C-NUCLEOSIDES. 22.[1] SYNTHESIS OF QUINOXALINE ACYCLO-C-NUCLEOSIDE

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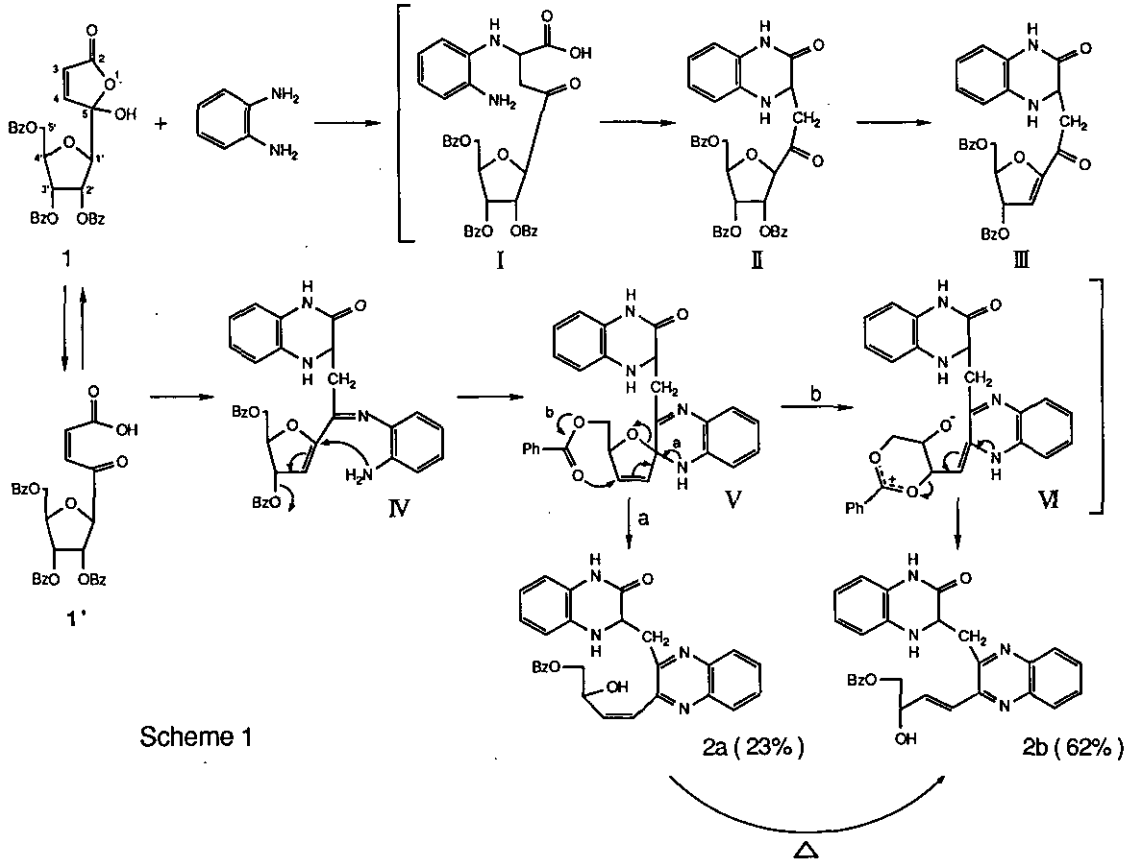
Abstract ----- The synthesis of quinoxaline acyclo-C-nucleoside, 2-[(3S)-3,4-dihydroxybutyl]-3-methylquinoxaline (**6**), is described. Treatment of furanone glycoside (**1**) with 1,2-diaminobenzene gave a mixture of Z- and E-3-[2-[4-O-benzoyl-(3S)-3-hydroxy-1-butenyl]-3-quinoxalinylmethyl]-1,2,3,4-tetrahydroquinoxalin-2-ones (**2a** and **2b**). Compound (**2a**) was treated with acetic acid to give three products, Z- and E- 2-[4-O-benzoyl-(3S)-3-hydroxy-1-butenyl]-3-methylquinoxalines (**3a** and **3b**) and quinoxalin-2-one (**4**). Catalytic hydrogenation of **3a,b** produced 2-[4-O-benzoyl-(3S)-3-hydroxybutyl]-3-methylquinoxaline (**5**). Removal of the protecting group in **5** afforded compound (**6**).

Our preceding paper[1] reported that the preparation of isoxazole C-nucleoside from 5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (**1**) *via* enaminone glycoside. The present paper describes the preparation of Z- and E-3-[2-[4-O-benzoyl-(3S)-3-hydroxy-1-butenyl]-3-quinoxalinylmethyl]-1,2,3,4-tetrahydroquinoxalin-2-ones (**2a** and **2b**) from furanone glycoside (**1**) and demonstrates the utility of **2a,b** through the construction of quinoxaline acyclo-C-nucleoside (**6**).

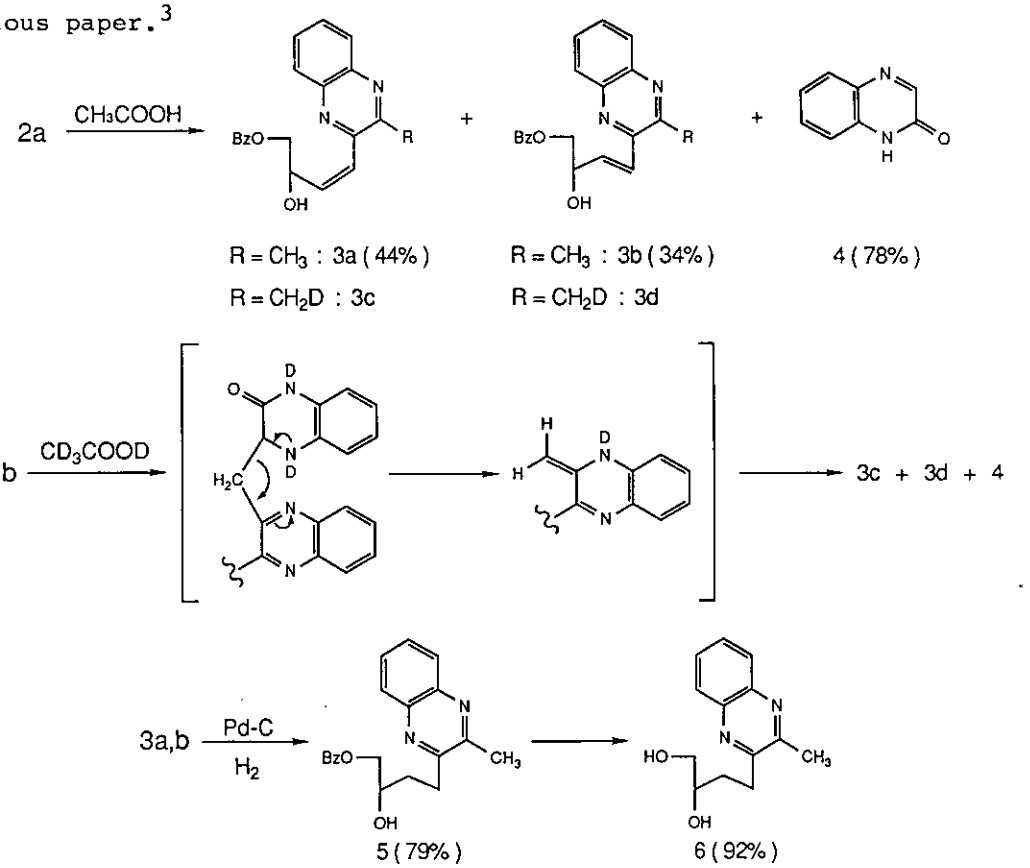
Treatment of 1,2-diaminobenzene with the furanone glycoside (**1**) in methanol at room temperature for 3 h gave the olefinic products (**2a,b**) in 85% combined yield. These products were assumed to be an E/Z mixture of quinoxaline products, in which the sugar moiety was ring-opened. This assumption was supported by the ^{1}H-nmr spectra, which showed chemical shifts for the olefinic protons at δ 6.20 and 6.95 for the Z-isomer (**2a**) (J = 11.2 Hz) and at δ 7.16 and 7.23 for the E-isomer (**2b**) (J = 15.1 Hz).

The ratio of the olefinic compounds (2a) : (2b) was approximately 1:3. This ratio did not change as the reaction time increased. However, when 2a was refluxed in benzene, the product of the E-compound (2b) was obtained in 71% yield. One plausible explanation for the formation of 2a,b involves Michael type addition of 1,2-diaminobenzene to ring opening tautomer (1') and subsequent formation of I, which then undergoes cyclization to tetrahydroquinoxalin-2-one (II). Loss of benzoic acid from II leads to compound (III), which is then condensed with 1,2-diaminobenzene to give Schiff's base (IV). A nucleophilic attack by the amino group of IV on the 1'-carbon of the sugar moiety, with a subsequent loss of benzoic acid, produces spiro compound (V), which then undergoes ring opening to the Z-compound (2a)(path a). In path b, a nucleophilic attack by the oxygen of carbonyl group of V on the 3'-carbon of the sugar moiety, with subsequent ring opening of dihydrofuran, produces dihydroquinoxaline (VI), which leads to a thermodynamically more stable isomer (2b). Scheme 1 outlines the reaction mechanism.



Scheme 1

Compound (2a) was treated with acetic acid at 40°C for 2 h to give three products, Z- and E-2-[4-O-benzoyl-(3S)-3-hydroxy-1-butenyl]-3-methylqinoxalines (3a and 3b) in 78% combined yield, and quinoxalin-2-one (4)[2] in 78% yield. The assignment of these structures (3a,b) was supported by their ^{1}H nmr spectra, which showed chemical shifts for the olefinic protons at δ 6.47 and 7.00 for the Z-isomer (3a) (J = 11.8 Hz) and at δ 7.25 (multiplet) for the E-isomer (3b). Isomerization (Z → E) was observed during this reaction experiment. When the same reaction of 2a,b in acetic-D_3 acid-D is performed, the corresponding deuterated methylquinoxaline compounds (3c,d) are obtained in 15% and 45% yield, respectively. In the ^{1}H nmr spectra of 3c,d, the relative intensity of the methyl proton represents exactly two protons when compared to two protons of apparent doublet in 3c or multiplet in 3d due to the methylene group or olefinic group. Therefore, we think that the formation of 3a,b proceeds by the similar mechanism for formation of quinoxalines in our previous paper.[3]



Scheme 2

The catalytic hydrogenation of 3a,b produced 2-[4-O-benzoyl-(3S)-3-hydroxybutyl]-3-methylquinoxaline (5) in 79% yield. Debenzoylation of 5 with methanolic sodium carbonate afforded 2-[(3S)-3,4-dihydroxybutyl]-3-methylquinoxaline (6) in 92% yield. The purine acyclonucleoside 9-(3,4-dihydroxybutyl)guanine exhibiting significant antiherpes activity has been reported.[4] Compound (6) showed no activity against herpes simplex virus type II in cell culture.

EXPERIMENTAL

Melting points were determined on a Yanagimito apparatus and are uncorrected. 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 spectrometer. ^{1}H and ^{13}C nmr spectra were measured with a JNM-GX-270 or a GX-400 (JEOL) spectrometer, with tetramethylsilane as an internal standard. J values are given in Hz. Analytical tlc was performed on glass plates coated with a 0.5-mm layer of silica gel GF_{254} (Merck). The compounds were detected by uv light (254 nm).

Z- and E-3-[2-[4-O-Benzoyl-(3S)-3-hydroxy-1-butenyl]-3-quinoxalinylmethyl]-1,2,3,4-tetrahydroquinoxalin-2-ones (2a and 2b). A solution of compound (1) (187.8 mg, 0.35 mmol) and 1,2-diaminobenzene (74.7 mg, 0.7 mmol) in methanol (6 ml) was stirred at room temperature for 3 h, then evaporated under reduced pressure to a syrup. Tlc (chloroform:methanol, 24:1) showed that the syrup contained two major compounents (Rf 0.33 and 0.31). The residue was chromatographed over a column of silica gel with chloroform-methanol (99.5:0.5) as the eluent. The first compound eluted, compound (2a) (38.6 mg, 23%, corresponding to Rf 0.33 on tlc), was obtained as colorless needles; mp 110-111°C: $[\alpha]^{25}_{D}$ -25.0° (c 1.9, $CHCl_3$); ^{1}H nmr [$(CD_3)_2SO$] δ 3.31, 3.48 (each 1H, each m, methylene), 4.46 (2H, m, 3-H qunoxalin-2-one and 4-Ha), 4.58 (1H, m, 4-Hb), 5.37 (1H, m, 3-H), 5.46, 6.04 (each 1H, NH or OH exchangable with D_2O), 6.20 (1H, m, 2-H olefin), 6.61-6.79 (4H, m, ArH), 6.95 (1H, d, J=11.2, 1-H olefin), 7.47-8.00 (9H, m, ArH), 10.38 (1H, NH exchangable with D_2O); ^{13}C nmr ($CDCl_3$ partial) δ 36.2, 36.3 (CH_2), 54.0 (C-3 quinoxalin-2-one), 66.3, 66.4 (C-4), 67.28 (C-3), 126.5 (C-1 olefin), 140.7, 140.8 (C-2 olefin), 166.5, 168.6 (C=O). Hrms Found: m/z 480.1782. Calcd for $C_{28}H_{24}N_4O_4$; M^+ 480.1795.

Compound (2b) was eluted as the second fraction (102.0 mg, 62%, corresponding to Rf 0.31 on tlc), was obtained as colorless needles; mp 208-209°C: $[\alpha]^{25}_{D}$ +5.3° (c 1.0, $CHCl_3$); ^{1}H nmr [$(CD_3)_2SO$] δ 3.33, 3.54

(each 1H, each m, methylene), 4.38 (2H, m, 4-H), 4.51 (1H, m, 3-H quinoxalin-2-one), 4.70 (1H, m, 3-H), 5.67, 6.07 (each 1H, NH or OH exchangable with D_2O), 6.61-6.79 (4H, m, ArH), 7.16 (1H, dd, J=5.9, 15.1, 2-H olefin), 7.23 (1H, d, J=15.1, 1-H olefin), 7.49-8.03 (9H, m, ArH), 10.38 (1H, NH exchangable with D_2O); ^{13}C nmr ([$(CD_3)_2SO$] partial) δ 36.8 (CH_2), 54.6 (C-3 quinoxalin-2-one), 67.7 (C-4), 68.8 (C-3), 124.8, 124.9 (C-1 olefin), 139.4 (C-2 olefin), 165.6, 166.7 (C=O). Hrms Found: m/z 480.1820. Calcd for $C_{28}H_{24}N_4O_4$; M^+ 480.1795.

Isomerization of 2a to 2b. A solution of compound (2a) (25.1 mg, 0.05 mmol) in benzene (4 ml) was heated under reflux for 5 h. Benzene was removed under reduced pressure, and the residue was purified by plc. This afforded 17.7 mg of compound (2b) (71%). Identifty was confirmed by comparing ^1H nmr spectrum with 2b.

Z- and E-2-[4-O-Benzoyl-(3S)-3-hydroxy-1-butenyl]-3-methylquinoxalines (3a and 3b) and Quinoxalin-2-one (4). A solution of compound (2a) (91.6 mg, 0.02 mmol) in acetic acid (11 ml) was heated at 40°C for 2 h. After this time, three new compounds were detected (tlc) in the reaction mixture which had Rf values of 0.44, 0.34, and 0.32 (chloroform-methanol, 24:1), respectively. The solvent was removed under reduced pressure. The mixture was separated by plc with chloroform-methanol (97:3) as the eluent.

Compound (3a): (27.8 mg, 44%, corresponding to Rf 0.44 on tlc) as colorless needles; mp 71-73°C; $[\alpha]^{25}_D$ -45.9° (c 1.8, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 2.82 (3H, s, CH_3), 4.62 (2H, apparent d, J=5.7, 4-H), 4.97 (1H, m, 3-H), 6.47 (1H, dd, J=6.7, 11.8, 2-H olefin), 7.00 (1H, dd, J=1.3, 11.8, 1-H), 7.38-7.77 (5H, m, ArH), 7.98-8.08 (4H, m, ArH); ^{13}C nmr (CD_3OD) δ 23.8 (CH_3), 68.7 (CH_2), 69.6 (CH), 127.8, 129.5, 130.3, 130.7, 131.3, 131.9, 132.2, 135.0, 142.0, 142.3, 142.7, 152.5 155.5 (Ar-, olefin-C), 168.7 (C=O). Hrms Found: m/z 334.1298. Calcd for $C_{20}H_{18}N_2O_3$; M^+ 334.1316.

Compound (3b): (21.4 mg, 34%, corresponding to Rf 0.34 on tlc) as colorless needles; mp 138-139°C; $[\alpha]^{25}_D$ +39.0° (c 1.8, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 2.80 (3H, s, CH_3), 4.45 (1H, dd, J=7.4, 11.4, 4-Ha), 4.63 (1H, dd, J=3.4, 11.4, 4-Hb), 4.90 (1H, m, 3-H), 7.25 (2H, m, 1-, 2-H olefin), 7.42-7.71 (5H, m, ArH), 7.96-8.10 (4H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 22.9 (CH_3), 68.3 (CH_2), 70.6 (CH), 126.4, 128.2, 128.4, 128.9, 129.2, 129.4, 129.7, 133.3, 137.0, 141.2, 141.4, 148.9, 152.3 (Ar- and olefin-C), 166.8 (C=O), Hrms Found: m/z 334.1314. Calcd for $C_{20}H_{18}N_2O_3$; M^+ 334.1316.

Compound (4): (21.7 mg, 78%, corresponding to Rf 0.32 on tlc) as colorless needles; mp 263-265°C. Cheeseman has given mp 267-269°C: ^1H nmr [$(CD_3)_2SO$] δ 7.31-7.56 (3H, m, ArH), 7.78 (1H, dd, J=1.4, 8.4, ArH), 8.17 (1H, s, 3-H), 12.42 (1H, s, NH). Hrms Found: m/z 146.0506. Calcd for $C_8H_6N_2O$; M^+

146.0480.

2-[4-*O*-Benzoyl-(3*S*)-3-hydroxybutyl]-3-methylquinoxaline (5). To a suspension of 10% palladium-on-carbon (10 mg) in ethanol (3 ml) was added a solution of the compound (3a) (24.4 mg, 0.07 mmol) in the same solvent (2 ml) and the mixture was stirred under hydrogen at atmospheric pressure for 15 min. After the catalyst was removed by filtration, the solvent was evaporated off under reduced pressure. The residue was purified by plc with chloroform-methanol (97:3) as the eluent. This afforded 19.4 mg of compound (5) (79%) as colorless needles; mp 129-130°C: $[\alpha]^{25}_{D}$ +4.1° (*c* 1.4, $CHCl_3$); ^{1}H nmr ($CDCl_3$) δ 2.24 (2H, m, CH_2), 2.78 (3H, s, CH_3), 3.28 (2H, m, CH_2), 4.15 (1H, m, CH), 4.43 (2H, m, CH_2), 7.41-7.71 (5H, m, ArH), 8.00-8.09 (4H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 22.9 (CH_3), 30.3, 31.7, 68.9 (CH_2), 69.6 (CH), 128.2, 128.3, 128.4, 129.1, 129.2, 129.7, 129.9, 133.1, 140.3, 141.0, 153.4, 155.6 (Ar-C), 166.7 (C=O). Hrms Found: *m/z* 336.1460. Calcd for $C_{20}H_{20}N_2O_3$; M^+ 336.1448.

2-[(3*S*)-3,4-Dihydroxybutyl]-3-methylquinoxaline (6). To a solution of compound (5) (19.4 mg, 0.06 mmol) in methanol (2 ml) was added 0.3 *N* aqueous sodium carbonate (0.5 ml, 0.11 mmol) at room temperature for 1 h, and then the reaction mixture was rendered neutral with acetic acid and evaporated. The residue was purified by plc with chloroform-methanol (19:1) as the eluent. This afforded 12.3 mg of compound (6) (92%) as colorless needles; mp 134-135° C; $[\alpha]^{25}_{D}$ -12.8° (*c* 0.9, methanol); ^{1}H nmr (CD_3OD) δ 1.96 (4H, m, CH_2CH_2), 2.78 (3H, s, CH_3), 3.56 (2H, m, CH_2), 3.75 (1H, m, CH), 7.58 (2H, m, ArH), 7.97 (2H, m, ArH); ^{13}C nmr (CD_3OD) δ 23.4 (CH_3), 33.1, 33.3, 68.1 (CH_2), 73.6 (CH), 129.5, 131.1, 131.2, 142.4, 142.9, 155.9, 159.2 (Ar-C). Hrms Found: *m/z* 232.1236. Calcd for $C_{13}H_{16}N_2O_2$; M^+ 232.1210.

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