ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF 1,5-DIHYDROXY-3-OXA-2-PENTYL DERIVATIVES OF NUCLEIC BASES

S. G. Zavgorodnii, E. V. Efimtseva,
S. N. Mikhailov, T. L. Tsilevich,
A. É. Yavorskii, and V. L. Florent'ev

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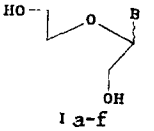
A convenient method for the synthesis of 1,5-dihydroxy-3-oxa-2-pentyl derivatives of nucleic bases, which consists in the condensation of trimethylsilyl derivatives of nucleic bases with 1,2,5-triacetoxy-3-oxapentane in the presence of $SnCl_4$, is proposed. Optically active derivatives – (R)- and (S)-1-(1,5-dihydroxy-3-oxa-2-pentyl)uracil, respectively – were obtained by periodate oxidation of α-L- and α-D-arabinopyranosyluracil.

The attention of chemists engaged in research on the synthesis of antiviral preparations has lately been riveted on acyclic analogs of nucleosides. Although the theoretical substantiation of the activity of this class of compounds was published more than 10 years ago [1], practical interest in it intensified after the antiviral activity of compounds such as 9-(4-hydroxy-2-oxabutyl)guanine (acyclovir), 9-(2,3-dihydroxypropyl)adenine (DHPA), 9-(3-hydroxymethyl-4-hydroxy-2-oxabutyl)guanine (BIOLF-62), and a number of others had been demonstrated (see [2, 3]).

The present communication is devoted to the synthesis of 1,5-dihydroxy-3-oxa-2-pentyl derivatives Ia-f of nucleic bases, the hydroxyalkyl residue of which models the $C_{(1')}$–$O_{(4')}$–$C_{(5')}$ fragment of the ribose ring of natural nucleosides.

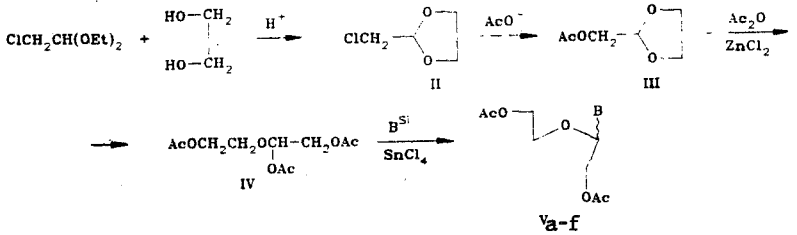


I a-f

Ia B=Ura-1, b Thy-1, c fl[5]Ura-1, d Cyt-1, e Ade-9, f Ade-3

Only the synthesis of (R,S)-9-(1,5-dihydroxy-3-oxa-2-pentyl)adenine (Ie) by alkylation of 6-chloropurine with 1-benzyloxy-2-iodo-5-trimethylsilyloxy-3-oxapentane with subsequent replacement of the chlorine atom by an amino group and hydrogenolysis of the benzyl group [4] and the synthesis of the (R) and (S) enantiomers of analogs of Ie [5], which was realized by periodate oxidation with subsequent reduction by sodium borohydride of 9-β-D-xylopyranosyladenine and 9-α-D-arabinopyranosyladenine, respectively, have been described in the literature.

A more convenient and simpler method for obtaining the racemic analogs Ia-f is described in the present paper:



V a B=Ura-1, b Thy-1, c fl[5]Ura-1, d Cyt-1, e bz[6]Ade-9, f bz[6]Ade-3

Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow 117984. Branch for the Development of Ready-Made Medicinals, Scientific-Research Institute for the Biological Testing of Chemical Compounds, Moscow 117246. T. G. Shevchenko Kiev State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 223-228, February, 1988. Original article submitted July 23, 1986; revision submitted November 5, 1986.

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TABLE 1. Synthesis and Properties of the Acyclic Analogs of Nucleosides

Protected analogs Va-f			Unprotected analogs Ia-f					
Compound	mp, °C (ethanol)	Yield, %	Compound	mp, °C (ethanol)	Yield, %	UV spectrum, λ_{max}, nm (ε)		
						0.1 M HCl	pH 7	0.1 M NaOH
Va	oil	97	I_a	124—125*	84	262,5 (9460)	262,5 (9940)	262,5 (7150); 222,5 (8320)
Vb	112—113	84	Ib	200—201	89	268,0 (9460)	267,5 (9620)	268,0 (7600)
Vc	oil	70	Ic	131—132	85	268,5 (8680)	269,0 (8300)	269,0 (7180); 225,0 (8700)
Vd	175—176	82	Id	143—144*	88	280,0 (12 630)	271,5 (8650); 229,0† (9000)	271,5 (7100); 228,0† (6630); 222,0 (6650)
Ve	oil	16	Ie	150—151	85	257,5 (14 180)	261,0 (14 590)	261,0 (14 590)
Vf	133—134	51	If	164—165	87	305,0† (4500); 295,0 † (5420); 281,0 † (9780); 274,0 (10 900); 217,0 (11 280)	298,0 † (3510); 283,0† (7920); 276,0 (9250); 246,0 † (6500)	305,0 † (2750); 283,0 † (6540); 274,0 (8540); 270,0 † (8450); 219,0 (12 370)

*From ethyl acetate—ethanol.
†Shoulder.

TABLE 2. PMR Spectra of the Acyclic Analogs of Nucleosides*

Compound	Chemical shift,† δ, ppm (SSCC, Hz)						
	6-H or 2-H	5-H or 8-H	2′-H	1′-CH_2	4′-CH_2(m)	5′-CH_2(m)	Other signals
Ia	7,51 d (8,0)	5,58 d (8,0)	5,54 t (6,2)	3,45 m			1′-OH: 5,03 t (5,5); 5′-OH: 4,60 t (5,6)
Va	7,35 d (8,0)	5,73 d (8,0)	5,93 t (6,0)	4,23 m	3,77	4,19	1′-$OCOCH_3$: 2,09 s; 5′-$OCOCH_3$: 2,07 s; 3-H: 9,26 br.s
Ib	7,39 q (0,6)	—	5,64 t (6,1)	3,46 m			5-CH_3: 1,85 d (0,6); 1′-OH: 5,04 t (5,3); 5′-OH: 4,64 t (5,5)
Vb	7,13 q (0,6)	—	5,92 t (6,1)	4,22 m	3,74	4,16	1′-$OCOCH_3$: 2,07 s; 5′-$OCOCH_3$: 2,05 s; 3-H: 9,15 br.s
Ic	7,61 d (6,3)	—	5,62 dt (5,8; 2,0)	3,47 m			1′-OH: 5,05 t (5,5); 5′-OH: 4,62 t (5,4)
Vc	7,44 d (6,2)	—	5,91 dt (5,6; 1,9)	4,23 m	3,80	4,19	1′-$OCOCH_3$: 2,10 s; 5′-$OCOCH_3$: 2,07 s; 3-H: 9,59 br.s
Id	7,50 d (7,6)	5,72 d (7,6)	5,64 t (5,9)	3,48 m			1′-OH: 4,99 t 5 (5,4); 5′-OH: 4,63 t (5,5); 4-NH_2: 7,07 br.s
Vd	7,51 d (7,6)	5,74 d (7,6)	5,85 t (5,9)	4,15 m	3,62	4,08	1′-$OCOCH_3$: 2,10 s; 5′-$OCOCH_3$: 2,08 s; 4-NH_2: 7,16 br.s
Ie	8,21 s	8,10 s	5,67 t (6,1)	4,87 d (6,1)	3,42 m		1′-OH: 5,15 t (5,3); 5′-OH: 4,60 t (5,5); 6-NH_2: 7,18 br.s
Ve	8,71 s	8,17 s	6,09 d.d (5,6; 6,4)	4,53 m	3,73	4,16	1′-$OCOCH_3$: 2,02 s; 5′-$OCOCH_3$: 1,97 s; 6-NH: 9,02 br.s Bz: 7,96—8,04 m
If	8,30 s	8,18 s	5,70 d.d (5,9; 6,8)	3,57 m		3,57	1′-OH: 5,18 t (5,5); 5′-OH: 4,74 t (5,7); 6-NH_2: 6,78 br.s
Vf	8,36 s	8,28 s	7,01 d.d (5,8; 6,6)	4,57 m	3,91	4,23	1′-$OCOCH_3$: 2,02 s; 5′-$OCOCH_3$: 1,96 s; 6-NH: 9,42 br.s Bz: 7,96—8,04 m

*The spectra of Ia-f were obtained from solutions in d_6-DMSO, while the spectra of the other compounds were obtained from solutions in $CDCl_3$.

†The assignment of the signals was made by double resonance.

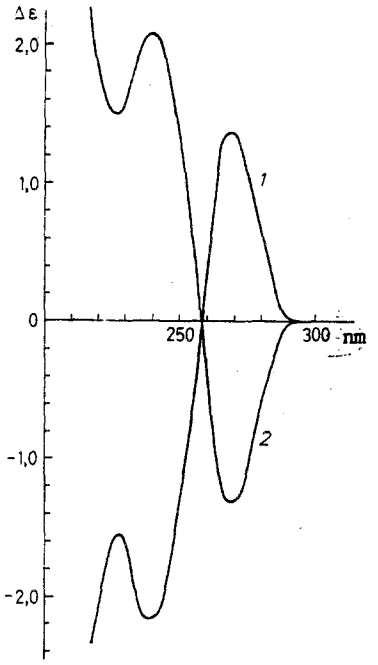


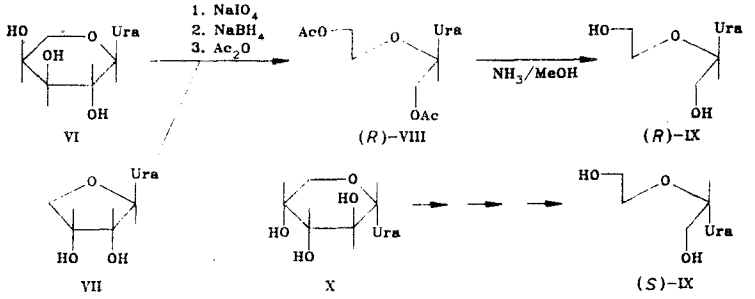
Fig. 1. Circular dichroism spectra of derivatives (R)-IX (1) and (S)-IX (2) in water at 20°C.

Acetate III was obtained by replacement of the halogen atom in 2-chloromethyldioxolane (II) [6] by an acetoxy group with subsequent opening of the dioxolane ring with acetic anhydride in the presence of $ZnCl_2$.

Virtually only 1-alkyl derivatives are formed in the alkylation of trimethylsilyl derivatives of pyrimidine bases, whereas a mixture of the 9- and 3-substituted isomers is formed in the case of 6-N-benzoyladenine. The yields of the compounds obtained are presented in Table 1.

The use of only acyl protective groups simplifies deblocking of the compounds obtained. Treatment of the protected analogs with a methanol solution of ammonia leads to the desired products Ia-f in good yields (Table 1).

Since a chiral center at $C_{(2)}$ is present in the compounds obtained, the optically pure enantiomers, which model the α and β anomers of uridine, were synthesized in the case of 1-(1,5-dihydroxy-3-oxa-2-pentyl)uracil.



Periodate oxidation of 1-(α-L-arabinopyranosyl)uracil (VI) and 1-(β-D-erythrofuranosyl)-uracil (VII) with subsequent reduction with dosium borohydride leads to (R) enantiomer (R)-IX. The same sequence of reactions converts 1-(α-D-arabinopyranosyl)uracil (X) to the corresponding (S) enantiomer (S)-IX.

The periodate oxidation is conveniently followed from the change in the PMR spectra. The three compounds VI, VII, and X all give the same dialdehyde as a result of oxidation. The spectrum of this dialdehyde is substantially simpler than the spectra of the starting compounds and consists of doublet and triplet signals (~5.2 ppm) of the protons of the hydrate form of the aldehyde groups and of the AB system (3.68 and 3.61 ppm) of the CH_2 group. In addition, a singlet signal at 8.32 ppm, which corresponds to the formic acid formed in the oxidation, appears in the oxidation of VI and X.

The circular dichroism (CD) spectra of enantiomers (R)-IX and (S)-IX are presented in Fig. 1.

The structures of the compounds obtained were confirmed by the UV (Table 1) and PMR (Table 2) spectra. The UV spectra make it possible to unambiguously establish the site of attachment of the hydroxyalkyl substituent to the nucleic base. The structure of the substituent itself shows up graphically in the PMR spectrum. We note the 2-H triplet and two triplets of hydroxy groups. The latter two signals indicate the presence of two unsymmetrically oriented primary hydroxy groups in the molecules of the compounds obtained.

EXPERIMENTAL

The UV spectra were recorded with a Varian Cary 210 spectrophotometer. The circular dichroism spectra were obtained with a Jobin-Ivon Mark III dichrograph. A Varian XL-100 spectrometer was used to record the PMR spectra. This-layer chromatography (TLC) was carried out on Silufol UV-254 plates in an ethanol–chloroform system (5-20% ethanol) with development in UV light. Silica gel L 40/100 (Czechoslovakian SSR) was used for column chromatography.

The results of elementary analysis (C, H, N) of the compounds obtained differed from the calculated values by no more than 0.3%.

2-Acetoxymethyl-1,3-dioxolane (III). A mixture of 49 g (0.4 mole) of 2-chloromethyl-1,3-dioxolane (II) [6] and 65.6 g (0.8 mole) of anhydrous sodium acetate in 500 ml of absolute DMF was refluxed for 48 h, after which the mixture was cooled and poured into 2 liters of water. The aqueous mixture was extracted with chloroform (four 250-ml portions), the extracts were washed with 250 ml of water and dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was distilled in vacuo to give 26.7 g (45%) of a product with bp 91-93°C (16 mm). PMR spectrum ($CDCl_3$): 5.09 (1H, t, CH), 4.09 (2H, d, J = 4.5 Hz, CH_2), 3.94 (4H, d, CH_2), 2.097 ppm (3H, s, CH_3CO_2).

1,2,5-Triacetoxy-3-oxapentane (IV). A 1-g sample of anhydrous $ZnCl_2$ was added with cooling (with ice water) and stirring to a solution of 14.6 g (0.1 mole) of acetoxydioxolane III in 30 ml of acetic anhydride, after which stirring was continued until the $ZnCl_2$ had dissolved (~1 h), and the resulting solution was allowed to stand at 20°C for 18 h. The mixture was evaporated in vacuo, and the residue was stirred with 200 ml of saturated $NaHCO_3$ solution. The resulting mixture was extracted with chloroform (four 50-ml portions), and the extracts were washed with 50 ml of 10% $NaHCO_3$ solution and water, dried with anhydrous Na_2SO_4, and evaporated. The residue was distilled in vacuo to give 20.4 g (82%) of a product with bp 125-126°C (1 mm). PMR spectrum ($CDCl_3$): 5.95 (1H, t, J = 4.4 Hz, CH), 4.18 (4H, m, 2-CH_2), 3.87 (2H, m, CH_2), 2.12 (3H, s, 2-$OCOCH_3$), 2.08 ppm (6H, s, 1- and 5-$OCOCH_3$).

Alkylation of the Nucleic Bases. A 1.24-g (5 mmole) sample of acetate IV and 0.75 ml (6.5 mmole) of $SnCl_4$ were added successively to a solution of 6 mmole of the trimethylsilyl derivative of the nucleic base, which was obtained by refluxing 6 mmole of the corresponding base with 20 ml of hexamethyldisilazane and 1 ml of trimethylchlorosilane until all of the solid had dissolved, after which the solution was evaporated in vacuo, in 30 ml of absolute acetonitrile, and the resulting solution was maintained at 20°C for 24 h in the synthesis of Va-d and at 20°C for 48 h in the synthesis of Ve and Vf. The solvent was removed in vacuo, the residue was stirred with 100 ml of chloroform, and the resulting mixture was poured into 250 ml of saturated $NaHCO_3$ solution. The aqueous mixture was filtered, the organic layer was separated, and the aqueous layer was extracted with chloroform (five 50-ml portions). The combined chloroform extracts were dried with anhydrous Na_2SO_4 and evaporated, and the residue was dissolved in 2 ml of chloroform and chromatographed with a column (4 by 9.5 cm) packed with silica gel by elution with ethanol–chloroform (1:39) (1:9 in the case of Vd). The fractions containing the reaction product were evaporated to dryness in vacuo, and the residue was crystallized from ethanol. The yields are presented in Table 1, and the PMR spectra are presented in Table 2.

Removal of the Protective Groups. A 1-mmole sample of the protected analog Va-f of the nucleoside was dissolved in 10 ml of a semisaturated (at 0°C) methanol solution of ammonia, and the solution was allowed to stand at 20°C for 16 h. It was then evaporated to dryness in vacuo, and the residue was recrystallized from a suitable solvent (Table 1) to give Ia-f (Tables 1 and 2).

(R)-1-(1,5-Dihydroxy-3-oxa-2-pentyl)uracil [(R)-IX]. A 0.46-g (2.2 mmole) sample of $NaIO_4$ was added in portions with stirring to a solution of 244 mg (1 mmole) of 1-(α-L-arabinopyranosyl)uracil [7] in 8 ml of water, and the solution was stirred at 20°C for 1 h. The solution was then treated with 5 M NaOH (to pH 6-7), 40 ml of ethanol was added, and the mixture was stirred for 15 min. The precipitate was removed by filtration and washed with 20 ml of ethanol. A 76-mg (2 mmole) sample of $NaBH_4$ was added in portions with stirring to the combined filtrate, and the mixture was stirred for 2 h at 20°C. The mixture was then treated with CH_3COOH (to pH 6-7) and evaporated in vacuo, and the residue was evaporated with absolute pyridine (three 10-ml portions), after which 10 ml of absolute pyridine and 5 ml of acetic anhydride were added. The reaction mass was stirred for 16 h at 20°C and then evaporated in vacuo. The residue was distributed between 20 ml of chloroform and 20 ml of water. The organic layer was separated, and the aqueous layer was extracted with chloroform (two 20-ml portions). The combined chloroform extracts were washed successively with saturated $NaHCO_3$ solution and water, dried with anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The residue was dried by evaporation with toluene (two 20-ml portions), dissolved in 1 ml of chloroform, and chromatographed with a column packed with silica gel (30 g) by elution with ethanol–chloroform (1:39). The fractions containing the reaction product were evaporated to give 0.27 g (90%) of acetate (R)-VIII. The PMR spectrum was identical to the spectrum of racemic Va.

A solution of 0.25 g (0.83 mmole) of acetate (R)-VIII in 7 ml of methanol semisaturated with ammonia at 0°C was maintained at 20°C for 20 h, after which it was evaporated to dryness in vacuo, and the residue was recrystallized from acetone to give 162 mg (75%) of product. The physical and spectral characteristics of the compound obtained were the same as those for racemic Ia.

Similarly, but with the use of a 1.1-fold excess of $NaIO_4$, (R)-IX was obtained from 1-(β-D-erythrofuranosyl)uracil [8].

(S)-1-(1,5-Dihydroxy-3-oxa-2-pentyl)uracil was obtained from 1-(α-D-arabinopyranosyl)-uracil via the method described above.

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