3-β-D-RIBOFURANOSIDES (C-NUCLEOSIDES) OF INDOLES*

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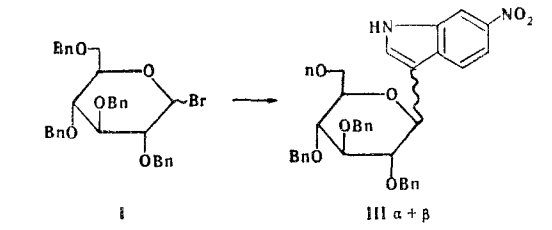
The possibilities of the direct glycosylation of indoles with glycosyl halides that do not contain participating groups in the 2 position were studied. The α and β anomers of the corresponding C-ribofuranosides were obtained by the reaction of indole or its 5-bromo and 5- or 6-nitro derivatives with 2,3-O-isopropylidene-5-O-p-nitrobenzoyl-D-ribofuranosyl bromide in refluxing benzene in the presence of silver oxide and molecular sieves. O-Substituted 3-α-D-ribofuranosides of indoles undergo isomerization to the 3-β-anomers. Mixtures of anomeric 3,2'-deoxy-D-ribofuranosyl-6-nitroindoles and 1,2'-deoxy-D-ribofuranosyl-6-nitroindoles were synthesized. The structures of the compounds obtained were confirmed by data from PMR, IR, UV, and circular dichroism spectroscopy and mass spectrometry.

In contrast to 1-nucleosides of indoles, the methods for the synthesis of which have been well developed, up until now 3-nucleosides of indoles and other condensed pyrrole-containing heterocycles were unknown. In contrast to C-nucleosides of pyrazolo[4,3-d]pyrimidines (antibiotics of the formicin group), C-nucleosides of pyrrolo[3,2-d]pyrimidines (for example, 9-deazaadenosine) have not yet been obtained, and the study of 3-nucleosides of indole can be regarded as the first stage in research in this area.

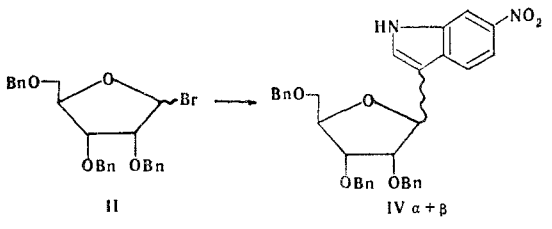
We have previously [2, 3] studied the reaction of indoles with glycosyl halides that contain acyloxy groups in the 2 position. We isolated 1- and 3-α-L-arabinopyranosides of indoles (N- and C-nucleosides); however, the principal reaction products were 1,2-O-[1-(1-indolyl)- or 1-(3-indolyl)]alkylidene derivatives of monosaccharides.

It was concluded that to obtain C- or N-nucleosides of indole by direct glycosylation it is necessary to use agents that do not contain participating groups in the 2 position.

In the present research we started with a study of the reaction of indoles in refluxing benzene in the presence of silver oxide and molecular sieves with 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl bromide (I) [4] and 2,3,5-tri-O-benzyl-D-ribofuranosyl bromide (II) [5].



I III α+β



II IV α+β

Bn=$CH_2C_6H_5$

*See [1] for our preliminary communication.

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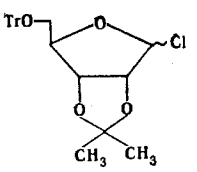
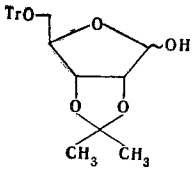
On the basis of I and 6-nitroindole we obtained a mixture of anomeric per-O-benzylated 3-D-glucopyranosyl-6-nitroindoles III in an overall yield of 17%. Similarly, the reaction of 6-nitroindole with II gave mixture IV also in an overall yield of 16%.

Attempts to isolate the individual anomers in both cases were unsuccessful. The PMR spectra of III and IV do not contain signals of indole 3-H protons but do contain signals of the NH group. A broad band of absorption of an NH group at 3400 cm^{-1} is observed in the IR spectra, and this confirms substitution of the indole ring in the 3 position. We did not observe the formation of N-nucleosides in these reactions.

Taking into account the low C-glycosylation yields and the complexities involves in the separation of the anomers and in the removal of the O-benzyl protective group we directed our attention to other glycosylating agents. Although 2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl chloride (V) [6] has been successfully used in the synthesis of C-nucleosides [7], it decomposed when it was refluxed with 6-nitroindole in benzene in the presence of silver oxide and molecular sieves, and we were unable to isolate any products of ribosylation of indole whatsoever. When we carried out the reaction in dry acetonitrile at room temperature, as described in [8], we also were unable to isolate indole ribosides.



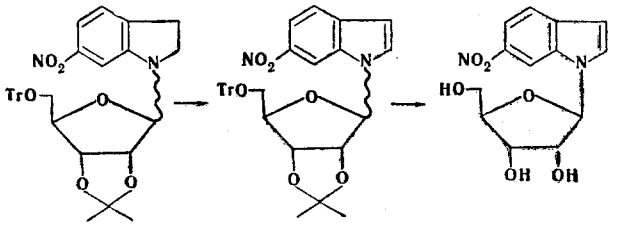
V



VI

Tr=$COC_6H_4CH_3$-p

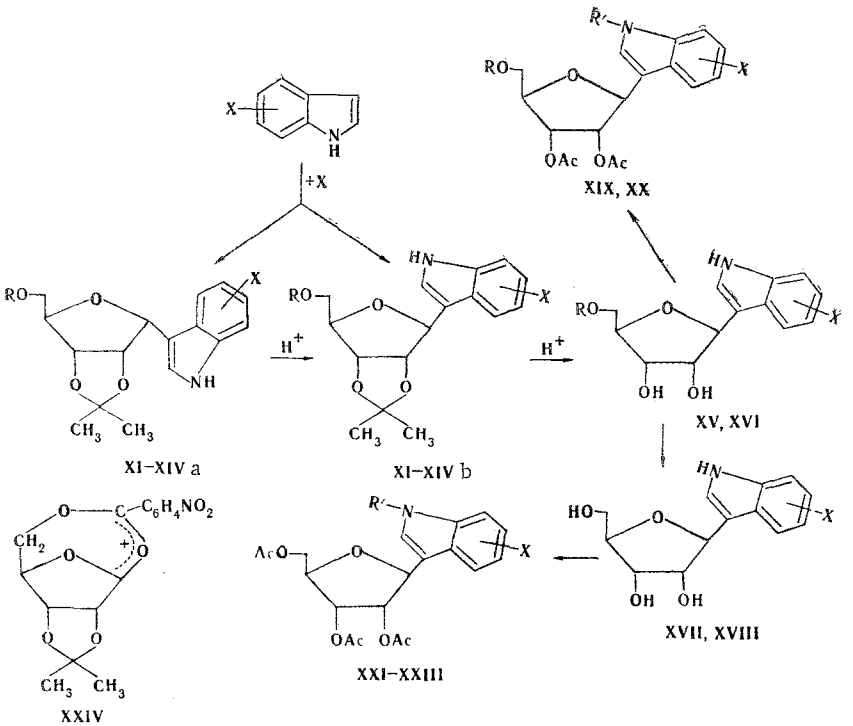
At the same time, 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (VI) has a rather high reactivity and condenses with 6-nitroindoline in refluxing ethanol to give the corresponding riboside VII in 60.5% yield. Nucleoside VIII was obtained in 65% yield by dehydrogenation of VII with active MnO_2 with azeotropic removal of the water in the benzene by distillation, and subsequent removal of the protective groups by the action of 80% acetic acid gave 1-β-D-ribofuranosyl-6-nitroindole (IX) (80%), which, according to the PMR data, was identical to the preparation obtained previously by another method [9].



VII VIII IX

It follows from the PMR spectra of VII and VIII that they are individual anomers; however, we were unable to assign their configuration. It is known that primarily the α anomers are formed when 2,3-O-isopropylidene-D-ribofuranosyl halides are used as the glycosylating agents [10, 11], while the action of acidic or alkaline agents on O-substituted 1-α-D-ribofuranosylindoles leads to the corresponding β anomers [12]. Thus it may be assumed that VII and VIII are the α anomers. In the case of VIII additional evidence in favor of this is provided by its circular dichroism (CD) spectrum (see Table 5), in which a positive Cotton effect ([θ] $2.25 \cdot 10^3$) is observed at 264 nm. A positive maximum is also observed in this region for 3-D-ribofuranosides that have an α configuration.

2,3-O-Isopropylidene-5-O-p-nitrobenzoyl-D-ribofuranosyl bromide (X) [13] proved to be the most successful glycosylating agent for the preparation of C-nucleosides of indole. Mixtures of α and β anomers of O-substituted 3-nucleosides of indole (XI-XIV) were obtained in 38-47% yields in its reaction with indole, 5- or 6-nitroindole, or 5-bromoindole in refluxing benzene in the presence of silver oxide and molecular sieves; the mixtures were separated by preparative thin-layer chromatography (TLC). As expected from general principles for ribofuranosides with a 2,3-O-isopropylidene protective group [10, 11], the α anomers predominate in the mixture of glycosylation products (the α:β ratio is 3:1 for XIII or 4:1 for the remaining pairs of anomers). In addition, the preponderant formation of the



R=$COC_6H_4NO_2$-*p*, Ac=$COCH_3$; XI X=H; XII X=5-Br; XIII, XV, XVII, XIX, XXI X=6-NO_2; XIV, XVI, XVIII, XX, XXII, XXIII X=5-NO_2; XIX R′=Ac; XX R′=H; XXI R′=Ac; XXII R′=H; XXIII R′=Ac

α anomers in the condensation is evidently associated with the effect of the participating 5′-O-acyl group and the contribution of an intermediate structure of the XXIV type. The properties of the compounds obtained are presented in Table 1, and the data from the PMR spectra are presented in Tables 2-4.

A distinct signal of an NH group is observed in the PMR spectra of XIIa, XIIIa, b, and XIVa, b, whereas for XIa, XIb, and XIIb it is overlapped by the signals of the protons of the indole ring and the benzoyl group; the spectra do not contain the signal of the indole 3-H proton at 6.0-7.0 ppm. The IR spectra of nucleosides XI-XIV contain an absorption band at 3400 cm^{-1}, which indicates the presence of an NH group.

The assignment of the configurations of the C-nucleosides obtained (XI-XIV) was made by comparison of the chemical shifts of the anomeric protons, for which the signal of the

TABLE 1. Properties of VIII, XI-XIV, XVI-XIX, XXI, XXXI, and XXXII

Compound	mp, °C (methanol)	$[\alpha]_D^{20}$ (c, chloroform)	Found, %			Empirical formula	Calc., %		
			C	H	N		C	H	N
VIII†	—*	−28,8 (1,0)	72,3	5,7	4,8	$C_{35}H_{32}N_2O_6 \cdot 0{,}25\ H_2O$	72,3	5,6	4,8
XIb†	—*	−17,0 (0,75)							
XIa†	—*	−20,0 (1,0)	61,3	5,0	6,6	$C_{23}H_{22}N_2O_7 \cdot 0{,}75\ H_2O$	61,1	5,2	6,2
XIIb†	—*	−21,5 (1,0)							
XIIa†	—*	−12,0 (1,0)	51,3	4,2	5,6	$C_{23}H_{21}BrN_2O_7 \cdot 1{,}0\ H_2O$	51,6	4,3	5,2
XIIIb	—*	−27,6 (0,5)	57,0	4,4	8,7	$C_{23}H_{21}N_3O_9$	57,1	4,4	8,7
XIIIa	—*	−16,8 (0,5)	56,1	4,7	8,5	$C_{23}H_{21}N_3O_9 \cdot 0{,}5\ H_2O$	56,1	4,5	8,5
XIVb†	—*	−15,0 (1,0)							
XIVa	—*	+3,5 (1,0)	55,2	4,4	8,8	$C_{23}H_{21}N_3O_9 \cdot 1{,}0\ H_2O$	55,1	4,6	8,4
XVI	—*		52,6	4,1	9,2	$C_{20}H_{17}N_3O_9 \cdot 0{,}75\ H_2O$	52,7	4,5	9,6
XVII	152—153	−33,0 (1,0‡)	51,4	5,2	9,3	$C_{13}H_{14}N_2O_6 \cdot 0{,}5\ H_2O$	51,5	5,0	9,2
XVIII	—*	−10,0 (1,0‡)	50,7	5,5	9,1	$C_{13}H_{14}N_2O_6 \cdot 0{,}75\ H_2O$	50,7	5,1	9,1
XIX	155—156	−16,4 (1,0)	54,0	4,1	7,9	$C_{26}H_{23}N_3O_{12} \cdot 0{,}5\ H_2O$	54,0	4,2	7,3
XXI†	—*		53,5	4,8		$C_{21}H_{22}N_2O_{10} \cdot 0{,}5\ H_2O$	53,5	4,9	
XXXI† (XXXII)	119—120	+13,0 (0,5‡)	54,3	4,4	7,5	$C_{27}H_{25}N_3O_{11} \cdot 1{,}5\ H_2O$	54,6	4,7	7,1

*Amorphous substance. †The structure was confirmed by data from the mass spectra. ‡Methanol.

TABLE 2. PMR Spectra of 3-D-Ribofuranosides of Indole and 5-Bromoindole (in $CDCl_3$ at 25°C)

Compound (configuration)	Chemical shifts, δ, ppm (SSCC, Hz)													
	indole ring protons						carbohydrate protons						$COC_6H_4NO_2$	$(CH_3)_2C$ ($\Delta\delta CH_3$)
	H	7-H	6-H	5-H	4-H	2-H	1′-H ($J_{1',2'}$)	2′-H	3′-H	4′-H	5′-H	5″-H		
XIb (β)	8,40					6,95	5,29 (4,2)	5,10				4,30	8,19	1,65 1,37 (0,28)
XIa (α)	8,20					7,08	5,39 (3,2)	5,00				4,35	8,22	1,55 1,34 (0,21)
XIIb (β)	8,36		7,32 a		7,80	—*	5,16 (4,0)	5,00	4,80	4,70		4,46	—*	1,65 1,38 (0,27)
XIIa (α)	8,41	7,15	7,32		7,87	7,11	5,30 (3,2)	5,00				4,28	8,21	1,56 1,34 (0,22)

*The signals are overlapped.

TABLE 3. PMR Spectra of 3-D-Ribofuranosides of 5-Nitroindole (in $CDCl_3$ at 25°C)

Compound (configuration)	Chemical shifts, δ, ppm (SSCC, Hz)													
	indole ring protons					carbohydrate protons								
	H	4-H	6-H	2-H	7-H	1′-H ($J_{1',2'}$)	2′-H	3′-H	4′-H	6′-H	5″-H	$COC_6H_4NO_2$	$(CH_3)_2C$ ($\Delta\delta CH_3$)	OAc (NAc)
XIVb (β)	9,21	8,61	8,00	7,40	7,34	5,26 (3,2)	5,00	4,80	4,80		4,30	8,14	1,66 1,39 (0,27)	
XIV* (α)	8,91	8,76	8,04	7,48	7,35	5,39 (3,2)	5,04				4,30	8,23	1,58 1,34 (0,24)	
XVI*		8,68	7,93	7,42	7,34	5,15 (4,4)	4,90				4,20	8,30—8,10		
XVIII*		8,76	8,01	7,51	7,43	5,08 (6,0)	4,30				3,40			
XX	8,96	8,69	8,08	7,50	7,30	5,74		5,36	4,80		4,40	8,18		2,18
XXII	9,28	8,72	8,08	7,41	7,36		5,32			4,41				2,12 2,16 2,13
XXIII		8,65	8,23	7,68	8,56	5,48		5,20		4,42				2,09 (2,67) 2,16 † 2,12 †

*In CD_3OD. †Three OAc groups.

β anomer is found at stronger field as compared with the signal of the α anomer [14]. The $J_{1',2'}$ values for β nucleosides are usually lower than for the α nucleosides [14], but in our case this principle is not observed. An anomalous ratio of the $J_{1',2'}$ values for pairs of anomers was also noted in the pyrrolopyrimidine [15] and benzimidazole [16] series. Imbach and co-workers have proposed a convenient method for the determination of the anomeric configuration of derivatives of nucleosides that is based on the differences in the chemical shifts of the protons of the two methyl groups of anomeric 2,3-O-isopropylidene-ribofuranosyl nucleosides ($\Delta\delta_{CH_3} < 0.15$ for the α anomer, and $\Delta\delta_{CH_3} > 0.15$ for the β anomer) [17]. This rule is not observed for nucleosides that have an anisotropic substituent in the 5′ position [18]. Imbach's criterion is also violated for our pairs of nucleosides; however, $\Delta\delta_{CH_3}$ in all cases for the α anomers has a lower value than for the corresponding β anomers. This principle was also noted during a study of the isopropylidene derivatives of anomeric C-nucleosides of other types [19]. For all pairs of XI-XIV anomers the 4-H signal for the α anomer is located at weaker field than in the case of the β anomer; in addition, the signals of the methyl groups of the α anomers are more shielded than in the case of the β anomers.

To remove the O-isopropylidene protective group we studied the effect of acidic agents on XI-XIV. For these compounds the addition of a proton is possible both at the oxygen atom

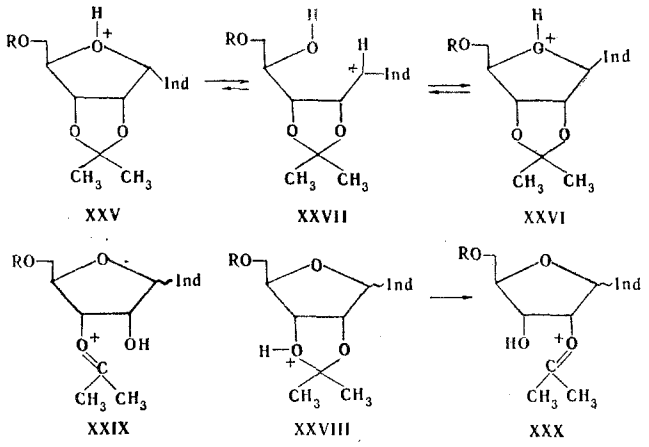
TABLE 4. PMR Spectra of D-Ribofuranosides of 6-Nitroindole (in $CDCl_3$ at 25°C)

Compound (configuration)	Chemical shifts, δ, ppm (SSCC, Hz)													
	indole ring protons					carbohydrate protons						$COC_6H_4NO_2$ [$C(C_6H_5)_3$]	$(CH_3)_2C$ ($\Delta\delta CH_3$)	OAc (NAc)
	NH (3-H)	7-H	5-H	4-H	2-H	1′-H ($J_{1',2'}$)	2′-H	3′-H	4′-H	5′-H	5″-H			
VIII	(6,50)	8,46	8,04	7,61	—*	6,12 (3,2)	4,90	4,80	4,46	3,50	3,10	(7,58—7,12) a	1,64 1,34 (0,30)	
XIIIb (β)	9,32	—*	7,81	7,61	7,46	5,25†	4,96				4,40	8,15a	1,67 1,42 (0,25)	
XIIIa (α)	9,24	—*	7,94	7,71	7,59	5,38 (3,0)	5,08				4,32	8,18a	1,55 1,35 (0,20)	
XV‡	8,44				7,64	5,40	4,24				4,00	8,28		
XVII**		8,32	7,90*	—*	7,67	5,04 (6,2)					3,60			
XIX		9,20	8,05	7,84	7,68	5,56		5,28	4,96		4,48	8,24		2,16 2,13 (2,60)
XXI		9,32	8,17	7,81	7,34		5,30			4,42				2,13†† 2,11 (2,69)

*The signals are overlapped. †The line width at half the height of the wave is 6.0 Hz. ‡In DMSO. **In CD_3OD. ††Three OAc groups.

of the ribofuranose ring and at the oxygen atoms of the dioxolidine ring. In the first case (XXV and XXVI) this leads to opening of the carbohydrate ring (XXVII) and its recyclization to give the thermodynamically favorable anomer. The higher stability of the β nucleosides of indole as compared with the α nucleosides is evidently determined by the sign and magnitude of the dipole of the indole aglycone.

The protonation of the dioxolidine ring (XXVIII, for example) is followed by its cleavage (for example, XXX or XXIX) and subsequent splitting out of the isopropylidene protective group.



R=$COC_6H_4NO_2$; ind = 3-indolyl

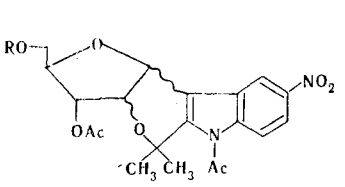
As a consequence of the electron-donor properties of the indole ring, protonation of the oxygen atom of the ribose ring evidently takes place very readily, and anomerization consequently proceeds readily (the presence of a p-nitrobenzoyl group in the 5' position excludes the possibility of the formation of ribopyranosides). The corresponding β anomers (XIb or XIIb) were isolated when α anomers XIa or XIIa were heated with picric acid in alcohol or dioxane. The nucleosides of indole (XI) or 5-bromoindole (XII) undergo cleavage under more severe conditions [by the action of hydrochloric or trifluoroacetic acid and Dowex (H^+) under various conditions].

Nucleoside XIIIa or XIIIb or a mixture of them gave 5'-O-p-nitrobenzoyl-3-β-D-ribofuranosyl-6-nitroindole (XV) when they were treated with 1 N hydrochloric acid in methanol,

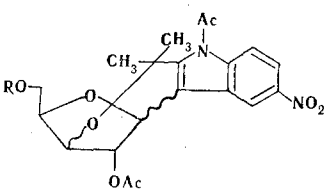
while 5'-O-p-nitrobenzoyl-3-β-D-ribofuranosyl-5-nitroindole (XVI) was obtained by the action of 90% trifluoroacetic acid on XIVb or XIVa or a mixture of them. Treatment of XIVa with a 1 N solution of hydrochloric acid in methanol gave a compound that was isolated after acetylation with acetic anhydride in pyridine and to which structure XXXI or XXXII can be assigned. The formation of this compound evidently takes place through an intermediate structure of the XXIX or XXX type. Treatment with acid results in cleavage of the bond of the O-isopropylidene grouping with the C_2' atom (structure XXIX) or with the C_3' atom (structure XXX) and subsequent cyclization of the indole C_2 atom, which leads to the formation of a dihydropyran ring. One cannot exclude the prior anomerization of the glycoside bond and conversion of the α nucleoside to the β nucleoside.

The structure of the isolated XXXI (XXXII) was confirmed by mass spectrometry. The spectrum contains a molecular ion with m/e 567, a fragment with splitting out of $-OC(CH_3)_2$ $[(M - 58)^+]$ with m/e 509, and peaks corresponding to $(B + 30)^+$ and B^+ fragments with m/e 232 and 202, respectively.

The PMR spectrum of XXXI (XXXII) in $CDCl_3$ at 25°C does not contain signals of pyrrole ring protons, but singlets at 7.65 and 6.68 ppm, which correspond to 1'-H and 2'-H protons, respectively, are present. The 3'-H proton is observed in the form of a broad doublet at 5.88 ppm, and the distance between the peaks is 6.8 Hz. The multiplet at 5.50-5.70 ppm corresponds to the 4'-H proton, while the doublets of doublets at 4.84 ($J_{4',5'}$ = 2.8, $J_{5',5''}$ = 12.4 Hz) and 4.53 ppm ($J_{4',5''}$ = 5.8 Hz) correspond to the protons at 5'-H and 5''-H. The three-proton singlets at 2.66 and 2.15 ppm correspond to the protons of the methyl groups in N-Ac and OAc, respectively. The three-proton singlets at 2.23 and 2.08 ppm correspond to the isopropylidene grouping. The data from the PMR spectra do not make it possible to determine the configuration of the C_1'—indole bond and the C—O bond in the dihydropyran ring. The $J_{1',2'}$ and $J_{2',3'}$ constants are close to zero, and this constitutes evidence that the H—C_1—C_2—H and H—C_2—C_3—H dihedral angles should be close to 90°. An examination of Dreiding models shows that this is possible in the case of a β configuration of the glycoside bond and a xylo configuration of the carbohydrate residue in structure XXXII. The mechanism of the epimerization at the C_3' atom remains unknown.



XXXI



XXXII

Deacylation of nucleoside derivatives XV or XVI with methanolic ammonia led to 6- or 5-nitroindole 3-β-D-ribofuranosides XVII or XVIII. The individuality of C-nucleosides XVII or XVIII was confirmed by high-resolution liquid chromatography with exit times of 23.92 or 23.33 min, respectively (isocritical conditions, 30% methanol at 30°C).

In the case of acetylation of XV with acetic anhydride in pyridine we isolated its 2,3-O,N-triacetyl derivative XIX, while 5-nitro isomer XVI gave per-O-acetylation product XX. Unsubstituted 6-nitronucleoside XVII also gave 2,3,5-O,N-tetraacetylated XXI upon acetylation, whereas a mixture of tri- and tetraacetates XXII and XXIII was obtained from 5-nitro derivative XVIII. The formation of N-acetyl derivatives of 3-ribosylindoles was noted only in the case of their nitro derivatives; the 6-nitro derivatives form N-acetates more easily than the 5-nitro derivatives. We also noted a similar principle for 5- or 6-nitroindole 3-α-L-arbinopyranoside. According to the data from a study of the UV spectra, 5- and 6-nitroindoles are considerably stronger acids (pK_a 15-16) than indole; the pK_a value of 6-nitroindole is 0.5 units lower than that of 5-nitroindole. The acidities of the 3-ribofuranosyl derivatives of nitroindole evidently determine the rather high concentrations of the anions of these compounds in the presence of bases under acetylation conditions, and this leads to the formation of N-acetyl derivatives. The signals of the O-acetyl groups attached to the C_2' and C_3' atom are located close to one another in the PMR spectra of XIX-XXIII (Tables 3 and 4), and this indicates the β configuration of both nucleosides XIX-XXIII and starting XVII or XVIII [20].

We recorded the circular dichroism (CD) spectra of the synthesized C-nucleosides of the indoles. Data on the most pronounced maxima and the molecular ellipticity are presented in

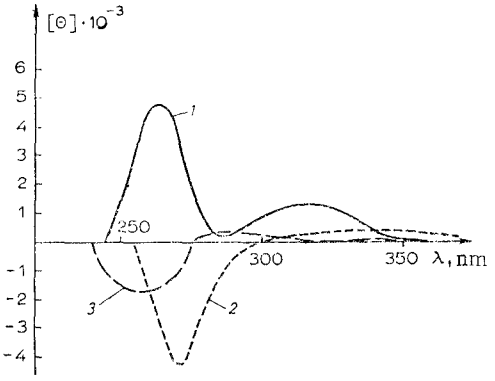


Fig. 1

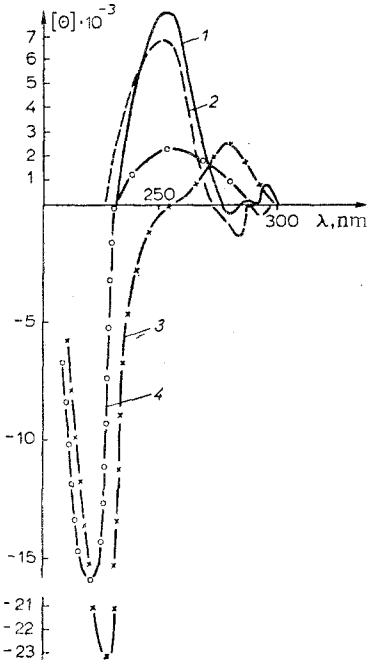


Fig. 2

Fig. 1. Circular dichroism (CD) curves in alcohol: 1) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-α-D-ribofuranosyl-6-nitroindole (XIIIa); 2) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-β-D-ribofuranosyl-6-nitroindole (XIIIb); 3) 3-β-D-ribofuranosyl-6-nitroindole (XVII).

Fig. 2. Circular dichroism (CD) curves in alcohol: 1) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-α-D-ribofuranosyl-5-bromoindole (XIIa); 2) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-α-D-ribofuranosylindole (XIa); 3) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-β-D-ribofuranosyl-5-bromoindole (XIIb); 4) 3-(2,3-O-isopropylidene-5-O-p-nitrobenzoyl)-β-D-ribofuranosylindole (XIb).

Table 5. We studied pairs of anomers: For the α anomers of XI-XIV we observed a positive Cotton effect, whereas for the corresponding β anomers we observed a negative Cotton effect at 230-270 nm (Figs. 1 and 2). A characteristic feature of the α anomers of C-nucleosides of nitroindoles is a 10 nm shift, as compared with the corresponding β anomers, of the position of the most pronounced maxima to the short-wave region (Fig. 1 and Table 5). This was previously noted also for the α and β anomers of 1-D-ribofuranosyl-5-fluorouracil [21]. A positive Cotton effect for the α anomers of XI or XII in the CD spectra of C-nucleosides of indole or 5-bromoindole is observed in the longer-wave region as compared with the negative Cotton effect for the corresponding β anomers (the maxima are shifted 27-34 nm, Fig. 2). A negative Cotton effect at 260 nm ($[\theta] - 1.65 \cdot 10^3$) is observed for 3-β-D-ribofuranosyl-6-nitroindole (XVII), and this also confirms its β configuration.

The empirical formulas of XIa, b, XIIa, b, XIVb, and XXI-XXIII were confirmed by mass spectrometry. Low intensity of the molecular ion is characteristic for all of these compounds. The mass spectra of XIa, c, XIIa, c, and XIVc contain peaks that correspond to those fragments that are characteristic for C-nucleosides, viz., $(B + 29)^+$ and $(S + 1)^+$, and peaks of $(B + 1)^+$ fragments that are characteristic for N-nucleosides are absent.

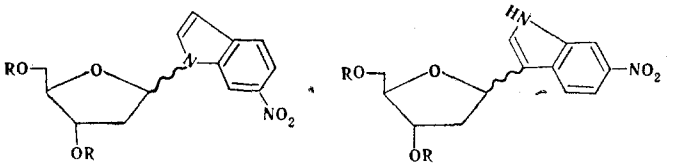
It was recently reported [22] that α- and β-1-2'-deoxy-D-ribofuranosides of indole were obtained by the reaction of indolylsodium in liquid ammonia with 3,5-di-O-p-toluyl-2-deoxy-D-ribofuranosyl chloride [23] and that, after deacylation, a mixture of indole 1-nucleosides with a β:α anomer ratio of 10:1 was obtained in an overall yield of 12%.

We studied the reaction of 6-nitroindole with 3,5-di-O-p-toluyl-2-deoxy-D-ribofuranosyl chloride in the presence of silver oxide and molecular sieves with refluxing in benzene. By preparative TLC on silica gel plates we isolated anomeric mixtures of 1- and 3-substituted

TABLE 5. Data From the Circular Dichroism (CD) Spectra of 3-D-Ribofuranosides of Indoles

Compound (configuration)	Most pronounced maxima	Less pronounced maxima
	λ, nm ($\theta \times 10^{-3}$)	
VIII (α)	264 (+2,25)	305 (+0,65), 355 (−1,25)
XIb (β)	220 (−15,8)	255 (+2,2)
XIa (α)	254 (+6,85)	285 (−1,45), 293 (−0,5)
XIIb (β)	228 (−23,2)	280 (+2,55)
XIIa (α)	255 (+7,95)	280 (−0,5), 287 (+0,15), 296 (+0,85)
XIIIb (β)	272 (−4,3)	228 (+0,8), 340 (+0,4), 245 (−1,1)
XIIIa (α)	262 (+4,8)	245 (−1,75), 320 (+1,35)
XIVb (β)	255 (−3,75), 275 (+4,0)	266 (+0,75), 360 (−0,8), 350 (−0,8)
XIVa (α)	245 (+4,0), 276 (−1,5), 308 (+2,4)	
XVII (β)	260 (−1,65)	230 (+0,55), 290 (+0,39), 350 (−1,03)
XXXI (XXXII)	230 (+6,27), 260 (−5,24), 280 (+3,37)	

deoxyribosides XXXIII and XXXIV in ∿30% yields. By means of Zemplén deacylation we obtained mixtures of anomers of detoluylated nucleosides XXXV and XXXVI, but we were unable to separate the anomers preparatively.



XXXIII α + β R = $COC_6H_4NO_2$-*p*

XXXIV α + β R = $COC_6H_4NO_2$-*p*

XXXV α + β R = H

XXXVI α + β R = H

The ratios of the anomers in the mixtures of deoxynucleosides were established by means of high-efficiency liquid chromatography. We found that the ratio of anomers in the mixture of N-deoxynucleosides XXXV is 5:6 with exit times of 16.87 and 17.24 min. In the case of C-deoxynucleosides XXXVI the ratio of the anomers is 2:3 with exit times of 13.97 and 14.40 min. We were unable to assign the anomers.

Signals of protons attached to C_3 of the indole ring are present in the PMR spectrum of a mixture of anomers of XXXV; signals of both isomers can be isolated in the spectrum. The PMR spectra of XXXIV and XXXVI do not contain the doublet of the proton attached to C_3 of the indole ring, whereas the PMR spectrum of XXXIV contains a signal of an NH group at 8.92 ppm, and the absorption band of an NH group is also observed in the IR spectrum of XXXIV at 3390 cm^{-1}. The mass spectrum of XXXV contains peaks with m/e 278 (M^+), 162 $(B + 1)^+$, and 117 $(S)^+$.

EXPERIMENTAL

The PMR spectra were recorded with a Jeol JNM-MH-100 spectrometer with tetramethylsilane as the internal standard at 25°C. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 or a Perkin-Elmer 283 spectrometer. The circular dichroism (CD) spectra of solutions in 96% ethanol were obtained with a Jobin Yvon Mark-III dichrograph. The UV spectra of solutions of the compounds in 96% alcohol were obtained with a Unicam SP-800 recording spectrophotometer. The specific rotation was determined with a Perkin-Elmer polarimeter. The mass spectra were obtained with a Varian MAT-311A mass spectrometer with direct introduction of the samples into the ion source at 100-200°C, an accelerating voltage of 3 kV, an electron energy of 80 eV, and a cathode emission current of 3 mA. High-efficiency liquid chromatography was carried out with a Hewlett-Packard 1084 B chromatograph (USA) (for XVII and XVIII) or a Jobin Yvon Lirec liquid chromatograph (France) (for XXXV and XXXVI). The Hibar column was 250 by 4 mm and was packed with LiChrosorb sorbent with a particle size of 10 mμ; the flow rate of the mobile phase was 1 ml/min, the detector was an Altex model 153 (USA), the wavelength was 254 nm, and the chromatograms were recorded by means of a Hewlett-Packard 3380 A integrator (USA). The chromatography of XXXV and XXXVI was carried out in a linear gradient water–methanol system, commencing with 20% methanol at a gradient rise rate of 2.86%/min at 25°C. Analytical TLC was carried out on Silufol UV-254, while preparative TLC was carried out on a loose layer of LSL 5/40 μ silica gel (Czechoslo-

vakia) with a layer thickness of 2 mm on 20 by 20 cm plates. After chromatography, the substances were eluted with methanol. Carbon tetrachloride–acetone solvent systems in ratios of 4:1 (A), 2:1 (B) and 1:2 (C) were used for the chromatography.

Condensation of 6-Nitroindole. A) With 2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl Bromide. A mixture of 162 mg (1 mmole) of 6-nitroindole and 232 mg (1 mmole) of silver oxide in 50 ml of absolute benzene was refluxed in the presence of molecular sieves (Wilfen Zeosorb 4 Å, Kugelform) in a nitrogen atmosphere, after which ∿10 ml of the solvent was removed by distillation, and a solution of the glucosyl bromide [obtained from 983 mg (1.5 mmole) of 1-p-nitrobenzoyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose] in 20 ml of absolute benzene was added dropwise in the course of 2.5 h, during which ∿20 ml of the solvent was removed by distillation. Refluxing was continued for 20 h, after which the reaction mass was filtered, and the solid residue was washed with benzene and chloroform. The filtrate and the wash waters were combined and evaporated, and the residue was dissolved in 20 ml of chloroform and chromatographed in system A with collection of the fraction with R_f 0.38 [120 mg (17%)], which was a mixture of anomers of III. PMR spectrum of III in $CDCl_3$ at 30°C: 8.93 (s, NH), 8.19 (d, 7-H), 7.85 (dd, 5-H), 7.38 (d, 4-H), 6.90-7.34 (m, 2-H, C_6H_5), 5.25 (broad doublet, $J_{1',2'} < 4.0$ Hz, 1'-H), and 3.44-5.04 ppm (2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 6''-H, CH_2, and 1-H of the second anomer).

B) With 2,3,5-Tri-O-benzyl-D-ribofuranosyl Bromide. The reaction of 162 mg (1 mmole) of 6-nitroindole and 232 mg (1 mmole) of silver oxide with the glucosyl bromide [obtained from 725 mg (1.5 mmole) of 1-p-nitrobenzyl-2,3,5-tri-O-benzyl-D-ribofuranose] was carried out similarly. Workup gave a mixture of the anomers of IV with R_f 0.50 [90 mg (16%)]. PMR spectrum of IV in $CDCl_3$ at 30°C: 8.89 (s, NH), 8.25 (d, 7-H), 7.90 (dd, 5-H), 7.45 (d, 4-H), 7.04-7.41 (m, 2-H, C_6H_5), 5.28 (broad singlet, 1'-H), and 3.24-4.64 ppm (2'-H, 3'-H, 4'-H, 5'-H, 5''-H, and CH_2 and 1'-H of the second anomer).

Condensation of 2,3-O-Isopropylidene-5-O-p-nitrobenzoyl-D-ribofuranosyl Bromide. A) With Indole. A mixture of 351 mg (3 mmole) of indole and 696 mg (3 mmole) of silver oxide in 100 ml of absolute benzene was treated with the glucosyl bromide [obtained from 1464 mg (3 mmole) of 1,5-di-O-p-nitrobenzoyl-2,3-O-isopropylidene-D-ribofuranose] as described above. Workup gave 510 mg (38%) of XIa with R_f 0.22 and 120 mg (9%) of XIc with R_f 0.37. Mass spectrum of XIa or XIb, m/e: M^+ 438 $(S + 1)^+$ 323, and $(B + 29)^+$ 145.

B) With 5-Bromoindole. A mixture of 588 mg (3 mmole) of 5-bromoindole and 696 mg (3 mmole) of silver oxide in 100 ml of absolute benzene was condensed with the glycosyl bromide [obtained from 1464 mg (3 mmole) of 1,5-di-O-p-nitrobenzoyl-2,3-O-isopropylidene-D-ribofuranose] as in method A. Workup gave 500 mg (31%) of XIIa with R_f 0.32 and 110 mg (7%) of XIIb with R_f 0.39. Mass spectrum of XIIa or XIIb, m/e: M^+ 516, 518; $(S + 1)^+$ 323, $(B + 28)^+$ 222, 224; $(B + 29)^+$ 223, 225.

C) With 6-Nitroindole. Workup of a reaction mixture consisting of 648 mg (4 mmole) of 6-nitroindole, 928 mg (4 mmole) of silver oxide, and a glycosyl bromide [obtained from 2928 mg (6 mmole) of 1,5-di-O-p-nitrobenzoyl-2,3-O-isopropylidene-D-ribufuranose] as in method A gave XIIIa [R_f 0.10, 570 mg (29%)] and XIIIb [R_f 0.14, 170 mg (9%).

D) With 5-Nitroindole. Workup of a mixture consisting of 972 mg (6 mmole) of 5-nitroindole, 1392 mg (6 mmole) of silver oxide, and a glycosyl bromide [obtained from 2928 mg (6 mmole) of 1,5-di-O-p-nitrobenzoyl-2,3-O-isopropylidene-D-ribofuranose] as in method A gave a mixture of anomers XIVa and XIVb [R_f 0.20, 1370 mg (46%)]. Analytical samples of the anomers were isolated by threefold chromatography in system A; α anomer XIVa had R_f 0.16, and β anomer XIVb had R_f 0.22. Mass spectrum of XIVb, m/e: M^+ 483, $(S + 1)^+$ 323, and $(B + 29)^+$ 190.

Condensation of 6-Nitroindole with 3,5-Di-O-p-toluyl-2-deoxy-D-ribofuranosyl Chloride. The reaction of 569 mg (3.5 mmole) of 6-nitroindole in 100 ml of benzene and 696 mg (3 mmole) of silver oxide with 1162 mg (3 mmole) of 3,5-di-O-p-toluyl-2-deoxy-D-ribofuranosyl chloride in 30 ml of benzene was carried out as in method A to give a mixture of anomers [R_f 0.50, 470 mg (30%)] and XXXIV [R_f 0.31, 500 mg (32%)]. Found for XXXIV: C 67.6; H 5.1; N 5.5%. $C_{29}H_{26}N_2O_7$. Calculated: C 67.7; H 5.1; N 5.4%.

1-(2-Deoxy-D-ribofuranosyl)-6-nitroindole (XXXV). A 15-ml sample of a 0.1 N solution of sodium methoxide was added to 470 mg of crude XXXIII, and the mixture was stirred at 20°C for 2 h. It was then treated with Dowex (H^+) to pH 7.0 and filtered, and the filtrate was

evaporated to dryness. The residue was dissolved in 1.5 ml of methanol and chromatographed in an ethyl acetate–methanol system (10:1) with collection of the fraction with R_f 0.56 [100 mg (12% based on the starting carbohydrate component)]. PMR spectrum of XXXV in CD_3OD: 8.55 (7-H), 8.02 (5-H), 7.87 (2-H), 7.63 (4-H), 6.65 (3-H), 6.47 (1'-H), 4.50 (3'-H), 4.07 (4'-H), 3.50-3.90 (5'-H, 5"-H), and 2.0-3.0 ppm (2'-H, 2"-H). Found: C 53.8; H 5.6%. $C_{13}H_{14}N_2O_5 \cdot 0.75H_2O$. Calculated: C 53.6; H 5.4%.

3-(2-Deoxy-D-ribofuranosyl)-6-nitroindole (XXXVI). Treatment of 300 mg (0.58 mmole) of XXXIV with 10 ml of 0.1 N sodium methoxide solution as in the preparation of XXXV gave XXXVI [R_f 0.36, 120 mg (71%)]. PMR spectrum of XXXVI in CD_3OD: 8.28 (7-H), 7.70-8.0 (4-H, 5-H), 7.60 (2-H), 5.46 (1'-H), 4.42 (3'-H), 3.99 (4'-H), 3.50-3.90 (5'-H), 5"-H), 2.66 (2'-H), and 2.24 ppm (2"-H and 2'-H, and 2"-H of the second anomer). Found: C 53.6; H 5.6%. $C_{13}H_{14}N_2O_5 \cdot 0.75H_2O$. Calculated: C 53.6; H 5.4%.

1-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-6-nitroindoline (VII). A mixture of 164 mg (1 mmole) of 6-nitroindoline and 433 mg (1 mmole) of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (VII) in 5 ml of absolute ethanol was refluxed for 20 h, after which it was evaporated, and the residue was chromatographed in system A with collection of the fraction with R_f 0.55 [350 mg (60.5%) of VII]. PMR spectrum in $CDCl_3$: 5.44 (1'-H, $J_{1',2'}$ = 4.0 Hz) and 1.59 and 1.36 ppm [$(CH_3)_2C$].

1-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-6-nitroindole (VIII). A 520-mg (5.98 mmole) sample of manganese dioxide was added to a solution of 260 mg (0.45 mmole) of VII in 50 ml of absolute benzene, and the mixture was refluxed for 14 h with removal of the water by azeotropic distillation. The mixture was filtered, the solid residue was washed with benzene and filtered, and the wash waters were combined and evaporated. The residue was chromatographed in a CCl_4–acetone system (16:1) to give 170 mg (65%) of VIII with R_f 0.21.

1-β-D-Ribofuranosyl-6-nitroindole (IX). A 110-mg (0.22 mmole) sample of VIII was refluxed in 5 ml of 80% acetic acid for 30 min, after which the mixture was evaporated, and the residue was chromatographed in system C to give 45 mg (81%) of IX (R_f 0.35).

3-(5-O-p-Nitrobenzoyl-β-D-ribofuranosyl)-6-nitroindole (XV). A 15-ml sample of a 1 N solution of hydrochloric acid in methanol was added to 330 mg (0.67 mmole) of XIIIa or XIIIb, and the mixture was stirred at 20°C for 1.5 h. The green amorphous precipitate was removed by filtration and washed with water to give 270 mg (89%) of XV.

1-Acetyl-3-(2,3-di-O-acetyl-5-O-p-nitrobenzoyl-β-D-ribofuranosyl)-6-nitroindole (XIX). A 2-ml sample of acetic anhydride was added to a solution of 50 mg (0.11 mmole) of XV in 3 ml of pyridine, and the mixture was allowed to stand at 20°C for 12 h. It was then evaporated to dryness, and the residue was dissolved in 1 ml of chloroform and chromatographed in system C to give XIX [R_f 0.43, 40 mg (63%)].

3-β-D-Ribofuranosyl-6-nitroindole (XVII). A 5-ml sample of methanolic ammonia was added to 150 mg (0.33 mole) of XV, and the mixture was allowed to stand at 20°C for 12 h. It was then evaporated, and the residue was chromatographed in system C to give XVII [R_f 0.22, 80 mg (80%)].

1-Acetyl-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-nitroindole (XXI). This compound was obtained from 20 mg (0.066 mmole) of XVII in the same way as XIX after chromatography in system B [R_f 0.41, 20 mg (64%)]. Mass spectrum of XXI, m/e: M^+ 462, $(M - NO)^+$ 432, and $(M_n - CH_3COOH)^+$ (n = 1, 2, 3), 402, 342, and 282, respectively; $(M_n - CH_3COOH - C_2H_2O)^+$ (n = 1, 2, 3) 360, 300, and 240, respectively; $(B + 30 - CH_3CO)^+$ 190.

3-(5-O-p-Nitrobenzoyl-β-D-ribofuranosyl)-5-nitroindole (XVI). A 250-mg (0.5 mmole) sample of XIVa or XIVb was dissolved in 10 ml of 90% trifluoroacetic acid, and the solution was allowed to stand at 20°C for 1 h. It was then evaporated to dryness, and the residue was chromatographed in system B to give XVI [R_f 0.25, 180 mg (79%)].

3-(2,3-Di-O-acetyl-5-O-p-nitrobenzoyl-β-D-ribofuranosyl)-5-nitroindole (XX). The acetylation of 30 mg (0.066 mole) of XVI was carried out as in the case of XIX; XX [R_f 0.50, 25 mg (72%)] was obtained after chromatography in system B.

3-β-D-Ribofuranosyl-5-nitroindole (XVIII). An 8-ml sample of methanolic ammonia was added to 310 mg (0.67 mmole) of XVI, and the mixture was worked up as in the case of XVII [R_f 0.33, 170 mg (82%)].

1-Acetyl-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-5-nitroindole (XXIII) and 3-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-5-nitroindole (XXII). The acetylation of 60 mg (0.19 mmole) of XVIII was carried out in 3 ml of pyridine and 2 ml of acetic anhydride to give XXII [R_f 0.28, 40 mg (49%)]. Mass spectrum of XXII, m/e: M^+ 420 $(M_n - CH_3COOH)^+$ (n = 1, 2, 3) 360, 300, and 240, respectively; $(B + 29)^+$ 190; $(B + 43)^+$ 204. Also obtained was XXIII [R_f 0.33, 20 mg (22%)]. Mass spectrum of XXIII, m/e: M^+ 462; $(M_n - CH_3COOH)^+$ (n = 1, 2, 3) 402, 342, and 282, respectively; $(M_n - CH_3COOH - C_2H_2O)^+$ (n = 1, 2, 3) 360, 300, and 240, respectively; $(B + 30 - CH_3CO)^+$ 190.

1-Acetyl-3-[(2-C,2(3)-O-isopropylidene)]-3-O-acetyl-5-O-p-nitrobenzoyl-D-glycosyl-5-nitroindole (XXXI or XXXII). An 11-ml sample of a 1 N solution of hydrochloric acid in methanol was added to 200 mg (0.4 mmole) of XIVa, and the mixture was stirred at 20°C for 12 h. It was then neutralized with a saturated solution of sodium bicarbonate and evaporated to dryness. The residue was dissolved in acetone, the solid residue was removed by filtration, and the filtrate was evaporated to 1 ml and chromatographed in system B with isolation of the zone with R_f 0.20 to give 120 mg of a compound, which was acetylated in a mixture of 4 ml of pyridine and 2 ml of acetic anhydride, with workup as in the case of XIX to give XXXI (XXXII) [R_f 0.42, 100 mg (42%)].

LITERATURE CITED

1. T. N. Sokolova, I. V. Yartseva, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 10, 1423 (1980).
2. T. N. Sokolova, V. E. Shevchenko, and M. N. Preobrazhenskaya, Carbohydr. Res., 83, 249 (1980).
3. T. N. Sokolova, V. I. Mukhanov, and M. N. Preobrazhenskaya, in: New Directions in the Chemistry of Nitrogen-Containing Heterocycles (Summaries of Papers Presented at the 2nd All-Union Conference on the Chemistry of Heterocyclic Compounds) [in Russian], Vol. 1, Zinatne (1979), p. 80.
4. M. N. Preobrazhenskaya and N. N. Suvorov, Zh. Obshch. Khim., 35, 888 (1965).
5. R. Barker and H. G. Fletcher, J. Org. Chem., 26, 4605 (1961).
6. R. S. Klein, H. Ohrui, and J. J. Fox, J. Carbohydr. Nucleosides, Nucleotides, 1, 265 (1974).
7. J. J. Fox, K. A. Watanabe, R. S. Klein, and C. K. Chu, S. Y.-K. Tam, U. Reichman, K. Hirota, J.-S. Hwang, F. G. de las Heras, and J. Wempen, in: The Chemistry and Biology of Nucleosides and Nucleotides, edited by R. E. Harmon, R. K. Robins, and L. B. Townsend, Academic Press, New York (1978), p. 415.
8. F. G. de las Heras, S. Y.-K. Tam, R. S. Klein, and J. J. Fox, J. Org. Chem., 41, 84 (1976).
9. V. I. Mukhanov, T. D. Miniker, and M. N. Preobrazhenskaya, Zh. Org. Khim., 13, 214 (1977).
10. H. Ohrui and S. Emote, J. Org. Chem., 42, 1951 (1977).
11. H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, J. Am. Chem. Soc., 97, 4602 (1975).
12. V. I. Mukhanov, M. N. Preobrazhenskaya, N. P. Kostyuchenko, T. Ya. Filipenko, and N. N. Suvorov, Zh. Org. Khim., 10, 587 (1974).
13. L. B. Townsend, in: Synthetic Procedures in Nucleic Acid Chemistry, edited by W. W. Zorbach and R. S. Tipson, Vol. 2, Wiley-Interscience, New York, p. 333.
14. S. De Barnardo and M. Weigele, J. Org. Chem., 41, 287 (1976).
15. L. V. Éktova, V. N. Tolkachev, M. N. Kornveits, and M. N. Preobrazhenskaya, Bioorg. Khim., 4, 1250 (1978).
16. J. Southon and W. Pfleiderer, Chem. Ber., 11, 996 (1978).
17. J. L. Imbach, J. L. Barascut, B. L. Kam, B. Rayner, C. Tamby, and C. Tapiero, J. Heterocycl. Chem., 10, 1069 (1973).
18. J. L. Imbach and B. L. Kam, J. Carbohydr. Nucleosides, Nucleotides, 1, 271 (1974).
19. S. Y.-K. Tam, R. S. Klein, F. G. de las Heras, and J. J. Fox, J. Org. Chem., 44, 4854 (1979).
20. J. A. Montgomery, Carbohydr. Res., 33, 184 (1974).
21. T. P. Nedorezova, S. Ya. Mel'nik, and M. N. Preobrazhenskaya, Bioorg. Khim., 2, 1205 (1976).
22. Huynh Dink Tam, M. R. Rayard, and J. Igolen, Compt. Rend., C, 283, 227 (1976).
23. M. Hoffer, Chem. Ber., 93, 2777 (1960).