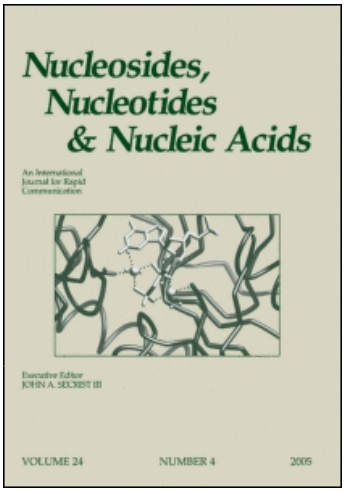

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Robert Vince[a]; Phuong T. Pham[a]
[a] Department of Medicinal Chemistry, College of Pharmacy, Minneapolis, MN

To cite this Article Vince, Robert and Pham, Phuong T.(1995) 'The Synthesis and Biological Evaluation of Sulfamoyl Nucleosides Related to Carbovir and AZT', Nucleosides, Nucleotides and Nucleic Acids, 14: 9, 2051 — 2060
To link to this Article: DOI: 10.1080/15257779508010723
URL: http://dx.doi.org/10.1080/15257779508010723

NUCLEOSIDES & NUCLEOTIDES, 14(9&10), 2051-2060 (1995)

THE SYNTHESIS AND BIOLOGICAL EVALUATION OF SULFAMOYL NUCLEOSIDES RELATED TO CARBOVIR AND AZT

Robert Vince* and Phuong T. Pham

Department of Medicinal Chemistry
College of Pharmacy
308 Harvard St. S.E.
University of Minnesota
Minneapolis, MN 55455-0343

Abstract. A series of 5'-O-sulfamoylated carbocyclic 2',3'-dideoxy nucleosides was synthesized and evaluated for antitumor and anti-HIV activities. In this study, we have combined the phosphate mimicking features of the sulfamoyl group with our previously reported antiviral carbocyclic nucleoside, carbovir. In a related strategy, the sufamoyl moiety was used as a replacement for the α-phosphate of AZT-triphosphate in an analog designed to examine a membrane permeable HIV reverse transcriptase inhibitor. Some of the analogs exhibited significant in vitro anticancer activity.

Introduction

Since the discovery of nucleocidin,[1,2] a naturally occurring 5'-sulfamoylated nucleoside, many nucleoside analogs containing the 5'-sulfamoyl group have been examined. These agents have been shown to exhibit antitumor,[3,4] antibacterial,[3,5,6] antiviral,[7,8-10] antiparisitic,[11-13] and herbicidal[5] activities. In a previous study, the first series of carbocyclic 5'-sulfamoylated nucleosides were reported from our laboratory.[14] The carbocyclic agents chosen each contained an adenine-like (6-substituted purine) base and a carbocyclic ribofuanosyl sugar moiety. In vitro studies demonstrated very potent cytotoxicities against P388 mouse leukemia cells. It was also determined that these compounds have a direct effect on protein biosynthesis.[14] These observations are consistant with previous studies on nucleocidin and related analogs in which the investigators concluded that the sulfamoyl nucleosides were acting as adenosine monophosphate analogs and interfering with the biosynthesis of aminoacyl-tRNA's.[3] Further evidence that a sulfamoyl moiety can substitute for a phosphate in certain enzyme

systems has recently been demonstrated by using crystal structures of seryl-tRNA synthetase.[15]

In this study, we have combined the phosphate mimicking features of the sulfamoyl group with our previously reported antiviral carbocyclic nucleoside, carbovir.[16,17] In a related strategy, the sulfamoyl moiety was used as a replacement for the α-phosphate of AZT-triphosphate in an analog designed to examine a membrane permeable HIV reverse transcriptase inhibitor. We have also incorporated a phosphonate moiety as an isosteric γ-phosphate in the same molecule. In 1986, an acyclo phosphonate nucleoside analog, (S)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine, was found to be active against a variety of viruses.[18] Since that time, the use of the membrane permeable phosphonate moiety has been intensively studied in the the design of more useful antiviral agents. It therefore seemed reasonable that the AZT analog incorporating both the sulfamoyl group and a phosphonate may have binding capacity for the HIV reverse transcriptase enzyme.

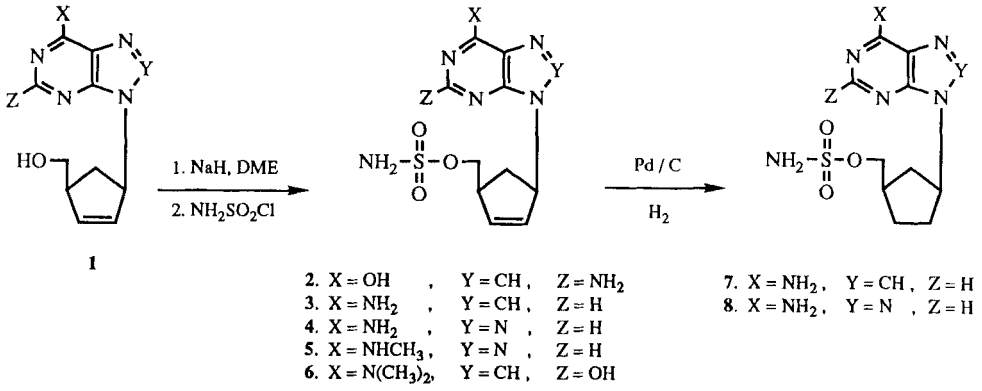
Chemistry

Carbovir **1** and the related starting carbocyclic dideoxydidehydro nucleosides were prepared as described previously.[17] The general synthetic procedure involved the reaction of sulfamoyl chloride with the carbocyclic nucleosides as illustrated in Scheme 1. Catalytic reduction of the cyclopentene moiety gave the corresponding saturated analogs as illustrated by the preparation of **7** and **8**.

The triphosphate analog of AZT was prepared as outlined in Scheme 2. Diethyl hydroxymethylphosphonate **9** was prepared as previously described.[19] Reaction of chlorosulfonyl isocyanate with **9** gave the intermediate **10** which was subsequently reacted with AZT in the presence of pyridine to yield the diethoxy blocked triphosphate analog **11**. The target compound was obtained from the diester using bromotrimethylsilane followed by hydrolysis with ammonium hydroxide. The ammonium salt was converted to the free phosphonate **12** using a weakly acidic amberlite resin.

Results

The compounds in Table 1 were evaluated for cytotoxicity against P388 mouse leukemia cells.[20] The adenine compound **3** and the corresponding 8-aza analog **4** manifested very potent activity (IC_{50}'s of 0.2 and 0.1 μg/mL). Methylation of the 6 amino group, as in compounds **5** and **6**, severely decreased cytotoxicity. The IC_{50} values of **7** and **8** indicate that reduction of the double bond in compounds **3** and **4** slightly decreases activity. It is interesting to note that replacement of the adenine moiety with a guanine greatly decreases activity. Thus, a preference for the adenine form seems to exist for the cytotoxic effect of the sulfamoyl compounds. The 5'-sulfamoylated compounds were found to be

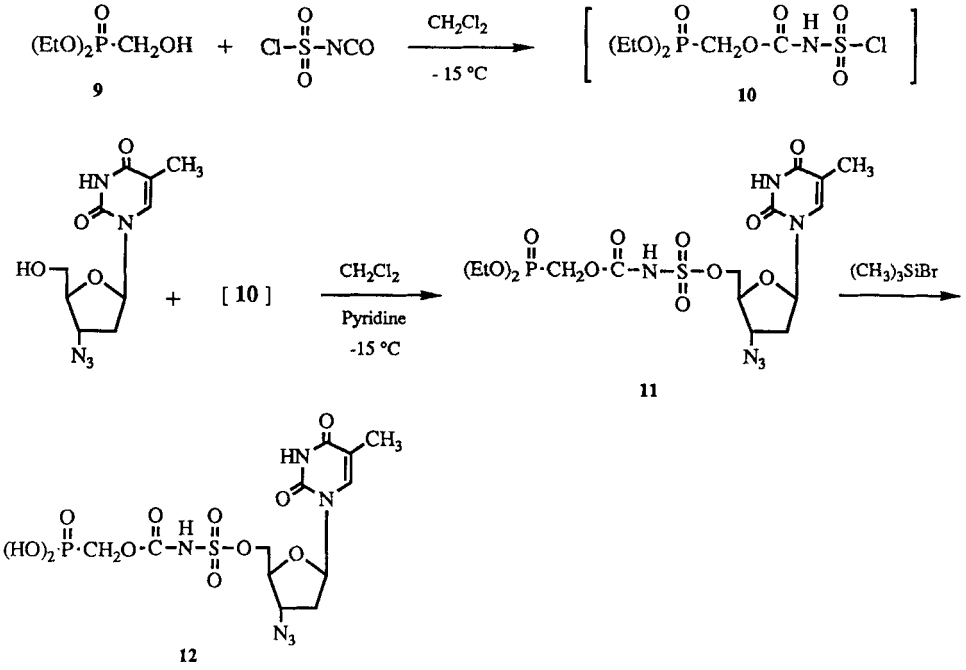


1

2. X = OH , Y = CH , Z = NH_2
3. X = NH_2 , Y = CH , Z = H
4. X = NH_2 , Y = N , Z = H
5. X = $NHCH_3$, Y = N , Z = H
6. X = $N(CH_3)_2$, Y = CH , Z = OH

7. X = NH_2 , Y = CH , Z = H
8. X = NH_2 , Y = N , Z = H

Scheme 1



9

10

11

12

Scheme 2

TABLE 1. Cytotoxicity to P388 Leukemia Cells

Cpd.	IC_{50} (μg/mL)
2	>50
3	0.20
4	0.15
5	>100
6	25
7	0.78
8	0.80

significantly more potent than the corresponding 5'-hyroxylated agents (IC_{50}'s >100 μg/mL). Thus, the cytotoxic activity of the sulfamoyl nucleosides was not a result of hydrolysis of the 5'-sulfamoyl group to the hydroxy compounds. Antiviral screening revealed that none of the compounds exhibited anti-HIV activity.

The AZT triphosphate analog **12** was tested as an inhibitor of recombinant HIV-1 reverse transcriptase using poly(rA):$p(dT)_{12-18}$ template.[21] The IC_{50} for **12** in this assay was 300 μM whereas the IC_{50} for AZT triphosphate was 1 μM. Although the binding of **12** was weak compared to AZT triphosphate, the results indicate that the modified phosphate moiety does exhibit binding recognition. Thus, no measurable inhibition of HIV reverse transcriptase was observed with unphosphorylated AZT.

Experimental. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Melting points were determined on a Mel-Temp apparatus and are corrected. Nuclear magnetic resonance spectra were obtained on a General Electric 300. IR spectra were determined with KBr pellets on a Perkin-Elmer 281 spectrometer, and UV spectra were determined on a Beckman DU-70-spectrophotometer. Thin-layer chromatography (TLC) was performed on 0.25 mm layers of Merck silica gel 60F-254 and column chromatography was done on Merck 60 (230-400 mesh). Mass spectra were obtained with an AEI Scientific Apparatus Limited MS-30 mass spectrometer

(-) Cis-2-amino-1,9-dihydro-9-[4-(sulfamoyloxymethyl)-2-cyclopenten-1-yl]-6H-purin-6-one (5'-sulfamoyl Carbovir, 2). (-) Carbovir (100 mg, 0.40 mmol) and NaH (30 mg, 1.25 mmol) in anhydrous DME (25 mL) was refluxed under N_2 for 24h. The suspension was then cooled in an ice bath and sulfamoyl chloride[14] (840

mg) was added in two equal portions. Stirring was continued overnight at room temperature. Excess NaH was then destroyed by addition of methanol until effervescence ceased. The resulting product mixture was concentrated and adsorbed onto silica gel. Compound **2** was isolated by flash chromatography on a column of silica gel (2.5 x 35 cm), eluted with ethyl acetate-methanol (20:3). The product was obtained as slightly off-white solid (95 mg, 73%). Recrystallization from ethanol yield very fine solid; m.p. 154°C dec; Rf = 0.47 (ethyl acetate-methanol 1:1); UVλ_{max} 253, sh 277 (pH 1), 252, sh 273 (pH 7), 269, sh 256 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 10.53 (s, 1H, NH), 7.58 (s, 1H, C8H), 7.49 (s, 2H, NH_2SO_2), 6.57 (s, 2H, C2NH_2), 6.10 (broad, 1H, C2'H), 5.85 (broad, 1H, C3'H), 5.35 (broad, 1H, C1'H), 4.10 (broad, 2H, C5'H), 3.13 (broad, 1H, C4'H), 2.59, 1.58 (m, 1H, C6'H). Anal. Calc'd for $C_{11}H_{14}N_6O_4S$: C, 40.49; H, 4.32; N, 25.75. Found: C, 40.26; H, 4.19; N, 25.59.

(±) Cis-9H-9-[4-(sulfamoyloxymethyl)-2-cyclopenten-1-yl] adenine (3). A suspension of (±) cis-9H-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] adenine (200 mg, 0.87 mmol) and NaH (278 mg, 11.6 mmol) in anhydrous DME (15 mL) was stirred under N_2 at 60-65°C for 2h. The suspension was then cooled in an ice bath and a solution of NH_2SO_2Cl (310 mg) in DME (5 mL) was added dropwise. Stirring was continued overnight and the reaction temperature maintained at 4°C. Excess NaH was then destroyed by addition of methanol until effervescence ceased. The resulting product mixture was concentrated and adsorbed onto silica gel. **3** was isolated by flash chromatography on a column of silica gel (2.5 x 30 cm), eluted with ethyl acetate-methanol (10:2). The product was obtained as slightly off-white solid (154 mg, 57%). Recrystallization from water-methanol (2:1) yield white crystals; m.p. 155°C started to dec., melt w/ bubbles at 230°C; Rf = 0.51 (ethyl acetate-methanol 1:1); UVλ_{max} 259 (pH 1), 261 (pH7), 262 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.09 (s, 1H, C2H), 8.01 (s, 1H, C8H), 7.46 (s, 2H, NH_2SO_2), 7.19 (s, 2H, C6NH_2), 6.10 (broad, 1H, C2'H), 5.98 (broad, 1H, C3'H), 5.61 (broad, 1H, C1'H), 4.11 (d, J = 7.5 Hz, 2H, C5'H), 3.14 (broad, 1H, C4'H), 2.75, 1.67 (2m, 2H, C6'H). Anal. Calc,d for $C_{11}H_{14}N_6O_3S$: C, 42.57; H , 4.55; N, 27.08; Found: C, 42.51; H , 4.56; N, 26.91.

(±) Cis-3H-3-[4-(sulfamoyloxymethyl)-2-cyclopenten-1-yl]-7-amino-1,2,3-triazolo-[4,5-d]pyrimidine (4). (±) Cis-3H-3-[4-(hydroxymethyl)-2-cycopenten-1-yl]-7-amino-1,2,3-triazolo-[4,5-d]pyrimidine (500 mg, 2.15 mmol) and NaH (120 mg, 5.0 mmol) in anhydrous DME (50 mL) was stirred under N_2 at room temperature overnight, when the solid turned off-white. The suspension was then cooled in an ice bath and NH_2SO_2Cl (1.2 g) was added at once. Stirring was continued overnight at 4°C. Methanol

was then added to destroy all excess NaH. Compound **4** was obtained pure by flash chromatography on a 4.5 x 25 cm column of silica gel eluted with ethyl acetate-methanol (10:0.5). Recrystallization from methanol gave white solid in 32% yield (215 mg); m.p. 134-136 °C; Rf = 0.70 (ethyl acetate-methanol 1:1); UVλ_{max} 264 (pH 1), 278 (pH 7), 214, 278 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.41 (broad, 1H, NH), 8.28 (s, 1H, C2H), 8.06 (broad, 1H, C6NH), 7.47 (s, 2H, NH_2SO_2), 6.14 (broad, 1H, C2'H), 6.06 (broad, 1H, C3'H), 5.93 (broad, 1H, C1'H), 4.13 (m, 2H, C5'H), 3.21 (broad, 1H, C4'H), 2.78, 1.97 (2m, 2H, C6'H). Anal. Calc'd for $C_{10}H_{13}N_7O_3S$: C , 38.58; H, 4.21; N, 31.50. Found: C ,38.38; H, 4.28; N, 31.39.

(±) **Cis-9H-9-[4-(sulfamoyloxymethyl)-2-cyclopenten-1-yl]-6-methylamino purine (5).** (±) Cis-9H-9[4-(hydroxymethyl)-2-cyclopenten-1-yl]-6-methylamino purine (200 mg, 0.82 mmol) and NaH (160 mg, 6.67 mmol) in anhydrous DME (50 mL) was stirred at 80°C for 1h when all the solid appeared off-white. The suspension was then cooled in an ice bath and NH_2SO_2Cl (760 mg) was added in about three equal portions. TLC showed about 90% conversion after 2/3 of sulfomoyl chloride was added. After complete addition, methanol was added to destroy all excess NaH. Compound **5** was obtained pure by flash chromatography on a 4.0 x 15 cm column of silica gel eluted with ethyl acetate-methanol (10:1). Recrystallization from methanol-ethanol (1:1) gave off-white crystals in 31 % yield (82 mg); m.p. 210°C dec.; Rf = 0.68 (ethyl acetate- methanol 1:1); UVλ_{max} 264 (pH 1), 268 (pH 7), 267 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1H, C2H), 7.99 (s, 1H, C8H), 7.47 (broad, 1H, C6N<u>H</u>CH_3), 7.47 (s, 2H, NH_2SO_2), 6.11 (m, 1H, C2'H), 5.99 (m, 1H, C3'H), 5.63 (broad, 1H, C1'H), 4.09 (d, J = 7.5 Hz, 2H, C5'H), 3.16 (broad, 1H, C4'H), 2.87 (broad, 3H, C6NHC<u>H</u>$_3$), 2.78, 1.67 (2m, 2H, C6'H). Anal. Calc'd for $C_{12}H_{16}N_6O_3S$: C , 44.44; H , 4.97; N, 25.91. Found: C, 44.56; H, 4.80; N, 25.77.

(±) **Cis-9H-9-[-4-(sulfamoyloxymethyl)-2-cyclopenten-1-ly]-6-dimethylamino purine (6).** (±) Cis-9H-9-[-4(hydroxymehtyl)-2-cylopenten-1-yl]-6-dimethylamino purine (80 mg, 0.31 mmol) and NaH (42 mg, 1.75 mmol) in anhydrous DME (25 mL) was stirred at room temperature, under N_2 for 2h. The suspension was then cooled in an ice bath and NH_2SO_2Cl (300 mg) in DME (15 mL) was added dropwise. After complete addition, stirring was continued overnight at 4°C. Methanol was then added to destroy all excess NaH. Compound **6** was obtained pure by flash chromatography on a 2.5 x 30 cm column of silica gel eluted with ethyl acetate-methanol (10:1). Recrystallization from methanol-ethyl acetate (3:1) gave white crystals in 86% yield (90 mg); m.p. 131-133 °C; Rf = 0.76 (ethyl acetate-methanol 1:1); UVλ_{max} 269, 212 (pH 1),

276, 214 (pH 7), 277, 215 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.09 (s, 1H, C2H), 7.99 (s, 1H, C8H), 7.45 (s, 2H, NH_2SO_2), 6.11 (m, 1H, C2'H), 5.97 (m, 1H, C3'H), 5.65 (broad, 1H, C1'H), 4.08 (d, J = 7.5 Hz, 2H, C5'H), 3.17 (broad, 1H, C4'H), 2.77, 1.63 (2m, 2H, C6'H). Anal. Calc'd for $C_{13}H_{18}N_6O_3S$: C, 46.14; H, 5.36; N, 24.84. Found: C, 46.26; H, 5.38; N, 25.02.

(±) **Cis-9H-9-[-4(sulfamoyloxymethyl)cyclopent-1-yl]adenine (7).** (±) Cis-9H-9[4-(sulfamoyloxymethyl)-2-cyclopenten-1-yl]adenine **3** (50 mg, 0.16 mmol) was dissolved in methanol (50 mL) and hydrogenated in the presence of 10% palladium-charcoal (5 mg) under 35 Psi of H_2 for 7hrs. The catalyst was removed and the solvent was evaporated. Recrystallization from ethanol yield 35 mg (74%) of **7** as white solid; m.p. 148-150 °C; Rf = 0.53 (ethyl acetate-methanol 1:1); UVλ_{max} 260, 211 (pH 1), 261 (pH 7), 261, 215 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.21 (s, 1H, C2H), 8.11 (s, 1H, C8H), 7.46 (s, 2H, NH_2SO_2), 7.18 (s, 2H, C6NH_2), 4.85 (m, 1H, C1'H), 4.06 (d, J = 6 Hz, 2H, C5'H), 3.44 (broad, 1H, C4'H), 2.39, 2.12, 1.82, 1.70 (4m, 4H, C2'H, C3'H and C6'H). Anal. Calc'd for $C_{11}H_{16}N_6O_3S$; C , 42.32; H, 5.17; N, 26.92. Found; C , 42.36; H, 5.37; N, 26.76.

(±) **Cis-3H-3-[4-(sulfamoyloxymethyl)cylopent-1-yl]-7-amino-1,2,3-triazolo-[4,5-d]pyrimidine (8).** (±) Cis-3H-3-[4-(sulfamoyloxymethyl)-2-cycopenten-1-yl]-7-amino-1,2,3-triazolo-[4,5-d]pyrimidine **4** (45 mg, 0.15 mmol) was dissolved in ethanol (50 mL) and hydrogenated in the presence of 10% palladium-charcoal (20 mg) under 35 Psi of H_2 overnight. The catalyst was removed and the solvent was evaporated. Recrystallization from methanol yield 25 mg (53%) of **8** as white solid; m.p. 148-150 °C dec; Rf = 0.7 (ethyl acetate-methanol 2:1); UVλ_{max} 264 (pH 1), 278 (pH 7), 278, 215 (pH 13); ^{1}H NMR (Me_2SO-d_6) δ 8.39 (broad, 1H, NH), 8.25 (s, 1H, C2H), 8.04 (broad, 1H, C6NH), 7.44 (s, 2H, NH_2SO_2), 5.22 (m, 1H, C1'H), 4.05 (d, J = 7.5 Hz, 2H, C5'H), 3.30 (broad, 1H, C4'H), 2.44, 2.20, 1.93, 1.70 (4m, 4H, C2'H, C3'H and C6'H). Anal. Calc'd for $C_{10}H_{15}N_7O_3S$; C, 38.33; H, 4.82; N, 31.29. Found; C, 38.53; H, 5.01; N , 31.10.

5'-O-[[[[(Diethylphosphono)methyloxy]carbonyl]amino]sulfonyl]-3'-azidothymidine (11). A solution of diethylhydroxymethyl phosphonate **9** (157 mg, 0.94 mmol) in anhydrous CH_2Cl_2 was cooled to -15°C and 1 eq. of chlorosulfonyl isocyanate (132 mg, 0.081 mL) was added. The mixture was stirred with cooling under nitrogen for 15 minutes and used directly in the following reaction.

A suspension of AZT (250 mg, 0.94 mmol) and 1 eq. of pyridine (75.7 mg, 0.77 mL) in anhydrous CH_2Cl_2 (10 mL) was slowly added to the above solution containing intermediate **10** at -15 °C under a nitrogen atmosphere. The reaction mixture was stirred for an hour with cooling and then overnight at room temperature. Solvent was removed under reduced pressure and the residue was purified by flash chromatography with ethyl acetate-methanol to give **11** (210 mg, 41 %): R_f = 0.67 (ethyl acetate-methanol, 2:1) ; m.p. 120 °C start to decompose; ^{1}H NMR [(Me_2SO-d_6), 300 MHz]: δ 11.28 (s, 1H, N3-H), 7.66 (s, 1H, C6-H), 6.09 (t, 1H, C1'-H $J_{1',2'}$ = 7 Hz), 4.46-4.44 (m, 1H, C3'-H), 4.10 (d, 2H, P(O)C$\underline{H}_2$, J_{PH} = 8 Hz), 4.09-3.97 (overlapping m, 7H, $CH_3C\underline{H}_2O$, C4'-H, C5'-H), 2.48-2.20 (m, 2H, C2'-H_2), 1.75 (s, 3H, C$\underline{H}_3$), 1.19 (t, 6H, $C\underline{H}_3CH_2O$, J_{PH} = 7 Hz). ^{31}P NMR: d 22.35. Anal. calc'd for $C_{16}H_{25}N_6O_{11}PS{\cdot}2H_2O$: C , 33.16; H , 4.50; N, 14.21. Found: C , 33.48; H, 4.88; N, 14.10.

5'-O-[[[[[(Phosphono)methyl]oxy]carbonyl]amino]sulfonyl]-3'-azido thymidine (12). Compound **11** (361 mg, 0.67 mmol) was dissolved in anhydrous DMF (20 mL) and freshly distilled bromotrimethylsilane (1 mL) was added. The reaction mixture was stirred at room temperature under nitrogen overnight, and then concentrated under reduced pressure. The residue was taken up in MeOH (5 mL) and 1N NH_4OH was added until pH of the solution turned basic (pH ~8-9). The precipitate formed was dissolved in H_2O (1mL) and passed through a weakly acidic amberlite (CG-50, 100-200 wet mesh) column to give **12** as off-white solid (60 mg, 19%): m.p. 162-164 °C; R_f = 0.49 (Isopropanol-ammonia-water, 7:1:2); MS (FAB): 485 (M+1). ^{1}H NMR [(Me_2SO-d_6), 300 MHz]: δ 11.31 (broad s, 1H, N3-H), 9.17 (s, 1H, C(O)$\underline{N}HSO_2$), 7.72 (s, 1H, C6-H), 6.12 (t, 1H, C1'-H, $J_{1'2'}$ = 7 Hz), 4.51-4.47 (m, 1H, C3'-H), 3.99-3.77 (overlapping m, 3H, C4'-H, C5'-H), 3.75 (d, 2H, P(O)C$\underline{H}_2$, J_{PH} = 8 Hz), 2.47-2.22 (m, 2H, C2'-H_2). ^{31}P NMR: δ 17.84. Anal. Calc'd for $C_{12}H_{17}N_6O_{11}PS$ (3/2 H_2O): C, 28.19; H, 3.94; N, 16.44. Found: C, 28.67; H, 4.23; N, 16.98.

Acknowledgments. This work was supported by Public Health Service Grant CA23263 from the National Cancer Institute.

REFERENCES

1. Bakus, E. J., Tresner, H. D., Campbell, T. H. *Antibiot. Chemother.* **1957**, 7, 532-541.

2. Thomas, S. O., Singleton, V. L., Lowery, J. A., Sharpe, R. W., Pruess, L. M., Porter, J. N., Mowat. J. H., Bohonos, N. *Antibiot. Annu.* 1956-57, **1957**,716-721.

3. Bloch, A., Coutsogeorgopoulos, C. *Biochemistry* **1971**, 10, 4394-4398.

4. Klien, E., Burgess, G. H., Bloch, A., Milgrom, H., Holtermann, O. A. *Ann. N. Y. Acad. Sci.* **1975**, 255, 216-224.

5. Iwata, M., Sasaki, T., Iwamatsu, H., Miyadoh, S., Tachibana, K., Matsumoto, K., Shomura, T., Sezaki, M., Watanabe, T. *Meiji Seika Kenkyu Nenpo.* **1987**, 26, 17-22.

6. Takahashi, E., Beppu, T. A. *J. Antibiot.* **1982**, 35, 939-947.

7. (a) Smee, D. F., Alaghamandan, H. A., Kini, G. D., Robins, R. K., *Antiviral Res.* **1988,** 10, 253-262. (b) Smee, D. F., In *Nucleotide Analogs as Antiviral Agents,* ACS Symposium Series 401, Martin J., Ed, American Chemical Society, Washington, D. C., **1989**, pp 124-139.

8. Camarasa, M. J., Fernandez-Resa, P., Garcia-Lopez, M. T., de Las Heras, F. G., Mendez-Castrillon, P. P., Alarcon, B., Carrasco, L. *J. Med. Chem.*, **1985**, 28, 40-56.

9. Castro-Pichel, J., Garcia-Lopez, M. T., de Las Heras, F. G., Herranz, R., *Arch. Pharm.* (Weinheim, Ger.) **1989**, 322, 11-15.

10. Vilas, P., Perez, C., Perez, S., Villalon, D.C., Gancedo, A. G., Gil-Fernandez, C., Garcia-Lopez, M. T., de Las Heras, F. G. *Chemotherapy* **1989**, 35, 58-63.

11. Jaffe, J. J., McCormack, J. J., Meymerian, E. *Exp. Parasitol.* **1970**, 28, 535-543.

12. Kini, G. D., Henry, E. M., Robins, R. K., Larson, S. B., Marr, J. J., Berens, R. L., Bacchi, C. J., Nathan, H. C., Keithly, J. S., *J. Med. Chem.* **1990**, 33, 44-48.

13. Alcina, A., Fresno, M,. Alarcon, B. *Antimicrob. Agents Chemother.* **1988**, 12, 113-132.

14. Peterson, E. M., Brownell, J., Vince, R. *J. Med. Chem.* **1992**, 35, 3991-4000.

15. Belrhali, H., Yaremchuk, A., Tukalo, M., Larsen, K., Berthet-Colominas, C., Leberman, R., Beijer, B., Sproat, B., Als-Nielsen, J., Grubel, G., Legrand, J-F., Lehmann, M., Cusack, S. *Science* **1994,** 263, 1432-1436.

16. Vince, R., Hua, M., Brownell, J., Daluge, S., Lee, F., Shannon, W. M., Lavelle, G. C., Qualls, J., Weislow, O. S., Kiser, R., Canonico, P. G., Schultz, R. H., Narayanan, V. L., Mayo, J. G., Shoemaker, R. H., Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988,** 156, 1046-1053.

17. Vince, R., Hua, M. *J. Med. Chem.* **1990**, 33, 17-21.

18. DeClercq, E., Holy, A., Rosenberg, I., Sakuma, T., Balzarini, J., Maudgal, P. C., *Nature* **1986**, 323, 464.

19. Phillion, D.P., Andrew, S.S., *Tetrahedron Lett.* **1986**, 27, 1447-1480.

20. Geran, R. I., Greenberg, N. H., McDonald, M. M., Schumacher, A.M., Abbott, B.J., Procols for Screening Chemical Agents and Natural Products Against Animal Tumors and Other Biological Systems (Third Edition). *Cancer Chemother. Rep., Part 3* **1972**, 3,1.

21. Data provided by E. Lucile White and William B. Parker, Southern Research Institute, Birmingham, Alabama.

Received July 24, 1995
Accepted September 13, 1995