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NEW CHIRAL ACYCLIC ANALOGS OF 2'-DEOXYNUCLEOSIDES

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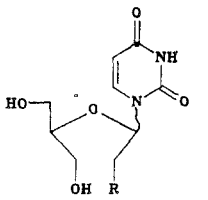
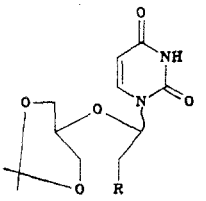
Convenient methods for the synthesis of chiral 2',3'-seco-2'-deoxynucleosides were developed. An isopropylidene protective group was used to block the 3',5'-hydroxy groups in 2',3'-seco-uridine. Conversion of the hydroxymethyl group to a methyl group was accomplished by chlorination with a mixture of CCl_4 and Ph_3P with subsequent reduction with n-Bu_3SnH. 2',3'-seco-2'-Deoxyuridine was obtained after deacetonation. The (S) enantiomer was similarly synthesized starting from 1-(α-D-arabinofuranosyl)uracil. 3'-O-tert-Butyldimethylsilyl-5'-O-(p-monomethoxytrityl)-2',3'-seco-2'-deoxyuridine, which has optically active centers at $C_{(1')}$ and $C_{(4')}$, was also synthesized.

This paper is a continuation of research devoted to obtaining chiral acyclic 2',3'-seconucleosides [1, 2] and is devoted to the development of methods for the synthesis of 5-hydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl derivatives of nucleic bases (2',3'-seco-2'-deoxynucleosides) in the case of uridine derivatives.

The conversion of uridine to redox derivative Ia was previously accomplished in low yields (see the literature cited in [1]). The use of chromatography on silica gel to isolate the product made it possible to increase the yield of analog Ia to 89%. Enantiomer Ib was similarly obtained in high yield starting from 1-(α-D-arabinofuranosyl)uracil [3]. It should be noted that the periodate oxidation of the trans-diol group takes place substantially slower [3] than that of the cis-diol group and is complete after 4 h at 20°C.



Ia,b; VIa,b



IIa,b-Va,b

I-VI a R-isomer; b S-isomer; I, II a,b R=OH; III a,b R=OBz; IV a, b R=Cl; V, VI a, bR=H

For the simultaneous blocking of the 3',5'-hydroxy groups* we used an isopropylidene protective group, the best method for the introduction of which was the reaction of triols Ia,b with acetone dimethylacetal in DMF in the presence of p-TsOH [4], which leads to acetonides IIa, b in 86-89% yields. The acetonation of analog Ia in the presence of 60% $HClO_4$ in acetone was described in [5]; the yield of product IIa was 45%.

The structures of the synthesized 2',3'-seco-nucleosides were confirmed by data from the PMR spectra (see Table 1), the complex character of which is explained by the presence of three $HOCH_2$ groups with diastereotopic protons. The spectra of analogs Ia, b and IIa, b correspond to the data in [1, 5]. For the subsequent proof of the structures of acetonides IIa, b we carried out benzoylation with benzoyl cyanide in dioxane in the presence of triethylamine [6]; derivatives IIIa, b were obtained in high yields. The benzoyl group shifts the signals of

*In the case of analogs I-XII for convenience we used the numbering of the atoms adopted for nucleosides.

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TABLE 1. PMR Spectra of the Synthesized Ia, b–VIa, b at 33°C*

Compound	Chemical shifts, δ, ppm (J, Hz)						
	NH (bs)	6-H** (d)	5-H (d)	1'-H ($J_{1',2'}$; $J_{1',2''}$)	2',2''-H ($J_{2',2''}$)	3',3'',4',5',5''-H (m)	Remaining protons
Ia, b		7,76	5,88	5,93 t (5,4; 5,4)	3,99—3,48 m		
IIa,b	9,15	7,46	5,71	5,84 t (5,3; 5,3)	4,10—3,40 m		1,43 s (2Me)
IIIa,b	8,92	7,46	5,78	6,14 dd (5,5; 6,0)	4,55 dd; 4,37 d.d (−11,5)	4,10—3,52	1,39 s (2Me); 8,07—7,25 m (Bz)
IVa,b	9,39	7,41	5,76	5,95 t (5,7; 5,7)	4,12—3,50 m		1,40 s (2Me)
Va,b	9,54	7,37	5,73	5,92 q (5,8)	1,46 d	4,06—3,35	1,39 s (Me); 1,37 s (Me)
VIa,b		7,79	5,93	6,07 q (6,0)	1,57 d	3,91—3,57	

*The spectra of I and VI were recorded in D_2O, and the spectra of II–V were recorded in $CDCl_3$.
**$J_{5,6}$ = 8.0 Hz.

the adjacent protons to weak field; this makes it possible to assign the signals of the 1'-, 2'-, and 2''-H protons, determine the spin-spin coupling constants (SSCC), and thus prove the presence of the benzoyl group in the 2' position and of the isopropylidene group in the 3' and 5' positions.

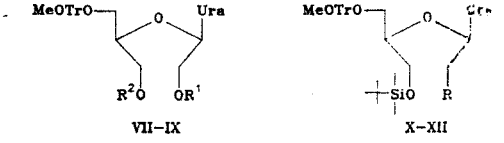
The hydroxymethyl group was converted to a methyl group by chlorination with a mixture of CCl_4 and Ph_3P in DMF [7] with subsequent reduction with tributyltin hydride [8]. While the reduction proceeded smoothly in high yields, chlorination was accompanied by side reactions: formylation [7] and deacetonation. Unsuccessful attempts to synthesize chloride IVa by refluxing the 2'-O-tosyl derivative of IIa with LiCl in DMF were reported in [5]. The only isolated product was 2',3'-seco-2'-deoxy-2'-chlorouridine [5]. The transition from 2'-chloro derivatives IVa, b to deoxynucleosides Va, b is accompanied by a strong-field shift of the signals of the 2'-H protons and a change in their multiplicity.

After acidic hydrolysis of the isopropylidene group, the desired 2',3'-seco-2'-deoxyuridines VIa, b were isolated by means of chromatography on silica gel. The structures of the synthesized compounds were confirmed by elementary analysis.

The circular dichroism (CD) spectra of Ia, b and VIa, b (Fig. 1) coincide in form and amplitude but are opposite in sign; this constitutes evidence for the optical purity of the acyclic derivatives. A large negative Cotton effect at 240-250 nm is characteristic for the R isomers Ia and VIa.

The synthesized enantiomers Ia, b and VIa, b have one optically active center at $C_{(1')}$. For retention of the chiral character at $C_{(4')}$ one must protect the 5'-OH group in the starting nucleoside prior to periodate oxidation and reduction with sodium borohydride. The synthesis of partially protected nucleosides VII was previously accomplished in [9]. Chiral derivatives of adenosine of this sort have been used for the synthesis of oligonucleotides [10]. A similar principle was also used in the present research.

Treatment of derivative VII with 1.3 equivalents of a solution of tert-butyldimethylsilyl chloride in pyridine led to a mixture of bis derivative VIII, monosubstituted IX and X, and starting VII, which were separated by chromatography on silica gel and were eluted from the column in the same order as in the case of 2',3'-seco-adenosine derivatives [10].



VII–IX X–XII

VII $R^1=R^2=H$; VIII $R^1=R^2=\overset{|}{\underset{|}{Si}}+$; IX $R^1=\overset{|}{\underset{|}{Si}}+$, $R^2=H$; X R=OH; XI R=Cl; XII R=H

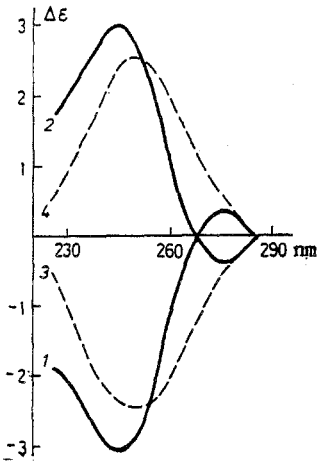


Fig. 1. Circular dichroism (CD) spectra in water at 20°C: 1) Ia; 2) Ib; 3) VIa; 4) VIb.

The successive chlorination of analog X and reduction gave the desired chiral compound XII in satisfactory yield.

The chlorination was carried out in pyridine in order to avoid side detritylation [11]. In addition to signals of protons of the protective groups, signals of protons of a uracil residue, 1'-H signals, and other signals of the carbohydrate residue are observed in the PMR spectra of VII-XII (see Table 2). The PMR spectrum of XII contains a doublet signal at 1.42 ppm and a quartet 1'-H signal with SSCC 5.8 Hz; as in the case of analogs Va, b and VIa, b, this proves the presence of a methyl group.

One should note the interesting stereochemical possibilities of synthone XII that arise as a consequence of free rotation about the $C_{(4')}$—$O_{(4')}$ and $C_{(1')}$—$O_{(4')}$ bonds. Derivative XII is the starting compound for the synthesis of analogs of oligonucleotides.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Varian XL-100 spectrometer with tetramethylsilane (TMS) as the internal standard. In the case of solutions in D_2O the measurements were made relative to tert-butyl alcohol (taken as 1.27 ppm) and were scaled relative to TMS.

The UV spectra of solutions in water (pH 7 and 13) were recorded with a Specord UV-vis spectrophotometer (East Germany). The UV spectra of analogs Ia, b and VIa, b coincided with the spectra of uridine. The CD spectra were recorded with a Jobin-Yvon Dichrograph III (France) using a 1-cm cuvette at a sensitivity of $5 \cdot 10^{-6}$. The melting points were determined with a TP apparatus (USSR) and were not corrected.

Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in the following systems: $CHCl_3$ (A), $CHCl_3$—EtOH (97.5:2.5) (B), $CHCl_3$—EtOH (95:5) (C), $CHCl_3$—EtOH (9:1) (D), $CHCl_3$—EtOH (4:1) (E), $CHCl_3$—EtOH (3:1) (F), and PhMe—EtOAc (1:1) (G). Silica gel L 40/100 (Czechoslovakian SSR) was used for column chromatography.

1-(α-D-Arabinofuranosyl)uracil was obtained from methyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside [12] by successive acetolysis and condensation with bis(trimethylsilyl)uracil in the presence of $F_3CSO_2OSiMe_3$ by the Vorbrüggen method [13]. After debenzoylation, the nucleoside was obtained in 42% overall yield in the form of a slowly crystallizing syrup, the characteristics of which were identical to those presented in [3].

1-[1,5-Dihydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl]uracil; 2',3'-seco-β- and -α-Uridine (Ia, b). A 2.35-g (11 mmole) sample of $NaIO_4$ was added in portions with stirring at 20°C to a solution of 2.44 g (10 mmole) of uridine or 1-(α-D-arabinofuranosyl)uracil in 30 ml of water, after which the solution was maintained for 0.5 h at 20°C (for uridine) or for 4 h at 20°C (for the α anomer). Alcohol (100 ml) was added, and the precipitate was removed by filtration and washed with alcohol. A 380-mg (10 mmole) sample of $NaBH_4$ was added in portions with stirring to the combined filtrates, and the suspension was stirred for 20 min at

TABLE 2. PMR Spectra of the Synthesized VIII–XII in $CDCl_3$ at 33°C

Compound	Chemical shifts, δ, ppm (J, Hz)								
	NH (bs)	6-H* (d)	5-H** (dd)	1'-H ($J_{1',2'}$; $J_{1',2''}$)	2',2''-H	3',3'',4'-H	5',5''-H (m)	t-Bu (s)	Me*** (s)
VIII	8,01	7,39	5,56	5,90 t (4,7; 4,7)	3,80—3,53m		3,14	0,85	0,02
IX	8,54	7,34	5,51	5,81 t (5,2; 5,2)	3,82—3,54m		3,19	0,88	0,07
X	8,32	7,40	5,52	5,85 t (5,0; 5,0)	3,80—3,57m		3,16	0,86	0,04
XI	8,97	7,52	5,58	6,19 t (4,7; 4,7)	3,84—3,62m		3,22	0,90	0,06
XII	8,47	7,38	5,52	6,03 q (5,8)	1,42 d	3,80—3,46 m	3,12	0,86	0,03

*$J_{5,6}$ = 8.0 Hz.
**$J_{5,NH}$ = 2.0 Hz.
***Signals of the protons of the MeOTr group: 7.10-7.40 m (12H), 6.76 d (2H, 8.7), 3.78 s (3H).

20°C. The mixture was then treated to pH 7 with 30% AcOH and evaporated to dryness in vacuo, and the residue was chromatographed with a column packed with 50 g of silica gel in system F. The products were obtained in the form of a viscous syrup with R_f 0.11 (E). The yield of R isomer Ia was 89%, and the yield of the S isomer was 86%.

1-[4',5-O-Isopropylidene-1,5-dihydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl]uracil; 3',5'-O-Isopropylidene-2',3'-seco-β- and -α-uridine (IIa, b). A solution of 2.5 g (10 mmole) of nucleoside Ia or Ib in 30 ml of DMF mixed with 12 ml of acetone dimethylacetal and 0.1 g of p-toluenesulfonic acid monohydrate was heated for 1.5 h at 70°C, after which the mixture was neutralized with 10% $NaHCO_3$ and evaporated to dryness in vacuo, and the residue was chromatographed with a column packed with 50 g of silica gel. The column was washed with system C and eluted with system D. The yields of IIa, b were 70–80% (slowly crystallizing syrup). The product had mp 131–132°C and R_f 0.70 (E).

1-[1-Benzoyloxy-4',5-O-isopropylidene-4-hydroxymethyl-5-hydroxy-3-oxa-2(R and S)-pentyl]-uracil; 2'-O-Benzoyl-3',5'-O-isopropylidene-2',3'-seco-β- and -α-uridine (IIIa, b). A 100-mg sample of benzoyl cyanide and 0.14 ml of NEt_3 were added to a solution of 143 mg (0.5 mmole) of nucleoside IIa or IIb in 5 ml of dioxane. After 3 h at 20°C, the solution was evaporated to dryness, and the residue was chromatographed with a column packed with 10 g of silica gel. The column was washed with system A and eluted with system B. The yields of IIIa, b were 92–95% (syrup). The product had R_f 0.64 (C). Found: C 58.1; H 5.5; N 7.0% (R isomer IIIa); C 58.0; H 5.4; N 7.0% (S isomer IIIb). $C_{19}H_{22}N_2O_7$. Calculated: C 58.4; H 5.7; N 7.2%.

1-[4',5-O-Isopropylidene-5-hydroxy-4-hydroxymethyl-1-chloro-3-oxa-2(R and S)-pentyluracil; 3',5'-O-Isopropylidene-2'-deoxy-2'-chloro-2',3'-seco-β- and -α-uridine (IVa, b). A 1.04-g (4 mmole) sample of Ph_3P and 0.6 ml (6 mmole) of CCl_4 were added to a solution of 572 mg (2 mmole) of nucleoside IIa or IIb in 10 ml of dry DMF, after which the solution was maintained for 16 h at 20°C. It was then evaporated to dryness in vacuo, and the residue was chromatographed with a column packed with 30 g of silica gel. The Ph_3PO was initially eluted with system A, after which the product (IVa, b) was eluted with system B. The product was obtained in 45–50% yield (syrup) and had R_f 0.29 (C). Found: C 46.9; H 5.3; N 9.0% (R isomer IVa); C 47.0; H 5.4; N 8.9% (S isomer IVb). $C_{12}H_{17}ClN_2O_5$. Calculated: C 47.3; H 5.6; N 9.2%.

1-[4',5-O-Isopropylidene-5-hydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl]uracil; 3',5'-O-Isopropylidene-2'-deoxy-2',3'-seco-β- and -α-uridine (Va, b). A solution of 0.3 g (1 mmole) of nucleoside IVa or IVb, 0.8 ml (3 mmole) of tributyltin hydride, and 20 mg of α,α'-azobisisobutyronitrile in 10 ml of dry toluene was refluxed for 2 h. In accordance with the TLC data in system G, the reaction was judged to be complete with respect to R_f 0.13 (for the starting IVa, b) and R_f 0.08 (for products Va, b). The solution was evaporated in vacuo, and the residue was chromatographed with a column packed with 20 g of silica gel. The column was washed with system A and eluted with system B. The yields of Va, b were 80–90% (slowly crystallizing syrup). The product had mp 69–70°C and R_f 0.29 (C). Found: C 53.2; H 6.6; N 10.4% (R isomer Va); C 53.0; H 6.5; N 10.2% (S isomer Vb). $C_{12}H_{18}N_2O_5$. Calculated: C 53.3; H 6.7; N 10.4%.

1-[5-Hydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl]uracil; 2'-Deoxy-2',3'-seco-β- and -α-uridine (VIa, b). A solution of 0.27 g (1 mmole) of nucleoside Va or Vb in 10 ml of 75%

acetic acid was heated for 1 h at 80°C, after which it was evaporated in vacuo. The residue was evaporated with alcohol (five 10-ml portions) and chromatographed with a column packed with 10 g of silica gel. Products VIa, b were eluted with system D and were obtained in 77-80% yields. The product had mp 142-144°C (acetone) and R_f 0.03 (C). Found: C 47.0; H 6.1; N 12.2% (R isomer VIa); C 47.2; H 6.0; N 12.1% (S isomer VIb). $C_9H_{14}N_2O_5$. Calculated: C 47.0; H 6.1; N 12.2.

1-[1-tert-Butyldimethylsilyloxy-4(R)-tert-butyldimethylsilyloxymethyl-5-(p-monomethoxytrityloxy)-3-oxa-2(R)-pentyl]uracil (VIII), 1-[1-tert-Butyldimethylsilyloxy-5-(p-monomethoxytrityloxy)-4(S)-hydroxymethyl-3-oxa-2(R)-pentyl]uracil (IX), and 1-[4(R)-tert-Butyldimethylsilyloxymethyl-5-(p-monomethoxytrityloxy)-1-hydroxy-3-oxa-2(R)-pentyl]uracil (X). A solution of 2.6 g (5 mmole) of nucleoside VII [9], 0.98 g (6.5 mmole) of tert-butyldimethylsilyl chloride, and 0.68 g (10 mmole) of imidazole in 20 ml of dry pyridine was maintained for 16 h at 20°C, after which 1 ml of methanol was added, and the mixture was evaporated to dryness in vacuo. The residue was dissolved in 100 ml of chloroform, and the organic layer was washed successively with 20 ml of 10% $NaHCO_3$ and 20 ml of water, dried with Na_2SO_4, and filtered. The filtrate was evaporated to dryness, and the residue was evaporated with toluene (two 10-ml portions) and chromatographed with a column packed with 100 g of silica gel in system A. Elution gave, initially, 0.7 g (19%) of bis derivative VIII (syrup) with R_f 0.81 (B). Found: C 65.4; H 7.5; N 3.6%. $C_{41}H_{58}N_2O_7Si_2$. Calculated: C 65.9; H 7.8; N 3.8%. Elution then gave 1.05 g (33%) of 2'-substituted IX with mp 139-141°C and R_f 0.35 (B). Found: C 66.5; H 7.2; N 4.2%. Subsequent elution gave 0.9 g (28%) of 3'-substituted X (syrup) with R_f 0.25 (B). Found: C 66.0; H 6.7; N 4.1%. $C_{35}H_{44}N_2O_7Si$. Calculated: C 66.4; H 7.0; N 4.4%. Elution with system B gave 0.5 g (19%) of starting VII with R_f 0.04 (B).

1-[4(R)-tert-Butyldimethylsilyloxymethyl-5-(p-monomethoxytrityloxy)-1-chloro-3-oxa-2(R)-pentyl]uracil (XI). A solution of 0.63 g (1 mmole) of X, 0.52 g (2 mmole) of Ph_3P, and 1 ml of CCl_4 in 10 ml of dry pyridine was maintained for 16 h at 20°C, after which 1 ml of MeOH was added to the mixture, and the solution was evaporated to dryness in vacuo. The residue was evaporated with toluene (three 10-ml portions) and chromatographed with a column packed with 30 g of silica gel in system A to give 300 mg (46%) of XI (syrup) with R_f 0.10 (A). Found: C 64.1; H 6.4; N 4.1%. $C_{35}H_{43}ClN_2O_6Si$. Calculated: C 64.6; H 6.7; N 4.3%.

1-[4(R)-tert-Butyldimethylsilyloxymethyl-5-(p-monomethoxytrityloxy)-3-oxa-2(R)-pentyl]-uracil (XII). A mixture of 0.3 g (0.46 mmole) of XI, 0.4 ml (1.5 mmole) of tributyltin hydride, and 10 mg of α,α'-azobisisobutyronitrile in 10 ml of toluene was refluxed for 3 h and evaporated to dryness in vacuo. The residue was chromatographed with a column packed with 10 g of silica gel in system A to give 0.25 g (88%) of XII with R_f 0.11 (A) (syrup). Found: C 67.8; H 7.0; N 4.3%. $C_{35}H_{44}N_2O_6Si$. Calculated: C 68.2; H 7.2; N 4.5%.

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