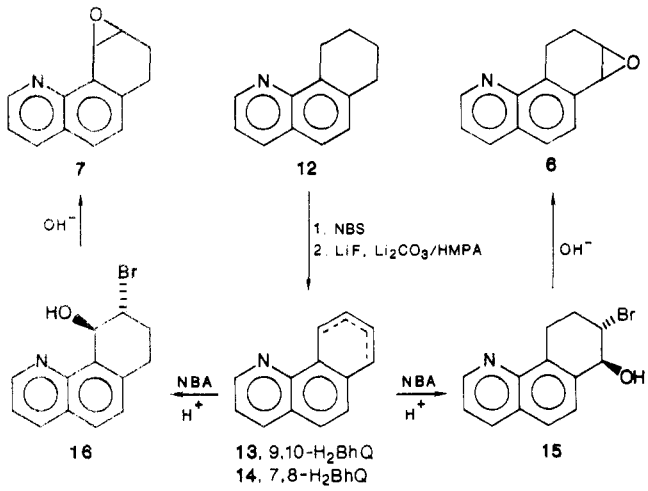
0022-3263/88/1953-1329$01.50/0

Scheme II



resistance of **3** toward N-oxidation is suspected to result from a presence of angular ring peri to the nitrogen atom. Such resistance toward N-oxidation has been noted previously with the analogous dihydro diols of benz[*c*]acridine,[13,14] dibenz[*c*,*h*]acridine,[15] and dibenz[*a*,*h*]acridine.[16] Treatment of **10** with *N*-bromoacetamide (NBA) produced the bromohydrin **11**, which on treatment with NaOMe produced the desired syn diol epoxide **5**. The anti diol epoxide **4** and syn diol epoxide **5** of BhQ showed comparable ^{1}H NMR spectra to the corresponding diol epoxides of phenanthrene[17] except for significant downfield shift of H_{10} of BhQ diol epoxides (δ 5.12–5.49) to that of H_4 in the corresponding diol epoxides of phenanthrene (δ 4.64–4.92) due to the presence of nitrogen in the bay region of BhQ diol epoxides.

BhQ tetrahydro epoxides **6** and **7** have been prepared from a common known starting material, 7,8,9,10-tetrahydro-BhQ (**12**)[18] as shown in Scheme II. The bromination (NBS, CCl_4) and dehydrobromination (LiF, Li_2CO_3, HMPA) resulted in a mixture of two alkenes 9,10-dihydro-BhQ (**13**) and 7,8-dihydro-BhQ (**14**). Due to their similar R_fs on TLC, these compounds were not separated but converted directly to a mixture of bromohydrins **15** and **16**. These bromohydrins were separable by column chromatography on dry column grade silica gel (Merck). The downfield shift of carbinol proton (H_{10}) in bromohydrin **16** compared to that (H_7) of in bromohydrin **15** confirmed the structures of these bromohydrins. The treatment of individual bromohydrins **15** and **16** with NaOH produced high yields of the corresponding tetrahydro epoxides **6** and **7**, respectively.

Preliminary studies have indicated that dihydro diol **3** is significantly more mutagenic than BhQ and that bay-region diol epoxide **4** and tetrahydro epoxide **7** of BhQ were highly mutagenic. In contrast, 7,8,9,10-tetrahydro-7,8-epoxy-BhQ (**6**), a non-bay-region tetrahydro epoxide, was only weakly mutagenic. Detailed mutagenic and carcinogenic studies with these compounds are to be reported elsewhere.

Experimental Section

The melting points are uncorrected. The NMR spectra were obtained on a JOEL FX-270 and/or FX-90Q spectrophotometer with tetramethylsilane as internal standard.

Benzo[*h*]quinoline-7,8-dione (9). A solution of 7-hydroxybenzo[*h*]quinoline (**8**)[11] (100 mg, 0.5 mmol) in benzene (50 mL) containing 5 drops of Adogen-464 was stirred at room temperature while a solution of potassium nitrosodisulfanate (400 mg, 1.5 mmol) in $^1/_6$ M KH_2PO_4 (15 mL) and water (15 mL) was added in one portion with vigorous stirring. The progress of the reaction was monitored by TLC (chloroform/ethyl acetate 20:1) and completed after 1.5 h at room temperature. The benzene layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried over Na_2SO_4, yielding **9** as dark red solid (80 mg, 76%) after evaporation of the solvent and recrystallization from benzene: mp 118 °C dec; mass spectrum, *m*/*e* (relative intensity) 211 (13), 182 (12), 181 (62), 153 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.62 (d, 1, H_9), 7.59 (dd, 1, H_3), 7.80–8.15 (m, 3), 9.15–8.85 (m, 2), $J_{2,3}$ = 3.6, $J_{3,4}$ = 9.0, $J_{9,10}$ = 10.8 Hz.

***trans*-7,8-Dihydro-7,8-dihydroxybenzo[*h*]quinoline (3).** Quinone **9** (75 mg, 0.35 mmol) was dissolved in THF (2 mL) and added to a stirred suspension of potassium borohydride (200 mg, 3.7 mmol) in 95% EtOH (50 mL) while air was bubbled through the solution. After 22 h, most of the solvent was removed under vacuum at room temperature and the residue was partitioned between EtOAc and water. The organic layer was washed with water and brine and dried over sodium sulfate. After evaporation of the solvents, the residue was treated overnight with 1 mL of dry pyridine and 0.75 mL of acetic anhydride at 0 °C. Water was added and the mixture was extracted with EtOAc. Organic layer was washed with 5% $NaHCO_3$, water, and brine and then dried (Na_2SO_4). After the solvent was evaporated, the residue was purified by flash chromatography (silica gel, benzene/ethyl acetate 10:1), yielding 21 mg (20%) of dihydro diol diacetate **10** as white solid after recrystallization (benzene–hexane) as needles: mp 144–145 °C; mass spectrum, *m*/*e* (relative intensity) 297 (0.4, M^+), 254 (0.3), 237 (6), 212 (2), 195 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.14 (s, 3), 2.32 (s, 3), 5.71 (m, 1, H_8), 6.24 (dd, 1, H_9), 6.35 (d, 1, H_7), 7.42 (dd, 1, H_3), 7.49 (d, 1, H_5), 7.75 (d, 1, H_6), 8.01 (dd, 1, H_{10}), 8.13 (dd, 1, H_4), 8.95 (dd, 1, H_2), $J_{2,3}$ = 4.1, $J_{2,4}$ = 1.8, $J_{3,4}$ = 8.2, $J_{5,6}$ = 8.3, $J_{7,8}$ = 5.7, $J_{8,9}$ = 4.3, $J_{8,10}$ = 1.0, $J_{9,10}$ = 10.1 Hz. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09. Found: C, 68.56; H, 5.02.

The diacetate **10** (20 mg, 72 μmol) was dissolved in dry THF (5 mL) and treated with 10 mL of methanol which was saturated with ammonia. The solution was allowed to stand in the dark under nitrogen for 48 h. The solvents were removed in vacuo and the residue was purified by flash chromatography on silica gel, eluting first with benzene–ethyl acetate (1:1) and then with ethyl acetate. Dihydro diol **3** (12 mg, 78%) was obtained as a white solid, mp 217–220 °C dec: UV (MeOH) λ_{max} (ϵ) 315 nm (600), 243 (3500), 219 (2700); mass spectrum, *m*/*e* (relative intensity) 213 (41, M^+), 196 (55), 167 (100), 166 (47), 156 (56), 154 (90); ^{1}H NMR (90 MHz, Me_2CO-d_6) δ 4.67 (d, 1, H_8), 4.95 (d, 1, H_7), 6.21 (dd, 1, H_9), 7.39 (dd, 1, H_3)e, 7.72 (dd, 1, H_{10}), 7.87 and 7.90 (s, 2, $H_{5,6}$) 8.28 (dd, 1, H_4), 8.90 (dd, 1, H_2), $J_{2,3}$ = 4.1, $J_{2,4}$ = 1.7, $J_{3,4}$ = 8.3, $J_{7,8}$ = 10.8, $J_{8,9}$ = 2.2, $J_{8,10}$ = 2.0, $J_{9,10}$ = 9.8 Hz; high-resolution mass spectrum, exact mass calcd for $C_{13}H_{11}NO_2$ 213.0790, obsd 213.0790.

7β,8α-Dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline (4). A solution of dihydro diol **3** (11.5 mg, 0.05 nmol) and *m*-chloroperoxybenzoic acid (MCPBA) (100 mg) in dry THF (100 mL) was stirred for 48 h under argon at room temperature. The excess of *m*-chloroperoxybenzoic acid and *m*-chlorobenzoic acid were removed by stirring the reaction mixture with anion exchange resin AG-1-X8 for 2 h at room temperature. After filtration, the solvent was removed in vacuo and the residue was triturated with ether to give 8.5 mg (69%) of diol epoxide as colorless solid: mp 71–72 °C; UV (THF) λ_{max} (ϵ) 321 nm (400), 290 (600), 231 (5200), 221 (5400); mass spectrum, *m*/*e* (relative intensity) 229 (10), 211 (40), 200 (27), 183 (94), 182 (100), 154 (99); ^{1}H NMR (90 MHz, Me_2CO-d_6) δ 3.83 (dd, 1, H_9), 3.99 (d, 1, H_8), 4.77 (d, 1, H_7), 5.49 (d, 1, H_{10}), 7.54 (dd, 1, H_3), 7.97 (s, 2, $H_{5,6}$), 8.53 (dd, 1, H_4), 8.97 (dd, 1, H_2), $J_{2,3}$ = 4.0, $J_{2,4}$ = 1.8, $J_{7,8}$ = 9.4, $J_{8,9}$ = 0.8, $J_{9,10}$ = 4.4 Hz; high-resolution mass spectrum, exact mass calcd for $C_{13}H_{11}NO_3$ 229.0739, obsd 229.0752.

7β,8α-Dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline (5). A solution of diacetate **10** (20 mg, 72 μmol), *N*-bromoacetamide (10.5 mg, 76 μmol) and a trace of HCl in 5 mL of THF and 1.5 mL of H_2O was stirred at 0–5 °C under Ar

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for 30 min. The mixture was extracted with EtOAc (20 mL) and the organic solution was washed with H_2O (2 × 5 mL), dried (Na_2SO_4), and distilled in vacuo to yield a colorless solid. The solid was recrystallized from EtOAc–petroleum ether to produce 20.5 mg (77%) of **11** as colorless crystals, mp 237–239 °C dec; ^1H NMR (360 MHz, DMSO-d_6) δ 2.11 (s, 3), 2.19 (s, 3), 4.76 (t, 1, H_9), 5.78 (dd, 1, H_8), 6.07 (m, 1, H_{10}), 6.35 (d, 1, H_7), 6.43 (d, 1, OH), 7.38 (d, 1, H_5), 7.63 (dd, 1, H_3), 8.02 (d, 1, H_6), 8.42 (dd, 1, H_4), 9.00 (dd, 1, H_2), $J_{2,3}$ = 4.1, $J_{2,4}$ = 1.7, $J_{3,4}$ = 8.3, $J_{5,6}$ = 8.6, $J_{7,8}$ = 8.5, $J_{8,9}$ = 2.7, $J_{9,10}$ = 3.2, $J_{10,OH}$ = 5.0 Hz.

A mixture of 15 mg of the bromohydrin **11**, ca. 5 mg of NaOMe, and dry THF (5 mL) was stirred at 0–5 °C for 30 min. EtOAc (15 mL) was added and the organic phase was washed with ice-cold H_2O (5 mL), dried (Na_2SO_4), and evaporated in vacuo to yield 5 mg (57%) of a colorless solid which decomposed without melting at 133 °C: ^1H NMR (360 MHz, DMSO-d_6) δ 3.82 (m, 1, H_9), 4.10 (m, 1, H_8), 4.64 (m, 1, H_7), 4.71 (d, 1, OH_7), 5.12 (d, 1, H_{10}), 5.51 (d, 1, OH_8), 7.59 (dd, 1, H_3), 7.65 (d, 1, H_5), 7.99 (d, 1, H_6), 8.40 (dd, 1, H_4), 9.00 (dd, 1, H_2), $J_{2,3}$ = 4.1, $J_{2,4}$ = 1.7, $J_{3,4}$ = 8.3, $J_{5,6}$ = 8.4, $J_{7,8}$ = 4.0, $J_{8,9}$ = 2.0, $J_{9,10}$ = 4.0, $J_{7,OH}$ = 8.2, $J_{8,OH}$ = 4.6 Hz; mass spectrum, m/e 229 (M^+).

***trans*-8-Bromo-7-hydroxy- and *trans*-9-Bromo-10-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline (15 and 16).** A mixture of 7,8,9,10-tetrahydrobenzo[*h*]quinoline[18] (**12**, 0.7g, 3.8 mmol), *N*-bromosuccinimide (0.7g, 3.9 mmol), and α,α'-azobis(isobutyronitrile) [AIBN, 5.0 mg] in dry CCl_4 (40 mL) was stirred at 70–75 °C under argon for 45 min. The mixture was cooled to 10 °C and filtered, and the filtrate was concentrated under reduced pressure to yield a mixture of **12**, **13**, and **14** (1.03 g). This mixture was stirred with LiF (1.0 g) and Li_2CO_3 (1.5 g) in redistilled HMPA (5 mL) at 80–85 °C for 60 min under argon. The reaction mixture was cooled to room temperature, diluted with ether (50 mL), and filtered. The filtrate was washed with water (5 × 25 mL), dried (Na_2SO_4), and concentrated to give a dark oil (0.62 g).

The above oil (0.62 g), *N*-bromoacetamide (NBA, 0.50 g), and 2 drops of concentrated HCl were dissolved in a mixture of THF (30 mL) and water (6 mL) and stirred at 0–5 °C under Ar for 4 h. The mixture was diluted with water (25 mL) and extracted with EtOAc (2 × 50 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product, thus obtained, was chromatographed on a dry column grade silica gel (Merck) using $CHCl_3$ as eluant to give 0.15 g (14%) of **16** [mp 165–167 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 1.8 (br s, exchangeable with D_2O, OH), 2.20–2.70 (m, 2 H_8), 3.10 (m, 2 H_7), 4.60 (m, H_9), 5.76 (d, H_{10}), 7.10–7.85 (m, H_3, H_5, and H_6), 8.17 (d, H_4), 9.83 (m, H_2), $J_{3,4}$ = 8.2, $J_{9,10}$ = 6.6; mass spectrum, m/e 276.97, 278.94 (M^+)] and 80 mg (8%) of **15** [mp 135–137 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 2.25–2.73 (m, 2 H_9), 3.15 (br s, exchangeable with D_2O, OH), 3.25–3.70 (m, 2 H_{10}), 4.45 (m, H_8), 5.07 (d, H_7), 7.40–7.72 (m, H_3, H_5, H_6), 8.13 (dd, H_4), 8.92 (dd, H_2), $J_{2,3}$ = 4.3, $J_{2,4}$ = 1.6, $J_{3,4}$ = 8, $J_{7,8}$ = 7 Hz; mass spectrum, m/e 277, 279 (M^+)].

7,8,9,10-Tetrahydro-7,8-epoxybenzo[*h*]quinoline (6). To a stirred solution of a mixture of bromohydrin **15** (25 mg) in acetone (5 mL) was added 10% NaOH (0.4 mL) under argon. The mixture was stirred at room temperature for 30 min and extracted with ether (50 mL), washed with water (1 × 15 mL), dried (Na_2SO_4), and evaporated under reduced pressure to produce **6** (13 mg, 74%) as a colorless crystalline solid after recrystallization from ether, mp 88–89 °C: ^1H NMR (270 MHz, $CDCl_3$) δ 1.83 (m, 1 H), 2.54–2.86 (m, 3 H), 3.88 (m, H_8), 4.02 (d, H_7), 7.37–7.72 (m, H_3, H_5, H_6), 8.15 (dd, H_4), 8.94 (dd, H_2), $J_{2,3}$ = 1.6, $J_{2,4}$ = 4.0, $J_{3,4}$ = 8.2, $J_{7,8}$ = 4.3 Hz; high resolution mass spectrum, exact mass calcd for $C_{13}H_{11}NO$ 197.0840, obsd 197.0840.

7,8,9,10-Tetrahydro-9,10-epoxybenzo[*h*]quinoline (7). The reaction of bromohydrin **16** (30 mg) in acetone (5 mL) containing 10% NaOH (0.4 mL) was affected as described for **5**. Workup gave crystalline **7** (15 mg, 71%) after recrystallization from petroleum ether: mp 128–129 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 1.87 (m, 1 H), 2.54–3.10 (m, 3 H), 3.91 (m, H_9), 5.46 (d, H_{10}), 7.20–7.75 (m, H_3, H_5, H_7), 8.13 (dd, H_4), 8.94 (m, H_2), $J_{2,4}$ = 1.2, $J_{3,4}$ = 8.5, $J_{9,10}$ = 4.3 Hz; high-resolution mass spectrum, exact mass calcd for $C_{13}H_{11}NO$ 197.0840, obsd 197.0821.

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Homogeneous Nucleophile Exchange. 1. Simple, High-Yield Synthesis of Some Heterodihalides

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Chemoselectivity holds a central position in organic synthesis.[1] To achieve this, differentiated di(poly)functional synthons often are used; heterodihalides would appear to be eminently employable to this end. However, although the halides are one of the most versatile sets of functions with which to create carbon–carbon bonds and introduce functional variations, the only readily and cheaply available heterodihalides, prior to this work, were the C_1–C_3 α,ω-bromochlorides; the C_4–C_6 bromochlorides and the C_1–C_6 chloroiodides are quite expensive. Higher homologues are prepared by methods so inconvenient and inefficient that they seldom are used in synthesis. This paper describes rapid, simple, inexpensive preparations of a range of bromochlorides and chloroiodides from readily available starting materials.

Our interest in this area arose initially because of a desire to rapidly convert an alkyl bromide to the corresponding chloride; we discovered that this could be accomplished nearly quantitatively by heating a neat mixture of the bromide with a large excess of 1-chlorobutane for 2–3 h in the presence of a catalytic amount of quaternary ammonium halide. A literature search for halide interconversion methodology yielded only two comparable examples. In 1981, Sasson and Yonovich-Weiss[2] reported homogeneously catalyzed exchange between primary alkyl bromides and chlorides. In 1984, Bidd and Whiting,[3] apparently unaware of the previous work, published a similar report; they also converted an iodide to the corresponding bromide or chloride but used more than an equivalent of the corresponding quaternary halide. The most cited work on halide interconversions, aside from Finkelstein (1910),[4] is the 1976 paper of Willy et al.[5] However, they employed metal halide catalyzed equilibrations, and although they usually achieved very high conversions, reactions often required 10 or more days, and the product had to be washed free of salts and solvent prior to distillation. They did not apply their method to synthesis of heterodihalides, although they discussed and demonstrated useful chemoselectivity of such reagents. Since then, most papers on bromide–chloride exchange,[6] citing Willy, have used metal halides, either as catalysts or as stoichiometric reagents in phase transfer catalyzed processes. It thus became clear that homogeneously catalyzed halide exchange is largely unappreciated and that its scope and limitations never have been systematically explored.

We soon realized that such an exchange has at least one major advantage over the Finkelstein reaction or any phase

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