Ready Access to 7,8-Dihydro- and 1,2,3,4-Tetrahydro-1,6-Naphthyridine-5(6*H*)-ones from Simple Pyridine Precursors

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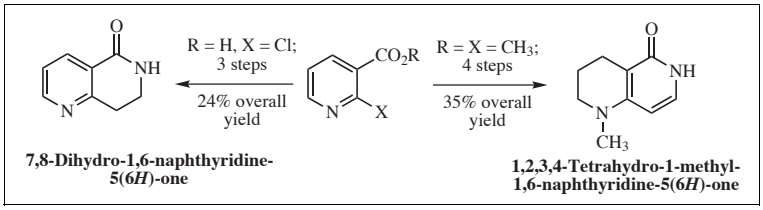

Short pathways are described for the synthesis of a representative example of each of the 7,8-dihydro- and 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6*H*)-one ring systems from simple pyridine precursors. An attempted synthesis of the related 4,6-dihydro-1,6-naphthyridin-5(1*H*)-one ring system from a common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

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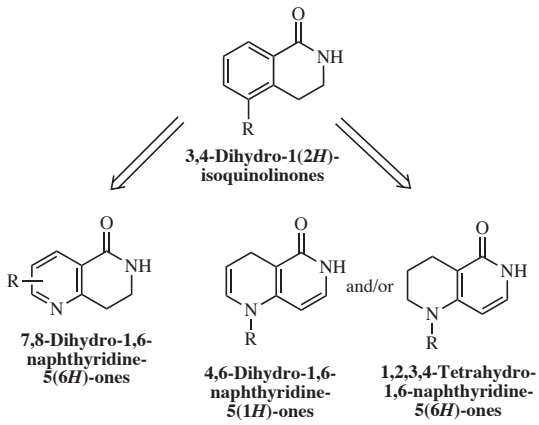
Introduction.

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(2*H*)-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(6*H*)-one ring system. Furthermore, we were interested in extending our studies to the synthesis of the isomeric 4,6-dihydro-1,6-naphthyridin-5(1*H*)-ones, and/or more highly reduced congeners, the 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6*H*)-ones (Chart 1).

Previous reports describing the synthesis of reduced 1,6-naphthyridine-5(6*H*)-ones are relatively sparse. Within the 7,8-dihydro-1,6-naphthyridine-5(6*H*)-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(1*H*)-pyridinone was annulated to the requisite bicyclic system. Neither synthesis is high-yielding nor general for the types of target molecules we

Chart 1



sought. In their synthesis of a number of 4,6,7,8-tetrahydro-1,6-naphthyridin-5(1*H*)-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(6*H*)-one intermediate [5]. Literature procedures describing the synthesis of 1,2,3,4-tetrahydro-1,6-naphthyridine-5(6*H*)-ones [6] and 4,6-dihydro-1,6-naphthyridin-5(1*H*)-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(1*H*)-ones from a common intermediate. A preliminary account of some of this work can be found in the patent literature [8]. This paper

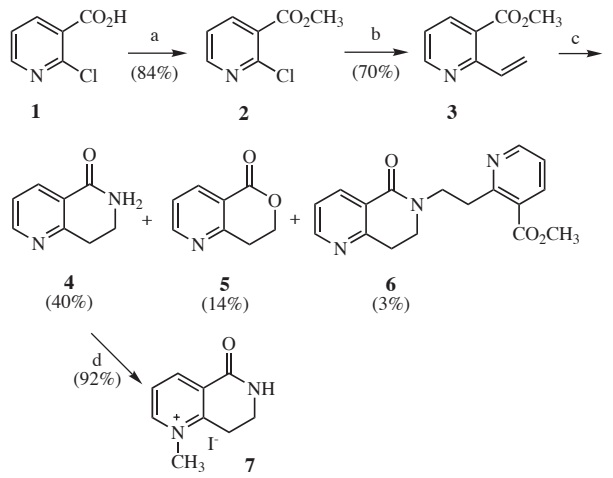
expands on this with complete experimental detail, including some larger scale reactions, and describes additional intermediates and side products not cited previously.

Results and Discussion.

Synthesis of 7,8-Dihydro-1,6-Naphthyridine-5(6*H*)-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(6*H*)-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 alkyne 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 pyridine **3** in 70% yield following

Scheme 1[a]



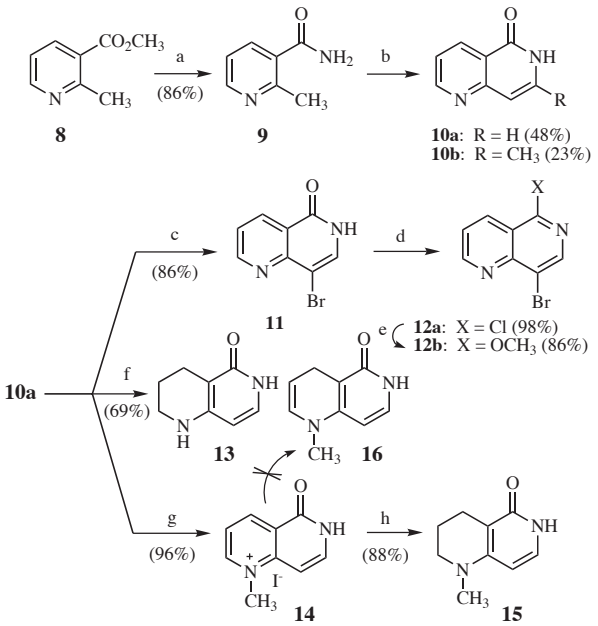
[a](a) dimethyl sulfate, K_2CO_3, acetone, rt, overnight; (b) vinyltributyltin, $(Ph_3P)_2Pd(II)Cl_2$, BHT, DMF, 40-25 ºC, 68 h; (c) excess NH_4Cl, 50% aq HOAc, reflux, 5 h; (d) MeI, DMF, rt, 60 h.

distillation. Compound **3** was somewhat sensitive to decomposition, thus was utilized directly in an annulative cyclization with ammonia to provide desired target **4**. We evaluated a range of solvents for this reaction, including alcohols (neat and aqueous), water, glacial acetic acid, and looked at an unsuccessful reaction with refluxing 1,1,1,3,3,3-hexamethyldisilazane/ammonium sulfate. While alcohols showed some promise, reactions tended to be sluggish and yields were lower than for our optimum conditions, which were found to be refluxing 50% aqueous acetic acid. This provided **4** in 40% yield after chromatography. The reaction also yielded the known lactone **5** [6b] as a prominent side product (14% yield), and **6** as minor by-product (3% yield). The structure of **6** was readily apparent from its electron impact and chemical ionization mass spectra, along with clearly defined peaks in its ^1H and ^{13}C nmr spectra. The ^{13}C nmr spectrum was especially diagnostic with its pattern of 17 well resolved lines. Mechanistically, we believe that the formation of **4** is due to an initial acid-catalyzed aza-Michael addition of ammonia to the C-2 vinyl of **3** to provide intermediate β-aminoethyl adduct, which then closes to bicycle **4**. Such acid-catalyzed additions of amines to vinyl pyridines are well precedented from the work of Cliffe *et al.* [10]. Target compound **4** was then further elaborated to the methylated derivative **7** in high yield under standard conditions.

Synthesis of 1,2,3,4-Tetrahydro-1,6-naphthyridine-5(6*H*)-one Ring System.

Our synthetic pathway to this target ring system begins with commercially available 2-methylnicotinic ester **8** (Scheme 2). Amidation of this was conducted by a more standard procedure to provide known compound **9** [11] in 86% yield. Reaction of **9** with *N*,*N*-dimethylformamide dimethyl acetal was then carried out by a modification of the procedure of Marecki *et al.* [12] to provide known naphthyridinone **10a** [13] in 48% yield. Extension of this procedure provided homologue **10b** [14] in an unoptimized 23% yield. Compound **10a** was then elaborated to several derivatives. Toward synthesizing potential reduced 1,6-naphthyridine-5(6*H*)-ones with additional substituents off the lactam ring, **10a** was brominated with *N*-bromosuccinimide to provide **11** in 86% yield. Phosphorus oxychloride chlorination of **11** proceeded uneventfully to give **12a** in 98% yield, which was further converted to methoxy congener **12b** in 86% yield with sodium methoxide. In an initial attempt to find conditions for a controlled reduction of the pyridine ring to access the targeted 4,6-dihydro-1,6-naphthyridin-5(1*H*)-one ring system (*e.g.*, **16**), we subjected **10a** to mild catalytic hydrogenation conditions. However, this resulted in four-electron reduction of the pyridine ring to give the 1,2,3,4-tetrahydro congener **13** in 69% yield. We then decided to quaternize the N-1 nitrogen of **10a**, which we believed might afford us greater control over generating the 4,6-dihydro reduction products via use of a metal hydride reagent. Prior work [15] showed that nicotinate alkylpyridinium salts would readily reduce to tetrahydro products under catalytic hydrogenation conditions, so these conditions were not pursued. Accordingly, treatment of **10a** with iodomethane gave the

Scheme 2[a]



[a](a) 6M aq KOH, MeOH, 5 ºC, 6 h, then isolate K salt; $(COCl)_2$, benzene, 5 ºC, 19 h, then anhyd NH_3, CH_2Cl_2, 5-15 ºC, 30 min; (b) $Me_2NC(OMe)_2R$, DMF or DMA, 50 ºC, 1.5-2h, then NaH, 80 ºC, 2.5-7 h; H_3O^+; (c) NBS, 1,2-DCE, rt, 3.5 h; (d) $POCl_3$, 100 ºC, 28 h; (e) NaOMe, MeOH, rt, overnight; (f) H_2 (1 atm), 20% Pd/C, 50% aq MeOH, rt, 3h; (g) MeI, DMF, rt, 40 h; (h) BH_3-pyridine, 88% formic acid, rt, 3 d.

alkylnaphthyridinium salt **14** in 96% yield. When we treated **14** under conditions described by Lounasmaa *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(2*H*)-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(6*H*)-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(6*H*)-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(6*H*)-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 (Kiesegel 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 ºC 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 ºC/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-pyridinecarboxylic 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-*t*-butyl-4-methylphenol, and 250 mL of *N*,*N*-dimethylformamide was stirred at 55 ºC 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 ºC for 61 h and concentrated at 60 ºC/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 ºC/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 ºC/0.15 mm to leave 13.6 g (70%) of **3** as a clear oil, >95% pure by GC; ^{1}H nmr (deuteriochloroform): δ 8.70 (dd, *J* = 5.7 Hz, 1.8 Hz, 1H), 8.16 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 7.62 (dd, *J* = 17 Hz, 10.7 Hz, 1H), 7.24 (dd, *J* = 7.9 Hz, 4.5 Hz, 1H), 6.50 (dd, *J* = 17 Hz, 2.2 Hz, 1H), 5.60 (dd, *J* = 10.7 Hz, 2.2 Hz, 1H), 3.93 (s, 3H). The ^{1}H nmr also showed the presence of small amounts of organotin contaminants, however the product was sufficiently pure to use directly in the next step. Ester **3** slowly discolors upon standing at room temperature, thus should be stored under refrigeration.

7,8-Dihydro-1,6-naphthyridin-5(6*H*)-one (**4**).

A mixture of 48.2 g (274 mmol) of 93% pure 2-ethenyl-3-pyridinecarboxylic acid, methyl ester (**3**), 200 g (3.74 mol) of ammonium chloride, and 550 mL of 50% aqueous acetic acid was brought to reflux and maintained there for 5 h. The solution was cooled and concentrated to a residue that was triturated in hot methanol and filtered. The filtrate was again concentrated, and then pumped *in vacuo*/45 ºC/30 min to leave a semi-solid residue that was diluted with methanol. While stirring, the solution was treated cautiously with excess sodium bicarbonate. The mixture was filtered, and the filtrate was concentrated to a solid that was boiled in 9:1 ethyl acetate:methanol. The hot suspension was filtered and the cooled filtrate was loaded onto a 17 cm x 68 cm column of silica gel. The column was eluted with 1.8 L of ethyl acetate followed by 1 L of 9:1 ethyl acetate:methanol and then 1 L of 85:15 ethyl acetate:methanol. The 85:15 ethyl acetate:methanol column fractions were concentrated to a solid residue that was crystallized from ethyl acetate to give **4**, fairly pure by TLC. Later ethyl acetate column fractions containing fairly pure **4** were combined with the 9:1 ethyl acetate:methanol column fractions and concentrated to a residue that was crystallized from 2-propanol to give 12.9 g of **4**, pure by TLC. The mother liquor was concentrated to a residue that was crystallized from ethyl acetate to provide an additional 1.5 g of pure **4**. The subsequent mother liquor was then combined with the initial ethyl acetate column fractions and concentrated to an oil that was dissolved in minimal ethyl acetate and loaded onto a 8 cm x 10 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 **4**, mp 163-166 ºC; R_f 0.17 (9:1 ethyl acetate:methanol); ^{1}H nmr (deuteriochloroform): δ 8.64 (dd, *J* = 4.9 Hz, 1.7 Hz, 1H), 8.33 (dd, *J* = 7.7 Hz, 1.6 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).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.92; H, 5.47; N, 19.19.

7,8-Dihydro-5*H*-pyrano[4,3-*b*]pyridin-5-one (**5**).

Pooling and concentration of the fractions containing pure R_f 0.43 (9:1 ethyl acetate:methanol) material from the ethyl acetate elution of the second silica gel chromatography described above in the synthesis of **4** provided an oil that solidified on standing. The solid was triturated in isopropyl ether, collected, and dried to leave 5.59 g (14%) of side product **5**, mp 90-93 ºC (lit [6b] mp 90-92 ºC); ^{1}H nmr (deuteriochloroform): δ 8.74 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.38 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.8 Hz, 4.9 Hz, 1H), 4.65 (t, *J* = 6.1 Hz, 2H), 3.30 (t, J = 6.1 Hz, 2H). EI ms: *m*/*z* (relative %): 150 (83), 149 (72, M^+), 119 (100), 91 (56).

Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.60; H, 4.65; N, 9.51.

2-[2-(5-Oxo-7,8-dihydro-5*H*-1,6-naphthyridin-6-yl)ethyl]-3-pyridinecarboxylic acid, methyl ester (**6**).

Prolonged storage of the concentrated mother liquor from the crystallization of the 85:15 ethyl acetate:methanol column fractions described above in the synthesis of **4** resulted in the formation of a solid. The solid was crystallized from 2-propanol and then recrystallized from ethyl acetate to afford 2.5 g (3%) of side product **6**, mp 102-103 ºC; ^{1}H nmr (deuteriochloroform): δ 8.63 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.57 (dd, *J* = 4.9 Hz, 1.7 Hz, 1H), 8.28 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 8.20 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 7.35-7.21 (m, 2H), 4.03 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.67 (t, *J* = 6.8 Hz, 2H), 3.55 (t, *J* = 7.2 Hz, 2H). 3.14 (t, *J* = 6.8 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 166.7, 163.3, 160.1, 158.0, 151.9, 151.6, 138.5, 135.8, 125.8, 125.2, 122.3, 121.4, 52.4, 47.2, 45.7, 34.9, 30.9; EI ms: *m*/*z* (relative %): 311 (34, M^+), 164 (50), 161 (100); CI ms: *m*/*z* (relative %): 312 (34, MH^+), 311 (37), 164 (36), 161 (44).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.62; H, 5.58; N, 13.41.

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(6*H*)-one (**4**), 0.2 mL of iodomethane, and 1 mL of anhydrous *N*,*N*-dimethylformamide was stirred at 25 ºC 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; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.11 (d, J = 6.0 Hz, 1H), 8.86 (d, J = 7.8 Hz, 1H), 8.69 (br s, 1H, D_2O exchangeable), 8.13-8.04 (m, 1H), 4.29 (s, 3H), 3.64-3.53 (m, 2H; with D_2O wash collapses to t), 3.40 (t, J = 6.5 Hz, 2H).

Anal. Calcd. for $C_9H_{11}N_2OI$: C, 37.26; H, 3.82; N, 9.66. Found: C, 37.07; H, 3.72; N, 9.34.

2-Methylnicotinamide (**9**).

To an ice-cold solution of 75.6 g (0.5 mol) of methyl 2-methylnicotinate (**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 resultant 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 at 200mm/90 ºC/14 h over potassium pentoxide to leave 88.6 g of the potassium salt, mp >280 ºC.

To a mechanically stirred, ice-cold suspension of the potassium salt in 500 mL of benzene was added dropwise over 45 min 45.8 mL (0.525 mol) of oxalyl chloride (**CAUTION**: vigorous evolution of carbon dioxide). After stirring at 25 ºC for 19 h, the olive-green suspension was filtered over Celite, and the pad was washed well with dichloromethane. The filtrate was concentrated to *ca*. 200 mL and then added as a thin stream over 5 min to an ice-cold solution of 500 mL of dichloromethane saturated with anhydrous ammonia. An additional 150 mL of dichloromethane was utilized to transfer the acid chloride. The cold suspension was saturated with additional ammonia over a 1 h period, the cooling bath was removed, and the mixture was stirred for 30 min more. The suspension was filtered and the collected solids were washed with dichloromethane. The combined filtrates were evaporated to leave additional solids which were collected as above. The solids were combined and dissolved in *ca*.1.3 L of methanol. The solution was treated with 100 g of anhydrous potassium carbonate, and then stirred for 15 min. The suspension was filtered over Celite, the filtrate evaporated to near dryness, diluted with *ca*.600 mL of acetonitrile, and then heated to effect solution. The hot solution was loaded onto a pad of silica gel, and the pad was washed with ethyl acetate:methanol (4:1) until all product had been collected. The filtrate was concentrated to *ca*. 600 mL, the resultant suspension was boiled, and then filtered hot to remove some insolubles. After cooling, the precipitated solids were collected and dried to leave 48 g (71%) of analytically pure **9**, mp 156-159 ºC (lit [11] mp 160-163 ºC). The ^{1}H nmr was identical to that reported earlier [11]. The mother liquor was concentrated to dryness and purified over silica gel as above to give 10.5 g (15%) of additional **9**, mp 151-154 ºC, sufficiently pure for further use.

1,6-Naphthyridine-5(6*H*)-one (**10a**).

A mixture of 27.23 g (0.2 mol) of 2-methylnicotinamide (**9**) and 38.5 mL (0.263 mol) of 90% pure *N*,*N*-dimethylformamide dimethyl acetal 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 hydride (60 % oil 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 ^{1}H nmr was identical to that reported earlier [13].

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.63; H, 4.28; N, 19.13.

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

A mixture of 272 mg (2 mmol) of 2-methylnicotinamide (**9**) and 0.34 mL (2.2 mmol) of 95% *N*,*N*-dimethylacetamide 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*-dimethylacetamide, 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, heated for an additional 4.5 h, and then quenched with excess glacial acetic acid. The mixture was concentrated at 2 - mm/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); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11-65-11.30 (br s, 1H, D_2O 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 $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.55; H, 5.08; N, 17.48.

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

A suspension of 1.46 g (10 mmol) of 1,6-naphthyridine-5(6*H*)-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; R_f 0.2 (1:1 ethyl acetate:hexanes); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.98-11.72 (br s, 1H, D_2O 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 $C_8H_5BrN_2O$: 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 $C_8H_5BrN_2O \cdot 0.9$ 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(6*H*)-one (**11**) and 2 mL (21.5 mmol) of phosphorus oxychloride was heated at 100 ºC 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 ºC; ^{1}H 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 $C_8H_4BrClN_2$: C, 39.46; H, 1.66; N, 11.50; Br, 32.82; Cl, 14.56. Found: C, 39.33; H, 1.30; N, 11.45; Br, 32.75; Cl, 14.59.

The above reaction was repeated on a 2.75 g (12.2 mmol) scale of **11** to provide 2.91 g (98%) of crude **12a** showing one spot by TLC; R_f 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 ºC for 30 min, and then at 25 ºC overnight. The mixture was concentrated, diluted with water, and extracted with dichloromethane (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 ºC; ^{1}H 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 $C_9H_7BrN_2O$: C, 45.22; H, 2.95; N, 11.72; Br, 33.42. Found: C, 45.20; H, 2.85; N, 11.70; Br, 33.28.

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

A suspension of 400 mg (2.7 mmol) of 1,6-naphthyridin-5(6*H*)-one (**10a**), 40 mg of 20% palladium/carbon, and 10 mL of 50% aqueous methanol was stirred under 1 atmosphere of hydrogen at 25 ºC for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated to leave a foam that was boiled in 2-propanol and then cooled. The solids were collected, washed with 2-propanol, and dried to leave 120 mg (29%) of **13**, mp >250 ºC (dec); R_f 0.2 (9:1 ethyl acetate:methanol). Processing of the mother liquor yielded 165 mg (40%) of a second crop; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 6.90 (d, *J* = 7 Hz, 1H), 6.47 (br s, 1H, D_2O exchangeable), 5.56 (d, *J* = 7 Hz, 1H), 3.12 (t, *J* = 5 Hz, 2H), 2.31 (t, *J* = 6 Hz, 2H), 1.78-1.60 (m, 2H).

Anal. Calcd. for $C_8H_{10}N_2O \cdot 0.1\ H_2O$: C, 63.22; H, 6.76; N, 18.43. Found: C, 62.98; H, 6.71; N, 18.44.

Treatment of 270 mg of the free base of **13** with 2-propanolic hydrogen chloride gave 210 mg (63%) of the hydrochloride salt, mp 178-180 ºC; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.50-11.90 (br m, 1.75H, D_2O exchangeable), 8.66 (br s, 0.75H, D_2O exchangeable), 7.49 (d, *J* = 7 Hz, 1H), 6.43 (d, *J* = 7 Hz, 1H), 3.24 (t, *J* = 5 Hz, 2H), 2.54 (t, *J* = 6 Hz, 2H), 1.82-1.66 (m, 2H).

Anal. Calcd. for $C_8H_{10}N_2O \cdot HCl$: C, 51.48; H, 5.94; N, 15.01; Cl^-, 19.00. Found: C, 51.28; H, 6.05; N, 15.13; Cl^-, 19.40.

5,6-Dihydro-1-methyl-5-oxo-1,6-naphthyridinium iodide (**14**).

A suspension of 10.84 g (74.2 mmol) of 1,6-naphthyridin-5(6*H*)-one (**10a**), 25.9 mL of iodomethane, and 593 mL of anhydrous *N*,*N*-dimethylformamide was stirred at 25 ºC for 40 h, and then poured slowly into 185 mL of stirring acetone. The solids were collected, washed with acetone, and dried to leave 19.35 g (91%) of **14** as a yellow solid, mp 249-252 ºC; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.62 (br s, 1H, D_2O exchangeable), 9.32 (d, *J* = 6.0 Hz, 1H), 9.12 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 8.04-7.96 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 4.34 (s, 3H).

Anal. Calcd. for $C_9H_9N_2OI$: C, 37.52; H, 3.15; N, 9.72; I^-, 44.05. Found: C, 37.43; H, 3.04; N, 9.75; I^-, 44.29.

The filtrate was concentrated to leave a residue that was triturated in hot 2-propanol and then recrystallized from methanol to give 1.18 g (5%) of a second crop, mp 242-247 ºC.

1,2,3,4-Tetrahydro-1-methyl-1,6-naphthyridin-5(6*H*)-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 removed and the solution was stirred for 3 d. The formed suspension was concentrated to a residue that was pumped *in vacuo*/50 ºC to leave a semisolid that was dissolved in methanol. The solution was treated with a large excess of Amberlite IRA-400 (OH^-), and the mixture was stirred at 25 ºC for 3 h. The resin was filtered off, and the solution was concentrated to a solid residue that was triturated in hot 2-propanol. After storage at 5 ºC, the solids were collected, washed with 2-propanol, and dried to leave 5.19 g (80%) of **15**, mp 260-261 ºC; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.65 (br s, 1H, D_2O exchangeable), 7.00 (d, *J* = 7.4 Hz, 1H), 5.83 (d, *J* = 7.4 Hz, 1H), 3.16 (t, *J* = 5.5 Hz, 2H), 2.88 (s, 3H), 2.31 (t, *J* = 6.3 Hz, 2H), 1.85-1.72 (m, 2H); ^{1}H nmr (dimethyl sulfoxide-d_6/1 drop trifluoroacetic acid): δ 7.64 (d, *J* = 7.4 Hz, 1H), 6.51 (d, *J* = 7.4 Hz, 1H), 3.44 (t, *J* = 5.6 Hz, 2H), 3.10 (s, 3H), 2.56 (t, *J* = 6.2 Hz, 2H), 1.92-1.80 (m, 2H).

Anal. Calcd. for $C_9H_{12}N_2O \cdot 0.1\ H_2O$: C, 65.12; H, 7.41; N, 16.87. Found: C, 65.10; H, 7.19; N, 16.70.

The filtrate was concentrated to a solid that provided 0.53 g (8%) of additional **15**, mp 260-261 ºC, after two crystallizations.

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