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SYNTHESIS OF 2-DEOXY-3-0-[AMINOETHYL]-5′-0-[4,4′-DIMETHOXYTRITYL]-α-ERYTHRO-PENTOFURANOSYL-4-AMIN-2(1H)-PYRIMIDINONE NULEOSIDE

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ABSTRACT

Methyl 2-deoxy-3-0-[2-(formylamino)ethyl]-5-0-trityl-α , β -erythro-pentofuranoside 3 has been prepared. On the reaction of 3 with silylated N-isobutyryl cytosine 4, using trimethylsilyl trifluoromethane sulfonate as a catalyst. Chromatographic separation afforded 5 and 6 anomers (4% and 55% yield).On refluxing α -anomer 6 with 80% acetic acid followed by chromatographic purification gave the deprotected nucleoside 7 in 68% yield. Treatment 7 with di-p-methoxytrityl chloride in dry pyridine gave protected nucleoside 8 (61% yield). Deprotected nuleoside 2-deoxy-3-0-[aminoethyl]-5′ -0-[4,4′ -dimethoxytrityl]-α -erythro-penofuranosyl)-4-amin-2(1H)-pyrimidinone 9 was obtained in a good yield (83%) by refluxing compound 8 with sodium methoxide in methanol overnight.

INTRODUCTION

The retrovirus human immunodeficiency virus (HIV)[1] has been recognized as the etiologic agent of AIDS.[2,3] Different 2′,3′-dideoxynucleosides have turned out to be promising antiviral agents against AIDS acting as inhibitors of the retrovirus transcriptase.[4-6] The

2′,3′-dideoxynucleosides[7] of which 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxycytidine (ddC) and 3′-deoxy-3′-fluorothymidine (dFT) were most potent, but they also caused difficulties due to side effects.[8] In the case of AZT, the key toxicity which should be obviated is the suppression of bone marrow while in the case of ddC, the key toxicity is peripheral neuropathy. Therefore, it would be of interest to synthesize a new group of nucleosides to offer a chance to find compounds with less prominent side effects than those observed for AZT and ddC.[8]

DISCUSSION

Methyl 2-deoxy-3-0-[2-(formylamino)ethyl]-5-0-trityl-α,β-erythro-pentofuranoside **3** was prepared in a previous work[9] includes **1** and **2**, N-isobutyryl cytosin[10] was silylated[11] to give **4** which coupled with **3** in dry acetonitrile using trimethylsilyl trifluoromethane sulfonate (TMS triflate) as a catalyst[12]. The obtained oil product was chromatographed on silica gel to give the protected nucleosides β-anomer **5** (4% yield) and α-anomer **6** (55% yield). Removal of the trityl group on treatment **6** with boiled acetic acid (80%) for 10 mints. afforded deprotected nucleoside **7** which was chromatographed on silica gel, using CH_2Cl_2/MeOH (95:5 v/v), in 68% yield. On treatment of compound 7 with di-p-methoxytrityl chloride in dry pyridine under stirring at room temperature for 5 h and the residue was chromatographed giving protected nucleoside **8** in 61% yield. The deformylated product **9** was obtained in a good yield (83%), by refluxing compound **8** with a mixtures of sodium methoxid/methanol overnight (Scheme-1).

The assignment of the anomeric configuration in these nucleosides was made by ^{1}H-NMR spectroscopy. The H-4′ proton of the α-anomers appear downfield from that observed for β-anomers and the H-5′ signals of the α-isomer appear upfield from those observed for the β-anomer.[13-15]

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 250 spectrometer, and FAB mass spectra were recorded on varian MAT 311 A Spectrometer. Chemical shifts are given in PPM(δ) relative to tetramethylsilane for ^{1}H-NMR and relative to DMSO-d_6 (39.44 PPM) or $CDCl_3$ (76.9 PPM) for ^{13}C-NMR.

2-Deoxy-[2-(formylamino)ethyl]-5-0-(trityl)-α,β-erythro-pento-furanosyl-4-(isobutyrylamino)-2(1H)-pyrimidinone 5 and 6.

N-Isobutyryl cytosine (15.12 m mol) and ammonium sulphate (40 mg) were heated under reflux for 6 h in 50 ml of hexamethyldisilazane (clear solution was obtained after 1 h) and the solvent was removed under reduced pressure. The oily residue was dissolved in dry acetonitrile (80 ml) and compound **3** (10.8 m mol) was added. The reaction mixture was stirred and cooled to -30°C. A solution of trimethylsilyl triflat (10.8 m mol) in dry acitonitrile (20 ml) was added dropwise to the reaction mixture and stirred for 3 h at -30°C, then stirring at room temperature overnight. After complete reaction detected by TLC, the reaction mixture was diluted with methylene chloride (300 ml), washed with a cold saturated aqueous solution of $NaHCO_3$ (150 ml), cold water (3x100 ml) and dried with anhydrous Na_2SO_4. The solvent was

evaporated under reduced pressure, and the residue chromatographed on silica gel (200 gm, 0.040-0.063 mm) with CH_2Cl_2/MeOH (95:5 v/v) to give a crude mixture from α-and β-anomers in 64% yield. The mixture was separated by column chromatography on silica gel (100 gm, 0.040-0.063 mm) with CH_2Cl_2/MeOH (98:2 v/v) to give a pure compounds of **5** and **6**.

5 yield (152 mg, 4%). ^{1}H-NMR ($CDCl_3$). δ 1.18-1.20 (d, J=6.5 Hz, 6H, $2CH_3$), 2.04-2.12 (m, 1H, H-2′), 2.67-2.72 (t, J=6.4 Hz, H-2′), 3.35-3.44 (m, 6H, $2CH_2$, H-5′), 4.07-4.08 (d, J=6.1 Hz, 1H, H-4′), 6.04 (t, 1H, J=7.1 Hz, H-1′), 7.27-7.40 (m, 15H, arom.) , 8.07-8.09 (d, J=5.7 Hz, 1H, H-6) , 8.16 (s, 1H, CHO) , 9.18 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 18.87 (CH_3), 36.19 (CH), 38.66 (0-CH_2-$\underline{CH_2}$-NH-), 41.80 (C-2′), 62.94 (C-5′), 67.94 (0-$\underline{CH_2}$-CH_2-NH-), 78.56 (C-3′), 84.03 (C-1′), 86.86 (C-4′), 87.24 (Cph_3), 96.11 (C-5), 127.26, 127.85, 128.38 (arom.), 143.01 (arom.C), 143.95 (C-6), 154.83 (C-2), 162.47 (CHO), 166.11 (C-4), 177.17 (CO).
FABMS ($CHCl_3$ + NBA): m/z = 611 (M^+ + 1).

6 yield (2.3 g, 55%). ^{1}H-NMR ($CDCl_3$). δ 1.17-1.20 (d, J=6.9 Hz, 6H, $2CH_3$) , 2.36-2.42 (d, J=14.7 Hz, 1H, H-2′α) , 2.62-2.74 (m, 1H, H-2′ β), 3.20-3.25 (m, 2H, H-5′), 3.29-3.42 (m, 4H, 2xCH_2), 3.95-3.97 (d, J=4.8 Hz, H-3′), 4.58-4.59 (d, J=3.7 Hz, 1H, H-4′), 6.20-6.22 (d, J=6.3 Hz, 1H, H-1′), 7.27-7.46 (m, 15H, arom.), 7.95-7.98 (d, J=7.6 Hz, 1H, H-6), 8.06 (s, 1H, CHO), 9.54 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 18.83, 19.01 (CH_3) , 35.88 (CH) , 37.97 (0-CH_2-$\underline{CH_2}$-NH-) , 42.22 (C-2′) , 63.94 (C-5′), 67.40 (0-$\underline{CH_2}$-CH_2-NH-), 80.19 (C-3′), 86.54 (C-1′), 86.90 (C-4′), 89.07 (Cph_3), 95.92 (C-5), 127.08, 127.76,

128.39 (arom.C), 143.31 (arom.c), 144.62 (C-6), 155.10 (C-2), 161.23 (CHO), 166.11 (C-4), 177.45 (CO).
FABMS ($CHCl_3$ + NAB): m/z = 611 (M^+ + 1).

2-Deoxy-[2-(formylamino)ethyl]-α-erythro-pentofuranosyl)-4-(isobutyrylamino)-2(1H) pyrimidinone 7.

Detritylation of the α-nucleoside **6** was carried by refluxing with aqueous 80% acetic acid (5 ml) for 10 mints. The reaction mixture was left at room temperature for 3 h, the priciptated triphenylmethanol was filtered off, and the filtrat was poured onto ice-water (30 ml), then water and acetic acid were evaporated under reduced preasure. The residue was chromatographed on silica gel with CH_2Cl_2/MeOH (90:10 v/v) to give a pure compound **7**.

7 yield (878 mg, 68%). ^{1}H-NMR (DMSO-d_6). δ 1.17-1.19 (d, J=6.8 Hz, 6H, $2CH_3$), 2.29-2.35 (d, J=14.8 Hz, 1H, H-2′α), 3.35 (s, 1H, OH), 3.61-3.62 (d , J=4.6 Hz , 4H, $2CH_2$) , 4.10-4.13 (d, J=5.3 Hz, H-3′), 4.58-4.62 (t, J=4.5 Hz, 1H, H-4′), 4.81 (s, 1H, NH), 6.15-6.17 (d, J=6.1 Hz, H-1′), 7.44-7.45 (d, J=3.4 Hz, 1H, H-6), 8.15-8.17 (d, J=3.8 Hz, 1H, CHO) . ^{13}C-NMR: δ 18.55, 19.32 (CH_3), 37.41 (CH() , 39.13 (0-CH_2-$\underline{CH_2}$-NH-) , 39.23 (C-2′) , 63.75 (C-5′) , 68.41 (0-$\underline{CH_2}$-CH_2-NH-) , 81.50 (C-3′) , 89.72 (C-1′) , 90.77 (C-4′), 97.54 (C-5), 146.96 (C-6), 158.07 (C-2), 164.13 (CHO), 164.63 (C-4), 179.93 (CO). FABMS (MeOH + Glycerol): m/z = 369 (M^+ + 1).

2-Deoxy-[2-(formylamino)ethyl]-5-0-(4,4′-dimethoxytrityl)-α-erythro-pentofuranosyl-4-(isobutyrylamino)-2(1H) pyrimidinone 8.

To a suspension of pure product 7 (2.17 m mol) in dry pyridine (10 ml), di-p-methoxytritylchloride (2.24 m mol) was added. The reaction mixture was stirred at room temperature for 5 h. After the starting material disappear at TLC, 1 ml of methanol was added. The solution was concentrated to gum at low temperature under reduced pressure. The residue was chromatographed on silica gel (50 g) with CH_2Cl_2/MeOH (98:2 v/v) to give the pure compound **8**.

8 yield (885 mg, 61%). ^{1}H-NMR ($CDCl_3$). δ 1.18-1.22 (m, 6H, $2CH_3$), 2.40-2.46 (d, J=15.01 Hz, H-2′α), 2.62-2.75 (m, 3H, H-2′, H-5′),3.18-3.40 (m, 4H, $2CH_2$), 3.78 (s, 6H, OCH_3), 3.98-4.00 (d, J=4.8 Hz, 1H, H-3′), 4.58-4.60 (d, J=5.7 Hz, 1H, H-4′), 6.20-6.23 (d, J=5.9 Hz, 1H, H-1′), 6.82-6.85 (d, J=8.7 Hz, 4H, arom.H ortho), 7.27-7.46 (m, 9H, arom.H), 7.93-7.96 (d, J=7.5 Hz, 1H, H-6), 8.07 (s, 1H, CHO), 9.64 (s, 1H, NH). ^{13}C-NMR: δ 18.74, 19.53 (CH_3), 35.85 (CH), 37.96 (0-CH_2-$\underline{CH_2}$-NH-), 42.55 (C-2′), 55.00 (OCH_3), 63.80 (C-5′), 67.38 (0-$\underline{CH_2}$-CH_2-NH-), 80.28 (C-3′), 86.26 (C-1′), 86.41 (C-4′), 89.17 (DMT), 95.18 (C-5), 113.04 (arom), 126.78, 127.77, 129.74 (arom) , 135.24 (C-6) , 144.19 (arom.) , 156.01 (C-2) , 158.02 (arom.) , 165.87 (C-4), 179.53 (CO).

2-Deoxy-3-0-[aminoethyl]-5′-0′-(4,4′-dimethoxytrityl) α-erythro-pentofuranosyl) 4-amin-2(1H) pyrimidinone 9.

A stirred solution of compound **8** (1.19 m mol) in methanol (15 ml) and sodium methoxide (5.97 m mol, 5 equiv.) in methanol (5 ml) was

refluxed overnight. After cooling, the solvent was evaporated, and the crude material purified by column chromatography silica gel (50 g) with CH_2Cl_2/MeOH (95:5 v/v) to give **9**.

9 yield (566 mg, 83%). ^{1}H-NMR ($CDCl_3$). δ 2.29-2.35 (d, J=14.6 Hz, 1H, H-2α), 2.53-2.59 (m, 1H, H-2′β), 2.79 (s, 2H, CH_2), 3.14-3.18 (t, J=4.7 Hz, 2H, H-5′), 3.40 (s, 2H, CH_2), 3.76 (s, 6H, OCH_3), 3.97-3.99 (d, J=4.8 Hz, 1H, H-3′), 4.50-4.51 (d, J=3.7 Hz, 1H, H-4′), 5.75-5.78 (d, J=7.3 Hz, 1H, H-1′), 6.21-6.24 (d, J=6.4 Hz, 2H, NH_2), 6.80-6.83 (d, J=8.6 Hz, 4H, arom.H ortho), 7.58-7.61 (d, J=7.3 Hz, 1H, H-6). ^{13}C-NMR. δ 38.02 (O-CH_2-$\underline{CH_2}$-NH_2), 40.97 (C-2′), 55.08 (O-CH_3), 64.05 (C-5′), 69.62 (O-$\underline{CH_2}$-CH_2-NH_2), 80.39 (C-3′), 86.28 (C-1′), 86.40 (C-4′), 88.18 (DMT), 93.32 (C-5′), 113.12 (arom.), 126.78, 127.77, 129.87 (arom.), 135.55 (arom.), 141.30 (C-6), 144.43 (arom.), 156.09 (C-2), 158.07 (arom.), 165.78 (C-4).

ACKNOWLEDGMENT

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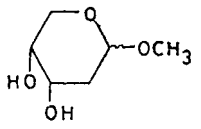

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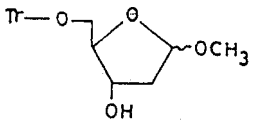

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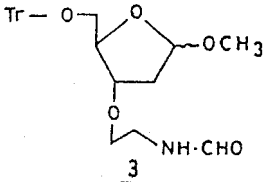

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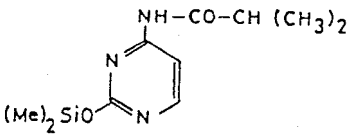

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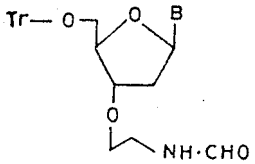

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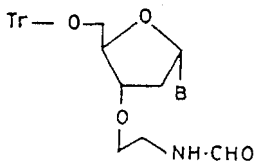

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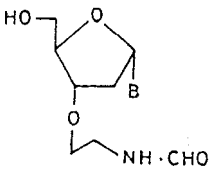

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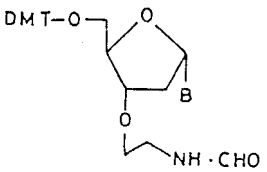

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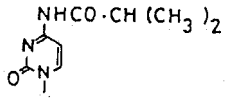

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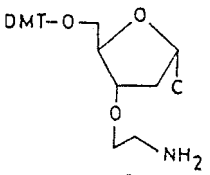

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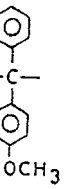

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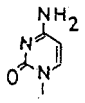

(Scheme-1)

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تخليق نيوكليوزيد ٢-دى أوكسى-[٢-إثيل أمينو]-O-o-(٤،٤ '-ثنائى ميثوكس تريتايل)-ألفا-إريثرو-بنتوفيوراندىد)-٤-أمينو-٢(١يد) بريميدينون

عبـد العليـم حسـن عبد العليـم

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ملخص البحث :

الهدف من هذا البحث هو تخليق أنواع جديدة من النيوكليوزيدات التى تحتـوى علـى السيتوزين كقاعدة جديدة تُستخدم فى تخليق بعض النيوكليوتيدات التى من المتوقـع تأثيرهـا البيولوجى ضد إلتهاب الكبد الوبائى والإيدز .

وقد تم ذلك بتفـاعل مثيـل ٢-دى أوكسـى-٣-O-[٢(فورميـل أمينـو)إثيـل]-O-o-(تريتايل)-ألفا ، بيتا-إريثرو-د-بنتوفيوراندىد) مع سيلايل السيتوزين بإستخدام ثلاثى ميثيـل سيلايل ثلاثى الفلور ليعطى المخلوط من الأيزوميرات الألفا والبيتا والتى بإستخدام العمـود الكرموتجرافى أمكن فصل الألفا-أيزومير بنسـبة ٥٥٪ والبيتـا-أيزومـير بنسـبة ٤٪ - ولـذا يفضل إستخدام الألفا-فى تحضير بعض النيوكليوتيدات الجديدة .

وقد تم إزاحة مجموعة التريتايل بتسخين الألفا-أيزومير مع حمض الخليك ٨٠٪ ثم حماية مجموعة الهيدروكسيل بمجموعة أخرى ٤،٤ '-ثنائى ميثوكس تريتـايل ليعطـى ٢-دى أوكسـى-[٢-(فورميـل أمينـو) إثيـل]-O-o-(٤،٤ '-ثنـائى ميثوكـس تريتـايل)-ألفـا-إريثرو-بنتوفيوراندىد)-٤-(أيزوبيوتيريل أمينو)-٢(١يد)-بريميدينون .

وقد أمكـن إزاحـة مجموعـة الفورميـل والأيزوبيوتـيريل بإسـتخدام ميثوكسـيد الصوديـوم والميثانول والغليان لمدة ٢٤ ساعة لنحصل على النيوكليوزيـد الحر والـذى يسـتخدم كمـادة أساسية فى تحضير النيوكليوتيدات الجديـدة . وقد تم إثبـات التركيب الكيميـائى للمركبـات بإستخدام الرنين النـووى المغناطيسـى والرنيـن النـووى المغناطيسـى للكربـون-١٣ وطيـف الكتلة لبعض المركبـات .