ANOMALOUS NUCLEOSIDES AND RELATED COMPOUNDS

XVIII.* SYNTHESIS OF 1- AND 2-GLYCOSYLBENZOTRIAZOLES

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N_1- and N_2-benzotriazolylribo-, -xylo-, and -glucopyranosides were synthesized in a search for nucleic exchange antimetabolites by the condensation of the silver or chloromercury salt of benzotriazole with acetobromo sugars with subsequent removal of the protecting groups. The silver salt results in the predominant formation of N_1-glycosides, while N_2-glycosides predominate in the mixture when the mercuric salt is used. The site of addition of the sugar to the base and the β configuration of the glycoside center were proved on the basis of the UV, IR, and PMR spectra. The antitumorigenic activity of the synthesized benzotriazolylglycosides was established.

Benzotriazole and a number of its derivatives, which are structural analogs of purine, have biological activity [2-5]. An increase in activity, a broadening of the spectrum of biological activity, and a reduction in toxicity can be expected when they are glycosylated.

The synthesis of N_1-benzotriazolylglycosides including ribofuranose, and gluco-, galacto-, and arabopyranose residues by the silyl method was described in [6,7]. There are no data on their biological activity.

We have synthesized N_1- and N_2-benzotriazolylribo- (IX and XII), -xylo- (X and XIII), and -glucopyranosides (XI and XIV).

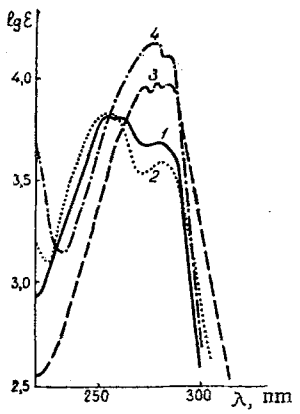
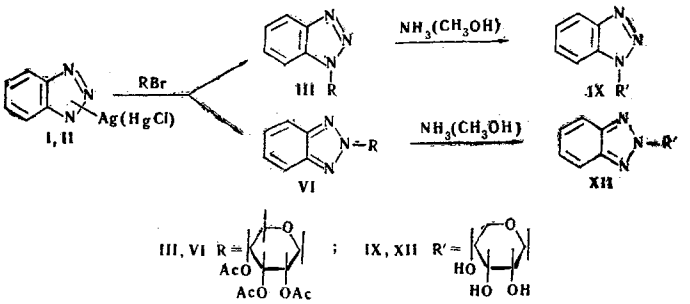


Fig. 1. UV spectra in ethanol: 1) 1-methylbenzotriazole; 2) 1-β-D-ribopyranosylbenzotriazole; 3) 2-methylbenzotriazole; 4) 2-β-D-ribopyranosylbenzotriazole.

The condensation of the chloromercury (I) or silver (II) salt of benzotriazole with acylated haloglycosides in refluxing xylene results in the formation of a mixture of isomeric acylated benzotriazolylglycosides. The silver salt gives predominantly N_1-substituted benzotriazoles, while the chloromercury salt gives primarily N_2-glycosides. The acetyl protecting group was removed with ammoniacal methanol.



*See [1] for communication XVII.

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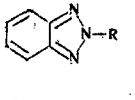
TABLE 1. Properties of 1- and 2-Glycosylbenzotriazoles

III-V, IX-XI



VI-VIII, XII-XIV

Comp.	R[a]	mp, °C	Empirical formula	N, % found	N, % calc.	R_f A	R_f B	R_f C	UV spectra, λ_{max}, nm (log ε)	Specific rotation $\alpha_D^{t°}$	Specific rotation solvent	Yield, %
III	Ac A	151—153[b]	$C_{17}H_{19}N_3O_7$	11,2	11,1	0,90	0	0,90	254(3,79); 282(3,72)	—52,3[22]	chloroform	27
IV	Ac B	154—155[c]	$C_{17}H_{19}N_3O_7$	10,9	11,1	0,93	0	0,95	254(3,86); 282(3,64)	—88,2[24]	chloroform	45
V[7]	Ac C	117—118[c]	—	—	—	—	—	—	254(3,46); 282(3,41)	—61,5[24]	chloroform	66
VI	Ac A	157—158[c]	$C_{17}H_{19}N_3O_7$	11,2	11,1	0,90	0	0,95	278(3,97); 285(3,89)	—37[22]	ethanol	52
VII	Ac B	161—162[b]	$C_{17}H_{19}N_3O_7$	11,0[d]	11,1	0,91	0	0,95	278(3,95); 285(3,87)	—86,5[24]	ethanol	38
VIII	Ac C	196—198[c]	$C_{20}H_{23}N_3O_9$	9,2	9,3	0,95	0	0,96	278(4,09); 286(4,03)	—40,5[22]	chloroform	70
IX	A	150—151[b]	$C_{11}H_{13}N_3O_4$	16,9	16,7	0,61	0,61	0,60	254(3,82); 282(3,0)	—	—	75
X	B	157—159[b]	$C_{11}H_{13}N_3O_4$	16,7	16,7	0,60	0,60	0,62	255(3,86); 282(3,65)	—	—	80
XI[7]	C	197—198[b]	—	—	—	0,60	0,70	0,70	254(3,82); 281(3,60)	—	—	86
XII	A	185[c]	$C_{11}H_{13}N_3O_4$	16,8[e]	16,7	0,85	0,82	0,75	278(4,16); 285(4,10)	—32[22]	water	91
XIII	B	217—219[c]	$C_{11}H_{13}N_3O_4$	16,8[f]	16,7	0,86	0,86	0,72	278(4,15); 285(4,09)	—43,2[22]	water	89
XIV	C	206—208[c]	$C_{12}H_{15}N_3O_5$	15,1	14,9	0,85	0,87	0,75	278(4,07); 285(4,00)	—45,3[18]	pyridine	85

[a]A is ribopyranosyl, B is xylopyranosyl, C is glycopyranosyl, AcA is 2,3,4-tri-O-acetyl-β-D-ribopyranosyl, AcB is 2,3,4-tri-O-acetyl-β-D-xylopyranosyl, and AcC is 2,3,4,6-tetra-O-acetylglucopyranosyl.

[b]The crystallization solvent was methanol.

[c]The crystallization solvent was ethanol.

[d]Found: C 54.3; H 5.0%. Calculated: C 54.1; H 5.0%.

[e]Found: C 52.6; H 5.4%. Calculated: C 52.6; H 5.2%.

[f]Found: C 53.0; H 5.1%. Calculated: C 52.6; H 5.2%.

The site of addition of the carbohydrate residue to the base was established by comparing the UV spectra with the spectra described in [8] for 1-methyl- and 2-methylbenzotriazoles (Fig. 1).

It is known that the stereochemistry of the glycoside bond in nucleosides obtained by this path is controlled by the 2-acyloxy group of the sugar. Regardless of the initial configuration of the atoms attached to C_1-C_2, nucleosides with a trans C_1-C_2 configuration are formed in the process. On the basis of this, one might have expected the formation of nucleosides with the β configuration of the glycoside center. In fact, the PMR spectrum of XIV contains a doublet signal from an anomeric proton with a chemical shift of τ 4.16 ppm and a spin–spin coupling constant of J_{1a2a} 8.9 Hz, which is characteristic for an axial hydrogen attached to the glycoside atom of β-nucleosides [10].

The IR spectra of the free benzotriazolylglycosides have bands of medium or strong intensity at 890-915 cm^{-1} that correspond to the deformation vibrations of an axial hydrogen atom attached to the glycoside atom of β-sugars.

The molecular rotation of XIII ($[M]_D$-108) coincides with the rotation of β-methylxylopyranoside [11].

The pyranose form of the ring in the benzotriazolylglycoside is confirmed by periodate oxidation [1.9 and 1.98 mole of sodium periodiate, respectively, were expended in the oxidation of 1 mole of the benzotriazolylribosides (IX, XII) and benzotriazolylxylosides (X, XIII)].

In acidic and alkaline media, the N_1-benzotriazolylglycosides are two to three times more stable than the corresponding N_2 derivatives.

According to preliminary data, some of the synthesized benzotriazolylglycosides have antitumorigenic activity in experimental tumors of mice and rats.

EXPERIMENTAL

Leningrad B paper was used for ascending chromatography in the following systems of solvents: water-saturated butyl alcohol (A), butyl alcohol-saturated water (B), or butyl alcohol–acetic acid–water (5:2:3) (C). The chromatograms were developed in UV light.

The UV spectra of ethanol solutions were recorded with an SF-4 spectrophotometer. The IR spectra of KBr pellets were recorded with a UR-10 spectrometer. The PMR spectra of D_2O solutions were recorded with a Varian-A60A spectrometer at 40°. The external standard was tetramethylsilane.

1-(2',3',4'-Tri-O-acetyl-β-D-ribopyranosyl)benzotriazole (III). A 4.5-g (13 mmole) sample of acetobromoribose in 30 ml of xylene was added to a refluxing suspension of 3 g (13 mmole) of II in 250 ml of dry xylene after one-fifth of the solvent was removed by distillation, and the mixture was refluxed for 3 h and cooled. The silver bromide was removed by filtration, and the filtrate was vacuum-evaporated. The syrup was diluted with a small amount of methanol, 15 ml of petroleum ether was added, and the mixture was allowed to stand for crystallization to give 1.35 g of III as colorless prisms. According to UV spectroscopy, the mother liquor contained a mixture of III and VI with predominance of the N_1-isomer.

Compound IV was similarly obtained (Table 1).

1-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)benzotriazole (V). This compound was similarly obtained. A small amount of absolute methanol was added to the syrupy residue after removal of the solvent, and the mixture was allowed to stand for crystallization. Compound VIII (14%) precipitated initially.

Compound V crystallized rapidly at room temperature after removal of VIII from the mother liquor.

2-(2',3',4'-Tri-O-acetyl-β-D-ribopyranosyl)benzotriazole (VI). Condensation of 3.5 g (10 mmole) of I with 3.35 g (10 mmole) of acetobromoribose was carried out by the method described for III. Compound I reacted completely in 5-10 min. The mixture was refluxed for another 20-30 min, cooled, and the HgClBr was removed by filtration. The filtrate was treated twice with 100 ml of 30% potassium iodide solution, washed with water, dried with sodium sulfate, and vacuum-evaporated. The syrup was diluted with a small amount of absolute ethanol and allowed to stand for crystallization to give 2.24 g of VI. A mixture of III and VI began to melt at 25° lower than the melting point of III. IR spectrum: $\nu_{C-H\,arom}$ 3072, 2995; $\nu_{C=O}$ 1753; ν_{C-O-C} 1230; $\delta_{CH\,arom}$ 1080, 1050, 950, 782, 748; δ_{C_1-H} 920 cm^{-1}. According to UV spectroscopy, the mother liquor contained a mixture of VI and III.

Compounds VII and VIII were similarly obtained (Table 1).

1-β-D-Ribopyranosylbenzotriazole (IX). A solution of 0.5 g of III in 50 ml of absolute methanol was saturated with ammonia at 0° for 1.5 h and allowed to stand in the cold for 2 days. The cleavage of the acetyl protecting groups was monitored by chromatography. The methanol solution was vacuum-evaporated to a small volume, ether was added until turbidity was produced, and the mixture was allowed to stand in the cold for crystallization to give 0.25 g of IX.

Compounds X-XIV were similarly obtained (Table 1). IR spectrum of X: ν_{OH} (broad) 3350; $\nu_{C-H\,arom}$ 2935, 2898, $\delta_{C-H\,arom}$ 1030, 995, 840, 790, 760; δ_{C_1-H} 916 cm^{-1}. IR spectrum of XII: ν_{OH} (broad) 3400; $\nu_{C-H\,arom}$ 2935, 2950; $\delta_{C-H\,arom}$ 1053, 990, 786, 755; δ_{C_1-H} 916 cm^{-1}.

Chloromercury Salt of Benzotriazole (I). A 5.95-g (50 mmole) sample of benzotriazole was dissolved in a mixture of 50 ml of 1 N sodium hydroxide in 50 ml of ethanol, and the mixture was added dropwise with stirring to a solution of 13.8 g (50 mmole) of mercuric chloride in 800 ml of 25% ethanol. The precipitate was removed by filtration, washed with 25% ethanol, and dried to give 16.6 g (91%) of I as a white, insoluble powder that did not melt up to 300°. Found: Cl 9.6%. $C_6H_4ClHgN_3$. Calculated: Cl 10.0%.

Silver Salt of Benzotriazole (II). This compound [32.4 g (89%)] was similarly obtained as a white powder from 27.2 g (160 mmole) of silver nitrate and 19.3 g (160 mmole) of benzotriazole dissolved in a mixture of 162 ml of 1 N sodium hydroxide and 162 ml of ethanol. Found: N 17.9%. $C_6H_4AgN_3$. Calculated: N 18.6%.

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