Conformational Studies of N,N-Disubstituted Nicotinamides. NMR Peak Assignments and Utilization of Shift Reagents with 2,6-Dichloronicotinamides[1]

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Europium-induced shift studies are reported for numerous substituted nicotinamides. Without ring substituents, the europium ion interacts with both the pyridine nitrogen and the amide oxygen; however, with 2,6 ring substituents interaction with the amide oxygen is favored. Simple correlations for the induced shifts of the pyridine ring hydrogens are presented and are useful in the conformational analysis of nicotinamides. A combination of variable-temperature nuclear magnetic resonance (VTNMR) studies and europium shift reagents is used to ascertain the preferred conformation in solution of both simple and complex, substituted nicotinamides.

Numerous conformational studies have been conducted on pyridine dinucleotides in order to better understand structural preferences in solution and then to apply these preferences to the design of biomimetic models.[3] In these models, the role of the amide function in the 3-position of the pyridine nucleus has been demonstrated.[4] Structural assignments have been ascertained for numerous N,N-disubstituted amides by rapid, easy, and accurate NMR procedures, such as aromatic solvent-induced[5] and lanthanide[6] shift studies. In view of these reports,[7] peak assignments of N,N-disubstituted nicotinamides have yet to be established, since these NMR procedures when applied to the nicotinamides are not useful due to the aromaticity of the heteroaromatic nucleus and/or the ability of metal ions to coordinate with the pyridine N-electrons.

During the course of our investigation of NADH models, several 2,6-disubstituted nicotinamides were found to interact with europium shift reagents, predominantly with their amide oxygen.[8] This paper deals with the conformational analyses of both simple and complex, substituted nicotinamides by a combination of variable-temperature nuclear magnetic resonance (VTNMR) studies and europium shift reagents.

Results and Discussion

Scheme I shows the europium-induced shifts of the NMR peaks for N,N-disubstituted nicotinamides with 10 mol % of added $Eu(fod)_3$ per amide group. From the magnitude of these shift results for 1, it is clear that the *Eu ion interacts with both the pyridine nitrogen and the amide oxygen*. Thus, utilization of Eu-shift reagents for the NMR peak assignments for other N,N-disubstituted nicotinamides might lead to erroneous conclusions, since the percent of site complexation is unknown. In the case of the 2,6-diethoxy derivative (3) the 6-ethoxy shifts are negligible in relation to those of the 2-ethoxy group, indicative of a predominant europium–amide oxygen rather than a europium–pyridine nitrogen interaction. From comparative shift data, the dominance of amide-oxygen coordination with the shift reagent is realized for the 2,6-diheterosubstituted nicotinamides; pyridine nitrogen interaction is retarded on the basis of the simple steric repulsion caused by these groups[8b,9,10] and the greatly diminished N-electron density.[11]

In every case, the peaks due to the ring hydrogens are shifted to lower magnetic field by the action of added shift reagent. The shift ion–proton distance relationship has been well documented.[12] In this study (1) the 4-pyridine hydrogens are influenced predominantly by Eu coordination to the amide oxygen, (2) the 6-pyridine hydrogens are affected primarily by pyridine nitrogen–shift reagent interaction, and (3) the 2- and 5-position ring hydrogens can be influenced by Eu ion coordination to *either* site. On the basis of these observations, the following correlations for the induced shifts of the 2- and 5-pyridine hydrogens ($\Delta\delta_2$ and $\Delta\delta_5$, respectively) can be derived (eq 1 and 2)

$$\Delta\delta_2 = \Delta\delta_6 + \Delta\delta'_4 \quad (1)$$

$$\Delta\delta_5 = 0.04\delta_4 + 0.3\delta_6 \quad (2)$$

where $\Delta\delta_4$ and $\Delta\delta_6$ are the induced shifts measured for the 4- and 6-pyridine hydrogens, respectively. For 2,6-disubstituted nicotinamides, $\Delta\delta_6$ in eq 2 is zero. The magnitude and sign of $\Delta\delta'_4$ are dependent on the amide oxygen–pyridine nitrogen orientation; $\Delta\delta'_4 \approx \Delta\delta_4$ when the plane of the pyridine ring and the C=O moiety is perpendicular.

For more rigorous discussion, arguments based on the π-electron distribution in the conjugated system must be considered because appreciable pure contact contribution to the resonance shifts is plausible.[12c] The 4-position ring hydrogen can be affected by pyridine nitrogen–shift reagent interaction, and the 6-position ring-hydrogen spin can be affected in part by the distant interaction of the

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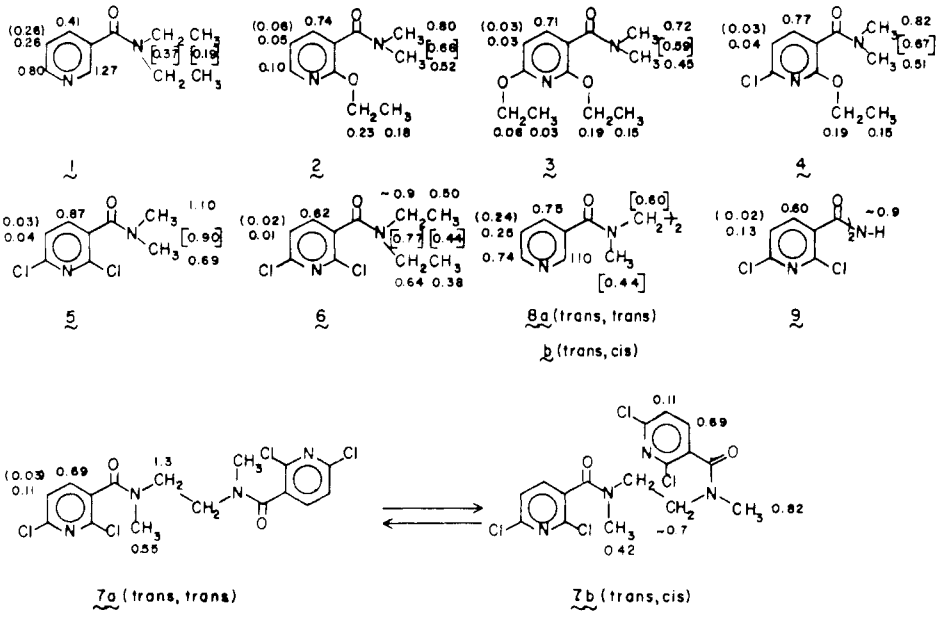
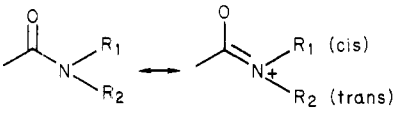
Scheme I. Shifts[a] Induced by Eu(fod)$_3$[b,c] (ppm)



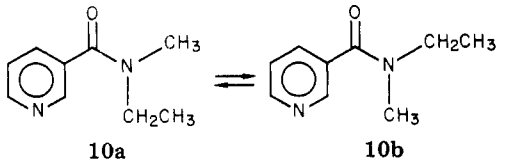
[a] Values in brackets show the mean chemical-shift differences for the cis and trans substituents. [b] Values in parentheses were derived from eq 2. [c] For 1-6 and for 7-9, 10 and 20 mol %, respectively, of Eu(fod)$_3$ was added.

Eu ion with the amide oxygen. Thus, in the ring-amide perpendicular conformation, $\Delta\delta_2$ must be less than $\Delta\delta_6 + \Delta\delta_4$. The Eu ion–pyridine nitrogen interaction is expected to cause a greater shift for the 2-hydrogen (vs. the 6-hydrogen), due to the spin-density localization within the pyridine nucleus. Consideration of spin density within the ring may lead to a slightly better but more complex equation for the ring-proton shifts. Estimation of the exact values of pure contact and pseudocontact shifts in substituted pyridines is still unrealizable. At this stage, eq 1 and 2 are strictly empirical but are straightforward and useful in the conformational analysis of nicotinamides.

Sarma, Moore, and Kaplan reported that *N*-methyl-*N*-ethylnicotinamide (**10**) existed as a mixture of the *cis*- and *trans*-methyl isomers, both being present to an equal ex-



tent.[13] The noncoplanarity of the amide groups and pyridine nucleus was suggested[13] on the basis of the steric hinderence between the ethyl moiety and pyridine nucleus.



10a **10b**

Application of this orientation to *N*,*N*-diethylnicotinamide (**1**) can be used to test the validity of eq 1. The Eu-induced shift for the 2-pyridine hydrogen ($\Delta\delta_2$ = 1.27 ppm) is close to the summation of the chemical shifts of the 6- and 4-pyridine hydrogens ($\Delta\delta_6 + \Delta\delta_4$ = 1.21 ppm), thus suggesting the *near* perpendicularity of the ring and amide groups. The fact that $\Delta\delta_2$ is slightly larger than $\Delta\delta_6 + \Delta\delta_4$ is suggestive of an orientation in which the pyridine nitrogen is *closer* to the carbonyl oxygen than the *N*-ethyl group. Equation 2 can be used with an error of 0.01 ppm,

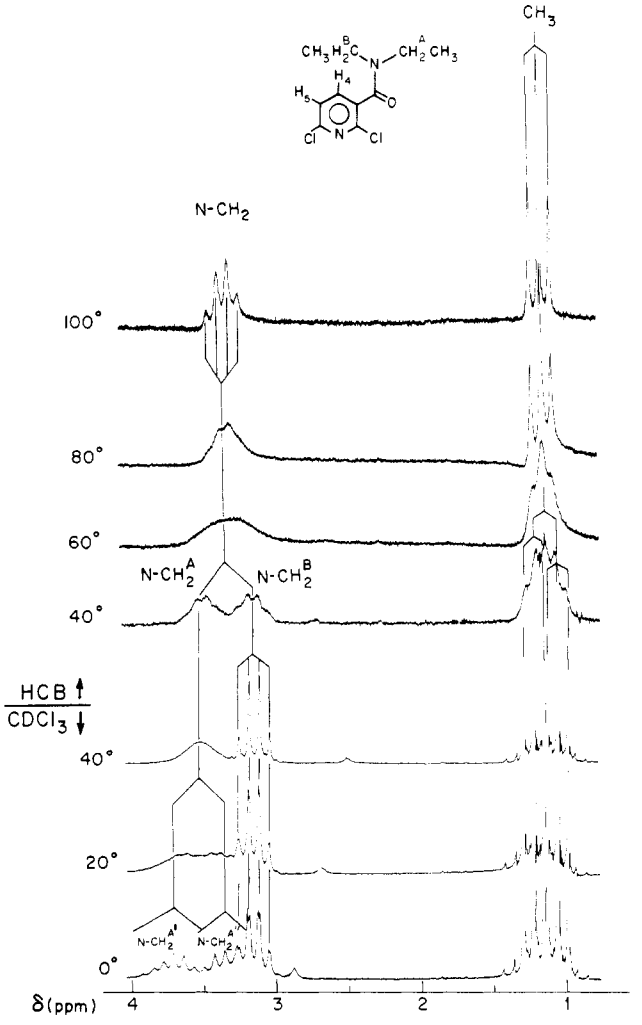


Figure 1. Variable-temperature NMR spectral data for **6** in $CHCl_3$ below 40 °C and in hexachlorobutadiene above 40 °C.

except for **7** and **9** (see later discussion).

The perpendicular conformation of the unsymmetrical ring to the amide carbonyl group causes the magnetic

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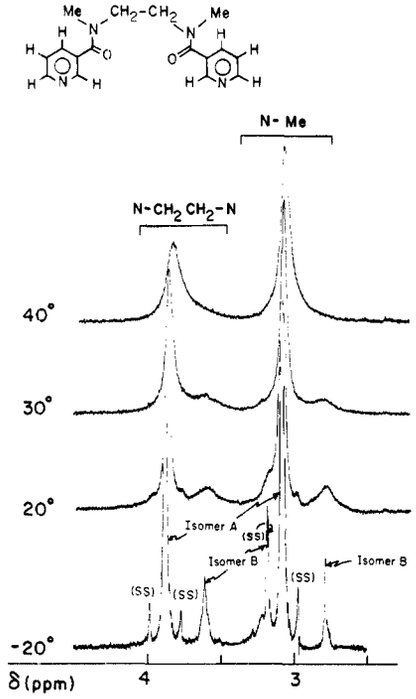
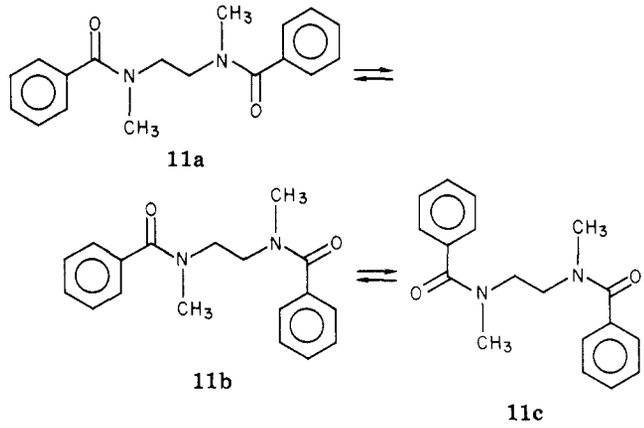


Figure 2. Variable-temperature NMR spectra data for 8 in CD_2Cl_2.

nonequivalence of the geminal hydrogens of methylene groups attached to the amide nitrogen.[14] In such cases, NMR peak assignments for the amide group are important since chemical-shift differences of the geminal protons for these N-substituents are not necessarily identical.[14] For this purpose, 2,6-dichloronicotinamides with Eu shift reagents are useful. Figure 1 shows the VTNMR of **6**. Two distinct ethyl peaks are exhibited at ambient temperature because of restricted C–N amide rotation. The downfield methylene group appears as a broad peak, showing nonequivalence of the geminal protons at 25 °C. From the Eu-induced shift data, the upfield methylene and methyl peaks were assigned to the ethyl group trans to the oxygen. Spin coupling of the ethyl hydrogens was confirmed by decoupling techniques.

The ethyl peaks were transformed into a typical first-order A_2B_3 pattern at temperatures above 373 K. From the coalescence temperature (T_c = 333 K) and the methylene chemical-shift difference ($\Delta\nu$ = 21.3 Hz), the activation energy ($\Delta G^{\ddagger}$) for C–N amide bond rotation was calculated to be 16.99 kcal/mol in hexachlorobutadiene. The nonequivalence of the geminal methylene protons was clearly demonstrated below 273 K. The methylene group whose geminal protons exhibited magnetically larger nonequivalence was assigned to be trans, i.e., farther from the unsymmetrical heteroaromatic ring. This result is similar to that of the NOE study of ortho-substituted *N,N*-dibenzylbenzamides.[14d]

In view of the interest in polymer chemistry, the conformation of *N,N'*-dimethyl-*N,N'*-ethylenebis(benzamide) (**11**) has been investigated.[15] In the crystalline state, **11** was determined by X-ray diffraction to be in the trans,-trans conformation (**11a**);[15c] however, in solution, several



conformational isomers existed. Their indentification and the conformational isomer ratio have not been established. *N,N'*-Dimethyl-*N,N'*-ethylenebis(nicotinamide) (**8**) also exists as a mixture of conformers at low temperatures (Figure 2) as shown from NMR data. The Eu-induced shift study for peak assignments of **8** appeared to be complicated as a result of Eu ion–pyridine nitrogen interaction; thus **6** and **7** were prepared. Amide **7** exhibited three singlets at δ 2.97, 3.03, and 3.25 for the *N*-methyl groups, and the integration ratio of 0.5:5:0.5, respectively, afforded insight into the isomer distribution. From the degree of Eu-induced shift, these peaks were assigned to the *cis*-methyl of **7b**, the *trans*-methyl of **7a**, and the *trans*-methyl of **7b**, respectively (Scheme I). The conformational ratio was subsequently determined to be 83% **7a** and 17% **7b**. This ratio was not altered by the addition of up to 20 mol % of $Eu(fod)_3$.[8,16] The difference between the methyl chemical shifts results from varied degrees of magnetic anisotropy of the pyridine nucleus, which by analogy with **1**, must be approaching orthogonality with the amide group but is not perpendicular to it. This fact affords a rationale why one isomer exists predominantly in solution in difference to **10**.

The C–C restricted rotation of the pyridine–carbonyl and the central ethylene bonds leads to the nonequivalence of the geminal methylene protons as depicted by the broad singlet for the ethylene group. By addition of $Eu(fod)_3$ to **7**, the ethylene peak was separated into two broad peaks due to the trans,trans (**7a**) and trans,cis (**7b**) conformers. With increased temperatures, the singlets at δ 2.54 and 3.10 for **7b** broadened then coalesced to a singlet at δ 2.77, similar to the position exhibited for **7a** in pyridine solution. Simultaneously, the broad absorption for the ethylene group was transformed into a sharp spike. From T_c (330 K) and $\Delta\nu$ (56 Hz) for the methyl peaks, the free energy of activation ($\Delta G^{\ddagger}$) for C–N rotation was calculated to be 16.68 kcal/mol in pyridine.

The methyl peaks for **8** appeared as singlets at δ 2.78, 3.07, and 3.19 at low temperatures in CD_2Cl_2 and were assigned to the *cis*-methyl of **8b**, the *trans*-methyl **8a**, and the *trans*-methyl of **8b**, respectively. The singlets for the methylenic hydrogens at δ 3.61 and 3.87 were assigned to **8b** and **8a**, respectively. From the intensity data, the ratio of **8a** and **8b** was calculated to be 83:17. The free energy of activation ($\Delta G^{\ddagger}$) for C–N amide rotation was shown to be 15.84 kcal/mol on the basis of the T_c (313 K) and $\Delta\nu$ (41 Hz) for the methyl peaks.

Addition of $Eu(fod)_3$ to **8** caused a downfield shift for all hydrogens, but most important is the shift ($\Delta\delta_2$ = 1.10 ppm) for the 2-pyridine hydrogen which is considerably

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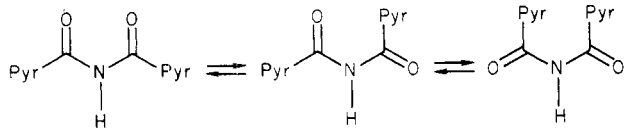
smaller than that predicted (Σ = 1.49) by eq 1. This difference is suggestive of a flattened conformation in which the pyridine nitrogen is further removed from the amide oxygen, e.g., a dihedral angle greater than 90°. This conformation can be one of the contributing reasons why the ratio of conformers is not identical in solution; further, the predominant conformer of **8** is quite different from conformer of **11** in the crystal structure.

Bis[nicotinamide] (**12**) is another model compound in the nicotinamide series and is of current pharmaceutical interest ("anticholesteremic").[17] Three conformational isomers of **12** are possible and are similar to those of the



9a, Pyr = $C_5H_2NCl_2$ **9b** **9c**
12a, Pyr = C_5H_4N **12b** **12c**

β-diketones.[18] In order to elucidate the preferred conformation(s) in **12**, we prepared 2,2′,6,6′-tetrachloronicotinamide **9** which was spectrally shown to possess a doublet at δ 7.42 (J = 8.0 Hz) due to the 5-pyridine hydrogen. The chemical shift of this doublet is almost the same as that of 2,6-dichloronicotinamide (δ 7.40) and thus excludes conformer **9c** in which the pyridine hydrogen must be shifted upfield by the magnetic anisotropy of the adjacent ring. Addition of Eu(fod)$_3$ did not segregate the ring hydrogens, indicating that the two pyridine rings are magnetically equivalent (**9a**) or that a fast equilibrium (**9a** $\rightleftarrows$ **9b**) exists in solution at 300 K. The presence of such an equilibrium for **9** could not be verified because of the low solubility in organic solvents at low temperatures. The larger ($\Delta\delta_5$ = 0.13 ppm) than predicted ($\Delta\delta_5$ = 0.02 ppm) Eu-induced shift for the 5-pyridine hydrogen indicates a small but significant contribution of **9b** to the equilibrium, in which one pyridine ring nucleus approaches the Eu ion on an adjacent amide oxygen.

In summary, the use of Eu shift reagents with 2,6-dichloronicotinamides is useful for accurate assignments of complicated NMR patterns as well as conformational analyses, including orientation of the heteroaromatic nuclei, of diverse nicotinamides. More qualitative and quantitative information can be obtained by application of these techniques to other polyfunctional heterocyclic systems.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded on a Varian Associates A-60A or HA-100 spectrometer. Unless otherwise noted, deuteriochloroform solutions were used with tetramethylsilane as the interal reference (δ 0). For the Eu-induced shift study, approximately 0.15 M solutions of the amide (**9** at 0.04 M) in $CDCl_3$ and 2.38×10^{-4} M solutions of Eu(fod)$_3$[19] in $CDCl_3$ were employed. IR spectra were recorded on a Beckmann IR-7 spectrophotometer. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Materials. *N,N*-Diethylnicotinamide (**1**) was prepared by the reaction of nicotinoyl chloride hydrochloride[20] with excess diethylamine in dichloromethane, distilled in vacuo [bp 118 °C (0.6 mm)], and spectrally compared with known IR and NMR data. *N,N*-Dimethyl-2-ethoxynicotinamide (**2**) [bp 115 °C (1.5 mm)], *N,N*-dimethyl-2,6-diethoxynicotinamide (**3**) [bp 140 °C (1 mm)], *N,N*-dimethyl-6-chloro-2-ethoxynicotinamide (**4**) (mp 65–65.5 °C), *N,N*-dimethyl-2,6-dichloronicotinamide (**5**) (mp 68.5–69 °C), and 2,2′,6,6′-tetrachlorodinicotinamide (**9**) (mp 182–183 °C dec) have been synthesized in our previous work.[9a,21]

***N,N*-Diethyl-2,6-dichloronicotinamide (6).** To an ice-cooled solution of 2,6-dichloronicotinoyl chloride [6.3 g, 0.03 mol; bp 117–118 °C (4.5 mm)][22] in dichloromethane (100 mL) was slowly added a solution of diethylamine (2.19 g, 0.03 mol) in dichloromethane (20 mL), followed by a solution of triethylamine (3.1 g, 0.03 mol) in dichloromethane (20 mL). The mixture was stirred at room temperature for 15 h. After filtration of triethylamine hydrochloride, the solution was washed with aqueous sodium carbonate and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was distilled in vacuo to give amide **6** as a colorless oil: bp 164 °C (0.5 mm); 6.2 g (84%); NMR δ 1.10 (t, CH_2CH_3, J = 7.1 Hz, 3 H), 1.27 (t, CH_2CH_3, J = 7.1 Hz, 3 H), 3.20 (q, CH_2CH_3, J = 7.1 Hz, 2 H), ~3.6 (br m, CH_2CH_3, 2 H), 7.33 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.62 (d, 4-pyr-H, J = 8.0 Hz, 1 H); IR (neat) 1640 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2OCl_2$: C, 48.60; H, 4.89; N, 11.34. Found: C, 48.29; H, 4.94; N, 11.26.

***N,N′*-Dimethyl-*N,N′*-ethylenebis(nicotinamide) (8).** Freshly prepared nicotinoyl chloride hydrochloride was generated from nicotinic acid (10 g, 80 mmol) and excess thionyl chloride. After removal of excess thionyl chloride, the crude acyl halide was dissolved in dichloromethane (150 mL), and *N,N′*-dimethylethylenediamine (2.5 g, 28 mmol) was added, followed by triethylamine (16 g, 160 mmol) in dichloromethane (50 mL) at 0–5 °C. The temperature was brought to 30 °C and the mixture stirred for 30 h. The mixture was washed with aqueous sodium carbonate and dried over anhydrous sodium sulfate. After concentration, the residue was treated with a mixture of dichloromethane–carbon tetrachloride to give the crystalline amide **8**, which was recrystallized from that mixed solvent: mp 140.5–141.5 °C; 4.4 g (52%); NMR δ 3.12 (br s, NMe, 6 H), 3.88 (br s, CH_2, 4 H), 7.31 (dd, 5-pyr-H, J = 8, 5 Hz, 2 H), 7.72 (td, 4-pyr-H, J = 8, 2, 2 Hz, 2 H), 8.66 (m, 6-pyr-H, 2 H), 8.70 (m, 2-pyr-H, 2 H); IR (KBr) 1630 (C=O) cm^{-1}.

Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.10; H, 6.14; N, 18.71.

Nicotinic acid anhydride was also isolated as white needles from this reaction: mp 123–124 °C (lit.[23] mp 123–124 °C); NMR δ 7.46 (dd, 5-pyr-H, J = 8.0, 5.0 Hz, 1 H), 8.43 (td, 4-pyr-H, J = 8.0, 2.4, 1.7 Hz, 1 H), 8.93 (dd, 6-pyr-H, J = 5.0, 1.7 Hz, 1 H), 9.38 (d, 2-pyr-H, J = 2.4 Hz, 1 H); IR (KBr) 1800 (C=O), 1725 (C=O) cm^{-1}.

***N,N′*-Dimethyl-*N,N′*-ethylenebis(2,6-dichloronicotinamide) (7).** The above procedure with 2,6-dichloronicotinoyl chloride (5.5 g, 26 mmol), *N,N′*-dimethylethylenediamine (1.1 g, 12 mmol), and triethylamine (2.7 g, 27 mmol) afforded amide **7**, which was recrystallized from ethanol to give white needles: mp 192–193 °C; 4.3 g (79%); NMR δ 2.79 (s, NMe^A, 0.5 H), 3.03 (s, NMe^B, 5 H), 3.25 (s, NMe^A, 0.5 H), ~3.9 (br s, CH_2CH_2, 4 H), 7.33 (d, 5-pyr-H, J = 8.1 Hz, 1 H), 7.71 (d, 4-pyr-H, J = 8.1 Hz, 1 H); IR (KBr) 1630 (C=O) cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_4O_2Cl_4$: C, 44.06; H, 3.23; N, 12.85. Found: C, 44.01; H, 3.24; N, 12.90.

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Registry No. **1**, 59-26-7; **2**, 70290-50-5; **3**, 70290-48-1; **4**, 70290-49-2; **5**, 70290-47-0; **6**, 72301-61-2; **7**, 72301-62-3; **8**, 72301-63-4; **9**, 70445-62-4; nicotinoyl chloride, hydrochloride, 20260-53-1; diethylamine, 109-89-7; 2,6-dichloronicotinoyl chloride, 58584-83-1; *N,N′*-dimethylethylenediamine, 110-70-3; nicotinic acid anhydride, 16837-38-0.

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