Synthesis of Potential Metabolites of Dibenz[a,j]acridine: Dihydro Diols and Phenols

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Received May 30, 1986

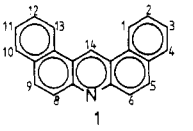
The potential trans dihydro diol metabolites of the carcinogen dibenz[a,j]acridine (1) were prepared. The dihydro diols *trans*-1,2-dihydro-1,2-dihydroxydibenz[a,j]acridine (12) and *trans*-3,4-dihydro-3,4-dihydroxydibenz[a,j]acridine (13) were prepared by Prevost reaction on appropriate reduced intermediates to form the diacetoxy tetrahydro derivatives followed by the introduction of the 3,4- or 1,2-unsaturation and hydrolysis. The trans 5,6-isomer (28) was made via the *cis*-5,6-dihydro-5,6-dihydroxydibenz[a,j]acridine (30) by oxidation to the 5,6-quinone (32) and subsequent reduction. Three phenols, 3-hydroxy- (37), 4-hydroxy- (36), and 6-hydroxydibenz[a,j]acridine (27), were also made. An improved synthesis of 12 and 13 through the sodium/liquid NH_3/EtOH reduction products of 1, 1,4,10,13-tetrahydrodibenz[a,j]acridine (16) and 1,4,8,9-tetrahydrodibenz[a,j]acridine (17), was developed. Other 1 reduction products characterized were reduced at the 5,6-, 5,6,8,9-, 1,2,3,4,10,13-, 1,4,7,7a,8,9,13b,14-, and 5,6,6a,7,14,14a-positions.

Introduction

Dibenz[a,j]acridine (1) is a polycyclic azaaromatic hydrocarbon found in tobacco smoke condensate[1] and urban atmosphere[2] and possesses carcinogenic properties.[3] It is expected, by analogy with other polycyclic hydrocarbons,[4] that the biological activation of 1 proceeds through dihydro diols and diol epoxides, and metabolism in vitro with liver microsomes from 3-methylcholanthrene pretreated animals has demonstrated the presence of these pathways.[5a] The bay-region theory[4] of chemical carcinogenesis predicts that for carcinogenic polycyclic aromatic hydrocarbons (PAH), or their heterocyclic analogues such as 1, the biologically most important dihydro diol is the 3,4-isomer (for 1, or the equivalent angular ring derivative of a PAH). This can be metabolized to a vicinal diol epoxide with the oxirane ring at the 1,2-position in 1, the bay region, and such diol epoxides are highly reactive species. They react readily with cellular constituents, alkylate macromolecules, and may produce genetic damage. Much support for this theory has come from experimental studies with PAH dihydro diols. This paper reports studies on the synthesis of the three isomeric dihydro diols of 1 as well as three phenols and other candidate metabolites. These were required to prove metabolite structures and for mutagenicity and carcinogenicity tests.

Results and Discussion

Many methods of synthesis of dihydro diol derivatives of polycyclic azaaromatic compounds involve dihydro derivatives as intermediates.[6-10] These may be prepared by halogenation/dehydrohalogenation[8,9] or hydroxylation/dehydration,[6a,8,9] reactions of tetrahydro intermediates which, in turn, may be formed by reduction of the parent azaaromatic hydrocarbon.[8] An appropriate starting point for synthesis of the dihydro diols of 1 was 1,2,3,4-tetrahydrodibenz[a,j]acridine (2). The fusion of 6-aminotetralin and the Mannich base, 1-[(dimethylamino)methyl]-2-naphthol gave a mixture of 2 together with 9,10,11,12-tetrahydrodibenz[a,i]acridine (3) from which 2 could be



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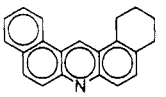

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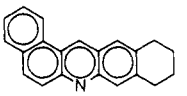

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isolated in poor yield (16%) by fractional recrystallization. Both 2 and 3 could be dehydrogenated with palladium on carbon and afforded 1 and dibenz[a,i]acridine,[11] respectively. Bromination of 2 with 0.55 molar equiv of 1,3-dibromo-5,5-dimethylhydantoin (dibromantin) afforded 1-bromo- and 4-bromo-1,2,3,4-tetrahydrodibenz[a,j]acridine (not isolated) and was followed by hydrolysis of the crude reaction mixture in aqueous acidic THF. Two alcohols were isolated, each in about 15% yield, and structures were assigned on the basis of the chemical shift of the methine protons of 5.58 and 4.80 ppm of 1-hydroxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (4) and 4-hydroxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (5), respectively. Dehydration of 4 and 5 with *p*-toluenesulfonyl chloride and pyridine gave 3,4-dihydrodibenz[a,j]acridine (6) and 1,2-dihydrodibenz[a,j]acridine (7), respectively, in excellent yield. In the ^1H NMR spectrum of 6 the doublet expected for H_1 was sufficiently deshielded to occur in the aromatic region (δ 7.55–8.19), while the signal from H_4 of the 1,2-dihydro compound, 7, appeared clear of the aromatic signals at 6.58. Prevost reaction of the dihydro compounds, 6 and 7, with silver benzoate and iodine was followed immediately by hydrolysis and acetylation to give *trans*-1,2-diacetoxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (8) and *trans*-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (9) in good overall yield from the dihydro compounds.

The dihydro diols 12 and 13 were prepared by ammonolysis of the dihydro diacetates 10 and 11, which were

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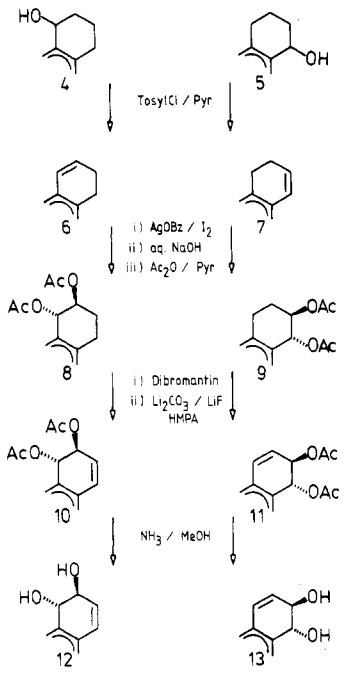
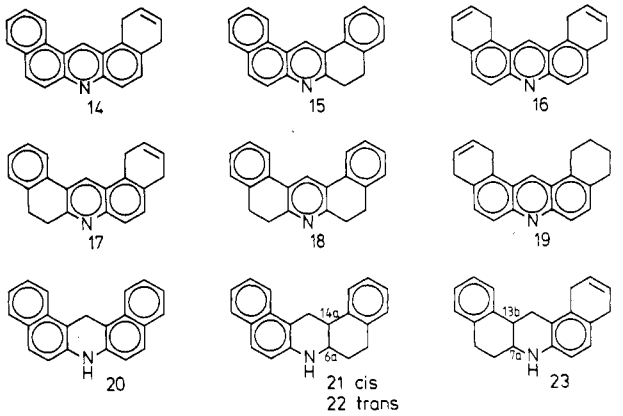


prepared by treatment of the trans tetrahydro diacetates **8** and **9** with dibromantin followed by dehydrobromination. The ^{1}H NMR spectra of the dihydro diols and their diacetates were analogous to those of the benz[*a*]anthracene,[12] dibenz[*a*,*h*]acridine,[6b] dibenz[*c*,*h*]acridine,[9b] and 7-methylbenz[*c*]acridine[9a] derivatives. The large coupling constant of the methine protons of the dihydro diol **13** compared with that of its diacetate **11** indicated that the vicinal hydroxyl groups in **13** are quasidiequatorial while the acetoxy groups of **11** are conformationally mobile.[18] The low values of $J_{1,2}$ (ca. 1.3 Hz) in the bay-region dihydro diol **12** and diacetate **10**[6b] are analogous with observations with benz[*c*]acridine[8] and other dibenzacridines[6b,9b] and indicated quasidiaxial conformations for the hydroxyl and acetoxyl groups in these compounds.

The routine preparation of tetrahydro diacetates in low yield was achievable by Prevost reaction with a mixture of the 3,4- and 1,2-dihydro compounds (**6** and **7**) prepared by bromination and dehydrobromination (DBU) of **2**. Routinely, no more than about 35–40% of a 1:1 mixture of 3,4- and 1,2-dihydro compounds together with both unchanged **2** and dibenz[*a*,*j*]acridine were obtained. Investigations of bromination with NBS or *N*-bromocaprolactam, more than 0.55 molar equiv of dibromantin and dehydrobromination with Li_2CO_3/LiF/HMPA failed to give better yields of alkenes or more selectivity. Quantitation in reaction mixtures was done by integration of the H_{14} signals which occurred at 9.72, 9.48, 9.38, and 10.23 for **6**, **7**, **2**, and **1**, respectively. Furthermore, in contrast to results obtained with 1,2,3,4-tetrahydrobenz[*c*]acridine[8] and 10,11,12,13-tetrahydrodibenz[*a*,*h*]acridine,[6b] reaction of **2** with mercuric acetate in glacial AcOH only afforded unchanged starting material.

An alternative starting material was 1,4-dihydrodibenz[*a*,*j*]acridine (**14**), analogous to the 1,4-reduced intermediates used in the benz[*a*]acridine and benz[*a*]anthracene series.[7] Reduction of **1** with Na in refluxing



xylene/EtOH or liquid NH_3/THF/EtOH gave acridan-derived products which were subjected to aerial oxidation to regenerate the heteroaromatic ring before examination of ^{1}H NMR spectra. Product compositions (Table I) were determined by integration of the characteristic H_{14} signals. The product distribution was dependent upon the atomic equivalents of sodium used and the percentage of THF used for solubilization of **1**, 7.0 equiv and 42% being optimal for the production of 1,4,10,13-tetrahydrodibenz[*a*,*j*]acridine (**16**) and 1,4,8,9-tetrahydrodibenz[*a*,*j*]acridine (**17**). These were isolated in 13% and 17% yield, respectively. Other products were 5,6-dihydrodibenz[*a*,*j*]acridine (**15**), 5,6,8,9-tetrahydrodibenz[*a*,*j*]acridine (**18**), and 1,2,3,4,10,13-hexahydrodibenz[*a*,*j*]acridine (**19**), but no 1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine was found. No conditions were found which gave good conversion to **14**.

The reduction of **1** with Na/liquid NH_3/THF/EtOH was shown to proceed through the acridan 7,14-dihydrodibenz[*a*,*j*]acridine (**20**) by reduction of the latter with 5.0 atomic equiv of sodium (Table I) which gave the same products as the reduction of **1** using 7.0 atomic equiv of sodium with virtually the same product distribution. Furthermore, treatment of **1** with only 2.3 atomic equiv of sodium gave only partial reduction (Table I). In this case the product distribution before aerial oxidation was determined by chromatographic separation of unchanged **1** (63%) from the much less polar "acridan" products (37%). Examination of the mixed "acridan" products by ^{1}H NMR showed that **20** (51% of the acridans) was present plus other reduction products. After aerial oxidation the product distribution was **1** (49%), **14** (20%), **15** (6%), **16** (17%), and **17** (8%). Thus the acridan, **20**, initially formed is more readily reduced than **1**.

The use of more than 7.0 atomic equiv of sodium in liquid NH_3/THF/EtOH gave products with reduced nitrogen heterocyclic rings that were resistant to aerial oxidation in hot acetic acid. Compounds isolated were *cis*- and *trans*-5,6,6a,7,14,14a-hexahydrodibenz[*a*,*j*]acridine (**21** and **22**, respectively) and *trans*-1,4,7,7a,8,9,13b,14-octahydrodibenz[*a*,*j*]acridine (**23**). In the 400-MHz NMR spectrum a relatively small coupling constant of 5.5 Hz between H_{6a} and H_{14a} in **21** indicated cis stereochemistry while a large coupling of 10.1 Hz in **22** indicated trans stereochemistry. For **23** the proton assigned as H_{7a} showed a large coupling of 10.3 Hz to H_{13b}, indicating trans stereochemistry of the fused reduced rings. The large coupling constant observed between H_{6a} and $H_{6'}$ (12.0 Hz) in **21** suggests a strong preference for one conformation in the cis-fused product. Compound **22** had an identical melting

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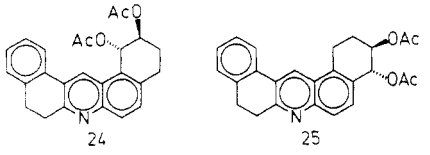
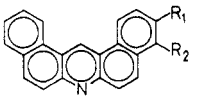
point and UV spectrum with a compound identified by Blout and Corley[13] as a hexa- or octahydro derivative of dibenz[a,j]acridine obtained by Zn/HCl reduction. However, the melting point and UV spectrum reported for a dihydrodibenz[a,j]acridine[13] did not correspond to any of the dihydro compounds (**6**, **7**, **14**, **15**, and **20**) isolated in the present work.

The synthetic value of **16** and **17** was investigated by base-catalyzed rearrangements followed by dehydrogenation and Prevost reaction. Dehydrogenation of **16** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1 molar equiv) gave **1** (19%), **14** (55%), and **16** (27%) and was less satisfactory in terms of potential yield of tetrahydro diol diacetates than sodium *tert*-butoxide catalyzed isomerization followed by DDQ (1 molar equiv) treatment. The latter gave 20%, 53%, and 3% of **1**, **7**, and **6**, respectively, as well as isomerized **16**. Prevost reaction followed by hydrolysis afforded the mixed tetrahydro diols, which were acetylated to **8** and **9** in yields of 5% and 32%, respectively, from **16**. Alternatively, dehydrogenation (DDQ) and then isomerization with sodium *tert*-butoxide of **16**, followed by Prevost reaction, hydrolysis, and acetylation gave **8** and **9** (14% and 41%, respectively, from **16**).

Treatment of the unsymmetrical tetrahydro derivative, **17**, with DDQ afforded only **15** (76%). However, refluxing **17** with sodium *tert*-butoxide/*tert*-butyl alcohol gave a mixture containing 7% of **17** (H_{14} at δ 8.51) and 50% and 43% of products with H_{14} signals at δ 8.60 and 8.67, respectively. The latter were isomerization products of **17** because dehydrogenation of the whole reaction mixture with DDQ afforded **7** (16%), **6** (30%), **15** (41%), and the fully aromatic **1** (12%). Prevost reaction of this base-catalyzed rearrangement product of **17** followed by hydrolysis and acetylation gave *trans*-1,2-diacetoxy-1,2,3,4,8,9-hexahydrodibenz[a,j]acridine (**24**) and *trans*-3,4-diacetoxy-1,2,3,4,8,9-hexahydrodibenz[a,j]acridine (**25**) as well as **8**, **9**, and **15** (8%), which were formed as a result of oxidation during the Prevost reaction. Treatment of **24** and **25** with DDQ afforded **8** and **9**, respectively, giving an overall yield from **17** of 15% for **8** and 22% for **9**.



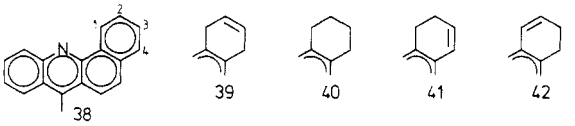
Dibenz[a,j]acridine 5,6-oxide[14a] (**26**) was obtained by phase-transfer oxidation of dibenz[a,j]acridine with sodium hypochlorite.[14b] Hydrolysis of **26** under basic conditions gave no dihydro diols (contrast with benzo[f]quinoline 5,6-oxide[15]) but under acidic conditions a phenol was obtained[14b] which, based on the sharpening of a singlet for H_5 at δ 7.45 on irradiation of H_1 (and H_{13}) but not on irradiation of H_{14}, was 6-hydroxydibenz[a,j]acridine (**27**). *trans*-5,6-Dihydro-5,6-dihydroxydibenz[a,j]acridine (**28**) was obtained by reduction of dibenz[a,j]acridine-5,6-quinone (**32**) with sodium borohydride.[16] The quinone was prepared from dibenz[a,j]acridine by initial osmium tetraoxide oxidation to *cis*-5,6-dihydro-5,6-dihydroxydibenz[a,j]acridine (**30**) and subsequent DDQ dehydrogenation[17] or by benzeneselenenic anhydride oxidation of **27**. The $J_{5,6}$ values (5.6 Hz) of the trans diacetate (**29**) and associated acetate methyl signals at 2.02 and 2.11 ppm indicate quasidiaxial conformations of the acetoxy groups.[18] In **31**, the pseudoaxial and pseudoequatorial methyl signals appeared at 2.34 and 1.97 ppm, respectively, indicating a strong preference for one conformation.[18] 7*H*-Dibenz[a,j]acridone (**34**) was obtained by acetic anhydride rearrangement[19] of dibenz[a,j]acridine *N*-oxide (**33**), in contrast to the literature synthesis in which the acridone was prepared by the Ullmann reaction.[20] Elimination products isolated after an attempted preparation of *trans*-3,4-diacetoxy-3,4-dihydrodibenz[a,j]acridine (**11**) were identified as 4-acetoxydibenz[a,j]acridine (**35**), 4-hydroxydibenz[a,j]acridine (**36**), and 3-hydroxydibenz[a,j]acridine (**37**).

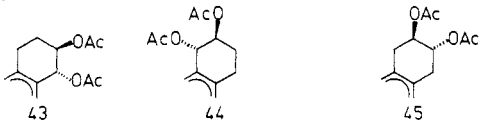


35 R_1=H R_2=OAc
36 R_1=H R_2=OH
37 R_1=OH R_2=H

In the course of the ^1H NMR studies of total reduction products derived from dibenz[a,j]acridine, it was noted that the change in chemical shifts of H_{14} of **1**, **14**, **15**, **16**, **17**, **18**, and **19** were linear with total concentration in $CDCl_3$ up to 0.14 M. The concentration dependencies of the H_{14} signal in compounds containing an acridine moiety, **1**, **14**, **16**, and **19** were greater than 2 ppm/M. Those compounds lacking this structural feature showed a much smaller concentration dependency for the H_{14} signal which was <0.5 ppm/M for **15**, **17**, and **18**. These effects arise from shielding of the H_{14} due to intermolecular solute–solute interactions and have been previously noted with acridine.[21]

Application of the Na reduction method to the preparation of precursors for the synthesis of dihydro diols of 7-methylbenz[c]acridine (**38**) was also attempted to improve yields of key intermediates. Treatment with Na in refluxing xylene/EtOH followed by reoxidation of the heterocyclic ring with CrO_3/HOAc afforded 7-methyl-1,4-dihydrobenz[c]acridine (**39**), 40% and 7-methyl-1,2,3,4-tetrahydrobenz[c]acridine[22] (**40**, 8%). The yield of **39** was increased to 64% by use of Na in liquid NH_3/EtOH followed by aerial reoxidation to the acridine system. Rearrangement of **39** by heating with polyphosphoric acid





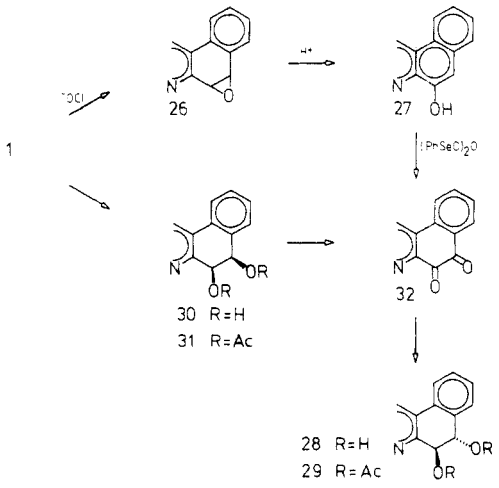


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Table I. Product Composition of Na/Liquid NH_3/EtOH Reduced[a] Dibenz[a,j]acridine (1)

reactn condtns		% composition[b]						
		1	14	15	16	17	18	19
Na, molar equiv	THF, %	10.23[c]	9.52	9.23	8.78	8.51	8.32	8.84
2.3	40	81	7	2	7	3	0	*e*
6.0	45	27	6	6	17	29	12	4
6.5	40	21	5	4	23	33	11	4
7.0	42	0	5	4	25	49	9	7
7.0	67	27	9	7	18	18	12	9
7.5	*d*	8	16	5	14	53	5	*e*
5.0[f]	38	5	13	4	21	51	6	*e*

[a] Crude products were refluxed in AcOH with air to rearomatize the heterocyclic ring. [b] Percentage composition determined by integration of the ^1H NMR H_{14} signals ($CDCl_3$ solvent). [c] Chemical shift of H_{14} signals at infinite dilution. [d] Reduction was carried out in xylene/EtOH. [e] Not determined due to overlapping signals from H_{13} of 14. [f] 7,14-Dihydrodibenz[a,j]acridine (**20**) was reduced in this experiment.

failed to give adequate yields of 1,2-dihydro-7-methylbenz[c]acridine (**41**). In refluxing sodium *tert*-butoxide-/*tert*-butyl alcohol, **39** was largely consumed in 1 h and at equilibrium, attained by about 4 h, 51%, 39%, and 9% of **41**, its 3,4-dihydro isomer, **42**, and **39**, respectively were present. These proportions were determined from the isolated yield of **42** and the yields of Prevost products obtained on reaction of a mixture of **41** and **39**. The products were hydrolyzed and acetylated to afford *trans*-3,4-diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]-acridine (**43**), *trans*-2,3-diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]acridine (**45**), and traces of *trans*-1,2-diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]acridine (**44**). This sequence afforded **43**, the dihydro diol with a bay-region double bond, in 18% overall yield from **38** and represents an improvement over the bromination/dehydrobromination sequence from **40**[9a] (3% from **40**).

In vitro metabolic experiments with **1** and liver microsomes[5a] and isolated hepatocytes[5b] showed the trans-3,4-dihydro diol (**13**) to be a major product and failed to show the presence of the 1,2-dihydro diol (**12**). The 3,4-isomer (**13**) is the biosynthetic precursor of the proposed ultimate carcinogen derived from **1**.

Experimental Section

^1H NMR spectra were recorded on a JEOL FX-90Q or a 400-MHz Bruker spectrometer in deuteriochloroform solution unless otherwise stated. Coupling constants (J) are recorded in Hz and chemical shifts (δ) in ppm with Me_4Si as an internal standard. Where possible, assignments of signals were confirmed by homodecoupling. Quantitation in crude reaction mixtures was carried out by integration of the H_{14} signals in dibenz[a,j]acridine derivatives and by isolation of products for dihydro-7-methylbenz[c]acridines. All melting points are uncorrected. Chemical ionization mass spectra were conducted by using methane as reagent gas and were performed on a Finnigan 3200E quad system with an INCOS data system. Ultraviolet spectra were measured on a Perkin-Elmer Lamda 5, UV/vis spectrophotometer in MeOH. Purifications were effected by using short column vacuum chromatography on silica gel.[23] High-resolution electron impact mass spectra were recorded on an AEI MS-9 mass spectrometer.

1,2,3,4-Tetrahydrodibenz[a,j]acridine (2). 6-Aminotetralin[24] (3.20 g) and 1-[(dimethylamino)methyl]-2-naphthol[25] (4.38 g) were heated at 260–280 °C for 30 min and then cooled. A CH_2Cl_2 solution of the resultant black tar was chromatographed (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) to afford 1-methyl-2-naphthol (0.32 g, mp 109–112 °C, lit.[26] mp 111 °C from CH_2Cl_2/pentane), and a brown solid (1.99 g), which on repeated recrystallization from EtOAc gave **2** as needles (0.50 g), mp 160–162 °C: ^1H NMR (400 MHz) δ 1.90 (m, 2 H_3), 2.00 (m, 2 H_2), 2.90 (m, 2 H_4), 3.22 (m, 2 H_1), 7.44 (d, H_5), 7.60 (dt, H_{11}), 7.65 (dt, H_{12}), 7.84 (dd, H_{10}), 7.88 (d, H_9), 7.96 (d, H_8), 7.98 (d, H_6), 8.65 (d, H_{13}), 9.38 (s, H_{14}), $J_{5,6} = J_{8,9} = 8.8$ Hz, $J_{10,11} = J_{11,12} = J_{12,13} = 7.3$ Hz, $J_{10,12} = J_{11,13} = 1.2$ Hz; CIMS, m/e (relative intensity) 284 (M + 1, 100); UV (λ_{max} nm (ϵ)) 387 (9000), 368 (8600), 290 (58 600), 282 (59 500), 277 (40 000). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.87; H, 5.83; N, 4.90. Crystallization of the mother liquor residue from EtOAc/hexane afforded yellow 9,10,11,12-tetrahydrodibenz[a,i]acridine (**3**, 0.13 g), mp 145–146 °C (lit.[27] mp 145 °C): ^1H NMR (400 MHz) δ 1.94 (m, 2 H_{10} and 2 H_{11}), 3.01–3.07 (m, 2 H_9 and 2 H_{12}), 7.62 (dt, H_3), 7.68 (dt, H_2), 7.72 (br s, H_{13}), 7.87 (dd, H_4), 7.89 (d, H_5), 7.96 (d, H_6), 7.96 (br s, H_8), 8.68 (dd, H_1), 9.23 (s, H_{14}), $J_{1,2} = 7.8$ Hz, $J_{1,3} = 1.2$ Hz, $J_{2,3} = 7.8$ Hz, $J_{2,4} = 1.2$ Hz, $J_{3,4} = 7.8$ Hz, $J_{5,6} = 9.0$ Hz; CIMS, m/e (relative intensity) 284 (M + 1, 100); UV (λ_{max} nm (ϵ)) 389 (14 500), 369 (12 300), 352 (8000), 281 (66 500), 250 (24 000), 240 (24 500), 226 (38 000).

Dehydrogenation of 2 and 3. A mixture of **2** (50 mg) and 10% palladium on charcoal (12 mg) was heated at 190 °C in *p*-cymene (7 mL) for 8 h. The catalyst was removed by filtration through Celite, the Celite was washed with CH_2Cl_2, and the solvent was removed under reduced pressure from the combined washings and filtrate. Chromatography (gradient CH_2Cl_2 to CH_2Cl_2/EtOAc 5:1) gave **1** (83%). Crystallization from benzene gave yellow needles, mp 216–218 °C (lit.[13] mp 215–216 °C), which showed the expected ^1H NMR spectrum.[28]

Similar treatment of **3** (10 mg) with 10% Pd/C (3 mg) in *p*-cymene (5 mL) gave 7.8 mg of a solid which, after recrystallization from EtOAc, gave yellow dibenz[a,i]acridine, mp 207–209 °C (lit.[29] mp 206–208 °C): ^1H NMR (3 mg/mL acetone-d_6), δ 6.76–6.87 (m, H_{10} and H_{11}), 6.90–7.06 (m, H_2 and H_3), 7.12 (d, H_6), 7.23 (d, H_4), 7.28 (d, H_5), 7.36–7.55 (m, H_9 and H_{12}), 8.13 and 8.16 (br s, H_8 and H_{13}), 8.23 (m, H_1), 9.19 (s, H_{14}), $J_{6,14} = 0.7$ Hz, $J_{5,6} = 10.0$ Hz.

1-Hydroxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (4) and 4-Hydroxy-1,2,3,4-tetrahydrodibenz[a,j]acridine (5). A solution of **2** (0.75 g), 1,3-dibromo-5,5-dimethylhydantoin (dibromantin, 0.375 g), and α,α'-azabis(isobutyronitrile) (2 mg) in dry CCl_4 was refluxed for 2 h in a N_2 atmosphere. The 5,5-dimethylhydantoin was removed from the cool reaction mixture by filtration. The solvent was removed under reduced pressure to afford an oil (0.79 g), which was dissolved in THF (50 mL). Water (10 mL) and concentrated HCl (5 drops) were added, and after overnight stirring, the THF was removed under reduced pressure and the mixture was extracted with EtOAc. The EtOAc was washed with 5% aqueous $NaHCO_3$ and water, dried with Na_2SO_4, and evaporated to afford a solid (0.77 g). Chromatography (gradient, CH_2Cl_2 to EtOAc) gave unchanged **2** (0.410 g, 55%), **4** (0.125 g, 16%), and **5** (0.109 g, 14%). Compound **4** gave pale yellow crystals from EtOAc, mp 239–241 °C: ^1H NMR (4 mg/mL, $CDCl_3$/Me_2SO-d_6 3:2) δ 1.78–2.36 (m, 2 H_2 and 2 H_3), 2.76–3.04 (m, H_4), 5.18 (d, OH_1), 5.58 (br s, H_1), 7.74–8.18 (m, 7 H), 8.95 (m, H_{13}), 10.03 (s, H_{14}), $J_{1,OH_1} = 7.0$ Hz; CIMS, m/e (relative intensity) 300 (M + 1, 100), 282 (62); UV (λ_{max} nm (ϵ)) 383 (10 400), 363 (9200), 346 (6900), 330 (5800 sh), 316 (4200 sh), 285 (57 200),

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276 (58 100), 236 (25 800), 222 (37 400); high-resolution electron impact MS, m/e 299.1304 ($C_{21}H_{17}NO$ requires 299.1310). Recrystallization of **5** from EtOAc gave a pale yellow solid, mp 212–214 °C: ^{1}H NMR δ 1.87–2.23 (m, 2 H_2 and 2 H_3), 3.30 (m, 2 H_1), 4.82 (m, H_4), 5.30 (d, OH_4), 7.58–8.25 (m, 7 H), 8.92 (m, H_{13}), 9.67 (s, H_{14}), J_{4,OH_4} = 7.0 Hz; CIMS, m/e (relative intensity) 300 (M + 1, 100), 282 (55); UV (λ_{max} nm (ϵ)) 383 (12 000), 363 (11 400), 344 (8700), 286 (71 000), 278 (74 000), 238 (31 600, sh), 222 (47 500); high-resolution electron impact MS, m/e 299.1310 ($C_{21}H_{17}NO$ requires 299.1310).

3,4-Dihydrodibenz[*a*,*j*]acridine (6). A solution of **4** (80 mg) and *p*-toluenesulfonyl chloride (160 mg) in toluene (60 mL) containing pyridine (1.0 mL) was refluxed under N_2 for 10 h. The residue remaining after removal of most of the toluene under reduced pressure was dissolved in CH_2Cl_2, and the solution was washed with water, dried (Na_2SO_4), and concentrated to afford an oil (76 mg). Chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 5:1) gave **6** (63 mg, 84%), which gave yellow crystals from EtOAc/hexane, mp 145–147 °C: ^{1}H NMR (5 mg/mL) δ 2.32–2.36 (m, H_3 and $H_{3'}$), 2.90–3.20 (m, 2 H_4), 6.44 (dt, H_2), 7.63–8.19 (m, 7 H), 7.47 (dt, H_1), 8.76 (m, H_{13}), 9.65 (s, H_{14}), $J_{1,2}$ = 9.7 Hz, $J_{1,3}$ = $J_{1,3'}$ = 1.7 Hz, $J_{2,3}$ = 4.6 Hz; CIMS, m/e (relative intensity) 282 (M + 1, 100); UV (λ_{max} nm (ϵ)) 388 (8400), 371 (7900), 353 (5300, sh), 337 (3500, sh), 290 (49 400), 283 (48 000, sh), 240 (32 700, sh), 230 (41 100). Anal. Calcd for $C_{21}H_{15}N$: C, 89.64; H, 5.38; N, 4.98. Found: C, 89.72; H, 5.48; N, 5.22.

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine (8).** To a benzene (30 mL) suspension of silver iodobenzoate prepared from silver benzoate (81 mg) and iodine (44 mg) under N_2 was added a solution of **6** (50 mg) in dry benzene (30 mL). The mixture was stirred for 0.5 h and then refluxed under N_2 for 12 h. EtOAc (50 mL) was added, the suspension was filtered through silica gel HF_{254}, and the filtrate and EtOAc washings of the silica gel were evaporated to afford a *trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine as a light brown solid (83 mg): ^{1}H NMR (2.0 mg/0.4 mL) δ 2.45–2.68 (m, H_3 and $H_{3'}$), 3.12–3.35 (m, 2 H_4), 5.79 (dd, H_2), 7.22–8.44 (m, 18 H), 8.84 (m, H_{13}), 9.75 (s, H_{14}), $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = $J_{2,3'}$ = 3.4 Hz; CIMS, m/e (relative intensity) 524 (M + 1, 6), 402 (37), 123 (100). The dibenzoate was hydrolyzed under N_2 in THF (20 mL) and MeOH (10 mL) with 5% aqueous NaOH (5 mL) at room temperature for 8 h. The bulk of the THF and MeOH was removed under reduced pressure, EtOAc was added, and the organic phase was washed with water, dried (Na_2SO_4), and evaporated to give a solid. This was acetylated with acetic anhydride (5.0 mL) and pyridine (0.5 mL) overnight. The reaction mixture was evaporated under reduced pressure, dissolved in EtOAc, and washed twice with cold 10% aqueous Na_2CO_3. After washing with water and drying (Na_2SO_4), evaporation of solvent gave a yellow solid (51 mg) which was chromatographed (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) to give **8** (48 mg). This formed needles: mp 210–211 °C (MeOH); ^{1}H NMR (2.0 mg/0.5 mL) δ 2.04 (s, 3 H), 2.10 (s, 3 H) 2.25–2.45 (m, H_3 and $H_{3'}$), 3.10–3.30 (m, 2 H_4), 5.42 (dd, H_2), 6.91 (d, H_1), 7.56–7.80 (m, 4 H), 7.99 (s, H_8 and H_9), 8.34 (d, H_6), 8.75 (m, H_{13}), 9.62 (s, H_{14}), $J_{1,2}$ = $J_{2,3}$ = 3.2 Hz, $J_{2,3'}$ = 3.4 Hz, $J_{5,6}$ = 8.2 Hz; CIMS, m/e (relative intensity) 400 (M + 1, 100), 340 (63), 308 (7), 280 (22); UV (λ_{max} nm (ϵ)) 388 (8100), 367 (7200), 350 (5100), 334 (4500, sh), 320 (2500, sh), 289 (46 600), 279 (43 300), 238 (22 900, sh), 226 (27 400, sh), 222 (29 100). Anal. Calcd for $C_{25}N_{21}NO_4$: C, 75.20; H, 5.26; N, 3.50. Found: C, 75.20; H, 5.22; N, 3.30.

***trans*-1,2-Diacetoxy-1,2-dihydrodibenz[*a*,*j*]acridine (10).** Compound **8** (0.300 g), α,α'-azabis(isobutyronitrile) (5 mg), and dibromantin (0.108 g) were refluxed in dry CCl_4 (150 mL) under N_2 for 30 min. After cooling and removal of the 5,5-dimethylhydantoin by filtration, the solvent was removed under vacuum to give a solid which was treated with Li_2CO_3 (1.0 g) and LiF (0.70 g) in freshly distilled hexamethylphosphoramide (HMPA, 10 mL). After being stirred under N_2 at 100 °C for 3 h, the reaction mixture was cooled, diluted with water, and extracted with EtOAc. The EtOAc was washed with water, dried (Na_2SO_4), and evaporated to give **10** (0.276 g, 92%), mp 205–206 °C (pale yellow needles from MeOH): ^{1}H NMR (1.0 mg/0.5 mL) δ 2.03 (s, 3 H), 2.06 (s, 3 H), 5.52 (dd, H_2), 6.42 (ddd, H_3), 6.98 (d, H_4), 7.12 (d, H_1), 7.72–7.99 (m, 4 H), 8.07 (s, H_8 and H_9), 8.43 (d, H_6), 8.95 (m, H_{13}), 9.97 (s, H_{14}), $J_{1,2}$ = 1.2 Hz, $J_{1,3}$ = 0.7 Hz, $J_{2,3}$ = 4.9 Hz, $J_{3,4}$ = 8.1 Hz, $J_{5,6}$ = 9.0 Hz; CIMS, m/e (relative intensity) 398 (M + 1, 43), 338 (100), 296 (25); UV (λ_{max} nm (ϵ)) 405 (14 300), 384 (11 600), 365 (7300), 352 (4900, sh), 299 (89 300), 288 (58 500), 268 (24 300, sh), 259 (18 000, sh), 239 (35 500, sh), 229 (38 000); high-resolution electron impact MS, 397.1315 ($C_{25}H_{19}NO_4$ requires 397.1314).

***trans*-1,2-Dihydro-1,2-dihydroxydibenz[*a*,*j*]acridine (12).** A solution of **10** (220 mg) in THF (30 mL) and MeOH (20 mL) was saturated with NH_3 gas and allowed to stand for 1.5 h. After the addition of 5% aqueous NaOH (50 mL), the reaction mixture was extracted with EtOAc (4 × 200 mL), and the organic extract was worked up in the usual fashion by washing, drying, and evaporation of the solvent. Recrystallization of the yellow solid (137 mg, 79%) from EtOAc gave yellow needles of **12**, mp 267–271 °C dec: ^{1}H NMR (3.0 mg/0.5 mL Me_2SO-d_6) δ 4.40 (m, H_2), 5.08 (d, OH_2), 5.58 (br s, H_1 and OH_1), 6.32 (dd, H_3), 6.78 (d, H_4), 7.66–8.23 (m, 7 H), 9.10 (m, H_{13}), 10.01 (s, H_{14}), $J_{1,2}$ = 1.5 Hz, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 4.6 Hz, J_{2,OH_2} = 5.9 Hz; CIMS, m/e (relative intensity) 314 (M + 1, 100), 296 (100), 280 (8); UV spectrum in MeOH (λ_{max} nm (ϵ)) 405 (9400), 384 (11 000), 364 (8000), 334 (7800), 320 (7000), 298 (78 300), 287 (55 300), 276 (36 000, sh), 266 (28 600, sh), 230 (51 600, sh); high-resolution electron impact MS, m/e 313.1109 ($C_{21}H_{15}NO_2$ requires 313.1102).

1,2-Dihydrodibenz[*a*,*j*]acridine (7). A solution of **5** (50 mg) in toluene (100 mL) was treated with *p*-toluenesulfonyl chloride (100 mg) in the presence of pyridine (0.5 mL) as described for the preparation of **6**. After chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 5:1) **7** (37 mg, 78%) was obtained which gave pale yellow needles, mp 176–178 °C, from EtOAc/hexane: ^{1}H NMR (5 mg/mL) δ 2.45–2.79 (m, H_2 and $H_{2'}$), 3.27–3.46 (m, H_1 and $H_{1'}$), 6.25 (dt, H_3), 6.58 (dt, H_4), 7.48–8.10 (m, 7 H), 8.67 (m, H_{13}), 9.48 (s, H_{14}), $J_{2,3}$ = $J_{2,3'}$ = 4.2 Hz, $J_{2,4}$ = $J_{2',4}$ = 1.7 Hz, $J_{3,4}$ = 9.5 Hz; CIMS, m/e (relative intensity) 282 (M + 1, 100); UV (λ_{max} nm (ϵ)) 412 (6600), 394 (7100), 302 (80 600), 294 (58 100), 291 (58 400), 230 (38 100). Anal. Calcd for $C_{21}H_{15}N$: C, 89.64; H, 5.38; N, 4.98. Found: C, 89.66; H, 5.48; N, 4.97.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine (9).** The Prevost reaction on compound **7** (20 mg) was effected by using conditions described above for preparation of the 1,2-diacetoxy derivative, **8**, to give pale brown solid (29 mg) of *trans*-3,4-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine: ^{1}H NMR (2.0 mg/0.4 mL) δ 2.43–2.77 (m, 2 H_2), 3.57–3.79 (m, 2 H_1), 5.63–5.89 (m, H_3), 6.77 (d, H_4), 7.36–8.26 (m, 17 H), 8.87 (m, H_{13}), 9.59 (s, H_{14}), $J_{3,4}$ = 5.9 Hz; CIMS, m/e (relative intensity) 524 (M + 1, 5), 402 (38), 123 (100). The dibenzoate was hydrolyzed, and the resulting diol was acetylated and worked up as described above to give a yellow solid (17 mg). Chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) gave *trans*-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*j*]acridine as pale yellow crystals from MeOH, mp 199–201 °C: ^{1}H NMR (2 mg/0.5 mL) δ 2.07 (s, 3 H), 2.18 (s, 3 H). 2.32–2.47 (m, 2 H_2), 3.55 (t, 2 H_1), 5.35 (dd, H_3), 6.30 (d, H_4), 7.67–8.10 (m, 4 H), 8.13 (s, H_8 and H_9), 8.28 (d, H_6), 8.93 (m, H_{13}), 9.77 (m, H_{14}), $J_{1,2}$ = 6.9 Hz, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 5.4 Hz, $J_{5,6}$ = 8.3 Hz; CIMS, m/e (relative intensity) 400 (M + 1, 78), 340 (100), 298 (8), 280 (36), 199 (13), 157 (23); UV (λ_{max} nm (ϵ)) 386 (10 100), 367 (9700) 349 (6900, sh), 289 (64 200), 281 (63 200), 242 (31 200), 229 (36 000), 221 (34 400). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.20; H, 5.26; N, 3.50. Found: C, 75.29; H, 5.29; N, 3.21.

***trans*-3,4-Diacetoxy-3,4-dihydrodibenz[*a*,*j*]acridine (11).** Bromination followed by dehydrobromination of **9** according to the method used above to prepare **10** gave **11** (90%), which formed pale yellow crystals from EtOAc, mp 205–207 °C: ^{1}H NMR (1.0 mg/0.5 mL) δ 2.09 (s, 3 H), 2.19 (s, 3 H), 5.73 (ddd, H_3), 6.47 (dd, H_2), 6.47 (d, H_4), 7.70–8.03 (m, 5 H), 8.02 (s, H_8 and H_9), 8.32 (d, H_6), 8.88 (m, H_{13}), 9.86 (s, H_{14}), $J_{1,2}$ = 10.2 Hz, $J_{1,3}$ = 1.1 Hz, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 5.4 Hz; CIMS, m/e (relative intensity) 398 (M + 1, 48) 338 (100), 296 (49), 103 (7); UV (MeOH (λ_{max} nm (ϵ)) 394 (11 500), 373 (11 500), 356 (7600, sh), 294 (62 500), 287 (59 700), 241 (44 800), 230 (41 200, sh). Anal. Calcd for $C_{25}H_{19}NO_4$: C, 75.56; H, 4.78; N, 3.52. Found: C, 75.61; H, 4.76; N, 3.34.

***trans*-3,4-Dihydro-3,4-dihydroxydibenz[*a*,*j*]acridine (13).** Hydrolysis of compound **11** as described for the preparation of **12** gave **13** as pale yellow needles from EtOAc (76%), mp 287–293 °C dec: ^{1}H NMR (2 mg/0.3 mL Me_2SO-d_6) δ 4.57 (m, H_3), 4.91 (dd, H_4), 5.42 (d, OH_3), 5.83 (d, OH_4), 6.17 (dd, H_2), 7.80–8.40 (m, 8 H), 9.41 (m, H_{13}), 10.20 (s, H_{14}), $J_{1,2}$ = 10.1 Hz, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 10.8 Hz, J_{3,OH_3} = 4.9 Hz, J_{4,OH_4} = 4.9 Hz; CIMS, m/e (relative

intensity) 314 (M + 1, 100), 296 (98), 280 (8); UV (MeOH) (λ_{max} nm (ϵ)) 392 (10700), 372 (10600), 354 (7300, sh), 293 (65900), 240 (41600), 231 (46300); high resolution electron impact MS, m/e 313.1111 ($C_{21}H_{15}NO_2$ requires 313.1103).

Bromination/Dehydrobromination of 1,2,3,4-Tetrahydrodibenz[a,j]acridine (2). Direct Conversion to Tetrahydro Diacetates 8 and 9. Compound **2** (8.0 g) was refluxed for 3 h with dibromantin (4.0 g) and α,α'-azobis(isobutyronitrile) (10 mg) under N_2 and worked up to the bromination products as described previously. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 8.0 mL) was added to a CH_2Cl_2 solution of these, the solvent was removed, and the residue was heated at 35–40 °C for 1 h. Chromatography afforded a solid (3.95 g) comprising a mixture of **1**, **6**, **7**, and **2** in a 3:2:2:5 ratio (determined by integration of their H_{14} signals at δ 10.2, 9.69, 9.39, and 9.33, respectively in the NMR). This mixture was treated under Prevost conditions with silver iodobenzoate prepared from silver benzoate (2.57 g) and iodine (1.42 g) as described above for the preparation of the tetrahydro diacetates **8** and **9**. Hydrolysis was followed by chromatography to separate **1** and **2** from the tetrahydro diols, which were then acetylated and chromatographed (gradient, CH_2Cl_2 to EtOAc) to afford **8** (1.5%) and **9** (5%).

Reduction of Dibenz[a,j]acridine (1). Method A. Sodium (8.7 g, 7 atomic equiv) was added to a vigorously stirred suspension of 1^{13} (15.1 g) in THF (660 mL), liquid NH_3 (880 mL), and EtOH (30 mL) over 15 min. The suspension dissolved after about one-quarter of the Na was added, and after 18 h of stirring and the evaporation of the ammonia, 20% NaCl was added. The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated to afford a residue which was dissolved in AcOH (600 mL) and stirred vigorously at 100–125 °C in air. After 18 h the bulk of the AcOH was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and extracted with 10% Na_2CO_3. The organic phase was dried and concentrated, pentane (1 vol) was added, and from the resultant solution 1,4,10,13-tetrahydrodibenz[a,j]acridine (**16**) (1.03 g) separated. Chromatography (gradient, pentane/CH_2Cl_2 1:1 to CH_2Cl_2/EtOAc 1:1) of the residual solution and fractional crystallizations gave a further batch of **16** (0.95 g). Recrystallization from CH_2Cl_2 gave yellow crystals, mp 233–234 °C: ^{1}H NMR (2 mg/0.3 mL, $CDCl_3$) δ 3.69 (m, 2 H_4 and 2 H_{10}), 3.84 (m, 2 H_1 and 2 H_{13}), 6.17 (m, 4 H), 7.63 (d, H_5 and H_9), 8.18 (d, H_6 and H_8), 8.84 (s, H_{14}), $J_{5,6}$ = $J_{8,9}$ = 9.0 Hz; CIMS, m/e (relative intensity) 284 (M + 1, 100); UV (MeOH) (λ_{max} nm (ϵ)) 390 (4000 sh), 362 (11900), 353 (8100, sh), 345 (8100), 262 (177900). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.79; H, 6.18; N, 4.64. A major fraction eluting with CH_2Cl_2/EtOAc 19:1 (6.45 g) on recrystallization from EtOAc/hexane gave 1,4,8,9-tetrahydrodibenz[a,j]acridine (**17**) (3.67 g) as yellow crystals, mp 154–156 °C: ^{1}H NMR (5 mg/0.3 mL) δ 3.18 (m, 4 H_8 and H_9), 3.68 (m, 4 H_1 and H_4), 6.05 (m, H_2 and H_3), 7.26–7.50 (m, 4 H), 7.82–7.98 (m, 2 H), 8.50 (s, H_{14}); CIMS, m/e (relative intensity) 284 (M + 1, 100), 283 (12), 282 (23); UV (EtOH) (λ_{max} nm (ϵ)) 344 (9000), 328 (9400), 315 (11900), 304 (10300, sh), 268 (33500), 263 (32800, sh). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 89.31; H, 5.73; N, 5.05. 5,6,8,9-Tetrahydrodibenz[a,j]acridine (**18**) isolated by further chromatography and fractional crystallization of the above filtrate was recrystallized from CH_2Cl_2/pentane to give pale yellow needles, mp 149–150 °C: ^{1}H NMR (1 mg/0.2 mL) δ 3.07 (m, H_5, H_6, H_8, H_9), 7.26–7.48 (m, 6 H), 7.75–7.87 (m, H_1 and H_{13}), 8.32 (s, H_{14}); CIMS, m/e (relative intensity) 284 (M + 1, 100), 283 (16), 282 (22). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.84; H, 6.10; N, 4.53. 1,2,3,4,10,13-Hexahydrodibenz[a,j]acridine (**19**) gave yellow needles after several recrystallizations from EtOAc of the fraction eluting with CH_2Cl_2/EtOAc 4:1, mp 214–216 °C: ^{1}H NMR (2.5 mg/0.4 mL) δ 1.98 (m, 4 H_2 and H_3), 2.95 (m, 2 H_4), 3.21 (m, 2 H_1), 3.46–3.71 (m, 2 H_{10}), 3.71–3.97 (m, 2 H_{13}), 6.08 (m, 2 H_{11} and H_{12}), 7.48 (d, 2 H), 7.95 (d, H_6), 8.03 (d, H_8), 8.82 (s, H_{14}), $J_{5,6}$ = 9.0 Hz, $J_{8,9}$ = 8.8 Hz; CIMS, m/e (relative intensity) 286 (M + 1, 100), 285 (14), 284 (11), 282 (9). Anal. Calcd for $C_{21}N_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.79; H, 6.50; N, 4.60.

Method B. Sodium (6.20 g) was added in small pieces to a stirred solution of **1** (10.0 g) in *p*-xylene (150 mL) and EtOH (20 mL), and after the metal had dissolved the solution was refluxed for 3 h. It was cooled and poured into water, and the products were isolated by CH_2Cl_2 extraction. After drying and evaporation of the solvent, the solid residue was dissolved in AcOH (80 mL) stirred under air overnight at approximately 100 °C and worked up as described in method A. Chromatography (gradient, CH_2Cl_2 to EtOAc) gave three major fractions, compound **17** (4.30 g, 42%), a 6:4 mixture of **1** and **14** (2.30 g), and 1,4,10,13-tetrahydrodibenz[a,j]acridine (**16**, 1.52 g, 15%). The mixture of **1** and **14** was rechromatographed to afford 1,4-dihydrodibenz[a,j]acridine **14** (31 mg), mp 206–209 °C: ^{1}H NMR (2.0 mg/0.3 mL) δ 3.57–3.79 (m, 2 H_4), 3.84–4.15 (m, 2 H_1), 6.17 (m, H_2 and H_3), 7.59–8.30 (m, 7 H), 8.90 (m, H_{13}), 9.45 (s, H_{14}); CIMS, m/e (relative intensity) 282 (M + 1, 100); UV (MeOH) (λ_{max} nm (ϵ)) 387 (7100), 367 (6800), 336 (3700, sh), 323 (3000 sh), 289 (47800), 283 (45600), 265 (24300), 240 sh (18700), 228 (32300); high-resolution electron impact MS, m/e 281.1213 ($C_{21}H_{15}N$ requires 281.1204).

Hexa- and Octahydro Derivatives of Dibenz[a,j]acridine (1). Reduction of **1** (7 g) by method A using 7.4 atomic equiv of sodium gave a crude product which on purification by repeated chromatography on silica gel H gave three major fractions which were recrystallized from hexane. *cis*-5,6,6a,7,14,14a-Hexahydrodibenz[a,j]acridine (**21**) (120.2 mg) was isolated as pale yellow crystals, mp 123–124 °C: ^{1}H NMR (400 MHz, 7.2 mg/0.4 mL) δ 1.86 (m, H_6), 2.05 (m, $H_{6'}$), 2.88 (dd, H_{14}), 2.96 (m, 2 H_5), 3.32 (dt, H_{14a}), 3.41 (dd, $H_{14'}$), 3.76 (dt, H_{6a}), 4.31 (br s, NH), 6.79 (d, H_8), 2.85–2.92 (m, 5 H), 7.38 (ddd, H_{11}), 7.52 (d, H_9), 7.66 (dd, H_{13}), 7.71 (d, H_{10}), $J_{6,6a}$ = 4.2 Hz, $J_{6',6a}$ = 12.0 Hz, $J_{6a,14a}$ = 5.5 Hz, $J_{8,9}$ = 8.7 Hz, $J_{10,11}$ = 8.5 Hz, $J_{11,12}$ = 6.8 Hz, $J_{11,13}$ = 1.3 Hz, $J_{12,13}$ = 8.1 Hz, $J_{14,14'}$ = 16.5 Hz, $J_{14,14a}$ = 11.3 Hz, $J_{14',14a}$ = 5.5 Hz; CIMS, m/e (relative intensity) 286 (M + 1, 100), 285 (30); UV (EtOH) (λ_{max} nm (ϵ)) 362 (2600), 302 (7900), 291 (8500), 253 (50300); high-resolution electron impact MS, m/e 285.1511 ($C_{21}H_{19}N$ requires 285.1517). *trans*-5,6,6a,7,14,14a-Hexahydrodibenz[a,j]acridine (**22**) (64.9 mg) was isolated as pale yellow crystals, mp 152–154 °C: ^{1}H NMR (400 MHz, 9.0 mg/0.4 mL) δ 1.94 (qd, H_6), 2.12 (dq, $H_{6'}$), 2.94 (dd, H_{14}), 3.22 (m, 2 H_5), 3.11 (td, H_{14a}), 3.33 (ddd, H_{6a}), 3.88 (dd, $H_{14'}$), 3.98 (br s, NH), 6.86 (d, H_8), 7.19–7.30 (m, 4 H), 7.47 (ddd, H_{11}), 7.55–7.59 (m, H_4 and H_9), 7.71 (dd, H_{13}), 7.88 (d, H_{10}), $J_{5,6}$ = 12.1 Hz, $J_{5',6}$ = 6.0 Hz, $J_{5,6'}$ = $J_{5',6'}$ = 3.2 Hz, $J_{6,6'}$ = 12.4 Hz, $J_{6,6a}$ = 11.5 Hz, $J_{6',6a}$ = 3.2 Hz, $J_{6a,14a}$ = 10.1 Hz, $J_{8,9}$ = 8.7 Hz, $J_{10,11}$ = 8.4 Hz, $J_{11,12}$ = 6.9 Hz, $J_{11,13}$ = 1.4 Hz, $J_{12,13}$ = 8.1 Hz, $J_{14,14'}$ = 15.8 Hz, $J_{14,14a}$ = 11.6 Hz, $J_{14',14a}$ = 5.5 Hz; CIMS, m/e (relative intensity) 286 (M + 1, 100), 285 (25); UV (EtOH) (λ_{max} nm (ϵ)) 351 (2400), 300 (5900 sh), 290 (7300), 273 (5400 sh), 249 (49400); high-resolution electron impact MS, m/e 285.1500 ($C_{21}H_{19}N$ requires 285.1517). *trans*-1,4,7,7a,8,9,13b,14-Octahydrodibenz[a,j]acridine (**23**) (254.1 mg) was isolated as very pale yellow crystals, mp 177–178 °C: ^{1}H NMR (400 MHz, 11.0 mg/0.4 mL) δ 1.86 (qd, H_8), 2.06 (dq, $H_{8'}$), 2.55 (dd, H_{14}), 2.90–3.07 (m, H_9, $H_{9'}$, and H_{13b}), 3.19 (td, H_{7a}), 3.23 (m, H_1), 3.35 (m, $H_{1'}$, H_4, and $H_{4'}$), 3.41 (dd, $H_{14'}$), 3.75 (br s, NH), 5.90 (m, H_2 and H_3), 6.50 (d, H_6), 6.83 (d, H_5), 7.14 (d, H_{13}), 7.18 (t, H_{12}), 7.24 (t, H_{11}), 7.45 (d, H_{10}), $J_{5,6}$ = 8.1 Hz, $J_{7a,8}$ = $J_{7a,13b}$ = 10.3 Hz, $J_{7a,8'}$ = 2.8 Hz, $J_{8,8'}$ = 12.5 Hz, $J_{8,9}$ = 12.0 Hz, $J_{8,9'}$ = 6.0 Hz, $J_{8',9}$ = $J_{8',9'}$ = 2.8 Hz, $J_{10,11}$ = 7.7 Hz, $J_{11,12}$ = 6.5 Hz, $J_{12,13}$ = 6.4 Hz, $J_{13b,14}$ = 12.1 Hz, $J_{13b,14'}$ = 5.5 Hz, $J_{14,14'}$ = 15.5 Hz; CIMS, m/e (relative intensity) 288 (M + 1, 100), 287 (40), 286 (22); UV (λ_{max} nm (ϵ)) 301 (2000), 250 (7900); high-resolution electron impact MS, m/e 287.1646 ($C_{21}H_{21}N$ requires 287.1674).

7,14-Dihydrodibenz[a,j]acridine (20) was prepared by the method of Blout and Corley[13] and purified by chromatography (solvent CH_2Cl_2) and recrystallization from CH_2Cl_2/pentane to give pale yellow plates, mp 215–222 °C (lit.[13] mp 218–220 °C): ^{1}H NMR (1.6 mg/0.3 mL) δ 4.79 (br s, H_{14} and $H_{14'}$), 6.28 (br s, NH), 6.98 (d, H_6 and H_8), 7.36–7.95 (m, 10 H), $J_{5,6}$ = $J_{8,9}$ = 8.5 Hz; CIMS, m/e (relative intensity) 282 (M + 1, 100), 281 (28), 280 (17); UV (EtOH) (λ_{max} nm (ϵ)) 386 (6600, sh), 373 (7100), 328 (18100), 316 (10600 sh), 285 (24000), 269 (42400), 261 (41200), 246 (26400), 236 (23800), 219 (75200).

5,6-Dihydrodibenz[a,j]acridine (15). Compound **17** (9.5 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (8.6 mg) were stirred and refluxed under N_2 in dioxane (5 mL) for 4 h. The solution was poured into 5% aqueous NaOH (20 mL) and extracted with CH_2Cl_2 (40 mL) and then the extract was washed with water and worked up to give a yellow crystalline solid (7.2 mg). Recrystallization from EtOAc/pentane gave **15** as pale yellow needles, mp 144–145 °C: ^{1}H NMR (400 MHz, 3.7 mg/0.4 mL)

δ 3.13 (m, 2 H_5), 3.33 (m, 2 H_6), 7.35 (m, 2 H), 7.43 (m, 1 H), 7.65 (ddd, H_{11}), 7.73 (ddd, H_{12}) 7.95 (dd, H_{10}), 7.96 (s, H_8 and H_9), 8.03 (d, H), 8.74 (br d, H_{13}), 9.23 (s, H_{14}), $J_{1,2}$ = 7.6 Hz, $J_{10,11}$ = 7.7 Hz, $J_{10,12}$ = 1.5 Hz, $J_{11,12}$ = 7.1 Hz, $J_{11,13}$ = 1.1 Hz, $J_{12,13}$ = 8.0 Hz; CIMS, *m/e* (relative intensity) 282 (M + 1, 100), 281 (9), 280 (4); UV (EtOH) (λ_{max} nm (ε)) 364 (12500), 347 (11300), 331 (7700 sh), 319 (22700), 306 (18500), 292 (18300), 280 (18300), 260 (29100, sh), 245 (34200), 224 (31200). Anal. Calcd for $C_{21}H_{15}N$: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.85; H, 5.06; N, 5.27.

Isomerization and Dehydrogenation of 1,4,10,13-Tetrahydrodibenz[*a,j*]acridine (16). Method A. Compound **16** (1.00 g) was refluxed under N_2 for 15 h in sodium *tert*-butoxide/*tert*-butyl alcohol prepared by dissolving sodium (2.50 g) in *tert*-butyl alcohol (200 mL). After evaporation of solvent and addition of water to the residue, the isomerization products were isolated by extraction into CH_2Cl_2, affording a solid (0.956 g). This was refluxed in dry dioxane (50 mL) with DDQ (0.765 g, 1 molar equiv) for 15 h, cooled, and poured into 10% NaOH (150 mL). Extraction of the aqueous phase with CH_2Cl_2 followed by the usual workup of the organic phase afforded a solid (0.87 g) which, by integration of the H_{14} ^1H NMR signals, contained **1** (20%), 3,4-dihydrodibenz[*a,j*]acridine (**6**, 3%), 1,2-dihydrodibenz[*a,j*]acridine (**7**, 53%) and isomers of **16**. Treatment under Prevost conditions described above gave after hydrolysis and acetylation **8** and **9** in 5% and 32% yields, respectively, from **16**. **Method B.** Compound **16** (0.200 g) was refluxed with DDQ (0.16 g, 1 molar equiv) and worked up as described above to afford a yellow solid (0.198 g), the composition of which was **1** (18%), 1,4-dihydrodibenz[*a,j*]-acridine, **14** (55%), and unchanged **16** (27%) as determined by integration of ^1H NMR H_{14} signals at δ 10.20, 9.27, and 8.46, respectively. The total product was refluxed with sodium *tert*-butoxide/*tert*-butyl alcohol (sodium (1.00 g) dissolved in *tert*-butyl alcohol (75 mL)) under nitrogen and worked up as before to afford a solid containing **1** (22%), **6** (24%), **7** (27%), 1,4-dihydrodibenz[*a,j*]acridine (**14**, 4%) and tetrahydrodibenz[*a,j*]acridine isomers (23%). Prevost reaction as described above gave **8** and **9** in 14% and 41% yield from **16**.

Isomerization of 1,4,8,9-Tetrahydrodibenz[*a,j*]acridine (17). Sodium (1.2 g) was dissolved in refluxing *tert*-butyl alcohol (250 mL), the hot solution was poured onto **17** (3.75 g), and the mixture was refluxed under N_2 for 18 h. After cooling, the reaction mixture was mixed with EtOAc (250 mL), washed with 20% aqueous NaCl, and worked up in the usual fashion. The residue was extracted with CH_2Cl_2 and filtered and the filtrate concentrated to give a partially crystalline residue (4.33 g). Analysis of the mixture by ^1H NMR (9 mg/0.4 mL, $CDCl_3$) showed signals due to **17** (7%) at δ 8.51 (H_{14}) and two new downfield signals at 8.60 (50%) and 8.67 (43%). Signals in the range 6.05–6.66 integrated for 100% of the original signal due to **17** at 6.05 (H_2 and H_3). A new multiplet at δ 2.26–2.64 integrated for two protons of the original **17**. A portion of the reaction mixture (16.0 mg) was refluxed and stirred for 3 h with DDQ (12.9 mg) and dioxane (8 mL). Workup as described previously gave a partially crystalline product (14.0 mg). Analysis of the mixture by ^1H NMR (14 mg/0.4 mL) showed downfield signals (H_{14}) at 9.18 (**15**) (41%), 9.56 (**6**) (30%), 9.63 (**7**) (16%), and 10.12 (**1**) (12%). Treatment of the remaining isomerization mixture (4.31 g) with silver iodobenzoate prepared from silver benzoate (11.56 g) and iodine (5.82 g) was followed by hydrolysis, acetylation, and chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 2:1) and gave fractions eluting with CH_2Cl_2/EtOAc 19:1 (2.37 g), 4:1 (0.71 g), and 2:1 compound **9** (0.60 g). The first fraction (2.37 g) gave on further chromatography 5,6-dihydrodibenz[*a,j*]acridine (**15**) and a mixture of **8** and *trans*-1,2-diacetoxy-1,2,3,4,8,9-hexahydrodibenz[*a,j*]acridine (**24**) (1.99 g). Further chromatography on a portion (ca. 100 mg) of this mixture gave **24** which was recrystallized from EtOAc/hexane, giving yellow crystals, mp 192–209 °C dec: ^1H NMR (1.8 mg/0.3 mL) δ 2.03 (s, 3 H), 2.09 (s, 3 H), 2.09–2.41 (m, 2 H), 2.91–3.37 (m, 6 H), 5.34 (m, 1 H_2), 6.65 (m, 1 H_1), 7.26–8.03 (m, 6 H), 8.53 (s, H_{14}), $J_{1,2}$ = 3.2 Hz; CIMS, *m/e* (relative intensity) 402 (M + 1, 28), 401 (6), 400 (7), 342 (100), 284 (18), 282 (16). The remainder of the mixture (1.98 g) was refluxed with DDQ (1.37 g) in dioxane (230 mL) under N_2 for 3 h. After partitioning between EtOAc and 10% aqueous Na_2CO_3, the organic layer was dried (Na_2SO_4) and evaporated to give a solid which after chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) and recrystallization from EtOAc/hexane gave **8** (1.34 g). The fraction eluting with CH_2Cl_2/EtOAc 4:1 (0.71 g) contained mainly *trans*-3,4-diacetoxy-1,2,3,4,8,9-hexahydrodibenz[*a,j*]acridine (**25**). A small portion (10 mg), after recrystallization from EtOAc/hexane, gave **25** as yellow needles, mp 172–174 °C: ^1H NMR (10 mg/0.3 mL) δ 2.06 (s, 3 H), 2.16 (s, 3 H), 2.21–2.45 (m, 2 H_2), 2.95–3.45 (m, 6 H), 5.30 (m, 1 H_3), 6.20 (d, 1 H_4), 7.26–7.42 (m, 3 H), 7.51 (d, 1 H), 7.92 (d, 1 H), 7.82–8.11 (m, 1 H), 8.59 (s, H_{14}), $J_{3,4}$ = 5.4 Hz, $J_{8,9}$ = 9.0 Hz; CIMS, *m/e* (relative intensity) 402 (M + 1, 24), 342 (100), 300 (3), 284 (5), 283 (2), 282 (5). Compound **25** (0.70 g) was treated with DDQ (0.59 g) as described above and gave **9** (0.44 g, 63%).

***cis*-5,6-Dihydro-5,6-dihydroxydibenz[*a,j*]acridine (30).** A solution of dibenz[*a,j*]acridine (2.00 g) in dry pyridine (80 mL) was stirred under N_2 with osmium tetraoxide (2.0 g) for 7 days. After removal of some solvent under vacuum, the reaction mixture was stirred with saturated aqueous $NaHSO_3$ (500 mL) for 4 h and extracted with EtOAc/tetrahydrofuran (1:1, 4 × 150 mL). The combined organic layers were washed, dried, and evaporated to dryness to afford a solid. Recrystallization (CH_2Cl_2/EtOAc, 1:1) gave pale yellow **30** (1.39 g, 62%), mp 231–233 °C: ^1H NMR (2 mg/0.3 mL) δ 2.81 (br s, OH), 5.08 (s, H_5 and H_6), 5.60 (br s, OH), 7.45–8.25 (m, 9 H), 8.86 (m, H_{13}), 9.38 (s, H_{14}); CIMS, *m/e* (relative intensity) 314 (M + 1, 100), 296 (56); UV (λ_{max} nm (ε)) 361 (10200), 344 (9500), 319 (23800), 306 (19900), 290 (20800), 280 (20000), 260 (30000, sh), 246 (33100), 224 (28300, sh); high-resolution electron impact MS, *m/e* 313.1102 ($C_{21}H_{15}NO_2$ requires 313.1102). Acetylation of **30** with acetic anhydride and pyridine at room temperature afforded *cis*-5,6-diacetoxy-5,6-dihydrodibenz[*a,j*]-acridine (**31**), which gave yellow crystals from MeOH, mp 165–168 °C: ^1H NMR (4 mg/0.5 mL) δ 1.96 (s, 3 H), 2.34 (s, 3 H), 6.35 (d, H_5), 6.52 (d, H_6), 7.37–8.21 (m, 10 H), 8.79 (m, H_{13}), 9.27 (s, H_{14}), $J_{5,6}$ = 3.5 Hz; CIMS, *m/e* (relative intensity) 398 (M + 1, 100), 338 (92), 296 (40); UV (MeOH) (λ_{max} nm (ε)) 363 (8400), 346 (8300), 320 (23100), 307 (19800), 290 (23800), 280 (24400), 262 (32000), 260 (31700), 248 (31700), 224 (31700); high-resolution electron impact MS, *m/e* 397.1317 ($C_{25}H_{19}NO_4$ requires 397.1314).

Dibenz[*a,j*]acridine-5,6-quinone (32). Method A. The cis dihydro diol **30** (80 mg) was refluxed under N_2 in dry dioxane (60 mL) with DDQ (300 mg) for 6 h. The dioxane was removed under reduced pressure, 10% aqueous NaOH (60 mL) was added, and the mixture was extracted with EtOAc. The usual workup afforded **32** as a red solid, mp >300 °C: ^1H NMR (2.2 mg/0.5 mL) δ 7.58–8.48 (m, 9 H), 8.86 (m, H_{13}), 9.64 (s, H_{14}); CIMS, *m/e* (relative intensity) 310 (M + 1, 100); IR (Nujol) 1680 cm^{-1} (carbonyl); high resolution electron impact MS, *m/e* 309.0770. ($C_{21}H_{11}NO_2$ requires 309.0789).

Method B. A solution of **27** (150 mg) in dry THF (15 mL) was added to a stirred suspension of benzeneselenenic anhydride (200 mg) in THF (50 mL). After being stirred at 50 °C for 5 h, the reaction mixture was cooled, and the red precipitate of quinone **32** was recrystallized from EtOAc to afford a 72% yield.

***trans*-5,6-Dihydro-5,6-dihydroxydibenz[*a,j*]acridine (28).** To the 5,6-quinone (**32**, 38 mg) suspended in MeOH was added sodium borohydride (40 mg), and the reaction mixture was stirred for 3 h. The MeOH was removed, water was added, and the products were extracted into EtOAc. After washing with water and drying (Na_2SO_4), evaporation of the EtOAc yielded a solid which was chromatographed to afford **28** (81%), mp 237–240 °C: ^1H NMR (2.0 mg/0.3 mL) δ 3.20 (br s, OH), 4.96 (s, H_5 and H_6), 5.40 (br s, OH), 7.45–8.26 (m, 9 H), 8.85 (m, H_{13}), 9.34 (s, H_{14}); CIMS, *m/e* (relative intensity) 314 (M + 1, 100), 296 (38); UV (MeOH) (λ_{max} nm (ε)) 363 (13000), 346 (11800), 320 (28300), 306 (23600), 290 (24600), 280 (26400), 261 (38700), 247 (37800), 223 (38000). Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47. Found: C, 80.48; H, 4.88; N, 4.75. Acetylation by the described method gave *trans*-5,6-diacetoxy-5,6-dihydrodibenz[*a,j*]acridine (**29**), mp 248–251 °C dec: ^1H NMR (400 MHz, 2 mg/0.3 mL) δ 2.02 (s, 3 H), 2.11 (s, 3 H), 6.31 (d, H_6), 6.35 (d, H_5), 7.44 (dt, H_3), 7.58 (d, H_4), 7.58 (dt, H_2), 7.69 (dt, H_{11}), 7.75 (dt, H_{12}), 7.95 (dd, H_{10}), 8.00 (d, H_9), 8.02 (d, H_8), 8.12 (d, H_1), 8.77 (d, H_{13}), 9.35 (s, H_{14}), $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 1.0 Hz, $J_{2,3}$ = $J_{3,4}$ = 7.5 Hz, $J_{5,6}$ = 5.7 Hz, $J_{8,9}$ = 8.0 Hz, $J_{10,12}$ = 1.4 Hz, $J_{10,11}$ = 7.5 Hz, $J_{11,13}$ = 1.3 Hz, $J_{12,13}$ = 8.0 Hz; CIMS, *m/e* (relative intensity) 398 (M + 1, 100), 338 (90), 296 (30), 280 (55); UV (λ_{max} nm (ε)) 365 (6100), 348 (6100), 321 (18200), 308 (15600), 289 (20700, sh), 267 (26700), 248

(24 500), 224 (29 900); high resolution electron impact MS, m/e 397.1310 ($C_{25}H_{19}NO_4$ requires 397.1314).

Dibenz[a,j]acridine 5,6-Oxide (26). Dibenz[a,j]acridine (1, 4.0 g), dissolved in CH_2Cl_2 (400 mL), was vigorously stirred with tetrabutylammonium hydrogen sulfate (400 mg) and 5% aqueous sodium hypochlorite (100 mL, buffered to pH 8.5 with 0.6 M phosphate) for 6 h. The organic layer was removed, washed with water, dried, and evaporated to give a solid (3.93 g) which was chromatographed (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) on silica gel H previously moistened with 10% aqueous Na_2CO_3 and dried). The eluted material contained unchanged starting material, and after recrystallization from CH_2Cl_2, the epoxide **26** (9%), mp 255–258 °C (lit.[14a] mp 252–254 °C), was obtained: ^1H NMR (3.0 mg/0.3 mL) δ 4.67 (d, H_5), 4.93 (d, H_6), 7.45–8.12 (m, 6 H), 8.04 (s, H_8 and H_9), 8.39 (m, H_1), 8.80 (m, H_{13}), 9.59 (s, H_{14}), $J_{5,6}$ = 3.9 Hz; CIMS, m/e (relative intensity) 296 (M + 1, 100), 280 (38); UV (λ_{max} nm (ϵ)) 367 (8400), 350 (8000), 325 (21 300), 311 (18 600), 292 (23 600), 270 (35 800), 255 (28 300, sh), 225 (36 200).

6-Hydroxydibenz[a,j]acridine (27). A solution of the epoxide (**26**, 30 mg) in dioxane (40 mL) was treated with 25% acetic acid for 36 h at room temperature. The dioxane was removed by evaporation, and the solution was extracted with CH_2Cl_2. After drying, removal of the solvent afforded a solid, which on chromatography gave **27** (78%) and unchanged epoxide **26** (9%). **27** gave yellow needles from CH_2Cl_2/hexane, mp 222–225 °C: ^1H NMR (2.0 mg/0.5 mL) δ 7.45 (s, H_5), 7.60–8.04 (m, 6 H), 8.12 (s, H_8 and H_9), 8.85 (m, H_1 and H_{13}), 10.18 (s, H_{14}), $J_{1,5}$ = 0.3 Hz ($w_{1/2}$); CIMS, m/e (relative intensity) 296 (M + 1, 100); UV (λ_{max} nm (ϵ)) 403 (3600, sh), 383 (4400, sh), 351 (6600, sh), 324 (35 800, sh), 314 (36 900), 307 (36 100, sh), 297 (42 800), 257 (28 500), 247 (27 700, sh), 228 (52 100); high-resolution electron impact MS, m/e 295.0988 ($C_{21}H_{13}NO$ requires 295.0997).

3-Hydroxydibenz[a,j]acridine (37) and 4-Hydroxydibenz[a,j]acridine (36). During an attempted preparation of **11** from **9** (0.74 g) as previously described, the crude brominated intermediates were exposed to a moist acidic atmosphere overnight before the usual dehydrohalogenation. Chromatography (gradient, CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) gave 4-acetoxydibenz[a,j]acridine (**35**, 46 mg), **36** (180 mg), and a fraction which on preparative thin-layer chromatography (silica gel) gave further **36** (8 mg) and **37** (26 mg). Compound **35** afforded yellow needles (from EtOAc), mp 255–262 °C: ^1H NMR (5.0 mg/0.3 mL) δ 2.52 (s, 3 H), 7.45 (dd, H_3), 7.66–8.10 (m, 8 H), 8.78 (br dd, H_1), 8.89 (m, H_{13}), 10.14 (s, H_{14}), $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 7.8 Hz, $J_{1,3}$ = 1.0 Hz; CIMS, m/e (relative intensity) 338 (M + 1, 100), 337 (10), 296 (24); high-resolution electron impact MS, m/e 337.1097 ($C_{23}H_{15}NO_2$ requires 337.1102). Compound **36** gave yellow crystals from EtOAc, mp 287–298 °C dec: ^1H NMR (400 MHz, 4.7 mg/0.4 mL Me_2SO-d_6) δ 7.21 (d, H_3), 7.67 (t, H_2), 7.78 (t, H_{11}), 7.87 (dt, H_{12}), 7.95 (d, H_9), 8.05 (d, H_5), 8.11 (dd, H_{10}), 8.20 (d, H_6), 8.46 (d, H_8), 8.86 (d, H_1), 9.42 (d, H_{13}), 10.44 (br s, OH), 10.56 (s, H_{14}), $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 7.6, $J_{5,6}$ = $J_{8,9}$ = 9.1 Hz, $J_{10,11}$ = 7.6 Hz, $J_{11,12}$ = $J_{12,13}$ = 8.1 Hz, $J_{10,12}$ = 1.5 Hz; CIMS, m/e (relative intensity) 296 (M + 1, 100). Anal. Calcd for $C_{21}H_{13}NO$: C, 85.40; H, 4.44; N, 4.74. Found: C, 85.08; H, 4.16; N, 4.84. **37** recrystallized from EtOAc, mp 310–313 °C dec: ^1H NMR (1.0 mg/0.3 mL, Me_2SO-d_6) δ 7.30 (d, H_2), 7.38 (s, H_4), 7.63–8.25 (m, 7 H), 9.24 (d, H_1), 9.37 (d, H_{13}), 10.09 (s, H_{14}), 10.45 (s, OH), $J_{1,2}$ = 9.8 Hz; CIMS, m/e (relative intensity) 296 (M + 1, 100), 295 (8); high-resolution electron impact MS, m/e 295.0994 ($C_{21}H_{13}NO$ requires 295.0997).

Dibenz[a,j]acridine *N*-Oxide (33). The following data were not previously reported.[27] Compound **1** (0.50 g) and *m*-chloroperbenzoic acid (0.40 g) were refluxed in $CHCl_3$ (400 mL) for 5 h. The reaction mixture was extracted with 5% aqueous sodium bicarbonate and water, dried, and evaporated to afford a solid which was chromatographed (gradient, CH_2Cl_2 to EtOAc). Unchanged **1** (5%) and **33** (84%), mp 263–264 °C (lit.[29] mp 264–265 °C), as needles from EtOAc were obtained. Compound **33**: ^1H NMR (2.0 mg/0.3 mL) δ 8.87 (m, H_1 and H_{13}), 7.63–8.13 (m, 10 H), 9.67 (s, H_{14}); CIMS, m/e (relative intensity) 296 (M + 1, 85), 280 (100); UV (λ_{max} nm (ϵ)) 420 (5300), 400 (9700), 381 (10 100), 326 (7800, sh), 324 (53 400), 308 (34 100), 270 (17 700), 260 (16 100), 245 (18 400), 224 (52 300).

7*H*-Dibenz[a,j]acridone (34). Compound **33** (20 mg) was refluxed with acetic anhydride (15 mL) for 4 h under N_2. After evaporation to dryness under reduced pressure the product was recrystallized from glacial acetic acid to afford straw-colored needles of **34** (67%), mp 307–309 °C (lit.[19] mp 308–309 °C).

1,4-Dihydro-7-methylbenz[c]acridine (39). Method A. Sodium (0.47 g, 5 molar equiv) was added over 1 h to a stirred solution of 7-methylbenz[c]acridine[30] (**38**) (1.0 g) in anhydrous THF (25 mL), liquid NH_3 (80 mL), and EtOH (2.0 mL). After evaporation of the ammonia (18 h), the residue was partitioned between 20% NaCl and pentane/EtOAc (4:1) and the organic phase was worked up to give a yellow syrup. This was dissolved in AcOH (25 mL), and after 2 days of stirring at room temperature, the reaction mixture was diluted with water and NaOH (18 g) in H_2O (180 mL) added. The products were extracted with CH_2Cl_2 and separation by short column vacuum chromatography on silica gel H (gradient, pentane/CH_2Cl_2 1:1 to CH_2Cl_2) afforded **39** (0.67 g, 64%). Recrystallization from pentane gave yellow plates, mp 140–142 °C: ^1H NMR (9.3 mg/0.3 mL, $CDCl_3$) δ 3.02 (s, 3 H), 3.58 (m, 2 H_4), 4.10 (m, 2 H_1), 6.02 (m, H_3), 6.22 (m, H_2), 7.21 (d, H_5), 7.46–7.80 (m, H_8 and H_4), 7.98 (d, H_6), 8.12–8.26 (m, H_9 and H_{10}), $J_{2,3}$ = 10.0 Hz, $J_{5,6}$ = 9.0 Hz; CIMS, m/e (relative intensity) 246 (M + 1, 100), 245 (10), 244 (15). Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 87.92; H, 5.87; N, 5.85.

Method B. Sodium (0.38 g, 8 atomic equiv) was slowly added to a refluxing solution of **38** (0.50 g) in xylene (4.0 mL) and absolute EtOH (2.2 mL), and after it had dissolved, water was added to the cool solution. The product was isolated by toluene extraction, and after Na_2SO_4 drying and evaporation of the solvent the residue was refluxed in AcOH (25 mL) with chromium trioxide (138 mg) for 5 min. The cooled mixture was basified (aqueous NaOH) and the product again isolated with toluene. Chromatography (gradient, hexane/CH_2Cl_2 3:1 to CH_2Cl_2/EtOAc 49:1) gave **38** (20%), **39** (40%), and **40** (8%).

Isomerization of 1,4-Dihydro-7-methylbenz[c]acridine. Sodium (3 g) was dissolved in refluxing *tert*-butyl alcohol (500 mL), the hot solution was added to **39** (8.20 g), and the solution was refluxed under N_2 for 19 h. The mixture was poured into 20% aqueous NaCl, the organic phase was separated, and the aqueous phase was washed with EtOAc (2 × 100 mL). Workup of the combined organic phases afforded a dark brown syrup which, on repeated chromatography (gradient, pentane/CH_2Cl_2 2:1 to CH_2Cl_2/EtOAc 19:1) gave two useful fractions. The first (2.39 g) was 3,4-dihydro-7-methylbenz[c]acridine[9a] (**42**) containing a small amount of **38**, and the second (3.68 g) was 1,2-dihydro-7-methylbenz[c]acridine[9a] (**41**) containing traces of **39**, **40**, and **42**.

***trans*-2,3-Diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]acridine (45).** Under N_2 a solution of crude alkene **41** (3.68 g) in benzene (38 mL) was added to a benzene suspension (75 mL) of silver iodobenzoate prepared from iodine (3.81 g) and silver benzoate (7.56 g). After being stirred at room temperature for 15 min and refluxing for 2 h, the warm solution was filtered through Celite and EtOAc washings (150 mL) were added. The yellow solid which separated from solution was hydrolyzed, acetylated, and purified as previously described[9a] to afford **43** (2.71 g, 50% from the crude alkene), mp 169–170 °C (lit.[9a] mp 170–172 °C). The filtrate from which the yellow solid was separated was hydrolyzed with 5% aqueous NaOH in THF/MeOH[9a] and chromatographed (gradient, CH_2Cl_2/EtOAc 3:1 to EtOAc) to give fractions which were acetylated with acetic anhydride and pyridine. Purification by chromatography gave *trans*-1,2-diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]acridine (**44**, 38 mg, 0.7%), mp 198–205 °C (lit.[9a] mp 194–204 °C), and *trans*-2,3-diacetoxy-7-methyl-1,2,3,4-tetrahydrobenz[c]acridine (**45**, 0.47 g, 9%), mp 201–204 °C: ^1H NMR (400 MHz, 8.4 mg/0.4 mL, $CDCl_3$) δ 2.08 (s, 3 H), 2.11 (s, 3 H), 3.09 (s, 3 H), 3.11 (dd, H_4), 3.47 (dd, $H_{4'}$), 3.60 (dd, H_1), 4.10 (dd, $H_{1'}$), 5.41 (m, H_3), 5.53 (m, H_2), 7.24 (d, H_5), 7.54 (m, H_8), 7.75 (m, H_{11}), 8.08 (d, H_6), 8.23 (m, H_9 and H_{10}), $J_{1,1'}$ = 18.2 Hz, $J_{1,2}$ = 6.5 Hz, $J_{1',2}$ = 5.7 Hz, $J_{2,3}$ = 8.1 Hz, $J_{3,4}$ = 6.5 Hz, $J_{3,4'}$ = 5.5 Hz, $J_{4,4'}$ = 17.4 Hz, $J_{5,6}$ = 9.0 Hz; CIMS, m/e (relative intensity) 364 (M + 1, 100), 304 (16), 262 (1), 244 (9), 243 (4); high resolution electron impact MS, m/e 363.1452 ($C_{22}H_{21}NO_4$ requires 363.1470).

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Acknowledgment. Financial assistance for this was received from the N.H. and M.R.C. and the Australian Tobacco Research Foundation. A scholarship for C.A.R. was provided by the Pharmacy Research Trust of N.S.W. The assistance of Bruce Tattam and Peter Burden in the running of NMR and mass spectra and of Sandra Lothian for the preparation of this manuscript is gratefully acknowledged.

Hydroxyl-Directed Regioselective Monodemethylation of Polymethoxyarenes

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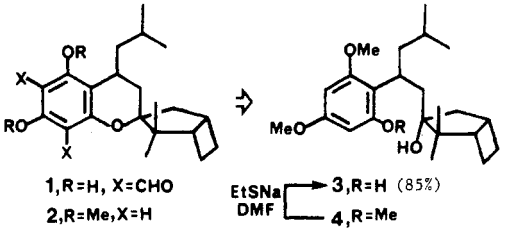
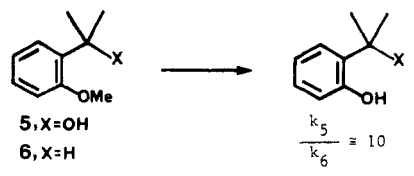
Received August 14, 1986

Methoxyl groups ortho to β-hydroxyethyl or γ-hydroxypropyl substituents in polymethoxybenzene derivatives were regioselectively demethylated with sodium thioethoxide in *N,N*-dimethylformamide. Methoxydihydrobenzofurans or methoxychromans were produced by cyclization of the monodemethylated β-hydroxyethyl or γ-hydroxypropyl derivatives, respectively.

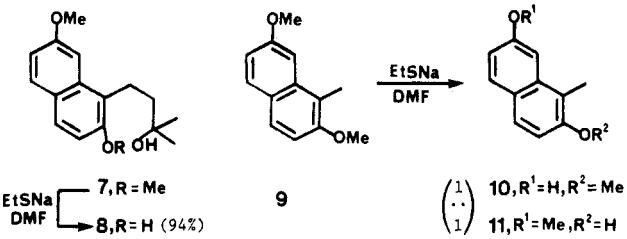
We recently achieved total syntheses of dialdehydes of structure **1**[1] which had been presumed[2] to correspond to robustadials, natural products isolated from *Eucalyptus robusta*. Our syntheses involved cyclization of phenol **3** to provide chroman intermediate **2**. Fortunately we found that monodemethylation of the trimethoxybenzene precursor **4** with sodium thioethoxide in *N,N*-dimethylformamide[3] was highly regioselective. Although a statistical



advantage of 66:33 for demethylation of a methoxyl ortho vs. para to the alkyl side chain could be anticipated, ortho demethylation product **4** was isolated in 85% yield. This favorable selectivity appeared to result from the regiodirecting influence of the remote hydroxyl group of the ortho hydroxyalkyl substituent. Previously, an ortho hydroxyalkyl substituent in **5** was shown to accelerate demethylation under these conditions by a factor of about 10 relative to demethylation of **6**.[4] Even more pertinent is the regioselective demethylation of dimethoxynaphthalene **7**



which produces **8** in 94% isolated yield.[5] The crucial role of the remote hydroxyl group in **7** was underscored by the demethylation of **9** under the same reaction conditions that nonselectively generates equal amounts of the isomeric mononaphthols **10** and **11**.[5] Since methyl ethers are important protecting groups,[6] a new general approach to regiocontrolled monodemethylation of polymethoxyarenes would be valuable for organic synthesis. We now report that such regiodirecting effects of remote hydroxyl groups are quite general.



Results and Discussion

Dimethoxybenzenes. The (polymethoxyaryl)alkanols **4** and **7** both incorporate tertiary hydroxyl groups appended to the arene ring by a three-carbon bridge. The (dimethoxyphenyl)alkanols **12d-14d** were prepared by reduction of the corresponding (dimethoxyphenyl)alkanoic acids with lithium aluminum hydride (see Experimental Section) to determine whether a primary hydroxyl group can exert a similar regiodirecting influence. In each case monodemethylation of these (dimethoxyphenyl)alkanols with sodium thioethoxide in *N,N*-dimethylformamide provided mixtures of monophenols in which demethylation of the methoxy group ortho to the alkanol substituent predominates. This regioselectivity was confirmed by conversion of each of the major demethylation products **12o-14o** into the corresponding cyclic ethers **12c-14c** by

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