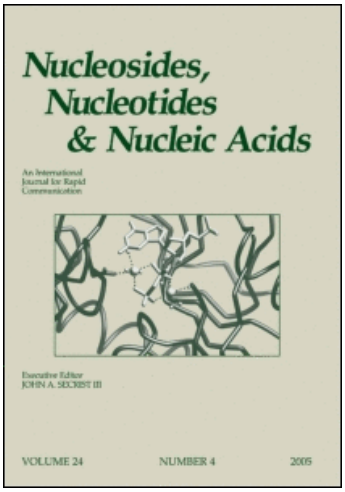


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Biological Evaluation of some Acyclic Nucleoside Cyclic Phosphoramidate Derivatives

Hiroshi Takaku[a]; Tsunehiko Ito[a]; Shiro Yoshida[a]; Tomoni Aoki[a]; Erik De Clercq[b]
[a] Laboratory of Bioorganic Chemistry, Chiba Institute of Technology, Chiba, Japan [b] Rega Institute for Medical Research, University of Leuven, Leuven, Belgium

To cite this Article Takaku, Hiroshi , Ito, Tsunehiko , Yoshida, Shiro , Aoki, Tomoni and De Clercq, Erik(1987) 'Synthesis and Biological Evaluation of some Acyclic Nucleoside Cyclic Phosphoramidate Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 6: 4, 793 — 802
To link to this Article: DOI: 10.1080/15257778708073425
URL: http://dx.doi.org/10.1080/15257778708073425

NUCLEOSIDES & NUCLEOTIDES, 6(4), 793-802 (1987)

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME ACYCLIC NUCLEOSIDE CYCLIC PHOSPHORAMIDATE DERIVATIVES

Hiroshi Takaku*,[1], Tsunehiko Ito[1], Shiro Yoshida[1], Tomoni Aoki[1] and Erik De Clercq[2]

[1]Laboratory of Bioorganic Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275, Japan
[2]Rega Institute for Medical Research, University of Leuven, B-3000 Leuven, Belgium

Abstract

The acyclic nucleosides 2 were treated with 2-chloro-3-methyl-1-oxa-3-aza-2-phosphacyclopentane (3) in the presence of diisopropylethylamine to give the corresponding phosphoramidite derivatives (4). The phosphoramidite intermediates (4) were oxidized with m-chloroperbenzoic acid to the phosphoramidate derivatives (5). Treatment of 5a,b with $ZnBr_2$ in CH_3NO_2 gave the corresponding acyclic nucleoside cyclic phosphoramidates (6a,b). Attempts to desilylation of 5c by tetrabutylammonium fluoride (TBAF) resulted in opening of the phosphoramidate ring. The newly synthesized compounds were evaluated for antiviral and antitumor cell activity.

INTRODUCTION

Recently, several workers reported[1] the chemical syntheses and biological evaluation of nucleoside cyclic phosphoramidate derivatives. These compounds are hydrolyzed under chemical or enzymic conditions and are a potential source of nucleoside 5'-phosphates in vivo. On the other hand, acyclic nucleoside analogues have gained increasing interest because of their biological activity, particularly as antiviral and anticancer compounds (1).[2]

We now report the synthesis of acyclic nucleoside phosphoramidate derivatives (6) which were evaluated for their antiviral and antitumor cell activity.

CHEMISTRY

The tritylation or silylation of acyclic nucleoside (1) was carried out as follows : the acyclic nucleoside 1 was treated with dimethoxytri-

tyl chloride (1.1 molar equiv.) in dry pyridine for 5 h to give the corresponding tritylated compounds 2a (56 %) and 2b (57 %), respectively along with bis-tritylated compounds, after separation by silica gel column chromatography. While treatment of 1a with tert-butyldimethylsilyl chloride (TBDMS-Cl) (1.1 molar equiv.) in dry DMF gave the silylated product (2c) (47 %).

Next we examined the phosphorylation of 2 by using 2-chloro-3-methyl-1-oxa-3-aza-2-phosphacyclopentane (3). The phosphitylating agent 3 was prepared according to the procedure reported by Martynov.[3] However, we observed that the phosphitylating agent 3 was lower than 90 % pure (by ^{31}P-NMR). Satisfactory ^{31}P-NMR data of 3 were obtained only after distillation over cesium fluoride. The phosphitylating agent 3 (1.5 molar equiv.) thus obtained was treated with 2a in the presence of diisopropylethylamine (1.5 molar equiv.) in dry THF at -50°C. After 30 min, the precipitated diisopropylethylammonium hydrochloride was removed by filtration and the filtrate was treated with m-chloroperbenzoic acid (MCPBA) at 20°C for 15 min.[4] After the usual work up, the corresponding acyclic nucleoside cyclic phosphoramidate (5a) was isolated in 79 % yield. As a more direct method for preparing 5a we examined the direct condensation reaction of 2-chloro-3-methyl-1-oxa-3-aza-2-phosphacyclopentane 2-oxide (7) with an acyclic nucleoside. However, compound 7 failed to react with 3 under several conditions. Compound 5a was characterized by UV and NMR spectroscopy and elemental analysis. The NCH_3 signal of the ^{1}H-NMR spectrum consists of a pair of doublets with a phosphorus coupling constant of 10 Hz. The further splitting of these signals is ascribed to the presence of diastereomers in the sample resulting from a chiral phosphorus centre. Two signals (22.63 and 22.29 ppm) observed in the ^{31}P-NMR spectrum could be assigned to the diastereomers, present in the ratio 2:1.

In a similar manner, the compounds 5b,c were obtained in 76 % and 79 % yield, respectively. The ^{1}H and ^{31}P-NMR spectra of these products were consistent with the assigned structures and showed the presence of diastereomers.

Finally, we examined the possibility of removing the hydroxyl protecting groups from 5. Compound 5c was treated with TBAF at low temperature. After 2 h, thin-layer chromatography (TLC) analysis (solvent B)

showed complete conversion of 5c (Rf 0.38) into base line material. From this result, the desilylation by TBAF treatment was accompanied by opening of the phosphorus heterocycle. To obtain compounds 6a,b from 5a,b, the reaction with $ZnBr_2$ was carried out in CH_3NO_2.[5] This gives selective removal of the hydroxyl protecting group from 5. The compounds had the expected characteristic UV and NMR spectra.

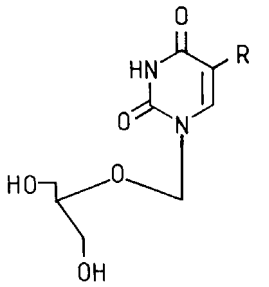
BIOLOGICAL ACTIVITY

Compounds 1a, 1b, 6a, 6b, 8a and 8b were evaluated for antiviral activity, cytotoxicity and antitumor cell activity according to well established procedures.[6] No cytotoxicity or antiviral activity was observed for any of these compounds under conditions where the reference compounds[7,8] tubercidin, (S)-DHPA [(S)-9-(2,3-dihydroxypropyl)adenine], ribavirin and carbocyclic 3-deazaadenosine showed the usual cytotoxicity or antiviral activity (Table 1). Also, compounds 1a and 6a were totally devoid of antitumor cell activity (Table 2). Compounds 1b, 6b, 8a and 8b did show some antitumor cell activity, but in terms of potency, they did not even come close to the antitumor cell potency exhibited by the standard fluorinated antitumor agents, 5-fluorouracil, 5-fluorouridine and 5-fluoro-2'-deoxyuridine (Table 2).

EXPERIMENTAL SECTION

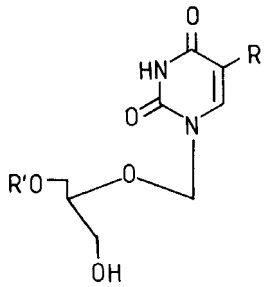
Ultraviolet spectra were recorded on a Shimazu UV 200 spectrometer. ^{1}H-NMR spectra were recorded in a JOEL JNMPS 100 spectrometer with TMS internal standard. Thin layer chromatography (TLC) was performed on precoated TLC plates of silica gel 60 F-254 (Merck, Art. No. 5715) and the R_f values of the acyclic nucleoside and acyclic nucleotide derivatives were determined after development with solvent A (CH_2Cl_2-MeOH, 95:5, v/v) and solvent B (ethyl acetate-EtOH-pyridine, 8:1:1, v/v). Column chromatography was performed with Silica gel C-200 purchased from Wako Co. Ltd. Pyridine was distilled twice from p-toluenesulfonyl chloride and from CaH_2 and then stored over molecular sieves 4Å. Compounds 1a,b and 8a,b were prepared according to published procedures.[9]

Tritylation of 1. Compound 1a (430 mg, 2 mmol) was treated with dimethoxytrityl chloride (758 mg, 2.2 mmol) in dry pyridine (40 ml) at room temperature for 5 h. The reaction mixture was quenched with ice-water (20 ml) and repeatedly extracted with CH_2Cl_2 (2 x 40 ml). Combined organic

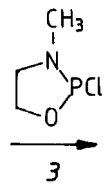


1 a R = H
b R = F

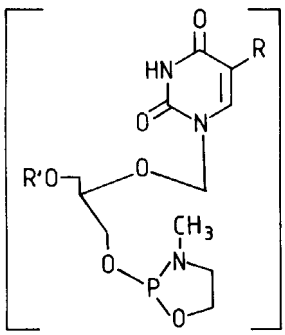
DMTrCl or TBDMSCl



2a R = H R' = DMTr
b R = F R' = DMTr
c R = H R' = TBDMS

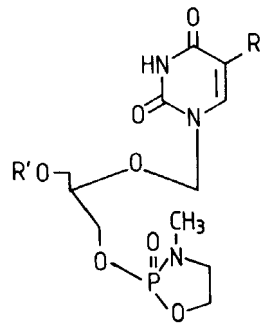


3



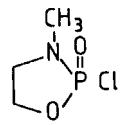
4

MCPBA

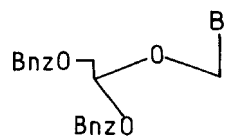


5a R = H R' = DMTr
b R = F R' = DMTr
c R = H R' = TBDMS

ZnBr2



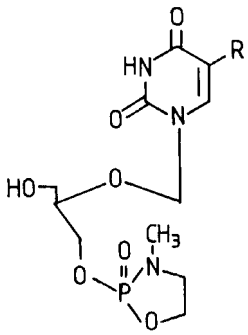
7



8a B = 5-fluorouracil
b B = adenine

TBAF

5



6a R = H
b R = F

COMPOUNDS

TABLE 1
Cytotoxicity and Antiviral Activity in Primary Rabbit Kidney Cells

Compound	Minimum cytotoxic concentration[a] (μg/ml)	Minimal inhibitory concentration[b] (μg/ml)			
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus
1a, 1b, 6a, 6b, 8a, 8b	> 400	> 400	> 400	> 400	> 400
Tubercidin	> 0.4	> 0.1	> 0.1	0.07	0.07
(S)-DHPA	> 400	> 400	> 400	70	40
Ribavirin	> 400	> 400	> 400	10	300
Carbocyclic 3-deazaadenosine	> 400	> 400	> 400	2	1

In HeLa Cells

Compound	Minimal cytotoxic concentration[a] (μg/ml)	Minimal inhibitory concentration[b] (μg/ml)		
		Vesicular stomatitis virus	Coxsackie virus B4	Polio virus-1
1a, 1b, 6a, 6b, 8a, 8b	> 400	> 400	> 400	> 400
Tubercidin	> 1	0.1	0.1	0.2
(S)-DHPA	> 400	> 400	> 400	> 400
Ribavirin	> 200	20	70	70
Carbocyclic 3-deazaadenosine	> 400	0.7	> 400	> 400

In Vero B Cell

Compound	Minimum cytotoxic concentration[a] (μg/ml)	Minimum inhibitory concentration[b] (μg/ml)				
		Para-influenza 3-virus	Reo-virus-1	Sindbis virus	Coxsackie virus B4	Semliki forest virus
1b	> 400	> 400	150	> 400	> 400	300
1a, 6a, 6b, 8b	> 400	> 200	> 200	> 400	> 400	> 200
8a	> 400	> 100	> 100	100	> 400	> 400
Tubercidin	> 0.4	> 0.1	> 0.1	0.2	0.2	0.2
(S)-DHPA	> 400	20	150	> 400	150	300
Ribavirin	> 400	70	70	70	200	> 400
Carbocyclic 3-deazaadenosine	> 400	0.7	1	70	1	> 200

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50 %.

TABLE 2

Inhibitory Effects on the Proliferation of Tumor Cells[a]

Compound	ID_{50}[b] (μg/ml)						
	L1210/0	L1210/BdUrd	Raji/0	Raji/TK^-	FM3A/0	FM3A/TK^-	Molt/4F
1a	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	ND
1b	13.4 ± 3.6	24.5 ± 2.5	353 ± 25	79.3 ± 8.9	2.51 ± 0.81	4.14 ± 0.31	ND
6a	> 1000	ND[c]	> 1000	ND	648 ± 145	ND	> 1000
6b	205 ± 39	ND	244 ± 20	ND	189 ± 61	ND	212 ± 28
8a	210 ± 28	260 ± 3	63.5 ± 17	38.8 ± 4.1	68.3 ± 27	93.5 ± 38	ND
8b	> 1000	627 + 76	26.6 ± 1.1	84.3 ± 42	945 ± 72	243 ± 122	ND
5-F-Ura	0.340 ± 0.023	0.451 ± 0.012	9.25 ± 1.66	3.8 ± 1.1	0.164 ± 0.038	0.099 ± 0.013	ND
5-F-dUrd	0.00365 ± 0.00030	4.27 ± 0.27	0.178 ± 0.029	1.57 ± 0.83	0.00188 ± 0.00065	0.810 ± 0.180	0.0848 ± 0.0489
5-F-Urd	0.0350 ± 0.0018	0.0354 ± 0.0049	0.126 ± 0.024	0.094 ± 0.024	0.0088 ± 0.0037	0.0246 ± 0.0036	ND
Ado	558 ± 55	505 ± 20	350 + 50	792 ± 131	790 ± 280	370 ± 5	ND

[a]Abbreviations : L1210/0, murine leukemia cells (wild type); L1210/BdUrd, murine leukemia cells (deoxythymidine kinase-deficient); Raji/0, human B-lymphoblast cells; Raji/TK^-, human B-lymphoblast cells (deoxythymidine kinase-deficient); FM3A/0, murine mammary carcinoma cells; FM3A/TK^-, murine mammary carcinoma cells (deoxythymidine kinase-deficient); Molt/4F, human T-lymphoblast cells.
[b]50 %-inhibitory dose ± standard deviation.
[c]Not determined.

extracts were washed with water (2 x 20 ml), and the CH_2Cl_2 was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and purified by silica gel column chromatography. The appropriate fractions [eluted with CH_2Cl_2-MeOH (95:5, v/v)] were evaporated to ca. 3-4 ml and poured into hexane (100 ml). A white precipitate was collected to give 2a (560 mg, 56 %); mp 83-85°C; R_f 0.13 (solvent A); UV (MeOH) λ_{max} 265, 254 nm, λ_{min} 234 nm, ^{1}H-NMR (DMSO-d_6) δ 11.37 (br s, 1H, NH), 7.75 (d, 1H, $J_{5,6}$=8 Hz, H-6), 7.40-6.70 (m, 13H, ArH), 5.59 (d, 1H, $J_{5,6}$=8 Hz, 5-H), 5.28 (s, 2H, O-CH_2-N), 4.65 (br s, 1H, OH), 4.45 (d, 1H, CH); 3.71 (s, 6H, OCH_3), 3.40 (m, 2H, CH_2-CH-CH_2), 3.00 (m, 2H, CH_2-CH-CH_2).

Compound (1b) (640 mg, 2.7 mmol) was treated with dimethoxytrityl chloride (1.01 g, 2.97 mmol) in dry pyridine (54 ml) at room temperature for 5 h, and the mixture was processed in the same manner as described above giving 2b (816 mg, 57 %); mp 82-86°C; R_f 0.23 (solvent A); UV (MeOH) λ_{max} 267, 237 nm, λ_{min} 253 nm; ^{1}H-NMR (DMSO-d_6) δ 10.83 (br s, 1H, NH), 8.20 (d, 1H, $J_{5,6}$=7 Hz, H-6) 7.37-6.74 (m, 13H, ArH), 5.20 (d, 2H, O-CH_2-N), 4.45 (br s, 1H, OH), 3.75 (s, 6H, OCH_3), 3.45 (m, 3H, CH_2-CH-CH_2), 3.00 (m, 2H, CH_2-CH-CH_2).

Silylation of 1a. Compound (1a) (362 mg, 1.68 mmol) and imidazole (137 mg, 2.1 mmol) were dissolved in DMF (12 ml). TBDMS-Cl[10] (254 mg, 1.85 mmol) was added in portions over 20 min period and the mixture was stirred for an additional 30 min. The solvent was removed at reduced pressure and the residue was chromatographed on a silica gel column using CH_2Cl_2-MeOH (95:5, v/v) as eluant. The appropriate fractions were evaporated in vacuo to give the silylated product (2c) (260 mg, 47 %); mp 86-88°C; R_f 0.20 (solvent A); UV (MeOH) λ_{max} 256 nm, λ_{min} 225 nm; ^{1}H-NMR ($CDCl_3$) δ 11.20 (br s, 1H, NH), 7.60 (d, 1H, $J_{5,6}$=7.5 Hz, H-6), 5.55 (d, 1H, $J_{5,6}$=7.5 Hz, H-5), 5.15 (s, 2H, O-CH-N), 4.60 (br s, 1H, OH), 3.45 (m, 5H, CH_2-CH-CH_2), 0.85 (s, 9H, $(CH_3)_3C$), 0.00 (s, 6H, $(CH_3)_2Si$); Anal Calcd for $C_{14}H_{26}N_2O_5Si$: C, 51.07; H, 8.18; N, 8.33 %, Found : C, 50.87; H, 7.93; N, 8.47 %.

2-Chloro-3-methyl-1-oxa-3-aza-2-phosphacyclopentane (3). A solution of 2-methylaminoethanol (5 ml, 62.4 mmol) and triethylamine (8.75 ml, 62.4 mmol) in dry CH_2Cl_2 (28 ml) was added dropwise to a stirred solution of phosphorus trichloride (5.44 ml, 62.4 mmol) in dry CH_2Cl_2 (28 ml) over a period of 45 min. The reaction mixture was maintained at -20°C under a nitrogen atmosphere. Stirring was continued under nitrogen atmosphere at

22°C for 30 min. After the precipitated triethylammonium hydrochloride was removed by filtration, the filtrate was evaporated in vacuo to give a colorless liquid. The crude material was fractionally distilled from cesium fluoride to afford 5.6 g (65 %) of 3; b.p. 77-80°C/3 mmHg; ^{1}H-NMR ($CDCl_3$) δ 4.5 (m, 2H, CH_2-O), 3.5-2.9 (m, 2H, CH_2-N), 2.60 (d, 3H, $J_{H,P}$=16 Hz, NCH_3); ^{31}P-NMR ($CDCl_3$, 85 % H_3PO_4) δ 167.

Phosphorylation of 2. A solution of 2a (1.22 g, 2.35 mmol) in dry THF (9.4 ml) and diisopropylethylamine (0.60 ml, 3.52 mmol) was cooled at -50°C and compound (3) (486 mg, 3.52 mmol) was added with vigorous stirring. After 30 min, the precipitated diisopropylethylammonium hydrochloride was removed by filtration and the filtrate was treated with MCPBA (603 mg, 3.52 mmol) at 20°C. After 15 min, pyridine was added, and the solvent was evaporated in vacuo. The residue was purified by chromatography on a column (3 x 10 cm) of silica gel which was eluted with ethyl acetate-ethanol-pyridine (8:1:1, v/v). The appropriate fractions were collected and the solvent was evaporated under reduced pressure to give the product (5a) which was isolated as a white powder (1.14 g, 79 %) by precipitation from hexane (100 ml); mp 69-72°C; UV (MeOH) λ_{max} 265 (sh), 233 nm; ^{1}H-NMR (pyridine-d_5) δ 7.45-7.05 (m, 14H, H-6 and ArH), 5.80 (d, 1H, $J_{5,6}$=7 Hz, H-5), 5.50 (br s, 2H, O-CH_2-N), 4.20 (m, 2H, CH_2-O), 3.70 (s, 6H, OCH_3), 3.60-2.95 (m, 7H, CH_2-N and CH_2-CH-CH_2), 2.55 (d, 3H, $J_{H,P}$=10 Hz, NCH_3); ^{31}P-NMR (pyridine-d_6, 85 % H_3PO_4) δ 22.63, 22.29. Anal Calcd for $C_{32}H_{34}N_3O_9P.3.5\ H_2O$: C, 55.00; H, 5.92; N, 6.02 %. Found : C, 54.99; H, 5.83; N, 6.00 %.

Compound 5b was prepared by a similar procedure as compound 5a, except that the acyclic nucleoside derivative 2b (1.05 g, 2.0 mmol) was treated with 3 (413 mg, 3.0 mmol). 5b was isolated as a white powder (950 mg, 76 %); mp 73-76°C; UV(MeOH) λ_{max} 261, 227 nm, λ_{min} 247 nm; ^{1}H-NMR (pyridine-d_5) δ 7.60-6.70 (m, 14H, H-6 and ArH), 5.27 (br s, 2H, O-CH_2-N), 4.25 (m, 2H, CH_2-O), 3.73 (s, 6H, OCH_3), 3.60-2.85 (m, 7H, CH_2-N and CH_2-CH-CH_2), 2.72 (d, 3H, $J_{H,P}$=10 Hz, N-CH_3); ^{31}P-NMR (pyridine-d_5, 85 % H_3PO_4) δ 21.95, 21.81. Anal Calcd for $C_{32}H_{33}O_9N_3PF.H_2O$: C, 57.20; H, 5.25; N, 6.25 %. Found : C, 57.14; H, 5.17; N, 6.13 %.

Compound 5c was prepared by a similar procedure as compound 5a except that the acyclic nucleoside derivative 2c (661 mg, 2.0 mmol) was treated with 3 (413 mg, 3.0 mmol). 5c was isolated as a white powder (707 mg, 79 %); UV (MeOH) λ_{max} 255 nm; ^{1}H-NMR ($CDCl_3$) δ 9.74 (br s, 1H, NH),

7.47 (d, 1H, $J_{5,6}$=8 Hz, H-6), 5.74 (d, 1H, $J_{5,6}$=8 Hz, H-5), 5.26 (s, 2H, O-CH_2-N), 4.20 (m, 2H, CH_2-O), 4.05-3.60 (m, 5H, CH_2-CH-CH_2), 3.30-3.05 (m, 2H, CH_2-N), 2.60 (d, 3H, $J_{H,P}$=10 Hz, NCH_3), 0.80 (s, 9H, $(CH_3)_3C$), 0.00 (s, 6H, $(CH_3)_2Si$); ^{31}P-NMR ($CDCl_3$, 85 % H_3PO_4) δ 21.74, 21.63. Anal Calcd for $C_{17}H_{30}N_3O_7PSi$: C, 45.62; H, 6.76; N, 8.80 %. Found : C, 45.73; H, 6.89; N, 8.65 %.

Removal of the trityl groups from 5a,b. Compound 5a (420 mg, 0.68 mmol) was treated with $ZnBr_2$ (1.53 g, 0.68 mmol) in dry CH_3NO_2 (17 ml) at 0°C for 15 min. The solvent was concentrated and applied onto a silica gel column (2 x 8 cm). The appropriate fractions [eluted with ethyl acetate-ethanol-pyridine (70:25:5, v/v)] were collected and the solvent was evaporated under reduced pressure to give the product (6a) as a white powder (192 mg, 85 %); mp 68-71°C; UV (MeOH) λ_{max} 261 nm; ^{1}H-NMR (pyridine-d_5) δ 10.52 (br s, 1H, NH), 7.35 (d, 1H, $J_{5,6}$=7 Hz, H-6), 5.64 (d, 1H, $J_{5,6}$=7 Hz, H-5), 5.23 (br s, 2H, O-CH_2-N), 4.50 (br s, 1H, OH), 4.06-3.36 (m, 9H, CH_2-CH-CH_2 and O-CH_2-CH_2-N), 2.87 (d, 3H, $J_{H,P}$=10 Hz, NCH_3).

Compound 6b was prepared by a similar procedure as compound 6a, except that the phosphorylated product (5b) (700 mg, 1.12 mmol) was treated with $ZnBr_2$. 6b was isolated as a white powder (305 mg, 81 %); mp 66-68°C; UV (MeOH) λ_{max} 265 nm; ^{1}H-NMR (pyridine-d_5) δ 11.02 (br s, 1H, NH), 7.27 (d, 1H, $J_{5,6}$=8 Hz, H-6), 5.33 (m, 2H, O-CH_2-N), 4.51 (br s, 1H, OH), 4.17-3.40 (m, 9H, CH_2-CH-CH_2 and O-CH_2-CH_2-N), 2.85 (d, 3H, $J_{H,P}$=10 Hz, NCH_3).

Acknowledgments

We thank TAIHO Pharmaceutical Co. Ltd. and YODOGAWA Pharmaceutical Co. Ltd. for the gift of 5-fluorouracil and uracil.

REFERENCES

1. G.E. Foley, O.M. Friedman, and B.P. Drolet, Cancer Res., 21, 57 (1961); N. Brock and H.-J. Hohorst, Arzneim.-Forsch., 13, 1021 (1963); D.L. Hill, W.R. Laster, and R.F. Struck, Cancer Res., 32, 658 (1972); M. Colvin, C.A. Padgett, and C. Fenselau, Cancer Res., 33, 915 (1973); N.E. Sladek, Cancer Res., 33, 1150 (1973); T.A. Connors, P.J. Cox, P.B. Farmer, A.B. Foster, and M. Jarman, Biochem. Pharmacol., 23, 115 (1974); A. Takamizawa, S. Matsumoto, T. Iwata, Y. Tochino, K. Katagiri, K. Yamaguchi, and O. Shiratori, J. Med. Chem., 18, 376 (1975); N. Brock, Cancer Treat. Rep., 60, 301 (1976); C. Fenselau, M.-N. Kan, S.S. Rao, A. Myles, O.M. Friedman, and M. Colvin, Cancer Res., 37, 2538 (1977); B.E. Domeyer, and N.E. Sladek, Cancer Res., 40, 174 (1980); R.N. Hunston, M. Jehangir, A.S. Jones, and R.T. Walker, Tetrahedron, 36, 2337 (1980); D. Farquhar, N.J.

Kuttesch, M.G. Wilkerson, and T. Winkler, J. Med. Chem., 26, 1153 (1983); A.S. Jones, C. McGuigan, and R.T. Walker, J. Chem. Soc. Perkin I, 1984, 1471 (1984); D. Farquhar, and R. Smith, J. Med. Chem., 28, 1358 (1985); A.S. Jones, C. McGuigan, and R.T. Walker, J. Chem. Soc. Perkin I, 1985, 199 (1985).

2. For reviews, see R.J. Remy and J.A. Secrist III, Nucleosides Nucleotides, 4, 411 (1985).
3. I.V. Martynov, Y.L. Kurglyak, and S.I. Malekin, Zh. Obshch. Khim., 38, 2343 (1968).
4. K. Imai, T. Ito, S. Kondo, and H. Takaku, Nucleosides Nucleotides, 4, 669 (1985).
5. V. Kohli, H. Blöcker, and H. Köster, Tetrahedron Lett., 21, 2683 (1980); M.D. Matteucci, and M.H. Caruthers, ibid., 21, 3243 (1985).
6. E. De Clercq, J. Descamps, G. Verhelst, R.T. Walker, A.S. Jones, P.F. Torrence, and D. Shugar, J. Infect. Dis., 141, 563 (1980); E. De Clercq, J. Balzarini, P.F. Torrence, M.P. Mertes, C.L. Schmidt, D. Shugar, P.J. Barr, A.S. Jones, G. Verhelst, and R.T. Walker, Mol. Pharmacol., 19, 321 (1981).
7. D.E. Bergstrom, A.J. Brattesani, M.K. Ogawa, P.A. Reddy, M.J. Schweickert, J. Balzarini, and E. De Clercq, J. Med. Chem., 27, 285 (1984).
8. E. De Clercq, and J.A. Montgomery, Antiviral Res., 3, 17 (1983); E. De Clercq, D.E. Bergstrom, A. Holy, and J.A. Montgomery, Antiviral Res., 4, 119 (1984).
9. K.K. Ogilvie, R.G. Hamilton, M.F. Gillen, B.K. Radatus, K.O. Smith, and K.S. Galloway, Can. J. Chem., 62, 16 (1984).
10. K.K. Ogilvie, N. Nguyen-ba, M.F. Gillen, B.K. Radatus, U.O. Cheriyan, H.R. Hanna, K.O. Smith, and K.S. Galloway, Can. J. Chem., 62, 241 (1984).

Received August 11, 1986.