Synthesis of *trans*-10,11-Dihydroxy-10,11-dihydrodibenz(*a*,*h*)acridine and Its Diastereomeric Epoxides. Possible Carcinogenic Metabolites of Dibenz(*a*,*h*)acridine

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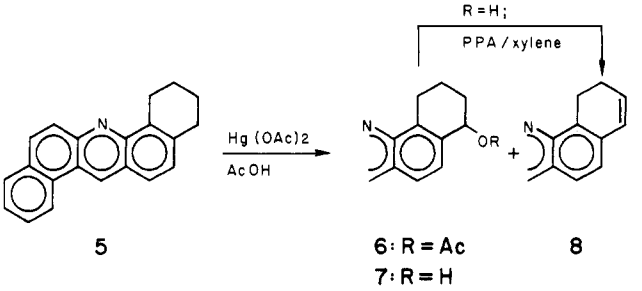
trans-10,11-Dihydroxy-10,11-dihydrodibenz(*a*,*h*)acridine (**12**), (±)-10α,11β-dihydroxy-8α,9α-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (**3**), and 10α,11β-dihydroxy-8β,9β-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (**4**), which are potentially proximate and ultimate carcinogens of dibenz(*a*,*h*)acridine (**1**), are synthesized. Regiospecific oxygenation at C-11 of 8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine with mercuric acetate in acetic acid resulted in an intermediate that was converted to the above dihydrodiol and diol epoxides. ^{1}H NMR, UV, and fluorescence emission spectra of dibenz(*a*,*h*)acridine derivatives are reported.

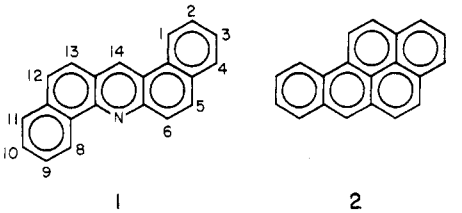
During the past decade, numerous studies have indicated that "bay region"[1] diol epoxides are the major ultimate carcinogenic metabolites of a large number of polycyclic aromatic hydrocarbons.[2,3] The importance of these molecules has stimulated strong interest in their synthesis and chemical and biological properties. The quest for ultimate carcinogenic metabolites of analogous aza-polynuclear aromatic hydrocarbons (aza-PAH), which are also environmental contaminants and which include a number of known carcinogens[4,7] has only recently begun. Kitahara et al.[5] demonstrated with a number of K-region oxides of aza-PAHs that these K-region oxides are not likely to be the bioactivated forms of the molecules (aza-PAHs).

The concept of the bay region theory[6] which predicts the ultimate carcinogens of PAHs has recently been extended to several aza-PAHs. The quantum chemical studies[8,9] predict that bay region diol epoxides of aza-PAHs are expected to be the most electrophilic and consequently mutagenic/tumorigenic metabolites. These studies have also predicted that bay region benz(*c*)acridine diol epoxides should be more electrophilic and biologically active than that of benz(*a*)acridine. Recently, synthesis[10,13] of diol epoxides and other derivatives of benz(*a*)- and benz(*c*)-acridines has made it possible to demonstrate experimentally that the bay region benz(*c*)acridine diol epoxide is much more mutagenic in *Salmonella typhimurium* strain TA98, TA100, and mammalian cells V-79, than other benz(*c*)acridine diol epoxides, and greatly exceeds the analogous bay region benz(*a*)acridine diol epoxide in mutagenicity.[14] Further, a study[15] of the tumor initiating activity of benz(*c*)acridine and its derivatives has revealed significant tumorigenic activity for those derivatives bearing a bay region epoxide. These limited studies strongly suggest that bay region theory may be extended to certain aza-PAHs of acridine series. These studies have become more significant as benz(*c*)acridine[16] and 7-methylbenz(*c*)acridine[17,18] have been shown to be metabolized to those dihydrodiols which are the precursors of the respective bay region diol epoxide(s).

Scheme I



In contrast to the weak carcinogenicity of benz(*c*)-acridine and benz(*a*)acridine, dibenz(*a*,*h*)acridine (**1**) is a potent carcinogen.[4] Andervont and Shimkin[19] reported



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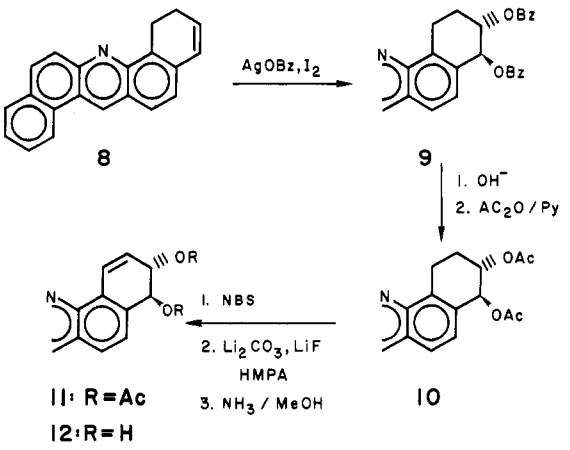
that 1 was generally more potent than benzo(*a*)pyrene (2) in inducing pulmonary adenomas but less active by percutaneous application and subcutaneous injection. The quantum chemical calculations developed by Lehr and Jerina[8] predict that the bay region diol epoxide derived from the 8,9,10,11-benzo ring of dibenz(*a,h*)acridine (1) will be more reactive ($\Delta E_{deloc}/\beta = 0.737$) than that derived from the 1,2,3,4-benzo ring ($\Delta E_{deloc}/\beta = 0.700$). In order to test the applicability of bay region theory in dibenz(*a,h*)-acridine, we require its dihydrodiol and diol epoxide derivatives. The present paper descries a highly regiospecific synthesis of *trans*-10,11-dihydro-10,11-dihydroxydibenz-(*a,h*)acridine (12) and its diastereomeric epoxide derivatives 3 and 4.

Results and Discussion

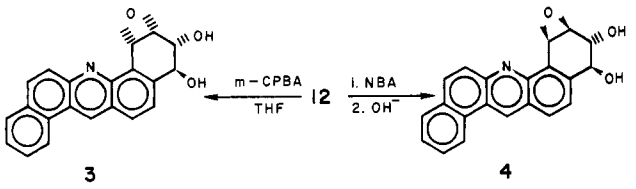
The recent advances in the synthesis of various dihydrodiols and diol epoxides of benz(*c*)acridine[10,11] and 7-methylbenz(*c*)acridine[20] prompted us to select 8,9,10,11-tetrahydrodibenz(*a,h*)acridine (5) (Scheme I) as the starting material. The compound 5 was synthesized in large quantity by a literature procedure.[21] We have examined a number of reactions of 5 with the hope of obtaining a regiospecific synthesis of 8,9-dihydrodibenz-(*a,h*)acridine (8). The chlorination of 5 with *tert*-butyl hypochlorite in CCl_4 produced a very small amount of benzylic chlorinated products (less than 10%). It is interesting to note that the analogous reaction with 1,2,3,4-tetrahydrodibenz(*c,h*)acridine produced more than 85% yield of 1:1 mixture of 1-chloro and 4-chloro derivatives.[22] Much more favorable results were obtained by reacting 5 with *N*-bromosuccinimide (~60% total conversion), but this reaction was not regiospecific and produced unfavorable ratios of brominated derivatives at C-8 and C-11 (2:1) as judged by the relative areas of the peaks at δ 3.05 and 3.70 (H_{11} and H_8, respectively, in the 10,11-dihydro- and 8,9-dihydrodibenz(*a,h*)acridines) in the ^1H NMR spectrum of the crude reaction product obtained by subsequent dehydrobromination.

The reaction of 5 with mercuric acetate in refluxing acetic acid produced a mixture of 11-acetoxy-8,9,10,11-tetrahydrodibenz(*a,h*)acridine 6 and 8 (Scheme I). Possibly, the later compound resulted by acid-catalyzed deacetoxylation of 6. Interestingly, mercuric acetate under analogous reaction condition failed to produce any oxidation products of 1,2,3,4-tetrahydrodibenz(*c,h*)acridine,[22] but has been shown to react with 1,2,3,4-tetrahydrobenz-(*c*)acridine[10] and 8,9,10,11-tetrahydrobenz(*c*)acridine,[10] exclusively at C-4 and C-11 positions, respectively. More likely, the facile coordination by mercury with the nitrogen lone pair of 5, 1,2,3,4-tetrahydrobenz(*c*)acridine, and 8,9,10,11-tetrahydrobenz(*c*)acridine is responsible for their reactivity with mercuric acetate. The similar coordination by mercury with the nitrogen lone pair of 1,2,3,4-tetrahydrodibenz(*c,h*)acridine may be difficult to achieve under similar conditions due to greater steric hindrance. 6 was isolated conveniently from the reaction mixture as the 11-hydroxy derivative 7 by column chromatography on silica gel. The comparatively nonpolar fractions contained 8 (45%), 5 (30%), and 1 (25%). The dehydration of 7 with polyphosphoric acid (PPA) by using xylene as cosolvent produced 79% yield of 8. Alternatively, the mercuric acetate oxidation product of 5 was hydrolyzed with base and subsequently the isolated product was treated with PPA/xylene to give a mixture of compounds containing 65% of 8 as judged by ^1H NMR.

Scheme II



Scheme III



The application of Prevost reaction (Scheme II) to 8 by using silver benzoate produced 58% yield (based on 5) of pure *trans*-10,11-bis(benzoyloxy)-8,9,10,11-tetrahydrodibenz(*a,h*)acridine (9). We preferred to convert tetrahydrodiol dibenzoate 9 into tetrahydrodiol diacetate 10 before the introduction of a double bond at the 8,9-position. We have found in the past[10,22] that tetrahydrodiol diacetates are better substrates for these types of chemical conversions and for monitoring the purity of the products by methyl signals of the acetoxy groups in ^1H NMR. Thus, tetrahydrodiol diacetate 10 was converted to dihydrodiol diacetate 11 in 71% yield by bromination with *N*-bromosuccinimide followed by dehydrobromination (Scheme II). The direct conversion of the alkene 8 to 10 with silver acetate is usually associated with lower yields. The usual hydrolysis of diester 11 with methanolic ammonia yielded 70% of *trans*-10,11-dihydroxy-10,11-dihydrodibenz(*a,h*)-acridine (12).

The diastereomeric bay region diol epoxides 3 and 4 were prepared from the dihydrodiol 12 (Scheme III). In each case the usual reaction conditions produced good yields of expected epoxides. Thus the reaction of 12 with *m*-chloroperoxybenzoic acid in dry THF gave anti diol epoxide 3 in 48% yield. The syn diol epoxide 4 was obtained in 33% overall yield from 12 by conversion to the bromo triol with *N*-bromoacetamide (NBA) in acidic aqueous THF, followed by cyclization with amberlite 400/OH^-.

^1H NMR data for the dibenz(*a,h*)acridine derivatives are reported in the Experimental Section. The dihydrodiol 12 and bay region diol epoxides 3 and 4 showed comparable ^1H NMR spectra to the corresponding benz(*c*)acridine dihydrodiol[10] and diol epoxides.[10,11] Moreover, there are close similarities with the ^1H NMR data reported for dibenz(*a,h*)anthracene derivatives[23,25] with the typical

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downfield shift of the protons in the bay region (H-1, H-8, and H-14). An additional downfield shift of H-8 and H-14 and dibenz(*a*,*h*)acridine derivatives is caused by the presence of nitrogen. The large coupling constant values for the carbinol protons of the dihydrodiol **12** compared to that of the protons of dihydrodiol diester **11** indicate that the vicinal hydroxyl groups in **12** are predominantly quasi-diequatorial.[24] As generally observed for bay region diol epoxides, the large coupling constant value ($J_{10,11}$ = 8.4) for diol epoxide **3** was consistent with a predominantly quasi-diequatorial conformation of the hydroxyl groups. The ultraviolet spectrum of the dihydrodiol **12** (see Experimental Section) was very similar to that of the corresponding dibenz(*a*,*h*)acridine derivative.[23] The ultraviolet spectra of both diol epoxides **3** and **4** (data not shown) were virtually identical with that of **5** [UV (EtOH–THF) λ_{max} (ϵ) 224 (35 500), 244 (23 000), 282 (57 000), 346 (6500), 355 (5900), 363 (9200), 383 (9500)]. Preliminary studies in our laboratory have indicated that the dihydrodiol **12** is one of the major metabolites when dibenz(*a*,*h*)acridine **1** is incubated with rat liver microsomes. The results of these studies and the mutagenic activity of the diol epoxides and other derivatives of **1** will be reported elsewhere.

Experimental Section

Ultraviolet spectra and fluorescence emission spectra were recorded on Perkin Elmer Model Lambda-3 UV–vis and LS-3 fluorescence spectrophotometers, respectively. ^{1}H NMR spectra were recorded on Joel-270 FX and Bruker WF-360 spectrometers. The Syracuse University high field NMR facility was used for 360-MHz spectra. Unless noted otherwise, $CDCl_3$ was used as the solvent. Coupling constants (J) are recorded in hertz (Hz) and chemical shifts in parts per million (μ) with Me_4Si as an internal standard. Mass spectra were obtained on AEI MS-902/CIS-2 spectrometer at Cornell University Mass Spectral facility. Elemental microanalyses were performed by Galbraith Laboratories, Inc, Knoxville, TN. Dry column grade silica gel was purchased from ICN Pharmaceuticals.

11-Hydroxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (7). A mixture of 8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (**5**, 2.8 g),[21] mercuric acetate (6.3 g), and glacial acetic acid (75 mL) was refluxed for 28 h under Ar. Most of the acetic acid was removed under reduced pressure, and the residue was made basic with saturated $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The ethyl acetate layer was washed with water (2 × 100 mL), dried over Na_2SO_4, and concentration to dryness to yield a brownish yellow semisolid. This solid was dissolved in THF (25 mL) and MeOH (25 mL), and 40% NaOH (3 mL) was added. The mixture was stirred at room temperature for 2 h. Most of the solvent was removed and the residue was partitioned between EtOAc (200 mL) and water (100 mL). The ethyl acetate layer was separated, washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a yellow solid. It was chromatographed over dry column grade silica gel with CH_2Cl_2 as the developing solvent to give a mixture of three compounds (1.35 g) **8**, **1**, and **5** which were present in the ratio of approximately 2:1:1, respectively, as judged by NMR. Further elution with ethyl acetate gave **7** (1.35 g, 47%) as a pale yellow crystalline solid of mp 225–227 °C: ^{1}H NMR (270-MHz, Me_2SO-d_6) δ 1.80–2.15 (4 H, m), 3.25–3.50 (2 H, m), 4.80 (H_{11}, m), 5.40 (OH, d), 7.65–8.11 (7 H, m), 9.0 (H_1, d), 9.80 (H_{14}, s), $J_{1,2}$ = 8, $J_{4,OH}$ = 6; high-resolution mass (AEI-MS-902) spectrum, obsd 299.1311, calcd 299.1310.

8,9-Dihydrodibenz(*a*,*h*)acridine (8). To a stirred mixture of polyphosphoric acid (3.8 g) and xylene (10 mL) at 85–90 °C under Ar was added **7** (1.15 g). The biphasic mixture was stirred for 90 min under Ar and cooled, and the xylene was decanted. The PPA phase, which was red, was triturated with hexane (3 × 50 mL) and then decomposed with water. The mixture was made basic with saturated Na_2CO_3 and then extracted with benzene–ether (1:1; 3 × 50 mL). The combined organic phase was washed with water (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **8** as a yellow aerosol (0.85 g, 79%): ^{1}H NMR (270 MHz) δ 2.54 (H_9, m), 3.68 (H_8, t), 6.29 (H_{10}, m), 6.64 (H_{11}, d), 7.24–8.10 (ArH, m) 8.70 (H_1, d), 9.28 (H_{14}, s), $J_{1,2}$ = 7.8, $J_{8,9}$ = 9.0, $J_{9,10}$ = 4.2, $J_{10,11}$ = 9.8.

***trans*-10,11-Bis(benzoyloxy)-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (9).** To a stirred suspension of dry silver benzoate (1.5 g) in dry benzene (100 mL) under Ar was added iodine (0.8 g), and the mixture was stirred at room temperature until the color of iodine disappeared. The alkene **8** (1.0 g) was added with the aid of dry benzene (75 mL) and the suspension was stirred under reflux for 15 h. The hot mixture was filtered, and the residue was washed with benzene (25 mL). The filtrate was cooled to room temperature and washed with 10% sodium thiosulfate solution (2 × 100 mL) and water (2 × 50 mL). After drying (anhydrous Na_2SO_4), the solution was concentrated under reduced pressure to yield a solid. This solid was dissolved in CH_2Cl_2 (15 mL), and the solution was diluted with petroleum ether (6 mL). On cooling **9** was separated out as colorless solid (1.2 g, 65%). A small sample was recrystallized from ethyl acetate as colorless crystals of mp 250–251 °C: ^{1}H NMR (270 MHz) δ 2.35–2.75 (H_9, m), 3.84 (H_8, t), 5.76 (H_{10}, m), 6.77 (H_{11}, d), 7.10–8.30 (7 H, m), 8.76 (H_1, d), 9.37 (H_{14}, s), $J_{1,2}$ = 7.7, $J_{8,9}$ = 6, $J_{9,10}$ = 1.5, $J_{10,11}$ = 6. Anal. Calcd for $C_{35}H_{25}NO_4$: C, 80.30; H, 4.78; N, 2.67. Found: C, 80.48; H, 4.71; N, 2.65.

***trans*-10,11-Diacetoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (10).** To a solution of tetrahydro dibenzoate **9** (3.8 g) in THF (50 mL) and MeOH (40 mL) was added 30% NaOH (5 mL). A dark red solution resulted, which was stirred at room temperature under Ar for 2.5 h. Solvents were removed under reduced pressure and the residue was triturated with CH_2Cl_2/H_2O (25 mL each). The suspended solid was filtered and washed with cold CH_2Cl_2 (10 mL) to give a light yellow crystalline solid (2.07 g, 90%). This solid was dissolved in acetic anhydride (80 mL) and pyridine (20 mL) upon warming and the solution was stirred for 18 h, under Ar, at room temperature. The mixture was poured gradually on ice cooled saturated Na_2CO_3 (200 mL) with stirring. A solid separated out which was filtered, washed with water, dried, and recrystallized from CH_2Cl_2–hexane to produce **10** as colorless granules (2.35 g, 90%) of mp 211–212 °C: ^{1}H NMR (270 MHz) δ 1.80–2.50 (H_9, m), 2.07 (CH_3, s), 2.19 (CH_3, s), 3.66 (H_8, m), 5.45 (H_{10}, m), 6.28 (H_{11}, d), 7.20–8.25 (7 H, m), 8.71 (H_1, d), 9.30 (H_{14}, s); mass spectrum (CI-CH_4), m/z 400 (M^+ + 1), 340 (M^+ + 1 – $C_2H_4O_2$), 298 (base peak). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.20; H, 5.26; N, 3.50. Found: C, 75.50; H, 5.25; N, 3.50.

***trans*-10,11-Diacetoxy-10,11-dihydrodibenz(*a*,*h*)acridine (11).** A mixture of **10** (1.6 g), recrystallized *N*-bromosuccinimide (0.8 g), α, α'-azobis(isobutyrodinitrile) (AIBN, 20 mg), and dry CCl_4 (175 mL) was heated 15 min at ca. 63–65 °C under a stream of Ar. The mixture was cooled and filtered. The filtrate was distilled under reduced pressure to leave a yellow solid, which was triturated with Et_2O–petroleum ether (25 mL each) and filtered to yield 8-bromo-10α,11β-diacetoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine as a yellow crystalline solid (1.85 g, 97%) of mp 151–154 °C dec.

The above bromo diacetate (1.0 g), Li_2CO_3 (2.0 g), LiF (1.5 g), and freshly distilled HMPA (15 mL) were stirred for 3 h, under Ar, at 85–90 °C. The mixture was cooled, diluted with water (50 mL), and extracted with 1:1 benzene–ether (2 × 100 mL). The organic phase was washed with water 4 × 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a yellow solid (0.73 g) that was recrystallized from ethyl acetate to give 0.59 g (71%) of **11** as light yellow crystals of mp 197–198 °C dec: ^{1}H NMR (270 MHz) δ 2.07 (CH_3, s), 2.16 (CH_3, s), 5.75 (H_{10}, m), 6.31 (H_9, dd), 6.41 (H_{11}, d), 7.58–8.15 (7 H, m), 8.31 (H_8, d), 8.76 (H_1, d), 9.37 (H_{14}, s), $J_{1,2}$ = 8, $J_{8,9}$ = 10, $J_{9,10}$ = 4.4, $J_{10,11}$ = 5.4; mass spectrum (CI-CH_4), m/z 398 (M^+ + 1), 338 (M^+ + 1 – $C_2H_4O_2$), 296 (base peak). Anal. Calcd for $C_{25}H_{19}NO_4$: C, 75.56; H, 4.78; N, 3.52. Found: C, 75.63; H, 4.76; N, 3.44.

***trans*-10,11-Dihydroxy-10,11-dihydrodibenz(*a*,*h*)acridine (12).** A solution of dihydro diacetate (**11**, 0.23 g) in dry THF (15 mL) and dry MeOH (30 mL) was saturated with NH_3 gas at 0–5 °C. The reaction flask was capped with a balloon, and the solution was stirred for an additional 2.5 h at room temperature. Most of the solvent was removed under reduced pressure and the residue was dissolved in EtOAc/H_2O (50-mL each). The aqueous phase

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was discarded and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a solid. The solid was triturated with ether to yield 0.12 g (70%) of **12** as a brownish yellow solid of mp 228–231 °C dec: ^1H NMR (270 MHz, Me_2SO-d_6 + CD_3OD) δ 4.46 (H_{10}, d), 4.85 (H_{11}, d), 6.21 (H_9, dd), 7.66–8.32 (8 H, m), 8.93 (H_1, d), 9.77 (H_{14}, s), $J_{1,2}$ = 7.2, $J_{8,9}$ = 10, $J_{9,10}$ = 2.6, $J_{10,11}$ = 11.2; mass spectrum, m/z 313 (M^+), 295 (base peak, $M^+ - H_2O$); UV (EtOH–THF) λ_{max} (ϵ) 224 (35600, sh) 288 (53000), 350 (5200), 367 (6600), 388 (7000); fluorescence emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (405,416).

(±)-10α,11β-Dihydroxy-8α,9α-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (3). A mixture of dihydrodiol **12** (60 mg) and purified *m*-chloroperoxybenzoic acid (450 mg) in anhydrous THF (20 mL) was stirred at room temperature under Ar for 1 h. The mixture was diluted with ether (30 mL), extracted with ice-cooled 2% NaOH (2 × 50 ml) and water (2 × 25 ml), dried (Na_2SO_4), and concentrated to give a solid that was triturated with ice-cooled anhydrous ether (3 × 5 mL) to give **3** as a colorless crystalline solid (30 mg, 48%) of mp 215–217 °C dec: ^1H NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 3.86 (H_9, d), 3.91 (H_{10}, d), 4.57 (H_{11}, d), 5.58 (H_8, d), 7.65–8.35 (7 H, m), 9.01 (H_1, d), 9.93 (H_{14}, s), $J_{1,2}$ = 8.4, $J_{8,9}$ = 6.3, $J_{9,10}$ = 0, $J_{10,11}$ = 8.4; high resolution mass (AEI-MS-902) spectrum, obsd 329.1034, calcd mass 329.1052; fluorescence emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (397, 408).

(±)-10α,11β-Dihydroxy-8β,9β-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (4). To a stirred solution of dihydrodiol **12** (90 mg) in THF (14 mL) at 0 °C under Ar was added H_2O (4 mL), *N*-bromoacetamide (NBA, 42 mg), and 1 drop of concentrated HCl. The solution was stirred at 0–5 °C for 30 min. EtOAc (30 mL) was added. The organic phase was washed with ice-cooled H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a solid. The solid was chromatographed over dry column grade silica gel with CH_2Cl_2 as developing solvent to give initially nonpolar impurities. Further elution with acetone gave desired bromo triol (80 mg, 68%) as yellow crystalline solid of mp 169–171 °C dec: ^1H NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 4.20 (H_{10}, dd), 4.67 (H_9, m), 6.11 (H_8, d), 7.70–8.27 (7 H, m), 9.01 (H_1, d), 9.89 (H_{14}, s), $J_{1,2}$ = 7.9, $J_{8,9}$ = 4.3, $J_{9,10}$ = 3.0, $J_{10,11}$ = 7.1.

To a stirred solution of the above bromo triol (46 mg) in dry THF (10 mL) was added amberlite-400 (4 g) that had been converted to the hydroxide form. The mixture was stirred at room temperature under Ar, for 5 h, and was quickly filtered, and the filtrate was concentrated under reduced pressure. The trituration of the solid with petroleum gave diol epoxide **4** (19 mg, 49%) as colorless solid of mp 254–257 °C dec: NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 3.93 (H_9, m), 4.22 (H_{10}, dd), 4.69 (H_{11}, dd), 5.38 (H_8, d), 7.69–8.29 (7 H, m), 8.98 (H_1, d), 9.85 (H_{14}, s), $J_{1,2}$ = 7.4, $J_{8,9}$ = 4.0, $J_{9,10}$ = 2.2, $J_{9,11}$ = 1.2, $J_{10,11}$ = 4.0; fluorescent emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (395, 404).

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Registry No. **1**, 226-36-8; (±)-**3**, 97135-11-0; (±)-**4**, 97169-68-1; **5**, 97135-12-1; (±)-**6**, 97135-13-2; (±)-**7**, 97135-14-3; **8**, 97135-15-4; (±)-**9**, 97135-16-5; (±)-10, 97135-17-6; **10** (8-bromo deriv), 97135-20-1; (±)-11, 97149-85-4; (±)-**12**, 97135-18-7; (±)-12 (8,9-dihydro), 97135-19-8; **12** (bromotriol), 97149-86-5.

Chemistry of Pyrimidine. 2. Synthesis of Pyrimidine *N*-Oxides and 4-Pyrimidinones by Reaction of 5-Substituted Pyrimidines with Peracids. Evidence for Covalent Hydrates as Reaction Intermediates

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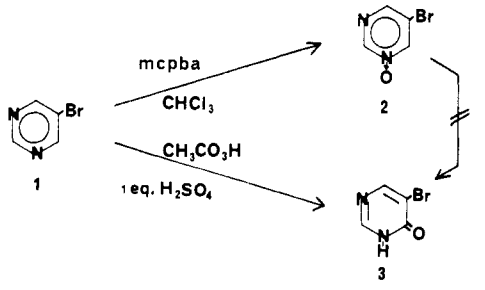
The reaction of 5-substituted pyrimidines with peracids has been found to take divergent pathways depending on the presence or absence of a strong acid. Reaction of 5-bromo- (**1**) or 5-methoxypyrimidine (**6**) with *m*-chloroperbenzoic acid afforded the corresponding *N*-oxides in 29% and 70% yields, respectively. The formation of an *N*-oxide was not observed when either **1** or **6** was treated with 40% peracetic acid in the presence of 1 equiv of sulfuric acid. In the case of **1**, the product was 5-bromo-4(3*H*)-pyrimidinone (**3**), formed in 70% yield. From **6**, two products, 5-methoxy-4(3*H*)-pyrimidinone (**8**) and 4(5)-carbomethoxyimidazole (**9**), were formed in a combined yield of 70% (3:2 ratio of **8** to **9**). The *N*-oxides were demonstrated to be stable to the above reaction conditions and are therefore not intermediates in the formation of **3**, **8**, or **9**. Evidence for the existence of covalent hydrates makes it reasonable to suggest their formation as reaction intermediates.

Heterocyclic *N*-oxides are valuable intermediates in promoting further functionality within a ring system.[1] Our interest in developing synthetic methodology for the elaboration of pyrimidine and 5-substituted pyrimidines led us to consider the preparation of their *N*-oxides. In general, simple substituted pyrimidines afford poor yields of *N*-oxide and are either largely destroyed or do not react during attempted N-oxidation.[2,3] The yield of *N*-oxide is substantially improved when the 2,4- and/or 4,6-positions are occupied by electron-releasing substituents. In

Scheme I



numerous instances under N-oxidation conditions, the pyrimidine ring appears to be more susceptible to other reactions such as hydrolysis, ring opening, and decomposition.[4] The variability in the outcome of these reactions

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