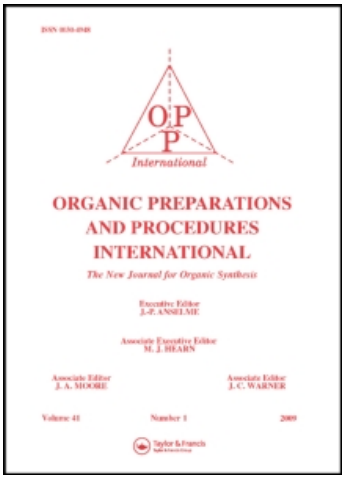

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PREPARATION OF NOVEL QUINO[3, 4-C]-, QUENO[4, 3-C], QUINO[5, 6-C]-, QUINO[6, 5-C]-, AND QUINO[7, 8-C][2, 7]NAPHTHYRIDINE

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PREPARATION OF NOVEL QUINO[3,4-C]-, QUINO[4,3-C], QUINO[5,6-C]-, QUINO[6,5-C]-, AND QUINO[7,8-C][2,7]NAPHTHYRIDINE

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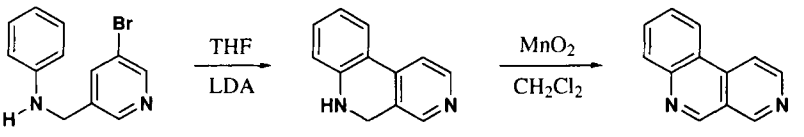
Polycyclic aromatic hydrocarbons containing one or more nitrogen atoms in place of a carbon atom (azaPAH or azaarenes) are ubiquitous environmental pollutants emanating from various sources, including the fossil fuel industry, tobacco smoking, wood preservation, pesticides, cooked high-protein foods and pharmaceuticals. Like their carbocyclic counterparts, azaarenes have been shown to possess mutagenic and carcinogenic activity that can vary greatly between regioisomers.[1] As a result, there continues to be interest in developing synthetic methodologies for the preparation of a large variety of azaarene ring systems so that a more complete structure-activity profile can be deduced.

For the past 15 years, we have been investigating an intramolecular pyridyne cyclization strategy for the synthesis of the benzo[c][2,7]naphthyridine ring system **3**, a structural feature common to many natural products exhibiting biological activity.[2]

The pyridyne cyclization precursors **1** can be readily obtained from reductive amination of 5-bromonicotinaldehyde and the appropriate aromatic amine. Utilizing this methodology,



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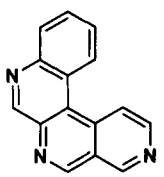
azaarenes have been previously prepared by us from 5-bromonicotinaldehyde and aniline, substituted anilines, 1-aminoanthracene, and aminopyridines[3]. A logical extension of this synthesis scheme is to investigate the pyridyne cyclization of the precursors obtained from 5-bromonicotinaldehyde and aminoquinolines. Because the 3-, 6-, and 7-aminoquinoline regioisomers have two different ortho cyclization sites available, this strategy can theoretically result in ten different quino[c][2,7]naphthyridines, all of which represent previously unreported heterocyclic ring systems. We now delineate the results of our investigations on the extension of this pyridyne cyclization methodology to the synthesis of azaarenes from the combination of 5-bromonicotinaldehyde and all seven aminoquinoline regioisomers.

Reductive amination of 5-bromonicotinaldehyde was successful for all of the aminoquinoline isomers except 8-aminoquinoline, which resulted in an extremely complex product mixture as evidenced by both thin layer chromatography and proton NMR spectroscopy. As the proton NMR spectrum showed little to no evidence of a successful reaction, separation or cyclization of the mixture was not attempted. While both 2-aminoquinoline and 4-aminoquinoline yielded reductive amination products, neither resulted in a viable preparation of their respective azaarene upon attempted cyclization and oxidation. The product mixture resulting from 2-aminoquinoline showed no evidence of a cyclization product by proton NMR spectroscopy due to absence of absorptions in the δ 9-10 region. Peaks in this region are due to the C-1 and C-8 protons of the 2,7-naphthyridine substructural unit. While the ^{1}H NMR spectrum of the product resulting from cyclization and subsequent oxidation of the reductive amination product from 4-aminoquinoline did show the presence of the expected azaarene, quino[4,3-c][2,7]naphthyridine (**5**), all attempts to purify the product by flash chromatrography were unsuccessful; only trace amounts (<1% overall yield from 4-aminoquinoline) of an impure product were obtained. The remaining aminoquinoline isomers all yielded azaarene products in overall purified yields of 5-31% for the four-step process. It is clear from these reactions that the α-carbons of quinoline are preferred over the β-carbons as cyclization sites. When only a β-carbon is available *ortho* to the amino group, little to no cyclization occurs (5% yield for the 5-amino isomer **6** and <1% yield for the 4-amino isomer **5**). When both an α- and β-carbon are available, the reaction appears to be completely regioselective for the α site as no conclusive evidence was apparent in the proton NMR spectra for the presence of regioisomers that would have resulted from cyclization on a β-carbon. As a result, five previously unreported heterocyclic ring systems have been prepared **4-8**, four of which can be obtained in pure form: **4**, **6**, **7**, **8**.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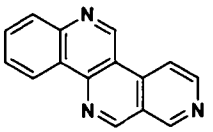
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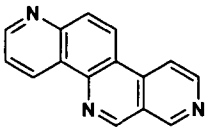
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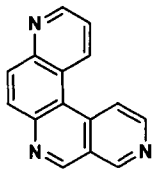
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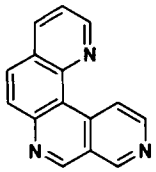
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For all of the aforementioned syntheses, the four-step sequence was carried out without purification of the intermediate products due to tedious, capricious chromatography for the reductive amination products and partial air oxidation of the cyclized dihydronaphthyridine products.

Studies are currently underway in our laboratories to further explore the scope and limitations of this protocol for the preparation of a wide variety of azaarenes.

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EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°C), and all lithiation reactions were performed under nitrogen. Lithium diisopropylamide (LDA) was prepared by standard procedures from diisopropylamine and n-butyllithium. Tetrahydrofuran was distilled from sodium/benzophenone. Thin layer chromatography was performed on precoated (0.25 mm) silica gel 60 F_{254} plastic sheets and was visualized with 254 nm ultraviolet light. Flash chromatography was performed with silica gel 60 (200-400 mesh).[4] Proton and carbon NMR spectra were recorded on a Jeol Eclipse400 FT-NMR spectrometer; chemical shifts are reported in parts per million relative to internal-TMS (proton) or the solvent chloroform-d (carbon). Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. All starting materials were commercially available except for 4-aminoquinoline and 7-aminoquinoline, which were prepared by literature procedures.[5]

Preparation of Quino[6,5-c][2,7]naphthyridine (7).- A magnetically stirred solution of 5-bromonicotinaldehyde (0.997 g, 5.36 mmol), 6-aminoquinoline (0.768 g, 5.33 mmol), and *p*-toluenesulfonic acid monohydrate (0.01 g, 0.053 mmol) in benzene (150 mL) was refluxed for 48 hrs with water removal *via* a Dean-Stark trap. The benzene was removed *in vacuo*, the oily residue was dissolved in methanol (50 mL), and sodium borohydride pellets (2.0 g, 53 mmol) were added over 15 min. The resulting mixture was magnetically stirred at room temperature for 24 hrs. The methanol was removed *in vacuo* and the viscous oily residue was partitioned between chloroform (50 mL) and water (50 mL). The aqueous layer was further extracted with chloroform (2 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated and dried *in vacuo* to afford a yellow-brown solid. A solution of the solid in dry THF (20 mL) was added over a period of 2 min, by means of a syringe, to a magnetically stirred solution of LDA (21 mmol) in dry THF (100 mL) under nitrogen at such a rate that the temperature remained below -100°C. The resulting mixture was allowed to warm

slowly to room temperature and stirred for 24 hrs. The dark reaction mixture was diluted with water (200 mL) and extracted with chloroform (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting brown oil was dissolved in methylene chloride (50 mL), manganese dioxide (2.3 g, 26 mmol) was added and the mixture was magnetically stirred for 24 hrs. The manganese dioxide was removed by filtering the reaction mixture through Celite and the Celite was washed with acetone until the filtrate eluting from the Celite was colorless. Silica gel was added to the filtrate and the mixture was concentrated *in vacuo* to a dry powder. Flash chromatography (1:1 hexanes/acetone to remove high Rf material followed by 1:2 hexanes/acetone) gave quino[6,5-c][2,7]naphthyridine (**7**) cleanly as an orange/brown solid (0.383 g, 31%) Recrystallization of a small amount from 5:1 hexanes/acetone gave a light grey solid, mp 198-200°C; ^{1}H NMR ($CDCl_3$): δ 9.58 (s, 1H), 9.54 (s, 1H), 9.37 (dd, J = 1.5, 9.0 Hz, 1H), 9.09 (dd, J = 1.5, 4.5 Hz, 1H), 8.99 (d, J = 6.0 Hz, 1H), 8.74 (d, J = 6.0 Hz, 1H), 8.43-8.38 (m, 2H), 7.69 (dd, J = 4.5, 9.0 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 153.4, 153.0, 150.4, 149.0, 148.6, 146.3, 136.5, 134.6, 133.4, 132.4, 125.2, 122.3, 121.6, 118.8, 118.4.

Anal. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.81; H, 3.96; N, 17.95.

Quino[3,4-c][2,7]naphthyridine (4).- was prepared analogously from 5-bromonicotinaldehyde and 3-aminoquinoline (10%) as a salmon-colored solid that was recrystallized from 5:1 hexanes/acetone: mp 187-189°C; ^{1}H NMR($CDCl_3$): δ 9.64 (s, 1H), 9.61 (s, 1H), 9.56 (s, 1H), 9.07 (d, J = 6.0 Hz, 1H), 9.02 (dd, J = 1.0, 8.0 Hz, 1H), 8.94 (d, J = 6.0 Hz, 1H), 8.36 (dd, J = 1.5, 8.0 Hz, 1H), 7.88 (td, J = 1.0, 8.0 Hz, 1H), 7.82 (td, J = 1.5, 8.0 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 154.3, 153.6, 153.4, 149.5, 146.6, 139.9, 135.8, 131.2, 129.5, 128.3, 126.0, 123.8, 123.5, 122.9, 119.5.

Anal. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.79; H, 4.02; N, 18.01.

Quino[5,6-c][2,7]naphthyridine (6).- was prepared analogously from 5-bromonicotinaldehyde and 5-aminoquinoline (5%) as a brown solid that was recrystallized from 5:1 hexanes/acetone: mp 245-247°C; ^{1}H NMR($CDCl_3$): δ 9.68 (dd, J = 1.5, 8.5 Hz, 1H), 9.60 (s, 1H), 9.56 (s, 1H), 9.12 (dd, J = 1.5, 4.5 Hz, 1H), 9.01 (d, J = 6.0 Hz, 1H), 8.73 (d, J = 9.0 Hz, 1H), 8.45 (d, J = 6.0 Hz, 1H), 8.35 (d, J = 9.0 Hz, 1H), 7.72 (dd, J = 4.5, 8.5 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 152.9, 152.0, 151.8, 149.6, 148.8, 143.3, 136.9, 133.7, 130.0, 127.3, 123.3, 122.4, 122.0, 119.5, 115.6.

Anal. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.96; H, 4.02; N, 18.02.

Quino[7,8-c][2,7]naphthyridine (8).- was prepared analogously from 5-bromonicotinaldehyde and 7-aminoquinoline (31%) as an orange solid that was recrystallized from 5:1 hexanes/acetone: mp 194-196°C; ^{1}H NMR($CDCl_3$): δ 10.63 (d, J = 6.0 Hz, 1H), 9.47 (s, 1H), 9.43 (s, 1H), 9.12 (dd, J = 2.0, 4.0 Hz, 1H), 8.95 (d, J = 6.0 Hz, 1H), 8.27 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.57 (dd, J = 4.0, 8.0 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 154.1, 152.5, 149.4, 149.3, 148.5, 147.9, 137.7, 136.5, 130.5, 129.9, 127.6, 122.5, 122.3, 121.7, 118.8.

Anal. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.72; H, 3.98; N, 18.04.

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