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On the Regioselectivity in Transformation of Benzo[*a*]pyrene 4,5-Oxide and 3-Methylcholanthrene 11,12-Oxide to the Corresponding β-Amino-Alcohol Derivatives

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Dedicated to Professor Amazya Y. Meyer who died untimely at the peak of his career

Abstract: β-Amino-alcohol derivatives of benzo[*a*]pyrene and 3-methylcholanthrene, **8**, **9** and **15** which are assumed to take part in the transformation of the K-region oxides **1** and **10** to the corresponding arene imines, have been prepared. The sequence of reactions consists of nucleophilic oxirane ring opening of the epoxides by azide ion, acetylation of the separated isomeric *trans*-azido alcohols so formed, and palladium catalyzed hydrogenation of the resulting β-acetyloxy azides under ambient conditions. The ratios between the isomeric azido-hydrins obtained from **1** and **10**, as well as the product distribution in azide-induced oxirane ring cleavage in other carbocyclic and heterocyclic arene oxides have been shown to correlate with Hückel-type calculations of Wheland's π-localization energies.

Arene oxides are primary metabolites of polycyclic aromatic hydrocarbons, capable of reacting *in vivo* with cellular nitrogen nucleophiles to give derivatives of amino-alcohols.[1] Since some β-amino-alcohols can be converted into carcinogenic azridines by sulfotransferases[2,3] we assume that one possible route to chemical carcinogenesis involves the transformation of arene oxides to arene imines *via* amino-alcohol derivatives.[4] Biological studies have already revealed that K-region imines of many aromatic polycyclics possess exceedingly high mutagenic potencies[5,6] which correlate with the mutagenicities of the corresponding arene oxides.[5] Furthermore, while sterically unhindered arene oxides (e.g. K-region epoxides) are readily detoxified in the presence of microsomal and cytosolic epoxide hydrolases, the respective arene imines are unaffected by cellular enzymes.[5] Consequently, imine analogues of some biologically inactive arene oxide are highly mutagenic.

In spite of these observations the theory on transformation of polycyclic arene oxides to the respective imines *via* amino-alcohol intermediates could not be verified because of lack of suitable standards and reference compounds. Although numerous studies have been conducted on the identification of the adducts of polycyclic epoxides to DNA components,[7] only a few stable ß-amino-alcohol derivatives of carcinogenic polyarenes have been prepared so far.[6,8,9] Therefore, we found it imperative to synthesize polycyclic amino-alcohols that may serve as biological markers in experiments on transformation of arene oxides to arene imines. In this paper we describe the preparation of β–amino-alcohols derived from the classical carcinogens benzo[*a*]pyrene and 3-methylcholanthrene. In addition, we report a simple theoretical method of general

utility for predicting the regioselectivity in the nucleophilic oxirane ring opening of 3b,4a-dihydrobenzo[1,2]pyreno[4,5-*b*]oxirene (benzo[*a*]pyrene 4,5-oxide (**1**)) and of 1a,10,11,11c-tetrahydro-3-methylbenz[7,8]aceanthryleno[9,10-*b*]oxirene (3-methylcholanthrene 11,12-oxide (**8**)) from which our amino-alcohols have been prepared.

RESULTS AND DISCUSSION

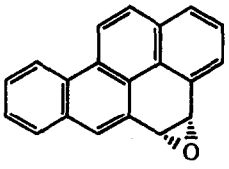
As shown previously,[10] the reaction of the K-region oxide of benzo[*a*]pyrene, **1** with N_3^- gives equal amounts of the two *trans*-azido-alcohols **2** and **3**. This isomer distribution is in accord with the predictions based on the MO calculations,[11-13] and resembles the results obtained in the reactions of **1** with other nucleophiles.[11,13] While only partial separation of **2** and **3** had been accomplished in the past by fractional crystallization,[10] preparative HPLC has now permitted complete separation and identification of the two isomers.

Since we have already found that neither the model *trans*-10-amino-9,10-dihydro-9-phenanthrenol (**17**)[14] nor its *N*-acetyl-derivative **18** is mutagenic in *Salmonella tiphimurium*, but the acetyloxy compound **19** *is* biologically active,[15] we found it of interest to convert **2** and **3** into the O-acetylated amino-alcohols **8** and **9** rather than into the free amino-alcohols **4** and **5**. Each of the azido-alcohols was acetylated and the acetates **6** and **7**, so formed were hydrogenated in the presence of palladium on carbon in tetrahydrofuran and ethyl acetate.[9] The acetates **8** and **9** had to be prepared close to their use in biological tests owing to their tendency to rearrange upon storage to the corresponding *N*-acetyl compounds.

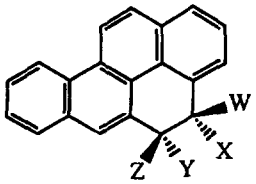
The reaction of the K-oxide of 3-methylcholanthrene **10**[16] with N_3^- was shown previously to give one of the possible *trans*-azido-alcohols in a large excess.[17] This azido-hydrin which has now been separated from the minor isomer by column chromatography, was assumed to be **12** on account of earlier predictions.[12] Since new calculations suggested that the major product in the nucleophilic ring opening of **10** is *trans*-12-azido-1,2,11,12-tetrahydro-3-methyl-11-benz[*j*]aceanthrylenol (**11**) (*vide infra*), we subjected its acetate ester **14** to X-ray diffraction analysis which indeed revealed that our earlier assignment was incorrect. An ORTEP drawing of **14** is shown in Figure 1.[18] Lithium aluminium hydride reduction of **11** afforded the free ß-amino-alcohol **13** and palladium catalyzed hydrogenation of the acetate **14** gave *trans*-11-acetyloxy-1,2,11,12-tetrahydro-3-methyl-12-benz[*j*]aceanthrylenamine (**15**).

Since the previous MO theoretical predictions for oxirane ring opening by nucleophiles,[11,12] based on the perturbational method of Dewar[19] had proven inapplicable to **10**, we performed Hückel calculations based on Wheland's seminal work.[20,21] Following our original work[21], the central assumption of the model is that the transition state to nucleophilic attack involves advanced ring opening, and may therefore be modeled by the corresponding carbonium ions shown in ***a*** and ***b*** for the ring opening of **10** (see Scheme 1). The Hückel models of ***a*** and ***b*** are the corresponding ***a'*** and ***b'***. In accord with this assumption, the more stable carbonium ion will determine the preferred regio-isomer of the nucleophilic ring opening shown in ***c*** or ***d***. The second assumption[21] is that the relative stability of the carbonium ions, and hence also the preferred regioselectivity, are given by the corresponding Hückel energy difference. In spite of the many assumptions involved in the Hückel theory and in the modeling of the transition state, the model has emerged very useful for predicting the regioselectivity in the oxirane and aziridine ring opening in various substituted phenanthrene 9.10-oxides and imines.[21] Now we have found that such theoretical calculations match the experimental results for the nucleophilic oxirane ring opening in both **1** (which gives equal amounts of **2** and **3**) and **10** (which gives a large excess of **11**). Furthermore, when we applied the calculations for the transformation of other non-symmetrical oxides studied previously in our laboratory[6,10,17,22-27] they proved to fit, without exception, the experimental results in respect to the regioselectivity of the products (see Tables 1 and 2).

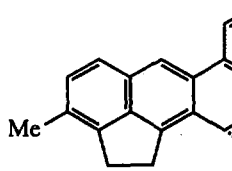
The Tables indicate that for differently substituted arene oxides having the *same* aromatic skeleton, the theoretical calculations provide a good quantitative prediction for the preferred product. Thus, e.g. the ΔE values for the benz[*a*]anthracenes derivatives, listed in Table 1, reflect well on the ratio between products **a**



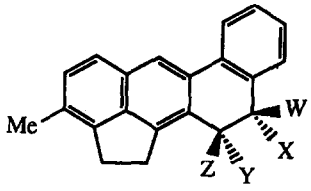
1



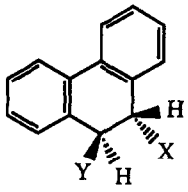
2, W = Y = H X = OH Z = N_3
3, W = N_3 X = Z = H Y = OH
4, W = Y = H X = OH Y = NH_2
5, W = NH_2 X = Z = H Y = OH
6, W = Y = H X = OCOMe Z = N_3
7, W = N_3 X = Z = H Y = OCOMe
8, W = Y = H X = OCOMe Z = NH_2
9, W = NH_2 X = Z = H Y = OCOMe



10



11, W = Y = H X = OH Z = N_3
12, W = N_3 X = Z = H Y = OH
13, W = Y = H X = OH Z = NH_2
14, W = Y = H X = OCOMe Z = N_3
15, W = Y = H X = OCOMe Z = NH_2



16, X = OCOMe Y = N_3
17, X = OH Y = NH_2
18, X = OH Y = NHCOMe
19, X = OCOMe Y = NH_2

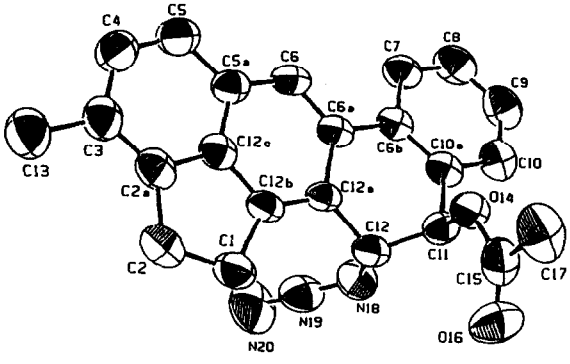
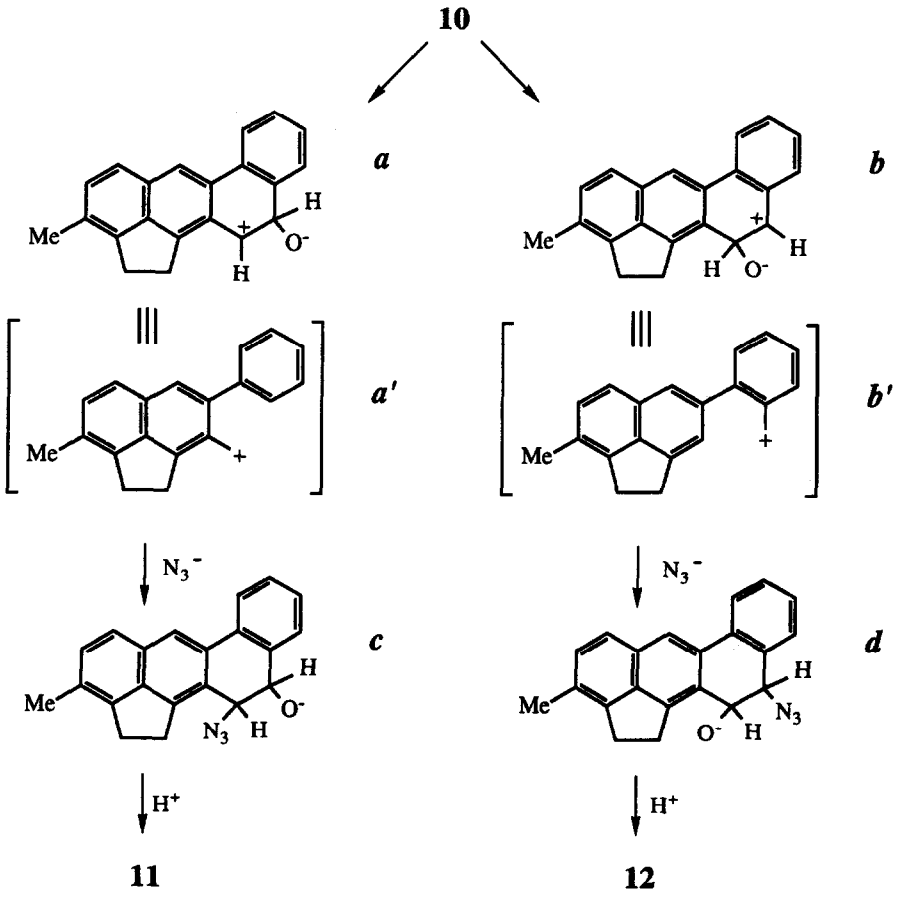


Fig. 1. Molecular structure (ORTEP) of **14**.



Scheme 1

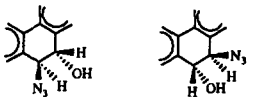
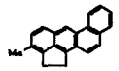
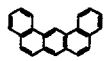
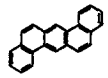
and **b**. Likewise, the data for the dibenzacridines and the benzophenanthrothiophenes given in Table 2 correlate with the observed ratios between the isomeric *trans*-azido-alcohols. For oxirane ring opening in arene oxides with *different* skeletons only qualitative information on the preferred product is obtained.

Since the calculations take into consideration only π electrons, the quality of the correlation between the theoretical predictions and the observed regioselectivity is reduced when the polyarene oxides are substituted with methyl groups. The correlation is also affected by dehydration and rearrangements which sometimes accompany the nucleophilic ring opening processes[23] (cf. also[11,28]). Nevertheless, we see that in spite of their simplicity the Hückel calculations have a wide scope of application for predicting the preferred mode of oxirane ring cleavage in many non-symmetrical arene oxides.

EXPERIMENTAL

***trans*-5-Azido-4,5-dihydro-4-benzo[*a*]pyrenol (2) and *trans*-4-Azido-4,5-dihydro-5-benzo[*a*]pyrenol (3).** By the method described previously[10] 3b,4a-dihydrobenzo[1,2]pyreno[4,5*b*]-oxirene (**1**) was converted in 89% yield into a 1:1 mixture of **2** and **3**. The mixture was separated by HPLC

TABLE 1: Calculated and Observed Regioselectivity in Oxirane Ring Opening in Various Carbocyclic K-Region Arene Oxides

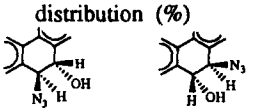
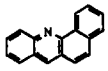
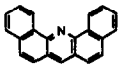
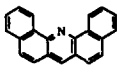
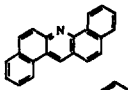
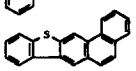
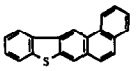
Parent polycyclic compound	Calculated ΔE (β units). Preferred product in parenthesis	Experimental distribution (%)  a b		Ref.
	0.0016 (**a**)	51	49	10
	0.0162 (**a**)	60	40	6
	0.1788 (**a**)	70	33	10
	0.1310 (**a**)	80	20	22
	0.1980 (**a**)	93	7	17
	0.0980 (**b**)	30	70	23
	0.0234 (**a**)	60	40	10
	0.0000	50	50	10
	0.0032 (**b**)	48	52	24
	0.0180 (**a**)	63	37	10

at 35°C on a preparative (250 x 10mm) Lichrosorb RP-18 column using a 2:3.3 mixture of THF-acetate buffer (pH 6) as eluent at a flow rate of 4.5 ml min^{-1}. The fractions with retention times of 49.35 min and 54.52 min proved to be pure **2** and **3**, respectively.

2: Pale orange crystals; mp 171°C (dec); IR (Nujol): 3320 (OH), 2110 cm^{-1} (N_3); 200- MHz ^1H NMR ($CDCl_3$): 5.172 (br s, 1, H5), 5.193 (br s,1, H4), 7.686-7.836 (m, 4H, Ar*H*), 7,979-8.075 (m, 4H, Ar*H*), 8.701-8.745 (m, 2, H11, H12); MS (70 eV, 130°C): *m/z* (rel. intensity) 311 ($M^{\cdot+}$,63), 284 ($C_{20}H_{13}NO^{\cdot+}$, 13), 283 ($C_{20}H_{12}NO^+$, 12), 282 ($C_{20}H_{11}NO^{\cdot+}$, 2), 269 ($C_{20}H_{13}O^+$, 60), 268 ($C_{20}H_{12}O^{\cdot+}$, 14), 255 ($C_{19}H_{11}O^+$, 24), 254 ($C_{19}H_{10}O^{\cdot+}$, 100), 253 ($C_{20}H_{13}^+$, 23), 226 ($C_{18}H_{10}^{\cdot+}$, 30).

3: Bright yellow crystals; mp 168-169°C (dec); IR (Nujol): 3350 (OH), 2108 cm^{-1} (N_3); 200-MHz ^1H NMR ($CDCl_3$): 5.057 (d,1, $J_{4,5}$= 6.4 Hz, H4), 5.168 (d,1, $J_{4,5}$= 6.4 Hz, H5), 7.686-7.836 (m, 4H, Ar*H*), 7,979-8.075 (m, 4, Ar*H*), 8.701-8.745 (m, 2, H11, H12); MS (70 eV, 130°C): *m/z* (rel. intensity) 311

TABLE 2: Calculated and Observed Regioselectivity in Oxirane Ring Opening in Various Heterocyclic K-Region Arene Oxides

Parent polycyclic compound	Calculated ΔE (β units). Preferred product in parentheses	Experimental distribution (%)  a b		Ref.
	0.0138 (**b**)	30	70	25
	0.0532 (**a**)	100	0	25
	0.0240 (**a**)	60	40	26
	0.0156 (**a**)	55	45	26
	0.0770 (**b**)	30	70	26
	0.0362 (**a**)	75	25	26
	0.0376 (**a**)	86[a]	14[a]	27
	0.0150 (**a**)	60	40	28

[a] These figures differ from those reported in the literature because the latter referred to the chromatographed products.

($M^{\cdot+}$, 58), 284 ($C_{20}H_{13}NO^{\cdot+}$,), 283 ($C_{20}H_{12}NO^{+}$, 15), 282 ($C_{20}H_{11}NO^{\cdot+}$, 5), 269 ($C_{20}H_{13}$, 65), 268 ($C_{20}H_{12}O^{\cdot+}$, 20), 255 ($C_{19}H_{11}O^{+}$, 28), 254 ($C_{19}H_{10}O^{\cdot+}$, 100), 253 ($C_{20}H_{13}^{+}$, 29), 226 ($C_{18}H_{10}^{\cdot+}$, 33).

***trans*-5-Azido-4,5-dihydro-4-benzo[*a*]pyrenol Acetate (6).** A solution of 100 mg (0.28 mmol) of **2** in 2 ml (20 mmol) of acetic anhydride and 0.55 ml (6.7 mmol) of dry pyridine was stirred at room temperature for 42 h. Addition of 10% aqueous Na_2CO_3, extraction (6x) with ether and chromatography of the resulting yellow product on silica gel (with a 4:1 mixture of hexane-ether as eluent), afforded 97 mg (86%) of yellow **6**. The compound proved to be isomerically pure (HPLC: RP-18, 2:3 mixture of THF:H_2O as eluent); mp 148-149°C; IR (Nujol): 2110 (N_3), 1740 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$): 2,171 (s, 3, CH_3), 5.219 (d,1, $J_{4,5}$= 4.9 Hz, H5), 6.393 (d,1, $J_{4,5}$= 4.9 Hz) 7.640-7.780 (m, 4, Ar*H*), 8.006-8.127 (m, 4, Ar*H*), 8.720-8.771 (m, 2, H11, H12); MS (70 eV, 110°C): *m/z* (rel. intensity) 353 ($M^{\cdot+}$, 26), 282 ($C_{20}H_{13}NO^{\cdot+}$, 6), 269 ($C_{20}H_{13}O^{+}$, 18), 268 ($C_{20}H_{12}O^{\cdot+}$, 14), 267 ($C_{20}H_{11}O^{+}$, 22), 266 ($C_{20}H_{12}N^{+}$, 100), 255 ($C_{19}H_{11}O^{+}$, 56), 254 ($C_{19}H_{10}O^{\cdot+}$, 61), 253 ($C_{20}H_{13}^{+}$, 29), 239 ($C_{19}H_{11}^{+}$, 30), 226 ($C_{18}H_{12}^{\cdot+}$, 25). Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.49; H, 3.99; N, 11.60.

***trans*-4-Azido-4,5-dihydro-5-benzo[*a*]pyrenol Acetate (7).** In the manner described for the preparation of **6**, 96 mg of **3** was converted into **7** in 86% yield. Mp 147-148°C; IR (Nujol): 2110 (N_3), 1740 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$): 1.950 (s, 3, CH_3), 5.149 (d,1, $J_{4,5}$= 5.2 Hz, H4), 6.460 (d,1, $J_{4,5}$= 5.2 Hz, H5), 7.636-7.785 (m, 4, Ar*H*), 8.002-8.127 (m, 4, Ar*H*), 8.720-8.770 (m, 2, H11, H12); MS (70 eV, 110°C): *m/z* (rel. intensity) 353 ($M^{\cdot+}$, 40), 282 ($C_{20}H_{12}NO^{\cdot+}$, 7), 269 ($C_{20}H_{13}O^+$, 17), 268 ($C_{20}H_{12}O^{\cdot+}$, 17), 267 ($C_{20}H_{11}O^+$, 18), 266 ($C_{20}H_{12}N^+$, 100), 255 ($C_{19}H_{11}O^+$, 61), 254 ($C_{19}H_{10}O^{\cdot+}$, 52), 253 ($C_{20}H_{13}^+$, 32), 239 ($C_{19}H_{11}^+$, 33), 226 ($C_{18}H_{12}^{\cdot+}$, 28). Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.48; H, 4.51; N, 11.68.

***trans*-4-(Acetyloxy)-4,5-dihydro-5-benzo[*a*]pyrenamine (8).** A solution of 50 mg (0.14 mmol) of **6** in a mixture of 3.5 ml of dry THF and 18.5 ml of ethyl acetate was hydrogenated at room temperature and 1 atm H_2 in the presence of 25 mg of 10% palladium on carbon. After 110 min, the catalyst was filtered off (through celite) and the filtrate concentrated. The resulting yellow solid was purified by chromatography on alumina deactivated with 15% H_2O using a 24:21:5 mixture of ethyl acetate-ether-hexane as eluent. There was obtained 21 mg (42%) of pale yellow crystals; mp 102.5-105°C; IR (Nujol): 3400 (NH), 1728 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$): 2,009 (s, 3, CH_3), 4.597 (d,1, $J_{4,5}$= 4.9 Hz, H5), 6.322 (d,1, $J_{4,5}$= 4.9 Hz, H4), 7.410-7.825 (m, 4, Ar*H*), 8.000-8.125 (m, 4, Ar*H*), 8.720-8.785 (m, 2, H11, H12); MS (70 eV, 90°C): *m/z* (rel. intensity) 327 ($M^{\cdot+}$, 33), 312 ($C_{21}H_{14}NO_2^+$, 6), 310 ($C_{22}H_{14}O_2^{\cdot+}$, 27), 284 ($C_{20}H_{14}NO^+$, 7), 268 ($C_{20}H_{14}N^+$, 72), 267 ($C_{20}H_{13}N^{\cdot+}$, 100), 240 ($C_{19}H_{12}^{\cdot+}$, 61), 238 ($C_{19}H_{10}^{\cdot+}$, 58). Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5,23; N, 4.28. Found: C, 80.45; H, 5.30; N, 4,17.

***trans*-5-(Acetyloxy)-4,5-dihydro-4-benzo[*a*]pyrenamine (9).** In the manner described for the preparation of **8**, the hydrogenation of **7** gave 42% of pale yellow **9**. Mp 105-107°C; IR (Nujol): 3400 (NH), 1725 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$): 1.986 (s, 3, CH_3), 4.545 (d,1, $J_{4,5}$= 5 Hz, H4), 6.371 (d,1, $J_{4,5}$= 5 Hz, H5), 7.410-7.820 (m, 4H, Ar*H*), 8.000-8.120 (m, 4, Ar*H*), 8.720-8.785 (m, 2, H11, H12); MS (70 eV, 90°C): *m/z* (rel. intensity) 327 ($M^{\cdot+}$, 34), 312 ($C_{21}H_{14}NO_2^+$, 8), 310 ($C_{22}H_{14}O_2^{\cdot+}$, 25), 284 ($C_{20}H_{14}NO^+$, 9), 268 ($C_{20}H_{14}N^+$, 74), 267 ($C_{20}H_{13}N^{\cdot+}$, 100), 240 ($C_{19}H_{12}^{\cdot+}$, 8), 238 ($C_{19}H_{10}^{\cdot+}$, 74). Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.45; H, 5.06; N, 3.98.

***trans*-12-Azido-1,2,11,12-tetrahydro-3-methyl-11-benz[*j*]aceanthrylenol(11) and *trans*-11-Azido-1,2,11,12-tetrahydro-3-methyl-12-benz[*j*]aceanthrylenol(12).** A mixture of 1.7 g (5.94 mmol) of 1a,10,11,11c-tetrahydro-3-methylbenz[7,8]aceanthryleno[9,10-*b*]oxirene (**10**),[16] 44 g (67.6 mmol) of NaN_3, 660 ml acetone and 330 ml H_2O was stirred at room temperature for 60 min. Removal of the acetone under reduced pressure yielded 1.75 g (90%) of a 14:1 mixture of **11** and **12** that was separated on silica gel with a 1:9 hexane-THF mixture as eluent. The initial small fraction of 10 mg of pure **12** was followed first by mixtures of **11** and **12** and, finally by a fraction of 1.048 g of pure **11**.

11: Mp 178-181°C (from THF-hexane); IR (Nujol): 3201 (OH), 2108 cm^{-1} (N_3); 200-MHz ^1H NMR ($CDCl_3$): 2.422 (s, 3, CH_3), 3.344, 3.514 (two m, 4 H1, H1', H2, H2'), 4.766 (d,1, $J_{11,12}$= 3.4 Hz, H12), 5.008 (d,1, $J_{11,12}$= 3.4 Hz, H11), 7.318-7.371 (m, 2, 4H, H9), 7.427-7.502 (m, 2, H8, H10), 7.582 (d,1, $J_{4,5}$= 8 Hz, H5), 8.002 (d,1, $J_{7,8}$= 7.2 Hz, H7) 8.075 (s, 1, H6); MS (70 eV, 130°C): *m/z* (rel. intensity) 327 ($M^{\cdot+}$, 64), 285 ($C_{21}H_{17}O^+$, 43), 270 ($C_{20}H_{14}O^{\cdot+}$, 100), 268 ($C_{21}H_{16}^{\cdot+}$, 17), 253 ($C_{20}H_{13}^+$, 16), 252 ($C_{20}H_{12}^{\cdot+}$, 17). Anal. Calcd. for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.11; H, 5.25; N, 12.71.

12: 200-MHz ^1H NMR ($CDCl_3$): 2.410 (s, 3, CH_3), 3.340, 3.510 (two m, 4 H1, H1', H2, H2'), 4.730 (d,1, $J_{11,12}$= 3.5 Hz, H11), 4.986 (d,1, $J_{11,12}$= 3.5 Hz, H12), 7.279-7.391 (m, 2, H4, H9), 7.412-7.523 (m, 2, H8, H10), 7.564 (d,1, $J_{4,5}$= 6.3 Hz), 8.019 (d,1, $J_{7,8}$= 6.2 Hz, H7) 8.048 (s, 1, H6).

***trans*-12-Amino-1,2,11,12-tetrahydro-3-methyl-11-benz[*j*]acenanthrylenol (13).** A mixture of 350 mg (1.07 mmol) of **11**, 210 mg (5.52 mmol) of $LiAlH_4$ and 220 dry ether was stirred under N_2 at room temperature for 2 h. The excessive reagent was decomposed with wet ether. Aqueous 10% NaOH was added with vigorous stirring until most of the precipitate of aluminium compounds dissolved.

After 20 min the remaining solid particles were filtered off. Phase separation, removal of the organic solvent and chromatogrphy on silica gel (1:1 mixture of hexane-THF) afforded 150 mg (47%) of colorless **13** as a hydrate. Mp 127-132°C (dec); IR (Nujol): 3300-3500 (NH, OH); 200-MHz ^{1}H NMR ($CDCl_3$): 1.670 (s, 2, H_2O), 2.408 (s, 3, CH_3), 3.408, 3.487 (two m, 4 H1, H1', H2, H2'), 4.344 (d,1, $J_{11,12}$= 3.7 Hz, H12), 4.720 (d,1, $J_{11,12}$= 3.7 Hz, H11), 7.299-7.363 (m, 2, H4, H9), 7.419-7.452 (m, 2, H8, H10), 7.553 (d,1, $J_{4,5}$= 8.2 Hz, H5), 7.961 (d,1, $J_{7,8}$= 7.2 Hz, H7) 8.023 (s, 1, H6); MS (70 eV, 140°C): *m/z* (rel. intensity) 301 ($M^{\cdot+}$, 20), 284 ($C_{21}H_{18}N^+$, 100), 283 ($C_{21}H_{17}N^{\cdot+}$, 23), 269 ($C_{20}H_{15}N^{\cdot+}$, 32), 267 ($C_{21}H_{15}^+$, 28), 255 ($C_{20}H_{15}^+$, 22), 239 ($C_{20}H_{11}^+$, 22). Anal. Calcd. for $C_{21}H_{19}NO{\cdot}H_2O$: C, 78.97; H, 6.57; N, 4.39. Found: C, 79.27; H, 6.88; N, 4.39.

***trans*-12-Azido-1,2,11,12-tetrahydro-3-methyl-11-benz[*j*]aceanthrylenol Acetate (14).** By the method described for the preparation of **6**, 0.4 g of **11**, was converted into **14** with the aid of 7.5 ml of acetic anhydride and 2.1 mg of pyridine. Chromatography on silica gel (4:1 mixture of hexane-ether as eluent) afforded 0.37 g (82%) of **14** as pale yellow crystals. Mp (172-174°C); IR (Nujol): 2804 (N_3); 1725 cm^{-1} (C=O); 400-MHz ^{1}H NMR ($CDCl_3$): 1.871 (s, 2, OCH_3), 2.440 (s, 3, CH_3), 3.408, 3.504 (two m, 4, H1, H1', H2, H2'), 5.027 (d,1, $J_{11,12}$= 3 Hz, H12), 5.971 (d,1, $J_{11,12}$= 3 Hz, H11), 7.337-7.369 (m, 2, H4, H9), 7.502-7.541 (m, 2, H8, H10), 7.629 (d,1, $J_{4,5}$= 8.1 Hz, H5), 8.029 (d,1, $J_{7,8}$= 7.7 Hz, H7) 8.119 (s, 1, H6); MS (70 eV, 140°C): *m/z* (rel. intensity) 369 ($M^{\cdot+}$, 67), 285 ($C_{20}H_{15}NO^{\cdot+}$, 87), 282 ($C_{21}H_{19}N^{\cdot+}$, 18), 281 ($C_{21}H_{15}N^{\cdot+}$, 100), 268 ($C_{21}H_{16}^{\cdot+}$, 39), 253 ($C_{20}H_{13}^+$, 40. Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.60; H, 5.34; N, 11.33.

A suitable crystal for X-ray diffraction analysis was obtained by slow crystallization from dichloromethane. Data were measured on an ENRAF-NONIUS CAD-4 automatic diffractometer. CuK_α (λ - 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used. The standard CAD-4 centering, indexing, and data collection programs were used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of $23 \leq \theta \leq 30°$. Intensity data were collected using the ω-2θ technique to a maximum 2θ of 110°. The scan width, $\Delta\omega$, for each reflection was 0.80 + 0.15·tanθ. An aperture with a height of 4 mm and a variable width, calculated as 2.0 + 0.5·tanθ mm was located 173 mm from the crystal. Reflections were first measured with a scan of 8.24° min^{-1}. The rate of the final scan was calculated from the preliminary scan results so that the ratio $I/\sigma(I)$ would be at least 40 and the maximum scan time would not exceed 60 s. If a preliminary scan $I/\sigma(I) < 2$, this measurement was used as the datum. Scan rates varied from 1.27 to 8.24° min^{-1}. Of the 96 steps in the scan, the first and the last 16 steps were considered to be background. During data collection the intensities of three standard reflections were monitored after every hour of X-ray exposure. No decay was observed. In addition, three orientation standards were checked after 100 reflections to check the effects of crystal movement. If the standard deviation of the h, k and l values of any orientation reflection exceeded 0.08, a new orientation matrix was calculated on the basis of the recentering of 24 reference reflections. Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[29] After several cycles of refinements[30] the positions of the hydrogen atoms were calculated, and added to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_o|-|F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.2 e/Å^3 scattered about the unit cell without a significant feature. The discrepancy indices, $R_w = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $[R_w = \Sigma w\,(|F_o|-|F_c|)^2/\Sigma w\,|F_o|^2\,]^{1/2}$ are presented with other pertinent crystallographic data in Table 3. An ORTEP drawing of **14** is shown in Figure 1.[18]

***trans*-11-(Acetyloxy)-1,2,11,12-tetrahydro-3-methyl-12-benz[*j*]aceanthrylenamine (15).** Hydrogenation of **14** was carried out in THF-ethyl acetate in the presence of Pd/C at room temperature under 1 atm H_2. Chromatography on alumina deactivated with 15% of H_2O (using a mixture of 50% hexane, 45% ether and 5% ethyl acetate as eluent) afforded 69% of colorless **15**. Mp 153-155°C; IR (Nujol): 3401 (NH); 1725 cm^{-1} (C=O); 200-MHz ^{1}H NMR ($CDCl_3$): 1.846 (s, 2, OCH_3), 2.420 (1, 3, CH_3), 3.414 (m, 4 H1, H1', H2, H2'), 4.401 (d,1, $J_{11,12}$= 2.9 Hz, H12), 5.939 (d,1, $J_{11,12}$= 2.9 Hz,

TABLE 3. Crystallographic Data for **14**

formula $C_{29}H_{19}N_3O_2$	$Z = 4$
molecular weight 441.49	ρ(calcd) = 1.31 g cm^{-3}
space group $P2_1/c$	$\mu(CuK_\alpha)$ = 6.47 cm^{-1}
a = 9.88 (1) Å	number of unique reflections 2450
b = 20.098 (2) Å	number of reflections with $I \geq 3\sigma(I)$ 1996
c = 9.994 (1) Å	R = 0.046
β = 109.28 (1)°	R_w = 0.077
V= 1873.4 (5) Å3	

H11), 7.212-7.369 (m, 2, H4, H9), 7.452-7.606 (m, 3, H5, H8, H10), 8.014 (d,1, $J_{7,8}$= 7.1 Hz, H7) 8.071 (s, 1, H6); MS (70 eV, 150°C): *m/z* (rel. intensity) 343 ($M^{\cdot+}$, 33), 326 ($C_{23}H_{18}O^{\cdot+}$, 16), 284 ($C_{21}H_{18}N^+$, 34), 283 ($C_{21}H_{17}N^{\cdot+}$, 100), 267 ($C_{21}H_{15}^+$, 84), 268 ($C_{21}H_{16}^{\cdot+}$, 12), 255 ($C_{20}H_{15}^+$, 25). Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.66; H, 6.30; N, 4.01.

***trans*-10-Azido-9,10-dihydro-9-phenanthrenol Acetate (16).** Acetylation of 10-azido-9.10-dihydro-9-phenanthrol[14] by the method described for **2** gave **16** in 89% yield. Pale yellow viscous oil; IR (neat): 2102 (N_3); 1752 cm^{-1} (C=O); 200-MHz ^{1}H NMR ($CDCl_3$): 2.036 (s, 3, C*H*$_3$), 4.768 (d,1, $J_{9,10}$= 5.3 Hz, H9), 6.053 (d,1, $J_{9,10}$= 5.3 Hz, H10), 7.329-7.542 (m, 6, Ar*H*), 7.834-7.913 (m, 2, Ar*H*), MS (70 eV, 70°C): *m/z* (rel. intensity) 279 ($M^{\cdot+}$, 6), 219 ($C_{14}H_9N_3^{\cdot+}$, 9), 192 ($C_{14}H_8N^+$, 100), 178 ($C_{14}H_9^+$, 89), 151 ($C_{12}H_7^+$, 35). Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.53; H, 4.80; N, 14.61.

***trans*-10-*N*-Acetylamino-9,10-dihydro-9-phenanthrenol (18).** A mixture of 72 mg (0.34 mmol) of *trans*-10-amino-9,10-dihydro-9-phenanthrenol (**17**)[14] 35 mg (0.34 mmol) of acetic anhydride and 31 mg (0.39 mmol) of dry pyridine was refluxed under N_2 for 30 min. Evaporation to dryness, treatment with water and chromatography on silica gel (using a 1:10 mixture of MeOH-ether as eluent) afforded 63 mg (73%) of **18** as colorless crystals. Mp 214-215°C. 300-MHz ^{1}H NMR ($CDCl_3$): 2.021 (s, 3, C*H*$_3$), 4.773 (d,1, $J_{9,10}$= 7 Hz, H10), 5.304 (dd,1, $J_{9,10}$= 7 Hz, $J_{H,OH}$ = 8 Hz, affected by D_2O, H9), 5.636 (d,1, $J_{H,OH}$ = 8 Hz, disappears upon addition of D_2O, O*H*), 7.31-7.47 (m, 5, Ar*H*), 7.834-7.913 (m, 2, Ar*H*), 7.566 (d,1, $J_{7,8}$= 9 Hz, H8), 7.800 (d,1, $J_{3,4}$= 7 Hz, H4), 7.823 (d,1, $J_{5,6}$= 7 Hz, H5). MS (70 eV, 210 eV): *m/z* (rel. intensity) 235 ($C_{16}H_{13}NO^{\cdot+}$, 5), 195 ($C_{14}H_{11}O^+$, 15), 194 ($C_{14}H_{10}O^{\cdot+}$, 100), 193 ($C_{14}H_9O^+$, 32), 166 ($C_{13}H_{10}^{\cdot+}$, 11), 165 ($C_{13}H_9^+$, 31). Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.97; N, 5.53. Found: C, 75.61, H, 5.92; N, 5.77.

***trans*-10-(Acetyloxy)-9,10-dihydro-9-phenanthrenamine (19).** Hydrogenation of **16** in a mixture of ethyl acetate and THF in the presence of Pd/C gave after chromatography on deactivated alumina (15% H_2O) 50% of pale yellow **19**. Mp 105-111°C (dec); IR (Nujol): 3401 (NH); 1736 cm^{-1} (C=O); 400-MHz ^{1}H NMR ($CDCl_3$): 1.963 (s, 3, C*H*$_3$), 4.182 (d,1, $J_{9,10}$= 4.2 Hz, H9), 5.934 (d,1, $J_{9,10}$= 4.2 Hz, H10), 7.277-7.518 (m, 5, Ar*H*), 7.816-7.839 (m, 2, H4, H5), MS (70 eV, 100°C): *m/z* (rel. intensity) 253 ($M^{\cdot+}$, 1), 236 ($C_{16}H_{12}O^{\cdot+}$, 8), 210 ($C_{14}H_{12}NO^+$, 8), 209 ($C_{14}H_{11}NO^{\cdot+}$, 9), 194 ($C_{14}H_{12}N^+$, 100). Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.65; H, 6.01; N, 5.38.

Hückel Calculations. The Hückel parameters used to obtain the ΔE(ß) data were obtained by using the standard Hückel software.[31]

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