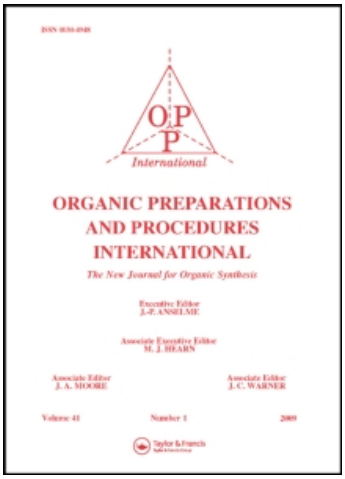

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PHOSPHORYLATED ADENINE DERIVATIVES AS POTENTIAL SYNTHONS FOR ANTIVIRAL AGENTS

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PHOSPHORYLATED ADENINE DERIVATIVES AS POTENTIAL SYNTHONS FOR ANTIVIRAL AGENTS

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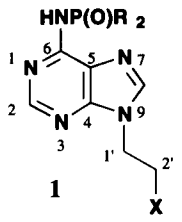
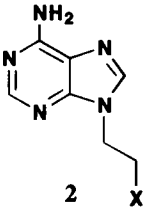
In studies directed towards the development of highly specific antiviral agents, we had need of certain *N*-phosphorylated adenine derivatives as potential synthons for such compounds. A search of the literature revealed that *N*-phosphorylated adenines of the type we required were essentially unknown. Our target systems were **1** and **2** both families of which possess highly reactive groups at the end of a chain attached at N(9). The rationale and incentive to include **1a-d** and **2a-d** for synthesis were different from that for **1e** and **1f**. Compounds **1a-d** and **2a-d** have excellent leaving groups at



1

a) R = C_6H_5O, X = Cl
b) R = 4-MeC_6H_4O, X = Cl
c) R = C_6H_5O, X = N_3
d) R = 4-MeC_6H_4O, X = N_3
e) R = C_6H_5O, X = $NHCH_2$-3-C_5H_4N
f) R = 4-MeC_6H_4O, X = $NHCH_2$-4-C_5H_4N

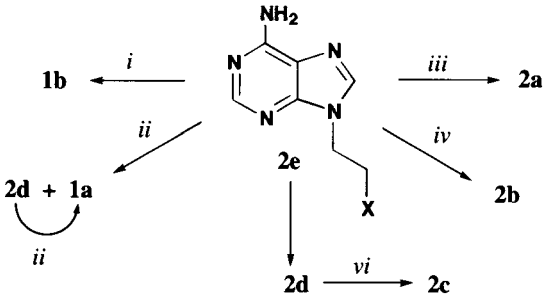


2

a) X = OP(O)(OPh)Ph
b) X = $OP(O)Ph_2$
c) X = N_3
d) X = Cl
e) X = OH

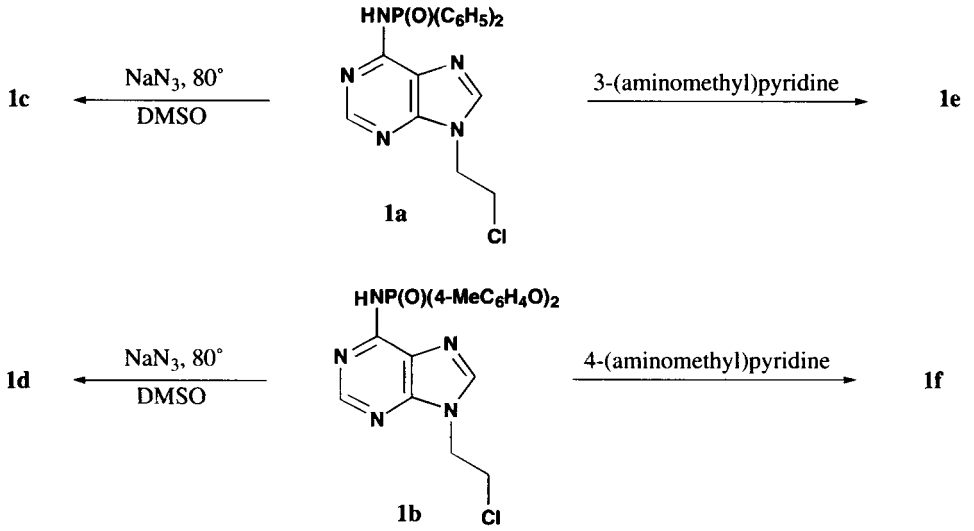
the terminus of the attached chain at N(9) and could serve as a site for elaboration such as for the addition of sugars or other potentially useful groups which could induce antiviral properties.[1] On the other hand, in **1e** and **1f** a ligand framework exists which could chelate metal ions such as zinc, for example.[2,3] Consequently, **1e** and **1f** could be useful in these types of investigations since they possess several binding sites and are hydrophilic which could maintain the metal in solution.

Derivatives of **1** and **2** were prepared *via* reaction of an adenine derivative with the corresponding phosphorus chloride in the presence of pyridine. The key reagent **2e**[4] was so treated with an appropriate phosphorus chloride/pyridine to yield **1a**, **1b**, or **2a-d** as shown. The greater nucleophilicity of the oxygen atom in the alcohol than that of the nitrogen atom in the attached amino group in **2e**[4] is obvious. We have no explanation as to why reagents with P-Ph groups led to O-phosphorylation to give **2a** and **2b** where reagents with only P-O-aryl groups led to *N*-phosphorylation to give **1a** and **1b**. The yields of products varied, but all reaction mixtures were complex and the products tended to be partially hygroscopic. Amine **2d**, obtained in trace amounts in **2e** →**1a**, was converted to **1a** independently.



i) 4-$MeC_6H_4OP(O)Cl$, pyr. *ii*) $(PhO)_2P(O)Cl$, C_6H_6, Δ *iii*) $(4\text{-}MeC_6H_4O)_2P(O)Cl$, C_6H_6, Δ
iv) $(PhO)_2P(O)Cl$/toluene/Et_3N *v*) $(4\text{-}MeC_6H_4O)_2P(O)Cl$, toluene, Et_3N *vi*) NaN_3, DMSO, 80°

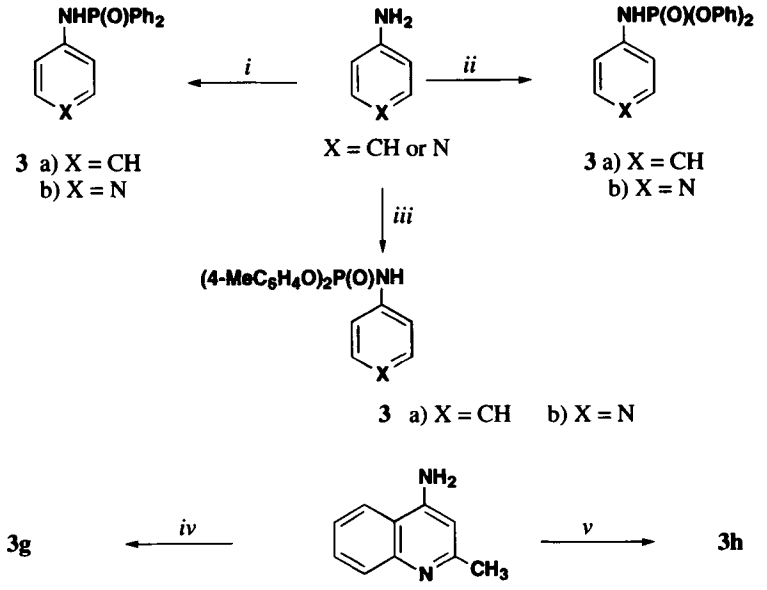
The syntheses of **1c** and **1e,** as well as that of **1d** and **1f,** were realized as illustrated from **1a** and **1b**, respectively. Azides **1c** and **1d** were non-hygroscopic, crystalline products, but potential



metal chelates **1e** and **1f** formed crystalline hydrates. All efforts to generate crystalline products void of the water of hydration were unsuccessful.

Few model systems are in the literature for comparison purposes in terms of physical and spectral properties of **1-2**. All proton, ^{13}C and ^{31}P NMR spectra supported the structures. Compounds **3a,b** with a $HNP(O)Ph_2$ unit had a positive ^{31}P chemical shift while **3c-h** with a $HNP(O)(OAr)_2$ group had a negative shift. Model systems employed were the respective aniline derivatives **3a**, **3c** and **3e**,[5-7] the pyridine derivatives **3b**, **3d** and **3f**,[7] and the 4-aminoquinaldine derivatives **3g** and **3h**. The correlation of ^{31}P shifts in **1a-f** with **3c-h** is obvious as is the correlation of **2a,b** with **3a,b**. Purity for **3a,c,e**[3] and **3b,d,f**[7] has been improved and **3g,h** were previously unknown. In addition, a variety of spectral properties of **3a-f** are reported herein for the first time. The syntheses for the members of **3** are outlined

in the Scheme. Procedures herein for **1-3** are facile for this rare group of P(O)-NH compounds.



i) $Ph_2P(O)Cl$, PhH, Δ *ii*) $(PhO)_2P(O)Cl$, PhH, Δ *iii*) $(4\text{-}H_3CC_6H_4O)_2P(O)Cl$, PhH, Δ
iv) $(PhO)_2P(O)Cl$, $PhCH_3$, Et_3N *v*) $(4\text{-}MeC_6H_4O)_2P(O)Cl$, $PhCH_3$, Et_3N

EXPERIMENTAL SECTION

All ^1H, ^{13}C and ^{31}P spectral data were taken on a Varian XL-300 or XL-400 NMR spectrometer operating at 299.94, 75.43 and 121.48 MHz and at 399.9, 100.6 and 161.9 MHz, respectively. Chemical shifts for ^1H and ^{13}C NMR were reported in δ or ppm values downfield from TMS while ^{31}P were reported in ppm from 85% H_3PO_4 as a reference. Such data have been included for all new compounds as well as for those not previously recorded. IR spectra were recorded in KBr pellets on a Perkin Elmer 681 IR unit. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Mass spectral data (FAB unless specified) were taken on a VG analytical instrument, ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Chromatographic purifications were performed on silica gel (60-200 mesh), alumina (neutral, 70-230 mesh), or silica gel with gypsum (60, PF_{254}). The Chromatotron was obtained from Harrison Research, Inc., 840 Moana Court, Palo Alto, CA 94306. Syntheses were executed under nitrogen unless otherwise specified. All reagents were purified before use either by distillation or recrystallization. Synthons **2d**[4] and **2e**[4] were prepared by literature methods, as were **3a,c,e**[5] and **3b,e,f**,[3] but procedures for the latter are included since those reported lacked details.

9-(2'-Chloroethyl)-*N*^{6}-*bis*(phenoxy)phosphinyladenine (1a).- A suspension of **2e**[4] (0.065 g, 0.23 mmol) in dry pyridine (2 mL) was treated dropwise with diphenyl chlorophosphate (2.65 g, 11.2 mmol) over 12 min. After stirring at reflux (1 hr) and then being allowed to cool (1 hr), the solution was filtered and the filtrate was evaporated to a yellow oil. The oil in $HCCl_3$ (2 mL) was chromatographed [silica gel with $HCCl_3$:H_3COH (30:1)] to give a solid which was recrystallized

($HCCl_3$:ether, 1:10) to yield **1a** (0.75 g, 53%), mp 175-176.5°. IR: 3100 (N-H), 1218 (P=O), 1194 (C-O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 3.9 [m, 2 H, H(2')], 4.5 [m, 2 H, H(1')], 7.1-7.3 [m, 10 H, Ar-H], 8.05 [s, 2 H, H(2) and H(8)], 8.7 [bs, 1 H, NH]; ^{13}C NMR ($DCCl_3$]: ppm 42.0 [C(2')], 45.8 [d, C(1')], 120.7 [C(5)]; Ar-C: 121.4, 125.5, 129.7, 140.9, 144.1 [C(8)], 150.2 [C(4)], 151.1 [C(2)], 151.2 [C(6)]; ^{31}P NMR (DMSO-d_6): δ -8.91. Mass spectrum calculated for $C_{19}H_{17}ClN_5O_3P$ *m/z* [$M^{+\cdot}$]: 428; Found: [428 + 1]$^+$.

Anal. Calcd for $C_{19}H_{17}ClN_5O_3P$: N, 16.29; P, 7.21. Found: N, 16.21; P, 7.13

A trace of **2d** was also obtained from the chromatography and had properties as reported.[7]

To a suspension of **2d** (0.065 g, 0.23 mmol) and dry pyridine (2 mL) was added dropwise diphenyl chlorophosphate (2.65 g, 11.2 mmol) over 12 min. The mixture was heated at reflux (1 hr) and then cooled to RT (1 hr). After filtration and evaporation, the thick yellow oil which remained was dissolved in $HCCl_3$ (2 mL) and the solution was chromatographed (silica gel). The fraction with R_f 0.44 was collected. Evaporation of the solvent and recrystallization ($HCCl_3$:ether, 1:10) gave crystalline **1a** (0.075 g, 53%), mp 175-176.5°) identical to that obtained above and which confirmed its structure.

9-(2'-Chloroethyl)-*N*^{6}-*bis*(4-tolyl)phosphinyladenine (1b).- As for **1a**, **2e**[4] (0.200 g, 1.11 mmol), anhydrous pyridine (4.5 mL) and *bis*(4-tolyl) chlorophosphate (1.021 g, 3.44 mmol) gave **1b** (0.06 g, 16%), mp 152.5-154°. IR: 3100 (N-H), 1225, 1200 cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.27 [s, 6 H, 2 CH_3], 3.9 [m, 2 H, H(2')], 4.5 [m, 2 H, H(1')], 7.06-7.21 [m, 8 H, Ar-H], 8.02 [s, 2 H, H(2) and H(8)], 8.7 [bs, 1 H, NH]; ^{13}C NMR ($DCCl_3$): ppm 20.7 [d, CH_3, $^6J_{P-C}$ = 5.6 Hz], 42.0 [C(2')], 45.8 [C(1')], 119.5 [C(5)]; Ar-C: 120.4, 130.2, 135.1, 143.8 [C(8)], 150.9 [C(4)], 151.2 [C(2)], 152.0 [d, C(6), $^2J_{P-C}$ = 5.5 Hz]; ^{31}P NMR (DMSO-d_6): δ -8.97. Mass spectrum calculated for $C_{21}H_{21}ClN_5O_3P$ *m/z* [$M^{+\cdot}$]: 457; Found: [457 + 1]$^+$.

Anal. Calcd for $C_{21}H_{21}ClN_5O_3P$: N, 15.29; P, 6.76. Found: N, 15.08; P, 6.76

9-(2'-Azidoethyl)-*N*^{6}-*bis*(phenoxy)phosphinyladenine (1c).- A mixture of **1a** (0.150 g, 0.35 mmol), sodium azide (0.068 g, 1.05 mmol) and DMSO (1.5 mL) was heated at 80° with stirring (4.5 hrs). After cooling to RT (30 min), the mixture was treated with water (2 mL) and $HCCl_3$ (3 mL) and two layers separated. Extracts ($HCCl_3$, 3 x 2 mL) of the aqueous layer were combined with the original organic layer and the resulting solution was washed (brine) and then dried ($MgSO_4$). Evaporation left an oil which solidified with cold ether and the solid was recrystallized [$HCCl_3$:ether (3:20)] to give **1c** (0.055g, 37%), mp 138-139°. IR: 3100 (N-H), 2100 (N_3), 1210 (P=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 3.77 [m 2 H, H(2')], 4.32 [m, 2 H, H(1')], 7.1-7.3 [Ar-H], 8.03 [bs, 2 H, H(2) and H(8)], 8.7 [bs, 1 H, NH]; ^{13}C NMR ($DCCl_3$): ppm 43.16 [C(2')], 50.03 [C(1')], 120.6 [C(5)], 143.8 [C(8)], 150.9 [C(4)], 151.1 [C(2)], 152.6 [C(6)]; Ar-C: 125.4, 129.6, 150.2; ^{31}P NMR ($DCCl_3$): δ -9.27. Mass spectrum calculated for $C_{19}H_{17}N_8O_3P$ *m/z* [$M^{+\cdot}$]: 436. Found: [436 + 1]$^+$.

Anal. Calcd for $C_{19}H_{17}N_8O_3P$: N, 25.68; P, 7.07. Found: N, 25.95; P, 7.14

9-(2'-Azidoethyl)-*N*^{6}-*bis*(4-tolyl)phosphinyladenine (1d).- A mixture of **1b** (0.303 g, 0.663 mmol), sodium azide (0.123 g, 1.98 mmol) and DMSO (3 mL) was treated as in the preparation of **1c** and

gave **1d** (0.12 g, 39%), mp 109.5-111° IR: 3105 (N-H), 2100 (N_3), 1230 (P=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 3.78 [t, 2 H, H(2')], 4.30 [t, 2 H, H(1')], 7.1-7.4 [Ar-H], 8.7 [bs, 1 H, NH], 8.00 [bs, 2 H, H(2) and H(8)]; ^{13}C NMR ($DCCl_3$): ppm 20.74 [s, CH_3], 43.2 [C(2')], 50.1 [C(1')], 120.4 [C(5)]; Ar-C: 120.34, 130.16, 135.04, 143.7 [C(8)], 148.03, 148.12 [C(4)], 151.19 [C(2)], 152.2 [C(6)]; ^{31}P NMR ($DCCl_3$): δ -9.23. Mass spectrum calculated for $C_{21}H_{21}N_8O_3P$ *m/z* [$M^{+\cdot}$]: 464. Found: [464 + 1]$^+$.

Anal. Calcd for $C_{21}H_{21}N_8O_3P$: N, 24.13; P, 6.67. Found: N, 24.54; P, 6.57

9-[2'-(*N*-3-Methylpyridinyl)aminoethyl-N^6-*bis*(phenoxy)]phosphinyladenine (1e).- Compound **1a** (2.00 g, 4.36 mmol), 3-(aminomethyl)pyridine (0.708 g, 6.6 mmol) and anhydrous pyridine (35 mL) were stirred (Δ-2.5 hr). Upon cooling (50 min), a precipitate formed and was filtered off and the filtrate was evaporated to a solid. Traces of pyridine were removed *via* co-evaporation with benzene. Chromatography [silica gel with $HCCl_3$:H_3COH (15:1)-Chromatotron] gave a yellow oil which was rechromatographed ($HCCl_3$:H_3COH; 25:1). The solid obtained recrystallized ($HCCl_3$) to give **1e** (0.024 g, 11%), mp 59.4-60.5°. IR: ($HCCl_3$) 1610-1590 (C=C, C=N), 1195 (C-O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 3.04 [t, 2 H, H(2')], 3.76 [s, 2 H, H(3')], 4.26 [t, 2 H, H(1')], 7.09-7.29 [m, 11 H, Ar-H and H(5')], 7.53 [d, 1 H, H(6')], 7.99 [s, 2 H, H(2) and H(8)], 8.42-8.49 [m, 2 H, H(7') and H(8')], 8.68 [s, 1 H, PNH]; ^{13}C NMR ($DCCl_3$): ppm 44.15 [C(2')], 47.8 [C(1')], 50.58 [C(3')], 120.60 [C(5)], 122.33 [C(5')], 134.90 [C(6')], 135.75 [C(4')], 144.16 [C(8)], 148.54 [C(7')], 149.55 [C(8')], 150.25 [C(4)], 151.06 [C(2)]; Ar-C: 120.66, 125.35, 129.65, 150.30, 151.2, 151.98. ^{31}P NMR ($DCCl_3$): δ -8.77. Mass spectrum calculated for $C_{25}H_{24}N_7O_3P$: *m/z* [$M^{+\cdot}$]: 501. Found: [501 + 1]$^+$.

Anal. Calcd for $C_{25}H_{24}N_7O_3P \cdot 4\ H_2O$: N, 17.09; P, 5.40. Found: N, 17.09; P, 5.17

9-[2'-(*N*-4-Methylpyridinyl)aminoethyl-N^6-*bis*(4-tolyl)]phosphinyladenine (1f).- A mixture **1b** (0.150 g, 0.327 mmol), 4-(aminomethyl)pyridine (0.389 g, 0.36 mmol) and anhydrous pyridine (5 mL) was stirred at reflux (2.5 hr). The remaining procedure was identical to that used for **1e** and afforded crude product which recrystallized ($HCCl_3$:ether; 3:25) to give **1f** (0.024 g, 14%), mp 71-72°. IR: ($HCCl_3$) 3350 (broad, N-H), 1610 (C=C), 1198 (C-O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 2.23 [s, two CH_3 and NH], 3.07 [m 2 H, H(2')], 3.79 [s, 2 H, H(3')], 4.32 [m, 2 H, H(1')], 7.00-7.27 [m, 10 H, Ar-H and H(5')], 8.04/8.05 [s, 2 H, H(2) and H(8)], 8.47 [d, 2 H, H(6')], 8.69 [s, 1 H, PNH]; ^{13}C NMR ($DCCl_3$): ppm 19.90 [s, two CH_3], 43.39 [C(2')], 47.30 [C(1')], 51.29 [C(3')], 120.08 [C(5)], 122.07 [C(5')], 142.98 [C(8')], 144.16 [C(8)], 147.29 [C(4')], 148.02 [C(4)], 148.54 [C(7')], 148.95 [C(6')], 151.17 [C(2)]; Ar-C: 119.43, 119.47, 129.34, 129.38, 138.18, 150.33. ^{31}P NMR ($DCCl_3$): δ -9.23. Mass spectrum calculated for $C_{27}H_{28}N_7O_3P$: *m/z* [$M^{+\cdot}$]: 529. Found: [529 + 1]$^{+\cdot}$.

Anal. Calcd for $C_{27}H_{28}N_7O_3P \cdot H_2O$: N, 17.91; P, 5.66. Found: N, 17.94; P, 5.32

9-(2'-*O*-Phenylphenoxyphosphinyl)ethyladenine (2a).- As for **1a**, there was used **2e**[4] (0.400 g, 2.23 mmol), anhydrous pyridine (9 mL) and phenyl phenylphosphonochloridate (0.648 g, 2.56 mmol) to give **2a** (0.44 g, 50%), mp 145.5-146°. The elution system for the chromatography was $HCCl_3$:H_3COH (10:1) and the recrystallization system was $HCCl_3$:ether (1:9). IR: 3100 (N-H), 1447 (P-Ph), 1225 (P=O), 1200 (C-O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.2-3.8 [bm, 2 H, NH_2], 4.53 [bs, 4 H, CH_2-CH_2], 6.99-7.64 [m, 10 H, Ar-H], 8.44-8.46 [two s, 2 H, H(2) and H(8)]; ^{13}C NMR (DMSO-d_6]:

ppm 44.05 [d, C(2'), $^2J_{P-C}$ = 6.7 Hz], 64.13 [d, C(1'), $^3J_{POC}$ = 5.6 Hz], 117.5 [C(5)]; Ar-C: 120.0, 125.0 125.2, 127.0, 128.7, 129.7, 131.3, 133.2, 143.9, 145.3, 148.6, 149.7, 150.6; ^{31}P NMR (DMSO-d_6): δ 15.32. Mass spectrum calculated for $C_{19}H_{18}N_5O_3P$ *m/z* [$M^{+\cdot}$]: 395 Found: [395 + 1]$^+$.

Anal. Calcd for $C_{19}H_{18}N_5O_3P$•2.5 H_2O: N, 15.90 P, 7.03 Found: N, 15.76 P, 7.14

9[2'-*O*-*bis*(Phenyl)phosphinyl)ethyladenine (2b). To a boiling suspension of **2e**[4] (0.385 g, 2.148 mmol) in pyridine (7 mL) was added dropwise diphenylphosphinyl chloride (0.610 g, 2.58 mmol) over a period of 12 min. After heating at reflux (1 hr), the mixture was allowed to cool to RT (1 hr) and it was then evaporated (clear yellow solution). Residual pyridine was removed *via* co-evaporation with benzene to give a viscous yellow oil which was dissolved in $HCCl_3$ and subjected to chromatography [silica gel with $HCCl_3$:H_3COH (10:1)]. Recrystallization (EtOH:ether; 1:25) of the solid obtained gave pure **2b** (0.126 g, 42%), mp 199-200°. IR: 3300-3120 (HN-H), 1448 (P-Ph), 1245 (P=O), 1030 P-O-C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.2 [m, 2 H, H(2')], 4.5 [t, 2 H, H(1'), $^3J_{H-H}$= 4. 8 Hz], 7.3-7.6 [s, NH_2], 7.3-7.6 [m, 12 H, Ar-H, H(2), H(8)]; ^{13}C NMR (DMSO-d_6): ppm 40.2 [C(1')], 43.4 [d, C(2')]; $^2J_{P-C}$ = 8 Hz], 118.7 [C(5)]; Ar-C: 128.4, 128.6, 129.9, 130.8, 130.9, 131.7, 132.2, 141.0 [C(8)], 149.5 [C(4)], 152.3 [C(2)], 155.9 [C(6)]; ^{31}P NMR (DMSO-d_6): δ 31.67. Mass spectrum calculated for $C_{19}H_{18}N_5O_2P$ *m/z* [$M^{+\cdot}$]: 379; Found: [379 + 1]$^+$.

Anal. Calcd for $C_{19}H_{18}N_5O_2P$: N, 18.46; P, 8.16. Found: N, 18.33; P, 8.20

9-(2'-Azidoethyl)adenine (2c).- A mixture of **2d**[4] (0.400 g, 2.024 mmol), sodium azide (0.395 g, 6.072 mmol) and DMSO (4 mL), was heated at 80° (4 hr). After cooling to RT, the mixture was treated with water (5 mL) and $HCCl_3$ (8 mL). Extracts ($HCCl_3$, 3 x 5 mL) of the aqueous layer and original organic layer were combined, but a solid formed during the extraction process. This solid was filtered off and retained. The combined organic solution was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent gave an identical solid which was combined with that isolated earlier. Additional extractions of the aqueous layer (warm $HCCl_3$) gave a final crop of the solid. Recrystallization ($HCCl_3$) gave **2c** (0.18 g, 36%), mp 182.5-183.5°. IR: 3300-3100 (broad, HN-H), 2100 (N_3) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 3.80 [t, 2 H, H(2')], 4.35 [t, 2 H, H(1')], 7.26 [bs, 2 H, NH_2], 8.17 [bs, 2 H, H(2) and H(8)]; ^{13}C NMR (DMSO-d_6): ppm 42.35 [C(2')], 49.61 [C(1')], 118.61 [C(5)], 140.7 [C(8)], 149.5 [C(4)], 152.43 [C(2)], 155.03 [C(6)]. Mass spectrum (EI) calculated for $C_7H_8N_8$ *m/z* [$M^{+\cdot}$]: 204.0871; Found: 204.0871.

Anal. Calcd for $C_7H_8N_8$: C, 41.17; H, 3.95; N, 54.87. Found: C, 40.95; H, 3.97; N, 54.85

***bis*(Phenyl)phosphinanilide (3a)**.- To a boiling solution of diphenylphosphinic chloride (1.61 g, 6.8 mmol) in dry benzene (5 mL) was added dropwise a solution of aniline (1.27 g, 13.63 mmol) in dry benzene (5 mL) over 15-min. The solid formed almost immediately and persisted during additional (1 hr) heating at reflux (stirring). The mixture was allowed to cool (1 hr) and then was filtered. The precipitate was washed (water) and then dried; yield of crude **3a** was 1.64 g (82%). Recrystallization (abs. ethanol) gave colorless prisms of **3a** (1.1 g, 55%), mp 238.5-239.5° (lit[5] 239-240°). ^{1}H NMR (DMSO-d_6): δ 6.8-7.8 [m, 15 H, Ar-H], 8.3 [d, NH, $^2J_{P-H}$ = 11.6 Hz]; ^{13}C NMR (DMSO-d_6):δ 118.1 [d, C(4'), $^4J_{P-C}$ = 7 Hz], 120.4 [s, C(4)], 128.4 [s, C(3)], [d, C(3'), $^3J_{P-C}$ = 2.1 Hz], 131.5 [d, C(2), $^3J_{P-C}$

= 9.8 Hz], 131.7 [d, C(2'), $^2J_{P-C}$ = 2.4 Hz], 132.3 [d, C(1'), $^1J_{P-C}$ = 126.6 Hz], 141.9 [s, C(1)]; ^{31}P (DMSO-d_6): δ 17.4. Mass spectrum calculated for $C_{18}H_{16}NOP$ *m/z* [$M^{+\cdot}$]: 293; Found: [293 + 1]$^+$.

4-[*N-bis*(Phenyl)phosphoryl]aminopyridine (3b).- To 4-aminopyridine (0.500 g, 5.31 mmol), triethylamine (0.74 mL, 5.31 mmol) and toluene (1.6 mL) was added dropwise diphenylphosphinyl chloride (1.26 g, 5.31 mmol) in toluene (1.1 mL) over a 12-min period with stirring. A solid formed during the period (3 hr) of reflux. After cooling (1 hr), the mixture was filtered and the solid was washed (toluene). Chromatography [silica gel with $HCCl_3$:-H_3COH (10:1)] gave crude **3b** which was recrystallized ($HCCl_3$:ether; 1:10) to yield white **3b** (0.58 g, 39%), mp 172.5-173.5° (lit[7] 173-174°). ^1H NMR ($DCCl_3$): δ 6.86 [dd, H(3) $^3J_{H-H}$ = 4.9 Hz, $^4J_{P-H}$ = 1.4 Hz], 7.3-7.8 [m , 12 H, Ar-H], 8.0 [d, NH, $^2J_{P-H}$ = 6.2 Hz]; ^{13}C NMR ($DCCl_3$): ppm 113.1 [d, C(4'), $^4J_{P-C}$ = 7 Hz], 128.8 [d, C(3')], $^3J_{P-C}$ = 13.2 Hz], 130.1 [s, C(3)], 131.7 [d, C(2'), $^2J_{P-C}$ = 10.2 Hz], 132.5 [d, C(1'), $^1J_{P-C}$ = 2.5 Hz], 148.8 [s, C(4)], 149.8 [s, C(2)]; ^{31}P (DMSO-d_6): δ 19.7. Mass spectrum calculated for $C_{17}H_{15}N_2OP$ *m/z* [$M^{+\cdot}$]: 294; Found: [294 + 1]$^+$.

***bis*(Phenoxy)phosphinanilide (3c).**- As for **3a**, there was utilized diphenyl chlorophosphate (1.83 g, 6.8 mmol) in benzene (5 mL) and aniline (1.27 g, 13.63 mmol) in benzene (5 mL). Recrystallization (95% ethanol) gave **3c** (1.18 g, 54%), mp 130-131° (lit[8] 129-130°). ^1H NMR ($DCCl_3$): δ 6.9 [d, NH, $^2J_{P-H}$ = 17.1 Hz], 7.0-7.3 [m, 15 H, Ar-H]; ^{13}C NMR ($DCCl_3$): ppm 118.1 [d, C(4), $^5J_{P-C}$ = 7.7 Hz], 120.3 [d, C(4')], $^5J_{P-C}$ = 4.7 Hz], 122.3, 125.3, 129.3, [C(3)], 129.7 [C(2)], 138.9 [s, C(1)], 150.2 [d, C(1'), $^2J_{P-C}$ = 6.3 Hz]; ^{31}P ($DCCl_3$) ppm -6.2. Mass spectrum calculated for $C_{18}H_{16}NO_3P$ *m/z* [$M^{+\cdot}$]: 324; Found: [324 + 1]$^+$.

4-[*N-bis*(Phenoxy)phosphoryl]aminopyridine (3d).- As for **3b**, there was employed 4-aminopyridine (0.500 g, 5.31 mmol), triethylamine (0.74 g, 5.31 mmol), toluene (1.6 mL) and diphenyl chlorophosphate (1.43 g, 5.31 mmol). Recrystallization (abs. ethanol) gave **3d** (0.46 g, 29%), mp 197.5-199° (lit[9] 190-191°). ^1H NMR ($DCCl_3$): δ 7.14 [d , 2 H, H(3) $^3J_{H-H}$ = 6.34 Hz], 7.2-7.4 [m, 12 H, Ar-H], 8.4 [d, NH, $^2J_{P-H}$ = 5.2 Hz]; ^{13}C NMR ($DCCl_3$): ppm 112.4 [d, C(2'), $^3J_{P-C}$ = 2.2 Hz], 119.9 [d, C(4')], $^5J_{P-C}$ = 4.6 Hz], 125.4 [s, C(3')], 129.9, [C(3)], 149.6 [C(4)], 149.7 [d, C(2)], 150.1-150.4 [broad]; ^{31}P ($DCCl_3$): δ -7.9. Mass spectrum calculated for $C_{17}H_{15}N_2O_3P$ *m/z* [$M^{+\cdot}$] 326; Found: [326+ 1]$^+$.

***bis*(4-Methylphenyl)phosphinanilide (3e).**- As for **3a**, there was used *bis*(4-tolyl) chlorophosphate (2.02 g, 6.8 mmol) in benzene (5 mL) and aniline (1.27 g, 13.63 mmol) in benzene (5 mL) to give **3e** (0.58 g, 24%), mp 130-131° (lit[6] 125°). ^1H NMR ($DCCl_3$): δ 2.2 [s, 3 H, CH_3], 6.7 [d, NH, $^2J_{P-H}$ = 10.6 Hz], 6.9-7.3 [m, 13 H, Ar-H]; ^{13}C NMR ($DCCl_3$): ppm 118.1 [d, C(4), $^5J_{P-C}$ = 7.6 Hz], 120.1 [d, C(4')], $^5J_{P-C}$ = 4.0 Hz], 122.2, 129.3, 130.1 [C(2)], 134.8, 139.0 [s, C(1)], 148.1 [d, C(1'), $^2J_{P-C}$ = 6.6 Hz]; ^{31}P ($DCCl_3$): δ -5.8. Mass spectrum calculated for $C_{20}H_{22}NO_3P$ *m/z* [$M^{+\cdot}$]: 353; Found: [353 + 1]$^+$.

4-[*N-bis*(4-Methylphenoxy)phosphoryl]aminopyridine (3f).- As for **3b,** there were used 4-aminopyridine (0.500 g, 5.31 mmol), triethylamine (1.57 g, 5.21 mmol), toluene (1.6 mL) and *bis*(4-tolyl) chlorophosphate (1.57 g, 5.31 mmol) to give **3f** (0.92 g, 48%), mp 226-227° (lit[8] 215-216°). ^1H

NMR (DMSO-d_6): δ 2.3 [s, 6 H, 2 CH_3], 7.1-7.2 [m, 12 H, Ar-H], 8.3 [d, NH, $^2J_{P-H}$ = 5.4 Hz]; interestingly, H(3) was not cleanly observed but was apparently under the signal pattern at δ 7.1-7.2; ^{13}C NMR (DMSO-d_6): ppm 20.1 [d, CH_3, $^6J_{P-C}$ = 2.1 Hz], 112.3 [d, C(2'), $^3J_{P-C}$ = 8.1 Hz], 119.6 [d, C(3')], 119.7 [s, C(4')], 130.2 [s, C(2)], 134.0 [s, C(3)], 147.5 [C(4), $^2J_{P-C}$ = 6.4 Hz], 150.3 [d, C(1')], $^4J_{P-C}$ = 1.4 Hz]; ^{31}P (DMSO-d_6): δ -41.1. Mass spectrum calculated for $C_{19}H_{19}N_2O_3P$ *m/z* [$M^{+\cdot}$]: 354; Found: [354+ 1]$^+$.

4-[*N-bis*(Phenoxy)phosphoryl]aminoquinaldine (3g).- As for **3f**, 4-aminoquinaldine (1.0 g, 6.32 mmol), triethylamine (1.76 mL, 12.64 mmol), toluene (2 mL) and diphenyl chlorophosphate (1.69 g, 6.32 mmol) in toluene (1.2 mL) were mixed. Recrystallization (benzene) gave **3g** (0.38 g, 15%), mp 159-160°. IR: 3260 (N-H), 1225 (P=O), 1200 (C-O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.5 [s, 3 H, CH_3], 6.9-7.7 [m, 15 H, Ar-H], 8.2 [d, NH, $^2J_{P-H}$ = 7.9 Hz]; ^{13}C NMR (DMSO-d_6): ppm 19.6 [s, CH_3], 107.7 [d, C(3), $^3J_{P-C}$ = 2.1 Hz], 120.1 [d, C(3'), $^4J_{P-C}$ = 4.7 Hz], 123.7, 124.4, 125.0 [d, C(4')], $^5J_{P-C}$ = 4.1 Hz], 129.4 [s, C(2')], 132.1, 132.2, 138.7, 150.2 [s, C(4)], 151.7 [d, C(1'), $^2J_{P-C}$ = 3.3 Hz], 164.7 [s, C(2)]; ^{31}P NMR (DMSO-d_6): δ -0.6. Mass spectrum calculated for $C_{22}H_{19}N_2O_3P$ *m/z* [$M^{+\cdot}$]: 390.4. Found: [390 + 1].

Anal. Calcd for $C_{22}H_{19}N_2O_3P$: N, 7.17; P, 7.93. Found: N, 7.11; P, 7.90.

4-[*N-bis*(4-Methylphenoxy)phosphoryl]aminoquinalidine (3h).- As for **3g**, there were employed 4-aminoquinaldine (1.0 g, 6.32 mmol), triethylamine (1.76 mL, 12.64 mmol), toluene (2 mL) and *bis*(4-tolyl) chlorophosphate (1.87 g, 6.32 mmol) in toluene (1.3 mL). Recrystallization (benzene:ether) yielded **3h** (0.52 g, 20%), mp 180-181°. IR: 3260 (N-H), 1225 (P=O), 1200 (C-O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.2 [s, 6 H, 2 CH_3], 2.4 [s, 3 H, CH_3], 6.9-7.7 [m, 13 H, Ar-H], 8.2 [d, NH, $^2J_{P-H}$ = 8.24 Hz] ^{13}C NMR (DMSO-d_6): ppm 19.6 [s, CH_3], 20.1 [d, CH_3', $^6J_{P-C}$ = 2.56 Hz], 107.6 [s, C(3)] 117.9, 119.8 [d, C(3'), $^2J_{P-C}$ = 4.6 Hz], 124.3, 125.1, 129.6 [s, C(2')], 132.1, 132.6, [s, C(4')], 138.6, 149.5 [d, C(1'), $^2J_{P-C}$ = 3.2 Hz], 149.9 [s, C(4)], 164.4 [s, C(2)]; ^{31}P NMR (DMSO-d_6): δ -1.5.

Anal. Calcd for $C_{24}H_{23}N_2O_3P$: N, 6.69; P, 7.40. Found: N, 6.44; P, 7.24.

REFERENCES

1. C. H. Kim, B. Y. Luh, P. F. Misco, J. J. Branson, M. J. M. Hitchcock, I. Ghazzouli and J. C. Martin , *J. Med. Chem.* **33**, 1207 (1990).

2. Certain phosphorylated guanines have recently been shown to inhibit human erythrocyte purine nucleoside phosphorylase; see J. L. Kelley, J. A. Lin, E. W. McLean, J. V. Tuttle *J. Med. Chem.*, **36**, 3455 (1993). For two other peripherally related examples, see R. Charubala and W. Plfeiderer *Heterocycles*, **15**, 761 (1981) and R. Vinayak, F. Hassske and M. J. Robins *J. Heterocyclic Chem.*, **30,** 1181 (1993).

3. R. L. Heinrikson and Z. Zhang, *Biochemistry*, **30**, 8717 (1991).

4. U. Nasuo, K. Koichi and K. Masatsngu, *Die Makromol. Chem.*, **120**, 13 (1968).

5. E. Slusarska and A. Zwierzak, *Synthesis*, 717 (**1980**).

6. W. Autenrieth and A. Geyer, *Ber.*, **41**, 146 (1908).

7. V. Gutman, G. Mortl and K. Utary, *Monatsh.*, **93**, 1114 (1962).

8. I. N. Zhmurova, I. Voitsekhovskaya and T. Yu, *J. Gen. Chem. USSR*, **31**, 3495 (1961).

9. G. F. Dregval. A. P. Martynyuk and N. V. Kovalenko, *Khim. Geterotsikl. Soedin., Sb. 1; Azot-soderzhashchie Geterotsikly*, 236 (**1967**); *Chem. Abstr.*, **70**, 87504j (1969).

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