7-Amino-2-pyrenecarboxylic Acid

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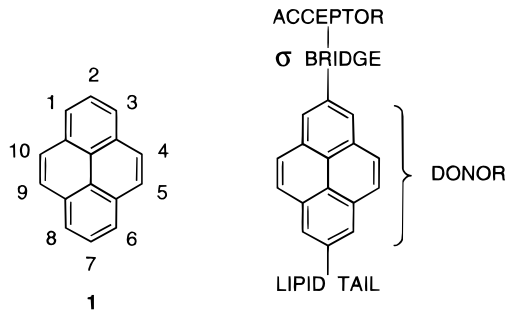
Pyrenes undergo initial electrophilic substitution in the 1 position; a second substitution typically occurs in the 3, 6, or 8 positions. We sought a pyrene with synthetically useful handles in the unusual 2,7 substitution pattern. To that end, 7-amino-2-pyrenecarboxylic acid was prepared by partial reduction of pyrene to 4,5,9,10-tetrahydropyrene, Friedel−Crafts acylation in the 2 position, and conversion to 2-carbethoxytetrahydropyrene through the haloform reaction and esterification. Nitration of the ester proceeded in the 7 position; rearomatization, reduction of the nitro group, and saponification gave the title compound.

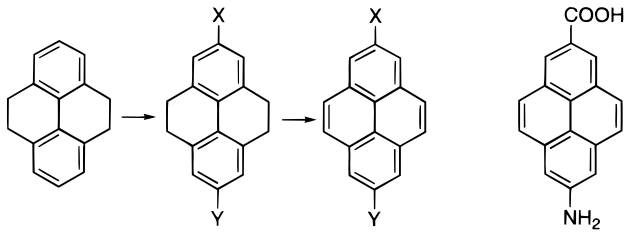
Pyrene (**1**) is a good one-electron donor. Its polarographic half wave oxidation potential is +1.16 volts vs SCE[1], and its ionization potential is 7.41 eV.[2] In our ongoing project preparing σ-bridged donor-σ-acceptor (D-σ-A) compounds as possible rectifiers of electrical current,[3,4] we wished to prepare a D-σ-A molecule with a pyrene group as the donor, D. Our target pyrene required two synthetic handles, one to attach the σ-A part, and the other to attach a lipid tail to help the molecules assemble into an oriented monolayer (Langmuir−Blodgett) film. Supposing that a stronger film would result from an elongated rather than a bent molecule, we sought a pyrene donor substituted at the 2 and 7 positions.



1

Standard electrophilic substitution of pyrene produces a mixture of 1,8-, 1,6-, and 1,3-disubstituted products.[5] 2-Substituted pyrenes are difficult to obtain,[6] and they react at the undesirable 6 and 8 positions.[7] A few 2,7-disubstituted pyrenes are known: for example, bis *tert*-butylation of pyrene gives the 2,7-disubstituted product for steric reasons,[8] and 2,7-disubstituted tetrahydropyrenes can be prepared by intramolecular coupling of *m*-cyclophanes[9] and can then be aromatized to pyrenes.[10,11] However, these routes did not seem likely to meet our needs.

We therefore turned to Harvey and co-workers' strategy[12,13] for obtaining 2,7-disubstituted pyrenes, which involves 4,5,9,10-tetrahydropyrene (**2**) as a crucial intermediate. Compound **2** behaves like a typical biphenyl, undergoing electrophilic substitution in the 2[14,15] and 7 positions. Aromatization then generates the pyrene nucleus.



2 **3**

We report here the preparation of target pyrene **3**, which contains a carboxyl group at one end and an amino group at the other. These versatile groups, which give the target the appearance of an expanded *p*-aminobenzoic acid, will allow us to do selective linking reactions at either end of the pyrene. As a variety of substituted pyrenes have been prepared for investigations into mechanisms of carcinogenicity,[15−17] **3** may also be a useful intermediate for the preparation of novel pyrenes of biochemical interest.

Results and Discussion

The synthesis began with the partial reduction of pyrene (**1**) to 4,5,9,10-tetrahydropyrene (**2**). Although

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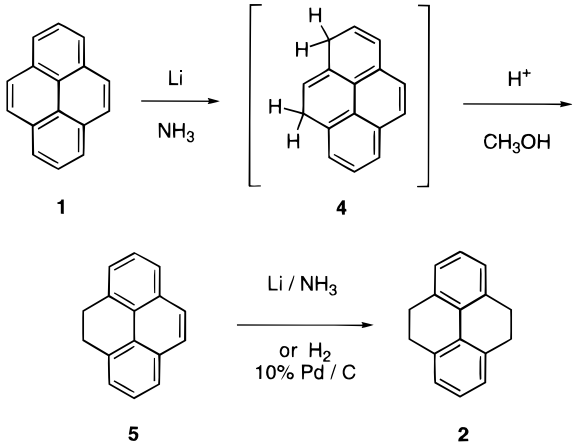
procedures for direct catalytic hydrogenation exist in the literature,[15,18,19] this method was not successful in our hands, even after careful purification of the starting pyrene. We therefore investigated a number of alternative reduction methods, including electrolytic[20] and diimide[21] reductions, without success. These efforts were similar to a study[22] of methods for partial reduction of phenanthrene to dihydrophenanthrene, which concluded that Birch reduction[23] was the best procedure.

Birch reduction of pyrene utilizing lithium in NH_3/THF has been reported by Harvey[24] to give the kinetic product 1,9-dihydropyrene (**4**). Warming an acidified methanol/THF solution of **4** rapidly isomerizes it to the desired **5**. We found this Birch reduction to be satisfactory (48−89% yield) if the pyrene was purified by column chromatography before use. In contrast, pyrene as supplied by Aldrich gave only a 5% conversion to **5**.



1 **4** **5** **2**

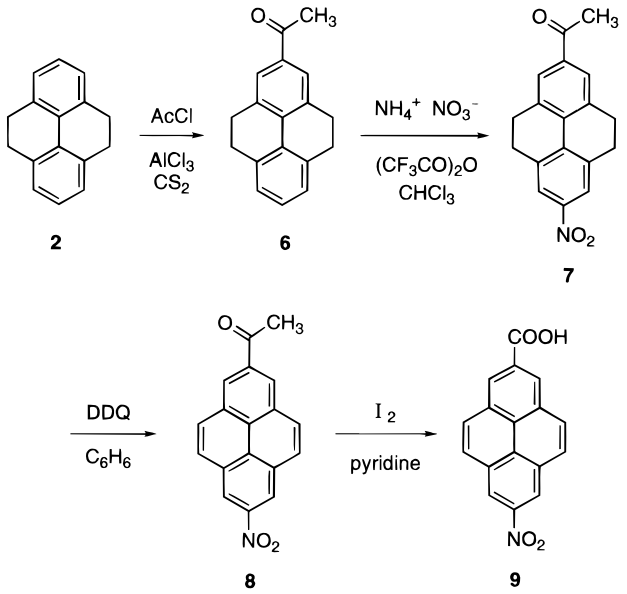
A second Li/NH_3 reduction could afford a satisfactory conversion to **2** as long as the starting **5** was purified by column chromatography (as opposed to crystallization). This Birch reduction was much more sensitive than the first. We found that reaction times of greater than 2 min led to over-reduction of **2**; over-reduction had not been a problem during the conversion of **1** to **4**. Rapid quenching (with ammonium chloride in methanol) was vital.

The crude product **2** typically contained a few percent of **1** as well as some **5**. Conventional column chromatography could not adequately separate these components. However, charge transfer chromatography,[20,25] using 10% caffeine on silica gel with petroluem ether as eluent, was successful: **2** eluted first, followed by **5** and then **1**.

We had varying success with a more convenient alternative, the Pd-catalyzed hydrogenation[12] of **5** to **2**. Conversions were initially low. Eventually we found that long reaction times in a Parr shaker, with occasional additions of fresh catalyst, gave adequate conversions, with yields over 85%.

Samples of **2** and **5** stored at room temperature for several months underwent substantial decomposition and color change and required repurification before use.

Harvey has reported[12] that the Friedel−Crafts acetylation of **2** with $AlCl_3$ can be controlled by the solvent: CS_2 leads to monoacetylation, while CH_2Cl_2 leads to diacetylation. In our hands, diacylation was a problem in both solvents, and use of only a slight excess of acetyl chloride in cold CS_2 was required to obtain **6** in 94% yield.



2 **6** **7** **8** **9**

At this point, nitration and ketone oxidation steps are required, as well as an aromatization step (which must follow nitration to assure the correct nitration regiochemistry). We chose to try nitration first, converting **6** to **7** with ammonium nitrate and trifluoroacetic anhydride (TFAA) at 0 °C.[26] However, DDQ aromatization[11,12] to **8** in freshly-dried benzene[27] did not give analytically pure material even after chromatography and crystallization. Further, the iodoform-reaction oxidation of ketone **8** to the corresponding acid **9** with iodine in pyridine[28,29] (conditions chosen due to the poor solubility of **8**) gave inconsistent results, low yields, and contaminated products, and this route was abandoned.

In our next attempt, haloform oxidation of **6** to the acid **10** (this time using bromine and NaOH in dioxane[30]) proceeded smoothly. However, nitration to **11** did not give analytically pure material after chromatography. Further, attempted DDQ oxidation of **11** to the corresponding pyrene **9** was slow and inconsistent and produced impurities that were difficult to remove. This route was also abandoned.

Suspecting that the carboxyl group was contributing to solubility problems, we next converted acid **10** to its ethyl ester **12** by Fischer esterification in 90% yield. Nitration of the ester with NH_4NO_3 and TFAA gave variable results; additional charges of reagents were sometimes needed to complete the reaction, and yields of **13** ranged from 30 to 90%. An alternative nitration

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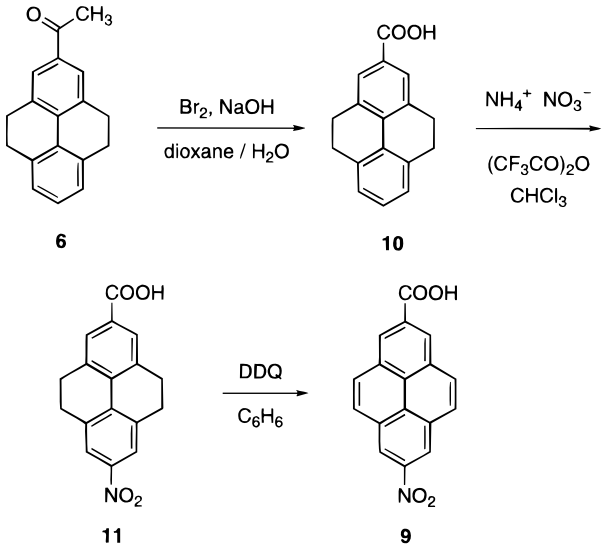
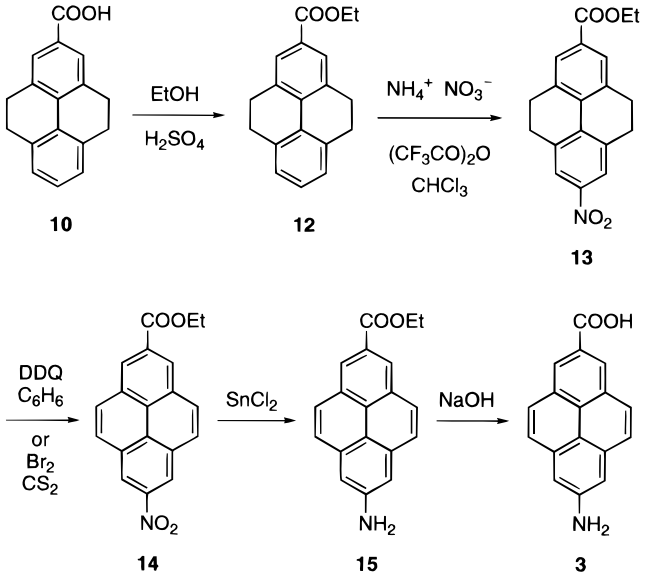


procedure, using nitronium tetrafluoroborate in sulfolane,[31] gave very low yields.



Aromatization of **13** with 2 equiv of DDQ in freshly-dried benzene afforded the desired 2,7-disubstituted pyrene **14**. Again, results were variable; sometimes additional charges of DDQ were required over several days, and yields ranged from 44 to 90%. An alternative aromatization procedure suggested by Harvey[13] utilized Br_2 in CS_2. Benzylic bromination followed by elimination accomplishes the formal dehydrogenation. In our hands, this easy method converted **13** to **14** in 60 to 92% yield.

Treatment of **14** with $SnCl_2$ in EtOH at reflux for 6 h[32] gave the amine **15**. Isolation as its apparent HCl salt gave a yellow solid in good yield with a sharp melting point and appropriate IR and NMR spectra. However, elemental analyses for C, H, and N were low, suggesting contamination by tin. When the reaction was worked up by washing with an aqueous solution of the chelating agent EDTA to remove tin, **15** was obtained in satisfactory purity in 74% yield. Saponification of the ester afforded the target amino acid **3** in quantitative yield; the yield was 24% following crystallization from EtOH/H_2O.

The coupling of **3** to acceptor and lipid moieties, and the evaluation of monolayers films of these products as potential rectifiers of electricity, will be reported elsewhere.[33]

Experimental Section

General Procedures. Reagents were purchased from Aldrich Chemical Co. Thin layer chromatography (TLC) was done on Aldrich silica gel/polyester plates with UV phosphor. Column chromatography utilized Merck 230−400 mesh or Davisil 100−200 mesh silica gel; charge-transfer chromatography used silica gel with 10% caffeine eluted with petrolum ether.[20] Melting points are uncorrected. Elemental analyses were carried out by Desert Analytics, Tuscon, AZ, or by Galbraith Laboratory, Knoxville, TN.

4,5-Dihydropyrene (5). Pyrene (**1**, 10.0 g, 49.4 mmol, purified by column chromatography) in 500 mL of THF was added to 750 mL of liquid ammonia at −78 °C in a 2 L round-bottom flask equipped with a mechanical stirrer. Lithium ribbon (1.27 g, 183 mmol) was then added and, after 60 min of stirring, the reaction was quenched by adding an excess of solid ammonium chloride. External cooling was removed and NH_3 was allowed to evaporate gradually. The solution was concentrated by rotary evaporation, and the residue was treated with 500 mL of water and extracted twice with ether. The ether layers were concentrated by rotary evaporation, and the residue of **4** was dissolved in 600 mL of hot CH_3OH and THF; a few drops of concd HCl were then added to isomerize **4** to **5**. After the solvent was removed by rotary evaporation, the residue was purified by column chromatography (hexane) to give 9.89 g of shiny light−yellow **5** (89%): mp 114−115 °C (lit.[34] mp 131−132 °C); ^{1}H-NMR ($CDCl_3$) δ 7.10−7.18 (8H, m), 3.5 (4H, s); MS *m*/*z* 204 (M^+, 88), 203 (100), 202 (56). Crude **5** could also be purified by crystallization from CH_3OH (white crystals, 86% yield, mp 122.5−123 °C) or by charge-transfer chromatography (48% yield, mp 127−128 °C); the last material was the most satisfactory in the next step.

4,5,9,10-Tetrahydropyrene (2). Birch Reduction Method. A solution of **5** (10.0 g, 49.0 mmol) in dry THF (500 mL) was added to liquid NH_3 (800 mL) at −78 °C. Li ribbon (0.85 g, 122.5 mmol) was then added, and after 2 min of vigorous mechanical stirring, the reaction was rapidly quenched with an excess of solid NH_4Cl and CH_3OH. The reaction was worked up as described above for **4**. Charge-transfer chromatography gave 9.6 g (95%) of shiny white **2**: mp 119−120 °C (lit.[12] mp 126−127 °C); TLC (9.1 petroleum ether:EtOAc) R_f 0.8; ^{1}H-NMR ($CDCl_3$) δ 7.10 (6H, m), 2.9 (8H, s); MS *m*/*z* 206 (M^+, 100), 205 (59), 203 (32), 191 (21).

Hydrogenation Method. A solution of **5** (2.16 g, 10.6 mmol) in 40 mL of distilled EtOAc was hydrogenated using 750 mg of 10% Pd/C in a Parr shaker at 50 psi for 3 days. The filtered solution was concentrated by rotary evaporation, and the crude residue was purified by column chromatography (petroleum ether) to give 1.93 g (88%) of **2**, mp 131−133 °C. No contamination from **5** was seen in the NMR spectrum. In cases where conversion was incomplete, hydrogenation of crude material was repeated.

2-Acetyl-4,5,9,10-tetrahydropyrene (6). A mixture of acetyl chloride (0.42 g, 5.4 mmol) and anhydrous $AlCl_3$ (0.78 g, 5.9 mmol) in CS_2 was cooled to 0 °C, and a solution of **2** (1.00 g, 4.90 mmol) in CS_2 was gradually added. The mixture was stirred at room temperature for 2 h; then 100 mL of water was added and the mixture was extracted 3 × with ether. The combined extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. The oily residue was purified by column chromatography (1:2 EtOAc:petroleum ether) to give yellow **6** (1.15 g, 94%): mp 112−113 °C (lit.[12] mp 113−114 °C); TLC (9:1 petroluem ether:EtOAc) R_f 0.5; ^{1}H-NMR ($CDCl_3$) δ 7.68 (2H, s), 7.20 (3H, s), 2.92 (8H, s), 2.61 (3H, s).

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4,5,9,10-Tetrahydropyrene-2-carboxylic Acid (10). A sodium hypobromite solution, prepared at 0 °C by reacting 1.56 mL (4.89 g, 30.6 mmol) of Br_2 with 4.92 g (123 mmol) of NaOH in 30 mL of water, was added slowly to a stirred solution of **6** (1.69 g, 6.75 mmol) in 60 mL of 1,4-dioxane at room temperature. The reaction mixture was stirred for 2 h and then treated with $NaHSO_3$ to destroy excess NaOBr. The reaction mixture was poured into 20 mL of ice−water and acidified to pH 2 with concd HCl. The resulting precipitate was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. The resulting solid was triturated with petroleum ether giving 1.67 g (98%) of insoluble, yellow **10**: mp 248 °C; TLC (1:1 petroleum ether: EtOAc) R_f 0.50; IR (KBr) 3000−2514, 1681 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.85 (2H, s), 7.20 (1H, t), 7.1 (2H, d), 2.95 (8H, s). This compound was used in the next step without purification.

Ethyl 4,5,9,10-Tetrahydro-2-pyrenecarboxylate (12). A solution of **10** (6.00 g, 23.9 mmol) and 5 mL of concd H_2SO_4 in 150 mL of EtOH was heated at reflux for 6 h. About half of the solvent was boiled off, and the cooled reaction mixture was poured into 100 mL of 5% $NaHCO_3$. The solution was made alkaline (pH > 10) with concd NH_4OH and extracted 2 × with 300 mL of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated by rotary evaporation to give **12** as an oil in 90% yield; TLC (1:5 EtOAc:petroleum ether) R_f 0.5; IR (KBr) 1707 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.80 (2H, s), 7.20 (1H, t), 7.1 (2H, d), 4.41 (2H, q), 2.95 (8H, s), 1.45 (3H, t). The analytical sample was crystallized from petroleum ether: off-white, 76% recovery, mp 64−65 °C. Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99%, H, 6.52%. Found: C, 81.85%; H, 6.31%.

Ethyl 7-Nitro-4,5,9,10-tetrahydro-2-pyrenecarboxylate (13). To a mixture of **12** (1.65 g, 5.91 mmol), NH_4NO_3 (0.95 g, 11.8 mmol), and TFAA (8.70 g, 5.80 mmol) kept at −5 °C was carefully added 50 mL of $CHCl_3$. After the reaction subsided, external cooling was removed and the reaction was allowed to stir at room temperature for 6 h. The mixture was poured into 200 mL of cold water and allowed to stir overnight. A precipitate formed which was collected, dried, and purified by column chromatography (1:4 EtOAc:hexane) and crystallization from EtOH to give 0.50 g of **13** in 26% yield; TLC (2:3 EtOAc:petroleum ether) R_f 0.63; IR (KBr) 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00 (2H, s) 7.80 (2H, s), 4.4 (2H, q), 3.00 (8H, s), 1.45 (3H, t). The analytical sample was crystallized from EtOH to give yellow crystals in 40% recovery, mp 176−177 °C. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58, H, 5.30; N, 4.33. Found: C, 71.03; H, 5.27; N, 4.39.

Ethyl 7-Nitro-2-pyrenecarboxylate (14). DDQ Method. A solution of **13** (0.50 g, 1.6 mmol) and DDQ (0.77 g, 3.4 mmol) in 30 mL of freshly-dried benzene was heated at reflux for two days. (In some cases, additional charges of DDQ were added periodically to complete the reaction.) After removing the solvent by rotary evaporation, the residue was triturated with cold EtOH to remove DDQ. The insoluble material was separated, dried, and crystallized from EtOH to give yellow **14** in 90% yield, mp 255−256 °C; TLC (2:3 EtOAc:petroleum ether) R_f 0.60; IR (KBr) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.05 (2H, s), 8.95 (2H, s), 8.25 (2H, d), 8.2 (2H, d), 4.58 (2H, q), 1.50 (3H, t). Anal. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.04; H, 3.80; N, 4.48.

Bromine Method. To a solution of **13** (515 mg, 1.67 mmol) in 41 mL of CS_2 was added dropwise Br_2 (0.19 mL, 3.6 mmol) in CS_2 (41 mL). The solution was stirred overnight, treated with 2 mL of 5% $Na_2S_2O_3$, and extracted with CH_2Cl_2. After rotary evaporation, the product was crystallized from EtOH/CH_2Cl_2 to give **14** in 92% yield, mp 260−261 °C.

Ethyl 7-Amino-2-pyrenecarboxylate (15). A turbid, bright yellow mixture of **14** (45 mg, 0.15 mmol) and $SnCl_2 \cdot 2H_2O$ (168 mg, 0.746 mmol) in 13 mL of dry EtOAc was refluxed overnight. The resulting light yellow mixture was cooled and washed 3 × with aqueous sodium EDTA to remove tin. The clarified organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to give 41 mg (96%) of crude brownish yellow solid which was purified by column chromatography (petroleum ether, EtOAc) to give yellow **15** in 74% yield, mp 198−199 °C; TLC (6:1 petroleum ether: EtOAc) R_f 0.25; IR (KBr) 3408, 3320, 1704 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.69 (2H, s), 8.13 (2H, d), 7.96 (2H, d), 7.46 (2H, s), 4.45 (2H, q), 1.43 (3H, t). The analytical sample was crystallized from $CHCl_3$ and petroleum ether followed by a short chromatography column. Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.90, H, 5.22; N, 4.64.

7-Amino-2-pyrenecarboxylic Acid (3). A solution of **15** (30 mg, 0.10 mmol) in 38 mL of EtOH was treated with 59 mg of NaOH (1.5 mmol) in 9.5 mL of H_2O and refluxed for 5 h. The solution was concentrated by rotary evaporation and acidified to pH 5 with 2.5% HCl, whereupon the mixture turned lemon yellow and a precipitate formed. The product was extracted with EtOAc, dried, and concentrated by rotary evaporation to give 30 mg (100%) of **3**. Crystallization from EtOH/H_2O gave dark yellow crystals (24%): mp > 400 °C; TLC (1:1 petroleum ether:EtOAc) R_f 0.3; IR (KBr) 3356, 3433, 1673 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.70 (2H, s), 8.10 (2H, d), 7.95 (2H, d), 7.45 (2H, s), 5.90 (2H, s). Anal. Calcd for $C_{17}H_{11}NO_2 \cdot H_2O$: C, 73.10; H, 4.69; N, 5.02. Found: C, 73.61; H, 4.69; N, 4.56.

Acknowledgment. We thank the National Science Foundation EPSCoR Program (OSR-9452857), the State of Mississippi, and the University of Mississippi for financial support of this work.

Supporting Information Available: IR peak data for **3**, **10**, **12**, **13**, **14**, and **15**; synthetic procedures for **7**, **8**, **9**, and **11**; ^{1}H NMR spectrum of **3** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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