C-NUCLEOSIDES. 17.[1] A SYNTHESIS OF 2-SUBSTITUTED 7-(β-D-RIBOFURANOSYL)-PYRROLO[2,1-f]-1,2,4-TRIAZINES. A NEW TYPE OF "PURINE LIKE" C-NUCLEOSIDE

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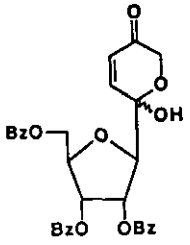
Abstract ------ A versatile intermediate pyranulose glycoside (1) for C-nucleoside synthesis was treated with semicarbazides (3a) and (3b) to give the corresponding semicarbazones (4a) and (4b) in good yield. Treatment of 4a with concentrated hydrochloric acid in dioxane yielded 1-ureido-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (5), which on heating in acetic acid gave 2-oxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazine (6a). Compound (4b) was treated by the same procedure to give 2-thioxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazine (7a) and 3-hydroxymethyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyridazine (8). The removal of the sugar protecting groups in 6a and 7a afforded the deprotected C-nucleosides (6b) and (7b).

Recent reports[2a,b] from our laboratory have described the synthesis of two new type of intermediates (1 and 2) useful for the preparation of a number of C-nucleosides. Pyranulose glycoside (1) has been utilized for the synthesis of pyrrole,[2a] quinoxaline,[2a] lumazine,[2c] pyridazine,[2d] and imidazole[2e] C-nucleosides while furanone glycoside (2) was transformed to pyrrolinone,[2b] pyridazinone,[2b] oxazinone,[2b] and benzodiazepinone[1] C-nucleosides. We wish to report here the utilization of 1 for the synthesis of 2-oxo- and 2-thioxo-7-(β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazines (6b) and (7b), new types of "purine like" C-



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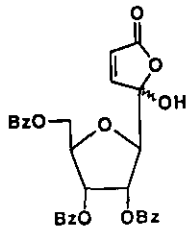

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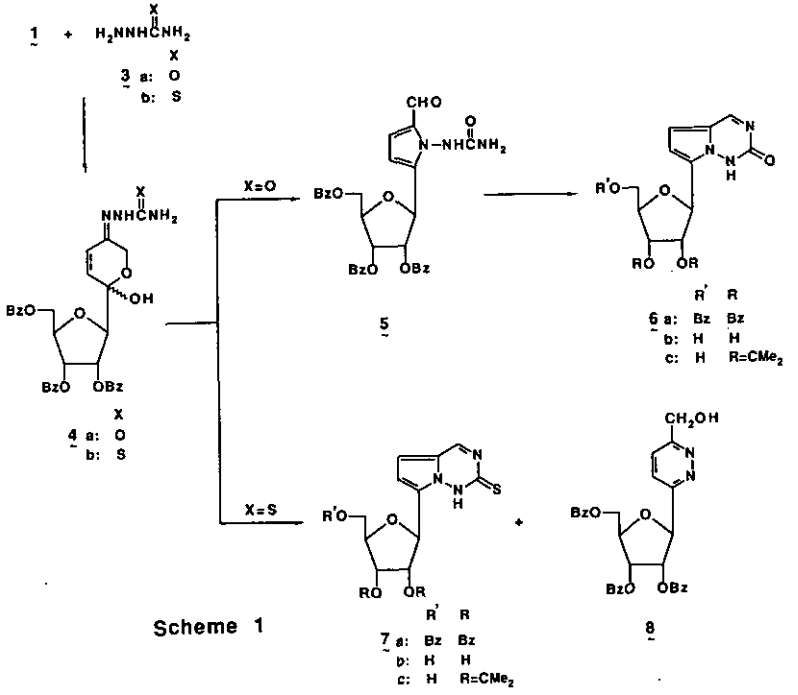
nucleoside. A number of reports[3] have dealt with the preparation of "purine like" C-nucleosides. A search of the literature revealed that the only representative of the synthesis of the pyrrolo[2,1-f]-1,2,4-triazine ring system was reported by O. Migliara, et al.[4] which resulted from the ring closure of 1-ureido-2-ethoxycarbonylpyrrole.

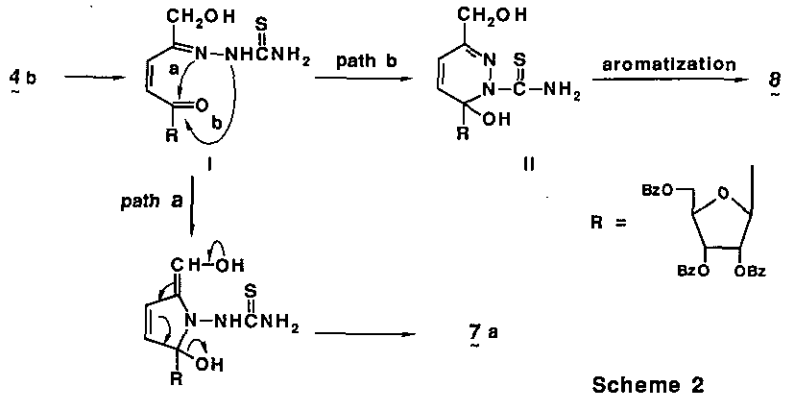
Treatment of pyranulose glycoside (**1**) with semicarbazides (**3a**) and (**3b**) in acetic acid at room temperature afforded the corresponding semicarbazones (**4a**) and (**4b**) in good yields after purification by silica gel column chromatography. Semicarbazones (**4a**) and (**4b**) are an inseparable mixture of diastereoisomers (differing in configuration only at C-6). The semicarbazone (**4a**) in dioxane was treated with hydrochloric acid solution at room temperature to afford 1-ureido-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (**5**) in 24% yield. Compound (**5**) in acetic acid was heated at 100 °C for 10 h, giving a 65% yield of 2-oxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazine (**6a**). Structure assignment of **6a** was supported by ^{1}H nmr spectrum, which exhibited the signals of the pyrrole moiety (H-5 and -6) at δ 6.89 and 6.93 (J=5.7 Hz) and the H-4 at δ 8.60. In the mass spectrum, the molecular ion peak was found at m/z 579 (M^+). However, **4b** was treated by the same procedure to give 17% yield of 2-thioxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazine (**7a**) without isolation of pyrrole-2-carboxaldehyde intermediate, and 23% yield of 3-hydroxymethyl-6-(2,3,5-tri-



Scheme 1

O-benzoyl-β-D-ribofuranosyl)pyridazine (8) which was found to be identical with the product previously prepared by the reported procedure.[2d]

Formation of 6a and 7a was assumed to proceed by the same mechanism (path a) for the formation of pyrroloquinoxaline described in a previous paper.[2a] Formation of 8 from 4b most probably proceeds via preferential reaction of carbonyl group in the intermediate (I) with the more basic amino group in I (path b) to give the cyclized intermediate (II), which is further converted to 8 by aromatization. The outline of the reaction mechanism is shown in Scheme 2. The removal of the sugar protecting groups in compounds (6a) and (7a) was readily accomplished with methanolic sodium hydroxide to afford the compounds (6b) and (7b). The assignments of anomeric configurations of compounds (6b) and (7b) were made on the basis of the difference in the chemical shifts of the two methyl signals of the corresponding 2,3-O-isopropylidene derivatives (6c) and (7c). The ^{1}H nmr chemical shift differential value ($\Delta\delta$) of the methyl groups in the isopropylidene derivatives is indicative of β stereochemistry in accordance with the Imbach's rule (<0.15 and >0.15 ppm for the α and β anomers, respectively) (see experimental). These data showed that the β-ribofuranoside configuration had been preserved during the reaction sequence.



Scheme 2

EXPERIMENTAL

Mass spectra were taken on a Hitachi M-80 instrument by direct insertion at 70 eV; fast-atom bombardment (fab) mass spectra were run on a JMS-HX 110. ^{1}H- and ^{13}C-Nmr spectra were measured with a JNM-GX-270 and a GX-400 (JEOL) spectrometers, with tetramethylsilane as internal standard. Analytical tlc was performed on glass plates coated with a 0.5-mm layer of silica gel GF_{254} (Merck). The compound were detected by uv light (254 nm).

6-Hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyran-3(2H,6H)-semicarbazone (4a). To a solution of 1 (68.1 mg, 0.12 mmol) in acetic acid (3 ml) at room temperature was added 13.8 mg

(0.18 mmol) of semicarbazide. The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was extracted with chloroform (3X10 ml). The extracts were combined, washed with water and dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was chromatographed on a column of silica gel with chloroform-methanol (9:1) as eluent, to give **4a** (61.2 mg, 81.5%) as a colorless syrup; ^{1}H nmr ($CDCl_3$) δ 4.37 (1 H, apparent d, 1'-H), 4.46-4.93 (5 H, m, 4'-, 5'- and 2-H), 5.62 (1/2 H, t, J=6.4 Hz, 3'-H), 5.73-5.79 (1 H, m, 2'- and 3'-H), 5.90 (1/2 H, dd, J=3.7 and 6.1 Hz, 2'-H), 6.18-6.28 (3/2 H, m, 4- and 5-H), 6.37 (1/2 H, d, J=10.4 Hz, 5-H), 7.30-8.09 (15 H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 57.81, 63.43 (C-5' and -2), 72.05, 73.15, 79.23, 87.11 (C-1', -2', -3' and -4'), 92.68 (C-6), 127.49-133.67 (Ar-C, C-4 and -5), 142.69 (C-3), 158.11, 165.29, 165.36, 166.19, 166.63 (C=O); ms (fab, nitrobenzyl alcohol as matrix) 616 (Found: MH$^+$ 616.1937. $C_{32}H_{30}N_3O_{10}$ requires 616.1931).

6-Hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyran-3(2H,6H)-thiosemicarbazone (4b). This compound was prepared from **1**, and thiosemicarbazide as described above for **4a**: yellow oil, 90.1%; ^{1}H nmr ($CDCl_3$) δ 4.25-4.96 (6 H, m, 1'-, 4'-, 5'- and 2-H), 5.62 (1 H, m, 3'-H), 5.82 (1 H, m, 2'-H), 6.21-6.58 (2 H, m, 4- and 5-H), 7.31-8.13 (15 H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 62.22, 63.46 (C-5' and -2), 71.91, 73.00, 79.36, 86.99 (C-1', -2', -3' and -4'), 92.77 (C-6), 126.71-136.64 (Ar-C, C-4 and -5), 143.95 (C-3), 165.33, 165.40, 166.06, 166.53, 166.66 (C=O), 179.27 (C=S); ms (fab, nitrobenzyl alcohol as matrix) 632 (Found: MH$^+$ 632.1731. $C_{32}H_{30}N_3O_9S$ requires 632.1702).

1-Ureido-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (5). A solution of **4a** (108 mg, 0.18 mmol) in dioxane (2 ml) containing 1 drop of concentrated hydrochloric acid was allowed to stir at room temperature for 4 h. Water was added, and the mixture was neutralized with saturated sodium hydrogen carbonate solution and then extracted with chloroform (3X10 ml). The extracts were combined, washed with water and dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was chromatographed on a column of silica gel with chloroform-methanol (97:3) as eluent, to give **5** (23 mg, 23.6%); ^{1}H nmr ($CDCl_3$) δ 4.55 (1 H, dd, J=4.0 and 12.1 Hz, 5'-Ha), 4.68 (1 H, m, 4'-H), 4.83 (1 H, dd, J=3.4 and 12.1 Hz, 5'-Hb), 5.40 (1 H, d, J=5.7 Hz, 1'-H), 5.80 (1 H, t, J=5.7 Hz, 3'-H), 5.95 (1 H, t, J=5.7 Hz, 2'-H), 6.31 (1 H, d, J=4.4 Hz, H-3), , 6.81 (1 H, d, J=4.4 Hz, 4-H), 7.34-8.05 (15 H, m, ArH), 9.52 (1 H, s, CHO); ^{13}C nmr ($CDCl_3$) δ 63.63 (C-5'), 72.26, 74.34, 74.87, 80.08 (C-1', -2', -3' and -4'), 107.61, (C-4), 121.17 (C-3), 128.42-133.53 (Ar-C and C-5), 138.95 (C-2), 165.32, 165.43, 166.25 (C=O), 179.27 (CHO); ms (fab, nitrobenzyl alcohol as matrix) 598 (Found: MH$^+$ 598.1818. $C_{32}H_{28}N_3O_9$ requires 598.1826).

2-Oxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-f]-1,2,4-triazine (6a). A solution of

5 (60.2 mg, 0.10 mmol) in acetic acid (3 ml) was heated at 100°C for 10 h. Acetic acid was removed under reduced pressure. The residual syrup was purified by preparative tlc with chloroform-methanol (96:4) as eluent, to give **6a** (38 mg, 65.1%) as a yellow foam; ^{1}H nmr ($CDCl_3$, D_2O) δ 4.66 (1 H, dd, J=4.4 and 11.8 Hz, 5'-Ha), 4.75 (1 H, apparent q, 4'-H), 4.84 (1 H, dd, J=3.4 and 11.8 Hz, 5'-Hb), 5.92 (1 H, d, J=5.7 Hz, 1'-H), 6.00 (1 H, t, J=5.4 Hz, 3'-H), 6.07 (1 H, t, J=5.7 Hz, 2'-H), 6.89 (1 H, d, J=5.0 Hz, 5-H), 6.93 (1 H, d, J=5.0 Hz, 6-H), 7.33-8.10 (15 H, m, ArH), 8.60 (1 H, s, 4-H); ^{13}C nmr ($CDCl_3$) δ 64.03 (C-5'), 72.56, 74.23, 74.29, 80.18 (C-1', -2', -3' and -4'), 109.80, 115.24 (C-5 and -6), 121.22, 128.23 (C-4a and -7), 128.35-133.44 (Ar-C), 146.12 (C-4), 156.38 (C-2), 165.26, 165.45, 166.19 (C=O); ms (fab, nitrobenzyl alcohol as matrix) 580 (Found: MH^+ 580.1687. $C_{32}H_{26}N_3O_8$ requires 580.1726).

2-Thioxo-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,1-f]-1,2,4-triazine (7a) and 3-Hydroxymethyl-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyridazine (8). Compounds (7a) and (**8**) were prepared from **4b** as described above for 5. **Compound 7a:** yellow foam, 17.4%, Rf 0.62 (hexane-ethyl acetate, 4:5); ^{1}H nmr ($CDCl_3$) δ 4.57 (1 H, dd, J=3.7 and 11.8 Hz, 5'-Ha), 4.64 (1 H, m, 4'-H), 4.77 (1 H, dd, J=3.7 and 11.8 Hz, 5'-Hb), 5.74 (1 H, d, J=6.1 Hz, 1'-H), 5.88 (1 H, t, J=5.4 Hz, 3'-H), 6.02 (1 H, t, J=5.4 Hz, 2'-H), 6.73, 6.92 (1 H each, each d, J=4.7 Hz, 5- and 6-H), 7.29-8.07 (15 H, m, ArH), 8.61 (1 H, s, 4-H); ^{13}C nmr ($CDCl_3$) δ 64.23 (C-5'), 72.59, 73.59, 75.31, 79.92 (C-1', -2', -3' and -4'), 105.20, 114.22 (C-5 and -6), 123.35, 127.85 (C-4a and -7), 128.23-133.34 (Ar-C), 150.97 (C-4), 158.28 (C-2), 165.21, 165.30, 166.16 (C=O); high resolution mass spectrum, m/z 595.1421. ($C_{32}H_{25}N_3O_7S$. requires 595.1411). **Compound 8:** yellow foam, 23%, Rf 0.17 (hexane-ethyl acetate, 4:5); Idetification was confirmed by comparing ^{1}H nmr spectra with the product previously prepared by the reported procedure.[2d]

General Deprotection Procedure. Sufficient methanolic sodium hydroxide was added to the protected C-nucleoside in methanol. The mixture was kept at room temperature for 5 h, rendered neutral with acetic acid, and evaporated. The residue was purified by plc to afford the free C-nucleoside.

2-Oxo-7-(β-D-ribofuranosyl)pyrrolo[1,2-f]-1,2,4-triazine (6b). pale yellow needles, 181-183°C (methanol), 51.3%; ^{1}H nmr (CD_3OD) δ 3.68 (1 H, dd, J=4.4 and 12.0 Hz, 5'-Ha), 3.81 (1 H, dd, J=3.0 and 12.0 Hz, 5'-Hb), 4.03 (1 H, m, 4'-H), 4.10 (1 H, t, J=5.1 Hz, 3'-H), 4.46 (1 H, t, J=5.4 Hz, 2'-H), 5.23 (1 H, d, J=6.1 Hz, 1'-H), 6.57, 6.60 (2 H, each d, J=4.7 Hz, 5- and 6-H), 8.56 (1 H, s, 4-H); ^{13}C nmr (CD_3OD) δ 64.63 (C-5'), 74.09, 75.66, 80.26, 87.05 (C-1', -2', -3' and -4'), 105.25, 112.69 (C-5 and -6), 123.49, 129.53 (C-4a and -7), 154.04 (C-4), 165.41 (C-2); ms (fab, glycerol as matrix) 290 (Found: MNa^+ 290.0770. $C_{11}H_{13}N_3O_5Na$ requires 290.0753).

2-Thioxo-7-(β-D-ribofuranosyl)pyrrolo[1,2-f]-1,2,4-triazine (7b). yellow needles, mp 228-230°C

(methanol), 50.9%; ^{1}H nmr (CD_3OD) δ 3.57 (1 H, dd, J=4.4 and 9.7 Hz, 5'-Ha), 3.65 (1 H, dd, J=3.7 and 9.7 Hz, 5'-Hb), 3.81 (1 H, m, 4'-H), 4.04 (1 H, t, J=5.4 Hz, 3'-H), 4.38 (1 H, t, J=6.1 Hz, 2'-H), 5.22 (1 H, d, J=6.1 Hz, 1'-H), 7.00 (1 H, d, J=4.7 Hz, 5-H), 7.05 (1 H, d, J=4.7 Hz, 6-H), 8.88 (1 H, s, 4-H); ^{13}C nmr (CD_3OD) δ 63.41 (C-5'), 72.76, 74.72, 77.93, 85.98 (C-1', -2', -3' and -4'), 107.21, 116.08 (C-5 and -6), 124.59, 129.86 (C-4a and -7), 152.20 (C-4), 158.77 (C-2); ms (fab, glycerol as matrix) 284 (Found: MH^+ 284.0724. $C_{11}H_{14}N_3O_4S$ requires 284.0705).

General Acetonization Procedure. To a solution of a deprotected C-nucleoside (0.01 mmol) in acetone (2 ml) was added acetone containing PTSA and the mixture was kept at room temperature for 2 h. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution. Water was added, and the mixture was extracted with chloroform, and dried over magnesium sulfate. The extracts, on evaporation, afforded a syrup, which was purified by plc with chloroform-methanol (97:3) as developer.

2-Oxo-7-(2,3-O-isopropylidene-β-D-ribofuranosyl)pyrrolo[1,2-f]-1,2,4-triazine (6c). pale yellow oil; ^{1}H nmr ($CDCl_3$) δ 1.35, 1.63 (3 H each, each s, isopropylidene Me, δ=0.28 ppm), 3.80 (1 H, d, J=12.1 Hz, 5'-Ha), 3.99 (1 H, d, J=12.1 Hz, 5'-Hb), 4.42 (1 H, br s, 4'-H), 5.09-5.16 (2 H, m, 1'- and 3'-H), 5.29 (1 H, t, J=6.1 Hz, 2'-H), 6.81, 6.88 (1 H each, each d, J=5.7 Hz, 5- and 6-H), 8.57 (1 H, s, 4-H).

2-Thioxo-7-(2,3-O-isopropylidene-β-D-ribofuranosyl)pyrrolo[1,2-f]-1,2,4-triazine (7c). yellow oil; ^{1}H nmr ($CDCl_3$) δ 1.15, 1.53 (3 H each, each s, isopropylidene Me, δ=0.38 ppm), 3.58 (2 H, m, 5'-H), 4.02 (1 H, m, 4'-H), 4.76 (1 H, dd, J=4.4 and 6.7 Hz, 3'-H), 5.21 (2 H, m, 1'- and 2'-H), 6.85, 6.92 (1 H each, each d, J=4.7 Hz, 5- and 6-H), 8.83 (1 H, s, 4-H).

REFERENCES

(1) Part 16: Y. Ito, C. Ito, and I. Maeba, Heterocycles, 1991, 32, 1955.

(2a) I. Maeba, T. Takeuchi, T. Iijima, and H. Furukawa, J. Org. Chem., 1988, 53, 1401; (b) I. Maeba, M. Suzuki, O. Hara, T. Takeuchi, T. Iijima, and H. Furukawa, ibid., 1987, 52, 4521; (c) I. Maeba, K. Kitaori, and C. Ito, ibid., 1989, 54, 3927; (d) I. Maeba, K. Osaka, N. Morishita, K. Fujioka, and C. Ito, J. Chem. Soc., Perkin Trans. 1, 1991, 939; (e) I. Maeba, K. Osaka, and C. Ito, Heterocycles, 1990, 31, 2225.

(3) S. P. Rao, K. V. B. Rao, B. A. Otter, R. S. Klein, and W. Ren, Tetrahedron Lett., 1988, 29, 3537, and references cited therein.

(4) O. Migliara, S. Petruso, and V. Sprio, J. Heterocycl. Chem., 1979, 16, 833.

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