Synthesis and Preliminary Antibacterial Activity of Some New Schiff's Base Compounds Derived From 5,5'- dimercapto-4,4'-diamin Bis-1,2,4-Triazole

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Summary

The present work consists of three parts, the first part deal with the synthesis of some new bis -1,2, 4-triazole involve five steps as show in scheme(1-1).

The second part (characterizatization):The synthesized compounds have been characterized on the basis of spectral analysis (IR and UV) spectroscopy ,there melting point and the results are compatible with their assigned structures .

The third part :Antibacterial Activity, some of the synthesized compounds were screened for antibacterial activity against ***Staphylococcus aureus***, ***Escherichia coli***, ***Salmonella typhi*** and ***Pseudo aerugenosa***, the preliminary results are shown in Table (3-1).

الخلاصة

يتألف البحث من ثلاثة أجزاء ، الجزء اللاول ويعنى بتحضير بعض المركبات الجديدة لـ بس-١، ٢ ، ٤- ترايازول والمتضمنة خمس خطوات وكما موضح بالمخطط (١-١) .

إما الجزء الثاني فقد اختص بتشخيص المركبات المحضرة وباستخدام طيف الأشعة فوق البنفسجية والأشعة تحت الحمراء وقياس درجات انصهار المركبات المحضرة وقد دلت النتائج المستحصلة على صحة التراكيب المقترحة .

إما الجزء الثالث فقد اختص بدراسة الفعالية البيولوجية ضد أنواع منتجة من البكتيريا الموجبة والسالبة لصبغة كرام . والجدول (٣ -١) يوضح النتائج الأولية لهذه الفعالية .

1.0 INTRODUCTION

Derivatives of 1,2 ,4- triazole constitute an important family of heteroeyelic compound[١]. Since many of them display a remarkable biological activity **,**their synthesis and transformations have been received particular interest for along time and has wide variety of therapeutically interesting drugs[2] **.** 1,2 ,4-triazole have been reported to show antibacterial [3-4] fungicidal[5] and nematocidal agents[6].

There are several method for the synthesized of 1,2,4-triazole[7-8-9-10] . In the present investigation the bis-1,2,4-triazole were synthesized by CS_2 \ KOH and hydrazine hydrate with oxalic dihydrazide[11-12] . Saris of new substituted bis-1,2,4- triazole derivatives (Schiff's base) were synthesized as antibacterial agent.

1.1 METERIALS AND METHODS

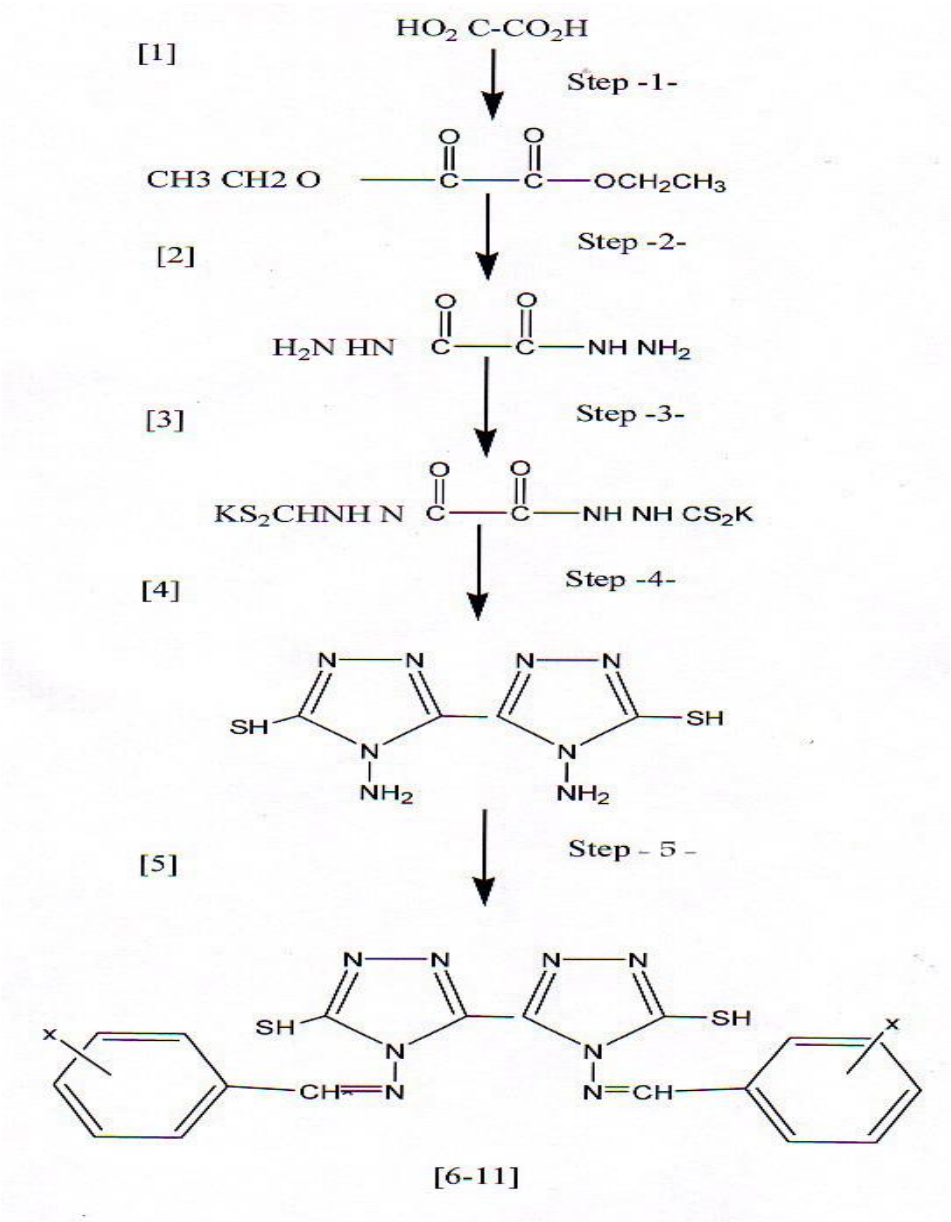
Melting point were recorded on electro thermal apparatus and are uncorrected . IR spectra were obtained on perkin - Elmer 1310 spectrophotometer .

UV spectra were recorded on ashinadzu spectrophotometer .

The stepwise synthesis of bis- 1,2,4 - triazole which were derived from oxalic acid are out lined in scheme (1-1) .

Step-1- Synthesis of diethyloxalate [13] ***[2]:***

Concentrated sulfuric acid (2.5 ml) was added drop wise with continuous stirring to (1 mol) of compound [1] in ethanol (100 ml). The mixture was refluxed for three hours, and then cooled to room temperature. Saturated sodium carbonate solution was added until solution became basic to litmus. The resulting oily product was extracted with ethyl acetate, the ethyl acetate layer, was collected dried and evaporated to give compound [2] as oil. yield (85%).



Scheme (1-1): Reagents and conditions: step-1- anhydrous ethanol, H_2SO_4, reflux (3h); step-2- hydrazine hydrate, EtOH, reflux (4h); step-3- CS_2, hydrazine hydrate, KOH, stirring (5h); step-4- hydrazine hydrate ,reflux (2h); step-5- appropriate aromatic aldehyde reflux (3h).

Step-2- Synthesis of oxalic dihyrazide [14][3]:

To a solution of (0.1 mol) of [2]in absolute ethanol (50 ml), was added (40 ml) of (50%) hydrazine hydrate, and the mixture was refluxed, for 4 hr. a white solid mass, which separated on cooling, was collected by filtration and re-crystallized from ethanol into white crystalline solid.The m.p.(245 C^o), yield (86%).

Step-3- Synthesis of dipotasium-bis-(dithio carbazoat)carbonyl[11-12] [4]:

Carbon disulfide (0.2 mol) was added to a solution of [3] (0.1mol) and KOH (0.2 mol) in ethanol (100ml) with continuous stirring at room temperature. Stirring was continued for (5h) and then the xanthate intermediate [4] was filtered, washed with ether. The Yield (68%) and the M.P > 360^{o}C .

Step-4- Synthesis of 5,5'- dimercapto-4,4'-diamin-bis -1,2,4-triazole[5] :

A solution from the xanthate salt(0.1 mol) and hydrazine hydrate(50%) (40ml) was suspend directly and heated under reflux for (2h). On cooling the mixture was diluted with water (100ml) and filtered, then neutralized with (10%) HCl. The separated crude produced was filtered,

dried and crystallized from aqueous ethanol, to give compound [5].The yield (55%),the M.P was (216^{o}C)

<u>Step-5-</u>Preparation of 5,5'-dimercapto-4,4'-diarylideneamino-bis-1,2,4-triazole[13][6-11]:

To a hot ethanolic solution of [5]. (0.01mol) A solution of substituted benzaldehyde (0.02 mol) in (10ml) ethanol was added, the reaction mixture was refluxed for (3) hours. On cooling the separated solid was filtered and recrystallized from ethanol . The Yield and the M.P in table (2-1).

2.1 RESULTS AND DISCUSSION:

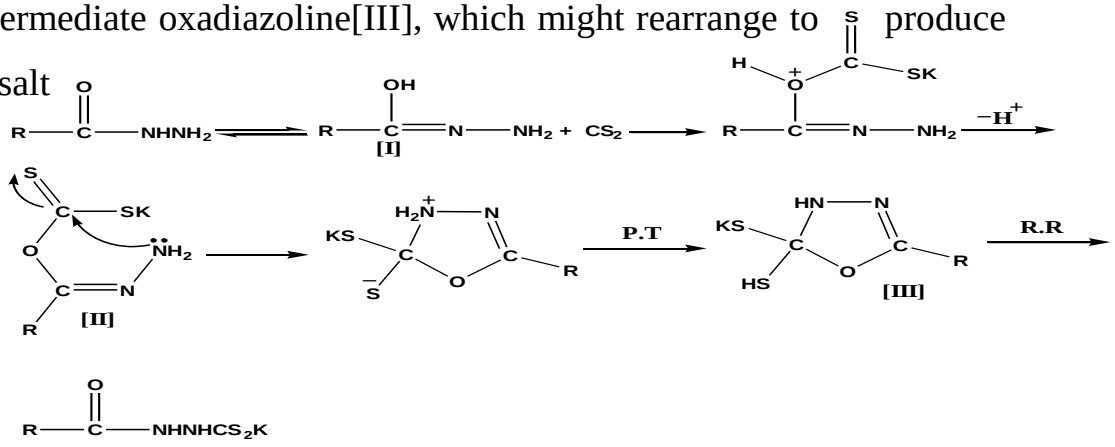
The structure of ester compound [2] was verified from the highly depressed melting point compared with melting point of compound [1] and by IR-spectrum. The disappearance of broad O-H stretching in the region (3350 cm^{-1}) and the appearance of carbonyl group of ester at the region (1725 cm^{-1}), and a stretching band of (C-H) aliphatic at (2900 cm^{-1}) , stretching band at (1375 and 1465 cm^{-1}) due to (CH_2) and (CH_3) respectively . Were utilized to confirm the esterification of compound [1].

Oxalic dihydrazide [3] was synthesized from compound [2] and hydrazine hydrate, as previously described by Gatterman [14]

The authenticity of product was confirmed by its melting point (245 ^{o}C) and by IR -spectrum. stretching bands at (3284, 3193 and 3041 cm^{-1}) which assigned to the asymmetrical and symmetrical stretching bands of NH_2 and (N-H) group. Also the IR -spectrum showed a shift in the carbonyl stretching band from (1725 cm^{-1}) in its ester [2] to (1680 cm^{-1}) (amide) in the hydrazide.

5,5'-dimercapto-4,4'-diamino-bis-1,2,4-triazole was prepared by stirring oxalic dihydrazide [3] with carbon disulfide in ethanolic potassium hydroxide gave the xanthate salt [4] namely dipotassium-bis-(dithiocarbazoat) carbonyl in good yield (m.p>360 ^{o}C).

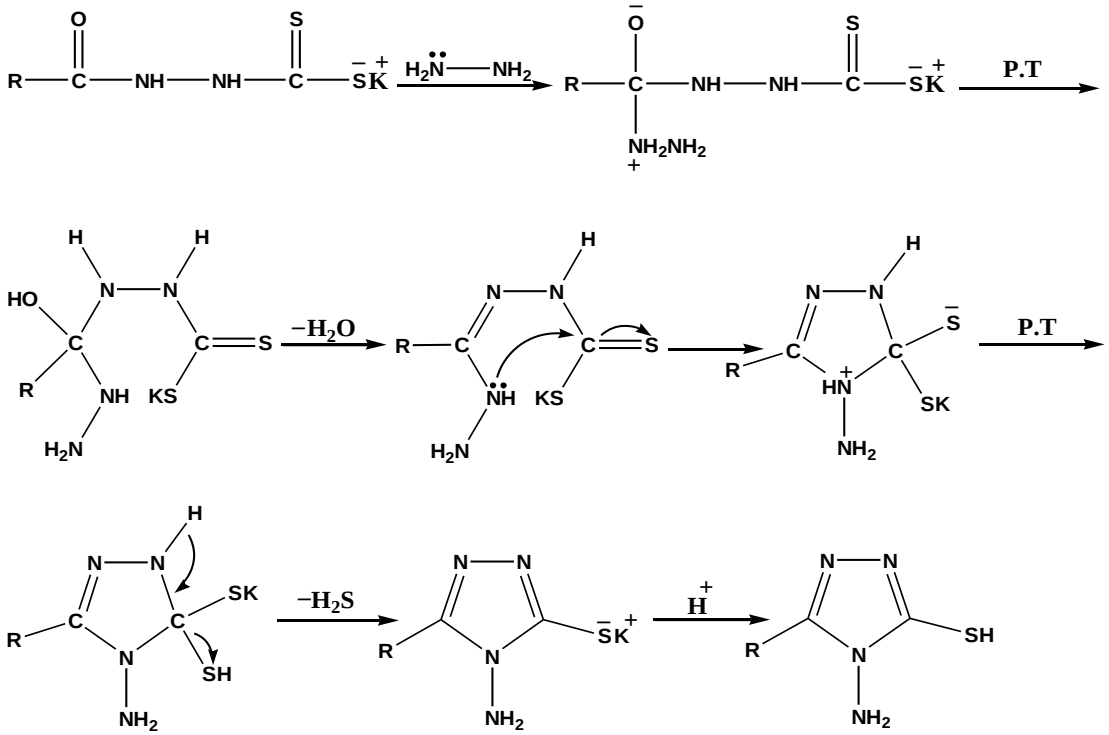
The formation steps of this salt [4] were suggested by Young and Wood[15]. The mechanism includes the attack of hydroxyl group of the enol of hydrazide [3] on the thione group of the carbon disulfide to form the salt (xanthate)[II], then undergoes interamolecular addition forming the intermediate oxadiazoline[III], which might rearrange to produce the salt [4] .



Scheme 2-1: The proposed mechanism for the formation of Xanthate Salt.

The xanthate salt [4] was characterized by IR-spectroscopy , the characteristic IR-features showed broad (N-H) stretching band at (3300cm^{-1}). Intense band at (1615cm^{-1}) due to (C=N) stretching vibration. The (C=O) appeared at (1650 cm^{-1}). The spectrum showed absorption

band at (1060 cm^{-1}) due to (C=S) stretching vibration . The reaction of xanthate salt [4] with hydrazine hydrate afforded the cyclization product [5].



Scheme 2-2: The proposed mechanism for the formation of 1,2,4- triazole ring

The structure of 1,2,4-triazole [5] was characterized from it is melting point (216^{o}C).The IR-spectrum showed the bands at (3330-3230cm^{-1})and (3150cm^{-1}), which are due to (NH_2) and (NH) asymmetrical and symmetrical stretching vibration, also the IR-spectrum displayed two bands, the first at(1060 cm^{-1}) which is due to (C=S) stretching and the weak one at (2240 cm^{-1}) which attributed to the (S-H)stretching. The bands at (1615cm^{-1}) due to (C=N) stretching vibration.

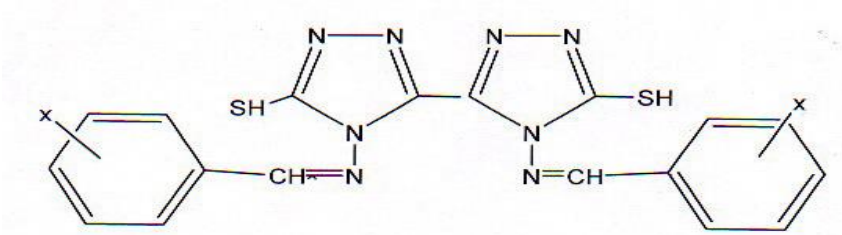
The triazole [5] was then condensed with the appropriate aromatic aldehydes in refluxing ethanol to afford the corresponding Schiff's bases [6-11].formation of these condensation products (Schiff's bases) was confirmed by measuring their melting points and spectral analysis. The IR characterization data are given in Table (٢-1).

The IR spectra displayed the disappearance of bands at (3330 cm^{-1}) and (3150 cm^{-1}) due to NH_2 stretching in the starting material bis-1,2,4-triazole [5] and also showed bands for (C-H) aromatic and (C=N) stretching vibration.

Ultraviolet-Visible spectrophotometer technique is also used to characterize the bis-1,2,4-triazole compounds , the ultraviolet-visible spectra of these compounds in solvent (DMSO). The characteristic absorption bands located at the wave length (λ_{max}) range between (285-335 nm).

These electronic spectral features are similar to those reported for 1,2,4-triazole compounds[16].

Table (2-1):The IR spectral and physical properties data information of compounds [6-11]



X=p-NO2[6],m-NO2[7],p-OH[8],p-Me[9],p-N(CH3)2[10],p-Cl[11]

3.1 Biological activity of the synthesized compounds:

The test was performed according to the disk diffusion method [17]. The prepared compounds were tested against one strain of Gram +ve bacteria (***Staphylococcus aureus***), and Gram –ve bacteria (***Ps. aerugenosa***). Prepared agar and Petridishes were sterilized by autoclaving for (15min) at 121 ^{o}C. The agar plates were surface

Compound no.	C-H Aromatic	C=N	yield	M.P	M.W calc.	other
6	**3100**	**1610**	٥٥	١٦٣	٤٩٦	**ν_{as}, ν_{s} (NO_2) at 1530-1350**
7	**3080**	**1650**	٤٥	١٤٢	٤٩٦	**ν_{as} ν_{s},(NO_2) at 1530 -1340**
8	**3100**	**1650**	56	١٢٣	٤٣٨	**brod (OH) at 3500-3150**
9	**3150**	**1610**	50	١١٩	٤٣٤	
10	**3090**	**1650**	52	١٧٠	٤٩٢	
11	**3120**	**1660**	40	١١٠	٤٧٤	

inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all (6mm) in diameter, were filled with 100µl of the prepared compounds (1mg of the compound dissolved in 1ml of DMSO solvent). These plates were incubated at (37^{o}C) for (24hrs.). The inhibition zones caused by the various compounds on the bacteria were examined. The results of the preliminary screening test are listed in Table (3-1).

Table (3-1): Antibacterial activity of the synthesized compounds.

Compound no.	Staph. aureus	E. coli	Sal. Typhi.	Ps. aerugenosa
5	++	+	-	++
6	+	+	+	+
10	+	+	+	++
11	++	+	+	-

Key to symbols:
Moderately active = ++ (inhibition zone 11-20mm).Slightly active = + (inhibition zone 5-10mm).
Inactive = - (inhibition zone <5mm).

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