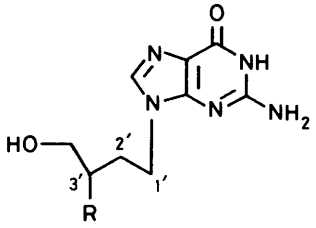
Analogues of the Antiviral Acyclonucleoside 9-(4-Hydroxy-3-hydroxymethylbutyl)guanine. Part 3.[1] Modification of a 3'-Hydroxymethyl Group

Michael R. Harnden and Richard L. Jarvest*
Beecham Pharmaceuticals Research Division, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ

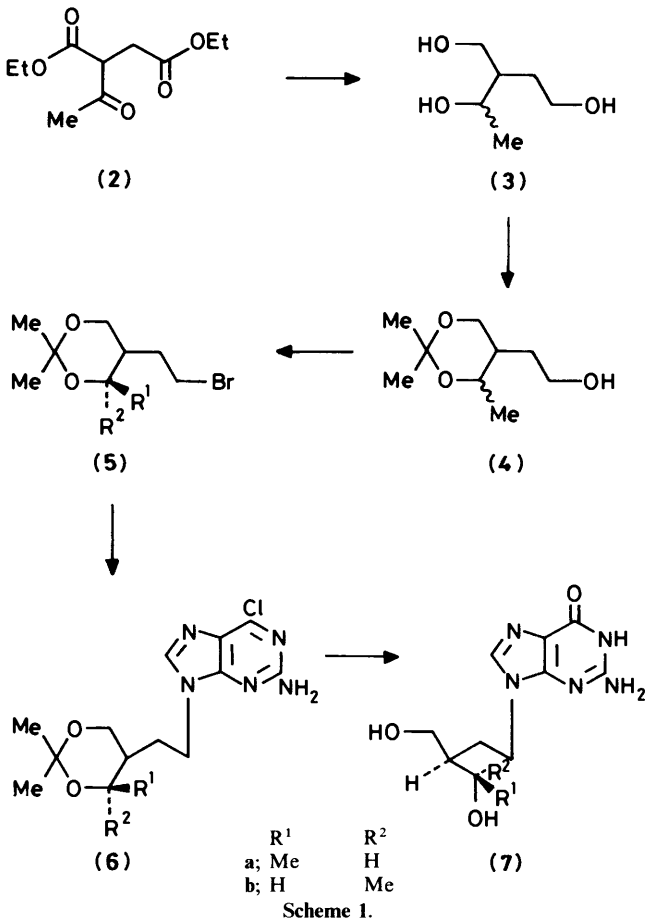
Syntheses of 3'-hydroxymethyl modified analogues of the potent antiviral agent 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**1c**) are described. These include methyl homologues (**7a, b**), chain-extended compounds such as the methylene homologue (**16**) and hydroxyalkyl ethers (**26b, c**), and methoxy (**26a**), bromo (**28**), azido (**29**), amino (**30**), and formamido (**31**) substituted analogues. Compounds (**7a, b**), (**16**), and (**26a—c**) were prepared by construction of an appropriately functionalised alkyl unit followed by purine alkylation and deprotection, whereas compounds (**28**)—(**31**) were prepared by selective modification of (**1c**). The formamido analogue (**31**) showed moderate anti-herpes virus activity and compounds (**16**), (**26b**), and (**29**) weak activity.

Certain 9-(4-hydroxybutyl)guanines (**1**) show potent and selective anti-herpes virus activity and have undergone extensive evaluation during the past few years. 9-(4-Hydroxybutyl)guanine (**1a**) itself exhibits quite high anti-herpes virus activity *in vitro*[2] but, due to poor pharmacokinetics and its inability to compete with endogenous thymidine, it is ineffective *in vivo*.[2,3] 9-(3,4-Dihydroxybutyl)guanine (DHBG) (**1b**) is somewhat more active and has been extensively investigated as an antiviral agent both *in vitro* and *in vivo*.[3–5] The anti-herpes virus activity of 9-(4-hydroxy-3-hydroxymethylbutyl)guanine



(**1**)
R
a; H
b; OH
c; CH_2OH

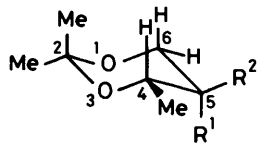
(**1c**) has been noted by us[6–8] and by others[9–11] and we have found that this compound is substantially more potent than DHBG. The increasing anti-herpes virus activity of the series (**1a**) to (**1c**) encouraged us to synthesize and evaluate the antiviral activity of compounds (**1**) in which the group R is further modified or extended. The synthesis of analogues of (**1c**) substituted at the positions designated as C-1', C-2', and C-3' of the alkyl chain is described in Parts 1 and 2 of this series of publications.[1,12]



Scheme 1.

Results and Discussion

The methyl homologues (**7a**) and (**7b**) were prepared by a route similar to the one that we have reported for the synthesis of (**1c**).[13] In this case diethyl acetylsuccinate (**2**) (Scheme 1) was reduced to the triol (**3**) in quantitative yield with methanol-activated sodium borohydride in t-butyl alcohol. Protection of the 1,3-diol system with the isopropylidene group was not selective and (**4**) was obtained in 19% yield as a mixture of *cis* and *trans* isomers. The alcohol (**4**) was brominated with carbon tetrabromide and triphenylphosphine in *N,N*-dimethylformamide (DMF) and column chromatography afforded the pure *cis* (**5a**) (32%) and *trans* (**5b**) (33%) isomers. Assignment of the stereochemistry of the isomers was made on the basis of their 270 MHz ^{1}H n.m.r. spectra; the relevant coupling constants are shown in the Table, along with the derived structures and conformations of the isomers. The conformation is dictated by the transannular axial steric interactions of 2-Me, 6-H and the 4-axial substituent so that both (**5a**) and (**5b**) have the methyl group equatorial. The bromoethyl group is then equatorial in (**5b**) (two axial-axial couplings to 5-H), which is thus the *trans* isomer, and it is axial in (**5a**) (no axial-axial coupling to 5-H), which is thus the *cis* isomer.



(5)

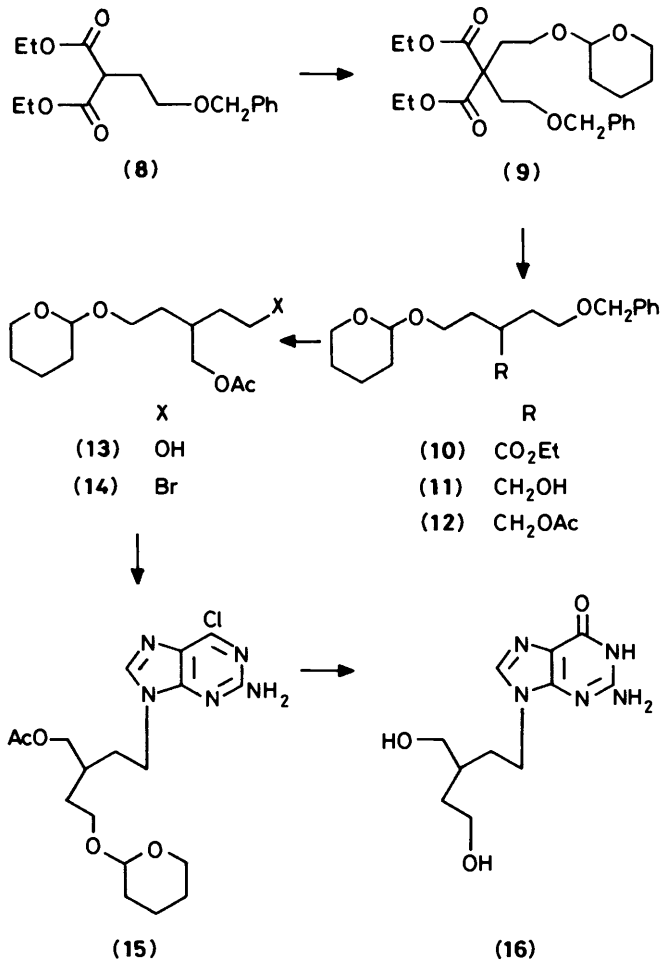
5a; $R^1 = CH_2CH_2Br$, $R^2 = H$ **b**; $R^1 = H$, $R^2 = CH_2CH_2Br$

Table. Selected ^1H n.m.r. parameters and conformation and stereochemistry of (**5a**) and (**5b**)

	δ	^3J	δ	^3J
6-H_{eq}	4.02	1.7 Hz (*eq-eq*)	3.85	4.9 Hz (*eq-ax*)
6-H_{ax}	3.75	1.4 Hz (*ax-eq*)	3.57	10.4 Hz (*ax-ax*)
4-H_{ax}	4.22	2.4 Hz (*ax-eq*)	3.70	9.7 Hz (*ax-ax*)

The bromides (**5**) were used to alkylate 2-amino-6-chloropurine in the presence of potassium carbonate in DMF to afford the 9-alkylated purines (**6a**) (60% yield) and (**6b**) (56% yield). Heating of (**6a**) and (**6b**) in dilute hydrochloric acid hydrolysed both the 6-chloro function and the isopropylidene protecting group to yield the desired guanines (**7a**) (86% yield) and (**7b**) (83% yield).

Synthesis of the methylene extended analogue (**16**) commenced from the malonate (**8**)[6] (Scheme 2). Tetrahydropyranyl



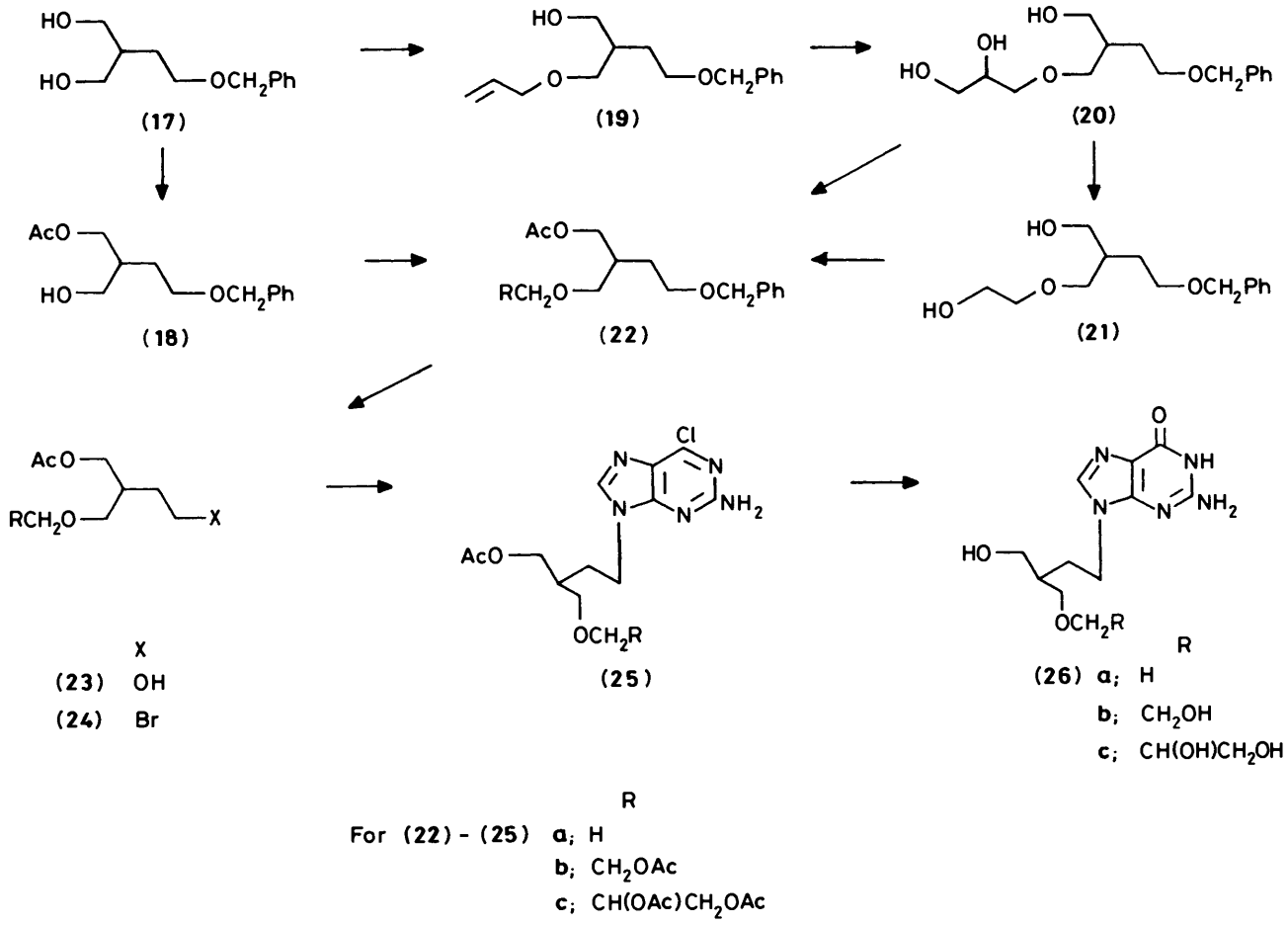
Scheme 2.

(THP) and benzyl protecting groups were used to differentiate the two hydroxyethyl groups attached to the branching carbon. Thus, alkylation of (**8**) with THP-protected bromoethanol (sodium hydride–tetrahydrofuran) gave (**9**) (64% yield), which was decarboxylated in hot dimethyl sulphoxide (DMSO) to give (**10**) in 28% yield. The ester group of (**10**) was reduced with lithium aluminium hydride in ether to afford the alcohol (**11**) (56% yield), which was acetylated with acetic anhydride and 4-dimethylaminopyridine (DMAP) in pyridine to afford the fully protected triol (**12**) in 93% yield. The alcohol (**13**) was obtained in 83% yield by catalytic hydrogenolysis of (**12**) in ethanol containing 1% acetic acid. Bromination of (**13**) to (**14**) and alkylation of 2-amino-6-chloropurine to afford the 9-substituted purine (**15**) were carried out as described above. Hydrolysis of (**15**) with 50% formic acid at 100 °C converted the 6-chloro into 6-oxo and also removed both the acetyl and THP groups to afford the guanine (**16**) in 47% yield.

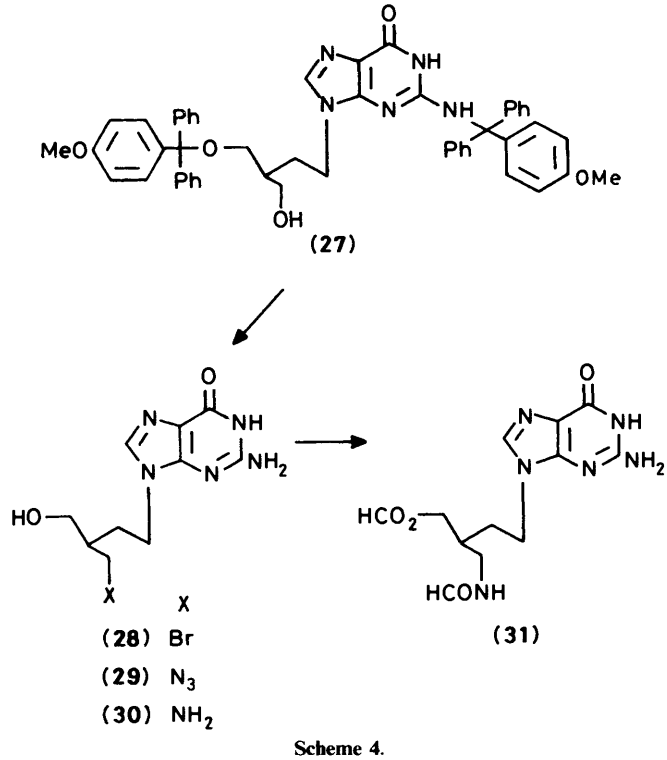
Synthesis of the ethers (**26a**—**c**) proceeded from the diol (**17**)[6] (Scheme 3). Differentiation of the two hydroxy groups was achieved either by monoester formation *via* a cyclic orthoester or by selective monoanion formation followed by alkylation. Reaction of (**17**) with triethyl orthoacetate catalysed by toluene-*p*-sulphonic acid followed by hydrolysis with 5% acetic acid gave the monoacetate (**18**) in 63% yield. Silver oxide catalysed methylation of (**18**) (iodomethane–DMF) afforded the methyl ether (**22a**) (67% yield), but attempted hydroxyethylation of (**18**) was not successful. Generation of the monoanion of (**17**) with 1.05 equiv. of sodium hydride in toluene followed by addition of allyl iodide gave the monoallyl ether (**19**) in 55% yield. *cis*-Hydroxylation of (**19**) with osmium tetroxide and *N*-methylmorpholine *N*-oxide gave the triol (**20**) (81% yield) and one-pot reaction of (**20**) with sodium periodate followed by sodium borohydride afforded the hydroxyethyl ether (**21**) (87% yield). Compounds (**20**) and (**21**) were peracetylated with acetic anhydride–DMAP–pyridine to give (**22c**) (86% yield) and (**22b**) (85% yield), respectively. Debenzylation of (**22a**) was effected by catalytic hydrogen transfer from ammonium formate and of (**22b**) and (**22c**) by catalytic hydrogenolysis in ethanol containing 1.5% acetic acid, the latter procedure being somewhat more efficient (yields of (**23a**—**c**) 49, 99, and 96% respectively). Bromination of the alcohols to (**24a**—**c**) and alkylation of 2-amino-6-chloropurine to the 9-substituted purines (**25a**—**c**) were carried out as described above. The deprotected guanines (**26a**—**c**) were obtained by hydrolysis of (**25a**—**c**) in refluxing dilute HCl in yields of 34, 62, and 73% respectively.

Selective functional group conversion of one hydroxy group of (**1c**) was achieved *via* the bis(monomethoxytrityl) derivative (**27**)[8] (Scheme 4). Reaction of (**27**) with carbon tetrabromide–triphenylphosphine in DMF followed by deprotection with 80% acetic acid afforded the bromo derivative (**28**). This compound was treated with sodium azide in DMF to give the azido analogue (**29**) in 54% yield. Reduction of (**29**) by catalytic hydrogen transfer from ammonium formate afforded the amine (**30**) which was isolated as the acetate salt (68% yield). Compound (**30**) was treated with formic acid and dicyclohexylcarbodi-imide in DMF and the major product was isolated by reverse-phase h.p.l.c. and was shown to be the diformyl derivative (**31**).

Biological Data.—The acyclonucleosides prepared in this study were tested at concentrations up to 100μg ml^{-1} for antiviral activity in cell cultures. Unlike the lead compound (**1c**),[6–11] none of the compounds (**7a**, **b**), (**16**), (**26a**—**c**) and (**28**—**31**) was highly active against herpes simplex virus types 1 and 2. The most active compound was the formamido derivative (**31**), for which the 50% inhibitory concentration (IC_{50}) against herpes simplex virus type 1 (SC16 strain) and herpes simplex



Scheme 3.



Scheme 4.

type 2 (MS strain) in MRC-5 (human fibroblast) cells was 20 and 33 μg ml^{-1}, respectively. Although (**31**) contains an additional *O*-formyl group, we believe that this would have been rapidly hydrolysed under the assay conditions.[8] Compounds in which the hydroxy group was further removed from the 3′-carbon by an extra methylene unit (**16**) or by an ethoxy group (**26b**) were slightly active against the type 1 virus with IC_{50} values of 33 and 100 μg ml^{-1}, respectively. Compounds (**26b**) and (**29**) were also slightly active against the type 2 virus with IC_{50} values of 100 and 59 μg ml^{-1}, respectively. None of the compounds prepared in this study inhibited the replication of influenza A (HK/1/68) virus or parainfluenza type 1 (Sendai) virus in Madin-Darby canine kidney cells. In these tests slight toxicity to the cell monolayer was observed only with compound (**29**) at 100 μg ml^{-1} in MRC-5 cells.

Experimental

M.p.s were determined using a Reichert Kofler apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded with a Varian EM-390 90 MHz or a Jeol GX-270 270 MHz spectrometer. I.r. spectra were recorded with a Perkin-Elmer 580 spectrometer and u.v. 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 analyser. Column chromatography was carried out on Merck 7736 silica gel. All compounds were homogeneous by t.l.c. on silica gel $60F_{254}$ coated aluminium sheets.

3-*Hydroxymethylpentane*-1,4-*diol* (**3**).—Methanol (12 ml) was added in three portions over 30 min to a refluxing solution of diethyl acetylsuccinate (21.6 g, 100 mmol) and sodium borohydride (10 g) in t-butyl alcohol (200 ml). The solution was heated under reflux for a further 30 min and then allowed to cool. It was then neutralised with 5M hydrochloric acid, filtered, and evaporated. The residue was extracted with ethanol (50 ml), and the extract filtered, and evaporated to afford the triol (**3**) as a viscous oil (14.4 g, quantitative); $\delta_H(D_2O)$ 1.20 (3 H, d, *J* 6 Hz, CH_3), 1.3—2.0 (3 H, m, $CHCH_2$), and 3.5—4.3 (5 H, m, 2 × CH_2OH and $CHOH$).

cis *and* trans 5-(2-*Hydroxyethyl*)-2,2,4-*trimethyl*-1,3-*dioxane* (**4**).—2,2-Dimethoxypropane (37 ml, 300 mmol) and toluene-*p*-sulphonic acid monohydrate (3.42 g, 18 mmol) were added to a solution of the triol (**3**) (100 mmol) in dry tetrahydrofuran (40 ml) and the solution was stirred at room temperature for 1 h. The solution was neutralised with triethylamine and evaporated. Column chromatography of the residue on silica gel, eluting with diethyl ether afforded a mixture of three isopropylidene acetals (9 g). This mixture was purified by column chromatography on silica gel eluting with hexane–diethyl ether mixtures to give the acetal (**4**) as a *cis*/*trans* mixture (3.36 g, 19%); $\delta_H(CDCl_3)$ 1.18 (3 H, d, *J* 6.6 Hz, $OCHCH_3$ isomer A) and 1.21 (3 H, d, *J* 6.1 Hz, $OCHCH_3$ isomer B) (Found: C, 61.1; H, 10.25. $C_9H_{18}O_3 \cdot 0.1H_2O$ requires C, 61.40; H, 10.42%).

Diethyl 2-*Benzyloxyethyl*(2-*tetrahydropyran*-2-*yloxyethyl*)-*malonate* (**9**).—Diethyl benzyloxyethylmalonate (14.7 g, 50 mmol) was added to a suspension of sodium hydride (60% dispersion in oil; 2.2 g, 55 mmol) in dry tetrahydrofuran (100 ml) and the mixture was stirred until effervescence ceased. 1-Bromo-2-(tetrahydropyran-2-yloxy)ethane (10.5 g, 50 mmol) was added to this solution and the mixture was heated under reflux for 16 h. It was then allowed to cool after which it was partitioned between ether (80 ml) and water (80 ml). The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane–acetone (5:1) to give the malonate (**9**) as a clear liquid (13.5 g, 64%); $\nu_{max.}$(film) 2 980, 2 940, 2 870, and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.20 (6 H, m, 2 × CH_3), 1.45—1.80 (6 H, m, 3 × $THPCH_2$), 2.15—2.35 (4 H, m, CH_2CCH_2), 3.30—3.60 (4 H, m, $CH_2CH_2CCH_2CH_2$), 3.74—3.82 (2 H, m, $THPCH_2O$), 4.13 (4 H, m, 2 × CH_2CO), 4.43 (2 H, s, $PhCH_2$), 4.51 (1 H, m, OCHO), and 7.30 (5 H, m, C_6H_5) (Found: C, 65.6; H, 8.1. $C_{23}H_{34}O_7$ requires C, 65.38; H, 8.11%).

Ethyl 4-*Benzyloxy*-2-(2-*tetrahydropyran*-2-*yloxyethyl*)*butyrate* (**10**).—A mixture of the malonate (**9**) (13.3 g, 31.5 mmol), sodium chloride (1.84 g, 31.5 mmol), and water (1.13 ml, 63 mmol) in Me_2SO (53 ml) was heated under reflux for 16 h after which it was partitioned between water (230 ml) and hexane (2 × 80 ml). The organic layers were combined, dried ($MgSO_4$), and evaporated and the residue was purified by column chromatography on silica gel, eluting with hexane–acetone (5:1) to afford compound (**10**) as a clear liquid (3.07 g, 28%); $\nu_{max.}$(film) 2 940, 2 860, and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.20 (3 H, m, CH_3), 1.5—2.05 (10 H, m, 3-H, CH_2CHCH_2 and 3 × $THPCH_2$), 2.70 (1 H, m, CH), 3.3—3.55 (4 H, m, 2 × CH_2OC), 3.70—3.83 (2 H, m, $THPCH_2O$), 4.11 (2 H, m, CH_2OCO), 4.43—4.57 (3 H, m, OCHO and $PhCH_2$), and 7.32 (5 H, m, C_6H_5) (Found: C, 68.2; H, 8.5. $C_{20}H_{30}O_5$ requires C, 68.54; H, 8.63%).

4-*Benzyloxy*-2-(2-*tetrahydropyran*-2-*yloxyethyl*)*butan*-1-*ol* (**11**).—A solution of the ester (**10**) (2.95 g, 8.4 mmol) in ether (5 ml) was added dropwise over 0.5 h to a suspension of lithium aluminium hydride (0.37 g) in ether (15 ml). After a further 0.5 h, water (0.4 ml) followed by 10% aqueous sodium hydroxide (0.6 ml) and water (1.0 ml) were added. The solution was filtered, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel, eluting with hexane–acetone (3:1) to afford the alcohol (**11**) as a clear liquid (1.45 g, 56%); $\nu_{max.}$(film) 3 440, 2 940, 2 860, and 1 030 cm^{-1}; $\delta_H(CDCl_3)$ 1.50—1.85 (11 H, m, CH_2CHCH_2, and 3 × $THPCH_2$) 3.17 (1 H, q, *J* 6.8 Hz, D_2O exchangeable, OH), 3.40—3.65 (6 H, m, 3 × CH_2O), 3.84 (2 H, m, $THPCH_2O$), 4.51 (2 H, s, $PhCH_2$), 4.59 (1 H, t, *J* 3.4 Hz, OCHO), and 7.33 (5 H, m, C_6H_5) (Found: C, 70.3; H, 9.1. $C_{18}H_{28}O_4$ requires C, 70.10; H, m, 9.15%).

4-*Benzyloxy*-2-(2-*tetrahydropyran*-2-*yloxymethyl*)*butyl Acetate*. (**12**).—The acetate (**12**), prepared in a similar way to compound (**22b**) but using the alcohol (**11**), was obtained as a clear liquid (1.46 g, 93%); $\nu_{max.}$(film) 2 940, 2 860, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.50—1.80 (10 H, m, CH_2CHCH_2, and 3 × $THPCH_2$), 1.95—2.05 (4 H, m, CH and CH_3), 3.40—3.55 (4 H, m, 2 × CH_2O), 3.82 (2 H, m, $THPCH_2O$), 4.05 (2 H, d, *J* 5.5 Hz, CH_2OAc), 4.50 (2 H, s, $PhCH_2$), 4.56 (1 H, t, *J* 3.4 Hz, OCHO), and 7.33 (5 H, m, C_6H_5) (Found: C, 68.7; H, 8.6. $C_{20}H_{30}O_5$ requires C, 68.54; H, 8.63%).

3-*Acetoxymethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentan*-1-*ol* (**13**).—10% Palladium-on-charcoal (1.0 g) was added to a solution of compound (**12**) (1.41 g, 4.0 mmol) in ethanol (20 ml) containing acetic acid (0.2 ml) and the mixture was stirred under hydrogen for 4 h. The solution was filtered, diluted with ether (25 ml), and washed with aqueous sodium hydrogen carbonate (15 ml) followed by water (10 ml). The aqueous layer was extracted with ether (25 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated to afford the alcohol (**13**) as a clear oil (0.86 g, 83%); $\nu_{max.}$(film) 3 460, 2 940, 2 870, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.55—1.85 (10 H, m, CH_2CHCH_2 and 3 × $THPCH_2$), 1.91 (1 H, t, *J* 5.7 Hz, D_2O exchangeable, OH), 2.06 (4 H, m, CH and CH_3), 3.48 (2 H, m, CH_2OCH), 3.73 (2 H, q, *J* 5.8 Hz, D_2O exchange gives t, CH_2OH), 3.83 (2 H, m, $THPCH_2O$), 4.05 (2 H, dd, *J* 5.7 Hz and 1.1 Hz, CH_2OAc), and 4.57 (1 H, t, *J* 2.0 Hz, OCHO) (Found: C, 59.6; H, 9.3. $C_{13}H_{24}O_5$ requires C, 59.98; H, 9.29%).

2-*Acetoxymethyl*-4-*benzyloxybutan*-1-*ol* (**18**).—Toluene-*p*-sulphonic acid monohydrate (0.3 g) was added to a solution of the diol (**17**) (5.8 g, 28 mmol) in trimethyl orthoacetate (15 ml) and the solution was stirred for 0.5 h. The solvent was then removed and the residue was taken up in 5% acetic acid (20 ml) and stirred vigorously for 10 min. The solution was extracted with chloroform and the organic layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (25:1) to afford the monoacetate (**18**) as a colourless liquid (4.47 g, 63%); $\nu_{max.}$(film) 3 440, 2 940, 2 870, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.68 (2 H, q, *J* 6 Hz, CH_2), 1.8—2.1 (1 H, m, CH), 2.07 (3 H, s, CH_3CO), 2.70 (1 H, br, D_2O exchangeable, OH), 3.55 (4 H, m, CH_2OH and CH_2OCH_2Ph), 4.10 (2 H, d, *J* 6 Hz, CH_2OAc), 4.53 (2 H, s, CH_2Ph), and 7.39 (5 H, s, C_6H_5) (Found: M^+, 252.1372. $C_{14}H_{20}O_4$ requires *M*, 252.1362).

2-*Allyloxymethyl*-4-*benzyloxybutan*-1-*ol* (**19**).—Sodium hydride (60% dispersion in oil; 1.68 g, 42 mmol) was added to a solution of the diol (**17**) (8.4 g, 40 mmol) in dry toluene (80 ml). After evolution of hydrogen ceased allyl iodide (6.4 ml, 70 mmol) was added and the mixture was stirred at 60 °C for 20 min. It was then washed with water (80 ml), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol (80:1) to afford the allyl ether (**19**) as a clear colourless liquid

(5.5 g, 55%); $\nu_{max.}$(film) 3 430, 2 920, 2 860, 1 645, 1 495, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.67 (2 H, q, *J* 6 Hz, $CHCH_2CH_2$), 2.00 [1 H, m, $CH(CH_2)_3$], 2.89 (1 H, t, *J* 6 Hz, D_2O exchangeable, OH), 3.4—3.7 [6 H, m, $(OCH_2)_2CHCH_2CH_2O$], 3.96 (2 H, m, CH_2=$CHCH_2O$), 4.53 (2 H, s, $PhCH_2O$), 5.1—5.4 (2 H, m, CH_2=CH), 5.88 (1 H, m, CH_2=CH), and 7.38 (5 H, s, C_6H_5); *m/z* (c.i., NH_3) 251 (MH^+, 100%).

4-*Benzyloxy*-2-(2,3-*dihydroxypropoxymethyl*)*butan*-1-*ol* (**20**).—Osmium tetroxide (catalytic) was added to a solution of the allyl ether (**19**) (5.3 g, 21 mmol) and *N*-methylmorpholine *N*-oxide (3.24 g, 24 mmol) in acetone (30 ml) and water (7 ml). The solution was stirred under nitrogen for 2 h at room temperature by which time it had become homogenous. It was then evaporated and the residue purified by column chromatography on silica gel, eluting with acetone–hexane (7:3) to afford compound (**20**) as a clear colourless oil (4.86 g, 81%); $\nu_{max.}$(film) 3 380, 2 920, 2 870, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.60 (2 H, q, *J* 6 Hz, $CHCH_2CH_2$), 1.96 [1 H, m, $CH(CH_2)_3$], 3.20 (2 H, m, D_2O exchangeable, 2 × CH_2OH), 3.4—3.9 (12 H, m, 1 H D_2O exchangeable, CHOH and 5 × CH_2O), 4.49 (2 H, s, $PhCH_2O$), and 7.34 (5 H, s, C_6H_5).

4-*Benzyloxy*-2-(2-*hydroxyethoxymethyl*)*butan*-1-*ol* (**21**).—A solution of sodium periodate (2.02 g, 9.45 mmol) in water (15 ml) was added to a solution of compound (**20**) (2.56 g, 9.0 mmol) in water (3 ml) and the mixture was stirred at room temperature. After 20 min ethanol (3 ml) was added and after a further 10 min sodium borohydride (0.34 g, 9.0 mmol) was added. After a further 15 min the solution was neutralised by addition of 5M hydrochloric acid. The solution was extracted with chloroform (3 × 30 ml) and the combined organic layers were washed with aqueous sodium thiosulphate (40 ml). The thiosulphate solution was extracted with chloroform (30 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel, eluting with acetone–hexane (1:1) to afford the hydroxyethyl ether (**21**) as a clear colourless oil (1.98 g, 87%); $\nu_{max.}$(film) 3 380, 2 920, 2 870, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.64 (2 H, q, *J* 6 Hz, $CHCH_2CH_2$), 1.98 (1 H, m, CH), 2.41 (1 H, br t, *J* 5 Hz, D_2O exchangeable, $CHCH_2OH$), 2.95 (1 H, br t, *J* 5 Hz, D_2O exchangeable, CH_2CH_2OH), 3.1—3.6 (10 H, m, 5 × CH_2O), 4.51 (2 H, s, $PhCH_2O$), and 7.36 (5 H, s, C_6H_5) (Found: C, 64.7; H, 8.6. $C_{14}H_{22}O_4 \cdot 0.3H_2O$ requires C, 64.74; H, 8.77%).

4-*Benzyloxy*-2-*methoxymethylbutyl Acetate* (**22a**).—Silver(I) oxide (3.7 g, 16 mmol) was added to a solution of the monoacetate (**18**) (2.02 g, 8 mmol) and iodomethane (3.12 ml, 40 mmol) in dry DMF (16 ml) and the mixture was stirred at 50 °C for 16 h. The solution was filtered and evaporated and the residue was extracted with chloroform. The extract was filtered and evaporated and the residue was purified by column chromatography on silica gel, eluting with chloroform to afford the methyl ether (**22a**) as a colourless liquid (1.43 g, 68%); $\nu_{max.}$(film) 2 930, 2 870, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.64 (2 H, q, *J* 6 Hz, CH_2), 2.03 (3 H, s, CH_3CO), 2.0—2.3 (1 H, m, CH), 3.3—3.4 (5 H, m, CH_2OCH_3), 3.50 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 4.05 (2 H, d, *J* 6 Hz, CH_2OAc), 4.49 (2 H, s, CH_2Ph), and 7.34 (5 H, s, C_6H_5) (Found: M^+, 266.1535. $C_{15}H_{22}O_4$ requires *M*, 266.1518).

2-*Acetoxyethoxymethyl*-4-*benzyloxybutyl Acetate* (**22b**).—Acetic anhydride (2.08 ml, 22 mmol) and DMAP (50 mg) were added to a solution of compound (**21**) (1.86 g, 7.3 mmol) in dry pyridine (22 ml) and the solution was stirred at room temperature for 15 min. Methanol (1 ml) was added and the solution was partitioned between ether (60 ml) and 5M hydrochloric acid (60 ml). The organic layer was washed with 5M hydrochloric acid (20 ml) and aqueous sodium hydrogen carbonate (60 ml), dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel, eluting with acetone–hexane (1:4) to afford the diacetate (**22b**) as a clear colourless liquid (2.11 g, 85%); $\nu_{max.}$(film) 2 950, 2 870, 1 740, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.69 (2 H, m, $CHCH_2CH_2$), 2.04 (3 H, s, CH_3), 2.07 (3 H, s, CH_3), 2.14 (1 H, m, CH), 3.44 (2 H, d, *J* 5.8 Hz, CH_2OCH_2CH), 3.54 (2 H, t, *J* 6.5 Hz, CH_2OCH_2Ph), 3.60 (2 H, m, CH_2OCH_2CH), 4.10 (2 H, d, *J* 5.7 Hz, $AcOCH_2CH$), 4.19 (2 H, m, $AcOCH_2CH_2$), 4.50 (2 H, s, $PhCH_2$), and 7.33 (5 H, s, C_6H_5) (Found: C, 63.9; H, 7.8%; M^+, 338.1731. $C_{18}H_{26}O_6$ requires C, 63.89; H, 7.74%; *M*, 338.1729).

4-*Benzyloxy*-2-(2,3-*diacetoxypropoxymethyl*)*butyl Acetate* (**22c**).—The triacetate (**22c**), prepared in a similar way to the diacetate (**22b**) but using compound (**20**), was obtained as a colourless liquid (2.33 g, 86%); $\nu_{max.}$(film) 2 940, 2 870, 1 740, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.66 (2 H, q, *J* 6.6 Hz, $CHCH_2CH_2$), 2.04—2.16 [10 H, m, $CH(CH_2)_3$ and 3 × CH_3], 3.43 [2 H, m, $CH_2OCH_2CH(CH_2)_2$], 3.53 (4 H, m, $OCHCH_2OCH_2$ and CH_2OCH_2Ph), 4.07 [2 H, d, *J* 5.5 Hz, $AcOCH_2CH(CH_2)_2$], 4.13 (1 H, dd, *J* 6.3 and 12.0 Hz, $AcOCH_2CHO$), 4.30 (1 H, dd, *J* 3.6 and 12.0 Hz, $AcOCH_2CHO$), 4.50 (2 H, s, $PhCH_2$), 5.17 (1 H, m, CHOAc), and 7.33 (5 H, s, C_6H_5) (Found: C, 62.0; H, 7.35%; M^+, 410.1942. $C_{21}H_{30}O_8$ requires C, 61.45; H, 7.37%; *M*, 410.1940).

4-*Acetoxy*-3-*methoxymethylbutan*-1-*ol* (**23a**).—10% Palladium-on-charcoal (2 g) was added to a solution of compound (**22a**) (1.23 g, 4.6 mmol), formic acid (0.94 ml, 25 mmol), ammonia (1.38 ml, 25 mmol), and acetic acid (2 ml) in methanol (40 ml) and the mixture was heated under reflux for 1 h. The solution was filtered and evaporated and the residue was taken up in chloroform and washed with brine and aqueous sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (25:1) to afford the alcohol (**23a**) as a colourless liquid (0.40 g, 49%); $\nu_{max.}$(film) 3 430, 2930, 2 890, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.61 (2 H, q, *J* 6 Hz, CH_2), 2.06 (3 H, s, CH_3CO), 2.21 (1 H, m, CH), 2.39 (1 H, s, D_2O exchangeable, OH), 3.4—3.5 (5 H, m, CH_2OCH_3), 3.67 (3 H, t, *J* 6 Hz, CH_2OH), and 4.05 (2 H, d, *J* 6 Hz, CH_2OAc); *m/z* (c.i., NH_3) 194 (MNH_4^+ 100%), 177 (MH^+, 56).

4-(2-*Acetoxyethoxy*)-3-*acetoxymethylbutan*-1-*ol* (**23b**).—10% Palladium-on-charcoal (0.7 g) was added to a solution of compound (**22b**) (1.89 g, 5.6 mmol) and acetic acid (0.5 ml) in ethanol (30 ml) and the mixture was stirred under hydrogen for 40 min. It was then filtered and evaporated to afford the alcohol (**23b**) as a clear colourless liquid (1.37 g, 99%); $\nu_{max.}$(film) 3 460, 2 950, 2 880, 1 735, and 1 440 cm^{-1}; $\delta_H(CDCl_3)$ 1.66 (2 H, m, $CHCH_2CH_2$), 2.06 (3 H, s, CH_3), 2.09 (3 H, s, CH_3), 2.14 (1 H, m, CH), 2.4 (1 H, br, D_2O exchangeable, OH), 3.50 (2 H, AB of ABX, J_{AB} 9.4 Hz, J_{AX} 6.3 Hz, and J_{BX} 4.9 Hz, CH_2OCH_2OH), 3.65 (2 H, m, CH_2OCH_2CH), 3.71 (2 H, m, CH_2OH), 4.07 (2 H, d, *J* 6.1 Hz, $AcOCH_2CH$), and 4.22 (2 H, m, $AcOCH_2CH_2$) (Found: C, 53.0; H, 8.0. $C_{11}H_{20}O_6$ requires C, 53.21; H, 8.12%).

4-*Acetoxy*-3-(2,3-*diacetoxypropoxymethyl*)*butan*-1-*ol* (**23c**).—The alcohol (**23c**), prepared in similar way to the alcohol (**23b**) but using compound (**22c**), was obtained as a clear colourless liquid (1.66 g, 96%); $\nu_{max.}$(film) 3 460, 2 940, 2 880, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.63 (2 H, m, $CHCH_2CH_2$), 2.0—2.2 (11 H, m, 1 H D_2O exchangeable, $CHCH_2CH_2OH$ and 3 × CH_3) 3.47 [2 H, m, $CH_2OCH_2CH(CH_2)_2$], 3.59 (2 H, m, $OCHCH_2OCH_2$), 3.71 (2 H, 2 × t, *J* 6.2 Hz, CH_2OH 2 isomers), 4.06 [2 H, d, *J* 6.0 Hz, $AcOCH_2CH(CH_2)_2$], 4.15 (1 H,

2 × dd, *J* 6.5 Hz and 11.9 Hz, $AcOCH_2CHO$ 2 isomers), 4.32 (1 H, 2 × dd, *J* 3.9 Hz and 12.1 Hz, $AcOCH_2CHO$ 2 isomers), and 5.20 (1 H, m, AcOCH) (Found: C, 52.4; H, 7.4. $C_{14}H_{24}O_8$ requires C, 52.44; H, 7.55%).

Preparation of the Bromo Compounds (**5a**), (**5b**), (**14**), (**24a**), (**24b**) *and* (**24c**).—Triphenylphosphine (0.39 g, 1.5 mmol) was added to an ice-cooled solution of the alcohol (1 mmol) and tetrabromomethane (0.50 g, 1.5 mmol) in DMF (3.1 ml) and the mixture was stirred at this temperature for 25 min. Aqueous sodium hydrogen carbonate (1.5 ml) and water (1.5 ml) were added and the mixture was extracted with hexane (3 × 4 ml, or more if necessary). The combined organic layers were dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography on silica gel: elution with hexane–ether (5:1) gave (**5a**, **b**); chloroform gave (**14**); and hexane-acetone [4:1 gave (**24a**) and 3:1 gave (**24b**, **c**)]. The bromo compounds were clear colourless liquids.

cis-5-(2-*Bromoethyl*)-2,2,4-*trimethyl*-1,3-*dioxane* (**5a**) *and* trans-5-(2-*Bromoethyl*)-2,2,4-*trimethyl*-1,3-*dioxane* (**5b**). The first product to be eluted was (**5a**) (1.20 g, 32%); $\nu_{max.}$(film) 2 990, 2 940, 2 870, 1 380, 1 260, and 1 200 cm^{-1}; $\delta_H(CDCl_3)$ 1.14 (3 H, d, *J* 6.6 Hz, 4-CH_3), 1.37 (3 H, s, 2-CH_3), 1.46 (3 H, s, 2-CH_3), 1.50 (1 H, m, 5-H), 1.98 (1 H, m, 5-CH_2) 2.30 (1 H, m, 5-CH_2), 3.48 (1 H, ddd, *J* 9.9, 9.9, and 6.1 Hz, CHBr), 3.65 (1 H, ddd, *J* 10.1, 6.8, and 4.4 Hz, CHBr), 3.75 (1 H, dd, *J* 12.2 Hz and 1.4 Hz, 6-H_{ax}), 4.02 (1 H, dd, *J* 12.1 and 1.7 Hz, 6-H_{eq}), and 4.22 (1 H, dq, J_d 2.4 Hz and J_q 6.4 Hz, 4-H) (Found: $[M - CH_3]^+$, 221.0178. $C_8H_{14}BrO_2$ requires 221.0178).

The second product to be eluted was (**5b**) (1.27 g, 33%); $\nu_{max.}$(film) 2 990, 2 940, 2 860 1 385, and 1 200 cm^{-1}; $\delta_H(CDCl_3)$ 1.21 (3 H, d, *J* 6.1 Hz, 4-CH_3), 1.55—1.80 (2 H, m, 5-H and 5-CH_2), 1.93 (1 H, ddt, J_d 13.8 Hz, J_d 3.2 Hz and *J*, 8.1 Hz, 5-CH_2), 3.25—3.45 (2 H, m, CH_2Br), 3.57 (1 H, dd, *J* 11.5 Hz and 10.4 Hz, 6-H_{ax}), 3.70 (1 H, dq, J_d 9.7 Hz and J_q 6.1 Hz, 4-H), and 3.85 (1 H, dd, *J* 11.5 Hz and 4.9 Hz, 6-H_{eq}) (Found: $[M - CH_3]^+$ 221.0180. $C_8H_{14}BrO_2$ requires 221.0178).

2-(2-*Bromoethyl*)-4-(*tetrahydropyran*-2-*yloxy*)*butyl Acetate* (**14**). Yield 0.67 g (69%); $\nu_{max.}$(film) 2 940, 1 740, and 1 240 cm^{-1}; $\delta_H(CDCl_3)$ 1.5—2.0 (10 H, m, CH_2CHCH_2, 3-H and 3 × $THPCH_2$), 2.07 (4 H, m, CH and CH_3), 3.47 (4 H, m, CH_2Br and CH_2OCH), 3.82 (2 H, m, $THPCH_2O$), 4.06 (2 H, m, CH_2OAc), and 4.58 (1 H, t, *J* 3.4 Hz, OCHO) (Found: M^+, 321.0702. $C_{13}H_{23}BrO_4$ requires *M*, 321.0701).

4-*Bromo*-2-*methoxymethylbutyl Acetate* (**24a**). Yield 0.24 g (53%); $\nu_{max.}$(film) 2 930, 2 900, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.95 (2 H, m, $CHCH_2$), 2.07 (3 H, s, CH_3CO), 2.17 (1 H, m, CH), 3.33 (3 H, s, CH_3O), 3.37 (2 H, m, CH_2OCH_3), 3.49 (2 H, t, *J* 7.1 Hz, CH_2Br), and 4.09 (2 H, AB of ABX, J_{AX} 5.7 Hz, J_{BX} 5.9 Hz and J_{AB} 11.2 Hz, CH_2OAc); *m*/*z* (e.i.) 206/208 ($[M - CH_3OH]^+$, 8%) and 43 (100).

2-*Acetoxyethoxymethyl*-4-*bromobutyl Acetate* (**24b**). Yield 1.10 g (68%); $\nu_{max.}$(film) 2 950, 2 870, and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.96 (2 H, m, CH_2CH_2Br), 2.07 (3 H, s, CH_3), 2.09 (3 H, s, CH_3), 2.19 (1 H, m, CH), 3.47 (4 H, m, CH_2OCH_2CH and CH_2Br), 3.63 (2 H, m, $CH_2CH_2OCH_2$), 4.09 (2 H, AB of ABX, J_{AB} 11.2 Hz, J_{AX} 5.5 Hz and J_{BX} 5.9 Hz, $AcOCH_2CH$), and 4.21 (2 H, m, $AcOCH_2CH_2$) (Found: C, 42.7; H, 6.1. $C_{11}H_{19}BrO_5$ requires C, 42.46; H, 6.15%).

4-*Bromo*-2-(2,3-*diacetoxypropoxymethyl*)*butyl Acetate* (**24c**). Yield 1.14 g (62%); $\nu_{max.}$(film) 2 960, 2 900, 1 740, and 1 440 cm^{-1}; $\delta_H(CDCl_3)$ 1.93 (2 H, m, CH_2CH_2), 2.05—2.10 (9 H, m, 3 × CH_3), 2.18 (1 H, m, $CHCH_2CH_2$), 3.47 [4 H, m, CH_2-$OCH_2CH(CH_2)_2$ and CH_2Br], 3.56 (2 H, m, $OCHCH_2OCH_2$), 4.07 [2 H, m, $AcOCH_2CH(CH_2)_2$], 4.14 (1 H, dd, *J* 6.3 and 11.8 Hz, $AcOCH_2CHO$), 4.31 (1 H, 2 × dd, *J* 3.9 and 12.0 Hz, $AcOCH_2CHO$ 2 isomers), and 5.18 (1 H, m, AcOCH) (Found: C, 43.9; H, 6.0. $C_{14}H_{23}BrO_7$ requires C, 43.88; H, 6.05%).

Preparation of the 9-*Alkyl*-2-*amino*-6-*chloropurines* (**6a**, **b**), (**15**), *and* (**25a**—**c**).—A mixture of 2-amino-6-chloropurine (178 mg, 1.05 mmol), potassium carbonate (145 mg, 1.05 mmol), and the bromo compound (1 mmol) in DMF (3.2 ml) was stirred for 16 h at room temperature. The solution was filtered and evaporated and the residue was taken up in chloroform. This too was filtered and evaporated and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (40:1—30:1) to afford the 9-alkylpurines as white solids.

2-*Amino*-6-*chloro*-9-[cis-2-(2,2,4-*trimethyl*-1,3-*dioxan*-5-*yl*)-*ethyl*]*purine* (**6a**).Yield 0.82 g, (56%), m.p. 171—173 °C; $\lambda_{max.}$(EtOH) 223 (ε 29 000), 248 (5 590), and 310 nm (7 700); $\nu_{max.}$(KBr) 3 420, 3 320, 3 210, 1 615, 1 560, 1 520, 1 470, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.14 (3 H, d, *J* 6.4 Hz, $OCHCH_3$), 1.22 (1 H, m, $CHCH_2CH_2$), 1.40 (3 H, s, CCH_3), 1.47 (3 H, s, CCH_3), 2.04 (1 H, m, $CHCH_2CH_2$), 2.26 (1 H, m, $CHCH_2CH_2$), 3.89 (1 H, dd, *J* 1.4 and 12.2 Hz, CH_2O), 4.06 (1 H, dd, *J* 2.7 and 12.2 Hz, CH_2O), 4.15—4.30 (3 H, m, $OCHCH_3$ and CH_2N), 5.24 (2 H, s, D_2O exchangeable, 2-NH_2), and 7.80 (1 H, s, 8-H) (Found: C, 51.3; H, 6.2; N, 21.6. $C_{14}H_{20}ClN_5O_2$ requires C, 51.61; H, 6.19; N, 21.50%).

2-*Amino*-6-*chloro*-9-[trans-2-(2,2,4-*trimethyl*-1,3-*dioxan*-5-*yl*)*ethyl*]*purine* (**6b**). Yield 0.88 g (60%), m.p. 166—168 °C (phase transition 140—142 °C); $\lambda_{max.}$(EtOH) 223 (ε 29 000), 248 (5 820), and 310 nm (7 800); $\nu_{max.}$(KBr) 3 460, 3 350, 3 220, 1 630, 1 620, 1 565, 1 520, 1 470, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.18 (3 H, d, *J* 6.0 Hz, $OCHCH_3$), 1.39 (3 H, s, CCH_3), 1.45 (3 H, s, CCH_3), 1.50—2.00 (3 H, m, $CHCH_2CH_2$), 3.60—3.75 (2 H, m, $OCHCH_3$ and CH_2O), 3.90 (1 H, dd, *J* 4.7 and 11.7 Hz, CH_2O), 4.07 (2 H, t, *J* 7.4 Hz, CH_2N), 5.23 (2 H, s, 2-NH_2), and 7.77 (1 H, s, 8-H) (Found: C, 51.3; H, 6.35; N, 21.7. $C_{14}H_{20}ClN_5O_2$ requires C, 51.61; H, 6.19; N, 21.50%).

9-[3-*Acetoxymethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentyl*]-2-*amino*-6-*chloropurine* (**15**). Yield 0.27 g (34%) $\lambda_{max.}$(EtOH) 223 (ε 29 000), 247 (5 890), and 310 nm (7 840); $\nu_{max.}$(film) 3 330, 3 210, 2 940, 1 735, 1 615, 1 560, 1 520, 1 465, and 1 410 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.15—1.6 (8 H, m, 4′-H and 3 × $THPCH_2$), 1.71 (1 H, m, 3′-H), 1.84 (2 H, m, 2′-H), 1.99 and 2.00 (total 3 H, each s, CH_3 -two isomers), 3.34 (2 H, m, 5′-H), 3.61 (2 H, m, $THPCH_2O$), 4.01 (2 H, m, CH_2OAc), 4.12 (2 H, t, *J* 6.9 Hz, 1′-H), 4.37 and 4.49 (total 1 H, each t, *J* 3 Hz, OCHO -two isomers), 6.88 (2 H, s, D_2O exchangeable 2-NH_2), and 8.15 (1 H, s, 8-H) (Found: C, 51.7; H, 6.4; N, 16.5%; M^+, 411.1662. $C_{18}H_{26}ClN_5O_4 \cdot 0.5CH_3OH$ requires C, 51.93; H, 6.60; N, 16.37%; *M*, 411.1673).

9-(4-*Acetoxy*-3-*methoxymethylbutyl*)-2-*amino*-6-*chloropurine* (**25a**). Yield 194 mg (74%), m.p. 132—135 °C; $\lambda_{max.}$(MeOH) 223 (ε 28 200), 247 (5 500), and 310 nm (7 500); $\nu_{max.}$(KBr) 3 430, 3 310, 3 210, 1 740, 1 630, 1 560, 1 520, and 1 470 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.84 (3 H, m, 2′-H and 3′-H), 1.98 (3 H, s, CH_3CO), 3.22 (3 H, s, CH_3O), 3.32 (2 H, d, *J* 3.0 Hz, CH_2OCH_3), 3.99 (2 H, AB of ABX, J_{AX} 5.4 Hz, J_{BX} 5.7 Hz, and J_{AB} 11.2 Hz, CH_2OAc), 4.12 (2 H, t, *J* 6.7 Hz, 1′-H), 6.86 (2 H, s, D_2O exchangeable, 2-NH_2), and 8.15 (1 H, s, 8-H) (Found: C, 47.7; H, 5.5; N, 21.2. $C_{13}H_{18}ClN_5O_3$ requires C, 47.64; H, 5.54; N, 21.37%).

9-[4-(2-*Acetoxymethoxy*)-3-*acetoxymethylbutyl*]-2-*amino*-6-*chloropurine* (**25b**). Yield 0.61 g (46%), m.p. 90—92 °C; $\lambda_{max.}$(MeOH) 223 (ε 29 500), 247 (5 700), and 310 nm (7 900); $\nu_{max.}$(KBr) 3 450, 3 310, 3 210, 1 735, 1 625, 1 560, 1 520, 1 470, and 1410 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.84 (3 H, m, 2′-H and 3′-H), 1.98 (3 H, s, CH_3), 1.99 (3 H, s, CH_3), 3.41 (2 H, d, *J* 3.9 Hz, 3′-CH_2OCH_2), 3.55 (2 H, m, 3′-CH_2OCH_2), 3.98 (2 H, AB of ABX, J_{AB} 11.0 Hz and $J_{AX} = J_{BX}$ 5.2 Hz, 3′-CH_2OAc), 4.11 (4 H, m, $AcOCH_2CH_2$ and 1′-H), 6.85 (2 H, s, D_2O exchangeable, 2-NH_2), and 8.14 (1 H, s, 8-H) (Found: C, 48.2; H, 5.4; N, 17.4. $C_{16}H_{22}ClN_5O_5$ requires C, 48.06; H, 5.55; N, 17.52%).

9-[3-*Acetoxymethyl*-4-(2,3-*diacetoxypropoxy*)*butyl*]-2-*amino*-6-*chloropurine* (**25c**). Yield 0.90 g (67%); $\lambda_{max.}$(EtOH) 223 (ε 29 200), 248 (5 900), and 310 nm (7 900); $\nu_{max.}$(film) 3 460, 3 330, 3 210, 2 950, 1 740, 1 610, 1 560, 1 520, 1 465, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.95 (3 H, m, 2′-H and 3′-H), 2.06—2.09 (9 H, m, 3 × CH_3), 3.49 (2 H, m, 3′-CH_2OCH_2), 3.57 (2 H, d, *J* 5.2 Hz, 3′-CH_2OCH_2), 4.08 (2 H, m, 3′-CH_2OAc), 4.19 (3 H, m, 1′-H and 1 of AcOCH_2CHO), 4.35 (1 H, 2 × dd, *J* 3.4 Hz and 12.0 Hz, AcOCH_2CHO 2 isomers), 5.21 (3 H, m, AcOCH and 2-NH_2), and 7.81, 7.82 (1 H, 2 × s, 8-H 2 isomers) (Found: C, 48.6; H, 5.4; N, 14.7. $C_{19}H_{26}ClN_5O_7$ requires C, 48.36; H, 5.55; N, 14.85%.

(3′R*,4′R*)-9-(4-*Hydroxy*-3-*hydroxymethylpentyl*)*guanine* (**7a**).—A solution of the purine (**6a**) (0.67 g, 2.05 mmol) in 2.5M hydrochloric acid (2.4 ml) was heated under reflux for 1 h. The solution was neutralised with 10% aqueous sodium hydroxide and the guanine (**7a**) crystallised on cooling (484 mg, 83%); $\lambda_{max.}$(H_2O) 252 (ε 12 900) and 268sh nm (9 690); $\nu_{max.}$(KBr) 3 330, 1 690, 1 630, and 1 605 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.01 (3 H, d, *J* 6.3 Hz, 5′-H), 1.30 (1 H, m, 3′-H), 1.68 (1 H, m, 2′-H), 1.86 (1 H, m, 2′-H), 3.39 (1 H, dd, *J* 6.4 and 10.6 Hz, 3′-CH_2), 3.52 (1 H, dd, *J* 5.5 and 10.6 Hz, 3′-CH_2), 3.70 (1 H, dq, J_d 5.5 Hz and J_q 6.4 Hz, 4′-H), 4.00 (2 H, m, 1′-H), 4.3—4.5 (2 H, br, D_2O exchangeable, 2 × OH), 6.41 (2 H, s, D_2O exchangeable, 2-NH_2), 7.68 (1 H, s, 8-H), and 10.52 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 46.25; H, 6.55; N, 24.5%; M^+, 267.1336. $C_{11}H_{17}N_5O_3$·H_2O requires C, 46.31; H, 6.71; N, 24.55%; *M*, 267.1331).

(3′R*,4′S*)-9-(4-*Hydroxy*-3-*hydroxymethylpentyl*)*guanine* (**7b**).—The guanine (**7b**), prepared in an analogous way to the guanine (**7a**) but using compound (**6b**), was obtained as a white solid (523 mg, 86%); $\lambda_{max.}$(H_2O) 252 (ε 12 200) and 268sh nm (9 230); $\nu_{max.}$(KBr) 3 330, 1 690, 1 630, and 1 605 cm^{-1}; δ_H[$(CD_3)_2SO$] 0.98 (3 H, d, *J* 6.3 Hz, 5′-H), 1.38 (1 H, m, 3′-H), 1.62 (1 H, m, 2′-H), 1.76 (1 H, m, 2′-H), 3.41 (2 H, AB of ABX system, J_{AB} 10.9 Hz and J_{AX} = J_{BX} 5.7 Hz, 3′-CH_2), 3.71 (1 H, dq, J_d 5.1 and J_q 6.2 Hz, 4′-H), 3.98 (2 H, t, *J* 7.4 Hz, 1′-H), 4.46 (2 H, br, D_2O exchangeable, 2 × OH), 6.44 (2 H, s, D_2O exchangeable, 2-NH_2), 7.70 (1 H, s, 8-H), and 10.57 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 47.8; H, 6.65; N, 25.2%; M^+, 267.1331. $C_{11}H_{17}N_5O_3$·0.5H_2O requires C, 47.82; H, 6.57; N, 25.35%; *M*, 267.1331).

9-(5-*Hydroxy*-3-*hydroxymethylpentyl*)*guanine* (**16**).—A solution of the purine (**15**) (230 mg, 0.56 mmol) in 50% aqueous formic acid (3 ml) was heated at 100 °C for 100 min. The solvent was removed and the residue was taken up in ammonia (*d*, 0.880; 2 ml) and methanol (2 ml). The solution was stirred at 50 °C for 1 h and then evaporated. The residue was purified by reverse-phase column chromatography on Spherisorb C18 300 silica eluting with water followed by 5 and 10% methanol to afford the guanine (**16**) (70 mg, 47%), m.p. 195—200 °C; $\lambda_{max.}$(H_2O) 252 (ε 11 600) and 270sh nm (8 680); $\nu_{max.}$(KBr) 3 320, 3 200, 2 910, 1 715, 1 690, 1 630, and 1 605 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.44 (3 H, m, 3′-H and 4′-H), 1.66 (1 H, m, 2′-H), 1.78 (1 H, m, 2′-H), 3.25—3.45 (4 H, m, 2 × CH_2O), 3.96 (2 H, t, *J* 7.4 Hz, 1′-H), 4.39 (1 H, t, *J* 5.1 Hz, D_2O exchangeable, OH), 4.49 (1 H, t, *J* 5.2 Hz, D_2O exchangeable, OH), 6.40 (2 H, s, D_2O exchangeable, 2-NH_2), 7.68 (1 H, s, 8-H), and 10.49 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 48.0; H, 6.4; N, 25.1%; M^+, 267.1334. $C_{11}H_{17}N_5O_3$·0.5H_2O requires C, 47.82; H, 6.57; N, 25.35%; *M*, 267.1331).

9-(4-*Hydroxy*-3-*methoxymethylbutyl*)*guanine* (**26a**).—A solution of the purine (**25a**) (0.16 g, 0.5 mmol) in 2M hydrochloric acid (1.0 ml) was heated under reflux for 40 min. The solution was neutralised with 10% aqueous sodium hydroxide and evaporated. The residue was purified by preparative h.p.l.c. on a reverse-phase C_{18} μ-Bondapak column eluting with 17% methanol in aqueous ammonium acetate (50mM; pH 4.5) and recrystallised from water containing one drop of saturated aqueous sodium hydrogen carbonate to give the guanine (**26a**) (46 mg, 34%), m.p. 222—224 °C; $\lambda_{max.}$(H_2O) 252 (ε 12 600) and 270sh nm (9 500); $\nu_{max.}$(KBr) 3 340, 3 170, 2 920, 1 690, 1 640, and 1 610 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.59 (1 H, m, 3′-H), 1.72 (2 H, m, 2′-H), 3.21 (3 H, s, CH_3), 3.25—3.45 (4 H, m, CH_2OH and CH_2OCH_3), 3.99 (2 H, t, *J* 7.3 Hz, 1′-H), 4.47 (1 H, t, *J* 5.2 Hz, D_2O exchangeable, OH), 6.39 (2 H, s, D_2O exchangeable 2-NH_2), 7.67 (1 H, s, 8-H), and 10.48 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 48.8; H, 6.3; N, 26.1%; M^+, 267.1344. $C_{11}H_{17}N_5O_3$·0.1H_2O requires C, 49.10; H, 6.44; N, 26.03%; *M*, 267.1331).

9-[4-(2-*Hydroxyethoxy*)-3-*hydroxymethylbutyl*]*guanine* (**26b**).—A solution of the purine (**26b**) (0.48 g, 1.2 mmol) in 1M hydrochloric acid (2.5 ml) was heated under reflux for 75 min. The solution was neutralised with 25% aqueous sodium hydroxide and allowed to cool. Filtration afforded the guanine (**26b**) as a white solid (220 mg, 62%), m.p. 110—112 °C followed by recrystallisation and melting again at 165—168 °C; $\lambda_{max.}$(H_2O) 252 (ε 12 400) and 270sh nm (9 200); $\nu_{max.}$(KBr) 3 390, 3 330, 3 160, 1 690, 1 635, 1 605, 1 580, 1 540, and 1 485 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.60 (1 H, m, 3′-H), 1.74 (2 H, m, 2′-H), 3.3—3.5 (8 H, m, 4 × CH_2O), 4.00 (2 H, t, *J* 7.2 Hz, 1′-H), 4.46 (1 H, br t, D_2O exchangeable, OH), 4.54 (1 H, br t, D_2O exchangeable, OH), 6.44 (2 H, s, D_2O exchangeable, 2-NH_2), 7.67 (1 H, s, 8-H), and 10.60 (1 H, br, D_2O exchangeable, 1-H) (Found: C, 47.6; H, 6.9; N, 23.0%; M^+, 297.1429. $C_{12}H_{19}N_5O_4$·0.3 H_2O requires C, 47.61; H, 6.53; N, 23.13%; *M*, 297.1437).

9-[4-(2,3-*Dihydroxypropoxy*)-3-*hydroxymethylbutyl*]*guanine* (**26c**).—A solution of the purine (**25c**) (0.76 g, 1.6 mmol) in 1M hydrochloric acid (3 ml) was heated under reflux for 1.5 h. The solution was neutralised with aqueous sodium hydroxide and evaporated. The residue was purified by preparative h.p.l.c. on a reverse-phase C_{18} μ-Bondapak column eluting with 10% methanol in water. Product-containing fractions were pooled, and evaporated and the residue was triturated with ethanol to afford the guanine (**26c**) as a white solid (0.38 g, 73%), m.p. 161—168 °C; $\lambda_{max.}$(H_2O) 252 (ε 12 600) and 270sh nm (9 300); $\nu_{max.}$(KBr) 3 340, 3 150, 2 920, 1 690, 1 635, 1 605, 1 580, 1 545, 1 480, and 1 410 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.60 (1 H, m, 3′-H), 1.74 (2 H, m, 2′-H), 3.35 (8 H, m, 4 × CH_2O), 3.58 (1 H, m, C*H*OH), 4.00 (2 H, t, *J* 7.3 Hz, 1′-H), 4.46 (2 H, m, D_2O exchangeable, 2 × CH_2OH), 4.59 (1 H, d, *J* 5.0 Hz, D_2O exchangeable, CHO*H*), 6.38 (2 H, s, D_2O exchangeable, 2-NH_2), 7.67 (1 H, s, 8-H), and 10.49 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 46.0; H, 6.3; N, 20.45%; M^+, 327.1547. $C_{13}H_{21}N_5O_5$·0.7H_2O requires C, 45.93; H, 6.64; N, 20.60%; *M*, 327.1543).

9-(4-*Bromo*-3-*hydroxymethylbutyl*)*guanine* (**28**).—Triphenylphosphine (2.36 g, 9.0 mmol) was added to a solution of the protected guanine (**27**) (4.84 g, 6.05 mmol) and tetrabromomethane (3.0 g, 9.0 mmol) in dry DMF (25 ml) at 0 °C and the solution was stirred at 0 °C for 30 min. Methanol (1 ml) was added and the solvent was removed. The residue was taken up in 80% acetic acid (60 ml) and the solution was stirred at 70 °C for 40 min. After cooling, the solution was extracted with hexane (3 × 60 ml). Additional water (20 ml) was added and the solution was extracted with chloroform (30 ml). The aqueous solution was collected, solvent removed, and the residue azeotroped with toluene (×3). The residue was purified by column chromatography on silica gel eluting with chloroform–

methanol mixtures (3:1—2:1) to give the title compound (**28**) (1.18 g, 62%), m.p. >250 °C (decomp.); $\lambda_{max.}$(MeOH) 255 nm (ε 12 200); $\nu_{max.}$(KBr) 3 400, 3 120, 1 680, and 1 605 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.64 (1 H, m, 3′-H), 1.78 (2 H, m, 2′-H), 3.40 (2 H, m, CH_2O), 3.65 (2 H, m, CH_2Br), 4.01 (2 H, t, *J* 7.0 Hz, 1′-H), 4.68 (1 H, t, *J* 5.2 Hz, D_2O exchangeable, OH), 6.41 (2 H, s, D_2O exchangeable, 2-NH_2), 7.70 (1 H, s, 8-H), and 10.51 (1 H, br s, D_2O exchangeable, 1-H); *m/z* (f.a.b. +ve ion; thioglycerol) 316/318.

9-(4-*Azido*-3-*hydroxymethylbutyl*)*guanine* (**29**).—A solution of compound (**28**) (348 mg, 1.1 mmol) and sodium azide (117 mg, 1.8 mmol) in DMF (5 ml) was stirred at 80 °C for 75 min. After cooling, the solvent was removed and ethanol was added and evaporated twice. The residue was triturated with water (2 ml) and filtered. The solid material was purified by column chromatography on silica gel, eluting with chloroform–methanol mixtures (5:2—2:1) to give the azido compound (**29**) (165 mg, 54%); $\nu_{max.}$(KBr) 3 120, 2 100, 1 685, and 1 610 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.55 (1 H, m, 3′-H), 1.74 (2 H, m, 2′-H), 3.40 (4 H, m, CH_2O and CH_2N_3), 4.00 (2 H, t, *J* 7.1 Hz, 1′-H), 4.65 (1 H, t, *J* 5.2 Hz, D_2O exchangeable, OH), 6.39 (2 H, s, D_2O exchangeable, 2-NH_2), 7.69 (1 H, s, 8-H), and 10.50 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 40.3; H, 4.7; N, 37.2%; M^+, 278.1249. $C_{10}H_{14}N_8O_2$·0.2$CHCl_3$ requires C, 40.55; H, 4.73; N, 37.08%; *M*, 278.1240).

9-(4-*Amino*-3-*hydroxymethylbutyl*)*guanine Acetate Salt* (**30**).—10% Palladium-on-charcoal (20 mg) was added to a suspension of the azide (**29**) (140 mg, 0.5 mmol) in methanol (5 ml) containing formic acid (0.075 ml, 2 mmol) and ammonia (*d* 0.880; 0.11 ml, 2 mmol) and the mixture was stirred at 65 °C for 1 h. The solution was filtered and the solvent removed. Excess of ammonium formate was removed *in vacuo* to give the product (140 mg). Some of this material (50 mg) was purified by preparative h.p.l.c. on a reverse-phase C_{18} μ-Bondapak column eluting with 3% methanol in aqueous ammonium acetate (pH 4.5; 50 mM) to give the amine (**30**) as the acetate salt (38 mg, 68%); $\nu_{max.}$(KBr) 3 410, 3 120, 1 695, 1 610, 1 575, and 1 540 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.44 (1 H, m, 3′-H), 1.71 (2 H, q, *J* 6.9 Hz, 2′-H), 1.83 (3 H, s, CH_3CO_2), 2.65 (2 H, d, *J* 3.9 Hz, CH_2NH_2), 3.43 (2 H, d, *J* 5.2 Hz, CH_2OH), 3.97 (2 H, d, *J* 7.3 Hz, 1′-H), 5.0 (7 H, vbr, D_2O exchangeable, 1-H, OH, NH_3^+, and H_2O), 6.56 (2 H, s, D_2O exchangeable, 2-NH_2), and 7.68 (1 H, s, 8-H) (Found: C, 43.5; H, 6.8; N, 24.9. $C_{12}H_{20}N_6O_4$·1.2 H_2O requires: C, 43.16; H, 6.76; N, 25.17%).

9-(4-*Formamido*-3-*formyloxymethylbutyl*)*guanine* (**31**).—A mixture of the amine (**30**) formate salt (50 mg, 0.17 mmol), dicyclohexylcarbodi-imide (45 mg, 0.22 mmol), formic acid (10 μl, 0.26 mmol), and DMAP (3 mg) in dry DMF (1 ml) was stirred at room temperature. Further portions of dicyclohexylcarbodi-imide (42 mg, 30 mg) and of formic acid (10 μl) were added and the mixture was stirred for a total of 4 h. Water was added, the solution filtered, and the filtrate evaporated. The residue was purified by preparative h.p.l.c. on a reverse phase C_{18} μ-Bondapak column eluting with 10% methanol in aqueous ammonium acetate (50mM; pH 4.5) and recrystallised from methanol–ethyl acetate to give the diformyl compound (**31**) (9 mg, 17%), m.p. 156—160 °C; $\lambda_{max.}$(H_2O) 254 and 270sh nm; $\nu_{max.}$(KBr) 3 400, 3 120, and 1 690 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.75 (3 H, m, 2′-H and 3′-H), 3.18 (2 H, t, *J* 5 Hz, D_2O exchange gives d, CH_2NH), 4.0—4.1 (4 H, m, 1′-H and CH_2O), 6.40 (2 H, s, D_2O exchangeable, 2-NH_2), 7.68 (1 H, s, 8-H), 8.0 (1 H, br, D_2O exchangeable, HCO*NH*), 8.04 (1 H, s, HCO), 8.22 (1 H, s, HCO), and 10.1 (1 H, br s, D_2O exchangeable, 1-H); *m/z* 308 (M^+, 15%), 262 (22), 204 (29), 164 (40), 152 (69), 105 (76), and 46 (100).

Acknowledgements

We thank Mr. M. R. Boyd and his colleagues for carrying out the antiviral tests.

References

1 Part 2, S. Bailey and M. R. Harnden, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper.
2 A. Larsson, S. Alenius, N.-G. Johansson, and B. Öberg, *Antiviral Res.*, 1983, **3**, 77.
3 A.-C. Ericson, A. Larsson, F. Y. Aoki, W.-A. Yisak, N.-G. Johansson, B. Öberg, and R. Datema, *Antimicrob. Agents Chemother.*, 1985, **27**, 753.
4 A. Larsson, B. Öberg, S. Alenius, C.-E. Hagberg, N.-G. Johansson, B. Lindborg, and G. Stening, *Antimicrob. Agents Chemother.*, 1983, **23**, 664.
5 K. Stenberg, A. Larsson, and R. Datema, *J. Biol. Chem.*, 1986, **261**, 2134.
6 M. R. Harnden and R. L. Jarvest, E. P. Appln. 141927A/1985 (to Beecham Group p.l.c.).
7 M. R. Boyd, T. H. Bacon, D. Sutton, and M. Cole, *Antimicrob. Agents Chemother.*, 1987, **31**, 1238.
8 M. R. Harnden, R. L. Jarvest, T. H. Bacon, and M. R. Boyd, *J. Med. Chem.*, 1987, **30**, 1636.
9 M. A. Tippie, J. C. Martin, D. F. Smee, T. R. Matthews, and J. P. H. Verheyden, *Nucleosides, Nucleotides*, 1984, **3**, 525.
10 A. Larsson, K. Stenberg, A.-C. Ericson, U. Hagland, W.-A. Yisak, N. G. Johansson, B. Öberg, and R. Datema, *Antimicrob. Agents Chemother.*, 1986, **30**, 598.
11 M. MacCross, R. L. Tolman, W. T. Ashton, A. F. Wagner, J. Hannah, A. K. Field, J. D. Karkas, and J. I. Germershausen, *Chem. Scr.*, 1986, **26**, 113.
12 M. R. Harnden, A. Parkin, and P. G. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2757.
13 M. R. Harnden and R. L. Jarvest, *Tetrahedron Lett.*, 1985, **26**, 4265.

Received 19*th October* 1988; *Paper* 7/1865