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Synthesis of *C*-Glycosyl Thiazoles

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Condensation of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (**1**) with α-chloroketo compounds yielded the corresponding 2-*C*-glycosyl thiazole nucleosides (**4a** and **7**) as the major products along with the 2-(thiazol-2-yl)-5-benzoyloxymethylfuran derivatives (**5a** and **8**). Reaction of **1** with ethyl bromopyruvate gave as the only resulting compound the 2-*C*-glycosyl thiazole nucleoside **12**. A similar series of reactions was carried out with 5-benzoyloxymethylfuran-2-thiocarboxamide (**2**) and α-halo ketones. Finally, treatment of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose (**24**) with thiourea afforded the 4-*C*-glycosyl thiazole **26**.

Of the several synthetic procedures described in the literature for obtaining thiazole derivatives, the reaction of thioamides and related compounds with α-halocarbonyl derivatives has been the most extensively used.[1] By application of this method, some acyclic sugar 2- and 4-thiazolyl nucleoside analogues have been prepared starting from suitable aldonic acid thioamides[2] or α-haloketoses,[3] respectively. More recently Tronchet et al.[4] have described the synthesis of 4-*C*-glycosyl thiazoles by reacting thiourea or thioacetamide with an α-halocarbonyl sugar derivative, namely 6-*S*-benzyl-6-chloro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-6-thiohexofuranos-5-ulose.

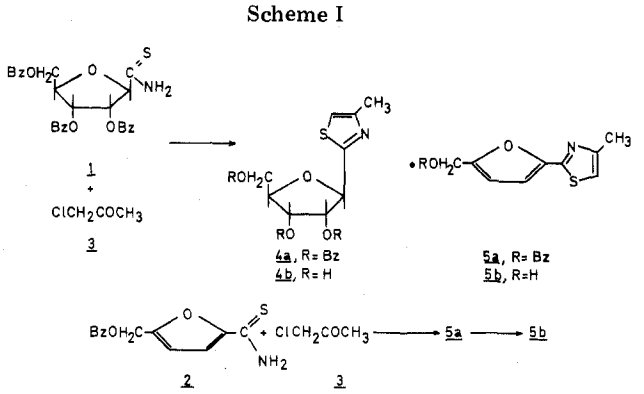
In a recent preliminary communication[5] we have reported on the synthesis of a 2-*C*-glycosyl thiazole nucleoside and also the synthesis of several acyclic sugar 4-thiazolyl nucleoside analogues. Now we wish to give a full account of this and related work.

The starting material in our synthesis of 2-glycosyl thiazole nucleosides, the hitherto unknown 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide[5,6] (**1**), was obtained in 20% yield as an amorphous solid by reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[7] with hydrogen sulfide. It should be noted that the furan derivative **2** resulting from the elimination of two benzoyloxy groups was also separated from the reaction. Similar base-catalyzed eliminations of these protecting groups have been already reported.[8]

The assignment of the anomeric configuration of **1** was made on the basis of the known configuration of the nitrile used as starting material, since the doublet corresponding to the anomeric proton of **1** (τ 4.92) showed a coupling constant larger than 1 Hz ($J_{1,2}$ = 5 Hz). This assignment was further supported by the consistent application of Imbach's criterion[9] on the 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl nucleoside **14**, obtained from **1** as described below.

Reaction of the thiocarboxamide **1** with chloroacetone in ethanol afforded a mixture of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthiazole (**4a**) in 32% yield and the furan derivative **5a** in 15% yield. Debenzoylation of these products with methanolic ammonia gave the deblocked compounds **4b** and **5b**, respectively (Scheme I). Similarly, reaction of the furan thiocarboxamide **2** with chloroacetone gave a 35% yield of **5a** identical with the compound obtained in the foregoing reaction.

Scheme I



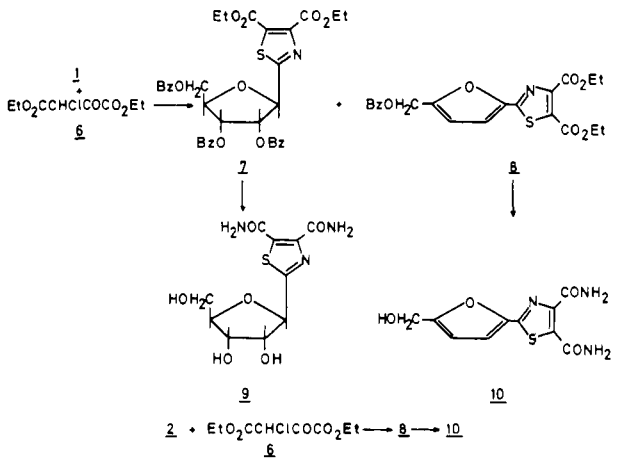
The thiocarboxamide **1** reacted smoothly with ethyl oxalochloroacetate to give a mixture of the blocked C-nucleoside **7** and the elimination product **8** which were isolated by preparative layer chromatography in yields of 31 and 27%, respectively. Compound **8** was also obtained from the reaction of furan thiocarboxamide **2** with ethyl oxalochloroacetate (Scheme II).

Treatment of compounds **7** and **8** with methanol saturated with ammonia gave the corresponding deblocked dicarboxamides in low yields. In the case of compound **7**, TLC of the crude reaction showed a complex mixture of products. Separation by preparative thick layer chromatography gave the expected deblocked β anomer **9** in 25% yield. ^1H NMR spectra of other minor bands showed the presence of the α anomer along with traces of compound **10**. It should be noted that no anomerization was detected in the debenzoylation reactions of the other 2-*C*-glycosyl thiazole nucleosides described in this paper.

In a similar fashion the thiocarboxamide **1**, when treated with ethyl bromopyruvate at reflux in ethanol solution, gave the protected *C*-glycosyl nucleoside **12** in 55% yield as a syrup. Although a furan derivative was expected, no compound of this type was found. Treatment of **12** with methanolic am-

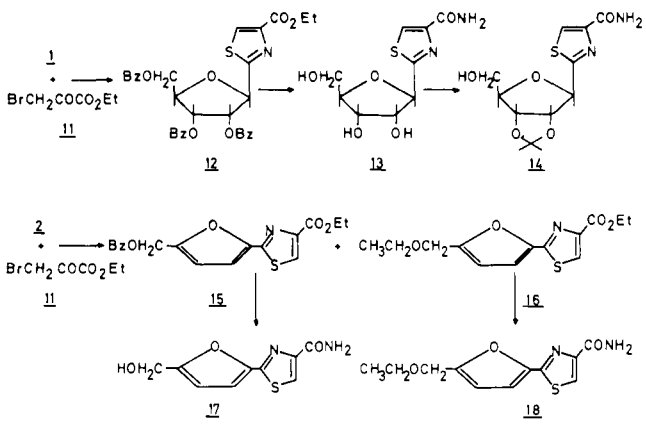
† The present paper is dedicated to the memory of Professor García-Muñoz.

Scheme II



monia afforded 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (13) as a crystalline product in 81% yield. This latter compound was then converted to the 2′,3′-*O*-isopropylidene derivative 14. Its NMR spectrum showed the protons of the isopropylidene methyl groups as two singlets at τ 8.50 and 8.68, respectively. This difference of 0.18 ppm has been shown to be consistent only with the β configuration[9] (Scheme III).

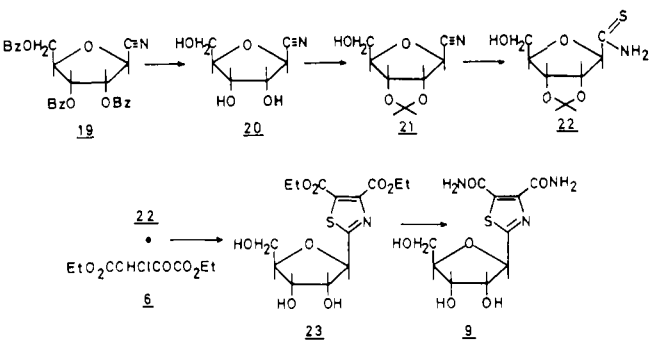
Scheme III



As before, the use of the thiocarboxamide 2 in the synthesis of nucleoside-related compounds having a furyl moiety was evaluated. Reaction of 2 with ethyl bromopyruvate in refluxing ethanol gave, besides the expected compound 15 in 30% yield, another compound in 27% yield that was identified as 2-(4-carboethoxythiazol-2-yl)-5-ethoxymethylfuran (16). The NMR spectrum of 16 indicated clearly the absence of benzoyl protons and the presence of signals corresponding to an ethoxy group, in addition to the signals of the carboethoxy thiazole substituent. Further evidence for the structure assignment for 16 stems from its conversion to the carboxamide 18, the NMR spectrum of which retains the characteristic pattern for the ethoxymethyl moiety. The formation of 16 can be explained taking account of the stability of the carbonium ion resulting from the cleavage of the C–O linkage of the benzoyloxy group due to the acidic media originated in the reaction. Attack of the carbonium ion by ethanol affords 16. Chemical evidence for this assumption was supported by the formation of 16 from 15, when this last compound was treated with ethanol–hydrogen bromide at reflux temperature. Attempts to find compounds similar to 16 in the reaction of 2 with chloroacetone or ethyl oxalochloroacetate were unsuccessful.

In order to avoid the formation of furan derivatives by loss of the benzoyl groups in the condensation of 1 with α-halo ketones, we synthesized the glycosyl thiocarboxamide 22 having an isopropylidene protecting group. The glycosyl nitrile 19 was debenzoylated at room temperature with methanolic ammonia to give the deblocked derivative 20, which was treated with ethyl orthoformate and acetone in the presence of hydrochloric acid to yield 2,3-*O*-isopropylidene-β-D-ribofuranosyl cyanide (21). Treatment of this product with hydrogen sulfide in ethanol containing triethylamine afforded 22 (Scheme IV).

Scheme IV

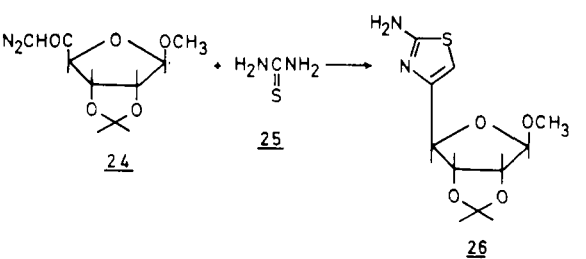


Reaction of thiocarboxamide 22 with ethyl oxalochloroacetate was then examined. As we expected, only one thiazole derivative was formed in a process involving the concomitant removal of the protecting isopropylidene group, due to the acidity of the reaction medium. Subsequent ammonolysis of the diester 23 gave the crystalline dicarboxamide derivative 9 identical with the compound obtained from 7.

It should be pointed out that compounds 7, 9, and 23 provide a series of valuable intermediates for synthesis, via cyclization, of new purinelike nucleosides.

Finally, since it has been reported that the reaction of α-diazo ketones with thioamides gives thiazole derivatives,[10] we then extended our studies to the synthesis of the 4-glycosyl thiazole derivative 26 by reaction in refluxing ethanol of the diazoketose 24[11] with thiourea (Scheme V). An analytically

Scheme V



pure sample of 26 was obtained via its picrate derivative, since all the attempts we made to obtain it from the repeatedly chromatographed reaction product were unsuccessful. The synthesis of compound 26 failed when the reaction was performed starting from the corresponding α-haloketose, probably due to the known instability of this compound.[11]

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 100 MHz on a Varian XL-100 spectrometer using Me_4Si as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Uv absorption spectra were taken with a Perkin-Elmer 350 spectrophotometer. Analytical thin layer chromatography was performed on glass plates coated with a 0.25 mm layer of silica gel GF_{254} (Merck), and preparative layer chromatography on 20 × 20 cm glass plates coated with a 2-mm layer of silica gel PF_{254} (Merck). The compounds were detected with a uv light (254 nm)

or by spraying the plates with 30% sulfuric acid in ethanol and heating at ca. 110 °C.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (1) and 5-Benzoyloxymethylfuran-2-thiocarboxamide (2). A mixture of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[7] (**19**, 1.41 g, 3 mmol), triethylamine (3.5 ml), and ethanol (60 ml) was stirred at room temperature for 2 h, while hydrogen sulfide was bubbled into the solution. The solvent was removed and the residue was chromatographed on plates using 20:1 benzene–ether as developing system. The two faster moving bands did not contain sulfur and were not further investigated. The third faster moving band yielded 0.19 g of a solid product that after crystallization from ethyl acetate–petroleum ether gave 0.11 g (14%) of compound **2** with mp 130–131 °C; NMR ($CDCl_3$) τ 3.45 (d, H-3, $J_{3,4}$ = 4 Hz), 4.71 (s, $-CH_2OBz$).

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.77; H, 4.21; N, 5.36; S, 12.26. Found: C, 59.85; H, 4.27; N, 5.06; S, 12.19.

The slowest moving band gave 0.46 g of product that was rechromatographed on preparative plates (1:9 ethyl acetate–chloroform) to provide 0.30 g (20%) of **1** as a yellow foam: $[\alpha]^{25}D$ + 2° (*c* 1, chloroform); NMR ($CDCl_3$) τ 4.02 (t, H-2, $J_{2,1} \simeq J_{2,3}$ = 5 Hz), 4.32 (m, H-3), 4.92 (d, H-1, $J_{1,2}$ = 5 Hz), 5.30 (m, H-4, 2 H-5).

Anal. Calcd for $C_{27}H_{23}NO_7S$: C, 64.15; H, 4.58; N, 2.77; S, 6.32. Found: C, 63.95; H, 4.75; N, 2.73; S, 6.59.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthiazole (4a) and 2-(4-Methylthiazol-2-yl)-5-benzoyloxymethylfuran (5a). A solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (**1**, 2.02 g, 4 mmol) and freshly distilled chloroacetone (**3**, 0.74 g, 8 mmol) in ethanol (15 ml) was heated under reflux for 7 h. The solvent was evaporated, the residue was dissolved in ethyl acetate, and the solution was washed with 5% aqueous sodium bicarbonate and with water and dried over sodium sulfate. After evaporation of the solvent the residue was purified by preparative TLC using 1:4 ethyl acetate–petroleum ether. The slowest moving band afforded 0.65 g (30%) of **4a** as a homogeneous syrup: $[\alpha]^{25}D$ −32° (*c* 1, chloroform); NMR ($CDCl_3$) τ 3.16 (H-5 thiazole ring), 4.36 (d, H-1′, $J_{1',2'}$ = 5 Hz), 7.57 (CH_3).

Anal. Calcd for $C_{30}H_{25}NO_7S$: C, 66.29; H, 4.63; N. 2.57; S, 5.88. Found: C, 66.06; H, 4.62; N, 2.48; S, 6.08.

The third band from the origin gave 0.18 g (15%) of **5a** with mp 72–73 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 3.20 (H-5 thiazole ring), 3.09 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.43 (d, H-4 furan ring, $J_{4,3}$ = 4Hz), 4.67 (s, CH_2OBz), 8.54 (CH_3).

Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.37; N, 4.68; S, 10.69. Found: C, 64.22; H, 4.44; N, 4.67; S, 10.80.

2-(4-Methylthiazol-2-yl)-5-benzoyloxymethylfuran (5a). A solution of the thiocarboxamide **2** (1.3 g, 5 mmol) and chloroacetone (**3**, 0.93 g, 10 mmol) in ethanol (25 ml) was refluxed for 7 h. The solvent was evaporated and the residue was purified by preparative TLC using 1:5 ethyl acetate–petroleum ether. The slowest moving band afforded 0.53 g (35%) of **5a** with physical properties identical with those previously reported for that compound.

2-(β-D-Ribofuranosyl)-4-methylthiazole (4b). A solution of **4a** (0.42 g, 0.73 mmol) in methanol saturated with ammonia at 0 °C (30 ml) was allowed to stand at room temperature for 48 h. The solvent was evaporated and the residue was purified by preparative TLC (9:1 chloroform–methanol) to give 0.14 g (80%) of **4b**: mp 122–124 °C (from ethyl acetate–petroleum ether); $[\alpha]^{25}D$ −24° (*c* 0.5, ethanol); uv λ_{max} (ethanol) 250 nm (ϵ 6700); NMR (Me_2SO-d_6–D_2O) τ 2.85 (H-5 thiazole ring), 5.12 (d, H-1′, $J_{1'2'}$ = 5 Hz), 7.68 (CH_3).

Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.75; H, 5.66; N, 6.05; S, 13.84. Found: C, 46.79; H, 5.56; N, 5.90; S, 14.01.

2-(4-Methylthiazol-2-yl)-5-hydroxymethylfuran (5b). A solution of **5a** (0.30 g, 1 mmol) in saturated methanolic ammonia was kept at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative TLC using 1:1 ethyl acetate–petroleum ether. Elution of the major band afforded 0.09 g (46%) of a solid which was recrystallized from ethyl acetate–petroleum ether to give pure **5b** with mp 151–153 °C; uv λ_{max} (ethanol) 219 nm (ϵ 8600), 318 (16 420); NMR (Me_2SO-d_6–D_2O) τ 2.79 (H-5 thiazole ring), 3.07 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.55 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.55 (s, CH_2OH), 7.63 (CH_3).

Anal. Calcd for $C_9H_9NO_2S$: C, 55.38; H, 4.64; N, 7.17; S, 16.40. Found: C, 55.14; H, 4.70; N, 7.32; S, 16.54.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dicarboethoxythiazole (7) and 2-(4,5-Dicarboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (8). A solution of **1** (1.01 g, 2 mmol) and ethyl oxalochloroacetate[12] (**6**, 0.89 g, 4 mmol) in ethanol (15 ml) was heated under reflux for 6 h. The solvent was removed and the residue was chromatographed by preparative TLC using 1:4 ethyl acetate–petroleum ether as developing system. The slowest moving band yielded 0.65 g of a syrup which was rechromatographed (1:4 ethyl acetate–petroleum ether) to give 0.42 g (31%) of **7** as a homogeneous syrup: $[\alpha]^{25}D$ −57° (*c* 0.5, chloroform); NMR ($CDCl_3$) τ 4.01–4.24 (m, H-2′ and H-3′), 4.39 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_{35}H_{31}NO_{11}S$: C, 62.40; H, 4.63; N, 2.07; S, 4.74. Found: C, 62.12; H, 4.69; N, 2.12; S, 5.02.

The next moving band gave 0.23 g (27%) of **8** with mp 82–83 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 2.87 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.39 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 4.66 (s, CH_2OBz), 5.56 and 5.66 (2 q, $2CH_2CH_3$), 8.60 and 8.65 (2t, $2CH_2CH_3$).

Anal. Calcd for $C_{21}H_{19}NO_7S$: C, 58.73; H, 4.46; N, 3.26; S, 7.45. Found: C, 58.50; H, 4.34; N, 3.14; S, 7.73.

2-(4,5-Dicarboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (8). Reaction of **2** (1.05 g, 4 mmol) with ethyl oxalochloroacetate (**6**, 1.78 g, 8 mmol) in refluxing ethanol (25 ml) for 7 h afforded after three successive preparative TLC (I, 1:5 ethyl acetate–petroleum ether; II and III, 1:2 ethyl acetate–petroleum ether) 0.47 g (27%) of **8** identical with that above described.

2-(β-D-Ribofuranosyl)thiazole-4,5-dicarboxamide (9). Treatment of **7** (0.30 g, 0.44 mmol) with methanolic ammonia (25 ml) for 20 h gave a complex mixture of compounds. The residue obtained after evaporation of the solvent was purified by two consecutive preparative TLC (the first using 9:1 chloroform–methanol and the second 7:3 chloroform–methanol). Crystallization from ethanol of the solid obtained gave 0.03 g (25%) of **9**: mp 212–214 °C; $[\alpha]^{25}D$ −33° (*c* 0.5, water); uv λ_{max} (ethanol) 220 nm (ϵ 14 100), 269 (8420); NMR (Me_2SO-d_6–D_2O) τ 5.12 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_{10}H_{13}N_3O_6S$: C, 39.60; H, 4.32; N, 13.85; S, 11.54. Found: C, 39.36; H, 4.55; N, 13.58; S, 11.20.

2-(4,5-Dicarboxamidothiazol-2-yl)-5-hydroxymethylfuran (10). A solution of **8** (0.43 g, 1 mmol) in methanolic ammonia (25 ml) was allowed to stand at room temperature for 20 h. The white solid precipitated was filtered off and after treatment with active charcoal was recrystallized from methanol to give 0.06 g (21%) of **10**: mp 260–261 °C dec; uv λ_{max} (ethanol) 239 nm (ϵ 15 370), 337 (16 990); NMR (Me_2SO-d_6–D_2O) τ 2.80 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.48 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, CH_2OH).

Anal. Calcd for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; N, 15.72. Found: C, 44.84; H, 3.49; N, 15.54.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-carboethoxythiazole (12). A mixture of **1** (2.02 g, 4 mmol) and ethyl bromopyruvate (**11**, 1.56 g, 8 mmol) in ethanol (15 ml) was refluxed for 5 h. The solvent was evaporated and the residue purified by preparative TLC using 1:9 ethyl acetate–chloroform. The product obtained from the major band was rechromatographed in a mixture of 1:2 ethyl acetate–petroleum ether to give 1.33 g (55%) of **12** as a homogeneous syrup: $[\alpha]^{25}D$ −45.5° (*c* 1, chloroform); NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 4.31 (d, H-1′, $J_{1',2'}$ = 5 Hz), 5.66 (q, CH_2CH_3), 8.67 (t, CH_2CH_3).

Anal. Calcd for $C_{32}H_{27}NO_9S$: C, 63.88; H, 4.52; N, 2.32; S, 5.32. Found: C, 63.58; H, 4.26; N, 2.14; S, 5.61.

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (13). Treatment of **12** (1 g, 0.17 mmol) with methanolic ammonia (50 ml) at room temperature for 48 h and evaporation of the solvent afforded a product which was purified by preparative TLC using 7:3 chloroform–methanol. Elution of the major band gave 0.35 g (81%) of **13**: mp 145–146 °C (from ethanol–ethyl acetate); $[\alpha]^{25}D$ −9° (*c* 0.5, ethanol); uv λ_{max} (ethanol) 215 nm (ϵ 9450), 237 (7625); NMR (Me_2SO-d_6–D_2O) τ 1.82 (s, H-5 thiazole ring), 5.04 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.54; H, 4.64; N, 10.76; S, 12.30. Found: C, 41.93; H, 4.67; N, 10.86; S, 12.10.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)thiazole-4-carboxamide (14). To a solution of **13** (0.20 g, 0.76 mmol), ethyl orthoformate (0.12 g, 0.80 mmol), and dry acetone (4 ml) was added a 1 M solution of hydrogen chloride in ether (0.1 ml). The mixture was stirred at room temperature until the solid was completely dissolved (24 h). The solution was neutralized with concentrated ammonium hydroxide and evaporated to dryness. The residue was dissolved in a small amount of water and the solution extracted several times with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated, leaving a residue which was purified by TLC using 1:2 ethyl acetate–petroleum ether. The solid obtained from the major band was recrystallized from ethyl acetate–petroleum ether to give 0.15 g (64%) of **14**: mp 119–120 °C; $[\alpha]^{25}D$ −32° (*c* 0.5, water); uv λ_{max} (ethanol) 215 nm (ϵ 7830), 237 (7390); NMR (Me_2SO-d_6–D_2O) τ 1.82 (s, H-5 thiazole ring), 4.86 (d, H-1′, $J_{1',2'}$ = 4 Hz), 5.00 (dd, H-2′, $J_{2',3'}$ = 6, $J_{2',1'}$ = 4 Hz), 5.28 (dd, H-3′, $J_{3',2'}$ = 6, $J_{3',4'}$ = 3 Hz), 8.50 and 8.68 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33; S, 10.65.

Found: C, 47.94; H, 5.40; N, 9.46; S, 10.62.

2-(4-Carboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (15) and 2-(4-Carboethoxythiazol-2-yl)-5-ethoxymethylfuran (16). A solution of **2** (1.05 g, 4 mmol) and ethyl bromopyruvate (**11**, 1.56 g, 8 mmol) in ethanol (15 ml) was refluxed for 5 h. After evaporation of the solvent the residue was purified by preparative TLC using 1:9 ethyl acetate–chloroform. The solid obtained from the slowest moving band was then rechromatographed in 1:2 ethyl acetate–petroleum ether. Elution of the major band afforded a solid material which was recrystallized from ethyl acetate–petroleum ether to give 0.30 g (27%) of **16**: mp 69–71 °C; NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 2.91 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.57 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, OCH_2), 5.59 and 6.44 (2 q, 2 CH_2CH_3), 8.60 and 8.78 (2 t, 2 CH_2CH_3).

Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.51; H, 5.33; N, 4.98; S, 11.38. Found: C, 55.68; H, 5.30; N, 5.09; S, 11.25.

The next moving band from the initial chromatography yielded a compound which was further purified by preparative TLC using 1:2 ethyl acetate–petroleum ether. The crystalline solid obtained, **15** (0.44 g, 30%), had mp 99–101 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 2.91 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.42 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 4.68 (s, OCH_2), 5.60 (q, CH_2CH_3), 8.61 (t, CH_2CH_3).

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.50; H, 4.23; N, 3.92; S, 8.95. Found: C, 60.72; H, 4.29; N, 4.12; S, 9.14.

2-(4-Carboxamidothiazol-2-yl)-5-hydroxymethylfuran (17). Compound **15** (0.18 g, 0.5 mmol) was treated with a saturated solution of ammonia in methanol for 24 h. Evaporation of the solvent left a residue which was crystallized from ethanol to give 0.09 g (80%) of **17**: mp 196–198 °C; uv λ_{max} (ethanol) 231 nm (ϵ 15 410), 315 (18 100); NMR (Me_2SO-d_6–D_2O) τ 1.79 (s, H-5 thiazole ring), 2.87 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.45 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.49 (s, OCH_2).

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.59; N, 12.49; S, 14.26. Found: C, 48.41; H, 3.67; N, 12.40; S, 14.11.

2-(4-Carboxamidothiazol-2-yl)-5-ethoxymethylfuran (18). Treatment of **16** (0.14 g, 0.5 mmol) according to the procedure described for **17** afforded 0.07 g (58%) of **18** after crystallization from ethanol: mp 154–156 °C; uv λ_{max} (ethanol) 231 nm (ϵ 15 140), 313 (18 100); NMR (Me_2SO-d_6–D_2O) τ 1.78 (s, H-5 thiazole ring), 2.88 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.36 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, OCH_2), 6.50 (q, CH_2CH_3), 8.86 (t, CH_2CH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.70. Found: C, 52.42; H, 4.54; N, 10.97; S, 12.98.

2,3-*O*-Isopropylidene-β-D-ribofuranosyl Cyanide (21). Treatment of **19** (4.71 g, 10 mmol) with methanolic ammonia at room temperature for 20 h yielded **20** which was used in the next step without further purification. Isopropylidination of **20** was carried out according to the procedure described for **14**. Column chromatography of the crude reaction product (~3.7 g) on silica gel (80 g) using 1:2 ethyl acetate–petroleum ether as eluent afforded a solid material which was crystallized from ethyl acetate–petroleum ether to give 0.64 g (32% total yield) of **21**: mp 63–65 °C; $[\alpha]^{25}D$ −35° (*c* 0.7, chloroform); NMR (Me_2SO-d_6–D_2O) τ 4.96 (dd, H-2, $J_{2,1}$ = 2, $J_{2,3}$ = 6 Hz), 5.10 (d, H-1, $J_{1,2}$ = 2 Hz), 5.22 (dd, H-3, $J_{3,2}$ = 6, $J_{3,4}$ = 1 Hz), 5.87 (m, H-4), 6.52 (m, 2 H-5), 8.60 and 8.74 ($2CH_3$, isopropylidene group).

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.08. Found: C, 54.41; H, 6.78; N, 6.98.

2,3-*O*-Isopropylidene-β-D-ribofuranosylthiocarboxamide (22). Hydrogen sulfide was bubbled into a solution of **21** (0.60 g, 3 mmol) in ethanol (30 ml) containing triethylamine (0.10 g, 1 mmol) for 2 h. The solvent was evaporated and the residue was purified by preparative TLC using 1:1 ethyl acetate–petroleum ether. Elution of the uv absorbing band (254 nm) afforded 0.60 g (86%) of **22** as a yellow syrup that crystallized on standing: mp 96–97 °C (from ethyl acetate–petroleum ether); $[\alpha]^{25}D$ −17° (*c* 1, chloroform); NMR (Me_2SO-d_6–D_2O) τ 5.21 (dd, H-2, $J_{2,1}$ = 4, $J_{2,3}$ = 6 Hz), 5.43 (dd, H-3, $J_{3,2}$ = 6, $J_{3,4}$ = 4 Hz), 5.50 (d, H-1, $J_{1,2}$ = 4 Hz), 5.93 (m, H-4), 8.54 and 8.72 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.34; H, 6.48; N, 6.00. Found: C, 46.65; H, 6.49; N, 5.93.

2-(β-D-Ribofuranosyl)-4,5-dicarboethoxythiazole (23). A solution of the thioamide **22** (0.47 g, 2 mmol) and ethyl oxalochloroacetate (**6**, 0.89 g, 4 mmol) in ethanol (15 ml) was refluxed for 6 h. The solvent was removed and the residue purified by preparative TLC using a mixture of 9:1 chloroform–methanol. Elution of the major band afforded a material which was further chromatographed using ethyl acetate, to give 0.23 g (32%) of **23** as a homogeneous syrup: $[\alpha]^{25}D$ −29° (*c* 0.5, chloroform); uv λ_{max} (ethanol) 213 nm (ϵ 13 890), 263 (13 890); NMR (Me_2SO-d_6–D_2O) τ 5.06 (d, H-1′, $J_{1',2'}$ = 5 Hz), 5.67 and 5.76 (2 q, 2 CH_2CH_3), 8.70 and 8.73 (2 t, 2 CH_2CH_3).

Anal. Calcd for $C_{14}H_{19}NO_8S$: C, 46.53; H, 5.26; N, 3.87. Found: C, 46.37; H, 5.60; N, 3.57.

2-(β-D-Ribofuranosyl)thiazole-4,5-dicarboxamide (9). Treatment of **23** (0.17 g, 0.47 mmol) with methanolic ammonia for 20 h gave after recrystallization from ethanol 0.08 g (56%) of **9** identical in all respects with **9** prepared from **7**.

Methyl 2,3-*O*-Isopropylidene-4-(2-aminothiazol-4-yl)-β-D-*ribo*-tetrafuranoside (26). A mixture of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose[11] (**24**, 0.80 g, 3.30 mmol) and thiourea (**25**, 0.76 g, 10 mmol) in ethanol (20 ml) was refluxed for 20 h, and then the solvent was evaporated. The residue was dissolved in chloroform and the unreacted thiourea removed by filtration. The filtrate was concentrated almost to dryness and the remaining residue was applied on preparative TLC plates which were developed with a mixture of 4:1 ethyl acetate–chloroform. Elution of the fastest moving band afforded 0.03 g of the starting diazo derivative **24**. The next band gave 0.28 g (32%) of **26** as a yellow syrup which was treated with a saturated ethanolic solution of picric acid. The picrate obtained was recrystallized from ethanol to yield 0.31 g of pure material with mp 167 °C.

Anal. Calcd for $C_{17}H_{19}N_5O_{11}S$: C, 40.71; H, 3.79; N, 13.97. Found: C, 40.89; H, 3.57; N, 13.62.

The free nucleoside **26** was obtained by passing the picrate through a short column of neutral alumina using ethyl acetate as eluent. This procedure afforded 0.14 g (16% total yield) of **26** as an analytically pure syrup: $[\alpha]^{25}D$ −31° (*c* 0.6, chloroform); NMR ($CDCl_3$) τ 3.65 (d, H-5 thiazole ring, $J_{5,4'} \simeq 1$ Hz), 4.93 (t, H-4′, $J_{4',3'} \simeq J_{4',5} = 1$ Hz), 4.94 (s, H-1′), 5.04 (dd, H-3′, $J_{3',2'}$ = 6, $J_{3',4'}$ = 1 Hz), 5.41 (d, H-2′, $J_{2',3'}$ = 6 Hz), 6.65 (s, OCH_3), 8.50 and 8.70 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.45; H, 6.08; N, 9.95.

Registry No.—**1**, 57944-10-2; **2**, 57944-12-4; **3**, 78-95-5; **4a**, 57944-11-3; **4b**, 60084-02-8; **5a**, 60084-03-9; **5b**, 60084-04-0; **6**, 34034-87-2; **7**, 60084-05-1; **8**, 60084-06-2; **9**, 60084-07-3; **10**, 60084-08-4; **11**, 70-23-5; **12**, 60084-09-5; **13**, 60084-10-8; **14**, 60084-11-9; **15**, 60084-12-0; **16**, 60084-13-1; **17**, 60084-14-2; **18**, 60084-15-3; **19**, 23316-67-8; **20**, 26882-26-8; **21**, 60084-16-4; **22**, 60084-17-5; **23**, 60084-18-6; **24**, 54622-96-7; **25**, 62-56-6; **26**, 60084-19-7; **26** picrate, 60084-20-0.

References and Notes

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(6) The chosen nomenclature for **1**, in our opinion, is more understandable and in better agreement with that of the rest of the compounds described in this paper than the alternative 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonthioamide.
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