calization in the carbonium ion of 7,12-DMBA, 3-MC, and 6,7,12-TMBA renders this intermediate chemically reactive on the methyl group(s) attached to the carbon atoms at which the charge is localized. Unfortunately, under the acidic conditions sufficiently mild to avoid decomposition, no exchange of the methyl group of other hydrocarbons could be observed. Nevertheless, from the kinetic study of deuterium ion exchange in the methylbenzanthracene series it can be inferred that a general mechanism of hydrocarbon activation by attack of the enzymically catalyzed oxygen species at the most reactive substituting positions with simultaneous formation of electrophilic centers at positions complementary to the points of activation[7] seems to be rather unlikely.

It will be seen in the accompanying paper how the one-electron oxidation of the hydrocarbon, which represents a more plausible mechanism of biological activation, generates radical cations with a significant degree of positive charge localization. Such an effect plays a decisive role in determining the reactivity toward nucleophilic trapping of these intermediates.

Acknowledgments. We wish to express our thanks to Dr. Melvin Newman for the monomethylbenzanthracene compounds and Dr. John Pataki for the dimethylbenzanthracene and trimethylbenzanthracene samples. The valuable comments of Dr. Robert Roth are much appreciated. The financial support of the Cancer Research Funds of the University of California, Berkeley, of the U.S. Atomic Energy Commission, and of the NCI-NIH PH-43-68-959 contract are gratefully acknowledged.

Registry No.—Anthracene, 120-12-7; BA, 56-55-3; 7-MBA, 2541-69-7; 12-MBA, 2422-79-9; 6,7-DMBA, 20627-28-5; 7,8-DMBA, 604-81-9; 8,12-DMBA, 20627-31-0; 7,12-DMBA, 57-97-6; 3-MC, 56-49-5; 6,7,12-TMBA, 20627-33-2; 6,8,12-TMBA, 20627-34-3; 2-MBA, 2498-76-2; 5-MBA, 2319-96-2; 6-MBA, 316-14-3; 8-MBA, 2381-31-9; 11-MBA, 6111-78-0; 6,12-DMBA, 568-81-0; 7,12-DMBA$^+$, 59230-87-4; 7,12-DMBA$^+$-d_4, 59230-88-5; 7,12-DMBA-d_3, 59230-67-0; 3-MC$^+$, 59230-89-6; 3-MC-d_2, 59230-90-9.

Supplementary Material Available. The 220-MHz proton NMR spectra of 7,12-DMBA and 3-MC in different solvent systems (2 pages). Ordering information is given on any current masthead page.

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Reaction of Methylbenzanthracenes and Pyridine by One-Electron Oxidation. A Model for Metabolic Activation and Binding of Carcinogenic Aromatic Hydrocarbons

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A simple procedure for generation and trapping of polycyclic aromatic hydrocarbon radical cations in homogeneous solutions of pyridine and iodine is described. Radical cations of benz[*a*]anthracene and its alkyl derivatives are trapped by nucleophilic attack of pyridine on the aromatic nucleus in the order C-7 > C-12 > C-5. When positions 7 or 7 and 12 are blocked by a methyl group, pyridine substitution on the alkyl group competes with ring substitution. Mechanisms for the two types of substitution are proposed and trapping specificity is discussed in terms of charge density and steric factors in the radical ions.

Recently, there has been increasing speculation that radical cations might be the critical intermediates in carcinogenesis by polycyclic aromatic hydrocarbons. Following the original suggestion by Wilk[1] that these intermediates might be important, the conversion of aromatic hydrocarbons to carcinogenic metabolites via one-electron oxidation was demonstrated.[2] More recently Wilk and Girke[3] have reported that the benzo[*a*]pyrene (B[*a*]P) radical cation reacts with nucleic acid bases. Based on the capacity of Fe^{3+} to effect one-electron oxidation of aromatic hydrocarbons,[1,4] it was suggested that hexacoordinated Fe^{3+} in the form of cytochrome P-450 present in microsomes[5] and nuclei[6–8] might act as the cellular oxidant.

Despite the potential biological significance, most studies of aromatic hydrocarbon radical cations have been limited to ESR properties or the mechanistic details of electron transfer steps. While interest in reactions of radical cations with nucleophiles has increased, factors governing the site of nucleophilic attack have received little attention. Among biologically interesting molecules, well-characterized products from nucleophiles and radical cations have been reported only for B[*a*]P.[4,9–11] We have therefore undertaken a study of nu-

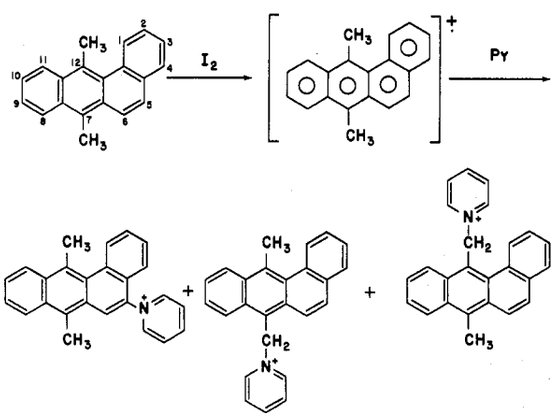
cleophilic trapping of radical cations derived from carcinogenic and noncarcinogenic benz[a]anthracenes.

The ability of iodine to effect a one-electron oxidation of aromatic hydrocarbons to radical cations is well established. The paramagnetic character of certain solid hydrocarbon–iodine complexes has long been known.[12,13] Recently the direct observation of ESR spectroscopy of radical cations in frozen solutions of iodine and several polycyclic aromatic hydrocarbons was reported.[14] The solid-phase reaction of iodine with B[a]P, 7,12-dimethylbenz[a]anthracene (7,12-DMBA), or 3-methylcholanthrene (3-MC) to give dimeric or oligomeric hydrocarbons[1] identical with those obtained through Fe^{3+} oxidation was interpreted as involving radical cation intermediates. In the case of the two former compounds, addition of pyridine gave pyridinium salts which were postulated to have arisen through nucleophilic trapping of the radical ions.[9] These results are paralleled when the radical cations are generated by anodic oxidation.[10,11]

Results

Generation and Trapping of Radical Cations. In seeking a practical system for generating and trapping aromatic radical cations on a synthetic scale, we were attracted to the system of Rochlitz[9] in which the hydrocarbon and pyridine adsorbed on thin layers of silica gel are exposed to iodine vapor. Initially several hydrocarbons were studied in this system with satisfactory results. After some experimentation, however, it was discovered that these reactions can be carried out in homogenous solutions with substantial improvement in yields and convenience.

Benz[a]anthracene (BA) and its alkyl derivatives, dissolved in pyridine in the presence of a high concentration of iodine, gave moderate to high yields of pyridinium salts which arose through nucleophilic trapping of the intermediate radical cations. The crude salts were quantitatively isolated from solutions containing the unreacted hydrocarbon by selective precipitation with ether and examined directly by NMR spectroscopy. Since an efficient method for the quantitative separation of pyridinium salt mixtures was not available, it was necessary to substitute NMR analysis of the gross mixture. Consequently minor products in some cases might not have been detected. For purification to analytical standards, the isolated iodides were converted to picrate or perchlorate salts. The results of these trapping experiments are summarized in Table I and illustrated below for 7,12-DMBA.



Structure Determinations. In the following discussion NMR chemical shifts are from spectra in Me_2SO solutions and are reported in δ units. No distinction is made between spectra of pyridinium iodides, perchlorates, or picrates, since the nature of the anion had no appreciable effect on chemical shifts or coupling constants. In general, structures of the pyridinium salts are readily evident from analysis of their NMR spectra, aided by comparisons with spectra of the hydrocarbons and the detailed chemical shift assignments for substituted benzanthracenes reported by Batterham et al.[15] In all cases where substitution was on the alkyl side chain, assignments were confirmed by spectral comparisons with authentic specimens.

Table I. Trapping Products of Alkyl Benzanthracene Radical Cations by Pyridine

Hydrocarbon[a]	Position(s) of substitution	Yield, %
BA	7	54
2-MBA	7	83
5-MBA	7	85
6-MBA	7	48
	12	14
7-MBA	7-CH_3	54
	12	23
8-MBA	7	58
	12	14
11-MBA	7	82
12-MBA	7	78
7-ETBA	12	68
7,12-DMBA	5	58
	7-CH_3	18
	12-CH_3	15
3-MC	1	96

[a] Abbreviations: MBA, methylbenz[a]anthracene; ETBA, ethylbenz[a]anthracene; DMBA, dimethylbenz[a]anthracene; 3-MC, 3-methylcholanthrene.

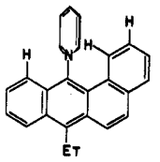
Common features in all spectra are signals arising from the pyridine ring hydrogens. In structures where pyridine is attached directly to the aromatic nucleus, the α protons appear as a doublet of multiplets at 9.5 ± 0.1; the γ proton as a triplet of multiplets at 9.1 ± 0.1; and the β protons as a triplet of multiplets at approximately 8.6. When the pyridine attachment is through an alkyl substituent, the pyridine protons are shifted upfield by approximately 0.5 ppm. The protons of the hydrocarbon nuclei exhibit small to moderate degrees of deshielding in the pyridinium derivatives relative to their parents. An important exception to this generalization is that protons having a peri relationship to the point of pyridine substitution are strongly shielded. This arises from the perpendicular orientation of the pyridine ring with respect to the hydrocarbon ring, and results in positioning of the peri protons within the shielding region of the pyridine ring.

The 100-MHz NMR spectrum of the single pyridinium salt obtained from BA exhibits the following distinctive features: a singlet at 10.02 (1 H), a multiplet at 7.3 (1 H), and a doublet at 7.05 (J = 9 Hz, 1 H). In the NMR spectra of the parent hydrocarbon, the singlet of H12 at 9.4 is at lowest field. The chemical shift of the singlet at 10.02 is most consistent with an assignment to H12 with moderate deshielding by the pyridine substituent at C-7. The multiplets at 7.3 and 7.05 are well upfield from all other protons, requiring that two protons of the hydrocarbon nucleus be simultaneously shielded by the pyridine ring. This could be consistent only with substitution at C-12 or C-7, in which cases the shielded pairs would be H1, H11 or H6, H8, respectively. The fact that the signal at 7.05 is a doublet with no observable long-range coupling strongly implies that it arises from H6, thus establishing substitution at C-7. This assignment is further supported by the observation that H5 and H7 of the structurally related 6-*N*-pyridiniumbenzo[a]pyrenyl perchlorate[4,16] give rise to a nearly identical pattern of chemical shifts and coupling constants. Moreover, the distinctive spectral features arising from substitution at C-12 are described below.

The NMR spectra of the single pyridinium salts obtained from each of the 2-, 11-, and 12-monomethylbenzanthracenes

were very similar, with each containing the characteristic signals of H6 and H8. In the spectrum of 7-*N*-pyridinium-5-MBA, H6 appears as a singlet at 6.9.

The spectrum of the single product obtained from 7-ETBA exhibited the following distinctive features: overlapping multiplets at 7.4–6.9 (2 H), a doublet at 6.19 (J = 8.2 Hz, 1 H), and ethyl group resonances at 3.75 and 1.45. The doublet at 6.19 must arise from an exceptionally strong shielding of a single proton by the pyridine ring. The two protons at 7.4–6.9 are simultaneously shielded to a degree more characteristic of the peri relationship discussed above. These features can only be consistent with substitution at C-12 as shown below.



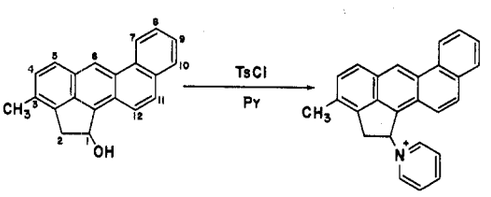
As can be seen in the drawing or more accurately from molecular models, H1 lies well within the shielding region of the pyridine ring and should experience a large upfield shift. The multiplets at 7.4–6.9 arise from H2 and H11, which would also be under the shielding influence of the pyridine ring but farther removed. The only inconsistency with this assignment is that the usual long-range coupling of H3 and H4 to H1 is not observed. This coupling could be reduced, however, by the degree of nonplanarity of the hydrocarbon nucleus induced by the bulky C-12 substituent.

The spectra of product mixtures from 6-MBA and 8-MBA indicated that both the 7-pyridinium and 12-pyridinium salts were present. The spectrum of the mixture from 6-MBA exhibited an abnormally shielded methyl group at 1.87 and a corresponding H8 multiplet at 6.85 for the 7-pyridinium isomer and a methyl singlet and H1 doublet at 2.86 and 6.06, respectively, for the 12-pyridinium isomer.

Likewise the spectrum of products from 8-MBA exhibited the shielded methyl singlet and H6 doublet of the 7 isomer at 1.89 and 6.6, respectively, along with the methyl singlet and H1 doublet of the 12 isomer at 2.92 and 6.1, respectively.

7,12-DMBA gave three trapping products, one of which resulted from ring substitution. The essential features of the NMR spectrum of this compound are a singlet at 8.73 (1 H) and a doublet of multiplets at 7.24 (J = ca. 8 Hz, 1 H), the highest field aromatic signal. These features alone require that the substitution be at C-5, since that position uniquely accounts for both the 8.7 singlet (H6) and the peri shielding of a single proton (H4). In most cases, additional assignment of NMR absorbances could be made by comparison of the hydrocarbon spectrum with that of the pyridinium salt and are reported in the Experimental Section.

The synthesis of authentic pyridinium alkyl benzanthracenes mentioned above involved simple nucleophilic displacement reactions of pyridine with the appropriate bromomethyl derivative. In the case of 3-MC, the tosyl ester, generated by the usual reaction of tosyl chloride with 1-hydroxy-3-methylcholanthrene in pyridine solution, underwent an in situ displacement reaction with pyridine resulting in a one-step synthesis of the desired pyridinium salt:



Discussion

Mechanisms of Radical Cation Trapping. It is to be expected that nucleophilic trapping of an aromatic cation radical should be governed by two main factors: (1) charge distribution in the radical ion and (2) the steric environment of centers on which the charge is preferentially localized. The fact that the benzanthracene radical cation is trapped exclusively at position 7 suggests that the greatest charge density exists at the site. Introduction of an alkyl substituent on the polycyclic nucleus should not dramatically alter the charge distribution. It is not surprising then that the 2-, 5-, 11-, and 12-monomethylbenzanthracenes, where the steric environment of C-7 is unaltered, also give specific C-7 substitution.

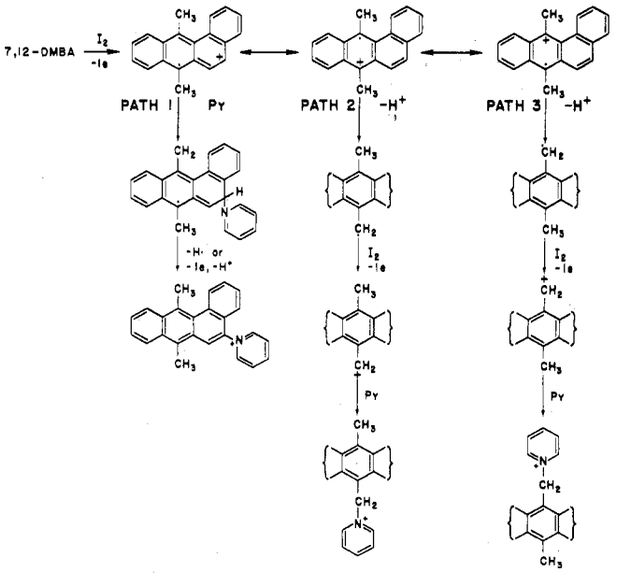
However, when the steric environment about C-7 is restricted and made to resemble more closely the environment inherent at C-12, e.g., by introduction of a methyl substituent at C-6 or C-8, substitution at C-12 begins to compete with that at C-7. This implies that the charge densities at C-7 and C-12 are of comparable magnitude.

When substitution at C-7 and C-12 is blocked, as in 7,12-DMBA, ring substitution proceeds specifically at C-5. Thus the experimental data suggest that the charge density distribution in the BA radical cation decreases in the order 7 > 12 > 5.

These observations are entirely in accord with theoretical calculations[17] which predict the following atomic charge densities in the benz[*a*]anthracene radical cation: C-7, 0.143; C-12, 0.126; C-8, 0.0918; C-5, 0.0904; C-2, 0.0812. Although C-8 is predicted to have slightly greater charge density than C-5, nucleophilic attack at C-8 would be significantly retarded by the steric influence of the 7-methyl substituent.

Introduction of alkyl substituents at C-7 or C-7 and C-12 provides a competitive reaction pathway leading to substitution on the alkyl substituent. The reaction path and proposed mechanism for 7,12-DMBA are illustrated in Scheme I.[18] Removal of one electron from the π system of 7,12-DMBA

Scheme I



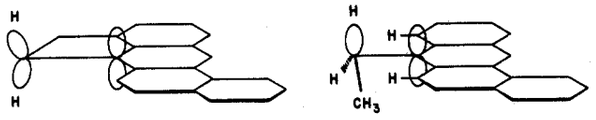
results in a radical ion with the heaviest charge densities at C-7, C-12, C-8, and C-5. With substitution at C-7 and C-12 blocked, and that at C-8 sterically retarded, ring attack proceeds at the position of next highest charge density, C-5 (path 1). The resulting radical can then either lose a hydrogen atom or be oxidized to an arenonium ion with loss of a proton to complete the substitution reaction.

The charge density at C-7 and C-12 is sufficient to induce appreciable acidity in the 7- and 12-methyl hydrogens. Loss of a proton from either group gives a benzylic radical which is rapidly oxidized to a carbonium ion with subsequent trapping by pyridine (path 2 and path 3). The mechanism of formation of pyridinium alkyl derivatives outlined in Scheme I is analogous to that proposed by Andrulis et al.[19] for the formation of anisyl acetate from the *p*-methoxytoluene radical cation. Those workers established from kinetic studies with *p*-methoxytoluene-α,α,α-d_3 that the rate-determining step was loss of a proton from the anisyl ion radical.

It is clear from the results of 7,12-DMBA that the substitution on an alkyl substituent is slow compared to direct attack on the corresponding ring position in the absence of the substituent. This is also apparent in comparing the BA radical ion, which is trapped only at C-7, with the 7-MBA radical ion, which is trapped at C-12 as well as the 7-methyl group.

In the 7-ETBA radical ion, no reaction at the alkyl methylene is observed, and trapping occurs only at C-12. At the other extreme the radical ion of 3-MC is trapped exclusively at the alkyl group. The distribution of substitution between C-12 and the C-7 alkyl substituent (C-1 in 3-MC) among 7-MBA, 7-ETBA, and 3-MC is most likely a reflection of the relative rates of proton loss from the radical ions, since no appreciable differences in charge distribution should exist.

We propose that these differences can be reasonably explained as follows. In 3-MC the C–H bonds of the C-1 methylene are forced into complete alignment with the adjacent aromatic p orbital by geometric constraints. The analogous C–H, p-orbital overlap in 7-ETBA is restricted, primarily by steric repulsion between the methyl group of the ethyl substituent and H6 or H8, and to a lesser extent by H6, or H8 methylene hydrogen repulsion. The situation for 7-MBA is intermediate between these two extremes. As the degree of this overlap decreases, hyperconjugation in the radical ion is minimized, and thus acidity is reduced. A similar argument applies to stabilization of the incipient benzylic radicals. Thus the relative rates of proton loss mentioned above are accounted for by predictable differences, either in hyperconjugation or benzylic radical stabilization.



As the data in this paper illustrate, nucleophilic trapping of aromatic radical ions is indeed controlled by charge distribution and steric factors. However, the potential importance of a third factor, namely the nucleophilicity of the trapping species, should not be ignored.

Studies of B[*a*]P reported in the literature illustrate this point. The B[*a*]P radical cation generated by chemical[3,4] or electrochemical[11] oxidation is trapped by pyridine specifically at C-6. However, Blackburn and Will[11] reported that the electrochemically generated radical ion is trapped by 1-methylimidazole at a site other than C-6, tentatively assigned as C-1. This difference in specificity can be understood by considering the charge distribution in the B[*a*]P radical cation and the relative nucleophilicities of the trapping reagents. Qualitatively, 1-methylimidazole (pK_a = ca. 7) is a significantly stronger nucleophile than pyridine (pK_a = 5). As the strength of the nucleophile is increased, trapping selectivity would become progressively less sensitive to differences in charge density. The highest calculated atomic charge densities[17] in the B[*a*]P radical cation are C-6, 0.131; C-1, 0.118; C-3, 0.100. These figures correctly predict that C-6 would be the primary trapping site with weaker nucleophiles. However, competitive reactions at C-1 and/or C-3 should be observed with sufficiently strong nucleophiles. Furthermore, attack at C-1 or C-3 is sterically more favorable, since these positions are effected by only one peri hydrogen interaction as compared to two such interactions at C-6.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained by the KBr disk method on a Beckman IR 9 spectrometer and are recorded in cm^{-1}. Ultraviolet spectra were obtained on a Cary 14 spectrometer, using methanol as the solvent, and are reported in nm. NMR spectra were recorded at 100 MHz on a Varian HA-100 spectrometer or at 80 MHz on a Varian CFT-20 Fourier transform instrument. Chemical shifts are reported in parts per million downfield from an internal Me_4Si standard. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

Chemicals. Reagent grade pyridine and iodine were used without further purification. Commercially obtained BA, 7,12-DMBA, and 3-MC were purified by column chromatography on Brinkmann silica gel, using hexane–benzene (9:1) followed by recrystallization from benzene–methanol. 7-MBA was prepared by the method of Wood and Fieser[20] and purified as described as above. Crude 12-MBA obtained by the procedure of Cook et al.[21] was purified by filtration through silica gel, followed by chromatography on a column of magnesium oxide–Celite 545, 2:1 w/w, using hexane–benzene (8:2) as the elutant, and subsequent recrystallization from acetic acid. 7-ETBA was prepared by a new synthetic procedure described below. We are indebted to Professor M. S. Newman of The Ohio State University for supplying samples of 2-, 3-, 6-, 8-, and 11-monomethylbenzanthracenes.

General Procedure for One-Electron Oxidation–Pyridine Coupling. Reaction mixtures were magnetically stirred in Erlenmeyer flasks closed with Teflon-lined screw caps. No effort was made to exclude air. Approximately 0.4 mmol of hydrocarbon and 2.0 g (7.9 mmol) of iodine were dissolved in 2.0 ml of pyridine and kept at 30–35 °C from 20 h. The mixture was then diluted with 70 ml of chloroform and washed with sufficient aqueous sodium thiosulfate to discharge the iodine color. Rapid quantitative separation of the pyridinium salts from any unreacted hydrocarbon was accomplished by dropwise addition of the dried (Na_2SO_4), concentrated chloroform solutions to 50–75 ml of ether with stirring. The yellow salts were collected by suction filtration, and the unreacted hydrocarbons were recovered from the filtrate by removal of the solvent. The crude salts were examined directly by NMR.

Conversion of Pyridinium Iodides to Perchlorates and Picrates. For analytical purposes, it was convenient to convert the iodides to picrates or perchlorates, which in many cases seemed to be more stable and have better recrystallization properties.

Perchlorates. Typically, a solution of 200–300 mg of pyridinium iodide in ca. 20 ml of methanol was gradually added to 10 ml of 70% perchloric acid, with cooling. Perchlorates which did not crystallize spontaneously were precipitated by addition of water. Suitable recrystallization solvents were acetone, methanol, or ethanol–water mixtures.

Picrates. Methanol solutions of pyridinium iodide and picric acid (5% molar excess) were mixed and kept at room temperature for 5 min and then poured into cold water. The crude picrates precipitated as bright yellow solids and were recrystallized from acetone–ethanol.

Benz[*a*]anthracene. From 110 mg (0.482 mmol) of BA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 113 mg (54%) of 7-*N*-pyridiniumbenz[*a*]anthracene iodide as the sole product. Perchlorate: mp ca. 310 °C (preheated bath), gradual decomposition above 250 °C; ir 3120, 3070, 2930, 1625, 1472, 1356, 1122, 1108, 1095, 1083, 1053, 812, 758, 685, 623 cm^{-1}; uv, λ_{max} (log ϵ) 389 (3.47), 369 (3.81), 353 (3.92), 337 (3.87), 323 (3.74), 303 (4.23), 292 (4.73), 281 (4.74), 274 (4.68); 100-MHz NMR (Me_2SO-d_6) 9.97 (s, 1 H, H12), 9.50 (d of m, J = 7 Hz, 2 H, Hα), 9.12 (m, 2 H, Hγ, H1), 8.75–8.4 (m, 3 H), 8.2–7.6 (m, 6 H), 7.3 (m, 1 H, H8), 7.05 (d, J = 10 Hz, 1 H, H6).

Anal. ($C_{23}H_{16}ClNO_4$) C, H, Cl, N.

7-Ethylbenz[*a*]anthracene. From 400 mg (1.56 mmol) of 7-ETBA, 10.0 g (39.4 mmol) of iodine, and 10.0 ml of pyridine was obtained 491 mg (68%) of 7-ethyl-12-*N*-pyridiniumbenz[*a*]anthracene iodide as the only product. The perchlorate had the following properties: mp 123–125 °C; ir 3118, 3073, 2980, 2940, 1627, 1475, 1370, 1150, 1120, 1108, 1095, 1082, 823, 772, 690, 625 cm^{-1}; uv λ_{max} (log ϵ) 398 (3.56), 374 (3.73), 3.60 (3.88), 348 (3.86), 338 (3.72), 292 (4.74), 282 (3.86), 272 (4.71), 262 (4.62), 233 (4.48); 80-MHz NMR (Me_2SO-d_6) 9.56 (d of m, J = 7 Hz, 2 H, Hα), 9.16 (t of m, J = 8 Hz, 1 H, Hγ),

8.8–8.2 (m, 4 H), 8.15–7.48 (m, 5 H), 7.42–6.92 (m, 2 H, H2, H11), 6.19 (d, J = 9 Hz, 1 H, H1), 3.8 (q, J = 7.8 Hz, 2 H, CH_2CH_3), 1.47 (t, J = 7.8 Hz, 3 H, CH_2CH_3).

Anal. ($C_{25}H_{20}ClNO_4$) C, H, Cl, N.

7-Methylbenz[*a*]anthracene. From 123 mg (0.508 mmol) of 7-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 174 mg (77% total) of a mixture consisting of 7-*N*-pyridiniummethylbenz[*a*]anthracene and 7-methyl-12-*N*-pyridiniumbenz[*a*]anthracene in a 2.4:1 ratio. The relative amount of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the area of the H12 singlet of 7-*N*-pyridiniummethylbenz[*a*]anthracene at 9.8 with that of the H1 doublet of 7-methyl-12-*N*-pyridiniumbenz[*a*]anthracene at 6.2. After conversion of the mixture to the perchlorates and fractional recrystallization from 95% ethanol, a pure sample of 7-*N*-pyridiniummethylbenz[*a*]anthracene perchlorate having a melting point and spectral properties identical with those of a synthetic specimen was obtained.

2-Methylbenz[*a*]anthracene. From 72.0 mg (0.297 mmol) of 2-MBA, 2.1 g (8.26 mmol) of iodine, and 2.1 ml of pyridine was obtained 111 mg (83%) of 2-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide as the sole product: 80-MHz NMR (Me_2SO-d_6) 9.92 (s, 1 H, H12), 9.45 (d of m, J = 6 Hz, 2 H, Hα), 9.08 (t of m, J = 8 Hz, 1 H, Hγ), 8.95 (s, 1 H, H1), 8.7–8.3 (m, 3 H, Hβ, H11), 8.05–7.4 (m, H3, H4, H5, H9, H10), (m, 1 H, H8), 6.9 (d, J = 9.4 Hz, H6), 2.65 (s, 3 H, CH_3).

5-Methylbenz[*a*]anthracene. From 85.0 mg (0.351 mmol) of 5-MBA, 2.1 g (8.3 mmol) of iodine, and 2.1 ml of pyridine was obtained 133 mg (85%) of 5-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide as the only product: 80-MHz NMR (Me_2SO-d_6) 9.88 (s, 1 H, H12), 9.45 (d of m, J = 6 Hz, 2 H, Hα), 9.15 (m, 2 H, H1, Hγ), 8.8–8.3 (m, 3 H), 8.1 (m, 1 H), 7.95–7.5 (m, 4 H), 7.2 (m, 1 H, H8), 6.9 (s, 1 H, H6), 2.6 (s, 3 H, CH_3).

6-Methylbenz[*a*]anthracene. From 100 mg (0.413 mmol) of 6-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 114 mg (62% total) of a mixture of 6-methyl-7-*N*-pyridiniumbenz[*a*]anthracene and 6-methyl-12-*N*-pyridiniumbenz[*a*]anthracene in a 3.5:1 ratio. The relative abundance of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the methyl singlets at 1.85 (6-methyl-7-*N*-pyridinium) and 2.85 (6-methyl-12-*N*-pyridinium). The H8 multiplet of the 6-methyl-7-*N*-pyridinium isomer was observed at 6.85 and the H1 doublet (J = 9 Hz) of the 6-methyl-12-*N*-pyridinium isomer at 6.1. The remainder of the NMR spectrum was unexceptional and consistent with the assigned structures.

8-Methylbenz[*a*]anthracene. From 110 mg (0.454 mmol) of 8-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 147 mg (72% total) of a mixture of 7-*N*-pyridinium-8-methylbenz[*a*]anthracene and 8-methyl-12-*N*-pyridiniumbenz[*a*]anthracene iodides in a ratio of 4.3:1. The relative abundance of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the methyl singlets at 1.89 (7-*N*-pyridinium) and 2.92 (12-*N*-pyridinium). The H6 doublet of the 7-pyridinium isomer appears at 6.6 (J = 9.6 Hz), while the H1 doublet of the 12-pyridinium isomer appears at 6.1 (J = 9 Hz). The remainder of the spectrum is unexceptional and consistent with the assigned structures.

11-Methylbenz[*a*]anthracene. From 92.0 mg (0.380 mmol) of 11-MBA, 2.7 g (10.6 mmol) of iodine, and 2.7 ml of pyridine was obtained 138 mg (82%) of 7-*N*-pyridinium-11-methylbenz[*a*]anthracene iodide as the only product: 80-MHz NMR (Me_2SO-d_6) 9.73 (s, 1 H, H12), 9.4 (d, J = 6 Hz, 2 H, Hγ), 9.14 (t of m, J = 8 Hz, 2 H, Hγ, H1), 8.6 (t of m, J = 6.6 Hz, 2 H, Hβ), 8.1–7.4 (m, 6 H, H2, H3, H4, H5, H9, H10), 7.0 (d, J = 9 Hz superimposed on a multiplet 2 H, H6, H8), 3.0 (s, 3 H, CH_3).

12-Methylbenz[*a*]anthracene. From 229 mg (0.946 mmol) of 12-MBA, 5.00 g (19.7 mmol) of iodine, and 5.0 ml of pyridine was obtained 332 mg (78%) of 7-*N*-pyridinium-12-methylbenz[*a*]anthracene iodide as the only detectable product. The perchlorate had the following properties: mp >260 °C dec; ir 3123, 3080, 1628, 1477, 1382, 1372, 1148, 1125, 1097, 1059, 870, 768, 688, 625 cm^{-1}; uv λ_{max} (log ϵ) 394 (3.37), 374 (3.77), 360 (3.88), 346 (3.80), 305 (4.22), 294 (4.53), 278 (4.66), 222 (4.52); 80-MHz NMR (Me_2SO-d_6) 9.4 (d of m, J = 7 Hz, 2 H, Hα), 9.05 (t of m, J = 7.5 Hz, 1 H, Hγ), 8.8–8.3 (m, 4 H), 8.2–7.5 (m, 6 H), 7.2 (m, 1 H, H8), 6.85 (d, J = 9.9 Hz, 1 H, H6), 3.48 (s, 3 H, CH_3).

7,12-Dimethylbenz[*a*]anthracene. From 100 mg (0.391 mmol) of 7,12-DMBA, 2.0 g (7.9 mmol) of iodine, and 2.0 ml of pyridine was obtained 164 mg (91% total) of a mixture consisting of 64% 5-*N*-pyridinium-7,12-dimethylbenz[*a*]anthracene iodide, 20% 7-*N*-pyridiniummethyl-12-methylbenz[*a*]anthracene iodide, and 16% 7-methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene iodide. The relative abundance of the three isomers was determined from the integrated NMR spectrum of the mixture by comparing the signals of 5-*N*-pyridinium-7,12-DMBA at 9.5 (Hα) and 7.2 (H4) with the methylene singlets of the 12-pyridiniummethyl and 7-pyridiniummethyl isomers at 7.06 and 6.95, respectively.

A mixture of the three salts (975 mg) was dissolved in a minimum volume of methylene chloride and diluted with 40 ml of acetone, whereupon the 5-pyridinium isomer selectively precipitated. The mother liquor was evaporated, and the residue was redissolved in the minimal volume of methylene chloride. After dilution with acetone as before, the 7-pyridiniummethyl isomer gradually crystallized with only minor amounts of isomeric contaminants. The mother liquor from the second crystallization contained the 12-pyridiniummethyl isomer as the chief component along with significant amounts of the two other isomers. Each of the three isomers was obtained in pure form after treatment of the fractions with perchloric or picric acid and recrystallization. The 7-pyridiniummethyl and 12-pyridiniummethyl picrates had melting points, ir, and NMR spectra identical with those of their synthetic counterparts. 5-*N*-Pyridinium-7,12-dimethylbenz[*a*]anthracene perchlorate had the following properties: mp 256–257 °C (lit.[9] 248–250 °C); ir 3120, 3070, 1622, 1470, 1120, 1110, 1090, 772, 760, 690, 685, 635, 623 cm^{-1}; uv λ_{max} (log ϵ) 406 (3.49), 366 (3.83), 300 (4.69), 290 (4.68), 279 (4.50), 256 (4.48), 234 (4.36); 100-MHz NMR (Me_2SO-d_6), 9.5 (d of m, J = 7 Hz, 2 H, Hα), 8.97 (t of m, J = 8 Hz, 1 H, Hγ), 8.73 (s, 1 H, H6), 8.6 (d of m, J = 8 Hz, 1 H, H1), 8.68–8.35 (m, 4 H, Hβ, H8, H11), 7.95–7.5 (m, 4 H, H2, H3, H9, H10), 7.24 (d of m, J = 8 Hz, 1 H, H4), 3.3 (s, 3 H, 12-CH_3), 3.1 (s, 3 H, 7-CH_3).

Anal. ($C_{25}H_{20}ClNO_4$) C, H, Cl, N.

3-Methylcholanthrene. From 112 mg (0.418 mmol) of 3-MC, 3.6 g (14.2 mmol) of iodine, and 3.6 ml of pyridine was obtained 190 mg (96%) of 1-*N*-pyridinium-3-methylcholanthrene iodide. The perchlorate had ir, uv, and NMR spectral properties identical with those of the synthetic specimen described below.

7-*N*-Pyridiniummethyl-12-methylbenz[*a*]anthracene Picrate. 7-Hydroxymethyl-12-methylbenz[*a*]anthracene was prepared by the method of Boyland and Sims.[22] A solution of 500 mg (1.85 mmol) of phosphorus tribromide in 4 ml of benzene was added over 5 min to a well-stirred suspension of 240 mg (0.904 mmol) of 7-hydroxymethyl-12-methylbenz[*a*]anthracene in 15 ml of benzene. After 1.5 h at room temperature, the reaction mixture was poured into 20 ml of water. The benzene layer was washed with saturated sodium bicarbonate solution and water, dried ($MgSO_4$), and evaporated to give 288 mg (96%) of crude 7-bromomethyl-12-methylbenz[*a*]anthracene: 100-MHz NMR ($CDCl_3$) 8.4–8.15 (m, 3 H), 7.86 (d, J = 9 Hz, 1 H), 7.8–7.3 (m, 6 H), 5.32 (s, 2 H, CH_2Br), 3.19 (s, 3 H, CH_3).

The crude bromomethyl-12-MBA (60 mg) was dissolved in 6 ml of pyridine. 7-Pyridiniummethyl-12-MBA bromide began to precipitate within minutes. After 2 h at room temperature, ether was added to complete the precipitation, and the product was collected, yield 73 mg (98%). The bromide was converted to the title picrate by the usual procedure: mp 178–179 °C; ir 3080, 1630, 1610, 1550, 1490, 1475, 1433, 1363, 1332, 1310, 1290, 1263, 1160, 1140, 1075, 920, 908, 818, 785, 750, 705, 678 cm^{-1}; uv λ_{max} (log ϵ) 363 (4.35), 348 (4.33), 295 (4.80), 284 (4.79), 275 (4.63), 260 (4.62); 100-MHz NMR (Me_2SO-d_6) 8.92 (d of m, J = 7 Hz, 2 H, Hα), 8.75–8.3 (m, 6 H, includes picrate hydrogen singlet at 8.55), 8.3–7.5 (m, 9 H), 6.95 (s, 2 H, CH_2N), 3.35 (s, 3 H, CH_3).

Anal. ($C_{31}H_{22}N_4O_7$) C, H, N.

7-Methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene Picrate. The synthesis described is analogous to that employed for the 7-pyridiniummethyl isomer. However, since the synthesis of 12-hydroxymethyl-7-methylbenz[*a*]anthracene via the lead tetraacetate oxidation of DMBA gives the 12-hydroxymethyl isomer in low yield,[22] a more efficient method of synthesis was sought. A mixture of 3.00 g (11.7 mmol) of 7,12-DMBA and 2.115 g (11.9 mmol) of *N*-bromosuccinimide in 60 ml of carbon tetrachloride was heated to reflux and irradiated with a sunlamp for 15 min. After removal of the succinimide and solvent, 4.0 g of solid residue was obtained. NMR analysis indicated a molar composition of 55% 12-bromomethyl-7-MBA (singlets at 2.66 and 5.24), 30% 7-bromomethyl-12-MBA (singlets at 2.94 and 5.08), and 15% unreacted DMBA (singlets at 2.76 and 3.10). The crude mixture, 1.33 g, was dissolved in 20 ml of tetrahydrofuran, mixed with 3 ml of 2 N sodium hydroxide solution, and stirred at room temperature for 40 h. The THF was removed on a rotary evaporator, and the residue was dissolved in benzene. After washing with water, drying ($MgSO_4$), and evaporating the solvent, 1.19 g of residue were obtained. Analysis of the residue by TLC confirmed the presence of the two isomeric alcohols and DMBA. Chromatography on an alumina column with benzene afforded 265 mg of pure 12-hydroxymethyl-7-methylbenzanthracene. A sample recrys-

tallized from ethanol melted at 264 °C (lit.[22] 264 °C). Reaction of the alcohol with phosphorus tribromide under the conditions described for 7-hydroxymethyl-12-MBA gave 12-bromomethyl-7-MBA in 85% yield: 100-MHz NMR ($CDCl_3$) 8.95 (m, 1 H), 8.49 (m, 1 H), 8.10 (m, 1 H), 7.75–7.2 (m, 7 H), 5.32 (s, 2 H, CH_2Br), 2.76 (s, 3 H, CH_3). The bromomethyl derivative was converted by the usual procedure to the title picrate: mp 164–165 °C dec; ir 3120, 3080, 1631, 1610, 1552, 1495, 1478, 1435, 1363, 1335, 1311, 1290, 1270, 1160, 1138, 1075, 785, 745, 708, 680 cm^{-1}; uv λ_{max} (log ϵ) 400 (4.08), 381 (4.22), 363 (4.32), 352 (4.31), 297 (4.76), 286 (4.77), 275 (4.61), 266 (4.56), 237 (4.51); 100-MHz NMR (Me_2SO-d_6) 8.88 (m, 2 H, Hα), 8.75–8.35 (m, 4 H, includes picrate hydrogen singlet at 8.55), 8.35–7.35 (m, 11 H), 7.06 (s, 2 H, CH_2N), 3.15 (s, 3 H, CH_3).

Anal. ($C_{31}H_{22}N_4O_7$) C, H, N.

7-*N*-Pyridiniummethylbenz[*a*]anthracene Perchlorate. 7-Bromomethylbenz[*a*]anthracene was prepared from BA by the bromomethylation procedure of Dipple and Slade[23] and converted to the title perchlorate by a procedure analogous to that described for the pyridiniummethylmethylbenz[*a*] anthracenes. The title compound exhibited the following properties: mp 212–213 °C; ir 3120, 3050, 1625, 1497, 1478, 1142, 1121, 1108, 1090, 1053, 830, 767, 755, 694, 683, 675, 622 cm^{-1}; uv λ_{max} (log ϵ) 390 (3.47), 372 (3.85), 356 (3.96), 341 (3.86), 326 (3.67) 292 (4.91), 281 (4.83), 271 (4.59), 254 (4.48), 230 (4.51); 100-MHz NMR (acetone-d_6) 9.62 (s, 1 H, H12), 8.98 (d of m, J = 7 Hz, 3 H, Hα, H1), 8.62 (t of m, J = 8 Hz, Hγ), 8.5–7.5 (m, 11 H), 7.05 (s, 2 H, CH_2N).

Anal. ($C_{24}H_{18}ClNO_4$) C, H, Cl, N.

1-*N*-Pyridinium-3-methylcholanthrene Perchlorate. A solution of 800 mg (2.62 mmol) of 1-hydroxy-3-methylcholanthrene[24] and 1.075 g (5.64 mmol) of *p*-toluenesulfonyl chloride in 25 ml of pyridine was kept at −4 °C for 3 days. The mixture was then diluted with 75 ml of cold water. After 20 min, the crude 1-*N*-pyridinium-3-MC tosylate was collected and dried by suction filtration. The tosylate was purified by dissolution in 50 ml of hot chloroform and addition of ether to the cooled solution to complete the precipitation. The tosylate was converted quantitatively to the perchlorate as described in the general procedure: mp <260 °C dec; ir 3060, 1628, 1495, 1482, 1120, 1108, 1090, 825, 795, 772, 750, 680, 635, 622 cm^{-1}; uv, λ_{max} (log ϵ) 393 (3.15), 375 (3.76), 358 (3.91), 341 (3.83), 327 (3.66), 295 (4.86), 283 (4.82), 273 (4.61), 233 (4.47), 222 (4.57); 100-MHz NMR (Me_2SO-d_6), 9.58 (s, 1 H, H6), 9.16–8.84 (m, 3 H, Hα, H7), 8.62 (t of m, J = 8 Hz, 1 H, Hγ), 8.3–7.4 (m, 10 H), 4.36 (d of d, J = 19 and 8 Hz, 1 H, H2), 3.76 (d, J = 19 Hz, 1 H, H2′), 2.46 (s, 3 H, CH_3).

Anal. ($C_{26}H_{20}ClNO_4$) C, H, Cl, N.

Synthesis of 7-Ethylbenz[*a*]anthracene. To a stirred solution of 2.80 g (12.3 mmol) of benz[*a*]anthracene and 5.80 g (73.9 mmol) of acetyl chloride in 20 ml of chloroform maintained at 0 to −5 °C was gradually added 3.30 g (24.7 mmol) of anhydrous aluminum chloride. After 30 min the mixture was allowed to warm to 10 °C, and water was added to decompose the complex. The chloroform layer was removed, and the aqueous layer was extracted with additional portions of chloroform. The combined chloroform solutions were washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina using hexane–benzene 4:1 as the elutant, to give 2.39 g (72%) of 7-acetylbenz[*a*]anthracene: 100-MHz NMR ($CDCl_3$) 8.92 (s, 1 H, H12), 8.55 (m, 1 H, H1), 8.0–7.3 (m, 9 H, 2.64 (s, 3 H, CH_3).

Lithium aluminum hydride (2.25 g, 59.3 mmol) was added to a solution of anhydrous aluminum chloride (15.7 g, 118 mmol) with stirring. After 30 min, solid 7-acetylbenz[*a*]anthracene (4.00 g, 14.8 mmol) was added in sufficiently small portions to keep the solution below reflux temperature. Within 5 min after the final addition, no starting material could be detected by TLC, and the excess $LiAlH_4$ was decomposed by adding ethyl acetate. The mixture was poured into water and extracted with chloroform. From the chloroform extracts was obtained 3.5 g of crude 7-ETBA which was purified by chromatography on a silica gel column using hexane–benzene (9:1) as elutant, and subsequent recrystallization from benzene–methanol: yield 3.3 g (87%); mp 112–113 °C (lit.[25] 113.5–114 °C); 100-MHz NMR ($CDCl_3$) 8.97 (s, 1 H, H12), 8.72 (m, 1 H, H1), 8.20 (m, 1 H), 8.1–7.9 (m, 2 H), 7.85–7.3 (m, 6 H), 3.50 (q, J = 8 Hz, 2 H, CH_2), 1.37 (t, J = 8 Hz, 3 H, CH_3).

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Registry No.—BA, 56-55-3; 2-MBA, 2498-76-2; 5-MBA, 2319-96-2; 6-MBA, 316-14-3; 7-MBA, 2541-69-7; 8-MBA, 2381-31-9; 11-MBA, 6111-78-0; 12-MBA, 2422-79-9; 7-ETBA, 3697-30-1; 7,12-DMBA, 57-97-6; 3-MC, 56-49-5; pyridine, 110-86-1; 7-*N*-pyridiniumbenz[*a*]-anthracene perchlorate, 59230-69-2; 7-ethyl-12-*N*-pyridiniumbenz[*a*]anthracene perchlorate, 59230-71-6; 2-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide, 59230-72-7; 5-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide, 59230-73-8; 7-*N*-pyridinium-11-methylbenz[*a*]anthracene iodide, 59230-74-9; 7-*N*-pyridinium-12-methylbenz[*a*]anthracene perchlorate, 59230-76-1; 5-*N*-pyridinium-7,12-dimethylbenz[*a*]anthracene perchlorate, 17066-30-7; 7-*N*-pyridiniummethyl-12-methylbenz[*a*]anthracene picrate, 59230-78-3; 7-hydroxymethyl-12-methylbenz[*a*]anthracene, 568-75-2; 7-bromomethyl-12-methylbenz[*a*]anthracene, 16238-56-5; 7-methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene picrate, 59230-80-7; 12-bromomethyl-7-MBA, 59230-81-8; 7-*N*-pyridiniummethylbenz[*a*]anthracene perchlorate, 59230-82-9; 1-*N*-pyridinium-3-methylcholanthrene perchlorate, 59230-84-1; 1-hydroxy-3-methylcholanthrene, 3342-98-1; acetyl chloride, 75-36-5; 7-acetylbenz[*a*]-anthracene, 59230-85-2.

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