Synthesis and Solvolysis of Acridine 1,2- and 3,4-Oxides: Crystal Structure of Acridine 1,2-Oxide

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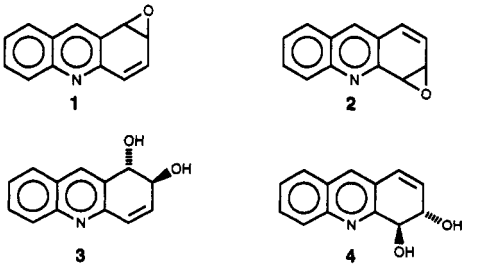
Acridine 1,2- and 3,4-oxides were synthesized from 3,4- and 1,2-dihydroacridine, respectively, *via* intermediate bromohydrin acetates. Crystals of acridine 1,2-oxide were sufficiently stable to allow the first determination of X-ray crystallographic structural features of a non-K-region arene oxide. Aqueous alkaline hydrolysis of the acridine 1,2- and 3,4-oxides produced *trans*-1,2-dihydroxy-1,2-dihydroacridine and *trans*-3,4-dihydroxy-3,4-dihydroacridine, respectively. The former dihydrodiol was also obtained by a six-step synthesis from 3,4-dihydroacridine. Acid-catalyzed hydrolysis of acridine 1,2-oxide yielded the corresponding *cis*- and *trans*-1,2-dihydrodiols (20%) in addition to 1-hydroxy- (12%) and 2-hydroxyacridine (68%). By contrast, solvolysis of acridine 3,4-oxide under acid conditions gave 4-hydroxyacridine as the exclusive product. pH–rate profiles for hydrolysis of the acridine oxides in 1:9 dioxane–water at 25 °C were compared with those for anthracene 1,2-oxide, naphthalene 1,2-oxide, and quinoline 5,6- and 7,8-oxides. Second-order rate constants for the hydronium ion-catalyzed ring opening of anthracene 1,2-, acridine 3,4-, and acridine 1,2-oxide are 585, 7.81, and 0.45 M^{-1} s^{-1}, respectively, and are 3–5 times larger than the rate constants for the corresponding naphthalene 1,2-, quinoline 7,8-, and quinoline 5,6-oxides. Rate constants for uncatalyzed ring opening of anthracene 1,2- and acridine 3,4-oxides (117×10^{-5} s^{-1} and 2.4×10^{-5} s^{-1}, respectively) are about two to three times larger than the corresponding rate constants for naphthalene 1,2- and quinoline 7,8-oxides, whereas the rate of nucleophilic ring opening by hydroxide ion to give the *trans*-dihydrodiols is accelerated by less than a factor of 2 for the acridine oxides as compared with their quinoline analogs. The pH–rate profiles for solvolysis of the acridine oxides, like those of the quinoline oxides, exhibit a pH-independent region at pH values below the pK_a of the ring nitrogen that is attributed to formation of an unreactive N-protonated species.

Introduction

Acridine, one of several aza-polycyclic aromatic hydrocarbons[1] resulting from partial combustion of fossil fuels and tobacco, has been detected in urban particulates,[2] motor vehicle exhaust emissions,[3] and cigarette smoke.[4] It is also prevalent in shale oil, crude petroleum distillates, coal tar, and coal liquefaction products. Metabolism of acridine has been reported to yield 2-hydroxy-9-acridone,[5-9] 9-acridone,[6,7] 2-hydroxyacridine,[8,9] and *trans*-1,2-dihydroxy-1,2-dihydroacridine (acridine 1,2-dihydrodiol)[8,9] (Scheme 1). Since it is likely that metabolically formed phenolic products and dihydrodiols arise *via* spontaneous rearrangement and enzymatic hydration, respectively, of unstable arene oxide intermediates, these arene oxides are of considerable interest. Thus, objectives of the present study were: (i) to synthesize acridine 1,2-oxide (1) and



acridine 3,4-oxide (2) and study their structure and stability, (ii) to synthesize *trans*-1,2-dihydroxy-1,2-dihydroacridine (3) and *trans*-3,4-dihydroxy-3,4-dihydroacridine (4) in order to examine their stability and to provide reference compounds for metabolism studies, and (iii) to examine the effects of the ring nitrogen on the rates and products of reactions of the arene oxides of acridine (1 and 2) in aqueous solution, as compared with their carbocyclic analog, anthracene 1,2-oxide.

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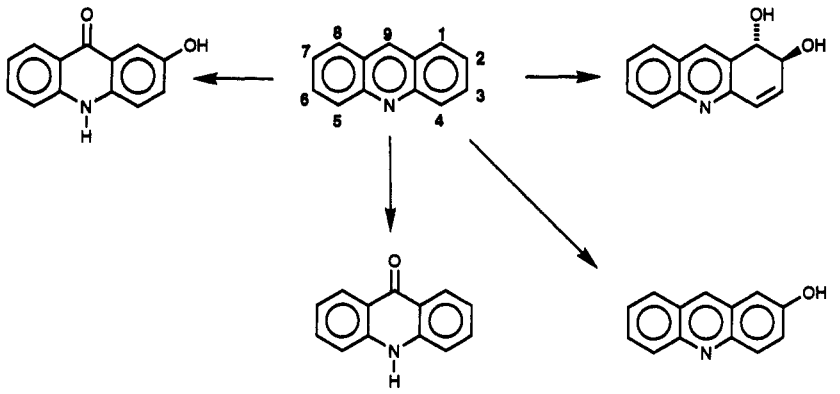
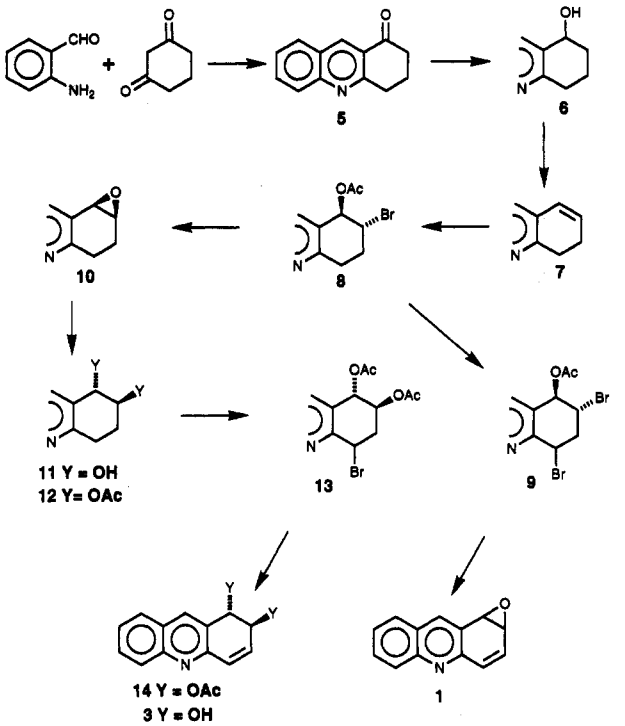
Scheme 1



Scheme 2



Results and Discussion

As had previously been the case for the quinoline 5,6- and 7,8-oxides,[10,11] acridine 1,2- and 3,4-oxides were synthesized by the bromohydrin acetate route.[12,13] Specifically, 1-oxo-1,2,3,4-tetrahydroacridine (**5**) was obtained (79% yield) by reaction of 1,3-cyclohexanedione with *o*-aminobenzaldehyde. Ketone **5** was in turn converted to acridine 1,2-oxide (**1**) *via* alcohol **6** (91%), alkene **7** (86%), bromoacetate **8** (86%), and dibromoacetate **9** (84%) intermediates with an overall yield of 46% (Scheme 2). The synthesis of acridine 3,4-oxide (**2**) was achieved in three steps from 1,2-dihydroacridine (overall yield 72%) using a route similar to that employed for acridine 1,2-oxide.

Both acridine oxides were found to be quite stable at room temperature. They tolerate preparative TLC on silica gel and storage as $CDCl_3$ solutions well. Both form colorless crystals which slowly turn brown on extended exposure to air at room temperature, perhaps due to oxidation. Crystals of acridine 1,2-oxide were, however, sufficiently stable at room temperature to permit X-ray crystallographic analysis. Crystallographic data for acridine 1,2-oxide (**1**) are summarized in Table 1.

Table 1. Crystallographic Data for Acridine 1,2-Oxide (1)

formula	$C_{13}H_9NO$
fw	195.2
crystal system	triclinic
space group	$P\bar{1}$ (No. 2)
a, Å	5.939(4)
b, Å	11.569(4)
c, Å	13.882(8)
α, deg	97.30(4)
β, deg	122.79(7)
γ, deg	92.45(4)
V, Å^3	945.2(9)
Z	4
D_x, mg m^{-3}	1.37
$F(000)$	408
diffractometer	Siemens P3/V2000
radiation	Mo Kα (λ = 0.710 73 Å)
μ (Mo Kα), cm^{-1}	0.49
scan method	θ–2θ
2θ scan range, deg	3–40 (1.2°)
unique reflns	1770

Prior to this study, X-ray crystal structure analyses have been carried out only on relatively stable K-region arene oxides: 7,12-dimethylbenz[*a*]anthracene 5,6-oxide,[14] phenanthrene 9,10-oxide,[14] and benzo[*a*]pyrene 4,5-oxide.[15,16] The generally less stable non-K-region, benzo-ring arene oxides are of particular interest in that some of them lie on the pathway to ultimately carcinogenic bay-region diol epoxides.[17] Crystal structure analysis of the non-K-region acridine 1,2-oxide shows two crystallographically independent, but chemically equivalent, molecules in the asymmetric unit cell. The epoxide ring (Figure 1) is fixed with respect to the conjugated planar portion of the molecule at an *average* external angle of 82° (80.2° and 83.4°, respectively, for the two independent molecules). Acridine 1,2-oxide is thus similar in structure to the K-region arene oxide series where the oxirane is also

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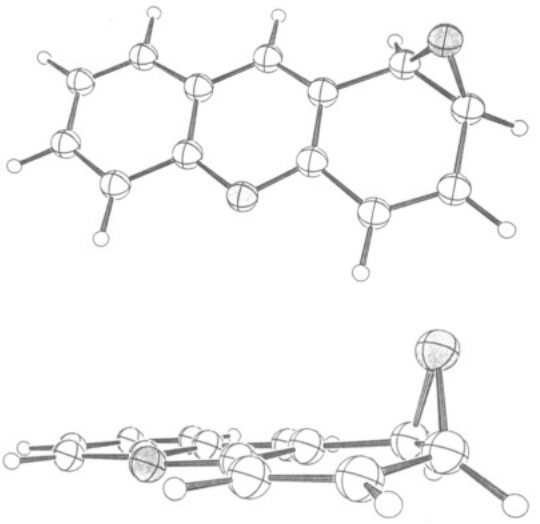

Figure 1. Top and edge views of one of the two crystallographically independent molecules of acridine 1,2-oxide.

inclined (77–81°)[14,15] to the arene plane. A similar value (73°) has been predicted for benzene oxide on the basis of molecular orbital calculations.[18] Although the oxirane carbon atoms of acridine 1,2-oxide are dissimilar (benzylic *vs* allylic), the two C–O bond lengths are the same (1.46 Å) and are practically identical to those of the K-region arene oxides (both carbons benzylic).

Synthesis of *trans*-1,2-dihydroxy-1,2-dihydroacridine (**3**) was achieved in a total yield of 23% from the bromoacetate precursor **8** *via* the tetrahydroepoxide **10**, *trans*-tetrahydrodiol **11**, *trans*-tetrahydrodiacetate **12**, bromodiacetate **13**, and dihydrodiacetate **14**. This synthetic route to **3** parallels that used previously to prepare carbocyclic *trans*-dihydrodiols[19,20] as well as *trans*-5,6-dihydroxy-5,6-dihydroquinoline.[10] Alkaline hydrolysis of acridine 1,2-oxide with KOH (0.065 M) in aqueous 2-methyl-2-propanol (45 °C for 72 h) also provides a route to **3** (55% yield). Although *trans*-dihydrodiol **3** discolored slowly in air, its ^{1}H NMR spectrum showed no observable changes when a neat sample was maintained at room temperature for 2 weeks. Selected ^{1}H NMR spectral data for the acridine oxides and dihydrodiols are compared in Table 2.

Kinetics. We have previously reported the effect of a ring nitrogen on the rates and products of solvolysis of quinoline 5,6- and 7,8-oxides[11] as compared with naphthalene 1,2-oxide. Several important differences between these azaarene oxides and their carbocyclic analog were observed. (i) Under acidic and neutral conditions, the rates of solvolysis of the two quinoline arene oxides were substantially slower than that of naphthalene 1,2-oxide, with quinoline 5,6-oxide less reactive (7–10-fold) than quinoline 7,8-oxide. The low solvolytic reactivity of the azaarene oxides results from the electron-withdrawing effect of the ring nitrogen, which destabilizes the carbocation intermediate in these reactions. (ii) The pH–rate profiles for solvolysis of the azaarene oxides in acidic solution exhibit breaks such that their observed pseudo-first-order rate constants increase with increasing hydronium ion concentration at pH 4–5 but become pH-independent as the pH is decreased below the pK_a of the ring nitrogen (~3–4). Solvolysis of the quinoline oxides in dilute aqueous acid was shown to involve protonation (by a hydronium ion) of the oxirane oxygen in the azaarene oxide species *that has an unprotonated nitrogen*.[11] Thus, the pH-independence of the rate below the pK_a of the nitrogen results from the opposing effects of pH on proton loss from nitrogen and proton addition at oxygen. (iii) Under strongly basic conditions (pH ~13), quinoline 5,6- and 7,8-oxides react with hydroxide ion to give the *trans* 5,6- and 7,8-dihydrodiols. In contrast, the rate of reaction of hydroxide ion with naphthalene 1,2-oxide[21] is insignificant relative to the extremely facile pH-independent reaction of this arene oxide.

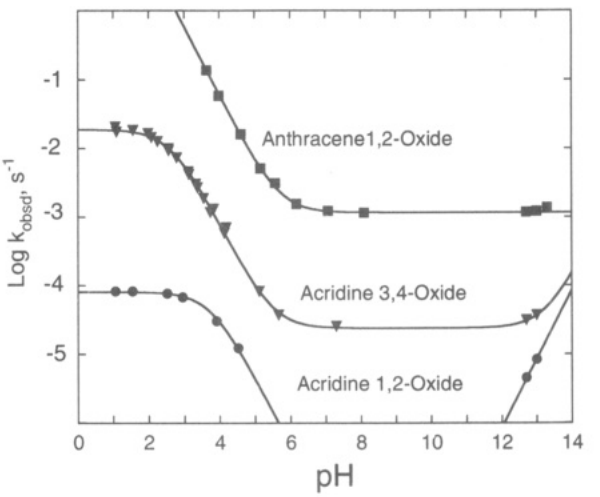

Figure 2. Dependence on pH of the observed pseudo-first-order rate constants for solvolysis of acridine 1,2-oxide (**1**), acridine 3,4-oxide (**2**), and anthracene 1,2-oxide, in 1:9 dioxane/water, ionic strength 0.1 M ($NaClO_4$) at 25 °C.

In the present study, acridine 1,2- and 3,4-oxides (**1** and **2**) and their carbocyclic analog, anthracene 1,2-oxide, exhibited kinetic behavior parallel to that of the arene oxides of quinoline (5,6 and 7,8) and naphthalene (1,2), respectively. Figure 2 shows the dependence on pH of the observed pseudo-first-order rate constants for solvolysis of the acridine and anthracene 1,2-oxides (1:9 dioxane–water; 25 °C; 0.1 M $NaClO_4$). As in the case of naphthalene 1,2-oxide, the rate law (eq 1) for solvolysis of anthracene

$$k_{obsd} = k_H a_{H^+} + k_o \qquad (1)$$

1,2-oxide corresponds to a simple biphasic pH–rate profile, in which the hydronium ion-catalyzed rate, k_H, dominates at low pH whereas the pH-independent rate, k_o, dominates at pH values above ~6. Like the quinoline arene oxides, the acridine oxides exhibit more complex pH–rate profiles with a break at pH 2–4 and a pH-independent region *below* this pH. Scheme 3 depicts a mechanism analogous to that for the quinoline arene oxides, in which an unreactive N-protonated species is in equilibrium with the neutral and O-protonated arene oxides at pH values below its pK_a. The rate law corresponding to this mechanism is given by eq 2, which describes the pH–rate profiles at pH values where reaction with hydroxide ion ($k_{OH}[OH^-]$) is insignificant. For acridine 3,4-oxide, both an acid catalyzed

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(20) An additional resonance contributor is available to the allylic *vs* the benzylic carbocation from benzo ring arene oxides. To our knowledge, there is only one example of the benzylic carbocation being favored on opening of a carbocyclic arene oxide: formation of 9-hydroxybenzo[a]-pyrene from the 9,10-oxide (Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 243–244) due to poor stabilization of a benzylic carbocation at the 2-position of pyrene.

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Table 2. ^{1}H NMR Data for Protons on the Substituted Rings of Acridine Oxides[a] and Dihydrodiols[b]

	vinyl protons		oxirane or diol protons	
compd	benzylic	nonbenzylic	benzylic	nonbenzylic
1,2-oxide (1)	7.10 (d)	6.85 (dd)	4.63 (d)	4.15 (m)
		($J_{1,2}$ = 4.1 Hz; $J_{2,3}$ = 3.8 Hz; $J_{3,4}$ = 9.8 Hz)		
3,4-oxide (2)	6.86 (dd)	6.52 (dd)	4.73 (d)	4.16 (m)
		($J_{1,2}$ = 9.6 Hz; $J_{1,3}$ = 1.6 Hz; $J_{2,3}$ = 3.7 Hz; $J_{3,4}$ = 3.7 Hz)		
trans-1,2-DHD (3)	6.63 (dd)	6.41 (dd)	4.91 (d)	4.53 (m)
		($J_{1,2}$ = 10.1 Hz; $J_{2,3}$ = 2.1 Hz; $J_{2,4}$ = 2.3 Hz; $J_{3,4}$ = 10.0 Hz)		
trans-3,4-DHD (4)[c]	6.67 (dd)	6.09 (dd)	4.78 (d)	4.56 (dt)
		($J_{1,2}$ = 9.5 Hz; $J_{1,3}$ = 2.3 Hz; $J_{2,3}$ = 2.3 Hz; $J_{3,4}$ = 10.0 Hz)		

[a] In $CDCl_3$. [b] In $(CD_3)_2CO$. [c] Aromatic protons were as follows: 7.54 (m), 7.70 (m), 7.90 (dd, J = 8.1, ~1 Hz), 7.98 (s), and 8.00 (d, J = 8.2 Hz).

Table 3. Kinetic Constants for the Solvolysis of Arene Oxides in 1:9 Dioxane/Water[a]

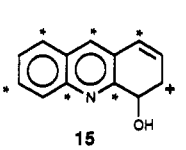
compd	k_H, M^{-1} s^{-1}	10^5 k_o, s^{-1}	10^5 k_{OH}, M^{-1} s^{-1}	pK_a[b]
anthracene 1,2-oxide	585	117		
naphthalene 1,2-oxide[c]	110	68		
acridine 1,2-oxide (1)	0.45	*d*	8.7	3.74
quinoline 5,6-oxide[c]	0.14	<0.1	~6	3.72
acridine 3,4-oxide (2)	7.81	2.4	13.2	2.61
quinoline 7,8-oxide[c]	1.54	0.72	9.8	2.96

[a] At 25 °C, ionic strength 0.1 M ($NaClO_4$). [b] Calculated from the negative x-intercept of plots of $1/k_{obsd}$ vs $1/a_{H^+}$, corresponding to the inverted form of eq 2 at low pH values where k_o does not contribute to the rate or by computer fitting[22] of eq 2 to the experimental data. [c] Data from ref 11. [d] Not determined.

$$k_{obsd} = (k_H a_{H^+} + k_o)\left(\frac{K_a}{a_{H^+} + K_a}\right) \quad (2)$$

(k_H) and a pH-independent (k_o) rate constant were measurable, whereas for acridine 1,2-oxide, k_o was too small ($t_{1/2}$ > 20 h) to permit its convenient determination. At pH ~13 (0.05–0.10 M NaOH), reaction with hydroxide ion provides a new pathway for the solvolysis of acridine 1,2-oxide. Under the same conditions, reaction with hydroxide ion contributes only marginally to the overall rate of solvolysis of acridine 3,4-oxide and not at all to that of anthracene 1,2-oxide, as a result of competition by the pH-independent reactions of these two compounds.

Rate constants and pK_a values for the anthracene and acridine oxides, as well as for the analogous quinoline and naphthalene oxides, are given in Table 3. The presence of a third aromatic ring in the anthracene and acridine systems increases k_H by a factor of 3–5 and k_o by a factor of 2–3, relative to the analogous naphthalene and quinoline derivatives. As expected for a nucleophilic substitution mechanism[23] for ring opening of arene oxides by base, values of k_{OH} are relatively insensitive to the presence of the third benzene ring in the acridine as compared with the quinoline oxides. The rate of reaction with hydroxide ion is only slightly affected by the position of the ring nitrogen (acridine 3,4- *vs* acridine 1,2-oxide and quinoline 7,8- *vs* quinoline 5,6-oxide). As in the case of the quinoline and naphthalene arene oxides, the presence of a ring nitrogen markedly decreases the rate of acid-catalyzed acridine oxide solvolysis relative to that of anthracene 1,2-oxide, and the magnitude of this rate effect depends on the position of the nitrogen atom in the ring system. Nitrogen at a position that is not in direct conjugation with the normally preferred[20] allylic carbocation (cf. structure 15) decreases k_H for acid-catalyzed solvolysis of



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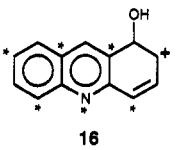

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both acridine 3,4-oxide and quinoline 7,8-oxide by a factor of 70–75 relative to the analogous anthracene or naphthalene oxides. A ring nitrogen in a position that is capable of direct resonance interaction with the allylic carbocation (structure 16) exerts an even larger effect (1300-fold decrease in k_H) on the solvolytic rate for acridine 1,2-oxide relative to anthracene 1,2-oxide. This rate retardation is slightly greater than the 785-fold decrease observed for quinoline 5,6-oxide relative to naphthalene 1,2-oxide. The relative rate for formation of the *allylic cation* from acridine 1,2-oxide is even slower than suggested by the above analysis, since the major phenolic product from this oxide results from ring opening at the alternative site to give a *benzylic cation* (see below).[20]

^{1}H NMR analysis of the products obtained upon solvolysis of anthracene 1,2-oxide in acid indicated the formation of 1- and 2-anthrol in a ratio of 9:1, whereas only 1-anthrol was observed upon neutral solvolysis. Under acidic and neutral conditions, solvolysis of acridine 3,4-oxide gave 4-hydroxyacridine as the only detectable product.[24] Thus, ring opening of these arene oxides by the k_H or k_o pathways occurs predominantly or exclusively to give a carbocation at the allylic position, as in the case of quinoline 7,8-oxide and naphthalene 1,2-oxide. In contrast, acid hydrolysis (both 100 and 1 mM perchloric acid) of acridine 1,2-oxide yielded a mixture of acridine *cis*- and *trans*-1,2-dihydrodiols (20%), 1-hydroxyacridine (12%), and 2-hydroxyacridine (68%). Thus, the major phenol formed from this oxide is derived from ring opening *at the benzylic carbon*. In the hydrolysis of the analogous quinoline 5,6-oxide, we had also observed the formation of the *trans*-5,6-dihydrodiol (20%) as well as 6-hydroxyquinoline, the phenol derived from the benzylic carbocation. However, this phenol was only a minor product (7%). The enhanced tendency of both acridine 1,2- and quinoline 5,6-oxides to open to a benzylic carbocation presumably results from destabilization of the allylic cation

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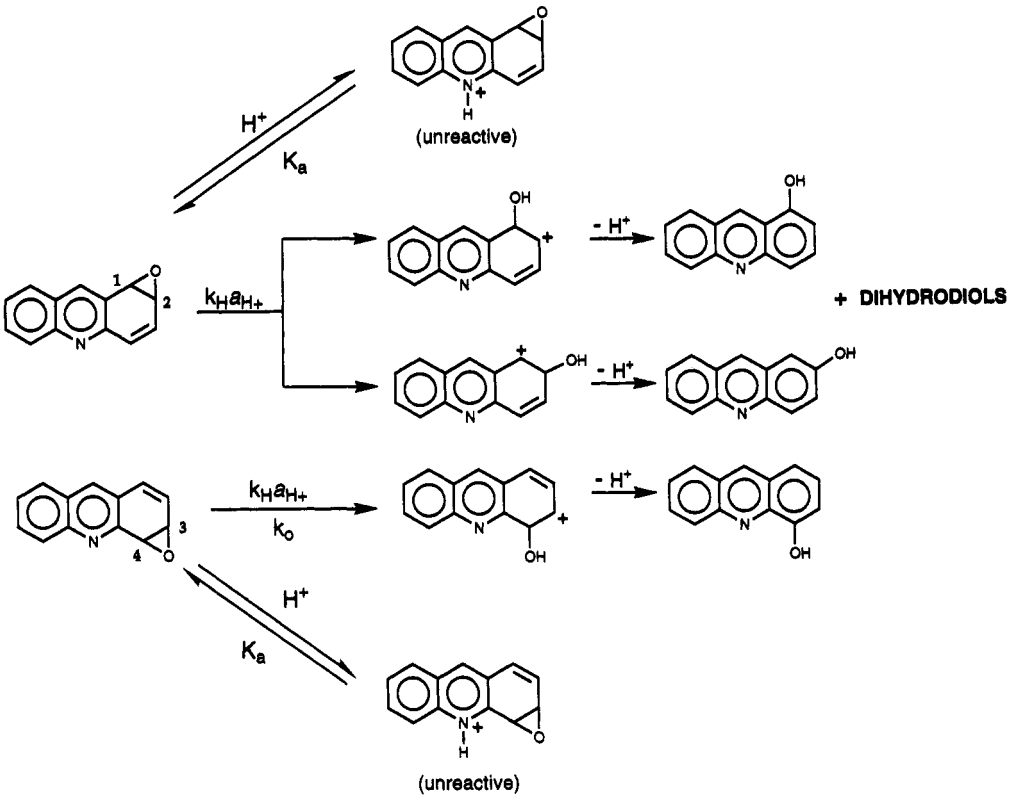
(24) The dramatic preference for formation of 4- *vs* 3-hydroxyacridine may be ascribed in part to conformational preferences of the initially formed carbocation. Axial opening of 2 to the allylic cation at C-3 leaves H-4 equatorial and poorly oriented for its requisite migration to C-3 such that 4-hydroxyacridine forms *via* its ketone precursor (see: Nashed, N. T.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 1723–1730). Conformational inversion (4-hydroxy equatorial and H-4 axial) could well be enhanced by hydrogen bonding between the nitrogen lone pair and the hydroxyl group. Computational studies suggest that the hydrogen of the hydroxyl group should orient away from the carbocation and toward the nitrogen lone pair.[23]

Scheme 3



by the effect of the unfavorable resonance contributor (cf. structure 16) in which a positive charge resides on the ring nitrogen. Although formation of dihydrodiols on solvolysis of the relatively unreactive K-region arene oxides is common,[23] quinoline 5,6-oxide and acridine 1,2-oxide are the only examples of benzo-ring arene oxides which hydrolyze to dihydrodiols. The presence of nitrogen in the ring is expected to destabilize the carbocations derived from these arene oxides, relative to their carbocyclic analogs. If, as in the case of K-region arene oxides, phenol formation requires a conformational inversion of the initially formed carbocation,[24] these unstable cations may have too short a lifetime to undergo this conformational isomerization and may react instead by solvent capture with resultant formation of diols.

Hydrolysis of acridine 3,4-oxide in 1:9 dioxane–water in the presence of 1.0 M sodium hydroxide gave the *trans*-3,4-dihydrodiol 4, which was identified by its ^{1}H NMR spectrum (Table 2). Similarly, only the *trans*-1,2-dihydrodiol 3 was obtained upon base hydrolysis of acridine 1,2-oxide under the kinetic conditions, as shown by comparison of the ^{1}H NMR spectrum of this product with that of 3 prepared as shown in Scheme 2.

Experimental Section

^{1}H NMR spectra were recorded at 250 or 300 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts (δ) are reported in ppm relative to internal TMS, and coupling constants (J) are in hertz. Flash chromatography and TLC were done on silica gel with the solvents indicated. Anthracene 1,2-oxide[25] and 1- and 2-anthrols[19] were prepared by published procedures.

1-Oxo-1,2,3,4-tetrahydroacridine (5). *o*-Aminobenzaldehyde (10.0 g, 83 mmol) in dry DMF (125 mL) was added dropwise under nitrogen to a solution of 1,3-cyclohexanedione (10.7 g, 95 mmol) in dry DMF (150 mL) at 100 °C. This temperature was maintained for 30 min, and then H_2O was removed at an elevated temperature. After the solution was refluxed for 30 min, the DMF was removed by distillation under reduced pressure (15 mmHg). Hydrochloric acid (300 mL, 20%) was added to the residue, which was in turn washed with Et_2O (500 mL) and made basic (NaOH) before extraction with chloroform (3 × 500 mL). The latter extracts were dried ($MgSO_4$) and concentrated to yield a crude product. Recrystallization from CH_2Cl_2/pentane gave ketone 5 (12.8 g, 79%): mp 110–112 °C; IR (KBr) 1680 cm^{-1} (ν C=O); ^{1}H NMR δ 2.27 (2H, m), 2.80 (2H, m), 3.31 (2H, m), 7.54 (1H, m), 7.81 (1H, m), 7.92 (1H, d, J = 8.2 Hz), 8.04 (1H, d, J = 8.5 Hz), 8.83 (1H, s). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.2; H, 5.6; N, 7.1. Found: C, 79.2; H, 5.7; N, 6.8.

1-Hydroxy-1,2,3,4-tetrahydroacridine (6). Sodium borohydride (10 g, 0.26 mol) was added portionwise to a solution of 1-oxo-1,2,3,4-tetrahydroacridine (5) (10.0 g, 50 mmol) in dry methanol (300 mL) at 0 °C, over 1 h. After being stirred overnight at rt, the reaction mixture was concentrated under reduced pressure and the residue diluted with H_2O (140 mL). The product was extracted into CH_2Cl_2, and after drying ($MgSO_4$), the solvent was removed under reduced pressure. The crude material thus obtained was recrystallized from CH_2Cl_2 to yield 1-hydroxy-1,2,3,4-tetrahydroacridine (6) (9.2 g, 91%): mp 167–169 °C; ^{1}H NMR δ 1.93 (2H, m), 2.19 (2H, m), 3.12 (2H, m), 5.00 (1H, m), 7.47 (1H, m), 7.66 (1H, m), 7.77 (1H, d, J = 8.0 Hz), 7.99 (1H, d, J = 8.4 Hz), 8.25 (1H, s). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.4; H, 6.5; N, 7.0. Found: C, 78.15; H, 6.6; N, 6.7.

3,4-Dihydroacridine (7). Alcohol 6 (5.0 g, 25 mmol) was heated and stirred with polyphosphoric acid (50 g) at ~110 °C. The reaction appeared to be complete after 1 h (by TLC analysis). The product mixture was then dissolved in H_2O (100 mL), cooled to 0 °C, made basic (NaOH), and extracted with CH_2Cl_2 (4 × 150 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (Et_2O) followed by recrystallization from hexane to yield 3,4-dihydroacridine (7) (3.9 g, 86%): mp 45–46 °C; ^{1}H NMR δ 2.58 (2H, m), 3.18 (2H, t, J = 7.8 Hz), 6.20 (1H, m), 6.61 (1H, d, J = 9.6 Hz), 7.45 (1H, m); 7.61 (1H, m), 7.65 (1H, s), 7.72 (1H, d, J = 8.1 Hz), 7.98 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{13}H_{11}N$: C, 86.2; H, 6.1; N, 7.7. Found: C, 85.9; H, 6.4; N, 8.0.

***trans*-1-Acetoxy-2-bromo-1,2,3,4-tetrahydroacridine (8).** 3,4-Dihydroacridine (7) (3.0 g, 17 mmol) was stirred in acetic

(25) Akhtar, M. N.; Hamilton, J. G.; Boyd, D. R.; Braunstein, A.; Seifried, H. E.; Jerina, D. M. *J. Chem Soc., Perkin Trans. 1* 1979, 1442–1446.

acid (90 mL) at rt with *N*-bromoacetamide (2.6 g, 19 mmol) and lithium acetate dihydrate (3.9 g, 38 mmol). After 4 h a portion (~50%) of the solvent was removed under reduced pressure, and the residual mixture was made basic (aqueous Na_2CO_3, 20%). The product was extracted with CH_2Cl_2 (3 × 150 mL), and the combined extracts were dried ($MgSO_4$) prior to removal of the solvent under reduced pressure. The crude product thus obtained was purified by flash chromatography (2% methanol in $CHCl_3$) to yield *trans*-1-acetoxy-2-bromo-1,2,3,4-tetrahydroacridine (**8**) (4.3 g, 81%): mp 112–114 °C (from hexane); IR (KBr) 1730 cm^{-1} (ν C=O); ^1H NMR δ 2.12 (3H, s), 2.40 (1H, m), 2.71 (1H, m), 3.29 (1H, m), 3.40 (1H, m), 4.56 (1H, m), 6.34 (1H, d, J = 4.4 Hz), 7.50 (1H, m), 7.72 (1H, m), 7.79 (1H, d, J = 7.9 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.14 (1H, s). Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.25; H, 4.4; N, 4.4. Found: C, 56.1; H, 4.1; N, 4.3.

1-Acetoxy-2,4-dibromo-1,2,3,4-tetrahydroacridine (9). To a solution of *trans*-1-acetoxy-2-bromo-1,2,3,4-tetrahydroacridine (**8**) (4.0 g, 12.5 mmol) in dry carbon tetrachloride (100 mL) was added NBS (2.46 g, 13.8 mmol) and AIBN (20 mg). The solution was irradiated (using a heat lamp) under a nitrogen atmosphere and heated at ~60 °C for ~1 h. Precipitated succinimide was removed by filtration and the solvent removed under reduced pressure to yield a crude product which appeared to be a mixture of stereoisomers of the dibromoacetate **9** (4.2 g, 84%). A small portion of this crude material was recrystallized from CH_2Cl_2 to yield a single, unstable isomer of 1-acetoxy-2,4-dibromo-1,2,3,4-tetrahydroacridine (**9**): mp 142–152 °C dec; ^1H NMR δ 2.31 (3H, s), 2.97 (1H, m), 3.14 (1H, m), 4.88 (1H, m), 5.67 (1H, m), 6.49 (1H, d, J = 8.8 Hz), 7.57 (1H, m), 7.75 (1H, m), 7.80 (1H, d, J = 8.1 Hz), 8.02 (1H, s), 8.08 (1H, d, J = 8.7 Hz); HRMS calcd for $C_{15}H_{13}{}^{79}Br_2NO_2$ (M^+) 396.9314, found 396.9314.

Acridine 1,2-Oxide (1). Sodium methoxide (4.0 g) was added to a solution of the dibromoacetate **9** (4.0 g, 10 mmol) in THF (150 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h and then at rt for 3 h. The solvent was removed under reduced pressure, and the residue was mixed with H_2O. The product was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were dried (K_2CO_3). The solvent was removed under reduced pressure, and the crude product was recrystallized from CH_2Cl_2/hexane to yield acridine 1,2-oxide (**1**) (1.7 g, 87%): mp 140–146 °C dec; ^1H NMR δ 4.15 (1H, m), 4.63 (1H, d, J = 4.1 Hz), 6.85 (1H, dd, J = 9.8, 3.8 Hz), 7.10 (1H, d, J = 9.8 Hz), 7.57 (1H, m), 7.75 (1H, m), 7.86 (1H, d, J = 8.1 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.37 (1H, s). Anal. Calcd for $C_{13}H_9NO$: C, 80.0; H, 4.6; N, 7.2. Found: C, 79.6; H, 4.7; N, 7.7.

1,2-Epoxy-1,2,3,4-tetrahydroacridine (10). Sodium methoxide (4.0 g) was added to a solution of *trans*-1-acetoxy-2-bromo-1,2,3,4-tetrahydroacridine (**8**) (4.0 g, 12.5 mmol) in dry THF (150 mL) under nitrogen, and the resulting suspension was stirred at rt for 4 h. The solvent was removed under reduced pressure, and the residue was mixed with H_2O. The aqueous suspension was extracted with CH_2Cl_2 (3 × 100 mL), the combined extracts were dried (K_2CO_3), and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography (Et_2O) yielded 1,2-epoxy-1,2,3,4-tetrahydroacridine (**10**) (1.9 g, 78%): mp 120–122 °C (CH_2Cl_2/hexane); ^1H NMR δ 2.00 (1H, m), 2.61 (1H, m), 3.03 (2H, m), 3.84 (1H, m), 4.04 (1H, d, J = 4.1 Hz), 7.51 (1H, m), 7.70 (1H, m), 7.80 (1H, d, J = 7.9 Hz), 8.02 (1H, d, J = 8.7 Hz), 8.16 (1H, s). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.2; H, 5.6; N, 7.1. Found: C, 79.2; H, 5.3; N, 7.0.

***trans*-1,2-Dihydroxy-1,2,3,4-tetrahydroacridine (11).** 1,2-Epoxy-1,2,3,4-tetrahydroacridine (**10**) (1.7 g, 8.6 mmol) was heated in formic acid (20 mL, 90%) at ~45 °C for 3 h. Following removal of the formic acid under reduced pressure, H_2O (20 mL) was added to the residue, and the solution was made basic with aqueous NaOH (20%). The mixture was then saturated with NaCl and extracted with EtOAc (5 × 50 mL). The combined extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (12% methanol in CH_2Cl_2) to yield *trans*-1,2-dihydroxy-1,2,3,4-tetrahydroacridine (**11**) (1.7 g, 75%): mp 159–161 °C (EtOAc/hexane); ^1H NMR δ 2.05 (1H, m), 2.33 (1H, m), 3.27 (2H, m), 3.93 (1H, m), 4.77 (1H, d, J = 8.5 Hz), 7.49 (1H, m), 7.68 (1H, m), 7.81 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 8.6 Hz), 8.37 (1H, s). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.6; H, 6.05; N, 6.5. Found: C, 72.3; H, 5.85; N, 6.3.

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydroacridine (12).** To a solution of *trans*-1,2-dihydroxy-1,2,3,4-tetrahydroacridine (**11**) (1.5 g, 7 mmol) in dry pyridine (10 mL) was added acetic anhydride (13 mL), and the solution was stirred at rt overnight. Solvent was removed under reduced pressure, and the residual oil was stirred with 2 M Na_2CO_3. The product was extracted into CH_2Cl_2 (3 × 50 mL) which was dried ($MgSO_4$) prior to evaporation under reduced pressure. Recrystallization of the product from Et_2O/pentane gave *trans*-1,2-diacetoxy-1,2,3,4-tetrahydroacridine (**12**) (1.7 g, 81%): mp 103–105 °C; ^1H NMR δ 2.04 (3H, s), 2.14 (3H, s), 2.25 (1H, m), 2.39 (1H, m), 3.26 (2H, m), 5.30 (1H, m), 6.23 (1H, d, J = 5.3 Hz), 7.51 (1H, m), 7.71 (1H, m), 7.79 (1H, d, J = 8.1 Hz), 8.01 (1H, d, J = 8.1 Hz), 8.13 (1H, s). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.5; H, 5.9; N, 4.4.

***trans*-1,2-Diacetoxy-4-bromo-1,2,3,4-tetrahydroacridine (13).** NBS (1.0 g, 5.6 mmol) and AIBN (10 mg) were added to a solution of *trans*-1,2-diacetoxy-1,2,3,4-tetrahydroacridine (**12**) (1.5 g, 5 mmol). The benzylic bromination and workup procedures were carried out as reported for compound **9**. The crude product was obtained as an oil (1.7 g, 89%) which appeared, from ^1H NMR analysis, to be a mixture of two stereoisomers of compound **13**. A small portion of the crude product was recrystallized from Et_2O to give the bromodiacetate **13**: mp 142–154 °C dec; ^1H NMR δ 2.10 (3H, s), 2.24 (3H, s), 2.64 (1H, m), 2.84 (1H, m), 5.68 (1H, dd, J = 4.3, 4.3 Hz), 5.82 (1H, m), 6.38 (1H, d, J = 8.0 Hz), 7.56 (1H, m), 7.75 (1H, m) 7.80 (1H, d, J = 8.2 Hz), 8.07 (1H, s), 8.09 (1H, d, J = 8.5 Hz); HRMS calcd for $C_{17}H_{16}{}^{79}BrNO_4$ (M^+) 377.0263, found 377.0272.

***trans*-1,2-Diacetoxy-1,2-dihydroacridine (14).** DBN (0.8 mL, 6.5 mmol) was added to a solution of the bromodiacetate **13** (1.2 g, 3.2 mmol) in dry THF. The solution was stirred under nitrogen at 0 °C for 1 h and then at rt for 3 h. The solvent was removed under reduced pressure, and excess phosphate buffer (aqueous KH_2PO_4 adjusted to pH 7.3 with NaOH) was added. The solution thus obtained (40 mL) was extracted with CH_2Cl_2 (3 × 60 mL), the extract was dried (K_2CO_3), and the solvent was removed under reduced pressure to give a relatively unstable product which decomposed during attempted purification by TLC (4% methanol in $CHCl_3$): yield of crude product 0.70 g (74%); ^1H NMR δ 2.07 (3H, s), 2.15 (3H, s), 5.69 (1H, m), 6.33 (1H, d, J = 4.0 Hz), 6.43 (1H, dd, J = 10.0, 3.9 Hz), 6.99 (1H, d, J = 10.0 Hz), 7.53 (1H, m); 7.71 (1H, m), 7.79 (1H, d, J = 8.0 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.06 (1H, s); HRMS calcd for $C_{17}H_{15}NO_4$ (M^+) 297.1001, found 297.1004.

***trans*-1,2-Dihydroxy-1,2-dihydroacridine (3).** Dry ammonia gas was bubbled through a solution of diacetate **14** (0.6 g, 2 mmol) in dry methanol (20 mL) at 0 °C for 2 h. The solution was stirred at rt for a further 2 h, and the solvent was removed under reduced pressure to afford the crude product. Purification by preparative TLC (5% methanol in $CHCl_3$) yielded *trans*-1,2-dihydroxy-1,2-dihydroacridine (**3**) (0.32 g, 75%), mp 202–212 °C dec from EtOAc: ^1H NMR (300 MHz, acetone-d_6) δ 4.53 (1H, m), 4.91 (1H, d, J = 10.1 Hz), 6.41 (1H, dd, J = 2.1, 10.0 Hz), 6.63 (1H, dd, J = 2.3, 10.0 Hz), 7.53 (1H, m), 7.67 (1H, m), 7.89 (1H, d, J = 8.0 Hz), 7.94 (1H, d, J = 8.4 Hz), 8.32 (1H, s); HRMS calcd for $C_{13}H_{11}NO_2$ (M^+) 213.0790, found 213.0790.

Acridine 1,2-oxide (**1**) (0.035 g, 0.18 mmol) was dissolved in a mixture of 2-methyl-2-propanol (3 mL) and H_2O (3 mL) containing KOH (0.022 g, 0.39 mmol) and was heated at ~45 °C for 72 h. The solution was diluted with H_2O (10 mL), saturated with NaCl, and extracted with EtOAc (5 × 10 mL). The extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude product. Purification by preparative TLC as above and recrystallization from EtOAc yielded *trans*-1,2-dihydroxy-1,2-dihydroacridine (**3**) (0.021 g, 55%), mp 200–210 °C dec. This sample was spectrally indistinguishable from the sample prepared by the multistep sequence **10** → **3**.

***trans*-4-Acetoxy-3-bromo-1,2,3,4-tetrahydroacridine.** 1,2-Dihydroacridine[26] (1.0 g, 5.5 mmol) was stirred with *N*-bromoacetamide (0.828 g, 6 mmol) and lithium acetate dihydrate (1.0 g, 9.5 mmol). The same reaction conditions and isolation procedure were employed as described for the synthesis of bromoacetate **8**. The isolated yield of 4-acetoxy-3-bromo-1,2,3,4-tetrahydroacridine was 1.5 g (85%): mp 103–105 °C from EtOAc/

(26) Al-Tai, F. A.; Sarkis, G. Y.; Al-Janabi, J. M. *Bull. Coll. Sci. (Baghdad)* **1966**, *9*, 55–58; *Chem. Abstr.* **1968**, *68*, 39436a.

Et_2O; ^1H NMR δ 2.14 (3H, s), 2.31 (1H, m), 2.54 (1H, m), 3.17 (1H, m), 3.31 (1H, m), 4.72 (1H, m), 6.23 (1H, d, J = 4.6 Hz), 7.51 (1H, m), 7.66 (1H, m), 7.79 (1H, d, J = 8.6 Hz), 7.96 (1H, s), 8.06 (1H, d, J = 8.5 Hz). Anal. Calcd for $C_{15}H_{14}O_2BrN$: C, 56.3; H, 4.4; N, 4.4. Found: C, 56.6; H, 4.0; N, 4.4.

4-Acetoxy-1,3-dibromo-1,2,3,4-tetrahydroacridine. Treatment of 4-acetoxy-3-bromo-1,2,3,4-tetrahydroacridine (0.5 g, 1.6 mmol) with NBS (0.313 g, 1.76 mmol) in carbon tetrachloride (30 mL) under similar conditions to those used in the synthesis of dibromoacetate **9** yielded 4-acetoxy-1,3-dibromo-1,2,3,4-tetrahydroacridine (0.62 g, 97%) as a highly unstable mixture of diastereomers: ^1H NMR δ 2.26 (3H, s), 2.88 (1H, m), 3.06 (1H, m), 4.85 (1H, m), 5.71 (1H, m), 6.30 (1H, d, J = 7.6 Hz), 7.52 (1H, m), 7.65–7.75 (3H, m), 8.04 (1H, s) for the major isomer. Due to instability this compound was used immediately without purification.

Acridine 3,4-Oxide (2). 4-Acetoxy-1,3-dibromo-1,2,3,4-tetrahydroacridine (0.620 g, 1.5 mmol) was stirred with sodium methoxide (1.0 g) in dry THF (50 mL). The reaction conditions and method used to isolate the product were identical to those described earlier for arene oxide **1**. This gave acridine 3,4-oxide (**2**) (0.280 g, 87%): mp 100–102 °C from pentane/Et_2O at −70 °C; ^1H NMR δ 4.16 (1H, m), 4.73 (1H, d, J = 3.7 Hz), 6.52 (1H, dd, J = 9.6, 3.7 Hz), 6.86 (1H, dd, J = 9.6, 1.6 Hz), 7.56 (1H, m), 7.70–7.80 (2H, m), 8.10 (1H, s), 8.14 (1H, d, J = 8.5 Hz); HRMS calcd for $C_{13}H_9NO$ (M^+) 195.0684, found 195.0684.

Crystal Data for Acridine 1,2-Oxide. Table 1 summarizes crystal parameters and details of crystal data collection for acridine 1,2-oxide. The structure was solved by direct methods (SHELXS86)[27] and refined by a least-squares procedure (SHELX76)[28] with non-hydrogen atoms anisotropic. Hydrogen atoms were included at calculated positions. In the final cycles the 674 data with $I > 4\sigma(I)$ gave R = 0.118, R_w = 0.130 with $w = 1/[\sigma^2(F) + 0.0256F^2]$. The structure approximates closely to the monoclinic space group $P2_1/n$ (a axis unique), the lowering of symmetry being due to the γ angle $\neq 90°$ (= 92.45°). The two independent molecules of the triclinic asymmetric unit are related by the approximate 2_1 axis of the monoclinic unit cell. Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Kinetics. Reaction rates were measured at 25 °C in 1:9 dioxane/water at an ionic strength of 0.1 M ($NaClO_4$). Dioxane was distilled from sodium. Constant pH in each reaction mixture was maintained with $HClO_4$ (10^{-1}–2.5×10^{-4} M) or buffers (1–2 mM acetic, formic, MES (4-morpholineethanesulfonic acid), and BES (*N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid)). Buffer catalysis was not observed at these concentrations. The pH of strongly basic reaction mixtures (0.05–0.2 M NaOH) was estimated from the relationship pH = (14 + log[OH^-]).

Rates of reactions of the acridine oxides at neutral and acidic pH values were measured spectrophotometrically (262 nm, acridine 1,2-oxide and 269 nm, acridine 3,4-oxide), as were the rates of reaction of anthracene 1,2-oxide (252 nm) throughout the pH range. Reactions were initiated by addition of 5–10 μL of a dioxane solution of each oxide (0.2 mg/mL) into 1.0 mL of the reaction mixture. At strongly basic pH (0.05 and 0.1 M NaOH), rates of acridine oxide hydrolysis were followed chromatographically: 0.2-mL samples of each reaction mixture were neutralized with 1 M NaH_2PO_4, and 0.1-mL portions were analyzed by HPLC on a Spherisorb 5-μm C_{18} column (4.6 × 250 mm) eluted at a flow rate of 1 mL/min with a linear gradient from 50% Tris-acetate buffer (0.05 M, pH 7.0) in MeOH to 100% MeOH in 20 min. The detection wavelength was 255 nm for the 1,2-oxide and 250 nm for the 3,4-oxide. Rates were quantified by following the decrease in the ratio of oxide to an internal standard of 4-(*p*-nitrophenyl)butanol. Retention times (min): standard (10.1), 1,2-dihydrodiol (6.7), 1,2-oxide (11.8), 3,4-dihydrodiol (7.5), 3,4-oxide (11.9).

Products. Products of the hydrolysis of acridine 1,2-oxide were analyzed by HPLC as described in the preceding section. To enable quantitation of the phenol and dihydrodiol products formed from acridine 1,2-oxide, HPLC detector responses were standardized against an NMR spectrum of the mixed products as follows. The oxide was allowed to react at 37 °C in 0.1 M $HClO_4$, and the ^1H NMR spectrum of the mixed products was measured in acetone. In this spectrum, the farthest downfield signal (s, δ 9.26) corresponds to H-9 of 1-hydroxyacridine, and a singlet at δ 8.72 corresponds to H-9 of 2-hydroxyacridine. The two furthest-upfield resonances of the phenols, H-2 of 1-hydroxyacridine, centered at δ 6.93 (dd, J = 1.3, 6.9 Hz), and H-1 of 2-hydroxyacridine at δ 7.34 (d, J = 2.6 Hz), are also characteristic. Molar ratios of the products, determined from the H-9 singlets or the H-2 and H-1 signals of 1-hydroxy- and 2-hydroxyacridine, respectively, as well as the H-3 signal at δ 6.41 for the *trans*-1,2-dihydrodiol, were compared with the areas of the HPLC peaks corresponding to these products in the same mixture. From these results, factors were derived for the conversion of HPLC peak areas (at 262 nm) to molar ratios of the products: the 1- and 2-hydroxyacridine areas were multiplied by 0.39 and 1.0, respectively, and the area corresponding to the *trans*-1,2-dihydrodiol was multiplied by 1.52. Retention times (min): acridine *trans*-1,2 dihydrodiol (6.7), 2-hydroxyacridine (11.6), and 1-hydroxyacridine (12.7). A small shoulder on the *trans*-1,2-dihydrodiol peak (6.5 min) that corresponded to less than 3% of the total products was tentatively assigned as the *cis*-1,2-dihydrodiol.

Acid hydrolysis of acridine 3,4-oxide was performed under the kinetic conditions in 0.1 M $HClO_4$ for 1 h. Because 4-hydroxyacridine did not give a quantifiable peak on HPLC, the mixture of hydrolysis products was acetylated prior to analysis. Upon completion of hydrolysis, the reaction mixture was adjusted to pH 6–8 with NaOH and extracted with EtOAc. After drying (Na_2SO_4) and evaporation of the organic solvent, the residual product was acetylated (pyridine/Ac_2O). The product was analyzed by HPLC (250 nm) on a 4.6 × 200-mm C_{18} column eluted at 1 mL/min with a linear gradient from 60% Tris-acetate buffer (0.05 M) in acetonitrile to 100% acetonitrile in 30 min.; t_R 9.1 min. A commercial sample of 4-hydroxyacridine (Fluka) upon acetylation gave a product with identical retention time and UV spectrum. Neither 3-hydroxyacridine nor the 3,4-dihydrodiol was detected upon examination of the ^1H NMR spectrum of the hydrolysis product prior to acetylation. 4-Hydroxyacridine was also the only product detected by the chromatographic method described upon hydrolysis of the 3,4-oxide at pH 4.2 ($t_{1/2}$ 990 s) and pH 7.3 ($t_{1/2}$ 7 h) for 17 and 48 h, respectively. The product formed upon base hydrolysis (1 M NaOH) was subjected to chromatography without prior acetylation and gave a single peak at 7.4 min, which was identified as the 3,4-dihydrodiol by its ^1H NMR spectrum (Table 2).

In order to determine the products formed from anthracene 1,2-oxide under the kinetic conditions, this arene oxide was allowed to react at rt in 1:9 dioxane/water containing 0.1 M $HClO_4$ for 5 min at 25 °C and in 0.01 M BES buffer, pH 7.6, ionic strength 0.1 M ($NaClO_4$), containing 10% dioxane, for 2 h. Upon completion of reaction, products were extracted from each reaction mixture with EtOAc, which was then dried with Na_2SO_4. The residues after solvent evaporation were dissolved in acetone-d_6 for measurement of ^1H NMR spectra.

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Supplementary Material Available: ^1H NMR spectra of compounds **1**, **2**, **3**, **9**, **13**, **14**, and 4-acetoxy-1,3-dibromo-1,2,3,4-tetrahydroacridine (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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