Short pathways are described for the synthesis of a representative example of each of the 7,8-dihydro- and 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6H)-one ring systems from simple pyridine precursors. An attempted synthesis of the related 4,6-dihydro-1,6-naphthyridin-5(1H)-one ring system from a common intermediate was unsuccessful.

Introduction.

Benzamides and nicotinamides represent classes of drugs that have experienced an unusually broad spectrum of clinical development in a number of therapeutic areas [1]. One of their principal targets is the nuclear DNA-binding protein poly(ADP-ribose) polymerase-1 (PARP-1), which is activated by nicks in DNA during inflammation, ischemia, neurodegeneration, and cancer therapy. When over-activated, PARP can cause extensive polymerization of ADP-ribose, leading to the depletion of NAD$^+$ and subsequently a decrease in the level of intracellular ATP. Such decreases can culminate in cell dysfunction and cell death through a necrotic pathway [2].

As part of a broad program to design bicyclic rigid analogues of these chemical classes as PARP inhibitors, we were interested in synthesizing aza-congeners of our 5-substituted-3,4-dihydro-1(2H)-isoquinolinone inhibitor leads [3]. This led us to explore synthetic pathways toward analogues of rigid nicotinamides, specifically compounds of the 7,8-dihydro-1,6-naphthyridine-5(6H)-one ring system. Furthermore, we were interested in extending our studies to the synthesis of the isomeric 4,6-dihydro-1,6-naphthyridin-5(1H)-ones, and/or more highly reduced congeners, the 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6H)-ones (Chart 1).

Previous reports describing the synthesis of reduced 1,6-naphthyridine-5(6H)-ones are relatively sparse. Within the 7,8-dihydro-1,6-naphthyridine-5(6H)-one ring system, Russian investigators [4a] have described an approach toward the synthesis of 6,7-diaryl substituted congeners via acid-catalyzed cyclization of 2-styrylnicotinamides, and German investigators [4b] have reported a synthesis in which an appropriately 3- substituted 4-amino-5,6-dihydro-2(1H)-pyridinone was annulated to the requisite bicyclic system. Neither synthesis is high-yielding nor general for the types of target molecules we sought. In their synthesis of a number of 4,6,7,8-tetrahydro-1,6-naphthyridin-5(1H)-ones bearing chiral auxiliaries off the lactam nitrogen as NADH model compounds, Combret et al. developed a sequence that proceeds through a 7,8-dihydro-1,6-naphthyridine-5(6H)-one intermediate [5]. Literature procedures describing the synthesis of 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6H)-ones [6] and 4,6-dihydro-1,6-naphthyridin-5(1H)-ones [7] are likewise scarce, and most are of limited utility toward procuring our target compounds.

Described herein are short pathways to the synthesis of two of the targeted reduced naphthyridinone systems shown in Chart 1, and a limited effort toward unsuccessfully accessing a single compound within the 4,6-dihydro-1,6-naphthyridin-5(1H)-ones from a common intermediate. A preliminary account of some of this work can be found in the patent literature [8]. This paper
expands on this with complete experimental detail, including some larger scale reactions, and describes additional intermediates and side products not cited previously.

Results and Discussion.

Synthesis of 7,8-Dihydro-1,6-Naphthyridine-5(6H)-one Ring System.

Our synthetic route is shown in Scheme 1, and is similar to that devised by Combret et al. [5]. Their synthesis of an intermediate 7,8-dihydro-1,6-naphthyridine-5(6H)-one proceeds in 21-38% overall yield via a 5-step, 3-pot sequence starting from 2-chloronicotinonitrile. However, rather than utilizing their strategy of building up an enamine from an alkyn moiety at the C-2 position of a nicotinate substrate, we favored incorporating a vinyl moiety at this position, then utilizing an acid-catalyzed aza-Michael addition of an amine, followed by in situ ring closure to provide our desired bicycle. Thus, commercially available 2-chloronicotinic acid was readily converted to the known ester 2 [9] in 84% yield, utilizing a simpler esterification method than previously described. Treatment of 2 with vinyltributyltin under standard Stille conditions (palladium-2 + catalysis) provided the vinyl moiety at this position, then utilizing an acid-catalyzed aza-Michael addition of an amine, followed by in situ ring closure to provide our desired bicycle. Thus, commercially available 2-chloronicotinic acid was readily converted to the known ester 2 [9] in 84% yield, utilizing a simpler esterification method than previously described. Treatment of 2 with vinyltributyltin under standard Stille conditions (palladium-2 + catalysis) provided the vinyl moiety at this position, then utilizing an acid-catalyzed aza-Michael addition of an amine, followed by in situ ring closure to provide our desired bicycle. Thus, commercially available 2-chloronicotinic acid was readily converted to the known ester 2 [9] in 84% yield, utilizing a simpler esterification method than previously described. Treatment of 2 with vinyltributyltin under standard Stille conditions (palladium-2 + catalysis) provided the vinyl moiety at this position, then utilizing an acid-catalyzed aza-Michael addition of an amine, followed by in situ ring closure to provide our desired bicycle.
alkynaphthyridinium salt 14 in 96% yield. When we treated 14 under conditions described by Lounamaa et al. [16] (sodium hydrosulfite, sodium bicarbonate, aqueous methanol), a slow discharge of the yellow solution color was observed. However, TLC revealed only the presence of decomposition products and starting material. This is in contrast to the work of Vitry et al. [7a], who utilized similar reduction conditions and were able to isolate a product closely related to our desired target 16 (but alkylated on the lactam nitrogen) under carefully controlled conditions (degassed solvents for all operations). Further attempts at controlled reduction of 14 under conditions of Booker et al. [17] (sodium cyanoborohydride, aqueous acetic acid) led instead to a slow generation of tetrahydro product 15 in low yield. The use of borane–pyridine in formic acid also proceeded slowly, but cleanly, to provide product 15 in 88% yield. This reaction was readily scaled up to provide gram quantities of 15 for biological studies.

**Biological Evaluation.**

When tested in vitro in an assay utilizing PARP prepared from calf thymus [18], compounds 4 (IC\(_{50} \) 2.5 μM), 7 (IC\(_{50} \) >100 μM), 10a (IC\(_{50} \) 1.0 – 10.0 μM), 10b (IC\(_{50} \) 1.2 μM), 11 (IC\(_{50} \) 1.0 – 10.0 μM), 13 (IC\(_{50} \) 1.0 – 10.0 μM), 14 (IC\(_{50} \) >10 μM) and 15 (IC\(_{50} \) 0.51 μM) displayed weaker potency than reference inhibitor, 3,4-dihydro-5-methyl-1(2H)-isoquinolinone (Chart 1, R = CH\(_{3}\)), with IC\(_{50} \) 0.11 μM [19].

**Conclusions.**

We have successfully developed synthetic pathways to two reduced congeners of the 1,6-naphthyridine-5(6H)-one ring system, and have described unsuccessful attempts to procure a third. Compound 4, the simplest member of the 7,8-dihydro-1,6-naphthyridine-5(6H)-one ring system, is derived from a short, fairly efficient synthesis (24% overall yield) from a readily available starting material. We believe this route can be further optimized and adapted to the combinatorial synthesis of numerous analogues possessing a wide range of substituents off either ring. The synthesis of compound 15, representative of the 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6H)-one ring system, is also readily accessible (35% overall yield) from a simple starting material along with functional variants of 10a (compounds 11 – 12b). These variants should allow for the construction of additional analogues of 15 possessing diversity off the tetrahydropyridine ring nitrogen as well as open positions on the lactam ring.

**EXPERIMENTAL**

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Proton and carbon magnetic resonance (\(^1\)H nmr and \(^13\)C nmr) spectra were obtained on a Bruker AM-250 spectrometer at 250 and 63 MHz, respectively. Chemical shifts are reported as δ values (parts per million) downfield from internal tetramethylsilane. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet. Mass spectra were obtained either in the electron impact (EI ms) or chemical ionization (CI ms; utilizing 1% ammonia in methane) mode on a VG Masslab Trio-2A mass spectrometer. Combustion analyses were determined on a CEC 440 Elemental Analyzer or by Robertson Microlit Laboratories, Inc., Madison, NJ. Column chromatography was carried out in the flash mode utilizing Merck 230-400 mesh silica gel. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light. All reaction solvents were reagent grade (methane) mode on a VG Masslab Trio-2A mass spectrometer. Combustion analyses were determined on a CEC 440 Elemental Analyzer or by Robertson Microlit Laboratories, Inc., Madison, NJ. Column chromatography was carried out in the flash mode utilizing Merck 230-400 mesh silica gel. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light. All reaction solvents were reagent grade or distilled-in-glass, and were stored over activated 3A (for lower alcohols) or 4A molecular sieves. Following normal workup procedures, organic extracts were dried over anhydrous magnesium sulfate prior to concentration. All reactions were run under a positive pressure of nitrogen.

2-Chloro-3-pyridinecarboxylic acid, methyl ester (2). A suspension of 22.06 g (140 mmol) of 2-chloro-3-pyridinecarboxylic acid (1), 14.6 mL (154 mmol) of dimethyl sulfate, 29 g (210 mmol) of anhydrous powdered potassium carbonate, and 140 mL of acetone was stirred at 25 °C overnight. The mixture was filtered, the filter pad was washed with...
acetone, and the filtrate was concentrated to an oil that was diluted with dichloromethane. The organic phase was washed with saturated aqueous sodium carbonate, dried, and then filtered through a pad of silica gel. The filtrate was concentrated to an oil that was distilled at 90-91 °C/0.17 mm to provide 20.2 g (84%) of analytically pure 2 as a colorless oil. The spectral properties were the same as previously reported [9].

2-Ethenyl-3-pyridinecarboxylic acid, methyl ester (3).

A mixture of 19.7 g (115 mmol) of 2-chloro-3-pyridine-carboxylic acid, methyl ester (2), 38.3 g (120.8 mmol) of vinyltributyltin, 1.48 g (2.1 mmol) of bis(triphenylphosphine)-palladium (II) chloride, 100 mg of 2,6-di-i-t-butyl-4-methylphenol, and 250 mL of N,N-dimethylformamide was stirred at 55 °C for 7 h, and then treated with 1.63 g (5.1 mmol) of additional vinyltributyltin and 1 g of the palladium catalyst. The mixture was heated further at 40 °C for 61 h and concentrated at 60 °C/5 mm to an oil that was dissolved in ethyl acetate. The solution was filtered through a pad of silica gel, and the filtrate was diluted with additional ethyl acetate, washed with water, dried, and concentrated to an oil that was distilled. Material was collected in the 80-95 °C/0.14 mm range to leave 24.5 g of an oil that was ca. 75% product by GC. The oil was dissolved in dichloromethane:hexanes (1:1) and loaded onto an 8 cm x 15 cm silica gel column. The column was eluted with dichloromethane:hexanes (1:1) with 500 mL fractions collected. Product fractions were combined and carefully distilled with material collected at 65-67 °C/0.15 mm to leave 13.6 g (70%) of additional vinyltributyltin and 1 g of the palladium catalyst. The mixture was heated further at 40 °C for 61 h and concentrated at 60 °C/5 mm to an oil that was dissolved in ethyl acetate. The solution was filtered through a pad of silica gel, and the filtrate was diluted with additional ethyl acetate, washed with water, dried, and concentrated to an oil that was distilled. Material was collected in the 80-95 °C/0.14 mm range to leave 24.5 g of an oil that was crystallized from ethyl acetate:methanol and then 1 L of 85:15 ethyl acetate:methanol. Column fractions containing 4 were concentrated and combined with nearly pure 4 from the crystallization of the 85:15 ethyl acetate:methanol column fractions discussed above. The combined solids were crystallized from ethyl acetate to provide 2.15 g of pure 4. All pure lots of 4 (16.55 g) were combined, triturated in ethyl acetate, collected, and dried to leave 16.23 g (40%) of material that was collected in the 80-95 °C/0.14 mm range to leave 24.5 g of an oil that was ca. 75% product by GC. The oil was dissolved in dichloromethane:hexanes (1:1) and loaded onto an 8 cm x 15 cm silica gel column. The column was eluted with dichloromethane:hexanes (1:1) with 500 mL fractions collected. Fraction 4 was collected and then pumped at 17 cm x 68 cm column of silica gel. The column was eluted with 1.5 L of ethyl acetate followed by 1 L of 9:1 ethyl acetate:methanol and then 1 L of 80:20 ethyl acetate:methanol. Column fractions containing 4 were concentrated and combined with nearly pure 4 from the crystallization of the 85:15 ethyl acetate:methanol column fractions discussed above. The combined solids were crystallized from ethyl acetate to provide 2.15 g of pure 4. All pure lots of 4 (16.55 g) were combined, triturated in ethyl acetate, collected, and dried to leave 16.23 g (40%) of material that was collected in the 80-95 °C/0.14 mm range to leave 24.5 g of an oil that was ca. 75% product by GC. The oil was dissolved in dichloromethane:hexanes (1:1) and loaded onto an 8 cm x 15 cm silica gel column. The column was eluted with dichloromethane:hexanes (1:1) with 500 mL fractions collected. Product fractions were combined and carefully distilled with material collected at 65-67 °C/0.15 mm to leave 13.6 g (70%) of 3 as a clear oil, >95% pure by GC; 1H nmr (deuteriochloroform): δ 8.70 (dd, J = 7.7 Hz, 1H), 7.54 (br s, 1H, D 2O exchangeable), 7.34 (dd, J = 7.8 Hz, 4.9 Hz, 1H), 3.75-3.65 (m, 2H; with D 2O wash collapses to δ 3.68, t, J = 6.8 Hz, 2H), 3.22 (t, J = 6.8 Hz, 2H).


5,6,7,8-Tetrahydro-1-methyl-5-oxo-1,6-naphthyridinium iodide (7).

A mixture of 100 mg (0.67 mmol) of 7,8-dihydro-1,6-naphthyridin-5(6H)-one (4), 0.2 mL of iodomethane, and 1 mL of anhydrous N,N-dimethylformamide was stirred at 25 °C for
60 h, and then poured slowly into 2 mL of stirring 2-propanol. The solids were collected, washed with 2-propanol, and dried to leave 180 mg (92%) of 7, mp 265-272 ºC; 1H nmr (dimethyl sulfoxide-d6): δ 9.11 (d, J = 6.0 Hz, 1H), 8.86 (d, J = 7.8 Hz, 1H), 8.69 (br s, 1H, D2O exchangeable), 8.13-8.04 (m, 1H), 4.29 (s, 3H), 3.64-3.53 (m, 2H; with D2O wash collapses to t), 3.40 (t, J = 6.5 Hz, 2H).

Anal. Calcd. for C10H11NO·HCl: C, 37.26; H, 2.31; N, 12.45.

4. To an ice-cold solution of 75.6 g (0.5 mol) of 2-methylnicotinamide (8) in 250 mL of methanol was added slowly 87.3 mL (0.524 mol) of 6 M aqueous potassium hydroxide. The mixture was stirred at 25 ºC for 6 h, and then diluted with 100 mL of water. The solution was washed with diethyl ether (3x), and then concentrated to dryness. The solid was coevaporated several times with ethanol, suspended in ca. 250 mL of 2-propanol, and the suspension was added to ca. 1.2 L of diethyl ether. The solids were collected, washed well with diethyl ether, and dried to leave 48 g (71%) of analytically pure insolubles. After cooling, the precipitated solids were collected suspension was boiled, and then filtered hot to remove some solvent. The mixture was heated at 50 ºC for 2 h. During the second hour, a 200 mm vacuum was applied to remove volatiles. The solution was cooled to 25 ºC, diluted with 200 mL of anhydrous N,N-dimethylformamide, and then treated carefully with batch-wise portions of 10.4 g (0.26 mol) of sodium hydroxide (60 % dispersion; CAUTION: vigorous evolution of hydrogen). The mixture was heated at 80 ºC for 2.5 h, ice-cooled, treated cautiously with 50 mL of 2-propanol, and then maintained at 0-5 ºC overnight. The solids were collected, and then dissolved in ca. 100 mL of hot water. The solution was filtered, the filtrate was ice-cooled and then treated dropwise with concentrated hydrochloric acid to pH 7.2. After storage at 0-5 ºC for 3 h, the precipitated solids were collected, washed with ice-cold water, and dried over potassium pentoxide to leave 13.9 g (48%) of 10a, mp 243-245 ºC (lit [13] mp 243-244.5 ºC); The 1H nmr was identical to that reported earlier [13].


Found: C, 65.63; H, 4.28; N, 19.13.

2-Methylnicotinamide (9).

A mixture of 272 mg (2 mmol) of 2-methylnicotinamide (9) and 0.34 mL (2.2 mmol) of 95% N,N-dimethylecetamide dimethyl acetal was heated at 50 ºC for 1.5 h, and then a vacuum was applied for 1 h with heating as described for 10a. The oil was diluted with 2 mL of dry N,N-dimethylecetamide, treated with 96 mg of 60% sodium hydride, and heated at 80 ºC for 2.5 h. The solution was treated with 70 mg more of 60% sodium hydride, and then quenched with excess glacial acetic acid. The mixture was concentrated at 25-70 ºC to leave a residual solid that was digested in hot chloroform. The suspension was filtered through a pad of silica gel that was washed with chloroform, and then acetone. Product fractions were concentrated to a solid that was dissolved in a minimum volume of hot water. The solution was stored at 5 ºC for 2 weeks, and the precipitated solids were collected, washed well with 2-propanol, and dried to give 73 mg (23%) of 10b, mp 244-245 ºC (lit [14] mp 244.5-246 ºC); 1H nmr (dimethyl sulfoxide-d6): δ 11.65-11.30 (br s, 1H, D2O exchangeable), 8.84 (d, J = 4.3 Hz, 1H), 8.42 (d, J = 7.3 Hz, 1H), 7.40 (dd, J = 7.9 Hz, 4.9 Hz, 1H), 6.45 (s, 1H), 2.27 (s, 3H).

Anal. Calcd. for C10H11NO: C, 67.49; H, 5.03; N, 17.49.

7-Methyl-1,6-naphthyridine-5(6H)-one (10b).

A mixture of 272 mg (2 mmol) of 2-methylnicotinamide (9) and 0.34 mL (2.2 mmol) of 95% N,N-dimethylecetamide dimethyl acetal was heated at 50 ºC for 1.5 h, and then a vacuum was applied for 1 h with heating as described for 10a. The oil was diluted with 2 mL of dry N,N-dimethylecetamide, treated with 96 mg of 60% sodium hydride, and heated at 80 ºC for 2.5 h. The solution was treated with 70 mg more of 60% sodium hydride, and then quenched with excess glacial acetic acid. The mixture was concentrated at 25-70 ºC to leave a residual solid that was digested in hot chloroform. The suspension was filtered through a pad of silica gel that was washed with chloroform, and then acetone. Product fractions were concentrated to a solid that was dissolved in a minimum volume of hot water. The solution was stored at 5 ºC for 2 weeks, and the precipitated solids were collected, washed well with 2-propanol, and dried to give 73 mg (23%) of 10b, mp 244-245 ºC (lit [14] mp 244.5-246 ºC); 1H nmr (dimethyl sulfoxide-d6): δ 11.65-11.30 (br s, 1H, D2O exchangeable), 8.84 (d, J = 4.3 Hz, 1H), 8.42 (d, J = 7.3 Hz, 1H), 7.40 (dd, J = 7.9 Hz, 4.9 Hz, 1H), 6.45 (s, 1H), 2.27 (s, 3H).

Anal. Calcd. for C10H11NO: C, 67.49; H, 5.03; N, 17.49.

8-Bromo-1,6-naphthyridine-5(6H)-one (11).

A suspension of 1.46 g (10 mmol) of 1,6-naphthyridine-5(6H)-one (10a), 1.96 g (11 mmol) of N-bromosuccinimide, and 30 mL of 1,2-dichloroethane was stirred at 25 ºC for 3.5 h. The mixture was filtered, the solids were washed successively with small amounts of chloroform, water, and diethyl ether, and then dried to leave 2.0 g of nearly pure product, mp 245-250 ºC. The solids were triturated in 13 mL of hot water, collected, and dried to leave 1.94 g (86%) of 11, mp 247-251 ºC; Rf 0.2 (1:1 ethyl acetate:hexanes); 1H nmr (dimethyl sulfoxide-d6): δ 11.98-11.72 (br s, 1H, D2O exchangeable), 9.03 (d, J = 5.3 Hz, 1H), 8.54 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.61 (dd, J = 8.0 Hz, 4.7 Hz, 1H).

Anal. Calcd. for C10H11BrN2O: C, 42.70; H, 2.24; N, 12.45.

Found: C, 42.80; H, 2.02; N, 12.40.

A suspension of 360 mg of the free base of 11 in methanol was treated with an excess of 2-propanolic hydrogen chloride, heated for 5 min, and stored at 25 ºC for 1.5 h. The solids were collected, washed with 2-propanol, and dried to give 410 mg (99%) of the hydrochloride salt; mp >245 ºC (dec).

Anal. Calcd. for C10H9BrN2O·0.9 HCl: C, 37.26; H, 2.31; N, 10.86; Cl, 12.37. Found: C, 37.19; H, 2.25; N, 10.75; Cl, 12.74.
4-Bromo-1-chloro-1,6-naphthyridine (12a).

A suspension of 450 mg (2 mmol) of 8-bromo-1,6-naphthyridine-5-(6H)-one (11) and 2 mL (21.5 mmol) of phosphorus oxychloride was heated at 100 °C for 28 h. The solution was concentrated to an oil that was diluted with dichloromethane. The resultant solution was added cautiously to cold saturated aqueous potassium bicarbonate. The phases were separated and aqueous layer was further extracted with dichloromethane. The combined organic extracts were washed with water, dried, and concentrated to a solid that was triturated in ethyl acetate. The precipitate was collected and recrystallized from ethyl acetate to provide 150 mg (31%) of 12a in two crops; mp 127-128 °C; 1H nmr (deuteriochloroform): δ 9.26 (d, J = 4.2 Hz, 1H), 8.77 (s, 1H), 8.67 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 7.73 (dd, J = 8.5 Hz, 4.2 Hz, 1H).

Anal. Calcd. for C9H6BrN2O: C, 45.22; H, 2.95; N, 11.72; Br, 33.28. Found: C, 45.28; H, 3.04; N, 11.75; Br, 32.75; Cl, 14.59.

The above reaction was repeated on a 2.75 g (12.2 mmol) scale of 11 to provide 29% (986e) of crude 12a showing one spot by TLC; Rf 0.6 (1:1 ethyl acetate:hexanes). This material was used directly for the synthesis of 12b below.

4-Bromo-1-methoxy-1,6-naphthyridine (12b).

A stirred suspension of 2.91 g (12 mmol) of crude 4-bromo-1-chloro-1,6-naphthyridine (12a) in 50 mL of dry, ice-cold methanol was treated portion-wise with ca. 0.85 g (36 mmol) of sodium metal. The temperature was maintained at 5 °C for 30 min, and then at 25 °C overnight. The mixture was concentrated, diluted with water, and extracted with dichlormethane (3x). The combined extracts were washed with brine, dried, and filtered over a small pad of silica gel, washing the pad with ethyl acetate to strip off the product. Concentration of the filtrate left a solid that was crystallized from 2-propanol to give 2.46 g (86%) of 12b in three crops; mp 97-99 °C; 1H nmr (deuteriochloroform): δ 9.16 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 8.56 (dd, J = 8.3 Hz, 1.6 Hz, 1H), 8.45 (s, 1H), 7.55 (dd, J = 8.3 Hz, 4.4 Hz, 1H), 4.14 (s, 3H).

Anal. Calcd. for C8H10N2O: C, 63.22; H, 6.76; N, 16.70. Found: C, 63.10; H, 7.19; N, 16.70.

1,2,3,4-Tetrahydro-1,6-naphthyridine-5-(6H)-one (13).

A suspension of 400 mg (2.7 mL of 1,6-naphthyridine-5-(6H)-one (10a), 40 g of 20% palladium/carbon, and 10 mL of 50% aqueous methanol was stirred under 1 atmosphere of hydrogen at 25 °C for 3 h. The solids were collected, washed with 2-propanol, and dried to leave 120 mg (29%) of 13, mp >250 °C (dec); Rf 0.2 (9:1 ethyl acetate:methanol). Processing of the mother liquor yielded 165 mg (40%) of a second crop; 1H nmr (dimethyl sulfoxide-d6): δ 6.90 (br, J = 7 Hz, 1H), 6.47 (br s, 1H, D2O exchangeable), 5.56 (d, J = 7 Hz, 1H, 3.12 (t, J = 5 Hz, 2H), 2.31 (t, J = 6 Hz, 2H), 2.78-1.60 (m, 2H).

Anal. Calcd. for C15H11NO: C, 73.42; H, 7.41; N, 16.87. Found: C, 73.50; H, 7.42; N, 16.79.

1,2,3,4-Tetrahydro-1,6-naphthyridine-5-(6H)-one (15).

An ice-cold solution of 11.2 g (38.9 mmol) of 5,6-dihydro-1-methyl-5-oxo-1,6-naphthyridinium iodide (14) in 18.5 mL of 88% formic acid was treated dropwise over a 10 min period with 9.4 mL (93 mmol) of borane-pyridine complex. The bath was maintained at 5 °C, the solids were collected, washed with 2-propanol, and dried to leave 5.19 g (80%) of 15.

Acknowledgment.

Special thanks are extended to Barbara Miller for her assistance in the construction of this manuscript.

REFERENCES AND NOTES

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