ANOMALOUS NUCLEOSIDES AND RELATED COMPOUNDS

XXVIII.* SYNTHESIS OF N-GLYCOSIDES OF 5-AMINO- AND 5-ALKYLAMINO-6-AZAURACILS

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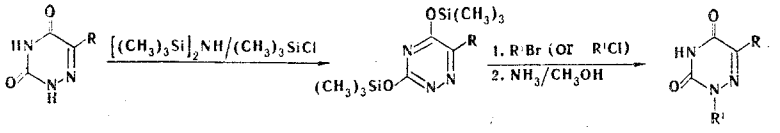
β-N_1-Glycosides of the azapyrimidine series were synthesized by reaction of trimethylsilyl derivatives of 5-amino- and 5-alkylamino-6-azauracils with protected 1-halo-substituted sugars (in benzene at room temperature for 72 h) in the presence of $HgO/HgBr_2$ or $Hg(OCOCH_3)_2$. Some of the physicochemical properties of the new anomalous nucleosides were studied.

During an experimental and clinical study of 5- and 6-azapyrimidine nucleosides it was established that they are promising antimetabolites with antitumorigenic and antivirus action [2-6]. Continuing our study of 6-azapyrimidine derivatives, we synthesized and studied the products of glycosylation of 5-amino- and 5-alkylamino-6-azauracils. To obtain the azapyrimidine nucleosides we used the "silyl condensation" method [7], which makes it possible to realize the specific synthesis of N_1-glycosides (see the scheme below).

Compounds I-IV were converted to trimethylsilyl ethers by heating in a mixture of hexamethyldisilazane and trimethylchlorosilane at 170°C for a few hours. The silylation time was dependent on the basicities of the 5-substituted 6-azauracils and increased on passing from I to IV. Silyl derivatives V-VIII were condensed, without additional purification, with the acyl halogenose in the presence of a mercury catalyst: $HgO/HgBr_2$ or $Hg(OCOCH_3)_2$ in an inert solvent (in benzene at 20°C for 72 h). As a result of the condensation we obtained acylated azapyrimidine nucleosides IX-XIV. Compounds XV-XIX were isolated after deacylation of derivatives IX-XIII with a methanol solution of ammonia at 0°C.

The 5-substituted 6-azapyrimidine nucleosides are colorless, very hygroscopic substances that are soluble in water and other polar solvents. Like uridine [8], they are resistant to acid hydrolysis: when they are refluxed in 1 N HCl, traces of the base that is split out appear on the chromatogram only after 3 h.

The position of the glycoside bond in the 5-substituted azapyrimidine nucleosides was established on the basis of the UV spectra. It is known [9-11] that in the glycosylation of 5-methyl-, 5-hydroxymethyl-, and 5-trifluoromethyl-6-azauracils the monosaccharide residue is attached to N_1, shifting the absorption maximum of the N-glycoside to the short-wave region as the pH of the medium increases. In analogy with the behavior of known azapyrimidine nucleosides [9-12], the free N-glycosides that we obtained display a hypsochromic shift of the UV absorption maximum of 10-13 nm when neutral solutions are made alkaline; this proves glycosylation in the N_1 position.



I-IV V-VIII IX-XIX

The β configuration of the glycoside center of the synthesized nucleosides was predetermined by the selected conditions for the carrying out of the "silyl condensation" and was confirmed by the circular dichroism

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TABLE 1. 5-Substituted 6-Azapyrimidine Nucleosides (IX-XIX)

Compound	R	R[1a]	mp, °C	N found, %	Empirical formula	N calc., %	λ_{max}, nm (ε · 10⁻³) pH 1	pH 7	pH 13	$[\alpha]_D^{20}$ deg, (C)[e]	R_f in system A	Yield, %
IX	NH_2	Glc(OAc)$_4$	215–217	12,4	$C_{17}H_{22}N_4O_{11}$	12,2		302(5,16)		−62,0(1,03)	0,82	90
X	$NHCH_3$	Glc(OAc)$_4$	109–110	10,3	$C_{18}H_{24}N_4O_{11}\cdot C_6H_6$[b]	10,2		311(4,56)		−63,4(1,04)	0,86	87
XI	$N(CH_3)_2$	Glc(OAc)$_4$	Amorphous	10,5	$C_{19}H_{26}N_4O_{11}$	10,5		318(4,42)		−83,3(1,14)	0,87	90
XII		Glc(OAc)$_4$	124–126	10,6	$C_{21}H_{28}N_4O_{12}$	10,6		311(5,43)		−123,8(1,05)	0,84	88
XIII	NH_2	Rib(OBz)$_3$	Amorphous	9,5	$C_{29}H_{24}N_4O_9$	9,8		231(45,2) 300(4,26)		—	0,86	93
XIV	$N(CH_3)_2$	Xyl(OAc)$_3$	176–178	13,6	$C_{16}H_{22}N_4O_9$	13,5		320(5,34)		−136,5(1,08)	0,92	54
XV	NH_2	Glc	173–175	18,5	$C_9H_{14}N_4O_7\cdot H_2O$[c]	18,2	300(5,09)	300(5,06)	290(4,30)	−31,4(1,00)	0,31	60
XVI	$NHCH_3$	Glc	250–251	18,5	$C_{10}H_{16}N_4O_7$	18,5	311(5,02)	311(5,09)	299(4,79)	−32,1(1,00)	0,43	73
XVII	$N(CH_3)_2$	Glc	Amorphous	17,3	$C_{11}H_{18}N_4O_7$	17,6	318(3,64)	318(4,45)	301(3,96)	−20,1(1,00)	0,52	44
XVIII		Glc	169–170	15,3	$C_{13}H_{20}N_4O_8$	15,5	309(4,33)	309(4,25)	309(4,27)	−17,6(1,00)	0,46	58
XIX	NH_2	Rib	228–230	21,6	$C_8H_{12}N_4O_6$	21,5	300(4,99)	300(5,17)	293(4,92)	−14,3(1,00)	0,34	60

[a]Abbreviations: Glc(OAc)$_4$ = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl, Rib(OBz)$_3$ = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl, Xyl(OAc)$_3$ = 2,3,4-β-D-xylopyranosyl, Glc = β-D-glucopyranosyl, and Rib = β-D-ribofuranosyl.

[b]Found for X: C 52.3, H 5.6%. Calculated: C 52.4, H 5.5%.

[c]Found for XV: C 35.3, H 5.6%. Calculated: C 35.1, H 5.2%.

[d]The UV absorption of IX-XIV was measured in ethanol, and the UV absorption of XV-XIX was measured in aqueous solutions.

[e]The specific rotation of IX-XIV was determined in chloroform, and the specific rotation of XV-XIX was determined in water.

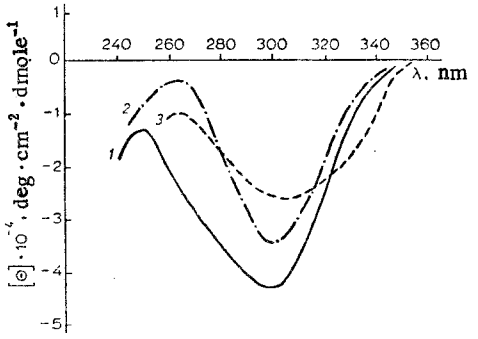

Fig. 1. Circular dichroism spectra in methanol: 1) 1-β-D-ribofuranosyl-5-amino-6-azauracil (XIX); 2) 1-β-D-glucopyranosyl-5-amino-6-azauracil (XV); 3) 1-β-D-glucopyranosyl-5-methylamino-6-azauracil (XVI).

(CD) and IR spectra. Like 6-azauridine [13], the 5-substituted azanuclosides have a large negative Cotton effect (Fig. 1). The frequencies of C_1-H deformation vibrations that are characteristic for β-glycosides [14] were identified in the IR spectra at 890-900 cm^{-1}.

EXPERIMENTAL

The UV spectra of water and ethanol solutions of the compounds were recorded with a Specord UV-Vis spectrophotometer. The CD spectra and the specific rotation were recorded with a Spectropol-1 apparatus. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. Chromatography on Filtrak FN-12 paper (German Democratic Republic) was carried out in system A [n-butanol–acetic acid–water (5 : 2 : 3)], and column chromatography was carried out in a column filled with LK-40/100 silica gel (Czechoslovakian SR) in system B [benzene–acetone (2 : 1)]. The characteristics of the compounds obtained are presented in Table 1.

1-(2',3',4',6'-Tetra-O-acetyl)-β-D-glucopyranosides of 5-Amino- and 5-Alkylamino-6-azauracils (IX-XII). Hexamethyldisilazane (37 ml) and 8 ml of trimethylchlorosilane were added to 20 mmole of I-IV, and the mixture was heated at 170°C for 1-3 h (until the starting base dissolved completely). The excess of the silylating agents was removed by vacuum distillation, and the silyl derivative (V-VIII) was dissolved in 20 ml of dry benzene. The solution was mixed with 20 mmole of acetobromoglucose [15], and the mixture was added to a previously dried suspension of 5 g of HgO and 5 g of $HgBr_2$ in benzene. The mixture was allowed to stand at room temperature for 2 to 3 days. At the end of the condensation (after the spot of the starting compound disappeared on the chromatogram), 5 ml of ethanol and 300 ml of chloroform were added to the mixture. The mercury salts were removed by filtration, and the filtrate was washed successively with saturated NaCl solution, 30% KI solution (acidified to pH 3 with acetic acid), saturated $NaHCO_3$ solution, and water. It was then dried over magnesium sulfate, the chloroform was evaporated, and the reaction products were purified by chromatography on silica gel and crystallization from a mixture of hexane with benzene or ethyl acetate.

1-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-5-amino-6-azauracil (XIII). A 0.64-g (5 mmole) sample of I was silylated as described above, and the product was condensed in the presence of mercuric acetate (0.01 g) with 1-chloro-2,3,5-tri-O-benzoylribofuranose [16], obtained from 2.7 g (5.1 mmole) of 1-O-acetyl-tri-O-benzoylribofuranose. The mixture was worked up as in the preparation of IX-XII to give 2.1 g of XIII.

1-(2',3',4'-Tri-O-acetyl-β-D-xylopyranosyl)-5-dimethylamino-6-azauracil (XIV). The product of silylation of 3.12 g (20 mmole) of III was condensed with 1-bromo-2,3,4-tri-O-acetylxylopyranose [17], by the method used to obtain IX-XII. White needles of XIV (3.44 g) were isolated from ethyl acetate–cyclohexane (1 : 1).

1-β-D-Glycosides of 5-Amino- and 5-Alkylamino-6-azauracils (XV-XIX). A 10-mmole sample of IX-XIII was dissolved in 250 ml of absolute methanol, and the solution was cooled to −5°C and saturated with ammonia in the course of 2.5 h. It was then maintained at 0°C until the splitting out of the acyl groups was complete (monitored by paper chromatography). After deacylation, the ammonia was removed from the solution by bubbling in air, and the methanol was vacuum evaporated. The residue was dissolved in aqueous ethanol, the solution was refluxed with activated charcoal, and the reaction products were dried with ethyl acetate. The products were crystallized: XV from aqueous alcohol, XVI from ethanol–ether, XVIII from nitromethane, and XIX from aqeuous methanol.

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SYNTHESIS AND SOME PROPERTIES OF 2-METHYLPHTHALAZONE HYDRAZONES*

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The reaction of 1-chloro- and 1,4-dichloro-2-methylphthalazinium salts with hydrazine leads to the formation of hydrazones and azines of the corresponding 2-methylphthalazones, the ratio of which depends on the reaction conditions. Symmetrical azines of 4-substituted phthalazones exist in the EE'E" form, while azines of 2-methyl-4-substituted phthalazones exist in the ZE'Z" form.

During a study of the structure of 1-hydrazinophthalazines [2] it was found necessary to synthesize model compounds having a fixed hydrazone structure – 2-methyl- and 2-methyl-4-chlorophthalazone hydrazones (Ia,b). Hydrazones Ia,b and phthalazones IIIa,b in close ratios were obtained from the hygroscopic 1-chloro- (IIa) and 1,4-dichloro-2-methylphthalazinium (IIb) chlorides and 1,4-dichloro-2-methylphthalazinium methylsulfate (IIc) (the analogous 3,6-dichloro-4-methylpyridazinium methylsulfate is stable in water [3]) under the influence of aqueous hydrazine solution. In the reaction of salts IIa-c (without isolation after synthesis) with aqueous hydrazine solution we isolated, in addition to hydrazones Ia,b and phthalazones IIIa,b, azines of 2-methyl-4-substituted phthalazones (IVa,b), the ratio of which depends on the hydrazine concentration. An increase in the hydrazine concentration increases the yield of the hydrazone, whereas a decrease in its concentration raises the yields of phthalazones IIIa,b and azines IVa,b. The use of anhydrous hydrazine in organic solvents raises the yields of hydrazones Ia,b considerably.†

*Communication LII of the series "Hydrazones." See [1] for communication LI.

† The synthesis of 2-methyl-4-chlorophthalazone dimethylhydrazone in low yield by reaction of methylsulfate salt IIc with aqueous 1,1-dimethylhydrazine solution was described in [2]. The yield increases to 85-90% in anhydrous methanol.

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