SYNTHESIS OF SOME ANTIBIOTICS RELATED TO PENICILLIN AND CEPHALOSPORIN

A THESIS

Submitted in Partial Fulfilment of the Requirements of

M.Sc. Degree in

Organic Chemistry

Presented By

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B.Sc.(Chemistry)

Department of Chemistry

Faculty of Science

Ain-Shams University

Cairo , Egypt

1995

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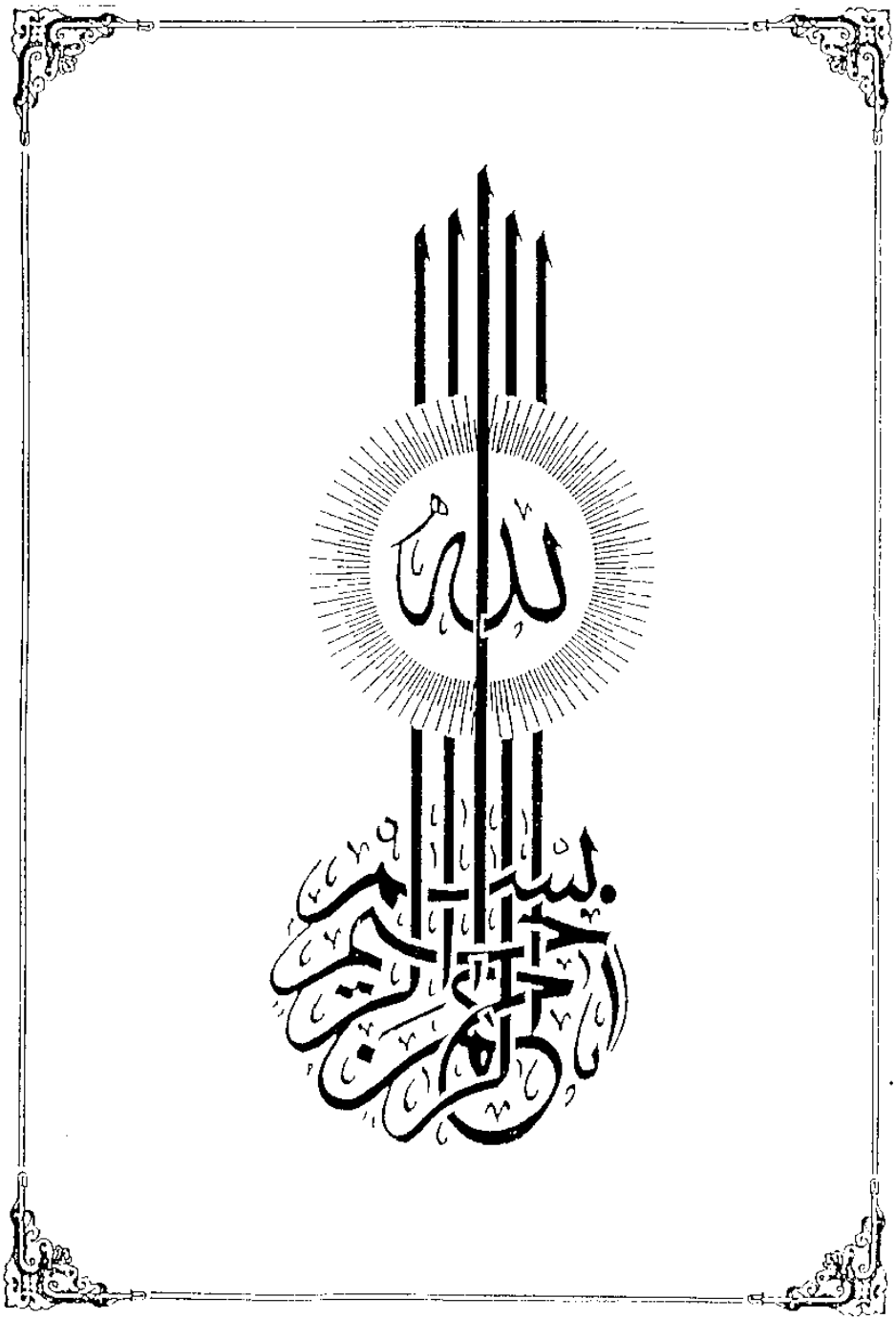
1995



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POST GRADUATE STUDIES FOR M.Sc.STUDENT IN ORGANIC CHEMISTRY (89-90)

This is to certify that Gamal Abdel-Naser Mohamed Ibrahim has attended passed successfully the following postgraduate courses as partial fulfilment for the Degree of Master of Science.

1- Advanced studies in physical organic chemistry :

i) Polar reaction mechanism.

ii)Pericyclic reaction mechanism.

2- Advanced studies in heterocyclic chemistry.

3- Advanced studies in applied spectroscopy analysis.

Electronic spectra, Infrared, H^1NMR,C^{13}-NMR and mass spectroscopy of organic chemistry.

4- Advanced studies in natural products.

5- Advanced studies in microanalysis.

6- Advanced studies in organometallic compounds.

7- Advanced studies in photochemistry.

8- Advanced studies in thermodynamics.

9- Advanced studies in kinetics.

10- Advanced studies in quantum chemistry.

11- English language course.

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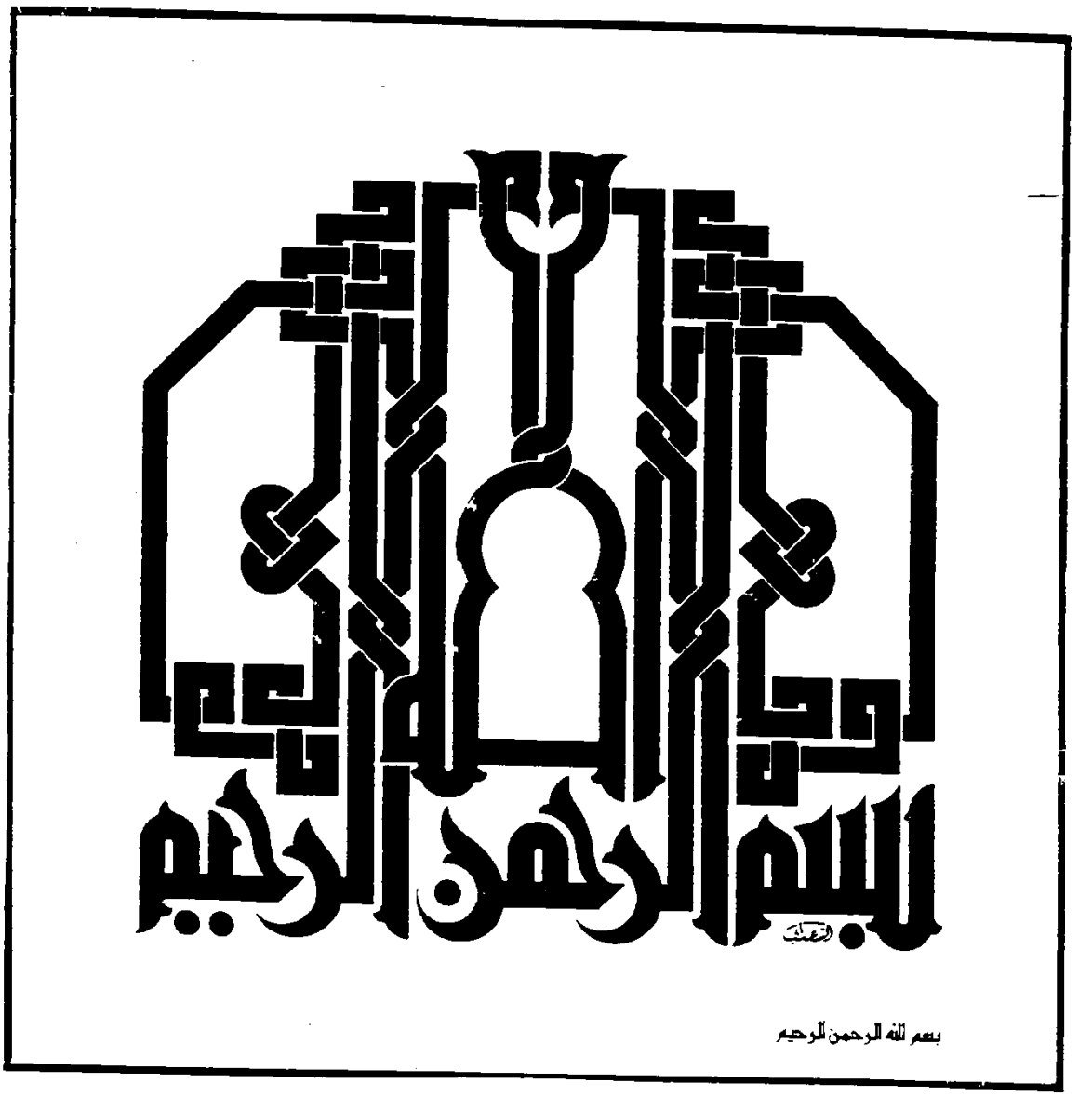
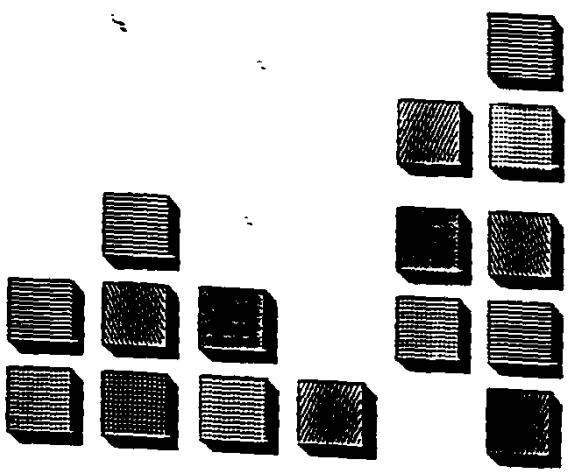


AIM OF THE WORK



Aim of The Work

This thesis deals with the synthesis of some new antibiotics of the penicillin and cephalosporin groups , and the study of their antimicrobial activities . It is hoped that the results obtained here , might contribute to the efforts of the research section at our company : El Nasr Pharmaceutical Chemicals Company, which is intersted in the production and development of synthetic drugs.

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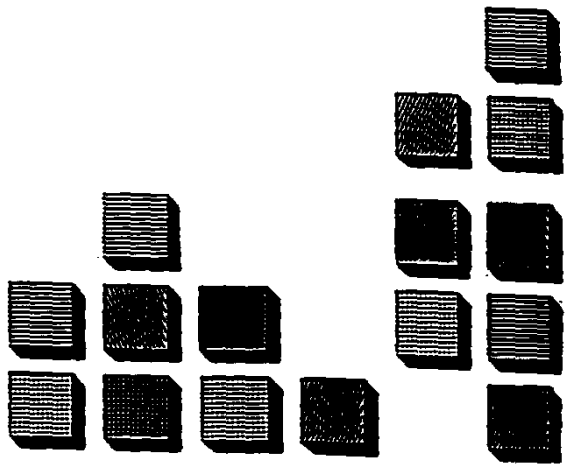
SUMMARY



Summary

Penicillins and cephalosporins represent two important classes of antibiotics those having a β-lactam group. The β-lactam moiety is responsible for the antimicrobial activity of these antibiotics , and therefore ,any changes of the substituents at this group , may cause changes in the activity .

In this investigation, some penicillin and cephalosporin derivatives are synthesized , with a study of their antimicrobial activity . 6-Aminopenicillanic acid (6-APA) and 7-aminodeacetoxy-cephalosporanic acid (7-ADCA) are used as the key starting materials

The reaction of 6-APA with 4-acetylaminobenzenesulphonyl chloride , phenylacetic-4- sulphonyl chloride and uracil-5-sulphonyl chloride leads to the formation of the corresponding 6-sulphonamido penicillanic acids (165a) ,(165b) and 165c) respectively . When 6-APA is allowed to react with α-(cyclohexa-1,3-dienyl) glycyl chloride hydrochloride , an ampicillin-like antibiotic (167) is obtained.

Similarly, 7-ADCA reacts with the previously mentioned sulphonyl chlorides to give the corresponding 7-sulphonamido-cephalosporanic acids (169a) ,(169b) and (169c) respectively. The reaction of 7-ADCA also with α-(cyclohexa-1,3-dienyl)-glycyl chloride hydrochloride leads to the formation of a cephalexin -like antibiotic (170) .

The reactions of the acid chlorides mentioned with 6-APA or 7 ADCA involve three main steps :

(i) Protection of the carboxyl group : since the carboxyl group of 6-APA or 7-ADCA is known to be sensitive to decarboxylation.

(ii) Coupling with the acid chloride : this step is carried out at low temperature ranging from -25 to -10 °C to avoid rupture of the β-lactam ring

(iii) Removal of the protecting group : removal of the protecting group to obtain the final product is usually affected either by water or 25% ammonium hydroxide solution depending on the nature of the protecting group .

The structures of the new products are based upon their microanalytical and spectral data .

The synthesized penicillin and cephalosporin derivatives are tested for their antimicrobial activity . Four Gram-positive bacterial strains : Sarcina lutea, Staphylococcus aureus , Bacillus subtilis and Streptococcus faecalis (enterococcus -groups D); and Five Gram-negative strains: Escherichia coli, Haemophilus influnzae,Proteus sp., klebsiella aerogenes, and Serratia marcescens were utilized.Ampicillin and cephalexin are used as standard antibiotics for comparison of the activities of the penicillin and cephalosporin derivatives respectively .Most of the tested compounds show significant inhibitory effect as antibacterial agents.

Generally , the uracyl derivatives show the most promising antibacterial activity , having broad spectra superier to ampicillin and cephalexin against certain strains.

ACKNOWLEDGEMENT

The author wishes to express his deep thanks and gratitude to Prof Dr.AHMED ISMAIL HASHEM, Professor of Organic Chemistry , Faculty of Science, Ain Shams University , and Dr.RAGAB MOHAMED ABDEL-AZIZ ,Head of Research Sector, El Nasr Pharmaceutical Chemicals Company , Not only for suggesting the subjects of this work, but also for his valuable discussions and citicism during the course of this work .

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TO MY FAMILY