Pyrimido[5,4-c]quinol-4-one (II). A. To a solution of 0.5 g (2.58 mmole) of the pyrimidone (V) in 5 ml of glacial acetic acid was added 0.3 ml of a 10% solution of dimethylamine in dry benzene, and the mixture was boiled for 4 h, evaporated, triturated with water, and the (II) (0.37 g, 74%) filtered off, mp 359-361°C (from DMF); literature value [2], mp 360-362°C.

B. To a solution of 0.8 g (3.74 mmole) of (VI) in 8 ml of glacial acetic acid was added 0.3 ml of a 10% solution of dimethylamine in dry benzene. The mixture was boiled for 4 h, evaporated to 2/3 of its volume, cooled, and the solid which separated was filtered off to give 0.55 g (75%) of (II), mp 360-361°C (from DMF).

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ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF CHIRAL 1,5-DIHYDROXY-4-METHYL-3-OXAPENT-2-YL DERIVATIVES OF URACIL

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A convenient method has been developed for the synthesis of optically active 1-[1,5-dihydroxy-4-(R)-methyl-3-oxapent-2(R and S)-yl]uracils. 5'-Deoxyuridine is obtained from 2',3'-O-isopropylideneuridine, and its periodate oxidation followed by reduction with sodium tetrahydroborate leads to the desired 4(R), 2(R)-isomer. The acetonide of α-uridine is converted into the 4(R),2(S)-isomer analogously.

Interest in acyclic analogs of nucleosides is due to the fact that some of them possess unique antiviral properties [1, 2]. However, only a few syntheses of chiral acyclic nucleoside derivatives have been described: so-called oxidized-reduced derivatives of ribonucleosides (without the $C_{(2')}$–$C_{(3')}$ bond, 2',3'-seco-nucleosides) [3], 3',4'-seco-nucleosides [4], and 1',2'-seco-nucleosides [5] containing all the functional groups of the natural compounds. Oligonucleotides based on acyclic derivatives possess increased resistance to the action of nucleases [6, 7].

The present paper is devoted to a development of methods for the synthesis of 1,5-dihydroxy-4(R)-methyl-3-oxapent-2(R and S)-yl derivatives of nucleic bases, using uridine bases as examples. The initial compounds that we selected were the readily accessible 2',3'-O-isopropylideneuridine (Ia) [8] and its α anomer (Ib) [9].

The hydroxymethyl group was converted into a methyl group by chlorination with a mixture of CCl_4 and Ph_3P [10], followed by reduction with tributyltin hydride [11]. The isopropylidene protective group was eliminated by boiling in water in the presence of Dowex-50 in the H^+ form [12]. The 5'-deoxyuridines (IVa, b), obtained in high yields, were oxidized with sodium periodate and reduced with sodium tetrahydroborate [3]. The acyclic analogs (Va, b) were isolated by chromatography on silica gel.

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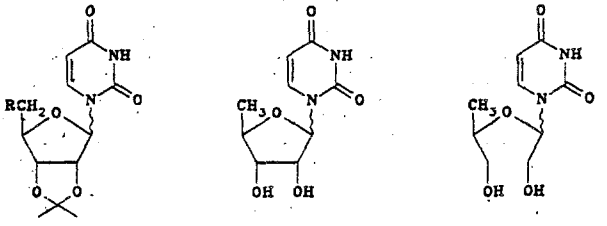
TABLE 1. PMR Spectra of the Compounds Synthesized*

Compound	Chemical shifts, δ, ppm (J, Hz)								
	NH, br.s	6-H ($J_{6,5}$), d	5-H ($J_{5,NH}$), d	1'-H ($J_{1',2'}$), d	2'-H ($J_{2',3'}$), d.d	3'-H ($J_{3',4'}$), d.d	4'-H ($J_{4',5'}$; $J_{4',5''}$)	5',5''-H ($J_{5',5''}$), d	isopropylidene, s
IIa	9,57	7,27 (8,0)	5,70	5,64 (2,0)	4,97 (6,5)	4,84 (3,5)	4,33d.t (5,0; 5,0)	3,79** 3,69** (−11,5)	1,57; 1,35
IIb	8,34	7,30 (8,0)	5,57** (2,2)	6,17 (4,0)	4,85 (6,0)	4,73 (1,0)	4,50 d.t (4,3; 4,3)	3,54	1,35; 1,23
IIIa	9,13	7,20 (8,0)	5,68	5,60 (2,0)	4,91 (6,5)	4,51 (4,5)	4,29d.q (6,5)	1,37	1,55; 1,34
IIIb	9,45	7,45 (8,0)	5,64	5,97 (4,0)	4,85 (5,9)	4,50 (0,8)	4,42 d.q (6,5)	1,24	1,42; 1,28
IVa		7,65 (8,0)	5,89	5,81 (4,0)	4,36 (5,5)	3,96 (6,0)	4,18 d.q (6,0)	1,35	
IVb		7,77 (8,0)	5,87	6,18 (4,0)	4,52 (4,5)	4,06 (7,5)	4,34 d.q (6,0)	1,42	
Va***		7,77 (8,0)	5,91	5,89** (5,5)	3,94—3,44 m (6,0)			1,12	
Vb***		7,79 (8,0)	5,93	5,89** (5,5)	3,90—3,50 m (6,0)			1,24	

*The PMR spectra were taken at 33°C; compounds (II) and (III) in $CDCl_3$, (IV) and (V) in D_2O.
**Doublet of doublets.
***For (IVa, b) the numbering of the atoms adopted for nucleosides has been used.
****Triplet.



I=IIIa, b IVa, b Va, b

I—V a β-anomer (R-isomer); b α-anomer (S-isomer); Ia,b R=OH; IIa,b R=Cl; IIIa,bR=H

The structures of the compounds synthesized (IIa, b)-(Va, b) were confirmed by PMR results (Table 1), CD and UV spectra (Fig. 1) elemental analysis, and chromatography, and also by comparison with the figures for nucleosides synthesized previously (IIa) [10] and (IVa) [13]. The empirical rules developed for demonstrating anomeric configurations of nucleosides with the aid of PMR spectroscopy (see the discussion and the references in [9]) are also applicable to the compounds synthesized (IIa, b)-(IVa, b). The 1'-H chemical shifts for 1',2'-cis-substituted furanoses lie in a weaker field than the 1'-H chemical shifts for the 1',2'-trans-substituted compounds. The difference between the chemical shifts of the protons of the methyl groups of the dioxolane ring, Δδ, is greater than 0.15 ppm for β-nucleosides and less than 0.15 ppm for α-nucleosides. The passage from the 5'-chloro derivatives (IIa, b) to the 5'-deoxynucleosides (IIIa, b) is accompanied by an upfield shift of the signals of the 5'-protons and by a change in their multiplicities. The elimination of the dioxolane ring leads to an increase in the sum of the SSCCs $J_{1',2'} + J_{3',4'}$ to 10-11.5 Hz. The PMR spectra of the acyclic derivatives (Va, b) are considerably more complex, which is explained by the presence of the two $HOCH_2$ groups with diasteriomeric protons. In these compounds, the 1'-H signals appear in the form of triplets.

The CD spectra of derivatives (Va, b) (Fig. 1) were opposite in sign and differed somewhat in the absolute values of the Cotton effects. They were close to the CD spectra of the R- and S-enantiomers, respectively, of 1-(1,5-dihydroxy-4-hydroxymethyl-3-oxapent-2-yl)uracil, which agrees with the additive scheme proposed in [3] according to which the greatest contribution to Cotton effect is made by the asymmetric centers closest to the chromophore.

Thus, for the synthesis of chiral acyclic analogs of deoxynucleosides it is promising to use derivatives of the natural nucleosides and their α-anomers.

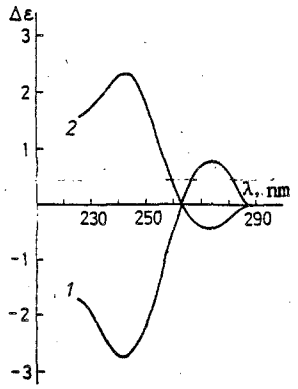


Fig. 1. CD spectra in water at 20°C: compound (Va); 2) compound (Vb).

EXPERIMENTAL

PMR spectra were recorded on a Varian XL-100 spectrometer for solutions in $CDCl_3$ with TMS as internal standard. For solutions in D_2O the measurements were performed relative to tert-butanol (taken as 1.27 ppm) and were recalculated relative to TMS. UV spectra were taken on a Specord UV-VIS spectrophotometer in water (pH 7 and 13). The UV spectra of the compounds synthesized (IIa, b)-(Va, b) coincided with the spectra of the initial compounds (Ia, b) and uridine. The CD spectra were recorded on a Jobin-Yvon Dichrographe III dichrograph (France) using 1-cm cells at a sensitivity of $5 \cdot 10^{-6}$. Melting points were determined on TP instrument (USSR) and are not corrected. TLC was performed on Silufol UV-254 plates in the following systems: $CHCl_3$ (A); $CHCl_3$–EtOH (98:2) (B); $CHCl_3$–EtOH (9:1) (C); $CDCl_3$–EtOH (4:1) (D); PhMe–EtOAc (1:1) (E). Silica gel L 40/100 (Czechoslovakia) was used for column chromatography.

According to the results of elemental analysis, compounds (IIIa), (IVb), and (Vb), obtained after chromatography on silica gel in the form of syrups, contained 1-3% of silica gel: the C, H, and N contents were low although their ratios were correct. The crystalline compounds gave satisfactory elemental analyses.

2',3'-O-Isopropylidene-5'-chloro-5'-deoxyuridine (IIa). A solution of 1.42 g (5 mmole) of nucleoside (Ia) in 10 ml of absolute DMFA was evaporated in vacuum to dryness. The residue was treated with 2.6 g (10 mmole) of Ph_3P, 0.97 ml (10 mmole) of CCl_4, and 25 ml of absolute DMFA. The resulting solution was kept at 20°C for 16 h. According to TLC in system C, the reaction was complete [R_f 0.48 for the initial (Ia), 0.78 for (IIa)]. After the addition of 1 ml of methanol, the solution was evaporated in vacuum and the residue was chromatographed on a column containing 100 g of silica gel. The system A eluted, first, Ph_3PO and then product (IIa). The fractions containing the (IIa) were combined and evaporated, and the residue was recrystallized from a mixture of methylene chloride and hexane. The yield of (IIa) was 1.25 g (83%). mp 178-179°C. According to the literature [10], mp 180-181°C.

1-(2,3-O-Isopropylidene-5-chloro-5-deoxy-α-D-ribofuranosyl)uracil (IIb) was obtained similarly. Yield 94%. mp 208-210°C (CH_2Cl_2–hexane). Found: C 47.7; H 4.8; N 9.5%. $C_{12}H_{15}ClN_2O_5$. Calculated: C 47.6; H 5.0; N 9.3%.

2',3'-O-Isopropylidene-5'-deoxyuridine (IIIa). A mixture of 2.4 g (7.93 mmole) of the nucleoside (IIa), 50 mg of α,α'-azobisisobutyronitrile and 4 ml (15 mmole) of tributyltin hydride in 50 ml of dry toluene was boiled for 2 h. According to TLC in system E, the reaction was complete [R_f 0.25 for the initial (IIa), and 0.20 for (IIIa)]. The solution was evaporated in vacuum and the residue was chromatographed on a column containing 50 g of silica gel. The column was washed with system A, and the reaction product was eluted with system B. The yield of compound (IIIa) was1.7 g (80%) (a slowly crystallizing syrup). mp 89-92°C. Found: C 53.2; H 5.8; N 10.2%. $C_{12}H_{16}N_2O_5$. Calculated: C 53.7; H 6.0; N 10.4%.

1-(2,3-O-Isopropylidene-5-deoxy-α-D-ribofuranosyl)uracil (IIIb) was obtained similarly. Yield 90%. mp 145-146°C (CH_2Cl_2–hexane). Found: C 53.6; H 5.7; N 10.2%. $C_{12}H_{16}N_2O_5$. Calculated: C 53.7; H 6.0; N 10.4%.

5'-Deoxyuridine (IVa). A mixture of 1.5 g (5.6 mmole) of nucleoside (IIIa) and 5 ml of Dowex-50×8 (H^+ form) in 30 ml of water was boiled for 2 h. According to TLC in system C the reaction was complete (R_f for the initial (IIIa), 0.83; R_f for the product (IVa), 0.33). The resin was filtered off and washed with water, the combined filtrates were evaporated in vacuum, the residue was evaporated with ethanol (2 × 10 ml) and dissolved in 10 ml of ethanol,

5 g of silica gel was added to the solution, and the suspension was evaporated in vacuum and transferred to a column containing 20 g of silica gel. The product was eluted with system C. The yield of (IVa) was 1.1 g (86%). mp 186-187°C (MeOH). According to the literature [13], mp 193-194°C.

1-(5-Deoxy-α-D-ribofuranosyl)uracil (IVb) was obtained similarly. Yield 90% (syrup, crystallizing on standing). mp 142-144°C. Found: C 46.8; H 5.3; N 12.1%. $C_9H_{12}N_2O_5$. Calculated: C 47.4; H 5.3; N 12.3%.

5'-Deoxy-2',3'-seco-uridine; 1-[1,5-Dihydroxy-4(R)-methyl-3-oxapent-2-R)-yl]uracil (Va). With stirring, 516 mg (2.4 mmole) of sodium periodate was added in portions to a solution of 500 mg (2.19 mmole) of nucleoside (IVa) in 20 ml of water. The solution formed was kept at 20°C for 30 min. According to the results of TLC in system D, oxidation was complete (R_f of the initial (IV), 0.62; R_f of the dialdehyde derivative 0.75). The solution was treated with 60 ml of ethanol, and the resulting suspension was stirred at 20°C for 10 min. The precipitate of $NaIO_3$ was filtered off and was washed with 20 ml of ethanol, and to the combined filtrate was added 83 mg (2.2 mole) of sodium tetrahydroborate with stirring, and the mixture was kept at 20°C for 30 min. According to TLC in system D, the reaction was complete (R_f of the reaction product (Va), 0.58). The mixture was treated with 30% AcOH to give pH 6 and was evaporated in vacuum. The residue was evaporated in vacuum with ethanol (3 × 10 ml) and was dissolved in 10 ml of ethanol; the solution was treated with 5 g of silica gel, the suspension was evaporated in vacuum, and the residue was transferred to a column containing 20 g of silica gel. The substance was eluted with system D. The fractions containing the reaction product were evaporated in vacuum, and the residue was recrystallized from acetone. The yield of compound (Va) was 400 mg (79%). mp 130-131°C. Found: C 46.7; H 6.0; N 12.3%. $C_9H_{14}N_2O_5$. Calculated: C 47.0; H 6.1; N 12.2%.

5'-Deoxy-2',3'-seco-α-uridine; 1-[1,5-Dihydroxy-4(R)-methyl-3-oxapent-2(S)-yl]uracil (Vb) was obtained similarly. Yield 72% (syrup). Found: C 45.8; H 5.9; N 11.8%. $C_9H_{14}N_2O_5$. Calculated: C 47.0; H 6.1; N 12.2%

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