Synthesis of Ara-doridosine, A New Arabinosyl Nucleoside Resistant to Adenosine Deaminase. *X*-Ray Structure Determination of 6-*N*,9(*N*)-Diacetyl-1(*N*)-methylisoguanine

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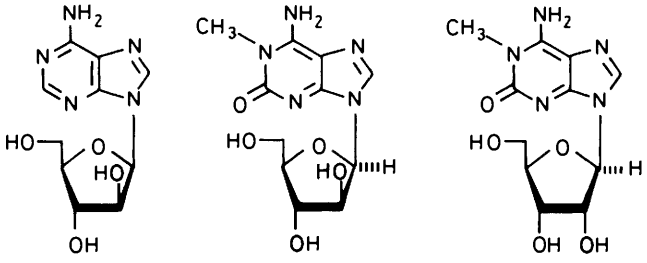
9-(β-D-Arabinofuranosyl)-1-(*N*)-methylisoguanine (**2**) (ara-doridosine) has been prepared *via* two stereochemically complementary synthetic routes, one of which utilized a recently described, novel nucleoside-base rearrangement reaction. The structural determination of several intermediates, some with unusual tautomeric forms stabilized by hydrogen bonding, was facilitated by use of ^{13}C–^{1}H long-range coupling values. An *X*-ray diffraction analysis and a mass-spectral isotope fragmentation experiment also facilitated the structure elucidation of the key intermediates, 6-*N*,9(*N*)-diacetyl-1(*N*)-methylisoguanine (**6**) and 6-*N*-methylisoguanine (**7**), respectively. The potential long acting antiviral agent (**2**) has been shown to be resistant to the enzyme adenosine deaminase.

The effectiveness of 9-(β-D-arabinosyl)adenine (ara-A) (**1**), an antiviral agent with approved status for clinical treatment of human and animal *Herpes* diseases, and several other arabinosyl nucleoside analogues is severely limited due to inactivation *in vivo* by adenosine deaminase.[1–5] The nucleoside 9-(β-D-arabinofuranosyl)-1(*N*)-methylisoguanine (ara-D) (**2**) was chosen[6] as an attractive synthetic goal by analogy with the related riboside analogue doridosine (**3**), a long acting *in vivo*



(**1**) (**2**) (**3**)

antihypertensive agent isolated from a marine nudibranch.[6–9] As doridosine has been reported to be completely resistant to adenosine deaminase, it was hoped that the coupling of the doridosine base, 1(*N*)-methylisoguanine, with the arabinosyl sugar moiety in 'ara-D' (**2**) would create a new nucleoside with the potential of prolonged antiviral activity. The prolonged activity of doridosine has been attributed to steric inhibition of approach by adenosine deaminase to the N-6 amino group caused by the adjacent *N*-methyl group.[7–10]

Two approaches to the synthesis of ara-D seemed apparent, namely introduction of the methyl group onto the nucleoside base either before or after attachment of the arabinosyl sugar moiety. These two synthetic approaches complement each other in that in the first the position of the methyl group is known absolutely, whereas in the second the stereochemistry of the anomeric centre of the arabinosyl moiety is predetermined by the choice of starting material. The former approach utilized a recently described, novel rearrangement reaction[11] to position correctly the methyl group.

Synthetic Route I—Methylation before Arabinosylation.—Commercially available 6-*N*-methyladenine (**4**) (Scheme) in aqueous tetrahydrofuran (THF) was treated with a large excess

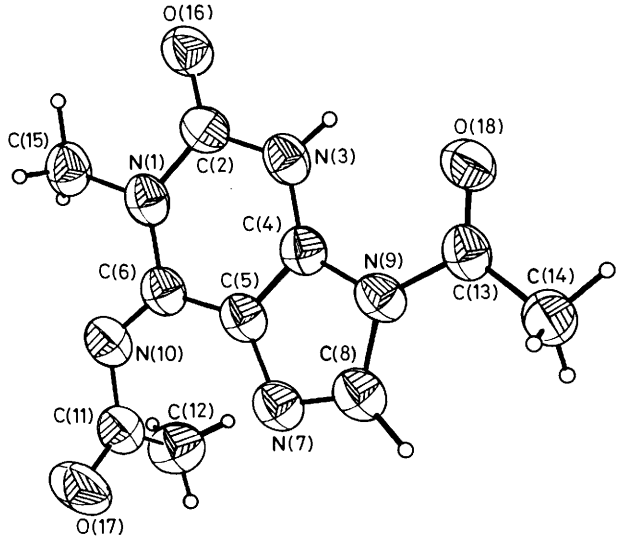
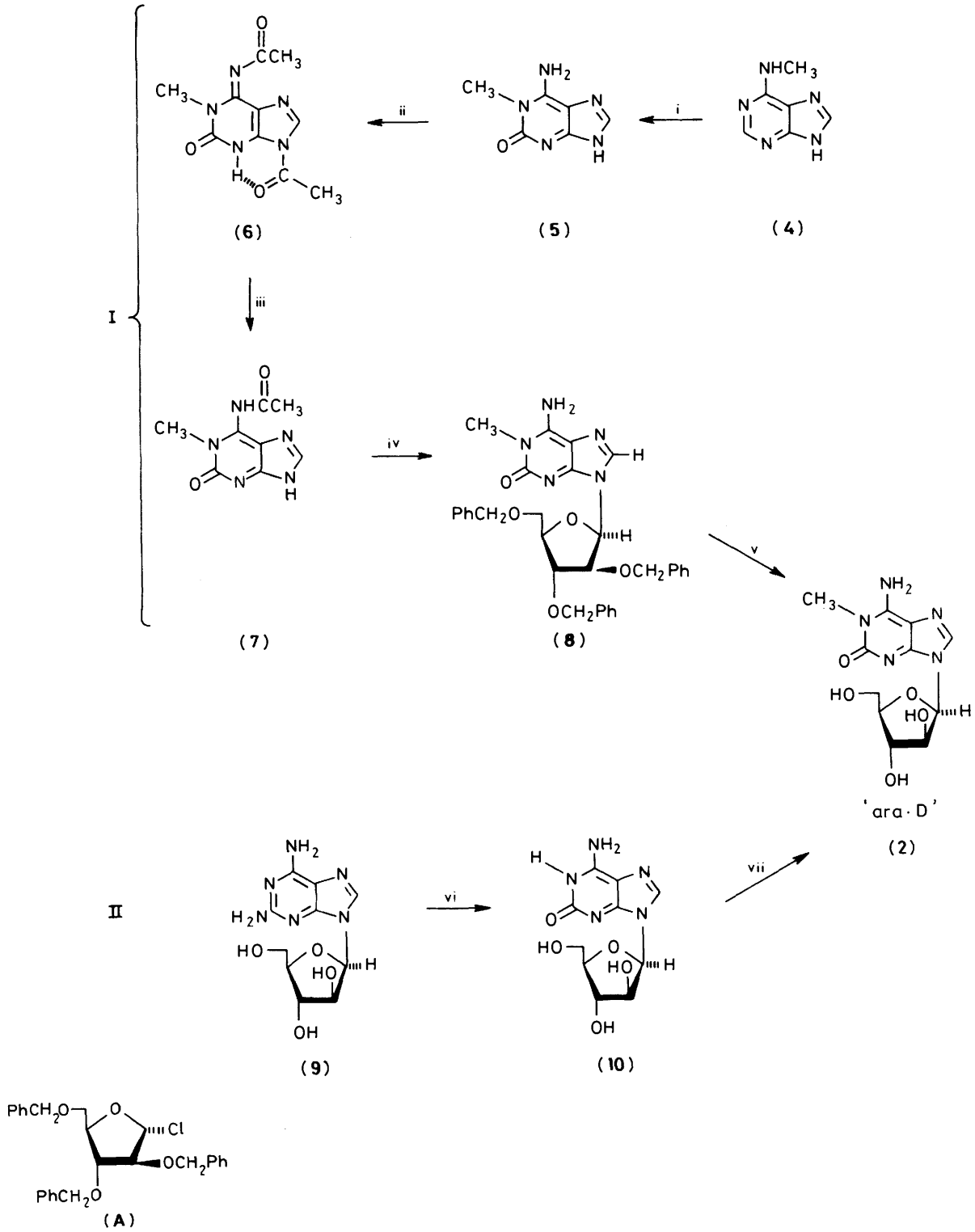


Figure 1. Perspective view of 6-*N*,9(*N*)-diacetyl-1(*N*)-methylisoguanine (**6**) with the atom numbering system. Thermal ellipsoids are depicted at the 50% probability level and H atoms are depicted with 0.1 Å radii

of phenyl chloroformate to yield 1-methylisoguanine (**5**) (Scheme). Following formation of an *O*-phenylcarbamate at N-3 and subsequent nucleophilic attack of water at the activated C-2 position, ring opening allows for rotation about the C-6–C-5 bond and ring re-formation occurs involving the methylamino and the N-3 phenylcarbamate groups in this reaction. While no specific conditions or yield for this transformation were mentioned in the original mechanistic study,[11] modification of the general conditions allowed achievement of a 45% yield, demonstrating the synthetic utility of this rearrangement to prepare 1(*N*)-methylisoguanine.

Treatment of compound (**5**) with acetic anhydride in THF led to a crystalline diacetate, identified as (**6**), in 65% yield. *X*-Ray crystallographic data on (**6**) demonstrated the presence of acetate groups at N-9 and N-6 (Figure 1). The acetate at N-9 forms a hydrogen bond with the N-3 hydrogen, in turn forcing the formation of the *unusual* imine tautomeric form at N-6 in the solid state. As the low-field chemical shift of the N-3 proton in [$^{2}H_6$]DMSO (DMSO is dimethyl sulphoxide) (δ 11.3) suggests that this hydrogen bond also exists in solution; it is presumably



Scheme. The two stereochemically complementary synthetic routes to 9-(β-D-arabinofuranosyl)-1(*N*)-methylisoguanine (ara-doridosine or ara-D) (**2**); I, Synthetic Route I; II, Synthetic Route II. Details of the synthetic routes are given in the text. *Reagents*: i, $ClCO_2Ph$, THF–water; ii, Ac_2O, THF; iii, MeOH, heat; iv, (**A**), 4 Å mol. sieves, CH_2Cl_2, then NH_3–MeOH; v, NH_3–MeOH; vi, $NaNO_2$, HOAc; vii, MeI, DMSO

responsible for the observed preferential susceptibility of the N-9 acetate to methanolysis.

Monoacetate (**7**) was obtained on selective methanolysis of diacetate (**6**) in 91% yield. Analysis of the magnitudes of the C-4 and C-5 to 8-H three-bond coupling values of compounds (**6**) and (**7**) indicated that migration of the imidazolide double bond had occurred from the N-7–C-8 [(**6**), $^3J_{5,8\text{-H}}$ 13 Hz] to the N-9–C-8 position [(**7**), $^3J_{4,8\text{-H}}$ 12 Hz] during the methanolysis reaction, providing evidence that the N-9 acetate group was removed. Recent reports have noted that the ^1H–^{13}C three-

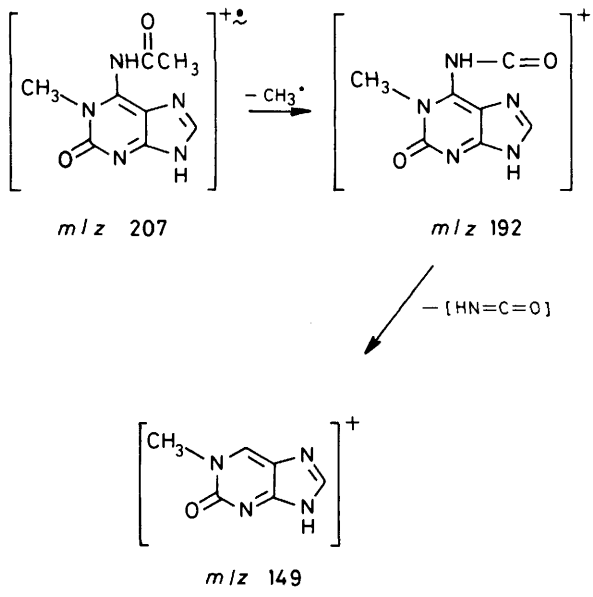
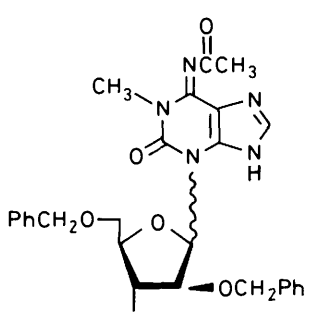


Figure 2. The fragmentation pattern of the ion with *m/z* 207 to ions with *m/z* 192 and 149 in the monoacetate (**7**)

bond coupling-value magnitude in the imidazolide portion of the purine ring system is largest when an intervening double bond is present.[12-14] The mass spectrum of diacetate (**7**) provided more significant evidence that the N-6 acetate group was retained. A prominent $(M - CH_3)^+$ ion (*m/z* 192) in the electron ionization (e.i.) mass spectrum underwent subsequent loss of isocyanic acid to give a peak with *m/z* 149. Constant precursor metastable ion scans[15] for the ion with *m/z* 149 in compound (**7**) support the fragmentation mechanism of Figure 2 by showing that the peak at *m/z* 192 is the sole source of the peak at *m/z* 149 and that the neutral fragment has composition CHNO. Additionally, loss of ^{13}C label in the isocyanic acid from the precursor ion labelled at the acetate carbonyl carbon rules out possible involvement of ring carbonyl in the fragmentation.

While coupling of the acetate (**7**) with 2,3,5-tri-*O*-benzyl-D-arabinosyl chloride in CH_2Cl_2 with activated 4Å molecular sieves[10,16-19] and such catalysts as $SnCl_4$[19,20] or pyridine led to the undesirable, relatively unstable, adduct (**11**), the elimination of catalyst in the reaction mixture provided 1(*N*)-methyl-9(*N*)-(2′,3′,5′-tri-*O*-benzyl-β-D-arabinofuranosyl)isoguanine (**8**) upon treatment of the crude product with NH_3–MeOH. Long-range ^{13}C–^1H coupling observed between C-8 and the C-1′ hydrogen (^3J = 5 Hz) of compound (**8**) confirmed that the arabinosyl moiety was attached at either N-9 or N-7 of the base.

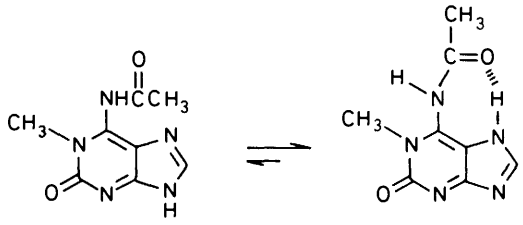


(**11**)

The relative magnitudes of the C-4–8-H and C-5–8-H coupling values, indicative of a double bond between N-7 and C-8, pinpointed the location of the sugar attachment at N-9. Long-range ^{13}C–^1H coupling between C-8 and the C-1′ hydrogen in purine nucleosides, utilized previously by physical organic chemists to determine the base–sugar conformation about the glycosidic bond in known nucleosides,[21] can therefore also be a powerful tool to synthetic chemists in the determination of the location of base–sugar attachment in these multiheteroatom systems.

Application of the sodium and liquid ammonia debenzylation procedure[22] to compound (**8**) led to a product assigned the 9-(β-D-arabinofuranosyl)-1-(*N*)-methylisoguanine or ara-D structure (**2**) and completed the synthesis. However, an absolute determination of the stereochemistry about the anomeric centre awaited a comparison of this material with that produced upon completion of synthetic route II.

The relatively low yield from the simple molecular sieve-aided coupling reaction between (**7**) and tribenzyl-D-arabinosyl chloride was attributed to the unusual preponderance of the N-7 over the N-9 hydrogen tautomer, perhaps stabilized by a hydrogen bond between the N-6 acetyl carbonyl and 7-H as depicted in structure (**7b**). As already mentioned, the magnitudes of the three-bond coupling values between C-4 and C-5 and 8-H indicated the unusual presence of a double bond between N-9 and C-8. A chemical shift of δ 12.1 for the 7-H resonance in the ^1H n.m.r. spectrum and of δ_C 180.2 p.p.m. for the N-6 acetyl carbonyl resonance in the ^{13}C n.m.r. spectrum of the acetate (**7**) are consistent with the proposed hydrogen-bond structure depicted in tautomeric structure (**7b**).



(**7a**) (**7b**)

Synthetic Route II—Methylation of Arabinosyl Nucleoside Precursor.—In order to confirm the stereochemistry about the anomeric centre and to facilitate formation of larger quantities of ara-D (**2**) for bioassay, a second, complementary, synthetic route was developed. In this second approach, the methyl group was introduced onto an intact nucleoside precursor with known anomeric stereochemistry. 2,6-Diamino-9-(β-D-arabinofuranosyl)purine (**9**)[23] (Scheme 1) was treated with $NaNO_2$ in aqueous HCl to afford 9-(β-D-arabinofuranosyl)isoguanine (**10**)[16] in 50% yield. Upon utilization of a modification of the selective methylating procedure (MeI, DMSO, K_2CO_3) we used to prepare doridosine (**3**) from isoguanosine,[7,10] a 40% yield of ara-D was obtained and the product was found to be identical with the sample prepared from the first synthesis.

The Cs^+ ion, fast-atom bombardment (FAB) spectrum of ara-D, with MH^+ = 298, and the u.v. spectrum were virtually identical with those of doridosine (**3**)[6,10] with absorptions at 250 nm (ε 9 300) and 294 nm (ε 11 500) at pH 5.3. The ^1H n.m.r. spectrum in $(CD_3)_2SO$ revealed signals at δ 3.35 (NCH_3), 7.80 (8-H), and 8.08 (6-NH_2), virtually identical with the analogous signals of doridosine (**3**),[10] and major signals at δ 5.98 (1′-H, $J_{1',2'}$ 4 Hz), 5.65 and 5.50 (2′-OH and 3′-OH), 5.10 (5′-OH), and 4.06 (5′-H_2) for the arabinosyl portion. Similarly, the ^{13}C n.m.r. signals for the purine portion of ara-D were similar to those of doridosine, at δ_C 29.9 (N–CH_3), 107.6 (C-5), 138.2 (C-8), 151.2

(C-6), 152.5 (C-4) and 154.1 p.p.m. (C-2), while the resonances in the sugar portion differed considerably.

Resistance to Adenosine Deaminase.—Samples of both ara-D and doridosine incubated with adenosine deaminase were resistant to deamination whereas under the same conditions a sample of adenosine was deaminated to the extent of 97%. The extent of reaction was based on analysis of the quantity of released ammonia.[24,25] The antiviral properties of ara-D (**2**) will be the subject of further investigation.

Experimental

M.p.s were determined using a Thomas Hoover Unimelt and a Melt-Temp apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded on either a Varian EM-390 or a Nicolet 200 spectrometer, except at 300 MHz when spectra were recorded on a Nicolet NP300 instrument (Stanford University Chemistry Dept. NMR Facility). ^{13}C N.m.r. spectra were recorded on a JEOL JNM-PFT-100 spectrometer at 25 MHz. Samples for n.m.r. measurements were dissolved in [$^2H_6$]DMSO unless otherwise stated. Mass spectra were obtained on a MM 70/70 HS spectrometer (V. G. Organic Ltd., Manchester, England). E.i. spectra (70 eV) were obtained by use of a standard direct-introduction probe, at a source temperature of 190 °C. Accurate mass measurements, obtained with a VG 2035 data system, were on full-scan spectra at 7 000 resolution. Constant daughter-ion scans for the first field-free region M.I. decompositions, obtained using a computerized B^2/E linked-scanning system,[15] yielded information on the genesis of particular ions. A fast atom (FAB) source using Cs^+ ion bombardment,[26] installed on the 70/70 HS, was used to obtain the spectra of compounds (**2**) and (**11**). For FAB, optimal spectra were obtained by dissolving the powdered sample directly in a glycerol–0.1M HCl matrix on the probe tip.[27] Glycerol is abbreviated as G in labelling fragment peaks of FAB spectra. I.r. spectra were obtained on a Perkin-Elmer 727B instrument. Optical rotations were measured in 1-dm cells on a Perkin-Elmer 241 Automatic polarimeter and u.v. spectra were determined on a Hewlett Packard 8451A Diode Array spectrophotometer. A Model 7924 Chromatotron (Harrison Research Inc., Palo Alto, CA) with either 1- or 2-mm silica gel circular plates was used for centrifugal circular preparative t.l.c. (c.c.p.l.c.). Analytical t.l.c. was conducted on 2.5 × 10 cm aluminium sheets precoated with silica gel 60 F-254 (E. Merck).

Adenosine Deaminase Assay.—The enzyme used was purified calf intestinal mucosa adenosine deaminase (Sigma Chemical Co., type III) with an activity of 260 units mg^{-1} protein (15 mg protein ml^{-1}). The enzyme solution (50 ml) was incubated with ara-D (**2**), doridosine (**3**) or adenosine (3 μM) and sodium phosphate buffer, pH 6.5 (500 μl). After 4 h incubation at 37 °C, the reaction was terminated and released ammonia was determined according to the procedure of Guisti.[25] The concentration of the blue indophenol was determined spectrophotometrically at 630 nm and compared with an ammonium sulphate standard. The assay indicated that whereas 97% of the adenosine had deaminated after 4 h, no deamination could be detected with either ara-D (**2**) or doridosine (**3**).

9-(β-D-*Arabinofuranosyl*)*isoguanine* (**10**).[28]—To a stirred solution of 2,6-diamino-9-(β-D-arabinofuranosyl)purine (**9**) (Burroughs–Welcome Co.) (1 g, 3.5 mmol) in water (44 ml) and acetic acid (4.6 ml) were added 1M-HCl (3.3 ml) and $NaNO_2$ (260 mg, 3.8 mmol). Further $NaNO_2$ (260 mg) was added after 1.5 h and 18 h from commencement of the reaction. After 24 h the gel was broken up, washed into a sintered glass Buchner funnel, and filtered. The residue was triturated with 1M-NaOH (20 ml) and washed with more base (5 ml). The filtrate was neutralized to pH 6 *via* addition of glacial acetic acid and was then allowed to cool for 2 h at 5 °C. The resulting white precipitate was filtered off, washed copiously with distilled water, and air-dried to yield the isoguanine (**10**) (492 mg, 50%) as a light yellow powder, m.p. 269—272 °C (decomp.); δ_H (90 MHz) 3.55—3.80 (3 H, br m, 2′-, 3′-, and 4′-H), 4.0—4.3 (2 H, br m, 5′-H_2), 6.00 (1 H, d, *J* 4 Hz, 1′-H), and 7.77 (1 H, s, 8-H); δ_C 60.9 (C-5′), 75.2 and 75.6 (C-2′ and C-3′), 83.3 (C-4′), 84.0 (C-1′), 108.5 (C-5), 138.7 (C-8), 152.0 (C-6), 154.0 (C-4), and 156.2 p.p.m. (C-2); *m/z* (Cs^+ positive-ion FAB) 284 [$(M + 1)^+$, 11%], 277 (G_3H^+, 1), 225 (GCs^+, 2), 207 (NaG_2^+, 3), 185 (G_2H^+, 32), 152 [(base + 1)$^+$, 9], 133 [(arabinose)$^+$, 4], 115 (133 − H_2O, 13), 93 (GH^+, 100), and 75 (93 − H_2O, 38); $\lambda_{max.}$(water, pH 1.5) 243 sh and 286 nm (ε 12 100); (pH 11.5) 254 (ε 7 200) and 287 nm (ε 9 800); $[\alpha]_D^{24}$ 29.5° (*c* 0.50 g/100 ml in water). These values closely matched unpublished values for 9-(β-arabinofuranosyl)isoguanine.[16,23,28]

9-(β-D-*Arabinofuranosyl*)-1(N)-*methylisoguanine* (**2**) *from* 9-(β-D-*Arabinofuranosyl*)*isoguanine* (**10**).—Methyl iodide (220 μl) was added to a stirred solution of 9-(β-D-arabinofuranosyl)-isoguanine (**10**) (500 mg, 1.8 mol), in anhydrous DMSO (20 ml) and, after 25 h K_2CO_3 (1.4 g) was added. After an additional 5 h the suspension was filtered and the DMSO was removed *via* lyophilization; the resulting powder was dissolved in 95% EtOH and the solution was cooled to 5 °C until precipitation occured. The precipitate was dissolved in distilled water cooled to 5 °C to aid precipitation of unchanged reagent (**10**). Four cycles of dissolution and precipitation from water led to the pure *N*-methylated product (**2**) which recrystallized as plates from water. A total of 94 mg of recovered (**11**) and 142 mg of crystalline (**2**) [35% based on consumed (**10**)] was obtained. Compound (**2**) had m.p. 223—225 °C (decomp.); δ_H (200 MHz) 3.34 (3 H, s, NCH_3), 3.63 (1 H, d, $J_{5a',5b'}$ 5 Hz, 5a′-H), 3.66 (1 H, d, $J_{5b',5a'}$ 5 Hz, 5b′-H), 3.74 (1 H, m, D_2O-exchangeable, 5′-CH_2OH), 5.49 (1 H, d, *J* 5 Hz, D_2O-exchangeable, 3′-OH), 5.65 (1 H, d, *J* 5 Hz, D_2O-exchangeable, 2′-OH), 5.98 (1 H, d, $J_{1',2'}$ 4.5 Hz, 1′-H), 7.79 (1 H, s, 8-H), and 8.08 (1 H, br s, D_2O-exchangeable, NH_2); δ_C 29.9 (q, ^1J 140 Hz, NCH_3), 61.0 (br t, ^1J 141 Hz, C-5′). 75.3 and 75.5 (2 × br d, $^1J \simeq 151$ Hz, C-3′ and C-2′), 82.9 (br d, ^1J 161 Hz, C-4′ or C-1′), 84.0 (br d, ^1J 148 Hz, C-1′ or C-4′), 107.6 (d, $^3J_{5,8-H}$ 13 Hz, C-5), 138.2 (dd, ^1J 216, $^3J_{8,1'-H}$ 5 Hz, C-8), 151.2 (br s, C-6), 152.5 (d, $^3J_{4,8-H}$ 5 Hz, C-4), and 154.1 p.p.m. (br s, C-2); *m/z* (FAB, Cs^+) and 298 [$(M^+ + 1)$, 15%]; $\lambda_{max.}$ (water; pH 1.5) 282 (ε 9 300) and 294 nm (ε 11 500); (pH 11.8) 263 (ε 11 000) and 281 nm (ε 12 400); $[\alpha]_D^{24}$ +25.5° (*c* 0.50 g/100 ml in water) (Found: C, 44.3; H, 5.1; N, 23.25. $C_{11}H_{15}N_5O_5$ requires: C, 44.45; H, 5.09; N, 23.56%).

1(N)-*Methylisoguanine* (**5**).—Phenyl chloroformate (60 g, 385 mmol) was quickly added to a vigorously stirred solution of 6-*N*-methyladenine (**4**)[11] (Sigma Chemical Co.) (12 g, 81 mmol) in 50% aqueous THF (1 l). The pH was maintained between 2.5 and 3.0 for the first 45 min *via* addition of saturated aqueous sodium hydroxide. The pH was then brought to *ca.* 4.5 and the solution was stirred for 18 h. The greenish precipitate that had formed in the two-phase reaction mixture was collected and washed copiously with both cold water and methanol. Reprecipitation from 1M-NH_4OH gave the title compound (**5**) (6.79 g, 48%) as a white powder, m.p. >300 °C; δ_H (200 MHz) 3.37 (3 H, s, NCH_3), 3.4 (br s, HOD + NH_2 + NH), and 7.91 (1 H, s, 8-H); δ_H (1-M-NaOD–D_2O)[21] 3.46 (3 H, s, NCH_3) and 7.70 (1 H, s, 8-H); δ_C[10] 30.1 (NCH_3), 108.5 (C-5), 138.7 (C-8), 151.2 (C-4), 153.2 (C-6), and 153.9 p.p.m. (C-2); $\lambda_{max.}$ (pH 12.5) 250 (ε 6 700) and 294 nm (ε 11 500); $\nu_{max.}$ (KBr) 1 710 and 1 690 cm^{-1} (C=O). [An *X*-ray diffraction study[29] of 1(*N*)-methylisoguanine in the solid state confirmed its structure as (**5**).] The organic

layer of the filtrate above was evaporated to give a white crystalline solid, recrystallization of which from methanol provided diphenyl carbonate (3 g). The m.p., ^{1}H n.m.r. spectrum, ^{13}C n.m.r. spectrum, and R_F value (SiO_2; 100% EtOH) of these crystals matched those of an authentic sample of diphenyl carbonate (Aldrich Chemical Co.). The formation of this side-product at least partially explains the necessity for a large excess of phenyl-chloroformate reagent.

6-N,9(N)-*Diacetyl*-1(N)-*methylisoguanine* (6-*Imino Tautomer*) (**6**).—A suspension of 1(*N*)-methylisoguanine (**5**) 4.93 g, 29.9 mmol) in acetic anhydride (40 ml) and THF (40 ml) was refluxed for 24 h. The prismatic crystals which had formed were broken up, filtered off, washed copiously with methylene dichloride, and dried (yield 904 mg). The crystal utilized in the *X*-ray diffraction study was obtained from this group. Further concentration of the crude reaction mixture led to several more crops of *compound* (**6**) (total: 3.45 g, 65%), m.p. 222—223 °C (decomp.); δ_H (200 MHz) 2.20 [3 H, s, C=N(CO)CH_3], 2.75 [3 H, s, N(CO)CH_3], 3.36 (3 H, s, NCH_3), 8.51 (1 H, s, 8-H), and 11.29 (1 H, br s, D_2O-exchangeable, 3-H); δ_C 23.4 [q, ^1J 129 Hz, 9(N)-C(O)*C*H$_3$], 24.6 [q, ^1J 131 Hz, C=N(CO)*C*H$_3$], 32.5 (q, ^1J 142 Hz, NCH_3), 117.4 (d, $^3J_{5,8-H}$ 13 Hz, C-5) 140.7 Hz (d, ^1J 222 Hz, C-8), 154.3 (C-4), 144.8 (C-6), 154.6 (C-2), 167.8 [q, ^2J 7 Hz, C=N(CO)CH_3], and 170.6 p.p.m. [br m, 9(N)-*C*(O)CH_3]; *m/z* M^+, 249.0855 ($C_{10}H_{11}N_5O_3$ requires *M*, 249.0862) (M^+, 8%), 234 ($M^+ - CH_3$, 13), 207.0762 ($M^+ - H_2C{=}C{=}O$, 50), 192.0529 (207 − CH_3, 100), 165.0663 (207 − $H_2C{=}C{=}O$, 50), 148 (24), 136 (18), 135 (13), 108 (165 − $CH_3N{=}C{=}O$, retro-Diels–Alder fragmentation, 12), and 43 ($CH_3C{\equiv}O^+$, 90); $\lambda_{max.}$ (95% EtOH) 253 (ε 5 600) and 324 nm (ε 10 400); $\nu_{max.}$ (KBr) 3 270 (amide-bonded N–H), and 1 720 and 1 690 cm^{-1} (carbonyl); R_F (95% EtOH; SiO_2) 0.48 (Found: C, 48.3; H, 4.6; N, 28.0. $C_{10}H_{11}N_5O_3$ requires C, 48.19; H, 4.46; N, 28.10%).

The ^{13}C-labelled diacetate (**6**) was prepared as above with a 1:1 mixture of acetic anhydride and $(CH_3{}^{13}CO)_2O$ (Merck and Co., 90%): *m/z* 251 (M^+ for $^{13}C_2$ isotopomer, 0.2%), 250 M^+ for ^{13}C, isotopomer, 0.5), 249 (M^+, 0.2), 236 ([$^{13}C_2 - M^+$] − CH_3, 0.4), 235 ([$^{13}C - M^+$] − CH_3, 0.8), 234 ($M^+ - CH_3$, 0.5), 208 (251 − $H_2C{=}^{13}C{=}O$, 40), 207 (250 − $H_2C{=}^{13}C{=}O$ and $M^+ - H_2C{=}C{=}O$, 44), 193 (208 − CH_3, 92), 192 (207 − CH_3, 100), 165 (208 − $H_2C{=}^{13}C{=}O$ and 207 − $H_2C{=}C{=}O$, 61), 149 (193-$HN{=}^{13}C{=}O$ and 192 − $HN{=}C{=}O$, 69), 148 (16), 136 (21), 135 (14), 108 (165 − $CH_3N{=}C{=}O$, retro-Diels–Alder fragmentation, 21), 44 ($CH_3{}^{13}C{\equiv}O^+$, 41), and 43 ($CH_3C{\equiv}O^+$, 57).

Crystal Data.—6-*N*,9(*N*)-Diacetyl-1(*N*)-methylisoguanine (**6**), $C_{10}H_{11}N_5O_3$, triclinic, space group $P\bar{1}$, a = 5.403(3), b = 10.292(6), c = 10.729(8) Å, α = 74.27(5)°, β = 75.11(5)°, γ = 84.45(5)°, V = 554.7(6) Å^3, Z = 2, D_c = 1.49 g cm^{-3}, D_m not determined, M = 249.3, F(000) = 260, μ(Cu-K_α) = 9.22 cm^{-1}.

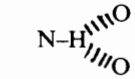
Intensity data were measured on a Nicolet R3 diffractometer with graphite monochromated Cu-K_α radiation (λ = 1.5418 Å) by the $\theta/2\theta$ scan technique with variable scan speed (4—30° min^{-1}) at room temperature. The unit-cell dimensions were determined by a least-squares fit to the setting angles of 20 independent reflections measured on the diffractometer. A total of 1 476 independent reflections were measured within the range $3° \leqslant 2\theta \leqslant 114°$, 1 229 of which were considered as observed by the criterion $|F_o| \leqslant 4\sigma|F_o|$. During data collection two check reflections, which were monitored periodically for crystal and instrument stability, showed only statistical fluctuations. Intensity data were corrected for background, Lorentz, and polarization effects, but not for absorption or extinction. The crystal structure was solved by using the direct-methods program SHELXTL.[30] Atomic co-ordinates, thermal parameters, and scale factors were refined by means of the 'cascade matrix' least-squares method with SHELXTL. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = [\sigma^2(F_o) + 0.008 F_o^2]^{-1}$. The scattering factors were taken from ref. 31; those of oxygen and nitrogen were corrected for anomalous dispersion. Positions of all hydrogen atoms were located on difference Fourier maps and included in the structure factor calculation. Least-squares refinement of the parameters of the 18 non-hydrogen atoms with anisotropic temperature factors converged at R = 0.111. Inclusion of the 11 hydrogen atoms with isotropic temperature factors with no restriction on their positional parameters in the structure refinement reduced the R-value to 0.081 and R_w = 0.082. The average parameter-shift in the final refinement cycle is 0.16σ; final difference Fourier synthesis excursions are within ±0.5e Å^{-3}. Lack of better agreement is believed to be due to the poor quality of the crystal. Crystals of the diacetate (**6**), crystallized from 50% Ac_2O–THF, appeared opaque and fractured; however, they seemed to be stable during data collection. Attempts to improve crystal quality by recrystallization from a variety of solvents were unsuccessful.

Table. Atom co-ordinates ($\times 10^4$)

Atom	*x*	*y*	*z*
N(1)	6 406(5)	3 030(2)	4 946(3)
C(2)	4 879(6)	2 452(3)	4 360(3)
N(3)	3 345(5)	1 420(2)	5 225(3)
C(4)	3 473(5)	983(3)	6 514(3)
C(5)	4 996(5)	1 522(3)	7 076(3)
C(6)	6 485(6)	2 656(3)	6 290(3)
N(7)	4 750(5)	843(3)	8 407(3)
C(8)	3 097(6)	−83(3)	8 652(3)
N(9)	2 220(5)	−62(2)	7 518(3)
N(10)	7 863(5)	3 359(3)	6 673(3)
C(11)	7 908(6)	3 178(3)	7 996(4)
C(12)	5 792(8)	3 879(4)	8 777(5)
C(13)	422(6)	−902(3)	7 379(4)
C(14)	−738(7)	−1 949(4)	8 573(4)
C(15)	7 989(7)	4 147(4)	4 033(4)
O(16)	4 890(4)	2 824(2)	3 200(2)
O(17)	9 662(5)	2 593(3)	8 450(3)
O(18)	−20(5)	−698(2)	6 294(2)
H(3)	2 316(68)	1 013(35)	4 956(33)
H(8)	2 475(56)	−732(28)	9 567(28)
H(12a)	5 675(72)	3 656(37)	9 648(34)
H(12b)	4 139(109)	3 733(56)	8 728(50)
H(12c)	5 862(72)	4 861(38)	8 365(35)
H(14a)	−1 389(78)	−1 767(41)	9 469(40)
H(14b)	550(109)	−2 604(53)	8 657(50)
H(14c)	−1 874(96)	−2 460(52)	8 243(45)
H(15a)	7 911(80)	4 396(44)	3 034(47)
H(15b)	9 573(106)	3 922(52)	3 855(46)
H(15c)	7 684(159)	5 190(89)	4 399(69)

A perspective view of 6-*N*,9(*N*)-diacetyl-1-(*N*)-methylisoguanine (**6**), shown in Figure 1, depicts the molecular conformation, atomic thermal motions, and the numbering scheme used in the *X*-ray investigation. The final atomic co-ordinates, and their estimated standard deviations are listed in the Table. Unlike 1-methylisoguanine (**5**)[29], the isoguanine moiety in the diacetate (**6**) is significantly non-planar. The six-membered ring is slightly puckered in such a manner that the substituent atoms C-12 and O-17 are appreciably out-of-plane and displaced by −1.416(7) and +0.919(6) Å, respectively; furthermore, there is a folding along the C-4–C-5 bond, the dihedral angle between the planes of the five- and six-membered rings being 2.0(1)°. The observed orientation of the acetyl group on the imidazole ring is noteworthy. It assumes a position with its carbonyl oxygen, O-18, directed approximately towards the hydrogen atom of the imino nitrogen, N-3, on the pyrimidine ring, thus forming a strong hydrogen bond between them

[N-3 • • • O-18 = 2.777(5) Å]. The condition here favours the formation of this intramolecular hydrogen bond since it also enhances the formation of a six-membered chelate ring (N-3, C-4, N-9, C-13, O-18, and 3-H). The observed values for the exocyclic angles at N-9 ⟨C-8–N-9–C-13 = 129.2(3)°, being slightly larger than ⟨C-4–N-9–C-13 = 125.2(3)°, may be a result of this intramolecular hydrogen-bond formation. The imino nitrogen group, N-3–H, is involved in a slightly asymmetric bifurcated hydrogen bond. In addition to being shared between N-3 and O-18 intramolecularly, 3-H is also attracted to an equal extent by the nearby O-18 atom of an adjacent molecule related by the centre of symmetry [N-3 • • • O-18′ = 2.976(6) Å], forming a bifurcated hydrogen bond



; the observed distances of 3-H • • • O-18, 3-H • • • O-18′, and O-18 • • • O-18′ are 2.21(9), 2.15(9), and 2.755(7) Å respectively. Besides these hydrogen bonds, all other intermolecular distances not involving hydrogen atoms exceed 3.10 Å. The bond lengths and angles in the purine ring are generally compatible with those found in 1-methylisoguanine and other related purine structures.[32,33] The eight endocyclic C–N bonds, varying from 1.298 to 1.412 Å, have an average bond length of 1.378(5) Å. The mean C–C bond length [1.478(6) Å] of the two acetyl groups are shorter than a normal single C–C bond length of 1.537(5) Å.[34] The three carbonyl bond lengths do not differ significantly from the mean of 1.205(5) Å. The atomic thermal vibrational parameters in the structure are within the normal range except for the slightly higher values for the methyl groups. A list of the anisotropic thermal parameters with their estimated standard deviations for the non-hydrogen atoms, and tables of bond lengths and angles, have been deposited as Supplementary Publication No. SUP 56226 (4 pp.).*

6-N-*Acetyl*-1(N)-*methylisoguanine* (**7**).—6-*N*,9(*N*)-Diacetyl-1(*N*)-methylisoguanine (**6**) (762 mg, 0.3 mmol) was dissolved in methanol (100 ml) and the solution was chilled at 5 °C for 18 h. 6-*N*-Acetyl-1(*N*)-methylisoguanine (**7**) (576 mg, 91%) was collected by filtration as a white crystalline solid and was washed with CH_2Cl_2, m.p. > 274 °C (decomp.); δ_H (200 MHz) 2.20 [3 H, s, NH(CO)CH_3], 3.32 (3 H, s, NCH_3), 7.87 (1 H, s, 8-H), and 12.13 (1 H, br s, D_2O-exchangeable, 9-H); δ_C 27.0 [q, ^1J 127 Hz, NH(CO)CH_3], 30.1 (q, ^1J 142 Hz, NCH_3), 105.6 (d, $^3J_{5,8-H}$ 7 Hz, C-5), 141.2 (d, ^1J 220 Hz, C-8), 147.0 (d, $^3J_{4,8-H}$ 12 Hz, C-4), 147.1 (m, C-6), 150.5 (m, C-2), and 180.3 p.p.m. [q, ^2J 6 Hz, NH(*C*O)CH$_3$]; *m/z* M^+, 207.0745 (52%) ($C_8H_9N_5O_2$ requires *M*, 207.0756), 192.0518 ($M^+ - CH_3$, 100), 165 (6), 149.0459 (192 − HN=C=O, 24), 136 (8), 108 (165 − CH_3N=C=O, retro-Diels–Alder fragmentation, 11), and 43 ($CH_3C{\equiv}O^+$, 30); a B^2/E M.I.-linked scan[15] established the ion of *m/z* 192 as the precursor ion to the ion of *m/z* 149; $\nu_{max.}$ (KBr) 1 690 cm^{-1} (amide); $\lambda_{max.}$ (95% EtOH) 321 (ε 12 000) and 255 nm (ε 6 600); R_F (95% EtOH; SiO_2) 0.43 (Found: C, 46.4; H, 4.4; N, 33.90. $C_8H_9N_5O_2$ requires C, 46.37; H, 4.38; N, 33.81%).

[1-^{13}C]acetyl-labelled (**7**) was prepared *via* methanolysis of the labelled diacetate (**6**), according to the procedure described above; *m/z* 208 (^{13}C-M^+, 40%) 207 (M^+, 47), 193 ([^{13}C-M^+] − CH_3, 85), 192 ($M^+ - CH_3$, 100), 165 ($M^+ - H_2C{=}C{=}O$, 58), 149 (193 − HN=^{13}C=O and 192 − HN=C=O, 61), 136 (27), 108 (165 − CH_3N=C=O, retro-Diels–Alder fragmentation, 21), 44 ($CH_3{}^{13}C{\equiv}O^+$, 61), and 43 ($CH_3C{\equiv}O^+$, 90).

6-N-*Acetyl*-1(N)-*methyl*-3(N)-(2′,3′,5′-*tri*-O-*benzyl*-D-*arabinofuranosyl*)*isoguanine* (6-*Imino Tautomer*) (**11**).—To a stirred suspension of 6-*N*-acetyl-1(*N*)-methylisoguanine (**7**) (100 mg, 0.48 mmol) and an equimolar quantity of anhydrous 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[16,17] in anhydrous CH_2Cl_2 (100 ml) was added $SnCl_4$ (35 μl) and the mixture was kept for 24 h. After addition of an excess of saturated aqueous sodium hydrogen carbonate the organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure to give a syrup which was chromatographed in portions by c.c.p.l.c. [SiO_2, 2 mm plate; EtOAc–95% EtOH–C_6H_6 (5:1:1)]. A chromatographically homogeneous [R_F 0.54 (EtOAC; SiO_2)] constituent was collected as a relatively unstable oil, spectroscopically consistent with structure (**11**); δ_H (200 MHz w/decoupling) 2.3 [3 H, s, 6-N(CO)CH_3], 3.32 (3 H, s, NCH_3), 3.52 (1 H, dd, $J_{5a',5b'}$ 12, $J_{5a',4'}$ 5 Hz, 5a′-H), 3.62 (1 H, dd, $J_{5b',5a'}$ 12, $J_{5b',4a'}$ 3 Hz, 5b′-H), 4.20 (1 H, dd, $J_{3',2'}$ 8, $J_{3',4'}$ 6 Hz, 3′-H), 4.40 (1 H, d, *J* 12 Hz, 5′-OC*H*HC$_6$H$_5$), 4.43 (1 H, d, *J* 12 Hz, 5′-OCH*H*C$_6$H$_5$), 4.51 (1 H, d, *J* 12 Hz, 3′-OC*H*HC$_6$H$_5$), 4.52 (1 H, *J* 12 Hz, 3′-OCH*H*C$_6$H$_5$), 4.59 (1 H, ddd, $J_{4',5a'}$ 5, $J_{4',5b}$ 3, $J_{4',3'}$ 6 Hz, 4′-H), 4.61 (1 H, d, *J* 12 Hz, 2′-OC*H*HC$_6$H$_5$), 4.71 (1 H, d, *J* 12 Hz, 2′-OCH*H*C$_6$H$_5$), 5.19 (1 H, dd, $J_{2',3'}$ 7, $J_{2',1'}$ 6 Hz, 2′-H), 6.29 (1 H, d, $J_{1',2'}$ 6 Hz, 1′-H), 7.14 (5 H, m, $OCH_2C_6H_5$), 7.31 (10 H, m, 2 × $OCH_2C_6H_5$), 7.89 (1 H, s, 8-H), and 12.33 (1 H, br s, 9-H); δ_C (purine portion) 28.1 [q, ^1J 128 Hz, 6-N(CO)*C*H$_3$], 31.0 (q, ^1J 143 Hz, NCH_3), 106.3 (d, $^3J_{5,8-H}$ 6 Hz, C-5), 139.1 (d, ^1J 212 Hz, C-8), 146.8 (dd, $^3J_{4,8-H}$ 13, $^3J_{4,1'-H}$ 3 Hz, C-4), 148.1 (br s, C-6), 149.7 (br s, C-2), and 183.4 p.p.m. [br m, 6-N(*C*O)CH$_3$]; *m/z* 609 (M^+, 3%), 594 ($M^+ - CH_3$, 0.2), 567 ($M^+ - H_2C{=}C{=}O$, 0.4), 518 ($M^+ - CH_2C_6H_5$, 3), 503 (518 − CH_3, 1), 380 (0.9), 356 (0.9), 298 (4), 297 (3), 236 (15), 207 (M^+ − arabinosyl moiety, 51), 192 (207 − CH_3, 20), 181 (45), 149 (192 − HN=C=O, 12), and 91 ($CH_2C_6H_5{}^+$, 100).

1(N)-*Methyl*-9-(2′,3′,5′-*tri*-O-*benzyl*-β-D-*arabinofuranosyl*)-*isoguanine* (**8**) *and* 9-(β-D-*Arabinofuranosyl*)-1(N)-*methylisoguanine* (**2**).—A solution of 6-*N*-acetyl-1(*N*)-methylisoguanine (**7**) (110 mg, 0.5 mmol) and anhydrous 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[16,17] was stirred under Ar with 4Å molecular sieves (100 mg) for 7 days. The crude reaction mixture was filtered through a Celite pad and the filtrate was evaporated to afford a syrup which was dissolved in saturated NH_3–MeOH solution and kept at room temperature for 3 h. The solvent was then evaporated off under reduced pressure and the residue was chromatographed by c.c.p.l.c. [silica gel; EtOAc–95% EtOH–C_6H_6 (8:1:1); 2 mm plate]. A chromatographically homogeneous constituent (R_F 0.38; SiO_2), *compound* (**8**), was isolated as an oil (42 mg, 15%); δ_H (300 MHz, w/decoupling) 3.34 (3 H, s, NCH_3), 3.69 (1 H, dd, $J_{5a',5b'}$ 11, $J_{5a',4'}$ 4 Hz, 5a′-H), 3.75 (1 H, dd, $J_{5b',5a'}$ 11, $J_{5b',4'}$ 6 Hz, 5b′-H), 4.12 (1 H, m, $J_{4',5a'}$ 4, $J_{4',5b'}$ 6, $J_{4',3'}$ 5 Hz, 4′-H), 4.33 (1 H, dd, $J_{3',4'}$ 5, $J_{3',2'}$ 5 Hz, 3′-H), 4.43 (1 H, dd, $J_{2',3'}$ 5, $J_{2',1'}$ 5 Hz, 2′-H), 4.45 and 4.29 (2 H, 2 d, *J* 12 Hz, $OCH_2C_6H_5$), 4.58 and 4.54 (2 H, 2 d, *J* 13 Hz, $OCH_2C_6H_5$), 4.71 and 4.63 (2 H, 2 d, *J* 12 Hz, $OCH_2C_6H_5$), 6.18 (1 H, d, $J_{1',2'}$ 5 Hz, 1′-H), 7.73 (1 H, s, 8-H), and 8.12 (2 H, br s, D_2O-exchangeable, NH_2); δ_C 29.9 (q, ^1J 141 Hz, NCH_3), 69.3 (m, C-5′), 71.1 (m, 5′-$OCH_2C_6H_5$), 71.6 (m, 3′-$OCH_2C_6H_5$), 72.2 (m, 2′-$OCH_2C_6H_5$), 79.5 (d, ^1J 150 Hz, C-2′), 80.6 (d, ^1J 164 Hz, C-3′), 81.2 (d, ^1J 164 Hz, C-4′), 81.4 (d, ^1J 164 Hz, C-1′), 107.4 (d, $^3J_{5,8-H}$ 12 Hz, C-5), 127.4, 127.6, 128.1, and 128.2 (d, $^1J \simeq 160$ Hz, 2′-, 3′, and 5′-$OCH_2C_6H_5$ non-quaternary aromatic carbons), 137.1, 137.8, and 138.1 (3 × brs, 2′-, 3′-, and 5′-OCH_2CH_5, quaternary aromatic carbons), 137.7 (dd, ^1J 215 Hz, $^3J_{8,1'-H}$ 5 Hz, C-8), 151.3 (d, $^3J_{4,8'-H}$ 4 Hz, C-4), 152.4 (C-6), and 154.1 p.p.m. (C-2); *m/z* M^+, 567.2471 (0.1%) ($C_{32}H_{33}N_5O_5$ requires *M*, 567.2478), 476.1929 ($M^+ - CH_2C_6H_5$, 3), 354.1581 (2), 284.1171 (1.5), 256.1200 (3), 249.1228 (2), 194.0683 (6), 181.1018 (3), 179.0812 (1.5), 175.0752 (1), 166.0710 (7), 165.0645 (M^+ −

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 1*, 1985, issue 1. Structure factor tables are available from the editorial office on request.

arabinosyl moiety, 16), 108.0542 (165 − $CH_3N{=}C{=}O$, retro-Diels–Alder fragmentation, 3), and 91.0549 ($CH_2C_6H_5^+$, 100); $\lambda_{max.}$(EtOH) 252 (ε 7 900) and 299 nm (ε 10 200).

Sodium was added in small portions to a stirred suspension of the tribenzyl ether (**8**) (40 mg, 70.5 μmol) in liquid NH_3 (5 ml) until the deep blue colour persisted. The colour was discharged by careful addition of NH_4Cl and the reaction mixture was then allowed to evaporate in a stream of N_2. The solid residue was triturated with benzene (10 ml) and dissolved in water, and the solution was cooled until formation of a precipitate of the free arabinofuranose (**2**) (11 mg, 53%) occurred. This material was reprecipitated from water to give pure compound (**2**) and was shown to be identical with a sample of compound (**2**), prepared *via* the alternate route (above), by m.p., m.s., ^1H n.m.r., ^{13}C n.m.r., u.v., and optical rotation.

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References

1 R. J. Whitely, S. Soong, R. Dolin, G. J. Galasso, L. T. Chien, and C. A. Alford, *N. Engl. J. Med.*, 1977, **297**, 289.
2 D. P. Gustafson, *J. Am. Vet. Med. Assoc.*, 1980, **176**, 1081.
3 D. P. Gustafson, J. H. Moser, and G. Scherba, 'Abstracts of the 1976 Annual Meeting of the American Society for Microbiology,' 1977, 257.
4 W. Plunkett and S. S. Cohen, *Ann. N. Y. Acad. Sci.*, 1977, **284**, 91.
5 T. W. North and S. S. Cohen, *Pharm. Ther.*, 1979, **4**, 81.
6 R. J. Nachman, Ph.D. Dissertation, Stanford University, 1981, p. 261.
7 Y. H. Kim, R. J. Nachman, L. Pavelka, H. S. Mosher, F. A. Fuhrman, and G. J. Fuhrman, *J. Nat. Prod.* (*Lloydia*), 1981, **44**, 206.
8 F. A. Fuhrman, G. J. Fuhrman, Y. H. Kim, L. A. Pavelka, and H. S. Mosher, *Science*, 1980, **207**, 193.
9 F. A. Fuhrman, G. J. Fuhrman, R. J. Nachman, and H. S. Mosher, *Science*, 1981, **212**, 557.
10 A. F. Cook, R. T. Bartlett, R. P. Gregson, and R. J. Quinn, *J. Org. Chem.*, 1980, **45**, 4020.
11 R. F. Pratt and K. K. Kraus, *Tetrahedron Lett.*, 1981, **22**, 2431.
12 M. Schumacher and H. Gunther, *J. Am. Chem. Soc.*, 1982, **104**, 4167.
13 M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Parzica, and L. B. Townsend, *J. Am. Chem. Soc.*, 1975, **97**, 4626.
14 M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Parzica, and L. B. Townsend, *J. Am. Chem. Soc.*, 1975, **97**, 4636.
15 W. F. Haddon, *Anal. Chem.*, 1979, **51**, 983.
16 G. B. Elion, J. L. Rideout, P. deMiranda, P. Collins, and D. J. Bauer, *Ann. N. Y. Acad. Sci.*, 1975, **255**, 468.
17 B.P. 1 338 905/1973.
18 F. Keller, I. J. Botvinick, and J. E. Bunker, *J. Org. Chem.*, 1967, **32**, 1644.
19 U. Niedballa and H. Vorbruggen, *J. Org. Chem.*, 1974, **39**, 3654.
20 E. J. Reist, V. J. Bartuska, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, 1965, **30**, 3401.
21 J. Donahue and K. N. Trueblood, *J. Mol. Biol.*, 1960, **2**, 363.
22 E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, 1964, **29**, 3725.
23 T. A. Krenitsky, G. W. Koszalka, J. V. Tuttle, J. L. Rideout, and G. B. Elion, *Carbohydr. Res.*, 1981, **97**, 139.
24 L. P. Davies, K. M. Taylor, R. P. Gregson, and R. J. Quinn, *Life Sci.*, 1980, **26**, 1079.
25 P. Guisti, in 'Methods of Enzymatic Analysis,' ed. H. U. Bergmeyer, Academic Press, New York, **1974**, p. 1092.
26 W. Aberth, K. M. Straub, and A. L. Burlingame, *Anal. Chem.*, 1982, **54**, 2029.
27 D. F. Hunt, J. Shabanowitz, F. K. Botz, and D. A. Brent, *Anal. Chem.*, 1977, **49**, 1160.
28 J. L. Rideout, personal communication and unpublished data.
29 R. Y. Wong and R. J. Nachman, *Acta Crystallogr.*, 1984, **C40**, 1409.
30 G. M. Sheldrick SHELXTL—an Integrated System for Solving, Refining and Displaying Crystal Structures from Diffractometer Data, University of Göttingen, Federal Republic of Germany, 1979.
31 'International Tables for X-ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. IV.
32 D. J. Sutor, *Acta Crystallogr.*, 1958, **B11**, 83.
33 D. J. Sutor, *Acta Crystallogr.*, 1958, **B11**, 453.
34 L. E. Sutton, 'Tables of Interatomic Distances and Configuration in Molecules and Ions,' Special Publication No. 18, The Chemical Society, London, 1965.

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