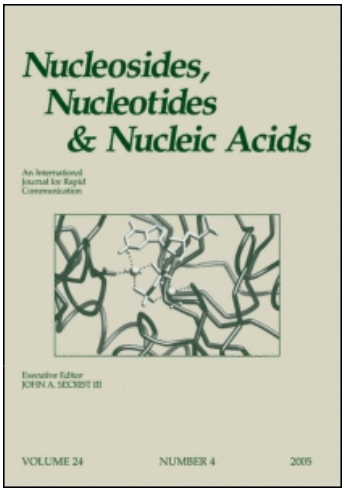


**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# The Synthesis of Some 5-Substituted and 5,6-Disubstituted 2'-Deoxyuridines

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**To cite this Article** Basnak, I. , Balkan, A. , Coe, P. L. and Walker, R. T.(1994) 'The Synthesis of Some 5-Substituted and 5,6-Disubstituted 2'-Deoxyuridines', Nucleosides, Nucleotides and Nucleic Acids, 13: 1, 177 — 196
**To link to this Article: DOI:** 10.1080/15257779408013234
**URL:** http://dx.doi.org/10.1080/15257779408013234

NUCLEOSIDES & NUCLEOTIDES, 13(1-3), 177-196 (1994)

# THE SYNTHESIS OF SOME 5-SUBSTITUTED AND 5,6-DISUBSTITUTED 2'-DEOXYURIDINES

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ABSTRACT: 5-Alkyl(cycloalkyl)-2'-deoxyuridines VIa-VIf were synthesised in high yields by condensation of the corresponding silylated bases with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride in chloroform and subsequent deblocking with sodium methoxide in methanol. The β-configuration, anti-glycosidic conformation and C2'-endo (S) sugar pucker of all of these compounds has been established from their $^1$H NMR, $^{13}$C NMR, UV and mass spectra. Under the same conditions, the condensation of silylated 5,6-trimethyleneuracil, resulted in 1:2/α:β anomeric mixture (overall yield 71%) and syn-conformation of the 5,6-trimethylene-2'-deoxyuridine [Xg]. The results of the condensation of the silylated 5,6-dimethyluracil are discussed as well. No significant antiviral activity has been found in testing the synthesised compounds against a range of herpes, influenza and HIV-1 viruses.

The antiviral activity of 5-substituted -2'-deoxyuridines has been known since the early years of nucleoside chemistry[1]. The substitution of the methyl group in the natural nucleoside thymidine for an ethyl group, resulted in the high antiviral activity of 5-ethyl-2'-deoxyuridine[2,3]. The ability of this nucleoside to be incorporated into DNA has not been connected with mutagenicity, therefore, in spite of its rather low antiherpetic selectivity[1] this compound became an antiviral drug[4]. As a logical

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

consequence of this, the synthesis of different 5-alkyl-(cycloalkyl)-2'-deoxyuridines have followed[5-9] and notable antiviral activities were found, connected in particular with n-propyl, isopropyl[1] as well as with the cyclopropyl[10] group. The 5-alkyl(cycloalkyl)-2'-deoxyuridines[11] are of increasing importance with their use in the synthesis of the base-modified oligodeoxynucleotides with the aim of improving their selectivity (e.g. cellular uptake, stability to nucleases, hybridisation)[11].

On the other hand, 6-alkyl-2'-deoxyuridines have only been studied to a very limited extent and no antiviral activity of these compounds has been reported so far[12-17]. Also, incorporation of the methyl group into the 6-position in 5-iodo- and 5-bromo-2'-deoxyuridines results in the complete loss of the parental broad-spectrum of antiviral activity[18].

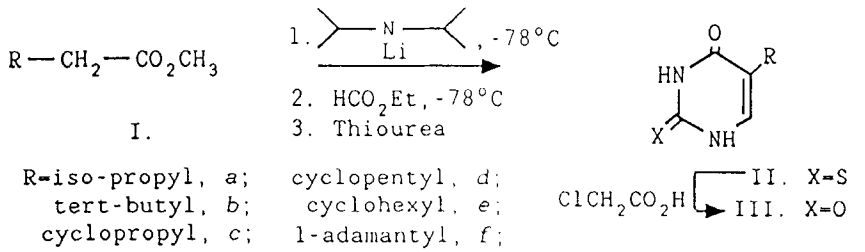
Although the synthesis of different 5,6-dialkyluridines has been reported[19-22], there is to our knowledge no information available about the synthesis of 5,6-dialkyl-2'-deoxyuridines, except one paper published recently[39]. The lack of significant effort in the field is apparently connected with the prevailing view, that 6-substituted, as well as 5,6-disubstituted pyrimidine nucleosides, generally have an "unnatural" syn-conformation around the glycosidic bond, which precludes any significant antiviral activity[18]. The experimental evidence for such syn-conformation based on CD-spectra[24] proved to be ambiguous in the case of 6-substituted and 5,6-disubstituted-2'-deoxyuridines[18]. However, NMR spectroscopy ($^1H$; $^{13}C$) gives an unequivocal answer with regard to the conformation of the glycosidic bond in virtually all cases of pyrimidine nucleosides[9,19,23,25]. For example $^1H$ and $^{13}C$ NMR analysis of 5,6-trimethyleneuridine in $D_2O$ revealed a "high-syn"-conformation for the glycosidic bond, in which the $H_{1'}$ proton is more shielded by the $C_2$-carbonyl group, than it is in the case of 6-methyluridine and 5,6-dimethyluridine[25]. In general, when an alkyl group is introduced into the 6-position of the pyrimidine ring, the steric demand of the $C_5$-$C_6$ side of the pyrimidine ring is bigger than the space available over the furanose ring and as a result the syn-conformation is observed. The extension of these findings to the 5,6-dialkyl-2'-deoxyuridines has not been possible so far because these compounds have not been available. Similarly, the steric limits imposed by 5-alkyl groups in 2'-deoxyuridines with regard to anti-conformation and antiviral activity have not been known, especially for the case of branched, bulky alkyl, as well as for cycloalkyl groups. The common reason for this situation has been the lack of reliable methods for the synthesis of 5-alkyl- and 5,6-dialkyl-β-D-2'-deoxyuridines.

There are different possibilities for the synthesis of $C_5$-alkyl-(cycloalkyl)-2'-deoxyuridines. For example an attractive method of Bergstrom *et al.*[26-29] uses

organopalladium chemistry and 5-chloro-mercury- or 5-iodo-2'-deoxyuridines as starting materials, to give different 5-alkyl-2'-deoxyuridines. The use of this approach with highly branched and bulky $C_5$-alkyl groups has not been reported. A more "classical" synthetic approach uses the condensation of a suitably protected 2-deoxyribose, usually as chlorosugar, with the corresponding 2,4-bis-*O*-trimethylsilyluracil[30]. A whole range of different conditions (solvent, catalyst, temperature) have been used for this condensation, mostly leading to a mixture of α and β-anomers of the blocked nucleosides[30,5-9,40]. The conditions favourable for the creation of either one of the anomers remained unclear until Hubbard *at al.*[31], studied in detail (by means of $^1$H NMR spectroscopy), the factors governing the α:β ratio of the product in 2'-deoxynucleoside synthesis. Chloroform as the solvent, room temperature and no catalyst were found to be the best conditions for an $S_N2$ reaction giving in high yields predominantly (or exclusively) the β-nucleosides for the majority of the good nucleophilic pyrimidine bases. These findings were later confirmed by Freskos[40] who found that an equimolar amount of CuI could sometimes further improve the already established high yield β-selectivity of this condensation reaction.

With 6-alkyl- or 5,6-dialkyluracils, the problem of regiospecificity of the condensation reaction arises when an $N_3$-$C_1$ glycosidic bond can be created in addition to the "natural" $N_1$-$C_1$ bond. The ratio of $N_1/N_3$ glycosidation of these bases varies substantially according to the nature of the 5,6-substituents, solvent, catalyst, as well as some other reaction conditions. The product is often a complicated mixture of $N_1$(α or β) and $N_3$(α or β) isomers[16,19-22].

The availability of the particular 5-alkyl(cycloalkyl)uracil is another limiting factor for a synthesis of 5-alkyl(cycloalkyl)-2'-deoxyuridines by the condensation of the corresponding base with the blocked sugar. Different modifications of the Burckhalter and Scarborough method[33], based on Claisen formylation of the corresponding alkylacetates, subsequent condensations of formylacetates with thiourea and finally desulfuration with dilute aqueous chloroacetic acid, generally gives rather low yields of 5-alkyluracils, especially when the alkyl group is branched and/or bulky[34-38]. The use of lithium diisopropylamide (LDA) as a base in the Claisen condensation, finally opened the way to a general synthesis of uracils, substituted in the 5- or 5- and 6-position with alkyl or cycloalkyl groups, in acceptable yields[32]. In an attempt to solve some of the problems of 5-alkyl(cycloalkyl)- as well as 5,6-dialkyl-2'-deoxyuridines, we have synthesised and studied the following series of nucleosides.




SCHEME 1

TABLE 1. 5-Alkyl(cycloalkyl)-2-thiouracils

| Comp | Yield (%) | $^1$H NMR (DMSO-$d_6$) | $^{13}$C NMR (DMSO-$d_6$) |
|---|---|---|---|
| * IIa | 46 | 12.38, 12.20 (2NH); 7.10 (dd, 1H, H6); 2.80-2.65 (m, 1H, R); 1.07(d, 6H, R) | 161.07 (C-2); 174.47 (C-4); 123.66 (C-5); 136.06 (C-6); 25.41: 20.96 (both R) |
| ** IIb | 43 | 12.35, 12.20 (2NH); 7.01 (s, 1H, H6); 1.20 (s, 9H, R) | 160.69 (C-2); 174.58 (C-4); 125.07 (C-5); 136.17 (C-6); 33.67, 28.21 (both R) |
| *** IIc | 44 | 12.38(bs, 2NH); 7.02(s, 1H, H6); 1.6 (m, 1H, R); 0.73, 0.60 (2m, 4H, R) | 167.71 (C-2); 174.14 (C-4); 119.66 (C-5); 135.71 (C-6); 7.91, 5.90 (both R) |
| **** IId | 10 | 12.3, 12.20 (2NH); 7.14 (d, 1H, H6); 2.75 (m, 1H, R); 1.52 (m, 8H, R) | 161.12 (C-2); 174.41 (C-4); 121.23 (C-5); 136.16 (C-6);37.25, 30.78, 24.65 (all R) |
| IIe | 63 | 12.38, 12.20 (2NH); 7.07 (s, 1H, H6); 2.39 (m, 1H, R); 1.69, 1.20 (2m, 10H, R) | 161.12 (C-2); 174.31 (C-4); 122.95 (C-5); 136.33 (C-6); 34.08, 31.13, 26.18, 25.65 (R) |
| ***** IIf | 46 | 12.33, 12.20 (2NH); 6.88 (s, 1H, 6H); 1.98, 1.86, 1.67 (3m, 3H, 6H, 6H, R) | 160.34 (C-2); 174.14 (C-4); 125.07 (C-5); 136.32 (C-6); 36.38, 34.48, 27.88 (all R) |

* Lit.[32], yield 31%; ** Lit.[32], yield 25%; *** Lit.[32], yield 44%; ***** Lit.[42], yield 18%.

**** Lithium bis(trimethylsilyl)amide as a base, instead of LDA

TABLE 2. 5-Alkyl(cycloalkyl)-and-5,6-dialkyluracils

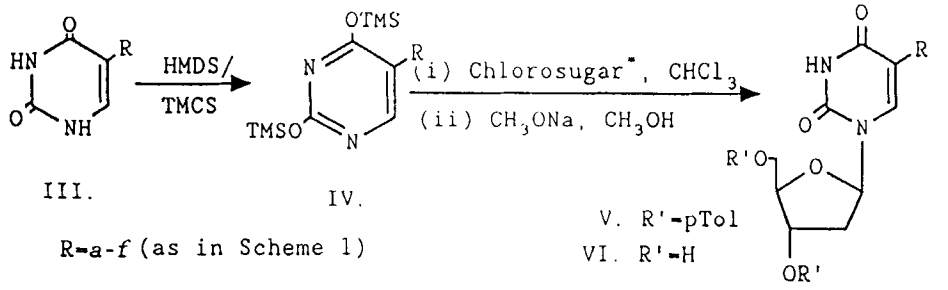
| Comp. | Yield (%) | $^1$H NMR (DMSO-$d_6$) | $^{13}$C NMR (DMSO-$d_6$) |
|---|---|---|---|
| * IIIa | 94 | 10.98, 10.63, (2NH); 6.65 (dd, 1H, H6); 2.69 (m, 1H, R) 1.06 (d, 6H, R) | 151.21 (C-2); 164.13 (C-4); 117.99 (C-5); 135.91 (C-6); 25.16, 21.46 (both R) |
| ** IIIb | 92 | 10.94, 10.61 (2NH); 6.91 (d, 1H, H6); 1.19 (s, 9H, R) | 151.25 (C-2); 163.65 (C-4); 119.43 (C-5); 135.94 (C-6); 32.21, 28.60 (both R) |
| * IIIc | 88 | 11.00, 10.63 (2NH); 6.99 (s, 1H, H6); 1.53 (m, 1H, R); 0.58 (m, 4H, R) | 151.17 (C-2); 164.75 (C-4); 113.72 (C-5); 135.97 (C-6); 7.76, 5.44 (both R) |
| ** IIId | 80 | 10.98, 10.62 (2NH); 7.10 (d, 1H, H6); 2.70 (m, 1H, R); 1.70 (m, 8H, R) | 151.25 (C-2); 164.36 (C-4); 115.36 (C-5); 136.03 (C-6); 37.18, 31.08, 24.57 (all R) |
| ** IIIe | 95 | 11.00, 10.63 (2NH); 7.04 (s, 1H, H6); 2.35 (m, 1H, R); 1.45, 1.21 (2m, 10H, R) | 151.10 (C-2); 164.19 (C-4); 117.38 (C-5); 136.22 (C-6); 34.65, 31.67, 26.34, 25.75 (R) |
| *** IIIf | 83 | 10.86, 10.60 (2NH); 6.88 (s, 1H, H6); 1.97, 1.86, 1.67 (3m, 3H, 6H, 6H, R) | 150.97 (C-2); 163.47 (C-4); 119.77 (C-5); 136.28 (C-6); 36.49, 34.10, 28.02 (all R) |
| * VIIg | 33 (1st crop) | 11.05, 10.75 (2NH); 2.63 (t, 2H, $CH_2$); 2.44 (t, 2H, $CH_2$); 1.95 (m, 2H, $CH_2$) | 156.08 (C-2); 162.08 (C-4); 109.67 (C-5); 152.37 (C-6); 31.06, 26.42, 21.00 ($R_1$-$R_2$) |
| VIIh | - | 1.92, 10.61 (2NH); 2.03 ($CH_3$-6); 1.71 ($CH_3$-5) | 150.83 (C-2); 164.69 (C-4); 104.13 (C-5); 147.49 (C-6); 16.25, 9.57 ($R_1$, $R_2$) |

(2-thiouracil : chloroacetic acid : water; all in grams):
* 1:3:15; ** 1:3:40; *** 1:3:40 ($H_2O$) : 20 (DMSO)



## RESULTS AND DISCUSSION

The series of 5-alkyl(cycloalkyl)-2-thiouracils [IIa-IIf] was prepared according to the published procedure[32](SCHEME 1) with the following modifications of the Claisen formylation. Instead of diethyl ether as the only solvent and the reaction temperature -40°C to -30°C a mixture of diethyl ether/n-hexane at a temperature below -60°C was used. Also, in some cases the excess of n-BuLi in an *in situ* preparation of LDA from diisopropylamine proved to be beneficial, as can be seen from the yields of the synthesised compounds in TABLE 1. The high yields of 2-thiouracils with branched and bulky substituents (tert-butyl, IIb, 43% and 1-adamantyl, IIf, 46%) are particularly noticeable and confirm the broad applicability of this method. 5-(1-Adamantyl)-2-thiouracil [IIf] was reported to be prepared also from 1-adamantanol via ethyl 2(1-adamantyl)-2-formylacetate (68%) and its subsequent condensation with thiourea (27%; overall yield 18%)[42]. The low yield of 5-cyclopentyl-2-thiouracil [IId; 10%] is due to use of lithium bis(trimethylsilyl)amide as a base, instead of LDA. This yield is comparable to the similar yield of 5-isopropyl-2-thiouracil [IIa; 13%] using lithium bis(trimethlysilyl)amide[32] and confirms




SCHEME 2

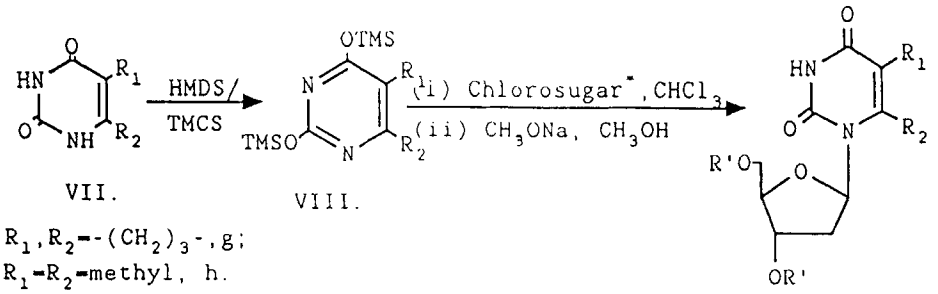
conclusively the inefficiency of this base in this Claisen condensation. The 2-thiouracils IIa-IIf were transformed in high yields (≥80%; TABLE 2) into the corresponding uracils IIIa-IIIf by heating under the reflux in a solution of chloroacetic acid/water (13-20%). In the case of the uracil IIIf, the addition of DMSO was necessary, because of the very poor solubility of the substrate. 5,6-Trimethyleneuracil [VIIg] was prepared according to the literature[41].

The 3',5'-di-*O*-*p*-toluoyl-2'-deoxyuridines Va-Vf (SCHEME 2) were prepared by the condensation of the crude, silylated bases IVa-IVf with freshly prepared crystalline 2-deoxy-3,5-di-*O*-*p*-toluoyl-*erythro*-pentosyl chloride[43] in dry chloroform without any catalyst[31]. The reaction was performed at room temperature, with a reaction time 20-24 hrs. In preliminary experiments, an excess of the silylated base (up to 40% molar) was used, in an attempt to use all the chlorosugar and to recycle, if possible, the unreacted base. This approach was found not to be optimal, because the base was not easily separable from the product either by crystallisation or by column chromatography. Therefore all the condensations were finally done with a 10% molar excess of the chlorosugar and byproducts from this excess were easily removed as the fastest eluates from the chromatography column. The high yields of the products Va-Vf are shown in TABLE 3 and represent overall yields of the blocked nucleosides after column chromatography. In the case of nucleosides Vb-Ve these were pure β-anomers. In the case of nucleosides Va and Vf the overall yield contained 89-91% of the β-anomer and 9-11% of α-anomer. The latter (faster moving in the solvent system used) was in both cases separated by column chromatography as a mixture with some β-anomer and was not worked up further. The identity and the ratio of α and β-anomers in the crude condensation product was

TABLE 3 The synthesised 3', 5'-di-O-pTol-2'-deoxyuridines

| Comp. | Yield | $R_f(S_1)$ | % Calculated | | | % Found | | |
|---|---|---|---|---|---|---|---|---|
| | (%) | | C | H | N | C | H | N |
| Va | 95 | 0.46 | | | | Not analysed (see Lit.[7]) | | |
| Vb | 98 | 0.58 | 66.91 | 6.20 | 5.38 | 66.78 | 6.40 | 5.28 |
| Vc | 92 | 0.32 | | | | Not analysed (see Lit.[9]) | | |
| Vd | 96 | 0.45 | 67.65 | 6.06 | 5.26 | 67.88 | 6.06 | 5.37 |
| Ve | 99 | 0.49 | 68.11 | 6.27 | 5.13 | 68.39 | 6.03 | 5.33 |
| Vf | 92 | 0.65 | 70.21 | 6.40 | 4.68 | 70.08 | 6.49 | 4.62 |
| IXg | 55 | *0.39 | 66.65 | 5.59 | 5.55 | 66.38 | 5.38 | 5.29 |
| XIg | 16 | *0.39 | 66.65 | 5.59 | 5.55 | 66.36 | 5.50 | 5.23 |

* Solvent system $S_2$




VII.

$R_1, R_2$=-$(CH_2)_3$-, g;
$R_1$=$R_2$=methyl, h.

VIII.

(β-anomer) IX.*g*; R'=pTol X.*g*; R'=H
(α-anomer) XI.*g*; R'=pTol XII.*g*; R'=H
(α-and β-anomer) XIII.*h*; R'=pTol XIV.*h*; R'=H

SCHEME 3.

obtained from $^1H$ NMR and MS spectra of the crude condensation product when compared with that of chromatographically separated β and α+β anomers.

The condensation of silylated 5,6-trimethyleneuracil [VIIIg] with the chlorosugar under the conditions as above (SCHEME 3) provided a crude product of the $N_1$-glycoside with a 1:2/α:β ratio, from which the crystalline pure β-anomer IXg was obtained in 55% yield by fractional crystallisation. The pure α-anomer XIg was isolated from the mother liquor in 16% yield by column chromatography and

TABLE 4. The synthesised 2'-deoxyuridines

| Comp. | Yield (%) | $R_f(S_3)$ | * Mp °C | % Calculated | | | % Found | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N |
| VIa | 58 | 0.39 | 175-6 | | | | Not analysed (see Lit.[7]) | | |
| VIb | 88 | 0.43 | 151-2 | 54.91 | 7.09 | 9.86 | 54.62 | 7.24 | 9.66 |
| VIc | 56 | 0.37 | 193-4 | | | | Not analysed (see Lit.[9]) | | |
| VId | 70 | 0.44 | 134-5 | 56.74 | 6.80 | 9.46 | 56.78 | 6.66 | 9.76 |
| VIe | 90 | 0.54 | **180-1 | 58.05 | 7.15 | 9.03 | 57.75 | 7.10 | 8.92 |
| VIf | 73 | 0.50 | ***204-5 | 62.96 | 7.23 | 7.73 | 63.25 | 7.28 | 7.54 |
| Xg | 85 | 0.30 | ***147-8 | 53.72 | 6.01 | 10.45 | 53.42 | 6.02 | 10.32 |
| XIIg | 77 | 0.34 | 159-60 | 53.72 | 6.01 | 10.45 | 53.76 | 5.66 | 10.61 |

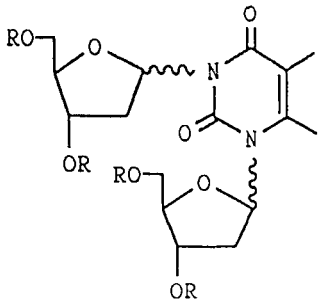
* Amorphous solid after treatment with diethyl ether, ** Ethyl acetate, *** Methanol / Diethyl ether



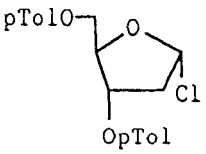
subsequent crystallisation. The separation was complicated by very close chromatographic mobility of both anomers (TABLE 3).

Compounds Va-Vf, IXg and XIg were deblocked with sodium methoxide in methanol (SCHEME 2 and 3). After neutralisation, removal of methyl p-toluate by column chromatography, the 2'-deoxyuridines VIa-VIf, Xg and XIIg were obtained in good to excellent yields (TABLE 4).

However, the condensation of silylated 5,6-dimethyluracil [VIIIh, SCHEME 3] under the same conditions (no catalyst) resulted (2 experiments) in a complicated mixture of at least eight different UV-absorbing components (TLC), including unreacted base VIIh and byproducts from the chlorosugar. The experiment when repeated with the addition of 0.1 equivalent of $ZnCl_2$, resulted in the same mixture, but this time two components of the mixture ($R_f$0.28 and 0.59; $S_1$) were relatively more abundant. These components were separated by column chromatography and deblocked with sodium methoxide in methanol. The combined investigation by $^1H$ and $^{13}C$ NMR, MS and UV spectra of the blocked nucleosides $R_f$0.28 and $R_f$0.59, their deblocked products and comparison with similar data for the 5,6-trimethylene derivatives IXg-XIIg, as well as with all four possible isomers of 6-methyl-2'-deoxyuridine[16,13] revealed the following identity for the isolated condensation products:




XVh; R=pTol
XVIh; R=H




*Chlorosugar

SCHEME 4.



The component with $R_f$0.28 was identified as an anomeric mixture (α:β/1:2) of 3',5'-di-O-p-toluoyl-5,6-dimethyl-2'-deoxyuridine [XIIIh; 9.4%]. The compound with $R_f$0.59 was identified as the N1/N3 diglycoside XVh(3.3%), with at least two out of four possible isomers [($N_1$(α)/$N_3$(α); $N_1$(α)/$N_3$(β); $N_1$(β)/$N_3$(β); $N_1$(β)/$N_3$(α)] present. It was not possible to establish the exact ratio of the isomers in the mixture on the basis of the information available. The deblocked mixture XIIIh contained, after column chromatography, an anomeric mixture (α:β/1:1.6) of 5,6-dimethyl-2'-deoxyuridine [XIV;55%]. The deblocked mixture of diglycoside XVh, after column chromatography, contained an isomeric mixture of 5,6-dimethyl-$N_1$,$N_3$-di-[1'-(2'-deoxyribofuranosyl)]uracil [XVIh; 60%, SCHEME 4]. Again, it was not possible to establish the exact ratio of the isomers in the product, but according to the $^1$H NMR spectrum, β-anomeric configurations of both $N_1$ and $N_3$-glycosidic bonds prevailed.

The results from the condensation experiments with 5,6-trimethyleneuracil [VIIg] and 5,6-dimethyluracil [VIIh] can be interpreted with the help of the conclusions from the study of Hubbard *et al.*[31] 5,6-Trimethyleneuracil apparently has steric demands with regard to the 6-position of the pyrimidine ring, which results in a lower condensation reactivity in comparison with the 5-substituted bases IIIa-IIIf. Nevertheless, these demands are smaller than in the case of the 6-methyl group and also, the 5,6-trimethylene ring may positively influence the condensation reactivity of this base, to give some α-condensation product. The considerable steric demands of 5,6-dimethyluracil with regard to $N_1$ condensation are comparable to those of 6-methyluracil. This explains the observed low reactivity under the noncatalysed condensation conditions. On the other hand, $ZnCl_2$ catalyses N-condensation in general and as a result, $N_1$/$N_3$-diglycoside XVh is formed. At the same time, $ZnCl_2$

TABLE 5. $^1$H NMR Spectra of the synthesised 3',5'-di-O-pTol-2'-deoxyuridines ($CDCl_3$)

| Comp | H-1' | H-2' | H-2" | H-3' | H-4' | H-5' | H-5" | H-R or $R_1/R_2$ |
|---|---|---|---|---|---|---|---|---|
| Va | 6.45 dd, 1H | 2.34 m, 1H | 2.75 dd, 1H | 5.64 m, 1H | 4.55 m, 1H | 4.76 dd, 1H | 4.65 dd, 1H | 7.22 (s, 1H, H6); 2.68 (m, 1H, R); 0.96, 0.90 (2d, 6H, R) |
| Vb | 6.40 dd, 1H | 2.35 m, 1H | 2.75 dd, 1H | 5.62 m, 1H | 4.55 m, 1H | 4.50 dd, 1H | 4.63 dd, 1H | 7.23 (s, 1H, H6); 1.08 (s, 9H, R); |
| Vc | 6.41 dd, 1H | 2.29 m, 1H | 2.72 m, 1H | 5.62 m, 1H | 4.53 m, 1H | 4.75 dd, 1H | 4.67 dd, 1H | 7.18 (d, 1H, H6); 1.46 (m, 1H, R); 0.70-0.28 (3m, 4H, R). |
| Vd | 6.46 dd, 1H | 2.34 m, 1H | 2.73 m, 1H | 5.65 m, 1H | 4.54 m, 1H | 4.78 dd, 1H | 4.61 dd, 1H | 7.22 (s, 1H, H6); 2.53 (m, 1H, R); 0.75-1.10 (3m, 8H, R) |
| Ve | 6.45 dd, 1H | 2.33 m, 1H | 2.72 m, 1H | 5.65 m, 1H | 4.53 m, 1H | 4.76 dd, 1H | 4.61 dd, 1H | 7.16 (s, 1H, H6); 2.35 (m, 1H, R); 1.67-0.70 (3m, 10H, R) |
| Vf | 6.47 dd, 1H | 2.37 m, 1H | 2.76 dd, 1H | 5.66 m, 1H | 4.56 m, 1H | 4.74 dd, 1H | 4.62 dd, 1H | 7.18 (s, 1H, H6); 1.78 (bs), 1.69 (m) 1.59 (m), 1.47 (m), 15H all R |
| IXg | 6.17 t, 1H | 2.47 m, 1H | 3.06 m, 1H | 5.71 m, 1H | 4.43 m, 1H | 4.75 dd, 1H | 4.61 dd, 1H | 2.97 (m, 2H, $CH_2$); 2.66 (t, 2H, $CH_2$); 2.00 (m, 2H, $CH_2$). |
| XIg | 6.13 t, 1H | 3.10 m, 1H | 2.81 m, 1H | 5.50 m, 1H | 4.92 m, 1H | 4.60 m, 1H | 4.49 m, 1H | 3.10 (m, 2H, $CH_2$); 2.69 (t, 2H, $CH_2$); 2.09 (m, 2H, $CH_2$); |

TABLE 6. $^1$H NMR Spectra of the synthesised 2'-deoxyuridines, (DMSO-$d_6$)

| Comp | H-1' | H-2' H-2" | H-3' | H-4' | H-5' H-5" | H-R or R1/R2 |
|---|---|---|---|---|---|---|
| VIa | 6.19 t, 1H | 2.15 - 2.05 m, 2H | 4.26 m, 1H | 3.79 m, 1H | 3.65 - 3.52 m, 2H | 7.70 (s, 1H, H6); 2.72 (m, 1H, R) 1.07 (d, 6H, R) |
| VIb | 6.22 t, 1H | 2.14 - 2.07 m, 2H | 4.26 m, 1H | 3.80 m, 1H | 3.64 - 3.51 m, 2H | 7.64 (s, 1H, H6); 1.20 (s, 9H, R) |
| VIc | 6.15 t, 1H | 2.10 - 2.03 m, 2H | 4.23 m, 1H | 3.76 m, 1H | 3.65 - 3.52 m, 2H | 7.59 (s, 1H, H6); 1.62-1.52 (m, 1H, R); 0.73-0.44 (m, 4H, R) |
| VId | 6.20 t, 1H | 2.14 - 2.03 m, 2H | 4.25 m, 1H | 3.79 m, 1H | 3.64 - 3.51 m, 2H | 7.71 (s, 1H, H6); 2.82-2.64 (m, 1H, R); 1.85-1.33 (m, 8H, R) |
| VIe | 6.19 t, 1H | 2.14 - 2.03 m, 2H | 4.26 m, 1H | 3.79 m, 1H | 3.66 - 3.52 m, 2H | 7.67 (s, 1H, H6); 2.38 (m, 1H, R); 1.80-1.60, 1.37-1.06 (2m, 10H, R) |
| VIf | 6.22 t, 1H | 2.12 - 2.05 m, 2H | 4.25 m, 1H | 3.80 m, 1H | 3.63 - 3.51 m, 2H | 7.51 (s, 1H, H6); 1.98 (bs, 3H, R); 1.88 (bs, 6H, R); 1.68 (m, 6H, R) |
| Xg | 6.02 t, 1H | 3.12 - 2.80 m, 2H | 4.23 m, 1H | 3.62 m, 1H | 3.58 & 3.49 2m, 2H | 2.60-2.42 (m, 4H, 2x$CH_2$); 2.07-1.87(m, 2H, $CH_2$) |
| XIIg | 5.96 t, 1H | 2.47 2.26 m, 1H m, 1H | 4.15 m, 1H | 3.98 m, 1H | 3.65 - 3.45 m, 2H | 3.38 (m, 2H, $CH_2$); 3.00 (t, 2H, $CH_2$); 1.96 (pent, 2H, $CH_2$) |

catalyses the anomerization of the starting α-chlorosugar, which explains the presence of α-glycosidic bonds (either $N_1$ or $N_3$).

$^1H$ NMR spectra of the synthesised blocked nucleosides are shown in TABLE 5. Very close chemical shift vales of each sugar proton in the series of nucleosides Va-Vf indicates the same anomeric configuration and the same or very similar conformation around the gycosidic bond, as well as in the pucker of the sugar ring. The stereochemistry of the nucleoside Vc (5-cyclopropyl-2'-deoxyuridine) has already been studied in detail by $^1H$ NMR under the same conditions (CDCl3) and the chemical shift values, including the multiplicity of the signals [H-1', 6.41; H-2', 2.30; H-2", 2.72; H-3', 5.62; H-4', 4.53; H-5', 4.75; H-5", 4.67; H-6, 7.18; R-5/CH, 1.47; R-5/$CH_2$-$CH_2$, 0.30-0.45, 0.51-0.71][9] were nearly identical with those found in this study. $^1H$ NMR data of the deblocked 2'-deoxyuridines are shown in TABLE 6 and again, they are very similar to each other with in the series of the nucleosides VIa-VIf. The chemical shift vales of 5-cyclopropyl-2'-deoxyuridine [VIc] cannot be compared directly with those from the literature[9], which had been obtained in $D_2O$. Never the less, the relative position of the signals on the chemical shift scale, as well as their multiplicity, remain the same. The overall conclusion, based on the data in TABLES 5 and 6 and on the already published data for VIc[9], is unequivocal. All the nucleosides VIa-VIf are β-anomers, with anti-conformation around the glycosidic bond and with a predominant C2'-endo (S) pucker of the sugar ring. The size of the alkyl(cycloalkyl) substituent in the 5-position apparently does not influence the glycosidic or sugar conformation to a major extent. It would require a much more rigorous analysis at high field to determine the precise proportion of each component present at equilibrium[46].

$^{13}C$ NMR spectra of the synthesised 2'-deoxyuridines are shown in TABLE 7. Also included is the spectrum of thymidine, which was measured under the same conditions for comparison. The chemical shift values of the particular carbon atoms were assigned with the help of the literature data of 5-substituted uracils[45], uridines[23,25] and 2'-deoxyuridines[44]. The nucleosides VIa-VIf provide very close chemical shift values of the same carbon atoms in this series, which are as a whole, very similar to the corresponding values in thymidine. The values for the carbon C-5 are the exception, as they vary according to the inductive (or conjugative) effects of the R-5 alkyl(cycloalkyl) group; the highest value (121.50 ppm) being associated with 1-adamantyl and the lowest one (115.36 ppm) with the cyclopropyl group. This effect is observed to a much smaller extent (less than 1.3 ppm difference) in the chemical

TABLE 7. $^{13}C$ NMR Spectra of the synthesised 2'-deoxyuridines (DMSO-$d_6$)

| Comp. | C-2 | C-4 | C-5 | C-6 | C-1' | C-3' | C-4' | C-5' | C-R or $R_1/R_2$ |
|---|---|---|---|---|---|---|---|---|---|
| VIa | 150.18 | 163.03 | 119.57 | 134.66 | 84.24 | 70.50 | 87.43 | 61.24 | 25.49; 21.47 |
| VIb | 150.23 | 162.53 | 121.15 | 134.82 | 84.23 | 70.75 | 87.46 | 61.32 | 32.80; 28.67 |
| VIc | 150.11 | 163.62 | 115.36 | 134.43 | 84.18 | 70.38 | 87.41 | 61.18 | 8.02; 5.74; 5.58 |
| VId | 150.22 | 163.26 | 117.14 | 134.62 | 84.13 | 70.57 | 87.41 | 61.30 | 37.39; 31.06; 24.50 |
| VIe | 150.10 | 163.08 | 118.95 | 134.98 | 84.20 | 70.50 | 87.40 | 61.23 | 34.97; 31.73; 31.66; 26.31, 25.73 |
| VIf | 150.01 | 162.34 | 121.50 | 135.20 | 84.16 | 70.77 | 87.41 | 61.33 | 36.47; 34.75; 28.02 |
| * Xg | 155.80 | 160.77 | 112.44 | 151.32 | 85.12 | 70.01 | 86.90 | 61.41 | 31.96; 26.34; 21.05 |
| ** XIIg | 155.49 | 160.89 | 112.58 | 151.57 | 85.95 | 70.14 | 86.22 | 61.53 | 32.09; 26.37; 21.22 |
| *** XIVh,β | 150.29 | 160.05 | 107.59 | 148.65 | 84.79 | 70.26 | 86.96 | 61.64 | 16.48($R_2$); 10.81($R_1$) |
| **** XIVh,α | 150.47 | 160.05 | 107.59 | 148.47 | 85.54 | 70.42 | 85.98 | 61.55 | 16.48($R_2$); 10.81($R_1$) |
| ***** Thdr | 150.53 | 163.80 | 109.42 | 136.18 | 83.82 | 70.50 | 87.32 | 61.41 | 18.60 |

*C-2': 37.68 ppm; **C-2': 38.28 ppm; ***C-2': 37.83 ppm; ****C-2': 37.47 ppm

*****ThdR: Thymidine (measured under the same conditions, C-2'; 39.49 ppm).



shifts of the c-4 and C-6 atoms. The chemical shifts of the C-2' atoms of the nucleosides VIa-VIf are not resolved from the multiplet of DMSO-$d_6$. Very small differences in chemical shifts for the same sugar carbon atoms in this series (C-1', C-3', C-4', and C-5', all less than 0.3 ppm) point to the same anomeric configuration (β) and very similar glycosidic conformation (anti), as well as sugar pucker (C2'-endo or S) of the nucleosides VIa-VIf.

The assignment of β-configuration to the nucleosides IXg and Xg was possible because of the higher chemical shift values of H-1' and the lower vales for H-4' when compared to the equivalent protons in the α-anomers XIg and XIIg[9,16]. On the other hand, significantly lower chemical shifts for H-1' and H-4' for the nucleosides IXg and Xg, when compared with equivalent protons in the nucleosides Va-Vf and VIa-VIf, clearly indicates the syn-conformation in the nucleosides IXg and Xg[23]. This finding is further supported by higher $^{13}C$ chemical shifts of C-1' and lower values for C-4', when the compared to the values for the same carbons in VIa-VIf[23]. Not surprisingly, the most striking difference in the $^{13}C$ chemical shifts in the

nucleosides Xg and XIIg, when compared with VIa-VIf, is connected with the carbons of the pyrimidine base, particularly C-2 (up to 5.8 ppm) and C-6 (up to 17 ppm).

$^{13}C$ NMR spectra of both anomers of 5,6-dimethyl-2'-deoxyuridine [XIVh,β; XIVh,α] were well resolved and are presented in TABLE 7. The interpretation of the values obtained is quite similar to those of 5,6-trimethylene-2'-deoxyuridine (Xg; XIIg]. Unfortunately, the $^1H$ NMR spectra of 5,6-dimethyluracil nucleosides XIIIh, XIVh, XVh, and XVIh are too complex for the presentation in TABLE 5 or 6, therefore they are presented in the Experimental part of this paper. The relative position of the protons on the scale of chemical shifts in the case of all four possible isomers of 6-methyl-2'-deoxyuridine ($N_1$ or $N_3$, α or β), especially H-1' and C6-$CH_3$[16], were together with the available data for 5,6-trimethyleneuracil nucleosides, sufficient information for the interpretation of the $^1H$ NMR spectra of the synthesised 5,6-dimethyl-2'-deoxyuridines. A final conclusion about the stereochemistry of these compounds is not possible until it is possible to separate all the isomers.

The UV-spectra of the synthesised 2'-deoxyuridines (except those of VIa and VIc - see lit.[7,9]) are shown in TABLE 9. The lack of significant bathochromic shift in 0.1N NaOH, when compared with the vales obtained in 0.1N HCl, unequivocally confirms the presence of the $N_1$-glycosidic bond in all synthesised nucleosides and is in agreement with the $N_1/N_3$-diglycosidic character of the compounds in the mixture XIVh.

The mass spectra of all synthesised nucleosides (blocked or deblocked) are shown in TABLE 8. All compounds (except blocked dinucleoside XVh) give a molecular peak and a fairly similar fragmentation picture, confirming the proposed structures. The molecular peaks of the blocked nucleosides are of rather low intensity, which might explain the missing molecular peak in the mixture of blocked nucleosides XVh. On the other hand, the molecular peaks of the deblocked nucleosides are quite intensive and in the case of the diglycosidic mixture XVIh, unequivocally confirm the proposed structure.

All the compounds presented here have been subjected to antiviral screening for a range of herpes viruses, influenza virus and HIV-1. No significant activity (≤ 100μM) was found for any compound, which is in direct contrast to the activity found for the corresponding 4'-thio-nucleosides of compounds VIa and VIc. It is likely that the present range of compounds is sensitive to nucleoside phosphorylase and therefore the activity seen for 5-cyclopropyl- and 5-isopropyl-4'-thio-2'-deoxyuridines is because of the stability of those analogues in the test system used.

TABLE 8. Mass spectrum of synthesised 3',5'-di-O-pTol-2'-deoxyuridines and 2'-deoxyuridines

| Comp. | *M/Z* (FAB) | Comp. | *M/Z* (FAB) |
|---|---|---|---|
| Va | 507$(m+1)^+$; 371$(M-135)^+$; 353$(M\text{-base})^+$ | VIa | 271$(m+1)^+$;192$(M-78)^+$;176$(M-94)^+$;165$(M-105)^+$ |
| *Vb | 521$(m+1)^+$; 385$(M-135)^+$; 353$(M\text{-base})^+$ | VIb | 285$(m+1)^+$; 169(M of base +1)$^+$; 117$(M-167)^+$ |
| Vc | 505$(M+1)^+$; 369$(M-135)^+$; 353$(M\text{-base})^+$ | VIc | 269$(m+1)^+$; 176$(M-92)^+$; 165$(M-103)^+$ |
| Vd | 533$(M+1)^+$; 397$(M-135)^+$; 353$(M\text{-base})^+$ | *VId | 297$(m+1)^+$; 207$(M-89)^+$; 181(M of base +1)$^+$ |
| Ve | 547$(M+1)^+$; 412$(M-134)^+$; 353$(M\text{-base})^+$ | *VIe | 311$(m+1)^+$; 221$(M-89)^+$; 195(M of base +1)$^+$ |
| Vf | 599$(M+1)^+$; 464$(M-134)^+$; 353$(M\text{-base})^+$ | VIf | 363$(m+1)^+$; 247(M of base +1)$^+$ |
| IXg | 505$(M+1)^+$; 369$(M-135)^+$; 353$(M\text{-base})^+$ | Xg | 269$(m+1)^+$; 153(M of base +1)$^+$ |
| XIg | 505$(M+1)^+$; 369$(M-135)^+$; 353$(M\text{-base})^+$ | XIIg | 269$(m+1)^+$; 153(M of base +1)$^+$ |
| XIIIh | 493$(M+1)^+$; 391$(M-101)^+$; 353$(M\text{-base})^+$ | XIVh | 257$(m+1)^+$; 141(M of base +1)$^+$ |
| XVh | 493$(M-352)^+$; 353$^+$; 259$^+$; 221$^+$ | XVIh | 373$(m+1)^+$; 257$(M-115)^+$; 141(M of base +1)$^+$ |

* CI Spectrum



## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded on a Brucker AC300 and AMX400 and the chemical shift values are in ppm. Mass spectra were recorded on a Kratos MS580. Electron-impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) were used as necessary. Ultraviolet spectra were recorded on a Perkin Elmer 552 spectrophotometer in the solvents specified in TABLE 9. Precoated Merck silica gel 60 $F_{254}$ plates were used for TLC and the spots were detected under UV light (254 nm). Column chromatography was performed using Kieselgel 60, 230-400 mesh ASTM, type 9385. Glass columns were slurry-packed under gravity. Solvent systems used for TLC and column chromatography were $S_1$=1:1 (n-hexane/ethyl acetate), $S_2$=1:2(n-hexane/ethyl acetate) and $S_3$=85:15($CHCl_3$/ $CH_3OH$). Chloroform used in condensations was dried by heating under reflux over phosphorus pentoxide, distilled and stored over type-4A molecular sieves. Methanol was dried by heating under reflux over magnesium methoxide, distilled and stored over type-4A molecular sieves. Diethyl ether was dried by sodium wire. Methyl acetates Ia-If were prepared according to the literature[32] or by esterification of the

TABLE 9. UV Spectra of the synthesised 2'-deoxyuridines

| Comp. | MeOH | | 0.1 N HCl | | 0.1 N NaOH | |
|---|---|---|---|---|---|---|
| | λmax (ε) | λmin (ε) | λmax (ε) | λmin (ε) | λmax (ε) | λmin (ε) |
| VIb | 260 (11240) | 232 (5300) | 261 (9920) | 230 (2880) | 261 (8790) | 242 (6730) |
| VId | 265 (11780) | 233 (3350) | 266 (10800) | 233 (2900) | 265 (8620) | 243 (5450) |
| VIe | 264 (9060) | 233 (2410) | 265 (8930) | 233 (2430) | 263 (8810) | 243 (6960) |
| VIf | 263 (8690) | 232 (2420) | 264 (8750) | 233 (2750) | 261 (6960) | 242 (5390) |
| Xg | 265 (9840) | 235 (1830) | 267 (8520) | 235 (1310) | 267 (6520) | 243 (3030) |
| XIIg | 266 (9750) | 235 (2450) | 269 (8780) | 237 (2290) | 268 (7970) | 243 (3580) |
| *XIVh | 265 (9220) | 235 (3140) | 266 (10440) | 235 (3380) | 266 (8070) | 244 (5000) |
| **XVIh | 267 | 240 | 269 | 234 | 270 | 242 |

*Anomeric mixture (α:β/1:1.16)

**ε-not measured (complicated mixture)



commercially available alkyl(cycloalkyl)acetic acids. Ethyl formate was dried with molecular sieves. Melting points are not corrected.

**5-Alkyl(cycloalkyl)-2-thiouracils IIa-IIf** (general method). To 80 mmol of freshly distilled diisopropylamine in 80 ml of dry ether in a round bottomed flak under a slight stream of dry nitrogen was syringed in small portions 120 mmol of n-BuLi (2.5 M n-hexane soln, ALDRICH) with intensive stirring (magnetic stirrer) and external cooling (dry ice/acetone) to -78°C, so that the inner temperature of the reaction mixture was always below -60°C.

Then 78 mmol of compound Ia-If in 70 ml of dry ether was added in the same way and finally 310 mmol of ether formate in 120 ml of dry ether, the inner temperature of the reaction mixture being kept below -60°C all the time. Then the reaction mixture was stirred further (-78°C, $N_2$, 6 hrs), the reaction flask stoppered and kept at -12°C overnight. The ether was evaporated under vacuum (35°C) and to the gummy-like yellow to orange residue, 80 mmol of thiourea and 20 ml of freshly dried methanol

was added. The reaction mixture was heated under reflux with the exclusion of moisture for 6 hrs, cooled in an ice/salt bath under vigorous stirring, acidified (dropwise) with 20% aqueous HCl to pH≤3. The acidified reaction mixture was left in the ice/salt bath for another 0.5-1 hr, then a white solid which separated, was collected with suction and dried over $P_2O_5$. In some cases the mother liquor was concentrated using rotary evaporation and a small amount of a second crop was obtained (the yields presented in TABLE 1 are overall). Except for compound IIf, which was crystallised from tetrahydrofuran/water, all synthesised 2-thiouracils were used in the next step without purification.

**5-Alkyl(cycloalkyl)uracils IIIa-IIIf** (general method). The 2-thiouracils IIa-IIf were heated under reflux in the reaction mixture, which is shown (TABLE 2) for each compound in .

The reaction was monitored by TLC (ethyl acetate). When all the 2-thiouracil in the reaction mixture was consumed, the reaction mixture was cooled in ice and left in a refrigerator for a few hours. The white crystalline product was collected with suction, washed with a small amount of ice water and dried over $P_2O_5$. In some cases the mother liquor was concentrated using rotary evaporation and a small amount of a second crop was obtained (the yields presented in TABLE 2 are overall). All the synthesised uracils were used in the next step without purification.



**The silylation of the uracils IIa-IIf, VIg, VIh** (general method). To the base (10 mmol; IIa-IIf, VIg or VIh), was added hexamethyldisilazane (HMDS, 20 ml) and 2 ml of trimethylchlorosilane (TMCS) in a 100 ml round bottomed flask with a reflux condenser (protection against moisture) and was heated under reflux (oil bath,130°C) with magnetic stirring until the reaction mixture became clear (14-46 hrs, depending on the base used). The excess of HMDS and TMCS were distilled of at room temperature under high vacuum, leaving the silated base as a thick oil or an amorphous solid (colourless or slightly yellowish). This crude product was directly used in the next step.

**3',5'-Di-*O*-*p*-toluoyl-2'-deoxyuridines Va-Vf** (general method). The crude silylated base (IIIa-IIIf; 10 mmol) was dissolved in 20 ml of dry chloroform and 4.3 mg (11 mmol) of freshly prepared crystalline 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride[43] in 40 ml of dry chloroform was added. The resulting clear solution was

magnetically stirred in the stoppered reaction flask at room temperature for 20-24 hrs. The reaction mixture was filtered and the filtrate evaporated. The residue was purified on a silica column ($S_1$), fractions containing the β-anomer only were combined and evaporated, then dried over $P_2O_5$; yields of the pure products are presented in TABLE 3. The samples for elemental analysis were obtained by crystallisation from the ethyl acetate/ether.

**3',5'-Di-*O*-*p*-toluoyl-2'-deoxyuridines IXg and Xg.** The silylated base VIIIg was condensed with the chlorosugar as described above. To the filtered and evaporated reaction mixture, 40 ml of ethyl acetate/n-hexane (3:1) was added and after intensive stirring (0.5 hr), a white solid of the pure β-anomer IXg was collected with suction and dried over $P_2O_5$, giving a yield of 55%. The mother liquor was evaporated and purified on a silica column ($S_2$) as described above, giving 16% yield of the α-anomer XIg. The samples of both anomers for elemental analysis were obtained by crystallisation from ethyl acetate/ether.



**3',5'-Di-*O*-*p*-toluoyl-2'-deoxyuridine XIIIh and diglycoside XVh.** The silyated base VIIIl was condensed with the chlorosugar as described above, except that 1 mmol of $ZnCl_2$ was added. The filtered and evaporated reaction mixture was separated on a silica column ($S_1$). The fractions with $R_f$0.28 were combined, evaporated and dried, giving a anomeric mixture of XIIIh (α:β/1:2) in 9.4% yield. Similarly, the fractions with $R_f$0.59 were combined, evaporated and dried, giving an isomeric mixture of XVh in 3.3% yield.

**2'-Deoxyuridines VIa-VIf, Xg, XIIg, XIVh, XVIh** (general method). The 1.0 mmol of blocked nucleoside Va-Vf, IXg, XIg, XIIIh or XVh was stirred in a solution of sodium methoxide, freshly prepared by dissolving 58 mg (2.5 mmol) of sodium in 25 ml of dry methanol. The reaction was monitored by TLC ($S_3$) and stopped after all the starting material and monodeblocked intermediates disappeared (4-6 hrs). The reaction mixture was diluted with the same volume of methanol, neutralised with Dowex 50($H^+$, prewashed with methanol) and the resin filtered off (washed with methanol until UV absorption in the filtrate disappeared). The combined filtrates were evaporated and purified on a silica column ($S_3$). The fractions containing the product were combined, filtered and evaporated to dryness; the yields obtained are those presented in TABLE 4 for the products VIa-VIf, Xg and XIIg, The samples for

elemental analysis were obtained as shown in TABLE 4. Similarly, the anomeric mixture of 5,6dimethyl-2'-deoxyuridine [XIVh] was obtained in 55% yield (α:β /1:1.6) and isomeric mixture XVIh in 60% yield. $^1$H NMR (DMSO-$d_6$) of XIVh: 11.78(NH, α), 11.75(NH, β), 6.15(t, H-1', α), 6.06(t, H-1', β), 5.25(d, OH-3', α). 5.14(d, OH-3', β), 4.68(t, OH-5', α and β), 4.27(m, H-3', β), 4.12(m, H-3', α), 4.01(m, H-4', α), 3.62(m, H-4', β), 3.55-3.35(m, H-5', H-5", α and β), 2.66(m, H-2', β), 2.44 (m, H-2", β), 2.05-1.94(m, H-2', H-2", α and β), 2.27(s, $CH_3$, α and β), 1.82(s, $CH_3$, α), 1.80 (s, $CH_3$, β). $^1$H NMR (DMSO-$d_6$) of the isomeric mixture XVIh: 6.62-6.44(m, $N_3$-anomeric protons), 6.21-6.02(m, $N_1$-anomeric protons). 5.28-5.05(3d, H-3 protons), 4.70(m, OH-5 protons), 4.30(m, H-3', all β), 4.20-4.00(m, all H-3' and H-4', α), 3.62(m, H-4', all β), 3.50-3.30(m, all H-5', H-5"), 2.72-2.35(m, all H-2', H-2"), 2.30(2s, $CH_3$), 1.85(3s, $CH_3$).

**Acknowledgement.** This project was supported by the Wellcome Foundation (Fellowship to I.B. and provision of testing facilities) and by the Scientific and Technical Research Council of Turkey (Fellowship to A.B.).



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Received 8/4/93
Accepted 9/14/93