Analogues of the Antiviral Acyclonucleoside 9-(4-Hydroxy-3-hydroxymethylbutyl)guanine. Part 1. Substitutions on C-2′ of the Acyclic N-9 Substituent

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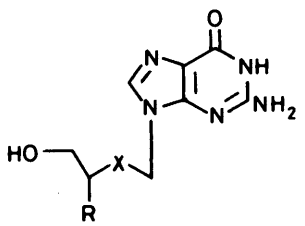
Syntheses of 9-(4-hydroxy-3-hydroxymethyl-2-methylbutyl)guanine (**4**), 9-(4-hydroxy-3-hydroxymethyl-2-methoxybutyl)guanine (**5**), 9-[4-hydroxy-2,3-bis(hydroxymethyl)butyl]guanine (**6**), 9-(2,4-dihydroxy-3-hydroxymethylbutyl)guanine (**7**), and 9-(2-fluoro-4-hydroxy-3-hydroxymethylbutyl)-guanine (**8**) are described. These analogues of the antiviral acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**3**) were prepared by a route involving alkylation of 2-amino-6-chloropurine with a protected bromide or trifluoromethanesulphonate ester derived from the appropriately substituted alcohol (**9a—e**). Subsequent hydrolysis and deprotection afforded the required 9-substituted guanine. None of this series of acyclonucleosides (**4**)—(**8**) was highly active in antiviral tests in cell cultures.

The discovery of the potent and selective anti-herpes virus activity of 9-(2-hydroxyethoxymethyl)guanine [acyclo-guanosine, acyclovir, (**1**)][1–3] has stimulated extensive research into the preparation and evaluation of similar purine derivatives.[4,5] In the majority of cases, variation of the acyclic 9-substituent has resulted in compounds with substantially diminished anti-herpes virus activity. Some such modifications have, however, provided compounds with very high antiviral activity, the most potent compound to have been synthesized to date being 9-[(1,3-dihydroxypropan-2-yloxy)methyl]guanine [BIOLF-62, 2′-NDG, DHPG, (**2**)].[6–8] Our interest has been focussed on the closely related acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**3**) and its synthesis[9] and selective anti-herpes virus activity[10–12] have recently been reported. The presence in (**3**) of a methylene moiety at the position occupied by the ether oxygen of acyclovir and DHPG



	R	X
(**1**)	H	O
(**2**)	CH_2OH	O
(**3**)	CH_2OH	CH_2

(designated the 2′-position) allows the introduction of additional substituents at this position, whereas this is not possible with the latter two compounds. In this publication we describe the synthesis of a series of novel acyclonucleosides in which small atoms or groups with varying steric requirements and electronic properties have been introduced at the 2′-position of (**3**). The antiviral activity of these compounds in cell cultures has been determined. Syntheses of additional analogues of (**3**) modified at other positions on the acyclic N-9 substituent will be described in subsequent papers in this series.

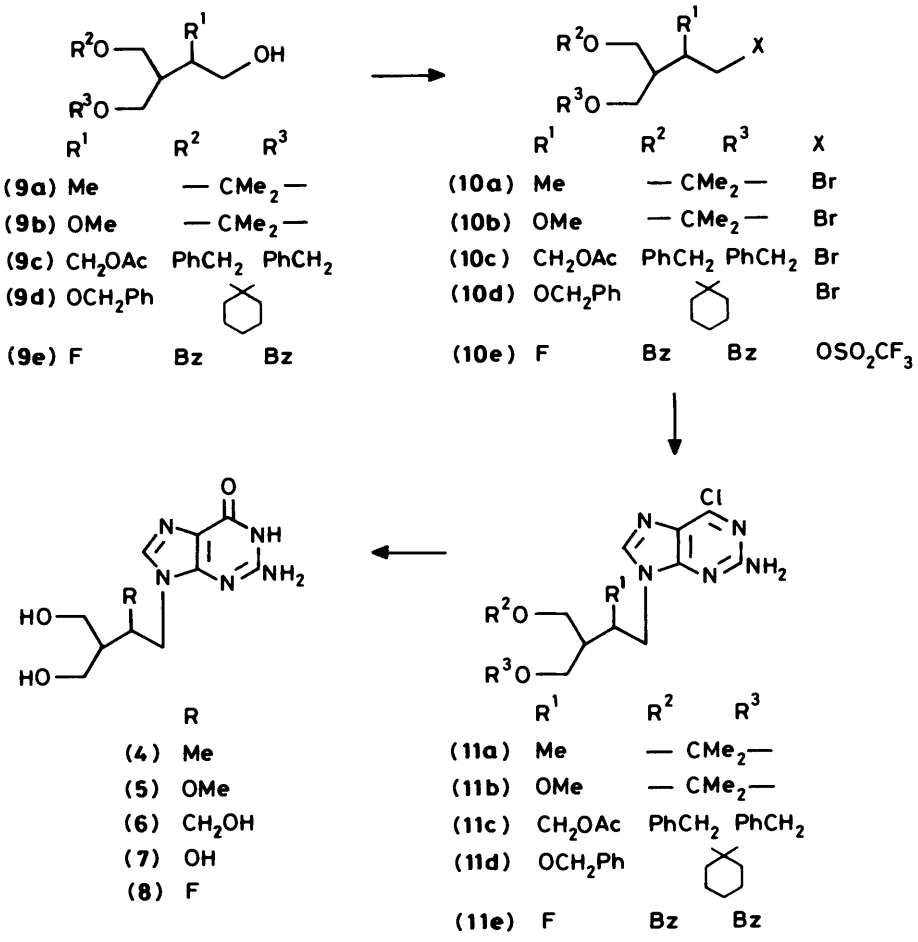
Results and Discussion

The racemic acyclonucleosides (**4**)—(**8**) were prepared by a route involving alkylation of 2-amino-6-chloropurine. The strategy employed for synthesis of the 9-substituent involved preparation of partially protected alcohols (**9a—e**) which were, in general, converted into bromides (**10a—d**) by reaction with triphenylphosphine–carbon tetrabromide prior to reaction with the purine (Scheme 1). In the case of the fluorinated alcohol (**9e**), however, bromination could not be achieved with these reagents, even at elevated temperatures. This problem was circumvented by conversion of (**9e**) into its trifluoromethane-sulphonate ester (**10e**), which was used for alkylation of 2-amino-6-chloropurine.

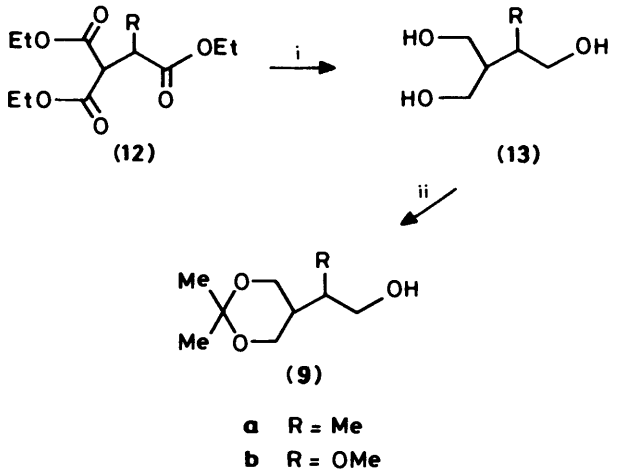
The alcohols (**9a—e**) were prepared as shown in Schemes 2—4. In our published synthesis of (**3**),[9] an efficient and convenient route to the precursor of the 9-substituent was reported. This involved reduction of a triester to a triol using sodium borohydride–methanol in refluxing t-butyl alcohol, followed by selective protection of the 1,3-diol system by acetonide formation with 2,2-dimethoxypropane (Scheme 2; R = H). These procedures proved less satisfactory for the preparation of the alcohols (**9a**) and (**9b**). Reduction of (**12a**) with sodium borohydride afforded the triol (**13a**), but in the case of (**12b**) elimination of the methoxy group occurred. We have observed substantially decreased efficiency of metal hydride reducing agents in several systems containing acidic hydrogens and in such situations have employed the mild reducing agent borane–dimethyl sulphide. Using this reagent, the synthesis of (**13b**) from (**12b**) was achieved in 60% yield, after chromatography. Protection of the 1,3-diol system in (**13a**) and (**13b**) was accomplished with little selectivity and, in addition to the required alcohols (**9a**) and (**9b**), isomeric 7-membered ring products were obtained. The alcohols were subsequently converted into the bromides (**10a**) and (**10b**), which were isolated by chromatography.

Preparation of the alcohol precursor of the 2′-hydroxymethyl analogue (**6**) was accomplished by reaction of 1,3-dibenzyloxy-2-mesyloxypropane (**14**) with diethyl malonate (Scheme 3). The crude diester (**15**) was reduced with lithium aluminium hydride, affording the diol (**16**) in 11% overall yield from (**14**). Treatment of (**16**) with trimethyl orthoacetate gave a cyclic orthoester intermediate which, on acid hydrolysis, afforded the mono-acetate (**9c**) in 84% yield.

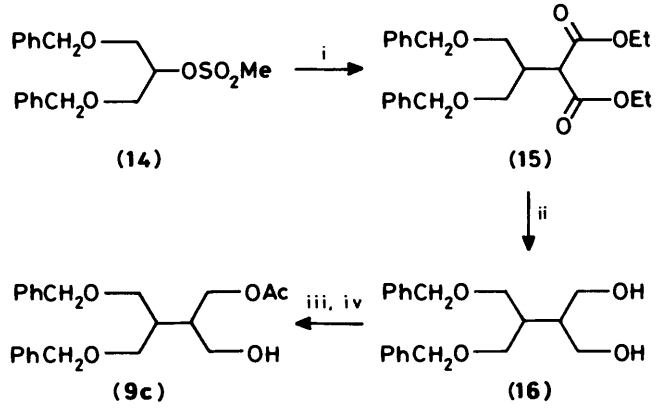
The alcohol precursors of the 2′-hydroxy and 2′-fluoro



Scheme 1.

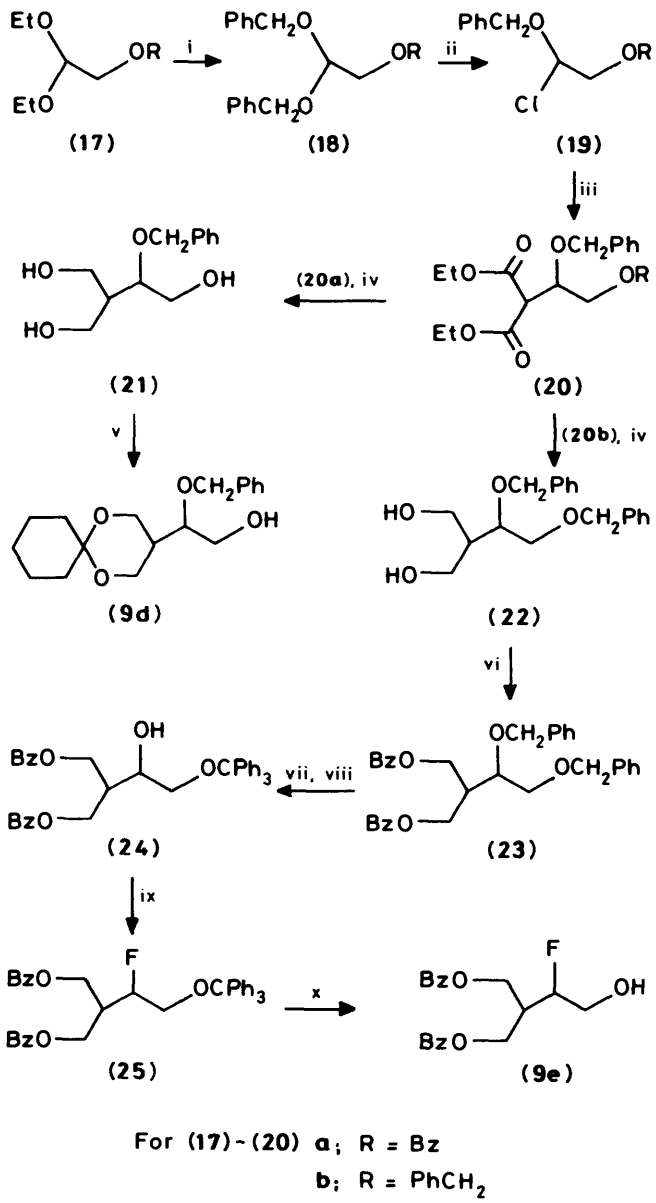


Scheme 2. *Reagents:* i, **a** $NaBH_4$, **b** 10M BH_3·Me_2S, THF; ii, $(MeO)_2CMe_2$



Scheme 3. *Reagents:* i, $(EtOCO)_2CHNa$; ii $LiAlH_4$, Et_2O; iii, $(MeO)_3CMe$, TsOH; iv, 5% HOAc

analogues, (**7**) and (**8**) respectively, were prepared by reaction of α-chlorobenzyl ethers with diethyl malonate (Scheme 4). The chloro ethers (**19a**) and (**19b**) were synthesized in high overall yield from *O*-protected glycolaldehyde diethyl acetals (**17a**, **b**). Transacetalisation afforded the dibenzyl acetals (**18a**) and (**18b**) in 90% yield and these were cleanly converted into (**19a**) and (**19b**) with phosphorus pentachloride in refluxing 1,2-dichloroethane. Reaction of (**19a**) and (**19b**) with diethyl malonate anion in dry benzene gave in each case a mixture of products from which the diesters (**20a**) and (**20b**) were obtained in 40 and 60% yield, respectively, after chromatography. Reduction of (**20a**) and (**20b**) with borane–dimethyl sulphide then afforded the alcohols (**21**) and (**22**), in 54 and 57% yield, respectively. Treatment of (**21**) with cyclohexanone and toluene-*p*-sulphonic acid gave the cyclohexylidene derivative (**9d**) in 43% yield. A



Scheme 4. *Reagents*: i, $PhCH_2OH$, TsOH; ii, PCl_5 $C_2H_4Cl_2$; iii, $(EtOCO)_2CHNa$; iv, 10M BH_3·Me_2S, THF; v, $C_6H_{10}O$, TsOH; vi, BzCl, C_5H_5N; vii, H_2, 5% Pd-C; viii, Ph_3CCl, C_5H_5N; ix, Et_2NSF_3, THF, Et_3N; x, HOAc

small amount of the isomeric 7-membered ring product was also formed in this reaction. The diol (**22**) was converted into its dibenzoate ester (**23**), the *O*-benzyl groups removed by hydrogenolysis and the triphenylmethyl ether (**24**) prepared. Attempts to fluorinate (**24**) using diethylaminosulphur trifluoride in dichloromethane in the presence of either organic or inorganic bases were unsuccessful. In the absence of a large excess of an organic base, migration of a benzoate moiety to the secondary hydroxy group occurred. When (**24**) was treated with diethylaminosulphur trifluoride in tetrahydrofuran–triethylamine (1:1), the required fluoro compound (**25**) was, however, obtained in 60% yield. Although detritylation of (**25**) could not be effected by catalytic hydrogenolysis using palladium on carbon at atmospheric pressure, deprotection was accomplished in acetic acid at 70 °C, but the alcohol (**9e**) was isolated in only 40% yield.

The 9-substituted 2-amino-6-chloropurines (**11a**—**e**) were obtained by alkylation of 2-amino-6-chloropurine with the bromides (**10a**—**d**) and the triflate (**10e**). Yields in the range 40—53% were obtained, with traces of 7-substituted purines being detected in some cases. Conversion of (**11a**—**e**) into guanine derivatives was accomplished by acidic hydrolysis. With the isopropylidene derivatives (**11a**) and (**11b**) hydrolysis of the 6-chloro group occurred with concomitant removal of the protecting group, affording (**4**) and (**5**) directly. For compounds (**11c**—**e**), standard deprotection procedures were employed in addition to acidic hydrolysis. The acyclonucleosides (**4**)—(**8**) or their hydrochloride salts were isolated in 32—78% overall yield from the 6-chloropurine derivatives (**11a**—**e**).

Biological Data.—The acyclonucleosides prepared in this study were tested for antiviral activity in cell cultures. Unlike the lead compound (**3**),[10–12] none of the compounds (**4**)—(**8**) was highly active against herpes simplex virus types 1 and 2. The 50% inhibitory concentration (IC_{50}) against two strains (HFEM and SC-16) of herpes simplex virus type 1 in Vero (African green monkey kidney) cells and MRC-5 (human fibroblast) cells, respectively, was in each case >100 μg/ml. Against herpes simplex virus type 2 (MS) in Vero cells, compounds (**4**), (**6**), and (**8**) had an IC_{50} of 32, 64, and 72 μg ml^{-1}, respectively, but when the compounds were tested against the MS strain in MRC-5 cells, only (**4**), with an IC_{50} of 74 μg ml^{-1}, showed any activity at concentrations up to 100 μg ml^{-1} Additionally, at concentrations up to 100 μg ml^{-1}, none of (**4**)—(**8**) 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 for the cell monolayer was observed only with compound (**6**) at 100 μg ml^{-1} in Vero cells.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 580 instrument; u.v. spectra were obtained on a Cary 219 spectrometer. N.m.r. spectra were recorded on JEOL GX270 and Bruker AM 400 spectrometers. Mass spectrometry was performed using a V.G. 70-70F instrument operating at 70 eV. M.p.s were determined using a Reichert-Kofler apparatus and are uncorrected. Elemental analysis was carried out on a Carlo Erba model 1106 analyser. Organic solutions of products were dried using magnesium sulphate and chromatography was performed on Merck 7736 60 H silica gel. All compounds were homogeneous by t.l.c. on silica gel $60F_{254}$ coated aluminium sheets.

5-(2-*Hydroxy*-1-*methylethyl*)-2,2-*dimethyl*-1,3-*dioxane* (**9a**).—Methanol (6 ml) was added in three portions, over a period of 0.5 h to a refluxing solution of the triester (**12a**) (14 g, 54 mmol) in t-butyl alcohol (100 ml) and sodium borohydride (5.3 g, 140 mmol). The mixture was heated at reflux temperature for a further 0.5 h and then cooled and neutralised by careful addition of 5M hydrochloric acid. The mixture was filtered and the residue extracted with ethanol (70 ml) and refiltered. The ethanol was removed under reduced pressure to give a crude oil (7.8 g), which was dissolved in tetrahydrofuran (25 ml) and treated with 2,2-dimethoxypropane (8 ml, 64 mmol) and toluene-*p*-sulphonic acid (0.7 g). The mixture was stirred at room temperature for 2 h and then neutralised by addition of triethylamine. The solvent was removed and the residue chromatographed on silica gel, eluting with acetone–hexane (1:3) to give, as the second component to be eluted, (**9a**) as an oil (1.4 g, 15%); $\nu_{max.}$(film) 3 450, 2 995, 2 960, 2 940, 2 880, and 1 460 cm^{-1}; $\delta_H(CDCl_3)$, 0.98 (3 H, d, *J* 7 Hz, CH_3), 1.4 (6 H, s, 2 × CH_3), 1.68 (2 H, m, 2 × CH), 2.4 (1 H, br t, *J* 4 Hz, D_2O exchangeable OH), and 3.5—4.1 (6 H, m, 3 × CH_2); *m/z* 159

(M^+ − 15, 55%), 99 (75), 81 (40), 69 (65), 59 (100), 57 (50), 55 (55), and 43 (85) (Found: C, 60.8; H, 10.2%; M^+ 159.1022. $C_9H_{18}O_3 \cdot 0.25H_2O$ requires C, 60.5; H, 10.4%. $C_9H_{18}O_3 - CH_3$ requires M^+, 159.1021).

5-(2-*Bromo*-1-*methylethyl*)-2,2-*dimethyl*-1,3-*dioxane* (**10a**).—Carbon tetrabromide (4.1 g, 12.4 mmol) and triphenylphosphine (3.25 g, 12.4 mmol) were added to a stirred solution of the alcohol (**9a**) (1.08 g, 6.2 mmol) in dichloromethane (40 ml) at 0 °C. The solution was stirred at room temperature for 1 h and then neutralised by shaking with saturated aqueous sodium hydrogen carbonate (200 ml). The layers were separated and the organic phase was washed with aqueous sodium hydrogen carbonate (2 × 50 ml) and water (50 ml). The organic phase was dried and evaporated to leave an oil which was chromatographed on silica gel, eluting with ethyl acetate–cyclohexane (1:6) to give, as the second component to be eluted, (**10a**) as an oil (0.52 g, 35%); $\nu_{max.}$(film) 2 990, 2 970, 2 940, 2 870, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.05 (3 H, d, *J* 7 Hz, CH_3), 1.39 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.77 (1 H, m, CH), 1.90 (1 H, m, CH), 3.45 (2 H, m, CH_2), 3.72 (2 H, dd, *J* 7.5 and 12 Hz, 2 × CH of CH_2), and 3.94 (2 H, dd, *J* 4.5 Hz, and 12 Hz, 2 × CH of CH_2).

2-*Amino*-6-*chloro*-9-[2-(2,2-*dimethyl*-1,3-*dioxan*-5-*yl*)-*propyl*]*purine* (**11a**).—A mixture of the bromide (**10a**) (0.5 g, 2.1 mmol), 2-amino-6-chloropurine (0.4 g, 2.3 mmol) and potassium carbonate (0.5 g, 3.5 mmol) in dry *N*,*N*-dimethylformamide (10 ml) was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The organic phase was washed with water (2 × 25 ml), dried, and evaporated under reduced pressure to afford a residue which was chromatographed on silica gel, eluting with ethyl acetate to give (**11a**) as a solid (0.26 g, 38%); $\nu_{max.}$(KBr) 3 400, 3 320, 3 200, 2 990, 2 940, 2 880, 1 610, 1 560, 1 520, 1 465, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 0.89 (3 H, d, *J* 6 Hz, CH_3), 1.41 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 1.68 (1 H, m, CH), 2.17 (1 H, m, CH), 3.7—4.3 (6 H, m, 3 × CH_2), 5.08 (2 H, s, D_2O exchangeable NH_2), and 7.72 (1 H, s, CH); *m*/*z* 325 (M^+, 15%), 310 (40), 239 (30), 238 (25), 211 (10), 183 (70), 169 (40), 134 (25), 45 (100), and 43 (55) (Found: C, 51.3; H, 6.3; N, 21.0%; M^+, 325.1308. $C_{14}H_{20}ClN_5O_2$ requires C, 51.6; H, 6.2; N, 21.5%; M^+, 325.1305).

9-(4-*Hydroxy*-3-*hydroxymethyl*-2-*methylbutyl*)*guanine* (**4**).—A solution of compound (**11a**) (100 mg, 0.3 mmol) in 2.5M hydrochloric acid (1 ml) was heated at reflux temperature for 2 h. It was then neutralised with aqueous sodium hydrogen carbonate and cooled. The product precipitated out and was filtered off (47 mg) and a second crop (3 mg) was obtained by evaporation of the filtrate (61%). Recrystallisation from water gave (**4**), m.p. 245 °C (decomp.); $\lambda_{max.}(H_2O)$ 253 (ε 10 360) and 273sh nm; $\nu_{max.}$(KBr) 3 600—2 700, 1 690, 1 620, 1 580, 1 540, 1 480, and 1 410 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 0.75 (3 H, d, *J* 7 Hz, CH_3), 1.51 (1 H, m, CH), 2.21 (1 H, m, CH), 3.42 (4 H, m, 2 × CH_2), 3.87 (1 H, dd, *J* 9 and 13.5 Hz, CH of CH_2), 4.01 (1 H, dd, *J* 6.5 and 13.5 Hz, CH of CH_2), 4.43 (2 H, br s, D_2O exchangeable OH), 6.50 (2 H, s, D_2O exchangeable NH_2), 7.62 (1 H, s, CH), and 10.78 (1 H, br s, D_2O exchangeable NH) (Found: C, 47.2; H, 6.2; N, 24.7%. $C_{11}H_{17}N_5O_3 \cdot 0.75H_2O$ requires C, 47.1; H, 6.6; N, 24.9%).

5-(2-*Bromo*-1-*methoxyethyl*)-2,2-*dimethyl*-1,3-*dioxane* (**10b**).—Compound (**12b**) (14 g, 37.2 mmol) was added to a stirred solution of 10M borane–dimethyl sulphide complex (11.14 ml, 111 mmol) in dry THF (56 ml) under nitrogen. The solution was heated at 70 °C for 1.5 h, liberated dimethyl sulphide being distilled out. The solution was cooled to room temperature, water was added slowly, and the solution was neutralised by addition of potassium carbonate (10 g). The resulting suspension was evaporated to dryness and the residue co-evaporated with ethanol. After the resultant solid had been extracted twice with ethanol the combined solutions were evaporated to dryness under reduced pressure. The residue was dissolved in ethanol (75 ml), filtered, and evaporated to dryness. The resultant syrup was purified by chromatography on silica gel, eluting with chloroform–methanol (6:1) to yield (**13b**) as an oil (4.5 g, 62%).

Toluene-*p*-sulphonic acid (0.16 g, 0.84 mmol) was added to a solution of (**13b**) (4.2 g, 28 mmol) and 2,2-dimethoxypropane (3.8 ml, 30.8 mmol) in dry THF. After 0.5 h at room temperature the solution was neutralised by addition of triethylamine (1 ml) and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with chloroform–methanol (15:1) to give (**9b**) as an impure oil.

Carbon tetrabromide (7.56 g, 22.8 mmol) and triphenylphosphine (5.98 g, 22.8 mmol) were then added to a stirred solution of the crude alcohol (**9b**) in dry *N*,*N*-dimethylformamide at 0 °C. After 0.5 h the solution was allowed to warm to room temperature and stirred for 3 h. The solution was then added to water (20 ml) and extracted with ether. The combined ether extracts were dried and evaporated under reduced pressure to afford a syrup. The residue was chromatographed on silica gel, eluting with hexane–acetone (20:1) to give, as the second component to be eluted, (**10b**) as an oil (0.73 g, 23%); $\delta_H(CDCl_3)$ 1.39 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 1.9 (1 H, m, CH), 3.45 (3 H, s, OCH_3), 3.51 (1 H, dd, *J* 4 and 11 Hz, CH of CH_2), 3.61 (1 H, dt, *J* 4 and 8 Hz, CH), 3.75 (2 H, m, 2 × CH of CH_2), and 3.9—4.1 (3 H, m, CH_2Br and CH of CH_2).

2-*Amino*-6-*chloro*-9-[2-(2,2-*dimethyl*-1,3-*dioxan*-5-*yl*)-2-*methoxyethyl*]*purine* (**11b**).—A mixture of the bromide (**10b**) (0.73 g, 2.89 mmol), 2-amino-6-chloropurine (0.53 g, 3.18 mmol), and potassium carbonate (0.43 g) in dry *N*,*N*-dimethylformamide (5 ml) was stirred at room temperature for 4 days. The mixture was treated with chloroform (10 ml) and filtered. The filtrate was evaporated under reduced pressure to afford a syrup which was then treated with chloroform and filtered. The filtrate was evaporated to dryness and the residue purified by chromatography on silica gel, eluting with ethanol–chloroform (1:80) to give (**11b**) (640 mg, 65%) as a solid, m.p. 158—159 °C; $\nu_{max.}$(KBr) 3 300, 1 610, 1 560, 1 460, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.41 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 1.61 (1 H, m, CH), 3.31 (3 H, s, OCH_3), 3.68 (1 H, dt, *J* 3 and 7 Hz, CH), 3.8—4.1 (4 H, m, 2 × CH_2), 4.2 (1 H, dd, *J* 7 and 15 Hz, CH of CH_2), 4.45 (1 H, dd, *J* 3 and 15 Hz, CH of CH_2), 5.15 (2 H, br s, D_2O exchangeable NH_2), and 7.87 (1 H, s, CH) (Found: C, 49.4; H, 5.9; N, 20.5%. $C_{14}H_{20}ClN_5O_3$ requires C, 49.2; H, 5.9; N, 20.5%).

9-(4-*Hydroxy*-3-*hydroxymethyl*-2-*methoxybutyl*)*guanine* (**5**).—A solution of compound (**11b**) (0.64 g, 1.87 mmol) in 2M hydrochloric acid (2 ml) was heated at reflux temperature for 2.5 h. The solution was cooled to room temperature, neutralised with 10% aqueous sodium hydroxide, and evaporated to dryness. The residue was purified by chromatography on XAD-4 resin and recrystallised from water to give (**5**) (170 mg, 32%), m.p. 225—228 °C; $\lambda_{max.}(H_2O)$ 253 (ε 13 000) and 275sh nm; $\nu_{max.}$(KBr) 3 310, 3 170, 1 720, 1 630, 1 600, and 1 530 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.7 (1 H, m, CH), 3.1 (3 H, s, OCH_3), 3.4—3.7 (5 H, m, 2 × CH_2 and CH), 4.1 (2 H, m, CH_2), 4.4 (1 H, br s, D_2O exchangeable OH), 4.5 (1 H, br s, D_2O exchangeable OH), 6.65 (2 H, br s, D_2O exchangeable NH_2), 7.6 (1 H, s, CH), and 10.8 (1 H, br s, D_2O exchangeable NH); *m*/*z* (f.a.b. +ve ion, thioglycerol) MH^+ 284 (Found: C, 43.3; H, 5.9; N, 22.6. $C_{11}H_{17}N_5O_4 \cdot 1.2H_2O$ requires C, 43.3; H, 6.4; N, 23.0%).

4-*Benzyloxy*-3-*benzyloxymethyl*-2-*hydroxymethylbutan*-1-*ol* (**16**).—Mesyl chloride (31.35 ml, 0.4 mol) was added dropwise to a stirred solution of 1,3-dibenzyloxypropan-2-ol (55 g, 0.2 mol) and triethylamine (41.8 ml, 0.3 mol) in dichloromethane (150 ml) at −30 °C. After 0.5 h the reaction mixture was poured onto a mixture of ice-cooled 1M hydrochloric acid (150 ml) and chloroform (100 ml) and the organic layer separated; the aqueous layer was then extracted with chloroform (100 ml). The combined organic layers were washed with 1M hydrochloric acid (2 × 50 ml) and water (2 × 50 ml), dried, and evaporated to give crude (**14**) as a syrup. A small sample was purified by chromatography on silica gel, eluting with hexane–ethyl acetate (3:1); $\delta_H(CDCl_3)$ 3.0 (3 H, s, CH_3), 3.7 (4 H, d, *J* 5 Hz, 2 × CH_2), 4.5 (4 H, s, 2 × CH_2), 4.8 (1 H, m, CH), and 7.3 (10 H, s, 2 × C_6H_5).

Diethyl malonate (46.1 ml, 0.3 mol) was added dropwise with stirring to a dispersion of sodium hydride in oil (60%; 12.13 g, 0.30 mol) in dry *N*,*N*-dimethylformamide (130 ml) at 0 °C. After addition the suspension was stirred for 20 min at room temperature and then treated dropwise with a solution of the crude 1,3-dibenzyloxy-2-mesyloxypropane (**14**) in *N*,*N*-dimethylformamide (20 ml). The solution was heated at 150 °C overnight and then cooled, poured into water (150 ml), and neutralised with 5M hydrochloric acid. The suspension was extracted with hexane (3 × 50 ml) and the combined hexane extracts were washed with water (50 ml), dried, and evaporated to afford a syrup, which was chromatographed on silica gel, eluting with hexane–ethyl acetate (3:1) to give crude (**15**). This was added to a suspension of lithium aluminium hydride (10 g) in dry diethyl ether and the mixture heated under reflux overnight. It was then cooled and successively treated, dropwise and with stirring, with water (10 ml), 10% aqueous sodium hydroxide (10 ml), and water (20 ml). The organic phase was separated, dried, and evaporated to afford a syrup, which was purified by chromatography on silica gel, eluting with chloroform–ethanol (50:1) to give (**16**) (7.2 g, 11%), as an oil; $\delta_H(CDCl_3)$ 1.90 (1 H, m, CH), 2.20 (1 H, m, CH), 3.40 (2 H, s, 2 × D_2O exchangeable OH), 3.50 (4 H, d, *J* 5 Hz, 2 × CH_2), 3.65 (4 H, d, *J* 5 Hz, 2 × CH_2), 4.50 (4 H, s, 2 × CH_2), and 7.3 (10 H, s, 2 × C_6H_5).

2-*Acetoxymethyl*-4-*benzyloxy*-3-*benzyloxymethylbutan*-1-*ol* (**9c**).—A mixture of the diol (**16**) (7.19 g, 23.8 mmol), toluene-*p*-sulphonic acid monohydrate (0.4 g, 2.1 mmol), and trimethyl orthoacetate (20 ml) was stirred for 0.5 h at room temperature. The mixture was then evaporated under reduced pressure and the residue treated with 5% acetic acid (20 ml). The resultant suspension was then stirred for 0.5 h after which the solvent was removed and the product purified by chromatography on silica gel, eluting with chloroform, to give (**9c**) as an oil (6.89 g, 84%); $\nu_{max.}$(film) 3 450, 2 850, 1 740, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.90 (1 H, m, CH), 2.0 (3 H, s, CH_3), 2.1 (1 H, m, CH), 3.55—3.70 (6 H, m, 3 × CH_2), 4.2 (2 H, d, *J* 5 Hz, CH_2OAc), 4.5 (4 H, s, 2 × CH_2), and 7.3 (10 H, s, 2 × C_6H_5).

1-*Acetoxy*-4-*benzyloxy*-3-*benzyloxymethyl*-2-*bromobutane* (**10c**).—Carbon tetrabromide (9.95 g, 30 mmol) and triphenylphosphine (7.87 g, 30 mmol) were added to a stirred solution of the alcohol (**9c**) (6.8 g, 20 mmol) in dry *N*,*N*-dimethylformamide (30 ml) at 0 °C. After 0.5 h at 0 °C, the solution was stirred for 2 h at room temperature and then poured into water (30 ml). The suspension was extracted with hexane (3 × 30 ml) and the combined hexane extracts were washed with water (30 ml), dried, and evaporated to afford a syrup, which was purified by chromatography on silica gel, eluting with chloroform–hexane (7:3) to give (**10c**) (3.29 g, 40%) as an oil; $\nu_{max.}$(film) 2 930, 2 860, 1 740, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 2.03 (3 H, s, CH_3), 2.17 (1 H, m, CH), 3.01 (1 H, m, CH), 3.5—3.7 (6 H, m, 3 × CH_2), 4.13 (1H, dd, *J* 11.5 and 7 Hz, CH of CH_2), and 4.32 (1 H, dd, *J* 11.5 and 5 Hz, CH of CH_2); *m*/*z* 343.0554 (M^+; $C_{22}H_{27}BrO_4$ − C_7H_7 required M^+, 343.0546).

9-(2-*Acetoxymethyl*-4-*benzyloxy*-3-*benzyloxymethylbutyl*)-2-*amino*-6-*chloropurine* (**11c**).—A mixture of the bromide (**10c**) (3.29 g, 8.1 mmol), 2-amino-6-chloropurine (1.51 g, 8.9 mmol), potassium carbonate (1.23 g, 8.9 mmol), and dry *N*,*N*-dimethylformamide (10 ml) was stirred at room temperature for 4 days. The mixture was treated with chloroform (30 ml), filtered, and the filtrate evaporated to afford a syrup, which was purified by chromatography on silica gel, eluting with chloroform–ethanol (100:1) to give (**11c**) (1.7 g, 43%), m.p. 113—115 °C; $\nu_{max.}$(EtOH) 3 240, 1 735, 1 630, 1 620, 1 560, and 1 470 cm^{-1}; $\delta_H(CDCl_3)$ 1.92 (3 H, s, CH_3), 2.11 (1 H, m, CH), 2.75 (1 H, m, CH), 3.57 (4 H, d, *J* 6 Hz, 2 × CH_2), 4.0—4.3 (4 H, m, 2 × CH_2), 4.77 (2 H, s, CH_2Ph), 4.78 (2 H, s, CH_2), 5.04 (2 H, br s, D_2O exchangeable NH_2), 7.30 (10 H, m, 2 × C_6H_5), and 7.67 (1 H, s, CH) (Found: C, 61.1; H, 5.9; N, 13.1%. $C_{27}H_{30}ClN_5O_4 \cdot 0.4H_2O$ requires C, 61.0; H, 5.9; N, 13.2%).

9-(2,3-*Bishydroxymethyl*-4-*hydroxybutyl*)*guanine* (**6**).—A solution of compound (**11c**) (0.41 g, 0.9 mmol) in 2M hydrochloric acid (4 ml) and dioxane (1 ml) was heated at reflux for 1.25 h. It was then cooled to room temperature, neutralised with 10% aqueous sodium hydroxide and extracted with ethyl acetate (3 × 5 ml). The combined organic layers were dried, evaporated to dryness, and the residue was chromatographed on silica gel, eluting with chloroform–ethanol (7:1). The product (0.25 g) was dissolved in a mixture of ethanol (10 ml), water (25 ml) and 5M hydrochloric acid (5 ml) and treated with 10% palladium-on-charcoal. The stirred mixture was hydrogenated under atmospheric pressure for 1.5 h, and then filtered, neutralised with 10% aqueous sodium hydroxide, and evaporated to dryness. The residue was recrystallised from water to give (**6**) (0.11 g, 53%), m.p. 268—270 °C; $\lambda_{max.}(H_2O)$ 253 (ε 13 000) and 270sh nm: $\nu_{max.}$(KBr) 3 340, 3 160, 1 690, 1 645, 1 615, 1 545, 1 485, and 1 400 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.6 (1 H, m, CH), 2.1 (1 H, m, CH), 3.2—3.5 (6 H, m, 3 × CH_2), 4.0 (2 H, d, *J* 7 Hz, CH_2), 6.04 (2 H, br s, D_2O exchangeable NH_2), 7.6 (1 H, s, CH), and 10.5 (1 H, br s, D_2O exchangeable NH) (Found: C, 46.6; H, 6.0; N, 24.8. $C_{11}H_{17}N_5O_4$ requires 46.6; H, 6.1; N, 24.7%).

1-*Benzoyloxy*-2,2-*diethoxyethane* (**17a**).—Benzoyl chloride (19.3 ml, 165 mmol) was added dropwise to a stirred solution of glycoaldehyde diethyl acetal (21 ml, 150 mmol) in pyridine (100 ml) and di-isopropylethylamine (10 ml) cooled in an ice-bath. The solution was stirred at 0 °C for a total of 1 h and then at room temperature for 1.5 h. It was evaporated under reduced pressure and the residue treated with ice-cooled saturated aqueous sodium hydrogen carbonate (500 ml) and extracted with ethyl acetate (2 × 500 ml). The organic phase was washed with 5M hydrochloric acid (100 ml), aqueous sodium hydrogen carbonate (100 ml), and water (50 ml), and dried. The solvent was removed under reduced pressure and the residual pale yellow liquid was distilled under reduced pressure to give (**17a**) as a liquid (32 g, 90%) (b.p. 200 °C at 25 mmHg). An analytical sample was obtained by chromatography on silica gel, eluting with ethyl acetate–cyclohexane (1:8); $\nu_{max.}$(film) 2 980, 2 940, 2 900, 1 725, 1 600, 1 585, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.24 (6 H, t, *J* 7 Hz, 2 × CH_3), 3.70 (4 H, m, 2 × CH_2), 4.35 (2 H, d, *J* 6 Hz, CH_2), 4.85 (1 H, t, *J* 6 Hz, CH), and 7.3—8.5 (5 H, m, C_6H_5) (Found: C, 65.3; H, 7.5%. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%).

1-*Benzoyloxy*-2,2-*dibenzyloxyethane* (**18a**).—A stirred solution of compound (**17a**) (25 g, 10.5 mmol) and toluene-*p*-

sulphonic acid (0.5 g) in benzyl alcohol (250 ml) was heated at 90—100 °C under reduced pressure (25 mmHg) for 3 h, the ethanol formed during the reaction being distilled off. After complete reaction the excess of benzyl alcohol was removed by distillation *in vacuo* (0.05 mmHg), and the residue was dissolved in chloroform (250 ml) and washed with saturated aqueous sodium hydrogen carbonate (100 ml) and water (100 ml). The organic phase was dried and evaporated under reduced pressure to leave an oil, which was chromatographed on silica gel, eluting with ethyl acetate–cyclohexane (1:5) to give (**18a**) as a liquid (34 g, 89%); $\nu_{max.}$(film) 3 090, 3 060, 3 030, 2 960, 2 920, 2 880, 1 725, 1 600, 1 585, 1 500, 1 450, and 1 405 cm^{-1}; $\delta_H(CDCl_3)$ 4.44 (2 H, d, *J* 6 Hz, CH_2), 4.61 (2 H, d, *J* 12 Hz, 2 × CH of $OCH_2C_6H_5$), 4.78 (2 H, d, *J* 12 Hz, 2 × CH of $OCH_2C_6H_5$), 5.04 (1 H, t, *J* 6 Hz, CH), and 7.2—8.2 (15 H, m, 3 × C_6H_5) (Found: C, 75.9; H, 6.1%. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%).

Diethyl (2-*Benzoyloxy*-1-*benzyloxyethyl*)*malonate* (**20a**).—A dispersion of sodium hydride in oil (60%; 3.5 g, 87 mmol) was washed with dry benzene (3 × 50 ml) under nitrogen. After the solvent had been decanted, the solid was suspended in dry benzene (120 ml) and diethyl malonate (22 ml, 145 mmol) was added, dropwise with stirring. The mixture was then left overnight at room temperature.

A solution of compound (**18a**) (10.5 g, 29 mmol) and phosphorus pentachloride (6 g, 29 mmol) in dry dichloroethane (80 ml) was heated at 60 °C for 40 min. The solvent and phosphorus oxychloride were removed under reduced pressure to leave crude (**19a**) as a liquid; $\nu_{max.}$(film) 3 090, 3 060, 3 030, 2 940, 2 880, 1 725, 1 600, 1 585, 1 500, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 4.60 (3 H, m, CH_2 and CH of CH_2), 4.98 (1 H, d, *J* 12 Hz, CH of CH_2) 5.84 (1 H, t, *J* 6 Hz, CH), and 7.2—8.2 (10 H, m, 2 × C_6H_5).

The preformed suspension of diethyl malonate anion was treated with a solution of the crude (**19a**) in dry benzene (15 ml) with mechanical stirring. The mixture was stirred for 4 h at room temperature and then treated with brine (100 ml) and ethyl acetate (100 ml). The layers were separated and the organic phase was extracted with ethyl acetate (50 ml). The combined organic phases were washed with brine (5 × 50 ml), dried, and the solvent removed under reduced pressure. The excess of diethyl malonate was distilled off under reduced pressure to leave an oil (11.8 g), which was chromatographed on silica gel eluting with acetone–hexane (1:6). The first fraction to be eluted (6.8 g) contained crude (**20a**), which was purified by further chromatography on silica gel, eluting with ethyl acetate–cyclohexane (1:5) to give (**20a**) as an oil (4.8 g, 40%); $\nu_{max.}$(film) 3 090, 3 060, 3 040, 2 980, 2 940, 2 900, 2 880, 1 750, 1 730, 1 600, 1 585, 1 500, 1 475, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.25 (6 H, t, *J* 7 Hz, 2 × CH_3), 3.85 (1 H, d, *J* 6 Hz, CH), 4.17 (4 H, m, 2 × CH_2), 4.43 (2 H, m, CH_2), 4.70 (3 H, m, CH_2 and CH), and 7.8—8.1 (10 H, m, 2 × C_6H_5); *m/z* 415 (MH^+, < 1%), 255 (10), 203 (10), 187 (10), 186 (35), 113 (45), 105 (70), 91 (100), and 77 (25) (Found: C, 66.5; H, 6.4%. $C_{23}H_{26}O_7$ requires C, 66.7; H, 6.3%).

2-*Benzyloxy*-3-*hydroxymethylbutane*-1,4-*diol* (**21**).—A 10M solution of borane–dimethyl sulphide complex in tetrahydrofuran (1.2 ml, 12 mmol) was added to a stirred solution of the triester (**20a**) (1.68 g, 4 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. The solution was heated at 70 °C for 4 h liberated dimethyl sulphide being distilled out. Additional borane–dimethyl sulphide was added (0.6 ml, 6 mmol) and heating continued for 1 h. The solution was cooled to room temperature and water (7 ml) was added slowly. After effervescence had ceased, potassium carbonate (1.5 g) and tetrahydrofuran (20 ml) were added. The layers were separated and the aqueous phase was extracted with chloroform (10 ml). The organic layers were combined and tetrahydrofuran (100 ml) was added. After being washed with brine (20 ml) the organic phase was dried and evaporated under reduced pressure to give an oil (1.4 g), which was chromatographed on silica gel eluting with chloroform–methanol (10:1). The most polar component was collected, giving (**21**) (0.5 g, 54%); $\nu_{max.}$(film) 3 350, 2 940, 2 880, 1 500, 1 455, and 1 400 cm^{-1}; $\delta_H(CDCl_3)$ 2.00 (1 H, m, CH), 3.00 (3 H, s, 3 × D_2O exchangeable OH), 3.77 (7 H, m, 3 × CH_2 and CH), 4.53 (1 H, d, *J* 12 Hz, CH of CH_2), 4.65 (1 H, d, *J* 12 Hz, CH of CH_2), and 7.30 (5 H, s, C_6H_5) (Found: C, 63.7; H, 8.1%. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%).

3-(1-*Benzyloxy*-2-*hydroxyethyl*)-1,5-*dioxaspiro*[5.5]*undecane* (**9d**).—A solution of the triol (**21**) (1.1 g, 4.9 mmol) in cyclohexanone (25 ml) was treated with toluene-*p*-sulphonic acid (0.1 g, 0.5 mmol). The stirred solution was treated with triethylamine (0.3 ml) at room temperature for 20 h after which the solvent was removed under reduced pressure to leave an oil which was chromatographed on silica gel, eluting with ethyl acetate–cyclohexane (1:1). The most polar fraction was collected to give (**9d**) (0.66 g, 44%); $\nu_{max.}$(film) 3 440, 3 060, 3 030, 2 940, 2 960, 1 495, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.3—2.1 (11 H, m, 5 × CH_2 and CH), 2.20 (1 H, br s, D_2O exchangeable OH), 3.6—4.2 (7 H, m, 3 × CH_2 and CH), 4.60 (2 H, m, CH_2), and 7.30 (5 H, m, C_6H_5); *m/z* 306 (M^+, 5%), 263 (2), 262 (3), 208 (3), 207 (2), 160 (5), 159 (4), 141 (3), 117 (15), 99 (8), 98 (5), 92 (10), 91 (100), 83 (4), 70 (5), 69 (4), 65 (4), 57 (5), and 55 (10) (Found: C, 70.6; H, 8.6%; M^+, 306.1838. $C_{18}H_{27}O_4$ requires C, 70.3; H, 8.9%; M^+, 306.1831).

2-*Amino*-9-{2-*benzyloxy*-2-(1,5-*dioxaspiro*[5.5]*undecan*-3-*yl*)*ethyl*}-6-*chloropurine* (**11d**).—Carbon tetrabromide (0.83 g, 2.5 mmol) and triphenylphosphine (0.65 g, 2.5 mmol) were added to a stirred, ice-cooled solution of compound (**9d**) (0.51 g, 1.7 mmol) in dry *N*,*N*-dimethylformamide (8 ml). The mixture was stirred at 0 °C for 3 h, followed by 1 h at room temperature: it was then treated with saturated aqueous sodium hydrogen carbonate (8 ml), water (8 ml), and hexane (30 ml). The layers were separated and the aqueous phase was extracted with hexane (30 ml). The combined organic phases were dried and evaporated under reduced pressure to leave an oil which was stirred with hexane (15 ml). The hexane layer was decanted off and evaporated to dryness to give an oil (0.42 g), which was dissolved in dry *N*,*N*-dimethylformamide (5 ml) and treated with 2-amino-6-chloropurine (0.2 g, 1.2 mmol) and potassium carbonate (0.23 g, 1.6 mmol). The mixture was stirred at room temperature for 18 h and additional 2-amino-6-chloropurine (0.1 g, 0.6 mmol) and potassium carbonate (0.12 g, 0.8 mmol) were added. After the mixture had been stirred for a total of 3 days at room temperature the solvent was removed and the residue partitioned between chloroform (30 ml) and brine (20 ml). The layers were separated and the insoluble material present filtered off. The aqueous phase was extracted with chloroform (20 ml), and the combined organic layers were dried and evaporated to dryness. The resulting oil (0.48 g) was chromatographed on silica gel, eluting with ethyl acetate–cyclohexane (5:1) to give (**11d**) as an oil (0.18 g, 24%); $\nu_{max.}$(film) 3 420, 3 340, 3 210, 2 940, 2 860, 1 615, 1 565, 1 520, 1 465, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.65 (11 H, m, 5 × CH_2 and CH), 4.25 (9 H, m, 4 × CH_2 and CH), 5.13 (2 H, s, D_2O exchangeable NH_2), 7.2 (5 H, m, C_6H_5), and 7.82 (1 H, s, CH); *m/z* 457 (M^+, 10%), 416 (12), 414 (30), 351 (12), 169 (12), and 91 (100) (Found: C, 60.4; H, 6.2; N, 14.8%. $C_{23}H_{28}ClN_5O_3$ requires C, 60.3; H, 6.2; N, 15.3%).

9-(2,4-*Dihydroxy*-3-*hydroxymethylbutyl*)*guanine* (**7**).—A solution of compound (**11d**) (0.12 g, 0.26 mmol) in 2M hydrochloric acid (4 ml) was heated at reflux temperature for 1.5 h. The solution was cooled to room temperature and palladium-

charcoal catalyst (15 mg) was added. The mixture was subjected to atmospheric pressure hydrogenolysis for 2.5 h at room temperature and then filtered through a glass fibre pad. The solvent was removed and the residue subjected to high vacuum for 2 h. The white solid obtained was dissolved in a 1% solution of HCl in methanol (10 ml), and the solvent removed under reduced pressure to give (**7**) as its hydrochloride salt (68 mg, 78%), which was recrystallised from ethanol, m.p. 225 °C (decomp.); $\lambda_{max.}(H_2O)$ 252 (ε 13 400) and 275sh nm; $\nu_{max.}$(KBr) 3 360, 3 200, 3 130, 2 930, 2 900 2 850, 2 750, 1 730, 1 690, 1 635, 1 610, 1 570, 1 540, 1 480, and 1 410 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.60 (1 H, m, CH), 3.25—5.00 (> 10 H, m, 3 × CH_2, CH, D_2O exchangeable OH's and H_2O), 6.80 (2 H, s, D_2O exchangeable NH_2), 8.32 (1 H, s, CH), and 11.05 (1 H, s, D_2O exchangeable NH) [Found: C, 37.7; H, 5.1; N, 21.6%; M^+ (free base), 269.1124. $C_{10}H_{16}ClN_5O_4 \cdot 0.6H_2O$ requires C, 37.9; H, 5.5; N, 22.1%; $C_{10}H_{15}N_5O_4$ requires M^+, 269.1124].

1-*Benzyloxy*-2,2-*diethoxyethane* (**17b**).—A dispersion of sodium hydride in oil (60%; 12.1 g, 302 mmol) was washed with dry benzene (2 × 30 ml) under nitrogen. After decanting the solvent, the solid was suspended in dry tetrahydrofuran (500 ml) and treated dropwise with glycoaldehyde diethyl acetal (40.5 g, 302 mmol) in tetrahydrofuran (50 ml) over a period of 15 min, the temperature being maintained at 20—25 °C by ice cooling. The mixture was stirred for 2 h and left at room temperature overnight. Benzyl bromide (36 ml, 303 mmol) was added dropwise to the stirred mixture over a period of 1.5 h. Stirring was continued for an additional 5.5 h and the precipitated sodium bromide was filtered off. The solvent was removed and the residual oil dissolved in ethyl acetate (250 ml) and washed with brine (2 × 100 ml). The layers were separated and the organic phase dried and evaporated under reduced pressure to give an oil which was distilled *in vacuo* to give (**17b**) as a liquid (46 g, 69%), b.p. 84 °C, 0.06 mmHg. An analytically pure sample of (**17b**) was obtained by chromatography on silica gel, eluting with ethyl acetate–cyclohexane (1:4); $\nu_{max.}$(film) 3 090, 3 060, 3 030, 2 970, 2 930, 2 920, 2 870, 1 500, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.22 (6 H, t, *J* 7 Hz, 2 × CH_3), 3.65 (6 H, m, 3 × CH_2), 4.65 (3 H, m, CH_2 and CH), and 7.35 (5 H, s, C_6H_5) (Found: C, 69.6; H, 9.0%. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%).

1,2,2-*Tribenzyloxyethane* (**18b**).—A stirred solution of compound (**17b**) (8 g, 36 mmol) and toluene-*p*-sulphonic acid (80 mg) in benzyl alcohol (50 ml) was heated at 70 °C under reduced pressure (25 mmHg) for 2 h, the ethanol formed during the reaction being distilled off. After complete reaction, excess of benzyl alcohol was removed by distillation *in vacuo* (0.05 mmHg) and the residue was dissolved in chloroform (50 ml) and washed with aqueous sodium hydrogen carbonate (2 × 20 ml) and brine (20 ml). The organic phase was dried and evaporated under reduced pressure to leave an oil, which was chromatographed on silica gel, eluting with ethyl acetate–cyclohexane (1:4) to give (**18b**) as an oil (11 g, 89%); $\nu_{max.}$(film) 3 090, 3 060, 3 030, 2 910, 2 870, 1 950, 1 875, 1 810, 1 605, 1 585, 1 495, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 3.63 (2 H, d, *J* 6 Hz, CH_2), 4.65 (6 H, m, 3 × CH_2), 4.92 (1 H, t, *J* 6 Hz, CH), and 7.37 (15 H, s, 3 × C_6H_5) (Found: C, 79.3; H, 6.7%. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.9%).

Diethyl 1,2-*Dibenzyloxyethylmalonate* (**20b**).—A dispersion of sodium hydride in oil (60%; 4.8 g, 120 mmol) was washed with dry benzene (3 × 50 ml) under an atmosphere of dry nitrogen. After decanting the solvent, the solid was suspended in dry benzene (240 ml) and diethyl malonate (30 ml, 200 mmol) was added dropwise with stirring. The mixture was then left overnight at room temperature.

A solution of compound (**18b**) (14 g, 40 mmol) and phosphorus pentachloride (9.2 g, 44 mmol) in dry dichloroethane (210 ml) was heated at 60 °C for 35 min. The solvent and phosphorus oxychloride were removed under reduced pressure to leave crude (**19b**); $\nu_{max.}$(film) 3 090, 3 060, 3 030, 2 930, 2 870, 1 500, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 3.78 (2 H, m, CH_2), 4.70 (4 H, m, 2 × CH_2), 5.65 (1 H, t, *J* 6 Hz, CH), 7.29 (5 H, s, C_6H_5), and 7.30 (5 H, s, C_6H_5).

The preformed suspension of diethyl malonate anion was treated with a solution of the crude (**19b**) in dry benzene (20 ml) with mechanical stirring. The mixture was stirred for 16 h at room temperature and then treated with brine (150 ml) and ethyl acetate (150 ml). The layers were separated and the organic phase extracted with ethyl acetate (100 ml). The combined organic phases were washed with brine (3 × 100 ml), dried, and evaporated under reduced pressure. The excess of diethyl malonate was distilled off under reduced pressure to leave an oil (16 g), which was chromatographed on silica gel eluting with ethyl acetate–hexane (1:4). After recovery of unchanged (**18b**) (1.7 g), the major product to be eluted was (**20b**) as an oil (8.5 g, 60%); $\nu_{max.}$(film) 3 090 3 060, 3 040, 2 980, 2 940, 2 910, 2 870, 1 750, 1 735, 1 500, 1 465, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 1.20 (6 H, t, *J* 7 Hz, 2 × CH_3), 3.68 (2 H, m, CH_2), 3.80 (1 H, d, *J* 9 Hz, CH), 4.13 (4 H, m, 2 × CH_2), 4.30 (1 H, m, CH), 4.47 (1 H, d, *J* 12 Hz, CH of CH_2), 4.55 (1 H, d, *J* 12 Hz, CH of CH_2), 4.60 (1 H, d, *J* 11.5 Hz, CH of CH_2), 4.70 (1 H, d, *J* 11.5 Hz, CH of CH_2), and 7.30 (10 H, m, 2 × C_6H_5); *m/z* 400 (M^+, 1%), 309 (6), 270 (3), 204 (10), 203 (75), 187 (40), 175 (20), 129 (10), 10 (15), 107 (10), 92 (25), 91 (100), and 65 (15) (Found: M^+, 400.1880. $C_{23}H_{28}O_6$ requires M^+, 400.1887).

3,4-*Dibenzyloxy*-2-*hydroxymethylbutan*-1-*ol* (**22**).—A 10M solution of borane–dimethyl sulphide complex in tetrahydrofuran (7.5 ml, 75 mmol) was added to a stirred solution of the diester (**20b**) (12 g, 30 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. The solution was heated at 80 °C for 4 h the liberated dimethyl sulphide being distilled out. Additional borane–dimethyl sulphide was added (2 ml, 20 mmol) and heating was continued for 2 h.

The solution was cooled to room temperature and treated with tetrahydrofuran (50 ml) and then water (25 ml) was added slowly. After effervescence had ceased, potassium carbonate (20 g) was added. The emulsion which formed was filtered and the layers were separated. The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (3 × 50 ml). The combined organic phases were dried and evaporated to dryness. The oily residue was dissolved in chloroform and washed with 5M hydrochloric acid (10 ml). The organic layer was dried and evaporated under reduced pressure to give an oil (7.1 g), which was chromatographed on silica gel, eluting with ethyl acetate to give (**22**) as an oil (5.4 g, 57%). Subsequent chromatography on silica gel, eluting with chloroform–methanol (25:1) afforded an analytically pure sample of (**22**); $\nu_{max.}$(film) 3 400, 3 090, 3 070, 3 030, 2 870, 1 495, 1 455, and 1 420 cm^{-1}; $\delta_H(CDCl_3)$ 1.96 (1 H, m, CH), 2.45 (2 H, br s, 2 × D_2O exchangeable OH), 3.80 (7 H, m, 3 × CH_2 and CH), 4.62 (4 H, m, 2 × CH_2), and 7.30 (10 H, m, 2 × C_6H_5) (Found: C, 72.1; H, 7.9%. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.7%).

1-*Benzoyloxy*-2-*benzoyloxymethyl*-3,4-*dibenzyloxybutane* (**23**).—Benzoyl chloride (1.7 ml, 15 mmol) was added dropwise to an ice-cooled, stirred solution of the diol (**22**) (1.85 g, 5.9 mmol) and 4-*N*,*N*-dimethylaminopyridine (1.8 g, 15 mmol) in dry pyridine (30 ml). The mixture was stirred for 18 h at room temperature and then treated with additional benzoyl chloride (0.69 ml, 5.9 mmol). After being stirred for a further 24 h, the mixture was poured into ice–brine (200 ml) and extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with 5M hydrochloric acid (3 × 100 ml), saturated

aqueous sodium hydrogen carbonate (100 ml), and brine (100 ml) and dried. The solvent was removed under reduced pressure to leave an oil (2.7 g), which was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:4) to give (**23**) as an oil (2.05 g, 67%); $\nu_{max.}$(film) 3 090, 3 070, 3 040, 2 960, 2 900, 2 870, 1 720, 1 600, 1 585, 1 495, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.70 (1 H, m, CH), 3.75 (2 H, m, CH_2), 3.95 (1 H, m, CH), 4.63 (8 H, m, 4 × CH_2), and 7.2—8.1 (20 H, m, 4 × C_6H_5) (Found: C, 75.4; H, 6.1%. $C_{33}H_{32}O_6$ requires C, 75.6; H, 6.2%).

4-*Benzoyloxy*-3-*benzoyloxymethyl*-1-*triphenylmethoxybutan*-2-*ol* (**24**).—A solution of compound (**23**) (3.4 g, 6.5 mmol) in 90% aqueous tetrahydrofuran (20 ml) and 5M hydrochloric acid (0.5 ml) was treated with 5% palladium-charcoal catalyst (150 mg) and hydrogenated at atmospheric pressure and room temperature for 7 h. The mixture was filtered through a glass fibre pad, and the catalyst washed with tetrahydrofuran (30 ml). The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried and the solvent removed to leave 4-benzoyloxy-3-benzoyloxymethyl-2-hydroxybutan-1-ol as an oil (2.02 g, 90%). An analytically pure sample was obtained by chromatography on silica gel, eluting with chloroform–methanol (25:1); $\nu_{max.}$(film) 3 460, 3 060, 2 980, 2 950, 2 900, 1 720, 1 600, 1 585, 1 490, 1 460, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.43 (2 H, m, CH plus D_2O exchangeable OH), 3.20 (1 H, br s, D_2O exchangeable OH), 3.85 (3 H, m, CH_2 and CH), 4.56 (4 H, m, 2 × CH_2), and 7.3—8.1 (10 H, m, 2 × C_6H_5); *m/z* 344 (M^+ < 1%), 220 (5), 192 (8), 191 (30), 162 (10), 123 (25), 122 (8), 106 (25), 105 (100), 77 (100), and 51 (35) (Found: C, 66.6; H, 5.8%. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.9%).

A solution of 4-benzoyloxy-3-benzoyloxymethyl-2-hydroxybutan-1-ol (1.8 g, 5.2 mmol) and triphenylmethyl chloride (1.75 g, 6.3 mmol) in dry pyridine (10 ml) was heated at 70 °C for 4 h. The cooled mixture was poured into ice–brine (150 ml) and the mixture was extracted with ethyl acetate (3 × 50 ml). The combined organic phases were washed with 5M hydrochloric acid (3 × 50 ml), saturated aqueous sodium hydrogen carbonate (50 ml), and brine (50 ml), dried, and evaporated under reduced pressure to leave an oil (3.4 g) which was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:3) to give (**24**) as an oil (2.6 g, 85%); $\nu_{max.}$(film) 3 500, 3 090, 3 060, 3 040, 2 960, 2 930, 2 880, 1 720, 1 600, 1 585, 1 490, 1 470, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.49 (1 H, m, CH), 2.65 (1 H, d, *J* 4 Hz, D_2O exchangeable OH), 3.40 (2 H, m, CH_2), 4.00 (1 H, m, CH), 4.45 (4 H, m, 2 × CH_2), and 7.1—8.0 (25 H, m, 5 × C_6H_5) (Found: C, 77.9; H, 5.7%. $C_{38}H_{34}O_6$ requires C, 77.8; H, 5.8%).

1-*Benzoyloxy*-2-*benzoyloxymethyl*-3-*fluoro*-4-*triphenylmethoxybutane* (**25**).—A solution of the alcohol (**24**) (1.14 g, 1.9 mmol) in dry tetrahydrofuran (4 ml) and triethylamine (4 ml) was cooled to −50 °C under nitrogen. The solution was treated, dropwise, with diethylaminosulphur trifluoride (0.3 ml, 2.5 mmol) and allowed to warm to room temperature slowly. Dry *N,N*-dimethylformamide (4 ml) was added to the mixture and the solution was stirred at room temperature for 20 h. It was then treated with water (3 ml), and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (30 ml) and washed with 5M hydrochloric acid (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and brine (20 ml). The organic phase was dried and evaporated under reduced pressure and the residue subjected to a second fluorination using conditions identical with those described above. After work-up, the residual oil was chromatographed on silica gel, eluting with chloroform–hexane (5:1) to give (**25**) as an oil (0.7 g, 61%); $\nu_{max.}$(film) 3 090, 3 060, 3 040, 2 960, 2 940, 2 880, 1 725, 1 605, 1 585, 1 495, 1 450, and 1 400 cm^{-1}; $\delta_H(CDCl_3)$ 2.77 (1 H, m, CH), 3.47 (2 H, dm, J_{HF} 25 Hz, CH_2), 4.45 (4 H, m, 2 × CH_2), 4.89 (1 H, dm, J_{HF} 47 Hz, CH), and 7.1—8.0 (25 H, m, 5 × C_6H_5); *m/z* 588 (M^+ < 1%) 511 (4), 329 (5), 259 (20), 244 (30), 243 (100), 233 (5), 165 (30), 105 (100), and 77 (30) (Found: C, 77.1; H, 5.8%; M^+, 588.2300. $C_{38}H_{33}FO_5$ requires C, 77.5; H, 5.7%; M^+, 588.2314).

4-*Benzoyloxy*-2-*benzoyloxymethyl*-3-*fluorobutan*-1-*ol* (**9e**).—A suspension of compound (**25**) (3.4 g, 5.8 mmol) in 80% aqueous acetic acid (40 ml) was heated at 60 °C for 4 h. The solvent was removed and the residue dissolved in chloroform (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried and evaporated under reduced pressure and the residue was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:2) to give (**9e**) as an oil (0.8 g, 40%); $\nu_{max.}$(film) (3 500, 3 060, 2 980, 2 910, 1 725, 1 605, 1 585, 1 495, 1 470, and 1 455 cm^{-1}; $\delta_H(CDCl_3)$ 2.77 (1 H, m, CH), 4.00 (2 H, dd, *J* 4 and 25.5 Hz, CH_2), 4.60 (4 H, m, 2 × CH_2), 4.90 (1 H, dm, J_{HF} 48 Hz, CH), and 7.35—8.1 (10 H, m, 2 × C_6H_5) (Found: C, 65.7; H, 5.7%. $C_{19}H_{19}FO_5$ requires C, 65.9; H, 5.5%).

2-*Amino*-9-(4-*benzoyloxy*-3-*benzoyloxymethyl*-2-*fluorobutyl*)-6-*chloropurine* (**11e**).—A solution of compound (**9e**) (330 mg, 0.95 mmol) and 4-*N,N*-dimethylaminopyridine (182 mg, 1.5 mmol) in dry dichloromethane (5 ml) was cooled to 0 °C under nitrogen. Trifluoromethanesulphonic anhydride (0.25 ml, 1.5 mmol) was added dropwise to the stirred solution. The mixture was stirred for 15 min at 0 °C and at room temperature for 15 min and then treated with ice–water (5 ml). Chloroform (10 ml) was added to this mixture and the layers separated. The organic phase was dried and evaporated to dryness to give crude (**10e**): $\delta_H(CDCl_3)$ 2.80 (1 H, m, CH), 4.59 (4 H, m, 2 × CH_2), 4.87 (2 H, m, CH_2), 5.10 (1 H, dm, J_{HF} 50 Hz, CH), and 7.35—8.15 (10 H, m, 2 × C_6H_5).

A dispersion of sodium hydride in oil (60%; 57 mg, 1.4 mmol) was washed with dry hexane (5 ml) under nitrogen. After decanting the hexane, the solid was suspended in dry *N,N*-dimethylformamide (2 ml) and 2-amino-6-chloropurine (320 mg, 1.9 mmol) was added. Effervescence occurred and the mixture was stirred for 1 h at room temperature, after which time dissolution was complete.

A solution of the crude (**10e**) in dry *N,N*-dimethylformamide (2 ml) was added to the above mixture, and the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between chloroform (20 ml) and water (20 ml). The solid precipitate was filtered off and the chloroform layer was dried. The solvent was removed under reduced pressure and the residual oil was chromatographed on silica gel, eluting with ethyl acetate–hexane (3:1) to give, as a foam, (**11e**) (250 mg, 53%); $\nu_{max.}$(KBr) 3 480, 3 400, 3 320, 3 200, 2 960, 2 920, 1 720, 1 615, 1 565, 1 520, 1 465, 1 450, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 2.68 (1 H, m, CH), 4.38—4.80 (6 H, m, 3 × CH_2), 4.95 (2 H, s, D_2O exchangeable NH_2), 5.13 (1 H, dm, J_{HF} 48 Hz, CH), and 7.35—8.10 (11 H, m, 2 × C_6H_5 plus CH); *m/z* 497 (M^+, 20%), 392 (10), 376 (15), 270 (10), 240 (10), 234 (10), 169 (10), 146 (5), 134 (10), 105 (100), 101 (10), 77 (35), and 51 (5) (Found: C, 57.2; H, 4.3; N, 13.6%; M^+, 497.1254. $C_{24}H_{21}FClN_5O_4 \cdot 0.4H_2O$ requires C, 57.1; H, 4.3; N, 13.9%; M^+, 497.1266).

9-(2-*Fluoro*-4-*hydroxy*-3-*hydroxymethylbutyl*)*guanine* (**8**).—A suspension of compound (**11e**) (107 mg, 0.2 mmol) in dioxane (1 ml) and 2M hydrochloric acid (3 ml) was heated at 100 °C for 0.5 h. The solution was concentrated under reduced pressure to *ca.* 2 ml and extracted with chloroform (50 ml). Saturated aqueous sodium hydrogen carbonate was added until the

mixture became basic and the chloroform phase, in which some white solid was suspended, was separated off and evaporated to dryness. Water was removed from the residue by co-evaporation with methanol. The residue was stirred with 0.1M sodium methoxide in methanol (2 ml) for 3 h at room temperature. The solution was then neutralised by cautious addition of Amberlite IR 120 (H) and filtered quickly as soon as neutrality was reached. The filtrate was evaporated to dryness and the residue was dissolved in water (40 ml) and washed with chloroform (5 × 25 ml). The aqueous phase was evaporated to dryness and the residue crystallised from methanol to give, as a hygroscopic solid, (**8**) (19 mg, 33%), m.p. 260—265 °C; $\lambda_{max.}(H_2O)$ 250.5 (ε 11 920) and 275sh nm; $\nu_{max.}$(KBr) 3 400, 3 320, 3 220, 3 120, 2 950, 2 900, 2 760, 1 690, 1 610, 1 580, 1 540, 1 480, and 1 410 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.82 (1 H,m, CH), 3.55 (4 H, m, 2 × CH_2), 4.30 (2 H, m, CH_2), 4.68 (2 H, br s, D_2O exchangeable OH), 4.90 (1 H, dm, J_{HF} 51 Hz, CH), 6.58 (2 H, s, D_2O exchangeable NH_2), 7.62 (1 H, s, CH), and 11.0 (1 H, br s, D_2O exchangeable NH); $\delta_F[(CD_3)_2SO]$ −194.0 (reference $CFCl_3$); *m/z* 271 (M^+, 50%), 251 (35), 232 (20), 220 (40), 216 (10), 202 (30), 197 (10), 165 (15), 164 (25), 152 (100), 151 (90), 147 (10), 135 (25), 134 (15), 122 (10), 119 (12), 110 (35), 109 (45), 81 (10), 69 (35), 68 (15), 55 (15), and 43 (65) (Found: C, 43.0; H, 5.2; N, 24.6%; M^+, 271.1083. $C_{10}H_{14}FN_5O_3 \cdot 0.5H_2O$ requires C, 42.9; H, 5.4; N, 25.0%; M^+, 271.1081).

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