Acyclic Analogues of Purine and Imidazole Nucleosides

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Hydroxyl-protected derivatives of 1- and 3-(2-hydroxyethoxymethyl)imidazoles (**4,5,7-10**) have been prepared from 5-amino-4-carbamoylimidazoles (**2**). The protected derivatives were converted to acyclic analogues of imidazole nucleosides (**6**) or subjected to various cyclisation reactions leading to 9-(2-hydroxyethoxymethyl)-substituted 2-methyl-, 2-phenyl- and 2-azahypoxanthines (**18,13** and **20**, respectively) and 1-methylguanine (**28**). For assignment of structures to isomeric imidazole and purine derivatives, ^{13}C chemical shifts have been used.

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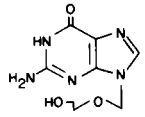
In recent years a number of nucleoside analogues in which the carbohydrate moiety has been replaced by an acyclic substituent have been reported (1-11). Several of these compounds possess antiviral activity (1-4) and one, 9-(2-hydroxyethoxymethyl)guanine (acycloguanosine, **1**), is a highly specific inhibitor of herpes viruses both *in vitro* and in animals and is showing considerable promise in the treatment of herpes virus infections in man (1,12-18).



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The potent antiviral activity and lack of effect upon uninfected host cell metabolism observed with **1** results from its ability to act as a substrate for the herpes virus specified enzyme thymidine kinase, by which it is phosphorylated 30-120 times faster than by the cellular thymidine kinase (12,13). The product of subsequent phosphorylations, acycloguanosine triphosphate, is additionally 10-30 times more effective as an inhibitor of herpes virus specified DNA polymerase than of cellular DNA polymerase (12,13).

It is surprising that **1**, a purine nucleoside analogue, can act as a substrate for a pyrimidine nucleoside kinase. Although additional purines and pyrimidines bearing the 2-hydroxyethoxymethyl substituent have been synthesized (2,5,9), only the 8-azapurine and 2,6-diaminopurine analogues have been reported to possess antiviral activity (2). We were therefore interested in determining to what extent the base moiety of **1** could be varied while retaining antiviral activity.

Several well documented general procedures for the preparation of purine nucleosides modified at positions 1 and 2 involve cyclisations of imidazole intermediates (19-25). Since the 1-substituted imidazoles required for conversion to analogues of **1**, because of their structural relationship to the purine nucleotide precursor 5-amino-4-carbamoyl-1-β-D-ribofuranosylimidazole (AICA-riboside), were also themselves of interest as potential inhibitors of enzymes involved in nucleic acid biosynthesis (26,27), we elected to investigate synthetic routes involving the intermediacy of these imidazoles.

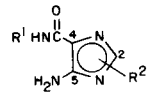
The preparation of the 1-(2-hydroxyethoxymethyl)-imidazoles **6a,b** is outlined in Scheme 1. After initial protection of the amino group in **2a,b** by benzoylation, **3a,b** were alkylated using the procedure described by Schaeffer (2,28,29). Mixtures of isomers substituted at position 3 (**4a,b, 7a,b**) (10-20% yields) and position 1 (**5a,b, 8a,b**) (40-50% yields) of the imidazole ring were obtained and separated using column chromatography. Treatment of **5a,b** with hydrazine hydrate (30) afforded **6a,b** in 80% yield.

When **7a,b** and **8a,b** were subjected to treatment with hydrazine hydrate selective removal of the benzamido group was effected, giving **9a,b** and **10a,b**. The latter were converted to the 2-hydroxyethoxymethyl derivatives **6a,b** by catalytic hydrogenolysis.

The ^{13}C chemical shifts for the imidazole ring carbons in the isomers **9a,10a** and **9b,10b** are shown in Table 1, and are in agreement with values reported in other systems (24). The upfield shift of 10 ppm is consistent with substitution at position 3; similarly, substitution at position 1 in isomers **10a,b** causes a shielding of carbon 5 of the same order of magnitude.

Table 1

^{13}C Chemical Shifts of Imidazoles (a,b)

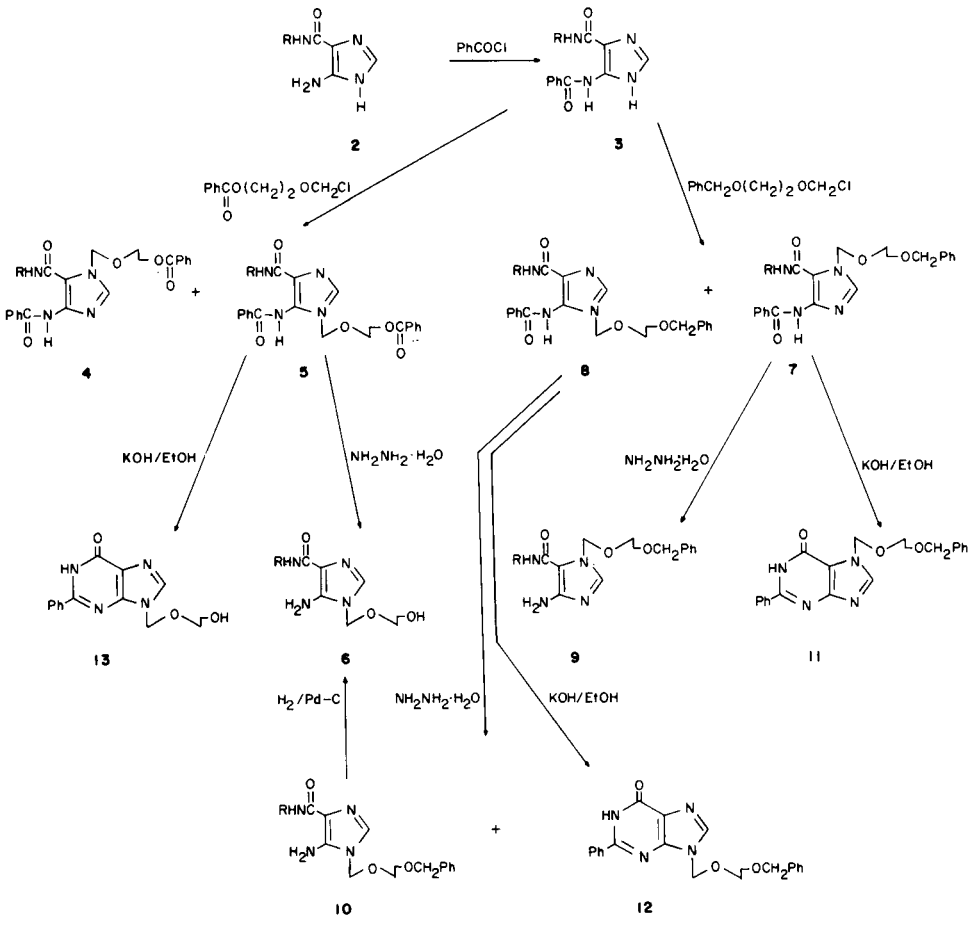


(c,d)

Compound	C-2	C-4	C-5
9a	138.6	104.5	156.0
10a	129.7	114.3	143.4
9b	137.4	105.6	154.5
10b	131.8	115.1	142.2

(a) Values in ppm from internal tetramethylsilane. (b) Solvent deuteriochloroform. (c) R^1 = H (**9a,10a**) or Me (**9b,10b**). (d) R^2 = $PhCH_2OCH_2CH_2OCH_2$-.

Scheme 1

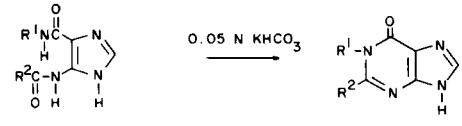


For 2—10
a, R = H
b, R = Me

Treatment of **7a,8a** with hydrazine hydrate resulted not only in deprotection of the amino function, but also in formation of small amounts of substituted hypoxanthines **11** and **12** which were also obtained by heating **7a,8a** with ethanolic potassium hydroxide. Under the latter conditions **5a** gave 9-(2-hydroxyethoxymethyl)-2-phenylhypoxanthine (**13**). However, treatment of the 4-*N*-methylcarbamoylimidazoles **7b,8b** with hydrazine, boiling ethanolic potassium hydroxide or boiling aqueous potassium hydroxide resulted only in recovery of starting material or loss of the benzamido group.

These observations led us to examine further the contribution made by the *N*-methyl group in inhibition of the cyclisation. The related 5-acylamino-4-carbamoylimidazoles **14,3a** and **3b** were subjected to conditions known (31) to result in the formation of hypoxanthine from 5-formamido-4-carbamoylimidazole (Scheme 2). Upon boiling with 0.05*N* potassium bicarbonate, **14** and **3a** cyclised to 1-methylhypoxanthine (**15**) and 2-phenylhypoxanthine (**16**), respectively (32,33), but **3a** remained unchanged. Allowing for the more facile cyclisation of **14** due to the presence of the 5-formyl grouping, comparison of the reac-

Scheme 2



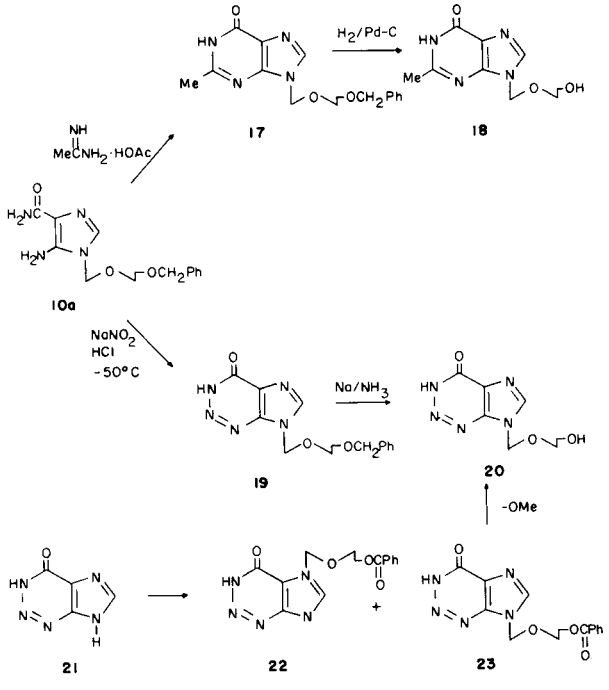
14, R^1 = Me, R^2 = H
3a, R^1 = H, R^2 = Ph
3b, R^1 = Me, R^2 = Ph

15, R^1 = Me, R^2 = H
16, R^1 = H, R^2 = Ph

tivities of **3b**,**7b** and **8b** with those of **3a**,**7a** and **8a** suggests that steric factors may be important in these cyclisation reactions.

Analogues of **1** modified at position 2 were prepared *via* 5-amino-4-carbamoyl-1-(2-benzoxyethoxymethyl)imidazole (**10a**) (Scheme 3). Treatment of **10a** with acetamidine acetate (34) yielded the 2-methylhypoxanthine **17** and diazotisation at -50° (35-38) yielded the 2-aza analogue **19**. The 9-(2-hydroxyethoxymethyl)purines **18** and **20** were obtained either by catalytic hydrogenolysis or treatment with sodium/liquid ammonia (39,40), the latter procedure giving generally better yields.

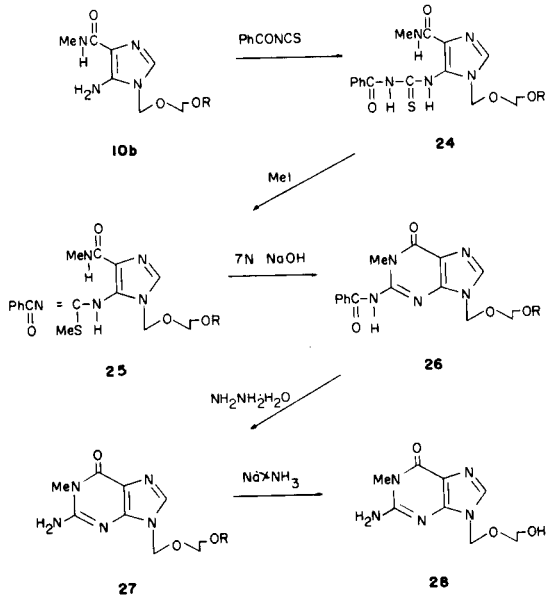
Scheme 3



Direct alkylation of 2-azahypoxanthine (**21**) (35) gave low yields of products, the major one being the 7-substituted isomer **22**. The 9-substituted derivative **23** was formed in only 6% yield. The position of substitution in isomers **22** and **23** was determined from their ^{13}C nmr spectra (41) (Table 2). In the 9-substituted derivatives **19** and **23** C-4 appears upfield from the C-4 signal in the 7-substituted derivative **22**. Deprotection of a small sample of **23** gave a product with a tlc mobility identical to that of **20**, supporting the structural assignments.

The synthesis of 9-(2-hydroxyethoxymethyl)-1-methylguanine (**28**, 1-methylacycloguanosine) from 5-amino-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**10b**) was achieved using a modification (42) of the procedure reported for the preparation of guanosine from AICA riboside (43) (Scheme 4). Treatment of **10b** with benzoylisothiocyanate gave **24** (65% yield), which was converted to the *S*-methyl derivative **25** in 82% yield. Cyclisation of **25** by treatment with aqueous alkali gave **26** in 93% yield. On heating **26** with hydrazine hydrate **27** was obtained in 66% yield and was converted to **28** in 73% yield by treatment with sodium in liquid ammonia.

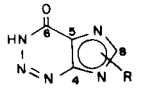
Scheme 4



For **10b**, **24-27**, R = $PhCH_2$

Table 2

^{13}C Chemical Shifts of Azahypoxanthines (a,b)



(c)

Compound	C-4	C-5	C-6	C-8
22	154.4	116.8	151.8	145.5
23	145.5	126.9	154.7	143.3
19	145.5	126.9	154.8	143.1

(a) Values in ppm from internal tetramethylsilane. (b) Solvent deuteriochloroform. (c) R = $PhCH_2OCH_2CH_2OCH_2$- (**19**) or $PhCOOCH_2CH_2OCH_2$- (**22**,**23**).

None of the compounds prepared in this study had significant activity against herpes simplex type 1 or influenza A viruses *in vitro*.

EXPERIMENTAL

Melting points were determined with a Reichert hot-stage apparatus and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer 580 spectrophotometer, using potassium bromide discs, unless otherwise stated. Nuclear magnetic resonance (nmr) spectra were deter-

mined for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as an internal reference. Proton spectra were recorded at 90 MHz on a Varian DM 390 spectrometer and carbon spectra at 20.15 MHz on a Brucker WP 80 DS spectrometer. Mass spectra were obtained with a VG 70-70F instrument operating at 70eV. The R_f values were measured on Merck silica gel 60F precoated plates, layer thickness of 0.25 mm and column chromatography was carried out under pressure using Merck silica gel 60H.

5-Benzamido-4-carbamoylimidazole (**3a**).

To a stirred suspension of 3.52 g (22 mmoles) of **2a** and 50 mg of dimethylaminopyridine in 100 ml of dry pyridine, 3 ml (26 mmoles) of benzoyl chloride was added dropwise and the mixture stirred at room temperature for 0.5 hour, then heated at 50° for 5 hours. The reaction products were then poured into 600 ml of ice-water and the precipitate filtered, washed with water, air dried and recrystallised from ethanol to give 3.43 g (68%) of 5-benzamido-4-carbamoylimidazole (**3a**), mp 253-254°; ir: 3500-3000 cm^{-1} (NH), 1660, 1620 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 7.38 (s, deuterium oxide exchangeable NH_2, 2H), 7.45 (s, CH, 1H), 7.4-8.1 (m, aromatic, 5H), 11.1 (s, deuterium oxide exhangeable NH, 1H), 12.75 (s, deuterium oxide exchangeable NH, 1H); ms: 230 (M^+, 80), 105 (100), 77 (90).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.62; H, 4.33; N, 24.65.

5-Benzamido-4-methylcarbamoylimidazole (**3b**).

To a stirred suspension of 2.25 g (13 mmoles) of **2b** and 100 mg of dimethylaminopyridine in 60 ml of dry pyridine, 1.8 ml (15 mmoles) of benzoyl chloride was added dropwise. The mixture was heated at 50° for 7 hours and then poured onto 500 ml of ice-water. A white solid precipitated and was filtered, washed with water, dried and recrystallised from ethanol to give 1.97 g (63%) of 5-benzamido-4-methylcarbamoylimidazole (**3b**), mp >260°; ir: 3500-3200 cm^{-1} (NH), 1625 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 2.79 (d, CH_3, 3H, J = 4 Hz), 7.43 (s, 1H, CH), 7.5-8.2 (m, aromatic, 5H, deuterium oxide exchangeable NH, 1H), 11.17 (s, deuterium oxide exchangeable NH, 1H); ms: 244 (M^+, 35), 105 (100), 77 (40).

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; N, 4.95; N, 22.94. Found: C, 59.12; H, 4.68; N, 22.49.

5-Benzamido-3-(2-benzoyloxyethoxymethyl)-4-carbamoylimidazole (**4a**) and 5-Benzamido-1-(2-benzoyloxyethoxymethyl)-4-carbamoylimidazole (**5a**).

To a stirred suspension of 2.1 g (9 mmoles) of **3a** and 2.5 ml of triethylamine (18 mmoles) in 25 ml of dry *N,N*-dimethylformamide, 3.86 g (18 mmoles) of 1-benzoyloxy-2-chloromethoxyethane was added dropwise. Heat was evolved, the imidazole dissolved and triethylamine hydrochloride precipitated out. The mixture was stirred at room temperature for 16 hours and the solvent removed under reduced pressure. The resulting oil was treated with a mixture of 100 ml of ethyl acetate and 70 ml of water. A precipitate of 0.66 g of unreacted starting material was filtered off.

The layers were separated and the organic phase washed with two 50 ml portions of water. After drying over magnesium sulphate the solvent was removed to leave an oil which was column chromatographed on silica eluting with chloroform-ethanol (50:1).

The first product collected was 1.18 g (46%) of 5-benzamido-1-(2-benzoyloxyethoxymethyl)-4-carbamoylimidazole (**5a**) which was recrystallised from ethanol-water, mp 143-145°; R_f 0.24 (chloroform-ethanol 10:1); ir: 3470, 3290 cm^{-1} (NH), 1710, 1690, 1665 cm^{-1} (C=O); nmr: δ 3.78 (t, CH_2, 2H, J = 4 Hz), 4.42 (t, CH_2, 2H, J = 4 Hz), 5.67 (s, CH_2, 2H), 6.85 (broad s, 1H, deuterium oxide exchangeable NH, 1H), 7.2-8.1 (m, aromatic, 10H, CH, 1H, deuterium oxide exchangeable NH, 1H), 10.00 (s, deuterium oxide exchangeable NH, 1H); ms: 408 (M^+, 30), 231 (10), 179 (20), 149 (40), 105 (100), 77 (70).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.45; H, 5.01; N, 13.61.

On further elution the column yielded 0.22 g (9%) of a second component, 5-benzamido-3-(2-benzoyloxyethoxymethyl)-4-carbamoylimidazole (**4a**) which was recrystallised from ethanol-water, mp 160-162°; R_f 0.16 (chloroform-ethanol, 10:1); ir: 3500-3200 cm^{-1} (NH), 1715, 1670, 1650 cm^{-1}; nmr: δ 3.90 (t, CH_2, 2H, J = 4 Hz), 4.46 (t, CH_2, 2H, J = 4 Hz), 5.68 (s, CH_2, 2H), 7.00 (s, deuterium oxide exchangeable NH, 2H), 7.3-8.1 (m, aromatic, 10H, CH, 1H), 10.45 (s, deuterium oxide exchangeable NH, 1H); ms: 408 (M^+, 20), 242 (10), 231 (20), 230 (10), 212 (10), 179 (30), 149 (70), 105 (100).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.55; H, 4.56; N, 13.44.

5-Benzamido-3-(2-benzoyloxyethoxymethyl)-4-methylcarbamoylimidazole (**4b**) and 5-Benzamido-1-(2-benzoyloxyethoxymethyl)-4-methylcarbamoylimidazole (**5b**).

To a stirred suspension of 6.15 g (25 mmoles) of **3b** and 2 ml (152 mmoles) of triethylamine in 80 ml of dry *N,N*-dimethylformamide, 32.5 g (152 mmoles) of 1-benzoyloxy-2-chloromethoxyethane was added dropwise. The mixture was stirred at room temperature for 16 hours and the solvent removed under reduced pressure. The resulting oil was treated with a mixture of 250 ml of ethyl acetate and 175 ml of water.

The layers were separated and the organic phase washed with two 125 ml portions of water. After drying with magnesium sulphate the solvent was removed to leave an oil which was column chromatographed on silica eluting with chloroform-ethanol (50:1). The first product collected was 4 g (38%) of 5-benzamido-1-(2-benzoyloxyethoxymethyl)-4-methylcarbamoylimidazole (**5b**), recrystallised from ethanol-water, mp 85-87°; R_f 0.29 (chloroform-ethanol, 20:1); ir: 3500-2800 cm^{-1} (NH), 1720, 1680, 1640 cm^{-1} (C=O); nmr: δ 2.94 (d, CH_3, 3H, J = 5 Hz), 3.78 (m, CH_2, 2H), 4.40 (m, CH_2, 2H), 5.65 (s, CH_2, 2H), 7.0 (broad s, deuterium oxide exchangeable NH, 1H), 7.2-8.2 (m, aromatic, 10H, CH, 1H), 10.08 (s, deuterium oxide exchangeable NH, 1H); ms: 422 (M^+, 10), 245 (5), 179 (5), 149 (15), 105 (100), 77 (20).

Anal. Calcd. for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.60; H, 5.10; N, 13.23.

The second component to be eluted was 1.5 g (14%) of 5-benzamido-3-(2-benzoyloxyethoxymethyl)-4-methylcarbamoylimidazole (**4b**) recrystallised from carbon tetrachloride, mp 121-122°; R_f 0.08 (chloroform-ethanol, 20:1); ir: 3600-2800 cm^{-1} (NH), 1720, 1670 cm^{-1} (C=O); nmr: δ 2.85 (d, CH_3, 3H, J = 5 Hz), 3.95 (m, CH_2, 2H), 4.50 (m, CH_2, 2H), 5.60 (s, CH_2, 2H), 7.2-8.2 (m, aromatic, 10H, CH, 1H, deuterium oxide exchangeable NH, 1H), 9.88 (s, deuterium oxide exchangeable NH, 1H); ms: 422 (M^+, 2), 245 (5), 149 (15), 105 (100), 77 (55).

Anal. Calcd. for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.78; H, 5.52; N, 13.19.

5-Benzamido-3-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**7a**) and 5-Benzamido-1-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**8a**).

To a stirred suspension of 1.97 g (8.6 mmoles) of **3a** and 2.4 ml (17 mmoles) of triethylamine in 25 ml of dry *N,N*-dimethylformamide was added 3.4 g (17 mmoles) of 1-benzoxy-2-chloromethoxyethane and the mixture stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the resulting oil was treated with a mixture of 200 ml of ethyl acetate and 140 ml of water. A precipitate of 0.41 g of unreacted starting material was filtered off. The layers were separated and the organic phase washed with two 100 ml portions of water. After drying with magnesium sulphate the solvent was removed to leave an oil which was column chromatographed on silica eluting with chloroform-ethanol (20:1) to give 1.17 g (44%) of 5-benzamido-1-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**8a**) which was recrystallised from carbon tetrachloride, mp 115-117°; R_f 0.26 (chloroform-ethanol 10:1); ir: 3600-3100 cm^{-1} (NH), 1670 cm^{-1} (C=O); nmr: δ 3.55 (s, CH_2CH_2, 4H), 4.45 (s, CH_2, 2H), 5.59 (s, CH_2, 2H), 5.85 (broad s, deuterium oxide exchangeable NH, 1H), 6.90 (broad s, deuterium oxide exchangeable NH, 1H), 7.2-8.1 (m, aromatic, 10H, CH, 1H), 9.99 (s, deuterium oxide exchangeable NH, 1H); ms: 394 (M^+, 10), 320 (10), 303 (40), 288 (15), 105 (100), 91 (70), 77 (30).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found: C, 63.82; H, 5.92; N, 14.55.

The second component was obtained from the column contaminated with starting material and further column chromatography was required, followed by recrystallisation from ethanol-water to give 0.28 g (10%) of 5-benzamido-3-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**7a**), mp 145-146°; R_f 0.18 (chloroform-ethanol, 10:1); ir: 3280, 3000 cm^{-1} (NH), 1680 cm^{-1} (C=O); nmr: δ 3.68 (m, CH_2CH_2, 4H), 4.49 (s, CH_2, 2H), 5.57 (s, CH_2, 2H), 6.60 (broad s, deuterium oxide exchangeable NH, 2H), 7.2-8.1 (m, aromatic, 10H, CH, 1H), 10.40 (s, deuterium oxide exchangeable NH, 1H); ms: 394 (M^+, 10), 320 (15), 303 (25), 288 (15), 105 (100), 91 (70), 77 (30).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found: C, 63.56; H, 5.68; N, 13.88.

5-Benzamido-3-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**7b**) and 5-Benzamido-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**8b**).

To a stirred suspension of 4.2 g (17 mmoles) of **3b** with 14.3 ml (100 mmoles) of triethylamine in 50 ml of dry *N,N*-dimethylformamide, 20.7 g (100 mmoles) of 1-benzoxy-2-chloromethoxyethane was added dropwise. The mixture was stirred for 16 hours and the solvent removed under reduced pressure. The resulting oil was treated with a mixture of 200 ml of ethyl acetate and 140 ml of water. The layers were separated and the organic phase washed with two 100 ml portions of water. After drying with magnesium sulphate the solvent was removed to leave an oil which was column chromatographed on silica eluting with chloroform-ethanol (50:1). The first product collected was 3.2 g (46%) of 5-benzamido-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**8b**) which was recrystallised from cyclohexane, mp 57-59°; R_f 0.39 (chloroform-ethanol 20:1); ir: 3600-3100, 2940 cm^{-1} (NH), 1650 cm^{-1} (C=O); nmr: δ 2.92 (d, CH_3, 3H, J = 5 Hz), 3.55 (s, CH_2CH_2, 4H), 4.45 (s, CH_2, 2H), 5.61 (s, CH_2, 2H), 6.99 (s, deuterium oxide exchangeable NH, 1H), 7.2-8.1 (m, aromatic, 10H, CH, 1H), 9.99 (s, deuterium oxide exchangeable NH, 1H); ms: 408 (M^+, 10), 303 (15), 105 (100), 91 (70), 77 (30).

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.78; H, 6.22; N, 13.50.

The second product to be eluted was 1.4 g (20%) of 5-benzamido-3-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**7b**), an oil which was crystallised from chloroform-cyclohexane, mp 76-78°; R_f 0.21 (chloroform-ethanol 20:1); ir: 3600-2800 cm^{-1} (NH), 1660 cm^{-1} (C=O); nmr: δ 2.82 (d, CH_3, 3H, J = 5 Hz), 3.65 (m, CH_2CH_2, 4H), 4.48 (m, CH_2, 2H), 5.52 (s, CH_2, 2H), 7.2-8.1 (m, aromatic, 10H, CH, 1H, deuterium oxide exchangeable NH, 1H), 10.41 (s, deuterium oxide exchangeable NH, 1H); ms: 408 (M^+, 3), 334 (10), 303 (15), 245 (10), 229 (20), 105 (100), 91 (85), 77 (30).

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.64; H, 5.81; N, 13.66.

5-Amino-4-carbamoyl-1-(2-hydroxyethoxymethyl)imidazole (**6a**) from **5a**.

To a solution of 0.50 g (1.2 mmoles) of **5a** in 20 ml of ethanol was added 5 ml of hydrazine hydrate. The mixture was boiled under reflux for 16 hours, and the solvent removed to leave a solid which was column chromatographed on silica, eluting with chloroform-ethanol (5:1). The second component to be eluted was 0.2 g (82%) of 5-amino-4-carbamoyl-1-(2-hydroxyethoxymethyl)imidazole (**6a**), R_f 0.16 (chloroform-ethanol, 2:1), which was treated with 1% hydrogen chloride in methanol to form the hydrochloride which was recrystallised from methanol, mp >140° dec; ir: 3500-2500 cm^{-1} (NH,OH), 1690, 1640 cm^{-1} (C=O); nmr (free base) (deuteriodimethylformamide): δ 3.57 (s, CH_2CH_2, 4H), 4.77 (s, deuterium oxide exchangeable OH, 1H), 5.37 (s, CH_2, 2H), 5.89 (s, deuterium oxide exchangeable NH, 2H), 6.72 (s, deuterium oxide exchangeable NH, 2H), 7.29 (s, CH, 1H); ms: 200 (M^+, 40), 126 (100), 109 (60).

Anal. Calcd. for $C_7H_{13}ClN_4O_3$: C, 35.53; H, 5.54; N, 23.67. Found: C, 35.76; H, 5.30; N, 23.32.

5-Amino-4-methylcarbamoyl-1-(2-hydroxyethoxymethyl)imidazole (**6b**) from **5b**.

A solution of 4.2 g (10 mmoles) of **5b** in 130 ml of ethanol was treated with 40 ml of hydrazine hydrate as described above for **6a**. Upon column chromatography (chloroform-ethanol, 10:1), 1.7 g (80%) of 5-amino-4-methylcarbamoyl-1-(2-hydroxyethoxymethyl)imidazole (**6b**) was obtained as the second component to be eluted and was recrystallised as its hydrochloride from ethanol; mp >150° dec; R_f 0.11 (chloroform-ethanol 5:1); ir: 3500-2500 cm^{-1} (NH, OH), 1660 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 2.76 (s, CH_3, 3H), 3.54 (s, CH_2CH_2, 4H), 4.45 (broad s, deuterium oxide exchangeable NH, OH, water), 5.49 (s, CH_2, 2H), 8.30 (broad s, deuterium oxide exchangeable NH, 1H), 8.62 (s, CH, 1H); ms: 214 (M^+, 40), 140 (60), 110 (40), 45 (100).

Anal. Calcd. for $C_8H_{15}ClN_4O_3$: C, 38.33; H, 6.03; N, 22.35. Found: C, 38.30; H, 5.87; N, 22.21.

5-Amino-3-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**9a**) and 7-(2-Benzoxyethoxymethyl)-2-phenylhypoxanthine (**11**).

To a solution of 0.7 g (1.8 mmoles) of **7a** in 25 ml of ethanol was added 7 ml of hydrazine hydrate. The solution was boiled under reflux for 16 hours and the solvent removed to leave an oil which was column chromatographed on silica, eluting with ethyl acetate-ethanol (20:1). The first product to be eluted was 0.12 g (18%) of 7-(2-benzoxyethoxymethyl)-2-phenylhypoxanthine (**11**), which was recrystallised from ethyl acetate, mp 188-189°; R_f 0.26 (chloroform-ethanol, 20:1) ir: 3300-2800 cm^{-1} (NH), 1685 cm^{-1} (C=O); nmr: δ 3.65 (m, CH_2CH_2, 4H), 4.45 (s, CH_2, 2H), 5.86 (s, CH_2, 2H), 7.26 (s, aromatic, 5H), 7.50 (m, aromatic, 3H), 8.10 (s, CH, 1H), 8.30 (m, aromatic, 2H), 12.18 (s, deuterium oxide exchangeable NH, 1H); ms: 376 (M^+, 10), 302 (10), 301 (10), 270 (40), 242 (15), 241 (20), 226 (15), 225 (30), 213 (40), 212 (100), 91 (98).

Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.31; H, 5.04; N, 14.63.

The second component to be eluted was benzoyl hydrazine followed by 0.2 g (39%) of 5-amino-3-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**9a**), which was recrystallised from chloroform-carbon tetrachloride, mp 92-93°; R_f 0.07 (chloroform-ethanol, 20:1); ir: 3500-2800 cm^{-1} (NH), 1650 cm^{-1} (C=O); nmr: δ 3.65 (s, CH_2CH_2, 4H) 4.49 (s, CH_2, 2H), 4.90 (broad s, deuterium oxide exchangeable NH, 2H), 5.39 (s, CH_2, 2H), 6.14 (broad s, deuterium oxide exchangeable NH, 2H), 7.14 (s, CH, 1H), 7.30 (s, aromatic 5H); ms: 290 (M^+, 45), 216 (15), 199 (15), 91 (100).

Anal. Calcd. for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.02; H, 6.07; N, 19.48.

5-Amino-3-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**9b**).

To a solution of 1.5 g (3.6 mmoles) of **7b** in 50 ml of ethanol was added 15 ml of hydrazine hydrate. The mixture was boiled under reflux for 16 hours. The solvent was removed and the residue column chromatographed on silica, eluting with ethyl acetate-ethanol (20:1). After benzoyl hydrazine, the second component to be eluted was 0.58 g (52%) of 5-amino-3-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**9b**), obtained as an oil which could not be crystallised; R_f 0.09 (chloroform-ethanol 20:1); ir (film): 3600-2800 cm^{-1} (NH), 1620 cm^{-1} (C=O); nmr: δ 2.81 (d, CH_3, 3H, J = 5 Hz), 3.68 (s, CH_2CH_2, 4H), 4.53 (s, CH_2, 2H), 4.96 (broad s, deuterium oxide exchangeable NH, 2H), 5.38 (s, CH_2, 2H), 7.15 (s, CH, 1H), 7.32 (m, aromatic, 5H, deuterium oxide exchangeable NH, 1H); ms: observed 304.1530 (M^+, 30), (M^+ theoretical 304.1535), 230 (15), 199 (10), 169 (10), 152 (10), 140 (10), 110 (10), 92 (20), 91 (100).

5-Amino-1-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**10a**) and 9-(2-Benzoxyethoxymethyl)-2-phenylhypoxanthine (**12**).

To a solution of 1.49 g (3.8 mmoles) of **8a** in 50 ml of ethanol was added 15 ml of hydrazine hydrate. The mixture was boiled under reflux for 16 hours, the solvent removed and the residue column chromatographed on silica, eluting with ethyl acetate-ethanol (20:1). The first material to be eluted was benzoyl hydrazine, followed by 0.06 g (4%) of 9-(2-benzoxyethoxymethyl)-2-phenylhypoxanthine (**12**), recrystallised from ethyl

acetate, mp 171-173°; R_f 0.15 (chloroform-ethanol, 20:1); ir: 3500-2800 cm^{-1} (NH), 1695 cm^{-1} (C=O); nmr: δ 3.69 (m, CH_2CH_2, 4H), 4.50 (s, CH_2, 2H), 5.68 (s, CH_2, 2H), 7.30 (s, aromatic, 5H), 7.53 (m, aromatic, 3H), 7.94 (s, CH, 1H), 8.27 (m, aromatic, 2H), 12.40 (broad s, deuterium oxide exchangeable NH, 1H); ms: 376 (M^+, 15), 302 (20), 301 (20), 270 (40), 242 (30), 241 (50), 226 (25), 225 (30), 213 (20), 212 (60), 104 (15), 91 (100).

Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.77; H, 5.46; N, 14.58.

Further elution of the column yielded the major product, 0.78 g (71%) of 5-amino-1-(2-benzoxyethoxymethyl)-4-carbamoylimidazole (**10a**), which was recrystallised from chloroform-carbon tetrachloride, mp 120-121°; R_f 0.07 (chloroform-ethanol 20:1); ir: 3380, 3200 cm^{-1} (NH), 1660, 1630 cm^{-1} (C=O); nmr: δ 3.66 (s, CH_2CH_2, 4H), 4.54 (s, CH_2, 2H), 5.27 (s, CH_2, 2H, deuterium oxide exchangeable NH, 4H), 7.02 (s, CH, 1H), 7.35 (s, aromatic, 5H); ms: 290 (M^+, 25), 91 (100).

Anal. Calcd. for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.18; H, 6.15; N, 19.22.

5-Amino-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**10b**).

To a solution of 0.6 g (1.5 mmoles) of **8b** in 20 ml of ethanol was added 5 ml of hydrazine hydrate. The mixture was boiled under reflux for 16 hours, the solvent removed and the oily residue was column chromatographed, eluting with chloroform-ethanol (50:1). The first product to be eluted was 0.35 g (78%) of 5-amino-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**10b**), R_f 0.24 (chloroform-ethanol, 20:1), which was converted to its hydrochloride by treatment with 1% hydrogen chloride in methanol and recrystallised from ethanol, mp 144-146°; ir: 3400, 3240, 3100 cm^{-1} (NH), 2850, 1660 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 2.73 (s, CH_3, 3H), 3.61 (m, CH_2CH_2, 4H), 4.45 (s, CH_2, 2H), 4.5 (broad s, deuterium oxide exchangeable NH, water), 5.49 (s, CH_2, 2H), 7.30 (s, aromatic, 5H), 8.35 (s, deuterium oxide exchangeable NH, 1H), 8.68 (s, CH, 1H); ms: 304 (M^+, 30), 91 (100).

Anal. Calcd. for $C_{15}H_{21}ClN_4O_3$: C, 52.86; H, 6.21; N, 16.44. Found: C, 52.77; H, 6.78; N, 16.41.

5-Amino-1-(2-hydroxyethoxymethyl)-4-carbamoylimidazole (**6a**) from **10a**.

Hydrogenation of 0.1 g (0.3 mmole) of **10a** over 0.1 g of palladium charcoal catalyst in 5 ml of methanol and 1 ml of water was carried out at atmospheric pressure for 4 hours, after which time tlc indicated complete reaction. The solution was filtered through Celite, evaporated under reduced pressure and the residue column chromatographed on silica, eluting with chloroform-ethanol (5:1), to give 37 mg (54%) of 5-amino-1-(2-hydroxyethoxymethyl)-4-carbamoylimidazole (**6a**), having spectral data identical with those reported above.

5-Amino-1-(2-hydroxyethoxymethyl)-4-methylcarbamoylimidazole (**6b**) from **10b**.

Hydrogenation of 0.2 g (0.66 mmole) of the hydrochloride of **10b** over 0.1 g of palladium charcoal catalyst in 18 ml of methanol and 2 ml of water was carried out at atmospheric pressure for 10 minutes, after which time tlc indicated complete reaction. After filtration through Celite, the solution was neutralised with Amberlite IR 45 (OH) resin and filtered again. On removal of the solvent under reduced pressure the residue was column chromatographed on silica, eluting with chloroform-ethanol (10:1). The first component to elute was 25 mg of unreacted starting material, followed by 45 mg (37%) of 5-amino-1-(2-hydroxyethoxymethyl)-4-methylcarbamoylimidazole (**6b**), having spectral data identical with those reported above.

9-(2-Benzoxyethoxymethyl)-2-phenylhypoxanthine (**12**).

A solution of 0.2 g (0.5 mmole) of **8a** in 10 ml of 0.1*N* alcoholic potassium hydroxide was boiled under reflux for 16 hours. The solvent was removed under reduced pressure and the residue dissolved in 10 ml of water and neutralised with 2*N* hydrochloric acid. The solution was extracted with three 10 ml portions of chloroform, the organic layers combined, washed with 10 ml of water and dried with magnesium sulphate. After removal of the solvent the residue was recrystallised from ethyl acetate to give 94 mg (49%) of 9-(2-benzoxyethoxymethyl)-2-phenylhypoxanthine (**12**), having spectral properties identical with those reported above.

7-(2-Benzoxyethoxymethyl)-2-phenylhypoxanthine (**11**).

A solution of 0.22 g (0.56 mmole) of **7a** in 12 ml of 0.1*N* alcoholic potassium hydroxide was boiled under reflux for 16 hours. The solvent was removed under reduced pressure and the residue dissolved in 12 ml of water and neutralised with 2*N* hydrochloric acid. The solution was extracted with three 12 ml portions of chloroform, the organic layers combined, washed with 12 ml of water and dried with magnesium sulphate. After removal of the solvent the residue was recrystallised from ethyl acetate to give 0.10 g (48%) of 7-(2-benzoxyethoxymethyl)-2-phenylhypoxanthine (**11**), having spectral properties identical with those reported above.

9-(2-Hydroxyethoxymethyl-2-phenylhypoxanthine (**13**).

A solution of 0.2 g (5 mmoles) of **5a** in 10 ml of 0.1*N* ethanolic potassium hydroxide was boiled under reflux for 16 hours, after which time a white solid had precipitated. The solvent was removed, the residue dissolved in 20 ml of water and acidified with 5*N* hydrochloric acid. The resulting precipitate was collected, washed and dried to give 73 mg (52%) of 9-(2-hydroxyethoxymethyl)-2-phenylhypoxanthine (**13**), recrystallised from methanol-water, mp 258-260°; ir: 3500-2800 cm^{-1} (NH, OH), 1680 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 3.54, (m, CH_2CH_2, 4H), 4.70 (s, deuterium oxide exchangeable OH, 1H), 5.62 (s, CH_2, 2H), 7.54 (m, aromatic, 3H), 8.16 (m, aromatic, 2H), 8.26 (s, CH, 1H); ms: 286 (M^+, 30), 241 (15), 226 (30), 225 (35), 213 (15), 212 (100), 211 (20), 109 (60), 104 (40), 77 (15), 45 (40).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.51; H, 4.91; N, 19.29.

1-Methylhypoxanthine (**15**).

To 100 ml of 0.05*N* potassium bicarbonate solution was added 0.5 g (3 mmoles) of **14** and the mixture boiled under reflux for 4 hours. The solution was then concentrated to 5 ml and the *p*H adjusted to 7 by addition of glacial acetic acid. The precipitate which formed was collected, washed with water, and dried to give 0.18 g (40%) of 1-methylhypoxanthine (**15**), recrystallised from ethanol, mp >300°; ir: 3300-2500 cm^{-1} (NH), 1710, 1690 cm^{-1} (C=O); nmr (trifluoroacetic acid plus deuteriodimethylsulphoxide): δ 3.93 (s, CH_3, 3H), 8.78 (s, CH, 1H), 9.29 (s, CH, 1H); ms: 150 (M^+, 100), 122 (20), 121 (15), 95 (10), 68 (10), 54 (10).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.96; H, 4.27; N, 37.08.

2-Phenylhypoxanthine (**16**).

To 100 ml of 0.05*N* potassium bicarbonate solution was added 0.5 g (2.2 mmoles) of **3a** and the mixture boiled under reflux for 4 hours. The solution was then concentrated to 20 ml and the *p*H adjusted to 5 by addition of glacial acetic acid. The precipitate which formed was collected, washed with water and dried to give 0.24 g (52%) of 2-phenylhypoxanthine (**16**) recrystallised from ethanol, mp >300°; ir: 3300-2700 cm^{-1} (NH), 1690 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 7.52 (m, aromatic, 3H), 8.12 (m, aromatic, 2H, CH, 1H), 12.70 (s, deuterium oxide exchangeable NH, 2H); ms: 212 (M^+, 100), 109 (70), 104 (35), 77 (25).

Anal. Calcd. for $C_{11}H_8N_4O{\cdot}H_2O$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.63; H, 4.46; N, 24.40.

9-(2-Benzoxyethoxymethyl)-2-methylhypoxanthine (**17**).

To a solution of 0.34 g (1.2 mmoles) of **10a** in 2 ml of amyl alcohol was added 0.9 g (7.6 mmoles) of acetamidine acetate. The mixture was boiled under reflux for 48 hours. The solvent was then removed under reduced pressure, the residue dissolved in chloroform and the chloroform solution washed with water. After drying with magnesium sulphate and removal of the solvent the residue was subjected to high vacuum for several hours to remove traces of amyl alcohol, then column chromatographed on silica, eluting with ethyl acetate-ethanol (50:1) to give 0.13 g (35%) of 9-(2-benzoxyethoxymethyl)-2-methylhypoxanthine (**17**), recrystallised from ethyl acetate, mp 139-140°; ir: 3600-2600 cm^{-1} (NH),

1700 cm^{-1} (C=O); nmr: δ 2.62 (s, CH_3, 3H), 3.68 (m, CH_2CH_2, 4H), 4.05 (s, CH_2, 2H), 4.12 (s, deuterium oxide exchangeable NH, 1H), 5.60 (s, CH_2, 2H), 7. 30 (s, aromatic, 5H), 7.90 (s, CH, 1H); ms: 314 (M^+, 5), 208 (15), 91 (100).

Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 60.90; H, 5.59; N, 17.60.

9-(2-Hydroxyethoxymethyl)-2-methylhypoxanthine (**18**).

Hydrogenation of 0.2 g (0.6 mmole) of **17** over 0.1 g palladium charcoal catalyst in 20 ml of methanol and 3 ml of 1*N* hydrochloric acid was carried out under atmospheric pressure for 15 minutes. After filtration through Celite the solution was neutralised with Amberlite IR 45 (OH) resin, filtered, the solvent removed and the residue column chromatographed on silica, eluting with chloroform-ethanol (3:1) to give 40 mg (28%) of 9-(2-hydroxyethoxymethyl)-2-methylhypoxanthine (**18**), mp 245° dec; ir: 3500-2500 cm^{-1} (NH, OH), 1680 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 2.37 (s, CH_3, 3H), 3.30 (s, deuterium oxide exchangeable OH, water), 3.47 (s, CH_2CH_2, 4H), 4.63 (broad s, deuterium oxide exchangeable NH, 1H), 5.50 (s, CH_2, 2H), 8.12 (s, CH, 1H); ms: 224 (M^+, 20) 163 (30), 150 (100), 109 (20).

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.47; H, 5.19; N, 24.58.

2-Aza-9-(2-benzoxyethoxymethyl)hypoxanthine (**19**).

To 5 ml of 6*N* hydrochloric acid, precooled to -30°, was added 0.2 g (0.7 mmole) of **10a**. After dissolution, 0.48 g (0.7 mmole) of sodium nitrite in a few drops of water was added. The solution remained colourless and, after stirring for 30 minutes at -30°, 30 ml of ethanol was slowly added, keeping the temperature at -30°. The *p*H of the solution was adjusted to between 7 and 7.5 by addition of ammonium hydroxide solution, again keeping the temperature at -30°. After neutralisation the solution was allowed to warm to room temperature. On warming it developed an orange colouration. After addition of 10 ml of water, the ethanol was removed under reduced pressure until a fine suspension of the product could be seen. The mixture was treated with 30 ml of chloroform, the aqueous phase extracted and the layers separated. The aqueous phase was further extracted with three 10 ml portions of chloroform and the chloroform solutions combined and dried with magnesium sulphate. After removal of the chloroform the dark residue obtained was column chromatographed, eluting with chloroform-ethanol (20:1) to give 98 mg (47%) of 2-aza-9-(2-benzoxyethoxymethyl)hypoxanthine (**19**), recrystallised from ethyl acetate, mp 113-114°; ir: 3300-2700 cm^{-1} (NH), 1710 cm^{-1} (C=O); nmr: δ 3.69 (m, CH_2CH_2, 4H), 4.48 (s, CH_2, 2H), 5.80 (s, CH_2, 2H), 7.28 (s, aromatic, 5H), 8.15 (s, CH, 1H), 13.2 (broad s, deuterium oxide exchangeable NH, 1H).

2-Aza-9-(2-hydroxyethoxymethyl)hypoxanthine (**20**).

To a solution of 40 mg (0.13 mmole) of **19** in 15 ml of liquid ammonia at -50°, was added 50 mg (22 mmoles) of sodium metal in portions. The solution was kept at -50° for 30 minutes and then allowed to warm up to room temperature so that the ammonia evaporated off. The residue was column chromatographed on silica, eluting with ethyl acetate-ethanol-water (10:3:2) to give 20 mg (71%) of 2-aza-9-(2-hydroxyethoxymethyl)-hypoxanthine (**20**), recrystallised from ethanol, mp 178-179° dec; ir: 3500-2500 cm^{-1} (NH, OH), 1720 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 3.52 (m, CH_2CH_2, 4H), 4.70 (broad s, deuterium oxide exchangeable OH, 1H), 5.77 (s, CH_2, 1H), 8.60 (s, CH, 1H), 11.94 (broad s, deuterium oxide exchangeable NH, 1H); ms: 211 (M^+, 5), 181 (20), 138 (30), 137 (50), 45 (100).

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.16. Found: C, 40.08; H, 3.92; N, 32.87.

2-Aza-7-(2-benzoyloxyethoxymethyl)hypoxanthine (**22**) and 2-Aza-9-(2-benzoyloxyethoxymethyl)hypoxanthine (**23**).

To a solution of 2 g (14.6 mmoles) of **21** and 4.1 ml (30 mmoles) of triethylamine in 40 ml of dry *N,N*-dimethylformamide was added 6.4 g (30 mmoles) of 1-benzoyloxy-2-chloromethoxyethane. The solution became hot and darkened in colour. The solution was stirred for 16 hours and the solvent was removed under reduced pressure to leave an oil which was extracted with 100 ml of ethyl acetate and 50 ml of water. The layers were separated and the organic phase washed with two 50 ml portions of water and dried with magnesium sulphate. On removal of the solvent, the resulting oil was column chromatographed on silica, eluting with chloroform-ethanol (20:1) to give 1.14 g (25%) of 2-aza-7-(2-benzoyloxyethoxymethyl)hypoxanthine (**22**), recrystallised from methanol as an orange solid, mp 145-146° dec; R_f 0.53 (chloroform-ethanol, 5:1); ir: 3400-3100, 2950 cm^{-1} (NH), 1710, 1680 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 3.90 (m, CH_2, 2H), 4.36 (m, CH_2, 2H), 5.82 (s, CH_2, 2H), 7.3-8.0 (m, aromatic, 5H), 8.72 (s, CH, 1H), 15.2 (broad s, deuterium oxide exchangeable NH, 1H); ms: 315 (M^+, 5), 149 (40), 105 (100), 77 (50).

Anal. Calcd. for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 53.23; H, 4.30; N, 22.29.

Further elution yielded 0.29 g (6.3%) of 2-aza-9-(2-benzoyloxyethoxymethyl)hypoxanthine (**23**), recrystallised from ethanol-water as an orange solid, mp 131-132° dec; R_f 0.47 (chloroform-ethanol, 5:1); ir: 3400, 3100, 2940 cm^{-1} (NH), 1715 cm^{-1} (C=O); nmr (deuteriodimethylsulphoxide): δ 3.92 (m, CH_2, 2H), 4.38 (m, CH_2, 2H), 5.84 (s, CH_2, 2H), 7.3-8.0 (m, aromatic, 5H), 8.63 (s, CH, 1H), 15.0 (broad s, deuterium oxide exchangeable NH, 1H).

Anal. Calcd. for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 53.22; H, 4.07; N, 21.99.

1-(2-Benzoxyethoxymethyl)-5-(*N*-benzoylthiocarbamoyl)amino-4-methylcarbamoylimidazole (**24**).

To a solution of 0.39 g (5.1 mmoles) of ammonium thiocyanate in 7 ml of dry acetone at 50°, 0.55 ml (4.7 mmoles) of benzoyl chloride was added dropwise. A precipitate of ammonium chloride appeared immediately.

The mixture was stirred at 50° for 5 minutes and then treated with a solution of 1.3 g (4.3 mmoles) of 5-amino-1-(2-benzoxyethoxymethyl)-4-methylcarbamoylimidazole (**10b**) in 8 ml of warm acetone. The mixture was then boiled under reflux for 30 minutes after which time tlc (chloroform) showed the reaction to be complete. The solvent was removed under reduced pressure and the residue extracted with 20 ml of chloroform and 10 ml of water. The layers were separated, the organic phase washed with water and dried with magnesium sulphate. The residue obtained on evaporation of the solvent was column chromatographed on silica, eluting with chloroform. The first fast running component was discarded and the product was collected as the second component, 1.3 g (65%) of 1-(2-benzoxyethoxymethyl)-5-(*N*-benzoylthiocarbamoyl)amino-4-methylcarbamoylimidazole (**24**), recrystallised from chloroform-cyclohexane, mp 56-58°; ir: 3600-2800 cm^{-1} (NH), 1655 cm^{-1} (C=O); nmr: δ 2.90 (d, CH_3, 3H, J = 4.5 Hz), 3.60 (s, CH_2CH_2, 4H), 4.48 (s, CH_2, 2H), 5.40 (s, CH_2, 2H), 7.00 (broad s, deuterium oxide exchangeable NH, 1H), 7.16-8.0 (m, aromatic, 10H, CH, 1H), 9.41 (s, deuterium oxide exchangeable NH, 1H), 12.33 (s, deuterium oxide exchangeable NH, 1H).

1-(2-Benzoxyethoxymethyl)-5-(*N*-benzoyl-*S*-methylisothiocarbamoyl)-amino-4-methylcarbamoylimidazole (**25**).

To a solution of 1.1 g (2.3 mmoles) of **24** in 20 ml of 0.2*N* aqueous sodium hydroxide, cooled in an ice bath, was added 0.8 ml (13 mmoles) of methyl iodide. The solution turned cloudy immediately. After 2 hours, tlc indicated complete reaction and the *p*H of the solution was adjusted to 4-5 by addition of a few drops of acetic acid. The oil which had separated was extracted with 20 ml of chloroform and the chloroform layer was washed with water, dried with magnesium sulphate, filtered and evaporated to give an oil which was column chromatographed on silica, eluting with chloroform-cyclohexane (20:1) to give 0.93 g (82%) of 1-(2-benzoxyethoxymethyl)-5-(*N*-benzoyl-*S*-methylisothiocarbamoyl)amino-4-methylcarbamoylimidazole (**25**), recrystallised from ethyl acetate-cyclohexane, mp 107-108°; ir: 3400, 3210, 2900 cm^{-1} (NH), 1695, 1645 cm^{-1} (C=O); nmr: δ 2.50 (s, SCH_3, 3H), 2.95 (d, CH_3, 3H, J = 4.5 Hz), 3.60 (s, CH_2CH_2, 4H) 4.50 (s, CH_2, 2H), 5.36 (s, CH_2, 2H), 7.18-8.05 (m, aromatic, 10H, CH, 1H, deuterium oxide exchangeable NH, 1H), 11.89 (s, deuterium oxide exchangeable NH, 1H); ms: 481 (M^+, 30), 434 (40), 360 (20), 105 (100), 91 (70).

Anal. Calcd. for $C_{24}H_{27}N_5O_4S$: C, 59.86; H, 5.65; N, 14.54. Found: C, 59.99; H, 5.53; N, 14.39.

2-Benzamido-9-(2-benzoxyethoxymethyl)-1-methylpurin-6-one (**26**).

To a solution of 1.2 g (2.5 mmoles) of **25** in 5 ml of dioxane was added 35 ml of 7*N* sodium hydroxide and the solution was boiled under reflux for 6 hours. Some material precipitated out of solution during this time. The solution was neutralised with 5*N* hydrochloric acid and extracted with 30 ml of chloroform. The chloroform solution was dried with magnesium sulphate and evaporated to give 1 g (93%) of 2-benzamido-9-(2-benzoxyethoxymethyl)-1-methylpurin-6-one (**26**); ir (film): 3300-2800 cm^{-1} (NH), 1690 cm^{-1} (C=O); nmr: δ 3.63 (s, CH_3, 3H), 3.68 (s, CH_2CH_2, 4H), 4.50 (s, CH_2, 2H), 5.50 (s, CH_2, 2H), 7.1-8.9 (m, aromatic, 10H, CH, 1H, deuterium oxide exchangeable NH, 1H); ms: 433.1752 (M^+, 20), (M^+ theoretical 433.1750), 358 (15), 327 (20), 298 (15), 282 (20), 269 (25), 105 (80), 91 (100), 77 (30).

9-(2-Benzoxyethoxymethyl)-1-methylguanine (**27**).

To a solution of 1 g (2.3 mmoles) of **26** in 30 ml of ethanol was added 10 ml of hydrazine hydrate and the mixture was boiled under reflux for 16 hours. The solvent was removed and the residue column chromatographed on silica, eluting with chloroform-ethanol (20:1). The second component to be eluted was 0.57 g (66%) of 9-(2-benzoxyethoxymethyl)-1-methylguanine (**27**); ir: 3600-2400 cm^{-1} (NH), 1680, 1640 cm^{-1} (C=O); nmr: δ 3.47 (s, CH_3, 3H), 3.64 (s, CH_2CH_2, 4H), 4.50 (s, CH_2, 2H), 5.40 (s, CH_2, 2H), 6.13 (s, deuterium oxide exchangeable NH, 2H), 7.30 (s, aromatic, 5H), 7.60 (s, CH, 1H); ms: 329.1489 (M^+, 10), (M^+ theoretical 329.1488), 255 (10), 223 (20), 195 (10), 194 (10), 178 (15), 165 (20), 91 (100).

9-(2-Hydroxyethoxymethyl)-1-methylguanine (**28**).

To a solution of 100 mg (0.3 mmole) of **27** in 15 ml of liquid ammonia at -50°, 20 mg (0.9 mmole) of sodium was added in small portions. The ammonia was allowed to evaporate and the residue column chromatographed on silica, eluting with chloroform-ethanol (20:1) to give 53 mg (73%) of 9-(2-hydroxyethoxymethyl)-1-methylguanine (**28**). Treatment with 1% hydrogen chloride in methanol yielded the hydrochloride, recrystallised from methanol, mp >300°; ir: 3600-2200 cm^{-1} (NH, OH), 1710, 1640 cm^{-1} (C=O); nmr (free base) (deuteriodimethylsulphoxide): δ 3.32 (s, CH_3, 3H), 3.48 (s, CH_2CH_2, 4H), 4.61 (broad s, deuterium oxide exchangeable OH, 1H), 5.35 (s, CH_2, 2H), 7.02 (s, deuterium oxide exchangeable NH, 2H), 7.80 (s, CH, 1H); ms: 239 (M^+, 5), 166 (10), 165 (100), 135 (10), 110 (15), 109 (15), 83 (15), 57 (20).

Anal. Calcd. for $C_9H_{14}ClN_5O_3$; C, 39.21; H, 5.12; N, 25.40. Found: C, 38.88; H, 4.84; N, 25.06.

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