John Hannah*, Richard L. Tolman, John D. Karkas, Richard Liou,
Helen C. Perry† and A. Kirk Field††

Merck Sharp & Dohme Research Laboratories,
Rahway, NJ 07065, and West Point, PA 19486

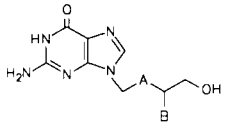
Received April 10, 1989

Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Ganciclovir **2** and 2′-carba-ganciclovir **5a** are anti-viral agents differing structurally only in the replacement of an oxygen by a methylene group and yet expressing their biological properties along mechanistically independent pathways. Methoxy, hydroxy and fluoro derivatives of 2′-carba-ganciclovir were prepared to examine the effect of re-introducing a binding site close to that in the original oxa side chain. The cyclic phosphate of carba-ganciclovir was also prepared.

J. Heterocyclic Chem., **26**, 1261 (1989).

An excellent review of the chemistry and antiviral activities of the acyclonucleosides has recently been published [1]. It is at once evident that potent antiviral properties have been found for guanine derivatives with the side chains (2-hydroxyethoxy)methyl-, **1**, (acyclovir); (1,3-dihydroxy-2-propoxy)methyl-, **2**, (ganciclovir); and *R*-3,4-dihydroxybutyl-, **3**, (buciclovir), at position 9.

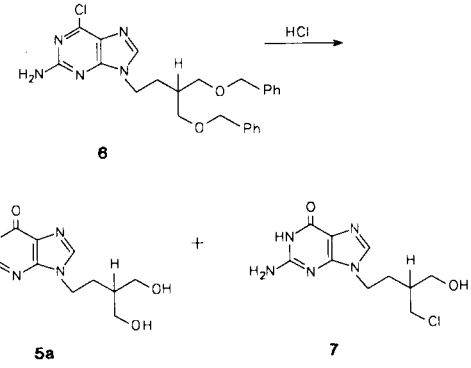


	A	B
1	O	H
2	O	CH_2OH
3	CH_2	OH
4	CH_2	H
5a	CH_2	CH_2OH

The simple hydroxybutyl analog **4** (carba-acyclovir) displayed modest antiherpetic action in our enzyme and cell culture assays, (Table 1) enough to suggest that 9-(4′-hydroxy-3′-hydroxymethyl)butylguanine, **5a** (carba-ganciclovir) could be of interest. Compound **5a** had already been reported in the chemical literature [2], but no biological data was available. We therefore followed the literature procedure to prepare a sample of **5a** for comparison in all our assays with the highly active ganciclovir **2**. The side chain oxygen was thought to be an important binding site and its removal was expected to cause considerable change in the biological profile of the molecule.

Since beginning this work, two research groups [3,4] have published genuine syntheses of **5a**, each commenting that the published conditions had given a mixture (mp 170-175°) of the desired product and residual *O*-benzylated derivatives. In our hands, (Scheme 1) hydrolysis of compound **6** with refluxing hydrochloric acid left very little *O*-benzylated material, and reverse phase chromatography of the mixture gave compound **5a** (mp 272-275° dec) and the mono chloro derivative **7** (mp 188-190° dec).

SCHEME 1



It was soon apparent that the good antiviral activity of **5a** must be expressed by a mechanism different from that of ganciclovir and other members of the acyclovir class. We therefore decided to make more carba-ganciclovir by a route amenable to some variation in the new side chain, with easily chromatographed penultimate structures, and a mild, final deprotection step (Scheme 2).

The malonate derivatives **8a,b,c** were readily converted to 1,3-propanediols **9a,b,c** which were protected as cyclic ketals **10a,b,c**. In each case, the allyl substituent served as a masked 2-hydroxyethyl function, later exposed by ozonolysis and borohydride reduction of the somewhat unstable aldehydes. The tosylates of the primary alcohols were reactive viscous oils which were characterized by tlc and nmr, then used to alkylate 2-amino-6-benzyloxypurine **13** [5]. The latter substrate was prepared from the 6-chloro analog in the hope that the bulky 6-benzyloxy substituent would lead to exclusive alkylation at position 9. In this we were disappointed: a 2:1 ratio of 9 over 7 alkylation was observed, except in the case of the tertiary hydroxyl substituent, where only the 9-isomer **14d** could be isolated from a complex mixture. Consistently, the 9-isomers were less

TABLE 1

COMPOUND	STAGGERED ENZYME ASSAY [ag]						ANTIVIRAL ACTIVITY[fg] in CELL CULTURE	
	STEP I [bc]	STEP II [cd]			DNA POLYMERASE [e] INHIBITION %		ED_{50} μg/ml	
	MP, %	MP, %	DP, %	TP, %	HSV-1	HeLa	HSV-1 (Schooler)	HSV-2 (Curtis)
1	17	3	9	60	79	40	3	3
2	90	3	10	84	60	22	3	3
3	96	6	22	72	0	15	50 (tox)	50 (tox)
4	55	0	10	17	20	20	3–12	12–25
5a	37	3	13	75	0	8	6–12	12–50
5b	21	8	8	74	2	0	>100	>100
5c	14	1	2	47	12	7	1.6–3.1 (tox @ 100)	3.1 (tox @ 100)
5d	50	0	23	75	5	5	12–25	50
23	100	100	0	0	0	0	6–12	25
2cp	100	100	0	0	6	0	6–50	12–50
16a	3	0	0	0	6	0	>100	>100
16b	1	0	0	0	8	13	>100	>100
16c	NT	NT	NT	NT	NT	NT	NT	NT

[a]Average of three experiments. MP, DP, TP = mono-, di-, triphosphate. [b]Incubation with HSV-1 thymidine kinase. [c]Calculated percentages based on total phosphorylated and unphosphorylated compound. [d]Continued incubation of the mixture from step I with GMP kinase and crude extract of HSV-1 infected HeLa cells. [e]Following further incubation of the mixture from step II. [f]Drug concentration to inhibit plaque development by 50% on MRC-5 cell monolayers. [g]Experimental details in ref. 6.

polar, possessed a 30% more intense uv absorption at a shorter (Δ 12 nm) wavelength, and showed C_8-H resonance in the nmr spectrum at higher field (Δ 0.16 ppm) than the 7-isomer.

In the related pathway (Scheme 3) to 2'-carba-ganciclovir cyclic phosphate **23** the original intention was to carry the *cis/trans* mixtures of intermediates **17-21** through to the final product, where the geometric isomerism would be lost.

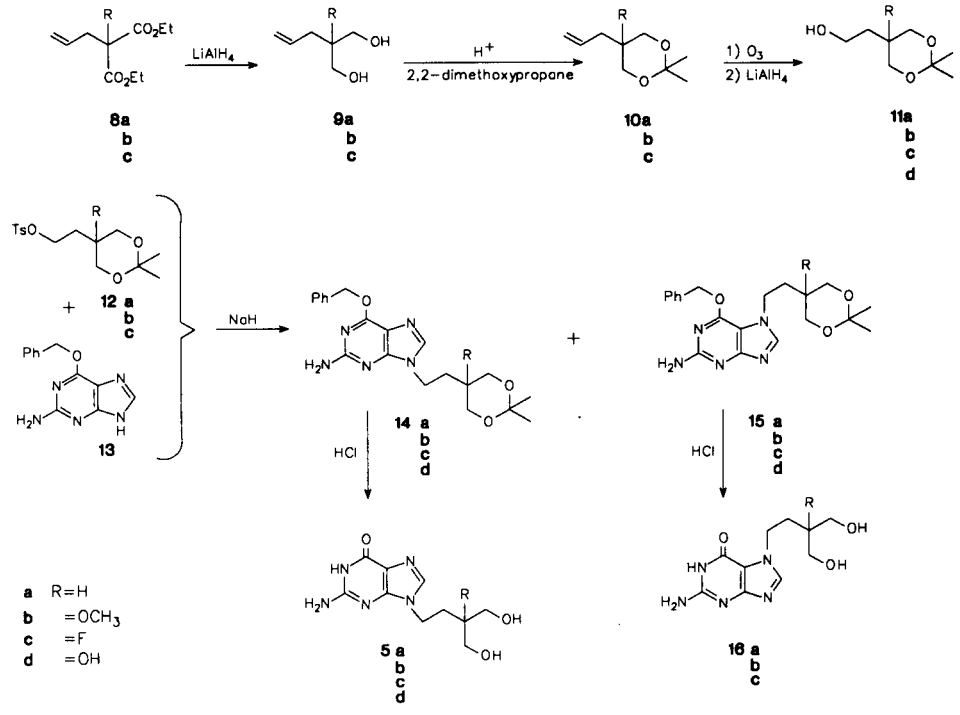
One component, however, readily crystallized from the mixture of *cis/trans* tosylates **20**, and was thereafter used exclusively. X-ray crystallographic analysis [5a] showed that this crystalline tosylate was the *trans* isomer in diaxial conformation **20**, which allowed unequivocal assignment of proton resonances in the nmr spectrum for both isomers.

Biological Studies.

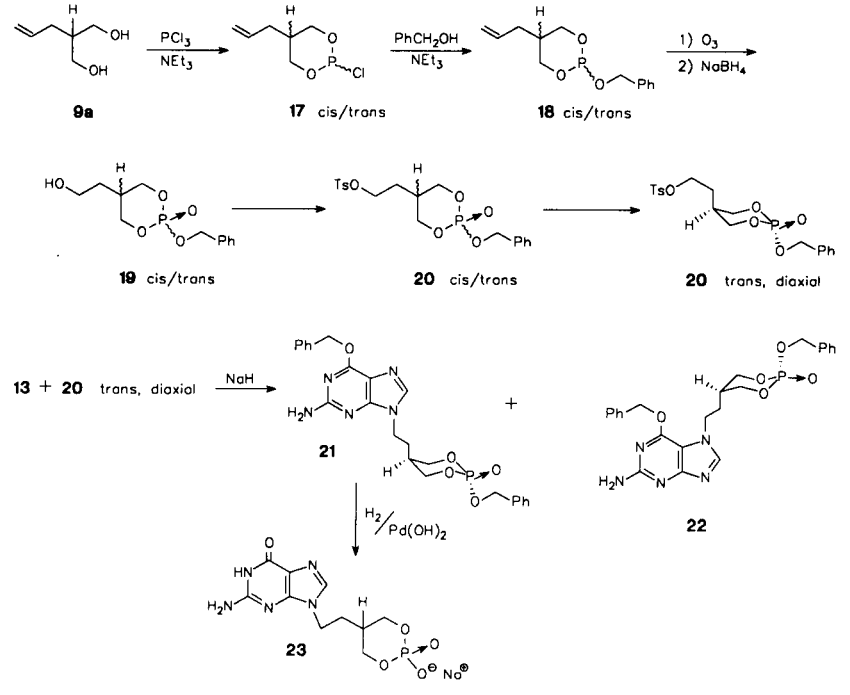
Acyclovir **1** and ganciclovir **2** are selectively monophosphorylated in infected cells by HSV thymidine kinase with additional phosphorylation by host cell enzymes to their triphosphates which are believed to be the actual anti-viral agents operating by inhibition of viral DNA polymerase.

Table 1 summarizes the evaluation of compounds **5a-d**, **16a,b** and **23** in a series of enzyme and cell culture assays [6]. Enzymic phosphorylation was measured by incubation with HSV-1 thymidine kinase at 37° for 4 hours with a chromatographic readout of the mono-phosphate formed. GMP kinase and a crude extract of HSV-infected cells was

Scheme 2



Scheme 3



then added and the incubation was continued overnight. Chromatography of another aliquot showed the mono-, di- and triphosphate components of the mixture. Aliquots of this mixture were finally incubated for 1 hour with a DNA polymerase mixture (either viral or cellular) to measure inhibitory activity. Carba-ganciclovir **5a** was revealed as a good substrate for thymidine kinase, and was easily converted to the triphosphate. The latter was, however, a very poor inhibitor of DNA polymerase.

In cell culture, the test compounds were added to confluent MRC-5 cells and incubated at 37°. The complete system was then challenged with either HSV-1, or HSV-2,

or no virus, and incubation was continued. Cells were evaluated after 4-5 days for cytopathology or toxicity. Carbaganciclovir **5a** appeared as an active anti-viral agent despite its poor performance against DNA polymerase which indicated that a mechanism of antiviral action in addition to that postulated for ganciclovir **2** must be operative.

The next compound prepared was the cyclic phosphate **23**. In the chromatographic system used [6], cyclic phosphates and monophosphates are not separated. The cyclic phosphate **23** remained in the monophosphate-cyclic phosphate elution position. This indicates that the cyclic ester of **23** was not opened during the conditions of this experiment, since open monophosphate of **5a** was readily converted to triphosphate under these conditions. Just as its non-phosphorylated precursor, cyclic phosphate **23** did not inhibit DNA polymerase *in vitro* but was active in cell culture, which again is consistent with the existence of an additional pathway for antiviral action. Ganciclovir cyclic phosphate **2cp** [7] is included in Table 1 for comparison with **23**, and appears to operate in a remarkably similar manner. Although **2cp** has been shown to be converted to some extent to ganciclovir triphosphate when incubated with high concentrations of cellular extracts there is evidence that it also has an additional, triphosphate-independent mode of action [7a].

The methoxy and hydroxy derivatives **5b** and **5d** were both good substrates for thymidine kinase, easily converted to their triphosphates, but differing markedly in their cell culture properties. The fact that activity was restored in **5d** drew attention to probable polarity and size requirements at a binding site, which pointed clearly to replacement of the tertiary hydroxyl with the smaller, more electronegative fluorine. This proposal was reinforced by reference to nucleocidin, an adenine glycosidic antibiotic having a fluoro substituent at position C-4′ [8].

The fluoro derivative **5c** [9] was the last of the series, and by the criteria in Table 1 was reasonably accepted as a substrate by thymidine kinase with subsequent conversion to the triphosphate. Compound **5c** was equally active with acyclovir **1** and ganciclovir **2** in the cell culture assay, a situation somewhat compromised by evidence of toxicity found at 100 μg/ml. Possibly a better therapeutic ratio would be achieved with **5c** cyclic phosphate which should operate in an analogous manner to compounds **23** and **2cp**.

The two examples tested in the isomeric 7-alkylated guanine series, **16a,b** were not enzymically phosphorylated, showed only a low order of activity against DNA polymerase, and were inactive in cell culture.

EXPERIMENTAL

Melting points were determined on an electrically heated block and are uncorrected. The ^{1}H nmr spectra were taken on a Varian XL-200 spectrometer in solvents specified in the text. The uv spectra were obtained on a Perkin Elmer 552A spectrometer, and mass spectra were determined on Finnegan MAT 731 (FAB) and MAT 212 (high resolution *e.i.*) instruments.

2-Amino-1,9-dihydro-9-(4′-hydroxy-3′-hydroxymethyl)butyl-6-oxo-6*H*-purine (**5a**) and 2-amino-1,9-dihydro-9-(4′-chloro-3′-hydroxymethyl)butyl-6-oxo-6*H*-purine (**7**).

(2)-Amino-9-(4′-benzyloxy-3′-benzyloxymethyl)butyl-6-chloro-9*H*-purine (**6**) (300 mg) was dissolved in hot ethanol (6 ml)/aqueous 2*N* hydrochloric acid (6 ml). The ethanol was distilled off and the residual aqueous acidic solution was boiled under reflux for 6 hours. Evaporation in a stream of nitrogen/100° then at 100°/0.5 mm gave a pale brown foam (204 mg). Tlc (silica GF, chloroform/methanol/water, 60/40/4 showed a trace of starting material and two major products R_f 0.46 and 0.68 which were easily separated by reverse phase hplc (Whatman, Partisil M9, ODS-2 column, aqueous 4-20% methanol, uv monitor at 290 mm for 40 mg x 5 injections) Eluates were evaporated at 70°/0.5 mm and the residues were recrystallized from water. The more polar product **5a** was colorless matted needles (42 mg), mp 272-275°; uv (aqueous 0.01*N* sodium hydroxide): λ max 215 nm (ε 18,140), 255 (sh) (10,020), 268 (10,710); ^{1}H nmr (deuterium oxide/TSP): δ 1.68 (heptet, 1 H, J = 6 Hz, CH), 1.86 (dt, 2 H, J = 7 and 7 Hz, CH_2), 3.64 (d, 4 H, J = 6 Hz, $[CH_2O]_2$), 4.13 (t, 2 H, J = 7 Hz, NCH_2), 7.83 (s, 1 H, C_8-H); ms: (FAB) m/e 254 ($M^+ + 1$).

Anal. Calcd. for $C_{10}H_{15}N_5O_3$: C, 47.43; H, 5.97; N, 27.65. Found: C, 47.67; H, 5.86; N, 27.56.

The less polar product **2** was colorless prisms (24 mg) (aqueous ethanol): mp 188-190° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 213 nm (ε 24,500), 256 (sh) (10,390), 268 (10,970); ^{1}H nmr (deuterium oxide/TSP): δ 1.93 (m, 3 H, CH + CH_2), 3.67 (d, 2 H, J = 5 Hz, CH_2O or Cl), 3.73 (d, 2 H, J = 4 Hz, CH_2Cl or O); ms: (FAB) m/e 272 and 274 ($M^+ + 1$).

Anal. Calcd. for $C_{10}H_{14}N_5O_2Cl$: C, 44.20; H, 5.19; N, 25.78. Found: C, 44.35; H, 5.17; N, 25.75.

Diethyl Methoxymalonate.

Clean sodium (9.74 g, 0.42 mole) was added to anhydrous ethanol (124 ml) and the mixture was boiled under reflux to give a clear solution. Ethyl methoxyacetate (50.0 g, 0.42 mole) and diethyl carbonate (350 ml, 2.89 mole) were added and the solution was slowly distilled for 1 hour, 30 minutes, removing approximately 210 ml. The reaction mixture was now a slurry of sodium salt at 120°. The mixture was cooled to 23° and filtered. The solids were washed with benzene, dried at 25°/0.25 mm, and obtained as a tan powder (60.75 g). All of it was suspended in benzene (200 ml). Crushed ice (100 g) was added followed by aqueous 4*N* sulfuric acid to *p*H 2. The organic phase was washed with saturated aqueous sodium chloride then dried over magnesium sulfate, filtered and evaporated to give an oil which was distilled at reduced pressure, 33.87 g, bp 73-76°/0.4 mm, $n_D^{22°}$ 1.4222 (lit [10] bp 95°/3 mm, $n_D^{22°}$ 1.4229). Tlc (silica GF, hexane/50% ethyl acetate) showed two products, R_f 0.68 and 0.84, by iodine staining. Both uv and ceric sulfate charring detected only the more polar component. The ^{1}H nmr (deuteriochloroform): clearly showed the product to be a mixture, a portion (29.10 g) of which was separated by chromatography over silica. Hexane/15% ethyl acetate eluted the less polar component (18.25 g) and ethyl acetate the more polar component (9.43 g). Each was distilled at

reduced pressure to give colorless oils. The less polar was diethyl methoxymalonate (17.38 g), bp 69°/0.2 mm, $n_D^{22°}$ 1.4175; ^{1}H nmr (deuteriochloroform): δ 1.31 (t, 6 H, J = 7 Hz, $[CH_3]_2$); 3.52 (s, 3 H, OCH_3); 4.29 (q, 4 H, J = 7 Hz, $[OCH_2]_2$), 4.41 (s, 1 H, CH).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.40; H, 7.16.

The more polar was ethyl 2,4-dimethoxyacetoacetate (7.99 g), bp 73°/0.2 mm, $n_D^{23°}$ 1.4297; ^{1}H nmr (deuteriochloroform): δ 1.32 (t, 3 H, J = 7 Hz, CH_3); 3.43 (s, 3 H, OCH_3); 3.49 (s, 3 H, OCH_3); 4.31 (q, 2 H, J = 7 Hz, OCH_2); 4.35 (s, 2 H, CH_2); 4.46 (s, 1 H, CH).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.58; H, 7.59.

Diethyl Allylmethoxymalonate (**8b**).

n-Butyllithium (2.5 *M*, 35.8 ml, 89.4 mmoles) in hexane was added dropwise in 10 minutes by hypodermic syringe through a rubber septum to a magnetically stirred solution of diethyl methoxymalonate (17.0 g, 89.4 mmoles) in anhydrous *t*-butyl alcohol (85 ml) at 22°. The very vigorous reaction was controlled by cooling in an ice bath. With the ice bath still in place, re-distilled allyl bromide (8.51 ml, 98.3 mmoles) was added in 4 minutes in the same manner. After 10 more minutes the ice bath was removed and the mixture was allowed to stand at room temperature for 1 hour becoming a crystalline slurry. The mixture was partitioned between ether (500 ml) and water (100 ml), dried over magnesium sulfate, filtered and evaporated at 70°/100 mm to give a pale yellow oil (19.70 g); tlc (silica GF, hexane/25% ethyl acetate, ceric sulfate single spot R_f 0.60). A portion was distilled at reduced pressure, bp 110°/3.5 mm, $n_D^{26°}$ 1.4310; ^{1}H nmr (deuteriochloroform): δ 1.30 (t, 6 H, J = 7 Hz $[CH_3]_2$, 2.84 (m, 2 H, CH_2), 4.27 (q, 4 H, J = 7 Hz $[OCH_2]_2$), 5.14 (m, 2 H, $=CH_2$); 5.75 (m, 1 H, =CH-).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.16; H, 7.77.

Diethyl Allylfluoromalonate (**8c**).

A freshly prepared solution of clean sodium (1.21 g, 52 meq) in anhydrous ethanol (20 ml) was added in 3 minutes to a magnetically stirred solution of diethyl allylmalonate (20.0 g, 50 mmoles) in sieve-dried pyridine (40 ml) maintained just short of freezing (−40° to −35°) by means of an acetone/solid carbon dioxide bath. A stream of dry nitrogen was bubbled through the solution at −35° *via* a fine porosity gas inlet tube for 5 minutes. By means of a Y connector, the nitrogen was shut off and perchloryl fluoride ($FClO_3$, Pennwalt) from a cylinder was bubbled through the same gas inlet at a rate not to exceed an internal temperature of −35° for the vigorously exothermic reaction. The perchloryl fluoride passage was stopped when no further heat evolution was observed (15 minutes, 17 g used). The pale yellow suspension was flushed with nitrogen for 5 minutes, and was then partitioned between ether (200 ml) and water (60 ml). The ethereal layer was washed with water (2 x 60 ml) and the combined aqueous solutions were back extracted with ether (100 ml). The second ethereal extract was washed with water (2 x 20 ml), and was then combined with the main extract, dried (magnesium sulfate), filtered and evaporated. The residue was distilled to give a colorless oil (9.73 g), bp 63°/0.2 mm; $n_D^{22°}$ 1.4192; ^{1}H nmr (deuteriochloroform): δ 1.31 (t, 6 H, J = 7.0 Hz, $[CH_3]_2$), 2.92 (dd, 2 H, J_{HH} = 7.0 Hz, J_{HF} = 24.1 Hz, CH_2), 4.30 (q, 4 H, J = 7.0 Hz, $[OCH_2]_2$), 5.22 (m, 2 H, $=CH_2$), 5.77 (m, 1 H, =CH-).

Anal. Calcd. for $C_{10}H_{15}FO_4$: C, 55.04; H, 6.93; F, 8.71. Found: C, 55.02; H, 6.95; F, 8.58.

2-Allylpropane-1,3-diol (**9a**).

Diethyl allylmalonate (96.0 g, 0.48 mole) was added in a rapid stream in 30 minutes to a mechanically stirred 1.0 *M* solution of lithium aluminum hydride in THF (Aldrich) (530 ml). The vigorously exothermic reaction was controlled by a reflux condenser and the occasional use of an ice bath. The completed reaction solution was allowed to cool to room temperature for 30 minutes, then the complex was decomposed by the dropwise addition of saturated aqueous sodium chloride (400 ml) (ice bath) with very vigorous stirring to disperse an initially gelatinous mass to a final granular precipitate. After adding magnesium sulfate (100 g), the mixture was cooled to 25° and filtered. The insolubles were washed with ether (2 x 100 ml) and the combined organic solutions were evaporated to a residue which was distilled to give a colorless oil (40.0 g) bp 85°/0.2 mm; $n_D^{23°}$ 1.4656 [lit (11) bp 136-139°/15 mm; $n_D^{20°}$ 1.474]; ^{1}H nmr (deuterium oxide): δ 1.91 (heptet, 1 H, J = 6 Hz, CH), 2.14 (dddd, 2 H, J = 1, 1, 7 and 7 Hz, CH_2), 3.60 (d, 4 H, J = 6 Hz, $[OCH_2]_2$), 5.15 (m, 2 H, $=CH_2$), 5.92 (ddt, 1 H, J = 7, 10 and 17 Hz, =CH-).

2-Allyl-2-methoxypropane-1,3-diol (**9b**).

In a similar manner, diethyl allylmethoxymalonate (**8b**) (19.7 g, 85.5 mmoles) was reduced to 2-allyl-2-methoxypropane-1,3-diol (10.0 g), bp 88°/0.1 mm, $n_D^{24°}$ 1.4706; ^{1}H nmr (deuteriochloroform): δ 2.27 (d, 2 H, J = 8 Hz, CH_2), 3.21 (br s, 2 H, $[OH]_2$), 3.34 (s, 3 H, OCH_3), 3.64 (d, 2 H, J = 12 Hz, $[CH_AO]_2$), 3.72 (d, 2 H, J = 12 Hz, $[CH_BO]_2$), 5.14 (m, 2 H, $=CH_2$) 5.78 (ddt, 1 H, J = 8, 9 and 17 Hz, =CH-).

Anal. Calcd. for $C_7H_{14}O_3 \cdot 0.30\ H_2O$: C, 55.46; H, 9.71. Found: C, 55.44; H, 9.73.

2-Allyl-2-fluoropropane-1,3-diol (**9c**).

In a similar manner, with temperature control (−30°/7 minute addition; 30°/20 minute intermittent cooling; 20°/30 minutes), diethyl allylfluoromalonate (**8c**) (20.0 g, 0.15 mole) was reduced to 2-allyl-2-fluoropropane-1,3-diol (12.3 g). The crude product R_f 0.54, (tlc silica GF, hexane/75% ethyl acetate, ceric sulfate) contained a more polar impurity, R_f 0.40, which was not removed by distillation (bp 60°/0.1 mm). Chromatography over silica (hexane/40% ethyl acetate) gave pure material in the early fractions (6.35 g total) [**A**], followed by increasingly contaminated fractions (4.41 g total) [**B**]. Distillation of a fraction of [**A**] gave a colorless oil, bp 75°/0.15 mm, $n_D^{22°}$ 1.4513; ^{1}H nmr (deuteriochloroform): XL400, δ 2.25 (t, 2 H, J = 6.4 Hz, $[OH]_2$), 2.48 (dddd, 2 H, J_{HH} = 1.2, 1.2 and 7.5 Hz, J_{HF} = 19.3 Hz, CH_2), 3.76 (ddd, 2 H, J_{HH} = 6.4 and 12.0 Hz, J_{HF} = 19.2 Hz, $[CH_AO]$), 3.78 (ddd, 2 H, J_{HF} = 6.4 and 12.0 Hz, J_{HF} = 16.8 Hz, $[CH_BO]_2$), 5.17 (m, 2 H, $=CH_2$, 5.82 (ddt, 1 H, J = 7.3, 9.7 and 17.0 Hz, =CH-).

Anal. Calcd. for $C_6H_{11}FO_2$: C, 53.79; H, 8.27; F, 14.16. Found: C, 53.79; H, 8.19; F, 14.00.

5-Allyl-2,2-dimethyl-1,3-dioxane (**10a**).

p-Toluenesulphonic acid monohydrate (68 mg) was added to a solution of 2-allylpropane-1,3-diol (**9a**) (6.80 g) in a 10 fold excess of freshly distilled 2,2-dimethoxypropane (72 ml) at 23°. After 1 hour the solution was shaken with fresh aqueous 5% sodium bicarbonate (5 ml), then saturated aqueous sodium chloride (20 ml) was added and the mixture was again shaken. The lower aqueous layer was run off and the organic phase was washed with more

saturated aqueous sodium chloride (20 ml), dried over magnesium sulfate, filtered and evaporated at 60°/120 mm to give a colorless oil. Attempted distillation of this product at pressures from 5 to 120 mm was abandoned because of extensive, persistent frothing. Distillation at atmospheric pressure however, gave a colorless oil (8.17 g), bp 182-186° $n_D^{24°}$ 1.4384 which was then easily redistilled in high yield, bp 85°/28 mm $n_D^{24°}$ 1.4383; ^1H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.91 (m, 1 H, CH), 2.00 (m, 2H, CH_2), 3.62 (dd, 2 H, J = 8.7 and 12.0 Hz, $[CH_AO]_2$), 3.86 (dd, 2 H, J = 4.4 and 12.0 Hz, $[CH_BO]_2$), 5.05 (m, 2 H, $=CH_2$), 5.72 (m, 1 H, =CH-).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.09; H, 10.19.

5-Allyl-2,2-dimethyl-5-methoxy-1,3-dioxane (**10b**).

In a similar manner, 2-allyl-2-methoxypropane-1,3-diol (**9b**) (8.88 g) was converted to the 1,3-dioxane (9.17 g), bp 76-77°/4.5 mm, $n_D^{23°}$ 1.4430; ^1H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.36 (m, 2 H, CH_2), 3.33 (s, 3 H, OCH_3), 3.69 (d, 2 H, J = 11.9 Hz, $[CH_AO]_2$), 3.76 (d, 2 H, J = 11.9 Hz, $[CH_BO_2)$, 5.15 (m, 2 H, $=CH_2$), 5.80 (m, 1 H, =CH-).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.17; H, 9.60.

5-Allyl-2,2-dimethyl-5-fluoro-1,3-dioxane (**10c**).

In a similar manner, 2-allyl-2-fluoropropane-1,3-diol (**9c**) (14.0 g) was converted to the 1,3-dioxane (8.02 g), bp 62°/5.5 mm, $n_D^{23°}$ 1.4300. The low yield was due to sudden onset of decomposition on attempted distillation at atmospheric pressure. Rapid cooling, neutralization with aqueous sodium bicarbonate extraction with ether and chromatography over silica (hexane/20% ethyl acetate) recovered about half the product which then was smoothly distilled at reduced pressure; ^1H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.36 (m, 2 H, CH_2), 3.79 (dd, 2 H, J_{HH} = 12.8 Hz, J_{HF} = 23.2 Hz, $[CH_AO]_2$), 3.82 (dd, 2 H, J_{HH} = 12.8 Hz, J_{HF} = 16.8 Hz, $[CH_BO]_2$), 5.19 (m, 2H, $=CH_2$), 5.82 (m, 1 H, =CH-).

Anal. Calcd. for $C_9H_{15}FO_2$: C, 62.05; H, 8.68; F, 10.91. Found: C, 62.06; H, 8.74; F, 11.10.

2,2-Dimethyl-5-(2′-hydroxyethyl)-1,3-dioxane (**11a**).

5-Allyl-2,2-dimethyl-1,3-dioxane (**10a**) (14.36 g, 91.9 mmoles) was dissolved in acetonitrile (280 ml) and the solution was cooled to −15° in a methanol/ice bath. A stream of oxygen/ozone from a Welsbach T816 generator (approx. 0.7 mmole ozone/minute) was bubbled through the solution *via* a fine porosity gas inlet tube, and the disappearance of starting material (R_f 0.67) was monitored by tlc (silica GF, hexane/25% ethyl acetate, ceric sulfate). Passage of ozone was stopped after 130 minutes. To the solution of ozonide was now added an excess of 1.0 *M* lithium aluminum hydride in THF (92 ml) at a rate not to exceed a reaction temperature of 20°, with stirring and cooling in methanol/ice: time required was 15 minutes. After 10 minutes at 22° the reaction complex was decomposed by the dropwise addition of saturated aqueous sodium chloride (46 ml) with cooling and very vigorous mechanical stirring. Magnesium sulfate (20 g) was added and the mixture was filtered. The solids were washed with ether (2 x 50 ml) and the combined organic solutions were evaporated to a residue (tlc silica GF, ethyl acetate, ceric sulfate, R_f 0.50) which was distilled to give a colorless oil (10.47 g), bp 76°/0.1 mm, $n_D^{22°}$ 1.4528; ^1H nmr (deuteriochloroform): δ 1.42 (s, 3H, CH_3), 1.43 (s, 3 H, CH_3), 1.53 (dt, 2 H, J = 6.5 and 6.5 Hz, CH_2), 1.94 (m, 1 H, CH), 2.33 (br s, 1 H, OH), 3.64 (dd, 2 H, J = 8.2 and 12.0 Hz, $[CH_AO]_2$), 3.69 (t, 2 H, J = 6.5 Hz, CH_2O), 3.93 (dd, 2 H, J = 4.5 and 12.0 Hz, $[CH_BO]_2$).

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.89; H, 10.00.

2,2-Dimethyl-5-(2′-hydroxyethyl)-5-methoxy-1,3-dioxane (**11b**).

In a similar manner, 5-allyl-2,2-dimethyl-5-methoxy-1,3-dioxane (**10b**) (8.87 g, 47.6 mmoles) was converted to 2,2-dimethyl-5-(2′-hydroxyethyl)-5-methoxy-1,3-dioxane. The crude product was chromatographed over silica gel (ethyl acetate, 0-5% methanol, with extensive tailing) to give single spot material (6.79 g) (tlc silica GF, ethyl acetate, ceric sulfate R_f 0.39) which was distilled as a colorless oil (5.09 g) bp 84°/0.16 mm, $n_D^{25°}$ 1.4554; ^1H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3); 1.81 (t, 2 H, J = 6.1 Hz, CH_2), 2.75 (br s, 1 H, OH), 3.38 (s, 3 H, OCH_3), 3.75 (d, 2 H, J = 12.4 Hz, $[CH_AO]_2$), 3.77 (t, 2 H, J = 6.0 Hz, OCH_2), 3.88 (d, 2 H, J = 12.4 Hz, $[CH_BO]_2$).

Anal. Calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.72; H, 9.49.

2,2-Dimethyl-5-fluoro-5-(2′-hydroxyethyl)-1,3-dioxane (**11c**).

In a similar manner, 5-allyl-2,2-dimethyl-5-fluoro-1,3-dioxane (**10c**) (7.92 g, 45.4 mmoles) was converted to 2,2-dimethyl-5-fluoro-5-(2′-hydroxyethyl)-1,3-dioxane. The crude product was chromatographed over silica gel (hexane/40-75% ethyl acetate, with extensive tailing) to give single spot material (4.99 g) (tlc silica GF, ethyl acetate, ceric sulfate R_f 0.47) a portion of which was distilled as a colorless oil, bp 85°/0.15 mm, $n_D^{22°}$ 1.4464, which readily crystallized as needles, mp 47-52°. ^1H nmr (deuterium oxide): δ 1.43 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.86 (dt, 2 H, J_{HH} = 6.0 Hz, J_{HF} = 19.7 Hz, CH_2), 3.86 (t, 2 H, J = 6.0 Hz, OCH_2); 3.88 (dd, 2 H, J_{HH} = 12.5 Hz, J_{HF} = 24.1 Hz, $[CH_AO]_2$), 3.94 (dd, 2 H, J_{HH} = 12.5 Hz, J_{HF} = 16.6 Hz, $[CH_BO]_2$); ^1H nmr (deuterium oxide): δ 1.45 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.83 (dt, 2 H, J_{HH} = 6.6 Hz, J_{HF} = 21.0 Hz, CH_2), 3.76 (t, 2 H, J = 6.6 Hz, OCH_2), 3.94 (dd, 2 H, J_{HH} = 13.3 Hz, J_{HF} = 13.7 Hz, $[CH_AO]_2$), 4.12 (dd, 2 H, J_{HH} = 13.3 Hz, J_{HF} = 36.0 Hz, $[CH_BO]_2$).

Anal. Calcd. for $C_8H_{15}FO_3$: C, 53.92; H, 8.48; F, 10.66. Found: C, 53.72; H, 8.45; F, 10.93.

2,2-Dimethyl-5-hydroxy-5-(2′-hydroxyethyl)-1,3-dioxane (**11d**).

Freshly cut, clean lithium (219 mg, 31.5 meq) in five equal pieces was added to a magnetically stirred solution of 2,2-dimethyl-5-(2′-hydroxyethyl)-5-methoxy-1,3-dioxane (**11b**) (2.0 g, 10.5 mmoles) in anhydrous ethylamine (50 ml) at reflux (17°) under an acetone/solid carbon dioxide condenser topped with a Drierite exit tube. Blue coloration spread entirely through the solution in 35 minutes and had discharged completely in 1 hour, 30 minutes. More lithium (146 mg, 21 meq) was added which permanently restored the blue color. After 4 hours, 40 minutes, the color was discharged by adding dropwise an excess of methanol (5 ml, *violent reaction*) which formed a gelatinous mass from which ethylamine was evaporated (water bath, 35°). The residue was dried at 60°/0.5 mm to give a colorless powder, which was dissolved in water (20 ml) and titrated to *p*H 8.5 by adding aqueous 2*N* hydrochloric acid. The solution was extracted with chloroform (4 x 20 ml). The combined extracts were dried (magnesium sulfate), filtered and evaporated. The residue was distilled to give a colorless viscous oil (728 mg), bp approximately 115°/0.18 mm, $n_D^{24°}$ 1.4644; ^1H nmr (deuteriochloroform): δ 1.43 (s, 3 H, CH_3), 1.45 (s,

3 H, CH_3), 1.69 (t, 2 H, J = 5.9 Hz, CH_2), 3.67 (d, 2 H, J = 11.4 Hz, $[CH_AO]_2$), 3.80 (d, 2 H, J = 11.4 Hz, $[CH_BO]_2$), 3.83 (t, 2 H, J = 5.9 Hz, OCH_2).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.30; H, 9.14.

2,2-Dimethyl-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12a**).

A solution of 2,2-dimethyl-5-(2'-hydroxyethyl)-1,3-dioxane (1.27 g, 7.9 mmoles) (**11a**) in sieve-dried pyridine (6.5 ml) was cooled in an ice bath, and with magnetic stirring, recrystallized *p*-toluenesulphonyl chloride (1.66 g, 8.7 mmoles) was added in portions in 3 minutes. After 10 more minutes, the ice bath was removed and the reaction mixture was left at room temperature for 2 hours. The mixture was then partitioned between ether (60 ml) and water (20 ml). The organic phase was washed with fresh aqueous 5% sodium bicarbonate (10 ml), with water (10 ml), dried (magnesium sulfate), filtered and evaporated to give a pale orange viscous oil (2.31 g); tlc essentially a single spot (silica GF, hexane/50% ethyl acetate, ceric sulfate, R_f 0.55); ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.73 (t, 2 H, J = 6.0 Hz, CH_2), 1.81 (m, 1 H, CH), 2.45 (s, 3 H, $TsCH_3$), 3.53 (dd, 2 H, J = 6.6 and 11.9 Hz, $[CH_AO]_2$), 3.86 (dd, 2 H, J = 3.8 and 11.9 Hz, $[CH_BO]_2$), 4.08 (t, 2 H, J = 6.0 Hz, OCH_2), 7.36 and 7.78 (ABq, 4 H, J = 8.2 Hz, Ar). Material of this quality was used directly in the next step.

2,2-Dimethyl-5-methoxy-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12b**).

In a similar manner 2,2-dimethyl-5-(2'-hydroxyethyl)-5-methoxy-1,3-dioxane (**11b**) (1.00 g, 5.3 mmoles) was converted to 2,2-dimethyl-5-methoxy-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane. The crude product was shaken with petroleum ether/ether, 1:1 (25+10 ml) decanting the clear supernatant layers from traces of orange gum. The combined extracts were evaporated to give a colorless, viscous oil (1.71 g); tlc single spot (silica GF, hexane/50% ethyl acetate, ceric sulfate, R_f 0.59); ^{1}H nmr (deuteriochloroform): δ 1.36 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.93 (t, 2 H, J = 6.9 Hz, CH_2), 2.45 (s, 3 H, CH_3, $TsCH_3$), 3.25 (s, 3 H, OCH_3), 3.63 (d, 2 H, J = 12.1 Hz, $[CH_AO]_2$), 3.74 (d, 2 H, J = 12.1 Hz, $[CH_BO]_2$), 4.13 (t, 2 H, J = 6.9 Hz, OCH_2), 7.36 and 7.80 (ABq, 4 H, J = 8.3 Hz, Ar).

2,2-Dimethyl-5-fluoro-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12c**).

In a similar manner, 2,2-dimethyl-5-fluoro-5-(2'-hydroxyethyl)-1,3-dioxane (**11c**) (2.0 g, 11.2 mmoles) was converted to 2,2-dimethyl-5-fluoro-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane as a pale yellow viscous oil (3.92 g); tlc essentially a single spot (silica GF, hexane/50% ethyl acetate, ceric sulfate, R_f 0.59); ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.97 (dt, 2 H, J_{HH} = 6.2 Hz, J_{HF} = 19.7 Hz, CH_2), 2.46 (s, 3 H, $TsCH_3$), 3.79 (dd, 2 H, J_{HH} = 13.0 Hz, J_{HF} = 22.3 Hz, $[CH_AO]_2$), 3.82 (dd, 2 H, J_{HH} = 13.0 Hz, J_{HF} = 19.8 Hz, $[CH_BO]_2$), 4.19 (t, 2 H, J = 6.2 Hz, OCH_2), 7.37 and 7.80 (ABq, 4 H, J = 8.2 Hz, Ar).

2,2-Dimethyl-5-hydroxy-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12d**).

In a similar manner 2,2-dimethyl-5-hydroxy-5-(2'-hydroxyethyl)-1,3-dioxane (**11d**) (533 mg, 3.0 mmoles) was converted to 2,2-dimethyl-5-hydroxy-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane as a pale orange viscous oil (969 mg); tlc essentially a single spot (silica GF, hexane/50% ethyl acetate, ceric sulfate, R_f 0.49); ^{1}H nmr (deuteriochloroform): δ 1.42 (s, 6 H, $[CH_3]_2$), 1.73 (t, 2 H, J = 6.2 Hz, CH_2), 2.45 (s, 3 H, $TsCH_3$), 3.25 (s, 1 H, OH), 3.52 (d, 2 H, J = 11.9 Hz, $[CH_AO]_2$), 3.81 (d, 2 H, J = 11.9 Hz, $[CH_BO]_2$), 4.22 (t, 2 H, J = 6.2 Hz, OCH_2), 7.36 and 7.79 (ABq, 4 H, 8.3 Hz, Ar).

2-Amino-6-benzyloxy-9-[2'-(2,3-dimethyl-1,3-dioxan-5-yl)-ethyl]-9*H*-purine (**14a**) and 2-Amino-6-benzyloxy-7-[2'-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15a**).

A 57% sodium hydride oil dispersion (0.51 g, 12.1 mmoles) was added to a magnetically stirred solution of 2-amino-6-benzyloxypurine (**13**) (1.93 g, 8.0 mmoles) in sieve-dried DMF (25 ml) at 22° under dry nitrogen. When effervescence ceased (20 minutes), a solution of 2,2-dimethyl-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12a**) (2.29 g, 7.3 mmoles) in sieve dried DMF (5 ml) was added and stirring was continued overnight. The reaction mixture was then partitioned between ethyl acetate (200 ml) and water (50 ml). The organic layer was washed with more water (2 x 25 ml), dried (magnesium sulfate), filtered and evaporated at 60°/0.5 mm to give a sticky crystalline residue (2.24 g) which was chromatographed in chloroform/methanol/water, 95:5:0.5, over a 4.2 x 36.5 column of silica gel (200 g), collecting 10 ml fractions which were monitored by tlc (silica GF, chloroform/methanol/water, 95:5:0.5, ceric sulfate. Fractions 52-86 were combined, evaporated, and the residue was recrystallized twice from ethyl acetate to give colorless compact prisms of **14a** (530 mg), mp 157-163°, tlc single spot, R_f 0.57. Repeated crystallization raised the mp to 161-163°, but microanalyses were unsatisfactory. A 30 mg aliquot was finally purified by reverse phase hplc using a Whatman Partisil M20 10/50 ODS-3 column; aqueous 70% methanol, 10 ml/minute, UV monitor at λ 254 nm. The dominant peak at 31 minutes was collected and evaporated at 50°/0.5 mm to give a colorless solid (27 mg) which was crystallized from ethyl acetate to give microprisms (24 mg), mp 163.5-165°; uv (methanol): λ max 211 nm (ϵ 27,700), 250 (8,400), 283 (10,000); ^{1}H nmr (deuteriochloroform): δ 1.41 (s, 6 H, $[CH_3]_2$), 1.75 (m, 1 H, CH), 1.89 (dt, 2 H, J = 7.3 and 7.9 Hz, CH_2), 3.65 (dd, 2 H, J = 7.3 and 11.9 Hz, $[CH_AO]_2$), 3.93 (dd, 2 H, J = 4.1 and 11.9 Hz, CH_BO_2), 4.09 (t, 2 H, J = 7.3 Hz, NCH_2), 4.87 (br s, 2 H, NH_2), 5.57 (s, 2 H, CH_2O); 7.27-7.54 (m, 5 H, Ar), 7.59 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{20}H_{25}N_5O_3$: C, 62.64; H, 6.57; N, 18.27. Found: C, 62.62; H, 6.62; N, 17.98.

Column fractions 87-104 were combined and evaporated. The residue was extracted with hot ethyl acetate (10 x 5 ml) and the insoluble fraction was recrystallized from ethanol to give colorless matted needles of **15a** (284 mg), mp 234-237°; tlc single spot, R_f 0.33; uv (methanol): λ max 211 nm (ϵ 28,200), 295 (7,100), ^{1}H nmr (deuteriochloroform) δ 1.34 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.65 (m, 1 H, CH), 1.77 (dt, 2 H, J = 7.8 Hz, CH_2), 3.41 (dd, 2 H, J = 7.5 and 11.9 Hz, $[CH_AO]_2$), 3.74 (dd, 2 H, J 4.2 and 11.9 Hz, $[CH_BO]_2$), 4.16 (t, 2 H, J = 7.8 Hz, NCH_2), 4.86 (br s, 2 H, NH_2), 5.52 (s, 2 H, CH_2O), 7.43 (m, 5 H, Ar), 7.75 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{20}H_{25}N_5O_3$: C, 62.64; H, 6.57; N, 18.27. Found: C, 62.58; H, 6.29; N, 18.42.

2-Amino-6-benzyloxy-9-[2'-(2,2-dimethyl-5-methoxy-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14b**) and 2-Amino-6-benzyloxy-7-[2'-(2,2-dimethyl-5-methoxy-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15b**).

In a similar manner, 2-amino-6-benzyloxypurine (**13**) (1.43 g, 5.9 mmoles) was alkylated with 2,2-dimethyl-5-methoxy-5-(2'-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12b**) (1.70 g, 4.9 mmoles).

Chromatography and crystallization from ethyl acetate gave **14b** as colorless matted needles (748 mg), mp 174-175°; tlc, single spot R_f 0.40 (silica GF, chloroform/methanol/water, 90:10:1, ceric sulfate; uv (methanol): λ max 210 nm (ε 27,000), 249 (8,880), 283 (10,600); ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3); 1.44 (s, 3 H, CH_3), 2.12 (m, 2 H, CH_2), 3.36 (s, 3 H, OCH_3), 3.70 (d, 2 H, J = 12.1 Hz, $[CH_AO]_2$), 3.82 (d, 2 H, J = 12.1 Hz, $[CH_BO]_2$), 4.12 (m, 2 H, NCH_2), 4.86 (br s, 2 H, NH_2), 5.57 (s, 2 H, OCH_2), 7.32-7.54 (m, 5 H, Ar), 7.62 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58; N, 16.94. Found: C, 61.02; H, 6.51; N, 17.04.

Similarly, **15b** was obtained as colorless compact prisms (357 mg) mp 147-149°; tlc, single spot R_f 0.26; uv (methanol): λ max 211 nm (ε 29,500), 295 (7,000); ^{1}H nmr (deuteriochloroform): δ 1.29 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.99 (m, 2 H, CH_2), 3.12 (s, 3 H, OCH_3), 3.50 (d, 2 H, J = 12.2 Hz, $[CH_AO]_2$), 3.68 (d, 2 H, J = 12.2 Hz, $[CH_BO_2]$), 4.20 (m, 2 H, NCH_2), 4.92 (br s, 2 H, NH_2), 5.53 (s, 2 H, OCH_2), 7.27-7.50 (m, 5 H, Ar), 7.77 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58; N, 16.94. Found: C, 61.04; H, 6.59; N, 16.66.

2-Amino-6-benzyloxy-9-[2′-(2,2-dimethyl-5-fluoro-1,3-dioxan-5-yl)-ethyl]-9*H*-purine (**14c**) and 2-Amino-6-benzyloxy-7-[2′(2,2-dimethyl-5-fluoro-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15c**).

In a similar manner, 2-amino-6-benzyloxypurine (**13**) (3.25 g, 13.5 mmoles) was alkylated with 2,2-dimethyl-5-fluoro-5-(2-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12c**) (8.73 g, 11.2 mmoles). In this case, the original aqueous washings were back extracted with ethyl acetate which recovered approximately 20% of the calculated weight. Chromatography and crystallization from ethyl acetate/trace dichloromethane gave colorless prisms of **14c** (1.69 g), mp 186-188°; tlc single spot, R_f 0.53 (silica GF, chloroform/methanol/water, 90:10:1, ceric sulfate; uv (methanol): λ max 212 nm (ε 29,600), 249 (8,400), 284 (9,800); ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.19 (dm, 2 H, J_{HF} = 19.8 Hz, CH_2), 3.80 (dd, 2 H, J_{HH} = 12.6 Hz, J_{HF} = 24.3 Hz, $[CH_AO]_2$), 3.86 (dd, 2 H, J_{HH} = 12.6 Hz, J_{HF} = 14.6 Hz, $[CH_BO]_2$), 4.22 (m, 2 H, NCH_2), 4.87 (s, 2 H, NH_2), 5.57 (s, 2 H, OCH_2), 7.30-7.53 (m, 5 H, Ar), 7.61 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{20}H_{24}FN_5O_3$: C, 59.84; H, 6.03; F, 4.73; N, 17.45. Found: C, 59.86; H, 6.02; F, 4.93; N, 17.48.

Similarly **15c** was obtained as colorless, matted needles (945 mg), mp 237-239°; tlc single spot, R_f 0.33; uv (methanol): λ max 211 nm (ε 30,600), 295 (6,500); ^{1}H nmr (deuteriochloroform): δ 1.27 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.04 (dm, 2 H, J_{HF} = 19.0 Hz, CH_2), 3.51 (dd, 2 H, J_{HH} = 12.8 Hz, J_{HF} = 25.7 Hz, $[CH_AO]_2$), 3.69 (dd, 2 H, J_{HH} = 12.8 Hz, J_{HF} = 13.3 Hz, $[CH_BO]_2$), 4.29 (m, 2 H, NCH_2), 4.88 (s, 2 H, NH_2), 5.53 (s, 2 H, OCH_2), 7.38-7.50 (m, 5 H, Ar), 7.78 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{20}H_{24}FN_5O_3$: C, 59.84; H, 6.03; F, 4.73; N, 17.45. Found: C, 60.02; H, 5.89; F, 5.03; N, 17.66.

2-Amino-6-benzyloxy-9-[2′-(2,2-dimethyl-5-hydroxy-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14d**).

Similarly, 2-amino-6-benzyloxypurine (**13**) (803 mg, 3.3 mmoles) was alkylated with 2,2-dimethyl-5-hydroxy-5-(2-*p*-toluenesulphonyloxyethyl)-1,3-dioxane (**12d**) (1.0 g, 3.0 mmoles). The crude product (783 mg) was purified by reverse phase hplc using a Whatman Partisil M20 10/50 ODS-3 column; 60% aqueous methanol: 10 ml/minute uv monitor at 260 nm. Five consecutive injections of 150 mg in 2.0 mg of 60% aqueous methanol were made interspersed with column regeneration with 100% methanol. The combined product fractions (49 minute peak) were evaporated at 60°/0.5 mm and the residue was recrystallized twice from ethanol to give colorless platelets of **14d** (184 mg), mp 176-178°; tlc single spot R_f 0.49 (silica GF, chloroform/methanol/water, 90:10:1, ceric sulfate; λ max 211 nm (ε 30,500), 249 (8,900), 283 (10,600); ^{1}H nmr (deuteriochloroform): δ 1.42 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.95 (t, 2 H, J = 7.5 Hz, CH_2), 3.54 (d, 2 H, J = 11.4 Hz, $[CH_AO]_2$), 3.75 (d, 2 H, J = 11.4 Hz, $[CH_BO]_2$), 3.76 (s, 1 H, OH), 4.24 (t, 2 H, J = 7.5 Hz, NCH_2), 4.87 (br s, 2 H, NH_2), 5.58 (s, 2 H, OCH_2), 7.37-7.52 (m, 5 H, Ar), 7.63 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{20}H_{25}N_5O_4$: C, 60.13; H, 6.31; N, 17.53. Found: C, 60.16; H, 6.34; N, 17.59.

2-Amino-1,9-dihydro-9-(4′-hydroxy-3′-hydroxymethyl)butyl-6-oxo-6*H*-purine (**5a**).

2-Amino-6-benzyloxy-9-[2′-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14a**) (443 mg, 1.16 mmoles) was dissolved in hot methanol (9 ml) and treated with aqueous *N* hydrochloric acid (2.31 ml). The clear solution was boiled on the steam bath for 10 minutes, removing most of the methanol. The cold solution was filtered from traces of insolubles, and was then neutralized by adding aqueous 2.5 *N* sodium hydroxide to *p*H 7.0. The resultant precipitate was filtered off, washed with water (1 ml), with ethanol (1 ml), dried at 23°/0.5 mm and obtained as a colorless crystalline powder (232 mg), mp 270-276° dec. Recrystallization twice from water gave **5a** as colorless matted needles (156 mg), mp 272-275° dec.

2-Amino-1,9-dihydro-9-(4′-hydroxy-3′-hydroxymethyl-3′-methoxy)-butyl-6-oxo-6*H*-purine (**5b**).

Similarly, 2-amino-6-benzyloxy-9-2′-(2,2-dimethyl-5-methoxy-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14b**) (600 mg, 1.45 mmoles) was hydrolysed to **5b** (397 mg), mp 278-283° dec. Recrystallization of a portion (53 mg) twice from water gave colorless microprisms (31 mg) mp 282-284° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 213 nm (ε 22,560) 255 (9,700), 268 (10,500); ^{1}H nmr (deuterium oxide): δ 2.06 (t, 2 H, J = 7.8 Hz, CH_2), 3.25 (s, 3 H, OCH_3), 3.63 (d, 2 H, J = 12.2 Hz, $[CH_AO)_2]$), 3.68 (d, 2 H, J = 12.2 Hz, $[CH_BO)_2]$), 4.18 (t, 2 H, J = 7.8 Hz, NCH_2), 7.85 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.63; H, 6.05; N, 24.72. Found: C, 46.87; H, 6.22; N, 24.56.

2-Amino-1,9-dihydro-9-(3′-fluoro-4′-hydroxy-3′-hydroxymethyl)-butyl-6-oxo-6*H*-purine (**5c**).

Similarly, 2-amino-6-benzyloxy-9-[2′-(2,2-dimethyl-5-fluoro-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14c**) (1.38 g, 3.44 mmoles) was hydrolysed to **5c** (875 mg), mp 256-275° dec. All of it was crystallized from water (45 ml) to give colorless matted needles (771 mg) mp 274-277° dec; uv (aqueous 0.01*N* sodium hydroxide) λ max 215 nm (ε 19,400), 256 (10,600), 268 (11,200); ^{1}H nmr (deuterium oxide): δ 2.28 (dt, 2 H, J_{HH} = 7.7 Hz, J_{HF} = 19.3 Hz, CH_2), 3.75 (d, 4 H, J_{HF} = 19.2 Hz, $[CH_2O]_2$), 4.26 (t, 2 H, J = 7.7 Hz, NCH_2), 7.85 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{10}H_{14}FN_5O_3$: C, 44.28; H, 5.20; F, 7.00; N, 25.82. Found: C, 44.62; H, 5.17; F, 7.10; N, 25.69.

2-Amino-1,9-dihydro-9-(3′,4′-dihydroxy-3′-hydroxymethyl)butyl-6-oxo-6*H*-purine (**5d**).

Similarly, 2-amino-6-benzyloxy-9-[2′-(2,2-dimethyl-5-hydroxy-1,3-dioxan-5-yl)ethyl]-9*H*-purine (**14d**) (170 mg, 0.43 mmole) was

hydrolysed to **11d** (108 mg) mp 270-282° dec. Recrystallization twice from water gave colorless microcrystals (80 mg) mp 287-290° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 212 nm (ε 23,200), 255 (10,100), 268 (11,000); ^{1}H nmr (deuterium oxide): δ 2.06 (t, 2 H, *J* = 8 Hz, CH_2), 3.58 (s, 4 H, $[CH_2O]_2$), 4.22 (t, 2 H, *J* = 8 Hz, NCH_2), 7.85 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{10}H_{15}N_5O_4$: C, 44.60; H, 5.62; N, 26.01. Found: C, 44.32; H, 5.57; N, 25.74.

2-Amino-1,7-dihydro-7-(4'-hydroxy-3'-hydroxymethyl)butyl-6-oxo-6*H*-purine (**16a**).

Similarly, 2-amino-6-benzyloxy-7-[2'-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15a**) (280 mg, 0.73 mmole) was hydrolysed to **16a** forming colorless microneedles (143 mg) mp 300-304° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 217 nm (ε 19,000), 280 (6,800); ^{1}H nmr (deuterium oxide): δ 1.65 (heptet, 1 H, *J* = 6 Hz, CH), 1.90 (dt, 2 H, *J* = 6 and 7 Hz, CH_2), 3.61 (d, 4 H, *J* = 5.6 Hz, $[CH_2O]_2$), 4.36 (t, 2 H, *J* = 7 Hz, NCH_2), 7.99 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{10}H_{15}N_5O_3$: C, 47.43; H, 5.97; N, 27.65. Found: C, 47.57; H, 6.06; N, 27.40.

2-Amino-1,7-dihydro-7-(4'-hydroxy-3'-hydroxymethyl-3'-methoxy)-butyl-6-oxo-6*H*-purine (**16b**).

Similarly, 2-amino-6-benzyloxy-7-[2'-(2,2-dimethyl-5-methoxy-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15b**) (257 mg, 0.62 mmole) was hydrolysed to **16b** (158 mg) mp 294-306° dec. Recrystallization of a portion (30 mg) from water gave colorless microprisms (25 mg) mp 305-308° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 214 nm (ε 22,400), 280 (7,000); ^{1}H nmr (deuterium oxide): δ 2.10 (t, 2 H, *J* = 7.9 Hz, CH_2), 3.28 (s, 3 H, OCH_3), 3.62 (d, 2 H, *J* = 12.3 Hz, $[CH_AO]_2$), 3.68 (d, 2 H, *J* = 12.3 Hz, $[CH_BO]_2$), 4.37 (t, 2 H, *J* = 7.9 Hz, NCH_2), 8.00 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.63; H, 6.05; N, 24.72. Found: C, 46.72; H, 5.89; N, 24.62.

2-Amino-1,7-dihydro-7-(3'-fluoro-4'-hydroxy-3'-hydroxymethyl)-butyl-6-oxo-6*H*-purine (**16c**).

Similarly, 2-amino-6-benzyloxy-7-[2'-(2,2-dimethyl-5-fluoro-1,3-dioxan-5-yl)ethyl]-7*H*-purine (**15c**) (830 mg, 2.1 mmoles) was hydrolysed to **16c** (533 mg) mp 273-278°. Recrystallization from water gave colorless microprisms (448 mg) mp 286-289° dec; uv (aqueous 0.01*N* sodium hydroxide): λ max 213 nm (ε 24,200), 280 (7,300); ^{1}H nmr (deuterium oxide): δ 2.32 (dt, 2 H, J_{HH} = 7.6 Hz, J_{HF} = 19.0 Hz, CH_2), 3.74 (d, 4 H, J_{HF} = 19.6 Hz, $[CH_2O]_2$), 4.46 (t, 2 H, *J* = 7.6 NCH_2), 8.01 (s, 1 H, C_8-H).

Anal. Calcd. for $C_{10}H_{14}FN_5O_3$: C, 44.28; H, 5.20; F, 7.00; N, 25.82. Found: C, 44.72; H, 5.23; F, 6.98; N, 25.83.

cis/*trans*-5-Allyl-2-chloro-1,3,2-dioxaphosphorinane (**17**).

2-Allylpropane-1,3-diol (**4a**) (20.0 g, 0.17 mole) and sieve-dried triethylamine (34.84 g, 0.34 mole) were mixed, then ether was added to a solution volume of 100 ml. Freshly distilled phosphorus trichloride (23.65 g , 0.17 mole) was similarly dissolved in ether to a volume of 100 ml. The two solutions were added simultaneously, at the same rate, to more ether (400 ml) with vigorous mechanical stirring at 0° (ice bath) under dry nitrogen. Time of addition was 1 hour, with the mixture becoming a thick slurry of triethylamine hydrochloride. After 30 more minutes of stirring at 0°, the mixture was filtered; the precipitate was washed with ether and the combined filtrates were evaporated to give a colorless oil (31.88 g). Distillation gave 18.72 g, bp 53-61°/0.50 mm. Re-distillation through a short column gave 16.14 g, bp 42-44°/0.15 mm, $n_D^{25°}$ 1.4892; ^{1}H nmr (deuteriochloroform): approximately 2.9:1 *cis*:*trans* mixture; *cis* δ 1.92 (m, 2 H, $-CH_2-$), 2.45 (m, 1 H, -CH), 4.00 (m, 2 H, $[OCH_A]_2$), 4.25 (m, 2 H, $[OCH_B]_2$), 5.14 (m, 2 H, $CH_2=$), 5.72 (m, 1 H, =CH-); *trans* δ 1.77 (m, 1 H, -CH), 2.56 (m, 2 H, $-CH_2$), 3.90 (m, 2 H, $[OCH_A]_2$), 4.78 (m, 2 H, $[OCH_B]_2$), 5.14 (m, 2 H, $CH_2=$), 5.72 (m, 1 H, =CH-).

Anal. Calcd. for $C_6H_{10}ClO_2P$: C, 39.90; H, 5.58; Cl, 19.64. Found: C, 39.95; H, 5.55; Cl, 19.24.

cis/*trans*-5-Allyl-2-benzyloxy-1,3,2-dioxaphosphorinane (**18**).

A solution of 5-allyl-2-chloro-1,3,2-dioxaphosphorinane (**17**) (10.00 g, 55.4 mmoles) in anhydrous ether (50 ml) was added dropwise in 10 minutes to a magnetically stirred solution of benzyl alcohol (6.28 g, 58.1 mmoles) and sieve-dried triethylamine (5.60 g, 55.4 mmoles) in anhydrous ether (200 ml) at 0° (ice bath) under dry nitrogen. The ice bath was removed and stirring continued for 30 minutes. Precipitated triethylamine hydrochloride was filtered off and washed with anhydrous ether (2 x 100 ml). The ethereal filtrates were combined and evaporated to give **18** as a colorless oil (14.50 g); ^{1}H nmr (deuteriochloroform): approximately 1:3.3 *cis*:*trans* mixture; *cis* δ 1.80 (m, 2 H, $-CH_2-$), 2.35 (m, 1 H, -CH), 3.76 (m, 2 H, $[OCH_A]_2$), 4.04 (m, 2 H, $[OCH_B]_2$), 4.85 (d, 2 H, *J* = 9 Hz, OCH_2Ph), 5.08 (m, 2 H, $CH_2=$), 5.71 (m, 1 H, =CH-), 7.39 (m, 5 H, Ph); *trans* δ 1.62 (m, 1 H, -CH), 2.54 (m, 2 H, $-CH_2-$), 3.63 (m, 2 H, $[OCH_A]_2$), 4.55 (m, 2 H, $[OCH_B]_2$), 4.88 (d, 2 H, *J* = 9 Hz, OCH_2Ph), 5.08 (m, 2 H, $CH_2=$), 5.71 (m, 1 H, =CH-), 7.39 (m, 5 H, Ph). This product, particularly the *trans* component, tended to decompose on chromatography over silica gel and was accordingly used directly in the next stage.

cis/*trans*-2-Benzyloxy-5-(2'-hydroxyethyl)-1,3,2-dioxa-2-oxophosphorinane (**19**).

Cis/*trans*-5-allyl-2-benzyloxy-1,3,2-dioxaphosphorinane (**18**) (14.50 g) was dissolved in acetonitrile (280 ml) and the solution was cooled to 0° in an ice bath. A stream of oxygen/ozone from a Welsbach T816 generator (approximately 0.7 mmole ozone/minute) was bubbled through the solution *via* a fine porosity gas inlet tube. After 2 hours 35 minutes, wet starch/potassium iodide paper gave a strong reaction for ozone in the effluent gas. The system was degassed with nitrogen for 10 minutes, then an excess of dimethyl sulfide (8.2 ml) was added and the solution was allowed to warm to room temperature for 30 minutes. Sodium borohydride (2.10 g) was added in portions in 2 minutes to the magnetically stirred solution at 23°, and stirring was continued for 30 minutes. The mixture was cooled to 0° and was treated rapidly dropwise with a saturated solution of sodium chloride in aqueous *N* hydrochloric acid (50 ml) with vigorous stirring. The organic supernatant was separated and the aqueous phase (*p*H 5) was extracted with ether (3 x 50 ml). The ether and acetonitrile solutions were combined, dried (magnesium sulfate), and evaporated at 60°/1 mm to give a viscous oil (19 g) which was chromatographed over silica gel (380 g) in ethyl acetate/0-5% methanol. The eluate was monitored by tlc (silica GF, chloroform/methanol/water, 90:10:1, ceric sulfate, and appropriate fractions (R_f 0.39) were combined and evaporated to give a viscous oil, (**19**) (7.00 g); ^{1}H nmr (deuteriochloroform): approximately 1:2.7 *cis*/*trans* mixture; *cis* δ 1.34 (dt, 2 H, *J* = 6 and 6 Hz, CH_2), 2.53 (m, 1 H, -CH), 3.63 (t, 2 H, *J* = 6 Hz, OCH_2), 3.98 (dd, 2 H, *J* = 11 and 11 Hz, $[OCH_A]_2$), 4.38 (m, 2 H, $[OCH_B]_2$), 5.10 (d, 2 H, *J* = 8 Hz, OCH_2Ph), 7.41 (m, 5 H, Ph); *trans* δ 1.86 (dt, 2 H, *J* = 6 and 6 Hz, CH_2), 2.06 (m, 1 H, -CH), 3.71 (t, 2 H, *J* = 6 Hz, OCH_2), 4.24 (ddd,

2 H, J = 3.5, 11.5, and 18.5 Hz, $[OCH_A]_2$), 4.38 (m, 2 H, $[OCH_B]_2$), 5.10 (d, 2 H, J = 8 Hz, OCH_2Ph), 7.41 (m, 5 H, Ph).

Anal. Calcd. for $C_{12}H_{17}O_5P$: C, 52.94; H, 6.29. Found: C, 52.59; H, 6.44.

Chromatography (silica gel, 30:1) using ethyl acetate alone gave a long tailing chromatogram with pure *trans* **19** in the later fractions.

trans-Diaxial-2-benzyloxy-5-(2′-*p*-toluenesulphonyloxyethyl)-1,3,2-dioxa-2-oxophosphorinane (**20**).

Recrystallized *p*-toluenesulphonyl chloride (5.03 g, 26.3 mmoles) was dissolved in a solution of *cis*/*trans*-2-benzyloxy-5-(2′-hydroxyethyl)-1,3,2-dioxa-2-oxophosphorinane (**19**) (6.00 g, 22.0 mmoles) in sieve-dried pyridine (24 ml) at 0°. *p*-Dimethylaminopyridine (DMAP) (2.69 g, 22.0 mmoles) was also dissolved in the reaction solution which was left at 0° for 2 hours. DMAP.HCl was then filtered off and the solution was evaporated at 50°/1 mm to remove most of the pyridine. The residue was dissolved in ethyl acetate (100 ml) and was washed in sequence with 20 ml portions of water, aqueous *N* hydrochloric acid, and fresh aqueous 5% sodium bicarbonate. The solution was dried over magnesium sulfate, filtered and evaporated at 50°/1 mm to give a viscous oil (6.13 g). Trituration with ethanol induced crystallization. The solids were filtered off, washed with ethanol (2 x 4 ml), dried at 22°/1 mm and *trans* diaxial **20** was obtained as a colorless powder (1.77 g), mp 114-120°. Evaporation of the filtrates gave a viscous oil (4.48 g) which was chromatographed in ethyl acetate over silica gel. The eluate was monitored by tlc (silica GF, ethyl acetate cerous sulfate) and appropriate fractions (R_f 0.63) were combined and evaporated to give *cis*/*trans* **20** (approximately 4:3) as a viscous oil (1.23 g). A portion (270 mg) of *trans* diaxial **20** was recrystallized twice from ethanol to give matted needles (217 mg), mp 118-121° with recrystallization and remelting at 126-128°; ^{1}H nmr (deuteriochloroform): δ 2.03 (t, 2 H, J = 5 Hz, CH_2), 2.06 (m, 1 H, -CH), 2.47 (s, 3 H, CH_3), 4.12 (dd, 2 H, J_{HH} = 11 Hz, J_{HP} = 21 Hz, $[OCH_A]_2$), 4.14 (t, 2 H, J = 5 Hz, CH_2OTs), 4.36 (dd, 2 H, J_{HH} = 11 Hz, J_{HP} = 3 Hz, $[OCH_B]_2$), 5.11 (d, 2 H, J = 8 Hz, $POCH_2Ph$), 7.37 and 7.78 (ABq, 4 H, J = 8 Hz, Ts), 7.41 (m, 5 H, Ph).

Anal. Calcd. for $C_{19}H_{23}O_7PS$: C, 53.51; H, 5.44. Found: C, 53.32; H, 5.34.

Assignments for *cis* **20** were made differentially with the *cis*/*trans* mixture: δ 1.52 (dt, 2 H, J = 6 and 6 Hz, CH_2), 2.15 (m, 1 H, -CH), 2.47 (s, 3 H, CH_3), 3.92 (m, 2 H, $[OCH_A]_2$), 4.04 (t, 2 H, J = 6 Hz, CH_2OTs), 4.28 (m, 2 H, $[OCH_B]_2$), 5.11 (d, 2 H, J = 8 Hz, OCH_2Ph), 7.37 and 7.78 (ABq, 4 H, J = 8 Hz, Ts), 7.41 (m, 5 H, Ph).

trans-5-[2′-(2-Amino-6-benzyloxy-9*H*-purin-9-yl)ethyl]-2-benzyloxy-1,3,2-dioxa-2-oxophosphorinane (**21**) and *trans*-5-[2′-(2-Amino-6-benzyloxy-7*H*-purin-7-yl)ethyl]-2-benzyloxy-1,3,2-dioxa-2-oxophosphorinane (**22**).

In a manner analogous to the preparation of **14a** and **15a**, 2-amino-6-benzyloxypurine (**13**) (0.848 g, 3.5 mmoles) was alkylated with *trans*-2-benzyloxy-5-(2′-*p*-toluenesulphonyloxyethyl)-1,3,2-dioxa-2-oxophosphorinane (**20**) (1.5 g, 3.5 mmoles). Reaction time was cut to 2 hours 30 minutes and the usual work up gave the crude product as a gum (1.292 g) which was chromatographed in chloroform/0-10% methanol over a 2.5 x 24.7 cm column of silica gel (52 g). The eluate was monitored by tlc (silica GF, chloroform/methanol/water, 80:20:2, ceric sulfate). Appropriate fractions were combined, evaporated, and the residue was crystallized from ethanol to give **21** as colorless prisms (511 mg), mp 161-165°; tlc single spot R_f 0.63; 50 mg was recrystallized to give 43 mg, mp 162-165°; uv (methanol): λ max 210 nm (ϵ 36,000), 248 (9,100), 284 (10,700); ^{1}H nmr (deuteriochloroform): δ 1.57 (m, 1 H, -CH), 2.20 (dt, 2 H, J = 6.8 and 6.8 Hz, CH_2), 4.15 (t, 2 H, J = 6.8 Hz, NCH_2), 4.22-4.34 (m, 4 H, $[OCH_2]_2$), 4.99 (s, 2 H, NH_2), 5.33 (d, 2 H, J = 8.2 Hz, $POCH_2Ph$), 5.54 (s, 2 H, OCH_2Ph), 7.28-7.51 (m, 10 H, Ph_2), 7.59 (s, 1 H, C_8-H); high resolution ms: m/e 495.1663 (M^+ Calcd. 495.1672).

Anal. Calcd. for $C_{24}H_{26}N_5O_5P$: C, 58.18; H, 5.29; N, 14.54. Found: C, 58.08; H, 5.31; N, 14.26.

More polar column fractions gave colorless microprisms of **22** (112 mg), mp 73-78°; tlc single spot R_f 0.54, which were recrystallized from ethanol to give 94 mg, mp 75-78° with recrystallization and remelting 110-116°; uv (methanol): λ max 212 nm (ϵ 33,600), 295 (6,700); ^{1}H nmr (deuteriochloroform): δ 1.45 (m, 1 H, -CH), 2.08 (dt, 2 H, J = 7.2 and 7.2 Hz, CH_2), 3.92 (ddd, 2 H, J_{HH} = 11.5 and 1 Hz, J_{HP} = 20 Hz, $[OCH_A]_2$), 4.15 (m, 2 H, J_{HH} = 11.5 and $<$1 Hz, J_{HP} = 4 Hz, $[OCH_B]_2$), 4.20 (t, 2 H, J = 7.2 Hz, NCH_2), 5.08 (d, 2 H, J = 8 Hz, $POCH_2Ph$), 5.26 (s, 2 H, NH_2), 5.47 (s, 2 H, OCH_2Ph), 7.34-7.43 (m, 10 H, Ph_2), 7.77 (s, 1 H, C_8-H); high resolution ms: m/e 495.1663 (M^+ Calcd. 495.1672) and 585.2154 ($C_{31}H_{32}N_5O_5P$ Calcd. 585.2141).

Anal. Calcd. for $C_{24}H_{26}N_5O_5P$: C, 58.18; H, 5.29; N, 14.54. Found: C, 58.38; H, 5.40; N, 14.29.

5-[2′-(2-Amino-1,9-dihydro-6-oxo-6*H*-purin-9-yl)ethyl]-1,3,2-dioxa-2-oxophosphorinane Sodium Salt (**23**).

Twenty percent palladous hydroxide on carbon catalyst (100 mg) was added to a solution of 5-[2′-(2-amino-6-benzyloxy-9*H*-purin-9-yl)ethyl]-2-benzyloxy-1,3,2-dioxa-2-oxophosphorinane (*trans* **21**) (460 mg) in methanol (30 ml), and the mixture was hydrogenated at 23° and atmospheric pressure for 3 hours. Insoluble product and catalyst was filtered on to a pad of Fisher Celite analytical filter aid, which was washed with more methanol (3 x 5 ml). The product was extracted with fresh aqueous 3% sodium bicarbonate (2 x 5 ml) and water (2 x 5 ml). The clear aqueous filtrate was evaporated at 40°/0.5 mm to 5.0 ml and repetitive 1.0 ml injections were made on a Whatman Partisil M20 10/50 ODS-3 reverse phase column using aqueous 1% tetrahydrofuran as mobile phase at 10 ml/minute. The eluate was monitored off-peak at 295 nm and the product was collected as a dominant peak at approximately 15 to 17 minutes. The combined product fractions were lyophilised to give **19** as a colorless powder (265 mg); uv (aqueous 0.01*N* sodium hydroxide): λ max 211 nm (ϵ 23,900), 255 (9,900), 268 (10,700); ^{1}H nmr (deuterium oxide): δ 1.95 (m, 1 H, -CH), 1.95 (t, 2 H, J = 6 Hz, CH_2), 4.09 (ddd, 2 H, J = 5, 11.5 and 11.5 Hz, $[OCH_A]_2$), 4.17 (t, 2 H, J = 6 Hz, NCH_2), 4.33 (ddd, 2 H, J = 2, 11.7 and 11.7 Hz, $[OCH_B]_2$), 7.97 (broad s, 1 H, C_8-H).

Anal. Calcd. for $C_{10}H_{13}N_5O_5PNa \cdot 0.4\ H_2O$: C, 34.87; H, 4.04; N, 20.34. Found: C, 35.09; H, 4.26; N, 20.45.

Acknowledgement.

We thank Mrs. J. T. Wu, Mrs. J. E. Perkins and Mr. M. Valenciano for the elemental analyses.

REFERENCES AND NOTES

† West Point, Pa.

†† Present address: Squibb Institute for Medical Research,

Princeton, NJ 08540.

[1] Chung K. Chu and Stephen J. Cutler, *J. Heterocyclic Chem.*, **23**, 289 (1986).

[2] U. K. Pandit, W. F. A. Grose and T. A. Eggelte, *Synth. Commun.*, **2**, 345 (1972).

[3] M. A. Tippie, J. C. Martin, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, *Nucleosides and Nucleotides*, **3**, 525 (1984).

[4] M. R. Harnden and R. L. Jarvest, *Tetrahedron Letters*, **26**, 4265 (1985).

[5] M. MacCoss, A. Chen and R. L. Tolman, *Tetrahedron Letters*, **26**, 1815 (1985).

[5a] J. P. Springer and (the late) J. Hirshfield, unpublished results, Merck, Sharp and Dohme Research Laboratories.

[6] W. T. Ashton, L. F. Canning, G. F. Reynolds, R. L. Tolman, J. D. Karkas, R. Liou, M. M. Davies, C. M. DeWitt, H. C. Perry and A. K. Field, *J. Med. Chem.*, **28**, 926 (1985).

[7] R. L. Tolman, A. K. Field, J. D. Karkas, A. F. Wagner, J. Germershausen, C. Crumpacker and E. M. Scolnick, *Biochem. Biophys. Res. Commun.*, **128**, 1329 (1985).

[7a] J. Germershausen, R. Bostedor, R. Liou, A. K. Field, M. MacCoss, R. L. Tolman and J. D. Karkas, *Antimicrob. Agents Chemother.*, **29**, 1025 (1986).

[8] G. O. Morton, J. E. Lancaster, G. E. Van Lear, W. Fulmar and W. E. Meyer, *J. Amer. Chem. Soc.*, **91**, 1535 (1967).

[9] As this paper was being written, the synthesis of **5c** by a different route was published: S. Bailey and M. R. Harnden, *J. Chem. Soc., Perkin Trans. 1.*, 2767 (1988).

[10] D. E. Ames and R. E. Bowman, *J. Chem Soc.*, 1079 (1951).

[11] M. S. Kharasch and G. Büchi, *J. Org. Chem.*, 84 (1949).