Synthesis of 9-Hydroxyalkyl-substituted Purines from the Corresponding 4-(*C*-Cyanoformimidoyl)imidazole-5-amines

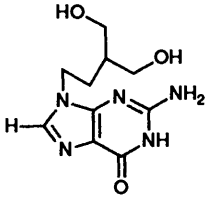
Brian L. Booth,[a] Alice M. Dias[b] and M. Fernanda Proença[*,b]
[a] *Department of Chemistry, University of Manchester Institute of Science and Technology, Manchester M60 1QD, UK*
[b] *I.N.I.C. Centre of Pure and Applied Chemistry, University of Minho, Braga, Portugal*

The amino alcohols $HO(CH_2)_nNH_2$ (n = 2, 3 and 5) react readily with ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **5** to give the amidines **6a–c**, which cyclize in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to give the corresponding 4-(cyanoformimidoyl)imidazole-5-amines **7a–c**, which can be isolated in the cases where n = 2 or 3.

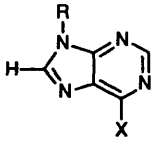
In the presence of aldehydes and ketones, the imidazoles **7a–d** lead to the 6-carbamoyl-1,2-dihydropurines **9a–f** which, in some cases, are oxidised to the corresponding 6-carbamoylpurines.

The reaction of the imidate **5** with 2-methoxyethylamine leads to the amidine **6d** and, on treatment with DBU, the reactive imidazole **7d** which can be used directly for further reaction.

Since the discovery of acyclovir great research effort has been devoted to the synthesis of new acyclic nucleoside analogues as potential anti-herpes (HSV) and anti-human cytomegalovirus (HCMV) agents.[1] Potent antiviral activities have been found for 'carbo-acyclic' nucleoside analogues such as **1**,[1,2] and purine derivatives with simple 9-hydroxyalkyl substituents, such as



1



2 X = NH_2·HCl; R = $CH(CHMeOH)(CH_2)_5CH_3$
3 X = OH; R = $CH(CHMeOH)(CH_2)_5CH_3$
4 X = OH; R = $(CH_2)_5OCONH(CO_2H)(CH_2)_3NHC(=NH)NH_2$

2 and **3**, have biological activity.[3,4] The hydroxyalkyl side chain is also useful for the introduction of further side chain functionality as, for example, with 6-chloro-9-(5-hydroxypentyl)-purine, which is an intermediate for the synthesis of the arginyl hypoxanthine derivative, PCF-39 **4**.[5] This, *in vitro*, activates human neutrophil chemiluminescence[6] and suppresses NK (natural killer) cell activity.[7]

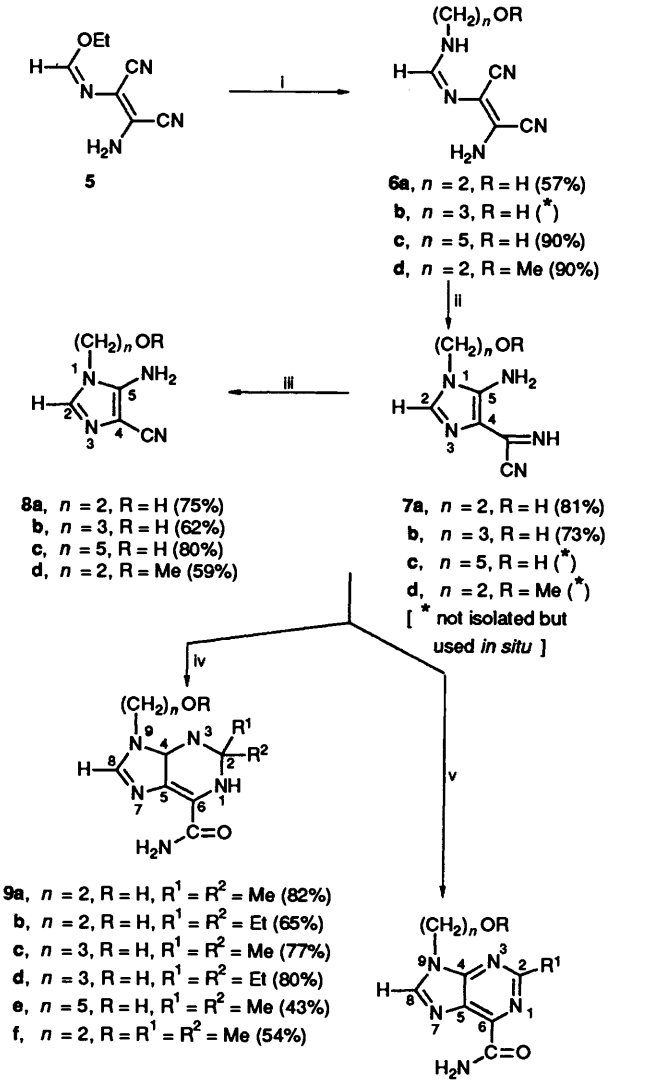
As part of a general study[8] of the synthesis of (*C*-cyanoformimidoyl)imidazole-5-amines we now report the preparation and reactions of new 1-(hydroxyalkyl)-4-(*C*-cyanoformimidoyl)-imidazole-5-amines and 1-(2-methoxyethyl)-4-(*C*-cyanoformimidoyl)imidazole-5-amine. These have been found to be useful intermediates for the synthesis of 9-(2-hydroxyalkyl)- and 9-(2-methoxyethyl)-1,2-dihydropurine and -purine derivatives.

Results and Discussion

The reaction of 2-aminoethanol, 2-methoxyethylamine and 5-aminopentanol with ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)-formimidate **5**, prepared according to a previously described procedure,[8] occurs readily at room temperature to give the corresponding amidines **6a–c** in up to 90% yield (Scheme 1). The IR spectra of the compounds prepared showed typical N–H and O–H stretching vibrations in the 3300–3400 cm^{-1} region and two characteristic strong (C≡N) absorptions around 2200 and 2220 cm^{-1}. The C–O stretching vibration is a medium intensity band in the 1056–1075 cm^{-1} region. In the ^1H NMR spectra, the proton directly attached to C-8 always showed up as a sharp singlet in the region 7.6–7.8 ppm. In the amidine **6a**, the $-NCH_2-$ protons resonate at lower field than do those of the $-OCH_2-$ group, which can be easily identified by the observed coupling to the hydroxy proton. In amidines **6b** and **6c** these two signals collapse to either a broad singlet or a distorted multiplet.

When 3-aminopropanol was used the reaction with formimidate **5** could not be stopped at the amidine stage, and was carried on through to the imidazole **7b** directly. The cyclization of these amidines to the imidazoles **7** occurs in the presence of base and both the choice of base and the solvent are critical if the pure product is to be isolated. The use of mild aqueous bases (Na_2CO_3, $NaHCO_3$) leads to a mixture of imidazoles **7** and **8**, as elimination of HCN from compound **7** is accelerated under these conditions. The use of $Ba(OH)_2$ in either methanol or ethanol, a method successfully used for the cyclization of similar amidines,[8] led in this case to a mixture of imidazoles **7** and **8** together with darkening of the solution due to decomposition. The use of $Ba(OH)_2$ in propan-2-ol, keeping the temperature around 0 °C, enabled imidazole **7a** to be isolated in yields of approximately 50% after 7 d. The best procedure for the cyclization of *N'*-hydroxyalkylamidines requires the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in ethyl acetate. Under these conditions the imidazoles **7a** and **b** were formed within 1–2 h at room temperature and isolated in 70–80% yield. The IR spectra of both these imidazole derivatives showed a complex set of peaks in the 3100–3400 cm^{-1} region, typical of the N–H and O–H stretching vibrations. A characteristic spectroscopic feature of these compounds is that the C≡N stretching vibration, is either absent or present as only a very weak band in the 2200 cm^{-1} region of the IR spectrum. Three intense bands at *ca.* 1630, 1658 and 1545 cm^{-1} are also typical of these compounds. In the ^1H NMR spectra the proton at C-8 is a sharp singlet in the region 7.1–7.3 ppm and the $-NCH_2-$ protons always resonate at lower field than do the $-OCH_2-$ protons.

The cyclization of *N'*-methoxyalkylamidine **6d**, isolated in 90% yield, is slow even with DBU in ethyl acetate. After 4 d at room temperature, all the amidine had been consumed, but attempts to isolate the imidazole **7d** led to a viscous oil which rapidly turned deep green and further evolved to the



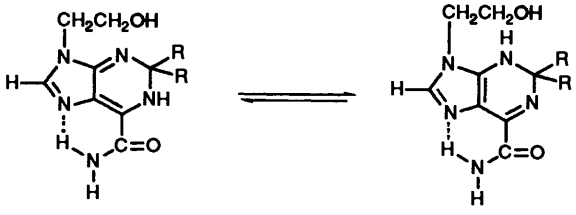
Scheme 1 *Reagents and conditions:* i, $NH_2(CH_2)_nOH$; EtOAc, room temp.; ii, DBU (2 drops), CH_3CN or EtOAc, room temp.; iii, 1 mol dm^{-3} KOH, room temp.; iv, excess R^1COR^2, room temp.; v, R^1COR^2, room temp.

corresponding 5-aminoimidazole-4-carbonitrile **8d**. Nevertheless, imidazole **7d** could be prepared *in situ* from the corresponding amidine either in ethyl acetate or acetonitrile in the presence of DBU, and the reaction was complete (by TLC) after 24 h at room temperature. Contamination with imidazole **8d** could never be avoided and the resulting solution was used directly for further reaction. Addition of acetone led to the 1,2-dihydropurine **9f** in 54% yield after 2 d at room temperature.

The formation of 1-hydroxyalkyl-5-aminoimidazole-4-carbonitriles **8a–d** can be accelerated in the presence of a stronger base (1 mol dm^{-3} aqueous KOH at room temperature or 0 °C) either from the corresponding 4-(*C*-cyanoformimidoyl)imidazol-5-amines **7a** and **b** or directly from the amidine structure **6c** and **d** in 60–80% yield. In contrast to the compounds of type **7** these compounds show a strong C≡N IR stretching vibration in the 2200 cm^{-1} region and two intense bands at *ca.* 1660 and 1587 cm^{-1}. The C–OH stretching vibration occurs at *v* 1062 cm^{-1} while two intense peaks at 1123 and 1014 cm^{-1} were assigned to the same vibration with the C–O–CH_3 substituent. In the ^1H NMR spectra the proton at C-8 is again a sharp signal in the region δ 7.1–7.3 and once again the $-NCH_2-$ protons resonate at lower field than do the $-OCH_2-$ protons, which in some cases couple with the OH proton.

Imidazoles **7a–c** were also allowed to react with carbonyl compounds. The use of acetone or pentan-3-one produces 9-substituted-6-carbamoyl-1,2-dihydropurines **9a–c** while in the presence of aldehydes (acetaldehyde and crotonaldehyde) or β-diketones (acetylacetone and trifluoroacetylacetone), oxidation of the intermediate dihydropurines occurs to give the corresponding 9-substituted-6-carbamoylpurines **10a–f**.

It is a general observation that the imidazoles **7a–c**, which possess a free hydroxy group, appear to react with aldehydes and ketones at a faster rate than imidazole **7d**. So, for example, reaction of the 1-(5′-hydroxypentyl)imidazole **7c** with acetone at room temperature is complete after only 4 h, while the 3′-hydroxypropyl- and 2′-hydroxyethyl-imidazoles **7a** and **b**, respectively, require 24 h for complete reaction under similar conditions. Reaction of the 2′-methoxyethyl derivative **7d** is particularly slow and complete reaction is achieved only after more than 2 d at room temperature. The reason for these rate differences is not yet apparent, but it demonstrates that in these reactions it is not only unnecessary to protect the hydroxy

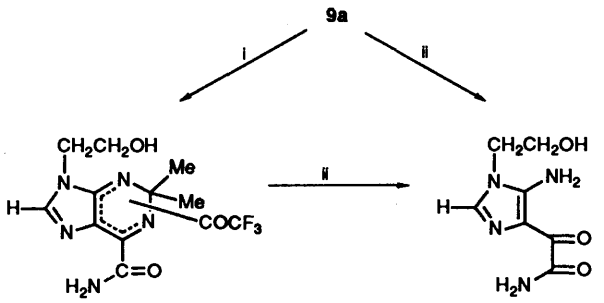


Scheme 2

group but it is undesirable and offers the possibility that this methodology could be used to synthesise new *N*-nucleosides without the need for extensive protection–deprotection strategies.

It is interesting that the signal for the proton on C-8 (δ 7.5 **9a** and 7.4 **9b**) appears as a broad signal with an integration <1. Similarly, the signal for the proton of the 9-NCH_2 group (δ 3.8) is also broadened and integrates for <2 H in contrast to the signal for the OCH_2 protons which are sharp and have the expected integration value. Raising the temperature to 75 °C after addition of water results in the appearance of the C-8 proton as a sharp singlet, while those for the 9-NCH_2 group appear as a well-defined triplet (J 5 Hz) having the anticipated integration value. The ^{13}C NMR spectra of compounds **9a–f** also show evidence of an exchange process. The signals for the C atoms of the substituents on the 9-N and C-2 positions are sharp, as are the signals for C-2 and the C=O of the carboxamido substituent. In contrast, the signals for C-4, C-5, C-6 and C-8 are broadened considerably and reduced in intensity. In some cases these signals are lost in the noise and cannot be observed. The spectroscopic evidence suggests that in solution these dihydropurine derivatives exist as an equilibrium mixture of the two tautomers shown in Scheme 2. Support for this comes from the synthesis of the trifluoroacetyl derivative **11** by reaction of **9a** with trifluoroacetic anhydride (Scheme 3). The acylation product is a single compound but the position of acylation (*i.e.* 1- or 3-) has not yet been established unambiguously. The ^1H NMR spectrum of this compound has sharp signals for all the protons and in the ^{13}C NMR spectrum the signals for C-4 (δ_C 156.3), C-5 (δ_C 120.0), C-6 (δ_C 149.1) and C-8 (δ_C 148.2 by DEPT 135) appear as sharp singlets.

Compound **11** decomposes readily in water to give green-



11 (76%) 12 (67%)

Scheme 3 *Reagents and conditions:* i, $(CF_3CO)_2O$, 0 °C→room temp.; ii, excess H_2O, room temp.

ish-yellow crystals shown by microanalysis and spectroscopic data to be 1-(2′-hydroxyethyl)-4-oxamoylimidazole-5-amine **12**. Hydrolytic decomposition to compounds of type **12** appears to be a general property of the dihydropurines. So, for example, when **9a** is stored at room temperature with water, compound **12** is obtained in 67% yield. The hydrolysis is accelerated by silica, and attempted purification of these and similar dihydropurines by flash chromatography on silica often leads to partial decomposition to compounds of type **12**.

Although the compounds described above have only simple, achiral hydroxyalkyl substituents it is clear that similar reactions could, in theory, be carried out using more complex, chiral amino alcohols leading to valuable 4-(*C*-cyanoformimidoyl)imidazole-5-amine and 5-aminoimidazole-4-carbonitrile intermediates.

The IR spectra of purines **10** show a strong carbonyl absorption in the 1683–1703 cm^{-1} region and an intense C–O stretching vibration at ν 1052–1066 cm^{-1}. In the NMR spectra, the proton at C-6 is a sharp singlet in the region δ 8.5–9.0, and the $-OCH_2-$ protons, at higher field than the $-NCH_2-$ protons, usually couple with the OH protons.

All the 6-carbamoyl-1,2-dihydropurines prepared showed typical N–H stretching vibrations in the 3100–3340 cm^{-1} region and strong carbonyl absorptions in the 1684–1700 cm^{-1} region. The C–O stretching vibration could always be identified as an intense band around 1080 cm^{-1}.

Experimental

^1H NMR spectra were recorded on Hitachi–Perkin-Elmer R-24B (60 MHz) or Bruker XL300 (300 MHz) instruments, ^{13}C NMR spectra either on a Bruker WP80 or XL300 instrument. All *J* values are given in Hz. IR spectra were recorded on a Shimadzu IR-435, mass spectra on a Kratos Concept instrument, and UV spectra on a Perkin-Elmer Lamda 15 UV–VIS spectrometer. M.p.s are uncorrected. Physical and spectroscopic data for compounds **6**–**12** are given in Tables 1–9.

Preparation of (Z)-N-(2-*Amino*-1,2-*dicyanovinyl*)-N′-(2′-*hydroxyethyl*)*formamidine* **6a**.—2-Aminoethanol (0.47 g, 7.7 mmol) was added to a solution of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (1.0 g, 6.4 mmol) in ethyl acetate (10 cm^3) and the mixture was stirred at room temperature. After 2 h an off-white solid precipitated out of the red solution, and, shortly after, it was indicated by TLC that all the imidate had been consumed. The product was filtered off and washed with chloroform to give *title compound* **6a** (0.65 g, 3.67 mmol; 57%) as an off-white solid.

Preparation of (Z)-N-(2-*Amino*-1,2-*dicyanovinyl*)-N′-(5′-*hydroxypentyl*)*formamidine* **6c**.—Ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (1.59 g, 9.7 mmol) was added to a solution of 5-aminopentan-1-ol (1.50 g, 14.6 mmol) in chloroform (20 cm^3), containing a catalytic amount (0.01 g) of anilinium hydrochloride and the mixture was stirred at room temperature. After 2 h, all the imidate had been consumed (evidence by TLC) and an off-white solid precipitated out of solution. The product was filtered off to give *title compound* **6c** (1.92 g, 8.7 mmol; 90%).

Preparation of (Z)-N-(2-*Amino*-1,2-*dicyanovinyl*)-N′-(2′-*methoxyethyl*)*formamidine* **6d**.—Ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (0.71 g, 4.3 mmol) was added to 2-methoxyethylamine (0.75 cm^3, 8.7 mmol) and a catalytic amount (0.01 g) of anilinium hydrochloride was added. The viscous mixture was scratched with a spatula, at room temperature for 15 min, until the reaction was complete. Chloroform (8 cm^3) was added to the resulting viscous suspension and the solid was filtered and washed with diethyl ether–chloroform (1:1) leading to an off-white solid identified as *title compound* **6d** (0.74 g, 3.9 mmol; 90%).

Preparation of 4-(*Cyanoformimidoyl*)-1-(2′-*hydroxyethyl*)-*imidazole*-5-*amine* **7a**.—Two drops of DBU were added to a suspension of **6a** (0.27 g, 1.5 mmol) in ethyl acetate (10 cm^3) and the mixture was stirred at room temperature. After 2 h all the amidine had been consumed, as evidenced by TLC. The off-white suspension was filtered and washed with a few drops of ethyl acetate followed by chloroform, to give *title compound* **7a** (0.22 g, 1.23 mmol; 81%) as an off-white solid.

Preparation of 4-(*Cyanoformimidoyl*)-1-(3′-*hydroxypropyl*)-*imidazole*-5-*amine* **7b**.—3-Aminopropan-1-ol (0.54 cm^3, 7.05 mmol) was added to a solution of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (1.0 g, 7.05 mmol) in ethyl acetate (10 cm^3) and the mixture was stirred at room temperature. After 2 h, the imidate was no longer present, as evidenced by TLC, and 2 drops of DBU were added to the reaction mixture. After 1 h, an off-white solid started to precipitate out of solution and within a few minutes all the amidine had been converted into the *title compound* **7b** which was filtered off and washed with ethyl acetate and chloroform (0.86 g, 4.5 mmol; 73%).

Preparation of 4-(*Cyanoformimidoyl*)-1-(2′-*methoxyethyl*)-*imidazole*-5-*amine* **7d**.—Two drops of DBU were added to a suspension of **6d** (0.15 g, 0.77 mmol) in ethyl acetate (10 cm^3) and the mixture was stirred at room temperature for 4 d, when all the amidine had been consumed. The imidazole **8d** was already present in solution, as evidenced by TLC. Compound **7d** could not be isolated and the solution was used directly for further reaction.

Preparation of 5-*Amino*-1-(*hydroxyalkyl*)*imidazole*-4-*carbonitriles* **8**.—A mixture of **7** and aqueous 1 mol dm^{-3} KOH (1 equiv.) was stirred either at room temperature or in an ice bath for 20–45 min. The resulting suspension was filtered off and washed with a few drops of iced water and diethyl ether to give *title compound* **8** (**8a**, 75%; **8b**, 62%).

In the preparation of **8c** (80%) and **8d** (59%), compound **6** was used as starting material, instead of **7**.

Reaction of 4-(*Cyanoformimidoyl*)-1-(2′-*hydroxyethyl*)*imidazole*-5-*amine with Ketones*.—(*a*) *Acetone*. A suspension of the imidazole (0.39 g, 2.2 mmol) in acetone (5 cm^3) was stirred at room temperature overnight. The orange solid was filtered, washed with diethyl ether and dried to give 6-carbamoyl-2,2-dimethyl-9-(2′-hydroxyethyl)-1,2-dihydropurine **9a** (0.43 g, 1.8 mmol; 82%). An analytical sample was obtained after flash chromatography (silica 60; dry acetone eluent) which gave orange crystals.

(*b*) *Pentan*-3-*one*. A suspension of the imidazole (1.0 g, 5.6

Table 1 Physical data for compounds **6–12**

Compound	M.p. (T/°C)	Molecular Formula	Found (%) C	H	N	Requires (%) C	H	N	Found: m/z	Requires: M
6a	>100 (decomp.)	$C_7H_9N_5O$	46.6	5.1	38.8	46.9	5.0	39.1	180 $(M + 1)^+$, 153 (base)	179
6c	>113 (decomp.)	$C_{10}H_{15}N_5O$	54.3	7.1	32.0	54.3	6.8	31.7	222 $(M + 1)^+$, 195 (base)	221
6d	>141 (decomp.)	$C_8H_{11}N_5O$	50.0	5.3	36.1	49.7	5.0	36.3	194 $(M + 1)^+$	193
7a	137.6–141.0 (decomp.)	$C_7H_9N_5O$	46.8	4.7	38.8	46.9	5.0	39.1	180 $(M + 1^+$, 153 (base)	179
7b	>143 (decomp.)	$C_8H_{11}N_5O$	49.8	5.3	36.0	49.7	5.0	36.3	$(M + 1)^+$,[a] 167 (base)	193
8a	192–195 (decomp.)	$C_6H_8N_4O$	47.1	5.2	36.8	47.4	5.3	36.8	153 $(M + 1)^+$	152
8b	132.9–134.7	$C_7H_{10}N_4O$	50.5	5.9	33.9	50.6	6.0	33.7	167 $(M + 1)^+$	166
8c	136.8–137.0	$C_9H_{14}N_4O$	55.7	7.2	28.8	55.7	7.2	28.9	195 $(M + 1)^+$	194
8d	124.1–125.8	$C_7H_{10}N_4O$	50.3	5.8	33.7	50.6	6.0	33.7	167 $(M + 1)^+$	166
9a	168.4–169.4 (decomp.)	$C_{10}H_{15}N_5O_2$	50.9	6.7	29.8	50.6	6.4	29.5	238 $(M + 1)^+$, 204 (base)	237
9b	>141 (decomp.)	$C_{12}H_{19}N_5O_2$	54.0	7.4	26.5	54.3	7.2	26.2	266 $(M + 1)^+$	265
9c	150.4–151.9 (decomp.)	$C_{11}H_{17}N_5O_2$	52.8	6.8	28.2	52.6	6.8	27.9	252 $(M + 1)^+$, 236 (base)	251
9d	138.8–141.1 (decomp.)	$C_{13}H_{21}N_5O_2$	55.6	7.6	24.8	55.9	7.5	25.1	280 $(M + 1)^+$	279
9e	>149 (decomp.)	$C_{13}H_{21}N_5O_2$	HRMS[b] 279.1696			HRMS[b] 279.1695			280 $(M + 1)^+$, 264 (base)	279
9f	139.3–139.7 (decomp.)	$C_{11}H_{17}N_5O_2$	52.3	6.9	27.7	52.6	6.8	27.9	252 $(M + 1)^+$, 233 (base)	251
10a	218–223	$C_9H_{11}N_5O_2$	48.6	4.9	31.6	48.9	5.0	31.7		221
10b	219.2–220.4	$C_9H_8F_3N_5O_2$	39.1	2.8	25.6	39.3	2.9	25.9	276 $(M + 1)^+$	275
10c	235–238	$C_{11}H_{13}N_5O_2$	53.8	5.4	28.6	53.5	5.3	28.3	248 $(M + 1)^+$	247
10d	>241 (decomp.)	$C_{14}H_{13}N_5O_2$	59.0	4.4	24.7	59.4	4.6	24.7		283
10e	189.9–191.0	$C_{10}H_{13}N_5O_2$	HRMS[b] 235.1079			HRMS[b] 235.1069			236 $(M + 1)^+$	235
10f	185.4–186.6	$C_{10}H_{10}F_3N_5O_2$	41.2	3.4 F, 19.5	23.9	41.5	3.5 F, 19.7	24.2	290 $(M + 1)^+$	289
11	146–152 (decomp.)	$C_{12}H_{14}F_3N_5O_3H_2O$	41.2	4.6 F, 16.1	19.9	41.0	4.6 F, 16.1	19.9	334 $(M + 1)^+$, 238 (base)	333
12	211–214 (decomp.)	$C_7H_{10}N_4O_3$	42.6	5.2	28.6	42.4	5.1	28.3	199 $(M + 1)^+$, 128 (base)	198

[a] $(M + 1)^+$ is absent in the spectrum. [b] High-resolution mass spectrum.

Table 2 UV Spectroscopic data for compounds **6–12**

Compound	λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1})	Compound	λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1})
6a	330 (18 165)	**9c**	431 (3 190)
	228 (10 950)		219 (11 420)
6c	331 (24 720)	**9f**	429 (3 507)
	230 (9 569)		219 (12 417)
6d	330 (24 748)	**10a**	252 (10 080)
	228 (11 751)		205 (19 060)
7b	348 (7 669)	**10b**	282 (7 278)
	227 (10 335)		211 (22 387)
8a	244 (14 416)	**10c**	316 (7 990)
			242 (31 821)
			206 (17 890)
8b	245 (12 627)	**10d**	316 (7 980)
			251 (25 256)
			206 (30 751)
8c	245 (13 932)	**10e**	291 (7 527)
			205 (22 490)
8d	245 (12 295)	**10f**	282 (7 287)
			210 (22 378)
9a	430 (3 236)	**11**	407 (4 723)
	220 (11 576)		251 (3 618)
			220 (11 281)
9b	443 (3 147)	**12**	344 (7 399)
	219 (11 676)		220 (11 619)

mmol) in freshly distilled pentan-3-one (12 cm^3) was stirred at room temperature. After 3 d, an orange solid started to precipitate, and the reaction was complete 7 d later. Addition of the chloroform and partial removal of the solvent on the rotary evaporator led to an orange solid, which was washed with chloroform and diethyl ether, and identified as 6-carbamoyl-2,2-diethyl-9-(2′-hydroxyethyl)-1,2-dihydropurine **9b** (0.97 g, 3.7 mmol; 65%). An analytical sample was obtained after flash chromatography (silica 60; dry acetone eluent) which gave bright orange crystals.

(*c*) *Acetylacetone.* A suspension of the imidazole (0.4 g, 2.2 mmol) in acetylacetone (2 cm^3) was stirred at room temperature. After 4 d, no imidazole was present in solution (as evidenced by TLC) and a white solid had been formed. Ethanol (5 cm^3) was added to the mixture and the solid was filtered and washed with a few drops of ethanol and diethyl ether. White crystals were obtained, which were identified as 6-carbamoyl-9-(2′-hydroxyethyl)-2-methylpurine **10a** (0.33 g, 1.4 mmol; 63%). An analytical sample was obtained from hot ethanol, which gave white needle crystals.

(*d*) *Trifluoroacetylacetone.* Trifluoroacetylacetone (0.1 cm^3, 0.13 g, 0.84 mmol) was added dropwise to a suspension of imidazole (0.1 g, 0.6 mmol) in acetonitrile (5 cm^3), kept in an ice bath, with efficient stirring. After the addition was complete, the temperature was allowed to rise to room temperature and the orange mixture was stirred for 2 h, when all the imidazole had been consumed. Attempts to isolate the dihydropurine by concentrating the solvent in the rotary evaporator and adding chloroform were unsuccessful as the purine was already present, as evidenced by TLC. The mixture was then stirred at room temperature for 1 d, leading to a white suspension which was filtered. The solid was recrystallized from hot ethanol to give white needles identified as 6-carbamoyl-9-(2′-hydroxyethyl)-2-trifluoromethylpurine **10b** (0.14 g, 0.5 mmol; 85%).

Reaction of 4-(*Cyanoformimidoyl*)-1-(2′-*hydroxyethyl*)*imidazole-5-amine with Aldehydes.*—(*a*) *Acetaldehyde.* Acetaldehyde (large excess) was added to a solution of the imidazole (0.10 g, 0.56 mmol) in dry acetonitrile (50 cm^3), kept in an ice bath. After 15 min at room temperature only dihydropurine and purine were present in solution (evidenced by TLC). The reaction was complete after 1 week. Dry flash chromatography (silica 60; acetone eluent) led to a white solid identified as 6-carbamoyl-9-(2′-hydroxyethyl)-2-methylpurine **10a** (0.014 g, 0.063 mmol; 12%).

(*b*) *Crotonaldehyde.* Crotonaldehyde (0.31 g, 4.48 mmol) was added to a suspension of the imidazole (0.40 g, 2.24 mmol) in absolute ethanol (10 cm^3) and the mixture was stirred at room temperature for 30 min, when all the starting material had been

Table 3 IR and ^{1}H NMR spectroscopic data for compounds **6–8**

Compound	ν_{max}[a](Nujol)/cm^{-1}	δ_H[b][$^2H_6$]-DMSO
6a	2210s, 2203s, 1647s, 1633s, 1600s, 1552s, 1056m	3.4 (2 H, q, *J* 6, NCH_2), 3.5 (2 H, t, *J* 6, OCH_2), 4.7 (1 H, br s, OH), 6.1 (2 H, br s, NH_2), 7.6 (1 H, d, *J* 4, 2-H) and 7.7 (1 H, br d, *J* 4, NH)
6c	2222s, 2199s, 1636s, 1614s, 1594s, 1545s, 1075s	1.3–1.6 (6 H, complex m, $CH_2(CH_2)_3CH_2$), 3.3 [2 H, dt, *J* (CH_2NH) 6 and *J* (CH_2CH_2) 7, NCH_2], 3.4 (2 H, m, OCH_2), 4.4 (1 H, t, *J* 5, OH), 6.1 (2 H, br s, NH_2), 7.7 (1 H, d, *J* 4, 2-H) and 7.8 (1 H, br d, *J* 4, NH)
6d	2224s, 2200s, 1634s, 1609s, 1595s, 1531s, 1114s, 1075m	3.4 (3 H, s, OMe), 3.5–3.6 (4 H, complex m, NCH_2CH_2O), 6.2 (2 H, br s, NH_2), 7.7 (1 H, d, *J* 4, 2-H) and 7.9 (1 H, d, *J* 4, NH)
7a	2221w, 1634s, 1584s, 1545s, 1508s, 1065s	3.7 (2 H, t, *J* 5, OCH_2), 3.9 (2 H, t, *J* 5, NCH_2), 6.7 (? H, br s, NH_2), 7.3 (1 H, s, 2-H) and 10.9 (1 H, s, NH)
7b	2202m, 1659m, 1625s, 1585s, 1546s, 1515m, 1056s	1.9 (2 H, quint, *J* 6, $CH_2CH_2CH_2$), 3.5 (2 H, t, *J* 6, OCH_2), 3.9 (2 H, t, *J* 7, NCH_2), 4.8 (1 H, br s, OH), 6.8 (2 H, br s, NH_2) and 7.3 (1 H, s, 2-H)
8a	2193s, 1664s, 1633w, 1588s, 1530m, 1062s	3.7 (2 H, dt, *J* 5, OCH_2), 3.9 (2 H, t, *J* 5, NCH_2), 5.1 (1 H, t, *J* 5, OH), 6.2 (2 H, s, NH_2) and 7.2 (1 H, s, 2-H)
8b	2205vs, 1660s, 1588s, 1559w, 1069m	1.9 (2 H, quint, *J* 6, $CH_2CH_2CH_2$), 3.6 (2 H, m, OCH_2), 4.0 (2 H, t, *J* 6, NCH_2), 4.9 (1 H, t, OH), 6.4 (< 2 H, s, NH_2) and 7.3 (1 H, s, 2-H)
8c	2208m, 1662m, 1592m, 1532m, 1074m	1.2 (2 H, quint, *J* 7, $CH_2CH_2CH_2$), 1.4 (2 H, quint, *J* 7, OCH_2CH_2), 1.6 (2 H, quint, *J* 7, NCH_2CH_2), 3.3 (2 H, m, OCH_2), 3.7 (2 H, t, *J* 7, NCH_2), 4.3 (1 H, t, *J* 4, OH), 6.2 (2 H, s, NH_2) and 7.1 (1 H, s, 2-H)
8d	2203s, 1659s, 1586s, 1531s, 1123s, 1014s	3.3 (3 H, s, OMe), 3.6 (2 H, t, *J* 5, OCH_2), 4.0 (2 H, t, *J* 5, NCH_2), 6.2 (< 2 H, br s, NH_2) and 7.7 (1 H, s, 2-H)

[a] All spectra show strong bands in the range 3470–3100 for O–H and N–H stretching vibrations. [b] *J* Values are given in Hz.

Table 4 IR and ^{1}H NMR spectroscopic data for compounds **9**

Compound	ν_{max}[a](Nujol)/cm^{-1}	δ_H[c][$^2H_6$]-DMSO
9a	1648s, 1618s, 1542s, 1529s, 1520m, 1507m, 1080s	1.5 (6 H, s, 2-Me_2), 3.7 (2 H, t, *J* 5, OCH_2), 3.8 (1–2 H, br s, NCH_2), 5.2 (< 1 H, br s, OH), 6.3 (1 H, br s, 1-H), 7.5 (1 H, s, 8-H), 7.95 (< 1 H, br s, CONH) and 8.3 (1 H, s, CONH)
9b	1697s, 1664s, 1625s, 1604s, 1553m, 1526s, 1084s	0.9 (6 H, t, *J* 7, CH_2Me), 1.6 and 1.75 (each 1 H, dq, *J* 7 and 14, CH_2Me), 3.7 (2 H, t, *J* 5, OCH_2), 3.8 (< 2 H, br s, NCH_2), 5.1–6.25 (1 H, vbr, s, OH), 7.4 (< 1 H, br s, 8-H), 7.95 (1 H, br s, CONH) and 8.3 (1 H, s, CONH)
9c	1684m, 1654s, 1625m, 1593, 1527s, 1082s	1.4 (6 H, s, 2-Me_2), 1.9 (2 H, quint, *J* 5, CH_2), 3.5 (2 H, t, *J* 5, OCH_2), 3.8 (< 2 H, br s, NCH_2), 7.5 (< 1 H, br s, 8-H), 7.9 (< 1 H, br s, CONH) and 8.3 (< 1 H, br s, CONH)
9d	1688m, 1660s, 1626m, 1602s, 1530s, 1084m	1.1 (6 H, t, *J* 5, CH_2Me), 1.8 and 1.9 (each 1 H, dq, *J* 7 and 14, CH_2Me), 2.0 (2 H, quint, *J* 5, CH_2), 3.6 (2 H, t, *J* 5, OCH_2), 3.9 (2 H, br s, NCH_2), 7.6 (vbr s, 8-H), 8.1 (vbr s, CONH), 8.4 (< 1 H, br s, CONH) and 8.9 (< 1 H, br s, NH)
9e	1686s, 1653s, 1624s, 1588m, 1576m, 1523s, 1041s	1.5 (2 H, br s, $CH_2CH_2H_2$), 1.6 (8 H, br s, 2-Me_2, OCH_2CH_2), 1.9 (2 H, br s, NCH_2CH_2), 3.9 (2 H, br s, NCH_2), 4.6 (1 H, br s, OH), 6.6 (vbr s, NH), 7.7 (vbr s, 8-H), 8.0 (< 1 H, br s, CONH) and 8.5 (< 1 H, br s, CONH)
9f	1689s, 1658s, 1633m, 1593m, 1521m, 1111m, 1006m	1.4 (6 H, s, 2-Me_2), 3.8 (3 H, s, OCH_3), 3.5 (< 2 H, br s, OCH_2), 3.7 (< 2 H, br s, NCH_2), 7.5 (< 1 H, br s, 8-H), 8.0 (vbr s, CONH) and 8.2 (vbr s, CONH)[b]

[a] All spectra show strong bands in the range 3470–3100 for O–H and N–H stretching vibrations. [b] [$^2H_6$]-Acetone was used as solvent. [c] *J* Values are given in Hz.

Table 5 IR and ^{1}H NMR spectroscopic data for compounds **10–12**

Compound	ν_{max}[a](Nujol)/cm^{-1}	δ_H[b][$^2H_6$]-DMSO
10a	1819w, 1688s, 1649w, 1639w, 1594m, 1580s, 1504m, 1066s	2.7 (3 H, s, 2-Me), 3.95 (4 H, s, OCH_2CH_2N) and 8.5 (1 H, s, 8-H)
10b	1800w, 1703s, 1591m, 1580w, 1559w, 1541w, 1503m, 1216m, 1187s, 1140s, 1067m	3.85 (2 H, br s, OCH_2), 4.4 (2 H, t, NCH_2), 5.0 (1 H, br s, OH), 8.3 (2 H, br s, NH_2) and 8.8 (1 H, s, 8-H)
10c	1685s, 1656m, 1630m, 1594m, 1576s, 1503s, 1067s	2.1 (3 H, dd, *J* 7 and 2, Me), 3.9 (2 H, dt, *J* 5, OCH_2), 4.4 (2 H, t, *J* 5, NCH_2), 5.2 (1 H, t, *J* 5, OH), 6.7 (1 H, dq, *J* 16 and 2, $=CH_A$), 7.3 (1 H, dq, *J* 7 and 15.5, $=CH_B$), 8.2 (1 H, s, CONH), 8.5 (1 H, s, CONH) and 8.7 (1 H, s, 8-H)
10d	1684s, 1625w, 1604w, 1586m, 1568m, 1540w, 1503w, 1066m	3.9 (2 H, t, *J* 4, OCH_2), 4.5 (2 H, t, *J* 5, NCH_2), 5.0 (1 H, br s, OH), 8.0 (1 H, br s, NH), 8.6 (1 H, br s, NH) and 8.8 (1 H, s, 8-H)
10e	1695s, 1656w, 1625m, 1594s, 1588s, 1501m, 1088m	2.0 (2 H, m, CH_2), 2.7 (3 H, s, 2-Me), 3.4 (2 H, t, OCH_2), 4.3 (2 H, t, NCH_2), 4.4 (1 H, br s, OH), 7.8 (1 H, br s, CONH), 8.2 (1 H, br s, CONH) and 8.4 (1 H, s, 8-H)
10f	1668s, 1594s, 1512m, 1226s, 1192s, 1144s, 1072m	2.0 (2 H, quint, *J* 7, CH_2), 3.4 (2 H, dt, *J* 5 and 6.5, OCH_2), 4.4 (2 H, t, *J* 7, NCH_2), 4.6 (1 H, t, *J* 5, OH), 8.3 (1 H, br s, NH), 8.4 (1 H, br s, NH) and 9.0 (1 H, s, 8-H)
11	1710s, 1678s, 1659s, 1583m, 1523m, 1510m, 1213s, 1186s 1120s, 1069s	2.7 (6 H, s, 2-Me_2), 3.7 (2 H, t, *J* 5, OCH_2), 4.1 (2 H, t, *J* 5, NCH_2), 7.9 (1 H, s, 8-H), 8.5 (1 H, s, CONH) and 8.9 (1 H, s, CONH)
12	1687m, 1656s, 1547s, 1511s, 1067s	3.7 (2 H, dt, *J* 5, OCH_2), 4.0 (2 H, t, *J* 5, NCH_2), 5.2 (1 H, t, *J* 5, OH), 7.2 (2 H, s, NH_2), 7.3 (1 H, s, 2-H), 7.7 (1 H, s, CONH) and 8.4 (1 H, s, CONH)

[a] All spectra show strong bands in the range 3470–3100 for O–H and N–H stretching vibrations. [b] *J* Values are given in Hz.

Table 6 ^{13}C Chemicals shifts (δ_C[$^2H_6$]-DMSO) for amidines **6**

Compound	C-2	C-4	C-5	C≡N	OCH_2	NCH_2	$(CH_2)_x$	OCH_3
6a	154.9	119.2	110.6	120.3 120.8	63.2	47.2		
6c	154.8	119.1	111.0	120.3 120.6	64.7	44.4	27.1 32.2 36.1	
6d	154.7	119.2	110.3	120.3 121.0	62.0	44.2		74.0

Table 7 ^{13}C Chemicals shifts (δ_C[$^2H_6$]-DMSO) for imidazoles **7**, **8** and **12**

Compound	C-2	C-4	C-5	C≡N	C=NH	OCH_2	NCH_2	$(CH_2)_x$	OCH_3
7a	137.0	117.7	147.1	120.3	148.6	49.5	63.4		
7b	136.4	117.7	147.2	120.3	148.4	43.7	61.4	35.7	
8a	138.5	95.4	152.9	122.8		51.0	64.5		
8b	136.7	94.2	151.6	121.6		44.0	61.2	35.9	
8c	136.5	94.0	151.4	121.5		46.8	64.4	26.3 32.7 35.8	
8d	137.2	94.2	151.6	121.5		46.9	73.7		62.1
12[a]	137.6	122.3	153.7			49.5	63.2		

[a] Additional signals are 170.6 ($CONH_2$) and 183.5 (C=O).

Table 8 ^{13}C Chemicals shifts (δ_C[$^2H_6$]-DMSO) for dihydropurines **9** and **11**

Compound	C-2	C-4	C-5	C-6	C-8	C=O	OCH_2	NCH_2	$(CH_2)_x$	R^1,R^2
9a	76.0	130–165[a]	121.0 (br)	130–165[a]	130–165[a]	167.7 (br)	49.4	63.8		32.5 (Me)
9b	63.8	160.5	120.2 (br)	151.5 (vbr)	137 (vbr)	167.6 (br)	49.2	63.2		12.0 (Me) 36.3 (br) (C_2Me)
9c	76.0	130–165[a]	121.1 (br)	130–165[a]	130–165[a]	167.6 (br)	43.5	61.4	36.0	32.4 (Me)
9d	82.0	—[b]	120.0 (br)	—[b]	—[b]	167.5	43.5	61.3	35.9	11.9 (Me) 36.4 (br) (C_2Me)
9e	75.9	?	121.0 (br)	153.1	136.7 (br)	167.8	46.3	66.4	26.4 32.5 35.8	32.3 (Me)
11[c]	75.2	156.3	120.0	149.1	148.2	163.2	50.9	62.8		30.4 (Me)

[a] Very broad band likely to include broad signals for C-8, C-6 and C-4. [b] Not visible in the spectrum. [c] Additional signals for **11** are 121.2 (CF_3, *J* 289) and 162.8 (*C* CF_3, *J* 32).

Table 9 Chemical shifts (δ_C[$^2H_6$]-DMSO) for purines **10**

Compound	C-2	C-4	C-5	C-6	C-8	C=O	OCH_2	NCH_2	CH_2	R^1
10b	151.6 (*J* 36.6)	157.9	136.2	152.0	155.4	167.35	50.7	62.8		124.0 (CF_3) (*J* 275)
10d	157.0	154.7	130.0	147.4	149.2	164.8	46.3	59.1		128.2 (*o*-C?) 128.7 (*m*-C?) 130.5 (*p*-C) 137.3 (C'?)
10e	164.6	157.9	132.9	151.1	151.7	168.5	44.8	61.7	35.95	29.6 (2-Me)
10f	151.6 (*J* 36)	157.7	136.2	151.9	155.2	167.3	45.6	61.7	35.6	124.0 (CF_3) (*J* 275)

converted into the orange dihydropurine. The solvent was removed in the rotary evaporator to give a brown oil, from which no solid could be isolated. The oil was dissolved in ethanol and stirred at room temperature for another 2 d leading to an off-white suspension. After addition of diethyl ether and cooling in an ice bath, the solid was filtered and washed with diethyl ether. A brownish solid was isolated and identified as 6-carbamoyl-9-(2′-hydroxyethyl)-2-[(*E*)-prop-1-enyl]purine **10c** (0.21 g, 0.85 mmol; 38%). An analytical sample was obtained by recrystallization from hot ethanol leading to off-white shiny crystals (38% yield).

(*c*) *Benzaldehyde.* Benzaldehyde (0.20 g, 1.9 mmol) was added to a suspension of the imidazole (0.30 g, 1.7 mmol) in acetonitrile (5 cm^3) and the mixture was stirred for 5 weeks at room temperature. The homogeneous yellow solution containing imidazole, dihydropurine and purine (as evidenced by TLC), slowly turned pale yellow and a white solid precipitated out of solution. Partial removal of acetonitrile by rotary evaporation, addition of absolute ethanol (5 cm^3) and standing for a further week at room temperature led to 6-carbamoyl-9-(2′-hydroxyethyl)-2-phenylpurine **10d** (0.18 g, 6.4 mmol; 38%) as an off-white solid. An analytical sample was obtained after flash chromatography (silica 60; acetonitrile eluent) to give white needle crystals.

Reaction of 4-(*Cyanoformimidoyl*)-1-(3′-*hydroxypropyl*)*imidazole-5-amine with Ketones.*—(*a*) *Acetone.* A solution of imidazole (0.23 g, 1.2 mmol) in acetone (20 cm^3) was stirred at room temperature for 24 h. The acetone was partially removed by rotary evaporation and the orange crystals were isolated, washed with chloroform, and identified as 6-carbamoyl-2,2-dimethyl-9-(3′-hydroxypropyl)-1,2-dihydropurine **9c** (0.23 g, 0.92 mmol; 77%). An analytical sample was obtained after flash chromatography (silica 60; acetone as eluent) to give orange needle crystals.

(*b*) *Pentan-3-one.* A mixture of the imidazole (0.25 g, 1.3 mmol) and pentan-3-one (2 cm^3) was stirred for 3 d at room temperature. The crystals were filtered and identified as 6-carbamoyl-2,2-diethyl-9-(3′-hydroxypropyl)-1,2-dihydropurine **9d** (0.29 g, 1.1 mmol; 80%). An analytical sample was obtained after flash chromatography (silica 60; dry acetone eluent) to give red crystals.

(*c*) *Acetylacetone.* Acetylacetone (0.12 cm^3, 0.12 g, 1.2 mmol) was added to a suspension of the imidazole (0.11 g, 0.6 mmol) in dry acetonitrile (5 cm^3) and the mixture was stirred at room temperature. After 8 d, all the imidazole had been converted into dihydropurine, which in turn had partially evolved to the purine (as evidenced by TLC). After 20 d, the purine was the only product present, and the suspension was filtered and washed with chloroform to give an off-white solid identified as 6-carbamoyl-9-(3′-hydroxypropyl)-2-methylpurine **10e** (0.10 g, 0.4 mmol; 70%). The product was treated with charcoal and recrystallized from hot ethanol to give white crystals.

(*d*) *Trifluoroacetylacetone.* Trifluoroacetylacetone (0.26 g, 1.67 mmol) was added to a stirred suspension of the imidazole (0.29 g, 1.48 mmol) in dry acetonitrile (8 cm^3), kept at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 2 d when all the orange dihydropurine had been converted into the colourless purine. The resulting suspension was filtered and the solid washed with a few drops of acetone and chloroform. The grey solid isolated (0.24 g) was purified by flash chromatography (silica 60; acetonitrile eluent), leading to white crystals identified as 6-carbamoyl-9-(3′-hydroxypropyl)-2-trifluoromethylpurine **10f** (0.18 g, 0.6 mmol; 43%).

Reaction of 4-(*Cyanoformimidoyl*)-1-(3′-*hydroxypropyl*)*imidazole-5-amine with Acetaldehyde.*—(*a*). Acetaldehyde (large excess) was added to a suspension of the imidazole (0.12 g, 0.6 mmol) in dry acetonitrile (10 cm^3) kept in an ice bath, with efficient stirring. After 15 min at room temperature a mixture of dihydropurine and a small amount of purine were present in solution (as evidenced by TLC). Only purine was present after 5 d and the solution was flash chromatographed (silica 60; chloroform, ethyl acetate and acetonitrile eluents). Partial removal of the solvent from the ethyl acetate fraction led to a white solid identified as 6-carbamoyl-9-(3′-hydroxypropyl)-2-methylpurine (0.015 g, 0.06 mmol; 10%) **10e** by comparison of its IR spectrum with that of an authentic sample.

(*b*). (3-Aminopropan-1-ol (0.15 cm^3, 1.98 mmol) was added to a solution of imidazole (0.22 g, 1.3 mmol) in acetonitrile (5 cm^3) and the reaction mixture was stirred at room temperature for 2 h. The excess of 3-aminopropan-1-ol was removed by flash chromatography (silica 60; acetonitrile eluent) and the resulting solution containing 4-(cyanoformimidoyl)-1-(3′-hydroxypropyl)imidazole-5-amine was concentrated in the rotary evaporator and treated with DBU (2 drops). Acetonitrile (large excess) was added to the previous solution, which was stirred at room temperature for 2 d, when the imidazole was no longer present by TLC. The solvent was removed by rotary evaporation leading to an oil which was solubilized in absolute ethanol and stirred at room temperature for 4 d. Dry flash chromatography (silica 60; acetone eluent) led to a white solid identified as 6-carbamoyl-9-(3′-hydroxypropyl)-2-methylpurine **10e** (0.12 g, 0.5 mmol; 50%) by comparison of its IR spectrum with that of an authentic sample.

Reaction of 4-(*Cyanoformimidoyl*)-1-(2′-*methoxyethyl*)*imidazole-5-amine with Acetone.*—4-(Cyanoformimidoyl)-1-(2′-methoxyethyl)imidazole-5-amine was prepared from formamidine **6d** (0.15 g, 0.77 mmol) and DBU (2 drops) in ethyl acetate (10 cm^3) and used *in situ* for further reaction. Acetone (5 cm^3) was added to the above solution, and the reaction was complete after 2 d at room temperature with magnetic stirring. Removal of the solvent on the rotary evaporator led to orange crystals which were filtered and washed with chloroform and diethyl ether. The product was identified as 6-carbamoyl-2,2-dimethyl-9-(2′-methoxyethyl)-1,2-dihydropurine **9f** (0.10 g, 0.40 mmol; 54%).

Reaction of 4-(*Cyanoformimidoyl*)-1-(5′-*hydroxypentyl*)*imidazole-5-amine with Acetone.*—4-(Cyanoformimidoyl)-1-(5′-hydroxypentyl)imidazole-5-amine was prepared from the corresponding formamidine **6c** (0.13 g, 0.59 mmol) and DBU (2 drops) in acetonitrile (5.0 cm^3). This compound was isolated as an oil after flash chromatography (silica 60; acetonitrile eluent) and removal of the solvent on the rotary evaporator. The oil was solubilized in acetone (7 cm^3) and the reaction was complete after 4 h at room temperature, under magnetic stirring. Removal of the solvent on the rotary evaporator and addition of chloroform, led to orange crystals which were filtered and washed with dry diethyl ether. The product was identified as 6-carbamoyl-2,2-dimethyl-9-(5′-hydroxypentyl)-1,2-dihydropurine **9e** (0.07 g, 0.25 mmol; 43%).

Reaction of 6-*Carbamoyl*-9-(2′-*hydroxyethyl*)-2,2-*dimethyl*-1,2-*dihydropurine with Trifluoroacetic Anhydride.*—Trifluoroacetic anhydride (0.09 cm^3, 0.14 g, 0.61 mmol) was added to a suspension of 6-carbamoyl-9-(2′-hydroxyethyl)-2,2-dimethyl-1,2-dihydropurine (0.14 g, 0.61 mmol) in acetone (40 cm^3). The mixture was stirred at room temperature for 10 min until the starting material was no longer present in solution. Partial removal of the solvent on the rotary evaporator led to a greenish-yellow solid identified as 6-carbamoyl-9-(2′-hydroxyethyl)-2,2-dimethyl-3-trifluoroacetyl-1,2-dihydropurine **11** (0.16 g, 0.46 mmol; 76%).

Synthesis of 1-(2′-*Hydroxyethyl*)-4-*oxamoylimidazole-5-amine* **12**.—A solution of 6-carbamoyl-9-(2′-hydroxyethyl)-2,2-dimethyl-1,2-dihydropurine (0.37 g, 1.56 mmol) in water (3 cm^3) was stirred at room temperature for 19 h, when all the dihydropurine had been consumed. The resulting suspension was filtered and washed with ethanol and diethyl ether to give *title compound* **12** (0.24 g, 1.06 mmol; 67%). An analytical sample was obtained after dry flash chromatography (silica 60; acetone eluent), leading to greenish-yellow crystals.

Acknowledgements

Thanks are due to the Instituto Nacional de Investigação Cientifica, and the Junta Nacional de Investigação Cientifica e Tecnológica, Portugal, for financial support.

References

1 C. K. Chu and S. J. Cutler, *J. Heterocycl. Chem.*, 1986, **23**, 289 and refs. therein.
2 M. R. Harnden, R. L. Jarvest, T. H. Bacon and M. R. Boyd, *J. Med. Chem.*, 1987, **30**, 1636; M. R. Harnden and R. L. Jarvest, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2207 and refs. therein.
3 R. J. Suahadolnik, *Nucleosides as Biological Probes*, Wiley-Interscience, New York, 1979, p. 217.
4 S. L. Norton and J. W. Hadden, Eur. Pat. Appl., 9154 (1980).

5 M. Giovarelli, R. Arione, C. Jemma, T. Musso, G. Benetton, G. Forni and P. Carnaglia-Ferraris, *Int. J. Immunopharmacol.*, 1987, **9**, 659.
6 P. Carnaglia-Ferraris, L. S. Perezzani, R. Stradi and C. Riccardi, *Drugs of the Future*, 1987, **12**, 134.
7 P. Carnaglia-Ferraris, L. Carnara and A. Melodia, *Int. J. Immunopharmacol.*, 1986, **8**, 463.
8 M. J. Alves, B. L. Booth and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1705.

Paper 2/01292H
Received 10*th March* 1992
Accepted 28*th April* 1992