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SYNTHESIS AND REACTIONS OF 2',3'-ANHYDRO-1-β-D-RIBOFURANOSYL-URACIL DERIVATIVES: MOLECULAR STRUCTURES OF 3-METHYL-2',3'-ANHYDROURIDINE AND 3,5-DIMETHYL-2',3':0⁶,5'-DIANHYDROURIDINE

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Abstract—2',3'-anhydro-1-β-D-ribofuranosyl-uracil derivatives, which are formed under basic conditions in an equilibrium from the corresponding 2,2'-anhydro isomers could be trapped by 3-N-methylation (**3**, **8**). The 3-methyl-5-bromo-2',3'-epoxide **8** gave on further methylation the 5-methyl-2',3':0⁶,5'-dianhydro derivative **16**, representing a method for converting uracil derivatives into thymidine nucleosides. The 2',3'-epoxides could be hydrolyzed to the corresponding arabinosyl derivatives, whereas 2'-bromo-2'-deoxy nucleosides with "ribo" configuration were obtained on treatment with HBr. All structures were proved by ^{1}H NMR. The molecular structures of **3** and **16** were also substantiated by X-ray analysis. The impact of the oxirane rings and the additional 0⁶-5'-ring closure on the puckering of the ribofuranose moiety is discussed.

The importance of anhydro-nucleosides (cyclo-nucleosides) in the pyrimidine series is well documented in the literature.[1-5] In these compounds the anhydro bridge is formed between the pyrimidine and the carbohydrate moiety, but in some of their reactions the corresponding ribo-2',3'-anhydro derivatives were postulated as hypotetical intermediates.

Brown, Todd *et al.*[6] proposed already in 1958 2',3'-anhydrouridine (**2**) as an intermediate, when 2,2'-anhydrouridine (**1**) was treated with thioethoxide in DMF. In 1961 Yung and Fox[7] suggested a benzoylated derivative of **2** as an intermediate in the rearrangement reaction of benzoylated 2,3'-anhydrouridine at its melting point into the 2,2'-anhydro isomer.

A detailed study of the theoretically possible interconversion of 2,2'-anhydrouridine (**1**) and its 2,3'-anhydro isomer into each other was carried out by Buchanan and Clark,[8] using sodium t-butoxide as base. They came to the conclusion that the hypothetical 2',3'-anhydride **2** must be present as an intermediate, but they did not succeed in preparing or even detecting it.

For synthesizing this latter, unknown 2',3'-riboanhydride **2**, we decided to "trap" it by treating the 2,2'-anhydride **1** with base and subsequently with methyl iodide. Kikugawa *et al.*[9] have already studied the reaction of **1** with methyl iodide in DMF, but in the absence of base, and the only compound they could isolate was N-methyl-2'-deoxy-2'-iodo-ribofuranosyluracil. This must have been formed via an attack of the iodide at C(2'), which has become strongly polarized by the 3-N-methylation of the pyrimidine ring.

When the 2,2'-anhydride **1** was treated in dry methanol with 1 equivalent of sodium methoxide and the formed salt, obtained after evaporation, was treated with methyl iodide in DMSO, the expected 3-N-methyl-2',3'-anhydrouridine (**3**) could be isolated as the main product after column chromatography. The ^{1}H NMR spectrum was in accordance with the proposed structure, as the N-Me signal appeared at 3.19 ppm and the original coupling of H(1) ($J_{1,2}$ = 6.0 Hz) was changed to $J_{1,2} \cong 0.0$ Hz, according to the inversion at C(2'). The structure of **3** was finally corroborated by X-ray diffraction.

As a by-product the 3-N-methyl-5'-O-methyl derivative **4** was isolated in the methylation reaction mentioned above, which could be obtained in higher yield when two equivalents of sodium methoxide and methyl iodide were applied, respectively. The same result was achieved, when the sodium salt of **2** was prepared directly, using a slurry of **1** in DMSO and sodium hydride as base.

The epoxide ring in **3** is sensitive to hydrolysis and is partly cleaved even during column chromatography on silicagel. When compounds **3** and **4** were hydrolyzed with 0.2 M HCl in ethanol, the corresponding arabinosyl derivatives **5** and **6** were formed exclusively, and no *xylo* isomer could be detected. This means that the N-methylation of the pyrimidine ring does not influence significantly the polarity of the neighbouring carbonyl groups. Consequently, O(2) will attack C(2') of the protonated oxirane ring, and the formed cation **12** is hydrolyzed in the usual way[1] to afford the nucleosides with *arabino* configuration.

The structure of compounds **5** and **6** was established unambiguously since **5** was identical with 3-N-methyl-arabino-furanosyluracil described in the literature,[9] while

Table 1. ^{1}H NMR data[a] of compounds **3–6, 8–11, 13, 16 and 18–20**

com-pound	chemical shifts (δ, ppm)								coupling constants (Hz)					others
	H(1')	H(2')	H(3')	H(4')	H(5')	H(5)	H(6)	N(3)CH_3	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5,6}$	
3	5.89s	(4.10)d	(4.21)d	4.16t	3.62d	5.76d	7.92d	3.19s	0	2.5	0	3.5	8.5	
4	5.89s	(4.11)d	(4.23)d	4.28t	3.58d	5.78d	7.77d	3.18s	0	2.5	0	4.0	8.5	CH_3O-5: 3.29 ppm, s
5	6.03d	4.01dd	3.87t	3.73m	3.59d	5.69d	7.69d	3.17s	4.5	3.5	3.5	4.0	8.5	
6	6.07d	4.06m	~3.9m	~3.9m	3.57d	5.75d	7.56d	3.19s	4.5	4.0	c	4.0	8.5	CH_3O-5: 3.34 ppm, s
8	5.97s	(4.16)d	(4.30)d	4.23t	3.71d	-	8.67s	3.29s	0	2.5	0	4.0	-	
9	5.98s	(4.20)d	(4.31)d	4.36t	3.67d	-	8.37s	3.26s	0	2.5	0	3.0	-	CH_3O-5: 3.37 ppm, s
10	5.99d	4.02t	3.91t	3.74q	3.61d	-	8.11s	3.21s	4.5	3.5	3.5	3.5	-	CH_3O-5: 3.37 ppm, s
11	6.04d	4.09dd	~3.9m	~3.9m	3.58d	-	8.02s	3.25s	4.5	3.5	c	3.0	-	
13	5.91s	(3.81)d	(3.91)d	4.39d	4.09d 3.68dd	5.06s	5.06s	3.04s	0	2.5	0	0 2.5	c	J_{AB}= 13.0 Hz[b]
16	6.49s	(4.13)d	(4.22)d	4.57d	4.67d 4.09dd	-	-	3.22s	0	2.5	0	0 1.5	-	J_{AB}= 13.0 Hz
18	6.17d	4.61dd	4.13t	4.0m	3.74dd 3.63dd	5.80d	8.05d	3.18s	4.2	4.8	4.8	3.0 3.0	8.5	J_{AB}= 12.3 Hz
19	6.05d	4.61dd	4.10t	3.92m	3.72dd 3.59dd	-	8.52s	-	4.2	4.8	4.8	2.4 3.0	-	J_{AB}= 12.5 Hz
20	6.09d	4.64dd	4.10dd	3.95m	3.80dd 3.62dd	-	8.65s	3.21s	3.6	4.5	6.0	2.4 2.1	-	J_{AB}= 12.3 Hz

[a]values in brackets are arbitrary assignments [b]J_{AB} refers to the 5'-methylene protons [c]not determined

6 showed a similar ^{1}H NMR spectrum to it, differing only in the presence of the 5'-O-Me group (Table 1).

For studying the influence of the polarizing effect of a substituent at C(5) on the anhydro-equilibrium, 5-bromo-2,2'-anhydrouridine[10] (**7**) was also submitted to similar methylation conditions as described above. The presence of the electron-withdrawing group at C(5) did not influence the reaction, as depending on the amount of base and methyl iodide applied, the 2',3'-epoxide **8** or its 5'-O-Me derivative **9** could be obtained as the main product. The stability of these 3-N-methyl derivatives towards hydrolysis was not influenced by the presence of the Br at C(5) either since both **8** and **9** gave readily the expected arabinosyl derivatives **10**[11] and **11**, respectively. The structures of **10** and **11** were established not only by NMR (Table 1), but also chemically, as the N-methyl-arabinosyl derivatives **5** and **6** could be converted by bromination with NBS in chloroform into **10** and **11**, respectively.

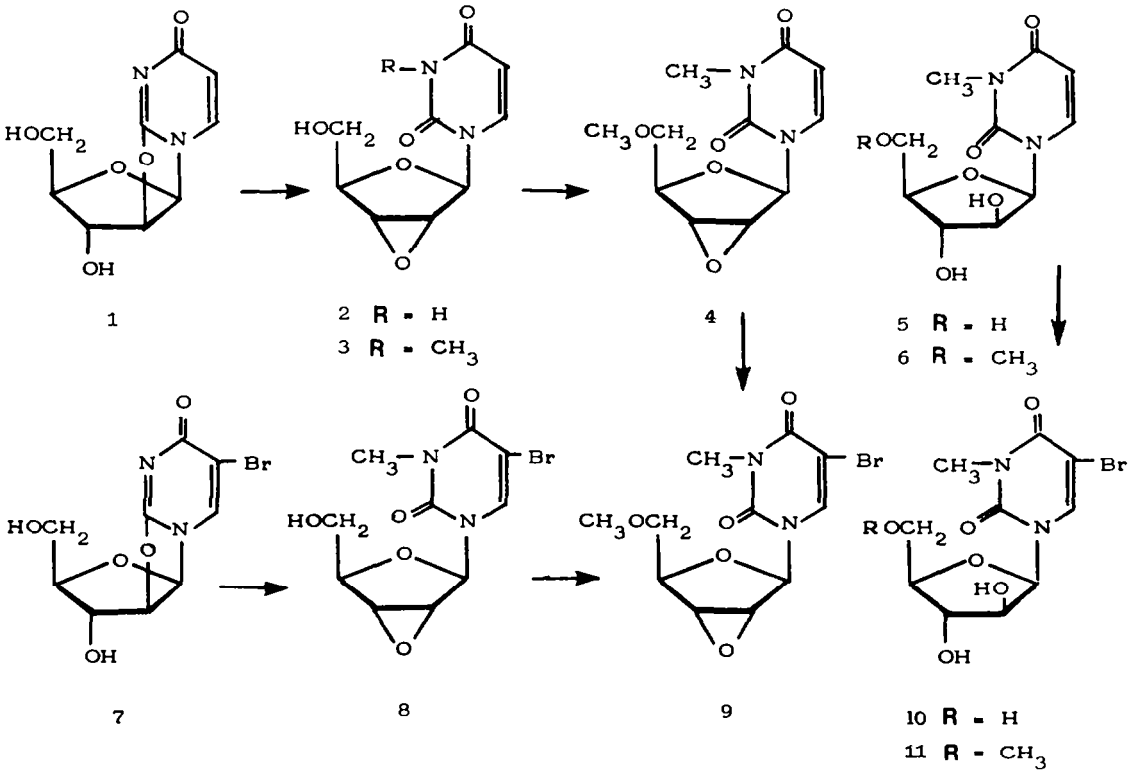
NBS was successfully applied for the conversion of the 5'-O-methyl-2',3'-epoxide **4** into its 5-bromo derivative **9**, too. But when the 2',3'-epoxide **3**, carrying a free OH group at C(5') was treated with NBS, the 2',3': 0^6,5'-dianhydro compound **13** was formed. This means, that besides bromination at C(5) the addition of the primary OH group of the carbohydrate moiety to the C(5)–C(6) double bond of the pyrimidine ring took place.

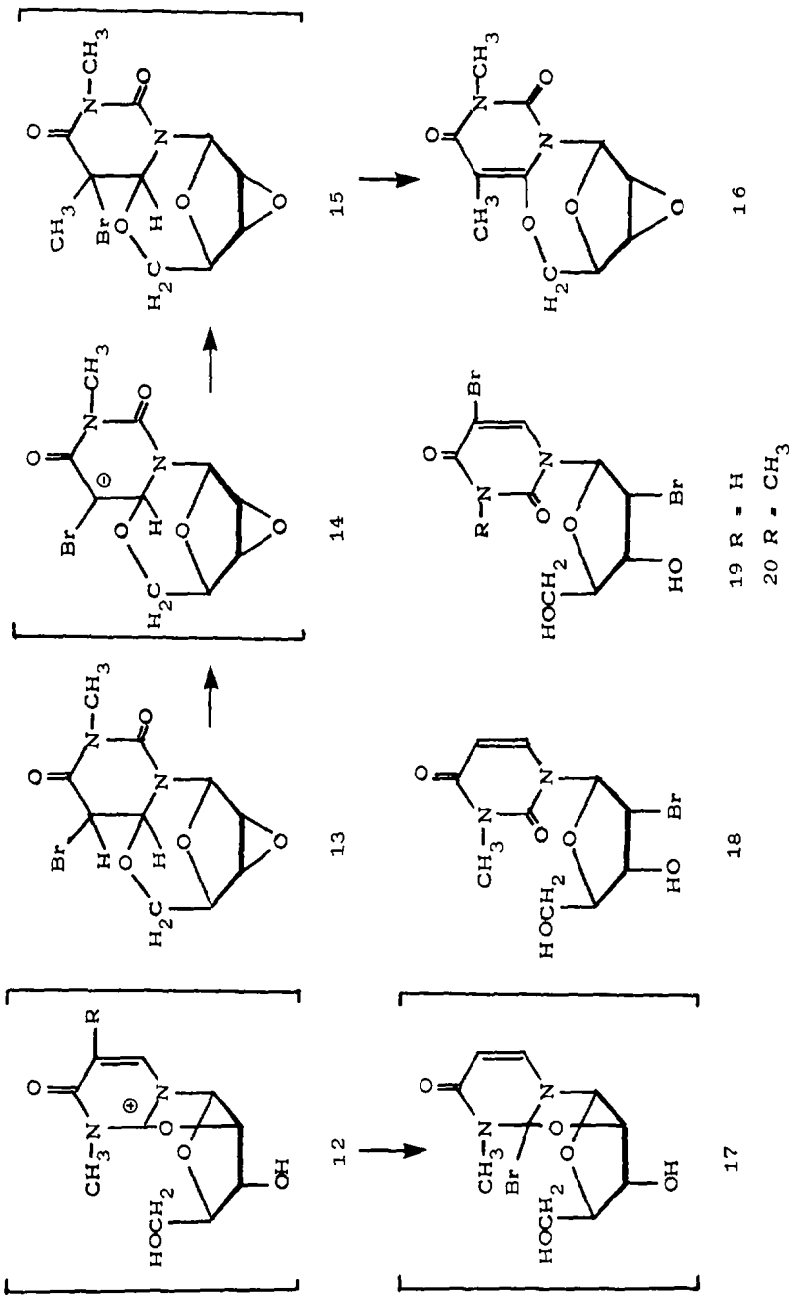
The ^{1}H NMR spectrum of **13** is in agreement with the proposed cyclic structure in which the 5'-methylene group is fixed in a ring, too. Consequently, its protons appear as an AB pattern with J_{AB} 13 Hz, being typical for 0^6,5'-anhydro-cyclonucleosides.[4] A similar reaction was described by Lipkin *et al.*[14] iodinating thymidine with N-iodo-succinimide. When the crystalline dianhydride **13** was dissolved in DMSO, a slow cleavage of the 0^6,5'-anhydro ring took place, affording the "open" isomer **8**.

The formation of an 0^6,5'-anhydro bridge was first observed by Chang,[15] who iodinated 2'-deoxycytidine and obtained as a by-product 0^6,5'-anhyhdro-2'-deoxy-5-iodo-uridine. Later it was shown by Lipkin *et al*,[4,16] as well as by Fox *et al.*[17] that 2'-deoxy-5-halogeno-pyrimidine nucleosides or their 2',3'-0-protected derivatives formed readily 0^6,5'-anhydro bridges on treatment with base. According to these facts the 5-bromo-2,2'-anhydrouridine **7** should give on treatment with an excess of base and subsequent methylation with methyl iodide the 3-N-methyl-0^6,5'-anhydride **13** via **8**. The crystalline compound, isolated from the reaction mixture had, however, a different structure and corresponded to the thymidine derivative **16**. The structure of this compound was established by ^{1}H- and ^{13}C NMR as well as by X-ray investigations.

It is very probable that the conversion of the uridine derivative **7** into the thymidine derivative **16** goes via the intermediate **13** as proposed for the similar reactions in the literature,[4,16,17] but in the latter compound H(5) is activated. Consequently, it is readily split off by base and the formed anion **14** is immediately attacked by methyl iodide, yielding the 5-methyl-5-bromo compound **15**. From the latter HBr is eliminated in the presence of base, resulting in the stable 0^6,5'-anhydro nucleoside **16**. The importance of this reaction is, that it offers a possibility to convert uridine derivatives into thymidine nucleosides.

Since 2',5-dihalogeno pyrimidine nucleosides possess significant biological activity,[18] the synthesis of similar, N-methylated derivatives was attempted by cleaving the 2',3'-epoxide ring in **3** and **8** with hydrobromic acid. The reaction proved to be stereo- and regiospecific in both cases, yielding besides the corresponding hydrolyzed arabinosides **5** and **10** only the 2'-deoxy-2'-bromo derivatives **18** and **20** with D-"ribo" configuration. This means, that the direct attack of bromide on the protonated




19 R = H
20 R = CH3

2',3'-epoxide ring is much slower, than the intramolecular attack of O(2) of the pyrimidine ring, yielding the 2,2'-anhydride cation **12**. This intermediate can be attacked by bromide either at C(2) or at C(2'). In the first case the "bromoacetal" **17** is formed and since it is unable to undergo any rearrangement it will be present only in an equilibrium concentration. On the other hand, the attack at C(2')—which is a much slower process—leads to the stable 2'-bromo "ribo" isomers. During separation of the reaction mixture by column chromatography, the reactive "bromoacetal" **17** is hydrolyzed, yielding the rearranged arabinosides. The "ribo" configuration of **20** was proved unambiguously, as its ^{1}H NMR spectrum was identical with the N-methylated compound, obtained on methylation of the known 2',5-dibromide[10] **19** with diazomethane.

The 5'-O-Me derivative **9** remained unchanged when treated with HBr under similar conditions, which might be due to the steric effect of the bulky OMe group, preventing O(2) from approaching C(2').

Some of the L-enantiomers of the corresponding N-methylated nucleosides were also prepared and according to biological investigations only two of the latter, L-**5** and L-**8** showed a weak cytostatic activity on P-388 and Rauscher leukemia, respectively.

X-ray determination of the molecular structures of **3** *and* **16**

Figure 1 shows a perspective view of the structures computed from the final relative atomic coordinates given with their e.s.d.'s in Tables 3 and 4. The majority of the corresponding bond lengths and angles for **3** and **16** listed in Tables 5 and 6 agree within experimental error with each other and with those found in the literature. Both pyrimidine rings are fairly planar (max. deviation from the least squares plane (Table 8) is 0.023 and 0.030 Å, respectively). The Me groups are slightly bent out of the best planes. The endocyclic C–N bonds exhibit somewhat different amount of multiple bond character, while the exocyclic bond lengths (1.463(2)–1.483(4)) indicate C(sp^3)–N(sp^3) character. Altogether, as estimated by virtue of the Pauling's formula[19] 60–70% of the lone pairs of N atoms are delocalized on their neighbourhood. C(2)–O(2) in **16** is slightly longer than the usual value about 1.21 Å (*cf* e.g. in 5-ethyl-2'-deoxyuridine[20]). The C(2)–N(3)–C(4) angles (mean value 124.5(4)°) are by 3.0° smaller than those where N(3) bears H atom.[20,21] This, of course, has a slight impact on the other *endo* bond angles. The 7-membered ring closure at C(6) does not alter visibly the bonding around C(6), e.g. the C(6) = C(5)–C(4) = O(4) conjugated system is unaffected.

In the sugar ring of both molecules the fused oxirane ring, characterized by the mean bond angle 60.0(2)° shortens the C(2')–C(3') bond (mean bond length: 1.430(3) Å) considerably (*cf* 1.522(2) in 5-ethyl-2'-deoxy-uridine[20]) and affects also the neighbouring C(3')–C(4') bond (mean bond length: 1.504(4) Å) which is somewhat shorter than the usual value about 1.54 Å. As shown by the r.m.s. value (5.9°) of the *endo* torsion angles[22] (Table 5) in **3** the

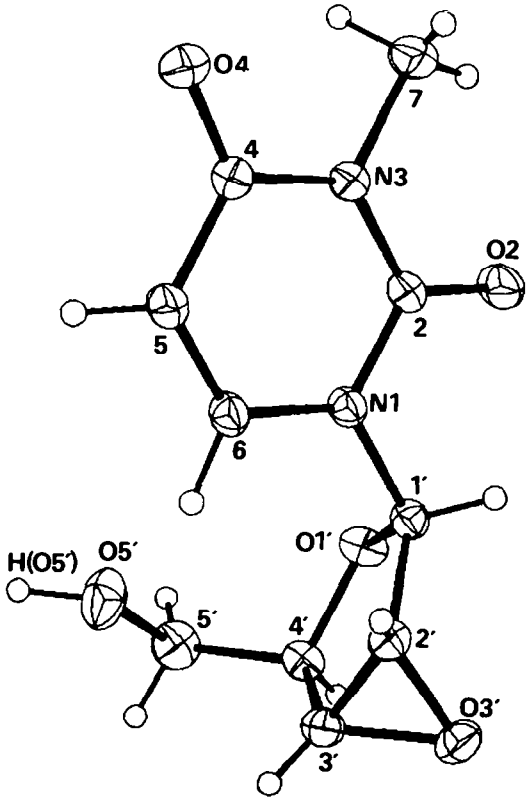


Fig. 1(a).

Fig. 1. Perspective views of the molecules 3 (a) and 16 (b) with atomic numbering. Atoms are carbon unless indicated otherwise. The H atoms are shown but not labelled except H(O5') in 3.

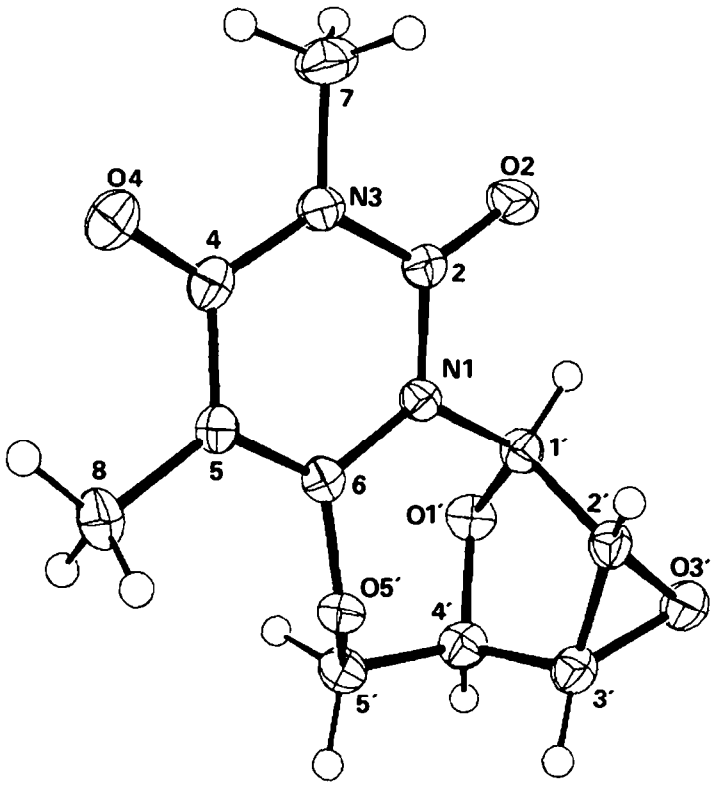


Fig. 1(b).

Table 2. Analytical data of compounds **3**, **4**, **6**, **8**, **9**, **11**, **16**, **18** and **20**

	MW		C	H	N	Br
3 $C_{10}H_{12}N_2O_5$	240.2	Found:	50.1	5.3	11.5	
		Required:	50.0	5.0	11.7	
4 $C_{11}H_{14}N_2O_5$	254.2	Found:	50.2	6.1	10.8	
		Required:	51.9	5.5	11.0	
6 $C_{11}H_{16}N_2O_6$	272.2	Found:	48.2	6.2	10.1	
		Required:	48.5	5.9	10.3	
8 $C_{10}H_{11}BrN_2O_5$	319.1	Found:	37.9	3.7	8.7	25.0
		Required:	37.7	3.5	8.8	25.0
9 $C_{11}H_{13}BrN_2O_5$	333.1	Found:	39.8	4.1	8.3	24.1
		Required:	39.7	3.9	8.4	24.0
11 $C_{11}H_{15}BrN_2O_6$	351.2	Found:	37.9	4.5	7.8	22.5
		Required:	38.0	4.3	8.0	22.6
16 $C_{11}H_{12}N_2O_5$	252.2	Found:	52.4	4.9	10.9	
		Required:	52.4	4.8	11.1	
18 $C_{10}H_{13}BrN_2O_5$	321.1	Found:	37.0	4.5	8.5	24.2
		Required:	37.4	4.1	8.7	24.9
20 $C_{10}H_{12}Br_2N_2O_5$	400.0	Found:	29.7	3.4	6.8	39.9
		Required:	30.0	3.0	7.0	40.0

Table 3. Final fractional coordinates and anisotropic vibrational parameters ($\times 10^4$) for compounds **3** and **16**. The anisotropic vibrational parameters are given in the form: $\exp[-2\pi^2 \sum_i \sum_j a_i^* a_j^* h_i h_j U_{ij}]$ with U_{ij} in Å^2. Estimated standard deviations are given in parentheses

Molecule 3

	x/a	y/b	z/c	U11	U22	U33	U12	U13	U23
N(1)	-6355(3)	-1148(1)	-731(1)	361(7)	326(6)	390(7)	-22(7)	37(7)	-3(6)
C(2)	-7217(4)	-1993(1)	-1113(1)	400(10)	342(8)	425(8)	-51(9)	6(9)	11(8)
O(2)	-8943(4)	-2467(1)	-785(1)	600(9)	495(7)	599(9)	-217(8)	168(9)	-74(7)
N(3)	-5956(4)	-2273(1)	-1910(1)	471(9)	362(7)	389(7)	-65(8)	35(8)	-28(7)
C(4)	-3946(5)	-1773(1)	-2319(1)	440(10)	383(9)	363(8)	-0(10)	13(9)	18(8)
O(4)	-2899(4)	-2093(1)	-3010(1)	690(10)	490(7)	452(7)	-65(9)	151(9)	-91(7)
C(5)	-3271(5)	-883(1)	-1898(1)	480(10)	377(8)	434(9)	-70(10)	77(9)	8(8)
C(6)	-4469(4)	-608(1)	-1137(1)	394(9)	332(8)	438(9)	-49(9)	55(9)	-9(8)
C(7)	-6858(6)	-3160(2)	-2348(2)	710(20)	470(10)	530(10)	-160(10)	70(10)	-100(10)
O(1')	-9562(3)	-245(1)	61(1)	295(6)	454(7)	599(8)	23(6)	-16(7)	-130(7)
C(1')	-7438(4)	-883(1)	153(1)	357(8)	342(8)	388(8)	-7(8)	46(9)	-0(8)
C(2')	-5542(4)	-381(1)	758(1)	396(9)	427(9)	335(8)	4(9)	-1(9)	2(8)
C(3')	-6546(4)	573(1)	952(1)	406(9)	429(9)	408(9)	-23(9)	4(9)	-46(8)
O(3')	-6665(4)	-183(1)	1627(1)	600(10)	587(8)	339(6)	15(9)	35(8)	2(7)
C(4')	-9064(4)	686(1)	457(1)	349(9)	421(9)	480(10)	28(9)	33(9)	-68(9)
C(5')	-9033(6)	1464(2)	-242(2)	540(10)	480(1)	690(10)	130(10)	-50(10)	30(10)
O(5')	-6823(4)	1384(1)	-787(1)	810(10)	622(9)	670(10)	190(10)	200(10)	226(8)

Molecule 16

	x/a	y/b	z/c	U11	U22	U33	U12	U13	U23
N(1)	637(3)	-228(2)	577(2)	399(9)	450(10)	338(9)	-25(9)	-7(9)	-3(9)
C(2)	-194(4)	-896(3)	1319(2)	420(10)	500(10)	420(10)	-10(10)	30(10)	10(10)
O(2)	341(4)	-935(3)	2210(2)	670(10)	880(20)	370(10)	-150(10)	-30(10)	80(10)
N(3)	-1651(3)	-1491(2)	1023(2)	420(1)	460(10)	440(10)	-30(10)	40(10)	20(10)
C(4)	-2280(4)	-1512(2)	15(2)	390(10)	410(10)	570(20)	-0(10)	-20(10)	-50(10)
O(4)	-3581(3)	-2099(2)	-184(2)	530(10)	640(10)	730(10)	-190(10)	-80(10)	-10(10)
C(5)	-1320(3)	-850(2)	-730(2)	390(10)	390(10)	440(10)	-20(10)	-40(10)	-20(10)
C(6)	103(3)	-258(2)	-442(2)	410(10)	360(10)	380(10)	40(10)	-10(10)	-29(9)
C(7)	-2494(5)	-2248(4)	1803(3)	670(20)	720(20)	710(20)	-230(20)	110(20)	120(20)
C(8)	-1905(5)	-926(3)	-1833(2)	580(20)	650(20)	520(20)	20(20)	-170(10)	-60(20)
O(1')	1991(3)	1683(2)	624(1)	620(10)	380(9)	540(10)	-5(9)	30(10)	-77(8)
C(1')	2144(4)	478(2)	929(2)	470(10)	420(10)	440(10)	-50(10)	-40(10)	-20(10)
C(2')	3804(4)	48(3)	433(2)	400(10)	480(10)	510(10)	-30(10)	-50(10)	-0(10)
C(3')	4265(4)	923(3)	-344(2)	430(10)	620(20)	560(20)	-70(10)	10(10)	0(10)
O(3')	5168(3)	882(2)	618(2)	470(10)	750(10)	620(10)	-190(10)	-70(10)	40(10)
C(4')	2809(4)	1812(3)	-371(3)	560(10)	410(10)	610(20)	-70(10)	20(10)	30(10)
C(5')	1525(4)	1483(3)	-1192(2)	570(10)	420(10)	480(10)	-10(10)	10(10)	60(10)
O(5')	1171(3)	210(2)	-1164(1)	480(9)	422(8)	358(8)	-20(8)	44(8)	5(7)

oxirane ring hinders the puckering of the sugar ring. This automatically involves opening of the bond angles especially at O(1') (112.7(2)°) relative to those observed in thymidine[23] and other nucleosides for which the mean C–C–C, C–C–O and C–O–C bond angles[24] are 103.0(4), 104.4(3) and 109.7(3)°, respectively. Thus the sum of the *endo* bond angles is 539.5°. Nevertheless, the C(5')–O(5') bond preserves its usual *gauche–gauche* ($\Psi = 47.7(3)°$, O(5')–C(5')–C(4')–O(1') = −70.9(3)°) position and the conformation about the glycosidic C(1')–N(1) bond remains in the anti range with $\chi = 88.1(3)°$. The dihedral angles between the best planes for molecule **3** are given also in Table 8.

In **16** the formation of an additional 7-membered ring between O(5') and C(6) exerts further strain on the sugar ring. This spoils then the planarity imposed previously on the sugar ring in **3** by the strained oxirane ring. The r.m.s. value of the torsion angles (23.2°) is almost as high as 23.9° which pertains, for example, to 5-isopropyl-2'-deoxyuridine.[21] This sugar ring embedded between the planar oxirane and the 7-membered ring is, however, forced into a rare C3'/C2'-*exo* conformation. More accurately, it has a transition between E_{01} and $^4T_{01}$ canonical forms described by the Schwarz's notations[25] in accord with the puckering parameters (Q = 29.5 pm, $\varphi = 315.5°$)[26] and asymmetry factors[27] (fC_2[C2'] = 3.8, fC_s[O1'] = 4.4 pm) computed by the program RING.[28] This conformation seems to provide an optimum of sterical araangement for the ring closure between O(5') and C(6) sustaining the characteristic *gauche–gauche* position of O(5')–C(5') bond ($\Psi = 44.2(4)°$, O(5')–C(5')–C(4')–O(1') = −69.3(4)°) and *anti*-conformation ($\chi = 53.8(4)°$)

Table 4. Fractional coordinates ($\times 10^3$) for hydrogen atoms of compounds 3 and 16. Except H(O5') they are numbered according to the carbon atoms to which they are linked

	Molecule 3				Molecule 16			
	x/a	y/b	z/c	B_{iso}, Å^2	x/y	y/b	z/c	B_{iso}, Å^2
H(5)	-192	-46	-218	4.0				
H(6)	-416	0	-82	4.0				
H(7A)	-584	-354	-230	4.0	-354	-263	150	6.5
H(7B)	-834	-332	-209	4.0	-167	-288	204	6.5
H(7C)	-709	-291	-293	4.0	-285	-175	240	6.5
H(8A)					-299	-141	-187	6.6
H(8B)					-213	-11	-210	6.6
H(8C)					-98	-132	-225	6.6
H(1')	-791	-146	41	4.0	217	39	169	4.5
H(2')	-375	-63	63	4.0	370	-84	48	4.6
H(3')	-541	104	104	4.0	467	95	-107	5.2
H(4')	-1041	82	82	4.0	322	264	-52	5.1
H(5'A)	-875	207	0	4.0	201	170	-188	4.8
H(5'B)	-1043	146	-63	4.0	43	193	-107	4.8
H(O5')	-668	188	-125	4.0				

Table 5. Bond distances (Å) with their e.s.d. 's in parentheses

	Mol. 3	Mol. 16		Mol. 3	Mol. 16
N(1)-C(2)	1.379(2)	1.381(4)	N(1)-C(1')	1.463(2)	1.483(4)
N(1)-C(6)	1.371(2)	1.390(4)	C(1')-C(2')	1.499(2)	1.517(4)
C(2)-O(2)	1.212(3)	1.233(4)	C(2')-C(3')	1.457(2)	1.454(4)
C(2)-N(3)	1.397(2)	1.366(4)	C(2')-O(3')	1.430(2)	1.431(4)
N(3)-C(7)	1.471(3)	1.476(5)	C(3')-O(3')	1.449(2)	1.435(4)
N(3)-C(4)	1.390(3)	1.400(4)	C(3')-C(4')	1.502(3)	1.505(5)
C(4)-O(4)	1.235(2)	1.231(4)	C(4')-C(5')	1.494(3)	1.506(5)
C(4)-C(5)	1.430(2)	1.430(4)	C(5')-O(5')	1.402(4)	1.454(4)
C(5)-C(8)		1.508(4)	C(4')-O(1')	1.446(2)	1.449(4)
C(5)-C(6)	1.335(2)	1.340(3)	O(1')-C(1')	1.422(2)	1.413(3)
C(6)-O(5')		1.357(3)			

Table 6. Bond angles (°)with their e.s.d. 's in parentheses

	Mol. 3	Mol. 16		Mol. 3	Mol. 16
C(1')-N(1)-C(2)	116.9(2)	116.1(4)	N(1)-C(6)-O(5')		118.1(4)
C(1')-N(1)-C(6)	121.4(2)	122.8(4)	N(1)-C(1')-O(1')	111.8(2)	110.9(4)
C(2)-N(1)-C(6)	121.5(3)	121.1(4)	N(1)-C(1')-C(2')	113.2(2)	111.4(4)
N(1)-C(2)-N(3)	115.4(3)	116.9(4)	O(1')-C(1')-C(2')	105.8(2)	104.8(4)
N(1)-C(2)-O(2)	122.9(3)	121.4(5)	C(1')-O(1')-C(4')	112.7(2)	108.1(4)
N(3)-C(2)-O(2)	121.8(3)	121.7(5)	O(1')-C(4')-C(3')	104.8(2)	103.9(4)
C(2)-N(3)-C(4)	125.0(3)	124.1(5)	O(1')-C(4')-C(5')	112.2(3)	108.8(5)
C(2)-N(3)-C(7)	117.0(3)	116.9(5)	C(3')-C(4')-C(5')	113.6(3)	110.4(5)
C(4)-N(3)-C(7)	118.1(3)	118.8(4)	C(2')-C(3')-C(4')	108.1(2)	106.2(4)
N(3)-C(4)-C(5)	115.6(3)	116.5(4)	O(3')-C(3')-C(4')	111.8(2)	114.0(4)
N(3)-C(4)-O(4)	120.2(3)	119.4(4)	C(2')-C(3')-O(3')	59.0(2)	59.4(3)
C(5)-C(4)-O(4)	124.2(3)	124.1(4)	C(2')-O(3')-C(3')	60.8(2)	61.0(3)
C(4)-C(5)-C(6)	119.8(3)	119.7(4)	O(3')-C(2')-C(3')	60.2(2)	59.7(3)
C(4)-C(5)-C(8)		117.4(4)	C(1')-C(2')-C(3')	108.0(2)	106.9(3)
C(6)-C(5)-C(8)		122.8(4)	C(1')-C(2')-O(3')	110.7(2)	110.2(4)
C(5)-C(6)-N(1)	122.6(3)	121.6(4)	C(4')-C(5')-O(5')	110.1(4)	110.3(4)
C(5)-C(6)-O(5')		119.9(4)	C(5')-O(5')-C(6)		120.8(4)

Table 7. Relevant torsion angles (°) with their e.s.d. 's in parentheses

		Mol. 3	Mol. 16
(τ_0)	C(4')-O(1')-C(1')-C(2')	7.8(2)	29.7(4)
(τ_1)	O(1')-C(1')-C(2')-C(3')	-3.9(2)	-14.9(4)
(τ_2)	C(1')-C(2')-C(3')-C(4')	-1.0(2)	-4.7(4)
(τ_3)	C(2')-C(3')-C(4')-O(1')	5.4(2)	22.1(4)
(τ_4)	C(3')-C(4')-O(1')-C(1')	-8.3(2)	-32.7(4)
(τ_1')	N(1)-C(1')-C(2')-C(3')	118.7(3)	105.1(4)
(χ)	O(1')-C(1')-N(1)-C(6)	88.1(3)	53.8(4)
	C(1')-N(1)-C(6)-O(5')	-	11.5(4)
(ω)	N(1)-C(6)-O(5')-C(5')	-	-67.0(4)
(ζ)	C(6)-O(5')-C(5')-C(4')	-	77.7(4)
	O(5')-C(5')-C(4')-O(1')	-70.9(3)	-69.3(4)
	C(5')-C(4')-O(1')-C(1')	115.4(3)	85.0(4)
	C(4')-O(1')-C(1')-N(1)	-115.8(3)	-90.7(4)
(ψ)	O(5')-C(5')-C(4')-C(3')	47.7(3)	44.2(4)
(ψ')	C(5')-C(4')-C(3')-O(3')	179.6(3)	-157.6(5)
	O(1')-C(1')-C(2')-O(3')	60.2(2)	48.3(4)

Table 8. Equations of atomic planes in the form AX + BY + CZ = D, where X, Y, Z are orthogonal (Å) coordinates. Deviations (Å × 10^3) of relevant atoms from the planes are given in square brackets. Values for molecule 3 precede those for molecule 16

Plane (1): N(1), C(2), N(3), C(4), C(5), C(6)
-0.6786X + 0.4913Y - 0.5460Z = 2.0569
0.5641X - 0.8031Y - 0.1918Z = 0.3696
[N(1) -22, -30; C(2) 9, 23; N(3) 13, -4; C(4) -23, -8; C(5) 12, 1; C(6) 11, 18; O(2) 28, 69; O(4) -56, 2; C(7) 74, 115; C(8) -, 90; C(1') -168, -95]

Plane (2): C(1'), C(2'), C(3'), C(4'), O(1')
0.4543X + 0.3455Y - 0.8211Z = -2.3954
-0.6155X + 0.4770Y - 0.6274Z = -2.1674
[C(1') 34, 131; C(2') -8, -25; C(3') -19, -78; C(4') 40, 163; O(1') -48, 191; N(1) 1228, 1514; O(3') -1225, -1272; C(5') 1266, 1621,

Plane (3): C(2'), C(3'), O(3')
-0.8958X - 0.2757Y - 0.3487Z = 2.3311
0.6584X - 0.6430Y - 0.3912Z = 1.6842
[C(1') 1383 -1409; C(4') 1377, -1369]

Dihedral angles (°) between planes (1)-(2), 72.0, 81.0; (1)-(3) 48.5, 15.7; (2)-(3) -77.5, 81.6.

about the glycosidic C(1')–N(1) bond. Only the pyrimidine base oriented usually in *β-pseudo*-equatorial direction (τ_1' = 140–160°)[24] is forced into a *β-pseudo*-axial position (τ_1' = 105.1(4)°). The least-squares plane of the sugar ring in **16** forms the dihedral angles of 81.0 and 81.6° with that of the pyrimidine and oxirane rings (Table 8). The 7-membered ring with Q = 75 pm puckering amplitude[26] and fC_2[N1] = 10.0 and fC_s[C4'] = 12.8 pm asymmetry factors[27] exhibits a transition form between the twist-chair (TC) $\left(-\frac{+-+}{+-+}\right)$ and chair (C) $\left(0\frac{+-+}{-+-}\right)^{29}$ conformations. There is only one active H atom in **3** which forms an intermolecular H-bond between the atoms O(5')–H(5')...O(4) [x − 1/2, x + 1/2, z − 1/2] with the following parameters: O....O 2.676, H....O 1.811 Å, ∠OH..H 166.6°.

EXPERIMENTAL

M.ps are uncorrected. TLC was carried out on Kieselgel HF_{254} coated microscope slides using EtOAc (A), EtOHc/CCl_4 1:1 (B) and EtOAc/MeOH 19:1 (C) for elution. Detection was effected

by UV light and with 0.1 N $KMnO_4$ and 2 N H_2SO_4 (1:1) and heating to 105°. For column chromatography Kieselgel 40 (0.063–0.200 mm) was used. ^1H NMR spectra were recorded with a JEOL C-60-HL (60 MHz) and a VARIAN EM-390 (90 MHz) spectrometer, using DMSO-d_6 as solvent and DSS as the internal standard. The ^{13}C NMR spectrum was recorded on a VARIAN XL-100 spectrometer at 25.16 MHz in pyridine-d_5 solution and TMS was used as internal standard.

All evaporations were carried out in a rotary evaporator under diminished pressure. Analytical data are given in Table 2.

1 - (*β* - D - 2',3' - *anhydro* - *ribofuranosyl*) - 3 - *methyl* - *uracil* (**3**). To a stirred slurry of **1**[18] (2.3 g) in dry MeOH (20 ml) methanolic NaOMe (4.3 M, 2.3 ml; 1 equiv) was added at room temp and after 15 min the mixture was evaporated. To the solid residue DMSO (20 ml) and MeI (1.4 g, 0.6 ml, 1 equiv) was added. The orange-red soln was then evaporated at 60°. Purification of the crystalline residue was carried out by column chromatography (solvent A). The fraction having R_f 0.6 (A) was evaporated to yield **4** as an oil (0.2 g; 8%). The main fraction having R_f 0.45 (A) was evaporated and recrystallized from EtOH affording **3** (1.15 g; 48%), m.p. 156–158°, $[\alpha]_D^{20}$ +12.1° (c 0.6 MeOH). The fraction having R_f 0.15 (A) was evaporated and recrystallized from EtOH yielding the arabinosyl derivative **5** (0.15 g; 6%), m.p. 158–160° (see Hydrolysis).

1 - (*β* - L - 2',3' - *anhydro* - *ribofuranosyl*) - 3 - *methyl* - *uracil* (**L-3**) was prepared as described for **3**, starting from 2,2'-anhydro-1-*β*-L-arabinofuranosyl-uracil, yield 54%, m.p. 159–161°, $[\alpha]_D^{20}$ −5.8° (c 0.6 MeOH).

1 - (*β* - D - 2',3' - *anhydro* - 5' - O - *methyl* - *ribofuranosyl*) - 3 - *methyl* - *uracil* (**4**). To a slurry of NaH (50%; 1.2 g; 2 equiv) in DMSO (20 ml) 2,2'-anhydro - 1 - *β* - D - arabinofuranosyl - uracil (2.3 g) was added and the mixture was stirred at room temp. for 15 min. Then MeI (2.8 g; 1.2 ml; 2 equiv) was added, when an exothermic reaction took place raising the temp. to 60°. The mixture was kept at room temp for 24 h, and was then evaporated at 60°. The residue was separated by column chromatography (solvent A). The fraction having R_f 0.6 gave on evaporation **4** as colourless oil (1.36 g; 55%), $[\alpha]_D^{20}$ +8.6° (c 0.5 MeOH). The fraction having R_f 0.35 (A) gave on evaporation and recrystallization from EtOH derivative **6** (0.15 g; 6%), m.p. 123° (see Hydrolysis).

1 - (*β* - D - 2',3' - *anhydro* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**8**). A soln of **7**[10] (3.0 g) in dry MeOH (50 ml) and methanolic NaOMe (4.3 M, 2.4 ml; 1 equiv) was kept for 15 min at room temp and was then evaporated. DMSO (40 ml) and MeI (1.4 g; 0.6 ml; 1 equiv) was added to the dry residue and the mixture was kept overnight at room temp. After evaporation at 60° the residue was chromatographed on silica gel (solvent B then A). The fraction having R_f 0.7 (B) gave on evaporation **9** (0.05 g; 2%). The main fraction having R_f 0.5 (B) was evaporated and recrystallized from EtOH to yield **8** (1.6 g; 50%), m.p. 184–185°, $[\alpha]_D^{20}$ + 11.0° (c 0.5 MeOH). The fraction having R_f 0.4 (A) was crystallized after evaporation from EtOH affording **10** (0.5 g; 15%), m.p. 184–185° (see Hydrolysis).

1 - (*β* - L - 2',3' - *anhydro* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**L-8**) was prepared as described for **8** starting from 2.2' - anhydro - 1 - *β* - L - arabinofuranosyl - 5 - bromo - uracil, yield 43%, m.p. 184–186°, $[\alpha]_D^{20}$ −10.8° (c 0.5 MeOH).

1 - (*β* - D - 2',2' - *anhydro* - 5' - O - *methyl* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**9**) The soln of **7** (0.75 g) and methanolic NaOMe (4.3 M; 1.2 ml; 2 equiv) in dry MeOH (12.5 ml) was kept at room temp for 15 min. After evaporation to dryness DMSO (10 ml) then MeI (0.7 g; 0.3 ml; 2 equiv) was added, when the temp rose to 60–65°. After standing at room temp. overnight the mixture was evaporated at 60° and chromatographed on silicagel (solvent B) yielding after recrystallization from EtOH **9** (0.15 g; 18%), m.p. 180–190° (subl), R_f 0.7 (B), $[\alpha]_D^{20}$ +3.1° (c 0.5 DMF).

1 - (*β* - D - 2',3' - *anhydro* - 5' - O - *methyl* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**L-9**) was prepared in the same manner as described for **9** starting from the L-isomer of **7**, yield 20%, m.p. 185–190° (subl), $[\alpha]_D^{20}$ −2.9° (c 0.5 DMF).

Hydrolysis of compounds **3**, **4**, **8** and **9**. A soln of the 2',3' - anhydro derivatives **3**, **4**, **8** or **9** (0.002 M) in EtOH (50 ml) and HCl (0.2 M; 2.5 ml; 0.25 equiv) was boiled for 6 h and was then evaporated. The residue was purified by column chromatography to give after recrystallization from EtOH **5** (60%)-m.p. 160–164°, lit[9] m.p. 163–164°, R_f 0.15 (A); **6** (63%), m.p. 122–123°, R_f 0.35 (A); **10** (65%), m.p. 185–186°, lit[11] m.p. 184–186°, R_f 0.4 (A) and **11** (61%), m.p. 228–230°, R_f 0.5 (A), respectively.

Bromination of compounds **3**, **4**, **5** and **6**. A slurry of **3**, **4**, **5** or **6** (0.002M) and N-bromo-succinimide (0.36 g; 1 equiv) in dry $CHCl_3$ (20 ml) was boiled for 2 h. The residue obtained after evaporation was purified by column chromatography (solvent B) or by crystallization from MeOH, yielding **13** (8%; cryst.), m.p. 175–177°, R_f 0.5 (B) R_f 0.8 (A); **9** (48%; chrom.) m.p. 185–190° (subl) R_f 0.7 (B); **10** (68%; cryst.), m.p. 184–186°, R_f 0.4 (A) and **11** (50%; cryst.), m.p. 228–230°, R_f 0.5 (A), respectively.

O^6,5' - *Anhydro* - 1 - (*β* - D - 2',3' - *anhydro-ribofuranosyl*) - 3,5 - *dimethyl* - *uracil* (**16**). To a stirred slurry of NaH (50%, 2.0 g; 4 equiv) in DMSO (40 ml) **7** (3.0 g) was added. Stirring was continued for 15 min, then MeI (2.5 ml; 4 equiv) was added when the temp. rose to 60–65°. After 15 min stirring the orange-red soln was kept at room temp. overnight and was then evaporated at 60°. The residue was chromatographed on silicagel (solvent B). The fraction having R_f 0.7 was evaporated and crystallized from EtOH yielding **9** (0.05 g; 5%), m.p. 180–185° (subl.). The main fraction having R_f 0.4 (B) was evaporated and recrystallized from MeOH affording **16** (0.47 g; 20%), m.p. 206–207°, $[\alpha]_D^{20}$ +94.9° (c 0.5 MeOH). ^{13}C NMR data: *δ* (ppm) C(1'): 83.9(d), C(2') and C(3'): 54.7 and 53.1(d), C(4'): 76.6(d), C(5'): 75.6(dd), C(5): 99.1(s), (3)NCH_3: 28.4(q), 5-CH_3: 8.5(q), C(2), C(4) and C(6) not determined.

O^6,5' - *Anhydro* - 1 - (*β* - L - 2',3' - *anhydro* - *ribofuranosyl*) - 3,5 - *dimethyl* - *uracil* (**L-16**) was prepared as described for **16**, starting from the L-isomer of **7**, yield 18%, m.p. 205–206°, $[\alpha]_D^{20}$ −104.8° (c 0.5 MeOH).

1 - (*β* - D - 2' - *bromo* - 2' - *deoxy* - *arabofuranosyl*) - 3 - *methyl* - *uracil* (**18**). To a boiling soln of **3** (0.48 g) in EtOH (20 ml) a soln of HBr in AcOH (1.9 M, 1.1 ml, 1 equiv) was added. The soln was kept at room temp. overnight, then it was evaporated and the residue separated by column chromatography (solvent C). The fractions having R_f 0.75 gave on evaporation and recrystallization from EtOH **18** (0.2 g; 31%), m.p. 171–173°. The fractions having R_f 0.55 gave on similar treatment arabinoside **5** (0.15 g; 22%), m.p. 158–160°.

1 - (*β* - D - 2' - *bromo* - 2' - *deoxy* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**20**).

Method b. The dibromide **20** was prepared as described for **18**, starting from **8** and using solvent A for chromatography. Yield 50%, m.p. 195–197°, no depression with authentic material obtained via method a.

Method a. To a soln of **19**[10] (3.0 g) in dry EtOH (150 ml), diazomethane in ether (~2%, ~45 ml) was added to yellow colour. After standing at room temp overnight the mixture was evaporated, and the oily residue was crystallized from EtOH to yield **20** (2.1 g; 52%), m.p. 196–198°, R_f 0.75 (A), $[\alpha]_D^{20}$ −34.6° (c 1 DMF).

1 - (*β* - L - 2' - *bromo* - 2' - *deoxy* - *ribofuranosyl*) - 3 - *methyl* - 5 - *bromo* - *uracil* (**L-20**) was prepared as described for **20** starting from 1 - (*β* - L - 2' - bromo - 2' - deoxy - ribofuranosyl) - 5 - bromo - uracil, yield (45%), m.p. 193–195°, $[\alpha]_D^{20}$ +33.8° (c 1 DMF).

Crystal structure determination of 3 - *methyl* - 2',3' - *anhydrouridine* (**3**) *and* 2,5 - *dimethyl* - 2',3': O^6,5' - *dianhydrouridine* (**16**)

Symmetry independent reflexions for both compounds were collected on an Enraf-Nonius CAD-4 computer controlled four-circle diffractometer with graphite monochromated CuK_α-($\bar{\lambda}$ = 1.5418 Å) radiation. Cell constants were determined by least-squares from the setting angles of 25 reflexions. No absorption correction was applied in either case. Both crystal structures were solved by direct methods by the use of program MULTAN.[30] Full-matrix least-squares refinement of the positional and anisotropic vibrational parameters of non-H atoms resulted in the final conventional R values given above. The H positions were

located in both cases in difference Fourier syntheses. Scattering factors were taken from International Tables for X-ray Crystallography.[31] All calculations were performed on a PDP 11/34 (64K) computer with Enraf-Nonius SDP-34 system.

Crystal data

	3	16
Chemical formula	$C_{10}H_{12}O_5N_2$	$C_{11}H_{12}O_5N_2$
Crystal symmetry	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a:	5.183(1)	7.743(1) Å
b:	13.943(1)	11.210(1)
c:	14.695(1)	13.019(4)
U:	1062.0(4)	1130.0(6) Å^3
D_c:	1.502	1.482 g.cm^{-3}
Z:	4	4
F(000)	504	528
$N(F_{tot})$	1337	1392
$N(F_{obs})$ with $F > 1.7\sigma(F)$	1248	1304
R_{obs}	0.035	0.047
R_w	0.055	0.069

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