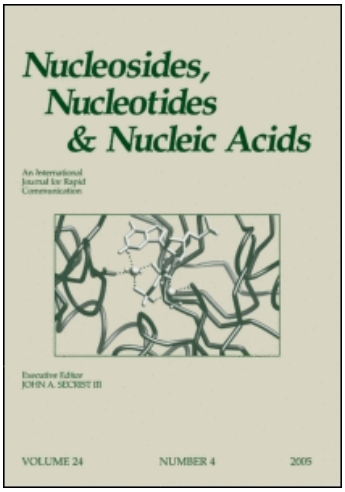

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SYNTHESIS OF 2-(β-D-RIBOFURANOSYL)THIAZOLE-4-CARBOXAMIDE 5'-PHOSPHATE ISOSTERES

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SUMMARY. The syntheses of 5'-O-sulfamoyl and 5'-O-carbamoyl tiazofurin (9 and 12) are described. One pot reaction of 2',3'-O-isopropylidene-tiazofurin (7) with hexabutyldistannoxane and sulfamoyl chloride gave the corresponding 5'-O-sulfamoyl ester, which was deprotected to yield 9. Compound 7 reacted with phenyl chloroformate to give the 5'-O-carbophenoxy derivative which on treatment with ammonium hydroxide followed by deisopropylidenation afforded 12. Improvements on the synthetic route to the starting tiazofurin are also reported.

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide, tiazofurin[1,2] (1), is an antitumor agent, currently undergoing phase I clinical trials, which shows potent activity against several murine tumors[3,4]. Tiazofurin is firstly metabolized to its 5'-phosphate 2 which is converted to the NAD analog, appropiately abbreviated TAD, which is an inhibitor of IMP dehydrogenase[5,6]. This fact prompted us to synthesize compounds 9 and 12 in which the 5'-O-phosphate of 2 has been replaced by sulfamate and carbamate groups simulating phosphate. These isosteres could substitute 2 to form the NAD analog of they could have an antitumor effect by themselves.

Since tiazofurin was required as starting material, we considered it of interest to improve its synthesis. Tiazofurin was first synthesized in our laboratory[1] by condensation of the thiocarboxamide 5 with ethyl bromopyruvate in refluxing ethanol followed by ammonolysis of the only resulting product, namely ethyl 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) thiazole-4-carboxylate (6) which was obtained in 55% yield. The starting thiocarboxamide 5 was also first synthesized by us by treatment of the glycosyl cyanide 4 with gaseous hydrogen sulfide in ethanol containing triethylamine[1,7]. Under these conditions, compound 5 was obtained in only 20% yield along with 5-benzoyloxymethylfuran-2-thiocarboxamide in 14% yield. Later, Robins and co-workers reported the synthesis of 5 in 83% yield with no benzoate elimination by treatment of 4 with liquid hydrogen

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sulfide in the presence of 4-dimethylaminopyridine[2]. These authors also reported the synthesis of tiazofurin via the condensation of 5 with ethyl bromopyruvate in acetonitrile at room temperature. In this case, besides the desired 2-β-ribosylthiazole 6 (42%) and a small amount of the (furan--2-yl)thiazole derivative resulting from benzoate elimination, the corresponding 2-α-ribosylthiazole, anomer of 6, was obtained in 22% yield. We have now investigated this unusual anomerization and found that treatment of the allonothioamide 5 and the 2-β-ribosylthiazole 6 with hydrogen bromide in acetonitrile gave no anomerization. This seems to indicate that the anomerization takes place in the course of the condensation of 5 with ethyl bromopyruvate when the reaction is achieved in acetonitrile, since no anomerization occurred using ethanol as solvent[1] or in closely related reactions using other solvents[2,7,8,9,10]. Therefore, it should be concluded that acetonitrile must not be used as solvent in order to avoid the formation of the undesired α-ribosylthiazole. Recently, a new route for the synthesis of tiazofurin via the reductive diazotization of ethyl 5-amino--2-(β-D-ribofuranosyl)thiazole-4-carboxylate has been reported[11]. However, this new route is longer than that involving the condensation of 5 with ethyl bromopyruvate. Now, following our initial route, we have succeeded in the improvement on the synthesis of the 2-β-ribosylthiazole-4-carboxylate 6, and therefore of tiazofurin, in relation to both earlier reports[1,2]. Thus, the ribofuranosyl cyanide 4 was quantitatively obtained by reaction of the commercially available 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (3), instead of the corresponding ribosyl bromide, with $(Me)_3SiCN$[12]. Treatment of 4 with gaseous hydrogen sulfide in ethanol containing a catalytic amount of 4-dimethylaminopyridine provided the thiocarboxamide 5 in 90% yield. Under these conditions, no appreciable benzoate elimination occurred and the yield was similar to that reported when liquid hydrogen sulfide, more difficult to handle than gaseous hydrogen sulfide, was used[2]. Finally, the condensation of 5 with ethyl bromopyruvate to give the precursor of tiazofurin 6 was achieved in ethanol in the manner reported by our laboratory[1]. It should be noted that several of these condensations were achieved in ethanol in order to detect if formation of some quantity of the corresponding 2-α-ribosylthiazole took place. However, this nucleoside was never detected.

According to the method described by Moffatt[13] for the conversion of nucleosides to their sulfamoyl esters by way of intermediate 5'-O-tributyltin derivatives, 2-(2,3-O-isopropylidene-5-O-sulfamoyl-β-D-ribofuranosyl) thiazole-4-carboxamide (8) was obtained in 63% yield by reaction of 2-(2,3--O-isopropylidene-β-D-ribofuranosyl)thiazole-4-carboxamide (7)[1] with hexa-

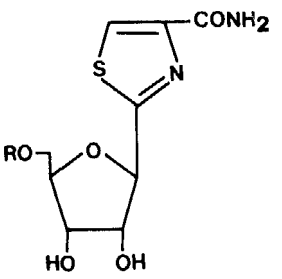
butyldistannoxane, followed by in situ reaction of the resulting 5'-O-tributyltin ether with sulfamoyl chloride. The 5'-O-carbamoyl analogue 11 was prepared by the route involving the previous preparation of the corresponding 5'-O-carbophenoxy derivative[14]. Thus, reaction of 7 with phenyl chloroformate afforded 2-(2,3-O-isopropylidene-5-O-carbophenoxy-β-D-ribofuranosyl) thiazole-4-carboxamide (10) in 51% yield which was treated with methanolic ammonium hydroxide to give 2-(2,3-O-isopropylidene-5-O-carbamoyl-β-D-ribofuranosyl)thiazole-4-carboxamide (11) in 91% yield. Removal of the 2',3'-O--isopropylidene protecting groups of 8 and 11 by treatment with 90% trifluoroacetic acid gave the target compounds 2-(5-O-sulfamoyl- and 5-O-carbamoyl-β-D-ribofuranosyl)thiazole-4-carboxamide (9 and 12).

The structures of these 5'-O-substituted tiazofurin derivatives were confirmed by analytical and spectroscopic data. The attachment of the sulfamoyl, carbophenoxy and carbamoyl groups to the 5'-O-position of the tiazofurin in 8, 10 and 11 was demonstrated by the downfield shift of the H-5' protons, which appeared at δ 4.04, 4.30 and 3.94 respectively, as compared to the same protons of 2',3'-O-isopropylidenetiazofurin, which appeared at δ 3.43.

EXPERIMENTAL

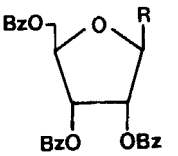
Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 90 MHz on a Varian EM-390 spectrometer using Me_4Si as internal standard. Analytical thin-layer chromatography was performed on aluminium sheets coated with a 0.2 mm layer of silica gel $60F_{254}$ (Merck). Preparative layer chromatography was performed on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Column chromatography was performed on silica gel 60 (Merck, 70-230 mesh). Compounds were detected with UV light (254 nm) or by spraying the plate with an ethanol-sulfuric acid (3:7) mixture and heating.

2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allonothioamide (5). A mixture of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide[12] (4.6 g, 9.8 mmol), 4-dimethylaminopyridine (0.1 g) and ethanol (50 mL) was stirred at room temperature for 3 h, while hydrogen sulfide was bubbled into the solution. The solvent was removed and the residue was purified on a silica gel column (2.5 x 40 cm) using benzene-ether as eluent to provide 5 (4.4 g, 90%) identical in all respects to that described[1,2].



1 : R = H

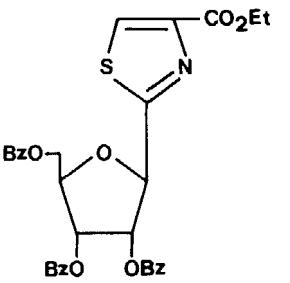
2 : R = PO_3H_2



3 : R = OAc

4 : R = CN

5 : R = $CSNH_2$



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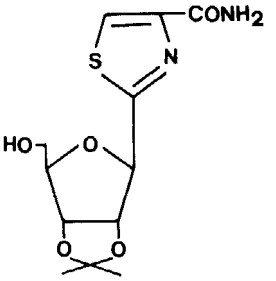

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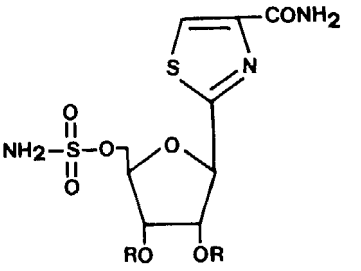
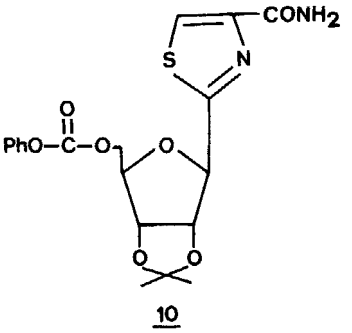


8 : R = $C(CH_3)_2$

9 : R = H



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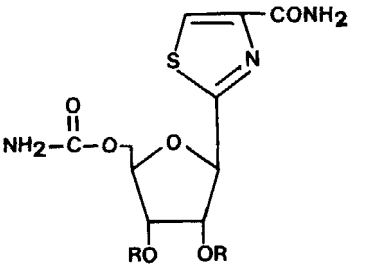

11 : R = $C(CH_3)_2$

12 : R = H

2-(2,3-O-Isopropylidene-5-O-sulfamoyl-β-D-ribofuranosyl)thiazole-4--carboxamide (8). A suspension of 2-(2,3-O-isopropylidene-β-D-ribofuranosyl)thiazole-4-carboxamide(7[1], 0.45 g, 1.5 mmol) in benzene (50 mL) containing hexabutyldistannoxane (2.98 g, 5 mmol) was heated under reflux in anhydrous conditions for 1.5 h. The resulting clear solution was cooled to 0-5°C in a dry box and a solution of sulfamoyl chloride (0.55 g, 4.75 mmol) in dioxane (15 mL) was added dropwise. After stirring for an additional 30 min the solvents were evaporated and the residue was extracted with hot hexane. The insoluble residue was quickly treated with methanolic ammonia, evaporated and purified by preparative TLC using $CHCl_3$-MeOH (9:1). Elution of the major band gave 8 (0.36 g, 63%) as a chromatographically homogeneous foam. ^{1}H NMR (DMSO) δ 1.32 and 1.52(2s, 6H, isopropylidene) 4.04(m, 2H, H-5'), 4.38(m, 1H, H-4'), 5.28(d, 1H, H-1', $J_{1',2'}$= 4.0 Hz), 7.53 and 7.70(2 br s, 4H, $CONH_2$ and SO_2NH_2, D_2O exchangeable), 8.23(s, 1H, H-5).

Anal. Calcd. for $C_{12}H_{17}N_3O_7S_2$: C, 37.99; H, 4.48; N, 11.07; S, 16.89. Found: C, 37.72; H, 4.53; N, 10.97; S, 16.98.

2-(5-O-Sulfamoyl-β-D-ribofuranosyl)thiazole-4-carboxamide (9). A solution of 8 (0.25 g, 0.66 mmol) in 90% aqueous trifluoroacetic acid (10 mL) was kept at room temperature for 15 min and then evaporated to dryness. The residue was treated with methanolic ammonium hydroxide (1:1, 7 mL) and evaporated to dryness leaving a residue which was chromatographed on a column of silica gel using $CHCl_3$-MeOH (9:1) to give 9 (0.22 g, 98%) as a chromatographically homogeneous foam. ^{1}H NMR (DMSO + D_2O) δ 5.00(d, 1H, H-1', $J_{1',2'}$= 5.0 Hz), 8.21(s, 1H, H-5).

Anal. Calcd. for $C_9H_{13}N_3O_7S_2$: C, 31.86; H, 3.83; N, 12.39; S, 18.88. Found: C, 32.05; H, 4.02; N, 12.11; S, 19.03.

2-(2,3-O-Isopropylidene-5-O-carbophenoxy-β-D-ribofuranosyl)thiazole--4-carboxamide (10). A suspension of 7 (0.90 g, 3.0 mmol) in pyridine (20 mL) was cooled to 0°C, and phenyl chloroformate (0.90 mL, 7.2 mmol) was added dropwise with stirring. The solution was stirred at 0°C for 1 h and then at room temperature for 1 h. Evaporation of the solvent left a residue which was triturated with H_2O (10 mL), evaporated and coevaporated with MeOH. The residue was purified by preparative TLC using $CHCl_3$-acetone (3:2) to afford 10 (0.64 g, 51%) as a chromatographically homogeneous foam. ^{1}H NMR (DMSO) δ 1.34 and 1.53(2s, 6H, isopropylidene group), 4.30(m, 2H, H-5'), 4.43(m, 1H, H-4'), 5.30(d, 1H, H-1', $J_{1',2'}$= 3.0 Hz), 7.10-7.47(m, 5, C_6H_5), 7.53 and 7.72(2 br s, 2H, $CONH_2$), 8.27(s, 1H, H-5).

Anal. Calcd. for $C_{19}H_{20}N_2O_7S$: C, 54.28; H, 4.76; N, 6.67; S, 7.62. Found: C, 54.47; H, 4.93; N, 6.31; S, 7.86.

2-(2,3-O-Isopropylidene-5-O-carbamoyl-β-D-ribofuranosyl)thiazole-4-carboxamide (11). A solution of 10 (0.54 g, 1.28 mmol) in methanol (10 mL) and concentrated ammonium hydroxide (30 mL) was stirred at room temperature for 2 h. Evaporation of the solvent left a residue which was purified by preparative TLC using $CHCl_3$-MeOH (9:1) to provide 11 (0.4 g, 91%), mp 155-156°C (from EtOAc-petroleum ether); ^{1}H NMR (DMSO) δ 1.30 and 1.50 (2s, 6H, isopropylidene group), 3.94(m, 2H, H-5'), 4.33(m, 1H, H-4'), 5.20(d, 1H, H-1', $J_{1',2'}$= 2.0 Hz), 6.47(br s, 2H, $OCONH_2$-5', D_2O exchangeable), 7.50 and 7.67 (2 br s, 2H, $CONH_2$-4, D_2O exchangeable), 8.20 (s, 1H, H-5).

Anal. Calcd. for $C_{13}H_{17}N_3O_6S$: C, 45.48; H, 4.96; N, 12.24; S, 9.33. Found: C, 45.79; H, 5.02; N, 11.92; S, 9.21.

2-(5-O-Carbamoyl-β-D-ribofuranosyl)thiazole-4-carboxamide (12). A solution of 11 (0.3 g, 0.87 mmol) in 90% aqueous trifluoroacetic acid (10 mL) was kept at room temperature for 30 min and then worked up as described for 9. Purification by preparative TLC using $CHCl_3$-MeOH (4:1) afforded 12 (0.23 g, 85%), mp 96-98°C (from EtOH-ether); ^{1}H NMR (DMSO + D_2O) δ 4.98(d, 1H, H-1', $J_{1',2'}$= 5.0 Hz), 8.21(s, 1H, H-5).

Anal. Calcd. for $C_{10}H_{13}N_3O_6S$: C, 39.60; H, 4.29; N, 13.86; S, 10.56. Found: C, 39.92; H, 4.23; N, 13.51; S, 10.38.

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REFERENCES

1. M. Fuertes, M.T. García-López, G. García-Muñoz, M. Stud, J. Org. Chem., 41, 4074 (1976).
2. P.C. Srivastava, M.V. Pickering, L.B. Allen, D.G. Streeter, M.T. Campbell, J.T. Witkowski, R.W. Sidwell, R.K. Robins, J. Med. Chem., 20, 256 (1977).
3. R.K. Robins, P.C. Srivastava, V.L. Narayanan, J. Plowman, K.D. Paull, J. Med. Chem., 25, 107 (1982).
4. P.C. Srivastava, G.R. Revankar, R.K. Robins, J. Med. Chem., 27, 266 (1984).
5. D.A. Cooney, H.N. Jayaram, G. Gebeyehu, C.R. Betts, J.A. Kelley, V.E. Marquez, D.G. Johns, Biochem. Pharmacol. 31, 2133 (1982).

6. G. Gebeyehu, V.E. Marquez, A. Van Cott, D.A. Cooney, J.A. Kelley, H.N. Jayaram, G.S. Ahluwalia, R.L. Dion, I.A. Wilson, D.G. Johns, J. Med. Chem., 28, 99 (1985) and references therein.
7. M. Fuertes, M.T. García-López, G. García-Muñoz, R. Madroñero, J. Carbohydr., Nucleosides, Nucleotides, 2, 277 (1975).
8. M.C. Clingerman, J.A. Secrist III, J. Org. Chem., 48, 3141 (1983) and references therein.
9. M.T. García-López, R. Herranz, P.P. Méndez-Castrillón, Nucleosides, Nucleotides, 1, 127 (1982).
10. T.J. Cousineau, J.A. Secrist III, J. Org. Chem., 44, 4351 (1979).
11. W.J. Hennen, B.C. Hinshaw, T.A. Riley, S.G. Wood, R.K. Robins, J. Org. Chem., 50, 1741 (1985).
12. F.G. De las Heras, P. Fernández-Resa, J. Chem. Soc. Perkin I, 903 (1982).
13. I.D. Jenkins, J.P.H. Verheyden, J.G. Moffatt, J. Am. Chem. Soc., 98, 3346 (1976).
14. W.C. Fleming, W.W. Lee, D.W. Henry, J. Med. Chem., 16, 570 (1973).

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