# Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 2. Analogues of 3-Aminopyridin-2(1*H*)-one†

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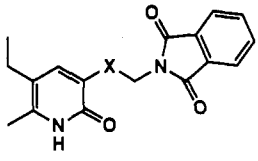
A series of nonnucleoside 3-aminopyridin-2(1*H*)-one derivatives was synthesized and evaluated for HIV-1 RT inhibitory properties. Several analogs proved to be potent and highly selective antagonists with in vitro $IC_{50}$ values as low as 19 nM in the enzyme assay using rC·dG as template·primer. Two compounds from this series, 3-[[(4,7-dimethylbenzoxazol-2-yl)methyl]-amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (**34**, L-697,639) and the corresponding 4,7-dichloro analogue (**37**, L-697,661) inhibited the spread of HIV-1 IIIb infection by 95% in MT4 cell culture at concentrations of 25–50 nM and were selected for clinical trials as antiviral agents.

As initially reported in previous communications[1,2] and in more detail in the previous report of this series,[3] phthalimide derivative **1** was found to be a potent and selective inhibitor of human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT). Unfortunately, **1** proved to be unstable under physiological conditions in vitro, as evidenced by the elimination of phthalimide, $t_{1/2}$ = 120 min, and therefore was not suitable for further development.

Since (aminomethyl)phthalimide derivatives such as **1** would appear to have limited clinical utility, various strategies were explored for the development of more stable analogues from this lead with retention of potency. An initial attempt[3] to improve stability involved replacement of the aminomethylene linker of **1** with ethylene to give **2**. Although this carbon analogue proved to be hydrolytically stable, it was more than 100-fold weaker than **1** as an RT enzyme inhibitor.



**1**, X = NH
**2**, X = $CH_2$

An alternate approach which has led to potent and stable inhibitors in both the aminomethylene and ethylene linker series proved to be replacement of the phthalimide moiety by various aromatic and heterocyclic groups. In this report, we present detailed structure–activity relationships which led to the selection of two such candidates from the 3-aminopyridin-2(1*H*)-one series for clinical investigation as inhibitors of HIV-1 replication.

## Chemistry

The N-substituted 3-aminopyridin-2(1*H*)-ones reported in Tables I–V were prepared either by alkylation of the appropriate 3-aminopyridinone with the corresponding haloalkyl derivative, path a, Scheme I (methods A–H), or by reductive alkylation with a ketone or aldehyde, path b, Scheme I (methods I–K). In general, higher yields were observed with (iodomethyl)benzoxazoles as alkylating agents in path a compared to the chloromethyl derivatives. Preparation of the dichlorobenzoxazole analogue **37** by this procedure is typical and is outlined in Scheme II.

Intermediate 2-(chloromethyl)benzoxazole derivatives were readily prepared from the corresponding 2-aminophenols by condensation with ethyl (chloroimino)acetate hydrochloride in $CH_2Cl_2$.[4] The (chloromethyl)benzoxazoles could be conveniently converted to the more reactive iodo derivatives by reaction with NaI in $Me_2CO$ (see method S) and were used without purification. Required aminophenols were obtained by reduction of the corresponding nitrophenols either catalytically or with $Na_2S_2O_4$ (sodium hydrosulfite). During preparation of the dichlorobenzoxazole required for synthesis of **37**, no dechlorination could be detected during catalytic reduction of 2-nitro-3,6-dichlorophenol over 5% Pt/C in EtOH–HOAc. This reduction was also successful with Raney Ni catalyst, but required over 24 h for completion.

The 7-chloro- and 4,7-dichloro-2-(chloromethyl)benzo[*b*]furan precursors of **48** and **49** were prepared by the method of Anderson, Bottaro and Halat.[5]

The 3-aminopyridin-2(1*H*)-ones were obtained by catalytic reduction of the corresponding 3-nitropyridinones and were generally used without purification. An efficient

† Presented in honor of Dr. Ralph F. Hirschmann on the occasion of his 70th birthday.

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∥ Department of Virus and Cell Biology.

(1) Saari, W. S.; Hoffman, J. M.; Wai, J. S.; Fisher, T. E.; Rooney, C. S.; Smith, A. M.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Stern, A. M.; Anderson, P. S. 2-Pyridinone Derivatives: A New Class of Nonnucleoside, HIV-1-Specific Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1991**, *34*, 2922–2925.

(2) Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. Pyridinone Derivatives: Specific Human Immunodeficiency Virus Type 1 Reverse Transcriptase Inhibitors with Antiviral Activity. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6863–6867.

(3) Hoffman, J. M.; Wai, J. S.; Thomas, C. M.; Levin, R. B.; O'Brien, J. A.; Goldman, M. E. Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 1. Phthalimidoalkyl and -alkylamino Analogues. *J. Med. Chem.*, preceding paper in this issue.

(4) Kristinsson, H. Synthese von Heterocyclen; IV. Neuer Syntheseweg zur Herstellung von Heterocyclischen Nitrilen. *Synthesis* **1991**, 102–103.

(5) Anderson, W. K.; Bottaro, J. C.; Halat, M. J. New Compounds: Synthesis of 2-Chloromethylbenzo[*b*]furans. *J. Pharm. Sci.* **1980**, *69*, 232–233.

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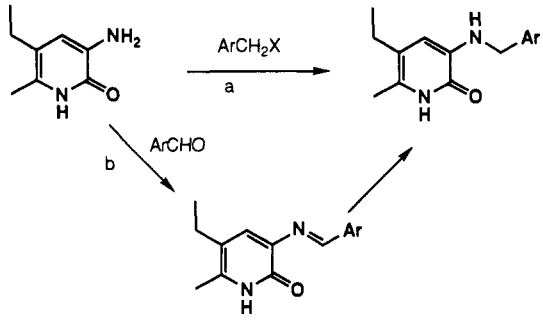
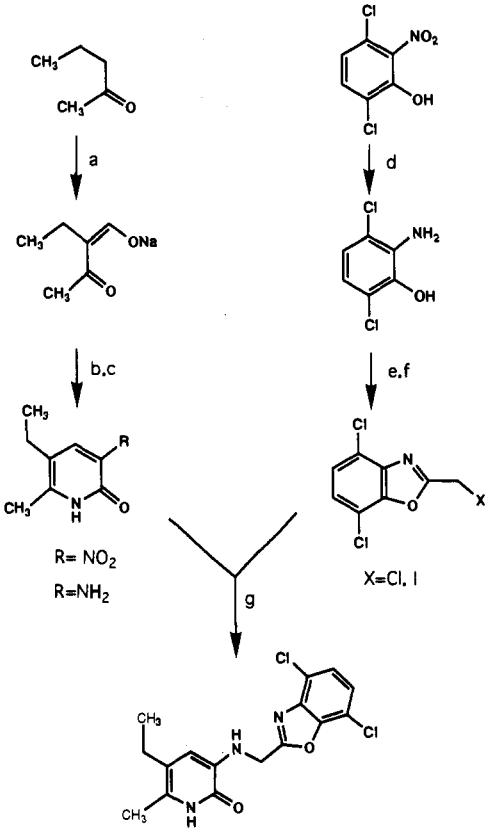
**Scheme I.** Synthesis of 3-[(Arylmethyl)amino]pyridin-2(1*H*)-ones




**Scheme II.** Synthesis of **37**[a]




**37**

[a] (a) $HCO_2Et$, NaOMe, EtOH–$Et_2O$, 44%; (b) $O_2NCH_2CONH_2$, aqueous piperidinium acetate, 80%; (c) $H_2$, Pd/C, 1:1 MeOH–THF, 68%; (d) $H_2$, Pt/C, EtOH–HOAc, quantitative; (e) ethyl (chloroimino)acetate hydrochloride, $CH_2Cl_2$, 86%; (f) NaI, $Me_2CO$, 84%; (g) MeCN, $(i\text{-}Pr)_2NEt$, 42%.

route to the nitropyridinones has been described previously[3] and is illustrated for the 5-ethyl-6-methyl derivative in Scheme II. A variety of functionality is tolerated in this nitropyridinone synthesis as evidenced by successful syntheses of the 5-(alkylthio), 5-methoxy, 5-acetyl, and 5-(ethoxycarbonyl) derivatives by this procedure.

*N*-methyl and *N*-ethyl groups were introduced on the 3-amino moiety of the pyridinone by $NaCNBH_4$ reductive alkylation with paraformaldehyde or acetaldehyde (method M). Pyridine-2(1*H*)-thione derivatives **59** and **71** were obtained by dealkylation of the corresponding *tert*-butyl thioethers with pyridine hydrochloride at 140 °C (method O). Other intermediates used to prepare the final products listed in Tables I–V and their sources are recorded in Table VII.

Many studies on related compounds indicate that the pyridinone structure is highly favored over the hydroxypyridine tautomer at near neutral pH.[6] It is also generally accepted that 3-aminopyridines exist overwhelmingly in the amino form.[6] Therefore the compounds listed in Tables I–V are depicted as the aminopyridinone tautomer.

## Results and Discussion

Replacement of the phthalimide moiety of lead structure **1** by various aromatic and heterocyclic groups led to the series of compounds shown in Table I. Initially, the HIV-1 RT inhibitory activity of these derivatives was determined in an in vitro enzyme assay using rC·dG as template·primer.[2] As indicated in Table I, the benzoxazole and benzofuran analogues, **3** and **4**, exhibited high potency in this RT enzyme assay and, unlike phthalimide **1**, were hydrolytically stable under physiological conditions in vitro. Tetrahydrobenzoxazole **5** showed comparable activity to the parent **3**. Replacement of the O of **3** and **4** by S led to the less potent benzothiazole and benzothiophene derivatives **7** and **9**. The benzimidazole **19** and indole **17** and **23** analogues were even less active. These results were suggestive that this portion of the molecule resides in a hydrophobic area of the enzyme–template·primer complex which appears to disfavor a hydrogen bond donor.

Of the bicyclic groups examined which contained two fused six-membered rings, the 3-quinolyl derivative **6** proved to be the most potent RT inhibitor with the 2-naphthyl (**8**), 2-quinolyl (**10**), 1-naphthyl (**13**), and tetralin (**20**) compounds being less active. Attempts to improve potency by introduction of a carbonyl group, as in the lead phthalimide **1**, to give **11** and **15**, were not effective. Conversion of the benzo rings of **3** and **4** to pyridyl yielded heterocycles **12**, **25**, and **26** which proved to be considerably less potent than the corresponding benzo analogues.

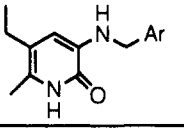
Extension of the potent benzoxazole compound **3** to the tricyclic naphthoxazoles **16** and **21** led to reduced activity. Analogues containing unsubstituted monocyclic phenyl, pyridyl, or furyl rings, **18**, **22**, **24**, **27**, and **28**, were weak RT inhibitors. The 5-phenyloxazole derivative **14** was also considerably less potent than the fused benzoxazole analogue **3**. These results suggest that optimal RT inhibitory activity resides in a relatively nonpolar bicyclic moiety containing five- and six-membered rings.

Having identified the benzoxazole moiety as a suitable replacement for phthalimide, the effect of introducing nuclear substituents into the benzoxazole ring was explored next. Systematic introduction of methyl groups into available positions on the benzoxazole ring of **3** was investigated as an initial approach to improving inhibitory potency. As can be seen from Table II, this strategy led to identification of the 4- and 7-positions as potency enhancing, cf. **29** and **32** vs **30** and **31**. However the decreased activity seen with the 7-ethyl analogue **33** suggests a limiting size requirement at this position.

Disubstitution at the 4- and 7-positions with either methyl or chloro (**34** and **37**, respectively) yielded even more potent RT inhibitors. This same pattern was also observed with the smaller fluoro substituent. Again, the 4- and 7-fluoro derivatives **38** and **41** were more potent RT inhibitors than the corresponding 5- and 6-substituted analogues **39** and **40**. However in this case, the 4,7-difluoro

(6) Katritzky, A. R.; Lagowski, J. M. Prototropic Tautomerism of Heteroaromatic Compounds: 2. Six-Membered Rings. *Adv. Heterocycl. Chem.* **1963**, *1*, 347–352, 406.

**Table I.** 3-[(Arylmethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one Derivatives



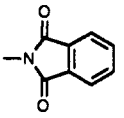
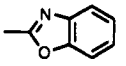
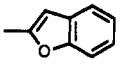
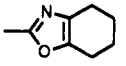
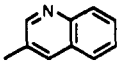
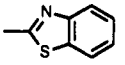
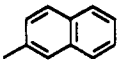
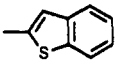
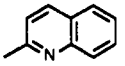
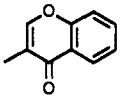
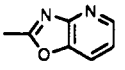
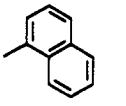
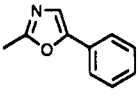
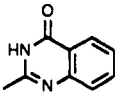
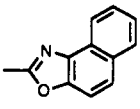
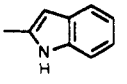
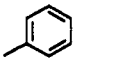
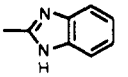
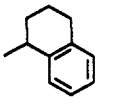
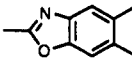
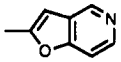
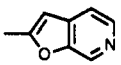
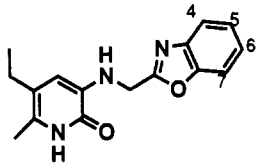
| no. | Ar | prep method | yield, % | mp, °C | recryst solvent | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|
| **1b** |  | | | | | 0.030 ± 0.001 |
| **3** |  | B | 34 | 202–3 | EtOH–$H_2O$ | 0.21 ± 0.02 |
| **4** |  | J | 24 | 195–7[c] | EtOAc | 0.33 + 0.09 |
| **5** |  | A | 52 | 63–8[d] | EtOAc–hexane | 0.280 |
| **6** |  | I | 42 | 228–9 | EtOH–$CHCl_3$ | 0.335 |
| **7** |  | C | 26 | 209–16 | EtOH–$H_2O$ | 0.35 ± 0.09 |
| **8** |  | B | 42 | 205–6[e] | $CHCl_3$–hexane | 0.46 ± 0.04 |
| **9** |  | E | 26 | 214–5.5 | EtOH–$H_2O$ | 0.500 |
| **10** |  | A | 18 | 163–5 | EtOAc–hexane | 0.530 |
| **11** |  | F | 41 | 225–6 | EtOH | 1.10 |
| **12** |  | A | 32 | 223–5 | *f* | 1.90 |
| **13** |  | B | 18 | 222–3[e] | $CHCl_3$–hexane | 2.10 |
| **14** |  | G | 15 | 194–7[g] | EtOAc–hexane | 2.35 |
| **15** |  | C[h] | 45 | >250[e,i] | DMF–$H_2O$ | 2.50 |
| **16** |  | B | 16 | | *j,p* | 2.70 |
| **17** |  | I | 54 | 235–8 | EtOH–$H_2O$ | 4.40 |
| **18** |  | A | 7 | 197–8[k] | EtOAc–hexane | 5.33 ± 1.25 |
| **19** |  | H | 43 | 252–4[c] | MeOH–$H_2O$ | 7.58 ± 1.17 |
| **20**[b] |  | I | 54 | 230–2 | *f* | 9.50 |
| **21** |  | F | 37 | >250 | DMF–$H_2O$ | 10.0 |

**Table I (Continued)**

| no. | Ar | prep method | yield, % | mp, °C | recryst solvent | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|
| 22 |  | C | 19 | 161–5[m,n] | EtOAc–hexane | 15.0 |
| 23 |  | I | 66 | 215–8 | EtOH | 22.5 |
| 24 |  | I | 53 | 152–4 | *h* | 29.0 |
| 25 |  | K | 35 | 172–4 | *q* | 32.3 |
| 26 |  | K | 48 | 234–6 | *i*-PrOH | 105 |
| 27 |  | I | 35 | 158–8.5 | EtOH–hexane | 145 |
| 28 |  | A | 10 | 180–2[m] | EtOAc–hexane | 300 |

[a] The HIV-RT assay using rC·dG as template·primer was performed as previously described.[1,2] Reported $IC_{50}$ values are the mean of at least two experiments. $IC_{50}$ values with mean and SEM were tested at least three times. [b] Reference 3. [c] Contains $0.15H_2O$. [d] Contains 0.25 EtOAc. [e] Hemihydrate. [f] Not recrystallized. [g] Calcd C, 69.88. Found: C, 69.06. [h] Not chromatographed. [i] Contains 0.05DMF. [j] Contains TFA. [k] Contains 0.10EtOAc. [l] 5-Ethyl-6-methyl-3-(1,2,3,4-tetrahydronaphthyl-1-amino)pyridin-2(1*H*)-one. [m] Contains 0.15EtOAc. [n] Calcd C, 68.36. Found: C, 67.93. [o] Contains $0.30H_2O$. [p] Purified by preparative HPLC. [q] Triturated with $Et_2O$.

**Table II.** 3-[(Benzoxazol-2-ylmethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one Derivatives



| no. | substituent | prep method | yield, % | mp, °C | recryst solvent | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|
| 3 | none | | | | | 0.21 ± 0.02 |
| 29 | 4-Me | F | 37 | >250 | DMF–$H_2O$ | 0.12 ± 0.01 |
| 30 | 5-Me | F | 25 | 150–2 | EtOH–$H_2O$ | 1.25 |
| 31 | 6-Me | F | 48 | 203–5 | EtOH–$H_2O$ | 1.65 |
| 32 | 7-Me | F | 26 | 190–0.5 | MeOH | 0.055 |
| 33 | 7-Et | A | 51 | 165–7 | $Et_2O$ | 0.26 |
| 34 | 4,7-$Me_2$[b] | A | 44 | 204–5 | EtOH–$CHCl_3$ | 0.020 ± 0.004 |
| 35 | 4-Cl | A | 35 | 222–3 | EtOH–$CHCl_3$ | 0.15 ± 0.03 |
| 36 | 7-Cl | A | 40 | 219–20 | EtOH–$CHCl_3$ | 0.065 ± 0.013 |
| 37 | 4,7-$Cl_2$[c] | A | 31 | 198–8.5 | EtOH–$CHCl_3$ | 0.019 ± 0.004 |
| 38 | 4-F | A | 42 | 205–6 | EtOH–$CHCl_3$ | 0.110 ± 0.013 |
| 39 | 5-F | A | 35 | 173–4 | EtOH–$CHCl_3$ | 0.470 |
| 40 | 6-F | A | 38 | 197–7.5 | EtOH–$CHCl_3$ | 1.25 |
| 41 | 7-F | A | 43 | 183–4 | EtOH–$CHCl_3$ | 0.092 ± 0.011 |
| 42 | 4-F,7-Cl | A | 46 | 179–80 | EtOH–$CHCl_3$ | 0.105 |
| 43 | 4,7-$F_2$ | A | 32 | 216–7 | EtOH–CHCl | 0.070 ± 0.014 |
| 44 | 4-OMe | C | 12 | 180–2 | EtOH–$CHCl_3$ | 0.180 |
| 45 | 4-OH | F | 42 | 216–8 | EtOH | 0.440 |
| 46 | 4-$NO_2$ | F | 8 | 266 dec | EtOH | 24.5 |
| 47 | 4-$NH_2$ | L | 19 | >250 | DMF–$H_2O$ | 67.0 |

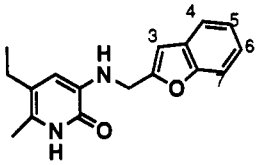
[a] See footnote *a*, Table I. [b] L-697,639. [c] L-697,661.

**43** and 4-fluoro-7-chloro **42** derivatives were not significantly more potent than the corresponding monohalo compounds. Other more polar nuclear substituents such as methoxy, hydroxy, nitro, and amino, **44–47**, were not effective in enhancing potency.

Although benzofuran appeared to be a comparable replacement for benzoxazole (**4** vs **3**), only a small number of substituted benzofuran derivatives, Table III, were prepared because of the lengthy syntheses involved. However in the benzofuran series, dichlorination at the 4- and 7-positions, **48**, yielded a more potent HIV-1 RT inhibitor as was observed in the benzoxazole series. In contrast to the benzoxazoles though, the 7-chloro derivative **49** had comparable activity to the unsubstituted parent benzofuran. Methyl substitution at the benzofuran 3-position, **50**, reduced RT inhibitory activity.

Alkyl substitution of the aminomethylene linker, Table IV, generally led to a significant reduction in potency. However this effect was minimal with the *N*-methyl derivative **51** of the highly potent dichlorobenzoxazole **37**. In contrast, N-methylation of the equally potent dimethyl analogue **34** or the dichlorobenzofuran derivative **48** to give **53** and **55**, respectively, yielded more substantial reductions in RT activity. Potency was not improved by methylation of the linker methylene carbon to give racemic **54** and **56**.

**Table III.** 3-[(Benzo[*b*]furan-2-ylmethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one Derivatives



| no. | substituent | prep method | mp, °C | recryst solvent | $IC_{50}$[a] μM |
|---|---|---|---|---|---|
| 4 | none | | | | 0.33 ± 0.09 |
| 48 | 4,7-$Cl_2$ | A | 217–20[b] | EtOH–$CHCl_3$ | 0.057 ± 0.022 |
| 49 | 7-Cl | A | 215–16 | EtOH–$CHCl_3$ | 0.335 ± 0.065 |
| 50 | 3-Me | I | 232–3 | EtOH–$CHCl_3$ | 1.95 |

[a] See footnote *a*, Table I. [b] Contains $0.20H_2O$.

Derivatives with variations in the pyridinone ring are presented in Table V. Conversion of the 5-ethyl group to 5-SMe either reduced activity, **58** vs **37**, or retained it, **65** vs **3**, depending upon the substitution pattern of the benzoxazole ring. In the latter case, increasing chain length to 5-SEt, **66**, decreased activity, suggesting a size limitation at this position. Higher sulfur oxidation states of **65**, the sulfoxide **70**, and sulfone **68** were detrimental to activity as was the 5-carbethoxy substitution in **69**. The 5-methoxy analogue **61** showed reduced RT inhibitory potency. However the vinyl substitutent, **57**, proved to be an effective replacement for ethyl. Hydroxylation and oxidation of the 5-ethyl group, **63** and **62**, led to a substantial reduction in activity. Apparently, a nonpolar group is necessary at this position for maximum activity. Introduction of a methyl group at the 4-position, **64** and **67**, led to substantial reductions in activity. The fused cyclohexano and benzo analogues **60** and **73**, respectively, were also less potent.

Methylation at the 1-position, **72**, secured the pyridinone tautomer but still led to a significant reduction in potency compared to the unmethylated parent **8**. However this result does not rule out the amide tautomer as the one primarily interacting with the enzyme–template·primer complex since the steric effect of methyl vs H at this position may be dominant. A series of phenol derivatives related to the pyridinol tautomer have been prepared and were found to be considerably less potent than the corresponding pyridinones of this report. Although not conclusive, this result suggests that the active tautomer is the pyridinone.

The marked contribution of the 5-ethyl group in the pyridinone series[3] to inhibition of HIV-1 RT parallels findings in the HEPT series[7] where the 5-ethyl substituent (a coincidence of numbering) was also superior to H or methyl at that position. The present results suggest that replacement of the HEPT 5-ethyl group by vinyl or methylthio might also lead to potent RT inhibitors.

In the TIBO[8,9] and nevirapine[10] series, thioureas and thiolactams were observed to be generally more potent than the corresponding ureas and lactams. However in this pyridinone series, the corresponding thiones **59** and **71** were not appreciably more active than the O analogues **37** and **8**.

Compounds inhibiting in vitro HIV-1 RT activity were evaluated for antiviral activity in cell culture. As shown in Table VI, pyridinones that were potent enzyme inhibitors effectively prevented the spread of HIV-1 strain IIIb infection in both MT-4 and H9 human T-lymphoid cell culture. No evidence of cytotoxicity was observed in these experiments at concentrations as high as 60 μM. The excellent correlation ($r^2$ = 0.92, slope = 0.99)[2] observed between in vitro inhibitory potency towards HIV-1 RT and efficacy in inhibiting viral spread in cell culture suggests that the antiviral effect of these compounds is mediated via direct inhibition of RT.

Subsequent experiments have shown that serial passage of the HIV-1 virus in cell culture in the presence of either a pyridinone inhibitor[11a] or nevapine[11b] have yielded viral strains which are resistant to the nonnucleoside inhibitors discussed here. These data are consistent with the possibility that the various nonnucleoside inhibitors share a common binding site.

The 2-pyridinones described in this report constitute a novel series of potent, nonnucleoside, HIV-1-specific RT inhibitors structurally distinct from other known classes of inhibitors such as the TIBO, nevirapine, and HEPT series. On the basis of potency, selectivity, oral bioavailability, and appropriate safety and tolerability studies in two species, benzoxazole derivatives **34** and **37** were selected from this series of aminopyridinones for phase I clinical trials to determine these parameters in man.[12] Following these studies, the dichloro derivative **37** progressed to clinical biological activity trials as an HIV-1 antiviral agent.

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(11) (a) Nunberg, J. H.; Schleif, W. A.; Boots, E. J.; O'Brien, J. A.; Quintero, J. C.; Hoffman, J. M.; Emini, E. A.; Goldman, M. E. Viral Resistance to Human Immunodeficiency Virus Type 1-Specific Pyridinone Reverse Transcriptase Inhibitors. *J. Virol.* **1991**, *65*, 4887–4892. (b) Richman, D.; Shih, C.-K.; Lowy, I.; Rose, J.; Prodanovich, P.; Goff, S.; Griffin, J. Human immunodeficiency virus type 1 mutants resistant to nonnucleoside inhibitors of reverse transcriptase arise in tissue culture. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 11241–11245.

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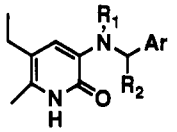
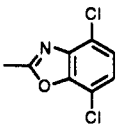
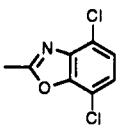
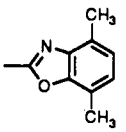
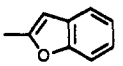
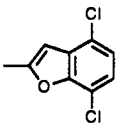
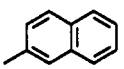
**Table IV.** Alkyl Analogues of the Aminomethylene Linker of 3-[(Arylmethyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-ones



| no. | $R_1$ | $R_2$ | Ar | prep method | yield, % | mp, °C | recryst solvent | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|---|---|
| 51 | Me | H |  | M | 86 | 230–2 | EtOH–$CHCl_3$ | 0.058 ± 0.013 |
| 52 | Et | H |  | M | 75 | 240–1 | EtOH–$CHCl_3$ | 0.654 ± 0.041 |
| 53 | Me | H |  | M | 80 | 175–7 | EtOH–$CHCl_3$ | 0.103 |
| 54 | H | Me |  | I | 25 | 148–50 | *b* | 0.970 |
| 55 | Me | H |  | M | 30 | 181–3 | EtOH–$CHCl_3$ | 1.05 |
| 56 | H | Me |  | B | 16 | 171–6[c] | EtOAc–hexane | 1.13 |

[a] See footnote 4a, Table I. [b] Not recrystallized. [c] Contains $0.25H_2O$.

## Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries and are uncorrected. Analytical results are indicated by atom symbols and are within 0.4% of theoretical values except where indicated. $^1H$ NMR spectra were recorded for all intermediates and final products on either a Varian XL-300 or a Unity-300 instrument using $Me_4Si$ as internal standard and are consistent with assigned structures. Intermediates were prepared by literature procedures except where included in the Experimental Section. E. Merck silica gel, 200–400 mesh, was used for the flash chromatographies. Yields are not optimized.

**Preparation of 3-(Substituted amino)pyridin-2(1*H*)-one Derivatives. Method A. 3-[[(4,7-Dichlorobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (37).** A mixture of 3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one[3] (0.93 g, 6.1 mmol), 2-(chloromethyl)-4,7-dichlorobenzoxazole (1.45 g, 6.1 mmol) (**80**) and diisopropylethylamine (1.06 mL, 6.1 mmol) in MeCN (30 mL) was heated at reflux under $N_2$ for 20 h. After cooling to 0 °C, the precipitated solid was removed by filtration and subjected to flash chromatography on silica gel. Elution with 4% MeOH–96% $CHCl_3$ yielded 0.76 g of product which was recrystallized from EtOH–$CHCl_3$ to give 0.66 g (31%) of analytically pure product: mp 198.0–8.5 °C; $^1H$ NMR ($CDCl_3$) δ 7.28 (br s, 2 H), 6.48 (s, 1 H), 5.40 (t, *J* = 6.8, 1 H), 4.67 (d, *J* = 6.8, 2 H), 2.35 (q, *J* = 7.8, 2 H), 2.18 (s, 3 H), 1.09 (t, *J* = 7.8, 3 H).

**Method B.** The procedure described in method A was followed except that triethylamine was substituted for diisopropylethylamine.

**Method C.** The procedure described in method B was followed except that EtOH was substituted for MeCN.

**Method D.** The procedure described in method A was followed except that 1,8-bis(dimethylamino)naphthalene was used as the base.

**Method E.** One additional equiv of the aminopyridinone was used as base in place of the $iPr_2EtN$ of method A.

**Method F.** The procedure described in method A was used with EtOH as solvent.

**Method G.** The procedure of method A was followed except that the iodo derivative was used as alkylating agent and the reaction time was 2 h.

**Method H.** The procedure of method E was used with EtOH as solvent.

**Method I. 5-Ethyl-3-[(3-furanylmethyl)amino]-6-methylpyridin-2(1*H*)-one (27).** A solution of 3-amino-5-ethyl-6-methylpyridin-2(1*H*)-one (152 mg, 1.0 mmol), 3-furaldehyde (96.1 mg, 1.0 mmol), and *p*-TsOH (19 mg, 0.10 mmol) in MeOH (10 mL) was stirred under $N_2$ at room temperature overnight. $NaCNBH_4$ (30 mg, 0.48 mmol) was added in 3 portions over 30 min. After addition was complete, the reaction mixture was stirred at room temperature for 1 h and then concentrated. The residue was flash chromatographed over silica gel and product eluted with 3% MeOH–97% $CHCl_3$. Recrystallization from EtOH–hexane gave 82 mg (35%) of analytically pure product: mp 158–8.5 °C; $^1H$ NMR ($CDCl_3$) δ 1.01 (t, 3 H), 2.04 (s, 3 H), 2.25 (q, 2 H), 4.06 (s, 2 H), 6.17 (s, 1 H), 6.46 (s, 1 H), 7.61 (d, 2 H).

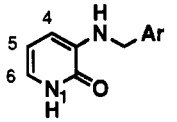
**Method J.** The procedure of method I was followed except that EtOH was used as solvent, and $NaBH_4$ was the reducing agent.

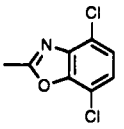
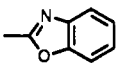
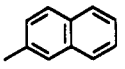
**Method K.** The procedure of method I was followed except that a catalytic amount of HOAc was used in place of TsOH, and EtOH was used as solvent.

**Method L. 3-[[(4-Aminobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (47).** A solution of the corresponding 4-nitro derivative **46** (113 mg, 0.34 mmol) in absolute EtOH (40 mL) was hydrogenated over a 5% Pd/C catalyst (50 mg) at atmospheric pressure and room temperature for 17 h. After filtering through a pad of diatomaceous earth and concentrating under reduced pressure, the residue was flash chromatographed over silica gel, and product (27 mg, 29%) was eluted with 4% MeOH–96% $CHCl_3$. An analytical sample was obtained upon recrystallization from DMF–$H_2O$.

**Method M. 3-[*N*-[(4,7-Dichlorobenzoxazol-2-yl)methyl]-*N*-methylamino]-5-ethyl-6-methylpyridin-2(1*H*)-one (51).** A solution of 3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (**37**) (74 mg, 0.211 mmol),

**Table V.** Derivatives of 3-[(Arylmethyl)amino]pyridin-2(1*H*)-one



| no. | substituent | Ar | prep method | yield, % | mp, °C | recryst solvent | $IC_{50}$,[a] μM |
|---|---|---|---|---|---|---|---|
| **37** | 5-Et,6-Me |  | | | | | 0.019 ± 0.004 |
| **57** | 5-CH=$CH_2$,6-Me | *b* | N | 17 | 224–7 | MeOH | 0.023 ± 0.009 |
| **58** | 5-SMe,6-Me | *b* | D | 69 | 254–7 | *c* | 0.043 ± 0.013 |
| **59** | 2-thio,5-Et,6-Me | *b* | O | 6 | | MeOH | 0.042 ± 0.010 |
| **60** | 4,5-($CH_2$)-,6-Me | *b* | D | 34 | 243–8 | MeOH | 0.113 ± 0.029 |
| **61** | 5-OMe,6-Me | *b* | D | 13 | 215 dec[d] | MeCN | 0.115 |
| **62** | 5-acetyl,6-Me | *b* | D | 36 | 300–4 dec | *c* | 0.300 |
| **63** | 5-CH(OH)$CH_3$,6-Me | *b* | D | 27 | 236–8 dec | *c* | 1.05 |
| **64** | 4,6-$Me_2$ | *b* | D | 21 | 193–8 | MeCN | 2.85 |
| **3** | 5-Et,6-Me |  | | | | | 0.21 ± 0.02 |
| **65** | 5-SMe,6-Me | *b* | A | 33 | 180–1 | MeOH | 0.19 |
| **66** | 5-SEt,6-Me | *b* | D | 35 | 197–200 | MeCN | 0.43 |
| **67** | 4,6-$Me_2$,5-Et | *b* | D | 19 | 165–8 | MeCN | 0.60 |
| **68** | 5-$SO_2$Me,6-Me | *b* | P | 14 | 247–50 | *e* | 1.15 |
| **69** | 5-$CO_2$Et,6-Me | *b* | A | 40 | 233–5[f] | *c* | 1.75 |
| **70** | 5-S(O)Me,6-Me | *b* | Q | 47 | 216–8 | MeCN | 31.5 |
| **8** | 5-Et,6-Me |  | | | | | 0.46 ± 0.04 |
| **71** | 2-thio,5-Et,6-Me | *b* | O | 36 | 200–2[g] | *h* | 0.30 |
| **72** | 1,6-$Me_2$,5-Et | *b* | R | *k* | 140–1[i] | hexane | 11 |
| **73** | 5,6-benzo | *b* | A | 42 | 230–1[j] | MeCN | >300 |

[a] See footnote *a*, Table I. [b] Same as above. [c] Not recrystallized. [d] Calcd C, 50.87. Found: C, 50.22. [e] Digested in hot MeOH. [f] Contains 0.20 $H_2O$. [g] EtOAc solvate. [h] $Et_2O$ trituration. [i] Hemihydrate. [j] MeCN solvate. [k] Not recorded.

**Table VI.** Antiviral Properties of Selected Compound in Cell Culture

| compd | $CIC_{95}$, μM[a] H9 cells | $CIC_{95}$, μM[a] MT-4 cells |
|---|---|---|
| **3** | | 0.20 |
| **34** | 0.10–0.15 | 0.025–0.050 |
| **37** | 0.10–0.20 | 0.025–0.050 |
| **48** | | 0.050 |
| **58** | | 0.10 |
| AZT | 20.0 | 0.012–0.025 |
| R82150[b] | | 0.20 |
| nevirapine[c] | | 0.10 |

[a] Cell culture inhibitor concentrations ($CIC_{95}$) are defined as those which inhibited by >95% the spread of HIV-1 IIIb infection in susceptible cell culture. Assays were performed as previously described.[1,2] [b] Reference 9. [c] Reference 10.

paraformaldehyde (63.4 mg, 2.11 mmol), $NaCNBH_4$ (40 mg, 0.63 mmol), and HOAc (51.3 mg, 0.63 mmol) in MeCN (0.57 mL) was stirred at room temperature overnight. The resultant solution was concentrated and the residue flash chromatographed over silica gel. Elution with 5% MeOH–95% $CHCl_3$ gave the *N*-methyl derivative. An analytical sample, mp 230–2 °C, was obtained upon recrystallization from EtOH–$CHCl_3$: $^1H$ NMR ($d_6$-DMSO) δ 7.49 (q, *J* = 8.5 Hz, 2 H), 6.60 (s, 1 H), 5.12 (s, 2 H), 2.82 (s, 3 H), 2.29 (q, *J* = 7.5 Hz, 2 H), 2.09 (s, 2 H), 1.01 (t, *J* = 7.5 Hz, 3 H).

**Method N. 3-[[(4,7-Dichlorobenzoxazol-2-yl)methyl]amino]-5-vinyl-6-methylpyridin-2(1*H*)-one (57).** A mixture of 3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-5-[1(*R,S*)-hydroxyethyl]-6-methylpyridin-2(1*H*)-one (**63**) (100 mg, 0.27 mmol) and pyridinium *p*-toluenesulfonate (1 mg) in $CDCl_3$ was heated at 60 °C for 1.5 h. $CHCl_3$ was added and the solution washed with saturated $NaHCO_3$ followed by brine. After evaporation, the residue was recrystallized from MeCN and then MeOH to give 16 mg (17%) of analytically pure product: $^1H$ NMR ($d_6$-DMSO) δ 2.14 (s, 3 H), 4.73 (d, 1 H), 5.02 (d, *J* = 11 Hz, 1 H), 5.41 (d, *J* = 17 Hz, 1 H), 6.63 (dd, *J* = 11, 17 Hz, 1 H), 6.69 (s, 1 H), 7.52 (d, *J* = 8.7 Hz, 1 H), 7.55 (d, *J* = 8.7 Hz, 1 H).

**Method O. 5-Ethyl-6-methyl-3-[(2-naphthylmethyl)amino]pyridine-2(1*H*)-thione (71).** A mixture of 2-(*tert*-butylthio)-5-ethyl-6-methyl-3-[(2-naphthylmethyl)amino]pyridine (98 mg, 0.27 mmol) (**96**) and pyridine hydrochloride (450 mg, 3.8 mmol) was heated at 140 °C under $N_2$ until evolution of gas ceased (about 45 min). After adding $H_2O$ and extracting three times with $CHCl_3$, the organic extracts were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was subjected to flash chromatography over silica gel. Elution with 2% MeOH–98% EtOAc yielded 32 mg (36%) of thione **71**.

**Method P. 3-[(Benzoxazol-2-ylmethyl)amino]-6-methyl-5-(methylsulfonyl)pyridin-2(1*H*)-one (63).** To 3-[(Benzoxazol-2-ylmethyl)amino]-6-methyl-5-(methylthio)pyridin-2(1*H*)-one (**65**) (45 mg, 0.15 mmol) in $CH_2Cl_2$ (5 mL) cooled in an ice bath was added 80% *m*-chloroperbenzoic acid (74 mg, 0.34 mmol) in $CH_2Cl_2$ solution. After stirring for 6 h, additional *m*-chloroperbenzoic acid (50 mg) was added and the reaction allowed to stir overnight at room temperature. The mixture was evaporated to dryness and the residue extracted four times with $Et_2O$. The residue was chromatographed over silica gel and developed with 2, 5, and 10% *i*-PrOH–$CH_2Cl_2$ to give 9 mg (18%) of product. Digestion with warm MeOH and cooling gave 4 mg of pure sulfone: $^1H$ NMR ($CDCl_3$) δ 2.65 (s, 3 H), 3.01 (s, 3 H), 4.66 (d, *J* = 6.3 Hz, 1 H), 5.62 (t, *J* = 6.3 Hz, 1 H), 6.89 (s, 1 H), 7.35 (m, 2 H), 7.5 (m, 1 H), 7.7 (m, 1 H); FAB MS, 234 (M + H).

**Method Q. 3-[(Benzoxazol-2-ylmethyl)amino]-6-methyl-5-(methylsulfinyl)pyridin-2(1*H*)-one (70).** A mixture of 3-[(benzoxazol-2-ylmethyl)amino]-6-methyl-5-(methylthio)pyridin-2(1*H*)-one (**65**) (20 mg, 0.066 mmol) and 80% *m*-chloroperbenzoic acid (14 mg, 0.079 mmol) in $CH_2Cl_2$ (5 mL) was allowed to stir at ice bath temperature for 1.5 h. Following evaporation of solvent, the solid residue was washed several times with $Et_2O$. The insoluble residue was dissolved in MeCN with heating. After filtration, the solvent was partially evaporated and cooled to give the sulfoxide: $^1H$ NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.66 (s, 3 H),

**Table VII.** Intermediates for the Preparation of Compounds Listed in Tables I–V

| product | intermediate | source |
|---|---|---|
| 3 | 2-(chloromethyl)benzoxazole | *a* |
| 4 | benzo[*b*]furan-2-carboxaldehyde | *n* |
| 5 | 2-(iodomethyl)-4,5,6,7-tetrahydrobenzoxazole (74) | *b* |
| 6 | quinoline-3-carboxaldehyde | *c* |
| 7 | 2-(chloromethyl)benzothiazole | *a* |
| 8 | 2-(bromomethyl)naphthalene | *c* |
| 9 | 2-(chloromethyl)benzo[*b*]thiophene | *d* |
| 10 | 2-(chloromethyl)quinoline hydrochloride | *c* |
| 11 | 3-(bromomethyl)-4*H*-1-benzopyran-4-one (75) | *b* |
| 12 | 2-(chloromethyl)oxazole[4,5-*b*]pyridine | *e* |
| 13 | 1-(bromomethyl)naphthalene | *c* |
| 14 | 2-(iodomethyl)–5-phenyloxazole (76) | *b* |
| 15 | 2-(chloromethyl)quinazolin-4(3*H*)-one | *f* |
| 16 | 2-(chloromethyl)naphth[1,2-*d*]oxazole | *a* |
| 17 | indole-2-carboxaldehyde | *m* |
| 18 | benzylbromide | *c* |
| 19 | 2-(chloromethyl)benzimidazole | *c* |
| 20 | 3,4-dihydronaphthalen-1(2*H*)-one | *c* |
| 21 | 2-(chloromethyl)naphth[2,3-*d*]oxazole | *a* |
| 22 | 2-(chloromethyl)pyridine hydrochloride | *c* |
| 23 | indole-3-carboxaldehyde | *c* |
| 24 | 2-furaldehyde | *c* |
| 25 | furo[3,2-c]pyridine-2-carboxaldehyde (77) | *b* |
| 26 | furo[2,3-c]pyridine-2-carboxaldehyde (78) | *b* |
| 27 | 3-furaldehyde | *c* |
| 28 | 3-(chloromethyl)pyridine hydrochloride | *c* |
| 29 | 2-(chloromethyl)-4-methylbenzoxazole | *a* |
| 30 | 2-(chloromethyl)-5-methylbenzoxazole | *a* |
| 31 | 2-(chloromethyl)-6-methylbenzoxazole | *a* |
| 32 | 2-(chloromethyl)-7-methylbenzoxazole | *a* |
| 33 | 7-ethyl-2-(iodomethyl)benzoxazole (79) | *b* |
| 34 | 2-(chloromethyl)-4,7-dimethylbenzoxazole | *a* |
| 35 | 4-chloro-2-(chloromethyl)benzoxazole | *a* |
| 36 | 7-chloro-2-(chloromethyl)benzoxazole | *a* |
| 37 | 2-(chloromethyl)-4,7-dichlorobenzoxazole (80) | *b* |
| 38 | 2-(chloromethyl)-4-fluorobenzoxazole | *a* |
| 39 | 2-(chloromethyl)-5-fluorobenzoxazole | *a* |
| 40 | 2-(chloromethyl)-6-fluorobenzoxazole | *a* |
| 41 | 2-(chloromethyl)-7-fluorobenzoxazole | *a* |
| 42 | 7-chloro-2-(chloromethyl)-4-fluorobenzoxazole | *a* |
| 43 | 4,7-difluoro-2-(iodomethyl)benzoxazole (81) | *b* |
| 44 | 2-(chloromethyl)-4-methoxybenzoxazole | *a* |
| 45 | 2-(chloromethyl)-4-hydroxybenzoxazole (82) | *b* |
| 46 | 2-(chloromethyl)-4-nitrobenzoxazole (83) | *b* |
| 47 | 46 | *g* |
| 48 | 4,7-dichloro-2-(iodomethyl)benzo[*b*]furan (84) | *b* |
| 49 | 7-chloro-2-(iodomethyl)benzo[*b*]furan | *o* |
| 50 | 3-methylbenzo[*b*]furan-2-carboxaldehyde (85) | *b* |
| 51 | 37 | *h* |
| 52 | 37 | *h* |
| 53 | 34 | *h* |
| 54 | 2-acetylbenzo[*b*]furan | *c* |
| 55 | 48 | *h* |
| 56 | 2-(1-chloroethyl)naphthalene | *q* |
| 57 | 63 | *i* |
| 58 | 3-amino-6-methyl-5-(methylthio)pyridin-2(1*H*)-one (86) | *b* |
| 59 | 2-(*tert*-butylthio)-3-[[(4,7-dichlorobenzoxazol-2-yl)-methyl]amino]-5-ethyl-6-methylpyridine (87) | *b* |
| 60 | 4-amino-1-methyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one (88) | *b* |
| 61 | 3-amino-5-methoxy-6-methylpyridin-2(1*H*)-one (89) | *b* |
| 62 | 5-acetyl-3-amino-6-methylpyridin-2(1*H*)-one (90) | *b* |
| 63 | 3-amino-5-(1-hydroxymethyl)-6-methylpyridin-2(1*H*)-one (91) | *b* |
| 64 | 3-amino-4,6-dimethylpyridin-2(1*H*)-one (92) | *b* |
| 65 | 3-amino-6-methyl-5-(methylthio)pyridin-2(1*H*)-one (86) | *b* |
| 66 | 3-amino-5-(ethylthio)-6-methylpyridin-2(1*H*)-one (93) | *b* |
| 67 | 3-amino-4,6-dimethyl-5-ethylpyridin-2(1*H*)-one | *j* |
| 68 | 65 | *k* |
| 69 | 3-amino-5-(ethoxycarbonyl)-6-methylpyridin-2(1*H*)-one (94) | *b* |
| 70 | 65 | *l* |
| 71 | 2-(*tert*-butylthio)-5-ethyl-6-methyl-3-[(2-naphthylmethyl)-amino]pyridine (95) | *b* |
| 72 | 8 | *p* |
| 73 | 3-aminoquinolin-2(1*H*)-one (96) | *b* |

[a] Prepared by the method of ref 4. [b] See Experimental Section. [c] Commercially available. [d] Reference 13. [e] Reference 14. [f] Reference 15. [g] Method L. [h] Method M. [i] Method N. [j] Reference 3. [k] Method P. [l] Method Q. [m] Reference 16. [n] Reference 17. [o] The corresponding chloromethyl derivative[5] was converted to iodomethyl by method S. [p] Method R. [q] Reference 18.

4.70 (d, $J$ = 6.3 Hz, 2 H), 5.66 (t, $J$ = 6.3 Hz, 1 H), 6.93 (s, 1 H), 7.34 (m, 2 H), 7.52 (m, 1 H), 7.71 (m, 1 H).

**Method R. 3-[(2-Naphthylmethyl)amino]-1,6-dimethyl-5-ethylpyridin-2(1*H*)-one (72).** A mixture of 3-[(2-naphthyl-

methyl)amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (8) (100 mg, 0.34 mmol) and NaH (9.0 mg, 0.38 mmol) in DMF (4 mL) was stirred at room temperature for 15 min. Methyl iodide (73 mg, 0.51 mmol) was added and the reaction stirred at room temperature for 12 h. After removal of DMF under reduced pressure, the residue was chromatographed over silica gel and product eluted with 2% MeOH–98% $CHCl_3$.

**Preparation of Intermediates Listed in Table VII. Method S. 2-(Iodomethyl)-4,5,6,7-tetrahydrobenzoxazole (74).** To a cooled solution of 2-aminocyclohexanone hydrochloride[19] (1.5 g, 10 mmol) and chloroacetyl chloride (1.69 g, 15 mmol) in $CHCl_3$ (20 mL) was added a solution of $Et_3N$ (2.78 mL, 20 mmol) in $CHCl_3$ (8 mL). After stirring overnight at room temperature, the reaction mixture was washed with $H_2O$, dried ($Na_2SO_4$), filtered, and concentrated. Recrystallization from EtOAc–hexane afforded 0.68 g (36%) of analytically pure amide, mp 79–81 °C.

A solution of this amide (0.50 g, 2.6 mmol) in $POCl_3$ (8.7 mL) was stirred at reflux for 7 h and then concentrated under reduced pressure. Ice was added to the residue and product extracted into $Et_2O$. After washing the $Et_2O$ extract with saturated $NaHCO_3$ solution, it was dried ($Na_2SO_4$), filtered, and concentrated to give 390 mg (87%) of the (chloromethyl)benzoxazole as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.75–1.90 (m, 4 H), 2.5 (m, 2 H), 2.65 (m, 2 H), 4.57 (s, 2 H).

A mixture of the (chloromethyl)benzoxazole (350 mg, 2.04 mmol) and NaI (974 mg, 6.5 mmol) in $Me_2CO$ (14 mL) was stirred at reflux under $N_2$ for 17 h. After concentration, the residue was extracted with $CHCl_3$ and washed with $H_2O$. The $CHCl_3$ extract was concentrated and the residue flash chromatographed over silica gel. Elution with $CHCl_3$ gave 0.27 g (50%) of the (iodomethyl)benzoxazole as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.75–1.90 (m, 4 H), 2.5 (m, 2 H), 2.6 (m, 2 H), 4.37 (s, 2 H).

**3-(Bromomethyl)-4*H*-1-benzopyran-4-one (75).** Bromination of 3-methyl-4*H*-1-benzopyran-4-one with NBS in refluxing $C_6H_6$ gave, after flash chromatography over silica gel and elution with 6–10% EtOAc–94–90% hexane, a 58% yield of product: $^1H$ NMR ($CDCl_3$) $\delta$ 8.26 (dd, $J$ = 7.9, 1.6 Hz, 1 H), 8.12 (s, 1 H), 7.70 (ddd, $J$ = 8.5, 7.1, 1.6 Hz, 1 H), 7.44 (m, 2 H), 4.41 (s, 2 H).

**2-(Iodomethyl)-5-phenyloxazole (76)** was prepared in 36% overall yield from 2-aminoacetophenone hydrochloride by method S: $^1H$ NMR ($CDCl_3$) $\delta$ 7.6 (d, 2 H), 7.3–7.5 (m, 4 H), 7.25 (d, 2 H), 4.47 (s, 2 H).

**Furo[3,2-*c*]pyridine-2-carboxaldehyde (77).** A solution of *n*-BuLi in hexane (1.6 M, 18.8 mL, 30 mmol) was added to a solution of distilled *i*-$Pr_2EtN$ (4.2 mL, 30 mmol) in dry THF (40 mL) under an inert atmosphere while maintaining the temperature below −20 °C. After 15 min, the temperature was lowered to −70 °C and a solution of furo[3,2-c]pyridine (2.85 g, 24 mmol)[20] in dry THF (15 mL) was added dropwise to give a gummy residue. This mixture was warmed to −30 °C, and with vigorous stirring the gum solidified into a powder. The mixture was again cooled to −70 °C and dry DMF (2.6 mL, 34 mmol) was added. The reaction mixture was allowed to warm slowly to room temperature, quenched with HOAc (2.2 mL), and extracted with $CH_2Cl_2$. The organic extract was washed with $H_2O$ and dilute NaOH solution and dried ($Na_2SO_4$). After filtration through a pad of charcoal and concentration, the residue was triturated with $Et_2O$ to give several crops of crystalline product (769 mg, 22%): mp 126–7 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 9.92 (s, 1 H), 9.13 (s, 1 H), 8.67 (d, $J$ = 5.9 Hz, 1 H), 7.63 (d, $J$ = 1 Hz, 1 H), 7.57 (d, $J$ = 5.9 Hz, 1 H). Anal. ($C_8H_5NO_2$) C, H, N.

**Furo[2,3-*c*]pyridine-2-carboxaldehyde (78)** was prepared in 21% yield from furo[2,3-c]pyridine[21] by the same procedure used to prepare furo[3,2-c]pyridine-2-carboxaldehyde (77): mp 120–1 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 10.02 (s, 1 H), 9.09 (s, 1 H), 8.57 (d, $J$ = 5.4 Hz, 1 H), 7.71 (dd, $J$ = 1.1, 5.4 Hz, 1 H), 7.57 (d, $J$ = 0.9 Hz, 1 H). Anal. ($C_8H_5NO_2$) C, H, N.

**7-Ethyl-2-(iodomethyl)benzoxazole (79).** 2-Ethylphenol (7.5 g, 61 mmol) was added slowly to a stirred solution of $NaNO_3$ (16.5 g, 194 mmol), concentrated $H_2SO_4$ (7 mL), and $H_2O$ (20 mL) maintained at 10–20 °C. After addition was complete, the reaction mixture was stirred at 20 °C for 1 h and then extracted with $CH_2Cl_2$. The organic extract was washed (brine), dried ($Na_2SO_4$), filtered, and concentrated. The residue was flash chromatographed over silica gel and 2-ethyl-6-nitrophenol (2.4 g, 23%) eluted with toluene. Catalytic hydrogenation in EtOH over a Pt/C catalyst provided the corresponding aniline which was converted to the (iodomethyl)benzoxazole by method S: $^1H$ NMR ($CDCl_3$) $\delta$ 7.55 (d, 1 H), 7.3 (t, 1 H), 7.2 (d, 1 H), 4.53 (s, 2 H), 2.9 (q, 2 H), 1.35 (t, 3 H).

**2-(Chloromethyl)-4,7-dichlorobenzoxazole (80).** A yellow solution of 2,5-dichloro-6-nitrophenol[24] (10.0 g, 48.0 mmol) in EtOH (200 mL) and HOAc (13.8 mL) at 0 °C was reduced in the presence of 5% Pt/C catalyst (0.15 g) under an atmosphere of $H_2$ (25 psi) for 1 h in a Parr apparatus. The resultant colorless solution was filtered and concentrated under reduced pressure to yield 8.52 g (100%) of 2-amino-3,6-dichlorophenol: $^1H$ NMR ($d_6$-DMSO) $\delta$ 9.3 (br s, 1 H), 6.78 (d, $J$ = 8.6 Hz, 1 H), 6.58 (d, $J$ = 8.6 Hz, 1 H), 5.1 (br s, 2 H).

To a solution of 2-amino-3,6-dichlorophenol (23.9 g, 134 mmol) in $CH_2Cl_2$ (270 mL) was added solid ethyl (chloroimino)acetate hydrochloride (31.9 g, 202 mmol). The resultant slurry was stirred at room temperature overnight and then filtered through a pad of diatomaceous earth and concentrated under reduced pressure. The solid residue was subjected to flash chromatography on silica gel. Elution with $CHCl_3$ yielded 26.6 g (86%) of 2-(chloromethyl)-4,7-dichlorobenzoxazole: $^1H$ NMR ($CDCl_3$) $\delta$ 7.34 (s, 2 H), 4.81 (s, 2 H). Anal. ($C_8H_4Cl_3NO$) C, H, N.

**4,7-Difluoro-2-(iodomethyl)benzoxazole (81).** To a mixture of concentrated $H_2SO_4$ (15 g) and 20% fuming $H_2SO_4$ (20 g) at 0 °C was added 2,5-difluorophenol (10 g, 77 mmol). The resultant slurry was stirred with a mechanical stirrer and heated to 80–90 °C for 30 min. After cooling to 0 °C, the slurry was diluted with concentrated $H_2SO_4$ (15 mL), and a mixture of concentrated $HNO_3$ (15 g) and 20% fuming $H_2SO_4$ (8 mL) added dropwise over a period of 30 min. This mixture was stirred at 0 °C for 30 min and then at room temperature overnight. The resultant mixture was then heated to 60 °C over a period of 2 h and held at that temperature for 3 h. After cooling to room temperature, $H_2O$ (20 mL) was added and the product steam distilled. The yellow distillate was extracted twice with $CH_2Cl_2$, and the extracts were combined and washed with brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography on silica gel eluted with 1% MeOH–99% $CHCl_3$ to give 2,5-difluoro-6-nitrophenol.

A yellow solution of 2,5-difluoro-6-nitrophenol (1.22 g, 7.0 mmol) in EtOH (70 mL) and HOAc (0.42 g) was catalytically reduced in the presence of 5% Pt/C (61 mg) under an atmosphere of $H_2$ at room temperature overnight. The colorless solution was filtered through a pad of diatomaceous earth and concentrated to yield 0.83 g (85%) of the amine. Reaction with ethyl (chloroimino)acetate hydrochloride by the procedure used for the corresponding dichloro derivative gave an 80% yield of

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2-(chloromethyl)-4,7-difluorobenzoxazole: $^1$H NMR ($CDCl_3$) δ 7.12 (ddd, $J$ = 9, 9, 3.6 Hz, 1 H), 7.03 (ddd, $J$ = 9, 9, 3.6 Hz, 1 H), 4.78 (s, 2 H).

The corresponding (iodomethyl)benzoxazole was prepared from the chloromethyl derivative by the procedure of method S.

**2-(Chloromethyl)-4-hydroxybenzoxazole (82).** Catalytic reduction of 2-nitroresorcinol in EtOH with a 5% Pd/C catalyst provided 2-aminoresorcinol in 99% yield. Conversion to the (chloromethyl)benzoxazole by method S gave 2-(chloromethyl)-4-hydroxybenzoxazole, mp 146–7 °C in 34% yield: $^1$H NMR ($d_6$-DMSO) δ 10.43 (s, 1 H), 7.22 (t, $J$ = 8.1 Hz, 1 H), 7.13 (d, $J$ = 8.2 Hz, 1 H), 6.76 (d, $J$ = 8.0 Hz, 1 H), 5.02 (s, 2 H).

**2-(Chloromethyl)-4-nitrobenzoxazole (83).** A solution of 2-amino-3-nitrophenol (1.5 g, 10 mmol) and 1-chloro-2,2,2-trimethoxyethane (1.5 g, 10 mmol)[14] in absolute EtOH (5 mL) was heated at 65 °C for 3 h. Additional 1-chloro-2,2,2-trimethoxyethane (1.0 g) and $p$-TsOH·$H_2O$ (20 mg) were added, and the mixture was heated at 65 °C for 19 h. After cooling, the precipitated solid was collected, washed with absolute EtOH, and dried to give 1.47 g (69%) of product: $^1$H NMR ($CDCl_3$) δ 4.9 (s, 2 H), 7.6 (t, 1 H), 7.95 (d, 1 H), 8.25 (d, 1 H).

**4,7-Dichloro-2-(iodomethyl)benzo[*b*]furan (84).** A mixture of 2,5-dichlorophenol (41 g, 0.25 mol), 2,3-dichloro-1-propene (28 g, 0.25 mol), and $K_2CO_3$ (35 g, 0.25 mol) in $Me_2CO$ (100 mL) was heated at reflux overnight. The residue was dissolved in $Et_2O$ and washed twice with 1 N NaOH and three times with brine. The $Et_2O$ solution was dried ($Na_2SO_4$), filtered, and concentrated to yield 41 g (68%) of 2,5-dichlorophenyl 2-chloroprop-2-enyl ether.

A solution of 2,5-dichlorophenyl 2-chloroprop-2-enyl ether (10 g, 23 mmol) in 1,4-diisopropylbenzene (50 mL) was heated at reflux under $N_2$ for 48 h. The resultant mixture was then subjected to flash chromatography over silica gel eluting first with hexane then with 2% $CH_2Cl_2$–98% hexane to give 8.7 g (87%) of 2-(2-chloroprop-2-enyl)-3,6-dichlorophenol.

A solution of 2-(2-chloroprop-2-enyl)-3,6-dichlorophenol (8.7 g, 37 mmol), $Ac_2O$ (4.5 g, 44 mmol), $i$-$Pr_2NEt$ (5.7 g, 44 mmol), and 4-(dimethylamino)pyridine (0.45 g, 3.7 mmol) in $CH_2Cl_2$ was stirred at room temperature overnight. After concentration, the residue was subjected to flash chromatography on silica gel. Elution with 4% $CH_2Cl_2$–96% hexane yielded 8.9 g (87%) of the acetate.

A solution of 2-(2-chloroprop-2-enyl)-3,6-dichlorophenyl acetate (8.9 g, 32 mmol) and 80% $m$-chloroperbenzoic acid (10 g) in $CH_2Cl_2$ (85 mL) was stirred at room temperature for 8 days. The mixture was then concentrated and the residue dissolved in $Et_2O$. The etheral solution was washed successively with saturated $NaHCO_3$ and brine. Drying ($Na_2SO_4$), filtration, and concentration gave the corresponding chloroepoxide.

Without further purification, the chloroepoxide was dissolved in $CH_2Cl_2$ and stirred under an atmosphere of HCl gas at room temperature for 2 days. Concentration gave a quantitative yield of 1-(2-acetoxy-3,6-dichlorophenyl)-3-chloro-2-propanone.

A suspension of 1-(2-acetoxy-3,6-dichlorophenyl)-3-chloro-2-propanone (2.0 g, 6.6 mmol) in concentrated HCl (50 mL) was heated at 90 °C for 1 h. After cooling to room temperature, the white solid that precipitated was dissolved in $CHCl_3$. The $CHCl_3$ extract was washed three times with brine, dried ($Na_2SO_4$), filtered, and concentrated. The residue was then subjected to flash chromatography on silica gel. Elution with 1:1 $CHCl_3$–hexane gave 0.67 g (42%) of 2-(chloromethyl)-4,7-dichlorobenzo[*b*]furan. Treatment with NaI in $Me_2CO$ at 60 °C overnight yielded the corresponding 2-(iodomethyl) derivative in 90% yield.

**3-Methylbenzo[*b*]furan-2-carboxaldehyde (85).** A mixture of 3-methylbenzo[*b*]furan-2-carboxylic acid (1.76 g, 10 mmol), iodomethane (1.42 g, 10 mmol), and DBU (1.52 g, 10 mmol) in $C_6H_6$ (20 mL) was stirred at room temperature for 2 h. The resultant slurry was filtered through a bed of diatomaceous earth and concentrated under reduced pressure to afford a quantitative yield of the methyl ester: $^1$H NMR ($CDCl_3$) δ 7.64 (d, $J$ = 8 Hz, 1 H), 7.55 (d, $J$ = 8 Hz, 1 H), 7.45 (t, $J$ = 8 Hz, 1 H), 7.31 (t, $J$ = 8 Hz, 1 H), 3.99 (s, 3 H), 2.60 (s, 3 H).

A 1 M solution of DIBAL in hexane (11.5 mL, 11.5 mmol) was added to a solution of methyl 3-methylbenzo[*b*]furan-2-carboxylate (0.73 g, 3.8 mmol) in THF at 0 °C. The mixture was stirred at room temperature for 1 h, quenched with 1 M aqueous HCl (50 mL), and diluted with $Et_2O$. The organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to give 0.58 g (87%) of 2-(hydroxymethyl)-3-methylbenzo[*b*]furan: $^1$H NMR ($CDCl_3$) δ 7.49 (d, $J$ = 7 Hz, 1 H), 7.36 (d, $J$ = 7 Hz, 1 H), 7.33 (m, 2 H), 4.76 (d, $J$ = 6 Hz, 2 H), 2.26 (s, 3 H), 1.84 (t, $J$ = 6 Hz, 1 H).

A mixture of the alcohol (0.58 g, 3.3 mmol) and $MnO_2$ (2 g) in $C_6H_6$ (30 mL) was stirred at room temperature overnight. The mixture was then filtered through a bed of diatomaceous earth and concentrated under reduced pressure to give 0.37 g (65%) of the aldehyde: $^1$H NMR ($CDCl_3$) δ 10.00 (s, 1 H), 7.66 (d, $J$ = 8 Hz, 1 H), 7.5 (m, 2 H), 7.31 (t, $J$ = 8 Hz, 1 H), 2.60 (s, 3 H).

**3-Amino-6-methyl-5-(methylthio)pyridin-2(1*H*)-one (86).** To a mixture of the Na salt of 2-(methylthio)-3-oxo-1-butanal (1.54 g, 10 mmol) (prepared by the procedure of ref 22) and 2-nitroacetamide (1.10 g, 10.5 mmol) in $H_2O$ (10 mL) was added aqueous 3.4 M piperidinium acetate (0.71 mL). After stirring overnight at room temperature, the yellow solids were removed by filtration and washed with $H_2O$ to give 0.874 g (43.7%) of analytically pure yellow solid, mp 199–203 °C. Anal. ($C_7H_8N_2O_3S$) C, H, N.

To a mixture of the 3-nitro compound (600 mg, 3.0 mmol) in MeOH (30 mL) at room temperature was added an aqueous solution of $Na_2S_2O_4$ (1.74 g, 10 mmol). When the yellow color disappeared after addition of more $Na_2S_2O_4$ (1.7 g), the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous $NaHCO_3$ and brine and then dried ($MgSO_4$). Filtration and concentration gave 0.20 g (39.4%) of product as a light yellow solid which was used without further purification.

**2-(*tert*-Butylthio)-3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridine (87).** A mixture of 5-ethyl-6-methyl-3-nitropyridin-2(1*H*)-one[3] (2.38 g, 13 mmol) and $PCl_5$ (3.3 g, 15.6 mmol) was heated under $N_2$ at 140–150 °C for 15 min. $H_2O$ was added and product extracted into $CHCl_3$. The organic extract was washed three times with brine, dried ($Na_2SO_4$), filtered, and concentrated. The residue was added to a small plug of silica gel and eluted with 2% MeOH–98% $CHCl_3$ to give 1.5 g (57.7%) of the corresponding chloropyridine as a clear pale brown oil.

2-Methyl-2-propanethiol (1.0 mL, 8.0 mmol) was added to a stirred suspension of NaH (0.23 g, 9.6 mmol) in DMF (20 mL) under $N_2$. After stirring at room temperature for 15 min, a clear solution was obtained. A solution of 2-chloro-5-ethyl-6-methyl-3-nitropyridine (1.5 g, 7.5 mmol) in DMF (2 mL) was then added and the black solution stirred for an additional 15 min at 0 °C. After concentration under reduced pressure, the residue was subjected to flash chromatography on silica gel. Elution with 30% $CHCl_3$–70% hexane yielded 0.5 g (26%) of the 2-(*tert*-butylthio)pyridine as a bright yellow solid: mp 113.5–4.5 °C; $^1$H NMR ($CDCl_3$) δ 8.16 (s, 1 H), 2.67 (q, $J$ = 7.6 Hz, 2 H), 2.59 (s, 3 H), 1.64 (s, 9 H), 1.28 (t, $J$ = 7.6 Hz, 3 H).

To a yellow solution of 2-(*tert*-butylthio)-5-ethyl-6-methyl-3-nitropyridine (0.5 g, 2.0 mmol) in MeOH (50 mL) at room temperature was added a solution of $Na_2S_2O_4$ (2.5 g, 14 mmol) in $H_2O$ (25 mL). The resulting white suspension was stirred for an additional 5 min and then concentrated under reduced pressure. After trituration three times with $CHCl_3$, the extracts were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was added to a small plug of silica gel and eluted with 3% MeOH–97% $CHCl_3$ to yield 0.3 g (68%) of the aminopyridine: mp 103.5–5.0 °C; $^1$H NMR ($CDCl_3$) δ 6.80 (s, 1 H), 4.17 (br s, 2 H), 2.54 (q, $J$ = 7.6 Hz, 2 H), 2.41 (s, 3 H), 1.40 (s, 9 H), 1.20 (t, $J$ = 7.6 Hz, 3 H).

Reaction of 2-(*tert*-butylthio)-5-ethyl-6-methyl-3-aminopyridine with 4,7-dichloro-2-(iodomethyl)benzoxazole by the procedure of method A afforded 3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-2-(*tert*-butylthio)-5-ethyl-6-methylpyridine as an oil in 25% yield: $^1$H NMR ($CDCl_3$) δ 7.28 (m, 2 H), 6.94 (s, 1 H), 5.81 (br s, 1 H), 4.71 (d, $J$ = 4.9 Hz, 2 H), 2.56 (q, $J$ = 7.6 Hz, 2 H), 2.41 (s, 3 H), 1.40 (s, 9 H), 1.20 (t, $J$ = 7.6 Hz, 3 H).

**4-Amino-1-methyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one (88).** A mixture of 2-acetylcyclohexanone (2.80 g, 20 mmol), 2-cyanoacetamide (1.68 g, 20 mmol), and $Et_2NH$ (0.8 mL) in EtOH (40 mL) was heated at 50 °C overnight. After cooling to room temperature, the solid product, a mixture of two regio-

isomers, was removed by filtration. Recrystallization from hot DMF gave nearly pure desired isomer, mp >319 °C. Structure of this product was confirmed by NOE experiments: $^1$H NMR ($d_6$-DMSO) δ 1.67 (m, 4 H), 2.21 (s, 3 H), 2.37 (m, 2 H), 2.72 (m, 2 H). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

A mixture of the cyano derivative (500 mg, 2.7 mmol) and concentrated HCl (4 mL) was heated in a sealed tube at 150 °C overnight. After cooling, the slurry was evaporated to dryness, $H_2O$ added, and the mixture made basic with concentrated $NH_4OH$ to give a grey solid (0.39 g) mp 207–20 °C. Nitration of this intermediate was accomplished by dissolving in concentrated $H_2SO_4$, cooling in an ice–$Me_2CO$ bath, and adding dropwise 70% $HNO_3$ (0.23 mL). After stirring for 1 h, the reaction was quenched with ice and the solid collected (0.23 g, 50%). Hydrogenation in EtOH (60 mL) with 10% Pd/C (43 mg) at atmospheric pressure and room temperature gave the amine.

**3-Amino-5-methoxy-6-methylpyridin-2(1*H*)-one (89).** A mixture of 1-methoxy-2-propanone (4.41 g, 50 mmol) and ethyl formate (4.07 g, 55 mmol) was added dropwise to a solution of NaOEt in MeOH [prepared by dissolving Na (1.15 g) in MeOH (60 mL)] cooled in an ice–$Me_2CO$ bath. After stirring for 1 h, the bath was removed and the mixture allowed to warm to room temperature. Some colorless solids were removed by filtration, and the filtrate was allowed to stir at room temperature overnight. The darkly colored reaction mixture was concentrated under high vacuum to constant weight.

A portion of the crude 1-(hydroxymethylene)-1-methoxy-2-propanone sodium salt (4.9 g) and 2-nitroacetamide ammonium salt (5.08 g, 43 mmol) were dissolved in $H_2O$. To this mixture was added 3.4 M piperidinium acetate (10.6 mL) and HOAc (2.52 g, 42 mmol). After heating at 50 °C for 4.5 h, the aqueous mixture was extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue flash chromatographed on silica gel. Elution with 2% *i*-PrOH–98% $CH_2Cl_2$ followed by 3% *i*-PrOH–97% $CH_2Cl_2$ gave 0.31 g of the nitropyridinone, mp 204–7 °C dec. Anal. ($C_7H_8N_2O_4$) C, H, N.

A mixture of 5-methoxy-6-methyl-3-nitropyridin-2(1*H*)-one (72 mg, 0.39 mmol) and 10% Pd/C (30 mg) in EtOH (20 mL) was stirred in an atmosphere of $H_2$ at atmospheric pressure and room temperature for 1.5 h. After filtering, solvent was removed under reduced pressure to give the amino compound which was used directly in the next reaction.

**5-Acetyl-3-amino-6-methylpyridin-2(1*H*)-one (90).** A mixture of 3-[(dimethylamino)methylene]-2,4-pentanedione (6.20 g, 40 mmol) and 2-nitroacetamide (2.08 g, 40 mmol) in THF (80 mL) was heated at 55–60 °C under $N_2$ for 48 h. After evaporation to dryness, the residue was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract and digestion of the residue with *i*-PrOH gave upon filtration 1.83 g (20.2%) of the nitropyridinone, mp 202–7 °C. An analytical sample had mp 207–10 °C: $^1$H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 2.87 (s, 3 H), 8.95 (s, 1 H). Anal. ($C_8H_8N_2O_2$) C, H, N.

The corresponding 3-amino derivative was prepared by catalytic hydrogenation of the nitro intermediate in EtOH at atmospheric pressure and room temperature over a 10% Pd/C catalyst and was used without further purification.

**3-Amino-5-(1-hydroxyethyl)-6-methylpyridin-2(1*H*)-one (91).** A mixture of 5-acetyl-6-methyl-3-nitropyridin-2(1*H*)-one (800 mg, 48 mmol) and 10% Pd/C (210 mg) in EtOH (200 mL) was stirred under an atmosphere of $H_2$ at atmospheric pressure and room temperature for 2 h. Following filtration and evaporation, the residue was dissolved in EtOH (200 mL), and $NaBH_4$ (550 mg) was added to the solution in portions. After stirring for 24 h, the reaction mixture was acidified with HOAc and concentrated. The crude product was washed twice with MeOH and then flash chromatographed over silica gel. Elution with 5–15% MeOH–95–85% $CH_2Cl_2$ gave 440 mg of product: mp >290 °C; $^1$H NMR ($d_6$-DMSO) δ 1.18 (d, $J$ = 6.3 Hz, 3 H), 2.05 (s, 3 H), 4.63 (m, 1 H), 4.72 (s, 2 H), 4.78 (d, $J$ = 3.3 Hz, 1 H), 6.61 (s, 1 H), 11.07 (s, 1 H). Anal. ($C_8H_{12}N_2O_2 \cdot 0.25H_2O$) C, H, N.

**3-Amino-4,6-dimethylpyridin-2(1*H*)-one (92).** A mixture of 2,4-pentanedione (1.0 g, 10 mmol), nitroacetamide ammonium salt (1.33 g, 11 mmol), and 3.4 M aqueous piperidinium acetate (2.94 mL, 10 mmol) in $H_2O$ (20 mL) was heated overnight at 50 °C. The yellow solid which appeared upon cooling weighed 0.11 g (7%): mp 255–8 °C; $^1$H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.37 (s, 3 H), 6.01 (s, 1 H); FAB MS 169 (M + H). Anal. ($C_7H_8N_2O_3$) C, H, N.

A mixture of the nitro compound (299 mg, 18 mmol) and 10% Pd/C (50 mg) in EtOH (25 mL) was stirred for 2 h under $H_2$. Filtration followed by evaporation afforded a solid (210 mg, 85%) which was utilized without further purification: $^1$H NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.24 (s, 3 H), 2.9–3.3 (br s, 2 H), 5.83 (s, 1 H).

**3-Amino-5-(ethylthio)-6-methylpyridin-2(1*H*)-one (93)** was prepared by the same route used to prepare the 5-(methylthio) derivative 86. The corresponding 3-nitro intermediate, mp 190–1 °C was obtained in 43.6% yield from the Na salt of 2-(ethylthio)-3-oxo-1-butanal which in turn was prepared by the procedure of ref 22.

**3-Amino-5-(ethoxycarbonyl)-6-methylpyridin-2(1*H*)-one (94).** A solution of 2-(ethoxycarbonyl)-3-oxobutanal[23] (1.6 g, 10 mmol) and nitroacetamide (1.0 g, 10 mmol) in $H_2O$ (50 mL) containing 300 mg of piperidine acetate was stirred at room temperature for 20 h. A pale yellow solid separated and was recovered by filtration. This solid was dissolved in a solution of EtOH (20 mL) and THF (40 mL), 10% Pd/C (80 mg) added, and the mixture was hydrogenated at 40 psi on a Parr apparatus. When $H_2$ uptake ceased, the reaction was filtered. The clear filtrate was concentrated to yield 700 mg (31%) of the amine, mp 214–6 °C. Anal. calcd ($C_9H_{10}N_2O_5$) C, H, N.

**2-(*tert*-Butylthio)-5-ethyl-6-methyl-3-[(2-naphthylmethyl)amino]pyridine (95).** A mixture of 3-amino-2-(*tert*-butylthio)-5-ethyl-6-methylpyridine (0.15 g, 0.67 mmol), 2-(bromomethyl)naphthalene (0.15 g, 0.67 mmol), and *i*-$Pr_2NEt$ (86 mg, 0.67 mmol) in MeCN (5 mL) was heated at reflux under $N_2$ for 16 h. After concentration, the residue was subjected to flash chromatography on silica gel. Elution with 1% MeOH–99% $CHCl_3$ provided 98 mg (40%) of the [(naphthylmethyl)amino]pyridine: $^1$H NMR ($CDCl_3$) δ 7.85–7.78 (m, 4 H), 7.49–7.44 (m, 3 H), 6.68 (s, 1 H), 5.52 (br t, 1 H), 4.52 (d, $J$ = 5.8 Hz, 2 H), 2.49 (q, $J$ = 7.6 Hz, 2 H), 2.40 (s, 3 H), 1.42 (s, 9 H), 1.11 (t, $J$ = 7.6 Hz, 3 H).

**3-Aminoquinolin-2(1*H*)-one (96).** A solution of 2-aminobenzaldehyde (1.93 g, 16 mmol) and ethyl 2-nitroacetate (2.21 g, 16 mmol) in DMF (50 mL) was heated at 70 °C overnight. The orange cloudy mixture was concentrated and the residue subjected to flash chromatography over silica gel. Elution with 9% MeOH–91% $CHCl_3$ yielded 0.3 g (10%) of 3-nitroquinolin-2(1*H*)-one: $^1$H NMR ($d_6$-DMSO) δ 8.96 (s, 1 H), 7.92 (d, $J$ = 8 Hz, 1 H), 7.74 (t, $J$ = 8 Hz, 1 H), 7.39 (d, $J$ = 8 Hz, 1 H), 7.34 (t, $J$ = 8 Hz, 1 H), 2.49 (q, $J$ = 7.6 Hz, 2 H), 2.40 (s, 3 H), 1.42 (s, 9 H), 1.11 (t, $J$ = 7.6 Hz, 3 H).

A solution of the nitroquinolinone (0.3 g) in MeOH (100 mL) was hydrogenated over 5% Pd/C catalyst (50 mg) at atmospheric pressure and room temperature for 2 h. After filtering, the filtrate was concentrated to give 21 mg (82%) of 3-aminoquinolin-2(1*H*)-one: $^1$H NMR ($CDCl_3$) δ 7.38 (d, $J$ = 8 Hz, 1 H), 7.35–7.25 (m, 2 H), 7.16 (t, $J$ = 8 Hz, 1 H), 4.41 (br s, 2 H).

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