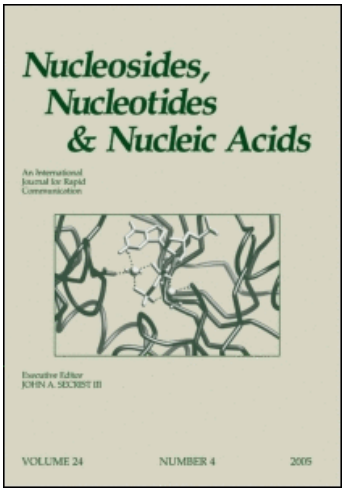

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Precursors for the Synthesis of Substituted 1,3,4-Thiadiazolf, C-Nucleosides, Analogues of Tiazofurin and Related Compounds

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PRECURSORS FOR THE SYNTHESIS OF SUBSTITUTED 1,3,4-THIADIAZOLE C-NUCLEOSIDES, ANALOGUES OF TIAZOFURIN AND RELATED COMPOUNDS

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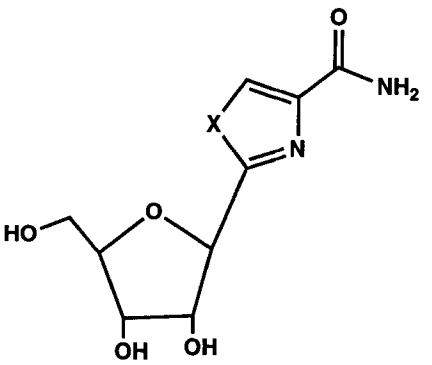
Abstract: The synthesis of 2-substituted 1,3,4-thiadiazole C-glycosides is described by building a heterocyclic system at the aldehyde end of a series of sugar derivatives. Acid catalyzed dehydration of the polyhydroxylic chain resulted in C-nucleoside, an analogue of tiazofurin.

Tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide, **1a**) and selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide, **1b**) are effective preclinical antitumor agents both *in vitro* and *in vivo*[1-3]. However, oxazofurin (2-β-D-ribofuranosyloxazole-4-carboxamide, **1c**), a structural analogue of tiazofurin, was recently reported to be inactive against either DNA or RNA viruses[4]. Antitumor activities of tiazofurin and selenazofurin are related to inhibition of guanine nucleotide synthesis due to the production of the dinucleotide anabolites TAD and SAD which act as an inhibitors of IMPD[5-8].

In our present work, we focused on another ring system of this family, namely 1,3,4-thiadiazole which possesses a good deal of structural resemblance such as ring size, charge distribution and ring basicity[9] to the thiazole moeity of the tiazofurin. The C-nucleosides derived from this ring system are expected to show the similar conformations about C-glycosidic bond as tiazofurin, in which the thiadiazole sulphur is cis to the furanose ether oxygen[10]. The close S-O contact has been reported[11,12] to be attributed to an electrostatic attraction between the positively charged sulphur and the lone-pair of electrons on the furanose oxygen which constrains rotation about the C-glycosyl bond, a feature necessary for the biological activity[4].



1a X = S, Tiazofurin
1b X = Se, Selenazofurin
1c X = O, Oxazofurin

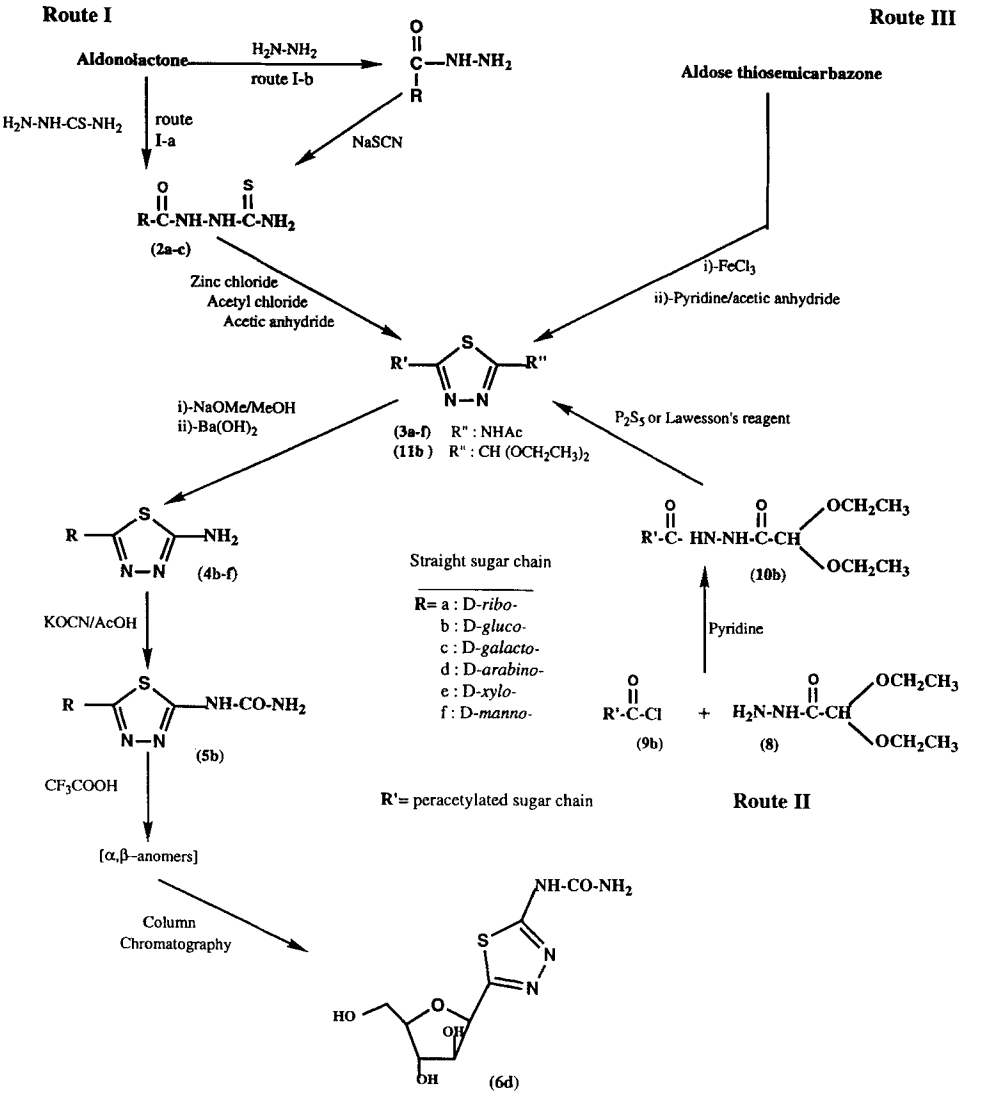
Chemistry

One of the methods of preparation of C-nucleoside, involve dehydration of the polyhydroxyl chains joined to aromatic heterocycles[13]. In our present work, synthesis of a series of 2-substituted (amino, acetamido, ureido and diethoxymethinyl)-1,3,4-thiadiazole C-glycosides was achieved by constructing a heterocyclic system at the aldehyde end of the straight sugar chain. Acid catalyzed dehydration of polyhydroxyalkyl-heterocycles between C-1' and C-4' produced the corresponding 2-substituted-1,3,4-thiadiazole C-nucleosides. The choice of such a synthetic method was based on the following reasoning; (i) ease availability of the starting material (sugars), (ii) configurational variability of the sugar components and (iii) generalization and verification of viability of some synthetic routes.

from acyl thiosemicarbazides:

Route I: Aldonic acid thiosemicarbazides **[2a-c]** were prepared by the reaction of aldonic acid lactone with thiosemicarbazide and also by the reaction of aldonic acid hydrazide with sodium thiocyanate as routes I-a and I-b respectively . Cyclization of acyl-thiosemicarbazides to the acetylated 1,3,4-thiadiazoles derivatives **[3a-c]** was carried under dehydrating and acetylating condition using zinc chloride, acetic anhydride and acetyl chloride. Sequential O- and N-deacetylation offered corresponding 2-amino-5-(D-polyhydroxyalkyl)-1,3,4-thiadiazoles **[4b-c]**.

Route II: The first step involved the preparation of a suitable substituted asymmetric dihydrazides by the reaction of hydrazine hydrate with ethyl diethoxyacetate to yielded 2,2-diethoxyacetic hydrazide **[8]** which upon reaction with penta-O-acetyl-D-gluconyl acid chloride **[9b]** produced an acylsemicarbazide intermediate **[10b].** Cyclization by phosphorous pentasulphide or (Lawesson's reagent) with elimination of hydrogen sulphide resulted in 2-(diethoxymethinyl)-5-*gluco*-pentaacetoxypentyl)-1,3,4-thiadiazole **[11b]**. Derivatization of the diethoxymethinyl group to other functions such as oxime, nitrile and amide is under investigation.



from sugar thiosemicarbazones:

Route III: Utilized the aldose thiosemicarbazones of D-*arabino*, -*xylo* and -*manno*- (cyclic or acyclic)[14] which were oxidatively cyclized to the corresponding 2-amino-1,3,4-thiadiazole derivatives by means of ferric chlodide[15]. In the case of those sugars presenting difficulties during the isolation of the crystalline product from the muddy mixture, the dried syrup was subjected to conventional acetylating and deacetylating procedure which yielded 2-amino derivatives of 1,3,4-thiadiazole C-glycosides **[4d-f]** respectively.

Trifluoroacetic acid -catalysed dehydration of **[5b]** at room temperture yields an α,β-mixture of anomers, which were separated by silica gel column chromatographgy. Compounds **[6d]**, consumed 1 mol. equiv. of sodium metaperiodate in accord with the proposed furanoid structure.

Experimental

General Methods: Melting points were determined on Gallenkamp apparatus. UV was performed in methanolic solution of the compounds using a Perkin Elmer spectrometer. The ^{1}H-NMR spectra were obtained on a Perkin Elmer-90, Burker WM-250 and WM-400. Spin decoupling and COSY techniques were used where required. ^{13}C-NMR spectra were recorded on the Bruker WM-250. Off resonance and INDEPT techniques were used to find the nature of the carbon signals.

preparation of aldonic acid thiosemicarbazides.

Route I-a: A mixture of aldonic acid lactone (0.1 moles) and thiosemicarbazide (0.1moles) in dry ethanol (200 ml) was heated under reflux for 3 days. The mixture concentrated and the solid was recrystallized in ethanol to give compounds **[2a-c].**

Route I-b: The aldonic acid lactone (0.1 moles) was treated with an excess of hydrazine hydrate (90%, 0.2 moles) in ethanol (200 ml) at room temperature. The product was concentrated and the excess of hydrazine was removed by repeated azeotropic distillations with water at 15 Torr and 90°C. The resulting syrup was reacted with sodium thiocyanate (0.1 moles) and 10% aqueous HCl at 20°C for 6h and then evaporated. The solid was recrystallized from ethanol to give the compounds **[2a-c]**, identical to those obtained by the previous method.

D-*ribonic* acid thiosemicarbazide [2a]. Yield: 80%, M.P. 162°C. Anal. Calcd. for $C_6H_{13}N_3O_5S$: C, 30.11; H, 5.47; N, 17.56; S, 13.40. Found: C, 30.48; H, 5.44; N, 17.12; S, 13.47.

D-*gluconic* acid thiosemicarbazide [2b]. Yield: 88%, M.P. 158°C (Lit, 159°C)[16] Anal. Calcd. for $C_7H_{15}N_3O_6S$: C, 31.22; H, 5.61; N, 15.60; S, 11.91. Found: C, 31.51; H, 6.74; N, 15.27; S, 11.77.

D-*galactonic* acid thiosemicarbazide [2c]. Yield 84%, M.P. 172°C. Anal. Calcd. for $C_7H_{15}N_3O_6S$: C, 31.22; H, 5.61; N, 15.60; S, 11.91. Found: C, 31.13; H, 5.58; N, 15.16; S, 11.36.

Cyclization of aldonic acid thiosemicarbazides:

Compounds 2a-c reacted with a cold mixture of fused zinc chloride (0.1 moles), acetyl chloride (0.4 moles) and acetic anhydride (300 ml) at 0°C for 2h. The product was extracted with chlorofrom and then concentrated to give an oil which solidified on trituration with a small amount of ethanol. Recrystallization from ethanol-chloroform yielded the 2-acetamido-5-(D-polyhydroxyalkyl)-1,3,4-thiadiazoles **[3a-c]** in practical yields.

Sequential O-and N-deacetylation:

Treatment of the above N, O per-acetylated compounds with catalytic amount of sodium methoxide in dry methanol yielded the 2-acetamido-5-(D-polyhydroxyalkyl)-1,3,4-

thiadiazoles which were recrystallized from methanol. Further reaction of these compounds with saturated aqueous barium hydroxide at 100°C for 24h offered 2-amino-5-(polyhydroxyalkyl)-1,3,4-thiadiazoles derivatives which was recrystallized from methanol-water to give **[4b-c]** respectively.

2-acetamido-5-(D-*ribo*-tetraacetoxybutyl)-1,3,4-thiadiazole [3a]. Yield: 83%, M.P. 122°C. Anal. Calcd. for $C_{16}H_{21}N_3O_9S$: C, 44.54; H, 4.90; N, 9.74; S, 7.43. Found: C, 44.70; H, 4.81; N, 9.89; S, 7.21.

2-acetamido-5-(D-*gluco*-pentaacetoxypentyl)-1,3,4-thiadiazole [3b]. Yield: 95%, M.P. 134°C. Anal. Calcd. for $C_{19}H_{25}N_3O_{11}S$: C, 45.32; H, 5.00; N, 8.34; S, 6.37. Found: C, 45.39; H, 5.02; N, 8.51; S, 6.49.

2-acetamido-5-(D-*galacto*-pentaacetoxypentyl)-1,3,4-thiadiazole [3c]. Yield: 88%, M.P. 117°C. Anal. Calcd. for $C_{19}H_{25}N_3O_{11}S$: C, 45.32; H, 5.00; N, 8.34; S, 6.37. Found: C, 45.20; H, 5.16; N, 8.43; S, 6.52.

2-amino-5-(D-*gluco*-pentahydroxypentyl)-1,3,4-thiadiazole [4b]. Yield: 88%, M.P. 185°C. Anal. Calcd. for $C_7H_{13}N_3O_5S$: C, 33.46; H, 5.21; N, 16.72; S, 12.76. Found: C, 33.59; H, 5.34; N, 16.90; S, 12.88.

2-amino-5-(D-*galacto*-pentahydroxypentyl)-1,3,4-thiadiazole [4c]. Yield: 85%, M.P. 195°C. Anal. Calcd. for $C_7H_{13}N_3O_5S$: C, 33.46; H, 5.21; N, 16.72; S, 12.76. Found: C, 33.49; H, 5.42; N, 16.60; S, 12.84.

Route III: Thiosemicarbazones of the three monosaccharides, D-*arabinose*, D-*xylose* and D-*mannose* were subjected to cyclooxidation reaction with 2M solution of ferric chloride and concentrated. The crude sample was then acetylated with pyridine and acetic anhydride at 20°C. Conventional work up of the reaction mixture yielded **[3d-f]** which after sequential O- and N-deacetylation (described above), offered corresponding 2-amino derivatives **[4d-f]**.

2-acetamido-5-(D-*arabino*-tetraacetoxybutyl)-1,3,4-thiadiazole [3d]. Yield: 86%, M.P. 112°C. Anal. Calcd. for $C_{16}H_{21}N_3O_9S$: C, 44.54; H, 4.90; N, 9.74; S, 7.43. Found: C, 44.59; H, 5.10; N, 9.91; S, 7.62.

2-acetamido-5-(D-*xylo*-tetraacetoxybutyl)-1,3,4-thiadiazole [3e]. Yield: 87%, M.P. 110°C. Anal. Calcd. for $C_{16}H_{21}N_3O_9S$: C, 44.54; H, 4.90; N, 9.74; S, 7.43. Found: C, 44.61; H, 4.93; N, 9.64; S, 7.57.

2-acetamido-5-(D-*manno*-pentaacetoxypentyl)-1,3,4-thiadiazole [3f]. Yield: 75%, M.P. 104°C. Anal. Calcd. for $C_{19}H_{25}N_3O_{11}S$: C, 45.32; H, 5.00; N, 8.34; S, 6.37. Found: C, 45.37; H, 5.30; N, 8.63; S, 6.53.

2-amino-5-(D-*arabino*-tetrahydroxybutyl)-1,3,4-thiadiazole [4d]. Yield: 82%, M.P. 203°C. Anal. Calcd. for $C_6H_{11}N_3O_4S$: C, 32.57; H, 5.01; N, 18.99; S, 14.49. Found: C, 32.59; H, 5.19; N, 18.75; S, 14.78.

2-amino-5-(D-*xylo*-tetrahydroxybutyl)-1,3,4-thiadiazole [4e]. Yield: 80%, M.P. 175°C. Anal. Calcd. for $C_6H_{11}N_3O_4S$: C, 32.57; H, 5.01; N, 18.99; S, 14.49. Found: C, 32.65; H, 5.28; N, 18.91; S, 14.64.

2-amino-5-(D-*manno*-pentahydroxypentyl)-1,3,4-thiadiazole [4f]. Yield: 75%, M.P. 188°C. Anal. Calcd. for $C_7H_{13}N_3O_5S$: C, 33.46; H, 5.21; N, 16.72; S, 12.76. Found: C, 33.66; H, 5.45; N, 16.69; S, 12.51.

TABLE 1. Characterization Data for Compounds 2a-c, 3a-f, 4b-f

Compound	Carbohydrate moiety	UV[a] λ_{max}	^{1}H-NMR[b,c,d] δ	^{13}C-NMR[e] δ
			H-2'	C-2'
2a	D-*ribo*-	243	4.15 d, $J_{2',3'}$ 2.80	73.47
2b	D-*gluco*-	245	4.20 d, $J_{2',3'}$ 4.60	73.70
2c	D-*galacto*-	245	4.16 d, $J_{2',3'}$ 1.70	71.59
			H-1'	C-1'
3a	D-*ribo*-	254	6.33 d, $J_{1',2'}$ 3.60	69.58
3b	D-*gluco*-	256	6.33 d, $J_{1',2'}$ 7.00	70.20
3c	D-*galacto*-	254	6.24 d, $J_{1',2'}$ 2.50	69.20
3d	D-*arabino*-	254	6.37 d, $J_{1',2'}$ 2.50	70.29
3e	D-*xylo*-	254	6.35 d, $J_{1',2'}$ 6.40	70.71
3f	D-*manno*-	254	6.15 d, $J_{1',2'}$ 7.80	69.40
4b	D-*gluco*-	257	4.81 d, $J_{1',2'}$ 6.50	72.01
4c	D-*galacto*-	258	5.04 d, $J_{1',2'}$ 1.20	72.35
4d	D-*arabino*-	257	5.00 d, $J_{1',2'}$ 4.00	73.54
4e	D-*xylo*-	258	4.81 d, $J_{1',2'}$ 5.10	72.90
4f	D-*manno*-	258	4.65 d, $J_{1',2'}$ 8.70	72.06

a. Maximum wave length, λmax in nm. b. Chemical shifts, δ: are relative to[$(CH_3)_4Si$ (0 ppm)].
c. Coupling constants, *J* value in Hertz. d. Solvent used for compounds: 2a-c and 4b-f, d.m.s.o.-d_6; for 3a-f, $CDCl_3$. e. Assignments based on Off Resonance and INDEPT techniques.

2-ureido-5-(D-*gluco*-tetrahydroxybutyl)-1,3,4-thiadiazole [5b]. A solution of compound [4b], (1g, 3.9 mmoles) in acetic acid-water (20%, 25 ml) and potassium cyanate (0.214g, 3.9 mmoles) stirred at 5°C for 2h and then at 50-60°C for another 2h. Concentration of the reaction mixture and crystallization of the crude from ethanol-water (50%) yielded 0.7g (60%) of a white crystalline compound, M.P. 165°C. ^{1}H-NMR data (d.m.s.o.-d_6): δ 3.25–3.50 (m, skeletal sugar protons, H-5', H-5'', H-4', H-3'), 3.75 (dd, 1H, H-2', $J_{2',1'}$=6.70Hz, $J_{2',3'}$=1.60Hz), 4.81 (d, 1H, H-1', $J_{1',2'}$=6.50Hz), 4.38-5.76 (5d, 5H, five OH protons), 7.02 (s, 2H, NH_2), 12.40 (bs, 1H, NH). ^{13}C-NMR data (d.m.s.o.-d_6): δ 63.31–72.01 (C-5', C-4', C-3', C-2', C-1'), 163.65 (C-5), 168.63 (C-2), 173.82 (NH-CO-NH_2). Anal. Calcd. for $C_8H_{14}N_4O_6S$: C, 32.65; H, 4.76; N, 19.04; S, 10.88. Found: C, 33.02; H, 4.83; N, 19.24; S, 10.55 .

2,2-diethoxyacetyl hydrazide [8]. To a solution of hydrazine hydrate (10 ml, 0.2 moles) in ethanol (30 ml), ethyl diethoxyacetate (35 ml, 0.2 moles) was added dropwise and heated under reflux for 3h and then concentrated. The excess of hydrazine was removed by repeated azeotropic distillations with water at 15 Torr and 90°C to give an oil which solidified on cooling. M.P. 45°C, ^{1}H-NMR data ($CDCl_3$): δ 1.22 (t, 6H, $2CH_3$), 3.62 (2 overlaping q, 4H, $2CH_2$) 4.87 (s, 1H, CH). ^{13}C- NMR data (CD_3OD): δ 15.39 ($-CH_3$), 63.31 ($-CH_2$-), 99.29 {CO-CH $(OEt)_2$}, 168.86 (NH-CO-). Anal. Calcd. for $C_6H_{14}N_2O_3$: C, 44.42; H, 8.69; N, 17.27 S. Found: C, 44.68; H, 8.34; N, 17.22.

Penta-O-acetyl-D-gluconyl chloride [9b]. this compound was prepared with reference to the procedure published in the literature[17]. M.P. 67°C.

N-(2,2-diethoxyacetyl)-N$_1$-(penta-O-acetyl-D-gluconyl)-hydrazide [10b] To a mixture of compound [8], (3.72 g, 23 mmoles) in dry pyridine (50 ml), a solution of compound [9b], (10 g, 23 mmoles) in dry ether was added drop by drop. The mixture was heated under reflux for 3h and filtered. The filterate was poured into ice water (300 ml) and extracted with chloroform (4 X 50 ml). The organic extract was washed with water (3 X 15 ml), dried, and then concentrated. On trituration with ether, the residue yielded 30g (90%) of pure compound. M.P. 50-51°C. ^{1}H-NMR data ($CDCl_3$) δ: 1.25 (t, 6H, $2CH_3$), 2.02-2.19 (5s, 15H, CO-CH_3), 3.72 (m, 4H, $2CH_2$), 4.13 (dd, 1H, H-6', $J_{6',6"}$= 12.40Hz, $J_{6',5'}$=5.50Hz), 4.25 (dd,1H, H-6", $J_{6",6'}$=12.30, $J_{6",5'}$=3.70Hz), 4.96 {s, 1H, CH$(OEt)_2$}, 5.05 (m, 1H, H-5'), 5.41 (d, 1H, H-2', $J_{2',3'}$=5.10Hz), 5.50 (dd, 1H, H-4', $J_{4',5'}$=6.60Hz, $J_{4',3'}$=4.70Hz), 5.68 (dd, 1H, H-3', $J_{3',4'}$= 4.80Hz, $J_{3',2'}$=4.90Hz), 8.92 and 9.27 (2bs, 2H, two amide protons). ^{13}C-NMR data ($CDCl_3$): δ 15.04 ($-CH_3$), 20.49-20.47 (CO-CH_3), 61.57 (C-6'), 62.58 ($-CH_2$), 68.72-70.76 (C-5', C-4', C-3', C-2'), 97.66 {CO-CH$(OEt)_2$}, 163.78 and 164.79 (two amide carbon), 169.58-170.67 (CO-CH_3). Anal. Calcd. for $C_{22}H_{34}N_2O_{14}$: C, 47.99; H, 6.22; N, 5.08. Found: C, 47.74; H, 5.89; N, 5.36.

2-(diethoxymethinyl)-5-(D-*gluco*-pentaacetoxypentyl)-1,3,4-thiadiazole [11b]. A mixture of compound [10b], (6.5 g, 11.8 mmoles) and phosphorus pentasulphide (26 g, 0.1 moles) in dry pyridine (30 ml) were heated under reflux for 6h and evaporated. The residue was dissolved in water and extracted with chloroform to yielded 1.8 g (27%) of an impure syrupy material. Purification of the crude by silica gel column chromatography using toluene/chloroform as eluents resulted in separation of 1.0 g (15.5%) of the desired compound. ^{1}H-NMR data ($CDCl_3$) δ: 1.25 (t, 6H, $2CH_3$), 2.05-2.10 (5s, 15H, CO-CH_3), 3.72 (m, 4H, $2CH_2$), 4.06 (dd, 1H, H-5', $J_{5',5"}$= 12.20Hz, $J_{5',4'}$=5.40Hz), 4.20 (dd, 1H, H-5", $J_{5",5'}$=12.00, $J_{5",4'}$=4.7Hz), 5.12 (m, 1H, H-4'), 5.39 (dd, 1H, H-3', $J_{3',4'}$=7.70Hz, $J_{3',2'}$=3.70Hz), 5.78 {s, 1H, CH$(OEt)_2$}, 5.89 (dd, 1H, H-2', $J_{2',3'}$=3.70Hz, $J_{2',1'}$=6.80Hz), 6.37 (d, 1H, H-1', J1',2'= 6.80Hz). ^{13}C-NMR data ($CDCl_3$): δ 15.06($-CH_3$), 20.54-20.87 (CO-CH_3), 61.57 (C-5'), 62.96 ($-CH_2$), 68.70-70.34 (C-4', C-3', C-2', C-1'), 98.72 {CO-CH$(OEt)_2$}, 165.91 (C-5), 169.64 (C-2) 169.72-171.28 (CO-CH_3). Anal. Calcd. for $C_{22}H_{32}N_2O_{12}S$: C, 48.16; H, 5.88; N, 5.10; S, 5.48. Found: C, 48.28; H, 6.04; N, 5.16; S, 5.62.

2-ureido-5-(β-D-*arabino*furanosyl)-1,3,4-thiadiazole [6d]. A solution of compound [5b], (500 mg, 1.7 mmoles) in water (25 ml) was treated with trifluoroacetic

acid (0.15 ml) at 0°C for 30 minutes. After this period, analysis by thin layer chromatography revealed the absence of [5b], and presence of a mixture corresponding to α,β anomers. The mixture was neutralized with Amberlite IR-45 (HO^-) resin and concentrated. Separation of the resulting syrup by preparative t.l.c. (R_F 0.66) offered β-anomer **[6d]** in low (15%) yield which reduced 1 mole equivalent of sodium metaperiodate, in accord with a furanoid structure. M.P. 165°C. ^{1}H-NMR data (d.m.s.o.-d_6): δ 3.3–4.1 (m, skeletal sugar protons, H-5', H-5", H-4', H-3', H-2'), 5.42 (d, 1H, H-1', $J_{1',2'}$=2.8Hz), 7.1 (s, 2H, NH_2), 12.35 (bs, 1H, NH). ^{13}C- NMR data (d.m.s.o.-d_6): δ 62.29 (C-5'), 77.52-71.31(C-4', C-3', C-2'), 90.70 (C-1'), 162.18 (C-5), 168.03 (C-2), 174.34 (NH-CO-NH_2). Anal. Calcd. for $C_8H_{12}N_4O_5S$: C, 34.78; H, 4.34; N, 20.28; S, 11.94. Found: C, 34.04; H, 4.83; N, 20.10; S, 12.05.

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