Synthesis and Study the Biological Activity of Some New Isoxathiozolidines by 1,3-Dipolar Cycloaddition of Nitrones and Thioacetamide

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Abstract:

A series of new isoxathozolidines (4-6) were synthesized by 1,3-dipolar cycloaddition reaction of different nitrones with thioacetamide under reflux condition . The yields of products following recrystallization from various solvents, and characterized by spectral methods (IR , UV , TLC , M.P), were used for identification of these compounds. The biological activety show that the compounds have antibacterial activity.

Key Word: Nitrones , Cycloaddition , Isoxathiozolidines , Antibacterial activity.

Introduction:

Nitrones are important synthetic intermediates that have been used extensively in organic chemistry [(1-7).] Some nitrones have been used for the trapping and identification of free radicals [(7)], particularly in biological studies[(4)]. Various synthetic approaches for the synthesis of nitrones have been reported by several group[(8,9)]. The most general approach for the preparation of nitrones is the condensation reaction between aldehydes or ketones with N-monosubstituted hydroxylamines.[(8)] Nitrones can react as 1,3-dipolar cycloaddition with variety of dipolarophiles, which are important in the synthesis of 5-membered heterocyclic compounds .[(10,11)] In 1973, Black and Watson described 1,3-cycloadducts of five nitrones and the sterically hindered aliphatic thioketones [(12)]. Thiourea react with nitrones to give oxathiazolidine .[(13)] The purpose of the present work is to synthesis some new oxathiazolidine by 1,3-dipolar cycloaddition reaction of nitrones to thioacetamide, and studies the biological activity of these compounds.

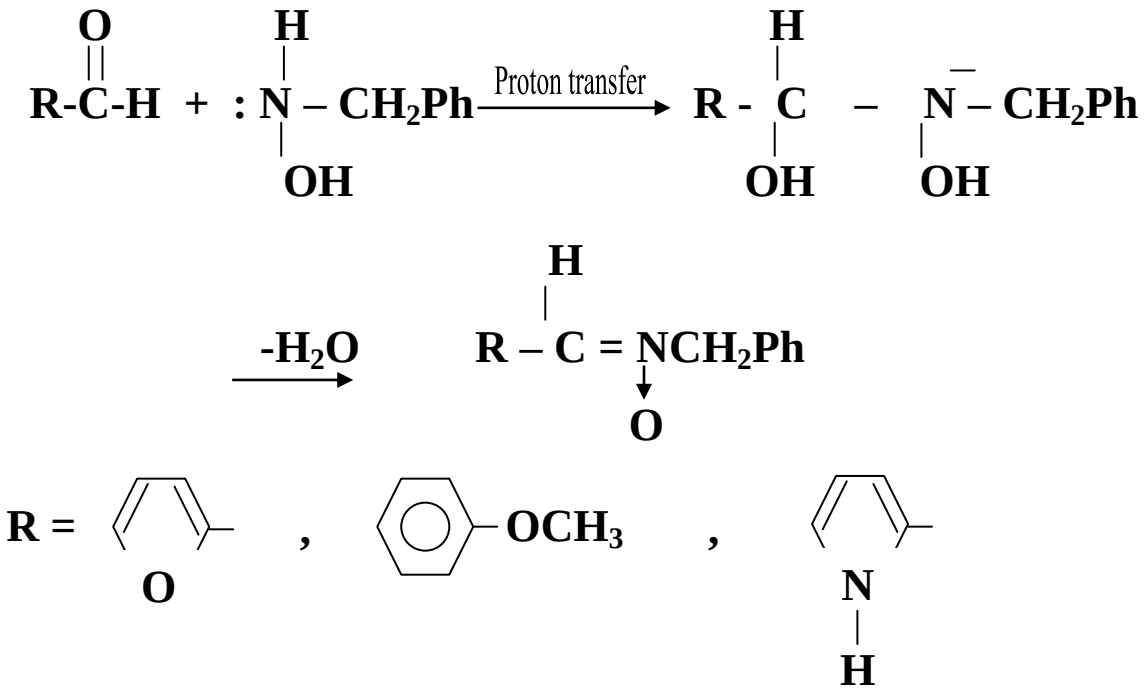
Experiment

General:

Melting points (mp) were determined with an electrothermal digital point apparatus type (GallenKamp). IR spectra were obtained using (Pye – Unicam) SP3-3005 spectrophotometer at secines college, university of basrah. All the spectra were recoreded as KBr discs.UV spectra were recorded on Hitachi-U-15000 UV / NIR .TLC is performed on silica gel 60 F_{254} sheet layer (Merck) .The materials from (Merk , Ridel , and Fluka) companies .The solvents were dried by the usual methods .

General Procedure For Preparation Of Nitrones[14]

Nitrones (1,2,3) were synthesized using the condensation reaction between corresponding aldehdes(furfural, pyrrole -2-carbaldehyde, 4-methoxy phenyl benzaldehyde) and N- benzyl hydroxylamine in ethanol solution to give (4,5,6) .



Prepration [2- benzyl -5- methyl -5-amino -3-(2-Furyl)-(1,4,2) oxathiozolidine][15,16] (4)

To the stirred solution of thioacetamide (0.0002 mole, 0.15 gm) in dichloroethane (20 ml) were added α –(2-Furyl)-N-benzyl nitrone (0.002 mol , 0.47 gm). The resulting mixture was reflux with stirring for (24 hr .) the reaction mixture was followed by TLC which showed that a new spot with R_f =(0.42) appeares, at the end of the reaction the mixture was

cooled , the white precipitate was optanide, filtered, recrystallization by hexane to give crystal compound(4) .

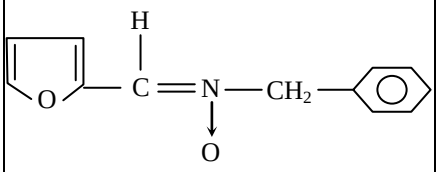
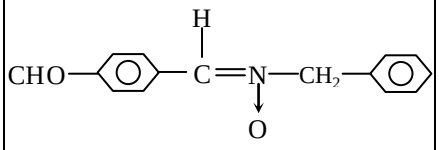
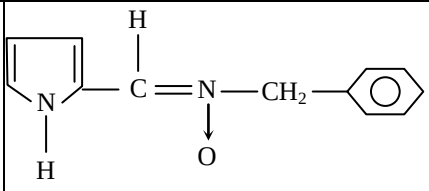
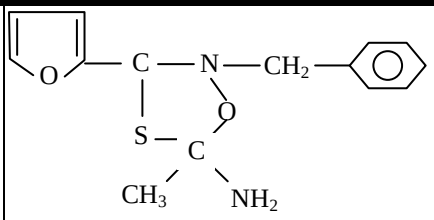
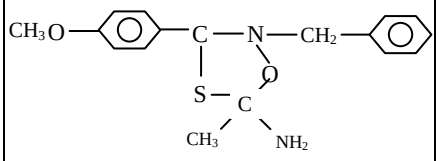
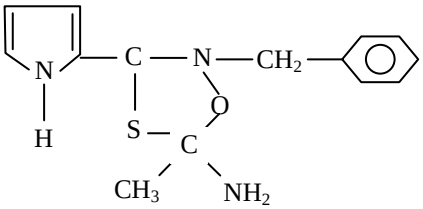
Preparation[2-benzyl-5-methyl -5- amino -3-(4-methoxy phenyl)-(1,4,2) oxathiozolidine](5)

To the stirred solution of thioacetamide (0.005 mole , 0.413 gm) in dichloroethane (20ml) were added α –(4- methoxy phenyl) –N – benzyl nitrone (0.005 mol , 0.75 gm) . The resulting mixture was reflux with stirring for (48 hr .) , the reaction mixture was followed by TLC which showed that a new spot with R_f = (0.35) appeares at the end of the reaction the mixture was cooled , the white precipitate was optanide, filtered , recrystallization by Toluene to give (5) .

Preparation [2-benzyl -5-methyl -5-amino -3-(2- pyrryl) – (1,4,2) – oxathiozolidine](6)

The method described above to prepare (4,5) was carried out using thioacetamide (0.011 mol, 0.082gm) with α-(2-pyrrle)– N-benzyl nitrone (0.0011 mol, 0.24 gm) in (20 ml) dichloroethane, the mixture reflux for (2hr.), cooled, filtered, recrystallized the product by using acetone to give (6) .

Table (1): Physical Properties of Nitrones and Isoxathiozolidines.

Comp.	Structures	M.P C^0	R_f	Solvent Recry.	Eluents	Yield
1		188-190	0.31	Cyclohexane	Dichloroethane	71
2		178-180	0.73	Dichloromethane	THF:$CHCL_3$ 8: 2	98
3		110-112	0.64	Ethanol	Dichloroethane	75
4		122-124	0.42	Hexane	Methanol:Toluene 3:7	80
5		112-113	0.54	Toluene	Methanol:Toluene 3:7	73
6		130-132	0.35	Acetone	Methanol:Toluene 3 : 7	85

Results and Discussion

Infrared Spectra

The IR Spectra of the studied prepared compounds as KBr discs and most of their representative spectra are shown in figs (1-3) and Table (2) .The spectra of Isoxathiozolidine (4,5,6) are characterized by the six bands corresponding the stretching vibration of ($-NH_2$) group in rang (3100-3220) cm^{-1} broad bands due to Hydrogen bonding , So appear the mean stretching vibration of the (C- N) band in the rang (1290- 1330) cm^{-1} and (N-O) band in rang (1020-1070) cm^{-1} . (C-S) band give strong band in rang (600-800) cm^{-1}, but the (C-O) band give us mean stretching vibration in the rang (1130- 1230) cm^{-1} , while those of (C=C) aromatic give two bands appear stretching vibration in rang (1390-1480) cm^{-1} .In general , it is clear that the frequency of the (C=N) band which related to nitrones is diappear in isoxathiozolidine compounds and that referenc to 1,3-dipolarcycloaddition and appear of new stretching vibration absorption related to (C-O) , (C-S) , (C-N) and NH_2 group. The suggest structures indicat that the reaction was take place the cycloaddition.

Table (2) : IR Spectral Data of Nitrones and Isoxathiozolidines (cm^{-1}).

Comp.	C=C Ar.Str.	C=N Str.(Cm^{-1})	C-N Str. (Cm^{-1})	C-O Str.(Cm^{-1})	$-NH_2$ Str.(Cm^{-1})	N-O Str.(Cm^{-1})	C-S Str. (Cm^{-1})
1	1440-1480	1580(w)	1140(w)	-	-	1065(s)	-
2	1400-1530	1590-1600(w)	1288(s)	-	-	1165(s)	-
3	1460-1500	1580(w)	1170(w)	-	-	1080(m)	-
4	1450-1490	-	1329(m)	1230(w)	3200-3220(b)	1060(s)	730(s)
5	1440-1480	-	1330(m)	1220(w)	3110-3200(b)	1070(m)	720(s)
6	1390-1400	-	1290(m)	1130(m)	3100-3140(b)	1020(m)	680(s)

Str. =Stretching br. = broad S =Strong m = medium w = weak .

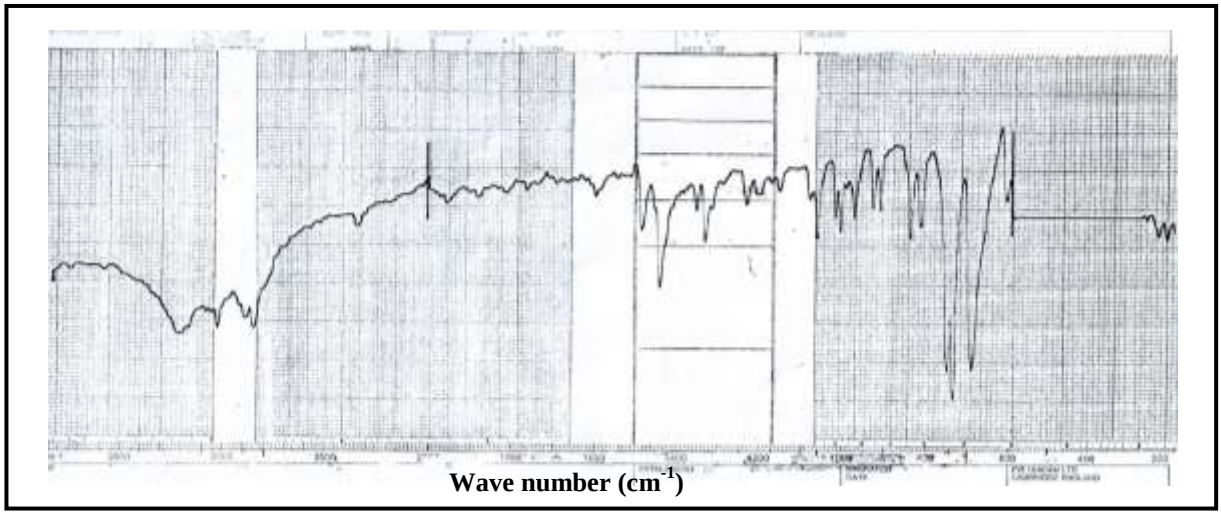


Figure (1): IR Spectra of compound (4)

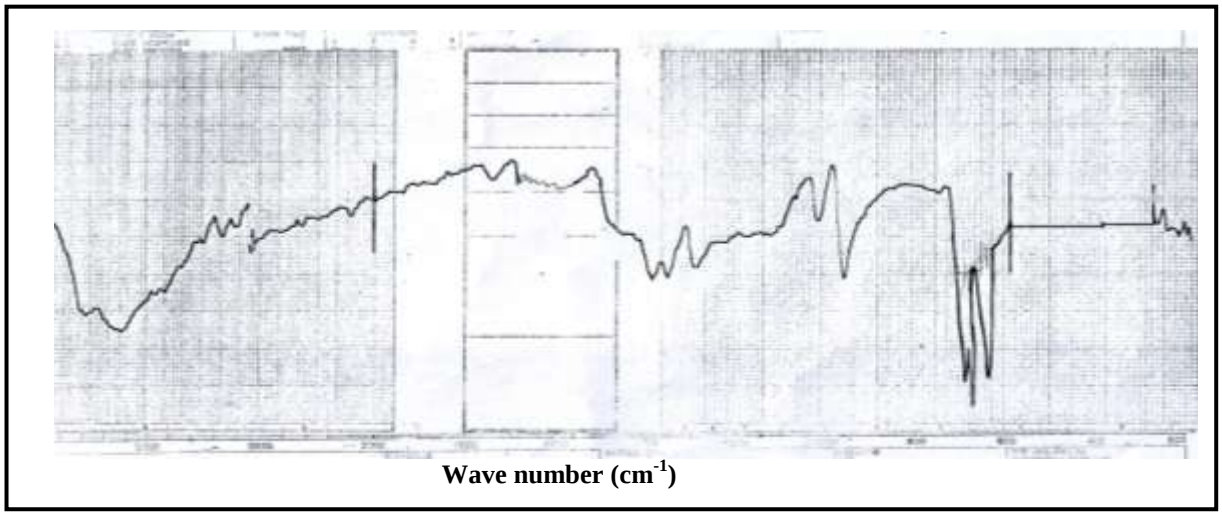


Figure (2): IR Spectra of compound (5)

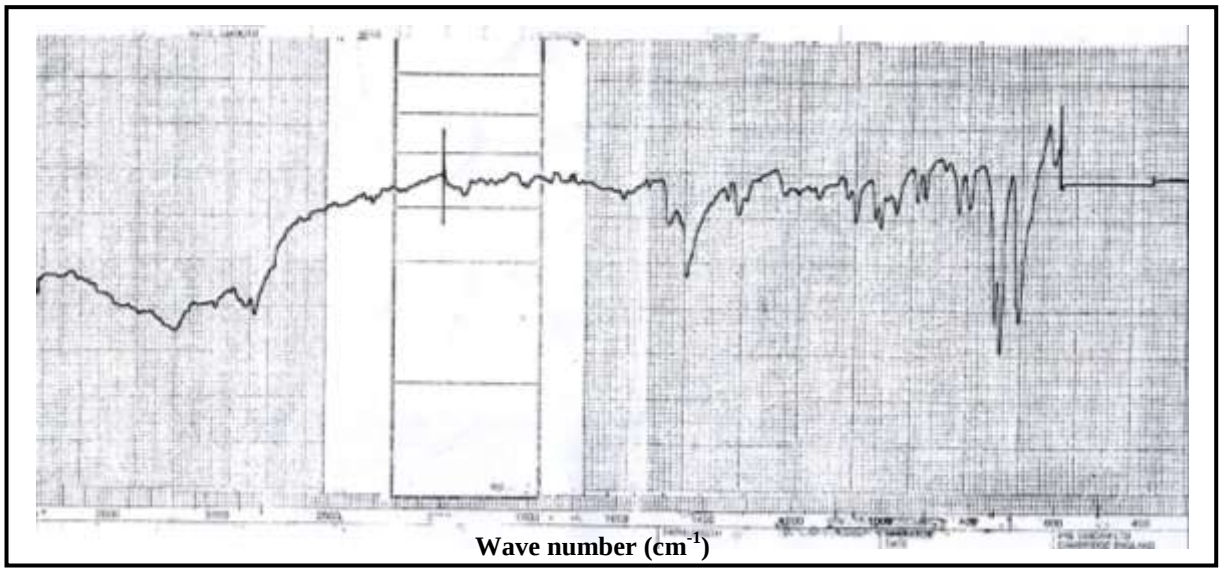


Figure (3): IR Spectra of compound (6)

Ultraviolet Spectra

The electronic absorption data of the investigated synthesized compounds are gathered in table (3) and the spectra of the prepared compounds are shown in figs (4-6) . The spectra of isoxathiozolidins compounds 4,5 and 6 are characterized by two bands , the week band is within the range (210-230) nm which related to aromatic system , and the strong band is within the range (250-270) nm attributed to the electronic transition $\pi \rightarrow \pi^*$ of the conjugated electronic system of phenyl groug. when we compared between the spectra of isoxathiozolidines compounds and the spectra of the nitrones compounds that prepared in otherstudies[15], we find that the bands related tothenitrones (N→O) group (n→ π^*) transition were disappear in position(288-300)[14] nm.

Table 3: UV Spectral data of Nitrones and Isoxathiozolidines .

Compounds	Band I λ max (nm)	Band II λ max(nm)	Solvent
1	214	293	$CHCL_3$
2	237	288	$CHCL_3$
3	238	300	$CHCL_3$
4	210	272	$CHCL_3$
5	230	280	$CHCL_3$
6	220	263	$CHCL_3$

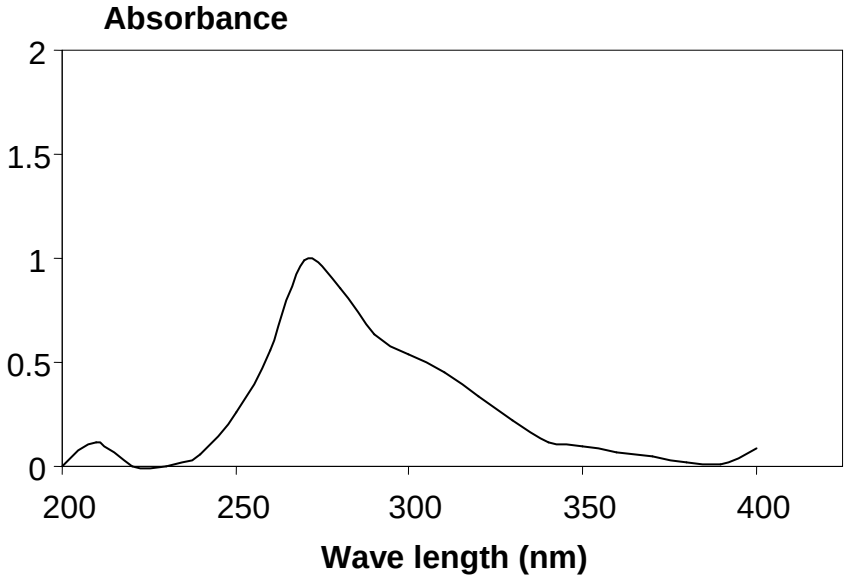


Figure (4): UV spectra of compound (4) in $CHCL_3$ (1×10^{-4})M

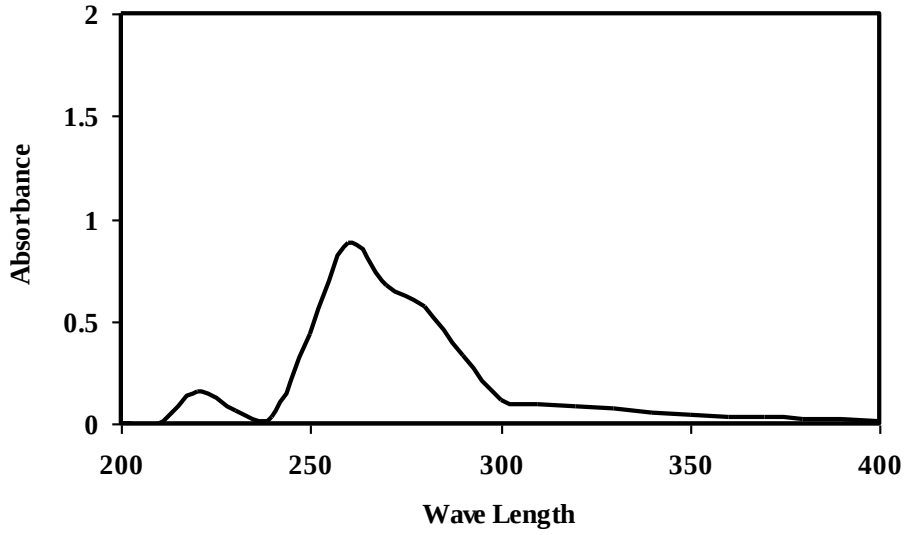


Figure (5): UV spectra of compound (5) in $CHCL_3$ (1×10^{-4}) M

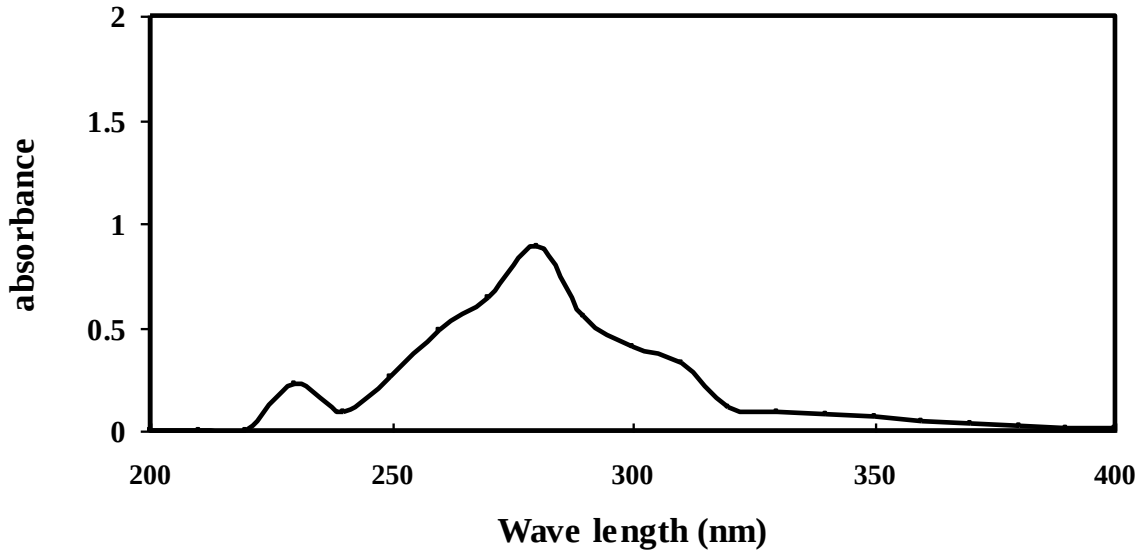


Figure (6): UV spectra of compound (6) in $CHCL_3$ (1×10^{-4}) M

Biological Activity

Experimental:

The Hahn (1979) method [17] was followed by using discs (6mm diameter) of whattman filter paper no.3. They were sterilized by the autoclave apparatus at 121^0c for 15 min under 1 atm and then they were spread in dry sterilized dishes.

The Bauer *et al*. (1966) method [18] was followed to determine the diameter of inhibition zone by preparing the Muller Hinton agar medium plates, and a micro – organismal suspension was prepared from the standard micro – organisms by taking 4-5 pure colony from every kind of micro – organisms. They are *Staphylococcus aureas*(NcTc 6571) and *Escherichia coli* (NcTc 5933) which have grown in the nutrient broth medium and were kept at 37^0c for 4-6 hr. till the appearance of the turbidity which was measured by the Philips spectrophotometer (number of cells 10^6 cell / ml and optical density = 0.1) .

Results and Discussion

Table (4) shown that all the Nitrones and Isoxathiozolidines to primary screening of anti – microbial activity of inhibition zone diameter (Z)mm against the test organisms *Staphylococcus aureas*(NcTc 6571) (gr. Positive) and *Escherichia coli* (NcTc 5933) (gr. Negative) . The data of table (4) confirm that the (Z) of Nitrones against standard micro – organisms are much more than of the(Z) of Isoxathiozolidines , for example the(Z) of [1,2,3] are [12,11,12] mm respectively, concn. =500 µg / ml while the(Z) of [4,5,6] are [9,10,11] mm respectively, concn. = 500 µg / ml against *S. aureas*.

Table(4) : Inhibition diameters(mm)of Nitrones and Isoxathiozolidines anti-Standard micro – organisms at concn. 500 µg / ml

Micro – organisms		
Compounds	**S. aureas NcTc 6571 Gr. (+)**	**E. Coli NcTc 5933 Gr.(-)**
1	**12**	**13**
2	**11**	**10**
3	**12**	**14**
4	**9**	**10**
5	**10**	**8**
6	**11**	**9**

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