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TETRAHEDRON

Convenient Syntheses of 9-[4-Hydroxy-3-(hydroxymethyl)butyl]-guanine (Penciclovir) and 9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-9*H*-purine (Famciclovir)

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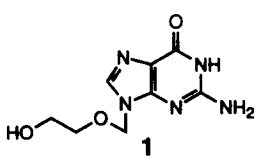
Abstract: Guanine **11** was converted, in a one pot reaction, into 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** in 88% isolated yield. 4-Acetoxy-3-(acetoxymethyl)butanol **23** was prepared from 2-chloroethanol in five steps and in 46% overall yield. The mesylate ester of compound **23** reacted with **9a** in the presence of potassium carbonate with a high degree of regioselectivity (89%) to give the *N*-9 alkylated product **26** which was isolated in 80% yield. Acidic hydrolysis of the latter compound **26** gave penciclovir **4** in virtually quantitative yield. Penciclovir **4** and famciclovir **5** were prepared from 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** in four and five steps, respectively, by procedures involving initial alkylation with 1,2-dibromoethane. The overall yields obtained were 65 and *ca.* 60%, respectively.

Keywords: antivirals, purines, alkylation, regioselection

INTRODUCTION

A number of nucleoside analogues in which the sugar residues have been replaced by acyclic side-chains have been found to exhibit high antiviral activity.[1] An especially notable group of such analogues which have found application in chemotherapy are achiral 9-alkylguanine and closely related 9-alkyl-2-amino-9*H*-purine derivatives. This group of compounds includes acyclovir[2,3] **1**, its 6-deoxy-derivative[4] **2**, ganciclovir[5-8] **3**, penciclovir[9-10] **4**, and famciclovir[11,12] **5**. A rational strategy for the synthesis of these and indeed of other related alkylated purines consists essentially of three main parts. The first part involves the preparation of a purine derivative that undergoes highly regioselective (or preferably regiospecific) alkylation on *N*-9, and is so designed that the resulting alkylation product can easily be converted into the corresponding 9-alkylguanine or 9-alkyl-2-amino-9*H*-purine. The second part is concerned with the introduction of the appropriate side-chain, and the third part involves the transformation of the alkylated purine derivative so obtained into the target compound.



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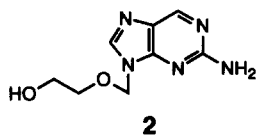

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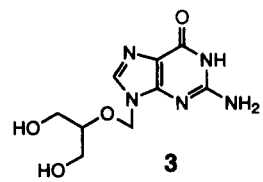

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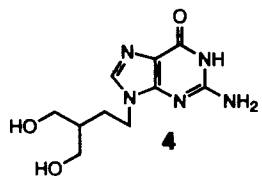

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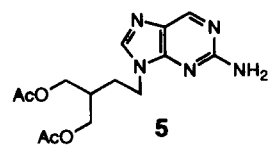

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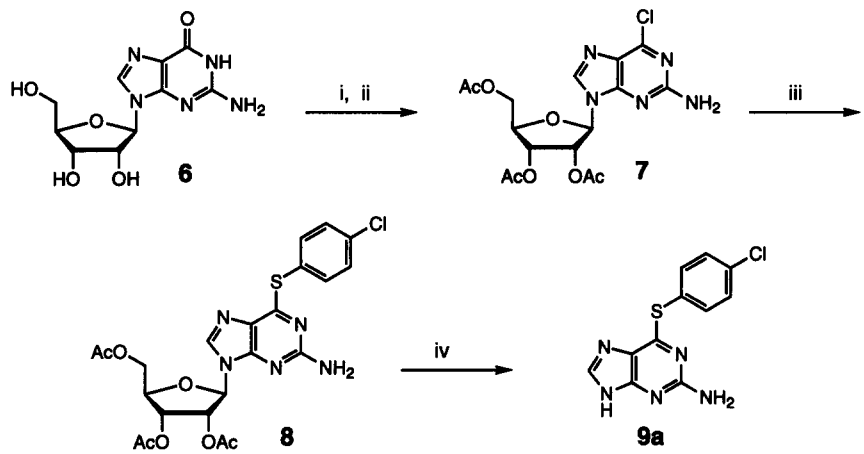
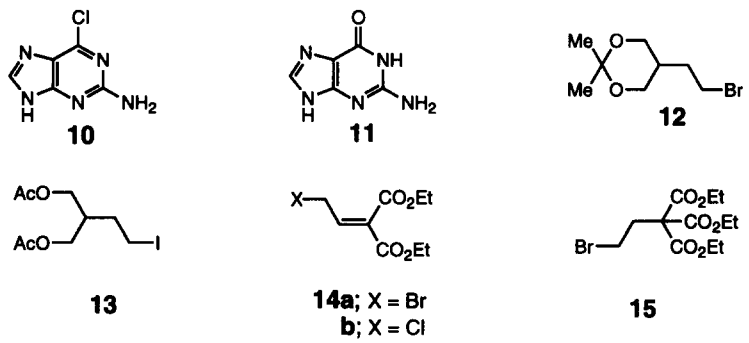


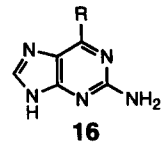
Scheme 1 *Reagents and conditions*: i, Ac_2O, C_5H_5N, DMF, 75°C: ii, $POCl_3$, $PhNMe_2$, Et_4NCl, reflux; iii, (4-chloro)thiophenol, Et_3N, MeOH, room temp.; iv, $Et_2O{\cdot}BF_3$, PhOH, CH_2Cl_2, reflux

In a previous publication, we reported[13] the conversion (Scheme 1) of guanosine **6** into 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** which proved to be a useful intermediate in the preparation of acyclovir **1** and its 6-deoxy-derivative **2**. We now report a considerably improved preparation of 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a**, and describe its conversion into 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir **4**)[9,10] and 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-9*H*-purine (famciclovir **5**).[11,12]



As far as we are aware, the purine derivative used in all but one[14] of the reported syntheses of penciclovir[10,14-16] **4** and famciclovir[11,12,16] **5** has been 2-amino-6-chloropurine[17,18] **10**. Due partly to its solubility in water, the direct preparation[18] of the latter compound **10** from guanine **11** (by treatment with phosphoryl trichloride and tetraethylammonium chloride in acetonitrile) is inconvenient to carry out on a laboratory scale, and usually leads only to a modest yield of the desired product **10**. Furthermore, although 2-amino-6-chloropurine **10** undergoes alkylation predominantly on *N*-9, significant quantities (sometimes more than 15%) of the *N*-7 isomer are usually also obtained.[19] The alkylating agents that have been used in the preparation of penciclovir **4** and famciclovir **5** include 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxane[10] **12**, 4-acetoxy-3-acetoxymethyl-1-iodobutane[20] **13**, diethyl (2-bromoethylidene)malonate[12] **14a**, diethyl (2-chloroethylidene)malonate[12] **14b** and triethyl 3-bromopropane-1,1,1-tricarboxylate[16] **15**.

RESULTS AND DISCUSSION



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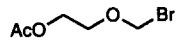

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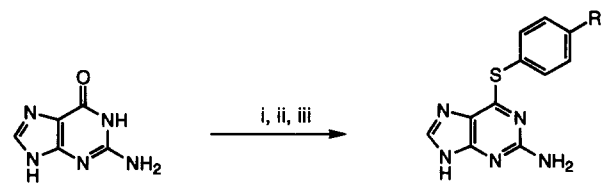
Geen *et al.*[20] showed that the *N*-9 : *N*-7 ratio observed in the alkylation of 6-substituted 2-aminopurine derivatives varies considerably for different *C*-6 substituents. In the latter study,[20] the worst ratio (i.e. the greatest proportion of *N*-7 isomer) was observed for the 6-methoxy derivative **16**; R = OMe and the best ratio was observed for the 6-isopropyl derivative **16**; R = Me_2CH. The *N*-9 : *N*-7 ratio observed for the 6-chloro derivative **10** was somewhere in between. We had previously found[13] that the trimethylsilyl derivative of 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** reacted with (2-acetoxyethoxy)methyl bromide[21] **17** in the presence of mercury(II) cyanide virtually regiospecifically on *N*-9. However, the conversion of guanosine **6** into the latter purine derivative **9a**, which involves four steps[13] (Scheme 1), is rather cumbersome and leads to an overall yield of less than 60%. We now report that when guanine **11** was allowed to react with trifluoroacetic anhydride in anhydrous pyridine,[22] and the products were treated first with (4-chloro)thiophenol and then with aqueous ammonia followed by hydrogen peroxide (Scheme 2), 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** was obtained and was isolated as an almost colourless solid in 88% yield. Thus 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** can easily be prepared from guanine **11** in what is essentially a one pot reaction. The fact that the latter purine derivative **9a** is relatively lipophilic no doubt makes it much easier to isolate than 2-amino-6-chloropurine **10**. Guanine **11** was similarly converted (Scheme 2) into 2-amino-6-[(4-methylphenyl)sulfanyl]purine **9b** and 2-amino-6-(phenylsulfanyl)purine **9c** in 76 and 75% yield, respectively. As neither of the latter preparations has been optimized, the somewhat lower yields obtained may not be significant. However, as thiophenol is a particularly disagreeable reagent to work with, both the 6-[(4-chlorophenyl)sulfanyl]- and the 6-[(4-methylphenyl)sulfanyl]- derivatives (**9a** and **9b**, respectively) are perhaps to be preferred over the 6-phenylsulfanyl-derivative.



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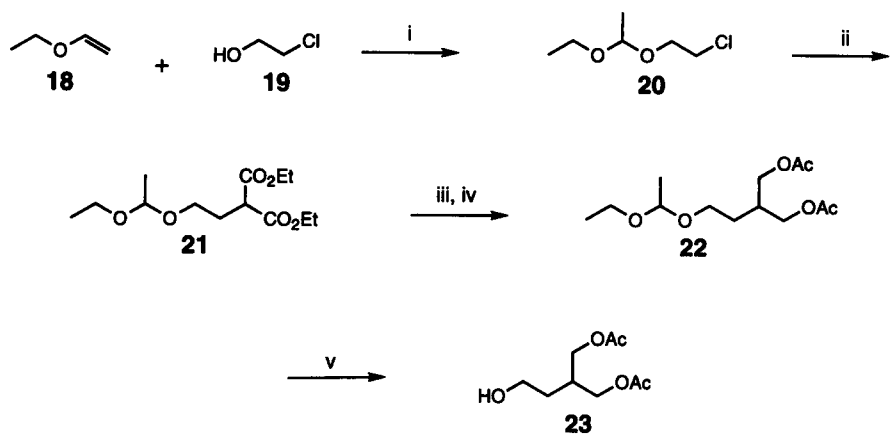
9 **a**; R = Cl
b; R = CH_3
c; R = H

Scheme 2 *Reagents and conditions*: i, $(CF_3CO)_2O$, C_5H_5N, 0°C, 35 min; ii, (4-chloro)thiophenol (for **9a**), (4-methyl)thiophenol (for **9b**) or thiophenol and MeCN (for **9c**), room temp.,2 h; iii, a, aq. NH_3 (*d* 0.88), b, 27% H_2O_2, room temp. (for **9a** and **9b**) or $MeNH_2$ (in EtOH) for **9c**.

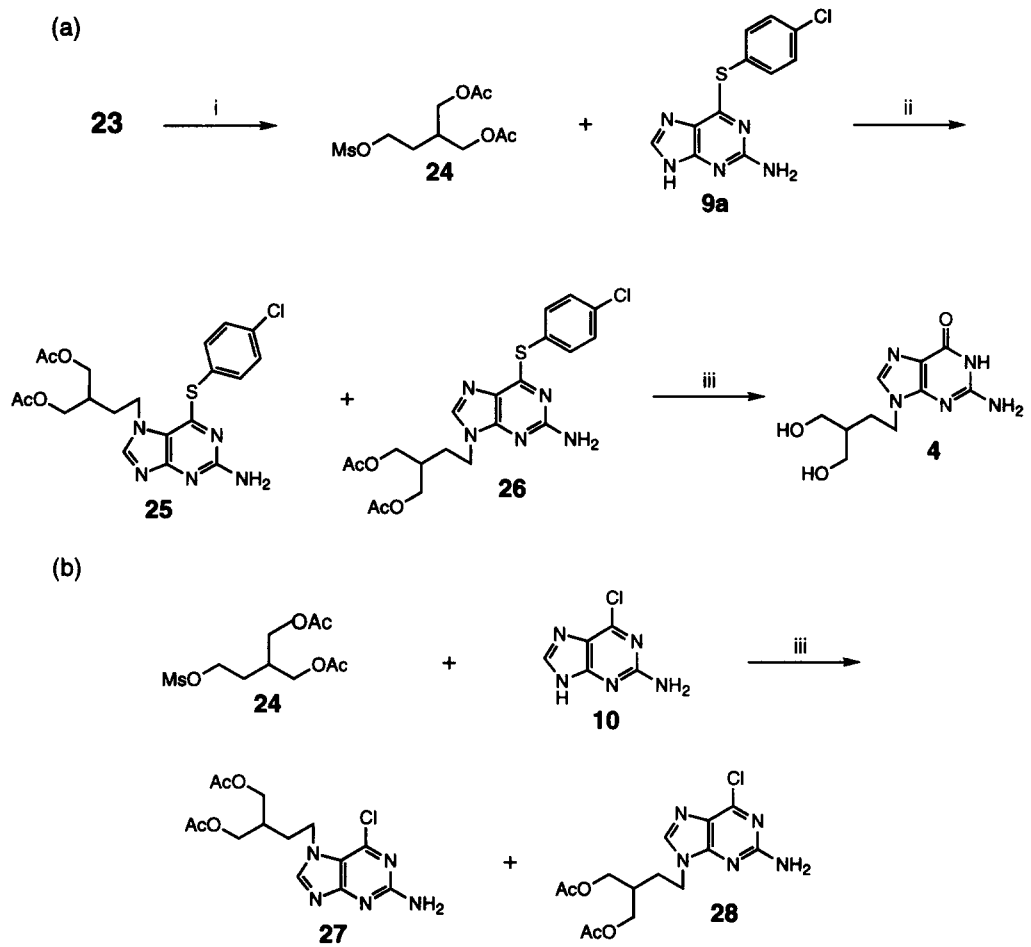
The preparation of penciclovir **4** from the 6-[(4-chlorophenyl)sulfanyl] derivative **9a** and 4-acetoxy-3-(acetoxymethyl)butanol[20] **23** was undertaken first. The latter diacetoxy compound **23** was prepared (Scheme 3) from 2-chloroethanol **19** in five steps. First, the acetal **20** was obtained in 94% isolated yield by allowing 2-chloroethanol

19 to react with ethyl vinyl ether **18** in the presence of a catalytic quantity of trifluoroacetic acid. Alkylation of the sodio derivative of diethyl malonate with compound **20** gave the diester **21** as a distillable liquid in 75% isolated yield. Reduction of this compound **21** with sodium borohydride, followed by acetylation of the resulting diol gave the diacetoxy-acetal **22** as a distillable liquid in *ca.* 70% isolated yield. Finally, hydrolysis with acetic acid-water (4 : 1 v/v) gave the required 4-acetoxy-3-(acetoxymethyl)butanol **23** as a colourless distillable liquid in 94% isolated yield. It should be noted that removal of the 1-ethoxyethyl protecting group leads to volatile and readily removable by-products (i.e. acetaldehyde and ethanol). This would not have been the case if, for example, the tetrahydropyran-2-yl protecting group had been used instead.



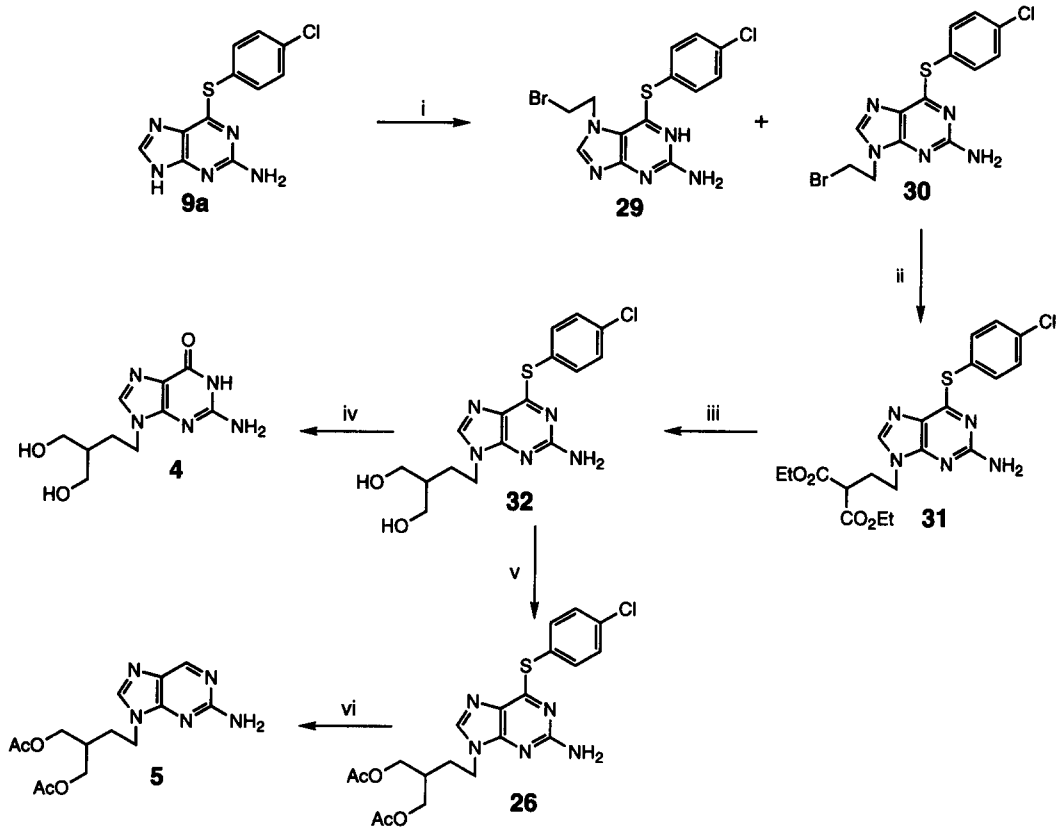
Scheme 3 *Reagents and conditions*: i, CF_3CO_2H (*ca.* 0.5 mol %), 0°C to room temp., 1 h; ii, $CH_2(CO_2Et)_2$; NaOEt, EtOH, reflux, 20 h; iii, $NaBH_4$, MeOH, t-BuOH, reflux, 3.5 h; iv, Ac_2O, C_5H_5N, room temp., 20 h; v, AcOH - H_2O (4 : 1 v/v), 30°C, 20 h

In the preparation of penciclovir **4**, 4-acetoxy-3-(acetoxymethyl)butanol **23** was first converted (Scheme 4a) into its mesylate[20] **24** which was then allowed to react with 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** and potassium carbonate in *N,N*-dimethylformamide (DMF) solution. A mixture of 7-[4-acetoxy-(3-acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-7*H*-purine **25** and the desired 9-isomer **26** was thereby obtained in high yield. Integration of the signals at δ 8.04 and 8.30 p.p.m. (assigned to the resonances of the *H*-8 protons of the two compounds) in the ^1H NMR spectrum [in $(CD_3)_2SO$] of this mixture indicated that the isomeric ratio was 89 : 11 in favour of the compound with the higher field (i.e. δ 8.04 p.p.m.) *H*-8 resonance signal. It has been reported[23] that the *H*-8 protons of 9-alkylpurines are generally more shielded than the *H*-8 protons of isomeric 7-alkylpurines. It was therefore concluded that the 9-isomer **26** was the major product. Following fractionation of the mixture by short column chromotography, the 9- and 7- isomers (**26** and **25**) were isolated as pure crystalline solids (mps 132-134°C and 168-171°C) in 80 and 2.4% yields, respectively. When the 9-isomer **26** was heated, under reflux, with 2.0 mol dm^{-3} hydrochloric acid for 3 h, 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir, **4**) was obtained in 98% isolated yield. The fact that the ^1H and ^{13}C NMR spectra [in $(CD_3)_2SO$] of this product were closely similar to the spectra reported in the literature[16] for penciclovir **4** provides further confirmation that the major product obtained in the alkylation of 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** with the mesylate **24** (Scheme 4a) was indeed the 9-isomer **26**.



Scheme 4 *Reagents and conditions*: i, CH_3SO_2Cl, Et_3N, CH_2Cl_2, -5°C, 2 h; ii, K_2CO_3, DMF, 40°C, 18 h; iii, 2.0 mol dm^{-3} hydrochloric acid, reflux, 3 h

When the mesylate **24** was allowed to react with 2-amino-6-chloropurine **10** and potassium carbonate in DMF under closely similar conditions (see Scheme 4b and Experimental), a mixture of the corresponding 7- and 9-alkyl derivatives (**27** and **28**, respectively) was obtained. Integration of the signals at δ 8.17 and 8.40 p.p.m. (assigned to the resonances of the *H*-8 protons) in the ^1H NMR spectrum [in $(CD_3)_2SO$] of this mixture indicated that the isomeric ratio was 82 : 18 in favour of the component with the higher field (i.e. δ 8.17 p.p.m.) *H*-8 resonance signal. This was assumed to be the 9-isomer[20] **28**. Following fractionation of the mixture by short column chromatography, the 9- and 7-isomers (**28** and **27**) were isolated as pure crystalline solids in 66 and 8.1% isolated yields, respectively. It is noteworthy that 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** undergoes alkylation by the mesylate **24** more regioselectively on *N*-9 than 2-amino-6-chloropurine **10**.



Scheme 5 *Reagents and conditions*: i, $BrCH_2CH_2Br$, K_2CO_3, DMSO, 50°C, 1 h; ii, $CH_2(CO_2Et)_2$, K_2CO_3, DMSO, 50°C,1.5 h; iii, $NaBH_4$, MeOH, diglyme, 50°C, 18 h; iv, 2.0 mol dm^{-3} hydrochloric acid, reflux, 3 h; v, Ac_2O, C_5H_5N, room temp., 16 h; vi, Raney nickel, EtOH - H_2O (1 : 1 v/v), reflux, 1 h

Although 4-acetoxy-3-(acetoxymethyl)butanol **23** is a useful synthon in the preparation of penciclovir **4** (Scheme 4a) and famciclovir **5**, our synthesis of it involves five steps (Scheme 3). With a view to devising a potentially more convenient procedure for the large scale preparation both of penciclovir **4** and famciclovir **5**, we have developed a shorter synthetic route (Scheme 5). When 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** was allowed to react with an excess (*ca.* 5 mol equiv.) of 1,2-dibromoethane in the presence of potassium carbonate in dry dimethyl sulfoxide (DMSO) at 50°C, a 9 : 1 mixture of 2-amino-9-(2-bromoethyl)-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **30** (δ_H [$(CD_3)_2SO$] 8.05 p.p.m.) and the isomeric 7-(2-bromoethyl)-derivative **29** (δ_H [$(CD_3)_2SO$] 8.32 p.p.m.) was obtained in virtually quantitative yield. Following fractionation of the mixture by short column chromatography, the 9-(2-bromoethyl)-derivative **30** was obtained as a colourless crystalline solid in 86.6% isolated yield. Chromatographic purification was not necessary in any of the subsequent steps. Reaction between the 9-(2-bromoethyl)-derivative **30**, potassium carbonate and diethyl malonate in dry DMSO at 50°C gave the diester **31** which was isolated as a crystalline solid in 93% yield. When this compound **31** was reduced with sodium borohydride in the presence of methanol in diglyme solution, the corresponding diol **32** was obtained and isolated in 85% yield. Penciclovir **4** was obtained in 95% isolated yield when this diol **32** was heated, under reflux, with 2.0 mol dm^{-3} hydrochloric acid. Acetylation of the diol **32** and Raney nickel desulfurization[24] of the resulting diacetate **26** gave famciclovir **5** as a colourless crystalline solid in 87% isolated yield. The ^1H and ^{13}C NMR spectra of both

the penciclovir **4** and the famciclovir **5** prepared by this route (Scheme 5) were closely similar to the spectra reported in the literature.[16]

In certain respects, the preparations of penciclovir **4** and famciclovir **5** described above would appear to offer significant advantages over previously reported[9-12,14-16] preparations. First, on the laboratory scale, 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** can be prepared (Scheme 2) from guanine **11** very much more conveniently and in much higher yield than can 2-amino-6-chloropurine **10**. Secondly, 2-amino-9-[(4-chlorophenyl)sulfanyl]purine **9a** undergoes alkylation by, for example, the mesylate **24** on *N*-9 with a higher degree of regioselectivity (89%) than does 2-amino-6-chloropurine **10** (82%). This is doubly advantageous in that not only is a higher yield of the desired isomer obtained, but also its purification is likely to be facilitated. It is not clear what is the best way to introduce the 9-[4-hydroxy-3-(hydroxymethyl)butyl] side-chain in the preparation of penciclovir **4** or the 9-[4-acetoxy-3-(acetoxymethyl)butyl)] side-chain in the preparation of famciclovir **5**. However, the 1,2-dibromoethane approach (Scheme 5) described above, which is very straightforward and proceeds with a high degree of regioselectivity (90%), may very well be the method of choice. Finally, an additional important feature of the present approach, that is the use of Raney nickel rather than ammonium formate and palladized charcoal[11] in the defunctionalization of *C*-6, may prove to be more convenient and economical in the large-scale preparation of famciclovir **5**.

EXPERIMENTAL

Mps were measured with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra, unless otherwise stated, were measured at 360 MHz with a Bruker AM 360 spectrometer. ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as the internal standard, and *J* values are given in Hz. Merck silica gel 60 F_{254} plates were developed in solvent systems A [dichloromethane - methanol (19 : 1 v/v)], B [dichloromethane - methanol (9:1 v/v)] and C [dichloromethane - methanol (4 : 1 v/v)]. Merck silica gel H was used for short column chromatography. Pyridine, triethylamine and acetonitrile were dried by heating, under reflux, over calcium hydride and were then distilled. Diglyme and DMF were dried by distillation over calcium hydride under reduced pressure. Raney nickel (50% aqueous slurry) and (4-chloro)thiophenol were purchased from the Aldrich Chemical Company.

2-Amino-6-[(4-chlorophenyl)sulfanyl]purine 9a

Trifluoroacetic anhydride (42.4 mL, 0.30 mol) was added dropwise over a period of 15 min to a stirred suspension of guanine **11** (15.11 g, 0.10 mol) in dry pyridine (200 mL) at 0°C (ice-water bath). After 20 min, solid (4-chloro)thiophenol (36.16 g, 0.25 mol) was added, and the stirred reactants were allowed to warm up to room temperature. After a further period of 2 h, concentrated aqueous ammonia (*d* 0.88, 100 mL) was added dropwise over a period of 10 min, followed by 27% aqueous hydrogen peroxide (10 mL). After the reaction mixture had been stirred for a further period of 1 h, the products were evaporated to dryness under reduced pressure. The residue was re-evaporated with toluene (100 mL) under reduced pressure, and was then shaken with toluene (100 mL) and water (100 mL) in a separatory funnel. The resulting mixture was filtered, and the residue was washed first with toluene (50 mL) and then with water (50 mL) to give the *title compound* **9a** as an off-white solid (24.50 g, 88%). Crystallization of this material from acetonitrile gave colourless crystals (Found: C, 47.48; H, 2.80; N, 24.97. Calc. for $C_{11}H_8ClN_5S$: C, 47.57; H, 2.90; N, 25.22%), mp 227-228°C (lit.[13] mp 225°C); R_f 0.57 (system B); δ_H [$(CD_3)_2SO$] 6.27 (2 H, s), 7.50 (2 H, m), 7.63 (2 H, m), 7.98 (1 H, s), 12.63 (1 H, br); δ_C [$(CD_3)_2SO$] 123.2, 127.2, 129.1, 133.8, 136.4, 139.8, 152.7, 156.9, 159.7.

2-Amino-6-[(4-methylphenyl)sulfanyl]purine 9b

Trifluoroacetic anhydride (17.0 mL, 0.12 mol) was added dropwise over a period of 15 min to a stirred suspension of guanine (5.00 g, 33.1 mmol) in dry pyridine (50 mL) at 0°C (ice-water bath). After 30 min, solid toluene-4-thiol (10.37 g, 83.5 mmol) was added and the stirred reactants were allowed to warm up to room temperature. After a further period of 2 h, concentrated aqueous ammonia (*d* 0.88, 30 mL) was added dropwise over a period of 10 min, followed by 27% aqueous hydrogen peroxide (3 mL). After the reaction mixture had been stirred for a further period of 1 h, the solvents were removed under reduced pressure. The residue was re-evaporated with toluene (20 mL) under reduced pressure, and was then stirred with hot toluene (30 mL) (water bath temperature below 100°C) for 10 min and filtered: it was finally stirred with hot water (50 mL) for 10 min. The resulting mixture was cooled and filtered to give the *title compound* **9b** as a virtually colourless crystalline solid (6.51 g, 76.4%) (Found in material recrystallised from acetonitrile: C, 54.7; H, 4.2; N, 27.0; $C_{12}H_{11}N_5S \cdot 0.25\ H_2O$ requires: C, 55.05; H, 4.43; N, 26.74%) m.p. 179-180°C; R_f 0.58 (system B); δ_H [$(CD_3)_2SO$] 2.33 (3 H, s), 6.17 (2 H, br.s), 7.24 (2 H, d, *J* 7.9), 7.46 (2 H, m), 7.92 (1 H, s) and 12.55 (1 H, br.s); δ_C [$(CD_3)_2SO$] 20.85, 123.46, 124.45, 129.77, 134.85, 138.51, 139.24, 152.11, 158.11 and 159.73.

2-Amino-6-phenylsulfanylpurine 9c

Trifluoroacetic anhydride (17.0 mL, 0.12 mol) was added dropwise over a period of 10 min to a stirred suspension of guanine **11** (5.00 g, 31.1 mmol) in dry pyridine (50 mL) at 0°C (ice-water bath). After 15 min, a solution of thiophenol (9.2 g. 83.5 mmol) in dry acetonitrile (10 mL) was added dropwise over a period of 15 min. The reactants were allowed to warm up to room temperature and were stirred for a further period of 2 h. Ethanolic methylamine (8 mol dm^{-3}, 4 mL) was then added and the resulting solution was stirred at room temperature for 30 min. The products were concentrated under reduced pressure. The residue obtained was triturated with petroleum ether (b.p. 40-60°C, 20 mL) and was then collected by filtration; it was finally suspended in water (100 mL), stirred and filtered. Crystallization of the resulting solid from aqueous acetone gave the *title compound* **9c** (6.05 g, 75%) as a colourless crystalline solid (Found: C, 54.22; H, 3.53; N, 29.10. $C_{11}H_9N_5S$ requires: C, 54.31; H, 3.73; N, 28.79%), mp 205°C; R_f 0.56 (system B); δ_H [$(CD_3)_2SO$] 6.20 (2 H, s), 7.44 (3 H, m), 7.61 (2 H, m), 7.96 (1 H, s), 12.60 (1 H, brs); δ_C [$(CD_3)_2SO$] 112.3, 128.3, 128.8, 129.1, 134.6, 139.5, 159.8.

1-Chloro-2-(1-ethoxyethoxy)ethane 20

Trifluoroacetic acid (0.8 mL, 10 mmol) was added to a stirred solution of ethyl vinyl ether (200 mL, 2.09 mol) and 2-chloroethanol (140.5 mL, 2.09 mmol) at 0°C (ice-water bath). The reactants were allowed to warm up to room temperature. After 1 h, triethylamine (3.0 mL, 21.5 mmol) was added. The products were then distilled over anhydrous potassium carbonate to give the *title compound* **20** (300 g, 94%) as a colourless liquid, bp 161°C / 760 mmHg (lit.[25], b.p. 75-77°C / 31 mmHg); δ_H [$CDCl_3$] 1.21 (3 H, t, *J* 7.1), 1.33 (3 H, d, *J* 5.4), 3.51 (1 H, m), 3.62-3.75 (4 H, m), 3.82 (1 H, m), 4.78 (1 H, quart, *J* 5.4); δ_C [$CDCl_3$] 15.1, 19.5, 43.2, 60.9, 64.7, 99.5.

Diethyl [2-(1-ethoxyethoxy)ethyl]malonate 21

Diethyl malonate (120.7 mL, 0.795 mol) was added dropwise over a period of 1 h to a stirred solution of ethanolic sodium ethoxide [prepared by dissolving sodium metal (18.6 g, 0.809 g atom) in absolute ethanol (300 mL) at 60°C]. After 2 h, 1-chloro-2-(1-ethoxyethoxy)ethane **20** (122.4 g, 0.802 mol) was added and the stirred reactants were heated, under reflux, for 20 h. The cooled products were concentrated (bath temperature *ca.* 45°C) under reduced pressure (water pump), and partitioned between ethyl acetate (400 mL) and water (150 mL). The dried ($MgSO_4$) organic layer was separated and evaporated under reduced pressure. The residue was distilled to give the *title compound* **21** (165.0 g, 75%) as a colourless liquid (Found : M^+, 276.1591. $^{12}C_{13}{}^{1}H_{24}{}^{16}O_6$ requires M,

276.1573), bp 121°C/0.1 mmHg; δ_H [$CDCl_3$] 1.19 (3 H, t, *J* 7.0), 1.27 (9 H, m), 2.18 (2 H, m), 3.46 (2 H, m), 3.57 (1 H, t, *J* 7.4), 3.63 (2 H, m), 4.20 (4 H, m), 4.66 (1 H, quart, *J* 5.3); δ_C [$CDCl_3$] 14.1, 15.3, 19.7, 29.0, 49.0, 60.8, 61.4, 62.1, 99.5, 169.4.

1-Acetoxy-2-acetoxymethyl-4-(1-ethoxyethoxy)butane 22

Diethyl [2-(1-ethoxyethoxy)ethyl]malonate **21** (106.68 g, 0.38 mol), sodium borohydride (25.15 g, 0.66 mol) and *tert*-butanol (300 mL) were heated together, under reflux. Methanol (31.5 mL) was added in three portions over a period of 30 min to the boiling suspension. The reactants were heated, under reflux, for a further period of 3 h, and were then cooled to room temperature. The products were neutralized with aqueous sodium phosphate buffer (pH 4.0, 3 mol dm^{-3}) and filtered. The residue was washed with ethanol (150 mL). The combined filtrate and washings were concentrated (bath temperature *ca.* 50°C) under reduced pressure (water pump) to give a colourless oil. This material was dissolved in dry pyridine (200 mL) and acetic anhydride (152 mL, 1.6 mol) was added. The reaction solution was stirred at room temperature for 20 h, and was then cooled to 0°C (ice water bath). Triethylamine (440 mL, 3.16 mol) was added and, after 10 min, methanol (80 mL) was added dropwise. The products were allowed to stand at room temperature for 1 h, and were then concentrated under reduced pressure to *ca.* one-quarter volume. The resulting material was dissolved in chloroform (200 mL) and the solution was washed with saturated aqueous sodium hydrogen carbonate (3 x 120 mL). The chloroform layer was dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residue gave the *title compound* **22** (75.5 g, 70.7%, based on diethyl [2-(1-ethoxyethoxy)ethyl]malonate **21** as starting material) as a colourless liquid (Found : M^+, 276.1554. $^{12}C_{13}{}^{1}H_{24}{}^{16}O_6$ requires M, 276.1573), bp 123°C/0.1 mmHg; δ_H [$CDCl_3$] 1.21 (3 H, t, *J* 7.1), 1.30 (3 H, d, *J* 5.4), 1.65 (2 H, quart, *J* 6.6), 2.06 (6 H, s), 2.20 (1 H, m), 3.48 (2 H, m), 3.65 (2 H, m), 4.09 (4 H, m), 4.68 (1 H, quart, *J* 5.3); δ_C [$CDCl_3$] 15.3, 19.8, 20.9, 28.4, 34.6, 60.9, 62.4, 64.1, 99.7, 171.0.

4-Acetoxy-3-(acetoxymethyl)butanol 23

A solution of 1-acetoxy-2-(acetoxymethyl)-4-(1-ethoxyethoxy)butane **22** (40.0 g, 0.145 mol) in glacial acetic acid (48 mL) and water (12 mL) was stirred at 30°C for 20 h. The products were concentrated (bath temperature *ca.* 30°C) under reduced pressure (oil pump). The residue was evaporated with toluene (2 x 10 mL) and was then distilled to give the *title compound* **23** (28.0 g, 94%) as a colourless liquid. (Found : (M+H)$^+$, 205.1092. $^{12}C_9{}^{1}H_{17}{}^{16}O_5$ requires M, 205.1076), bp 135°C/0.1 mmHg; υ_{max}film 1737 cm^{-1}; δ_H [$CDCl_3$] 1.64 (2 H, quart, *J* 6.6), 2.07 (6 H, s), 2.23 (1 H, m), 3.75 (2 H, t, *J* 6.4), 4.08 (2 H, dd, *J* 6.2 and 11.2), 4.13 (2 H, dd, *J* 5.2 and 11.2); δ_C [$CDCl_3$] 20.8, 31.0, 34.3, 60.1, 64.2, 171.1.

9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine 26 and its 7-[4-Acetoxy-3-(acetoxymethyl)butyl] isomer 25

A solution of methanesulfonyl chloride (4.95 mL, 64 mmol) in dry dichloromethane (10 mL) was added dropwise to a stirred solution of 4-acetoxy-3-(acetoxymethyl)butanol **23** (6.5 g, 31.8 mmol) and triethylamine (10.4 mL, 75 mmol) in dry dichloromethane (35 mL) at -5°C (ice-salt bath). After a further period of 2 h, hydrochloric acid (1.0 mol dm^{-3}, 35 mL) was added. The organic layer was separated, washed with saturated sodium hydrogen carbonate (2 x 20 mL), dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was dissolved in dry DMF (20 mL), and 2-amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** (5.0 g, 18.0 mmol) and potassium carbonate (4.9 g, 35.5 mmol) were added. The reactants were stirred at 40°C. After 18 h, water (20 mL) was added, and the products were extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (5 x 30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. TLC (system A) of the residue revealed the 9-isomer **26** (R_f 0.60, see below) as the major component and a minor component (R_f 0.35) which was later identified (see below) as

its 7-isomer **25**. Integration of the signals at δ 8.04 and 8.30 (assigned to the resonances of the *H*-8 protons of the 9- and 7- isomers, respectively) in the ^{1}H NMR spectrum [$(CD_3)_2SO$] of this material suggested that the isomeric ratio was *ca.* 89 : 11 in favour of the 9-isomer **26**. The residue was fractionated by short column chromatography on silica gel. The column was eluted with dichloromethane - methanol (100 : 0 to 96 : 4 v/v): fractions that contained material with (a) R_f 0.60 (system A) and (b) R_f 0.35 (system A) were combined separately, and evaporated under reduced pressure.

Crystallization of the higher R_f material from aqueous methanol gave *9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9H-purine* **26** as a colourless solid (6.70 g, 80%) (Found : C, 51.45; H, 4.64; N, 14.93. $C_{20}H_{22}ClN_5O_4S$ requires: C, 51.78; H, 4.78; N, 15.10%), mp 132-134°C; R_f 0.60 (system A); δ_H [$(CD_3)_2SO$] 1.85 (2 H, m), 1.92 (1 H, m), 2.00 (6 H, s), 4.02 (4 H, d, *J* 5.5), 4.12 (2 H, t, *J* 7.1), 6.40 (2 H, brs), 7.52 (2 H, m), 7.63 (2 H, m), 8.04 (1 H, s); δ_C [$(CD_3)_2SO$] 20.6, 27.9, 34.4, 40.5, 63.5, 123.7, 127.0, 129.1, 133.9, 136.5, 141.4, 151.5, 157.7, 159.6, 170.4.

Crystallization of the lower R_f material from aqueous methanol gave *7-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-7H-purine* **25** as a colourless solid (0.20 g, 2.4%) (Found : C, 50.15; H, 4.98; N, 14.50. $C_{20}H_{22}ClN_5O_4S \cdot H_2O$ requires: C, 49.84; H, 5.02; N, 14.53%), mp 168-171°C; R_f 0.35 (system A); δ_H [$(CD_3)_2SO$] 1.92 (2 H, m), 1.97 (6 H, s), 2.05 (1 H, m), 4.06 (4 H, m), 4.42 (2 H, m), 6.14 (2 H, brs), 7.53 (2 H, m), 7.60 (2 H, m), 8.30 (1 H, s); δ_C [$(CD_3)_2SO$] 20.6, 30.3, 34.6, 44.8, 63.6, 116.2, 127.1, 129.4, 134.0, 135.9, 148.3, 149.9, 159.9, 162.2, 170.3.

Conversion of 9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine 26 into 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir) 4

9-[4-Acetoxy-(3-acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **26** (4.71 g, 10.2 mmol) and hydrochloric acid (2.0 mol dm^{-3}, 10 mL) were heated together under reflux. After 3 h, the cooled products were extracted with ethyl acetate (60 mL). The aqueous layer was carefully neutralized with aqueous sodium hydroxide (10 mol dm^{-3}). The resulting mixture was filtered, and the residue was recrystallized from water to give *9-[4-hydroxy-3-(hydroxymethyl)butyl]-guanine* **4** as a colourless solid (2.53 g, 98%) (Found : C, 46.89; H, 5.84; N, 27.11. Calc. for $C_{10}H_{15}N_5O_3 \cdot 0.25\ H_2O$: C, 46.60; H, 6.06; N, 27.17%), mp 274-279°C (lit.[16], mp 275-277°C); R_f 0.10 (system C); δ_H [$(CD_3)_2SO$] 1.44 (1 H, m), 1.71 (2 H, m), 3.32-3.46 (4 H, m), 4.00 (2 H, t, *J* 7.3), 4.45 (2 H, t, *J* 5.1), 6.44 (2 H, brs), 7.69 (1 H, s), 10.55 (1 H, s); δ_C [$(CD_3)_2SO$] 28.8, 40.8, 41.1, 61.3, 116.6, 137.4, 151.1, 153.5, 156.9.

9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-chloro-9*H*-purine 28 and its 7-[4-Acetoxy-3-(acetoxymethyl)butyl] isomer 27

4-Acetoxy-3-(acetoxymethyl)butanol **23** (3.60 g, 17.7 mmol) was treated with methanesulfonyl chloride (2.75 mL, 35.4 mmol) and triethylamine (5.0 mL, 36 mmol) in dry dichloromethane (25 mL), and the products were worked up according to the procedure described in the above experiment. The residue was dissolved in dry DMF (8 mL), and 2-amino-6-chloropurine **10** (1.0 g, 5.9 mmol) and potassium carbonate (1.20 g, 8.7 mmol) were added. The reactants were stirred at 40°C. After 18 h, water (15 mL) was added and the products were extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (5 x 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. TLC (system B) of the residue revealed the 9-isomer **28** (R_f 0.75, see below) as the major component and a minor component (R_f 0.61) which was later assumed (see below) to be the 7-isomer **27**. Integration of the signals at δ 8.17 and 8.40 (assigned to the resonances of the *H*-8 protons of the 9- and 7-isomers, respectively) in the ^{1}H NMR spectrum of this material suggested that the isomeric ratio was *ca.* 82:18 in favour of the 9-isomer **28**. The residue was fractionated by short column chromatography on silica gel. The column was eluted

with dichloromethane - methanol (100 : 0 to 96 : 4 v/v): fractions that contained material with (a) R_f 0.75 (system B) and (b) R_f 0.61 (system B) were combined separately, and evaporated under reduced pressure.

Crystallization of the higher R_f material from aqueous methanol gave *9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-chloro-9H-purine* **28** as a colourless solid (1.40 g, 66%) (Found : C, 46.78; H, 4.87; N, 19.41. Calc. for $C_{14}H_{18}ClN_5O_4 \cdot 0.2\ H_2O$: C, 46.78; H, 5.16; N, 19.49%), mp 133-135°C (lit.[20], mp 134-136°C); R_f 0.75 (system B); δ_H [$(CD_3)_2SO$] 1.91 (3 H, m), 2.01 (6 H, s), 4.03 (4 H, d, *J* 5.3), 4.17 (2 H, t, *J* 6.8), 6.88 (2 H, brs), 8.18 (1 H, s); δ_C [$(CD_3)_2SO$] 20.9, 28.1, 34.8, 41.2, 63.8, 123.7, 143.5, 149.7, 154.4, 160.1, 170.7.

Crystallization of the lower R_f material from aqueous methanol gave *7-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-chloro-7H-purine* **27** as a colourless solid (0.17 g, 8.1%) (Found : C, 46.43; H, 4.80; N, 19.29. Calc. for $C_{14}H_{18}ClN_5O_4 \cdot 0.3\ H_2O$: C, 46.58; H, 5.19; N, 19.39%), mp 172-175°C (lit.[20], mp 159-161°C); R_f 0.61 (system B); δ_H [$(CD_3)_2SO$] 1.85 (2 H, m), 1.99 (6 H, s), 2.00 (1 H, m), 4.03 (4 H, d, *J* 5.8), 4.37 (2 H, t, *J* 7.5), 6.64 (2 H, brs), 8.40 (1 H, s); δ_C [$(CD_3)_2SO$] 20.5, 29.7, 34.4, 44.0, 63.4, 114.5, 142.0, 149.3, 159.8, 164.2, 170.2.

2-Amino-9-(2-bromoethyl)-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine 30 and its 7-(2-bromoethyl) isomer 29.

2-Amino-6-[(4-chlorophenyl)sulfanyl]purine **9a** (15.0 g, 54 mmol), 1,2-dibromoethane (24.0 mL, 0.28 mol), potassium carbonate (30.0 g, 0.22 mol) and dry DMSO (50 mL) was stirred together at 50°C. After 1 h, water (100 mL) was added, and the products were extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (4 x 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. An examination of the ^1H NMR spectrum [$(CD_3)_2SO$] of the residue revealed that the ratio of the integrals of the resonance signals at δ 8.05 and 8.32, assigned to *H*-8 of the 9- and 7-(2-bromoethyl) isomers (**30** and **29**, respectively) was almost exactly 9:1. The products were fractionated by short column chromatography on silica gel: fractions that were eluted with dichloromethane - methanol (100 : 0 to 97 : 3 v/v) and contained material with R_f 0.6 (system A) were combined and evaporated under reduced pressure; fractions that were eluted with dichloromethane - methanol (97 : 3 to 96 : 4 v/v) and contained material with R_f 0.35 (system A) were combined separately and evaporated under reduced pressure.

Crystallization of the higher R_f material from absolute ethanol gave *2-amino-9-(2-bromoethyl)-6-[(4-chlorophenyl)sulfanyl]-9H-purine* **30** (18.0 g, 86.6%) as a colourless solid (Found : C, 40.75; H, 2.70; N, 18.10. $C_{13}H_{11}BrClN_5S$ requires: C, 40.59; H, 2.88; N, 18.21%), mp 185°C (lit[26] m.p. 182-183°C); R_f 0.61 (system A); δ_H [$(CD_3)_2SO$] 3.91 (2 H, t, *J* 6.2), 4.46 (2 H, t, *J* 6.1), 6.49 (2 H, br), 7.52 (2 H, d, *J* 8.5), 7.64 (2 H, d, *J* 8.5), 8.05 (1 H, s); δ_C [$(CD_3)_2SO$] 31.5, 44.7, 123.9, 127.1, 129.5, 134.3, 136.9, 141.7, 151.8, 158.2, 160.0.

Crystallization of the lower R_f material from absolute ethanol gave *2-amino-7-(2-bromoethyl)-6-[(4-chlorophenyl)sulfanyl]-7H-purine* **29** (1.50 g, 7.2%) as a colourless solid (Found : C, 40.75; H, 2.63; N, 18.04. $C_{13}H_{11}BrClN_5S$ requires: C, 40.59; H, 2.88; N, 18.21%), mp 194-196°C; R_f 0.35 (system A); δ_H [$(CD_3)_2SO$] 3.94 (2 H, t, *J* 6.1), 4.74 (2 H, t, *J* 6.0), 5.76 (2 H, brs), 7.25 (2 H, d, *J* 8.3), 7.61 (2 H, d, *J* 8.3), 8.32 (1 H, s); δ_C [$(CD_3)_2SO$] 33.2, 48.3, 116.5, 127.4, 129.7, 134.4, 136.2, 149.2, 150.2, 160.4, 162.7.

Diethyl 2-{[2-Amino-6-(4-chlorophenyl)sulfanyl]purin-9-yl}ethylmalonate 31

Diethyl malonate (17.7 mL, 0.117 mol) was added to a stirred solution of 2-amino-9-(2-bromoethyl)-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **30** (15.0 g, 39.0 mmol) and anhydrous potassium carbonate (16.3 g, 0.118 mol) in dry DMSO (60 mL) at 50°C. After 1.5 h, water (100 mL) was added to the cooled products and the resulting mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were extracted with brine (3 x 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with petroleum ether

(b.p. 40-60°C) to give the *title compound* **31** as a colourless solid (17.0 g, 93%) (Found, in material crystallized first from ethanol and then from acetonitrile: C, 51.84; H, 4.60; N, 14.95. $C_{20}H_{22}ClN_5O_4S$ requires: C, 51.78; H, 4.78; N, 15.10%), mp 117°C; R_f 0.70 (system A); δ_H [$(CD_3)_2SO$] 1.12 (6 H, t, *J* 7.1), 2.30 (2 H, m), 3.44 (1 H, t, *J* 7.2), 3.94-4.13 (6 H, m), 6.38 (2 H, brs), 7.49 (2 H, m), 7.61 (2 H, m), 7.93 (1 H, m); δ_C [$(CD_3)_2SO$] 13.8, 28.0, 40.7, 48.8, 61.2, 123.7, 127.0, 129.1, 133.9, 136.5, 141.4, 151.6, 157.7, 159.6, 168.3.

2-Amino-6-[(4-chlorophenyl)sulfanyl]-9-[4-hydroxy-3-(hydroxymethyl)butyl]-9*H*-purine 32

Methanol (3.5 mL) was added dropwise to a stirred solution of sodium borohydride (2.0 g, 53 mmol) and diethyl 2-{[2-amino-(4-chlorophenyl)sulfanyl]purin-9-yl}ethylmalonate **31** (4.0 g, 8.6 mmol) in dry diglyme (40 mL) at room temperature. The reactants were then heated at 50°C. After 18 h, the cooled products were carefully neutralized with concentrated hydrochloric acid and then extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (40 mL), dried, and evaporated under reduced pressure. The residue was triturated with petroleum ether (bp 40-60°C) - diethyl ether (2 : 3 v/v) (50 mL) to give the *title compound* **32** as a colourless solid (2.8 g, 85%) (Found, in material crystallized from acetonitrile: C, 50.61; H, 4.62; N, 18.17. $C_{16}H_{18}ClN_5O_2S$ requires: C, 50.59; H, 4.78; N, 18.44%), mp 142-143°C; R_f 0.32 (system B); δ_H [$(CD_3)_2SO$] 1.45 (1 H, m), 1.76 (2 H, m), 3.36 (2 H, m), 3.45 (2 H, m), 4.10 (2 H, m), 4.46 (2 H, t, *J* 5.2), 6.40 (2 H, brs), 7.51 (2 H, m), 7.63 (2 H, m), 8.02 (1 H, s); δ_C [$(CD_3)_2SO$] 28.4, 40.7, 41.0, 61.2, 123.6, 126.9, 129.0, 133.8, 136.4, 141.3, 151.4, 157.4, 159.5.

Conversion of 2-Amino-6-[(4-chlorophenyl)sulfanyl]-9-[4-hydroxy-3-(hydroxymethyl)butyl]-9*H*-purine 32 into 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir) 4.

2-Amino-6-[(4-chlorophenyl)sulfanyl]-9-[4-hydroxy-3-(hydroxymethyl)butyl]-9*H*-purine **32** (1.82 g, 4.8 mmol) and hydrochloric acid (2.0 mol dm^{-3}, 5 mL) were heated together under reflux. After 3 h, the cooled products were extracted with ethyl acetate (2 x 20 mL). The aqueous layer was carefully neutralized with aqueous sodium hydroxide (10 mol dm^{-3}). The resulting mixture was filtered, and the residue was recrystallized from water to give *9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine* **4** as a colourless solid (1.138 g, 95%) that was identical [^{1}H NMR, ^{13}C NMR, mp, R_f (system C)] to the material prepared above by the acidic hydrolysis of the corresponding diacetoxy derivative **26**.

Acetylation of 2-Amino-6-[(4-chlorophenyl)sulfanyl]-9-[4-hydroxy-(3-hydroxymethyl)butyl]-9*H*-purine 32

A solution of 2-amino-6-[(4-chlorophenyl)sulfanyl]-9-[4-hydroxy-3-(hydroxymethyl)butyl]-9*H*-purine **32** (4.0 g, 10.5 mmol) and acetic anhydride (9.9 mL, 0.15 mol) in dry pyridine (10 mL) was stirred at room temperature. After 16 h, triethylamine (14.6 mL, 0.15 mol) and methanol (5.2 mL) were added to the cooled (ice-water bath) products which were then concentrated to *ca.* one quarter volume. Chloroform (200 mL) was added and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate (3 x 120 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the residue from aqueous methanol gave *9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9H-purine* **26** as a colourless solid (4.72 g, 96%) that was identical [^{1}H NMR, ^{13}C NMR, mp, R_f (system A)] to the material described above.

9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-9*H*-purine (famciclovir) 5

9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **26** (3.0 g, 6.5 mmol), Raney nickel slurry (13.6 g) and ethanol - water (1:1 v/v; 80 mL) were stirred together and heated under gentle reflux. After 1 h, the products were filtered through Celite, and the filtrate was evaporated under reduced pressure.

Crystallization of the colourless glassy residue from aqueous acetone gave the *title compound* **5** (1.90 g, 91%) (Found : C, 52.17; H, 5.95; N, 21.58. Calc. for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96, N, 21.79%), mp 103-105°C (lit.[16], mp 102-103°C); R_f 0.61 (system B); δ_H [$(CD_3)_2SO$] 1.82-1.96 (3 H, m), 2.00 (6 H, s), 4.03 (4 H, d, *J* 5.4), 4.15 (2 H, t, *J* 6.9), 6.52 (2 H, brs), 8.12 (1 H, s), 8.58 (1 H, s); δ_C [$(CD_3)_2SO$] 21.0, 28.2, 34.8, 40.6, 63.8, 127.3, 143.0, 149.4, 153.3, 160.8, 170.7.

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