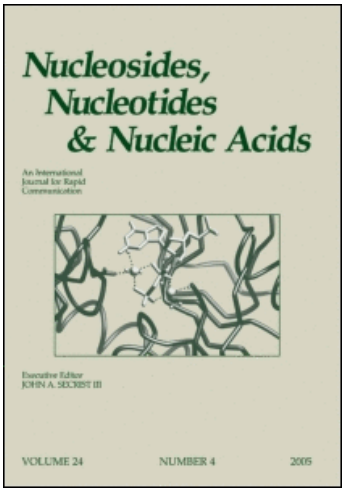


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis Of 6-Alkoxy-5-bromo-5,6-dihydropyrimidine Nucleosides Using Dibutyltin Alkoxide-Bromine

A. George Samuel[a]; Hari Babu Mereyala[a]; K. N. Ganesh[a]
[a] Division of Organic Chemistry, National Chemical Laboratory, Pune, INDIA

To cite this Article Samuel, A. George , Mereyala, Hari Babu and Ganesh, K. N.(1992) 'Synthesis Of 6-Alkoxy-5-bromo-5,6-dihydropyrimidine Nucleosides Using Dibutyltin Alkoxide-Bromine', Nucleosides, Nucleotides and Nucleic Acids, 11: 1, 49 — 60
To link to this Article: DOI: 10.1080/07328319208021152
URL: http://dx.doi.org/10.1080/07328319208021152

NUCLEOSIDES & NUCLEOTIDES, 11(1), 49-60 (1992)

SYNTHESIS OF 6-ALKOXY-5-BROMO-5,6-DIHYDROPYRIMIDINE NUCLEOSIDES USING DIBUTYLTIN ALKOXIDE-BROMINE

A. George Samuel, Hari Babu Mereyala and K.N. Ganesh*

Division of Organic Chemistry,
National Chemical Laboratory, Pune 411008, INDIA.

ABSTRACT: The pyrimidine nucleosides (1-3), on reaction with bromine and dibutyltin oxide in appropriate alcohols gave the titled compounds (5-7), which were characterised by derivatisation to 8-10, ^{1}H and ^{13}C NMR. The reported method of bromination of nucleosides in presence of DBTO under neutral and mild conditions facilitates the isolation of acid-labile 6-alkoxy-5-bromo-5,6-dihydro addition compounds of nucleosides which are otherwise difficult to obtain.

INTRODUCTION

Pyrimidine nucleosides functionally modified at the 5,6 double bond, have attracted significant attention, as antiviral and anticancer agents[1-4]. The 5-halopyrimidine nucleosides are known to effect inhibition of nucleic acid synthesis and to possess potential cytotoxic activity[3]. They have also recently emerged as useful intermediates for a variety of synthetic transformations[4,5], including introduction of non-radioactive labels in nucleic acids[6,7]. Besides, being present as unusual components of t-RNA, the 5,6-dihydropyrimidine nucleosides are also involved as key intermediates in photoinduced dimerizations and lesions[2,9]. Consequently, there is considerable interest in selective

---

+NCL Communication No. 4796

and efficient synthesis of 5-halo and 5,6-dihydropyrimidine nucleosides and their analogues.

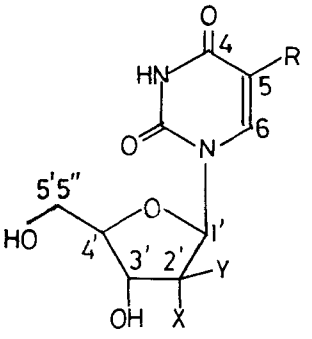
The pyrimidine nucleosides **1** and **3** on direct reaction with either halogens or with electrophilic sources of halogens such as N-halosuccinimide in alcoholic/non-aqueous media are known[5] to yield 5-halopyrimidine nucleosides **4**. In non-aqueous media, where the reaction proceeds by electrophilic addition of halogen at C5, the acidic reaction conditions often lead to cleavage of sensitive glycosidic linkage. In alcoholic media, the reaction involves addition of an alkoxide moiety at C6 to yield 5-halo-6-alkoxy-5,6-dihydropyrimidines (**5-7**). However, under the reaction conditions, these undergo a facile elimination of elements of alcohol from C5-C6 to yield 5-halopyrimidines **4**. The current methodologies are therefore not satisfactory for isolation of the intermediate 5,6-dihydro addition compounds

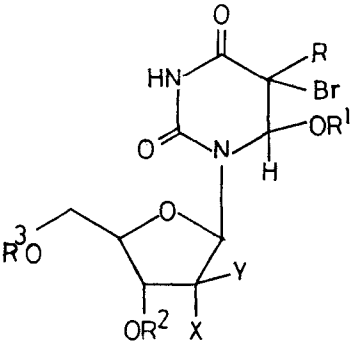
In this paper, we report a novel method for synthesis of 6-alkoxy-5-bromo-5,6-dihydropyrimidine nucleosides (**5-7**) by reaction of nucleosides with bromine and dibutyltin oxide in alcoholic media. The essentially neutral reaction conditions prevent the side reactions such as deglycosylation and elimination enabling a facile isolation of 5,6-addition intermediates (**5-7**). The versatality of this method is illustrated by the synthesis of 6-methoxy (**5a-7a**), 6-ethoxy (**5b-7b**) and 6-isopropyloxy (**5c-7c**) derivatives. These were characterized by ^{1}H and ^{13}C NMR after conversion into their corresponding acetates **(8-10)**.

RESULTS AND DISCUSSION

Reaction of ribo and arabinonucleosides with DBTO and Br_2

The nucleosides uridine (**1**), thymidine (**2**) and the arabinofuranosyl uracil (**3**) on refluxing with methanol and dibutyltin oxide (DBTO) gave a homogeneous solution, to which on cooling at $0^{o}C$, was added a molar equivalent of either bromine or dioxane dibromide. The reactions were complete within 15min, as seen by tlc which showed in each





R': **a=CH_3, b=CH_2CH_3, c=$CHMe_2$**

1 **R=Y=H, X=OH**

2 **R=CH_3, X=Y=H**

3 **R=X=H, Y=OH**

4 **R=Br, X/Y=OH/H**

5 **R=R^2=R^3=Y=H, X=OH**

6 **R=CH^3, R^2=R^3=X=Y=H**

7 **R=R^2=R^3=X=H, Y=OH**

8 **R=Y=H, R^2=R^3=X=OAc**

9 **R=CH_3, X=Y=H, R^2=R^3=OAc**

10 **R=X=H, R^2=R^3=Y=OAc**

case a faster moving compound. The solvent was completely removed from reaction mixtures to obtain white residues which were extracted directly into D_2O and characterised by ^1H NMR as **5a**, **6a** and **7a** respectively. On the other hand, treatment of the residues **5a**, **6a** and **7a** separately with pyridine-acetic anhydride, gave the corresponding acetate derivatives **8a-10a** as single products which could be isolated and characterised by ^1H and ^{13}C NMR. Attempts to purify **5a-7a** by complete removal of solvent, extraction and chromatography were not successful and led to isolation of the 5-bromo derivative **4** from **5a** whereas **6a** and **7a** gave a mixture of decomposed products. The use of bis(tributyltin) oxide instead of DBTO, in combination with bromine in methanol, also yielded the 5,6 addition compounds **5a-7a.** A similar reaction done on **1** without addition of DBTO gave **4**, whereas reaction of **2** and **3** led to the formation of mixtures of products inseparable by silica gel chromatography.

According to t.l.c., the reaction of uridine (**1**) with bromine in methanol at low temperature ($0^{o}C$) produces the 5,6-addition compound, which on work-up got converted into the 5-bromo derivative **4**. The 5,6-addition compound also resulted by mere addition of solid DBTO to a reaction mixture of uridine, alcohol and bromine. Replacing methanol with ethanol or 2-propanol, under similar conditions, led to formation of the corresponding 6-alkoxy-5-bromo-5,6-dihydro derivatives (**5b,c-7b,c**).

Spectroscopic characterization

The formation of 5,6-addition compounds in all cases was indicated by the disappearence of the characteristic UV absorption in the region 250-290nm due to the 5,6-double bond. The 5,6-addition compounds obtained after the reaction were directly extracted into D_2O for ^{1}H NMR in situ as these compounds could not be isolated for purification. However, the corresponding acetates could be isolated and fully characterised by ^{1}H and ^{13}C NMR.

In ^{1}H NMR, the olefinic signals due to H5 and H6 in **1** and **3** and that due to H6 in **2** disappeared in the reaction products and new signals appeared at 3.38 ppm and 5.26 ppm due to H5 and H6 respectively. The incorporation of an alkoxy moiety was clearly indicated by signals around 3.50-3.60 ppm. With all nucleosides, the product obtained was a diastereomeric mixture as evidenced by double signals due to H5 and H6 and the product ratio as estimated from relative intensity of these signals was 3:1. However, the products **5c-7c** from reaction of nucleosides **1-3** in 2-propanol were obtained as a single diastereomer as seen from ^{1}H NMR.

The 5,6-addition compounds **5-7** were converted into their corresponding 2',3',5'-tri-O-acetates **8-10** and characterised by both ^{1}H and ^{13}C NMR. The ^{1}H NMR of these exhibited apart from the characteristic acetate peaks around 2.00ppm downfield shifts for H2',H3' and H5'5" protons. In addition, acetate formation was not accompanied by

eliminations at C5-C6 to generate **4** as indicated by the chemical shifts of H5 and H6 protons. The alkyl protons of the 6-alkoxy groups OCH_3, OCH_2CH_3, and $OCH(CH_3)_2$ showed signals as expected in the relevant chemical shift regions.

The ^{13}C NMR spectrum of **8-10** also confirmed the structure of 5,6-addition compounds. The appearance of peaks around 39 ppm and 86 ppm respectively, due to C5 and C6 clearly prove the formation of 5,6-addition compounds. In the case of thymidine derivatives, the presence of methyl group caused chemical shift of C5 to be further downfield at 53 ppm. All other chemical shifts are according to the expected pattern, thus completely supporting the assigned structures.

Role of DBTO and reaction mechanism

The effective role of DBTO in the present reaction is realised by the fact that its absence led to (i) the formation of 5-halogenopyrimidine derivatives instead of the 5,6-addition compounds and (ii) slower overall rate of reaction. Alternatively, DBTO may be acting as a mild base in scavenging the acid liberated during the reaction.

$$R'OH + Br_2 = R'OBr + HBr$$

DBTO is also known to react with sugar hydroxyl groups to form cyclic 2':3'-dibutylstannylidene intermediates[10], which in present case may help solubilization of the nucleosides in alcoholic solvents.

It should be pointed out that deglycosylation is retarded when the reaction of nucleosides with bromine in methanol is conducted in the presence of silver carbonate[4]. The mild basicity of DBTO seems to be an important factor in arresting the reaction after the addition step and not permitting any elimination reaction. It is difficult to surmise on the origin of basicity of DBTO or its alkoxides, as their exact molecular structures are not known, although aggregates of dimeric to polymeric forms are reported to exist[13-15]. We have recently reported regioselective 5'-O-silylation of ribonucleosides[16] exploiting the mild basicity of DBTO.

Dibutyltin oxide is known to give dibutyltin alkoxides when heated with alcohols under reflux[10-12].

$$(Bu_2SnO)_n + R'OH = Bu_2Sn(OR')_2$$

It is also possible that these alkoxides on reaction with bromine, may generate alkyl hypobromites which add across the 5,6-double bond of nucleosides.

$$Bu_2Sn(OR')_2 + 2\ Br_2 = Bu_2SnBr_2 + 2\ R'OBr$$

However, at present, we do not have any direct evidence to support such a mechanistic path.

An interesting aspect of the reactions in presence of DBTO is the total non-observance of elimination reactions. If initially a <u>syn</u> addition occurs, then final elimination which would be <u>anti</u> can take place without difficulty. However, if initially, a <u>anti</u> addition happens, then epimerization at C5 must take place before the final <u>syn</u> elimination takes place. Such epimerizations are known to occur mainly under acidic conditions[17]. The presence of DBTO as a mild base within the reaction medium may supress eliminations, allowing the isolation of 5,6-addition compounds. Another novel feature of the present reaction is the non-participation of internal hydroxyls of sugar moiety. The 5,6-bromonium ion intermediate formed initially can, in principle, be attacked intramolecularly by 5'-OH to give 5',6-dihydro cyclonucleoside. However, this was not noticed during reactions in presence of DBTO. To further test this possibility, we did a similar reaction on arabinonucleosides **3** where the 2'-hydroxyl is orientated ideally for such an addition reaction. However, we failed to notice any intramolecular addition to form 2'6-anhydro nucleosides. The determination of stereochemistry of the products is under progress.

CONCLUSION

In this paper, we have reported a mild method for synthesis and isolation of 6-alkoxy-5-bromo-5,6-dihydro addition derivatives of nucleosides, using bromine in

presence of DBTO. These mild conditions enabled the isolation of 5,6-addition compounds of nucleosides which were characterized by chemical derivatization, ^{1}H and ^{13}C NMR. None of the internal sugar hydroxyls participate in intramolecular Michael type addition to the 5,6-double bond. The presently reported mild method of alkyl hypobromite addition to 5,6-double bond of pyrimidine nucleosides under neutral conditions may be valuable in preparation of halo-alkoxy derivatives of acid-labile compounds. It also opens up ways to synthesize varieties of 5,6-addition compounds of pyrimidine nucleosides which may have pharmacological and medicinal relevance.

EXPERIMENTAL PROCEDURE

All nucleosides were obtained from Aldrich, USA. Dibutyltin oxide was procured from Fluka whereas, bis(tributyl)tin oxide was from E.Merck. The precoated tlc sheets were from E.Merck and the solvent system used was ethyl acetate for 5-bromo addition compounds (**4-7**) and petroleum ether(60^{o}-80^{o}C):ethyl acetate (1:1,v/v) for the acetate derivatives (**8-10**). The spots were visualised by spray with perchloric acid-ethanol (60%, v/v) followed by charring. All ^{1}H and ^{13}C NMR spectra were recorded on Bruker ACF-200. All compounds (**8-10**) gave satisfactory C,H analysis.

General procedure for synthesis of 5-7

The nucleoside (1mmol) was heated under reflux in methanol (25ml) containing dibutyltin oxide (1mmol) until a homogeneous solution was obtained. The solution was then cooled to 0^{o}C and either bromine (1.6mmol) or dioxane dibromide (1.6mmol) was added to the solution and stirred at 0^{o}C until a pale yellow colour persisted. T.L.C showed a faster moving single spot indicating the completion of the reaction. A portion of the reaction mixture was concentrated under vacuum at low temperature and then extracted into D_2O for spectroscopic characterization (NMR, UV).

5-Bromo-6-methoxy-5,6-dihydrouridine(**5a**): Yield=85%,R_f=0.50, **^{1}H NMR:** 5.75(1H,d,5Hz,H1'), 5.24(1H,d,3Hz,H6), 4.26(1H,m, H3'), 4.05(2H,m,H4',H2'), 3.85(2H,m,H5'5"), 3.49(3H,s,OCH_3), 3.32(1H,d,3Hz,H5).

5-Bromo-6-ethoxy-5,6-dihydrouridine(**5b**): Yield=72%, R_f=0.45, **^{1}H NMR:** 5.75(1,d,5Hz,H1'), 5.28(1H,d,3Hz,H6), 4.28(1H,m,H3') 4.08(2H,m,H4',H2'), 3.85(2H,m,H5'5"), 3.70(2H,q,$O\underline{CH_2}CH_3$), 3.38(1H,d,3Hz,H5), 1.15(3H,t,$OCH_2\underline{CH_3}$).

5-Bromo-6-ispropyloxy-5,6-dihydrouridine(**5c**): Yield=78%, R_f= 0.40, **^{1}H NMR:** 5.60(1H,brd,H1'), 5.33(1H,br,H6), 4.28(1H,m, $O\underline{CH}(CH_3)_2$), 4.01(1H,m,H3'), 3.90(2H,m,H4',H2'), 3.75(1H,br, H5), 3.3(1H,br,H5), 1.21(6H,d,6Hz,$OCH(\underline{CH_3})_2$).

5-Bromo-6-methoxy-5,6-dihydrothymidine (**6a**): Yield=85%, R_f= 0.62, **^{1}H NMR:** 6.10(1H,dd,8Hz,H1'), 4.97(1H,s,H6), 4.35(1H, m,H3'), 4.10 (1H,m,H4'), 3.75(2H,m,H5'5"), 3.53(1H,s,OCH_3), 2.33(2H, m,H2'2"), 1.97(1H,s,$5CH_3$), 1.

5-Bromo-6-ethoxy-5,6-dihydrothymidine (**6b**): Yield=85%, R_f= 0.56, **^{1}H NMR:** 6.04(1H,dd,6Hz,H1'), 5.26(1H,s,H6), 4.32(1H, m,H3'), 4.20(1H,m,H4'), 3.78(2H,q,$O\underline{CH_2}CH_3$,overlapping with m for H5'5"), 2.38(2H,m,H2'2"), 1.96(3H,s,$5CH_3$), 1.12(3H,t, $OCH_2\underline{CH_3}$).

5-Bromo-6-ispropyloxy-5,6-dihydrothymidine(**6c**): Yield=82%, R_f=0.50, **^{1}H NMR:** 5.95(1H,dd,H1'), 5.19(1H,s,H6), 4.35(1H,m, H3'), 4.00(1H,m,H4',overlapping with $O\underline{CH}(CH_3)_2$), 3.75(1H,m, H5'), 2.31(2H,m,H2'2"), 1.97(1H,s,$5CH_3$), 1.19(6H,d,$OCH(\underline{CH_3})_2$

5-Bromo-6-methoxy-5,6-dihydroarabinofuranosyluracil (**7a**) : Yield=80%, R_f=0.58, **^{1}H NMR:** 5.86(1H,d,5Hz,H1'), 5.37(1H,d, 3Hz,H6), 4.3(1H,m,H3'), 4.1(2H,m,H4',H2"), 3.70(2H,m,H5'5"), 3.49(3H, s,OCH_3), 3.40(1H,d,3Hz,H5).

5-Bromo-6-ethoxy-5,6-dihydroarabinofuranosyluracil(**7b**): Yield=70%, R_f=0.54, **^{1}HNMR:**5.89(1H,d,6Hz,H1'), 5.75(1H,d,3Hz, H6), 4.34(1H,m,H3'), 4.08(2H,m,H4',H2'), 3.74(2H,m,H5'5"), 3.64 (2H,q,7Hz,$O\underline{CH_2}CH_3$), 3.35(1H,d,3Hz,H5), 1.17(3H,t,7Hz, $OCH_2\underline{CH_3}$).

5-Bromo-6-isopropyloxy-5,6-dihydroarabinofuranosyluracil(**7c**) : Yield=75%, R_f=0.46, **^{1}H NMR:** 5.70(1H,d, Hz,H1'), 5.55(1H,d, 3Hz,H6), 4.38(1H,m,H3'), 4.12(2H,m,H2',H4'), 3.85(1H,m,

$O\underline{CH}(CH_3)_2$), 3.78(2H,m,H5',5"), 3.42(1H,d,3Hz,H5), 1.13(6H,d, 6Hz,$OCH(\underline{CH_3})_2$).

Preparation of acetates (8-10)

The reaction mixture from preparations of **5-7** was concentrated and dried under vaccum and treated with pyridine (2ml) and acetic anhydride (1ml) for 4h. at 25°C. TLC at this stage showed a faster moving single spot indicating the completion of reaction. The mixture was extracted with chloroform (10-15ml). The chloroform extract were concentrated and chromatographed over a silica gel column (i.d. 3cm). Elution with petroleum ether(60°-80°C)/ethyl acetate (1:1,v/v) yielded the triacetates (**8-10**) as inseparable diastereomeric mixtures, which were then characterized by ^1H and ^{13}C NMR.

2',3',5'-Tri-O-acetyl-5-bromo-6-methoxy-5,6-dihydrouridine (**8a**): Yield=82%, R_f=0.60, **^{1}H NMR:** 9.10(1H,br,NH), 6.00(1H,d, 5.5Hz,H1'), 5.24(2H,m,H2',H3'),4.78(1H,d,2.7Hz,H6), 4.27(4H, m,H4',H5'5" overlapping with signal at 4.2,m,H2'), 3.32 (3H,s,OCH_3), 1.98, 2.05 and 2.1(each 3H,s,3x$OCOCH_3$). **^{13}CNMR:** 170.41, 169.82 and 169.62 (3x$O\underline{C}OCH_3$), 165.21 and 150.7 (CONHCO), 86.24(C6), 84.75(C1'), 79.61(C2'), 72.34(C3'), 70.13(C4'), 63.37(C5'), 56.99(CH_3), 38.41(C5), 20.41-20.80($OCO\underline{CH_3}$).

2',3',5'-Tri-O-acetyl-5-bromo-6-ethoxy-5,6-dihydrouridine (**8b**): Yield=85%, R_f=0.55; **^{1}H NMR:** 9.40(1H,br,NH), 6.00(1H,d, 5Hz,H1'), 5.29(2H,m,H2',H3'), 4.91(1H,d,3Hz,H6), 4.32-4.40 (4H,m, overlapping signals for H5,H4',H5'5"), 3.72(2H,q,7Hz $O\underline{CH_2}CH_3$), 2.10, 2.13 and 2.16 (each 3H,s,3x$COCH_3$), 1.13 (2H, t,7Hz,$OCH_2\underline{CH_3}$). **^{13}CNMR:** 170.47, 169.88 and 169.62(3x$O\underline{C}OCH_3$), 165.46 and 150.97(CONHCO),86.17(C6), 83.44(C1'), 79.48(C2'), 72.33(C3'), 70.05(C4'), 63.36(C5'), 38.79(C5), 20.73 and 20.34($OCO\underline{CH_3}$), 15.1($CH_2\underline{CH_3}$)

2',3',5'-Tri-O-acetyl-5-bromo-6-isopropyloxy-5,6-dihydrouridine(**8c**): Yield=80%, R_f=0.50. **^{1}H NMR:** 7.92(1H,br, NH), 5.94(1H,d,6Hz,H1'), 5.20(1H,m,6Hz,H2), 4.85(1H,d,2.5Hz,

H6), 4.23(3H,m,H4',H5'5"), 3.90(1H,m,O<u>CH</u>$(CH_3)_2$), 2.01 and 2.00(9H,s,3xOCO<u>CH</u>$_3$), 1.01(6H,d,6Hz,CH($\underline{CH_3}$)$_2$). **^{13}CNMR:** 170.32 170.81 and 169.61(3xO<u>CO</u>CH_3), 165.23 and 150.84 (2xCONHCO), 86.04(C6), 81.67(C1'), 79.62(C2'), 72.54(C3'), 71.75(C4'), 70.00(<u>CH</u>Me_2), 63.41(C5'), 39.67(C5), 22.95, 22.32 (CH($\underline{CH_3}$)$_2$) 20.98, 20.71 and 20.61 (3xOCO<u>CH</u>$_3$).

<u>3',5'-Di-O-acetyl-5-bromo-6-methoxy-5,6-dihydrothymidine</u>(**9a**) Yield=78%, R_f=0.68, **^{1}H NMR:** 7.55(1H,br,NH), 6.12(1H,t, 7Hz, H1'), 5.20(1H,m,H3'), 4.75(1H,s,H6), 4.23(3H,m,H4',H5'5"), 3.42(3H,s,OCH_3), 2.37(1H,m,H3'), 2.00,2.11(6H,2xs,$OCOCH_3$), 1.97(3H,s,5CH_3). **^{13}C NMR:** 170.59, 170.42(2xO<u>CO</u>CH_3), 167.35 and 150.87(CONHCO), 87.47(C6), 84.79(C1'), 81.60(C3'), 74.19 (C4'), 64.00(C5'), 58.08(OCH_3), 53.64(C5), 36.74(C2'), 22.86 (5CH_3), 21.73 and 21.22(OCO<u>CH</u>$_3$).

<u>3',5'-Di-O-acetyl-5-bromo-6-ethoxy-5,6-dihydrothymidine</u>(**9b**): Yield=75%, R_f=0.60. **^{1}H NMR:** 7.57(1H,br,NH), 6.08(1H,t,7Hz, H1'), 5.13(1H,m,H3'), 4.82(1H,s,H6), 4.22(2H,m,H4',H5'),3.77 (2H,q,O<u>CH</u>$_2$$CH_3$), 2.33(1H,m,H2'), 2.0(6H,s,2xCO<u>CH</u>$_3$), 1.95(3H,s 5CH_3), 1.06(3H,t,OCH_2<u>CH</u>$_3$). **^{13}C NMR:** 170.61 and 170.43(6H,s, 2xO<u>CO</u>CH_3), 167.20 and 150.80(CONHCO), 86.29(C6), 84.97(C1'), 81.67(C3'), 74.23(C4'), 66.4(O<u>CH</u>$_2$$CH_3$), 64.0(C5'), 53.87(C5), 36.94(C2'), 23.45(5CH_3), 21.61 and 21.07(6H,2xs,OCO<u>CH</u>$_3$).

<u>3'5'-Di-O-acetyl-5-bromo-6-isopropyloxy-5,6-dihydrothymidine</u> (**9c**): Yield=70%, R_f=0.55, **^{1}H NMR:** 8.00(1H,brs,NH), 6.11(1H, t,7Hz,H1'), 5.18(1H,m,H3'), 4.97(1H,s,H6), 4.22(3H,m,H4', H5'5"), 4.09(1H,q,6Hz,O<u>CH</u>$(CH_3)_2$), 2.38(2H,m,H2'2"), 2.12 and 2.10(6H,2xs,$OCOCH_3$), 1.95(3H,s,5CH_3), 1.0(6H,d,6Hz,OCH($\underline{CH_3}$)$_2$ **^{13}C NMR:** 170.61, 170.47(2xs,2x<u>CO</u>CH_3), 167.5, 151.22(CONHCO) 85.06(C6), 83.94(C1'), 81.62(C3'), 74.12(C4'), 70.93(O<u>CH</u>Me_2) 64.01(C5'), 54.21(C5) 37.19(C2'), 23.84(CH($\underline{CH_3}$)$_2$, 21.52 and 21.52(2xOCO<u>CH</u>$_3$).

<u>2',3',5'-Tri-O-acetyl-5-bromo-6-methoxy-5,6-dihydroarabino furanosyluracil</u>(**10a**) Yield=85%, R_f=0.64. **^{1}H NMR:** 8.00 (1H, br,NH), 5.94(1H,d,6Hz,H1'), 5.44(1H,d,3Hz,H6), 5.04(2H,t,H2' H3'), 4.35(3H,m,H4',H5'5"), 4.2(1H,d,3Hz,H5), 3.4(3H,s,CH_3), 2.11(9H,s,3x$OCOCH_3$). **^{13}C NMR:**170.67, 169.83 and 168.23 (3xO<u>CO</u>CH_3), 165.38, 150.32(CONHCO), 85.64(C6), 84.64(C1'),

80.41(C2'), 76.36(C3'), 75.37(C4'), 63.08(C5'), 57.08(OCH_3), 37.62(C5), 21.43($OCO\underline{CH_3}$).

2',3',5'-Tri-O-acetyl-5-bromo-6-ethoxy-5,6-dihydroarabino furanosyluracil(**10b**): Yield=82%, R_f=0.60 **^{1}H NMR:** 8.85 (1H, s,NH), 5.97(1H,d,4Hz,H1'), 5.46(1H,m,H6), 5.52-5.04(2H,brm, H2',H3'), 4.35(4H,m,H4',H5'5''and H5),3.65(2H,q,7Hz,$O\underline{CH_2}CH_3$) 2.1(9H,s,3x$COCH_3$), 1.17(3H,t,7Hz,$OCH_2\underline{CH_3}$). **^{13}CNMR:** 170.64, 169.83 and 169.23(3x$O\underline{CO}CH_3$), 165.53, 150.49(CONHCO), 84.47 (C6), 84.21(C1'), 80.39(C2'), 76.43(C3'), 75.41(C4'), 65.57 ($O\underline{CH_2}CH_3$), 63.12(C5'), 38.23(C5), 21.43($OCO\underline{CH_3}$), 15.26 ($OCH_2\underline{CH_3}$).

2',3',5'-Tri-O-acetyl-5-bromo-6-O-isopropyloxy-5,6-dihydro arabinofuranosyluracil (**10c**): Yield=78%, R_f=0.55. **^{1}H NMR:** 8.14(1H,s,NH), 5.87(1H,d, Hz,H1'), 5.42(1H,d, Hz,H6),5.52(2H m,H2',H3'), 4.4(4H,m,H4',H5'5",H5), 4.0(1H,q,6Hz,$O\underline{CH}(CH_3)_2$), 2.13(9H,s,3x$COCH_3$), 1.17(6H,d,6Hz,$OCH(\underline{CH_3})_2$. **^{13}C NMR:**170.75, 169.86, 168.19(3x$O\underline{CO}CH_3$), 165.86, 150.25(CONHCO), 86.60(C6), 82.23(C1'), 80.53(C2'), 78.83(C3'), 75.32(C4'),71.95($O\underline{CH}Me_2$) 63.78(C5'), 39.76(C5), 22.85($OCH(\underline{CH_3})_2$), 20.99($OCO\underline{CH_3}$).

REFERENCES

1. Baker B.R., (1967) " Design of Active Site Directed Irreversible Enzyme Inhibitors " Wiley N.Y.
2. Scheit K.H. (1980) " Nucleotide Analogs: Synthesis and Biological Functions ", John Wiley & Sons, Inc.
3. Jerkofsky M.A., Debersen M.J. and Greer S., Ann. N. Y. Acad. Sci., **1977**, 284, 389.
4. Duschinsky R., Gabriel T., Tautz W., Nausbaum A.W., Hoffer M. and Grunberg E., J. Med. Chem. **1967**,10, 47.
5. Bradshaw T. and Hutchinson D.W., Chem. Soc. Rev. **1977**, 6, 43.
6. Gilham I. C., Trends in Biotech,**1987**, 5, 332.
7. Kingsbury D.T., ibid, **1987**, 5, 107.
8. McClosky J.A. and Nishimura S., Acc. Chem. Res., **1977**, 10, 403.

9. Mizuno Y., (1986) " The Organic Chemistry of the Nucleic Acids", Elsevier Science Publishers B.V., Amsterdam.
10. Pereyere M., Quintard J.P. and Rahm A., (1987) "Tin in Organic Synthesis", Butterworth & Co. (Ltd.)
11. Poller R.C., (1970) " Chemistry of Organotin Compounds", Academic Press, New York.
12. Sauer A.K., (1971) " Organotin Compounds", Marcel Decker, New York.
13. Rouiller P., Delmau J. and Nofre C., Bull.Chem.Soc. France **1986**, 11, 3515.
14. Smith P.J.,White R.F. and Smith L., J.Organomet. Chem., **1972**, 40, 341.
15. Davies A.G., Smith P.J. and Wilkinson G., (1982) "Comprehensive Organometallic Chemistry" Volume II, Pergamon Press, p519.
16. Vidhya G., Samuel A.G., Mereyala H.B. and Ganesh K.N., Tetrahedron Lett., **1990**, 31, 1613.
17. Lipkin D. and Rabi J.A., J.Am.Chem.Soc.,**1971**, 93, 3308.

Received 3/13/91
Accepted 7/29/91