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C NUCLEOSIDES

II.* PREPARATION OF 2-β-D-RIBOFURANOSYLBENZOTHIAZOLE, 5-β-D-RIBOFURANOSYLTETRAZOLE, AND 5-β-GLYCOSYL-1,3,4-OXADIAZOLE DERIVATIVES

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The conversion of 5-β-D-ribofuranosyl cyanides to the corresponding 2-β-ribofuranosylbenzothiazoles (under the influence of 2-aminothiophenol) and to 5-β-glycosyltetrazoles (by reaction with sodium azide and ammonium chloride) is described. It is shown that acylation of the latter structures with acetic anhydride or benzoyl chloride is a convenient method for the synthesis of 5-β-glycosyl-1,3,4-oxadiazoles.

We have previously reported [1] the possibility of conversion of acylated β-D-ribo-, β-D-xylo-, and β-D-galactopyranosyl cyanides to the corresponding 2-β-glycosylbenzothiazoles by the action of 2-aminothiophenol and to 5-β-glycosyltetrazoles by means of a mixture of sodium azide and ammonium chloride. In the present paper we report the use of these reactions for 5-β-D-ribofuranosyl cyanides (I) and the conversion of 5-β-glycosyltetrazoles to 5-β-glycosyl-1,3,4-oxadiazoles.

Up until now C-glucosyloxadiazoles have been described in the literature only in a few cases. Thus several "inverse" 2-phenyl-C-glycosyl-1,3,4-oxadiazoles have been synthesized from aldehydodialdose derivatives by a different method, and 2-amino-5-(β-DL-ribofuranosyl)-1,3,4-oxadiazole has been synthesized by oxidation of 3,4-O-isopropylene-2,5-anhydro-DL-allose semicarbazone with lead tetraacetate [3]. Several 3-β-D-ribofuranosyl-1,2,4-oxadiazole derivatives [4] and acyclic compounds with structures similar to those

* See [1] for communication I.

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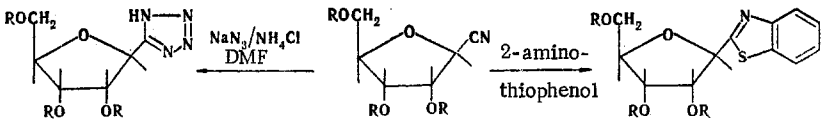
of C-glycosyl-1,3,4-oxadiazoles obtained by cyclization of the corresponding acylhydrazones [5-7] or by means of acid derivatives from 5-polyacetoxyalkyltetrazoles [8] are known.

Our experiments showed that 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide (I) [9] can be cyclized in the same way as acylated β-glycosyl cyanides to give crystalline 2-β-D-ribofuranosylbenzothiazole (IIb) and 5-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)tetrazole (III) in good yields:*

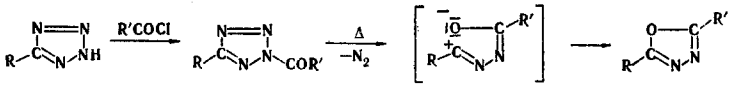


III I IIa,b

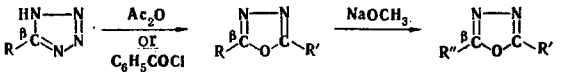
I, II a, III R = COC_6H_5; II b R = H

C-Substituted tetrazoles can be converted to 5-substituted 1,3,4-oxadiazole derivatives by vigorous acylation by the Huisgen method [10]. The reaction is based on cyclization of the unstable N-acylnitrilimine formed during the thermal decomposition of the corresponding 2-N-acyltetrazolium derivative.

This method was also recently used successfully for the synthesis of 5-(polyhydroxyalkyl)-1,3,4-oxadiazoles [8].



In conformity with this, by heating III and the previously obtained 5-β-glycosyltetrazoles (IV-VI) [1] with acetic anhydride and benzoyl chloride we were able to convert them to the corresponding 2-methyl-5-β-glycosyl- (VIIa-IXa, XIa) and 2-phenyl-5-β-glycosyl-1,3,4-oxadiazoles (Xa, XIIa). Except for IIIa, the transacylated compounds undergo deacylation under the influence of sodium methoxide to give VIIb-XIIb:



III-VI VII a-XII a VII b-XII b

V II-IX, XI R' = CH_3; X, XII R' = C_6H_5; III, VIIa R = tri-O-benzoyl-D-ribofuranosyl; IV, VIIIa R = tri-O-benzoyl-D-ribopyranosyl; V, IXa, Xa R = tri-O-acetyl-D-xylopyranosyl; VI, XIa, XIIa R = tetra-O-acetyl-D-galactopyranosyl; VIIb R = D-ribofuranosyl; VIIIb R = D-ribopyranosyl IXb, Xb R = D-xylopyranosyl; XIb, XIIb R = D-galactopyranosyl.

The skeletal vibration of the benzothiazole ring (1517 cm^{-1}) and the characteristic absorption of 1,2-disubstituted benzene derivatives (760 cm^{-1}) [11, 12] are observed in the IR spectrum of IIb. Signals of aromatic protons appear in the PMR spectrum. A system of NH bands (2700-3200 cm^{-1} with a maximum at ~3000 cm^{-1}) and skeletal vibrations of tetrazole (970 and 1550 cm^{-1}) [13, 14] are observed in the IR spectrum of III; the proton of the NH group (7.8-8.0 ppm) and protons of benzene groups (6.8-7.7 ppm) can be identified from the PMR spectrum. The structures of III-VI are also confirmed by their conversion to 1,3,4-oxadiazoles.

Skeletal vibrations of the heteroring (~970 cm^{-1}) and stretching vibrations of the C=N bond [15] appear in the IR spectra of 1,3,4-oxadiazole derivatives; ring methyl (~1390 cm^{-1}) and phenyl (670, 740, 1450 cm^{-1}) substituents can be identified on the basis of the spectra. Information regarding the β configuration of the pyranosides is also derived from the PMR spectra. There is no doubt regarding the configurations of IIb, III, VII, and VIIb, since the transformations of I do not involve the glycoside bond, and the anomeric configurations of the starting compound and the reaction products are always identical. The pyranose derivatives also displayed identical character of the anomeric configuration.

Thus our experiments provide evidence that 2-β-glycosyltetrazoles can be successfully used for the synthesis of 5-β-glycosyl-1,3,4-oxadiazole derivatives.

* After presentation of our paper for publication, we became aware of the paper by Likar and Yapel [Ann. New York Acad. Sci., 284, 182 (1977)] on the antiviral effect of III. The synthesis of this compound was previously unknown.

TABLE 1. Characteristics of the Compounds Obtained

Compound	m.p., °C (solvent)	$[\alpha]_D$ (solvent)	N found, %	Empirical formula	N calc., %	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
IIb	173—174 (ethanol)	−77,5° (pyridine)	5,2	$C_{12}H_{13}NO_4S$	5,2	760, 1517	5,66 (1H, d, J_{12}=4 Hz), 4,60—4,85 (3H, 2-H, 3-H, 4-H), 4,20 (2H, 5-H, 5′-H), 7,00—7,90 (4H, aromatic)	71
III	127 (aqueous ethanol)	−31,1° (chloroform)	10,8	$C_{27}H_{22}N_4O_7$	10,9	970, 1550 2700—3200 (max ~3000)	5,5—5,9 (4H, 1-H, 2-H, 3-H, 4-H), 4,6 (2H, 5-H, 5′-H); 7,8—8,0 (s, NH), 6,8—7,7 (15H, aromatic)	72
VIIa	130 (ethanol)	−65,2° (chloroform)	5,3	$C_{29}H_{24}N_2O_8$	5,3	950, 1390, 1575	5,35 (1H, d, 1-H, J_{12}=5 Hz), 5,7—6,0 (2H, 2-H, 3-H); 4,3—4,8 (3H, 4-H, 5-H, 5′-H); 2,3 (3H, s, CH_3)	67
VIIb	110 (ethanol—ether)	−49,8° (pyridine)	12,9	$C_8H_{12}N_2O_5$	13,0			67
VIIIa	139—140 (ethanol)	−103,8° (chloroform)	5,3	$C_{29}H_{24}N_2O_8$	5,3	955, 1396, 1575	5,28 (d, 1-H, J_{12}=8 Hz); 5,6 (1H, 2-H, J_{23}=3 Hz); 6,17 (1H, 3-H, J_{34}=3 Hz), 5,4 (1H, 4-H); 3,8—4,4 (2H, 5-H, 5′-H); 2,45 (3H, s, CH_3)	76
VIIIb	183—184 (ethanol)	−47,9° (pyridine)	12,9	$C_8H_{12}N_2O_5$	13,0			68
IXa		Syrupy compound						
IXb	145—146 (ethanol)	−10,9° (water)	12,7	$C_8H_{12}N_2O_5$	13,0	960, 1392, 1578, 1592	4,90 (d, 1-H, J_{12}=9 Hz); 3,5—4,5 (5H, 2-H, 3-H, 4-H, 5′-H, 5-H); 2,2 (3H, s, CH_3)	64
Xa	122—123 (aqueous ethanol)	−118,9° (chloroform)	6,8	$C_{19}H_{20}N_2O_8$	6,9	690, 740, 962, 1454, 1558	4,6—5,4 (3H, 1-H, 2-H, 3-H); 3,4—4,15 (3H, 4-H, 5-H, 5′-H), 7,2—7,9 (5H, aromatic)	89
Xb	207—208 (ethanol)	−106,9° (pyridine)	10,0	$C_{13}H_{14}N_2O_5$	10,1			91
XIa	135—136 (ethanol)	+10,2° (chloroform)	6,8	$C_{17}H_{22}N_2O_{10}$	6,8	951, 1390, 1572, 1593		75
XIb	185—186 (ethanol)	+30,1° (pyridine)	11,4	$C_9H_{14}N_2O_6$	11,4		4,57 (d, 1-H, J_{12}=8 Hz); 3,6—4,0 (6H, 2-H, 3-H, 4-H, 5-H, 6-H, 6′-H); 2,56 (3H, s, CH_3)	61
XIIa	117 (aqueous ethanol)	−42,5° (chloroform)	5,8	$C_{22}H_{24}N_2O_{10}$	5,9	690, 740, 960, 1450, 1550	4,77 (d, 1-H, J_{12}=9 Hz); 5,0—5,6 (4H, 2-H, 3-H, 4-H, 5-H); 4,1 (2H, 6-H, 6′-H); 7,1—7,8-(5H, aromatic)	76
XIIb	187 (ethanol)	+39,0° (water)	8,4	$C_{14}H_{16}N_2O_6$	8,3			79

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin–Elmer 283 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$, C_5D_5N (IIb and IXb), and D_2O (XIb) were recorded with a JEOL Minimar MH-100 spectrometer with tetramethylsilane as the internal standard. The melting points were determined in capillaries and were not corrected.

2-β-D-Ribofuranosylbenzothiazole (IIa). A 2-g (0.004 mole) sample of I [9] was refluxed in a stream of nitrogen with 0.8 ml (0.008 mole) of 2-aminothiophenol in 20 ml of ethanol on a water bath for 4 h, after which the solution was cooled and evaporated to dryness. The residual uncrystallizable syrup was dissolved in 20 ml of methanol, and the solution was made alkaline with sodium methoxide. After 16 h, the solution was neutralized with Dowex AG 50W-X12 (H^+) ion-exchange resin and evaporated to dryness. The residue was recrystallized from 30 ml of ethanol.

5-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)tetrazole (III). A mixture of 1 g (2.12 mmole) of I, 0.32 g (4.9 mmole) of sodium azide, 0.18 g (3.6 mmole) of NH_4Cl, and 5 ml of dimethylformamide was heated at 100°C for 2.5 h, after which it was evaporated to dryness, and the residue was triturated with water and acidified with hydrochloric acid (to pH 3). The acidic solution was extracted with chloroform, the chloroform extract was evaporated to dryness, and the residue was recrystallized from aqueous ethanol.

2-Methyl-5-(per-O-acyl-β-glycosyl)-1,3,4-oxadiazoles (VIIa-IXa, XIa). A 0.002-mole sample of III-VI was refluxed in 2 ml (0.02 mole) of acetic anhydride for 1 h, after which the mixture was cooled, and the acetic anhydride was decomposed with water. The syrupy residue was recrystallized from ethanol.

2-Phenyl-5-(per-O-acyl-β-glycosyl)-1,3,4-oxadiazoles (Xa, XIIa). A 0.001-mole sample of V or VI was refluxed with 0.8 ml (0.007 mole) of benzoyl chloride in 4 ml of pyridine for 1 h, after which the mixture was cooled and stirred with ice water. The resulting syrup was triturated with water, and the resulting crude solid was recrystallized from aqueous ethanol.

Compounds VIIa-XIIa were deacylated by means of sodium methoxide by the method used for IIa.

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