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SYNTHESIS OF GLYCOSYLPYRIMIDINES ON THE BASIS OF GLYCOSYLUREA

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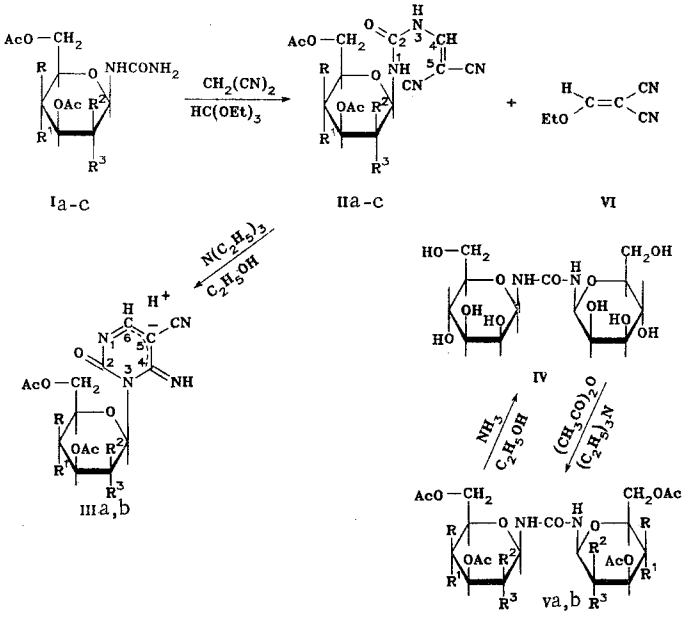
Acetylated derivatives of glycosylpyrimidines were synthesized on the basis of acetylated glycosylureas, malononitrile, and ethyl orthoformate. The spectral characteristics of the compounds obtained were studied.

We have previously developed a new method for the preparation of arabinosylpyrimidines by construction of the heterocyclic part of the molecule on the basis of arabinosyl derivatives of urea [1].

In the present research we used acetylated derivatives of 1-D-glucopyranosyl-, 1-D-mannopyranosyl-, and 1-D-galactopyranosylurea (Ia-c) as starting compounds. 1-(2',3',4',5'-Tetra-O-acetyl-β-D-glucopyranosyl)-, 1-(2',3',4',5'-tetra-O-acetyl-β-D-mannopyranosyl)-, and 1-(2',3',4',5'-tetra-O-acetyl-β-D-galactopyranosyl)ureidomethylenemalononitriles (IIa-c) were obtained by the reaction of Ia-c with malonitrile and ethyl orthoformate. In addition to nitriles IIa-c, ethoxymethylenemalononitrile (VI) is formed as an impurity. Attempts to subject unacetylated derivatives of glycosylureas to the described reaction were unsuccess-



Ia, IIa, IIIa R=R²=H, R¹=R³=OAc; Ib, IIb, IIIb R=R³=H, R¹=R²=OAc; Ic, IIc R¹=R²=H, R=R³=OAc; Va R=R³=H, R¹=R²=OAc; Vb R¹=R²=H, R=R³=OAc

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TABLE 1. PMR Spectra of Glycosylurea Derivatives Ia, c, IIa-c, IVb, and Va, b and Glycosylpyrimidines IIIa, b in d_6-DMSO

Compound	Chemical shifts, δ, ppm								SSCC, J, Hz						
	1′-H	2′-H	3′-H	4′-H	5′-H	6′-H	R	Ac	1′2′	2′3′	3′4′	4′5′	5′6′	6′6′	remaining protons
Ia	5,14	4,72	5,27	4,83	4,0	4,00	6,67 (NH); 5,80 (NH_2)	1,89; 1,95; 1,96; 1,98	9,4	9,0	9,0	9,0	—	—	9,1 ($NH—H'_1$)
Ic*	5,22	5,14	5,22	5,57	4,11	4,23	5,83 (NH); 4,88 (NH_2)	2,02; 2,07; 2,11; 2,18	—	—	—	<1	6,8	—	7,5 ($NH—H'_1$)
IIa	5,36	5,22	5,42	4,93	4,10	4,10	7,89 (N_1H); 10,67 (N_3H); 8,36 (CH)	1,94; 1,98; 1,99; 2,00	9,2	9,0	9,0	9,0	—	—	9,3 ($N_1H—H'_1$); 11,8 ($N_3H—CH$)
IIb	5,67	5,23	5,38	5,00	3,95	4,00	7,89 (N_1H); 10,38 (N_3H); 8,38 (CH)	1,84; 1,93; 1,94; 2,17	1,0	3,2	9,7	9,7	—	—	9,5 ($N_1H—N'_1$); 11,0 ($N_3H—CH$)
IIc	4,94	5,20—5,40			4,33	3,97	7,91 (N_1H); 10,60 (N_3H); 8,34 (CH)	1,89; 1,96; 2,01; 2,08	8,7	—	—	<1	5,6	—	8,7 ($N_1H—H'_1$)
IIIa	6,56	5,50	5,50	5,50	4,32	4,05 4,19	8,21 (CH); 8,40 (NH)	1,83; 1,94; 2,00; 2,01	8,5	—	—	10,0	7,0 1,8	12,0	—
IIIb	6,53	5,50	5,45	5,36	4,32	4,37 4,13	8,29 (CH); 8,30 (NH)	1,97; 2,07; 2,07; 2,10	0,7	3,2	9,8	9,7	5,5 2,0	11,5	—
IVb	4,82	3,48	3,30	3,23	2,99	3,60 3,35	7,16 (NH)	4,40 (6-OH); 4,63 (OH); 4,72 and 4,74 (OH)	<0,5	3,0	9,2	9,2	6,0	11,4	9,6 ($NH—H_1$)
Va*	5,54	5,48	5,22	5,30	3,85	4,37 4,13	5,54 (NH)	2,00; 2,08; 2,12; 2,25	<0,5	3,1	10,1	10,1	5,2 2,0	12,7	—
	5,59	5,19	5,34	5,00	3,97	4,12 3,97	6,84 (NH)	1,90; 1,99; 2,01; 2,19	<0,5	3,4	9,8	9,8	4,8 2,1	12,0	9,4 ($NH—H_1$)
Vb	4,94	5,1—5,3			4,25	3,94	6,92 (NH)	1,82; 1,96; 1,98; 2,09	10,0	—	—	<1	5,6	—	8,8 ($NH—H_1$)

*In $CDCl_3$.

ful. A product with an unidentified structure was isolated in the case of D-glucosylurea. The deacetylation of IIIa, dissolved in ethanol, with ammonia led to decomposition of the reaction product. D-Mannosylurea (Id) undergoes changes even during crystallization. When mannosylurea containing admixed urea is heated in ethanol in order to purify the mannosylurea by the method in [2], bis(β-D-mannopyranosyl)carbamide (IV) is formed. Bis(2′,3′,4′,5′-tetra-O-acetyl-β-D-mannopyranosyl)carbamide (Va) was obtained in the acetylation of carbamide IV. Treatment of Va, dissolved in ethanol, with ammonia leads to deacetylation to give IV.

Ureidomethylenemalononitrile derivatives IIa, b undergo cyclization to the corresponding glycosylpyrimidines IIIa, b when they are heated in ethanol in the presence of triethylamine. In contrast to IIa, b, IIc, dissolved in ethanol undergoes conversion to bis(2′,3′,4′,5′-tetra-O-acetyl-β-D-galactopyranosyl)carbamide (Vb) when triethylamine is added at room temperature.

The structures of all of the synthesized compounds were proved by the results of elementary analysis and UV, IR, PMR, and ^{13}C NMR spectral data. The parameters of the PMR spectra are presented in Table 1. On the basis of an analysis of the spin—spin coupling con-

TABLE 2. Calculated and Experimental ^{13}C Chemical Shifts for the α,α and β,β Anomers of Bis(mannopyranosyl)-carbamide IV

Configuration	C_1	C_2	C_3	C_4	C_5	C_6
Calc. for α,α	82,0	69,7	71,3	68,0	73,4	62,1
Calc. for β,β	81,6	70,3	74,1	67,8	77,2	62,1
Exptl.	79,8	71,6	74,6	67,7	78,5	62,1

stants (SSCC) of the sugar fragment it may be concluded that all of the compounds are β anomers and have a $^4C_1$ conformation. This conclusion is confirmed by the large 1'-H and 2'-H SSCC for IIa, c, IIIa, and Vb (9.2, 8.5, 8.7, and 10 Hz, respectively) in connection with the trans-diaxial orientation of the protons attached to the 1'-C and 2'-C atoms of the glucosyl and galactosyl rings [3]. Similarly, the small SSCC of the 1'-H and 2'-H protons for IIb, IIIb, and Va (1.0, 0.7, and <0.5 Hz, respectively) also demonstrate their β-anomeric structure and $^4C_1$ configuration, since the configuration of the 2'-OH group of mannose differs from that in glucose and galactose [4].

The interpretation of the PMR spectra presented above is in agreement with data from the ^{13}C NMR spectra for bis(mannosyl)urea IV. The calculated and experimental values for the α,α and β,β anomers of IV are presented in Table 2.

Thus the experimental results confirm the β,β configuration of the amino substituent, in complete agreement with the results of ^{13}C NMR spectroscopy [5].

The UV spectra of the synthesized compounds are of interest. Maxima at 280 and 313-314 nm (shoulder) are observed for IIa, b in a neutral medium (see the Experimental section), whereas the dissociated form of the ureidomethylenemalononitrile fragment is formed in an alkaline medium, as evidenced by the formation of a pronounced maximum at 315 nm and disappearance of the maximum at 280 nm. A maximum of an undissociated form is observed in an acidic medium at 280 mn. Hydropyrimidine derivatives IIIa, b form maxima at 247-248 and 309-310 nm in a neutral medium, as compared with maxima at 247 and 315-318 nm in an alkaline medium and at 224-227 and 285-290 nm in an acidic medium. The close values of the maxima in neutral and alkaline media and the hypsochromic shift in an acidic medium, together with the absence in the PMR spectra of a signal of a proton attached to N_1, as well as a separate signal from 5-H in DMSO, constitute evidence that IIIa, b exist in the ionized form at least in solution. The fact that the previously synthesized arabinosylpyrimidines exist in the ionized form was proved by x-ray diffraction analysis [1].

EXPERIMENTAL

The UV spectra were recorded with a Specord UV-vis spectrophotometer in ethanol, 0.1 N HCl in ethanol, 0.1 NaOH in ethanol, water, 0.1 N NaOH, and 0.1 N HCl. The PMR spectra were recorded in d_6-DMSO and $CDCl_3$ with tetramethylsilane as the internal standard, and the ^{13}C NMR spectra were recorded in D_2O with a Brucker WH-90 spectrometer (90 MHz). Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in the following systems: A) propanol—25% NH_4OH—H_2O (7:1:2), B) chloroform—ethyl acetate (3:1), and C) ethyl acetate—ethanol (3:1). The plates were developed in UV light, with Erlich's reagent, and with iodine vapors. Column chromatography was carried out on L 100/250 silica gel. The IR spectra of mineral oil suspensions were recorded with UR-20 and Specord 75IR spectrometers. The $[\alpha]_D^{20}$ values were determined with a Perkin-Elmer 141 polarimeter.

1-(2',3',4',5'-Tetra-O-acetyl-β-D-glucopyranosyl)ureidomethylenemalononitrile (IIa). A mixture of 3.9 g (10 mmole) of tetraacetylglucosylurea Ia, 1.12 g (17 mmole) of malononitrile, and 25 ml of ethyl orthoformate was stirred with a magnetic stirrer for 10 h until Ia had dissolved completely. The course of the reaction was monitored by means of TLC. The ethyl orthoformate was removed from the reaction mixture, which contained IIa (R_f 0.35, system B) and VI [7] (R_f 0.5, system B), by distillation, and the oily residue was purified with a column packed with silica gel by successive elution with chloroform and solvents with gradually increasing polarities up to the chloroform—ethyl acetate system (5:1). The fraction with R_f 0.35 (system B) was collected and evaporated to dryness to give 1.8 g (39%)

of a light-yellow crystalline substance with mp 85°C and $[\alpha]_D^{20}$ −18.2° (c 1.0, ethanol). IR spectrum: 1550, 1625, 1710 sh, 1760 (C=O); 2245 (C≡N); 3220, 3320-3350 cm^{-1} (N–H). UV spectrum (in ethanol), λ_{max} (log ε): 280 (4.29), and 314 (sh) nm (4.01); (in 0.1 N HCl in ethanol) 280 nm (4.08); (in 0.1 N NaOH in ethanol) 315 nm (4.10). Found: C 48.6; H 4.8; N 11.8%. $C_{19}H_{22}N_4O_{10}$. Calculated: C 48.9; H 4.7; N 12.0%.

2-Oxo-4-imino-5-cyano-1-(2',3',4',5'-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3,4-tetrahydropyrimidine (IIIa). A 0.4-ml sample of triethylamine was added to a solution of 4 g (9 mmole) of IIa in 200 ml of ethanol, after which the mixture was refluxed. A crystalline substance precipitated after refluxing for 15 min. The mixture was refluxed for 1.5 h, after which it was maintained at 5°C for 10-12 h. The mixture was then filtered to give 3.5 g (87%) of a white crystalline substance with mp <264°C (dec., from ethanol), $[\alpha]_D^{20}$ +45.0° (c 0.5, dimethylformamide), and R_f 0.87 (system B) and 0.76 (system A). IR spectrum: 1560, 1590, 1690, 1740, 1760 (C=O); 2230 (C≡N); 3150-3220 and 3320-3360 cm^{-1} (N–H). UV spectrum (in water), λ_{max} (log ε): 247 (4.19) and 310 nm (4.10); (in 0.1 N NaOH) 247 (4.09), 318 nm (4.19); (in 0.1 N HCl) 224 (4.15), 285 nm (4.10). Found: C 48.5; H 4.7; N 11.7%. $C_{19}H_{22}N_4O_{10}$. Calculated: C 48.9; H 4.7; N 12.0%.

1-(2',3',4',5'-Tetra-o-acetyl-β-D-mannopyranosyl)ureidomethylenemalononitrile (IIb). This compound was obtained by a method similar to that used for IIa by heating 3 g (7 mmole) of tetraacetylmannosylurea Ib, 1.02 g (15 mmole) of malononitrile, and 20 ml of ethyl orthoformate at 60°C for 2 h, after which the mixture, which contained IIb (R_f 0.34, system B) and VI (R_f 0.5, system B), was separated by a procedure similar to that described for IIb to give 1 g (28%) of a light-yellow crystalline substance with mp 80°C (from ethanol) and $[\alpha]_D^{20}$ −31.4° (c 0.5, ethanol). IR spectrum: 1545, 1621, 1750 (C=O); 2110, 2200, 2250 (C≡N); 3330 cm^{-1} (N–H). UV spectrum (in ethanol), λ_{max} (log ε): 280 (4.16) and 313 nm (2.63); (in 0.1 N HCl in ethanol) 270 nm (4.16); (in 0.1 N NaOH) 310 nm (4.17). Found: C 48.6; H 5.0; N 11.6%. $C_{19}H_{22}N_4O_{10}$. Calculated: C 48.9; H 4.7; N 12.0%.

2-Oxo-4-imino-5-cyano-1-(2',3',4',5'-tetra-O-acetyl-β-D-mannopyranosyl)-1,2,3,4-tetrahydropyrimidine (IIIb). This compound was obtained by a procedure similar to that used for IIb by heating 3 g (7 mmole) of tetraacetylmannosylurea Ib, 1.02 g (15 mmole) of malononitrile, and 20 ml of ethyl orthoformate at 60°C for 2 h. The reaction mixture, which contained IIIb and VI, was evaporated to give a viscous yellow syrup, which was maintained at 5°C for 10 h. It was then dissolved in 100 ml of ethanol, 0.4 ml of triethylamine was added, and the mixture was refluxed for 15 min. It was then maintained at 5°C for 24 h to precipitate 1 g (28%) of white crystals with mp < 255°C (dec., from ethanol) and R_f 0.76 (system A), 0.05 (system B), and 0.82 (system C). IR spectrum: 1560, 1587, 1693, 1760 (C=O); 2228 (C≡N); 3145-3195, 3320-3350 cm^{-1} (N–H). UV spectrum (in ethanol) λ_{max} (log ε): 248 (4.16) and 309 nm (4.07). Found: C 48.8; H 4.5; N 11.6%. $C_{19}H_{22}N_4O_{10}$. Calculated: C 48.9; H 4.7; N 12.0%.

1-(2',3',4',5'-Tetra-O-acetyl-β-D-galactopyranosyl)ureidomethylenemalononitrile (IIc). This compound was obtained by a procedure similar to that used for IIa by heating 3.9 g (10 mmole) of tetraacetylgalactosylurea Ic, 1.12 g (17 mmole) of malononitrile, and 25 ml of ethyl orthoformate with stirring with a magnetic stirrer at 70°C for 12 h. The reaction mixture, which contained VI (R_f 0.5, system B) and IIc (R_f 0.34, system B), was evaporated to give a viscous syrup, which was separated with a column packed with silica gel by elution as in the case of IIa. The fraction with R_f 0.34 (system B) was collected and evaporated to dryness to give 2.4 g (52%) of light-yellow crystals with mp 81-82°C (from ethanol) and $[\alpha]_D^{20}$ +26.8° (c 0.5, ethanol). IR spectrum: 1545, 1621, 1710 sh, 1750 (C=O); 2230 (C≡N); 3180-3225, 3280-3340 cm^{-1} (N–H). UV spectrum (in ethanol), λ_{max} (log ε): 278 nm (3.92). Found: C 48.5; H 4.9; N 11.7%. $C_{19}H_{22}N_4O_{10}$. Calculated: C 48.9; H 4.7; N 12.0%.

Bis(2',3',4',5'-tetra-O-acetyl-β-D-galactopyranosyl)carbamide (Vb). A 1-ml sample of triethylamine was added to a solution of 2 g (4 mmole) of IIc in 40 ml of absolute ethanol, during which a white crystalline precipitate formed. The mixture was maintained at 5°C for 10 h, after which 1 g (35%) of white crystals with mp 224-225°C (from ethanol) (mp 225°C [6]) was removed by filtration. Found: C 48.2; H 5.6; N 4.2%. $C_{29}H_{40}N_2O_{19}$. Calculated: C 49.3; H 5.6; N 3.9%.

Bis(2',3',4',5'-tetra-O-acetyl-β-D-mannopyranosyl)carbamide (Va). A 2.5-g (6.5 mmole) sample of IV was stirred with 14.5 ml of pyridine and 7.9 ml of acetic anhydride at room temperature for 15 min until bis(mannosyl)urea IV had dissolved completely. The reaction

mixture was filtered and evaporated, and the residue was treated with water to precipitate 3.5 g (49%) of white crystals with mp < 182°C (dec., from ethanol). Found: C 47.8; H 5.6; N 3.9%. $C_{29}H_{40}N_2O_{19}$. Calculated: C 48.3; H 5.6; N 3.9%.

Bis(1-β-D-mannopyranosyl)carbamide (IV). A) A 3-g (13 mmole) sample of mannosylurea Id obtained by the method in [2] and containing admixed urea was refluxed in ethanol for 3 h to give 4 g (77%) of white crystals of IV with mp < 223°C (dec.).

B) Dry ammonia was passed for 1 h through a solution of 3 g (4.5 mmole) of Va in ethanol to give white crystals that did not give the characteristic reaction for ureido derivatives with Erlich's reagent. Workup gave 1.5 g (87%) of a product with mp < 222°C (dec.). Found: C 40.2; H 6.5; N 6.7%. $C_{13}H_{24}N_2O_{11}$. Calculated: C 40.6; H 6.3; N 7.3%.

The identical character of the compounds obtained by methods A and B was established on the basis of the similarity in their NMR spectra.

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N-GLYCOSIDES.

4.* SYNTHESIS OF 3-GLYCOSYL-4-HYDROXYHEXAHYDROPYRIMIDINE-2-THIONES ON THE BASIS OF GLYCOSYL ISOTHIOCYANATES

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The reaction of peracetylgluco(galacto)pyranosyl isothiocyanates with β-aminopropionaldehyde diethylacetal gave the corresponding glycosylthioureas, which, after removal of the protective groups, are converted spontaneously to 3-gluco(galacto)pyranosyl-4-hydroxyhexahydropyrimidine-2-thiones.

We have previously described [2, 3] the synthesis of N_1-[2,3,4,6-tetra-O-acetyl-β-D-gluco(galacto)pyranosyl]-N_3-(4-methyl-2-oxo-4-pentyl)thioureas, which were obtained by the reaction of the corresponding glycosyl isothiocyanates with 4-amino-4-methyl-2-pentanone, and their deacetylation products. A characteristic peculiarity of the aglycone in the synthesized N-glycosides is its primary acyclic structure both in the crystalline state and in solutions, whereas the N-alkyl analogs, which do not contain a sugar residue, have the cyclic 4-hydroxy-3-alkyl-4,6,6-trimethylhexahydropyrimidine-2-thione structure [4]. An examination of Dreiding models of glycosyloxoalkylthioureas shows that cyclization of the aglycone hinders steric interaction of the CH_3CO group with the substituents attached to the $C_{(2')}$ atom or with the electron pairs of the $O_{(1')}$ atom.

*See [1] for communication 3.

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