Synthesis and Identification of Chiral open-chain sugar-derived nitrones and their 1,3-Dipolar Cycloaddition with maleimide and maleic acid

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ABSTRACT

The chiral open-chain sugar-derived nitrones (a,b) were prepared in a pure form. N-Sugar-derived isoxazolidines (2a,b-3a,b)) were synthesized regiospecifically by 1,3-dipolar cycloaddition reaction of a nitrone (a,b) with maleimide and maleic acid. N-sugar-derived isoxazolidine (3a) showed high activity against staphylococcus aurous, and Escherichia coli and complete inhibition of growth against pathogenic fungi candida albicans and microsporum gypseum

Keywords: sugar-derived nitrones, 1,3-dipolar cycloaddition , N-sugar-derived isoxazolidines .

Introduction

Many natural and synthetic products containing heterocyclic rings were reported to possess varied pharmacological activities . [(1-4)] Many of these biological activities were attributed to the presence of N-bridge heterocyclic nuclei of some pyrazoles and isoxazoles which are described to have antiviral and antimicrobial activities . [(5)] In this context , synthetic nucleoside analogues have been emerged as major therapeutic agents and several reports have appeared concerning their synthesis , therapeutic applications and mechanism of action [(6)] A very extensive and exhaustive research program by Tronchet and Co-workers [(7)] and by others [(8-10)] has been devoted to synthesis the analogues of natural glycosides containing an isoxazole or isoxazolidine ring directly linked to the sugar residue by 1,3-

dipolar cycloaddition reaction . In the 1,3-dipolar cycloaddition reaction of nitrones with alkenes , up to three new contiguous chiral centers can be formed , in the adduct , in single step [11.12] . In this paper we report the synthesis of chiral open-chain sugar-derived nitrones , the stereoselectivity of 1,3-dipolar cycloaddition with maleimide and maleic acid and the antimicrobial evaluation of nitrones (a,b) and isoxazolidine (2a) .

Experimental

General methods : Melting points were determined on SMP1 apparatus and are uncorrected . Reactions were monitored by thin layer chromatography (TLC) on silica gel F_{254} , with detection by the exposure to iodine vapour or by spraying with sulphuric acid in ethanol and heating the TLC plate at 80 0C . Column chromatography was performed on silica gel (lachema, 230-400 mesh) . Nuclear magnetic resonance spectra (NMR) were carried out using a Varian VXR 300 spectrometer at 300MHz , ^{13} C-NMR Spectra were determined using a Varian VXR 300 spectrometer at 300MHz (Al-Baath University / Faculty of Science / Chemistry Department /Homes/Syria) . Chemical shifts are denoted in δ units (ppm) field in relation to the internal standard tetramethylsilane (TMS) at δ=0.00 ppm , J in Hz . The splitting patterns are designated as follows : (s) singlet , (d) doublet , (t) triplet , (q) quartet , and (m) multiple .

All starting materials and reagents are commercially available (Fluka , Aldrich, Merckkvailable (Fluka , Aldrich, Mer commercially stand).

Synthetic procedures

Synthesis of open-chain sugar-derived nitrones:

***Preparation ofC-(D-Riboso)-N-methyl nitrone*(a):**

D-ribose (900mg,6mmol) was dissolved in 40ml dry absolute ethanol, N-methylhydroxylaminehydrochloride (500mg,6mmol)and (504 mg,6mmol) of sodium bicarbonate were added , After stirring at 40c0 under reflux for 6-7hr when TLC shows completion of the reaction, filtered , the solvent has evaporated and resulting product was dried and recrystallized by hot ethanol

The mixture was stirred for (7hr) ; yield 70%; mp Syrup ; Rf 0.49. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ (ppm) = 3.90 (S, 3H, N-CH_3), 7.43 (S,1H,CH=N), 3.50-3.65 (m, 4H, OH-sugar), 1.25-2.20 (m, 5H, C-H-sugar).

***Preparation of C-(D-Glucoso)-N-methyl nitrone*(b)**

D-glucose anhydrate (108mg,6mmol) was dissolved in (40ml)dry absolute ethanol, N-methylhydroxylaminehydrochloride (500mg,6mmol) and (504mg,6mmol) of sodium bicarbonate were added , after stirring at 40C^0 under reflux for (6-7hr), when TLC shows completion of the reaction. Filtered the solvent has evaporated and resulting product was dried and recrystallized by hot ethanol.

The mixture was stirred for (7hr) ; yield **72**%; mp **Syrup** ; Rf **0.53**

Preparation of N-Sugar-derived isoxazolidines (2a,b-3a,b)

Nitrones (a,b) and dipolarophile which were dissolved in dry toluene (25ml) were heated under reflux for (14-18)hr,the reaction mixture was followed by TLC (benzene: Methanol 8:2) which indicated that the reaction is completed and after concentration in vacuum gave a syrup residue, which was purified by column chromatography (chloroform) and then crystallized from chloroform-petroleum ether

Preparation of 2-Methyl-3-(D-Riboso)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d] isoxazolidine(2a)

The mixture was stirred for (14hr) ; yield 68%; mp Syrup ; Rf 0.55

Preparation of (2-Methyl-3-(D-Riboso)-4,5-dicarboxylicacid isoxazolidene (2b)

The mixture was stirred for (18hr) ; yield 70%; mp Syrup ; Rf 0.50

Preparation of 2-Methyl-3-(D-glucoso)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo [3,4-d] isoxazolidine(3a)

The mixture was stirred for (15hr) ; yield 77%; mp Syrup ; Rf 0.66

Preparation of *(2-Methyl-3-(D-glucoso)-4,5-dicarboxylicacid isoxazolidene (116b)*

The mixture was stirred for (18hr) ; yield 58%; mp Syrup ; Rf 0.71

1H-NMR (300 MHZ, $CDCl_3$): 3.90(s, 3H, N-CH_3) , 4.05(s,1H, C3-H) , 4.29(d,1H, C3a-H) , 5.01(d,1H , C6a-H) , 2.30-2.43(m ,4H, -OH sugar) ,1.25-1.92(m ,5H, C-H sugar).

Results and Discussion

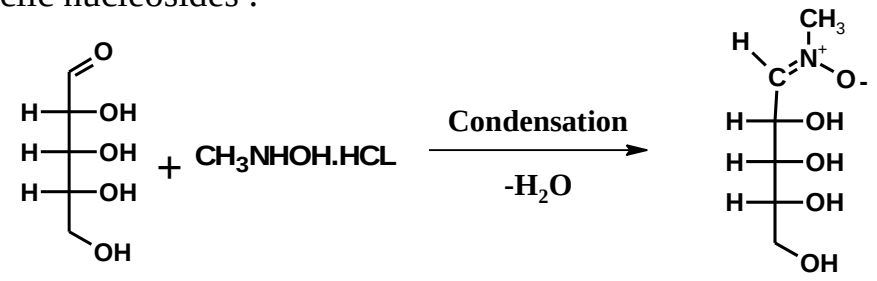
Synthesis of Chiral open-chain sugar-derived nitrones and 1,3-Dipolar Cycloaddition with maleimide and maleic acid

Two novel open chain –sugar nitrones were prepared , isolated ,and treated with maleimide. The nitrones used , together with details of the products isolated.

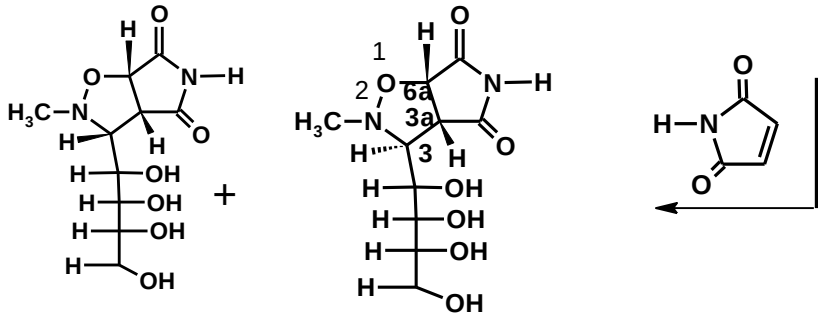
Nitrones (a ,b) derived from D-glucose and D-ribose without employing any protection of hydroxyl group have been prepared .

The preparation of nitrones was accomplished from the corresponding sugar with N-methyl hydroxylamine in ethanol under reflux for (6-7)hrs. schemes (1),(2).We have focused our attention to the preparation of chiral nitrones .Among the chiral nitrones a fundamental role was played by sugar –derived nitrones (a ,b) . Only few papers deal

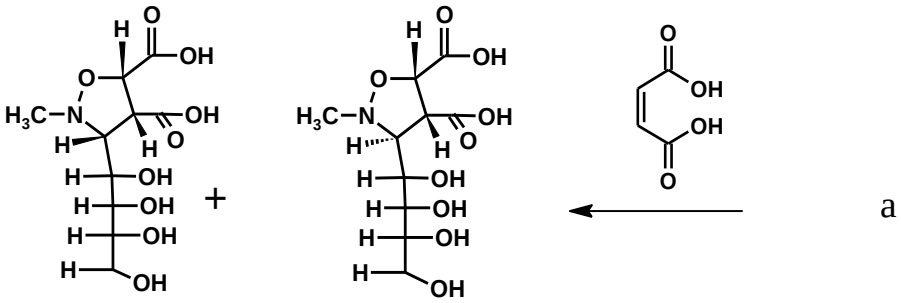
with chiral nitrones possessing a sugar moiety on their carbon substituent. Here we report now 1,3-dipolar cycloaddition of two closely related C-sugar substituted nitrones to maleimide and maleic acid to synthesis new acyclic nucleosides .



D-Ribose a

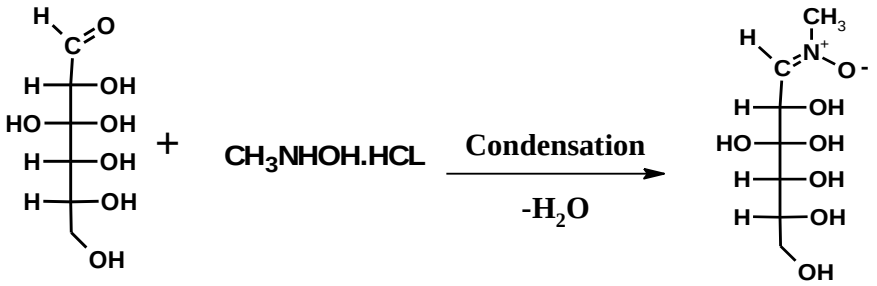


(2a') (2a)

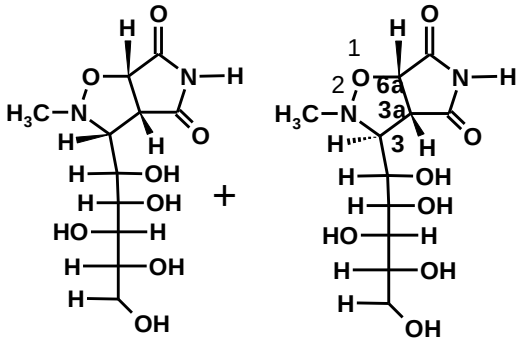


(2b') (2b) a

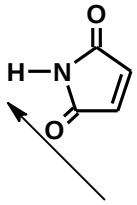
Scheme(1)



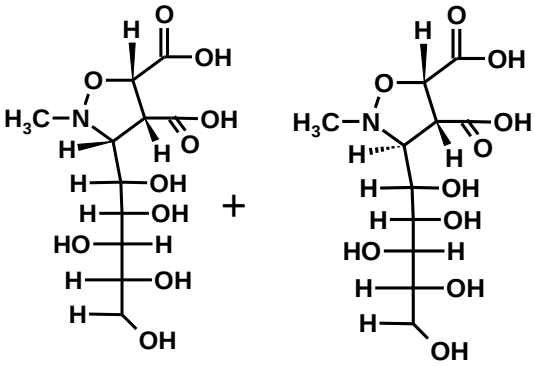
D-Glucose b



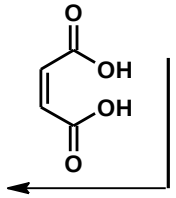
(3a') (3a)



b

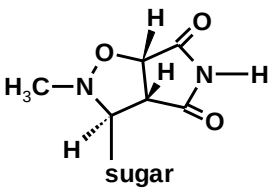


(3b') (3b)

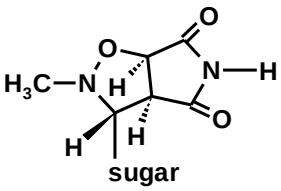


Scheme(2)

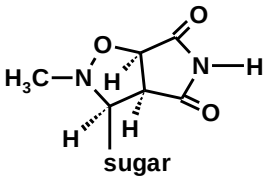
Three asymmetric centers C-6a , C-3a, and C-3 were generated in the cycloaddition process, since the condensed adducts have a cis-arrangement of H-3a and H-6a bridgehead protons , four diastereomeric cycloadducts were possible scheme(3) .



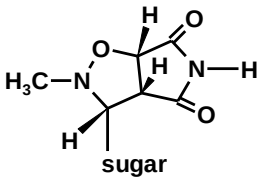
(I)



(II)



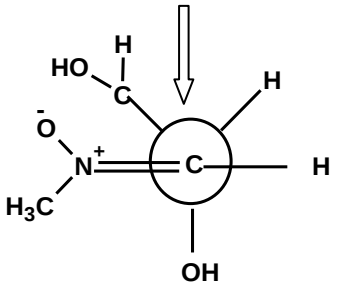
(III)



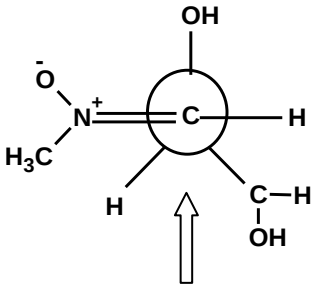
(IV)

(Scheme 3)Four possible diastereomeric cycloadducts of isoxazolidines

Stereochemical assignment of H-3,H-3a and H-6a atom were made to the condensed isoxazolidine on the basis of spectroscopic data. The ring junction between two rings was always cis which was indicated to coupling constant and examination of molecular models . The cycloaddition via transition state(A) Scheme (4) would afford syn product through the exo-attack.Conversely the cycloaddition via transition state (B) would afford anti cycloadducts through the endo-attack.



(A)Exo attack ⟶ syn

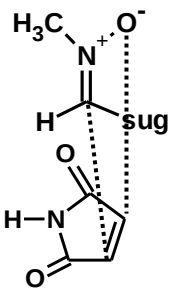


(B) Endo attack ⟶anti

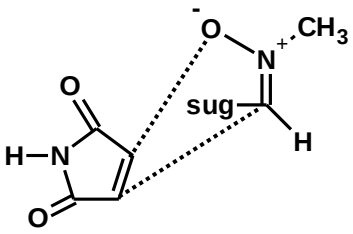
Scheme (4): The cycloaddition via transition state(A),(B).

It was not possible from the spectroscopic data available to decide whether the anti isoxazolidine (2a) obtained from D-ribosyl nitrone and maleimide corresponding to anti (I) or to anti (II) .The anti-isoxazolidine

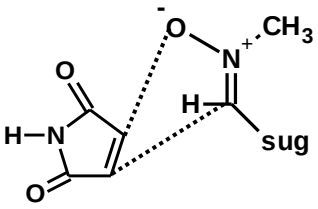
(2a) arise from cycloaddition of Z-nitrone through an endo-transition state or the E-nitrone in an exo-mode ,while the syn-isoxazolidines (2a') could be formed by the Z-nitrone reacting in the exo-fashion or the E-nitrone in an endo-mode (2a)(scheme 5) .



Endo TS ⟶ anti(2a)



Exo TS ⟶ syn (2a')



Exo TS ⟶ anti(2a)

Scheme(5)

Thus the cycloaddition of the C-ribosyl nitrones to maleimide would appear to proceed with useful stereoselectivity, but the nature of the stereoselectivity depends upon the precise functionality present in the nitrone(a). We have found how small a structure change in the nitrone needs to be to effect a significant change in the stereoselectivity of the cycloaddition [13,14,15].Proton NMR analysis of major isoxazolidines (2a) shows the anti relationship between H-3,H-3a and signals for H-6a and H-3a appear as doublets with very small coupling constant .

Fig.1-^{1}*H-NMR spectrum for C-(D-Riboso)-N-methyl nitrone(a)*

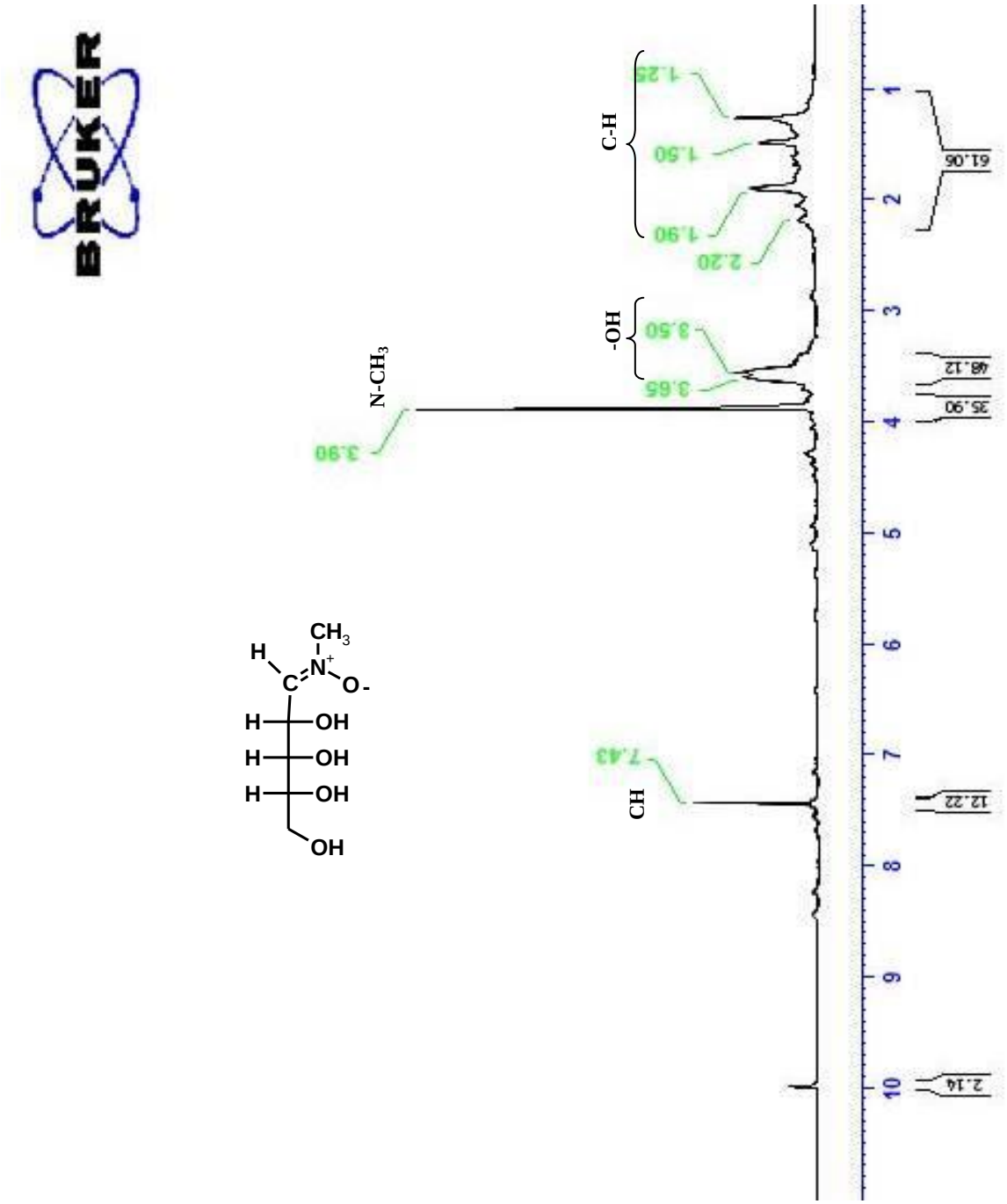
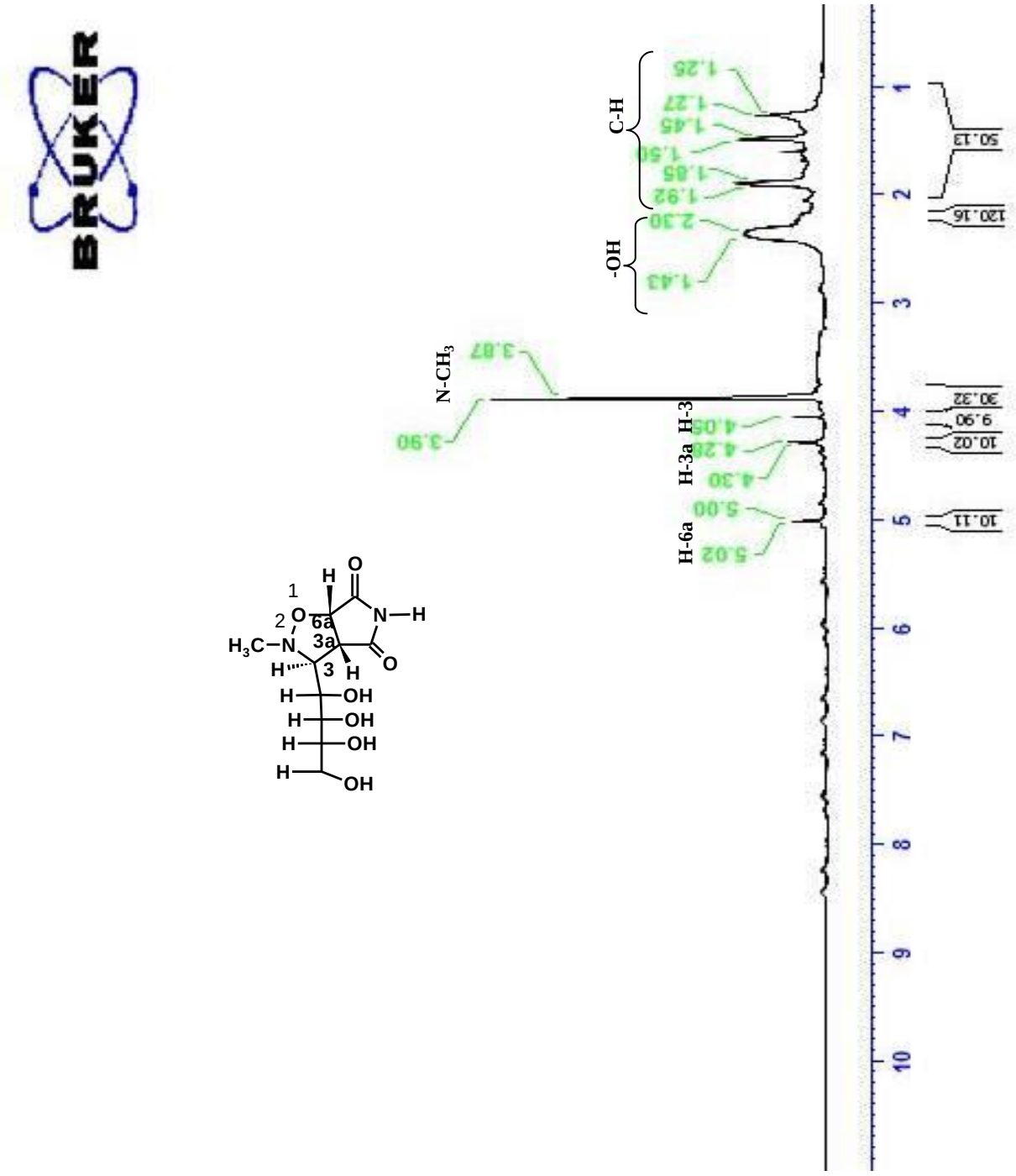


Fig.2-^{1}*H-NMR spectrum for 2-Methyl-3-(D-Riboso)-4,6- dioxo2,3 ,3a,4,6 ,6a-hexahydro-pyrrolo[3,4-d] isoxazolidine(2a)*



The results illustrated in table 1, show the biological activity of the Prepared open chain –sugar nitrones(a,b) isoxazolidines(3a,2b). As we can see from this table(1,2,3) compound (3a) has very high activity against microorganism(2b) showing a high activity against S.aureus and moderated activity against E.coli, Candida,(a,b)were found to be inactive against all microorganisms used.

Compound	*Microorganism*		
	S.aureus	**E.coli**	**candida**
3a	+ + +	+ + +	+ + +
2b	-	+	+ +
a	-	-	-
b	-	-	-

Table (1):Antimicrobial screening results of the tested compounds (first concentration (0.25eq/ l):

Table (2): Antimicrobial screening results of the tested compounds (second concentration (0.1eq/m l):

Compound	*Microorganism*		
	s.aureus	**E.coli**	**Candida**
3a	+ + +	+ + +	+ + +
2b	+ + +	+ +	+ +
a	-	-	-
b	-	-	-

Table(3):Antimicrobial screening results of the tested compounds (third

compound	*Microorganism*		
	S.aureus	**E.coli**	**candida**
3a	+ + +	+ + +	+ + +
2b	**-**	**-**	**-**
a	**-**	**-**	**-**
b	**-**	**-**	**-**

concentration (0.01eq/m l):

Table(4):M.gypsum screening results of the tested compounds

number	compound	First concentration (0.25eq/ml)	Second concentration (0.1eq/ml)	Third concentration (0.01eq/ml)
		T%	T%	T%
1	3a	45.1	2.03	1.29
2	2b	2	1.26	0.92
3	b	1.2	1.06	0.72
4	a	1.1	0.82	0.65

The results revealed that the highest transmission is clear for examined compounds (3a) ,this mean that compound (3a) revealed the highest activity against fungus of microsporum gypseum and high inhibition of this compounds. Finally remainder examined compounds(a,b, 2b) revealed weak activity against fungus .

Conclusions

Based on the Regio and Stereoselectivity of 1,3-dipolar cycloaddition reactions of nitrones to alkenes the following conclusions can be drawn from this research work:

1- 1,3-Dipolar cycloaddition of C-(D-Riboso)-N-methyl nitrones and maleimide affords anti-isoxazolidines, and the formation of anti-adduct has been rationalized by Z/E isomerization of nitrones and by NMR spectroscopic study.

2- Regio and stereoselectivity synthesis of new acyclic nucleosides by 1,3-dipolar cycloaddition of sugar-derived nitrones with maleimide was assigned.

3- This paper described the synthesis of 6 compounds which have not been prepared yet in any previous study, and examined the antimicrobial evaluation of nitrones (a,b) and isoxazolidines (3a ,2b) .

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