*Bulgarian Chemical Communications, Volume 41, Number 4 (pp. 422–426) 2009*

# Synthesis and antimicrobial activity of 2,10-dichloro-6-substituted amino acid ester-12*H*-dibenzo[d,g][1,3,2]dioxaphosphocin-6-oxides

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Received September 29, 2008; Revised February 10, 2009

A new class of 2,10-dichloro-6-substituted amino acid ester-12*H*-dibenzo[d,g][1,3,2]dioxaphosphocin-6-oxides have been synthesized in good yields via the condensation of 2,10-dichloro-6-chloro-12*H*-dibenzo[d,g][1,3,2]dioxaphosphocin with various amino acid esters in the presence of triethylamine. The title compounds were characterized by elemental analysis, IRS, NMR ($^1$H, $^{13}$C and $^{31}$P) and mass spectral studies and found to exhibit moderate antimicrobial activity.

**Key words:** Dioxaphosphocin-6-oxides, amino acid esters, spectral studies, antimicrobial activity.

## INTRODUCTION

Phosphoramide compounds substituted with amino acid esters are important class of rationally designated therapeutics especially with antineoplastic properties. Phosphate triester derivatives of nucleotides have been prepared as the memberane-soluble prodrug of the bio-active nucleotides and were found to contain good activity against HIV-1 in-vitro [1]. The aryloxyphosphoramidates were found to exhibit enhanced activity against HIV-1 and HIV-2 in cellular culture, compared to their parent ddN's with full retention of activity in thymidine kinase – deficient cell lines [2,3]. This type of nucleosides have been shown to be potent inhibitors of HIV and to display reduced toxicity in progenitorcells [4-6]. Exhaustive modifications to the amino acid moiety in aryloxyphosphoramidate have established L-alanine to be optimal for antiviral activity [7]. Hence synthesis of the title compounds were contemplated and accomplished. They have been characterised by elemental analysis, IRS, multi NMR and mass spectral analysis.

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and were uncorrected. IR spectra ($\nu_{max}$ in cm$^{-1}$) were recorded in KBr pellets on Perkin Elmer 1000 unit. The $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded on Varian Gemini 300 and Varian AM X 400 MHz NMR spectrometer operating at 300 or 400 MHz for $^1$H, 75.46 or 100.57 MHz for $^{13}$C and 121.7 MHz for $^{31}$P. All the compounds were dissolved in DMSO-$d_6$ and chemical shifts were referenced to TMS ($^1$H and $^{13}$C) and 85% $H_3PO_4$ ($^{31}$P). Micro analytical data were obtained from Central Drug Research Institute, Lucknow, India.

## RESULT AND DISCUSSION

The synthetic route (Scheme 1) involves the cyclocondensation of 5,5'-dichloro-2,2'-dihydroxy biphenyl methane (**1**) with phosphorus oxychloride at 0°C under inert and anhydrous conditions in dry toluene to afford the 2,10-dichloro-6-chloro-12*H*-dibenzo[d,g][1,3,2]dioxaphosphocin-6-oxide (**3**) and its subsequent condensation with various amino acid esters in the presence of triethylamine in dry tetrahydrofuran at room temperature. The final products were purified by column chromatography using hexane, ethyl acetate as step gradient mixtures as eluents.

IR spectra of **4a**–**i** showed absorption bands at 3383–3333, 1759–1733 and 1241–1219 cm$^{-1}$ for NH [8], C=O and P=O [9, 10], respectively (Table 1). Their $^1$H NMR spectra gave complex multiplets at δ 6.72–7.91 for aromatic protons (Table 2). The splitting pattern of bridged methylene protons showed their non-equivalance [11]. One of the bridging protons appeared as doublet of doublet in the region 4.21–4.41 (dd, $^2J_{HH}$ = 12.9–13.9 Hz and $^5J_{PH}$ = 3.5–4.3 Hz) due to the germinal coupling with the another bridging proton and long range coupling with the phosphorus. Second bridging proton resonated as doublet in the region δ 3.57–3.65 ($^2J_{HH}$ = 13.6–14.9 Hz) due to germinal coupling with

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germinal proton and its arrangement masked it from coupling with phosphorus.

The dioxaphosphocin ring in all these compounds appeared to exist in boat like configuration, in which one of the bridging protons protruded away from the phosphorus. The NH proton resonated as a broad singlet in the region δ 3.82–5.43.

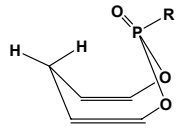
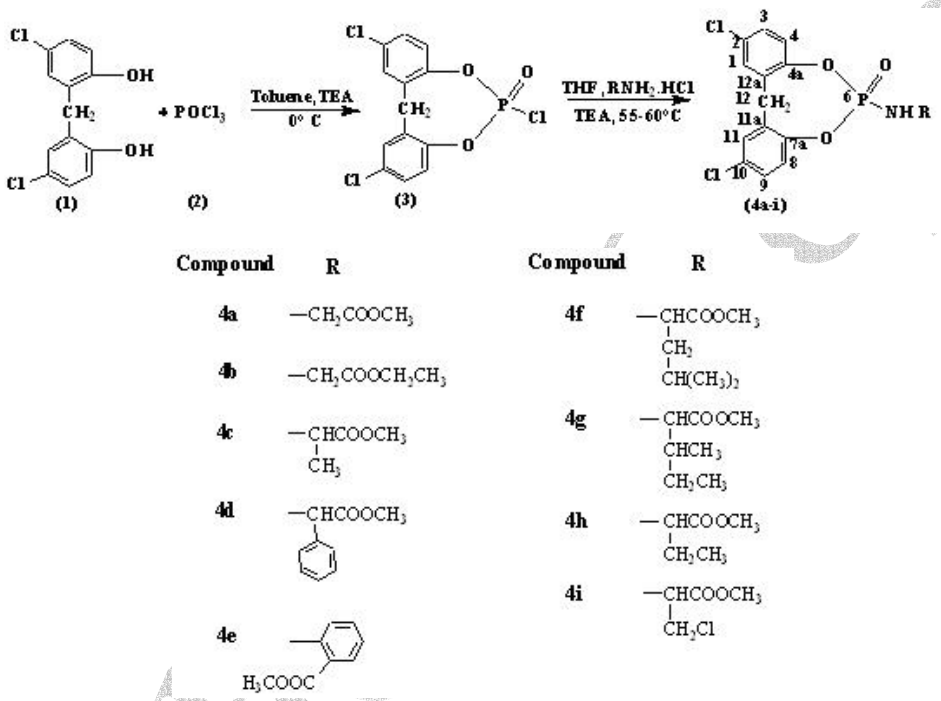


**Table 1**. Infrared spectral data of compounds **4a**–**i**.

| Comp. | IR band maximum, $cm^{-1}$ | | |
|---|---|---|---|
| | N–H | C=O | P=O |
| **4a** | 3351 | 1751 | 1231 |
| **4b** | 3374 | 1736 | 1238 |
| **4c** | 3333 | 1749 | 1230 |
| **4d** | 3371 | 1742 | 1231 |
| **4e** | 3342 | 1752 | 1239 |
| **4f** | 3356 | 1746 | 1224 |
| **4g** | 3364 | 1759 | 1241 |
| **4h** | 3383 | 1733 | 1237 |
| **4i** | 3341 | 1742 | 1219 |




Scheme 1.

**Table 2**. $^1$H NMR spectral data[a,b] of compounds **4a**–**i**.

| Comp. | Ar-H | $CH_2$ | N-H | Amino acid ester |
|---|---|---|---|---|
| **4a** | 6.82–7.74 (m, 6H) | 4.33 (dd, *J* = 13.2, 3.9 Hz), 3.61 (d, *J* = 13.5 Hz) | 3.92 (brs, 1H) | 4.47 (s, 3H, $OCH_3$), 3.87 (s, 2H, $CH_2$) |
| **4b** | 6.89–7.86 (m, 6H) | 4.25 (dd, *J* = 13.4, 3.5 Hz), 3.63(d, *J* = 13.8 Hz) | 4.12 (brs, 1H) | 4.39 (q, *J* = 7.1 Hz, 3H, $OCH_2$), 3.79 (s, 2H, $CH_2$), 3.12 (t, *J* = 6.9 Hz, 3H, $CH_3$) |
| **4c** | 6.72–7.79 (m, 6H) | 4.21 (dd, *J* = 13.7, 4.1 Hz), 3.65 (d, *J* = 13.9 Hz) | 4.62 (s, 1H) | 4.29 (s, 3H, $OCH_3$), 3.40 (m, 1H, CH), 1.41 (d, *J* = 7.9 Hz, 3H, CH–C<u>H</u>$_3$) |
| **4d** | 7.02–7.93 (m, 11H) | 4.23 (dd, *J* = 12.9, 3.5 Hz), 3.61 (d, *J* = 13.2 Hz) | 4.45 (s, 1H) | 4.79 (s, 1H, CH), 4.40 (s, 3H, $OCH_3$) |
| **4e** | 6.97–7.82 (m, 10H) | 4.22 (dd, *J* = 13.2, 3.6 Hz), 3.64 (d, *J* = 13.2 Hz) | 5.43 (s, 1H) | 4.11 (s, 3H, $OCH_3$) |
| **4f** | 6.93–7.91 (m, 6H) | 4.24 (dd, *J* = 13.5, 4.2 Hz), 3.59 (d, *J* = 14.2 Hz) | - | 4.32 (s, 3H, $OCH_3$), 3.41 (t, 1H, –C<u>H</u>–$CH_2$), 1.78–1.73 (m, 2H, –CH–C<u>H$_2$</u>–$CH(CH_3)_2$), 1.51–1.45 (m, 1H, –CH–$CH_2$–C<u>H</u>$(CH_3)_2$), 1.09–0.96 (m, 6H) |
| **4g** | 7.03–7.88 (m, 6H) | 4.31 (dd, *J* = 13.9, 3.7 Hz), 3.57 (d, *J* = 13.8 Hz) | 5.13 (s, 1H) | 4.19 (s, 3H, $OCH_3$), 3.58–3.52 (m, 1H, –C<u>H</u>–$CH(CH_3)$–$CH_2CH_3$), 2.21–2.25 (m, 1H, –CH–C<u>H</u>$(CH_3)CH_2CH_3$), 1.51–1.48 (m, 2H, $CHCH(CH_3)CH_2CH_3$), 1.09–0.94 (m, 6H) |
| **4h** | 7.01–7.74 (m, 6H) | 4.41 (dd, *J* = 13.2, 4.3 Hz), 3.61 (d, *J* = 13.6 Hz) | 3.83 (brs, 1H) | 4.24 (s, 3H, $OCH_3$), 3.51 (m, 1H, C<u>H</u>$(COOCH_3)CH_2$), 2.08–2.02 (m, 2H, C<u>H$_2$</u>–$CH_3$), 1.02 (t, *J* = 7.4 Hz, 3H, $CH_2$–C<u>H$_3$</u>) |
| **4i** | 6.82-7.71 (m, 6H) | 4.29 (dd, *J*= 13.5, 3.7Hz), 3.59 (d, *J* = 13.5 Hz) | 5.04 (s, 1H) | 4.23 (s, 3H, $OCH_3$), 4.10–3.91 (m, 2H, $CH_2Cl$), 3.58 (s, 1H, CH) |

a - Chemical shifts are in ppm from TMS and coupling constants (*J*) in Hz are given in parenthesis; b - Recorded in DMSO–$d_6$.

Their $^{13}C$ chemical shifts were interpreted based on comparison of basic units, present in them. Because of the symmetrical nature of dibenzophosphocin moiety only seven $^{13}C$ signals were observed for thirteen carbons (Table 3). The oxygen bearing C (4a) and C (7a) atoms gave signals in the down field 149.97–152.41 ppm as a doublet ($^2J_{POC}$ = 6.9–7.3 Hz). The doublets at δ 131.72–132.98 (d, $J$ = 3.7–4.5 Hz) were assigned to the C-11a and C-12a atoms. The chemical shifts in the region 130.98–131.92 ppm were assigned to chlorine bearing C-2 and C-10 atoms. The carbonyl carbon of amino acid ester moiety appeared at δ 169.49–176.2.

$^{31}P$ NMR chemical shifts [12] for all the title compounds were observed in the region 2.13–8.19 ppm (Table 4). The compounds **4a** and **4b** exhibited molecular ion peaks at their respective and relative molecular ion weights in their mass spectrum (Table 5).

*Antimicrobial activity*

Compounds **4a–i** were screened with respect to their antibacterial activity against *Staphylococcus aureus* (gram positive) and *Escherichia coli*(gram negative) by the disc-fusion method [13, 14] in nutrient agar medium at various concentrations (250, 500 ppm) in dimethyl formamide (DMF). These solutions were added to each filter disc and DMF was used as control. The plates were incubated at 35°C and examined for zone of inhibition around each disc after 24 h. The results were compared with the activity of the standard antibiotic Penicillin (250 ppm) (Table 6).

The antifungal activity of the synthesized compounds was evaluated against *Curvularia lunata* and *Aspergillus niger* at different concentrations (250, 500 ppm) and Griseofulvin was used as the reference compound. Fungal cultures were grown on potato dextrose broth at 25°C and spore suspension was adjusted to $10^5$ spore/mL. Most of the compounds showed moderate activity against bacteria and high activity against fungi (Table 7).

**Table 4**. Synthetic, elemental and $^{31}P$ NMR spectral data of compounds **4a**–**i**.

| Comp. | M. p., °C | Yield, % | Molecular Formula | Elemental analysis, % Found (Calc.) | | $^{31}P$ NMR, δ |
|---|---|---|---|---|---|---|
| | | | | C | H | |
| **4a** | 162–164 | 72 | $C_{16}H_{14}NO_5Cl_2P$ | 47.89 (47.78) | 3.63 (3.51) | 6.75 |
| **4b** | 171–173 | 76 | $C_{17}H_{16}NO_5Cl_2P$ | 49.21 (49.06) | 3.98 (3.87) | 6.82 |
| **4c** | 149–151 | 75 | $C_{17}H_{16}NO_5Cl_2P$ | 49.19 (49.06) | 3.99 (3.87) | 7.81 |
| **4d** | 197–199 | 71 | $C_{22}H_{18}NO_5Cl_2P$ | 55.39 (55.25) | 3.91 (3,79) | 7.99 |
| **4e** | 133–135 | 69 | $C_{21}H_{16}NO_5Cl_2P$ | 55.48 (54.33) | 3.61 (3.47) | 8.19 |
| **4f** | 204–206 | 77 | $C_{20}H_{22}NO_5Cl_2P$ | 52.57 (52.42) | 4.97 (4.84) | 2.13 |
| **4g** | 153–155 | 74 | $C_{20}H_{22}NO_5Cl_2P$ | 52.59 (52.42) | 5.01 (4.84) | 4.22 |
| **4h** | 187–189 | 79 | $C_{18}H_{18}NO_5Cl_2P$ | 50.39 (50.25) | 4.38 (4.22) | 2.20 |
| **4i** | 146–148 | 73 | $C_{17}H_{15}NO_5Cl_3P$ | 45.42 (45.31) | 3.46 (3.35) | 5.44 |

**Table 5**. Mass spectral data of compounds **4a** and **4c**.

| Compd. | m/z (%) |
|---|---|
| **6** | 404 [9, $M^{+\bullet}$+2], 402 [28, $M^{+\bullet}$], 369 (11), 358 (24), 343 (22), 325 (17), 314 (27), 268 (19) |
| **7** | 418 [9, $M^{+\bullet}$+2], 416 [31, $M^{+\bullet}$], 383 (17), 372 (16), 343 (21), 339 (19), 314 (21), 268 (16), 140 (32) |

Table **6**. Antibacterial activity of compounds **4a-i**.

| Comp. | Zone of inhibition | | | |
|---|---|---|---|---|
| | *Staphylococcus aureus* | | *Escherichia coli* | |
| | 250[a] | 500[a] | 250[a] | 500[a] |
| **4a** | 8 | 13 | 12 | 17 |
| **4b** | 7 | 11 | 14 | 19 |
| **4c** | 7 | 12 | 13 | 18 |
| **4d** | 6 | 11 | 15 | 18 |
| **4e** | 8 | 11 | 16 | 25 |
| **4f** | 7 | 12 | 14 | 22 |
| **4g** | 6 | 12 | 13 | 20 |
| **4h** | 5 | 10 | 13 | 19 |
| **4i** | 6 | 12 | 14 | 20 |
| Penicillin[b] | 12 | | 24 | |

a - Concentration in ppm; b - Standard reference.

**Table 7**. Antifungal activity of compounds **4a-i**.

| Comp. | Zone of inhibition | | | |
|---|---|---|---|---|
| | *Curvularia lunata* | | *Asperigillus niger* | |
| | 250[a] | 500[a] | 250[a] | 500[a] |
| **4a** | 16 | 27 | 20 | 27 |
| **4b** | 14 | 21 | 16 | 20 |
| **4c** | 16 | 23 | 19 | 25 |
| **4d** | 16 | 22 | 22 | 29 |
| **4e** | 14 | 20 | 19 | 26 |
| **4f** | 18 | 28 | 23 | 31 |
| **4g** | 15 | 27 | 13 | 17 |
| **4h** | 15 | 26 | 21 | 29 |
| **4i** | 16 | 21 | 15 | 20 |
| Griseofulvin[b] | 23 | | 26 | |

a - Concentration in ppm; b - Standard reference.

**Table 3.** $^{13}C$ NMR spectral data[a,b] of compounds **4a–i**.

| Comp. | C(1/11) | C(2/10) | C(3/9) | C(4/8) | C(4a/7a) | C(11a/12a) | C(12) | α | β | γ | Ar-H | | | | C=O | $OCH_2$/ $OCH_3$ | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | C-1' | C-2'/6' | C-3'/5' | C-4' | | | |
| **4a** | 129.38 | 131.84 | 128.62 | 124.50 | 150.14 [d, $J$ = 7.1 Hz] | 132.98 [d, $J$ = 3.7 Hz] | 33.41 | 54.89 [d, $J$ = 126.2 Hz] | – | – | – | – | – | – | 174.90 | 52.61 | – |
| **4b** | 129.48 | 131.85 | 128.67 | 124.53 | 150.16 [d, $J$ = 7.2 Hz] | 132.87 [d, $J$ = 4.5 Hz] | 33.48 | 54.70 [d, $J$ = 126.2 Hz] | – | – | – | – | – | – | 172.91 | – | 13.22 |
| **4c** | 129.51 | 131.89 | 128.61 | 124.51 | 150.15 [d, $J$ = 6.8 Hz] | 132.85 [d, $J$ = 4.5 Hz] | 33.39 | 54.79 [d, $J$ = 126.2 Hz] | 23.23 | – | – | – | – | – | 172.61 | 56.92 | – |
| **4d** | 129.11 | 131.67 | 128.32 | 124.47 | 149.97 [d, $J$ = 7.0 Hz] | 132.52 [d, $J$ = 4.1 Hz] | 33.12 | 54.21 [d, $J$ = 126.2 Hz] | – | – | 135.21 | 128.92 | 127.89 | 125.4 | 169.49 | 56.63 | – |
| **4e** | 129.69 | 131.53 | 128.11 | 124.82 | 151.31 [d, $J$ = 7.3 Hz] | 131.99 [d, $J$ = 4.0 Hz] | 34.09 | – | – | – | 149.62 | 116.8 | 132.9 | 118.12 | 179.32 | 53.91 | – |
| **4f** | 129.12 | 131.92 | 127.92 | 124.03 | 152.11 [d, $J$ = 7.1 Hz] | 132.91 [d, $J$ = 4.3 Hz] | 34.12 | 54.13 [d, $J$ = 121.3 Hz] | 26.3 | 15.7 13.3(γ') | – | – | – | – | 171.34 | 54.32 | – |
| **4g** | 128.97 | 131.62 | 128.41 | 124.53 | 151.31 [d, $J$ = 6.9 Hz] | 132.17 [d, $J$ = 3.9 Hz] | 33.79 | 55.03 [d, $J$ = 126.7 Hz] | 28.4 14.6(β') | 16.2 13.9 (β') | – | – | – | – | 172.37 | 52.31 | – |
| **4h** | 129.32 | 130.98 | 128.17 | 124.32 | 152.41 [d, $J$ = 7.0 Hz] | 131.72 [d, $J$ = 4.0 Hz] | 35.31 | 53.97 [d, $J$ = 120.3 Hz] | 29.3 | 14.1 | – | – | – | – | 176.20 | 51.20 | – |
| **4i** | 129.82 | 131.03 | 128.47 | 124.55 | 150.75 [d, $J$ = 6.9 Hz] | 132.11 [d, $J$ = 4.5 Hz] | 33.72 | 55.07 [d, $J$ = 123.7 Hz] | 9.3 | – | – | – | – | – | 173.11 | 51.37 | – |

a - Chemical shifts are in ppm from TMS and coupling constants ($J$) in Hz are given in parenthesis; b - Recorded in DMSO–$d^6$.

*Synthesis of 2,10-dichloro-6-glycene methyl ester-12H-dibenzo[d,g][1,3,2]dioxaphosphocin-6-oxid* ***4a****. General Procedure*

To a well stirred solution of 5,5'-dichloro-2,2'-dihydroxy biphenyl methane(**1**, 1.34 g, 0.005 mole) and triethylamine (1.01 g, 0.01 mole) in dry toluene (25 mL) phosphorous oxychloride (0.466 g, 0.005 mole) in dry toluene (15 mL) was added at 0°C. After the addition, the temperature of the reaction mixture was raised slowly and kept at 55–60°C for 2 hours. Completion of the reaction was monitored by TLC analysis. After cooling down to room temperature it was filtered to remove triethylamine hydrochloride and evaporated in rotary evaporator to obtain concentrated solution of 2,10-dichloro-6-chloro-12*H*-dibenzo[d,g][1,3,2]dioxaphosphocin-6-oxide (**3**), which is used for the next step without any further purification.

To the concentrated solution of compound **3** (1.748 g, 0.005 mole)and triethylamine (1.01 g, 0.01 mole) in dry tetrahydrofuran (30 mL), a solution of L-glycine methyl ester (0.698 g, 0.005 mole) was added at room temperature. Progress of the reaction was monitored by TLC analysis. Triethylamine hydrochloride was filtered and the filtrate was evaporated in rotary evaporator. Finally, the residue was purified by column chromatography by using hexane and ethyl acetate mixtures as eluents to yield 1.63 g (72%) m.p. 162–164°C.

Analogous compounds were prepared by adopting the same procedure.

## SUMMARY

A new class of phosphomides substituted with aminoacid esters having good anti-microbial activity were synthesized conveniently in good yields.

***Acknowledgements:*** *The authors express their thanks to Prof. C. Devendranath Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati for his academic interaction and Director IISc (SIC), Bangalore for providing the spectral data.*

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## SYNTHESIS AND АСИНТЕЗ И АНТИМИКРОБНА АКТИВНОСТ НА 2,10-ДИХЛОР-6-ЗАМЕСТЕНИ С ЕСТЕРИ НА АМИНОКИСЕЛИНИ-12*H*-ДИБЕНЗО[d,g][1,3,2]ДИОКСА-ФОСФОЦИН-6-ОКСИДИ

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Received September 29, 2008; Revised February 10, 2009

(Резюме)

Синтезирани са с добър добив нов клас 2,10-дихлор-6-заместени с естери на аминокиселини-12*H*-дибензо[d,g][1,3,2]ди-оксафосфоцин-6-оксиди чрез кондензация на 12*H*-дибензо[d,g][1,3,2]диоксафосфоцин с различни естери на аминокиселини в присъствие на триетиламин. Съединенията са охарактеризирани с елементен анализ, ИЧС, ЯМР ($^{1}$H, $^{13}$C и $^{31}$P) и масспектроскопия и показват умерена антимикробна активност.