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Phosphorus-Containing Purines and Pyrimidines: A New Class of Transition State Analogs[1]

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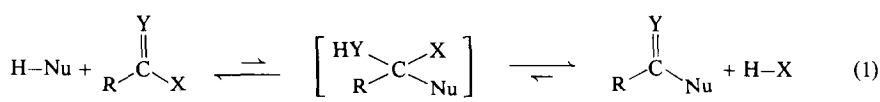
Synthetic routes to the [1,5,2]-diazaphosphorine ("4-phosphapyrimidine"), imidazo[4,5-e][1,5,2]-diazaphosphorine ("6-phosphapurine"), and imidazo[4,5-d][1,3,2]-diazaphosphorine ("2-phosphapurine") ring systems have been developed. Appropriately functionalized derivatives of these heterocycles are desired as possible transition state analogs of the nucleoside deaminases.

INTRODUCTION

An effective approach to the synthesis of potent, selective enzyme inhibitors has been the design of molecules which mimic the presumed transition state of the enzyme-catalyzed reaction (*1, 2*). This approach is based upon the expectation that at least part of the reduction in activation energy for the enzyme-catalyzed pathway is derived from a tighter binding interaction for the enzyme–transition state complex than for the enzyme–substrate or –product complexes. The transition state is by definition an unstable arrangement of the constituent atoms, and the major challenge in designing a transition state analog is to discover a stable mimic which deviates from the transition state structure as little as possible, both sterically and electronically.

An important class of enzyme-catalyzed reactions involves nucleophilic substitution at sp^2-hybridized carbon via an addition–elimination process and an sp^3-hybridized intermediate [Eq. (1)]. While this tetrahedral intermediate, **1**, is not the transition state for such a reaction, it is expected to lie close to it on the reaction coordinate (*3*), both in



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terms of energy and geometry. A number of strategies have therefore been developed for the synthesis of analogs of these intermediates. These approaches have involved substitution of boron (*4*) or sulfur (*5*) for the tetrahedral carbon, or replacement of one of the heteroatom substituents [e.g., X in Eq. (1)] with a hydrogen (*6*) or trifluoromethyl (*7*) group, to prepare compounds which are stable with the tetrahedral geometry.

[1] Dedicated to Professor William S. Johnson on the occasion of his 65th birthday to express appreciation for his guidance and admiration for his contributions to chemistry.

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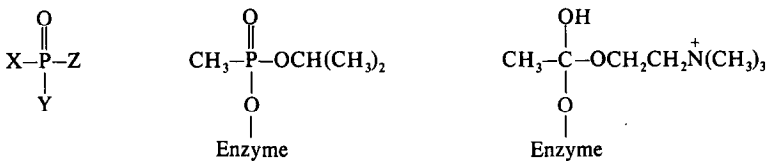
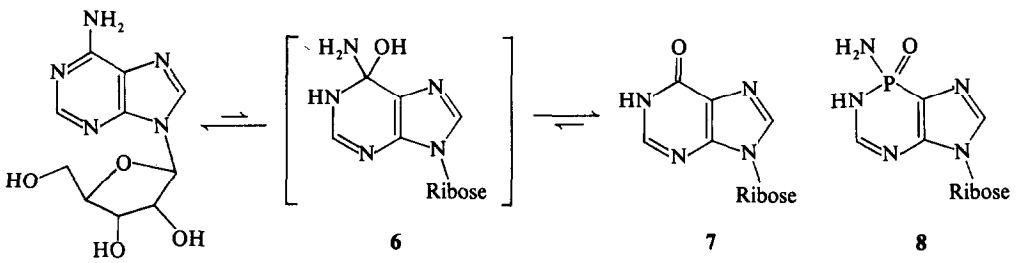
In these previous approaches to analogs of tetrahedal intermediates, significant sacrifices have been made in terms of steric or electronic similarity in order to gain tetrahedral stability. We are exploring the possibility that substitution of phosphorus for the tetrahedral carbon in question may minimize the necessary sacrifices, creating analogs which mimic the intermediate **1** more closely. Phosphorus derivatives of general formula **2** are stable in the tetrahedral geometry with any combination of carbon, nitrogen, or oxygen substituents. Furthermore, these substituents are not exchanged for hydroxyl groups in water. The bonds to phosphorus are only 10 to 15% longer than those to carbon (*8*), so the analogs will not be significantly bulkier than the actual intermediates. Although this strategy has not been previously investigated, Bernhard and Orgel have pointed out the similarity between organophosphate-inactivated acetylcholine esterase (e.g., **3**) and the tetrahedral intermediate of the normal transacylation step, **4** (*9*).

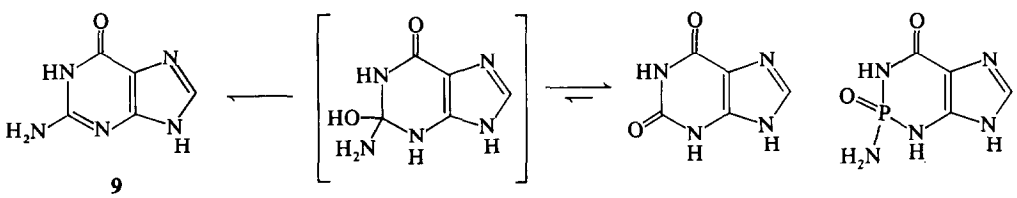


2 **3** **4**

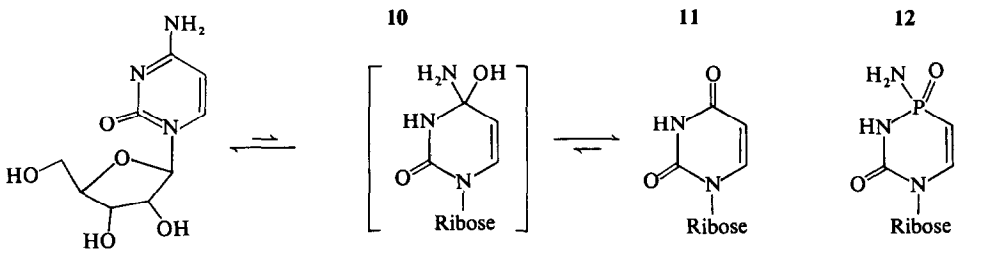
The metabolism of naturally occurring pyrimidines and purines includes several deamination reactions which probably proceed by a mechanism similar to that of Eq.



5 **6** **7** **8**

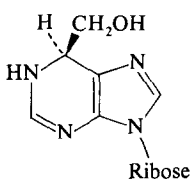


9 **10** **11** **12**



13 **14** **15** **16**

(1). Adenosine deaminase catalyzes the conversion of adenosine, **5**, to inosine, **7** (*10*), and guanine deaminase catalyzes the conversion of guanine, **9**, to xanthine, **11** (*11*), most reasonably via the tetrahedral intermediates **6** and **10**, respectively (*12*). Cytidine deaminase catalyzes the analogous hydrolysis of cytidine, **13**, to uridine, **15**, apparently via a noncovalently bound tetrahedral intermediate (**14**) as well (*13*). Several known inhibitors of these enzymes are regarded as analogs of the relevant tetrahedral intermediates, most notably the nebularine–methanol photoadduct, **17** (*14*), and coformycin, **18** (*15*), for adenosine deaminase, and tetrahydrouridine, **19** (*13*, *16*), for cytidine deaminase.



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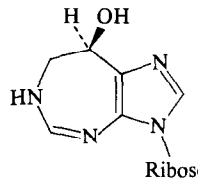

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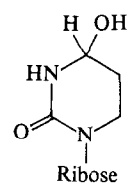

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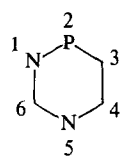
We have chosen the nucleoside deaminases as the initial focus of our study and the phosphorus-substituted purines **8** and **12** and pyrimidine **16** as the initial targets of our synthetic endeavors. Original syntheses of these compounds were required, since the bicyclic compounds represent previously unknown heterocyclic ring systems, and the only reported synthesis of a 1,5,2-diazaphosphorine (*17*) is not adaptable to the preparation of **16**. In this report, we describe syntheses of derivatives of the three heterocycles by routes which should prove to be applicable to the specific targets desired.

RESULTS

(*I*) *"4-Phosphapyrimidines": 2-Amino-2,5-dihydro-[1,5,2]-diazaphosphorin-6(1H)-one-2-oxide* (**32**) *and the 5-Benzyl Derivative* (**26**)



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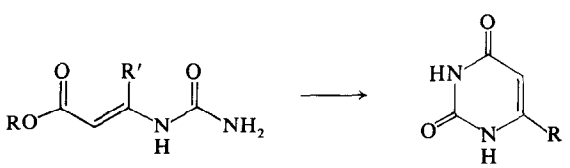
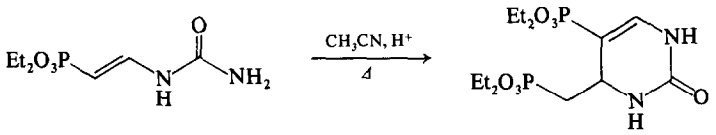


(2)

Our initial approach to the 1,5,2-diazaphosphorine ring system **20** was patterned after the facile cyclization of β-ureidoacrylic esters to uracil derivatives [Eq. (2)] (*18*). Condensation of urea and diethyl formylmethylphosphonate with acid catalysis gave

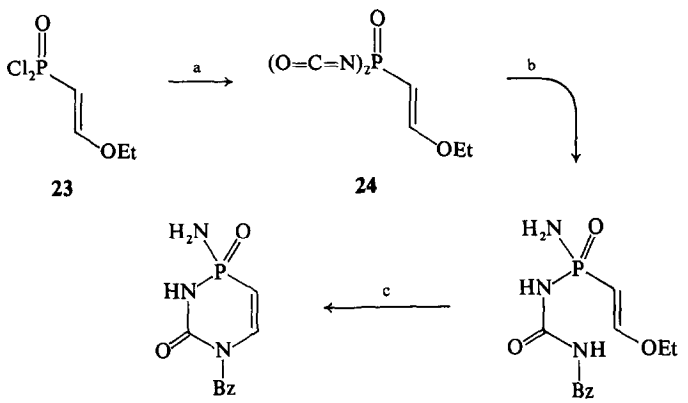
the adduct **21**, albeit in low yield. In contrast to the analogous transformations of carboxylic esters (*18*), this compound could not be induced to cyclize to the desired heterocycle. Instead, the cyclic dimer **22** was isolated on heating the urea **21** in acetonitrile with sulfuric acid. The structure was assigned from the ir, nmr, and mass spectra. The reluctance of the urea **21** to cyclize is probably due to the requirement of



21 **22**

two sequential, unfavorable steps for the transformation: *trans* to *cis* isomerization of the double bond, and ring closure by attack on the phosphonic ester moiety. In lieu of these two poor steps, side reactions such as dimerization and cyclization to **22** supravene.

A successful approach to the desired ring system introduces the phosphorus–nitrogen bonds early in the sequence and generates the ring by carbon–nitrogen bond formation. This route, which is outlined in Scheme 1, is analogous to Shaw's synthesis of uracil



23 **24** **26** **25**

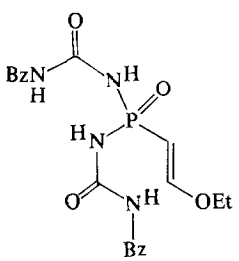
(a) KNCO, 18-crown-6, $CHCl_3$, Δ
(b) 1. H_2O; 2. benzylamine
(c) *p*-TsOH, $CHCl_3$, Δ; or
1. $Hg(OAc)_2$, CH_3CN, 25°C
2. $NaBH_4$, aq. NaOH

SCHEME 1

from β-ethoxyacryloyl isocyanate (*19*). 2-Ethoxyvinylphosphonic dichloride (**23**) is readily available from the reaction of ether with phosphorus pentachloride and sulfur dioxide (*20*). The halogens are replaced quantitatively with isocyanate groups using potassium cyanate (*21*), although in our hands this reaction requires 18-crown-6 catalysis in *vigorously* refluxing chloroform (bath temperature 95°C). Under normal reflux, the reaction was exceedingly capricious, affording mixtures of starting material

and mono- and diisocyanates which were unaltered by the addition of more reagents. We were unable to repeat the reported synthesis of **24** using sodium cyanate in benzene/acetonitrile (*21*).

The two isocyanate groups of **24** react with nucleophiles at different rates (*22*), with the result that sequential addition of one equivalent of water and one equivalent of benzylamine affords primarily the monoamide monoureide **25**. Treatment of this material with mercuric acetate in acetonitrile, followed by sodium borohydride, or with *p*-toluenesulfonic acid in chloroform provide the 5-benzyl derivative **26** in low yield (10–30%). This material was assigned the heterocyclic structure shown on the basis of its nmr and mass spectra as well as the distinctive uv absorption at 243 nm, which is characteristic of all the cyclic compounds we have prepared in this series. The major side product in the acid-catalyzed cyclization is benzylurea, arising from cleavage of the phosphorus–ureide bond.



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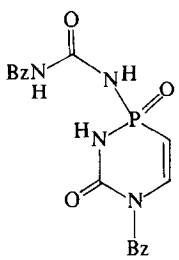

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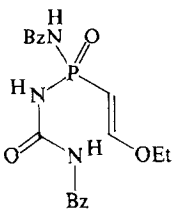

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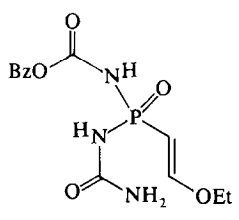
On the other hand, acid-catalyzed cyclization of the bis(ureide) **27** proceeds in essentially quantitative yield to give compound **28**. Why an electron-withdrawing substituent should facilitate cyclization is not immediately clear, but the ease with which the bis(ureide) undergoes ring closure is in marked contrast to the behavior of the monoureide **25**. The origin of this dichotomy is obscure, since the electronically similar monureide benzylamide **29** is also cyclized in good yield, with either acid or mercuric ion. Fortunately, the 5-benzyl derivative **26** is readily obtained by selective hydrolysis of the exocyclic ureide moiety of compound **28** using 3% water in acetic acid.

A characteristic of all the derivatives **25** through **29** referred to above is their low solubility in convenient solvents, which places limitations on methods for their purification and further reaction. The situation becomes even more critical in connection with synthesis of the unsubstituted 1,5,2-diazaphosphorine **32**, because the analogous intermediates (e.g., **27**, H instead of Bz) become essentially intractable.



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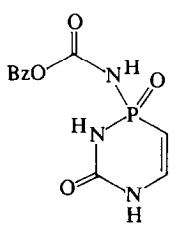

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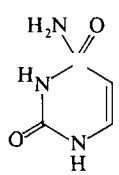

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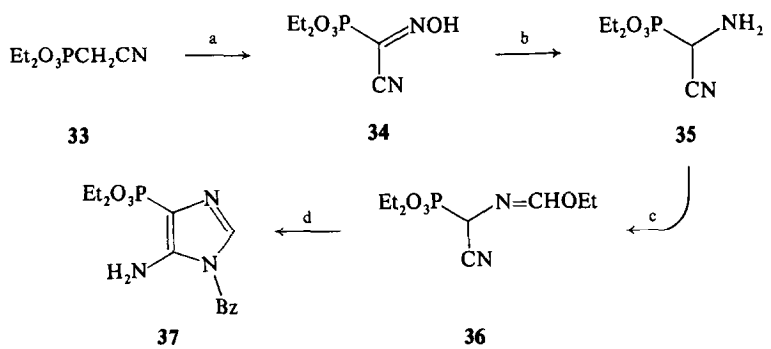
However, by taking advantage of the different reactivities of the isocyanate groups of **24**, a less polar and more easily removed protecting group for the exocyclic amide nitrogen can be introduced.

For instance, reaction of the diisocyanate **24** with one equivalent of benzyl alcohol in chloroform at −30°C to room temperature, followed by excess ammonia, provides the ureide carbamate **30** in 76% yield. Cyclization of this derivative using either *p*-toluenesulfonic or hydrochloric acid catalysis in chloroform or tetrahydrofuran proceeds smoothly to give **31** (80–90% yield). Finally, deprotection of the exocyclic amino group to afford **32** is accomplished by catalytic hydrogenolysis using palladium on charcoal in ethanol. Hydrogenolysis of the benzyloxy group occurs appreciably faster than does reduction of the 3,4-double bond, although evidence for this side reaction is seen on prolonged treatment.

The mild conditions required for the cyclization and deprotection steps and the efficiency with which the isocyanate groups can be derivatized selectively are key features of this route, which should facilitate formation of the desired riboside **16**, using a suitably protected ribosylamine (*23*).

(*II*) *"6-Phosphapurines": 1-Amino-5-benzyl-1,2-dihydro-5H-imidazo-[4,5-e][1,5,2]-diazaphosphorine-1-oxide* (**44**) *and the Dipropyl Derivative* (**43**)

The route developed by Shaw (*24*) for the synthesis of aminoimidazolecarboxylic acid derivatives was adapted for the synthesis of the aminoimidazolylphosphonate **37**, the key intermediate for construction of the "6-phosphapurine" ring system. An amino group is introduced into the α position of diethyl cyanomethylphosphonate (**33**) by oxidation, using sodium hydride and isoamyl nitrite at room temperature (80% yield), followed by aluminium amalgam reduction in refluxing ether (64% yield), as outlined in Scheme 2. Condensation of the amine **35** with excess triethyl orthoformate in refluxing acetonitrile is conveniently followed by nmr and proceeds with essentially quantitative conversion to the formimidate **36**. This material is not purified, but after removal of excess orthoester, is condensed directly with benzylamine in acetonitrile. The

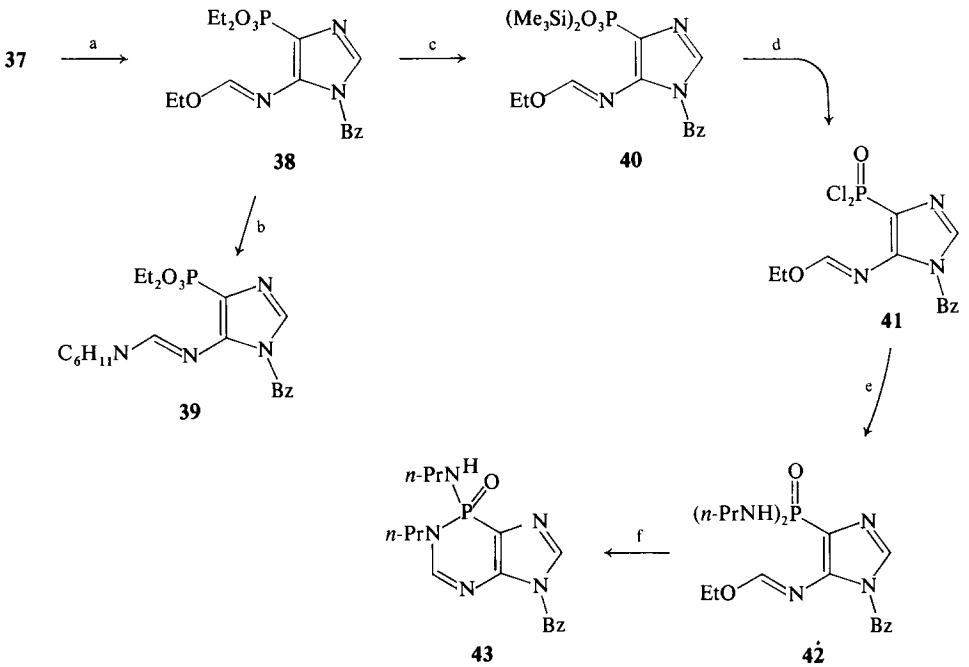


(a) NaH, *i*-amyl nitrite, THF, 0°C
(b) Al(Hg), ether, Δ
(c) $(EtO)_3CH$, CH_3CN, Δ
(d) Benzylamine, CH_3CN, Δ

SCHEME 2

aminoimidazolylphosphonate **37** is obtained in 70% overall yield from the amine **35** after recrystallization.

As in the case of the phosphapyrimidine **26**, several avenues were explored for the construction of the six-membered ring (Scheme 3). Introduction of the formimidate carbon of **38** is again accomplished smoothly with triethyl orthoformate in refluxing acetonitrile, in this instance with a catalytic amount of acetic acid. The formamidine **39**,



(a) $(EtO)_3CH$, HOAc, CH_3CN, Δ
(b) $C_6H_{11}NH_2$, CH_3CN, 25°C
(c) Me_3SiBr, $CHCl_3$, 25°C
(d) PCl_5, $CHCl_3$, 25°C
(e) *n*-$PrNH_2$, $CHCl_3$, 25°C
(f) AcOH, $ClCH_2CH_2Cl$, Δ or t-BuOK, THF, Δ

SCHEME 3

obtained on addition of cyclohexylamine, fails to cyclize on heating, as analogous carboxylic esters do (*25*). Again, side reactions take precedence over the two unfavorable steps required for cyclization: *trans* to *cis* isomerization, and ring closure by attack on the phosphonic diester.

To close the six-membered ring by formation of a carbon–nitrogen bond required a method for the functionalization of the phosphonic diester which was compatible with the other groups in the molecule. Phosphonamide derivatives are most generally available from the phosphonyl dichlorides; however, the usual methods (*26*) for the synthesis of the latter involve harsh or strongly acidic conditions which the amino or formimidate groups of intermediates **35** to **38** would not survive. Aprotic conditions can be maintained by reaction of a dialkyl phosphonate with phosphorus pentachloride, although elevated temperatures are required for complete reaction (*26*). Milder

temperatures are required for the reaction of a phosphonic acid, but the mixture is strongly acidic. A simple modification of these common procedures, involving conversion of the diethyl ester to the bis(trimethylsilyl) ester **40** with bromotrimethylsilane (*27*), avoids both the harsh and acidic conditions and enables smooth formation of the dichloride **41** with two equivalents of phosphorus pentachloride at room temperature. The by-products, phosphoryl chloride and chlorotrimethylsilane, are easily removed at reduced pressure.

Treatment of the formimidate dichloride **41** with excess propylamine at room temperature affords the formimidate diamide **42** as an oil. This material suffers ready loss of the formimidate group through hydrolysis and is therefore carried on without purification. Either acid (acetic acid in $ClCH_2CH_2Cl$) or base (potassium *t*-butoxide in tetrahydrofuran) are effective in catalyzing the loss of ethanol to give the bicyclic material **43**. This compound is obtained from the acid-catalyzed cyclization in 9% overall yield for the five steps from the aminoimidazole **37** after recrystallization. The 6-phosphapurine exhibits the nmr and mass spectral characteristics expected for the assigned structure as well as a significant bathochromic shift in the uv absorption spectrum (272 nm vs 260 nm for the formimidate diester **38**). The corresponding unsubstituted phosphonamide **44** is also accessible by this route, although its insoluble

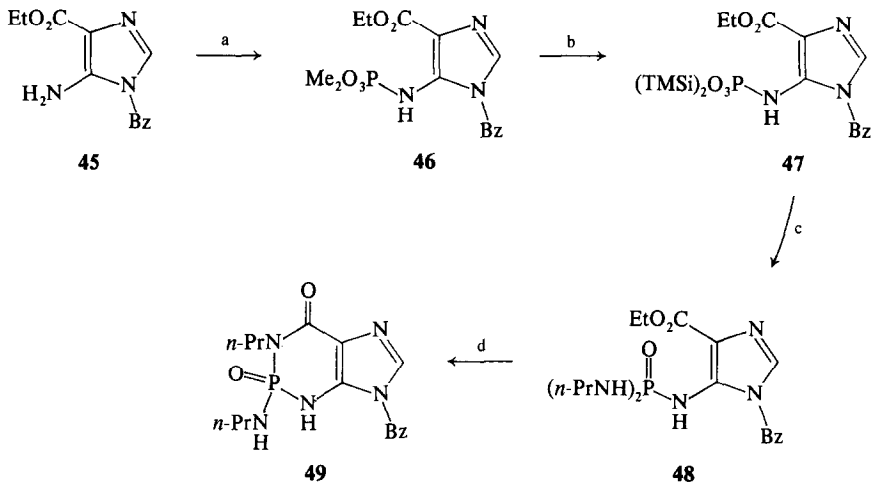
44

nature has so far frustrated our attempts to purify and to characterize it fully. The nmr, mass, and uv spectral properties of material isolated from chromatography on Sephadex LH-20 (25% methanol/acetone) are fully in accord with the bicyclic structure, however.

(III) "2-Phosphapurines": 7-Benzyl-2-propylamino-1,2-dihydro-3-propyl-7H-imidazo[4,5-d][1,3,2]-diazaphosphorine-4[3H]-one-2-oxide (**49**)

Ethyl 1-benzyl-5-aminoimidazole-4-carboxylate (**45**) was prepared according to Shaw's procedure (*24*) from ethyl aminocyanoacetate. Compounds of this type are readily condensed with urea, isocyanates, etc. (*25*) and are subsequently cyclized to the xanthine derivatives. Attempts to condense **45** with *N,N'*-dibenzylphosphorodiamidic chloride were unsuccessful, however, even under vigorous conditions, because of the poor reactivity of this phosphorylating agent and the hindered environment of the amino group. Phosphorylation of this amino group requires formation of the amide salt of **45** with potassium hydride and reaction with diethyl phosphorochloridate in refluxing tetrahydrofuran/hexamethylphosphoric triamide! A 48% yield of phosphoramide **46** can be obtained in this manner.

A functionalization procedure analogous to that applied to the synthesis of the phosphonic diamide **42** enables conversion of the phosphoramidic diester **46** to the triamide **48** (Scheme 4). Phosphorus ester exchange with bromotrimethylsilane in



(a) NaH, $ClPO_3Me_2$, THF/HMPA, Δ
(b) TMSiBr, $CHCl_3$, Δ
(c) 1. PCl_5, $CHCl_3$, 25°C
2. *n*-$PrNH_2$, $CHCl_3$, 25°C
(d) *t*-BuOK, THF, Δ

SCHEME 4

refluxing chloroform affords the bis(trimethylsilyl) phosphoramidate **47**, and subsequent reaction with two equivalents of phosphorus pentachloride and then excess propylamine provides the triamide **48** in 20% yield, after column chromatography.

The triamide **48** is reluctant to cyclize under acidic, neutral, or basic conditions. In the presence of trifluoroacetic acid in chloroform, slow hydrolysis of the phosphoramide occurs, returning free aminoimidazole **45**. In refluxing chloroform, no reaction occurs over 24 hr. In refluxing tetrahydrofuran with potassium *t*-butoxide as catalyst, only a 3% yield of the desired bicyclic material **49** is obtained after chromatographic purification; recovered starting material accounts for the bulk of the reaction product. The nmr spectrum of **49** exhibits resonances due to two nonequivalent propyl groups, similar to those seen in the nmr spectrum of the 6-phosphapurine **43**. The uv absorption at 265 nm confirms the bicyclic structure as well. Although this route constitutes the first synthesis of the 2-phosphapurine ring system, the problems encountered in the final cyclization step will have to be overcome before the desired analog **12** can be obtained.

EXPERIMENTAL

^1H nmr spectra are reported in parts per million on the δ scale relative to tetramethylsilane; data are presented as the chemical shift (multiplicity, integrated intensity, coupling constants, assignment). ^{13}C nmr spectra are reported in parts per million on the δ scale, relative to $CDCl_3$ as 77.0 ppm or DMSO-d_6 as 39.5 ppm; data are presented as the chemical shift (multiplicity in off resonance decoupled spectrum, carbon–phosphorus coupling constant, assignment). Ultraviolet spectra were recorded

in ethanol and are reported as λ_{max} (log ε) nm. Mass spectra were obtained at 70 eV, unless otherwise specified, and are reported as *m/e* (relative intensity) (assignment). Combustion analyses agreed with the theoretical values within ±0.3%.

Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl; acetonitrile was dried by distillation from Linde 4A molecular sieves. Ethanol-free chloroform was used for all reactions run in this solvent.

E-2-Ethoxyethenylphosphonic diisocyanate, **24**. A mixture of 2.8 g (20 mmol) of the phosphonic dichloride, **23**, 4.8 g (60 mmol) of potassium cyanate, and 300 mg of 18-crown-6 in 30 ml of chloroform was heated under reflux with an oil bath at 95°C for 6 hr. Nuclear magnetic resonance analysis indicated that no mono- or dichloride remained. The supernatant was decanted from the salts, concentrated, and distilled (Kugelrohr oven, 90°C/0.1 Torr) to give 2.0 g (67% yield) of the diisocyanate **24** (*21*) as a clear liquid: ir ($CHCl_3$) 1260 (P=O), 1605 (C=C), 2270 N=C=O), cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.4 (t, 3), 3.9 (q, 2), 4.94 (dd, 1, J_{HH} = 13 Hz, J_{HP} = 16 Hz, H-1), 7.33 (dd, 1, $J_{HH} = J_{HP}$ = 13, Hz, H-2).

5-Benzyl-2-(benzylcarbamoylamino)-2,5-dihydro-[1,5,2]-diazaphosphorin-6(1H)-one -2-oxide, **28**. To a vigorously stirred solution of 202 mg (1 mmol) of the diisocyanate **24** in 13 ml of chloroform at −40°C was added 214 mg (2 mmol) of benzylamine in 5 ml of chloroform. A precipitate of the bis(ureide) **27** formed immediately.

From a similar experiment, the bis(ureide) was isolated in pure form after filtration: mp 205–206°C after recrystallization from 100% ethanol; ir (mull) 1200 (P=O), 1620 (C=C), 1660 (C=O), 3270, 3320 (NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.2 (t, 3), 3.9 (q, 2), 4.2 (d, 4, J = 6 Hz, PhCH_2), 5.1 (dd, 1, $J_{HH} = J_{HP}$ = 13.5 Hz, H-1), 6.7–7.5 (m, 13, *Ph*Ch$_2$N*H*, H-2), 8.0 (d, 2, J = 9 Hz, CONHPO); uv 225 (3.49); mass spectrum 309 (0.23) (M-PhCH$_2$NH$_2$), 202 (1.8) (M-2[PhCH$_2$NH$_2$]), 187 (9.6), 173 (26), 107 (70), 106 (100).

Continued stirring of the suspension of the bis(ureide) **27** at 25°C with 10 mg of *p*-toluenesulfonic acid for 15 hr resulted in quantitative cyclization. The insoluble material was filtered, washed with chloroform, and dried to give 330 mg (89% overall yield) of the phosphapyrimidine ureide **28**: mp 190°C (dec); ir (mull) 1200 (P=O), 1620 (C=C), 1660 (C=O), 3280 (NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 4.3 (d, 2, J = 11 Hz, PhCH_2NH), 4.9 (s, 2, PhCH_2N), 5.3 (dd, 1, $J_{HH} = J_{HP}$ = 11 Hz, H-3), 6.8–7.6 (m, 12), 8.0 (d, 1, J = 8 Hz, exocyclic CONHPO), 9.8 (br s, 1, endocyclic CONHPO); uv 222 (4.08), 249 (4.00) nm; mass spectrum 263 (36) (M-PhCH$_2$NH$_2$), 106 (100). An analytical sample was prepared by recrystallization from 100% ethanol: mp 222–223°C.

Anal. ($C_{18}H_{19}N_4O_3P$) C, H, N, P.

2-Amino-5-benzyl-2,5-dihydro-[1,5,2]-diazaphosphorin-6(1H)-one-2-oxide, **26**. A 3.4 mmol sample of the crude benzylureide **28** was heated in a mixture of 15 ml of acetic acid and 0.5 ml of water at 85°C for 2.5 hr. After removal of the solvent at reduced pressure, the residue was chromatographed on silica gel (7.5% methanol–chloroform) to give 429 mg (34% recovery) of the starting material, **28**, and 366 mg (69% yield based on unrecovered starting material) of the hydrolyzed compound **26**: ir ($CHCl_3$) 1190 (P=O), 1630 (C=C), 1675 (C=O), 3200–3500 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.8 (s, 2, PhCH_2), 5.3 (dd, 1, $J_{HH} = J_{HP}$ = 10.8 Hz, H-3), 6.9 (dd, 1, J_{HH} = 10.8 Hz,

J_{HP} = 41 Hz, H-4); uv 222 (3.81), 243 (3.96) nm; mass spectrum 237 (63) (M^+), 106 (34), 91 (100). The analytical sample was obtained on recrystallization from methanol–water: mp 180–181°C.

Anal. ($C_{10}H_{12}N_3O_2P$) C, H, N, P.

2-Amino-2,5-dihydro-[1,5,2]-diazaphosphorin-6(1H)-one-2-oxide, **32**. A solution of 0.54 g (5 mmol) of benzyl alcohol in 7.5 ml of chloroform was added slowly to a solution of 2.0 g (10 mmol) of the diisocyanate **24** in 25 ml of chloroform at −30°C. After allowing the mixture to warm slowly to 25°C, it was recooled to −30°C and treated with another 5 mmol of benzyl alcohol in the same manner. After 2.5 hr at 25°C, ammonia was bubbled into the solution, causing an immediate, gelatinous precipitate of the ureide carbamate, **30**. This material was collected, washed with chloroform, and dried to give 2.47 g (76% yield) of white powder, contaminated with 2% of the bis(ureide): mp 200°C (dec); ir (KBr) 1200 (P=O), 1610 (C=C), 1685br (C=O), 3200br (NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.1 (t, 3), 3.7 (q, 2), 4.9 (s, 2, PhCH_2), 4.9 (dd, 1, $J_{HH} = J_{HP}$ = 13 Hz), 6.0 (br s, 2, $CONH_2$), 6.9 (dd, 1, $J_{HH} = J_{HP}$ = 13 Hz), 7.2 (br s, 2, CONHPO); ^{13}C nmr (DMSO-d_6) δ 14.0 (q), 65.5 (t), 66.0 (t), 92.4 (d, J_{CP} = 173 Hz), 127.5, 127.6, 128.1 (d, aryl *C*H), 136.0 (s, aryl *C*), 153.3 (s, J_{CP} = 3.5 Hz, O*C*ONH), 155.5 (s, NH*C*ONH), 161.3 (d, J_{CP} = 20 Hz, C-2); uv 208 (4.34) nm; mass spectrum 310 (2.5) (M-NH_3), 202 (13), 187 (67), 131 (76), 90 (100). This material was cyclized without further purification.

A 0.46-mmol sample of the crude ureide carbamate **30** was treated with 0.1 ml of 3 *N* HCl in 15 ml of THF at 40°C for 18 hr. After removal of the solvent, the product was dissolved in methanol and filtered through a column of silica gel, affording 110 mg (85% yield) of the cyclic material, **31**: mp 220°C (dec); ir (KBr) 1200 (P=O), 1625 (C=C), 1690, 1740 (C=O), 3200br (NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 4.9 (s, 2, PhCH_2), 4.9 (dd, 1, H-3), 6.8–7.8 (br m, 9, aryl, NH, H-4); ^{13}C nmr (DMSO-d_6) δ 66.1 (t), 88.7 (d, J_{CP} = 155 Hz, C-3), 127.8, 128.0, 128.4 (d, aryl *C*H), 136.1 (s, aryl *C*), 141.2 (d, J_{CP} = 0 Hz, C-4), 152.4 (s, C-6), 153.8 (s, J_{CP} = 3.9 Hz, O*C*ONH); uv 204 (3.83), 238 (3.81) nm; mass spectrum 187 (44), 173 (84) (M-$PhCH_2OH$), 131 (53), 107 (58), 79 (100).

A mixture of 100 mg (0.36 mmol) of the cyclic carbamate **31** and 10 mg of 10% Pd/C in 10 ml of 2:1 ethanol–water was stirred under a hydrogen atmosphere for 1 hr. Filtration and concentration of the solution afforded 51 mg (98% yield) of the deprotected phosphapyrimidine **32**, uncontaminated with starting material or over-reduced product: mp 220°C (dec); ir (KBr) 1150 (P=O), 1630 (C=C), 1660 (C=O), 3200br (NH) cm^{-1}; ^1H nmr (D_2O) δ 5.3 (dd, 1, J_{HH} = 11 Hz, J_{HP} = 13 Hz, H-4), 7.0 (dd, 1, J_{HH} = 11 Hz, J_{HP} = 40 Hz, H-3); ^{13}C nmr (DMSO-d_6) δ 93.8 (d, J_{CP} = 150 Hz, C-3), 136.8 (d, J_{CP} = 0 Hz, C-4), 152.3 (s, J_{CP} = 0 Hz, C-6); uv (H_2O), 235 (3.64) nm; mass spectrum 147 (97) (M^+), 130 (28), 104 (65), 47 (100). *Anal.* Calcd for $C_3H_6N_3O_2P$: 147.0197. Found: 147.0201.

Diethyl cyanohydroxyiminomethylphosphonate, **34**. To a stirred suspension of 8.5 g (0.17 mol) of 50% NaH/oil dispersion in 250 ml of THF was added 24.1 g (0.136 mol) of diethyl cyanomethylphosphonate, without external cooling. After hydrogen evolution ceased, the mixture was allowed to cool and the supernatant was transferred to a fresh flask by siphon. This solution was stirred mechanically at 0°C while 17.5 g (0.15 mol) of *i*-amyl nitrite was added and for another 1.5 hr at 25°C. The thick yellow suspension

was diluted with water, washed with three portions of ether, acidified, and extracted twice with ether. The latter ether layer was washed with brine, dried ($MgSO_4$), and concentrated to give 22.4 g (80% yield) of the oxime **34** as a colorless oil: ir (film) 1030 (P—O), 1250 (P=O), 2400–3600 (OH) cm^{-1}; ^1H nmr δ 1.4 (t, 6), 4.2 (dq, 4, $J_{HH} = 7$ Hz, $J_{HP} = 8.5$ Hz), 12.3 (br s, 1). *Anal.* Calcd for $C_6H_{11}N_2O_4P$: 206.0458. Found: 206.0457.

Diethyl aminocyanomethylphosphonate, **35**. A 10-g sample (48.5 mmol) of the oxime phosphonate **34** was disolved in 200 ml of ether and stirred with 2.2 g (81 mmol) of amalgamated aluminum foil, and 4 ml of water was added over a 20-min period to maintain reflux. After a further 40 min, the grey–green suspension was filtered through a pad of filter-aid, the residue was washed three times with ether, and the combined ether fractions were concentrated. The wet product was diluted with chloroform, dried (Na_2SO_4), and concentrated to give 6.0 g (64% yield) of the amino phosphonate **35** as an oil: ir ($CHCl_3$) 1030 (P—O), 1250 (P=O), 2260 (C≡N), 1620, 3360, 3430 (NH) cm^{-1}; ^1H nmr δ 1.4 (t, 6), 2.2 (br s, 2, NH_2), 4.3 (dq, 4, $J_{HH} = 7$ Hz, $J_{HP} = 8.5$ Hz), 4.3 (d, 1). The *p*-toluenesulfonate was prepared and recrystallized from 5% ethanol–ethyl acetate to provide a sample for analysis: mp 138–139°C.

Anal. ($C_{13}H_{21}N_2O_6PS$) C, H, N, P, S.

Diethyl 5-amino-1-benzyl-4-imidazolylphosphonate, **37**. A solution of 4.8 g (25 mmol) of the amino phosphonate **35** and 9 ml (54 mmol) of triethyl orthoformate in 50 ml of acetonitrile was heated at reflux for 18 hr and concentrated to give a quantitative yield (by nmr) of ethyl *N*-[cyano(diethoxyphosphinyl)methyl]methanimidate, **36**, as an oil: ir (film) 1030 (P—O), 1230 (P=O), 1640 (C=N), 2220w (C≡N) cm^{-1}; ^1H nmr δ 1.3 (t, 3), 1.4 (t, 6), 3.8 (dq, 4), 3.9 (q, 2), 4.7 (d, 1, $J_{HP} = 23$ Hz), 7.8 (d, 1, $J_{HP} = 3.5$ Hz).

A 10.5-mmol sample of the crude formimidate **36** and 1.26 ml (12.1 mmol) of benzylamine in 20 ml of acetonitrile were heated at reflux for 2 hr. The mixture was concentrated, diluted with chloroform, washed with saturated aqueous KH_2PO_4, dried ($MgSO_4$), and evaporated to give 3.18 g of a brown solid. Recrystallization from ethyl acetate afforded 2.26 g (70% overall yield from the amine **35**) of the imidazolylphosphonate **37** as colorless prisms: mp 126–127°C; ir ($CHCl_3$) 1040 (P—O), 1200 (P=O), 1560 (aryl), 3390, 3470 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.2 (t, 6), 4.1 (dq, 4), 5.0 (s, 2, Ph_2CH_2), 5.1 (s, 2, NH_2), 7.1 (d, 1, $J_{HP} = 3$ Hz, H-2), 7.2 (br s, 5); ^{13}C nmr ($CDCl_3$) δ 15.3 (q, $J_{CP} = 7.2$ Hz), 46.3 (t, PhCH$_2$), 61.0 (t, $J_{CP} = 4.9$ Hz, CH_2O), 103.6 (s, $J_{CP} = 253$ Hz, C-4), 126.4, 127.2, 128.1 (d, aryl CH), 132.8 (d, $J_{CP} = 21.7$ Hz, C-2), 134.5 (s, aryl C), 147.9 (s, $J_{CP} = 36.7$ Hz, C-5).

Anal. ($C_{14}H_{20}N_3O_3P$) C, H, N, P.

Ethyl N-[3-benzyl-5-(diethoxyphosphinyl)-4-imidazolyl]methanimidate, **38**. A mixture of 1.0 g (3.24 mmol) of the aminoimidazolylphosphonate **37**, 2 ml (12 mmol) of triethyl orthoformate, 100 μl of acetic acid, and 4 ml of acetonitrile was heated at reflux for 12 hr, at which time tlc analysis indicated complete conversion to the formimidate **38**. Removal of the solvent and excess reagent under vacuum afforded a brown oil which was carried on without purification: ir ($CHCl_3$) 1040 (P—O), 1235 (P=O), 1510 (aromatic), 1645 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.22 (t, 6), 1.27 (t, 3), 3.97 (dq, 4, $J_{HH} = J_{HP} = 7$ Hz), 4.22 (q, 2), 5.02 (s, 2), 7.27 (s, 5), 7.43 (s, 1, $J_{HP} = 3$Hz, H-2), 8.4 (s, 1, OCH=N); ^{13}C nmr ($CDCl_3$) δ 13.6 (q), 15.8 (q, $J_{CP} = 6.2$ Hz), 46.9 (t, PhCH$_2$), 61.7 (t, $J_{CP} = 5$ Hz), 62.6 (t), 113.3 (s, $J_{CP} = 249$ Hz, C-4), 126.9, 127.6, 128.4 (d, aryl

*C*H), 135.3 (d, J_{CP} = 22 Hz, C-2), 135.8 (s, aryl *C*), 144.8 (s, J_{CP} = 37 Hz, C-5), 160.8 (d, O*C*H=N); uv 216 (3.98), 260 (3.68). *Anal.* Calcd for $C_{17}H_{24}N_3O_4P$: 365.1504. Found: 365.1501.

5-Benzyl-2-propyl-1-propylaminoimidazo[4,5-e][1,5,2]-diazaphosphorine-1-oxide, **43**. A 1.13-mmol sample of the formimidate **38** was treated with 0.45 ml (3.4 mmol) of bromotrimethylsilane in 0.75 ml of chloroform for 10 min at 40°C. After removal of volatile material, the nmr spectrum indicated that complete conversion to the bis(trimethylsilyl) ester **40** had occurred. This material was dissolved in 8 ml of toluene and 2 ml of chloroform and stirred at 25°C with 483 mg (2.3 mmol) of phosphorus pentachloride. After 1.5 hr, the mixture was concentrated under vacuum to give a viscous gum. The ^1H and ^{13}C nmr spectra indicated that essentially complete conversion to the dichloride **41** had occurred. The crude dichloride **41** was stirred in 15 ml of chloroform at 0°C while 0.45 ml (6.0 mmol) of propylamine was added slowly. After 30 min at 25°C, the mixture was washed with saturated aqueous KH_2PO_4, dried (K_2CO_3), and evaporated to give the phosphonic diamide **42** as a brown gum: ^1H nmr ($CDCl_3$) δ 0.9 (t, 6), 1.3 (t, 3), 1.4 (m, 4), 2.9 (br m, 6, CH_2NH_2), 4.2 (q, 2), 5.0 (s, 2), 7.2 (br s, 6, aryl), 8.6 (s, 1, OC*H*=N).

A 2.2-mmol sample of the diamide **42**, prepared in this manner, in 10 ml of 1,2-dichloroethane was heated at reflux with 0.2 ml of acetic acid for 2 hr. The mixture was washed with 1 *M* $NaHCO_3$, the aqueous layer was extracted with chloroform, and the combined organic layer was dried ($MgSO_4$) and concentrated to give 0.46 g of crude product. Recrystallization from ethyl acetate–diisopropyl ether afforded 70 mg (9% overall yield for the five steps from the amino diester 37) of the 6-phosphapurine **43**: ir ($CHCl_3$) 1200 (P=O), 1575 (aromatic), 3475 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) ($CHCl_3$) δ 0.8 (t, 3), 1.0 (t, 3), 1.4 (m, 2), 1.9 (m, 2), 2.5 (m, 2, CH_2NH), 3.7 (m, 2, CH_2N), 5.24 (s, 2, PhCH_2), 7.0–7.3 (m, 5, Ph), 7.50 (d, 1, J_{HP} = 20 Hz, H-3), 7.57 (d, 1, J_{HP} = 3 Hz, H-6); ^{13}C nmr ($CDCl_3$) δ 10.9 (q), 11.1 (q), 24.2 (t, J_{CP} = 6.1 Hz, CH_2CH_2NP), 25.0 (t, CH_2CH_2NHP), 42.9 (t, PhCH$_2$), 46.6 (t, CH_2NHP), 47.3 (t, J_{CP} = 2.2 Hz, CH_2NP), 114.9 (s, J_{CP} = 207 Hz, C-7a), 127.1, 127.8, 128.6 (d, aryl *C*H), 135.9 (s, aryl *C*), 138.0 (d, J_{CP} = 24 Hz, C-6), 148.8 (s, J_{CP} = 25 Hz, C-4a), 149.4 (d, J_{CP} = 2.1 Hz, C-3); uv 218 (4.04), 272 (3.89) nm; mass spectrum 345 (75) (M^+), 302 (21), 287 (78), 261 (48), 91 (100). An analytical sample was prepared by recrystallization from ethyl acetate–diisopropyl ether: mp 199–200°C.

Anal. ($C_{17}H_{24}N_5OP$) C, H, N, P.

Ethyl 5-amino-1-benzylimidazole-4-carboxylate, **45**. The aminoimidazaolecarboxylic ester **45** was prepared according to the procedure of Shaw *et al.* (*24*), in 20% yield from ethyl aminocyanoacetate, after recrystallization from ethyl acetate: mp 164–167°C; ir ($CHCl_3$) 1560 (aromatic), 1680 (C=O), 3410, 3500 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.3 (t, 3), 4.3 (q, 2), 4.9 (br s, 4, PhCH_2, NH_2), 7.0 (s, 1, H-2), 7.0–7.4 (m, 5); ^{13}C nmr (DMSO-d_6) δ 14.5 (q), 45.8 (t, PhCH_2), 58.3 (t, CH_2O), 109.4 (s, C-4), 127.0, 127.4, 128.5 (d, aryl *C*H), 131.5 (d, C-2), 136.5 (s, aryl *C*), 146.3 (s, C-5), 163.8 (s, *C*=O). Recrystallization from acetonitrile afforded a sample for analysis: mp 168–169°C.

Anal. ($C_{13}H_{15}N_3O_2$) C, H, N.

Ethyl 1-benzyl-5-[(dimethoxyphosphinyl)amino]imidazole-4-carboxylate, **46**. A suspension of 18 mmol of NaH and 2.0 g (8.2 mmol) of the aminoimidazole **45** in 50 ml of THF and 1 ml of hexamethylphosphorictriamide was heated at reflux for 30 min to

complete hydrogen evolution. A solution of 1.01 ml (9.4 mmol) of dimethyl phosphorochloridate in 20 ml of THF was added over a 1-hr period while maintaining reflux. After 30 min more, the mixture was partitioned between ether and 1 *N* NaOH and the organic layer was extracted with a second portion of 1 *N* NaOH. The combined alkaline layer was washed with chloroform and acidified and saturated with NaCl, and the product was extracted with chloroform. After the phosphoramidate was dried ($MgSO_4$) and concentrated 1.4 g (48% yield) was obtained: ir ($CHCl_3$) 1035 (P–O), 1215 (P=O), 1585 (aromatic), 1690 (C=O), 3360 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.3 (t, 3), 3.7 (d, 6, J_{HP} = 12 Hz), 4.3 (q, 2), 5.3 (s, 2), 6.3 (br s, 1, NH), 7.0–7.4 (m, 6, Ph, H-2); uv 213 (3.93), 244 (3.95). Recrystallization from methanol/diisopropyl ether afforded an analytical sample: mp 146–148°C.

Anal. ($C_{15}H_{20}N_3O_5P$) C, H, N, P.

Ethyl 1-Benzyl-5-[(dipropylaminophosphinyl)amino]-imidazole-4-carboxylate, **48**. A solution of 0.87 g (2.5 mmol) of the dimethyl phosphoramidate **46** and 1.0 ml (6.4 mmol) of bromotrimethylsilane in 6 ml of chloroform was refluxed for 20 min and concentrated to give the bis(trimethylsilyl) ester **47** as an oil. Nuclear magnetic resonance analysis indicated that complete ester exchange had occurred. This material was dissolved in 6 ml of chloroform and stirred with 1.04 g (5.0 mmol) of phosphorus pentachloride for 2 hr at 25°C. After concentration, the residue was dissolved in 1 ml of toluene, reevaporated, and kept at 0.01 Torr overnight to remove the volatile by-products. The crude phosphoramidic dichloride was dissolved in 10 ml of chloroform and stirred at 0°C during the addition of 1.0 ml (12.5 mmol) of propylamine. After 30 min at 25°C, the mixture was diluted with chloroform, washed with water, dried ($MgSO_4$), and concentrated to give 0.64 g of crude product. This material was purified by chromatography on silica gel (3% ethanol–chloroform), affording 0.19 g (20% yield) of the phosphoric triamide **48** as an oil: ir ($CHCl_3$) 1245 (P=O), 1580 (aromatic), 1685 (C=O), 3450 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.7 (t, 6), 1.2–1.7 (m, 7, CH_3CH_2O, CH_2CH_2NH), 2.6–3.1 (m, 4, CH_2NH), 4.3 (q, 2), 5.0 (m, 3), 5.4 (s, 2, $PhCH_2$), 7.0–7.8 (m, 6, Ph, H-2); uv 210 (4.00), 251 (3.75) nm. *Anal.* Calcd for $C_{19}H_{30}N_5O_3P$: 407.2086. Found: 407.2087.

7-Benzyl-1,2-dihydro-3-propyl-2-propylamino-7H-imidazo[4,5-d][1,3,2]-diazaphosphorin-4(3H)-one-2-oxide, **49**. A mixture of 0.23 g (0.57 mmol) of the triamide **48** and 80 mg (0.71 mmol) of potassium *t*-butoxide in 5 ml of THF was refluxed for 2 days. After being diluted with chloroform and washed with saturated NH_4Cl, the product was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on Sephadex LH-20 (3% H_2O:20% CH_3OH:77% acetone) to give 5 mg of the bicyclic product **49** as an oil: ^1H nmr ($CDCl_3$) δ 0.85 (m, 6), 1.5 (m, 4), 2.5 (m, 2, CH_2NH), 3.4 (m, 2, CH_2N), 3.8 (m, 2, NH), 5.2 (m, 2, $PhCH_2$), 7.2 (br s, 6, Ph, H-6); uv 216 (4.00), 265 (3.79) nm; mass spectrum 361 (5) (M^+), 319 (12), 304 (2), 262 (7), 258 (71), 91 (100). *Anal.* Calcd for $C_{17}H_{24}N_5O_2P$: 361.1666. Found: 361.1658.

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