Synthesis and Antiviral Activity of 9-Alkoxypurines. 1. 9-(3-Hydroxypropoxy)- and 9-[3-Hydroxy-2-(hydroxymethyl)propoxy]purines

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Reaction of hydroxyl-protected derivatives of hydroxyalkoxyamines (**3a,b,c**) with either 4,6-dichloro-2,5-diformamidopyrimidine (**5**) or 4,6-dichloro-5-formamidopyrimidine (**31**) and subsequent cyclization of the resultant 6-(alkoxyamino)pyrimidines (**6, 17, 32, 35**) by heating with diethoxymethyl acetate afforded 9-alkoxy-6-chloropurines (**7, 18, 33, 36**), which were converted subsequently to 9-(3-hydroxypropoxy)- and 9-[3-hydroxy-2-(hydroxymethyl)propoxy] derivatives of guanine, 2-amino-6-chloropurine, 2-amino-6-alkoxypurines, 2-aminopurine, 2,6-diaminopurine, adenine, hypoxanthine, and 6-methoxypurine (**8, 12, 13, 19–21, 23–26, 34, 37–39**). Carboxylic acid esters (**9–11, 14–16, 27–29**) and a cyclic phosphate derivative (**22**) of the 9-(hydroxyalkoxy)guanines (**8, 21**) and 2-amino-9-(hydroxyalkoxy)purines (**13, 26**) were also prepared. The guanine derivatives (**8, 21**) showed potent and selective activity against herpes simplex virus types 1 and 2 and varicella zoster virus in cell cultures and **8** is more active than acyclovir. Although without significant antiviral activity in cell cultures, the 2-aminopurines (**13, 14–16, 26–29**) and 2-amino-6-alkoxypurines (**12, 23–25**) are well absorbed after oral administration to mice and are converted efficiently to the antiviral guanine derivatives (**8, 21**) in vivo.

In continuation of our studies on novel acyclonucleosides,[1-8] we have prepared a series of 9-alkoxypurines.

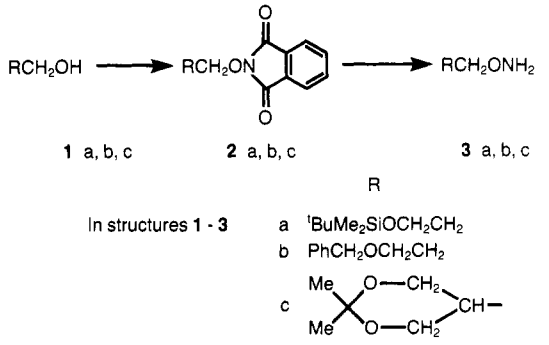
In the present paper we report the synthesis of 3-hydroxypropoxy and 3-hydroxy-2-(hydroxymethyl)propoxy analogues of the antiviral guanine derivatives acyclovir,[9-11] ganciclovir,[12-14] and BRL 39123[3,5] and corresponding derivatives of adenine, hypoxanthine, 6-methoxypurine, 2-aminopurine, 2,6-diaminopurine, and some 6-alkoxy-2-aminopurines. Esters of some of these compounds have also been prepared.

Results that we have obtained from evaluation of the activities of these acyclonucleosides against herpes viruses in cell culture tests are described. The derivatives of 2-aminopurine, 2,6-diaminopurine, and 6-alkoxy-2-aminopurines were synthesized as potential prodrugs of guanine derivatives possessing improved gastrointestinal absorption properties. The concentrations of antiviral guanine derivatives in the blood of mice after oral administration of these compounds are reported.

Chemistry

We have reported previously[15] our development of syntheses of 9-(3-hydroxypropoxy)guanine (**8**) from 3-(benzyloxy)propoxyamine (**3b**) via a 1-alkoxy-5-amino-4-carbamoylimidazole or a 6-(alkoxyamino)-4-chloro-2,5-diformamidopyrimidine. Of these two routes, the latter is shorter and more efficient. Moreover, since it proceeds via a 9-alkoxy-6-chloropurine intermediate, it has readily been adapted for syntheses of all of the additional 9-alkoxypurines reported in this publication. Although *O*-benzyl protection of the hydroxyl groups of the 9-alkoxypurine proved to be quite satisfactory in syntheses of guanine[15] and adenine derivatives (e.g. **8** and **34**), using a variety of experimental conditions we were unable to achieve hydrogenolytic debenzylation of the analogous 2-aminopurine derivatives without concomitant degradation of the purine. For this reason the more easily removed *tert*-butyldimethylsilyl and isopropylidene protecting groups (as in **3a** and **3c**) have been used in most subsequent studies.

Scheme I



Alkoxyamines. Synthesis of the alkoxyamines **3a–c** (Scheme I) was accomplished in high overall yield by reaction of a suitably protected alcohol (**1a–c**) with *N*-hydroxyphthalimide under Mitsunobu conditions, followed by cleavage of the resultant *N*-alkoxyphthalimide (**2a–c**) with either hydrazine hydrate in ethanol at reflux temperature or *N*-methylhydrazine in dichloromethane at ambient temperature.

9-Alkoxy Derivatives of Guanine, 2-Aminopurine, 2,6-Diaminopurine, and 6-Alkoxy-2-aminopurines. Although displacement of chloride from 2,5-diamino-4,6-dichloropyrimidine (**4**) with alkoxyamines did not occur readily, **4** was converted in 70% yield to its diformyl de-

(1) Parkin, A.; Harnden, M. R. *J. Heterocycl. Chem.* **1982**, *19*, 33.
(2) Bailey, S.; Shanks, C. T.; Harnden, M. R. *Nucleosides Nucleotides* **1985**, *4*, 565.
(3) Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1985**, *26*, 4265.
(4) Bailey, S.; Harnden, M. R. *Nucleosides Nucleotides* **1987**, *6*, 555.
(5) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. *J. Med. Chem.* **1987**, *30*, 1636.
(6) Harnden, M. R.; Parkin, A.; Wyatt, P. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2757.
(7) Bailey, S.; Harnden, M. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2767.
(8) Harnden, M. R.; Jarvest, R. L. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2777.
(9) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
(10) Elion, G. B.; Furman, P. A.; Fyfe, J. A. de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
(11) Collins, P.; Bauer, D. J. *J. Antimicrob. Chemother.* **1979**, *5*, 431.
(12) Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Ogilvie, K. K.; Radatus, B. K. *Antimicrob. Agents Chemother.* **1982**, *22*, 55.
(13) Ashton, W. T.; Karkas, J. K.; Field, A. K.; Tolman, R. L. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1716.
(14) Smee, D. F.; Martin, J. C.; Verheyden, J. P. H.; Matthews, T. R. *Antimicrob. Agents Chemother.* **1983**, *23*, 676.
(15) Harnden, M. R.; Parkin, A.; Wyatt, P. G. *Tetrahedron Lett.* **1988**, *29*, 701.

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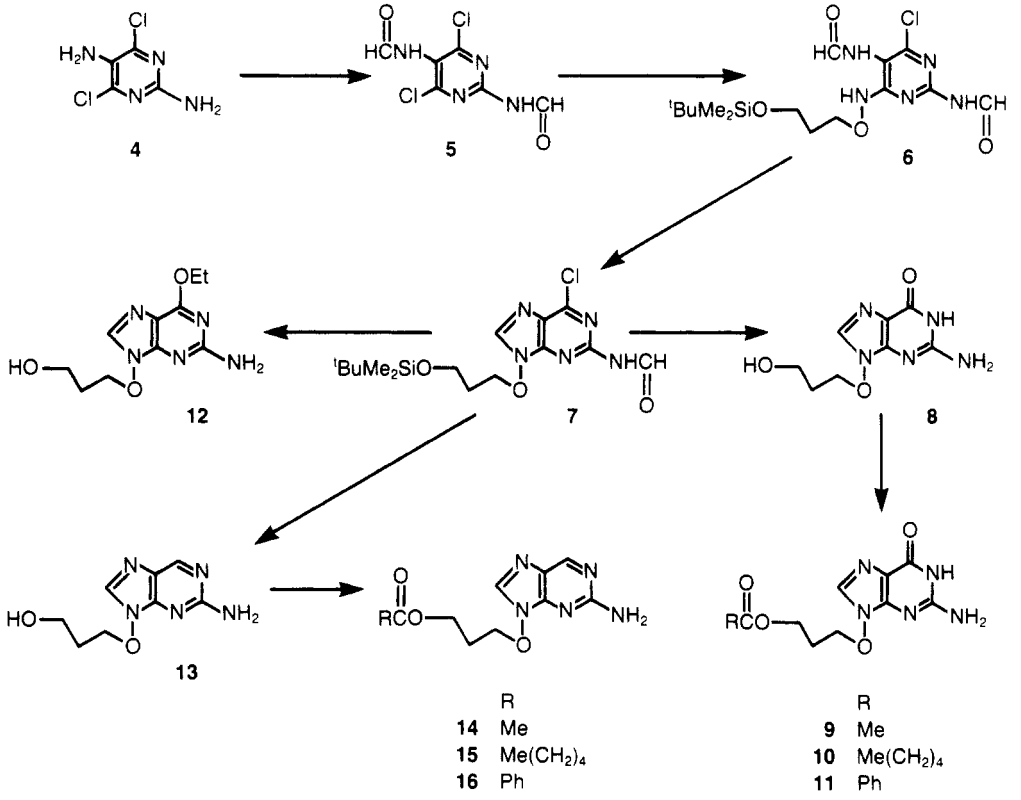
Scheme II



rivative **5**, which in the presence of diisopropylethylamine, reacted in diglyme with 3-[(*tert*-butyldimethylsilyl)oxy]-propoxyamine (**3a**) and [(2,2-dimethyl-1,3-dioxan-5-yl)-methoxy]amine (**3c**) to afford the (alkoxyamino)pyrimidines **6** (Scheme II) and **17** (Scheme III) in 67% and 77% yield, respectively. Closure of the imidazole ring by heating at 120 °C with diethoxymethyl acetate[16] and treatment with ammonia in methanol then gave purines **7** and **18**, which were both obtained in 81% yield.

The 6-chloro-2-formamidopurines **7** and **18** proved to be versatile intermediates to several 9-(hydroxyalkoxy)purines and their O-acylated derivatives. Thus, hydrolysis of **7** and **18** with 80% formic acid at 100 °C afforded 9-(3-hydroxypropoxy)guanine (**8**) and 9-[3-hydroxy-2-(hydroxymethyl)propoxy]guanine (**21**) in 58% and 45% yield, respectively.

The acyclonucleoside **8** was converted to its acetyl (**9**), hexanoyl (**10**), and benzoyl (**11**) esters in 46%, 39%, and 36% yield, respectively, by reaction with appropriate carboxylic acid anhydride and 4-(dimethylamino)pyridine (DMAP) in DMF. Treatment of the acyclonucleoside **21** with stannic chloride and phosphorus oxychloride afforded its cyclic phosphate derivative **22**, which was isolated in 10% yield.

Hydrogenolysis of **7** and **18** using catalytic hydrogen transfer from ammonium formate, followed by treatment with hydrazine hydrate and then acid hydrolysis, provided the 2-aminopurine derivatives **13** and **26** in 31% and 37% yield, respectively. Treatment of **13** and **26** with the appropriate carboxylic acid anhydride and DMAP in DMF afforded the esters **14–16**, **27–29** in high yield.

Reaction of **18** with a catalytic quantity of sodium ethoxide in ethanol, followed by hydrolysis with 80% aqueous acetic acid, provided the 2-amino-6-chloropurine derivative **19** in 69% yield. A series of 6-alkoxypurines (**23–25**) were obtained from **18** by reaction with the appropriate sodium alkoxide followed by acid hydrolysis. The methoxy (**23**), ethoxy (**24**), and isopropoxy (**25**) derivatives were obtained in 89%, 63%, and 64% yield, respectively. Treatment of **18** with ammonia in methanol at 110 °C, followed by acid hydrolysis, afforded the 2,6-diaminopurine derivative **20** in 49% yield.

9-Alkoxy Derivatives of Adenine, Hypoxanthine, and 6-Methoxypurine. 9-Alkoxy derivatives of adenine and hypoxanthine were obtained from 4,6-dichloro-5-formamidopyrimidine (**31**) (Schemes IV and V). Reaction of 5-amino-4,6-dichloropyrimidine (**30**) with formic acid–acetic anhydride afforded **31** in quantitative yield. Treatment of **31** with the hydroxyl-protected alkoxyamines **3b** and **3c** and triethylamine in dioxane gave the (alkoxyamino)pyrimidines **32** and **35** in 79% and 73% yield, respectively. Closure of the imidazole ring was achieved by reaction of **32** with triethyl orthoformate and concentrated hydrochloric acid, affording the 6-chloropurine **33** in 98% yield. Treatment of **33** with ammonia in methanol at 110 °C, followed by catalytic hydrogenolysis, then gave 9-(3-hydroxypropoxy)adenine (**34**) in 13% overall yield. The isopropylidene-protected (alkoxyamino)pyrimidine **35** was converted to the 6-chloropurine derivative **36** in 67% yield with diethoxymethyl acetate at 120 °C. Hydrolysis of **36** with 80% aqueous acetic acid at 100 °C provided 9-[3-hydroxy-2-(hydroxymethyl)propoxy]hypoxanthine (**39**) in 59% yield. Reaction of **36** with ammonia in methanol and sodium methoxide in methanol afforded, after acid hydrolysis, the analogous adenine and 6-methoxypurine derivatives **37** and **38** in about 50% yield.

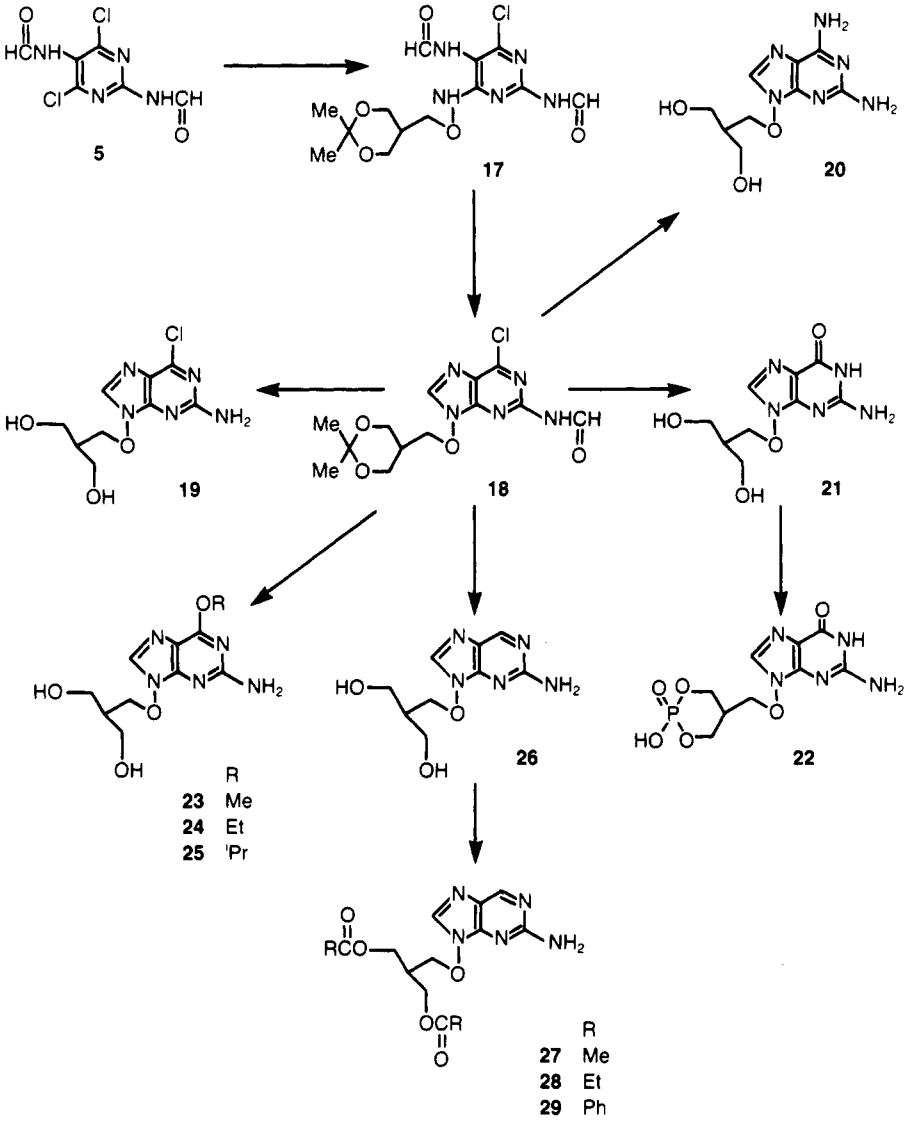
Chemical Stability of the N–O Bond

Although syntheses of 1-alkoxyimidazoles[17] and 9-(benzyloxy)purines[18] have been described, relatively little

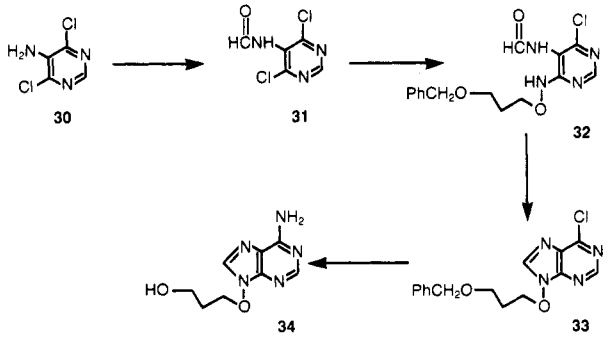
(16) Montgomery, J. A.; Temple, C., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5238.

(17) Bock, V.; Klötzer, W.; Singewald, N.; Strieder, G. *Synthesis* **1987**, 1058.

Scheme III



Scheme IV



information concerning the chemical stability of the N–O bond in these compounds has previously been available. 1-(Benzyloxy)-2,3-dihydroimidazol-2-one was prepared under acidic conditions and converted to the 1-hydroxy compound by catalytic hydrogenation, but this 1-(benzyloxy)imidazole is unstable and under alkaline conditions decomposes into benzaldehyde and 2,3-dihydroimidazol-2-one.[17] In contrast, 9-(benzyloxy)guanine was isolated in 67% yield by cyclization of a 1-(benzyloxy)imidazole in 1 N sodium hydroxide at 100 °C.[18] In the studies reported in this paper we have found that the N–O bond of 9-alkoxypurines is stable to a wide range of both acidic and basic conditions at temperatures up to 100 °C and also to catalytic hydrogenation.

Biological Results

The acyclonucleosides **8–16**, **19–29**, **34**, and **37–39** prepared in this study were tested in plaque reduction assays[19] for activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in Vero and MRC-5 cells, respectively, and against varicella zoster virus (VZV) in MRC-5 cells. The results obtained for active compounds (IC_{50} < 300 μM) are given in Table I.

Antiviral Activity in Cell Culture. The highly potent and selective activities of 9-(3-hydroxypropoxy)guanine (**8**, BRL 44385) and 9-[3-hydroxy-2-(hydroxymethyl)propoxy]guanine (**21**, BRL 45148) are particularly noteworthy. Against HSV-1 and HSV-2 **8** is about 3 times more potent than acyclovir and against VZV it is about 5 times more potent. Esters (**9–11**) of **8** are also active in cell cultures, but this is most probably attributable to their enzymatic and/or chemical hydrolysis to **8** under the test conditions. The bis(hydroxymethyl) analogue **21** has activity similar to that of acyclovir.

(18) Watson, A. A. *J. Org. Chem.* **1974**, *39*, 2911.

(19) Boyd, M. R.; Bacon, T. H. Sutton, D.; Cole, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1238.

Scheme V

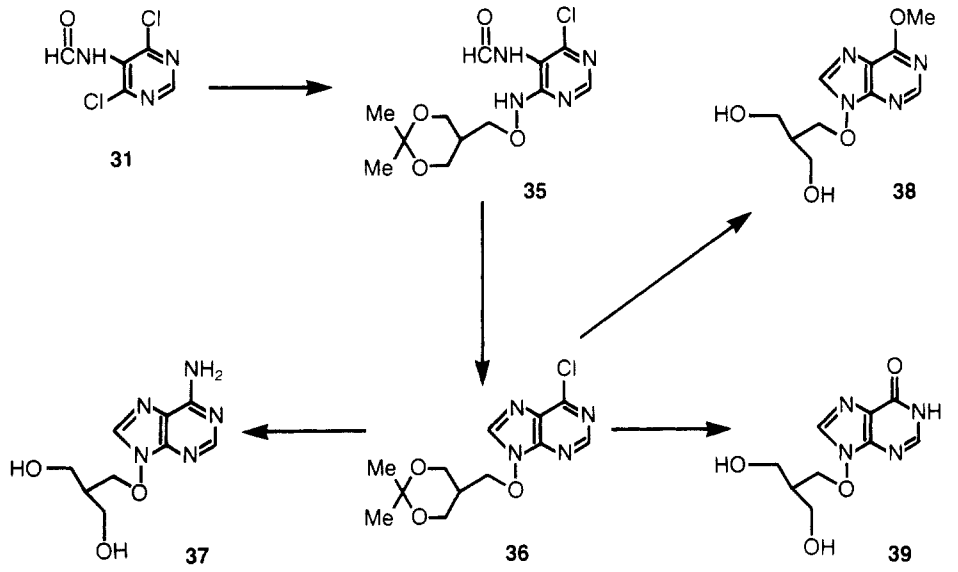


Table I. Antiviral Activity in Plaque Reduction Assays[a] against Herpes Simplex Virus Types 1 and 2 and Varicella Zoster Virus

	IC_{50}, μM		
compd[b]	HSV-1 (HFEM)	HSV-2 (MS)	VZV (Ellen)
8	2.1	0.71	4.4
9	16	4.1	45
10	2.1	0.22	7.4
11	8.5	6.4	>300
21	5.9	5.9	11
22	180	180	186
acyclovir	6.7	2.5	20

[a] Plaque reduction assays were performed as previously described,[19] using Vero or MRC-5 cell monolayers infected with about 50 PFU of HSV-1, HSV-2, or VZV. Monolayers were treated with various concentrations of the compounds that were present throughout the incubation period. Plaques were counted when they were clearly visible (usually 3 days for HSV-1, 1 day for HSV-2, and 5 days for VZV). The compound concentration required to reduce the plaque count to 50% of that in untreated control cultures was calculated (IC_{50}). [b] Test compounds were prepared as 10 mg/mL solutions in Me_2SO and aliquots further diluted in cell culture medium.

None of the compounds for which IC_{50} data are given was cytotoxic in Vero or MRC-5 cell monolayers at concentrations up to 100 μg/mL. Furthermore, in a cell growth experiment in which MRC-5 cells were incubated for 72 h with the acyclonucleosides, the concentrations required to inhibit the increase in cell number by 50% were 275 μM for **8** and >1000 μM for **21**. The cell number in untreated control cultures increased 9-fold.

Absorption and Conversion to Antiviral Acyclonucleosides in Mice. The gastrointestinal absorption of both acyclovir[20] and 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123)[21] after oral administration to rodents or humans has been reported to be rather poor. Consequently, there have been extensive investigations aimed at the development of prodrugs of these guanine derivatives with improved absorption properties. It was reported that higher concentrations of acyclovir in the blood were obtained following oral administration of its 6-amino-6-deoxy[22] and 6-deoxy[23] congeners which, after absorption, are converted to acyclovir by the enzymes adenosine deaminase and xanthine oxidase, respectively.[23,24] The 6-amino-6-deoxy congener of BRL 39123 did not prove to be an efficient prodrug of the 9-substituted guanine upon oral administration to mice. However, the 6-deoxy congener, several of its esters, and a number of 6-*O*-alkyl derivatives were better absorbed and converted with varying degrees of efficiency to the guanine, some of them providing substantially higher concentrations of BRL 39123 in the blood than were achieved after oral administration of the antiviral acyclonucleoside. Conversion of the 6-deoxy congener to the guanine was again accomplished efficiently by xanthine oxidase. Although the enzyme responsible for conversion of the 6-alkoxy derivatives to the guanine was not identified, the more efficient dealkylation observed for the 6-*O*-ethyl- and 6-*O*-isopropylguanines as compared with the 6-*O*-methylguanine[21] indicates that the transformation may involve enzymatic oxidative dealkylation.

Since similar problems of poor gastrointestinal absorption were anticipated with the novel 9-alkoxyguanines (**8** and **21**) reported in this publication, the relative efficiencies of the corresponding derivatives of 2-aminopurine, 2,6-diaminopurine, and 6-alkoxy-2-aminopurines as orally active prodrugs of the guanines have also been determined in mice (Table II).

The guanine derivative **8** and its esters (**9–11**) were, as expected, relatively poorly absorbed after oral administration of a single 0.2 mmol/kg dose and provided concentrations of **8** in the blood ≤8 μM. The 6-*O*-ethyl derivative **12** was better absorbed, but conversion to **8** was incomplete and no improvement in blood concentrations of **8** was seen. The 6-deoxy congener **13** and its esters (**14–16**) were, however, better absorbed and converted efficiently to the antiviral guanine derivative, providing concentrations of **8** in the blood that were from 5 to 8 times higher than those obtained after oral administration of **8**. The bis(hydroxymethyl)guanine derivative **21** was even less well absorbed than **8**, and the highest concentration of **21** detected in the blood was 2 μM. Like the corresponding

(20) de Miranda, P.; Blum, M. R. *J. Antimicrob. Chemother.* **1983**, *12*, Suppl. B, 29.
(21) Harnden, M. R. *Drugs Future* **1989**, *14*, 347.
(22) Good, S. S.; Krasny, H. K.; Elion, G. B.; de Miranda, P. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 644.
(23) Spector, T.; Jones, T. E.; Beecham, L. M., III *Biochem. Pharmacol.* **1983**, *32*, 2505.
(24) Krenitsky, T. A.; Hall, W. W.; de Miranda, P.; Beauchamp, L. M.; Schaeffer, H. J.; Whiteman, P. D. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3209.

Table II. Concentrations of Antiviral Guanine Derivatives (8 and 21) and Their Prodrugs Detected in the Blood of Mice after Oral Administration of 9-Alkoxypurines[a]

compd dosed	concn (μM) in blood at time (min) after dosing[b]: total 9-alkoxypurines 15	total 9-alkoxypurines 60	8 (BRL 44385) 15	8 (BRL 44385) 60	compd dosed	concn (μM) in blood at time (min) after dosing[b]: total 9-alkoxypurines 15	total 9-alkoxypurines 60	21 (BRL 45148) 15	21 (BRL 45148) 60
8	8	5	8	5	**21**	2	2	2	2
9	3	5	3	5	**19**	11	5	11	5
10	8	3	8	3	**20**	5	4	<2	<2
11	<2	<2	<2	<2	**23**	82	25	7	8
12	19	3	6	<2	**24**	127	15	37	15
13	49	3	43	3	**25**	119	38	29	26
14	54	3	45	3	**26**	39	16	31	16
15	79	4	66	4	**27**	64	10	53	10
16	56	4	46	4	**28**	62	12	49	12
					29	14	9	14	9

[a] Compounds were administered as single doses of 0.2 mmol/kg in 0.1 mL of 1% (carboxymethyl)cellulose by oral gavage to female Balb/c mice weighing 20 g. Food was withheld from the mice for 18 h prior to the start of the experiment. Blood was collected by cardiac puncture using heparinised syringes 15, 60, and 180 min after dosing. Equal volumes (0.2 mL) from three mice were pooled at each time point and 0.6 mL of 16% trichloroacetic acid was added. After centrifugation, 0.5 mL of supernatant was added to 0.1 mL of saturated aqueous $NaHCO_3$ followed by the addition of 0.6 mL of 0.4 M NH_4OAc (pH 6.0) and the mixture was analyzed by HPLC. [b] Only trace amounts (<2 μM) of 9-alkoxypurines were detected in the blood 180 min after dosing.

analogue of BRL 39123, the 6-amino-6-deoxy congener (**20**) of **21** was not an efficient prodrug, but the 6-chloro-6-deoxy congener **19** did provide a 5-fold increase in the concentration of **21** in the blood. The 6-*O*-alkyl derivatives (**23–25**) of **21** were very well absorbed and were converted to the antiviral guanine derivative, the 6-ethoxy (**24**) and 6-isopropoxy (**25**) derivatives providing concentrations of **21** in the blood that were 18 and 15 times higher, respectively, than those obtained after administration of **21**. The 6-deoxy congener (**26**) and some of its diesters (**27, 28**) were also well absorbed and converted efficiently to **21**, providing concentrations of the antiviral acyclonucleoside in the blood that were up to 25 times higher than those obtained after an oral dose of **21**.

With none of these compounds was there evidence of metabolic cleavage of the N–O bond. The high metabolic stability of 9-alkoxypurines was confirmed in an experiment in which **8** was unaffected during incubation with a mouse liver homogenate preparation.

In summary, 9-(3-hydroxypropoxy)guanine (**8**) and 9-[3-hydroxy-2-(hydroxymethyl)propoxy]guanine (**21**) have potent and selective activity against herpes viruses and we are continuing to investigate their antiviral activity in cell culture and in animal infection models. Additionally, from the novel 9-alkoxypurines described, the 2-aminopurine and 6-alkoxy-2-aminopurine analogues of **8** and **21** appear to be potentially useful prodrugs of the antiviral guanine derivatives with improved gastrointestinal absorption properties.

Experimental Section

Melting points were determined by using a Reichert Kofler apparatus and are uncorrected. ^1H NMR spectra were recorded with a Varian EM-390 90-MHz or a JEOL GX-270 270-MHz spectrometer. Infrared spectra were recorded with a Perkin-Elmer 580 spectrometer and ultraviolet spectra with a Cary 219 spectrometer. Mass spectra were recorded on a VG 70-70 instrument, and accurate masses were measured on a VG ZAB spectrometer. Microanalyses were performed on a Carlo-Erba Model 1106 analyzer and, where only the symbols for the elements are recorded, were within ±0.4% of the calculated values. Upon TLC of analytical samples using silica gel $60F_{254}$ precoated aluminum sheets (Merck Art. No. 5554) in each case only a single component was detected.

***N*-[3-[(*tert*-Butyldimethylsilyl)oxy]propoxy]phthalimide (2a).** Diethyl azodicarboxylate (19.9 mL, 126.3 mmol) was added to a solution of **1a**[25] (20.0 g, 105.3 mmol), triphenylphosphine (33.1 g, 126.3 mmol), and *N*-hydroxyphthalimide (20.6 g, 126.3 mmol) in THF (500 mL). The solution was stirred at room temperature for 22 h and then the solvent was removed. The residue was triturated with ether (200 mL) and filtered, and the filtrate was evaporated. The process was repeated and then the residue was purified by column chromatography on silica gel eluting with hexane–acetone mixtures (10:1, 5:1) to afford **2a** (29.08 g, 91%): IR (film) ν_{max} 2955, 2930, 2857, 1791, 1737 and 1468 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s, 2 CH_3), 0.90 (9 H, s, 3 CH_3), 1.90 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.80 (2 H, t, J = 6 Hz, CH_2O), 4.25 (2 H, t, J = 6 Hz, CH_2ON) and 7.75 (4 H, s, ArH); HRMS calcd for $C_{16}H_{22}NO_4Si - CH_3$, 320.1318, found 320.1324.

3-[(*tert*-Butyldimethylsilyl)oxy]propoxyamine (3a). Methylhydrazine (2.5 mL, 40.0 mmol) was added to **2a** (10.5 g, 31.3 mmol) in dichloromethane (70 mL) at 0 °C. The suspension was then allowed to warm to 20 °C and stirred for 1 h. The suspension was filtered, the solvent removed, and the residue triturated with ether (20 mL). The suspension was filtered and the solvent removed. The residue was purified by column chromatography on silica gel eluting with chloroform–hexane (10:1) to afford **3a** (5.13 g, 80%): IR (film) ν_{max} 2956, 2930, 2858, 1588, 1473, and 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (6 H, s, 2 CH_3), 0.85 (9 H, s, 3 CH_3), 1.70 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.60 (2 H, t, J = 6 Hz, CH_2O), 3.70 (2 H, t, J = 6 Hz, CH_2ON) and 5.20 (2 H, s, D_2O exchangeable, NH_2).

***N*-[3-(Benzyloxy)propoxy]phthalimide (2b).** Diethyl azodicarboxylate (15.6 mL, 99.4 mmol) was added to a solution of **1b**[26] (15.0 g, 90.4 mmol), *N*-hydroxyphthalimide (14.7 g, 90.1 mmol), and triphenylphosphine (23.7 g, 90.4 mmol) in THF (450 mL). After 16 h at room temperature the solvent was removed and the residue purified by column chromatography on silica gel, eluting with ethyl acetate–hexane (3:1) to afford **1b** (27.8 g, 99%): ^1H NMR ($CDCl_3$) δ 2.05 (2 H, quintet, J = 6.0 Hz, $CH_2CH_2CH_2$), 3.70 (2 H, t, J = 6.0 Hz, CH_2O), 4.35 (2 H, t, J = 6.0 Hz, CH_2ON), 4.50 (2 H, s, CH_2Ar), 7.35 (5 H, s, CH_2Ph), and 7.85 (4 H, s, HAr); HRMS calcd for $C_{18}H_{17}NO_4$ (MH^+) 312.1236, found 312.1230.

3-(Benzyloxy)propoxyamine (3b). A solution of **2b** (27.0 g, 86.8 mmol) and hydrazine hydrate (4.2 mL, 86.8 mmol) in ethanol (200 mL) was heated at reflux temperature for 1 h. After cooling, the suspension was added to a 3% sodium carbonate solution (500 mL). The aqueous solution was extracted with ether (2 × 250 mL), the combined ether extracts were dried ($MgSO_4$), and the solvent was removed. Ethereal hydrogen chloride was added to the residue and the white solid obtained was separated by fil-

(25) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
(26) Kutney, J. P.; Abdwahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727.

tration, washed with ether, and dried, to afford **3b** hydrochloride salt (15.2 g, 81%): IR (KCl) ν_{max} 2970, 2865, 2690, 2005, 1950, 1590, 1515, and 1455 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.50 (2 H, t, J = 6 Hz, CH_2O), 4.10 (2 H, t, J = 6 Hz, CH_2ON), 4.40 (2 H, s, CH_2Ar), 7.30 (5 H, s, HAr), and 11.20 (3 H, s, NH_3^+). Anal. ($C_{10}H_{16}ClNO_2$) C, H, N.

A solution of **3b**·HCl (10 mmol) in water (10 mL) was neutralized with aqueous sodium hydroxide. The solution was extracted twice with chloroform (2 × 10 mL). The combined organic extracts were washed with water (10 mL) and dried ($MgSO_4$), and the solvent was removed. The **3b** obtained was used without further purification: ^1H NMR ($CDCl_3$) δ 1.90 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.50 (2 H, t, J = 6 Hz, CH_2O), 3.70 (2 H, t, J = 6 Hz, CH_2ON), 4.50 (2 H, s, CH_2Ar), 5.30 (2 H, s, D_2O exchangeable, NH_2), and 7.30 (5 H, s, HAr); HRMS calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1101.

2,2-Dimethyl-5-(hydroxymethyl)-1,3-dioxane (1c). To a solution of borane–dimethyl sulfide complex (2 M, 170.5 mL) was added triethyl methanetricarboxylate (24.9 g, 0.107 mol) under nitrogen. The solution was heated under reflux for 8 h with distillation of dimethyl sulfide and then cooled. To the stirred solution was added methanol (100 mL) dropwise with stirring and the solution stirred for a further 15 h. The solvent was removed and the residue coevaporated with methanol (3 × 50 mL). The residue was purified by column chromatography on silica gel eluting with chloroform–methanol mixture (3:1) to afford 2-(hydroxymethyl)propane-1,3-diol (9.43 g, 83%): mp 65–68 °C; IR (KBr) ν_{max} 3267, 2944, 2801, 1489, and 1113 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6 (1 H, septet, J = 6 Hz, CH), 3.40 (6 H, t, J = 6 Hz, 3 CH_2), and 4.25 (3 H, t, J = 6 Hz, D_2O exchangeable, 3 OH). Anal. ($C_4H_{10}O_3$) C, H, N.

To a solution of 2-(hydroxymethyl)propane-1,3-diol (9.0 g, 62.0 mmol) and 4-toluenesulfonic acid monohydrate (0.49 g, 2.6 mmol) in THF (450 mL) was added 2,2-dimethoxypropane (11.7 mL, 95.2 mmol). The solution was stirred for 1 h at room temperature and was then neutralized by the addition of triethylamine (5 mL). The solvent was removed and the residue purified by column chromatography on silica gel eluting with a chloroform–ethanol mixture (10:1) to afford **1c** (9.6 g, 78%): IR (film) ν_{max} 3431, 2993, 2943, 2874, 1482, 1456, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (6 H, s, 2 CH_3), 1.69 (1 H, m, CH), 3.38 (2 H, dd, J = 5.2 Hz and 6.6 Hz, CH_2OH), 3.61 (2 H, dd, J = 11.8 Hz and 7.1 Hz, 2 H_{ax}), 3.82 (2 H, dd, J = 11.8 Hz and 4.4 Hz, 2 H_{eq}), and 4.53 (1 H, t, J = 5.2 Hz, D_2O exchangeable, OH). Anal. ($C_7H_{14}O_3$·0.1H_2O) C, H, N.

***N*-[(2,2-Dimethyl-1,3-dioxan-5-yl)methoxy]phthalimide (2c).** To a solution of **1c** (9.60 g, 66.0 mmol), triphenylphosphine (20.74 g, 79 mmol), *N*-hydroxyphthalimide (12.90 g, 79.0 mmol) in THF (300 mL) was added diethyl azodicarboxylate (12.45 mL, 79.0 mmol). The solution was stirred at room temperature for 16 h. The solvent was removed, the residue triturated with ether and filtered, and the filtrate evaporated. The process was repeated and then the residue was purified by column chromatography eluting with hexane–acetone mixtures (3:1 and 5:2) to give **2c** (16.4 g, 86%): IR (KBr) ν_{max} 3500, 2988, 2880, 1791, 1726, 1702, and 1466 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.32 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 2.04 (1 H, m, CH), 3.77 (2 H, dd, J = 11.9 Hz and 6.0 Hz, 2 H_{ax}), 4.00 (2 H, dd, J = 11.9 Hz and 4.1 Hz, 2 H_{eq}), 4.22 (2 H, d, J = 7.0 Hz, CH_2ON) and 7.86 (4 H, s, aromatic). Anal. ($C_{15}H_{17}NO_5$) C, H, N.

[(2,2-Dimethyl-1,3-dioxan-5-yl)methoxy]amine (3c). To a solution of **2c** (2.26 g, 14.0 mmol) in dichloromethane (15 mL) at 0 °C was added methylhydrazine (0.55 mL, 10.3 mmol). The solution was then allowed to warm to room temperature and stirred for 1 h. The suspension was filtered and the solvent removed. The residue was triturated with ether (20 mL) and filtered and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (100:1) to afford **3c** (0.87 g, 79%): IR (film) ν_{max} 3320, 3000, 2950, 2875, 1600, 1480, and 1435 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.29 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.95 (1 H, m, CH), 3.51 (2 H, d, J = 6.9 Hz, CH_2ON), 3.58 (2 H, dd, J = 11.8 Hz and 6.9 Hz, 2 H_{ax}), 3.84 (2 H, dd, J = 11.8 Hz and 4.4 Hz, 2 H_{eq}) and 5.97 (2 H, s, D_2O exchangeable, NH_2).

4,6-Dichloro-2,5-diformamidopyrimidine (5). Acetic anhydride (30 mL) was added to a solution of **4** (10 g, 55.87 mmol) in formic acid (100 mL) at 0 °C. After 15 min the solution was allowed to warm to room temperature and was stirred for a further 16 h. The solvent was then removed and the residue coevaporated twice with toluene to afford **5** (13.13 g, 100%). This material can be used without further purification or chromatographed on silica gel, eluting with hexane–acetone mixtures (3:2), to afford recoveries of 75%: IR (KBr) ν_{max} 3230, 1715, 1680, 1575, 1550, 1485, and 1415 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.30 (1 H, s, CHO), 9.25 (1 H, d, J = 9 Hz, CHO), 10.25 (1 H, s, D_2O exchangeable, NH) and 11.60 (1 H, d, J = 9 Hz, NH); HRMS calcd for $C_6H_4Cl_2N_4O_2$ 233.9709, found 233.9695. Anal. ($C_6H_4Cl_2N_4O_2$·0.1$(CH_3)_2CO$) C, H, N.

6-[[3-[(*tert*-Butyldimethylsilyl)oxy]propoxy]amino]-4-chloro-2,5-diformamidopyrimidine (6). A solution of **5** (10.15 g, 43.0 mmol), 3-[(*tert*-butyldimethylsilyl)oxy]propoxyamine (8.85 g, 43.2 mmol) and diisopropylethylamine (22.6 mL, 129.0 mmol) in diglyme (250 mL) was stirred at 100 °C for 3 h. The suspension was cooled and filtered and the solution evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol (50:1) to afford **6** (11.6 g, 67%): IR (KBr) ν_{max} 3250, 2930, 1705, 1650, 1590, and 1465 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.0 (6 H, s, 2 CH_3), 0.89 (9 H, s, 3 CH_3), 1.90 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.77 (2 H, t, J = 6 Hz, CH_2OSi), 4.07 (2 H, t, J = 6 Hz, CH_2ON), 7.85 (1 H, d, J = 10 Hz, D_2O exchangeable, NHCHO), 8.34 (1 H, s, NHC*H*O), 8.75 and 8.76 (1 H, 2 s, D_2O exchangeable, NH) and 9.40 (1 H, d, J = 10 Hz, NHC*H*O); FABMS (positive ion, 3-NOBA) 426 (MNa^+), 404 (MH^+).

9-[3-[(*tert*-Butyldimethylsilyl)oxy]propoxy]-6-chloro-2-formamidopurine (7). A solution of **6** (2.15 g, 5.3 mmol) in diethoxymethyl acetate (20 mL) was stirred at 120 °C for 1.5 h. The solution was then cooled and the solvent removed. The residue was dissolved in methanol (20 mL) and concentrated aqueous ammonia (0.5 mL). The solution was then stirred at room temperature for 30 min, the solvent removed, and the residue coevaporated with methanol. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (50:1) to afford **7** (1.66 g, 81%): IR (KBr) ν_{max} 3125, 2956, 2930, 1718, 1700, 1613, 1583, 1508, and 1439 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.04 (6 H, s, 2 CH_3), 0.85 (9 H, s, 3 CH_3), 1.90 (2 H, quintet, J = 6.2 Hz, $CH_2CH_2CH_2$), 3.79 (2 H, t, J = 6.2 Hz, CH_2OSi), and 4.50 (2 H, t, J = 6.2 Hz, D_2O exchangeable, NH). Anal. ($C_{15}H_{24}ClN_5O_3Si$) C, H, N.

9-(3-Hydroxypropoxy)guanine (8). A solution of **7** (6.0 g, 15.5 mmol) in 80% formic acid (50 mL) was stirred at 100 °C for 1 h. The solution was cooled, the solvent removed, and the residue coevaporated with water. The residue was dissolved in concentrated aqueous ammonia (20 mL) and stirred at room temperature for 1 h. The solvent was then removed and the residue coevaporated with toluene. Recrystallization from water gave **8** (2.04 g, 58%): mp 279–280 °C dec; UV λ_{max} 253 nm (ϵ 13500); IR (KBr) ν_{max} 3190, 1720, 1685, 1630, 1605, and 1475 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (2 H, quintet, J = 6.0 Hz and 6.6 Hz, $CH_2CH_2CH_2$), 3.55 (2 H, quartet, J = 5.5 Hz and 6.0 Hz, CH_2OH), 4.32 (2 H, t, J = 6.6 Hz, CH_2ON), 4.57 (1 H, t, J = 5.5 Hz, D_2O exchangeable, OH), 6.57 (2 H, s, D_2O exchangeable, NH_2), 7.91 (1 H, s, H-8), and 10.63 (1 H, s, D_2O exchangeable, H-1). Anal. ($C_8H_{11}N_5O_3$) C, H, N.

Preparations of Esters of 8, Compounds 9–11. Compound 8 (1.0 mmol) was treated with the appropriate acid anhydride (10–20 mmol) and 4-(dimethylamino)pyridine (0.2 mmol) in DMF (10 mL) at room temperature for 2–3 h. Ethanol (1 mL) was then added and the solution stirred for a further 15 min. The solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol mixtures. Recrystallization from methanol–water mixtures gave the pure compounds.

9-(3-Acetoxypropoxy)guanine (9): yield 46%; mp 251–255 °C; IR (KBr) ν_{max} 3330, 3168, 1736, 1696, 1648, 1602, 1589, and 1391 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.98 (2 H, quintet, J = 6.3 Hz and 6.6 Hz, $CH_2CH_2CH_2$), 2.02 (3 H, s, CH_3), 4.17 (2 H, t, J = 6.6 Hz, CH_2ON), 4.32 (2 H, t, J = 6.3 Hz, $CH_2OC{=}O$), 6.60 (2 H, s, D_2O exchangeable, NH_2), 7.94 (1 H, s, H-8), and 10.69 (1 H, s, D_2O exchangeable, H-1). Anal. ($C_{10}H_{13}N_5O_4$) C, H, N.

9-[3-(Hexanoyloxy)propoxy]guanine (10): yield 39%; mp 235–237 °C; IR (KBr) ν_{max} 3337, 3172, 2957, 2933, 1696, 1646, 1599, 1587, and 1390 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 0.84 (3 H, t, J = 6.9 Hz, CH_3), 1.24 (4 H, m, $CH_2CH_2CH_3$), 1.51 (2 H, m, CH_2), 1.98 (2 H, quintet, J = 6.6 Hz and 6.3 Hz, $OCH_2CH_2CH_2O$), 2.29 (2 H, t, J = 7.4 Hz, CH_2C=O), 4.19 (2 H, dd, J = 6.3 Hz and 6.6 Hz, CH_2ON), 4.32 (2 H, dd, J = 6.3 Hz and 6.6 Hz, CH_2OC=O), 6.58 (2 H, s, D_2O exchangeable, NH_2), 7.93 (1 H, s, H-8) and 10.66 (1 H, s, D_2O exchangeable, H-1). Anal. ($C_{14}H_{21}N_5O_4$) C, H, N.

9-[3-(Benzoyloxy)propoxy]guanine (11): yield 36%; mp 114–116 °C; IR (KBr) ν_{max} 3390, 3200, 1714, 1700, 1639, 1595, 1582, and 1391 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.13 (2 H, quintet, J = 6.3 Hz, $CH_2CH_2CH_2$), 4.43 (2 H, t, J = 6.3 Hz, CH_2ON), 4.46 (2 H, t, J = 6.3 Hz, CH_2OC=O), 6.60 (2 H, s, D_2O exchangeable, NH_2), 7.53 (2 H, m, HAr), 7.67 (1 H, m, HAr), 7.97 (3 H, m, H-8, 2 HAr), and 10.72 (1 H, s, D_2O exchangeable, H-1). Anal. ($C_{15}H_{15}N_5O_4$) C, H, N.

2-Amino-9-(3-hydroxypropoxy)purine (13). A mixture of **7** (1.60 g, 4.2 mmol), 10% palladium on charcoal (80 mg), ammonium formate (1.8 g, 24.9 mmol), and methanol (50 mL) was stirred under reflux for 3 h. Additional ammonium formate (0.8 g) was added after 1 and 2 h. The mixture was then cooled, the solvent removed, and the residue partitioned between ethyl acetate (50 mL) and water (50 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phases were washed with water (25 mL) and dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (30:1) to afford 9-[3-[(*tert*-butyldimethylsilyl)oxy]propoxy]-2-formamidopurine (0.81 g, 56%); IR (KBr) ν_{max} 3120, 2925, 1695, 1615, and 1410 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 0.04 (6 H, s, 2 CH_3), 0.85 (9 H, s, 3 CH_3), 1.90 (2 H, quintet, J = 6.3 Hz, CH_2), 3.79 (2 H, t, J = 6.3 Hz, CH_2O), 4.49 (2 H, t, J = 6.3 Hz, CH_2ON), 8.72 (1 H, s, H-8), 8.98 (1 H, s, H-6), 9.43 (1 H, d, J = 9.2 Hz, NHC*H*O), and 11.10 (1 H, d, J = 9.2 Hz, D_2O exchangeable, N*H*CHO).

A solution of 9-[3-[(*tert*-butyldimethylsilyl)oxy]propoxy]-2-formamidopurine (800 mg, 2.3 mmol) in 80% acetic acid (20 mL) was stirred at 90 °C for 20 min. After cooling, the solvent was removed and the residue coevaporated with water. The residue was dissolved in ethanol (20 mL) and hydrazine hydrate (1 mL) and stirred at reflux temperature for 1 h. After cooling, the solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol (8:1) to afford **13** (262 mg, 55%); mp 153–155 °C; UV λ_{max} 309 nm (ϵ 6750); IR (KBr) ν_{max} 3340, 3210, 1655, 1615, 1570, 1510, and 1430 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.84 (2 H, quintet, J = 6.5 Hz, $CH_2CH_2CH_2$), 3.58 (2 H, q, J = 6.5 Hz and 5.2 Hz, CH_2OH), 4.39 (2 H, t, J = 6.5 Hz, CH_2ON), 4.62 (1 H, t, D_2O exchangeable, J = 5.2 Hz, OH), 6.71 (2 H, s, D_2O exchangeable, NH_2), 8.31 (1 H, s, H-8), and 8.59 (1 H, s, H-6); HRMS calcd for $C_{18}H_{11}N_5O_2$ 209.0913, found 209.0914. Anal. ($C_8H_{11}N_5O_2$) C, H, N.

Preparation of Esters of 13, Compounds 14–16. Compound **13** (1.0 mmol) was treated with the appropriate acid anhydride (1.2 mmol) and 4-(dimethylamino)pyridine (0.2 mmol) in DMF (5 mL) at room temperature for 3 h. Ethanol (0.5 mL) was then added and the solution stirred at room temperature for a further 15 min. The solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol mixtures.

9-(3-Acetoxypropoxy)-2-aminopurine (14): yield 95%; mp 179–181 °C; IR (KBr) ν_{max} 3311, 3154, 1721, 1665, 1614, 1572, and 1430 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.02 (5 H, m, CH_3, CH_2), 4.20 (2 H, t, J = 6.5 Hz, CH_2OC=O), 4.39 (2 H, t, J = 6.3 Hz, CH_2ON), 6.70 (2 H, s, D_2O exchangeable, NH_2), 8.32 (1 H, s, H-8), and 8.59 (1 H, s, H-6); HRMS calcd for $C_{10}H_{13}N_5O_3$ 251.1018, found 251.1013. Anal. ($C_{10}H_{13}N_5O_3$·0.1H_2O) C, H, N.

2-Amino-9-[3-(hexanoyloxy)propoxy]purine (15): yield 74%; mp 67–70 °C; IR (KBr) ν_{max} 3337, 3187, 1724, 1656, 1616, 1578, 1511, and 1429 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 0.84 (3 H, t, J = 6.8 Hz, CH_3), 1.24 (4 H, m, $CH_2CH_2CH_3$), 1.52 (2 H, m, CH_2), 2.01 (2 H, quintet, J = 6.6 Hz, 6.3 Hz, $OCH_2CH_2CH_2O$), 2.30 (2 H, t, J = 7.3 Hz, CH_2C=O), 4.21 (2 H, t, J = 6.6 Hz, CH_2OC=O), 4.39 (2 H, t, J = 6.3 Hz, CH_2ON), 6.70 (2 H, s, D_2O exchangeable, NH_2), 8.32 (1 H, s, H-8), and 8.59 (1 H, s, H-6). Anal. ($C_{14}H_{21}N_5O_3$) C, H, N.

2-Amino-9-[3-(benzoyloxy)propoxy]purine (16): yield 69%; mp 85–88 °C; IR (KBr) ν_{max} 3351, 3324, 3195, 1713, 1646, 1620, 1573, 1511, and 1430 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.17 (2 H, quintet, J = 6.3 Hz, $CH_2CH_2CH_2$), 4.50 (4 H, m, CH_2ON, CH_2OC=O), 6.68 (2 H, s, D_2O exchangeable, NH_2), 7.53 (2 H, m, HAr), 7.67 (1 H, m, HAr), 7.99 (2 H, m, HAr), 8.35 (1 H, s, H-8), and 8.60 (1 H, s, H-6); HRMS calcd for $C_{15}H_{15}N_5O_3$ 313.1175, found 313.1176. Anal. ($C_{15}H_{15}N_5O_3$·0.3H_2O) C, H, N.

4-Chloro-2,5-diformamido-6-[[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]amino]pyrimidine (17). To a solution of 4,6-dichloro-2,5-diformamidopyrimidine (6.4 g, 27.2 mmol) and diisopropylethylamine (9.5 mL, 81.6 mmol) in diglyme (100 mL) was added **3c** (4.4 g, 27.2 mmol), and the solution was stirred at 100 °C for 2.5 h. The solvent was then removed and the residue purified by column chromatography on silica gel eluting with chloform–methanol (30:1) to afford **17** (7.54 g, 77%): IR (KBr) ν_{max} 3240, 1690, 1585, 1570, 1480, and 1420 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (3 H, s, CH_3), 1.34 (3 H, s, CH_3), 1.99 (1 H, m, CH), 3.70 (2 H, m, 2 H_{ax}), 3.93 (4 H, m, CH_2ON, 2 H_{eq}), 8.15, 8.31 (1 H, 2 s, NHC*H*O), 9.17, 9.42 (1 H, 2 s, D_2O exchangeable N*H*CHO), 9.26 (1 H, s, NHC*H*O), and 10.83 (2 H, s, D_2O exchangeable, N*H*CHO, NHO). Anal. ($C_{13}H_{18}ClN_5O_5$) C, H, N.

6-Chloro-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]-2-formamidopurine (18). A solution of **17** (1.90 g, 5.3 mmol) in diethoxymethyl acetate (25 mL) was stirred at 120 °C for 2 h. The solvent was removed and the residue dissolved in methanol (70 mL) and concentrated aqueous ammonia (2.5 mL). The solution was then stirred at room temperature for 1 h, and the solvent was removed. The residue was coevaporated with methanol and then purified by column chromatography on silica gel eluting with chloroform–methanol (50:1) to afford **18** (1.47 g, 81%): IR (KBr) ν_{max} 3419, 1720, 1616, 1579, 1513, 1507, and 1439 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.32 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 2.04 (1 H, m, CH), 3.80 (2 H, dd, J = 11.8 Hz and 5.5 Hz, 2 H_{ax}), 4.03 (2 H, dd, J = 12.1 Hz and 3.9 Hz, 2 H_{eq}), 4.51 (2 H, d, J = 7.3 Hz, CH_2ON), 8.84 (1 H, s, H-8), 9.38 (1 H, s, CHO), and 11.31 (1 H, s, D_2O exchangeable, NH); HRMS calcd for $C_{13}H_{16}ClN_5O_4$ 341.0891, found 341.0891.

2-Amino-6-chloro-9-[3-hydroxy-2-(hydroxymethyl)propoxy]purine (19). A solution of **18** (450 mg, 1.3 mmol) in sodium ethoxide in ethanol (0.5 N, 0.8 mL) and ethanol (10 mL) was stirred at reflux temperature for 1.5 h. After cooling, acetic acid (0.1 mL) was added and the solvent removed. The residue was dissolved in 80% acetic acid (10 mL) and stirred at room temperature for 4 h. The solvent was then removed and the residue coevaporated with toluene. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol (10:1) to afford **19** (247 mg, 69%): IR (KBr) ν_{max} 3320, 3200, 1645, 1625, 1565, 1510, and 1465 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.96 (1 H, m, CH), 3.53 (4 H, m, 2 CH_2OH), 4.34 (2 H, J = 6.3 Hz, CH_2ON), 4.58 (2 H, t, J = 5.3 Hz, D_2O exchangeable, 2 OH), 7.10 (2 H, s, D_2O exchangeable, NH_2), and 8.39 (1 H, s, H-8). Anal. ($C_9H_{12}ClN_5O_3$) C, H, N.

2,6-Diamino-9-[3-hydroxy-2-(hydroxymethyl)propoxy]-purine (20). A solution of **18** (630 mg, 1.8 mmol) and ammonia (10 mL) in methanol (15 mL) was heated at 110 °C for 7.5 h in an autoclave and then allowed to cool over 16 h. The solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol (20:1) to afford 2,6-diamino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine (340 mg, 63%); IR (KBr) ν_{max} 3409, 3321, 3158, 1669, 1640, 1589, 1488, 1457, and 1409 cm^{-1}: ^{1}H NMR (Me_2SO-d_6) δ 1.32 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 2.00 (1 H, m, CH_3), 3.77 (2 H, dd, J = 11.8 Hz and 6.1 Hz, 2 H_{ax}), 3.98 (2 H, dd, J = 11.8 Hz and 4.1 Hz, 2 H_{eq}), 4.32 (2 H, d, J = 7.1 Hz, CH_2ON), 5.91 (2 H, s, D_2O exchangeable, 6-NH_2), 6.78 (2 H, s, D_2O exchangeable, 2-NH_2) and 7.96 (1 H, s, H-8). Anal. ($C_{12}H_{18}N_6O_3$·0.2H_2O) C, H, N.

A solution of 2,6-diamino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)-methoxy]purine (310 mg, 1.1 mmol) in 80% acetic acid (5 mL) was stirred at room temperature for 4 h. The solvent was then removed and the residue coevaporated with toluene. The residue was purified by column chromatography on reverse phase silica gel (Spherisorb V.L.S. C18 300 pore), eluting with water and then water–methanol mixtures (19:1, 9:1), followed by recrystallization from water, to afford **20** (208 mg, 78%): mp 147–149 °C; UV λ_{max} 255 (ϵ 7800), 279 (9740) nm; IR (KBr) ν_{max} 3356, 3208, 1663, 1628,

1600, 1482, 1445, and 1409 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.95 (1 H, m, CH), 3.54 (4 H, m, 2 CH_2OH), 4.27 (2 H, d, J = 6.3 Hz, CH_2ON), 4.62 (2 H, t, J = 5.3 Hz, D_2O exchangeable, 2 OH), 5.92 (2 H, s, D_2O exchangeable, 6-NH_2), 6.80 (2 H, s, D_2O exchangeable, 2-NH_2), and 7.92 (1 H, s, H-8); HRMS calcd for $C_9H_{14}N_6O_3$ 254.1127, found 254.1124. Anal. ($C_9H_{14}N_6O_3 \cdot 0.9H_2O$) C, H, N.

9-[3-Hydroxy-2-(hydroxymethyl)propoxy]guanine (21). A solution of **18** (3 g, 8.8 mmol) in 80% aqueous formic acid (40 mL) was stirred at 100 °C for 2 h. The solvent was removed and the residue coevaporated with water. The residue was dissolved in concentrated aqueous ammonia (15 mL) and stirred at room temperature for 0.5 h. The solvent was then removed and the residue recrystallized from water to afford **21** (1.04 g, 45%): mp 288–290 °C; UV λ_{max} 253 nm (ϵ 9100); IR (KBr) ν_{max} 3380, 3183, 1679, 1637, 1605, 1541, 1479, and 1395 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.94 (1 H, m, CH), 3.53 (4 H, m, 2 CH_2OH), 4.26 (2 H, d, J = 6.3 Hz, CH_2ON), 4.57 (2 H, t, J = 5.2 Hz, D_2O exchangeable, 2 OH), 6.58 (2 H, s, D_2O exchangeable, NH_2), 7.92 (1 H, s, H-8), and 10.64 (1 H, s, D_2O exchangeable, H-1). Anal. ($C_9H_{13}N_5O_4$) C, H, N.

9-[3-Hydroxy-2-(hydroxymethyl)propoxy]guanine Cyclic Phosphate (22). To a stirred suspension of **21** (450 mg, 1.8 mmol) in dry acetonitrile (350 mL) was added stannic chloride (0.3 mL, 2.5 mmol). The mixture was stirred at room temperature for 1 h. To the resulting solution phosphoryl chloride (0.77 mL, 5.2 mmol) in acetonitrile (130 mL) was added dropwise with stirring over 1.5 h. When addition was complete the reaction was stirred for 16 h and then neutralized by addition of saturated aqueous sodium bicarbonate solution. The suspension was filtered and the filtrate evaporated to dryness. The residue was purified by reverse-phase HPLC eluting with ammonium acetate buffer at pH 4.5 containing 10% methanol. The resulting solid was recrystallized from aqueous ammonia, yielding the title compound as the ammonium salt (53 mg, 10%): IR (KBr) ν_{max} 3150, 1680, 1630, and 1475 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.00 (1 H, m, CH), 3.97 (2 H, dd, J = 11.4 Hz and 5.1 Hz, 2 H_{ax}), 4.16 (2 H, dd, J = 11.4 Hz and 3.4 Hz, 2 H_{eq}), 4.33 (2 H, d, J = 6.9 Hz, CH_2ON), 6.67 (2 H, br s, D_2O exchangeable, NH_2) and 7.94 (1 H, s, H-8). Anal. ($C_9H_{12}N_5O_6P \cdot 0.6NH_3 \cdot 2H_2O$) C, H, N.

Preparation of 6-Alkoxy Compounds 23–25. Compound **18** (1.0 mmol) was treated with sodium alkoxide (3.0 mmol) in THF or the respective alcohol (10 mL) at reflux temperature for 1–1.5 h. After cooling, acetic acid (0.2 mL) was added and the solvent removed. The residue was dissolved in 80% acetic acid (10 mL) and the solution stirred at 70 °C for 1 h or at room temperature for 4 h. The solvent was then removed and the residue coevaporated with toluene. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol mixtures.

2-Amino-9-[3-hydroxy-2-(hydroxymethyl)propoxy]-6-methoxypurine (23): yield 89%; mp 133–135 °C; UV λ_{max} 249 (ϵ 7760), 279 (9590) nm; IR (KBr) ν_{max} 3332, 3213, 1617, 1584, 1509, and 1491 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.95 (1 H, m, CH), 3.53 (4 H, m, 2 CH_2OH), 3.96 (3 H, s, CH_3), 4.29 (2 H, d, J = 6.3 Hz, CH_2ON), 4.59 (2 H, t, J = 5.2 Hz, D_2O exchangeable, 2 OH), 6.60 (2 H, s, D_2O exchangeable, NH_2), and 8.09 (1 H, s, H-8). Anal. ($C_{10}H_{15}N_5O_4$) C, H, N.

2-Amino-6-ethoxy-9-[3-hydroxy-2-(hydroxymethyl)propoxy]purine (24): yield 63%; mp 129–131 °C; IR (KBr) ν_{max} 3374, 3341, 3213, 1658, 1614, 1580, 1514, and 1455 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.35 (3 H, t, J = 7.2 Hz, CH_3), 1.95 (1 H, m, CH), 3.53 (4 H, m, 2 CH_2OH), 4.29 (2 H, d, J = 6.3 Hz, CH_2ON), 4.45 (2 H, q, J = 7.2 Hz, CH_2O), 4.59 (2 H, s, D_2O exchangeable, 2 OH), 6.55 (2 H, s, D_2O exchangeable, NH_2) and 8.09 (1 H, s, H-8). Anal. ($C_{11}H_{17}N_5O_4 \cdot 0.1H_2O$) C, H, N.

2-Amino-9-[3-hydroxy-2-(hydroxymethyl)propoxy]-6-isopropoxypurine (25): yield 64%; mp 128–129 °C; IR (KBr) ν_{max} 3390, 1610, 1580, and 1455 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.33 (6 H, d, J = 6.3 Hz, 2 CH_3), 1.94 (1 H, m, CH), 3.54 (4 H, m, 2 CH_2OH), 4.28 (2 H, d, J = 6.1 Hz, CH_2ON), 4.58 (2 H, t, J = 5.0 Hz, D_2O exchangeable, 2 OH), 5.47 (1 H, m, CHO), 6.52 (2 H, s, D_2O exchangeable, NH_2), and 8.07 (1 H, s, H-8). Anal. ($C_{12}H_{19}N_5O_4$) C, H, N.

2-Amino-9-[3-hydroxy-2-(hydroxymethyl)propoxy]purine (26). A mixture of **18** (1.47 g, 4.3 mmol), 10% palladium on charcoal (75 mg), ammonium formate (3.0 g, 47.6 mmol), and methanol (50 mL) was stirred at reflux temperature for 4 h. Additional ammonium formate (0.75 g) was added after 1.5, 2, and 3 h. After cooling, the solvent was removed and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (25 mL). The organic layers were combined, washed with water, and dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in methanol (25 mL) and hydrazine hydrate (2 mL). The solution was heated at reflux temperature for 45 min and cooled and the solvent removed. The residue was purified by column chromatography on silica gel eluting with a chloroform–methanol mixture (15:1) to afford 2-amino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine (530 mg, 43%): IR (KBr) ν_{max} 3327, 3193, 1655, 1622, 1580, 1515, and 1434 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.33 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 2.02 (1 H, m, CH), 3.79 (2 H, dd, J = 12.1 Hz and 5.8 Hz, 2 H_{ax}), 4.05 (2 H, dd, J = 12.1 Hz and 4.1 Hz, 2 H_{eq}), 4.39 (2 H, d, J = 7.1 Hz, CH_2ON), 6.70 (2 H, s, D_2O exchangeable, NH_2), 8.34 (1 H, s, H-8), and 8.59 (1 H, s, H-6). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

A solution of 2-amino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine (500 mg, 1.79 mmol) in 80% acetic acid was stirred at room temperature for 3 h. The solvent was removed and the residue coevaporated with toluene. The residue was purified by column chromatography on silica gel eluting with mixtures of chloroform–ethanol (5:1 and 5:2) to afford **26** (371 mg, 87%): mp 128–132 °C; UV λ_{max} 305 nm (ϵ 7170); IR (KBr) ν_{max} 3336, 3203, 1647, 1618, 1578, and 1430 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.97 (1 H, m, CH), 3.55 (4 H, m, 2 CH_2OH), 4.33 (2 H, d, J = 6.3 Hz, CH_2ON), 4.59 (2 H, t, J = 5.3 Hz, D_2O exchangeable, 2 OH), 6.70 (2 H, s, D_2O exchangeable, NH_2), 8.30 (1 H, s, H-8), and 8.59 (1 H, s, H-6). Anal. ($C_9H_{13}N_5O_3$) C, H, N.

Preparation of Diesters of 26, Compounds 27–29. Compound **26** (1.0 mmol) was treated with the appropriate acid anhydride (2.5 mmol) and 4-(dimethylamino)pyridine (0.2 mmol) in DMF (6 mL) at room temperature for 1.5–2.0 h. Ethanol (0.6 mL) was then added and the solution stirred for a further 15 min. The solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol mixtures (19:1).

9-[3-Acetoxy-2-(acetoxymethyl)propoxy]-2-aminopurine (27): yield 91%; mp 105–107 °C; IR (KBr) ν_{max} 3328, 3191, 1740, 1652, 1618, 1581, 1513, and 1431 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.03 (6 H, s, 2 CH_3), 2.50 (m, CH), 4.20 (4 H, m, 2 $CH_2OC{=}O$), 4.39 (2 H, d, J = 6.3 Hz, CH_2ON), 6.68 (2 H, s, D_2O exchangeable, NH_2), 8.32 (1 H, s, H-8), and 8.60 (1 H, s, H-6). Anal. ($C_{13}H_{17}N_5O_5$) C, H, N.

2-Amino-9-[3-(propionyloxy)-2-[(propionyloxy)methyl]propoxy]purine (28): yield 83%; mp 68–71 °C; IR (KBr) ν_{max} 3382, 3313, 1740, 1641, 1619, 1575, and 1429 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.02 (6 H, t, J = 7.4 Hz, 2 CH_3), 2.33 (4 H, q, J = 7.4 Hz, 2 $CH_2C{=}O$), 4.22 (4 H, m, 2 $CH_2OC{=}O$), 4.39 (2 H, d, J = 6.3 Hz, CH_2ON), 6.68 (2 H, s, D_2O exchangeable, NH_2), 8.32 (1 H, s, H-8), and 8.60 (1 H, s, H-6). Anal. ($C_{15}H_{21}N_5O_5$) C, H, N.

2-Amino-9-[3-(benzoyloxy)-2-[(benzoyloxy)methyl]propoxy]purine (29): yield 65%; mp 75–78 °C; IR (KBr) ν_{max} 3327, 1721, 1617, 1576, and 1426 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.82 (1 H, m, CH), 4.60 (6 H, m, 3 CH_2), 6.64 (2 H, s, D_2O exchangeable, NH_2), 4.51 (4 H, m, ArH), 7.65 (2 H, m, ArH), 7.97 (4 H, m, ArH), 8.39 (1 H, s, H-8), and 8.60 (1 H, s, H-6). Anal. ($C_{23}H_{21}N_5O_5$) C, H, N.

4,6-Dichloro-5-formamidopyrimidine (31). Acetic anhydride (60 mL) was added dropwise over 5 min to a mixture of **30** (12.6 g, 76.8 mmol) and formic acid (150 mL) at 0 °C and then stirred for a further 2 h at 20 °C. The solvent was then removed and the residue coevaporated with toluene to yield **31** (14.92 g, 100%): ^1H NMR (Me_2SO-d_6) δ 8.30 (1 H, s, H-2), 8.90 (1 H, s, CHO), and 10.50 (1 H, s, D_2O exchangeable, NH); HRMS calcd for $C_5H_3Cl_2N_3O$ 190.9683, found 190.9660.

6-[[3-(Benzyloxy)propoxy]amino]-4-chloro-5-formamidopyrimidine (32). A solution of **31** (2.0 g, 10.4 mmol), **3b** (2.27 g, 10.4 mmol), and triethylamine (5.8 mL, 41.6 mmol) in dioxane (50 mL) was stirred at 110 °C for 6 h. After cooling, the suspension was filtered and the solvent removed. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (50:1) to afford **32** (79%): ^1H NMR (Me_2SO-d_6)

δ 2.00 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 4.65 (2 H, t, J = 6 Hz, CH_2O), 4.10 (2 H, t, J = 6 Hz, CH_2ON), 4.55 (2 H, s, CH_2Ar), 7.35 (7 H, m, HAr, H-2, NHCHO), and 8.25 (1 H, s, CHO). Anal. ($C_{15}H_{17}ClN_4O_3$) C, H, N.

9-[3-(Benzyloxy)propoxy]-6-chloropurine (33). A mixture of **32** (2.65 g, 7.88 mmol), triethyl orthoformate (50 mL), 12 N hydrochloric acid (1.3 mL), and DMF (25 mL) was stirred at room temperature for 16 h. The solvent was removed and the residue partitioned between chloroform (50 mL) and water (50 mL). The phases were separated, and the water was washed with chloroform (20 mL). The combined organic phases were washed with water (2 × 30 mL) and dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (50:1) to afford **33** (2.35 g, 98%): IR (KBr) ν_{max} 2860, 1590, 1560, 1455, and 1435 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.10 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 3.70 (2 H, t, J = 6 Hz, CH_2O), 4.50 (4 H, m, CH_2Ar, CH_2ON), 7.30 (5 H, s, HAr), 8.2 (1 H, s, H-8), and 8.8 (1 H, s, H-2); HRMS calcd for $C_{15}H_{15}ClN_4O_2$ 319.0960, found 319.0964. Anal. ($C_{15}H_{16}ClN_4O_2$) H, N; C: calcd, 56.51; found, 55.91.

9-(3-Hydroxypropoxy)adenine (34). A solution of **33** (1.65 g, 7.2 mmol) and ammonia (10 mL) in methanol (15 mL) was heated in an autoclave at 110 °C for 48 h. The solvent was then removed and the residue purified on column chromatography on silica gel eluting with chloroform–methanol (20:1) to afford 9-[3-(benzyloxy)propoxy]adenine (254 mg, 17%): IR (KBr) ν_{max} 3290, 3140, 3100, 1670, 1605, 1580, and 1415 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.98 (2 H, quintet, J = 6.3 Hz, $CH_2CH_2CH_2$), 3.64 (2 H, t, J = 6.3 Hz, CH_2O), 4.45 (2 H, t, J = 6.3 Hz, CH_2ON), 4.50 (2 H, s, CH_2Ar), 7.33 (7 H, m, HAr, NH_2), 8.15 (1 H, s, H-8), and 8.38 (1 H, s, H-2).

A mixture of 9-[3-(benzyloxy)propoxy]adenine (170 mg, 0.57 mmol), 10% palladium on charcoal (100 mg), and 80% formic acid (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 45 min. The suspension was then filtered and the solvent removed. The residue was suspended in water (10 mL) and concentrated aqueous ammonia (1 mL) and stirred at 100 °C for 15 min. After cooling, the solvent was removed and the residue was purified by column chromatography on reverse-phase silica gel (Spherisorb V.L.S. C18 300 pore) to afford **34** (87.2 mg, 74%): mp 195–197 °C; UV λ_{max} 259 nm (ε 13 400); IR (KBr) ν_{max} 3267, 3142, 1684, 1666, 1609, 1581, and 1416 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.84 (2 H, quintet, J = 6.3 Hz, $CH_2CH_2CH_2$), 3.59 (2 H, dt, J = 6 Hz and 5.1 Hz, CH_2OH), 4.43 (2 H, t, J = 6.3 Hz, CH_2ON), 4.63 (1 H, t, J = 5.1 Hz, D_2O exchangeable, OH), 7.37 (2 H, s, D_2O exchangeable, NH_2), 8.15 (1 H, s, H-8), and 8.40 (1 H, s, H-2). Anal. ($C_8H_{11}N_5O_2$) C, H, N.

4-Chloro-6-[[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]amino]-5-formamidopyrimidine (35). A solution of **31** (1.19 g, 6.2 mmol), **3c** (1.0 g, 6.21 mmol), and triethylamine (2.6 mL, 18.6 mmol) in dioxane (15 mL) was stirred at reflux temperature for 2.5 h. After cooling, the suspension was filtered and the solvent removed. The residue was purified by column chromatography on silica gel eluting with chloroform–ethanol (20:1) to afford **35** (1.44 g, 73%): IR (KBr) ν_{max} 3210, 1690, 1635, 1575, and 1372 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.31 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.99 (1 H, m, CH), 3.69 (2 H, dd, J = 11.8 Hz and 6.3 Hz, 2 H_{ax}), 3.91 (4 H, m, 2 H_{eq}, CH_2ON), 8.00 (1 H, br s, CHO), 8.14 (1 H, s, H-2), 9.50 (1 H, s, D_2O exchangeable, NHO), and 11.20 (1 H, s, D_2O exchangeable, NHCHO); HRMS calcd for $C_{12}H_{17}ClN_4O_4$ 316.0938, found 316.0939.

6-Chloro-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine (36). A solution of **35** (1.40 g, 4.42 mmol) in diethoxymethyl acetate (20 mL) was stirred at 120 °C for 3 h. After cooling, the solvent was removed and the residue dissolved in methanol (30 mL) and concentrated aqueous ammonia (2.5 mL). After 0.5 h the solvent was removed and the residue purified by column chromatography on silica gel eluting with chloroform–ethanol (100:1) to afford **36** (1.21 g, 92%): IR (KBr) ν_{max} 3108, 2989, 1592, 1566, 1441, and 1330 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.33 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 2.10 (1 H, m, CH), 3.80 (2 H, dd, J = 12.0 Hz and 5.6 Hz, 2 H_{ax}), 4.03 (2 H, dd, J = 12.0 Hz and 3.9 Hz, 2 H_{eq}), 4.55 (2 H, d, J = 7.2 Hz, CH_2ON), 8.83 (1 H, s, H-8), and 9.06 (1 H, s, H-2); HRMS calcd for $C_{12}H_{15}ClN_4O_3$ 298.0833, found 298.0836. Anal. ($C_{12}H_{15}ClN_4O_3 \cdot 0.1H_2O$) C, H, N.

9-[3-Hydroxy-2-(hydroxymethyl)propoxy]adenine (37). A solution of **36** (320 mg, 1.1 mmol) in ammonia (10 mL) and methanol (10 mL) was heated at 100 °C in an autoclave for 8 h and allowed to cool over 16 h. The solvent was then removed and the residue purified by column chromatography on silica gel eluting with chloroform–methanol (20:1) to afford 9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]adenine (195 mg, 65%): IR (KBr) ν_{max} 3239, 3153, 1678, 1604, and 1579 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.32 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 2.03 (1 H, m, CH), 3.80 (2 H, dd, J = 11.8 Hz and 6.1 Hz, 2 H_{ax}), 4.01 (2 H, dd, J = 12.1 Hz and 4.1 Hz, 2 H_{eq}), 4.44 (2 H, d, J = 6.9 Hz, CH_2ON), 7.38 (2 H, s, D_2O exchangeable, NH_2), 8.15 (1 H, s, H-8), and 8.44 (1 H, s, H-2). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

A solution of 9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]adenine (180 mg, 0.60 mmol) in 80% acetic acid (10 mL) was stirred at room temperature for 4 h. The solvent was removed and the residue coevaporated with water. The residue was dissolved in water and the solution made basic by addition of aqueous $NaHCO_3$. The solution was applied to a chromatographic column of reverse-phase silica gel and eluted with water and then water–methanol (19:1) to afford a white solid. Recrystallization from water gave **37** (116 mg, 82%): mp 84–86 °C; IR (KBr) ν_{max} 3410, 3290, 3110, 1675, 1645, 1605, and 1300 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.98 (1 H, m, CH), 3.57 (4 H, m, 2 CH_2OH), 4.38 (2 H, d, J = 6.3 Hz, CH_2ON), 4.62 (1 H, t, J = 4.8 Hz, D_2O exchangeable, OH), 7.39 (2 H, s, D_2O exchangeable, NH_2), 8.15 (1 H, s, H-8), and 8.40 (1 H, s, H-2); HRMS calcd for $C_9H_{13}N_5O_3$ (MH^+) 240.1097, found 240.1091. Anal. ($C_9H_{13}N_5O_3 \cdot 0.75H_2O$) C, H, N.

9-[3-Hydroxy-2-(hydroxymethyl)propoxy]-6-methoxypurine (38). A solution of **36** (270 mg, 0.90 mmol) and sodium methoxide (147 mg, 2.7 mmol) in methanol (10 mL) was heated at reflux temperature for 1.5 h. After cooling, acetic acid (0.16 mL) was added and the solvent was removed. The residue was dissolved in 80% acetic acid (10 mL) and stirred at room temperature for 4 h. The solvent was then removed and the residue coevaporated with toluene. A portion of the residue was purified by reverse-phase chromatography eluting with water and then water–methanol mixtures (9:1 and 4:1) to afford **38** (65 mg); mp 116–118 °C; UV λ_{max} 250 nm (ε 10 590); IR (KBr) ν_{max} 3440, 3316, 1602, 1482, and 1318 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.99 (1 H, m, CH), 3.56 (4 H, m, 2 CH_2OH), 4.11 (3 H, s, CH_3O), 4.43 (2 H, d, J = 6.1 Hz, CH_2ON), 4.60 (2 H, t, J = 5.2 Hz, D_2O exchangeable, 2 OH), 8.57 (1 H, s, H-8), and 8.68 (1 H, s, H-2); HRMS calcd for $C_{10}H_{14}N_4O_4$ 254.1015, found 254.1022. Anal. ($C_{10}H_{14}N_4O_4 \cdot 0.2H_2O$) C, H, N.

9-[3-Hydroxy-2-(hydroxymethyl)propoxy]hypoxanthine (39). A solution of **36** (0.5 g, 1.68 mmol) in 80% acetic acid (10 mL) was stirred at 100 °C for 1 h. After cooling, the solvent was removed and the residue coevaporated with water. The residue was dissolved in methanol (2 mL) and concentrated aqueous ammonia (2 mL) and stirred at room temperature for 0.5 h. The solvent was removed and the residue recrystallized from water–methanol to afford **39** (239 mg, 59%): mp 220–223 °C; UV λ_{max} 250 nm (ε 11 220); IR (KBr) ν_{max} 3390, 3290, 1690, 1593, 1557, and 1413 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.97 (1 H, m, CH), 3.55 (4 H, m, 2 CH_2OH), 4.38 (2 H, d, J = 6.3 Hz, CH_2ON), 4.59 (2 H, s, D_2O exchangeable, NH_2), 8.08 (1 H, s, H-8), and 8.36 (1 H, s, H-2). Anal. ($C_9H_{12}N_4O4$) C, H, N.

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Registry No. **1a**, 73842-99-6; **1b**, 4799-68-2; **1c**, 4728-12-5; **2a**, 114778-45-9; **2b**, 114809-45-9; **2c**, 114778-38-0; **3a**, 114778-46-0; **3b**, 114809-62-0; **3b**·HCl, 114809-46-0; **3c**, 114778-39-1; **4**, 55583-59-0; **5**, 116477-30-6; **6**, 123240-58-4; **7**, 123240-59-5; **8**, 114778-60-8; **9**, 114778-61-9; **10**, 114778-69-7; **11**, 114778-62-0; **12**, 114778-63-1; **13**, 114778-68-6; **14**, 114778-79-9; **15**, 114778-80-2; **16**, 114778-81-3; **17**, 123240-60-8; **18**, 123240-61-9; **19**, 123240-62-0; **20**, 114800-63-4; **21**, 114809-39-1; **22**, 123240-63-1; **22**·$^1/_2NH_3$, 123240-76-6; **23**, 114778-78-8; **24**, 123240-64-2; **25**, 123240-65-3; **26**, 114778-74-4; **27**, 114809-42-6; **28**, 114778-76-6; **29**, 114778-77-7; **30**, 5413-85-4; **31**, 123240-66-4; **32**, 123240-67-5; **33**, 123240-68-6; **34**, 123240-69-7; **35**, 123240-70-0; **36**, 123240-71-1; **37**, 123240-72-2; **38**, 123240-73-3; **39**, 123240-74-4; $CH_3(CH_2)_4CO_2CO(CH_2)_4CH_3$, 2051-49-2; $PhCO_2COPh$, 93-97-0; $EtCO_2COEt$, 123-62-6; *N*-

hydroxyphthalimide, 524-38-9; triethyl methanetricarboxylate, 6279-86-3; 2-(hydroxymethyl)propane-1,3-diol, 4704-94-3; 9-[3-[(*tert*-butyldimethylsilyl)oxy]propoxy]-2-formamidopurine, 123240-75-5; 2,6-diamino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine, 114778-44-8; 2-amino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine, 114778-42-6; 9-[3-(benzyloxy)propoxy]adenine, 123240-77-7; 9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]adenine, 123240-78-8.

Benzodiazepine Receptor Binding Activity of 8-Substituted-9-(3-substituted-benzyl)-6-(dimethylamino)-9*H*-purines

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A series of 8-substituted analogues of 9-(3-aminobenzyl)-6-(dimethylamino)-9*H*-purine (**8**) were synthesized and tested for their ability to bind to the benzodiazepine receptor (BZR) in rat brain tissue. The most active compound was the 8-bromo-9-(3-formamidobenzyl) analogue **16** (IC_{50} = 0.011 μM), which was 1000-fold more active than the parent 9-benzyl-6-(dimethylamino)-9*H*-purine (**1**) and nearly as active as diazepam. Although substitution of a *m*-formamido group and an 8-bromo substituent on **1** imparted potent BZR binding activity, neither **16** nor 11 analogues exhibited significant anxiolytic activity on a modified Geller–Seifter conflict schedule.

High-affinity binding sites or receptors through which benzodiazepines exert their pharmacological activities have been identified in the central nervous system.[1-3] Compounds of diverse structure bind to the benzodiazepine receptor (BZR).[4] Purines were proposed as possible endogenous ligands,[5,6] and several papers describe structure–activity studies on the interaction of purines with the BZR.[7-9] We recently reported the BZR binding activity of a series of 6,9-disubstituted purines;[10] one of the most active compounds was 9-(3-aminobenzyl)-6-(dimethylamino)-9*H*-purine (**8**) which had an IC_{50} = 0.9 μM. We report the structure–activity relationships for binding to the BZR of a series of 8-substituted analogues of **8**; the most potent compounds have BZR binding affinity comparable to that of diazepam.

Chemistry

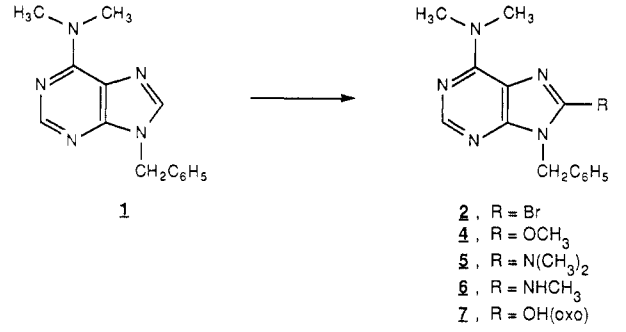
The 9-benzyl-8-substituted-purines **2** and **4–7** were prepared from **1** as outlined in Scheme I. Bromination of **1** with aqueous bromine in sodium acetate buffer gave **2**, which was converted to **4** with sodium methoxide, to **5** with aqueous dimethylamine, and to **6** with aqueous methylamine. The 8-oxopurine **7** was formed as a byproduct in the preparation of **4**.

The 8-methylpurine **3** was prepared in four steps from 4,6-dichloro-5-nitropyrimidine (**27**) as outlined in Scheme II. Amination of **27** with benzylamine gave **28**, which was reacted with dimethylamine to give **29** in fair yield. The nitro group was reduced with palladium on carbon to give **30**, which was cyclized with triethyl orthoacetate to give **3** in low overall yield.

The 8-bromopurine **9** was prepared as outlined in Scheme III. The 9-(3-nitrobenzyl)purine **31** was brominated by using a modification of the method for preparation of **2** to give **20** in high yield. The use of tetrahydrofuran as a cosolvent gave a homogeneous reaction, and the shorter reaction time circumvented formation of a monomethylamino side product. The nitro group of **20** was reduced with Raney nickel without detectable dehalogenation to give the 8-bromopurine **9** in good yield.

The 8-chloropurine **10** was prepared in three steps from 6,8-dichloropurine (**32**) (Scheme IV). Alkylation of **32** with 3-nitrobenzyl chloride gave **33**, which was selectively aminated to give the 6-(dimethylamino)purine **34**. The

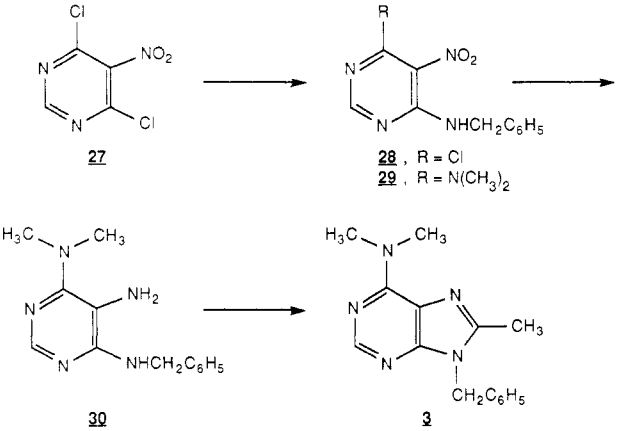
Scheme I



1

2, R = Br
4, R = OCH_3
5, R = $N(CH_3)_2$
6, R = $NHCH_3$
7, R = OH(oxo)

Scheme II



27

28, R = Cl
29, R = $N(CH_3)_2$

30 **3**

structures of **33** and **34** were confirmed by reaction of **34** with methylamine to give **37**, which was identical with **37**

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(1) Squires, R. F.; Braestrup, C. *Nature (London)* **1977**, *266*, 732.
(2) Möhler, H.; Okada, T. *Science* **1977**, *198*, 849.
(3) Braestrup, C.; Squires, R. F. *Eur. J. Pharmacol.* **1978**, *48*, 263.
(4) Haefely, W.; Kyburz, E.; Gerecke, M.; Mohler, H. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press: London, 1985; Vol. 14, pp 165–299.
(5) Skolnick, P.; Marangos, P. J.; Goodwin, F. K.; Edwards, M.; Paul, S. *Life Sci.* **1978**, *23*, 1473.
(6) Asano, T.; Spector, S. *Proc. Natl. Acad. Sci.* **1979**, *76*, 977.
(7) Davies, L. P.; Cook, A. F.; Poonian, M.; Taylor, K. M. *Life Sci.* **1980**, *26*, 1089.
(8) Grozinger, K.; Freter, K. R.; Farina, P.; Gladczuk, A. *Eur. J. Med. Chem.* **1983**, *18*, 221.
(9) Sung, S.-C.; Saneyoshi, M. *Biochem. Pharmacol.* **1984**, *33*, 1737.

0022-2623/90/1833-0196$02.50/0