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NUCLEOSIDES OF 4-METHYLTHIO-1,2,3-TRIAZOL-5-YL-CARBOXYLIC ACID DERIVATIVES

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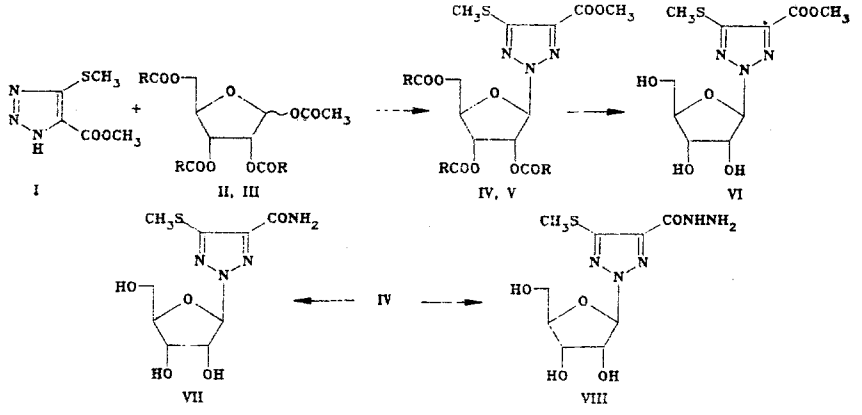
2-β-D-Ribofuranosyl-4-methylthio-5-methoxycarbonyl-1,2,3-triazole was obtained by fusing 4-methylthio-5-methoxycarbonyl-1,2,3-triazole together with tetraacyl-D-ribofuranose, followed by deacylation, and its amide and hydrazide were prepared. The structures of the new nucleosides were established by converting them into known 2-nucleosides of 1,2,3-triazol-4-yl-carboxylic acid derivatives.

Nucleosides of azoles, including 1,2,3-triazole, are of interest as potential inhibitors of nucleic acid metabolism in tumor and virus-infected cells. Among the nucleosides of 1,2,4-triazole, thiazole, pyrazole, and other azoles, compounds with pronounced antitumor or antiviral activity were discovered (for example, Virazol, pyrazofurin, thiazofurin, etc.) [1].

In the present work, we studied the ribosylation under fusion reaction conditions of 4-methylthio-5-methoxycarbonyl-1,2,3-triazole (I) obtained by T. S. Safonova et al. by rearrangement of 6-methylthio-5-diazouracil [2]. Fusion of triazole (I) with 1,2,3,5-tetra-O-acetyl-D-ribofuranose (II), or 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (III) at 120°C, in vacuo and in the presence of catalytic amounts of bis-p-nitrophenyl phosphate, led to the formation of 2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-methylthio-5-methoxycarbonyl-1,2,3-triazole or to the corresponding per-O-benzoyl derivative V in yields of 89 and 96%, respectively. In a control by TLC, the formation of noticeable amounts of isomeric nucleosides was not revealed.



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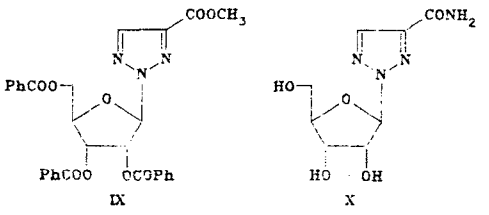


II, IV R=CH_3; III, V R=Ph

Deacylation of nucleoside IV by a methanolic solution of HCl or nucleoside V by a solution of sodium methylate in methanol gave 2-β-D-ribofuranosyl-4-methylthio-5-methoxycarbonyl-1,2,3-triazole (VI). In the aminolysis of ester IV, amide VII was isolated. By the action of hydrazine hydrate in methanol on nucleoside IV, a hydrazide of 2-β-D-ribofuranosyl-4-methylthio-1,2,3-triazol-5-yl-carboxylic acid (VIII) is formed, which was isolated in 49% yield from the reaction mixture after holding for 24 days at 20°C.

To establish the structure of the nucleosides obtained, we converted nucleoside V into 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxy-carbonyl-1,2,3-triazole (IX) and nucleoside VII into the previously described 2-β-D-ribofuranosyl-4-carbamoyl-1,2,3-triazole (X) [3]. This was done by the desulfuration of nucleosides V and VII by boiling them in methanol with Raney nickel.

By comparing PMR spectra obtained for ester IX and amide X (Table 1) with previously reported PMR spectra for the isomeric 1- and 2-nucleosides of 1,2,3-triazol-4-yl-carboxylic acid derivatives (Table 2) [3, 4], the synthesized nucleosides could be assigned to 2-substituted triazoles. The obtained data of UV spectra of compound X and the previously described 2-β-D-ribofuranosyl-4-carbamoyl-1,2,3-triazole (Table 2) [3] coincide completely.

EXPERIMENTAL

The PMR spectra were run on a Bruker WH-360 spectrometer (360 MHz), using TMS as internal standard. The IR spectra were recorded on a Perkin-Elmer 283 spectrophotometer in KBr tablets UV spectra on a Specord UV-vis spectrophotometer in ethanol, and for compound X, on a Cary-219 apparatus at a concentration of $1 \cdot 10^{-4}$ mole. Silufol UV-254 plates were used for the analytical TLC. The preparative chromatography was carried out on plates (20 × 20 cm) with a LSL_{254} 5-40 μm (Chemapol) nonstationary layer of silica gel at a layer thickness of 1 mm. The following systems were used for the chromatography: A (benzene–acetone, 9:1), B (chloroform–methanol, 4:1), C (chloroform–methanol, 6:1) D (chloroform–methanol, 3:1). The specific rotation was determined on a Perkin-Elmer 241 polarimeter. For fusion, bis-p-nitrophenyl phosphate was used, 10% with respect to the weight of the heterocycle.

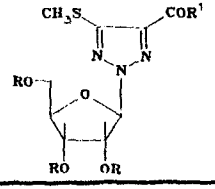
The initial 4-methylthio-5-methoxycarbonyl-1,2,3-triazole was kindly provided by fellow workers of the S. Orzhonikidze All-Union Pharmaceutical Chemistry Research Institute, T. S. Safonova, M. P. Nemeryuk, and A. L. Sedov.

2-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-methylthio-5-methoxycarbonyl-1,2,3-triazole (IV). A 0.17-g portion (1 mmole) of heterocycle I and 0.31 g (1 mmole) of tetra-O-acetyl-D-ribofuranose (II) are fused in vacuo at 120°C in the course of 40 min in the presence of 20 mg of bis-p-nitrophenyl phosphate. The dark melt is dissolved in 2 ml of chloroform, the solution is deposited on nine plates and chromatographed in system A. After elution from silica gel by system B and evaporation of the solvent, 0.4 g (89%) of an oily colorless compound IV is obtained, R_f 0.39 (A).

2-(2,3,5-Tri-O-Benzoyl-β-D-ribofuranosyl)-4-methylthio-5-methoxycarbonyl-1,2,3-triazole (V). A 0.17-g portio (1 mmole) of heterocycle I and 0.5 g (1 mmole) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (III) are fused together. The experimental conditions are similar as in the preceding case. By TLC in system A on 10 plates, 0.6 g (96%) of a colorless oily compound V are isolated, R_f 0.54 (A).

2-β-D-Ribofuranosyl-4-methylthio-5-methoxycarbonyl-1,2,3-triazole (VI). A. A 0.6-g portion (1.3 mmole) of nucleoside IV is dissolved in 15 ml of a 1% HCl solution in anhydrous methanol, and the solution is left to stand at 20°C for 20 h. The solvent is distilled in vacuo, and the residue is chromatographed in system C to yield 0.37 g (88%) of crystalline compound, R_f 0.63 (B), mp 115-117°C (from methanol). UV spectrum, λ_{max} (ε): 215 (10,350),

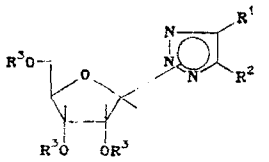
TABLE 1. PMR Spectra of Compounds IV-X



Compound	Chemical shifts, δ, ppm									SSCC, Hz						Solvent
	1′-H	2′-H	3′-H	4′-H	5′-H	5″-H	R	S—CH_3	R^1	$J_{1'2'}$	$J_{2'3'}$	$J_{3'4'}$	$J_{4'5'}$	$J_{4'5''}$	$J_{5'5''}$	
IV	6,18	5,87	5,75	4,47	4,44	4,21	2,13 2,12 2,08	2,59	3,95	3,2	5,1	5,5	3,5	5,0	11,5	$CDCl_3$
V	6,49	6,32	6,24	4,89	4,79	4,65	8,10— 7,30	2,50	3,93	3,0	5,1	5,9	4,0	5,1	12,1	$CDCl_3$
VI	5,98	4,58	4,46	4,15	3,80	3,68	—	2,56	3,90	3,1	4,5	5,5	3,6	5,0	12,0	CD_3OD
VII	6,12	4,76	4,61	4,27	3,91	3,79	—	2,64	—	3,2	4,8	5,2	3,3	5,5	12,2	CD_3OD+H_2O
VIII	5,97	4,59	4,48	4,12	3,79	3,68	—	2,54	—	3,2	4,7	5,5	3,6	5,5	12,3	CD_3OD
IX	6,56	6,31—6,23		4,89	4,79	4,63	8,08— 7,30	8,10*	3,94	3,5			3,9	4,9	11,8	$CDCl_3$
X	5,90	4,51	4,26	3,98	3,58	3,46	—	8,15*	7,85 7,53	4,0	4,5	4,5	4,7	5,8	12,1	DMSO plus CD_3OD

*5-H – proton of a heterocycle in a desulfurated product.

TABLE 2. PMR and UV Spectra of 1,2,3-Triazole Nucleosides Described in Literature



Position of attachment of heterocyclic rings	R¹	R²	R³	Chemical shifts, δ, ppm (SSCC, Hz)		Solvent	λ_{max}, nm (alcohol)	ε	Ref. for PMR and IR spectra
				H of heterocyclic ring	1'-H				
$N_{(1)}$	CH_3COO	H	C_6H_5CO	8,38	6,52 ($^3J_{1'2'}$ =2,8);	$CDCl_3$	229	49 250	[4, 4]
				9,11	6,8 ($^3J_{1'2'}$ =2,4)	DMSO			[4]
				8,35		$CDCl_3$			[3]
				9,15		DMSO			[3]
$N_{(1)}$	H	CH_3COO	C_6H_5CO	8,18; 8,41	7,15 ($^3J_{1'2'}$ =1,3)	$CDCl_3$	231	49 235	[4, 4]
						DMSO			[4]
$N_{(2)}$	CH_3COO	H	C_6H_5CO	8,12	6,59 ($^3J_{1'2'}$ =1,3)	$CDCl_3$			[3]
$N_{(2)}$	CH_3COO	H	C_6H_5CO	8,50	6,87 ($^3J_{1'2'}$ =2,2)	DMSO			[3]
$N_{(1)}$	$CONH_2$	H	H				213	10 600	[3]
$N_{(1)}$	H	$CONH_2$	H	8,30	6,76 ($^3J_{1'2'}$ =3,0)	DMSO	217	9 800	[4, 3]
$N_{(2)}$	$CONH_2$	H	H	8,28	5,97 ($^3J_{1'2'}$ =4,0)	DMSO	226	11 450	[3, 3]

239 (8600), 282 nm (5100). IR spectrum: 1730 cm^{-1} (C=O) $[\alpha]_D^{20}$ −5.8° (c 0.1 methanol). Found: C 39.5; H 4.9; N 14.3; S 10.5%. $C_{10}H_{15}N_3O_6S$. Calculated: C 39.3; H 4.9; N 13.8; S 10.5%.

B. A 0.38-g portion (0.6 mmole) of nucleoside V is stirred for 1 h at 20°C with 15 ml of 0.1 N solution of sodium methylate in methanol. The solution is neutralized by Dowex (H^+) resin. The resin is filtered, thoroughly washed with methanol, the filtrate is evaporated, and the residue is chromatographed in system C on six plates to yield 0.17 g (90%) of a compound, which, according to the PMR and IR data, is identical with a product obtained by method A.

2-β-D-Ribofuranosyl-4-methylthio-5-carbamoyl-1,2,3-triazole (VII). A 0.17-g portion (0.55 mmole) of ether (VI) is placed in 10 ml of anhydrous methanol, saturated with ammonia, and the mixture is allowed to stand at 20°C for 24 h. The solvent is evaporated, and compound VII is isolated in quantitative yield, R_f 0.4 (B), mp 175-179°C (from methanol). UV spectrum, λ_{max} (ε): 213 (10,450), 236 (8200), 282 nm (5100). IR spectrum: 1670 (C=O), 1612 cm^{-1} (C=N); $[\alpha]_D^{20}$ −5.0° (c 0.1 methanol). Found: C 37.3; H 4.8; N 19.6; S 10.8%. $C_9H_{14}N_4O_5S$. Calculated: C 37.2; H 4.9; N 19.3; S 11.0%.

2-β-D-Ribofuranosyl-1-methylthio-1,2,3-triazol-5-yl-carboxylic acid hydrazide (VIII). A 0.7-g portion (1.6 mmole) of ester IV is dissolved in 15 ml of anhydrous methanol containing 1 ml of hydrazine hydrate and the solution is allowed to stand at 20°C for 24 days. The solvent is distilled with methanol, and the residue is chromatographed in system D on nine plates, twice passing the system of solvents. Yield, 0.24 g (49%) of a foamy compound VIII, R_f 0.17 (B). IR spectrum: 1676 (C=O), 1600 cm^{-1} (C=N), $[\alpha]_D^{20}$ −36.2° (c 0.8 methanol). Found: C 35.3; H 5.0; N 22.4%. $C_9H_{15}N_5O_5S$. Calculated: C 35.4; H 4.9; N 22.9%.

2-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxycarbonyl-1,2,3-triazole (IX). A 0.1-g portion (0.16 mmole) of nucleoside V is boiled in 10 ml of anhydrous methanol containing 1 g of Raney nickel. The catalyst is filtered and washed thoroughly with methanol. The filtrate is evaporated and the residue is chromatographed in system A to yield 0.03 g of the starting compound V and 0.03 g of compound IX (50%, based on the starting compound which entered into th reaction).

2-β-D-Ribofuranosyl-4-carbamoyl-1,2,3-triazole (X). A 0.12-g portion (0.41 mmole) of nucleoside VII is boiled in 15 ml of anhydrous methanol, containing 1.2 g of Raney nickel. The catalyst is filtered, washed with methanol, and the filtrate is evaporated. The residue is chromatographed in system B to yield 0.04 g (40%) of compound X, R_f 0.26 (B). UV spectrum., λ_{max} (ε): 227 nm (10,000).

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ESTIMATION OF THE σ_R-CONSTANTS OF THE TETRAZOLYL GROUPS ON THE BASIS OF ^{13}C NMR SPECTRA OF VINYLTETRAZOLES

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On the basis of ^{13}C NMR spectra of tetrazole-containing vinyl monomers, the resonance σ_R constants of a series of tetrazolyl groups have been estimated.

Investigation of the reactivity of new monomers in polymerization processes requires some quantitative information on the electronic nature of the substituent at the vinyl group, especially on the σ_I and σ_R Taft constants which characterize the contribution of the inductive and resonance effects to the Hammett σ-constant. This information is especially important in the case of the monomers in which the substituent at the vinyl group is ambident. Recently, vinylazoles have been widely employed as such compounds. Their azolyl radicals appear to be electron-withdrawing groups; however, due to the conjugation they can also behave as electron donors and cause the appropriate polarization of the vinyl bond [1].

In the present work, we estimated the resonance σ_R Taft constants on the basis of the ^{13}C NMR spectra of several tetrazolyl groups. Calculation of these constants using the Swain–Lupton equation is tedious and requires a complex mathematical treatment [2]. The calculation was carried out using a correlation relationship which satisfactorily correlates the ^{13}C NMR chemical shifts of the terminal vinyl carbon atoms (C_β) of the olefins RCH = CH_2 with the inductive and resonance constants for substituents R [3, 4]:

$$\Delta\delta_{C_\beta} = 11.9\sigma_I + 63.5\sigma_R,$$

where $\Delta\delta C$ is the difference between the values of the chemical shifts of the vinyl derivative and ethylene (the δ_C value for ethylene is equal to 123.3 ppm [4]).

The data concerning the chemical shifts of the carbon atoms in the ^{13}C NMR spectra of the investigated tetrazole containing monomers are presented in Table 1. The σ_I values of the inductive constants for 1-tetrazolyl, 5-tetrazolyl, and N-methyl-5-tetrazolyl groups are taken from [6, 7] and those for 5-amino-1-tetrazolyl, and 5-methyl-1-tetrazolyl groups are calculated according to the pK_a values of the corresponding tetrazolylacetic acids [6] using the Charton correlation equation [8]:

$$\sigma_I = -0.251pK_a + 1.186.$$

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