Purines, Pyrimidines and Imidazoles. Part 66.[1] New Syntheses of Some Uridine and *N*-Alkoxycarbonyl 5-carboxamides, *N*-carbamoyl 5-carboxamides and 5-carboxamides

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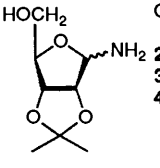
Ethoxymethylene-*N,N'*-(methoxy-, ethoxy- and benzyloxy-carbonyl)malonamides have been prepared from the corresponding *N,N'*-alkoxycarbonylmalonamides with triethyl orthoformate and acetic anhydride. The three ethoxymethylene derivatives with primary alkyl- or aryl-amines including 2,3-*O*-isopropylidene-D-ribofuranosylamine gave 1-substituted-*N*-alkoxycarbonyluracil-5-carboxamides. The three isopropylidene nucleosides were isolated as β-anomers but in one example (benzyloxy) the α-anomer was also produced in small yield. The four isopropylidene nucleosides were deblocked with 50% aqueous trifluoroacetic acid to afford *N*-methoxy-, ethoxy- and benzyloxy-carbonyluridine-5-carboxamides and *N*-benzyloxycarbonyl-1-α-D-ribofuranosyluracil-5-carboxamide. Hydrolysis of each of the three β-anomeric isopropylidene nucleosides with sodium hydroxide produced 1-(2,3-*O*-isopropylidene)uridine-5-carboxamide which with aqueous trifluoroacetic acid gave uridine-5-carboxamide. Benzyloxycarbonyluridine-5-carboxamide however with aqueous ammonia (*d* 0.88) at room temperature soon gave *N*-carbamoyluridine-5-carboxamide in good yield. *N*-Carbamoyluridine-5-carboxamide was obtained directly from *N,N'*-ethoxycarbonylethoxymethylenemalonamide and aqueous ammonia. *N*-Benzyloxycarbonyluridine-5-carboxamide was converted into *N*-benzyloxycarbonyl-2'-deoxyuridine-5-carboxamide by successive reaction with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, *p*-tolyl chlorothioformate and tributyltin hydride followed by deblocking with tetrabutylammonium fluoride. The deoxyuridine with aqueous ammonia (*d* 0.88) at room temperature gave *N*-carbamoyl-2'-deoxyuridine 5-carboxamide in high yield. Structures were confirmed by elemental analysis, and FAB mass and ^{1}H NMR spectroscopy.

We have earlier described[2] the synthesis of uridine-5-carbonitrile by reaction of 2,3-*O*-isopropylidene-D-ribofuranosylamine 1 with α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide under mild conditions followed by acid deblocking of the resulting 2,3-*O*-isopropylideneuridine-5-carbonitrile. We have been interested to extend this synthesis to prepare 5-substituted uridines with additional hydrogen bonding capacity in the 5-substituent as potential antitumour or antiviral agents. *N,N'*-Ethoxycarbonylmalonamide **2** prepared by reaction of malonic acid, urethane and acetic anhydride,[3] when heated with triethyl orthoformate and acetic anhydride for 1 h readily gave the crystalline ethoxymethylene derivative **5** (described briefly in an earlier communication[4]). When a solution of **5** in methanol was heated for 15 min with a slight molar excess of methylamine or benzylamine, *N,N'*-ethoxycarbonyl-1-methyl(or benzyl)uracil-5-carboxamides **8** and **9** respectively were produced in good yield.



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$CH_2(CONHCO_2R)_2$ $EtOCH{=}C(CONHCO_2R)_2$

2; R = Et **5**; R = Et
3; R = Me **6**; R = Me
4; R = CH_2Ph **7**; R = CH_2Ph

In contrast, preparation of *N*-ethoxycarbonyl-1-phenyluracil-5-carboxamide **10**, from **5** and aniline required additional brief warming with sodium hydroxide (1 mol dm^{-3}) followed by acidification.

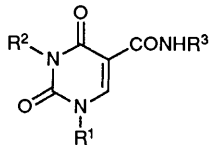
In a similar manner the crystalline ethoxymethylene derivatives **6** and **7** were readily prepared in good yield from the corresponding malonamides **3** and **4**. Prolonged treatment of **9** with sodium hydroxide (2 mol dm^{-3}) on a steam bath for 5 min produced the corresponding carboxamide **11** in excellent yield. Also it is noteworthy that the 5-*N*-alkoxycarbonyluracils were found to be methylated under exceptionally mild conditions. Thus **9** and **10** with methyl iodide and triethylamine in DMF (dimethylformamide) solution at room temperature over 1 h gave high (>80%) yields of the 3-methyl derivatives **12** and **13** respectively.

Having established conditions for production of the uracils, especially the stability of the carbamate group to basic and acidic conditions, we further examined the reaction of **7** with 2,3-*O*-isopropylideneribofuranosylamine[2] **1**. A solution of the two substances in methanol containing triethylamine was warmed for 15 min and then acidified to give a precipitate of the pure *N*-benzyloxycarbonyl-2',3'-*O*-isopropylideneuridine-5-carboxamide **14** in good (57%) yield. The corresponding α-anomer **17** (15% yield) separated from the filtrate when it was stored at 0 °C overnight. Similarly the ethoxymethylene derivatives **5** and **6** produced the corresponding isopropylideneuridines **15** and **16** respectively. In each of the last two reactions no α-isomer separated from the acidified filtrates. The reactions offer a particularly facile route to 5-substituted uridine derivatives.

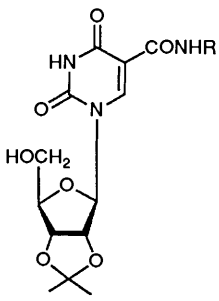
The four isopropylidene nucleosides were readily deblocked by treatment with 50% aqueous trifluoroacetic acid over 30 min at room temperature to produce the nucleosides **18**, **19**, **20** and **21** in yields of 62–85%. The structures assigned to the nucleosides were confirmed by elemental analysis, mass (FAB MH^+, 462, 400, 386 and 462 respectively) and ^{1}H NMR spectra. In particular, the α-anomer **21** had δ 6.05 (1'-H) compared to δ 5.78 (1'-H) for the β-anomer **18**.

Also for the isopropylidene α-anomer **17** $\Delta\delta = 0.04$ whereas the related β-anomer **14** had $\Delta\delta = 0.19$ in agreement with Imbach's rules.[5]

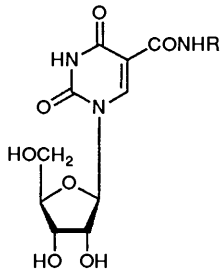
In addition, a solution of one of the isopropylidene nucleosides **14**, **15** or **16** in aqueous triethylamine and sodium



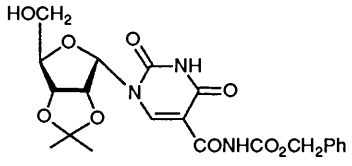
8; R^1 = Me, R^2 = H, R^3 = CO_2Et
9; R^1 = CH_2Ph, R^2 = H, R^3 = CO_2Et
10; R^1 = Ph, R^2 = H, R^3 = CO_2Et
11; R^1 = CH_2Ph, R^2 = R^3 = H
12; R^1 = CH_2Ph, R^2 = Me, R^3 = CO_2Et
13; R^1 = Ph, R^2 = Me, R^3 = CO_2Et
25; R^1 = R^2 = H, R^3 = $CONH_2$



14; R = CO_2CH_2Ph
15; R = CO_2Et
16; R = CO_2Me
22; R = H



18; R = CO_2CH_2Ph
19; R = CO_2Et
20; R = CO_2Me
23; R = H
24; R = $CONH_2$



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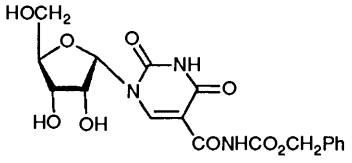

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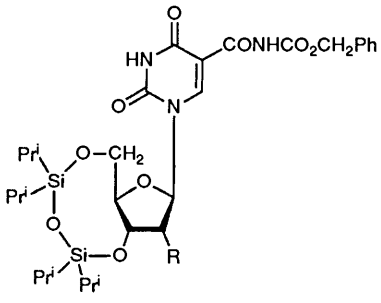
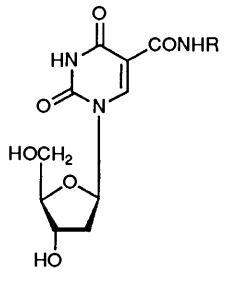
hydroxide (2 mol dm^{-3}) when warmed for 5 min gave, after acidification, a precipitate of 2,3-*O*-isopropylideneuridine-5-carboxamide **22**. This was readily deblocked by treatment with 50% aqueous trifluoroacetic acid to produce uridine-5-carboxamide **23**. The structure of **23** was confirmed by elemental analysis and mass (FAB MH^+ 288) and ^1H NMR spectroscopy.

In contrast, reaction of the nucleoside **18** with aqueous ammonia (*d* 0.88) gave a smooth conversion into *N*-carbamoyluridine-5-carboxamide **24** in high (85%) yield. The corresponding aglycone, *N*-carbamoyluracil-5-carboxamide **25** was obtained directly from the ethoxymethylene derivative **5** with aqueous ammonia in good yield.

Reaction of the nucleoside **18** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine produced the cyclic derivative **26** which with *p*-tolylchlorothioformate in acetonitrile solution



26; R = OH
27; R = OCSPhMe (*p*)
28; R = H



29; R = CO_2CH_2Ph
30; R = $CONH_2$

containing 4-dimethylaminopyridine at room temperature gave the thiocarbonate **27**. When this was heated in toluene solution with tributyltin hydride 'in the presence of 2,2'-azo(2-methylpropane nitrile) *N*-benzyloxycarbonyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-2'-deoxyuridine-5-carboxamide **28** was produced in 70% yield. This was readily deblocked by treatment with tetrabutylammonium fluoride in THF at room temperature to afford the crystalline *N*-benzyloxycarbonyl-2'-deoxyuridine-5-carboxamide **29**. The structure was readily confirmed by elemental analysis and mass (FAB, MH^+ 406) and ^1H NMR spectroscopy. Reaction of **29** with aqueous ammonia (*d* 0.88) gave a high yield (88%) of *N*-carbamoyl-2'-deoxyuridine-5-carboxamide **30**.

Experimental

^1H NMR spectra were measured at 270 MHz on a JEOL GX 270 spectrometer using $(CH_3)_4Si$ (TMS) as internal standard with $(CD_3)_2SO$ as solvent, *J* values are given in Hz. FAB mass spectra were provided by the SERC MS service centre, University College of Swansea with 3-nitrobenzyl alcohol as a matrix. Analytical TLC was carried out on DC-ALUFOLIEN Kieselgel 60 F_{254} plates and Merck 9385 Kieselgel 60 (230–400 mesh) was used for flash column chromatography.

General Procedure for the Preparation of N,N'-*(Alkoxycarbonyl)malonamides.*—A suspension of malonic acid (0.5 mol) and methyl, ethyl or benzyl carbamate (1 mol) in acetic anhydride (200 cm^3) was heated on a steam bath until the temperature of the resulting solution reached 100–110 °C. The solution was allowed to cool to 100 °C and then evaporated under reduced pressure to syrup which rapidly crystallised on addition of ether. The solid was collected and washed with ether. N,N'-*(Methoxycarbonyl)malonamide* **3** (90 g, 82.5%) crystallised from ethanol as needles, m.p. 156 °C (Found: C, 38.4; H, 4.7; N, 12.8%; M^+, 218. $C_7H_{10}N_2O_6$ requires C, 38.53; H, 4.62; N, 12.84%; *M*, 218); N,N'-*(benzyloxycarbonyl)malonamide* **4** (156 g, 84%) crystallised from ethanol, as needles, m.p. 178 °C (Found: C, 6.5; H, 4.8; N, 7.5%; M^+, 370. $C_{19}H_{18}N_2O_6$ requires C, 61.62; H, 4.9; H, 7.56%; *M*, 370. *N,N'*-(Ethoxycarbonyl)-malonamide **3** (86 g, 70%) had m.p. and mixed m.p. 123 °C (lit.,[3] 124 °C).

*General Procedure for the Preparation of Ethoxymethylene-*N,N'-*alkoxycarbonylmalonamides.*—A solution of the crude malonamides produced in the latter procedure (sufficiently pure for this procedure) with triethyl orthoformate (84 cm^3) and acetic anhydride (136 cm^3) was boiled under reflux for 40 min. The cooled solution gave a crystalline precipitate which was collected and washed with ether. The compounds were sufficiently pure to use in the later steps but could be crystallised from ethyl acetate. *Ethoxymethylene*-N,N'-*(methoxycarbonyl)-malonamide* **6** (90 g, 66% yield based on the malonic acid used in the first procedure), m.p. 176–178 ° (Found: C, 43.7; H, 5.15 N, 10.15%; M^+, 274. $C_{10}H_{14}N_2O_7$ requires, C, 43.79; H, 5.14; N, 10.22%; *M*, 274); δ_H 1.53 (3 H, t, *J* 7.0, CH_3CH_2), 3.76 (3 H, s, CH_3O *trans* to OEt), 3.83 (3 H, s, CH_3O *cis* to OEt), 4.52 (2 H, q, *J* 7.0, CH_2), 8.34 (1 H, s, CH), 9.24 (1 H, br s, NH, *trans* to OEt) and 11.28 (1 H, br s, NH, *cis* to OEt).

N,N'-*(Ethoxycarbonyl)ethoxymethylenemalonamide* **5** (70% yield), m.p. 122 °C (Found: 47.5; H, 5.9; N, 9.15%; M^+, 302. $C_{12}H_{18}N_2O_7$ requires C, 47.68; H, 6.0; N, 9.27%; *M*, 302); δ_H 1.25–1.36 (6 H, 2 t, 2 × $CO_2CH_2CH_3$, *J* 7.1), 1.53 (3 H, t, *J* 7.0, $CHOCH_2CH_3$), 4.25 (4 H, 2q, *J* 7.1, 2 × $CO_2CH_2CH_3$), 4.53 (2 H, q, *J* 7.0, $CHOCH_2CH_3$), 8.34 (1 H, s, CH), 9.20 (1 H, bs, NH, *trans* to OEt) and 11.25 (1 H, br s, NH *cis* to OEt).

N,N'-*(Benzyloxycarbonyl)ethoxymethylenemalonamide* **7** (60% yield) m.p. 124–126 °C (Found: C, 61.85; H, 5.35; N, 6.5%; M^+, 426. $C_{22}H_{22}N_2O_7$ required C, 61.97; H, 5.2; N, 6.57%; *M*, 426); δ_H 1.48 (3 H, t, *J* 6.96, CH_3), 4.48 (2 H, q, *J* 6.96, CH_2-

CH_3), 5.18 (2 H, s, CH_2Ph *trans* to OEt), 5.23 (2 H, s, CH_2Ph *cis* to OEt), 7.37 (10 H, m, Ar), 8.31 (1 H, s, CH), 9.23 (1 H, br s, NH *trans* to OEt) and 11.33 (1 H, br s, NH *cis* to OEt).

N-*Ethoxycarbonyl*-1-*methyluracil*-5-*carboxamide* **8**.—A solution of the ethoxymethylenemalonylurethane **5** (3.6 mmol) and methylamine (3.8 mmol) in methanol (20 cm^3) was heated on a steam bath for 15 min. The precipitate was collected and washed with ethanol to produce **8** (0.56 g, 65% yield) which recrystallised from butan-2-one as needles, m.p. 245–250 °C (Found: C, 44.75; H, 4.7; N, 17.3%; M^+, 241. $C_9H_{11}N_3O_5$ requires C, 44.8; H, 4.6; N, 17.42%; *M*, 241); δ_H 1.23 (3 H, t, CH_3CH_2), 3.34 (3 H, s, NCH_3), 4.14 (2 H, q, CH_2CH_3), 8.68 (1 H, s, 6-H), 11.19 (1 H, s, CONH exch. with D_2O) and 12.14 (1 H, br s, 3-NH exch. with D_2O).

1-*Benzyl*-N-*ethoxycarbonyluracil*-5-*carboxamide* **9**.—The method used for the 1-methyl derivative was adopted. The product **9** (82% yield) separated from butan-2-one as needles, m.p. >270 °C (Found: C, 56.6; H, 4.85; N, 13.1%; M^+, 317. $C_{15}H_{15}N_3O_5$ requires C, 56.78; H, 4.76; N, 13.25%; *M*, 317); δ_H 1.31 (3 H, t, *J* 6.96, CH_3), 4.09 (2 H, q, *J* 6.96, CH_2O), 4.95 (2 H, s, CH_2Ph), 7.52 (5 H, m, Ph), 11.15 (1 H, s, CONH, exch. with D_2O) and 12.34 (1 H, br s, 3-NH exch. with D_2O).

1-*Benzyluracil*-5-*carboxamide* **11**.—A solution of the foregoing uracil (0.5 g) in a little triethylamine–water (50%; 2 cm^3) and sodium hydroxide (2 mol dm^{-3}; 2 cm^3) was heated on a steam bath for 5 min. The cooled solution was acidified with hydrochloric acid (2 mol dm^{-3}) to give a solid precipitate of the carboxamide **11** (0.4 g), m.p. 262 °C (decomp.) (Found: C, 58.5; H, 4.65; N, 17.05%; M^+, 245. $C_{12}H_{11}N_3O_3$ requires C, 58.77; H, 4.5; N, 17.14%; *M*, 245); δ 5.05 (2 H, s, CH_2Ph), 7.34 (5 H, m, Ph), 7.5 (1 H, br s, $CONH_a$), 8.15 (1 H, s, $CONH_b$), 8.79 (1 H, s, 6-H), 11.91 (1 H, s, 3-NH, exch. with D_2O).

1-*Benzyl*-N-*ethoxycarbonyl*-3-*methyluracil*-5-*carboxamide* **12**.—A solution of 1-benzyl-*N*-ethoxycarbonyluracil-5-carboxamide (1.89 mmol) in dry triethylamine (5 cm^3) and dimethylformamide (10 cm^3) with methyl iodide (4.93 mmol) was set aside at room temperature for 1 h then evaporated under reduced pressure to dryness. The residue with water gave a solid which was collected. The 3-*methyluracil* (82% yield) crystallised from methanol as needles, m.p. 185 °C (Found: C, 57.95; H, 5.1; N, 12.63%; MH^+, 332. $C_{16}H_{17}N_3O_5$ requires C, 58.0; H, 5.17; N, 12.68%; *M*H, 332); δ_H 1.23 (3 H, t, *J* 6.96, CH_3CH_2O), 3.22 (3 H, s, NCH_3), 4.14 (2 H, q, *J* 6.96, CH_3CH_2O), 5.16 (2 H, s, CH_2Ph), 7.36 (5 H, m, Ph), 8.87 (1 H, s, 6-H) and 11.23 (1 H, s, CONH exch. with D_2O).

N-*Ethoxycarbonyl*-3-*methyl*-1-*phenyluracil*-5-*carboxamide* **13**. Prepared by the method used for the 1-benzyl derivative. Yield (80%), m.p. 179 °C (Found: C, 56.6; H, 4.8; N, 13.1%; MH^+, 318. $C_{15}H_{15}N_3O_5$ requires C, 56.78; H, 4.77; N, 13.25%; *M*H, 318). δ_H 1.24 (3 H, t, *J* 6.96, CH_3CH_2), 3.28 (3 H, s, NCH_3), 4.16 (2 H, q, *J* 6.96, CH_3CH_2O), 7.52 (5 H, m, Ph), 8.41 (1 H, s, 6-H and 11.22 (1 H, s, CONH, exch. with D_2O).

N-*Carbamoyluracil*-5-*carboxamide* **25**.—Ethoxymethylene-*N,N'*-ethoxycarbonylmalonamide (0.5 g) was set aside with aqueous ammonia (*d* 0.88, 40 cm^3) for 1 h then evaporated to dryness. The residue was co-evaporated with ethanol to give N-*carbamoyluracil*-5-*carboxamide* which separated from ethanol as needles (0.25 g), m.p. >280° (Found: C, 36.25; H, 3.1; N, 28.4%; M^+, 198. $C_6H_6N_4O_4$ requires C, 36.36; H, 3.03; N, 28.28%; *M*, 198); δ_H 7.45 (1 H, s, $CONH_a$), 7.79 (1 H, s, $CONH_b$), 8.32 (1 H, s, 6-H), 10.63 (1 H, s, CONHCO exch. with D_2O) and 11.93 (1 H, br s, 3-NH, exch. with D_2O); 1-NH signal not seen.

General Procedure for the Preparation of N-*Alkoxycarbonyl*-1-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)*uracil*-5-*carboxamide*.—Solutions of 2,3-*O*-isopropylidene-D-ribofuranosylamine toluene-*p*-sulphonate[2] (3.9 mmol) in triethylamine (8 cm^3) and methanol (8 cm^3) and the appropriate ethoxymethylenemalonylurethane (3.3 mmol) in methanol (10 cm^3) were mixed and heated on a steam bath for 15 min. The solution was evaporated under reduced pressure to about half volume and then acidified to pH 6 with HCl (2 mol cm^{-3}) to give a solid precipitate. The isopropylidene nucleosides recrystallised from ethanol as hydrated needles.

1-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-*methoxycarbonyluracil*-5-*carboxamide* **16**. (41% yield), m.p. 226–228 °C (Found: C, 45.2; H, 4.7; N, 10.6%; MH^+, 386. $C_{15}H_{19}N_3O_9 \cdot \frac{3}{4}H_2O$ requires C, 45.17; H, 5.18; N, 10.54%; *M*H, 386); δ_H 1.29, 1.49 (6 H, 2s, Me_2C), 3.6 (2 H, m, 5'-H, 5''-H), 3.69 (3 H, s, OMe), 4.3 (1 H, m, 4'-H), 4.75 (1 H, m, 3'-H), 4.93 (1 H, m, 21-H), 5.21 (1 H, br s, 5'-HO exch. with D_2O), 5.85 (1 H, d, *J* 1.83, 1'-H), 8.83 (1 H, s, 6-H), (1 H, br s, CONH, exch. with D_2O) and 12.24, 11.16 (1 H, s, 3-NH, exch. with D_2O).

N-*Ethoxycarbonyl*-1-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)*uracil*-5-*carboxamide* **15**. (45% yield), m.p. 228–230 °C (Found: C, 47.72; H, 5.23; N, 10.83%; MH^+, 400. $C_{16}H_{21}N_3O_9 \cdot \frac{1}{4}H_2O$ requires C, 47.58; H, 5.32; N, 10.41%; *M*H, 400); 1.23–1.48 (9 H, m, CMe_2, CH_2Me), 3.60 (2 H, br s, 5',5''-H), 4.14 (2 H, q, CH_2Me), 4.30 (1 H, m, 4'-H), 4.76 (1 H, m, 3'-H), 4.92 (1 H, m, 2'-H), 5.20 (1 H, m, 5'-HO exch. with D_2O), 5.85 (1 H, d, *J* 1.8, 1'-H), 8.83 (1 H, s, 6-H), 11.10 (1 H, s, CONH, exch. with D_2O) and 12.53 (1 H, br s, 3-NH exch. with D_2O).

N-*Benzyloxycarbonyl*-1-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)*uracil*-5-*carboxamide* **14**. (57% yield), m.p. 232–234 °C (Found: C, 54.15; H, 4.9; N, 9.05%; MH^+, 462. $C_{21}H_{23}N_3O_9 \cdot \frac{1}{4}H_2O$ requires C, 54.13; H, 5.05; N, 9.02%; *M*H 462); δ_H 1.29, 1.48 (6 H, 2s, Me_2C), 3.60 (2 H, m, 5'5''-H), 4.29 (1 H, m, 4'-H), 4.76 (1 H, m, 3'-H), 4.93 (1 H, m, 2'-H), 5.18 (2 H, s, CH_2Ph), 5.20 (1 H, m, 5'-HO, exch. with D_2O), 5.85 (1 H, d, *J* 1.8, 1'-H), 7.38 (5 H, m, Ph), 11.21 (1 H, s, CONH, exch. with D_2O) and 12.25 (1 H, s, 3-NH, exch. with D_2O); N-*benzyloxycarbonyl*-1-(2,3-O-*isopropylidene*-α-D-*ribofuranosyl*)*uracil*-5-*carboxamide* **17** (15% yield) separated from the acidified mother liquor upon storage at 0 °C overnight; it had m.p. 116–118 °C (Found: C, 54.2; H, 5.0; N, 9.2%; MH^+, 462. $C_{21}H_{23}N_3O_9$ requires C, 54.66; H, 5.02; N, 9.11%; *M*H, 462); δ_H 1.27, 1.31 (6 H, 2s, Me_2C), 3.61 (2 H, m, 5',5''-H), 4.46 (1 H, m, 4'-H), 4.85 (2 H, m, 3'-H, 2'-H), 5.18 (2 H, s, CH_2Ph), 5.27 (1 H, d, *J* 4.03, 1'-H), 7.36 (5 H, m, Ph), 11.19 (1 H, s, CONH, exch. with D_2O) and 12.34 (1 H, br s, 3-NH, exch. with D_2O).

General Procedure for the Preparation of N-*Alkoxycarbonyl*-1-α- *and* -β-D-*ribofuranosyluracil*-5-*carboxamides*.—The foregoing appropriate isopropylidene derivative (7.5 mmol) was dissolved in aqueous trifluoroacetic acid (20 cm^3) and set aside at room temperature for 30 min. The solution was evaporated to dryness under reduced pressure and the residue co-evaporated under reduced pressure several times with ethanol to give a solid residue. The nucleosides recrystallised from ethanol as needles:

N-*Methoxycarbonyl*-1-β-D-*ribofuranosyluracil*-5-*carboxamide* **20**. (62% yield) m.p. 198–200 °C (Found: C, 41.7; H, 4.25; N, 12.35%; MH^+, 346. $C_{12}H_{15}N_3O_9$ requires C, 41.75; H, 4.4; N, 12.15%; *M*H, 346); δ_H 3.54 (2 H, m, 5',5''-H), 3.69 (3 H, s, Me), 3.96 (2 H, m, 3'-H, 4'-H), 4.00 (1 H, m, 2'-H), 5.13 (1 H, d, *J* 5.13, 3'-HO, exch. with D_2O), 5.25 (1 H, m, 5'-HO, exch. with D_2O) and 5.51 (1 H, d, *J* 5.11 2'-HO, exch. with D_2O).

N-*Ethoxycarbonyl*-1-β-D-*ribofuranosyluracil*-5-*carboxamide* **19**. (74% yield), m.p. 208–221 °C (Found: C, 43.05; H, 4.6; N, 12.0%; MH^+, 360. $C_{13}H_{17}N_3O_9$ requires C, 43.45; H, 4.77; N, 11.7%; *M*H, 360); δ_H 1.23 (3 H, t, *J* 7.3, Me), 3,54 (2 H, m, 5',5''-H), 3.93–4.15 (5 H, m, CH_2, 2'-H, 3'-H, 4'-H), 5.13 (1 H, m,

3′-HO, exch. with D_2O), 5.24 (1 H, m, 5′-HO, exch. with D_2O), 5.51 (1 H, m, 2′-HO, exch. with D_2O), 5.81 (1 H, d, *J* 3.66, 1′-H), 9.08 (1 H, s, 6-H), 11.10 (1 H, s, CONH, exch. with D_2O) and 12.18 (1 H, bs, 3-NH, exch. with D_2O).

N-*Benzyloxycarbonyl*-1-α-D-*ribofuranosyluracil*-5-*carboxamide* **21** (85% yield), m.p. 115–118 °C (Found: C, 51.0; H, 4.5; N, 9.65%; MH^+, 422). $C_{18}H_{19}N_3O_9$ requires C, 51.3; H, 4.54; N, 9.98%; *M*H, 422); δ_H 3.65 (2 H, m, 5′,5″-H), 4.08 (2 H, m, 3′-H, 4′-H), 4.19 (1 H, m, 2′-H), 4.91 (1 H, m, 3′-HO, exch. with D_2O), 5.18 (3 H, m, CH_2Ph, 5′-HO, latter exch. with D_2O), 5.60 (1 H, d, *J* 4.4, 2′-HO, exch. with D_2O), 6.05 (1 H, d, *J* 3.3, 1′-H), 7.4 (5 H, m, Ph), 11.24 (1 H, s, CONH, exch. with D_2O) and 12.22 (1 H, br s, 3-NH, exch. with D_2O).

N-*Benzyloxycarbonyl*-1-β-D-*ribofuranosyluracil*-5-*carboxamide* **18**. (79% yield), m.p. 148–150 °C (Found: C, 49.8; H, 4.3; N, 9.95%; MH^+, 422. $C_{18}H_{19}N_3O_9 \cdot \frac{3}{4}H_2O$ requires C, 49.71; H, 4.75; N, 9.65%; *M*H, 422); δ_H 3.66 (2 H, m, 5′,5″-H), 3.79 (2 H, m, 3′-H, 4′-H), 4.09 (1 H, m, 2′-H), 5.14 (1 H, d, 3′-HO, exch. with D_2O), 5.52 (1 H, d, *J* 5.12, 2′-HO, exch. with D_2O), 5.78 (1 H, d, *J* 3.67, 1′-H), 7.40 (5 H, m, Ph), 11.23 (1 H, s, CONH, exch. with D_2O) and 12.2 (1 H, br s, 3-NH exch. with D_2O).

N-*Carbamoyluridine*-5-*carboxamide* **24**.—A solution of the foregoing nucleoside (1.6 mmol) in aqueous ammonia (*d* 0.88; 40 cm^3) was set aside at room temperature for 1 h; a precipitate formed after 30 min. The solution was evaporated to dryness and the residue co-evaporated several times with ethanol. The *nucleoside* (85% yield) crystallised from ethanol as needles, m.p. 204–206 °C (Found: C, 39.6; H, 4.3; N, 16.8%; MH^+, 331. $C_{11}H_{14}N_4O_8$ requires C, 40.0; H, 4.27; N, 16.97%; *M*H, 331); δ_H 3.56–3.73 (2 H, m, 5′,5″-H), 3.97 (2 H, m, 2′-H, 3′-H), 4.09 (1 H, m, 4′-H), 5.16 (2 H, 5′-HO, 3′-HO, both exch. with D_2O), 5.54 (1 H, d, *J* 4.93, 2′-HO, exch. with D_2O), 5.78 (1 H, d, *J* 3.66, 1′-H), 7.46 (1 H, s, $CONH_a$), 7.77 (1 H, s, $CONH_b$), 9.05 (1 H, s, 6-H), 10.63 (1 H, s, CONHCO exch. with D_2O) and 12.2 (1 H, s, 3-NH, exch. with D_2O).

2,3-O-*Isopropylideneuridine*-5-*carboxamide* **22**.—A solution of either of the isopropylidene nucleosides **14**, **15** or **16** (1 mmol) in 50% aqueous triethylamine (2 cm^3) and sodium hydroxide (2 mol dm^{-3}; 1.5 cm^3) was warmed on a steam bath for 5 min then cooled and adjusted to pH 7.5 with hydrochloric acid (2 mol dm^{-3}). The precipitate was collected, washed with water and dried to give the *isopropylidene nucleoside* (73% yield), m.p. 218–220 °C (decomp.) (Found: C, 47.7; H, 5.2; N, 12.8%; MH^+, 328. $C_{13}H_{17}N_3O_7$ requires C, 47.7; H, 5.2; N, 12.84%; *M*H, 328); δ_H 1.29, 1.48 (6 H, 2s, 2 × CH_3), 3.57 (2 H, m, 5′,5″-H), 4.2 (1 H, m, 4′-H), 4.75 (1 H, m, 3′-H), 4.93 (1 H, m, 2′-H), 5.13 (1 H, br s, 5′-HO, exch. with D_2O), 5.82 (1 H, d, *J* 2.2, 1′-H), 7.56 (1 H, bs, $CONH_a$), 8.13 (1 H, bs, $CONH_b$), 8.61 (1 H, s, 6-H) and 11.89 (1 H, br s, 3-NH exch. with D_2O).

Uridine-5-*carboxamide* **23**.—A solution of the foregoing isopropylidene derivative (0.6 g) in 50% aqeuous trifluoroacetic acid (15 cm^3) was set aside at room temperature for 30 min and then evaporated to dryness under reduced pressure. The residue was co-evaporated with ethanol to give a solid. The *nucleoside* (0.4 g, 77%) recrystallised from ethanol as needles, m.p. 198–200 °C (decomp.) (Found: C, 41.8; H, 4.5; N, 14.6%; MH^+, 288. $C_{10}H_{13}N_3O_7$ requires C, 41.8; H, 4.5; N, 14.63%; *M*H, 288), δ_H 3.53–3.70 (2 H, m, 5′,5″-H), 3.94 (2 H, mm, 2′-H, 3′-H), 4.08 (1 H, m, 4′-H), 5.14 (2 H, m, 3′-HO, 5′-HO, both exch. with D_2O), 5.46 (1 H, d, *J* 4.76, 1′-H), 7.57 (1 H, br s, $CONH_a$), 8.12 (1 H, br s, $CONH_b$), 8.73 (1 H, s, 6-H) and 11.89 (1 H, br s, 3-NH, exch. with D_2O).

N-*Benzyloxycarbonyl*-3′,5′-O-1,1,3,3-*Tetraisopropyldisiloxan*-1,3-*diyl*)*uridine*-5-*carboxamide* **26**.—1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (2.4 cm^3, 7.62 mmol) was added dropwise to a solution of **18** (3 g, 7.1 mmol) in dry pyridine (35 cm^3) with cooling. The solution was set aside at room temperature overnight then evaporated under reduced pressure to dryness. The residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated to a solid which as purified by flash column chromatography using chloroform followed by chloroform and methanol (0.6%) as eluting solvents. The *uridine* (3 g, 69%) had m.p. 68–70 °C; δ_H 1.03–1.07 (28 H, m, 4 × Me_2CH), 3.25 (1 H, m, 2′-HO, exch. with D_2O), 4.07 (3 H, m, 5′,5″-H and 4′-H), 4.28 (1 H, m, 3′-H), 4.51 (1 H, t, 2′-H), 5.22 (2 H, s, CH_2Ph), 5.69 (1 H, d, *J* 1.46, 1′-H), 7.25–7.43 (5 H, m, Ph), 8.68 (1 H, s, 6-H), 9.31 (1 H, br s, CONH, exch. with D_2O) and 10.83 (1 H, s, 3-NH); (Found: MH^+, 664. $C_{30}H_{45}N_3O_{10}Si_2$ requires MH 664).

N-*Benzyloxycarbonyl*-2′-*deoxy*-3′,5′-O-(1,1,3,3-*tetraisopropyldisiloxan*-1,3-*diyl*)*uridine*-5-*carboxamide* **28**.—A mixture of the foregoing nucleoside (2.9 g, 4.37 mmol), 4-dimethylaminopyridine (1.1 g, 9 mmol) and *p*-tolyl chlorothioformate (0.9 g, 4.81 mmol) in dry acetonitrile (55 cm^3) was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with cold hydrochloric acid (1 mol dm^{-3}), aqueous sodium hydrogen carbonate and water, and then dried ($MgSO_4$) and evaporated to dryness under reduced pressure to an oil which was dissolved in degassed dry toluene (60 cm^3) and tributyltin hydride (1.31 g, 4.5 mmol) and 2,2′-azo(2-methylpropanenitrile) (0.16 g, 0.97 mmol) added. The solution was boiled under reflux for 2 h and then evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (chloroform used as eluting solvent) to give **28** as a colourless oil (2 g, 71%); δ_H 1.02–1.05 (28 H, m, 4 × Me_2CH), 2.31–2.58 (2 H, m, 2′,2″-H), 3.86 (1 H, m, 4′-H), 4.06 (2 H, m, 5′,5″-H), 4.52 (1 H, m, 3′-H), 5.23 (2 H, s, CH_2Ph), 7.40 (5 H, m, Ph), 9.55 (1 H, br s, CONH, exch. with D_2O) and 10.89 (1 H, s, NH-3).

N-*Benzyloxycarbonyl*-2′-*deoxyuridine*-5-*carboxamide* **29**.—The foregoing uridine derivative **26** (2 g, 3.1 mmol) was stirred at room temperature with tetrabutylammonium fluoride in THF (1 mol dm^{-3}) for 1 h. The solvent was evaporated under reduced pressure and the residue partitioned between water and ether. The aqueous layer was collected and evaporated to dryness under reduced pressure. The residue was flash chromatographed on silica gel (chloroform–methanol, 20:1 as eluting solvent) to give the *deoxyuridine* (0.5 g) which recrystallised from ethanol–ether as needles, m.p. 180 °C (Found: C, 52.9; H, 4.6; N, 10.4%; MH^+, 406. $C_{18}H_{19}N_3O_8$ requires C, 53.33; H, 4.72; N, 10.37%; *M*H, 406); δ_H 2.14–2.27 (2 H, m, 2′,2″-H), 3.6 (2 H, m, 5′,5″-H), 3.89 (1 H, m, 4′-H), 4.23 (1 H, m, 3′-H), 5.13 (1 H, m, 3′-HO, exch. with D_2O), 6.03 (1 H, t, *J* 6.23 and *J* 4.76, 1′-H), 7.40 (5 H, m, Ph), 11.23 (1 H, s, CONH, exch. with D_2O) and 12.19 (1 H, bs, 3-NH, exch. with D_2O).

N-*Carbamoyl*-2′-*deoxyuridine*-5-*carboxamide* **30**.—The foregoing nucleoside (1.6 mmol) was set aside at room temperature with aqueous ammonia (40 cm^3, *d* 0.88) for 1 h. The solution was evaporated to dryness and the residue co-evaporated several times with ethanol. The *nucleoside* (88% yield) separated from ethanol as needles, m.p. 218–220 °C (Found: C, 41.95; H, 4.35; N, 17.7%; MH^+, 315. $C_{11}H_{14}N_4O_7$ requires C, 42.04; H, 4.49; N, 17.83%; *M*H, 315); δ_H 2.5 (2 H, m, 2 × 2′-H), 3.59 (2 H, m, 2 × 5′-H), 3.88 (1 H, m, 3′-H), 4.24 (1 H, m, 4′-H), 5.3 (1 H, m, 5′-H, exch. with D_2O), 5.32 (1 H, d, *J* 4.03, 2′-HO, exch. with D_2O), 6.09 (1 H, m, 1′-H), 7.46 (1 H, s, $CONH_a$), 7.79 (1 H, s, $CONH_b$), 8.93 (1 H, s, 6-H) 0.63 (1

H, s, CONHCO, exch. with D_2O) and 12.18 (1 H, s, NH-3, exch. with D_2O).

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