SYNTHESIS AND PMR SPECTRA OF α- AND β-D-ARABINOFURANOSYLURACILS

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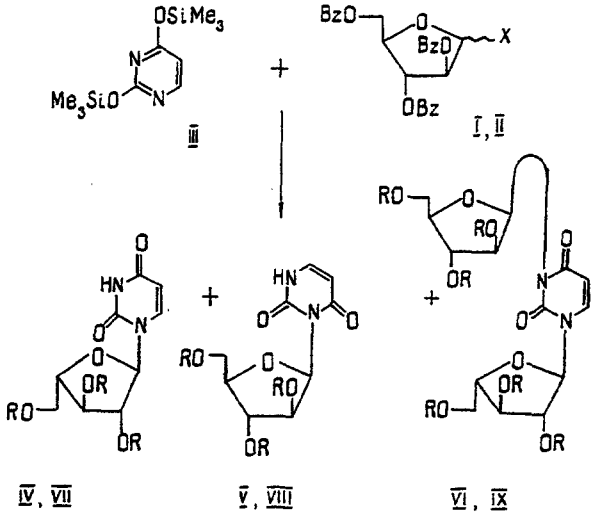
The α- and β-anomers of N^1- and N^3-monoglycosylated and N^1,N^3-diglycosylated nucleosides have been synthesized by the condensation of 1-OMe- or 1-O-acetyl-2,3,5-tri-O-benzoyl-D-arabinose with bis(trimethylsilyl)uracil in the presence of $SnCl_4$. The structures of the compounds obtained were established from their NMR spectra.

Arabinofuranosylnucleosides possess a high biological activity [1]. In order to obtain arabinofuranosyluracil [2], we have studied the interaction of 1-O-methyl- and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-arabinofuranoses (I and II, respectively) with bis(trimethylsilyl)-uracil in the presence of $SnCl_4$ in dichloroethane solution. In this case a mixture of three substances was obtained: 1-(2',3',5'-tri-O-benzoyl-α-arabinofuranosyl)uracil (IV), 3-(2',3',5'-tri-O-benzoyl-α-arabinofuranosyl)urcil (IV), 3-(2',3',5'-tri-O-benzoyl-β-D-arabinofuranosyl)uracil (V), and 1-(2',3',5'-tri-O-benzoyl-β-D-arabinofuranosyl)uracil (VI), their ratio depending on the conditions (Table 1). Where the 1-O-methyl derivtive (I) was used, the addition of acetic anhydride to the reaction mixture led to a sharp increase in the amount of the 1,3-diglycosylated product (VI). However, in the case of the 1-O-acetyl derivative (II) the addition of acetic anhydride did not change the ratio of the compounds (IV-VI) obtained.



I X=α-OMe
II X=OAc

R = Bz (IV, V, VI), H (VII, VIII, IX)

The removal of the protective groups of compounds (IV)-(VI) was effected with MeONa in methanol. The yields of the nucleosides (VII)-(IX) amounted to 73-80%. In 0.1 M aqueous NaOH solution the absorption maximum in the UV spectrum of compound (VIII) underwent a bathochromic shift of 29 nm, while for the N^1-arabinofuranoside (VII) the shift was only 0.5 nm (in comparison with the spectra in aqueous solutions) (Table 2). For the $N^{1,3}$-diglycosylated product (IX) no shift of the absorption maximum was observed.

The structures of the anomeric centers and the positions of attachment of the carbohydrate residues – at the N^1 or the N^3 atom of uracil – were established on the basis of NMR spectra. It was shown that in the ^{13}C NMR spectra of the N^1,N^3-diglycosylated nucleo-

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TABLE 1. Yields and Ratios of Products (IV-VI)*

Compound (I) or (II), X	Yields, %			Total yield, %
	IV	V	VI	
OMe**	27	13	30	70
OAc	37	17	8.3	62.3
OAc**	35	18	9	62

*Reaction conditions: solvent – dichloroethane; catalyst – $SnCl_4$; reaciton time – 3 h.
**With the addition of acetic anhydride.

TABLE 2. Physicochemical Characteristics of the Compounds

Compound	mp, °C, (EtOH)	$[\alpha]_D^{20}$, deg	UV spectrum		
			solvent	λ_{max}, nm	λ_{min}, nm
IV	191—192	−35,2 (c, 3; $CHCl_3$)	A	234 265	216 241
V	78	−11,6 (c 2; $CHCl_3$)	A	232 264	212 240
	99—102	−32,35 (c 3,4; $CHCl_3$)	A	231,5 260	210,8 251
VII	128—131	+22,5 (c 0,1; H_2O)	B C	262,6 263,1	230,6 241,7
VIII	179–181	+79,4 (c 0,06; H_2O)	B C	263,7 262,6	231,5 246,5
IX	—*	+44,6 (c 1,3; H_2O)	B C	268,0 268,1	233,6 231,4

*Hygroscopic powder.
**Solvents: A – MeOH; B – H_2O; C – 0.1 M aqueous NaOH.

sides (VI) and (IX) the chemical shifts of the anomeric carbon atoms were 91-92 ppm for N^1-addition and 86-87 ppm for N^3-addition. In this way we established the positions of the carbohydrate residues for the monosubstituted uracils (IV), (V), (VII), and (VIII) (Table 3).

It is known that the vicinal SSCCs between H-1' and H-2' of α-D-arabinofuranosides are small [4]. However, in this case the differences in the SSCC values are not characteristic. For the α-configuration the substituents at C-1' and C-2' are in the trans-position and for the β-configuration they are in the cis- position. It is known that an anomeric effect is observed in such structures; i.e., the substituent at C-1' preferentially occupies the pseudoaxial position [5]. Then the interaction between H-1' and H-2' for the α- anomer becomes as it is between two pseudoequatorial substituents, and for the β- anomer as between pseudo-a,e. In the first case, the SSCC should be small (1-3 Hz), and in the second it should be medium (4.5-6.5 Hz) [6]. The assignments to the α- and β- configurations of the anomeric centers of nucleosides (IV-IX) were made on this basis (Table 4). The SSCCs of the vicinal interactions of the other protons corresponded to these hypotheses. Thus, in the α-anomers all the substituents were present in the trans-state and occupied pseudoaxial positions and the SSCCs were small. In the β-anomers the substituent at C-2' had the cis- position and was located pseudoequatorially, and since the interaction between H-2' and H-3' was pseudo-a,e the SSCC was 5-7 Hz.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were taken on a Bruker AM-300 instrument with working frequencies of 300 and 75 MHz. Values of δ (ppm) and spin-spin coupling constants (Hz) are given. UV absorption spectra were taken on a Shimadzu UV 365 instrument. Specific angles of rotation were determined with the aid of a Perkin-Elmer 241 MS instrument. Column chromatography was conducted on silica gel L 5/40 μ. For the disubstituted uracils, in order to establish the interactions between the protons and to determine the spectral parameters, we performed 2D experiments by the COSY method.

TABLE 3. Parameters of the ^{13}C NMR Spectra of Compounds (V-IX)* (δ, ppm, TMS)

Compound	C'	C'-1'	C'-2'	C'-3'	C'-4'	C'-5'	C-3	C-4	C-6	C-1''	C'	C''	C''	C-5'	Solvent
V	86,69 d	77,08 d	80,18 d	81,96 d	64,29 t	152,45 s	163,05 s	102,41 d	139,29 d						$CDCl_3$
VI	92,90 d	80,88 d	77,23 d	85,14 d	63,86 t	150,06 s	162,22 s	102,30 d	138,65 d	86,90 d	77,62 d	80,22 d	82,02 d	64,25 d	$CDCl_3$
VII	91,18 d	80,00 d	75,54 d	87,76 d	61,33 t	150,33 s	163,22 s	100,79 d	140,79 d						DMSO-d_6
VIII	86,26 d	76,30 d	76,02 d	83,90 d	61,52 t	151,62 s	164,02 s	100,66 d	141,57 d						DMSO-d_6
IX	91,65 d	79,51 d	75,52 d	87,73 d	61,16 t	150,20 s	162,77 s	100,46 d	140,41	86,29 d	75,78 d	75,07 d	83,64 d	61,28 d	DMSO-d_6

*The CSs of the signals of the carbon atoms of the benzoate groups are not given in the Table; they lay in the 127-133 ppm region.

TABLE 4. PMR Spectra of Compounds (IV-IX) (δ, ppm, J, Hz)

Compound	Solvent	H-5 H-6 $J_{5,6}$	H-1' $J_{1',2'}$	H-2' $J_{2',3'}$	H-3' $J_{3',4'}$	H-4' $J_{5'a,4'}$ $J_{4,5'6}$	H-5' H-5'' J_{gem}
IV	$CDCl_3$	5,81d, 7,91 d 8.16	6,23 d 3,11	5,98t 2,90	5,78dd 3,70	4,98 ddd 4.55, 5.70	4,76dd 4,66 dd −11.96
	DMSO-d_6	5.70d, 7,91 d 8.10	6,23d 4,06	6,07t 4,12	5,89dd 5,09	5,08 m	4.66s 4,69 s
V	$CDCl_3$	5,72d, 7.05d 7.74	6,70 d 4,31	6,42dd 5,07	6,07dd 7,69	5,12 ddd 3,23, 4,36	4,61dd, 4,77dd −12,16
	DMSO-d_6	5,70d, 7,43 d 7,60	6,62 d 4,50	6.40t 4.82	5,88dd 7,47	5.02	4,57—4,62 (m)
VI	$CDCl_3$	5,86d, 8,02 d 8,16	6,24 d 2.04	6,02t 2,00	5,70dd 2.70	5,02 m 3,20, 4,20	4.72dd, 4,5?dd −12,20
		5,62d, 7,70 d 8,09	6.60d 4,35	6,45t 5,12	6,07dd 7,60	5,15 m 6.20, 4,15	4,67dd −4,77 dd −11,80
VII	$CDCl_3$	5.55d, 7,42 d 7.58	5,72 d 3,97	3,92t 4,42	4,11dd 4.80	4,08 ddd, 5,45d 4,44	3,45 dd −3,65dd
VIII	DMSO-d_6	5,75d, 7,60 d 8,02	6,16 d 6,38	4,80t 7,20	4,11dd 3,95	4,05 m 5,30, 6,90	3,37 dd, 3.80 dd −12,50
IX	DMSO-d_6		5,74 d 3,30	3,94 t 4,80			
			6.15 d 6.32	4.80t 6.90		3,35—3,95 (m)	

1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)uracil (V), 3-(2,3,5-Tri-O-benzoyl-β-D-arabinofuranosyl)uracil (IV), and 1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl-3-(2,3,5-tri-O-benzoyl-β-D-arabinofuranosyl)uracil (VI). A mixture of 2.75 g (1.1 mmole) of bis(trimethylsilyl)uracil [7], 5.04 g (10 mmole), of 1-O-acetyl-2,3,5-tri-O-benzoylarabinofuranose [4] (or 1-O-methyl-2,3,5-tri-O-benzoylarabinofuranose) in 60 ml of dry dichloroethane was treated with 1.45 ml (12 mole) of $SnCl_4$ and was left at room temperature for 3 h. Then 33 ml of 10% aqueous $NaHCO_3$ solution was added to the reaction mixture and, after being stirred for 0.5 h, it was filtered through a layer of silica gel*, and this was washed with chloroform (4 × 30 ml). The combined filtrates were washed with 10% $NaHCO_3$ (50 ml) and with water (2 × 100 ml), and dried with Na_2SO_4. The solvent was eliminated in vacuum, and the residue was chromatographed on silica gel L 5/40 μ (400 g), with chloroform as the eluent. The experiments with the addition of an equimolar amount of acetic anhydride were performed similarly. The physicochemical characteristics of the compounds are given in Tables 2-4.

1-(α-D-Arabinofuranosyl)uracil (VII). Nucleoside (IV) (1 mmole) was dissolved in 40 ml of 0.1 M methanolic MeONa, and the solution was left at room temperature (24 h). Then the reaction mixture was neutralized with KU-2 cation-exchanger. The resin was washed with methanol (2 × 10 ml), and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of water and extracted with chloroform (2 × 25 ml). The aqueous part was heated with carbon, filtered, and evaporated to dryness in vacuum. The residue was recrystallized from ethanol (95%). Yield 80%.

3-(β-D-Arabinofuranosyl)uracil (VIII) (yield 77%) and 1-(α-D-arabinofuranosyl)-3-(β-D-arabinofuranosyl)uracil (IX) (yield 73%) were obtained similarly. The elementary analyses of all the compounds isolated agree with the calculated figures.

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*A step (layer separation/extraction?) has perhaps been omitted [Translator].