Synthesis of Phenanthro[9,10-*g*]isoquinoline

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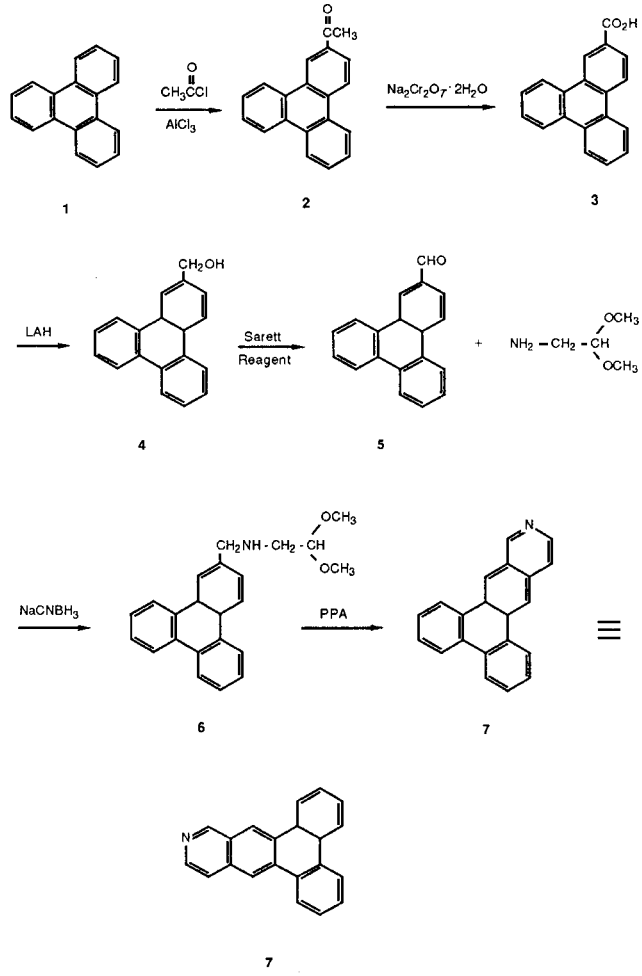
Numerous aza-polycyclic aromatic hydrocarbons (aza-arenes) that are found in the environment are largely uncharacterized, except by molecular weight distribution. Identifications are only tentative due to the lack of reference data. Few aza-arenes of high molecular weight are known, consequently, reference compounds and spectra are unavailable. Biological test data are also unavailable for the same reason, although some of the known compounds exhibit carcinogenic and mutagenic activity [1,2,3]. Aza-arenes are formed during the pyrolytic decomposition of organic matter [4]. The study of aza-arenes pollutants is important, since production of liquid fuels by gasification of nitrogen-rich oil shale and coal could release increasing amounts of these compounds into the environment.

As part of a continuing effort to develop an understanding of the potential environmental hazard posed by aza-arenes we synthesized phenanthro[9,10-*g*]isoquinoline. In surface sediments, street dust as well as crude oil samples, composite mass spectra obtained by probe distillation/low voltage mass spectrometry of the aza-aromatic fractions showed a component which could be phenanthro[9,10-*g*]-isoquinoline [5]. To our knowledge the synthesis and physical data on this compound have not previously been reported.

The synthetic route is shown in Scheme I. Triphenylene (**1**) was converted to the acetyl **2** by a Friedel-Crafts reaction using acetyl chloride and aluminum chloride. The acetyl compound **2** was oxidized to the carboxylic acid **3** using sodium dichromate dihydrate in acetic acid [6]. Reduction of the acid **3** to the alcohol **4** was accomplished using lithium aluminum hydride. The alcohol **4** was oxidized to the aldehyde **5** using Sarett's reagent [7,8]. Reductive alkylation of the aldehyde **5** with aminoacetaldehyde dimethyl acetal and sodium cyanoborohydride yielded the acetal **6**. Cyclization of the acetal **6** with polyphosphoric acid gave only the desired product phenanthro[9,10-*g*]isoquinoline (**7**).

To assist in making the spectral assignments COSY (shift correlation spectrum), HETCOR (heteronuclear chemical shift correlation), DEPT (distortionless enhancement by polarization transfer), and APT (attached proton test) nmr experiments were done [9,10,11]. The COSY and

Scheme I. Syntesis of phenanthro[9,10-g]isoquinoline (7)



HETCOR experiments provided connectivity information about the molecules. The proton spectrum of phenanthro-[9,10-*g*]isoquinoline (**7**) has a doublet at δ 7.79 (J = 5.7 Hz) for H-4 and a doublet at δ 8.53 (J = 5.7 Hz) for H-3. There are singlets at δ 8.92 for H-14, δ 9.10 for H-5 and δ 9.46 for H-1, and multiplets at δ 7.65 (H-7, H-8, H-11, H-12), δ 8.52 (H-9, H-10), and δ 8.69 (H-6, H-13) which are as expected for the protons in the rest of the molecule. In the carbon spectrum of **7**, C-1 is at δ 153.37 and C-3 is at δ 142.25, while C-4 is at δ 120.20. It was not possible to unambiguously assign C-7 and C-11 (δ 123.50 or δ 123.54).

The syntheses of aza-arene pollutants are necessary to evaluate the health hazard posed by them. Phenanthro-[9,10-*g*]isoquinoline (**7**) is currently undergoing evaluation for mutagenic and carcinogenic activity. The biological results will be reported elsewhere.

EXPERIMENTAL

Melting points (uncorrected) were obtained using a Thomas-Hoover melting point apparatus. The nmr spectra were recorded on a Jeol FX90Q or a Varian XL400 spectrometer. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The nmr multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad. The ir spectra were recorded on a Perkin Elmer 1310 spectrometer. The uv spectra were determined on a varian DMS90 spectrometer. 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.

2-Acetyltriphenylene (**2**).

To 50 ml of dry nitrobenzene under argon was added 4.9 g (21.4 mmoles) of triphenylene (**1**) and 5.7 g (42.8 mmoles) of aluminum chloride. The mixture was cooled in ice water and 2.1 ml (30.0 mmoles) of acetyl chloride was added in one portion. The mixture was stirred with cooling for 1.5 hours and at room temperature for 12 hours. The excess aluminum chloride was decomposed by addition of 20 g of ice and the nitrobenzene was steam distilled. The residue was extracted with chloroform, dried (magnesium sulfate) and evaporated. Silica gel chromatography using 75% chloroform and 25% hexane yielded 5.1 g (92%). Recrystallization from 99% chloroform and 1% methanol gave white crystals, mp 155-156°C; ^{1}H nmr (deuteriochloroform): δ 2.80 (s, CH_3), 7.70 (m, H-6, H-7, H-10, H-11), 8.18 (dd, J = 1.8 and 8.8 Hz, H-3), 8.70 (m, H-4, H-5, H-8, H-9, H-12), 9.26 (d, J = 1.8 Hz, H-1); ^{13}C nmr (deuteriochloroform): δ 26.67 (methyl), 123.21, 123.26, 123.37, 123.86, 125.97, 127.27, 127.38, 127.65, 128.19, 128.74, 129.33, 129.76, 130.58, 133.07, 134.97, 197.75 (CO); ir (potassium bromide): 1685 (CO), 1625, 1410, 1365, 1270, 1240, 765, 730 cm^{-1}; uv (95% ethanol): λ max 235 nm (ε 37,426), 268 (101,880), 289 (24,559), 301 (21,327), 315 (16,039).

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.76; H, 5.28.

Triphenylene-2-carboxylic Acid (**3**).

To 1.33 g (5.0 mmoles) of ketone **2** in a 100 ml three necked round-bottomed flask equipped with stirrer, reflux condenser and dropping funnel was added 13 ml of glacial acetic acid. After the ketone was in solution by heating (approximately 90°), 9.0 g (30.0 mmoles) of sodium dichromate dihydrate, previously ground to a course powder, was carefully added in small portions. Heating and stirring were continued throughout the addition, which took about 15 minutes. The reaction mixture was brought to a gentle reflux and 4 ml (42.3 mmoles) of acetic anhydride was added using the dropping funnel. The mixture was then refluxed for 18 hours. The hot solution was stirred into 180 ml of hot water. The suspension was stirred for 15 minutes and then filtered. The filter cake was washed with four 10 ml portions of 2% sulfuric acid solution. The wet filter cake was transferred to a beaker with 20 ml of 5% potassium hydroxide solution. The mixture was heated (approximately 80°), and the hot solution was filtered. The alkali-insoluble material (if any) was washed with 10 ml of hot 5% potassium hydroxide solution. The solution of the potassium salt was heated with stirring to 70° and 18% hydrochloric acid solution was added dropwise until the *p*H was 4. The mixture was cooled, filtered, and the filter cake washed with water. The yellow-orange filter cake was heated (100°) with 100 ml of 10% hydrochloric acid solution for 1 hour. After cooling a pale yellow precipitate was filtered off, washed with 20 ml of water and dried. Recrystallization from methanol yielded 0.82 g (60%), mp 157-158°; ^{1}H nmr (d_6 dimethyl sulfoxide): δ 7.70 (m, H-6, H-7, H-10, H-11), 8.21 (dd, J = 1.8 and 8.8 Hz, H-3), 8.79 (m, H-4, H-5, H-8, H-9, H-12), 9.26 (d, J = 1.8 Hz, H-1); ^{13}C nmr (d_6 dimethyl sulfoxide): δ 123.41, 123.63, 124.06, 124.22, 124.71, 127.42, 127.80, 128.96, 128.07, 128.34, 128.61, 129.31, 129.42 (C-1), 129.91 (C-10b), 132.40 (C-4a), 167.24 (CO); ir (potassium bromide): 3450 (-OH), 1620, 1600 (CO), 1570, 1540, 1410, 1050, 750, 730 cm^{-1}; uv (95% ethanol): λ max 254 nm (ε 54,575), 263 (80,350), 282 (14,116), 298 (7688), 306 (4537).

Anal. Calcd. for $C_{19}H_{12}O_2 \cdot H_2O$: C, 78.60; H, 4.86. Found: C, 78.38; H, 4.54.

2-Hydroxymethyltriphenylene (**4**).

To 3.09 g (11.3 mmoles) of the acid **3** in 700 ml of dry tetrahydrofuran under argon was added 1.00 g (26.3 mmoles) of lithium aluminum hydride. The mixture was refluxed for 10 hours and the excess lithium aluminum hydride decomposed by addition of saturated ammonium chloride solution. The mixture was filtered and the filtrate evaporated. Silica gel chromatography using chloroform yielded 2.81 g (96%) of a white solid, mp 149-150°; ^{1}H nmr (deuteriochloroform): δ 1.53 (s, OH), 4.97 (br s, CH_2), 7.66 (m, H-3, H-6, H-7, H-10, H-11), 8.65 (m, H-1, H-4, H-5, H-8, H-9, H-12); ^{13}C nmr (deuteriochloroform): δ 65.57 (CH_2), 121.48, 123.32, 123.70, 126.03, 127.22, 127.33, 129.93; ir (potassium bromide): 3300 (OH), 3050, 2900, 1410 (OH), 1030, 1010 (OH), 820, 750 cm^{-1}; uv (95% ethanol): λ max 251 nm (ε 76,634), 259 (129,601), 273 (17, 806), 286 (15,477).

Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.31; H, 5.77.

Triphenylene-2-carboxaldehyde (**5**).

To 4 ml of dry pyridine under argon at 10° was added 50 mg (0.50 mmole) of chromium trioxide. **Caution**: reverse addition causes the mixture to inflame. A yellow precipitate formed and the mixture was stirred for 30 minutes, warming to room temperature. To the slurry was added 35 mg (0.14 mmole) of the alcohol **4** dissolved in 3 ml of dry pyridine. After stirring for 4 days, the mixture was poured onto ice, extracted with chloroform, and the organic layer was washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution and then water. The solution was dried (magnesium sulfate) and evaporated. Silica gel chromatography using chloroform yielded 31 mg (86%), mp 155-156°; ^{1}H nmr (deuteriochloroform): δ 7.57 (m, H-6, H-7, H-10, H-11), 8.14 (dd, J = 1.3 and 8.4 Hz, H-3), 8.74 (m, H-4, H-5, H-8, H-9, H-12), 9.15 (d, J = 1.3 Hz, H-1), 10.28 (s, HCO); ^{13}C nmr (deuteriochloroform): δ 123.37, 124.18, 126.24, 126.73, 127.54, 127.65, 127.98, 128.68, 129.87, 134.59, 192.17 (CO); ir (potassium bromide): 2720, 2820 (HCO), 1690 (CO), 1610, 1350, 1270, 830, 760, 720 cm^{-1}; uv (95% ethanol): λ max 242 nm (ε 35,357), 252 (45,714), 260 (59,999), 269 (77,678), 304 (17,500), 321 (13,749).

Anal. Calcd. for $C_{19}H_{12}O \cdot 0.10\ H_2O$: C, 88.41; H, 4.77. Found: C, 88.16; H, 4.97.

2-(2′,2′-Dimethoxyethylaminomethyl)triphenylene (**6**).

To 20 ml of dry methanol under argon was added 0.19 g (0.74 mmole) of aldehyde **5**, 28 mg (0.44 mmole) of sodium cyanoborohydride, and 0.48 ml (4.44 mmoles) of freshly distilled aminoacetaldehyde dimethyl acetal. The reaction mixture was stirred for 6 hours, during which time the *p*H was periodically adjusted to 7 with glacial acetic acid. The solvent was evaporated and the residue was partitioned between saturated sodium bicarbonate solution and dichloromethane. The organic layer was dried (magnesium sulfate) and evaporated. Chromatography on silica gel eluting with 97% chloroform and 3% methanol yielded 0.18 g (71%); ^{1}H nmr (deuteriochloroform): δ 1.63 (s, NH), 2.85 (d, J = 5.3 Hz, CH_2), 3.38 (s, -OCH_3), 4.08 (s, CH_2), 4.55 (t, J = 5.3 Hz, -CH), 7.65 (m, H-2, H-6, H-7, H-10, H-11), 8.75 (m, H-1, H-4, H-5, H-8, H-9, H-12); ^{13}C nmr (deuteriochloroform): δ 50.62 (-CH_2NHCH_2), 54.03 (OCH_3, 103.92 (CHO_2), 122.67 (C-3), 123.26, 123.37, 123.54, 127.06 (C-1), 127.17, 127.44, 128.84 (C-4a), 129.71 (C-12b), 129.82, 129.93, 138.98 (C-2); ir (neat): 3340 (NH), 2940, 2860, 1195, 1135, 1065 (acetal), 830, 760, 720 cm^{-1}; uv (95% ethanol): λ max 251 nm (ε 93,799), 259 (159,863), 273 (22,893), 286 (19,361); ms: m/e 345 (15%) (MI), 270 (20%), 241 (100%).

Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.58; H, 6.50; N, 4.50.

Phenanthro[9,10-*g*]isoquinoline (**7**).

To 23 mg (0.07 mmole) of acetal **6** was added 10 ml of polyphosphoric acid. The mixture was heated at 130° under argon for 8 hours, then poured onto ice water (50 ml) and extracted with chloroform. The aqueous phase was basified with concentrated aqueous ammonia solution, extracted with chloroform, dried (magnesium sulfate), and evaporated. Silica gel chromatography with 5% methanol and 95% chloroform yielded 5 mg (27%), mp 139-150° dec; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 7.65 (m, H-7, H-8, H-11, H-12), 7.79 (d, J = 5.7 Hz, H-4), 8.52 (m, H-9, H-10), 8.53 (d, J = 5.7, H-3), 8.69 (m, H-6, H-13), 8.92 (s, H-14), 9.10 (s, H-5), 9.46 (s, H-1); ^{13}C nmr (deuteriochloroform, 400 MHz): 120.20 (C-4), 120.48 (C-14), 122.25 (C-5), 123.50 (C-7 or C-11), 123.54 (C-7 or C-11), 123.71 (C-8), 124.14 (C-12), 127.29 (C-14a), 127.69 (C-9), 127.78 (C-10), 128.24 (C-13), 128.69 (C-6), 129.24 (C-13b), 129.54 (C-5b), 129.70 (C-9b), 130.00 (C-9a), 130.67 (C-13a), 132.24 (C-5a), 133.57 (C-4a), 142.25 (C-3), 153.37 (C-1); ir (potassium bromide): 3025, 1622, 1500, 1255, 880, 765, 720 cm^{-1}; uv (methanol): λ max 205 (ε 41,160), 248 (34,375), 255 (35,535), 266 (40,892), 277 (61,875), 287 (71,249), 304 (11,339), 318 (6517), 357 (3125), 379 (1785); ms: m/e 279 (100%) (MI).

Anal. Calcd. for $C_{21}H_{13}N \cdot 0.6\ H_2O$: C, 86.93; H, 4.93; N, 4.83. Found: C, 86.99; H, 4.94; N, 4.71.

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REFERENCES AND NOTES

[1] M. J. Tanga and E. J. Reist, *Mutat. Res.*, **158**, 125 (1985).

[2] M. J. Tanga, R. M. Miao, and E. J. Reist, *Mutat. Res.*, **172**, 11 (1986).

[3] R. M. Miao, M. J. Tanga, W. A. Suk, A. Miller, and E. J. Reist, *Int. J. Cancer*, **37**, 613 (1986).

[4] T. K. Rao, J. L. Epler, M. R. Guerin, B. R. Clark, and C. H. Ho, "Mutagenicity of Nitrogen Compounds from Synthetic Crude Oils: Collection, Separation, and Biological Testing," Natl. Technol. Info. Service, Springfield, VA, CONF-800-323-1, W-7405-ENG-26 (1980).

[5] S. G. Wakeham, *Environ. Sci. Technol.*, **13**, 1118 (1979).

[6] G. Rieveschland and F. E. Ray, *Org. Synth. Coll. Vol.* **3**, 420-422 (1955).

[7] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 425 (1953).

[8] J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

[9] J. N. Shoolery, *J. Nat. Prod.*, **47**, 226 (1984).

[10] A. Bax, "Two-Dimensional Nuclear Magnetic Resonance in Liquids", Delft University Press and D. Reidel Publishing Co., Boston, 1982.

[11] R. Ben and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **22**, 350 (1983).