Synthesis and characterization of some new heteroaldonitrones

Zienab. A. Ameer*, Nezar. L. Shihab Aldain*, Nisreen . N. Majeed**, Ali. H. AI – Mowali**

*Chemistry Dept., Education college, Basrah University
****Chemistry Dept., Science college, Basrah University**

Abstract:

　　　　Two series of new heteroaldonitrones were prepared and identified . Series A was prepared by reaction of benzyl hydroxyl amine with helroaldehydes derived from (pyrrol, thiophene , furan and pyridine) while series B was prepared by reaction of phenyl hydroxyl amine with the same set of hetroadlehydes, then various spectroscopic studies and other analysis (l.R , U.V , NMR and elemental analysis) were done for the prepared nitroncs to prove its validity. The spin trapping properties of these compounds have been evaluated by using ESR technique . All tested nitrones were trapped by methyl radical which was generated by (Fe^{+2} /H_2O) in a mixture of H_2O / DMSO to form a relatively stable nitroxide radicals .

:

(　　　)

　　　　A　　　　.

.(　　　　　　)

A

)　　　　　　　　　B

(

.

(　　　/　　/　)

.
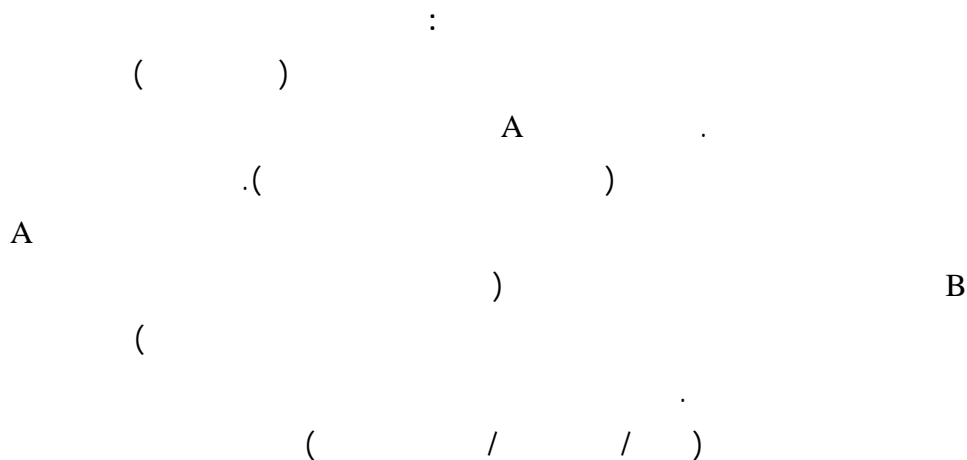
Introduction :

Nitrones have the following general form :

$$\diagdown C = N \diagup ^{\nearrow O}$$
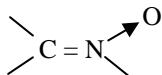
It was prepared firstly (Smith , 1938) by alkylating the nitrogen oxime, the phrase *nitrone* was refers to nitrogen - ketone .

There are two types of nitrones; aldonitrones ($RCH = N$) and ketonitrones ($R_2C = N$) depend on the source of C_α weither from substituided aldehydes or substituted ketones .

One of the common methods (Torset *.et.al,* 1988) for the preparation of nitrones like

oxidation of disubstituted hydroxyl amine with oxygen , HgO ,'potassium permanganate and ter - butyl hydroperoxide , is alkylaling the oxime and oxidation of enamine by using peroxide acid to give three member cyclic ring like oxazardine

derivative and nitrones .

Nitrones compound   specified with the delocalization of π bond between the oxygen and the nitrogen atom and this delocalizalion of charge depends upon the type of

substitutenl attached with the carbon atom of nitrone (Bruer , 1982).
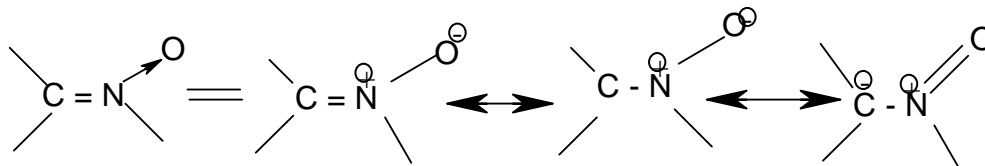
Nitrones were easily oxidized by many reagent like ferric chloride , ozone , lead tetra acetate (LTA) potassium , ferricyanide and also with photooxidation .

This type of nitrone could be reduced by different reducing agent like sodium metal to give a radical anion (Hamer and Macaluso , 1964) . PCl_3, PO_3 and PO_4 could be used to capture the oxygen of nitrone . The selectivity of Lewis acid (Zinc / $AlCl_3$/ THF) derived the oxygen of nitrone to give a highly yield of amine. Other metal hydrides like $LiALH_4$ and $NSaBH_4$ may be also used like

$$Ph - CH = \underset{O}{\overset{\downarrow}{N}} - Bu^t \xrightarrow{\text{LiAlH}_4} Ph - CH_2 \underset{OH}{\overset{\downarrow}{N}} — Bu^t$$
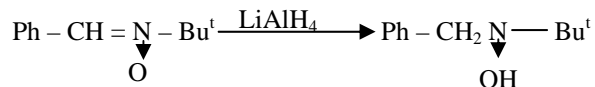
　　　　Rearrangement of nitrones take place by proteolysis to give the corresponding amide. Captodalive olefins 1 - acetyl vinyl carboxylates were proved by (Rafael.et.al, 2001) to be highly regioselective dipolarphiles in 1,3 - dipolar cyclo addition to propionitrile oxide, aryl phenyl nitrile imines , diazoalkancs and the nitrones yield the corresponding 5-substituted heterocyclic and here the sddition was also stereosclective. Many applications of nitrones, (Soloand Picrre , 2000) used it as drugs and the radical induced oxidation damage which was extremely harmful to tissues and organs due to molecules modification brought to poly unsaturated membrane lipids , proteins-and nucleic acid . Oxidative stress was believed to be one of the pathological, ischemia mechanisms that operate in neutrodegeneratie disorders such as cerebral is chemise , amyotrophie laleral sclerosis .

　　　　Other examples the synthesis of 2 - amino - 8 - nitronaptho [1,2 - d] thiazole and its utilization as diazo component lo prepare arrange of heterocyclic azo disperse dyes . These dyes were studied by (Rangnekar and Maladkar, 2000 with respect to their color , constitution relationship-and evaluate their application on polyester fiber.

　　　　The aim of this research is to synthesize some new hetroaldonitrones and characterized them by CHN and spectroscopy techniques. The spin traping properties of these compounds have been determined by ESR method.

Experimental:

　　　　The NMR was obtained with NMR - Mercury - 300 MHz Locethz apparatus using DMSO and CD_3OD solvents in Zeorich university switz. The ESR obtained with Varian - E 109 in science college using aqueous solution and quartz cell using standard diphenyl picryl hydrazil .

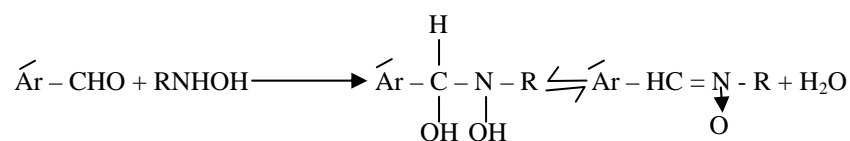U.V studies were done by G - E377407 spectrum using dried $CDCL_3$ and EtOH as solvents .

l.R data were obtained by PYE - Unicam (200 - 4000 cm^{-1}) SP3 - 3005 apparatus using KBr disc .

Elemental analysis were done in science college by using CARLO - ERBA EA 1108 apparatus.

Procedure:

N - Benzyl hydroxylamine :

A mixture of 7g (0.1007) mole hydroxyl amine hydrochloride 25g (0.197 mole) benzyl chloride and 30g (0.283 mole) sodium carbonate were refluxed for two hours .

Then filtrate and cool (0 °C)-A crystalline product were formed recrystilization from diethyl ether its m.p 129 - 130 °C .

Nitrones compounds

(Series A)

$$Ar – CHO + RNHOH \longrightarrow \underset{OH\ OH}{Ar – \overset{H}{\underset{|}{C}} – \overset{|}{N} – R} \rightleftharpoons \underset{O}{Ar – HC = N - R} + H_2O$$

Ar = 2 - Pyrryl , 3 – thienyl 2 - furyl, 4 – pyridiyl, R = phenyl or benzyl

α- (4 - Pyridiyl) - N - benzyl nitrone (A$_1$)

In round bottom flask (RBF) 1.23 g (0.01 mole) of N - benzyl hydroxyl aminc was dissolved in dry toluene then 1.22 g (0.0114 mole) of pyridine - 4 - carbaldehyde was added gradually with stirring in room temperature . a yellow precipitate was formed re crystallization from dry EtOH . A yellow clean crystal were found for this nitrone . (A$_1$) its m.p 120- 122°C, yield. 71 % .

α- (2- Furyl) - N - benzyl nitrone (A$_2$)

In round bottom flask 1.23 g (0.01 mole) of N - benzyl hydroxyl amine was dissolved in dry toluene then 1.11 g (0.0115 mole) of furfural was added to dissolved the stirred mixture . The resulting mixture was refluxed for 24 hrs then left it for 20 hrs at dark with continuos stirring . A yellow precipitate was formed. Recrystalized from dry eyclohexanc to give a yellow needles from A2. Its m.p 198 - 199 °C , yield 74 %.

α – (3 - thienyl) - N - benzyl nitrone (A $_3$)

In RBF 1,23 g (0.01 mole) of N - benzyl hydroxyl amine was dissolved in dry toluene then 1.36 g (0.122 mole) thiophen - 3 - carbaldehyde was added to the stirred mixture . The resulting mixture was refluxed for 1.5 hrs then left it for 12 hrs at dark place a yellow precipitate were formed crystallized from dry methanol to give a yellow crystal from nitrone (A.i) its m.p 103 - 105C , yield 70 % .

α - (2 - pyrryl) - N - benzyl nitrone (A$_4$)

In RBF 1.23 g (0.01 mole) of N - benzyl hydroxyl amine and 0.95 g (0.0099 mole) pyrrole - 2 - carbaldehyde was dissolved in dry to luene . Then mixture was refluxed for 24 hrs. Then left it for 4 hrs at dark place. The product with time becomes deep blacky. Then cooled and filtrate. Recryslalized from dry EtOH . Orange needles will be formed from nitrone A$_4$ its m.p 110 - 112 ℃ , yield 75 % .

N - phenyl hydroxyl amine :

In RBF fitted with mechanical stirred fitted with a condenser and a thermometer 20g (0.37 mole) ammonium chloride was dissolved in 640 ml water then 8.3 ml nitrobenzene was added to the stirred mixture at room temperature then 47.2gm zinc dust was added gradually with keeping the temperature below 50 ℃ for $\frac{1}{2}$ hr filtrate then wash the precipitate with 80 ml hot H$_2$O to remove zinc oxide the filtrate was saturated with sodium chloride then cool it in ice bath for I hr to complete crystalaztion . Filter the' product then extract with diethyl ether to remove the traces of salt, the ether was evaporated , crystallization from benzene then it will precipitate from petroleum ether to give a sharp m.p at 81 ℃ .

(Series B)

α - (4 - Pyridiyl) - N - phenyl nitrone (B$_1$)

In RBF fitted with a condenser 1.09g (0.0099 mole) N - phenyl hydroxyl amine was dissolved in a smallest amount of dry ethanol, the solution was heated with stirring at 40 - 60 ℃ to complete the dissolving then 1.22g (0.0114 mole) pyridine - 4

- carbaldehyde were added gradually to the hot solution with stirring , then the mixture was left at room temperature for 24 hrs a yellow product was formed . Recrystallizcd from dry toluene a yellow powder was found , its m.p 123 - 125 ℃ , yield 76%.

α - (2 - Furyl) - N - phenyl nitrone (B_2)

In RBF filled with a condenser 1.09g (0.0099 mole) N - phenyl hydroxyl amine was dissolved in a smallest amount of dry ethanol, the solution was heated with stirring at 40 - 60 ℃ to complete the dissolvalion then 1.11 g (0.0115) mole furfural was added to the hot solution gradually with stirring , the mixture was refluxed for 1 hr the mixture was kept in ice bath for 24 hrs at dark place a yellow precipitate was found, recrystallizalion from dry cyclohexan, a yellow crystal was found , its m.p 80 - 82 ℃ yield 80% .
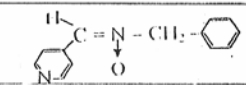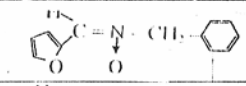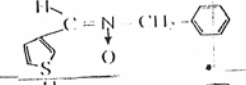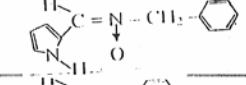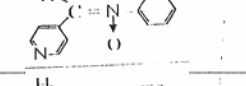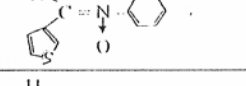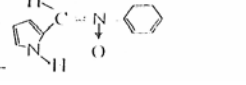
α- (3 - thienyl) - N - phenyl nitrone (B_3)

In RBF fitted with a condenser 1.09g (0.0099 mole) N - phenyl hydroxyl amine was dissolved in a smallest amount of dry elhanol, the solution was heated with stirring at 40 - 60°C to complete the salvation then 1.36g (0.0122 mole) thiophenfe 3 - carbaldehyde was added to the hot solution gradually with stirring. Then the mixture was refluxed for 16 hrs with stirring in a dark place . The RBF was closed with an adapter and lift it in ice bath a yellow precipitate was formed. Filtrate and recrystallizcd from cyclohexan . A yellow crystal was represented• Its m.p 105-107 °C, yield 75%.

α - (2 - Pyrryl) - N - phenyl nitrone (B_4)

In RBF fitted with a condenser 1.09g(0.0099 mole) N - phenyl hydroxyl amine were mixed with 0.95g (0.0099 mole) pyrrol - 2 - carbaldehyde with dry ethanol as a solvent then the mixture were refluxed for 4 hrs. Then left in at room temperature stirred 2hrs at dark place. II was shown that the reaction mixture decomposed with time, filter it. Recryslalized from cyclohexane. A yellow crystal were found Its m.p 116 -118 ℃ , yield 81%. The completion data of reaction and the purity of product were checked by TLC Using dichloroethanc , Benzene / chloroform 3 : 7 as **Eluent .**

Table (I) Show the name and the chemical structure of the new prepared nitroncs

Term	Nitrouse structure	Structures
A_1	$\alpha - (4 - Pyridiyl) - N - benzyl\ nitrone$	
A_2	$\alpha - (2 - furyl) - N - benzyl\ nitrone$	
A_3	$\alpha - (3 - Thienyl) - N - benzyl\ nitrone$	
A_4	$\alpha - (2 - Pyrryl) - N - benzyl\ nitrone$	
B_1	$\alpha - (4 - Pyridiyl) - N - phenyl\ nitrone$	
B_2	$\alpha - (2 - Furyl) - N - phenyl\ nitrone$	
B_3	$\alpha - (3 - Thienyl) - N - phenyl\ nitrone$	
B_4	$\alpha - (2 - Pyrryl) - N - phenyl\ nitrone$	

Result and discussion :

Infrared spectra :

Table (2) shows the infrared spectra for the prepared nitrones were measured as KBr disk shows selective band for the N   O stretching at 1050 cm^{-1} , 1085 cm^{-1} for all compounds, also   a weak to a medium band for the stretching of C - N at 1120 cm^{-1} and C = M stretch about 1570 - 1590 cm^{-1}. All spectra were given the aromatic bending band (= CH) about 600 - 950 cm^{-1} as strongly band. Series A gave a melhylene stretching at 2820 - 2910 cm^{-1} an aromatic combination bands appear as conjugated band at 1750 - 2000 cm^{-1} .

Spectra of compound A_4, *B_4* shows bands at 3225 , 3280 cm^{-1} respectively for N - H stretching also compounds A_3, B_3 shows in its spectra bands at 1330 cm^{-1}, 1345 cm^{-1} respectively for the C - S stretching and compounds A_2 . B_2, show bands at 1220, 1230 cm^{-1} respectively for C - O stretching. The spectra of all new

compounds specified in disappearance of the C = O stretching which comes about 1720 - 1750 cm^{-1} (for the aldehydes) also the disappearance of O - H stretching belongs to the hydroxyl amine which comes in 3130 - 3510 cm^{-1}. This proved the expected product as in literature (Joseph. *et. al,* 1987).

Ultra Violet Spectra

The standard solution of series A were determined in dried chloroform which show two absorption peaks . Table three shows the all data, l'ig(1) and Fig (11) as examples for the U.V spectra . The first transmission at 288 - 297 nm which belong to the nilronc group it is due to the nitrone group that due to π - π^* transition. (silverstien .et.al, 1981)

Table (2) : I.R data foe series A and B

C-H ben, Ar	N-O str	N-H str ring	C-S str Ring	C-O str Ring	C-N str Ar.	C-N str Alip	C=N str	C=N str ring	C=C str Ar.	=C-H str Ar.	$-CH_3$ str	Compound
980-600	1070(m)	·	·	·	·	1120 (w)	1580 (w)		1540 - 1440	3060 - 3020 (w)	2910 –2820 (w)	A₁
980-600	1065(s)	-	-	1220(m)	·	1140 (w)	1580 (w)		1480,1440	3020 - 3000 (w)	2900 – 2825 (w)	A₂
980-600	1060(m)	-	1330 (m)	-	-	1190 (w)	1570 (w)		1540,1440	3040 - 3000 (w)	2860–2910 (w)	A₃
980-600	1080(m)	3225 (b)	·	-	-	1170 (w)	1580 (w)		1500,1460	3040 - 3020 (w)	2860–2910 (w)	A₄
990-600	1085(s)	-	-	-	1200 (m)	-	1575 (w)	1540 - 1400	3120 - 3085 (w)	-		B₁
960-600	1060(s)	-	-	1230 (s)	1290 (m)	-	1580 (w)		1555 ,1460	3080 – 3035 (w)	-	B₂
960-600	1050(s)	-	1345(m)	·	1285(m)	-	1570 (w)		1530,1440	3075 – 3020 (w)	-	B₃
950-600	1075(s)	3280 (b)	-	-	1250(m)	-	1590 (w)		1570,1450	3100 - 3040 (w)	-	B₄

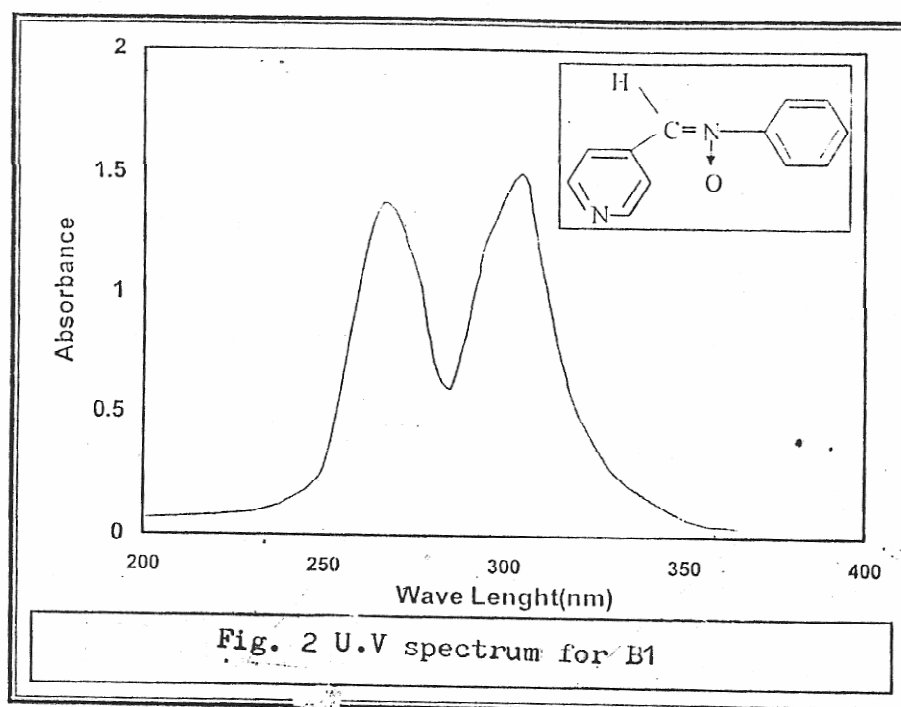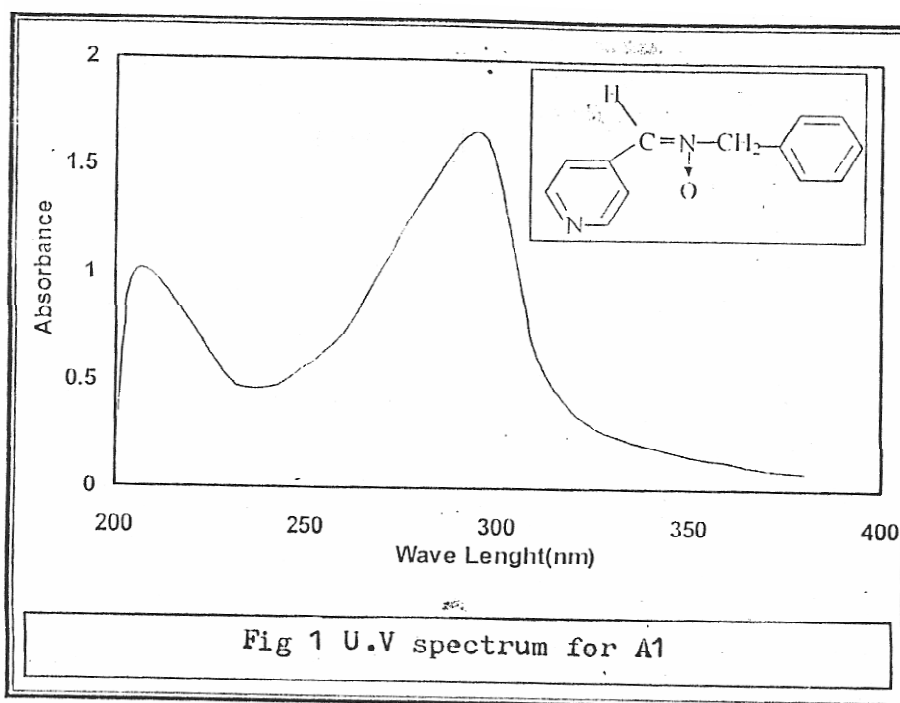Bending : ben , Stretching : Str , Broad : b , Weak : W , Medium : m , Strong : (S)

Fig 1 U.V spectrum for A1

Fig. 2 U.V spectrum for B1

Table (3) U .V data for scries A and B

Compound	λnm	$m^2\,mol^{-1}$	λnm	$m^2\,mol^{-1}$	Solvent
A_1	206	10170	296	16510	CHCl3
A_2	214	1142(1	293	14530	CHCl3
A_3	220	12210	297	13960	CHCl3
A_4	237	II 720	288	15810	CHCl3
B_1	265	13420	305	13350	ETOH
B_2	258	12790	300	15840	ETOH
B_3	261	10280	310	15480	ETOH
B_4	249	14560	308	16230	ETOH

The second peak shows at 206 - 237 nm belongs to the electronic transition of aromatic ring.

Series B were measured in dry ethanol, also shows two peaks , the first one appeared in highly at 300 - 310 nm for the nitrone group while the second appear at 249 - 265 mn for the aromatic ring . Important case noticed from the spectra of A and 13, which shows that B spectra absorbs in highly wave length than A spectra due to the increase of conjugation which stabilized the compound due to the nearest of the energy level to each other , so bathchromic shift π - π^* was happened .

1H - NMR Spectroscopy

DMSO, CD_3OD were used as solvent for (B_1 B_2) and (A_2, A_3) respectively. Table (IV) shows the details of signals, chemical shift and some of the coupling constant for the prepared nitrones, which shows identity with the literature measurements (smith, 1964) for the nitrones protons.

Table (4): The NMR data for prepared compounds

Compound	Functional group	Chemical shift (ppm)	Coupling Constant	Solvent
B_1	CH=N →O, 1H,S Arom 3Hm, H-6, H-1, H-2 Arom 2Hm, H-5, H-3 Arom (py) 2H, dd, H-6, H-2 Arom (py) 2H, dd, H-5, H-3	8.629 7.559 – 7.582 7.933 – 7.900 8.728 – 8.708 8.285 – 8.264	4.8 4.8	DMSO
B_2	CH=N →O, 1H,S Arom 3Hm, H-6, H-4, H-2 Arom 2Hm, H-5, H-3 Arom (fu) 1H, d, H-3 Arom (fu) 1H, q, H-4	8.732 7.550 – 7.495 7.957 – 7.925 7.853 6.748	3.6 3.6, 3.4	DMSO
A_2	CH$_2$, 2H, S Arom 5H, m CH=N →O, 1H,S Arom (fu) 1H, d, H-3 Arom (fu) 1H, s, H-4 Arom (fu) 1H, d, H-5	4.876 7.383 – 7.267 7.387 7.243 7.218 7.315	1.24 1.24	CD$_3$OD
A_3	Arom 5H, arom (th) 3H& 9H,M CH=N →O CH$_2$, 2H, S	7.389 – 7.208 4.876		CD$_3$OD

S — Singlet, d = doublet, dd= doublet of doublet, in = multiplet Thiophene: Th, Furan: fu, Pyridine: Py

Elemental analysis :

Table (V) shows the result of the elemental analysis to the prepared compounds which proved the validity of these products .

Table (5) Elemental analysis for the new compounds

	Found			Calculated			Comp
	%N	%ll	%C	%N	%11	%C	
$C_{13}H_{12}N_2O$	13.16	5.71	73.58	13.20	5.65	73.60	A_1
$C_{12}H_{11}NO_2$	6.98	5.42	71.63	6.96	5.46	71.66	A_2
$C_{12}H_{11}SNO$	6.32	5.12	66.34	6.44	5.06	66.36	A_3
$C_{12}H_{12}N_2O$	13.86	5.92	72.08	13.99	5.99	72.01	A_4
$C_{12}H_{10}N_2O$	14.34	5.22	72.86	14.13	5.04	72.74	B_1
$C_{11}H_9NO_2$	7.46	4.82	70.40	7.48	4.81	70.61	B_2
$C_{11}H_9SNO$	6.82	4.42	65.12	6.89	4.42	65.02	B_3
$C_{11}H_{10}N_2O$	15.03	5.34	70.97	15.05	5.37	70.98	B_4

ESR study

Nilrones ability to capture the unstable free radicals like alkyl, hydroxyl and oxygen radicals have an important site in Biological activity in human body also . It causes oxidized damage for some tissues and others part, also it will induced some chain reaction for polylipo tissues (unsaturated) protein and Lipo acid. Nitroncs as organic molecules have in its structure the ability to relief

the oxidized damage through fastly capturing to the free radical   like : (T orsell .et.al, 1988).

$$R-C(H)=N^+(R)-O^- \xrightarrow{X} H-C(R)(X)-N(R)-O \qquad X = CH_3, OH, O$$

Nitrone   Nitroxide radical
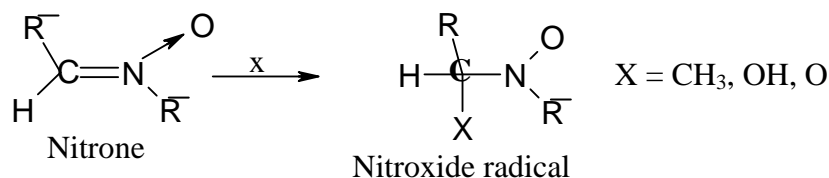
Then we used for this purpose 5.5 - dimethyl - 1 - pyrrolidinc - N -oxide. DMPO and α - phenyl - N - butyl - nitrone (PBN) which used to capture the bromine in many biological and chemical reactions. The spin products were prepared from suitable nitrones (10 M) with the free methyl radical which was formed (Fe^{+2} / H_2O) in equal ratio of DMSO/ H_2O in room temperature by using Varian E - 109 and diphenylpicrylhydrazil as a standard. PBN was prepared as in literature. The electron spin resonance spectrum was generated the nitroxide radical. From reaction of methyl radical with nitrones(B). Three signals were shown, they come from the interaction of electron with the nitrogen atom (1 =1) and by using the selection rule ($\Delta Ms =1$) ($\Delta Ms =0$) Fig Vll shows the effect of magnetic field on the energy levels between the electron and the nitrogen atom. every major signal will be divided into two signals due to the interaction between the uni electron with the hydrogen atom attached to C in the nitrone. Table (6) shows the hyperfine coupling of the unpaired electron with nitrogen and proton nuclei of the formed nitroxide radicals and (PBN) radical.

Table (6) ESR data for some nitrone standard compound

Nitrones	Nitroxide	aN gauss	aHα gauss	aHα gauss
B2	I	15.20	2.30	—
B3	2	15.25	2.28	—
B4	3	15.03	2.33	—
A1	4	12.7	3.2	5.7
A2	5	12.6	3.2	5.8
A3	6	12.5	3.5	5.6
PBN	7	14.8	2.8	—

 References :

1. Breucr . *E*, "The chemistry of amino nitroso and nitro compounds and their
    derivatives " Eds , patai, Inc , New york , I , 459 (1982).

2. Hamer .J and Macaluso. A, Nitroso (chemical Rev) 64, 473 (1964).

3. Joseph B. L, Herbert, F. S, David, A. L and Gram R. C "Introduction to
    organic spectroscopy "Macmillan publishing company, Inc (USA) (1987)

4. Rangnekar, D. W and Maladkar, G. J, Synthesis and application of 2-
    (arylazo) - 8 - nitronapho [1, 2-d] thiazole disperse dyes. phosphorus,
    sulfur silicon Relal. elem (2000), 164: 199-205(2000).

5. Rafael, H, Arumugam. N. Miguel. A. Francisco. M. and Gerardo L, Regio
    and stereoslectivily of captodativc olefins in 1, 3- Dipolar cycloaddition AD
    FT /HSAB. Theory Rationale for the observed Regio chemistry of nitrones
    J. Org. Chem 66 (4), 1252(2001).

6. Smith, L. 1 "Nitrones in chem. Rev, 23, 222 (1938).

7. Silverstein, R. M, Brasscr, G. C and Morrill, T. C "Spectrometric
    identification of organic compounds 4th ed (1981).

8. Solo, G and Pierre. L. "chemical and pharmacological aspects of heteroaryl
    nilrones Curr. Med. Chein. 7(12)1255 (2000).

9. Torsell, K. B. G "Nilrones in organic synthesis Feur, H. Ed, VCH puplisher,
    Inc, New York, chap. 3. 85(1988).