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The environmental contaminants 1-azapyrene **15**, 2-azapyrene **13** and several other azapyrene derivatives were synthesized from a common intermediate, 2,2a,3,4-tetrahydrocyclopenta[*cd*]phenalen-1-one oxime **6**. The synthesis of 1-azapyrene **15** completes the series of azapyrenes.

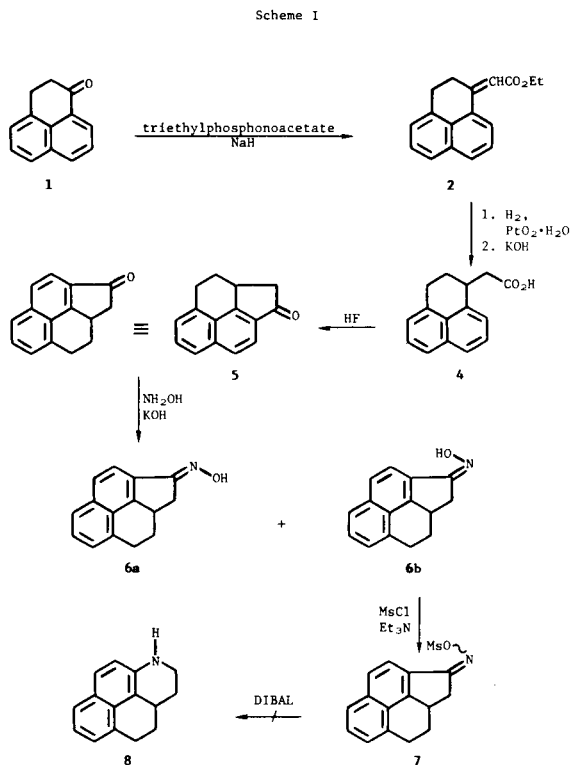
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### Introduction.

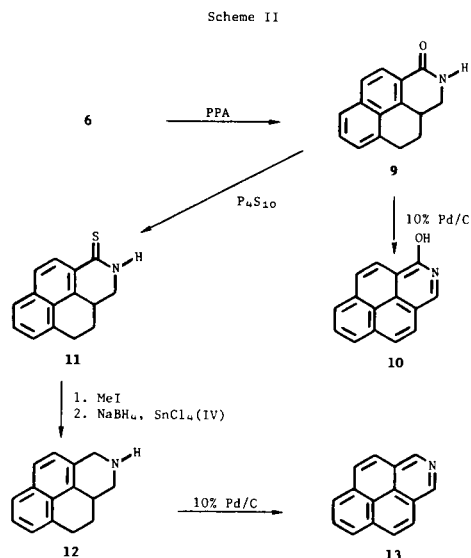
Azapyrenes have been detected in gc/ms spectra of samples of recent lake sediment [1], street dust [1-3] and suspended urban particulate [4]. Like polynuclear aromatic hydrocarbons, azapyrenes are pyrosynthesized during combustion and are therefore widely distributed in the environment [3]. Azapyrenes are the nitrogen isosteres of pyrene, the parent compound of a series that contains many highly carcinogenic derivatives. The aza-analogs may be responsible for the mutagenic activity which has been reported in the basic fraction of environmental pollutants. The synthesis and characterization of 1-azapyrene have not previously been reported in the literature and its synthesis completes the series of azapyrenes.

### Results and Discussion.

The strategy for the synthesis of 1-azapyrene involved construction of the cyclopenta[*cd*]phenalene ring system



(structure **5**), followed by ring expansion of an oxime using a Beckmann reaction and aromatization (Scheme I). This procedure offered the advantage that the needed carbon-carbon bonds could be synthesized by acid catalyzed condensation prior to introduction of the basic nitrogen atom with its deactivating effect under such conditions. The intermediate **5** was synthesized from 2,3-dihydrophenalene-1-one **1** [7] by a Horner-Emmons reaction followed by reduction and a Friedel-Crafts alkylation giving an improved synthesis of the ketone **5** [5] in 60% overall yield.

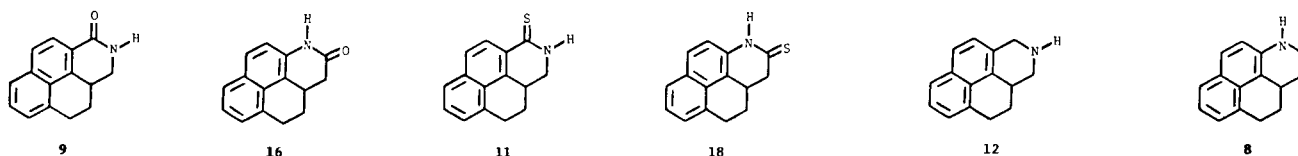


The proposed synthesis featured a reductive Beckmann reaction using the method of K. Muruoka *et al* [6] to give the amine **8** from the oxime mesylate **7**. When various attempts failed to form the ring expanded product, other Beckmann conditions were investigated (phosphorus oxychloride, phosphorus pentachloride, sulfuric acid, polyphosphoric acid). Polyphosphoric acid gave the lactam **9** in high yield (Scheme II), while only starting material was recovered from the other methods. Although the oxime **6** was a mixture of *syn* **6a** and *anti* **6b** isomers (9/1) and in a stereospecific Beckmann rearrangement the *syn* oxime **6** should have given the desired lactam **16** for the 1-azapyrene ring system, only the undesired lactam **9** was ever isolated. In fact the separated isomers of **6** each gave only

Table I

 $^{13}\text{C}$  NMR Chemical Shift [a] Data for Compounds **8**, **9**, **11**, **12**, **16**, and **18**

## Structures



No.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-3a	C-5a	C-8a	C-10a	C-10b	C-10c
<b>9</b>	167.04		46.12	26.89	29.54	126.68	127.71	126.08	124.78	123.64	35.23	136.70	134.49	127.71	135.29	123.64
<b>16</b>		172.02	37.78	29.65	29.92	125.86	127.71	124.24	124.84	116.28	32.42	134.42	128.95	132.53	118.23	130.25
<b>11</b>	208.97		47.42	27.00	29.49	126.24	126.57	126.24	126.24	125.16	34.96	135.56	127.49	137.40	133.56	128.19
<b>18</b>		202.80	45.89	31.67	29.60	125.97	125.32	127.87	127.87	115.41	29.26	134.91	131.07	141.58	125.82	131.28
<b>12</b>	55.74		54.82	26.60	30.07	126.01	127.31	125.36	123.30	125.85	36.30	132.64	128.74	129.93	135.29	128.46
<b>8</b>		41.90	30.79	29.11	29.76	127.00	124.51	121.48	125.76	117.47	34.53	130.36	127.76	138.38	114.98	133.94

[a] The chemical shifts are reported in ppm with tetramethylsilane as internal reference. The solvent is deuteriochloroform.

the lactam **9** when treated with polyphosphoric acid.

The lactam **9** had unexpected stability. Efforts to reduce it to the amine **12** by standard methods failed. The lactam **9** was aromatized using 10% palladium on carbon to give the hydroxyl compound **10**. Subsequent efforts to remove the hydroxyl group by displacement and/or reduction also failed. The hydroxyl compound **10** was converted to the mesylate, but it too was resistant to reduction.

The lactam **9** was converted to the thioamide **11** using phosphorus pentasulfide, but could not be desulfurized using Raney nickel. However, alkylation of **11** using iodomethane [8] gave a methylthio compound which was reduced using sodium borohydride and anhydrous stannic chloride to yield the amine **12**. Aromatization of the amine **12** using 10% palladium on carbon gave 2-azapyrene **13**. The product, 2-azapyrene **13**, was identical to material prepared by the method of Kirchlechner and Jutz [9] and thus confirmed the structural assignment of the lactam **9**.

Other approaches to the synthesis of 1-azapyrene were now considered (Scheme III). Reduction of the ketone **5** using sodium borohydride gave the alcohol **14**. Treatment of **14** in a modified Schmidt reaction using sodium azide and methanesulfonic acid, similar to the method described

by Eguchi *et al* [10], gave 1-aza-4,5-dihydropyrene, which was aromatized using 10% palladium on carbon to give 1-azapyrene **15**. The modified Schmidt reaction proceeded in very low yield and attempts to increase the yield were unsuccessful.

Another approach (Scheme IV) was then taken, in view of a reported change in isomeric yields of lactams using diethylaluminum chloride [11]. Reaction of the oxime mesylate **7** with diethylaluminum chloride [11] or aluminum chloride gave the desired lactam **16**. Aluminum chloride gave a higher yield of desired lactam. Lactam **16**

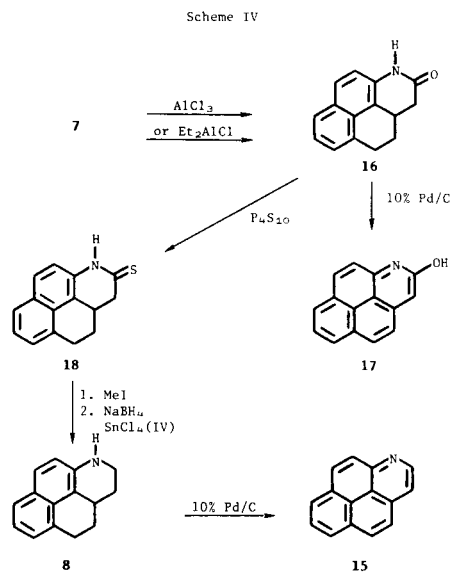
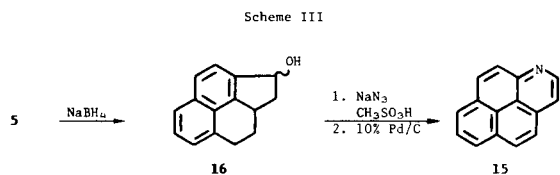


Table II

<sup>13</sup>C NMR Chemical Shift [a] Data for Compounds **10**, **13**, **15**, and **17**

No.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-3a	C-5a	C-8a	C-10a	C-10b	C-10c
<b>10</b> [b]	160.09		129.97	126.02	123.31	123.47	125.69	123.47	124.46	128.94	119.46	133.98	133.98	113.01	133.00	124.44
						or 123.58		or 123.58								
<b>17</b> [b] [c]		162.04	112.42	127.64	132.95	124.99	125.20	124.99	131.92	128.35	138.91	128.51	128.51	141.35	116.92	127.21
<b>13</b>	144.31		144.31	128.22	124.48	125.22	127.64	125.22	124.48	128.22	124.83	131.58	131.58	124.83	127.03	122.67
<b>15</b> [c]		146.84	117.65	128.76	131.35	126.79	126.56	126.79	131.95	125.40	146.80	130.64	129.93	149.10	117.68	126.63
						or 127.20		or 127.24								

[a] The chemical shifts are reported in ppm with tetramethylsilane as internal reference. The solvent is deuteriochloroform. [b] The solvent is *d*<sub>6</sub>-methylsulfoxide. [c] The spectrum was taken on the Varian XL-400 spectrometer.

was isomeric with the lactam **9** formed using polyphosphoric acid. Reduction of the lactam **16** was done in a similar manner to the method used successfully for the reduction of the lactam **9**. Thus **16** was converted to the thioamide **18**, alkylated with iodomethane and the resulting methylthio derivative was reduced with sodium borohydride and stannic chloride to the amine **8**.

Comparison of the nmr spectra of amine **8** and **12** verified the structural assignments. Amine **12** has a multiplet worth 2 protons at  $\delta$  4.20 indicative of benzylic protons adjacent to an amine. In the carbon spectrum (Table I) it has two methylene carbons next to nitrogen at  $\delta$  54.82 (C-3) and  $\delta$  55.74 (C-1). The proton spectrum of amine **8** has a multiplet at  $\delta$  3.50 worth 2 protons for the methylene group next to the nitrogen. The carbon spectrum of **8** has only one methylene carbon next to nitrogen  $\delta$  41.90 (C-2) and one aromatic quaternary carbon next to nitrogen  $\delta$  138.38 (C-11a).

Aromatization of amine **8** using 10% palladium on carbon gave 1-azapyrene **15**. The nmr spectra of 1-azapyrene **15** and 2-azapyrene **13** are readily distinguishable due to the symmetry of 2-azapyrene **13**. To assist in making the spectral assignments COSY (chemical shift correlation spectroscopy), DEPT (distortionless enhancement by polarization transfer), APT (attached proton test), and HETCOR (heteronuclear chemical shift correlation) nmr experiments were done [12,13,14]. The proton spectrum of 1-azapyrene **15** has a doublet at  $\delta$  9.22 ( $J = 5.3$  Hz) for H-2 and a doublet at  $\delta$  7.96 ( $J = 5.3$  Hz) for H-3, while the spectrum of 2-azapyrene **13** has a singlet at  $\delta$  9.43 which integrates for two protons for H-1 and H-2. The proton,

COSY and HETCOR spectra of 1-azapyrene **15** established the proton assignments. The COSY and HETCOR experiments provided connectivity information. It was not possible from the experiments to determine which doublet ( $\delta$  8.27 and  $\delta$  8.32,  $J = 7.2$  Hz) was H-6 and which was H-8. Similarly H-4 and H-5 ( $\delta$  8.30 and  $\delta$  8.34,  $J = 9.3$  Hz) could not be definitely assigned. The proton spectrum of 2-azapyrene **13** was unambiguously assigned with the information provided by the nmr experiments. In the carbon spectra (Table II), 2-azapyrene **13** has a peak at  $\delta$  144.31 for C-1 and C-3, while 1-azapyrene **15** has a peak at  $\delta$  146.84 for C-2 and a peak at  $\delta$  117.65 for C-3. In 1-azapyrene it was not possible to unambiguously assign C-6 and C-8 ( $\delta$  126.79 or  $\delta$  127.24).

In this study 1-azapyrene **15**, 2-azapyrene **13**, and several azapyrene derivatives were synthesized from a common intermediate, oxime **6**. These compounds are currently undergoing testing to determine their carcinogenicity and mutagenicity. Biological results will be reported elsewhere.

## EXPERIMENTAL

### General Methods.

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer as potassium bromide pellets. Ultraviolet spectra were recorded on a Varian DMS-90. The nmr spectra were recorded on a Varian XL-400 or a Jeol FX90Q spectrometer, using tetramethylsilane as the internal standard. The nmr multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Mass spectra were deter-

mined on a Ribermag R10-10C CG-MS. Column chromatography was done using E. Merck silica gel 40 (70-230 mesh ASTM). Tetrahydrofuran was distilled from sodium with benzophenone ketyl as an indicator. All other solvents were dried over 3A molecular sieves. Microanalyses were performed by W. Galbraith Laboratories, Knoxville, TN.

#### Ethyl 2-(2,3-Dihydro-1-phenalenylidene)acetate (2).

To a suspension of 0.43 g (9.07 mmoles) of sodium hydride in 25 ml of tetrahydrofuran under argon, was added dropwise, with cooling 1.8 ml (9.07 mmoles) of triethylphosphonoacetate. The mixture was stirred for 10 minutes at 23° to give a clear suspension. In 20 ml of tetrahydrofuran 2,3-dihydrophenalenone I [7] (1.7 g, 9.07 mmoles) was slowly added to the solution. After stirring 48 hours at 23°, 10 ml of ethanol was added to the mixture. The mixture was poured into water, extracted with ethyl acetate, dried (magnesium sulfate) and evaporated to give an oil. Chromatography on silica gel eluting with toluene separated the two isomers, 0.68 g and 1.19 g (*Z:E*) with a combined yield of 82%; <sup>1</sup>H nmr (deuteriochloroform): (*Z* isomer) δ 1.33 (t, J = 8 Hz, 3H, CH<sub>3</sub>), 3.17 (m, 2H, CH<sub>2</sub>-aromatic), 3.47 (m, 2H, CH<sub>2</sub>), 4.18 (q, J = 8 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.38 (s, 1H, =CH-), 7.30 (m, 3H, aromatic), 7.69 (m, 3H, aromatic); <sup>1</sup>H nmr (deuteriochloroform): (*E* isomer) δ 1.20 (t, J = 6 Hz, 3H, CH<sub>3</sub>), 2.69 (m, 2H, CH<sub>2</sub>), 3.16 (m, 2H, CH<sub>2</sub>-aromatic), 4.12 (q, J = 6 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.89 (s, 1H, =CH-), 7.29 (m, 3H, aromatic), 7.72 (m, 3H, aromatic); ir (neat): 1710 (C=O), 1625 (C=CH), 1180 (C-O-C), 1125 (C-O-C) cm<sup>-1</sup>.

#### Ethyl 2-(2,3-Dihydrophenalenyl)acetate (3).

A mixture of 1.31 g (5.15 mmoles) of the olefin 2, 250 ml of absolute ethanol and 0.09 g of PtO<sub>2</sub>·H<sub>2</sub>O (Adam's Catalyst) was hydrogenated at 50 psi for 24 hours. The mixture was filtered through celite and evaporated. The yellow oil was chromatographed on silica gel using 40% chloroform/60% petroleum ether to yield 1.28 g (98%); <sup>1</sup>H nmr (deuteriochloroform): δ 1.20 (t, J = 7 Hz, 3H, CH<sub>3</sub>), 1.99 (m, 2H, CH<sub>2</sub>), 2.65 (m, 2H, CH<sub>2</sub>CO), 3.06 (m, 2H, CH<sub>2</sub>-aromatic), 3.62 (m, 1H, CH-aromatic), 4.12 (q, J = 7 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.22 (m, 4H, aromatic), 7.59 (m, 2H, aromatic); ir (neat): 1720 (C=O), 1275 (C-O-C), 1170 (C-O-C) cm<sup>-1</sup>.

#### 2-(2,3-Dihydrophenalenyl)acetic Acid (4).

A mixture of 1.78 g (7.0 mmoles) of the ester 3, 100 ml of 0.18 M potassium hydroxide in methanol (10 mg/ml) and 20 ml of water was refluxed for 3 hours. The methanol was evaporated and 20 ml of water was added. After washing with chloroform, the solution was made acidic with concentrated hydrochloric acid. The acidic fraction was extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated to yield 1.48 g (92%); <sup>1</sup>H nmr (deuteriochloroform): δ 2.11 (m, 2H, CH<sub>2</sub>), 2.68 (m, 2H, CH<sub>2</sub>CO), 3.13 (m, 2H, CH<sub>2</sub>-aromatic), 3.69 (m, 1H, CH-aromatic), 7.27 (m, 4H, aromatic), 7.64 (m, 2H, aromatic), 10.91 (br s, 1H, CO<sub>2</sub>H); ir (neat): 2920 (-OH), 1700 (C=O), 1430 (-OH), 1290 (-OH) cm<sup>-1</sup>.

#### 2,2a,3,4-Tetrahydrocyclopenta[cd]phenalen-1-one (5).

To 6.40 g (27.8 mmoles) of the acid 4 in a 1 l polyethylene bottle (wide mouth) was added 150 ml of cold anhydrous hydrogen fluoride. The bottle was sealed, and after 24 hours was slowly opened. The hydrogen fluoride was allowed to evaporate under slight vacuum. Ice was added and the solution was stirred for 2 hours, followed by extraction with chloroform. The organic layer washed with saturated sodium carbonate solution, dried (magnesium sulfate) and evaporated. Chromatography on silica gel eluting with chloroform yielded 4.70 g (80%), mp 143-144° C [5]; <sup>1</sup>H nmr (deuteriochloroform): (400 MHz) δ 1.72 (ddd, J = 4.5, 12.4, 26.1 Hz, 1H, CH<sub>2</sub>CH), 2.48 (dd, J = 5.2, 17.6 Hz, 1H, CH<sub>2</sub>CO), 2.52 (m, 1H, CH<sub>2</sub>CH), 3.08 (dd, J = 6.6, 17.6 Hz, 1H, CH<sub>2</sub>CO), 3.24 (m, 1H, CH<sub>2</sub>-aromatic), 3.28 (m, 1H, CH<sub>2</sub>-aromatic), 3.48 (m, 1H, CH-aromatic), 7.38 (dd, J = 1.2, 7.1, 8.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.75 (apparent t, J = 7.5, 7.8 Hz, 2H); <sup>13</sup>C nmr (deuteriochloroform): δ 29.09 (C-3), 29.96 (C-4), 36.35 (C-2), 45.34 (C-2a), 119.29 (C-7), 124.98 (C-8), 125.47 (C-9), 127.36 (C-6), 129.37 (C-5, C-9c), 131.54 (C-7a), 135.60 (C-4a), 136.95

(C-9b), 159.71 (C-9a), 204.67 (C-1); ir: 1695 (C=O) cm<sup>-1</sup> (1); uv (chloroform): λ max 246 nm (ε 95,319), 253 (137,446), 280 (12,978), 288 (14,148), 298 (7765), 335 (7446), 350 (9999).

#### 2,2a,3,4-Tetrahydrocyclopenta[cd]phenalen-1-one Oxime (6).

To 0.485 g (2.28 mmoles) of the ketone 5 in 25 ml of methanol was added 0.240 g (3.42 mmoles) of hydroxylamine hydrochloride and 0.78 ml of aqueous 50% potassium hydroxide solution. After refluxing for 4 hours, the solution was evaporated. The compound was chromatographed on silica gel using 5% methanol/95% chloroform as the eluant. Recrystallization from methanol/water yielded 0.48 g (95%), mp 173-174° dec; <sup>1</sup>H nmr (d<sub>6</sub>-methylsulfoxide): δ 1.60 (m, 1H, CH-aromatic), 2.44 (m, 2H, CH<sub>2</sub>), 3.27 (m, 4H, CH<sub>2</sub>C=N, CH<sub>2</sub>-aromatic), 7.55 (m, 5H, aromatic), 10.82 (s, 1H, OH); ir: 3245 (O-H), 1650 (C=N-), 955 (N-O stretch) cm<sup>-1</sup>; uv (methanol): λ max 247 nm (ε 41,042), 253 (43,160), 280 (9435), 296 (10,879), 307 (8469), 330 (3909), 346 (4690); ms: m/e (relative intensity) 223 (100%) MI.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.69; H, 5.87; N, 6.27; O, 7.17. Found: C, 80.42; H, 5.98; N, 6.18; O, 7.21.

The *syn* and *anti* oximes were separated on silica gel using 1/1 hexane/chloroform; <sup>13</sup>C nmr (deuteriochloroform): (*syn*) δ 29.71 (C-3), 30.19 (C-4), 34.85 (C-2), 39.08 (C-2a), 119.15 (C-7), 124.40 (C-8), 125.32 (C-9), 127.06 (C-6), 127.27 (C-5), 127.60 (C-9c), 130.04 (C-7a), 133.61 (C-4a), 135.94 (C-9b), 149.59 (C-9a), 163.46 (C-1).

#### 2,2a,3,4-Tetrahydrocyclopenta[cd]phenalen-2-one Oxime Mesylate (7).

To 0.050 g (0.22 mmole) of the oxime 6 slurried in 0.05 ml (0.33 mmole) of dry triethylamine and 2 ml of dry dichloromethane under argon at -20° was added 0.02 ml (0.24 mmole) of methanesulfonyl chloride. After stirring 0.5 hours at -20° the solution was washed sequentially with cold 1N hydrochloric acid, cold saturated sodium bicarbonate solution and cold saturated sodium chloride solution, dried (sodium sulfate) and evaporated. Silica gel chromatography eluting with chloroform yielded 0.055 g (83%) of *syn* and *anti* isomers, mp 126° dec; <sup>1</sup>H nmr (deuteriochloroform): δ 1.70 (br m, 1H), 2.70 (br m, 2H, CH<sub>2</sub>), 3.22 (m, 2H, CH<sub>2</sub>-aromatic), 3.32 (s, 3H, CH<sub>3</sub>), 3.65 (br m, 2H, CH<sub>2</sub>C=N), 7.55 (m, 5H, aromatic); ir: 1610 (C=N stretch), 1345 (R-SO<sub>2</sub>OCH<sub>3</sub> stretch), 1170 (R-SO<sub>2</sub>OCH<sub>3</sub> stretch) cm<sup>-1</sup>; uv (chloroform): λ max 229 nm (ε 11,734), 244 (s) (22,021), 252 (32,639), 260 (36,983), 283 (5761), 293 (6244), 302 (4132), 332 (3046), 348 (4313); ms: m/e (relative intensity) 301 (80%) MI, 222 (30%), 206 (50%), 192 (100%), 79 (60%).

*Anal.* Calcd. for C<sub>16</sub>H<sub>15</sub>NSO<sub>3</sub>: C, 63.76; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.63; H, 5.25; N, 4.50; S, 10.69.

#### 3,3a,4,5-Tetrahydro-2-azapyren-1(2H)-one (9).

To 0.369 g (1.72 mmoles) of the oxime 6 was added 25 ml of polyphosphoric acid. After the slurry was well mixed, it was heated to 130° over 0.5 hours, and then poured onto ice. The solution was stirred until all gummy material was dissolved. The lactam was extracted with chloroform, dried (magnesium sulfate) and evaporated. Silica gel chromatography using 75% ethyl acetate/25% toluene yielded 0.332 g (90%), mp 214-215°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.86 (m, 1H), 2.22 (m, 1H), 3.15 (m, 2H, CH<sub>2</sub>-aromatic), 3.49 (m, 3H), 7.00 (m, 1H, NH), 7.38 (m, 2H), 7.71 (m, 2H), 8.08 (d, J = 7 Hz, 1H); ir: 1678 cm<sup>-1</sup> (CONH); uv (ethanol): λ max 242 nm (ε 61,594), 278 (6000), 289 (7000), 301 (5219), 327 (2906), 341 (3594); ms: m/e (relative intensity) 223 (80%) MI, 194 (100%), 165 (80%).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.70; H, 5.87; N, 6.27. Found: C, 80.77; H, 6.02; N, 6.11.

#### 2-Azapyren-1-ol (10).

To 0.259 g (1.16 mmoles) of lactam 9 was added 0.030 g of 10% palladium on carbon. The mixture was heated under argon from 230-320° over 1 hour. The solid was placed in a soxhlet thimble and extracted with chloroform. The extract was filtered through celite, evaporated and chromatographed on silica gel using 5% methanol/95% chloroform to yield 0.236 g (93%), mp 286-289°; <sup>1</sup>H nmr (d<sub>6</sub>-methylsulfoxide): δ 7.32 (d, J = 9 Hz, 1H), 7.47 (d, J = 9 Hz, 1H), 7.77 (d, J = 3

H<sub>z</sub>, 1H), 7.92 (d, J = 3 Hz, 1H), 7.92 (d, J = 14 Hz, 1H), 8.00 (s, 1H), 8.04 (d, J = 8 Hz, 1H), 8.30 (d, J = 9 Hz, 1H), 12.46 (s, 1H, OH); ir: 3450, 1650, 1648, 1550 cm<sup>-1</sup>; uv (ethanol): λ max 236 nm (ε 32,492), 250 (27,201), 274 (19,338), 285 (27,633), 346 (12,468), 381 (6667), 403 (9211), 426 (8397); ms: m/e (relative intensity) 220 (100%) M + 1.

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>NO-0.4 H<sub>2</sub>O: C, 79.57; H, 4.36; N, 6.18. Found: C, 79.77; H, 4.71; N, 5.82.

### 3,3a,4,5-Tetrahydro-2-azapyren-1(2H)-thione (11).

To 0.023 g (0.10 mmole) of lactam **9** in 30 ml of tetrahydrofuran was added 0.045 g (0.10 mmole) of phosphorus pentasulfide. The mixture was refluxed under argon for 1 hour, filtered and the solvent evaporated. Silica gel chromatography eluting with 5% methanol/95% chloroform gave 0.020 g (84%) of a yellow solid, mp 224-225°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.80 (m, 1H), 2.30 (m, 1H), 3.27 (m, 2H), 3.51 (m, 3H), 7.26-7.57 (m, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.71 (br s, 1H, N-H); ir: 1575 (C-N), 1200 (C=S) cm<sup>-1</sup>; uv (ethanol): λ max 344 nm (ε 3471), 283 (9256), 255 (48,843), 247 (45,702), 213 (21,488).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NS-0.4 H<sub>2</sub>O: C, 73.07; H, 5.64; N, 5.68; S, 13.01. Found: C, 73.06; H, 5.76; N, 5.63; S, 13.37.

### 1,2,3,3a,4,5-Hexahydro-2-azapyrene (12).

To 0.125 g (0.52 mmole) of thioamide **11** in 18 ml of tetrahydrofuran under argon was added 400 μl (6.42 mmoles) of methyl iodide. The mixture was stirred for 18 hours at 23° and then the solvent was removed *in vacuo*. To the solid was added 18 ml of dry dimethoxyethane, 0.163 g (4.29 mmoles) of sodium borohydride and 98 μl (0.84 mmole) of anhydrous tin(IV) chloride [8]. The mixture was stirred at 23° under argon for 3 hours and then carefully hydrolyzed with water. The solution was made basic with potassium carbonate solution, extracted with chloroform, dried (magnesium sulfate) and evaporated. Chromatography on silica gel eluting with chloroform yielded 78 mg (72%) of a white solid, mp 202-203°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.61 (m, 1H), 2.23 (m, 1H), 2.88 (m, 2H), 3.15 (m, 2H, CH<sub>2</sub>-aromatic), 3.60 (m, 1H), 4.20 (m, 2H), 7.20-7.50 (m, 3H, aromatic), 7.65 (m, 2H, aromatic); ir: 3450 (NH) cm<sup>-1</sup>; uv (chloroform): λ max 237 nm (ε 11,893), 277 (5000), 286 (5533), 294 (4368), 306 (1067), 323 (728).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N-0.95 H<sub>2</sub>O: C, 79.57; H, 7.52; N, 6.19. Found: C, 79.67; H, 8.01; N, 5.91.

### 2-Azapyrene (naphth[2,1,8-def]isoquinoline) (13).

To 0.027 g (0.13 mmole) of amine **12** was added 0.004 g of 10% palladium on carbon. The solid was heated under argon from 270-340° over 1 hour. The mixture was extracted with chloroform, filtered and evaporated. The material was chromatographed on silica gel eluting with 5% methanol/95% chloroform to yield 0.025 g (94%), mp 167-168°, lit mp 162-165° [9]; <sup>1</sup>H nmr (deuteriochloroform): (400 MHz) δ 8.09 (d, J = 9.5 Hz, 2H, H-5, H-9), 8.10 (t, J = 8.3 Hz, 1H, H-7), 8.14 (d, J = 9.5 Hz, 2H, H-4, H-10), 8.22 (d, J = 8.3 Hz, 2H, H-6, H-8), 9.41 (s, 2H, H-1, H-3); ir (nujol): 3250, 1450, 1360, 1240, 890, 845 cm<sup>-1</sup>; uv (95% ethanol): λ max 239 nm (ε 46,200), 261 (18,440), 271 (19,560), 294 (4100), 304 (9800), 317 (24,200), 332 (37,700), 356 (3,600), 370 (1600), 375 (6100).

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>N: C, 88.64; H, 4.46; N, 6.90. Found: C, 88.61; H, 4.40; N, 6.90.

### 2H3,4-Dihydrocyclopenta[cd]phenalene-1-ol (14).

To 1.035 g (4.71 mmoles) of ketone **5** in 50 ml of absolute ethanol was added 0.206 g (5.44 mmoles) of sodium borohydride. The mixture was stirred at 23° for 24 hours, then saturated ammonium chloride solution was carefully added. The solvent was evaporated and the resulting solid was dissolved in chloroform/water, extracted with chloroform, dried (magnesium sulfate) and evaporated to yield 0.94 g (93%) of a white solid, mp 148-149°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.65 (m, 3H), 2.35 (m, 1H), 3.17 (m, 4H), 5.58 (br m, 1H, OH), 7.27 (m, 2H, aromatic), 7.41 (d, J = 5 Hz, 1H, aromatic), 7.63 (m, 2H, aromatic); <sup>13</sup>C nmr (deuteriochloroform): δ 29.47 (C-3), 30.01 (C-4), 38.95 (C-2a), 46.43 (C-2), 77.36 (C-1),

121.30 (C-9), 123.68 (C-7), 125.14 (C-5), 125.96 (C-6), 126.33 (C-8), 127.36 (C-9c), 132.46 (C-7a), 135.60 (C-9a), 138.80 (C-4a), 141.67 (C-9b); ir: 3300 (OH) cm<sup>-1</sup>; uv (chloroform): λ max 239 nm (ε 13,969), 268 (2481), 280 (4060), 290 (4586), 295 (3894), 309 (1278), 324 (1293).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>O: C, 85.68; H, 6.71. Found: C, 85.48; H, 6.86.

### 3,3a,4,5-Tetrahydro-1-azapyren-2(1H)-one (16).

#### Method A.

To 0.455 g (1.51 mmoles) of the mesylate **7** dissolved in 200 ml of dry dichloromethane under argon was added 0.403 g (3.02 mmoles) of anhydrous aluminum chloride. The mixture was refluxed for 6 hours, then ice was added and the solution was transferred to a separatory funnel. The organic layer was washed with saturated potassium carbonate solution, then water, dried (magnesium sulfate) and evaporated. Chromatography on silica gel using 5% methanol/95% chloroform yielded 0.171 g (51%) of product, mp 235-237°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.20-3.25 (m, 7H), 7.00 (d, J = 7 Hz, 1H, aromatic), 7.25 (m, 2H, aromatic), 7.65 m, 2H, aromatic), 8.28 (br s, 1H, NH); ir: 1680 (CONH) cm<sup>-1</sup>; uv (chloroform): λ max 232 nm (ε 21,509), 252 (40,943), 260 (29,811), 282 (5094), 294 (6414), 306 (6037), 324 (2452), 339 (1886); ms: m/e (relative intensity) 223 (100%) M1.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO-0.4 H<sub>2</sub>O: C, 78.17; H, 6.03; N, 6.08. Found: C, 78.15; H, 5.99; N, 5.87.

### 3,3a,4,5-Tetrahydro-1-azapyren-2(1H)-one (16).

#### Method B.

To 0.055 g (0.18 mmole) of mesylate **7** in 15 ml of dry dichloromethane under argon was added 0.500 ml (0.50 mmole) of diethylaluminum chloride in hexane (**1M**). The mixture was stirred at 23° for 30 hours and then quenched with 1 ml of 0.2 N sodium hydroxide. The solution was extracted with chloroform, dried (magnesium sulfate) and evaporated. Chromatography on silica gel eluting with 3% methanol/97% chloroform yielded 0.011 g (27%) of the lactam **16**.

### 3,3a,4,5-Tetrahydro-1-azapyren-2(1H)-thione (18).

The same procedure used to prepare **11** was followed, using 0.021 g (0.09 mmole) of the lactam **16** in 15 ml of tetrahydrofuran and 0.041 g (0.09 mmole) of phosphorus pentasulfide. Chromatography on silica gel using chloroform yielded 0.021 g (97%) of a pale yellow solid, mp 246-248° dec; <sup>1</sup>H nmr (deuteriochloroform): δ 1.95 (m, 1H), 2.39 (m, 1H), 3.10 (m, 3H), 3.45 (m, 2H), 7.00 (d, J = 7 Hz, 1H, aromatic), 7.32 (m, 2H, aromatic), 7.65 (m, 2H, aromatic), 9.60 (br s, 1H, NH); ir: 1540 (C-N), 1110 (C=S) cm<sup>-1</sup>; uv (ethanol): λ max 207 nm (ε 22,004), 227 (24,608), 243 (5867), 259 (4718), 269 (9523), 281 (20,400), 291 (28,361), 340 (16,161); ms: m/e (relative intensity) 239 (100%) M1, 206 (20%) M-SH.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NS-H<sub>2</sub>O: C, 70.00; H, 5.88; N, 5.44; S, 12.46. Found: C, 70.36; H, 5.51; N, 5.39; S, 12.67.

### 1,2,3,3a,4,5-Hexahydro-1-azapyrene (8).

The same procedure described for the preparation **12** was followed, using 0.040 g (0.17 mmole) of the thioamide **18** in 18 ml of tetrahydrofuran under argon and 131 μl (2.10 mmoles) of iodomethane. The resulting thiomethyl compound was dissolved in 6 ml of dry dimethoxyethane with 0.053 g (1.40 mmoles) of sodium borohydride and 32 μl (0.27 mmole) of anhydrous tin(IV) chloride. Silica gel chromatography using chloroform yielded 0.031 g (87%) of white product, mp 125-126°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.63 (m, 2H), 2.15 (m, 2H), 3.10 (m, 3H), 3.50 (m, 2H), 6.70 (d, J = 7.5 Hz, 1H, aromatic), 7.10 (m, 2H, aromatic), 7.50 (m, 2H, aromatic); ir: 3380, 2920, 1610, 1600, 1518, 1350, 1330, 1180, 820 cm<sup>-1</sup>; uv (chloroform): λ max 240 nm (ε 10,256), 266 (3917), 278 (5293), 286 (5761), 295 (4568), 309 (1330), 324 (1073); ms: m/e (relative intensity) 209 (100%) M1.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N-0.25 H<sub>2</sub>O: C, 84.27; H, 7.54; N, 6.55. Found: C, 83.84; H, 7.29; N, 6.26.

### 1-Azapyren-2-ol (17).

The same procedure was followed as for the preparation **10** using

0.010 g (0.04 mmole) of the lactam **16** and 0.001 g 10% palladium on carbon. Chromatography on silica gel with 3% methanol/97% chloroform yielded 0.006 g (61%) of a yellow solid, mp 298-300°; <sup>1</sup>H nmr (d<sub>6</sub>-methylsulfoxide): δ 6.81 (s, 1H), 7.52 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.91 (m, 2H), 8.22 (d, J = 8.8 Hz, 1H), 8.32 (d, J = 9.2 Hz, 1H), 12.60 (br s, 1H, -OH); ir: 3430, 1660, 1540, 1450, 1190, 960, 850 cm<sup>-1</sup>; uv (95% ethanol): λ max 238 nm (ε 35,119), 250 (34,293), 258 (39,653), 283 (8853), 320 (3226), 334 (9253), 350 (17,546), 369 (3013), 390 (7119), 409 (11,546), 432 (10,213); ms: m/e (relative intensity) 219 (100%) M<sup>+</sup>, 191 (40%) M-CO.

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>NO: C, 82.17; H, 4.14; N, 6.39. Found: C, 81.89; H, 4.19; N, 6.27.

#### 1-Azapyrene (Naphtho[2,1,8-def]quinoline) (**15**).

The same procedure was followed as for the preparation of compound **13** using 0.070 g (0.33 mmole) of the amine **8** and 0.007 g of 10% palladium on carbon. Chromatography on silica gel eluting with 5% methanol/95% chloroform yielded 0.063 g (94%), mp 111-112°; <sup>1</sup>H nmr (deuteriochloroform): (400 MHz) δ 7.96 (d, J = 5.3 Hz, 1H, H-3), 8.01 (d, J = 8.9 Hz, 1H, H-10), 8.07 (t, J = 7.2 Hz, 1H, H-7), 8.26 (d, J = 8.9 Hz, 1H, H-9) 8.27 (d, J = 7.2 Hz, 1H, H-6 or H-8), 8.30 (d, J = 9.3 Hz, 1H, H-4 or H-5), 8.32 (d, J = 7.2 Hz, 1H, H-6 or H-8), 8.34 (d, J = 9.3 Hz, 1H, H-4 or H-5) 9.22 (d, J = 5.3 Hz, 1H, H-2); ir: 1630, 1600, 1580, 1390, 1240, 1180, 860 cm<sup>-1</sup>; uv (95% ethanol): λ max 237 nm (ε 39,113), 261 (14,810), 271 (19,113), 304 (4177), 323 (12,658), 335 (18,101), 351 (8734), 361 (3797), 369 (12,151); ms: m/e (relative intensity) 203 (100%) M<sup>+</sup>.

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>N·0.20 H<sub>2</sub>O: C, 87.10; H, 4.58; N, 6.77. Found: C, 87.20; H, 4.60; N, 6.56.

#### Modified Schmidt Reaction for the Preparation of 1-Azapyrene (**15**).

To 3.6 ml of 98% methanesulfonic acid and 3 ml of dry dichloromethane under argon at 0° was added 0.12 g (1.90 mmoles) of sodium azide. After 15 minutes 0.03 g (1.43 mmoles) of the alcohol **14** was added. After an additional 15 minutes 0.25 g (3.8 mmoles) of sodium azide was added in two portions. The mixture was slowly warmed to 23° and stirred for 18 hours, then poured onto ice. The aqueous portion was washed with chloroform and then basified with potassium carbonate. The basic fraction was extracted with chloroform, dried (magnesium sulfate) and evaporated. Chromatography on silica gel eluting with chloroform gave 1-aza-4,5-dihydropyrene which was heated under argon with 3 mg of 10%

palladium on carbon from 270-320° over 30 minutes. The mixture was extracted with chloroform and chromatographed on silica gel using 5% methanol/95% chloroform to yield 8.4 mg (1%).

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#### REFERENCES AND NOTES

- [1] S. Wakeham, *Environ. Sci. Technol.*, **13**, 1118 (1979).
- [2] M. Blumer and W. W. Youngblood, *Science*, **188**, 53 (1974).
- [3] M. W. Dong, D. C. Locke and D. Hoffmann, *Environ. Sci. Technol.*, **11**, 612 (1977).
- [4] W. Cautreels and K. Van Cauwenberghe, *Atmos. Environ.*, **10**, 477 (1976).
- [5] I. Murato, K. Nakesuji, K. Yamamoto, T. Nakazawa, Y. Kayne, A. Kimura and O. Hara, *Angew. Chem., Int. Ed. Engl.*, **14**, 170 (1975).
- [6] K. Muroka, T. Mijazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 2831 (1983).
- [7] L. F. Fieser and M. D. Gates Jr., *J. Am. Chem. Soc.* **62**, 2335 (1940).
- [8] R. J. Sundberg, C. P. Walters and J. D. Bloom, *J. Org. Chem.*, **46**, 3730 (1981).
- [9] R. Kirchlechner and C. Jutz, *Angew. Chem., Int. Ed. Engl.*, **7**, 376 (1968).
- [10] S. Eguchi, K. Asai and T. Sasaki, *J. Chem. Soc., Chem. Commun.*, 1147 (1984).
- [11] K. Hayokawa, M. Yodo, S. Ohsuki and K. Kanematsu, *J. Amer. Chem. Soc.*, **106**, 6735 (1984).
- [12] J. N. Shoolery, *J. Nat. Prod.*, **47**, 226 (1984).
- [13] A. Bax, "Two-Dimensional Nuclear Magnetic Resonance in Liquids", Delft University Press and D. Reidel Publishing Co., Boston, 1982.
- [14] R. Benn and H. Günther, *Angew. Chem., Int. Ed. Engl.*, **22**, 350 (1983).