Synthesis and Characterization of Some New Derivatives of Heterocyclic Compounds and its Polymers with study their Biological Activity

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Abstract:
Three series of heterocyclic compounds were synthesized derived from 2-amino-5-styryl-1,3,4-thiadiazole[1]. The first series includes the Schiff bases(II) prepared from the reaction between 2-amino 5-styryl-1,3,4-thiadiazole(I) with different substituted benzaldehydes in presence of glacial acetic acid and absolute ethanol. Then these derivatives have transformed to its polymers(III) by using dibenzyloperoxide as initiator. The third series was prepared from the reaction of the Schiff bases and 2,3-dimethyl maleic anhydride to give oxazepine compounds(IV). The reactions was followed by TLC., and then these identified by FTIR, UV./Vis., ¹H-NMR,¹³C-NMR for some of them) spectra and melting points. The biological activity for some of the prepared compounds was studied against Staphylococcus Sal. Typhi, Ps. Arugenosa and Escherichia Coli.

Introduction:
2-amino-1,3,4-thiadiazole constitute an important class of compounds having a wide spectra of biological activity. A great number of variously substituted 1,3,4-thiadiazole derivatives have been synthesized and tested for their fungicidal¹⁻³, nematocidal⁴⁻⁶, antibacterial⁷⁻⁹ and anti-inflammatory activities⁵, besides the industrial applications⁶. Most of the substitution reactions have been carried out of (2) and (5) position of the thiadiazole ring. The synthesis of these heterocycles has received considerable attention in recent years¹⁷⁻²⁰. Khasrow et. al.¹⁹ have synthesized some new substituted 1,3,4-thiadiazole and their derivatives through the intermolecular cyclization of 1,4-disubstitution thiosemicarbazides. The 5-amino 1,3,4-thiadiazole analogues were also reported to be active against vaccinia¹⁰ substituted 1,3,4-thiadiazole with aryl mercurium chloride have been synthesized under microwave irradiation in dry media¹¹. In view of these observations, synthesis of series of derivatives of amino thiadiazole with its polymers have been synthesized.

Experimental Part:
Materials:
Chemicals employed were of analytical reagent and used without further purification. Melting points were determined by using an "Electrothermal" melting apparatus IR spectra were recorded on a SHIMADZU Infrared spectrophotometer Fourier transform FTIR-8400S in the 4000-200 cm⁻¹ range using KBr disc. The reactive process was monitored by TLC until the starting material nearly disappeared. All reactions were followed by TLC (benzene/methanol) (2:1). NMR Ultra Shield 300 MHz, Bruker 2003, Switzerland. UV./Vis.spectra:Ultraviolet visible spectrophotometer company HITACHU U2000 spectrophotometer.

1-Preparation of 2-amino 5-styryl-1,3,4-thiadiazole [I]:

A mixture of (0.01mole) of cis-cinnamic acid and (0.01mole) of thiosemicarbazide in (10ml) of POCI₃ was refluxed for 4hrs. The excess of POCI₃ was removed and the residue dissolved in distilled water (50ml) and heated for 1hr. Then, the resulting product cooled, filtered and the filtrate was neutralized with KOH. The precipitate was filtered, dried and re-crystallized from ethanol.

2-Preparation of Schiff bases [II]:

The hot ethanol solution of 2-amino 5-styryl-1,3,4-thiadiazole (0.01mole) mixed with a solution of the corresponding substituted benzaldehyde (0.01mole) in (10 ml) of absolute ethanol with some drops of glacial acetic acid. The mixture was refluxed for 30 minutes. The product was separated by filtration. The physical properties of these compounds are listed in Table (1).
3-The polymerization (III):
The polymerization of these monomers was carried out in THF by using AIBN or dibenzoyl peroxide as initiator. A solution of the monomer (0.5gm) in THF (15ml) and (6mg) of initiator were mixed in a flask. The mixture was refluxed in water bath. After 24hrs., the contents of the flask were poured into a large amount of methanol/water to precipitate the polymer. See Table(2).

Table (2): Physical properties of the prepared polymers (III).

<table>
<thead>
<tr>
<th>Comp.No.</th>
<th>R</th>
<th>M.P.°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>IIb</td>
<td>p-Br</td>
<td>110</td>
</tr>
<tr>
<td>IIc</td>
<td>p-NO₂</td>
<td>120</td>
</tr>
<tr>
<td>IIId</td>
<td>p-Ni(CH₃)₂</td>
<td>&gt;250</td>
</tr>
<tr>
<td>IIe</td>
<td>p-OH</td>
<td>150</td>
</tr>
<tr>
<td>IIIf</td>
<td>2,4-diOH</td>
<td>122</td>
</tr>
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</table>
| IIg      | p-Me       | 220 dec.

4-Preparation of 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-aryl-2,3-dihydro-1,3-oxazepine-4,7-dione (IV).
2-N-Arylidene imino (III ) added 2,3-di methyl maleic anhydride to give 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-arylidene-2,3-di hydro -1,3-oxazepine-4,7-diones (IV ). These compounds were identified by their melting points and IR spectra. See Table (3).

Table (3): Physical properties of the compounds (IV).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>M.P.°C</th>
<th>Yield %</th>
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<tr>
<td>IVA</td>
<td>H</td>
<td>C₅H₄N₂O₅S</td>
<td>417</td>
<td>220</td>
<td>70</td>
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<tr>
<td>IVb</td>
<td>p-Br</td>
<td>C₅H₄N₂O₅SBr</td>
<td>496</td>
<td>205</td>
<td>75</td>
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<tr>
<td>IVc</td>
<td>p-Ni(CH₃)₂</td>
<td>C₅H₄N₂O₅SBr</td>
<td>460</td>
<td>210</td>
<td>70</td>
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<tr>
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<td>p-Me</td>
<td>C₅H₄N₂O₅S</td>
<td>431</td>
<td>200</td>
<td>70</td>
</tr>
<tr>
<td>IVf</td>
<td>2,3-dioH</td>
<td>C₅H₄N₂O₅S</td>
<td>462</td>
<td>180</td>
<td>75</td>
</tr>
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</table>

Results and discussion:
Thiadiazole derivatives were prepared by the direct reaction between the corresponding cinnamic acid and dry powder of thiosemicarbazide in presence of phosphorus oxychloride to give compound I.

The IR spectrum of compound I Fig.(1), exhibited significant two bands in the region 3110-3250 cm⁻¹, which could be attributed to a symmetric stretching vibration of NH₂ group¹² besides this, a band at about 1612 cm⁻¹, due to cyclic C=N, stretching is also observed.

The Shiff bases compounds were synthesized from 2-amino 5-styryl-1,3,4-thiadiazole with different substituted aldehydes in presence of glacial acetic acid. The synthesis of these compounds was carried out according to the steps outlined in scheme 1, and the physical properties are given in Table (1).

The reaction was followed by disappearance of NH₂ absorption band at 3500 cm⁻¹ and appearance of C=N absorption band in the IR spectra of the products Table(4). ¹H-NMR spectrum Fig.(2a) of compound (IIIh) showed a signals at δ 3.0(6H-singlet ), δ 6.7(1H-doublet), δ 7.6 (2H-doublet) and δ 9.3(5H-singlet).

In the ¹³C-NMR spectrum Fig(2b), the appearance of the two carbons of di-methyl rings at 40ppm. The signals at 145 and 190 ppm attributed to the benzene rings. The thiadiazole carbon atoms appeared at 125 and the signal at 111ppm due to carbon of azomethine group. The signal at 132ppm may attributed to the carbon of styrene ring.

Table (4): Infra-red and Uv./Vis. spectral data for compounds (II).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>v =C=C Ar.</th>
<th>v =C-H Ar.</th>
<th>v C=N</th>
<th>v C-H Aliph.</th>
<th>C=N</th>
<th>N-N</th>
<th>C-S</th>
<th>UV,λmax (nm),DMSO</th>
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<tr>
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<td>1590,1461</td>
<td>3080</td>
<td>1610</td>
<td>2900</td>
<td>1390</td>
<td>1102</td>
<td>650</td>
<td>250</td>
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<tr>
<td>IIb</td>
<td>p-OH</td>
<td>1585,1473</td>
<td>3100</td>
<td>1600</td>
<td>2890</td>
<td>1400</td>
<td>1177</td>
<td>681</td>
<td>270</td>
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<td>IIc</td>
<td>p-Cl</td>
<td>1589,1482</td>
<td>3090</td>
<td>1600</td>
<td>2980</td>
<td>1385</td>
<td>1180</td>
<td>677</td>
<td>260,370</td>
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<td>IIId</td>
<td>p-NO₂</td>
<td>1560,1466</td>
<td>3100</td>
<td>1600</td>
<td>2900</td>
<td>1400</td>
<td>1178</td>
<td>645</td>
<td>280,320</td>
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<tr>
<td>IIe</td>
<td>m-NO₂</td>
<td>1590,1501</td>
<td>3100</td>
<td>1620</td>
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<td>1395</td>
<td>1166</td>
<td>684</td>
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<td>IIIf</td>
<td>2,4-diOH</td>
<td>1580,1455</td>
<td>3090</td>
<td>1630</td>
<td>2890</td>
<td>1387</td>
<td>1165</td>
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<td>IIg</td>
<td>p-Br</td>
<td>1580,1494</td>
<td>3100</td>
<td>1620</td>
<td>2890</td>
<td>1400</td>
<td>1170</td>
<td>680</td>
<td>250,370</td>
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<tr>
<td>IIh</td>
<td>p-Ni(CH₃)₂</td>
<td>1590,1488</td>
<td>3080</td>
<td>1630</td>
<td>2900</td>
<td>1378</td>
<td>1132</td>
<td>671</td>
<td>260,370</td>
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<tr>
<td>IIi</td>
<td>p-Me</td>
<td>1590,1467</td>
<td>3100</td>
<td>1620</td>
<td>2900</td>
<td>1388</td>
<td>1169</td>
<td>653</td>
<td>280,370</td>
</tr>
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</table>
Fig (1): The IR spectrum of compound (I).
Fig(2a): The $^1$H-NMR spectrum of compound (IIh).
Fig 2b: The $^{13}$C-NMR spectrum of compound (IIh).
R=H, p-OH, p-Cl, p-N(CH₃)₂, p-NO₂, p-CH₃, m-NO₂, 3,4 Di-OH.

Scheme (I): The synthetic routes of the prepared compounds.

2- The polymers:
These polymers were prepared according to Kapzuk’s method[13]. The polymerization of the monomers (II) was carried out in tetrahydrofuran (THF) with dibenzoyl peroxide as initiator. The structures of the obtained polymers were confirmed from their melting points, IR, UV/Vis. spectra and the viscosity were measured. The IR spectra for these polymers, showed the disappearance of the absorption band of 1600-1610 cm⁻¹ assigned to the double bond (C=C) in the monomer, it also showed the characteristic band of the monomer. The absorption band at 1620 cm⁻¹ which is typical to the azomethine group of Schiff bases, it also showed the absorption bands which characteristic to(C=C) aromatic and at 600-800 cm⁻¹ that belongs to the para-substitution of benzene ring. The UV/Vis. spectra of these compounds are shown in Table (5). It showed the absorption band at 260 nm and 362-400 nm which attributed to the (C=O) and(C=C) groups respectively, that represents the n-π and π- π* vibration. All these polymers were soluble in all common organic solvents, such as dimethyl formamide (DMF), dimethyl sulphoxide(DMSO), chloroform (CHCl₃), and THF. The viscosity measurements of synthesized polymers of this study were determined by using viscometer (type Ubbelohod viscometer) was placed in water bath, the temperature was controlled by using a thermostat(Table 6).
Synthesis of 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-aryl-2,3-dihydro-1,3-oxazepine-4,7-dione IV.

The reaction of Schiff bases with maleic anhydride is a sort of cycloaddition reaction. Cycloaddition is a ring formation that results from the addition of π bonds to either δ or π bonds with formation of new δ bonds. This class of reaction and its reverse encompasses a large number of individual types (12).

Huisgen (15) has formulated a useful classification of diverse cycloadditions in terms of the new σ bonds, the ring size of the product, and the number of atoms in the components taking part in the cycloaddition. This cycloaddition is classified as 5+2→7, implying a 5-membered heterocyclic ring, but the mechanism involves addition of one σ bond (CH=CH₂) to one π bond (N=C) to give 4-membered cyclic transition state which opens into maleic anhydride (5-membered ring) to give 7-membered heterocyclic ring.

It is obvious that N-aryl-1,3,4-thiadiazole contains both a (C=C) function and an azomethine function (C=N) and either one or both are able to react with maleic anhydride. The reaction, actually, involves interaction between the Homo orbital of maleic anhydride with Lumo orbital of (C=O) or (C=N), since the oxygen has higher electronegativity than nitrogen, the energy gap between its Lumo orbital and the Homo orbital of maleic anhydride is larger than it is between the Lumo orbital of azomethine and the Homo orbital of maleic anhydride. Energetically, the interaction between the Homo orbital of maleic anhydride and the Lumo orbital of azomethine is more favorable. Incidentally, even in the absence of (C=N) no interaction between the Homo orbital of maleic anhydride and the Lumo orbital of (C=C) is observed for the same reason. It is obvious that the two absorption bands at (1740-1780)cm⁻¹ and at (1800-1850)cm⁻¹ in the IR spectrum of pure maleic anhydride (12) have disappeared when the anhydride became part of the 7-membered heterocyclic ring. The (C=O) group of the title compounds absorbs at (1700-1750)cm⁻¹ (oxazepine) and (C-O), (O=C-O-) at (1000-1300)cm⁻¹. This confirms the assigned 7-membered heterocyclic ring structure.

Biological activity:

In this work, the anti-microbial test was performed according to agar well diffusion method (16). The prepared compounds were tested against four pathogenic microorganism, *staphylococcus Aurus*, *E. Coli*, *Sal. Typh* and *Ps. aerugenosa*. In the solidified media (Nutrient agar), suitable spaced apart holes were made (6mm in diameter) these holes were filled with (0.1ml) of prepared compounds concentration that dissolve in DMSO (Dimethyl sulphoxide) after spread the bacteria on agar, these plates were incubated at 37°C for 24 hour, the zone of inhibition of bacteria growth around the hole was observed and measured in mm and are represented by (-), (+), (++), and (+++) depending upon the diameter and clarity as in Table (7).

The preliminary screening results reveal that the compounds contained (NO₂ -), compound [IIe ] exhibit the highest antibacterial activity against while the other compounds showed either low or no activity against both or all organisms.

<table>
<thead>
<tr>
<th>Comp.No.</th>
<th>Staphaureus</th>
<th>E.Coli</th>
<th>Sal. Typhi</th>
<th>Ps.aerugenosa</th>
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<tr>
<td>IIa</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>IIb</td>
<td>-</td>
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<td>IIc</td>
<td>+</td>
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<td>IID</td>
<td>+</td>
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<td>±</td>
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<tr>
<td>IIIF</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

Key to symbols: (-) =No inhibition, (±)=6- 9mm, (+)=10-14mm, (++)=15-22mm.
تحضير وتشخيص بعض المشتقات الجديدة غير المتجانسة الحلقة وبينوليراتها
مع دراسة تأثيراتها البايولوجية.

ابتسام خليفة جاسم
خالدة عباس عمران
وغزوان حسن الصميدعي

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قسم الكيمياء، كلية العلوم، جامعة تكريت، جمهورية العراق

الملخص:
تم تحضير عدّة مشتقات من مشتقات المركب 2-إمينو-5-ستاريل من ثلاثاءيد ألتدابير الحديدية. وتم تحضير 2-إمينو-5-ستاريل من حمض البنفسجية. وتم تحضير منiform POCI 3، وتم قواعد بنفسجية (I) ومن POCI 3، وتم قواعد بنفسجية (I) ومن POCI 3
(IV) وتم قواعد بنفسجية (IV) وتم قواعد بنفسجية (IV)
(IV) وتم دراسة تأثير هذه المشتقات على بعض أنواع البكتريات المقاومة لعلاج ثلاثية-ثائيابات (III)
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