Conversion of Guanosine into Isoguanosine and Derivatives

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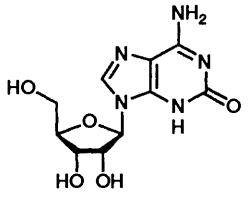
Treatment of 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **7**, which is readily prepared from guanosine **2** in two steps, with toluene-4-thiol and triethylamine followed by sodium nitrite in aqueous acetic acid gives 6-[(4-methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9**. When the latter compound (**9**) is treated with ammonia in aqueous ethanol at 70 °C, methylamine in industrial methylated spirit at room temperature, dimethylamine in industrial methylated spirit at 50 °C, and aniline, under reflux, in pyridine solution followed by methanolic ammonia at room temperature, isoguanosine **1**, 6-*N*-methylisoguanosine **12a**, 6,6-di-*N*-methylisoguanosine **12b**, and 6-*N*-phenylisoguanosine **12c**, respectively, are obtained in satisfactory yields.

Isoguanosine **1**, which is sometimes referred to as crotonoside or 2-hydroxyadenosine, is a naturally occurring, biologically active isomer of guanosine **2**; it was first isolated[1] in 1932 from *Croton tiglium* L. Isoguanosine is incorporated into mammalian but not into bacterial nucleic acids,[2] and is reported to stimulate the accumulation of cyclic-AMP in the brain;[3] it is an inhibitor of IMP pyrophosphorylase,[4] and its 5′-di- and -tri-phosphates inhibit glutamic acid dehydrogenase.[5]



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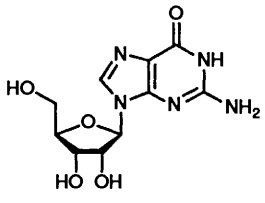

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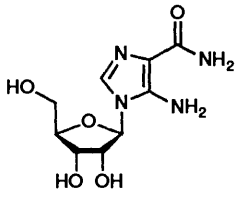

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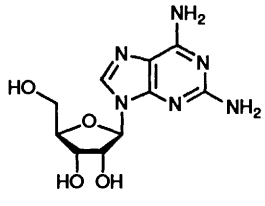

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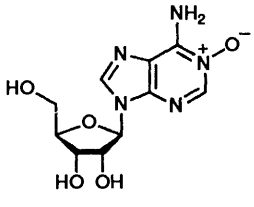

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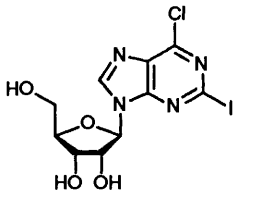
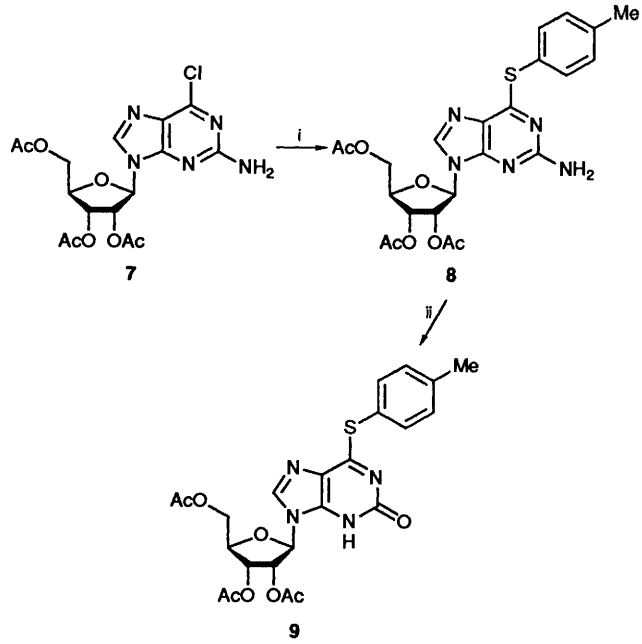


6

Several methods for the synthesis of isoguanosine **1** have been reported in the literature; some of the methods are based[6,7] on the relatively inaccessible 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide **3** as starting material and some involve the modification of other 9-(β-D-ribofuranosyl)purines, such as 2-aminoadenosine[8] **4** or adenosine 1-oxide[9] **5**. We now report a very convenient procedure for the conversion of guanosine **2**, a relatively cheap starting material, into isoguanosine **1** and its 6-*N*-methyl, 6,6-di-*N*-methyl and 6-*N*-phenyl derivatives. Our procedure is related to a previously reported method[10] involving 6-chloro-2-iodo-9-(β-D-ribofuranosyl)purine **6** as an intermediate, and involves the same number of steps; however, unlike the latter method, it avoids a relatively low yielding and possibly scale-limiting photochemical step and leads to an intermediate which is a common precursor both of isoguanosine **1** and its 6-*N*-alkyl and -aryl derivatives (see below).



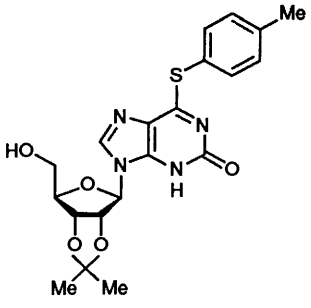
7 **8** **9**

Scheme 1 *Reagents and conditions:* i, toluene-4-thiol, triethylamine, DMF, 100 °C, 1 h; ii, $NaNO_2$, acetic acid–water (1:1 v/v), 50 °C, 1 h

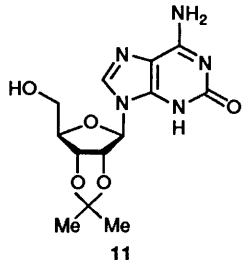
2-Amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine **7** was prepared from guanosine **2** in 71% overall yield, using Robins and Uznánski's chlorination procedure.[11] When compound **7** was heated (see Scheme 1) with *ca.* 2.0 mol equiv. of toluene-4-thiol and 1.0 mol equiv. of triethylamine in anhydrous dimethylformamide (DMF) at 100 °C for 1 h, 2-amino-6-[(4-methylphenyl)thio]-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine **8** was obtained as a crystalline solid in 92% isolated yield. Treatment of compound **8** with a very large excess of sodium nitrite in aqueous acetic acid at 50 °C gave 6-[(4-methylphenyl)-thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** which was isolated as a glassy material in almost quantitative yield. The latter compound is the key intermediate

in the synthesis of isoguanosine **1** and its derivatives by the present approach.

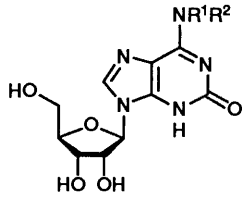
As we had previously prepared 2′,3′-*O*-isopropylideneisoguanosine **11** by a totally independent route,[12] we set out first to convert compound **9** into isoguanosine **1**, *via* its 2′,3′-*O*-isopropylidene derivative **11**. 6-[(4-Methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** was treated with an excess of *ca.* 0.8 mol dm^{-3} methanolic sodium methoxide at room temperature for 15 min, and the resulting deacetylated product was allowed to react with 2,2-dimethoxypropane in the presence of toluene-4-sulphonic acid (PTSA) in DMF solution to give the corresponding 2′,3′-*O*-isopropylidene derivative **10** in *ca.* 53% overall yield for the two steps. When the latter compound **10** was heated in a closed vessel with ammonia in aqueous 1,4-dioxane solution at 70 °C for 6 h, 2′,3′-*O*-isopropylideneisoguanosine **11**, identical with authentic material,[12] was obtained as a crystalline solid in *ca.* 75% isolated yield. When a solution of compound **11** in formic acid–water (4:1 v/v) solution was kept at room temperature for 4 h, isoguanosine **1** was obtained and was isolated as a crystalline solid in 86% yield.



10



11



12 a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = H, R^2 = Ph

Isoguanosine **1** was then prepared more directly by heating the intermediate triacetate **9** with ammonia in aqueous ethanol solution in a closed vessel at 70 °C; it was obtained in *ca.* 73% isolated yield and was identical with the material obtained (see above) by the action of 80% formic acid on compound **11**. When the intermediate triacetate **9** was allowed to react with a 33% solution of methylamine in industrial methylated spirit at room temperature for 3 h, 6-*N*-methylisoguanosine[6] **12a** was obtained and was isolated as a crystalline solid in *ca.* 90% yield. 6,6-Di-*N*-methylisoguanosine[6] **12b** was similarly obtained by heating the triacetate **9** with a 33% solution of dimethylamine in industrial methylated spirit at 50 °C, and was isolated as a crystalline solid in >90% yield. The intermediate triacetate **9** not surprisingly was much less susceptible to nucleophilic attack at C-6 by aromatic amines; however, when it was heated with aniline in pyridine solution, under reflux, under nitrogen for 53 h and the products were then treated with methanolic ammonia, 6-*N*-phenylisoguanosine **12c** was obtained and was isolated as a crystalline solid in >60% overall yield for the two steps.

We have previously found[13,14] other nucleoside derivatives with 6- or 8-arylthio substituents to be useful synthetic intermediates. It is noteworthy that, while the key intermediate **9** undergoes deacetylation in satisfactory yield (see Experimental section) without concomitant substitution at C-6 when it is treated with sodium methoxide in methanol, it readily undergoes nucleophilic substitution at C-6 when it is allowed to react with methylamine in industrial methylated spirit solution at room temperature. In some related studies, nucleophilic substitution at C-6 or C-8 has been facilitated by first oxidizing the arylthio derivatives to the corresponding sulphoxides[14] or sulphones.[13,14]

Experimental

NMR Spectra were measured at 250 MHz with a Bruker WM 250 spectrometer and at 360 MHz with a Bruker AM360 spectrometer; tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. Merck silica gel 60H was used for short-column chromatography; Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [chloroform–methanol (9:1 v/v)] and B [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 isocratically with water–methanol mixtures. Acetonitrile 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-[(4-methylphenyl)thio]-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine* **8**.—Triethylamine (2.93 cm^3; 21.04 mmol) was added dropwise to a stirred solution of 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **7**[11] (9.00 g, 21.04 mmol) and toluene-4-thiol (5.23 g, 42.1 mmol) in anhydrous DMF (90 cm^3) at room temperature. The reactants were then heated at 100 °C for 1 h, and the resulting products were cooled, and concentrated under reduced pressure. The gummy solid obtained was triturated several times with light petroleum. Crystallization of the residue from absolute ethanol gave the *title compound* **8** (10.0 g, 92%) (Found: C, 53.45; H, 5.0; N, 13.4. $C_{23}H_{25}N_5O_7S$ requires C, 53.6; H, 4.9; N, 13.6%), m.p. 175–177 °C; R_f 0.77 (system A); $\delta_H[(CD_3)_2SO]$ 2.04 (6 H, s), 2.12 (3 H, s), 2.36 (3 H, s), 4.25–4.45 (3 H, m), 5.55 (1 H, dd, *J* 3.8 and 5.8), 5.88 (1 H, t, *J* 6.0), 6.09 (1 H, d, *J* 6.1), 6.47 (2 H, br s), 7.27 (2 H, d, *J* 8.1), 7.48 (2 H, d, *J* 8.1) and 8.22 (1 H, s); $\delta_C[(CD_3)_2SO]$ 20.15, 20.34, 20.47, 20.81, 63.05, 70.38, 71.94, 79.68, 84.68, 123.81, 123.96, 129.98, 135.09, 138.95, 139.47, 151.16, 159.82, 159.88, 169.46, 169.61 and 170.27.

*6-[(4-Methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine* **9**.—Sodium nitrite (25.2 g, 0.365 mol) was added slowly during 1 h to a stirred solution of 2-amino-6-[(4-methylphenyl)thio]-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **8** (9.0 g, 17.5 mmol) in acetic acid–water (1:1 v/v, 180 cm^3) at 50 °C. When the deamination process was complete [as indicated by TLC (system A)], the products were concentrated under reduced pressure. The residue was dissolved in chloroform (200 cm^3) and the resulting solution was washed with ice-cold saturated aq. sodium hydrogen carbonate (250 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residual material was fractionated by short-column chromatography on silica gel to give the desired product **9** as a glass (8.84 g, *ca.* 98%); R_f 0.71 (system A); λ_{max}(95% EtOH)/nm 301; λ_{infl}/nm 252; λ_{min}/nm 271; $\delta_H[(CD_3)_2SO]$ 2.04 (6 H, s), 2.12 (3 H, s), 2.38 (3 H, s), 4.25–4.45 (3 H, m), 5.56 (1 H, m), 5.91 (1 H, t, *J* 5.8), 6.15 (1 H, d, *J* 5.6), 7.29

(2 H, d, *J* 8.0), 7.49 (2 H, d, *J* 8.0) and 8.39 (1 H, s); δ_C[$(CD_3)_2SO$] 20.12, 20.29, 20.42, 20.79, 62.84, 70.09, 71.86, 79.61, 85.13, 123.18, 125.71, 129.98, 135.12, 139.24, 141.51, 151.04, 160.61, 169.22, 169.37 and 170.03.

2′,3′-O-*Isopropylidene*-6-[(4-*methylphenyl*)*thio*]-2-*oxo*-9-(β-D-*ribofuranosyl*)-2,3-*dihydropurine* **10**.—Methanolic sodium methoxide (*ca.* 4.4 mol dm^{-3}; 8.8 cm^3, *ca.* 38.5 mmol) was added to a stirred solution of compound **9** (5.19 g, *ca.* 10.1 mmol) in methanol (40.2 cm^3) at room temperature. After 15 min, the products were neutralized by the addition of Dowex 50 × 8 (H^+-form) cation-exchange resin. The mixture was then filtered and the residue was washed with ethanol several times. The combined filtrate and washings were concentrated under reduced pressure. The residual glass was dissolved in the minimum quantity of chloroform–ethanol (1:1 v/v), and the resulting solution was added dropwise to light petroleum. The white solid [2.99 g, R_f 0.34 (system A)] thus obtained was collected by centrifugation, washed with light petroleum and dried.

2,2-Dimethoxypropane (10.16 cm^3, 82.6 mmol) was added to a stirred solution of the above product (2.99 g) and PTSA monohydrate (1.80 g, 9.5 mmol) in anhydrous DMF (19 cm^3) at room temperature. After 2 h, the products were neutralized (pH paper) with methanolic ammonia (half-saturated at 0 °C), and then concentrated under reduced pressure. The residue obtained was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–ethanol (95:5 v/v), were combined, and evaporated under reduced pressure to give a glass (2.31 g, *ca.* 53% overall yield for the two steps); R_f 0.53 (system A); δ_H($CDCl_3$) 1.36 (3 H, s), 1.62 (3 H, s), 2.16 (3 H, s), 3.79 (1 H, dd, *J* 2.3 and 12.7), 3.97 (1 H, dd, *J* 1.8 and 12.7), 4.47 (1 H, m), 5.10 (1 H, dd, *J* 1.4 and, 6.0), 5.21 (1 H, dd, *J* 4.7 and 5.9), 5.79 (1 H, d, *J* 4.6), 7.14 (2 H, d, *J* 7.9), 7.46 (2 H, d, *J* 8.1) and 7.86 (1 H, s); δ_C($CDCl_3$) 21.13, 25.24, 27.54, 63.18, 81.54, 82.70, 86.32, 93.28, 114.09, 119.54, 123.45, 131.04, 135.34, 141.73, 142.97, 153.19, 156.82 and 157.25.

2′,3′-O-*Isopropylideneisoguanosine* **11**.—Conc. aq. ammonia (*d* 0.88; 1.09 cm^3) was added to a solution of 2′,3′-*O*-isopropylidene-6-[(4-methylphenyl)thio]-2-oxo-9-(β-D-ribofuranosyl)-2,3-dihydropurine **10** (0.30 g, *ca.* 0.70 mmol) in 1,4-dioxane (7 cm^3) and the reactants were heated at 70 °C in Pierce Reacti-Vials for 6 h. The product was then cooled, and concentrated under reduced pressure. After the residue had been triturated with diethyl ether, it was crystallized from absolute ethanol to give 2′,3′-*O*-isopropylideneisoguanosine **11** (0.17 g, *ca.* 75%) as crystals, m.p. 280 °C, identical [^1H and ^{13}C NMR, UV, TLC (system A)] with material prepared [12] by another route.

Isoguanosine **1**.—(*a*) A stirred solution of 2′,3′-*O*-isopropylideneisoguanosine **11** (0.50 g, 1.55 mmol) in formic acid–water (4:1, v/v; 5 cm^3) was kept at room temperature for 4 h. The products were then concentrated under reduced pressure and the residue was co-evaporated three times with absolute ethanol. Crystallization of the resultant material from water gave the title compound **1** (0.39 g, 86%) (Found, in material dried *in vacuo* at 100 °C: C, 41.0; H, 4.75; N, 23.5. Calc. for $C_{10}H_{13}N_5O_5$·0.6H_2O: C, 40.8; H, 4.9; N, 23.8%), m.p. 236–238 °C (decomp.) (lit.,[9,10] 237–241 °C); λ_{max}(water)/nm 292 (ε 11 000) and 247 (8800); λ_{min}/nm 264 (ε 2900) and 229 (4200); R_f 0.58 (system B); t_R[water–methanol (95:5 v/v)] 7.0 min; δ_H[$(CD_3)_2SO$–D_2O] 3.56 (1 H, dd, *J* 2.8 and 12.3), 3.66 (1 H, dd, *J* 2.8 and 12.3), 3.98 (1 H, m), 4.11 (1 H, dd, *J* 2.7 and 4.9), 4.50 (1 H, m), 5.67 (1 H, d, *J* 6.4) and 7.97 (1 H, s); δ_C[$(CD_3)_2SO$] 61.63, 70.71, 72.98, 85.94, 87.69, 109.67, 138.07, 152.59, 156.03 and 160.61.

(*b*) Conc. aq. ammonia (*d* 0.88; 9 cm^3) was added to a solution of 6-[(4-methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** (0.35 g, *ca.* 0.68 mmol) in ethanol (3 cm^3). The resulting solution was heated at 70 °C in Pierce Reacti-Vials for 17 h. The products were then concentrated under reduced pressure and ethanol (5 cm^3) was added. The resulting mixture was re-evaporated under reduced pressure, and this process was repeated twice more. The residue was triturated several times with diethyl ether and was then dissolved in a hot mixture of ethanol (12.5 cm^3) and water (12.5 cm^3). The resulting solution was heated with activated charcoal, under reflux, for *ca.* 5 min, and was then cooled, and filtered through Celite. Concentration of the filtrate gave isoguanosine **1** (0.141 g, *ca.* 73%) as a solid. After recrystallization from methanol, the product was identical [m.p., ^1H and ^{13}C NMR, LC] with the material obtained in section (*a*) above.

6-N-*Methylisoguanosine* **12a**.—6-[(4-Methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** (1.00 g, *ca.* 1.94 mmol) was dissolved in a 33% solution of methylamine in industrial methylated spirit (14 cm^3; *ca.* 0.116 mol of methylamine), and the resulting solution was stirred at room temperature for 3 h. The products were then concentrated under reduced pressure and the residue was triturated several times with diethyl ether. The residual solid was crystallized from ethanol to give the title compound **12a** (0.52 g, *ca.* 90%) (Found, in material dried *in vacuo* at 80 °C: C, 41.7; H, 5.1; N, 22.0. Calc. for $C_{11}H_{15}N_5O_5$·H_2O: C, 41.9; H, 5.4; N, 22.2%); m.p. 188–190 °C; λ_{max}(95% EtOH)/nm 281 (ε 7600) and 247 (8600); λ_{infl}/nm 300 (ε 5800); λ_{min}/nm 265 (ε 5800) and 237 (6700); R_f 0.58 (system B); t_R[water–methanol (95:5 v/v)] 14.3 min; δ_H[$(CD_3)_2SO$] 2.95 (3 H, br s), 3.62 (2 H, m), 3.98 (1 H, m), 4.12 (1 H, m), 4.50 (1 H, m), 5.20 (1 H, br), 5.47 (1 H, br), 5.71 (1 H, d, *J* 6.3) and 7.94 (1 H, s); δ_C[$(CD_3)_2SO$] 38.13, 61.48, 70.54, 73.27, 85.60, 87.45, 113.77, 136.18, 151.17, 154.13 and 158.65.

6,6-*Di*-N-*Methylisoguanosine* **12b**.—6-[(4-Methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** (1.00 g, *ca.* 1.94 mmol) was dissolved in a 33% solution of dimethylamine in industrial methylated spirit (14 cm^3, *ca.* 78 mmol of dimethylamine), and the resulting solution was heated at 50 °C for 3 h. The products were then concentrated under reduced pressure and the residue was triturated several times with diethyl ether. The residual solid was crystallized from methanol to give the title compound (0.57 g, *ca.* 93%) (Found, in material dried *in vacuo* at 80 °C: C, 46.0; H, 5.6; N, 22.0. Calc. for $C_{12}H_{17}N_5O_5$·0.2H_2O: C, 45.8; H, 5.6; N, 22.2%); m.p. 230–232 °C (decomp.); λ_{max}(95% EtOH)/nm 278 (ε 10 800) and 253 (11 500); λ_{infl}/nm 306 (ε 4400); λ_{min}/nm 266 (ε 8300) and 241 (ε 9300); R_f 0.72 (system B); t_R[water–ethanol (85:15 v/v)] 8.7 min; δ_H[$(CD_3)_2SO$] 3.41 (6 H, br s), 3.54 (1 H, dd, *J* 3.2 and 12.1), 3.65 (1 H, dd, *J* 3.2 and 12.0), 3.93 (1 H, m), 4.10 (1 H, m), 5.14 (1 H, d, *J* 4.2), 5.40 (2 H, m), 5.76 (1 H, d, *J* 6.2) and 8.03 (1 H, s); δ_C[$(CD_3)_2SO$] 38.07, 61.48, 70.52, 73.27, 85.59, 87.45, 113.84, 136.11, 151.27, 154.27 and 159.01.

6-N-*Phenylisoguanosine* **12c**.—6-[(4-Methylphenyl)thio]-2-oxo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine **9** (1.00 g, *ca.* 1.94 mmol) and freshly distilled aniline (0.36 cm^3, 3.95 mmol) were heated together, under reflux, in anhydrous pyridine (24 cm^3) solution under nitrogen, for 53 h. The products were then concentrated under reduced pressure, and the residue was fractionated by short-column chromatography on silica gel to give a light-purple coloured glass (0.64 g); R_f 0.63 (system A). A portion of this material (0.20 g) was dissolved in methanolic ammonia (half-saturated at 0 °C). After the solution had been kept at room temperature for 15 h, it was concentrated under reduced pressure and the residue was triturated several times with diethyl ether. Crystallization of the solid residue from

water gave the *title compound* **12c** (0.14 g, *ca.* 61% overall yield) (Found: C, 50.5; H, 5.0; N, 18.4. $C_{16}H_{17}N_5O_5 \cdot H_2O$ requires C, 50.9; H, 5.1; N, 18.6%); m.p. 156–158 °C; λ_{max}(95% EtOH)/nm 301 (ε 22 900) and 240 (7900); λ_{min}/nm 265 (ε 5800) and 237 (6700); R_f 0.09 (system A), 0.60 (system **B**); $\delta_H[(CD_3)_2SO]$ 3.58 (1 H, dd, *J* 3.2, 12.1), 3.69 (1 H, dd, *J* 3.3, 12.0), 3.97 (1 H, m), 4.14 (1 H, m), 4.51 (1 H, m), 5.20 (1 H, br), 5.48 (1 H, br), 5.82 (1 H, d, *J* 6.3), 7.03 (1 H, t, *J* 7.3), 7.31 (2 H, m), 7.96 (2 H, d, *J* 7.7), 8.19 (1 H, s) and 9.79 (1 H, br); $\delta_C[(CD_3)_2SO]$ 61.44, 70.55, 73.39, 85.66, 87.45, 114.97, 120.86, 122.66, 128.30, 137.77, 139.39, 153.07 and 159.71.

Acknowledgements

We thank the Cancer Research Campaign for generous financial support; one of us (M. M.) thanks the SERC for the award of a research studentship.

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Paper 0/04758I
Received 23*rd October* 1990
Accepted 14*th November* 1990