Structural Elucidation of an Oxazolo[5,4-*b*]pyridine: an Alternative Cyclization Product Related to Nevirapine

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An unexpected cyclization product was isolated in the final step of the synthesis of nevirapine, a non-nucleoside inhibitor of HIV-1 reverse transcriptase. Based on infrared spectrometry, mass spectrometry, and a number of two-dimensional nmr experiments, the structure of this product was assigned to be 2-((2'-cyclopropylamino)-3'-pyridyl)-7-methyloxazolo[5,4-*b*]pyridine, **9**. Results of a single crystal X-ray analysis confirmed this structural assignment. This product arises from cyclization of *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamine)-3-pyridinecarboxamide, **8**, by displacement of the chlorine with the amide carbonyl oxygen. A competitive reaction occurs when **8** is deprotonated prior to cyclization to form nevirapine, 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one, **2**.

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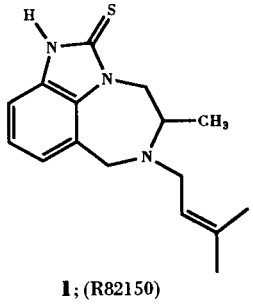
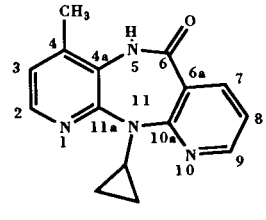
Introduction.

Recently a number of studies have been published that report the discovery of non-nucleoside inhibitors of HIV-1 reverse transcriptase [1-5]. The first such publication, from the Janssen Research Foundation, reported the development of a novel series of tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and -thione (TIBO) derivatives such as **1** (R82150) [1]. These derivatives inhibit the replication of HIV-1, the major etiologic agent of AIDS, at nanomolar concentrations. Subsequent reports from Boehringer Ingelheim Pharmaceuticals, Inc., describe the discovery of a unique class of non-nucleoside reverse transcriptase inhibitors that are exemplified by nevirapine, 11–cyclopropyl–5,11–dihydro–4–methyl–6*H*–dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**2**, (BI-RG-587)) [2]. This novel dipyridodiazepinone is a selective, noncompetitive inhibitor of HIV-1 reverse transcriptase with a high therapeutic index in culture. It has been postulated that non-nucleoside inhibitors of HIV-1 reverse transcriptase such as these could provide potent therapeutic agents for the fight against AIDS.



1; (R82150)



2; (nevirapine)

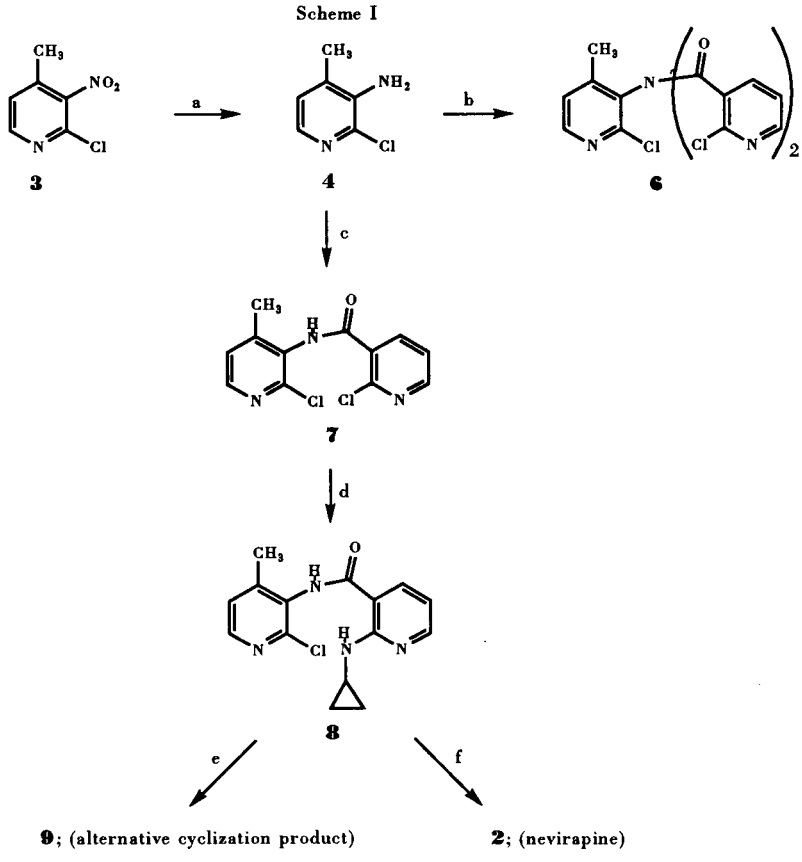
To study the effects of these and related inhibitors, it was necessary to prepare these compounds as pharmacological standards. Synthetic efforts directed toward the preparation of nevirapine, **2**, resulted in the isolation and identification of an interesting alternative cyclization product, **9**. The preparation and structural elucidation of this product is reported herein.

Chemistry.

The synthetic sequence directed toward the preparation of **2** is outlined in Scheme I. Commercially available 2-chloro-4-methyl-3-nitropyridine (**3**) was reduced with stannous chloride in hydrochloric acid to give 3-amino-2-chloro-4-methylpyridine (**4**) in 98% yield. Amine **4** was acylated with 2-chloro-3-pyridinecarbonyl chloride (**5**) (prepared by the treatment of 2-chloro-3-pyridine carboxylic acid with thionyl chloride) to provide an 87% yield of 2-chloro-*N*-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide (**7**). When this acylation was run under concentrated conditions with triethylamine as an acid scavenger, the bisacylated adduct **6** was obtained as the major product. Formation of the bis-acylated product was avoided through the use of dilute reaction conditions and without the addition of an external base.

The penultimate intermediate, *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (**8**), was obtained in 94% yield by heating dichloropyridinecarboxamide, **7**, with cyclopropylamine at 140° in a Teflon-capped pressure bottle.

Scheme I



a) $SnCl_2 \cdot 2H_2O/HCl$, Et_2O; b) CH_2Cl_2, NEt_3, 2-chloro-3-pyridinecarbonyl chloride (**5**); c) CH_2Cl_2, 2-chloro-3-pyridinecarbonyl chloride (**5**); d) cyclopropylamine, 140 °C; e) DMF, Na_2CO_3, reflux; f) NaH, diglyme, reflux.

Under these conditions only one of the chlorine atoms underwent displacement, and no ring-closed product was observed. It was envisaged that closure of this intermediate would be straightforward to provide nevirapine, **2**, as the required pharmacological standard. This, however, was not the case. Heating amide **8** with sodium carbonate in refluxing dimethylformamide provided a 90% yield of a light yellow powder, which appeared to be the desired dipyridodiazepinone upon initial examination of the spectral data. Shortly after the completion of our synthesis, however, experimental and spectral data for nevirapine was reported by Hargrave, *et al.* [2]. It was apparent by comparison of our data with literature values that an unexpected reaction had occurred during the final cyclization process. When the cyclization of amide **8** was carried out under the published reaction conditions (heating the corresponding dianion, generated by deprotonation with sodium hydride, in bis(2-methoxyethyl) ether (diglyme)) the requisite pharmacological standard, nevirapine (**2**), was obtained. With the two products resulting from the common precursor **8** in hand, experiments were conducted to elucidate the structure of the unknown cyclization product. The results of these studies are discussed below.

Results and Discussion.

The unknown cyclization product obtained by heating the 2'-alkylamino-amide **8** with sodium carbonate in dimethylformamide was analyzed by CHN combustion analysis, EI-ms, FT-ir, and FT-nmr techniques.

Determination of the molecular weight and molecular formula was accomplished by CHN combustion analysis and high-resolution mass spectrometric measurements. Elemental analysis of the unknown was consistent with theoretical values expected for the desired cyclization product. The mass spectrum of the cyclized product showed a strong molecular ion at m/z 266, along with fragment ions at m/z 251 (base peak) and m/z 238, which correspond to the losses of CH_3 and C_2H_2, respectively. The elemental compositions of the molecular ion and two fragment ions were confirmed by high resolution mass measurements

(Table 1). As shown in Table 1, the difference between the experimental and theoretical exact masses for the three ions is less than 3.0 millimass units. Again, these data were consistent for the desired dipyridodiazepinone, **2**.

Table 1

Exact Mass Measurements of Oxazolo[5,4-*b*]pyridine **9** and Prominent Ions

Experimental Mass (mu)	Theoretical Mass (mu)	Deviation (mmu)	Empirical Formula
266.1160	266.1168	-0.8	$C_{15}H_{14}N_4O$
251.0916	251.0933	-1.7	$C_{14}H_{11}N_4O$
238.0885	238.0855	3.0	$C_{13}H_{10}N_4O$

Infrared spectra were taken of compounds **2** and **9** in the solid state (potassium bromide pellet). Spectral data observed for nevirapine, **2**, were highly characteristic of the 7-membered lactam group in this molecule. In contrast, ir data observed for **9** were distinctly different, providing strong evidence that an alternative product had formed. Frequencies assigned to NH stretching and bending vibrations (3192, 3063, and 1415 cm^{-1}) of **2** were diagnostic of the hydrogen-bonded *cis* conformation of this 7-membered lactam [6]. In addition, the amide carbonyl was characterized by the intense absorption at 1642 cm^{-1}. The FT-ir spectrum of product **9**, in contrast, showed no evidence of an amide functionality, either open chain or cyclic. The intense carbonyl absorption at 1642 cm^{-1} and the broad NH bands between 3300 and 3190 cm^{-1} that characterized the lactam group in nevirapine were absent. These data indicated that **9** did not contain an amide moiety. Furthermore, the lack of strong bands between 1640 and 1750 cm^{-1} conclusively demonstrated that there were no carbonyl groups of any type in this molecule. The ir data observed for this molecule did contain evidence of three types of functional groups not found in nevirapine: a secondary arylalkyl amine, an imine, and a fully conjugated ether (=C-O-C=).

The presence of a secondary arylalkyl amine group was supported by bands at 3317 and 1514 cm^{-1}. These were assigned to NH stretching and bending vibrations, respectively. Assignment of the 1514 cm^{-1} band to an NH bending mode was confirmed by deuterium exchange. Assignment of these bands to vibrational modes of a secondary amine rather than a hydroxyl group were supported by (1) the sharp band shape at 3317 cm^{-1} and (2) the frequency of the bending vibration at 1514 cm^{-1}. Alcohols and phenols have broad band shapes in the 3300 cm^{-1} region, and bending vibrations near 1400 cm^{-1}.

The FT-ir data observed for product **9** in the solid state and in solution also provided evidence of an N-conjugated imine group. Moderately strong absorption at 1632 cm^{-1} was attributed to the C=N stretching mode of this group. This assignment was favored over the C=C stretching vibration of an olefin because the band intensities arising from C=C stretching are, with few exceptions, very weak in the ir, while those arising from C=N stretching are intermediate between C=O and C=C. *N*-Conjugation of the imine was supported by data observed for a very dilute chloroform solution of product **9**, where a moderately intense band was again observed at 1632 cm^{-1}. This band frequency lies very close to the frequency where the C=N stretching mode of *N*-conjugated imines typically absorb (1630 cm^{-1}) and is lower than those where non-conjugated and *C*-conjugated imines generally absorb (1650 cm^{-1} and 1640 cm^{-1}, respectively) under these same conditions [7].

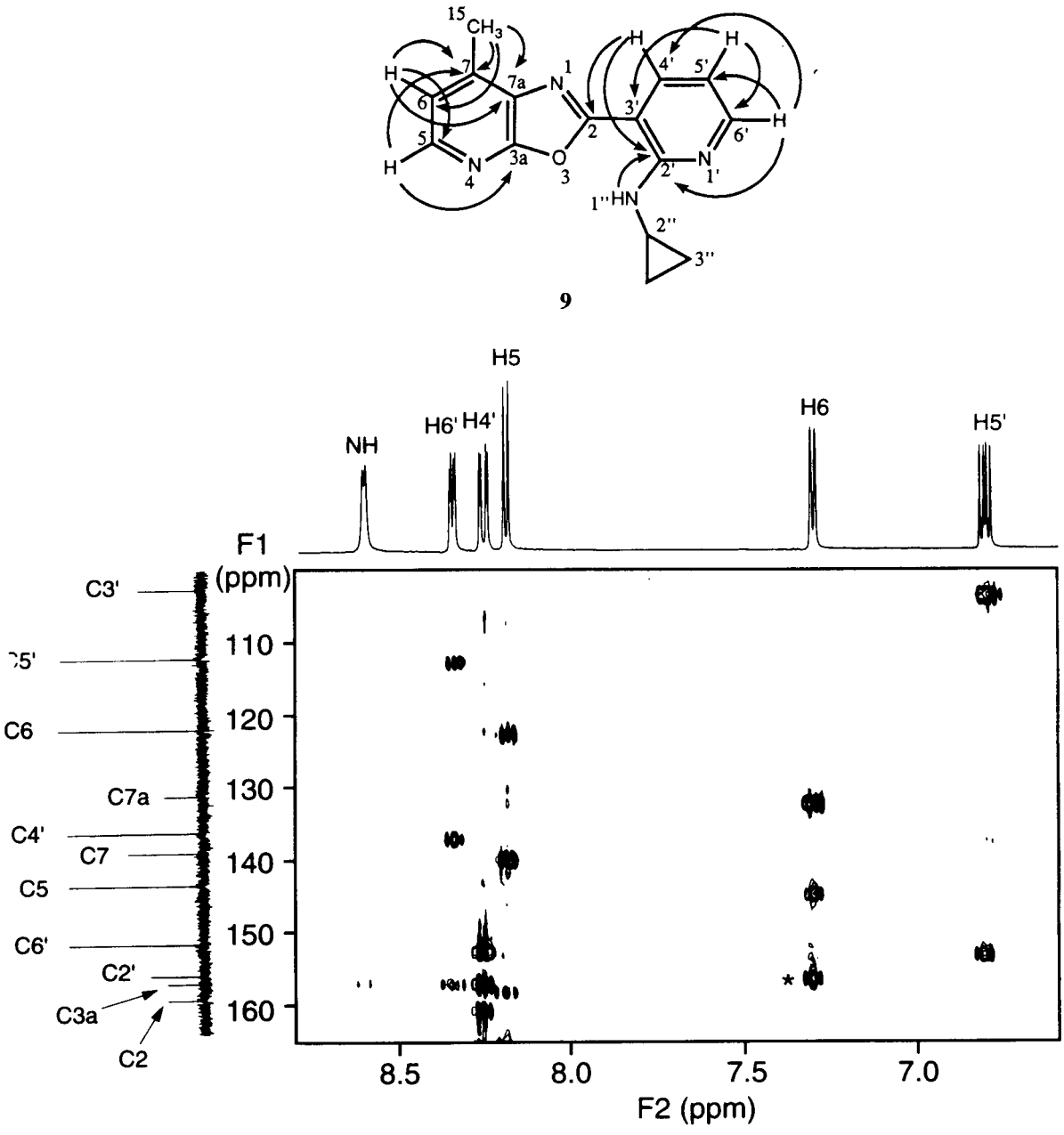
Finally, FT-ir data provided evidence of a fully conjugated ether group (=C-O-C=) in **9**. The strong band at 1226 cm^{-1} in this spectrum was not observed in the spectrum of nevirapine (**2**). This band occurred in the region where C-O stretching vibrations of conjugated ether groups (=C-O-) are found (1310-1210 cm^{-1}). Assignment of this band to the C-O stretching mode of a fully conjugated ether instead of an arylalkyl ether was based upon the absence of a second strong band between 1150 and 1060 cm^{-1}, where the alkyl C-O stretching vibration of these ethers occurs.

In summary, FT-ir data for **9** indicated that this molecule did not contain any carbonyl functionality. These data did indicate the presence of arylalkyl

Table 2

Proton and Carbon NMR Chemical Shift Assignments, Homonuclear Coupling Constants, and Long-range Connectivities Observed for Oxazolo[5,4-*b*]pyridine **9** in DMSO-d_6 at 400 MHz.

Position	Chemical Shift (δ) ^1H	Chemical Shift (δ) ^{13}C	Coupling J (Hz)	Long-Range Correlations (^1H-^{13}C)
2		160.2		
7a		131.8		
7		139.7		
6	7.31	122.5	5.1	C7a, C7, C5
5	8.19	144.2	5.2	C7, C6, C3a
3a		157.9		
2'		156.8		
3'		102.8		
4'	8.26	136.8	7.7, 1.8	C2, C2', C6'
5'	6.81	112.4	7.6, 4.8	C3', C4', C6'
6'	8.34	152.3	4.6, 1.7	C2', C4', C5'
1"NH	8.60		3.1	C2'
2"	2.96	24.1	mult.	
3"	0.84	7.1	mult.	
	0.56		mult.	
7-CH_3	2.59	15.8	*s*	



9

Figure 1. HMBC spectrum of oxazolo[5,4-*b*]pyridine **9**. Long-range couplings observed in the 63 msec (8 Hz) optimized HMBC spectrum are as indicated.
*Correlation H6-CH_3 folded in F_1.

amine, *N*-conjugated imine, and fully conjugated ether groups in this molecule, all of which were subsequently confirmed by X-ray diffraction and supported by long-range heteronuclear couplings observed in the HMBC spectrum (*vide infra*).

The proton nmr spectrum of the unexpected cyclization product at 400 MHz was essentially first order. Resonances corresponding to the two-spin and three-spin systems of the two pyridine-derived moieties, an *N*-methyl, resonances for the aminocyclopropyl, and an NH resonance at 8.60 ppm were observed. It is important to note that the NH resonance appeared as a doublet rather than the singlet that would be expected for the amide proton of nevirapine (**2**). Other than this inconsistency, the proton data were reasonable for the structure of **2**. The carbon nmr spectrum also contained resonances that could be interpreted in a manner consistent with the initially anticipated product, **2**. There were no obviously unaccountable resonances based on the structure of **2**.

Resonances which could potentially be assigned as the amide carbonyl were, however, shifted upfield from 3-10 ppm relative to the normal chemical shift anticipated for a carbonyl of the type contained in **2**.

Protonated aromatic carbon chemical shift assignments were made from an inverse-detected heteronuclear shift correlation (HMQC) spectrum [8] . A long-range correlation (HMBC) spectrum was also acquired using the pulse sequence of Bax and Summers [9]. Long-range correlations were typical for pyridine-derived heterocycles. When the data were interpreted in light of the infrared data (*vide supra*) only a single long-range connectivity was inconsistent with the anticipated product **2**. Specifically, the NH, H6', and H4' resonances at 8.60, 8.34, and 8.26 ppm (refer to numbering for **9**), respectively, all long-range couple to a quaternary carbon resonating at 156.8 ppm. The latter two correlations are expected and would be consistent with **2**. For **2**, correlations would be expected and should be observed from both H7 and H9 to the C10a quaternary carbon. The correlation from the NH to the quaternary carbon resonance at 156.8 ppm was weak and was not observed when the data set was initially acquired. The acquisition of a second HMBC spectrum with a longer interpulse delay uncovered the weak correlation from the NH to the quaternary carbon resonating at 156.8 ppm. If **2** was the correct structure, the correlation from the NH to the 156.8 ppm quaternary carbon, which could only reasonably be assigned as C10a, would be *via* $^{4}J_{CH}$. Although four-bond couplings in HMBC spectra are not without precedent, they are uncommon [10]. Alternately, for structure **9**, the correlation from the NH to C2' would arise *via* $^{2}J_{CH}$. Two-bond long-range couplings are much more commonly encountered and are also frequently weak. Furthermore, the attachment of the aminocyclopropyl moiety at the 2' position of **9** also accounts for the splitting of the NH resonance, which would be inexplicable in the case of **2**. There was no coupling observed between the NH resonance and a resonance assignable as either C11a or C4 *via* three-bonds or to C4a *via* two-bonds (refer to numbering for **2**). If indeed **2** was the correct structure, at least one of these coupling pathways should have given an observable response in the HMBC spectrum. In contrast, for **9**, couplings to the corresponding C7a, C3a, and C7 carbons from the NH are obviously impossible. Long-range couplings observed in the HMBC spectrum are shown in Figure 1. Complete proton and carbon resonance assignments, homonuclear coupling constants, and a summary of observed long-range correlations are contained in Table 2.

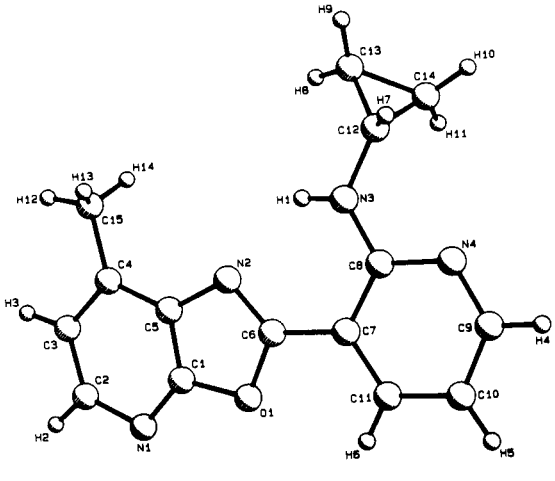


Figure 2. ORTEP representation of the X-ray crystal structure of oxazolo[5,4-*b*]pyridine **9**.

From the data outlined above, the alternative cyclization product was assigned 2-((2'-cyclopropylamino)-3'-pyridyl)-7-methyloxazolo[5,4-*b*]pyridine, **9**. To confirm this structural assignment, crystals suitable for X-ray analysis were obtained by recrystallization from ethyl acetate/hexanes, and the crystal structure was determined. The resultant ORTEP representation is shown in Figure 2. The crystal data, positional parameters, bond lengths, and bond angles of the single X-ray crystal structure of **9** are reported in Tables 3-6. Estimated standard deviations in the least significant figure are given in parentheses.

Table 3

Crystal Data for Compound **9**

Empirical Formula	$C_{15}H_{14}N_4O$
Formula weight	266.30
Crystal Dimensions	0.350 x 0.120 x 0.100 mm
Crystal System	monoclinic
No. Reflections Used for Unit Cell Determination (2θ range)	24 (80.9 - 100.2°)
No. Reflections Measured	Total: 2265 Unique: 2202 (R_{int} = 0.068)
No. Observations (I>3.00σ(I))	1099
No. Variables	185
Omega Scan Peak Width at Half-height	0.39
Lattice Parameters:	
a	24.090(8)Å
b	5.72(1)Å
c	19.23(1)Å
β	95.14(4)°
v	2640 (5)Å^3
Space Group	C2/c (#15)
z value	8
d_{calcd}	1.340 g cm^{-3}
μ(CuKα)	6.75 cm^{-1}
Temperature	23°C
$2\theta_{max}$	120.3°
Residuals	R: 0.050 R_w: 0.051

Table 4

Positional Parameters and B[eq] for Compound **9**

Atom	x	y	z	B[eq]
O1	0.2145(1)	0.0917(6)	0.4244(1)	4.6(2)
N1	0.2790(1)	0.3799(7)	0.3969(2)	5.2(2)
N2	0.1397(1)	0.2000(7)	0.3519(2)	4.3(2)
N3	0.0427(2)	-0.0396(9)	0.3670(2)	5.1(2)
N4	0.0464(1)	-0.3639(7)	0.4374(2)	5.1(2)
C1	0.2289(2)	0.2860(8)	0.3871(2)	4.1(2)
C2	0.2820(2)	0.572(1)	0.3561(3)	5.4(3)
C3	0.2396(2)	0.6581(9)	0.3109(2)	5.0(2)
C4	0.1877(2)	0.5495(9)	0.3022(2)	4.5(2)
C5	0.1840(2)	0.3536(8)	0.3439(2)	4.0(2)
C6	0.1596(2)	0.0553(8)	0.3998(2)	3.9(2)
C7	0.1310(2)	-0.1394(8)	0.4296(2)	4.0(2)
C8	0.0733(2)	-0.1792(9)	0.4114(2)	4.2(2)
C9	0.0756(2)	-0.500(1)	0.4820(3)	5.4(3)
C10	0.1314(2)	-0.4759(9)	0.5045(2)	5.1(3)
C11	0.1586(2)	-0.2894(9)	0.4766(2)	4.7(2)
C12	-0.0155(2)	-0.069(1)	0.3475(2)	5.2(3)
C13	-0.0486(2)	0.142(1)	0.3288(3)	6.4(3)
C14	-0.0563(2)	0.015(1)	0.3944(3)	7.2(3)
C15	0.1411(2)	0.634(1)	0.2532(3)	6.1(3)
H1	0.057(2)	0.085(8)	0.352(2)	6(1)
H2	0.3163	0.6549	0.3592	6.5
H3	0.2458	0.7952	0.2848	6.0
H4	0.0565	-0.6281	0.5005	6.5
H5	0.1500	-0.5808	0.5371	6.1
H6	0.1970	-0.2646	0.4903	5.6
H7	-0.0257	-0.2052	0.3214	6.2
H8	-0.0312	0.2912	0.3304	7.7
H9	-0.0769	0.1376	0.2910	7.7
H10	-0.0896	-0.0714	0.3988	8.7
H11	-0.0439	0.0822	0.4382	8.7
H12	0.1525	0.7705	0.2302	7.3
H13	0.1311	0.5161	0.2197	7.3
H14	0.1100	0.6697	0.2784	7.3

Table 5

Bond Lengths (Å) for Compound **9**

Bond		Length	Bond		Length
O1	C1	1.383(5)	C3	C4	1.392(6)
O1	C6	1.379(5)	C4	C5	1.386(6)
N1	C1	1.320(5)	C4	C15	1.480(6)
N1	C2	1.357(6)	C6	C7	1.454(6)
N2	C5	1.401(5)	C7	C8	1.423(6)
N2	C6	1.297(5)	C7	C11	1.373(6)
N3	C8	1.340(6)	C9	C10	1.382(6)
N3	C12	1.428(6)	C10	C11	1.384(6)
N4	C8	1.359(6)	C12	C13	1.471(7)
N4	C9	1.316(6)	C12	C14	1.472(6)
C1	C5	1.360(6)	C13	C14	1.484(7)
C2	C3	1.372(6)			

Table 6

Bond Angles (°) for Compound **9**

Bond			Angle	Bond			Angle
C1	O1	C6	102.8(3)	O1	C6	C7	116.9(4)
C1	N1	C2	110.1(4)	N2	C6	C7	127.7(4)
C5	N2	C6	104.0(4)	C6	C7	C8	120.8(4)
C8	N3	C12	124.7(5)	C6	C7	C11	121.4(4)
C8	N4	C9	117.1(4)	C8	C7	C11	117.8(4)
O1	C1	N1	121.5(4)	N3	C8	N4	116.4(4)
O1	C1	C5	108.8(4)	N3	C8	C7	122.1(4)
N1	C1	C5	129.7(5)	N4	C8	C7	121.5(4)
N1	C2	C3	125.5(5)	N4	C9	C10	126.4(5)
C2	C3	C4	121.8(5)	C9	C10	C11	115.9(5)
C3	C4	C5	113.3(5)	C7	C11	C10	121.3(4)
C3	C4	C15	123.5(5)	N3	C12	C13	117.8(5)
C5	C4	C15	123.2(4)	N3	C12	C14	119.7(4)
N2	C5	C1	109.0(4)	C13	C12	C14	60.6(3)
N2	C5	C4	131.3(4)	C12	C13	C14	59.8(3)
C1	C5	C4	119.6(4)	C12	C14	C13	59.7(3)
O1	C6	N2	115.4(4)				

Scheme II

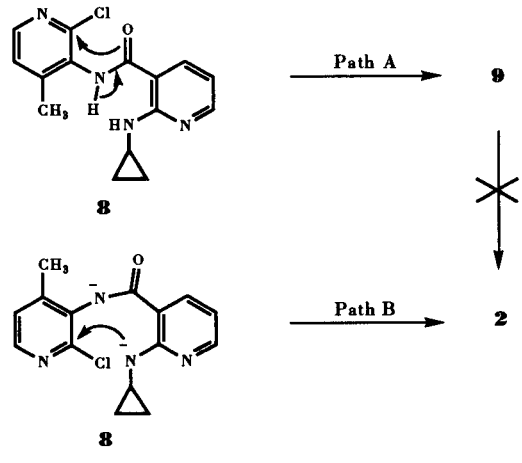


Table 7

Reaction Conditions vs. Product Distribution.

8 ⟶ **9** + **2**

Entry	Solvent	Base	equivalents	Product Ratios (%) 8 : 9 : 2		
1	DMF	Na_2CO_3	1	0	100	0
2	DMF	NaH	4	0	100	0
3	Diglyme	Na_2CO_3	1	90	10	0
4	Diglyme	NaH	1	45	55	0
5	Diglyme	NaH	2	0	25	75
6	Diglyme	NaH	4	0	0	100

The factors controlling the two modes of cyclization of amino-amide **8** were investigated (Table 7). A profound solvent effect was observed in the formation of the two products. When dimethylformamide was employed as the solvent with the addition of either sodium carbonate or sodium hydride, the oxazolo[5,4-*b*]pyridine, **9**, was obtained as the sole product [11] (Table 7, entries 1 and 2). This product arises from

displacement of the chlorine atom by the amide carbonyl oxygen as shown in Scheme II, Path A. Alternatively, when diglyme was used as the solvent, varying amounts of the dipyridodiazepinone, **2**, were obtained (Scheme II, Path B). Under mildly basic conditions, which did not deprotonate the aromatic amine, the oxazolo[5,4-*b*]pyridine product dominated (Table 7, entries 3 and 4). However, when the dianion of amide-amine **8** was formed by treatment with sodium hydride, the amine was the preferred nucleophile, leading to the formation of nevirapine, **2** (Table 7, entry 6). Under conditions that allowed only partial deprotonation of the amine the two reaction pathways were competitive, resulting in the formation of a mixture of both cyclization products (Table 7, entry 5). Treatment of oxazolo[5,4-*b*]pyridine **9** with either 1 or 4 equivalents of sodium hydride in refluxing diglyme for 1.5 hours did not result in the formation of dipyridodiazepinone **2**, suggesting that **9** is unlikely to be an intermediate in the formation of dipyridodiazepinone **2**.

Conclusion.

We have developed synthetic procedures to *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamine) 3-pyridine carboxamide (**8**) that represent significant improvements to the methods described previously. Amide **8** was obtained in an 80% overall yield from **3**, whereas the corresponding literature method yields only 41% of this intermediate [2]. Furthermore, we have isolated and characterized two products arising from cyclization of this intermediate under a variety of conditions (oxazolo[5,4-*b*]pyridine, **9**, and dipyrridodiazepinone, **2**). The relative formation of these two products was shown to be dependent on the solvent employed and on the degree of deprotonation of the precursor amide, **8**.

EXPERIMENTAL

General.

Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Anhydrous solvents such as dichloromethane and dimethylformamide (DMF) were obtained from Aldrich Chemical Company in Sure Seal bottles. Triethylamine was distilled from calcium hydride prior to use. Flash chromatography [12] was performed using EM Science silica gel 60 (230-400 mesh ASTM). Thin-layer chromatography (tlc) was performed with Analtech silica gel FG tlc plates (250 mm). All nmr experiments for compound **9** were performed using a Varian Unity 400 operating at an observation frequency of 399.952 MHz for ^{1}H observation and 100.577 MHz for ^{13}C and equipped with a 5 mm Z•Spec inverse-detection probe from Nalorac Cryogenics Corp., Martinez, CA. All data for compound **9** were acquired using a sample prepared by dissolving 5 mg of **9** in 0.7 ml of 99.96% DMSO-d_6 (Merck), except for the carbon spectrum which was recorded on a 20 mg sample. The HMQC spectrum was acquired using the pulse sequence of Bax and Subramanian [8] as 320 x 16 points for the aromatic region of the spectrum. The one-bond delay was optimized for 160 Hz. The data were zero-filled to 1024 x 128 points and were processed using Gaussian multiplication prior to the first Fourier transform and cosine multiplication prior to the second. The HMBC spectra were acquired as 1024 x 64 points using the pulse sequence of Bax and Summers [9]. The long-range delay was optimized for 63 msec (8 Hz). The one-bond delay in the low-pass J-filter was optimized for 160 Hz. The data were zero filled to 2048 x 256 points and were processed using hypercomplex processing with multiplication by a combination of a Gaussian/phase-shifted Gaussian prior to the first Fourier transform and cosine multiplication prior to the second. All proton and carbon spectra for intermediates **4-8** were acquired using either a Varian XL-300 or a Varian Gemini-200 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H nmr data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hz. The electron impact (EI) mass spectra were obtained using a VG 70S mass spectrometer under the following conditions: accelerating voltage 7 KV; ionization energy 70 eV; trap current 200 microamps, probe temperature 110°C; source temperature 200°C; low resolution 1,000 (10% valley definition), scan range 40-800 amu; high resolution 8,000 (10% valley definition), scan range 100-300 amu. Accurate mass measurements were performed using perfluorokerosene as the secondary reference standard. All mass spectra were recorded using a VG 11-250J data system, and the data were analyzed using a Kratos Mach 3 work station. The FT-ir spectra were recorded with an Analect FX6260 FT-IR operating at 2 cm^{-1} resolution. The spectrometer was equipped with a DTGS detector and an FXA 510/520 beam condenser (9x) that held the potassium bromide pellets and solution cells examined in this study. Spectra of samples in potassium bromide pellets were obtained by dividing 32 co-added sample spectra (sample + potassium bromide) by 32 co-added background spectra (blank potassium bromide pellet). Solution studies were performed using a Spectra Tech potassium bromide microcavity cell (0.5 mm nominal cell length). A background spectrum of the empty potassium bromide cell was obtained by co-adding 125 scans. Solution spectra were then obtained by co-adding 125 scans for each solution and dividing by the background spectrum. Solvent bands were removed from solution spectra by digital subtraction. Data smoothing (9-point) and peak locations were accomplished using software supplied with the instrument. The solvent used in this study was deuteriochloroform (MSD Isotopes). The potassium bromide (99+ %) was obtained from Aldrich Chemical Company. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Thomas-Hoover capillary melting point

apparatus and are uncorrected.

3-Amino-2-chloro-4-methylpyridine (**4**).

To a 250-ml, round-bottomed flask was added 2-chloro-4-methyl-3-nitropyridine (4.53 g, 26.3 mmoles) and anhydrous ether (25.0 ml). A solution of stannous chloride dihydrate (23.1 g, 102 mmoles, 3.9 equivalents) in concentrated hydrochloric acid (25.0 ml) was added dropwise to the colorless solution. As the stannous chloride solution was added, the reaction mixture turned light yellow and the ether was allowed to evaporate as the reaction became exothermic. The reaction mixture was allowed to stir at room temperature for 20 minutes. As the reaction proceeded, the yellow solution became colorless. The reaction mixture was cooled in an ice/water bath, distilled water (85.0 ml) was added, and the solution was allowed to stir at 0° for 0.5 hour. An aqueous solution of 50% sodium hydroxide was added to the reaction mixture until the solution was basic (*p*H 11-12). White solids precipitated from solution and redissolved as more base was added. The aqueous solution was extracted with dichloromethane (3 x 75 ml). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give 3.65 g (98%) of **4** as a white solid, mp: 68-70° (lit [2] mp: 65-66°); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 2.21 (s, 3), 4.02 (br s, 2), 6.93 (d, 1, J = 4.8), 7.72 (d, 1, J = 4.8); ^{13}C nmr (deuteriochloroform, 75.43 MHz): δ 17.41, 124.70, 131.87, 136.58, 137.92, 138.16.

Anal. Calcd. for $C_6H_7N_2Cl$: C, 50.54; H, 4.95; N, 19.65. Found: C, 50.62; H, 5.00; N, 19.65.

2-Chloro-3-pyridinecarbonyl chloride (**5**).

To an oven-dried, 200-ml, round-bottomed flask was added 2-chloronicotinic acid (20.0 g, 0.127 mole) as a white powder. Thionyl chloride (55.5 ml, 90.6 g, 0.762 mole, 6.0 equivalent) was slowly added to the acid *via* an addition funnel. The resulting white slurry was placed under nitrogen and heated at reflux for 1 hour. The mixture became a light yellow, homogeneous solution upon heating. The reflux condenser was replaced with a distillation head, and the excess thionyl chloride was removed by distillation under aspirator pressure. Toluene (10.0 ml) was added to the distillation pot and then distilled under reduced pressure. Upon cooling, the pot residue slowly solidified to give 22.09 g (99%) of **5** as a tan solid, mp: 39-42°; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 7.45 (dd, 1, J = 4.8, 7.9), 8.41 (dd, 1, J = 1.9, 7.9), 8.59 (dd, 1, J = 1.9, 4.8); ^{13}C nmr (deuteriochloroform, 125.70 MHz): δ 121.91, 129.26, 141.35, 148.95, 152.86, 163.85.

Anal. Calcd. for $C_6H_3NOCl_2$: C, 40.95; H, 1.72; N, 7.96. Found: C, 40.94; H, 1.73; N, 7.94.

2-Chloro-*N*-(2-chloro-4-methyl-3-pyridyl)-3-pyridinecarboxamide (**7**).

To an oven-dried, 100-ml, round-bottomed flask were added 3-amino-2-chloro-4-methylpyridine (**4**)(0.25 g, 1.8 mmoles) and anhydrous dichloromethane (20.0 ml). The solution was placed under nitrogen and cooled to -78° in a dry ice / acetone bath. A solution of 2-chloro-3-pyridinecarbonyl chloride (**5**)(0.31 g, 1.8 mmoles) in dichloromethane (20.0 ml) was added to the amine over a 0.5 hour period. The reaction mixture was allowed to stir at -78° for 1 hour and at room temperature for 23 hours. Saturated aqueous potassium carbonate was added, and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 0.48 g of a white solid. The product was purified by flash chromatography with 2:1 ethyl acetate:hexanes as eluant to give 0.43 (87%) of **7** as a white powder, mp: 191-192° (lit [2] mp: 189-191°). The ^{1}H nmr spectral data were identical to that previously reported [2]; ^{13}C nmr (DMSO-d_6, 75.43 MHz): δ 17.90, 123.19, 125.27, 129.77, 132.31, 138.16, 146.34, 147.51, 148.86, 148.97, 150.79, 168.77.

Anal. Calcd. for $C_{12}H_9N_3OCl_2$: C, 51.09; H, 3.22; N, 14.89. Found: C, 51.16; H, 3.26; N, 14.82.

N-(2-Chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (**8**).

To an oven-dried, 50-ml, pressure bottle was added 2-chloro-*N*-(2-chloro-4-methyl-3-pyridyl)-3-pyridinecarboxamide (**7**) (2.60 g, 9.22 mmoles) and cyclopropylamine (25.0 ml). The solution was placed under a nitrogen atmosphere and the bottle was closed tightly with a Teflon screw cap. The cloudy reaction mixture was heated in an oil bath at 130-150° for 4 hours. As the reaction progressed, the solution became clear and a white solid precipitated. The pressure bottle was allowed to cool to room temperature and cooled further in an ice-water bath before opening. The reaction mixture was dissolved in dichloromethane and washed with saturated aqueous potassium carbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give 3.82 g of a sticky, light-yellow solid. This material was purified by flash chromatography with 1:1 hexanes:ethyl acetate as eluant to give 2.63 g (94%) of **8** as a white solid, mp: 127-129° (lit [2] mp: 127-129°). The ^{1}H nmr spectral data were identical to that previously reported [2]; ^{13}C nmr (deuteriochloroform, 75.43 MHz): δ 7.06, 18.90, 23.83, 108.47, 111.20, 125.16, 129.96, 136.06, 146.97, 148.31, 148.33, 153.26, 159.31, 166.90.

Anal. Calcd. for $C_{15}H_{15}N_4OCl$: C, 59.51; H, 4.99; N, 18.50. Found: C, 59.59; H, 5.01; N, 18.55.

2-((2'-Cyclopropylamino)-3'-pyridyl)-7-methyloxazolo[5,4-*b*]-pyridine (**9**).

To an oven-dried, 100-ml, round-bottomed flask was added *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (**8**) (1.50 g, 4.95 mmoles), sodium carbonate (0.58 g, 5.45 mmoles, 1.1 equivalents) and anhydrous dimethylformamide (50.0 ml). The reaction mixture was placed under a nitrogen atmosphere and heated at reflux for 19 hours. The dimethylformamide was removed with a rotary evaporator under reduced pressure. The resulting dark orange residue was taken up in ethyl acetate and washed with distilled water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 1.27 g of an orange-yellow solid. The crude material was purified by flash chromatography with 3:1 hexanes:ethyl acetate as eluant to give 1.19 g (90%) of **9** as a yellow

powder, mp: 158-159°; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 0.66 (m, 2), 0.95 (m, 2), 2.66 (s, 3), 3.03 (m, 1), 6.74 (dd, 1, J = 7.8, 4.9), 7.14 (d, 1, J = 5.1), 8.18 (d, 1, J = 5.1), 8.33 (dd, 1, J = 7.8, 1.9), 8.41 (dd, 1, J = 4.9, 1.9), 8.36 (br s, 1); ^{13}C nmr (deuteriochloroform, 75.43 MHz): δ 7.33, 16.21, 23.98, 103.72, 112.05, 122.07, 132.61, 137.12, 139.73, 144.07, 152.36, 157.48, 158.45, 160.90. ^{1}H and ^{13}C nmr data recorded in DMSO-d_6 are reported in Table 2.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.70; H, 5.30; N, 21.02.

11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin -6-one (**2**).

To an oven-dried, 25-ml, round-bottomed flask was added *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (**8**) (0.530 g, 1.75 mmoles), diglyme (5.0 ml) and sodium hydride (0.157 g of an 80% oil dispersion, 5.25 mmoles, 3.0 equivalents). The solution was placed under nitrogen and slowly heated in an oil bath. The reaction mixture was allowed to heat at 180-190° for 1.5 hours. The solution was allowed to cool, poured into ice water and allowed to stir for 1 hour. The resulting white precipitate was filtered, washed with water and dried in a vacuum oven to give 0.367 g of an off-white solid. This material was purified by flash chromatography with 1:1 hexanes:ethyl acetate as eluant to give 0.310 g (67%) of **2** as a white solid, mp: 242-244° [lit [2] mp: 247-249°]. The ^{1}H nmr spectral data were identical to that previously reported [2]; ^{13}C nmr (deuteriochloroform, 75.43 MHz): δ 8.88, 9.15, 17.86, 29.65, 118.99, 120.35, 122.13, 124.97, 139.52, 140.36, 144.47, 152.15, 154.17, 160.73, 169.06.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.74; H, 5.31; N, 20.93.

X-ray Crystallography of 2-((2'-Cyclopropylamino)-3'-pyridyl)-7-methyloxazolo [5,4-*b*]pyridine (**9**).

The single crystal X-ray analysis of oxazolo[5,4-*b*]pyridine **9** was performed by Molecular Structure Corporation, The Woodlands, TX. Compound **9** was recrystallized from a mixture of ethyl acetate and hexanes to yield light-yellow, prism-shaped crystals. A crystal having approximate dimensions of 0.350 x 0.120 x 0.100 mm was selected for data collection. All measurements were made at 23° on a Rigaku AFC5R diffractometer with graphite monochromated CuKα radiation and a 12KW rotating anode generator. Crystal survey, unit cell determination, and data collection were performed using copper radiation at room temperature. The structure was solved by direct methods [13] and refined by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. The hydrogen atom attached to the nitrogen atom was located by difference Fourier techniques and refined isotropically. The positions of the remaining hydrogen atoms were calculated assuming ideal geometries.

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