(±)-2-Amino-3-(6-hydroxy-2-naphthyl)propanoic Acid Hydrobromide (2·HBr). **2g** (3.00 g, 8.60 mmol) was refluxed in 48% HBr (20 mL) overnight under argon, decolorized over activated charcoal, and filtered through a Celite pad that was washed with warm water (40 mL), and the aqueous solution was cooled to room temperature. The remaining workup as with 1·HCl gave 2·HBr as a pink solid (2.30 g, 86%): mp 248–251 °C (dec, sealed tube); UV (MeOH) 230 (ε 58500) nm; IR (KBr pellet 3600–2400 (broad), 1732 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (d, 1 H, H8), 7.63–7.65 (m, 2 H, H1, H4), 7.28 (dd, 2 H, H3), 7.10 (d, 1 H, H5), 7.08 (dd, 1 H, H7), 4.23 (t, CH_α), 3.21 (d, 2 H, $ArCH_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 170.4 (CO), 155.3 (C6), 133.8 (C10), 129.0 (C8), 128.8 (C2), 128.1, 127.6 (C3), 126.4, 118.8 (C5), 108.5 (C7), 53.2 (CH_α), 35.7 (CH_2); MS (FAB/MS/MS) *m/z* 232 (M - Br), 215, 186, 173, 145. HR-MS (FAB, M - Br + H) calcd 232.0974, obsd 232.0972.

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Registry No. 1·HCl, 126216-15-7; **1a**, 7770-45-8; **1b**, 126190-58-7; **1c**, 126190-60-1; **1d**, 126190-62-3; **1e**, 126190-64-5; **1f**, 126190-66-7; 2·HBr, 126190-57-6; **2c**, 3453-33-6; **2d**, 126190-59-8; **2e**, 126190-61-2; **2f**, 126190-63-4; **2g**, 126190-65-6; **2h**, 126190-67-8; hippuric acid, 495-69-2; 1-naphthol, 90-15-3; 2-naphthol, 135-19-3; 6-bromo-2-naphthol, 15231-91-1; 6-bromo-2-methoxynaphthalene, 5111-65-9.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters, bond distances, and bond angles for **1c**, **1f**, and **1d** (12 pages). Ordering information is given on any current masthead page.

New Syntheses of Cyclopenta[*cd*]pyrene 3,4-Oxide and 4-Pyrenylacetic Acid

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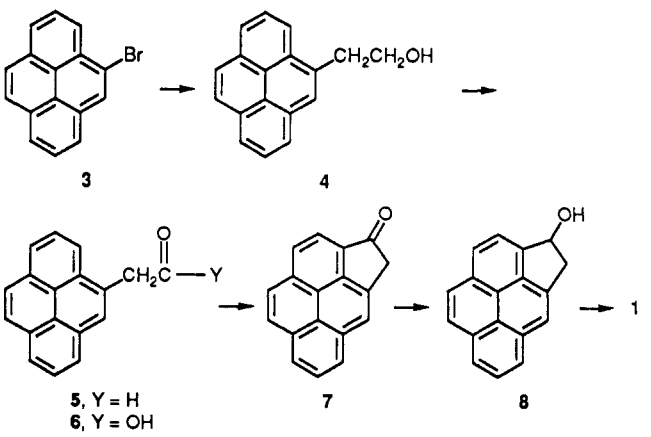
New syntheses of cyclopenta[*cd*]pyrene 3,4-oxide (CPPE) and 4-pyrenylacetic acid, a key intermediate in the synthesis of cyclopenta[*cd*]pyrene and CPPE, are described starting from 1,2,3,6,7,8-hexahydropyrene. 4-Pyrenylacetic acid is prepared from the corresponding alcohol, 2-(4-pyrenyl)ethanol, by applying two mild oxidation reactions. 4-Pyrenylacetaldehyde was obtained by *N*-chlorosuccinimide dimethyl sulfide oxidation, and this was converted smoothly to the desired 4-pyrenylacetic acid by silver oxide oxidation, an approach that has potential for a new route to arylacetic acids from arylethanols. The epoxide CPPE is prepared by cyclization of the 3,4-*trans*-dihydroxycyclopenta[*cd*]pyrene via its monotosylate, prepared in situ, with powdered sodium hydroxide.

Polycyclic aromatic hydrocarbons (PAH), produced during combustion of coal, gasoline, and diesel fuel, are genotoxic environmental pollutants. The biological activity of PAH requires metabolic activation to a variety of oxygenated products, more easily excreted by the organism, in the form of epoxides and/or dihydroxy epoxides.[1,2] Cyclopenta[*cd*]pyrene (CPP), 1, which contains a *cd* fused ring and lacks a bay region, was identified as a component of carbon black[3,4] and automobile exhaust.[5] It was found to be a potent mutagen to bacteria[6] and carcinogenic to mice.[7] Cyclopenta[*cd*]pyrene 3,4-oxide (CPPE, 2) was predicted to be a highly mutagenic metabolite of CPP. Eisenstadt and Gold proposed, on the basis of experimental observation and perturbational molecular orbital calculations, that an electrophilic species is formed by

Scheme I



opening of the epoxide ring at C(3) to give a benzylic carbonium ion capable of reacting with nucleophilic sites of cellular macromplecules such as DNA and proteins.[6]

For further in vivo and in vitro studies on the interaction of CPP and CPPE with DNA and proteins we needed relatively large amounts of CPP and CPPE. A number of syntheses for CPP have been published to date[8-14] and

(1) Singer, B.; Grunberger, D. *Molecular Biology of Mutagens and Carcinogen*; Plenum Press: New York, 1983.
(2) Dipple, A.; Moschel, R. C.; Bigger, C. A. H. Polynucleararomatic Carcinogens. In *Chemical Carcinogens*, 2nd ed.; Searle, C., Ed.; ACS monograph 182, American Chemical Society: Washington, DC, 1984; p 41.
(3) Gold, A. *Anal. Chem.* **1975**, *47*, 1469.
(4) Wallcave, L.; Nagel, D. L.; Smith, J. W.; Waniska, R. D. *Environ. Sci. Technol.* **1975**, *9*, 143.
(5) Grimmer, G. In *Air Pollution and Cancer in Man*; Mohr, V., Schmahl, D., Tomatis, L., Eds.; IARC: Lysons, France, 1977; pp 29–39.
(6) Eisenstadt, E.; Gold, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 1667.
(7) Neal, J.; Trieff, N. M. *Health Lab. Sci.* **1972**, *9*, 32.
(8) Gold, A.; Schultz, J.; Eisenstadt, E. *Tetrahedron Lett.* **1978**, 4491.

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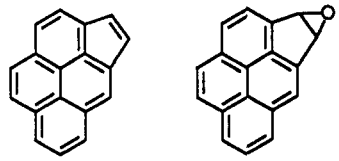
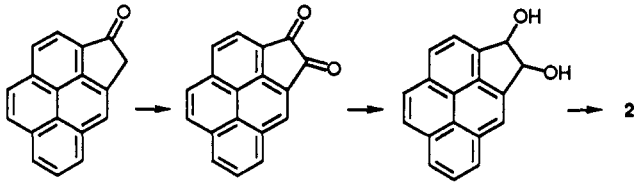


1 2

fewer syntheses for CPPE.[13,15,16] However, more convenient synthetic methods are needed, especially for CPPE. A key intermediate compound used for the synthesis of CPP and CPPE is 4-pyrenylacetic acid, **6**. Since the method for obtaining CPP from **6** is a known and convenient pathway (Scheme I), the recently published syntheses deal mainly with the synthesis of **6**. A traditional general method for arylacetic acid synthesis (from acetophenones) is the Willgerodt–Kindler reaction,[17] which requires the use of sealed tubes as well as high temperatures. A newer methodology for arylacetic acid synthesis, again from acetophenones, is the McKillope thallium(III) nitrate oxidative rearrangement.[18] Both of these methods were applied to the synthesis of 4-pyrenylacetic acid.[8,13]

Only three syntheses of CPPE have been published, and all lack efficiency in regard to yield and/or the number of steps involved. We report herein a new convenient synthesis for CPPE (**2**) from the starting material 1,2,3,6,7,8-hexahydropyrene through 4-pyrenylacetic acid, **6**. The acid **6**, prepared as described below, was cyclized to the ketone **7** by anhydrous HF,[11] and this was converted to the 3,4-dihydro-3,4-*trans*-dihydroxycyclopenta[*cd*]-pyrene, **10**, following a published procedure.[13] The diol **10** was cyclized to the epoxide **2** in 86% yield through its monotosylate, prepared in situ, in the presence of powdered sodium hydroxide.[19] This method is more convenient than the Sangaiah method of converting the same diol by using triphenylphosphine and EtOOEt (50% yield) or the other methods of converting CPP to CPPE via the bromohydrin or via the chloroacetate. We believe that this route offers a general method for other polycyclic aromatic hydrocarbon epoxides as it was also applied successfully in our laboratory to the synthesis of benzo[*e*]pyrene 9,10-oxide.[20]



7 9 10

The strategy for the synthesis of **6** is based on mild oxidation reactions of the corresponding alcohol 2-(4-pyrenyl)ethanol, **4**. In fact Harvey et al. first described the route to CPP through 2-(4-pyrenyl)ethanol but omitted experimental details.[21] 4-Bromopyrene, **3**, prepared from 1,2,3,6,7,8-hexahydropyrene,[11,22] was converted to 2-(4-pyrenyl)ethanol (**4**) in very good yield (85%) by lithiation of **3** followed by addition of ethylene oxide. One step oxidation of the alcohol **4** directly to the corresponding acid **6** by PDC[23] was complicated by the formation of 4-pyrenecarboxylic acid as a major side product. The ratio of 4-pyrenecarboxylic acid to **6** was 2:3 as determined by GC–MS analysis of the methylated products. In order to avoid such side reactions the oxidation of the alcohol **4** to the acid **6** was performed in two mild oxidation steps. The oxidation of alcohol **4** to aldehyde **5** was performed in excellent yield by the *N*-chlorosuccinimide dimethyl sulfide method.[24] Oxidation of the alcohol **4** by PCC was unsatisfactory, yielding 4-pyrenecarboxaldehyde and the desired aldehyde **5** in the ratio of 3:7, respectively. Attempts to cyclize the aldehyde **5** directly to CPP using PPA[25] were unsuccessful, and unidentified products were obtained instead. The reagent of choice for the oxidation of aldehyde **5** to the acid **6** was silver oxide, one of the mildest oxidation agents for aldehydes.[26] Acid **6** was obtained in good yield with some modification of the original procedure. This approach may open a new route to arylacetic acids in the cases where preparation of the corresponding arylethanol is possible. The conversion of **6** to CPP as previously reported[11] and outlined in Scheme I completes the synthesis.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained on a Bruker WM-270 MHz or a Varian XL-300 instrument. IR spectra were obtained on a Perkin-Elmer 397 infrared spectrophotometer. HRMS were determined on a Finnigan MAT system 8200 double-focusing, magnetic sector, mass spectrometer. GC–MS and low-resolution MS analyses were performed using a Hewlett-Packard 5987A GC–MS with standard EI source and a 15 m × 0.25 mm DB-5 fused silica capillary column. Ether and monoglyme were dried over sodium. 1,2,3,6,7,8-Hexahydropyrene was purchased from Aldrich.

2-(4-Pyrenyl)ethanol (4). To a solution of 4-bromopyrene (**3**) (3 g, 10.7 mmol) in dry ether (150 mL) containing lithium (190 mg, 27 mmol) was added a solution of *n*-BuLi (2.5 M, 2.0 mL) to initiate the reaction. The mixture was stirred 2 h at room temperature, and then it was transferred by a dry syringe to a second flask and cooled down with a salt–ice bath. Ethylene oxide (0.58 mL, 11.5 mmol) was added by precooled syringe in portions over 15 min, and the reaction mixture was stirred for 45 min at this temperature. The cooling bath was removed, and the reaction mixture was stirred for additional 15 min at room temperature. The reaction was cooled to 0 °C again, and water (100 mL) was added carefully. The organic phase was separated, and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed over silica gel to yield 2.3 g of the alcohol **4**; mp 88–89.5 °C (recrystallized from toluene); IR ($CHCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 8.35–7.98 (m, 9 H), 4.13

(9) Ittah, Y.; Jerina, D. M. *Tetrahedron Lett.* **1978**, 4495.
(10) Ruehle, P. H.; Fischer, D. L.; Wiley, J. C., Jr. *J. Chem. Soc., Chem. Commun.* **1979**, 302.
(11) Konieczny, M.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 2158.
(12) Tintel, C.; Cornelisse, J.; Lugtenbereger, J. *Recl.: Neth. Chem. Soc.* **1983**, *102*, 14.
(13) Sangaiah, R.; Gold, A. In *PAH-Mechanisms and Metabolism*, 8th International Symposium; Battelle: Columbus, OH, 1983; p 1147.
(14) Veeraraghavan, S.; Jostmeyer, S.; Myers, J.; Wiley, J. C., Jr. *J. Org. Chem.* **1987**, *52*, 1355.
(15) Gold, A.; Brewster, J.; Eisenstadt, E. *J. Chem. Soc., Chem. Commun.* **1979**, 903.
(16) McCaustland, D. J.; Ruehle, P. H.; Wiley, J. C., Jr. *J. Chem. Soc., Chem. Commun.* **1980**, 93.
(17) (a) Carmack, M.; Spielman, M. A. *Org. React.* **1947**, *3*, 83. (b) Asinger, F.; Schafer, W.; Halcour, K. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 19. (c) Wegler, R.; Kuhle, E.; Schafer, W. *Newer Method of Preparative Organic Chemistry*; Academic Press: New York, 1964; Vol. 3, p 1.
(18) McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, 95, 3340.
(19) Holland, S.; Epstein, R. *Synthesis* **1977**, 706.
(20) Day, B. W.; Sahali, Y.; Naylor, S.; Gan, L.-S.; Nguyen, T. T.; Skipper, P. L.; Wishnok, J. S., Tannenbaum, S. R., paper in progress.
(21) Harvey, G. H.; Raddo, P. D. In *Polymuclear Aromatic Hydrocarbons: A Decade of Progress*; Cooke, M., Dennis, A. J., Eds.; Battele Press: Columbus, OH, 1989; pp 363–375.
(22) Streiweiser, A., Jr.; Lawler, R. G.; Schwaab, D. *J. Org. Chem.* **1965**, *30*, 1470.
(23) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(24) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(25) No experiment was performed to cyclize **5** using HF.
(26) Walbarsky, H. M.; Davis, R. H.; Howton, R. D. *J. Am. Chem. Soc.* **1951**, *73*, 2590.

(t, 2 H), 3.53 (t, 3 H); MS, found for $C_{18}H_{14}O$ m/z 246.1046 (calcd m/z 246.1045).

4-Pyrenylacetic Acid (6). Methyl sulfide (0.6 mL, 8.2 mmol) was added to a stirred solution of *N*-chlorosuccinimide (800 mg, 6.0 mmol) in toluene (20 mL) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and then cooled down to −25 °C. A solution of the alcohol **4** (980 mg, 4.0 mmol) in methylene chloride (4 mL) was added dropwise. The reaction mixture was stirred 2 h at −25 °C, and then a solution of triethylamine (606 mg, 6.0 mmol) in toluene (1 mL) was added dropwise. The cooling bath was removed, and after 5 min ether (40 mL) was added. The organic layer was washed with 1% HCl (10 mL) and water (2 × 30 mL), dried ($MgSO_4$), and concentrated to give 970 mg of crude aldehyde **5** (95% yield according to GC–MS), which was used directly for the next step: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 9.92 (t, 1 H), 8.28–7.9 (m, 9 H), 4.22 (d, 2 H); MS, found for $C_{18}H_{12}O$ m/z 244.0888 (calcd m/z 244.0888).

The crude aldehyde from the last step (970 mg) was dissolved in ethanol (30 mL) and added to a solution of silver nitrate (1.4 g, 8.25 mmol) in ethanol (50 mL). To the well-stirred solution of the aldehyde was added dropwise over 10 min 5 N aqueous NaOH (3 mL) diluted to 25 mL with ethanol. The black mixture was stirred at room temperature for 4 h and then centrifuged. The supernatant was decanted, and the solvent was removed under reduced pressure. The residual solid was taken up in water (25 mL) and washed with pentane (2 × 15 mL), acidified with concentrated HCl, filtered, and dried to give 840 mg of acid **6** (81%), mp 241–243 °C (for a small amount that was recrystallized from chlorobenzene): IR (Nujol) 3300–2400, 1700 cm^{-1}; NMR (acetone-d_6) δ 8.4–7.95 (m, 9 H), 4.3 (s, 2 H); MS of the methyl ester of **6** m/z (rel intensity) 274 (38, M^+), 215 (100).

3,4-Dihydrocyclopenta[*cd*]pyrene 3,4-Oxide (2). A solution of the diol **10** (26 mg, 0.1 mmol) and tosyl chloride (1.05 equiv, 20 mg, 0.105 mmol) in monoglyme (0.8 mL) was added slowly to a suspension of sodium hydroxide (10 equiv, 40 mg, 1 mmol) in monoglyme (0.8 mL) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature and filtered, and the filtrate was concentrated. The crude product was chromatographed over a neutral alumina (activity IV) column with benzene under nitrogen stream. The solvent was removed by nitrogen stream to give 20.8 mg of epoxide **2** (86%): mp 204–206 °C; NMR (acetone-d_6) δ 8.32–8.02 (m, 8 H), 5.18 (s, 2 H); MS m/z (rel intensity) 242 (100, M^+), 214 (88), 213 (77).

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Registry No. **2**, 73473-54-8; **3**, 1732-26-9; **4**, 125996-95-4; **5**, 125996-96-5; **6**, 22245-55-2; **10**, 72273-60-0.

Synthesis and X-ray Crystal Structure of 1,3,3-Trinitroazetidine

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1,3,3-Trinitroazetidine (1) was synthesized and its structure elucidated by X-ray crystallography. Reaction of 1-*tert*-butyl-3-((methylsulfonyl)oxy)azetidine (**3a**) with sodium nitrite gave 1-*tert*-butyl-3-nitroazetidine (**4a**), which was converted to 1-*tert*-butyl-3,3-dinitroazetidine (**5a**) by oxidative nitration. Nitrolysis of **5a** with acetyl nitrate gave **1**. 1-Benzhydryl-3,3-dinitroazetidine (**5b**) did not undergo a similar nitrolysis. Single-crystal X-ray analysis of **1** showed that the ring is puckered, with a dihedral angle of 13.6 (5)° between the C–C–C and C–N–C planes, and that the nitramino group exhibits an unusually high (39.4°) out-of-plane deformation. A structural optimization with MNDO reproduced the ring pucker and the nitramino bend to within 5°. The large bend at the ring nitrogen atom indicates sp^3 rather than sp^2 for its hybridization. However, the N–N bond length, 1.351 (6) Å, falls in the normal range for planar (sp^2) nitramines and is ca. 0.1 Å shorter than N–N bonds previously observed in bent nitramines.

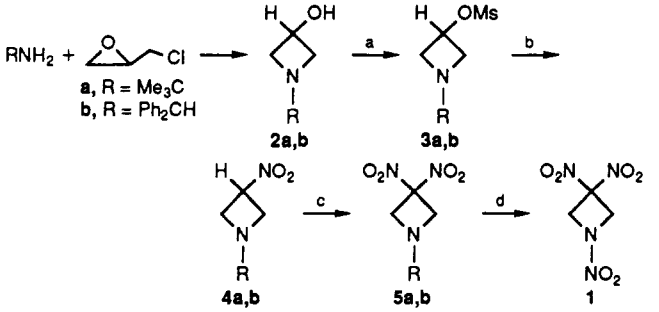
Introduction

Cyclic polynitramines[1] as well as cyclic nitramines containing *gem*-dinitro groups[2] are of interest for structural and decomposition mechanism studies.[3] 1,3,3-Trinitroazetidine (**1**), the simplest member of the latter class, has been synthesized in these laboratories, and thermolysis[4] infrared dynamic motion studies[5] of this material have been reported elsewhere. Herein we report the synthesis and crystallographic characterization of **1**.

Synthesis

The Mannich condensation reaction between amines and nitro alcohols[6] has been employed to synthesize cyclic compounds containing both *C*-nitro and nitramino groups.[2,7] This approach depends on the use of a sterically demanding blocking group on the amine to control the course of the ring formation.[2b] Subsequent nitrolysis of the N-blocking group yields the nitramine. Both acyl and alkyl groups have been used, although results are highly dependent on the system.[8] However, the Mannich condensations used in the synthesis of relatively unstrained

Scheme I[a]



[a] Reagents: (a) Et_3N, $MeSO_2Cl$; (b) $NaNO_2$; (c) $AgNO_3$, $NaNO_2$ or $C(NO_2)_4$; (d) HNO_3, $(CH_3CO)_2O$.

[†] Fluorochem, Inc.

[‡] Naval Research Laboratory.

(1) (a) Koppes, W. M.; Chaykovsky, M.; Adolph, H. G.; Gilardi, R.; George, C. *J. Org. Chem.* **1987**, *52*, 1113. (b) Willer, R. L.; Atkins, R. L. *J. Org. Chem.* **1984**, *49*, 5147. (c) Willer, R. L. *J. Org. Chem.* **1984**, *49*, 5151.

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