The Demethylation Chemistry of 3-Substituted 2-Methoxypyridines

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Upon acylation of 3-amino-2-methoxypyridines, two side products were discovered, a pyridone, **5**, **6**, and **8**, and a pyridyloxazine, **4** and **9**. The ratios of these products can be affected by changes in the reaction parameters. When oxalyl chloride was the acylating agent a pyridone **13** was isolated.

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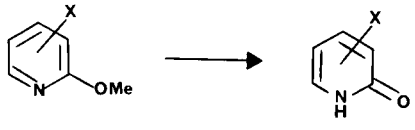
The cleavage of an alkyl group from a 2-alkoxy pyridine, Scheme I, has been the subject of only a limited number of publications [1,2]. The most cited example is the demethylation of 2-methoxy-3-nitropyridine in the presence of hydrochloric acid under mild conditions to give 3-nitro-2-pyridine [1]. Our interest in the area was stimulated when we found to our surprise that in the synthesis of compounds like **3** an unexpected demethylation also occurs and two new types of substituted pyridines were obtained. The first unexpected product identified was the pyridyloxazine **4** and the second was pyridone **5**. Both are the result of a demethylation of pyridylamide **3**. This manuscript then describes our research into this unique demethylation reaction.

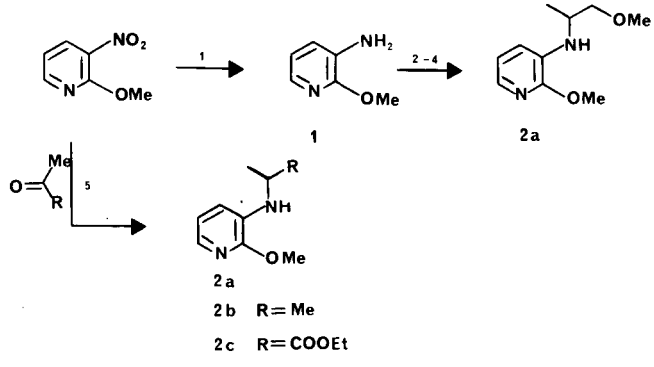
Scheme I



The synthesis of the requisite amine precursor **2a**, leading to compounds **3-5**, begins with readily available 2-methoxy-3-nitropyridine (Scheme II). Hydrogenation of 2-methoxy-3-nitropyridine to 2-methoxy-3-aminopyridine, **1**, [3] followed by condensation with ethyl pyruvate (benzene, magnesium sulfate) gave the imine in good yield. Subsequent reduction of both imine and ester readily occurred with sodium borohydride (ethanol, reflux) to give the amino alcohol. Selective *O*-alkylation with sodium hydride and methyl iodide gave the desired amine **2a**. Alternatively amine **2a** could also be made by a reductive alkylation of **1**. In this reaction **1** is treated with methoxy acetone in the presence of hydrogen and sulfided platinum under pressure to give amine **2a** directly in very good yield. This procedure is also applicable to the synthesis of other pyridyl amines. When amine **1** was treated with acetone with hydrogen and sulfided platinum under pressure, the *N*-isopropylamino pyridine **2b** was obtained. Likewise, when amine **1** was treated with ethyl pyruvate under the same conditions, the *N*-pyridylalanine **2c** was isolated.

Anticipating a straightforward acylation, we reacted

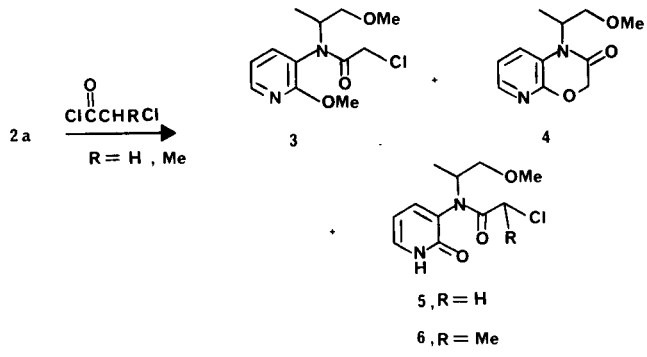
Scheme II



1, H_2, Pd ; 2, MeCOCOOEt ; 3, $NaBH_4$; 4, NaH, MeI ; 5, H_2, Pt—S

amine **2a** with chloroacetyl chloride in the presence of 4-vinylpyridine polymer [4] as an acid scavenger in tetrahydrofuran (THF). After an aqueous workup with diethyl ether, the expected acylated amine **3** was isolated and purified by chromatography in a 55% yield. However, when the above aqueous layer was extracted again with methylene chloride, a white solid was obtained which after recrystallization was identified as the pyridone **5** (9% yield). The combined mother liquors from the recrystallization of compound **5** were chromatographed to give yet another pyridine product the pyridyloxazine **4** (19% yield). Both compounds **4** and **5** were easily identified by proton nmr, mass spectra, and combustion analysis. Both compounds lack the methyl group on the pyridyl oxygen which was easily detected by nmr. Finally in the case of **4**, the chlorine was found to be missing when the analysis and mass spectrum were examined. Both compounds are thus the result of a demethylation process at some point during the reaction, with subsequent cyclization of pyridine **5** to produce the oxazine **4**. This method thus provided an interesting as well as simple route to substituted pyridones and pyridyloxazines. We therefore began an exploration of this reaction to see if we could prepare either the pyridone **5** or pyridyloxazine **4** as the only product.

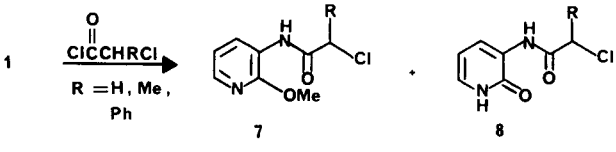
Scheme III



Although many parameters of the reaction were changed in order to affect the product ratio, only two changes altered the ratio significantly. In the first case, when the reaction was carried out in refluxing THF (4 hours), only the pyridyloxazine **4** (in 60% yield) was obtained. In the second case when no solvent was used only the pyridone **5** was isolated in 20% yield. We then looked at what effect the acylating agent had on the reaction. Treating amine **2a** with 2-chloropropionyl chloride (THF, reflux) gave only the pyridone **6** (Scheme III). In summary, by changing the conditions of the acylation of **2a** using different acid chlorides, one can obtain the direct acylation product **3**, the pyridyloxazine **4**, or the pyridine **5** as the major or only product.

With the above results in hand we looked at what other 3-amino-2-methoxy pyridines would do under similar demethylation conditions. The three amines chosen were amines **1**, **2b**, and **2c**. It was surprising to find that the isopropyl amine **2b** and the aniline **2c** when treated with chloroacetyl chloride under numerous sets of conditions (no base, base, heating, *etc.*) gave only the *N*-acylated products (see experimental for details). No demethylation products, either the pyridyloxazine or the pyridone, were ever seen. In the case of pyridyl amine **1**, however, products resulting from demethylation were again seen. Therefore when amine **1** was treated with chloroacetyl chloride (methylene chloride) the direct acylation product **7** (R = H) was obtained in 100% yield (Scheme IV). When the reaction was repeated using a mixture of solvents (methylene chloride and dimethyl formamide, reflux) only the pyridone **8** (R = H) was isolated in 92% yield.

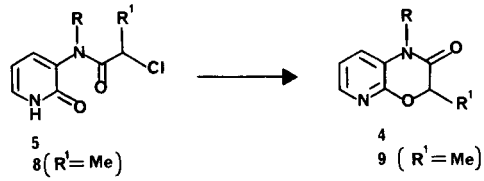
Scheme IV



Treatment of amine **1** with other acylating agents gave similar reuslts. Reaction of amine **1** with propionyl chloride gave the acylated product, **7**, (R = Me) as the minor product (12% yield) and the pyridone, **8**, (R = Me) as the major product (50% yield). The reaction of amine **1** with 2-chlorophenylacetyl chloride gave only the pyridone **8** (R = Ph) in 80% yield. In all cases the acylation of **1** gave no pyridyloxazine, unlike the case of **2a**. It is of interest to us that thusfar only in the cases of **1** and **2a** do we see demethylation occur. In addition only with amine **2a** did we isolate the pyridyloxazine.

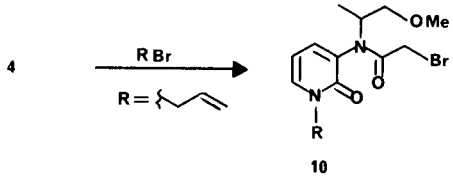
Since the pyridyloxazine was not isolated from the reaction of amine **1** with chloroalkanoyl chlorides, we attempted to make them *via* the pyridones **5** and **8** (R = Me). Initial attempts to cyclize the pyridones by heating or in the presence of a weak base such as triethylamine, pyridine or 4-vinylpyridine polymer, even at elevated temperatures, gave no pyridyloxazine. When pyridone **5** or pyridone **8** (R = Me) were treated with sodium hydride in THF, cyclization occurred and the pyridyloxazines **4** and **9**, respectively, were obtained (Scheme V).

Scheme V



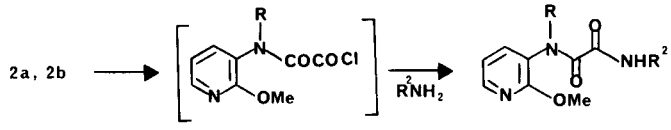
A publication by Wiesner and co-workers [2] had shown that reaction of a 2-methoxy-5-substituted pyridine with benzyl bromide gave initially the pyridinium ion then demethylation to the *N*-benzylpyridones. Under similar conditions, reaction of allyl bromide with the pyridyloxazine **4** (in the presence of sodium hydride) gave the bromoacetamide *N*-allylpyridone **10** (R = allyl) where bromide ion opened the oxazine ring (Scheme VI). This compound was readily identified by proton nmr and mass spectrometry.

Scheme VI



Finally, we changed the acylating agent from chloroacetyl chloride to oxalyl chloride. Our intention was to isolate the pyridyloxazine dione **12**. However, after several unsuccessful attempts, we decided to trap **12** by adding an

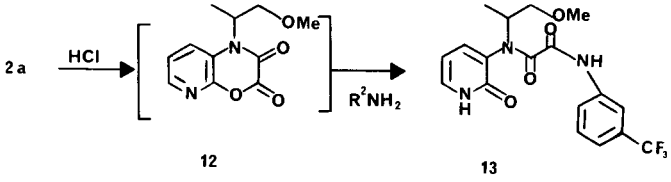
Scheme VII



amine to the reaction (Scheme VII). Thus amines **2a** and **2b** were treated with oxalyl chloride (THF) then with an amine (either 3-methoxy aniline, 3-trifluoromethylaniline, or aniline). Under these conditions no pyridones (*e.g.* **13**) were isolated. Instead the 2-methoxypyridylethanediamides **11a-d** were isolated.

When **2a** was treated with gaseous hydrochloric acid in benzene, then treated with oxalyl chloride, followed by *m*-aminobenzotrifluoride, the pyridone oxamide **13** was isolated (Scheme VIII). We speculate that dione **12** is the intermediate in the reaction. The formation of this intermediate was apparently accelerated by the presence of hydrochloric acid.

Scheme VIII



In conclusion, we have found that 2-methoxy pyridines can readily undergo, under mild conditions, demethylation to new pyridine compounds, *e.g.* pyridones **3** and **7**, and a new fused ring system, the pyridyloxazines **4** and **8**.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bechmann spectrometer neat or as nujol mulls. Proton magnetic resonance spectra were determined with a Bruker 250 MHz or IBM 80 MHz instrument using tetramethylsilane as an internal standard. Low pressure liquid chromatography with silica gel was used for all chromatographic separations. Mass spectra were obtained on a Hewlett Packard mass spectrometer.

2-Methoxy-*N*-(2-methoxy-1-methylethyl)-3-amino pyridine, **2a**, *via* Sodium Borohydride Route.

A solution of 10.0 g of 2-methoxy-3-aminopyridine, **1**, and 10.8 g of ethyl pyruvate in 100 ml of benzene containing 10.8 g of magnasium sulfate was refluxed for two hours. The mixture was allowed to stir at room temperature overnight and was filtered and concentrated under reduced pressure to provide 17.8 g of 2-[(2-methoxy-3-pyridinyl)imino]propanoic acid, ethyl ester. This was used immediately.

A solution of 17.8 g of 2-[(2-methoxy-3-pyridinyl)imino]propanoic acid, ethyl ester and 4.6 g of sodium borohydride in 175 ml of ethanol was refluxed for approximately 16 hours. The reaction mixture was cooled and added to water. The aqueous solution was extracted with chloroform. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was chromatogrpahed with 90% Skellysolve B/10% ethyl acetate to provide 6.0 g of 2-methoxy-*N*-(2-hydroxy-1-methylethyl)-3-aminopyridine in 41% yield as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6, 3H), 3.35 (s, 3H), 3.40 (m, 3H), 3.95 (s, 3H); 4.2 (broad s, 1H), 6.7 (d, J = 3, 2H), 7.4 (d of d, J = 3, 1H).

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.57; H, 7.48; N, 15.27.

Approximately 2.8 g of 50% sodium hydride in mineral oil was suspended in 100 ml of THF. Next, 5.5 g of 2-methoxy-*N*-(2-hydroxy-1-methylethyl)-3-aminopyridine was added to the stirring suspension over a five minute period. The reaction mixture was stirred at room temperature for approximately 30 minutes whereupon 4.3 g of methyl iodide was added dropwise. The mixture was stirred at room temperature for three hours at which point water was added to the solution. The solution was twice extracted with diethyl ether, and the organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel eluting with 90% Skellysolve B/10% ethyl acetate. Fractions containing the first major component were combined and the solvent was evaporated therefrom to provide 4.2 g of 2-methoxy-*N*-(2-methoxy-1-methylethyl)-3-aminopyridine, **2a**, in 71% yield as a colorless oil; ir (neat): 3410, 1585 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 5, 3H), 3.32 (s, 3H), 3.4 (m, 3H), 3.9 (s, 3H), 4.2 (broad s, 1H), 6.7 (d, J = 3, 2H), 7.4 (m, 1H).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.16; H, 8.04; N, 14.02.

Formation of *N*-Alkyl-3-amino-2-methoxypyridines by Reductive Alkylation. Compound **2a**.

To 86.3 g (0.56 mole) of 2-methoxy-3-nitropyridine in 1.8 l of ethanol was added 97 g of methoxyacetone and 40 g of 5% sulfided platinum. This mixture was placed under a hydrogen atmosphere at 1000 psi at 150° for 8 hours. The mixture was then filtered and the solvent removed *in vacuo*. The remaining oil was chromatographed (methylene chloride) yielding 100 g (91%) of a colorless oil, **2a** (see spectral data above). The following compounds were made in this manner.

N-(1-Methylethyl)-2-methoxy-3-aminopyridine, **2b**.

Compound **2b** was obtained in a yield of 60% as a colorless oil; ir (neat): 3400, 1580 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.21 (d, J = 1, 6H), 3.5 (m, 1H), 3.96 (s, 3H), 6.75 (m, 2H), 7.45 (m, 1H).

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49: N, 16.85. Found: C, 64.95; H, 7.99; N, 16.46.

N-(2-Methoxy-3-pyridinyl)-D,L-alanine, Ethyl Ester, **2c**.

Compound **2c** was obtained in 67% yield as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 1.1 (t, J = 6, 3H), 1.4 (d, J = 6, 3H), 3.8 (s, 3H), 3.85 (m, 1H), 3.95 (q, J = 6, 2H), 4.55 (m, 1H), 6.55 (m, 2H), 7.32 (m, 1H).

Anal. Calcd. for $C_{11}H_{15}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.77; H, 7.16; N, 12.58.

2-Chloro-*N*-(2-methoxy-1-methylethyl)-*N*-(2-methoxy-3-pyridinyl)acetamide, **3**.

1-(2-Methoxy-1-methylethyl)-1*H*-pyrido[2,3-*b*][1,4]oxazine-2(3*H*)-one, **4**.

2-Chloro-*N*-(1,2-dihydro-2-oxo-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)-acetamide, **5**.

To 200.0 g (1.0 mole) of **2a** in 500 ml of THF was added 140 g of 4-vinylpyridine polymer then 90.6 ml of chloroacetyl chloride. The mixture was then refluxed for two hours, cooled to room temperature, filtered, then poured into 200 ml of 1*N* aqueous sodium hydroxide and 500 ml of diethyl ether. The layers were separated and the organic layer was filtered through phase separation paper then evaporated *in vacuo* to 170 g of a green solid (mp 68-73°). The aqueous layer was extracted with 500 ml of methylene chloride which was then filtered through phase separation paper and solvent removed *in vacuo* to give a white solid.

The green solid was chromatographed (pentane/methylene chloride) to give 121.1 g (55%) of **3** as a colorless oil; ir (potassium bromide): 1675, 1580 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.95 and 1.23 (2ds, J = 1, 3H), 3.3 (m, 2H), 3.35 (s, 3H), 3.75 (m, 2H), 4.0 and 4.05 (2s, 3H), 4.45 and 5.1 (2m, 1H), 7.0 (m, 1H), 7.6 (m, 1H), 7.25 (m, 1H).

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3$: C, 52.85; H, 6.28; N, 10.27; Cl, 13.00. Found: C, 52.65; H, 6.44; N, 10.33; Cl, 13.22.

In addition 14.0 g of impure **3** was also isolated the following:

The isoalted white solid was triturated with diethyl ether then recrystallized from pentane/ethyl acetate to give 23.2 g (9%) of the pyridone **5**, as a mixture of stereoisomers, mp 114-115°; ir (neat): 1685, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.9 and 1.25 (2 doublets, J = 3, 3H), 3.25 and 3.3 (2 singlets, 3H), 3.27 (m, 2H), 3.7 (d of d, J = 6, 1H), 4.5 and 5.1 (m, 1H), 6.95 (m, 1H), 7.6 (d of d, J = 8, 1H), 8.25 (m, 1H).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 51.06; H, 5.80; N, 10.83; Cl, 13.73. Found: C, 51.05; H, 5.72; N, 10.71; Cl, 13.90.

The mother liquor from this recrystallization was evaporated and the resulting oil was chromatographed (methylene chloride) to give 42.1 g (19%) of an oil, which was the pyridyloxazine, **4**; ir (potassium bromide): 3270, 1650, 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5 (d, J = 7, 3H), 3.3 (s, 3H), 3.6 (m, 2H), 4.5 (m, 1H), 4.65 (s, 2H); 6.9 (m, 1H), 7.55 (m, 1H), 7.85 (m, 1H); ms: m/e 222, 177, 151, 119, 149, 78.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60; Cl, 0.00. Found: C, 59.33; H, 6.21; N, 12.42; Cl, 0.00.

2-Chloro-*N*-(1,2-dihydro-2-oxo-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)-propanamide, **6**.

To 4.0 g (0.02 mole) of **2a** in 50 ml of THF was added 2.4 ml of 2-chloropropionyl chloride. This mixture was refluxed 18 hours. Upon cooling to room temperature 50 ml of diethyl ether was added and the mixture washed with 25 ml of water. Upon addition of water a white precipitate formed. The solvent mixture was filtered and the solid collected. Upon recrystallization (pentane/ethyl acetate) 1.1 g (20%) of **6** as a white solid was obtained, mp 169-170°; ir (potassium bromide): 3200, 1660, 1635, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.9 and 1.25 (2 doublets, J = 3, 3H), 3.25 and 3.3 (2 singlets, 3H), 3.27 (m, 2H), 3.7 (d of d, J = 6, 1H), 4.5 and 5.1 (2 multiplets, 1H), 6.95 (m, 1H), 7.6 (d of d, J = 8, 1H), 8.25 (m, 1H).

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3$: C, 52.84; H, 6.23; N, 10.27. Found: C, 52.60; H, 6.02; N, 10.43.

2-Chloro-*N*-(2-methoxy-3-pyridinyl)-*N*-(1-methylethyl)acetamide.

To 5.0 g of 2-methoxy-*N*-(methylethyl)-3-aminopyridine in 50 ml of THF was added 6.0 ml of chloroacetyl chloride. This mixture was stirred 18 hours at room temperature. The mixture was then refluxed 3 hours, cooled to room temperature, then poured into 25 ml of 0.5 *N* aqueous sodium hydroxide and 100 ml of diethyl ether. The layers were separated and the organic layer passed through phase separation paper. The solvent was removed *in vacuo* and the resulting oil was chromatographed (methylene chloride) to provide 6.3 g (86%) of the acylated product as a colorless oil; ir (potassium bromide): 1675, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.97 (d, J = 1, 3H), 1.16 (d, J = 1, 3H), 3.75 (q, J = 3, 2H), 3.96 (s, 3H), 4.9 (m, 1H), 7.0 (m, 1H), 7.47 (m, 1H), 8.24 (m, 1H).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.44; H, 6.23; N, 11.54. Found: C, 54.17; H, 5.97; N, 11.24.

N-(Chloroacetyl)-*N*-(2-methoxy-3-pyridinyl)-D,L-alanine, Ethyl Ester.

To 5.0 g (0.022 mole) of *N*-(2-methoxy-3-pyridinyl)alanine, ethyl ester in 50 ml of THF was added 4.0 g of 4-vinylpyridine polymer then 4.0 ml of chloroacetyl chloride. This mixture was stirred 18 hours. The solvent was then removed *in vacuo* and the resulting oil was chromatographed (methylene chloride). This yielded 4.4 g (64%) of a colorless oil; ir (neat): 1735, 1690, 1670, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2 (t, J = 6, 3H), 1.35 and 1.6 (2d, J = 7, 3H), 3.75 (s, 2H), 3.92 (s, 3H), 4.18 (q, J = 6, 2H), 5.1 (q, J = 7, 1H), 6.9 (m, 1H), 7.8 (m, 1H), 8.1 (m, 1H).

Anal. Calcd. for $C_{13}H_{14}ClN_2O_4$: C, 52.09; H, 5.38; N, 9.35. Found: C, 51.86; H, 5.51; N, 9.14.

2-Chloro-*N*-(2-methoxy-3-pyridinyl)acetamide, **7** (R = H).

To 3.7 g (0.03 mole) of **1** in 50 ml of THF was added 2.7 ml of chloroacetyl chloride. The mixture was stirred at room temperature 3 days. It was then added to 25 ml of water and 100 ml of methylene chloride. The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution, filtered through phase separation paper, and the solvent removed *in vacuo* leaving a colorless oil 5.9 g (100%) identified as the acylated product **7**; ir (potassium bromide): 3360, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.05 and 4.25 (2 singlets, 3H), 6.9 (d of d, J = 3, 1H), 7.9 (d, J = 3, 1H), 8.5 (d, J = 3, 1H), 8.85 (broad s, 1H).

Anal. Calcd. for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.63; H, 4.33; N, 13.83.

2-Chloro-*N*-(1,2-dihydro-2-oxo-3-pyridinyl)acetamide, **8** (R = H).

To 5.0 g (0.04 mole) of **1**, in 175 ml of methylene chloride was added 9.0 ml of chloroacetyl chloride. Immediately a solid formed and 12 ml of DMF was added to solubilize this mixture at reflux. After refluxing 72 hours, the solution was cooled to room temperature and washed with 50 ml of water. After discarding the aqueous layer, 50 ml of chloroform was added. The organic phase was filtered through phase separation paper and evaporated *in vacuo* leaving 6.0 g (82%) of an analytically pure white solid, **8** (R = H), mp 215-216°; ir (potassium bromide): 2800 (broad), 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.4 (s, 3H), 6.15 (t, J = 5, 1H), 7.1 (d of d, J = 1, 5, 1H), 8.1 (d of d, J = 1, 5, 1H).

Anal. Calcd. for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 44.79; H, 3.69; N, 14.74.

2-Chloro-*N*-(1,2-dihydro-2-oxo-3-pyridinyl)propanamide, **8** (R = Me).

To 2.5 g (0.02 mole) of **1** in 50 ml of methylene chloride was added 4.0 ml of 2-chloropropionoyl chloride. This mixture was refluxed 18 hours. After cooling to room temperature 50 ml of water was added. The layers were separated and the organic layer was passed through phase separation paper then evaporated *in vacuo*. Chromatography (4:1, methylene chloride/ethyl acetate) gave two products. The first product, 2.0 g (50%) was the pyridone, **8** (R = Me), mp 141-142°; ^1H nmr (deuteriochloroform): δ 1.8 (d, J = 7, 3H), 3.95 (s, 3H), 4.5 (q, J = 7, 1H), 6.85 (d of d, J = 5, 7, 1H), 7.65 (m, 1H), 8.45 (d of d, J = 1, 7, 1H), 8.6 (broad s, 1H).

Anal. Calcd. for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 48.10; H, 4.53; N, 13.72.

The second product, 0.5 g (12%) was 2-chloro-*N*-(2-methoxy-3-pyridinyl)propanamide; ^1H nmr (deuteriochloroform): δ 1.75 (d, J = 7, 3H), 4.55 (q, J = 7, 1H), 6.32 (d of d, J = 7, 8, 1H), 7.1 (m, 1H), 8.45 (d of d, J = 1, 7, 1H), 9.3 (broad s, 1H).

Anal. Calcd. for $C_9H_{11}ClN_2O_2$: C, 50.36: H, 5.16; N, 13.05. Found: C, 50.57; H, 5.20; N, 12.96.

2-Chloro-*N*-(1,2-dihydro-2-oxo-3-pyridinyl)benzene acetamide, **8** (R = Ph).

To 4.8 g (0.04 mole) of **1**, in 50 ml of chloroform was added 16 ml of 2-chlorophenylacetyl chloride. The mixture was refluxed 16 hours. After cooling to room temperature, the solution was washed with 20 ml of 1*N* aqueous sodium hydroxide and then 50 ml of water. The organic layer was passed through phase separation paper and then the solvent removed *in vacuo*. Chromatography followed by recrystallization (pentane/ethyl acetate) of the resultant solid gave 1.4 g (11%) of a white crystalline material **8** (R = Ph), mp 160-161°; ir (potassium bromide): 2800, 1645 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.25 (m, 2H), 7.4 (m, 6H), 8.26 (m, 1H), 9.91 (s, 1H), 12.11 (s, 1H).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66; Cl, 13.50. Found: C, 59.64; H, 4.23; N, 10.41; Cl, 13.34.

Treatment of **5** With Sodium Hydride to Give **4**.

To 5.0 g (0.02 mole) of pyridone **5** in 200 ml of THF was added 1.0 g of sodium hydride (50% in mineral oil). This mixture was refluxed 20 hours. After cooling to room temperature, the solution was poured into 50 ml of water then neutralized with 2*N* hydrochloric acid (*p*H 7). This solution was extracted with ethyl acetate (3 × 100 ml), and the combined ethyl acetate extracts filtered through phase separation paper then evaporated *in vacuo* to an oil. Chromatography (methylene chloride) gave 2.7 g (50%) of an colorless oil, compound **4**. Spectral data are given above.

3-Methyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-one, **9**.

To 1.5 g of pyridone **8b** in 30 ml of THF was added 0.6 g of sodium hy-

dride (50% in mineral oil). This mixture was refluxed 4 hours. After cooling to room temperature, the reaction mixture was poured into 25 ml water and extracted with chloroform (3 × 50 ml). After drying with sodium sulfate, the organic solvent was passed through phase separation paper and evaporated *in vacuo*. The resulting solid was recrystallized (ethyl acetate) to give 0.25 g (20%) of pyridyloxazine **9**, mp 225-226°; ^{1}H nmr (DMSO-d_6): δ 1.45 (d, J = 1, 3H), 4.9 (q, J = 1, 1H), 7.0 (m, 1H), 7.22 (m, 1H), 7.80 (m, 1H), 8.80 (s, 1H).

Anal. Calcd. for $C_7H_6N_2O_2$: C, 58.53; H, 4.88; N, 17.07. Found: C, 58.26; H, 4.78; N, 16.85.

2-Bromo-*N*-(1-(1-propenyl)-2-oxo-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)acetamide, **10a**.

To 6.0 g (0.027 mole) of **5** in 50 ml of dry THF under nitrogen was added slowly in portions 1.2 g of sodium hydride (60% dispersion in mineral oil). After complete addition the mixture was refluxed for 2 hours then 8 ml of allyl bromide was added. After refluxing 3 days the mixture was cooled and water was cautiously added. Hydrogen evolution occurred. One hundred milliliters of methylene chloride was added. The layers were separated. The organic layer was passed through phase separation paper, and the solvent removed *in vacuo* leaving an oil. Chromatography (ethyl acetate) gave 1.3 g (15%) of a colorless oil: **10a**; ^{1}H nmr (deuteriochlorofrom): δ 1.0 and 1.27 (2d, J = 7, 3H), 3.30 (m, 2H), 3.35 (s, 3H), 3.65 (s, 2H), 4.6 (m, 2H), 5.1 (m, 3H), 5.9 (m, 1H), 6.3 (d of d, J = 5, 8, 1H), 7.4 (m, 2H); ms: m/e 342, 270, 231, 177, 135. Repeated analyses gave no correct C, H, N. Also isolated was unreacted **5**.

General Procedure for the Synthesis of *N*-(Alkyl)-*N'*-arylethanediamides.

N-(2-Methoxy-3-pyridinyl)-*N*-(1-methylethyl)-*N'*-(3-trifluoromethylphenyl)-ethanediamide, **11a**.

To 5.0 g (0.025 mole) of **2a** in 100 ml of THF was added 6.0 ml of oxalyl chloride. After stirring at room temperature for 18 hours hexane was added and a solid precipitated. This solid was filtered and washed with hexane. The hesane extracts were evaporated *in vacuo* leaving an oil which appeared to be the chlorocarbonylamide **10**. This was used immediately. To 3 g (0.01 mole) of crude **10** in 100 ml of THF was added 5 ml of *m*-aminobenzotrifluoride. After 4 hours the mixture was poured into 25 ml of 1*N* aqueous hydrochloric acid and 75 ml of chloroform. The layers were separated and the organic layer was filtered through phase separation paper. The solvent was removed *in vacuo* and the resulting solid was recrystallized from hexane to give 2.4 g (58%) of a white solid, mp 97-98°; ir (potassium bromide): 3300, 1715, 1640, 1560 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.06 (d, J = 1, 3H), 1.26 (d, J = 1, 3H), 3.89 (s, 3H), 4.9 (m, 1H), 6.98 (m, 1H), 7.4 (m, 3H), 7.75 (m, 2H), 8.1 (m, 1H), 9.41 (s, 1H); ms: m/e 381, 165, 151, 136, 43.

Anal. Calcd. for $C_{18}H_{18}F_3N_3O_3$: C, 56.69; H, 4.76; N, 11.02. Found: C, 56.43; H, 4.78; N, 10.81.

The following compounds were prepared in this manner.

N-(2-Methoxy-3-pyridinyl)-*N*-(1-methylethyl-*N'*-phenylethanediamide, **11b**.

This compound was obtaine in a yield of 40% as a white solid, mp 96-97°; recrystallized from hexane; ir (potassium bromide): 3140, 1705, 1635, 1590 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.06 (d, J = 1, 3H), 1.26 (d, J = 1, 3H), 3.88 (s, 3H), 4.9 (m, 1H), 6.94 (m, 1H), 7.23 (m, 1H), 7.26 (m, 1H), 7.4 (m, 2H), 7.43 (m, 3H), 8.1 (m, 1H), 9.15 (s, 1H); ms: m/e 313, 165, 151, 136, 92, 77, 43.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.00; H, 5.84; N, 13.26.

N-(2-Methoxy-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)-*N'*-(3-trifluoromethylphenyl)ethanediamide, **11c**.

This compound was obtained in a yield of 42% as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.99 and 1.34 (2d, J = 1, 3H), 3.33 (s, 3H), 3.4 (m, 2H), 3.9 (s, 3H), 4.6 and 5.1 (2m, 1H), 6.95 (m, 1H), 7.3 (m, 2H), 7.8 (m, 2H), 8.1 (m, 1H), 9.7 (s, 1H).

Anal. Calcd. for $C_{19}H_{20}F_3N_3O_4$: C, 55.47; H, 4.90; N, 10.21. Found: C, 55.45; H, 5.04; N, 10.02.

N-(2-Methoxy-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)-*N'*-(3-methoxyphenyl)ethanediamide, **11d**.

This compound was obtained in a yield of 15% as a colorless oil; ir (neat): 3270, 1680, 1650, 1635, 1595 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.99 and 1.35 (2d, J = 1, 3H), 3.35 (m, 4H), 3.73 (s, 3H), 3.86 and 3.89 (2s, 3H), 4.6 and 5.1 (2m, 1H), 6.65 (d, J = 1, 1H), 7.1 (m, 4H), 7.55 (m, 1H), 8.13 (m, 1H), 9.1 and 9.15 (2s, 1H).

Anal. Calcd. for $C_{19}H_{23}N_3O_5$: C, 61.61; H, 5.44; N, 11.34. Found: C, 61.37; H, 5.64; N, 11.07.

N-(1,2-Dihydro-2-oxo-3-pyridinyl)-*N*-(2-methoxy-1-methylethyl)*N'*-(3-trifluoromethylphenyl)ethanediamide, **13**.

A solution of 4.0 g (0.02 mole) of **2a** in 5 ml of dry benzene was saturated with gaseous hydrochloric acid for 2 hours. After cooling to room temperature, 5.0 ml of oxalyl chloride was added and the mixture stirred 72 hours at room temperature. To this solution was added 200 ml of ethyl acetate and then 20 g of 4-vinylpyridine polymer. After 30 minutes the mixture was filtered and the solvent removed *in vacuo*. To the resulting oil was added 50 ml of ethyl acetate then 5 ml of *m*-aminobenzotrifluoride and the mixture was refluxed 72 hours. After cooling to room temperature, the mixture was poured into 20 ml of water and 50 ml of chloroform. The organic layer was separated and washed with 20 ml of 1*N* aqueous hydrochloric acid then filtered through phase separation paper. After evaporation of the solvent *in vacuo*, the crude product was chromatographed (diethyl ether) twice to give 2.1 g (28%) of a white solid, mp 97-98°; ir (potassium bromide): 3300, 1665 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15 and 1.2 (2d, J = 7, 3H), 3.4 (s, 3H), 3.45 (m, 2H), 4.6 and 5.0 (2m, 1H), 6.15 (m, 1H), 7.5 (m, 6), 10.0 (s, 1H), 13.6 (s, 1H); ms: m/e 397, 352, 326, 281, 254, 209, 137.

Anal. Calcd. for $C_{18}H_{18}F_3N_3O_4$: C, 54.41; H, 4.57; N, 10.57. Found: C, 54.13; H, 4.43; N, 10.38.

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