SYNTHESIS, REACTIONS AND PROPERTIES OF SOME CITRAZINIC ACID DERIVATIVES

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SYNTHESIS, REACTIONS AND PROPERTIES OF SOME CITRAZINIC ACID DERIVATIVES

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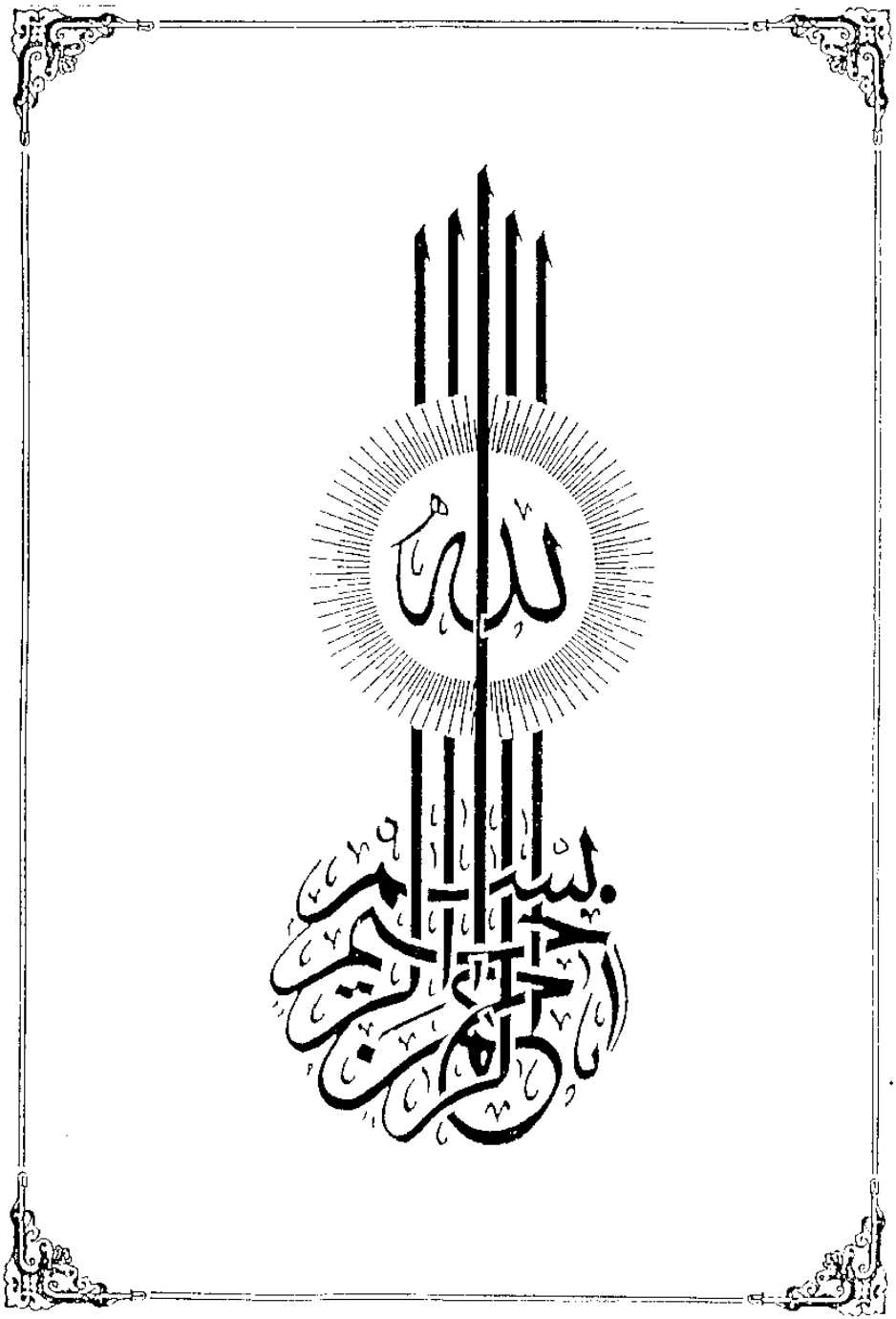

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N O T E S

Besides the work carried out in this thesis, the candidate ABD EL-GELEIL E. ABD EL-RAHMAN AMR has pursued postgraduate studies for the partial fulfilment of the M.Sc. degree, during the academic year 1989/1990, in the following topics:

1. Physical Organic Chemistry.
2. Chemical Spectroscopy.
3. Advanced Heterocyclic Chemistry.
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CONTENTS

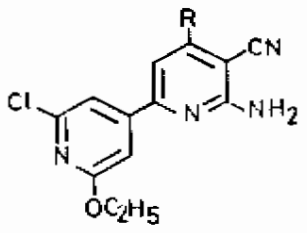
SUMMARY

S U M M A R Y

1. The thesis starts with an introduction covering a general review for the chemistry of citrazinc acid till 1991. It includes also a special part presenting the obtained results followed by the experimental part and ended with a list of 129 references.
2. The thesis includes a course of investigation to synthesize a series of some heterocyclic nitrogen compounds drived from citrazinic acid. It includes the new synthesis of 2-chloro-6-ethoxy-4-acetylpyridine **(65)**, a key product to prepare some α,ß-unsaturated ketones **66**.

(65) (66)

3. The obtained ß-acryloyl derivatives **66** were allowed to react with active methylene compounds, namely, malononitrile, ethyl cyanoacetate and cyano acetamide where two serise of cyanopyridines **67** and **69** were obtained by different methods.



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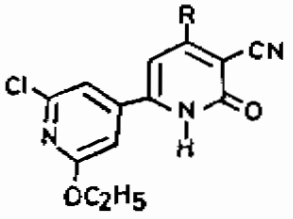
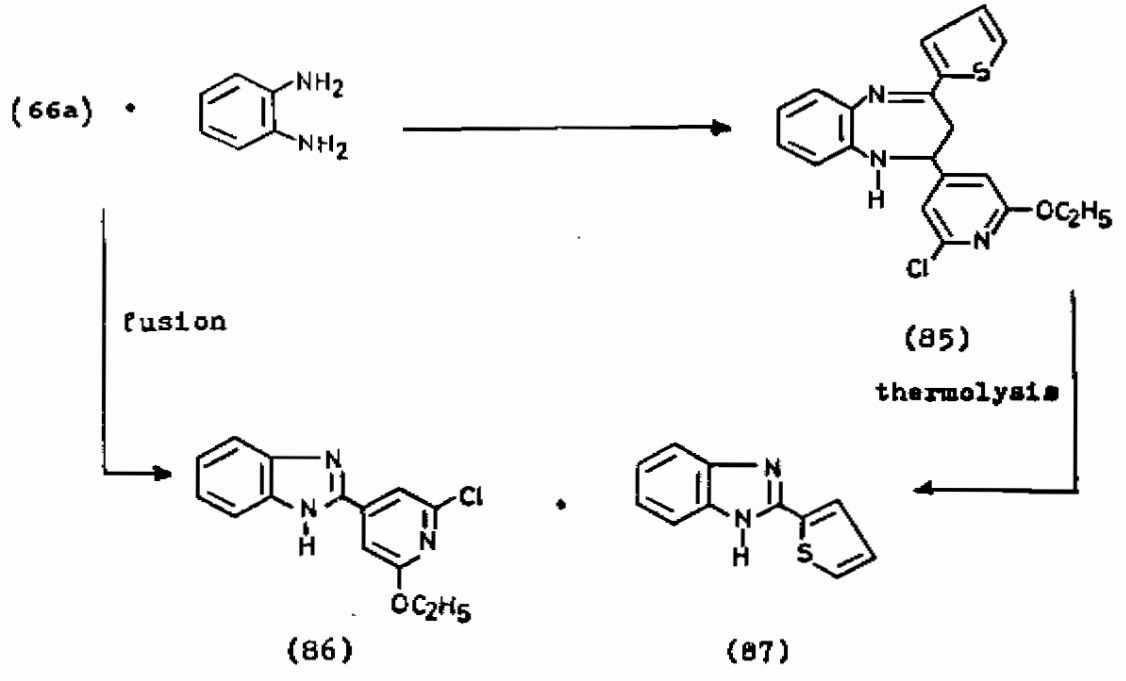
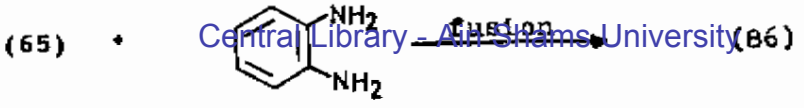


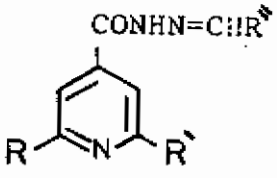
(69)

4. Condensation of the present β-acryloyl derivatives **66** with o-phenylenediamine was undertaken affording different products depending on reactior conditions. Diazipine **85** and benzimidazole derivatives **86** & **87** were isolated via different methods and their formation was investigated.





5. Some hydrazones **88** have been prepared from the reaction of 2,6-disubstituted isonicotinic acid hydrazides **39** and **53** with aldehydes. Meanwhile, the hydrazides were reacted with isocyanates and iso-thiocyanates with the formation of the corresponding semi- and thiosemicarbazides **89**.



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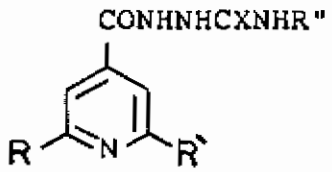
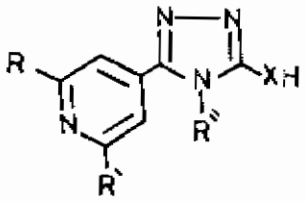


(89)

6. The semi- and thiosemicarbzide derivatives **89** were subjected to the action of sodium hydroxide or sulphuric acid to afford cyclized products, namely, triazoles **90**, oxadiazoles and thiadiazoles **91**, respectively.



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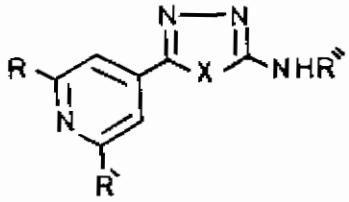


(91)

7. Formation of the obtained products was also explained and necessary path-ways for the undertaken reactions, are presented.

8. Structures of the obtained products were studied in light of their spectroscopic features (IR,UV and mass spectra).
9. The antimicrobial activity of the synthesized compounds has been tested against variuos species representing bacteria and fungi at 50 ϒ /ml, using the bioassay antibiotic sensitivity technique specified in USA pharmacopoiea in comparison with AMPCILLIN as a standard. Some of the tested products showed equal or higher effect than that resulted by Ampcillin

CHAPTER (I)

General Part

CHEMISTRY OF CITRAZINIC ACID

INTRODUCTION

Isonicotinic acid hydrazide (INH, isoniazid) is well known as a potent antitubercular agent used in the treatment of tuberculosis[1-3]. Other nicotinic and isonicotinic acid derivatives possess also well defined biological activities in several directions[4-18] and also as antimicrobial[19], anticonvulsant[20,21], antihistaminic[22], antidepressant[23] and antispasmodic[24] agents.

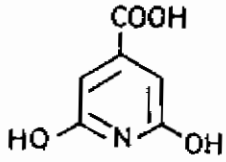
In continuation of our course of investigations in the field of pyridine chemistry[4-15] and in light of the afforementioned importance of pyridine carboxylic acid derivatives, the present study is dealing with the synthesis of citrazinic acid derivatives. It describes a study of its reactions with various electrophilic and nucleophilic reagents. Some of the isolated products were subjected to cyclization reactions with the formation of different ring systems. The obtained products are designed to be of expected biological activity and of pharmacological properties.

In the present review, it is not intended to cover the whole literature on the subject covering the chemistry of all pyridine carboxylic acids and related

analogues. Thus, the review which surveys the primary literature until 1991 and chemical abstracts to volume **114**, has been restricted on the reactions leading to citrazinic acid and related derivatives, in addition to their reactions and biological properties, as well.

I. Synthesis of citrazinic acid

Carboxylic acids of the pyridine series with carboxylic group in position-4 are known to be prepared with difficulty[25]. 2,6-Dihydroxy isonicotinic acid **(1)**, known as citrazinic acid was early reported[25] (in 1929) to be synthesized in 19% yield from citric acid as starting material.



(1)

Citrazinic acid **(1)** is existed mainly in formula **(a)** and the possible formulae **(b)** and **(c)** were excluded on the bases of IR study[26] of H-bridges and of the changes in the spectra caused by deuteration. The esters of **1** were found to exist predominatly in the 2-pyridone form **(d)** in methanol