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# Synthesis and Structure of Novel Phosphonodipeptides Containing a Uracil or Thymine Group

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ABSTRACT: *A series of novel phosphonodipeptides containing a uracil or thymine group was synthesized in 54.2–74.1% yields by means of a peptide coupling reaction with DCC as the dehydrating agent and 1-hydroxybezotriazole as the activating agent of the carboxyl group. All products were characterized by $^1H$ NMR, $^{31}P$ NMR and IR spectra, and by elemental analyses. The crystal and molecular structure of compound* **6c** *has been determined by X-ray diffraction.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:422–427, 2000

## *INTRODUCTION*

The introduction of a peptide backbone into some biologically active molecules is very attractive to organic chemists. For example, peptide nucleic acids (PNAs) [1], used as potential antisense therapeutic and diagnostic tools [2–5], were synthesized by introducing a peptide group into the nucleoside structure. As mimics of amino acids and peptides, $\alpha$-aminophosphonic acids and phosphonopeptides exhibit various interesting biological activities [6–9]. Some of them have been used as anticancer, antibacterial, and antibiotic agents [10–12].

Various uracil and thymine derivatives have been synthesized and tested as anticancer or antiviral drugs [13–17]. Pyrimidin-1-yl or purin-9-yl phosphonic acids were also found to be a new class of antiviral agents with a broad spectrum of activities against retroviruses and DNA virus for inhibiting DNA polymerase [18–19]. To the best of our knowledge, there are few studies on the synthesis and biological activities of phosphonopeptide-containing nucleosides.

In order to search for a novel biologically active peptide, we designed and synthesized a number of novel phosphonodipeptides containing a uracil or thymine group, and their structures and intermolecular hydrogen bond were studied by the X-ray crystal diffraction method.

## *RESULT AND DISCUSSION*

### *Synthesis of α-[(Uracil-1-yl or thymin-1-yl)methylformyl]amino-α-arylmethyl-O,O-diphenylphosphonates* (**6**)

The title compounds **6a** and **6i** were synthesized by the route shown in Scheme 1. The thymin-1-ylacetic acid **2** or uracil-1-ylacetic acid **2′** was obtained by the reaction of bromoacetic acid with thymine 1 (or uracil **1′**) in water at 40°C in the presence of potassium hydroxide [20]. The $\alpha$-aminophosphonic acid esters **4** were prepared according to literature methods [21–22]. The compounds **2** and **2′** were converted into the acetyl chlorides **3** and **3′** by the addition of $SOCl_2$ to solutions of the acetic acids **2** and **2′** in $CHCl_3$ at 0°C. The $\alpha$-aminophosphonic acid ester **4** was then added to the acetyl chloride **3**(or **3′**)

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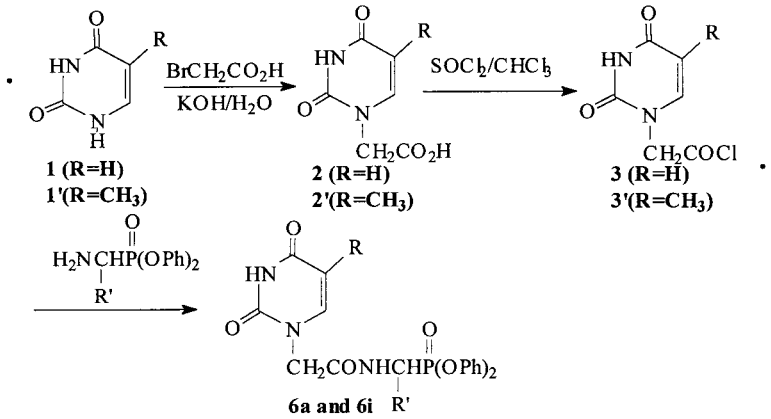
to afford the title compounds **6a** and **6i** in poor yields (24 and 31%).

In order to improve the yields of the products, the route shown in Scheme 2 was selected, DCC and 1-hydroxybenzotriazole (BtOH) were used as the dehydrating agent and the activating reagent of the carboxyl group, respectively. Thus, the acetic acids **2** and **2′** and BtOH formed the intermediates **5** by the action of DCC/BtOH, and $\alpha$-aminophosphonic acid esters were added to the crude intermediates **5** to produce compounds **6** smoothly and in good yields (54.2–74.1%). It was found that two main factors affected the conversion of **5** to **6**. One is the apparent steric hindrance of an $\alpha$-aryl group having a bulky substituent at the *ortho*-position. Another is the electronic effect of the substituent of the $\alpha$-aryl groups. The electron-withdrawing groups decrease the nucleophilicity of the amino group. The yields of all products containing the nitro group were lower than those of other products. In fact, the desired products containing a nitro group at the *ortho*-position were not obtained. All the products (**6a–p**) were purified by flash column chromatography on silica-gel.

## *The Structure of the Products*

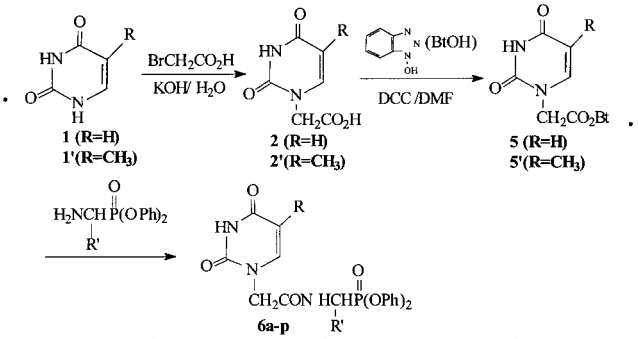
The molecular structures of the compounds **6a–p** were confirmed by $^1$H NMR, $^{31}$P NMR, and IR spectroscopy and by elemental analyses. The experimental data for **6a–p** are listed in Tables 1, 2.

In the $^1$H NMR spectra of compounds **6,** the methylene protons of the resonances of the acetyl group appear as a set of characteristic doublet of doublet peaks in the range of 4.45–4.56 ppm ($^2J_{\text{H-C-H}}$ = 14.6–16.8 Hz). It is noteworthy that the proton of the CH group linking with the phosphorus atom exhibits doublet of doublet peaks at 5.78–46.40 ppm ($^2J_{\text{H-C-P}}$ = ~23Hz) due to the splitting and coupling of both the phosphorus atom and the hydrogen atom of the amino group. The $^1$H NMR spectrum also re-




**6a. R=CH$_3$, R′ =C$_6$H$_5$; 6i. R=H, R′ =C$_6$H$_5$**

**SCHEME 1**




**6a. R=CH$_3$, R′ =C$_6$H$_5$; 6b. R=CH$_3$, R′ =C$_6$H$_4$-Cl-4; 6c. R=CH$_3$, R′ =C$_6$H$_4$-OMe-2; 6d. R=CH$_3$, R′ =C$_6$H$_4$-NO$_2$-4; 6e. R=CH$_3$, R′ =C$_6$H$_4$-OMe-4; 6f. R=CH$_3$, R′ =C$_6$H$_3$-OCH$_2$O-3, 4; 6g. R=CH$_3$, R′ =C$_6$H$_4$-NO$_2$-3; 6h. R=CH$_3$, R′ =C$_6$H$_4$-Me-4; 6i. R=H, R′ =C$_6$H$_5$; 6j. R=H, R′ =C$_6$H$_4$-Cl-4; 6k. R=H, R′ =C$_6$H$_4$-OMe-2; 6l. R=H, R′ =C$_6$H$_4$-NO$_2$-4; 6m. R=H, R′ =C$_6$H$_4$-OMe-4; 6n. R=H, R′ =C$_6$H$_3$-OCH$_2$O-3, 4; 6o. R=H, R′ =C$_6$H$_4$-NO$_2$-3; 6p. R=H, R′ =C$_6$H$_4$-Me-4**

**SCHEME 2**

**TABLE 1** $^{1}$H NMR(DMSO, $\delta$, ppm) of Compounds **6**

| *No.* | $^{31}$P NMR | $^{1}$H NMR |
|---|---|---|
| **6a** | 19.73 | 1.73(s, 3H, $=CCH_3$) 4.48(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.8 Hz) 5.85(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 23.2 Hz, $^{3}J_{HCNH}$ = 9.9 Hz) 7.60–6.91(m, 16H, 3 × $C_6H_5$ + C = C**H**N) 9.66(d, 1H, $^{3}J_{HONH}$ = 9.9 Hz, N**H**CHP) 11.21(s, 1H, $(CO)_2$N**H**) |
| **6b** | 19.12 | 1.72(s, 3H, $=CCH_3$) 4.47(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 14.6 Hz) 5.86(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 23.8 Hz, $^{3}J_{HCNH}$ = 9.8 Hz) 7.64–6.96(m, 15H, 2 × $C_6H_5$ + 4-$ClC_6H_4$ + C=C**H**N) 9.70(d, 1H, $^{3}J_{HCNH}$ = 9.8 Hz, N**H**CHP) 11.28(s, 1H, $(CO)_2$N**H**) |
| **6c** | 20.00 | 1.73(s, 3H, $=CCH_3$) 3.74(s, 3H, $CH_3OC_6H_4$) 4.45(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 15.7 Hz) 6.40(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 23.4 Hz, $^{3}J_{HCNH}$ = 10.0 Hz) 7.67–6.85(m, 15H, 2 × $C_6H_5$ + 2-$MeOC_6H_4$ + C = C**H**N) 9.50(d, 1H, $^{3}J_{HCNH}$ = 10.0 Hz, N**H**CHP) 11.29(s, 1H, $(CO)_2$N**H**) |
| **6d** | 18.19 | 1.72(s, 3H, $=CCH_3$) 4.50(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 15.4 Hz) 6.14(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 22.3 Hz, $^{3}J_{HCNH}$ = 9.8) 8.31–7.00(m, 15H, 2 × $C_6H_5$ + 4-$NO_2C_6H_4$ + C=C**H**N) 9.80(d, 1H, $^{3}J_{HCNH}$ = 9.8 Hz, N**H**CHP) 11.28(s, 1H, $(CO)_2$N**H**) |
| **6e** | 20.01 | 1.73(s, 3H, $=CCH_3$) 3.75(s, 3H, $CH_3OC_6H_4$) 4.48(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 15.9Hz) 5.82(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 24.1Hz, $^{3}J_{HCNH}$ = 9.7) 7.48–6.94(m, 15H, 2 × $C_6H_5$ + 4-$MeOC_6H_4$ + C=C**H**N) 9.50(d, 1H, $^{3}J_{HCNH}$ = 9.7 Hz, N**H**CHP) 11.26(s, 1H, $(CO)_2$N**H**) |
| 6f | 19.64 | 1.72(s, 3H, $=CCH_3$) 4.45(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 15.9 Hz) 5.84(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 22.8 Hz, $^{3}J_{HCNH}$ = 9.5) 6.02(s, 2H, $OCH_2O$) 7.33–6.94(m, 14H, 2 × $C_6H_5$ + 3.4-$OCH_2OC_6H_3$ + C=C**H**N) 9.54(d, 1H, $^{3}J_{HCNH}$ = 9.5 Hz, N**H**CHP) 11.21(s, 1H, $(CO)_2$N**H**) |
| **6g** | 18.48 | 1.72(s, 3H, $=CCH_3$) 4.50(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.8 Hz) 6.21(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 23.2 Hz, $^{3}J_{HCNH}$ = 9.1 Hz) 8.55–7.00(m, 15H, 2 × $C_6H_5$ + 3-$NO_2C_6H_4$ + C=C**H**N) 9.82(d, 2H, $^{3}J_{HCNH}$ = 9.1 Hz, N**H**CHP) 11.32(s, 1H, $(CO)_2$N**H**) |
| **6h** | 19.87 | 1.73(s, 3H, $=CCH_3$) 2.36(s, 3H, $CH_3C_6H_4$) 4.46(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 14.9 Hz) 5.78(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 23.0 Hz, $^{3}J_{HCNH}$ = 9.0 Hz) 7.48–6.94(m, 15H, 2 × $C_6H_5$ + 4-$MeC_6H_4$ + C=C**H**N) 9.57(d, 1H, $^{3}J_{HCNH}$ = 9.04 Hz, N**H**CHP) 11.27(s, 1H, $(CO)_2$N**H**) |
| **6i** | 19.80 | 4.54(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.3 Hz) 5.56(d, 1H, $^{3}J_{HCCH}$ = 7.9 Hz, C**H**=CN) 5.86(dd, H, PC**H**, $^{2}J_{PCH}$ = 23.0 Hz, $^{3}J_{HCNH}$ = 7.5 Hz) 7.57–6.91(m, 16H, 3 × $C_6H_5$ + C=C**H**N) 9.68(d, 1H, $^{3}J_{HCNH}$ = 7.5 Hz, N**H**CHP) 11.27(s, 1H, $(CO)_2$N**H**) |
| **6j** | 19.56 | 4.52(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.7 Hz) 5.55(d, 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 5.89(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 24.8 Hz, $^{3}J_{HCNH}$ = 7.5 Hz) 7.63–6.96(m, 15H, 2 × $C_6H_5$ + 4-$ClC_6H_4$ + C=C**H**N) 9.68(d, 1H, $^{3}J_{HCNH}$ = 7.5 Hz, N**H**CHP) 11.26(s, 1H, $(CO)_2$N**H**) |
| **6k** | 19.96 | 3.74(s, 3H, $CH_3OC_6H_4$) 4.48(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 14.6Hz) 5.54(d, 1H, $^{3}J_{HCCH}$ = 7.6Hz, C**H**=CN) 6.38(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 23.4Hz, $^{3}J_{HCNH}$ = 9.1Hz) 7.62–6.84(m, 15H, 2 × $C_6H_5$ + 2-$MeOC_6H_4$ + C=C**H**N) 9.48(d, 1H, $^{3}J_{HCNH}$ = 9.14Hz, N**H**CHP) 11.27(s, 1H, $(CO)_2$N**H**) |
| **6l** | 18.17 | 4.56(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 15.8 Hz) 5.54(d, 1H, $^{3}J_{HCCH}$ = 7.7Hz, C**H**=CN) 6.20(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 23.0Hz, $^{3}J_{HCNH}$ = 9.2Hz) 8.36–7.01(m, 15H, 2 × $C_6H_5$ + 4-$NO_2C_6H_4$ + C=C**H**N) 9.80(d, 1H, $^{3}J_{HCNH}$ = 9.2Hz, N**H**CHP) 11.24(s, 1H, $(CO)_2$N**H**) |
| **6m** | 19.98 | 3.76(s, 3H, $CH_3OC_6H_4$) 4.54(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 14.7Hz) 5.58(d, 1H, $^{3}J_{HCCH}$ = 7.8Hz, C**H**=CN) 5.82(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 23.1 Hz, $^{3}J_{HCNH}$ = 9.2 Hz) 7.58–6.85(m, 15H, 2 × $C_6H_5$ + 4-$MeOC_6H_4$ + C=C**H**N) 9.50(d, 1H, $^{3}J_{HCNH}$ = 9.2 Hz, N**H**CHP) 11.26(s, 1H, $(CO)_2$N**H**) |
| **6n** | 19.66 | 4.56(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.5Hz) 5.58(d, 1H, $^{3}J_{HCCH}$ = 7.7Hz, C**H**=CN) 5.88(dd, 1H, PC**H**, $^{2}J_{PCH}$ = 22.5Hz, $^{3}J_{HCNH}$ = 9.3 Hz) 6.02(s, 2H, $OCH_2O$) 7.52–6.90(m, 14H, 2 × $C_6H_5$ + 3,4-$OCH_2OC_6H_3$ + C=C**H**N) 9.46(d, 1H, $^{3}J_{HCNH}$ = 9.3 Hz, N**H**CHP), 11.20(s, 1H, $(CO)_2$N**H**) |
| **6o** | 18.49 | 4.54(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = = 15.4 Hz) 5.54(d 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 6.22(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 23.3 Hz, $^{3}J_{HCNH}$ = 9.2 Hz) 8.55–7.00(m, 15H, 2 × $C_6H_5$ + 3-$NO_2C_6H_4$ + C=C**H**N) 9.78(d, 1H, $^{3}J_{HCNH}$ = 9.2 Hz, N**H**CHP) 11.25(s, 1H, $(CO)_2$N**H**) |
| **6p** | 19.89 | 2.30(s, 3H, $CH_3C_6H_4$) 4.52(dd, 2H, $CH_2CO$, $^{2}J_{HCH}$ = 16.8 Hz) 5.54(d, 1H, $^{3}J_{HCCH}$ = 7.3 Hz, C**H**=CN) 5.80(dd., 1H, PC**H**, $^{2}J_{PCH}$ = 23.9 Hz, $^{3}J_{HCNH}$ = 9.4 Hz) 7.55–6.04(m, 15H, 2 × $C_6H_5$ + 4-$MeC_6H_4$ + C=C**H**N) 9.59(d, 1H, $^{3}J_{HCNH}$ = 9.4 Hz, N**H**CHP) 11.28(s, 1H, $(CO)_2$N**H**) |

veals two sets of peaks at 1.72–1.73 ppm (singlet signals), 11.21–11.32 ppm (singlet signal), and 5.54–5.58 ppm (doublet signal), 11.20–11.28 ppm (singlet signal) supporting the thymine and uracil structure, respectively. The hydrogen at position-6 of thymine and uracil appears in the range of the peaks of the hydrogens of the aryl groups. The $^{31}$P NMR spectrum of all products exhibited chemical shifts at 18.17–20.01 ppm. The IR spectra of compounds **6** showed normal stretching absorption bands to indicate the existence of the groups NH (~3400 $cm^{-1}$), C=O (1670 ~ 1719$cm^{-1}$), P=O (1214 ~ 1245$cm^{-1}$), P–O–C (1159 ~ 1188$cm^{-1}$).

### *The Molecular Structure and Crystal Structure of Compound* **6c**

In order to obtain information about the molecular structure and hydrogen bonding of the compound

**6c,** a single crystal of **6c** was analyzed by X-ray diffraction. The colorless crystal of α-[(thymin-1-yl) methylformyl]amino-α-(2′-methoxyphenyl)methyl-*O,O*-diphenylphosphonate, $C_{27}H_{26}N_3O_7P$, **6c,** was obtained by evaporation from its saturated methanol solution. A crystal with a size of 0.1 × 0.250 × 35 mm was examined on a BRUKER SMART 1000 four-circle diffractometer with MoK radiation ($\lambda$ = 0.71073Å). The compound **6c** crystallized in the triclinic space group $P\bar{1}$ with cell dimensions $a$ = 9.0086(9) Å, $b$ = 9.9294(11) Å, $c$ = 15.0207(15) Å, $\alpha$ = 84.201(2)°, $\alpha$ = 72.792(2)°, $\alpha$ = 80.346(2)°, $V$ = 1263.4(2) Å $^3$, $Z$ = 2, and $D_c$ = 1.408Mg/m$^3$. The structure was solved by the direct method and refined by the full-matrix least squares on $F^2$, and the final crystallographic discrepancy factor is 0.0553 for 6418 observed reflections (see Table 3–4). The structure of compound **6c** is shown in Figure 1.

In the crystal cell, the amino H atom of the nucleoside base does not take part in forming intramolecular or intermolecular hydrogen bonds; there are only intermolecular hydrogen bonds formed between the O atom of the phosphoryl group and the amino H atom of the α-aminophosphonate (see Figure 2).

## *EXPERIMENTAL*

### *Instruments*

Elemental analyses were performed with a CHNCORDERD MT-3 elementary analyzer. NMR spectra were recorded with a BRUKER AC-P200 spectrometer with TMS and 85% $H_3PO_4$ as internal and external references, respectively, and DMSO as the solvent. A SHIMADZU-435 instrument was used to measure IR spectra. Melting points were determined with a Thomas-Hoover melting point apparatus, and the thermometer was uncorrected. The determination of unit cell and the data collection were performed with MoK radiation (= 0.71073Å) on a BRUKER SMART 1000 diffractometer. Column chromatography was performed on silica gel $GF_{254}$ (Qing dao Hai yang Chemical Group Co. of China).

### *Thymin-1-yl Acetic Acid* **2** *or Uracil-1-yl Acetic Acid* **2**

Thymine or uracil (30 mmol) was dissolved in a solution of potassium hydroxide (6.45 g, 115 mmol) in

**TABLE 2** Experimental Data of Compounds **6**

| | | *IR(ν, cm$^{-1}$)* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *No.* | (*NH*), | (*C*=*O*), | (*P*=*O*), | (*P–O–C*) | *Yield* (%) | *State* | *m.p.* (°*C*) | *Element Analyses C, H, N* (*Calculation*) |
| **6a** | 3421 | 1696 | 1215 | 1162 | 69.2 | Solid | 200–201 | 61.75, 4.89, 8.08 (61.78, 4.79, 8.31) |
| **6b** | 3420 | 1701 | 1226 | 1184 | 69.3 | Solid | 221–222 | 57.74, 4.45, 7.32 (57.85, 4.29, 7.78) |
| **6c** | 3410 | 1709 | 1245 | 1172 | 61.6 | Solid | 185–186 | 60.13, 4.99, 7.53 (60.56, 4.89, 7.85) |
| **6d** | 3430 | 1704 | 1226 | 1170 | 54.6 | Solid | 234(dec.) | 56.63, 4.20, 10.31 (56.73, 4.21, 10.18) |
| **6e** | 3432 | 1704 | 1223 | 1186 | 72.1 | Solid | 207–208 | 60.19, 4.61, 8.10 (60.56, 4.89, 7.85) |
| **6f** | 3437 | 1680 | 1223 | 1159 | 68.5 | Solid | 188–189 | 58.87, 4.78, 8.01 (59.02, 4.40, 7.65) |
| **6g** | 3430 | 1719 | 1214 | 1160 | 55.5 | Solid | 179–180 | 56.68, 4.15, 10.33 (56.73, 4.21, 10.18) |
| **6h** | 3430 | 1704 | 1222 | 1184 | 74.1 | Solid | 210.5–211.5 | 60.45, 5.12, 9.46 (60.42, 5.07, 9.72) |
| **6i** | 3420 | 1670 | 1213 | 1174 | 70.6 | Solid | 204–205 | 56.89, 4.17, 7.89 (57.10, 4.02, 7.99) |
| **6j** | 3430 | 1673 | 1222 | 1188 | 69.8 | Solid | 197–198 | 60.88, 4.27, 8.64 (61.10, 4.51, 8.55) |
| **6k** | 3427 | 1676 | 1239 | 1186 | 68.5 | Solid | 117–118 | 59.60, 4.58, 8.11 (59.89, 4.64, 8.06) |
| **6l** | 3424 | 1680 | 1234 | 1180 | 56.7 | Solid | 223–224 | 55.82, 3.97, 10.54 (55.98, 3.95, 10.44) |
| **6m** | 3429 | 1682 | 1237 | 1187 | 72.0 | Solid | 206–207 | 59.77, 4.75, 8.02 (59.89, 4.64, 8.06) |
| **6n** | 3437 | 1687 | 1237 | 1185 | 69.8 | Solid | 184–185 | 58.41, 4.54, 8.16 (58.32, 4.14, 7.85) |
| **6o** | 3421 | 1687 | 1237 | 1183 | 54.2 | Solid | 170–171 | 55.58, 4.31, 10.63 (55.98, 3.95, 10.44) |
| **6p** | 3459 | 1682 | 1237 | 1183 | 72.2 | Solid | 196–197 | 61.35, 4.65, 8.23 (61.78, 4.78,8.31) |

**TABLE 3** Selected Bond Lengths (Å) of Compound **6c**

| | | | | | |
|---|---|---|---|---|---|
| P(1)–O(4) | 1.4553(17) | N(3)–C(3) | 1.453(3) | C(27)–O(5) | 1.431(3) |
| P(1)–O(4) | 1.5813(17) | C(1)–C(2) | 1.514(3) | N(2)–C(44) | 1.364(3) |
| O(1)–C(42) | 1.229(3) | O(5)–C(26) | 1.372(3) | N(2)–C(1) | 1.464(3) |
| N(1)–C(43) | 1.379(3) | O(7)–C(31) | 1.419(3) | N(3)–C(2) | 1.348(3) |
| O(2)–C(43) | 1.212(3) | P(1)–O(3) | 1.5691(18) | O(3)–C(11) | 1.407(3) |
| N(2)–C(43) | 1.372(3) | P(1)–C(3) | 1.812(2) | C(2)–O(6) | 1.212(3) |
| C(40)–C(41) | 1.493(4) | N(1)–C(42) | 1.375(3) | C(3)–C(21) | 1.518(3) |

**TABLE 4** The Selected Bond Angles (°) of Compound **6c**

| | | | | | |
|---|---|---|---|---|---|
| O(4)–P(1)–O(3) | 116.13(11) | C(32)–C(31)–O(7) | 120.4(2) | O(6)–C(2)–N(3) | 124.1(2) |
| O(3)–P(1)–O(7) | 104.25(10) | O(2)–C(43)–N(1) | 122.8(3) | N(3)–C(2)–C(1) | 113.2(2) |
| O(3)–P(1)–C(3) | 100.79(10) | O(5)–C(26)–C(25) | 122.9(3) | N(3)–C(3)–C(21) | 113.65(18) |
| C(42)–N(1)–C(43) | 127.2(2) | O(2)–C(43)–N(2) | 123.2(2) | C(21)–C(3)–P(1) | 110.71(15) |
| C(44)–N(2)–C(1) | 120.9(2) | C(44)–C(41)–C(40) | 123.2(3) | O(1)–C(42)–C(41) | 124.1(3) |
| C(2)–N(3)–C(3) | 121.58(19) | N(1)–C(42)–C(41) | 115.5(2) | C(41)–C(44)–N(2) | 123.6(2) |
| N(2)–C(1)–C(2) | 112.7(2) | C(16)–C(11)–O(3) | 114.9(2) | C(12)–C(11)–O(3) | 122.8(2) |
| O(6)–C(2)–C(1) | 122.6(2) | O(4)–P(1)–O(7) | 113.72(10) | C(22)–C(21)–C(3) | 119.5(2) |
| C(26)–O(5)–C(27) | 116.9(2) | O(4)–P(1)–C(3) | 113.62(10) | C(36)–C(31)–O(7) | 117.8(2) |
| N(3)–C(3)–P(1) | 105.71(15) | O(7)–P(1)–C(3) | 107.02(10) | N(2)–C(43)–N(1) | 113.9(2) |
| C(31)–O(7)–P(1) | 122.02(14) | C(44)–N(2)–C(43) | 122.0(2) | O(1)–C(42)–N(1) | 120.4(2) |
| C(26)–C(21)–C(3) | 121.2(2) | C(43)–N(2)–C(1) | 117.1(2) | | |
| O(5)–C(26)–C(21) | 116.8(2) | C(11)–O(3)–P(1) | 126.75(17) | | |

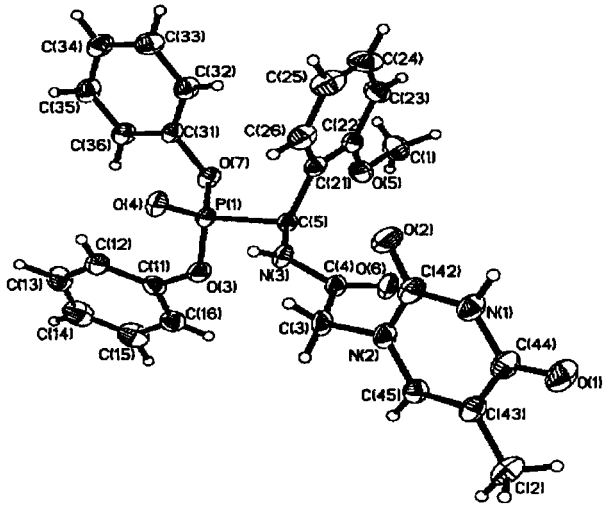



**FIGURE 1** Molecular structure of compound **6c**.

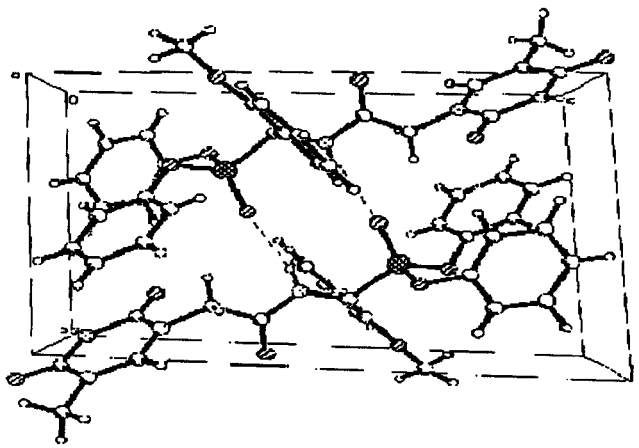


**FIGURE 2** Packing of molecules of compound **6c** in unit cell.

20 mL of water. While this solution was warmed in a 45°C water bath, a solution of bromoacetic acid (6.25 g, 45 mmol) in 10 mL of water was added over 30 minutes. The reaction mixture was stirred for another 4 hours at this temperature. It was allowed to cool to room temperature, and the pH was adjusted to 5.5 with conc. HCl. The solution was then cooled in a refrigerator for 2 hours. Any precipitate (unreacted thymine or uracil) formed was removed by filtration. The solution was then adjusted to pH = 2 with conc. HCl and placed in a freezer for 2 hours. The white precipitates were collected by filtration and dried in a vacuum oven at 40°C for 6 hours. The yields were 86% and 91% of theoretical, based on thymine and uracil, respectively. **2**: m.p. > 270°C, $^1$H NMR 4.40 (s, 2H) 5.57 (d, 1H, $^3J_{HCCH}$ = 7.90 Hz) 7.59 (d, 1H, $^3J_{HCCH}$ = 7.90 Hz) 11.33 (s, 1H); **2′**: m.p. 270°C, $^1$H NMR 1.74 (s, 3H), 4.34 (s, 2H) 7.47 (s, 1H) 11.31 (s, 1H).

### *α-[(Uracil-1-yl or Thymin-1-yl)methylformyl]amino-α-arylmethyl-O,O-diphenylphosphonates* (**6**)

*General Procedure.* The thymin-1-yl acetic acid **2** or uracil-1-yl acetic acid **2′** and 1-hydroxybenzotriazole were dissolved in 15 mL of DMF. While this solution was cooled in an ice bath, a solution of DCC (1.2 mmol, 0.25 g) in DMF (10 mL) was added dropwise over 40 minutes at 0°C under $N_2$. The mixture was allowed to warm to room temperature and stirred for 2 hours; the α-aminophosphonate **4** was added to the reaction mixture, and stirring was continued for 18 hours. The precipitate was filtered off. The solvent was removed under vacuum from the filtrate and the residue was then purified by flash chromatography on silica gel ($CHCl_3$: $CH_3OH$ =

15:1) to give the title compounds **6a–p**. The appropriate experimental data are listed in Tables 1 and 2.

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