Synthesis and study of antibacterial activity of some new bis 1,3,4-oxadiazole derivatives

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Abstract
Some of succinic acid hydrazide derivatives were prepared from the reaction of succinic acid hydrazide(3) with different benzaldehydes, then cyclization of hydrazones (4a-e) in glacial acetic acid and lead dioxide resulted into the formation of new bis-1,3,4-oxadiazole derivatives (5a-e). The reactions were followed by TLC and the synthesized compounds were confirmed by their IR and U.V. spectra. The antibacterial activity of the synthesized compounds against the four bacterial species was also studied.

Keywords: Hydrazone, 1,3,4-Oxadiazole, Antibacterial Activity.

Introduction
Hydrazone and their derivatives have versatile applications in the biological fields as antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular, antitumoral and antibacterial activities1,2,3,4,5,6,7. The synthesis of 1,3,4-oxadiazoles is also of considerable interest due to their various biological activities, such as, nervous system depressing6,7, analgesic8,9, herbicidal10, muscle relaxant11 and tranquilizing activities12.

Experimental
Uncorrected melting points were determined using Electrothermal melting point apparatus(Electrothermal Engineering LTD S-N 10853), IR spectra were recorded by Shimadzu FT-IR spectrophotometer as KBr disc. The UV measurements were obtained using Schimadzu (UV-Visible) spectrophotometer UV-1650 PC. Dimethyl succinate (1) was prepared according to a published procedure20. Dimethyl succinate dihydrazide (2) was prepared following literature reported procedure21. See Fig.(1).

Preparation of 1,2- bis (1-(4-substituted benzylidene)hydrazon-3-oyl)ethane (4a-e).
A mixture of compound (3) (0.01 mole) and substituted benzaldehydes (0.01 mole) in ethanol 25 ml was refluxed for 3 hrs. The precipitate was filtered and crystallized from ethanol. Melting points, yield and (U.V.,IR) spectral data are listed in Table (1), See Fig.(2,3).

Preparation of 1,2- bis (2-(substituted phenyl)-1,3,4-oxadiazole-5-y)ethane (5a-e).
(0.01 mole) of compound (4) was dissolved in 40 ml of glacial acetic acid with stirring for until the obtaining of a homogeneous solution. Lead dioxide (0.01 mole) was added with stirring at 25 °C for 1 hr. The product was poured on crushed ice. The crude material was filtered off and washed with cold water and recrystallized from ethanol. Physical and (U.V.,IR) spectral data are illustrated in Table (2), See Fig.(4,5).

The biological activity
The bacteria species used are listed in Table (3). All strains were obtained from College of Medicine, Tikrit University. They were grown up to the stationary phase nutrient bath at 37 °C and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate22.

Antibacterial assay23
Disc of filter paper (6 mm diameter) were sterilized at 140 °C for 1 hr and impregnated with the germs, absolute ethanol was used as a solvent for compounds (4a-e) and (5a-e). The same solvent was used for antibiotics, blank paper discs of absolute ethanol was used as control. The inoculated plates were incubated at 37 °C for 24 hrs., and the inhibition zone (mm) were measured24. In all experiments, the mean of each triplicate was measured25.

Results and Discussion
Hydrazone compounds (4a-e) were prepared by the condensation reaction of succinic acid hydrazide with substituted benzaldehyde.

The IR characteristic absorption bands of the hydrazones compounds (4a-e) were given appeared at (1606-1656) cm⁻¹ and (1660-1677) cm⁻¹ for (C=N) and (C=O) respectively. While single band at (3193-3247) cm⁻¹ for (N-H).See Fig.(2,3).

The 1,3,4-oxadiazoles (5a-e) was synthesized by the reaction of equimolar amounts of hydrazone (4a-e) with lead dioxide in glacial acetic acid.

The IR spectra of compounds (5a-e) showed the following vibrational absorption bands (1167-1261), (1062-1176), (1008-1087) and (1610-1662) cm⁻¹ which are assigned to (C-O-C, asymmetric, symmetric), (N=N) and (C=N), respectively.

The U.V. spectra gave absorption band at different wave lengths for the resulted hydrazones and 1,3,4-oxadiazoles (in % 95 EtOH), due to n→π* and π→π* transition and all these transition are listed in Table (1,2).

Antimicrobial activity of the compounds (4a-e) and (5a-e) was examined by the agar diffusion method using four different bacterial species i.e. Escherichia coli, Staphylococcus aureus, Salmonella typhi and Pseudomonas aeruginosa.

The results indicated that all the assayed compounds showed activity against the tested organism up to 3.2 mg/disc.

The prepared compounds (4a-e) and (5a-e) showed higher activity towards Staph. aureus and E. coli compared with the other germs.

The hydrazones (4a-e) were more active than 1,3,4-oxadiazoles(5a-e) but the last were more selective with E. coli (Table 3).
Table (1): Physical and spectral data for the compounds (4a-e)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Color</th>
<th>UV nm $\lambda_{max}$</th>
<th>C=N</th>
<th>C=O</th>
<th>N-H</th>
<th>Other</th>
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<tbody>
<tr>
<td>4a</td>
<td>229-231</td>
<td>96</td>
<td>White</td>
<td>308</td>
<td>1652</td>
<td>1672</td>
<td>3193</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>214-216</td>
<td>80</td>
<td>White/ Yellow</td>
<td>338</td>
<td>1606</td>
<td>1660</td>
<td>3247</td>
<td>3326 (OH)</td>
</tr>
<tr>
<td>4c</td>
<td>260-262</td>
<td>87</td>
<td>White</td>
<td>310</td>
<td>1656</td>
<td>1677</td>
<td>3201</td>
<td>-</td>
</tr>
<tr>
<td>4d</td>
<td>241-243</td>
<td>97</td>
<td>White</td>
<td>292</td>
<td>1654</td>
<td>1677</td>
<td>3201</td>
<td>-</td>
</tr>
<tr>
<td>4e</td>
<td>214-215</td>
<td>95</td>
<td>Yellow</td>
<td>332</td>
<td>1656</td>
<td>1676</td>
<td>3195</td>
<td>-</td>
</tr>
</tbody>
</table>

Table (2): Physical and spectral data for the compounds (5a-e)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. °C</th>
<th>Color</th>
<th>UV nm $\lambda_{max}$</th>
<th>IR $\nu$ cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>215</td>
<td>White</td>
<td>306</td>
<td>C-O-C</td>
</tr>
<tr>
<td>5b</td>
<td>246-248</td>
<td>Chocolate</td>
<td>308</td>
<td>N-N</td>
</tr>
<tr>
<td>5c</td>
<td>218-220</td>
<td>Milky</td>
<td>298</td>
<td>C=N</td>
</tr>
<tr>
<td>5d</td>
<td>228-229</td>
<td>White</td>
<td>318</td>
<td>as.</td>
</tr>
<tr>
<td>5e</td>
<td>252</td>
<td>Pale Yellow</td>
<td>352</td>
<td>s.</td>
</tr>
</tbody>
</table>

Table (3): biological activity for hydrazones (4a-e) and 1,3,4-oxadiazoles (5a-e)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Staph. aureus</th>
<th>E. coli</th>
<th>Sal. typhi</th>
<th>Ps. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>4c</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>4d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>4e</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>5a</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>5b</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>5c</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>5d</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5e</td>
<td>-</td>
<td>++</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: (-) = no inhibition, (±) = 5-10mm, (+) = 10-20mm, (++)= more than 20mm.
Fig. (1): IR spectrum of the compound (3)

Fig. (2): IR spectrum of the compound (4a)
Fig. (3): IR spectrum of the compound (4e)

Fig. (4): IR spectrum of the compound (5b)
Fig.(5): IR spectrum of the compound (5d)

References
تحضير ودراسة الفعالية البيولوجية لبعض المشتقات الجديدة من بس، 4-أوكساديازول

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قسم الكيمياء، كلية العلوم، جامعة الموصل، الموصل، العراق


الملخص

تم تحضير بعض مشتقات هيدروزون حامض السكستيك من تفاعل هيدرازيد حامض السكستيك (3) مع بزلديهيدات مختلفة، ثم حوافقة الهيدرازونات المكونة (4a-e) بواسطة حامض الخليك البلجي و ثنائي أوكسيد الرصاص إلى مشتقات جديدة من 4،2-أوكساديازول الثنائية (5a-e)، تم متابعة سير التفاعلات كروموتوغرافيا الطبقية الوقاقة وقد وصفت المركبات المحضرة باستخدام أطياف الأشعة تحت الحمراء وفوتو البنفسجية، كما تمت دراسة الفعالية البيولوجية للمركبات المحضرة ضد أربعة أنواع من البكتريا.

الكلمات المفتاحية: الهيدرازون، 4،2-أوكساديازول، الفعالية المضادة للبكتريا.