GLYCOSYLATION OF N_4-BENZOYLCYTOSINE AND N_6-BENZOYLADENINE WITH ACETYLATED GLYCALS

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The glycosylation of silyl derivatives of N_4-benzoylcytosine and N_6-benzoyladenine with D-xylal and L-arabinal diacetates in the presence of $SnCl_4$ as the condensing agent was studied. It is shown that the character of the products depends on the heterocyclic base subjected to the condensation. Primarily N_1-nucleosides with a double bond in the 2' position, in which the heterocyclic base is attached to the C_1 atom of the carbohydrate fragmnet, are formed with N_4-benzoylcytosine, whereas only N_9-nucleosides in which the C_3 atom of the carbohydrate fragment is bonded to the heterocyclic base are obtained with N_6-benzoyladenine under the investigated conditions. The catalytic hydrogenation of the double bond in the carbohydrate fragment of the nucleosides obtained was investigated. The structures of all of the compounds obtained were proved by means of PMR and circular dichroism (CD) spectroscopy.

The utilization of acyl derivatives of glycals for the synthesis of diverse modified nucleosides expands the possibilities of the preparation of compounds of this class substantially. The possibilities of the use of Lewis acids as condensing agents have been studied in the case of the reaction of bis(trimethylsilyl)uracil with acylated glycals [1-3]; however, the bis(trimethylsilyl) derivative of cytosine could not be subjected to the reaction [3]. In the present research we studied the condensation of bis(trimethylsilyl) derivatives of N_4-benzoylcytosine and N_6-benzoyladenine with peracetyl-D-xylal and L-arabinal in the presence of $SnCl_4$, as well as some chemical transformations and the spectral properties of the nucleosides obtained. The preliminary results of this research were published in [4].

We have found that the condensation of N_4,O-bis(trimethylsilyl)-N_4-benzoylcytosine (I) with 3,4-di-O-acetyl-D-xylal (II) in dichloroethane with $SnCl_4$ as the condensing agent gives 1-(4-O-acetyl-2,3-dideoxy-β-D-glyceropent-2-enopyranosyl)-N_4-benzoylcytosine (III) as the principal reaction product. Removal of the protective groups by the action of a methanol solution of ammonia gives cytosine IV, the selective acetylation of which by the action of acetic anhydride in ethanol [5] led to N_4-acetyl derivative V. The catalytic selective hydrogenation of the double bond of IV proceeded most smoothly when palladium on strontium carbonate was used as the catalyst. Under these conditions 1-(2,3-dideoxy-β-D-glyceropentopyranosyl)cytosine (VII) was obtained in 67% yield based on IV. The use of palladium on carbon and on barium sulfate as hydrogenation catalysts led to a reaction product, the UV spectrum of which did not contain the absorption band characteristic for the cytosine chromophore. The products of hydrogenation of IV with Pd/C and $Pd/BaSO_4$ as the catalysts were not investigated in greater detail.

In contrast to IV, the hydrogenation of peracyl derivative III in the presence of $Pd/SrCO_3$ led to a more complex mixture of reaction products, from which VI was isolated in 18% yield. Acetate VIII was therefore obtained by selective acetylation [5] of VII (see scheme, top of following page).

The reaction mixture remaining after isolation of III was subjected to deacylation by the action of ammonia in methanol and chromatographic separation on silica gel, as a result of which α-D-anomer IX and nucleoside XI, together with small amounts of IV, were obtained. Dihydro derivative X was obtained by hydrogenation ($Pd/SrCO_3$) of IX. Oily glycal nucleoside XI was converted to crystalline acetate XII by selective acetylation.

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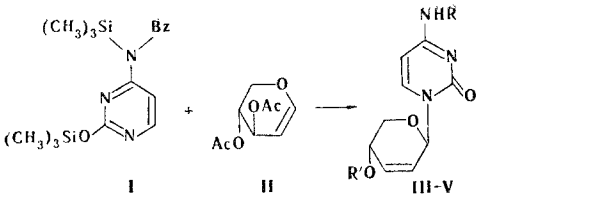
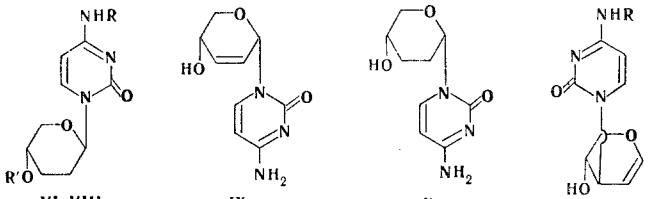


I II III-V

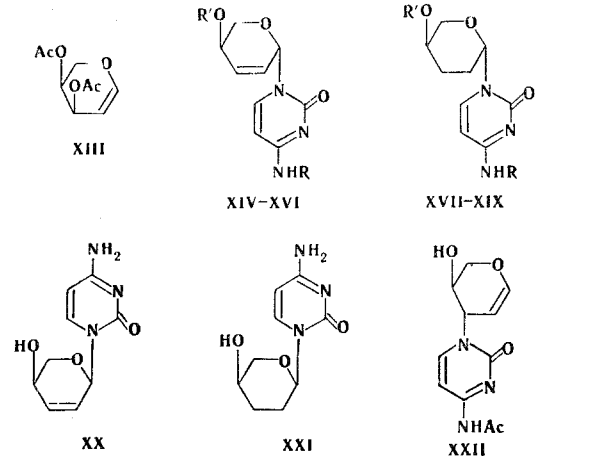


VI-VIII IX X XI, XII

III, VI R=Bz, R′=Ac; IV, VII, XI R=R′=H; V, VIII, XII R=Ac, R′=H

The structural and stereochemical course of the reaction of 3,4-di-O-acetyl-L-arabinal (XIII) with silyl derivatives of cytosine I in the presence of $SnCl_4$ is similar to that described above for D-xylal. N_4-Benzoylcytosine XIV was obtained as the chief reaction product. α-L-Anomer XX and a glycal nucleoside were also obtained from the reaction products after removal of the protective groups and chromatographic separation; the glycal nucleoside was isolated in the crystalline state in the form of N_4-acetyl derivative XXII. Nucleosides XV-XIX and XXI were obtained by a method similar to that described above for IV-VIII and X.

The physicochemical and spectral properties of XXI are completely identical to those for the natural nucleoside antibiotic pentopyranine A [6].



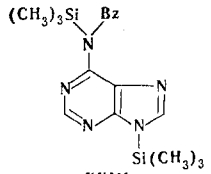
XIII XIV-XVI XVII-XIX

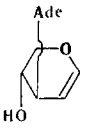
XX XXI XXII

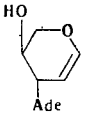
XIV, XVII R=COC_6H_5, R′=Ac; XV, XVIII R=R′=H; XVI, XIX R=Ac, R′=H

In contrast to what was described above for silylcytosine I, the condensation of N_6N_9-bis(trimethylsilyl)-N_6-benzoyladenine (XXIII) with glycals II and XIII gives as the chief reaction products after removal of the protective groups glycal nucleosides XXIV and XXV, by hydrogenation ($Pd/SrCO_3$) of which we obtained the corresponding XXVI and XXVII derivatives. (see scheme, top of following page).

The structures of all of the synthesized compounds were confirmed by a combination of spectral methods of investigation. Compounds III and XIV, IV and XV, V and XVI, VI and XVII, VII and XVIII, VIII and XIX, IX and XX, X and XXI, and XII and XXII have identical physicochemical and spectral properties; this, together with Cotton effects on the circular dichroism (CD) curves that are equal in magnitude but opposite in sign, constitutes evidence that they


XXIII


XXIV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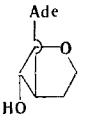
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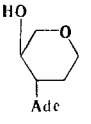
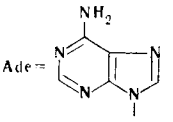

XXVII



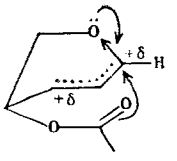
are enantiomeric pairs. It should be noted that, in contrast to natural cytosine β-nucleosides, which have a positive Cotton effect in the long-wave region of the spectrum (~260 nm), compounds with a double bond in the 2' position display a negative Cotton effect in the same region. Thus in the investigated group of compounds the transition from nucleosides with a double bond to saturated derivatives is accompanied by inversion of the sign of the Cotton effect and a substantial decrease in the absolute value of the molar ellipticity [θ]. Similar facts have been previously noted for nucleosides that have a double bond in the carbohydrate fragment of the molecule [7, 8]. A detailed discussion of the CD spectra of the investigated group of compounds will be published separately.

The structures of the investigated compounds were confirmed by data from PMR spectroscopy (see Table 1); the resonance signals were assigned by means of the double-resonance technique. A comparison of our data with the data for related compounds [9] reveals good agreement, but in the case of 2',3'-unsaturated pyranoses it exhibits certain difficulties in the unambiguous establishment of the anomeric configuration. Our noted correlations between the Cotton effect and the anomeric configuration therefore are of considerable interest for establishment of the anomeric structure.

The principal element in the establishment of the structures of XI and XII, XXII, XIV, and XXV was proof of the mutual orientation of the substituents in the pyranose ring. We were unable to solve this problem for pyrimidine nucleosides in view of the complete overlapping of the signals of the 3'-H, 5'-H, and 5''-H protons, which made it impossible to find the values of the corresponding spin–spin coupling constants (SSCC). In the case of adenine nucleosides XXIV and XXV the $J_{3',4'} = 5$, $J_{4',5'} = 3.5$, and $J_{4',5'} = 7$ Hz values constitute evidence in favor of a trans orientation of the substituents. However, these values show that the C_3–C_4–C_5 fragment has substantial mobility and that the constants indicated above are average values for a number of conformations. Reduction of the double bond in XXIV and XXV leads to derivatives XXVI and XXVII, respectively, which are more rigid structures in a conformational sense with a trans-diaxial orientation of the heterocyclic base and the hydroxy group. The latter follows from the SSCC ($J_{3',4'} = J_{4',5'a} = 10.5$ Hz), which is characteristic for the trans-diaxial protons of the pyranose ring. The structure of XI and XII with a trans orientation of the substituents of the pyranose ring was adopted in analogy with the structure for adenine nucleosides.

The site of addition of the carbohydrate residue to the cytosine and adenine heterorings (N_1 and N_9, respectively) was proved by a study of the UV spectra of the nucleosides at various pH values [10, 11].

It seems expedient to make a number of general comments relative to the stereochemical and structural principles of the investigated condensations of bis(trimethylsilyl) derivatives of N_4-benzoylcytosine and N_6-benzoyladenine with peracylglycals in the presence of $SnCl_4$ as the condensing agent. The stereochemical result of the reaction, viz., the preponderant formation of nucleosides with 1,4- and 3,4-trans orientations of the substituents, can be explained, in our opinion, by 1,4- and 3,4-coparticipation of the 4-O-acetyl group in the intermediate carbonium ion, which is illustrated by structures XXVIII and XXIX. Coparticipation of the 3,4 type of the acetyl group has a number of well-known analogies [12], and there is no doubt that it determines the stereochemical result of the formation of nucleosides at the C_3 atom. Stereochemical control of attack of the heterocyclic base at the C_1 atom is more unexpected. However, a comparison of the literature data [3, 9] with our data makes it possible to confidently assume that 1,4 coparticipation plays a significant role in carbonium ion XXVIII in the determination of the stereochemistry of the reaction.


XXVIII

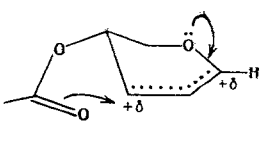

XXIX

TABLE 1. PMR Spectroscopic Data for the Synthesized Compounds

Compound	δ, ppm							J, Hz							
	1-H	2-H	3-H	4-H	5e-H	5a-H	others	1,2	1,3	2,3	3,4	4,5e	4,5a	5a,5e	others
III	6,44	6,05	6,36	5,22	4,05	3,82	2,10 (CH_3)	3—3,5	2,0	10,0	4,0	3,7	3,7	13,0	<1 (2,4)
IV	6,50	6,10	6,65	4,30	4,00	3,85		3,0	2,0	10,0	4,4	3,5	3,5	12,5	1,0 (2,4)
V	6,25	5,90	6,20	4,00	3,80	3,50	2,00 (CH_3), 5,16 (OH)			10,0		4,5	6,0	12,0	
VII	5,65	2,4	1,5	4,10	3,85	3,50		9 (1,2a) 4 (1,2e)				5,0	10,0	10,0	
VIII	5,53	2,2	1,4	3,90	3,50	3,20	2,00 (CH_3), 4,93 (OH)	9 (1,2a) 2,5 (1,2e)				4,0	10,0	10,0	
IX	6,30	5,90	6,40	4,20	4,00	3,80		2,0	2,0	10,0	4,5	3,5	3,5	12,0	1,0
XI	6,73	4,53		4,85											(2,4)
XII	6,73	4,56	3,66—3,84	4,88	3,66—4,84		2,10 (CH_3), 5,48 (OH)	6,0 6,0	1,5 1,5	4,0 4,0					4,0 (4,04)
XXIV	6,70	4,80	4,90	4,20	4,00	3,84	5,68 (OH)	6,0	1,7	3,5	5,0	3,5	7,0	11,5	5,0 (4,04)
XXVI	3,50	2,3—30	4,80	5,00	4,65—4,15						10,5	4,0	10,5	11	

*The PMR spectra were recorded with the following solvents: d_6-DMSO for III, V, VIII, XII, and XXIV, D_2O for IV, VII, IX, and XI, and trifluoroacetic acid for XXVI.

The structural specificity of the condensation as a function of the character of the heterocyclic base is also of considerable interest. The structure of the carbohydrate carbonium ion (for example, XXVIII and XXIX) predetermines the ambiguity of nucleophilic attack. The structural selectivity that we observed, viz., primary attack at the C_1' atom of silylcytosine I and the C_3' atom of silyladenine XXIII undoubtedly reflects the differences in the nucleophilicities of the N_1 and N_9 atoms. As far as we know, this is the first example that demonstrates differences in the nucleophilicities of pyrimidines and purines.

EXPERIMENTAL

The PMR spectra were obtained with a JNM PS 100 spectrometer with tetramethylsilane as the internal standard. The UV spectra were recorded with a Specord spectrophotometer. The $[\alpha]_D$ values were obtained with a JASCO J-20 spectropolarimeter.

The bis(trimethylsilyl) derivatives of N_4-benzoylcytosine [13] and N_6-benzoyladenine [14] were obtained by the action on the indicated heterocyclic compounds of equimolar amounts of trimethylchlorosilane and triethylamine in anhydrous benzene. The constants and yields of the compounds obtained are presented in Table 2.

1-(4-O-Acetyl-2,3-dideoxy-β-D-glyceropent-2-enopyranosyl)-N_4-benzoyl-cytosine (III). A 0.5-ml (4.3 mmole) sample of $SnCl_4$ was added to a solution of 1.0 g (2.8 mmole) of silylcytosine I in 15 ml of dry dichloroethane, the solution was cooled to 0°C, and a solution of 1.1 g (5.5 mmole) of 3,4-di-O-acetyl-D-xylal (II) [15] in 10 ml of dichloroethane was added dropwise with stirring in the course of 10 min. The mixture was diluted with 50 ml of chloroform, and the resulting solution was washed twice with water, once with sodium bicarbonate solution, and once again with water. The organic layer was dried with Na_2SO_4, the drying agent was removed by filtration, and the solvent was removed *in vacuo*. The resulting semicrystalline mass was dissolved by heating in methanol, the solution was cooled, and the white crystals were removed by filtration, washed on the filter with methanol, and dried.

Compound XIV was similarly obtained. In the case of XXIV-XXVII the oily residue after removal of the solvent by distillation was treated with 100 ml of a saturated solution of ammonia in methanol, and the mixture was allowed to stand at 20°C for 48 h. The solution was concentrated *in vacuo* to a volume of 10 ml, and the concentrate was cooled. The precipitated crystals were removed by filtration, washed thoroughly with cold methanol and ether, and dried.

1-(2,3-Dideoxy-β-D-glyceropent-2-enopyranosyl)cytosine (IV). A 0.40-g sample of III was treated with 50 ml of a saturated solution of ammonia in methanol, and the mixture was allowed to stand at 20°C for 48 h. The solution was concentrated *in vacuo* to a volume of ~5 ml, and the precipitated crystals were removed by filtration, washed thoroughly with ether, and dried. Compound XV was similarly obtained.

TABLE 2. Properties of the Synthesized Compounds

Compound	mp, °C	$[\alpha]_D^{20}$ (c, solvent)	UV spectrum		Found, %			Empirical formula	Calc., %			Yield, %
			λ_{max}, nm	log ε	C	H	N		C	H	N	
III	225—226	+104 (2, MeOH)	261, 304	4,4; 4,0	61,1	4,9	11,6	$C_{18}H_{17}N_3O_5$	60,8	4,8	11,8	47
IV	214—215	+75 (2, H_2O)	269	4,0	52,0	5,5	20,0	$C_9H_{11}N_3O_3$	51,7	5,3	20,1	91
V	214—216	+177 (1, MeOH)	249, 299	4,2; 3,8	52,6	5,3	17,0	$C_{11}H_{13}N_3O_4$	52,6	5,2	16,7	92
VI	236—238	+148 (0,5, MeOH)	261, 304	4,4; 4,0	60,4	5,4	11,8	$C_{18}H_{19}N_3O_5$	60,5	5,4	11,8	18
VII	247 (dec.)	+23 (1, H_2O)	270	3,9	51,2	6,3	20,0	$C_9H_{13}N_3O_3$	51,2	6,2	19,9	67
VIII	211—213	+118 (1, MeOH)	248, 299	4,2; 3,8	52,3	5,9	16,6	$C_{11}H_{15}N_3O_4$	52,2	6,0	16,6	84
IX	210—212	+115 (0,5, H_2O)	269	4,0	51,9	5,3	19,9	$C_9H_{11}N_3O_3$	51,7	5,3	20,1	
X	258 (dec.)	−24 (0,5, H_2O)	270	4,0	51,3	6,4	19,6	$C_9H_{13}N_3O_3$	51,2	6,2	19,9	50
XII	204—206	−98,7 (1, MeOH)	247, 302	4,1; 3,9	52,3	5,2	16,7	$C_{11}H_{13}N_3O_4$	52,6	5,2	16,7	50
XIV	225—226	−107 (2, MeOH)	261, 304	4,4; 4,0	60,7	4,9	11,7	$C_{18}H_{17}N_3O_5$	60,8	4,8	11,8	53
XV	214—215	−68 (2, H_2O)	269	4,0	51,7	5,3	19,8	$C_9H_{11}N_3O_3$	60,8	4,8	11,8	94
XVI	213—215	−171 (1, MeOH)	249, 299	4,2; 3,8	52,8	5,1	16,4	$C_{11}H_{13}N_3O_4$	52,6	5,2	16,7	92
XVII	236—238	−139 (0,5, MeOH)	261, 304	4,3; 4,0	60,6	5,2	11,9	$C_{18}H_{19}N_3O_5$	60,5	5,4	11,8	15
XVIII	247 (dec.)	−21 (1, H_2O)	270	4,0	51,5	6,2	19,6	$C_9H_{13}N_3O_3$	51,2	6,2	19,8	60
XIX	211—213	−125 (1, MeOH)			52,5	6,0	16,7	$C_{11}H_{15}N_3O_4$	52,2	6,0	16,6	82
XX	210—212	−120 (0,5, H_2O)	269	3,9	51,6	5,4	19,8	$C_9H_{11}N_3O_3$	51,7	5,3	20,1	
XXI	258 (dec.)	+28 (0,5, H_2O)	270	3,9	51,4	6,3	19,8	$C_9H_{13}N_3O_3$	52,2	6,2	19,9	50
XXII	204—206	+96,5 (1, MeOH)	247, 302	4,2; 3,9	52,4	5,3	16,5	$C_{11}H_{13}N_3O_4$	52,6	5,2	16,7	
XXIV	240—241	−242 (1, H_2O)	262	4,2	51,4	4,9	29,8	$C_{10}H_{11}N_5O_2$	51,5	4,8	30,0	71
XXV	240—241	+245 (1, H_2O)	262	4,2	51,7	4,8	29,9	$C_{10}H_{11}N_5O_2$	51,5	4,8	30,0	66
XXVI	306 (dec.)	−37,5 (1, H_2O)	262	4,2	51,1	5,6	29,8	$C_{10}H_{13}N_5O_2$	51,1	5,6	29,8	87
XXVII	306 (dec.)	+37,5 (1, H_2O)	262	4,2	51,3	5,9	29,6	$C_{10}H_{13}N_5O_2$	51,1	5,6	29,8	

1-(2,3-Dideoxy-β-D-glyceropent-2-enopyranosyl)-N_4)acetylcytosine (V). A 0.10-g (0.48 mmole) sample of IV was dissolved in 5 ml of dry ethanol, 0.1 ml (1.06 mmole) of acetic anhydride was added, and the mixture was refluxed for 4 h. It was then cooled, and the precipitated crystals were removed by filtration and washed successively with ethanol and ether to give 0.07 g of product V. The filtrate was concentrated *in vacuo*, and the residue was evaporated several times with dry ethanol. The resulting oil was dissolved in 5 ml of ethanol, 0.1 ml of acetic anhydride was added, and the mixture was refluxed for 3 h. It was then cooled, and the precipitated crystals were removed by filtration to give an additional 0.04 g of V.

Compounds VIII, XII, XVI, XIX, and XXII were similarly obtained.

1-(4-O-Acetyl-2,3-dideoxy-β-D-glyceropentopyranosyl)-N_4-benzoylcytosine (VI). A 0.1-g sample of III was dissolved in 10 ml of ethanol, 0.02 g of Pd/$SrCO_3$ (30%) was added, and the mixture was stirred at room temperature in a hydrogen atmosphere for 1 h. The catalyst was removed by filtration, and the filtrate was evaporated. The substance was isolated by preparative thin-layer chromatography (TLC) on silica gel with subsequent crystallization from ethanol.

Compound XVII was similarly obtained.

1-(2,3-Dideoxy-β-D-glyceropentopyranosyl)cytosine (VII). A 0.15-g sample of IV was hydrogenated in ethanol over 30 mg of Pd/$SrCO_3$ (30%). Crystallization of the product from ethanol gave 0.1 g of VII. Compound XVIII was similarly obtained.

1-(2,3-Dideoxy-α-D-glyceropent-2-enopyranosyl)cytosine (IX). The residue from the crystallization of III and the wash waters were combined and concentrated *in vacuo*, and the concentrate was dried. The oily residue was treated with 70 ml of a saturated solution of ammonia in methanol, and the solution was allowed to stand at 20°C for 48 h. The volatile substances were removed by vacuum distillation, and the residue was chromatographed with a column filled with silica gel. Elution with chloroform–methanol (9:1) gave initially XI and then 0.12 g of an oily substance, which was crystallized from ethanol to give 0.06 g of nucleoside IX. Compound XX was similarly obtained.

1-(2,3-Dideoxy-α-D-glyceropentopyranosyl)cytosine (X). A 0.04-g sample of IX was hydrogenated in ethanol over 0.01 g of Pd/$SrCO_3$ (30%). After stirring for 1 h, the catalyst was removed by filtration, the filtrate was concentrated *in vacuo*, and the concentrate was subjected to preparative TLC on silica gel.

Compound XXI was similarly obtained.

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