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

Utilization of Nitrogen and Oxygen Compounds as Building Blocks of some Heterocycles

A Thesis Submitted for the Degree of Ph.D

In

Organic Chemistry

Presented

By

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Approval of Chemistry Department Council **/ /2017**
Approval of Faculty Council **/ /2017**
Approval of University Council **/ /2017**

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

The author wishes to refer her 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, *Professor of Organic Chemistry, Chemistry Department, Faculty of Science, Ain Shams University.*

&

Prof. Dr. Magdy Mohamed Hemdan Mohamed, *professor of Organic Chemistry, Chemistry Department, Faculty of Science, Ain Shams University.*

For

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

QUALIFICATION

Name: Heba Allah Ezzat Hashem Fawzy

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Ph.D. Graduation Year: 2017

Contents

The proposed plane of this research work aims to utilize 2-methyl-4H-benzo[*d*][3,1]oxazin-4-one (**76a)** in the synthesis of some new derivatives of quinazoline and their annulated system of potent biological activity. The syntheses of the target heterocycles are addressed in three parts.

Part (1)

The aim of this part was the syntheses of quinazoline derivatives and their fused ring systems by the utility of 2-methyl-4H-benzo[*d*][3,1]oxazin-4-one(**76a)** with (Z)-N-(3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl)benzamide (**58a**) under different conditions. Thus, reaction of the concerned compound with **(58a)** in glacial acetic acid and in the presence of fused sodium acetate afforded the quinazolinone derivative **203**. On the other hand, reaction in boiling pyridine produced pyrazoloquinazolinone **204.** However, heating in glacial acetic acid or absolute ethanol didn't give the desired quinazoline derivatives; instead the reaction yielded amino imidazolone derivative **57** or N-acetyl amino imidazolone **202.**

Treatment of benzoxazinone **76a** with amino imidazolone derivative **57** afforded quinazolinone derivative **206**. Moreover, refluxing **(76a)** with hydrazine hydrate in ethanol or acetic acid furnished amino quinazolinone derivative **207** or pyrazoloquinazolinone **208**. The reaction of amino quinazolinone derivative **207** with 2-chloro-quinolin-3-carbaldehyde or 1,3-oxazolone **25** gave quinazolinone derivative **210** or benzoic acid derivative **211**. Heating of compound **211** with acetic anhydride produced pyrazoloquinazolinone **208** in a good yield together with the oxazolone derivative **25**.

Part (2)

In this part we aimed to synthesize quinazoline derivatives functionalized with 3-heterocycle side chain. Thus the reaction of 2-methyl-4*H*-benzo[*d*][3,1]oxazin-4-one (**76a**) with 2-cyanoacetohydrazide in absolute ethanol in the presence of a few drops of glacial acetic acid produced the quinazolinone derivative **212** in a good yield. Compound **212** is used as a useful building block for the synthesis of the target heterocycles.

Treatment of quinazolinone derivative **212** with hydrazine hydrate in refluxing dioxane afforded the quinazoline derivative **213**. Fusion of quinazoline **212** in presence of piperidine afforded the pyrazoloquinazoline derivative **214.** Treatment an ethanolic solution of quinazoline **212** with an equivalent amount of malononitrile and a catalytic amount of pipridine yielded the pyridoquinazoline derivative **215.** Moreover, refluxing with salicylaldehyde in ethanol in presence of a catalytic amount of ammonium acetate yielded quinazoline derivative **216** bearing a coumarine nucleus. Treatment of quinazoline derivative **216** with hydrazine hydrate or phenyl hydrazine produced tetrazinoquinazoline **217** or quinazolinone derivative **218**. Furthermore, refluxing of compound **212** with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde in 10 % alcoholic KOH yielded 3-(4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-oxoazet-1(2H)-yl)-2-methylquinazolin-4(3H)-one **219**. Heating compound **219** with hydrazine hydrate in n-butanol produced a mixture of amino quinazolinone **207** and pyrazolylpyrazole derivative **220**.

Treatment a solution of compound **212** in dimethylformamide with an equivalent amount of phenyl isothiocyanate in the presence of a catalytic amount of potassium hydroxide produced azetine derivative **221.** On the

other hand, heating of compound **212** under similar conditions in the presence of elemental sulfur gave the thiazole derivative **222.** The reaction of quinazolinone derivative **212** with phenyl isothiocyanate and ethyl bromide at room temperature in dimethylformamide and a catalytic amount of KOH afforded quinazolinone derivative **223**. However, its reaction under similar conditions with two molar equivalents of ethyl chloroacetate afforded the thiazolidinone derivative **224**.

Part (3)

Further stage for the syntheses of quinazoline derivatives were achieved by reaction of benzoxazinone **76a** with thiocarbonohydrazide. Thus refluxing an equimolar amounts of the benzoxazinone **76a** with thiocarbonohydrazide in ethanol and few drops of acetic acid furnished 4-(2-methyl-4-oxo quinazolin-3(4H)-yl)thiosemicarbazide (**225)**. Compound **225** is used as a useful building block for the synthesis of further quinazoline derivatives functionalized with a 3-substitued side chain. Heating of compound **225** with benzoyl chloride in dry benzene gave thiosemicarbazide derivative **226**. Boiling thiosemicarbazide **226** in a mixture of acetic and hydrochloric acids afforded thiadiazole derivative **227** in a good yield.

The reaction of thiosemicarbazide derivative **225** with aromatic aldehydes namely 2-chloroquinoline-3-carbaldehyde and 4-methoxybenzaldehyde afforded the thiosemicarbazones **228** and **229,** respectively. Treatment of the thiosemicarbazone derivative **228** with hydrazine hydrate or phenyl hydrazine furnished the tetrazine derivatives **230a,b**, respectively. Similar treatment of the thiosemicarbazone derivative **229** with hydrazine hydrate gave the tetrazine derivative **231**.

Structural assignments of the newly synthesized compounds were based on their infrared, mass spectrum and proton nuclear magnetic resonance.

Part (4)

The possible antimicrobial activities of some of the synthesized heterocyclic compounds were investigated against six reference microbial isolates including; Fungi: *Aspergillus fumigatus* (RCMB 02568) (Af), *Aspergillus niger* (RCMB 02724) (An) and *Candida albicans* (RCMB 05036) (Ca); Gram-positive bacteria: *Staphylococcus epidermidis* (RCMB 010024) (Se), *Bacillis cereus* (RCMB 010064) (Bc) and *Staphylococcus aureus* (RCMB 010027) (Sa); Gram-negative bacteria: *Pseudomonas aeruglnosa* (RCMB 010043) (Pa), *Escherichia coli* (RCMB 010052) (Ec), and *Klebsiella pneumonia* (RCMB 01002 23-5) (Kp).

The *in vitro* evaluation of antimicrobial against several pathogenic bacterial and fungal strains revealed that all the synthesized compounds have high activity.

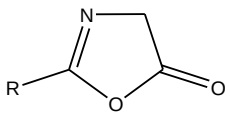
Compound2-((2-benzamido-3-phenylacryloyl)hydrazinyl)ethylideneamino) benzoic acid (**211**) is the most potent compound against the tested fungi and the Gram-positive bacteria comparable with other tested compounds. Compounds **211** and 3-(6-methyl- 4*H*-[1,2,4,5]tetrazino[1,6-*c*]quinazolin-3-yl)-2*H*-chromen-2-one (**217**) are the most potent compounds against the tested Gram negative bacteria and they also showed significant activity comparable with standard gentamicin and ciprofloxacin.

Introduction

Since many decades, active heterocyclic compounds are one of the main topics of interest for the medicinal chemists as it displays a number of pharmacological activities. Nitrogen, sulphur and 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.

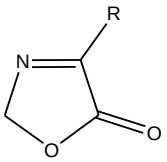
Oxazolones

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



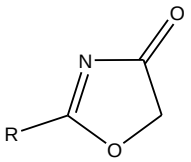
2-oxazolin-5-one
or 5(4H)-oxazolone
Azlactone

(1)



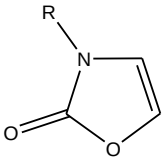
3-oxazolin-5-one
or 5(2H)-oxazolone
or pseudoxazolone

(2)



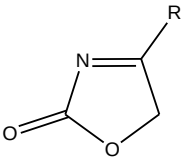
2-oxazolin-4-one
or 4(5H)-oxazolone

(3)



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

(4)



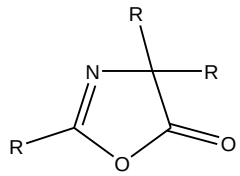
3-oxazolin-2-one
or 2(5H)-oxazolone

(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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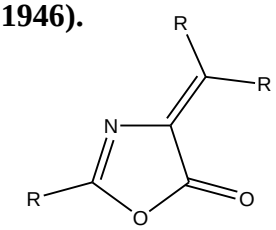
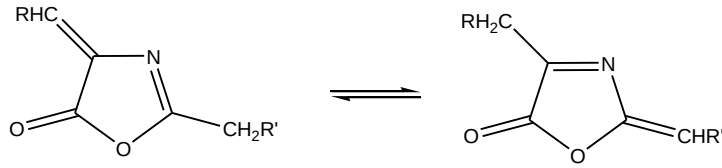


(7)

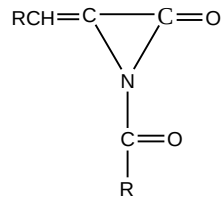
The unsaturated azlactone **7** possible to be found in tautomerism between the real one **8** and the pseudo **9** form of oxazolones **(Kildisheva et al., 1957).**

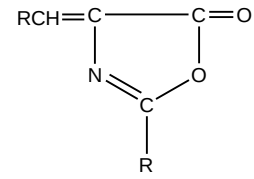


(8) (9)

Structure of azlactones:

Several different structures have been suggested for azlactones. Of these only two (formulas **10** and **11**) have received serious consideration. .



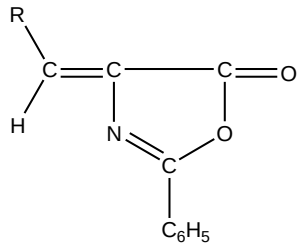


(10) (11)

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).**

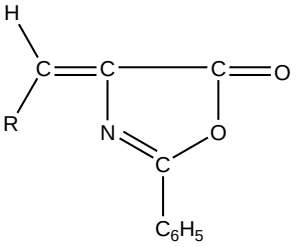
Stereochemistry of azlactones:

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



R= CH_3, Ph

(12)

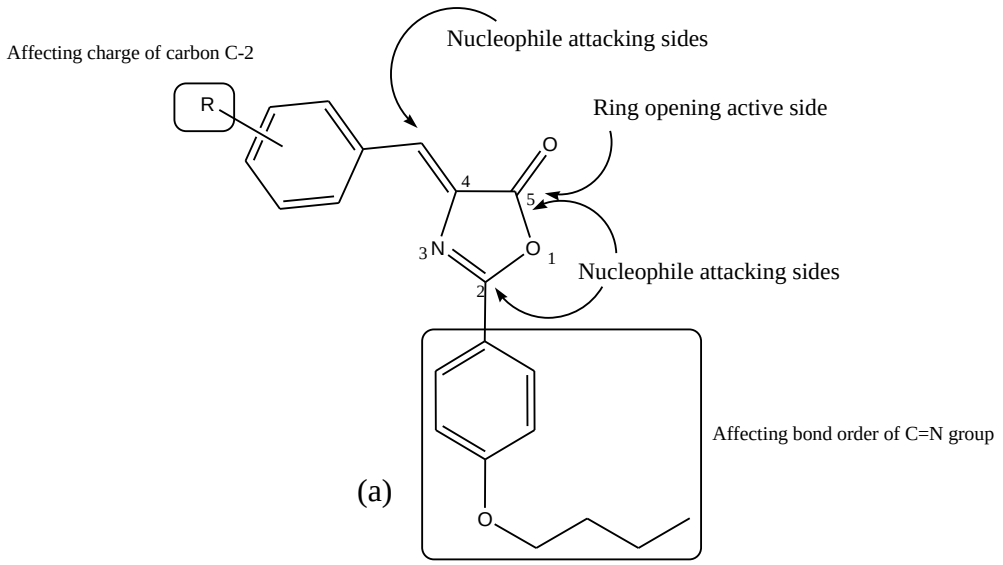


(13)

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)