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SYNTHESIS OF ENANTIOMERS OF 3',4'-seco-2'-DESOXYTHYMIDINE

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The glycosylation of 1,3,4-tri-O-benzoyl-2-desoxy-β-D-ribopyranose by bis-trimethylsilylthymine in the presence of $SnCl_4$ and $F_3CSO_2OSiMe_3$ was studied. It was shown that the stereo-selectivity and directivity of the reaction are dependent on the choice of catalyst. The 1-(2-desoxy-β- and α-D-ribopyranosyl)-thymines obtained were converted into 3',4'-seco-2'-desoxythymidines.

In a continuation of our investigations on the synthesis of chiral acyclic analogs of nucleosides [1, 2], we synthesized 3',4'-seco-2'-desoxythymidine (preliminary communication, see [3]), a representative of a new class of analogs of 2'-desoxynucleosides without the $C_{(3')}$—$C_{(4')}$ bond.

As starting compound, we chose 1,3,5-tri-O-benzoyl-2-desoxy-β-D-ribopyranose (I), which is readily obtained from 2-desoxy-D-ribose [4]. We studied the condensation of pyranose I with bistrimethylsilylthymine in dichloroethane in the presence of $SnCl_4$ and $F_3CSO_2OSiMe_3$, two of the most frequently used catalysts in nucleoside synthesis [5]. When the reaction is carried out in the presence of $SnCl_4$, a complex mixture of products is formed. By using chromatography and crystallization, two main products IIa and IIIa were isolated and characterized. They are obtained in yields of 36% and 17%, respectively. The complex character of the occurrence of this reaction is probably explained by splitting of benzoic acid to form a glycal, followed by glycosylation. The formation of unsaturated nucleosides of type III has already been observed in the condensation of glycals [6, 7] and 1,3,4,6-tetra-O-acetyl-2-desoxy-D-glucopyranose [8] with trimethylsilyl derivatives of heterocyclic bases in the presence of Friedel—Crafts catalysts. (See scheme on page 780.)

The glycosylation of pyranose I in the presence of $F_3CSO_2OSiMe_3$ led to β- and α-anomers IIa and IVa in a ratio of 1:2.5, in an overall yield of 88%.

It should be noted that the use of the two above glycosylation reaction catalysts leads to different products: In the case of $F_3CSO_2OSiMe_3$, the α-anomer IVa is preferentially formed, while when $SnCl_4$ is used the main product is the β-anomer IIa.

Debenzoylation of compounds IIa-IVa led to high yields of nucleosides IIb-IVb, and subsequent acetylation gave derivatives IIc-IVc.

In the PMR spectra of the unsaturated compounds IIIa-c, a SSCC $J_{2',3'}$ 10.0-10.8 Hz is observed and a long-range SSCC, characteristic of 2-enopyranosides [6, 7]. The negative Cotton effect (CE) in the circular dichroism (CD) spectrum of nucleoside IIIb serves as a proof of the β-anomeric configuration [6, 7].

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TABLE 1. PMR Spectra of Compounds II-VI Synthesized at 33°C[a]

Compound	Chemical shifts δ, ppm									
	NH (av)	6-H (q) / 5-Me (d) ($J_{6,5}$=1.2)		1′-H ($J_{1',2'}$; $J_{1',2''}$)	2′,2″ H ($J_{2'',3'}$; $J_{2'',3'}$)	3′-H ($J_{3',4'}$)	4′-H ($J_{4',5'}$; $J_{4',5''}$)	5′-H ($J_{5',5''}$)	5″-H	remaining signals
IIa	8,42	7,29	1,97	6,21 d d (3,0; 10,0)	2,42 d t[b] 2,23 d d d (3,0; 3,0)	5,95 q (3,0)	5,37 d d d (7,0; 9,0)		4,22 m	8,26—7,34 m (2Bz)
IIb	—	7,61	1,90	5,96 d d (4,2; 9,4)	2,11 m		4,40—3,80 m			—
IIc	8,55	7,12	1,92	5,94 d d (3,5; 10,0)	2,07 m (3,0; 3,0)	5,50 q (3,0)	4,98 d d d (7,0; 9,0)		3,92 m	2,16 s (Ac), 2,01 s (Ac)
IIIa	8,53	7,11	1,94	6,49 m (1,7)	5,94 d d d[c] (10,8)	6,49 m	5,63 m (4,8; 6,5)	4,27 d d (−11,9)	3,94 d d	8,15—7,37 m (Bz)
IIIb	—	7,45	1,87	6,33 m[d] (2,9)	5,99 d d d (10,1)	6,53 m (4,3)	4,30 m (3,2; 3,5)	4,05 d d (−12,5)	3,88 d d d	—
IIIc	8,47	6,99	1,89	6,35 m[d] (2,5)	5,80 d d d (10,0)	6,25 m (3,0)	5,31 m (5,0; 6,0)	4,11 d d (−12,0)	3,75 d d	2,09 s (Ac)
IVa	9,27	7,25	1,95	5,92 d d (6,0; 7,5)	2,35 m	5,61—	5,36 m (1,5; 0,5)	4,37 d d (−13,0)	3,96 d d	8,10—7,31 m (2Bz)
IVb	—	7,69	1,93	5,69 d d (4,0; 9,0)	2,09 m		4,20—3,60 m			
IVc	9,25	7,17	1,94	5,74 d d (6,0; 7,5)	2,06 m	5,23—	5,00 m (2,0; 1,0)	4,11 d d (−13,0)	3,78 d d	2,19 s (Ac), 2,02 s (Ac)
Va, VIa[f]	9,38	7,10	1,92	5,81 d d (6,0; 7,0)	2,08 m	4,13 m	3,64 m		4,13 m	2,04 s (Ac) 2,01 s (Ac)
Vb, VIb[f]	—	7,54	1,94	5,84 t (6,6; 6,6)	2,09 m	3,79—	3,55 m			

a) IIa-IVa, IIc-IVc, Va, VIa in $CDCl_3$, IIb-VIb in D_2O. b) $J_{2',2''}$ − 14.0. c) $J_{2',4'}$ − 1.5. d) $J_{1',3'}$ − 2.0; $J_{1',4'}$ − 1.0; $J_{2',4'}$ − 1.1; $J_{3',5''}$ − 0.9, e) $J_{1',3'}$ − 2.0) $J_{2',4'}$ − 1.5. f) For Va, b, VIa, b, numeration of atoms accepted for nucleosides was used.

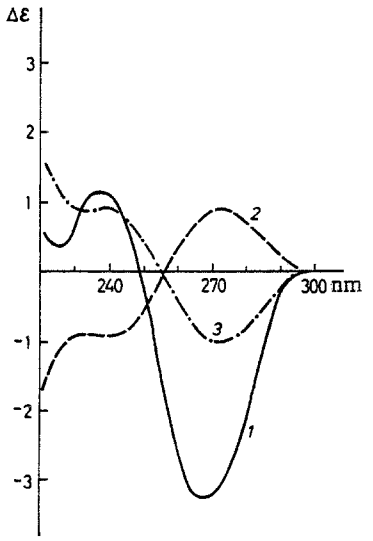
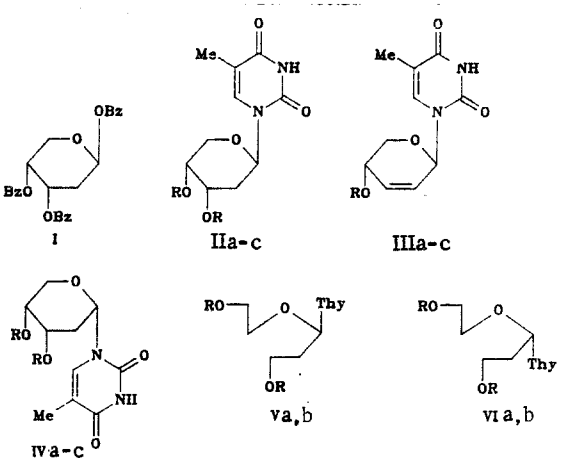


Fig. 1. CD spectra in water at 20°C: 1) nucleoside IIIb; 2) compound Vb; 3) compound VIb.



II—IVa R=Bz; b R=H; c R=Ac; V, VI a R=Ac; b R=H

The oxidation of the diastereomers IIb and IIc by sodium periodate leads to the formation of enantiomeric dialdehyde derivatives. Their PMR spectra coincide and becomes noticeably simplified [10]. The aldehyde derivatives, without being isolated, were reduced by $NABH_4$, and the acyclic analogs obtained were isolated by chromatography on silica gel in the form of diacetates Va and VIa. After diacetylation, the acyclic nucleosides Vb and VIb were synthesized to give good yields. The PMR spectra of nucleosides Vb and VIb and their acetates Va and VIa coincide, while the CD spectra were mirror images, which indicates the optical purity of the compound synthesized.

EXPERIMENTAL

The PMR spectra were recorded on a Varian XL-100 spectrometer for solutions in $CDCl_3$, using TMS as internal standard. For solutions in D_2O, the measurements were carried out relative to tert-butanol (accepted as 1.27 ppm) and were converted relative to TMS. The ^{13}C NMR spectra were obtained on a Bruker-Physik WP-60 spectrometer at 15.08 MHz, and the chemical shifts were measured relative to TMS. The UV spectra were run on a Specord UV-vis spectrophotometer in water. The CD spectra were recorded on a Jobin—Vyon Dichrograph III (France), using 1 cm cuvettes with a sensitivity of $5 \cdot 10^{-6}$. The melting points were determined on a TP apparatus (USSR), and were not corrected.

The TLC was carried out on Silufol UV-254 plates in systems $CHCl_3$ (A); $CHCl_3$–EtOH, 95:5 (B); $CHCl_3$–EtOH, 4:1 (C). A silica gel L 40/100 (CSSR) was used for the column chromatography.

1-(3,4-Di-O-benzoyl-2-desoxy-β-D-ribopyranosyl)thymine (IIa) and 1-(4-O-Benzoyl-2,3-dideoxy-β-D-glyceropent-2-enopyranosyl)thymine (IIIa). A suspension of 1 g (8 mmoles) of thymine in 10 ml of dry pyridine and 10 ml of hexamethylidisilazane is boiled to complete dissolution (~3 h), and the solution is evaporated in vacuo to dryness. The residue is distilled with dry toluene (2 × 10 ml), 40 ml of dry 1,2-dichloroethane, 2.8 g (6.25 mmoles) of benzoate I and 0.9 ml (7.5 mmoles) of $SnCl_4$ are added. The solution is held for 2 h at 20°C. A 50 ml portion of chloroform and 20 ml of 10% $NaHCO_3$ are added, the mixture is stirred for 20 min at 20°C, filtered through Hyflo Super Cel, and the precipitate is washed with 20 ml of chloroform. The organic layer is separated, washed with water, dried over Na_2SO_4, and filtered. The filtrate is evaporated, and the residue is chromatographed on a column with 100 g of silica gel in system A. The fractions containing the product are evaporated and the residue is crystallized from alcohol. The yield of nucleoside IIa is 1.0 g (36%), mp 224-225°C. R_f 0.37 (B). ^{13}C NMR spectrum ($CDCl_3$): 166.2 (1-C), 166.0 (1-C), 134.0 (1-C), 133.9 (1-C), 130.1 (4-C), 129.1 (2-C), 128.8 (3-C), 129.4 (1-C), (Bz), 165.1 (4-C), 151.1 (2-C), 135.9 (6-C), 111.9 (5-C), 12.5 (Me), 78.4 (1'-C), 68.2 (3'-C), 67.8 (4'-C), 64.7 (5'-C), (2'-C) ppm. Found, %: C 63.7; H 4.7; N 6.2. $C_{24}H_{22}N_2O_7$. Calculated, %: C 64.0; H 4.9; N 6.2.

Further elution by system A leads to 0.85 g of a mixture of products, from which, by crystallization from alcohol, 0.35 g of nucleoside IIIa is obtained. Yield 17%, mp 218-219°C. R_f 0.34 (B). ^{13}C NMR spectrum (DMSO-D_6): 165.3 (1-C), 133.7 (1-C), 129.3 (3-C), 128.9 (2-c) (Bz), 163.9 (4-C), 150.8 (2-C), 137.4 (6-C), 109.1 (5-C), 11.9 (Me), 129.9 (3'-C), 128.4 (2'-C), 76.0 (1'-C), 63.8 (4'-C), 63.5 ppm (5'-C). Found, %: C 61.9; H 4.7; N 8.4. $C_{17}H_{16}N_2O_5$. Calculated, %: C 62.2; H 4.9; N 8.5.

1-(3,4-Di-O-benzoyl-2-desoxy-β-D-ribopyranosyl)thymine (IIa) and 1-(3,4-Di-O-benzoyl-2-desoxy-α-D-ribopyranosyl)thymine (IVa). A solution of bis-trimethylsilylthymine (from 5 mmoles of thymine), 3.5 mmoles of benzoate I in 30 ml of dry dichloroethane and 4 ml of a 1 M solution of $F_3CSO_2OSiMe_3$ in dichloroethane is held for 16 h at 20°C. The treatment is carried in a similar way as in the above procedure. Yield 0.4 g (25%) of nucleoside IIa. Further elution by system A leads to nucleoside IVa. Yield 1.0 g (63%), mp 122-123°C (from alcohol). R_f 0.35 (B). Found, %: C 64.1; H 4.8; N 6.0. $C_{24}H_{22}N_2O_7$. Calculated, %: C 64.0; H 4.9; N 6.2%.

1-(2-Desoxy-β-D-ribopyranosyl)thymine (IIb). A solution (1 mmole) of 0.4 g of nucleoside IIa in 10 ml of 5 M ammonia in methanol is held for 16 h at 20°C, and evaporated in vacuo to dryness. Then 10 ml of water and 10 ml of chloroform are added to the residue. The aqueous layer is evaporated, and the residue is recrystallized from alcohol. Yield, 170 mg (70%), mp 220-221°C. R_f 0.40 (C). mp 222-224°C [9].

1-(2,3-Didesoxy-β-D-glyceropent-2-enopyranosyl)thymine (IIIb) is obtained in a similar way. Yield 76%, mp 171-172°C. R_f 0.57 (C). UV spectrum, λ_{max} (ε) (pH 7): 268 nm (9200); (pH 13): 268 nm (7100). Found: C 53.7; H 5.3; N 12.6. $C_{10}H_{12}N_2O_4$. Calculated, %: C 53.6; H 5.4; N 12.5%.

1-(2-Desoxy-α-D-ribopyranosyl)thymine (IVb) is obtained in a similar way. Yield 88%, mp 223-225°C. R_f 0.32 (C), mp 226°C [9].

1-(3,4-Di-O-acetyl-2-desoxy-β-D-ribopyranosyl)thymine (IIc). A solution of 242 mg (1 mmole) of nucleoside IIb in mixture of 0.5 ml of acetic anhydride and 3 ml of dry puridine is held for 16 h at 20°C. A 1 ml portion of methanol is added, the mixture is evaporated in vacuo to dryness, the residue is distilled with toluene (2 × 10 ml). The product is extracted by chloroform and isolated by chromatography on silica gel. The yield of nucleoside IIc is 86%, mp 210-211°C (ethanol). R_f 0.13 (B), mp 212°C [9].

1-(4-O-Acetyl-2,3-didesoxy-β-D-3-glyceropent-2-enopyranosyl)thymine (IIIc) is obtained in a similar way. Yield 89%, mp 173-174°C. R_f 0.28 (B).

1-(3,4-Di-O-α-D-ribopyranosyl)thymine (IVc) is obtained in a similar way. Yield 85% (syrup). R_f 0.29 (B).

1-[1,6-Dihydroxy-4-oxahex-3(R)-yl]thymine: 3',4'-seco-2'-desoxythymidine (Vb). Sodium periodate (225 mg, 1.05 mmole) is added in portions, with stirring, to a solution of 242 mg (1 mmole) of nucleoside IIb in 8 ml of water. The solution is held for 2 h at 20°C, and 20 ml of ethanol are added, the precipitate is filtered and washed with 10 ml of alcohol. A 38

mg portion (1 mmole) of $NaBH_4$ is added to the filtrates, the mixture is held for 1 h at 20°C, neutralized by 30% AcOH, evaporated in vacuo to dryness, and evaporated with dry pyridine (3 × 10 ml). A 10 ml portion of dry pyridine and 5 ml of acetic anhydride are added to the residue, and the mixture is stirred for 16 h at 20°C. After the usual treatment and chromatography on silica gel, 0.3 g of nucleoside Va are obtained. R_f 0.25 (B). Subsequent deacetylation by an ammonia solution in methanol gives the nucleoside Vb. Yield 0.15 g (61%), mp 115-116°C (from alcohol). R_f 0.30 (C). UV spectrum, λ_{max} (ε), (pH 7): 268 nm (9500); (pH 13): 268 nm (7200). Found, %: C 49.0; H 6.5; N 11.2%. $C_{10}H_{16}N_2O_5$. Calculated, %: C 49.2; H 6.6; N 11.4.

1-[1,6-Dihydroxy-4-oxahex-3(S)-yl]thymine: 3',4'-seco-2'-desoxy-α-thymidine (VIb) was obtained in a similar way. Yield 70%. The scalar characteristics of nucleosides Va, b and VIa, b are identical. Found, %: C 49.0; H 6.4; N 11.1.

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SYNTHESIS, STRUCTURE, AND ACID–BASE CHARACTERISTICS OF ENAMINONES OF THE BARBITURIC ACID SERIES

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Enaminones were obtained by a tricomponent condensation of barbituric acids, aniline and triethyl orthoformate. The acid–base properties, PMR, UV and IR spectra of 5-anilinomethylene- and 1,3-dimethyl-5-anilinomethylenebarbituric acids are discussed. The properties of these compounds conform with a bipolar structure, in which the positive charge is distributed over the exocyclic part of the molecule, while the negative charge is distributed on the β-dicarbonyl fragment of the heterocyclic ring.

Interest in enaminones of the barbituric acid series arose because of their diverse biological activity [1, 2]. These compounds are formed in the reaction of barbituric acids with aniline and triethyl orthoformate [3, 4]. The reaction with an unsubstituted barbituric acid (Ia) was carried out in ethylene glycol at 140°C, and with 1,3-dimethylbarbituric acid (Ib), in boiling ethyl or butyl alcohols. The presence of water in the solvent strongly decreases the yield of the product. (See scheme on top of following page.)

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