Elaboration of 1,8-Naphthyridine-2,7-Dicarboxaldehyde into Novel 2,7-Dimethylimine Derivatives

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The known 1,8-naphthyridine-2,7-dicarboxaldehyde was prepared by SeO_2 oxidation of 2,7-dimethyl-1,8-naphthyridine. The dimethylated naphthyridine molecule was assembled from an adaptation of the Skraup synthesis using 2-amino-6-methylpyridine and crotonaldehyde to afford a reproducible 37% yield, and constitute a significant advance over the literature of this reaction. The condensation of 1,8-naphthyridine-2,7-dicarboxaldehyde with various primary amines (R = $-C_6H_{11}$, $-CH_2C_6H_5$, $-C(CH_3)_3$, $-C_{10}H_{15}$, and $CH_2CH_2SCH_2CH_3$) in alcohol affords diimines **1(a-e)**. The inherent crystallinity of **1(a-e)** affords pure compounds in reasonable to excellent yields (*ca*. 70%) after evaporation of solvent and recrystallization. The anticipated spectroscopic features of (N=C-H) ^{1}H nmr shift and ν(C=N) in the ir spectrum appear around 8.50 δ and 1640 cm^{-1}, respectively, for the series **1(a-e)**. These novel naphthyridines typically display the signature ^{1}H nmr doublets at *ca*. 8.15-8.30 δ ascribed to the 3 and 4 naphthyridine protons, consistent with a mirror plane (through the quaternary carbons) perpendicular to the naphthyridine plane, and *syn, syn* relationships of the naphthyridine moiety with each imine nitrogen lone pair. Complexation studies of **1(a-e)** with transition metals of biological relevance such as copper(I) and copper(II) will be reported elsewhere.

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Introduction.

Simple 1,8-naphthyridines have been found to form metal complexes in a variety of different binding modes, such as the "linear" [1] type shown below (Figure 1). Linear complexes such as the dicopper(I) and disilver(I) 1,8-naphthyridines have shown relatively short metal-metal distances consistent with metal-metal bonding interactions [1], yet they show little tendency to lose a naphthyridine ligand and "open up" the metals to possible interesting and novel reactivity.

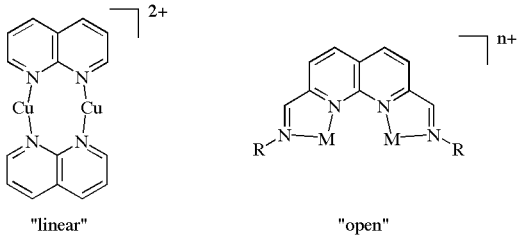

Figure 1. Representations of known and possible types of naphthyridine complex.

We have elaborated and extended the ligating power of the 1,8-naphthyridine system by generating methylimine functionality at the 2 and 7 positions. The resulting novel "diimines" **1** are potentially tetradentate chelating ligands with the power to accommodate two metals in close proximity to each other. In addition, these novel ligands offer variable steric capacity of the R groups on the imine nitrogen. It should be possible therefore to inhibit the formation of dimers, as was observed with the linear complexes cited earlier [1], and prepare "open" novel complexes (Figure 1).

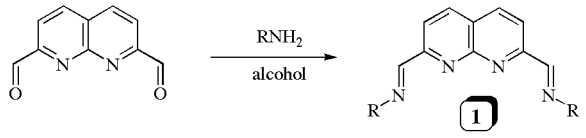

Figure 2. Synthesis of **1** from 1,8-naphthyridine-2,7-dicarboxaldehyde.

As shown in Figure 2, when 1,8-naphthyridine-2,7-dicarboxaldehyde is treated with primary alkyl amines the corresponding novel imines, **1(a-e)** (with R = cyclohexyl, benzyl, *t*-C_4H_9, 1-adamantyl, and thioethylethyl, Figure 3) are obtained in good yields *via* the Schiff base reaction. We prepared 1,8-naphthyridine-2,7-dicarboxaldehyde from 2,7-dimethyl-1,8-naphthyridine in *ca*. 60% yield, following the selenium dioxide protocol of Chandler and co-workers [2]. The dimethyl compound was generated from an adaptation of the Skraup synthesis, adapted by Good and co-workers, which we modified to improve the reported yield to *ca*. 40% [3]. Other syntheses of 2,7-dimethyl-1,8-naphthyridine offering comparable overall yields have also been developed [4,5], although the number of reaction steps, and reaction time, is more than we report here.

Diiminenaphthyridines in general are novel compounds and potentially good ligands, which are likely to confer rigidity, crystallinity, and presumably stability on their complexes. Five commercially available amines with a range of steric and solubility properties were chosen for

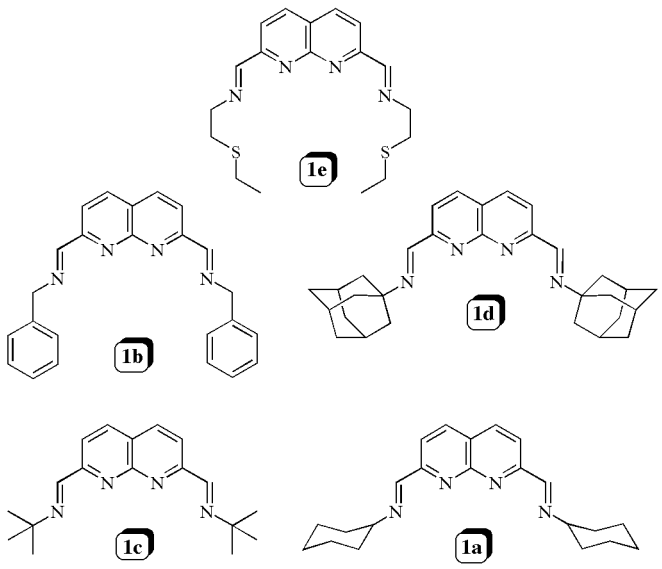

Figure 3. Diiminenaphthyridines **1(a-e)**.

reaction with the dialdehyde (Figure 2), and the series of novel diimines **1a-e** (Figure 3) prepared and isolated as crystalline solids. Complexation studies of **1a-e** will be reported elsewhere.

EXPERIMENTAL

All reagents except benzylamine were purchased from the Aldrich Chemical Company; benzylamine was purchased from the Acros Company. All solvents were reagent grade and were used without further purification. Melting points were recorded using an electrothermal EM-6 apparatus, and were not corrected. Nuclear magnetic resonance spectra were recorded using a Jeol Eclipse 300 MHz spectrometer. Mass spectrometry measurements were recorded using the electron impact (70 eV) technique on a Finnigan Mat GCQ instrument. Infrared spectra of compounds were recorded as potassium bromide pellets or Nujol mulls on a Perkin-Elmer Paragon FTIR spectrometer. Elemental analyses were performed by Desert Analytics of Tucson, Arizona.

Preparation of "Sulfo-mix".

This preparation, presumably that of nitrobenzenesulfonic acid, was adapted from several previous reports [2,3]: in a 1.00 L three-necked flask equipped with a stir bar was charged 30% oleum (230.0 g, 861.6 mmol) and at a steady temperature of 25° was added nitrobenzene (52.6 g, 427.3 mmol) over a 30 minute period. Stirring was maintained at ca. 60° for 2 hours, at which point miscibility with water (and implicit consumption of nitrobenzene) was achieved. This solution was allowed to cool overnight and used in the next step.

2,7-Dimethyl-1,8-naphthyridine.

This compound was prepared through modification of an adaptation of the Skraup synthesis, as applied by Good and co-workers, which utilized the "sulfo-mix" reagent [3]. In a 1.00 L three-necked flask equipped with overhead stirrer, in an ice-water bath, crotonaldehyde (41.60 g; 593.5 mmol) was added dropwise to a stirring solution of 2-amino-6-methylpyridine (18.00 g; 166.4 mmol) in water (75 mL). The water bath was removed and the creamy suspension stirred for *ca*. 3 hours until thin layer chromatography (tlc) on alumina, with chloroform as eluant, showed complete conversion of starting pyridine into a single lower fluorescent spot. The sulfo-mix solution was then added dropwise while maintaining temperature at 25° (water bath), and was accompanied by the appearance of a red solution, which darkened as the addition proceeded. This solution was stirred at 110° for 30 minutes, and then poured hot on to ice (400 g) in a large beaker, and allowed to stand until the ice melted. A substantial amount of crumbly solid was then filtered off, washed with water, and discarded; the pale brown filtrate and washings (*ca*. 1 L) was then stirred in an ice-water bath, and 50% NaOH (aq) carefully added until pH ~ 10. The mixture gradually darkened as base was added, and upon standing in the ice water bath for *ca*. 1 hour an off-white slurry formed. This slurry was suction-filtered using a large Buchner funnel, and the solids washed copiously with water (*ca*. 1 L), and allowed to air dry to yield an ecru product (17.10 g). From this crude compound was sublimed (at 18 mm Hg, 125°) beautiful white needles of product (9.66 g, 37%). Alternatively, the crude compound could be dissolved in hot cyclohexane, filtered, allowed to cool, collected and dried to again give a white crystalline product, in comparable yield; mp 193-195°; ir (potassium bromide): 3002, 1604, 1541, 1507, 1446, 1312, 850, 809, 780 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.72 (s, $-CH_3$, 3H), 7.24 (d, 1H, 3-napH, J = 8.0 Hz), 7.94 (d, 1H, 4-napH, J = 8.0 Hz).

1,8-Naphthyridine-2,7-dicarboxaldehyde.

This compound was prepared with minor modification according to the report of Chandler and co-workers [2]. To a stirring refluxing mixture of selenium dioxide (22.50 g, 202.8 mmol), 1,4-dioxan (750 mL) and 4 Å molecular sieves (5.50g), in 2 L three-necked, round bottom flask was added 2,7-dimethyl-1,8-naphthyridine (10.00 g, 63.2 mmol) *via* funnel. The mixture was heated at reflux for 2 hours, filtered hot, and the filtrate concentrated *in vacuo* to about 500 mL volume. Chloroform (500 mL) was added and the solution extracted with water (3 x 250 mL); the aqueous extracts were then further extracted with chloroform (3 x 250 mL). The combined organic extracts were then washed once with 5% sodium bicarbonate (aq) (500 mL), dried ($MgSO_4$), and the solvent evaporated to yield 7.25 g of tan powdery solid. This solid was redissolved in hot ethyl acetate (500 mL), filtered hot, and allowed to precipitate 6.80 g (59%) of microcrystalline pale brown powder. mp 225-227°; ir (potassium bromide): 2960, 1714 (C=O), 1603, 1540, 1458, 1380, 1291, 876, 813, 774 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.21 (d, 1H, 3-napH, J = 8.0 Hz), 8.85 (d, 1H, 4-napH, J = 8.0 Hz), 10.20 (s, -CHO, 1H).

(*syn, syn*)-2,7-Bis(*N*-cyclohexylmethylimino)-1,8-naphthyridine (**1a**).

In a 250 mL round-bottom flask equipped with a stir bar was charged methanol (50 mL) and 1,8-naphthyridine-2,7-dicarboxaldehyde (2.003 g, 10.76 mmol). To the stirring suspension was added cyclohexylamine (2.666 g, 26.88 mmol), and the ensuing cloudy solution stirred overnight. Next day, the brown solution was filtered to remove reddish insoluble matter, and evaporated

to yield a tan paste that was washed with water (100 mL), filtered, and dried *in vacuo* to yield 3.159 g (84%) of beige powder. Recrystallization was effected from either methanol/water to yield fluffy beige microcrystals, or hot methyl *tert*-butyl ether to yield off-white needles; mp 159-160°; ir (Nujol): 2925, 2854, 1642 (C=N), 1598, 1536, 1505, 1461, 1377, 1150, 1078, 958, 888, 862, 811, 722 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.37-1.84 (m, 11H, -CH_2-cyclohexyl), 8.19 (d, 1H, 3-napH, J = 8.3 Hz), 8.25 (d, 1H, 4-napH, J = 8.3 Hz), 8.59 (s, 1H, N=C-H); ms: (70 eV, electron impact) m/z 348 (molecular ion), 305, 265.

Anal. Calcd. for $C_{22}H_{28}N_4$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.62; H, 8.24; N, 15.86.

(*syn*, *syn*)-2,7-Bis(*N*-benzylmethylimino)-1,8-naphthyridine (**1b**).

In a 250 mL Erlenmeyer flask equipped with a stir bar was charged a suspension of methanol (80 mL) and 1,8-naphthyridine-2,7-dicarboxaldehyde, (3.505 g, 18.8 mmol). A solution of benzylamine (4.096 g, 38.23 mmol) in methanol (10 mL) was introduced in one shot, and within seconds a clear brown solution formed. A crystalline solid precipitated within minutes, and the reaction mixture was allowed to stir over night. Next day, a tan solid was collected by filtration, washed with methanol (20 mL), and air-dried to yield 4.708 g (69%) of product. A portion of this compound was recrystallized by evaporation from acetone to yield white needles; mp 154-155°; ir (potassium bromide): 3085, 3062, 3028, 2924, 2851, 1644 (C=N), 1602, 1580, 1495, 1452, 1378, 1342, 1260, 1218, 1075, 1027, 800, 752 cm^{-1}; ^1H nmr ($CDCl_3$): δ 4.98 (s, 2H, -CH_2-), 7.36 (m, 5H, phenyl), 8.20 (d, 1H, 3-napH, J = 8.4 Hz), 8.32 (d, 1H, 4-napH, J = 8.4 Hz), 8.70 (s, 1H, N=C-H); ms: (70 eV, electron impact) m/z 364 (molecular ion), 287, 273, 244.

Anal. Calcd. for $C_{24}H_{20}N_4$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.30; H, 5.23; N, 16.23.

(*syn*, *syn*)-2,7-Bis(*N*-1,1-dimethylethylmethylimino)-1,8-naphthyridine (**1c**).

In a 1000 mL round-bottom flask equipped with a stir bar was charged methanol (200 mL) and 1,8-naphthyridine-2,7-dicarboxaldehyde, (5.550 g, 29.81 mmol). To the stirring solution was added *tert*-butylamine (6.950 g, 95.03 mmol) and stirring was maintained overnight. Next day, the solution was concentrated to dryness to yield a microcrystalline orange solid (8.60 g). Of this, 1.27 g was dissolved in hot cyclohexane, filtered, and allowed to cool to yield 0.89 g (68%) of white crystals upon filtration and drying. A further 1.27 g of the crude product was heated *in vacuo* to sublime a white powder (0.73 g, 56%) that was dissolved in hot cyclohexane, and allowed to stand to yield beautiful white crystals; mp 227-228°; ir (potassium bromide): 2923, 2854, 1646 (C=N), 1604, 1538, 1506, 1459, 1377, 1339, 1209, 1169, 1108, 958, 906, 866, 816, 774 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.34 (s, 9H, -C_4H_9), 8.18 (d, 1H, 3-napH, J = 8.4 Hz), 8.27 (d, 1H, 4-napH, J = 8.4 Hz), 8.57 (s, 1H, N=C-H); ms: (70 eV, electron impact) m/z 297 (molecular ion + 1), 281, 240, 213, 157.

Anal. Calcd. for $C_{18}H_{24}N_4$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.99; H, 7.96; N, 18.76.

(*syn*, *syn*)-2,7-Bis(*N*-1-adamantylmethylimino)-1,8-naphthyridine (**1d**).

In a 125 mL Erlenmeyer flask equipped with a stir bar was dissolved 1-adamantanamine (0.8124 g, 5.371 mmol) in methanol (40 mL). To the stirring solution was added 1,8-naphthyridine-2,7-dicarboxaldehyde, (0.500 g, 2.686 mmol) to produce a yellow solution from which a copious solid deposited within minutes. After 2 hours the solid was collected by filtration, washed with methanol (10 mL), and dried *in vacuo* to yield off-white microcrystalline solid **1d** (0.892 g, 73%). A portion of this compound was recrystallized from hot acetone to yield cream-colored needles; mp 308-310°; ir (Nujol): 2924, 2854, 1639 (C=N), 1604, 1505, 1458, 1377, 1306, 1138, 1115, 1090, 1033, 984, 862, 816, 724 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.74 (s, 6H, -CH_2), 1.86 (s, 6H, -CH_2), 2.19 (s, 3H, -CH), 8.19 (s, 1H, 3-napH, J = 8.2 Hz), 8.30 (d, 1H, 4-napH, J = 8.2 Hz), 8.57 (s, 1H, N=C-H); ms: (70 eV, electron impact) m/z 452 (molecular ion), 425, 135.

Anal. Calcd. for $C_{30}H_{36}N_4$: C, 79.61; H, 8.01; N, 12.38. Found: C, 79.72; H, 7.79; N, 12.34.

(*syn*, *syn*)-2,7-Bis(*N*-2-ethylthioethylmethylimino)-1,8-naphthyridine (**1e**).

In a 50 mL round-bottom flask equipped with a stir bar was charged methanol (30 mL) and 1,8-naphthyridine-2,7-dicarboxaldehyde, (0.200 g, 1.07 mmol). To the stirring suspension was added 2-(ethylthio)ethylamine hydrochloride (0.380 g, 2.68 mmol) followed by sodium carbonate (0.284 g; 2.68 mmol). The mixture was stirred at room temperature for four hours, then the solvent removed *in vacuo* to yield a solid yellow paste to which was added water (20 mL) to precipitate an ecru solid; this was allowed to air dry to furnish 0.27 g (70%) of compound **1e**. A portion of this solid was recrystallized from acetone to produce large pale-yellow plates; mp 100-102°; ir (potassium bromide) 2990, 2910, 2724, 1647 (C=N), 1603, 1536, 1506, 1468, 1377, 1262, 1016, 976, 924, 866, 814, 761 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.25 (t, 3H, -CH_3), 2.58 (q, 2H, -CH_2S-), 2.91 (t, 2H, S-CH_2-), 3.95 (t, 2H, -CH_2N=), 8.21 (d, 1H, 3-napH), 8.25 (d, 1H, 4-napH), 8.59 (s, 1H, N=C-H); ms: (70 eV, electron impact) m/z 360 (molecular ion), 345, 286, 213, 157.

Anal. Calcd. for $C_{18}H_{24}N_4S_2$: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.36; H, 6.90; N, 15.22.

Results and Discussion.

The synthesis of the 2,7-dimethyl-1,8-naphthyridine "synthon" using sulfo-mix was improved in several useful ways: one was the use of 30% oleum in the preparation of sulfo-mix as opposed to 20%, as cited previously [3]. It is found that miscibility of sulfo-mix with water is reliably achieved within 2 hours with our improvement, whereas the literature method with 20% oleum appeared unpredictable, and could take up to several days. The second improvement simply arose from our order of addition: since the Skraup reaction classically involves conjugate bond formation between aromatic amine and the alkenyl portion of crotonaldehyde, we gave this reaction a chance to occur prior to addition of sulfo-mix. From tlc, we observed the complete conversion of starting 2-amino-6-methylpyridine into a highly fluorescent lower spot within three hours at room temperature. We then added sulfo-mix, which would presumably drive ring closure, subsequent loss of water, and aromatization during heating; the reaction was then quenched over ice, and worked up to produce a crystalline solid after basification from which we could sublime or recrystallize the dimethyl compound in much improved yield. The literature [3] cites addition of crotonaldehyde to an already formed solution of amine and sulfo-mix at 110°; in our hands this method gave a best yield of 15%, whereas our improved method

reliably gave at least 30% of solid, with a work-up which avoided extraction with large volumes of solvents.

As for 1,8-naphthyridine-2,7-dicarboxaldehyde, this was prepared with only minor modification from the literature method [2]. We found that washing the organic extracts with weak base removed a low spot on tlc, which we therefore suspect was a carboxylic acid compound. Furthermore, the use of molecular sieves during the reaction inhibited the formation of a higher spot, so that essentially a tlc-pure compound was produced during the synthesis. Recrystallization from ethyl acetate afforded overall 59% yield.

As anticipated, the Schiff base reaction between the dialdehyde, 1,8-naphthyridine-2,7-dicarboxaldehyde, and primary alkylamines yielded crystalline imines in good yield, typically close to 70%. All imines could be recrystallized without significant loss to yield analytically pure compounds, and all melted sharply and cleanly. To further attest to its stability, **1c** could even be sublimed, although recrystallization gave much better isolated yields. Interestingly, all compounds except **1c** gave mass spectra where the molecular ion peak was strongly manifested. For **1c**, however, there was only a small peak at m/z = 296 corresponding to the molecular ion and this was *ca*. 5% of the base peak which appeared at m/z = 297. Although all the diimines studied here comprise four basic nitrogen atoms, and all might be likely to undergo some decomposition at probe temperatures approaching 250°, it is possible that for **1c** in particular, a combination of its basicity and decomposition at the probe created the necessary conditions to yield its monoprotonated form as the base peak.

The Schiff base reaction for **1(a-e)** was followed by tlc on alumina using chloroform as eluant. Typically, after 5 minutes, tlc showed two closely spaced spots of about equal intensity with R_f in the range 0.7-0.8. On the same tlc plate, the dialdehyde appeared with R_f = 0.5. As time proceeded, tlc showed a gradual diminution of the lower spot, and enhancement of the upper. After 1 hour, typically only the upper spot was apparent. This observation is most likely the result of initial formation of monoimine-monoaldehyde (the lower spot), which eventually converts to the diimine (the upper spot). For example, for **1c**, reaction quench after 5 minutes and workup gave a mixture which in the ^{1}H nmr showed an aldehyde proton peak, and extra doublets in the naphthyridine region, in addition to the known spectrum of the diimine. These observations are consistent with the proposed monoimine-monoaldehyde assignment, where the nmr spectral features can be explained in terms of loss of the mirror plane along the quaternary carbon-quaternary carbon bond (*vide infra*). The strategic isolation of unsymmetrical imines will be the focus of a future endeavor.

Spectroscopy.

Comparison of the IR spectra of 1,8-naphthyridine-2,7-dicarboxaldehyde with **1(a-e)** reveals loss of ν(C=O) formerly at 1714 cm^{-1} and the emergence of a relatively strong new peak around 1640 cm^{-1}, assigned therefore to ν(C=N). Formulating the compounds **1(a-e)** as $R_2N{=}CHR_1CH{=}NR_2$, where R_1 is the naphthyridine moiety, the C=N double bonds afford the potential for geometric isomers: these are (*syn, syn*), (*syn, anti*), and (*anti, anti*) based on the relationship between R_1 and the imine-nitrogen lone pair as being the determining relationship. For steric reasons, for the ligand to accommodate two metals in close proximity to each other, only the (*syn, syn*) scenario will suffice.

The ensuing ^{1}H nmr spectra of all the imines **1(a-e)** display only one sharp singlet for the imine C-H proton in the region 8.50-8.70 δ. Furthermore, the observed two simple doublet pairs of the 3 and 4-naphthyridine protons appear in the range 8.15-8.30 δ. All the spectra are therefore consistent with reflection across a mirror plane containing the quaternary carbon atoms, which is perpendicular to the plane of the naphthyridine itself, and grossly represent either (*syn, syn*) or (*anti, anti*) regiochemistry. Steric consideration of the R groups employed, however, militates against (*anti, anti*) and realistically favors only the desired (*syn, syn*) isomer. The mirror in question would be lost in a (*syn, anti*) arrangement, of course, and we would then expect four distinct doublets for the 3,4,5,6-naphthyridine protons, as well as two distinct singlets for the two respective imine C-H protons. Similar loss of the mirror was observed when the putative monoimine-monoaldehyde compounds were being made (*vide supra*).

For **1e** (Figure 3), the assignment of the three distinct methylene groups is made as follows: the most downfield shifted, the triplet at 3.95 δ, is assigned to the methylene adjoining the imine nitrogen atom. The other two methylenes flanking the thioether sulfur atom are in different environments, of course; the observed quartet at 2.58 δ is therefore assigned to the methylene adjacent to the terminal methyl group, and the observed triplet at 2.91 δ assigned by default to the other methylene of the two-carbon bridge between the sulfur and imine nitrogen.

All imines **1(a-e)** react with excess borohydride ion in alcohol to yield a single low spot on tlc upon quench and extraction into ether. The ^{1}H nmr of crude reaction products in every case shows complete loss of the former imine proton at ca. 8.50 δ, and appearance of a sharp singlet at ca. 4.20 δ, integrating to 2 proton equivalents, as well as a shift upfield to *ca*. 7.50 δ for the 3-naphthyridine signal. Furthermore, ir spectra of all crude products show a new broad and strong absorption at *ca*. 3300 cm^{-1}. These observations together are consistent with collapse of the extended aromaticity of the naphthyridine system that had been conferred by the imine, and conversion into the analogous amines. Purification and further study of these reduced products will also be the subject of a future endeavor.

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