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Conversion of Guanosine into Acyclovir and its 6-Deoxy Derivative

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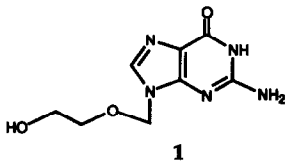
Abstract: 2-Amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11**, which is readily prepared by allowing the corresponding 6-chloro-compound **10** to react with 4-chloro(thiophenol) and triethylamine in methanol solution at room temperature, reacts with boron trifluoride diethyl etherate in boiling dichloromethane solution to give 2-amino-6-(4-chlorophenylthio)-9*H*-purine **12** in high isolated yield. 9-[(2-Acetoxyethoxy)methyl]-2-amino-6-(4-chlorophenylthio)-9*H*-purine **13**, prepared from the latter aglycone **12** in good yield, is converted by a four-step process into acyclovir **1** and by a two-step process into 6-deoxyacyclovir **2**.

A number of nucleoside analogues in which the sugar residues have been replaced by acyclic side-chains have been found to possess high antiviral activity[1]. A particularly notable group of such analogues which have either already found or are likely to find application in chemotherapy are achiral 9-alkylguanine or closely related 9-alkyl-2-aminopurine derivatives. This group of compounds includes acyclovir[2] **1**, its 6-deoxy-derivative[3] **2**, ganciclovir[4] **3**, penciclovir[5] **4** and famciclovir[6] **5**. A possible overall strategy for the synthesis of these and indeed other related alkylated purines consists essentially of two main parts. The first such part involves the preparation of a purine derivative that undergoes alkylation highly regioselectively (or preferably regiospecifically) on *N*-9, and is so designed that the resulting alkylation product can readily be converted into the corresponding 9-alkylguanine or 9-alkyl-2-aminopurine. The other main part involves the preparation of the synthons required for the introduction of the appropriate acyclic side-chains. The present study has been directed towards the first part of the overall strategy, that is the synthesis of a suitable purine derivative. The possible utility of the purine derivative selected (see **12** below) is illustrated by its conversion into both acyclovir **1** and the corresponding prodrug 6-deoxyacyclovir **2**.



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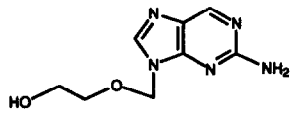

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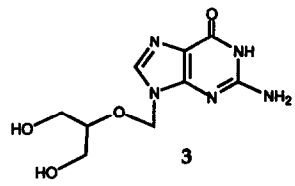

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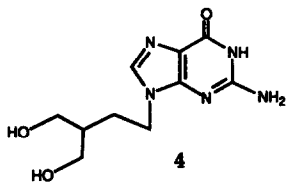

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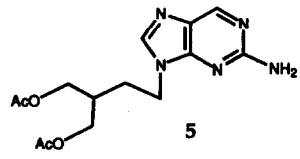

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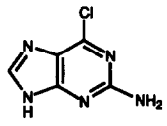

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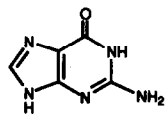

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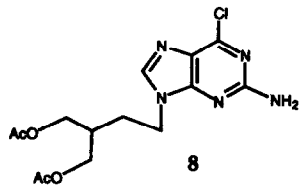

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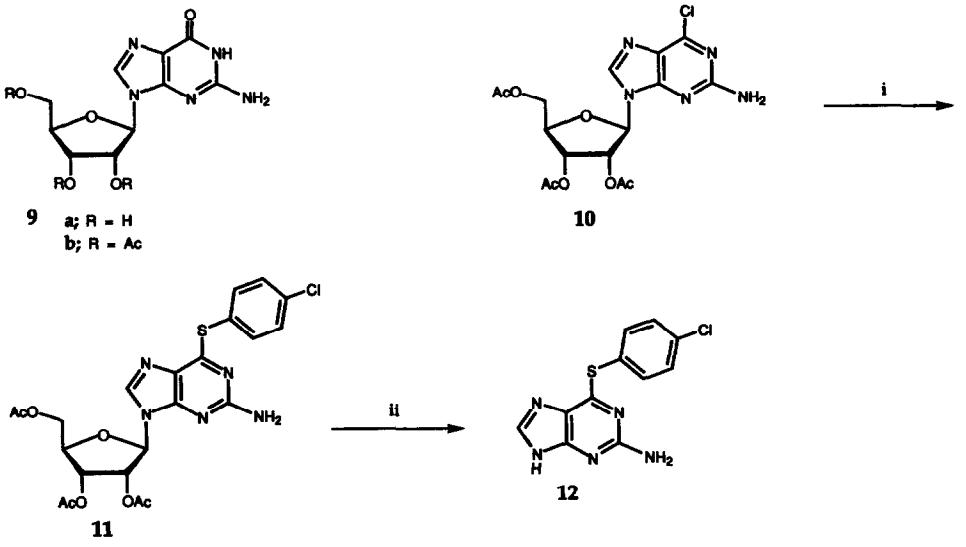
2-Amino-6-chloropurine[7] **6**, which is a potential precursor both of guanine and 2-aminopurine derivatives, is an obvious candidate for the purine component required in the synthesis of the above antiviral agents **1**-**5** and related compounds, and indeed has been used[5,6,8] for this purpose. However, there is a possible disadvantage to be taken into consideration in connection with the use of the latter compound **6** in that, although it undergoes alkylation predominantly on *N*-9, significant quantities of 7-alkyl derivatives are often also obtained[9,10]. For example, compound **6** reacts with benzyl bromide in the presence of potassium carbonate to give[9] the isomeric 9-*N*- and 7-*N*-benzyl derivatives in the proportions of 3.5 : 1; under similar conditions, it reacts with 4-acetoxy-3-(acetoxymethyl)-1-iodobutane to give[10] mainly compound **8** which is a precursor both of penciclovir **4** and famciclovir **5**, but the isomeric 7-*N*-alkyl derivative accounts for *ca.* 15% of the products obtained.

Since 2',3',5'-tri-*O*-acetylguanosine **9b**, which may be prepared[11] in very high (94%) yield from guanosine **9a**, reacts with phosphorus oxychloride in the presence of *N*,*N*-dimethylaniline and tetraethylammonium chloride in acetonitrile solution to give[11] 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **10** directly and in 85% isolated yield, it occurred to us that guanosine **9a** might be a more convenient starting material for the preparation of the purine component than guanine **7**, the most accessible precursor[7c] of 2-amino-6-chloropurine **6**. A recent study has suggested[10] that the lipophilicity of the 6-substituent as well as its bulk might influence the *N*-9/*N*-7 alkylation ratio. With this

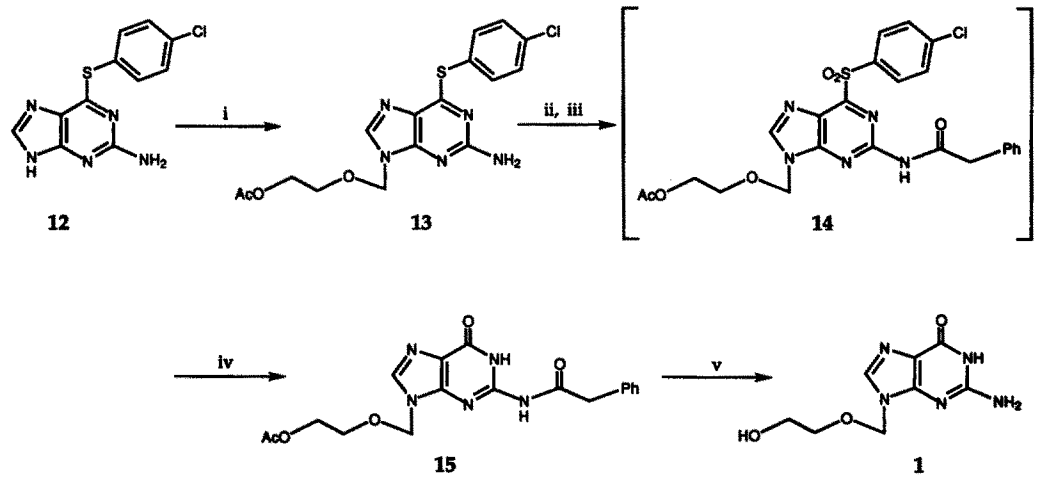
in mind we thought that 2-amino-6-(4-chlorophenylthio)-9*H*-purine **12** which may readily be prepared in two steps (Scheme 1) from the 6-chloro-compound **10** might well prove to be a suitable purine derivative for the synthesis of compounds **1-5** and indeed for 9-alkylguanine and related derivatives in general.



Scheme 1 *Reagents and conditions:* i, 4-ClC_6H_4SH, Et_3N, MeOH, N_2, RT, 4 hr; ii, conc. H_2SO_4, 0°C to RT or $Et_2O \rightarrow BF_3$, PhOH, CH_2Cl_2, reflux, 2 hr.

The 6-chloro-compound **10** reacted with a slight excess each of 4-chloro(thiophenol) and triethylamine in methanol solution[12] at room temperature to give (Scheme 1) the corresponding thioether **11** which was isolated as a crystalline solid in 81% yield. The key reaction in this synthetic approach is the conversion of the latter nucleoside derivative **11** into the corresponding aglycone **12**. Initially this was effected with concentrated sulfuric acid at room temperature (Scheme 1, reaction ii) and the required purine derivative **12** was obtained as a crystalline solid in 70% isolated yield. We then found that a better yield (89%) was obtained when the cleavage of the glycosidic linkage was effected by treatment with an excess of boron trifluoride diethyl etherate in the presence of phenol in boiling dichloromethane solution. The presence of phenol was found to be beneficial but whether or not it reacted with the released sugar moiety has not been investigated. If the glycosidic cleavage reaction is effected by the latter procedure, the four-step conversion of guanosine **9a**, which is a relatively inexpensive starting material, into the required 2-amino-6-(4-chlorophenylthio)-9*H*-purine **12** proceeds in *ca.* 57% overall yield. A clear advantage of the present approach is that, if any alkylation reaction of

compound 12 should prove not to be virtually regiospecific, alkylation on *N*-7 could be further suppressed by replacing the 4-chlorophenyl by a much bulkier aryl group. It is not anticipated that such a modification would be accompanied by synthetic complications.

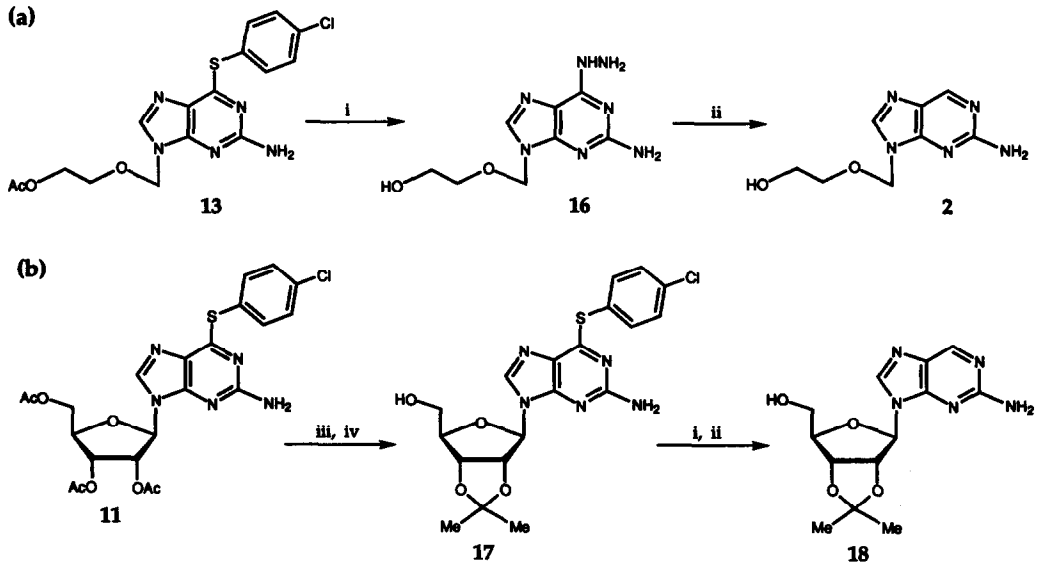


Scheme 2 *Reagents and conditions*: i, a, $(Me_3Si)_2NH$, $(NH_4)_2SO_4$, reflux, 30 min, b, $Hg(CN)_2$, $AcOCH_2CH_2OCH_2Br$, benzene, reflux; ii, $PhCH_2COCl$, 2,6-lutidine, MeCN, 0 °C; iii, 3-$ClC_6H_4CO_3H$, CH_2Cl_2, RT, 3 hr; iv, Ac·C(Me) = NOH, $(Me_2N)_2C$ = NH, MeCN, RT, 15 min; v, 8 mol dm^{-3} NH_3, MeOH, RT, 24 hr.

The purine derivative 12 was first trimethylsilylated by treatment (Scheme 2) with an excess of hexamethyldisilazane in the presence of ammonium sulfate. The product was then heated with (2-acetoxyethoxy)methyl bromide[8] and mercury(II) cyanide in benzene solution to give the 9-[(2-acetoxyethoxy)methyl] derivative 13 in 70% isolated yield. The isomeric 7-[(2-acetoxyethoxy)methyl] derivative was not detected in the products. Compound 13 was phenylacetylated on *N*-2 and the product was then oxidized to the sulfone 14 by treatment with 3-chloroperbenzoic acid in dichloromethane solution[12]. The latter product 14 was not isolated but was treated directly with butan-2,3-dione monoxime[13] and N^1,N^1,N^3,N^3-tetramethylguanidine in dry acetonitrile (Scheme 2, reaction iv) to give the diacyl acyclovir derivative 15 as a crystalline solid in 53% isolated yield for the three steps, starting from the thioether 13. The phenylacetylation step, which may at first sight appear to be superfluous, proved to be beneficial inasmuch as it improved the solubility of the intermediates in organic solvents and facilitated the isolation of a pure acyclovir derivative (i.e. 15) in satisfactory yield. 2-*N*-Acylation of such purine systems is also believed[14] to facilitate nucleophilic attack on *C*-6 by oximate ions. When the diacyl derivative 15 was treated with ammonia in methanol solution at room temperature,

acyclovir **1** was obtained and was easily isolated from the products as a pure crystalline solid in 84% yield.

While the conversion of 9-[(2-acetoxyethoxy)methyl]-2-amino-6-(4-chlorophenylthio)-9*H*-purine **13** into acyclovir **1** (Scheme 2) involved four steps, its conversion into the corresponding prodrug, 6-deoxyacyclovir[3] **2** required only two steps (Scheme 3a and Experimental), and proceeded in almost 66% overall yield. When the thioether **13** was heated with an excess of hydrazine hydrate in boiling ethanol solution overnight, the 6-hydrazino-



Scheme 3 *Reagents and conditions*: i, $N_2H_4 \cdot H_2O$, EtOH, reflux; ii, yellow HgO, $MeOCH_2CH_2OH$ or EtOH, *ca.* 80 °C; iii, 8 mol dm^{-3} NH_3, MeOH, RT, 16 hr; iv, $Me_2C(OMe)_2$, $TsOH \cdot H_2O$, MeCN, RT.

compound **16** was obtained in nearly quantitative yield. Thus smooth nucleophilic substitution by hydrazine at *C*-6 can readily be effected without first oxidizing the thioether to the corresponding sulfone. Treatment of the hydrazino-compound **16** in 2-methoxyethanol solution with yellow mercury(II) oxide[15] at 80°C for 2 hr gave 6-deoxyacyclovir **2** which was isolated as a colourless crystalline solid in 70% yield. This two-step desulfurization process was also carried out on 2-amino-6-(4-chlorophenylthio)-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine **17**. The latter compound **17** was converted (Scheme 3b and Experimental) into 2-amino-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine[16] **18** in 57% overall yield. The two-step conversion (Scheme 3b and Experimental) of 2-amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11** into the corresponding isopropylidene derivative **17** was effected in 55% overall yield.

It is not proposed to review here the methods that have been used previously for the synthesis of acyclovir 1, its 6-deoxy-derivative 2 and related compounds. In conclusion, it may be supposed that 2-amino-6-(4-chlorophenylthio)-9*H*-purine 12, which is best prepared by the action of boron trifluoride diethyl etherate on 2-amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11** (Scheme 1), will also prove to be a suitable purine derivative for the synthesis of ganciclovir[4] 3, penciclovir[5] 4 and famciclovir[6] 5. Studies directed towards testing this supposition experimentally are now in progress in our laboratory.

EXPERIMENTAL

NMR Spectra were measured at 250 MHz with a Bruker WM 250 spectrometer and at 360 MHz with a Bruker AM 360 spectrometer; tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [chloroform-ethanol (98:2 v/v)], B [chloroform-ethanol (95:5 v/v)] and C [butan-1-ol - acetic acid - water (5:2:3 v/v)]. Liquid chromatography (LC) was carried out on a Jones Apex Octadecyl 5μ column which was eluted with 0.1 mol dm^{-3} aqueous triethylammonium acetate - acetonitrile (97:3 v/v). Dichloromethane was dried by heating over phosphorus pentoxide, under reflux, and was then distilled. Acetonitrile, 2,6-lutidine, pyridine and triethylamine were dried by heating, under reflux, with calcium hydride and were then distilled. *N*,*N*-Dimethylformamide (DMF) was dried by distillation over calcium hydride under reduced (water-pump) pressure. Light petroleum refers to the fraction boiling in the range 30-40°C.

2-Amino-6-chloro-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine **10**. - *N*,*N*-Dimethylaniline (3.2 cm^3, 25.2 mmol) and freshly distilled phosphorus oxychloride (13.7 cm^3, 0.147 mol) were added to a stirred solution of 2',3',5'-tri-*O*-acetylguanosine[11] **9b** (10.23 g, 25.0 mmol) and tetraethylammonium chloride (8.30 g, 50.1 mmol; dried *in vacuo* over phosphorus pentoxide at 85°C) in an atmosphere of nitrogen at room temperature. The reaction flask was placed in an oil-bath which had been preheated to 100°C, and the reactants were heated, under reflux, for 10 min. The cooled products were then evaporated under reduced pressure, and the residue was dissolved in chloroform (150 cm^3). Crushed ice (150 g) was added and the resulting mixture was stirred for 15 min. After the layers had separated, the aqueous layer was extracted with chloroform (5 × 50 cm^3). The combined organic layers were then washed with cold water (6 × 30 cm^3), saturated aqueous sodium hydrogen carbonate (3 × 50 cm^3), dried ($MgSO_4$) and concentrated (to *ca.* 40 cm^3) under reduced pressure. After propan-2-ol (60 cm^3) had been added, the solution was concentrated under reduced pressure to *ca.* 40 cm^3 and kept at 4°C overnight to give the *title compound* **10** (9.0 g, 84%) (Found: C, 45.0; H, 3.9; N, 16.1. Calc for $C_{16}H_{18}ClN_5O_7$: C, 44.9; H, 4.2; N, 16.4%) as a crystalline solid, m.p. 140-142°C, (lit[12]. 152-153°C); R_f 0.27 (system A); δ_H [$(CD_3)_2SO$] 2.04 (3 H, s), 2.05

(3 H, s), 2.13 (3 H, s), 4.29 (1 H, dd, *J* 5.1 and 10.9), 4.35-4.45 (2 H, m), 5.55 (1 H, dd, *J* 4.1 and 5.8), 5.89 (1 H, t, *J* 5.9), 6.12 (1 H, d, *J* 5.2), 7.09 (2 H, br.s), 8.38 (1 H, s); δ_C [$(CD_3)_2SO$] 20.12, 20.31, 20.44, 62.88, 70.18, 71.83, 79.63, 84.80, 123.43, 141.20, 149.84, 153.62, 159.84, 169.21, 169.36, 170.02.

2-Amino-6-(4-chlorophenylthio)-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine **11**. - 4-Chloro(thiophenol) (1.70 g, 11.8 mmol) and triethylamine (1.6 cm^3, 11.5 mmol) were added to a stirred suspension of 2-amino-6-chloro-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **10** (4.15 g, 9.7 mmol) in methanol in an atmosphere of nitrogen at room temperature. After 4 hr, the products were filtered and the residue was washed with light petroleum. Crystallization of this material from ethanol gave the *title compound* **11** (4.23 g, 81%) (Found: C, 49.1; H, 4.0;, N, 12.9. $C_{22}H_{22}ClN_5O_7S$ requires: C, 49.3; H, 4.1; N, 13.1%), m.p. 170°C; R_f 0.30 (system A); δ_H [$(CD_3)_2SO$] 2.04 (6 H, s), 2.13 (3 H, s), 4.28 (1 H, dd, *J* 5.5 and 11.2), 4.35 (1 H, m), 4.41 (1 H, dd *J* 3.7 and 11.2), 5.55 (1 H, dd, *J* 4.2 and 5.7), 5.89 (1 H, t, *J* 5.9), 6.10 (1 H, d, *J* 6.1), 6.57 (2 H, br.s), 7.53 (2 H, d, *J* 8.5), 7.64 (2 H, d, *J* 8.5), 8.25 (1 H, s); δ_C [$(CD_3)_2SO$] 20.19, 20.37, 20.52, 63.01, 70.31, 71.88, 79.63, 84.57, 123.66, 126.52, 129.18, 134.11, 136.63, 139.53, 151.23, 158.65, 159.70, 169.30, 169.46, 170.11.

2-Amino-6-(4-chlorophenylthio)-9H-purine **12**. - (a) 2-Amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11** (3.48 g, 6.5 mmol) was added in small portions with stirring to concentrated sulfuric acid (15 cm^3) at 0-5°C (ice-water bath). The reaction mixture was stirred at 0-5°C for 5 min, and then at room temperature for 30 min. The resulting solution (an ultrasonic bath may be used, if necessary, to effect complete solution) was poured onto crushed ice (200 g), and the mixture was stirred vigorously for 5 min. The products were then carefully neutralized (to *ca.* pH 7) with concentrated aqueous ammonia and extracted with ethyl acetate (1 × 100 cm^3, 2 × 50 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* **12** as a colourless solid (1.26 g, 70%) which was recrystallized from aqueous methanol (Found: C, 47.5; H, 2.85; N, 25.0. $C_{11}H_8ClN_5S$ requires: C, 47.6; H, 2.9; N, 25.2%), m.p. 225°C; R_f 0.05 (system A); δ_H [$(CD_3)_2SO$] 6.28 (2 H, br.s), 7.51 (2 H, d, *J* 8.5), 7.63 (2 H, d, *J* 8.5), 7.97 (1 H, s), 12.62 (1 H, br.s); δ_C [$(CD_3)_2SO$] 123.39, 127.08, 128.97, 133.71, 136.35, 139.42, 152.27, 157.01, 159.63.

(b) Phenol (2.076 g, 22 mmol) and boron trifluoride diethyl etherate (11 cm^3, 89 mmol) were added to a stirred solution of 2-amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11** (5.91 g, 11.0 mmol) in dry dichloromethane (100 cm^3), and the resulting solution was heated, under reflux, for 2 hr. The cooled products were evaporated under reduced pressure. The residue obtained was dissolved in ethyl acetate (250 cm^3) and the resulting solution was washed with saturated aqueous sodium carbonate (3 × 50 cm^3),

dried ($MgSO_4$) and evaporated under reduced pressure. The residue was washed with diethyl ether (3 × 20 cm^3) to give the *title compound* **12** as a colourless solid (2.735 g, 89%) that was identical [m.p., TLC (system B), ^1H and ^{13}C NMR] to the material described in (a) above.

9-[(2-Acetoxyethoxy)methyl]-2-amino-6-(4-chlorophenylthio)-9H-purine **13**. - 2-Amino-6-(4-chlorophenylthio)-9*H*-purine **12** (1.11 g, 4.0 mmol), ammonium sulfate (0.18 g, 1.36 mmol) and hexamethyldisilazane (20 cm^3) were heated together, under reflux. After 3 hr, the cooled products were evaporated to dryness under reduced pressure, and dry benzene (45 cm^3) and mercury(II) cyanide (1.38 g, 5.46 mmol) were added. The mixture was heated, under reflux, for 30 min and a solution of (2-acetoxyethoxy)methyl bromide[8] (0.78 g, 3.96 mmol) in benzene (10 cm^3) was added. After the reaction mixture had been heated, under reflux, for a further period of 2 hr, the cooled products were evaporated under reduced pressure and chloroform (300 cm^3) was added. The resulting solution was extracted with 1.0 mol dm^{-3} aqueous potassium iodide (150 cm^3) and saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was fractionated by chromatography on silica gel. The appropriate fractions, eluted with chloroform, were combined and evaporated under reduced pressure to give the *title compound* **13** as a colourless glass (1.10 g, 70%), which was crystallized from ethyl acetate - cyclohexane (Found: C, 48.75; H, 3.9; N, 17.4. $C_{16}H_{16}ClN_5O_3S$ requires: C, 48.8; H, 4.1; N, 17.8%), m.p. 99-101°C; R_f 0.26 (system A); δ_H [$(CD_3)_2SO$] 1.95 (3 H, s), 3.69 (2 H, m), 4.07 (2 H, m), 5.45 (2 H, s), 6.50 (2 H, br.s), 7.52 (2 H, d, *J* 8.5), 7.63 (2 H, d, *J* 8.5), 8.15 (1 H, s); δ_C [$(CD_3)_2SO$] 20.46, 62.68, 66.61, 71.78, 123.36, 126.67, 129.05, 133.90, 136.45, 141.44, 151.66, 157.97, 159.87, 170.16.

9-[(2-Acetoxyethoxy)methyl]2-N-phenylacetylguanine **15**. - 2,6-Lutidine (1.0 cm^3, 8.6 mmol) was added to a stirred solution of 9-[2-(acetoxyethoxy)methyl]-2-amino-6-(4-chlorophenylthio)-9*H*-purine **13** (1.10 g, 2.8 mmol) in dry acetonitrile (30 cm^3), and the solution was cooled to 0°C (ice-bath). Phenylacetyl chloride (0.56 cm^3, 4.2 mmol) was added followed, after 30 min, by water (0.8 cm^3). After a further period of 10 min, the products were evaporated under reduced pressure. A solution of the residue in chloroform (100 cm^3) was washed with cold 1.0 mol dm^{-3} sulfuric acid (50 cm^3) and then with saturated sodium hydrogen carbonate (2 × 50 cm^3). The latter washings were back extracted with chloroform (50 cm^3), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue obtained was fractionated by chromatography on silica gel. The appropriate fractions, eluted with chloroform were evaporated under reduced pressure to give a colourless glass (1.18 g), R_f 0.29 (system A), 0.40 (system B).

3-Chloroperbenzoic acid (*ca.* 55%; 2.0 g, *ca.* 6.4 mmol) was added to a stirred solution of the latter material (1.10 g) in dichloromethane (50 cm^3) at room temperature. After 3 hr, more dichloromethane (50 cm^3) was added and the products were washed with aqueous sodium hydrogen sulfite (50 cm^3) and saturated aqueous sodium hydrogen carbonate

(2×50 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was redissolved in dry acetonitrile (15 cm^3). Butan-2,3-dione monoxime (0.33 g, 3.3 mmol) and N^1,N^1,N^3,N^3-tetramethylguanidine (0.40 cm^3, 3.2 mmol) were added, and the reactants were stirred at room temperature. After 15 min, the products were concentrated under reduced pressure, the residue was redissolved in chloroform (50 cm^3) and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate (2×50 cm^3). The dried ($MgSO_4$) chloroform layer was evaporated under reduced pressure and the residue was fractionated by chromatography on silica gel. The appropriate fractions, eluted with chloroform-ethanol (96:4 v/v), were combined and evaporated under reduced pressure to give a colourless glass. Crystallization of this material from propan-2-ol gave the *title compound* **15** (0.53 g, 53% overall yield based on **13**) (Found: C, 56.1; H, 4.9; N, 17.9. $C_{18}H_{19}N_5O_5$ requires: C, 56.1; H, 5.0; N, 18.2%), m.p. 148-150°C; R_f 0.05 (system A), 0.15 (system B); δ_H [$(CD_3)_2SO$] 1.95 (3 H, s), 3.70 (2 H, m), 3.82 (2 H, s), 4.09 (2 H, m), 5.50 (2 H, s), 7.25 - 7.40 (5 H, m), 8.16 (1 H, s), 12.03 (2 H, br.); δ_C [$(CD_3)_2SO$] 20.47, 42.49, 62.61, 66.55, 72.37, 120.23, 126.92, 128.37, 129.30, 134.20, 140.07, 148.05, 148.74, 154.79, 170.18, 174.09.

9-[(2-Hydroxyethoxy)methyl]-guanine (Acyclovir) **1**. - 9-[(2-Acetoxyethoxy)methyl]-2-*N*-phenylacetylguanine **15** (0.53 g, 1.38 mmol) was dissolved in 8 mol dm^{-3} methanolic ammonia (20 cm^3) at room temperature. After 24 hr, the products were evaporated under reduced pressure and the residue was crystallized from aqueous ethanol to give the *title compound* **1** (0.26 g, 84%) (Found: C, 42.45; H, 5.0; N, 30.8. Calc. for $C_8H_{11}N_3O_3$: C, 42.7; H, 4.9; N, 31.1%) as colourless crystals, m.p. 255-260°C (lit.[8] m.p. 265-266°C); λ_{max} (0.1 mol dm^{-3} hydrochloric acid)/nm 254 (ϵ 11 800); λ_{infl}/nm (ϵ 7800); λ_{min}/nm 226 (ϵ 2400); R_f 0.25 (system C); t_R 4.6 min (100%); δ_H [$(CD_3)_2SO$] 3.48 (4 H, m), 4.70 (1 H, m), 5.36 (2 H, s), 6.54 (2 H, br.s), 7.84 (1 H, s), 10.69 (1 H, br.s); δ_C [$(CD_3)_2SO$] 59.79, 70.26, 71.92, 116.34, 137.69, 151.32, 153.75, 156.73. This material was identical to that purchased from the Sigma Chemical Co.

2-Amino-6-hydrazino-9-[(2-hydroxyethoxy)methyl]-9H-purine **16**. - Hydrazine monohydrate (1.40 cm^3, 28.9 mmol) was added to a stirred solution of 9-[(2-acetoxyethoxy)methyl]-2-amino-6-(4-chlorophenylthio)-9*H*-purine **13** (1.345 g, 3.4 mmol) in absolute ethanol (25 cm^3). The resulting solution was heated, under reflux, for 18 hr and then cooled. The products were filtered and the filtrate was evaporated under reduced pressure. The residue was triturated with diethyl ether (3×30 cm^3) to give the *title compound* **16** (0.77 g, 94%) (Found in material recrystallized from absolute ethanol: C, 40.6; H, 5.3; N, 40.8. $C_8H_{13}N_7O_2$ requires: C, 40.2; H, 5.5; N, 41.0%), m.p. 178-180°C; R_f 0.19 (system B); δ_H [$(CD_3)_2SO$] 3.47 (4 H, s), 4.45 (2 H, br), 4.72 (1 H, m), 5.39 (2 H, s), 6.05 (2 H, s), 7.85 (1 H, s), 8.58 (1 H, br.s); δ_C [$(CD_3)_2SO$] 59.81, 70.18, 71.64, 111.73, 137.46, 151.34, 155.83, 160.29.

2-Amino-9-[(2-hydroxyethoxy)methyl]-9H-purine **2**. - Yellow mercury(II) oxide (2.18 g, 10.1 mmol) was added to a stirred solution of 2-amino-6-hydrazino-9-[(2-hydroxyethoxy)-methyl]-9*H*-purine **16** (0.80 g, 3.3 mmol) in dry 2-methoxyethanol (60 cm^3) and the resulting suspension was heated at 80°C for 2 hr. The products were filtered and the filtrate was concentrated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with chloroform-methanol (95:5 v/v), were combined and evaporated under reduced pressure to give 2-amino-9-[(2-hydroxyethoxy)methyl]-9*H*-purine **2** as a colourless solid (0.49 g, 70%) (Found in material crystallized from absolute ethanol: C, 46.1; H, 5.4; N, 33.4. Calc. for $C_8H_{11}N_5O_2$: C, 45.9; H, 5.3; N, 33.5%), m.p. 185°C (lit.[3], 187-189°C); R_f 0.11 (system B); δ_H [$(CD_3)_2SO$] 3.49 (4 H, m), 4.70 (1 H, t, *J* 5.3), 5.48 (2 H, s), 6.62 (2 H, s), 8.20 (1 H, s), 8.62 (1 H, s); δ_C [$(CD_3)_2SO$] 59.79, 70.49, 71.67, 126.54, 142.77, 149.16, 153.08, 160.69.

2-Amino-6-(4-chlorophenylthio)-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine **17**. - 2-Amino-6-(4-chlorophenylthio)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **11** (5.50 g, 10.26 mmol) and methanolic ammonia (8 mol dm^{-3}, 100 cm^3) were stirred together at room temperature. After 16 hr, the products were concentrated under reduced pressure to give a colourless solid residue. 2,2-Dimethoxypropane (12.0 cm^3, 95.5 mmol) and toluene-4-sulfonic acid monohydrate (1.97 g, 10.36 mmol) were added to a stirred solution of the latter material in acetonitrile (50 cm^3) at room temperature. After 30 min, the products were neutralized (pH paper) with methanolic ammonia, and then filtered. The filtrate was evaporated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane-methanol (99:1 v/v), were combined and concentrated under reduced pressure to give the *title compound* **17** as a colourless glass (2.56 g, 55%) (Found in material crystallized from absolute ethanol: C, 50.8; H, 4.6; N, 15.4. $C_{19}H_{20}ClN_5O_4S$ requires: C, 50.8; H, 4.5; N, 15.6%), m.p. 205-207°C; R_f 0.26 (system A); δ_H [$(CD_3)_2SO$] 1.32 (3 H, s), 1.52 (3 H, s), 3.52 (2 H, m), 4.15 (1 H, m), 5.03 (2 H, m), 5.28 (1 H, dd, *J* 2.4 and 6.2), 6.03 (1 H, d, *J* 2.4), 6.51 (2 H, br.s), 7.51 (2 H, dd, *J* 1.9 and 6.6), 7.62 (2 H, dd, *J* 1.9 and 6.6), 8.20 (1 H, s); δ_C [$(CD_3)_2SO$] 25.23, 27.02, 61.56, 81.27, 83.43, 86.99, 88.65, 112.94, 123.69, 126.71, 129.13, 133.99, 136.52, 139.78, 150.96, 158.21, 159.59.

2-Amino-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine **18**. - Hydrazine monohydrate was added to a solution of 2-amino-6-(4-chlorophenylthio)-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine **17** (0.50 g, 1.1 mmol) in absolute ethanol (10 cm^3). The resulting solution was heated, under reflux for 6 hr, and the products were cooled and evaporated under reduced pressure. The residue was triturated with diethyl ether (3 × 10 cm^3) and then dissolved in absolute ethanol (15 cm^3). Yellow mercury(II) oxide (0.72 g, 3.3 mmol) was added and the stirred suspension was heated, under reflux, for 1 hr. The cooled products were filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate

fractions, which were eluted with chloroform-ethanol (98:2 v/v), were combined and evaporated under reduced pressure to give the *title compound* **18** as a colourless glass (0.196 g, 57%) (Found in material crystallized from ethyl acetate - cyclohexane: C, 50.8; H, 5.8; N, 22.45. Calc. for $C_{13}H_{17}N_5O_4$: C, 50.8; H, 5.6; N, 22.8%), m.p. 118-120°C; R_f 0.25 (system B); δ_H [$(CD_3)_2SO$] 1.33 (3 H, s), 1.54 (3 H, s), 3.54 (2 H, m), 4.17 (1 H, m), 5.03 (1 H, dd, *J* 2.9 and 6.2), 5.07 (1 H, t, *J* 5.2), 5.32 (1 H, dd, *J* 2.6 and 6.2), 6.08 (1 H, d, *J* 2.6), 6.64 (2 H, br.s), 8.28 (1 H, s), 8.61 (1 H, s); δ_C [$(CD_3)_2SO$] 25.15, 26.97, 61.49, 81.19, 83.29, 86.74, 88.32, 112.91, 126.81, 140.96, 149.36, 152.36, 160.39.

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