SYNTHESIS OF 7H-1,2,4-TRIAZOLO[1,5-*d*]TETRAZOLE ACYCLO *C*-NUCLEOSIDES

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Abstract: Condensation of 1.5-diaminotetrazole 1 with 2.3.4.5.6-penta-*O*-acetyl-*D*-gluconoyl chloride 2 or 2.3.4.5-tetra-*O*-acetylgalactaroyl dichloride 6 gave the corresponding 2.3.4.5.6-penta-*O*-acetyl-*D*-gluconic-1-(5-aminotetrazole)amide 3 or 2.3.4.5-tetra-*O*-acetylgalactaric 1.6-bis[(5-aminotetrazole)amide] 7, respectively which upon dehydrative cyclization with phosphoryl chloride gave the corresponding 6-(1.2.3.4.5-penta-*O*-acetyl-*D*-*gluco*-pentitol-1-yl) 7H-1.2.4-triazolo[1.5-*d*]tetrazole 4 or 1.2.3.4-tetra-*O*-acetyl-1.4-bis(7H-1.2.4-triazolo[1.5-*d*]tetrazol-6-yl)*galacto*-tetritol 8, respectively. De-*O*-acetylation of the acyclo *C*-nucleoside peracetates 4 and 8 with methanolic ammonia or sodium ethoxide in ethanol gave the corresponding acyclo *C*-nucleosides 5 and 9.

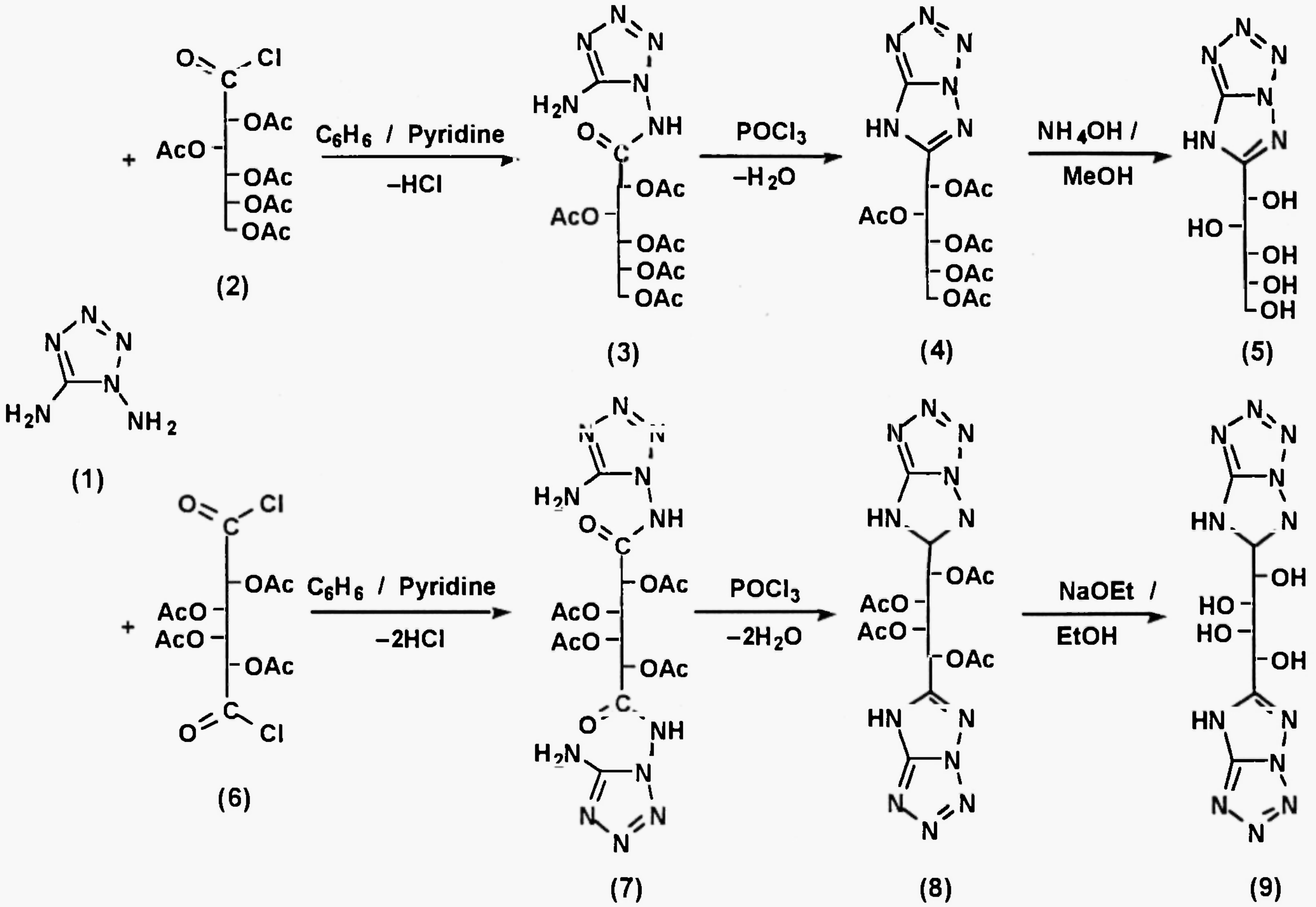
Introduction :

The synthesis (1-4) of *C*-nucloeosides and their acyclo analogs has attracted the attention of many investigators as a result of their various biological activities (5). contributed to the importance of acyclo-*C*-nucleosides also was the isolation and synthesis of the acyclo *C*-nucleoside antibiotic CV-1 [5-hydroxy-4-(D-*arabino*-tetritol-1-yl)imidazolidine-2,5-dione]from a strain of Streptomyces sp. II (6). Other acyclo *C*-nucleoside analogs were found to posses antiviral (7), antibacterial (8) and antifungal (9) activities. Thus, this article deals with the synthesis of new members of acyclo *C*-nucleosides as part of a program (10-13) on the synthesis of acyclo *C*-nucleosides of potential activites .

Resultes and Discussion :

Whereas the condensation of equimolar amounts of 2,3,4,5,6-penta-*O*-acetyl-*D*-gluconoyl chloride 2 or 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride 6 with 1,5-diaminotetrazole (14) 1 gave products 3 and 7. The IR spectra of these products showed NH_2, NH, OAc, CON, and N=N absorptions and their ^{1}H NMR spectra revealed signals for exchangeable protons (NH and NH_2), alditolylidene group protons and four or five *O*-acetyl groups. These data, together with elemental analysis indicated that the structures 3 and 7 .

Dehydrative cyclization of 3 or 7 by heating with phosphoryl chloride gave products the elemental analyses of which showed the loss of one or two molecules of water per molecule of the parent amides 3 and 7. The product showed NH and OAc absorptions and lacked the amide absorption of the starting amides. The ^{1}H NMR spectra of the products showed signals for



exchangeable proton NH, alditolyl group protons and four or five *O*-acetyl groups. The cyclization products were thus assigned the structures 4 and 8. Treatment of 4 with a saturated solution of methanolic ammonia at ambient temperature resulted in removal of the *O*-acetyl groups to give the corresponding structure 5. . Attempted de -*O*-acetylation of 8 with saturated solution of methanolic ammonia was unsuccessful; the unchanged starting material was recovered even after extended rection time. De-*O*-acetylation was successfully achieved, however, upon treatment with sodium ethaoxide solution in ethanol to give the corresponding structure 9.

Experimental:

All melting points are uncorrected. The IR spectra were recorded in potassium bromide discs on a Pye-Unicam SP 1025 spectrophotometer. The ^{1}H NMR were measured in $CDCl_3$ or $(CD_3)_2SO$ on a varian EM 390 spectrometer. Microanalyses were performed by the Microanalytical Data Unit at Cairo University, Cairo, Egypt.

2,3,4,5,6-Penta-*O*-acetyl-*D*-gluconic-1-(5-aminotetrazole)amide 3 :

A solution of 2,3,4,5,6-penta -*O*-acetyl-*D*-gluconoyl chloride 2 (5 mmol) in dry benzene was added dropwise to a cold and stirred solution of 1,5-diaminotetrazole 1 (5 mmol) in pyridine (5 ml) at ambient temperature. The mixture was stirred for 1h and the crystalline product which separated, was filtered and recrystallized from methanol. m.p. 250°C; yield: 78%. TLC ($CHCl_3$/MeOH, 9:1), R_F: 0.45. (Found: C, 41.5; H, 4.7; N, 17.3. $C_{17}H_{24}N_6O_{11}$ requires: C, 41.8, H, 4.9; N, 17.2%). IR: 3360 (NH_2), 3280 (NH), 1750 (OAc), 1690 (CON), 1620 (C=N), 1570 cm^{-1} (N=N); ^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H, exchangeable, NH), 6.75 (d, 1H, pentitolylidene H-1), 6.10 (s, 2H, exchangeable, NH_2), 5.80, 5.45 (2m, 1H each, pentitolylidene H-2, H-3), 5.30 (m, 1H, pentitolylidene H-4), 4.05 (m, 2H, pentitolylidene H+5 + H-5′), 2.30 (s, 9H, 3 0Ac), 2.05, 1.90 ppm (2s, 3H each, 2 OAc).

6-(1,2,3,4,5-Penta-*O*-acetyl-*D*-*gluco*-pentitol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole 4:

A suspension of 3 (5 mmol) in phosphoryl chloride (10 ml) was heated under reflux for 30 min. After attaining ambient temperature, the mixture was evaporated under reduced pressure and the residue was dissolved in chloroform (30 ml), washed with a cold 10% aqueous sodium hydrogencarbonate (100 ml) and water and then dried (anhydrous sodium sulfate). Evaporation of the solvent yielded a residue was crystallized from methanol m.p. 290°C; yield: 65%. TLC ($CHCl_3$/ MeOH, 9:1), R_F = 0.55. (Found : C, 43.1; H, 5.0; N, 20.1. $C_{17}H_{22}N_6O_{10}$ requires: C, 43.4; H, 4.7; N, 19.9%). IR: 3270 (NH), 1760 (OAc), 1620 (C=N), 1560 cm^{-1} (N=N); ^{1} NMR ($CDCl_3$): δ 9.04 (s, 1H, exchangeable, NH), 6.74 (d, 1H, pentitolyl H-1) 5.90, 5.60 (2m, 1H each, pentitolyl H-2, H-3), 5.20 (m, 1H, pentitolyl H-4), 4.00 (m, 2H, pentitolyl H-5 + H-5′), 2.40 ppm (s, 15H, 5 OAc).

6-(*D*-*Gluco*-pentitol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole 5 :

A solution of 4 (5 mmol) in methanol (10 ml) was treated with a saturated solution (15 ml) of ammonium hydroxide (10 ml) and kept at ambient temperature for 24h. Evaporation of the solvents under reduced pressure gave a residue which crystallized from a methanol- water mixture. m.p .> 300 °C; yield : 68%. TLC ($CHCl_3$ /MeOH, 1:1), R_F: 0.45. (Found: C, 32.0; H, 4.8; N, 32.0. $C_7H_{12}N_6O_5$ requires: C, 32.3; H, 4.6; N, 32.3 %). IR: 3440 (OH), 3200 (NH), 1610 (C=N), 1550 cm^{-1} (N=N); ^{1}H NMR [$(CD_3)_2SO$]: δ 9.00 (s, 1H, exchangeable, NH), 5.69 (m, 1H, exchangeable, OH); pentitolyl chain protons together with the solvent absorption were gathered in a broad signal at δ 3.35 ppm.

2,3,4,5-Tetra-*O*-actylgalactaric 1,6-bis[(5-aminotetrazole)amide] 7:

A solution of 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride 6 (5 mmol) in dry benzene was added dropwise to a cold and stirred solution of 1 (5 mmol) in pyridine (5 ml) at ambient temperature. The mixture was stirred for 1.5h and the crystalline product which seperated, was filtered and recrystallized from methanol. m.p. 295 °C; yield: 65%. TLC ($CHCl_3$/MeOH, 9:1), R_F: 0.40. (Found: C, 35.9; H, 4.0; N, 31.5. $C_{16}H_{22}N_{12}O_{10}$ requires: C, 35.4; H, 4.1; N. 31.0 %). IR: 3350 (NH_2), 3275(NH), 1760 (OAc), 1680 (CON), 1620 (C=N), 1575 cm^{-1} (N=N); ^{1}H NMR [$(CD_3)_2SO$]: δ 9.10 (s, 2H, exchangeable, 2NH), 6.00 (s, 4H, exchaneable, $2NH_2$), 5.20, 5.00 (2s, 2H each, tetritolylidene H) 2.35, 2.15 ppm (2s, 6H each, 4 OAc).

1,2,3,4-Tetra-*O*-acetyl-1,4-bis (7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl)*galacto*-tetritol 8 :

A suspension of 7 (5 mmol) in phosphoryl chloride (10 ml) as described for the prepartion of 4. Crystallization from methanol. m.p. > 300 °C; yield: 55%. TLC ($CHCl_3$/MeOH, 9:1), R_F: 0.45. (Found:

C, 38.3; H, 3.2; N, 33.7. $C_{16}H_{18}N_{12}O_{8}$ requires: C, 37.9, H, 3.6; N, 33.2%). IR: 3290 (NH), 1750 (OAc), 1620 (C=N), 1570 cm^{-1} (N=N). ^{1}H NMR [$(CD_3)_2SO$]: δ 9.00 (s, 2H, exchangeable, 2NH), 5.70, 5.20 (2 s, 2H each, tetritolyl H), 2.35, 2.10 ppm. (2s, 6H each, 4 OAc).

1,4-Bis (7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl)*galacto*-tetritol 9 :

A mixture of 8 (5 mmol) and freshly prepared 0.2M sodium ethoxide solution (50 ml) in ethanol was stirred at ambient temperature for 24h. The resulting solution was stirred with Dowex- 50 cation exchange resin, H^- form) for 15 min. The resin was filtered and evaporated the solution, the separated product was filtered and crystallized form a methanol-water. m.p. > 300 °C; yield: 60%. TLC ($CHCl_3$/MeOH, 1:1), R_F : 0.40 (Found : C, 29.0; H, 2.1; N, 50.2. $C_8H_{10}N_{12}O_4$ requires: C, 28.4; H, 3.0; N, 49.7%). IR: 3500 (OH), 3300 (NH), 1600 (C=N), 1520 cm^{-1} (N=N).

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