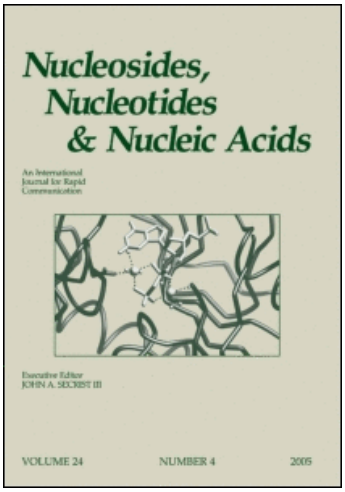

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Basnak, I. , Coe, P. L. and Walker, R. T.(1994) 'The Synthesis of Some 5-Substituted-6-aza-2'-deoxyuridines', Nucleosides, Nucleotides and Nucleic Acids, 13: 1, 163 — 175
To link to this Article: DOI: 10.1080/15257779408013233
URL: http://dx.doi.org/10.1080/15257779408013233

NUCLEOSIDES & NUCLEOTIDES, 13(1-3), 163-175 (1994)

THE SYNTHESIS OF SOME 5-SUBSTITUTED-6-AZA-2'-DEOXYURIDINES

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ABSTRACT: 5-(2-Thienyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil [VIII] and 5-cyclopropyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil [X] were obtained in high yields (93.5% and 81.3% respectively) exclusively as β anomers, by condensation of the corresponding silylated triazine bases with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride in chloroform. After deblocking both nucleosides with sodium methoxide in methanol, 5-(2-thienyl)-6-aza-2'-deoxyuridine [IX] and 5-cyclopropyl-6-aza-2'-deoxyuridine [XI] were obtained. The nucleoside IX was further acetylated, brominated with Br_2/CCl_4 and deblocked with methanolic ammonia to give 6-aza-5[2-(5-bromothienyl)]-2'-deoxyuridine [XIV].

The high activity and selectivity of 5-(2-halovinyl)-2'-deoxyuridines against herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV)[1] has expanded in recent years to include 5-substituted-2'-deoxyuridines in which the 5-(halovinyl)-group was replaced by different heteroaryl substituents. The most potent compounds of this series against HSV-1 and VZV replication so far found are 5-[2-(5-halothienyl)]-2'-deoxyuridines, possessing activity comparable with that of 5-(2-bromovinyl)-2'-deoxyuridine[2-4]. In contrast to the well documented antiviral activity of 5-substituted-2'-deoxyuridines[5], the analogues 5-substituted-6-aza-2'-deoxyuridines have been studied in much less detail and have not provided compounds of notable activity until recently. The situation changed with the synthesis

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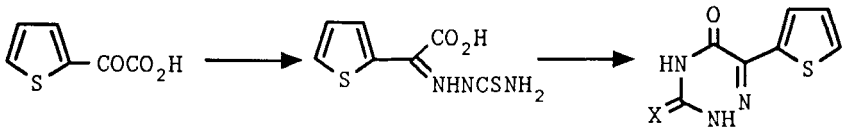
This paper is dedicated to the memory of Professor R. K. Robins.

of 5-(2-bromovinyl)-6-aza-2'-deoxyuridine[6] which showed modest activity (ID_{50} 8μg/ml) against HSV-1. This finding proved that 5-substituted-aza-2'-deoxyuridines possess potential antiviral structures. Therefore we decided to prepare 6-aza-5-[2-(5-bromothienyl)]-2'-deoxyuridine. Similarly, 5-cyclopropyl-2'-deoxyuridine[7] has been claimed to be highly active against human immunodefficiency virus type 1 (HIV-1)[8]. Moreover, the cyclopropyl group due to its unique bonding, is very sensitive towards conjugation and/or inductive properties of the rest of the molecule, which is reflected in its changing stereochemical behaviour[9, 10]. This prompted us to synthesise 5-cyclopropyl-6-aza-2'-deoxyuridine.

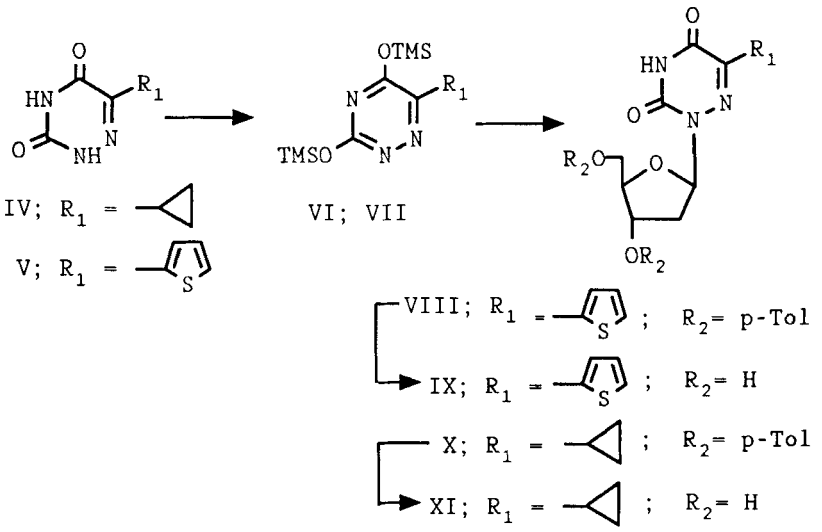
RESULTS AND DISCUSSION

5-Cyclopropyl-6-aza-uracil [V] was prepared from cyclopropylglyoxylic acid following the published procedure[11]. By analogy, starting with commercially available 2-thienylglyoxylic acid [I], condensation with thiosemicarbazide in hot water gave, in 97% yield, thiosemicarbazone II which was subsequently heated under reflux in 5% $NaOH/H_2O$, resulting in the isolation of 78% yield of 5-(2-thienyl)-6-aza-2-thiouracil [III]. Desulfuration of III with CH_3I[11] did not produce any detectable amount of the 2-oxo-derivative IV. By heating under reflux for 12 hr in 17% $ClCH_2CO_2H/H_2O$, the 2-thio-derivative III was converted to 5-(thienyl)-6-aza-uracil [IV] in 69% yield (scheme1). Resistance of the compound III towards desulfuration apparently reflects the different influence of the thienyl group on the 6-azauracil ring when compared with that of the cyclopropyl group. The required 2'-deoxyuridines were prepared via the usual series of reactions, comprising silylation of the base, condensation with chlorosugar and removal of the blocking groups under basic conditions (scheme 2). The silylation presents no problems and was very quick especially in the case of the thienyl base IV, when compared with thymine or similar uracil bases. Both bis-trimethylsilyl derivatives VI and VII were used without purification and characterization and were condensed with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride[12] in chloroform at room temperature without any catalyst. This, the first reported case of the condensation of a 6-azauracil type base under such conditions gave, in high yields, blocked nucleosides VIII (93.5%) and X (81.3%) with exclusively the β-anomeric configuration, thus supporting the general applicability and advantage of this method[13] in the synthesis of the β-anomer of pyrimidine 2'-deoxyribonucleosides. This method depends upon the fact that the



I II III; X=S
IV; X=O

Scheme 1

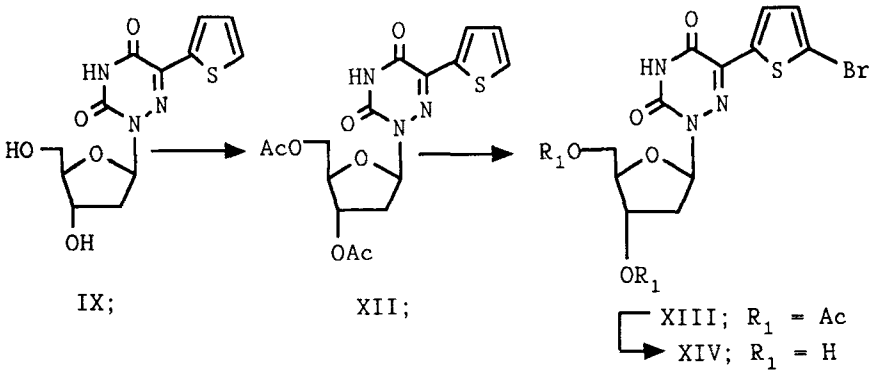


IV; R_1 =
V; R_1 =
VI; VII
VIII; R_1 = ; R_2= p-Tol
IX; R_1 = ; R_2= H
X; R_1 = ; R_2= p-Tol
XI; R_1 = ; R_2= H

Scheme 2

starting sugar has the α-configuration at C-1 and in pure chloroform does not anomerize, such that attack by the pyrimidine base takes place under SN_2 conditions with inversion of configuration to give almost entirely the β-nucleoside. The treatment of the blocked nucleoside VIII and X with 0.1M sodium methoxide in methanol gave nucleosides IX (84.9%) and XI (64.2%).

For the incorporation of bromine into the thiophene ring in compound XI the same approach was used (scheme 3) as in the case of its 2'-deoxyuridine counterpart[3]. The nucleoside XI was acetylated with acetic anhydride in pyridine (100%) and the chloroform solution of the resulting 3',5'-diacetate XII was brominated with Br_2/CCl_4. The slight excess of Br_2 and sufficient reaction time proved to be crucial



Scheme 3

for complete bromination and easy isolation of the desired nucleoside XIII (77%), otherwise a nonseparable mixture of the product XIII contaminated with starting material was obtained. Finally, the acyl groups were removed with methanolic ammonia giving 5-[2-(5-bromothienyl)]-6-aza-2'-deoxyuridine (XIV, 62.3%).

There is only limited information in the literature concerning the conformation of the 6-aza-2'-deoxyuridines. A PCILO molecular orbital study on the conformation of 6-azauridine, 6-azacytidine and 6-azathymidine[15] brings out the essential differences between the conformations of these nucleosides and their "natural" pyrimidine counterparts. In contrast to the clear anti-conformation of the glycosidic bond and prevailing S($C_{2'}$-endo) pucker of the 2-deoxyribose moiety in thymidine[16], 6-azathymidine, in addition to its prevailing N($C_{3'}$-endo) sugar pucker, seems to prefer the syn-glycosidic conformation, which may be the result of intramolecular hydrogen bonding between O(5')-H(05') of the sugar and O(2) of the base in the preferred conformation.

The comparison of the 1H-NMR data of the nucleosides IX, XI and XIV (TABLE 1 and 2) allows the following qualitative conclusions.

The values of chemical shifts, as well as coupling constants for the protons in 5-cyclopropyl-6-aza-2'-deoxyuridine [XI] are close to those of 6-azathymidine, thus indicating an overall very similar conformation of both nucleosides. The chemical shifts of the protons in the nucleosides IX and XIV are very similar to each other so that substitution of the thiophene ring with a bromine atom in XIV does not influence the overall conformation of the nucleoside IX.

TABLE 1. ^{1}H NMR Spectra of 5-substituted-6-aza-2'-deoxyuridines (DMSO-d_6).

Comp.	H-1'	H-2'	H-2"	H-3'	H-4'	H-5'	H-5"	H-R5
IX	6.41 dd,1H	2.45 m,1H	2.14 m,1H	4.42 m,1H	3.74 dd,1H	3.56 m,1H	3.42 m,1H	7.98 (dd, 1H, H-5") 7.71 (dd, 1H, H-3") 7.71 (dd,1H, H-4")
XI	6.30 dd,1H	2.33 dd,1H	2.03 dd,1H	4.24 m,1H	3.65 dd,1H	3.44 m,1H	3.32 m,1H	2.14 (m, 1H, CH) 0.97-0.79(m. 4H, CH_2-CH_2)
XIV	6.40 dd,1H	2.44 m,1H	2.14 m,1H	4.41 m,1H	3.74 dd,1H	3.54 m,1H	3.42 m,1H	7.74 and 7.31(2d, 2H, $H_{3"}$ and $H_{4"}$)
*6-ATD	6.31 dd,1H	2.40 m,1H	2.04 m,1H	4.27 dd,1H	3.70 dd,1H	3.46 dd,1H	3.34 dd,1H	2.09(s, 3H, CH_3)

*Lit. [14](6-ATD: 6-Azathymidine)

TABLE 2. 1H NMR Coupling constants of 5-substituted-6-aza-2'-deoxyuridines (Hz)

Comp.	$J_{1'2'}$	$J_{1'2"}$	$J_{2'3'}$	$J_{2'3"}$	$J_{3'4'}$	$J_{4'5'}$	$J_{4'5"}$	$J_{2'2"}$	$J_{5'5"}$	$J_{H\text{-}R1}$
IX	4.5	7.1	6.5	6.5	3.8	5.2	6.4	-13.2	-12.0	$J_{3,4}$ = 4.6; $J_{5,4}$ = 3.5 $J_{3,5}$ = 1.0
XI	5.0	7.5	6.5	5.5	4.0	5.0	6.0	-13.5	-11.5	Not analysed
*6-ATD	5.31	6.63	5.75	4.42	4.86	5.31	6.19	-13.27	-11.50	-

*Lit. [14](6-ATD: 6-Azathymidine)

Because ^{13}C-NMR data of 6-azathymidine has not been available, the chemical shifts for the nucleosides IX, XI and XIV were assigned with the help of literature data on uracil as-triazine derivatives [17,18](base, as well as those of 2'-deoxyuridines[3] (sugar moiety and thienyl bases) and finally by comparison with measured ^{13}C-NMR of thymidine (TABLE 3)

As would be expected, the chemical shifts of the carbon atoms of triazine rings in IX, XI and XIV differ from the corresponding carbons in thymidine particularly for the position C-5, due to the strong electronegative effect of N-6. The conjugation ability of thienyl [IX] or the 2-(5-bromothienyl) [XIV] group, better compensates for nitrogen electronegativity than that of the cyclopropyl group in XI (δC_5 146.70 ppm versus δC_5 137.51 or 136.55 ppm). The chemical shifts of C_2 in the triazine nucleosides are very close and are only slightly different from those in thymidine. Three distinctive signals (comparable intensity) for the carbons in the cyclopropyl group (XI; 9.08, 8.85 and 8.24 ppm) strongly support the preferred φ=120° (gauche)

TABLE 3. ^{13}C NMR Spectra of 5-(R_5)-6-aza-2'-deoxyuridines (DMSO-d_6)

Compd.	C_2	C_4	C_5	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C-R_5
IX	148.15	155.30	137.51	84.95	37.63	70.72	87.74	62.53	134.81 ($C_{2''}$): 129.50 ($C_{5''}$); 129.05 ($C_{4''}$); 127.92 ($C_{3''}$)
XI	148.31	156.41	146.70	84.19	36.85	70.39	87.01	61.89	9.08; 8.85; 8.24; (all c-C_3H_5)
XIV	148.07	155.30	136.55	84.97	37.64	70.55	87.66	62.26	136.31 ($C_{2''}$); 131.19 and 129.25 ($C_{3''}$ and $C_{4''}$); 115.67 ($C_{5''}$)
* 6-AUR	148.7	156.8	136.6	(89.7)	(72.6)	(70.6)	(84.9)	(62.3)	-
** 5-TdU	149.4	161.4	108.4	85.0	40.5	70.1	87.7	61.0	135.7 (C_6); 134.1 ($C_{2''}$); 126.5 ($C_{5''}$); 125.6($C_{4''}$); 122.7 ($C_{5''}$)
*** 5-MdU	150.53	163.80	109.42	83.82	39.49	70.50	87.32	61.41	136.18 (C_6); 121.31 (CH_3)

*Lit. [18](6-AUR: 6-Azauridine)

**Lit. [3](5-TdU: 5-(2-Thienyl)-2'-deoxyuridine)

***5-MdU: 5-Methyl-2'-deoxyuridine (Thymidine)

conformation of the cyclopropyl ring with respect to the triazine ring, as calculated by the PCILO method for 5-cyclopropyl-2'-deoxyuridine[7]. The chemical shifts of the carbons in 2'-deoxyribose in IX, XI and XIV differ from those in thymidine, particularly for $C_{2'}$, which could be connected with the prevailing syn-conformation of the glycosidic bond and resulting shielding effect of the C-2 carbonyl and /or with the prevailing N($C_{3'}$-endo) pucker of the 2-deoxyribose moiety in triazine nucleosides IX, XI and XIV as is speculated for 6-azathymidine from PCILO calculations[15].

The UV-spectra of the nucleosides IX, XI and XIV compared with that of 6-azathymidine[14] are presented in TABLE 4.

The lack of bathochromic shift of the λ_{max} in the spectra measured under alkaline conditions confirms the N-1 character of these nucleosides. The bathochromic shift of the λ_{max} in XI compared with that in 6-azathymidine is apparently the result of the conjugation of the cyclopropane with the triazine ring as was already referred to in the literature[11]. The UV-spectra of the nucleosides IX and XIV are very similar to those of their 2'-deoxyuridine counterparts[3], with the bathochromic shift of the long-wavelength maximum (ca. 14-15 nm) as a characteristic property of the triazine ring,

TABLE 4. UV-Spectra of 5-substituted-6-aza-2'-deoxyuridines.

Comp	Methanol				0.1N-HCl/H_2O				0.1N-NaOH/H_2O			
	λ_{max} (ε)		λ_{min} (ε)		λ_{max} (ε)		λ_{min} (ε)		λ_{max} (ε)		λ_{min} (ε)	
IX	330	244	281	255	332	246	284	226	321	246	283	231
	(11400)	(8900)	(3950)	(5900)	(9750)	(8100)	(3600)	(5700)	(9950)	(10150)	(3900)	(7750)
XI	270		238		270		236		260		shoulder	
	(5700)		(2300)		(6400)		(2950)		(5550)		-	
XIV	337	252	288	227	337	253	289	229	329	252	285	232
	(13030)	(8060)	(2620)	(4750)	(10290)	(7280)	(2640)	(3260)	(12060)	(9460)	(4270)	(6090)

Lit[14]: 5-Methyl-6-aza-2'-deoxyuridine-(6-azathymidine), in Ethanol. λ_{max} 267nm(ε 7750), λ_{min} 236nm(ε 3800); 0.1N-HCl λ_{max} 264nm. (ε 6550); 0.1N-NaOH λ_{max} 254 (ε 7800).

compared with the uracil ring[11]. Both thiophene nucleosides IX and XIV demonstrated very intensive UV and visible fluorescence which is the object of further investigation.

The three nucleosides, IX, XI and XIV were submitted for antiviral testing but none showed any activity against a range of DNA- and RNA-containing viruses, including herpesviruses and HIV. These are yet another example of compounds in which one modification produces a compound which is active but when more than one change is combined in one molecule, activity is lost. This is in distinction to the normal basis of SAR studies in medical chemistry and results from the fact that for most nucleosides to show antiviral activity, these need to be kinase (preferably specific viral) substrates. One modification sometimes confers viral kinase specificity but multiple changes invariably result in complete loss of enzyme recognition.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Perkin Elmer 552 spectrophotometer in the solvents specified in TABLE 4. Mass spectra were recorded on a Kratos MS80 mass spectrometer with DSS data system with automatic digital readout or a Kratos MS580. Electron-impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) were used as necessary. The ^1H and ^{13}C-NMR spectra were recorded on

Brucker AC300 and AMX400 and the chemical shift values are in ppm. Precoated Merek silica gel 60 F_{254} plates were used for TLC, and the spots were detected under UV light (254 nm). The solvent systems used were S_1, n-hexane : ethylacetate/1 : 1 and S_2, chloroform : methanol/85 : 15. Column chromatography was performed using Kieselgel 60, 230-400 mesh ASTM, type 9385. Glass columns were slurry packed under gravity. Chloroform was dried under reflux over phosphorus pentoxide, distilled and stored over type-4A molecular sieves.

2-Thienylglyoxylic acid thiosemicarbazone [II]. Thiosemicarbazide (2.7 g; 29.6 mmol) in 30 ml of hot distilled water was added at once to the 2-thienylglyoxylic acid (5 g; 32.1 mmol; LANCASTER, 98%). The reaction mixture was allowed to cool to room temperature (ca. 1 hr) and fine yellow needles were collected with suction and washed with cold distilled water (ca. 20 ml). The product II was dried in vacuo over P_2O_5, 4.92 g (67.3%). EI mass spectrum m/e 229(M^+), 211(M-H_2O), 185(M-CO_2). ^{1}H-NMR δ(DMSO-d_6) 784(1H, dd, H-5', $J_{5'4'}$=3.7 Hz, $J_{5'3'}$=1 Hz, thiophene), 7.62(1H, dd, H3', $J_{3'4'}$=5 Hz, thiophene), 7.09(1H, dd, thiophene). The compound was used in the next step without any purification.

6-(2-Thienyl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-one [III]. Compound II(4.58 g; 20 mmol) was heated under reflux in 100 ml of 5% sodium hydroxide in distilled water for 3 hr. The reaction mixture was diluted to ca. 200 ml with methanol and neutralised by dropwise addition (intensive stirring) of 10% HCl. After standing at room temperature overnight, fine, slightly yellow crystals were collected by suction and dried under vacuum over P_2O_5 to give 2.13 g (50.5%) of III. By evaporation of the mother liquor, 1.16 g (27.5%) of a second crop was obtained. The product was crystallised from methanol, M.p. 281-282 °C(dec.). TLC S_2, R_f 0.71. EI mass spectrum m/e 211(M^+). ^{1}H-NMR δ(DMSO-d_6) 13.54(1H, bs, NH), 13.34(1H, bs, NH), 8.02(1H, dd, H-5', $J_{5'4'}$=3.7 Hz, $J_{5'3'}$=1Hz, thienyl), 7.77(1H, dd, H-3', $J_{3'4'}$=5Hz, thienyl), 7.18(1H, dd, H-4' thienyl). ^{13}C-NMR δ(DMSO-d_6) 172.47(C-4), 151.92(C-2), 141.67(C-5), 134.27(C-2'thienyl), 130.27(C-5'thienyl), 129.80(C-4'thienyl), 128.07(C-3'thienyl). Elemental analysis $C_7H_5N_3OS_2$(211.25) calculated C, 39.8; H, 2.4; H, 19.9; found C, 39.9; H, 2.3; N, 19.8.

5-(2-Thienyl)-6-azauracil [IV]. III(1.1 g; 5.2 mmol) was heated under the reflux in a solution of 2.5 g of chloroacetic acid in distilled water (ca. 17%) for 13 hr and then

left at the room temperature overnight. The crystalline product IV was collected with suction and dried under vacuum over P_2O_5, 0.7 g(69%). The product was crystallised from water M.p. 274-275 °C(dec.). TLC S2, R_f 0.61. EI mass spectrum m/e 195(M^+). ^{1}H-NMR δ(DMSO-d_6) 12.47(1H, bs, NH), 12.19(1H, bs, NH), 7.94(1H, dd, H-5', $J_{5'4'}$=3.7 Hz, $J_{5'3'}$=1 Hz, thienyl), 7.67(1H, dd, H-3', $J_{3'4'}$=5 Hz, thienyl), 7.14(1H, dd, H-4', thienyl). ^{13}C-NMR δ(DMSO-d_6) 155.98(C-4), 149.01(C-2), 137.31(C-5), 135.06(C-2' thienyl), 128.80(C-5' thienyl), 128.33(C-4' thienyl), 127.74(C-3' thienyl). Elemental analysis $C_7H_5N_3O_2S$(195.19) calculated, 43.1; H, 2.6; N, 21.5; found C, 43.4; H, 2.3; N, 21.8.

5-Cyclopropyl-6-azauracil [V]. This compound was prepared following the published procedure[11]. ^{1}H-NMR δ(DMSO-d_6) 11.95(1H, s, NH); 11.89(1H, s, NH); 2.12-2.02(1H, m, CH, cyclopropyl); 0.92-0.74(4H, m, $2CH_2$, cyclopropyl). ^{13}C-NMR δ(DMSO-d_6) 157.35(C-4); 149.31(C-2); 145.94(C-5); 9.24(CH, cyclopropyl)); 7.79(CH_2, cyclopropyl). Lit[11], ^{1}H-NMR δ(DMSO-d_6) 11.79(1H, s, NH); 2.10(1H, m, CH, cyclopropyl); 0.84(4H, m, $2CH_2$, cyclopropyl).

5-2(Thienyl)-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil [VIII]. IV(0.69 g, 3.5 mmol) was heated under reflux and dry conditions with stirring in a mixture of 15 ml of hexamethyldisilazane (HMDS) and 1.5 ml of trimethylchlorosilane (TMCS). After 10 minutes the reaction mixture gave a yellow clear solution and heating was continued for 4 hrs. The excess of HMDS was removed under high vacuum at room temperature leaving crude 2,4-bis-*O*-trimethylsilyl-5-(2-thienyl)-6-azauracil [VI], which was directly used in the next step. The mixture of the silylated base VI (3.5 mmol) and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (1.2 g, 3.1 mmol)[12] in 30 ml of dry chloroform was stirred in the stoppered flask at room temperature for 12 hrs. TLC in S_1 showed the major spot of the expected product VIII, as well as very weak spot of the unreacted base IV. The reaction mixture was evaporated under vacuum to dryness (45°C) and the residue treated with 25 ml of methanol. The resulting crystalline solid (homogenous by TLC) was collected by suction and dried under high vacuum over P_2O_5, giving 1.58 g(93.5%) of the product VIII, which according to the ^{1}H-NMR spectrum proved to be exclusively the β-anomer. For elemental analysis the product was recrystallised from methanol, M.p. 229-233°C. TLC S_1, R_f 0.51. ^{1}H-NMR δ ($CDCl_3$) 9.16(1H, s, NH); 8.14(1H, dd, H-5", $J_{5'4'}$=3.7, $J_{5'3'}$=1 Hz, thienyl); 7.95(2H,

d, p-Tol); 7.87(2H, d, p-Tol); 7.46(1H, dd, H-3", $J_{3'4'}$=5Hz, thienyl); 7.26(2H, d, p-Tol); 7.10(2H, d, p-Tol); 7.09(1H, dd, H-4", thienyl); 6.73(1H, dd, $J_{1'2'}$=5 Hz, $J_{1'2'}$=7.5 Hz, H-1); 5.85(1H, m, H-3'); 4.70-4.48(3H, m, H-4', H-5', H-5"); 3.07(1H, m, H-2'); 2.56(1H, m, H-2"); 2.43(3H, s, CH_3, p-Tol); 2.35(3H, s, CH_3, p-Tol). FAB mass spectrum m/e 548$(M+1)^+$. Elemental analysis $C_{28}H_{25}N_3O_7S$(547.56) calculated C, 61.4; H, 4.6; N, 7.7; found C, 61.4; H, 4.3; N, 7.9.

5-(2-Thienyl)-6-aza-β-2'-deoxyuridine [IX]. The mixture of the blocked nucleoside VIII(1.1 g, 2 mmol) and 0.1M sodium methoxide in dry methanol (50 ml, freshly prepared from 115 mg of Na) was stirred in the stoppered flask at room temperature overnight. The reaction mixture was neutralised with Dow 50(H^+, washed with methanol) which caused the precipitation of a white solid. 100 ml of Methanol(100 ml) and 10 ml of distilled water was added to the mixture, which was gently heated until the precipitate dissolved. The resin was filtered off and washed with hot methanol until UV-absorption in the filtrate was negligible. The filtrate (ca. 200 ml) was left overnight, when fine, slightly yellow needles of the product IX were collected by suction, washed with ether and dried under high vacuum over P_2O_5, 430 mg(69.1%). From the mother liquor, the second crop was isolated upon concentration, 92 mg(14.8%). For elemental analysis the product was recrystallized from methanol/ether. M.p. 254-255 °C. TLC S_2, R_f0.46. CI mass spectrum m/e 312$(M+1)^+$. Elemental analysis $C_{12}H_{13}N_3O_5S$(311.30) calculated C, 46.3; H, 4.2; N, 13.5; found C, 46.4; H, 4.4; N,13.5.

5-Cyclopropyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil [X]. Compound V(0.84 g, 2.8 mmol) was silylated in the same way as compound IV. The mixture of 2.8 mmol of the crude 2,4-bis-*O*-trimethylsilyl-5-cyclopropyl-6-azauracil [VII] and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (1.0g, 2.8 mmol) in 40 ml of dry chloroform was stirred in a stoppered flask at room temperature overnight. The reaction mixture was evaporated in vacuo and the residue coevaporated with toluene(40 ml). The resulting viscous oil by standing overnight at the room temperature crystallised. Treatment on standing overnight with a mixture of n-hexane(20 ml) and toluene(1 ml) gave fine white crystals which were collected by suction, washed with 50 ml of the mixture of n-hexane/toluene(10 : 1) and dried under high vacuum over P_2O_5. 1.08g(81%) of the product X (M.p. 125-130 °C) was homogenous in TLC (S_1, R_f0.52). ^{1}H-NMR

spectrum confirmed that the product was pure β-anomer. For elemental analysis, the product was recrystallized from ethanol M.p. 146-148 °C. ^{1}H-NMR δ($CDCl_3$) 9.34(1H, s, NH); 7.95 and 7.25(8H, 2m, p-Tol); 6.67(1H, t, H-1'); 5.67(1H, m, H-3'); 4.58-4.40(3H, m, H-4', H-5', H-5"); 2.97-2.82(1H, m, H-2'); 2.50-2.35(1H, m, H-2"); 2.44 and 2.38(6H, 2s, $2CH_3$, p-Tol); 2.35-2.20(1H, m, CH, cyclopropyl); 1.05(4H, m, $2CH_2$ cyclopropyl). CI mass spectrum m/e 506$(M+1)^+$. Elemental analysis $C_{27}H_{27}N_3O_7$(505.53) calculated C, 64.2; H, 5.4; N, 8.3; found C, 64.0; H, 5.5; N, 8.1.

5-Cyclopropyl-6-aza-2'-deoxyuridine [XI]. A mixture of the blocked nucleoside X (260 mg, 0.51 mmol) and 0.1 M sodium methoxide in dry methanol (15 ml) was stirred at room temperature for 23 hrs, then diluted with 15 ml of methanol and neutralised with Dow 50(H^+, washed with methanol). The resin was filtered off and washed with methanol, until the UV-absorption in the filtrate was negligible. The combined filtrates were evaporated under vacuum and the residue purified on a column (5×15 cm) with the solvent system chloroform/methanol (85 : 15). The fractions containing only the product XI were combined, evaporated to dryness under vacuum (40 °C) and treated with 15 ml of ether overnight at room temperature. The resulting white crystalline solid was collected by suction, washed with ether and dried under high vacuum over P_2O_5, 75.3 mg(54.3%). By concentration of the mother liquor, a second crop was obtained, 13.7 mg(9.9%). M.p. 166-167 °C. TLC S_2, R_f0.38. CI mass spectrum m/e 270$(M+1)^+$, Elemental analysis $C_{11}H_{15}N_3O_5$(269.25) calculated C, 49.1; H, 5.6; N, 15.6; found C, 49.1; H, 5.5; N, 15.5.

5-[2-(5-Bromothienyl)]-1-(2-deoxy-3,5-di-O-acetyl-*erythro*-pentofuranosyl)-6-azauracil [XIII]. Compound IX(2.18 mg;0.7 mmol) was dissolved with vigorous shaking in 15 ml of dry pyridine and 3 ml of acetic anhydride was added. After 1 hr at room temperature, the mixture was evaporated to the dryness and coevaporated twice with toluene. The smell of pyridine and acetic anhydride completely disappeared and the residual white amorphous diacetate XII was homogenous according to TLC (S_2, R_f0.78). The crude XII was dissolved in 25 ml of dry chloroform and 115 mg(0.71 mmol) of bromine in 5 ml of tetrachloromethane was added dropwise with cooling within 20 minutes. The solution was stirred for 45 minutes (red colour of the solution turned to slightly orange) and then left aside overnight. The resulting colourless solution was washed with distilled water (2×25

ml) and the organic layer dried with magnesium sulphate. The magnesium sulphate was filtered off and the filtrate evaporated to dryness, giving 302 mg(91%) of the crude XIII, which was subsequently treated with 10 ml of ether. The white solid of pure XIII was collected with suction, washed on a filter with ether and dried under high vacuum over P_2O_5, 256 mg(77%). This product was without further purification used for deblocking. CI mass spectrum m/e 474(M^+), 476(M^+ for ^{81}Br isotope containing molecule). ^{1}H-NMR δ($CDCl_3$) 8.79(1H, s, NH); 7.89(1H, d, H-3", $J_{3"4"}$4Hz, thienyl); 7.09(1H, d, H-4", thienyl); 6.63(1H, dd, $J_{1'2'}$=5Hz, $J_{1'2"}$=7.5Hz, H-1'); 5.44(1H, m, H-3'); 4.40-4.15(3H, m, H-4', H-5', H-5"); 2.88(1H, m, H-2'); 2.40(1H, m, H-2").

5-[2-(5-Bromothienyl)]-6-aza-2'-deoxyuridine [XIV]. The diacetate XIII(118.5 mg; 0.25 mmol) was dissolved in 20 ml of dry methanol saturated with ammonia and left a room temperature for 30 hrs. The reaction mixture was evaporated under vacuum and the glassy residue was purified on a column (2×40 cm) in the solvent system 85 : 15 chloroform/methanol. The fractions containing only the product were combined and evaporated to dryness. The amorphous solid was dissolved in 3-4 ml of the mixture 85 : 15 chloroform/methanol and left in the fridge to crystallize. The white crystals of the first crop were collected by suction and dried under high vacuum over P_2O_5, 27 mg(27.7%) of the XIV. The mother liquor was evaporated to dryness and the residue was treated with 1 ml of the same solvent mixture to yield a second crop, 33.8 mg(34.6%). Both crops were homogenous and identical according to the TLC(S_2, R_f0.41) and ^{1}H-NMR spectra. FAB mass spectrum m/e 391$(M+1)^+$ and 393$(M+1)^+$ for the molecule containing ^{81}Br isotope.

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Received 7/7/93
Accepted 9/13/93