

the same conditions as the assay except without vitamin K₁ epoxide. At various time intervals (0, 1, 2, 3, 4, 5 h) aliquots (40 μ L) were withdrawn from the incubation mixtures, diluted into an assay mixture containing 40 μ M vitamin K₁ epoxide, 3 mM DTT, and 0.02% Emulgen 911 (total volume 500 μ L), and assayed for vitamin K₁ epoxide reductase activity as described above.

Competitive Inhibition of Vitamin K₁ Epoxide Reductase by Substrate Analogues. Vitamin K₁ epoxide reductase activity (0.8 mg of microsomes) was measured by varying concentrations (10, 12.5, 16.5, 25, and 40 μ M) of vitamin K₁ epoxide and 5 mM DTT in the absence and presence of the analogues (0, 20, 40, and 60 μ M). Enzyme assays were the same as described above. Double-reciprocal plots of enzyme activity versus vitamin K₁ epoxide concentration at various concentrations of the substrate analogues were constructed. Inhibition constants (K_i) were determined from replots of $K_{m,app}$ versus the concentration of the substrate analogues.

The experiment also was carried out at varying DTT concentrations (0.33, 0.50, 0.67, 1.0, 2.0 mM) and 40 μ M vitamin K₁ epoxide in the presence of 1 ($R = CH_2F$) (0, 20, 40, 60 μ M). Assays were done as described above.

Substrate Activity of 1 ($R = CH_2OH$), 7, 11, 13, and 16. The assay (minus vitamin K₁ epoxide) was carried out as above with the alternative substrates 1 ($R = CH_2OH$), 7, 11, 13, and 16) at 100, 66.7, 50, 40, 33, 25, 20, 16.5, 14.5, 12.5, 11, and 10 μ M. The corresponding quinone products generated (2-hydroxyvitamin K₁,¹⁷ 6, 10, 18, 15) were used as standards to quantitate the amount of enzyme-generated product. No epoxide reduction occurred under the same conditions when either microsomes or DTT was omitted.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (Grant No. GM 35855) for financial support of this work.

Synthesis and Antiviral Activity of (S)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]guanine

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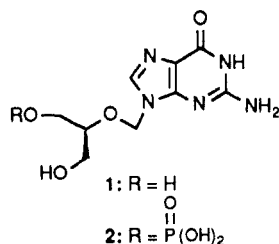
The synthesis of (S)-9-[4-hydroxy-3-(phosphonomethoxy)butyl]guanine (**3**), starting from (S)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**4**), is described. Alkylation of trityl derivative **7** with (diethylphosphono)methyl triflate provided phosphonate **8**, which was readily converted to mesylate **12** in three steps. Nucleophilic substitution of the mesylate group of **12** by 2-amino-6-chloropurine sodium salt led to (S)-2-amino-6-chloro-9-[3-[(diethylphosphono)methoxy]-4-(tetrahydro-2H-pyran-2-yloxy)butyl]purine (**13**). Sequential treatment of **13** with trimethylsilyl bromide and then with 2 N HCl furnished **3**. Preliminary in vitro screening indicated that **3** exhibited a potent activity against human cytomegalovirus (HCMV) but was not active against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The adenine and cytosine derivatives (**14** and **15**) did not exhibit activity against HSV-1 and -2 and HCMV.

The discovery of the potent selective antiherpes agents 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir)¹ and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, ganciclovir, **1**)²⁻⁴ has led to an extensive search for novel nucleoside analogues with improved properties. DHPG is an exceptionally potent agent against a broad range of herpesviruses including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2),²⁻⁴ human cytomegalovirus (HCMV),^{3,4}

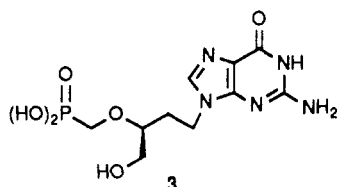
varicella-zoster virus,³ and Epstein-Barr virus.³ Although the clinical use of DHPG for the treatment of cytomegalovirus retinitis has been approved, some adverse toxicological effects of DHPG in humans⁵ prompted further search for a more effective agent against HCMV. Recently, HCMV has also been recognized as one of the most important pathogens in immunocompromised and acquired immune deficiency syndrome (AIDS) patients.⁶ As the essential feature of the biochemical mechanism, DHPG is known to be converted to its monophosphate **2** by HSV thymidine kinases (TKs) or host kinases and then to the triphosphate by host cell kinases.³ This triphosphate, in turn, acts as a viral DNA polymerase inhibitor.⁷ Since HCMV is not known to code for a viral TK, a phosphonate

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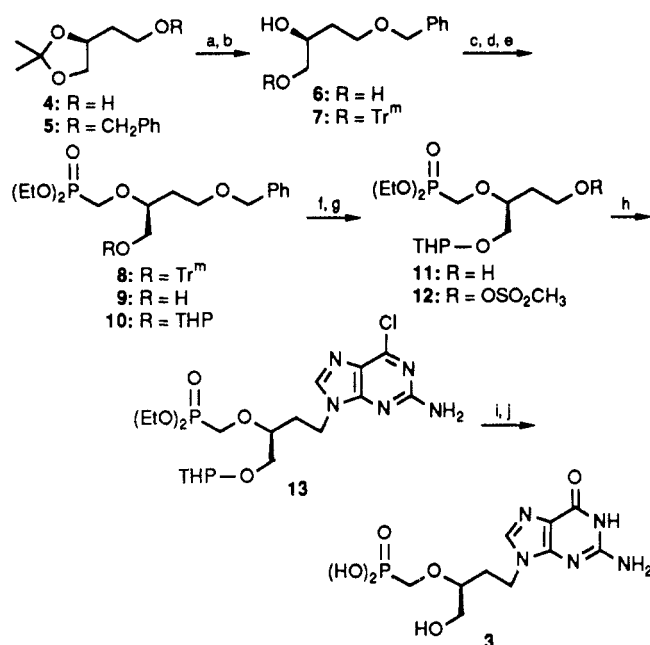
analogue such as 3 which mimics monophosphate 2, thus



bypassing the initial enzymatic phosphorylation, would be promising as a potential chemotherapeutic agent against HCMV. Furthermore, the initial phosphorylation of DHPG by HSV-TK has been demonstrated to generate stereospecifically the *S* isomer of 2,⁸ therefore, we have set our goal to synthesize 3 with the *S* chirality.

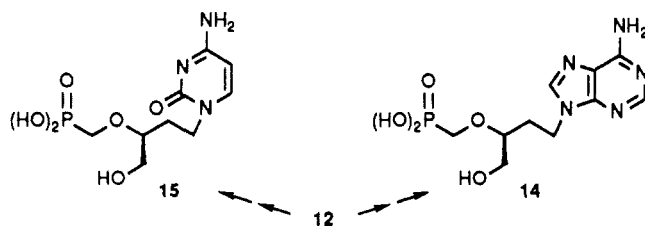
Recently, new [(phosphonomethoxy)alkyl]purine and -pyrimidine derivatives have emerged as potent antiviral agents.⁹ These analogues effectively inhibited a wide array of DNA viruses and retroviruses.⁹ The characteristic phosphonomethyl ether functionality present in [(phosphonomethoxy)alkyl]purine and -pyrimidine derivatives is expected to be chemically and metabolically stable.¹⁰ Moreover, the β -oxygen atom in the phosphonomethyl ether functionality enhances the acidity of the phosphonate and brings its second pK_a closer to that of the phosphate ester.¹¹ In addition to this isoelectronic nature, the oxygen atom in the immediate vicinity of phosphorus has been demonstrated to play a critical role for the enzymatic phosphorylation and thus for antiviral activity.¹¹

Although 3 was designed as a mimic of DHPG monophosphate 2, it may also be regarded as a one carbon homologated analogue of 9-[(3-hydroxy-2-(phosphonomethoxy)propyl]guanine (HPMPG), which is reported^{9f} to exhibit broad-spectrum antiviral activity. In the present paper, we report on the synthesis and in vitro antiviral

Scheme I^a

^a(a) 3 N HCl, MeOH; (b) (4-methoxyphenyl)diphenylmethyl chloride, TEA; (c) NaH, (diethylphosphono)methyl triflate; (d) Amberlyst 15, MeOH; (e) 3,4-dihydro-2H-pyran, *p*-TSA; (f) Pd/C, H₂; (g) CH₃SO₂Cl, TEA; (h) 2-amino-6-chloropurine, NaH; (i) TMSBr, DMF; (j) 2 N HCl.

Scheme II



activity of 3 and the related adenine and cytosine analogues (14, 15).

Chemistry

As shown in Scheme I, the synthesis of 3 commenced with (*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (4), which was obtained by acid-catalyzed cyclization of (*S*)-1,2,4-butanetriol 2-(1-methyl-1-methoxyethyl ether) according to the procedure of Meyers and his co-workers.¹² The hydroxyl functionality of 4 was protected first as the benzyl ether by alkylation with benzyl bromide. Diol 6, generated by acid-catalyzed hydrolysis of 5, reacted smoothly with 4-methoxytrityl chloride in CH₂Cl₂ to give monotrityl derivative 7 in 84% yield. This site-selective tritylation was crucial to distinguish the primary and the secondary hydroxyl groups in diol 6. At this stage, the sodium salt of 7 was alkylated with (diethyl phosphono)methyl triflate¹³ in THF to give the desired phosphonate 8 in 58% yield. The use of the triflate was necessary in this case, because (diethylphosphono)methyl *p*-toluenesulfonate¹⁴ was found to be ineffective for this alkylation. Since catalytic hydrogenolysis of 8 removed both benzyl and trityl protecting groups, conversion of the trityl group

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Table I. Antiherpes and Anticellular Activities of Acyclic Phosphonates in Tissue Culture

virus or cell	ID ₅₀ , ^a $\mu\text{g/mL}$			
	3	14	15	DHPG
HSV-1 (BWS) ^b	>100	>100	>100	0.2
HSV-2 (G)	97	>100	>100	1.6
HCMV (AD-169)	1.0	>100	>100	5.0
vero cells	>100	>100	>100	>100
MRS-5 cells	10	>100	>100	>100

^a Determined by plaque-reduction assays in vero (HSV) or MRC-5 cells (HCMV) or cell-proliferation assays in uninfected cell. ^b The strain is given in parentheses.

to the hydrogenolysis-stable protecting group was necessary. Selective removal of the trityl group was achieved under mild acidic conditions to give alcohol **9**, which was then converted to tetrahydropyranyl ether **10** in almost quantitative yield. Catalytic hydrogenolysis of **10** removed the benzyl protecting group, and the resulting alcohol **11** was converted to mesylate **12** by treatment with methanesulfonyl chloride and triethylamine. The coupling between the mesylate **12** and 2-amino-6-chloropurine sodium salt in DMF provided the N-9 purine derivative **13** in 52% yield with no observable N-7 isomer after silica gel chromatography. Final deprotection of **13** was effected in 47% yield by treatment with bromotrimethylsilane in DMF followed by acidic hydrolysis of the 6-chloropurine. The side-chain attachment at the N-9 position in **3** was ascertained by its ¹³C NMR (δ 117.816 for the C-5 signal)¹⁵ and UV (λ_{max} 252 and 274 nm)¹⁶ spectra which were consistent with the published data of N-9 alkylated isomers. In a similar manner to that described above, the adenine and the cytosine analogues (**14** and **15**) were also prepared from mesylate **12** (Scheme II).

Biological Results and Discussion

Results of antiviral activity testing by the plaque-reduction assay against herpesviruses are listed in Table I. Since the DHPG triphosphate and the diphosphoryl derivative of (R,S)-HPMPG have been demonstrated to be selective inhibitors of viral DNA polymerase,^{7,9f} a prerequisite for **3** to have antiherpetic activity is assumed to be that it be phosphorylated further to its diphosphate. Despite poor activity against HSV-1 and HSV-2, compound **3** exhibited a very potent activity against HCMV, comparable to that of DHPG. This result appears to suggest a significant level of phosphorylation of **3** by host enzymes; however, its diphosphate may be a poor inhibitor of HSV-1 and HSV-2 DNA polymerase, but an effective inhibitor of the HCMV DNA polymerase. A similar trend of antiviral activity against herpesviruses was also reported for 9-[[1-(dihydroxyphosphinyl)-4-hydroxy-3-butoxy]-methyl]guanine,¹⁷ an isosteric isomer of **3**. The cytotoxic effect of **3** is somewhat dependent on the cell line used in the assay. Thus, **3** exhibited ID₅₀'s of >100 $\mu\text{g/mL}$ in vero cells and 10 $\mu\text{g/mL}$ in MRC-5 cells (human lung fibroblast).

Compounds **14** and **15** had no antiviral activity at concentrations up to 100 $\mu\text{g/mL}$. The inactivity of **15** against HCMV is somewhat surprising because 9-[(1,3-dihydroxy-2-propoxy)methyl]cytosine,¹⁸ a cytosine analogue

of DHPG, has potent activity against HCMV that is comparable to the activity of DHPG.

Experimental Section

General Methods. Nuclear magnetic resonance (¹H, ¹³C NMR) spectra were run on a Varian Gemini-300 300-MHz spectrometer with trimethylsilane 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 $\pm 0.4\%$ of the calculated values.

(S)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolane (5). To a suspension of 57% sodium hydride in mineral oil (6.6 g, 0.16 M) in THF (250 mL) at 25 °C was added (S)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**4**) (21.3 g, 0.15 M) and the mixture was heated at reflux for 2 h under nitrogen. To this solution at 10 °C was added benzyl bromide (25.2 g, 0.15 M). After stirring at 25 °C for 2 h, the mixture was heated at reflux for 1 h. Insoluble material was removed by filtration, and the filtrate was concentrated to dryness. The residual oil was chromatographed on silica gel using CH₂Cl₂-hexane as eluent to give **5** (25.0 g, 72.6%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.35 (s, 3 H), 1.402 (s, 3 H), 1.9 (m, 2 H), 3.55 (q, J = 2.7, 5.4 Hz, 1 H), 3.58 (q, J = 5.1, 7.5 Hz, 2 H), 4.06 (q, J = 5.4, 8.1 Hz, 1 H), 4.22 (m, 1 H), 4.5 (s, 2 H), 7.33 (s, 5 H). Anal. (C₁₄N₂O₃) C, H.

(S)-3-(Benzyloxy)-1-[[diphenyl(4-methoxyphenyl)methoxy]methyl]propanol (7). To a solution of **5** (25 g, 0.11 M) in methanol (200 mL) was added 3 N HCl (4 mL). After stirring for 4 h at 25 °C, the solution was evaporated in vacuo, taken up in CH₂Cl₂, and washed with aqueous NaHCO₃. The CH₂Cl₂ was dried over MgSO₄ and evaporated to give diol **6** as a colorless oil. This material was used for the next step without further purification. Thus, to a solution of diol **6** (20 g, 0.1 M) in CH₂Cl₂ (300 mL) and [(4-methoxyphenyl)diphenyl]methyl chloride (31 g, 0.1 M) in CH₂Cl₂ (300 mL) was added at 0 °C triethylamine (13 g, 0.13 M) over 5 min. After stirring at 0 °C for 90 min, the mixture was stirred for 16 h and filtered through Celite. The filtrate was washed with 10% H₃PO₄, aqueous NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH₂Cl₂ as eluent to give **7** (42 g, 84%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.78 (m, 2 H), 3.58 (m, 2 H), 3.76 (s, 3 H), 3.84 (m, 2 H), 3.99 (m, 1 H), 4.45 (s, 2 H), 6.8–7.2 (m, 14 H).

(S)-Diethyl [[3-(Benzyloxy)-1-[[diphenyl(4-methoxyphenyl)methoxy]methyl]propoxy]methyl]phosphonate (8). To a suspension of 57% sodium hydride in mineral oil (2.8 g, 70 mmol) in dry THF (300 mL) was added 28 g (59.6 mmol) of **6** and the mixture was heated at 60 °C for 3 h under nitrogen. To this solution was added at 5 °C a solution of (diethylphosphono)methyl triflate (20 g, 66.7 mmol) in THF (20 mL). After stirring at 25 °C for 16 h, the mixture was evaporated in vacuo, taken up in CH₂Cl₂ (600 mL), washed with water, 10% H₃PO₄, aqueous NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH₂Cl₂-3% MeOH as eluent to give **8** (21.2 g, 58%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.20–1.35 (m, 6 H), 1.82 (m, 2 H), 3.17 (m, 2 H), 3.5–3.7 (m, 4 H), 3.78 (s, 3 H), 4.45 (s, 2 H), 6.8–7.5 (m, 19 H).

(S)-Diethyl [[3-(Benzyloxy)-1-[(tetrahydro-2H-pyran-2-yloxy)methyl]propoxy]methyl]phosphonate (10). To a solution of **8** (26.3 g, 43 mmol) in MeOH (120 mL) was added Amberlyst 15 ion-exchange resin (6.0 g). After stirring at 25 °C for 4 h, the mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residual oil was chromatographed on silica gel using CH₂Cl₂ as eluent to give **9** (13.9 g, 93%) as a colorless oil. To a solution of **9** (11.5 g, 33.3 mmol) and 3,4-dihydro-2H-pyran (3.4 g, 40 mmol) in CH₂Cl₂ (200 mL) was added a solution of *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) in ether (10 mL) at 25 °C. After stirring at 25 °C for 2 h, the solution was washed with aqueous NaHCO₃, dried over

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MgSO₄, and concentrated in vacuo. The oily residue was chromatographed on silica gel using CH₂Cl₂ as eluent to give 10 (13.6 g, 95%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.27 (m, 6 H), 1.4-1.9 (m, 8 H), 3.3-3.9 (m, 13 H), 4.45 (s, 2 H), 4.55 (br s, 1 H), 7.28 (m, 5 H). Anal. (C₂₁H₃₅O₅P) C, H.

(S)-Diethyl [[3-[(Methylsulfonyl)oxy]-1-[(tetrahydro-2H-pyran-2-yloxy)methyl]propoxy)methyl]phosphonate (12). A mixture of 10 (11.3 g, 26.3 mmol) and 10% palladium on activated carbon (5.6 g) in EtOH (200 mL) was hydrogenated in a Parr hydrogenator at 50 psi for 16 h. The catalyst was filtered through Celite and washed with MeOH, and the combined solvents were evaporated to give 11 (8.4 g, 93%) as a colorless oil. This material was used for the next step without purification. Thus, a solution of 11 (3.8 g, 11.2 mmol) and methanesulfonyl chloride (1.6 g, 13.6 mmol) in CH₂Cl₂ (60 mL) was added at 0 °C to a solution of triethylamine (2.35 g, 23 mmol) in CH₂Cl₂ (5 mL). After stirring at 0 °C for 2 h, the CH₂Cl₂ was washed with 30% H₃PO₄ and brine, dried over MgSO₄, and evaporated in vacuo. The crude oil was chromatographed on silica gel using CH₂Cl₂ as eluent to give 12 (4.0 g, 85%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.25 (m, 6 H), 1.4-2.0 (m, 8 H), 2.95 (s, 3 H), 3.40 (m, 2 H), 3.6-4.4 (m, 11 H), 4.55 (br s, 1 H).

(S)-2-Amino-6-chloro-9-[3-[(diethylphosphono)methoxy]-4-(tetrahydro-2H-pyran-2-yloxy)butyl]purine (13). To a suspension of 57% sodium hydride in mineral oil (200 mg, 14.6 mmol) in dry DMF (30 mL) was added 2-amino-6-chloropurine (1.35 g, 8 mmol) under nitrogen. After stirring at 25 °C for 45 min, the mixture was heated at 55 °C for 2 h. To this solution was added at 25 °C a solution of 12 (3.28 g, 8 mmol) in DMF (8 mL) and the mixture was heated at 65 °C for 5 h. The solution was then concentrated in vacuo, taken up in CH₂Cl₂, washed with water, 30% H₃PO₄, aqueous NaHCO₃, and brine, dried over MgSO₄, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH₂Cl₂-5% MeOH as eluent to give 13 (2.1 g, 52%) as a slightly yellow, hard oil: ¹H NMR (CDCl₃) δ 1.25 (t, J = 7.2 Hz, 6 H), 1.3-2.1 (m, 8 H), 3.40 (m, 2 H), 3.6-4.4

(m, 13 H), 4.65 (br s, 1 H), 5.51 (s, 2 H), 7.86 (s, 1 H). Anal. (C₁₉H₃₁N₅O₅PCl) C, H, N.

(S)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]guanine Disodium Salt (3). To a solution of 13 (2.5 g, 5.1 mmol) in CH₃CN (40 mL) was added at 0 °C bromotrimethylsilane (3 mL) under nitrogen. After stirring at 0 °C for 3 h, the volatiles were removed in vacuo, the residual oil was dissolved in 2 N HCl (10 mL), and the solution was heated at 110 °C. Water was then evaporated in vacuo and the residue was adjusted to pH 8 with aqueous NaHCO₃. Evaporation of water gave an amorphous solid which was purified by C-18 reverse phase column under 8 psi of pressure using water as eluent to give 3 (800 mg, 47%) as a white solid: ¹H NMR (D₂O) δ 1.95 (m, 2 H), 3.36 (m, 1 H), 3.435 (dd, J = 3.8, 12.3 Hz, 1 H), 3.54 (d, J = 9.4 Hz, 2 H), 3.7 (dd, J = 3.8, 12.3 Hz, 1 H), 4.12 (t, J = 7.2 Hz, 2 H), 7.88 (s, 1 H); ¹³C NMR (D₂O) δ 32.570, 42.340, 64.005, 67.833, 69.854, 80.793, 80.947, 117.816, 142.079, 153.300, 155.502, 160.889; UV max (H₂O) 252 nm (ε 12159), 274 nm (ε 8882). Anal. Calcd for C₁₀H₁₄N₅O₆PN₂·2.5H₂O: C, 28.42; H, 4.55; N, 16.65. Found: C, 28.36; H, 5.14; N, 16.15.

In a manner similar to that described for the synthesis of 3, compounds 14 and 15 were prepared by coupling of 12 and adenine and cytosine. The spectroscopic data are as follows.

(S)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]adenine disodium salt (14): ¹H NMR (D₂O) δ 1.98 (m, 2 H), 3.30 (m, 1 H), 3.43 (dd, J = 3.6, 12.3 Hz, 1 H), 3.48 (d, J = 10.0 Hz, 2 H), 3.67 (dd, J = 3.6, 12.3 Hz, 1 H), 4.2 (t, J = 7.2 Hz, 2 H), 7.92 (s, 1 H), 8.03 (s, 1 H); UV max (H₂O) 262 nm (ε 12642). Anal. Calcd for C₁₀H₁₄N₅O₆PN₂·3.5H₂O: C, 28.12; H, 3.91; N, 16.05. Found: C, 28.30; H, 4.45; N, 16.55.

(S)-1-[4-Hydroxy-3-(phosphonomethoxy)butyl]cytosine (15): ¹H NMR (D₂O) δ 1.91 (m, 2 H), 3.45 (m, 1 H), 3.53 (d, J = 9.6 Hz, 2 H), 3.6-3.9 (m, 4 H), 6.03 (d, J = 7.2 Hz, 1 H), 6.72 (d, J = 7.2 Hz, 1 H); UV max (H₂O) 282 nm (ε 9486). Anal. Calcd for C₁₁H₁₆N₃O₆P: C, 34.74; H, 5.14; N, 13.50. Found: C, 34.64; H, 5.35; N, 13.02.

Synthesis and Dopamine Receptor Affinities of Enantiomers of 2-Substituted Apomorphines and Their *N-n*-Propyl Analogues

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Received November 30, 1989

Syntheses of (R)-(-)-2-methoxyapomorphine (R-8), its antipode S-8, and its (R)-(-)-*N-n*-propyl R-9 derivative are described. The dopaminergic receptor affinities of these compounds and their 2-unsubstituted counterparts (R)-(-)-apomorphine (R(-)-APO, R-1), (S)-(+)-apomorphine (S(+)-APO, S-1), and (R)-(-)-*N-n*-propylnorapomorphine (R(-)-NPA, R-2), as well as those of (R)-(-)-2-chloroapomorphine (R(-)-2-Cl-APO, R-6), (R)-(-)-2-bromoapomorphine (R(-)-2-Br-APO, R-6), were determined with tissue membrane preparations of corpus striatum from rat brain. Contribution of both an *N-n*-propyl and a 2-hydroxy in (R)-(-)-2-hydroxy-*N-n*-propylnorapomorphine (R(-)-2-OH-NPA, R-7) or a methoxy group in (R)-(-)-2-methoxy-*N-n*-propylnorapomorphine (R(-)-2-OCH₃-NPA, R-9) produced the highest D₂ affinity (0.053 and 0.17 nM) and D₂ over D₁ selectivity (17300 and 10500 times) of the compounds evaluated. The structure-affinity relationships of these 2-substituted apomorphines suggest that secondary binding sites of D₂ receptors interact with 2-substituents on the A ring of apomorphines through H-bonding.

The rigid structure of aporphine alkaloids can be related to several conformations of the neurotransmitter dopamine (DA) (cis,trans- α -rotamer and trans- β -rotamer).^{1,2} This unique character of aporphine derivatives has stimulated extensive study of the structure-activity relationship (SAR) of a large number of such compounds.³ This work supports the conclusion that the α -rotamer is the biologically relevant conformation in aporphines to provide high affinity and dopaminergic activity, such as the prototype

DA agonists (R)-(-)-apomorphine (1, R(-)-APO) and (R)-(-)-*N-n*-propylnorapomorphine (2, R(-)-NPA).

Novel 2-substituted (R)-(-)-apomorphines have been prepared in our laboratories.⁴ These compounds, with

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