Synthesis of Phenanthro[2,3-*h*]isoquinoline and Phenanthro[3,2-*h*]isoquinoline

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The suspected environmental contaminants phenanthro[2,3-*h*]isoquinoline **12** and phenanthro[3,2-*h*]isoquinoline **11** were synthesized in four steps from a common intermediate 1,4-phenanthroquinone **3**, using a Diels-Alder reaction.

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Introduction.

Aza-arenes are nitrogen-containing polyaromatic hydrocarbons that are formed as trace pollutants by incomplete combustion of nitrogen-containing organic matter in a manner similar to the formation of polyaromatic hydrocarbons. Many of these compounds have never been synthesized or characterized, making their identification in basic sample fractions very difficult, and as a result little is known about their biological activity.

As part of our study of the chemistry and biological activity of aza-arenes, we have synthesized phenanthro[2,3-*h*]isoquinoline **12** and phenanthro[3,2-*h*]isoquinoline **11**. The synthesis and characterization of these compounds have not previously been reported in the literature. Compounds of this molecular weight have been identified in gc-mass spectra of street dust samples [1], air samples [2], samples of smoked foods [3], oil and synthetic fuel extracts [4], and auto exhaust [5]. In an extraction study of roadside soil, we found this molecular weight in the polar fraction. When aza-arenes are present in oil and synthetic fuels, the potential exists for them to pollute water as the result of spills or seepage. Some studies have shown that higher-molecular-weight compounds bioaccumulate. In our biological testing program we found that phenanthro[2,3-*h*]-isoquinoline **12** and phenanthro[3,2-*h*]isoquinoline **11** show mutagenic activity in the Ames *Salmonella typhimurium* assay [6].

Results and Discussion.

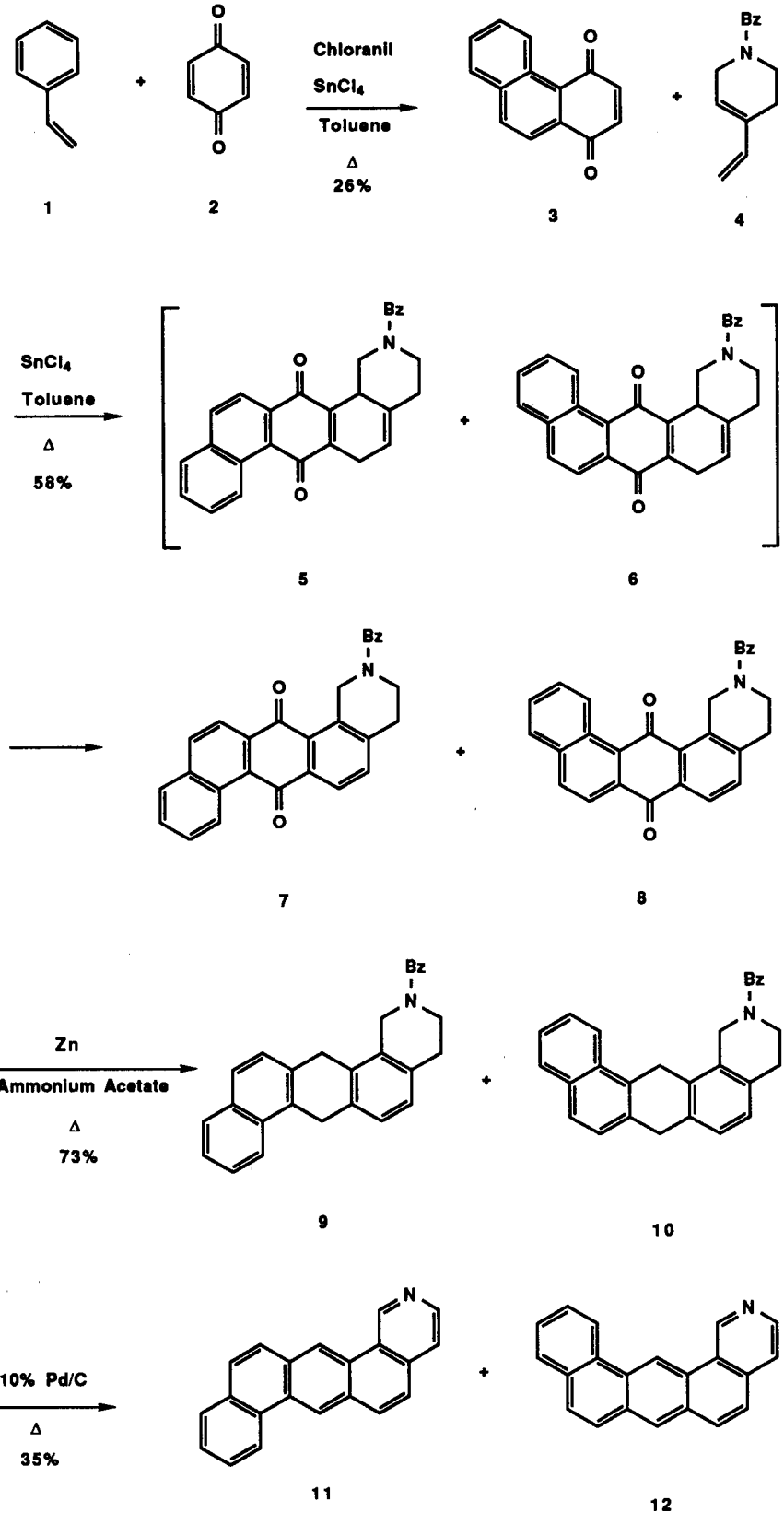
The strategy for the synthesis of phenanthro[2,3-*h*]isoquinoline **12** and phenanthro[3,2-*h*]isoquinoline **11** involved construction of the necessary ring systems *via* Diels-Alder reactions as outlined in Scheme I. We were interested in further exploring the utility of anhydrous stannic chloride as a catalyst in Diels-Alder reactions having quinones as dienophiles [7]. The dienophile for the synthesis of the necessary ring system was 1,4-phenanthroquinone **3**. Compound **3** was synthesized by reacting styrene **1** with 1,4-benzoquinone **2** and anhydrous stannic chloride in refluxing toluene for 18 hours (Scheme I). This reaction is faster and gives a better yield than has been reported in the literature [8,9].

The 1,4-phenanthroquinone **3** thus prepared was reacted with *N*-benzoyl-4-vinyl-1,2,5,6-tetrahydropyridine **4**. The diene **4** was prepared by a literature procedure from *N*-benzoyl-4-piperidone *via* a Grignard reaction followed by dehydration [10]. Finkelstein and Perchonock observed that **4** is quite unreactive and required highly activated dienophiles, (*e.g.*, dimethyl acetylenedicarboxylate) in order to form condensation products [10]. This result was confirmed when reacting **4** with 1,4-naphthoquinone required a catalyst in order to form condensation products [7]. The diene **4** introduces all the necessary functionality to synthesize the desired compounds. In addition, it provides an excellent test of the general utility of anhydrous stannic chloride to catalyze this type of Diels-Alder reaction. The reaction mixture was refluxed in toluene for 18 hours to give the two quinones **7** and **8**. Under the reaction conditions the Diels-Alder adducts **5** and **6** aromatize to give only the quinones **7** and **8**. The two quinones **7** and **8** were not separated at this step, as the separation is difficult.

The quinones **7** and **8** were reduced using zinc and ammonium acetate. This is a much cleaner reduction than using lithium aluminum hydride or sodium borohydride. The methylene compounds, **9** and **10**, were isolated, but not purified due to their instability. The crude mixture was aromatized using 10% palladium on carbon at 350° under argon. After extraction, the two phenanthroisoquinoline compounds **11** and **12** were separated on a silica gel column, eluting with 1/1 hexanes/ethyl acetate. The ratio of **11** to **12** is 4:1. This ratio is probably the result of steric hindrance in the formation of **12**.

The phenanthroisoquinolines **11** and **12** were identified by spectral analysis. The chemical shifts of the protons at 7-H and 14-H are very characteristic for the two compounds. In compound **12** the position of 7-H is at δ 8.37; in compound **11** it is at δ 9.18, as expected because in compound **11** 7-H should be shifted downfield due to the proximity of the aromatic ring. Similarly, in compound **12** 14-H is at δ 10.07 whereas in compound **11** it is at δ 9.12. In compound **12** 7-H and 14-H are in very different chemical environments and, as a result, 14-H is shifted downfield, since it is in the bay region of the aromatic

SCHEME I


Chloranil
SnCl4
Toluene
Δ
26%
Bz
N
O
1
2
3
4
SnCl4
Toluene
Δ
58%
5
6
7
8
Zn
Ammonium Acetate
Δ
73%
9
10
10% Pd/C
Δ
35%
11
12

rings. In compound **11** the chemical environments of 7-H and 14-H are not very different as each is adjacent to an aromatic ring; therefore, 7-H is shifted only slightly downfield from 14-H, δ 9.18 versus 9.12. The chemical shift of 14-H is very different for compound **12** and compound **11**: δ 10.07 versus δ 9.12, which is consistent with the structures of the two compounds.

In this research two compounds, phenanthro[2,3-*h*]isoquinoline **12** and phenanthro[3,2-*h*]isoquinoline **11**, were synthesized in the same reaction and separated. Testing of these compounds has shown them to be mutagenic in the Ames assay [6]. The synthesis and characterization of aza-arenes is necessary in order to assess the health hazard posed by them. In addition, the synthesis and characterization of aza-arenes provides the much needed standards for the identification of various aza-arenes in complex environmental mixtures.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 1620 FT spectrophotometer as potassium bromide pellets. Ultraviolet spectra were recorded on a Varian DMS-90. The nmr spectra were recorded on a Varian XL-400 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. Column chromatography was done using E. Merck silica gel 40 (70-230 mesh ASTM) Solvents were dried over 3A molecular sieves. Microanalyses were performed by Desert Analytics, Tucson, AZ.

1,4-Phenanthroquinone (**3**).

A mixture of 1.18 g (10.2 mmoles) of 1,4-benzoquinone (**2**) and 1.25 g (5.10 mmoles) of chloranil in 700 ml of toluene was refluxed with a Dean-Stark trap under argon for 4 hours. The reaction mixture was cooled to 23°, and 2.10 ml (18.3 mmoles) of styrene (**1**) and 1.27 ml (12.7 mmoles) of anhydrous stannic chloride were added. The mixture was refluxed for 18 hours and then poured onto ice and filtered. The mother liquor was extracted with toluene, dried (magnesium sulfate), and evaporated. The material was dissolved in chloroform and filtered to remove the insoluble chloranil. It was then applied to a silica gel column and eluted with 3:1 chloroform/petroleum ether and the yellow band was collected, yield 0.56 g (26%), mp 146°, lit 148° [8].

N-Benzoyl-1,2,3,4-tetrahydrophenanthro[3,2-*h*]isoquinoline-7,14-dione (**7**) and *N*-Benzoyl-1,2,3,4-tetrahydrophenanthro[2,3-*h*]isoquinoline-7,14-dione (**8**).

To 350 ml of toluene was added 0.44 g (2.12 mmoles) of 1,4-phenanthroquinone (**3**) and 2.26 g (10.61 mmoles) of *N*-benzoyl-4-vinyl-1,2,5,6-tetrahydropyridine (**4**) [10]. The mixture was refluxed with a Dean-Stark trap under argon for 1 hour, then cooled to 23°. Then 268 μl (2.33 mmoles) of anhydrous stannic chloride was added and the reaction mixture was refluxed for 18 hours. The reaction mixture was cooled, poured onto ice, extracted with chloroform, dried (magnesium sulfate), and evaporated. The material was chromatographed on silica gel, eluting with 20% ethyl acetate/80% hexane, yield 0.51 g (58%). From the chromatography, 0.30 g of the diene **4** and 0.17 g of 1,4-phenanthroquinone (**3**) were recovered.

N-Benzoyl-1,2,3,4,7,14-hexahydrophenanthro[3,2-*h*]isoquinoline (**9**) and *N*-Benzoyl-1,2,3,4,7,14-hexahydrophenanthro[2,3-*h*]isoquinoline (**10**).

To 2.50 g, (5.99 mmoles) of quinones **7** and **8** was added 1.60 g, (24.4 mmoles) of activated zinc dust [11] and 90.0 g of ammonium acetate. The reaction mixture was heated at 150° for 18 hours and then poured into water. After extraction with chloroform, the mixture was washed with water then saturated sodium bicarbonate solution and water, dried (magnesium sulfate), and evaporated, crude yield 1.70 g (73%), R_f 0.68 and 0.75 on silica gel eluting with 5% methanol/95% chloroform.

Phenantho[2,3-*h*]isoquinoline (**12**) and Phenanthro[3,2-*h*]isoquinoline (**11**).

To the 1.70 g (4.36 mmoles) of compounds **9** and **10** was added 0.17 g of 10% palladium on carbon. The solid was heated under argon from 250 to 350° over 45 minutes. The mixture was extracted with chloroform/methanol, filtered, and evaporated. The material was chromatographed on silica gel, eluting with 1/1 hexanes/ethyl acetate to yield 0.58 g (35%), yield of **11** 0.46 g and **12** 0.12 g.

Compound **11** had the following physical data: mp 238-239°; ^{1}H nmr (deuteriochloroform): δ 7.64 (d, 1H, 13-H, $J_{12,13}$ = 9.0 Hz), 7.65 (m, 1H, 10-H, $J_{8,10}$ = 0.8, $J_{9,10}$ = 7.0, $J_{10,11}$ = 8.1 Hz), 7.69 (d, 1H, 4-H, $J_{3,4}$ = 5.1 Hz), 7.71 (m, 1H, 9-H, $J_{9,11}$ = 1.5, $J_{9,10}$ = 7.0, $J_{8,9}$ = 8.1 Hz), 7.78 (d, 1H, 5-H, $J_{5,6}$ = 9.2 Hz), 7.91 (dd, 1H, 11-H, $J_{9,11}$ = 1.5, $J_{10,11}$ = 8.1 Hz), 7.94 (d, 1H, 12-H, $J_{12,13}$ = 9.0 Hz), 8.10 (d, 1H, 6-H, $J_{5,6}$ = 9.2 Hz), 8.74 (br d, 1H, 3-H, $J_{3,4}$ = 5.1 Hz), 8.82 (dd, 1H, 8-H, $J_{8,10}$ = 0.8, $J_{8,9}$ = 8.1 Hz), 9.12 (s, 1H, 14-H), 9.18 (s, 1H, 7-H), 10.15 (s, 1H, 1-H); ^{13}C nmr (deuteriochloroform): δ 121.35, 121.55, 122.75, 122.86, 124.88, 127.03, 127.19, 127.35, 127.67, 128.08, 128.77, 129.67, 130.12, 130.61, 131.54, 132.11, 132.32, 136.28, 145.78, 145.81, 146.49; ir (potassium bromide): 3423, 3048, 1922, 1604, 1508, 1447, 1423, 1226, 1156, 1072, 1020, 885, 841, 809, 774, 742, 662, cm^{-1}; uv (methanol): λ max 218 nm (ε 39,627), 232 (17,978), 274 (49,574), 278 (54,840), 288 (76,808), 321 (14,574), 336 (12,712), 351 (11,063), 370 (2819), 391 (1595).

Anal. Calcd. for $C_{21}H_{13}N$: C, 90.29; H, 4.69; N, 5.02. Found: C, 90.36; H, 4.45; N, 4.90.

Compound **12** had the following physical characteristics: mp 211-213°; ^{1}H nmr (deuteriochloroform): δ 7.65 (d 1H, 5-H, $J_{5,6}$ = 9.0 Hz), 7.67 (m, 1H, 11-H, $J_{11,13}$ = 1.0, $J_{11,12}$ = 6.8, $J_{10,11}$ = 7.9 Hz), 7.71 (br d, 1H, 4-H, $J_{3,4}$ = 5.1 Hz), 7.76 (d, 1H, 8-H, $J_{8,9}$ = 9.0 Hz), 7.78 (m, 1H, 12-H, $J_{10,12}$ = 1.4, $J_{11,12}$ = 6.8, $J_{12,13}$ = 7.9 Hz), 7.85 (d, 1H, 9-H, $J_{8,9}$ = 9.0 Hz), 7.91 (dd, 1H, 10-H, $J_{10,12}$ = 1.4, $J_{10,11}$ = 7.9 Hz), 8.04 (d, 1H, 6-H, $J_{5,6}$ = 8.0 Hz), 8.37 (s, 1H, 7-H), 8.75 (br d, 1H, 3-H, $J_{3,4}$ = 5.1 Hz), 8.97 (d, 1H, 13-H, $J_{11,13}$ = 1.0, $J_{12,13}$ = 7.9 Hz), 10.07 (s, 1H, 14-H), 10.29 (s, 1H, 1-H); ^{13}C nmr (deuteriochloroform): δ 115.76, 115.81, 121.49, 122.97, 125.01, 126.64, 127.20, 127.45, 127.98, 128.04, 128.86, 129.11, 129.77, 130.30, 130.68, 131.36, 131.77, 132.24, 136.39, 145.69, 146.37; ir (potassium bromide): 3443, 3045, 1603, 1460, 1418, 1229, 1163, 1072, 1030, 1010, 887, 841, 807, 742 cm^{-1}; uv (methanol): λ max 203 nm (ε 37,616), 222 (34,352), 246 (26,891), 255 (30,414), 270 (31,398), 288 (49,533), 299 (78,031), 318 (17,823), 335 (14,196), 372, (1709), 391 (1295).

Anal. Calcd. for $C_{21}H_{13}N$: C, 90.29; H, 4.69; N, 5.02. Found: C, 90.91; H, 4.50; N, 5.00.

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