Ain Shams University
Faculty of Women
for Arts, Science, and
Education
Department of Chemistry

Synthesis and Reactions of Some New Heterocycles Containing Nitrogen and Sulphur of anticipated Biological Activity

A Thesis Submitted for the Degree of M. Sc

In

Organic Chemistry

Presented

By

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(2014)

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Approval of Chemistry Department Council **/ /2014**
Approval of Faculty Council **/ /2014**
Approval of University Council **/ /2014**

DEDICATION

To my distinguished parents:

I do appreciate my God for giving me such wonderfully parents for their continuous support, encouragement, and enlighting my life.

ACKNOWLEDGEMENT

I wish to refer my deep appreciation and gratitude

To

Prof. Dr. Fatma Abdel Rahman El-Mariah, *Professor of Organic Chemistry, Chemistry Department, Faculty of Women for Arts, Science and Education, Ain Shams University.*

Prof. Dr. Ahmed Said Ahmed Youssef, *Professor of Organic Chemistry, Chemistry Department, College of Science, Ain Shams University.*

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Suggesting the subject, interpreting the results, their valuable scientific guidance, help, and encouragement during the work of this thesis.

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QUALIFICATION

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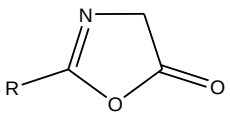
Contents

Introduction

Since many decades, active hetero cyclic compounds are one of the main topics of interest for the medicinal chemists as it displays a number of pharmacological activities. Nitrogen, sulphur, oxygen containing five and six membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry**.** Medicinal or pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. Now with every possible bacterial infection, the research still on antimicrobial agent is continuously going on to develop new molecules.

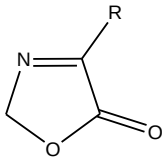
Oxazolones:

Oxazolones can exist in five isomeric forms, all of which are known



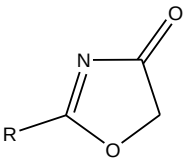
2-oxazolin-5-one
or 5(4H)-oxazolone
Azlactone

(1)



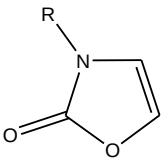
3-oxazolin-5-one
or 5(2H)-oxazolone
or pseudoxazolone

(2)



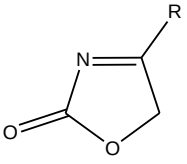
2-oxazolin-4-one
or 4(5H)-oxazolone

(3)



4-oxazolin-2-one
or 2(3H)-oxazolone

(4)



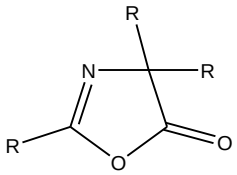
3-oxazolin-2-one
or 2(5H)-oxazolone

(5)

All of these isomers, azlactones or 2-oxazolin-5-ones (oxazolones) may be regarded as cyclic esters of α-acyl amino acids. Their chemistry has been investigated very thoroughly. This interest may be attributed in large measure to structural studies on penicillin and the fact that oxazolones are starting materials for the synthesis of α-amino acids, peptides, α-keto and aryl acetic acids, and a host of other heterocyclic compounds **(Turchi I.J., 1986).** Oxazolones play very vital roles in the manufacturing of various biologically active drugs as analgesic, anti-inflammatory, antidepressant, anti-cancer, anti-microbial, anti-diabetic and anti-obesity **(Conway et al., 2009 and Taile et al., 2009).**

Azlactones (5(4H)-oxazolones):

These compounds are classified into two types, saturated azlactones **6** and unsaturated azlactones **7**, since the two types show characteristic differences in properties **(Roger Adams, 1946).**



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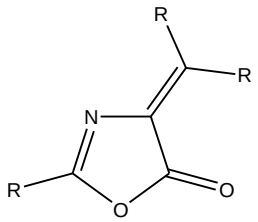
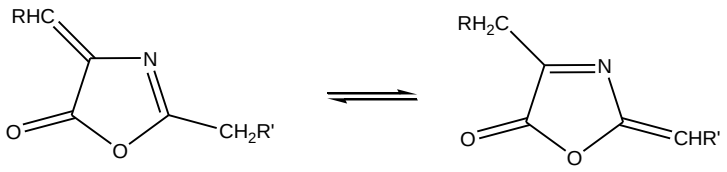


(7)

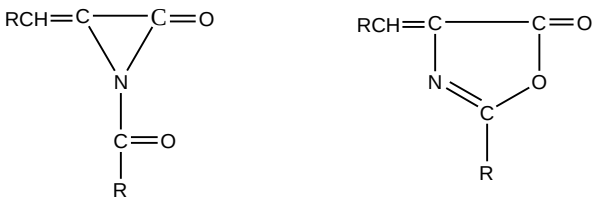
The unsaturated azlactone **7** possible to be found in tautomerism between the real one **8** and the pseudo **9** form of oxazolones **(Kildisheva et al., 1957).**



(8) (9)

Structure of azlactones:

Several different structures have been suggested for azlactones. Of these only two (formulas **8** and **9**) have received serious consideration. .

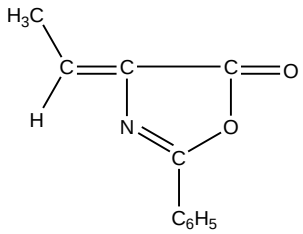


(10) (11)

The three-membered ring structure **10** (called Lactimide) was proposed by Rebuffat and accepted by Erlenmeyer**.** However, in 1900 Erlenmeyer abandoned this formula in favor of the five-membered ring **11** for which he later proposed the term "azlactone"**.** The term "lactimone" also has been applied to these compounds **(Roger Adams, 1946).**

Stereochemistry of azlactones:

Geometric isomerism is possible in the unsaturated azlactones, the (cis) and (trans) isomers of benzoyl aminocrotionic azlactone and of benzoyl aminocinnamic azlactone have been isolated **(Roger Adams, 1946)**.



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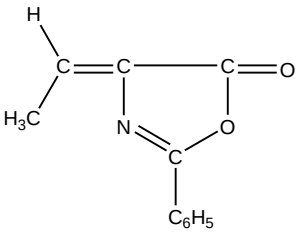
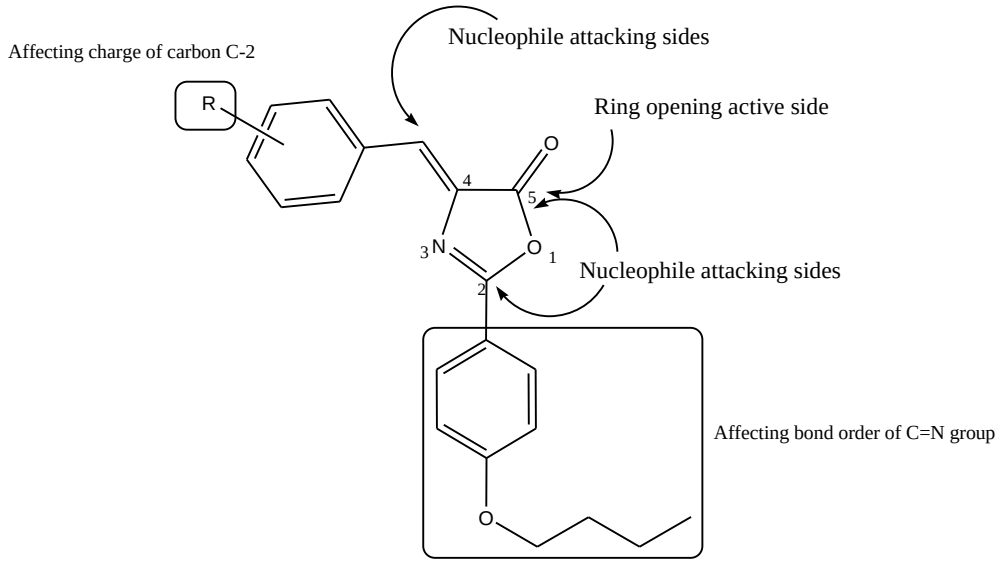


(13)

Physical Properties of azlactones :

Saturated azlactones are colorless liquids or low-melting solids. Unsaturated azlactones are solids, often high melting, and the majority has colors ranging from light yellow to dark red. The color is most intense in 2-aryl-4-arylidene-5-oxazolones; the 2-alkyl-4- alkylidene-5-oxazolones are colorless **(Roger Adams, 1946).**

Chemistry and reaction of azlactones:



(a)

Lewis acid activation of the carbonyl group of unsaturated oxazolones gives electrophilic character to the β-carbon **(Avenoza et al., 2002).** The structure of (4Z)-4-benzylidine-2-phenyl-1,3-oxazol-5(4H)-ones **(a)** has multiple electrophilic reaction centers for an attack of the nucleophile. Mostly they attack the carbonyl group often leading to a ring opening. The rate of oxazolone ring-opening reaction decreased with an increase of the electron donating properties of the substituent of the phenyl ring at C-2 position **(Betlakowska et al., 2002).** The positive charge of the C-2 increases by m-NO_2 group which may be easily attacked by any nucleophile.

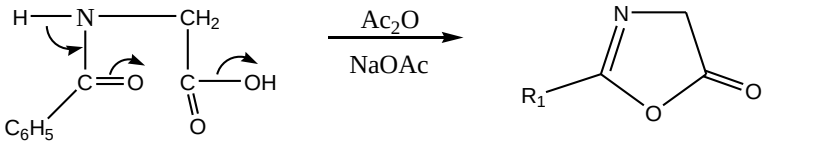
An alkoxy group at the *para* position of the phenyl ring decreases the negative effect of the nitro group and the electron withdrawing effect of this group may support the attack of the C═N group. The bond order of the C═N group decreases by the presence of m-NO_2 group at the benzylidene ring **(Leod et al., 1983 and Palcut, 2009).** Substitution of functional group at C-2 and C-4 position plays a vital role in the activity of oxazolone **(Abdel-Aty, 2009)**. An extension of conjugation through an aliphatic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity **(Khan et al., 2006),** for example; substituted p-nitro exocyclic phenyl group at C-4 in oxazolone moiety greatly influences the immunosuppressive activity **(Mesaik et al., 2004).**

Synthetic Methods:

a) Erlenmeyer synthesis:

The Erlenmeyer reaction was first described in 1893 by Friedrich Gustav Carl Emil Erlenmeyer. The Erlenmeyer azlactone synthesis consists of the condensation of an aldehyde (or ketone) with an α-acyl amino acid

(e.g.,hippuric acid) **14** in the presence of acetic anhydride and anhydrous sodium acetate as a catalyst. The reaction may be considered as a special case of the Perkin condensation but it takes place under much milder conditions **(Ahmed El-Mekabaty, 2013).**



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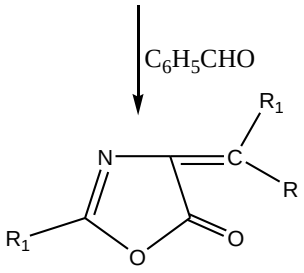
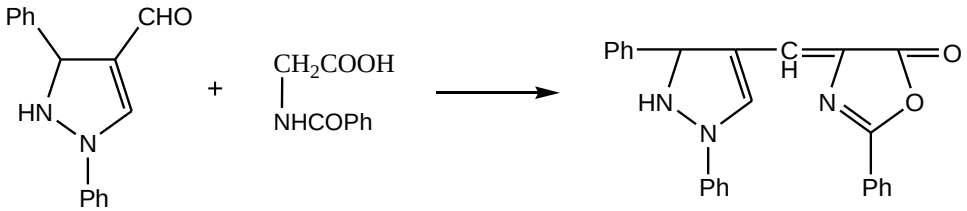


(7) R=H; $R_1=C_6H_5$

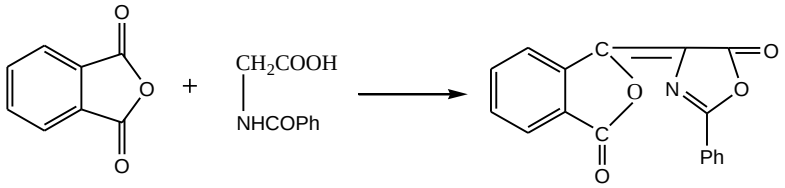
Aliphatic aldehydes and ketones also condense with saturated azlactones when heated for 3h at 50^{o}C, the yields increase markedly when lead acetate is added to the reaction mixture, with shorter reaction times **(Turchi, 1986)**.

Treatment of 1,3-diphenyl-4-pyrazolin-4-aldehyde **(15)** with hippuric acid afforded the corresponding (1,3-diphenyl-4-pyrazolin)-4-methylene-2-oxazolin-5-one **(16) (El-Kaschef et al., 1974).**



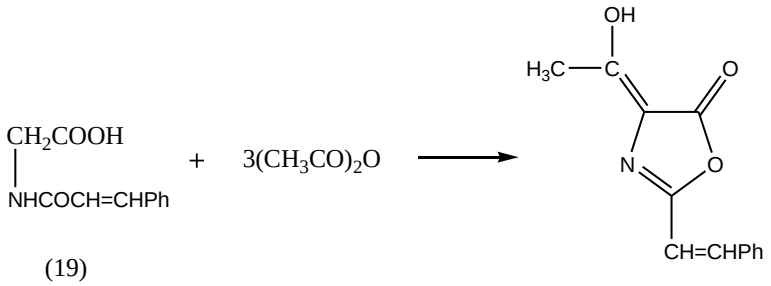
(15) (16)

When phthalic anhydride **(17)** was condensed with hippuric acid, 2-phenyl-4-phthalyl-2-oxazolin-5-one **(18)** was obtained **(Ahmed El- Mekabaty, 2013).**



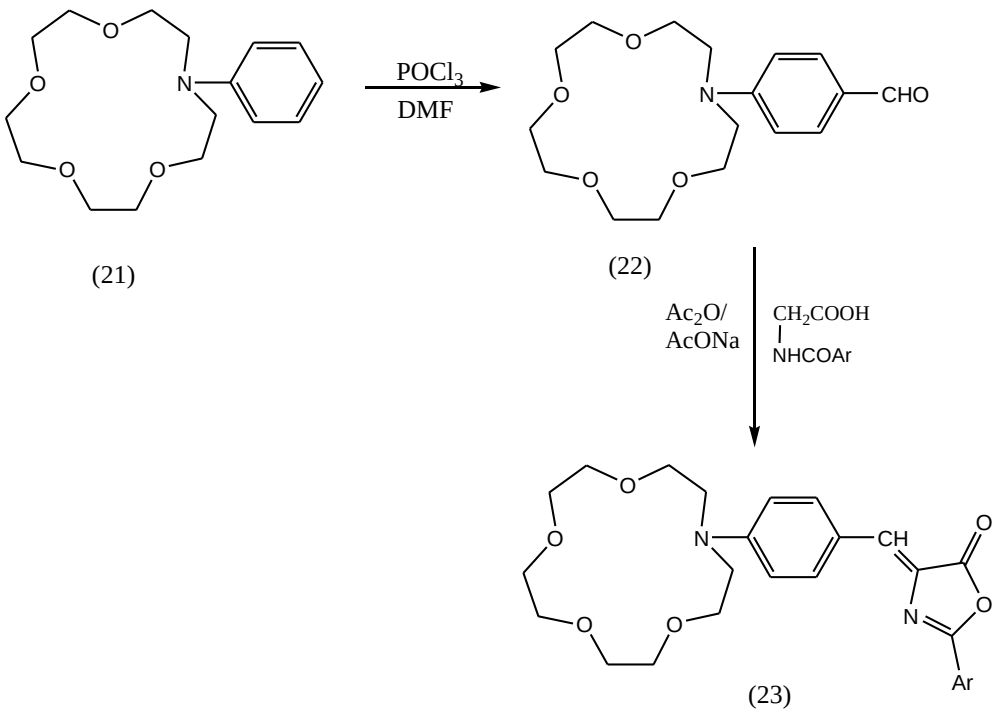
(17) (18)

Clarke and Johnson, 1949 reported that the Condensation of cinnamoylglycine **(19)** with acetic anhydride and sodium acetate gave a low yield of 2-styryl-4-(α-hydroxyethylidene)-2-oxazolin-5-one **(20).**



(19) (20)

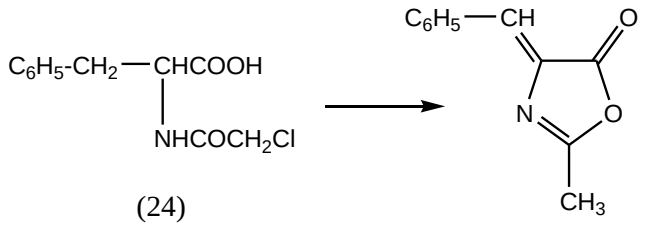
2-Aryl-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)-benzylidene]-5-oxazolone derivatives **(23)** were prepared by the cyclocondensation of 4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl) benzaldehyde **(22)** that obtained from the action of $POCl_3$ in DMF on (1,4,7,10-tetraoxa-13-azacyclopentadecyl)benzene **(21)** with aroyl glycine derivatives in the presence of acetic anhydride **(Ozturk et al., 2007).**



(21) (22) (23)

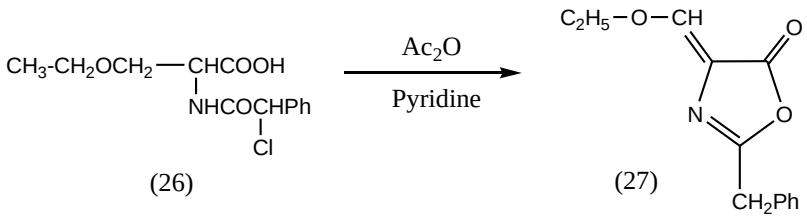
b) Bergmann Synthesis:

Bergmann and Stern, 1926 stated that oxazolones can be prepared by the action of acetic anhydride on certain α-(α-haloacyl)-aminoacids. Thus, refluxing N-chloroacetyl phenylalanine **(24)** with acetic anhydride gave 4-benzylidene-2-methyl-2-oxazolin-5-one **(25).**



(24) (25)

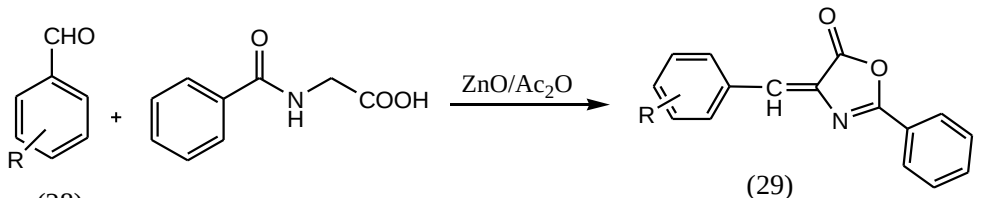
Ahmed El-Mekabaty, 2013 reported that the formation of 2-benzyl-4-ethoxymethylene-2-oxazolin-5-one **(27)** by treatment of N-(α-chlorophenylacetyl)-o-ethylserine **(26)** with acetic anhydride in pyridine.



(26) (27)

c) New methods using benzoyl glycine under different conditions:

Pasha et al., 2007 reported the synthesis of 4-arylmethylidene-2-aryl-5(4H)-oxazolones **(29)** by stirring a suspension of substituted benzaldehyde **(28),** hippuric acid, ZnO (catalyst) and acetic anhydride. The reaction was completed at room temperature with a good yield of oxazolone **(29).**



(28) (29)

Tikdari et al., 2008 synthesized 2-phenyl-5(4H)-oxazolone **(31)** by microwave irradiation from hippuric acid and aldehydes or ketones **(30)**, in the presence of acetic anhydride and corresponding catalysts (dodecatungstophosphoric acid, samarium and ruthenium (III) chloride) and stated that the rate of the reaction was very fast and leads to a good yield of oxazolone **(31)**.