J.Thi-Qar Sci. Vol.3 (2) Feb./2012

ISSN 1991- 8690 **الترقيم الدولي 8690 - 1991**

Website: http://jsci.utq.edu.iq Email: utjsci@utq.edu.iq

A new procedure for preparation of Sulfon-Z compounds.

Alaa H. K. Al- Daraji

Chemistry Dept. - College of Science - Maissan University.

Email: alaa_h_k@yahoo.com

Abstract :

Four compounds (Sulfon – Z) were prepared by a new procedure where Z is; N, S, O, and relating moieties. This procedure have many advantages comparing with other methods, its simple and easy, short time for preparation process (45 minutes in maximum), available starting materials (such as compounds; A, B, C, and others), cheap, relativily high percentage yield (60 – 96 %). However, above points are depending on the nature of starting materials.

The products were identified by; melting point, thin- layer chromatography technique and Infra-red spectra. In addition, biological activity of these compounds have been studied against three different species (St.aureus, E . coli and Candida albicans).

Introduction:

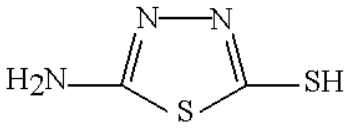
Microbes have ability to resistant a lot of drugs (Weisblum B., 1985; Courvalin P. and Fiaudt M., 1980; Loncle V. and *et. al.*, 1993; Lyon BR. and Skurray RA., 1987), as example penicillin was introduced into clinical use during 1940, and it resistaned by St.aureus strains have rapidly arose since 1946 (Barber M. and Rozwadowska-Dowzenko M., 1948). As resultant of this resistance many compounds have been prepared to be a new drugs instead of the old drugs which microbes were resisted. One of these old resistance drugs is sulfonamide antibiotics (Landy M. and *et. al.*, 1943), it is an old chemotherapeutic agents contain (RSO_2 –NHR) sulfonamide bond, and many of these compounds contain heterocyclic ring (specially thiadiazol moiety) (Bertram G. Katzung, 1998; H.K. Alaa, 2000).

Aim of this research is to make reseachers able to prepare some compounds of sulfonamides drugs instead of old drugs which the microbes have resisted. Hoping to find sufonamide compounds that are more active as drugs.

Experimental part:

Following (1, 2, 3, and 4) compounds and (A, B, and C) compounds have been prepared by following proceduers:-

1- Preparation of (2-amino –1,3,4- thiadiazol-5-thiol) (A) (Petrow V. and *et. al.*, 1958):-

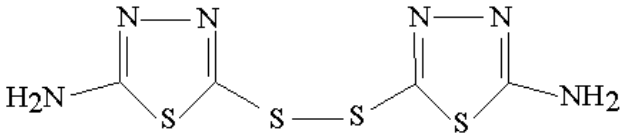


Compound (A)

Thiosemicarbazide (0.3 mole,27.3g) in absolute ethanol (105ml),anhydrous sodium carbonate (15.9g), and carbon disulfide (0.36 mmole, 27.6g) were added and mixed then refluxed with stirring for 6 hr. The reaction mixture was then allowed to cool at room temperature and filtered to collect compound (A), 70% product yield, and melting point = 231 –232 º C.

2- Preparation of bis (5-amino- 1,3,4-thiadiazol - 2-yl) disulfide. (B).

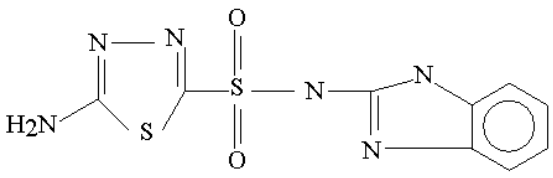
The compound was prepared by oxidation of compound (A) using hydrogen peroxide (Gula A., 1922):



Compound (**B**)

Hydrogen peroxide (31ml, 3% w/v) was added drop wise to a solution of compound (A) (45.8 mmole, 6g) in ethanol solution (50ml) with continuous stirring for one hour at room temperature. A yellow precipitate of (B) was formed and collected by filtration. Washed with distilled water and dried in oven at 70 ˚ C.

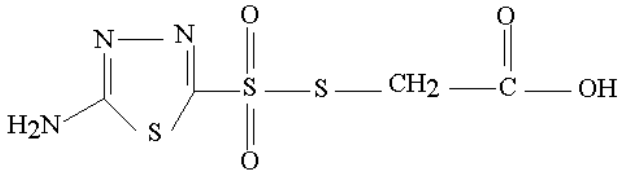
3- Preparation of (5-amino-1,3,4-Thiadiazol-2-yl)-2- benzimidazol sulfonamide (1):



Compound (1)

In a (250 ml) beaker, it was put compound (B) (30.1mmole, 2.01g) and hydrogen peroxide (10 ml, 30w/v). Beaker's solution was mixing with continuous stirring for 15 seconds. The process continuous until the color of the mixture became yellow, depending on the reaction mixture. Then 2-amino-benzimidazole (30.1mmole, 2.4g) and sodium bicarbonate (1g) was added. After 30 sec. the precipitate was filtered and collected, the product compound (1) was obtained 93% product yield, 241-243° C melting point. This procedure was followed in preparation of sulfon-amine or sulfon-sulfur compounds.

4- Preparation of (5-amino-1,3,4-thiadiazol-2-yl) thio sulfon acetic acid (2):-

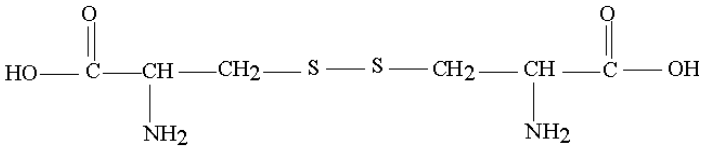


Compound (2)

Compound (2) was prepared by same procedure of preparation of (1) compound.

Compound (B) (5.6 mmole, 2.1g), hydrogen peroxide (8ml, 30w/v), thio acetic acid (5.6mmole, 1.4g) the product was collected by filtration, the yield was 92%, melting point 222-223 ˚C.

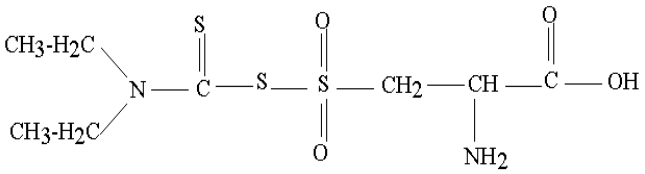
5- Preparation of bis (2-amino - propanoic acid) disulfide (cystine compound) (C).



Compound (C)

Compound (C) was prepared by adding hydrogen peroxide (31ml, 3% w/v) drop wise to a solution of cysteine compound in ethanol solution (50ml) with continuous stirring for 45 minutes at room temperature. A pale yellow precipitate was formed to collect by filtration, washed with distilled water and dried in oven at 70 ˚ C to give compound (C).

6- Preparation of 1-(N, N-diethyl carbondisulfid (2) sulfon)-2-amine propanoic acid. (3):

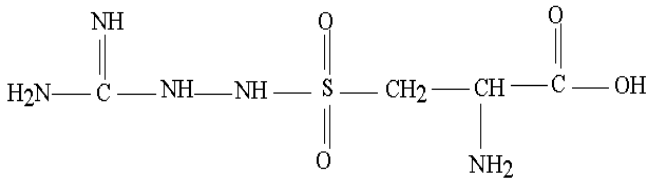


Compound (3)

Compound (3) was prepared by the same procedure of compound (1);

Compound (C) or Cystine (17mmole, 3.1g), hydrogen peroxide (12 ml, 30w/v), N,N-diethyl carbon disulfide (17 mmole, 2.516g), sodium bicarbonate (17 mmole, 0.758g) were used. The product was collected by filtration the product yield was 94%.

7- Preparation of 1-semicarbazide-2-amino-propanoic acid sulfonamide, (4): -



Compound (4)

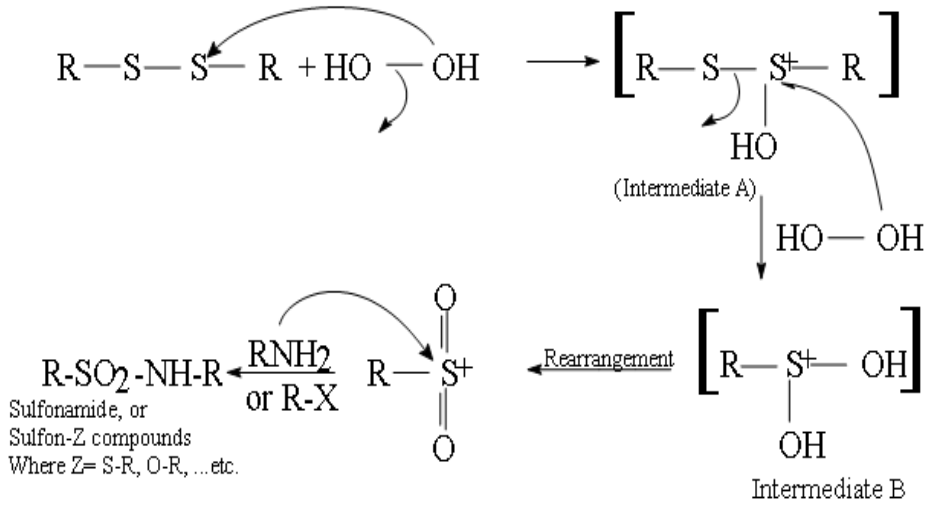
Compound (4) was prepared as same as that for compound (1);

Compound (C) or Cystine compound (18mmole,3- 4g), hydrogen peroxide (13ml,30w/v), amino-semicarbazide (18mmole,1-3g), sodium bicarbonate (18mmole,0.91g) were used, the product was collected by filtration and product yield was 95% , with melting point 147-148 ºC.

Results and discussion:

Prepared compounds were characterized by; Melting point, thin layer chromatography, and I.R. spectra which has indicated that all products are as expected.

A possible mechanism for the reaction, depending on the nature of starting materials that involved, is:



Hydrogen peroxide is well known compound as oxidation agent, it is highly active compound. It is more active than oxygen molecule because oxygen atom has higher electronegativity value than all atoms periodic table except florin atom . This value of electronegativity makes hydrogen peroxide more active than oxygen due to the number of bonds between the atoms of the two active oxygen atoms. Hydrogen peroxide has one bond between its oxygen atoms while oxygen molecule has double bond between its atoms this mean that in case of oxygen molecule, oxygen atoms are less flexible due to double bond than hydrogen peroxide with one bond more flexible atoms. This may the reason of higher activity of hydrogen peroxide or this activity comes from the two connected oxygen atoms because electronegativity mean that the atom prefer to keep the electron around it and atom like with high value means it prefer to keep the electrons around it, but in case of hydrogen peroxide the two connected atoms are oxygen therefore each one of these atoms wants to keep bonding electrons around it for this molecules like hydrogen peroxide the two atoms one of them have partial positive charge whereas the other has partial negative charge. In case of hydrogen peroxide it can be written as:

$$HO^{\delta+}\_\_\_\ ^{\delta-}OH$$

Therefore, oxygen atom with partial negative charge more electron density will attach the disulfide bond because according to the reference, it acts as elecrophile compound searching for electrons this why this research reaction is easy and fast reaction (Vogel's, 1978).

Therefore the mechanism is the partial negative charge oxygen atom of hydrogen peroxide will attach sulfur atom of disulfide bond resultant of intermediate (A), another highly active partial negative charge oxygen atom will attack the intermediate (A) to produce intermediate (B) rearrangement process will be happen to give sulfoxide molecule which its easy to attack by an amine compound to give sulfonamide compounds or any compound with high electron density such as; S-R, O-R, N-R…etc can attach sulfoxide molecule to produce different compounds with Sulfon-Z bond where Z= S-R, N-R, O-R and relating moieties, such as it was prepared of compounds (2) and (3) in this research.

However, This research reaction is proceeded through S_N2-like reaction in which the nucleophilic reagent is highly active nagative charge oxygen atom will attack the electrophile (disulfide bridge) resulting formation of a metastable intermediate (H.K. Alaa, 2000).

The main role of disulfide bond is to stabilize the three dimensional structure of the molecmles (Cecil R. and Neutrath H., 1963). Pryor (Pryor W.A., 1962) suggested that bivalent sulfur bond is nearly pure (p) orbital the bond angle for two atoms attacked to sulfur was about 105 º, the four electrons that still left on a sulfur atom were assigned as two to the (S) orbital and two to the third (P) orbital .In disulfide bond, the pairs of the non-bonded (P) electrons on adjacent atom were considered to repel each other, so that to minimized repulsion, R groups of R-S-S-R take the dihedral angle of about 90º, as a Result of this situation, the disulfide bond was found to have one (P) orbital of the three 4P orbital empty from electrons make it behave as electrophile easy to attach by any nucleophile or it searching for electrons to be stable. One of most suitable nucleophile for attching disulfide bond is hydrogen peroxide compound which is able to attack it through S_N2 like reaction (H.K. Alaa, 2000; Vogel's, 1978).

I.R. spectra of the products was measured in Al-Nahrain University-College of science /Chemistry Department and they will be discussing which they are showed the following characteristics absorption bands (KBr disc cm^{-1}) as follow (Robert M. Silverstein and *et. al.*, 1981; L. Ralph shriner *et. al.*, 1980): -

1-Compound (1):

In the compound (1), the asymmetric stretching vibration of $-NH_2$ group appeared as a

weak peak at (3248 cm^{-1}),while the symmetric stretching vibration at (3093.6 cm^{-1}) due to H-bonding, also at (1929.7 cm^{-1}) for (C = NH) group indicate this phenomena at (2866 cm^{-1})str*., (1541 cm^{-1}) moiety stretching and bending vibration , at (842 cm^{-1}),and (721.3 cm^{-1}) peaks for (C-S-C) bonds stretching vibration ,another peaks at (1629.7 cm^{-1}),(1585.4 cm^{-1}),and (1502.4 cm^{-1}) for aromatic imidazole ring stretching vibration, for (C = N) bond str. At (1685.7 cm^{-1}), at (1346.2 cm^{-1}) and (1072.3 cm^{-1}) sharp peaks for the sulfonamide bond str. and bending vibration respectively, (C-S) bond has sharp peak at (918.1 cm^{-1})str. Vibration .
These most of I.R. spectrum peaks have indicated that the structure of compound (1) as expected.

2- Compound (2):

The peaks at (3396.4 cm^{-1}), and (3276.8cm^{-1}) are assingned to (N-H) str.asymmetric and symmetric vibration respectively. Also At (3091.7 cm^{-1}) broad peak for (O-H) bond str.vibration, (2920 cm^{-1}) and (2773.4 cm^{-1}) peaks for (-CH_2CO) group due to aliphatic (C-H). At (1058.8 cm^{-1}) for (CH_2-S) group str., (746.4 cm^{-1}) for (C-S-C) group str., (1600.8 cm^{-1})(C = O) group, (1328.9 cm^{-1}) (C-O-H) group str., (1535.2 cm^{-1}) (C =NH) bond str., (1496.7 cm^{-1}) (N-H) bending vibration, (1363.6 cm^{-1}) and (1114.8 cm^{-1})(S-SO_2) group str., also (1058.8 cm^{-1}) for S → O str. Or S =O str., (559.3 cm^{-1})(SO_2-S) group bending.
All these peaks were indicated that the compound (2) structure is as suggested.

3- Compound (3):

The I.R. spectrum of this compound has been gave the following peaks for their groups:-
At (3310-2662cm^{-1}) (broad with multiple bard of $^{(+)}NH_3$ Str.), (2582.5cm^{-1}) (S-H) Str. Also (962.4 cm^{-1}) bending because of the resonance phenomena make the (C = S) group change to (C-SH) group., in the broad band (2868cm^{-1}) (-C_2H_5) group, (1632 cm^{-1}),and (1407 cm^{-1}) carboxylate ion str. Vibration, (1583.4) (N-H) of -$^{+}NH_3$ bending,(1334.6cm^{-1}) (C=S)str., (1124.4 cm^{-1}) (C-H) bending vibration, (1380.9 cm^{-1}), and (1193-9 cm^{-1}) (SO_2 – S) str. Vibration,(611.4 cm^{-1}) (SO_2 – S) bending vibration, (844.8cm^{-1}) and (777.3cm^{-1}) (CH_3-S-S-) Str., (1632 cm^{-1}) (CS-NR_2) str.
The I.R. spectrum has indicate that the structure of compound (3) as suggested for it in the Method.

4- Compound (4):

It has been showed the following peaks and for them specific groups:-
At (3321-3484 cm^{-1}) (N-H) str. for amine, (3174-2362cm^{-1}) broad with multiple band of $^{+}NH_3$ str., (1585.4) (C=N)str., (1634 cm^{-1}) (N-H) of $^{+}NH_3$ bending, (1667), and (1407cm^{-1}) for carboxylate ion str. vibration respectively, (1336.6cm^{-1}), (1193.9cm^{-1}), and (540 cm^{-1}) stretching and bending vibration of sulfonamide group. The peaks were indicated that the structure of compound (4) as expected.

Str*: stretching vibration.

Biological activity:

Biological activity or antimicrobial activity has tested for the four compounds against St.aureus, E . coli, and Candida albicans species by agar diffusion method (Barry A.L., 1976).
millimeter (m.m) inhibition zone was used to determine the activity of the prepared four compounds, the data are listed in following table:-

Compound no.	Conc. (µg/ml)	St. aureus (mm)	E – coli (mm)	Candida albicans (mm)
(1)	**75**	32	19	25
	50	23	15	17
	25	20	14	11
(2)	**75**	27	19	29
	50	20	14	24
	25	15	11	23
(3)	**75**	33	26	30
	50	27	18	29
	25	21	17	24
(4)	**75**	37	28	26
	50	35	26	24
	25	27	25	20

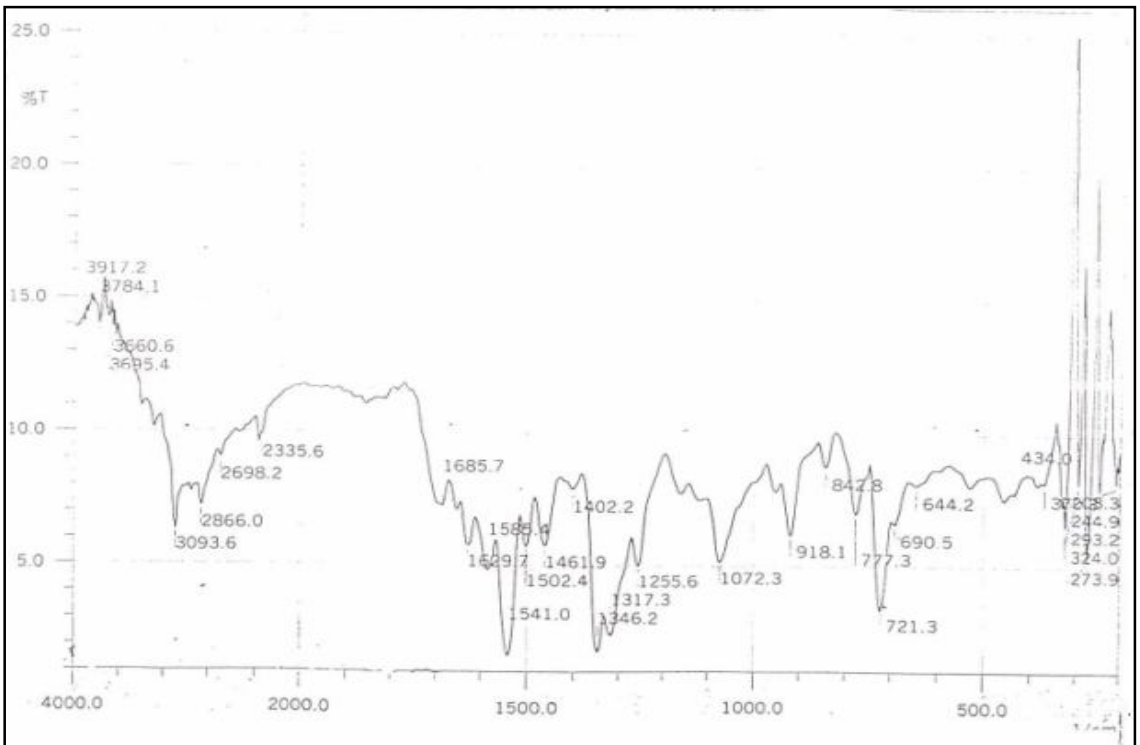


Figure (1): I.R. spectrum of compound (1).

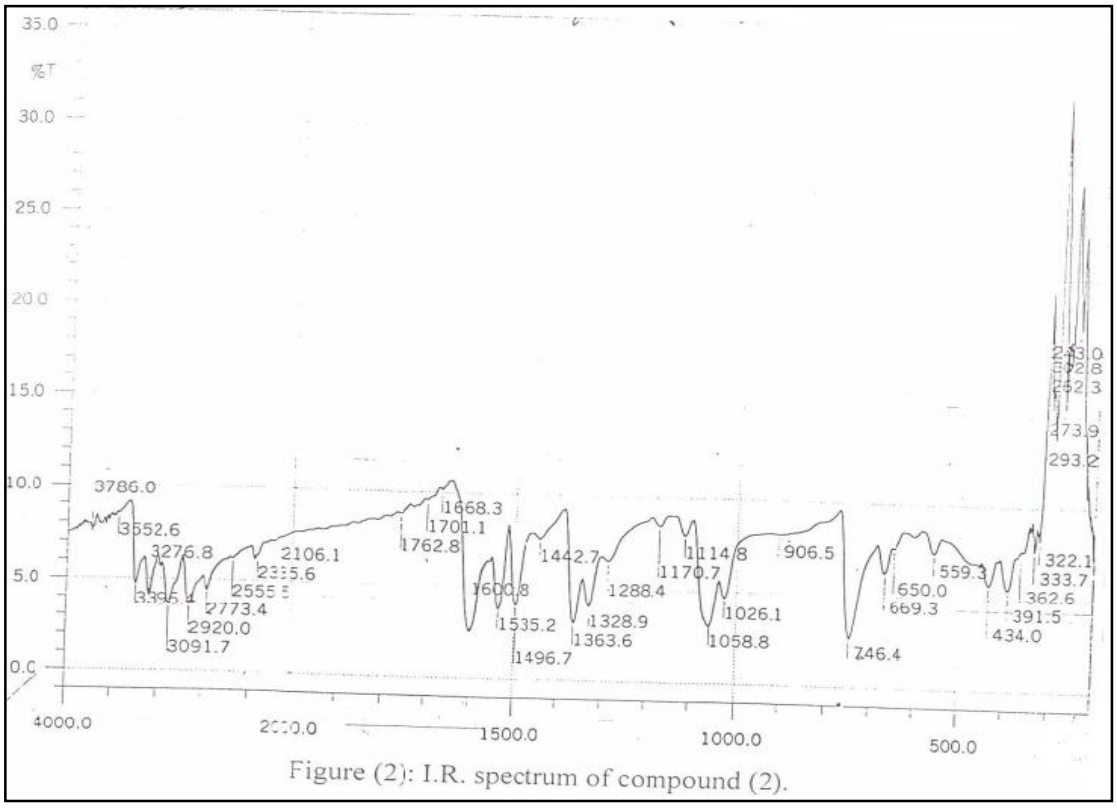


Figure (2): I.R. spectrum of compound (2).

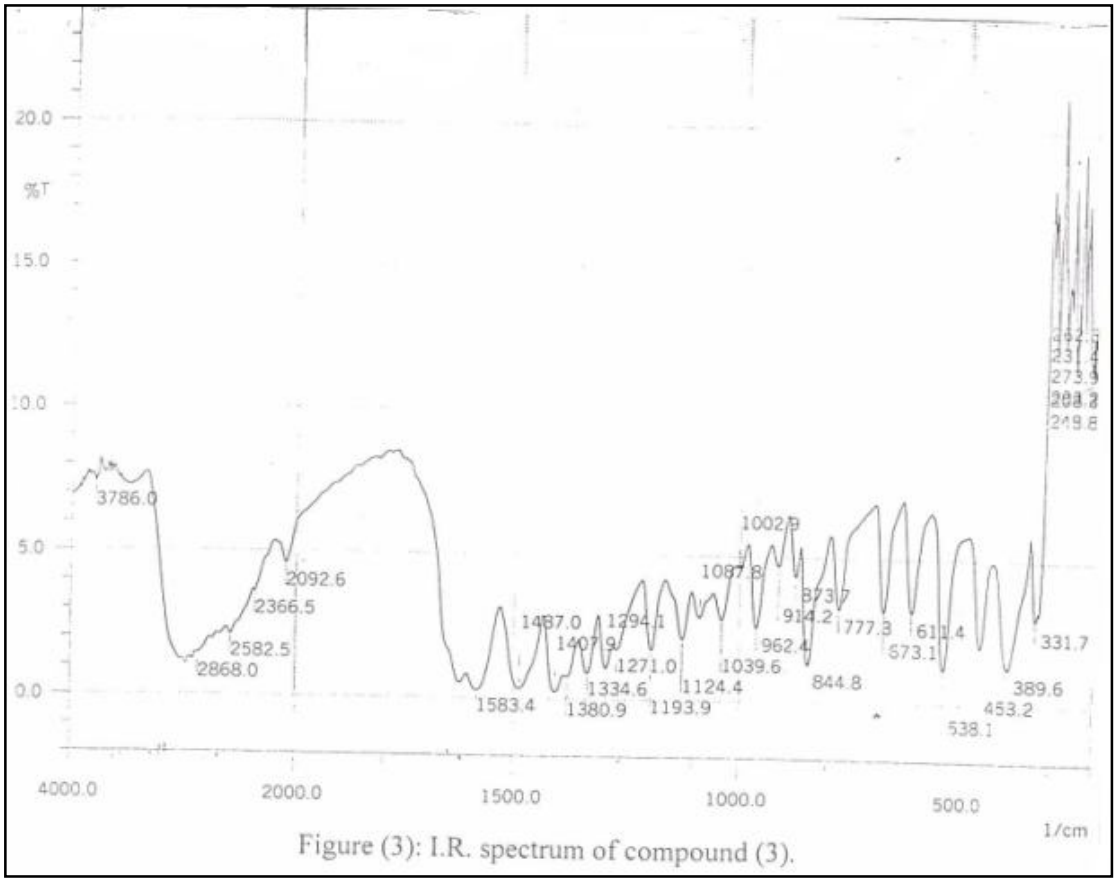


Figure (3): I.R. spectrum of compound (3).

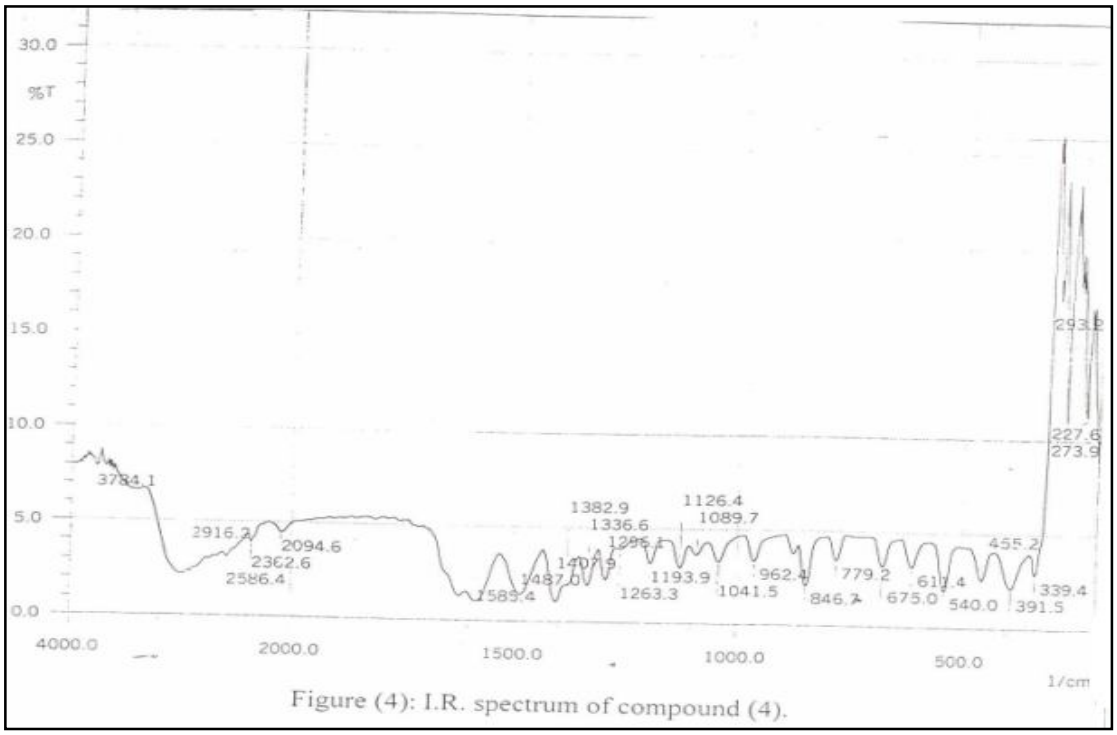


Figure (4): I.R. spectrum of compound (4).

References:

- Barber M. and Rozwadowska- Dowzenko M. (1948) "Infection by penicillin – resistant staphylococci". Lancet,2:64.
- Barry A.L. (1976) "The Antimicrobiological Susceptibility Test practical and practices", Illus LCO and Febiger, Philadelphia, p.180.
- Bertram G. Katzung (1998) "Basic and Clinical pharmacology". Seventh Edition: pp.762.
- Cecil R., and Neutrath H.,(Editor) (1963) " The proteins" vol.12,2nd , Academic press, New York, pp.379.
- Courvalin P. and Fiaudt M. (1980) "aminoglycoside-modifying enzymes of staphylococcus aureus", expression in Escherichia coli, Gene, 9,247.
- Gula A. (1922) J. Amer. , chem. Soc., 44,1502.1922.
- H.K. Alaa (2000), M.Sc. Thesis, Nahrin University, Iraq, 2000.
- L. Ralph shriner, *et. al.*. (1980) "The Systematic Identificationof organic compounds". Sixth Edition,John Wiley&sons ,New York.
- Landy M., Larkum NW., Oswald EJ. and streighoff P. (1943) "Increased Synthesis of p-amino-benzoic acid associated with the development of sulfonamide resistance in staphylococcus aureus", science ,97,265.
- Loncle V., Caseha A., Buu-Hoi A. and Elsolh N. (1993) "analysis of pristinamycin – resistance staphylococcus epidermidis isolates responsible for an outbreak in a parisian hospital", Antimicrob.agents chemother., 37,2159.
- Lyon BR. and Skurray RA. (1987) "antimicrobial resistance of staphylococcus aureus", genetic basis, microbiol. Rev., 51:88.
- Petrow V., stephanson O., Thomas A.J. ,and Will A.M. (1958) J.chem. Soc., 1508.

- Pryor W.A. (1962) " Mechanism of sulfur reaction". MeGraw-Hill, New York, pp. 16-70.
- Robert M. Silverstein, G. Clayton Bassler, and terence C.Morrill (1981) "Spectrometric identification of organic compound", fourth edition, John Wiley &sons, New York.
- Vogal's (1978) "Text Book of practical organic chemistry".
- Weisblum B. (1985) " Inducible resistance to macrolides,Lincosamides and streptogramin type B antibiotics, the resistance phenotype, itsBiological diversity and structure elements that regulate expression- a review." J antimicrob. Chemother., suppl A,63,16.

طريقة جديدة لتحضير المركبات الحاوية على الاصرة سلفون- ز.

علاء حسين الدراجي

قسم الكيمياء - كلية العلوم - جامعة ميسان

الخلاصة:

في هذا البحث تم تحضيرها اربع مركبات (سلفون- ز) حيث س= نايتروجين، اوكسجين، كبريت، و غيرها من الجذور المشابه لها بواسطة طريقة جديدة ، تمتاز هذه الطريقة بانها؛ بسيطة و سهلة، تتطلب وقت قصير في عملية التحضير (45) دقيقة كحد اقصى،من مواد اولية متوفرة، رخيصة نسبياً، نسبة انتاج عالية (75-96%)، لكن جميع هذه المميزات تعتمد على طبيعة المواد المستخدمة في هذه الطريقة. جميع نتائج البحث تم تشخيصها بواسطة؛ تقنية درجة الانصهار، الفصل بواسطة الطبقة الرقيقة، و تقنية الاشعة تحت الحمراء. بالاضافة الى الفعالية الحياتية حيث قيست للمركبات المحضرة في هذا البحث و تمت دراسة المركبات المحضرة على انواع مختلفة من الكائنات الدقيقة.