Methyl 2-(1-methyl-2-pyrrolidinylidene)acetate (27): mp 50.5–51.5 °C; IR ($CHCl_3$) 1595, 1670 cm^{-1}; NMR (CCl_4) δ 1.93 (qu, J = 7.5, 2 H, CH_2), 2.80 (s, 3 H, NCH_3), 3.07 (t, J = 7.5, 2 H, $=CCH_2$), 3.33 (t, J = 7.5, 2 H, NCH_2), 3.50 (s, 3 H, OCH_3), 4.32 (s, 1 H, =CH); mass spectrum, m/e (relative intensity) 155 (42), 124 (100), 97 (18), 96 (18); exact mass calcd for $C_8H_{13}NO_2$ m/e 155.0946, found m/e 155.0952.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 62.14; H, 8.51.

3-(1-Methyl-2-pyrrolidinylidene)-2,4-pentanedione (28):[4d] NMR ($CDCl_3$) δ 2.03 (qu, J = 7.5, 2 H, CH_2), 2.27 (s, 6 H, $COCH_3$), 2.82 (s, 3 H, NCH_3), 3.17 (t, J = 7.5, 2 H, $=CCH_2$), 3.63 (t, J = 7.5, 2 H, NCH_2).

1-(1-Methyl-2-pyrrolidinylidene)-2-propanone (29):[2] NMR (CCl_4) δ 1.70–2.10 (q, J = 7, with s at 1.90, 5 H, $COCH_3$ and CH_2), 2.83 (s, 3 H, NCH_3), 3.07 (t, J = 7, 2 H, $=CCH_2$), 3.33 (t, J = 7, 2 H, NCH_2), 4.80 (s, 1 H, =CH).

***tert*-Butyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxobutanoate (30)**: mp 65.5–66.5 °C; IR ($CHCl_3$) 1545, 1615, 1670 cm^{-1}; NMR (CCl_4) δ 1.52 (s, 9 H, O-*t*-Bu), 2.00 (qu, J = 7.5, 2 H, CH_2), 2.17 (s, 3 H, $COCH_3$), 2.77 (s, 3 H, NCH_3), 3.07 (t, J = 7.5, 2 H, $=CCH_2$), 3.60 (t, J = 7.5, 2 H, NCH_2); mass spectrum, m/e (relative intensity) 239 (3), 238 (18), 182 (16), 167 (30), 165 (23), 164 (23), 149 (21), 118 (19), 103 (100); exact mass calcd for $C_{13}H_{21}NO_3$ m/e 239.1521, found m/e 239.1516.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85. Found: C, 65.25; H, 8.99.

***tert*-Butyl 2-(1-methyl-2-pyrrolidinylidene)acetate (31)**: IR ($CHCl_3$) 1590, 1670 cm^{-1}; NMR (CCl_4) δ 1.43 (s, 9 H, O-*t*-Bu), 1.93 (qu, J = 7.5, 2 H, CH_2), 2.78 (s, 3 H, NCH_3), 3.03 (t, J = 7.5, 2 H, $=CCH_2$), 3.30 (t, J = 7.5, 2 H, NCH_2), 4.27 (s, 1 H, =CH); mass spectrum, m/e (relative intensity) 197 (31), 96 (100); exact mass calcd for $C_{11}H_{19}NO_2$ m/e 197.1416, found 197.1418.

α-(1-Methyl-2-pyrrolidinylidene)acetophenone (35): mp 100–101 °C; IR ($CHCl_3$) 1540, 1580, 1620 cm^{-1}; NMR (CCl_4) δ 1.97 (qu, J = 6, 2 H, CH_2), 2.90 (s, 3 H, NCH_3), 3.33 (q, J = 6, 4 H, NCH_2, allyl), 5.53 (s, 1 H, =CH), 7.20–7.50 (m, 3 H, ortho and para Ar H), 7.63–7.90 (m, 2 H, meta Ar H); mass spectrum, m/e (relative intensity) 201 (64), 200 (55), 184 (30), 124 (100), 115 (8), 105 (26), 96 (44); exact mass calcd for $C_{13}H_{15}NO$ m/e 201.1154, found m/e 201.1158.

Acknowledgment. We thank Dr. Chuck Cottrell and Richard Weisenberger for their assistance in obtaining ^{13}C NMR and mass spectra, respectively. Financial support from the National Institutes of Health is gratefully acknowledged.

Registry No. 8, 25355-40-2; 9, 25355-41-3; 10, 78167-63-2; 11, 75-52-5; 12, 108-59-8; 13, 105-56-6; 14, 141-97-9; 15, 105-45-3; 16, 123-54-6; 17, 1694-31-1; 18, 26171-05-1; 19, 26924-97-0; 20, 53583-61-2; 21, 21985-16-0; 22, 60624-10-4; 23, 78167-64-3; 24, 78167-65-4; 25, 78167-66-5; 26, 78167-67-6; 27, 78167-68-7; 28, 60624-11-5; 29, 39178-30-8; 30, 78167-69-8; 31, 78167-70-1; 32, 542-05-2; 33, 614-20-0; 34, 1071-46-1; 35, 39178-28-4; 36, 64679-38-5; 37, 78167-71-2; 38, 78167-72-3; 39, 75533-98-1; i, 78167-73-4; ii, 78167-74-5; 1-methyl-2-pyrrolidinone, 872-50-4; 1-methyl-2-piperidone, 931-20-4; *rel*-(3a*S*,5a*R*,9a*R*)-dodecahydropyrrolo[1,2-*a*]quinolin-1-one, 75533-96-9.

Synthesis of Dihydrodiol and Other Derivatives of Benz[*c*]acridine

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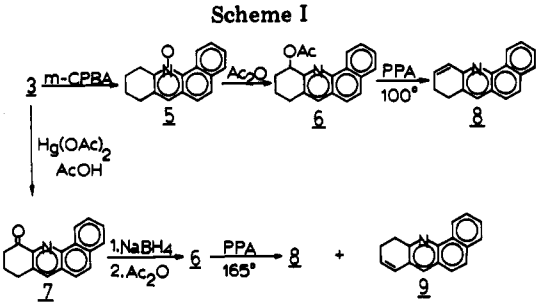
Received March 30, 1981

The K-region and non-K-region *trans*-dihydrodiols and the cis and trans bay-region diol epoxides of benz[*c*]acridine have been synthesized. Regiospecific oxygenation at C-11 of 8,9,10,11-tetrahydrobenz[*c*]acridine and at C-4 of 1,2,3,4-tetrahydrobenz[*c*]acridine with mercuric acetate in acetic acid afforded intermediates that were converted to the 10,11- and 3,4-dihydrodiols, respectively. The 1,2- and 8,9-dihydrodiols were prepared by routes involving separation of their precursors from analogous precursors of the 3,4- and 10,11-dihydrodiols. The K-region *trans*-dihydrodiol was prepared by acid-catalyzed hydration of the K-region oxide. The *cis*- and *trans*-3,4-diol 1,2-epoxides, which are structurally analogous to the most mutagenic and tumorgenic of the benzo[*a*]anthracenediol epoxides, were prepared from the 3,4-dihydrodiol in good yields by base-catalyzed bromotriol cyclization and direct epoxidation with *m*-chloroperoxybenzoic acid, respectively.

It is well established that metabolism of polycyclic aromatic hydrocarbons to dihydrodiols and diol epoxides is an important event in the activation of these molecules to ultimate mutagens and carcinogens.[1] The analogous aza aromatics, which are also environmental contaminants and which include a number of known carcinogens,[2] have received scant attention. Kitahara et al.[3] prepared K-region oxides of several aza aromatics and have observed mutagenicity levels in *S. typhimurium* TA 100 insufficient to support their involvement as likely bioactivated forms of the molecules. Reports of the preparation of dihydrodiols and other derivatives of dibenzo[*c*,*h*]acridine[4] and of the K-region oxide of 7-methylbenz[*c*]acridine[5] have appeared recently, but the biological data reported for these molecules has been fragmentary.

Scheme I



Benz[*c*]acridine (1) was chosen as the initial target for the several reasons. The analogous polycyclic aromatic hydrocarbon, benz[*a*]anthracene (BA, 2) has been exten-

(1) For a recent review, see M. Nordqvist, D. R. Thakker, H. Yagi, R. E. Lehr, A. W. Wood, W. Levin, A. H. Conney, and D. M. Jerina in "Molecular Basis of Environmental Toxicity", R. S. Bhatnagar, Ed., Ann Arbor Science Publishers, Ann Arbor, MI, 1980, pp 329–357.

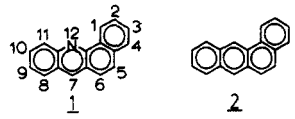
(2) A. Dipple in "Chemical Carcinogens", C. E. Searle, Ed., American Chemical Society, New York, 1976, p 245.

(3) Y. Kitahara, H. Okuda, K. Shudo, T. Okamoto, M. Nagao, Y. Scino, and T. Sugimura, *Chem. Pharm. Bull. Jpn.*, 26, 1950 (1978).

(4) Y. Kitahara, K. Shudo, and T. Okamoto, *Chem. Pharm. Bull. Jpn.*, 28, 1958 (1980).

(5) L. J. Boux, H. T. A. Cheung, G. M. Holder, and L. Moldovan, *Tetrahedron Lett.*, 21, 2923 (1980).

0022-3263/81/1946-3675$01.25/0



1 2

sively studied, and mutagenicity and tumorigenicity data are available for an extensive series of synthetic derivatives.[6] The effect of aza substitution at C-12 upon both metabolism and biological properties could thus be readily assessed once the analogous derivatives of benz[c]acridine were prepared. Furthermore, structure–activity relationships are more easily determined if a relatively large number of closely related derivatives are available. Benz[c]acridine, like BA, has, in addition to the K-region *trans*-5,6-dihydrodiol, four diastereomeric non-K-region *trans*-dihydrodiols and eight diastereoisomeric diol epoxides derived from them.

Results and Discussion

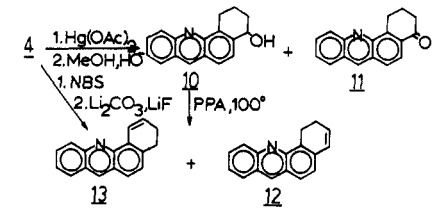
There are a wide variety of routes available for dihydro diols and other derivatives of polynuclear aromatic hydrocarbons (PAH), with dihydrobenzo ring derivatives analogous to 8 and 9 (Scheme I), being required intermediates in all reported schemes. For the aza PAH, tetrahydrobenzo ring derivatives are frequently easily accessible through condensation reactions, and 3 and 4 were

3 4

chosen as synthetic starting points for the benz[c]acridine derivatives. Compound 3 (8,9,10,11-tetrahydrobenz[c]acridine) is available in large quantities by a straightforward literature procedure,[7] but 1,2,3,4-tetrahydrobenz[c]acridine (4) has previously been described only as a minor byproduct[8] in a mechanistic study. Compound 4 was synthesized in quantity by reduction of benz[c]acridine[9] with sodium in refluxing amyl alcohol to 1,2,3,4,7,12-hexahydrobenz[c]acridine, followed by oxidation of the acridan to 4 with ferric chloride in concentrated hydrochloric acid.

Preparation of Dihydrobenz[c]acridines. The most productive and effective route to dihydrodiols and other benzo ring derivatives of 3 and 4 would entail the development of conditions for the introduction of oxygen functionality regiospecifically into the two different benzylic positions in both 3 and 4 followed by conversion to the alkene. For 3, it has proven possible to introduce functionality regiospecifically at C-11 but not at C-8. Two synthetic routes have been found effective. Treatment of 3 with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 yielded a mixture of the *N*-oxide 5 and unreacted 3 (3:1 ratio). Treatment of the mixture, without purification, with excess acetic anhydride on a steam bath afforded 11-acetoxy-8,9,10,11-tetrahydrobenz[c]acridine (6) in 92% yield based upon recovered 3. The regiospecific production of a C-11 acetate in this reaction is consistent with previous results and proposed mechanisms for the reaction.[10] A

Scheme II



more novel approach involved treatment of 3 with mercuric acetate in acetic acid at reflux to give 11-oxo-8,9,10,11-tetrahydrobenz[c]acridine (7). Again, derivatization occurred exclusively at C-11. This 11-oxo derivative 7 on reduction with sodium borohydride in ethanol followed by treatment with acetic anhydride–pyridine yielded 6 in 55–60% overall yield (Scheme I) from 3. Conversion of acetate 6 to the desired alkene 8 was accomplished in good yield with polyphosphoric acid at 100 °C. The isomeric alkene 9 could not be prepared in a regiospecific manner but was produced by heating 6 at 160 °C in polyphosphoric acid. Under these conditions a ca. 3:1 mixture of 8/9 is produced from 6 in 67% yield. As discussed later, further reaction of the alkene mixture leads to derivatives that permit separation of the 8,9 and 10,11 series in quantity and consequently to a route to the 8,9-dihydrodiol.

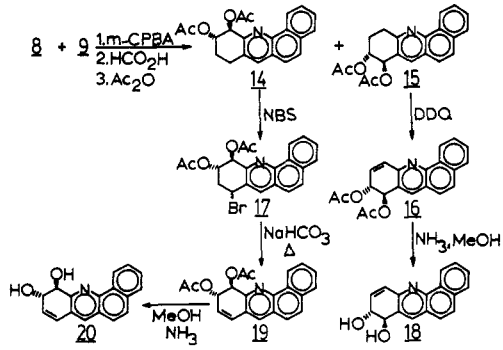
Attempts to apply the *N*-oxide/acetic anhydride procedure to prepare 4-acetoxy-1,2,3,4-tetrahydrobenz[c]acridine were unsuccessful, since rupture of the heterocyclic ring occurred in the reaction of 4 with *m*-chloroperoxybenzoic acid. An analogous ring opening of acridine to produce 2-(2-hydroxyanilino)benzaldehyde has been reported by Acheson and Adcock.[11] Successful oxidation at C-4 of 4 was achieved by the mercuric acetate/acetic acid method (Scheme II). Under these conditions a mixture of 4-acetoxy-1,2,3,4-tetrahydrobenz[c]acridine, 4-hydroxy-1,2,3,4-tetrahydrobenz[c]acridine (10), and 4-oxo-1,2,3,4-tetrahydrobenz[c]acridine (11) is produced which upon hydrolysis with a methanolic sodium hydroxide gave 10 in 62–70% yield based on recovered 4. Dehydration of 10 at 100 °C in a biphasic mixture of polyphosphoric acid and xylene gave a high yield of 1,2-dihydrobenz[c]acridine (12), contaminated by a small amount (ca. 15%) of 3.4-dihydrobenz[c]acridine (13).

Derivatives of 4 at C-1 are formed, but nonselectively, through free-radical bromination with *N*-bromosuccinimide. Under these conditions, roughly equal amounts of 1-bromo- and 4-bromo-1,2,3,4-tetrahydrobenz[c]acridines are produced. A direct determination of relative amounts has not proven possible due to the high reactivity of the 1-bromo isomer, which partially dehydrobrominates during workup unless the temperature is controlled below 25 °C. However, careful workup of the bromination mixture, followed by hydrolysis to the alcohols in acidic aqueous THF, gives a high recovery of 1- and 4-hydroxy-1,2,3,4-tetrahydrobenz[c]acridines (83% based on recovered 4) as a 1:1 mixture, which could be separated by dry-column chromatography on alumina. For synthetic purposes, the crude mixture of bromo compounds was dehydrobrominated with LiF and Li_2CO_3 in HMPA to give a mixture of alkenes 12 and 13, which afforded, upon further reaction, easily separated derivatives of the 1,2 and 3,4 series and thereby a route to the 1,2-dihydrodiol.

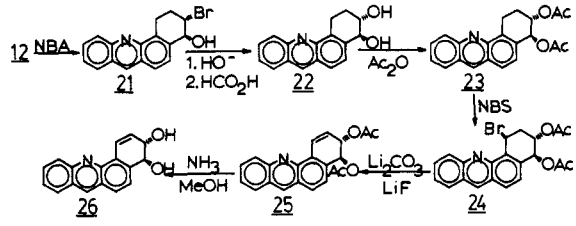
Preparation of Diacetoxytetrahydrobenz[c]acridines. Typically, dihydrobenzo ring derivatives of

(6) (a) A. W. Wood, W. Levin, R. L. Chang, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 3176 (1977); (b) W. Levin, D. R. Thakker, A. W. Wood, R. L. Chang, R. E. Lehr, D. M. Jerina, and A. H. Conney, *Cancer Res.*, 38, 1705 (1978); (c) T. J. Slaga, E. Huberman, J. K. Selkirk, R. G. Harvey, and W. M. Bracken, *ibid.*, 38, 1699 (1978).
(7) G. E. Hall and James Walker, *J. Chem. Soc. C*, 2237 (1968).
(8) R. N. Carde and G. Jones, *J. Chem. Soc., Perkin Trans. 1*, 2066 (1974).
(9) J. von Braun and P. Wolff, *Chem. Ber.*, 55, 3675 (1922).
(10) For a discussion, see L. A. Paquette, "Principles of Modern Heterocyclic Chemistry", W. A. Benjamin, New York, 1968, pp 257–261.
(11) R. M. Acheson and B. Adcock, *J. Chem. Soc. C*, 1045 (1968).

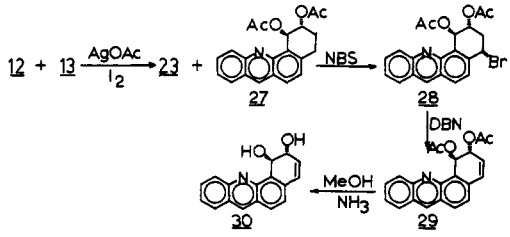
Scheme III



Scheme IV



Scheme V



PAH are successfully converted to *trans*-tetrahydro diesters via the Prévost reaction.[12] However, attempts to prepare *trans*-10,11-diacetoxy-8,9,10,11-tetrahydrobenz[c]acridine (**14**) in that manner were unsuccessful, as alkene **8** was evidently refractory to addition of iodoacetate. However, epoxidation of **8** with *m*-CPBA followed by ring opening with formic acid, hydrolysis, and acetylation with Ac_2O/pyridine (Scheme III) gave **14** in 55% overall yield.

Application of the same reaction sequence to the mixture of alkenes **8** and **9** yielded *trans*-8,9- and 10,11-diacetoxy-8,9,10,11-tetrahydrobenz[c]acridine (**14** and **15**) as a mixture that could be readily separated by dry-column chromatography on silica gel (Scheme III).

Attempted epoxidation of 1,2-dihydrobenz[c]acridine (**12**) with *m*-CPBA was unsuccessful due to formation of a complex mixture. However, the epoxide could be obtained by cyclization of the bromohydrin formed from **12** and *N*-bromoacetamide/aqueous THF (Scheme IV), and was directly converted to *trans*-3,4-diacetoxy-1,2,3,4-tetrahydrobenz[c]acridine (**23**) in the manner described for **14**. Alkene **12** could also be converted to **23** via the Prévost reaction in acceptable yield (38%).

Application of the Prévost reaction to the mixture of 1,2- and 3,4-dihydrobenz[c]acridine (Scheme V) gave **23** and *trans*-1,2-diacetoxy-1,2,3,4-tetrahydrobenz[c]acridine (**27**), which were easily separated by dry column chromatography on silica gel. The overall yield of **27** from **4** was 14%.

Preparation of Dihydrodiols from Tetrahydro Diacetates. Benzylic bromination with NBS in CCl_4, followed by dehydrobromination, afforded the best route to dihydrodiol diesters **19**, **25**, and **29**. In all cases the yields of bromo diesters were high. However, dehydrobromination yields were sensitive to reaction conditions. In our hands, the different dehydrobromination procedures cited in Schemes III–V appear to provide the best yields, with **19**, **25**, and **29** being obtained in 55%, 82%, and 84% yields, respectively, from the corresponding bromo diesters. For **16**, direct dehydrogenation of tetrahydro diester **15** with excess DDQ in refluxing dioxane afforded the best yield (45%).

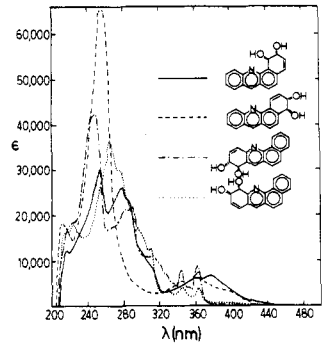


Figure 1. Ultraviolet spectra of non-K-region dihydrodiols of benz[c]acridine in EtOH. The K-region dihydrodiol *trans*-5,6-dihydroxy-5,6-dihydrobenz[c]acridine had the following spectrum in EtOH [λ_{max} (ϵ_{max})]: 223 (28 800, sh), 259 (30 100, sh), 263 (31 000), 296 (8800); 313 (8100), 328 (9800), 343 (10 500).

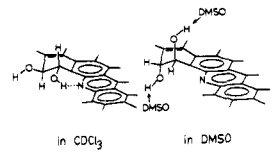


Figure 2. Predominant conformations of *trans*-1,2-dihydroxy-1,2-dihydrobenz[c]acridine in $CDCl_3$ and in Me_2SO-d_6.

In all cases, the dihydrodiol diesters could be hydrolyzed to the corresponding dihydrodiols with ammonia in methanol, with isolated yields ranging from 60 to 86%.

Spectral Properties of the Dihydrodiols and Dihydrodiol Diesters. The NMR spectra of the dihydro diol diesters and dihydrodiols are recorded in Table I. The NMR spectra of these compounds are very similar to those of the analogous benz[a]anthracene derivatives. In this case also, the larger coupling constant values for the carbinol protons of dihydrodiols **18**, **20**, and **26** compared with those of the corresponding dihydrodiol diester protons indicate that the vicinal hydroxyl groups in those compounds are predominantly quasi-diequatorial.[11] The low values of $J_{1,2}$ for the bay-region substituted diester **29** ($J_{1,2}$ = 1.8 Hz) and for the corresponding dihydrodiol **30** in Me_2SO ($J_{1,2}$ = 3.8 Hz) are consistent with a predominantly quasi-diaxial conformation for the hydroxyl and acetoxy groups. Interestingly, the conformation of the hydroxyl groups in **30** becomes predominantly quasi-diequatorial in $CDCl_3$, as judged by an increase of $J_{1,2}$ to 11.5 Hz. This is not the case with similar derivatives of polynuclear aromatic hydrocarbons, e.g., *trans*-9,10-dihydroxy-9,10-dihydrobenzo[e]pyrene, for which the corresponding coupling constants are very small both in Me_2SO-d_6 and in $CDCl_3$. Evidently, the benzylic hydroxyl group in **30** is extensively hydrogen bonded intramolecularly to the nitrogen atom when $CDCl_3$ is the solvent, whereas in Me_2SO the presence of stronger intermolecular hydrogen bonds to solvent results in the usual quasidiaxial conformation for the hydroxyl groups (Figure 1). The ultraviolet spectra, recorded in EtOH, also bear a marked resemblance to the corresponding spectra of the BA dihydro diols (Figure 2). As for BA, the dihydrodiols substituted in the

(12) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *J. Org. Chem.*, **42**, 736 (1977).

Table I. ^{1}H NMR Spectral Data of Diesters/Diols[a]

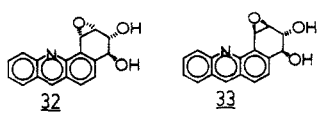
compd	ester/carbinol hydrogen		vinyl hydrogen		acetyl hydrogens	aromatic hydrogens
	benzylic	nonbenzylic	benzylic	nonbenzylic		
19	6.51 (H_{11})	5.95 (H_{10})	6.77 (H_8)	6.11 (H_9)	2.14, 2.33	7.63-7.93 (6 H), 9.15-9.23 (H_1)
	$J_{8,9}$ = 9.2, $J_{10,11}$ = 8.1, $J_{8,10}$ = 2.7, $J_{9,10}$ = 3.2					
16	6.36 (H_8)	5.70 (H_9)	7.10 (H_{11})	6.40 (H_{10})	2.06, 2.40	7.61-7.92 (5 H), 8.07 (H_7), 9.22-9.30 (H_1)
	$J_{8,9}$ = 6.1, $J_{10,11}$ = 10.1, $J_{9,10}$ = 4.0					
25	6.40 (H_4)	5.73 (H_3)	8.32 (H_1)	6.30 (H_2)	2.05, 2.14	7.48-8.28 (5 H), 8.74 (H_7)
	$J_{1,2}$ = 8.4, $J_{2,3}$ = 4.0, $J_{3,4}$ = 4.7					
29	H_1[c]	5.59 (H_2)	6.92 (H_4)	6.43 (H_3)	2.00, 2.00	7.32-8.30 (6 H, H_1)
	$J_{1,2}$ = 1.8, $J_{2,3}$ = 5.0, $J_{3,4}$ = 10					
20	4.97 (H_{11})	4.68 (H_{10})	6.73 (H_8)	6.16 (H_9)		7.62-8.17 (6 H), 9.27-9.47 (H_1)
	$J_{8,9}$ = $J_{10,11}$ = 10, $J_{8,10}$ = $J_{9,10}$ = 2.1					
18	4.88 (H_8)	4.46 (H_9)	6.80 (H_{11})	6.43 (H_{10})		7.66-8.14 (5 H), 8.38 (H_7), 9.06-9.28 (H_1)
	$J_{8,9}$ = $J_{10,11}$ = 10, $J_{8,10}$ = 1.5, $J_{9,10}$ = $J_{9,11}$ = 2					
26	4.86 (H_4)	4.46 (H_3)	H_1[c]	6.22 (H_2)		7.48-8.32 (6 H, H_1), 9.04 (H_7)
	$J_{1,2}$ = 10, $J_{1,3}$ = $J_{2,3}$ = 2.5, $J_{3,4}$ = 10.7					
30[b]	5.89 (H_1)	4.31 (H_2)	6.74 (H_4)	6.30 (H_3)		7.45-8.31 (6 H), 9.05 (H_7)
	$J_{1,2}$ = 3.8, $J_{2,3}$ = 4.7, $J_{3,4}$ = 9.5					

[a] J values are in hertz. For **19**, **16**, **25**, and **29** spectra were recorded in $CDCl_3$, with Me_4Si as an internal standard; for **20**, **18**, **26**, and **30** spectra were recorded in Me_2SO d_6 with Me_4Si as an internal standard; for **29**, **20**, **18**, **26**, and **30** spectra were recorded at 100 MHz; for **16**, **19**, and **25** spectra were recorded at 270 MHz. [b] ^{1}H NMR (100 MHz, $CDCl_3$-CD_3OD) δ 4.74 (dt, H_2), 5.62 (d, H_1), 6.12 (dd, H_3), 6.42 (dd, H_4), 7.14-8.10 (6 H), 8.66 (H_7); $J_{1,2}$ = 11.5, $J_{2,4}$ = 2.0, $J_{3,4}$ = 10 Hz. [c] The resonance of the indicated bay-region hydrogen occurs within the aromatic absorption envelope owing to edge deshielding by the proximate heterocyclic ring.

angular benzo ring exhibit long-wavelength absorptions absent in dihydrodiols substituted in the nonangular benzo ring.

K-Region Oxide and Dihydrodiol of Benz[*c*]acridine. Benz[*c*]acridine 5,6-oxide (**31**) was prepared in 42% yield from benz[*c*]acridine by using sodium hypochlorite and the method of Krishnan.[13] Hydrolysis of the oxide under acidic conditions in aqueous dioxane gave, after chromatography on silica gel, *trans*-5,6-dihydroxy-5,6-dihydrobenz[*c*]acridine (23%), which was rigorously purified by conversion to the diacetate, recrystallization, and hydrolysis back to the diol.

Diol Epoxides of *trans*-3,4-Dihydroxy-3,4-dihydrobenz[*c*]acridine. The bay-region diol epoxides analogous to the most mutagenic and tumorigenic diol epoxides of BA were prepared from the 3,4-dihydrodiol, **27**. In each case, the usual reaction conditions[14] gave good yields of the expected epoxides. Thus, reaction of **27** with *m*-CPBA in dry THF gave the *trans*-diol epoxide **32** in 72% yield.



32 **33**

The *cis*-diol epoxide **33** was obtained in 59% overall yield from **27** by conversion to the bromotriol (90% yield) with *N*-bromoacetamide in acidic, aqueous THF, followed by cyclization with KO-*t*-Bu in anhydrous THF (66% yield). Preliminary experiments indicate that **32** and **33** are mutagenic toward muant strains of *Salmonella typhimurium*.[15]

Experimental Section

Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3 spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian T-60, XL-100, and 270-MHz spectrometers. Unless noted otherwise, $CDCl_3$ was used as the solvent. Coupling constants (J) are recorded in hertz and chemical shifts in parts per million (δ) with Me_4Si, as an internal standard. Melting points are uncorrected. The designations α and β are used to indicate relative stereochemistry.

11-Acetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (6). A solution of 8,9,10,11-tetrahydrobenz[*c*]acridine (**3**, 11.5 g)[7] and *m*-chloroperoxybenzoic acid (20.6 g) in methylene chloride (150 mL) was stirred at room temperature for 20 h. More *m*-chloroperoxybenzoic acid (10.3 g) was added, and the mixture was refluxed for 24 h, cooled, and extracted twice with ice-cold 5% NaOH and water. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure to give a mixture of **5** (H_1, δ 9.20–9.38) and **3** (H_1, δ 8.82–9.02) in a 7:3 ratio on the basis of integration of the indicated NMR peaks.

To the above (11.5 g) was added acetic anhydride (12.2 mL), and the mixture was heated on a steam bath for 2 h, poured onto saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to dryness to give a reddish oil (13.3 g). The crude product was chromatographed over dry column grade silica gel (Woelm Pharma) with benzene as the developing solvent. Compound **3** (7.5 g) was eluted followed by **6** (4.44 g, 92% based on recovered **3**). It was recrystallized from EtOAc–hexane to give a colorless crystalline solid: mp 97.5–98.5 °C; ^{1}H NMR (100 MHz) δ 1.82–2.36

(13) S. Krishnan, D. G. Kuhn, and G. A. Hamilton, *J. Am. Chem. Soc.*, **99**, 8131 (1977).
(14) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *Tetrahedron Lett.*, 539 (1977).
(15) Experiments performed by A. W. Wood, Hoffmann-LaRoche, Inc.

(4 H, m), 2.20 (s, 3 H), 2.88–3.10 (m, 2 H), 6.30 (t, H_{11}), 7.48–7.94 (m, 5 H), 9.16–9.36 (m, H_1); $J_{10,11}$ = 2.7 Hz. Anal. Calcd for $C_{19}H_{17}NO$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.32; H, 5.88; N, 4.69.

Method II. A mixture of **3** (5.0 g) and mercuric acetate (13.6 g) in glacial acetic acid (100 mL) was refluxed for 20 h under N_2. Most of the acetic acid was removed under reduced pressure, and the residue was made alkaline with cold 10% NaOH. The product separated out and was extracted with CH_2Cl_2. The usual workup of the organic phase gave a grayish solid which was recrystallized from CH_2Cl_2 to yield grayish needles of 11-oxo-8,9,10,11-tetrahydrobenz[c]acridine (**7**): 4.1 g (77%); mp 225–228 °C; ^1H NMR (100 MHz) δ 2.26–2.48 (m, 2 H_9), 2.98 (t, 2 H_{10}), 3.28 (t, 2 H_8), 7.6–8.0 (m, 5 H), 8.11 (s, H_7), 9.36–9.58 (m, H_1); $J_{8,9}$ = 6 Hz, $J_{9,10}$ = 7 Hz.

The above ketone **7** (4.1 g) and $NaBH_4$ (2.0 g) in ethanol (150 mL) were heated under relux for 20 h. Most of the ethanol was removed, and the residue was treated with dilute AcOH and extracted with EtOAc to give 3.6 g (88%) of 11-hydroxy-8,9,10,11-tetrahydrobenz[c]acridine which upon treatment with acetic anhydride (100 mL) and pyridine (20 mL) for 15 h at ambient temperature gave **6**.

***trans*-10,11-Diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (14).** A well-stirred mixture of **6** (4.44 g) and polyphosphoric acid (50 g) was heated under N_2 at 100 °C for 2 h. The mixture was cooled and stirred with cold 40% NaOH to make it alkaline. An oily product separated and was extracted with ether (2 × 200 mL). The ether solution was washed with water, dried over Na_2SO_4 and distilled to give 8,9-dihydrobenz[c]acridine **8** (3.2 g, 91%) as a semisolid: ^1H NMR (100 MHz) δ 2.28–2.70 (m, 2 H), 3.4 (t, 2 H_8), 6.38–6.62 (m, H_{10}), 6.96 (d, H_{11}), 7.46–7.96 (m, 6 H), 9.20–9.38 (m, H_1); $J_{8,9}$ = 7.7 Hz, $J_{9,10}$ = 5.2 Hz, $J_{10,11}$ = 10 Hz. A solution of **8** (2.7 g) and *m*-chloroperoxybenzoic acid (2.19 g) in dry CH_2Cl_2 (40 mL) was stirred for 17 h. The mixture was extracted with cold 5% NaOH (2 × 20 mL) and water, dried over Na_2SO_4, and distilled under reduced pressure to give 10,11-epoxy-8,9,10,11-tetrahydrobenz[c]acridine (2.71 g). The epoxide thus obtained was dissolved in formic acid (88%, 40 mL) and stirred under N_2 at 60–65 °C for 3 h. Most of the formic acid was removed under reduced pressure, and the residue was made alkaline and extracted with EtOAc. The organic phase was washed with water, dried over Na_2SO_4, and concentrated to give a solid which was triturated with CH_2Cl_2 to give colorless crystalline solid of *trans*-10,11-dihydroxy-8,9,10,11-tetrahydrobenz[c]acridine, mp 157–158 °C; ^1H NMR (60 MHz, $CDCl_3$ + D_2O) δ 1.91–2.70 (m, 2 H_9), 2.91–3.31 (m, 2 H_8), 3.75–4.35 (m, H_{10}), 4.73 (d, H_{11}); $J_{10,11}$ = 9.2 Hz. This diol (1.89 g) was dissolved in a warm solution of acetic anhydride (40 mL) and pyridine (12 mL), and the resulting clear solution was stirred under N_2 for 24 h at ambient temperature. The mixture was poured slowly into a cold solution of saturated Na_2CO_3 (200 mL), and the mixture was extracted with ether to give tetrahydro diol diacetate **14** which was recrystallized from benzene–hexane as a colorless crystalline solid: 2.35 g (92%); mp 134–135 °C; ^1H NMR (100 MHz) δ 1.88–2.54 (m, 2 H_9), 2.08 (s, 3 H), 2.16 (s, 3 H), 3.09 (t, 2 H_8), 5.30–5.54 (m, H_{10}), 6.34 (d, H_{11}), 7.50–7.94 (m, 6 H), 9.06–9.24 (m, H_1); $J_{8,9}$ = 6.5 Hz, $J_{10,11}$ = 7 Hz. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.46; H, 5.56; N, 3.80.

8-Bromo-10α,11β-diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (17). A mixture of **14** (310 mg), *N*-bromosuccinimide (180 mg), α,α'-azobis(isobutyrodinitrile) (AIBN, 5 mg), and CCl_4 (55 mL) was heated for 30 min at ca. 70–75 °C under a stream of N_2. The mixture was cooled and filtered. The filtrate was distilled under reduced pressure to leave a yellow oily residue that crystallized as a yellow solid upon addition of ether to give **17** as a ca. 1:1 stereoisomeric mixture: 295 mg (77%); mp 133–136 °C; ^1H NMR (60 MHz) δ 2.13 (s, 3 H), 2.26 (s, 1.5 H), 2.33 (s, 1.5 H), 2.46–3.26 (m, 2 H_9), 5.20–6.07 (m, H_8, H_{10}), 6.43 (m, H_{11}), 7.20–8.33 (m, 6 H), 8.93–9.33 (m, H_1).

***trans*-10,11-Diacetoxy-10,11-dihydrobenz[*c*]acridine (19).** To a stirred mixture of boiling xylene (30 mL) and anhydrous $NaHCO_3$ (3.0 g) was added bromo diacetate **17** (520 mg). The mixture was heated under Ar for 30 min with continuous removal of water. The mixture was cooled and filtered, and the xylene was removed under reduced pressure to leave a semisolid which was recrystallized from ether to give **19** (190 mg, 55%) as a colorless solid: mp 154–155 °C; ^1H NMR (see Table I); mass spectrum (molecular ion), calcd for $C_{21}H_{17}NO_4$ *m/e* 347.1157, found 347.1142.

***trans*-10,11-Dihydroxy-10,11-dihydrobenz[*c*]acridine (20).** A solution of dihydro diol diacetate **19** (46 mg) in dry THF (2.0 mL) was diluted with anhydrous MeOH (40 mL) and anhydrous NH_3 was bubbled through the solution for 15 min. The reaction vessel was capped with a balloon, and the reaction mixture was stirred at room temperature for 30 min. The methanol was removed under reduced pressure, and the residue was dissolved in EtOAc and water. The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated to give dihydro diol **20** as a light gray solid: 30 mg (86%); mp 135–137 °C; ^1H NMR (see Table I).

***trans*-8,9-Diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (15).** A mixture of **6** (4.5 g) and polyphosphoric acid (50 g) was stirred under N_2 at 160–170 °C for 3 h, and the mixture was worked up as described for **8** to give a mixture (2.4 g) of alkenes **8** and **9** in a 3:1 ratio as estimated by NMR. This mixture of alkenes was subjected to the subsequent reactions described in the preparation of **14** to give the mixture of tetrahydro diol diacetates **14** and **15** as a dark oil (2.2 g). The mixture was chromatographed on dry column grade silica gel with EtOAc/hexane (20:80) as the developing solvent. Compound **15** (420 mg, 8% based on **6**) eluted first followed by **14** (470 mg, 9%). Compound **15** was recrystallized from CH_2Cl_2–petroleum ether to give colorless needles: mp 158–160 °C; ^1H NMR (100 MHz) δ 2.06 (s, 3 H), 2.16 (s, 3 H), 2.26–2.54 (m, 2 H_{10}), 3.38 (t, 2 H_{11}), 5.26–5.44 (m, H_9), 6.30 (d, H_8), 7.58–8.00 (m, 5 H), 8.1 (s, H_7), 9.22–9.40 (m, H_1); $J_{8,9}$ = 5.4 Hz, $J_{10,11}$ = 7 Hz. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.10; H, 5.19; N, 3.82.

***trans*-8,9-Diacetoxy-8,9-dihydrobenz[*c*]acridine (16).** A mixture of **15** (150 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (260 mg) in freshly distilled peroxide-free dioxane (20 mL) was refluxed under Ar for 7 h. The mixture was cooled, diluted with ether (100 mL), and extracted with ice-cooled 1% NaOH (2 × 50 mL) followed by water. The usual workup gave **16** as colorless flakes after recrystallization from ether: 68.3 mg (45%); mp 175.5–177 °C; ^1H NMR (see Table I). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.35; H, 4.84; N, 3.85.

***trans*-8,9-Dihydroxy-8,9-dihydrobenz[*c*]acridine (18).** Dihydrodiol diacetate **16** (50 mg) was treated with ammonia in dry THF (2 mL) and anhydrous methanol (40 mL) as described for **20** except that a reaction time of 2 h was employed. The crude product was triturated with 30% EtOAc–hexane to give colorless solid: 22 mg (55%); mp 177–179 °C; ^1H NMR (see Table I).

1,2,3,4-Tetrahydrobenz[*c*]acridine (4). Sodium (115 g) was added in portions to a refluxing and well-stirred solution of benz[c]acridine (50 g)[9] in amyl alcohol (1700 mL). Each portion of sodium was allowed to react completely before addition of the next one. After being refluxed for an additional 1 h, the mixture was cooled and treated with water (500 mL), and the amyl alcohol was steam distilled. The residue was extracted with $CHCl_3$. The $CHCl_3$ solution was worked up as usual to give 1,2,3,4,7,12-hexahydrobenz[c]acridine as a yellow solid: 50.2 g; ^1H NMR (60 MHz) δ 1.5–2.1 (m, 4 H), 2.3–3.0 (m, 4H), 4.0 (s, 2 H_7), 5.82 (br s, 2 H_{12}), 6.46–7.2 (m, 6 H). This solid was refluxed in 10 N HCl (600 mL) with ferric chloride (250 g) for 2 h. The mixture was cooled in an ice-bath and neutralized with ammmonium hydroxide. The heterogeneous mixture was well extracted with $CHCl_3$ three times. The combined organic phase was washed with water, dried (Na_2SO_4), and concentrated to give a dark oily product which was chromatographed over silica gel with benzene as the developing solvent to give 43.5 g (86% based on benz[c]acridine) of **4**: mp 77–78.5 °C (lit.[8]) mp 79–80 °C; ^1H NMR (100 MHz) δ 1.68–2.18 (m, 4 H), 2.94 (m, 2 H_4), 3.48 (m, 2 H_1), 7.12–8.32 (m, 6 H), 8.55 (s, H_7).

4-Hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine (10). A mixture of **4** (3.0 g), mercuric acetate (8.2 g), and glacial AcOH (75 mL) was refluxed for 20–24 h under N_2. Most of the AcOH was removed under reduced pressure, and the residue was made basic with 10% Na_2CO_3 and extracted with EtOAc. The usual workup gave a reddish oil which was dissolved in MeOH (75 mL) and 20% NaOH (5 mL) and refluxed for 10 min on a steam bath. Most of the methanol was removed, and the residue was dissolved

in an EtOAc–water mixture. The ethyl acetate layer was separated, washed with water, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to give a yellow solid. It was chromatographed over dry column grade silica gel with CH_2Cl_2 as the developing solvent to give recovered **4** (550 mg). Further elution with 40% EtOAc–hexane gave 4-oxo-1,2,3,4-tetrahydrobenz[*c*]acridine (**11**) [250 mg (10%); ^1H NMR (100 MHz) δ 2.28–2.60 (m, 2 H_2), 2.85 (t, 2 H_3), 3.82 (t, 2 H_1), 7.34–8.40 (m, 6 H), 8.70 (s, H_7); $J_{2,3}$ = 7 Hz, $J_{1,2}$ = 6.5 Hz] and then **10**, 1.8 g (70% based on recovered **4**). Recrystallization of **10** from acetone gave a colorless crystalline solid: mp 166–168 °C; ^1H NMR (100 MHz) δ 1.82–2.40 (m, 4 H), 3.52 (m, 2 H), 4.96 (m, H_4), 7.42–8.34 (m, 6 H), 8.66 (s, H_7). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.92; H, 6.02; N, 5.62. Found: C, 81.83; H, 5.89; N, 5.31. A small sample of **10** was converted by Ac_2O and pyridine into 4-acetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine which upon recrystallization from acetone–water yielded a colorless crystalline solid: mp 120–120.5 °C; ^1H NMR (100 MHz) δ 2.16 (s, 3 H), 2.00–2.32 (m, 4 H), 3.16–3.98 (m, 2 H_1), 6.14–6.30 (m, H_4), 7.34–8.38 (m, 6 H), 8.68 (s, H_7). Anal. Calcd for $C_{19}H_{17}NO$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.26; H, 5.86; N, 4.89.

***trans*-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine (21).** To a stirred mixture of polyphosphoric acid (7.0 g) and xylene (20 mL) at 95–100 °C under N_2 was added **10** (1.65 g). The biphasic mixture was stirred for 1 h and cooled, and the xylene was decanted. The PPA phase which was red, was decomposed with water and made alkaline by addition of ice-cold 20% NaOH.

The mixture was extracted with ether, washed with water, and worked up as usual to give 1,2-dihydrobenz[*c*]acridine (**12**) as an oil: ^1H NMR (100 MHz) δ 2.38–2.76 (m, 2 H_2), 3.68 (t, 2 H_1), 6.18–6.42 (m, H_3), 6.62 (dt, H_4), 7.14–8.32 (m, 6 H), 8.62 (s, H_7); $J_{1,2}$ = 9 Hz, $J_{2,4}$ = 2 Hz, $J_{3,4}$ = 10 Hz. This was contaminated with 15–20% of 3,4-dihydrobenz[*c*]acridine (**13**): ^1H NMR (100 MHz) δ 3.04 (t, 2 H_4); $J_{3,4}$ = 8 Hz. The crude alkene **12** (1.46 g) was dissolved in THF (80 mL) and water (20 mL) and cooled to 0–5 °C. To this stirred solution under Ar was added recrystallized *N*-bromoacetamide and 2 drops of concentrated HCl. The mixture was stirred at 0–5 °C under N_2 for 3 h, diluted with EtOAc (100 mL) and extracted with water (2 × 40 mL). After being dried over Na_2SO_4, the organic solution was concentrated under reduced pressure to give a semisolid which was recrystallized twice from EtOAc to yield bromohydrin **21** (0.98 g 47%) as light yellow needles: mp 165–167 °C; ^1H NMR (100 MHz) δ 2.24–2.92 (m, 2 H_2), 3.68 (t, 2 H_1), 4.62 (m, H_2), 5.06 (m, H_4), 5.38 (d, OH), 7.46–8.38 (m, 6 H), 8.74 (s, H_7); $J_{3,4}$ = 7 Hz, J_{4OH} = 6.4 Hz $J_{1,2}$ = 6.2 Hz. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.19; H, 4.26; N, 4.26. Found: C, 61.98; H, 3.95; N, 4.06. The mother liquor was found to be enriched with the isomeric *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine: ^1H NMR (100 MHz) δ 2.18–2.80 (m, 2 H_3), 3.15 (t, 2 H_4), 4.67 (m, H_2), 5.90 (d, H_1), 7.20–8.40 (m, 6 H), 8.74 (s, H_7); $J_{1,2}$ = 6.5 Hz, $J_{3,4}$ = 7 Hz.

***trans*-3,4-Dihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine (22).** To a stirred mixture of bromohydrin **21** (1.4 g) in acetone (140 mL) was added 10% NaOH (20 mL) dropwise at room temperature under N_2. This solution was stirred vigorously for 5 h, most of the acetone was removed, and ether and water were added. The usual workup gave the epoxide as a yellow crystalline solid which was dissolved in 88% HCOOH (50 mL) and stirred under N_2 at 70 °C for 90 min. The formic acid was removed under reduced pressure, and the residue was made alkaline with 10% NaOH, extracted with EtOAc, dried (Na_2SO_4), and concentrated to dryness. The resulting semisolid was stirred in MeOH (100 mL) and 10% NaOH (10 mL) at room temperature for 15 min. Most of the methanol was removed under reduced pressure without heating, and the residue was diluted with EtOAc–H_2O. The usual workup yielded a solid residue which was triturated with CH_2Cl_2 to give **22** as pale yellow needles: 820 mg (71% based on bromohydrin **21**): mp 203–205; ^1H NMR (100 MHz, Me_2SO-d_6 δ 1.72–2.34 (m, 2 H_2), 3.44 (t, 2 H_1), 3.72–3.96 (m, H_3), 4.50 (m, H_4), 4.88 (d, OH), 5.50 (d, OH), 7.46–8.24 (m, 6 H), 8.96 (s, H_7); $J_{1,2}$ = 6.5 Hz, $J_{3,4}$ = 6 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (23).** In the manner described for **14**, diol **22** (800 mg) was treated with Ac_2O (20 mL) and dry pyridine (4.5 mL) to yield tetrahydrodiol diacetate **23** as a colorless crystalline solid: 950 mg (90%); mp 125–126 °C (after recrystallization from EtOAc/hexane); ^1H NMR (100 MHz) δ 2.05 (s, 3 H), 2.16 (s, 3 H), 2.24–2.44 (m, 2 H_2), 3.65 (t, 2 H_1), 5.28–5.50 (m, H_3), 6.28 (d, H_4), 7.46–8.36 (m, 6 H), 8.64 (s, H_7); $J_{1,2}$ = 6.5 Hz, $J_{3,4}$ = 5.5 Hz. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.02; H, 5.47; N, 3.85.

1-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (24). The reaction of tetrahydro diacetate **23** (700 mg), NBS (466 mg), and AIBN (10 mg) in CCl_4 (120 mL) was effected as described for **17**. The aerosol so obtained was treated with ether to give yellowish orange crystalline solid **24**: 840 mg (98%); 125–129 °C; ^1H NMR (100 MHz) δ 2.12 (s, 3 H), 2.24 (s, 3 H), 2.34–3.10 (m, 2 H_2), 5.96–6.34 (m, H_3), 6.53 (d, H_4), 6.88 (m, H_1), 7.18–8.52 (m, 6 H), 8.69 (s, H_7); $J_{3,4}$ = 9 Hz.

***trans*-3,4-Diacetoxy-3,4-dihydrobenz[*c*]acridine (25).** A mixture of **24** (820 mg), anhydrous Li_2CO_3 (2.46 g), and anhydrous LiF (1.64 g) in freshly distilled HMPA (40 mL) was stirred under N_2 at 90–95 °C for 6 h. The mixture was cooled, diluted with water (100 mL), and extracted with ether–benzene. The organic layer was washed with water three times and worked up as usual to leave an oily residue which solidified on treatment with aqueous acetone. Recrystallization from acetone–petroleum ether (bp 30–60 °C) gave **25** as light yellow needles: 550 mg (82%); mp 167.5–168.5 °C; ^1H NMR (see Table I). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.78; H, 4.88; N, 4.03.

***trans*-3,4-Dihydroxy-3,4-dihydrobenz[*c*]acridine (26).** The hydrolysis of dihydrodiol diacetate **25** (100 mg) with methanolic ammonia was effected as described for the preparation of **20** except that the reaction time was 2 h. The product thus obtained was triturated with ether–hexane (1:1) to give **26** as a yellow solid: 64 mg (85%); mp 182–184 °C; ^1H NMR (see Table I).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (27).** A mixture of **4** (2.1 g), NBS (1.7 g), and AIBN (2.5 mg) in dry CCl_4 (150 mL) was refluxed under N_2 for 3 h. The mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure. The resulting reddish semisolid (2.8 g) was stirred under N_2 with Li_2CO_3 (6.0 g) and LiF (4.0 g) in freshly distilled HMPA (30 mL) at 100 °C for 3 h. The mixture was cooled, diluted with water (75 mL), and extracted twice with ether. The usual workup gave a reddish yellow oil (1.95 g, 96% based on **4**) which was a ca. 1:1 mixture of **12** and **13** as judged by NMR.

To a stirred suspension of silver acetate (3.0 g) in dry benzene (20 mL) under N_2 was added iodine (2.75 g), and the mixture was stirred at room temperature until the color of iodine disappeared. The above mixture of **12** and **13** was added, and the suspension was stirred at room temperature for 6 h and then refluxed for 17 h. The hot mixture was filtered, and the residue was washed with dry benzene. The filtrate was distilled under reduced pressure to leave a crude oily product which was chromatographed over dry column grade silica gel with 18% EtOAc–hexane as the developing solvent to give first a mixture of benz[*c*]acridine and 1,2,3,4-tetrahydrobenz[*c*]acridine (0.93 g). Further elution gave **23** (0.23 g, 8%) followed by **27** [0.37 g (12.5%); mp 167–170 °C] which was recrystallized from EtOAc–hexane as light yellow crystals: mp 178–181 °C; ^1H NMR (100 MHz) δ 2.02 (s, 6 H), 2.12–2.36 (m, 2 H_3), 2.94–3.15 (m, 2 H_4), 5.46 (m, H_2), 7.04 (d, H_1), 7.20–8.24 (m, 6 H), 8.68 (s, H_7); $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 8.6 Hz. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 71.90; H, 5.57; N, 3.77.

4-Bromo-1β,2α-diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (28). The reaction of **27** (223 mg), NBS (124 mg), and AIBN (5 mg) in CCl_4 (75 mL) was effected as described for **17**. Addition of ether to the oily crude product yielded **28** as a yellow crystalline solid: 190 mg (70%); mp 147–152 °C; ^1H NMR (100 MHz) δ 2.00 (s, 3 H), 2.05 (s, 3 H), 2.74–3.12 (m, 2 H_3), 5.52 (m, H_2), 5.66 (dd, H_4), 7.34 (d, H_1), 7.46–8.40 (m, 6 H), 8.82 (s, H_7); $J_{1,2}$ = 3 Hz.

***trans*-1,2-Diacetoxy-1,2-dihydrobenz[*c*]acridine (29).** To an ice-cooled solution of bromo diacetate **28** (190 mg) in freshly distilled dry THF (20 mL) under Ar was added DBN (1.6 mL). The reaction mixture was kept at 0 °C for 24 h. EtOAc (50 mL) was added to the reaction mixture, and the EtOAc solution was washed with 0.1% HCl (2 × 40 mL), water (20 mL), 5% $NaHCO_3$ (20 mL), and water (20 mL) successively. The ethyl acetate phase was dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue which was recrystallized from ether–petroleum ether to give **29** as a yellow crystalline solid: 130 mg (84%); mp

197–198.5 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.28; H, 5.01; N, 3.83.

***trans*-1,2-Dihydroxy-1,2-dihydrobenz[*c*]acridine (30).** Hydrolysis of dihydrodiol diacetate **29** (140 mg) in dry THF (6 mL) and anhydrous MeOH (250 mL) with ammonia gas was effected as described for the preparation of **20**, except that the reaction time was 20 h. Workup as described previously gave brownish crystalline solid **30**: 70 mg (64%); mp 160–162 °C; ^{1}H NMR (see Table I).

Benz[*c*]acridine 5,6-Oxide (31). Benz[*c*]acridine (100 mg) was dissolved in 15 mL $CHCl_3$ and added to a solution of 12 mL of Chlorox buffered to pH 8.5 with 0.8 M sodium phosphate containing tetrabutylammonium hydrogen phosphate (74 mg). The biphasic solution was stirred in a glass-stoppered flask at room temperature for 5 h. The mixture was diluted with 60 mL of ether. The usual workup gave a colorless crystalline solid from which **31** was obtained after two recrystallizations from ether as colorless needles: mp 153–154 °C; yield 45 mg (42%); NMR (60 MHz, $CDCl_3$) δ 4.47, 4.60 ($H_{5,6}$, $J_{5,6}$ = 4.2 Hz), 7.26–8.33 (m, 8 H), 8.25 (s, H_7), 8.80–9.13 (m, H_1).

***trans*-5,6-Dihydroxy-5,6-dihydrobenz[*c*]acridine.** A solution of the above epoxide (300 mg) was dissolved in 50 mL dioxane and 10 mL 25% aqueous AcOH. The solution was stirred at 35 °C under N_2 for 48 h. Most of the dioxane was removed, and the residue was stirred with 10% ice-cold NaOH (20 mL) and extracted with EtOAc. The EtOAc layer was washed with water, dried over Na_2SO_4, and distilled to give a residue. It was chromatographed over silica gel, and the most polar major product was eluted with EtOAc to give 75 mg of the colorless solid. It was treated with Ac_2O (10 mL) and pyridine (2 mL) at room temperature for 20 h to give the diacetate, which was recrystallized twice from ethyl acetate–hexane to yield 71 mg of pale yellow needles: mp 157–158 °C; ^{1}H NMR (100 MHz) δ 1.95 (s, 3 H), 1.98 (s, 3 H), 6.16, 6.26 ($H_{5,6}$, J = 4.7 Hz), 7.36–8.32 (m, 8 H), 8.56–8.80 (m, H_1). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.76; H, 4.83; N, 3.88.

The hydrolysis of this diacetate was effected in 50 mL of methanol saturated with NH_3 gas at room temperature for 6 h. Most of the methanol was removed, and the residue was diluted with water. The colorless solid so separated was centrifuged and triturated with 3% EtOAc–hexane to give 42 mg of *trans*-diol: mp 182–184 °C; ^{1}H NMR (100 MHz, CD_3COCD_3 + CD_3OD) δ 4.86 (br s, 2 H), 7.40–8.22 (m, 7 H), 8.40–8.64 (m, 2 H).

(±)-3α,4β-Dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (32). A mixture of 3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (50 mg) and *m*-CPBA (250 mg) in anhydrous THF (25 mL) was stirred at room temperature under N_2 for 1 h. The mixture was diluted with ether, extracted with ice-cold 2% NaOH and water, dried (Na_2SO_4), and concentrated to give diol epoxide **32** (38 mg, 72%) as a pale yellow solid: mp 198–200 °C dec; ^{1}H NMR (100 MHz, Me_2SO-d_6) 3.72–4.0 (m, H_2, H_3), 4.40–4.68 (m, H_4), 5.56 (d, H_1), 5.64 (d, OH_3), 5.86 (d, OH_4), 7.5–8.4 (m, 6 H), 9.15 (s, H_7); $J_{1,2}$ = 4.0 Hz, $J_{3,4}$ = 8.4 Hz, $J_{4,OH}$ = 6.5 Hz, $J_{3,OH}$ = 6.6 Hz.

(±)-3α,4β-Dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (33). To a stirred solution of dihydrodiol **27** (26 mg) in THF (8 mL) at 0 °C under argon was added H_2O (2 mL), *N*-bromoacetamide (16 mg), and 1 drop of concentrated HCl. The solution was stirred for 1 h at 0–5 °C. EtOAc was added, and the reaction was worked up in the usual manner to give a solid, which was triturated with ether to give the bromo triol (±)-2α-bromo-1β,3α,4β-trihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine as a colorless, crystalline solid: 32 mg (90%); mp 142–144 °C dec; NMR (Me_2SO-d_6, CD_3OD) δ 4.26 (dd, H_3), 4.6–4.8 (m, H_2, H_4), 6.08 (d, H_1), 7.42–8.78 (m, 6 H), 9.04 (s, H_7); $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 2.2 Hz, $J_{3,4}$ = 7.0 Hz.

To a stirred solution of the bromotriol (45 mg) in anhydrous THF (20 mL) was added KO-*t*-Bu (75 mg), and the mixture was stirred under Ar for 14 min at room temperature. EtOAc was added, and the organic phase was extracted twice with cold water. The usual workup gave a solid which was triturated with petroleum ether to give diol epoxide **33**: 23 mg (66%); mp 190–191 °C dec; NMR (Me_2SO-d_6, CD_3OD) 3.89 (m, H_2), 4.16 (m, H_3), 4.67 (d, H_4), 5.33 (d, H_1), 7.52–8.32 (m, 6 H), 8.12 (s, H_7); $J_{3,4} \approx 2.5$ Hz, $J_{1,2}$ = 4.0 Hz.

Acknowledgment. This investigation was supported, in part, by Grant No. CA 22985, awarded to R.E.L. by the National Cancer Institute, DHEW. We thank Patrick Cohenour, Thomas Douchinsky, and Raymond Daffner for assistance with portions of the syntheses.

Registry No. 1, 225-51-4; 3, 19730-91-7; 4, 54538-09-9; 5, 78167-75-6; (±)-6, 78167-76-7; 7, 78167-77-8; 8, 78186-15-9; 9, 78167-78-9; (±)-10, 78167-79-0; 11, 78167-80-3; 12, 77305-66-9; 13, 78167-81-4; (±)-14, 78167-82-5; (±)-15, 78167-83-6; (±)-16, 78167-84-7; (±)-17 (isomer 1), 78167-85-8; (±)-17 (isomer 2), 78215-27-7; (±)-18, 78167-86-9; (±)-19, 78167-87-0; (±)-20, 78167-88-1; (±)-21, 78167-89-2; (±)-22, 78167-90-5; (±)-23, 78167-91-6; 24, 78215-28-8; (±)-25, 78167-92-7; (±)-26, 78167-93-8; (±)-27, 78167-94-9; 28, 78167-95-0; (±)-29, 78167-96-1; (±)-30, 78167-97-2; (±)-31, 78167-98-3; (±)-32, 78167-99-4; (±)-33, 78215-29-9; (±)-11-hydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-00-0; (±)-10,11-epoxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-01-1; (±)-*trans*-10,11-dihydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-02-2; 1,2,3,4,7,12-hexahydrobenz[*c*]acridine, 78168-03-3; (±)-4-acetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-04-4; (±)-*trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-05-5; (±)-*trans*-5,6-dihydroxy-5,6-dihydrobenz[*c*]acridine, 78186-09-1; (±)-*trans*-5,6-diacetoxy-5,6-dihydrobenz[*c*]acridine, 78168-06-6; (±)-2α-bromo-1β,3α,4β-trihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-07-7.

Guanine Analogues. Allyl-Substituted Aminoimidazo[1,5-*a*]-1,3,5-triazinones Formed by Cyclization–Rearrangement

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Received April 30, 1981

Syntheses of allylimidazo[1,5-*a*]-1,3,5-triazinones, which are analogues of N(9)-substituted guanines, have been accomplished by cyclization–rearrangement. Condensation of ethyl 2-cyano-2-formamido-4-pentenoate and ethyl 2-acetamido-2-cyano-4-pentenoate with guanidine yielded substituted 5-allyl-4,5-dihydropyrimidin-4-ones. Treatment of these 5-allyl-4,5-dihydropyrimidin-4-ones with chlorotrimethylsilane and hexamethyldisilazane in pyridine gave the correspondingly substituted allylimidazo[1,5-*a*]-1,3,5-triazinones by a rearrangement that appears to proceed through 5-allylguanines as transient intermediates. Structures were established in this series on the basis of precursors and routes of synthesis, IR spectra, ^{1}H and ^{13}C NMR spectra, mass spectra, and a final catalytic hydrogenation.

Recently, we reported that treatment of 4,5-dihydropyrimidin-4-ones **1a–e** in pyridine with chlorotrimethylsilane and hexamethyldisilazane[1] leads effectively to the correspondingly substituted imidazo[1,5-*a*]-1,3,5-triazin-

0022-3263/81/1946-3681$01.25/0