Purines, Pyrimidines and Imidazoles. Part 67.[1] Some *N*-Substituted *o*-(2-Hydroxyethyl)benzyl-purines, -pyrimidines and -imidazoles as Aromatic Acylonucleoside Analogues

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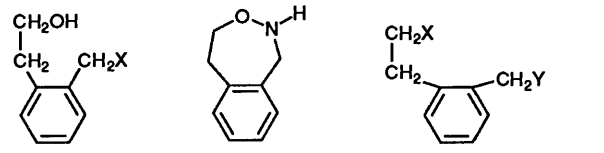
Reaction of isochromane with hydrogen bromide in acetic acid and further reaction of the products formed with potassium phthalimide gave a mixture of *N*-[*o*-(2-bromoethyl)benzyl]phthalimide and *N*-[*o*-(2-acetoxyethyl)benzyl]phthalimide. The mixture, on reaction with silver acetate, gave the latter compound, which with hydrazine gave *o*-(2-hydroxyethyl)benzylamine. The amine, on reaction with 2-cyano-2-(ethoxymethylenamino)acetamide, gave 5-amino-1-[*o*-(2-hydroxyethyl)benzyl]imidazole-4-carboxamide, which was cyclised to 9-[*o*-(2-hydroxyethyl)benzyl]-guanine, -hypoxanthine and -adenine. With *N*-ethoxycarbonyl-3-methoxy-2-methylacrylamide, 3-methoxy-2-methylacryloyl isothiocyanate and ethoxymethylenemalonylurethane, the amine produced 1-[*o*-(2-hydroxyethyl)-benzyl]thymine, -2-thiothymine and -*N*-ethoxycarbonyluracil-5-carboxamide respectively. The latter, on reaction with alkali, gave 1-[*o*-(2-hydroxyethyl)benzyl]uracil-5-carboxylic acid, which was decarboxylated to 1-[*o*-(2-hydroxyethyl)benzyl]uracil. Structures were confirmed by EI, FAB and ^{1}H NMR spectra.

We have observed[2] that the efficiency of 5'-O-phosphorylation of some imidazole ribonucleosides using a phosphotransferase from wheat shoots was greatly enhanced by the presence of an aromatic ring in the molecule. This led us to suggest that this might have some relevance to the mechanism of action of the phosphotransferase. These observations, together with the well publicised antiviral activity of various acylonucleosides, led us to investigate in the first instance the preparation of a series of aromatic nucleoside analogues of type **1** in which the carbon skeletal structure of a ribo- or 2-deoxyribo-nucleoside is broadly maintained.



1 X = base
2 X = NH_2

3

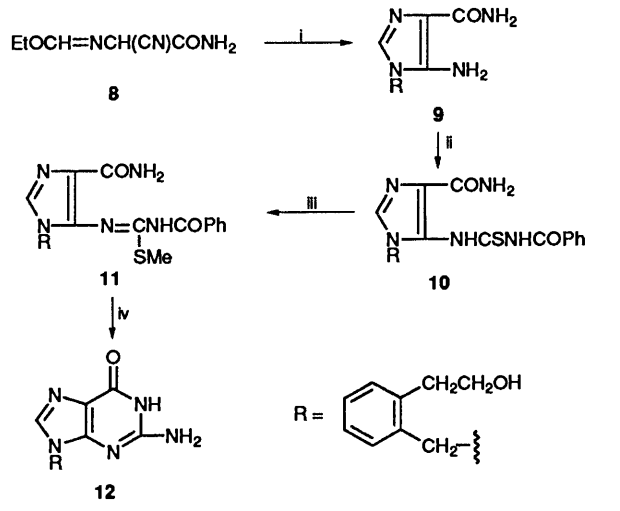
4 X = Y = Br
5 X = OAc, Y = Br
6 X = Br, Y = phthalimido
7 X = OAc, Y = phthalimido

Our proposed synthetic (Shaw syntheses)[3-8] routes (which give unambiguously substituted derivatives) to both pyrimidine and purine derivatives, required the preparation of *o*-(2-hydroxyethyl)benzylamine **2**. This compound has been described as a hydrochloride in the literature[9] by hydrogenolysis of the tetrahydrobenzoxazepine **3** which was prepared in turn in low yield by a multistage series of reactions involving separation of mixtures from *o*-(2-bromoethyl)benzaldehyde. We now describe a much simpler practical method for the preparation of compound **2** which does not involve chromatography. The proposed synthesis of compound **2** required preparation of the dibromide **4**. This compound has been earlier prepared[10] by the reaction of isochromane with hydrogen bromide in acetic acid. Preliminary experiments in our hands showed that this reaction results in the formation of a mixture of the dibromide **4** and the bromo acetate **5**. Thus when the crude reaction product of isochromane and hydrogen bromide in acetic acid was treated with potassium phthalimide in dimethylformamide (DMF), a mixture of the phthalimido bromo and related acetate derivatives **6** and **7** respectively was obtained. On a small scale these were separated by column chromatography and identified by elemental analysis, and mass and ^{1}H NMR spectroscopy.

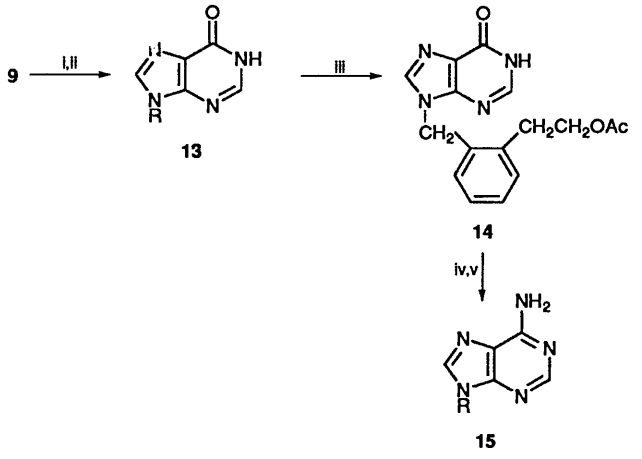
In particular, in the ^{1}H NMR spectra of compounds **6** and **7** the signals for the benzylic hydrogen atoms were identical (δ 4.96) and compared well with that of the CH_2 group in *N*-benzylphthalimide (δ 4.84). These observations have enabled us to produce a good synthesis of the phthalimido acetate **7** by reaction of the mixture of bromides **4** and **5** with potassium phthalimide followed by reaction of the crude mixture of phthalimides so produced with silver acetate in acetic acid. This produced an overall yield of at least 50% of pure recrystallised acetate **7** without the need for chromatography. The phthalimido acetate **7** reacted with hydrazine hydrate in ethanol solution when heated on a steam-bath for a few minutes to give a 90% yield of the amine **2**, which was readily converted into a crystalline hydrochloride by treatment with hydrochloric acid.

The amine **2** was converted into a series of purine, pyrimidine and imidazole acylonucleoside analogues by using methods developed earlier by one of us.[3-8] In particular, reaction of amine **2** with the ethoxymethylenimino derivative **8**[5] (prepared from aminocyanoacetamide and triethyl orthoformate) gave the aminoimidazole derivative **9** [a 5-amino-1-ribofuranosyl-imidazole-4-carboxamide 5'-phosphate (AICAR) analogue] which, with benzoyl isothiocyanate in DMF at room temperature gave, after 1.5 h, the thiourea **10**. This, on reaction with aq. sodium hydroxide or triethylamine and methyl iodide, produced the *S*-methyl isothiourea derivative **11** which, when heated with aq. ammonia, gave the guanine analogue **12** in 51% yield (Scheme 1).

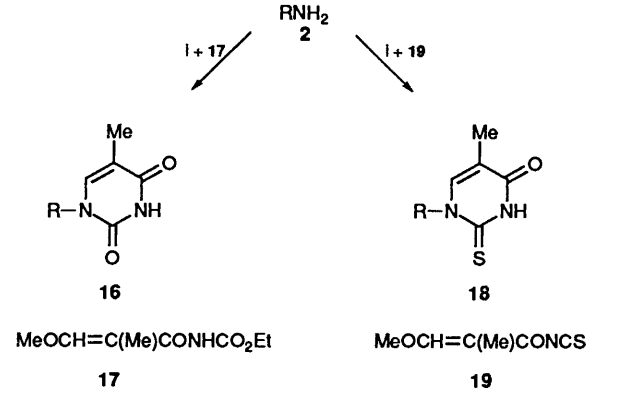
The hypoxanthine derivative **13** was prepared from compound **9** in 96% yield by reaction with formic acetic anhydride followed by aq. sodium hydrogen carbonate. Treatment of the hypoxanthine **13** with acetic anhydride in pyridine produced the *O*-acetate **14** which, with tetraethylammonium chloride, *N*,*N*-dimethylaniline and phosphoryl trichloride, gave presumably the corresponding 6-chloropurine (not isolated) which, with hot aq. ammonia, readily gave the adenine **15** in 50% yield (Scheme 2). The thymine derivative **16** was prepared by reaction of the amine **2** with *N*-ethoxycarbonyl-3-methoxy-2-methyl-acrylamide[4] **17** followed by sodium hydroxide, and the corresponding 2-thiothymine derivative **18** by a similar reaction of



Scheme 1 *Reagents:* i, RNH_2; ii, PhCONCS; iii, MeI, base; iv, NH_3



Scheme 2 *Reagents:* i, HCO_2H, Ac_2O; ii, aq. $NaHCO_3$; iii, Ac_2O, Py; iv, NEt_4Cl, $PhNMe_2$, $POCl_3$; v, NH_3. R (see Scheme 1).

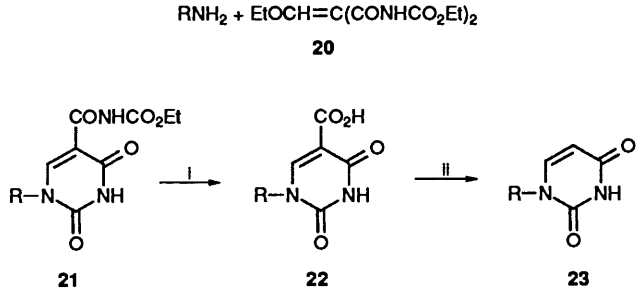


Scheme 3 *Reagent:* i, 2 mol dm^{-3} NaOH. R (see Scheme 1).

the amine **2** with the acyl isothiocyanate **19** and sodium hydroxide (Scheme 3).

Reaction of the amine **2** with ethoxymethylenemalonylurethane[1] **20** readily produced the uracil derivative **21**, hydrolysis of which with 2 mol dm^{-3} sodium hydroxide gave the uracil-5-carboxylic acid **22**. When the latter compound was refluxed in *N*-ethylmorpholine solution for 1 h, the uracil derivative **23** was obtained in good yield (62%) (Scheme 4).

The compounds were tested for antiviral activity against Herpes Simplex 1 (HSV 1) in Veros cells. They were essentially inactive except at high concentrations, when the guanine derivative **12** was the most active (EC_{50} 150 μg cm^{-3}) (Table 1).



Scheme 4 *Reagents and conditions:* i, 2 mol dm^{-3} NaOH; ii, *N*-ethylmorpholine, reflux, 1 h. R (see Scheme 1).

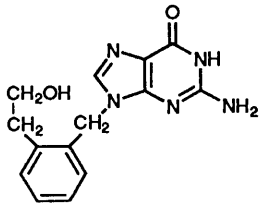
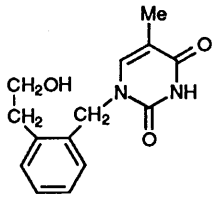
Experimental

Reactions were monitored by TLC on silica gel sheets 60 F254 (0.2 mm thick) (Merck); m.p.s were measured on a Gallenkamp m.p. apparatus and are uncorrected, ^1H NMR spectra (δ; *J*-values in Hz) were recorded with a JEOL JNM-GX270 spectrometer (tetramethylsilane as internal standard) for solutions in $(CD_3)_2SO$ or $CDCl_3$, FAB mass spectra (3-nitrobenzyl alcohol) were determined by the SERC MS Service Centre, Swansea and EI mass spectra were measured using an AE1 MS 903 spectrometer. Evaporations were carried out under reduced pressure (water-pump) with a flask temperature of below 40 °C.

N-[o-(2-*Acetoxyethyl*)*benzyl*]*phthalimide* **7**.—Isochromane (25 g, 0.19 mol) and hydrogen bromide in acetic acid (45%, w/v; 145 cm^3) were heated on a steam-bath for 4 h. The solution was cooled, water (500 cm^3) was added, and the mixture was extracted with chloroform. The extract was washed successively with aq. sodium hydrogen carbonate and water, then was dried (anhyd. $MgSO_4$) and evaporated to give a pale brown oil (45 g). This, in DMF (200 cm^3), was treated with potassium phthalimide (30 g, 0.16 mol) and the suspension was heated on a steam-bath for 2 h. The mixture was diluted with both chloroform (200 cm^3) and water (150 cm^3). The organic layer was separated and the aqueous phase was extracted with chloroform (150 cm^3). The combined organic phases were washed successively with 0.2 mol dm^{-3} sodium hydroxide (100 cm^3) and water (100 cm^3), dried (anhyd. $MgSO_4$), then evaporated to give a thick syrup which solidified on cooling. TLC examination revealed that this consisted of two products (see later). A solution of the crude solid (33 g) and silver acetate (33 g, 0.2 mol) in acetic acid (330 cm^3) was boiled under reflux for 5 h, then was filtered, and the filtrate was diluted with water (200 cm^3). The resulting precipitate was extracted into chloroform. The extract was washed successively with aq. sodium hydrogen carbonate (2 × 150 cm^3) and water (100 cm^3), dried (anhyd. $MgSO_4$), and evaporated to leave a solid. Crystallisation of this from ethanol gave the *title compound* (30 g, 50%), m.p. 109–110 °C; δ($CDCl_3$) 2.05 (3 H, s, Me), 3.23 (2 H, t, *J* 7.33 and 6.96, CH_2CH_2O), 4.33 (2 H, t, *J* 7.33 and 6.96, CH_2O), 4.96 (2 H, s, CH_2N) and 7.15–7.9 (8 H, m, ArH) (Found: C, 70.5; H, 5.4; N, 4.25%; MH^+, 323, 325. $C_{19}H_{17}NO_4$ requires C, 70.59; H, 5.3; N, 4.33%; MH, 323, 325).

N-[o-(2-*Bromoethyl*)*benzyl*]*phthalimide* **6**.—The mixture of solids obtained in a small-scale repetition of the latter experiment was separated by chromatography on silica gel (chloroform as eluting solvent) to give the *title compound*, m.p. 131–132 °C; δ($CDCl_3$) 3.44 (2 H, t, *J* 7.33, CH_2CH_2Br), 3.63 (2 H, t, *J* 7.33, CH_2CH_2Br) 4.96 (2 H, s, CH_2N) and 7.2–7.88 (8 H, m, ArH) (Found: C, 59.25; H, 4.2; N, 4.1%; MH^+, 344, 346. $C_{17}H_{14}BrNO_2$ requires C, 59.3; H, 4.09; N, 4.07%; MH, 344, 346). Compound **7** was also isolated and the ratio **6**:**7** formed was approximately 1:3.

Table 1 Anti-Herpes simplex activity[a]

Compound	Conc. (μg cm^{-3})	Mean number of plaques per well (pfu[b]/well)	As percentage of control value	EC_{50} (μg cm^{-3})	TC_{50} (μg cm^{-3})
 **12**	500	30	40		
	200	34	45		
	100	40	53		
	40	51	68	150	1000
	20	55	73		
	8	72	96		
	4	74	99		
 **16**	1000	20	27		
	500	30	40		
	200	39	52		
	100	55	73	250	> 1000
	40	56	75		
	20	61	81		
	8	66	88		
	4	79	105		
Control		75	100		

[a] The compounds were tested in Veros cells infected with HSV-1 17-I by using a plaque-reduction assay. [b] Plaque forming units.

o-(2-Hydroxyethyl)benzylamine {2-[o-(*Aminomethyl*)*phenyl*]*ethanol*} **2**.—A mixture of the phthalimido acetate **7** (30 g, 0.09 mol), hydrazine hydrate (7 cm^3, 0.14 mol) and ethanol (60 cm^3) was heated on a steam-bath for 10 min. A clear solution formed, which rapidly became a thick paste. Hydrochloric acid (100 cm^3, 10 mol dm^{-3}) was added slowly to the cooled mixture and the resulting mixture was heated on a steam-bath for 15 min. The cooled mixture was filtered and the filtrate was evaporated to ~30 cm^3. Solid potassium hydroxide was added (to pH 11 using test papers) and the solution was extracted with chloroform (4 × 50 cm^3). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated to afford the title compound as an oil (12.7 g, 90.7%). A portion (0.5 g) of the amine was treated with hydrochloric acid (5 cm^3; 10 mol dm^{-3}) and the solution was evaporated to leave a gum which rapidly crystallised. Recrystallisation from propan-2-ol gave the title compound hydrochloride (0.4 g), m.p. 161 °C (lit.,[10] 168–169 °C); δ([$^2H_6$]Me_2SO) 2.82 (2 H, t, *J* 6.23, ArCH_2), 3.62 (2 H, t, *J* 6.23, CH_2O), 4.05 (2 H, s, CH_2N), 5.5 (1 H, br s, OH, exch. with D_2O), 6.84–7.22 (4 H, m, Ar) and 8.4 (3 H, br s, NH_3^+, exch. with D_2O) [Found: C, 57.7; H, 7.75; N, 7.25; Cl, 19.0%; MH^+ (−Cl), 152. Calc. for $C_9H_{14}ClNO$: C, 57.6; H, 7.52; N, 7.46; Cl, 18.88%; MH(−Cl), 152].

5-Amino-1-[o-(2-hydroxyethyl)benzyl]imidazole-4-carboxamide **9**.—A solution of 2-amino-2-cyanoacetamide (1.5 g, 15 mmol), and triethyl orthoformate in acetonitrile (30 cm^3) was boiled under reflux for 45 min. A solution of the foregoing amino alcohol **2** (1.8 g, 10 mmol) in acetonitrile (5 cm^3) was added and the solution was boiled under reflux for 15 min. The *title compound* (2.2 g, 76%) precipitated from the cooled solution and was recrystallised from ethanol; m.p. 183–184 °C (decomp.); δ([$^2H_6$]Me_2SO) 2.81 (2 H, t, *J* 6.96, C$H_2$$CH_2$OH), 3.64 (2 H, t, *J* 6.96, CH_2CH_2OH), 4.79 (1 H, br s, OH, exch. with D_2O), 5.13 (2 H, s, CH_2N), 5.8 (2 H, br s, NH_2, exch. with D_2O), 6.63 (2 H, br s, $CONH_2$, exch. with D_2O) and 6.79–7.2 (5 H, m, Ar and CH=) (Found: C, 60.1; H, 6.25; N, 21.4%; MH^+, 261. Calc. for $C_{13}H_{16}N_4O_2$ requires C, 60.0; H, 6.19; N, 21.54%; MH, 261). The compound gave a strong Bratton-Marshall test[11] for a primary aromatic amine.

5-[N′-Benzoyl(thioureido)]-1-[o-(2-hydroxyethyl)benzyl]imidazole-4-carboxamide **10**.—A mixture of the foregoing aminoimidazole **9** (3 g, 11.5 mmol) and benzoyl isothiocyanate (1.8 cm^3, 13 mmol) in dry DMF (60 cm^3) was stirred at room temperature for 1.5 h. The solvent was evaporated off and the residue was triturated with water, when it readily solidified. The *title compound* (4.5 g, 92%) was crystallised from ethanol; m.p. 157–158 °C; δ([$^2H_6$]Me_2SO) 2.75 (2 H, t, *J* 6.96, C$H_2$$CH_2$OH), 3.5 (2 H, t, *J* 6.96, CH_2OH), 4.69 (1 H, br s, OH, exch. with D_2O), 5.25 (2 H, s, CH_2N), 6.95–8.0 (12 H, $CONH_2$, Ar and CH=N, former exch. with D_2O), 11.96 (1 H, s, N*H*COPh, exch. with D_2O) and 12.0 (1 H, s, CSNH, exch. with D_2O) (Found: C, 59.35; H, 4.8; N, 16.2%; MH^+, 424. $C_{21}H_{21}N_5O_3S$ requires C, 59.57; H, 5.0; N, 16.55%; MH, 424).

5-(1-Benzoyl-2-methyl-3-isothioureido)-1-[o-(2-hydroxyethyl)benzyl]imidazole-4-carboxamide **11**.—A solution of the foregoing thiourea **10** (2 g, 4.72 mmol) in 0.5 mol dm^{-3} sodium hydroxide (25 cm^3) was stirred with methyl iodide (0.6 cm^3, 9.6 mmol) for 1 h. The solution was adjusted to pH 6–7 using test papers with 2 mol dm^{-3} hydrochloric acid. The title compound (1.6 g, 77%) precipitated, was collected by filtration, and was washed with water. A similar yield was obtained when using methyl iodide and triethylamine in DMF. *Compound* **11** was crystallised from ethanol; m.p. 131–132 °C; δ($CDCl_3$) 2.48 (3 H, s, Me), 2.78 (2 H, t, *J* 6.96, C$H_2$$CH_2$OH), 3.77 (2 H, t, *J* 6.96, CH_2OH), 5.15 (2 H, s, CH_2N), 5.62 (1 H, br s, OH, exch. with D_2O), 6.94–7.93 (12 H, ArH, CH=N, $CONH_2$, latter exch. with D_2O) and 11.59 (1 H, s, NH, exch. with D_2O) (Found: C, 60.1; H, 5.0; N, 15.9%; MH^+, 438. $C_{22}H_{23}N_5O_3S$ requires C, 60.27; H, 5.29; N, 15.98%; MH, 438).

9-[o-(2-Hydroxyethyl)benzyl]guanine **12**.—The foregoing methylthio derivative **11** (0.6 g, 1.37 mmol) and aq. ammonia (30 cm^3; 33%) was heated at 100 °C in a sealed tube for 2 h. The solvent was evaporated off to give a solid. Crystallisation from methanol gave the *title compound* (0.2 g, 51%), m.p. 275 °C (decomp.); δ([$^2H_6$]Me_2SO) 2.87 (2 H, t, *J* 6.96, C$H_2$$CH_2$OH), 3.59 (2 H, t, *J* 6.96, CH_2OH), 4.78 (1 H, br s, OH, exch. with

D_2O), 5.20 (2 H, s, CH_2N), 6.82–7.24 (4 H, m, ArH), 7.72 (3 H, br s, CH=N, NH_2, latter exch. with D_2O) and 10.64 (1 H, br s, NH, exch. with D_2O) (Found: C, 58.8; H, 5.2; N, 24.4%; MH^+, 286. $C_{14}H_{15}N_5O_2$ requires C, 58.95; H, 5.3; N, 24.56%; MH, 286).

9-[o-(2-*Hydroxyethyl*)*benzyl*]*hypoxanthine* **13**.—A solution of the aminoimidazole **9** (1 g, 3.8 mmol) in a pre-mixed solution of formic acid (30 cm^3) and acetic anhydride (100 cm^3) was set aside overnight at room temperature. The solution was evaporated to leave a solid. This was heated on a steam-bath with saturated aq. sodium hydrogen carbonate (50 cm^3) for 15 min. The resulting solution was adjusted to pH 6–7 using test papers with 2 mol dm^{-3} hydrochloric acid to precipitate the *title compound* (1 g, 96%), m.p. 225–226 °C; $\delta([^2H_6]Me_2SO)$ 2.89 (2 H, t, *J* 6.96, CH_2CH_2OH), 3.6 (2 H, t, *J* 6.96, CH_2OH), 4.75 (1 H, br s, OH, exch. with D_2O), 5.45 (2 H, s, CH_2N), 6.84–7.22 (4 H, m, ArH), 8.05 (1 H, s, 8-H), 8.08 (1 H, s, 2-H) and 12.34 (1 H, br s, NH, exch. with D_2O) (Found: C, 62.1; H, 5.7; N, 20.55%; M^+, 270) $C_{14}H_{14}N_4O_2$ requires C, 62.2; H, 5.2; N, 20.74%; M, 270).

9-[o-(2-*Acetoxyethyl*)*benzyl*]*hypoxanthine* **14**.—A solution of compound **13** (1 g, 3.7 mmol) in pyridine (30 cm^3)–acetic anhydride (2.5 cm^3) was left at 5 °C overnight. The solution was evaporated and a solution of the residue in chloroform was washed successively with water (20 cm^3), saturated aq. sodium hydrogen carbonate (20 cm^3) and water (20 cm^3). The dried extract (anhyd. $MgSO_4$) was evaporated to leave a solid. The *title compound* (1 g, 87%) was crystallised from ethanol; m.p. 193–194 °C; $\delta(CDCl_3)$ 2.2 (3 H, s, Me), 2.87 (2 H, t, *J* 6.96, CH_2CH_2OAc), 4.16 (2 H, t, *J* 6.96, CH_2OAc), 5.2 (2 H, s, CH_2N), 6.92–7.35 (6 H, ArH, 2- and 8-H) and 8.89 (1 H, br s, NH, exch. with D_2O) (Found: C, 61.3; H, 5.1; N, 18.05%; M^+, 312. $C_{16}H_{16}NO_3$ requires C, 61.53; H, 5.16; N, 17.95%; M, 312).

9-[o-(2-*Hydroxyethyl*)*benzyl*]*adenine* **15**.—A solution of the acetate **14** (0.7 g, 2.24 mmol) in acetonitrile (15 cm^3) was treated with tetraethylammonium chloride (0.9 g, 5.44 mmol, previously dried over P_2O_5) and *N*,*N*-dimethylaniline (0.4 cm^3, 3.15 mmol) followed by phosphoryl trichloride (1.6 cm^3, 17.12 mmol). The mixture was heated on a steam-bath for 30 min and the solvents were evaporated off. The residue was dissolved in chloroform (50 cm^3) and the solution was added to ice-water (30 cm^3). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 50 cm^3) and the combined organic phases were washed successively with 10% aq. sodium hydrogen carbonate (3 × 25 cm^3) and water (2 × 25 cm^3). The dried (anhyd. $MgSO_4$) solution was evaporated to give an oil (1 g). This was heated in a sealed tube with saturated methanolic ammonia (50 cm^3) at 120 °C for 4 h. The solvent was evaporated off and the residue was triturated with water. The *title compound* (0.3 g, 49%) was crystallised from ethanol; m.p. 214–215 °C; $\delta([^2H_6]Me_2SO)$ 2.92 (2 H, t, *J* 6.96, CH_2CH_2OH), 3.56 (2 H, q, *J* 6.96 and 5.13, CH_2OH), 4.76 (1 H, t, *J* 6.96 and 5.13, OH, exch. with D_2O), 5.44 (2 H, s, CH_2N), 6.85–7.27 (6 H, ArH, NH_2, the latter exch. with D_2O), 8.13 (1 H, s, 8-H) and 8.14 (1 H, s, 2-H) (Found: C, 62.1; H, 5.5; N, 25.75%; M^+, 269. $C_{14}H_{15}N_5O$ requires C, 62.45; H, 5.62; N, 26.02%; M, 269).

1-[o-(2-*Hydroxyethyl*)*benzyl*]*thymine* **16**.—A solution of *N*-ethoxycarbonyl-3-methoxy-2-methylacrylamide **17**[4] (1 g, 5.35 mmol) and the amine **2** (1 g, 6.62 mmol) in butan-1-ol (5 cm^3) was boiled under reflux for 1 h. The solution was evaporated to dryness and the residue was treated with 2 mol dm^{-3} sodium hydroxide then was heated on a steam-bath for 5 min. The cooled solution was acidified with hydrochloric acid to precipitate a gummy solid. The aqueous phase was decanted and the gum was triturated with ethanol to give a solid. The *title compound* (0.7 g, 41%) was crystallised from ethanol; m.p. 179–180 °C; $\delta([^2H_6]Me_2SO)$ 1.75 (3 H, s, Me), 2.80 (2 H, t, *J* 6.96, CH_2CH_2OH), 3.54 (2 H, q, *J* 6.96 and 5.13, CH_2OH), 4.72 (1 H, s, OH, exch., with D_2O), 5.42 (2 H, s, CH_2N), 6.97–7.24 (4 H, m, ArH), 7.49 (1 H, s, 6-H) and 11.37 (1 H, s, 3-NH, exch. with D_2O) (Found: 64.4; H, 6.1; N, 10.6%; M^+, 260. $C_{14}H_{16}N_2O_3$ requires C, 64.61; H, 6.2; N, 10.77%; M, 260).

1-[-(2-*Hydroxyethyl*)*benzyl*]-2-*thiothymine* **18**.—A solution of 3-methoxy-2-methylacryloyl isothiocyanate[3] **19** (1 g, 6.32 mmol) and the amine **2** (0.96 g, 6.36 mmol) in diethyl ether (5 cm^3) was warmed on a steam-bath for 5 min, then 2 mol dm^{-3} sodium hydroxide (4 cm^3) was added and the mixture was heated on a steam-bath for 5 min. Any excess of diethyl ether was removed by evaporation and the resulting aqueous solution was acidified with hydrochloric acid to precipitate a gum which rapidly solidified. It was collected, and washed with water. The *title compound* (0.8 g, 46%) was crystallised from methanol; m.p. 197–198 °C; $\delta([^2H_6]Me_2SO)$ 1.73 (3 H, s, Me), 2.81 (2 H, t, *J* 6.96, CH_2CH_2OH), 3.62 (2 H, t, *J* 6.96, CH_2OH), 4.75 (1 H, s, OH, exch. with D_2O), 5.47 (2 H, s, CH_2N), 6.83–7.24 (4 H, m, ArH), 7.7 (1 H, s, 6-H) and 12.7 (1 H, s, 3-NH, exch. with D_2O) (Found: C, 59.7; H, 5.7; N, 10.0%; M^+, 276. $C_{14}H_{16}N_2S{\cdot}\frac{1}{4}H_2O$ requires C, 59.89; H, 5.93; N, 9.98%; M, 276).

5-(*Ethoxycarbonylcarbamoyl*)-1-[o-(2-*hydroxyethyl*)*benzyl*]-*uracil* **21**.—A solution of ethoxymethylenemalonylurethane[1] **20** (3 g, 10 mmol) and the amine **2** (1.5 g, 10 mmol) in methanol (5 cm^3) was heated on a steam-bath for 10 min. The *title compound* was precipitated as a crystalline solid (2.8 g, 78%) and was recrystallised from ethanol; m.p. 270 °C; $\delta([^2H_6]Me_2SO)$ 1.22 (3 H, t, *J* 6.96, Me), 2.79 (2 H, t, *J* 6.95, CH_2CH_2OH), 3.6 (2 H, t, *J* 6.96, CH_2OH), 4.14 (2 H, q, *J* 6.96, CH_2Me), 4.71 (1 H, br s, OH, exch. with D_2O), 5.15 (2 H, s, CH_2N), 7.06–7.28 (4 H, m, ArH), 8.57 (1 H, s, 6-H), 11.15 (1 H, s, 3-NH, exch. with D_2O) and 12.27 (1 H, s, CONH, exch. with D_2O) (Found: C, 56.2; H, 5.25; N, 11.6%; MH^+, 362. $C_{17}H_{19}N_3O_6$ requires C, 56.51; H, 5.31; N, 11.63%; MH, 362).

1-[o-(2-*Hydroxyethyl*)*benzyl*]*uracil*-5-*carboxylic Acid* **22**.—A solution of the uracil **21** (2 g, 5.54 mmol) in 2 mol dm^{-3} sodium hydroxide (25 cm^3) was boiled under reflux for 3 h. The solution was acidified with hydrochloric acid to give a solid precipitate. The *title product* (1.3 g, 81%) was collected, and was crystallised from ethanol; m.p. 197–198 °C; $\delta([^2H_6]Me_2SO)$ 2.83 (2 H, t, *J* 6.23, CH_2CH_2OH), 3.75 (2 H, t, *J* 6.23, CH_2OH), 4.72 (1 H, br s, OH, exch. with D_2O), 5.16 (2 H, s, CH_2N), 7.08–7.22 (4 H, m, ArH), 8.59 (1 H, s, 6-H) and 12.5 (2 H, br s, NH, CO_2H, both exch. with D_2O) (Found: C, 57.9; H, 4.7; N, 9.7%; M^+, 290. $C_{14}H_{14}N_2O_5$ requires C, 57.9; H, 4.86; N, 9.65%; M, 290).

1-[o-(2-*Hydroxyethyl*)*benzyl*]*uracil* **23**.—A solution of the acid **22** (0.5 g, 1.72 mmol) in *N*-ethylmorpholine (8 cm^3) was boiled under reflux for 1 h. The solution was evaporated and the residue was treated with water to produce a solution, which was acidified with hydrochloric acid to give a solid precipitate. The *title compound* (0.26 g, 62%) was collected and was crystallised from ethanol; m.p. 145–146 °C; $\delta([^2H_6]Me_2SO)$ 2.8 (2 H, t, *J* 6.96, CH_2CH_2OH), 3.6 (2 H, t, *J* 6.96, CH_2OH), 4.73 (1 H, br s, OH, exch. with D_2O), 4.95 (2 H, s, CH_2N), 6.98–7.61 (6 H, m, ArH, 5- and 6-H) and 11.37 (1 H, br s, 3-NH, exch. with D_2O) (Found: C, 63.3; H, 5.4; N, 11.3%; M^+, 246. $C_{13}H_{14}N_2O_3$ requires C, 63.41; H, 5.73; N, 11.38%; M, 246).

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