# Synthesis and Pharmacology of a Series of 3- and 4-(Phosphonoalkyl)pyridine- and -piperidine-2-carboxylic Acids. Potent *N*-Methyl-D-aspartate Receptor Antagonists

Paul L. Ornstein,* John M. Schaus, John W. Chambers, Diane L. Huser, J. David Leander, David T. Wong, Jonathan W. Paschal, Noel D. Jones, and Jack B. Deeter

*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285.* *Received July 8, 1988*

We recently prepared a series of 3- and 4-(phosphonoalkyl)pyridine- and -piperidine-2-carboxylic acids as antagonists of neurotransmission at *N*-methyl-D-aspartate (NMDA) preferring receptors. NMDA antagonists may prove to be useful therapeutic agents, for instance, as anticonvulsants, in the treatment of neurodegenerative disorders such as Alzheimer's disease and in the prevention of neuronal damage that occurs during cerebral ischemia. The compounds prepared were evaluated for their ability to displace [$^3$H]CPP binding (an assay shown to be selective for compounds that bind at the NMDA receptor) and for their ability to block NMDA-induced lethality in mice (an assay that is also specific for competitive and noncompetitive NMDA antagonists). Two of the compounds, *cis*-4-(phosphonomethyl)piperidine-2-carboxylic acid (**11a**) and *cis*-4-(3-phosphonoprop-1-yl)piperidine-2-carboxylic acid (**11c**) proved to be potent NMDA antagonists. **11a** and **11c** displaced [$^3$H]CPP binding with $IC_{50}$'s of 95 and 120 nM, respectively, and both protected mice from NMDA-induced lethality, with MEDs (minimum effective dose, the dose at which three of the five animals tested survived) of 10 and 40 mg/kg ip, respectively. The rest of the compounds prepared were weakly active or inactive in these assays. The pattern of activity observed for this series parallels that observed for the acyclic series of $\omega$-phosphono-$\alpha$-amino acids, where AP5 and AP7 possessed NMDA antagonist activity while AP6 and AP8 were inactive. Reduction of conformational mobility by incorporation of the piperidine ring led to enhanced potency relative to the acyclic analogues.

Excitatory amino acid transmission is emerging as an important area of investigation in the central nervous system (CNS).[1] Glutamic and aspartic acids are the putative endogenous ligands effecting excitatory neurotransmission in the mammalian CNS;[2] however, their actions are nonselective. At least three distinct excitatory amino acid receptor subtypes have been classified by selective agonists by using electrophysiological[3] and biochemical[4] techniques. The three agonists are (Figure 1) *N*-methyl-D-aspartic acid (**1**, NMDA), L-quisqualic acid (**2**), and L-kainic acid (**3**).

The NMDA receptor is probably the most heavily studied of the three receptor subtypes, owing in part to the availability of potent and selective antagonists.[5] Antagonists of excitatory amino acid neurotransmission at the NMDA receptor may prove to be useful therapeutic agents in the treatment of a variety of neurological disorders.[6] These compounds have been shown to be anticonvulsant in sound[7a-d] and chemical[7e] induced convulsions, and they protect against NMDA-induced lethality.[8] NMDA antagonists may also have useful applications in the treatment of neurodegenerative disorders such as Alzheimer's disease[9] and in the prevention of neuronal damage that occurs during cerebral ischemia.[10]

Structural features common to all known selective NMDA receptor antagonists are as follows: two acidic functional groups, with separation of these groups by four or six atoms giving the best antagonist activity; an amino group adjacent to one of the acidic functions, preferably as an $\alpha$-amino acid; and, the nitrogen of the amino group can be unsubstituted or carry a small alkyl group. Watkins developed a series of acyclic $\omega$-phosphono-$\alpha$-amino acids (**4**, Figure 2) that are very potent and selective NMDA antagonists.[5a] Of this series, the five and seven carbon compounds, AP5 (**4**, $n$ = 1) and AP7 (**4**, $n$ = 3), respectively, are the most potent. More recently, Watkins reported[11a] the cyclic piperazine analogue of AP7, 4-(3-phosphonoprop-1-yl)piperazine-2-carboxylic acid (**5**, CPP, Figure 2). This compound is 4–10 times more potent than AP5 and AP7 in a variety of assays[11] and is equally selective for the NMDA receptor.

We felt that a series of phosphonoalkyl-substituted piperidine and pyridine derivatives, e.g., **6** and **7** (Figure 3), would have the potential of serving as more potent

(1) (a) Davies, J.; Evans, R. H.; Jones, A. W.; Mewett, K. N.; Smith, D. A. S.; Watkins, J. C. *Excitotoxins*; Plenum Press: New York, 1983; pp 43–54. (b) Watkins, J. C.; Evans, R. H. *Annu. Rev. Pharmacol. Toxicol.* **1981**, *21*, 165.

(2) (a) Fagg, G. E.; Foster, A. C. *Neuroscience* **1983**, *9*, 701. (b) Fonnum, F.; *J. Neurochem.* **1984**, *42*, 1. (c) Ottersen, O. P.; Storm-Mathisen, J. *Handbook of Chemical Neuroanatomy*; Elsevier, New York, 1984; Vol. 3, pp 141–246.

(3) (a) Evans, R. H.; Watkins, J. C. *Life Sci.* **1981**, *28*, 1303. (b) Davies, J.; Evans, R. H.; Jones, A. W.; Smith, D. A. S.; Watkins, J. C. *Comp. Biochem. Physiol.* **1982**, *72C*, 211.

(4) (a) Monoghan, D. T.; Holets, V. R.; Toy, D. W.; Cotman, C. W. *Nature (London)* **1983**, *306*, 176. (b) Monoghan, D. T.; Yao, D.; Cotman, C. W. *Brain Res.* **1984**, *340*, 378. (c) Greenamyre, J. T.; Olson, J. M. M.; Penny, J. B., Jr.; Young, A. B. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 254. (d) Foster, A. C.; Fagg, G. E. *Eur. J. Pharmacol.* **1987**, *133*, 291.

(5) (a) For a recent review of NMDA receptor function, see: *Trends Neurosci.* **1987**, *10*, 263–302. (b) Watkins, J. C.; Olverman, H. J. *Ibid.* **1987**, *10*, 265. (c) Evans, R. H.; Francis, A. A.; Jones, A. W.; Smith, D. A. S.; Watkins, J. C. *Br. J. Pharmacol.* **1982**, *75*, 65.

(6) (a) Turnbull, J. *Can. J. Neurol. Sci.* **1987**, *14*, 122. (b) Meldrum, B. *Clinical Sci.* **1985**, *68*, 113.

(7) (a) Chapman, A. G.; Meldrum, B. S.; Nanji, N.; Watkins, J. C. *Eur. J. Pharmacol.* **1987**, *139*, 91. (b) Croucher, M. J.; Collins, J. F.; Meldrum, B. S. *Science* **1982**, *216*, 899. (c) Meldrum, B. S.; Croucher, M. J.; Czuczwar, S. J.; Collins, J. F.; Curry, K.; Joseph, M.; Stone, T. W. *Neuroscience* **1983**, *9*, 925. (d) Jones, A. W.; Croucher, M. J.; Meldrum, B. S.; Watkins, J. C. *Neurosci. Lett.* **1984**, *45*, 157. (e) Czuczwar, S. J.; Meldrum, B. S. *Eur. J. Pharmacol.* **1982**, *83*, 335.

(8) Leander, J. D.; Lawson, R. R.; Ornstein, P. L.; Zimmerman, D. M. *Brain Res.* **1988**, *448*, 115.

(9) Maragos, W. F.; Greenamyre, J. T.; Penny, J. B., Jr.; Young, A. B. *Trends Neurosci.* **1987**, *10*, 65.

(10) Gill, R.; Foster, A. C.; Woodruff, G. N. *J. Neurosci.* **1987**, *7*, 3343. (b) Rothman, S. M.; Olney, J. W. *Ann. Neurol.* **1986**, *19*, 105.

(11) (a) Davies, J.; Evans, R. H.; Herrling, P. L.; Jones, A. W.; Olverman, H. J.; Pook, P.; Watkins, J. C. *Brain Res.* **1986**, *382*, 169. (b) Lehman, J.; Schneider, J.; McPherson, S.; Murphy, D. E.; Bernard, P.; Tsai, C.; Bennett, D. A.; Pastor, G.; Steel, D. J.; Boehm, C.; Cheney, D. L.; Liebman, J. M.; Williams, M.; Wood, P. L. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 737.

0022-2623/89/1832-0827$01.50/0 

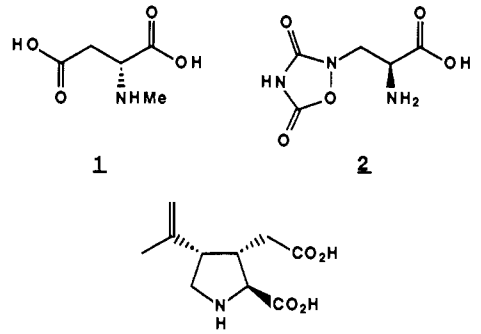


**Figure 1.** Selective receptor agonists.

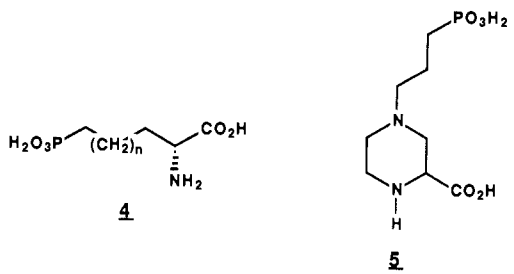


**Figure 2.** Selective NMDA antagonists.

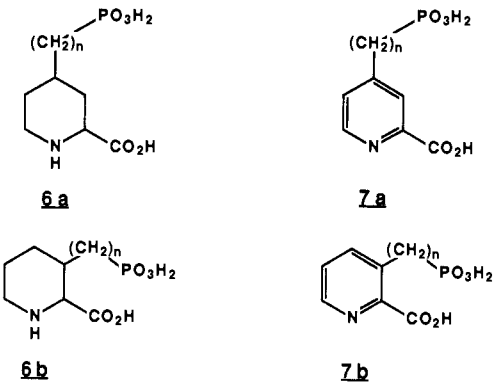


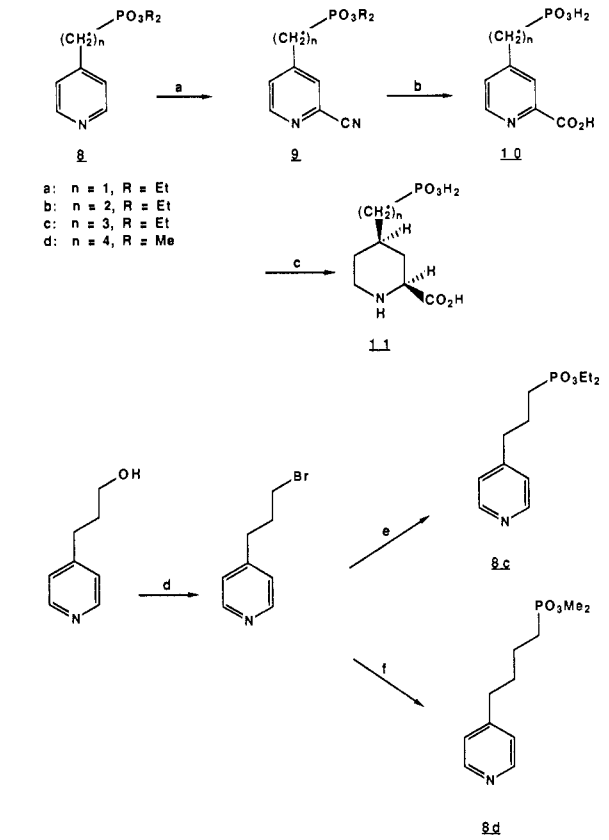
**Figure 3.** Piperidine and pyridine amino acids.

antagonists of NMDA-mediated neurotransmission, owing to the enhanced conformational rigidity provided by the introduction of the carbocyclic ring. Where therefore wish to report our efforts at development of novel 3- and 4-phosphonoalkyl-substituted piperidine- and pyridine-2-carboxylic acids and their evaluation as NMDA antagonists.[12]

## Chemistry

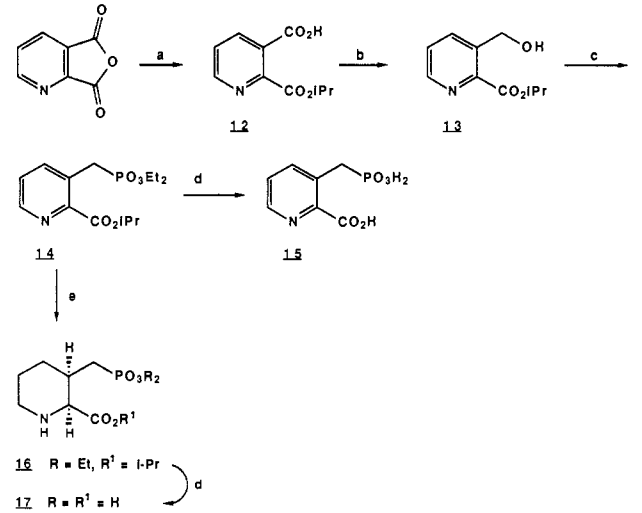
4-(Phosphonoalkyl)piperidine- and -pyridine-2-carboxylic acids were prepared by the route shown in Scheme I. Oxidation of 8 with *m*-CPBA in acetone afforded the corresponding *N*-oxide, which was then treated with trimethylsilyl cyanide and *N,N*-dimethylcarbamoyl chloride in dichloromethane[13] to give the 2-cyanopyridine 9. Hydrolysis of 9 with 6 N HCl afforded the desired pyridine diacids 10, and catalytic hydrogenation of 10 then gave the corresponding piperidines 11. The stereoselectivity of the reduction is very high, and only the 2,4-cis-substituted piperidines 11 were obtained (vide infra). The

**Scheme I**[a]



[a] a. i. *m*-CPBA, acetone, room temperature. ii. TMSCN, $Me_2NCOCl$, $CH_2Cl_2$. b. 6 N HCl, reflux. c. $H_2$, $PtO_2$, $H_2O$, 60 °C, 60 psi. d. $Ph_3PBr_2$, $CH_2Cl_2$, $C_5H_5N$, 0 °C. e. $(EtO)_2POH$, NaH, THF, room temperature to reflux. f. $(MeO)_2PMe$, *n*-BuLi, THF, −78 °C to room temperature.

**Scheme II**[a]



[a] a. *i*-PrOH, reflux. b. i. $SOCl_2$, reflux. ii. $NaBH_4$, THF, 0 °C. c. i. $Ph_3PBr_2$, $CH_2Cl_2$, room temperature. ii. $P(OEt)_3$, toluene, reflux. d. 6 N HCl, reflux. e. $H_2$, $PtO_2$, 60 °C, 60 psi.

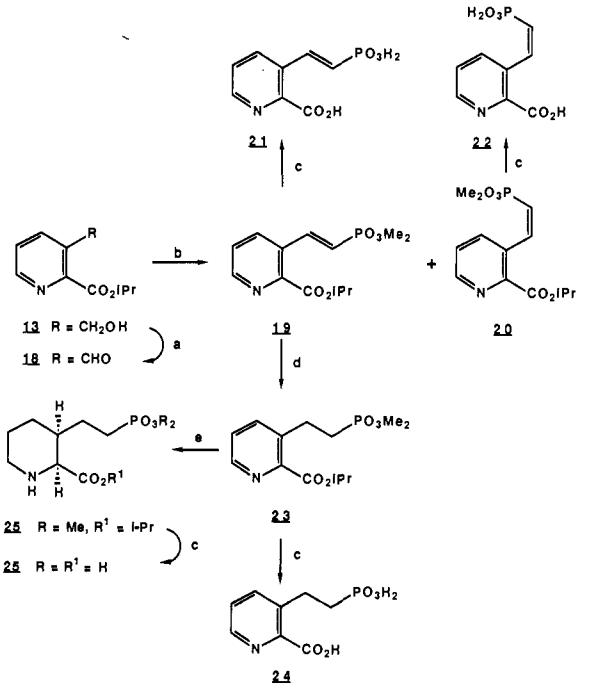
phosphonates **8c** and **8d** were prepared by treatment of 4-(3-bromoprop-1-yl)pyridine (in turn prepared by bromination of the corresponding alcohol with triphenylphosphine dibromide) with sodium diethyl phosphite and dimethyl lithiomethylphosphonate, respectively, in tetrahydrofuran (Scheme I).

Synthesis of the 3-substituted-pyridine and -piperidine-2-carboxylic acids proceeded from quinolinic acid (Scheme II). Ring opening of quinolinic anhydride with

(12) During the course of this work, a patent application appeared on these compounds from Ciba-Geigy AG: Hutchinson, A. J.; Shaw, K. R.; Schneider, J. A. E.P. 0203891A2.

(13) Fife, W. *J. Org. Chem.* **1983**, *48*, 1375.

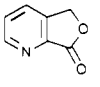
**Scheme III**[a]



[a] a. PCC, $CH_2Cl_2$, room temperature. b. R = CHO: $(Me_2O_3P)_2CH_2$, THF, NaH. c. 6 N HCl, reflux. d. $H_2$, 5% Pd/C. e. $H_2$, $PtO_2$.

2-propanol provided a single monoester which was assumed to be quinolinic acid 2-monoisopropyl ester on the basis of literature precedent that the carbonyl at C-2 of quinolinic anhydride is known to be the more electrophilic one.[14] The regiochemistry of this ring opening was proven at a later stage in this work by an X-ray crystal structure of one of the products (vide infra). Chemoselective reduction of the carboxylic acid group of **12** was achieved by conversion to the acyl chloride[15] and subsequent reduction with sodium borohydride.[16] The resulting alcohol **13** was converted to the primary bromide with triphenylphosphine dibromide. Michaelis–Arbuzov reaction of the bromide with triethyl phosphite provided the phosphonate **14**. Acidic hydrolysis of **14** yielded amino acid **15**. Hydrogenation of **14** over platinum oxide gave the cis piperidine derivative **16**, which upon hydrolysis in 6 N HCl solution provided amino acid **17**.

The homologous compounds were prepared as follows. Oxidation of **13** with pyridinium chlorochromate gave aldehyde **18** (Scheme III). Wittig reaction of this aldehyde with the sodium salt of tetramethyl methylenediphosphonate provided the corresponding vinyl phosphonates **19** and **20** as a mixture of olefin isomers (*E*:*Z* = 9:1). The stereochemistry of **19** and **20** was assigned by proton NMR analysis of the coupling constants of the olefinic protons. For **19**, the coupling constant for the olefinic protons was 17 Hz, while for **20** the olefinic coupling



i

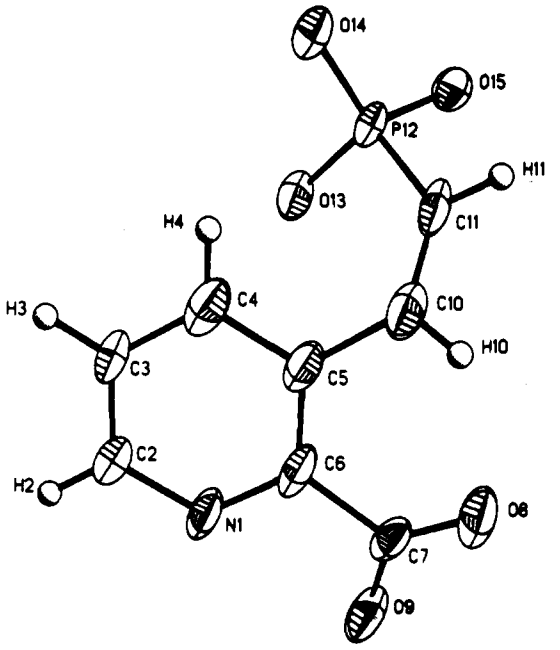
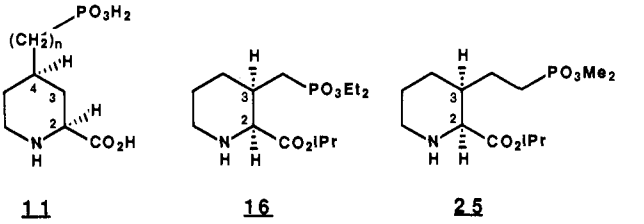



**Figure 4.** ORTEP plot of amino acid **22**.



**11** **16** **25**

**Figure 5.** Stereochemistry of piperidine acids.

constant was 14 Hz, indicating *E* and *Z* stereochemistry, respectively. Hydrolysis of the esters **19** and **20** yielded the corresponding amino acids **21** and **22**, respectively. A crystal of amino acid **22** suitable for X-ray diffraction studies was grown from water/acetone. Compound **22** crystallized in the space group $P2_1/c$, with four molecules in a unit cell having the dimensions $a$ = 7.766 (1) Å, $b$ = 8.921 (1) Å, $c$ = 13.654 (2) Å, $B$ = 103.787 (1)° and a calculated density of 1.658 g cm$^{-3}$. A total of 1297 unique reflections with $2\theta$ less than 116.0° were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved by using the direct methods routine SOLV of the SHELXTL program library[18] and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms, except those of the carboxyl and phosphonate groups, were included with isotropic temperature factors at calculated positions. The final *R* factor was 0.082 for 964 observed reflections. Figure 4 shows an ORTEP plot of the molecule and Tables I–VI in the supplementary material section give the atomic coordinates, bond lengths, bond angles, anisotropic temperature factors, and other crystallographic data. X-ray crystal structure determination of phosphonate **22** confirmed both the assignment of the olefin stereochemistry and the regiochemistry of the ring opening of quinolinic anhydride with 2-propanol. Catalytic hydrogenation of the *E* phosphonate **19** over 5% palladium on carbon in ethanol gave the phosphonoethyl compound **23**. Hydrolysis with 6 N HCl solution yielded the amino acid **24**. Catalytic hy-

(14) (a) Kirpal, A. *Monatshefte* **1900**, *21*, 957. (b) Blicke, F. F.; Jenner, E. L. *J. Am. Chem. Soc.* **1942**, *64*, 1721. (c) Fibel, L. R.; Spoerri, P. E. *Ibid.* **1948**, *70*, 3908.

(15) Miescher, K.; Kagi, H. *Helv. Chim. Acta* **1941**, *24*, 1471.

(16) Analogous reduction of the methyl ester of **12** gave good yields of lactone i,[17] presumably resulting from cyclization of the corresponding alcohol. This was overcome by the use of the more hindered isopropyl ester.

(17) Zincke, T. *Justus Liebigs Ann. Chem.* **1896**, *290*, 353.

(18) Sheldrick, G. M. SHELXTL, Revision 4, Nicolet Analytical Instruments, August, 1983.

drogenation of **23** over platinum oxide afforded the ester **25** and hydrolysis then gave the desired amino acid **26**.

**Assignment of Stereochemistry of the Piperidine Amino Acids.** The stereochemistry of the 2,4-disubstituted compounds **11** was determined by $^1$H NMR decoupling at 500 MHz or $^{13}$C NMR spectroscopy (the NMR data are summarized in the Experimental Section). H-2 (Figure 5) shows a large coupling (~12 Hz) and a small coupling (~3 Hz) to the protons on the C-3 methylene. Assuming a chairlike conformation for the piperidine ring would require that H-2 has an axial orientation. The observation of the H-4 proton resonance was hindered by the overlap of several resonances; however, H-3 axial was usually partially resolved so that we could determine that it was seeing only large couplings (that is, all couplings were ~12 Hz). The large coupling to H-4 requires that it, like H-2, have an axial orientation. This allows the relationship between the groups at C-2 and C-4 to be assigned as cis, if we assume that the piperidine ring adopts a chairlike conformation. Overlap in the $^1$H NMR spectrum of **11d** was so severe that the measurement of appropriate coupling constants was not possible. In this case, the $^{13}$C NMR spectrum of **11d** and a compound that had been identified previously were compared with the observation that there were only small differences in the ring carbons. The conclusion was that both compounds have the same stereochemistry, e.g., cis.

The stereochemistry of the amino acids **17** and **26** was determined through measurement of the $J_{23}$ coupling constants of the corresponding esters **16** and **25**, respectively (Figure 5). The value is 3.03 Hz for **16** and 3.35 Hz for **25**, which, assuming a chairlike conformation for the piperidine ring, strongly suggests an axial/equatorial relationship between the groups at C-2 and C-3. Therefore, the stereochemistry must be cis.

## Binding Studies

A number of ligands have been evaluated for their potential to selectively label the NMDA receptor, including [$^3$H]-L-glutamate[19a] and [$^3$H]-D-AP5.[19b] Problems with the stability and selectivity of these ligands have precluded their general use in binding studies. However, the selective antagonist CPP (**5**, Figure 3) has been radiolabeled and Murphy[20a] and Wong[20b] have reported on the use of this ligand as a stable and selective means for evaluating the affinity of compounds for the NMDA receptor.

All of the amino acids that we prepared were evaluated in the [$^3$H]CPP receptor binding assay, and the results are reported in Table I. The trend for the 4-phosphonoalkyl-substituted piperidine-2-carboxylic acids (**11a–d**) closely paralleled that observed for the series of acyclic amino acids AP5 to AP8,[5a,19b] where the 4-phosphonomethyl and 4-phosphonopropyl compounds **11a** and **11c**, respectively, had the highest affinity (Table I) for the NMDA receptor. The $IC_{50}$'s for compounds **11a** and **11c** were 95 and 120 nM, respectively, making these some of the highest affinity ligands for the NMDA receptor described to date. Very weak NMDA receptor affinity was observed for the AP6 analogue **11b**, with an $IC_{50}$ of 6600 nM.

Of the 3-phosphonoalkyl-substituted piperidine-2-carboxylic acids, only the AP5-like compound **26** showed any affinity for the NMDA receptor, with an $IC_{50}$ of 1000 nM. The other piperidine analogues as well as the 3- and 4-phosphonoalkyl-substituted pyridines did not significantly displace [$^3$H]CPP binding.

Table I. Receptor Affinities and Pharmacology of Amino Acids

| compd[a] | $IC_{50}$ (nM) or % displacement (concn) versus [$^3$H]CPP | MED[b] versus NMDA lethality (mg/kg, ip)[c] |
|---|---|---|
| **10a** | 4% (10 μM) | >160 |
| **11a** | 95 ± 28 | 10 |
| **10b** | 3500 ± 831 | >160 |
| **11b** | 6600 ± 1279 | >160 |
| **10c** | 34% (10 μM) | >160 |
| **11c** | 120 ± 19 | 40 |
| **10d** | 25% (10 μM) | >160 |
| **11d** | 26% (10 μM) | >160 |
| **15** | −18% (10 μM) | >160 |
| **17** | 19% (10 μM) | >160 |
| **21** | 26% (10 μM) | >160 |
| **22** | 20% (10 μM) | >160 |
| **24** | 3500 ± 728 | >160 |
| **26** | 1000 ± 226 | 160 |
| AP7 | 320 ± 66 | 160 |
| CPP | 72 ± 16 | 2.5 |

[a] All compounds are racemic. [b] MED = minimum effective dose. This is the dose at which at least three of the five animals tested survived for more than 30 min after NMDA injection. [c] Animals were given the test compound 30 min prior to a dose of 200 mg/kg of NMDA. All drugs were given intraperitoneally.

## Pharmacology

To determine the in vivo potency of the compounds prepared in this study as antagonists at the NMDA receptor, they were evaluated for their ability to protect against NMDA-induced lethality in mice. Leander[8] has recently demonstrated that this assay is very specific for NMDA antagonist activity. The only compounds that afford protection against NMDA-induced lethality are the competitive NMDA receptor antagonists, such as AP5 and AP7, and the noncompetitive NMDA receptor antagonists, such as phencyclidine and dexoxadrol. Anticonvulsant activity versus sound-induced convulsions in DBA/2 mice[7a–d] and against a number of chemical convulsants,[7e] including NMDA, has previously been used as a means of evaluating NMDA antagonist activity. However, these assays are not specific, since compounds without an excitatory amino acid mechanism of action, such as diazepam, are active against NMDA-induced convulsions.[21]

While all of the new compounds prepared were evaluated for their ability to protect against NMDA-induced lethality in mice, only those compounds which showed high affinity for the NMDA receptor (as evidenced by potent inhibition of [$^3$H]CPP binding) were active in this assay (Table I). Compounds **11a** and **11c** were the most active in protecting against lethality, showing minimum effective doses (MED, the dose at which at least three of the five mice which were tested survived) of 10 and 40 mg/kg ip, respectively. This compares to a MED of 160 mg/kg for AP7 to afford protection. The AP5 analogue **26**, which had moderate affinity for the NMDA receptor, also afforded protection in this assay, with an MED of 160 mg/kg. The other analogues were all inactive at 160 mg/kg, the highest dose tested.

## Conclusions

One problem that has plagued the acyclic amino acids AP5 and AP7 is very poor blood–brain barrier penetra-

(19) (a) Foster, A. C.; Fagg, G. E. *Eur. J. Pharmacol.* **1987**, *133*, 291. (b) Olverman, H. J.; Jones, A. W.; Watkins, J. C. *Nature* **1984**, *307*, 460.

(20) (a) Murphy, D. E.; Schneider, J.; Boehm, C.; Lehman, J.; Williams, M. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 778. (b) Wong, D. T.; Threlkeld, P. G. *Life Sci.*, in press.

(21) Czuczwar, S. J.; Frey, H.; Loscher, W. *Eur. J. Pharmacol.* **1985**, *108*, 273.

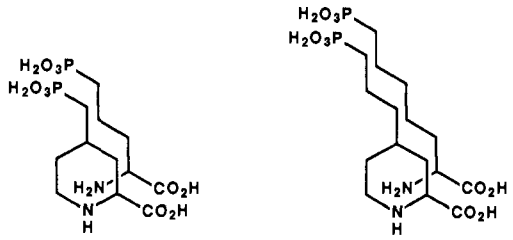



**Figure 6.** Comparison of cyclic and acyclic amino acids.

bility.[22] Therefore, we had hoped that incorporation of the piperidine ring would serve to increase the lipophilicity of these amino acids and enhance their ability to penetrate the blood–brain barrier. We also hoped that the piperidine ring would serve as a means to restrain conformational mobility, and thus provide the potential for increased potency. Our results appear to support these concepts. The cyclic compounds **11a** and **11c**, which can overlap with AP5 and AP7 (Figure 6), respectively, not only show a greater affinity for the NMDA receptor relative to their acyclic counterparts, they are also much more active in providing protection from NMDA-induced lethality in mice. One may conclude from the increase in affinity at the NMDA receptor (as evidenced by displacement of [$^3$H]CPP binding) relative to the increase in potency in vivo (see Table I) that we are observing enhanced systemic availability; however, further experiments would be necessary to verify this hypothesis.

None of the pyridine analogues that we prepared had appreciable affinity for the NMDA receptor in vitro, or any significant activity in vivo. This could be a result of either decreased basicity of the pyridine nitrogen or the lack of $sp^3$ hybridization at C-2 and/or C-4.

The analogues that we prepared allow us to begin to understand some of the structural requirements necessary for antagonist activity at the NMDA receptor. The increase in potency of the 2,4-disubstituted piperidine analogues **11a** and **11c** versus the 2,3-disubstituted piperidine analogues **17** and **26** suggests that the extended conformation available in **11** may allow for better interaction of the substituents with the receptor. Our overall results with the pyridine analogues would imply that either a more basic $\alpha$-amine or a $sp^3$-hybridized atom at C-2 and/or C-4 is required for activity.

## Experimental Section

All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium or sodium/benzophenone ketyl prior to use. All other solvents and reagents were used as obtained. $^1$H NMR spectra were obtained on a GE QE-300 spectrometer at 300.15 MHz, a Bruker AM-500 spectrometer at 500 MHz, or a JEOL FX90Q spectrometer at 90 MHz, and $^{13}$C NMR spectra were obtained on a GE QE-300 spectrometer at 75.48 MHz with tetramethylsilane as an internal standard. Coupling constants reported for $^{13}$C NMR refer to $^{13}$C–$^{31}$P couplings. Where indicated, a small amount of 40% aqueous KOD was added to aid solution of NMR samples run in $D_2O$.

**[$^3$H]CPP Binding.** The methodology used for the [$^3$H]CPP binding assay has been published.[20b]

**NMDA-Induced Lethality in Mice.** The methodology used for the NMDA-induced lethality assay has been published.[8]

**Preparation of 2-Cyano-4-[3-(diethylphosphono)prop-1-yl]pyridine (9c) (Includes General Procedure for 2-Cyanation of Pyridines).** To a 0 °C solution of triphenylphosphine (82.6 g, 0.31 mol) in 400 mL of $CH_2Cl_2$ was added bromine (50.3 g, 0.31 mol, 16.1 mL) via dispo-pipet over 5 min. Triphenylphosphine was added (<0.5 g) until the yellow color disappeared, and then a solution of 3-(4-pyridyl)-1-propanol (28.8 g, 0.21 mol) in 50 mL of $CH_2Cl_2$ was added dropwise for 30 min. After 15 min more at 0 °C and 1 h at room temperature, 800 mL of ether was added and the mixture extracted twice with 150 mL each of water and twice with 100 mL each of 1 N HCl (aqueous). The combined aqueous washes were extracted once with 200 mL of ether and then made basic (pH >13) with 5 N NaOH (aqueous). The now basic aqueous layer was extracted five times with 150 mL each of ether, and then the combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 4-(3-bromopropyl)pyridine as an oil.

To a room temperature suspension of NaH (16.8 g of a 60% suspension in oil, 0.42 mol, washed thrice with hexane to remove the oil) in 400 mL of THF was added diethyl phosphite (58.0 g, 0.42 mol, 54 mL) dropwise via addition funnel at a rate to maintain vigorous hydrogen evolution (about 1.5 h), and then the mixture was stirred 2 h more at room temperature. The above bromide in 100 mL of THF was added in one portion (2 × 25 mL rinses with THF). The solution was stirred overnight at room temperature and then quenched with 500 mL of 2 N NaOH (aqueous). The organic layer was separated and the aqueous layer extracted twice with 400 mL each of ether, and then the combined organics were washed with 500 mL of 2 N NaOH (aqueous) and 300 mL of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 45.4 g (84% crude yield) of diethyl 3-(4-pyridyl)propylphosphonate (**8c**) as an orange oil.

To a room temperature solution (flask immersed in an ambient temperature water bath) of the above phosphonopyridine in 250 mL of acetone was added *m*-CPBA (45.7 g of material 80% by weight active peracid, 0.21 mol) in 150 mL of acetone dropwise over 0.5 h. After stirring 4 h more at room temperature, the mixture was concentrated in vacuo. The resultant oily residue was partitioned between 500 mL each of water and ether, the aqueous layer separated, and the ether layer washed once with 100 mL of water. The combined aqueous washes were extracted once with 300 mL of ether, and then the aqueous layer was concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$, dried ($Na_2SO_4$), filtered, and concentrated in vacuo to afford the corresponding pyridine *N*-oxide. This material was dissolved in 400 mL of $CH_2Cl_2$ and then treated at room temperature with trimethylsilyl cyanide (20.8 g, 0.21 mol, 28 mL). After 5 min, *N*,*N*-dimethylcarbamoyl chloride (22.2 g, 0.21 mol, 19 mL) was added in three portions over 30 min (8 mL; after 15 min, 6 mL; then after another 15 min, 5 mL; after the second addition, $CO_2$ evolution was evident. The reaction was mildly exothermic). After the mixture was stirred overnight at room temperature, the reaction was *carefully quenched* with 200 mL of 10% $K_2CO_3$ (aqueous) and stirred 15 min at room temperature. The organic layer was separated and the aqueous layer extracted twice with 200 mL each of $CH_2Cl_2$, and then the combined organics were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residue was purified by Prep 500 HPLC to afford 39.6 g (67%, four steps) of **9c** as a clear, slightly yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 8.62 (d, $J$ = 6.0 Hz, 1 H), 7.59 (s, 1 H), 7.40 (d, $J$ = 6.0 Hz, 1 H), 4.12 (m, 4 H), 2.83 (t, $J$ = 7.5 Hz, 2 H), 2.00 (m, 2 H), 1.77 (m, 2 H), 1.35 (t, $J$ = 7 Hz, 6 H).

**2-Cyano-4-[(diethylphosphono)methyl]pyridine (9a)**: 76% yield; $^1$H NMR ($CDCl_3$) $\delta$ 8.62 (d, $J$ = 4.4 Hz, 1 H), 7.63 (s, 1 H), 7.45 (m, 1 H), 4.06 (quintet, $J$ = 7.1 Hz, 4 H), 3.16 (d, $J$ = 22.9 Hz, 2 H), 1.26 (t, $J$ = 7.1 Hz, 6 H).

**2-Cyano-4-[2-(diethylphosphono)eth-1-yl]pyridine (9b)**: 71% yield; $^1$H NMR ($CDCl_3$) $\delta$ 8.64 (d, $J$ = 4.8 Hz, 1 H), 7.60 (s, 1 H), 7.41 (d, $J$ = 4.8 Hz, 1 H), 4.11 (quintet, $J$ = 7.5 Hz, 4 H), 3.00 (m, 2 H), 2.09 (m, 2 H), 1.33 (t, $J$ = 7.5 Hz, 6 H).

**2-Cyano-4-[4-(dimethylphosphono)but-1-yl]pyridine (9d)**: 54% yield; $^1$H NMR ($CDCl_3$) $\delta$ 8.61 (d, $J$ = 4.8 Hz, 1 H), 7.53 (s, 1 H), 7.35 (d, $J$ = 4.8 Hz, 1 H), 3.76 (d, $J$ = 10.0 Hz, 6 H), 2.72 (t, $J$ = 7.5 Hz, 2 H), 1.77 (m, 6 H).

**General Procedure for the Hydrolysis of 9 to 10.** The 4-(phosphonoalkyl)-2-cyanopyridine (**9a–d**) was dissolved in 6 N aqueous hydrochloric acid and heated to reflux overnight. The mixture was cooled and concentrated in vacuo. The residue was

(22) For a study of AP5 and AP7 administered icv and ip, see: Meldrum, B. S.; Croucher, M. J.; Czuczwar, S. J.; Collins, J. F.; Curry, K.; Joseph, M.; Stone, T. W. *Neuroscience* **1983**, *9*, 925.

Table II. Analytical Data for Novel Compounds

| compd | formula | anal. | mp, °C | solvent[a] |
|---|---|---|---|---|
| 9a | $C_{11}H_{15}N_2O_3P$ | C, H, N | | |
| 10a | $C_7H_8NO_5P \cdot 0.65H_2O$ | C, H, N | 260–263.5 | water |
| 11a | $C_7H_{14}NO_5P$ | C, H, N | 287–288 | |
| 9b | $C_{12}H_{17}N_2O_3P$ | C, H, N | | |
| 10b | $C_8H_{10}NO_5P \cdot 0.3H_2O$ | C, H, N | 250–252 | water |
| 11b | $C_8H_{16}NO_5P \cdot 0.4H_2O$ | C, H, N | >270 | |
| 9c | $C_{13}H_{19}N_2O_3P \cdot 0.2CH_2Cl_2$ | C, H, N | | |
| 10c | $C_9H_{12}NO_5P \cdot 1.3H_2O$ | C, H, N | 134–137 | water |
| 11c | $C_9H_{18}NO_5P$ | C, H, N | 257–260 | |
| 8d | $C_{11}H_{18}NO_3P$ | C, H, N | | |
| 9d | $C_{12}H_{17}N_2O_3P$ | C, H, N | | |
| 10d | $C_{10}H_{14}NO_5P$ | C, H, N | 178–180 | water |
| 11d | $C_{10}H_{20}NO_5P \cdot 0.5H_2O$ | C, H, N | 265–267 | |
| 12 | $C_{10}H_{11}NO_4$ | C, H, N | 149–153 | EtOAc |
| 13 | $C_{10}H_{13}NO_3$ | C, H, N | 67–70 | EtOAc/hexanes |
| 15 | $C_7H_8NO_5P \cdot 0.7H_2O$ | C, H, N | 238 | water/acetone |
| 17 | $C_7H_{14}NO_5P \cdot 0.7H_2O$ | C, H, N | >230 | water/acetone |
| 18 | $C_{10}H_{11}NO_3$ | C, H, N | | |
| 21 | $C_8H_8NO_5P$ | C, H, N | 244 | water |
| 22 | $C_8H_8NO_5P \cdot 0.4H_2O$ | C, H, N | 240 | water/acetone |
| 24 | $C_8H_{10}NO_5P$ | C, H, N | 235 | methanol[b] |
| 26 | $C_8H_{16}NO_5P \cdot HCl \cdot H_2O$ | C, H, N | 195 | 10% aq HCl/acetone |

[a] Solvent for recrystallization. [b] Isolation by trituration.

dissolved in water and treated with 3 equiv of propylene oxide for 1.5 h at 50 °C (pH change from <1 to ~2–3) and then concentrated in vacuo. Acetone or ethanol was added, and the resulting solid was filtered and washed with ethanol, acetone, and ether. The resulting solid was recrystallized (see Table II) and filtered as above to afford the desired amino acid **10a–d** after drying in vacuo at 60–80 °C.

**4-(Phosphonomethyl)pyridine-2-carboxylic acid (10a)**: 76% yield; $^1$H NMR ($D_2O$/KOD) δ 8.29 (d, $J$ = 5.0 Hz, 1 H), 7.67 (s, 1 H), 7.32 (m, 1 H), 2.84 (d, $J$ = 21.0 Hz, 2 H).

**4-(2-Phosphonoeth-1-yl)pyridine-2-carboxylic acid (10b)**: 85% yield $^1$H NMR ($D_2O$/KOD) δ 8.81 (d, $J$ = 6.0 Hz, 1 H), 8.56 (s, 1 H), 8.22 (d, $J$ = 6.0 Hz, 1 H), 3.35 (m, 2 H), 2.32 (m, 2 H).

**4-(3-Phosphonoprop-1-yl)pyridine-2-carboxylic acid (10c)**: 53% yield; $^1$H NMR ($D_2O$) δ 8.32 (d, $J$ = 6.0 Hz, 1 H), 7.69 (s, 1 H), 7.30 (d, $J$ = 6.0 Hz, 1 H), 2.65 (t, $J$ = 7.5 Hz, 2 H), 1.76 (m, 2 H), 1.31 (m, 2 H).

**4-(4-Phosphonobut-1-yl)pyridine-2-carboxylic acid (10d)**: 44% yield; $^1$H NMR ($D_2O$/KOD) δ 8.30 (d, $J$ = 4.8 Hz, 1 H), 7.66 (s, 1 H), 7.25 (d, $J$ = 4.8 Hz, 1 H), 2.59 (t, $J$ = 7.5 Hz, 2 H), 1.2–1.6 (m, 6 H).

**General Procedure for the Hydrogenation of 10 to 11.** The 4-(phosphonoalkyl)pyridine-2-carboxylic acid (**10a–d**) was hydrogenated with 10–20% by weight of $PtO_2$ in water at 40 °C and 60 psi overnight. The mixture was filtered through Celite and concentrated in vacuo to afford a solid. Acetone was added, and the precipitate was filtered and washed with acetone and ether and then dried in vacuo at 60–80 °C.

***cis*-4-(Phosphonomethyl)piperidine-2-carboxylic acid (11a)**: 82% yield; $^1$H NMR ($D_2O$) δ 3.83 (d, $J$ = 12.0 Hz, 1 H), 3.46 (d, $J$ = 12.0 Hz, 1 H), 3.02 (t, $J$ = 12.0 Hz, 1 H), 2.46 (d, $J$ = 15.0 Hz, 1 H), 2.08 (m, 2 H), 1.69 (m, 2 H), 1.42 (m, 2 H); $^{13}$C NMR ($D_2O$/KOD) δ 182.3, 61.8, 45.5, 39.2 (d, $J$ = 11.3 Hz), 37.9 (d, $J$ = 129.8 Hz), 34.3 (d, $J$ = 7.6 Hz).

***cis*-4-(2-Phosphonoeth-1-yl)piperidine-2-carboxylic acid (11b)**: 81% yield; $^1$H NMR ($D_2O$/KOD) δ 3.05 (m, 2 H), 2.50 (m, 1 H), 1.99 (m, 1 H), 1.80 (m, 1 H), 1.42 (m, 5 H), 0.94 (m, 2 H); $^{13}$C NMR ($D_2O$/KOD) δ 182.6, 61.8, 45.5, 38.1 (d, $J$ = 16.6 Hz), 37.1, 32.4, 27.1 (d, $J$ = 129.8 Hz).

***cis*-4-(3-Phosphonoprop-1-yl)piperidine-2-carboxylic acid (11c)**: 90% yield; $^1$H NMR ($D_2O$) δ 3.79 (m, 1 H), 3.50 (m, 1 H), 3.03 (m, 1 H), 2.34 (m, 1 H), 1.97 (m, 1 H), 1.10–1.86 (m, 9 H); $^{13}$C NMR ($D_2O$) δ 173.8, 58.9 (d, $J$ = 2.3 Hz), 44.4, 36.9 (d, $J$ = 15.9 Hz), 34.0, 33.0, 28.3, 27.8 (d, $J$ = 128.3 Hz), 20.3 (d, $J$ = 3.0 Hz).

***cis*-4-(4-Phosphonobut-1-yl)piperidine-2-carboxylic acid (11c)**: 87% yield; $^1$H NMR ($D_2O$/KOD) δ 2.97 (m, 2 H), 2.46 (m, 1 H), 1.94 (m, 1 H), 1.61 (m, 1 H), 1.14–1.50 (m, 9 H), 0.89 (m, 2 H); $^{13}$C NMR ($D_2O$/KOD) δ 182.6, 61.9, 45.6, 37.4, 37.1, 36.5, 32.8, 30.4 (d, $J$ = 139.6 Hz), 28.6 (d, $J$ = 17.4 Hz), 25.2.

**Preparation of 4-[4-(Dimethylphosphono)but-1-yl]pyridine.** To a −78 °C solution of dimethyl methylphosphonate (11.75 g, 94.7 mmol) in 150 mL of THF was added *n*-butyllithium (76 mL of a 1.15 M solution in hexane, 84.4 mmol), and the mixture was allowed to stir for 1.5 h at −78 °C. To this solution was added 4-(3-bromoprop-1-yl)pyridine (prepared as described above, 11.6 g, 60.0 mmol) in 50 mL of THF (2X 10 mL THF rinses). The mixture was stirred 1 h at −78 °C and then warmed to room temperature and stirred overnight. The reaction was quenched with 150 mL of water, the organic layer separated, and the aqueous layer extracted with 3 × 50 mL each of dichloromethane and 2 × 50 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. Prep 500 HPLC afforded 6.4 g (45%) of **8d**: $^1$H NMR ($CDCl_3$) δ 8.69 (d, $J$ = 6.0 Hz, 2 H), 7.10 (d, $J$ = 6.0 Hz, 2 H), 3.73 (d, $J$ = 11.0 Hz, 6 H), 2.63 (t, $J$ = 7.5 Hz, 2 H), 1.74 (m, 6 H).

**2,3-Pyridinedicarboxylic Acid 2-(Isopropyl ester) (12).** A suspension of quinolinic anhydride[23] (48.1 g, 0.32 mol) in 250 mL of 2-propanol was warmed to reflux until the reaction became homogeneous. The solution was stirred at 80 °C overnight, cooled to room temperature, and concentrated in vacuo. The resulting yellow solid was recrystallized from ethyl acetate to give the desired monoester **12** as a tan solid (43.8 g, 65%): mp 149–153 °C; $^1$H NMR (DMSO-$d_6$) δ 8.66 (dd, $J$ = 2, 5 Hz, 1 H), 8.18 (dd, $J$ = 2, 8 Hz, 1 H), 7.57 (dd, $J$ = 5, 8 Hz, 1 H), 5.14 (septet, $J$ = 6 Hz, 1 H), 1.31 (d, $J$ = 6 Hz, 6 H).

**Isopropyl 3-(Hydroxymethyl)pyridine-2-carboxylate (13).** A suspension of the monoester **12** (158.2 g, 0.76 mol) in 800 mL of thionyl chloride was heated to reflux until the reaction was homogeneous and then concentrated in vacuo. Residual thionyl chloride was removed by dissolving the residue in THF and concentrating the resulting solution. This process was repeated twice. The resulting acid chloride was dissolved in 800 mL of THF and cooled to 0 °C. Sodium borohydride (28.6 g, 0.76 mol) in 200 mL of THF was added and the resulting solution stirred at 0 °C for 1 h. The reaction was carefully poured onto ice (foaming) and extracted with $CH_2Cl_2$. The extract was dried ($Na_2SO_4$) and concentrated in vacuo to give the crude alcohol as a yellow oil. Purification by flash chromatography (3% methanol in $CH_2Cl_2$) gave the desired crude alcohol **13** (105.6 g, 71%), which was used directly in subsequent reactions: $^1$H NMR ($CDCl_3$) δ 8.57 (dd, $J$ = 2, 5 Hz, 1 H), 7.82 (dd, $J$ = 2, 8 Hz, 1 H), 7.37 (dd, $J$ = 5, 8 Hz, 1 H), 5.28 (septet, $J$ = 7 Hz, 1 H), 4.77 (m, 2 H), 1.43 (d, $J$ = 7 Hz, 6 H).

**Isopropyl 3-[(Diethylphosphono)methyl]pyridine-2-carboxylate (14).** Bromine (9.8 g, 62 mmol) was added to a solution of triphenylphosphine (16.1 g, 62 mmol) in 200 mL of $CH_2Cl_2$ at 0 °C. Triphenylphosphine (~50 mg) was added to the resulting orange solution and the solution became colorless. The solution was warmed to room temperature and alcohol **13** (10.0 g, 51 mmol) in 100 mL of $CH_2Cl_2$ was added. After the mixture was stirred at room temperature for 30 min, the reaction was washed with water (3 × 100 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuo to give a mixture of the corresponding crude bromide and triphenylphosphine oxide as a light yellow solid. Purification by flash chromatography (2% methanol in $CH_2Cl_2$) gave the corresponding bromide (10.1 g, 77%): $^1$H NMR ($CDCl_3$) δ 8.53 (dd, $J$ = 2, 5 Hz, 1 H), 7.74 (dd, $J$ = 2, 8 Hz, 1 H), 7.32 (dd, $J$ = 5, 8 Hz, 1 H), 5.30 (septet, $J$ = 7 Hz, 1 H), 4.80 (s, 2 H), 1.43 (d, $J$ = 6.5 Hz, 6 H).

A solution of the above bromide (10.1 g, 39 mmol) and triethyl phosphite (16.3 g, 100 mmol) in 250 mL of toluene was heated to reflux overnight. The reaction was poured into water and extracted with $CH_2Cl_2$. The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated in vacuo to give the crude phosphonate **14** (12.1 g). Purification by flash chromatography (3% methanol in $CH_2Cl_2$) gave the desired phosphonate **14** as an oil (10.16 g, 82%): $^1$H NMR ($CDCl_3$) δ 8.57–8.42 (m, 1 H), 7.71 (td, $J$ = 2, 8 Hz, 1 H), 7.29 (dd, $J$ = 5, 8 Hz, 1 H), 5.26 (septet,

(23) We found that commercial samples of quinolinic anhydride were contaminated by ca. 30% quinolinic acid, which made isolation of **12** troublesome. We used quinolinic anhydride prepared by essentially the method of Blicke and Jenner.[14b]

$J$ = 7 Hz, 1 H), 3.99 (quintet, $J$ = 7 Hz, 4 H), 3.68 (d, $J$ = 29 Hz, 2 H), 1.43 (d, $J$ = 7 Hz, 6 H), 1.23 (t, $J$ = 7 Hz, 6 H).

**Isopropyl *cis*-3-[(Diethylphosphono)methyl]piperidine-2-carboxylate (16).** A solution of phosphonate **14** (3.6 g, 11.4 mmol) in 95 mL of ethanol was hydrogenated at 40–50 °C and 60 psi overnight with 700 mg of platinum oxide as catalyst. The reaction was filtered and concentrated in vacuo to give the crude phosphonate. Purification by flash chromatography (3% methanol in $CH_2Cl_2$) gave isopropyl *cis*-3-[(diethylphosphono)-methyl]piperidine-2-carboxylate (**16**) as an oil (2.5 g, 68%): $^1$H NMR ($CDCl_3$) $\delta$ 5.07 (septet, $J$ = 7 Hz, 1 H), 4.15–4.03 (m, 4 H), 3.49 (t, $J$ = 3.02 Hz, 1 H), 3.09–3.02 (m, 1 H), 2.70–2.63 (m, 1 H), 2.56–2.46 (m, 1 H), 2.20–2.08 (m, 3 H), 1.71–1.56 (m, 3 H), 1.50–1.42 (m, 1 H), 1.31 (dt, $J$ = 1.5, 7 Hz, 6 H), 1.27 (d, $J$ = 7 Hz, 6 H).

**2-Carboisopropoxypyridine-3-carboxaldehyde (18).** A solution of alcohol **13** (26.8 g, 0.14 mol) in 100 mL of $CH_2Cl_2$ was added to a mixture of pyridinium chlorochromate (50.4 g, 0.23 mol), sodium acetate (19.2 g, 0.23 mol), and 4-Å molecular sieves in 260 mL of $CH_2Cl_2$. The resulting dark mixture was stirred vigorously for 48 h at room temperature. The reaction was diluted with 400 mL of ether, poured onto a silica gel column, and eluted with ether. Fractions containing the desired aldehyde were combined and concentrated in vacuo to give a yellow oil. This oil was taken up in $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and concentrated in vacuo to give **18** as an oil (11.4 g, 43%): $^1$H NMR ($CDCl_3$) $\delta$ 10.44 (s, 1 H), 8.77 (dd, $J$ = 2, 5 Hz, 1 H), 8.13 (dd, $J$ = 2, 8 Hz, 1 H), 7.51 (dd, $J$ = 5, 8 Hz, 1 H), 5.34 (septet, $J$ = 7 Hz, 1 H), 1.46 (d, $J$ = 7 Hz, 6 H).

**Isopropyl (*E*)- and (*Z*)-3-[2-(Dimethylphosphono)ethen-1-yl]pyridine-2-carboxylates (19 and 20).** Sodium hydride (60% in mineral oil, 1.66 g, 41 mmol) was washed with hexanes to remove the mineral oil and then suspended in 50 mL of THF. A solution of tetramethyl methylenediphosphonate (9.6 g, 41 mmol) in 20 mL of THF was added at room temperature, forming a clear solution. A solution of aldehyde **18** (4.0 g, 21 mmol) in 20 mL of THF was added and the solution stirred at room temperature for 2 h. The reaction was poured into water and extracted with $CH_2Cl_2$. The organic layer was dried ($Na_2SO_4$) and concentrated in vacuo to give a crude mixture of vinylphosphonates **19** and **20** as an oil (5.7 g). Purification by flash chromatography (3% methanol in $CH_2Cl_2$) gave the pure *E* phosphonate **19** ($R_f$ = 0.26, 3.8 g, 60%), the pure *Z* phosphonate **20** ($R_f$ = 0.22, 430 mg, 7%), along with a mixture of the two isomers (300 mg, 5%). **19**: $^1$H NMR ($CDCl_3$) $\delta$ 8.61 (dd, $J$ = 2, 5 Hz, 1 H), 7.97 (dd, $J$ = 17, 22 Hz, 1 H), 7.86 (dd, $J$ = 2, 8 Hz, 1 H), 7.40 (dd, $J$ = 5, 8 Hz, 1 H), 6.12 (t, $J$ = 17 Hz, 1 H), 5.29 (septet, $J$ = 6 Hz, 1 H), 3.78 (d, $J$ = 11 Hz, 6 H), 1.44 (d, $J$ = 6 Hz, 6 H). **20**: $^1$H NMR ($CDCl_3$) $\delta$ 8.62 (bd, $J$ = 5 Hz, 1 H), 7.99 (bd, $J$ = 8 Hz, 1 H), 7.68 (dd, $J$ = 14, 50 Hz, 1 H), 7.38 (dd, $J$ = 5, 8 Hz, 1 H), 7.87 (dd, $J$ = 14, 17 Hz, 1 H), 5.14 (septet, $J$ = 7 Hz, 1 H), 3.52 (d, $J$ = 10 Hz, 6 H), 1.42 (d, $J$ = 7 Hz, 6 H).

**Isopropyl 3-[2-(Dimethylphosphono)eth-1-yl]pyridine-2-carboxylate (23).** A solution of **19** (3.8 g, 12.7 mmol) in 200 mL of ethanol was hydrogenated at room temperature and 50 psi for 3 h with 760 mg of 5% palladium on carbon as catalyst. The reaction was filtered and concentrated in vacuo to give phosphonate **23** as a colorless oil (3.5 g, 91%): $^1$H NMR ($CDCl_3$) $\delta$ 8.52 (dd, $J$ = 2, 5 Hz, 1 H), 7.61 (dd, $J$ = 2, 8 Hz, 1 H), 7.29 (dd, $J$ = 5, 8 Hz, 1 H), 5.28 (septet, $J$ = 7 Hz, 1 H), 3.74 (d, $J$ = 10 Hz, 6 H), 3.30–2.92 (m, 2 H), 2.34–1.92 (m, 2 H), 1.44 (d, $J$ = 7 Hz, 6 H).

**Isopropyl *cis*-3-[2-(Dimethylphosphono)ethyl]-piperidine-2-carboxylate (25).** A solution of **23** (5.60 g, 17 mmol) in 93 mL of ethanol was hydrogenated overnight at 60 psi and 40–50 °C with 6.72 g of platinum oxide as catalyst. The reaction was filtered and concentrated in vacuo to give the crude phosphonate as an oil (5.7 g). Purification by flash chromatography (3–5% methanol in $CH_2Cl_2$ containing 0.5% $NH_4OH$) gave isopropyl *cis*-3-[2-(dimethylphosphono)ethyl]piperidine-2-carboxylate (**25**) as an oil (4.8 g, 84%): $^1$H NMR ($CDCl_3$) $\delta$ 5.07 (septet, $J$ = 7 Hz, 1 H), 3.66 (d, $J$ = 11 Hz, 6 H), 3.50 (d, $J$ = 3.35 Hz, 1 H), 3.20–2.92 (m, 1 H), 2.79–2.44 (m, 1 H), 2.06–1.20 (m, 10 H), 1.31 (d, $J$ = 7 Hz, 6 H).

**General Procedure for the Synthesis of the Amino Acids.** The amino acids were synthesized by hydrolysis of the corresponding esters with 6 N HCl as illustrated for amino acid **15**.

**3-(Phosphonomethyl)pyridine-2-carboxylic Acid (15).** A solution of **14** (2.0 g, 6.35 mmol) in 200 mL of 6 N HCl solution was heated to reflux for 3 h. Lyophilization of the resulting solution gave 1.7 g of a white solid. Recrystallization from water and acetone gave **15** as partially hydrated white crystals (1.1 g, 76%); mp 238 °C. Recrystallization of the mother liquors gave a second crop of **15** as a white solid (200 mg, 14%): $^1$H NMR (DMSO-$d_6$) $\delta$ 8.65 (m, 1 H), 8.14 (bd, $J$ = 8 Hz, 1 H), 7.75 (dd, $J$ = 5, 8 Hz, 1 H), 3.36 (d, $J$ = 29 Hz).

***cis*-3-(Phosphonomethyl)piperidine-2-carboxylic Acid (17):** 51% yield, white solid (10% aqueous HCl/acetone); mp >230 °C; $^1$H NMR ($D_2O$) $\delta$ 4.02 (s, 1 H), 3.45 (d, $J$ = 12 Hz, 1 H), 3.04 (bt, $J$ = 11 Hz, 1 H), 2.82–2.68 (m, 1 H), 2.25–2.10 (m, 1 H), 1.97–1.72 (m, 4 H), 1.53 (bt, $J$ = 18 Hz, 1 H).

**(*E*)-3-(2-Phosphonoethen-1-yl)pyridine-2-carboxylic acid (21):** 72% yield, off-white solid ($H_2O$), mp 244 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.49 (bd, $J$ = 5 Hz, 1 H), 8.20 (d, $J$ = 8 Hz, 1 H), 7.76–7.32 (m, 2 H), 6.57 (t, $J$ = 15 Hz, 1 H).

**(*Z*)-3-(2-Phosphonoethen-1-yl)pyridine-2-carboxylic acid (22):** 44% yield, colorless crystals ($H_2O$/acetone); mp 240 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.58 (dd, $J$ = 5, 2 Hz, 1 H), 8.19 (bd, $J$ = 7 Hz, 1 H), 7.57 (dd, $J$ = 5, 7 Hz, 1 H), 7.50 (dd, $J$ = 13, 45 Hz, 1 H), 6.00 (t, $J$ = 13 Hz, 1 H).

**3-(2-Phosphonoeth-1-yl)pyridine-2-carboxylic acid (24):** 51% yield, white solid (triturated with methanol), mp 235 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.47 (dd, $J$ = 2, 5 Hz, 1 H), 7.83 (dd, $J$ = 2, 9 Hz, 1 H), 7.49 (dd, $J$ = 5, 9 Hz, 1 H), 3.06–2.92 (m, 2 H), 1.93–1.74 (m, 2 H).

***cis*-3-(2-Phosphonoeth-1-yl)piperidine-2-carboxylic acid (26):** 36% yield, white crystals (10% aqueous HCl/acetone), mp 195 °C; $^1$H NMR ($D_2O$) $\delta$ 4.18 (d, $J$ = 4 Hz, 1 H), 3.48 ($J$ = 11 Hz, 1 H), 3.14–2.99 (m, 1 H), 2.50–2.39 (m, 1 H), 2.02–1.48 (m, 8 H).

**Acknowledgment.** We thank Ron Lawson and Penny Threlkeld for their technical assistance and the Physical Chemistry Department of Lilly Research Laboratories for spectral data and elemental analyses.

**Registry No.** 1, 6384-92-5; (±)-4, 78966-69-5; (±)-5, 100828-16-8; 8a, 77047-42-8; 8a (*N*-oxide), 35469-52-4; 8b, 66934-89-2; 8b (*N*-oxide), 118892-64-1; 8c, 118892-58-3; 8c (*N*-oxide), 118892-65-2; 8d, 118892-59-4; 8d (*N*-oxide), 118892-66-3; 9a, 118892-60-7; 9b, 118892-61-8; 9c, 118892-62-9; 9d, 118892-63-0; 10a, 113190-82-2; 10b, 118892-67-4; 10c, 118892-68-5; 10d, 118892-69-6; (±)-11a, 113229-84-8; (±)-11b, 118892-70-9; (±)-11c, 118892-71-0; (±)-11d, 118892-72-1; 12, 118892-73-2; 12 (2-methyl ester), 24195-07-1; 13, 118892-74-3; 13 (bromide), 118892-76-5; 14, 118892-75-4; 15, 118892-83-4; (±)-16, 118892-77-6; (±)-17, 118892-84-5; 18, 118892-78-7; 19, 118892-79-8; 20, 118892-80-1; 21, 118892-85-6; 22, 118892-86-7; 23, 118892-81-2; 24, 118892-87-8; (±)-25, 118892-82-3; (±)-26, 118892-88-9; i, 4733-69-1; $(EtO)_2P(O)H$, 762-04-9; $(MeO)_2P(O)H$, 868-85-9; $(MeO)_2P(O)Me$, 756-79-6; $P(OEt)_3$, 122-52-1; $(Me_2O_3P)_2CH_2$, 16001-93-7; 4-pyridylmethanol, 586-95-8; 2-(4-pyridyl)ethanol, 5344-27-4; 3-(4-pyridyl)-7-propanol, 2629-72-3; 4-(4-pyridyl)-1-butanol, 5264-15-3; 4-(bromomethyl)-pyridine, 54751-01-8; 4-(2-bromoethyl)pyridine, 39232-05-8; 4-(3-bromopropyl)pyridine, 40337-66-4; 4-(4-bromobutyl)pyridine, 109315-44-8; quinolinic anhydride, 699-98-9.

**Supplementary Material Available:** X-ray crystallographic data for **21** (7 pages). Ordering information is given on any current masthead page.