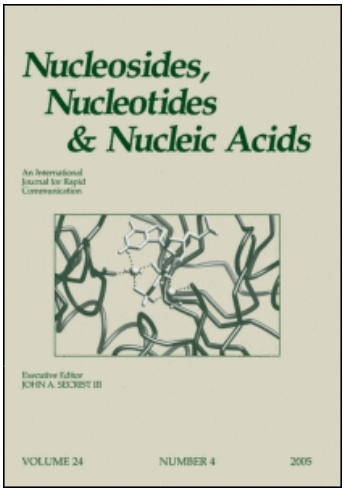


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis of Novel 5-Trifluoroethoxy Pyrimidine Nucleosides

P. Kumar[a]; L. I. Wiebe[a]
[a] Division of Bionucleonics and Radiopharmacy, University of Alberta, Edmonton, Canada

To cite this Article Kumar, P. and Wiebe, L. I.(1990) 'The Synthesis of Novel 5-Trifluoroethoxy Pyrimidine Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 9: 6, 861 — 873
To link to this Article: DOI: 10.1080/15257779008043151
URL: http://dx.doi.org/10.1080/15257779008043151

NUCLEOSIDES & NUCLEOTIDES, 9(6), 861-873 (1990)

THE SYNTHESIS OF NOVEL 5-TRIFLUOROETHOXY PYRIMIDINE NUCLEOSIDES

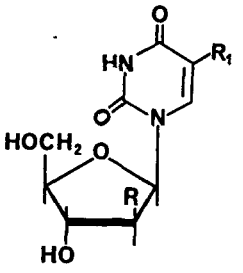
P. Kumar and L.I. Wiebe*
Division of Bionucleonics and Radiopharmacy
University of Alberta, Edmonton, T6G 2N8 Canada

ABSTRACT: The syntheses of 5-(2,2,2-trifluoroethoxy)uracil, 5-(2,2,2-trifluoroethoxy)arabinouridine and 5-(2,2,2-trifluoroethoxy) uridine are described.

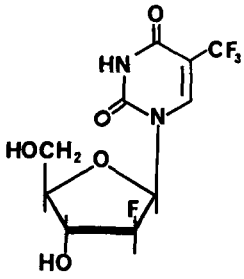
INTRODUCTION

The fluorinated pyrimidines were first developed in 1957, primarily as potential drugs for the treatment of advanced cancer.[1,2] Chemical elaboration of this class of xenobiotics has yielded many 5-substituted pyrimidine nucleoside analogs which are effective antiviral agents.[3] The most potent and selective pyrimidine nucleosides, 5-(2-bromovinyl)-arabinouridine (BVAU, 1),[4] 5-(2-chlorovinyl)-arabinouridine (CVAU, 2),[4] and 5-(2-iodovinyl)-arabinouridine (IVAU, 3),[5] have been shown to exert marked inhibition of the development of cytopathogenic effects induced by herpes simplex virus type 1 (HSV-1) infection and on the multiplication and plaque formation by HSV-1, but do not show significant activity against HSV type 2 (HSV-2).[5-7] BVAU and CVAU showed extremely strong inhibition of deoxyribonucleic acid synthesis in HSV-1 infected cells, whereas their inhibitory effect on deoxyribonucleic acid synthesis in HSV-2 infected cells was much lower than that in HSV-1 infected cells.[5] Trifluridine (TFT, 4), the trifluoromethyl analog of thymidine which is useful in treating herpetic eye infections in man,[8] is not selectively antiviral *per se*, because it is also phosphorylated in uninfected cells, where it inhibits normal cell DNA synthesis.[9] However, the 2'-fluoro-arabinosyl analog of TFT 5 has been reported to be a selective inhibitor of HSV-1 and HSV-2 in cell culture.[10]

Other modifications to the physiological nucleosides can also result in improved therapeutic specificity and efficacy. 5-Methoxymethyl-2′-deoxyuridine (MMdUrd, 6) for example, has been reported to exhibit antiviral activity against strains of HSV-1 in primary rabbit kidney cell cultures.[11] 5-Methylamino- (7), 5-methoxy- (8) and 5-methylthio- (9) derivatives of 2′-deoxyuridine have also been reported to exhibit good antiviral activities.[12,13]



1-4; 6-8



5

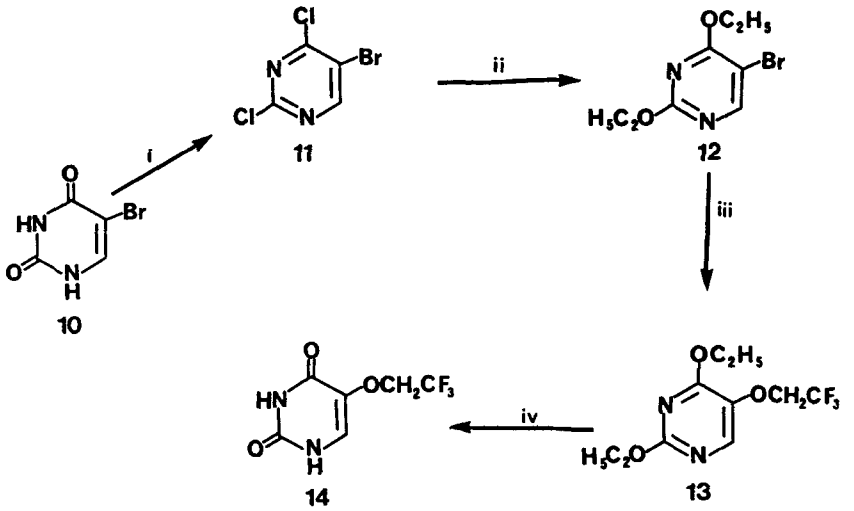
1. R_1= (E)CH=CHBr , R=OH
2. R_1= (E)CH=CHCl, R=OH
3. R_1= (E)CH=CHI, R=OH
4. R_1= CF_3, R=H
6. R_1= CH_2OCH_3, R=H
7. R_1= $NHCH_3$, R=H
8. R_1= OCH_3, R=H
9. R_1= SCH_3, R=H

We now report the synthesis of novel C-5 substituted 5-(2,2,2-trifluoroethoxy)pyrimidine nucleosides.

CHEMISTRY

Attempts to synthesize 5-(2,2,2-trifluoroethoxy)-2,4-diethoxy-pyrimidine 13 by simple condensation of sodium trifluoroethoxide with 5-bromo-2,4-diethoxy pyrimidine 12 were futile. However, this reaction proceeded smoothly with potassium trifluoroethoxide, trifluoroethanol and copper bronze in catalytic amount (Scheme 1).

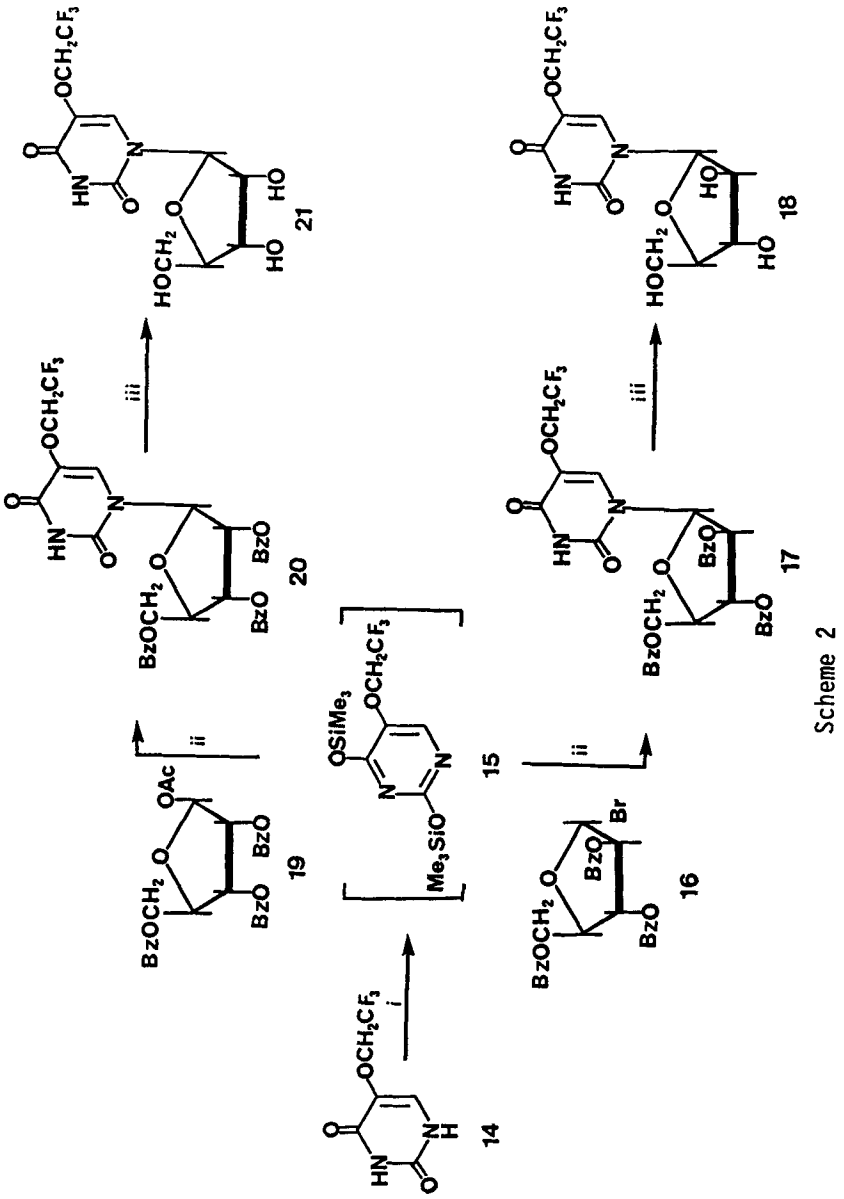
Deprotection of 13 in glacial acetic acid gave 5-(2,2,2-trifluoro-ethoxy) uracil 14, the ^1H NMR spectrum of which showed a quartet ($J_{F,H}$=8.5 Hz) at a chemical shift of δ 4.28 for 5-OCH_2CF_3 protons. The ^{19}F NMR spectrum of 14 exhibited a triplet ($J_{H,F}$=8.5 Hz) at δ 89.45 with hexafluorobenzene as an internal standard. 5-(2,2,2-Trifluoro-ethoxy) uracil 14, on conversion to its 2,4-di-O-(trimethylsilyl)



Scheme 1

i = $POCl_3$/diethylaniline; ii = $NaOCH_2CH_3$; iii = CF_3CH_2OK/Cu Bronze; iv = glacial acetic acid

derivative 15 and subsequent condensation with 1-α-bromo-2′,3′-5′-tri-O-benzoyl arabinofuranose 16 or 1-β-acetyl-2′,3′-5′-tri-O-benzoyl ribofuranose 19, in the presence of $SnCl_4$, gave 5-(2,2,2-trifluoroethoxy)-2′,3′,5′-tri-O-benzoyl arabinouridine 17 (56.5%) and 5-(2,2,2-trifluoroethoxy)-2′,3′,5′-tri-O-benzoyluridine 20 (54%), respectively (Scheme 2). An exclusive formation of the β-anomer of 17 is akin to the stereoselectivity observed in Hilbert-Johnson, silyl type reactions with tri-O-benzoyl-α-D-arabinofuranosyl bromide[14] and can be explained on the fact that ^1H NMR spectrum of 16 showed it to be the α-anomer. Moreover, the presence of an electron-withdrawing benzoyl group should make the dissociation of bromide ion from the sugar more difficult. Consequently, condensation of the sugar bromide with silylated base 15 would proceed in large measure by the S_N2 mechanism resulting in the predominant formation of the β-arabinoside.[15] The proton resonance spectrum of 18, which showed a clear doublet ($J_{2',1'}$=~3Hz) at δ 5.85, confirmed its β-anomeric configuration around C-1.[16] The ^1H NMR spectrum of 17 exhibited a



i = HMDS/(NH_4), SO_4; ii = $SnCl_4$; iii = NH_3/MeOH; B_Z = benzoyl

Scheme 2

quartet at δ 4.32 ($J_{F,H}$=8.4 Hz) for $OC\underline{H}_2CF_3$ protons. The ^{19}F NMR spectrum of 17 displayed a triplet at δ 87.62 ($J_{H,F}$=8.4 Hz). It was interesting to observe that the fluorine atoms in 17 were shielded in comparison to 14, since the chemical shift for fluorine in 17 was upfield by δ 1.8 ppm. The ^{13}C NMR spectrum of 17 showed a quartet at δ 68.55 ($J_{F,C}$=35.2 Hz) for $OCH_2\underline{C}F_3$, the quartet for $\underline{C}F_3$ being weak and merged in the base line. In the case of the ^1H NMR spectrum of 20, the quartet for the methylenic protons of $OC\underline{H}_2CF_3$ appeared at δ 4.25 ($J_{F,H}$=8.2 Hz), and the triplet for fluorine in the ^{19}F NMR appeared at δ 87.18 ($J_{H,F}$=8.2 Hz) which was upfield by δ 2.25 ppm, reconfirming that the fluorine atoms are shielded in benzoylated nucleosides. A ^{13}C Jmod spectrum of 20 exhibited two quartets, one at δ 124.00 ($J_{F,C}$=277 Hz) for the tertiary carbon ($\underline{C}F_3$) and the other at δ 68.44 ($J_{F,C}$=35.6 Hz) for the methylenic carbon ($OCH_2\underline{C}F_3$). Their debenzoylation, using ammonia/methanol solution, produced 5-(2,2,2-trifluoroethoxy)arabinouridine 18 (89%) and 5-(2,2,2-trifluoroethoxy)uridine 21 (93%), respectively. It was of interest to note that the fluorine spectra of 18 and 21 shifted downfield by δ 1.9 and δ 2.3, respectively, as compared to their benzoylated derivatives 17 and 20. ^{13}C Jmod spectra of 18 and 21 showed two quartets for each compound, one in the region of δ 126.30-124.80 for the coupling of fluorine with the tertiary carbon ($\underline{C}F_3$) and the other around δ 69.50 because of coupling of fluorine atoms with the neighboring methylenic carbon. Pertinent NMR data are summarized in Table 1.

EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker AM 300 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane (^1H NMR) and hexafluorobenzene (^{19}F NMR) as internal standard. ^1H NMR assignments were confirmed by double irradiation experiments. ^{13}C NMR resonances were assigned by using the J modulation spin echo technique (Jmod), where methyl and methine peaks are plotted above the

TABLE 1. ^{1}H, ^{19}F, ^{13}C NMR Chemical Shifts and Coupling Constants for the OCH_2CF_3 Group as Exhibited by Compounds 15-23.

Compound	^{1}H $OC\underline{H}_2CF_3$ Chemical Shift (δ)	$J_{F,H}$(Hz)	^{19}F $OCH_2C\underline{F}_3$ Chemical Shift (δ)	$J_{H,F}$(Hz)	^{13}C $O\underline{C}H_2CF_3$ Chemical Shift (δ)	$J_{F,C}$(Hz)	^{13}C $OCH_2\underline{C}F_3$ Chemical Shift (δ)	$J_{F,C}$ (Hz)
13	4.28 (q)	8.3	87.54 (t)	8.3	-	-	-	-
14	4.43 (q)	8.5	89.45 (t)	8.5	-	-	-	-
17	4.32 (q)	8.4	87.62 (t)	8.4	68.55 (q)	35.2	embedded	-
18	4.43 (q)	8.9	89.49 (t)	8.9	69.50 (q)	35.0	126.28 (q)	264
20	4.25 (q)	8.2	87.17 (t)	8.2	68.44 (q)	35.6	124.00 (q)	277
21	4.41 (q)	8.5	89.51 (t)	8.5	69.08 (q)	35.7	124.86 (q)	278

baseline and methylene and quaternary carbon resonances appear below the baseline, to determine the number of attached hydrogens. Thin layer chromatography (TLC) was performed on Whatman MK6F silica gel microslides (250 um thickness). The TLC solvent systems employed were: chloroform/ methanol=90/10 and 95/5 (v/v). Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 mesh particle size). Pyridine and acetonitrile were distilled over calcium hydride and used fresh at the time of reaction. Dichloromethane was dried over phosphorous pentoxide and freshly distilled just before use.

5-Bromo-2,4-dichloropyrimidine (11). 5-Bromouracil 10 (25 g; 131 mmole) was mixed with phosphorous oxychloride (100 mL) and diethylaniline (15 mL, 94.3 mmole), and the mixture was refluxed for 5 h (until the starting material was not evident on TLC) with mechanical stirring and under an inert atmosphere. Excess $POCl_3$ was removed by distillation under water pump vacuum and the crude mass was recrystallized from hexane; yield 26 g (87%); B.P. 111-113°C; 112-113°C (lit).[17]

5-Bromo-2,4-diethoxypyrimidine[18] (12). Sodium (4.5 g; 195 mmole) was dissolved in absolute ethanol (20 mL), then diluted with an additional 50 mL of ethanol, followed by gradual addition of 11 (22 g, 96.5 mmole). The reaction mixture was then heated under reflux for 2 h, cooled to room temperature and filtered. The solid was washed with absolute ethanol (2 x 50 mL), the filtrate and the washings were combined, neutralized with Dowex cation exchange resin to pH 7.0 and evaporated on a rotoevaporator to get the crude product, which was recrystallized from hexane to give 21.5 g (89%) of pure 12: mp 69°C; ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H, H-6), 4.45 (q, J_{CH_3,CH_2}=7.4 Hz, 2H of $OC\underline{H}_2CH_3$ at C-2), 4.30 (q, 2H of $OC\underline{H}_2CH_3$ at C-4, J_{CH_3,CH_2}=7.4 Hz), and 1.36 (two t, merged, 6H of two $OCH_2C\underline{H}_3$ groups).

5-(2,2,2-Trifluoroethoxy)-2,4-diethoxypyrimidine (13). Potassium hydroxide (354 mg, 6.3 mmole) was added to 2,2,2-trifluoroethanol (3 mL) and the mixture was heated under reflux for 48 h. Excess of trifluoroethanol was removed by distillation *in vacuo* and the salt was dried on high vacuum overnight. Trifluoroethanol (2 mL),

12 (0.4 g, 1.62 mmole) and copper bronze (31.5 mg) were added to the residue, and the contents were heated at reflux for 48 h, under an inert atmosphere with mechanical stirring. The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was filtered to remove the copper bronze, and the precipitate was washed with ethyl ether (10 mL). The filtrate and the washings were combined, evaporated and purified on a silica gel column using gradients of toluene/ethyl acetate (1%, 2%, 5%) to recover 0.25 g (58%) of pure 13: mp 57°C; ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H, H-6), 4.45 (q, J_{CH_3,CH_2}=7.4 Hz, 2H of $OC\underline{H}_2CH_3$ attached at C-2), 4.32 (q, J_{CH_3,CH_2}=7.4 Hz, 2H of $OC\underline{H}_2CH_3$ attached at C-4), 4.28 (q, $J_{F,H}$=8.3 Hz, 2H, $OC\underline{H}_2CF_3$) and 1.37 (two triplets of $OCH_2C\underline{H}_3$ at C-2 and C-4 positions, J_{CH_2,CH_3}=7.4 Hz, 6H); LRMS for $C_{10}H_{13}F_3N_2O_3$ (266.20) M^+ (100%).

5-(2,2,2-Trifluoroethoxy)uracil (14). A solution of 13 (0.4 g, 1.88 mmole) in glacial acetic acid (20 mL) was added to 2N HCl solution (1.6 mL)[19] and the mixture was heated to reflux for 45 minutes. The solvent was removed *in vacuo*, and the crude solid recrystallized from methanol: yield 0.2 g(63%); mp 276°C; ^{1}H NMR (CD_3OD) δ 7.35 (s, 1H, H-6), 4.43 (q, $J_{F,H}$=8.5 Hz, 2H, $OC\underline{H}_2CF_3$); ^{19}F NMR (CD_3OD+C_6F_6) δ 89.45 (t, $J_{H,F}$=8.5 Hz); anal calc. for $C_6H_5F_3N_2O_3$ (210.2); C, 34.29; H, 13.33; N, 2.40; found; C, 34.34; H, 13.20; N, 2.30; LRMS M^+ (54.2%).

5-(2,2,2-Trifluoroethoxy)-2′,3′,5′-tri-O-benzoyl arabinouridine (17). 1-α-Bromo-2′,3′,5′-tri-O-benzoyl arabinofuranose, 16, was prepared from 1-α-methoxy-2′,3′,5′-tri-O-benzoyl arabinofuranose by reaction with HBr,[20] and 5-(2,2,2-trifluoroethoxy)-2,4-trimethylsilyloxy pyrimidine 15,[21] was generated *in situ* by reaction of 14 (88 mg, 0.42 mmole) with hexamethyl disiloxane (4 mL) under a nitrogen atmosphere in the presence of a pinch of ammonium sulphate. Excess HMDS was evaporated, the contents were dried on the vacuum pump for 5 minutes and were then added to a solution of 16 (0.28 mmole) in anhydrous dichloromethane (5 mL) under an inert atmosphere. Anhydrous $SnCl_4$ (0.28 mmole) was also added to this mixture and the contents were stirred overnight. A few drops of methanol were added to stop the reaction, the solvent was evaporated *in vacuo* and the crude product

was recovered from a silica gel column, using gradients of toluene/ethyl acetate (1%, 2% and 5%), to give 155 mg (56.5%) of pure 17: mp 91°C; ^{1}H NMR ($CDCl_3$) δ 8.68 (s, broad, exchanges with D_2O, 1H, NH), 8.06-7.92 (m, 6 ortho protons of three phenyl groups), 7.60-7.28 (m, remainder, 9H, of three phenyl groups), 7.20 (s, 1H, H-6), 6.21 (d, $J_{2',1'}$=2.9 Hz, 1H, H-1'), 5.80 (d, $J_{1',2'}$=2.9 Hz of d, $J_{3',2'}$=3.7 Hz, 1H, H-2'), 5.70 (m, 1H, H-3'), 4.89 (m, 1H, H-4'), 4.70 (d, $J_{4',5'}$=4.64 Hz of d, J_{gem}=12.4 Hz, 1H, H-5'), 4.59 (d, $J_{4',5"}$=4.64 Hz of d, J_{gem}= 12.4 Hz, 1H, H-5") and 4.32 (q, $J_{F,H}$=8.4 Hz, 2H, OCH_2CF_3); ^{19}F NMR ($CDCl_3$ + C_6F_6) δ 87.62 (t, $J_{H,F}$=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.39 and 165.27 (C=O of two benzoyls), 158.86 (C-4), 148.65 (C-2), 134.06 (C-6), 134.00-129.31 (carbons of phenyls and C-5), 91.26 (C-1'), 83.71 (C-4'), 80.74 (C-2'), 77.45 (C-3'), 68.55 (q, $J_{F,C}$=35.2 Hz, OCH_2CF_3) and 63.67 (C-5'); anal. calc. for $C_{32}H_{25}F_3N_2O_{10}$ (656.54); C, 58.72; H, 3.85; N, 4.28; found; C, 58.87; H, 4.19; N, 4.33.

5-(2,2,2-Trifluoroethoxy)arabinouridine (18). Compound 17 (130 mg, 0.2 mmole) was taken up in a saturated solution of ammonia in methanol (10 mL) and stirred overnight at 25°C. The solvent was evaporated *in vacuo* and the residue was loaded in the form of a slurry on a silica gel column. An elution gradient, starting with chloroform and ending with 8% methanol in chloroform, yielded 62 mg (89%) of pure 18: mp 215°C (dec.); ^{1}H NMR (CD_3OD) δ 7.66 (s, 1H, H-6), 5.85 (d, $J_{2',1'}$=3.0 Hz, 1H, H-1'), 4.43 (q, $J_{F,H}$=8.9 Hz, 2H, OCH_2CF_3), 4.30 (d, $J_{5',4'}$=3.75 Hz of d, $J_{3',4'}$=3.8 Hz, 1H, H-4'), 4.20 (d, $J_{1',2'}$= 3.0 Hz of d, $J_{3',2'}$=3.8 Hz, 1H, H-2'), 4.09 (d, $J_{2',3'}$=3.8 Hz of d, $J_{4',3'}$=3.8 Hz, 1H, H-3'), 3.76 (d, $J_{4',5'}$=3.8 Hz of d, J_{gem}=12.0 Hz, 1H, H-5') and 3.70 (d, $J_{4',5"}$=3.8 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"); ^{19}F NMR (CD_3OD + C_6F_6) δ 89.49 ($J_{H,F}$=8.9 Hz); ^{13}C NMR (CD_3OD) δ 161.73 (C-4), 151.23 (C-2), 134.70 (C-5), 130.32 (C-6), 126.28 (q, J_{F-C}=264 Hz, CF_3), 93.90 (C-1'), 89.83 (C-4'), 82.00 (C-2'), 77.39 (C-3'), 69.50 (q, J_{F-C}=35 Hz, OCH_2CF_3), and 63.08 (C-5'); anal. calc. for $C_{11}H_{13}F_3N_2O_7 \cdot ½\ H_2O$ (351.24); C, 37.61; H, 4.02; N, 7.97; found C, 37.74; H, 3.98; N, 7.59; LRMS M^+ (2.4%).

5-(2,2,2-Trifluoroethoxy)-2',3',5'-tri-O-benzoyluridine (20). Compound 14 (89 mg, 0.42 mmole) was dissolved in hexamethyl disiloxane

(4 mL) and refluxed under argon for 5 h together with a pinch of ammonium sulphate. Excess HMDS was evaporated *in vacuo* and the oily mass 15 was used as such for further reaction. A solution of 19 (143 mg, 0.28 mmole) in anhydrous acetonitrile (4 mL) was added to 15 under argon in the presence of two drops of anhydrous $SnCl_4$, and the mixture was stirred overnight at 25°C.[22] A few drops of methanol were added to this mixture and the solvent was evaporated *in vacuo* to leave an oily mass which, after purification on a silica gel column using gradients of toluene/ethyl acetate (1%, 2% and 5%), gave 150 mg (54%) of pure 20:mp 81°C; ^{1}H NMR ($CDCl_3$) δ 8.74 (s, broad, D_2O exchangeable, 1H, NH), 8.16-7.90 (three d, 6H of three phenyls), 7.66-7.30 (m, 10H, 9H of three phenyls and 1H of H-6), 6.43 (d, $J_{2',1'}$=6.4 Hz, 1H, H-1'), 5.88 (d, $J_{2',3'}$=6.4 Hz of d, $J_{4',3'}$=3.8 Hz, 1H, H-3'), 5.72 (t, $J_{1',2'}$= $J_{3',2'}$=6.4 Hz, 1H, H-2'), 4.84-4.68 (m, 1H, H-4', 2H, H-5') and 4.25 (q, $J_{F,H}$= 8.2 Hz, 2H of OCH_2CF_3); ^{19}F NMR (CD_3OD+C_6F_6) δ 87.18 (t, $J_{H,F}$= 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.14, 165.35 (C=O carbons of two benzoyl groups), 158.57 (C-4), 148.80 (C-2), 134.09-128.56 (C-6 plus phenyl carbons), 127.91 (C-5), 124.00 (q, $J_{F,C}$=277 Hz, CF_3), 87.78 (C-1'), 80.89 (C-4'), 73.39 (C-3'), 71.31 (C-2'), 68.43 (q, $J_{F,C}$=35.6 Hz, methylenic carbon of OCH_2CF_3) and 63.84 (C-5'); anal. calc. for $C_{32}H_{25}F_3N_2O_{10}$ (654.54); C, 58.50; H, 3.85; N, 4.10; found; C, 58.87; H, 4.19; N, 4.33.

5-(2,2,2-Trifluoroethoxy)uridine (21). Compound 20 (0.22 mmole) was dissolved in a saturated solution of methanolic ammonia (10 mL) and stirred overnight at 25°C. TLC, at this time, showed complete conversion of the starting material to its debenzoylated product. Excess solvent was evaporated and the crude product loaded in the form of a slurry on a silica gel column. A sequential elution with 2%, 5% and 8% methanol gave the fraction containing the product which on evaporation *in vacuo* yielded 70 mg (93%) of pure 21: mp 170°C; ^{1}H NMR(CD_3OD) δ 8.10 (s, 1H, H-6), 5.91 (d, $J_{2',1'}$=3.71 Hz, 1H, H-1'), 4.41 (q, $J_{F,H}$=8.5 Hz, 2H, OCH_2CF_3), 4.19 (m, 2H, H-2' and H-3'), 4.05 (m, 1H, H-4'), 3.90 (d, $J_{4',5'}$=2.6 Hz of d, $J_{5',5''}$=12.0 Hz, 1H, H-5'), and 3.76 (d, $J_{4',5''}$=2.6 Hz of d, $J_{5',5''}$=12.0 Hz, 1H, H-5"); ^{19}F NMR (CD_3OD+ C_6F_6) δ 89.51 (t, $J_{H,F}$=8.5 Hz); ^{13}C NMR (CD_3OD) δ 161.44 (C-4), 151.28 (C-2), 135.16 (C-6), 128.56 (C-5), 124.86 (q, $J_{F,C}$=278 Hz, CF_3), 90.86

(C-1′), 86.30 (C-4′), 75.93 (C-3′), 71.07 (C-2′), 69.08 (q, $J_{F,C}$=35.7 Hz, O<u>C</u>H_2CF_3) and 61.91 (C-5′); anal. calc. for $C_{11}H_{13}F_3N_2O_7$ (342.23); C, 38.60; H, 3.83; N, 8.19; found; C, 38.25; H, 3.99; N, 7.94.

ACKNOWLEDGEMENTS

This work was carried out with financial support from the Medical Research Council of Canada, grant number MA9684. The authors wish to thank Mrs. Carolyn Hartwig for her patience in typing the manuscript.

REFERENCES

1. Curreri, A.R.; Ansfield, R.J.; McIver, F.H.; Waisman, H.A.; Heidelberger, C.; *Cancer Res.* **1958**, *18*, 478.

2. Chaudhary, N.K.; Montag, B.J.; Heidelberger, C.; *Cancer Res.* **1958**, *18*, 318.

3. De Clercq, E.; Pyrimidine nucleoside analogues as antiviral agents. In: Targets for the Design of Antiviral Agents (De Clercq, E. and Walker, R.T., eds.), Plenum Publishing Corp., **1984**, 203-230.

4. Sakata, S.; Shibuya, H.; Machida, H.; Yoshino, H.; Hirota, K.; Senda, S.; Ikeda, K.; Mizuno, Y.; *Nucleic Acids Res. Symp. Ser.* **1980**, *8*, s39.

5. Machida, H.; Sakata, S.; Kuminaka, A.; Yoshino, H.; *Antimicrob. Agents. Chemother.*, **1981**, *20*, 47.

6. Machida, H.; Sakata, S.; *Antiviral Res.*, **1984**, *4*, 135.

7. Cheng, Y-C.; Dutschman, G.; Fox, J.J.; Watanabe, K.A.; Machida, H.; *Antimicrob. Agents Chemother.*, **1981**, *20*, 420.

8. Carmine, A.A.; Brogden, R.N.; Heel, R.C.; Speight, T.M.; Avery, G.S.; *Drugs*, **1982**, *23*, 329.

9. Tone, H.; Heidelberger, C.; *Mol. Pharmacol.*, **1973**, *9*, 783.

10. Smee, D.F.; Chernow, M.; Kraft, M.; Okamoto, P.M.; Prisbe, E.J.; *Nucleosides and Nucleotides*, **1988**, *7(2)*, 155.

11. Gupta, S.V.; Tourigny, G.; Stuart, A.L.; De Clercq, E.; Quail, J.W.; Ekiel, I.; El-Kabbani, O.A.L.; Delbaere, L.T.J.; *Antiviral Res.*, **1987**, *7*, 69.

12. Nemes, M.M.; Hilleman, M.R.; *Proc. Soc. Exp. Biol. Med.*, **1965**, *119*, 515.

13. Sidwell, R.W.; Huffman, J.H.; *Appl. Microbiol.*, **1971**, *22*, 797.

14. Shen, T.Y.; Lewis, H.M.; Ruyle, W.V.; *J. Org. Chem.*, **1965**, *30*, 835, Keller, F.; Bunker, J.; Tyrrill, A.R.; *J. Med. Chem.*, **1967**, *10*, 979; Keller, F.; Tyrrill, A.R.; *J. Org. Chem.*, **1966**, *31*, 1289.

15. Watanabe, K.A.; Su, T-L.; Reichman, U.; Greenberg, N.; Lopez, C.; Fox, J.J., *J. Med. Chem.*, **1984**, *27*, 91.

16. Stevens, J.D.; Fletcher, H.G. Jr.; *J. Org. Chem.*, **1968**, *33*, 1799.

17. Schreiber, K.C.; *J. Chem. Soc.*, **1953**, 1646.

18. Hilbert, G.C.; Johnson, T.B.; *J. Am. Chem. Soc.*, **1930**, *52*, 2001.

19. Abrams, D.N.; In: Ph.D. Thesis, The University of Alberta, Edmonton, Canada, **1983**, 73.

20. Zorbach, W.W.; Pietsch, G.; *Annal.*, **1962**, *655*, 26.

21. Gut, J.; *Collec. Czech. Chem. Commun.*, **1958**, *23*, 1588.

22. Stevens, C.L.; Blumbergs, P.; In: "Synthetic Procedures in Nucleic Acid Chemistry" (Zorbach, W.W., Tipson, R.S., eds.), Wiley Interscience Publisher, New York, **1968**, *1*, 317.

Received February 24, 1990.