Registry No.—**6**, 36803-49-3; **7**, 36803-48-2; **8**, 26870,38-2; **10**, 20606-25-1; **10**, semicarbazone, 50803-78-6; **11**, 50803-79-7; **12**, 50803-80-0; **14**, 33371,95-8; **14** semicarbazone, 50803-81-1; **16**, 50803-82-2; **17**, 1010-77-1; **26**, 6684-66-8; cycloheptanone, 502-42-1; methyl 5-bromopentanoate, 5454-83-1; 2-cyclohexylcyclohexan-1-one, 90-42-6.

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Synthesis and Photorearrangement of 4,5-Epoxy-4,5-dihydropyrene

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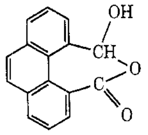
The title compound, 4,5-epoxy-4,5-dihydropyrene, which is important in cancer research was synthesized from pyrene *via* its ozonide and 4,5-phenanthrenedicarboxaldehyde. On ultraviolet irradiation, this epoxide rearranges to 2,3:3,4:4,5-tribenzoxepin, a new oxepin, 4-hydroxypyrene, pyrene, and other not yet identified products.

The importance of epoxides as intermediates in the metabolic detoxification of aromatic hydrocarbons has been established.[1] Aromatic epoxides can react to form a variety of products, including phenols and oxepins.[1,2] In recent years there has been considerable interest in synthesizing the K-region epoxides of carcinogenic hydrocarbons such as dibenz[*a,h*]anthracene,[3] benzo[*a*]pyrene, and 7,12-dimethylbenz[*a*]anthracene,[4] since these have been suggested as the possible carcinogenic metabolic intermediates in carcinogenesis by aromatic hydrocarbons.[5] Pyrene, a related noncarcinogenic hydrocarbon, is useful for comparative metabolic studies in laboratory animals and in *in vitro* cell culture studies.[6] Although important, the oxides of pyrene have not been successfully synthesized up to now. Boyland and Sims[6a] reported that in the oxidation of pyrene with perbenzoic acid an intermediate is formed which they believed to be 4,5-epoxy-4,5-dihydropyrene. This epoxide has also been detected as a microsomal metabolite of pyrene.[6c] The present paper describes the first reported synthesis of pure 4,5-epoxy-4,5-dihydropyrene (**4**). This epoxide is photochemically unstable and rearranges to form several products. It was of added importance, therefore, to study its photochemical rearrangement, as the intermediates formed therein may be of significance in the carcinogenic or detoxification processes of aromatic hydrocarbons.

Two general approaches have been used for the synthesis of K-region epoxides: (1) the conversion of dialdehydes[7] obtained by chemical oxidation of polycyclic aromatic hydrocarbons to the epoxide by the use of Mark's reagent, tris(dimethylamino)phosphine; (2) the cyclization of trans dihydrodiols with the dimethyl acetal of dimethylformamide.[4]



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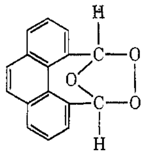

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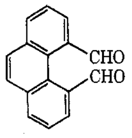

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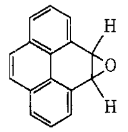

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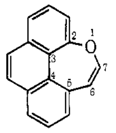

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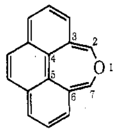

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Previous attempts[8] to synthesize 4,5-phenanthrenedicarboxaldehyde by the catalytic hydrogenation of pyrene ozonide under various experimental conditions have resulted in the formation of 5-formyl-4-phenanthroic acid in the lactol form, I.[8] However, Sturrock and Duncan[9a] reported the formation of unstable, uncrystallizable, and impure dialdehyde in poor yield from the iodide reduction of pyrene monozonide. Criegee,[10] who prepared the dialdehyde by oxidation of *trans*-4,5-dihydroxy-4,5-dihydropyrene with lead tetraacetate, also reported similar findings. Both methods thus seemed unsuitable as preparative procedures.

In the present work, ozonization of a dilute solution of pyrene in anhydrous methylene chloride at −70° using 1 mol of ozone afforded mainly a colorless compound, mp 159–161°, in good yield. Based on its uv, ir, nmr, mass spectral, and C, H analysis, it was characterized as the monomeric monozonide of pyrene, **2**.[9a,b] Catalytic hydrogenation of the ozonide **2** over Pd/C in ethyl acetate

Table I
Fluorescence Characteristics of Pyrene Epoxide and Photoproducts[a]

Compd	Conditions	Excitation maxima, mμ	Wavelength of analysis, mμ	Emission maxima, mμ	Wavelength of excitation, mμ
Pyrene epoxide	Ethanol, 2 μg/ml	*260*, 279 (sh), 298, 319	354	354, *379*, 396, 415 (sh)	262
	Cyclohexane, 2 μg/ml, deoxygenated	*260*, 278 (sh), 285 (sh), 298, 320	354	353, *373*, 392, 412 (sh)	262
	Cyclohexane–benzene (1:9), 2 μg/ml			(332) 355, *377*, 396, 418 (sh)	302
4-Hydroxypyrene	Ethanol, 0.08 μg/ml, deoxygenated	*239*, 270 (sh), 279, 342, 355 (sh), 377	380	*380*, 400, 420, 450 (sh)	262
4-Hydroxypyrene	Cyclohexane, 0.08 μg/ml, deoxygenated	*239*, 265 (sh), 275, 315 (sh), 328, 342, 347 (sh)	376	*376*, 396, 417, 440 (sh)	262
4-Methoxypyrene	Ethanol, deoxygenated	*239*, 268 (sh), 276, 315 (sh), 327, 339, 350 (sh)	375	*375*, 395, 417, 441	276
2,3:3,4:4,5-Tribenzoxepin	Ethanol, 2 μg/ml	*233*, 273, 290, 301	455	426, *455*, 488, 525, 570 (sh)	292
Pyrene	Ethanol, deoxygenated	*237*, 259, 269, 304, 317, 332	391	372, 382, *391*, 410 (sh), 437 (sh)	332

[a] 5-mμ slides were used both on the analyzer and exciter side; corrected excitation maxima in energy units and corrected emission maxima in quantum units; major peaks are italicized and shoulders are indicated in parentheses as sh.

yielded **1**, instead of the expected dialdehyde. Reduction of **2** with sodium iodide in glacial acetic acid yielded **1** and a crystalline solid in good yield. This solid was identified as 4,5-phenanthrenedicarboxaldehyde (**3**) by spectral and elemental analyses. In contrast to the earlier reports,[9a,10] compound **3** is stable and readily crystallized. The dialdehyde **3** was reduced to 4,5-bis(hydroxymethyl)phenanthrene by lithium aluminum hydride. When refluxed with tris(dimethylamino)phosphine in dry benzene, the dialdehyde **3** was converted to 4,5-epoxy-4,5-dihydropyrene (**4**). The structure was confirmed by its uv, nmr, mass spectral, and combustion analysis.

Upon attempting to obtain fluorescence spectra in a deoxygenated cyclohexane solution, the epxide **4** was found to be photochemically unstable. This observation led to photochemical decomposition studies of pyrene epoxide in various solvents. Pyrene epoxide in deoxygenated anhydrous methylene chloride was irradiated at 254 mμ. Changes in the uv absorption maxima and intensities were noted while monitoring the reaction. Silica gel tlc of the reaction mixture showed eight distinct spots. The major product isolated (36%) has the structure 2,3:3,4:4,5-tribenzoxepin (**5**) as determined by mass spectrum, C, H analysis, and nmr, which was definitive in deciding between **5** and its isomer 3,4:4,5:5,6-tribenzoxepin (**6**). 4-Hydroxypyrene and pyrene, although present in small amounts, were also identified as irradiation products.

Pyrene epoxide **4** is quite stable in methylene chloride and cyclohexane solutions in the dark at −10° and its decomposition to 4-hydroxypyrene is negligible over a period of several months, as shown by uv absorption and thin layer chromatography. A summary of the fluorescence characteristics of pyrene epoxide and its derivatives is given in Table I.

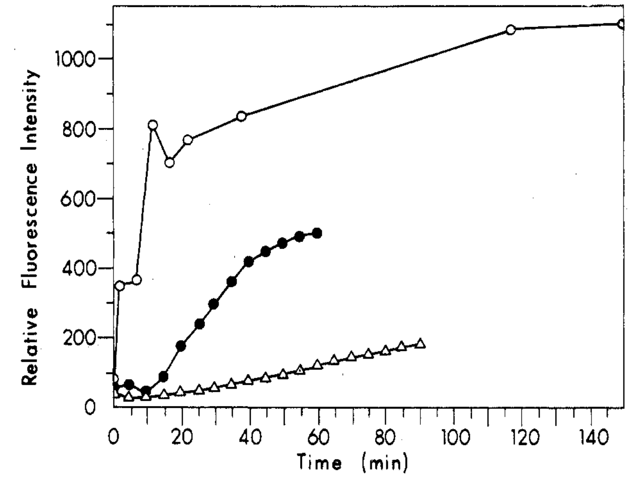
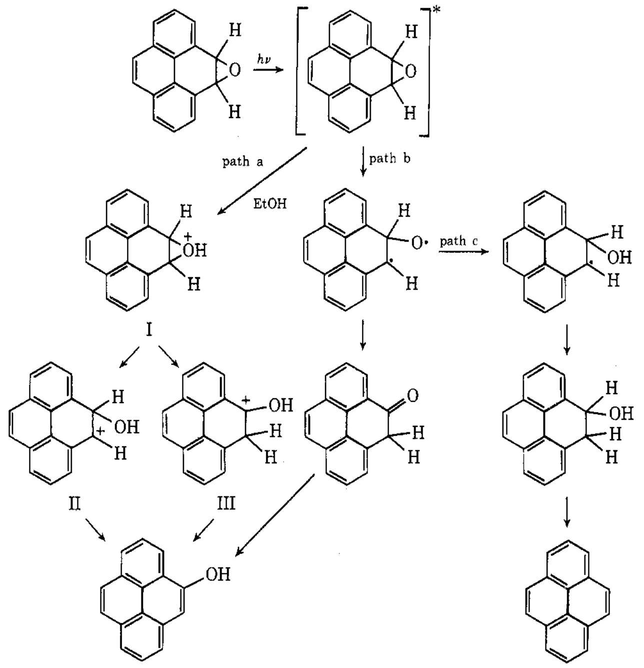


Figure 1. Photodecomposition of pyrene epoxide: ○, in absolute ethanol, $\lambda_{ex} = 262$, $\lambda_{anal} = 380$ mμ; ●, in cyclohexane, $\lambda_{ex} = 262$, $\lambda_{anal} = 375$ mμ; △, in 1:9 (v/v) cyclohexane-benzene, $\lambda_{ex} = 302$, $\lambda_{anal} = 377$ mμ.

In order to determine the effects of solvents in the photodecomposition, dilute solutions of pyrene epoxide in absolute ethanol, cyclohexane, and 1:9 (v/v) cyclohexane–benzene were irradiated in a fluorescence cuvette using a xenon lamp as light source. Since even short exposure of pyrene epoxide to ultraviolet light resulted in a strong phenol emission, the photodecomposition was monitored with respect to phenol formation. Figure 1, a plot of irradiation time *vs.* phenol fluorescence intensity, shows that the phenol concentration is significantly greater in ethanol than in cyclohexane or cyclohexane–benzene. Extrapolation of plots of fluorescence intensity *vs.* 1/time to infinite time (not shown) yield the final fluorescence intensity due to 4-hydroxypyrene formed. Since the fluorescence intensity was determined for 4-hydroxypyrene solutions of known concentrations, per cent conversion of epoxide to the phenol can be calculated. Thus 48 and 19% of epoxide is converted to the phenol in ethanol and cyclohexane, respectively. Although a direct comparison cannot be made, it appears that ~10% conversion to the phenol takes place in cyclohexane–benzene. These data indicate that as the hydrogen-donating ability of the solvent decreases, epoxide is largely converted to products other than phenol. For example, in methylene chloride, a poor hydrogen donor, the tribenzoxepin **5** is the major product of the photodecomposition of pyrene epoxide.

Chart I



At present, a definitive mechanism for photolytic phenol formation cannot be postulated. The decomposition studies point to solvent participation by hydrogen-donating solvents. It is well known that molecules may become stronger bases (or acids) in the first excited singlet state.[11] Thus, in protolytic solvents such as ethanol, 4-hydroxypyrene may be formed according to path a in Chart I. This mechanism is similar to the ground-state mechanism postulated for acid-catalyzed cleavage of 1,3-cycloheptadiene oxide.[12] The protonated ground state intermediate (I) may undergo ring opening by C–O cleavage to form II or by an NIH shift[13] to form III. Both II and III can form the phenol by loss of a proton.

In nonprotolytic solvents such as cyclohexane and cyclohexane–benzene, the excited epoxide species may undergo homolytic C–O cleavage, yielding a stable benzylic biradical as shown in path b in Chart I. A 1,2-hydrogen shift, the equivalent of a free-radical type NIH shift, followed by tautomerization, would lead to 4-hydroxypyrene. A similar mechanism involving homolysis to a stable biradical followed by a 1,2-hydrogen shift has been postulated for the photodecomposition of epoxy olefins[14] and phenyloxirane.[15] Alternatively, the biradical might abstract hydrogen atoms from the solvent and form the reduced product pyrene after dehydration, as shown in path c, Chart I. The photolytic formation of benzene from benzene epoxide has been reported.[16] Since the experimental conditions for photolysis in cyclohexane and cyclohexane–benzene were not the same and since the nature of all major products is not known in these systems, it is at present not possible to explain why more phenol is formed during photolysis in cyclohexane than in cyclohexane–benzene.

The photochemical formation of 2,3:3,4:4,5-tribenzoxepin from pyrene epoxide may occur by a mechanism similar to that proposed for the formation of 2,3:4,5-dibenzoxepin from 9,10-dihydro-9,10-epoxyphenanthrene.[17] This mechanism involves a concerted rearrangement of the excited epoxide species followed by valence tautomerization to the oxepin.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 421 spectrophotometer as KBr pellets, and ultraviolet spectra with a Cary Model 14. Proton magnetic resonance spectra were recorded on the Varian Associates Model A-60A spectrometer in $CDCl_3$ using TMS as an internal standard. A custom-designed multipurpose luminescence spectrophotometer[18] was used to record the emission and excitation spectra. Corrected emission spectra were recorded in quantum units and corrected excitation spectra in energy units. The mass spectra reported below were obtained from the Morgan Schaffer Corp., Montreal, Canada. The sample was introduced through a direct inlet in most cases. The ozonizer used was a Welsbach Corp. Model T-408. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (tlc) was carried out on precoated silica gel G plates (thickness 0.25 mm for analytical and 2.0 mm for preparative); spots were visualized with short- and long-wavelength uv hand lamps.

Pyrene Monozonide (2). Pyrene (2.02 g) dissolved in dry CH_2Cl_2 (400 ml) was cooled to −70° and treated with ozonized oxygen until 1 molar equiv had been added. It was immediately flushed with nitrogen to sweep out unreacted ozone. The brown residue obtained on evaporation of the pale yellow solution under reduced pressure at 35° was chromatographed on a silica gel column. A mixture of hexane–CH_2Cl_2 (6:4, v/v) eluted most of the unreacted pyrene (strong fluorescent band in uv) as the first fraction and then the monozonide, which crystallized from CH_2Cl_2–hexane mixture as colorless, shiny plates (1.3 g, 52.0%), mp 156–161° dec.[9] It exhibited the following spectral properties: uv max (EtOH) 212, 257, 263, 280, 292, 300, 338, and 355 nm (ϵ 34,700, 41,100, 44,300, 13,900, 12,500, 9300, 1300, 1400); ir[9a] 9.20, 9.50 (m-w), 10.5 (vs), 12.0 μ (m, twin peaks); nmr ($CDCl_3$) δ 6.70 (s, 2 H), 7.70 ppm (m, 8 H, aromatic); mass spectrum *m/e* 250 (parent ion); fluorescence excitation maxima (cyclohexane, deoxygenated, λ_{anal} 375 mμ) 255, 263, 290, 300, 338, 355 mμ; fluorescence emission maxima (λ_{ex} 255 mμ) 357, 375, 394, 413 mμ. *Anal.* Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.67; H, 4.12. Tlc in CH_2Cl_2–hexane (1:1, v/v) shows a single spot of R_f 0.7. It is sensitive to heat and light and does not form a precipitate with 2,4-dinitrophenylhydrazine. It releases iodine from sodium iodide solution in aqueous methanol and is stable at −10° for several months.

4,5-Phenanthrenedicarboxaldehyde (3). A mixture of the monozonide (1.0 g), sodium iodide (2.0 g), and acetic acid (45 ml) was allowed to stand at room temperature overnight and the liberated iodine was reduced with sodium thiosulfate solution. The mixture was extracted with CH_2Cl_2 and washed with sodium bicarbonate solution and water. The dried extract on concentration yielded colorless needles of 1, mp 272–276° dec (lit.[8c] mp 272–276°), which were filtered. The filtrate was concentrated and chromatographed on a silica gel column. Elution with CH_2Cl_2 gave first a colorless solid (0.2 g), mp 172–175° dec. The second fraction was the pale yellow dialdehyde (0.38 g). This was dissolved in dry ethyl acetate and filtered. The residue obtained on evaporation of the filtrate crystallized from CH_2Cl_2–hexane mixture as creamy-white needles (0.26 g, 28%), mp 169–171° (lit.[9,10] mp 169–171°). It had the following spectral characteristics: uv max (EtOH) 225, 251, 268 (sh), 296, 340 nm (sh) (ϵ 40,000, 26,900, 21,500, 22,700, 4800); ir 3.51, 3.62 (C–H stretch), 5.90, 5.92 μ (C=O stretch); nmr ($CDCl_3$) δ 7.91–8.23 (m, 8 H, aromatic), 10.13 ppm (s, 2 H, -CHO). *Anal.* Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.82; H, 4.39. Lithium aluminum hydride reduction of the dialdehyde afforded 4,5-bis(hydroxymethyl)phenanthrene which crystallized from CH_2Cl_2 as colorless needles, mp 159–161° (lit.[8b] mp 152–159°).

4,5-Epoxy-4,5-dihydropyrene (4). The dialdehyde (0.220 g) was dissolved in hot, dry benzene (10 ml) and tris(dimethylamino)phosphine (0.6 ml) was added to it. The mixture was heated to reflux under a nitrogen atmosphere. On addition of hexane and cooling, colorless crystals (0.145 g, 70.7%), mp 177–180° dec, were obtained. The product gives a single spot, R_f 0.34, on a silica gel plate using cyclohexane–dioxane (85:15, v/v) as solvent. However, some decomposition takes place when benzene is used as the eluent. The epoxide showed uv max (cyclohexane) 215, 256, 262, 270 (sh), 282, 288, 300 nm (ϵ 49,200, 48,600, 54,800, 30,800, 16,200, 16,100, 20,100) (*cf.* uv of the ozonide, 2); ir 8.1, 9.6, 12.1 μ; nmr ($CDCl_3$) δ 4.82 (s, 2 H), 7.88 (m, 8 H, aromatic); mass spectrum *m/e* 218 (parent ion). *Anal.* Calcd for $C_{16}H_{10}O$: C, 88.05; H, 4.62. Found: C, 87.68; H, 4.79. When refluxed in acetone with a few drops of HCl, it hydrolyzed to 4-hydroxypyrene. An authentic sample of the latter was prepared by acid-catalyzed dehydration of 4,5-dihydroxy-4,5-dihydropyrene,[19] mp 199–201° dec from

CH_2Cl_2-hexane mixture (lit.[20] mp 204-210° dec). The uv absorption spectrum of the phenol is identical with that reported in the literature.[6a] Its tlc in cyclohexane-dioxane (85:15, v/v) has R_f 0.13.

Irradiation of 4,5-Epoxy-4,5-dihydropyrene (4) in Methylene Chloride. Isolation of 2,3:3,4:4,5-Tribenzoxepin (5). The epoxide (0.110 g) dissolved in dry CH_2Cl_2 (200 ml) in a quartz vessel was irradiated at 254 nm using two mineral light uv lamps while N_2 was bubbled through the solution. The uv absorption of aliquots of the photolysis mixture showed an increase in the intensity of a new peak at 241 nm (4-hydroxypyrene) and later of another peak at 232 nm while the intensity of the epoxide peaks at 262 and 300 nm was decreasing. At the end of 15 hr, when all the epoxide has reacted, the solution was concentrated under reduced pressure and preparative tlc of the residue was carried out in the cyclohexane-dioxane (85:15, v/v) mixture.

The greenish fluorescent band of R_f 0.79 was identified to be pyrene by tlc, uv, fluorescence, and mass spectrum. In order to determine whether pyrene is indeed a photoproduct, the epoxide was chromatographed for contamination by pyrene. Although minute amounts of pyrene were detected by fluorescence emission spectroscopy, the amount of pyrene found after irradiation far exceeded that present as a contaminant of the starting epoxide.

The major band with R_f 0.71 on rechromatography and crystallization from hexane yielded colorless plates (0.04 g, 36.4%), mp 130-131°. It had the following spectral characteristics: uv max (EtOH) 232, 240 (sh), 276 (sh), 293, and 305 nm (ϵ 63,000, 48,200, 13,500, 14,400 and 13,000); ir 3.28, 6.00, 7.90, 8.10, 9.48, 9.50, 12.0, 12.8, 13.8, and 14.2 μ; nmr ($CDCl_3$) δ 5.90 and 6.53 (2 H, olefinic, J = 6.5 Hz), 7.42 ppm (m, 8 H, aromatic); mass spectrum m/e 218 (parent ion). *Anal.* Calcd for $C_{10}H_{16}O$: C, 88.05; H, 4.62. Found: C, 87.96; H, 4.75.

The band of R_f 0.26 was characterized as 4-hydroxypyrene by fluorescence excitation and emission spectra and uv and by converting it to 4-methoxypyrene by treating its methanolic solution with a solution of diazomethane in ether. This had identical tlc, fluorescence, and uv absorption characteristics with those of an authentic sample prepared similarly, mp and mmp 122-124° (lit.[19] mp 128-129°). However, 4-hydroxypyrene was present in small amounts in the irradiated mixture.

Effects of Solvents on the Photodecomposition of 4,5-Dihydro-4,5-epoxypyrene Pyrene epoxide was dissolved in three different solvents: (1) ethanol, (2) cyclohexane, and (3) 1:9 (v/v) cyclohexane-benzene. The concentration of pyrene epoxide in each solvent was 2 μg/ml. In order to preclude catalysis by impurities, the fluorescence cuvette was soaked in chromic acid for 15 min, rinsed thoroughly with distilled water, washed with nonfluorescent soap to destroy residual acid, and rinsed again with distilled water. The epoxide solution in the cuvette was deoxygenated by vigorously passing dry nitrogen through the sample for 12 min. The cuvette was stoppered with a glass stopper and sealed with parafilm to prevent oxygen from entering. Since the absorption maximum of pyrene epoxide is at 262 mμ, the samples in ethanol and cyclohexane were excited at this wavelength. In the cyclohexane-benzene system, 302 mμ was used as the excitation wavelength since benzene absorbed too strongly at 262 mμ. Fluorescence emission spectra were recorded every 5 min except for pyrene epoxide in ethanol, where photochemical decomposition proceeded extremely fast. In this case, fluorescence intensities were measured at the epoxide and phenol emission maxima at the beginning of the irradiation and spectra were recorded as the reaction slowed down; 5-mμ slits were used both on the analyzer and the exciter side.

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Registry No.—**1**, 50803-86-6; **2**, 16203-57-9; **3**, 16162-34-8; **4**, 37496-00-7; **5**, 50803-87-7; pyrene, 129-00-0; 4-hydroxypyrene, 31700-39-7; 4-methoxypyrene, 50803-88-8.

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