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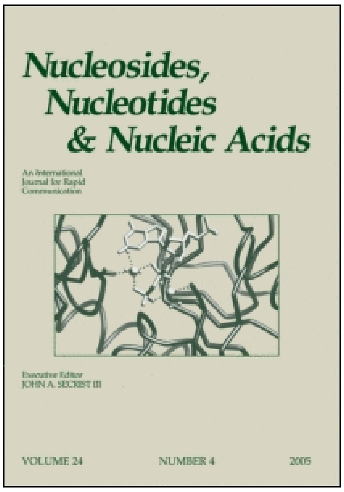

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Synthesis of 9-[(Phosphonomethoxy)methyl]guanine and 9-[2-Hydroxy-1-(phosphonomethoxy)ethyl]guanine

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NUCLEOSIDES & NUCLEOTIDES, 9(4), 579-585 (1990)

SYNTHESIS OF 9-[(PHOSPHONOMETHOXY)METHYL]GUANINE AND 9-[2-HYDROXY-1-(PHOSPHONOMETHOXY)ETHYL]GUANINE

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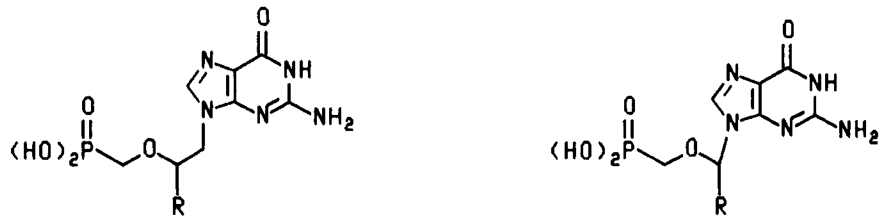
Abstract: The synthesis of 9-[(phosphonomethoxy)methyl]guanine (3) and 9-[2-hydroxy-1-(phosphonomethoxy)ethyl]guanine (4) is described.

Recently, 9-[(2-phosphonomethoxy)ethyl]guanine (PMEG, 1)[1] and (R,S)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]guanine (HPMPG, 2)[2] have been described as potent and broad spectrum antiviral agents. As a part of our program to study structure-activity relationships of this class of compounds, guanine derivatives with various lengths of the phosphonomethoxy alkyl side chain were prepared to examine the importance of the distance between the phosphorous atom and the guanine base for antiviral activity. Among longer alkyl chain derivatives, 9-[(3-phosphonomethoxy)propyl]guanine[3] and (S)-9-[4-hydroxy-3-(phosphonomethoxy)butyl]-guanine[4] exhibited a potent activity against human cytomegalovirus (HCMV). Since these compounds are one carbon homologated analogues of compounds 1 and 2, we further became interested in synthesizing 9-[(phosphonomethoxy)methyl]guanine (3) and 9-[2-hydroxy-1-(phosphonomethoxy)ethyl]guanine (4), in which the side chain was shorter by one carbon from compounds 1 and 2.

The synthesis of compound 3 is shown in Scheme I. The requisite chloromethyl ether 6 was prepared from dimethyl hydroxymethylphosphonate (5)[5] and 1,3,5-trioxan in the presence of HCl gas. Coupling of 6 with 2-amino-6-chloropurine sodium salt readily afforded 7 in 45% overall yield. The chloro group in 7 was first displaced with sodium methoxide



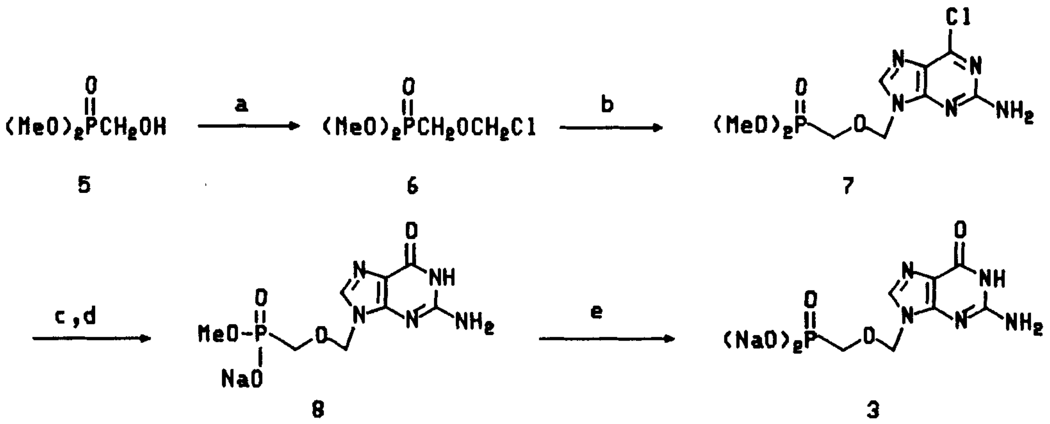
1 R=H
2 R=CH_2OH

3 R=H
4 R=CH_2OH

CHART I

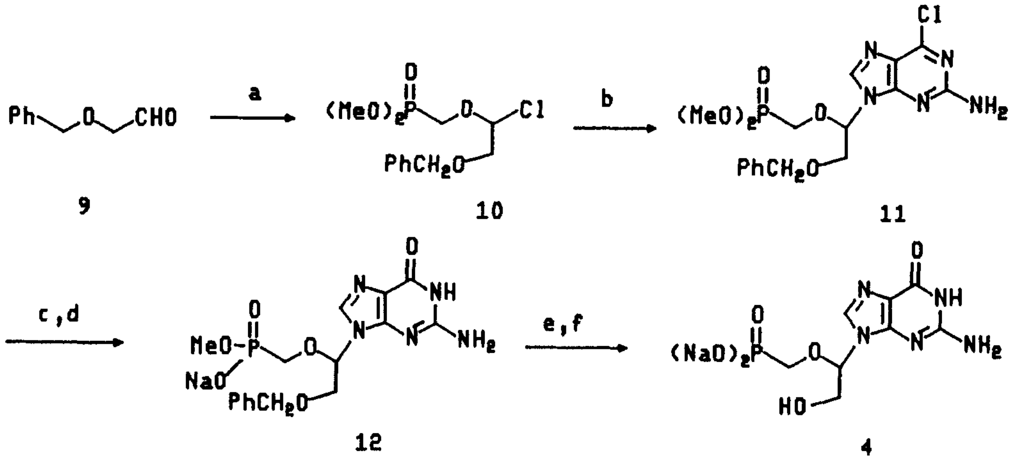
and the resulting methoxy intermediate was further saponified by sodium hydroxide to give the guanine derivative 8 in 67% yield. Final conversion of 8 to 3 was effected in 54% yield by treatment with bromotrimethylsilane followed by sodium bicarbonate neutralization. The side chain attachment at the N-9 position in 3 was ascertained by its ^{13}C NMR (δ 118.194 for the C_5 signal) and UV (λmax 252 and 274 nm) spectra which were consistant with the published data of N-9 alkylated guanine derivatives.[6]

Analogous to the synthesis of 3, the α-chloroalkyl ether intermediate 10 was required for the preparation of 4 (Scheme II). Condensation of benzyloxyacetaldehyde (9) with dimethyl hydroxymethylphosphonate[5] in the presence of HCl gas gave the α-chloroalkyl ether (10)[7] with 40-50% purity, as estimated from NMR analysis. Coupling of the crude 10 with 2-amino-6-chloropurine sodium salt provided the purine derivative 11 in 16% overall yield. Sequential treatment of 11 with sodium methoxide followed by sodium hydroxide gave the guanine derivative 12 in 72% yield. Conversion of 12 to 4 was effected in 29% yield by action of bromotrimethylsilane followed by palladium catalyzed hydrogenolysis. The attachment of the side chain at the N-9 position in 4 was also confirmed by its ^{13}C NMR and UV spectra in a same manner described for 3.



[a] (a) HCl-1,3,5-trioxane; (b) 2-amino-6-chloropurine sodium salt; (c) CH_3ONa; (d) H_2O; (e) TMSBr.

SCHEME I[a]



[a] (a) $(MeO)_2P(O)CH_2OH/HCl$; (b) 2-amino-6-chloropurine sodium salt; (c) CH_3ONa; (d) H_2O; (e) TMSBr; (f) Pd/C.

SCHEME II[a]

Both compounds 3 and 4 did not exhibit activity against herpes simplex virus type 1 and type 2, and HCMV up to the concentration of 100 μg/ml. This result demonstrates that the two or three carbon spacers between the phosphonomethoxy functionality and guanine base are optimal for 9-phosphonoalkylguanine derivatives as anti-herpes agents.

EXPERIMENTAL

Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were run on a Varian Gemini-300 MHz spectrometer with tetramethylsilane as the internal reference. The chemical shift values are expressed in δ values (parts per million). Ultraviolet spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Analytical results for compounds indicated by the molecular formula were within ±0.4% of calculated values.

2-Amino-6-chloro-9-[[(dimethylphosphono)methoxy]methyl]purine (7). A solution of dimethylhydroxymethylphosphonate[5] (3.1g, 22.4 mmol) and 1,3,5-trioxane (730 mg, 24 mmol) in 1,2-dichloroethane (20 mL) was saturated with HCl gas at 5°C. After stirring at 25°C for 16 h, the resulting solution was purged with a stream of N_2 to remove excess HCl and then dried with Na_2SO_4. Concentration of the filtrate in vacuo gave 6 (3.7 g, 60% purity as estimated by nmr): ^1H NMR ($CDCl_3$) δ 3.880 (d, J=12 Hz, 6H), 3.962 (d, J=10.5 Hz, 2H), 5.470 (s, 2H). This material was used for the next step without further purification.

To a suspension of 57% sodium hydride in mineral oil (730 mg, 13.2 mmol) in DMF (50 mL) was added 2-amino-6-chloropurine (2.2 g, 13 mmol), and the mixture was stirred for 1 h at 20°C under nitrogen. To this solution was added a solution of 6 (2.5 g, 13 mmol) in DMF (2 mL). The resulting mixture was stirred for 15 h at 25°C. The mixture was then concentrated in vacuo, taken up in CH_2Cl_2 and washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as eluent to give 7 (1.9 g, 45%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.706 (d, J=10.8 Hz, 6H), 3.841 (d, J=8.9 Hz, 2H), 5.517 (s, 2H), 5.579 (broad s, 2H, 7.874 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 53.505, 53.594, 61.653, 63.888, 73.802, 73.957, 125.330, 142.737, 152.357, 154.761, 160.403. Anal. ($C_9H_{13}N_5O_4PCl$) C, H, N.

9-[[(Methoxyhydroxyphosphinyl)methoxy]methyl]guanine sodium salt (8).

To a solution of 7 (720 mg, 2.24 mmol) in MeOH (10 mL) was added 1N MeONa in MeOH (25 mL) and the solution was heated at 80°C for 2 h under nitrogen. After removal of MeOH, water (25 mL) was added and the solution was heated at reflux for 90 min. The cooled (5°C) solution was then adjusted to pH 8 with concentrated HCl. The resulting solution was evaporated in vacuo, and the residual solid was purified by C_{18} reverse phase column using water as eluent under 8 psi pressure to give 8 (550 mg, 67%) as a white solid: UV max (H_2O) 252 nm (ε 12471), 274 nm (ε 8882); ^1H NMR (D_2O) δ 3.472 (d, J=10.4 Hz, 6H), 3.681 (d, J=9.6 Hz, 2H), 5.466 (s, 2H), 7.908 (s, 1H). Anal. $C_8H_{11}N_5O_5PNa\cdot 3H_2O$) C, H, N.

9-[(Phosphonomethoxy)methyl]guanine disodium salt (3).

A solution of 8 (520 mg, 1.67 mmol) and bromotrimethylsilane (5 mL) in DMF (10 mL) was stirred at 25°C for 2 h under nitrogen. The volatiles were removed in vacuo and the residual oil was taken up in aqueous $NaHCO_3$ (3 mL) and neutralized with 10% HCl. Water was evaporated in vacuo and the residual solid was purified by C_{18} reverse phase column using water as eluent under 8 psi pressure to give 3 (290 mg, 54%) as a white solid: UV max (H_2O) 254 nm (ε 12375), 274 nm (ε 8960); ^1H NMR (D_2O) δ 3.475 (d, J=9.3 Hz, 2H), 5.458 (s, 2H), 7.921 (s, 1H). Anal. $C_7H_8N_5O_5PNa_2\cdot(4H_2O + 5\%\ NaCl)$) C, H, N.

2-Amino-6-chloro-9-[2-benzyloxy-1-[(dimethoxyphosphono)methoxy]-ethyl]purine (11).

A mixture of benzyloxyacetaldehyde (1.0 g, 6.6 mmol), dimethyl hydroxymethylphosphonate (919 mg, 6.6 mmol) and Na_2SO_4 (2.5 g) in 1,2-dichloroethane (15 mL) was stirred at 5°C as a stream of HCl was bubbled through it. After 5 h at 5°C, the mixture was continuously stirred at 25°C for 14 h. The resulting mixture was purged with a stream of N_2 and filtered. Concentration of the filtrate in vacuo gave 10 (50% purity as estimated by nmr) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.690 (d, J=11.5 Hz, 3H), 3.756 (d, J=11.5 Hz, 3H), 3.5-4.2 (m), 4.451 (d, J=13 Hz, 1H), 4.552 (d, J=13 Hz, 1H), 5.640 (q, J=3.0, 5.4 Hz, 1H), 7.20 (broad s, 5H). This material was used for the next step without further purification.

To a suspension of 57% NaH in mineral oil (270 mg, 6.6 mmol) in DMF (25 mL) was added 2-amino-6-chloropurine (1.1 g, 6.6 mmol), and the mixture was stirred for 1 h at 25°C under nitrogen. To this solution was added a solution of crude 10 in DMF (2 mL). The mixture was stirred at 25°C for 5 h and then concentrated in vacuo. The residual oil was taken up in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo. Column chromatography of the residual oil on silica gel using CH_2Cl_2-10%MeOH as eluent gave 11 (460 mg, 16%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.695 (d, J=10.5 Hz, 3H), 3.745 (d, J=10.5 Hz, 3H), 3.7-4.0 (m, 4H), 4.450 (d, J=7.8 Hz, 1H), 4.520 (d, J=7.8 Hz, 1H), 5.720 (t, J=5.5 Hz, 1H), 7.0-7.3 (m, 5H), 7.90 (s, 1H).

9-[2-Benzyloxy-1-[(methoxyhydroxyphosphinyl)methoxy]ethyl]guanine sodium salt (12).

A solution of 11 (600 mg, 1.36 mmol) in 1N MeONa in MeOH (15 mL) was heated at 80°C for 2 h under nitrogen. Concentration of MeOH gave a yellow oil, which was dissolved in water (15 mL) and the resulting solution was heated at 110°C for 2 h. The cooled (5°C) solution was then adjusted to pH 8 with concentrated HCl. The resulting solution was evaporated in vacuo, and the residual solid was purified by C_{18} reverse phase column using water as eluent under 8 psi pressure to give 12 (400 mg, 72%) as a white solid: ^1H NMR (D_2O) δ 3.464 (d, J=10.8 Hz, 3H), 3.607 (m, 2H), 4.00 (m, 2H), 4.402 (d, J=12 Hz, 1H), 4.532 (d, J=12 Hz, 1H), 5.600 (t, J=5.1 Hz, 1H), 7.0-7.3 (m, 5H), 7.834 (s, 1H).

9-[2-Hydroxy-1-(phosphonomethoxy)ethyl]guanine disodium salt (4).

A solution of 12 (400 mg, 0.98 mmol) and bromotrimethylsilane (5 mL) in DMF (5 mL) was stirred at 25°C for 2 h under nitrogen. The volatiles were removed in vacuo, and the residual oil was taken up in aqueous $NaHCO_3$ (4 mL) and diluted with EtOH (20 mL). To the resulting solution was added 10% palladium on activated carbon (200 mg), and the mixture was hydrogenated in the Parr hydrogenator at 50 psi for 12 h. The mixture was filtered through celite, washed with MeOH, and the combined filtrate was evaporated in vacuo. The residual solid was purified with C_{18} reverse phase column chromatography using water as eluent under 8 psi pressure to give 4 (29%) as a white solid: UV max (H_2O) 252 nm (ε 12630), 274 nm (ε 8694); ^1H NMR (D_2O) δ 3.424 (d, J=8.4 Hz, 1H), 3.456 (d, J=8.4 Hz, 1H), 3.94 (dd, J=5.1, 11.4 Hz, 1H), 4.08 (dd, J=5.1, 11.4 Hz, 1H), 5.586 (t, J=5.1 Hz, 1H), 7.973 (s, 1H); ^{13}C NMR (D_2O) δ 64.293, 68.046, 70.031, 88.226, 88.403, 140.327, 153.445, 156.038, 161.115. Anal. ($C_8H_{10}N_3O_6PNa_2 \cdot 3H_2O$) C, H, N.

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