J = 8 Hz, 2 H), 2.25 (two overlapping singlets, 6 H). An analogous sequence of reactions was performed for the *O*-((β-ethoxyethoxy)methyl) series of derivatives. The yield in this coupling step was 71%.

(+)-Sparsomycin (1). Compound **32** (15 mg) was dissolved in 5 mL of methanol, and to this solution was added 1 N hydrochloric acid solution (5 mL). The resulting solution was heated at 50 °C for 5 h and then concentrated in vacuo to afford a white solid which was purified on a silica gel column (ethyl acetate/methanol v 1:1). The synthetic sparsomycin was obtained as a white solid (8.9 mg, 65%). However there were some minor impurities present and several attempts to further purify this material failed: $[\alpha]^{25}_D$ +71° (*c* 0.009, H_2O) (lit.[1] +69° (*c* 0.5, H_2O), lit.[16a] +75° (*c* 0.245, H_2O)); ^1H NMr (D_2O) δ 7.29 (d, J = 15.56 Hz, 1 H), 3.83 (d, J = 14.95 Hz, 1 H), 3.65 (m, 3 H), 3.06 (m, 1 H), 2.28 (s, 3 H), 2.17 (s, 3 H).

***O*-(Methoxymethyl)-*S*-episparsomycin.** Following the same procedure described in the synthesis of amine **19**, a mixture of two diastereoisomers **29** and **29a** (1.53 g, 4.9 mmol) was allowed to react with sodium (0.10 g, 4.3 mmol) in liquid ammonia to give the corresponding amine sulfoxides as an oil (0.7 g, 81%): ^1H NMR ($CDCl_3$) δ 4.64 (s, 2 H), 3.56 (m, 3 H), 3.37 (s, 3 H), 2.86 (m, 2 H), 2.63 (s, 3 H), 1.86 (br s, 2 H).

The amine sulfoxide (0.42 g, 2.32 mmol) was sulfenylated, according to the procedure described in the synthesis of compound **21**, to give a mixture of compounds. Upon column purification (methanol/methylene chloride = 1:10, containing 2 mL of aqueous ammonium hydroxide per liter of solvent) the diastereoisomer with the opposite configuration at the chiral sulfur center (compared to the amine sulfoxide **31**) could be obtained in 13% yield (68 mg): ^1H NMR ($CDCl_3$) δ 4.66 (s, 2 H), 3.93 (d, J = 13.5 Hz, 1 H), 3.71 (d, J = 13.5 Hz, 1 H), 3.58 (br s, 1 H), 3.38 (s, 3 H), 3.09 (dd, J = 13.2, 4.8 Hz, 1 H), 2.81 (dd, J = 13.2, 7.5 Hz), 2.33 (s, 3 H), 1.9 (br s, 2 H).

Following the procedure described in the synthesis of compound **32**, the O-protected *S*-episparsomycin was prepared in 62% yield: ^1H NMR (D_2O) δ 7.5 and 7.7 (AB quartet, J = 15.6 Hz, 2 H), 4.8 (m, 1 H), 4.36 and 4.50 (AB quartet, J = 13.8 Hz, 2 H), 4.18 (m, 2 H), 3.62 (d, 2 H), 2.80 (s, 3 H), 2.71 (s, 3 H).

***S*-Episparsomycin (33).** Following the procedure described in the synthesis of (+)-sparsomycin, *S*-episparsomycin (**33**) was obtained: $[\alpha]^{25}_D$ +45° (*c* 0.007, H_2O) (lit.[16a] +48° (*c* 0.175, H_2O)); ^1H NMR (D_2O) δ 7.27 (d, J = 15.56 Hz, 1 H), 6.91 (d, J = 15.56 Hz, 1 H), 4.374 (m, 1 H), 4.04 (d, J = 13.93 Hz, 1 H), 3.85 (d, J = 13.93 Hz, 1 H), 3.652 (m, 2 H), 3.28 (dd, J = 13.5, 5.26 Hz, 1 H), 3.03 (dd, J = 13.5, 8.4 Hz, 1 H), 2.27 (s, 3 H), 2.18 (s, 3 H).

Acknowledgment. We are pleased to acknowledge the financial support of this research provided by a grant from the National Institutes of Health (Grant No. CA 20701) and a William and Florence Catacosinos Cancer Research Award. We are also very grateful to Professor H. C. J. Ottenheijm and Dr. R. M. J. Liskamp (University of Nijmegen, The Netherlands) for many valuable and stimulating discussions and to Dr. P. F. Wiley (Upjohn Co.) for providing an authentic sample of natural sparsomycin.

Registry No. **1**, 1404-64-4; **2**, 28277-67-0; **5**, 56-45-1; **6**, 626-48-2; **7**, 147-61-5; **8**, 24048-74-6; **9**, 28277-68-1; **10**, 52-89-1; **11**, 1187-84-4; DL-**12**, 19651-44-6; DL-**13**, 95406-97-6; **14**, 95406-98-7;]4-*l*-ephedrine, 95406-99-8; **15**, 95407-00-4; **16**, 95407-01-5; **17a**, 95407-02-6; **17b**, 95407-03-7; **18**, 95463-96-0; **19**, 95463-97-1; **20**, 95463-98-2; (±)-**21**, 26547-93-3; (±)-**22**, 95407-04-8; **23**, 1145-80-8; **24**, 1676-81-9; **25**, 95407-05-9; **26**, 95407-06-0; **27**, 95407-07-1; **28**, 95407-08-2; **29**, 95407-09-3; **29a**, 95407-10-6; **30**, 95407-11-7; (*S*)-*epi*-**30**, 95407-12-8; **31**, 95407-13-9; (*S*)-*epi*-**31**, 95407-14-0; **32**, 95407-15-1; (*S*)-*epi*-**32**, 95407-16-2; **33**, 77880-77-4; $Ph_3P{=}CHCO_2Et$, 1099-45-2; $(CH_3)_2CHCH_2SCH_3$, 5008-69-5; $(CH_3)_2CHCH_2SH$, 513-44-0.

A Highly Efficient One-Flask Method for the Preparation of the Individual Diastereoisomers of Ribonucleoside 3′,5′-Cyclic N-Substituted Phosphoramidates via the Direct Appel Reaction. X-ray Structure of *trans*-5-Isopropyl-2′-deoxyuridine 3′,5′-Cyclic *N*-Benzylphosphoramidate

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Received June 18, 1984

A superior method for the preparation of 3′,5′-cyclic N-substituted phosphoramidates of purine and pyrimidine ribo- and deoxyribonucleosides is reported. An Appel-type reaction of various 3′,5′-cyclic nucleoside monophosphates using a Ph_3P/CCl_4 pretreatment followed by addition of the requisite amine gives the corresponding phosphoramidate as a mixture of diastereomers in 31–85% isolated yields. Separation of the individual diastereomers is accomplished by chromatography on SiO_2. Most notably the reactions proceed readily with 3′,5′-cyclic ribonucleoside monophosphates *without protection* of the 2′-OH or potentially reactive functionality on the nitrogen base. In most instances both diastereomers are formed in useful amounts. Amino groups used included $C_6H_5CH_2NH$, C_6H_5NH, and $(CH_2)_5N$. Nucleosides employed were adenosine, deoxyadenosine, uridine, 5-isopropyl-2′-deoxyuridine, and 5-iodo-2′-deoxyuridine. An X-ray crystallographic study of one diastereomer of the *N*-benzylphosphoramidate based on the 3′,5′-cyclic diester of adenosine established the trans relationship of the $PhCH_2NH$ and nitrogen base as well as the equatorial position of the $PhCH_2NH$ on the chair form of the 1,3,2-dioxaphosphorinane ring. The structural parameters observed for the five- and six-membered rings are consistent with those of other neutral cyclic nucleotide derivatives.

Nucleoside 3′,5′-cyclic phosphoramidates, neutral derivatives of nucleoside 3′,5′-cyclic monophosphates, have proved to be valuable for the determination of binding and activation requirements for the active sites of protein kinases and phosphodiesterases.[1] They and other neutral derivatives have been useful in the study of the chair-twist conformational equilibrium available to the phosphate ring of such compounds derived from thymidine.[2] Recently, the anilidates of protected cAMP and other nucleotide

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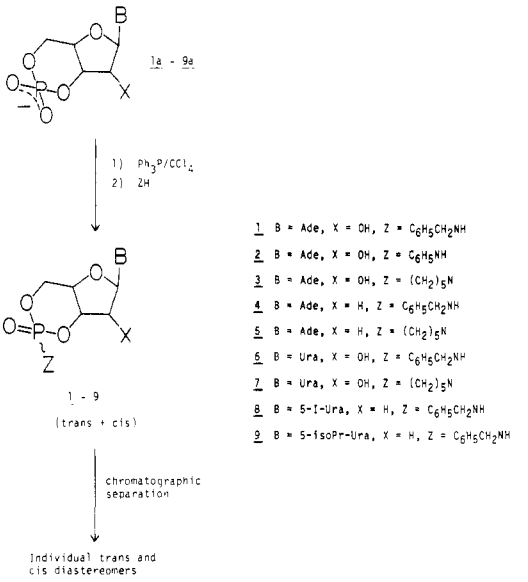
cyclic 3′,5′-diesters have been employed in a Wadsworth–Emmons type reaction with CS_2 to give cyclic phosphorothioates with sulfur stereospecifically axial or equatorial on phosphorus.[3] Such phosphorothioates are also important as probes of the binding and activation requirements of phosphodiesterases and protein kinases.[1] With isotopic oxygen-labeled aldehydes or CO_2, the above anilidates yield cyclic 3′,5′-monophosphates with ^{17}O or ^{18}O introduced stereospecifically.[3,4] Both the oxygen-labeled diesters and phosphorothioates have demonstrated their utility in studies of the stereochemistry about phosphorus of various enzyme-catalyzed phosphoryl-transfer reactions.[5]

Routes to cyclic phosphoramidates based on nucleoside cyclic 3′,5′-monophosphates have often employed the 3′,5′-monophosphate as starting material and normally have involved activation of a P–O bond followed by nucleophilic substitution. Early studies utilized $(PhO)_2P(O)Cl$[6] or $POCl_3$[7] as activating agents and generally required multistep protection–deprotection sequences to avoid involvement of a potentially reactive functionality on the base and sugar moieties. Following the same approach, the Appel reaction[8] was used to convert $N^6,O^{2'}$-benzoylated adenosine cyclic 3′,5′-monophosphate to its *N,N*-dimethylphosphoramidates[9] and phosphoranilidates.[3] Both could be separated into the individual diastereomers and then deblocked. Direct reaction of unblocked *deoxyribonucleoside* 3′,5′-cyclic phosphates also could be readily carried out. Recently, a simple two-step method was demonstrated for the preparation of ribonucleoside (adenine, guanine, uridine, and cytidine) cyclic 3′,5′-*N,N*-dimethylphosphoramidates *directly* from the *ribonucleoside* cyclic 3′,5′-monophosphate *without* blocking of the NH_2 of the heterocyclic base and the 2′-OH.[10] The classic activating agent 2,4,6-triisopropylbenzenesulfonyl chloride was used. Yields (18–33%) were considerably improved over those reported for the Appel route.[9] Unfortunately, only one diastereomer was obtained with cGMP. The ratio of diastereomers, trans/cis, was generally high (>5.6), as well. No survey of reaction scope with respect to amine was conducted as only *N,N*-dimethyl derivatives were synthesized.

In this paper we report an efficient one-flask route to the phosphoramidates of nucleoside cyclic 3′,5′-monophosphates. This approach, which might be termed a direct Appel method, uses commercially available, *unprotected* 3′,5′-cyclic diesters. Isolated yields are relatively high (31–85%), and both diastereomers are formed in all nine nucleosides studied with the trans/cis ratio of diastereomers no greater than 2.4 for seven of the nine examples. Both ribo- and deoxyribonucleoside cyclic 3′,5′-monophosphates were used as well as several different

Scheme I

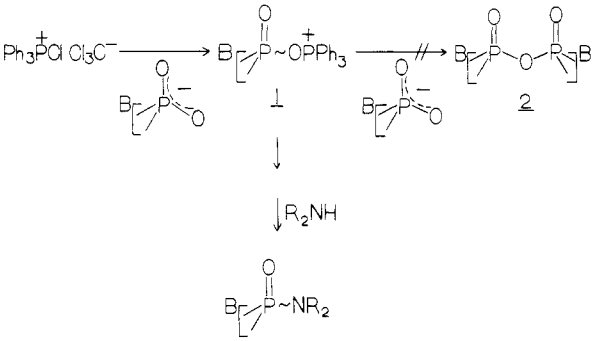


amines, and the reaction is equally applicable to pyrimidine and purine cases.

In view of the relatively high yields of the anilidates obtained, the present method may prove advantageous for the preparation of the very valuable corresponding cyclic phosphorothioates[3] and isotopic oxygen labeled cyclic phosphate diesters.[3,4] This should only require subsequent protection of the 2′-OH of the anilidates before conversion to the desired phosphorothioates and labeled cyclic diesters.

Results and Discussion

The nucleoside cyclic 3′,5′-monophosphate trialkylammonium salts, **1a–9b**, were reacted at 25 °C with three molar equivalents each of Ph_3P and CCl_4 in anhydrous pyridine followed by addition of the appropriate amine (Scheme I). It is advantageous to use the tri-*n*-butylammonium salts because of their superior solubilities in pyridine. The cyclic 3′,5′-monophosphate, Ph_3P, and CCl_4 are allowed to undergo a short prereaction before addition of the amine. Since yields can be greater than 50%, it is clear that the anhydride, **2**, is not the primary activated



intermediate. (We were unable to detect intermediate **2** by ^{31}P NMR[12] on samples examined just before addition of amine.) It is reasonable that **1** represents the initial reactive species, which in pyridine solvent may be further transformed to the pyridinium salt[13] before reaction with

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Table I. Synthetic and ^{31}P NMR Data for 1–9

compd	formula	analyses[a]	conversion,[b] %	yield[c] %	trans/cis[d]	δ ^{31}P[e] trans	δ ^{31}P[e] cis	R_f[f] trans	R_f[f] cis	(solvent)
1	$C_{17}H_{19}N_6O_5P$	C, H, N, P	50	34	1.2	7.51	5.09	0.22	0.26	($CHCl_3$/MeOH, 5/1)
2	$C_{16}H_{17}N_6O_5P$	C, H, N, P	86	78	0.5	1.06	−2.54	0.20	0.22	($CHCl_3$/MeOH, 5/1)
3	$C_{15}H_{21}N_6O_5P$	C, H, N, P	40	31	3.6	6.34	4.33	0.35	0.39	($CHCl_3$/MeOH, 5/1)
4	$C_{17}H_{19}N_6O_4P$	C, H, N, P	57	45	2.4	6.99	5.12	0.39	0.35	($CHCl_3$/MeOH, 5/1)
5	$C_{15}H_{21}N_6O_4P$	C, H, N, P	100	76	5.7	5.83	3.86	0.51	0.47	($CHCl_3$/MeOH, 5/1)
6	$C_{16}H_{18}N_3O_7P$	C, H, N, P	62	46	0.7	7.89	5.93	0.34	0.37	($CHCl_3$/EtOH, 5/1)
7	$C_{14}H_{20}N_3O_7P$	C, H, N, P	100	85	1.4	6.46	4.50	0.37	0.28	($CHCl_3$/EtOH, 10/1)
8	$C_{16}H_{17}IN_3O_6P$	C, H, I, N, P	*i*	10[h]	1.5	7.38[g]	5.32[g]	0.31	0.21	($CHCl_3$/EtOH, 20/1)
9	$C_{19}H_{24}N_3O_6P$	C, H, N, P	*i*	19[h]	1.5	7.17[g]	5.48[g]	0.38	0.26	($CHCl_3$/EtOH, 20/1)

[a] On mixtures of diastereomers. Found ±0.4% of theory. [b] Based on integrated ^{31}P NMR areas of products and remaining reactants assuming no other cyclic nucleotide-related peaks appear in the spectrum. [c] Yields of isolated mixtures of diastereomers unless otherwise specified. [d] From integrated ^{31}P NMR spectra. [e] In ppm downfield from external 85% H_3PO_4 in Me_2SO-d_6 on mixtures of diastereomers unless otherwise specified. [f] On 0.2-mm silica gel TLC plates. [g] On individual diastereomers in $CDCl_3$. [h] Total yield of both isomers after separation. [i] Not determined.

the amine. ^{31}P NMR showed the reactions to be very clean. Furthermore, the isolated yields, though slightly lower, were commensurate with percentage conversions. The yields were increased by 10–15% by use of a 24-h rather than shorter, 2-h, reaction times, although the yields of individual reactions were not fully maximized.

Whereas $PhNH_2$, $PhCH_2$, and piperidine all reacted readily in these systems, *i*-Pr_2NH could not be induced to give the corresponding *N,N*-diisopropylphosphoramidate. Steric hindrance may play a role in the unreactivity of *i*-Pr_2NH. Since Appel reaction conditions have been shown to convert both the 2′- and 5′-hydroxyls of pyrimdine nucleosides to the corresponding chlorides,[14] the lack of involvement of the 2′-OH in these reactions is noteworthy.

Separation of the individual diastereomers of 1–9 (Scheme I) was readily effected by absorption chromatography on SiO_2 following column chromatographic isolation of the pure diastereomer mixtures. Indeed, the trans and cis diastereomers of 1 were cleanly separated by simple column chromatography. For the other cases, silica gel TLC on a 0.2–0.5-mm plate effectively separated 5–20 mg of the diastereomeric mixtures. Typically 20–100-mg amounts of individual diastereomers were isolated. No doubt MPLC techniques, which we used to separate the individual diastereomers of thymidine 3′,5′-cyclic *N,N*-dimethylphosphoramidates in several hundred milligram amounts,[2] would make available the individual diastereomers of 1–9 in larger quantities. Assignment of geometry about phosphorus was based on relative ^{31}P chemical shifts following the well-established order.[15] Thus the diastereomer with axial amino substituent, which we refer to as the cis diastereomer, is the more upfield shifted (amino and nitrogen base, cis). For *trans*-**9**, this assignment was confirmed by X-ray crystallography, as described below.

The structures of 1–9 were further verified by mass spectrometry and by ^1H (Table II) and ^{13}C NMR spectroscopy, all of which confirmed the lack of modification of other parts of the molecules. A full analysis of coupling constants, both J_{HH} and J_{HP}, will be reported elsewhere along with a detailed discussion of the conformational properties of these molecules.

^{13}C NMR spectroscopy not only confirmed the structure of **1**, **8**, and **9** but also revealed correlations useful in assignment of specific geometries to the individual diastereomers. Pertinent data are abstracted in Table III. The enclosure of phosphorus in a six-membered ring is attested to by the carbon–phosphorus couplings to both C3′ and C5′. Indeed, $^2J_{PC}$ for the cis diastereomer is invariably 1–3 Hz greater than that for its trans counterpart. The reliability of this correlation will be tested with a wider variety of phosphoramidates. More dramatic is the greater $^3J_{PC}$ for C4′ of the cis diastereomers. The same correlation was noted for the *N,N*-dimethylphosphoramidates of thymidine cyclic 3′,5′-monophosphate.[15a] As we will show in a subsequent publication, the increase in $^3J_{PC}$ for the cis diastereomer is a consequence of the population of the twist conformation. Indeed the large reported $^3J_{PC}$ (11.8 Hz) for C4′ of *cis*-thymidine cyclic 3′,5′-*N,N*-dimethylphosphoramidate[15a] reflects a relatively large population of the twist conformation.[2] By contrast the corresponding alkyl triesters of nucleoside cyclic 3′,5′-monophosphates show just the opposite correlation $^3J_{PC}$ (C4′, trans) > $^3J_{PC}$ (C4′, cis).[16] The trans rather than cis triesters partially populate the twist conformation.[17]

Noteworthy, as well, is the correlation δ C3′ (cis) > δ C3′ (trans) and δ C5′ (cis) > δ C5′ (trans). The correlation δ ^{31}P (trans) > δ ^{31}P (cis) noted earlier is that expected for a normal γ-gauche effect dependent on whether the amino group is axial or equatorial. However, the influence on the C3′ and C5′ chemical shifts is just the opposite of that predicted by the influence of the γ alkyl- or phenylamino group. Evidently the phosphoryl oxygen plays an overriding role, perhaps both steric and polar. It is perhaps surprising that $^2J_{PC}$ for the PN*C*H_2 functionality of both diastereomers of **1**, **8**, and **9** is less than 0.6 Hz, whereas $^2J_{PC}$ for the *Me*$_2$NP grouping of the corresponding 3′,5′-cyclic *N,N*-dimethylphosphoramidates of thymidine ranged 2.9–4.9 Hz.[15a,18]

trans-**9** was subjected to X-ray crystallographic analysis. A perspective view of the resulting structure is given in Figure 1. As predicted by the ^{31}P chemical shifts, the $PhCH_2NH$ is indeed trans to the thymin-1-yl ring and furthermore is attached equatorially to the chair-form 1,3,2-dioxaphosphorinane ring. The dioxaphosphorinane ring, as shown by the torsion angles listed in Table IV, has a distorted chair conformation. Nevertheless, it is less distorted (puckering parameters: Q = 0.57 (1) Å, ϕ = 37.5 (33)°) than, e.g., is 5-iodo-2′-deoxyuridine 3′,5′-cyclic monophosphate P–O methyl ester.[19] In the P–O-methyl ester, the methoxy group is in the *axial* position with

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Table II. ^{1}H NMR Chemical Shifts of Individual Diastereomers of 1-9[a]

compd	diastereomer	sugar ring H1′	H2′	H2″	H3′	H4′	H5′	H5″	base	other
1	trans	6.23	4.69		5.12	4.18	4.49	4.36	8.19 (H2), 8.40 (H8), ~7.40 (NH_2)	6.08 (PNH), 4.05 (CH_2), 7.25–7.35 (C_6H_5)
	cis	6.26	4.61		5.05	4.25	4.56	4.31	8.12 (H2), 8.27 (H8), under aromatic (NH_2)	5.98 (PNH), 4.09 (CH_2), 7.24–7.41 (C_6H_5)
2	trans	6.08	4.74		5.29	4.38	4.63	4.49	8.21 (H2), 8.42 (H8), 7.37 (NH_2)	6.02 (PNH), 6.95–7.25 (C_6H_5)
	cis	6.04	4.62		5.23	4.28	4.66	4.50	8.07 (H2), 8.34 (H8), 7.36 (NH_2)	6.33 (PNH), 6.95–7.29 (C_6H_5)
3	trans	6.02	4.66		5.08	4.16	4.52	4.37	8.19 (H2), 8.40 (H8), 7.37 (NH_2)	3.08, 1.46 ($(CH_2)_5N$)
	cis	6.04	4.67		5.19	4.34	4.58	4.17	8.15 (H2), 8.35 (H8), 7.37 (NH_2)	3.06, 1.58 ($(CH_2)_5N$)
4	trans	6.47	2.80	2.65	5.32	3.95	4.45	4.35	8.19 (H2), 8.40 (H8), ~7.33 (NH_2)	6.04 (PNH), 4.04 (CH_2), 7.22–7.35 (C_6H_5)
	cis	6.48	~2.72	~2.72	5.24	4.03	4.50	4.29	8.14 (H2), 8.28 (H8), under aromatic (NH_2)	5.96 (PNH), 4.06 (CH_2), 7.23–7.44 (C_6H_5)
5	trans	6.47	2.79	2.69	5.29	3.95	4.47	4.35	8.19 (H2), 8.41 (H8), 7.34 (NH_2)	3.07, 1.39–1.59 ($(CH_2)_5N$)
	cis[c]	6.49	~2.75	~2.75	5.32	~4.15	~4.53	~4.15	8.16 (H2), 8.37 (H8), 7.35 (NH_2)	3.05, 1.56 ($(CH_2)_5N$)
6	trans[c]	5.71	4.43		4.58	4.06	4.48	4.40	5.60 (H5), overlapped (H6)	6.02 (PNH), 4.01 (CH_2), 7.25–7.34 (C_6H_5)
	cis	6.10	4.29		4.46	4.12	4.54	4.36	5.65 (H5), 7.57 (H6)	5.98 (PNH), 4.04 (CH_2), 7.22–7.40, 7.66–7.94 (C_6H_5)
7	trans	5.98	4.29		4.57	4.03	4.51	4.39	6.15 (H5), 7.72 (H6)	3.06, 1.43–1.63 ($(CH_2)_5N$)
	cis[c]	5.97	4.33		~4.56	~4.20	~4.56	~4.20	6.18 (H5), 7.69 (H6)	3.02, 1.50 ($(CH_2)_5N$)
8[b]	trans	6.34	2.65	2.58	4.99	3.95	4.55	4.49	8.15 (H6)	possible exchange with HOD (PNH), 4.15 (CH_2), 7.23–7.40 (C_6H_5)
	cis	6.32	~2.90	~2.92	4.90	4.09	4.57	4.43	7.94 (H6)	possible exchange with HOD (PNH), 4.15 (CH_2), 7.23–7.44 (C_6H_5)
9[b]	trans	6.34	2.60	2.54	4.94	3.91	4.49	4.47	overlapped (H6), 2.78 (CH), 1.17 (Me_2C)	5.00 (PNH), 4.15 (CH_2), 7.24–7.39 (C_6H_5)
	cis	6.26	~2.57	~2.55	4.89	4.02	4.55	4.34	7.22 (H6), 2.83 (CH), 1.14 (Me_2C)	4.97 (PNH), 4.15 (CH_2), 7.24–7.45 (C_6H_5)

[a] In Me_2SO-d_6 unless otherwise specified. [b] In acetone-d_6. [c] Approximate values.

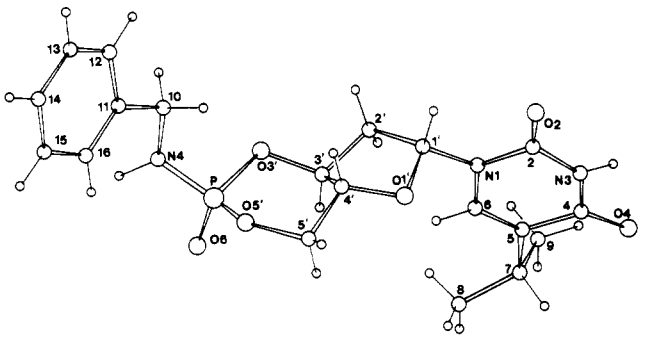

Figure 1. Perspective view of *trans*-9 showing atomic numbering. The bare numbers are carbon atoms unless indicated otherwise. The H atoms are shown but not labeled.

Table III. Important ^{13}C NMR Parameters for 1, 8, and 9

	δ ^{13}C (J_{CP}, Hz) C3′	C4′	C5′	solvent
cis-1	77.54 (5.4)	70.52 (7.1)	68.76 (9.3)	Me_2SO-d_6
trans-1	76.60 (4.1)	70.70 (4.1)	67.90 (8.0)	Me_2SO-d_6
cis-8	76.45 (5.0)	73.99 (9.0)	68.70 (8.4)	Me_2SO-d_6/$CDCl_3$
trans-8	75.38 (3.8)	74.00 (4.9)	67.83 (6.9)	Me_2SO-d_6/$CDCl_3$
cis-9	76.96 (4.9)	73.82 (9.0)	68.80 (8.1)	Me_2SO-d_6/$CDCl_3$
trans-9	76.04 (3.9)	74.16 (4.5)	68.19 (6.9)	Me_2SO-d_6/$CDCl_3$

C(3′)–O(3′)–P–O(6) = 75.9 (9)°. In the title compound, by contrast, the NH group is linked *equatorially*. Although one of the bridging oxygens is replaced by an NH moiety, the coordination of the phosphorus atom is almost perfectly trigonal pyramidal. The P=O double bond, in accord with the VSEPR theorem,[20] exerts a repulsion on

Table IV. Relevant Torsion Angles with Their ESD's in Parentheses

χ	O(1′)–C(1′)–N(1)–C(6)	73.1 (9)
	O(1′)–C(1′)–N(1)–C(2)	143.0 (11)
	C(3′)–C(2′)–C(1′)–N(1)	121.3 (9)
τ_0	C(4′)–O(1′)–C(1′)–C(2′)	-30.8 (7)
τ_1	O(1′)–C(1′)–C(2′)–C(3′)	1.9 (7)
τ_2	C(1′)–C(2′)–C(3′)–C(4′)	25.8 (7)
τ_3	C(2′)–C(3′)–C(4′)–O(1′)	-46.2 (7)
τ_4	C(3′)–C(4′)–O(1′)–C(1′)	47.4 (8)
	C(5′)–C(4′)–O(1′)–C(1′)	167.8 (11)
ω'	O(5′)–P–O(3′)–C(3′)	46.8 (6)
ϕ	P–O(3′)–C(3′)–C(4′)	-63.1 (6)
ψ'	O(3′)–C(3′)–C(4″)–C(5′)	69.5 (8)
ψ	C(3′)–C(4′)–C(5′)–O(5′)	-58.0 (8)
	P–O(5′)–C(5′)–C(4′)	49.4 (6)
ω	C(5′)–O(5′)–P–O(3′)	-43.2 (8)
	O(5′)–C(5′)–C(4′)–O(1′)	-172.9 (10)
	O(6)–P–O(3′)–C(3′)	-77.1 (7)
	N(4)–P–O(3′)–C(3′)	157.4 (7)
	C(10)–N(4)–P–O(3′)	-51.4 (7)
	C(11)–C(10)–N(4)–P	-136.4 (9)
	C(12)–C(11)–C(10)–N(4)	18.5 (10)
	C(8)–C(7)–C(5)–C(6)	-17.7 (11)
	C(9)–C(7)–C(5)–C(6)	107.9 (13)
	O(10)–N(4)–P–O(6)	176.4 (10)

(20) Gillespie, R. J. *J. Chem. Educ.* **1963**, *40*, 295.

the three other bonds around P, resulting in an average of 113.7° (rms deviation 0.3°) for the three O(6)–P–X (X = O(3′), O(5′), and N(4)) bond angles. Consequently, the three other bonds maintain three almost equal bond angles (their mean is 105.0 (9)°) with each other, while the P=O double bond coincides with a threefold axis. It is worth noting that a quasi-similar coordination of the phosphorus atom can be found in 2′-acetyluridine 3′,5′-cyclic monophosphate benzyl triester[21] in which the *O*-benzyl group is also *equatorial* to the dioxaphosphorinane ring. The orientation of the N(4)–C(10) bond to the dioxaphosphorinane ring across the N(4)–P bond is *synclinal*.

A useful way of looking at the geometry of the dioxaphosphorinane ring is to consider the angle between the extension of the best plane through atoms O(5′)–C(5′)–C(3′)–C(3′) and the plane defined by O(3′)–P–O(5′). For *trans*-**9** this angle is 39.2 (2)°, which shows the ring to be considerably flattened at the phosphorus end. This angle is unusually small for 2-oxo-1,3,2-dioxaphosphorinanes bearing axial phosphoryl oxygen, being normally 50–56°.[22] The analogous Me_2N phosphoramidate from thymidine has a corresponding angle of 52°.[23] That for the neutral cyclic triester derived from adenosine with phosphoryl oxygen equatorial is 35°.[21] The angle between O(5′)–C(5′)–C(3′)–O(3′) and C(5′)–C(4′)–C(3′), 59.4 (3)°, reflects normal six-membered chain geometry at that end of the ring.

The molecules of the title compound are bound together by two infinite intermolecular hydrogen bond chains along the [110] direction. One of them is formed by the N(3)–H(3) group with O(6) of another molecule at $(1 + x, 1 + y, z)$ with the parameters: N···O = 2.80 (1) Å, H···O = 1.95 (6) Å, ∢NH···O = 164 (4)°. The second hydrogen bridge utilizes the interaction of atoms N(4)–H(4) with O(2) at the position of $(x - 1, y - 1, z)$ and has the following parameters: N···O = 3.00 (1), H···O = 2.14 (6) Å, ∢NH···O = 173 (5)°.

The bonding of the fairly planar pyrimidine ring [χ^2 = 7.8 at 95% probability level for the least-squares plane given by eq $0.59722X - 0.40279Y - 0.69360Z = 5.16814$; max deviation 0.030 (5) Å] agrees well with the corresponding values observed in 5-isopropyl-2′-deoxyuridine[24] (hereinafter 5-ipr-dU) within experimental error. The ring itself is more planar than in 5-ipr-dU and C(7) lies practically in this plane (Δ = 0.032 (7) Å.) Similarly to 5-ipr-dU one of the isopropyl methyl groups assumes a *synperiplanar* conformation about the C(5)–C(7) bond [C(8)–C(7)–C(5)–C(6) = 17.7 (11)° vs. 12.8° in 5-ipr-dU]. Consequently, as can be seen from Figure 1, the other methyl group of the isopropyl moiety once again protrudes markedly from the best plane of the base (1.43 (1) Å). However, in contrast to the dimeric associates of 3′,5′-diacetyl-5-ethyl- and 3′,5′-diacetyl-5-isopropyl-2′-deoxyuridines,[25] in the crystal structure of the title compound, no conformational disorder of the 5-alkyl substituents could be detected. These facts taken together weaken the hypothesis put forth earlier[26] concerning the limited incorporation of 5-ipr-dU in enzymatic DNA synthesis inferred from the structure analyses of these and other 3′-5′-diacetyl-5-alkyl-2′-deoxyuridine derivatives[25] and seem to support the model suggested by Czugler and co-workers.[24] The χ torsion angle [C(6)–N(1)–C(7)–O(1′)] about the N(1)–C(1′) glycosidic bond (73.1 (9)°) is also quite close to that of 64.4° observed in 5-ipr-dU.[24]

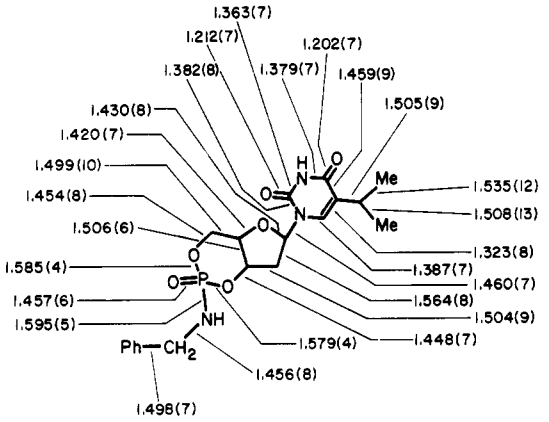

Figure 2. Pertinent bond lengths (esd's) in Angstroms for *trans*-**9**.

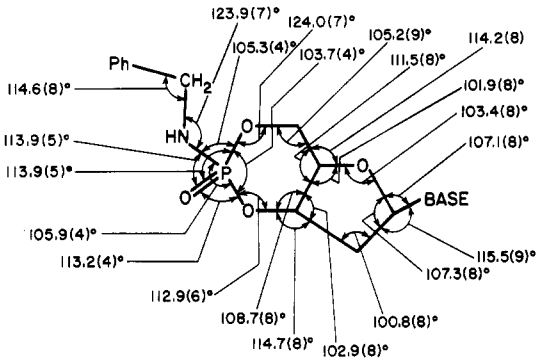

Figure 3. Pertinent bond angles (esd's) for *trans*-**9**.

Of course, because of the dioxaphosphorinane ring, there is a conspicuous difference between the conformations of the ribofuranose rings of nucleosides and their 3′,5′-cyclic nucleotides. In the title compound, as with numerous nucleoside 3′,5′-cyclic monophosphates,[21,23,27] the sugar ring assumes an envelope shape with C(3′) on the flap. This ring puckering can also be termed as C(3′)-*endo*.[28] The corresponding puckering parameters[29] and the related lowest asymmetry factor[25] are as follows: Q = 0.45 (1) Å, ϕ = 145 (1)°, fC_s(C4′) = 0.9 pm.

Bond lengths and pertinent bond angles for *trans*-**9** appear in Figures 2 and 3. Comparable parameters are similar to those for other neutral derivatives of 3′,5′-cyclic monophosphates and the cyclic diesters themselves.[21,23,27] The P–N(4) bond length (1.595 (5) Å) is similar to that found for other 2-oxo-1,3,2-dioxaphosphorinanes with substituted amino groups equatorial on a chair-form ring or pseudoequatorial on a ring in the twist conformation.[30] An important torsional angle is C(10)–N(4)–P–O(6). Its value of 176 (10)° means that the C(10)–N(4)–H(N4) and P–O(6) are nearly in the same plane. (The C(10)–N(4)–P angle of 123.7 (9)° suggests that there is close to trigonal planarity at N(4).) This arrangement is common to 2-oxo-1,3,2-dioxaphosphorinane and 1,3,2-oxazaphosphori-

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nane rings with an equatorial or pseudoequatorial substituted amino group at phosphorus[30] and apparently reflects optional bonding interaction between N(4) and P. Most probably the antiperiplanar C(10)–N(4)–P–O(6) arrangement is a result of the minimization of vicinal steric interactions along the P–N(4) bond.

Experimental Section

cAMP monohydrate and cUMP sodium salt were generous gifts from Professor Roland K. Robins. 5-Iodo- and 5-isopropyl-2′-deoxyuridine 3′,5′-cyclic phosphates were synthesized according to a procedure to be published elsewhere.[31] The trialkylamines and the ammonium bicarbonate were reagent grade and were used without purification. Nucleoside 3′,5′-cyclic phosphate trialkylammonium salts were dried under vacuum (0.13 Pa) over P_2O_5 at room temperature for at least an overnight period. 2′-Deoxyadenosine monohydrate was purchased from the Aldrich Chemical Co. Triphenylphosphine was crystallized from ethanol. Carbon tetrachloride, pyridine, and phosphoryl chloride were distilled from P_2O_5. Benzylamine, aniline, and trimethyl phosphate were vacuum distilled before use. Piperidine was freshly distilled from KOH. The Appel-type reactions were performed with the exclusion of air and moisture using syringe techniques.

Amberlite IR-120 was purchased from Fluka Chemical Corp. DEAE Sephadex A-25 was the product of Pharmacia Fine Chemicals, Sweden, and purchased from Sigma Chemical So. Silica gels used for absorption column chromatography were the products of Merck, Darmstadt, FRG. (Kieselgel 40, 0.063–0.200 mm and Kieselgel 60, 0.040–0.063 mm), and J. T. Baker Chemical Co. (silica gel, 0.070–0.200 mm). Precoated TLC plates (silica gel 60 F_{254}, 0.2 mm × 20 cm × 20 cm and 0.5 mm × 20 cm × 20 cm) used to separate the diastereoisomers were the product of Merck, Darmstadt. *trans*- and *cis*-**1**–**9** were extracted from silica gel with 1/1 $CHCl_3$/MeOH or 1/1 $CHCl_3$/EtOH at ambient temperature. The ratios of the solvents in the solvent mixtures used are always expressed in v/v. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. ^{31}P and ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer operating at 32.2 and 20.0 MHz, respectively. Positive chemical shifts for ^{31}P are in ppm downfield from external 85% H_3PO_4. The ^1H and, for **1**, ^{13}C NMR spectra were collected on a Varian SC-300 spectrometer operating at 300.3 and 75.5 MHz, respectively. In the former case, 32K points were used over a 3 kHz sweep width giving a digital resolution of ±0.18 Hz. In the latter case, 16K points were used over 15 kHz giving reported chemical shifts accurate to ±0.02 ppm. The ^{13}C spectrum of *trans*-**1** also was run at 75.5 MHz with ±0.27 Hz resolution. Where appropriate, computer simulation of proton spectra were performed by using a modified LAOCOON NMR simulation program on either a DEC-20 or VAX 11/750 computer. Samples were prepared by dissolving 5–20 mg of compounds in 0.5 mL of deuterated solvent which also served as the field/frequency lock. ^{13}C NMR spectra of *trans*- and *cis*-**8** and **9** were recorded on a disk-augmented Varian XL-100/15 spectrometer operating at 25.2 MHz. ^1H and ^{13}C chemical shifts are expressed in ppm downfield from internal Me_4Si.

Electron-impact mass spectra of *trans*- and *cis*-**1** were acquired by using a Varian MAT 112S mass spectrometer with ionizing energy of 80 eV and an ion source temperature of 270 °C. Mass spectral measurements for *trans*- and *cis*-**8** and **9** were carried out on an AEI MS-902 double-focusing instrument with ionizing energy of 70 eV and ion source temperature of 180 °C. All samples were introduced by direct probe techniques. Trimethylsilylation of the cyclic nucleotides prior to EI-MS analysis was carried by the addition of 90 μL of BSTFA and 10 μL of pyridine to approximately 0.2 mg of compound in a glass capillary; reaction time at 100 °C was 1 h. UV spectra were recorded in methanol with a Varian Cary 17D UV–vis spectrophotometer system.

General Procedure for the Synthesis of Diastereomeric Nucleoside 3′,5′-Cyclic N-Substituted Phosphoramidates. Adenosine 3′,5′-Cyclic *N*-Benzylphosphoramidates (1). To a stirred mixture of cAMP monohydrate (0.347 g, 1.0 mmol) in 10 mL of water was added triethylamine (0.208 mL, 1.5 mmol). The solution, obtained after a few minutes of stirring, was evaporated to dryness and further dried in vacuum over P_2O_5. A mixture of the resulting cAMP triethylammonium salt, **1a**, (0.430 g, 1.0 mmol) and Ph_3P (0.787 g, 3.0 mmol) in 5 mL of pyridine was vigorously stirred and to it was added successively CCl_4 (0.461 g, 3.0 mmol) and, dropwise, benzylamine (0.643 g, 6.0 mmol) at ambient temperature. After 24 h the reaction mixture was evaporated to dryness in vacuum (2 kPa, <40 °C) and then coevaporated with toluene (3 × 30 mL) to remove the pyridine. The oily residue was dissolved in a small volume (5 mL) of chloroform/methanol (3/1). The solution was applied to a silica gel (Merck) column (2.5 × 40 cm). Compound **1** (0.142 g, both isomers) was eluted (5 mL/6 min/fraction) with chloroform/methanol (5/1) and appeared in fractions 46–55. The chromatography was monitored by UV spectroscopy at 260 nm. After this prepurification, the trans and cis diastereoisomers of compound **1** (0.131 g) were separated by repeating the above column chromatographic procedure under the same conditions (*trans*-**1**, 0.060 g; *cis*-**1**, 0.052 g).

***trans*-1.** UV: λ_{max} 258 nm; λ_{min} 226 nm. EI-MS, *m/e* (relative intensity %): 635, $M^+ + 3\ Me_3Si$ (3.3); 620, $M^+ + 3\ Me_3Si - 15$ (3.3). ^{13}C NMR (75.5 MHz, Me_2SO-d_6): δ 44.35 (CH_2NH, J_{PC} < 1.9 Hz), 67.90 (C5′, d, J_{PC} = 8.0 Hz), 70.70 (C4′, d, J_{PC} = 4.1 Hz), 71.67 (C2′, d, J_{PC} = 7.3 Hz), 76.60 (C3′, d, J_{PC} 4.1 Hz), 92.06 (C1′), 119.30 (C5), 127.04 (*p*-C_6H_5), 127.48 (*m*-C_6H_5), 128.42 (*o*-C_6H_5), 140.46 (C8), 149.08 (C4), 153.26 (C2), 156.49 (C6), ipso-C_6H_5 (not observed).

***cis*-1.** UV: λ_{max} 258 nm; λ_{min} 230 nm. EI-MS, *m/e* (relative intensity %): 635, $M^+ + 3\ Me_3Si$ (16.8); 620, $M^+ + 3\ Me_3Si - 15$ (24.5). ^{13}C NMR (75.5 MHz, Me_2SO-d_6): δ 43.91 (CH_2NH, J_{PC} < 1.9 Hz), 68.76 (C5′, d, J_{PC} = 9.3 Hz), 70.52 (C4′, d, J_{PC} = 7.1 Hz), 71.54 (C2′, d, J_{PC} = 7.3 Hz), 77.54 (C3′, d, J_{PC} = 5.4 Hz), 91.90 (C1′), 127.12 (*p*-C_6H_5), 127.51 (*m*-C_6H_5), 128.45 (*o*-C_6H_5), 140.06 (C8), 153.14 (C2), 156.47 (C6); not observed, C4, C5, and ipso-C_6H_5.

Adenosine 3′,5′-Cyclic *N*-Phenylphosphoramidates (2). cAMP monohydrate (0.347 g, 1.0 mmol) and tri-*n*-butylamine (0.36 mL, 1.5 mmol) were refluxed in 10 mL of methanol until a clear solution was obtained. After evaporation to dryness, the glassy residue was dried under vacuum and used as starting compound, **2a**. Aniline (0.56 g, 6.0 mmol), as the last component, was added after a 5-min prereaction of cAMP with Ph_3P and CCl_4. After 21 h at room temperature, the solvent was evaporated, and the oily residue was chromatographed on a silica gel (Baker) column (2.7 × 24 cm) eluted with $CHCl_3$/EtOH (5/1) at a rate of 13 mL/8 min/fraction. Compound **2** (both isomers) appeared in fractions 21–40. The trans and cis isomers were separated on silica gel TLC plates (~10 mg/0.2 mm thick plate), developing them twice in $CHCl_3$/MeOH (5/1). In this and other preparations, of the order 20–100 mg, the diastereomers were separated by TLC.

Adenosine 3′,5′-Cyclic *N*,*N*-Pentamethylenephosphoramidates (3). cAMP triethylammonium salt was used as starting material. After a 22-h reaction, the oily residue of the evaporated reaction mixture was chromatographed on a silica gel (Merck) column (2.7 × 22 cm) eluted with $CHCl_3$/MeOH (5/1) at 15 mL/5 min/fraction. Compound **3** appeared in fractions 7–12. The trans and cis isomers were separated on silica gel TLC plates (~9 mg/0.2 mm thick plate), developed with $CHCl_3$/MeOH (7/1).

2′-Deoxyadenosine 3′,5′-Cyclic Phosphate (cdAMP). 2′-Deoxyadenosine 5′-phosphate (dAMP), as precursor for cdAMP, was synthesized in a Yoshikawa phosphorylation reaction[32] by using a modification of the procedure of Ludwig.[33] Previously dried (110 °C, 0.13 kPa, 2 h) 2′-deoxyadenosine (1.0 g, 4 mmol) was dissolved in 10 mL of trimethyl phosphate at 120–130 °C. The solution thus obtained was cooled (−20 °C), and phosphoryl chloride (0.48 mL, 5.2 mmol) was added with vigorous stirring. After reaction at −20 °C for 2 h, the mixture was poured into ice–water containing NH_4HCO_3 (2,4 g, 31.2 mmol). This solution (pH 6) was applied to a DEAE Sephadex A-25 (HCO_3^-) column (2.7 × 53 cm). The column was first washed with water (350 mL). The 5′-phosphate was then eluted (18 mL/9 min/fraction) using

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a linear gradient of water (1.5 L) and 1 M NH_4HCO_3 solution (1.5 L). dAMP appeared in fractions 71–85 (diammonium salt, yield 88%). cdAMP was prepared as described earlier[34] (ammonium salt, yield 76%). The free acid was precipitated as a white powder (81% yield) on adding aqueous 1 M HCl to a solution of cdAMP ammonium salt in water until a pH of 2 was attained.

2'-Deoxyadenosine 3',5'-Cyclic *N*-Benzylphosphoramidates (4). cdAMP tri-*n*-butylammonium salt (**4a**) was used as starting material. The volume of pyridine was doubled (10 mL per 1 mmol of starting material). The benzylamine was added after a 5-min prereaction period. The oily residue of the evaporated reaction mixture (24 h reaction) was chromatographed on a silica gel (Baker) column (2.7 × 23 cm) eluted with $CHCl_3$/MeOH (20/1) at 12 mL/8 min/fraction. Compound **4** appeared in fractions 35–54. The trans and cis isomers were separated on silica gel TLC plates (~6 mg/0.2 mm thick plate), developed three times with $CHCl_3$/EtOH (6/1).

2'-Deoxyadenosine 3',5'-Cyclic *N*,*N*-Pentamethylenephosphoramidates (5). cdAMP tri-*n*-butylammonium salt was used as starting compound. Piperidine was added after a 10-min prereaction. The oily residue of the evaporated reaction mixture (24 h reaction) was chromatographed on a silica gel (Baker) column (2.7 × 23 cm) eluted with $CHCl_3$/MeOH (20/1) at 12 mL/8 min/fraction. Compound **5** appeared in fractions 19–36. The trans and cis isomers were separated on silica gel TLC plates (~5 mg/0.2 mm thick plate), developed twice with $CHCl_3$/MeOH (8/1).

Uridine 3',5'-Cyclic *N*-Benzylphosphoramidates (6). Uridine 3',5'-cyclic phosphate sodium salt (0.328 g, 1.0 mmol) was dissolved in 5 mL of distilled water and applied to an Amberlite IR-120 (H^+) column (1.4 × 20 cm). The column was washed with distilled water until no more UV absorbance appeared. The eluate was evaporated to dryness, and tri-*n*-butylamine (0.36 mL, 1.5 mmol) in 10 mL of methanol was added to the residue. The solution thus obtained was evaporated and dried in vacuum (0.2 Pa). The oily residue from evaporation of the solvent following a 21-h Appel reaction was applied to a silica gel (Baker) column (2.7 × 24 cm). Compound **6** was eluted at a rate of 12 mL/8 min/fraction with $CHCl_3$/MeOH (20/1). Fractions 34–43 contained mainly the cis isomer, while most of the trans one appeared in fractions 44–52. The trans and cis isomers were completely separated on silica gel TLC plates (~10 mg/0.2 mm thick plate) after three developments with $CHCl_3$/MeOH (10/1).

Uridine 3',5'-Cyclic *N*,*N*-Pentamethylenephosphoramidates (7). cUMP triethylammonium salt (**7a**) was used as starting compound. Following an 18-h reaction, oily residue of the evaporated reaction mixture was applied to a silica gel (Baker) column (2.7 × 23 cm) and eluted (10 mL/6 min/fraction) with $CHCl_3$/EtOH (20/1). Fractions 14–24 contained mainly the trans isomer while most of the cis one appeared in fractions 25–40. The final separation of the isomers was achieved on silica gel TLC plates (~15 mg/0.2 mm thick plate), developed twice with $CHCl_3$/EtOH (10/1).

5-Iodo-2'-deoxyuridine 3',5'-Cyclic *N*-Benzylphosphoramidates (8). 5-Iodo-2'-deoxyuridine 3',5'-cyclic phosphate triethylammonium salt (**8a**) was used as starting material. Following a 24-h reaction, the solvent was evaporated, and the oily residue was dissolved in 60 mL of 1/1 $CHCl_3$ and water. The aqueous phase was washed with additional portions (3 × 30 mL) of $CHCl_3$. The combined organic layer was dried ($MgSO_4$) and evaporated to dryness. Purification of this residue was performed on a silica gel (Merck) column (2.5 × 40 cm) using $CHCl_3$/EtOH (20/1) for elution (10 mL/5 min/fraction). Both isomers appeared in fractions 14–22. The trans and cis diastereoisomers were separated on preparative silica gel TLC plates (~20 mg/0.5 mm thick plate), developed twice with $CHCl_3$/EtOH (20/1).

***trans*-8.** ^{13}C NMR (Me_2SO-d_6/$CDCl_3$): δ 34.89 (C2', d, J_{PC} = 8.6 Hz), 44.62 (CH_2NH, J_{PC} < 0.6 Hz), 67.83 (C5', d, J_{PC} = 6.9 Hz), 69.94 (C5), 74.00 (C4', d, J_{PC} = 4.9 Hz), 75.38 (C3', d, J_{PC} = 3.8 Hz), 85.23 (C1'), 126.84 (*p*-C_6H_5), 127.19 (*m*-C_6H_5), 128.10 (*o*-C_6H_5), 139.88 (ipso-C_6H_5), 145.30 (C6), 149.85 (C2), 160.38 (C4).

***cis*-8.** EI-MS, *m*/*e* (relative intensity %): 649, M^+ + 2 Me_3Si (65); 634, M^+ + 2 Me_3Si − 15 (45); 577, M^+ + Me_3Si (100); 562, M^+ + Me_3Si − 15 (33). ^{13}C NMR (Me_2SO-d_6/$CDCl_3$): δ 35.38, (C2', d, J_{PC} = 7.9 Hz), 44.81 (CH_2NH, J_{PC} < 0.6 Hz), 68.70 (C5', d, J_{PC} = 8.4 Hz), 69.83 (C5), 73.99 (C4', d, J_{PC} = 9.0 Hz), 76.45 (C3', d, J_{PC} = 5.0 Hz) 86.20 (C1'), 127.29 (*p*-C_6H_5), 127.63 (*m*-C_6H_5), 128.45 (*o*-C_6H_5), 139.66 (ipso-C_6H_5), 144.88 (C6), 149.85 (C2), 160.46 (C4).

5-Isopropyl-2'-deoxyuridine 3',5'-Cyclic *N*-Benzylphosphoramidates (9). 5-Isopropyl-2'-deoxyuridine 3',5'-cyclic phosphate triethylammonium salt (**9a**) was used as starting material. The synthesis (24 h), the purification (fractions 11–19), and the separation (~20 mg/0.5 mm thick plate) were essentially the same as described for **8**.

***trans*-9.** UV: λ_{max} 261 nm; λ_{min} 231 nm. EI-MS, *m*/*e* (relative intensity %): 565, M^+ + 2 Me_3Si (15); 550, M^+ + 2 Me_3Si − 15 (8); 493, M^+ + Me_3Si (13); 478, M^+ + Me_3Si − 15 (6); 421, M^+ (6). ^{13}C NMR (Me_2SO-d_6/$CDCl_3$): δ 21.33, 21.37 (*Me*$_2$CH), 26.11 (CH), 35.26 (C2', d, J_{PC} = 8.5 Hz), 45.00 (CH_2NH, J_{PC} < 0.6 Hz), 68.19 (C5', d, J_{PC} = 6.9 Hz), 74.16 (C4', d, J_{PC} = 4.5 Hz), 76.04 (C3', d, J_{PC} = 3.9 Hz), 85.32 (C1'), 121.53 (C5), 127.13 (*p*-C_6H_5), 127.31 (*m*-C_6H_5), 128.30 (*o*-C_6H_5), 134.02 (C6), 139.48 (ipso-C_6H_5), 150.07 (C2), 163.16 (C4).

***cis*-9.** EI-MS, *m*/*e* (relative intensity %): 565, M^+ + 2 Me_3Si (0.3); 550, M^+ + 2 Me_3Si − 15 (0.2); 493, M^+ + Me_3Si (0.5); 478, M^+ + Me_3Si − 15 (0.2); 421, M^+ (0.1). ^{13}C NMR (Me_2SO-d_6/$CDCl_3$): δ 21.35 (*Me*$_2$CH), 25.97 (CH), 34.93 (C2', d, J_{PC} = 7.9 Hz), 44.62 (CH_2NH, J_{PC} < 0.6 Hz), 68.80 (C5', d, J_{PC} = 8.1 Hz), 73.82 (C4', d, J_{PC} = 9.0 Hz), 76.96 (C3', d, J_{PC} = 4.9 Hz), 86.66 (C1'), 121.00 (C5), 127.12 (*p*-C_6H_5), 127.50 (*m*-C_6H_5), 128.32 (*o*-C_6H_5), 135.07 (C6), 139.78 (ipso-C_6H_5), 149.89 (C2), 163.24 (C4).

X-ray Analysis of *trans*-9. $C_{19}H_{24}N_3O_6P$ (MW = 421.39) crystallized in the noncentrosymmetric triclinic space group *P*1. The size of the crystal selected for X-ray measurements was about 0.30 × 0.30 × 0.15 mm^3. The precise cell dimensions: a = 6.524 (3) Å, b = 8.564 (2) Å, c = 9.996 (2) Å, α = 72.94 (2)°, β = 78.09 (3)°, γ = 85.44 (2)°, V = 522.3 (4) Å^3 (Z = 1, D_c = 1.340 g cm^{-3}) $F(000)$ = 222 were determined by least-squares refinement of diffractometer angles for 25 automatically centered reflections. The reflection intensities were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer at 22 °C using graphite monochromated Mo K_α radiation (λ = 0.71073 Å) with $\omega/2\theta$ scan (scan width 0.35 ± 0.35 tan θ) in the range $1.5 \leq \theta \leq 28.0°$. The scan rate for each reflection was determined by a rapid prescan at 10° min^{-1} in θ at which point any reflection with $I < \sigma(I)$ was coded as unobserved. Three standard reflections (525, $1\bar{5}3$, $2\bar{4}4$) were monitored every hour and showed no significant deviation (~1.1%). The total exposure time was 35 h during which 3037 reflections were recorded. After correction of Lorentz and polarization effects, 2432 with $|F|^2 > 2.0\sigma(F^2)$ were taken as observed. The phase problem was solved by direct methods using the MULTAN program.[35] In the calculations of the phase relationships, 293 normalized structure factors having $E \geq 1.51$ were used. The *E*-map computed from set 24 of best consistency revealed the position of 6 out of 29 non-hydrogen atoms (R = 0.40). Subsequent structure factor and Fourier calculations revealed the positions of the other non-hydrogen atoms (R = 0.27).

The structural model could only reflected isotropically by full-matrix least-squares to an R value of 0.145 for 2331 reflections ($|F|^2 > 3.0\sigma(F^2)$). Consequently, a spherical empirical absorption correction was calculated by using the DIFABS program.[36] The minimum and maximum absorption corrections are 0.676 and 1.518, respectively. This reduced R to 0.119. Coordinates of H atoms bound to C atoms were generated from assumed geometries while those belonging to the NH groups were located in difference electron density maps.

The positional parameters of H atoms together with their isotropic temperature factors were refined at the end of the anisotropic treatment of the non-hydrogen parameters which led to a final R = 0.064 (R_w = 0.072, R_{tot} = 0.074). The function minimized during the refinement was $\sum w(|F_o| - |F_c|)^2$ using the

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weighting scheme $w = [\sigma^2(F_o) + 0.25(pF_o)^2]^{-1}$ ($p = 0.01$). The error in an observation of unit weights $S = 3.8$. Scattering factors were taken from standard tables.[37] All calculations were performed on a PDP-11/34 minicomputer with an Enraf-Nonius SDP program package and local programs. The final positional and isotropic temperature factors of the non-hydrogen atoms are given in the supplementary material.

Acknowledgment. We thank Professor Roland K. Robins for gifts of cAMP and cUMP. This research was supported by Grant CA 11045 (to W.G.B.) from the National Cancer Institute of the Public Health Service. Thanks are also extended to Professor W. J. Stee in whose laboratory J. Beres became aquainted with the use of the Appel reaction to prepare protected 3',5'-cyclic phosphoramidates.

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Registry No. 1 (*R* isomer), 94903-45-4; 1 (*S* isomer), 94903-46-5; **1a**, 51642-68-3; 2 (*R* isomer), 71960-54-8; 2 (*S* isomer), 71960-53-7; **2a**, 59618-81-4; 3 (*R* isomer), 94903-47-6; 3 (*S* isomer), 94903-48-7; 4 (*R* isomer), 94844-12-9; 4 (*S* isomer), 94844-13-0; **4a**, 94844-11-8; 5 (*R* isomer), 94844-14-1; 5 (*S* isomer), 94844-15-2; 6 (*R* isomer), 94844-17-4; 6 (*S* isomer), 94844-18-5; 7 (*R* isomer), 94844-19-6; 7 (*S* isomer), 94844-20-9; **7a**, 20212-92-4; 8 (*R* isomer), 94844-23-2; 8 (*S* isomer), 94844-24-3; **8a**, 94844-22-1; 9 (*R* isomer), 94844-27-6; 9 (*S* isomer), 94844-28-7; **9a**, 94844-26-5; Ph_3P, 603-35-0; CCl_4, 56-23-5; dAMP·$2NH_3$, 94844-09-4; cdAMP·NH_3, 94844-10-7; benzylamine, 100-46-9; aniline, 62-53-3; piperidine, 110-89-4; 2'-deoxyadenosine, 958-09-8; uridine 3',5'-cyclic phosphate tributyl ammonium salt, 94844-16-3.

Supplementary Material Available: Listings of fractional atomic coordinates of hydrogen and non-hydrogen atoms, bond lengths, bond angles, torsion angles, weighted least-squares planes and lines, and general temperature factor expressions for the title compound **9**, and analytical data for compounds **1-9** (9 pages). Ordering information is given on any current masthead page.

Synthesis of Heterocyclic Compounds Containing Phosphorus Residues by Cycloaddition of 1,3-Dipoles to Cyclobutenylphosphorus Compounds

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Received September 27, 1984

The cycloaddition reactions of 1-cyclobutenylphosphorus compounds with 1,3-dipoles such as diazomethane, nitrile oxides, and a nitrone regiospecifically gave Δ^1-pyrazolin-3-yl-, Δ^2-isoxazolin-5-yl-, and isoxazolidin-4-ylphosphorus compounds, respectively. The reactivity of 1-cycloalkenylphosphonium salts toward diazomethane was investigated.

1,3-Dipolar cycloadditions of 1,3-dipoles such as diazoalkanes,[1] nitrones,[2] and nitrile imines[3] to vinylphosphonates and related phosphoryl compounds as well as a variety of olefins have been well studied so far. Similar cycloadditions of diazoalkanes,[4] an azide anion,[5] and nitrile ylides[6] to vinyl- and alkenylphosphonium salts and use of the resulting cycloadducts in syntheses of heterocyclic compounds such as pyrazoles, triazoles, and pyrroles as useful intermediate reagents have been reported. However, the reaction of 1,3-dipoles with their homologues, cycloalkenylphosphonium salts, has not been studied to date. On the other hand, we have recently reported the general synthesis[7] and some synthetic applications[8] of cycloalkenylphosphonium salts. In connection with our continuing interest in the utilization of 1-cycloalkenylphosphonium salts, we have examined herein the cycloaddition reactions of 1,3-dipoles with 1-cyclobutenylphosphorus compounds, which provide strained bicycloheterocyclic compounds retaining the phosphorus moiety. Furthermore, the influence of ring sizes of 1-cycloalkenylphosphonium salts on the cycloaddition reaction with diazomethane was investigated.

Results and Discussion

Reaction with Diazomethane. The reaction of 1-cyclobutenyltriphenylphosphonium perchlorate (**1a**) with diazomethane occurred even under mild conditions (0 °C, 5 h) to give only a Δ^1-pyrazolin-3-ylphosphonium salt **3a** in 80% yield. The similar reaction using 1-cyclobutenyldiphenylphosphine oxide (**2**) produced the corresponding Δ^1-pyrazolinylphosphine oxide **4** in 72% yield although rather prolonged reaction time (10 h) was necessitated. On the other hand, similar treatment of **1a** with diphenyldiazomethane led to none of the cycloadduct. In order to investigate the influence of ring sizes of 1-cyclo-

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