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5-ARYLIDENE DERIVATIVES OF 3-β-D-RIBOFURANOSYLTHIAZOLIDINE-2,4-DIONE

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The synthesis of modified nucleosides, viz., 5-arylidene derivatives of 3-β-D-ribofuranosyl-thiazolidine-2,4-dione, the structures of which were confirmed by data from the IR and PMR spectra, is described. The compounds have weak activity with respect to smallpox vaccine virus.

Thiazolidine derivatives are of interest both from the point of view of their ability to participate in diverse chemical transformations and owing to the broad spectrum of biological activity displayed by them, including bactericidal, pesticidal, anti-inflammatory, and antivirus activity [1].

Compounds with antivirus activity have also been detected among 2-thioxo-4-thiazolidinone (rhodanine) N-glycosides, viz., in a number of its 5-arylidene derivatives [2]. In this connection, it seemed of interest to synthesize and study the antivirus activity of N-glycosides of 5-arylidene derivatives of an oxygen-containing analog of rhodanine, viz., thiazolidine-2,4-dione. We selected β-D-ribofuranose, which is included in the composition of natural nucleosides, as the carbohydrate component.

We studied two approaches to the synthesis of such compounds. One of them was the synthesis of thiazolidine-2,4-dione N-ribosides [3] and their reaction with aromatic aldehydes through the reactive 5-methylene group of the thiazolidine ring, while the second approach was the synthesis of 5-arylidene derivatives of thiazolidine-2,4-dione itself with subsequent glycosylation of these compounds at the $N_{(3)}$ atom of the thiazolidine ring. We selected the conditions for glycosylation, condensation, and removal of the protective groups in such a way as to avoid anomerization of the glycoside bond and hydrolytic cleavage of the labile thiazolidine ring.

Thus in the first case 2',3',5'-tri-O-acetyl-3-β-D-ribofuranosylthiazolidine-2,4-dione (I), or directly, 3-β-D-ribofuranosylthiazolidine-2,4-dione (II) [3] was condensed with aromatic aldehydes IIIa-f in isopropyl alcohol in the presence of piperidine, and 5-arylidene derivatives IVa-f and Va-f, respectively, were obtained. The condensation products were isolated from the reaction mixture by column chromatography on silica gel. The yields of condensation products varied as a function of the aldehyde used in the reaction (but not as a function of the nucleoside) and ranged from 16% to 62% (see Table 1). (Scheme, following page.)

The traditional methods for removal of the acetyl protective groups by means of solutions of ammonia or sodium methoxide in methanol were unsuitable for IVa-f because of the instability of the thiazolidine ring under these conditions. We were able to realize the deacetylation of IVa-f to give the products in quantitative yields by means of a 5% solution of acetyl chloride in methanol at room temperature.

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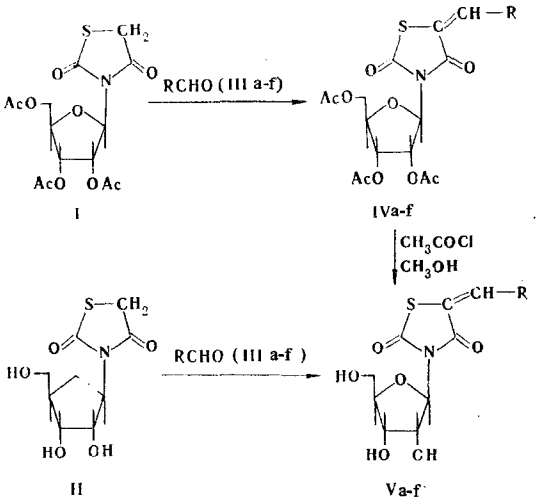
TABLE 1. 5-Arylidene Derivatives of 3-β-D-Ribofuranosylthiazolidine-2,4-dione (Va-f)

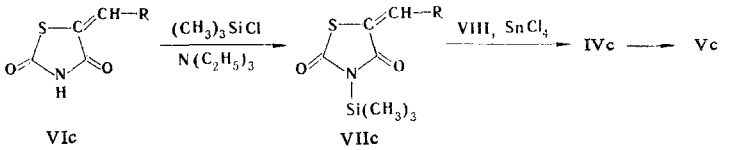
Compound	mp,[a] deg C	Found, %				Empirical formula[b]	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
Va	173—176	53,6	4,8	4,0	8,6	$C_{15}H_{15}NO_6S$	53,4	4,4	4,2	9,5	38,4
Vb	112—115	52,4	4,7	3,6	—	$C_{16}H_{17}NO_7S$	52,3	4,6	3,8	—	36,8
Vc	220—225	53,9	5,7	—	—	$C_{17}H_{20}N_2O_6S$	53,7	5,3	—	—	62,6
Vd	137—142	—	—	4,0	—	$C_{15}H_{14}FNO_6S$	—	—	3,9	—	51,4
Ve	157—162	43,3	3,7	3,5	7,6	$C_{15}H_{14}BrNO_6S$[c]	43,3	3,4	3,4	7,7	31,3
Vf	155—159	—	—	7,4	—	$C_{15}H_{14}N_2O_8S$	—	—	7,3	—	16,0

[a]All of the compounds were purified by column chromatography in a chloroform—methanol system (19:1). [b]Compounds Va,b were colorless, Vc was orange-yellow, Vd,e were yellow, and Vf was reddish brown. [c]Found: Br 19.1%. Calculated: Br 19.2%.



III—V a R=C_6H_5; b R=$C_6H_4OCH_3$-*p*; c R=$C_6H_4N(CH_3)_2$-*p*; d R=C_6H_4F-*p*; e R=C_6H_4Br-*p*; f R=$C_6H_4NO_2$-*p*

We showed that IV and V can also be obtained by another method. Thus riboside Vc was obtained in 61% yield starting from 5-(p-dimethylaminobenzylidene)thiazolidine-2,4-dione (VI). The latter was silylated with trimethylchlorosilane in dioxane in the presence of triethylamine, and the resulting reactive N-trimethylsilyl derivative (VII) was subjected to reaction with β-D-ribofuranose 1,2,3,5-tetraacetate (VIII) in acetonitrile in the presence of stannic chloride by the method in [4]; the resulting peracyl derivative of nucleoside IVc was deacetylated with a 5% solution of acetyl chloride in methanol, and Vc was isolated by column chromatography on silica gel.



We used a similar procedure to obtain ribosides Va,b,d-f, for which, however, we were unable to achieve satisfactory yields because of the difficulties involved in their isolation from the reaction mixture and purification to remove the admixed starting 5-arylidene derivatives of thiazolidine-2,4-dione, which have close R_f values.

The structures of the glycosides obtained were proved by IR and PMR spectroscopic data and the result of elemental analysis. Thus all of the 5-arylidene derivatives (Va-f) of the nucleosides have IR spectra that contain absorption bands at 1725-1750 cm^{-1} that are due to

the stretching vibrations of the exocyclic C=O bonds of thiazolidine-2,4-dione, and this also confirms the addition of the carbohydrate residue to the $N_{(3)}$ atom in the preparation of riboside Vc by glycosylation of VI. The presence of aromatic substituents is confirmed by the presence of absorption bands at 1585-1610 cm^{-1}; the absorption bands of the hydroxy groups of the carbohydrate fragment appear at 3400 cm^{-1}.

In the PMR spectra of Va-f (Table 2) the signals of the 5-arylidene protons are shifted to weak field to 7.72-7.90 ppm as compared with the signals of the protons of the aromatic ring, which are located at 6.70-7.62 ppm. This shift is probably caused by the dual effect of deshielding due to the anisotropy of the arylidene double bond and the phenyl substituent [5]. The signals of the anomeric protons have almost identical chemical shifts at 5.54-5.56 ppm with spin–spin coupling constant $J_{1',2'}$ = 4.5 Hz, which is characteristic for ribosides with a 1,2-trans orientation of the substituents [6].

The antivirus properties of glycosides Va-f were determined in experiments performed on tissue monolayer cultures infected by a number of DNA- and RNA-containing viruses by the methods in [7, 8]. Of all of the synthesized compounds, glycosides Vc,d,f displayed slight activity with respect to the smallpox vaccine virus.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Jeol PS-100 spectrometer with tetramethylsilane as the internal standard. The melting points were not corrected. The individuality of the compounds obtained was confirmed by chromatography on Silufol UV-254 plates in a chloroform–methanol system (19:1). For preparative chromatography we used L 40/100 μm silica gel (Czechoslovakian SSR). The properties of Va-f are presented in Tables 1 and 2.

The 5-arylidene derivatives of thiazolidine-2,4-dione, including VI, were obtained by condensation of thiazolidine-2,4-dione with aromatic aldehydes in alcohol in the presence of piperidine [9] or in glacial acetic acid in the presence of sodium acetate [10].

5-(p-Dimethylaminobenzylidene)-3-β-D-ribofuranosylthiazolidine-2,4-dione (Vc). A) A 0.25-g (1 mmole) sample of 3-β-D-ribofuranosylthiazolidine-2,4-dione was dissolved in 10 ml of isopropyl alcohol, 0.22 g (1.5 mmole) of p-dimethylaminobenzaldehyde (IIIc) and a few drops of piperidine were added, and the mixture was heated at 60-70°C for 7 h. The reaction solution was then concentrated in the vacuum created by a water aspirator until it became syrupy, after which 1 g of silica gel used for preparative chromatography was added, and the mixture was evaporated to dryness with a rotary evaporator. The dry residue was applied to a column and chromatographed successively with a hexane–ethyl acetate system (7:5) and a chloroform–methanol system (19:1). The fractions containing chromatographically pure product Vc were combined, and the solvent was removed *in vacuo* to give 238 mg (62.6%) of Vc in the form of yellow crystals with mp 220-225°C. Compounds Va,b,d-f were similarly obtained.

B) A 0.19-g (0.5 mmole) sample of 3-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)thiazolidine-2,4-dione was dissolved in 10 ml of isopropyl alcohol, 0.075 g (0.5 mmole) of p-dimethylaminobenzaldehyde and a few drops of piperidine were added, and the mixture was stirred at 70-80°C for 7-8 h. It was then concentrated *in vacuo*, silica gel was added, and the solvent was removed completely. The dry residue was applied to a column and chromatographed in a hexane–ethyl acetate system (7:5). The chromatographically homogeneous fractions were combined, and the solvent was removed *in vacuo* to give 0.15 g (59.3%) of 3-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-5-(p-dimethylaminobenzylidene)thiazolidine-2,4-dione in the form of a viscous reddish-orange syrup, to which 15 ml of a 5% solution of acetyl chloride in absolute methanol was added, and the mixture was stirred at 20°C for 10-15 h. The reaction solution was evaporated in the vacuum created by a water aspirator, after which it was evaporated twice with methanol to decompose the excess acetyl chloride. The residue contained the chromatographically pure 5-(p-dimethylaminobenzylidene) derivative of 3-β-D-ribofuranosylthiazolidine-2,4-dione, which was identical to Vc obtained by method A, according to the results of elemental analysis, data from the IR and PMR spectra and TLC, and the absence of a melting-point depression. The yield was 0.11 g (59.3%). Compounds Va,b,d-f were similarly obtained.

C) A 299-mg (2.75 mmole) sample of trimethylchlorosilane was added all at once to a solution of 0.62 g (2.5 mmole) of 5-(p-dimethylaminobenzylidene)thiazolidine-2,4-dione in 25 ml

TABLE 2. Data from the PMR Spectra of 3-β-D-Ribofuranosyl-5-arylidene Derivatives (Va-d) of Thiazolidine-2,4-dione in d_6-DMSO

Compound	Chemical shifts, δ, ppm (J, Hz)														
	—CH=	C_6H_5	3″,5″-Ar	2″,6″-Ar	1′-H	2′-OH	3′-OH	2′-H, 5′-OH	2′-H	5′-OH	3′-H	4′-H	5′,5″-H	4′-H, OCH_3	$N(CH_3)_2$
Va	7,86 s	7,46 m 5H			5,56 d $J_{1',2'}=4,5$	5,30 d $J_{OH,2'}=5,0$	5,06 d $J_{OH,3'}=5,5$	4,62 m $J_{2',1'}=4,5$, $J_{OH,2'}=5,0$, $J_{2',3'}=4,5$, 2H			4,06 m, $J_{3',2'}=4,5$, $J_{OH,3'}=5,5$, $J_{3',4'}=4,5$	3,74 m	3,46 m		
Vb	7,86 s		7,56 d $J=10,0$	7,06 d $J=10,0$	5,58 d $J_{1',2'}=4,5$	5,38 dd $J_{OH,2'}=4,5$	5,12 dd $J_{OH,3'}=5,0$		4,62 dd $J_{2',1'}=4,5$, $J_{2',3'}=5,0$[a]	4,76 m	4,06 dd $J_{3',2'}=5,0$, $J_{3',4'}=5,0$[a]			3,84 s 4H	
Vc	7,72 s		7,36 d $J=10,0$	6,70 d $J=10,0$	5,54 d $J_{1',2'}=4,5$				4,58 dd $J_{2',1'}=4,5$, $J_{2',3'}=5,0$		4,02 dd $J_{3',2'}=5,0$, $J_{3',4'}=5,0$	3,68 m	3,46 m		2,98 s
Vd	7,90 s		7,62 m	7,32 m	5,56 d $J_{1',2'}=4,5$	5,20 dd	5,08 dd	4,58 dd $J_{2',1'}=4,5$, $J_{2',3'}=5,0$, 2H			4,06 dd $J_{3',2'}=5,0$, $J_{3',4'}=5,0$	3,70m	—[b]		

[a]After exchange with D_2O. [b]Overlapped by the H_2O peak.

of absolute dioxane, after which a solution of 278 mg (2.75 mmole) of triethylamine in 5 ml of absolute dioxane was added dropwise with stirring in the course of 30 min, and stirring at 20°C was continued for 6 h. The precipitated triethylamine hydrochloride was removed by filtration and washed with dioxane. The combined filtrates were evaporated *in vacuo*, and the dry bright-yellow residue was treated successively with 12.5 ml of absolute acetonitrile and 875 mg (2.75 mmole) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (all at once). A solution of 2.6 g (10 mmole) sample of anhydrous stannic chloride in 6 ml of absolute acetonitrile was then added dropwise with stirring, and the mixture was stirred at 20°C for 2 days. The reaction solution was diluted with 100 ml of chloroform, and the mixture was treated with a saturated aqueous solution of sodium bicarbonate until it gave a neutral reaction. The extract was dried with magnesium sulfate, and the solvent was removed *in vacuo* to give an orange-yellow crystalline powder, which, according to the TLC data, was 3-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-5-(p-dimethylaminobenzylidene)-thiazolidine-2,4-dione mixed with the starting 5-(p-dimethylaminobenzylidene) derivative of thiazolidine-2,4-dione. A 40-ml sample of a 5% solution of acetyl chloride in absolute methanol was added, and the mixture was stirred at 20°C for 10-15 h. The solvent was removed *in vacuo*, the residue was evaporated with methanol twice, and the residue was chromatographed successively in the usual way with a column in a hexane–ethyl acetate system (7:5) and a chloroform–methanol system (19:1). The chromatographically homogeneous fractions were combined, and the solvent was removed to give 0.58 g (61.0%) of Vc in the form of a viscous orange-yellow syrup that crystallized upon trituration to give a product with mp 220-225°C. Compounds Va,b,d-f were similarly obtained.

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