1-Substituted 2′-deoxyinosine analogues

Lorenzo De Napoli, Anna Messere, Daniela Montesarchio, Gennaro Piccialli* and Michela Varra

Dipartimento di Chimica Organica e Biologica, Università di Napoli 'Federico II', Via Mezzocannone 16, I-80134 Napoli, Italy

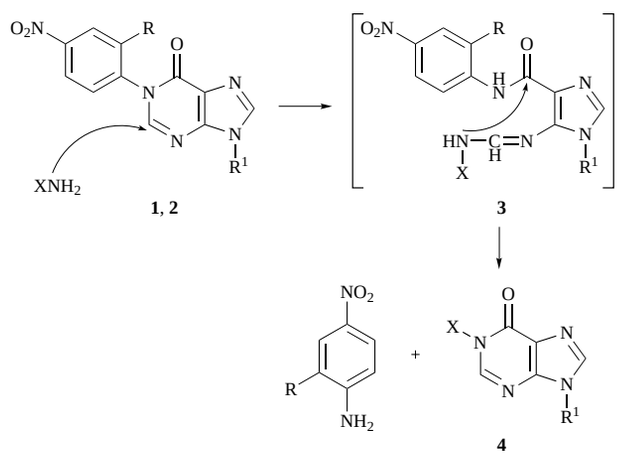
The base 2-carbon of 2′,3′-di-*O*-acetyl-2′-deoxyinosine is strongly activated towards nucleophilic attack when either the 4-nitrophenyl or 2,4-dinitrophenyl group is attached to its N-1 position (product 1 or 2). 1-(ω-Aminoalkyl)- and 1-(ω-hydroxyalkyl)-2′-deoxyinosine derivatives 5, 8–10 have been efficiently synthesized by a rearrangement of the purine ring upon treatment of compound 1 or 2 with the appropriate α,ω-diamine or α,ω-hydroxyamine. Moreover 1-amino-2′-deoxyinosine 11 and 1-hydroxy-2′-deoxyinosine 13 have been easily prepared in high yields by reaction of substrate 1 or 2, respectively, with hydrazine or hydroxylamine.

Introduction

It is well known that alkaline treatment of 1-substituted hypoxanthine nucleosides causes a ring-opening reaction at the 2-carbon to give 5-aminoimidazole-4-carboxamide riboside (AICAR)[1] or 2′-deoxyriboside (AICA-2′dR, **7**).[2] Our previous studies[3] showed that when a strongly electron-withdrawing group (such as 4-nitrophenyl) was attached to the 1-nitrogen atom of the hypoxanthine ring, the 2-carbon became electrophilic enough to react with aminic nucleophiles (XNH_2, Scheme 1) leading to a fast ring reclosure of the formamidine intermediate **3**, favoured by the loss of 4-nitroaniline as the leaving group, to give the inosine derivative **4**. Following this route 2′-deoxy-[1-^{15}N]inosine and some 1-alkyl derivatives of 2′-deoxyinosine[3,4] were efficiently synthesized by reaction of 3′,5′-di-*O*-acetyl-2′-deoxy-1-(4-nitrophenyl)-inosine **1** respectively with $^{15}NH_4OH$ and amines. We reasoned that this strategy could provide an easy and profitable two-step access to 1-(ω-hydroxyalkyl)purine nucleosides[5] and particularly to 1-(ω-aminoalkyl) derivatives, the preparation of which is otherwise not obvious. Among their possible applications in nucleoside chemistry, such substrates, incorporated into an oligonucleotide chain, can be used for a specific post-synthetic conjugation with labels (for example intercalators, photoreactive or cleaving agents). Several methods are available in the literature to derivatize pyrimidine nucleotides with such linker arms.[6] On the other hand, few syntheses concerning this kind of modification of purine nucleosides (*i.e.*, essentially alkylations of exocyclic amino functions) have been described;[6] this is probably due both to the limited nucleophilicity of the exocyclic amino groups of adenine and guanine and to the reduced stability of the N-glycosidic bond in N-alkylated purines. With the aim of introducing linker units easily and in high yields at the 1-position of purines, we herein explore the reactivity of 1-(4-nitrophenyl)- and 1-(2,4-dinitrophenyl)-2′-deoxyinosine derivatives **1**, **2** towards a number of binucleophilic amino compounds (**a**–**f**, Table 1).

The starting substrates **1** and **2** were obtained by treatment of 3′,5′-di-*O*-acetyl-2′-deoxyinosine (**4**; X = H) with 2.5 mol equiv. of 4-nitrofluorobenzene or 2,4-dinitrochlorobenzene, respectively, together with K_2CO_3 (2.5 mol equiv.) in dimethylformamide (DMF). Purification by silica gel chromatography afforded the desired compounds in 92 and 91% yield, respectively. Product **2** was obtained as a 1:1 mixture of atropisomers.[7] The reactions of compounds **1** and **2** with α,ω-diamines **a**, **b** and with α,ω-hydroxyamines **c**, **d** are summarized in Table 1. Particularly, treatment with 1,6-diaminohexane **b**, ethanolamine **c** or 5-aminopentan-1-ol **d** gave the expected corresponding 1-substituted compounds **8**–**10**, Scheme 2) in high yields. In the case of ethylenediamine **a**, different results were obtained depending on whether compounds **1** or **2** were used as the starting material. Compound **1**, with ethylenediamine, furnished a mixture of the target compound **5** (70%) and 5-amino-1-(2′-deoxy-β-D-ribofuranosyl)imidazole-4-[*N*-(4-nitrophenyl)]carboxamide **6**[3] (21%) as side product. The formation of compound **6** can be ascribed to the degradation of the formamidine group of intermediate **3** by aminolysis. On the other hand, treatment of compound **2** with ethylenediamine under the same conditions gave AICA-2′dR **7** in almost quantitative yield and with only traces of the cyclization product **5**. A similar result was observed even when compound **2** was treated with an equimolar amount of ethylenediamine in DMF solution giving a mixture of mono- and di-acetyl derivatives of compound **7**. Such behaviour for substrate **2** could be explained by hypothesizing in intermediate **3** ($X = CH_2CH_2NH_2$) a fast intramolecular nucleophilic attack of the primary amino function on the more reactive 1-carbon of the 2,4-dinitrophenyl ring. This hypothetical reaction mechanism, involving an 11-membered ring intermediate, seemed plausible also in the light of the different behaviour shown by 1,6-diaminohexane **b**, which with substrate **1**, as well as with dinitro derivative **2**, yielded only the cyclization product **8**.

It is to be noted that this is a more convenient synthesis of AICA-2′dR (overall yield 78% starting from 2′-deoxyinosine) with respect to that already reported in the literature.[2]

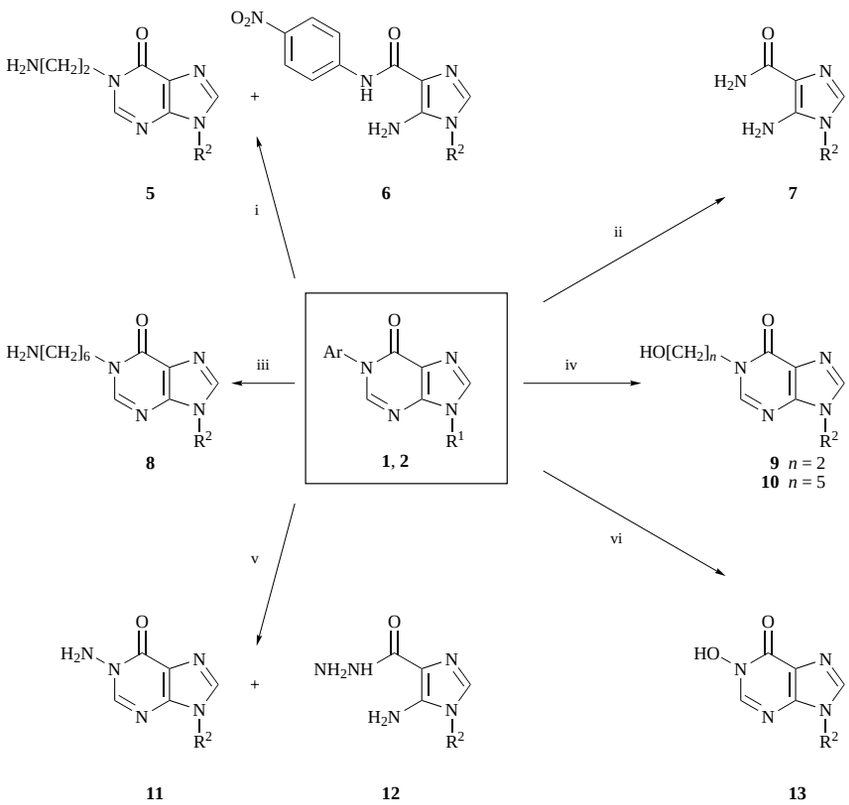


1 R = H
2 R = NO_2
R^1 = 3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl

Scheme 1

Table 1 Reactions of substrates **1** and **2** with nucleophiles **a**–**f**

Nucleophiles	Substrates	Products	Yield (%)	Reaction conditions
a $NH_2[CH_2]_2NH_2$	**1**	**5** and **6**	70 and 21	**a** neat, 4 h, 50 °C
	2	**7**	94	**a** neat, 2 h, 50 °C
b $NH_2[CH_2]_6NH_2$	**1**	**8**	92	**b** (10 mol equiv.), DMF, 4 h, 50 °C
	2	**8**	80	**b** (10 mol equiv.), DMF, 3 h, 50 °C
c $NH_2[CH_2]_2OH$	**1**	**9**	90	**c** neat, 4 h, 50 °C
	2	**9**	88	**c** neat, 2 h, room temp.
d $NH_2[CH_2]_5OH$	**1**	**10**	92	**d** neat, 4 h, 50 °C
	2	**10**	90	**d** neat, 4 h, 50 °C
e NH_2NH_2	**1**	**11** and **12**	75 and 23	**e** (50% aq.), 14 h, 50 °C
	2	**11** and **12**	75 and 23	**e** (50% aq.), 4 h, 50 °C
f NH_2OH	**1**	**6**	25	**f** (10 mol equiv.), DMF–EtOH, KOH (10 mol equiv.), 4 h, 80 °C
	2	**13**	75	**f** (10 mol equiv.), DMF–EtOH, KOH (10 mol equiv.), 4 h, 80 °C



1 Ar = 4-nitrophenyl
2 Ar = 2,4-dinitrophenyl
R^2 = 2-deoxy-β-D-ribofuranosyl
R^1 = 3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl

Scheme 2 *Reagents:* i, **a** on **1**; ii, **a** on **2**; iii, **b**; iv, **c** or **d**; v, **e**; vi, **f** on **2**

The reactivity of compounds **1** and **2** with hydrazine **e** and hydroxylamine **f** was investigated in the expectation of the formation of 1-amino and 1-hydroxy derivatives, respectively. With hydrazine (50% aq.), substrate **1** or **2** gave in both cases a mixture of 1-amino-2′-deoxyinosine **11** (75%) and the hydrazide derivative **12** (23%). For product **11** we excluded the other possible structure containing a seven-membered ring on the basis of literature data, which reported a higher stability for the 1-aminohypoxanthine ring,[8] and spectroscopic evidence. In the ^{1}H NMR spectrum ([$^2H_6$]DMSO) the presence of a singlet at δ 5.82 (2 H, exchangeable in D_2O) is diagnostic for the exocyclic 1-amino function. The formation of compound **12** as a by-product can be explained by hydrazinolysis[8] of amide **6** (or its 2,4-dinitrophenyl analogue) or of carboxamide **7**. Treatment of compound **2** with hydroxylamine hydrochloride **f** dissolved in EtOH–DMF in the presence of KOH produced a mixture of 2′-deoxy-1-hydroxyinosine **13** and its 3′,5′-di-*O*-acetyl and monoacetyl derivatives, which were then converted into compound **13** by deprotection with NH_4OH (75% overall yield). On the other hand, the same reaction, when performed on mononitrophenyl substrate **1**, led to a complex mixture in which the main product was identified as **6** (25 %).

It is noteworthy that this route to **11** and **13** is a valuable alternative to that already reported for 1-amino-[9] and 1-hydroxy-derivatives[10] of hypoxanthine nucleosides.

In all the above reactions leading to 1-substituted purine nucleosides, 4-nitroaniline (or 2,4-dinitroaniline) was isolated in an equimolar ratio with respect to the cyclization product, confirming the proposed purinic rearrangement pathway.

Experimental

General

TLC plates (Merck, silica gel 60, F254) were developed in one of several solvent systems: A [$CHCl_3$–MeOH (95:5, v/v)]; B [$CHCl_3$–MeOH (7:3, v/v)]; C [ethyl acetate–acetone–water

(5:10:1, v/v)]; D [butan-1-ol–acetic acid–water (60:15:25, v/v)]. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 0.063–0.200 mm). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 270 instrument (270 MHz); *J*-Values are given in Hz. Fast-atom bombardment (FAB) mass spectra (positive) were determined on a ZAB 2SE spectrometer. UV spectra were taken on a Perkin-Elmer lambda 7 spectrophotometer. Mps were determined on a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter at 25 °C and are quoted in units of 10^{-1} deg cm^2 g^{-1}.

3′,5′-Di-*O*-acetyl-2′-deoxy-1-(2,4-dinitrophenyl)inosine 2

A mixture of 3′,5′-di-*O*-acetyl-2′-deoxyinosine (336 mg, 1 mmol), 2,4-dinitrochlorobenzene (577 mg, 2.5 mmol) and K_2CO_3 (345 mg, 2.5 mmol) was suspended in stirred, anhydrous DMF (5 cm^3) at 80 °C for 2.5 h. After cooling, the mixture was filtered and the solid was washed with $CHCl_3$. The filtrates and washings, evaporated to dryness *in vacuo*, were purified on a silica gel column (3 × 50 cm) eluted with increasing amounts of MeOH in $CHCl_3$ (from 0 to 4%) to give *title compound* **2** as a diastereoisomeric mixture (456 mg, 91%); R_f 0.5 (system A); mp 192–194 °C (from MeOH) (Found: C, 47.95; H, 3.71; N, 16.70. $C_{20}H_{18}N_6O_{10}$ requires C, 47.81; H, 3.61; N, 16.73%); λ_{max}(CHCl$_3$)/nm 248 (ε/dm^3 mol^{-1} cm^{-1} 20 100); *m/z* (FAB) 503 (MH$^+$); $[\alpha]_D$ 2.8 (*c* 0.05, $CHCl_3$); δ_H($CDCl_3$) 9.06 (1 H, ss, 3-H phenyl), 8.68 (1 H, ds, 5-H nitrophenyl), 8.03, 8.04, 8.04 and 8.05 (2 H, ss, 2- and 8-H), 7.72 (1 H, ss, 6-H nitrophenyl), 6.40 (1 H, m, 1′-H), 5.42 (1 H, m, 3′-H), 4.40 (3 H, m, 4′-H and 5′-H_2), 3.07–2.63 (2 H, ms, 2′-H_2) and 2.16 and 2.11 (3 H each, ss, Ac); δ_C($CDCl_3$) 170.3 and 170.2 (CH_3CO), 155.0 (C-6), 148.1, 147.1, 146.2 and 135.5 (quaternary carbons of dinitrophenyl and C-4), 144.9 (C-2), 139.0 and 138.4 (C-8), 131.8, 128.8, 121.3 (CH dinitrophenyl), 124.2 and 124.3 (C-5), 85.1 and 84.6 (C-4′), 82.8 (C-1′), 74.2 (C-3′), 63.6 (C-5′) and 38.0 and 37.6 (C-2′).

Reaction of compound 1 with ethylenediamine: 1-(2-aminoethyl)-2′-deoxyinosine 5 and 6[3] 5-amino-*N*-(4-nitrophenyl)imidazole-4-carboxamide

Compound **1** (250 mg, 0.55 mmol) was treated with 3 cm^3 of ethylenediamine and the mixture was heated at 50 °C for 4 h and stirred. The resulting solution, dried *in vacuo*, was purified on silica gel plates (20 × 20 cm, 0.5 mm), developed in eluent system B. The bands at R_f 0.15 and 0.85, scratched from the plates and eluted with $CHCl_3$–MeOH (1:1, v/v) afforded compounds **5** (162 mg, 70%) and **6** (42 mg, 21%), respectively. *Compound* **5**: mp 113–116 °C (amorphous solid) (Found: C, 48.73; H, 5.90; N, 23.85. $C_{12}H_{17}N_5O_4$ requires C, 48.81; H, 5.80; N, 23.72%); λ_{max}(MeOH)/nm 246 (7600), 251 (7700) and 256sh (4300); *m/z* (FAB) 296 (MH$^+$); $[\alpha]_D$ −8.6 (*c* 0.06, water); δ_H-(CD_3OD) 8.32 and 8.30 (2 H, s, 2- and 8-H), 6.43 (1 H, dd, *J* 6.5 and 6.5, 1′-H), 4.58 (1 H, m, 3′-H), 4.17 (2 H, t, *J* 6.3, 1-CH_2), 4.04 (1 H, m, 4′-H), 3.77 (2 H, m, 5′-H_2), 3.01 (2 H, t, *J* 6.3, CH_2NH$_2$), 2.75 (1 H, m, 2′-H^a) and 2.44 (1 H, m, 2′-H^b); δ_C(D_2O) 158.2 (C-6), 149.7 (C-2), 148.2 (C-4), 141.1 (C-8), 122.3 (C-5), 88.3 (C-4′), 85.4 (C-1′), 71.9 (C-3′), 62.4 (C-5′), 50.2 (1-CH_2), 42.1 (C-2′) and 39.9 (CH_2NH_2).

Reaction of compound 2 with ethylenediamine

5-Amino-1-(2′-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide 7 (AICA-2′dR). Compound **2** (250 mg, 0.50 mmol) was treated with ethylene diamine (2 cm^3) and the mixture was heated at 50 °C for 4 h. The mixture was dried *in vacuo* and then chromatographed on a silica gel column (3 × 50 cm) eluted with increasing amounts of MeOH in $CHCl_3$ (from 10 to 30%) to give pure compound **7** (115 mg, 94%); R_f 0.45 (system B); mp 175–177 °C (MeOH–$CHCl_3$; lit.,[2a] 177–178 °C); λ_{max}-(water)/nm 267 (11 500); *m/z* (FAB) 243 (MH$^+$); ^{1}H NMR data in agreement with lit. values.[2a]

1-(6-Aminohexyl)-2′-deoxyinosine 8

Compound **1** (200 mg, 0.44 mmol) [or **2** (200 mg, 0.40 mmol)] was treated in DMF (3 cm^3) with 1,6-diaminohexane (510 mg, 4.4 mmol) and the mixture was heated at 50 °C for 4 h (3 h for compound **2**). The solution, dried *in vacuo*, was chromatographed on a silica gel column (3 × 50 cm) eluted with increasing amounts of MeOH in $CHCl_3$ (from 0 to 25%) to give pure *title compound* **8** (150 mg, 92%; or 80% starting from **2**); R_f 0.15 (system B); mp 112–118 °C (amorphous solid) (Found: C, 54.81; H, 7.26; N, 20.05. $C_{16}H_{25}N_5O_4$ requires C, 54.69; H, 7.17; N, 19.93%); λ_{max}(MeOH)/nm 251 (12 900) and 267 (11 400); *m/z* (FAB) 352 (MH$^+$); $[\alpha]_D$ −8.0 (*c* 0.04, MeOH); δ_H(CD_3OD) 8.31 (2 H, br s, 2- and 8-H), 6.42 (1 H, dd, *J* 7.2 and 7.2, 1′-H), 4.56 (1 H, m, 3′-H), 4.10 (2 H, t, *J* 7.6, 1-CH_2), 4.03 (1 H, m, 4′-H), 3.76 (2 H, m, 5′-H_2), 2.72 (1 H, m, 2′-H^a), 2.61 (2 H, t, *J* 6.7, CH_2NH$_2$), 2.47 (1 H, m, 2′-H^b) and 1.55–1.30 (8 H, complex signal, 4 × CH_2); δ_C(CD_3OD) 158.6 (C-6), 149.8 (C-2), 148.9 (C-4), 141.3 (C-8), 125.2 (C-5), 89.9 (C-4′), 86.7 (C-1′), 73.0 (C-3′), 63.6 (C-5′), (1-CH_2, submerged by the solvent signal), 42.7 and 42.1 (C-2′ and CH_2NH_2) and 34.0, 31.0, 27.8 and 27.7 (4 × CH_2).

2′-Deoxy-1-(2-hydroxyethyl)inosine 9

Compound **1** (200 mg, 0.44 mmol) [or **2** (200 mg, 0.40 mmol)] was treated with 2 cm^3 of ethanolamine and the mixture was heated at 50 °C for 4 h (2 h at room temp. for compound **2**). The solution, dried *in vacuo*, was purified on silica gel plates (20 × 20 cm, 0.5 mm), developed in eluent system B. The band at R_f 0.40, scratched from the plates and eluted with $CHCl_3$–MeOH (1:1, v/v), afforded pure *title compound* **9** (117 mg, 90%; or 88% starting from **2**), mp 172–175 °C (from MeOH) (Found: C, 48.70; H, 5.59; N, 19.06. $C_{12}H_{16}N_4O_5$ requires C, 48.65; H, 5.44; N, 18.91%); λ_{max}(water)/nm 247 (10 400) and 267sh (5300); *m/z* (FAB) 297 (MH$^+$); $[\alpha]_D$ −16.2 (*c* 0.07, water); δ_H(D_2O) 8.32 and 8.28 (1 H each, ss, 2- and 8-H), 6.44 (1 H, dd, *J* 6.5 and 6.5, 1′-H), 4.64 (1 H, m, 3′-H), 2.25 (2 H, t, *J* 5.1, 1-CH_2), 4.15 (1 H, m, 4′-H), 3.89 (2 H, t, *J* 5.1, CH_2OH), 3.80 (2 H, m, 5′-H_2), 2.82 (1 H, m, 2′-H^a) and 2.58 (1 H, m, 2′-H^b); δ_C-([$^2H_6$]DMSO) 156.0 (C-6), 149.0 (C-2), 147.3 (C-4), 139.0 (C-8), 123.8 (C-5), 88.0 (C-4′), 83.7 (C-1′), 70.8 (C-3′), 61.7 (C-5′), 58.5 (CH_2OH) and 48.0 (1-CH_2) (signal for C-2′ submerged by the solvent signal).

2′-Deoxy-1-(5-hydroxypentyl)inosine 10

Compound **1** (200 mg, 0.44 mmol) [or **2** (150 mg, 0.30 mmol)] was treated in DMF (3 cm^3) with 5-aminopentan-1-ol (903 mg, 8.8 mmol) and the mixture was heated at 50 °C for 4 h (2 h at room temp. for compound **2**). The solution, dried *in vacuo*, was purified on silica gel plates (20 × 20 cm, 0.5 mm), developed in eluent system B. The band at R_f 0.35, scratched from the plates and eluted with $CHCl_3$–MeOH (1:1, v/v), afforded pure *title compound* **10** (137 mg, 92%; or 88% starting from **2**) which could not be induced to crystallize (Found: C, 53.30; H, 6.60; N, 16.64. $C_{15}H_{22}N_4O_5$ requires C, 53.25; H, 6.55; N, 16.56%); λ_{max}-(MeOH)/nm 246 (10 800), 250 (11 000) and 268sh (6300); *m/z* (FAB) 339 (MH$^+$); $[\alpha]_D$ −11.3 (*c* 0.06, MeOH); δ_H(CD_3OD) 8.32 (2 H, br s, 2- and 8-H), 6.42 (1 H, dd, *J* 6.6 and 6.6, 1′-H), 4.54 (1 H, m, 3′-H), 4.11 (2 H, t, *J* 5.5, 1-CH_2), 4.02 (1 H, m, 4′-H), 3.77 (2 H, m, 5′-H_2), 3.55 (2 H, t, *J* 5.5, CH_2OH), 2.73 (1 H, m, 2′-H^a), 2.44 (1 H, m, 2′-H^b) and 1.89–1.38 (6 H, ms, 3 × CH_2); δ_C(CD_3OD) 159.2 (C-6), 150.4 (C-2), 149.8 (C-4), 141.9 (C-8), 126.3 (C-5), 90.5 (C-4′), 87.3 (C-1′), 73.6 (C-3′), 64.2 and 63.5 (C-5′ and CH_2OH), 48.6 (1-CH_2), 42.6 (C-2′) and 34.0, 31.4 and 24.8 (3 × CH_2).

Reaction of substrate 1 or 2 with hydrazine; products 11 and 12

Compound **1** (150 mg, 0.33 mmol) [or **2** (150 mg, 0.30 mmol)] was treated with 4 cm^3 of hydrazine (50%, w/w) and the mixture was heated at 50 °C for 14 h (4 h at room temp. for compound **2**). The mixture, dried *in vacuo*, was purified on silica gel plates

(20 × 20 cm, 0.5 mm), developed in eluent system B. The bands at R_f 0.33 and 0.45, scratched from the plates and eluted with $CHCl_3$–MeOH (1:1, v/v), afforded pure products **11** (66 mg, 75%) and **12** (19 mg, 23%), respectively.

1-*amino*-2′-*deoxyinosine* **11**, mp 189–191 °C (from MeOH) (Found: C, 45.09; H, 4.97; N, 26.35. $C_{10}H_{13}N_5O_4$ requires C, 44.94; H, 4.90; N, 26.21%); λ_{max}(MeOH)/nm 247 (8400) and 254sh (4800); *m/z* (FAB) 268 (MH^+); $[\alpha]_D$ −8.2 (*c* (0.03, MeOH); δ_H([$^2H_6$]DMSO) 8.38 and 8.31 (1 H each, ss, 2- and 8-H), 6.30 (1 H, dd, *J* 6.0 and 6.0, 1′-H), 5.82 (2 H, s, exchangeable in D_2O, 1-NH_2), 5.31 (1 H, d, exchangeable in D_2O, 3′-OH), 4.92 (1 H, t, exchangeable in D_2O, 5′-OH), 4.39 (1 H, m, 3′-H), 3.88 (1 H, m, 4′-H), 3.56 (2 H, m, 5′-H_2), 2.62 (1 H, m, 2′-H[a]) and 2.31 (1 H, m, 2′-H[b]); δ_C(CD_3OD) 158.8 (C-6), 150.2 (C-2), 148.6 (C-4), 141.5 (C-8), 125.2 (C-5), 89.9 (C-4′), 86.6 (C-1′), 72.9 (C-3′), 63.5 (C-5′) and 42.0 (C-2′).

5-*Amino*-1-(2′-*deoxy*-β-D-*ribofuranosyl*)*imidazole*-4-*carboxylic acid hydrazide* **12**, amorphous solid which could not be induced to crystallize (Found: C, 42.15; H, 5.98; N, 27.30. $C_9H_{15}N_5O_4$ requires C, 42.02; H, 5.88; N, 27.22%); λ_{max}(MeOH)/nm 268 (9500); *m/z* (FAB) 258 (MH^+); $[\alpha]_D$ −13.1 (*c* 0.065, MeOH); δ_H(CD_3OD) 7.34 (1 H, s, 2-H), 6.00 (1 H, dd, *J* 6.4 and 6.1, 1′-H), 4.50 (1 H, m, 3′-H), 3.95 (1 H, m, 4′-H), 3.74 (2 H, m, 5′-H_2), 2.62 (1 H, m, 2′-H[a]) and 2.26 (1 H, m, 2′-H[b]); δ_C(D_2O) 166.7 (CO), 143.8 (C-5), 131.0 (C-2), 130.4 (C-4), 87.6 (C-4′), 84.8 (C-1′), 71.5 (C-3′), 62.1 (C-5′) and 39.1 (C-2′).

Reaction of substrate 1 or 2 with hydroxylamine hydrochloride

2′-Deoxy-1-hydroxyinosine 13. To hydroxylamine hydrochloride (208 mg, 4.0 mmol), dissolved in EtOH (5 cm^3) at reflux, was added a solution of KOH (224 mg, 4 mmol) in EtOH (2 cm^3) and the mixture was kept at room temp. After 10 min a solution of compound **2** (200 mg, 0.4 mmol) in DMF (5 cm^3) was added and the mixture was heated at 80 °C for 4 h. The mixture was dried *in vacuo* and then was treated with conc. NH_4OH (5 cm^3) at room temperature. After 5 h the mixture was dried, and purified on a silica gel column (3 × 60 cm) eluted with increasing amounts of MeOH in $CHCl_3$. The fractions eluted with 40–50% of MeOH contained product **13** (R_f 0.25 system D) which was further purified by HPLC on a reversed-phase C-18 column eluted with MeOH–water (2:3, v/v). The appropriate fractions, dried *in vacuo*, afforded pure *compound* **13** (80 mg, 75%). The same reaction performed on substrate **1** furnished product **6** (36 mg, 25%), mp (MeOH) >170 °C (decomp.). For *compound* **13** (Found: C, 44.60; H, 4.70; N, 21.07. $C_{10}H_{12}N_4O_5$ requires C, 44.78; H, 4.51; N, 20.89%); λ_{max}(water)/nm 226 (8200), 252 (2000) and 289 (950); *m/z* FAB 269 (MH^+); $[\alpha]_D$ −113 (*c* 0.019, water); δ_H(D_2O) 8.49 and 8.30 (1 H each, ss, 2- and 8-H), 6.45 (1 H, dd, *J* 6.6 and 6.6, 1′-H), 4.69 (1 H, m, 3′-H), 4.20 (1 H, m, 4′-H), 3.83 (2 H, m, 5′-H_2), 2.86 (1 H, m, 2′-H[a]) and 2.61 (1 H, m, 2′-H[b]); δ_C(water) 160.4 (C-6), 145.8 (C-2), 144.9 (C-4), 141.8 (C-8), 123.8 (C-5), 88.0 (C-4′), 85.2 (C-1′), 71.9 (C-3′), 62.3 (C-5′) and 39.6 (C-2′).

Acknowledgements

We are grateful to CNF and MURST for grants in support of these investigations and to the 'Centro di Metodologie Chimico-Fisiche dell' Universita' di Napoli Federico II' for NMR facilities and to Istituto P.I.T.A.G.O.R.A., Napoli for the stimulating cultural support. A. M. thanks 'Istituto Superiore di Sanita' for a fellowship 'Borse di Studio AIDS-Italia.' We are also indebted to Miss Rita Carolla for competent technical assistance.

References

1 E. Shaw, *J. Am. Chem. Soc*., 1959, **81**, 6021; L. B. Townsend, *Nucleoside Analogues: Chemistry, Biology and Medical Applications*, ed. R. T. Walker, E. De Clercq and F. Eckstein, Plenum, New York, 1979, p. 209.

2 (*a*) N. Minakawa, Y. Sasabuchi, A. Kiyosue, N. Kojima and A. Matsuda, *Chem. Pharm. Bull*., 1996, **44**, 288; (*b*) S. Pochet and R. D'Ari, *Nucleic Acids Res*., 1990, **18**, 7127; (*c*) D. Betbeder and D. W. Hutchinson, *Nucleosides, Nucleotides*, 1990, **90**, 569.

3 L. De Napoli, A. Messere, D. Montesarchio and G. Piccialli, *J. Org. Chem*., 1995, **60**, 2251.

4 L. De Napoli, A. Messere, D. Montesarchio, G. Piccialli, C. Santacroce and M. Varra, *J. Chem. Soc*., *Perkin Trans. 1*, 1994, 923.

5 1-(ω-Hydroxyalkyl)hypoxanthine derivatives can be prepared from 1-(ω-hydroxyalkyl)adenine derivatives by a deamination process (*a*) T. Fujii, T. Saito and N. Terahara, *Chem. Pharm. Bull*., 1986, **34**, 1094; or by a 1-alkylation procedure for 9-substituted hypoxanthines (*b*) A. Montgomery and H. J. Thomas, *J. Org. Chem*., 1963, **28**, 2304).

6 J. L. Ruth, *Oligonucleotides and Analogues; a Practical Approach*, ed. F. Eckstein, IRL Press, Oxford, 1991, pp. 255–281.

7 Molecular mechanics calculations confirmed the presence of an energy barrier created by the interactions of the 2-nitro group with the 6-O and 2-H atoms of the purine ring, hindering the complete rotation of the 2,4-dinitrophenyl ring. The same results were obtained when the corresponding 2-nitrophenyl derivative was synthesized (data not shown).

8 P. Scheiner, S. Arwin, M. Eliacin and J. Tu, *J. Heterocycl. Chem*., 1985, **22**, 1435.

9 For example see: (*a*) A. D. Broom and R. K. Robins, *J. Org. Chem*., 1969, **34**, 1025; (*b*) G.-F. Huang, M. Maeda, T. Akamoto and Y. Kawazoe, *Tetrahedron*, 1975, **31**, 1363; (*c*) J. A. Montgomery and H. J. Thomas, *J. Med. Chem*., 1972, **15**, 1334.

10 For example see: (*a*) A. R. Katritzky and J. M. Lagowsky, *Chemistry of Heterocyclic* N-*Oxides*, Academic Press, London, 1971; (*b*) E. C. Taylor, C. C. Cheng and O. Vogl, *J. Org. Chem*., 1959, **24**, 2019; (*c*) H. Siegel, *Helv. Chim. Acta*, 1965, **48**, 433; (*d*) J. C. Parham, J. Fissekis and G. B. Brown, *J. Org. Chem*., 1966, **31**, 966; (*e*) Ref. 9*c*.

Paper 7/00987I
Received 11*th February* 1997
Accepted 27*th March* 1997