Chemical Properties and Bioactive Study of (Benzanil and Oxazepam)-Derivatives

Dr. Nagham Mahmood Aljamali(1), Jehaan Razaq(2), Fatima Abed-Wannase(3)

Asist. Prof. Chemistry Dep., College of Education, University of Kufa, IRAQ.

Abstract:
This bio-chemical study aimed to preparation of cyclic compounds are containing of more than one heteroatoms in their structures like ( N )-nitrogen atome. A seven-membered ring compounds were prepared by condensation of N,N-di methyl amino benzaldehyde with aromatic amines to give compounds \([N_2N_2] \), these compounds were found to react with maleic anhydride to give 7-membered ring \([N_3N_3] \). All these compounds \([N_1N_3] \) were prepared by pericyclic reactions. All compounds have been characterized by (( FT.IR , C.H.N, some them by H.NMR )) biological study and study of chemical properties like solubility.

Keywords: solubility, oxa, azepame, benzene, interaction.

Introduction:
A seven-membered ring have reviewed cyclo addition reaction of alkenes , the cyclic transition state must correspond to one arrangement of the participating orbitals that can maintain a bonding interaction between the reaction components. A pericyclic reaction is one step-process, take place through a single transition state (T.S) with relatively high yield and frequently no side reaction. There are many reactions in organic chemistry that give no evidence of involving intermediates when they are subjected to the usual probes employed for studying reaction mechanisms.

A pericyclic reaction were very puzzling to chemist because they are generally not sensitive to any kind of catalyst or to a change in solvent that involves the cyclization of a conjugated polyne. One \( \pi \)-bond is broken, the other \( \pi \)–bond change position, a new \( \sigma \)–bond is formed and a cyclic compound results. synthesis of these compounds in this work is a class of a pericyclic reaction which is classified as a \( 5+2 \rightarrow 7 \), implying 5-atom component plus 2-atom component leading to 7-membered cyclic ring.

Experimental:
• All chemicals used were supplied from Merck and BDH-chemical company.
• All measurements were carried out by:
• Melting points: Electrothermal 9300, melting point Engineering LTD, U.K
• FT-IR spectra: Fourier transform infrared shimadzu (8300) (FT-IR), Kbr disc was performed by Co. S. Q. Iraq.
• Elemental Analysis (C, H, N): EA-017 mth in center Lab- Institute of Earth and Environmental science, Al-bayt University Jordan.
• UV-Visible spectra: Shimadzu-1700, double beam with computerized, Japan.
• HNMR spectra: in center Lab-Institute of Earth and Environmental Science, Al-bayt University Jordan.
• Biological study in bio-Lab of biology department of science college.
Synthetic Methods:

Synthesis of \( p\)-N,N-dimethyl amine benzylidenearene amino (Schiff's bases) \([N_2-N_{17}]\)

General procedure\(^6,11,13\)

A mixture of equimolar amounts (0.05 mole, 6.30 ml) of \( p\)-N,N-dimethyl amine benzaldehyde \([N_1]\) and primary aromatic amine dissolved in (50 ml) of absolute ethanol with some drops of acetic acid was refluxed for (3 hrs). The reaction mixture was then allowed to cool to room temperature and solid product was filtered and recrystallized from ethanol to give colored crystals from compounds \([N_2-N_{17}]\)

![Synthesis of p-N,N-dimethyl amine benzylidenearene amino (Schiff’s bases)](image)

Synthesis of 2-(\( p\)-N,N-dimethyl amine benzyl)-3-aryl-2,3-dihydro [1,3]-oxazepine-4,7-diones (Oxazepine derivatives) \([N_{18}-N_{33}]\).

General procedure \(^{11,12,18}\):

A mixture of equimolar amounts (0.02 mole) of Schiff's bases \([N_2-N_{17}]\) and maleic anhydride in dry benzene was refluxed for (4-5 hrs), the solvent was removed and the resulting colored crystalline solid was recrystallized from dry 1,4-dioxane to give the title products of compounds \([N_{18}-N_{33}]\).

![Synthesis of 2-(p-N,N-dimethyl amine benzyl)-3-aryl-2,3-dihydro [1,3]-oxazepine-4,7-diones](image)

Results and Discussion:

The reaction of any anhydride with anil compounds are classified as a [5+2=7], 5-atom component plus 2-atom component leading to 7-membered ring, the pericyclic reactions in this work involves synthesis of compounds by condensation with aromatic amines to give Schiff's base \([N_2-N_{17}]\) according to well-known procedure\(^{6,11,13}\). Compounds \([N_2-N_{17}]\) react with maleic anhydride to produce 7-membered heterocyclic compounds \([N_{18}-N_{33}]\) of oxazepine.
If (Ar):

\[
\begin{align*}
\text{Ar} &= \begin{array}{c}
\text{NH}_2 \text{CH} - \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}, \\
\text{Ar} &= \begin{array}{c}
\text{NH} \text{COCH}_2 \text{H} \text{Ar} \text{CH}_2 \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}, \\
\text{Ar} &= \begin{array}{c}
\text{NH} \text{COCH}_2 \text{H} \text{Ar} \text{CH}_2 \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}, \\
\text{Ar} &= \begin{array}{c}
\text{NH} \text{COCH}_2 \text{H} \text{Ar} \text{CH}_2 \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}, \\
\text{Ar} &= \begin{array}{c}
\text{NH} \text{COCH}_2 \text{H} \text{Ar} \text{CH}_2 \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}, \\
\text{Ar} &= \begin{array}{c}
\text{NH} \text{COCH}_2 \text{H} \text{Ar} \text{CH}_2 \\
\text{OH} - \\
\text{OH} - \\
\text{H}
\end{array}
\end{align*}
\]

Synthesized compounds \([N_{17} - N_{33}]\) have been characterized by their melting point and spectroscopic methods (UV-Visible, FT-IR, H.NMR spectrum, and (C. H. N) analysis), study of biological activity and study of chemical properties like solubility of compounds in various solvents.

H.NMR-spectrum:

H.NMR-spectrum of compound \([N_{17} - N_{33}]\) showed:
singlet signal at δ 9.92-9.97 for one proton of anil group (-CH=N) in compound [N2-N7], singlet signal at δ 10.2 that could be attributed to the proton of oxazepine (O-CH-N) group in compound [N12-N33], and other peaks shown in figures of H.NMR.

FT.IR spectra:
FT.IR showed appearance band at (1620-1640) cm⁻¹ due to imine (C=N) group of compounds [N2-N33], while this band is disappear and two bands are appear at (1700,1670) cm⁻¹ due to (lactone/lactam) group of oxazepine compounds [N12-N33], this evidence to formation of compounds [N2-N33]. Other data of functional groups shown in the following in figures of I.R.

Figure (1) H-NMR spectrum of compound [N20]

Figure (2) I.R- spectrum of compound [N20]
UV-spectra & (C. H. N)-Analysis:
Uv spectra, most of compounds have electron transition (n-π) due to the hetero atoms (O,N) in these compounds beside of transition (π-π) of conjugated system. The UV-spectra of compounds show Uv-Vis spectrum Table (3) of compounds [N_{18}-N_{33}], showed the absorbance bands data were appeared at (λ_{max} = 315 - 400 nm), these compounds have chromophore group with oxochromic group due to hyperchromic effect such as conjugated system and carbonyl group in oxazepine compound with (-OH) group as oxochromic group of compound [N_{8}], (iodine) in compound [N_{19}], (-NH-CO-) group in compound [N_{20,N_{21}}], (C=N), (C=S) in compound [N_{22}, N_{23}, N_{24}], (-N=C-N=) group in compounds [N_{25},N_{26}, N_{27}], (-NO_{2}) group in compound [N_{1}], (COOH) groups in compounds [N_{28},N_{29}], for this reason, the bands shift to the maximum wave length data for compounds [N_{8}-N_{33}].

Table (1) - C.H.N. - analysis data of 1,3-oxazepine compounds

![Diagram of 1,3-oxazepine compounds]
Assay of antimicrobial activity:

All materials and bacteria supplied from bio-lab in college education. Antimicrobial activity was tested by the filter paper disc diffusion method against gram positive bacteria (Staphylococcus aureus) and gram negative bacteria (Pseudomonas aeruginosa). 0.1 ml of the bacterial suspensions was seeded on agar. To determine minimum inhibitory concentration (MIC) for each compound were ranged between (6-30) mg/ml by dissolved in (DMSO) and preparation 0.1 mg/ml standard antibiotic amoxyline as positive standard and reference.

The positive results or sensitivity were established by the presence of a clear zone of inhibition around active compounds which were measured with a meter rule and diameters were recorded based on (mm). The assays were performed with two replicates. Generally, the results showed that the compounds have good inhibitory effect against tested bacteria as compared with synthetic antibiotic Amoxyline.

Table (4) showed the zone of inhibition of the compounds in this study ranged (from 3 to 8) mm. From results, we noted that the compounds [22, 23, 25, 32, 33] have higher antibacterial activity against (S. aureus and P. aeruginosa) is due to the presence more than one of nitrogen atoms (N) and sulfur atom (S) in their structures in (thiazole, imidazole, pyrimidine) rings. These compounds become more effective in precipitating proteins on bacteria cell walls.

Table (2): Antibacterial activity of the compounds.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>G+: Staphylococcus aureus</th>
<th>G+: Pseudomonas aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>compounds[1]</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>compounds[2]</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>compounds[18]</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>compounds[19]</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>compounds[20]</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>compounds[22]</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>compounds[23]</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>compounds[25]</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>compounds[32]</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>compounds[33]</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Amoxyline**</td>
<td>38</td>
<td>28</td>
</tr>
</tbody>
</table>

*Minimum Inhibitory concentration (MIC) of compounds[1] (5 mg/ml).
**Amoxyline (0.1 mg/ml).
Study of Solubility of compounds in Solvents:
Several solvent were tested solubility of prepared compounds in this work., the results shown in Table (3)

Table (3) :Solubility of Compounds[1,2] in Solvents.

<table>
<thead>
<tr>
<th>Solvents</th>
<th>(Schiff Bases)All</th>
<th>All (Oxazepam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Methanol</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Benzene</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Dioxan</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Di Ethyl Ether</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

References:
13. Leovac.V; (2005)., "preparation of cyclic compounds from schiff bases through condensation reaction",Serb .Chem .Soc.70 (3), 393-399..
15. Nagham M Aljamali.,Chemistry and Material Research ,.(2014), 6 ,8.,54-59.