which was identical with a known sample (NMR δ 3.68 (s, CH_2CH_2O, 20 H), ~3.3 (bs, 2 H). Two minor slow moving fractions were shown to possess a cyano stretching frequency. **Fraction A**: NMR δ 4.3 (bm, CH_2), 3.68 (s, CH_2), ~2.5 (bs, OH or NH), 2.48 (s, CH_2); IR 2200 (C≡N), 1710 (b, C=O), 1640 (b, C=O), 1590 (C=C). **Fraction B**: NMR δ ~4.6 (bs, CH_2), ~3.7 (bm, CH_2), 3.68 (s, CH_2), ~2.0 (bs, OH or NH); IR 2200 (C≡N), 1730 (b, C=O), 1640 (b, C=O), 1585 (C=C). Attempted purification was unsuccessful and due to the limited amount and apparent instability of material further analysis was not considered.

Reduction of 9b with Lithium Aluminum Hydride. To a stirred solution of **9b** (150 mg, 0.44 mmol) in dry tetrahydrofuran (30 mL) was added lithium aluminum hydride (20 mg, 0.53 mmol) at 25 °C under nitrogen. The reaction conditions and workup were similar to those of the above reaction. A trace of 3-(aminomethyl)pyridine macrocycle **13** (7.6 mg, 5%) was identified (NMR δ ~3.0 (b, CH_2, 2 H), 3.56 (s, ϵ-CH_2, 4 H), 3.68 (b, γ- and δ-CH_2, 8 H), 3.90 (t, β-CH_2, J = 5 Hz, 4 H), 4.55 (t, 6-α-CH_2, J = 5 Hz, 2 H), 4.64 (t, 2-α-CH_2, J = 5 Hz, 2 H), 6.32 (d, 5-pyr-H, J = 8 Hz, 1 H), 7.45 (d, 4-pyr-H, J = 8 Hz, 1 H)) and compared with related macrocyclic nicotinamides.[7]

The major product was suggested to be nitrile **14**, isolated as an unstable oil: NMR δ ~4.3 (bm, CH_2), 3.68 (s, OCH_2), 2.9 (m, CH_2), 2.3 (m, CH_2), 1.7 (m, CH_2); IR 2190 (C≡N), 1595 (C=C), 1535 (C=C, C=N), 1460 (CH_2), 1300 (CO), 1100 (b, CO) cm^{-1}. Under hydrolytic conditions, nitrile **14** underwent decomposition to afford pentaethylene glycol along with other products similar to those of the above reaction.

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Registry No. **6**, 62068-78-4; **7**, 70445-62-4; **8**, 40381-90-6; **9a**, 70445-63-5; **9b**, 70445-64-6; **9c**, 70445-65-7; **10a**, 70445-66-8; **10b**, 70445-67-9; **13**, 70445-68-0; **14**, 70445-69-1; **15**, 4792-15-8; 2,6-dichloronicotinoyl chloride, 58584-83-1.

Nicotinic Acid Crown Ethers.[1] Synthesis and Reactions of 2,6-Disubstituted *N,N*-Dimethylnicotinamides

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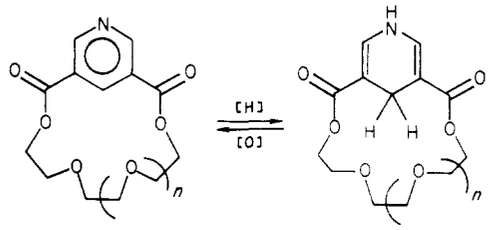
N,N-Dimethyl-2,6-dichloronicotinamide (**3**), prepared from the corresponding disubstituted nicotinic acid, was converted into macrocyclic nicotinamides **10**. Amide **3** was also subjected to sodium ethoxide in hot xylene to afford initially *N,N*-dimethyl-2-ethoxy-6-chloronicotinamide, which was proven by NMR spectral data and chemical degradation. Reduction of **10** with "Vitride" afforded exclusively the corresponding amine **11** in high yield. Enhanced protonation and metal ion coordination to the amide oxygen have been shown by NMR. Without the carboxamide function, $Eu(fod)_3$ complexed predominantly with the central ethereal oxygens as suggested by the dramatic chemical shift of the ϵ-methylene groups. Crown ether fragmentation has been demonstrated to give open-chain pyridones, e.g., **16**, when **15** was treated with either *tert*-butyllithium or, to a lesser extent, reducing agents under rigorous conditions.

Since the initial discovery of coenzyme β-nicotinamide adenine dinucleotide (NAD) in 1904 by Harden and Young,[3] substantial effort has been conducted on the mechanistic and stereochemical aspects of hydrogen transfer.[4] Mimesis of the stereospecific reduction with NAD dehydrogenases has been a direction of numerous organic research efforts.[5] Recently, even the inclusion of a Hantzsch 1,4-dihydropyridine fragment into a crown ether (**1**) was completed and this moiety was shown to mimic reactions of NAD(H).[6] We herein report our initial



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studies on the synthesis and chemistry of simple 2,6-disubstituted *N,N*-dimethylnicotinamides as well as the related 2,6-nicotinamide crown ethers in an attempt to more closely model NAD.

Results and Discussion

The pivotal starting material for the construction of our pyridine-linked nucleotide models was *N,N*-dimethyl-2,6-dichloronicotinamide (**3**), which was prepared by

(1) Part 43 of the series "Chemistry of Heterocyclic Compounds". Presented in part at the 175th National Meeting of the American Chemical Society, Miami, Fla., September 1978.

(2) (a) On leave from Kyushu University, Fukuoka, Japan (1977–1979); (b) On leave from Sambalpur University, Sambalpur (Orissa), India (1975–1977).

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(4) C. Carruthers, *J. Tech. Arch. Biochem. Biophys.*, **56**, 441 (1955); A. L. Lehninger, *J. Biol. Chem.*, **190**, 345 (1951); F. H. Westheimer, H. F. Fisher, E. E. Conn, and B. Vennesland, *J. Am. Chem. Soc.*, **73**, 2403 (1951); H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964); W. Hanstein and K. Wallenfels, *ibid.*, **23**, 585 (1967).

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(6) T. J. van Bergen and R. M. Kellogg, *J. Am. Chem. Soc.*, **99**, 3882 (1977); *J. Chem. Soc., Chem. Commun.*, 964 (1976); O. Piepers and R. M. Kellogg, *ibid.*, 383 (1978); D. M. Hedstrand, W. H. Kruizina, and R. M. Kellogg, *Tetrahedron Lett.*, 1255 (1978); R. H. v. d. Veen, R. M. Kellogg, A. Vos, and T. J. v. Bergen, *J. Chem. Soc., Chem. Commun.*, 923 (1978). Also see: L. E. Overman, *J. Org. Chem.*, **37**, 4214 (1972); D. C. Dittmer and B. B. Blinder, *ibid.*, **38**, 2873 (1973).

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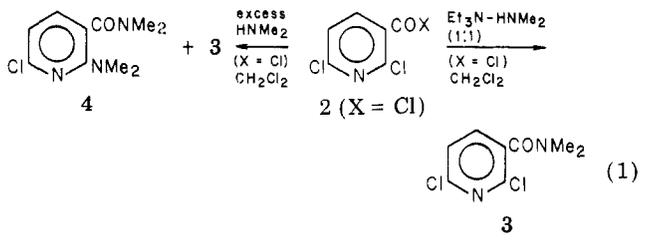
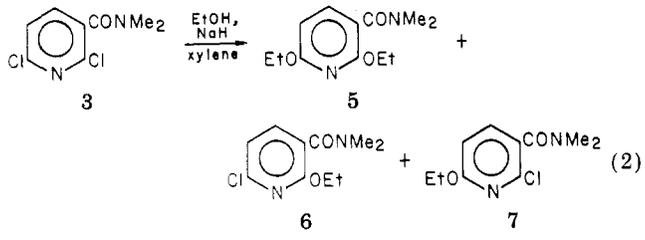
careful treatment of **2** with an equimolar quantity of dimethylamine hydrochloride in dichloromethane in the presence of excess triethylamine at 0–20 °C. The acyl chloride **2** was synthesized from 2,6-dichloronicotinic acid by an established procedure.[7] When **2** was subjected to either excess dimethylamine in diethyl ether or benzene and/or elevated temperatures with greater than 1 equiv of dimethylamine, a mixture of **3** and **4** resulted (eq 1).



4 **2** (X = Cl) **3** (1)

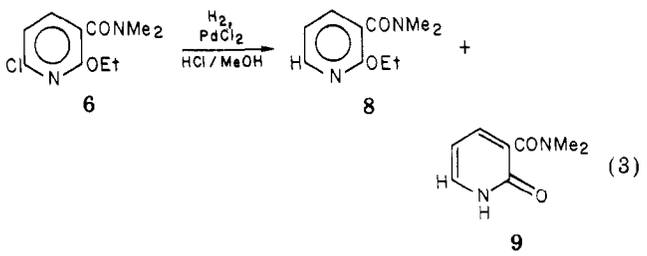
Moreover with commercial chloroform as solvent, sufficient stabilizer (ethanol) was present to give rise to the corresponding ethyl ester (**2**, X = OCH_2CH_3)[7] under the reaction conditions. An alternate amide synthesis was attempted, in which an equimolar mixture of **2** and *N,N*-dimethylformamide in dry toluene was refluxed for several hours; only starting material (**2**) was recovered, even though numerous related dimethyl amides have been prepared by this procedure.[8]

In order to ascertain the preferred site for nucleophilic attack on the pyridine nucleus as well as to establish the best reaction conditions for macrocycle formation, we subjected **3** to sodium ethoxide under widely varied conditions. Treatment of **3** with 2.2 equiv of sodium ethoxide at 135 °C (in refluxing xylene) afforded the disubstituted **5** in 60% isolated yield as well as **6** (27%) (see eq 2). Under less drastic reaction conditions, e.g.,



3 **5** **6** **7** (2)

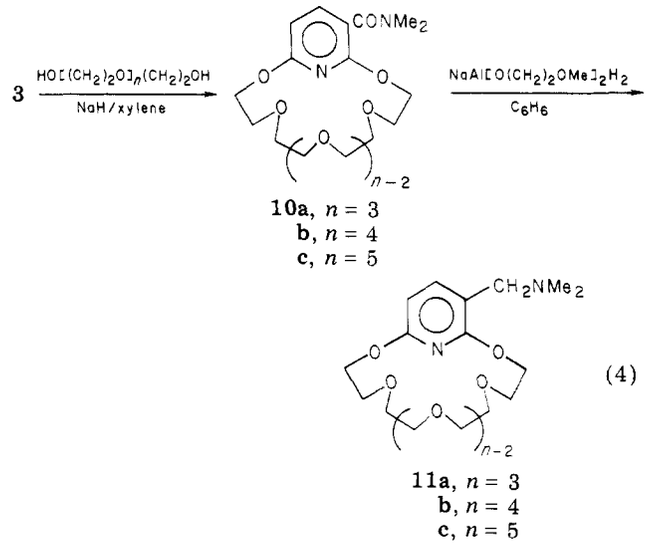
refluxing toluene, the percentage of **6** increased, whereas the treatment of **3** with 1 equiv of ethoxide ion afforded the 2-ethoxy isomer **6** in >95% yield along with traces of **7**.[9] On the other hand, the use of a large excess (more than 4 equiv) of sodium ethoxide in this reaction at 140 °C gave **5**, exclusively. The structure of the monosubstituted product, **6**, was ascertained by the H-5 proton upfield shift relative to starting material ($\Delta\delta_3^{H\text{-}5} - \delta_6^{H\text{-}5} = 0.42$); however with **5**, a dramatic upfield shift ($\Delta\delta_3^{H\text{-}5} - \delta_5^{H\text{-}5} = 1.05$) was observed. Further substantiation was obtained by dehalogenation of **6** by treatment with palladium chloride in methanolic hydrochloric acid[10] to give **8** (see eq 3), which exhibits the characteristic multiplet at δ 8.18 for an H-6 proton. The related pyridone **9** was also isolated from this reaction. Treatment of **3** with 1 equiv of dimethylamine similarly afforded predominantly **4**, whose structure was



6 **8** **9** (3)

correlated with known disubstituted pyridines.[11] Thus from these preliminary results, *the preferred site for nucleophilic displacement is the 2 position.* The rationale for this preferential displacement of the "middle" substituent will be considered in theoretical detail elsewhere.[12]

In view of the above results, macrocycle **10b** was prepared in 32% isolated yield by treatment of **3** with pentaethylene glycolate in refluxing xylene for 24 h (eq 4).



10a, $n = 3$
b, $n = 4$
c, $n = 5$

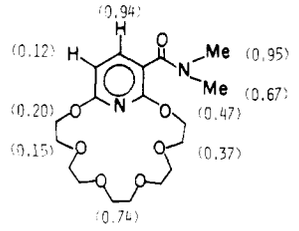
11a, $n = 3$ (4)
b, $n = 4$
c, $n = 5$

The 1:1 macrocycles **10a,c** were prepared in a parallel manner in 20 and 17% yield, respectively. Along with the anticipated uncyclized intermediates,[13] an isomeric 2:2 macrocycle mixture could be separated in low yield; none of these compounds were characterized further. Since polyethylene glycols slowly but easily undergo thermal fragmentation and/or oligomerization in basic media at 140 °C,[14] traces of the oligomeric macrocycles could also be detected.

Attempted 1,4 reduction of these nicotinamide macrocycles **10** with sodium dithionate, sodium hydride, sodium borohydride, or L-Selectride gave only starting material in near-quantitative recovery. With sodium bis(2-methoxyethoxy)aluminum hydride ("Virtride"), **10** was reduced to give exclusively the corresponding amine macrocycle **11**.

The absence of the amide carbonyl absorption in the IR spectrum of **11** coupled with the appearance of two singlets for the methylene group (δ 3.28–3.37) and the *N*-methyls (δ 2.15–2.23) is consistent with this transformation. Under the same reduction procedure with Vitride, the noncyclic **5** gave the corresponding amine **12** as well as aldehyde **13**

(7) F. Mutterer and C. D. Weis, *Helv. Chim. Acta*, **59**, 222 (1976).
(8) G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954).
(9) *N,N*-Dimethyl-2-chloro-6-ethoxynicotinamide (**7**) could not be completely purified by repetitive recrystallization and/or chromatography; however, it could be confirmed by NMR spectral data, which are consistent with assigned structure: NMR δ 1.36 (t, CH_2CH_3, J = 7.2 Hz, 3 H), 2.92 (s, NMe^A, 3 H), 3.10 (s, NMe^B, 3 H), 4.39 (q, CH_2CH_3, J = 7.2 Hz, 2 H), 6.68 (d, 5-pyr-H, J = 8.2 Hz, 1 H), 7.52 (d, 4-pyr-H, J = 8.2 Hz, 1 H).
(10) J. R. Stevens, R. H. Beutel, and E. Chamberlin, *J. Am. Chem. Soc.*, **64**, 1093 (1942).
(11) V. Majestic, LSU, unpublished results.
(12) G. R. Newkome and T. Kawato, unpublished data.
(13) G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khoshboo, and J. Broussard-Simpson, *J. Org. Chem.*, **42**, 1500 (1977); G. R. Newkome, G. L. McClure, J. Broussard-Simpson, and F. Danesh-Khoshboo, *J. Am. Chem. Soc.*, **97**, 3232 (1975).
(14) E. Stande and F. Patat in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967, pp 46–49; R. E. Lubowicz and R. P. Reich, *Chem. Eng. Prog.*, **67**, 59 (1971).



10b

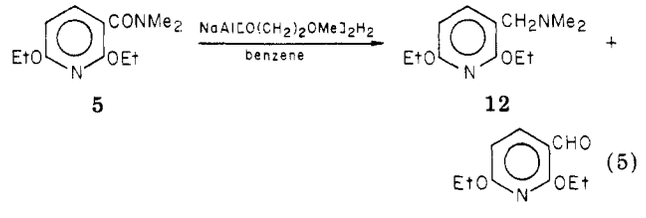
Figure 1. Shifts (parts per million) induced by 20 mol % $Eu(fod)_3$.

Table I. Free Energies of Activation for Restricted Rotation around the C-N Bond

compd	solvent	T_c, K	$\Delta\nu$, H	$\Delta G^{\ddagger}$, kcal/mol
10a	$CDCl_3$	327	12.0	17.04
10b	$CDCl_3$	330	11.7	17.22
10c	$CDCl_3$	329	12.5	17.13
5	$CDCl_3$	328	12.0	17.10
3-pyrCONMe$_2$	$CDCl_3$[a]	301	10.0	15.75

[a] H.-J. Sattler and W. Schunack, *Chem. Ber.*, **108**, 730 (1975).

in a 4:1 ratio as determined by NMR integration of the 4-pyridyl hydrogens ($\delta_{13}^{H\text{-}4}$ = 8.04, $\delta_{12}^{H\text{-}4}$ = 7.47) (eq 5).



5 12 13 (5)

Enhanced coordination of the metal ion(s) with the oxygen of the amide group, thus affording a rationale for the greater susceptibility of the amide group to nucleophilic attack, can be demonstrated by utilization of $Eu(fod)_3$ shift reagent. Even though **10b** has multiple sites for metal ion coordination, at low shift reagent concentrations, the carbonyl oxygen is the preferred site of complexation. Figure 1 shows the greater shift induced by $Eu(fod)_3$, for H-4, α-CH_2, and *one* *N*-Me group, in relation to the other hydrogens. The strongly polarized character of the amide group can be further demonstrated by the presence of diastereotopic *N*-methyl groups. Rotational barriers around the C–N bond of these macrocyclic amides have been ascertained by VT NMR studies. Table I shows the free energies of activation ($\Delta G^{\ddagger}$) of the diastereotopic *N*-methyl signals of these macrocycles which can be easily compared to those of known related 2,6-disubstituted nicotinamides.[15] By addition of traces of HCl gas, the two singlets for the *E* and *Z* amide methyl groups of **10** were transformed to a sharp spike even below 300 K; the shifts of the pyridine peaks were negligible. These results are consistent with the view that the amide C–N rotational barriers were lowered by the oxygen protonation effect;[15] thus, even the protonation of these substituted macrocycles occurred predominantly at the amide oxygen at low proton concentrations. The magnitude of the C–N rotational barriers of these macrocycles is indicative of enhanced C–N amide double-bond character and an orthogonality of the amide group to the pyridine nucleus caused by the steric interaction of the 2-oxygen atom.

(15) G. R. Newkome and T. Kawato, *Tetrahedron Lett.*, 4639 (1978).

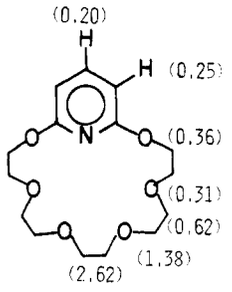


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Figure 2. Shifts (parts per million) induced by 20 mol % $Eu(fod)_3$.

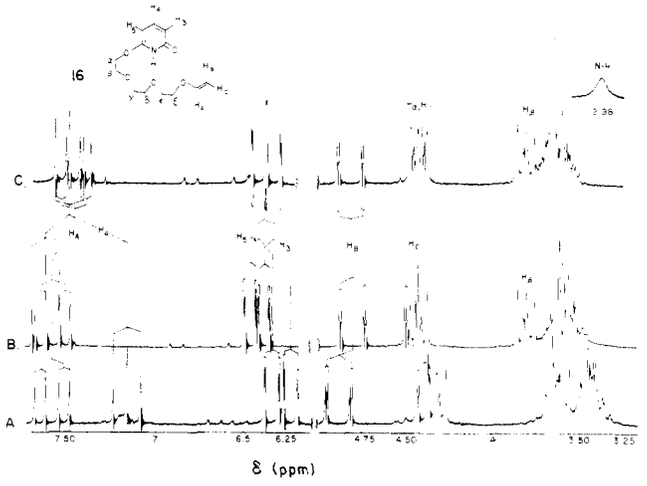
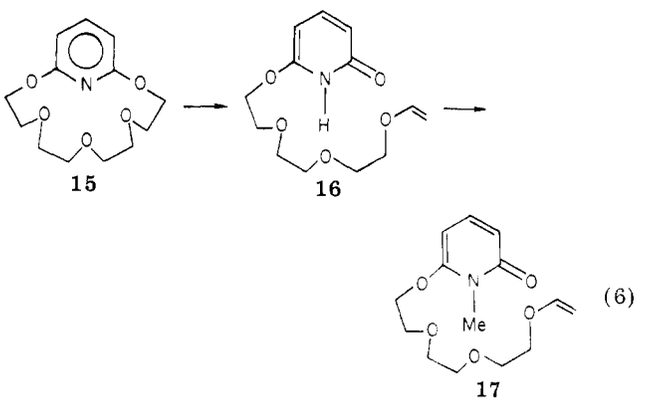


Figure 3. NMR spectra of pyridone **16**: (A) $CDCl_3$; (B) 5% C_6D_6 in $CDCl_3$; (C) 20% C_6D_6 in $CDCl_3$.

Without the carboxamide group as in **14**, the shift reagent at low concentrations appears to be coordinated preferentially with the bridge ethereal oxygens—generally centered and external to the ring cavity. If $Eu(fod)_3$ were equally distant from the ethereal groups, the observed shift would be approximately equal for the equidistant methylene groups; however, the observed shift is greatest (Figure 2) for the ϵ-methylene groups and diminishes proportionally with distance from the central part of the bridge. Coordination of the shift reagent with the central bridging ethereal atoms of **10b** also occurs but to a lesser extent, as demonstrated by the minor enhanced shift for the central methylene hydrogens.

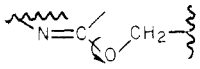
With a smaller cation, e.g., Li, which can form an inner-cavity complex with **15**, ring-cleavage reactions can be demonstrated (eq 6). Treatment of **15** with strong nucleophiles such as *tert*-butyllithium caused facile cleavage of the ethereal ring by β elimination; the vinyl pyridone **16** was isolated in >20% yield along with unchanged



(6)

starting material, **15**. The structure of **16** was confirmed by NMR data with different solvents (Figure 3). Subsequent treatment of **16** with sodium ethoxide followed by methyl iodide in DMF gave the expected *N*-methyl pyridone **17**. Numerous reducing agents under diverse reaction conditions failed to reduce **15** to the desired 1,4-dihydro species; however, under drastic reaction conditions, **15** was cleaved as above in low yield to **16**. Thus, some substituent(s) except for amide groups at the 3 (or 5) position(s) was deemed necessary for 1,4 reduction.

The exclusive reduction of the amide group in macrocycles **10b** rather than 1,2 or 1,4 ring reduction is indicative of little or no positive character generated on the pyridine nitrogen atom via metal ion chelation prior to hydride attack. Recently, by X-ray analysis[16] and MO calculations,[17] insight into the molecular geometry of the juxtapositioned groups has been ascertained for closely related 2,6-disubstituted aza aromatic compounds which possess at least one OCH_2R group. These data indicate a near-zero (±10°) dihedral angle for the α- and/or α′-methylene group(s):



thus, direct N–metal ion complexation will be greatly hindered in such macrocyclic systems.

Studies are currently underway to quantitatively evaluate and subsequently circumvent this structural handicap.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt melting point apparatus and are uncorrected. The NMR spectra were recorded on either a Varian Associates A-60A or HA-100 spectrometer with tetramethylsilane as an internal standard ($\delta = 0$). For the Eu-induced shift study, a ~0.15 M solution of compounds in $CDCl_3$ and a 0.238 M solution of $Eu(fod)_3$[18] in $CDCl_3$ were employed. Chemical shifts were recorded before and after the microaddition (1–20 mol %) of the standardized $Eu(fod)_3$ solution to the compound in an NMR tube. Mass spectral (MS) data were obtained on a Hitachi Perkin-Elmer RMS-4 spectrometer. Infrared (IR) spectra were recorded on a Beckman IR-7 spectrophotometer. The recorded R_f values were determined by a standardized thin-layer chromatography (TLC) procedure: 0.25-mm Brinkmann silica gel 60 HF-254-366 plates eluting with ethyl acetate, unless otherwise stated. For preparative-thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Sodium hydride (50% oil dispersion) was first washed with dry petroleum ether (bp 30–60 °C) and then dried under nitrogen prior to use.

***N,N*-Dimethyl-2,6-dichloronicotinamide (3).** Into an ice-cooled mixture of 2,6-dichloronicotinoyl chloride [**2**: 8.5 g (0.04 mol); bp 117–118 °C (4.5 mm) (lit.[7] bp 72–74 °C (0.01 mm)); mp 28–28.5 °C] and dimethylamine hydrochloride (3.2 g, 0.04 mol) in dichloromethane (200 mL), triethylamine (8 g) was added dropwise at 0 °C and the mixture was allowed to warm slowly to room temperature. After 12 h of stirring, the reaction mixture was filtered. The filtrate was washed with aqueous sodium carbonate solution (20 mL) and then water and dried over anhydrous sodium sulfate. After removal of the solvent, 8.4 g (95%) of amide **3** was obtained; recrystallization from aqueous ethanol afforded colorless crystals as an analytical sample: mp 68.5–69 °C; NMR δ 2.91 (s, NMe^A, 3 H), 3.13 (s, NMe^B, 3 H), 7.34 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.64 (d, 4-pyr-H, J = 8.0 Hz, 1 H); IR (KBr) 1635 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_8N_2OCl_2$: C, 43.86; H, 3.68; N, 12.79. Found: C, 43.67; H, 3.69; N, 12.63.

***N,N*-Dimethyl-6-chloro-2-(dimethylamino)nicotinamide (4).** A solution of 2,6-dichloronicotinoyl chloride (1.05 g, 5 mmol) in diethyl ether (50 mL) was cooled to 0–5 °C and gaseous dimethylamine, generated from the corresponding hydrochloride (2 g) upon treatment with aqueous base, was slowly bubbled with a nitrogen stream into the mixture while the temperature was maintained *below* 5 °C with stirring. After addition, the temperature was raised slowly to 30 °C. After removal of the amine hydrochloride, the mixture was washed with aqueous sodium carbonate, dried over anhydrous sodium sulfate, and concentrated in vacuo to give a viscous oil, which was chromatographed (ThLC), eluting five times with ethyl acetate, to afford two major fractions.

Fraction A gave *N,N*-dimethyl-2,6-dichloronicotinamide (**3**): 200 mg (18%); R_f 0.44.

Fraction B yielded the amino amide **4**: bp 139–140 °C (1.1 mm); 730 mg (72%); R_f 0.38; NMR δ 2.87 (s, $CONMe^A$, 3 H), 3.01 (s, 2-pyr-NMe, 6 H), 3.10 (s, $CONMe^B$, 3 H), 6.64 (d, 5-pyr-H, J = 7.8 Hz, 1 H), 7.38 (d, 4-pyr-H, J = 7.8 Hz, 1 H); IR (neat) 1630 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_3OCl$: C, 52.75; H, 6.20; N, 18.46. Found: C, 52.20; H, 6.17; N, 18.23.

***N,N*-Dimethyl-6-chloro-2-ethoxy- and -2,6-diethoxynicotinamides (6 and 5).** To a suspension of sodium hydride (500 mg, 10 mmol) in dry xylene (80 mL) was added dropwise ethanol (600 mg, 13 mmol) in dry xylene (20 mL) under nitrogen. The mixture was stirred for 10 min and then **3** (1.1 g, 5 mmol) in xylene (50 mL) was added. After the initial reaction, the mixture was refluxed for 15 h and then water (50 mL) was carefully added. The organic layer was separated, dried, and concentrated in vacuo affording a viscous oil, which was chromatographed (ThLC), eluting eight times with ethanol–cyclohexane (1:5), to afford two major fractions.

Fraction A gave *N,N*-dimethyl-2,6-diethoxynicotinamide (**5**) as a colorless oil: bp 140 °C (1 mm); 720 mg (60%); R_f 0.35 [ethanol–cyclohexane (1:5)]; NMR δ 1.34 (t, 2-pyr-$OCH_2\mathbf{CH_3}$, J = 7.1 Hz, 3 H), 1.36 (t, 6-pyr-$OCH_2\mathbf{CH_3}$, J = 7.1 Hz, 3 H), 2.93 (bs, $CONMe^A$, 3 H), 3.08 (bs, $CONMe^B$, 3 H), 4.32 (q, 6-pyr-$\mathbf{OCH_2}$, J = 7.1 Hz, 2 H), 4.40 (q, 2-pyr-$\mathbf{OCH_2}$, J = 7.1 Hz, 2 H), 6.29 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.53 (d, 4-pyr-H, J = 8.0 Hz, 1 H); IR (neat) 1630 (br, C=O), 1260 (CO), 1030 (CO) cm^{-1}; MS m/e 238 (M^+, 61%).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.28; H, 7.81; N, 11.57.

Fraction B afforded the ether **6** as colorless needles: mp 65–65.5 °C (hexane); 310 mg (27%); R_f 0.30 [ethanol–cyclohexane (1:5)]; NMR δ 1.36 (t, $\mathbf{OCH_2CH_3}$, J = 7.2 Hz, 3 H), 2.87 (s, $CONMe^A$, 3 H), 3.09 (s, $CONMe^B$, 3 H), 4.44 (q, $\mathbf{OCH_2}CH_3$, J = 7.0 Hz, 2 H), 6.92 (d, 5-pyr-H, J = 7.8 Hz, 1 H), 7.55 (d, 4-pyr-H, J = 7.8 Hz, 1 H); IR (KBr) 1630 (C=O), 1270 (CO), 1030 (CO) cm^{-1}.

Anal. Calcd for $C_{10}H_{13}N_2O_2Cl$: C, 52.52; H, 5.73; N, 12.25. Found: C, 52.80; H, 5.87; N, 12.41.

***N,N*-Dimethyl-2-ethoxynicotinamide (8) and *N,N*-Dimethyl-1,2-dihydro-2-oxonicotinamide (9).** To a stirred solution of palladium chloride (30 mg) in 2.5 N hydrochloric acid (1 mL) was added a solution of **6** (480 mg, 2.1 mmol) in methanol (15 mL) and acid-washed charcoal (300 mg) under a hydrogen atmosphere (20–30 psi). After 3 h, the catalyst was filtered off and the filtrate concentrated in vacuo. The residue was chromatographed (ThLC) eluting two times with ethyl acetate to afford three major fractions.

Fraction A gave unchanged starting material: 90 mg (19%).

Fraction B yielded the dehalogenated ether **8**: bp 115 °C (1.5 mm); 200 mg (49%); R_f 0.38; NMR δ 1.37 (t, $\mathbf{CH_2CH_3}$, J = 7.1 Hz, 3 H), 2.88 (s, $CONMe^A$, 3 H), 3.12 (s, $CONMe^B$, 3 H), 4.44 (q, $\mathbf{CH_2}CH_3$, J = 7.1 Hz, 2 H), 6.90 (dd, 5-pyr-H, J = 7.4, 5.0 Hz, 1 H), 7.60 (dd, 4-pyr-H, J = 7.4, 2.0 Hz, 1 H), 8.18 (dd, 6-pyr-H, J = 5.0, 2.0 Hz, 1 H); IR (neat) 1630 (C=O), 1265 (CO), 1050 (CO) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2 \cdot {}^1/_6H_2O$: C, 60.89; H, 7.32; N, 14.20. Found: C, 60.93; H, 7.37; N, 14.11.

(16) (a) G. R. Newkome, A. Nayak, J. D. Sauer, P. K. Mattschei, S. F. Watkins, and F. Fronczek, submitted for publication; (b) F. Fronczek, A. Nayak, and G. R. Newkome, *Acta Crystallogr., Sect. B*, **35**, 775 (1979); (c) G. R. Newkome, V. Majestic, F. Fronczek, and J. L. Atwood, *J. Am. Chem. Soc.*, **101**, 1047 (1979).

(17) MINDO calculations (0°): R. D. Gandour and B. K. Kruelskie, LSU, unpublished results. STO-3G calculations (0°): R. D. Gandour, LSU, unpublished results.

(18) Purchased from Kary Laboratories.

Fraction C gave the pyridone **9**: mp 153–154 °C (recrystallized from $CHCl_3$–CCl_4); 60 mg (11%); R_f ~0; NMR δ 3.03 (bs, $CONMe^A$, 3 H), 3.08 (bs, $CONMe^B$, 3 H), 6.33 (dd, 5-pyr-H, J = 6.7, 6.7 Hz, 1 H), 7.49 (dd, 4-pyr-H, J = 6.7, 2.3 Hz, 1 H), 7.60 (dd, 6-pyr-H, J = 6.7, 2.3 Hz, 1 H), ca. 10 [bs, NH (exchanged with D_2O), 1 H]; IR (KBr) 1650 (C=O, br) cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.13; H, 6.40; N, 16.47.

Reaction of *N,N*-Dimethyl-2,6-dichloronicotinamide with Pentaethylene Glycol. General Procedure. To a suspension of sodium hydride (500 mg, 10 mmol) in xylene (200 mL) was slowly added pentaethylene glycol (1.19 g, 5 mmol) under nitrogen. The mixture was stirred at room temperature for 30 min and then **3** (1.1 g, 5 mmol) in xylene (50 mL) was added. The mixture was refluxed for 24 h, cooled, and quenched with water. The organic layer was separated and washed with water. The combined aqueous layer was extracted with dichloromethane, added to the xylene layer, and dried over anhydrous sodium sulfate. After concentration, the viscous residue was chromatographed (ThLC), eluting with ethyl acetate, to afford the 1:1 macrocycle **10b** as a thick viscous liquid: bp 220 °C (0.4 mm); 620 mg (32%); R_f 0.08; NMR δ 2.89 (bs, $CONMe^A$, 3 H), 3.06 (bs, $CONMe^B$, 3 H), 3.4–3.8 (m, γ-ε-CH_2, 12 H), 3.84 (t, 2-β-CH_2, J = 5.5 Hz, 2 H), 3.87 (t, 6-β-CH_2, J = 5.5 Hz, 2 H), 4.55 (t, 6-α-CH_2, J = 5.5 Hz, 2 H), 4.60 (t, 2-α-CH_2, J = 5.5 Hz, 2 H), 6.35 (d, 5-pyr-H, J = 8 Hz, 1 H), 7.54 (d, 4-pyr-H, J = 8 Hz, 1 H); IR (neat) 1630 (br, C=O), 1260 (CO), 1120 (br, CO), 1040 (br, CO) cm^{-1}; MS m/e 384 (M^+, 25%).

Anal. Calcd for $C_{18}H_{28}N_2O_7$: C, 56.24; H, 7.34; N, 7.29. Found: C, 55.99; H, 7.57; N, 7.24.

Reaction of 3 with tetraethylene glycol was conducted as described above except for the substitution of 960 mg (5 mmol) of tetraethylene glycol. After chromatographic (ThLC) workup, the desired 1:1 macrocycle **10a** was isolated as a viscous, colorless oil: bp 205 °C (0.3 mm); 340 mg (20%); R_f 0.1; NMR δ 2.93 (bs, $CONMe^A$, 3 H), 3.07 (bs, $CONMe^B$, 3 H), 3.4–3.8 (m, γ- and δ-CH_2, 8 H), 3.86 (t, 2-β-CH_2, J = 5.5 Hz, 2 H), 3.90 (t, 6-β-CH_2, J = 5.5 Hz, 2 H), 4.61 (t, 6-α-CH_2, J = 5.5 Hz, 2 H), 4.65 (t, 2-α-CH_2, J = 5.5 Hz, 2 H), 6.33 (d, 5-pyr-H, J = 8 Hz, 1 H), 7.53 (d, 4-pyr-H, J = 8 Hz, 1 H); IR (neat) 1630 (br, C=O), 1260 (CO), 1110 (CO), 1040 (CO) cm^{-1}; MS m/e 340 (M^+, 66%).

Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.63; H, 6.87; N, 8.21.

Reaction of 3 with hexaethylene glycol followed the above general procedure except for the substitution of 1.42 g (5 mmol) of hexaethylene glycol. After chromatography (ThLC), the 1:1-macrocycle **10c** was isolated as a thick, colorless oil: bp 240 °C (0.3 mm); 370 mg (17%); R_f 0.04; NMR δ 2.92 (bs, $CONMe^A$, 3 H), 3.06 (bs, $CONMe^B$, 3 H), 3.4–3.8 (m, γ-ξ-CH_2, 16 H), 3.83 (t, 2-β-CH_2, J = 5.7 Hz, 2 H), 3.87 (t, 6-β-CH_2, J = 5.7 Hz, 2 H), 4.53 (t, 6-α-CH_2, J = 5.7 Hz, 2 H), 4.58 (t, 2-α-CH_2, J = 5.7 Hz, 2 H), 6.37 (d, 5-pyr-H, J = 8.1 Hz, 1 H), 7.56 (d, 4-pyr-H, J = 8.1 Hz, 1 H); IR (neat) 1630 (C=O), 1270 (CO), 1120 (CO), 1040 (CO) cm^{-1}; MS m/e 428 (M^+, 11%).

Anal. Calcd for $C_{20}H_{32}N_2O_8$: C, 56.06; H, 7.53; N, 6.54. Found: C, 55.86; H, 7.77; N, 6.48.

Reduction of 10b with Sodium Bis(2-Methoxyethoxy)aluminum Hydride ("Vitride"). General Procedure. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (500 μL, 1.8 mmol, 70% benzene solution) in anhydrous benzene (10 mL) was added dropwise to a benzene solution of **10b** (530 mg, 1.4 mmol) at 5 °C with stirring under nitrogen. The reaction mixture was refluxed for 30 min and then cooled in ice. Water (10 mL) was added and the mixture was stirred vigorously for 10 min. The organic layer was decanted and the aqueous layer was extracted with chloroform. The combined organic fraction was dried over anhydrous sodium sulfate and concentrated in vacuo to give the amine macrocycle **11b** as a colorless oil: bp 190 °C (0.15 mm); 490 mg (96%); NMR δ 2.15 (s, NMe_2, 6 H), 3.28 (s, CH_2N, 2 H), 3.47 (s, ε-CH_2, 4 H), 3.57 (bs, γ- and δ-CH_2, 8 H), 3.81 (t, β-CH_2, J = 5.6 Hz, 4 H), 4.45 (t, 6-α-CH_2, J = 5.6 Hz, 2 H), 4.50 (t, 2-α-CH_2, J = 5.6 Hz, 2 H), 6.22 (d, 5-pyr-H, J = 7.9 Hz, 1 H), 7.40 (d, 4-pyr-H, J = 7.9 Hz, 1 H); IR (neat) 2820 (N–Me), 2770 (N–Me), 2730 (N–Me), 1250 (CO), ~1120 (br, CO), 1030 (CO) cm^{-1}.

Anal. Calcd for $C_{18}H_{30}N_2O_6$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.34; H, 8.32; N, 7.31.

Reduction of 10a and 10c with Vitride in a similar manner gave the amine macrocycles **11a** and **11c**, respectively, in near-quantitative yields. Further purification was not undertaken but their structures were confirmed by spectral data.

11a: NMR δ 2.23 (s, NMe_2, 6 H), 3.37 (s, CH_2N, 2 H), 3.75–3.45 (m, γ- and δ-CH_2, 8 H), 3.88 (t, 6-β-CH_2, J = 5.5 Hz, 2 H), 3.90 (t, 2-β-CH_2, J = 5.5 Hz, 2 H), 4.60 (t, 6-α-CH_2, J = 5.5 Hz, 2 H), 4.64 (t, 2-α-CH_2, J = 5.5 Hz, 2 H), 6.28 (d, 5-pyr-H, J = 7.8 Hz, 1 H), 7.47 (d, 4-pyr-H, J = 7.8 Hz, 1 H); IR (neat) 2815 (N–Me), 2770 (N–Me), 2720 (N–Me), 1250 (CO), 1120 (b, CO), 1040 (CO) cm^{-1}.

11c: NMR δ 2.23 (s, NMe_2, 6 H), 3.36 (s, NCH_2, 2 H), 3.5–3.7 (m, γ-ε-CH_2, 16 H), 3.86 (t, β-CH_2, J = 5.6 Hz, 4 H), 4.50 (t, 6-β-CH_2, J = 5.6 Hz, 2 H), 4.56 (t, 2-α-CH_2, J = 5.6 Hz, 2 H), 6.30 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.48 (d, 4-pyr-H, J = 8.0 Hz, 1 H); IR (neat) 2820 (N–Me), 2770 (N–Me), 2720 (N–Me), 1250 (CO), ~1120 (br, CO), 1030 (CO) cm^{-1}.

3-(*N,N*-Dimethylaminomethyl)-2,6-diethoxypyridine (12). A solution of **5** (660 mg, 2.8 mmol) in benzene (20 mL) was added dropwise to a solution of Vitride (1.2 mL, 8.4 mmol) in benzene (20 mL) at 40 °C with stirring under nitrogen. The mixture was refluxed for 1 h and cooled, and then 5 N aqueous hydrochloric acid (10 mL) was added slowly with external cooling. After separation of the organic layer, solid potassium hydroxide (3 g) was added to the aqueous solution. Amine **12** was extracted from the aqueous layer with benzene. The extract was dried over anhydrous sodium sulfate and concentrated in vacuo to give the amine as a colorless oil: bp 90 °C (0.8 mm); 540 mg (86%); NMR δ 1.36 (t, $CH_2\mathbf{CH_3}$, J = 7.0 Hz, 6 H), 2.22 (s, NMe_2, 6 H), 3.36 (s, NCH_2, 2 H), 4.31 (q, 6-pyr-$\mathbf{OCH_2}$, J = 7.0 Hz, 2 H), 4.37 (q, 2-pyr-$\mathbf{OCH_2}$, J = 7.0 Hz, 2 H), 6.24 (d, 5-pyr-H, J = 8.0 Hz, 1 H), 7.47 (d, 4-pyr-H, J = 8.0 Hz, 1 H); IR (neat) 2810 (N–Me), 2765 (N–Me), 2720 (N–Me), 1240 (CO), 1040 (CO) cm^{-1}.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 63.95; H, 8.63; N, 12.43.

The first organic extract was dried over magnesium sulfate and concentrated in vacuo. Without further purification, the following spectral data for **13** were obtained: NMR δ 1.40 (t, 2-$OCH_2\mathbf{CH_3}$, J = 7.1 Hz, 3 H), 1.43 (t, 6-$OCH_2\mathbf{CH_3}$, J = 7.1 Hz, 3 H), 4.42 (q, 6-$\mathbf{OCH_2}CH_3$, J = 7.1 Hz, 2 H), 4.50 (q, 2-$\mathbf{OCH_2}CH_3$, J = 7.1 Hz, 2 H), 6.34 (d, 5-pyr-H, J = 8.2 Hz, 1 H), 8.04 (d, 4-pyr-H, J = 8.2 Hz, 1 H), 10.23 (s, CHO, 1 H); IR (neat) 1673 (C=O), 1275 (CO), 1030 (CO) cm^{-1}.

Reaction of 2,6-Pyridino-5-crown (15) with *tert*-Butyllithium. To a solution of **15**[13] (538 mg, 2 mmol) in anhydrous benzene (400 mL), *tert*-butyllithium (6 mL, 0.75 M in pentane) was added dropwise with stirring under nitrogen at 20 °C. The mixture was stirred for 12 h and then concentrated in vacuo to 25 mL and decomposed carefully by addition of ice water (10 mL), followed by 6 N hydrochloric acid (6 mL). Excess acid was neutralized with aqueous sodium carbonate and then extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to give a pale yellow oil, which was chromatographed (ThLC), eluting with cyclohexane-ethyl acetate (1:1), to afford two fractions.

Fraction A gave unchanged starting material: mp 72–74 °C; 100 mg (70%).

Fraction B gave an oily liquid corresponding to pyridone **16**: bp 175–180 °C (1 mm); 106 mg (20%); R_f 0.18; NMR ($CDCl_3$), see Figure 3; IR (neat) 3440 (NH, OH), 2900, 1640 (w, amide), 1590, 1430, 1310, 1135, 1030, 940, 785 cm^{-1}; mol wt (MS) m/e 269 (M^+, 26%).

Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.20; H, 7.25; N, 5.06.

Methylation of 16. Pyridone 17. Metallic sodium (23 mg, 1 mmol) was dissolved in absolute ethanol (25 mL) and **16** (270 mg, 1 mmol) was added with stirring. After 12 h of stirring at 20 °C, the solvent was removed in vacuo affording a residue, which was extracted several times with ether. The residue was dried under vacuum and then dissolved in anhydrous dimethylformamide (5 mL) containing an excess of methyl iodide (1 mL). The mixture was stirred overnight at 30 °C and after concentration the oily material was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1), to give the N-methylated product **17** as a viscous oil: bp 200–203 °C (1 mm, short path); 200 mg (60%); R_f 0.1; NMR ($CHCl_3$) δ 3.35 (s, NMe, 3 H), 3.63 (m,

γ-ξ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 6 Hz, 2 H), 4.40 (t, α-CH_2O, J = 6 Hz, 2 H), 4.50 (dd, H_C, J = 7, 1 Hz, 1 H), 4.85 (dd, H_B, J = 14, 1 Hz, 1 H), 6.63 (dd, H_3, J = 4, 1 Hz, 1 H), 6.45 (dd, H_5, J = 4, 1 Hz, 1 H), 7.48 (t, H_4, J = 7.5 Hz, 1 H), 7.55 (dd, H_A, J = 14, 8 Hz, 1 H); IR (neat) 2930, 1675 (amide), 1580, 1425, 1370, 1300, 1235, 1120, 1080, 790 cm^{-1}; mol wt (MS) m/e 283 (M^+, 22%).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.15; H, 7.14; N, 4.93. Found: C, 58.98; H, 7.42; N, 4.75.

Acknowledgments. We are grateful to the National Institutes of Health and the National Science Foundation for partial support of this work. We also thank Dr. Weis of CIBA-GEIGY, Basel, Switzerland, for the generous sample of 2,6-dichloronicotinic acid.

Registry No. **2**, 58584-83-1; **3**, 70290-47-0; **4**, 70445-78-2; **5**, 70290-48-1; **6**, 70290-49-2; **7**, 70445-79-3; **8**, 70290-50-5; **9**, 70290-51-6; **10a**, 70290-41-4; **10b**, 70290-42-5; **10c**, 70290-43-6; **11a**, 70290-44-7; **11b**, 70290-45-8; **11c**, 70290-46-9; **12**, 70445-80-6; **13**, 70445-81-7; **14**, 61463-74-9; **15**, 56446-73-2; **16**, 70445-82-8; **17**, 70445-83-9; pentaethylene glycol, 4792-15-8; tetraethylene glycol, 112-60-7; hexaethylene glycol, 2615-15-8; ethanol, 64-17-5.

Functionalization of 5-Methyl-2-halonicotinic Acid Derivatives

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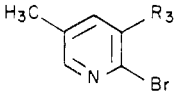
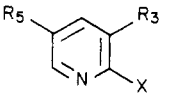
Methodology is described for the preparation of pyridines containing versatile functional groups in the 2, 3, and 5 positions via di and tri NBS brominations of the C-5 methyl group of 2-halonicotinic acid derivatives. Reductive dehalogenation of the 2-bromo substituent provides for a facile synthesis of unsymmetrical pyridines in which the oxidation state of the C-3 and C-5 groups can be effectively controlled.

Recently, we described a method for the synthesis of 5-methyl-2-halonicotinic acid derivatives of the type **1** via



1

R_3 = CO_2Et, CN



2

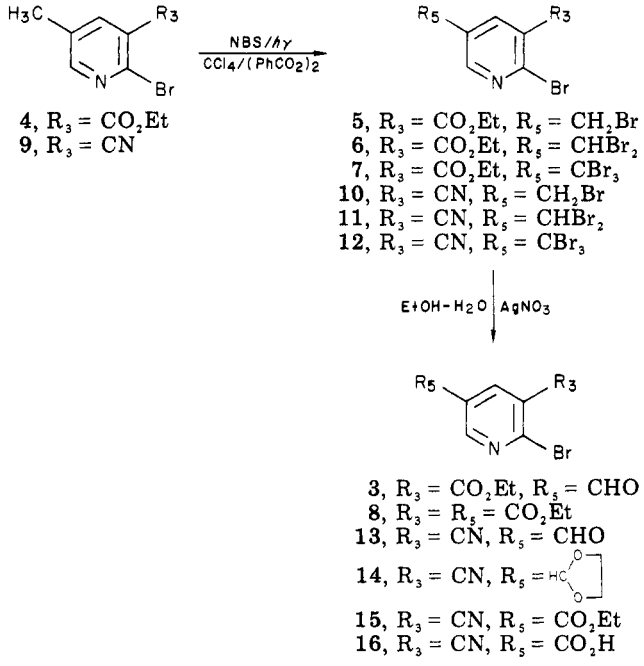
R_3 = CO_2Et, CN
R_5 = CHO, CO_2Et
X = Br, H

enamine cyclization.[1] The ready availability of **1** by this procedure prompted an investigation into the utilization of these compounds as intermediates en route to the preparation of more highly functionalized derivatives. We now report on the functionalization of the C-5 methyl group of **1** as an approach to compounds of the type **2**, a class unknown in the pyridine literature.[2]

Initially, we attempted the synthesis of ethyl 2-bromo-5-formylnicotinate (**3**) via SeO_2 oxidation of **4**. Unfortunately, SeO_2, under various conditions, failed to oxidize the C-5 methyl group. In fact, the starting material **4** was recovered quantitatively, even after prolonged treatment. This failure of the SeO_2 oxidation of **4** necessitated a search for an alternate route for the conversion of **4** to **3**. As outlined in Scheme I, this functionalization was accomplished by *N*-bromosuccinimide (NBS) bromination of the C-5 methyl group.

When **4** was treated with a slight excess over 2 equiv of NBS, ethyl 2-bromo-5-(dibromomethyl)nicotinate (**6**) was isolated as the major product in 35% yield. In addition to **6**, the mother liquors from the crystallization contained

Scheme I



varying amounts of **4**, **5**, and **7**. Chromatography of this mixture yielded **7** (6%). Although not isolated, the presence of **5** is clearly supported by the appearance of a singlet at δ 4.4 for the bromomethyl group in the ^1H NMR spectrum.

Treatment of **4** with a slight excess over 3 equiv of NBS gave ethyl 2-bromo-5-(tribromomethyl)nicotinate (**7**) in 49% yield as well as a minor amount of **6**. These compounds, **6** and **7**, were easily separated by chromatography on silica gel. Unlike the previous example, no trace of **5** could be observed in the ^1H NMR spectrum of the crude reaction mixture.

(1) J. J. Baldwin, A. W. Raab, and G. S. Ponticello, *J. Org. Chem.*, 43, 2529 (1978).
(2) R. A. Abramovitch, Ed., "Pyridine and Its Derivatives", Wiley, New York, N.Y., Parts 1-4.

0022-3263/79/1944-2702$01.00/0