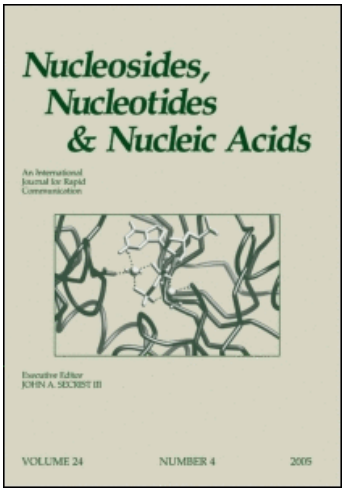


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Novel Acyclonucleosides. Part I. 2,3-Dihydroxy-1-Methoxypropyl-and 3-Hydroxy-1-Methoxypropyl-Substituted Pyrimidines

Stuart Bailey[a]; Colin T. Shanks[a]; Michael R. Harnden[a]
[a] Beecham Pharmaceuticals, Research Division, Biosciences Research Centre, Great Burgh, Epsom, Surrey, England

To cite this Article Bailey, Stuart , Shanks, Colin T. and Harnden, Michael R.(1985) 'Novel Acyclonucleosides. Part I. 2,3-Dihydroxy-1-Methoxypropyl-and 3-Hydroxy-1-Methoxypropyl-Substituted Pyrimidines', Nucleosides, Nucleotides and Nucleic Acids, 4: 5, 565 — 585
To link to this Article: DOI: 10.1080/07328318508081890
URL: http://dx.doi.org/10.1080/07328318508081890

NUCLEOSIDES & NUCLEOTIDES, 4(5), 565-585 (1985)

NOVEL ACYCLONUCLEOSIDES. PART I. 2,3-DIHYDROXY-1-METHOXYPROPYL- AND 3-HYDROXY-1-METHOXYPROPYL-SUBSTITUTED PYRIMIDINES

Stuart Bailey, Colin T. Shanks and Michael R. Harnden*
Beecham Pharmaceuticals, Research Division,
Biosciences Research Centre, Great Burgh, Epsom,
Surrey KT18 5XQ, England.

ABSTRACT

Novel pyrimidine nucleoside analogues in which the N-1 ribosyl moiety is replaced by a 2,3-dihydroxy-1-methoxypropyl or 3-hydroxy-1-methoxypropyl substituent have been synthesized and tested for antiviral activity.

INTRODUCTION

It is now well established that purine nucleoside analogues in which the carbohydrate moiety is replaced by an acyclic substituent can act as alternative substrates for and/or competitive inhibitors of enzymes involved in nucleic acid synthesis, thus interfering with processes essential for virus replication.

For example, (S)-9-(2,3-dihydroxypropyl)adenine (DHPA) is an inhibitor of S-adenosyl-L-homocysteine hydrolase[1] and inhibits the replication of both DNA and RNA viruses.[2] 9-(2-Hydroxyethoxymethyl)-guanine (acyclovir),[3] 9-(dihydroxyisopropoxymethyl)guanine (DHPG)[4-7] and 9-(3,4-dihydroxybutyl)guanine (DHBG)[8] are substrates for herpes virus specified thymidine kinases and their triphosphates are inhibitors of herpes virus DNA polymerases. The latter three compounds are consequently potent and highly selective inhibitors of the replication of viruses of the herpes family.[9]

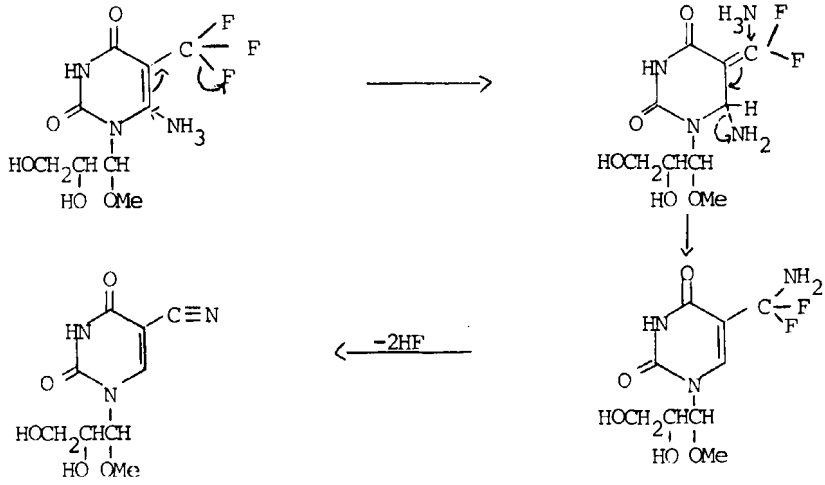
In this publication we report the synthesis of a series of pyrimidine nucleoside analogues in which the carbohydrate moiety is replaced with a 2,3-dihydroxy-1-methoxypropyl or 3-hydroxy-1-methoxypropyl substituent. These substituents can be regarded as the C(4')-O-C(1')-C(2')-C(3') portions of ribose and 2'-deoxyribose, respectively. Although others have reported syntheses of acyclic analogues of pyrimidine nucleosides,[10-15] the only 1-methoxypropyl derivative to have been described previously is 1-(3-hydroxy-1-methoxyprop-1-yl)-5-fluorouracil (14c),[14] which was included in a communication published whilst our manuscript was in preparation.

0732-8311/85/0405-0565$3.50/0

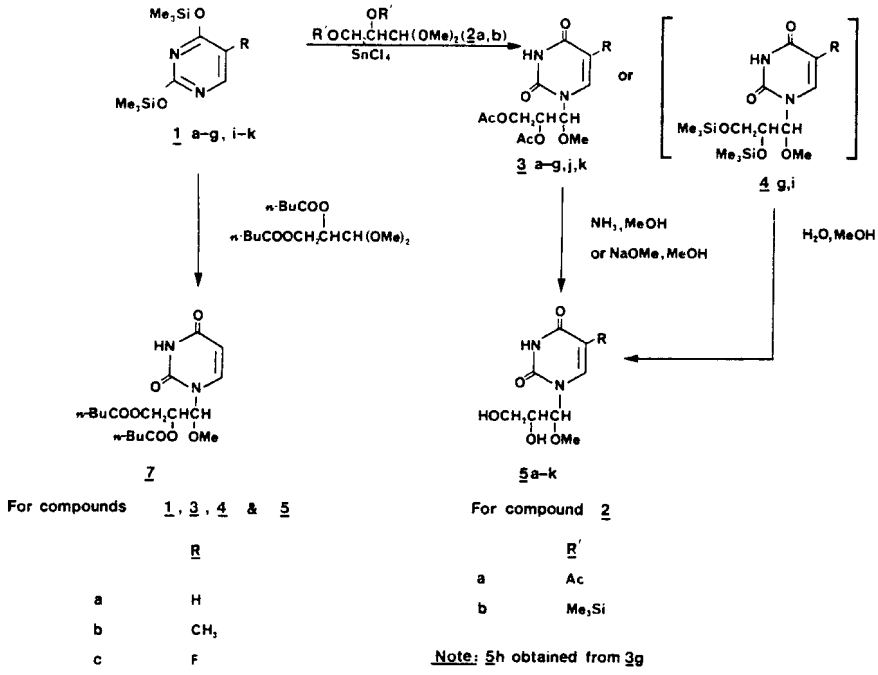
RESULTS AND DISCUSSION

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-(3a-g,j,k,9,16) and 1-(3-acetoxy-1-methoxyprop-1-yl)pyrimidines (12a-c,e,f,i,18) were prepared, usually in about 50% yield, by reaction of 2,3-diacetoxy-1,1-dimethoxypropane (2a) and 1,3-diacetoxy-1-methoxypropane (11), respectively, with bis-O-trimethylsilyluracils (1 a-g, i-k, 8) and N,O-bis-trimethylsilyl-N-acetylcytosine (15) in anhydrous acetonitrile in the presence of stannic chloride, a modification of the Hilbert - Johnson reaction.[16] 1-(2,3-Divaleryloxy-1-methoxyprop-1-yl)uracil (7) was obtained in 48% yield by reaction of bis-O-trimethylsilyluracil (1a) with 2,3-divaleryloxy-1,1-dimethoxypropane (6) under similar conditions. Acetyl groups were subsequently removed from most of the protected acyclic nucleoside analogues by treatment with ammonia in aqueous methanol at 25°C, affording the required 1-(2,3-dihydroxy-1-methoxyprop-1-yl)- (5a-f,j,10) and 1-(3-hydroxy-1-methoxyprop-1-yl)uracils (14 a-c,e,f,i) in yields varying from 50-90% (Schemes 1-3). Under these conditions the 4-N-acetyl group was also removed from the cytosine derivatives (16,18), affording 1-(2,3-dihydroxy-1-methoxyprop-1-yl)- (17) and 1-(3-hydroxy-1-methoxyprop-1-yl) cytosine (20) in about 90% yield (Scheme 4).

Upon reaction of 1-(2,3-diacetoxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (3g) with ammonia in aqueous methanol the sole product obtained was 1-(2,3-dihydroxy-1-methoxyprop-1-yl)-5-cyanouracil (5h), isolated in 48% yield. Since fluoride ion is normally a poor leaving group in displacement[17] and elimination [18,19] reactions, direct displacement of fluoride by ammonia seems unlikely and a more plausible mechanism for this transformation involves initial attack of ammonia at C-6.



5h



For compounds 1, 3, 4 & 5

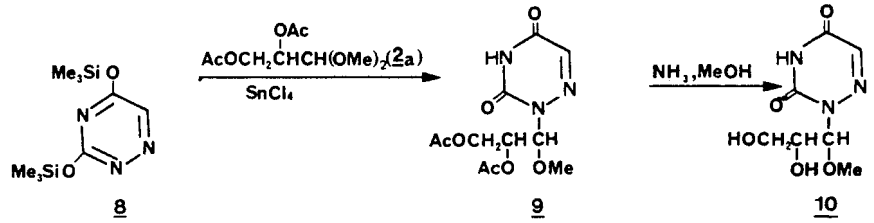
	R
a	H
b	CH_3
c	F
d	Cl
e	Br
f	I
g	CF_3
h	CN
i	NO_2
j	$CH=CH_2$
k	$C \equiv CH$

For compound 2

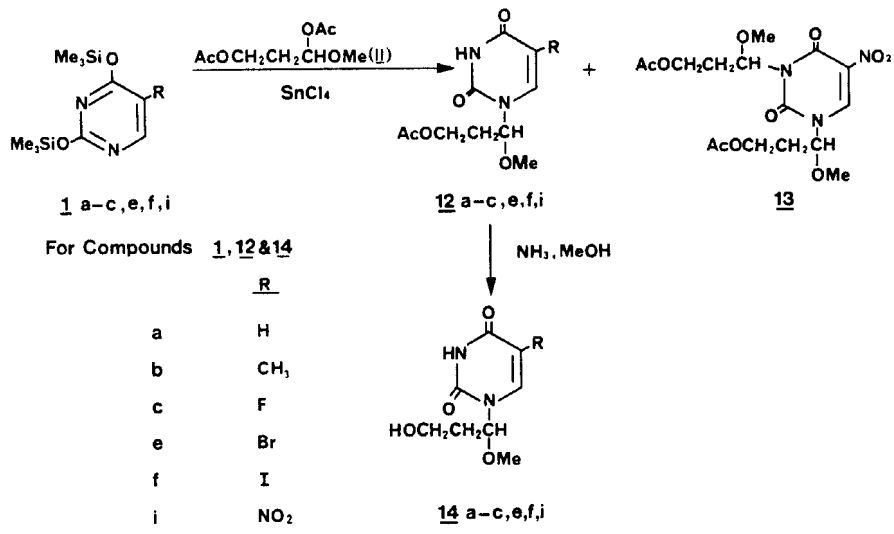
	R′
a	Ac
b	Me_3Si

Note: 5h obtained from 3g

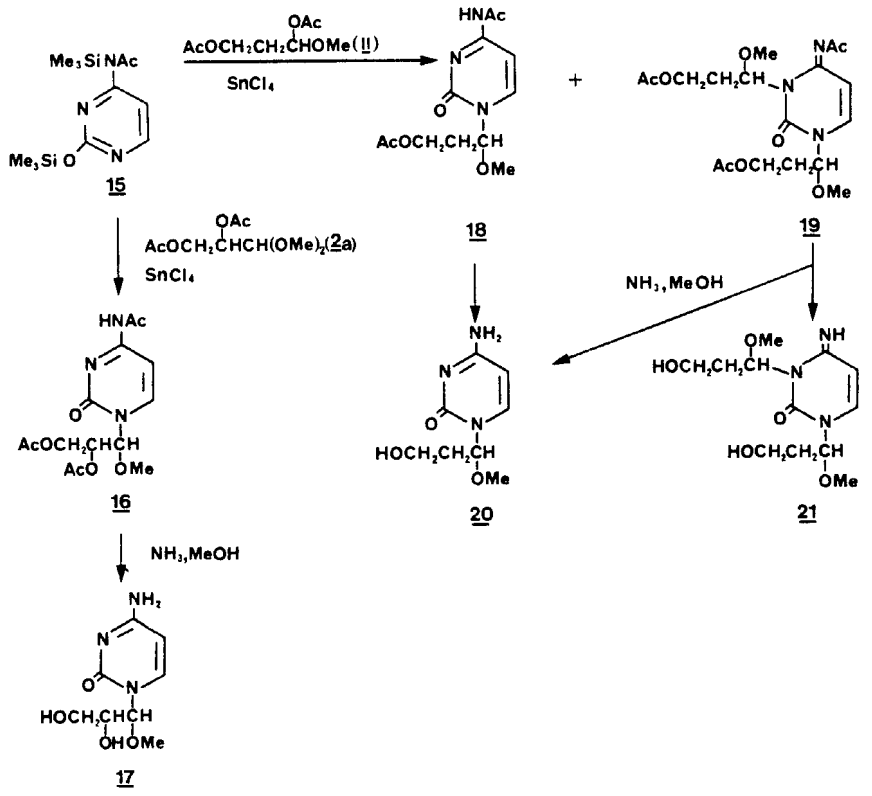
SCHEME 1



SCHEME 2



SCHEME 3



SCHEME 4

Analogous conversions of the CF_3 group in 2-trifluoromethylimidazoles to CN, $C(OR)_3$, CO_2H and CO_2R have been reported and it was suggested that these involved diazafulvene intermediates.[20]

The preparation of 1-(2,3-dihydroxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (5g) and 1-(2,3-dihydroxy-1-methoxyprop-1-yl)-5-nitrouracil(5i) was achieved in 76% and 12.5% yield, respectively, by an alternative procedure involving reaction of 2,3-bis-(trimethylsilyloxy)-1,1-dimethoxypropane (2b) with the trimethylsilylated pyrimidine (1g,i) and subsequent removal of the O-trimethylsilyl groups under neutral aqueous conditions (Scheme 1). 1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-ethynyluracil (5k) was obtained in 23% yield by deacetylation of 1-(2,3-diacetoxy-1-methoxyprop-1-yl)-5-ethynyluracil (3k) using sodium methoxide in methanol at 25°C.

Under the reaction conditions employed, condensation of bis-O-trimethylsilyl-5-nitrouracil (1i) and N,O-bis-trimethylsilyl-N-acetylcytosine (15) with 1,3-diacetoxy-1-methoxypropane (11) afforded, not only the 1-N alkylated products 12i and 18, but also the 1,3-disubstituted pyrimidines 13 and 19 in 14% and 5% yield, respectively (Schemes 3 and 4). Reaction of 13 with ammonia in aqueous methanol led to a complex mixture, from which no single product was isolable. Deacetylation of the 1,3-disubstituted cytosine derivative 19 under these conditions was accompanied by substantial loss of the 3-N-substituent and from this reaction 1,3-bis-(3-hydroxy-1-methoxyprop-1-yl) cytosine (21) was isolated in 23% yield and the 1-N-monosubstituted derivative 20 in 66% yield.

The ^1H and ^{13}C nmr spectra (Table 1) of the 1-(2,3-diacetoxy-1-methoxyprop-1-yl)-(3a-g,j,k,9,16) and 1-(2,3-dihydroxy-1-methoxyprop-1-yl)pyrimidines (5a-k,10,17) in each case indicated the presence of the two possible diastereoisomers. No attempt was made to separate the isomers and the fact that they were not always present in equal amounts is probably attributable to differences in their behaviour during the isolation procedures rather than to any stereoselectivity during the initial condensation with the pyrimidine base. Such differences in behaviour were most clearly demonstrated when 1-(2,3-divaleryloxy-1-methoxyprop-1-yl)uracil (7) was recrystallised from acetone-n-hexane and a single diastereoisomer was isolated.

All of the acyclonucleosides prepared in this study (5a-k,10,14a-c, e,f,i,17,20,21) were tested for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 100 µg/mL, none of them inhibited the replication of influenza A (HK/1/68) virus of

TABLE 1
^{13}C Chemical Shifts[a] for 1-(2,3-Dihydroxy-1-methoxyprop-1-yl)uracils

Compound	C2	C4	C5	C6	C-OMe	CH_3O	CHOH	CH_2OH	5-Subst.
5a	151.6 151.0	163.2 163.1	101.6 100.8	141.4 141.1	85.5 85.2	56.4 55.8	72.0 71.3	62.3 61.9	- -
5b	151.7 151.0	163.8	109.2 108.3	136.9 136.5	85.4 84.9	56.2 55.8	72.1 71.1	62.4 61.9	CH_3 12.1 12.0
5c	150.3 149.5	157.7 156.5	140.1 J_{CF} = 229.3Hz 139.6 J_{CF} = 229.3Hz	125.6 J_{CCF} = 33.3Hz 125.4 J_{CCF} = 33.3Hz	85.9 85.7	56.5 55.9	71.8 71.0	62.2 61.8	- -
5d	150.7 150.0	159.1 159.0	107.3 106.4	138.4	86.1 86.0	56.7 26.1	71.7 71.1	62.2 61.7	- -
5e	150.9 150.2	159.1	95.8 94.9	140.9	86.1 86.0	56.7 56.1	71.7 71.2	62.2 61.7	- -
5f	151.3 150.6	160.4	69.3 68.1	145.7 145.5	85.9 85.7	56.6 56.0	71.7 71.2	62.1 61.7	- -
5g	150.9 150.1	159.4	103.1 J_{CCF} = 31.4 Hz	142.9	86.7	57.2 56.6	71.8	62.3 61.9	CF_3, 123.0 J_{CF} = 268.2Hz
5h	150.7 150.2	160.2 160.0	88.8 87.8	149.5	87.4 87.0	57.0 56.5	71.2	62.0 61.6	CN, 114.4 114.1

TABLE 2
^{13}C Chemical Shifts[a] 1-(3-Hydroxy-1-methoxyprop-1-yl)pyrimidines

Compound	C2	C4	C5	C6	C-OMe	CH_2	CH_2OR	CH_3O	5-Subst.
14a	151.1	163.1	102.3	140.0	83.5	37.1	56.4	55.6	
14b	151.1	163.7	109.9	135.5	83.1	37.1	56.4	55.5	CH_3 12.0
14c	149.7	157.1 J_{CCF} = 25.9Hz	140.4 J_{CF} = 231.9Hz	124.4 J_{CCF} = 33.3Hz	84.1	36.8	56.3	55.7	
14e	150.4	159.0	96.4	139.7	84.5	36.9	56.3	55.8	
14f	150.7	160.3	69.9	144.3	84.3	36.9	56.3	55.8	
20	159.2	167.2	97.9	142.6	86.7	37.5	58.5	57.5	

[a] Determined in $(CD_3)_2SO$ and quoted in ppm downfield from TMS.

parainfluenza type 1 (Sendai) virus in Madin-Darby canine kidney cells nor of herpes simplex type 1 (HFEM) virus in Vero (African green monkey kidney) cells. At the concentrations examined, none of the compounds was toxic for the cell monolayer.

EXPERIMENTAL

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 197 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM-360 60MHz or EM-390 90 MHz spectrometer. ^{13}C NMR spectra were recorded with a Bruker 20.15 MHz instrument. Mass spectra were determined using a V.G. 70-70 mass spectrometer and, unless otherwise stated, were performed at 70 e.v. and a source temperature of 200°C. Chromatography was performed on Merck 7736 60H silica gel. Elemental analysis was carried out on a Carlo Erba model 1106 analyzer.

2,3-Diacetoxy-1,1-dimethoxypropane (2a)

Acetic anhydride (5.0 g, 50 mmol) was added to a solution of DL-glyceraldehyde dimethyl acetal[21] (1.17 g, 8.6 mmol) in anhydrous pyridine (20 mL) at 0°C. The mixture was allowed to warm to 25°C and stirred for 2h. It was then poured into iced water (150 mL) and the aqueous solution extracted with dichloromethane (2 x 50 mL). The combined extracts were washed with 2N hydrochloric acid (100 mL), saturated sodium bicarbonate solution (2 x 100 mL) and water (100 mL), and then dried (anhydrous magnesium sulphate). Evaporation of the solvent under reduced pressure afforded 2a (1.70 g, 90%) as an oil; IR ν_{max} (film) 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 3.38 (s, 3H, CH_3O), 3.42 (s, 3H, CH_3O), 3.95-4.50 (m, 3H, CH_2OAc and $CH(OMe)_2$), 5.05-5.25 (m, 1H, CHOAc); MS (Ammonia CI) m/z 238 (MNH_4^+, 5%), 189 ($M^+ - OCH_3$, 95%).

2,3-Bis-trimethylsilyloxy-1,1-dimethoxypropane (2b)

A solution of DL-glyceraldehyde dimethyl acetal (1.36 g, 10 mmol) and N-trimethylsilylimidazole (5.6 g, 40 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred at 25°C for 16h. The solvent was evaporated under reduced pressure and the residue extracted with anhydrous ether (100 mL). The ether solution was washed with water (30 mL), dried (anhydrous magnesium sulphate) and evaporated, affording 2b (2.80 g, 100%); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H, $(CH_3)_3$ Si), 0.15 (s, 9H, $(CH_3)_3Si$), 3.44 (s, 3H, CH_3O), 3.48 (s, 3H, CH_3O), 3.60 (m, 3H, CH_2OSiMe_3 and $CH(OMe)_2$), 4.25 (m, 1H, $CHOSiMe_3$); MS m/z 249 ($M^+ - OCH_3$, 11%).

1,3-Diacetoxy-1-methoxypropane (11)

A solution of 1,3-dichloro-1-methoxypropane[22] (13.6 g, 95 mmol) and potassium acetate (18.6 g, 190 mmol) in acetonitrile (400 mL) was stirred at 25°C for 2h (solution A). A solution of potassium acetate (9.3 g, 95 mmol) and 18-crown-6 (25 g, 95 mmol) in acetonitrile (500 mL) was also

stirred at 25°C for 2h (solution B). Solution A was added to solution B and heated at reflux temperature for 18h. The solution was then filtered and the solvent evaporated under reduced pressure. The residue was dissolved in ether (500 mL) and the solution washed with water (3 x 500 mL) and dried (anhydrous magnesium sulphate). Removal of the solvent under reduced pressure afforded 11 (8.1 g, 45%) as a pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 2H, CH_2CH) 2.05 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 3.40 (s, 3H, CH_3O), 4.20 (t, 2H, J = 8Hz, CH_2O), 5.80 (t, 1H, J = 6Hz, CH).

General Procedure for Synthesis of 1-(2,3-Diacetoxy-1-methoxyprop-1-yl) uracils (3a-g, j, k, 9) and 1-(3-Acetoxy-1-methoxyprop-1-yl)uracils (12a-c, e, f, i)

A mixture of the appropriate uracil (7 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (30 mL) was heated at 160°C for 20h in the presence of a catalytic amount of ammonium sulphate. Evaporation under reduced pressure afforded the 2,4-bis-O-trimethylsilyluracil (1a-g, i-k) as a mobile oil, which was used without further purification.

2,3-Diacetoxy-1,1-dimethoxypropane (2a, 1.52 g, 7 mmol) or 1,3-diacetoxy-1-methoxypropane (11, 1.46 g, 7.7 mmol) was added to a solution of the 2,4-bis-O-trimethylsilyluracil (7 mmol) in anhydrous acetonitrile (50 mL). The solution was cooled to -78°C and, under nitrogen, stannic chloride (0.14 - 0.28 mmol) added. The reaction mixture was maintained under nitrogen at -78°C for an additional 15 mins. and then at 25°C for 20h. The reaction mixture was reduced to ca 10 mL under reduced pressure and saturated sodium bicarbonate solution (50 mL) added. The aqueous slurry was extracted with chloroform (2 x 100 mL) and the combined extracts dried (anhydrous magnesium sulphate) and the solvent evaporated under reduced pressure. 1-(2,3-Diacetoxy-1-methoxyprop-1-yl)uracils were then chromatographed on silica gel, eluted with 10-40% acetone in n-hexane, and the required products (3a-g, j, k, 9) recrystallised from acetone-n-hexane mixtures. 1-(3-Acetoxy-1-methoxyprop-1-yl)uracils (12a-c, e, f, i) were isolated pure either after chromatography on silica gel, eluted with the solvent specified, or by recrystallisation of either the crude product or the material isolated after chromatography.

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)uracil (3a), isolated in 40% yield, m.p. 151-152°C; IR ν_{max} (KBr) 1750 (ester C=O), 1695 (amide C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 6H, 2 x CH_3CO), 3.30 (s, 3H, CH_3O), 4.00-4.55 (m, 2H, CH_2OAc), 5.20-5.45 (m, 1H, CHOAc), 5.60-5.85 (m, 2H, CHOMe and 5-H), 7.30 (d, 0.4H, J = 8Hz, 6-H), 7.34 (d, 0.6H, J = 8Hz, 6-H), 10.15

(br.s, 1H, NH); MS (Ammonia CI) m/z 318 (MNH_4^+, 100%), 301 (MH^+, 6%).

Anal. Calcd. for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.33; N, 9.33
Found : C, 47.99; H, 5.04; N, 9.07%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-methyuracil (3b), isolated in 64.5% yield, m.p. 146-153°C; IR ν_{max} (KBr) 3170 (NH), 1747 (ester C=O), 1695 and 1685 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (m, 3H, 5-CH_3), 2.07 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 3.40 (br.s, 3H, CH_3O), 4.10-4.40 (m, 2H, CH_2OAc), 5.15-5.50 (m, 1H, CHOAc), 5.70 (s, 0.45H, CHOMe), 5.80 (s, 0.55H, CHOMe), 7.25 (m, 1H, 6-H), 9.50 (br.s, 1H, NH); MS m/z 314 (M^+, 0.22%).

Anal. Calcd. for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.73; N, 8.91
Found : C, 49.36; H, 5.66; N, 8.46%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-fluorouracil (3c), isolated in 60% yield, m.p. 132-134°C; IR ν_{max} (KBr) 1755 (ester C=O), 1725 and 1695 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 3.25 (s, 1.5H, CH_3O), 3.30 (s, 1.5H, CH_3O), 3.95-4.40 (m, 2H, CH_2OAc), 5.15-5.40 (m, 1H, CHOAc), 5.55-5.75 (m, 1H, CHOMe), 7.80 (d, 0.5H, $J_{H,F}$ = 13Hz, 6-H), 7.87 (d, 0.5H, $J_{H,F}$ = 13Hz, 6-H), 11.90 (br.s, 1H, NH); MS (Ammonia CI) m/z 336 (MNH_4^+, 39%).

Anal. Calcd. for $C_{12}H_{15}FN_2O_7$: C, 45.28; H, 4.71; F, 5.97; N, 8.80
Found : C, 45.39; H, 4.53; F, 5.59; N, 8.47%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-chlorouracil (3d), isolated in 56% yield, m.p. 158-160°C; IR ν_{max} (KBr) 1760 and 1745 (ester C=O), 1675 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO), 3.40 (s, 1.8H, CH_3O), 3.44 (s, 1.2H, CH_3O), 4.15-4.55 (m, 2H, CH_2OAc), 5.20-5.55 (m, 1H, CHOAc), 5.65-5.85 (m, 1H, CHOMe), 7.80 (s, 0.6H, 6-H), 8.00 (s, 0.4H, 6-H), 11.90 (br.s, 1H, NH); MS (Ammonia CI) m/z 352 (MNH_4^+, 26%), 335 (MH^+, 7%).

Anal. Calcd. for $C_{12}H_{15}ClN_2O_7$: C, 43.04; H, 4.48; Cl, 10.61; N, 8.37
Found : C, 43.43; H, 4.65; Cl, 10.63; N, 8.64%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-bromouracil (3e), isolated in 49% yield, m.p. 159-161°C; IR ν_{max} (KBr) 1765 and 1745 (ester C=O), 1683 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 3.38 (s, 1.2H, CH_3O), 3.42 (s, 1.8H, CH_3O), 4.00-4.65 (m, 2H, CH_2OAc), 5.10-5.40 (m, 1H, CHOAc), 5.65-5.90 (m, 1H, CHOMe), 7.64 (s, 0.4H, 6-H), 7.68 (s, 0.6H, 6-H), 9.50 (br.s, 1H, NH); MS m/z 378/380 (M^+, 0.22%).

Anal. Calcd. for $C_{12}H_{15}BrN_2O_7$: C, 37.99; H, 3.95; Br, 21.10; N, 7.38
Found : C, 37.81; H, 3.85; Br, 21.20; N, 7.37%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-iodouracil (3f), isolated in 49% yield, m.p. 152-160°C; IR ν_{max} (KBr) 1756 and 1740 (ester C=O), 1666 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (br.s, 6H, 2 x CH_3CO), 3.41 (s, 1.2H, CH_3O), 3.45 (s, 1.8H, CH_3O), 4.00-4.75 (m, 2H, CH_2OAc), 5.10-5.55 (m, 1H, CHOAc), 5.80-5.95 (m, 1H, CHOMe), 7.77 (s, 0.4H, 6-H), 7.82 (s, 0.6H, 6-H), 9.67 (br.s, 1H, NH); MS m/z 426 (M^+, 0.27%).

Anal. Calcd. for $C_{12}H_{15}IN_2O_7$: C, 33.80; H, 3.52; I, 29.81; N, 6.57
Found : C, 33.80; H, 3.28; I, 30.05; N, 6.56%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (3g), isolated in 65% yield, m.p. 129-134°C; IR ν_{max} (KBr) 1730 (ester C=O), 1690 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 6H, 2 x CH_3CO), 3.40 (s, 1.55H, CH_3O), 3.43 (s, 1.45H, CH_3O), 3.90-4.65 (m, 2H, CH_2OAc), 5.10-5.50 (m, 1H, CHOAc), 5.81 (m, 1H, CHOMe), 7.65-8.00 (m, 1H, 6-H), 11.70 (br.s, 1H, NH); MS m/z 337 (M^+-OCH_3, 1.4%)

Anal. Calcd. for $C_{13}H_{15}F_3N_2O_7$: C, 42.39; H, 4.07; N, 7.60
Found : C, 42.50; H, 3.68; N, 7.77%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-nitrouracil (3i), isolated in 24% yield, m.p. 131-140°C; IR ν_{max} (KBr) 1738 (ester C=O), 1720 (amide C=O), 1525 and 1340 (N=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 2.06 (br.s, 6H, 2 x CH_3CO), 3.46 (s, 0.6H, CH_3O), 3.50 (s, 0.4H, CH_3O), 4.05-4.75 (m, 2H, CH_2OAc), 5.25-5.60 (m, 1H, CHOAc), 5.85-6.10 (m, 1H, CHOMe), 8.74 (s, 0.4H, 6-H), 8.85 (s, 0.6H, 6-H), 12.40 (br.s, 1H, NH); MS (Ammonia CI) m/z 363 (MNH_4^+, 7%).

Anal. Calcd. for $C_{12}H_{15}N_3O_9$: C, 41.73; H, 4.34; N, 12.17
Found : C, 41.88; H, 4.34; N, 11.89%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-vinyluracil (3j), isolated in 53% yield, m.p. 192°C (decomp.); IR ν_{max} (KBr) 1745 (ester C=O), 1685 (amide C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.98 (s, 3H, CH_3CO), 2.25 (s, 3H, CH_3CO), 3.30 (s, 2.45H, CH_3O), 3.34 (s, 0.55H, CH_3O), 3.95-4.50 (m, 2H, CH_3OAc), 5.10-5.50 (m, 2H, CHOAc and CH=CH_2), 5.75 (m, 1H, CHOMe), 5.80-6.20 (m, 1H, CH=CH_2), 6.30-6.70 (m, 1H, CH=CH_2), 7.60 (s, 0.18H, 6-H), 7.75 (s, 0.82H, 6-H), 11.45 (br.s, 1H, NH); MS m/z 326 (M^+, 1%).

Anal. Calcd. for $C_{14}H_{18}N_2O_7$: C, 51,53; H, 5.52; N, 8.58
Found : C, 51.59; H, 5.70; N, 8.38%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-5-ethynyluracil (3k), isolated in 54% yield, m.p. 188°C (decomp.); IR ν_{max} (KBr) 3257 (C≡CH), 1745 (ester C=O), 1705 and 1673 (amide C=O) cm^{-1}; ^1H NMR [(CD_3) SO] δ 2.00 (m, 6H, 2 x CH_3CO), 3.30 (m, 4H, CH_3O and C≡CH), 4.00-4.50 (m, 2H, CH_2OAc), 5.10-5.50 (m, 1H, CHOAc), 5.65-5.80 (m, 1H, CHOMe), 7.75 (s, 0.6H, 6-H), 7.95 (s, 0.4H, 6-H), 11.45 (br.s, 1H, NH); MS m/z 324 (M^+, 3%), 293 (M^+-OCH_3, 5%).

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.93; N, 8.64
Found : C, 51.50; H, 4.90; N, 8.53%

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-6-azauracil (9), isolated in 42% yield, as a glass; IR ν_{max} ($CHCl_3$) 1730 (ester C=O), 1693 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 3.45 (br.s, 3H, CH_3O), 4.05-4.80 (m, 2H, CH_2OAc), 5.20-5.75 (m, 1H, CHOAc), 5.80 (br.s, 0.4H, CHOMe), 5.93 (br.s, 0.6H, CHOMe), 7.50 (br.s, 1H, 5-H), 10.25 (br.s, 1H, NH); MS (Ammonia CI) m/z 319 (MNH_4^+, 92%), 302 (MH^+, 7%, 270 (MH^+-CH_4O, 100%).

Anal. Calcd. for $C_{11}H_{15}N_3O_7$: C, 43.85; H, 4.98; N, 13.95
Found : C, 43.74; H, 5.25; N, 13.73%

1-(3-Acetoxy-1-methoxyprop-1-yl)uracil (12a), isolated in 58% yield after chromatography (eluting solvent chloroform-methanol, 50:1) and recrystallisation from chloroform-cyclohexane, m.p. 116-117°C; IR ν_{max} Nujol) 3150 (NH), 1735 (ester C=O), 1700 and 1670 (amide C=O) cm^{-1}; H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.10 (m, 2H, CH_2CH), 3.34 (s, 3H, H_3O), 4.17 (t, 2H, J = 6Hz, CH_2OAc), 5.67 (d, 1H, J = 8Hz, 5-H), 5.86 d, 1H, J = 3Hz, CH), 7.30 (d, 1H, J = 8Hz, 6-H), 9.70 (br.s, 1H, NH); IS m/z 242 (M^+, 0.19%).

nal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56
Found : C, 49.49; H, 5.93; N, 11.27%

-(3-Acetoxy-1-methoxyprop-1-yl)-5-methyluracil (12b), isolated in 64% ield after recrystallisation from chloroform-n-hexane, m.p. 133-134°C; R ν_{max} (Nujol) 3170 (NH), 1730 (ester C=O), 1710 and 1660 (amide C=O) m^{-1}; H NMR ($CDCl_3$) δ 1.94 (s, 3H, 5-CH_3), 2.02 (s, 3H, CH_3CO), 2.06 m, 2H, CH_2CH), 3.31 (s, 3H, CH_3O), 4.14 (t, 2H, J = 6Hz, CH_2OAc), .73 (t, 1H, J = 6Hz, CH), 7.12 (s, 1H, 6-H), 9.65 (br.s, 1H, NH); 3 m/z 256 (M^+, 3%).

nal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93
Found : C, 51.15; H, 5.97; N, 10.75%

-(3-Acetoxy-1-methoxyprop-1-yl)-5-fluorouracil (12c), isolated in 47% ield after chromatography (eluting solvent ethyl acetate-methanol, 50:1) nd recrystallisation from acetone-n-hexane, m.p. 123-125°C; IR ν_{max} Nujol) 3160 (NH), 1740 (ester C=O), 1720, 1700 and 1660 (amide C=O) cm^{-1}, I NMR ($CDCl_3$) δ 2.08 (s, 3H, CH_3CO), 2.10 (m, 2H, CH_2CH), 3.40 (s, 3H, H_3O), 4.18 (t, 2H, J = 6Hz, CH_2OAc), 5.76 (t, 1H, J = 6Hz, CH), 7.40 l, 1H, $J_{H,F}$ = 6Hz, 6-H), 10.07 (br.s, 1H, NH).

nal. Calcd. for $C_{10}H_{13}FN_2O_5$: C, 46.15; H, 5.04; N, 10.77
Found : C, 45.93; H, 5.10; N, 10.71%

1-(3-Acetoxy-1-methoxyprop-1-yl)-5-bromouracil (12e), isolated in 44% yield after recrystallisation from chloroform-cyclohexane, m.p. 179-180°C; IR ν_{max} (Nujol) 3160 (NH), 1740 (ester C=O), 1720 and 1680 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.10 (m, 2H, CH_2CH), 3.37 (s, 3H, CH_3O), 4.17 (t, 2H, J = 6Hz, CH_2OAc), 5.71 (t, 1H, J = 6Hz, CH), 7.62 (s, 1H, 6-H), 9.60 (br.s, 1H, NH); MS m/z 320/322 (M^+, 0.2%).

Anal. Calcd. for $C_{10}H_{13}BrN_2O_5$: C, 37.40; H, 4.08; Br, 24.88; N, 8.72
Found : C, 37.63; H, 4.23; Br, 25.01; N, 8.62%

1-(3-Acetoxy-1-methoxyprop-1-yl)-5-iodouracil (12f), isolated in 48% yield after chromatography (eluting solvent chloroform-methanol, 50:1) and recrystallisation from chloroform-cyclohexane, m.p. 195-197°C; IR ν_{max} (Nujol) 3150 (NH), 1740 (ester C=O), 1720 and 1670 (amide C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.98 (s, 3H, CH_3CO), 2.13 (m, 2H, CH_2CH), 3.23 (s, 3H, CH_3O), 4.02 (t, 2H, J = 6Hz, CH_2OAc), 5.55 (t, 1H, J = 6Hz, CH), 7.96 (s, 1H, 6-H), 11.74 (br.s, 1H, NH); MS m/z 368 (M^+, 2.5%).

Anal. Calcd. for $C_{10}H_{13}IN_2O_5$: C, 32.63; H, 3.56; I, 34.47; N, 7.61
Found : C, 32.63; H, 3.86; I, 34.24; N, 7.39%

Alkylation of 2,4-bis-O-trimethylsilyl-5-nitrouracil (1i) under the conditions described in the general procedure afforded two products, which were separated by chromatography on silica gel, eluted with chloroform-methanol, 20:1, and identified as:

1-(3-Acetoxy-1-methoxyprop-1-yl)-5-nitrouracil (12i), isolated in 18% yield after recrystallisation from chloroform-cyclohexane, m.p. 130-132°C; IR ν_{max} (Nujol) 3150 (NH), 1740 (ester C=O), 1720 and 1690 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3CO), 2.14 (m, 2H, CH_2CH), 3.46 (s, 3H, CH_3O), 4.20 (t, 2H, J = 6Hz, CH_2OAc), 5.74 (t, 1H, J = 6Hz, CH), 8.80 (s, 1H, 6-H), 9.44 (br.s, 1H, NH); MS (Ammonia CI) m/z 305 (MNH_4^+, 26%).

Anal. Calcd. for $C_{10}H_{13}N_3O_7$: C, 41.82; H, 4.56; N, 14.63
Found : C, 41.67; H, 4.20; N, 14.46%

and 1,3-Bis-(3-acetoxy-1-methoxyprop-1-yl)-5-nitrouracil (13), isolated in 14% yield as an oil;

IR ν_{max} (Nujol) 1740 (ester C=O), 1700 and 1640 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 6H, 2 x CH_3CO), 2.07 (m, 2H, CH_2CH), 2.46 (m, 2H, CH_2CH), 3.35 (s, 3H, CH_3O), 3.40 (s, 3H, CH_3O), 4.15 (m, 4H, 2 x CH_2OAc), 5.73 (t, 1H, J = 6Hz, CH), 6.06 (t, 1H, J = 6Hz, CH), 8.67 (s, 1H, 6-H); MS (Ammonia CI) m/z 435 (MNH_4^+, 38%).

Anal. Calcd. for $C_{16}H_{23}N_3O_{10}$: C, 46.04; H, 5.55; N, 10.07
Found : C, 46.07; H, 5.49; N, 9.92%

2,3-Divaleryloxy-1,1-dimethoxypropane (6)

Valeryl chloride (12.1 g, 100 mmol) was added to a solution of DL-glyceraldehyde dimethyl acetal (5.44 g, 40 mmol) in anhydrous pyridine (40 mL) at 0°C. The mixture was allowed to warm to 25°C and then stirred for 2h. It was then poured into iced water (200 mL) and the aqueous solution extracted with chloroform (2 x 150 mL). The combined extracts were washed with 5N hydrochloric acid (2 x 150 mL), saturated sodium bicarbonate solution (2 x 200 mL) and water (100 mL) and then dried (anhydrous magnesium sulphate). The crude product obtained upon evaporation of the solvent under reduced pressure was chromatographed on silica gel, eluted with 10-20% acetone in n-hexane, affording 6 (10.96 g, 90%) as an oil; IR ν_{max} (film) 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60-2.00 (m, 14H, 2 x $CH_3(CH_2)_2$), 2.15-2.60 (m, 4H, 2 x CH_2CO), 3.44 (s, 3H, CH_3O), 3.48 (s, 3H, CH_3O), 3.95-4.70 (m, 3H, $CH(OMe)_2$ and CH_2O), 5.25 (m, 1H, CHO).

Reaction of 2,4-bis-O-trimethylsilyluracil (20 mmol) with 2,3-divaleryloxy-1,1-dimethoxypropane (6.1 g, 20 mmol) under conditions identical to those described in the above general procedure afforded 1-(2,3-divaleryloxy-1-methoxyprop-1-yl)uracil (7) in a 48% yield, m.p. 137-141°C; IR ν_{max} (KBr) 1737 (ester C=O), 1684 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.40-1.85 (m, 14H, 2 x $CH_3(CH_2)_2$), 1.90-2.50 (m, 4H, 2 x CH_2CO), 3.30 (br.s, 3H, CH_3O), 3.80-4.60 (m, 2H, CH_2O), 4.99-5.40 (m, 1H, CHO), 5.50-6.05 (m, 2H, CHOMe and 5-H), 7.23 (d, 0.33H, J = 8Hz, 6-H), 7.28 (d, 0.66H, J = 8Hz, 6-H), 10.15 (br.s, 1H, NH); MS (Ammonia CI) m/z 402 (MNH_4^+, 80%).

Fractional crystallisation of this mixture of isomers from acetone-n-hexane afforded the major diastereoisomer in 20% yield; ^1H NMR ($CDCl_3$) δ 0.63-1.95 (m, 14H, 2 x $CH_3(CH_2)_2$), 2.00-2.50 (m, 4H, 2 x CH_2CO), 3.38 (s, 3H, CH_3O), 4.20 (m, 2H, CH_2O), 5.28 (m, 1H, CHO), 5.75 (m, 2H, CHOMe and 5-H), 7.35 (d, 1H, J = 8Hz, 6-H), 9.30 (br.s, 1H, NH).

Anal. Calcd. for $C_{18}H_{28}N_2O_7$: C, 56.25; H, 7.29; N, 7.29

Found : C, 56.28; H, 7.04; N, 7.23%

General Procedure for Synthesis of 1-(2,3-Dihydroxy-1-methoxyprop-1-yl) uracils (5a-f, h, j, 10) and 1-(3-Hydroxy-1-methoxyprop-1-yl)uracils (14a-c, e, f, i)

A solution of the 1-(2,3-diacetoxy-1-methoxyprop-1-yl)uracil (3a-g, j, k) (9 mmol) and 0.88 ammonia (80 mL) in methanol (20 mL) was stirred at 25°C for 16h. The solvent was evaporated under reduced pressure and acetamide removed by sublimation (80°C, 1 mm Hg). 1-(2,3-Dihydroxy-1-methoxyprop-1-yl)uracils were chromatographed on silica gel, eluted with

25-50% acetone in n-hexane, and the required products (5a-f, h, j, 10) recrystallised from a mixture of methanol-acetone-n-hexane (1:5:4). 1-(3-Hydroxy-1-methoxyprop-1-yl)uracils (14a-c, e, f, i) were obtained by recrystallisation of the crude reaction product from the solvent specified.

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)uracil (5a), isolated in 51% yield, m.p. 134-142°C; IR ν_{max} (KBr) 3340(OH), 1680 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.10-3.80 (m, 6H, CH_3O, CH_2O, CHO), 4.70 (br.s, 1H, $CH_2\underline{OH}$), 5.10 (br.s, 1H, CHOH), 5.40-5.75 (m, 2H, CHOMe and 5-H), 7.55 (d, 0.66H, J = 8Hz, 6-H), 7.60 (d, 0.34H, J = 8Hz, 6-H), 11.16 (br.s, 1H, NH); MS m/z 216 (M^+, 7.5%).

Anal. Calcd. for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.55; N, 12.96
Found : C, 43.99; H, 5.66; N, 12.90%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-methyluracil (5b), isolated in 76% yield, m.p. 147-155°C; IR ν_{max} (KBr) 3250 (OH), 1725 and 1665 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.82 (s, 3H, CH_3), 3.22 (s, 1.2H, CH_3O), 3.27 (s, 1.8H, CH_3O), 3.30-3.80 (3H, m, CHO and CH_2O), 4.70 (br.s, 1H, $CH_2\underline{OH}$), 5.10 (br.s, 1H, CHOH), 5.45-5.65 (m, 1H, CHOMe), 7.50 (s, 1H, 6-H), 11.20 (br.s, 1H, NH); MS m/z 230 (M^+, 15.5%).

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.08; N, 12.17
Found : C, 46.80; H, 5.93; N, 12.25%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-fluorouracil (5c), isolated in 53% yield, m.p. 155-161°C; IR ν_{max} (KBr) 3350 (OH), 1710 and 1664 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.30 (s, 1.5H, CH_3O), 3.34 (s, 1.5H, CH_3O), 3.55-4.00 (m, 3H, CH_2O and CHO), 4.90 (br.s, 2H, $CH_2\underline{OH}$ and CHOH), 5.50-5.80 (m, 1H, CHOMe), 7.82 (d, 0.5H, $J_{H,F}$ = 10Hz, 6-H), 7.90 (d, 0.5H, $J_{H,F}$ = 10Hz, 6-H), 10.90 (br.s, 1H, NH); MS M/z 234 (M^+, 7%).

Anal. Calcd. for $C_8H_{11}FN_2O_5$: C, 41.02; H, 4.70; N, 11.96
Found : C, 40.99; H, 4.59; N, 11.90%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-chlorouracil (5d), isolated in 56% yield, m.p. 180-184°C; IR ν_{max} (KBr) 3455 (OH), 1710 and 1680 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.10-4.00 (m, 6H, CH_3O, CH_2O and CHO), 4.78 (br.s, 1H, $CH_2\underline{OH}$), 5.15 (br.s, 1H, CHOH), 5.40-5.60 (m, 1H, CHOMe), 7.76 (s, 0.5H, 6-H), 7.92 (s, 0.5H, 6-H), 11.80 (br.s, 1H, NH); MS m/z 250 (M^+, 8%).

Anal. Calcd. for $C_8H_{11}ClN_2O_5$: C, 38.32; H, 4.39; Cl, 14.17; N, 11.17
Found : C, 38.14; H, 4.57; Cl, 14.21; N, 11.06%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-bromouracil (5e), isolated in 74.5% yield, m.p. 195-202°C; IR ν_{max} (KBr) 3400 (OH), 1730 and 1682 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.10-3.90 (m, 6H, CH_3O, CH_2O and CHO),

4.70 (br.s, 1H, $CH_2\underline{OH}$), 5.15 (br.s, 1H, $CHO\underline{H}$), 5.40-5.60 (m, 1H, CHOMe), 7.82 (s, 0.38H, 6-H), 7.97 (s, 0.62H, 6-H), 11.75 (br.s, 1H, NH); MS m/z 294 (M^+, 4%).

Anal. Calcd. for $C_8H_{11}BrN_2O_5$: C, 32.54; H, 3.72; N, 9.49
Found : C, 32.75; H, 3.65; N, 9.55%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-iodouracil (5f), isolated in 66% yield, m.p. 201-207°C (decomp.); IR ν_{max} (KBr) 3365 (OH), 1715 and 1665 (C=0) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.20-3.90 (m, 6H, CH_3O, CH_2O and CHO), 4.75 (br.s, 1H, $CH_2\underline{OH}$), 5.15 (br.s, 1H, $CHO\underline{H}$), 5.40-5.60 (m, 1H, CHOMe), 7.92 (s, 0.4H, 6-H), 7.97 (s, 0.6H, 6-H), 11.60 (br.s, 1H, NH); MS m/z 342 (M^+, 21%).

Anal. Calcd. for $C_8H_{11}IN_2O_5$: C, 28.07; H, 3.21; N, 8.18; I, 37.13
Found : C, 28.29; H, 2.83; N, 8.12; I, 36.92%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-vinyluracil (5j), isolated in 63% yield, m.p. 242°C (decomp.); IR ν_{max} (KBr) 3465 (OH), 1685 (C=0) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 2.90-3.85 (m, 6H, CH_3O, CH_2O and CHO), 4.40-4.80 (m, 2H, 2 x OH), 4.90-5.20 (m, 1H, $CH=C\underline{H}_2$), 5.40-5.60 (m, 1H, CHOMe), 5.75-6.15 (m, 1H, $CH=C\underline{H}_2$), 6.30-6.60 (m, 1H, $C\underline{H}=CH_2$), 7.65 (s, 0.34H, 6-H), 7.72 (s, 0.66H, 6-H), 11.33 (br.s, 1H, NH); MS m/z 242 (M^+, 9%).

Anal. Calcd. for $C_{10}H_{14}N_2O_5.0.5H_2O$: C, 47.80; H, 5.97; N, 11.15
Found : C, 48.23; H, 6.20; N, 11.01%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-6-azauracil (10), isolated in 76% yield, m.p. 133-136°C; IR ν_{max} (KBr) 3510 (OH), 1710 (C=0) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.26 (s, 1.2H, CH_3O), 3.30 (s, 1.8H, CH_3O), 3.40-4.00 (m, 3H, CH_2O and CHO), 4.50 (br.s, 1H, $CH_2\underline{OH}$), 4.70-5.20 (m, 1H, $CHO\underline{H}$), 5.30-5.70 (m, 1H, CHOMe), 7.52 (s, 0.4H, 6-H), 7.58 (s, 0.6H, 6-H), 12.10 (br.s, 1H, NH); MS (Ammonia CI) m/z 235 (MNH_4^+, 100%), 218 (MH^+, 41%).

Anal. Calcd. for $C_7H_{11}N_3O_5$: C, 38.70; H, 5.06; N, 19.35
Found : C, 38.43; H, 4.77; N, 18.98%

1-(3-Hydroxy-1-methoxyprop-1-yl)uracil (14a), isolated in 63% yield after recrystallisation from chloroform-cyclohexane, m.p. 126-127°C; IR ν_{max} (Nujol) 3340 (OH), 3170 (NH), 1680 (C=0) cm^{-1}; ^1H NMR [$CDCl_3$-$(CD_3)_2SO$] δ 1.94 (m, 2H, $C\underline{H}_2CH$), 3.30 (s, 3H, CH_3O), 3.60 (m, 1H, OH), 3.64 (m, 2H, J = 6Hz, CH_2O), 5.74 (d, 1H, J = 8Hz, 5-H), 5.78 (t, 1H, J = 6Hz, CH), 7.35 (d, 1H, J = 8Hz, 6-H), 8.77 (br.s, 1H, NH); MS m/z 200 (M^+, 4%).

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99
Found : C, 48.06; H, 6.16; N, 14.07%

1-(3-Hydroxy-1-methoxyprop-1-yl)-5-methyluracil (14b), isolated in 81% yield after recrystallisation from chloroform-cyclohexane, m.p. 141-142°C; IR ν_{max} (Nujol) 3380 (OH), 3160 (NH), 1710 and 1660 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.82 (s, 3H, 5-CH_3), 1.90 (m, 2H, CH_2CH), 3.20 (s, 3H, CH_3O), 3.45 (m, 2H, J = 6Hz, CH_2O), 4.58 (t, 1H, J = 5Hz, OH), 5.65 (t, 1H, J = 6Hz, CH), 7.44 (s, 1H, 6-H), 11.26 (br.s, 1H, NH); MS m/z 214 (M^+, 7.5%), 196 ($M^+ - H_2O$, 2.5%).

Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08
Found : C, 49.97; H, 6.50; N, 12.97%

1-(3-Hydroxy-1-methoxyprop-1-yl)-5-fluorouracil (14c), isolated in 88% yield after recrystallisation from chloroform-cyclohexane, m.p. 131-133°C; IR ν_{max} (Nujol) 3420 (OH), 3150 (NH), 1710 and 1660 (C=O); ^1H NMR [$(CD_3)_2SO$] δ 1.90 (m, 2H, CH_2CH), 3.21 (s, 3H, CH_3O), 3.45 (m, 2H, J = 6Hz, CH_2O), 4.48 (m, 1H, OH), 5.63 (t, 1H, J = 6Hz, CH), 7.90 (d, 1H, $J_{H,F}$ = 7Hz, 6-H), 11.76 (br.s, 1H, NH); MS m/z 218 (M^+, 1.8%).

Anal. Calcd. for $C_8H_{11}FN_2O_4$: C, 44.04; H, 5.08; N, 12.84
Found : C, 44.02; H, 5.17; N, 12.67%.

1-(3-Hydroxy-1-methoxyprop-1-yl)-5-bromouracil (14e), isolated in 78% yield after recrystallisation from chloroform-cyclohexane, m.p. 194-196°C; IR ν_{max} (Nujol) 3400 (OH), 3150 (NH), 1680 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.94 (m, 2H, CH_2CH), 3.28 (s, 3H, CH_3O), 3.41 (m, 2H, J = 6Hz, CH_2O), 4.56 (t, 1H, J = 5Hz, OH), 5.62 (t, 1H, J = 6Hz, CH), 8.00 (s, 1H, 6-H), 11.85 (br.s, 1H, NH); MS m/z 278/280 (M^+, 3.8%).

Anal. Calcd. for $C_8H_{11}BrN_2O_4$: C, 34.43; H, 3.97; Br, 28.63; N, 10.04
Found : C, 34.26; H, 3.99; Br, 28.54; N, 10.07%

1-(3-Hydroxy-1-methoxyprop-1-yl)-5-iodouracil (14f), isolated in 83% yield after recrystallisation from chloroform-methanol, m.p. 203-205°C; IR ν_{max} (Nujol) 3400 (OH), 3150 (NH), 1720 and 1680 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.90 (m, 2H, CH_2CH), 3.22 (s, 3H, CH_3O), 3.40 (m, 2H, J = 6Hz, CH_2O), 4.55 (t, 1H, J = 5Hz, OH), 5.57 (t, 1H, J = 6Hz, CH), 7.90 (s, 1H, 6-H), 11.66 (br.s, 1H, NH); MS m/z 326 (M^+, 4%).

Anal. Calcd. for $C_8H_{11}IN_2O_4$: C, 29.47; H, 3.40; I, 38.92; N, 8.59
Found : C, 29.65; H, 3.54; I, 38.67; N, 8.49%

1-(3-Hydroxy-1-methoxyprop-1-yl)-5-nitrouracil (14i), isolated in 68% yield after recrystallisation from aqueous acetone, m.p. 160-161°C; IR ν_{max} (Nujol) 3420 (OH), 3150 (NH), 1680 and 1650 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.94 (m, 2H, CH_2CH), 3.34 (s, 3H, CH_3O), 3.50

(m, 2H, CH_2O), 4.60 (m, 1H, OH), 5.71 (t, 1H, J = 6Hz, CH), 8.77 (s, 1H, 6-H), 11.80 (br.s, 1H, NH); MS (Ammonia CI) m/z 263 (MNH_4^+, 8%).

Anal. Calcd. for $C_8H_{11}N_3O_5$: C, 39.19; H, 4.52; N, 17.14
Found : C, 38.80; H, 4.25; N, 17.30%

Treatment of 1-(2,3-diacetoxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (3g) with methanolic ammonia following the above general procedure afforded

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-cyanouracil (5h), isolated in 48% yield, m.p. 215-222°C (decomp); IR ν_{max} (KBr) 3480 and 3370 (OH), 2227 (C≡N) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.00-3.90 (m, 6H, CH_3O, CH_2O and CHO), 5.30-5.50 (m, 1H, CHOMe), 6.30 (br.s, 2H, 2OH), 8.20 (s, 0.5H, 6-H), 8.50 (s, 0.5H, 6-H); MS m/z 241 (M^+, 3%).

Anal. Calcd. for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.56; N, 17.42
Found : C, 44.52; H, 4.21; N, 16.85%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-ethynyluracil (5k)

A solution of sodium methoxide in methanol (0.25M, 12mL) was added to a solution of 1-(2,3-diacetoxy-1-methoxyprop-1-yl)-5-ethynyluracil (3k) (0.45g, 1.39 mmol) and the solution stirred at 25°C for 4h. The solution was then neutralised by addition of Amberlite IR 120 (H) ion exchange resin, filtered and the resin washed with warm methanol (125mL). The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel, eluted with 30% acetone in n-hexane. Crystallisation from a mixture of methanol-acetone-n-hexane (1:5:4) afforded 5k in 23% yield, m.p. 184°C (decomp.); IR ν_{max} (KBr) 3350 (OH), 3250 (C≡CH), 1700 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 2.80-3.90 (m, 7H, CH_3O, CH_2O, CHO and C≡CH), 4.65 (br.s, 1H, CH_2OH), 5.15 (br.s, 1H, CHOH), 5.35-5.55 (m, 1H, CHOMe), 7.74 (s, 0.5H, 6-H), 7.87 (s, 0.5H, 6-H), 11.50 (br.s, 1H, NH); MS m/z 240 (M^+, 23%).

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (5g) and 1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-nitrouracil (5i)

A mixture of the appropriate uracil (25 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (50mL) was heated at 160°C for 18h. Evaporation under reduced pressure afforded the 2,4-bis-O-trimethylsilyluracil (1g,i) as an oil, which was dissolved in anhydrous acetonitrile (75mL) and a solution of 2,3-bis-trimethylsilyloxy-1,1-dimethoxypropane (2b) (25 mmol) in anhydrous acetonitrile (75mL) added. The solution was cooled to -78°C and, under nitrogen, stannic chloride (2mL) added. The reaction mixture was maintained under nitrogen at -78°C for an additional 15mins. and then at 25°C for 18h. The reaction mixture was then reduced to ca 30mL under reduced pressure and saturated sodium

bicarbonate solution (150mL) added. The aqueous slurry was extracted with ethyl acetate (2 x 150mL) and the combined extracts dried (anhydrous magnesium sulphate) and the solvent evaporated under reduced pressure. The oil thus obtained was dissolved in methanol-water (4:1, 50mL) and the solution heated at 60°C for 6h. The solvent was then evaporated under reduced pressure and the residue chromatographed on silica gel, eluted with 20-50% acetone in n-hexane. The required products were recrystallised from methanol-acetone-n-hexane (1:5:4)

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-trifluoromethyluracil (5g), isolated in 76% yield, m.p. 166-170°C; IR ν_{max} (KBr) 3425 (OH), 1700 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.10-3.90 (m, 6H, CH_3O, CH_2O and CHO), 4.80 (br.s, 1H, $CH_2\underline{OH}$), 5.25 (br.s, 1H, $CH\underline{OH}$), 5.50-5.70 (m, 1H, CHOMe), 7.95 (s, 0.5H, 6-H), 8.06 (s, 0.5H, 6-H), 11.75 (br.s, 1H, NH); MS (Ammonia CI) m/z 302 (MNH_4^+, 77%), 285 (MH^+, 100%).

Anal. Calcd. for $C_9H_{11}F_3N_2O_5$: C, 38.02; H, 3.87; N, 9.85
Found : C, 37.72; H, 4.00; N, 9.79%

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)-5-nitrouracil (5i), isolated in 12.5% yield, m.p. 203-207°C (decomp.); ν_{max} (KBr) 3440 (OH), 1710 (C=O), 1540 and 1353 (N=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 3.10-3.70 (m, 5H, CH_3O and CH_2O), 3.75-3.95 (m, 1H, CHO), 5.40 (br.s, 2H, 2xOH), 5.50-5.75 (m, 1H, CHOMe), 8.80 (s, 0.2H, 6-H), 8.80 (s, 0.8H, 6-H), 11.45 (br.s, 1H, NH); MS (Ammonia CI) m/z 279 (MNH_4^+, 52%), 262 (MH^+, 100%).

Anal. Calcd. for $C_8H_{11}N_3O_7$: C, 36.78; H, 4.21; N, 16.09
Found : C, 36.70; H, 4.06; N, 16.35%

N-Substituted-4-N-acetylcytosines (16, 18 and 19)

A mixture of 4-N-acetylcytosine (4.59g, 30 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (70mL) was heated at 160°C for 18h. Evaporation under reduced pressure afforded, in quantitative yield, the N,O-bis-trimethylsilyl derivative (15), which was immediately dissolved in anhydrous acetonitrile (100mL) and a solution of either 2,3-diacetoxy-1,1-dimethoxypropane (2a, 6.80g, 30 mmol) or 1,3-diacetoxy-1-methoxy-propane (11, 5.70g, 30 mmol) in anhydrous acetonitrile (150mL) added. The solution was cooled to -78°C and, under nitrogen, stannic chloride (3mL) added. The reaction mixture was maintained under nitrogen at -78°C for an additional 15min. and then at 25°C for 20h. The reaction mixture was reduced to ca 50mL under reduced pressure and saturated sodium bicarbonate solution (150mL) added. The aqueous slurry was extracted with chloroform (2 x 150mL) and the combined extracts dried (anhydrous magnesium sulphate) and the solvent evaporated under reduced pressure.

1-(2,3-Diacetoxy-1-methoxyprop-1-yl)-4-N-acetylcytosine (16)

The crude product, obtained as described above, was chromatographed on silica gel, eluted with 10-40% acetone in n-hexane, affording 16 in 39% yield as a glass; IR ν_{max} ($CHCl_3$) 1750 (ester C=O), 1670 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (br.s, 6H, 2 x CH_3COO), 2.35 (s, 3H, CH_3CON), 3.37 (s, 1.2H, CH_3O), 3.40 (s, 1.8H, CH_3O), 3.90-4.65 (m, 2H, CH_2OAc), 5.15-5.60 (m, 1H, CHOAc), 5.80-6.15 (m, 1H, CHOMe), 7.53 (d, 1H, J = 8Hz, 6-H), 7.78 (d, 1H, J = 8Hz, 5-H), 10.75 (br.s, 1H, NH); MS m/z 341 (M^+, 1%).

1-(3-Acetoxy-1-methoxyprop-1-yl)-4-N-acetylcytosine (18)
and 1,3-Bis-(3-acetoxy-1-methoxyprop-1-yl)-4-N-acetylcytosine (19)

The crude product, obtained as described above, was chromatographed on silica gel, eluted with chloroform-methanol (50:1). Two compounds were isolated and identified as the monoalkylated cytosine 18, obtained in 84% yield as a yellow gum; IR ν_{max} (Nujol) 3230 (NH), 1740 (ester C=O), 1720, 1660 and 1620 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H, CH_3COO), 2.08 (m, 2H, CH_2CH), 2.30 (s, 3H, CH_3CON), 3.35 (s, 3H, CH_3O), 4.15 (t, 2H, J = 6Hz, CH_2OAc), 5.82 (t, 1H, J = 6Hz, CH), 7.47 (d, 1H, J = 8Hz, 6-H), 7.78 (d, 1H, J = 8Hz, 5-H), 10.70 (br.s, 1H, NH); MS m/z 283 (M^+, 2%).

Anal. Calcd. for $C_{12}H_{17}N_2O_5$: C, 50.88; H, 6.05; N, 14.83
Found : C, 50.67; H, 5.97; N, 14.58%

and the 1,3-dialkylated cytosine 19, obtained in 5% yield as an oil; IR ν_{max} (Nujol) 1740 (ester C=O), 1660 and 1620 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (m, 4H, 2 x CH_2CH), 2.05 (s, 6H, 2 x CH_3COO), 2.42 (s, 3H, CH_3CON), 3.37 (s, 3H, CH_3O), 3.40 (s, 3H, CH_3O), 4.15 (m, 4H, 2 x CH_2OAc), 5.75 (t, 1H, J = 6Hz, CH), 5.99 (t, 1H, J = 6Hz, CH), 6.64 (d, 1H, J = 8Hz, 5-H), 7.67 (d, 1H, J = 8Hz, 6-H); MS m/z 414 (MH^+, 0.28%), 370 (M^+-$COCH_3$, 21%).

Anal. Calcd. for $C_{18}H_{27}N_3O_8$: C, 52.29; H, 6.58; N, 10.16
Found : C, 52.57; H, 6.69; N, 9.96%

N-Substituted Cytosines (17, 20 and 21)

A solution of the N-substituted-4-N-acetylcytosine (16, 18, 19) (10 mmol) and 0.88 ammonia (100 mL) in methanol (50 mL) was stirred at 25°C for 16h. The solvent was then evaporated under reduced pressure to afford the crude product.

1-(2,3-Dihydroxy-1-methoxyprop-1-yl)cytosine (17)

The crude product was triturated with methanol (50 mL) and the undissolved solid collected by filtration, washed with methanol (50 mL) and dried affording, in 91% yield, 17, m.p. 233-236°C (decomp.);

^{1}H NMR [$(CD_3)_2SO$] δ 3.10-3.70 (m, 6H, CH_3O, CH_2O and CHO), 4.55 (br.s, 1H, $CH_2\underline{OH}$), 4.90 (d, 1H, CHOH), 5.40-5.85 (m, 2H, CHOMe and 5-H), 7.15 (br.s, 2H, NH_2), 7.40 (s, 0.5H, 6-H), 7.52 (s, 0.5H, 6-H); MS (Ammonia CI) m/z 216 (MH^+, 57%).

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.04; N, 19.53
Found : C, 44.56; H, 6.14; N, 19.48%

1-(3-Hydroxy-1-methoxyprop-1-yl)cytosine (20)

The crude product obtained from 18 was recrystallised from methanol affording, in 88% yield, 20, m.p. 247-249°C; IR ν_{max} (Nujol) 3400-3200 (OH, NH), 1670 and 1620 (C=O) cm^{-1}; ^{1}H NMR (CF_3CO_2D) δ 2.20 (m, 2H, $\underline{CH_2}CH$), 3.54 (s, 3H, CH_3O), 4.10 (t, 2H, J = 6Hz, CH_2O), 5.97 (t, 1H, J = 6Hz, CH), 6.50 (d, 1H, J = 8Hz, 5-H), 8.00 (d, 1H, J = 8Hz, 6-H); MS m/z 199 (M^+, 1.3%).

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 42.23; H, 6.58; N, 21.09
Found : C, 48.19; H, 6.72; N, 20.83%

1,3-Bis-(3-Hydroxy-1-methoxyprop-1-yl)cytosine (21)

The crude product obtained from 19 was recrystallised from methanol, affording the monalkylated cytosine 20 in 66% yield. The filtrate was evaporated under reduced pressure and the residue chromatographed on silica gel, eluted with chloroform-methanol (5:1) affording, in 23% yield, the dialkylated cytosine 21 as a foam; ^{1}H NMR [$(CD_3)_2SO$] δ 1.75 (m, 4H, 2 x $\underline{CH_2}CH$), 3.20 (s, 3H, CH_3O), 3.30 (s, 3H, CH_3O), 3.48 (m, 4H, 2 x CH_2O), 4.52 (m, 2H, 2 x OH), 5.50 (t, 1H, J = 6Hz, CH), 5.68 (t, 1H, J = 6Hz, CH), 5.93 (d, 1H, J = 8Hz, 5-H), 7.56 (d, 1H, J = 8Hz, 6-H), 7.96 (d, 1H, J = 9Hz, NH).

Anal. Calcd. for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63
Found : C, 49.86; H, 7.39; N, 14.92%

ACKNOWLEDGEMENT

We thank Mr. M.R. Boyd and his colleagues for biological evaluation of the compounds reported.

REFERENCES

1. Y. Votruba and A. Holý, Collect. Czechoslov. Chem. Commun., 45, 3039 (1980).
2. E. De Clercq, J. Descamps, P. De Somer and A. Holý, Science, 200, 503 (1978).
3. G.B. Elion, P.A. Furman, J.A. Fyfe, P. De Miranda, L. Beauchamp and H.J. Schaeffer, Proc. Natl. Acad. Sci. U.S.A., 74, 5716 (1977).

4. K.O. Smith, K.S. Galloway, W.L. Kennell, K.K. Ogilvie and B.K. Radatus, Antimicrob. Agents Chemotherapy, 22, 55 (1982).
5. W.T. Ashton, J.D. Karkas, A.K. Field and R.L. Tolman, Biochem. Biophys. Res. Commun., 108, 1716 (1982).
6. M.H. St. Clair, W.H. Miller, R.L. Miller, C.U. Lambe and P.A. Furman, Antimicrob. Agents Chemotherapy, 25, 191 (1984).
7. J.C. Martin, G.A. Jeffrey, D.P.C. McGee, M.A. Tippie, D.F. Smee, T.R. Matthews and J.P. Verheyden, J. Med. Chem., 28, 358 (1985).
8. A. Larsson and P.-Z. Tao, Antimicrob. Agents Chemotherapy, 25, 524, (1984).
9. J.L. Kelley and L. Beauchamp, Ann. Reports in Med. Chem., 18, 139 (1983).
10. M.L. Wolfrom, W. von Bebenburg, R. Pagnucco and P. McWain, J. Org. Chem., 30, 2732 (1965).
11. J.L. Kelley, J.E. Kelsey, W.R. Hall, M.P. Krochmal and H.J. Schaeffer, J. Med. Chem., 24, 753 (1981).
12. K.K. Ogilvie and D.M. Dixit, Nucleosides and Nucleotides, 2, 147 (1983).
13. A.C. Schroeder, R.G. Hughes, Jr. and A. Bloch, J. Med. Chem., 24, 1078 (1981).
14. J.E. McCormick and R.S. McElhinney, J. Chem. Res. (S), 176 (1983).
15. S.H. Chu, Z.H. Chen, E.C. Rowe, F.N.M. Naguib, M.H. el Kouni and M.Y. Chu, Nucleosides and Nucleotides, 3, 303 (1984).
16. U. Niedballa and H. Vorbruggen, J. Org. Chem., 39, 3654 (1974).
17. D.S. Noyce and J.A. Virgilio, J. Org. Chem., 37, 2643 (1972).
18. C.H. Depuy and C.A. Bishop, J. Amer. Chem. Soc., 82, 2535 (1960).
19. H.C. Brown and R.L. Klimisch, J. Amer. Chem. Soc., 88, 1425 (1966).
20. H. Kimoto and L.A. Cohen, J. Org. Chem., 45, 3831 (1980).
21. E.J. Witzemann, W.L. Evans, H. Hass and E.F. Schroeder, Organic Synthesis, Coll. Vol. II, 307 (1959).
22. R. Voet, Bull. Soc. Chim., 41, 1308 (1927).

Received March 25, 1985.