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Synthesis Of Nucleosides Analogues Substituted With Oxy Amino Acetylenic Derivatives

Hala M. AL-Zahawyi*

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Abstract

This work describes the synthesis of 5-(5'-(4-disubstituted amino-butyn-2-yl)oxy-b-D-ribofuranose) uracil.

For the synthesis of these compounds, 5-(b-D-ribofuranose) uracil was converted to its 5-(2',3'-O-isopropylidene-b-D-ribofuranose) uracil (1), it contains the free hydroxyl group at C-5 for the required chemical modification. Accordingly (1) was prepared from 5-(b-D-ribofuranose) uracil and acetone using anhydrous ferric chloride ($FeCl_3$) as Lewis acid catalyst. The treatment of (1) with propargyl bromide in benzene in a phase transfer conditions in presence of tetrabutyl amonium bromide and 2% sodium hydroxide solution yielded acetylenic ether derivative 5-(2',3'-O-isopropylidene-5'-(propyn-2-yl) oxy-b-D-ribofuranose) uracil (2), which was subjected to Mannich reaction with secondary aliphatic amines and paraformaldehyde to give the acetylenic amino oxy derivatives (3a-f). The treatment of (3a-f) with sulfuric acid at room temperature affected selectively the removal of acetal group at 2',3'-position giving (4a-f) in good yield.

The aim of the present work is the preparation of new carbohydrate derivatives containing acetylenic amines soluble in water, which possess a possible biological activity.

Keyword: Nudeosides analogues, Amino acetylenic

تكوين أشباه النيوكلوسيدات معوضة بمشتقات اوكسي امينو استيلينية

الخلاصة

تضمن هذا البحث تحضير ٥-(٥'-(٤-ثنائي التعويض بيوتاين-٢-يل)-اوكسي-b-D-رايبوفيورانوز) يوراسيل.

للحصول على هذه المشتقات تطلب تحضير ٥-(٢',٣'-O-ايزوبروبليدين-b-D-رايبوفيورانوز) يوراسيل (1)، حيث تحوي على مجموعة هيدروكسيل حرة في موقع ذرة كاربون-٥' ، ويمكن الحصول على (1) بسهولة من تفاعل ٥-b-D-رايبوفيورانوز يوراسيل مع الاسيتون الجاف وبوجود كلوريد الحديد. بعد ذلك تمت مفاعلة مشتق الايزوبروبليدين (1) مع بروميد البروبارجيل في البنزين وبظروف الانتقال الطوري المحفز ببروميد رباعي بيوتيل امونيوم وبوجود محلول ٢% هيدروكسيد الصوديوم تكون المشتق الاستيليني ٥-(٢',٣'-O-ايزوبروبليدين-٥-(بروباين-٢-يل)اوكسي-b-D-رايبوفيورانوز) يوراسيل (2). وقد أجريت بعد ذلك تفاعل مانش مع كل من ثنائي اثيل امين، ثنائي بيوتيل امين، ٣-مثيل ببرازين، ببرازين، بريدين ومورفلين تم الحصول على مشتقات الاوكسي امينو استيلينية ليوريدين (3a-f). بعد ذلك تمت معاملة (3a-f) مع حامض الكبريتيك في درجة حرارة الغرفة الذي أدى إلى تحلل مجموعة الاستايل في موقع ٢',٣' وإعطاء اشباه النيوكلوسيدات المعوضة بمشتقات اوكسي امينو استيلينية (4a-f).

* Department of Chemical Engineering/ University of Technology, Baghdad/Iraq

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2412-0758/University of Technology-Iraq, Baghdad, Iraq

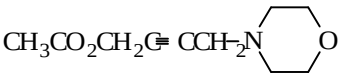
إن الهدف من تحضير هذه المشتقات هو الحصول على مشتقات كاربوهيدراتية جديدة تحتـــوي على امينات استيلينية سهلة الذوبان في الماء ومن المحتمل أن تمتلك هذه المشـــتقات فعاليـــة بايولوجية.

Introduction

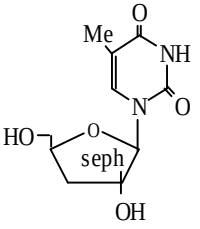
Carbohydrates and carbohydrate - containing structural moieties are usually involved in active biochemical and bioorganic processes (1).

Acetylenic amines having the general formula $\left(RCH_2C \equiv CCH_2R\right)$ have been used in Parkinson disease treatment. It has been shown that 1-acetoxy-2-butynyl trimethyl amonium iodide has strong parasymphathetic activity (2).

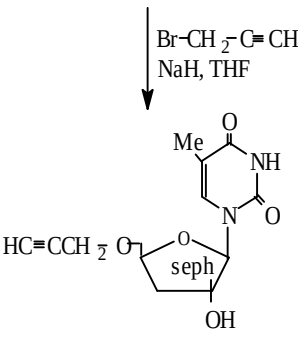
The butyne moity was, also found to be of great importance in the new generation of anti-cancer drugs (3,4), such as for example, N-(4-morpholino-2-butynyl) acetate.



Chemical modification of naturally occurring nucleoside has been of interest



(1)

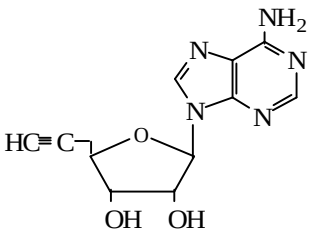


(2)

for over 30 years and numerous nucleoside analogous were synthesized in order to selectively interfere with DNA and RNA. The structural modification involves either the hetrocyclic ring or the sugar moiety (5).

Carbohydrate acetylenic ether has also been prepared. Treatment of the nucleoside (1) with the propargyl bromide in the presence of sodium hydride in (THF) at room temperature afforded the acetylenic ether derivative (2) in 89% yield (6).

The acetylenic analogue of adenosine 9-(5,6-dideoxy-β-*D*-ribo-hex-5'-ynofuranosyl) adenine (3) has been synthesized recently, and its behavior as inhibitor of bovine-S-adenosylhomocystei-ne hydrolase has been examined (7).



(3)

Several 1- (2-substituted-2-deoxy-β-*D*-arabino - furanosyl) pyrimidine nucleosides have shown anti-tumor (8) and / or antiviral activities (9).

Most of the known acetylenic amines possess low solubility in water. Therefore, in the present work , efforts have been directed toward the synthesis of new class of acetylenic amines; carbohydrate acetylenic derivatives start from uridine, such derivatives are expected to possess high solubility in water.

Experimental

Melting points were determined with a Gallen – Kamp apparatus and we uncorrected. IR spectra (KBr disc or liquid smear) were recorded on a Pye - Unicam SP3-100 and SP3-300 spectrophotometers. ^{1}HNMR spectra were taken in Mosul University with Hitachi - Perkin - Elmer 60A, R-24B spectrophotometer, using deuterated chloroform as solvent and tetramethyl Silane as internal standard. Microanalysis was performed by Oil Exploring Company, Baghdad, Iraq. Thin layer chromatography was performed with aluminum sheets protected with silica - gel F254 supplied by Merck under trade name Al-Sil G, UV spots were detected with iodine vapur.

5-(2',3'-O-isopropylidene-5'-(propyn -2-yl)oxy-b-*D*-ribofuranose) uracil (2):

To 5-(2',3'-O-isopropylidene-β -*D*-ribofuranosyl) uracil [10] (1) (2 gm, 10 mmol) in benzene (50 ml) was added drop-wise propargyl bromide (1.2 gm, 10 mmol) and resulting mixture was stirred in presence of (0.6 M) sodium hydroxide (0.1 gm) for 18 hrs at room temperature. The aqueous phase was then separated and extracted with benzene (3×20 ml).

The combined organic layers were dried (magnesium sulphate) and evaporated to afford a syrup which was purified on a silica-column eluted with benzene.

Compound (2) was obtained as a colourless syrup (1.3 gm, 65%), IR (film) 3210 cm^{-1} ($C \equiv CH$), 2145 cm^{-1} ($C \equiv C$), ^{1}HNMR (see table 2). Anal. for $C_{15}H_{18}N_2O_6$:

Calc. C 55.9 H 5.59 N 8.7
Found C 55.7 H 5.56 N 8.43

General Method for the Mannich Reactions:

To a mixture of (2) (10 mmol), paraformaldehyde was added portionwise, followed by appropriate secondary amine (10 mmol) and cuprous chloride (0.12 gm). The resulting mixture was heated under reflux with stirring for 5 hrs. The reaction mixture was cooled, filtered and the filtrate was poured on to cold water (100 ml). The solid residue was filtered, dried and purified by column chromatography, the spectral data are given in tables 1, 2 and 3.

Acid Hydrolysis of (3):

D 25 N H_2SO_4 (25 ml) was added to (3) (10 mmol) in methanol (25 ml) and the mixture was stirred for 7 hrs at room temperature. Neutralized with Amberlite IR-400. Removal of solvent, repeated extraction of the residue with ethyl acetate, evaporation of the extract and drying the residue over P_2O_5 gave (4a) in 89% yield as chromatographically uniform compound.

The same method was used for the synthesis of (4b-f).

Results and Discussion:

For the synthesis of these type of the acetylenic nucleoside derivatives, 5-(β-*D*-ribofuranose) uracil was first converted to its 5-(2',3'-*O*-isopropylidene-β-*D*-ribofura-nose) uracil (1).

Acetals are stable toward alkaline condition but are readily hydrolysed by dilute acids, as groups at C-2', C-3'

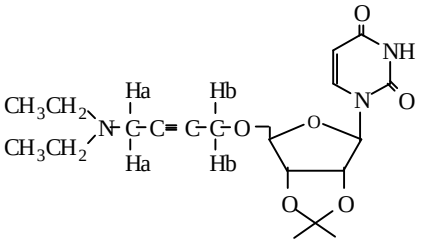
and leaving the hydroxyl group at C-5' free for the required chemical modification. A number of methods using different acid catalysts are available for the isopropylidene derivative of uridine.
These include ferric chloride (9), sulfuric acid and copper sulfate(11). Accordingly,5-(2',3'-*O*-isopropylidene -β-*D*-ribofuranosyl) uracil (1) was prepared from uridine and acetone using anhydrous ferric chloride ($FeCl_3$) as Lewis acid catalyst (12). This method was chosen because it gives (1) in good yield and high purity.

The reaction of 5-(2',3'-*O*-isopropylidene-β-*D*-ribofuranosyl) uracil (1) with propargyl bromide in benzene under phase transfer condition using tetrabutyl ammonium bromide and 2% sodium hydroxide solution for 18 hrs gave 5-(2',3'-*O*-isopropylidene-5'-(propyn-2-yl) oxy-β-*D*-ribofuranose) uracil (2) in 76% yield. The propargyl ether nucleoside derivative (2) shows in the IR spectrum the characteristic ($C \equiv C$) and ($C \equiv CH$) band at 2145 and 3210 cm^{-1} respectively (see figure 1).

The terminal propargyl ether nucleoside derivative (2) reacted with diethyl amine and cuprous chloride as catalyst in dioxan as solvent afforded the expected acetylenic amine derivative (3a). Similarly the reaction of (2) with dibutyl amine, 3-methyl piprazine, piperidine, piprazine and morpholine gave (3b), (3c), (3d), (3e) and (3f) respectively in good yields. Table (1) shows the physical properties and elemental analyses for the prepared (3). These derivatives were purified on a silica-gel column chromatography with 1:3 (V/V) ethyl acetate-hexane as eluent. They are characterized by spectroscopic methods. The IR spectra are showed in table (2).

The n.m.r. spectra of compound (3a) shows poorly resolved triplet at δ 3.2 ppm assigned to H-a proton; triplet at δ 4.2 ppm for H-b protons, the H-1 proton appeared as a doublet at δ 2.8 ppm, H-4 always appears as a quartet at δ 4.5 ppm, while the doublet at δ 3.65 ppm were assigned to the H-5 proton. A multiplet at δ 4.2 ppm integrated for 2H is due for H-2 and H-3 protons, a quartet at δ 2.38 ppm for the methylene of diethyl group whereas the methyl protons appeared overlapped with the signals for the methyl protons of the isopropylidene rings at δ 1.2-1.43 ppm (see Table 3).

To increase the solubility of the prepared acetylenic ether nucleoside derivatives (3a-f), treatment of (3a) with sulfuric acid at room temperature for 6 hrs affected selectively the removal of acetal group at 2',3'-position giving (4a) in good yield. This derivative is characterized by its IR spectrum which shows a distinguished hydroxyl stretching band at 3250 cm-1, Table (2) and n.m.r., Table (3).



(3a)

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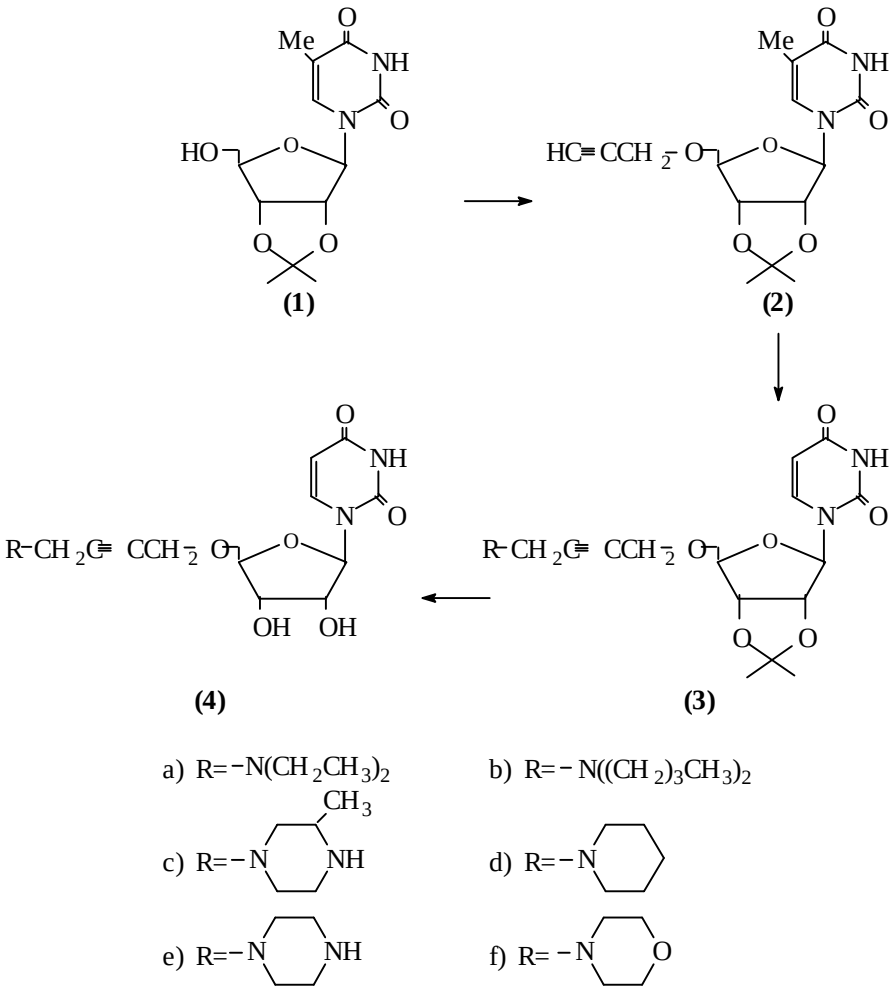
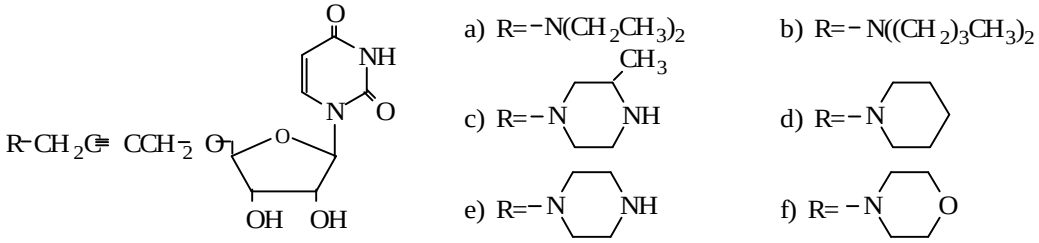


Scheme: Synthesis of Nucleosides Analogues Substituted with Oxy Amino Acetylenic Derivatives

Table (1): Physical Properties for Compounds (4a-f)



S: syrup

No. Comp.	Name of compounds	Melting point	Percentage (%)	Molecular formula	The C.H.N. analysis		
					C%	H%	N%
4a	5-(5' (4-N,N-diethylamino-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	168-169°	72.15	$C_{17}H_{25}O_6N_3$	Calc. 66.53 Found 66.29	Calc. 5.13 Found 4.99	Calc. 8.62 Found 8.31
4b	5-(5' (4-N,N-dibutylamino-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	S	66.45	$C_{21}H_{33}O_6N_3$	Calc.59.57 Found 59.40	Calc. 7.80 Found 7.91	Calc. 9.93 Found 9.79
4c	5-(5' (4-(3-methylpiprazino-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	144-145°	59.33	$C_{18}H_{26}O_6N_4$	Calc. 54.82 Found 54.95	Calc. 6.60 Found 6.29	Calc. 14.21 Found 14.13
4d	5-(5' (4-piperidino-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	160-161°	55.42	$C_{18}H_{25}O_6N_3$	Calc. 56.99 Found 56.78	Calc. 6.60 Found 6.41	Calc. 11.08 Found 10.93
4e	5-(5' (4-piprazino-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	178-179°	67.12	$C_{17}H_{24}O_6N_4$	Calc. 53.68 Found 53.41	Calc. 6.32 Found 6.22	Calc. 14.74 Found 14.85
4f	5-(5' (4-morpholeno-butyn-2'-yl)oxy-5'-deoxy)-β-*D*-ribofuranose uracil	S	56.5	$C_{17}H_{23}O_7N_3$	Calc. 53.43 Found 53.52	Calc. 6.04 Found 6.19	Calc. 11.02 Found 10.21

Table (2): IR spectral data

Comp. No.	$\nu_{max}(O-H)cm^{-1}$	$\nu_{max}(C\equiv C)cm^{-1}$	$\nu_{max}(C\equiv CH)cm^{-1}$	$\nu_{max}(C-N)cm^{-1}$	$\nu_{max}(C=O)cm^{-1}$	$\nu_{max}(N-H)cm^{-1}$
1	3450	-	-	1450	1730	3460
2	-	2145	3210	1422	1710	3465
3a	-	2115	-	1470	1700	3465
3c	-	2160	-	1435	1690	3460
3d	-	2155	-	1420	1690	3450
3f	-	2110	-	1445	1720	3460
4a	3410	2130	-	1455	1680	3460
4d	3480	2135	-	1425	1725	3470
4e	3455	2125	-	1460	1710	3465
4f	3390	2150	-	1440	1715	3450

Table (3): HNMR spectral data

Comp. No.	N.M.R. data ppm (d)				Remarks
	H-1	H-2, H-3	H-4	H-5	
2	2.90 (d, 1H)	4.50 (m, 2H)	4.60 (q, 1H)	3.50 (d, 2H)	(1.10-1.35) m for isopropylidene rings, 2-45(t, 1H) for the acetylenic proton (H-a), 4.25 (d, 2H) for methylene protons H-b
3a	2.80 (d, 1H)	4.20 (m, 2H)	4.50 (q, 1H)	3.65 (d, 2H)	3.2 (t, 2H) for H-a, 4.24 (t, 2H) for H-b, 2.38 (q, 4H) for $(CH_2)_2$ of diethyl group, $(CH_3)_2$ of diethyl group appeared overlapped with isopropylidene ring protons at 1.22-1.43 (m)

d = doublet m = multiplate q = quartet

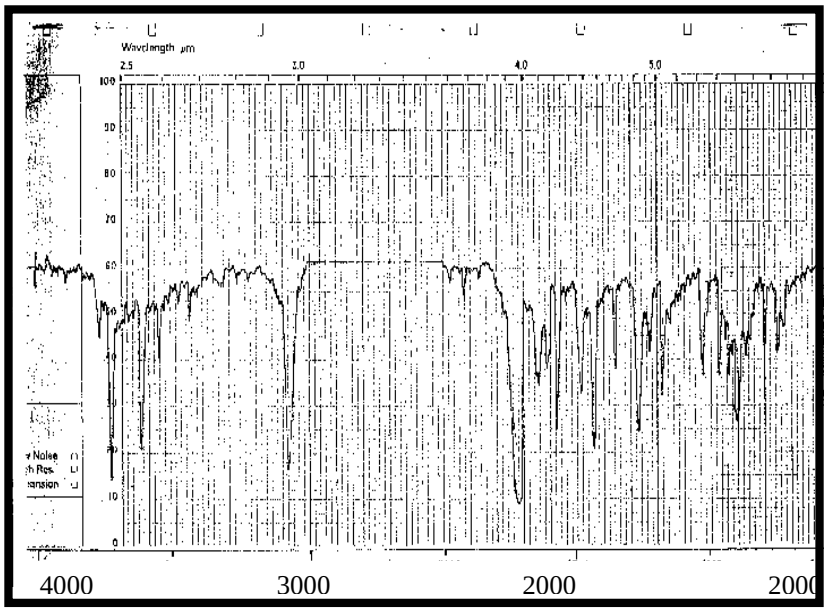


Figure (1): IR spectrum of compound (2)

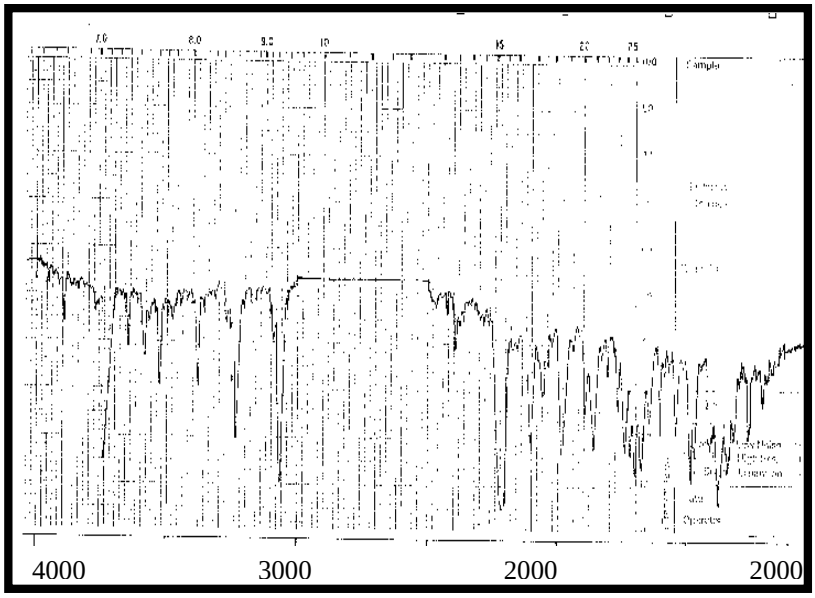


Figure (2): IR spectrum of compound (3a)