

# Synthesis and study the biological activity of Schiff base derivatives of 1,3-Oxazepines

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## Abstract

Reaction of *m*-nitrobenzaldehyde with semicarbazide hydrochloride in dry benzene give *m*-nitrophenyl semicarbazone (Schiff bases) . These Schiff bases were found to react smoothly with maleic anhydride , phthalic anhydride , 3-nitrophthalic anhydride and succinic anhydride to give seven membered heterocyclic system:1,3-Oxazepines. The new compounds characterized by elemental analysis, physical and spectral data. All the 1,3-Oxazepines have been screened for antibacterial activity against, *Escherichia coli* (G-), *Staphylococcus aureus* (G+) , *Pseudomonas aureus* (G-) .Some compounds were found to be active antibacterial.

## Introduction

For several years ,the diels-Alder reaction (1) was the only widely useful example of the So-called cycloaddition reactions. The extensive generalization by Huosgen and his School (2) of the concept of 1,3-dipolar cycloadditions ,has opened new avenues for investigations .The dimerization of olefins, as well as the addition of carbones and nitrogens to unsaturated centers has extended the series to include three,four,five and six-membered ring system ,here we will deal with various cycloaddition of the a somethine bond C=N .The seven-membered heterocyclic ring system: 1,3-Oxazepine has already been reported and thoroughly reviewed in the literature (3-6).

1,3-Oxazepines are prepared by condensation of Schiff bases with anhydrides (maleic, anhydride, phthalic anhydride-nitrophthalic anhydride ,succinic anhydride) ,to give corresponding cycloaddition products. The reaction of these anhydrides with Schiff bases is classified as a  $5+2 \rightarrow 7$  ,implting 5-atom component plus 2-atom component leading to 7-membered cyclic ring.

Some of these compounds show biological activity like ASENDIN is an antipressant of the dibenzoxazepine class. ASENDIN is an antidepressant with a mild sedative component to its action (7). According to above facts ,we decided to synthesize new 1,3-Oxazepines derivatives which are expected to have biological activity.

## Experimental

Chemicals: Most of chemicals used were supplied from Aldrich ,Merck and BDH chemicals Co. and were used are received.

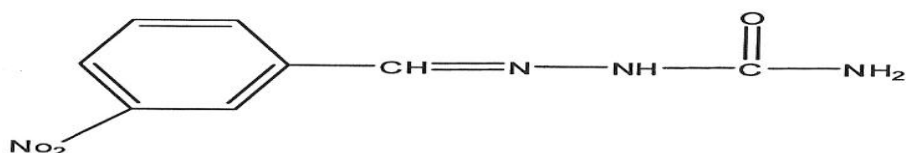
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Techniques: Melting points were determined by using an (Electrothermal) melting point apparatus and are uncorrected. FTIR spectra were recorded with SHIMADZU FTIR-4800S Infrared spectrophotometer in (KBR). Elemental analysis were carried out with Perkin Elmer B-240 Elemental Analyzer. U.V. spectra were recorded in (absolute ethanol) by SHIMADZU Recc-160 Spectrophotometer (M)  $\times 10^3$ .

### Synthesis

#### N-(*m*-nitrobenzylidene) Semicarbazone)[1]

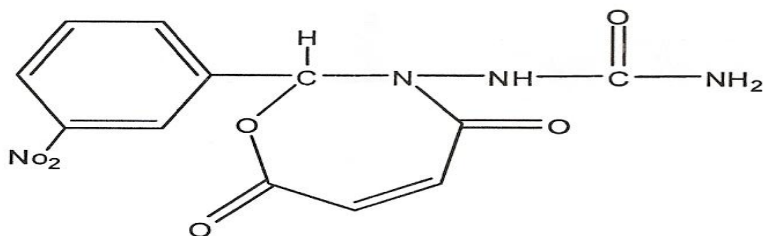
A mixture of equimolar amounts (7 gm, 0.046 mole) of *m*-nitrobenzaldehyde and semicarbazide hydrochloride (5.12 gm, 0.046 mole) dissolved in (30 ml) of absolute ethanol was refluxed in water bath for (7 hr). The reaction mixture was then allowed to cool to room temperature, and the solid product was filtered and recrystallized from ethanol (95%) to give colored crystals of [1]. Physical properties and maximum absorption in the U.V. region of synthesized compound was given in table (1), (3) shows FT-IR absorption bands to the same compound.



#### N-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3-dihydro[1,3]-Oxazepine-4,7-dione [Ia]

A mixture of equimolar amounts (0.2 gm, 0.00096 mole) of Schiff bases [I] and (0.094 gm, 0.00096 mole) of maleic anhydride dissolved in (20 ml) of dry benzene was refluxed and the resulting crystalline solid was recrystallized from absolute ethanol to give the product.

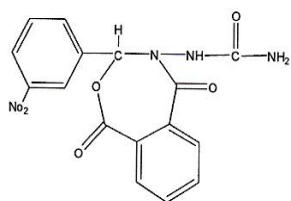
The corresponding derivatives of using another anhydride (phthalic anhydride, *m*-nitrophthalic anhydride, succinic anhydride) were obtained by following the same procedure and using the same amounts of Schiff bases and anhydrides to give [Ib], [Ic], [Id] respectively.



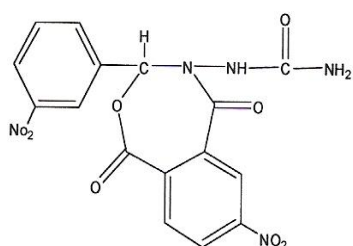
2-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3-dihydro-(1,2-e)-[1,3]-Oxazepine-4,7-dione.

2-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3-dihydro-[1,3]-Oxa-*m*-nitrophthalazine-4,7-dione.

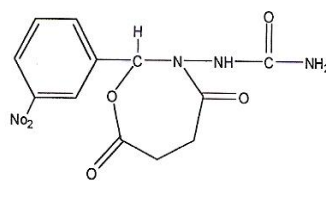
2-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3,5,6-tetrahydro-[1,3]-Oxazepine-4,7-dione.



Ib



Ic



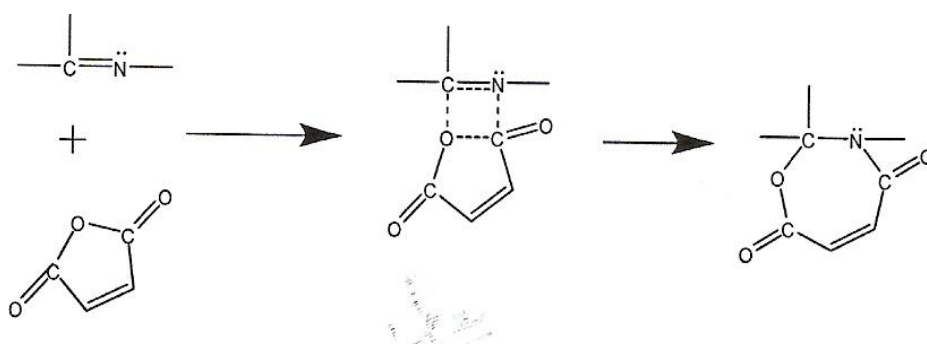
Id

Physical properties and maximum absorption in the U.V. region of the synthesized compounds are given in the table (2). FT.IR absorption for these compounds were show in table (4).

### Results and Discussions

N-(*m*-nitrobenzylidene) semicarbazone (Schiff bases) [I], are prepared by condensation of *m*-nitrobenzaldehyde with semicarbazide hydrochloride using absolute ethanol as the solvent in basic medium (fused CH<sub>3</sub>COONa), identified by their m.p, elemental analysis, U.V. spectra (table 1). IR of this compound show the appearance of stretching band at (1608) cm attribute to the Imines C=N group (table3). The Schiff bases are known to react smoothly with acid halides and anhydrides (8) to give corresponding cycloaddition products. Therefore N-(*m*-nitrobenzylidene) Semicarbazone [I] are expected to react with maleic anhydride to give 2-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3-dihydro-[1,3]-Oxazepine-4,7-dione[Ia].

The reaction is followed by disappearance of (C=N) absorption band at (1608) cm and appearance of (C-N) absorption band at (1170) cm. The product [Ia] are identified by the m.p., elemental analysis, U.V. (table 2), and FT.IR spectra (table 4). We should release the reaction of maleic anhydride with Schiff bases is a sort of cycloaddition reaction. Our cycloaddition reaction is classified as 5+2 → 7, leading to 7-membered heterocyclic ring. The reaction requires mild conditions (benzene, 80°C, 7hrs). The mechanism involves addition of one σ bond (-C-O) to one π bond (N=C) to give 4-membered cyclic transition state which opens in to maleic anhydride (5-membered cyclic ring) to give 7-membered cyclic ring.



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Similar results are obtained by the reaction of phthalic anhydride with N-(*m*-nitrobenzylidene) Semicarbazone to give 2-(*m*-nitrophenyl)-3-(Semicarbazone)-2,3-dihydro-(1,2-*e*)-[1,3]-Oxazepine-4,7-dione [Ib]. The product [Ib] is identified by their m.p., U.V. spectra and elemental analysis (table 2).

It is impressive to note that the absorption bands at (1740-1780) cm and at (1800-1850) cm (10,11) in the IR spectra of pure maleic anhydride have disappearance when the anhydride became part of the 7-membered ring of [1,3]-Oxazepine-4,7-dione. This may be attributed to the fact that the combine (C=O) of the lacton and (C=O) of the lactam absorbs in the same region of the IR spectra of these cyclic products. However, the IR spectra of pure phthalic anhydride maintains these two absorption bands, when it became part of the 7-membered cyclic ring of benz [1,2-*e*][1,3]-Oxazepine-4,7-dione, this may be attributed to the interaction of the benzene ring with carbonyl groups of this anhydride.

### Biological screening: Antibacterial activity test.

Many of the benzodiazepines and their oxides show interesting sedatives, muscle relaxant and anticonvulsant properties in animals (9). Since the discovery of the central nervous system activity of the 1,4-benzodiazepines, several clinically useful drugs have been found which contain a heterocyclic moiety fused into the seven-membered ring (10). In our study the synthesized compounds table 5 have been screened for their antibacterial activity against *E. coli*, *Staph. aureus*, & *Pseudo. Aeruginosa* by agar diffusion technique (11) by using nutrient agar & brain heart infusion agar. Each compound was dissolved in DMSO to give a final concentration of 0.01 mg / ml. From the data obtained in table 5, it is clear that the compounds [Ib], [Ic] exhibited biological activity against bacteria G- and G+ but in different range, while the compounds [Ia], [Id] have no any biological activity against bacteria G- and G+ (Inhibition zone = zero).

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**Table (1): The physical properties ,U.V. data and elemental analysis of N-(*m*-nitrobenzylidene) Semicarbazide.**

| Comp.No. | Formula   | m.p.(°C) | Yield% | Color  | $\lambda$<br>max(nm) |
|----------|---|----------|--------|--------|----------------------|
| I        | C <sub>8</sub> H <sub>8</sub> O <sub>3</sub> N <sub>4</sub> | 217-219  | 90     | Yellow | 273                  |

**Table (2): The physical properties , U.V. data and elemental analysis of the compound [Ia] to [Id].**

| Comp.No. | Formula   | m.ps. (°C) | Yields (%) | Color    | $\lambda$ max (nm) | Calc  |      |       | Found |      |       |
|----------|---|------------|------------|----------|--------------------|-------|------|-------|-------|------|-------|
|          |   |            |            |          |                    | C%    | H%   | N%    | C%    | H%   | N%    |
| Ia       | C <sub>12</sub> H <sub>10</sub> O <sub>6</sub> N <sub>4</sub> | 113-115    | 50         | Offwhite | 205                | 47.05 | 3.26 | 18.3  | 47.66 | 4.59 | 18.68 |
| Ib       | C <sub>16</sub> H <sub>12</sub> O <sub>6</sub> N <sub>4</sub> | 142-144    | 47.6       | White    | 250                | 53.93 | 3.37 | 15.73 | 54.26 | 3.47 | 15.99 |
| Ic       | C <sub>16</sub> H <sub>11</sub> O <sub>8</sub> N <sub>5</sub> | 180-184    | 80.1       | Offwhite | 217                | 47.88 | 2.74 | 17.45 | 47.22 | 2.99 | 18.11 |
| Id       | C <sub>16</sub> H <sub>12</sub> O <sub>6</sub> N <sub>4</sub> | 155-158    | 65         | White    | 271                | 62.33 | 3.89 | 18.18 | 63.01 | 4.37 | 17.99 |

**Table (3): Characteristic IR absorption bands (cm<sup>-1</sup>) of N-(*m*-nitrobenzylidene) Semicarbanzone [I].**

| Comp. | $\gamma$ N-H            | $\gamma$ Arom. C-N | $\gamma$ Imime C=N | $\gamma$ Arom. C=C | Others                                     |
|-------|-------------------------|--------------------|--------------------|--------------------|--|
| I     | 3464 Asym.<br>3361 Sym. | 2929               | 1608               | 1529               | C-NO <sub>2</sub><br>aromatic<br>1581,1315 |

Table (4) : Characteristic IR absorption bands (cm ) of the compounds [Ia] to [Id].

| Comp. No. | $\gamma$ N-H Asym. Sym. | $\gamma$ C-N Arom. | $\gamma$ C=O Lacton | $\gamma$ C=O Lactam | $\gamma$ C=C Arom. | $\gamma$ C-N | Others                       |
|-----------|-------------------------|--------------------|---------------------|---------------------|--------------------|--------------|------------------------------|
| Ia        | 3115-3000               | 2629               | 1734                | 1718                | 1570               | 1170         | C-NO <sub>2</sub> :1537,1321 |
| Ib        | 3000-3100               | 2700               | 1730                | 1715                | 1570               | 1175         | C-NO <sub>2</sub> :1530,1320 |
| Ic        | 3100-3000               | 2700               | 1730                | 1715                | 1570               | 1170         | C-NO <sub>2</sub> :1540,1321 |
| Id        | 3120-3000               | 2770               | 1740                | 1720                | 1575               | 1170         | C-NO <sub>2</sub> :1545,1330 |

Table (5) results of biological activity of the compounds [Ia],[Ib],[Ic] and [Id].

| Comp.No. | <i>E. coli</i> (G-) | <i>Staph.aureus</i> (G+) | <i>Pseudo. aeruginosa</i> (G+) |
|----------|---------------------|--------------------------|--------------------------------|
| Ia       | -                   | -                        | -                              |
| Ib       | ++                  | +                        | +                              |
| Ic       | +++                 | +                        | +                              |
| Id       | -                   | -                        | -                              |

Moderately active = ++ (inhibition zone 10-14 mm) Slightly active =+ (inhibition zone 6-9 mm), Inactive = - (inhibition zone < 6mm).

## تحضير ودراسة الفعالية الحيوية لشتقات قواعد شف ١, ٣ -

### او كسازبين

هدى اسماعيل ابراهيم

قسم الكيمياء ، كلية التربية - ابن الهيثم ، جامعة بغداد

### الخلاصة

شمل هذا البحث تحضير احدى (قواعد شيف) بتكاثف ميتا - نيتروبنزلديهايد مع سيمي كاربازيد هايديروكلورايد في البنزين الجاف . وجد ان قواعد شيف هذه تتفاعل بسهولة مع انهيدريد المالك ، انهيدريد الفثاليك ، ٣- نيتروفتاليك انهيدريد وانهيدريد الساكسينيك لتعطي نظاما حلقيًا سباعيًا غير متجانس : ١ و ٣ - او كسازبين . وقد شخصت هذه المركبات الجديدة من خلال تحليل العناصر الدقيق والقياسات الطيفية والفيزيائية . كما اظهرت بعض هذه المركبات فعالية حيوية تجاه البكتريا المستخدمة بنوعها بكتريا القولون (G-) ، والعنقوديات الذهبية (G+) ، والزنجارية (G-) .