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The Synthesis and Antiviral Activities of 2-Substituted azino-3- β -D-ribofuranosyl and α and β -D-arabinofuranosyl-5- -carbamoylmethylenethiazolidine-4-ones

Jože Kobe, Boris Rusjakovski

Boris Kidrič Institute of Chemistry Hajdrihova 19, 61000 Ljubljana;
KRKA Pharmaceutical and Chemical Works, C. herojev 45, 68000 Novo mesto,
Yugoslavia

and

Branko Brdar

Central Institute for Tumours and Allied Diseases, Ilica 197, 41000 Zagreb, Yugoslavia

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2-(1-Isopropylidene and Methylbenzylidene)azino- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one **3** were prepared by acid catalyzed fusion of 2-(1-Isopropylidene and 1-Methylbenzylidene)azino-5-carbamoylmethylenethiazolidine-(3H)-4-one **1**, with 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose and from derivative **7** through intermediates **9** and **10**, subsequent ringclosure to **11** and final deprotection. α and β -arabino furanosyl derivatives were synthesised using a direct aminolysis of protected derivative **5**. All derivatives are totally inactive against herpes simplex virus, while showing moderate activity against poliovirus **2**.

INTRODUCTION

Viruses and virus-infected cells exhibit some characteristics which are quantitatively or qualitatively different from normal uninfected cells. It is now evident that quite a few specific events may occur only in virus infected cells and these could serve as appropriate targets for the action of antiviral drugs¹. One of the targets, i. e. inhibition of the synthesis of viral DNA or RNA, was often achieved by inhibition of virus-specific DNA polymerases with selective antiviral agents. These agents are therefore the main synthetic aim. We have been involved with the synthesis of nucleoside analogues of some derivatives of thiazolidine acetic acids^{2,3} for quite some time and unfortunately were not able to establish possible connections between *in vitro* and *in vivo* biological results obtained within this series of compounds^{3,4}. Namely, the sugar component at position 3 showed a moderate enhancement in VR (virus racing) in comparison to the parent base, but the data were too scarce to allow any definite conclusions³. Nevertheless, the carboxamide group introduced on the exocyclic function at position 5 was considered a reasonable substituent for

the purpose of collecting additional data to conclude the study of the *in vitro* structure-activity relationship within this series.

RESULTS AND DISCUSSION

Chemistry

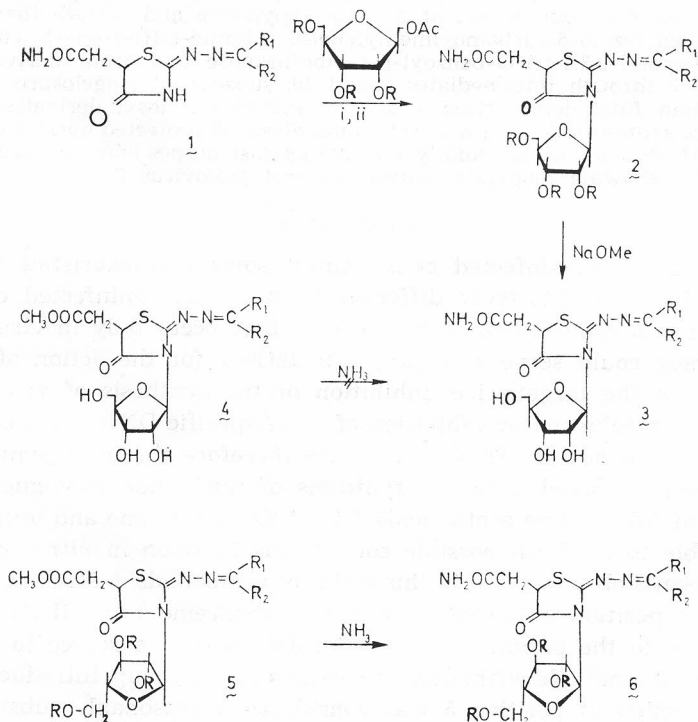
The first attempt to synthesize 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one **3**, ($R_1 = R_2 = \text{CH}_3$, $R = \text{H}$), following our previous approach³, proved to be unsuccessful due to the cleavage of the glycosidic bond, which suggested differences in the stability of the D-ribofuranosyl **3**, and D-arabinofuranosyl derivatives **6**. Two other possibilities were thus considered:

a) glycosidation of 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one **1**, and

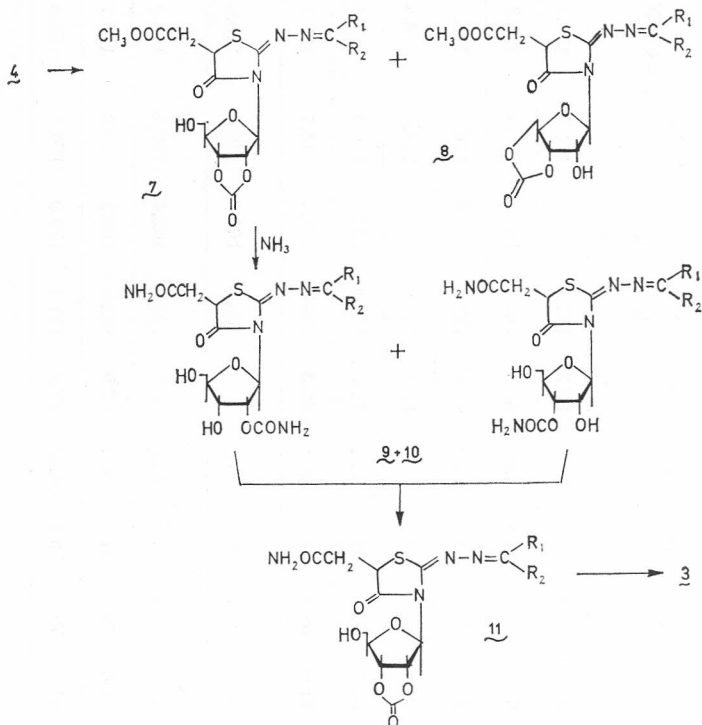
b) aminolysis of more stable derivatives prepared by modifications of the ribose moiety.

a) The fusion procedure was used first². 2-(1-isopropylidene)azino-5-carbamoylmethylenethiazolidine-4-one (**1**) was fused with 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose in the presence of I_2 . Optimum fusion procedure conditions (180 °C) afforded 2-(1-isopropylidene)azino-3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one **2**, in a 30% yield.

SCHEME 1



SCHEME 2



yield. The temperature was lowered by 20 °C and the reaction time shortened by 15 minutes when using the crude silylated derivative of 1, which was prepared by allowing 1, to react with a mixture of hexamethyldisilazane and trimethylchlorosilane in the ratio 10 : 1.

This procedure afforded a slightly improved yield (33%). The condensation of silylated derivative 1 in dry acetonitrile with 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose and SnCl_4 afforded an identical product; however, the yield was not improved. Benzoyl groups were removed with sodium methoxide to yield the white crystalline nucleoside 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one 3 ($\text{R}_1=\text{R}_2=\text{CH}_3$).

To prove that ribosylation took place at position 3, as well as the beta configuration of this nucleoside analogue, an approach based on starting material already possessing the desired configuration has been suggested. In fact pathway b) corresponds to this approach, and we decided to carry out some additional experiments with derivatives 4 possessing a suitably protected ribose moiety. The reaction of 4 ($\text{R}_1=\text{R}_2=\text{CH}_3$, $\text{R}=\text{H}$) with diphenylcarbonate in *N,N*-dimethylformamide as solvent and sodium hydrogen carbonate as catalyst, gave 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidine-4-one-2',3'-carbonate 7 in fair yield, together with a minor product identified as 3',5'-carbonate 8. Derivative 7 was submitted to aminolysis (methanolic ammonia at room temperature), and a mixture of 9 and 10 was

obtained. Even though the five-membered cyclic carbonate ester was opened, the glycosidic bond remained uninterrupted, and the exocyclic methoxycarbonyl group was transformed to the desired carbamoyl function. Derivative 9 was fused in vacuo at 160 °C to yield 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one-2',3'-carbonate 11, which was readily deprotected to 3 ($R_1=R_2=CH_3$), identical in all respects to the product prepared by pathway a). It seemed that the 2',3'-cyclic carbonate function stabilized the glycosidic bond, at least long enough for aminolysis of the ester function to be achieved in 42% yield. It has been noticed that this function significantly stabilized the glycosidic bond towards acidic hydrolysis⁶, and our attempts confirmed the stability of this particular glycosidic bond in weakly basic conditions.

Since both routes lead to the same product 3, the assignments of the anomeric configuration were correct. Additional support was provided by ¹³C NMR measurements (see Table I). The shifts observed at C1' and C2' resonances correspond to the shifts which belong to the stereoisomer α -arabinofuranosyl derivatives 6. The indicative diminished coupling constant $J_{1'2'} = 2.5$ Hz of 11 is conclusive as well.

When 2-(isopropylidene)azino-3-(2,3,5-tri-O-benzyl- α and β -D-arabinofuranosyl)-5-methoxycarbonylmethylenethiazolidine-4-ones 5 were treated with methanolic ammonia the corresponding amides 6 were isolated in fair yields, indicating greater stability of arabinofuranosyl derivatives 5 in comparison to 4. Deprotection was performed using boron trichloride at -77 °C in methylene chloride, and the corresponding nucleoside analogues 6 were obtained. 2-(1-isopropylidene)azino- α -D-arabinofuranosyl-5-carbamoylmethylenethiazolidine-4-one 6 was identical in all respects to the compound listed in Ref. 3, thus confirming the assignments of the anomeric configurations on the basis of ¹³C NMR data (see Table I).

Antiviral activity

Table II presents the results of *in vitro* investigations of the antiviral activity of 2-(1-isopropylidene)azino-3- α -D-arabinofuranosyl and - β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-ones. The results indicate that a moderate activity against poliovirus 2 is present, in contrast to the parent nucleoside ($R_1=R_2=CH_3$, R=H) where selective activity against herpes simplex virus was observed³.

EXPERIMENTAL

A) Chemistry

Melting points were determined with a Kofler microscope and are uncorrected. ¹H-NMR spectra were obtained at 100 MHz in a Jeol PS 100 spectrometer. ¹³C-NMR spectra were determined with a JEOL FX 90Q instrument and the assignments made with the off resonance technique. Ultraviolet spectra were recorded with a Beckman Mo 25 spectrophotometer.

Mass spectra were run in a CEC 21-110B mass spectrometer using the FAB method.

Elemental analyses were performed by Dr. Tasovac at the Institute of Chemistry of the University of Natural and Mathematical Sciences, Belgrade, Yugoslavia.

Thin layer chromatography (TLC) was performed with Merck silica gel 60 F₂₅₄ plates. Preparative chromatography was carried out with 20 × 20 plates covered with a 2 mm layer of Merck silica gel PF₂₅₄. Merck silica gel (0.05–0.2 mm) was

TABLE II
Comparative *in Vitro* Antiviral Activity^a

Comparative	VIRUS RATING	
	Herpes simplex virus	Poliovirus 2
Ribavirin ⁷	1.10	1.10
2-(1-Isopropylidene)azino-5-carbamoylmethylene-thiazolidine-4-one 1 (R ₁ =R ₂ =CH ₃)	0	1.10
2-(1-Isopropylidene)azino-3-β-D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one 3 (R ₁ =R ₂ =CH ₃)	0	0.7
2-(1-Isopropylidene)azino-3-α-D-arabinofuranosyl-5-carbamoylmethylenethiazolidine-4-one 6 (R ₁ =R ₂ =CH ₃)	0	0.7
2-(1-Isopropylidene)azino-3-(2'-carbamoyl-D-ribofuranosyl)-5-carbamoylmethylene-3-β-thiazolidine-4-one 9 (R ₁ =R ₂ =CH ₃)	0	0.2

used for chromatographic separations. The purity of products was determined by thin layer chromatography on silica gel.

Biological Screening

All the experiments reported in this paper were performed with monolayer cultures of HeLa cells. Cells were maintained and propagated in Minimum Essential Medium supplemented with 5–10% foetal bovine serum in a humid CO₂ atmosphere. Herpes simplex virus and poliovirus 2 were grown and assayed as previously described⁸.

2-(1-isopropylidene)azino-3-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (2, R₁ = R₂ = CH₃)

Method A

Dry 2-(1-isopropylidene)azino-5-carbamoylmethylenethiazolidine-(3H)-4-one (1) 170 mg (0.514 mmoles) was refluxed with stirring in a mixture of hexamethyldisilazane and trimethylchlorosilane 10:1 (20 ml), 67 mg (0.5 mmoles) of ammonium sulphate and in the absence of moisture for 40 minutes. The excess solvent was removed under reduced pressure, leaving a crude silylated derivative which was used without further purification. 250 mg (0.5 mmoles) of dry 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose and a catalytic amount of I₂ was added and the mixture heated with stirring in vacuo to 160 °C for 5 minutes. The residue was dissolved in CHCl₃ and applied to a silica gel column (16 g) prepacked in CHCl₃. Elution was started with CHCl₃. The solvent was changed to CHCl₃-acetone of 9:1, and finally to CHCl₃-acetone of 9:3. 150 mg (33.5%) of 2-(1-isopropylidene)azino-3-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (2) R₁ = R₂ = CH₃) was isolated as a syrup.

Method B

1 1.2 g (5.27 mmoles) and 2.5 g (4.97 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose with a catalytic amount of I₂ was fused in vacuo at 180 °C for

20 minutes. The same work-up procedure yielded 950 mg (30%) of a product identical to 2 ($R = C_6H_5-CO$) isolated by procedure A.

Method C

To a 150 mg (0.658 mmoles) of silylated 1, dissolved in 60 ml of dry acetonitrile, were added 292 mg (0.58 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose and 0.12 ml (1.03 mmoles) of $SnCl_4$ in 10 ml acetonitrile, and the mixture refluxed for 2 hours; 80 ml of dichloromethane was then added to the cold reaction mixture. This mixture was poured into 100 ml of a saturated solution of sodium hydrogen carbonate. The organic layer was filtered through celite, washed several times with 30 ml of NaCl solution and finally with water. The solution was separated, dried over anhydrous sodium sulphate and the solvent removed. The residue was purified as before, yielding 120 mg (27 %).

1H -NMR ($CDCl_3$) δ_{TMS} — 2.1, 2.12 (two, s, 6, $C(CH_3)_2$); 3.05 (m, 2, CH_2); 4.4 (m, 1, CH); 4.75 (m, 3, H_4 H_5^4); 7.5, 8.05 (m, 15, C_6H_5)

Anal. $C_{34}H_{32}O_9N_4S$ calc'd: C 60.71; H 4.79; N 8.33%
found: C 60.20; H 4.56; N 8.03%

2-(1-methylbenzylidene)azino-3-(2',3',5'-tri-O-benzoyl- β -D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (2, $R_1 = CH_3$, $R_2 = C_6H_5$) was obtained by method A in a 35% yield.

1H -NMR ($CDCl_3$) δ_{TMS} — 2.52 (s, 3, CH_3), 2.95 (m, 2, CH_2)

Anal. $C_{39}H_{34}O_9N_4S$ calc'd: C 63.75; H 4.66; N 7.63%
found: C 63.68; H 4.73; N 7.71%

2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one (3, $R_1 = R_2 = CH_3$)

To a solution of 2 ($R_1 = R_2 = CH_3$) 0.6 g (0.96 mmoles) in 30 ml MeOH was added 4 ml 1N sodium methoxide solution. The reaction mixture was stirred at room temperature for 2 hours, neutralized with Dowex, filtered and the solvent removed. The residue was adsorbed onto silica gel (500 mg) and chromatographed on a silica gel column (15 g). Elution was started with $CHCl_3$ and carried on with $CHCl_3$ -acetone of 9:1, 7:3 and 1:1 to give 95 mg (44%) of crystalline 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylthiazolidine-4-one (3, $R_1 = R_2 = CH_3$), m. p. 182—184 °C.

1H -NMR ($DMSO-d_6$) δ_{TMS} — 1.94 (s, 6, $C(CH_3)_2$); 2.5 (br. m., 2, CH_2); 3.5 (br. m., 3, H_4 , H_5^4); 4.6 (m, 2, H_2 , NH) 5.6 (d, 1, H_1 ; $J_{1,2} = 4.5$ Hz)

UV_{max} (MeOH) $\lambda = 255$ nm, $\epsilon = 11376$ M. S: $m/e = 360$ ($m + 1$)

Anal. $C_{13}H_{20}O_6N_4S$ calc'd: C 43.33; H 5.95; N 15.55%
found: C 43.82; H 5.72; N 15.20%

2-(1-methylbenzylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one (3, $R = CH_3$, $R_2 = C_6H_5$) was isolated by the same procedure in a 45% yield. m. p. 211—214 °C (hygroscopic)

1H -NMR ($DMSO-d_6$) δ_{TMS} — 2.41 (s, 3, CH_3); 2.95 (m, 2, CH_2); 4.75 (m, 2, H_2 , NH); 5.79 (d, 1, H_1 , $J_{1,2} = 4$ Hz); 7.45, 7.83 (m, 5, C_6H_5)

UV_{max} (MeOH) $\lambda = 290$ nm, $\epsilon = 17259$ $m/e = 422$ ($m + 1$)

Anal. $C_{18}H_{22}O_6N_4S \cdot 2H_2O$ calc'd: C 47.16; H 5.72; N 12.22%
found: C 47.78; H 5.43; N 11.90%

2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidine-4-one-2',3'-carbonate (7, $R_1 = R_2 = CH_3$)

To a solution of 2-(isopropylidene)azino-3- β -D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidine-4-one (1.1 g, 2.93 mmoles) in N,N -dimethylformamide (2 ml) were added diphenylcarbonate (0.81 g, 4.45 mmoles) and a catalytic amount of sodium hydrogen carbonate. The reaction mixture was heated for 20 minutes at 115 °C. Solvent was removed at 90 °C under reduced pressure, the residue dissolved in 5 ml of $CHCl_3$ and applied to a silica gel column (45 g) prepacked in $CHCl_3$. Elution

with CHCl_3 , CHCl_3 -acetone of 9:1 and finally CHCl_3 -acetone of 8:2, provided 580 mg (40%) of 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidine-4-one-2',3'-carbonate as a foam (recrystallization from MeOH yielded 510 mg (41%), 7, ($R_1=R_2=\text{CH}_3$) of white solid. m.p. 159–162 °C). Of the residue, 180 mg of crude product after repeated column chromatography (8 g) and with CHCl_3 -acetone of 9.5:0.5 gave 100 mg (12%) of pure 3',5'-carbonate derivative with a m. p. of 142–145 °C.

7, $^1\text{H-NMR}$ (CDCl_3) δ_{TMS} — 2.08, 2.11 (2s, 6, $\text{C}(\text{CH}_3)_2$); 3.15 (d, 2, CH_2); 3.78 (s, 3, OCH_3); 5.45 (m, 1, H_3'); 5.81 (m, 1, H_2'); 6.38 (d, 1, H_1' , $J_{1'2'} = 3$ Hz)
 UV_{max} (CHCl_3), $\lambda = 259$ nm, $\epsilon = 12048$ m/e = 401 ($m + 1$)

Anal. $\text{C}_{15}\text{H}_{19}\text{O}_8\text{N}_3\text{S}$ calc'd: C 44.88; H 4.77; N 10.47%
 found: C 44.37; H 4.91; N 10.37%

8, $^1\text{H-NMR}$ (CDCl_3) δ_{TMS} — 2.1 (s, 6, $\text{C}(\text{CH}_3)_2$); 3.12 (m, 2, CH_2); 3.77 (s, 3, OCH_3); 5.45 (m, 1, H_3'); 5.75 (dd, 1, H_2'); 6.52 (d, 1, H_1' , $J_{1'2'} = 5$ Hz) m/e = 401 ($m + 1$)

Anal. $\text{C}_{15}\text{H}_{19}\text{O}_8\text{N}_3\text{S}$ found: C 45.03; H 4.88; N 10.29%

2-(1-Isopropylidene)azino-3-(2'-carbamoyl and/or 3'-carbamoyl)- β -D-ribofuranosyl-5-thiazolidine-4-one-2',3'-carbonate (7, $R_1=\text{CH}_3$, $R_2=\text{C}_6\text{H}_5$)

The same procedure provided 7 ($R_1=\text{CH}_3$, $R_2=\text{C}_6\text{H}_5$)

7, $^1\text{H-NMR}$ (CDCl_3) δ_{TMS} — 2.48 (s, 3, CH_3); 3.14 (d, 2, CH_2); 3.75 (s, 3, OCH_3); 6.46 (d, 1, H_1' , $J_{1'2'} = 3$ Hz)

UV_{max} (CHCl_3): $\lambda_{\text{max}} = 295$ nm, $\epsilon = 25280$

Anal. $\text{C}_{20}\text{H}_{21}\text{O}_8\text{N}_3\text{S}$ calc'd: C 51.84; H 4.57; N 9.05%
 found: C 51.62; H 4.63; N 9.18%

2-(1-Isopropylidene)azino-3-(2'-carbamoyl and/or 3'-carbamoyl)- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one (9, 10, $R_1=R_2=\text{CH}_3$)

2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidine-4-one (730 mg, 1.82 mmoles) was dissolved in methanolic ammonia (70 ml). The solution was kept in a pressure bottle for 90 minutes. The solvent was removed and the residue adsorbed onto 500 mg of silica gel. and added to a column (20 g prepacked in chloroform). Elution was carried out with CHCl_3 and mixtures of CHCl_3 -acetone of 1:1, 1:2, 1:3 and finally 1:4. 300 mg (42%) of a crude product, containing a mixture of 2-(1-isopropylidene)azino-2'-carbamoyl and 3'-carbamoyl-(β -D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one in crystalline form, was isolated with a m. p. of 178–182 °C.

$^1\text{H-NMR}$ (D_2O) δ_{DSS} — 2.12, 2.20 (2s, 6, $\text{C}(\text{CH}_3)_2$); 3.18 (d, 2, CH_2); 3.88 (m, 2, H_5 , H_5''); 5.28 (d, 1, H_1' , $J_{1'2'} = 3$ Hz)

UV_{max} (MeOH) $\lambda_{\text{max}} = 257$ nm; $\epsilon = 11042$ m/e = 404 ($m + 1$)

Anal. $\text{C}_{14}\text{H}_{21}\text{O}_7\text{N}_5\text{S}$ calc'd: C 41.68; H 5.25; N 17.36%
 found: C 41.18; H 5.35; N 17.18%

2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one (3, $R_1=R_2=\text{CH}_3$)

A catalytic amount of sodium methoxide in methanol was added to a solution of 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one-2',3'-carbonate (11) (10 mg, 0.025 mmoles) in methanol (10 ml), and the resulting solution stirred for 1 hour. The reaction mixture was neutralized with Dowex 50 WX8/ H^+ , filtered and the solvent removed. 7 mg (75%) of 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one was obtained. The product was identical in all respects to the compound 3, ($R_1=R_2=\text{CH}_3$) isolated by the fusion procedure.

2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one-2',3'-carbonate (11, $R_1=R_2=\text{CH}_3$)

2-(1-isopropylidene)azino-3-(2'-carbamoyl- β -D-ribofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (9, $R_1=R_2=\text{CH}_3$) was fused in vacuo at 160 °C until no further

release of ammonia was noticeable. The residue was dissolved in methanol, adsorbed onto 100 mg of silica gel and chromatographed on a silica gel column (10 g) prepacked in CHCl_3 . The solution solvent was changed from CHCl_3 to a mixture of CHCl_3 -acetone of 1:4. 45 mg (24%) of pure 2-(1-isopropylidene)azino-3- β -D-ribofuranosyl-5-carbamoylmethylenethiazolidine-4-one-2',3'-carbonate was isolated as a syrup.

$^1\text{H-NMR}$ (D_2O) δ_{DSS} — 2.08 (s, 3, CH_3); 2.15 (s, 3, CH_3); 3.15 (m, 2, CH_2); 3.88 (m, 2, H_5' , H_5''); 6.1 (t, 1, H_2'); 6.42 (d, 1, H_1' ; $J_{1'2'} = 2.5$ Hz)

UV_{max} (MeOH): $\lambda_{\text{max}} = 257$ nm, $\epsilon = 12815$ $m/e = 386$ ($m + 1$)

Anal. $\text{C}_{34}\text{H}_{38}\text{O}_6\text{N}_4\text{S}$ calc'd: C 64.74; H 6.07; N 8.88%
found: C 64.73; H 5.86; N 8.66%

2-(1-isopropylidene)azino-3-(2',3',5'-tri-O-benzyl- α -D-arabinofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (6, $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{benzyl}$)

$^1\text{H-NMR}$ (CDCl_3) δ_{TMS} — 2.02, 2.08 (2s, 6, $\text{C}(\text{CH}_3)_2$); 2.75 (m, 2, CH_2); 3.2 (m, 1, CH); 4.5—4.8 (m, 10, H_3' , H_4' , H_5' , H_5'' , CH_2); 5.25 (dd, 1, H_2'); 61.8 (d, 1, H_1' ; $J_{1'2'} = 6$ Hz); 7.3 (m, 15, benzyl)

Anal. $\text{C}_{34}\text{H}_{38}\text{O}_6\text{N}_4\text{S}$ found: C 64.76; H 6.19; N 8.79%

2-(1-methylbenzylidene)azino-3-(2',3',5'-tri-O-benzyl- α -D-arabinofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (6, $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{C}_6\text{H}_5$, $\text{R}_3 = \text{benzyl}$)

$^1\text{H-NMR}$ (CDCl_3) δ_{TMS} — 2.34 (s, 3, CH_3); 2.8 (m, 2, CH_2); 4.2 (m, 2, H_4' , CH); 4.45—4.85 (m, 9, H_3' , H_5' , H_5'' , CH_2); 5.3 (dd, 1, H_2'); 6.15 (d, 1, H_1' ; $J_{1'2'} = 6$ Hz); 7.25 (m, 15, benzyl)

Anal. $\text{C}_{39}\text{H}_{40}\text{O}_6\text{N}_4\text{S}$ calc'd: C 67.61; H 5.82; N 8.09%
found: C 67.70; H 5.92; N 7.89%

2-(1-isopropylidene)azino- α -D-arabinofuranosyl-5-carbamoylmethylenethiazolidine-4-one (6, $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{H}$)

A solution of 2-(1-isopropylidene)azino-3-(2',3',5'-tri-O-benzyl- α -D-arabinofuranosyl)-5-carbamoylmethylenethiazolidine-4-one (500 mg, 0.795 mmoles) in 50 ml of dry methylene chloride was cooled to -77°C . Boron trichloride (7.36 g, 63 mmoles) was then added and the mixture was allowed to stand at -77°C for 24 hours. The reaction mixture was then slowly dropped into a cooled (-77°C) mixture (70 ml) of methylene chloride and methanol (1:1) and left at -20°C for an additional 20 hours. Solvent was then removed at room temperature, MeOH (50 ml) was added to the residue, and this treatment was repeated twice. The residue was then redissolved in MeOH (50 ml) and neutralized with Amberlite 45. The resin was filtered off, washed with MeOH, and the filtrate evaporated to dryness. The residue was adsorbed onto silica gel (250 ml) and placed on top of a chromatographic column (6 g silica gel prepacked in CHCl_3). The column was eluted with CHCl_3 , elution continued with a mixture of CHCl_3 -acetone 2:1, 1:1 and finally with 3:7. The desired product was collected, and the solvent was concentrated to a small volume. White crystals were separated to give 90 mg (31%) of 2-(1-isopropylidene)azino- α -D-arabinofuranosyl-5-carbamoylmethylenethiazolidine-4-one, m. p. 198—200 $^\circ\text{C}$ (from acetone- CHCl_3), identical in all respects to the compound listed in ref. 1.

$^1\text{H-NMR}$ (D_2O) δ_{DSS} — 2.15, 2.2 (2s, 6, $\text{C}(\text{CH}_3)_2$); 3.15 (d, 2, CH_2); 3.88 (m, 2, H_5' , H_5''); 5.28 (dd, 1, H_2'); 6.08 (d, 1, H_1' ; $J_{1'2'} = 7$ Hz)

UV_{max} (MeOH) $\lambda_{\text{max}} = 255$ nm; $\epsilon = 10296$ $m/e = 360$ ($m + 1$)

Anal. $\text{C}_{13}\text{H}_{20}\text{O}_6\text{N}_4\text{S}$ calc'd: C 43.33; H 5.59; N 15.59%
found: C 43.99; H 5.51; N 15.38%

2-(1-methylbenzylidene)azino-3- α -D-arabinofuranosyl-5-carbamoylmethylenethiazolidine-4-one (6) was isolated in a 23% yield using the same procedure

m. p. 216—218 $^\circ\text{C}$ (hygroscopic)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ_{TMS} — 2.52 (s, 3, CH_3); 3.05 (m, 2, CH_2); 5.15 (dd, 1, H_2'); 5.85 (d, 1, H_1' ; $J_{1'2'} = 7$ Hz); 7.55, 7.97 (m, 5, C_6H_5)

UV_{max} (MeOH) $\lambda_{\text{max}} = 725$; $\epsilon = 9663$ $m/e = 422$ ($m + 1$)

Anal. $\text{C}_{18}\text{H}_{22}\text{O}_6\text{N}_4\text{S} \cdot 2\text{H}_2\text{O}$ calc'd: C 47.16; H 5.72; N 12.22%
found: C 46.80; H 5.56; N 12.83%

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 4 ($R_1 = R_2 = CH_3$, R=Benzoyl) and 5 ($R_1 = CH_3$, $R_2 = C_6H_5$; R=Benzoyl) were prepared by the improved procedure in 48% and 58% yield. Namely; 2 g (8.24 mmoles) of 1 ($R_1 = R_2 = CH_3$) were dissolved in 150 ml CH_3CN , 4 g (2.95 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose and 0.5 ml trimethylchlorosilane and 0.9 ml of hexamethyldisilazane with 1.35 ml $SnCl_4$ and 25 ml CH_3CN was added. The reaction mixture was heated for 80 minutes at 80 °C. The general work-up procedure followed this modification.
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IZVLEČEK

Sinteza in antivirusna aktivnost 2-substituiranih azino-3- β -D-ribofuranozil in α in β -D-arabinofuranozil-5-karbamoilmetilentiazolidin-3-onov

J. Kobe, B. Rusjakovski in B. Brdar

Pripravili smo 2-(1-izopropiliden in metilbenziliden)azino-3- β -D-ribofuranozil-5-karbamoilmetilentiazolidin-4-on 3 s katalizirano talilno metodo 2-(1-isopropiliden in 1-metilbenziliden)azino-5-karbamoilmetilentiazolidin-(3H)-4-ona 1 z 1-O-acetil-2,3,5-tri-O-benzoil- β -D-ribofuranozo ter iz derivata 7 preko intermediatov 9 in 10 in nadaljno ciklizacijo v 11 ter odstranitvijo zaščitnih skupin, α in β arabinofuranozil derivate smo pripravili z direktno aminolizo zaščitnih derivatov 5. Produkti kažejo šibko aktivnost proti poliovirusu 2, medtem ko so neaktivni protiv virusu herpes simpleks.