References and Notes

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(2) Portions of this work were presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975, Abstract INOR-122.
(3) Postdoctoral research associate, 1971–1974.
(4) Postdoctoral research associate, 1974–1975, on leave from the National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa.
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Synthesis and Spectral Properties of the Isomeric Hydroxybenzo[*a*]pyrenes

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Syntheses of the 12 isomeric hydroxybenzo[*a*]pyrenes are described. Previous syntheses of eight of these isomers have been repeated and improved upon. New syntheses of the 1-, 2-, 4-, 10-, and 12-hydroxybenzo[*a*]pyrenes are reported. Infrared, ultraviolet, fluorescence, and ^{1}H NMR spectra of the 12 phenols are provided to facilitate study of the metabolism of this important environmental carcinogen.

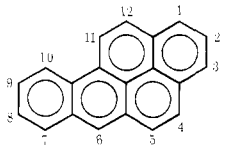
This laboratory has had a long-standing interest in the fundamental mechanisms and pathways through which aromatic compounds undergo oxidative metabolism within the cell.[4] Much of this interest was stimulated by our observation that aromatic ring substituents undergo intramolecular migration and retention (i.e., the NIH shift)[5] during the course of aromatic hydroxylation by monoxygenase enzymes.[6] Occurrence of the NIH shift suggested that aromatic hydroxylation was mediated by arene oxides and led ultimately to the identification of naphthalene 1,2-oxide as the obligatory intermediate in route to the several oxidative metabolites of naphthalene by mammals.[7] The past 5 years have seen a growing interest in the chemistry[8] and biochemistry[9] of arene oxides as this class of compounds has been shown to be potent frameshift mutagens in bacterial test systems, implicated in certain forms of metabolism induced cytotoxicity and necrosis, and shown to induce transformation of mammalian cells in culture (cf. ref 9). Although transformation of cells in culture cannot be directly equated with carcinogenesis in vivo, the possibility does exist that arene oxides are ultimate carcinogens[10] in mammals. For this reason, we have undertaken a comprehensive study of the carcinogen benzo[*a*]pyrene (BP).

Although BP must be classified as a relatively weak carcinogen[11] when compared to 3-methylcholanthrene or 7,12-dimethylbenzo[*a*]anthracene, BP is one of the most prevalent and ubiquitous environmental carcinogens to which man is exposed.[12] In addition, definitive studies of the metabolism of this hydrocarbon should be possible through the use of presently available techniques such as gas chromatography and high-pressure liquid chromatography. Interestingly, BP was the first chemical compound for which a causal relationship with cancer was established.[13]

An initial goal of this program has been the chemical synthesis of primary metabolites, arene oxides and phenols, of BP for use as reference standards in the study of the metabolism of BP. Despite the wide interest in the metabolism and carcinogenicity of this hydrocarbon, the synthesis of only eight of the 12 possible phenols had been described, and none of these were readily available for biological examination. The present study describes synthesis of the unknown phenols of BP and improvements on the prior synthetic procedures. Additionally, spectral and chemical properties of these isomers are reported.

Results and Discussion

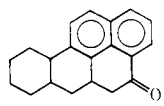
From a synthetic standpoint, the hydrocarbon BP can be considered to have four distinct regions into which the hydroxyl group must be introduced: the 1, 2, and 3 positions which are peculiar to pyrene residues in polycyclic aromatic hydrocarbons, the 4,5- and 11,12-K regions, the highly reactive 6 position which can be considered similar to 9,10 (meso) positions in anthracene, and the 7, 8, 9, and 10 positions in the benzo ring. Only two highly selective reactions



are known for the parent hydrocarbon, substitution at the 6 position and reaction of the 4,5-K region with osmium tetroxide to form the 4,5-dihydrodiol on hydrolysis of the osmate ester.[14] Thus, the only phenol which has been obtained by direct modification of the parent hydrocarbon is 6-hydroxy BP, which Fieser and Hershberg[15] obtained in good yield by acetoxylation of BP with lead tetracetate.

Synthesis of one of the two possible phenols at each of the K regions has been achieved via intramolecular cyclization of polycyclic hydrocarbon acetic acids in liquid HF to ketones which spontaneously isomerize to phenols. Thus, Fieser and Johnson[16] described the cyclization of 4-chrys-

Table I. Methods, Yields, and Melting Points of the Isomeric Phenols of BP Obtained from the Indicated Precursors[c]

Position of hydroxyl	Precursor	Method	Yield, % (mp,[a] °C)	Ref to prior synthesis
1	1e (Scheme I)	Pd, -3H$_2$ 27 h	90[b] (dec)	20a, 21, 24
2	2e (Scheme III)	Pd, -3H$_2$ 15 h	61 (227–228)	
3	3e (Scheme II)	Pd, 3H$_2$ 7 h	95 (226–227)	20a
4		Pd, -4H$_2$ 20 h	48 (220–222)	
5	4-Chryseneacetic acid (Scheme IV)	HF 0.5 h	43 (195–196)	16
6	6-Acetoxy BP	1. Pb(OAc)$_4$ 2. CH_3MgBr	62 (207–209)	15
7	7 (Scheme VI)	Pd, -H$_2$ 4 h	62 (218–219)	18
8	8 (Scheme VI)	Pd, -H$_2$ 10 h	67 (228)	19
9	9 (Scheme VI)	Pd, -H$_2$ 10 h	80 (196)	19
10	10 (Scheme VI)	Pd, -H$_2$ 10 h	70 (200–201)	
11	1-Benzo[a]anthraceneacetic acid	HF 1 h	71 (220)	17
12	12c diacetate (Scheme V)	1. DDQ, -HOAc, -H$_2$ 2. hyd	66 (230–231)	

[a] For the most part, these numbers represent decomposition temperatures rather than true melting points. [b] Yield based on recovered ketone. See Experimental Section. [c] Previously undescribed phenols gave combustion analyses within ±0.3% calculated for $C_{20}H_{12}O$.

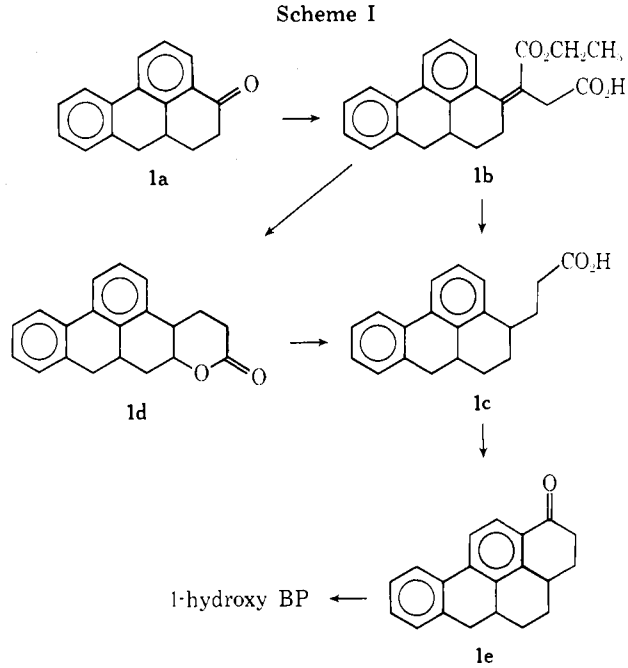
eneacetic acid to 5-hydroxy BP and Fieser and Heymann[17] the cyclization of 1-benzo[a]anthraceneacetic acid to 11-hydroxy BP. Prior to this study, syntheses of 4- and 12-hydroxy BP had not been described. For convenience, the immediate precursors to the hydroxy BP isomers are indicated in Table I.

For the 7, 8, and 9 positions on the benzo ring, the corresponding ketones of 7,8,9,10-tetrahydro BP have been dehydrogenated to the corresponding phenols.[18,19] 10-Hydroxy BP had not been previously reported.

Synthesis of the phenols at the 1, 2, and 3 positions have proved the most difficult. Cook et al.[20a] devised a multistep synthesis of a hexahydro BP ketone (Table I) which was then dehydrogenated to 3-hydroxy BP. Direct synthesis of 1-hydroxy BP[20a] was also described by acetoxylation of 6-chloro BP. The resulting 1-acetoxy-6-chloro BP was then converted to 1-methoxy BP in very low overall yield. Subsequently, we described a multistep synthesis of 1-hydroxy BP[21] which confirmed the structure of the material from the initial synthesis. 2-Hydroxy BP had not previously been reported.

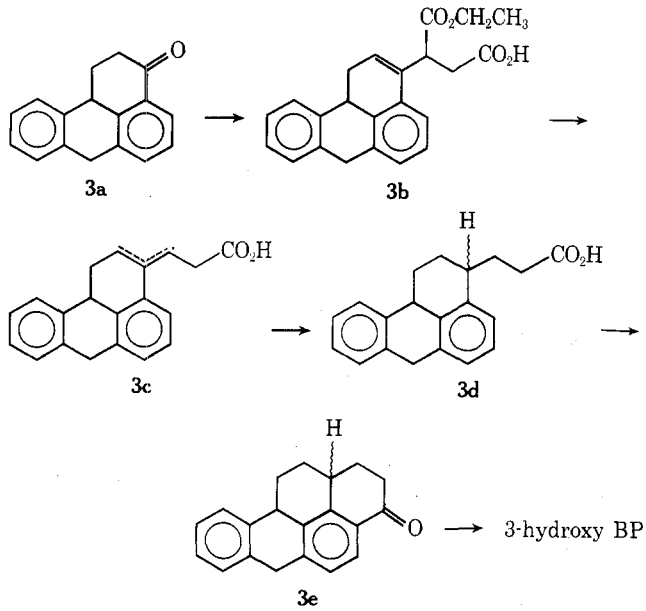
Synthesis. Since our initial report,[21] we have modified the synthetic route to 1-hydroxy BP such that the overall yield from 5,6,6a,7-tetrahydrobenz[de]anthracen-4-one (**1a**) was increased from 8% to 32%. Stobbe condensation of **1a** with diethyl succinate by the procedure of Daub and Johnson[22] afforded β-carbethoxy-β-(5,6,6a,7-tetrahydro-4*H*-benz[de]anthracen-4-ylidene)propionic acid (**1b**) in 85% yield. Previously, decarboxylation of **1b** was accompanied by disproportionation to **1c** (Scheme I) and β-(7*H*-benz[de]anthracen-4-yl)propionic acid (**7** in ref 21), which on cyclization with HF spontaneously dehydrogenated to 1-hydroxy BP.[21] Decarboxylation of the Stobbe product **1b** under reducing conditions provided the desired β-(5,6,6a,7-tetrahydro-4*H*-benz[de]anthracen-4-yl)propionic acid (**1c**) along with a small amount of lactone **1d** which was convertible to **1c**. Cyclization of **1c** to 3,3a,4,5,5a,6-hexahydrobenzo[a]pyren-1-(2*H*)-one (**1e**) proceeded as described.[21] The ketone **1e** was then dehydrogenated to 1-hydroxy BP. Our purpose in suppressing disproportionation during decarboxylation of **1b** and thereby improving the synthesis of **1e** resides in the possibility for conversion of **1e** into the presently unknown benzo[a]pyrene 1,2-oxide.[23] Once it had become clear through these synthetic studies[21] that the acetoxylation of 6-halo BP does indeed proceed at C-1 as described by Cook et al.,[20] Harvey and Cho[24] were able to improve greatly the original synthesis of 1-hydroxy BP through the use of modern techniques.

Scheme I



Both 2- and 3-hydroxy BP have been prepared by modification of the procedure which Cook et al.[20a] developed for the synthesis of 3-hydroxy BP. In this synthesis, 9-anthral-

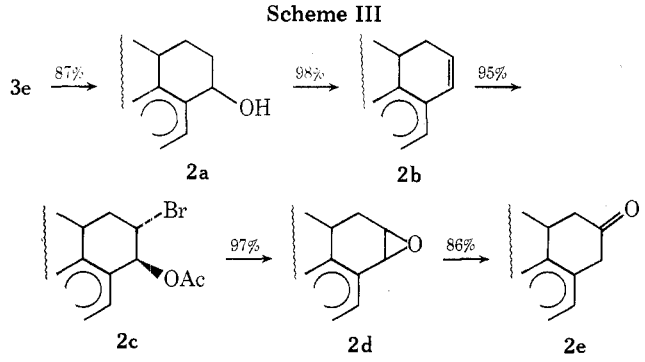
Scheme II



dehyde was converted through several steps to the ketone **3a** (Scheme II). Subsequently Daub and Doyle described an improved preparation of the precursors leading to **3a** via anthrone.[20b] Stobbe condensation of **3a** provided **3b** which appears to be mainly the isomer with the endocyclic double bond. Attempted decarboxylation of **3b** with hydrobromic acid resulted in disproportionation as well as decarboxylation in a fashion similar to that shown in Scheme I. This difficulty has been avoided by simply substituting hydrochloric acid for hydrobromic acid to obtain instead the acid **3c** which was reduced to a mixture of diastereomeric acids **3d** (XVA and XVB in ref 20) by sodium and amyl alcohol. The acids were cyclized to the diastereomeric ketones **3e,** both of which dehydrogenate smoothly to 3-hydroxy BP.

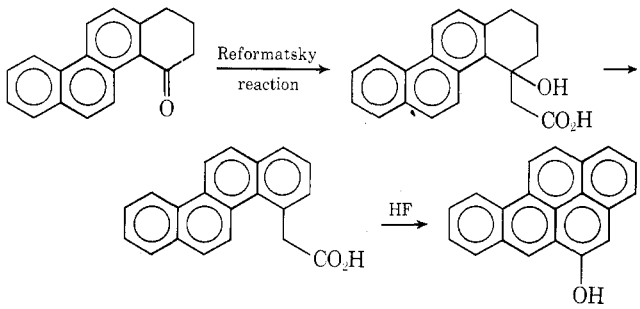
2-Hydroxy BP was synthesized by isomerization of 1,6,10b,11,12,12a-hexahydrobenzo[a]pyren-3-(2*H*)-one (**3e,** isomer XVIA in ref 20a) to the ketone at the 2 position (Scheme III, **2e**) and subsequent dehydrogenation (76% yield). Isomerization of the ketone **3e** was accomplished by (1) reduction to the alcohol **2a,** (2) dehydration to the hexahydro BP **2b,** (3) formation of the *trans*-bromohydrin acetate **2c,** (4) cyclization to epoxide **2d,** and (5) isomerization to the desired ketone **2e.** While the number of steps in this transformation is large, the method is highly practical in that the overall conversion was accomplished in nearly 70% yield.

Scheme III



Fieser's general approach to the synthesis of K-region phenols, particularly 5-hydoxy BP[16] and 11-hydroxy BP,[17] was found quite satisfactory. The general concept is typified by Scheme IV. We experienced little of the solubility

Scheme IV

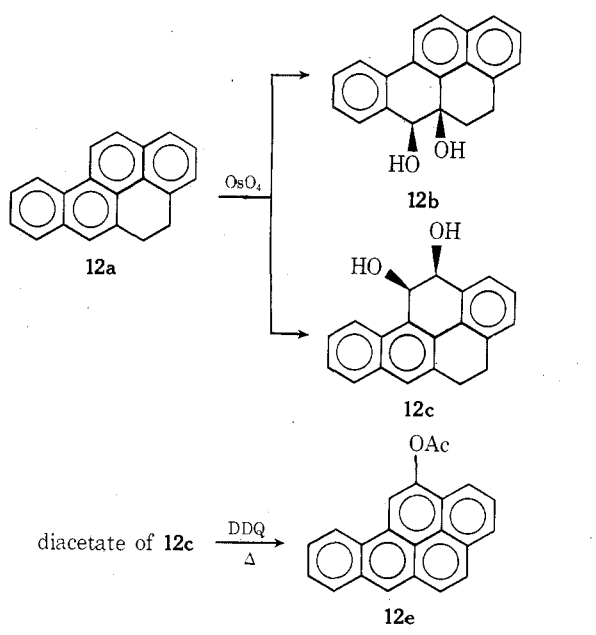


problem[16] which was observed in the Reformatsky reaction leading to 4-chryseneacetic acid, possibly because highly purified zinc was used. In addition, direct distillation of the crude Reformatsky products with sulfur, thus by-passing several intermediate steps, significantly improved the overall yield. Typical experiments en route to 11-hydroxy BP are described.

For synthesis of the unknown 4-hydroxy BP, dehydrogenation (Table I) of the known 5a,6,6a,7,8,9,10,10a-octahydrobenzo[a]pyren-4-(5*H*)-one[25] was found to proceed in 58% yield. In general, multiple dehydrogenations such as this proceed slower and in lower yield. Cyclization of 5-chryseneacetic acid, which could have been prepared en route to the above ketone, would probably represent a more convenient synthesis of 4-hydroxy BP.

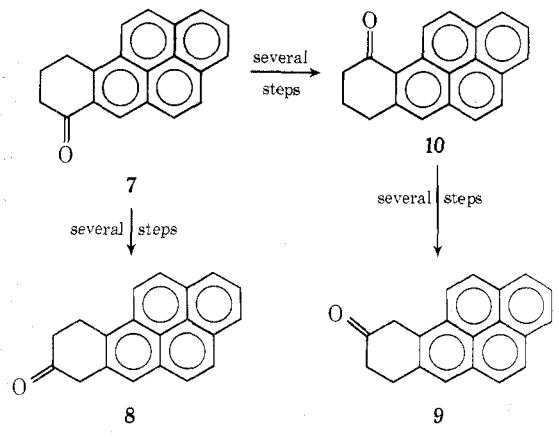
The route employed for the synthesis of the remaining unknown K-region phenol, 12-hydroxy BP, was dictated by a desire to introduce functionality at the 11,12 position which would also be useful in the synthesis of the unknown BP 11,12-oxide.[23] In an attempt to direct the reaction of osmium tetroxide to the 11,12-K region, the more reactive 4,5-K region was first reduced to produce 4,5-dihydro BP (**12a,** Scheme V) and then the osmium tetroxide reaction

Scheme V



was conducted. The two possible cis dihydro diols at the 5a,6- and 11,12-K regions (**12b**[26] and **12c**) were formed. Prior studies[27] on the dehydration of cis dihydro diols at the "bay region" of polycyclic hydrocarbons established that the hydroxyl group in the bay region occupies a highly axial environment and is thereby predisposed to elimination because of the trans-diaxial nature of such dehydrations. As expected, heating the diacetate of **12c** with DDQ

Scheme VI



in toluene cleanly produced 12-acetoxy BP which was readily hydrolyzed to the desired phenol. Less vigorous conditions for the oxidation allowed isolation of *cis*-11,12-diacetoxy-11,12-dihydro BP.[23]

The prior synthesis of 6-hydroxy BP was found to occur exactly as described.[15] This phenol was also obtained as a product from an attempted synthesis of BP 5a,6-oxide.[28]

The four isomeric phenols in the benzo ring of BP, including the unknown 10-hydroxy BP, were obtained by dehydrogenation (Table I) of the corresponding ketones of tetrahydro BP (**7–10**, Scheme VI). All of these ketones originate from 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[18] (**7**). Conversion to 10-hydroxy-7,8,9,10-tetrahydro BP has been described.[29,30] Oxidation with chromium trioxide–pyridine provided ketone **10** (Scheme VI). Ketones **8** and **9** had ppreviously been obtained[19] by dehydration of tetrahydrodiols of BP at the 7,8 and 9,10 positions, respectively. Sequences analogous to that shown in Scheme III have proved far more satisfactory.

Spectral Properties. Complete infrared spectra of the phenols in KBr, ultraviolet and fluorescence spectra of the phenols and their corresponding phenolate anions, and 220-MHz ^{1}H NMR spectra of the phenols in tetrahydrofuran-d_8 are presented in the supplemental data provided with the microfilm version of this article. These spectra were determined on analytically pure samples of the 12 isomeric phenols and represent the first collection of data of this type for a carcinogenic polycyclic aromatic hydrocarbon. The absence of such tabulations has greatly hampered the study of the carcinogenicity and particularly the metabolism of aromatic carcinogens in the past.

Comparison of the infrared spectra for these phenols established that sufficient differences exist in fine structure to allow ready identification of individual isomers as well as identification and possible quantitation of complex mixtures. Fourier transform infrared coupled with gas or liquid chromatography could prove invaluable to quantitative metabolism studies. None of the phenols exhibited detectable amounts of keto tautomers in solid KBr.

Mass spectra of the hydroxy BP isomers (Table II) are characterized by intense molecular ions which, in most cases, show a fragment ion at M − 29 which is typical of phenols.[31] For the 2-, 3-, 5-, 9-, and 10-hydroxy BP isomers, the electron impact spectra show base peaks in the region of *m/e* 100, the intensities of which were variable among separate runs, possibly owing to variation in source pressure. The spectra, either by electron impact or chemical ionization with ammonia, do not appear to provide a suitable means of distinguishing among isomers. Mass spectrometry has been employed to confirm the molecular weight of phenols produced on metabolism of BP,[32] but

Table II. Electron Impact and Chemical Ionization Mass Spectra of the Isomeric Hydroxybenzo[*a*]pyrenes[a]

Position of hydroxyl	Electron impact (70 eV)		Chemical ionization (NH_3)	
	M^+ (268)	$M^+ - 29$	M^+ (269)	$M^+ - 29$
1	100	0	100	0
2	100	14	100	60
3	100	46	100	45
4	100	60	100	50
5	100	33	100	0
6	100	55	100	50
7	100	50	100	80
8	100	55	100	50
9	100	50	100	50
10	100	57	100	70
11	100	45	100	0
12	100	45	100	0

[a] Mass spectra were determined with a Finnigan Model 1015D gas chromatograph–mass spectrometer. Samples were introduced through the direct inlet port. Relative intensities are given for the molecular ion and the fragment after loss of 29, which are the only significant high mass signals.

should not be taken as evidence for the position of the hydroxyl group.

^{1}H NMR spectra of the phenols were determined at 220 MHz in tetrahydrofuran-d_8. This solvent was selected because of the generally low solubility of the phenols in other solvents. 6-Hydroxy BP was studied as the acetate since the free phenol rapidly decomposed in tetrahydrofuran. A very broad envelope of absorption in the aromatic region suggested that radicals were present.

Chemical shifts (Table III) for the ring hydrogens in BP and the twelve phenols were assigned with the aid of double resonance and comparison with the spectra of related hydrocarbons.[33,34] Absolute assignment of H_1 vs. H_3 and H_4 vs. H_5 is particularly difficult because decoupling experiments do not allow distinction between these pairs. Hydrogens H_1 and H_3 are identical in the symmetric hydrocarbon pyrene. For BP, however, H_1 should be more deshielded relative to H_3 because of the ring current produced by asymmetric introduction of the additional ring.[34] A similar argument applies to H_4 and H_5. This principle was applied in making the assignments of Table III and may be subject to revision for the indicated pairs. The same assignment for BP has been made by Haight and Mallion[35] without justification for the relative assignment within these pairs. Cavalieri and Calvin[36] initially assigned H_1 and H_3 opposite to that in Table III but later revised[37] the assignment.[38]

In general, the H_{10} and H_{11} hydrogens of BP and the isomeric phenols appear at lowest field owing to van der Waals effects and edge deshielding by the aromatic ring in the bay position.[33,34] Introduction of the hydroxyl group into BP results in characteristic[34] upfield displacements in chemical shifts at positions equivalent to ortho, meta, and para hydrogens in the same ring by about 0.38–0.80, 0.13–0.21, and 0.48–0.47 ppm, respectively. Characteristic[34] downfield shifts of 0.33–0.45 ppm were observed for hydrogens at positions peri to a hydroxyl group. Similarily, pronounced downfield shifts of ~1.2 ppm were observed for the bay region hydrogen in 10- and 11-hydroxy BP. The above considerations adequately explain the chemical shifts presented in Table III.

BP represents a one-spin (H_6), a three-spin (H_1,H_2,H_3), a four-spin (H_7,H_8,H_9,H_{10}), and a pair of two-spin (H_4,H_5 and H_{11},H_12) systems. Magnitudes of the coupling constants are fairly characteristic[33,34] for polycyclic aromatic hydrocarbons in that J_{ortho} = 6.0–9.4, J_{meta} = 1.2–1.6, and

Table III. Chemical Shifts (ppm) Downfield from Internal Me_4Si for BP and the 12 Isomeric Phenols[a]

Registry no.	Compd	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{11}	H_{12}
50-32-8	BP	8.23	7.95	8.08	7.92	8.00	8.54	8.28	7.73	7.80	9.11	9.12	8.33
13345-23-8	1-OH	(9.52)[b]	7.37	7.89	7.77[c]	7.77[c]	8.39	8.21	7.69	7.73	9.07	9.04	8.66
56892-30-9	2-OH	7.59	(8.93)	7.56	7.80	7.94	8.47	8.23	7.63	7.75	9.02	9.02	8.16
13345-21-6	3-OH	8.06	7.48	(9.34)	8.26	7.87	8.38	8.21	7.68	7.72	9.01	8.86	8.18
37574-48-4	4-OH	8.26	7.97	8.52	(9.37)	7.24	8.30	8.17	7.65	7.70	9.04	9.08	8.30
24027-84-7	5-OH	8.03	7.87	7.87	7.17	(9.39)	8.98	8.34	7.71[c]	7.82[c]	9.09	9.08	8.28
53555-67-2	6-OAc	8.23	7.94	8.08	7.95	8.02		8.31	7.79[c]	7.82[c]	9.14	9.10	8.29
37994-82-4	7-OH	8.18	7.91	8.04	7.87	8.03	8.99	(9.45)	7.07	7.59	8.54	9.03	8.26
13345-26-1	8-OH	8.18	7.88	8.04	7.86	7.93	8.34	7.51	(8.75)	7.38	8.95	9.00	8.26
17573-21-6	9-OH	8.15	7.89	8.01	7.81	7.94	8.44	8.15	7.35	(8.95)	8.31	8.91	8.24
56892-31-0	10-OH	8.20	7.91	8.03	7.89	7.96	8.48	7.80	7.53	7.16	(9.71)	10.32	8.25
56892-32-1	11-OH	8.00	7.85[c]	7.90[c]	7.82	7.96	8.55	8.25	7.71[c]	7.71[c]	10.27	(9.76)	7.63
56892-33-2	12-OH	8.61	7.92	8.09	7.84	7.96	8.33	8.22	7.67[c]	7.70[c]	8.87	8.33	(9.58)

[a] 6-Hydroxy BP was measured as the acetate owing to instability of the free phenol. Spectra were measured with a Varian 220-MHz spectrometer on degassed and sealed samples which contained 15 mg of each compound in 0.8 ml of tetrahydrofuran-d_8. Decoupling experiments with a Varian HA-100 spectrometer aided in the spectral assignments. [b] Numbers in parentheses indicate the chemical shift of the hydroxyl hydrogens. [c] In these pairs of signals, distinction between the two hydrogens was not possible.

Table IV. Ultraviolet Absorption Data for the Phenols (Methanol) and Phenolate Anions (0.1% NaOH in 90% Methanol)[c]

Position of hydroxyl	Phenols				Phenolate anions			
1	257.5							
	266	(4.64)	298	398	261.5	(4.61)	310	424.5
	276.5							
2[a]	286.5	(4.67)	301[b]	382	264	(4.77)	302	387
3	258	(4.67)	307	380	237	(4.68)	314	394
4	267	(4.84)	299	375	271	(5.02)	311	390
5	262	(4.70)	302	381	257	(4.82)	317	405
6	256		302.5	(4.70) 391	251.5	(4.39)	312.5	433
				379				
7	268		303.5	(4.71) 399	251	(4.73)	318	438
8[a]	279	(4.75)	306[b]	383.5	264		296	(4.82) 386
9[a]	267	(4.75)	301.5	379	269	(4.75)	292	396
	250							
10	256	(4.57)	302	379	250.5	(4.61)	325	(4.61) 402
11	268	(4.80)	301	382	276	(4.80)	308[b]	395
12	255		295	(4.65) 380	260	(4.62)	308	418

[a] Unusual shifts in absorption were observed in alkali (see Discussion). [b] Not actual peaks but inflections or shoulders. [c] Logarithms of molar extinction coefficients for the most intense peak(s) are given. Samples were freshly prepared and read immediately for experiments in base.

$J_{para} < 1.0$ Hz. For BP, coupling constants of $J_{1,2} = 7.8$, $J_{1,3} = 1.0$, $J_{2,3} = 7.6$, $J_{4,5} = 9.1$, $J_{7,8} = 7.5$, $J_{7,9} = 1.5$, $J_{8,9} = 7.5$, $J_{8,10} = 1.8$, $J_{9,10} = 7.5$, and $J_{11,12} = 9.2$ Hz were observed. These values are nearly identical with the values of Haight and Mallion.[35] The corresponding values for the isomeric phenols were within ±0.2 Hz except when the presence of a hydroxyl group eliminated individual couplings.

Ultraviolet and fluorescence spectra of the phenols and their phenolate anions are tabulated in Tables IV and V. The ultraviolet spectra of the phenols are characterized by two broad absorption bands, the stronger in the 250–300-nm region and the weaker in the 360–400-nm region. The phenolate anions also show two broad absorption bands with a bathochromic shift relative to the phenol for both the long-wavelength band and the 300-nm component of the short-wavelength band with minor exceptions. Long-wavelength shifts of 10–15 nm from the ~300-nm region in the phenol appear as shoulders or inflections for the 2, 8, and 9 isomers. In addition, the 2 and 8 isomers show little shift for the long-wavelength band. Fluorescence of the phenols were relatively similar both in intensity and emission maxima with vibrational fine structure present in most instances. Greater variation in emission maxima and intensity were observed for the phenolate anions with the anions of the 5, 7, 8, and 10 isomers being only weakly or not fluorescent.

In general, the ultraviolet spectra of the phenols are sufficiently similar that distinction between single isomers and mixtures in which a single isomer substantially predominates is not possible. This has led some workers to the possibly erroneous conclusion that metabolism of BP produces only 3- and 9-hydroxy BP as phenolic metabolites.[39] Metabolism of BP is commonly monitored by the production of alkali extractable, fluorescent products and quantitated by comparison with the fluorescence observed from the phenolate anion of 3-hydroxy BP.[40] Since only the 3- and 9-hydroxy isomers are strongly fluorescent in alkali,[41] the assay selects for these products. When the assay was conducted by measuring the fluorescence of alkali extractable metabolites in acid where the fluorescence intensity of individual phenols are more comparable, increases in metabolism turnover numbers of up to 50% were found, suggesting that phenols were formed which were not fluorescent in alkali.[41]

Keto Tautomers. Recently Newman and Olson[42] reported the remarkably facile conversion of 5- and 6-acetoxy-7,12-dimethylbenzo[a]anthracene (K-region acetates) to the corresponding methyl ethers by simple treatment with methanolic HCl. Inspection of the ^1H NMR and infrared spectra of the corresponding phenols established that both exist largely as the keto tautomers, and thus formation of hemiketals followed by dehydration was suggested as the probable mechanism for the transformation.

Table V. Fluorescence Data[a] for the Phenols (Methanol) and Phenolate Anions (0.1% NaOH in 90% Methanol)[c]

Position of hydroxyl	Phenols		Phenolate anions, nm
	Maxima, nm	Intensity[b]	
1	427	350	520
2	417	198	508
3	434	1000	518
4	420	240	519
5	428	258	560
6	438	165	516
7	441	359	560
8	424	151	522
9	427	450	513
10	427	238	Nil
11	423	366	540
12	418	330	519

[a] Measured with a Perkin-Elmer Model MPF-3L fluorescence spectrophotometer in the direct mode with slit width settings of 2 nm for the excitation and emission monochromaters. [b] Relative fluorescence intensities of phenols measured with the above spectrofluorimeter settings at λ excitation 380 nm, and λ emission 434 nm. These are optimum for 3-hydroxy BP which has been arbitrarily set to 1000. The measurements were carried out on approximately 10^{-6} M solutions. [c] Samples were freshly prepared and read immediately for experiments in base.

Table VI. Methylation of Hydroxy BP Isomers with Methanol Saturated with Dry HCl[c]

Position of hydroxyl	Conditions		% conversion	
	Temp, °C	Time, h	Methyl ether	Chlorinated products
1	85	2	0	0
2	85	2	0	30[a]
3	85	2	0	0
4	5	48	100	
5	5	24	>95	Trace[a,b]
6	5	48	0	0
7	85	2	50	
8	85	2	50	
9	85	2	80	
10	85	2	50	
11	5	24	90	Trace[a]
12	5	24	50	Trace[a]

[a] The mass spectrum indicated that the product was a chlorinated phenol. [b] The mass spectrum indicated that the product was a methylated and chlorinated phenol. [c] Reactions were conducted in the dark under the indicated conditions. Products were isolated by TLC and conversions estimated by uv. Structures were confirmed by chemical ionization mass spectrometry with isobutane which showed losses of 15 mass units from the molecular ion characteristic of methyl ethers.

These authors proceeded to suggest that such a mechanism could account for the metabolism induced binding[10] of polycyclic hydrocarbons to biopolymers and thereby induce cancer. While there is no apparent correlation between carcinogenicity and the extent to which selected phenols exist as their keto tautomers,[43] this mechanism presently cannot be discounted as a potential pathway to explain some portion of the covalent binding of hydrocarbons to biopolymers in vivo, whether or not this mechanism of binding is associated with carcinogenesis. Dipple et al.[44] have studied the carcinogenicity of 5- and 6-hydroxy-7,12-dimethylbenzo[a]anthracene in mice and have found both phenols inactive in comparison to the parent hydrocarbon. However, comprehensive studies of all the possible phenols from any carcinogenic polycyclic hydrocarbon are presently unavailable.

The effect of methanolic HCl on the isomeric phenols of BP is shown in Table VI. Treatment for 24 h at 5 °C resulted in extensive O-methylation of all four K-region phenols. In addition, the four isomers in the benzo ring showed small amounts of reaction. When the reaction mixtures containing these phenols were heated at 85 °C for 2 h, extensive conversion was observed, whereas the 1-, 2-, 3-, and 6-hydroxy isomers were completely inactive under all conditions.

Neither infrared nor ^{1}H NMR gave indication that keto tautomers were present in dynamic equilibrium with the 12 phenols in this study. Results of the methylation studies indicate that tautomerism is quite facile for K-region phenols and does occur to a significant extent for the phenols in the benzo ring. Enhanced reactivity at the K region is anticipated on electronic grounds and parallels the observed[43] stability of the keto tautomers of 1-naphtol vs. 9-phenanthrol (K region). Methylation of the phenols in the benzo ring is understandable in light of the observation by Newman[45] that even 1- and 2-naphthol are converted to methyl ethers by methanolic HCl. The mechanism of these conversions has been confirmed by the observation that 9-phenanthrol is readily converted to the thio ether in thioethanol–HCl.

Biological Studies. Availability of all 12 of the isomeric phenols possible for BP has allowed a comprehensive approach to be taken in the study of the metabolism and carcinogenicity of the hydrocarbon. High-pressure liquid chromatography on Du Pont permaphase ODS columns with a water–methanol gradient has established that the phenols are eluted from the column in two unresolved peaks with the 2, 6, 8, and 9 isomers contained in the first peak.[46] A similar situation exists for the five phenanthrols where the 2 and 3 isomers elute first as a single peak.[27] In a study of the eight phenols for the two terminal rings of benzo[a]anthracene, the 2, 3, 9, and 10 isomers eluted first.[47] In almost all of these cases, the isomers which emerge from the column first correspond in position on the hydrocarbon to the 2 position on naphthalene. Metabolism of ^{14}C-BP[46] results in substantially higher production of phenols in the second peak, largely because unsymmetrical arene oxides tend to display highly directional opening[8,48] which favors the most stable carbonium ion intermediate. For the six metabolically probable arene oxides from BP,[23] only BP 9,10-oxide[46] should lead to substantial amounts of phenol in the first of the two groups of phenols emerging from the column. Interestingly, the only K-region arene oxide whose isomerization has been adequately studied[48] was found to produce the trans dihydrodiol exclusively on solvolysis at physiological pH.

We are presently examining the biological activity[49] of the 12 isomeric phenols of BP. Tests for mutagenicity toward histidine dependent *Salmonella typhimurium* and toward 8-azaguanine sensitive Chinese hamster V79 cells in culture have shown all 12 compounds to be relatively inactive[50] when compared to BP 4,5-oxide. The 1, 3, 6, 7, and 12 isomers are weakly mutagenic toward the bacterial strain TA 1538 while the 2, 3, 6, and 8 isomers show significant toxicity toward the mammalian cells. Mutagenicity of the 12 phenols after metabolic activation by hepatic microsomes, ability to transform mammalian cells in culture, and carcinogenicity on repeated application to the skin of mice are under study. The biological activity of the phenols will be compared to that of the corresponding arene oxides of BP of which the 4,5-, 7,8-, 9,10-, and 11,12-oxides[23,29] are presently available. The 7-, 9-, and 10-hydroxy BP isomers are relatively effective inhibitors of epoxide hydrase activity toward the 7,8- and 9,10-oxides, respectively, while the K-region phenols caused little inhibition of the hydration of the two K-region arene oxides. All 12 of the phenols gave

very low or negligible binding to polyguanylic acid when compared to 7,12-dimethylbenzo[a]anthracene 5,6-oxide.[51] BP 7,8-oxide is a potent carcinogen on mouse skin.[54]

Experimental Section

Routine ^{1}H NMR spectra were recorded with Varian A-60 and HA-100 instruments. High-resolution ^{1}H NMR spectra were recorded with a Varian HR-220 spectrometer. Tetrahydrofuran-d_8 was used as solvent for the phenols. Ultraviolet spectra were recorded with a Cary 15 recording spectrophotometer. Infrared spectra were determined in KBr disks with a Perkin-Elmer Model 421 grating infrared spectrophotometer. Fluorescence spectra of the phenols and the phenolate anions were determined with a Perkin-Elmer Model MPF-3L fluorescence spectrophotometer. Melting points were determined in open capillary tubes and are uncorrected. Microanalyses were performed by the Section on Analytical Services in this laboratory and were within ±0.3% for the indicated elements.

General Procedure for Dehydrogenation of Ketones to Phenols. Both sulfur and palladium black at high temperature have been employed in the final dehydrogenation step to convert ketones to phenols. Examination of both methods has shown palladium black to be generally superior. In a typical procedure, 2 mmol of ketone and 15 mmol of palladium black (Engelhard) were heated near reflux (>240 °C) for the indicated times (Table I) in 1-methylnaphthalene with a stream of argon gas passing through the solution. The use of high-quality 1-methylnaphthalene is essential. Commercial material was passed through a column of basic alumina (activity grade I) and eluted with petroleum ether. Prior to use, the material was distilled under vacuum. The crude reaction mixtures containing 1-, 2-, 3-, 4-, 7-, 8-, 9-, or 10-hydroxy BP were diluted with benzene and applied directly to a chromatographic column of 100 g of acidic alumina (activity grade I). Elution with benzene removes unreacted starting ketone, 1-methylnaphthalene, and nonpolar impurities. Further elution with acetone–benzene or acetone provided phenols of high purity. Final purification was by sublimation (190–210 °C, 0.03 mm) or recrystallization. Increase of the bath temperature above 210 °C usually results in faster decomposition than sublimation. All operations on the phenolic isomers were conducted in subdued light and samples were stored at −80 °C under argon gas.

1-Hydroxy BP.[21,24] A solution of 5,6,6a,7-tetrahydrobenz[*de*]anthracen-4-one (**1a**,[21] 1.0 g, 4.27 mmol) and diethyl succinate (2.23 g, 12.8 mmol) in dry Me_2SO[22] (10 ml) was added to a well-stirred suspension of NaH (8.6 mmol) in Me_2SO (3 ml) under argon. The dark mixture was stirred for 1.5 h at room temperature, cooled to 0 °C, quenched with acetic acid (5 ml), poured into water, and extracted into ether. Back extraction into 10% aqueous sodium carbonate, acidification of the aqueous phase, and extraction of the acid into ether provided 1.32 g (85%) of the Stobbe product **1b** on work-up: mp 189–191 °C dec from ethanol–water; mass spectrum *m/e* 362 (M^+). Anal. ($C_{23}H_{22}O_4$) C, H. ^{1}H NMR (100 MHz, $CDCl_3$) 3 H ester 1.05 (J = 7 Hz), H_{6a} 1.75, 2 H_5, 2 H_6, and 2 H_7, 2.2–3.1, 2 H allyl 3.59, 2 H ester 4.08 (J = 7 Hz), 5 aromatic protons 7.2–7.4, 2 aromatic protons 7.7–7.8 ppm.

A solution of crude **1b** (1.0 g, 2.8 mmol), acetic acid (21 ml), concentrated HCl (10.5 ml), water (15 ml), 2-propanol (10 ml), and triethylsilane (5 ml) was refluxed under argon for 16 h. Acetic acid (25 ml) and *p*-toluenesulfonic acid (100 mg) were added and reflux was continued for 5 h. The solution was poured into water and the products extracted into ether. Work-up as above provided a neutral fraction and an acidic fraction. Brief reduction of the latter with hydrogen in the presence of 5% palladium on carbon (50 mg) in THF to reduce a minor amount of olefinic material provided 0.62 g of acid **1c**, mass spectrum *m/e* 292 (M^+). The neutral fraction (**1d**) was refluxed for 16 h under nitrogen in a mixture of acetic acid (20 ml), concentrated HCl (3.5 ml), water (5 ml), and triethylsilane (2 ml). Work-up and reduction as above provided an additional 0.10 g of **1c**. Cyclization with liquid HF of the combined samples of acid **1c** as previously described[21] provided ketone **1e** in overall yield of 42% from the half-ester **1b**.

Conditions for dehydrogenation of **1e** to 1-hydroxy BP are given in Table I. The yield for this step was 90% after correction for recovered starting material (32% conversion). The phenol can be safely purified by column chromatography or vacuum sublimation (195 °C, 0.02 mm) but suffers extensive decomposition on attempted recrystallization.

3-Hydroxy BP. Cook et al.[20a] assigned the Stobbe condensation product from **3a** as the exocyclic isomer, β-(1,2,3,11b-tetrahydro-7*H*-benz[*de*]anthracen-3-yl)-β-ethoxycarbonylpropionic acid. However, the ^{1}H NMR spectrum (60 MHz, $CDCl_3$) of **3b** shows that it consists mainly of the isomer (mp 114–118 °C, lit.[20a] mp 115–116 °C) with the endocyclic double bond, β-(1,11b-dihydro-7*H*-benz[*de*]anthracen-3-yl)-β-ethoxycarbonylpropionic acid, based on a broad signal (~1 H) at δ 6.1. To 44 g of **3b**[20a] dissolved in 280 ml of acetic acid was added 140 ml of concentrated hydrochloric acid and 200 ml of water. The mixture was refluxed with stirring under argon gas for 8 h, cooled in ice, and 200 ml of water was added. The resultant solid was crystallized from ethyl acetate–cyclohexane to give 30.3 g (91.7%) of β-(7*H*-1,2-dihydrobenz[*de*]anthracen-3-yl)propionic acid (**3c**): mp 191–192.5 °C; mass spectrum *m/e* 290 (M^+); λ_{max} 218 nm (ε 21 500), 262 (ε 7500) in ethanol. Anal. ($C_{20}H_{18}O_2$) C, H.

To a refluxing solution of 30.0 g of **3c** in 2 l. of amyl alcohol under argon was added 67 g of sodium in pieces over 5 h. Reflux was continued for 30 h and the amyl alcohol was removed by steam distillation. Cooling and acidification gave a solid which on crystallization from ethanol–water gave 23.4 g (91.7%) of β-(1,2,3,11b-tetrahydrobenz[*de*]anthren-3-yl)propionic acid (**3d**) as a mixture of isomers: mp 149–152 °C; mass spectrum *m/e* 292 (M^+). Anal. ($C_{20}H_{20}O_2$) C, H.

To 300 ml of hydrogen fluoride cooled in ice and stirred was added 23.4 g of the isomeric mture **3d.** The resulting red solution was stirred at room temperature for 18 h before the hydrogen fluoride was removed in a stream of nitrogen. The residue was taken up in methylene chloride, washed with sodium bicarbonate solution, dried ($MgSO_4$), and concentrated in vacuo to an oil which slowly crystallized. Recrystallization from ethanol gave 12.0 g of 1,6,10b,11,12,12a-hexahydrobenzo[*a*]pyren-3(2*H*)-one (**3e**), isomer A: mp 183–184 °C (lit.[20] mp 185.5 °C); ^{1}H NMR (220 MHz, $CDCl_3$) 2 H_1, H_{10b}, 2 H_{11}, 2 H_{12}, and H_{12a}, 1.22–3.0, 2 H_6 3.64, 2 H_2 3.91 (J = 10 and 7 Hz), five aromatic protons 7.1–7.35, and H_4 7.80 ppm ($J_{4,5}$ = 10 Hz). Two recrystallizations of the solid obtained from ethanol filtrate gave 5.0 g of **3e,** isomer B: mp 147–153 °C (lit.[20] mp 156 °C); ^{1}H NMR (220 MHz, $CDCl_3$) 2 H_1, H_{10b}, 2 H_{11}, 2 H_{12} and H_{12a} 1.22–3.0, 2 H_6 3.64, 2 H_2 3.91 (J = 10 and 7 Hz), five aromatic protons 7.1–7.35, and H_4 7.83 ppm ($J_{4,5}$ = 10 Hz). Dehydrogenation of either isomer to 3-hydroxy BP and purification was as described.[20]

2-Hydroxy BP. To a suspension of 177 mg of the ketone **3e** (isomer A) in 40 ml of methanol was added 200 mg of sodium borohydride in portions with stirring. Stirring was continued for 1 h at room temperature, the bulk of solvent was evaporated, and the residue was treated with 50 ml each of water and chloroform. The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to leave a solid which was recrystallized from chloroform–petroleum ether to give 156 mg (87%) of colorless needles of 1,2,3,6,10b,11,12,12a-octahydro-3-hydroxybenzo[*a*]pyrene (**2a**): mp 135–136 °C; ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_6 3.92, H_3 4.74 and six aromatic protons 7.10–7.50 ppm. Anal. ($C_{20}H_{20}O$) C, H.

A mixture of 2.5 g of the alcohol **2a,** 120 ml of acetic acid, and 2 drops of concentrated hydrochloric acid was heated at 110 °C for 1.5 h with stirring. After cooling, the reaction mixture was poured into 200 ml of water and extracted with chloroform. The chloroform extract was washed with water, 10% ammonium hydroxide, and water and dried (K_2CO_3). Evaporation of the solvent gave an oil which was distilled (bp 225–230 °C, 0.1 mm) to give 2.28 g (98.5%) of colorless crystals which were recrystallized from methanol to give colorless prisms of 1,6,10b,11,12,12a-hexahydrobenzo[*a*]pyrene (**2b**): mp 87–88 °C; ^{1}H NMR (100 MHz, $CDCl_3$) three methylene protons and two methine protons 1.20–3.70, 2 H_6 3.79, H_2 5.90 ($^3J_{2,3}$ = 10, $^3J_{2,1}$ = 4, $^3J_{2,1}$ = 2 Hz), H_3 6.45 ($^3J_{3,2}$ = 10, $^3J_{3,1}$ = 1.5 Hz), and six aromatic protons 7.0–7.5 ppm. Anal. ($C_{20}H_{18}$) C, H.

A solution of 500 mg of the olefin **2b,** 268 mg of *N*-bromoacetamide, and 200 mg of lithium acetate in 100 ml of acetic acid was stirred at room temperature for 2.5 h. The reaction mixture was poured into 250 ml of water and the resulting crystals were collected by filtration. The crystals were dissolved in chloroform, washed with water, and dried (K_2CO_3). Evaporation of the solvent gave 700 mg (94.5%) of colorless crystals which were recrystallized from methanol to give colorless prisms of 3-acetoxy-2-bromo-1,2,3,6,10b,11,12,12a-octahydrobenzo[*a*]pyrene (**2c**): mp 120–122 °C; ^{1}H NMR (100 MHz, $CDCl_3$) $CH_3C{=}O$ 1.92, 2 H_6 3.91, H_2 4.48 ($^3J_{2,1}$ = 5, $^3J_{2,3}$ = 3 Hz), H_3 6.20 ($^3J_{3,2}$ = 3 Hz), and six aromatic protons 6.90–7.70 ppm. Anal. ($C_{22}H_{21}BrO_2$) C, H.

To a stirred suspension of 1.2 g of the bromohydrin acetate **2c** in 30 ml of dry tetrahydrofuran was added 1 g of dry sodium methoxide. Stirring was continued for 1.5 h at room temperature and the

reaction mixture was poured into 150 ml of water and extracted with chloroform (100 ml × 2). The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to leave crystals which were recrystallized from ether to give 840 mg (97%) of colorless needles of 2,3-epoxy-1,2,3,6,10b,11,12,12a-octahydrobenzo[*a*]pyrene (**2d**): mp 145–147 °C; ^{1}H NMR (60 MHz, $CDCl_3$) H_2 3.60, H_3 3.78 ($^3J_{3,2}$ = 4 Hz), 2 H_6 3.88, and six aromatic protons 7.1–7.6 ppm; mass spectrum *m/e* 274 (M^+). Anal. ($C_{20}H_{18}O$) C, H.

To a stirred solution of 700 mg of the epoxide **2d** in 75 ml of benzene was added 0.1 ml of boron trifluoride etherate under cooling at 5 °C. Stirring was continued for 30 min and the reaction mixture was decomposed with 50 ml of water. The benzene extract was dried (K_2CO_3) and evaporated to leave slightly yellowish crystals which were recrystallized from ethanol to give 600 mg (86%) of colorless prisms of 1,6,10b,11,12,12a-hexahydrobenzo[*a*]pyren-2(3*H*)-one (**2e**): mp 155–156 °C; ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_3 3.59, 2 H_6 3.90, and six aromatic protons 6.9–7.6 ppm; mass spectrum *m/e* 274 (M^+). Anal. ($C_{20}H_{18}O$) C, H.

Dehydrogenation (Table I) of **2e** provided 2-hydroxy BP, which was purified by chromatography and recrystallization from benzene in 61% yield. An additional 20% yield of partially dehydrogenated ketones of unknown structure was recovered. All of the starting **2e** was consumed.

4-Hydroxy BP. Dehydrogenation of 5a,6,6a,7,8,9,10,10a-octahydrobenzo[*a*]pyren-4(5*H*)-one[25] provided 4-hydroxy BP (Table I) in 48% yield after chromatography and sublimation. An additional 17% yield of partially dehydrogenated ketones free of starting material was also isolated. As was the case for the synthesis of 2-hydroxy BP, dehydrogenation was terminated once all the starting ketone had been consumed. Further dehydrogenation results in loss of the phenol and does not improve the yield.

5-Hydroxy BP. Cyclization (Table I) of 4-chryseneacetic acid[16] (Scheme IV) in HF followed by sublimation provided 5-hydroxy BP in 43% yield.

11-Hydroxy BP. A mixture of 1.7 g of 3,4-dihydrobenzo[*a*]anthracen-1(2*H*)-one (V in ref 17), 3.4 g of arsenic-free zinc (prewashed with hydrochloric acid, water, and acetone and dried at 100 °C), ethyl bromoacetate (1.5 ml), dry benzene (70 ml), and absolute ether (17 ml) was refluxed for 6 h after addition of one crystal of iodine. Ethanol (15 ml) and acetic acid (20 ml) were added to decompose the complex, and the organic layer was washed with dilute NH_4OH. Routine work-up provided 1.9 g of yellow prisms from ethanol, mp 114–115 °C. Anal. ($C_{22}H_{22}O_3$) C, H. The corresponding methyl ester of the Reformatsky alcohol (VI, ref 17) had mp 139–148 °C dec. An intimate mixture of the Reformatsky alcohol (1.4 g) and sulfur (190 mg) was heated at 210 °C for 2 h. The crude product was hydrolyzed with KOH (0.8 g) and ethanol (20 ml) at reflux for 1 h. The solution was diluted with water and washed with benzene to remove sulfur. Routine work-up provided 0.75 g of 1-benzo[*a*]anthraceneacetic acid (IX in ref 17) as colorless needles on crystallization from benzene–ligroin, mp 203–204 °C (lit.[17] 203.6–204.6 °C). The overall yield from V to IX (ref 17) of 52% compares well with the 22% previously reported. Cyclization was conducted as described to provide pure 11-hydroxy BP in 71% yield on recrystallization from benzene. Attempted sublimation of this material results in extensive decomposition.

12-Hydroxy BP. A solution of BP (9 g) in benzene (450 ml) was stirred with 3 g of 10% palladium on $SrCO_3$[52] and 4 atm hydrogen for 26 h. Gas chromatography (270 °C, 3% OV-17, 1.5 m, N_2 30 ml/min)–mass spectrometry established that the reaction mixture contained 5% BP and 3% perhydro BP along with the desired 4,5-dihydro BP (**12a**). Crystallization of the product from cyclohexane provided 7.0 g of [purity (GLC) ≥ 96%] colorless plates: mp 143–144 °C (lit.[52] mp 148.5–149 °C); ^{1}H NMR (100 MHz, CCl_4) 2 H_4 and 2 H_5 3.28, eight aromatic protons centered at 7.6 (multiplets), H_{11} 8.52 ($J_{11,12}$ = 9.2 Hz), and H_{10} 8.55 ppm (multiplets).

A mixture of 7 g of 4,5-dihydro BP (**12a**), 80 ml of pyridine, and 7 g of osmium tetroxide was stirred under argon gas for 7 days. Hydrolysis of the resulting osmate ester was carried out by stirring the reaction mixture under argon gas for 5 h after addition of 14 g of sodium bisulfite, 200 ml of water, and 160 ml of pyridine. The reaction mixture was diluted with 1.8 l. of water and the resulting yellowish solid recrystallized from carbon tetrachloride to afford 3.9 g of a mixture of the diols **12b** and **12c**. Pure 5a,6-dihydroxy-4,5,5a,6-tetrahydrobenzo[*a*]pyrene (1.2 g, 15%) was isolated by fractional recrystallization from THF as colorless needles, mp 205–208 °C dec. Anal. ($C_{20}H_{16}O_2$) C, H. Both mother liquors from the crystallization were combined and, after evaporation of solvents, were acetylated with 7 ml of acetic anhydride and 5 ml of pyridine for 36 h at 20 °C to provide 5.5 g of an oil which was separated by column chromatography (Merck 60 silica gel, petroleum ether–CH_2Cl_2–methanol, 50:10:0.2, followed by CH_2Cl_2–methanol, 100:2): 1.8 g (25%) of 4,5-dihydro BP, 2.9 g (28%) of 11,12-diacetoxy-4,5,11,12-tetrahydro BP [mp 155 °C from cyclohexane; ^{1}H NMR (60 MHz, $CDCl_3$) C_{11} and C_{12} $COCH_3$ 1.92 and 2.28, 2 H_4 and 2 H_5 3.04, H_{12} 6.35 and H_{11} 7.09 ppm ($J_{11,12}$ = 4.2 Hz). Anal. ($C_{24}H_{20}O_4$) C, H], 1.0 g (11%) of 6-acetoxy-5a-hydroxy-4,5,5a,6-tetrahydro BP, amorphous powder [^{1}H NMR (60 MHz, $CDCl_3$) C_6 $COCH_3$ 2.40, 2 H_4 3.2 (m) and 2 H_5 2.0 (m), H_6 6.21, seven aromatic protons centered at 7.35, and H_{10} and H_{11} 7.9 ppm], and 100 mg of 12-acetoxy-4,5-dihydro BP were obtained.

A mixture of the diacetate of **12c** (100 mg), DDQ (75 mg, Aldrich), and toluene (20 ml) was refluxed for 16 h. After filtration to remove hydroquinone the filtrate was washed with $Na_2S_2O_3$ solution, Na_2CO_3 solution, and water and dried ($MgSO_4$). Evaporation of the solvent gave 63 mg (76%) of yellow needles of 12-acetoxy BP (**12e**): mp 153–156 °C from CCl_4; ^{1}H NMR (60 MHz, $CDCl_3$) C_{12} $COCH_3$ 2.56, eight aromatic protons from 7.0–8.0, H_6 8.33, H_{10} 8.80 (m), and H_{11} 8.75 ppm. Anal. ($C_{22}H_{14}O_2$) C, H.

A mixture of **12e** (600 mg), THF (10 ml), methanol (10 ml), and ammonium hydroxide (5 ml) was stored at 20 °C for 48 h with stirring. The reaction mixture was evaporated to dryness and the solid was chromatographe on acidic alumina (100 g, benzene–20% acetone) to give 456 mg (87%) of yellow crystals of pure 12-hydroxy BP, mp 230–231 °C from benzene–petroleum ether.

7-Hydroxy BP. Dehydrogenation of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[29] (**7**) (Aldrich Chemical Co.) into 7-hydroxy BP (Table I) occurs in 62% yield after purification by chromatography and sublimation. The use of palladium black greatly improves the yield of this phenol.

8-Hydroxy BP. Conversion of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[29] (**7**) (Aldrich Chemical Co.) into 7,8,9,10-tetrahydrobenzo[*a*]pyrene 7,8-epoxide was essentially as described.[53] Isomerization of this compound to ketone **8** (Scheme VI) was as described for the conversion of **2d** into **2e**: 94% yield; yellowish plates, mp 174–176 °C (lit.[19] mp 174–176 °C); ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_9 2.70 ($J_{9,10}$ = 7 Hz), 2 H_{10} 3.70, 2 H_7 3.60, and eight aromatic protons 7.80–8.30 ppm. Dehydrogenation (Table I) to the phenol proceeded in 67% yield after chromatography and sublimation.

9-Hydroxy BP. 10-Acetoxy-9-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene[29] was converted to 7,8,9,10-tetrahydrobenzo[*a*]pyrene 9,10-epoxide in 95% yield as described for the conversion of **2c** into **2d**: colorless plates, mp 148–149° (lit.[53] mp 149°); ^{1}H NMR (100 MHz, $CDCl_3$) H_9 3.88, H_{10} 4.85 ($^3J_{9,10}$ = 4 Hz), seven aromatic protons 7.6–8.3, and H_{11} 7.45 ($J_{11,12}$ = 10 Hz). The oxide was isomerized to ketone **9** (Scheme VI) with BF_3 in 90% yield as described for the formation of **2e**: mp 178 °C (lit.[19] mp 178 °C); ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_8 2.40, 2 H_7 2.92 ($J_{7,8}$ = 7 Hz), 2 H_{10} 3.67, and eight aromatic protons 7.30–8.20 ppm. Dehydrogenation (Table I) to the phenol proceeded in 80% yield after chromatography and sublimation.

10-Hydroxy BP. To a stirred mixture of chromium trioxide (1.11 g) and pyridine (10 ml) was added a solution of 10-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene[29,30] (1 g) in pyridine (7 ml) and stirring was continued at room temperature for 18 h. The mixture was decomposed with water (150 ml), and the product extracted into chloroform and filtered to remove insoluble material. The chloroform extract was washed with water, 10% hydrochloric acid, and water and dried (K_2CO_3). Evaporation of the solvent and sublimation of the resultant solid provided 760 mg (76%) of ketone **10** with mp 175–177 °C (lit.[30] mp 174–175 °C); ^{1}H NMR (100 MHz, $CDCl_3$) 2 H_8 2.25, 2 H_7 2.90 ($J_{7,8}$ = 7 Hz), 2 H_9 3.31 ($J_{9,8}$ = 7 Hz), seven aromatic protons 7.8–8.4, and H_{11} 8.6 ppm ($J_{11,12}$ = 10 Hz). Dehydrogenation (Table I) to the phenol proceeded in 70% yield after chromatography and sublimation.

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Supplementary Material Available. Spectroscopic data (^{1}H NMR, uv, and ir) on the 12 hydroxy BP isomers (25 pages). Ordering information is given on any current masthead page.

Registry No.—**1a,** 54522-80-4; **1b,** 57652-51-4; **1c,** 54522-83-7; **1d,** 57652-52-5; **1e,** 54522-84-8; **2a,** 57652-53-6; **2b,** 57652-54-7; **2c,** 57652-55-8; **2d,** 57652-56-9; **2e,** 57652-57-0; **3a,** 57652-58-1; **3b,** 57652-59-2; **3c,** 57652-60-5; *cis*-**3d,** 57652-61-6; *trans*-**3d,** 57652-62-7; *cis*-**3e,** 57652-63-8; *trans*-**3e,** 57652-64-9; **7,** 3331-46-2; **8,**

17573-25-0; **9**, 17573-26-1; **10**, 57652-65-0; **12a**, 57652-66-1; **12b**, 57652-67-2; **12b** 6-acetate, 57652-68-3; **12c**, 57652-69-4; **12c** diacetate, 57652-70-7; **12e**, 57652-71-8; 5a,6,6a,7,8,9,10,10a-octahydrobenzo[a]pyren-4(5-*H*)-one, 57652-72-9; 4-chryseneacetic acid, 57652-73-0; 3,4-dihydrobenzo[a]anthracen-1(2*H*)-one, 57652-74-1; 1,2,3,4-tetrahydro-1-hydroxybenzo[a]anthracene-1-acetic acid ethyl ester, 57652-75-2; ethyl bromoacetate, 105-36-2; 1-benzo[a]anthraceneacetic acid, 57652-76-3; 10-acetoxy-9-bromo-7,8,9,10-tetrahydrobenzo[a]pyrene, 57652-77-4; 7,8,9,10-tetrahydrobenzo[a]pyren 9,10-epoxide, 36504-68-4; 10-hydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, 17573-24-9; 6-hydroxybenzo[a]pyrene, 33953-73-0.

References and Notes

(1) G. M. Holder is a Fogarty International Fellow on leave from the University of Sydney.
(2) P. M. Dansette is a guest worker at the NIH supported by the French CNRS.
(3) A portion of these studies was conducted by Dr. R. A. LeMahieu at Hoffmann-La Roche, Inc.
(4) Current efforts from this laboratory have attempted to establish the role of non-arene oxide pathways in the metabolism of aromatic hydrocarbons. See J. E. Tomaszewski, D. M. Jerina, and J. W. Daly, *Biochemistry*, **14**, 2024 (1975), and H. G. Selander, D. M. Jerina, and J. W. Daly, *Arch. Biochem. Biophys.*, **168**, 309 (1975).
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