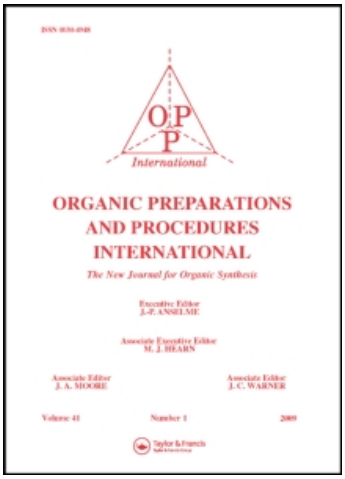

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SYNTHESIS OF ACETOXYLATED AND HYDROXYLATED NITROBENZO[a]PYRENE AND NUROBENZO[e]PYRENE

M. -J. Lee[a]; J. -S. Lai[a]; E. Cheng[a]; P. P. Fu[b]
[a] Institute of Chemistry, Providence University, Taiwan, Rep of CHINA [b] National Center for Toxicological Research, Jefferson, AR

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SYNTHESIS OF ACETOXYLATED AND HYDROXYLATED NITROBENZO[a]PYRENE AND NITROBENZO[e]PYRENE

Submitted by (01/05/95) M.-J. Lee, J.-S. Lai, E. Cheng and P. P. Fu*†

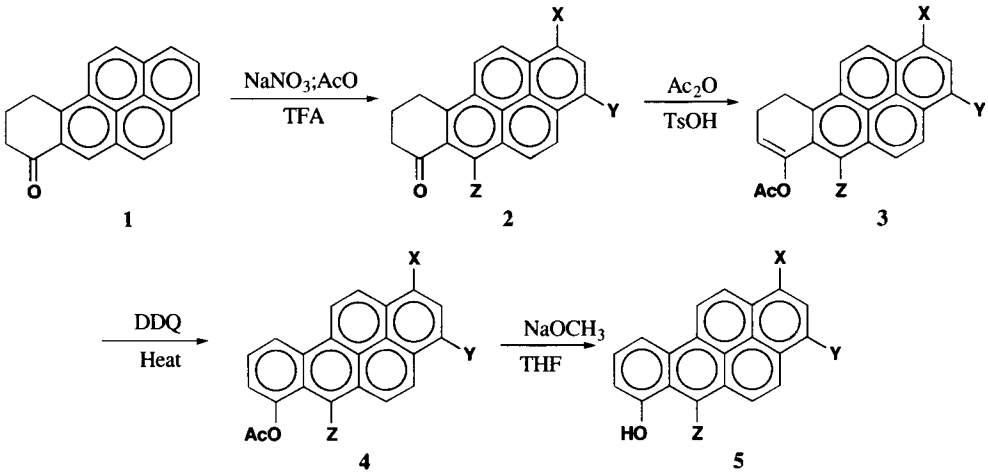
Institute of Chemistry, Providence University, Sha-lu Taichung, Taiwan, Rep. of CHINA

† *National Center for Toxicological Research, Jefferson, AR 72079*

Hydroxylated and acetoxylated polycyclic aromatic hydrocarbons (PAHs) have been detected in the environment[1,2] and some of these compounds exhibit higher mutagenic activity than their respective parent nitro-PAHs.[3-5] Hydroxylated nitro-PAHs are also principal metabolites of nitro-PAHs.[3,4] Thus, these compounds may pose possible adverse human health effects. Synthetic standards are required to study their genotoxic and other biological activity. This paper reports the synthesis of

six acetoxylated and hydroxylated nitrobenzo[a]pyrenes, 7-OAc-1-nitro-BaP (**4a**), 7-OAc-3-nitro-BaP (**4b**), 7-OAc-6-nitro-BaP (**4c**), 7-OH-1-nitro-BaP (**5a**), 7-OH-3-nitro-BaP (**5b**), 7-OH-6-nitro-BaP (**5c**), and 9-acetoxy-5-nitrobenzo[e]pyrene (9-OAc-5-nitro-BeP) (**9**).

The preparation of **4a-c** and **5a-c** started by nitration of 7-oxo-7,8,9,10-tetrahydro-BaP (**1**) with sodium nitrate in trifluoroacetic acid,[6] to afford compounds **2a-c** in 35, 22 and 30% yields, respectively. These three isomers were separated by column chromatography, and were converted to the corresponding enol acetates **3a-c** by treatment with acetic anhydride and *p*-toluenesulfonic acid (Scheme 1). Aromatization of **3a-c** each with DDQ gave **4a-c** in high yields. Compounds **5a-c** were

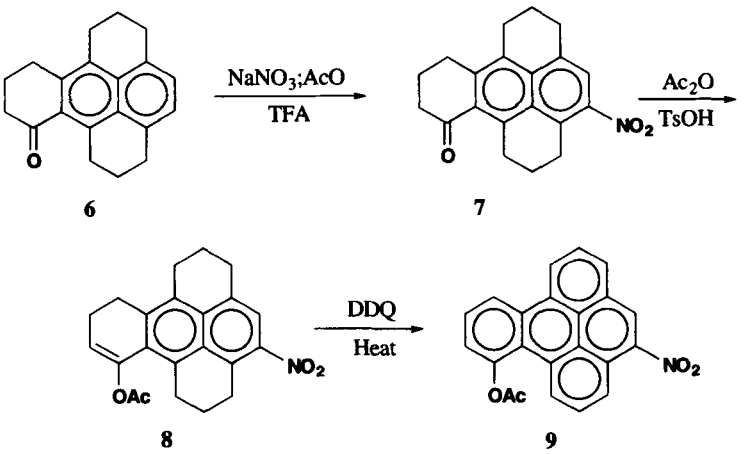


a) Y = Z = H, X = NO_2 b) X = Z = H, Y = NO_2 c) X = Y = H, Z = NO_2

Scheme 1

obtained in high yields by methanolysis of **4a-c** with sodium methoxide in methanol and THF at 65° for 40 min (Scheme 1). The overall yields of **4a-c** are 18, 25, and 11%, respectively, a combined yield of 54% of these three isomers. 9-OAc-5-nitro-BeP (**9**) was prepared by the same synthetic route by nitration of ketone **6**, affording compound **7** in a 52% yield. The location of the nitro substituent was determined after its conversion to compound **9** (Scheme 2).

Although direct nitration of acetoxylated PAHs can lead to acetoxylated nitro-PAHs in a single step, it provides geometric isomers that usually cannot be separated by conventional methods, including column chromatography.[7] However, nitration of a suitable tetrahydroketone followed by the steps depicted in Scheme 1, represents a simple and convenient method for the general synthesis of acetoxylated nitro-PAHs. Methanolysis of the acetoxylated nitro-PAHs by sodium methoxide in methanol affords the corresponding hydroxylated nitro-PAHs in nearly



6 7 8 9

Scheme 2

quantitative yields. Thus, the present method may constitute a general route for the synthesis of acetoxylated and hydroxylated nitro-PAHs.

EXPERIMENTAL SECTION

UV-vis absorption spectra measured in methanol were recorded on a Shimadzu UV-260 spectrophotometer. Mass spectra were obtained on a JEOL JMS-DX300 spectrometer, with a solid probe by electron impact (75 eV) at an ionizer temperature at 250°. All proton NMR spectra were obtained on a Bruker AM-500 spectrometer using acetone-d_6 as solvent. The chemical shifts are reported in δ downfield from TMS.

7-OAc-1-nitro-BaP (4a), 7-OAc-3-nitro-BaP (4b) and 7-OAc-6-nitro-BaP (4c).- To compound **1** (1.00 g, 3.7 mmol) in 200 mL of acetic acid in an ice bath was added slowly sodium nitrate (315 mg, 3.7 mmol) in 100 mL of trifluoroacetic acid. After addition of 150 mL of acetic anhydride, the reaction was allowed to proceed at ice-bath temperature for 30 min and then at ambient temperature for 2.5 hrs. The reaction mixture was poured into ice-water and the precipitated solid was collected and washed with water. The dried residue was chromatographed over silica gel (130-270 mesh, 2x20 cm). Elution with hexane-ethyl acetate (5:1, v/v) afforded **2a** (410 mg, 35% yield) as a yellowish solid, mp. 241-242.5°; UV-vis: λ_{max} 388 (ε = 10700), 267 (ε = 38400) and 202 nm (ε = 21500). MS: m/z 315 ($[M]^+$, 76%), 287 ($[M - CO]^+$, 100%), and 269 ($[M - NO_2]^+$, 12%).

Further elution gave **2b** (351 mg, 30% yield) as a yellowish solid, mp. 250.5-252°; UV-vis: λ_{max} 397 (ε = 9700), 291 (ε = 8300) and 233 nm (ε = 19000). MS (75 eV): m/z 315 ($[M]^+$, 100%), 285 ($[M - NO]^+$, 50%), 269 ($[M - NO_2]^+$, 18%), and 257 ($[M - CO - NO]^+$, 37%). Further elution with hexane-ethyl acetate (v/v, 5/1) resulted in **2c** (257 mg, 22% yield) as a yellowish solid, mp 212-213°; UV-vis:

λ_{max} 376 (ε = 24000), 289 (ε = 33000), 233 (ε = 54000), and 203 nm (ε = 47000). MS (75 eV): m/z 315 ([M]$^+$, 23%), 287 ([M - CO]$^+$, 100%), and 269 ([M - NO_2]$^+$, 11%).

Reaction of compound **2a** (140 mg, 0.44 mmol) and acetic anhydride (10 mL) catalyzed by *p*-toluenesulfonic acid (20 mg) under reflux for 22 hrs gave the crude **3a** which was heated in refluxing with DDQ (300 mg) in dioxane (30 mL) for 4 hrs. After workup, chromatography of the reaction product over silica gel and elution with hexane-ethyl acetate (v/v, 3/1) gave **4a** as an orange solid, mp. 239-240°; UV-vis: λ_{max} 427 (ε = 34000), 303 (ε = 42000), 266 (ε = 92000), and 225 nm (ε = 51000). MS m/z 355 (M$^+$, 33%), 325 ([M - NO]$^+$, 13%), 313 ([M - CH_2=C=O]$^+$, 100%), 283 ([M - NO - CH_2=C=O]$^+$, 35%) and 267 ([M - NO_2 - CH_2=C=O]$^+$, 44%); NMR: δ 2.61 (s, 3, OCH_3), 7.73 (d, 1, H_8), 8.01 (d, 1, H_9), 8.18 (d, 1, H_4), 8.35 (d, 1, H_3), 8.38 (d, 1, H_5), 8.78 (d, 1, H_2), 9.00 (s, 1, H_6), 9.10 (d, 1, H_{12}), 9.20 (d, 1, H_{10}), and 9.53 ppm (d, 1, H_{11}); $J_{2,3}$ = 8.3; $J_{4,5}$ = 9.0; $J_{8,9}$ = 7.5; $J_{9,10}$ = 8.6; $J_{11,12}$ = 9.6 Hz.
Anal. Calcd for $C_{22}H_{13}NO_4$: C, 74.36; H, 3.69; O, 18.01. Found: C, 74.42; H, 3.59; O, 17.98

Similar reaction of compound **2b** (95 mg, 0.30 mmol) gave **3b**, which upon dehydrogenation followed with chromatography afforded **2b** as an orange solid (74 mg, 69% yield), mp. 238-239°; UV-vis: λ_{max} 433 (ε = 4400), 400 (ε = 7000), 381 (ε = 4600), 359 (ε = 2800), 300 (ε = 7100), 266 (ε = 14000), and 253 nm (ε = 15000). MS: m/z 355 (M$^+$, 19%), 325 ([M - NO]$^+$, 10%), 313 ([M - CH_2=C=O]$^+$, 100%), 283 ([M - NO - CH_2=C=O]$^+$, 59%) and 267 ([M - NO_2 - CH_2=C=O]$^+$, 63%); NMR: δ 2.62 (s, 3, OCH_3), 7.73 (d, 1, H_8), 8.00 (d, 1, H_9), 8.47 (d, 1, H_5), 8.51 (d, 1, H_1), 8.59 (d, 1, H_{12}), 8.63 (d, 1, H_4), 8.64 (d, 1, H_2), 9.02 (s, 1, H_6), 9.19 (d, 1, H_{10}), and 9.46 ppm (d, 1, H_{11}); $J_{1,2}$ = 8.7; $J_{4,5}$ = 9.6; $J_{8,9}$ = 7.5; $J_{9,10}$ = 8.5; $J_{11,12}$ = 9.0 Hz.
Anal. Calcd for $C_{22}H_{13}NO_4$: C, 74.36; H, 3.69; O, 18.01. Found: C, 74.03; H, 3.82; O, 18.32

Similarly, reaction of **2c** (200 mg, 0.31 mmol) gave crude **3c** which upon dehydrogenation with DDQ (500 mg) afforded **4c** as a yellowish solid (74 mg, 69% yield), mp. 247-248°; UV-vis: λ_{max} 398 (ε = 10000), 378 (ε = 11000), 290 (ε = 22000), 278 (ε = 15000), 266 (ε = 25000), and 257 nm (ε = 24000). MS: m/z 355 (M$^+$, 41%), 325 ([M - NO]$^+$, 15%), 313 ([M - CH_2=C=O]$^+$, 57%), and 283 ([M - NO - CH_2=C=O]$^+$, 28%); NMR: δ 2.48 (s, 3, OCH_3), 7.78 (d, 1, H_8), 7.77 (d, 1, H_5), 8.04 (d, 1, H_9), 8.20 (d, 1, H_2), 8.34 (d, 1, H_4), 8.40 (d, 1, H_3), 8.54 (d, 1, H_1), 8.65 (d, 1, H_{12}), 9.29 (d, 1, H_{10}), and 9.31 ppm (d, 1, H_{11}); $J_{1,2}$ = 7.9; $J_{2,3}$ = 7.3; $J_{4,5}$ = 9.5; $J_{8,9}$ = 7.8; $J_{9,10}$ = 8.6; $J_{11,12}$ = 9.1 Hz.
Anal. Calcd for $C_{22}H_{13}NO_4$: C, 74.36; H, 3.69; O, 18.01. Found: C, 74.86; H, 3.54; O, 18.09

Synthesis of Hydroxynitrobenzo[a]pyrenes 5a, 5b, and 5c.- In general, a solution of 20 mg of an OAc-nitro-BaP in 5 mL of THF and 6 mg of $NaOCH_3$ in 5 mL of methanol was stirred at 65° for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was collected and dried over $MgSO_4$. After solvent was removed, pure OH-nitro-BaP was obtained in a near quantitative yield.

7-OH-1-nitro-BaP (5a), mp. 283-285°; UV-vis: λ_{max} 455 (ε = 7200), 317 (ε = 11000), 257 (ε = 22000), and 228 nm (ε = 16400). MS: m/z 313; NMR: δ 7.35 (d, 1, H_8), 7.82 (d, 1, H_9), 8.15 (d, 1, H_4), 8.32 (d, 1, H_3), 8.42 (d, 1, H_5), 8.76 (d, 1, H_2), 8.77 (d, 1, H_{10}), 9.26 (s, 1, H_6), 9.08 (d, 1, H_{12}), and 9.48 ppm (d, 1, H_{11}); $J_{2,3}$ = 8.4; $J_{4,5}$ = 9.1; $J_{8,9}$ = 7.6; $J_{9,10}$ = 8.6; $J_{11,12}$ = 9.7 Hz.

Anal. Calcd for $C_{20}H_{11}NO_3$: C, 76.67; H, 3.54; O, 15.32. Found: C, 76.43; H, 3.66; O, 15.18

7-OH-3-nitro-BaP (5b), mp. 292-292°; UV-vis: λ_{max} 455 (ε = 7100), 403 (ε = 7900), 383 (ε = 5000), 309 (ε = 12000), and 260 nm (ε = 26000). MS: m/z 313; NMR: δ 7.36 (d, 1, H_8), 7.81 (d, 1, H_9), 8.47 (d, 1, H_1), 8.52 (d, 1, H_5), 8.56 (d, 1, H_{12}), 8.63 (d, 1, H_2), 8.64 (d, 1, H_4), 8.76 (d, 1, H_{10}), 9.28 (s, 1, H_6), and 9.42 ppm (d, 1, H_{11}); $J_{1,2}$ = 8.7; $J_{4,5}$ = 9.6; $J_{8,9}$ = 7.6; $J_{9,10}$ = 8.6; $J_{11,12}$ = 9.2 Hz.

Anal. Calcd for $C_{20}H_{11}NO_3$: C, 76.67; H, 3.54; O, 15.32. Found: C, 76.60; H, 3.68; O, 15.28

7-OH-6-nitro-BaP (5c), mp. 280-281°; UV-vis: λ_{max} 395 (ε = 9500), 383 (ε = 9600), 307 (ε = 24000), 296 (ε = 21600), 268 (ε = 20300), 255 (ε = 21400), and 230 nm (ε = 19600). MS: m/z 313; NMR: δ 7.39 (d, 1, H_8), 7.76 (d, 1, H_5), 7.83 (d, 1, H_9), 8.15 (d, 1, H_2), 8.23 (d, 1, H_4), 8.33 (d, 1, H_3), 8.47 (d, 1, H_1), 8.56 (d, 1, H_{12}), 8.83 (d, 1, H_{10}), and 9.23 ppm (d, 1, H_{11}); $J_{1,2}$ = 7.8; $J_{2,3}$ = 7.6; $J_{4,5}$ = 9.4; $J_{8,9}$ = 7.6; $J_{9,10}$ = 8.5; $J_{11,12}$ = 9.3 Hz.

Anal. Calcd for $C_{20}H_{11}NO_3$: C, 76.67; H, 3.54; O, 15.32. Found: C, 76.81; H, 3.71; O, 15.47

Nitration of 7-OAc-BaP.- 7-OAc-BaP[7] (360 mg, 1.16 mmol) was nitrated with sodium nitrate (98 mg, 1.16 mmol) in trifluoroacetic acid (50 mL) and acetic anhydride (100 mL). After stirring for 30 min, the reaction was kept stirring at ambient temperature for 3 hrs, then poured into ice. The precipitate was purified over silica gel column. Elution with hexane-ethyl acetate (v/v, 3/1) afforded a mixture of compounds **4a, 4b** and **4c** (in a ratio of 1:1:25) in 110 mg (28% yield).

Synthesis of 9-OAc-5-nitro-BeP (9).- Nitration of **6** (500 mg) with sodium nitrate followed with purification yielded **7** (304 mg, 52% yield), mp. 194-195°; UV-vis: λ_{max} 376 (ε = 4200), 287 (ε = 19000), 249 (ε = 26000) and 202 nm (ε = 18000). MS: m/z 321 ($[M]^+$, 100%), 314 (50%), 291 (12%), and 275 (31%). Reaction of **7** with acetic anhydride afforded compound **8** which upon dehydrogenation with DDQ gave **9** as a light yellow solid in a 42% yield, mp 223-224°; UV-vis: λ_{max} 368 (ε = 12000), 275 (ε = 89000), 234 (ε = 72000), and 214 nm (ε = 96000). MS: m/z 355 (M^+, 51%), 324 ($[M - NO]^+$, 40%), 313 ($[M - CH_2{=}C{=}O]^+$, 100%), 283 ($[M - NO - CH_2{=}C{=}O]^+$, 31%) and 267 ($[M - NO_2 - CH_2{=}C{=}O]^+$, 4%); NMR: δ 2.59 (s, 3, OCH_3), 7.59 (d, 1, H_{10}), 7.87 (d, 1, H_{11}), 8.25 (d, 1, H_2), 8.28 (s, 1, H_7), 8.58 (d, 1, H_3), 8.67 (s, 1, H_6), 8.92 (d, 1, H_4), 9.05 (d, 1, H_{12}), 9.30 (d, 1, H_1), and 9.66 ppm (d, 1, H_8); $J_{1,2}$ = 8.0; $J_{2,3}$ = 7.7; $J_{6,7}$ = 8.2; $J_{7,8}$ = 8.3; $J_{10,11}$ = 7.7; $J_{11,12}$ = 8.3 Hz.

Anal. Calcd for $C_{22}H_{13}NO_4$: C, 74.36; H, 3.69; O, 18.01. Found: C, 74.68; H, 3.72; O, 17.87

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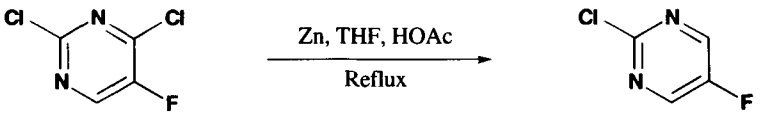
LARGE SCALE SYNTHESIS OF 2-CHLORO-5-FLUOROPYRIMIDINE

Submitted by (12/05/94) Audrey Dunaiskis, Tom Staigers, Tom Keltonic, Tom Chappie, Cliff Meltz, Robert Dugger and Mark A. Sanner*

Departments of Process Development, Process Research and Medicinal Chemistry Pfizer Central Research, Groton, CT 06340

The introduction of 2-amino-5-fluoropyrimidine functionality, found in neuroleptics such as the sigma receptor ligand BMY-14802,[1,2] is accomplished with derivatives of 5-fluorouracil such as 2,4-dichloro-5-fluoropyrimidine (**1**) and 2-chloro-5-fluoropyrimidine (**2**). Synthesis of 2-amino analogs from **1** requires initial protection of the 4-position with sulfur followed by later removal with Raney nickel; the regioselective protection is consistent with the preference for nucleophilic attack at the 4-chloro position.[1,3] Derivative **2** is available by a variation of the sulfur/Ra-Ni strategy,[4] or by hydrogenolysis of 2,4,6-trichloro-5-fluoropyrimidine.[5] While these methods are acceptable for preparing gram-quantities of **2** and its 2-amino derivatives, we required a method suitable for kilogram-scale synthesis.



1 **2**

Our investigation focused on a three-phase dechlorination of **1** using zinc in aqueous ammonium hydroxide and benzene.[6] A modification of this procedure with granular zinc and one mole equivalent of acetic acid in refluxing THF proved to be extremely useful for preparing as much as 1000 g of **2** in 55-65% yield. Granular zinc is preferred over more active forms such as zinc dust because the reaction rate can be difficult to control with zinc dust, especially when it is activated by