

**COMPARATIVE STUDIES OF SOME
SUBSTITUTED 4-HYDROXYCARBOSTYRILS
WITH SOME RELATED HETEROCYCLIC
COMPOUNDS**

A THESIS

Submitted to
The Faculty of Science
Ain Shams University

By

JEHAN MAHMOUD MORSY

B. Sc. (Chemistry)
Demonstrator of Chemistry
Faculty of Education
Ain Shams University

In Partial Fulfillment of the Requirements
of the Master's Degree
In Chemistry

Cairo, A. R. E.

1987

**TO
MY PARENTS**

**TO
MY HUSBAND**

**AND TO
MY DAUGHTER NOURAN**



COMPARATIVE STUDIES OF SOME SUBSTITUTED
4-HYDROXYCARBOSTYRILS WITH SOME RELATED
HETEROCYCLIC COMPOUNDS

THESIS ADVISORS

Prof. Dr. A.A. Sayed

Prof. Dr. A.L. Ibrahim

Assoc. Prof. Dr. E.A. Mohamed

APPROVED

A. A. Sayed

A. L. Ibrahim

E. A. Mohamed

Head of Chemistry Department

Prof. Dr. N. M. Guindy

ACKNOWLEDGEMENT

My deepest gratitude are due to Prof. Dr. A.A. Sayed; Prof. Dr. A.L. Ibrahim (Dean of Faculty of Education, Ain Shams University) and Associate Prof. Dr. E.A. Mohamed, Chemistry Department, Faculty of Education, Ain Shams University, not only for suggesting the main lines of this thesis and solving all the problems encountered but also for help given, advices offered and continual encouragement. Their interest and guidance throughout the work is highly appreciated too.

My thanks are due to Prof. Dr. Hamad Jaheen, Head of Chemistry Department, Faculty of Education, Ain Shams University, for the facilities introduced throughout the course of this thesis.

O

NOTE

Besides the work carried out in this thesis the candidate has attended post-graduate courses for one year in organic chemistry including the following topics:

- 1- Reaction mechanisms.
- 2- Physico-organic chemistry.
- 3- Electronic, Infrared, N.M.R, and Mass spectroscopy of organic molecules.
- 4- Quantum mechanics.
- 5- Free-Radical reactions.
- 6- Heterocyclic compounds.
- 7- Polymer.
- 8- Instrumental analysis.

She has successfully passed an examination of these topics.

Head of Chemistry

Department

CONTENTS

	Page
SUMMARY OF THE ORIGINAL WORK	i
GENERAL PART:	ii
<u>4. HYDROXYCARBOSTYRILS</u>	1
Biological Activity and Uses of 4-Hydroxycarbostryils	1
IR spectrum of 4-hydroxycarbostyrils	5
<u>SYNTHESIS OF 4-HYDROXYCARBOSTYRILS</u>	7
<u>REACTIONS OF 4-HYDROXYCARBOSTYRILS</u>	19
I. <u>Reactions at the Nitrogen atom of the heterocyclic</u>	
<u>ring</u>	19
A.N- Methylation	19
B.N-chlorination	23
II. <u>Reactions of the Hydroxyl group</u>	
A. Methylation	25
B. Replacement of the hydroxyl group by a halogen atom	36
C. O-Acylation	44
D. Reactions with amines	51
E. Replacement of the hydroxyl group by an amino group	53
F. Preparation of carbostyryl-4-phosphorothionates and	
carbostyryl-4-phosphonothionates	53
G. Reaction with phosgene and amonia derivatives.....	54

	Page
<u>III. Reactions at the 3-position:</u>	
A. Nitrosation	55
B. Acylation	58
C. Halogenation	60
1. Chlorination	60
2. Bromination	65
3. Iodination	70
D. Preparation of iodonium ylides	70
E. Nitration	71
F. Reactions with dibromo compounds	72
G. Reaction with chloroacetone	74
H. Reaction with diethylaminobutanone	75
I. Addition to unsaturated compounds	76
J. Reaction with 1-phenylbut-3-yn-1-ol	77
K. Reaction with azides	78
L. Reactions with aliphatic aldehydes	78
M. Reaction with thionyl chloride	81
N. Condensation with morpholino-and piperidino methanol	82
O. Reaction with acetic anhydride in dimethylsulphoxide	83
P. Coupling with diazonium salts	84
<u>IV. Miscellaneous reactions:</u>	
A. Reactions with malonate esters	90
B. Methylation	93
C. Reactions of 3-acyl derivatives	94
D. Sulphonation	98

N

	Page
E. Oxidation with potassium permanganate	98
F. Reaction with nitriles	99
G. Reactions with 3-dimethyl ally derivatives	99
SPECIAL PART	
ORIGINAL WORK	
The Chemistry of 3-acetyl (or 3-formyl) -1-butyl-4- hydroxycarboxylic acid	101
EXPERIMENTAL	158
REFERENCES	175
ARABIC SUMMARY.	

AIM OF THE WORK

Synthesis and reactions of 4-hydroxycarbo-tyrils in particular those with long acyl side chain in the 3-position, have recieved great interest because of their importance in medicine. This prompted us to deal in this thesis with the synthesis of some new 4-hydroxycarbo-tyrils containing long acyl groups in the 3-position and butyl group at position 1. This was acheived through synthesis and investigation of the chemistry of 3-acetyl (or formyl) 1-butyl-4-hydroxycarbo-tyrils.

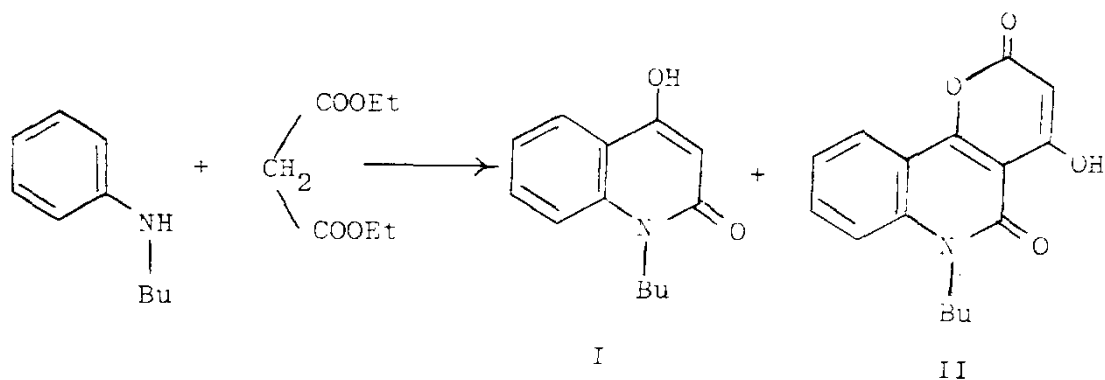
Compounds containing one or two carbonyl groups in the side chain at position-3 were also synthesized and investigated. Heterocyclic derivatives (namely; pyran, diazipin, pyrazol and isoxazol) fused to the carbo-tyril moiety at position 3,4-were also synthesized and their structures were discussed. Besides, we were able to prepare and investigate 1-butyl-4-hydroxycarbo-tyrils containing heterocycls as substituents at the 3-position.

Biological activity is expected for some of our new synthesized compounds.

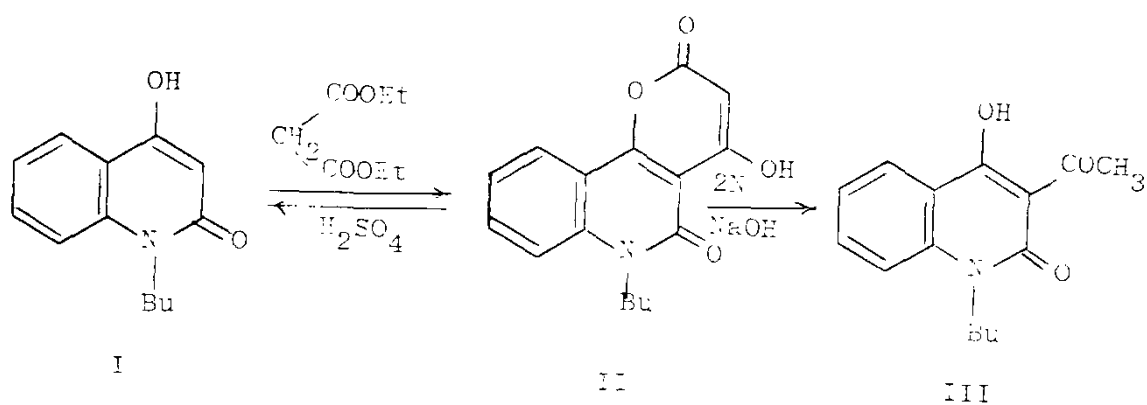
SUMMARY OF THE ORIGINAL WORK

SUMMARY OF THE ORIGINAL WORK

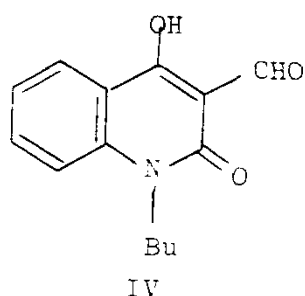
1- Butyl-4-hydroxycarbostyryl (I) and 4'-hydroxy 2'-oxo(5', 6':3,4) pyrano-1-butylcarbostyryl (II) were synthesized by the fusion of N-butylaniline with diethylmalonate.



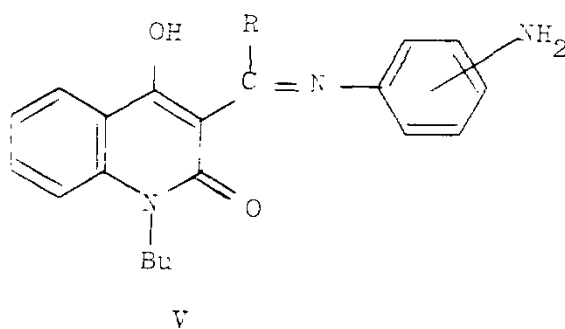
While acidic hydrolysis of II gave rise to I, alkaline hydrolysis led to the formation of the 3-acetyl-1-butyl-4-hydroxycarbostyryl (III). Whereas I reacted with diethylmalonate to give II.



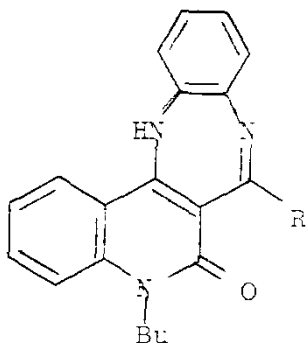
I underwent Riemer-Tieman reaction with chloroform and NaOH to give the 3-formyl derivative(IV) .



The reaction of III and/or IV with o-, m- and p-phenylenediamine was studied under different conditions and at different ratios of reactants. When the reaction was carried out in ethanol at the ratio 1:1, the obtained products were the imino derivatives(V) .

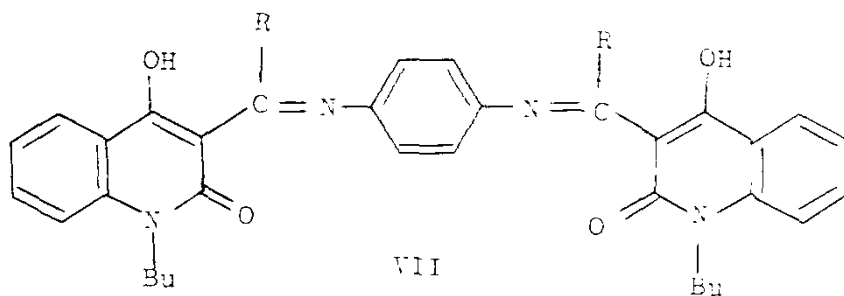


While upon carrying out the reaction with o-phenylenediamine in glacial acetic acid at the same ratio, the obtained products were the 1, 4-diazapin derivatives(VI), identical with those obtained by treating V_{a,d} with boiling acetic acid.



VI

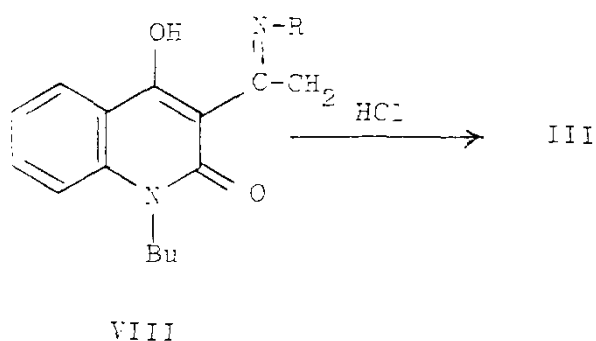
Whereas when the reaction of III and/or IV with p-phenylenediamine was carried out at the ratio 2:1, the products were the bis compounds VII, which were also obtained by reacting V_C with IV and/or V_F with III.



VII

On the other hand m-phenylenediamine reacted under all conditions and ratios to afford one and the same product V.

Compound III have been condensed with aliphatic and aromatic amines in alcohol to give the corresponding imino derivatives(VIII), which were readily converted to III on heating with dil HCl.



The acetyl derivative(III)underwent condensation reaction with hydrazine, phenylhydrazine and hydroxylamine in boiling alcohol, affording the hydrazone, phenylhydrazone and oxime derivatives(IX)respectively.

