

C-NUCLEOSIDES. 20.¹ RING TRANSFORMATION OF 5-HYDROXY-5-(2,3,5-TRI-O-BENZOYL- β -D-RIBOFURANOSYL)FURAN-2(5H)-ONE WITH 2-AMINOTHIOPHENOL AND 2-AMINOETHANETHIOL TO 1,5-BENZOTHAZEPINE AND 1,4-THIAZINE

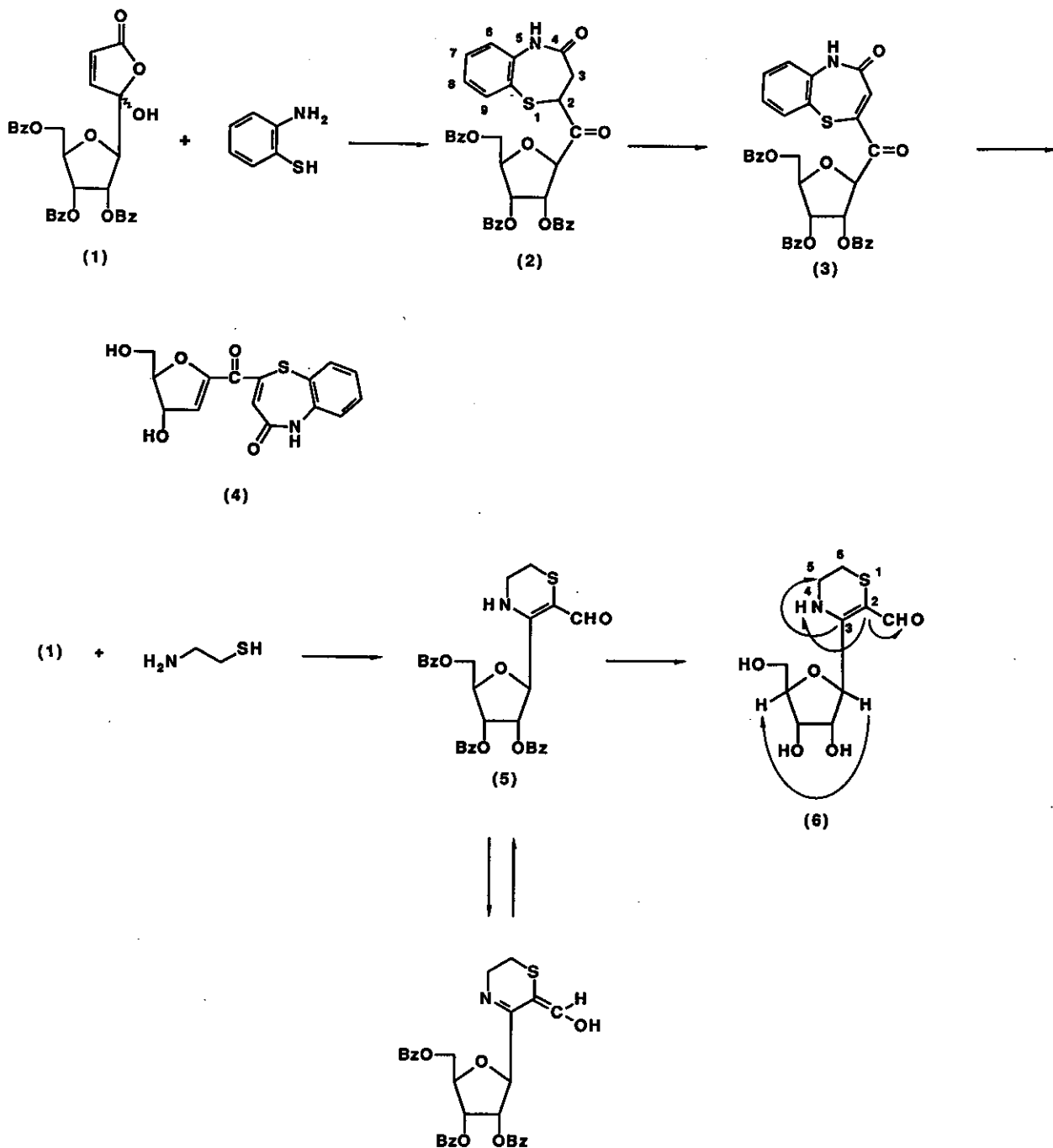
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Abstract----- Treatment of 1 with 2-aminothiophenol afforded 2-[1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (2). Dehydrogenation of 2 with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and a trace amount of *p*-toluenesulfonic acid in benzene afforded 2-[1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one (3). The removal of the sugar protecting groups in 3 afforded 2-[1-(1,4-anhydro-2-deoxy-D-erythro-pent-1-enofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one (4) resulting from the abstraction by base of H-1'. Compound (1) was treated with 2-aminoethanethiol to give 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-5,6-dihydro-4H-1,4-thiazine-2-carboxaldehyde (5). Deprotection of the compound (5) with aqueous sodium carbonate afforded the deprotected compound (6).

For several years, we have studied the transformation of 5-hydroxy-5-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)furan-2(5H)-one (1) into a variety of C-nucleosides.² In this paper, we describe the ring transformation of 1 with 2-aminothiophenol and 2-aminoethanethiol to 1,5-benzothiazepine and 1,4-thiazine. It is well known that 2-aminothiophenol can react with 1,3-bis carbon electrophiles to give various types of 1,5-benzothiazepine.³

Treatment of 2-aminothiophenol with the furanone glycoside (1) in chloroform at 10 °C afforded 2-[1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (2) in 94% yield. Compound (2) is an inseparable mixture of epimers at C-2. Dehydrogenation of 2 with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and a trace amount of *p*-toluenesulfonic acid (PTSA) in benzene at 50 °C afforded 2-[1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one (3) in 75% yield. Debenzoylation of 3 with alkaline did not afford the deprotected benzothiazepine nucleoside, leading to 2-[1-(1,4-anhydro-2-deoxy-D-erythro-pent-1-enofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one (4) resulting from the abstraction by base of



Scheme 1 : The $^1\text{H} - ^{13}\text{C}$ long range COSY and NOE experiments with 1,4-thiazinecarboxaldehyde (6)

H-1',⁴

The furanone glycoside (1) was allowed to react with 2-aminoethanethiol in chloroform at room temperature for 3 h to afford 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-5,6-dihydro-4H-1,4-thiazine-2-carboxaldehyde (5) in only 11% yield together with a number of unidentified products. Variation in the reaction temperature, time, reactant proportions, and solvent did not improve the above yield. The ^1H and ^{13}C nmr spectra of this substance (5) clearly showed the presence of a single formyl group at δ 9.74 and δ 180.87, respectively. In the ^{13}C nmr spectrum, the signal corresponding to the olefin carbon atom of position 2 was not observed. The missing signal may be attributed to exchange occurring between tautomeric forms (Scheme 1).⁵ In the mass spectrum, the molecular ion peak was found at m/z 573 (M^+). Removal of the sugar protecting groups in 5 was readily accomplished with aqueous sodium carbonate to afford 3-(β -D-ribofuranosyl)-5,6-dihydro-4H-1,4-thiazine-2-carboxaldehyde (6) in 75% yield. The stereochemistry of 5 was determined by a nuclear Overhauser effect experiment. Irradiation of the 1'-H signal (δ 5.10) in 6 gave a 4.1 % enhancement of the signal at δ 3.82 assignable to the 4'-H. In the ^{13}C nmr spectrum of 6, the missing C-2 signal was characteristically found at δ 99.06 under heating experimental condition (70°C). In the ^1H - ^{13}C long-range COSY experiment of 6, a correlation was observed between methylene proton of C-5 at δ 3.53 and C-3 at δ 155.17 and amino proton at δ 7.35 and C-2 at δ 99.06. In the mass spectrum, the molecular ion peak was found at m/z 261 (M^+). We can offer no convincing argument as to the mechanistic origin of the 1,4-thiazine carboxaldehyde, and the formation of this type of product does not appear to have been previously observed.

EXPERIMENTAL

Mass spectra were taken on a Hitachi M-80 instrument by direct insertion at 70 eV; high resolution mass spectra were run on a JMS-HX 110. ^1H - 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 GF₂₅₄ (Merck). The compounds were detected by uv light (254 nm).

2-[1-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one

(2). To a solution of 1 (104.4 mg, 0.20 mmol) in chloroform (3 ml) at 10 °C was added 28.8 mg (0.23 mmol) of 2-aminothiophenol and the resulting solution was stirred for 30 min and then evaporated. The residue was chromatographed over a column of silica gel with hexane-ethyl acetate (5:1) as developer to give 2 (117.7 mg, 94.2%) as a pale yellow oil; ^1H nmr (CDCl_3) δ 2.79, 2.86 (each 1/2 H, each t, $J=5.0$ Hz, 3-Ha), 3.47, 3.53 (each 1/2 H, each dd, $J=4.4$ and 8.1 Hz, 3-Hb), 4.13 (1 H, m, 2-H), 4.55-4.79 (3 H, m, 4'- and 5'-H), 4.85, 4.93 (each 1/2 H, each d, $J=4.7$ Hz, 1'-H), 5.67, 5.80 (each 1/2 H, each t, $J=4.7$ Hz, 3'-H), 5.95, 6.06 (each 1/2 H, each t, $J=4.7$ Hz, 2'-H), 6.84-7.24 (4 H, m, 6-, 7-, 8- and 9-H), 7.29-8.07 (15 H, m, ArH), 9.06, 9.11 (each 1/2 H, each br s, NH exchanges with D_2O); ^{13}C nmr (CDCl_3) δ 36.73, 36.82 (C-2), 37.20, 37.59 (C-3), 63.65, 63.97 (C-5'), 71.97, 72.18, 73.06, 73.47, 79.93, 80.24, 85.64, 85.79 (C-1', -2', -3' and -4'), 117.46-135.97 (Ar-C), 165.05, 165.26, 166.12, 166.21, 167.45 (C=O), 202.78, 203.63 (C-12). Hrms Found: m/z 407.0828. Calcd for $\text{C}_{22}\text{H}_{17}\text{NO}_5\text{S}$; M^+-2xBzOH , 407.0826.

2-[1-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one (3).

A solution of 2 (86.2 mg, 0.13 mmol) in benzene (3 ml) containing DDQ (58.2 mg, 0.25 mmol) and PTSA (5 mg) was heated at 50 °C for 9 h. Water was added, and the mixture was extracted with ethyl acetate. The extracts were combined, washed with water, and dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was purified by preparative tlc (plc) with hexane-ethyl acetate (1:1) as developer to give 3 (64.7 mg, 75.3%) as a yellow oil; ^1H nmr (CDCl_3) δ 4.61 (1 H, dd, $J=3.7$ and 12.1 Hz, 5'-Ha), 4.79 (1 H, m, 4'-H), 4.90 (1 H, dd, $J=3.4$ and 12.1 Hz, 5'-Hb), 5.00 (1 H, d, $J=4.4$ Hz, 1'-H), 5.76 (1 H, t, $J=4.4$ Hz, 3'-H), 6.01 (1 H, t, $J=4.4$ Hz, 2'-H), 6.99-8.09 (19 H, m, ArH), 8.01 (1 H, s, 3-H), 10.23 (1 H, s, NH exchanges with D_2O); ^{13}C nmr (CDCl_3) δ 63.71 (C-5'), 72.30, 73.96, 80.30, 85.35 (C-1', -2', -3' and -4'), 116.60, 117.46, 124.36, 125.57 (C-6, -7, -8 and -9), 127.86-133.62 (Ar-C and C-3), 142.74 (C-4), 156.53 (C-2), 165.24, 166.18, 171.61 (C=O), 194.86 (C-12). Hrms Found: m/z 405.0666. Calcd for $\text{C}_{22}\text{H}_{15}\text{NO}_5\text{S}$; M^+-2xBzOH , 405.0669.

2-[1-(1,4-Anhydro-2-deoxy-D-erythro-pent-1-enofuranosyl)carbonyl]-1,5-benzothiazepin-4(5H)-one

(4). To a solution of compound 3 (64.7 mg, 0.10 mmol) in methanol (6 ml) at 10 °C was added 0.5 N sodium carbonate (1 ml) and the mixture was kept at room temperature for 3 h. The reaction mixture was neutralized with acetic acid and evaporated. The residue was purified by plc with chloroform-methanol (9:1) as developer to give 4 (14.2 mg, 44.7%) as a yellow foam; ^1H nmr (CD_3OD)

δ 3.68 (2 H, d, $J=5.0$ Hz, 5'-H), 4.47 (1 H, apparent q, 4'-H), 4.93 (1 H, t, $J=3.0$ Hz, 3'-H), 6.12 (1 H, d, $J=3.0$ Hz, 2'-H), 7.10 (2 H, apparent q, 7- and 8-H), 7.26 (1 H, d, $J=8.1$ Hz, 6- or 9-H), 7.35 (1 H, dd, $J=1.3$ and 8.1 Hz, 6- or 9-H), 7.92 (1 H, s, 3-H); ^{13}C nmr (CDCl_3) δ 63.94 (C-5'), 77.04, 92.39 (C-3' and -4'), 113.20, 118.91, 125.78, 127.42, 129.72 (C-2', -3, -6, -7, -8 and -9), 118.11, 135.08 (C-10 and -11), 145.09, 157.41, 159.05 (C-1', -2 and -4), 183.83 (C-12). Hrms Found: m/z 319.0521. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_5\text{S}$; M^+ , 319.0513.

3-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)-5,6-dihydro-4H-1,4-thiazine-2-carboxaldehyde (5). To a solution of 1 (220 mg, 0.40 mmol) in chloroform (3 ml) at 10 °C was added 2-aminoethanethiol (183.3 mg, 1.6 mmol) and sodium carbonate (171.5 mg, 1.6 mmol). The mixture was stirred at room temperature for 3 h. Water was added, and the mixture was extracted with chloroform. The extracts were combined, washed with water, and dried over magnesium sulfate. The extracts, on evaporation, afforded a colorless oil which was purified by plc with hexane-ethyl acetate (1:1) as developer, to give 5 (24.4 mg, 10.5%) as a colorless syrup; ^1H nmr (CDCl_3) δ 2.76 (2 H, m, 6-H), 3.59 (2 H, m, 5-H), 4.69 (1 H, m, 4'-H), 4.75 (1 H, dd, $J=4.4$ and 12.1 Hz, 5'-Ha), 4.90 (1 H, dd, $J=2.4$ and 12.1 Hz, 5'-Hb), 5.44 (1 H, dd, $J=5.4$ and 8.1 Hz, 2'-H), 5.83 (2 H, m, 1'- and 3'-H), 6.35 (1 H, s, NH exchanges with D_2O), 7.34-8.14 (15 H, m, ArH), 9.74 (1 H, s, CHO); ^{13}C nmr (CDCl_3) δ 22.75 (C-6), 43.43 (C-5), 63.81 (C-5'), 72.42, 75.31, 75.73, 77.00 (C-1', -2', -3' and -4'), 128.29-133.86 (Ar-C), 150.69 (C-3), 165.16, 165.43, 166.82 (C=O), 180.87 (CHO). Hrms Found: m/z 573.1458. Calcd for $\text{C}_{31}\text{H}_{27}\text{NO}_8\text{S}$; M^+ , 573.1456.

3-(β -D-Ribofuranosyl)-5,6-dihydro-4H-1,4-thiazine-2-carboxaldehyde (6). To a solution of compound 5 (36.2 mg, 0.06 mmol) in methanol (3 ml) at 10 °C was added 0.5 N sodium carbonate (1 ml) and the mixture was kept at room temperature for 1 h. The reaction mixture was neutralized with acetic acid and evaporated. The residue was purified by plc with chloroform-methanol (9:1) as developer, to give 6 (12.3 mg, 74.6%) as a colorless needles; mp 198-199 °C; ^1H nmr [$(\text{CD}_3)_2\text{SO}$] δ 2.74 (2 H, m, 6-H), 3.53 (2 H, m, 5-H), 3.07 (1 H, dd, $J=2.9$ and 12.2 Hz, 5'-Ha), 3.69 (1 H, dd, $J=2.9$ and 12.2 Hz, 5'-Hb), 3.82 (2 H, m, 2'- and 4'-H), 3.91 (1 H, t, $J=5.4$ Hz, 3'-H), 5.10 (1 H, d, $J=5.4$ Hz, 1'-H), 4.75-5.28 (3 H, br, OH exchanges with D_2O), 7.35 (1 H, s, NH exchanges with D_2O), 9.44 (1 H, s, CHO); ^{13}C nmr [$(\text{CD}_3)_2\text{SO}$](70° C) δ 22.06 (C-6), 42.64 (C-5), 60.18 (C-5'), 70.12, 76.54, 78.57, 84.29 (C-1', -2', -3' and -4'), 99.06 (C-2), 155.17 (C-3), 179.70 (CHO). Hrms Found: m/z 261.0667. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_5\text{S}$; M^+ , 261.0670.

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