Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1 Specific Reverse Transcriptase Inhibitors. 1. Phthalimidoalkyl and -alkylamino Analogues†

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A potent (IC_{50} = 30 nM), specific nonnucleoside HIV-1 reverse transcriptase (RT) inhibitor 3-[*N*-(phthalimidomethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (**1**), was discovered through an in vitro screening program. This compound did not inhibit (IC_{50} > 300 μm) other DNA and RNA polymerases, including HIV-2 RT and SIV-RT. Unfortunately, hydrolytic instability of this (aminomethyl)phthalimide precluded use as an antiviral agent. In the first paper of this series, preliminary development efforts are described which produced ethylphthalimide **20**, a hydrolytically stable compound with reduced (100-fold) HIV-1 RT inhibitory activity and weak (CIC_{95} = 40 μM) antiviral activity in H9 cells. Structure–activity studies demonstrated the importance of the 5-ethyl, 6-methyl substituent pattern on the pyridinone ring and the need for a flexible two-atom linker between the pyridinone and phthalimide heterocycles. These leads, **1** and **20**, provided a basis for the further development of this structural class of inhibitors from which several compounds, the subject of accompanying reports, were selected for clinical evaluation.

The development of potent and effective antiviral drugs for the treatment of human immunodeficiency virus type 1 (HIV-1) infection has become one of the most intensely pursued goals of contemporary medicinal chemistry. Since retroviruses, such as HIV-1, possess a unique replication cycle, a variety of molecular targets are available for chemotherapeutic intervention.[1] One such target of considerable interest is the virally encoded reverse transcriptase (RT) which mediates conversion of the viral RNA genome to proviral DNA. Indeed, nucleoside analogues, such as 3′-azidothymidine (AZT) and dideoxyinosine (ddI), which inhibit the process of reverse transcription, are used clinically for the treatment of HIV-1 infection.[2-5] However, the utility of these nucleoside analogues is limited by significant toxicities, some of which may be attributed to inhibition of other cellular DNA polymerases.[4,6,7] The emergence of resistant viral strains has also become a major concern.[8-10]

Attention is therefore currently focused on the development of other nucleoside and nonnucleoside inhibitors as alternative or combination therapy. Potent, nonnucleoside, HIV-1-specific RT inhibitors have now been described in several chemically diverse series.[11-14] Recent communications from our laboratories have disclosed the discovery and characterization of the 2-pyridinone class of HIV-1 RT inhibitors.[15] In this series of reports, we present more detailed structure–activity relationships

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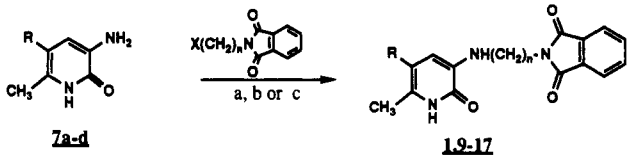
(SAR) which led to the selection of several candidates from the 2-pyridinone series for clinical evaluation as HIV-1 replication inhibitors.

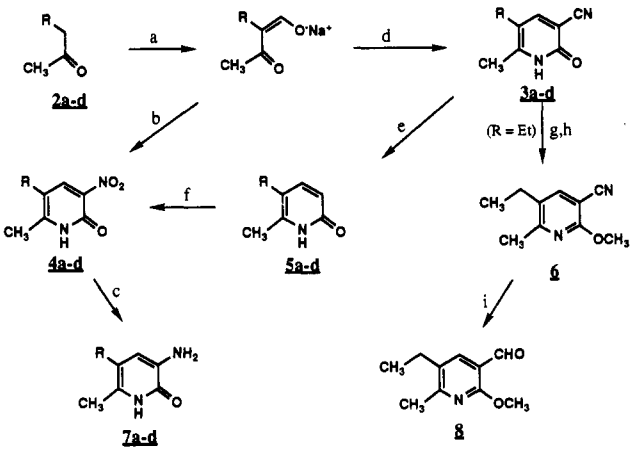
Our initial strategy to identify selective nonnucleoside inhibitors utilized an in vitro enzyme screen for HIV-1 RT inhibition, followed by a battery of secondary assays to exclude nonspecific inhibitors (i.e. other DNA and RNA polymerases). Using this approach, compound 1, a phthalimido pyridinone derivative from the Merck sample collection, was found to be a potent and selective inhibitor of HIV-1 RT. Unfortunately, this (aminomethyl)phthalimide was unstable under physiological conditions in vitro and eliminated phthalimide. This instability precluded further evaluation of 1 in a cell-based assay for inhibition of the spread of HIV-1 infection. While phthalimido pyridinone 1 was not suitable for antiviral studies, its potency and selectivity as an HIV-1 RT inhibitor encouraged further work designed to obtain chemical stability and elaborate key SAR issues. The results are described below.

Scheme I [a,b]



[a] (a) X = OH (n = 1), EtOH, 60 °C; (b) X = nosylate (n = 2), MeCN, 55 °C; (c) X = Br (n = 3), MeCN, diisopropylethylamine, NaI (cat.), reflux. [b] For **a**, R = Me; **b**, Et; **c**, n-Pr; **d**, n-Bu.

Scheme II [a,b]



[a] (a) HCO_2Et, NaOMe, EtOH/Et_2O; (b) nitroacetamide, aqueous piperidinium acetate; (c) H_2, Pd/C, 1:1 MeOH/THF; (d) cyanoacetamide, aqueous piperidinium acetate; (e) 6 N HCl, reflux; (f) HNO_3, H_2SO_4; (g) PCl_5, 120 °C; (h) MeONa, MeOH, reflux; (i) Dibal-H, THF, 0 °C. [b] For R see footnote *b*, Scheme I.

Chemistry

All of the required (aminoalkyl)phthalimides (**9–17**, Table I), including the screening lead 1, were prepared by procedures outlined in Scheme I. Originally 1 had been prepared by the condensation of formaldehyde with aminopyridinone **7b** and phthalimide. For this work, however, the reaction of *N*-(hydroxymethyl)phthalimide with an amine **7a–d** proved to be convenient. The longer chain analogues **16** and **17** required alkylation of **7b** with suitably activated alkylphthalimides (i.e. bromide or nosylate).

The aminopyridinones **7a–d** were obtained from nitriles **3a–d** as outlined in Scheme II. Hydrolysis and decarboxylation of these nitriles, nitration of the resultant pyridinone intermediates **5a–d**, and reduction of the nitro intermediates **4a–d** afforded aminopyridinones **7a–d**. The general route to the required cyanopyridinone intermediates **3a–d** is based on a literature procedure described by Paine[16] for the synthesis of cyanopyridinone **3a**. This route involved formylation of 2-butanone and cyclocondensation with cyanoacetamide. The substitution of higher homologs for 2-butanone gave isomeric mixtures of cyanopyridinones; however, the desired minor isomer was readily isolated by chromatography. A novel shorter synthesis of nitropyridinones **4a,b** was also developed by replacing the cyanoacetamide with nitroacetamide.

Successive chlorination (PCl_5) and methoxylation of cyanopyridinone **3b** generated methoxynitrile **6**. Upon reduction of **6** with diisobutylaluminum hydride (Dibal-H), nicotinaldehyde **8** was obtained. This compound is a

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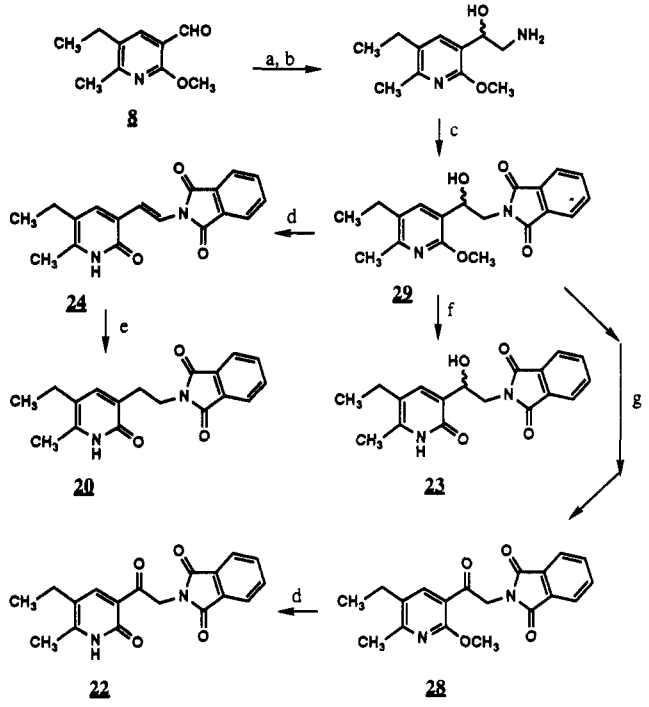
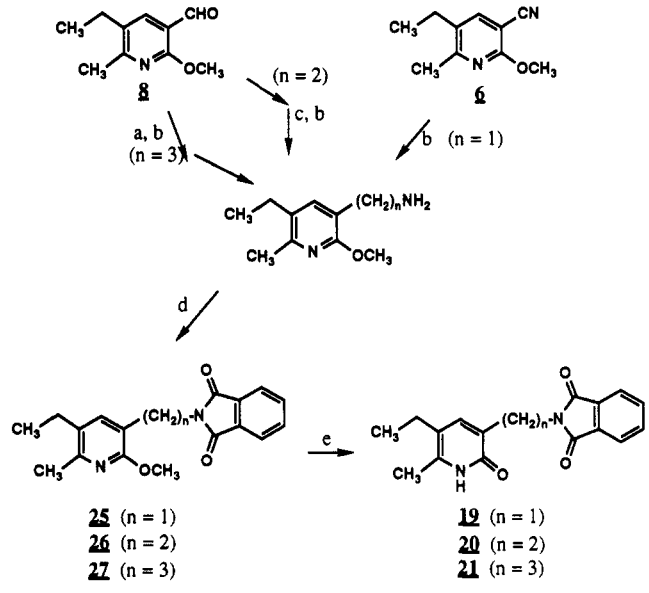
Scheme III [a]



[a] (a) TMSCN, ZnI_2; (b) $LiAlH_4$, Et_2O; (c) *N*-carbethoxyphthalimide, EtOH; (d) pyridine hydrochloride, 150 °C, 10 min; (e) H_2, Pd/C, 1:1 MeOH/THF; (f) BBr_3, CH_2Cl_2, room temperature; (g) MnO_2, $CHCl_3$.

Scheme IV [a]



[a] (a) $(EtO)_2P(O)CH_2CN$, NaH, THF; (b) H_2, Pd/C, MeOH, HCl; (c) excess CH_3NO_2, $MeNH_2$·HCl, KOH (cat), EtOH; (d) *N*-carbethoxyphthalimide, EtOH; (e) pyridine hydrochloride, 150 °C, 10 min.

key intermediate in the syntheses of alkylphthalimides **20–24** (Table I) which are outlined in Scheme III and IV.

In order to evaluate the effect of functionality at the alkyl link on inhibitory activity use was made of Evans technology[17] to prepare a β-hydroxyamine intermediate which was elaborated into the hydroxy (**23**) and keto (**22**) analogues. Reaction with *N*-carbethoxyphthalimide gave the 2-methoxypyridine **29**, and demethylation (BBr_3) of

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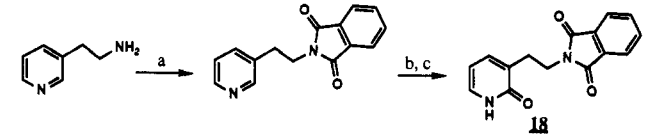
Scheme V [a]



[a] (a) *N*-Carbethoxyphthalimide, EtOH; (b) *m*-chloroperbenzoic acid, $CHCl_3$; (c) Ac_2O, reflux.

29 generated hydroxy pyridinone **23**. Keto pyridinone **22** was obtained by oxidation of **29** to **28** and subsequent demethylation (pyridine hydrochloride). A simultaneous dehydration/demethylation of **29** with pyridine hydrochloride (150 °C) led to vinyl pyridinone **24**. Catalytic reduction of **24** gave the saturated analogue **20**. An alternate route to **20** involved the condensation of nicotinaldehyde **8** with nitromethane, reduction to the ethylamine, reaction with *N*-carbethoxyphthalimide to give methoxypyridine **26**, and demethylation of **26**.

To obtain the three-carbon-link analogue **21**, nicotinaldehyde **8** was condensed with diethyl (cyanomethyl)phosphonate. The resultant nitrile was reduced to the propylamine which was trapped with *N*-carbethoxyphthalimide. The isolated methoxypyridine **27** was demethylated. The one-carbon-link analogue **19** was prepared in an analogous manner after reduction of nitrile **6** to the requisite amine.

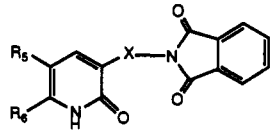
The unsubstituted pyridinone **18** required a different route (Scheme V) which involved the rearrangement of a pyridine *N*-oxide (acetic anhydride, reflux) obtained from *N*-(2-pyridin-3-ylethyl)phthalimide.

Biological Results and Discussion

Compound **1** was originally synthesized at Merck in 1972 during the course of an SAR study focused on antiinflammatory agents. The observed potency (IC_{50} = 30 nM) of this compound as an HIV-1 RT inhibitor as well as its selectivity for this enzyme versus other retroviral, bacterial, and mammalian polymerases generated interest in pursuing the development of this unique lead. In fact, Moloney murine leukemia virus (MMLV) and avian myeloblastosis virus (AMV) RT, calf thymus DNA polymerase α, human DNA polymerase β, δ, γ, Klenow fragment, *Micrococcus luteus* and *Escherichia coli* DNA polymerases, as well as, HIV-2 RT and simian immunodeficiency virus (SIV) RT were not significantly inhibited (IC_{50} > 300 μM).[15] An isomer of **1**, compound **14**, also available from this previous study, proved to be a selective HIV-1 RT inhibitor, but with substantially reduced potency. This result suggested that the alkyl substitution pattern on the pyridinone ring was important for inhibitory potency. Indeed, deletion of either both alkyl groups (**9**) or the 5-ethyl substituent (**10**), as well as replacement of 5-ethyl with 5-methyl (**11**) led to a decrease in inhibitory potency. Results obtained with the 5-propyl and 5-butyl analogs **12** and **13** suggested that the binding site for these inhibitors will tolerate greater steric bulk at this position than at the 6-position. The reduced activity observed with **15** is in accord with this view. While these results establish the importance of the pyridinone substituent pattern for inhibitor design, they did not address another important issue, chemical stability.

The poor chemical stability of **1** under in vitro physiological conditions can be attributed to a labile aminal link which leads to ready loss of phthalimide. The kinetics of the hydrolysis of **1** to aminopyridinone **7b** and phthal-

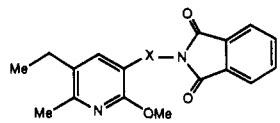
Table I. Inhibition of HIV-1 RT by 2-Pyridinones



no.	R_6	R_5	X	IC_{50} (μM)[a]
9	H	H	$-NHCH_2-$	1.66 ± 0.735
10	Me	H	$-NHCH_2-$	8.10 ± 0.733
11	Me	Me	$-NHCH_2-$	0.218 ± 0.019
1[b]	Me	Et	$-NHCH_2-$	0.03 ± 0.003
12	Me	*n*-Pr	$-NHCH_2-$	0.058 ± 0.018
13	Me	*n*-Bu	$-NHCH_2-$	0.128 ± 0.034
14[c]	Et	Me	$-NHCH_2-$	0.887 ± 0.088
15	$-(CH_2)_4-$		$-NHCH_2-$	3.70 ± 0.075
16	Me	Et	$-NH(CH_2)_2-$	45.0
17	Me	Et	$-NH(CH_2)_3-$	190
18	H	H	$-(CH_2)_2-$	>300
19	Me	Et	$-CH_2-$	26.5
20	Me	Et	$-(CH_2)_2-$	3.7 ± 0.377
21	Me	Et	$-(CH_2)_3-$	210
22	Me	Et		>300
23	Me	Et		>300
24	Me	Et		54

[a] The HIV-1 RT assay which used (poly)rC·(oligo)dG as the template/primer is described in ref 15. The concentration that produced 50% inhibition (IC_{50}) is stated as the mean of at least three experiments ± standard error (SE). All other values were obtained from one or two determinations. [b] L-345,516. Obtained from Merck sample collection and resynthesized (see Experimental Section).[c] L-619,757. Obtained from Merck sample collection.

Table II. Inhibition of HIV-1 RT by 2-Methoxypyridines



no.	X	IC_{50} (μM)[a]
25	$-CH_2-$	16
26	$-(CH_2)_2-$	6.2 ± 1.2
27	$-(CH_2)_3-$	>300
28		>300
29		>300

[a] See Table I, footnote *a*.

imide were determined, and the data are consistent with a pH-dependent aqueous hydrolysis at low pH, and a hydroxide-ion catalyzed hydrolysis at high pH. The approximate half-life of 1 under physiological conditions is 120 min, thus, accounting for its lack of antiviral activity. Several experiments suggested that the chemical reactivity of 1 was independent of its enzyme inhibitory activity. The hydrolysis products were not inhibitors. Preincubation of 1 alone led to a time-dependent loss of inhibitory activity, and incubation of 1 with stoichiometric enzyme, with or without substrates, did not lead to an enzyme-catalyzed transformation of 1. In addition, the hydrolysis rates for selected derivatives representing a range of inhibitory potencies were compared at pH 8.2, the pH at which RT enzyme measurements were determined (Table III). The fact that small differences in rate constants could not account for the range of inhibitory potencies observed further supported the concept that enzyme inhibition and

Table III. Comparison of Hydrolysis Rates and Inhibitory Potencies of Selected (Aminomethyl)phthalmides

		k_{obs}[b] (10^{-3} min^{-1})		
no.	IC_{50} (μM)[a]	pH 7	pH 8.2	pH 9.0
1	0.03	6.24	10.10	24.30
14	0.88	7.22	10.01	36.27
9	1.66	0.85	3.90	24.17
15	3.70	7.77	13.00	36.78
10	8.10	4.24	7.30	27.03

[a] See Table I, footnote a. [b] See Experimental Section.

chemical reactivity are not related. As a result, two strategies to improve chemical stability of 1 were explored. Initially, an analog (20) of 1 in which the exocyclic NH, the aminal NH, is replaced by a methylene group was synthesized. This chemically stable molecule retained HIV-1 RT inhibitory activity, albeit at a 100-fold reduced level. However, for the first time antiviral activity was demonstrated for this class of compounds in H9 human T-lymphoid cells infected with HIV-1 strain IIIb. The small differences in the data for enzyme inhibition potency (IC_{50} = 3.7 μM) and antiviral activity (CIC_{95} = 40 μM) for this compound, permitted establishment of the fact that this class of inhibitors could effectively cross cell membranes at concentrations to produce an antiviral effect.

Attempts to regain the potency lost on replacement of the NH with a methylene group did not succeed. Shortening the linker group to a single methylene unit (19) or expanding it to three carbons (21) resulted in further activity decreases. Structural changes which reduced the flexibility in the two-carbon linker and were formally derived by dehydrogenation (24) or oxidation (22 and 23) also resulted in a loss of inhibitory activity. These results did demonstrate, however, a requirement for a flexible two-atom linker between heterocycles to achieve maximum inhibitory potency. The low level of activity of one analog (18) in this series again illustrated the potency-enhancing effect of alkyl groups on the pyridinone ring.

In view of these results, a strategy to improve the chemical stability of 1 was reexamined. Addition of one (16) or two (17) methylene groups to the aminal spacer gave chemically-stable analogs; however, potency was substantially decreased. These results, again, highlighted the importance of the spacer composition and length for optimal enzyme inhibitory activity for this series of compounds.

One surprising aspect of this work for which we have no explanation is the similarity of the potency profiles between the precursor methoxypyridines 25–29 (Table II) and their corresponding pyridinones 19–23 (Table I) against the RT enzyme. Initial compound screening had established the need for the 3-substituted-2-pyridinone arrangement (data not shown).

Conclusions

A potent, specific HIV-1 reverse transcriptase inhibitor, pyridinone 1, was discovered through a screening program. This (aminomethyl)phthalimide analog is hydrolytically unstable, thus limiting its antiviral usefulness. Chemical modification of this lead produced a second lead, ethylphthalimide 20, which is hydrolytically stable and active as an HIV-1 antiviral agent in cell culture. Structure–activity studies demonstrated the importance of the 5-ethyl, 6-methyl substituent pattern on the pyridinone ring as well as a need for a flexible two-atom linker between the pyridinone and phthalimide heterocycles. Replace-

ment of the phthalimide group in these lead structures (1 and 20), the subject of accompanying reports, led to the development of several compounds which were selected for clinical evaluation.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.40% of the theoretical values. Routine ^{1}H NMR spectra, obtained on the Varian Associates XL-300 or Unity 300 using Me_4Si as an internal standard, are consistent with the structures indicated. Yields were not optimized. E. Merck silica gel, 200–400 mesh, are used for all flash chromatographies.

Preparation of 3-Aminopyridin-2(1*H*)-ones. 2-Aminopyridin-2(1*H*)-one was obtained from the catalytic reduction of commercial 2-hydroxy-3-nitropyridine while 3-amino-6-methylpyridin-2(1*H*)-one and 3-amino-5,6,7,8-tetrahydroquinolin-2(1*H*)-one were obtained from the Merck sample collection.[18] These compounds should be accessible by the procedures reported herein. All new aminopyridinones were prepared by the methods described below.

Method 1: 3-Amino-5-ethyl-6-methylpyridin-2(1*H*)-one (7b). To a stirred solution of sodium methoxide (38.6 g, 0.71 mol) in absolute ethanol (90 mL) under an atmosphere of nitrogen, anhydrous diethyl ether (600 mL) was added. The resultant solution was cooled to 0 °C, and a mixture of 2-pentanone (61.3 g, 0.71 mol) and ethyl formate (57.2 g, 0.77 mol) was added over a period of 3.5 h. The resultant white slurry was stirred at room temperature overnight, filtered, washed with anhydrous diethyl ether (100 mL), and vacuum-dried to yield regioselectivity 48 g (50%) of the desired 2-ethyl-3-oxobutanal, sodium salt. This material was used without further purification.

A mixture of 2-ethyl-3-oxobutanal, sodium salt (41.1 g, 342 mmol), nitroacetamide[19] (35.6 g, 342 mmol), aqueous piperidinium acetate (50 mL) [prepared from glacial acetic acid (42 mL), water (300 mL), and piperidine (72 mL)] in water (45 mL) was stirred at room temperature for 16 h. The yellow slurry was cooled to 0 °C, and the precipitate was collected by filtration. The yellow solid obtained was then dried under vacuum overnight to yield 31.9 g (51.4%) of the desired **5-ethyl-6-methyl-3-nitro-2(1*H*)-pyridinone (4b).** Recrystallization from methanol gave a pale yellow solid: 247–250 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1 H), 2.54 (ABq, 2 H, J = 7.6 Hz), 2.51 (s, 3 H), 1.22 (t, 3 H, J = 7.6 Hz). Anal. ($C_8H_{10}N_2O_3$) C, H, N.

A yellow solution of the 5-ethyl-6-methyl-3-nitropyridin-2(1*H*)-one (10 g, 55 mmol) in a mixture of methanol and tetrahydrofuran (100 mL, 1:1 v/v) was reduced catalytically in the presence of 5% palladium on charcoal (0.5 g) under an atmosphere of hydrogen (50 psi) at room temperature over a period of 3.5 h. The resultant mixture was filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure (15 torr) to provide 7.6 g (91%) of **3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one (7b).** Recrystallization from acetonitrile gave an off-white solid: mp 187–188 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.32 (s, 1 H), 4.70 (br s, 2 H), 2.21 (ABq, 2 H, J = 7.7 Hz), 2.01 (s, 3 H), 0.99 (t, 3 H, J = 7.6 Hz). Anal. ($C_8H_{12}N_2O$) C, H, N.

3-Amino-5,6-dimethylpyridin-2(1*H*)-one (7a): overall yield 51%; mp 196–197 °C; ^{1}H NMR ($CDCl_3$) δ 6.53 (s, 1 H), 3.68 (br s, 2 H), 2.21 (s, 3 H), 1.98 (s, 3 H). Anal. ($C_7H_{10}N_2O$) C, H, N.

Method 2: 3-Amino-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (7d). A suspension of 3-cyano-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (950 mg, 5.0 mmol) in 6 N hydrochloric acid (36 mL) was refluxed for 3 days. The reaction was cooled and extracted with methylene chloride to isolate product. The extract was then dried over sodium sulfate, filtered, and the solvent evaporated. The residue was triturated with diethyl ether to give 563 mg (68%) of solid **5-*n*-butyl-6-methylpyridin-2(1*H*)-one (5d):** ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1 H, J = 9 Hz), 6.76 (d, 1 H, J = 9 Hz), 2.50 (s, 3 H), 2.47 (t, 2 H, J = 6 Hz), 1.50 (m, 2 H), 1.37 (m, 2 H), 0.94 (t, 3 H, J = 9 Hz).

A solution of 5-*n*-butyl-6-methylpyridin-2(1*H*)-one (562 mg, 3.40 mmol) in concentrated sulfuric acid (4.3 mL) was cooled in an ice bath, and 70% nitric acid (0.4 mL) was added dropwise. After 1 h, the reaction mixture was poured into ice/water and the yellow product extracted into methylene chloride. This solution was dried, filtered, and evaporated. The residue (468 mg) was chromatographed on silica gel eluting with 1–2% methanol/chloroform to yield 293 mg (41%) of pure **3-nitro-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (4d):** ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1 H), 2.51 (s, 3 H), 2.48 (t, 2 H, J = 7.8 Hz), 1.56 (m, 2 H), 1.39 (m, 2 H), 0.97 (t, 3 H, J = 7.4 Hz).

A solution of 3-nitro-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (293 mg, 1.40 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) containing 5% palladium/carbon (120 mg) was hydrogenated at atmospheric pressure for 10–20 h. The catalyst was filtered off and the solvent evaporated. This residue was triturated with diethyl ether to give 224 mg (89%) of **3-amino-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (7d):** mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 6.54 (s, 1 H), 2.30 (t, 2 H, J = 7.8 Hz), 2.21 (s, 3 H), 1.45 (m, 2 H), 1.33 (m, 2 H), 0.92 (t, 3 H, J = 7.3 Hz). Anal. ($C_{10}H_{16}N_2O$) C, H, N.

3-Amino-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (7c): overall yield 38%; mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 6.53 (s, 1 H), 2.82 (t, 2 H, J = 7.8 Hz), 2.21 (s, 3 H), 1.49 (m, 2 H), 0.91 (t, 3 H, J = 7.4 Hz). Anal. ($C_9H_{14}N_2O$) C, H, N.

Preparation of 3-Cyanopyridin-2(1*H*)-ones. By extension of a procedure described by Paine[16] for the synthesis of **3-cyano-5,6-dimethylpyridin-2(1*H*)-one (3a)** the following pyridinones were prepared.

3-Cyano-5-ethyl-6-methylpyridin-2(1*H*)-one (3b). A solution of 2-ethyl-3-oxobutanal, sodium salt (136 g, 1 mol), cyanoacetamide (84 g, 1 mol), aqueous piperidinium acetate [214 mL, prepared from glacial acetic acid (42 mL), piperidine (72 mL), and water (100 mL)] in water (2.2 L) was refluxed for 16 h. Glacial acetic acid (150 mL) was added cautiously as the product precipitated. Upon cooling to room temperature, the product was collected by filtration, washed with water, and dried under vacuum overnight to give 83 g (51%): mp 243–244 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 2.45 (ABq, 2 H, J = 7.2 Hz), 2.45 (s, 3 H), 1.17 (t, 3 H, J = 7.2 Hz). Anal. ($C_9H_{10}N_2O$) C, H, N.

3-Cyano-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (3c). Solid sodium methoxide (20 g, 0.351 mol) was added to a solution of 2-hexanone (35.2 g, 0.351 mol) in diethyl ether (270 mL) and absolute ethanol (35 mL) which was cooled in an ice bath under a nitrogen atmosphere. Ethyl formate (28.4 mL, 0.351 mol) was added dropwise, and the mixture was stirred overnight. This reaction was diluted with diethyl ether, and a precipitated mixture of aldehydic salts was filtered off (6.65 g). Additional gummy precipitates were also collected (10.9 and 31 g).

This precipitate (6.65 g, 44 mmol) was dissolved in water, and cyanoacetamide (4.15 g, 47 mmol) and aqueous piperidinium acetate [prepared from acetic acid (1 mL), water (2.5 mL) and piperidine (1.8 mL)] were added to the reaction which was refluxed for 3.5 h. Acetic acid (5 mL) was added, the reaction was cooled to room temperature, and the product mixture extracted into methylene chloride. This solution was dried (Na_2SO_4), filtered through a pad of charcoal, and evaporated to give 1.33 g of crude product mixture. The two other precipitates (10.9 and 31 g) were treated as described above on a proportional scale-up to give 34.1 g of crude product mixture. All reaction products were combined (35.3 g) and chromatographed on silica gel eluting with 0–1% methanol/chloroform gradient. The appropriate fractions were combined and evaporated, and the residue was triturated with diethyl ether to give 6.9 g (11% yield) of pure product: mp 214–216 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 2.45 (s, 3 H), 2.39 (t, 2 H, J = 7.8 Hz), 1.54 (m, 2 H), 0.96 (t, 3 H, J = 7.5 Hz). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

3-Cyano-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (3d): overall yield 9%; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 2.46 (s, 3 H), 2.42 (t, 2 H, J = 9 Hz), 1.49 (m, 2 H), 1.37 (m, 2 H), 0.95 (t, 3 H, J = 7.2 Hz).

(18) These amines were prepared originally by B. Witzel (Merck Synthetic Chemical Research Dept., Rahway, NJ) as intermediates for an antiinflammatory program. See also Shen, T.-Y.; Clark, R. L.; Pessolano, A. A.; Witzel, B. E.; Lanza, T. J., Jr. Oxazolo- and thiazolopyridines. *Ger. Offen.* 2,330,109, Jan 1974.

(19) Brownstein, S. K. Reaction of Nitroacetamide with Hypobromite. *J. Org. Chem.* **1958**, *23*, 113–114.

Preparation of 3-[(Phthalimidomethyl)amino]pyridin-2(1*H*)-ones. 3-[*N*-(Phthalimidomethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (1). *N*-(Hydroxymethyl)phthalimide (89 mg, 0.50 mmol) was added to a suspension of 3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one (73 mg, 0.48 mmol) in absolute ethanol (1.5 mL) under a nitrogen atmosphere. This mixture was refluxed for 3 h during which time complete dissolution of reagent occurred, followed by precipitation of the bright yellow product. Upon cooling, the precipitated product was collected by filtration and rinsed with ethanol and then diethyl ether to yield 130 mg (87%) of 1: mp 245–247 °C; ^{1}H NMR (DMSO-d_6) δ 7.82–7.94 (m, 4 H), 6.60 (s, 1 H), 5.64 (br s, NHCH$_2$, 1 H), 5.12 (br s, 2 H), 2.25 (ABq, 2 H, J = 7 Hz), 2.02 (s, 1 H), 1.02 (t, 3 H, J = 7 Hz). Anal. ($C_{17}H_{17}N_3O_3$) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]pyridin-2(1*H*)-one (9): yield 30%; mp 235–236 °C; ^{1}H NMR (CDCl$_3$/DMSO-d_6) δ 7.84 (m, 2 H), 7.80 (m, 2 H), 6.82 (d, 1 H, J = 8.5 Hz), 6.64 (d, 1 H, J = 8.5 Hz), 6.09 (t, 1 H, J = 8.5 Hz), 5.84 (br t, NHCH$_2$, 1 H, J = 9 Hz), 5.12 (d, 2 H, J = 9 Hz). Anal. ($C_{14}H_{11}N_3O_3$) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]-6-methylpyridin-2(1*H*)-one (10): yield 82%; mp 235–236.5 °C; ^{1}H NMR (CDCl$_3$) δ 7.84 (m, 2 H), 7.70 (m, 2 H), 6.92 (d, 1 H, J = 9 Hz), 5.97 (d, 1 H, J = 9 Hz), 5.67 (br s, NHCH$_2$, 1 H), 5.15 (s, 2 H), 2.24 (s, 3 H). Anal. ($C_{15}H_{13}N_3O_3$) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]-5,6-dimethylpyridin-2(1*H*)-one (11): yield 72%; mp 263–266 °C; ^{1}H NMR (CDCl$_3$/DMSO-d_6) δ 7.85 (m, 2 H), 7.72 (m, 2 H), 6.8 (s, 1 H), 5.62 (t, NHCH$_2$, 1 H, J = 8.5 Hz), 5.14 (d, 2 H, J = 8.5 Hz), 2.14 (s, 3 H), 2.04 (s, 3 H). Anal. ($C_{16}H_{14}N_3O_3$) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]-5-*n*-propyl-6-methylpyridin-2(1*H*)-one (12): yield 43%; mp 243–245 °C; ^{1}H NMR (CDCl$_3$) δ 7.84 (m, 2 H), 7.70 (m, 2 H), 6.83 (s, 1 H), 5.64 (t, NHCH$_2$, 1 H, J = 7.9 Hz), 5.14 (d, 2 H, J = 7.9 Hz), 2.33 (t, 2 H, J = 7.3 Hz), 2.18 (s, 3 H), 1.51 (m, 2 H), 0.89 (t, 3 H, J = 7.3 Hz). Anal. ($C_{18}H_{19}N_3O_3$·0.1H$_2$O) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]-5-*n*-butyl-6-methylpyridin-2(1*H*)-one (13): yield 31%; mp 209–210 °C; ^{1}H NMR (CDCl$_3$) δ 7.84 (m, 2 H), 7.72 (m, 2 H), 6.83 (s, 1 H), 5.64 (br t, NHCH$_2$, J = 8.4 Hz), 5.15 (d, 2 H, J = 8.4 Hz), 2.34 (t, 2 H, J = 7.0 Hz), 1.47 (m, 2 H), 1.31 (m, 2 H), 0.90 (t, 3 H, J = 7.0 Hz). Anal. ($C_{19}H_{20}N_3O_3$) C, H, N.

3-[*N*-(Phthalimidomethyl)amino]-5,6,7,8-tetrahydroquinolin-2(1*H*)-one (15): yield 46%; mp 253–254 °C; ^{1}H NMR (DMSO-d_6) δ 7.82–7.95 (overlaping m, 4 H), 6.45 (s, 1 H), 5.66 (t, NHCH$_2$, 1 H, J = 7.0 Hz), 5.00 (d, 2 H, J = 7.0 Hz), 2.32 (br s, 4 H), 1.60 (br s, 4 H). Anal. ($C_{18}H_{17}N_3O_3$·0.25H$_2$O) C, H, N.

3-[*N*-(2-Phthalimidoethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (16). 3-Nitrobenzenesulfonyl chloride (12.2 g, 55 mmol) was added to a solution of *N*-(2-hydroxyethyl)-phthalimide (9.6 g, 50 mmol) and 4-(dimethylamino)pyridine (6.7 g, 55 mmol) in methylene chloride (50 mL), cooled in an ice bath. After stirring for 23 h, the solvent was evaporated and the residue triturated with diethyl ether to remove unreacted starting materials. The insoluble residue, a mixture of DMAP·HCl and product, was placed in a Soxhlet extractor. After continuous extraction with diethyl ether for 1.5 h, the diethyl ether extract was concentrated to give 1.0 g (5% yield) of purified **2-phthalimidoethyl 3-nitrobenzenesulfonate**: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 8.37 (m, 2 H), 8.35 (m, 1 H), 7.75–8.24 (m, 5 H), 4.45 (t, 2 H, J = 5.4 Hz), 3.84 (t, 2 H, J = 5.4 Hz). Anal. ($C_{16}H_{12}N_2O_7S$) C, H, N.

A solution of 2-phthalimidoethyl 3-nitrobenzenesulfonate (184 mg, 0.49 mmol) and 3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one (150 mg, 0.98 mmol) in acetonitrile (10 mL) was warmed at 55 °C for 5.5 h. The cooled reaction mixture was concentrated and the residue flash chromatographed on silica gel with 5% methanol/chloroform to give pure **3-[*N*-(2-phthalimidoethyl)-amino]-5-ethyl-6-methylpyridin-2(1*H*)-one** (6 mg, 3.7%): mp 205–206; ^{1}H NMR (CDCl$_3$) δ 7.87 (m, 2 H), 7.72 (m, 2 H), 6.36 (s, 1 H), 4.93 (br t, NHCH$_2$, 1 H, J = 5 Hz), 3.94 (t, 2 H, J = 7.0 Hz), 3.43 (ABq, 2 H, J = 5 Hz), 2.37 (ABq, 2 H, J = 7.5 Hz), 2.19 (s, 3 H), 1.12 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{19}N_3O_3$·0.75H$_2$O) C, H, N.

3-[*N*-(3-Phthalimidopropyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (17). A mixture of 3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one (300 mg, 2 mmol), *N*-(3-bromopropyl)-phthalimide (540 mg, 2 mmol), and diisopropylethylamine (260 mg, 2 mmol) in acetonitrile (25 mL) containing a catalytic amount of sodium iodide was refluxed overnight. The reaction mixture was concentrated and the residue chromatographed on silica gel eluting with 6.5% methanol/chloroform to give desired product. Trituration of the residual oil with diethyl ether gave solid **3-[*N*-(3-Phthalimidopropyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one**: mp 183–184 °C; ^{1}H NMR (CDCl$_3$) δ 7.73 (m, 2 H), 7.56 (m, 2 H), 6.10 (s, 1 H), 4.61 (br t, NHCH$_2$, J = 7.8 Hz), 3.70 (t, 2 H, J = 7.8 Hz), 3.04 (ABq, 2 H, J = 7.8 Hz), 2.21 (ABq, 2 H, J = 7.5 Hz), 2.07 (s, 3 H), 1.91 (m, 2 H), 0.96 (t, 3 H, J = 7.5 Hz). Anal. ($C_{19}H_{21}N_3O_3$·0.15H$_2$O) C, H, N.

2-Methoxy-5-ethyl-6-methylnicotinaldehyde (8). A mixture of 3-cyano-5-ethyl-6-methylpyridin-2(1*H*)-one (22.9 g, 0.14 mol) and phosphorus pentachloride (33 g, 0.15 mol) was heated at 110–120 °C for 1 h. The resultant melt was poured cautiously into ice–water, and the semisolid was extracted into methylene chloride. The organic extract was washed successively with water, saturated aqueous sodium bicarbonate, and brine. The methylene chloride extract was then dried over anhydrous sodium sulfate and filtered. The filtrate was passed through a small plug of silica gel, washed with methylene chloride, and concentrated under reduced pressure to yield 15.6 g (61%) of **2-chloro-3-cyano-5-ethyl-6-methylpyridine**. Recrystallization from hexane gave a white solid: mp 63–64 °C; ^{1}H NMR (CDCl$_3$) δ 7.72 (s, 1 H), 2.67 (q, 2 H, J = 7.6 Hz), 2.59 (s, 3 H), 1.26 (t, 3 H, J = 7.6 Hz). Anal. ($C_9H_9ClN_2$) C, H, N.

Sodium metal (3.3 g, 0.14 mol) was added to anhydrous methanol (180 mL) at 0 °C under an atmosphere of argon. After all the sodium metal was consumed, 2-chloro-3-cyano-5-ethyl-6-methylpyridine (18 g, 0.10 mol) was added and the resultant mixture refluxed overnight. This slurry was concentrated and the residue dissolved in water and extracted three times with chloroform. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then passed through a small plug of silica gel, washed with chloroform, and concentrated under reduced pressure to yield 23 g (94%) of **3-cyano-5-ethyl-2-methoxy-6-methylpyridine (6)**. Recrystallization from hexane gave a white solid: mp 59–61 °C; ^{1}H NMR (CDCl$_3$) δ 7.59 (s, 1 H), 4.01 (s, 3 H), 2.58 (q, 2 H, J = 7.6 Hz), 2.49 (s, 3 H), 1.19 (t, 3 H, J = 7.6 Hz). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

2-Methoxy-3-cyano-5-ethyl-6-methylpyridine (10.56 g, 60 mmol) was added in portions to a cold (0 °C) solution of diisobutylaluminum hydride in THF (1 M, 8.0 mL, 80 mmol) under an atmosphere of argon. The resultant yellow solution was stirred for 3–4 h and then poured into a mixture of ice-cooled 1 N hydrochloric acid (220 mL) and diethyl ether (200 mL). After 1 h the organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered through a pad of charcoal, and concentrated. The residue was crystallized from cold hexane to give several crops which were combined to give 6.69 g (62%) of **2-methoxy-5-ethyl-6-methylnicotinaldehyde (8)**. Recrystallization from methanol–water gave white solid: mp 53–55 °C; ^{1}H NMR (CDCl$_3$) δ 10.29 (s, 1 H), 7.83 (s, 1 H), 4.01 (s, 3 H), 2.58 (q, 2 H, J = 7.6 Hz), 2.47 (s, 3 H), 1.19 (t, 3 H, J = 7.6 Hz). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

2-Methoxy-3-(2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine (29). A mixture of 2-methoxy-5-ethyl-6-methylnicotinaldehyde (1.05 g, 5.86 mmol) and trimethylsilyl cyanide (0.85 mL, 6.37 mmol) containing zinc iodide (10 mg) was stirred, under a nitrogen atmosphere, at ambient temperature for 2 h.[17] This liquid was diluted with anhydrous diethyl ether, filtered, and then added dropwise to a suspension of lithium aluminum hydride (225 mg, 5.9 mmol) in diethyl ether (15 mL) under nitrogen. After 2 h the reaction was quenched with saturated aqueous sodium sulfate, diluted with methylene chloride, and filtered, and the solvents were evaporated to give a semisolid. This residue was triturated with cold diethyl ether and the crystalline **2-methoxy-3-(2-amino-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine** was collected by filtration to yield 346 mg (28%): ^{1}H NMR (CDCl$_3$) δ 7.42 (s, 1 H), 4.73 (m, 1 H), 3.93 (s, 3 H), 3.02 (dd, 1 H, J = 5 Hz, 13 Hz), 2.78 (dd, 1

H, J = 7 Hz, 13 Hz), 2.56 (ABq, 2 H, J = 8 Hz), 2.42 (s, 3 H), 1.17 (t, 3 H, J = 8 Hz).

To a suspension of 2-methoxy-3-(2-amino-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine (345 mg, 1.64 mmol) in ethanol (5 mL) was added *N*-carbethoxyphthalimide (373 mg, 1.70 mmol). The reaction was stirred for 6 h as the suspension dissolved. The solvent was evaporated, the viscous residue triturated with ethyl acetate/diethyl ether, and product crystallized. Upon filtration, 273 mg (49%) of pure **2-methoxy-3-(2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine** was collected, mp 134–135 °C. The mother liquors were flash chromatographed on silica gel and eluted with 20% ethyl acetate/hexane to give an additional 83 mg (15%) of product: ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.73 (m, 2 H), 7.37 (s, 1 H), 4.14 (dd, 1 H, J = 9 Hz, 14 Hz), 3.98 (s, 3 H), 3.96 (dd, 1 H, J = 4 Hz, 14 Hz), 3.40 (d, 1 H, J = 9 Hz), 2.51 (ABq, 2 H, J = 8 Hz), 2.30 (s, 3 H), 1.08 (t, 3 H, J = 8 Hz). Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

***trans*-3-(2-Phthalimidoethenyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (24).** A mixture of 2-methoxy-3-(2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine (172 mg, 0.50 mmol) and pyridine hydrochloride (600 mg, 5.3 mmol) was placed in a preheated oil bath at 150 °C for 10 min. The mixture was cooled and diluted with water, and the precipitated product was collected by filtration and air-dried to yield 145 mg (93%). Recrystallization from methanol gave analytically pure **3-(2-phthalimidoethenyl)-5-ethyl-6-methylpyridin-2(1*H*)-one**, mp 296–298 °C; ^{1}H NMR (DMSO-d_6) δ 8.24 (d, 1 H, J = 15 Hz), 7.84–7.97 (m, 4 H), 7.44 (s, 1 H), 7.39 (d, 1 H, J = 15 Hz), 2.30 (ABq, 2 H, J = 7.8 Hz), 2.23 (s, 3 H), 1.12 (t, 3 H, J = 7.8 Hz). Anal. ($C_{18}N_{16}N_2O_3$) C, H, N.

3-(2-Phthalimidoethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (20). A partial suspension of *trans*-3-(2-phthalimidoethenyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (145 mg, 0.47 mmol) in methanol (20 mL) and tetrahydrofuran (20 mL) containing 5% palladium/carbon (117 mg) was hydrogenated at atmospheric pressure for 10–20 h. The catalyst was filtered off, and the solvents were evaporated. This residue was recrystallized from methanol to give 110 mg (75%) of product: mp 232–233 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.69 (m, 2 H), 7.04 (s, 1 H), 4.01 (t, 2 H, J = 6.7 Hz), 2.90 (t, 2 H, J = 6.7 Hz), 2.27 (ABq, 2 H, J = 7.5 Hz), 2.25 (s, 3 H), 0.93 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

3-(2-Phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (23). To a solution of 2-methoxy-3-(2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine (180 mg, 0.53 mmol) in methylene chloride (6 mL) under a nitrogen atmosphere was added 1 M boron tribromide/CH_2Cl_2 (2.5 mL, 2.5 mmol), and the resultant precipitate was stirred for 15–20 h. The mixture was quenched with excess saturated aqueous sodium bicarbonate carefully and the crude product extracted into methylene chloride. The dried (Na_2SO_4) solution was evaporated and the residue chromatographed on silica gel and eluted with a 1–3% methanol/chloroform gradient to give a solid. This material was digested in hot ethanol and cooled and the solid collected to give pure **3-(2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one** (7 mg, 4%): mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2 H), 7.71 (m, 2 H), 7.22 (s, 1 H), 5.24 (d, 1 H, J = 9 Hz), 4.84 (m, 1 H), 4.28 (dd, 1 H, J = 9 Hz, 14 Hz), 3.93 (dd, 1 H, J = 5 Hz, 14 Hz), 2.39 (s, 3 H), 2.36 (ABq, 2 H, J = 7 Hz), 1.02 (t, 3 H, J = 7 Hz). Anal. ($C_{18}H_{18}N_2O_4 \cdot 0.3H_2O$) C, H, N.

2-Methoxy-3-(α-phthalimidoacetyl)-5-ethyl-6-methylpyridine (28). Activated manganese dioxide (510 mg) was added to a solution of 2-methoxy-3-[2-phthalimido-1(*R,S*)-hydroxyethyl)-5-ethyl-6-methylpyridine (152 mg, 0.44 mmol) in toluene (6 mL) and the mixture refluxed for 1.5 h. The cooled reaction was diluted with chloroform and filtered to remove MnO_2 and the solution evaporated. The residue was triturated with diethyl ether and the solid product collected (58 mg). This material was digested in diethyl ether, cooled, and collected to give 39 mg (26%) of pure **2-methoxy-3-(α-phthalimidoacetyl)-5-ethyl-6-methylpyridine**: mp 177–179 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1 H), 7.90 (m, 2 H), 7.76 (m, 2 H), 5.09 (s, 2 H), 4.10 (s, 3 H), 2.59 (ABq, 2 H, J = 7.8 Hz), 2.50 (s, 3 H), 1.18 (t, 3 H, J = 7.78 Hz). Anal. ($C_{19}H_{18}N_2O_4 \cdot 0.2H_2O$) C, H, N.

2-Methoxy-3-(2-phthalimidoethyl)-5-ethyl-6-methylpyridine (26). A mixture of 2-methoxy-5-ethyl-6-methylnicotinaldehyde (2.25 g, 12.6 mmol), nitromethane (1.9 g, 31.1 mmol), monomethylamine hydrochloride (69 mg), and sodium hydroxide (20 mg) in absolute ethanol (1.3 mL) was stirred at ambient temperature for 3 days. This mixture was diluted with methanol, and the yellow crystalline precipitate was collected by filtration to give 2.39 g (86%), of **2-methoxy-3-(2-nitroethenyl)-5-ethyl-6-methylpyridine**: mp 105–107 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1 H, J = 13 Hz), 7.92 (d, 1 H, J = 13 Hz), 7.46 (s, 1 H), 4.05 (s, 3 H), 2.60 (ABq, 2 H, J = 7 Hz), 2.98 (s, 3 H), 1.22 (t, 3 H, J = 7 Hz).

A suspension of 2-methoxy-3-(2-nitroethenyl)-5-ethyl-6-methylpyridine (445 mg, 2.0 mmol) in methanol (10 mL) and 4.7 M methanolic hydrogen chloride (2 mL) containing 5% palladium/carbon (110 mg) was hydrogenated at atmospheric pressure over 10–20 h. The catalyst was filtered off and the solvent evaporated. The residue was made basic with sodium hydroxide solution, the product extracted into methylene chloride, dried, and filtered, and the solvent evaporated to yield 332 mg of crude oily **2-methoxy-3-(2-aminoethyl)-5-ethyl-6-methylpyridine**. No further purification was performed.

To a solution of crude 2-methoxy-3-(2-aminoethyl)-5-ethyl-6-methylpyridine (332 mg) in ethanol (7 mL) was added *N*-carbethoxyphthalimide (406 mg, 1.85 mmol). After stirring at ambient temperature for 3 h the solvent was evaporated and the residue was chromatographed on silica gel by gradient elution with 20–100% ethyl acetate/hexane. The appropriate fractions were combined, the solvent was evaporated, and the residue was triturated with hexane as the product slowly crystallized out to yield 202 mg (31%) of pure **2-methoxy-3-(2-phthalimidoethyl)-5-ethyl-6-methylpyridine**: mp 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2 H), 7.70 (m, 2 H), 7.08 (s, 1 H), 3.94 (t, 2 H, J = 6.7 Hz), 3.83 (s, 3 H), 2.91 (t, 2 H, J = 6.7 Hz), 2.44 (ABq, 2 H, J = 7 Hz), 2.37 (s, 3 H), 1.02 (t, 3 H, J = 7 Hz). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

2-Methoxy-3-(phthalimidomethyl)-5-ethyl-6-methylpyridine (25). A solution of 2-methoxy-3-cyano-5-ethyl-6-methylpyridine (344 mg, 1.95 mmol) in methanol (8 mL) and 4.9 M methanolic HCl (5 mL) containing 5% palladium on carbon (100 mg) was hydrogenated at atmospheric pressure for 10–20 h. The catalyst was filtered off and the solvent evaporated. This residue was made basic with sodium hydroxide, and the product was extracted into methylene chloride, dried (Na_2SO_4), filtered, and evaporated to give 313 mg of oily crude **2-methoxy-3-(aminomethyl)-5-ethyl-6-methylpyridine**. No further purification was performed.

N-Carbethoxyphthalimide (441 mg, 2.0 mmol) was added to a solution of crude 2-methoxy-3-(aminomethyl)-5-ethyl-6-methylpyridine (310 mg) in ethanol (5 mL) and stirred at ambient temperature overnight. The solvent was evaporated, and the semisolid residue was flash chromatographed eluting with 20% ethyl acetate/hexanes to give 136 mg (24% overall yield) of **2-methoxy-3-(phthalimidomethyl)-5-ethyl-6-methylpyridine**: mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.73 (m, 2 H), 7.21 (s, 1 H), 4.80 (s, 2 H), 3.91 (s, 3 H), 2.50 (ABq, 2 H, J_{AB} = 7.5 Hz), 2.38 (s, 3 H), 1.13 (t, 3 H, J = 7.5 Hz). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

2-Methoxy-3-(3-phthalimidopropyl)-5-ethyl-6-methylpyridine (27). A solution of diethyl (cyanomethyl)phosphonate (0.50 mL, 3.1 mmol) in tetrahydrofuran (7 mL), under a nitrogen atmosphere, containing 60% sodium hydride/mineral oil (128 mg, 3.2 mmol) was stirred for about 0.5 h until gas evolution ceased. A solution of 2-methoxy-5-ethyl-6-methylnicotinaldehyde (567 mg, 3.0 mmol) in THF (5 mL) was added dropwise to give a pinkish gum. After stirring overnight, the reaction was diluted with water and methylene chloride. The organic layer was separated, dried (anhydrous Na_2SO_4) and evaporated. The residue was triturated with hexane to give 260 mg (43%) of pure ***trans*-2-methoxy-3-(2-cyanoethenyl)-5-ethyl-6methylpyridine**: ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1 H, J = 17 Hz), 7.35 (s, 1 H), 6.06 (d, 1 H, J = 17 Hz), 3.98 (s, 3 H), 2.57 (ABq, 2 H, J = 7 Hz), 2.45 (s, 3 H), 1.20 (t, 3 H, J = 7 Hz).

A solution of *trans*-2-methoxy-3-(2-cyanoethenyl)-5-ethyl-6-methylpyridine (242 mg, 1.2 mmol) in methanol (5 mL) containing 4.7 M methanolic HCl (3.0 mL) and 5% palladium/carbon (119

mg) was hydrogenated at atmospheric pressure. After 20 h, the catalyst was removed, the solvent evaporated, and the residue dissolved in water. This solution was made basic with NaOH. The product was extracted into methylene chloride, dried (anhydrous Na_2SO_4), and evaporated to give oily **2-methoxy-3-(3-aminopropyl)-5-ethyl-6-methylpyridine** (219 mg). This material was used without purification.

The amine was dissolved in ethanol (4 mL) and *N*-carbethoxyphthalimide (262 mg, 1.2 mmol) was added. After the reaction was stirred overnight, the solvent was removed and the residue chromatographed on silica gel and eluted with 10–15% ethyl acetate/hexane to give pure **2-methoxy-3-(3-phthalimidopropyl)-5-ethyl-6-methylpyridine** (246 mg, 61%). This glass slowly solidified and was triturated with hexane to give crystalline product: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.72 (m, 2 H), 7.16 (s, 1 H), 3.88 (s, 3 H), 3.74 (t, 2 H, J = 6 Hz), 2.57 (t, 2 H, J = 6 Hz), 2.50 (ABq, 2 H, J = 7 Hz), 2.36 (s, 3 H), 1.99 (m, 2 H), 1.15 (t, 3 H, J = 7 Hz). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

Demethylation of 2-Methoxypyridines: 3-(Phthalimidomethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (19). A mixture of 2-methoxy-3-(phthalimidomethyl)-5-ethyl-6-methylpyridine (56 mg, 0.18 mmol) and anhydrous pyridine hydrochloride (210 mg, 1.8 mmol) in a test tube under an inert atmosphere was placed in a preheated oil bath at 150 °C for 5–10 min. The mixture was cooled and diluted with water, and the precipitate produced was filtered off. Crystallization from methanol gave pure **3-(phthalimidomethyl)-5-ethyl-6-methylpyridin-2(1*H*)-one** (35 mg, 66%): mp 258–259 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.71 (m, 2 H), 7.22 (s, 1 H), 4.77 (s, 2 H), 2.34 (ABq, 2 H, J = 7.5 Hz), 2.21 (s, 3 H), 1.06 (t, 3 H, J = 7.5 Hz). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

3-(3-Phthalimidopropyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (21): yield 32%; mp 194–196 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.71 (m, 2 H), 7.17 (s, 1 H), 3.75 (t, 2 H, J = 6.7 Hz), 2.56 (t, 2 H, J = 6.7 Hz), 2.37 (ABq, 2 H, J = 7 Hz), 2.24 (s, 3 H), 2.04 (m, 2 H), 1.12 (t, 3 H, J = 7 Hz). Anal. ($C_{19}H_{20}N_2O_3 \cdot 0.7H_2O$) C, H, N.

3-(α-Phthalimidoacetyl)-5-ethyl-6-methylpyridin-2(1*H*)-one (22): yield 35%; mp 312–313 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1 H), 7.90 (m, 2 H), 7.75 (m, 2 H), 5.26 (s, 2 H), 2.48 (ABq, 2 H, J = 7.4 Hz), 2.46 (s, 3 H), 1.16 (t, 3 H, J = 7.4 Hz). Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

3-(2-Phthalimidoethyl)pyridin-2(1*H*)-one (18). A mixture of 3-(2-aminoethyl)pyridine[20] (1.22 g, 10 mmol) and *N*-carbethoxyphthalimide (2.30 g, 10.5 mmol) in ethanol (9 mL) was warmed at 60 °C for 0.5 h. Upon cooling, the reaction the product precipitated out and was filtered off to give 1.45 g (58%) of **3-(2-phthalimidoethyl)pyridine**: ^{1}H NMR ($CDCl_3$) δ 8.48 (m, 2 H), 7.84 (m, 2 H), 7.73 (m, 2 H), 7.63 (br d, 1 H, J = 8 Hz), 7.25 (dd, 1 H, J = 2 Hz, 7 Hz), 3.94 (t, 2 H, J = 7 Hz), 3.02 (t, 2 H, J = 7 Hz).

m-Chloroperbenzoic acid (80% pure, 592 mg, 2.7 mmol) was added in portions to a solution of 3-(2-phthalimidoethyl)pyridine (630 mg, 2.5 mmol) in chloroform (8 mL). After 2 h, the solvent was removed and the residue triturated with diethyl ether. This resultant solid was digested in warm diethyl ether twice to remove *m*-chlorobenzoic acid. Recrystallization from methylene chloride/diethyl ether afford pure **3-(2-phthalimidoethyl)pyridine *N*-oxide** (403 mg, 60%): mp 177–179 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (m, 2 H), 7.84 (m, 2 H), 7.74 (m, 2 H), 7.27 (m, 2 H), 3.97 (t, 2 H, J = 7 Hz), 3.00 (t, 2 H, J = 7 Hz). Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

A suspension of 3-(2-phthalimidoethyl)pyridine *N*-oxide (268 mg, 1.0 mmol) in acetic anhydride (1.5 mL) was refluxed for 7 h. The reaction was cooled to 100 °C, water (5 mL) was added, and product crystallized out as the reaction cooled. The collected solid was crystallized from methanol/chloroform to give pure **3-(2-phthalimidoethyl)pyridin-2(1*H*)-one** (76 mg, 28%): mp 289–291 °C; ^{1}H NMR (DMSO-d_6) δ 7.84 (m, 4 H), 7.21 (m, 2 H), 5.99 (t, 1 H, J = 7 Hz), 3.82 (t, 2 H, J = 7 Hz), 2.70 (t, 2 H, J = 7 Hz). Anal. ($C_{15}H_{12}N_2O_3 \cdot 0.1H_2O$) C, H, N.

Hydrolysis Studies on (Aminomethyl)phthalimides 1, 9, 10, 14, and 15. Hydrolysis rates were determined at three pH's (see Table III). Stock solutions (5 nM) of each compound were prepared in DMSO and then diluted 1:500 into the desired aqueous buffer. Aliquots were removed at specified times and analyzed by HPLC. The hydrolysis was followed by the disappearance of the HPLC peak for compound and the appearance of the peak for phthalimide. The data were then fit to a simple first order hydrolysis. The calculated rate was the same, within experimental error.

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