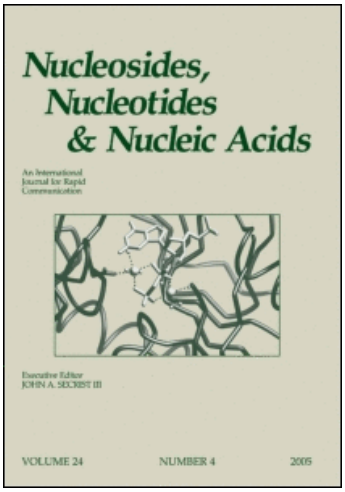

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THE SYNTHESIS OF SOME 5-VINYLURACIL-NUCLEOSIDE ANALOGUES

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Abstract: The reaction of 5-iodouridine with esters of acrylic acid in the palladium-catalysed Heck reaction was used to generate a series of esters of the acid (*E*)-5-(2-carboxyvinyl)uridine in poor to moderate yield. An alternative method starts from the acid by protection of the sugar moiety followed by *in situ* generation of the acid chloride then ester formation followed by simultaneous sugar deprotection. Treatment of the methyl ester with ammonia and methylamine gave the corresponding amides, while treatment with dimethylamine gave 5-(1-dimethylamino-2-carboxy)ethyluridine as the major product.

The Heck reaction, the coupling of an aryl iodide or aryl mercury halide with an activated olefin by an organopalladium complex has been widely used for the synthesis of substituted vinylic aromatic compounds. For the aryl component, it is possible to use a pyrimidine nucleoside functionalized at the 5-position with halogen (usually iodine) or alternatively the 5-chloromercury compound. Two organopalladium systems are possible; chloromercury nucleosides are reacted with molar equivalents of lithium palladium chloride in methanol whereas the 5-iodonucleoside is reacted with catalytic palladium complexes (0.05 molar equivalents) prepared *in situ*.[1]

The Heck reaction was first utilised for nucleoside analogues by Bergstrom and co-workers who published a series of papers which included the coupling reactions of nucleosides with allylic halides,[2] olefinic compounds[3,4] and allylic chlorides, alcohols and acetates.[5] Since the pioneering work of Bergstrom and co-workers, the Heck reaction has been widely used for the synthesis of nucleoside analogues. 5-Chloromercury nucleosides have been reacted with disulphides, RSSR', to give thioethers[5] and 5-acetoxymercury nucleosides/Li_2PdCl_4 have been used for the synthesis of C-5 biotinylated nucleosides[7] and for 5-vinylic carbocyclic analogues.[8]

A palladium (II) acetate, triphenyl phosphine and triethylamine catalyst system has been used in the synthesis of a series of halovinyl 2'-deoxyuridine and 2'-deoxycytidine analogues[9], molar equivalents of palladium (II) acetate in acetonitrile have also been used.[10] Palladium (II) acetate

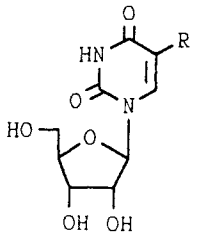
in N,N-dimethylformamide had been reported to couple 5-hydroxyuracil triflates with alkenes[11] while bis(triphenylphosphine)palladium (II) chloride in acetonitrile couples methyl acrylate.[12]

In a review of the literature some years ago, the known 5-vinyl substituted pyrimidine nucleosides were listed.[13] The review contained all the analogues synthesized since the synthesis[14] and antiviral activity[15] of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) were reported. This compound is a potent and selective inhibitor of the replication of the Herpes Simplex virus-1 (HSV-1) and Varicella-Zoster virus (VZV) at minimum inhibitory concentrations (MIC) of 0.007 and 0.002 μgml^{-1} respectively. None of the analogues subsequently synthesized has shown a significantly better activity than BVDU.

In a previous study,[16] it was found that (*E*)-5-(2-bromovinyl)uridine (4) and (*E*)-5-(2-carbomethoxyvinyl)uridine (2) had slight activity against the Yellow Fever virus (ID_{50} 60.1 and 20.9 µg/ml corresponding to therapeutic indices of 8.32 and 23.9 respectively). In the light of these results, a series of esters of the acid (*E*)-5-(2-carboxyvinyl)uridine (3) was required.

The coupling of methyl acrylate with 5-iodouridine has been reported to proceed in good yield to give the methyl ester.[17] Here, we report the coupling of other acrylic esters with 5-iodouridine.

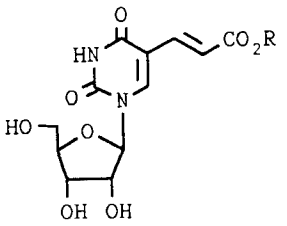
5-Iodouridine (1) was prepared in almost quantitative yield according to the method of Michelson[18] in which a solution of uridine in dilute aqueous nitric acid/dioxan is heated under reflux with iodine.



1. R = I
2. R = (*E*)-CH=CHCO$_2$CH$_3$
3. R = (*E*)-CH=CHCOOH
4. R = (*E*)-CH=CHBr

Most of the required esters were synthesized by the acid-catalysed transesterification of methyl acrylate. The *n*-propyl, *iso*-propyl, *n*-butyl, *n*-pentyl, *n*-octyl, 2-methoxyethyl, 2-ethoxyethyl, 2-butoxyethyl, 2-cyanoethyl, 2-chloroethyl and 2-bromoethyl esters were prepared from methyl acrylate according to the published procedures.[19a-e]

The acrylic esters were coupled with 5-iodouridine by first activating the catalyst of palladium (II) acetate, triphenylphosphine and triethylamine in dioxan by heating it to 70°C to give a deep red solution. Then, 5-iodouridine and the acrylic ester were added and the solution stirred under reflux. The esters, 5a-e were obtained in poor to moderate yield (Table 1) and in each case the configuration of the vinylic side chain was assigned as *trans* on the basis of large $J_{x,y}$ coupling constants observed in the NMR spectrum (Table 1).



5 R=

a	ethyl	j.	2-ethoxyethyl
b.	*n*-propyl	k.	2-butoxyethyl
c.	*iso*-propyl	l.	2-hydroxyethyl
d.	*n*-butyl	m.	4-hydroxybutyl
e.	*t*-butyl	n.	2-cyanoethyl
f.	*n*-pentyl	o.	2-chloroethyl
g.	*n*-octyl	p.	2-bromoethyl
h.	benzyl	q.	trifluoroethyl
i.	methoxyethyl	r.	tetrahydrofuryl

Although it has been reported in the literature using palladium chemistry,[12] the ethyl ester (5a) was synthesized here for antiviral evaluation.

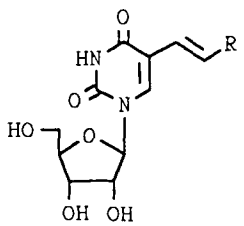
Under the same conditions, glycidyl and 2-nitroethyl[9] acrylates gave uridine as the only nucleosidic product. These heat-sensitive esters would be expected to decompose under the reaction conditions before the intermediate palladium/nucleoside complex $ArPdL_2X$ (Ar=uridin-5-yl; L,X=acetate, Ph_3P, I^- or Et_3N) could associate with the alkene to give the usual π-bonded intermediate.

The palladium-catalysed reaction of 5-iodouridine with the methyl- and ethyl acetals of acrolein, the allene 3-methylpent-1,2-diene[21] and nitroethylene[22] were also unsuccessful; the decomposition of nitroethylene being particularly violent.

5-(2-Cyanovinyl)uridine (6) has been reported in the literature where it was obtained as a mixture of *E* and *Z* isomers *via* a photochemical-induced-coupling of 5-iodouridine and acrylonitrile in 12% yield.[23] Here, using the palladium-catalysed method, the (*E*)-cyanovinyl isomer (6) was obtained in 25% yield which can be directly compared with the Li_2PdCl_4 system which has been used to prepare the analogous (*E*)-5-(2-cyanovinyl)-2'-deoxyuridine in 16% yield.[24].

The palladium-catalysed coupling of 3-nitrostyrene has previously been used to prepare the corresponding 2'-deoxy derivative from 5-chloromercuri-2'-deoxyuridine and Li_2PdCl_4.[25]

(*E*)-5-(2-*m*-Nitrophenylvinyl)uridine (7) has been obtained from poly(acetoxymercuryuridylic) acid followed by hydrolysis to the nucleoside.[26] We report here the reaction of 3-nitrostyrene with 5-iodouridine which proceeded in 41% yield to give the product (7) as fine yellow crystals.



6. R = CN
7. R = *m*-NO_2Ph

TABLE 1. ^{1}H-NMR data of compounds (5b-r). Resonances of ester side chain[a] and FAB mass spectra data.

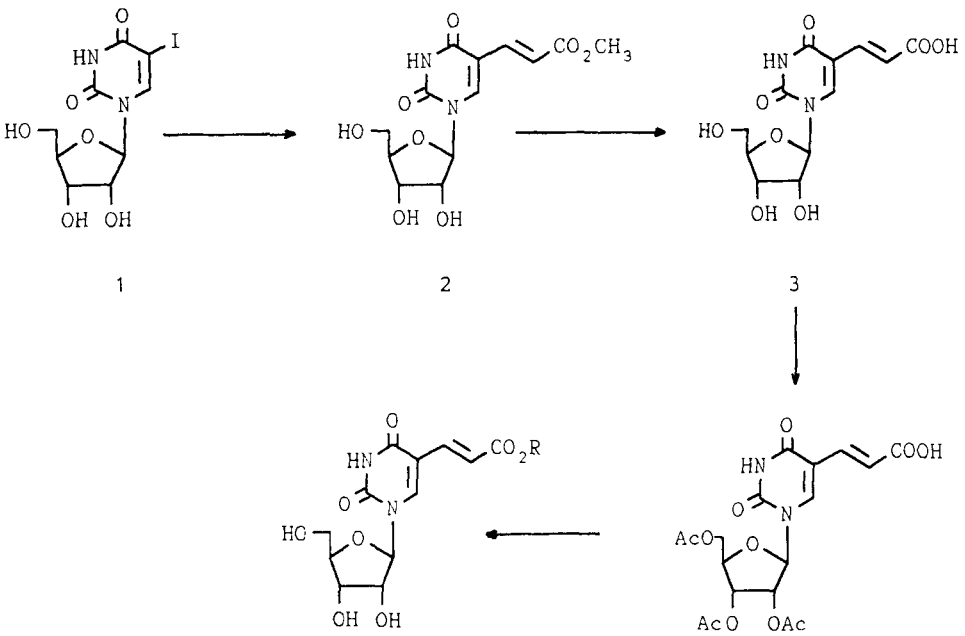
5	FAB mass spectrum m/e	assignment	^{1}H-NMR side chain resonances δ(DMSO-d_6), (vinylic H,J in Hz)
b	357	$(M+H)^+$	4.08(2-H,m,OCH_2-), 1.63(2-H,m,CH_2-) 0.90(3-H,m,CH_3) (16)
c	357	$(M+H)^+$	4.95(1-H,sept,-CH-), 1.23(6-H,s,2 CH_3 (16)
d	371, 741	$(M+H)^+$, $(2M+H)^+$	4.08(2-H,m,OCH_2), 1.80-0.75(7-H,m,$CH_2CH_2CH_3$) (16)
e	315	$(acid+H)^+$	1.45(9-H,s,$3CH_3$) (15)
f	385, 407	$(M+H)^+$, $(M+Na)^+$	4.08(2-H,m,OCH_2), 1.70-1.26(6-H,m,$CH_2CH_2CH_2$), 0.90(3-H,s,CH_3) (16)
g	427	$(M+H)^+$	4.08(2-H,m,OCH_2), 1.60(2H,m,$OCH_2C\underline{H}_2$), 1.25(10-H,m,$5CH_2$),0.86(3H,s,CH_3) (16)
h	405	$(M+H)^+$	7.36(5-H,s,Ph), 5.18(2H,s,$C\underline{H}_2$Ph)(16)
i	373	$(M+H)^+$	4.30-3.50(7-H,m,$CH_2CH_2OCH_3$) (17)
j	387	$(M+H)^+$	4.30-3.30(6-H,M,$OCH_2CH_2OCH_2$), 1.10(3-H,t,CH_3) (17)
k	415	$(M+H)^+$	4.30-3.30(6-H,m,CO_2CH_2,2 OCH_2), 1.60-1.10(4-H,m,2 CH_2), 0.85(3-H,t,CH_3) (16)
l	359	$(M+H)^+$	4.85(1-H,t,$CH_2O\underline{H}$), 4.20-3.40(4-H,m,$CO_2CH_2CH_2$) (17)
m	387	$(M+H)^+$	4.85(1-H,t,$CH_2O\underline{H}$), 4.30-3.30(4-H,m,2 OCH_2), 1.58(4-H,m,CH_2CH_2) (17)
n	236, 368	$(base+H)^+$, $(M+H)^+$	4.30(2-H,t,OCH_2), 2.90(2-H,t,CH_2CN) (17)
o	377	$(M+H)^+$	4.35(2-H,t,OCH_2), 3.70(2-H,t,CH_2Cl) (16)
p	421	(M)	4.30(2-H,t,OCH_2), 3.40(2-H,t,CH_2Br) (16)
q	39	$(M+H)^+$	4.80(2-H,q,CH_2CF_3) (16)
r	399	$(M+H)^+$	4.30-3.50(5-H,m,$CHOCH_2$), 2.10-1.50(4-H,m,CH_2CH_2 of ring) (16)

a. Other protons of compounds (5b-r) show little variation from the values δ(DMSO-d_6) 11.65(1-H,bs,N-H), 8.50(1-H,s,H-6), 7.35(1-H,d,vinylic H), 6.85(1-H,d,vinylic H), 5.75(1-H,d,H-1'), 5.45(1-H,d,2'-OH), 5.30(1-H,t,5'-OH), 5.10(1-H,d,3'-OH), 4.02(2-H,m,H-2',H-3'), 3.85(1-H,m,H-4'), 3.80-3.50(2-H,m,H-5').

As the yields of some of the esters 5a-r were poor and some of the longer chain esters were difficult to purify, an alternative synthesis *via* the acid chloride generated *in situ* was investigated (scheme 1). Initially, the synthesis of the acid chloride of (*E*)-5-(2-carboxyvinyl)uridine was investigated, the acid being obtained using the published procedure from the methyl ester.[17]

The methyl ester was prepared by the coupling of methyl acrylate with 5-iodouridine in good yield. Saponification with 1M aqueous sodium hydroxide

Scheme 1



1 2 3 8

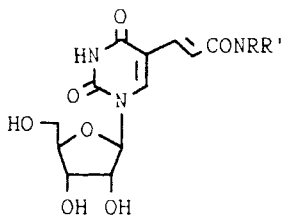
9. R = $CH_2CH(CH_3)_2$
10. R = $CH_2CH_2CH(CH_3)_2$

proceeded rapidly to give the acid. Treatment of the acid with thionyl chloride or oxalyl chloride in the absence or presence of pyridine followed by quenching with propan-1-ol gave much decomposition and no nucleosidic product. It was therefore decided to protect the sugar moiety of compound (3) which was acetylated in acetic anhydride/pyridine to give 2',3',5'-tri-*O*-acetyl-(*E*)-5-(2-carboxyvinyl)uridine (8) in 85% yield following purification by short column chromatography. This compound was treated with thionyl chloride and the resulting crude acid chloride, obtained after evaporation of the excess of thionyl chloride *in vacuo*, was heated under reflux with an excess of dry *iso*-butanol or *iso*-amyl alcohol.

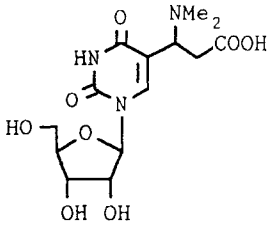
Ester formation was accompanied by deprotection of the sugar acetate groups and the 2-methylpropyl and 3-methylbutyl esters, compounds (9) and (10) were obtained in 71% and 58% yields respectively after purification by short column chromatography and these preliminary results suggest a more advantageous route than the palladium-catalysed method.

As no 5-vinylic amide nucleosides are known, their synthesis was undertaken from the methyl ester (2) by reaction with concentrated aqueous

solutions of the amine. The unsubstituted amide (11) was obtained in 58% yield as fine needles after recrystallization from water. The N-methyl-amide



11. R = R' = H
12. R = H, R' = CH_3
13. R = R' = CH_3



14

(12) was obtained in 41% yield while reaction with an aqueous solution of dimethylamine gave two nucleosidic products which were separated by fractional crystallization. The minority product was identified as compound (13) and was obtained in 7% yield. The majority product had an ^{1}H-NMR spectrum which showed the loss of the vinylic side chain and the presence of two new methyl groups which is consistent with the incorporation of one NMe_2 group. The FAB mass spectrum had an m/e 359 which is consistent with the compound having structure (14) and this was confirmed by elemental analysis.

The relatively high yield of (14) showed that although ammonolysis of the ester does occur to some extent, a Michael addition to the vinylic side chain followed by hydrolysis to the acid is prefered.

BIOLOGICAL RESULTS

Biological testing was done by the United States Army Medical Research Institute Of Infectious Diseases, Fort Detrick, MD. Compounds (5a-r), (6) and (11-14) were tested against Vesicular Stomatitus virus, Vaccinia Virus, Adenovirus Type 2, Japanese Encephalitis Virus and Rift Valley Fever Virus but no biological activity was observed.

EXPERIMENTAL

Ultraviolet spectra were recorded with a Perkin Elmer 552 spectrophotometer and were run in spectroscopic grade ethanol. Mass spectra were determined with a Kratos MS80 mass spectrometer with a DS 55 data system employing automatic digital readout of data. The ^{1}H-NMR spectra (s=singlet, d=doublet, t=triplet, br=broad, m=multiplet) were recorded on either a Jeol FX90Q (90MHz) or a Jeol GX270 (270MHz) spectrometer. Precoated Merck silica gel 60 F_{254} plates were used for TLC, and the spots were examined with UV light (254nm) and a sulphuric acid-cysteine spray. Column

TABLE 2

(5)	Yield (%)	λ_{max} (ε)	Elemental analysis calculated (C,H,N)	found (C,H,N)
b	21	303.0 (16330)	50.56, 5.65, 7.86	50.85, 5.5, 7.5
c	16	301.0 (19790)	50.56, 5.65, 7.86	50.3, 5.65, 7.6
d	19	301.0 (17430)	51.89, 5.99, 7.56	51.6, 6.0, 7.3
e	37	302.0 (23570)	51.89, 5.99, 7.56	51.6, 6.2, 7.3
f	12	300.5 (19180)	53.1, 6.3, 7.3	52.8, 6.2, 7.5
g	11	302.0 (14130)	56.32, 7.0, 7.0	56.3, 6.7, 6.3
h	46	304.4 (16070)	56.43, 5.00, 6.93	56.2, 5.0, 6.8
i	41	300.0 (20560)	48.38, 5.41, 7.52	48.4, 5.5, 7.6
j	42	302.0 (22540)	49.74, 5.70, 7.30	50.0, 5.4, 7.6
k	33	303.0 (20620)	52.17, 6.32, 6.76	52.2, 6.3, 6.9
l	32	303.0 (17180)	46.93, 5.06, 7.82	46.9, 4.8, 7.9
m	23	301.2 (20330)	49.74, 5.74, 7.25	49.4, 5.9, 7.0
n	36	302.0 (17540)	49.05, 4.66, 11.4	48.9, 4.4, 11.1
o	37	302.5 (19080)	44.63, 4.55, 7.46	44.3, 4.8, 7.3
p	23	301.6 (22540)	39.9, 4.1, 6.6	39.6, 4.1, 6.6
q	24	305.0 (18370)	40.6, 4.1, 6.76	40.9, 3.9, 6.5[a]
r	26	302.5 (19520)	51.25, 5.56, 7.03	51.0, 5.4, 6.9

a. +1 mol H_2O

chromatography was performed using Kieselgel 60, 70-230 mesh ASTM, type 7734, supplied by E. Merck A.G., Darmstadt, Germany. Columns were packed under gravity. Dimethylformamide was dried over P_2O_5 and distilled under high vacuum; pyridine and triethylamine were refluxed over calcium hydride then distilled; 1,4-dioxan was dried using potassium/benzophenone and thionyl chloride was purified by fractionation twice from linseed oil.

(*E*)-5-(2-Carboethoxyvinyl)uridine (5a) Palladium (II) acetate (0.06 g, 0.25 mmol), triphenylphosphine (0.14 g, 0.54 mmol) and redistilled triethylamine (1 ml) were combined in dry dioxan (10 ml) and the solution stirred at 70 °C until a deep red colouration had developed. Then, 5-iodouridine (2.00 g, 5.4 mmol) and ethyl acrylate (1.10 g, 10.8 mmol) were added. The mixture was stirred under reflux for 2 hours, filtered while hot and the crystals that separated on cooling overnight were filtered off and recrystallized from ethanol to give the product (0.438g, 24%). UV λ_{max} 302.0nm, ε=18530. ^{1}H-NMR δ(DMSO-d_6) 11.65(1-H,s,N-H), 8.50(1-H,s,H-6), 7.35(1-H,d,vinylic H,J=16Hz), 6.80(1-H,d,vinylic H,J=16Hz), 5.75(1-H,d,H-1'), 5.45(1-H,d,2'-OH), 5.30(1-H,t,5'-OH), 5.10(1-H,d,3'-OH), 4.30-3.80(5-H,m,H-2',H-3',H-4',-OCH_2), 3.70-3.50(2-H,m,H-5'), 1.20(3-H,t,CH_3). FAB mass spectrum m/e 345 $(M+H)^+$, 365 $(M+Na)^+$. Elemental analysis $C_{14}H_{18}N_2O_8$ calculated C, 49.12; H, 5.30; N, 8.18; found C, 48.8; H, 5.3; N, 7.9

Compounds (5b-r) These were prepared in an analogous manner to (5a) from 5-iodouridine (2.00 g, 5.4 mmol) and the appropriate acrylic ester (10.8 mmol) with purification by short column chromatography in a chloroform/methanol system followed by recrystallization from methanol or ethanol. All compounds gave correct ^{1}H-NMR spectra, FAB mass spectra and elemental analysis, see Tables 1 and 2.

(*E*)-5-(2-Cyanovinyl)uridine (6) To the activated catalyst based on 60 mg $Pd(OAc)_2$ in dry dioxan (8 ml) were added 5-iodouridine (2.00 g, 5.4 mmol) and acrylonitrile (0.57 g, 90.8 mmol) and the solution stirred under reflux for 2 hours. The solvent was then removed under reduced pressure and the reaction mixture purified by short column chromatography with elution in 80:20 then 70:30 chloroform/methanol. The crude product was then recrystallized from ethanol (0.40 g, 25%). UV λ_{max} 301.0nm, ε=19730. ^{1}H-

NMR δ(DMSO-D_6) 11.74(1-H,bs,N-H), 8.64(1-H,s,H-6), 6.16(1-H,d,vinylic H,J=16Hz), 6.50(1-H,d,vinylic H,J=16Hz), 5.73(1-H,d,H-1'), 5.49(1-H,bs,2'-OH), 5.26(1-H,bs,5'-OH), 5.10(1-H,bs,3'-OH), 4.03(2-H,m,H-2',H-3'), 3.89(1-H,m,H-4'), 3.70(2-H,dd,H-5'). FAB mass spectrum m/e 296 $(M+H)^+$. Elemental analysis $C_{12}H_{13}N_3O_6$ calculated C, 48.82; H, 4.44; N, 14.23; found C, 48.7; H, 4.5; N, 14.1

(*E*)-5-(2-*m*-Nitrophenylvinyl)uridine (7) To the activated catalyst based on 60 mg $Pd(OAc)_2$ in dry dioxan (10 ml) were added 5-iodouridine (2.00 g, 5.4 mmol) and 3-nitrostyrene (1.61 g, 10.8 mmol) and the mixture stirred under reflux for 2 hours. The solvent was removed under reduced pressure and the resulting oil purified by column chromatography with elution in 70:30 chloroform/methanol then 80:20 ethyl acetate/ethanol and was then recrystallized from ethanol to give fine yellow needles (0.86 g, 41%). UV λ_{max} ε=20640. ^{1}H-NMR δ(DMSO-d_6) 11.60(1-H,bs,N-H), 8.50-6.75(7-H,m,H-6, vinylics and 4 aromatic H), 5.85(1-H,d,H-1'), 5.70-5.00(3-H,bs,2'-OH,3'-OH,5'-OH), 4.10(1-H,s,H-2'), 3.90(1-H,s,H-3'), 3.85(1-H,m,H-4'), 3.70(2-H,m,H-5'). FAB mass spectrum m/e 392 $(M+H)^+$. Elemental analysis $C_{17}H_{17}N_3O_8$ calculated C, 52.2; H, 4.4; N, 10.7; found C, 51.9; H, 4.7; N, 10.4

2',3',5'-Tri-*O*-acetyl-(*E*)-5-(2-carboxyvinyl)uridine (8) (*E*)-5-(2-Carboxyvinyl)uridine (5.00 g, 15.9 mmol) was added to dry pyridine (80 ml) and after dissolution (5 minutes) acetic anhydride (80 ml) was added. The clear solution was stirred at room temperature for 24 hours and the solvent then removed by evaporation *in vacuo*. The white solid was coevaporated with toluene and ethanol and the resulting solid purified by column chromatography in 60:10 ethyl acetate/ethanol to give a white powder (5.97 g, 85%). UV λ_{max} 296.0nm, ε=12620. ^{1}H-NMR δ(DMSO-d_6) 11.75(1-H,bs,N-H), 8.25(1-H,s,H-6), 7.35(1-H,d,vinylic H,J=16Hz), 6.76(1-H,d,vinylic H,J=16Hz), 5.95(1-H,d,H-1'), 5.45(2-H,m,H-5'), 4.32(3-H,m,H-2',H-3',H-4'), 2.09(9-H,s,3 CO_2CH_3). FAB mass spectrum m/e 441 $(M+H)^+$. Elemental analysis $C_{18}H_{20}N_2O_{11}$ calculated C, 49.09; H, 4.57; N, 6.36; found C, 49.2; H, 4.7; N, 6.1

(*E*)-5-(2-carbo*iso*butoxyvinyl)uridine (9) Compound (8) (0.72 g, 1.63 mmol) was added to freshly redistilled thionyl chloride (20 ml) and the resulting solution heated under reflux for 20 minutes. The excess of thionyl chloride was then removed *in vacuo* with exclusion of moisture. Dry *iso*-butanol (2-methylpropan-1-ol, 3 ml) was added and the solution heated under reflux for 10 minutes. The excess of the alcohol was removed under high vacuum and the product isolated by column chromatography with elution in 80:20 chloroform/methanol followed by recrystallization from ethanol (0.43 g, 71%). UV λ_{max} 302.1nm, ε=18330. ^{1}H-NMR δ(DMSO-d_6) 11.70(1-H,s,N-H), 8.51(1-H,s,H-6), 7.35(1-H,d,vinylic H,J=16Hz), 6.86(1-H,d,vinylic H,J=16Hz), 5.76(1-H,d,H-1'), 5.48(1-H,bs,2'-OH), 5.32(1-H,t,5'-OH), 5.11(1-H,bs,3'-OH), 4.09(1-H,m,H-2'), 4.02(1-H,m,H-3'), 3.90(3-H,m,H-4',CO_2CH_2), 3.70-3.50(2-H,dd,H-5'), 1.92(1-H,septuplet, CH), 0.93(3-H,s,CH_3), 0.90(3-H,s,CH_3). FAB mass spectrum m/e 371 $(M+H)^+$. Elemental analysis $C_{16}H_{22}N_2O_8$ calculated C, 51.89; H, 5.98; N, 7.56; found C, 51.6; H, 6.0; N, 7.3

(*E*)-5-(2-Carbo*iso*pentoxyvinyl)uridine (10) This was prepared as for compound (9) from the acid (8) (1.00 g, 2.3 mmol), thionyl chloride (20 ml) and *iso*-amyl alcohol (3-methylbutan-1-ol, 10 ml) to give a white powder (0.51g, 58%). UV λ_{max} 302.5nm, ε=19710. ^{1}H-NMR δ(DMSO-d_6) 11.66(1-H,s,N-H), 8.48(1-H,s,H-6), 7.33(1-H,d,vinylic H,J=16Hz), 6.81(1-H,d,vinylic H,J=16Hz), 5.75(1-H,d,H-1'), 5.60-4.90(3-H,bs,2'-OH,3'-OH,5'-OH), 4.25-3.75(5-H,m,H-2',H-3',H-4', OCH_2), 3.75-3.50(2-H,m,H-5'), 1.50(3-H,m,-CH_2CH-), 1.00-0.80(6-H,2 s,2 CH_3). FAB mass spectrum m/e 385 $(M+H)^+$. Elemental analysis $C_{17}H_{24}N_2O_8$ calculated C, 53.1; H, 6.3; N,7.2; found C, 52.8; H, 6.3; N, 6.9

(*E*)-5-(2-Aminocarbonylvinyl)uridine (11) To (*E*)-5-(2-carbomethoxyvinyl)uridine (1.15 g, 0.46 mmol) was added concentrated aqueous ammonia solution (15 ml). The resulting solution was stirred at room temperature for 24 hours after which time TLC in 90:10 chloroform/methanol showed the disappearence of starting material. The excess ammonia solution was removed *in vacuo* and the resulting colourless solid recrystallized from

water to give long fine white needles (0.083g, 58%). UV λ_{max} 310.0nm, ε=12380. ^{1}H-NMR δ(DMSO-d_6) 11.50(1-H,s,N-H), 8.35(1-H,s,H-6), 7.50(1-H,s,H of NH_2), 7.15(1-H,d,vinylic H,J=16Hz), 6.90(1-H,d,vinylic H,J=16Hz), 6.90(1-H,s,H of NH_2), 5.76(1-H,d,H-1'), 5.40(1-H,m,2'-OH), 5.25(1-H,t,5'-OH), 5.05(1-H,m,3'-OH), 4.20-3.80(3-H,m, H-2',H-3',H-4'), 3.65(2-H,m,H-5'). FAB mass spectrum m/e 314 $(M+H)^+$. Elemental analysis $C_{11}H_{15}N_3O_7.H_2O$ calculated C, 43.5; H, 51.7; N, 12.69; found C, 43.6; H, 5.2; N, 12.4

(*E*)-5-(2-Methylaminocarbonylvinyl)uridine (12) To (*E*)-5-(2-carbomethoxyvinyl)uridine (1.50 g, 4.57 mmol) was added a 40% aqueous solution of methylamine (40 ml). After stirring for 2 hours at room temperature, TLC in 70:30 chloroform/methanol showed the absence of starting material. The reaction mixture was taken to dryness and the white solid purified by short column chromatography in 50:50 ethyl acetate/ethanol and then recrystallized from water to give fine white needles (0.63g, 41%). UV λ_{max} 310.0nm, ε=14280. ^{1}H-NMR δ(DMSO-d_6) 11.53(1-H,s,N-H), 8.34(1-H,s,H-6), 7.96(1-H,q,NHCH$_3$), 7.14(1-H,d,vinylic H,J=16Hz), 6.91(1-H,d,vinylic H,J=16Hz), 5.75(1-H,d,H-1'), 5.50-4.90(3-H,bs,2'-OH,3'-OH,5'-OH), 4.05(2-H,m,H-2',H-3'), 3.85(1-H,m,H-4'), 3.65(2-H,bs,H-5'), 2.62(3-H,d,NHCH$_3$). FAB mass spectrum m/e 328 $(M+H)^+$. Elemental analysis $C_{13}H_{17}N_3O_7$. H_2O calculated C, 45.21; H, 5.55; N, 12.16; found C, 45.5; H, 5.6; N, 12.0

(*E*)-5-(2-Dimethylaminocarbonylvinyl)uridine (13) To (*E*)-5-(2-carbomethoxyvinyl)uridine (0.50 g, 1.52 mmol) was added a 25/30% aqueous solution of dimethylamine (25 ml). After 48 hours at room temperature, TLC in 80:20 chloroform/methanol showed the presence of two new nucleosides, one with an Rf 0.52, the other on the baseline. The reaction mixture was taken to dryness and traces of amine removed by coevaporation with water. Recrystallization from water gave crystals with Rf 0.52 which were further purified by short column chromatography with elution in 80:20 chloroform/methanol then recrystallization from water. These were identified as the expected amide (0.0348 g, 7%). UV λ_{max} 302.7nm, ε=16670. ^{1}H-NMR δ(DMSO-d_6) 11.61(1-H,s,N-H), 8.45(1-H,s,H-6), 7.48(1-H,d,vinylic H,J=16Hz), 7.19(1-H,d,vinylic H,J=16Hz), 5.77(1-H,d,H-1'), 5.48(1-H,d,2'-OH), 5.35(1-H,t,5'-OH), 5.11(1-H,d,3'-OH), 4.08(1-H,m,H-2'), 4.01(1-H,m,H-3'), 3.87(1-H,m,H-4'), 3.80-3.50(2-H,m,H-5'), 3.05(3-H,s,NCH_3), 2.90(3-H,s,NCH_3). FAB mass spectrum m/e 342 $(M+H)^+$. Elemental analysis $C_{14}H_{19}N_3O_7.H_2O$ calculated C, 46.79; H, 5.89; N, 11.69; found C, 47.0; H, 5.6; N, 11.4

The filtrate contained mainly the more polar component. The filtrate was evaporated to dryness and the white solid recrystallized from methanol to give crystals identified as 5-(1-dimethylamino-2-carboxy)ethyluridine (14) (0.0852 g, 16%). UV λ_{max} 269.5nm, ε=7470. ^{1}H-NMR δ(DMSO-D_6) 11.37(1-H,s,N-H), 8.01(1-H,s,H-6), 5.78(1-H,d,H-1'), 5.50-5.00(3-H,bs,2'-OH,3'-OH,5'-OH), 4.23-4.10(1-H,m,-CH-), 4.10-4.00(2-H,m,H-2',H-3'), 3.89(1-H,m,H-4'), 3.72-3.57(2-H,m,H-5'), 2.76(1-H,m,1 of CH$_2$COOH), 2.36(1-H,m,1 of CH$_2$COOH), 2.14(3-H,s,NCH_3), 2.13(1-H,s,NCH_3). FAB mass spectrum m/e 359 (M). Elemental analysis $C_{14}H_{21}N_3O_8$ calculated C, 46.79; H, 5.89; N, 11.69; found C, 46.6; H, 5.9; N, 11.4

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