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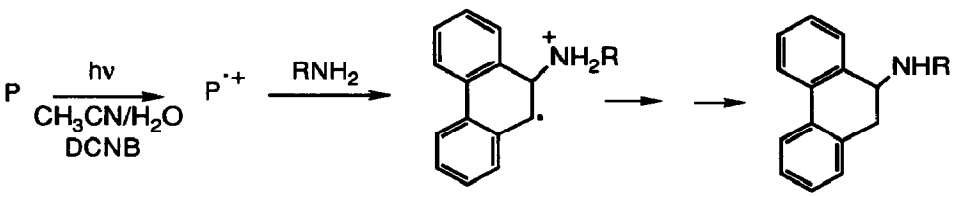
PHOTOSENSITIZED SYNTHESIS OF PHENANTHRENE HETEROCYCLES FROM 1- and 9-(AMINOALKYL)PHENANTHRENES

Frederick D. Lewis* , G. Dasharatha Reddy, and Bliss E. Cohen
Department of Chemistry, Northwestern University, Evanston, Illinois 60208-3113

Summary: The photosensitized electron transfer reactions of several 1- and 9-(aminoalkyl)phenanthrenes with meta-dicyanobenzene have been investigated. These reactions provide an efficient method of synthesis for the skeletal structures of the aporphine, phenanthropiperidine, and phenanthroazepine alkaloids.

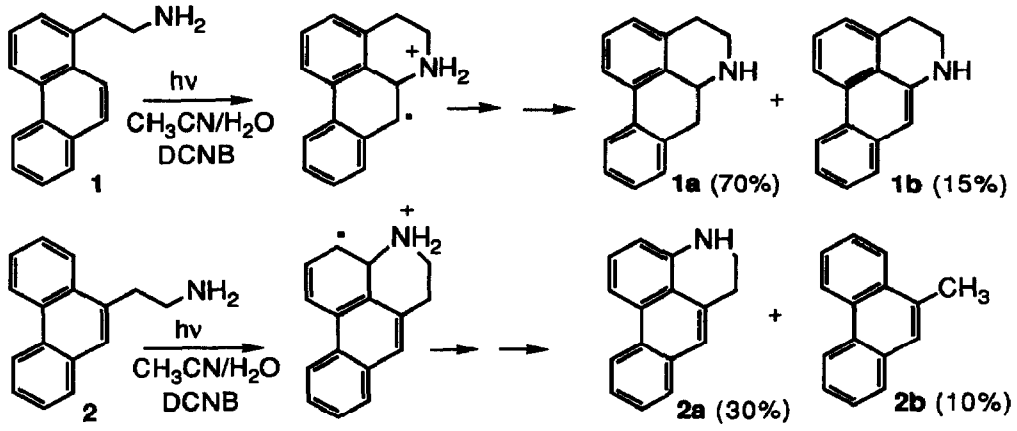
Photoamination of aromatic molecules with amines attached via an alkyl chain provides an efficient synthetic route to heterocyclic compounds.[1,2] Previous work in our laboratory demonstrated that under direct irradiation *ortho*-((N-methylamino)alkyl)stilbenes cyclize to form benzazepines[2a] and α- and β-((N-methylamino)alkyl)styrenes cyclize to form piperidine and pyrrolidine adducts.[2b,2c] Sugimoto and co-workers[1] have reported that irradiation of 9-(anilinoalkyl)phenanthrenes results in N-H addition to the phenanthrene 9,10 bond. The initial step in these reactions, electron transfer from ground state amine to singlet arene, is followed by N-H proton transfer and biradical cyclization. Thus when the initial electron transfer is endergonic, as is the case for singlet phenanthrene with primary amines or secondary N-methylamines, no adducts are formed. However, an indirect method for the photoamination of phenanthrene with ammonia and primary amines has been reported by Yasuda and co-workers.[3] Irradiation of phenanthrene (P) and an excess of primary amine with the electron-transfer sensitizer *meta*-dicyanobenzene (DCNB) in 9:1 (v/v) acetonitrile-water solution results in efficient photoamination (eq 1).[3] This reaction is initiated by electron transfer from singlet phenanthrene (P) to DCNB. The resulting phenanthrene cation radical is subject to nucleophilic attack by amine. Reduction of the intermediate by DCNB$^{\cdot-}$ and proton transfer yields the adduct and regenerates the sensitizer. Sensitized intramolecular photoamination has previously been reported for several (aminoethyl)benzenes[4] and *ortho*-(aminoalkyl)stilbenes.[2a] We report here our results for some 1- and 9-(aminoalkyl)phenanthrenes (**1-4**).[5]



(1)

Irradiation of **1** (0.01M) and *m*-DCNB (1 equiv) in nitrogen-purged 9:1 acetonitrile-water solution using a Rayonet reactor fitted with RPR 3000 lamps (300 nm light) for 2 h gives 70% of the aporphine **1a** and 15% of the dehydroaporphine **1b** with 87% conversion of starting material (eq 2).[6] The products were isolated via acid/basic extraction followed by column chromatography and identified with the aid of high field ^{1}H NMR decoupling experiments. Irradiation in the presence of oxygen results in a decreased ratio of **1a:1b** with time, indicating that **1b** is a secondary product

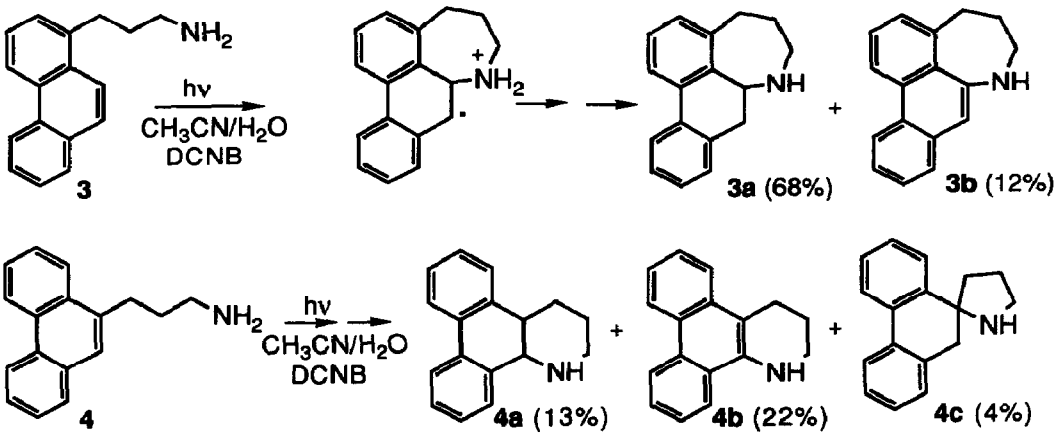
formed via the photooxidation of **1a**. Irradiation of **2** under identical conditions but for 70 h produces two major products with 55% conversion of starting material. After work up, phenanthro[1,10-d,e]-piperidine **2a**[6] and 9-methylphenanthrene **2b** were isolated in 30% and 10% yield respectively (eq 3). Similar product ratios are obtained in the absence and presence of oxygen.



(2)

(3)

Irradiation of **3** for 3 h results in the formation of the hexahydrophenanthro[10,1-bc]azepine **3a**[6] in 68% yield with 81% conversion of starting material (eq 4). A second product formed in 12% yield was not isolated but is tentatively assigned as the aromatized product **3b** on the basis of its increased yield in the presence of oxygen. Irradiation of **4** for 4 h results in 60% conversion of starting material and the formation of a complex mixture of photoproducts, three of which were isolated by chromatography: 9,10 dihydrophenanthrene[9,10-b]piperidine **4a** (13%), phenanthro-[9,10-b]piperidine **4b** (22%), and 1-aza[5,6;7,8-dibenzo]spiro[4,5]decane **4c** (4%, eq 5).[6] Irradiation of a **4** using monochromatic 313nm light (potassium chromate filter) with continuous purging with dry nitrogen and water bath cooling results in 60% conversion of **4** and the formation of **4a** (22%) and **4c** (6%), but no production of **4b**.



(4)

(5)

Comparison of the results obtained for electron-transfer sensitized irradiation of **1-4** indicates that both reactivity (**1** > **3** > **4** >> **2**) and products are dependent upon reactant structure. Ring closure of the phenanthrene cation radical to the distonic cation radical is presumed to be the rate determining step in these reactions. As is the case for the intermolecular photoamination of phenanthrene (eq 1), nucleophilic addition occurs at the 9,10 bond in the reactions of **1**, **3**, and **4**. The faster reaction rate for **1** vs **3** or **4** may reflect a smaller entropy of reaction for the aminoethyl vs. aminopropyl compounds. The ratio of products (**4a** + **4b**):**4c** presumably reflects the greater strain in the spiropyrrolidine intermediate. Most remarkable is the behavior of **2**. Formation of **2a** and not the phenanthropyrrolidine indicates that ring closure occurs at C-8 in preference to C-10. This result and the product ratio from **4** may reflect an inherent preference for the formation of 6- vs. 5-membered rings in these reactions. Another unusual feature of the behavior of **2** is the formation of the fragmentation product **2b**. Sugimoto and co-workers[1] report formation of the tautomer of **2b**, 9-methylene-9,10-dihydrophenanthrene, as a minor product upon direct irradiation of 9-(2-anilinoethyl)phenanthrene; however, no mechanistic details were given. Finally, no dihydro analog of **2a** is obtained upon irradiation of **2**, even in the absence of oxygen. The formation of dihydro products from the other (aminoalkyl)phenanthrenes may reflect the lower resonance energy of the phenanthrene 9,10 bond.

Established methods for the synthesis of phenanthrene alkaloids include the Pschorr cyclization and photocyclization reactions of substituted isoquinolines in which the phenanthrene C12-13 bond is formed last.[7] Electron-transfer sensitized intramolecular photoamination provides an alternative synthetic approach in which the phenanthrene-amine bond is formed last.

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5. **1** and **3** were synthesized via the Wittig reaction of *o* -tolualdehyde with $BnPPh_3^+Cl^-$ to yield *o*-methylstilbene. The stilbene was photochemically cyclized to 1-methylphenanthrene. NBS bromination gave 1-bromomethylphenanthrene. Reaction with NaCN followed by $LiAlH_4$ reduction gave **1**. Malonic ester condensation of 1-bromomethylphenanthrene followed

by decarboxylation and reaction with $NH_4^+OH^-$ gave the primary amide which was reduced with $LiAlH_4$ to give **3**. **2** and **4** were synthesized from a Grignard reaction between ethylene oxide and 9-bromophenanthrene. The resulting alcohol was converted to the chloride with $SOCl_2$. A Gabriel synthesis gave **2** whereas conversion of the halide to the nitrile followed by $LiAlH_4$ reduction provided **4**.

6. **1.** ^{1}H NMR ($CDCl_3$): δ8.65 (dd, 2H); 8.00 (d,1H); 7.90 (d, 1H); 7.77 (d, 1H); 7.67-7.55 (m, 3H); 7.45 (d, 1H); 3.27 (t, 2H); 3.12 (t, 2H); 1.65 (bs, 2NH). **1a.** δ7.73 (d, 1H); 7.58 (d, 1H); 7.32 (m, 1H); 7.28-7.23 (m, 3H); 7.09 (d, 1H); 4.04 (dd, 1H); 3.39 (m, 1H); 3.07 (m, 2H); 2.92 (dd, 1H); 2.84-2.75 (m, 2H); 1.74 (bs, NH). **1b.** δ8.50 (d, 2H); 7.60 (m, 2H); 7.46 (td, 1H); 7.36 (td, 1H); 7.32 (dd,1H); 6.78 (s, 1H); 3.55 (t, 2H); 3.28 (t, 2H); 1.25 (s, NH). **2.** δ8.70 (dd, 2H); 8.13 (d, 1H); 7.85 (d, 1H); 7.70-7.59 (m, 4H); 7.63 (s, 1H); 3.28 (t, 2H); 3.17 (t, 2H); 1.28 (bs, 2H). ^{13}C NMR: δ133.9, 131.7, 131.2, 130.9, 129.8, 128.2, 127.2, 126.8, 126.7, 126.3, 126.2, 124.4, 123.4, 122.5 (aromatic) 42.4, 37.7. MS: 221 (M^+, 14), 192 (100), 191 (30), 189 (17). HRMS: 221.1204 (obs); 221.1204 (calc). **2a.** δ8.59 (dd, 1H); 8.05 (d, 1H); 7.78 (dd, 1H); 7.55 (m, 2H); 7.43 (t, 1H); 7.34 (s, 1H); 6.78 (d, 1H); 4.38 (bs, NH); 3.54 (t, 2H); 3.27 (t, 2H). ^{13}C NMR: δ144.9, 132.3, 131.5, 131.0, 129.5, 127.8, 127.2, 126.7, 125.6, 123.2, 121.7, 119.1, 112.3, 109.7 (aromatic), 41.7, 31.1. MS: 219 (M^+), 204, 189, 108. HRMS: 219.1036 (obs); 219.1036 (calc). **3.** δ8.70 (dd, 2H); 8.13 (d, 1H); 7.85 (d, 1H); 7.70-7.60 (m, 4H); 7.59 (s, 1H); 3.14 (t, 2H); 2.85 (t, 2H); 1.96 (quin., 2H); 1.27 (s, 2H). ^{13}C NMR: δ136.3, 131.9, 131.2, 130.7, 129.7, 128.1, 126.7, 126.6, 126.2, 126.1, 126.0, 124.5, 123.3, 122.5 (aromatic) 42.3, 34.1, 30.8. MS: 235 (M^+, 40), 218 (36), 217 (26), 203 (38), 192 (100), 191 (33), 165 (17). HRMS: 235.1366 (obs); 235.1361 (calc). **3a.** δ7.69 (t, 2H); 7.31-7.21 (m, 4H); 7.11 (d, 1H); 4.17 (t, 1H); 3.25 (d, 1H); 3.18 (td, 2H); 3.14 (d, 1H); 3.03 (dd, 1H); 2.91 (dd, 1H); 1.79 (m, 1H); 1.72 (bs, NH); 1.52 (m, 1H). MS: 235 (M^+, 59), 234 (100), 192 (38), 191 (15), 189 (20). **4.** δ8.65 (dd, 2H); 8.00 (d, 1H); 7.88 (d, 1H); 7.77 (d, 1H); 7.59 (m, 3H); 7.45 (d, 1H); 3.16 (t, 2H); 2.83 (t, 2H); 1.92 (quin., 2H); 1.58 (bs, 2H). ^{13}C NMR: δ138.9, 131.6, 130.7, 130.1, 128.5, 127.2, 126.8, 126.6, 126.5, 126.2, 122.9, 122.6, 122.5, 121.1 (aromatic) 42.2, 35.2, 30.9. HRMS: 235.1364 (obs); 235.1361 (calc). **4a.** δ7.80 (d, 2H); 7.60 (d, 1H); 7.30 (m, 5H); 4.28 (d, 1H); 3.15 (quin., 1H); 2.95 (t, 2H); 1.95 (m, 1H); 1.80 (m, 1H); 1.68 (t, 2H); 1.29 (s, 1H). MS: 235 (M^+, 64), 234 (100), 206 (37), 179 (17), 178 (39). N-acetyl-**4b.** δ8.73 (m, 2H); 8.09 (dd, 1H); 7.97 (dd, 1H); 7.65 (m, 4H); 5.01 (m, 1H); 3.40 (m, 1H); 3.00 (m, 1H); 2.89 (m, 1H); 2.43 (m, 1H); 2.03 (m, 1H); 1.83 (s, 3H). MS: 275 (M^+), 233, 217, 202. HRMS: 275.1305 (obs); 275.1310 (calc). **4c.** δ7.76 (m, 2H); 7.59 (m, 1H); 7.35 (m, 5H); 3.58 (d, 1H); 3.36 (d, 1H); 2.82 (td, 1H); 2.60 (m, 1H); 2.49 (td, 1H); 1.98 (dt, 1H); 1.64 (m, 3H). MS: 235 (M^+), 234, 206, 178, 152, 119, 57. HRMS: 235.1372 (obs); 235.1361 (calc).

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