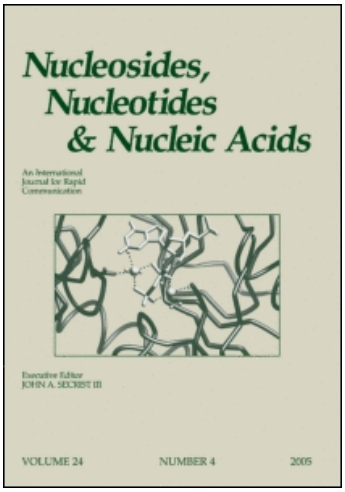

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Wei Chen[a]; Michael T. Flavin[a]; Robert Filler[b]; Ze-Qi Xu[a]
[a] MediChem Research Inc, Lemont, IL, USA [b] Department of Chemistry, Illinois Institute of Technology, Chicago, IL, USA

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AN IMPROVED SYNTHESIS OF 9-[2-(DIETHOXYPHOSPHONOMETHOXY)ETHYL]ADENINE AND ITS ANALOGUES WITH OTHER PURINE BASES UTILIZING THE MITSUNOBU REACTION

Wei Chen, Michael T. Flavin, Robert Filler[#], and Ze-Qi Xu*

MediChem Research, Inc., 12305 South New Avenue, Lemont, IL 60439, USA
[#] Department of Chemistry, Illinois Institute of Technology, Chicago, IL 60616, USA

Abstract: *Unprotected adenine, 6-chloropurine, 2,6-diaminopurine, and 2-amino-6-chloropurine have been directly coupled with 2-(diethoxyphosphonomethoxy)ethanol under Mitsunobu reaction conditions to provide acyclic phosphonate nucleotide analogues which are intermediates for antiviral agents such as PMEA.*

In the course of our research concerning new antitumor and antiviral agents, we identified the Mitsunobu reaction as an efficient method for direct coupling of adenine to a variety of free alcohol side chains. Although the Mitsunobu reaction has been widely used in the synthesis of nucleosides and nucleotides starting with protected purines and pyrimidines,[1-3] our literature survey identified only one example in which free adenine was employed in the Mitsunobu reaction.[4] Herein we wish to communicate our results concerning the synthesis of 9-[2-(diethoxyphosphonomethoxy)ethyl]adenine under Mitsunobu conditions, as well as the application of this method to the synthesis of other purine derivatives. Hydrolysis of these phosphonate nucleotide analogues should lead to formation of antiviral agent 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) and its analogues.

PMEA and (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine [(*S*)-HPMPA] have been reported to exhibit potent and selective activity against a broad spectrum of viruses,[5,6] including herpes simplex virus (types 1 and 2), varicella zoster virus, cytomegalovirus, hepatitis B virus,[7] as well as human immunodeficiency virus (HIV).[8-10] These compounds have been prepared by classical coupling of adenine,[11-13] or its precursors such as 6-chloropurine, with an appropriate phosphonate side chain (**2**) in the presence of a base such as NaH, K_2CO_3, or Cs_2CO_3 at elevated temperatures, followed by

hydrolysis. However, coupling reactions under these basic conditions often yield both N^7- and N^9-substituted derivatives;[11-13] the adenine salt generated during the reaction course also attacks the phosphonate ethyl ester to form N^9-ethyladenine.[13]

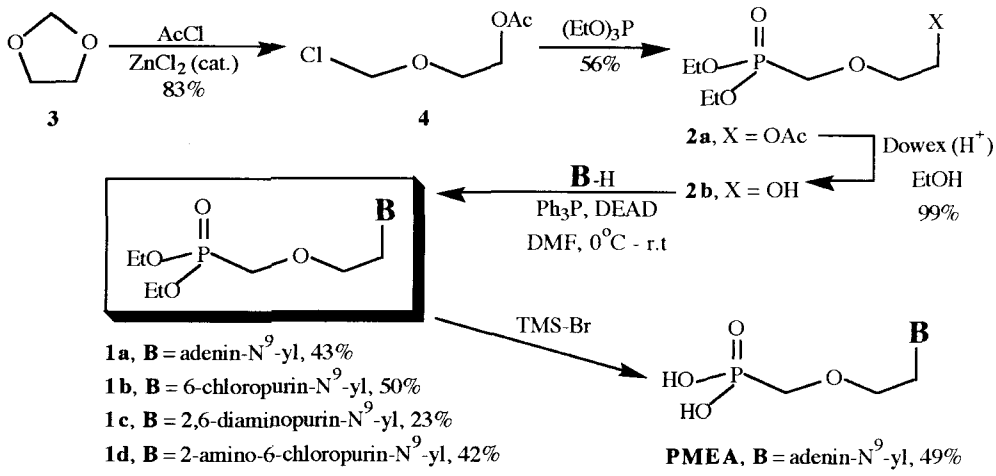
Thus, the free alcohol side chain **2b**, required for the Mitsunobu reaction, was prepared by literature procedures in a 3-step process, starting from 1,3-dioxolane, **3**;[11] however, a modified method[14,15] utilizing a catalytic amount of $ZnCl_2$ was found to be more effective for acylative cleavage of **3** to yield chloromethyl ether **4** (**Scheme 1**). Coupling of **2b** with adenine in THF in the presence of Ph_3P and DEAD formed the desired N^9-substituted derivative **1a** in only 5% yield. The low yield may be due to the insolubility of adenine in THF. After replacement of THF with DMF, compound **1a** was produced in 43% yield without any detection of the N^7- derivative or the N^9-ethyladenine.

The same procedure was applied to 6-chloropurine to afford compound **1b** in 50% yield. In contrast, when 2,6-diaminopurine was coupled with the side chain **2b** under the same conditions, N^9-ethyl-2,6-diaminopurine was the major product. It has been found that formation of the desired coupling product **1c** depends upon the reaction temperature. Compound **1c** became the predominant product, with minimal formation of N^9-ethyl-2,6-diaminopurine, when the reaction was carried out at -20°C (**Scheme 1**). The corresponding 2-amino-6-chloropurine derivative **1d** was also prepared at -10°C in 42% yield. The synthesized phosphonate nucleotide analogues (**1a** - **1d**) afforded satisfactory analytical and spectroscopic analyses. Hydrolysis of **1a** with TMS-Br led to PMEA.[11-13]

EXPERIMENTAL SECTION

General. Melting points were taken on a Laboratory Devices Mel-Temp apparatus and are corrected. TLC analyses were performed on analytical thin layer plates coated with silica gel 60 F_{254} (Merck) and components were visualized under UV light and/or stained with iodine. Column chromatography was performed using silica gel 60 (70-230 mesh from EM Science). ^1H and ^{13}C NMR spectra were recorded on a Varian VX-300 NMR spectrometer or a 300 MHz Varian Gemini 2000 NMR spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as an internal standard and were recorded in $CDCl_3$ solution unless otherwise stated. IR and mass spectra were recorded on a Midac M series FT-IR and a Finnegan MAT 90 mass spectrometer, respectively. UV spectra were measured in MeOH or aqueous solutions on a Hitachi U-2000 UV-VIS spectrophotometer. Elemental analyses were carried out at Midwest Microlab, Indianapolis, Indiana. All chemical reagents and anhydrous solvents were purchased from Aldrich Chemical Co.

1-Acetoxy-2-chloromethoxyethane (4).[15,16] To a 25 mL three-necked round bottom flask equipped with an addition funnel, a condenser, a thermometer, and a magnetic



Scheme 1

stirrer were added 1,3-dioxolane (5.0 g, 67.5 mmol) and a few crystals of freshly fused zinc chloride under N_2. A solution of acetyl chloride (5.3 g, 67.5 mmol) in anhydrous hexane (5 mL) was added dropwise to the stirred reaction mixture over 30 min. An exothermic reaction occurred immediately and the reaction temperature was maintained below 50 °C by using an ice-water bath. After addition, the reaction mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure and the residue was distilled under vacuum to afford **4** (8.6 g, 83% yield), bp. 57-59 °C/0.3 mm Hg (Lit[16] 70-72 °C/4.5 mm Hg). ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 2 H, CH_2Cl), 4.27 (m, 2 H, CH_2OAc), 3.90 (m, 2 H, CH_2O), 2.10 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.78 (CO), 82.51 (CH_2Cl), 68.00 (CH_2OAc), 62.14 (CH_2O), 20.79 (CH_3); IR (neat, cm^{-1}) 1742 (vs, C=O); MS (CI) *m/e* 123 and 125 (21.4, 6.3, M-CO), 117 (100, M-Cl).

Diethyl 2-Acetoxyethoxymethanephosphonate (2a).[11,16] 1-Acetoxy-2-chloromethoxyethane, **4**, (96.9 g, 0.583 mol) was added under N_2 to a 500 mL three-necked round bottom flask equipped with an addition funnel, a thermometer, and a magnetic stirrer. Triethylphosphite (92.5 g, 0.607 mol) was added dropwise to the stirred solution over a 1 h period. The reaction mixture was heated at 110 °C in an oil-bath for 1 h and then gradually cooled to ambient temperature. Vacuum distillation provided **2a** (82.1 g, 55.4% yield) as a colorless liquid, bp. 148-153 °C/0.6 mm Hg (Lit.[16] 136-137.5 °C/1.5 mm Hg). ^{1}H NMR ($CDCl_3$) δ 4.24 (t, J = 4.7 Hz, 2 H, CH_2OAc), 4.17 (q, J = 7.6 Hz, 4 H, 2 CH_2O), 3.85 (d, J = 8.2 Hz, 2 H, CH_2P), 3.81 (t, J = 4.7 Hz, 2 H, CH_2O), 2.08 (s, 3 H,

CH_3CO), 1.36 (t, J = 7.1 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 170.86 (CO), 70.97 (d, $^2J_{C,P}$ = 10.5 Hz, CH_2O), 65.25 (d, $^1J_{C,P}$ = 166.2 Hz, CH_2P), 63.20 (CH_2OAc), 62.49 (d, $^3J_{C,P}$ = 6.5 Hz, CH_2O), 20.85 (CH_3CO), 16.44 (d, $^3J_{C,P}$ = 5.7 Hz, CH_3); IR (neat, cm^{-1}) 1740 (vs, C=O), 1238 (vs, P=O), 1049 and 1033 (vs, P-O-C and C-O-C); MS (CI) *m/e* 255 (76.9, M+1), 213 (30.3, M-CH_2CO+1), 167 (50.4, M-C_2H_5O-CH_3CO+1), 166 (51.4, M-C_2H_5O-CH_3CO), 153 (100, M-C_2H_5O-CH_2CO-CH_3+1), 139 (68.7, M-C_2H_5O-CH_2CO-C_2H_5+1), 125 (96.6, M-2 C_2H_4-$CH_3CO_2CH_2$); Anal. calcd. for $C_9H_{19}O_6P$: C, 42.52; H, 7.53. Found: C, 42.32; H, 7.61.

Diethyl 2-Hydroxyethoxymethanephosphonate (2b).[11] To a 500 mL single-necked round bottom flask equipped with a condenser were added diethyl 2-acetylethoxy-methanephosphonate, **2a**, (30 g, 0.12 mol), ethanol (150 mL) and prewashed, with ethanol (4 x 50 mL), Dowex 50WX8 (H^+-form, 15 g). The mixture was heated to reflux for 18 h and completion of the reaction was determined by TLC analysis. The mixture was filtered, the resin washed with ethanol (3 x 30 mL), and the combined filtrates concentrated under reduced pressure. The residue was co-evaporated with anhydrous toluene (2 x 50 mL) under reduced pressure and dried under vacuum overnight to yield **2b** (24.8 g, 99% yield). ^1H NMR ($CDCl_3$) δ 4.19 (apparent quintet, J = 7.3 Hz, 4 H, 2 CH_2O), 3.89 (s, 1 H, OH), 3.87 (d, J = 8.1 Hz, 2 H, CH_2P), 3.70-3.77 (m, 4 H, 2 CH_2O), 1.36 (t, J = 7.1 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 75.7 (d, $^2J_{C,P}$ = 10.1 Hz, CH_2O), 65.28 (d, $^1J_{C,P}$ = 166.9 Hz, CH_2P), 62.59 (d, $^3J_{C,P}$ = 6.6 Hz, CH_2O), 61.46 (CH_2OH), 16.43 (d, $^3J_{C,P}$ = 5.7 Hz, CH_3); IR (neat, cm^{-1}) 3408 (vs, broad, OH), 1233 (vs, P=O), 1053 and 1024 (vs, P-O-C and C-O-C); MS (CI) *m/e* 213 (100, M+1); Anal. calcd. for $C_7H_{17}O_5P$: C, 39.63; H, 7.86. Found: C, 39.23; H 7.94.

9-(2-Diethoxyphosphonomethoxyethyl)adenine (1a).[11] A mixture of adenine (3.2 g, 23.6 mmol), diethyl 2-hydroxyethoxymethanephosphonate, **2b**, (5.0 g, 23.6 mmol) and triphenylphosphine (9.2 g, 35.4 mmol) in anhydrous DMF (70 mL) was stirred at ambient temperature under N_2 for 30 min. The reaction mixture was then cooled to 0 °C and diethyl azodicarboxylate (DEAD, 6.2 g, 35.4 mmol) in anhydrous DMF (25 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature gradually and stirred overnight. Any unreacted adenine was filtered and the filtrate concentrated to dryness under vacuum. The crude product was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH (9:1), to afford 3.3 g (43% yield) of the desired N^9-product **1a**. mp. 136-137 °C after recrystallization from EtOAc (Lit.[11] 137 °C). ^1H NMR ($CDCl_3$) δ 8.35 (s, 1 H, H-2), 7.96 (s, 1 H, H-8), 6.28 (s, 2 H, NH_2), 4.42 (t, J = 4.9 Hz, 2 H, CH_2N), 4.10 (apparent quintet, J = 7.1 Hz, 4 H, 2 CH_2O), 3.94

(t, J = 4.9 Hz, 2 H, CH_2O), 3.78 (d, J = 8.4 Hz, 2 H, CH_2P), 1.30 (t, J = 7.1 Hz, 6 H, 2 CH_3). ^{13}C NMR ($CDCl_3$) δ 155.67, 152.89, 149.83, 141.37, 119.32 (adenine ring carbons), 71.24 (d, $^2J_{C,P}$ = 10.6 Hz, OCH_2CH_3), 65.27 (d, $^1J_{C,P}$ = 166.7 Hz, CH_2P), 62.46 (d, $^3J_{C,P}$ = 6.6 Hz, CH_2O), 43.40 (CH_2N), 16.42 (d, $^3J_{C,P}$ = 5.7 Hz, CH_3); UV (MeOH) λ_{max} 260 (12,900) nm. IR (KBr, cm^{-1}) 3275 and 3111 (vs, broad, NH_2), 1671 and 1603 (vs, adenine ring), 1240 (vs, P=O), 1045 and 1024 (vs, P-O-C and C-O-C); MS (CI) *m/e* 330 (100, M+1); Anal. calcd. for $C_{12}H_{20}N_5O_4P$: C, 43.75; H, 6.12; N, 21.27. Found: C, 43.80; H, 6.03; N, 21.23.

6-Chloro-9-(2-diethoxyphosphonylmethoxyethyl)purine (1b). The procedure employed for synthesis of **1a** was followed for synthesis of **1b**. Thus, 6-chloropurine (0.73 g, 4.72 mmol) was treated with diethyl 2-hydroxyethoxymethanephosphonate **2b** (1.0 g, 4.72 mmol) in the presence of triphenylphosphine (1.6 g, 6.25 mmol) and diethyl azodicarboxylate (1.1 g, 6.25 mmol) in anhydrous DMF (14 mL). After purification by silica gel column chromatography eluting with CH_2Cl_2/MeOH (19:1), 0.82 g (50% yield) of the desired product **1b** was obtained as a thick oil. ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H, H-2), 8.27 (s, 1 H, H-8), 4.52 (t, J = 4.9 Hz, 2 H, CH_2N), 4.10 (apparent quintet, J = 7.5 Hz, 4 H, 2 OCH_2CH_3), 3.95 (t, J = 4.9 Hz, 2 H, CH_2O), 3.78 (d, J = 11.1 Hz, 2 H, CH_2P), 1.29 (t, J = 7.0 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 151.79, 151.65, 150.87, 146.19, 131.38 (purine ring carbons), 70.66 (d, $^2J_{C,P}$ = 10.1 Hz, OCH_2CH_3), 65.21 (d, $^1J_{C,P}$ = 166.9 Hz, CH_2P), 62.44 (d, $^3J_{C,P}$ = 6.5 Hz, CH_2O), 43.88 (CH_2N), 16.41 (d, $^3J_{C,P}$ = 4.1, CH_3); IR (KBr, cm^{-1}) 1593 and 1562 (s, purine ring), 1225 (vs, P=O), 1026 (vs, shoulder, P-O-C and C-O-C); MS (CI) m/e 351 and 349 (67.8, 100, M+1), 315 (73.6, M-Cl+2), 313 (25.5, M-Cl); UV (MeOH) λ_{max} 264 (9,593) nm; Anal. Calcd. for $C_{12}H_{18}ClN_4O_4P$: C, 41.31; H, 5.20; N 16.07. Found: C, 41.02; H, 5.32; N, 15.43.

2,6-Diamino-9-(2-diethoxyphosphonomethoxyethyl)purine (1c). A mixture of 2,6-diaminopurine (350 mg, 2.36 mmol), diethyl 2-hydroxyethoxymethanephosphonate **2b** (500 mg, 2.36 mmol) and triphenylphosphine (930 mg, 3.54 mmol) in anhydrous DMF (10 mL) was stirred at ambient temperature under N_2 for 30 min. The reaction mixture was then cooled to -30 °C and diethyl azodicarboxylate (0.56 mL, 3.54 mmol) was added dropwise at such a rate that the reaction temperature was maintained below -25 °C. The reaction mixture was stirred at that temperature for 2 h and then allowed to warm to ambient temperature gradually and stirred overnight. Any unreacted 2,6-diaminopurine was removed by filtration and the solvent removed under vacuum. The crude product was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH (9:1), to afford 190 mg (23 % yield) of the desired N^9- product **1c**. An

analytical sample was obtained from recrystallization using EtOAc/MeOH (5:1). mp. 152-154 °C. ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1 H, H-8), 6.67 (s, 2 H, NH_2), 5.79 (s, 2 H, NH_2), 4.13 (t, J = 5.0 Hz, 2 H, CH_2N), 3.95 (apparent quintet, J = 7.3 Hz, 4 H, 2 OCH_2CH_3), 3.84 (d, J = 8.4 Hz, 2 H, CH_2P), 3.81 (t, J = 5.0 Hz, 2 H, CH_2O), 1.17 (t, J = 7.1 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 160.01, 156.08, 151.87, 138.79, 114.03 (purine ring carbons), 71.36 (d, $^2J_{C,P}$ = 10.8 Hz, OCH_2CH_3), 65.26 (d, $^1J_{C,P}$ = 166.5 Hz, CH_2P), 62.50 (d, $^3J_{C,P}$ = 6.5 Hz, CH_2O), 42.92 (CH_2N), 16.44 (d, $^3J_{C,P}$ = 5.7 Hz, CH_3); UV (MeOH) λ_{max} 255 (10,300), 281 (12,000) nm; IR (KBr, cm^{-1}) 3345 and 3177 (s, broad, NH_2), 1669, 1636 and 1599 (s, purine ring), 1242 (s, P=O), 1020 (s, P-O-C); MS (CI) *m/e* 345 (100, M+1), 344 (29.5, M^+); Anal. calcd. for $C_{12}H_{21}N_6O_4P \cdot 1/4H_2O$: C, 41.32; H, 6.21; N, 24.09. Found: C, 41.36; H, 6.02; N, 23.72.

2-Amino-6-chloro-9-(2-diethoxyphosphonomethoxyethyl)purine (1d). A mixture of 2-amino-6-chloropurine (890 mg, 4.2 mmol), diethyl 2-hydroxyethoxymethanephosphonate **2b** (710 mg, 4.2 mmol) and triphenylphosphine (1.65 g, 6.3 mmol) in anhydrous DMF (10 mL) was stirred at ambient temperature under N_2 for 30 min. The reaction mixture was then cooled to -10 °C and diethyl azodicarboxylate (0.67 mL, 4.2 mmol) in DMF (2 mL) was added dropwise at such a rate that the reaction temperature was maintained at -10 °C. The reaction mixture was stirred at that temperature for 2 h and then allowed to warm to ambient temperature gradually and stirred for 5 h. Any unreacted 2-amino-6-chloropurine was removed by filtration and the solvent removed under vacuum. The crude product was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH (9:1), to afford 650 mg (42 % yield) of the desired N^9-product **1d**. ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H, H-8), 5.20 (s, broad, 2 H, NH_2), 4.30 (t, J = 4.8 Hz, 2 H, CH_2N), 4.12 (dq, J = 8.4 Hz, J = 7.0 Hz, 4 H, 2 OCH_2CH_3), 3.92 (t, J = 5.0 Hz, 2 H, CH_2O), 3.79 (d, J = 8.4 Hz, 2 H, CH_2O), 1.30 (t, J = 7.1 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 159.20, 153.78, 151.20, 143.29, 124.99 (purine ring carbons), 70.82 (d, $^2J_{C,P}$ = 10.3 Hz, OCH_2CH_3), 65.17 (d, $^1J_{C,P}$ = 166.0 Hz, CH_2P), 62.42 (d, $^3J_{C,P}$ = 5.7 Hz, CH_2O), 43.19 (CH_2N), 16.27 (d, $^3J_{C,P}$ = 5.7 Hz, CH_3); UV (MeOH) λ_{max} 247 (14,600), 310 (18,300) nm; IR (KBr, cm^{-1}) 3327 and 3210 (m, broad, NH_2), 1612 and 1562 (vs, purine ring), 1229 (s, P=O), 1026 (s, P-O-C); MS (CI) *m/e* 366 and 364 (40.5, 100, M+1), 3328 (22.3, M-Cl); Anal. calcd. for $C_{12}H_{19}ClN_5O_4P$: C, 39.63; H, 5.26; N, 19.25. Found: C, 39.53; H, 5.48; N, 18.99.

9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA). 9-[2-(Diethylphosphonomethoxy)ethyl]adenine, **1a** (100 mg, 0.30 mmol), was dissolved in anhydrous

dichloromethane (2 mL). Bromotrimethylsilane (0.4 mL, 3.0 mmol) was added dropwise to the stirred solution at ambient temperature. After the addition was completed, the reaction mixture was stirred for 2.5 h, whereupon the mixture was evaporated under vacuum to afford a white foam solid, mp. 145-150 °C, which was then dissolved in H_2O (1 mL). Acetone (2 mL) was added to the aqueous solution and a white solid precipitate was formed and collected by filtration to afford 40 mg (49% yield) of the desired product PMEA. mp. 278 °C (dec.) (Lit.[11] did not melt up to 250 °C). ^1H NMR (DMSO-d_6) δ 8.15 and 8.14 (2 s, 2 H, H-2, H-8), 7.35 (s, 2 H, NH_2, disappeared with D_2O exchange), 4.32 (t, J = 5.1 Hz, 2 H, CH_2N), 3.87 (t, J = 5.2 Hz, 2 H, CH_2O), 3.60 (d, J = 8.7 Hz, 2 H, CH_2P); IR (KBr, cm^{-1}) 3403-2733 (s, broad, OH and NH_2), 1694 (vs) and 1599 (m) (purine ring), 1225 (vs, P=O); MS (FAB) *m/e* 274 (100, M+1); UV (H_2O) λ_{max} 260 (13,900) nm; Anal. calcd. for $C_8H_{12}N_5O_4P \cdot 1/4H_2O$: C, 34.60; H, 4.54; N, 25.22. Found: C, 34.58; H, 4.66; N, 24.66.

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