C-NUCLEOSIDES. 16.[1] A SYNTHESIS OF A 1,5-BENZODIAZEPIN-2-ONE HOMO-C-NUCLEOSIDE THROUGH CONDENSATION OF 1,2-DIAMINOBENZENE WITH 5-HYDROXY-5-(2,3,5-TRI-O-BENZOYL-β-D-RIBOFURANOSYL)FURAN-2(5H)-ONE

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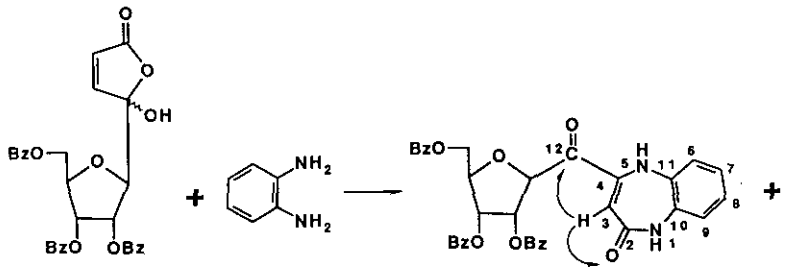
Abstract ----- The novel ring transformation of 5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (1) with 1,2-diaminobenzene to 1,5-benzodiazepin-2-one is described. Treatment of 1 with 1,2-diaminobenzene followed by dehydrogenation with 2,3-dicholo-5,5-dicyano-p-benzoquinone (DDQ) and p-toluenesulfonic acid afforded 4-[1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-oxo]-1,3-dihydro-2H-1,5-benzodiazepin-2-one (2) as the major product. A possible mechanism for this reaction is proposed. The removal of the sugar protecting groups in 2 afforded the deprotected homo-C-nucleoside (5).

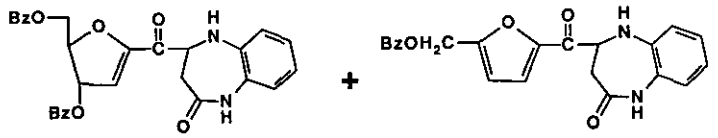
In recent years, the chemistry of homo-C-nucleosides has received considerable attention due to the biological activities.[2] In previous paper, we have reported the preparation of a functionalized C-glycoside, 5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (1) and its utilization in the synthesis of pyridazinone and oxazinone C-nucleosides.[3] This paper describes the preparation of 1,5-benzodiazepin-2-one homo-C-nucleoside by a novel ring transformation of furanone (1) with 1,2-diaminobenzene. The most widely used method for the synthesis of such a ring system involves the condensation of 1,2-diaminobenzenes with β-keto esters.[4] The key synthetic intermediate furanone (1) can be obtained readily from 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan by our previously published procedure.[3]

The condensation of 1 with 1,2-diaminobenzene was carried out in chloroform at room temperature. When the progress of the reaction was monitored by thin layer chromatography (tlc), complete disappearance of starting material (1) was observed after 3 h. The gradual disappearance of 1 was accompanied by the appearence of single distinct spot. Atttempted isolation of this product by preparative thin layer chromatography (plc), however, led to the formation of a number of unidentified products. Without isolation, 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and a trace amount of p-toluenesulfonic acid monohydrate were added and the mixture was stirred at room

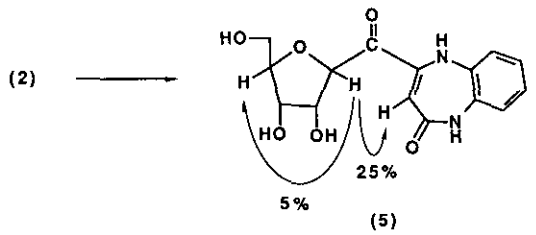
temperature for additional 1.5 h to give 4-[1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)oxo]-1,3-dihydro-2H-1,5-benzodiazepin-2-one (2) in 36% yield as the major product and 4-[1-(3,5-di-O-benzoyl-1,4-anhydro-2-deoxy-D-erythropent-1-enofuranosyl)oxo]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (3) and 4-[1-(5-benzoyloxymethylfuran-2-yl)oxo]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (4) in 3% and 6% yields. The structure of 2, 3 and 4 was established by ^{1}H and ^{13}C nmr and mass spectra. In particular, the ^{1}H-^{13}C long-range COSY spectrum of 2 exhibited a correlation between 3-H at δ 6.68 and C-2 and C-12 at δ 157.19 and 194.92. The ^{1}H nmr spectra of 3 and 4 show that, in the higher field region, 3-CH_2-4-CH- protons resonate as an ABX system.[5] The absolute stereochemistry of 4-position of compounds (3) and (4) was not readily obtainable from available spectra data.



(1) (2)



(3) (4)

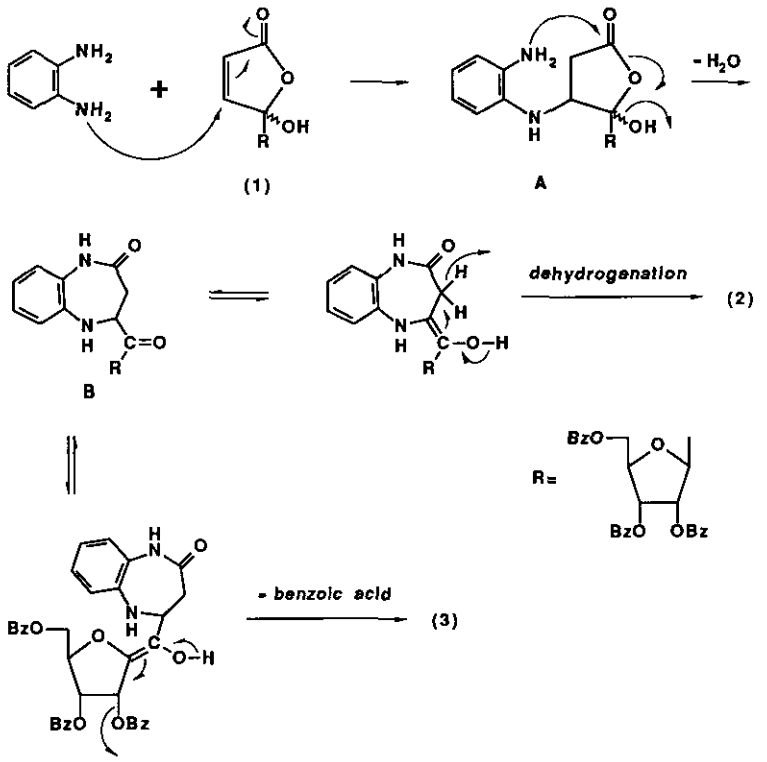


(5)

The ^{1}H ^{13}C long range COSY experiment with 2 .
NOE experiment with 5 .

Scheme 1

The removal of the sugar protecting groups in 2 was readily accomplished with aqueous sodium carbonate to afford the deprotected homo-C-nucleoside (5) in 34% yield. The stereochemistry of 5 was determined by a nuclear Overhauser effect experiment. Irradiation of the 1'-H signal (δ 4.19) in 5 gave a 5% enhancement of the signal at δ 3.82 assignable to the 4'-H. This showed the β-ribofuranoside configuration had been preserved during the condensation reaction. A plausible explanation for the formation of 2 involves Michael addition of 1,2-diaminobenzene to 1 with subsequent formation of A. Nucleophilic attack by the amino group of A on the carbonyl carbon of the furanone moiety would lead to tetrahydro-1,5-benzodiazepin-2-one B, which is then dehydrogenated to give 2. Loss of benzoic acid from B leads to the compound (3). The outline of the reaction mechanism is shown in Scheme 2.



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 Nmr spectra were measured with a JNM-GX-270 and a GX-400 (JEOL) spectrometers, with tetramethylsilane as internal standard. ^{13}C Nmr spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, 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).

4-[1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)oxo]-1,3-dihydro-2H-1,5-benzodiazepin-2-one (2), 4-[1-(3,5-Di-O-benzoyl-1,4-anhydro-2-deoxy-D-erythropent-1-enofuranosyl)oxo]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (3) and 4-[1-(5-Benzoyloxymethylfuran-2-yl)oxo]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (4). To a solution of **1** (79.6 mg, 0.15 mmol) in chloroform (2 ml) at 0 °C was added 23.7 mg (0.22 mmol) of 1,2-diaminobenzene. The mixture was stirred at room temperature for 3 h. After the tlc analysis indicated complete disappearance of starting material, DDQ (66.4 mg, 0.3 mmol) and PTSA (28 mg) were added, and the mixture was stirred for additional 1.5 h. Water was added, and the mixture was extracted with chloroform (3x10 ml). The extracts were combined, washed with water, dried over magnesium sulfate. The extracts, on evaporation, afforded a yellow oil which was separated by plc with chloroform-methanol (99:1) as eluent.

Compound 2: yellow needles, mp 184-186 °C; yield 36.3%; Rf 0.30 (hexane-ethyl acetate, 4:3); ^{1}H nmr ($CDCl_3$) δ 4.66 (1 H, dd, J=4.0 and 12.1 Hz, 5'-Ha), 4.79 (1 H, m, 4'-H), 4.88 (1 H, dd, J=3.4 and 12.1 Hz, 5'-Hb), 4.93 (1 H, d, J=3.7 Hz, 1'-H), 5.80 (1 H, t, J=3.7 Hz, 3'-H), 6.03 (1 H, t, J=3.7 Hz, 2'-H), 6.68 (1 H, s, 3-H), 7.09-8.05 (19 H, m, ArH), 11.45, 13.44 (2 H, each s, NH, exchanges with D_2O); ^{13}C nmr ($CDCl_3$) δ 64.00 (C-5'), 72.46, 74.71, 79.77, 85.13 (C-1', -2', -3' and -4'), 90.22 (C-3), 116.20, 124.68, 124.76, 126.00 (C-6, -7, -8 and -9), 128.17-133.38 (Ar-C), 145.47 (C-4), 157.19 (C-2), 165.29, 166.22 (C=O), and 194.92 (C-12). Anal. Calcd for $C_{36}H_{28}N_2O_9.1/2H_2O$: C, 67.39; H, 4.56; N, 4.37. Found: C, 67.23; H, 4.38; N, 4.46.

Compound 3: oil, yield 3%; Rf 0.39 (hexane-ethyl acetate, 4:3); ^{1}H nmr ($CDCl_3$) δ 3.10 (1 H, dd, J=10.1 and 18.8 Hz, 3-Ha), 3.65 (1 H, dd, J=2.4 and 18.8 Hz, 3-Hb), 4.46 (1 H, dd, J=10.1 and 2.4 Hz, 4-H), 4.60 (1 H, s, NH, exchanges with D_2O), 4.65 (2 H, m, 5'-H), 5.06 (1 H, q, J=3.0 Hz, 4'-H), 6.13 (1 H, t, J=3.0 Hz, 3'-H), 6.21 (1 H, d, J=3.0 Hz, 2'-H), 6.67-6.93 (4 H, m, 6-, 7-, 8- and 9-H), 7.40-8.05 (10 H, m, ArH), 8.45 (1 H, s, NH, exchanges with D_2O); ^{13}C nmr ($CDCl_3$) δ 41.33

(C-3), 52.09 (C-4), 63.81 (C-5'), 78.68, 84.80 (C-3' and -4'), 107.25 (C-2'), 114.54, 115.59, 119.77, 124.31 (C-6, -7, -8 and -9), 124.76-133.63 (Ar-C, C-10 and -11), 157.75 (C-1'), 166.02, 166.17, 167.69 (C-2 and C=O), and 191.72 (C-12). Although this compound was homogeneous by tlc, we were unable to obtain proper microanalytical data.

Compound 4: oil, yield 6%; Rf 0.28 (hexane-ethyl acetate, 4:3); ^{1}H nmr ($CDCl_3$) δ 3.23 (1 H, dd, J=10.4 and 18.1 Hz, 3-Ha), 3.76 (1 H, dd, J=2.4 and 18.1 Hz, 3-Hb), 4.54 (1 H, dd, J=10.4 and 2.4 Hz, 4-H), 4.80 (1 H, s, NH, exchanges with D_2O), 5.36 (2 H, s, CH_2), 6.63-6.93 (5 H, m, diazepine and furan 4-H), 7.24 (1 H, d, J=4.1 Hz, furan 3-H), 7.44 (2 H, t, J=9.1 Hz, benzene), 7.57 (1 H, t, J=9.1 Hz, benzene), 8.07 (2 H, d, J=9.1 Hz, benzene), 8.56 (1 H, s, NH, exchanges with D_2O); ^{13}C nmr ($CDCl_3$) δ 40.04 (C-3), 52.34 (C-4), 58.25 (CH_2), 112.84, 114.51, 115.52, 118.97, 119.58, 124.18, 124.92, 126.45, 128.48, 129.31, 129.84, 133.08, 133.43, 137.01 (Ar-C), 152.00, 154.51 (furan C-2 and -5), 165.98, 168.05 (C-2 and C=O), and 187.26 (C-12); high-resolution mass spectrum, m/z 390.1209 ($C_{22}H_{18}N_2O_5$ requires 390.1214).

4-[1-(β-D-Ribofuranosyl)oxo]-1,3-dihydro-2H-1,5-benzodiazepin-2-one (5). To a solution of 2 (45 mg, 0.07 mmol) in methanol (4 ml) was added 1 N aqueous sodium carbonate (0.5 ml, 0.6 mmol) at 0 °C, and the mixture was kept at room temperature for 4 h, then evaporated. The residue was purified by plc with chloroform-methanol (17:3) as eluent. Crystallization of the resulting solid from ether-dichloromethane afforded 5 (8.0 mg, 34.2%) as an yellow needles, 199-202 °C ; ^{1}H nmr [$(CD_3)_2SO$] δ 3.60 (2 H, m, 5'-H), 3.75 (1 H, t, J=4.4 Hz, 3'-H), 3.82 (1 H, q, J=4.4 Hz, 4'-H), 3.97 (1 H, t, J=4.4 Hz, 2'-H), 4.19 (1 H, d, J=4.4 Hz, 1'-H), 4.80 (4 H, br, OH and NH, exchanges with D_2O), 6.36 (1 H, s, 3-H), 7.08-7.45 (4 H, m, ArH), 13.14 (1 H, br s, NH, exchanges with D_2O); ^{13}C nmr [$(CD_3)_2SO$] δ 61.95 (C-5'), 71.31, 74.59, 84.13, 86.76 (C-1', -2', -3' and -4'), 89.39 (C-3), 115.31, 116.19, 123.44, 123.73, 123.91, 126.60 (C-6, -7, -8, -9, -10 and -11), 144.74 (C-4), 155.50 (C-2), and 178.32 (C-12); ms (fab, glycerol as matrix) 321 (MH^+, 34%) (Found: MH^+ 321.1115. $C_{15}H_{17}N_2O_6$ requires 321.1087).

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