A THESIS

ENTITLED

STUDIES ON SOME HETEROCYCLIC NITROGEN COMPOUNDS

Submitted by

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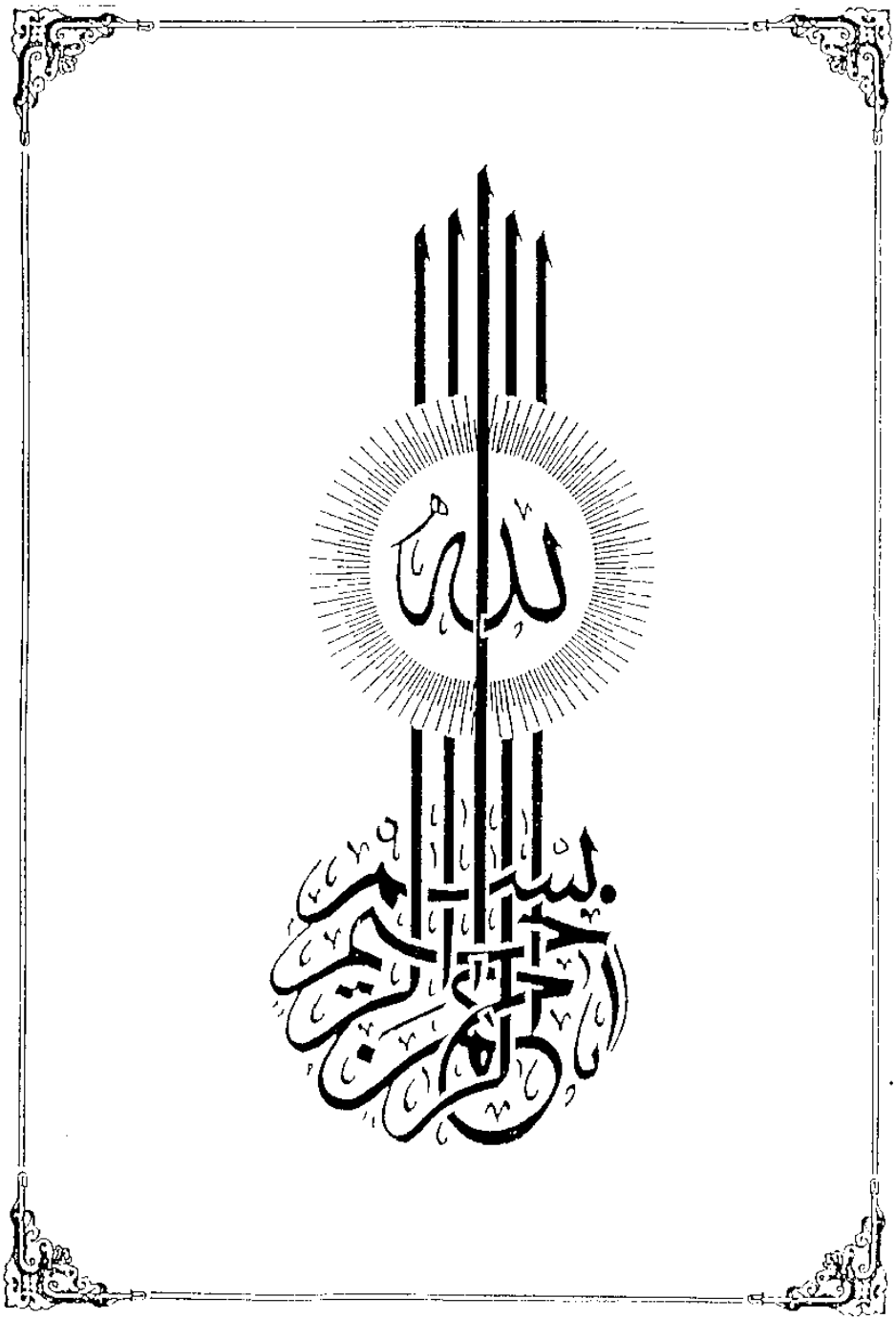

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V I T A E

Hanan Abd El-Rahman Mohamed Sallam, was born on October 27th 1963 in Cairo, Egypt. She attended her preuniversity studies at "Sarray El-Kobba secondary school. In 1981 she was enrolled in Faculty of Science, Ain Shams University, Cairo, Egypt, where she majored in chemistry and received the degree of Bachelor of Science in 1985 with Very Good.

In the same year, she was appointed as a demonstrator in Chemistry Department, Faculty of Science, Ain Shams University.

In 1988 she carried out this research under the supervision of Prof. Dr. M.F. Ismail, Professor of Organic Chemistry; Prof. Dr. E.I. Enayat, Professor of Organic Chemistry and Dr. O.E.A. Mustafa, Lecturer of Organic Chemistry, Faculty of Science, Ain Shams University.

N O T E

Besides the work carried out in this thesis, the candidate has attended postgraduate courses for one year in Organic Chemistry including the following topics :

(1) Reaction mechanism.

(2) Electronic, infrared, N.M.R. and Mass spectroscopy of Organic Compounds.

(3) Microanalysis of Organic Compounds.

(4) Organic reactions.

(5) Heterocyclic compounds.

(6) Quantum chemistry.

She had successfully passed on examination in these topics.

Prof. Dr. N.M. Guindy

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CONTENTS

S U M M A R Y

SUMMARY

The present investigation deals with the new convenient synthesis of 4-benzoylphthalazin-1(2H)-one (82) by the oxidation of 4-benzylphthalazin-1(2H)-one (30) using sodium dichromate in acetic acid. The presence of the ketonic carbonyl group in (82) was confirmed by its ready reaction with hydroxylamine hydrochloride or hydrazine hydrate to give the corresponding oxime (83) or hydrazone (84), respectively.

4-Benzoylphthalazin-1(2H)-one reacted, in the lactam form, with dimethyl sulphate to give 4-benzoyl-2-methylphthalazin-1(2H)-one (85). It reacted also with secondary amines in the presence of formaldehyde to give the Mannich bases (86a & b).

The base - catalysed reaction of 4-benzoylphthalazin-1(2H)-one (82) with acrylonitrile, for 4 hrs involved a Michael - type addition yielding 4-benzoyl-2-(2'-cyanoethyl)-phthalazin-1(2H)-one (87). When the reaction time was extended to 10 hrs, partial hydrolysis of the initially formed product (87) to 4-benzoyl-2-(2'-carbamidoethyl)-phthalazin-1(2H)-one (88) took place.

4-Benzoylphthalazin-1(2H)-one reacted, in the lactim form with acetic anhydride to give 1-O-acetyl-3-benzoylphthalazine (90). Similarly the reaction of (82) with phosphorus oxychloride involved the lactim form yielding 4-benzoyl-1-chlorophthalazine (91).

The reaction of Grignard reagents with 4-benzoylphthalazin-

1(2H)-one (82) gave products which were dependent upon the reagent. Thus, benzylmagnesium chloride reacted with (82) or its N-methyl derivatives (85) by 1,2-addition to the ketonic carbonyl group giving the carbinols (92a) or (92b), respectively. It was possible to get (92b) by the action of dimethyl sulphate on (92a). Arylmagnesium halides or methylmagnesium iodide reacted, on the other hand, with (82) by 1,2-addition to -C=N at position 4- giving the 3,4-dihydrophthalazinone derivatives (94a & b) and 95.

This investigation was extended to involve the application of the above method of oxidation to some substituted 4-benzoyl-phthalazine derivatives. Thus oxidation of 2-methyl- (96) and 2-(2'-carbamidoethyl)- (98) -4-benzylphthalazin-1(2H)-ones gave the expected 4-benzoylphthalazin-1(2H)-one derivatives (85) & (88), respectively while oxidation of 4-benzyl-2(2'-cyanoethyl)-phthalazin-1(2H)-one (97) gave the expected oxidation product (87) together with its partial hydrolysis product (88). However oxidation of 4-benzyl-2-piperidinomethylphthalazin-1(2H)-one (99) gave 4-benzoylphthalazin-1(2H)-one (82) which means that the oxidation process involved also cleavage of the piperidinomethyl group. Similarly, 1-O-acetyl-4-benzylphthalazine (100) gave (82) on oxidation with sodium dichromate in acetic acid indicating that the ester linkage is not stable under these reaction conditions.

Another part of this thesis involved a study of the reactivity of 4-benzoyl-1-chlorophthalazine (91) towards some nucleophilic reagents. The reaction of (91) with primary or secondary

amines in boliling ethanol involved the displacement of chlorine at position (1) giving 1-substituted amino-4-benzoylphthalazines (101a-c) & (103a & b). However, when the reaction of (91) with aniline was carried out at elevated temperature in the absence of solvent, the reaction involved both electrophilic centres, namely, the chlorine at position 1 and the ketonic carbonyl giving the Schiff base (102).

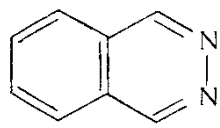
4-Benzoyl-1-chlorophthalazine (91) reacted with sodium azide in dimethylformamide to give the tetrazolophthalazine derivative (105) which is the cyclisation product of the originally formed 1-azido-4-benzoylphthalazine (104).

The reaction of (91) with alcoholic thiourea gave a good yield of 4-benzoylphthalazin-1(2H)-thione (106).

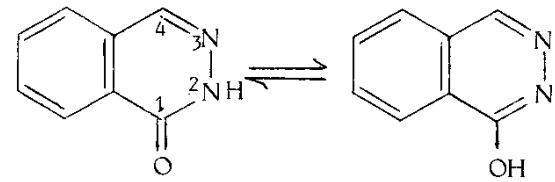
I N T R O D U C T I O N

CHEMISTRY OF PHTHALAZIN-1(2H)-ONES

Phthalazine is benzo-[d]-pyridazines (1). Phthalazin-1(2H)-one (2) carrying no substituents in the 2-position is tautomeric with 1-hydroxyphthalazine (2').



(1)



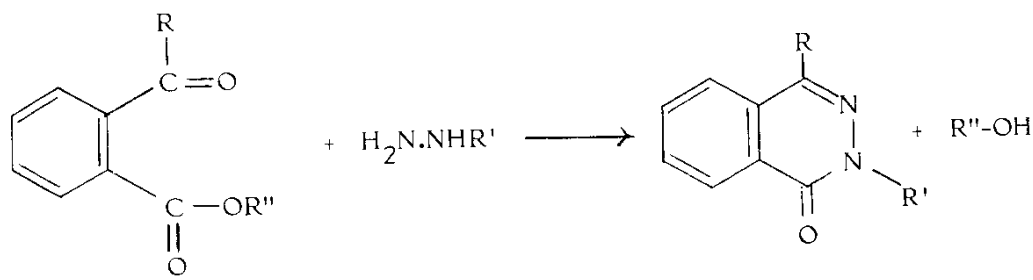
(2) (2')

SYNTHESIS OF PHTHALAZIN-1(2H)-ONES

1) From o-acylbenzoic acids

o-Acylbenzoic acids (3), their esters, or their azides, readily condense with hydrazines to yield 4-substituted phthalazin-1(2H)-ones (4)[1-6]. This method is the most commonly used for the synthesis of phthalazin-1(2H)-ones.

(2)



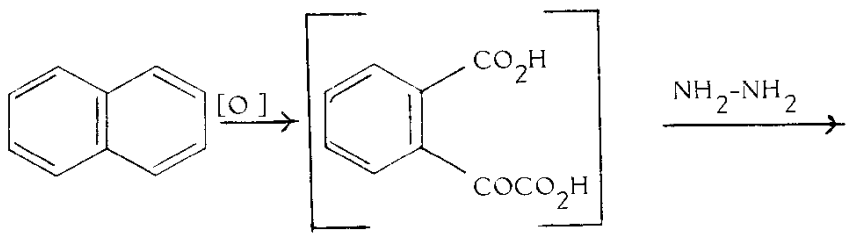
(3)

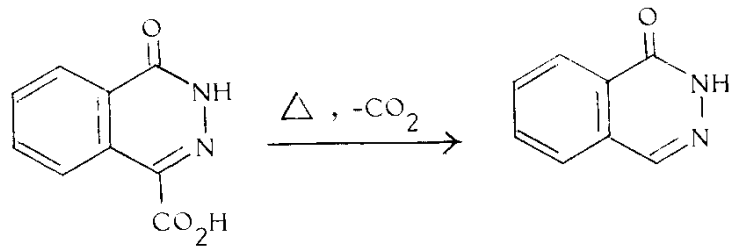
R = H, alkyl, aryl or $COOR'$

R' = H or alkyl

R'' = H, aryl or NH_2CO

Phthalazin-1(2H)-one (6) itself is prepared from naphthalene or tetralin by oxidation, subsequent treatment with hydrazine sulphate and decarboxylation of the formed phthalazinone carboxylic acid (5)[7,8].





(5) (6)