Sci. J. Fac. Sci. Monoufia Univ. Vol. VIII (1994).

FREE-RADICAL SYNTHESIS OF PROTECTED 3′(2-METHOXY-CARBONYLETHYL)-2′,3′-DIDEOXY-β-D-ERYTHRO-PENTO-FURANOSYL)THYMINE FOR APPLICATION IN THE SYNTHESIS OF POTENTIAL ANTIVIRAL NUCLEOSIDES.

Hamed M. Abdel-Bary

Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

ABSTRACT

β -Thymidine 1 was selectively protected at the 5′ -OH with 4-phenylbenzoyl chloride in pyridine at -20° to give 2. Treatment of 2 with sodium hydride, carbon disulphide and methyl iodide under N_2 atmosphere afforded the xanthate 3. Via free radical mechanism, 3, in the presence of α ,α ′ -azoisobutyronitrile (AIBN) as radical initiator, together with tributyltin hydride (n-Bu_3SnH) and methyl acrylate, gave 4. When 3 reacted under the same conditions with acrylonitrile, the dideoxy-β -D-thymidine derivative 5 was obtained. Compound 4 is the target compound for the preparation of diheaded nucleoside 7. All structures obtained were confirmed with ^{1}H-NMR , ^{13}C-NMR, FAB MS. EI MS spectra.

INTRODUCTION

During the last few years, interesting biological activities of several 2′,3′-dideoxy-3′-substituted nucleosides have been reported. Some compounds have inhibitory effects on retrovirus, particullarly the human immunodeficiency virus (HIV) and hence are of potential use in the therapy of AIDS[1,2]. From the great number of modified

nucleosides synthesized, it has been tried to determine structure activity relationships[3]. From these studies, the best suggestion is to modify the natural nucleosides at C-2′ and C-3′. Carbon branched substituents have been introduced at C-3′. Thus longer chains of 2′,3′-dideoxynucleosides like 3′-cyanomethyl[4] and 3′-hydroxymethyl[5] have been introduced.

Pyranosyl and Furanosyl radicals are known to react with radical acceptors like acrylonitrile, methyl acrylate in presence of n-Bu_3SnH to give C-glycosyl compounds[6,7]. Besides, similar routes have been used to introduce alkyl and allyl groups at carbon C-3′ in 2′-deoxynucleosides[8,9,10]. In this work, the author prepared nucleoside with lengthening in carbon atoms, more than two, at C-3′ hoping to increase the biological activity. Also compound **4** is the target compound for the synthesis of diheaded nucleosides.

DISCUSSION

β-Thymidine **1** reacted with 4-biphenylcarbonyl chloride in dry pyridine at -20° to give the protected nucleoside; 1-[5′-0-(4-phenylbenzoyl)-2′-deoxy-β-D-erythro-pentofuranosyl)] thymine **2** in 60% yield. The protection took place at the 5′-OH at -20°, while at 0 °C it will occur at the undesired 3′-OH position. Compound **2** when reacted with NaH and carbon disulphide, in dry xylene under N_2 atmosphere, and subsequent addition of methyl iodide, gave the xanthate **3**. The structural assignment of **3** was based on NMR spectra; ^{1}H-NMR spectrum shows a signal at 2.62 ppm corresponding to SCH_3 group-^{13}C-NMR shows bands at δ = 18.6 ppm (SCH_3) and 214.5 ppm (C=S), (c.f. Experimental). FAB MS of **3** shows: m/z = 513 ($M + H^+$), (Chart 1).

Compound **3** characterized by having a xanthate group (-$OCSSCH_3$) at C-3′, which is a good leaving group. Thus, **3**, in the presence of the radical initiator α,α′-azoisobutyronitrile (AIBN) together with tributyltin hydride (n-Bu_3SnH), as a source of hydrogen radical; generates the 3′-ribosyl-thymine radical, under nitrogen atmosphere. Subsequent reaction with methyl acrylate; which is used as radical acceptor afforded **4** in 29% yield. This is in accordance with that previously reported[11]. The structure of **4** was confirmed by NMR-spectra. ^{1}H-NMR spectrum, shows the absence of band characteristic for -SCH_3 (δ = 2.62 ppm) and the presence of signals at δ = 2.14-2.53 ppm as multiplit corresponding to 2′-H, 3′-H, 1″-H and 2″-H protons (Scheme-1), besides the signal δ = 3.59 ppm as singlet of -$COOCH_3$ (methyl ester group). In ^{13}C-NMR spectrum - the signals at δ = 18.6 ppm (SCH_3) and 214.5 ppm (C=S) disappeared, while signals (in ppm) at 26.58 (C-1″), 38.86 (C-2″), 51.42 (OCH_3) and 172.96 (CO-ester) are present to prove the proposed structure **4**. Also FAB MS determination shows m/z = 493 ($M + H^+$). When the author used acrylonitrile, as radical acceptor, to react with the xanthate **3**, under the same conditions using AIBN and n-Bu_3SnH in N_2 atmosphere, 2′,3′-dideoxy-β-D-thymidine derivative **5** was obtained. The structure of **5** was deduced from ^{1}H-NMR, ^{13}C-NMR and FAB MS spectra (c.f. Experimental). One can explain this by the fact that the methyl acrylate as radical acceptor is more faster than that the formed acrylonitrile one. Thus, in case of formation of **5**, hydrogen radical attacks the ribosyl-radical at C-3′, before the attack of acrylonitrile radical, which afforded the 2′,3′-dideoxy-derivative **5**. The author thinks that the aim of this work was fulfilled, because of the synthesis of **4**, the target compound for coupling with 5′-amino-β-D-thymidine[12] in a following work, later

on, to get the diheaded nucleoside **7** and its analogues for their evaluation against HIV.

EXPERIMENTAL

Treated dry solvents were used. All solvents for coloumn chromatography were used after distillation. Analytical TLC plates 60 F_{254} and silica gel (230-400 mesh) were purchased from Merck. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 250 FT NMR Spectrometer at 250 MHz for ^{13}C-NMR. EI mass spectra were obtained on Varian MAT 311 A Spectrometer.

1-[5′-0-(4-Phenylbenzoyl)-2′-deoxy-β-D-erythropentofuranosyl]-thymine (2):

4-Biphenylcarbonyl chloride (4.76 g, 0.022 mol) was added in small portions to a stirred solution of β-thymidine **1** (4.84 g, 0.02 mol) in dry pyridine (50 ml) at -20°. Stirring was continued for 4 h at -5°C. The reaction mixture was poured onto crushed ice with stirring. A white precipitate was formed, filtered off, washed several times with water. The obtained solid was triturated three times with $NaHCO_3$ solution. The solid product was chromatographed on silica gel with $CH_3OH/CHCl_3$ (1:5, v/v) to give compound **2**.

2: Yield 5.1 g (60%) - M.p. 220°C - ^{1}H-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 1.64 (s, 3H, CH_3), 2.24 (m, 2H, 2′-H), 4.12 (d, 1H, J = 3.7 Hz, 4′,-H), 4.48 (d, 2H, J = 5.0, 5.3, Hz, 5′-H), 4.61 (d, 1H, J = 3.4, 3.5 Hz, 3′-H), 5.50 (d, 1H, J = 3.7 Hz, 3′-OH), 6.26 (t, 1H, J = 6.8, 6.7 Hz, 1′-H), 7.43 (m, 4H, arom. H), 7.73 (d, 2H, J = 14.1 Hz, arom. H), 7.83 (d, 2H, J = 8.2 Hz, arom. + 6-H), 8.08 (d, 2H, J = 8.1

Hz, arom. H), 11.3 (s, 1H, NH)- ^{13}C-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 11.75 (CH_3), 38.72 (C-2′), 64.29 (C-5′), 70.22 (C-3′), 83.62 (C-1′), 83.853 (C-4′), 109.665 (C-5), 126.85, 126.89, 128.10, 128.30, 128.95, 129.75, 138.68, 144.84 (biphenyl), 135.52 (C-6), 150.27 (C-2), 163.48 (C-4), 165.3 (CO). FAB MS (DMSO 1% AcOH + 3-nitrobenzyl alcohol): m/z: 423 ($M + H^+$). EI MS: m/z (%) = 422 (M^+, 5). (Chart-1).

1-[5′-0-(4-Phenylbenzoyl)-3′-0-(methylthio)thiocarbonyl-2′,3′-dideoxy-β-D-erythropentofuranosyl) thymine (3):

To a solution of 5′-0-(4-phenylbenzoyl)-β-D-thymidine **2** (4.2 g; 0.01 mol) in dry tetrahydrofuran (500 ml) and CS_2 (1.5 ml, 0.25 mol); under N_2 atmosphere; was added sodium hydride (50%, dispersion, 1 g; 0.02 mol) in small portions. The addition takes about 1 h. The reaction mixture was stirred for 3 h, at room temperature. CH_3I (1.3 ml; 0.02 mol) was aded in one portion. After additional 2 h, the reaction mixture was quenched with acetic acid (0.5 ml). After 20 minutes the reaction mixture was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, filtered, washed with $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and the filtrate was evaporated under vacuo and subjected to coloumn chromatography, using silica gel, with Ether/Pet-ether (60-80) (1:1, v/v) to give **3**.

3: Yield 2.2 g (43%) - M.p. 140° - ^{1}H-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 1.64 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 2.66 (m, 2H, 2′-H), 4.59 (s, 1H, 4′-H), 4.65 (d, 2H, J = 6.2 Hz, 5′-H), 6.15 (d, 1H, J = 3.4 Hz, 3′-H), 6.28 (t, 1H, J = 6.7 Hz, 1′-H), 7.49 (m, 4H, arom.-H), 7.73 (m, 4H, arom.-H + 6-H), 8.08 (d, 2H, J = 7.8 Hz, arom.-H), 11.33 (s, 1H, N-H). ^{13}C-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 11.72 (CH_3).

18.6 (SCH_3) , 35.77 (C-2′) , 64.02 (C-5′), 80.65 (C-3′), 83.19 (C-1′), 84.51 (C-4′), 109.87 (C-5), 126.86, 127.89, 127.90, 128.30, 128.94, 129.80, 138.65, 144.92 (arom.C, biphenyl), 135.40 (C-6), 150.22 (C-2), 163.41 (C-4), 165.16 (C=O), 214.5 (C=S). FAB MS (DMSO + 1% AcOH + 3-nitrobenzyl alcohol): m/z = 513 ($M + H^+$), (Chart-1).

1-[5′-0-(4-Phenylbenzoyl)-3′-(2″-methoxycarbonylethyl)-2′,3′-dideoxy-β-D-erythropentofuranosyl) thymine (4):

A solution of **3** (2.56 g, 0.005 mol) and freshly distilled methyl acrylate (4.3 ml, 0.05 mol) in dry xylene (50 ml) was heated to 80-90° C under nitrogen atmosphere. A solution of tributyltin hydride (2 ml, 0.0086 mol) and AIBN (80 mg, 0.0003 mol) in dry xylene (20 ml) was added dropwise during 1 h at 90°C, under N_2 atmosphere. The mixture was heated further for 4 h and the solvent was then removed under reduced pressure. The crude product was purified by flash chromatography. Elution with pet-ether (60-80°C) (1.5 L) to remove excess AIBN and Bu_3SnH reagents.The product was then eluated with CH_3OH/CH_2Cl_2 (1:5, v/v) to give **4**.

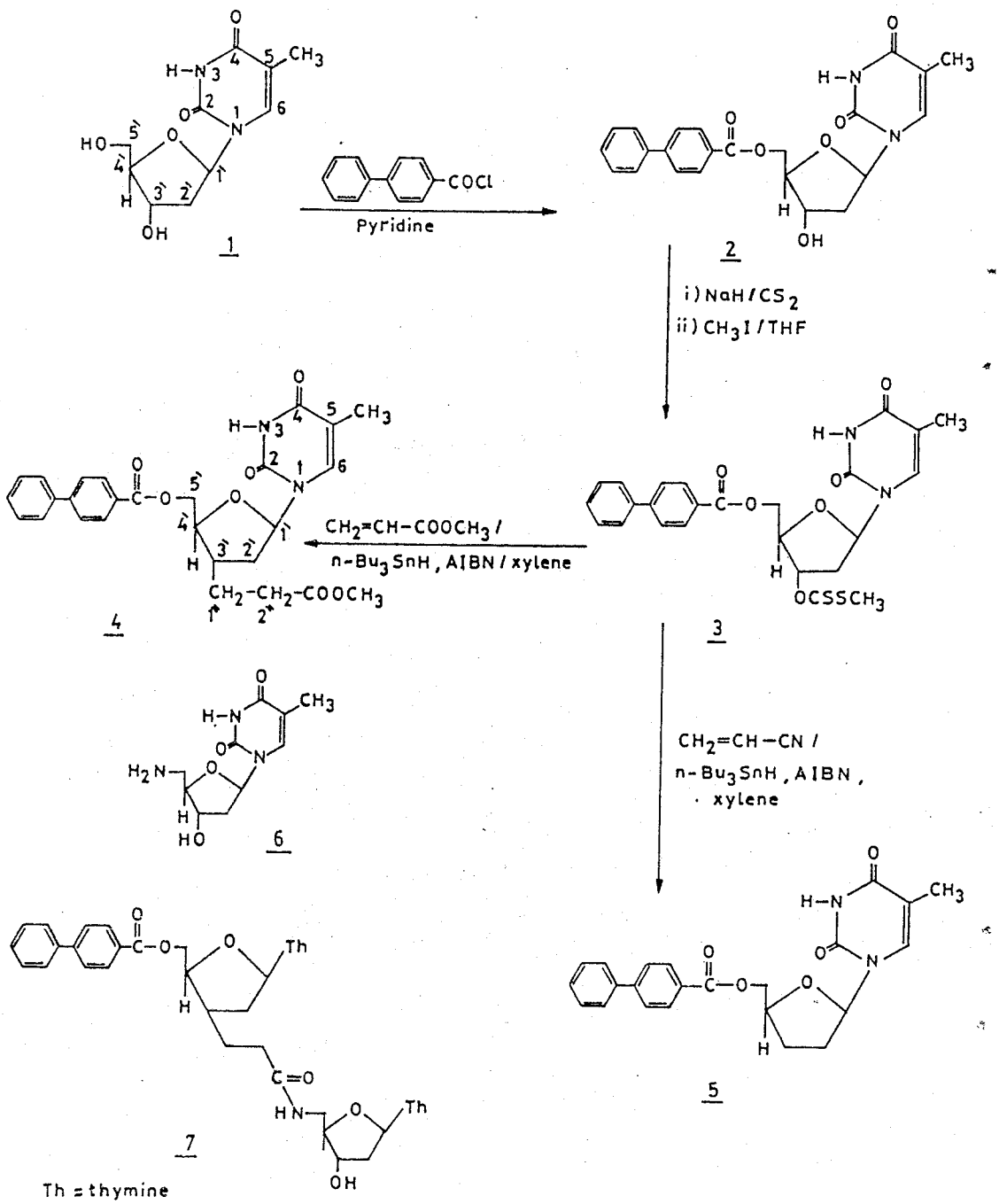
4: Yield 0.71 g (29%) - foam - ^{1}H-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 1.62 (s, 3H, CH_3), 2.14-2.53 (m, 7H, 2′-H, 3′-H, 1″-H, 2″-H), 3.59 (s, 3H, OCH_3), 4.48 (s, 1H, 4′-H), 4.63 (d, 2H, J = 6.7 Hz, 5′-H), 6.18 (t, 1H, J = 6.7 Hz, 1′-H), 7.48 (m, 4H, arom.-H), 7.79 (m, 4H, arom.-H + 6H), 8.06 (d, 2H, J = 7.8 Hz, arom.-H), 11.27 (s. 1H, NH). ^{13}C-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 11.89 (CH_3), 26.58 (C-1″), 33.66 (C-2′), 38.86 (C-2″), 51.42 (OCH_3), 64.29 (C-5′), 82.26 (C-1′), 83.94 (C-4′), 109.34 (C-5), 126.85, 127.79, 127.95, 128.24, 129.04, 129.78, 138.71, 144.81 (arom.-C, biphenyl), 135.51 (C-6), 150.20 (C-2), 163.52 (C-4), 165.30 (CO-thymine), 172.96 (CO-ester). FAB MS

(DMSO + 1% AcOH + 3-nitrobenzyl alcohol): m/z = 493 ($M + H^+$).

2′,3′-Dideoxy-5′-0-(4-phenylbenzoyl) thymidine (5):

A solution of **3** (2.56 g, 0.005 mol) and freshly distilled acrylonitrile (3.3 ml, 0.05 mol) in dry xylene (50 ml) was heated to 90° C under N_2 atmosphere. A solution of n-Bu_3SnH (2 ml, 0.0086 mol) and AIBN (80 mg, 0.0003 mol) in dry xylene (20 ml) was added dropwise during 1 h at 90°C. The reaction mixture was heated further 4 h. The solvent was then removed under reduced pressure. The residue was subjected to flash chromatography, elution with pet-ether (60-80) (1.5 L) and eluated with Ether/Pet-ether (2:8, v/v) to obtain **5**.

5: Yield 0.44 g (22%) - foam - ^{1}H-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 1.62 (s, 3H, CH_3) , 1.91-2.12 (m, 4H, 2′-H and 3′-H) , 4.41 (dd, 1H, J = 11.3 and 7.4 Hz , 5′-H), 4.52 (m, 2H, 4′-H and 5′-H), 5.09 (d,1H, J =4.2 Hz, 1′-H), 7.47 (m, 4H, arom.-H), 7.69 (d, 2H, J = 7.2 Hz, arom.-H and 6-H), 8.06 (d, 2H, J = 7.7 Hz, arom.-H), 11.31 (s, 1H, N-H). ^{13}C-NMR [$(D)_6$ DMSO/TMS]: δ (ppm) = 11.78 (CH_3) , 25.74 (C-3′), 34.85 (C-2′), 65.13 (C-5′), 82.91 (C-1′), 84.42 (C-4′), 109.78 (C-5),126.79, 127.84, 127.93, 128.29, 128.89, 129.76, 138.58, 144.85 (arom. C-biphenyl), 135.29 (C-6), 150.51 (C-2), 163.29 (C-4), 166.02 (CO). FAB MS (DMSO + 1% AcOH + 3-nitrobenzyl alcohol): m/z = 407 ($M + H^+$).


1
COCl
Pyridine
2
i) NaH / CS2
ii) CH3I / THF
3
CH2=CH-COOCH3 /
n-Bu3SnH, AIBN / xylene
4
CH2=CH-CN /
n-Bu3SnH, AIBN,
xylene
5
6
7
Th = thymine

Scheme-1

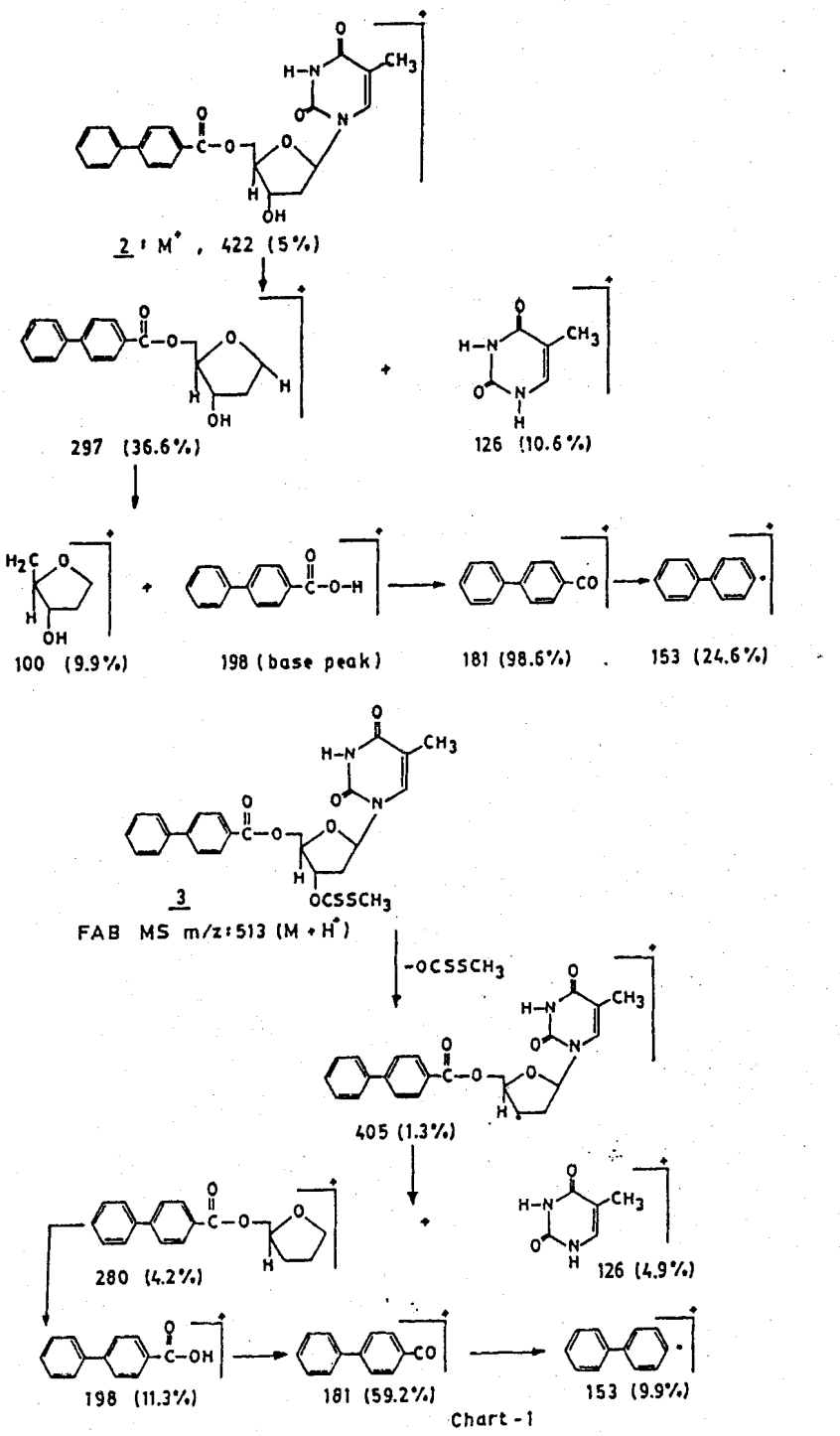

2 : M+ , 422 (5%)
297 (36.6%)
126 (10.6%)
100 (9.9%)
198 (base peak)
181 (98.6%)
153 (24.6%)
3
OCSSCH3
FAB MS m/z:513 (M + H+)
-OCSSCH3
405 (1.3%)
280 (4.2%)
126 (4.9%)
198 (11.3%)
181 (59.2%)
153 (9.9%)

Chart - 1

ACKNOWLEDGEMENT

DANIDA, and Danish Ministry of Foreign Affairs are gratefully acknowledged for their support to carry out this work at Odense University.

REFERENCES

1- T.S. Lin, M.S. Chen, C. McLaren, Y.S. Gao, I. Ghazzouli and W.H. Prusoff, J. Med. Chem., **30**, 440 (1987).

2- P. Herdewijin, J. Balazarini, E. De Clerq, R. Pauwels, M. Baba, S. Broder and H. Vanderhaeghe, J. Med. Chem., **30**, 1270 (1987).

3- E. De Clerq, A. Van Aerschot, P. Herdewijin, M. Baba, R. Pauwels, and J. Balzarini, Nucleosides & Nucleotides, **8**, 659 (1989).

4- T. Halmos, R. Montserret and K. Antonakis, Nucleic Acids Research, **17**, 7663 (1989).

5- E.M. Acton, R.N. Boerner, H.S. Uh, K.J. Ryan. and D.W. Henry, J. Med. Chem., **22**, 518 (1979).

6- B. Giese, J. Dupuis, M. Leising, M. Nix and H.J. Linder, Carbohyd. Res., **171**, 329 (1987).

7- B. Giese, Angew. Chem., **101**, 993 (1989).

8- E.M. Acton, R.N. Boerner, H.S. Uh, K.J. Ryan. and D.W. Henry, J. Med. Chem., **22**, 518 (1979).

9- C.K. Chu, B. Doboszewski, W. Schmidt, and G.V. Ullas, J. Org. Chem., **54**, 2767 (1989).

10- K. Agyei-Aye and D.C. Baker, Carbohyd. Res., **183**, 261 (1988).

11- J. Lau, K. Walczak, K. Pupek, C. Buch, C.M. Nielsen and E.B. Pedersen, Arch. Pharm., **324**, 953 (1991).

12- W.S. Mungall, G.I. Greene, G.A. Heavner and R.L. Letsinger, J. Org. Chem., **40**(11), 1659, (1975).

تخليق ٣ ′-(٢-ميثوكسى كربونيل إيثيل)-٢ ′-٣ ′-ثنائى دى أكسى بيتا-د-إريثرو-بنتوفيورانوزيل) ثايمين المحمى بتفاعلات الشق الطليق - لتطبيقها فى تخليق النيوكليوزيدات ضد الإلتهاب الكبدى الوبائى

حامد محمد عبد البارى

قسم الكيمياء - كلية العلوم - جامعة المنوفية - شبين الكوم - ج.م.ع

ملخص البحث :

تم حماية بيتا-ثيميدين (١) بتفاعلها مع ٤-فينيل بنزويل كلوريد فى البيريدين عند درجة حرارة -٢٠ °م ليعطى مركب (٢) حيث تمت على ذرة هيدروجين مجموعة الهيدروكسيل فى ذرة الكربون رقم ٥ ′. معالجة (٢) بهيدريد الصوديوم ، ثانى كبريتيد الكربون ويوديد الميثيل فى جو من النيتروجين أنتج الزانثات (٣) . بميكانيكية تفاعلات الشق الطليق - تفاعل المركب (٣) مع ألفا ، ألفا-آزو أيزوبيوتيرو نتريل (كمادة منشطة للطليق) ، تراى بيوتيل قصدير الهيدريد وإستر أكريلات الميثيل ليعطى المركب (٤) . عند تفاعل المركب (٣) مع نتريل الأكريليل فى نفس الظروف السابقة - تم الحصول على ثنائى دى إكسى-بيتا-د-ثايميدين (٥) - التركيب (٤) يُعتبر هو الهدف أو المركب المرغوب فيه لإستخدامه فى تخليق النيوكليوزيدات ذات الرأسين (المخلبين) (٧) . تم إثبات جميع المركبات الناتجة بأطياف البروتون النووى المغناطيسى وذرة الكربون (١٣) وطيف الكتلة .