held at 100 °C for 20 h. The product was worked up conventionally and chromatographed on Florisil eluted with benzene to furnish 1-methoxy-8-chlorobenzo[e]pyrene (**19b**, 1.7 g) as a white solid: NMR δ 4.0 (s, 3, OCH_3), 7.3–7.9 (m, 8, aromatic), 9.3–9.7 (m, 2, $H_{9,12}$).

A solution of **19b** (1.7 g) and *n*-butyllithium (20 mmol) in ether was heated at reflux for 30 min and then quenched with water to afford crude **20a**, 1.67 g (66%). Chromatography on a column of Florisil eluted with benzene followed by crystallization from benzene afforded pure **20a**: mp 206–208 °C; NMR δ 4.0 (s, 3, OCH_3), 7.4–8.2 (m, 8, aromatic), 8.55–8.9 (m, 2, $H_{8,9}$), 9.6–9.9 (m, 1, H_{12}).

1-Hydroxybenzo[e]pyrene (20b). A solution of ethanethiol (434 mg, 7 mmol) in dimethylformamide (1 mL) was added to a suspension of NaH (340 mg of a 50% oil dispersion) in DMF (1 mL) under N_2. The mixture was stirred for 5 min, **20a** (200 mg, 0.7 mmol) in DMF (1 mL) was added, and the solution was heated at reflux for 3 h. Conventional workup and passage through a column of Florisil eluted with benzene gave **20b**: 198 mg (99%); white solid; mp 180–181 °C (benzene); NMR, Table III.

2-Ethoxybenzo[e]pyrene (25a). A solution of benzanthrene (320 mg, 1.5 mmol), NaOMe (89 mg, 1.65 mmol), and 1,3-bis(dimethylamino)-2-ethoxytrimethinium perchlorate[15] (407 mg, 1.5 mmol) in pyridine (10 mL) was heated at 100 °C for 5 h under N_2. The pyridine was then replaced by quinoline (5 mL), and the solution was heated at reflux overnight. Conventional workup and passage through a column of Florisil eluted with benzene–hexane (1:1) gave **25a**: 142 mg (32%); white solid; mp 120–122 °C; NMR δ 1.5 (t, 3, CH_3), 4.2 (q, 2, CH_2), 7.4–8.1 (m, 7, aromatic), 8.22 (d, 1, H_1, $J_{1,3}$ = 2 Hz), 8.5–8.8 (m, 3, $H_{8,9,12}$).

2-Hydroxybenzo[e]pyrene (25b). Dealkylation of **25a** (140 mg, 0.47 mmol) was conducted by the procedure employed for the analogous reaction of **20a** to afford **25b**: 130 mg (99%); white solid; mp 229–230 °C (benzene); NMR, Table III.

2-Acetamidobenzo[e]pyrene (21). Potassium metal (98 mg, 2.5 mmol) and $FeCl_3$ (10 mg) were added to refluxing anhydrous liquid ammonia to generate KNH_2. Solid **1a** (166 mg, 0.5 mmol) was added to this solution over 15 min, and ether (50 mL) was added as a cosolvent. The deep red solution was stirred for 1 h, decomposed by addition of NH_4Cl, and worked up in the usual manner to afford crude 2-aminobenzo[e]pyrene (123 mg) as a yellow solid. Acetylation with acetic anhydride (10 mL) and pyridine (1 mL) gave **21** (150 mg) which was purified by chromatography on silica gel. Initial elution with benzene removed impurities (10 mg). Elution with $CHCl_3$ gave **21** (120 mg, 78%) contaminated with 6–7% (by HPLC) of an isomeric product, apparently 3-(AcNH)-BeP, which could not be removed by recrystallization. The analytical sample of **21** melted at 265–270 °C: NMR (Me_2SO-d_6, 270 MHz) δ 2.30 (s, 3, CH_3), 7.66 (m, 2, $H_{10,11}$), 7.88 (t, 1, H_7, $J_{6,7} = J_{7,8}$ = 8 Hz), 7.97 (d, 2, $H_{4,5}$, $J_{4,5}$ = 6.6 Hz), 8.11 (d, 1, H_6), 8.41 (s, 1, H_3), 8.58 (d, 1, H_8), 8.83 (m, 2, $H_{9,12}$), 8.99 (s, 1, H_1).

Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.49; H, 4.91; N, 4.51.

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Registry No. **1a**, 26105-52-2; **1b**, 77508-02-2; **2**, 77508-03-3; **3a**, 24909-10-2; **3b**, 66788-07-6; **4a**, 77508-04-4; **4b**, 28318-40-3; **5**, 68151-17-7; **5** β-hydroxy ester, 77508-05-5; *endo*-**6**, 77508-06-6; *exo*-**6**, 77508-07-7; **7**, 77508-08-8; **8a**, 77508-09-9; **8b**, 77508-10-2; **9**, 68151-08-6; **9** enol acetate, 77508-11-3; **10a**, 77508-12-4; **10b**, 77508-13-5; **14**, 77508-14-6; **15a**, 68151-11-1; **15b**, 77508-15-7; **16a**, 77508-16-8; **16b**, 77508-17-9; **17a**, 77508-18-0; **17b**, 77508-19-1; **17c**, 77508-20-4; **18**, 77508-21-5; **19a**, 77508-22-6; **19b**, 77508-23-7; **20a**, 77508-24-8; **20b**, 77508-25-9; **21**, 77508-26-0; **22**, 199-94-0; **23a**, 42784-01-0; **25a**, 77508-27-1; **25b**, 77508-28-2; BeP, 192-97-2; 2-aminobenzo[e]pyrene, 77508-29-3.

Synthesis of *trans*-3,4-Dihydroxy-3,4-dihydrobenz[a]- and -[c]acridines, Possible Proximate Carcinogenic Metabolites of Polycyclic Azaarenes

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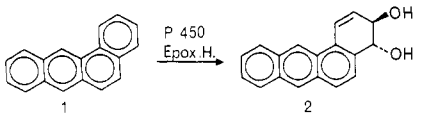
The vicinal *trans*-3,4-dihydro 3,4-diols of benz[a]- and -[c]acridine have been synthesized via modified Birch reduction of the parent heterocycles. Thus the pyridine moiety and the angular benzene ring could be reduced selectively. Controlled reoxidation re-formed the stable acridine part, leaving the angular ring partially hydrogenated. Isomerization of the isolated double bond led to 1,2-dihydrobenzacridines as key intermediates of the synthesis. Prêvost reaction, bromination, dehydrobromination, and hydrolysis of the 3,4-dihydrodioldiacetates in the angular ring did not interfere with the basic acridine moiety. This strategy has been applied to both series, i.e., benz[a]- and -[c]acridine. In some reaction steps the product ratio and total yield were strongly influenced by the position of nitrogen, indicating intrinsic differences in the chemical reactivity of the two systems. The new title compounds which have not been prepared previously are presumably the proximate carcinogenic metabolites of benzacridines. The benzacridines were chosen as model compounds of polycyclic azaarenes (PAA) which impose an increasing environmental risk with the industrial processing of synthetic fuel from shale and oil.

Studies with benz[a]anthracene (1), a model system for the carcinogenic polycyclic aromatic hydrocarbons (PAH), have clearly demonstrated that oxidative metabolism at the bay region (i.e., via the 3,4-dihydro diol 2) accounts



1 2

for its mutagenic and carcinogenic properties.[2] The carcinogenic polycyclic azaarenes (PAA) have not yet thoroughly been investigated in terms of their biological activity. Recently there has been renewed interest in this class of compounds as investigations of marine sediments

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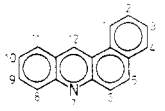
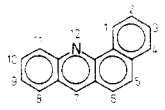
revealed that azaarenes are widely spread in the biosphere.[3] Environmental risk due to PAA may result from cigarette smoke, automotive exhausts,[4] or synthetic oil fractions.[5] In 1956 a comparative study of mono- and dibenzacridines showed a significant difference in carcinogenicity between the two series of [a]- and [c]acridines.[6] Generally, the [c] series where the nitrogen atom is located near the bay region of the polycycle was found to be more carcinogenic than the [a] series where nitrogen is far away from the bay region. A more recent report on skin painting and subcutanous injection tests with methylated benz[a]- and -[c]acridines fully confirmed those former results.[7] Of the two parent compounds, benz[a]acridine (**3a**) shows no carcinogenic effects whereas benz[c]acridine (**3c**) is reported to be a weak carcinogen.[8]

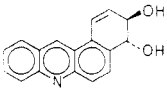


3a

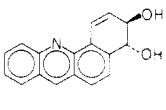


3c

In order to study the metabolic pathway of a carcinogen, one must first synthesize the postulated metabolites. Synthesis of the K-region oxides of dibenz- and methylbenzacridines and their biological testing revealed that these oxidation products are less mutagenic than the parent heterocycles.[9,10] These findings as well as theoretical calculations of reactivity indices of methylated benzacridines[11] point to a metabolic activation in the bay region of PAA. To test this hypothesis and to rationalize the relationship between carcinogenicity and the position of nitrogen in a given azaarene, we designed the synthesis of the *trans*-3,4-dihydro diols **12a** and **12c**, the possible



12a



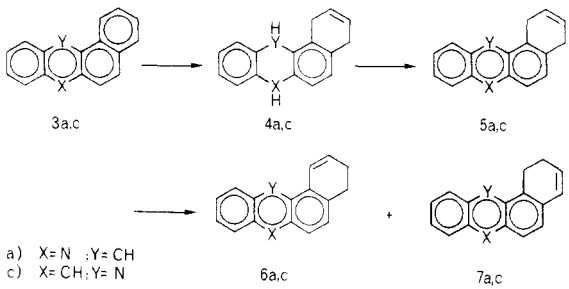
12c

proximate metabolites of both benz[a]- and -[c]acridines **3a** and **3c**. The presence of a heterocyclic moiety in these diols imposed a special difficulty on the synthetic strategy because of its sensitivity toward N-oxidation as well as reduction of the C=N bond.

Results and Discussion

A recently described method for the synthesis of 3,4-dihydro diols of PAA (e.g., **2**) involves bromination of the corresponding 3,4-quinone to a 1,2-dibromide followed by reduction of both bromo and keto functions with sodium borohydride.[12] In the benzacridine system, bromination

Scheme I



of the 3,4-quinone[13] only led to decomposition products, and direct reduction of the 3,4-quinone yielded polymerization products because of competing reduction and cross reaction of the C=N vs. the C=O functions.[13]

A quite different approach to the synthesis of diols **12a** and **12c** promised to be selective reduction of the parent heterocycles **3a** and **3c** which can be prepared by established procedures.[14,15] Partially hydrogenated aromatic systems are uniquely available by Birch reduction because of the specificity and selectivity of the method. This has been proven valid also for heterocyclic systems.[16]

For acridine, Li/NH_3 reduction in the presence of ethanol was reported to lead to 1,4,5,8-tetrahydroacridine whereas with NH_4OAc as proton donator the 9,10-dihydro product was obtained.[17] Therefore, we planned to direct the site of reduction so that the angular benzo ring became partially hydrogenated. For avoidance of any reduction in the linearly anellated benzo ring, the first step had to be reduction of the pyridine moiety. For the Li/NH_3 reduction of benz[a]- and -[c]acridines in the absence of ethanol we found that the pyridine moiety is reduced first, corresponding to the higher electron affinity of the C=N compared to the C=C bond:[18] addition of 2 equiv of lithium to the suspension of **3a** and **3c**, respectively, in liquid ammonia yielded the 7,12-dihydro aromatic amines which could be isolated by a common workup. To achieve reduction in the angular benzo ring, we reduced the dihydro compounds further with Li/NH_3 in the presence of methanol or ethanol to tetrahydrobenzacridines **4a** and **4c** in 40% and 50% yields, respectively (Scheme I). As with increasing amounts of lithium the molecules were reduced further, the reaction was stopped when the suspension turned from yellow to white.

On controlled reoxidation with equimolar amounts of *o*-chloranil at room temperature, the 1,4-dihydroacridines **5a** and **5c** could be obtained in 77% and 82% yields, respectively, without any dehydrogenation in the 1,4-position.

Isomerization of the isolated double bond should give the 1,2-dihydrobenzacridines **7a** and **7c**, the key intermediates in the synthesis of the 3,4-diols. The use of bis(benzonitrile)palladium dichloride as a catalyst[19] or Me_2SO/potassium *tert*-butylate[20] turned out to be unsuccessful, but isomerization proceeded smoothly when sodium ethoxide in refluxing ethanol was used (Scheme I). In the benz[a]acridine series **6a** and **7a** were obtained

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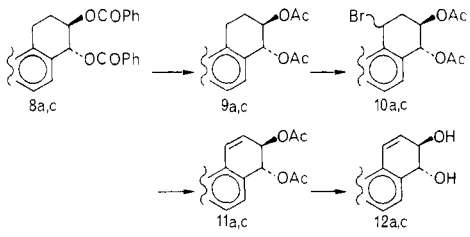
Scheme II



in a 2:3 ratio with a total yield of 55% for the desired 1,2-dihydro derivative **7a**. Separation of the isomers at this stage was not possible but could be achieved after the next step, i.e., by chromatography of the 1,2- and 3,4-dihydroxydibenzoates. In the benz[c]acridine series the desired isomer **7c** was formed predominantly (90%) and was characterized by spectroscopic means and by its melting point. At this step a remarkable difference in chemical reactivity between the [a] and [c] series of benzacridines is observed. While in both dihydrobenzacridines **5a** and **5c** position 4 is sterically favored vs. position 1 with respect to the ethoxide attack, resulting in a **7**/**6** ratio $\gg 1$, we can at present only speculate on the predominant formation of **7c** in the [c] series. Since the size of the nitrogen lone pair is comparable to the C–H bond, a steric effect of nitrogen at position 12 cannot account for the difference in the isomerization ratio. It seems reasonable, however, to assume that due to the "neighboring" nitrogen atom the C_1 anion of **5c** is thermodynamically less stable than the corresponding anion at C_4. Nevertheless, the observed regioselectivity caused by a neighboring nitrogen function indicates a considerable difference in chemical reactivity between the [a] and [c] series of PAA in general.

Having prepared the key intermediates **7a** and **7c**, we synthesized the title compounds according to a common procedure: Prévost reaction at the double bond, bromination, dehydrobromination, and finally hydrolysis of the ester bonds (Scheme II).

Compounds **7a** (together with **6a**) and **7c** were converted to *trans*-tetrahydro diol dibenzoates via Prévost reaction with silver benzoate and iodine in benzene in 40% yield. The dibenzoates were hydrolyzed with alkali in methanolic THF, and the resulting diols were acetylated with acetic anhydride/pyridine with 4-(dimethylamino)pyridine[21] as catalyst in 85% and 60% yields, respectively. Direct formation of the *trans*-diacetates **9a,c** was not successful.

To introduce the double bond in 1,2-position, we brominated the benzylic carbon atom with *N*-bromosuccinimide in refluxing carbon tetrachloride. In both cases two stereoisomeric bromides were formed. According to their proton nuclear magnetic resonance spectra, the major isomer of the bromides possesses the same relative stereochemistry as described for the benz[a]anthracene system[22] where the benzylic ester group and the bromine atom are cis.

The mixture of isomeric bromides **10a**, **10a′** and **10c**, **10c′**, respectively, was thermally dehydrobrominated in boiling xylene in the presence of $NaHCO_3$. Because of the interfering basicities of substrate and reagent, use of DBN is not recommended here. The total yield of the resulting dihydro diol diacetates **11a** and **11c** from tetrahydrodiacetates was 50% and 35%, respectively.

Conversion of **11a** and **11c** to the corresponding dihydro diols was readily achieved with dry ammonia in methanolic THF. Smooth reaction conditions were necessary because otherwise the products were degraded considerably. Compounds **12a** and **12c**, obtained in 95% and 85% yields, respectively, were purified by preparative TLC. The yellow solids decompose at 260 (**12a**) and 201 °C (**12c**). The spectroscopic data (see below) confirm the structure, and combustion analyses of the diols were obtained via their diacetates **11**.

The ^1H NMR data of the diols **12a** and **12c** are listed below. Chemical shifts are reported in parts per million (δ) and coupling constants in hertz; H-1 was determined by double resonance. For **12a** (Me_2SO-d_6, D_2O): 9.60 (s, 1 H, H-12), 7.5 (d, 1 H, H-1), 7.4–8.3 (m, 6 H, H-5, 6.8–11), 6.40 (dd, 1 H, H-2), 4.85 (m, 1 H, H-4), 4.45 (m, 1 H, H-3); $J_{1,2} = 10.2$, $J_{2,3} = 2.7$, $J_{3,4} = 10.8$. For **12c** (Me_2SO-d_6, D_2O): 9.13 (s, 1 H, H-7), 7.9 (d, 1 H, H-1), 7.4–8.3 (m, 6 H, H-5,6,8–11), 6.28 (dd, 1 H, H-2), 4.89 (m, 1 H, H-4), 4.50 (m, 1 H, H-3); $J_{1,2} = 9.9$, $J_{2,3} = 2.7$, $J_{3,4} = 10.2$. On comparison of the [a] and [c] series, the chemical shifts of the protons in the angular ring show a remarkable similarity. The coupling constants have comparable values in both series, indicating only a minor conformational disturbance caused by the nitrogen atom ($\Delta J_{3,4} = 0.6$ Hz). Moreover, there are close similarities with the data reported for 3,4-dihydrobenz[a]anthracene-3,4-diol (**2**)[22] with the typical downfield shift of the proton in the bay region (H-1). An additional downfield shift of H-1 is caused by the anisotropy effect of the C=N bond in the benz[c]acridine system, which is also known for the parent heterocycles **3a** and **3b**.

The ultraviolet spectra of diacetates and diols in the two series are very similar. Qualitative differences with the carbocyclic analogue like the higher absorption of the L_b band at higher wavelength correspond to general differences observed between the UV spectra of PAH and PAA. The title diols constitute the first 3,4-diols of benz[a]- and -[c]acridines. Testing the biological activity of these isomeric dihydro diols **12a** and **12c** will certainly disclose differences in the metabolic pathways of the two systems as compared to each other as well as in relation to the hydrocarbon analogue. Comparison of the [a] and [c] series of PAA in terms of their chemical as well as biological reactivity will thus allow new insight into structure–activity relations and enzyme–substrate interactions.

Experimental Section

Ultraviolet spectra were recorded on a Beckman 25 spectrophotometer; values are given as λ_{max} values in nanometers with ϵ values in parentheses. Proton magnetic resonance spectra were recorded on a Varian EM 390, 90-MHz spectrometer. 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 tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 283 spectrometer (values recorded in reciprocal centimeters) and mass spectra on a Finnigan 3200.

1,4,7,12-Tetrahydrobenz[a]acridine (4a). A solution of benz[a]acridine **3a**[14] (6.9 g, 0.03 mol) in anhydrous THF (100 mL) was added slowly to vigorously stirred liquid ammonia (1.5 L). Lithium (420 mg, 0.06 mol) was added in small pieces. The mixture was refluxed for 20 min, until the color changed from dark blue to yellow. Methanol (10 mL) was added, followed by lithium (1 g, 0.14 mol), until the reaction mixture appeared white. After evaporation of the ammonia, the residue was suspended in water (200 mL), and the aqueous phase was extracted with 200-mL portions of ether (600 mL). The etheral solution was washed with water, dried ($MgSO_4$), filtered, and concentrated. The resulting solid was recrystallized from methylene chloride/pentane to give **4a**: 2.9 g (42%); colorless plates; mp 171 °C; ^1H NMR 6.4–7.2 (m, 6 H), 5.9 (s, 2 H, H-2,3), 5.75 (s, 1 H, NH), 3.95 (s, 2 H, H-12), 3.3 (s, 4 H, H-1,4); IR (KBr) 3382 (NH); UV

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(dioxane) 292 (14 800); mass spectrum, m/e 233 (M^+).

1,4-Dihydrobenz[*a*]acridine (5a). 1,4,7,12-Tetrahydrobenz[*a*]acridine (**4a**; 2.33 g, 0.01 mol) was dissolved in anhydrous THF (200 mL), and a solution of *o*-chloranil (2.7 g, 0.011 mol) in THF (50 mL) was added. After 30 min, ethyl acetate (100 mL) was added, and the mixture was washed with 5% aqueous KOH and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated to 30 mL. The solution was filtered on alumina (short column) to give **5a**: 1.8 g (77%); pale yellow needles; mp 135 °C (after recrystallization from ether); ^1H NMR 8.8 (s, 1 H, H-12), 7.4–8.4 (m, 6 H), 6.1 (s, 2 H, H-2,3), 3.4–3.9 (m, 4 H, H-1,4); UV (dioxane) 258 (123 000), 357 (8500), 380 (3900). Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 87.75; H, 5.74; N, 6.13.

Isomerization of 1,4-Dihydrobenz[*a*]acridine (5a). Sodium (2.3 g, 0.1 mol) was dissolved in anhydrous ethanol (400 mL) (N_2 atmosphere). Compound **5a** (1.2 g, 5 mmol) was added, and the solution was refluxed for 7 h. After evaporation of the solvent (350 mL) water (250 mL) was added, and the aqueous phase was extracted with ether (500 mL). The ethereal layer was washed with water, dried ($MgSO_4$), filtered, and concentrated, leaving a mixture of the isomers **6a** and **7a** (1.1 g, 90%; ratio 2:3).

***trans*-3,4-Bis(benzoyloxy)-1,2,3,4-tetrahydrobenz[*a*]acridine (8a).** Silver benzoate (2.52 g, 0.011 mol) and iodine (1.28 g, 5 mmol) were added to dry benzene (20 mL). The mixture of isomers **6a** and **7a** (1.1 g, 5 mmol) was added, and the reaction mixture was stirred at 25 °C for 15 min and refluxed for 2 h. After addition of ethyl acetate (300 mL) the solution was filtered and washed with a saturated aqueous solution of $Na_2S_2O_3$ and with water (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to leave a solid (2 g, 87%) that was column chromatographed on silica gel with ethyl acetate/hexane (1:2). The 3,4-dibenzoate **8a** was eluted first. It forms pale yellow needles: 0.97 g (41%); mp 180 °C (after recrystallization from ethyl acetate/hexane); ^1H NMR 8.95 (s, 1 H, H-12), 7.3–8.4 (m, 16 H), 6.8 (d, 1 H, H-4), 5.6–5.9 (m, 1 H, H-3), 3.5 (t, 2 H, H-1), 2.4–2.8 (m, 2 H, H-2); $J_{3,4}$ = 6; IR (KBr) 1725 (C=O), 1277 (CO); UV (dioxane) 258 (174 000), 343 (7400), 360 (10 000), 380 (3700). Anal. Calcd for $C_{31}H_{23}NO_4$: C, 78.63; H, 4.90; N, 2.96. Found: C, 79.0; H, 4.92; N, 3.02.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrobenz[*a*]acridine (9a).** Dibenzoate **8a** (1.4 g, 3 mmol) was dissolved in THF (70 mL) and methanol (130 mL). A constant stream of N_2 was passed through the solution. A 1 N NaOH (24 mL) solution was added. After a few minutes a white solid separated. The mixture was stirred for 3 h at 25 °C. THF and methanol were removed under reduced pressure, leaving a yellow solid that was washed with water (50 mL), isolated by suction filtration, and washed once more with water. The tetrahydro diol thus obtained was dried in vacuo and added to a mixture of acetic anhydride (26 mL), pyridine (6 mL), and 10 mg of 4-(dimethylamino)pyridine.[21] The solution was stirred at 25 °C overnight. Ethyl acetate was added, and the solution was extracted with saturated $NaHCO_3$ (3 × 50 mL) and water (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to leave a yellow solid that was recrystallized from ethyl acetate/hexane. The pale yellow needles of **9a** (0.9 g, 85%) had the following: mp 181 °C; ^1H NMR 8.9 (s, 1 H, H-12), 7.5–8.3 (m, 6 H), 6.35 (d, 1 H, H-4), 5.2–5.5 (m, 1 H, H-3), 3.35 (t, 2 H, H-1), 2.1–2.5 (m, 2 H, H-2), 2.15 (s, 3 H, Me), 2.05 (s, 3 H, Me); $J_{3,4}$ = 5.5; IR (KBr) 1727 (C=O), 1250 (CO); UV (dioxane) 257 (182 000), 343 (7800), 358 (11 000), 380 (3900). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.25; H, 5.48; N, 4.10.

***trans*-3,4-Diacetoxy-3,4-dihydrobenz[*a*]acridine (11a).** A mixture of CCl_4 (20 mL), *N*-bromosuccinimide (98 mg, 0.55 mmol), **9a** (175 mg, 0.5 mmol), and α,α'-azobis(isobutyrodinitrile) (5 mg) was refluxed for 15 min while a stream of N_2 was passed through the solution. The completion of the reaction was checked by TLC (silica gel). The mixture was cooled (−20 °C) and filtered, the residue was washed, and CCl_4 was removed under reduced pressure to leave a yellow solid (isomeric mixture of bromides). Crystallization from ether/pentane forms yellow crystals: 182 mg (85%); dec at 155 °C. ^1H NMR (main isomer) 9.15 (s, 1 H, H-12), 7.4–8.4 (m, 6 H), 6.15 (t, 1 H, H-1), 6.6 (d, 1 H, H-4), 5.9 (m, 1 H, H-3), 2.5–3.2 (m, 2 H, H-2), 2.3 (s, 3 H, Me), 2.1 (s, 3 H, Me); $J_{3,4}$ = 8.6; ^1H NMR (minor isomer) 9.30 (s, 1 H, H-12), 7.4–8.4 (m, 6 H), 6.35 (d, 1 H, H-4), 6.2 (m, 1 H, H-1), 5.45 (m, 1 H, H-3), 2.5–3.2 (m, 2 H, H-2), 2.3 (s, 3 H, Me), 2.1 (s, 3 H, Me); $J_{3,4}$ = 2.5; mass spectrum, m/e 427/429 (M^+).

The crude mixture of bromides **10a** was added to a suspension of $NaHCO_3$ (2 g) in dry xylol (80 mL). The reaction mixture was refluxed for 15 min, cooled, and filtered. The filtrate was concentrated and column chromatographed on silica gel with ethyl acetate/hexane (1:1). The yellow fluorescent fraction yielded the diacetate **11a**: 86 mg (50% from **9a**); yellow needles; mp 168 °C (after recrystallization from ethyl acetate/hexane); ^1H NMR 9.05 (s, 1 H, H-11), 7.55 (d, 1 H, H-1), 7.4–8.3 (m, 6 H), 6.39 (d, 1 H, H-4), 6.33 (m, 1 H, H-2), 5.75 (t, 1 H, H-3); $J_{1,2}$ = 10.2, $J_{2,3}$ = 4.2, $J_{3,4}$ = 6.0; IR (KBr) 1743 (C=O), 1254 (CO); UV (dioxane) 260 (91 200), 350 (6500), 365 (10 700), 382 (7250), 402 (5400). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.66; H, 4.87; N, 4.01.

***trans*-3,4-Dihydroxy-3,4-dihydrobenz[*a*]acridine (12a).** A stream of dry ammonia was passed through the solution of diacetate **11a** (170 mg, 0.5 mmol) in THF (25 mL) and methanol (10 mL) for 30 min. The solution was stirred for an additional 16 h at 25 °C. Ethyl acetate (150 mL) was added, and the mixture was extracted with 5% NaOH and water (2 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and filtered. Evaporation of the solvent left a yellow brown solid that was purified by preparative TLC (silica gel; ethyl acetate/acetone, 1:1). The yellow dihydro diol **12a** (125 mg, 95%) decomposes at 260 °C: ^1H NMR (see Results and Discussion); IR (KBr) 2600–3600 (OH), 1070 (CO); UV (dioxane) 260 (79 000), 332 (2900, sh), 350 (4900), 366 (7400), 388 (4550), 406 (3400, sh); mass spectrum, m/e 263 (M^+). Compound **12a** could be retransformed to **11a** via acetylation.

1,4,7,12-Tetrahydrobenz[*c*]acridine (4c). The reduction of benz[*c*]acridine **3c**[15] (6.9 g, 0.03 mol) was effected as described for the preparation of **4a**. The crude product was recrystallized from ether/pentane to give **4c**: 3.4 g (50%); colorless plates; mp 125 °C; ^1H NMR 6.5–7.2 (m, 6 H), 5.9 (s, 2 H, H-2,3), 5.75 (s, 1 H, NH), 4.0 (s, 2 H, H-7), 2.9–3.4 (m, 4 H, H-1,4); IR (KBr) 3439 (NH); UV (dioxane) 292 (13 500); mass spectrum, m/e 233 (M^+).

1,4-Dihydrobenz[*c*]acridine (5c). Compound **4c** was oxidized with *o*-chloranil under the same conditions as described for **5a**. Recrystallization from hexane gave **5c**: 1.9 g (82%); yellow needles; mp 109 °C; ^1H NMR 8.7 (s, 1 H, H-7), 8.3 (d, 1 H, H-11), 7.2–8.1 (m, 5 H), 5.9–6.4 (m, 2 H, H-2,3), 3.9–4.2 (m, 2 H, H-1), 3.4–3.7 (m, 2 H, H-4); UV (dioxane) 257 (112 000), 286 (5400), 348 (6800), 357 (8000), 383 (3300). Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.25; H, 5.88; N, 6.01.

1,2-Dihydrobenz[*c*]acridine (7c). The isomerization of **5c** (1.2 g, 5 mmol) was achieved in refluxing ethanol as described for **7a** except that a reaction time of 24 h was applied. The workup led to a yellow oil that consisted mainly of **7c** (1.1 g, 90%) together with some benz[*c*]acridine. After recrystallization from ethyl acetate/hexane it was obtained as yellow rhombic crystals: mp 78 °C; ^1H NMR 8.5 (s, 1 H, H-7), 8.25 (d, 1 H, H-11), 7.1–7.4 (m, 5 H), 6.6 (d, 1 H, H-4), 6.1–6.4 (dt, 1 H, H-3), 3.6 (t, 2 H, H-1), 2.3–2.7 (m, 2 H, H-2); $J_{3,4}$ = 9.6; UV (dioxane) 242 (35 800), 257 (41 700), 272 (37 300), 279 (51 500), 289 (45 000), 358 (5400, sh), 364 (5700), 376 (6100), 384 (5900), 408 (2900, sh).

***trans*-3,4-Bis(benzoyloxy)-1,2,3,4-tetrahydrobenz[*c*]acridine (8c).** The Prévost reaction with **7c** (1.1 g, 5 mmol) to the *trans*-dibenzoate was achieved as described for **8a**. Recrystallization of the crude product from EtOAc/hexane gave **8c**: 0.9 g (40%); mp 190 °C; ^1H NMR 8.75 (s, 1 H, H-7), 7.3–8.4 (m, 16 H), 6.8 (d, 1 H, H-4), 5.7–5.9 (m, 1 H, H-3), 3.85 (t, 2 H, H-1), 2.2–2.7 (m, 2 H, H-2); $J_{3,4}$ = 6.3; IR (KBr) 1724 (C=O), 1276 (CO); UV (dioxane) 258 (183 000), 342 (7550), 358 (10 200), 379 (3600); mass spectrum, m/e 473 (M^+). Anal. Calcd for $C_{31}H_{23}NO_4$: C, 78.63; H, 4.90; N, 2.96. Found: C, 78.63; H, 4.86; N, 3.10.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (9c).** The conversion of the dibenzoate **8c** (1.4 g, 3 mmol) to the diacetate **9c** was effected as described for **9a**. The crude product was recrystallized from ethyl acetate/hexane, leaving **9c**: 0.62 g (60%); yellow needles; mp 126 °C; ^1H NMR 8.7 (s, 1 H, H-7), 8.3 (d, 1 H, H-11), 7.2–8.1 (m, 5 H), 6.3 (d, 1 H, H-4), 5.25–5.4 (m, 1 H, H-3), 3.6 (t, 2 H, H-1), 2.2–2.4 (m, 2 H, H-2), 2.18 (s, 3 H, Me), 2.07 (s, 3 H, Me); $J_{3,4}$ = 5.4; IR (KBr) 1745 (C=O), 1249 (CO); UV (dioxane) 257 (183 000), 341 (7400), 357 (10 300), 379 (4000). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01.

Found: C, 72.19; H, 5.54; N, 4.09.

***trans*-3,4-Diacetoxy-3,4-dihydrobenz[*c*]acridine (11c).** The reaction of **9c** (175 mg, 0.5 mmol) with NBS in CCl_4 was effected as described for **10a**. The isomeric bromides **10c** and **10c'** were obtained in the ratio 2:1: ^1H NMR (major isomer) 8.6 (s, 1 H, H-7), 8.3 (d, 1 H, H-11), 7.1–8.0 (m, 5 H), 6.85 (t, 1 H, H-1), 6.5 (d, 1 H, H-4), 5.95–6.3 (m, 1 H, H-3), 2.5–3.1 (m, 2 H, H-2), 2.25 (s, 3 H, Me), 2.1 (s, 3 H, Me); $J_{3,4}$ = 8.4; ^1H NMR (minor isomer) 8.6 (s, 1 H, H-7), 8.3 (d, 1 H, H-11), 7.1–8.0 (m, 5 H), 6.85 (t, 1 H, H-1), 6.35 (d, 1 H, H-4), 5.4 (m, 1 H, H-3), 2.5–3.1 (m, 2 H, H-2), 2.25 (s, 3 H, Me), 2.1 (s, 3 H, Me); $J_{3,4}$ = 3.

Dehydrobromination of **10c** was performed as described for **11a** except that a reaction time of 1 h was suitable. The dihydrodiacetate **11c** (60 mg, 35% from **9c**) forms yellow fluorescent needles: mp 167 °C (after recrystallization from ethyl acetate/hexane); ^1H NMR 8.67 (s, 1 H, H-7), 8.35 (d, 1 H, H-1), 8.25 (d, 1 H, H-11), 7.4–8.0 (m, 5 H), 6.4 (d, 1 H, H-4), 6.32 (dd, 1 H, H-2), 5.80 (t, 1 H, H-3); $J_{1,2}$ = 9.9, $J_{2,3}$ = 4.2, $J_{3,4}$ = 6.3; IR (KBr) 1734 (C=O), 1222 (CO); UV (dioxane) 260 (130 000), 333 (5800, sh), 347 (6300), 366 (10 600), 385 (6800), 403 (5100, sh). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.37; H, 5.03; N, 3.98.

***trans*-3,4-Dihydroxy-3,4-dihydrobenz[*c*]acridine (12c).** The hydrolysis of dihydro diol diacetate **11c** (250 mg, 0.7 mmol) was effected as described for the preparation of **12a**. Purification of **12c** by column chromatography with ethyl acetate (silica gel) gave **12c** as a yellow solid: mp 201 °C; 155 mg (85%); ^1H NMR (see Results and Discussion); IR (KBr) 3000–3500 (OH), 1090 (CO); UV (dioxane) 261 (94 000), 333 (2600, sh), 348 (5550), 365 (9400), 393 (5300), 415 (3700, sh); mass spectrum, *m/e* 263 (M^+). Compound **12c** could be retransformed to **11c** via acetylation.

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Registry No. 3a, 225-11-6; **3c**, 225-51-4; **4a**, 77305-60-3; **4c**, 77305-61-4; **5a**, 77305-62-5; **5c**, 77305-63-6; **6a**, 77305-64-7; **7a**, 77305-65-8; 7c, 77305-66-9; **8a**, 77305-67-0; **8a** tetrahydrodiol, 77305-77-2; **8c**, 77305-68-1; **9a**, 77305-69-2; **9c**, 77305-70-5; **10a**, 77305-71-6; **10a'**, 77397-57-0; **10c**, 77305-72-7; **10c'**, 77397-58-1; **11a**, 77305-73-8; **11c**, 77305-74-9; **12a**, 77305-75-0; **12c**, 77305-76-1.

Synthesis of Enamides and Amides by Hydrozirconation–Acylation of Schiff Bases

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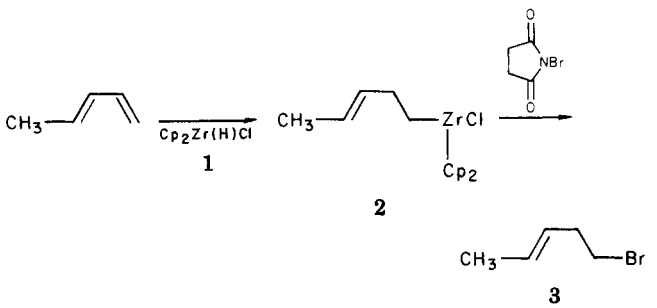
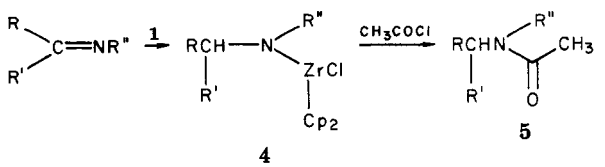
Schiff bases containing α-hydrogens react with hydridochlorodicyclopentadienylzirconium and then with acetyl or methyl oxalyl chloride to give enamides and imides or amides as products. Schiff bases derived from 2-methylcyclohexanone react with high regioselectivity, the thermodynamically more stable enamide being formed as the major or only unsaturated amide.

The hydrozirconation of olefins and dienes by hydridochlorodicyclopentadienylzirconium (1) is a useful reaction in organic chemistry.[2,3] Cleavage of the organozirconium intermediate, such as **2**, by electrophilic (e.g., *N*-bromosuccinimide) and other reagents can afford organic products not readily available by other methods (e.g., **3**).

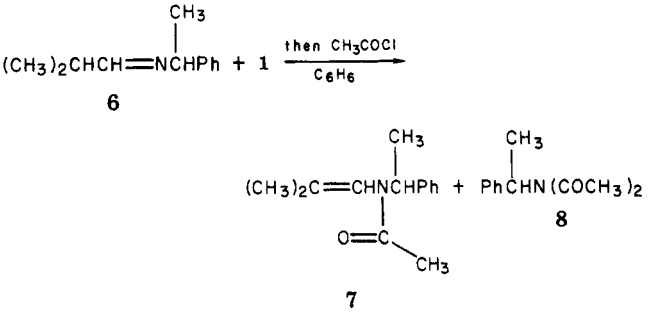


It seemed conceivable to us that Schiff bases would undergo hydrozirconation to give zirconium complexes of structural type **4** and that treatment of the latter with acid halides would afford amides such as **5**. We how report the results of this investigation.



Results and Discussion

We were surprised to observe that no reaction occurred between *N*-benzylidenemethylamine ($PhCH{=}NCH_3$) and the zirconium reagent **1** in benzene at room temperature, either in the presence or absence of an acid chloride. Reaction did take place, however, if the Schiff base function contained α-hydrogens. For example, treatment of imine **6** (derived from 2-methylpropanal and α-phenethylamine) first with **1** in benzene and then with acetyl chloride afforded the enamide **7** in 30% yield and the imide **8** in 20% yield. If one effected the reaction by first



treating **6** with acetyl chloride and then with **1**, **7** was obtained in 25% yield and α-phenethylacetamide (**9**) in 10% yield, but **8** was not detected. Enamides have been synthesized by exposure of imines to an acid chloride and triethylamine,[4] raising the possibility that the zirconium reagent is functioning in the same manner as triethylamine. However, the enamide **7** was obtained as the sole product

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