1,3,3-Trimethyl-2-methylene-5-benzoylaminomethyl-6-nitroindoline (XV). Benzoylation of indoline XIV is carried out analogously to the acylation of indoline I. The product is purified by reprecipitation from benzene with petroleum ether.

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SYNTHESIS OF 1-β-D-RIBOPYRANOSYL- AND RIBOFURANOSYL-6-NITROINDOLE AND INDOLINE FOR THE PHOSPHOTRIESTER OLIGONUCLEOTIDE SYNTHESIS

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The glycosylation reaction of 6-nitroindoline with 5-tritylribose led to the synthesis of the 1-β-D-ribofuranoside and 1-β-D-ribopyranoside of 6-nitroindoline, the dehydrogenation of which resulted in the isolation of the corresponding 1-β-D-ribopyranoside and 1-β-D-ribofuranoside of 6-nitroindole; the last with protecting groups are suitable for utilization in oligonucleotide synthesis.

The modification of natural nucleosides at the heterocyclic base or the carbohydrate residue and the synthesis of nucleosides by the glycosylation of various heterocycles give rise to nucleosides which are not naturally occurring and possess a broad spectrum of biological properties.

The chemical conversions of the monomeric artificial nucleosides in the metabolic cellular stock have been studied in detail. Less is known about their properties in the composition of the polynucleotide chain of RNA or DNA, and the character of the structural and functional changes in the nucleic acids containing artificial analogs of the nucleosides [1-7].

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TABLE 1. PMR Spectra of Compounds (II)-(IX)

Compound	δ, ppm (J, Hz)													
	indole and indoline							Ribose						
	H-Ph	7-H	6-H	4-H	3-H 1H (2H)	2-H 1H (2H)	CH₃ (Ac) 6H, 9H, S	1'-H	2'-H	3'-H	4'-H	5'-H (2H) H_a	5'-H (2H) H_b
II	19 H 7,80 ... 7,15				2,90 t ($J_{3,2}$=11,5)	3,64 t (J=11,5)	2,087; 2,035	5,57 broad s	5,39 m	—	4,092 ... 4,066 m	3,33 t ($J_{5',4'}$=2,5)		
III	19 H 7,80 ... 7,24				6,60 d (J=3,0)	7,80 ... 7,24 (19H)	2,11; 1,97	6,00 ... 5,94 d ($J_{1',2'}$=7,0)	5,63 m	4,35 ... 4,20 m (2H)		3,40 m (J=3,0)		
IV	—	7,25 d ($J_{7,5}$=2,0)	7,35q (J=2,0; $J_{5,4}$=6,0)	7,08 d (J=6,0)	6,60d (J=3,0)	7,40 d (J=3,0)	2,10; 2,00	6,15 d (J=5,0)	5,75 t ($J_{2',1'}$ = $J_{2',3'}$=5,0)	5,35 t (J=5,0; $J_{3',4'}$=3,5)	4,00m	3,85 m(J=3,0)		
V	—	7,25d ($J_{7,5}$=2,0)	7,35 q (J=2,0; $J_{5,4}$=6,0)	7,08 d (J=6,0)	6,60d (J=3,0)	7,40d (J=3,0)	2,10; 2,05; 1,89	6,20 d (J=5,5)	5,75t ($J_{2',1'}$ = $J_{2',3'}$=5,0)	5,35 t (J=5,0; $J_{3',4'}$=3,5)		4,18 ... 4,03 m (3H)		
VI	—	7,30 ... 7,15 m	7,45 q (J=7,0; J=3,0)	7,30 ... 7,15 m	2,90t (J=12,0)	3,60 t (J=12,0)	2,10; 1,95	6,17 s	5,75 t ($J_{2',1'}$ = $J_{2',3'}$=5,0)	5,35 t (J=5,0; $J_{3',4'}$=3,5)	4,05 m	3,85 m (J=3,0)		
VII	—	7,25 broad s	7,25 q (J=2,5; J=7,0)	7,15d (J=7,0)	2,90 t (J=12,0)	3,60 t (J=12,0)	2,02; 1,94	5,80 d (J=6,0)	4,70 dd (J=6; J=3,0)	5,06 q (J=3,0; J=3,0)	4,25 m ($J_{4',3'}$ = $J_{4',5'}$=3,0; $J_{4',OH\text{-}4'}$=5,0)	4,05 dd ($J_{5'a,4'}$=3,0) ($J_{5'a,5'b}$=10,0)	3,90 dd ($J_{5'b,4'}$=3,0)	
VIII	—	7,30	7,45	7,15d	6,70 d (J=3,0)	7,40 d (J=3,0)	2,00; 1,95; 1,90	6,00 d (J=6,0)	5,00 dd (J=6,0; J=3,0)	5,25 ... 5,10 m (2H)		4,05dd ($J_{5'a,4'}$=3,0) ($J_{5'a,5'b}$=10,0)	3,90dd ($J_{5'b,4'}$=3,0)	
IX	—	7,15 ... 7,00 m	7,40q (J=7,0; J=3,0)	7,15 ... 7,00 m	6,70 d (J=11,0)	3,45 t (J=11,0)	—	6,00 d (J=5,0)	4,60 t (J=5,0)	4,45 t (J=3,5)	4,25 q (J=3,5; J=3,2)	3,90dd (J=3,2; J=12,5)	3,75 dd (J=3,2; J=12,5)	

TABLE 2. ^{13}C NMR Spectrum of Compounds (IV)-(VII)

Compound	δ, ppm														
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	O ‖ —C—	O ‖ —C—CH_3
IV	130,0	104,6	120,9	115,9	143,5	106,9	134,0	134,0	86,8	73,5	71,2	83,0	61,9	—	20,8; 20,6
V	125,0	104,8	121,1	116,1	—	106,9	—	129,2	86,8	73,3	70,7	80,2	63,2	—	29,9
VI	46,1 t	27,9 t	124,5 d	115,2 d	148,3 s	102,2 d	150,9 s	138,2 s	80,5 d	66,8 d	65,9 d	70,9 d	65,4 t	169,6; 170,9	20,5; 20,8
VII	45,8 t	27,9 t	124,5 d	115,2 d	148,3 s	102,2 d	150,9 s	138,2 s	87,1 d	70,9 d	70,0 d	80,9 d	62,3 t	169,6; 170,9	20,5; 20,8

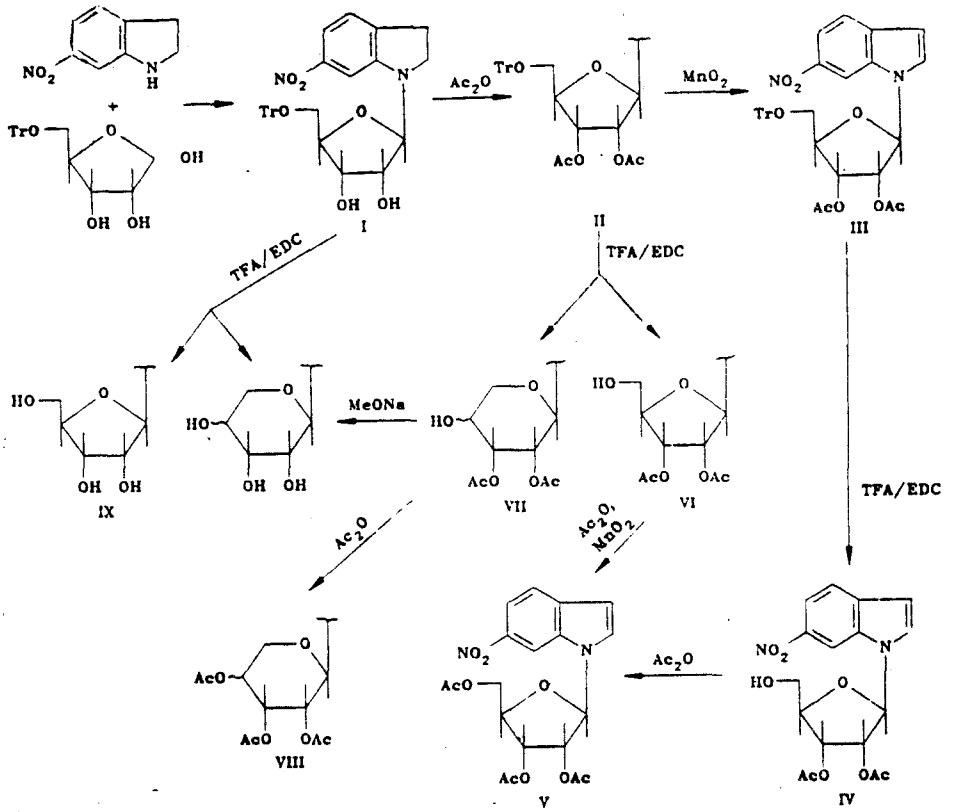
It was of interest to attempt the introduction of an artificial nucleoside of ribose and the tridesaza analog of purine [indole (particularly its 6-nitro derivative)] into the composition of oligonucleotides. The choice of the indole was determined by the high physiological activity of indole derivatives and the comparative stability of its 5- and 6-nitro derivatives. It was proposed to accomplish the introduction of the indole nucleoside into the composition of the synthetic oligonucleotides and DNA fragments by the isolation from it of 1-(5'-dimethoxytrityl-2'-O-acetyl-3'-(4-chlorophenyl-2-cyanethylphosphate)-β-D-ribofuranosyl)-6-nitroindole – the monomer synthon – in the phosphotriester oligonucleotide synthesis.

For the isolation of the 6-nitroindole nucleoside, we ribosylated 6-nitroindoline with 5-O-trityl-D-ribofuranose with the subsequent dehydration of the indoline derivative by the method of [8]. However, in contrast to [8], the glycosylation of the indoline and the detritylation of its derivative were accomplished under the conditions of the continuous distillation of the water formed in the reaction as the azeotrope with benzene. This displaces the equilibrium in favor of the formation of the desired product, the total yields of which comprised 65% for the three stages (glycosylation, acetylation, and dehydrogenation).

The detritylation of compound (III) is easily accomplished by the action of a 2% solution of trifluoroacetic acid in dry dichloroethane at room temperature.

The individual compounds were separated by adsorption column chromatography.

By analogy with 1-(β-D-ribofuranosyl)-6-nitroindole (IV), which may be utilized as a synthon in the phosphotriester oligonucleotide synthesis after a series of conversions, we synthesized the 2',3'-di-O-acetyl derivative of its dihydro analog – **1-β-D-ribofuranosyl-6-nitroindoline (IX). However, it was shown that isomerization with a change in the size of carbohydrate ring of the ribose accompanies the detritylation of compound (II).** The 1-(2',3'-di-o-acetyl-β-D-ribofuranosyl)-6-nitroindoline (VI) was only obtained as a by-product (15% of the overall total yield), whereas the main product of the detritylation was 1-(2',3'-di-O-acetyl-β-D-ribopyranosyl)-6-nitroindoline (VII) (70%). The ratio of the isomers comprises 18:82.



Tr is triphenylmethyl; Ac_2O is acetic anhydride; TFA/EDC is the 2% solution of trifluoroacetic acid in dry dichloroethane

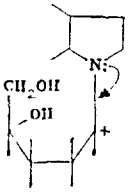
By comparison of the PMR and ^{13}C NMR spectra of compounds (VI) and (VII) (see Table 1), the following picture is obtained. When compound (VI) is O-acetylated and dehydrogenated for the isolation of compound (V), the 4'-H signal only shows insignificant change in the value of the chemical shift; the multiplicity of the signal is unchanged. At the same time, the CSs alter (by 0.3 ppm) and the multiplicity of the 5'-H_a and 5'-H_b signals are changed. Hence, it can be concluded that the 5'-OH undergoes the acetylation; this testifies in favor of the furanose form of the ribose in compounds (V) and (VI).

When compound (VII) is acetylated for the isolation of compound (VIII), the 4'-H signal shows a change in both the CS (by 1 ppm) and the multiplicity of the signal. This indicates the pyranose form of the ribose in compounds (VII) and (VIII).

The value of the CS of the signal of the $C_{(4')}$ atom, which equals 70 ppm, in the ^{13}C NMR spectrum of compound (VII) may serve as a direct demonstration of the pyranose form [9, 10] (see Table 2); the value of the CS of the $C_{(4')}$ atom in the ^{13}C NMR spectrum of compound (V) thereby comprises 80 ppm.

The acetylation and dehydrogenation of compound (VII) led to the isolation of the 6-nitroindoline-tri-O-acetylpyranoside (VIII). Previously described compounds were obtained by the deacetylation of compounds (IV), (V), and (VIII) [8, 11].

The isomerization of the carbohydrate ring of the 1-β-D-ribofuranoside and 1-β-D-ribopyranoside of indole by the action of acidic agents was noted previously [12-14]. Such isomerization was not observed for the 6-nitroindole ribosides; this is evidently associated with the fact that the electron-acceptor nitro group decreases the stabilization of the intermediate carbonium cation by the aglycone. Such stabilization becomes possible in the transition to the nitroindoline in which the electron pair at the nitrogen atom does not participate in the production of the aromatic indole system [13, 14].



The pyranoside (VII), which does not contain a primary hydroxyl, may not be blocked selectively by the tritylation with dimethoxytrityl chloride, and does not therefore present interest for oligonucleotide synthesis.

For the mass-spectrometric analysis of compounds (IV) and (VII), they were subjected to exhaustive silylation prior to the isolation of 1-(5'-trimethylsilyl-2',3'-di-O-acetyl-β-D-ribofuranosyl)-6-nitroindole and 1-(4'-trimethylsilyl-2',3'-di-O-acetyl-β-D-ribopyranosyl)-6-nitroindoline correspondingly. The silylation was performed immediately before the taking of the mass spectrum by the addition of a 10- to 20-fold excess of N,O-bistrimethylsilyltrifluoroacetamide to the solution of the substances in spectroscopic chloroform.

When compound (I) is detritylated, in contrast to compound (II), the ratio of the isomers changes in favor of the furanoside: 60% of the furanoside (IX) and 40% of the pyranoside [11] of 6-nitroindoline are formed. However, the furanoside gradually isomerizes to the pyranoside on storage. Therefore, in order to isolate the synthon of the phosphotriester oligonucleotide synthesis from the furanoside (IX), it should be blocked immediately either at the 5' position with the dimethoxytrityl group (for the isolation of the 3'-terminal unit) [15], or at the 5',3'-positions with the tetra-tert-butoxydisiloxane-1,3-diyl group [16] (for the isolation of the fully substituted nucleoside-3'-phosphate).

EXPERIMENTAL

Individual compounds were isolated by preparative column chromatography on silica gel L-40-100 in the following systems: the 0-33% gradient of acetone in CCl_4 (or benzene) and the 0-10% gradient of methanol in chloroform.

The monitoring of the course of the reaction and the evaluation of the discreteness of the substances were performed using TLC on Silufol UV-254 in the following systems: the 4:1 mixture of chloroform–acetone (A) and the 9:1 mixture of chloroform–methanol (B). Compounds were developed in UV light using a Khromatoskop M instrument as well as by heating or by color reactions, spraying the plates with acidic solutions of anil acetate [17] or 4-bromophenylhydrazine [18]; moreover, the trityl-containing compounds were developed with solutions of strong acids.

The UV spectra of the compounds were taken on a Specol UV-vis spectrophotometer. The PMR and ^{13}C NMR spectra were recorded on a Tesla NMR spectrophotometer (100 MHz). The internal standard was HMDS; the solvent was $CDCl_3$–CD_3OD. The mass spectra were taken on a Ribermag 10-10B mass spectrometer with the resolution of 1000 and the sensitivity of 5 ng. The spectra were taken by the direct introduction of the substance into the ionization source with the programmed heating of 0-250°C and the 70-eV energy of the ionizing electrons.

The data of the elemental analysis for C, H, and N correspond to the calculated data for compounds (I)-(IX).

Activated MnO_2. To the solution of 35 g of $KMnO_4$ in 200 ml of water is added dropwise with stirring and heating of the mixture on a steam bath, the solution of 45 g of $MnSO_4$ and 30 g of NaOH in 200 ml of water. After the completion of the addition, the mixture is maintained on the steam bath for 1 h more. The resulting finely dispersed residue of MnO_2 is filtered off on a glass filter No. 1 and repeatedly washed with distilled water until the complete decolorization of the filtrate and a neutral reaction are obtained. The product is dried at 120°C over P_2O_5; it is ground and stored in a paraffined bottle.

1-(5'-O-Trityl-β-D-ribofuranosyl)-6-nitroindoline (I) ($C_{32}H_{30}N_2O_6$). The mixture of 15 g (39 mmoles) of 5-O-tritylribose with 7.04 g (42.5 mmoles) of 6-nitroindoline in 250 ml of the 1:15 mixture of absolute ethanol–benzene is boiled in a flask of 0.5-liter capacity equipped with a fractionating column attachment.

The water formed in the reaction is simultaneously distilled off with benzene. The reaction mixture is boiled for 5 h; 100 ml of the mixture of absolute ethanol and benzene are added in each case, threefold, and the course of the reaction is monitored by TLC.

The solvents are distilled off in vacuo. The residue (a yellow oil) is purified by adsorption chromatography on 0.75 kg of silica gel with the elution by a gradient of acetone in CCl_4. Compound (I) is isolated; it has R_f 0.20 (A) and 0.60 (B), mp 80-83°C, yield 19.95 g (95%).

The detritylation of compound (I) (2.14 g, 4 mmoles) by the action of a 2% solution of trifluoroacetic acid in dry dichloroethane leads to the 3:2 mixture of the isomers **1-(β-D-ribofuranosyl)-6-nitroindoline (IX) and 1-(β-D-ribopyranosyl)-6-nitroindoline ($C_{13}H_{16}N_2O_6$).** The mixture obtained is purified chromatographically prior to the isolation of two substances. Compound (IX) (the furanoside) has R_f 0.50 (B), mp 194-198°C, and yield 0.6 g (54%), and the pyranoside has R_f 0.45 (B), mp 108-109°C (according to the data of [11]), mp 109-110°C, 115-116°C, and yield 0.43 g (36%). The furanoside (IX) undergoes isomerization to the pyranoside on storage.

1-(5'-O-Trityl-2',3'-di-O-acetyl-β-D-ribofuranosyl)-6-nitroindoline (II) ($C_{36}H_{34}N_2O_8$). Compound (I) (19.36 g, 36 mmoles) is concentrated twice with dry pyridine; the residue is dissolved in 750 ml of dry pyridine prior to the addition of 180 ml of acetic anhydride. The reaction mixture is left for 18 h; it is separated by the addition of 100 ml of water. The mixture is concentrated after 30 min and purified in a chromatography column containing 1 kg of silica gel in the 50:1 mixture of chloroform–methanol prior to the isolation of compound (II) with R_f 0.65 (A) and 0.90 (B), mp 75-85°C, yield 22.40 g (100%).

1-(5'-O-Trityl-2',3'-di-O-acetyl-β-D-ribofuranosyl)-6-nitroindole (III) ($C_{36}H_{32}N_2O_8$). The mixture of 7.46 g (12 mmoles) of compound (II) with 19 g (220 mmoles) of freshly prepared MnO_2 in 200 ml of absolute benzene is boiled for 4 h in a two-necked flask equipped with a mercury shutoff and a fractionating column attachment with continuous stirring. The water formed in the reaction is simultaneously distilled off with benzene. Dry benzene (2 × 100 ml) is added during of this time. The course of the reaction is monitored by TLC. The isolation of the reaction product is accomplished as indicated above. Compound (III) is isolated; it has R_f 0.62 (A) and 0.90 (B), mp 120-145°C, and yield 5.2 g (70%).

1-(2',3'-Di-O-acetyl-β-D-ribofuranosyl)-6-nitroindole (IV) ($C_{17}H_{18}N_2O_8$). Compound (III) (4.96 g, 8 mmoles) is dissolved in 20 ml of dry dichloroethane prior to the addition of 40 mmoles of CF_3COOH in the form of a 2% solution in dry dichloroethane (250 ml). The reaction mixture is neutralized to pH 8.0 by pouring it into 150 ml of an icy 5% solution of $NaHCO_3$ after 2-3 min. The mixture is extracted with chloroform or dichloroethane (2 × 100 ml) and dried over anhydrous Na_2SO_4. After concentration and the chromatographic purification on 250 g of silica gel in the 25:1 mixture of chloroform–methanol, compound (IV) is obtained; it has R_f 0.30 (A) and 0.60 (B), mp 103-194°C, and yield of 1.89 g (85%).

The silylation of compound (IV) in toluene with the 10- to 20-fold amount of N,O-bistrimethylsilylfluoroacetamide leads to isolation of the trimethylsilyl derivative, the mass spectrum of which contains the characteristic ions [m/z (I, %)]: 450 (47), 451 (17) [M, M + 1], 435 (20) [M – Me], 333 (14) [M – Ac, $-SiMe_3$], 331 (10) [M – 30], 315 (20) [M – AcOH, $-SiMe_3$], 289 (70), 290 (39), 291 (13) [S, S + H, S + 2H], 217 (13) [S – $SiMe_3$], 191 (14) [B + 30], 161 (4), and 162 (20) [B, B + H].

The deacetylation of (IV) by the 1 N alcoholic solution of NaOH (10 min, 20°C) leads to the isolation of 1-(β-D-ribofuranosyl)-6-nitroindole. It has yellow crystals with mp 161-163°C (from alcohol) and R_f 0.45 (the 1:1 mixture of benzene–acetone). According to the data of [8], the mp is 164-165°C, R_f 0.43 (the 1:1 mixture of benzene:acetone).

1-(2',3'-Di-O-acetyl-β-D-ribofuranosyl)-6-nitroindoline (VI) and 1-(2',3'-Di-O-acetyl-β-D-ribopyranosyl)-6-nitroindoline (VII) ($C_{17}H_{20}N_2O_8$). Compound (II) (12.44 g, 20 mmoles) is dissolved in 50 ml of dry dichloroethane prior to the addition of 100 mmoles of CF_3COOH (the 2% solution in dichloroethane). The reaction mixture is treated as in the synthesis of compound (IV). Chromatography is performed on 1 kg of silica gel with elution by 10:1

mixture of chloroform–methanol for the isolation of two substances: compound (VI) with R_f 0.27 (A), mp 167-170°C, and yield 1.14 g (15%), and compound (VII) with R_f 0.25 (A), mp 170-174°C, and yield 5.32 g (70%).

The silylation of compound (VII) by the action of N,O-bistrimethylsilyltrifluoroacetamide yields the trimethylsilyl derivatives, the mass spectrum of which contains the following characteristic ions [m/z (I, %)]: 453 (68), 454 (18) [M + H, M + 2M], 394 (6) [M – Me, – Ac], 350 (4) [M – AcOH, – Ac], 334 (4) [M – Me, – Ac, – AcOH], 247 (19) [M – 89], 248 (20), 290 (15) [S + H], 192 (25) [B + 30], and 164 (12) [B + H].

1-(2',3',4'-Tri-O-acetyl-β-D-ribopyranosyl)-6-nitroindoline (VIII) ($C_{19}H_{22}N_2O_9$). This is obtained by the acetylation of 0.7 g (2 mmoles) of compound (VII) under conditions analogous to the conditions of the synthesis of compound (II). Compound (VIII) is isolated; it has R_f 0.40 (A), mp 167-169°C, and yield 0.84 g (100%).

1-(2',3',4'-Tri-O-acetyl-β-D-ribopyranosyl)-6-nitroindole (V) ($C_{19}H_{20}N_2O_9$). This is obtained by the acetylation of 0.56 g (2 mmoles) of compound (IV) or the acetylation and dehydrogenation of 0.76 g (2 mmoles) of compound (VI). These reactions are accomplished under conditions analogous to the conditions of the synthesis of compound (III). Compound (V) is obtained in the form of an oil; it has R_f 0.37 (A) and yield 0.84 g (100%). The deacetylation of (V) with a 1 N alcoholic solution of NaOH yields 1-(β-D-ribopyranosyl)-6-nitroindole; it has R_f 0.60 (methanol) and mp 210-216°C (from alcohol). According to the data of [11], R_f 0.62 (methanol), mp 213.5-215°C.

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