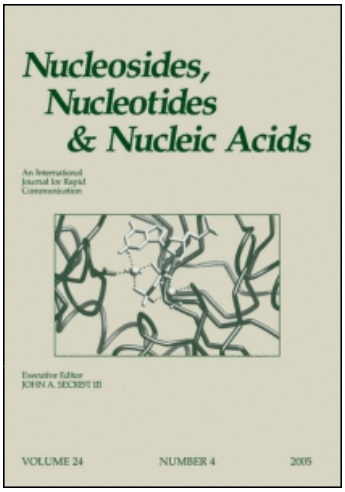


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

3'-Deoxy-3'-Hydroxyamino-β-D-Xylofuranosyluracil and Derivatives Thereof

Jean M. J. Tronchet[a]; Rachid Benhamza[a]; Naz Dolatshahi[a]; Michel Geoffroy[b]; Hans Türler[c]
[a] Departments of Pharmaceutical Chemistry, Physical, University of Geneva, Geneva 4, Switzerland [b] Chemistry and Molecular Biology University of Geneva, Geneva 4, Switzerland [c] Faculty of Sciences University of Geneva, Geneva 4, Switzerland

To cite this Article Tronchet, Jean M. J. , Benhamza, Rachid , Dolatshahi, Naz , Geoffroy, Michel and Türler, Hans(1988) '3'-Deoxy-3'-Hydroxyamino-β-D-Xylofuranosyluracil and Derivatives Thereof', Nucleosides, Nucleotides and Nucleic Acids, 7: 2, 249 — 269
To link to this Article: DOI: 10.1080/07328318808070208
URL: http://dx.doi.org/10.1080/07328318808070208

NUCLEOSIDES & NUCLEOTIDES, 7(2), 249-269 (1988)

3'-DEOXY-3'-HYDROXYAMINO-ß-D-XYLOFURANOSYLURACIL AND DERIVATIVES THEREOF

Jean M. J. Tronchet*[a], Rachid Benhamza[a], Naz Dolatshahi[a], Michel Geoffroy[b] and Hans Türler[c]

Departments of Pharmaceutical Chemistry[a], Physical Chemistry[b] and Molecular Biology[c] Faculty of Sciences, University of Geneva, 30 Quai Ernest Ansermet 1211 Geneva 4, Switzerland

ABSTRACT

The title compound was prepared by reduction of the oxime of the 3'-ketouridine. Condensation with aldehydes gave a series of nitrones whose reduction afforded "*second generation*" hydroxylamines, some of which showing antiviral activity. The nitroxide free radicals formed upon oxidation of hydroxylamines gave good e.s.r. spectra useful for configurational and conformational assignments.

INTRODUCTION

The high value of nucleoside analogs in medicinal chemistry, particularly for the treatment of cancers and viral diseases is well known. We describe here examples of a novel type of such analogs, compounds in which a hydroxyl group of the sugar moiety has been replaced by a hydroxyamino group. A further interest of these molecules resides in their spontaneous slow oxidation to nitroxide free radicals whose stationary concentration is sufficient to give good e.s.r. spectra but too low to alter significantly the resolution of the n.m.r. spectra of the parent hydroxylamine. We will show that this type of spin-labeling offers substantial advantages over the classical one[1] which consists in the "grafting" of an extraneous spin-label onto a peripheral site of the molecules :

- the spin-label is "right in the middle" of the molecule,

- the spin-labeling does not modify significantly the overall shape of the molecule,

- the e.s.r. spectra provide information on the structure (configuration and conformation) of these nucleoside analogs.

This work has been the object of a preliminary communication.[2]

RESULTS AND DISCUSSION

To synthesize 3'-deoxy-3'-hydroxyaminopentofuranosyluracil we needed 2',5'-di-blocked uridine. We first envisaged to use successively two blocking agents, first trityl chloride to specifically block the 5' position, then *tert*-butyldimethylsilyl chloride (TBDMSCl) to block selectively the 2' position[3]. 5'-O-trityluridine **2**[4] readily obtained from uridine (**1**) gave on treatment with TBDMSCl a resolvable mixture of mono-[**3** (40%) and **4** (16%)] and di-O-TBDMS [**5** (5%)] derivatives (Scheme 1). Oxidation of a mixture of **3** and **4** gave the corresponding ketouridine derivatives (68%) **6** and **7** which were oximated (70%) to the oximes **8** and **9**. Compounds **6**, **7**, **8** and **9** were obtained pure after column chromatography.

As both the yield and regioselectivity of the previous reactions were poorer than expected, we ressorted to a more classical approach and used as a starting material **10**[5], easily obtainable from uridine. As **10** was not reducible by the agents commonly used to affect the conversion of oximes into hydroxylamines, the BH_3-pyridine complex[6] and sodium cyanoborohydride[7] - this being probably the consequence of steric hindrance of the two trityl groups - it was hydrolyzed (HCl/MeOH) to **11** which was not isolated but directly reduced (BH_3-pyridine) to **12**, not isolated either, but used as such for the subsequent steps (Scheme 2). Some properties of the compounds prepared are collected in TABLE 1. Solutions of **12** could be kept for weeks at 4°C. The tetraacetyl derivative of **10**, **13**, was obtained in 37% yield from **10**, which corresponds to a 72% average yield per step, showing the usability of the procedure. The reduction step was stereospecific giving only the *xylo* derivative as established by n.o.e experiments on **12** and **13** showing population transfer observed on H-1' and H-4' when irradiating H-3' and confirmed by the easy formation and structure of cyclized compounds **20-25** (see below). ^{1}H-N.m.r. data of **12**, **13** and other 3'-deoxy-3'-hydroxyamino-nucleosides analogs are collected in TABLES 2 and 3. The "*first generation*" hydroxylamine **12** on treatment with aromatic aldehydes gave the corresponding nitrones **14-18**, some of

Scheme 1

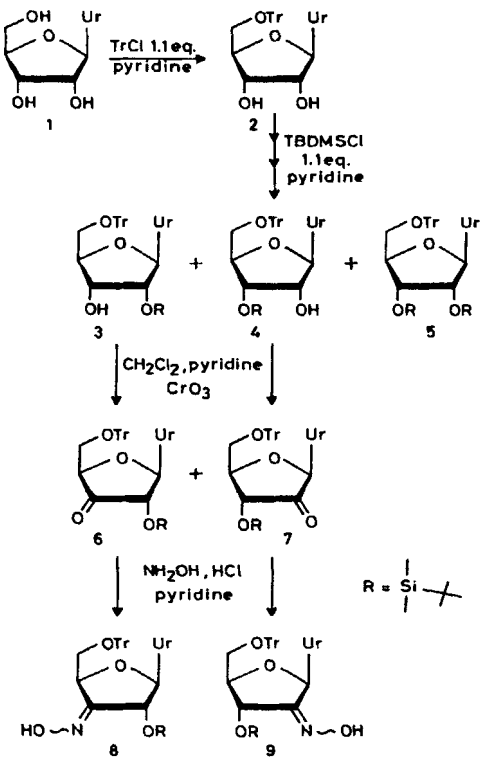


TABLE 1. Some properties of the compounds prepared

Compd	M.p.	$[\alpha]_D$		U.V.		I.R. (cm^{-1})
	°C	value °	c/t°C	λ_{max}	ε	
3	90-92	20[a]	1.05/22	260[d]	7400	3500(ν_{O-H}), 1680($\nu_{C=O}$)
4	63-64			262[a]	8500	
5	63-64			262[a]	8600	3200(ν_{N-H}), 1700($\nu_{C=O}$)
6	89-91	90.2[a]	1.33/22	260[a]	10400	3200(ν_{N-H}), 1750($\nu_{C=O}$), 1680($\nu_{C=O}$)
7	88-89	20.3[a]	0.57/23	258[a]	6300	3200(ν_{N-H}), 1780($\nu_{C=O}$), 1680($\nu_{C=O}$)
8	115-116	18.5[a]	1.4/22	260[a]	9800	3260(ν_{OH},ν_{NH}), 1680($\nu_{C=O}$)
9	101.9-102.5	3.7[a]	1.2/22			3280(ν_{O-H},ν_{N-H}), 1720($\nu_{C=N}$), 1680($\nu_{C=O}$)
13	83.1-83.8	24.4[a]	1.08/25	258[a]	8110	1803, 1747, 1696($\nu_{C=O}$)
14	129.4-130.5	32.7[c]	1.04/25	298[a]	18000	3338(ν_{O-H}), 3190(ν_{N-H}), 1716($\nu_{C=N}$), 1687($\nu_{C=O}$)
15	133.1-133.8	97.8[b]	1.0/26	310[a]	18870	3373(ν_{O-H}), 1710($\nu_{C=N}$), 1681($\nu_{C=C}$)
				260[a]	12200	
				242[a]	13420	
				238[a]	11740	
16	191.8-192.3	140.6[b]	0.96/23	336[a]	6260	3300(ν_{O-H}), 1760($\nu_{C=N}$), 1680($\nu_{C=O}$)
				378[a]	15760	
17	224.9-225.3			257[a]	30500	3338(ν_{O-H}), 1682($\nu_{C=O}$), 1345(ν_{NO2})
				344[a]	27100	
18	141.8-142.5	129.1[a]	0.91/24	318[a]	11850	3300(ν_{O-H}), 1680($\nu_{C=O,C=N}$)
				262[a]	7610	
19	74.7-75.4			260[a]	4700	1750 & 1680($\nu_{C=O}$), 1710($\nu_{C=N}$)
				300[a]	2000	
20	141.1-142.2			262[a]	15060	3387(ν_{O-H}), 1683($\nu_{C=O}$)
21	173.3-173.9	-68.7[b]	1.29/25	262[a]	11810	3350(ν_{O-H}), 1700($\nu_{C=O}$)
22	152.7-152.9	-10.4[b]	1.3/23	262[a]	10500	3380(ν_{O-H}), 1680($\nu_{C=O}$)
23	156.6-157.1	-3.36[b]	1.1/27	262[a]	9100	3400(ν_{O-H}), 1700 &1680($\nu_{C=O}$)
24	106.7-107.5	-132[a]	0.84/26	259[a]	10750	3200(ν_{N-H}), 1695($\nu_{C=O}$), 1772 & 1750($\nu_{C=O}$)
25	112.5-112.9	-34.11[a]	1.07/30	260[a]	6500	3217(ν_{N-H}), 1770 & 1749($\nu_{C=O}$), 1690($\nu_{C=O}$)
26	97-98	45.9[a]	0.74/26	260[a]	8700	3400(ν_{O-H}), 1700($\nu_{C=O}$)
27	108.9-109.4	56.9[a]	0.99/20			3300(ν_{O-H}), 1680($\nu_{C=O}$)
28	95-96.6	33,9[a]	1.09/23	264[a]	11860	3360(ν_{O-H}), 1690($\nu_{C=O}$)
29	109.5-111	34[b]	0.88/24	262[a]	10700	3380(ν_{O-H}), 1680($\nu_{C=O}$)
30	101-102	47.2[b]	0.91/23	265[a]	10070	3386(ν_{O-H}), 1685($\nu_{C=O}$)
31	85.8-86.7	39[b]	1.03/24	264[a]	11200	3386(ν_{O-H}), 1685($\nu_{C=O}$)
32	193.6-194.1			263[a]	9940	3379(ν_{O-H}), 1699 & 1668($\nu_{C=O}$)
33	119-120.6			262[a]	8320	3400(ν_{O-H}), 1690($\nu_{C=O}$)
34	182-183	33.8[b]	1.02/24	262[a]	10100	3430(ν_{O-H}), 1670($\nu_{C=O}$)
35	97.4-98.1	32.3[a]	0.77/24	261[a]	17660	3360(ν_{O-H}), 1690($\nu_{C=O}$)
				324[a]	39500	
36	110.6-111.2	5.5[b]	1.04/24	262[a]	9000	3408(ν_{O-H}), 1690($\nu_{C=O}$)
37	135.8-136.4	-30.3[a]	0.97/23	262[a]	9500	3420(ν_{O-H}), 1700($\nu_{C=O}$)
38	82.7-83.2	+164.3[f]	0.97/21	260[a]	8300	3200(ν_{O-H}), 1680($\nu_{C=O}$)
				236[a]	8500	

[a] in $CHCl_3$; [b] in MeOH; [c] in THF; [d] in dioxane; [e] in EtOH; [f] in acetone.

TABLE 2. ^{1}H-N.m.r. chemical shifts of 3'-deoxy-3'-hydroxyaminonucleosides derivatives 12, 13, 26-37 (in CD_3OD).

	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	CHN	H_5	H_6	Aromatics (or others)
12[a]	5.79	4.48	3.92	4.29	3.81		5.73	8.09	11.46(NH)
13[b]	6.02	5.73	4.82	4.68	4.34		5.84	7.81	8.49(NH), 2.20, 2.14, 2.08, 2.03(CH_3CO)
26	5.90	4.63	3.51	4.34	3.88	3.78	5.70	8.04	7.41-7.24
					4.01	4.14			
27	5.94	4.58	3.58	4.36	3.92	3.78	5.70	8.02	7.58-7.27
					4.00	4.36			
28	5.95	4.63	3.58	4.35	3.80	3.73	5.70	8.12	7.14, 6.80
					4.00	4.35			
29	5.98	4.56	3.62	4.35	3.79	3.98	5.71	8.05	7.28-7.08
					3.98	4.35			
30	5.88	4.51	3.46	4.33	3.86	4.07	5.68	8.05	7.0, 6.87, 3.8(CH_3O)
					4.00	3.70			
31	5.90	4.63	3.48	4.32	3.85	4.06	5.70	8.05	7.5-7.25, 7.02-6.80
					4.00	3.70			5.1(CH_2Ar), 3.85(CH_3O)
32	5.88	4.62	3.47	4.32	3.86	4.02	5.70	8.05	7.18, 6.73
					4.00	3.66			
33	5.85	4.44	3.40	4.31	3.83	2.64	5.68	8.02	5.09(HC=), 2.00(CH_2C=)
					4.00	2.97			1.66, 1.58(CH_3C=),
									1.66-1.09(CH_2,CH)
									0.87(CH_3-CH)
34	5.85	4.41	3.34	4.31	3.85	2.39	5.69	8.00	1.78, 1.26, 0.92
					4.00	2.78			
35	5.90	4.51	3.46	4.31	3.72	3.48	5.72	8.06	7.34, 6.60, 6.34, 6.08,
					3.85	3.80			2.02(CH_2), 1.95(C_3CH_3),
									1.85(C_7CH_3),
									1.70($C_{11}CH_3$),1.63(CH_2)
									1.48(CH_2), 1(CH_3)
36	5.85	4.44	3.44	4.29	3.85	2.83	5.69	8.00	1.46, 1.31 (Me_2C),
	5.83	4.64	3.70	4.44	3.96	3.28			3.36(CH_3O)
37	5.94	4.31	3.48	4.31	3.86	3.28	5.75	8.12	1.54, 1.41, 1.38 (Me_2C)
					4.01				
	5.50	4.40	4.68	4.31	4.18	2.80			
38	5.86	4.61	3.48	4.29	3.85	4.02	5.68	8.05	7.31, 7.00, 6.92
					4.00	4.28			

[a] in DMSO-d_6 ; [b] in $CDCl_3$

TABLE 3. ^{1}H-N.m.r. coupling constants (Hz) of 3'-deoxy-3'-hydroxyaminonucleosides derivatives 12, 13, 26-37 (in CD_3OD)

	J_{5-6}	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{5'a-5'b}$	J_{CHN}
12[a]	8	7	5	7	4.5		
13[b]	8.5	7	7	7.5	4.5		
26	8	6	5.5	7	3 6	13	13
27	8.5	6	6.5	7.5	3.5 5	13	14.5
28	8	6	7	7	3 4.5	13	13
29	8.3	6	6.5	7.2	3 5	13	13.5[c]
30	8.5	5.5	5.5	7	3 3.5	13	13
31	8	5.5	5.5	7.5	3.5 5	13	13
32	8	5.3	5.3	7.3	3.5 5.5	12.5	13
33	8.5	5.5	6	8	3.5 5.5	13	13[d]
34	8	6	6	7.5	3 5.5	13	13[e]
35	8.5	6	6	7	3 5.5	13	15
36	8.3	6	8	5.5	3.5 5	13	13.6 5.5, 7
		4.5	0	3.5			
37	8	5.5 5	6 2.5	7 8	2.5, 4 1.5	12.5	13 6, 7.5
38	8.2	5	5	7	3.5 5.5	12.5	14

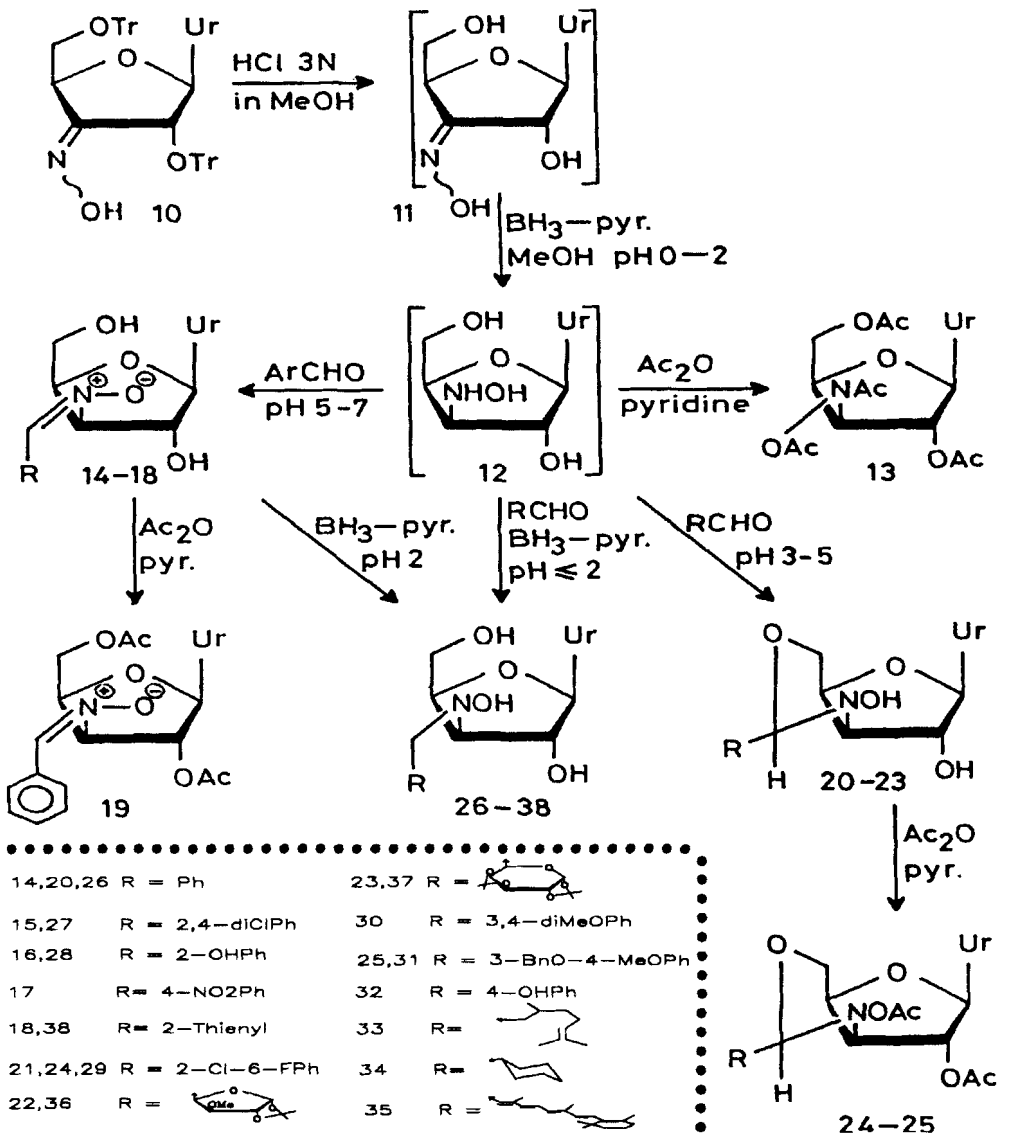
[a] in DMSO-d_6; [b] in $CDCl_3$; [c] J_{CHAN-F} = 1.2 Hz, J_{CHBN-F} = 1.7 Hz;
[d] $J_{CHANCH2}$ = 5.0 & 9.0 Hz, $J_{CHBN-CH2}$ = 6.0 & 9.0 Hz; [e] $J_{CHAN-H1''}$ = 7 Hz, $J_{CHBN-H1''}$ = 7.5 Hz

which (**14**,**16**) were reduced by borane-pyridine to the corresponding "*second generation*" hydroxylamines **26**,**27** or acetylated (**14** –> **19**). More generally, the "*second generation*" hydroxylamines **26-38** were obtained directly from **10** by a one-pot reaction effecting successively detritylation, reduction by an excess of borane-pyridine, condensation with an aldehyde and reduction of the nitrone formed by the unreacted borane-pyridine complex.

When **12** was treated in acidic medium (pH 3-5), without reducing agent, with an aldehyde - the reaction generally took a longer time for aromatic aldehydes and necessitated a lower pH than for aliphatic aldehydes - a cyclization occured to compounds of the type **20-23**, acetylable to **24-25**. ^{1}H-N.m..r data of the nitrones and their cyclization products are collected in TABLES 4 and 5.

The structural assignments of nitrones is straightforward from the typical azomethine proton in ^{1}H-n.m.r. (δ 7.46-8.45) and the C=N stretching in i.r. On the other hand, compounds bearing an hydroxyamino group on C-3' have a particularly shielded H-3'.

Scheme 2



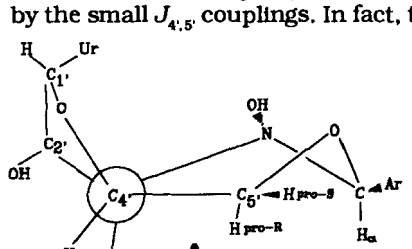
The structure of the perhydrooxazinofuranose derivatives **20-25** has been established in the following way. Compound **21**, for example, on acetylation gave a diacetyl derivative (**24**) while its ^{1}H-n.m.r. spectrum in DMSO-d_6 showed three exchangeable protons, the first one corresponding to H-N(3) [a doublet coupled to H-C(5)], the second one to NOH [a singlet] and the third one to HO-C(2') [a doublet coupled to H-2'], this proving that N-C(3') and O-C(5') were included in the perhydrooxazine ring. The configuration of the compounds **20-25** was found to be *xylo* from the null value of $J_{2',3'}$ (cf. TABLE 1) thus recursively establishing the configuration of all the series. The configuration of the new

TABLE 4. ^{1}H-N.m r. chemical shifts of nitrones 14-18 and their derivatives including their cyclic counterparts 20-25 (in CD_3OD)

	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	CH-N	H_5	H_6	Aromatics (or others)
14	6.05	5.00	4.84	4.52	3.75 3.89	7.96	5.80	8.31	8.31, 7.53
15	6.02	4.95	4.95	4.53	3.75 3.88	8.22	5.78	8.27	9.27, 7.61, 7.42
16	6.02	4.96	4.90	4.52	3.80 3.95	8.15	5.77	8.18	7.57, 7.42, 6.90, 6.87
17	6.04	4.95	4.95	4.52	3.72 3.87	8.12	5.78	8.27	8.52, 8.32
18	6.05	4.96	4.84	4.49	3.79 3.65	8.45	5.80	8.32	7.70, 7.68, 7.24
19[a]	6.24	5.76	4.68	4.56	4.48	7.46	5.88	8.37	8.13(NH), 8.24, 7.48, 2.17, 2.07(CH_3CO)
20	5.83	4.46	3.26	4.56	4.05 4.35	4.64	5.73	8.46	7.51-7.29
21	5.97	4.38	3.23	4.44	4.00 4.32	5.39	5.66	8.55	7.41-7.19, 7.12
22	5.77 5.87	4.39 4.66	3.16 3.83	4.50 4.25	3.82 4.27	4.11	5.59	8.30	3.40(OCH_3) 1.33-1.46(Me_2C)
23	5.79 5.55	4.39 4.39	3.21 4.60	4.39 4.39	3.90 4.30 4.11	4.11	5.60	8.27	1.49(Me_2C), 1.42, 1.36
24[a]	6.35	5.24	3.58	4.39	4.47 4.00	5.61	5.89	8.78	8.24(NH),7.39-7.00, 2.14, 1.78(CH_3CO)
25[a]	6.19	5.37	3.55	4.49	4.45 4.01	4.48	5.84	8.59	8.19(NH), 7.49-7.29, 6.86, 7.02, 5.18(CH_2O), 3.90(CH_3O). 2.15, 1.70(CH_3CO)

[a] In $CDCl_3$

asymetric carbon (α) was best established by e.s.r. (see below) but the ^{1}H-n.m.r. gave also some indications. From the $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$ values a conformation close to $^3T_{4'}$ of the furanose ring could be deduced. This conformation is only compatible with a $^{O(5')}C_{3'}$ conformation for the perhydrooxazine ring, the alternative chair $^{3'}C_O$ being further excluded by the small $J_{4',5'}$ couplings. In fact, the chair is somewhat distorted (flattened in the area C-5'-C-4'-C-3') and intermediate between the classical $^OC_{3'}$ chair and the flattened chair[8] $^{O,N}F$ **A** which explains the small difference between the two $J_{4',5'}$ values, $J_{4',5'pro\text{-}S}$ being the smaller. This conformation being established, the (*R*) configuration could be tentatively assigned to the α asymetric carbon from the absence of long-range W ^4J coupling between H-α and H-5'pro-s, the n.o.e. experiments showing a spin population transfer between H-3' and H-α and the probable thermodynamic control of the ring closure reaction leading to an equatorial position for the large (aryl or glycosyl) substituant on C-α.



A

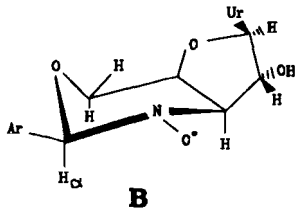
TABLE 5. ^{1}H-N.m.r. coupling constants of nitrones 14-18 and their derivatives including their cyclic counterparts (in CD_3OD).

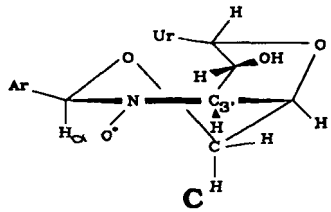
	J_{5-4}	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{5'a-5'b}$	J_{CHN}
14	8	5.5	4	7	5	12	
15	8.5	5			5	12	
16	8	5	3.5	0	6	12	
17	8	5	3		5.5	12	
18	8	5.5	4.5	7	5	12.5	
19[a]	8.5	5	2	6			
20	8.5	0	0	3.5	2	13.5	
					0		
21	8	0	0	4	2	13.5	
					0		
22	8	0	0	4	1.5	13.2	6
		4	1	4	0		
23	8	0			1.5	14	
		5	2	8	1		
24[a]	8	2	0	4	1.5	13.7	
					0		
25[a]	8.5	0	0	4	2	13.5	
					0		

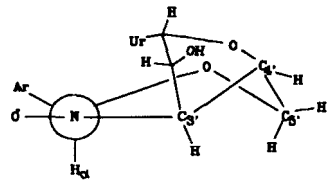
[a] In $CDCl_3$

TABLE 6. E.s.r. Data for the nitroxide free-radicals formed on oxidation of some Deoxy N-hydroxyamino Nucleosides (in diglyme).

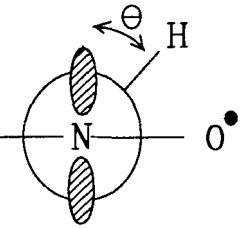
Compd	t°C	g	a_N	$a_{H-3'}$	a_{CH_2-N} or a_{CH-N}	Extra a_H
20'	20	2.0062	15.50	17.50	15.50	
21'	20	2.0055	15.60	20.33	17.53	
22'	20	2.0060	15.00	19.40	15.00	
	65		14.85	18.90	14.85	
26'	20	2.0062	14.20	2.80	9.25 & 9.25	
28'	20	2.0059	14.70	2.80	9.20 & 10.10	0.7
30'	20	2.0062	14.50	2.60	9.30 & 9.30	
31'	100	2.0059	14.50	3.00	9.40 & 9.40	0.8
	20		14.20	2.80	8.60 & 11.20	
33'	50	2.0060	14.20	3.00	10.40 & 10.80	0.8
34'	70	2.0060	14.10	2.80	9.15 & 11.10	
	90		14.30	3.00	9.30 & 10.40	
35'	20	2.0056	14.54	2.45	10.87 & 10.87	
36'	70	2.0064	14.00	2.80	8.80 & 11.40	0.9

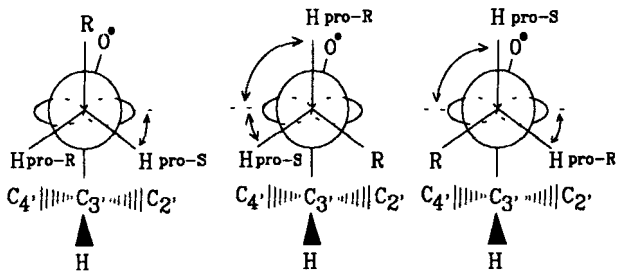

B


C


D

Compounds bearing a free N-OH group oxidized spontaneously in the air to give the corresponding nitroxide free radicals whose number have been primed (**26** — > **26'**, etc...). Their e.s.r. values, collected in TABLE 6 showed a hyperfine coupling with the nitrogen atom a_N, in the range 14.0-15.6 G, as well as with neighbouring protons, the last ones giving interesting structural information from the known[9] angular dependance of such hyperfine couplings $a_H \cong 26 \cos^2\theta$, θ being the dihedral angle between the H-C-C-N plane and the plane encompassing the C-N bond and the axis of the p_z orbital of the approximatively sp^2 hybridized nitrogen atom. For the cyclic nitroxides **20'-22'**, the two large a_H values indicated an approximate 1,3-*cis*-diaxial relationship of H-3' and H-α, thus establishing the (*R*) configuration of C-α. The larger of these two hyperfine couplings has been tentatively assigned to $a_{H3'}$, the distorted chair **B** seeming more probable than either the half-chair **C** or the flattened chair **D**. In any case, the e.s.r. data established definitively the configuration at C-α, proving its superiority over n.m.r. in this kind of situation where an asymetric carbon being flanked by two heteroatoms, no H-H coupling is available for configurational assignment.





E $a_{H\text{-pro-R}}$ = 19.5 G, $a_{H\text{-pro-S}}$ = 19.5 G

F $a_{H\text{-pro-R}}$ = 0, $a_{H\text{-pro-S}}$ = 19.5 G

G $a_{H\text{-pro-R}}$ = 19.5 G, $a_{H\text{-pro-S}}$ = 0

The preferred conformations for nitroxide free radicals are the eclipsed ones[10] (**E-G**) and, in the case of a methylene group, the two most populated conformations those in which one of the C-H bond eclipses the N-O bond as we have shown in several instances[11]. This is also the case here as shown (TABLE 6) by the fact that the sum of the two methylenic a_H was found to be close to 20 G. Increasing the temperature of measurement did not affect significantly this sum but decreased the difference between the two couplings, confirming the assignments and leaving the smallest value (2.45 - 3.00 G) to $a_{H\text{-}3'}$ which indicated that in the most favourable conformation H-C3' is in the σ plane of the nitroxide group.

Compounds **21**, **26-31**, **34** and **35** have been subjected to antibacterial testing against *Escherichia coli*, *Micrococcus luteus* and *Bacillis subtilis* where only **26** was found active against the three microorganisms at 50 μg/ml whereas, at the same concentration, **28** was active against *E. coli* and *B. subtilis*.

Cytotoxic and antiviral activities of compounds **13-15**, **18**, **20-22**, **26-32** and **34-38** have also been tested. Large differences in cytotoxicity were observed most compounds

being atoxic at 120 µg/ml whereas **28** was toxic at a concentration of 3 µg/ml in MRC5 cultures and **18**, **27**, **31**, **35** and **38** being active at *ca* 40 µg/ml. The only notable antiviral activities were found for **26** against *Herpes simplex virus I* (120 µg/ml) and *polyoma virus* (100 µg/ml) and **30** against *rhinovirus* (60 µg/ml). As compound **26** seemed the most promising agent against *polyoma virus*, it was submitted to a more detailed virological study.

In quiescent, primary mouse kidney cell cultures, *polyoma virus* induces a lytic infection, whereby mouse chromatin duplication (S-phase) parallels viral DNA replication.[12] During this period ^{3}H-thymidine incorporation is 4-6 fold higher in infected cultures than in uninfected control cultures. We used this property to test compound **26** for its ability to inhibit the lytic cycle of *polyoma virus* and virus-induced S-phase. Confluent, primary mouse kidney cell cultures[13] were grown to confluence on 22x22 mm microscope cover slips and infected or mock-infected with *polyoma virus*.[14] The compound to be tested was added in serum-free medium at the concentrations of 100 or 200 µg/ml after virus adsorption and was present throughout the experiment. The cultures were pulse-labeled for 1 hour with ^{3}H-thymidine 24 hours after infection. Then the coverslips were washed 3 times with cold phosphate-buffered saline,[14] ice-cold 5% trichloroacetic acid (15 min) and 96% ethanol. The air-dried coverslips were counted in scintillation liquid. The results showed that compound **26** at 100 µg/ml inhibited thymidine incorporation by 18-66%, while in uninfected cultures 0-20% inhibition was observed. With 200 µg compound **26** per ml little further increase of inhibitory activity was observed. Selective extraction of newly synthesized viral DNA and its analysis by velocity sedimentation[15] showed that incorporation of ^{3}H-thymidine into viral DNA was inhibited to a similar extent as total incorporation. Finally, as judged from an immunofluorescent assay,[14] synthesis of the early viral proteins (taking place before onset of viral DNA replication) occured in a similar proportion of the cells and to similar amounts both in presence and absence of compound **26**.

EXPERIMENTAL

Melting points (uncorrected) were determined under microscope with a Mettler FP52 melting-point apparatus. Thin layer chromatographies were performed on silica gel HF_{254} (Merck) with detection by UV light and phosphomolybdic-sulfuric acid.[16] Dry column chromatography[17] was conducted on silica gel $60F_{254}$ (0.063 - 0.200 mm). Silica gel 60 (0.040 - 0.200 mm) Merk was used for flash column chromatography.[18] IR spectra were recorded with a Perkin-Elmer Model 357 or a FT-IR Nicolet 20 SXB spectrometer. UV spectra were measured on a Kontron Uvicon 810 spectrophotometer. N.m.r. spectra were recorded at 20°C on a Brucker WP 200 SY spectrometer (^{1}H 200 MHz; ^{13}C 50.4 MHz; chemical shifts in ppm from TMS; d units; *b* : broad; *s* : singlet...). Optical rotations were measured with a Schmidt-Haensch polarimeter. E.s.r. spectra were recorded on a Varian E-9 spectrometer (X band, 100 KHz modulation) equipped with a variable temperature device. The g values were measured by using a DPPH sample and the magnetic field was calibrated with an n.m.r. marker. All the hyperfine coupling constants were checked by simulating the corresponding e.s.r. spectra with a 9830 Hewlett-Packard or Victor S1 desk computer, using a program developped in this Laboratory.

2'-O-Tert-butyldimethylsilyl(TBDMS)-5'-O-trityluridine **3**, *3'-O-TBDMS-5'-O-trityluridine* **4** *and 2',3'-di-O-TBDMS-5'-O-trityluridine* **5** : - To a stirred solution of **2** (1 g, 1.2 mmol) and $AgNO_3$ (0.4 g, 2.4 mmol) in 50 ml of distilled pyridine, was added *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.4 g, 2.4 mmol). After 2 h under stirring at room temperature **2** had disappeared (TLC). The pyridine was evaporated and the residue treated with 50 ml of a 5% aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4) and submitted to a flash chromatography giving :

- **3** in 40% yield (0.49 g, 0.8 mmol); R_F: 0.37 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r. ($CDCl_3$): δ 0.12 (*2s*, 6H, $2CH_3$), 0.85 (*s*, 9H, *tert*-Bu), 2.48 (*d*, 1H, OH), 3.44 (*d*, 2H, H-5'), 4.04 (*m*, 1H, H-4'), 4.31 (*m*, 2H, H-2', H-3'), 5.2 (*dd*, 1H, H-5), 5.85 (*d*, 1H, H-1'), 7.26 (*m*, 15H, Ph), 7.85 (*d*, 1H, H-6), 8.73 (*bs*, 1H, NH); ^{13}C-n.m.r ($CDCl_3$): d 17.95 (**C**$(CH_3)_3$), 25.61 (C(**C**$H_3)_3$), 62.35 (C-5'), 70.22 (C-3'), 83.32, 87.64, 88.73 (C-1', C-2', C-4'), 102.20 (C-5), 127.43, 127.73, 127.99, 128.19, 128.38, 128.59 (Ph), 140.11 (**C**Ph_3), 143.06 (C-6), 150.30 (C-2), 163.52 (C-4). Mass spectrum: *m/z* 543 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{34}H_{40}O_6N_2Si$ (600.79): C 67.97; H 6.71; N 4.66. Found: C 67.77; H 6.98; N 4.73.

- **4** in 16% yield (0.2 g, 0.33 mmol); R_F: 0.19 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r ($CDCl_3$): δ -0.12 (*s*, 2H, CH_3), 0 (*s*, 3H, CH_3), 0.8 (*s*, 9H, *tert*-Bu), 2.87 (*d*, 1H, OH), 3.27 (*dd*, 1H, H-5'a), 3.53 (*dd*, 1H, H-5'b), 4 (*m*, 1H, H-4'), 4.11 (*m*, 1H, H-2'), 4.33 (*m*, 1H, H-3'), 5.32 (*dd*, 1H, H-5), 5.91 (*d*, 1H, H-1'), 7.27 (*m*, 15H, Ph), 7.8 (*d*, 1H, H-6), 8.95 (*bs*, 1H, NH). Mass spectrum: *m/z* 543 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{34}H_{40}O_6N_2Si$ (600.79): C, 67.97; H, 6.71; N, 4.66. Found: C, 67.73; H, 6.92; N, 4.69.

- **5** in 5% yield (0.08 g, 0.11 mmol); R_F: 0.63 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r. ($CDCl_3$): δ -0.12, -0.02, 0.02, 0.09 (*4s*, 4x3H, $4xCH_3$), 0.7 (*s*, 9H, *tert*-Bu), 0.85 (*s*, 9H, *tert*-Bu), 3.29 (*dd*, 1H, H-5'a), 3.63 (*dd*, 1H, H-5'b), 4.12 (*m*, 3H, H-2', H-3', H-4'), 5.19 (*dd*, 1H, H-5), 5.78 (*d*, 1H, H-1'), 7.28 (*m*, 15H, Ph), 8.07 (*d*, 1H, H-6), 8.6 (*bs*, 1H, NH). Mass spectrum: *m/z* 699 ($M^{+\cdot}$ - CH_4), 657 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{40}H_{54}O_6N_2Si_2$ (715.06): C 67.19; H 7.61; N 3.92. Found: C 67.35; H 7.72; N 3.72.

2'-O-TBDMS-5'-O-trityl-β-D-erythro-pentofuranos-3'-ulosyluracil **6** *and 3'-O-TBDMS-5'-O-trityl-β-D-erythro-pentofuranos-2'-ulosyluracil* **7**. - A solution of oxidant was prepared by adding at 0°C 5g (0.05 mmol) of CrO_3 to a solution of 8 ml distilled pyridine and 100 ml of distilled CH_2Cl_2. The dark-brown solution was stirred 30 min and 2.5 g (4.1 mmol) of a 3:1 mixture of **3** and **4** was added. After 30 min, the solution was triturated with 100 ml of a saturated solution of $NaHCO_3$. Separation of the organic phase and extraction with 2x50 ml of CH_2Cl_2 afforded a brown solution which was dried over Na_2SO_4. Evaporation of the solvent and treatment with ether precipitated chromic salts. Filtration on activated charcoal then celite afforded a syrupy 3:1 mixture (68%) of **6** and **7**. Analytically pure samples were obtained by silica gel column chromatography.

- **6** (38%); R_F: 0.54 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r. ($CDCl_3$): δ 0.13 (*s*, 3H, CH_3), 0.22 (*s*, 3H, CH_3), 0.97 (*m*, 9H, *tert*-Bu), 3.45 (*dd*, 1H, H-5'a), 3.72 (*dd*, 1H, H-5'b), 4.31 (*m*, 1H, H-4'), 4.61 (*d*, 1H, H-2'), 5.47 (*d*, 1H, H-5), 6.30 (*d*, 1H, H-1'), 7.38 (*m*, 15H, Ph), 7.72 (*d*, 1H, H-6); ^{13}C-n.m.r. ($CDCl_3$): δ -5.35, -4.70 ($SiCH_3$), 18.18 (**C**$(CH_3)_3$), 25.38 (C(**C**$H_3)_3$), 63.18 (C-5'), 80.46, 85.04, 87.85 (C-4', C-2', C-1'), 103.51 (C-5), 127.61, 127.97, 128.13, 128.85 (Ph), 139.20 (**C**Ph_3), 142.77 (C-6), 150.18 (C-2), 162.57 (C-4), 208.19 (C-3'). Mass spectrum: *m/z* 541 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{34}H_{38}N_2O_6Si$ (598.7): C 68.20; H 6.39; N 4.67. Found: C 68.44; H 6.62; N 4.82.

- **7** (14%); R_F: 0.28 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r. ($CDCl_3$): δ 0 (*s*, 2H, CH_3Si), 0.14 (*s*, 2H, CH_3Si), 0.79 (s, 9H, *tert*-Bu), 3.41 (*dd*, 1H, H-5'a), 3.56 (*dd*, 1H, H-5'b), 4.12 (*ddd*, 1H, H-4'), 4.76 (*d*, 1H, H-3'), 5.15 (*s*, 1H, H-1'), 5.78 (*dd*, 1H, H-5), 7.24-7.56 (*m*, Ph, H-6), 8.78 (*bs*, 1H, NH). Mass spectrum: *m/z* 541 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{34}H_{38}N_2O_6Si$ (598.7): C 68.20; H 6.39; N 4.67. Found: C 68.13; H 6.26; N 4.68.

3'-Deoxy-3'-oximino-2'-TBDMS-5'-O-trityl-β-D-erythro-pentofuranosyluracil **8** *and 2'-deoxy-2'-oximino-3'-TBDMS-5'-O-trityl-β-D-erythro-pentofuranosyluracil* **9**. - A solution of a 73:27 mixture of **6** and **7** (1.2 g, 1 mmol) and hydroxylamine hydrochloride (1 g, 14.5 mmol) in dry pyridine (20 ml), was heated 2 h at 50°C. The solvent was evaporated and the residue treated with 150 ml of $CHCl_3$, washed with water (2x100 ml), then dried (Na_2SO_4). The evaporation of $CHCl_3$ and coevaporation with toluene afforded 1.2 g (98%) of a brown solid which was purified by silica gel column chromatography to yield **8** and **9** in isomeric percentage of 84% and 16%.

- **8** was obtained in 59% yield; R_F: 0.47 (AcOEt:$CHCl_3$, 1:6); ^{1}H.n.m.r. in $CDCl_3$ with progressive addition of DMSO-d_6 allowed the attribution of signals to the *E* (60%) and *Z* (40%) isomers : δ 0.12-0.19 (*m*, 6H, 2xCH_3), 0.9 (*m*, 9H, *tert*-Bu), 2.24 (*dd*, H-5'a, *E*), 3.60 (*m*, H-5', *Z*), 3.92 (*dd*, H-5'b, *E*), 5.04 (*m*, 2H, H-2', H-4'), 5.26 (*d*, 1H, H-5), 6.12, 5.95 (*d*, 1H, $J_{1',2'}$ = 8 Hz, *E*, $J_{1',2'}$ = 3 Hz, *Z*, H-1'), 7.36 (*m*, 15H, Ph), 7.60, 7.78 (*d*, 1H, H-6), 8.31, 8.75 (*bs*, 1H, OH), 8.80, 8.86 (*bs*, 1H, NH); ^{13}C-n.m.r. ($CDCl_3$): δ -4.77, -4.92, -5.19, -5.32 (Si(CH_3)$_2$), 18.04, 18.14 (**C**(CH_3)$_3$), 25.41, 25.51 (C(**C**H_3)$_3$), 62.81, 63.34 (C-5'), 74.11, 74.48, 75.58, 75.87, 78.21, 86.44, 87.35, 87.58, 91.64 (C-1', C-2', C-4'), 102.46, 102.99 (C-5), 127.28, 128.77 (Ph), 140.02, 140.51 (**C**Ph_3), 143.06, 143.16 (C-6), 150.13 (C-2), 158.37 (C-3), 162.76, 163.02 (C-4). Mass spectrum: *m/z* 556 ($M^{+\cdot}$ - *tert*-Bu).

Anal. Calcd for $C_{34}H_{39}O_6N_3Si$ (613.79): C 66.53; H 6.40; N 6.85. Found: C 66.35; H 6.20; N 6.75.

- **9** was obtained in 11% yield; R_F: 0.12 (AcOEt:$CHCl_3$, 1:6); ^{1}H-n.m.r. ($CDCl_3$): δ 0.06, 0.15 (*2s*, 6H, 2xCH_3Si), 0.84 (*s*, 9H, *tert*-Bu), 3.42 (*s*, 2H, H-5'), 4.20 (*m*, 1H, H-4'), 5.29 (*m*, 2H, H-5, H-3'), 6.84 (*s*, 1H, H-1'), 7.35 (*m*, 15H, Ph), 7.56 (*d*, 1H, H-6), 8.86 (*bs*, 1H, NH), 9.68 (*s*, 1H, OH). Mass spectrum: *m/z* 556 ($M^{+\cdot}$ - *tert*-Bu).

3'-Deoxy-3'-oximino-β-D-erythro-pentofuranosyluracil **11**. - Obtained from **10**[5] (1 g, 1.35 mmol) by detritylation in MeOH/HCl (pH ~ 2, 2-3 h, 1 ml). The product was unstable when subjected to classical purification methods, but could be kept in methanolic solution and used as such for the next steps; R_F: 0.41 (MeOH:CH_2Cl_2, 1:4); ^{1}H-n.m.r. (DMSO-d_6): two stereoisomers *Z* and *E* (23% and 77%): δ 3.65, 3.80 (*m*, 1H, H-5'), 4.56 (*t*, 1H, H-2'), 4.78 (*m*, 1H, N-H), 4.95 (*d*, 1H, OH-2'), 7.7, 7.9 (*d*, 1H, H-6), 11.09, 11.12 (*s*, 1H, NOH), 11.3 (*bs*, 1H, NH). Mass spectrum: *m/z* 274 ($M^{+\cdot}$ + H_2O).

3'-Deoxy-3'-hydroxyamino-β-D-xylofuranosyluracil **12**. - To the crude solution of **11**[4] obtained as described above, was added borane-pyridine complex[6] (4 equ., 0.5 ml) at pH = 0-2. The reduction occured in 2 hours. The solution was evaporated, and **12** extracted with water then washed with chloroform affording an essentially pure solution of **12** which was not purified further owing to its unstability but used as such; **12** could be kept for weeks at 4°C. R_F: 0.18 (MeOH:CH_2Cl_2, 1:4); ^{1}H-n.m.r. (DMSO-d_6): see TABLES 2 and 3; ^{1}H-n.m.r. (CD_3OD): δ 4.02 (*m*, 2H, H-3', H-5'), 4.64 (*m*, 1H, $J_{4',5'}$ = 9 Hz, $J_{3',4'}$ = 6 Hz, H-4'), 4.9 (*m*, 1H, $J_{2',3'}$ = 3.5 Hz, H-2'), 5.64 (*d*, 1H, $J_{1',2'}$ = 5 Hz, H-4), 5.77 (*d*, 1H, $J_{5,6}$ = 8 Hz, H-5), 7.85 (*d*, 1H, H-6).

3'-(N-Acetoxy acetamido)-2',5'-di-O-acetyl-3'-deoxy-β-D-xylofuranosyluracil **13**. - To a solution of **12** obtained as described above from **10** (1 g, 1.35 mmol) in 5 ml of pyridine, acetic anhydride (3 ml) was added at 0°C. The reaction occured in 30 min. After evaporation of the solvent, the residue was triturated with 20 ml of a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, then subjected to purification by silica gel column chromatography (AcOEt), and precipitated from chloroform/hexane to give 43 mg (0.1 mmol) of **13** (yield 37.2% from **10**, average yield for each step 72%): R_F: 0.41 (AcOEt); ^{1}H-n.m.r. ($CDCl_3$): see TABLES 2 and 3. Mass spectrum: *m/z* 113 (100, B+2H), 171 (87), 139 (78), 273 (75), 385 (71, $M^{+\cdot}$ - Ac), 231 (61), 69 (52), 97 (43), 196 (22), 54 (13), 316 (12), 427 (6, $M^{+\cdot}$).

Anal. Calcd for $C_{17}H_{21}N_3O_{10}$ (427.37): C 47.78; H 4.95; N 9.83. Found C 47.80; H 4.91; N 9.83.

General procedure for synthesis of **14** - **18**. - To a solution of **12** in methanol and at 5.5 < pH < 7.5 (corrected with a $NaHCO_3$ saturated solution), 1.2-3 equivalents of an aromatic aldehyde were added. After 2 to 10 h stirring at room temperature, the reaction was finished (t.l.c.). After evaporation of the solvent, the residue was chromatographed on silica gel dry column chromatography. Yield were calculated from **10** and an average yield for each step estimated.

3'-Benzylidenimino-3'-deoxy-β-D-xylofuranosyluracil-N'-oxide **14**. - A solution of **10** (501.7 mg, 0.67 mmol) in MeOH (30 ml) was successively detritylated to **11** with 3N HCl/MeOH (2ml) and reduced with the borane-pyridine complex (0.4 ml, 3.9 mmol). After evaporation of the solvent, extraction with water and washing with $CHCl_3$ to remove borane-pyridine and triphenylmethyl carbinol, water was evaporated and the residue redissolved in MeOH, then brought to pH = 4.9 with an aqueous $NaHCO_3$ saturated solution. Condensation with benzaldehyde (0.14 ml, 1.34 mmol) took place in 14 h and purification by silica gel column chromatography yielded 71.6 mg (0.2 mmol) of **14** which crystallized in methanol with inclusion of one molecule of methanol. Yield 27.9% from **10**, average 65% per step. R_F: 0.22 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5; (DMSO-d_6): δ 3.59 (*m*, 2H, H-5'), 4.36 (*q*, 1H, H-4'), 4.79 (*m*, 2H, H-2', H-3'), 5 (*t*, 1H, $J_{5',OH}$ = 6 Hz, OH-5'), 5.83 (*d*, 1H, $J_{5,6}$ = 8 Hz, H-5), 5.9 (*d*, 1H, $J_{1',2'}$ = 5 Hz, H-1'), 6.17 (*d*, 1H, $J_{2',OH}$ = 6 Hz, OH-2'), 7.46 (*m*, 2H, Ph), 8.03 (*s*, 1H, H-C =), 8.17 (*d*, 1H, $J_{5,6}$ = 8 Hz, H-6), 8.28 (*m*, 2H, Ph), 11.41 (*bs*, 1H, NH). Mass spectrum: *m/z* 113 (100, B + 2H), 105 (68), 91 (66), 330 (65), 122 (64), 241 (60), 77 (54), 194 (42), 218 (39), 70 (35), 160 (29), 148 (24), 347 (4, $M^{+\cdot}$).

Anal Calcd for $C_{16}H_{17}N_3O_6$, CH_3OH (379.37); C 53.82; H 5.58; N 11.08. Found: C 53.43, H 5.65; N 10.85.

3'-Deoxy-3'-[2.4-dichlorobenzylidenimino]-β-D-xylofuranosyluracil N'-oxide **15**. - A solution of **12** obtained from **10** (501 mg, 0.67 mmol) as described above was treated (2 h, pH 4.5, 20°C) with 2,4-dichlorobenzaldehyde (130 mg, 0.74 mmol). After crystallization (MeOH) 103 mg (36.6% from **10**, average yield 72% per step) of **15** were obtained. R_F: 0.27 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5. Mass spectrum: *m/z* 113 (100, B + 2H), 69 (92), 159 (66), 173 (58), 123 (55), 175 (51), 161 (43), 86 (34), 97 (30), 241 (24), 190 (17), 145 (14), 216 (9), 398 (7), 415 (6, $M^{+\cdot}$), 417 (4, $M^{+\cdot}$), 286 (4).

Anal. calcd for $C_{16}H_{15}N_3O_6Cl_2$ (416.22): C 46.17; H 3.63; N 10.10; Cl 17.04. Found: C 45.90; H 3.87; N 9.86; Cl 17.11.

3'-Deoxy-3'-[2-hydroxybenzylidenimino]-β-D-xylofuranosyluracil N'-oxide **16**. - A solution of **12** obtained from **10** (1 g, 1.35 mmol) as described above was treated (2 h, pH 7, 20°C) with salicylaldehyde (0.4 ml, 3.74 mmol). After crystallization (EtOH), 92 mg (18.8% from **10**, average yield 66% per step) of **16** were obtained. R_F: 0.49 (MeOH:CH_2Cl_2, 1:6); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5. Mass spectrum: *m/z* 121 (100), 56 (31), 69 (30), 113 (24, B + 2H), 345 (24, $M^{+\cdot}$ - H_2O), 176 (22), 92 (21), 112 (21, B + H), 77 (12), 132 (12), 162 (9), 148 (9), 233 (4), 363 (4, $M^{+\cdot}$), 251 (1).

Anal. calcd for $C_{16}H_{17}N_3O_7$ (363.33); C 52.89; H 4.72; N 11.59. Found: C 52.67; H 4.79; N 11.32.

3'-Deoxy-3'-[4-nitrobenzylidenimino]-β-D-xylofuranosyluracil N'-oxide **17**. - A solution of **12** obtained from **10** (501 mg, 0.67 mmol) as described above was treated (14 h, pH 6, 20°C) with *p*-nitrobenzaldehyde (139 mg, 0.92 mmol). After crystallization (MeOH) 37mg (14% from **10**, average yield 52% per step) of **17** were obtained. ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5. Mass spectrum: *m/z* 150 (100), 112 (66, B + H), 205 (57), 69 (48), 359 (42), 375 (37) 346 (33), 373 (32), 91 (28), 263 (23), 166 (14), 287 (10), 313 (10), 177 (9), 189 (10), 392 (3, $M^{+\cdot}$).

Anal. calcd for $C_{16}H_{16}N_4O_8$ (392.33); C 48.98; H 4.11; N 14.28. Found: C 48.75; H 4.07; N 14.07.

3'-Deoxy-3'-[thien-2-ylmethylidenimino]-β-D-xylofuranosyluracil N'-*oxide* **18**. - A solution of **12** obtained from **10** (1.23 g, 1.78 mmol) as described above was treated (14 h, pH 5.5, 20°C) with thiophene-2-carboxaldehyde (0.5 ml, 5 mmol) to yield 0.32 g (55% from **10**, average yield 82% per step) of **18**; R_F: 0.24 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5. Mass spectrum: *m/z* 111 (100), 97 (83), 113 (71, B + 2H), 69 (57), 128 (39), 85 (34), 55 (33), 154 (29), 165 (19), 224 (18), 206 (16), 336 (15), 182 (11), 136 (9), 195 (8), 241 (4), 269 (1), 252 (1), 353 (1, $M^{+\cdot}$).

Anal. calcd for $C_{14}H_{15}N_3O_6S$ (353.36); C 47.59; H 4.29; N 11.89; S 9.07. Found: C 47.34; H 4.56; N 11.69; S 8.95.

2',5'-Di-O-acetyl-3'-benzylidenimino-3'-deoxy-β-D-xylofuranosyluracil N'-*oxide* **19**. - Acetylation of **14** (14 mg, 0.04 mmol) was conducted in pyridine (1 ml) and acetic anhydride (0.5 ml) during 15 min. Concentration of the solution and treatment with water precipitated **19**. The product was collected by filtration, washed with hexane then dissolved in $CHCl_3$ and dried (Na_2SO_4). Evaporation afforded 12 mg of **19** : yield 69%; R_F: 0.41 (AcOEt); ^{1}H-n.m.r. ($CDCl_3$): see TABLES 4 and 5. Mass spectrum: *m/z* 105 (100), 200 (61), 97 (50), 77 (49), 139 (45), 242 (40), 260 (36), 112 (29, B + H), 69 (25), 160 (20), 188 (18), 172 (16), 304 (16), 414 (16, $M^{+\cdot}$ - OH), 218 (14), 372 (11), 277 (9), 230 (9), 431 (3, $M^{+\cdot}$), 388 (2, $M^{+\cdot}$ - Ac).

Anal. calcd for $C_{20}H_{21}N_3O_8$ (431.41); C 55.68; H 4.91; N 9.74. Found C 55.39; H 5.16; N 9.44.

General procedure for the synthesis of products **20** - **23** : - a methanolic solution of **12**, prepared from **10** as described above, was reacted with an aliphatic (pH 5, 1/2 hour) or an aromatic (pH 3-5, 15 min - 14 h) aldehyde. After evaporation of solvent, the residue was purified by silica gel column chromatography.

3'-N,5'-O-(R)-Benzylidene-3'-deoxy-3'-hydroxyamino-β-D-xylofuranosyluracil **20**. - A solution of **12** obtained from **10** (500.5 mg, 0.67 mmol) treated with benzaldehyde (0.07 ml, 0.73 mmol, 15 min, pH 5, 20°C) afforded a mixture of **14** (72 mg, 31% from **10**) and **20** (8 mg, 3.4% from **10**). R_F: 0.27 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5; e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 113 (100, B + 2H), 105 (77), 77 (73), 69 (62), 91 (57), 55 (49), 83 (34), 122 (21), 97 (16), 241 (14), 194 (12), 330 (11, $M^{+\cdot}$ - OH), 160 (9), 200 (6), 218 (6), 129 (5), 313 (1).

Anal. calcd for $C_{16}H_{17}N_3O_6$ (347.33); C 55.33; H 4.93; N 12.12. Found: C 55.42; H 5.13; N 11.84.

3'-N,5'-O-(R)-[2-Chloro-6-fluorobenzylidene]-3'-deoxy-3'-hydroxyamino-β-D-xylofuranosyluracil **21**. - A solution of **12** obtained from **10** (1.5 mg, 2.02 mmol) on treatment with 2-chloro-6-fluorobenzaldehyde (650 mg, 4 mmol, 14 h, pH 3, 20°C) afforded 0.15 g (18% from **10**) of **21**. R_F: 0.46 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5; e.s.r. (diglyme), see TABLE 6. Mass spectrum: *m/z* 113 (100, B + 2H), 70 (87), 159 (81), 157 (79), 143 (46), 83 (43), 97 (34), 241 (33), 212 (23), 129 (19), 174 (16), 198 (10), 184 (9), 251 (9), 382 (6, $M^{+\cdot}$ - OH), 270 (4).

Anal. calcd for $C_{16}H_{15}O_6N_3FCl$, 1 H_2O (417.78): C 46.00; H 4.10; N 10.06; F 4.55; Cl 8.49. Found: C 46.27; H 4.01; N 10.05; F 4.56; Cl 8.30.

3'-N,5'-O-(R)-[5''-Deoxy-1'',2''-isopropylidene-3''-O-methyl-α-D-xylofuranos-5''-ylidene]-3'-deoxy-3'-hydroxyamino-β-D-xylofuranosyluracil **22**. - A solution of **12** obtained from **10** (500 mg, 0.67 mmol) on treatment with 1,2-*O*-isopropylidene-3-*O*-methyl-α-*D*-

xylo-pentodialdo-1,4-furanose[19] (160 mg, 0.79 mmol, 30 min, pH 5, 20°C) gave 150 mg (50% from **10**, average yield 85% per step) of **22**. R_f: 0.27 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5 in ($CDCl_3$): δ 1.34 (*s*, 3H, CH_3), 1.53 (*s*, 3H, CH_3), 3.40 (*s*, 4H, CH_3O, H-3'), 3.86 (*m*, 1H, H-5'a), 3.9 (*bs*, 1H, H-3''), 4.24 (*bd*, 1H, H-5''), 4.35 (*bdd*, 1H, H-5'b), 4.58 (*m*, 3H, H-2'', H-4'', H-4'), 4.83 (*s*, 1H, H-2'), 5.66 (*d*, 1H, $J_{5,6}$ = 8.5 Hz, H-5), 5.73 (*s*, 1H, H-1'), 6 (*d*, 1H, $J_{1'',2''}$ = 4 Hz, H-1''), 8.12 (*d*, 1H, $J_{5,6}$ = 8.5 Hz, H-6), 8.43 (*s*, 1H, NOH), 10.1 (*bs*, 1H, NH); e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 270 (100), 113 (38, B + 2H), 85 (32), 97 (32), 69 (26), 142 (17), 254 (17), 125 (17), 385 (5), 428 (3), 310 (2), 336 (2), 350 (1), 410 (1), 364 (1), 442 (1, $M^{+\cdot}$ - H), 297 (1), 443 (1, $M^{+\cdot}$).

Anal. calcd for $C_{18}H_{25}N_3O_{10}$ (443.41): C 48.76; H 5.68; N 9.48. Found: C 48.84; H 5.95; N 9.20.

3'-N,5'-O-(R)-[6''-Deoxy-(1'',2'':3'',4'')-di-O-isopropylidene-α-D-galactopyranos-6''-ylidene]-3'-deoxy-3'-hydroxyamino-β-D-xylofuranosyluracil **23**. - A solution of **12** obtained from **10** (1 g, 1.35 mmol) on treatment with 1,2:3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose[20] (415 mg, 1.62 mmol, 30 min, pH 5, 20°C) afforded 0.16 g (63% from **10**, average yield 90% per step) of **22**. R_f: 0.39 (MeOH:CH_2Cl_2, 1:12); ^{1}H-n.m.r. (CD_3OD): see TABLES 4 and 5. Mass spectrum: *m/z* 97 (100), 59 (89), 71 (72), 270 (65), 112 (57, B + H), 85 (57), 484 (46), 142 (26), 158 (25), 254 (21), 3.12 (15), 441 (11), 124 (10), 171 (9), 387 (8), 366 (6), 500 (6, $M^{+\cdot}$), 466 (5), 329 (4), 424 (4), 200 (3), 354 (3), 408 (2), 266 (2).

Anal. calcd for $C_{21}H_{29}N_3O_{11}$ (499.48): C 50.50; H 5.85; N 8.41. Found: C 50.22; H 6.06; N 8.28.

(2'-O-Acetyl-3'-N,5'-O-(R)-[2-chloro-6-fluorobenzylidene]-3'-deoxy-3'-acetoxyamino-β-D-xylofuranosyl)uracil **24**. - To a solution of **21** (50.4 mg, 0.12 mmol) in pyridine (2 ml), acetic anhydride (1 ml) was added. After 1 h stirring, the solvent was evaporated and the residue purified by silica gel column chromatography using ethyl acetate, to afford 44 mg (75%) of **24**. Further purification could be done by reprecipitation from chloroform/hexane. R_f: 0.60 (AcOEt); ^{1}H-n.m.r. ($CDCl_3$): see TABLES 4 and 5. Mass spectrum: *m/z* 57 (100), 441 (92, $M^{+\cdot}$ - Ac), 139 (85), 97 (71), 69 (69), 113 (19, B + 2H), 157 (61), 329 (48), 126 (41), 443 (32), 171 (30), 287 (19), 198 (14), 216 (11), 424 (11), 312 (9), 241 (7), 483 (7, $M^{+\cdot}$).

Anal. calcd for $C_{20}H_{19}N_3O_8FCl$ (483.84): C 49.65; H 3.96; N 8.68; F 3.93; Cl 7.33; Found: C 49.39; H 4.25; N 8.52; F 3.90; Cl 7.39.

(2'-O-Acetyl-3'-N,5'-O-(R)-[5-benzyloxy-3-methoxybenzylidene]-3'-deoxy-3'-acetoxyamino-β-D-xylofuranosyl)uracil **25**. - A methanolic solution of **12**, prepared from **10** (500.3 mg, 0.67 mmol) as described above, was reacted with 4-benzyloxy-3-methoxybenzaldehyde (180 mg, 0.74 mmol, 14 h, pH 4, 20°C), and after distillation of the solvent and partial purification by silica gel column chromatography acetylated (acetic anhydride 3 ml, pyridine 6 ml). Classical trettment and silica gel column chromatography afforded 40 mg (10.4% from **10**, average yield per step 57%) of **25**. R_f: 0.53 (AcOEt); ^{1}H-n.m.r. ($CDCl_3$): see TABLES 4 and 5. Mass spectrum: *m/z* 91 (100), 57 (14), 69 (11), 112 (8, B + 4), 305 (4), 395 (4), 507 (4), 151 (3), 139 (3), 246 (29), 353 (2), 365 (2), 446 (1), 336 (1), 204 (1), 379 (1), 183 (1), 567 (0.2, $M^{+\cdot}$).

Anal. calcd for $C_{28}H_{29}N_3O_{10}$ (567.56): C 59.26; H 5.15; N 7.40. Found: C 59.00; H 5.27; N 7.24.

General procedure for the synthesis of products **26** -**38**.

1st procedure : Detritylation of **10** in 3N HCl/MeOH followed by reduction at pH 0-2 by an excess of borane-pyridine complex afforded **12**. Addition of 1.2 to 3 equivalents of

aldehyde in the same flask and stirring *ca* 1 h for aliphatic aldehyde or *ca* 12 h for aromatic ones afforded the expected hydroxylamine. Purification was performed by silica gel column chromatography.

2nd procedure : Starting from the nitrone, obtained as described above, the reduction by borane-pyridine afforded the hydroxylamine in good yield. Purification by silica gel column chromatography afforded the analytically pure product.

3'-N-*Benzyl-3'-deoxy-3'-hydroxyamino*-ß-D-*xylofuranosyluracil* **26**. - The 1st procedure applied to **10** (1 g, 1.35 mmol) borane-pyridine complex (0.5 ml, 4.9 mmol) and benzaldehyde (0.14 ml, 1.4 mmol) at pH 2 afforded **26** (0.16 g, 34% from **10**, average 77% per step). R_F: 0.46 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3. ^{1}H-n.m.r. (DMSO-d_6): δ 3.38 (*t*, 1H, H-3'), 3.66 (*m*, 2H, $J_{gemCH,N}$ = 14 Hz, H-5'b, H-CHN), 3.85 (*m*, 1H, $J_{4',5'}$ = 5.5 Hz, H-4'), 4.14 (*m*, 2H, H-5'a CH-N), 4.48 (*m*, 1H, $J_{5'\text{-}OH}$ = 6 Hz, OH-5'), 4.61 (*t*, 1H, $J_{2',3'}$ = 6 Hz, H-2'), 5.66 (*s*, 1H, OH-2'), 5.68 (*dd*, 1H, $J_{5\text{-}NH}$ = 3 Hz, $J_{5,6}$ = 8 Hz, H-5), 5.78 (*d*, 1H, $J_{1',2'}$ = 6 Hz, H-1), 7.3 (*m*, 5H, Ph), 7.95 (*d*, 1H, $J_{5,6}$ = 8 Hz, H-6), 8 (*bs*, 1H, NOH); ^{13}C-n.m.r. (CD_3OD): δ 63.08-64.24 (C-5', NCH_2), 73.54 (C-3'), 75.89 (C-2'), 82.87 (C-4'), 91.29 (C-1'), 102.59 (C-5), 128.22, 129.20, 130.62, 139.11 (Ph), 143.06 (C-6), 152.68 (C-2), 166.21 (C-4); e.s.r. (diglyme), see TABLE 6. Mass spectrum: *m/z* 91 (100), 288 (39), 204 (33), 237 (24), 220 (11), 331 (9, $M^{+\cdot}$ - H_2O), 106 (7), 178 (6), 301 (6), 349 (6, $M^{+\cdot}$), 113 (5, B + 2H), 77 (4), 254 (4), 132 (2), 148 (2).

Anal. Calcd for $C_{16}H_{19}O_6N_3$ (349.45): C 55.01; H 5.48; N 12.03. Found: C 55.31; H 5.67; N 11.78.

3'-Deoxy-3'-N-[*2,4-dichlorobenzyl*]-*3'-hydroxyamino*-ß-D-*xylofuranosyluracil* **27**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (0.6 ml, 5.9 mmol) and 2,4-dichlorobenzaldehyde (480 mg, 2.7 mmol) at pH 2 afforded **27** (0.107 g, 18.9% from **10**, average 66% per step). R_F: 0.45 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3. Mass spectrum: *m/z* 69 (100), 159 (85), 112 (70, B + H), 161 (52), 174 (25), 123 (23), 258 (16), 288 (9), 200 (9), 140 (6), 260(6), 185 (5), 290 (5), 230 (4), 212 (4), 272 (4), 241 (1).

Anal. Calcd for $C_{16}H_{17}N_3O_6Cl_2$ (418.24): C 45.95; H 4.10; N 10.25; Cl 16.95. Found: C 45.71; H 4.30; N 9.81; Cl 16.67.

3'-Deoxy-3'-hydroxyamino-3'-N-[*2'-hydroxybenzyl*]-ß-D-*xylofuranosyluracil* **28**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (0.6 ml, 5.9 mmol) and salicylaldehyde (502 mg, 4.05 mmol) at pH 2 afforded **28** (0.16 g, 32% from **10**, average 75% per step). R_F: 0.38 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3. ^{13}C-n.m.r. (CD_3OD): δ 60.63, 63.23 (C-5', NCH_2), 73.08 (C-3'), 75.86 (C-2'), 82.34 (C-4'), 90.77 (C-1'), 102.85 (C-5), 116.59, 120.53, 124.55, 129.79, 132.09, 157.53 (Ph), 142.98 (C-6), 152.74 (C-2), 166.20 (C-4); e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 78 (100), 106 (62), 112 (50, B + H), 113 (32, B + 2H), 96 (25), 149 (14), 186 (14), 165 (9), 199 (9), 218 (9), 333 (7), 347 (6), 243 (4), 270 (3), 281 (1), 305 (1).

Anal. Calcd for $C_{16}H_{19}N_3O_7$ (365.35): C 52.60; H 5.24; N 11.50. Found: C 52.34; H 5.14; N 10.93.

3'-N-[*2-Chloro-6-fluorobenzyl*]-*3'-deoxy-3'-hydroxyamino*-ß-D-*xylofuranosyluracil* **29**. - The 1st procedure applied to **10** (1g, 1.35 mmol), borane-pyridine complex (0.6 ml, 5.9 mmol) and 2-chloro-6-fluorobenzaldehyde (426 mg, 2.7 mmol) at pH 2 afforded **29** (0.17 g, 31% from **10**, average 75% per step). R_F: 0.46 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): see TABLES 2 and 3. Mass spectrum: *m/z* 57 (100), 99 (56), 149 (54),, 71 (51), 143 (42), 91 (29), 112 (23), 185 (23), 129 (22), 167 (16), 259 (16), 329 (4), 279 (3), 355 (3).

Anal. Calcd for $C_{16}H_{17}N_3O_6FCl$ (401.78): C 47.83; H 4.26; N 10.46; F 4.73; Cl 8.82. Found: C 48.00; H 4.08; N 10.32; F 4.93; Cl 8.90.

3'-Deoxy-3'-N-[*3,4-dimethoxybenzyl*]-*3'-hydroxyamino*-β-D-*xylofuranosyluracil* **30**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (1 ml, 10 mmol) and veratraldehyde (448 mg, 2.7 mmol) at pH 2 afforded **30** (0.15 g, 27% from **10**, average 72% per step). R_F: 0.61 (MeOH:CH_2Cl_2, 1:4); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3. ^{13}C-n.m.r. (CD_3OD): δ 56.47, 56.54 (2xOCH_3), 63.96, 63.20 (C-5', NCH_2), 73.28 (C-3'), 75.88 (C-2'), 82.87 (C-4'), 91.38 (C-1'), 102.60 (C-5), 112.78, 114.61, 123.29, 131.91, 149.83, 150.26 (Ph), 143.10 (C-6), 152.69 (C-2), 166.23 (C-4); e.s.r. (diglyme) see TABLE 6. Mass spectrum: *m/z* 151 (100), 166 (46), 69 (6), 112 (5, B + H), 207 (5), 222 (3), 137 (2), 391 (2, M^{+} - H_2O), 264 (1), 243 (1).

Anal. Calcd for $C_{18}H_{23}N_3O_8$ (409.40): C 52.81; H 5.66; N 10.26. Found: C 52.96; H 5.68; N 10.05.

3'-N-[*4-Benzyloxy-3-methoxybenzyl*]-*3'-deoxy-3'-hydroxyamino*-β-D-*xylofuranosyluracil* **31**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (1 ml, 10 mmol,) and 4-benzyloxy-3-methoxybenzaldehyde (653 mg, 2.7 mmol) at pH 2 afforded **31** (0.3 g, 44% from **10**, average 81% per step). R_F: 0.55 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; ^{13}C-n.m.r. (CD_3COCD_3): δ 56.19 (OCH_3), 63.01 (NCH_2), 63.40 (C-5'), 71.43 (CH_2Ph), 72.84 (C-3'), 75.69 (C-2'), 81.91 (C-4'), 90.20 (C-1'), 102.70 (C-5), 114.75 (C-2", C-2'"), 122.54 (C-4'"), 128.39, 128.48 (C-5", C-6"), 129.16 (C-3'"), 134.07 (C-1"), 138.69 (C-4"), 141.77 (C-6), 148.52 (C-3'"), 150.53 (C-1"), 151.98 (C-2), 163.77 (C-4); e.s.r. (Diglyme): see TABLE 6. Mass spectrum: *m/z* 91 (100), 465 (8), 467 (7), 65 (6), 242 (6), 112 (6, B + H, 137 (6), 277 (6), 340 (5), 185 (3), 376 (3), 355 (2), 390 (1), 406 (1), 481 (1, M^{+} - 4H).

Anal. Calcd for $C_{24}H_{27}N_3O_8$ (485.50): C 59.38; H 5.61; N 8.91. Found: C 59.02; H 5.87; N 8.66.

3'-Deoxy-3'-hydroxyamino-3'-N-[p-*hydroxybenzyl*]-β-D-*xylofuranosyluracil* **32**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (1 ml, 10 mmol) and *p*-hydroxybenzaldehyde (335 mg, 2.7 mmol) at pH 2 afforded **32** (69 mg, 14% from **10**, average 61% per step). R_F: 0.31 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 107 (100), 69 (97), 112 (75, B + H), 55 (71), 83 (34), 149 (22), 97 (20), 218 (18), 249 (7), 167 (4), 210 (3), 279 (2), 232 (1), 324 (1).

Anal. Calcd for $C_{16}H_{19}N_3O_7$ (365.35): C 52.60; H 5.24; N 11.39. Found: C 52.35; H 5.24; N 11.50.

3'-Deoxy-3'-N-[(R)-*3,7-dimethyl-6-octenyl*]-*3'-hydroxyamino*-β-D-*xylofuranosyluracil* **33**. - The 1st procedure applied to **10** (1 g, 1.35 mmol) and (R)-3,7-dimethyl-6-octenal (0.5 ml, 2.7 mmol) at pH 2 afforded **33** (60 mg, 11% from **10** average 59% per step). R_F: 0.53 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; ^{13}C-n.m.r. (CD_3COCD_3): δ 17.67, 19.89, 25.81 (3xCH_3), 26.10, 34.75,38.05 (3xCH_2), 57.49 (NCH_2), 63.17 (C-5'), 73.41 (C-3'), 75.79 (C-2'), 81.86 (C-4'), 90.00 (C-1'), 102.69 (C-5), 125.61 (C-7"), 131.36 (C-6"), 141.71 (C-6), 151.92 (C-2), 163.77 (C-4); e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 69 (100), 296 (65), 113 (37, B + 2H), 81 (37), 137 (23), 381 (20, M^{+} - OH), 226 (17), 210 (14), 166 (14), 312 (11), 336 (11), 256 (11), 395 (11, M^{+} - 2H), 270 (8), 397 (3, M^{+}).

Anal. Calcd for $C_{19}H_{31}N_3O_6$ (397.48): C 57.42; H 7.86; N 10.57. Found: C 57.19; H 8.02; N 10.41.

3'-N-[Cyclohexylmethyl]-3'-deoxy-3'-hydroxyamino-ß-D-*xylofuranosyluracil* **34**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (0.6 ml, 5.9 mmol) and cyclohexanecarbaldehyde (0.21 ml, 2.1 mmol) at pH 2 afforded **34** (90 mg, 18.5% from **10**, average 66% per step). R_F: 0.53 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; ^{13}C-n.m.r. (CD_3OD): δ 25.19, 25.91, 30.75, 34.52 (cyclohexyl), 61.49, 65.05 (NCH_2, C-5'), 72.8 (C-3'), 74.8 (C-2'), 80.75 (C-4'), 89.45 (C-1'), 100.93 (C-5), 140.75 (C-6), 150.78 (C-2), 163.93 (C-4); e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 55 (100), 97 (48), 184 (46), 69 (28), 115 (27), 254 (19), 294 (18), 270 (12), 167 (12), 243 (7), 154 (7), 337 (2), 355 (2, $M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{25}N_3O_6$ (355.39): C 54.07; H 7.09; N 11.82. Found: C 53.85; H 6.87; N 11.75.

3'-Deoxy-3'-hydroxyamino-3'-N-*retinyl*-ß-D-*xylofuranosyluracil* **35**. - The 1st procedure applied to **10** (1 g, 1.35 mmol), borane-pyridine complex (1 ml, 10 mmol) and retinal (780 mg, 2.7 mmol) afforded **35** (0.19 g, 26% from **10**, average 72% per step). R_F: 0.5 (MeOH 10% in CH_2Cl_2); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; ^{13}C-n.m.r. (CD_3OD): δ 12.79, 13.12 (C-19", C-20"), 20.33 (C-3"), 21.99 (C-18"), 29.45 (CH_3, C-16", C-17"), 33.94 (C-4"), 35.21 (C-1"), 40.75 (C-2"), 58.05 (NCH_2), 63.14 (C-5'), 73.29 (C-3'), 75.77 (C-2"), 82.72 (C-4'), 91.12 (C-1'), 102.66 (C-5), 125.26, 127.24, 128.36, 128.96, 129.90, 131.74, 136.32, 138.22, 139.28, 142.92, 143.36 (C-6), 152.68 (C-2), 166.14 (C-4); e.s.r. (diglyme): see TABLE 6. Mass spectrum: *m/z* 243 (100), 69 (75), 112 (71, B + H), 165 (66), 77 (43), 183 (37), 131 (28), 145 (19), 269 (16), 197 (9), 228 (9), 282 (9), 215 (7), 509 (7, $M^{+\cdot}$ - H_2O), 492 (4), 494 (3), 525 (1, $M^{+\cdot}$ - 2H).

Anal. Calcd for $C_{29}H_{41}N_3O_6$ (587.67): C 66.01; H 7.83; N 7.96. Found: C 65.98; H 7.73; N 7.77.

3'-Deoxy-3'-N-[*5"-deoxy-1",2"-isopropylidene-3"*-O-*methyl*-α-D-*xylofuranos-5"-yl*]-*3'-hydroxyamino*-ß-D-*xylofuranosyluracil* **36**. - The 1st procedure applied to **10** (500.8 mg, 0.87 mmol), borane-pyridine complex (0.5 ml, 4.9 mmol) and 1,2 *O*-isopropylidene-3-*O*-methyl-α-*D-xylo*-pentodialdo-1,4-furanose[19] (160 mg, 0.69 mmol) at pH 2-4 afforded **36** (75 mg, 25.8%, from **10**, average 71% per step). R_F: 0.29 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; e.s.r. (diglyme) see TABLE 6. Mass spectrum: *m/z* 71 (100), 87 (76), 59 (74), 113 (72, B + 2H), 97 (46), 144 (27), 256 (26), 300 (16), 270 (15), 254 (14), 379 (10), 310 (7), 163 (5), 366 (4), 389 (4), 428 (1, $M^{+\cdot}$ - OH).

Anal. Calcd for $C_{16}H_{27}N_3O_{10}$ (445.43): C 48.74; H 6.42. Found: C 48.54; H 6.11.

3'-Deoxy-3'-N-[*6"-deoxy-1",2":3',4"-di*-O-*isopropylidene*-α-D-galacto-*pyranos-6"-yl*]-*3'-hydroxyamino*-ß-D-*xylofuranosyluracil* **37**. - The 1st procedure applied to **10** (876.4 mg, 1.31 mmol), borane-pyridine complex (0.4 ml, 3.9 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose[20] (415 mg, 1.62 mmol) at pH 2 afforded **37** (500 mg, 75.7% from **10**, average 93% per step). R_F: 0.56 (MeOH:CH_2Cl_2, 1:12); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3; ^{1}H-n.m.r. ($CDCl_3$): δ 1.30, 1.33, 1.43, 1.50 (*4s*, 4x3H, 2C-Me_2), 2 (*bs*, 2H, 2OH), 2 (*bs*, 2H, 2OH), 3.01 (*m*, 2H, 2H-6"), 3.68 (*t*, 1H, $J_{2',3'}$ = 8 Hz, $J_{3',4'}$ = 8 Hz, H-3'), 3.78 (*dd*, 1H, $J_{5'a,5'b}$ = 2.5 Hz, $J_{4',5'a}$ = 13 Hz, H-5'a), 3.99 (*dd*, 1H, $J_{4',5'b}$ = 2 Hz, H-5'b), 4.12 (*bt*, 1H, $J_{4",5"}$ = 1.5 Hz, $J_{5",6"a}$ = 5.5 Hz, $J_{5",6"b}$ = 7 Hz, H-5"), 4.20 (*dd*, 1H, $J_{3",4"}$ = 8 Hz, H-4"), 4.33 (*m*, 2H, H-2", H-4'), 4.55 (*t*, 1H, $J_{1',2'}$ = 6 Hz, H-2'), 4.62 (*dd*, 1H, $J_{2",3"}$ = 2.5 Hz, H-3"), 5.56 (*d*, 1H, $J_{1",2"}$ = 5.5 Hz, H-1"), 5.79 (*d*, 1H, $J_{5,6}$ = 8 Hz, H-5), 5.98 (*d*, 1H, H-1'), 7.71 (*bs*, 1H, NOH), 8.11 (*d*, 1H, H-6), 10.3 (*bs*, 1H, NH). Mass spectrum: *m/z* 59 (100), 71 (86), 113 (70, B + 2H), 85 (60), 97 (57), 356 (24), 144 (23), 330 (21), 256 (19), 270 (14), 313 (13), 440 (13), 126 (12), 389 (11), 160 (10), 300 (8), 470 (7), 486 (6, $M^{+\cdot}$ - CH_3), 184 (5), 196 (2).

Anal. Calcd for $C_{21}H_{31}N_3O_{11}$ (501.49): C 50.30; H 6.23; N 8.38. Found: C 50.52; H 6.43; N 8.20.

3'-Deoxy-3'-hydroxyamino-3'-N-[*thien-2-ylmethyl*]-β-D-*xylofuranosyluracil* **38**. - The 2nd procedure applied to a solution of **18** (107.2 mg, 0.3 mmol) in MeOH (20 ml) using the borane-pyridine complex (0.7 ml, 6.9 mmol, 30 min, pH 0) as reducing agent afforded after silica gel column chromatography **38** (103 mg, 95.5%). R_f: 0.28 (MeOH:CH_2Cl_2, 1:10); ^{1}H-n.m.r. (CD_3OD): see TABLES 2 and 3. Mass spectrum: *m/z* 97 (100), 112 (31, B + H), 69 (25), 55 (16), 85 (6), 138 (5), 337 (3, $M^{+\cdot}$ - H_2O), 123 (2), 166 (2), 225 (1), 307 (1), 278 (1), 179 (1), 207 (1), 194 (1).

Anal. Calcd for $C_{14}H_{17}N_3O_6S$ (355.37): C 47.32; H 4.82; N 11.82; S 9.02. Found: C 47.60; H 5.05; N 11.57; S 9.26.

Antimicrobial, cytotoxic and antiviral screenings. - Microbiological experiments were performed by using a classical disk diffusion method[21]. Cytotoxicity has been measured on the following cell cultures : human embryonic fibroblasts (MRC5), dog kidney (MDCK), monkey kidney (CVI), mouse fibroblasts (3T6) or mouse kidney (MK) cells following classical procedures[22]. Antiviral activity has been measured[14] against *Herpes simplex virus I* on MRC5, *polyoma virus* on MK,[14] *rhinovirus 31* on MRC5, *influenza virus AWSN* on MDCK and *influenza virus* AH_1N_1 on CVI.

ACKNOWLEDGMENT

The authors thak M. G. Moret, Mrs J. Giust and M. B. Tschopp for their technical assistance, Mrs F. Barbalat-Rey and D. Cabrini for the n.m.r. spectra and Dr H. Eder for the elementary analyses. The investigation was supported by the Swiss National Science Foundation, Grants 2.846-0.83 and 2.671-0.85.

REFERENCES

1. T.Gnewuch and G. Sonnovsky, *Chem. Rev.* **86**, 203 (1986).

2. J.M.J. Tronchet, K. Mekhael,. J. Graf-Poncet and R. Benhamza, *Helv. Chim. Acta* **68**, 1893 (1985).

3. K.K. Ogilvie and N.Y. Theriault, *Tetrahedron Lett.* **(1979)** 2111; K.K. Ogilvie, A.L. Shifman and C.L. Penney, *Canad. J. Chem.* **57**, 2230 (1979); G.H. Hakimelahi, Z.A. Proba and K.K. Ogilvie, *Canad. J. Chem.* **60**, 1106 (1982).

4. P.A. Levene and R.S. Tipson, *J. Biol Chem.* **104**, 385 (1934).

5. A.F. Cook and J.G. Moffatt, *J. Am. Chem. Soc.* **89**, 2697 (1967).

6. Y. Kikugawa and M. Kawase, *Chem. Letters* **(1977)** 1279.

7. R.F. Borsch, M.D. Bernstein and H.D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).

8. J.M.J. TRONCHET, F. BARBALAT-REY and J.M. CHALET, *Carbohydr. Res.* **30**, 229 (1973).

9. C. HELLER and M.M. MCCONNEL, *J. Chem. Phys.* **32**, 1535 (1960).

10. A. RASSAT and H. LEMAIRE, *J. Chem. Phys.* **61**, 1576 (1964); H. LEMAIRE, R. RAMASSEUL and A. RASSAT, *Mol. Phys.* **8**, 557 (1964); A. ROCKENBAUER, M. GYOR, L. JOKAY and T. TUDOS, *Adv. Med. Relax. Int. Proc.* **15**, 311 (1979).

11. J.M.J. TRONCHET, D. SCHWARZENBACH, E. WINTER-MIHALY, C. DIAMANTIDES, U. LIKIC, G. GALLAND-BARRERA, C. JORAND, K.D. PALLIE, J. OGHA-PONCET, J. RUPP, G. MORET and M. GEOFFROY, *Helv. Chim. Acta* **65**, 1404 (1982); J.M.J. TRONCHET, E. WINTER-MIHALY, F. HABASHI, D. SCHWARZENBACH, U. LIKIC and M. GEOFFROY, *Helv. Chim. Acta* **64**, 610 (1981); J.M.J. TRONCHET, M. GEOFFROY, F. HABASHI, D. SCHWARZENBACH, E. WINTER-MIHALY, U. LIKIC, J. OGHA and C. JORAND, *Int. Carbohydr. Symp. XIth*, Vancouver, Canada **(1982)**, Abstr. I-77; F. HABASHI, *Ph.D. Thesis* No **2058**, University of Geneva, 1982; J.M.J. TRONCHET, E. WINTER-MIHALY, J. RUPP, F. BARBALAT-REY and M. GEOFFROY, *Carbohydr. Res.* **136**, 375 (1985); J.M.J. TRONCHET, J.-P. FASEL, E. WINTER, F. BARBALAT-REY, J. RUPP, J. OGHA-PONCET, G. ZOSIMO-LANDOLFO, K. MEKHAEL, C. JORAND, F.J. BUCHHOLZER, A. KAMATARI and F. HABASHI, *Int. Carbohydr. Symp. XIIth*, Utrecht, Netherlands **(1984)**, Abstr. A 1-23; C. JORAND, *Ph.D. Thesis* No **2211**, University of Geneva, 1986; J.M.J. TRONCHET, N. BIZZOZERO, J. GRAF, F. BARBALAT-REY and M. GEOFFROY, *Int. Carbohydr. Symp. XIIIth*, Ithaca N.Y., U.S.A. **(1986)**, Abstr. B-125.

12. J. TOOZE Ed "DNA tumor viruses", Cold Spring Harbor Laboratory, Cold Spring Harbor, N.-Y., 2nd ed (1980).

13. E. WINOCOUR, *Virology* **19**, 158 (1963).

14. H. TUERLER and P. BEARD in "Virology, a practical approach", B.W.J. Mahy Ed, IRL Press, Oxford (1985), pp 169-192.

15. B. HIRT, *J. Mol. Biol.* **26**, 365 (1967).

16. W. MEYER ZU RECKENDORF, *Chem. Ber.* **96**, 2019 (1963).

17. W. LOEW and M.M. GOODMAN, *Chem. Ind.* (London) **(1967)** 2026.

18. W.C. STILL, M. KAHN and A. MITRA, *J. Org. Chem.* **43**, 2923 (1978).

19. M.L. WOLFROM and S. HANESSIAN, *J. Org. Chem.* **27**, 1800 (1962).

20. D. HORTON, M. NAKADATE and J.M.J. TRONCHET, *Carbohydr. Res.* **7**, 56 (1968).

21. N. DOLATSHAHI, *Ph.D. Thesis* No **1928**, University of Geneva, 1979.

22. A.P. Wilson in "Animal Cell Culture. A practical Approach", R.I. Freshney Ed, IRL Press, Oxford (1986) pp 183-202.

Received May 12, 1987