SYNTHESIS AND REACTIONS WITH SOME NEW PHTHALAZINONES DERIVATIVES

THESIS

In Partial Fulfilment of the Requirement of

Master of Science Degree

By

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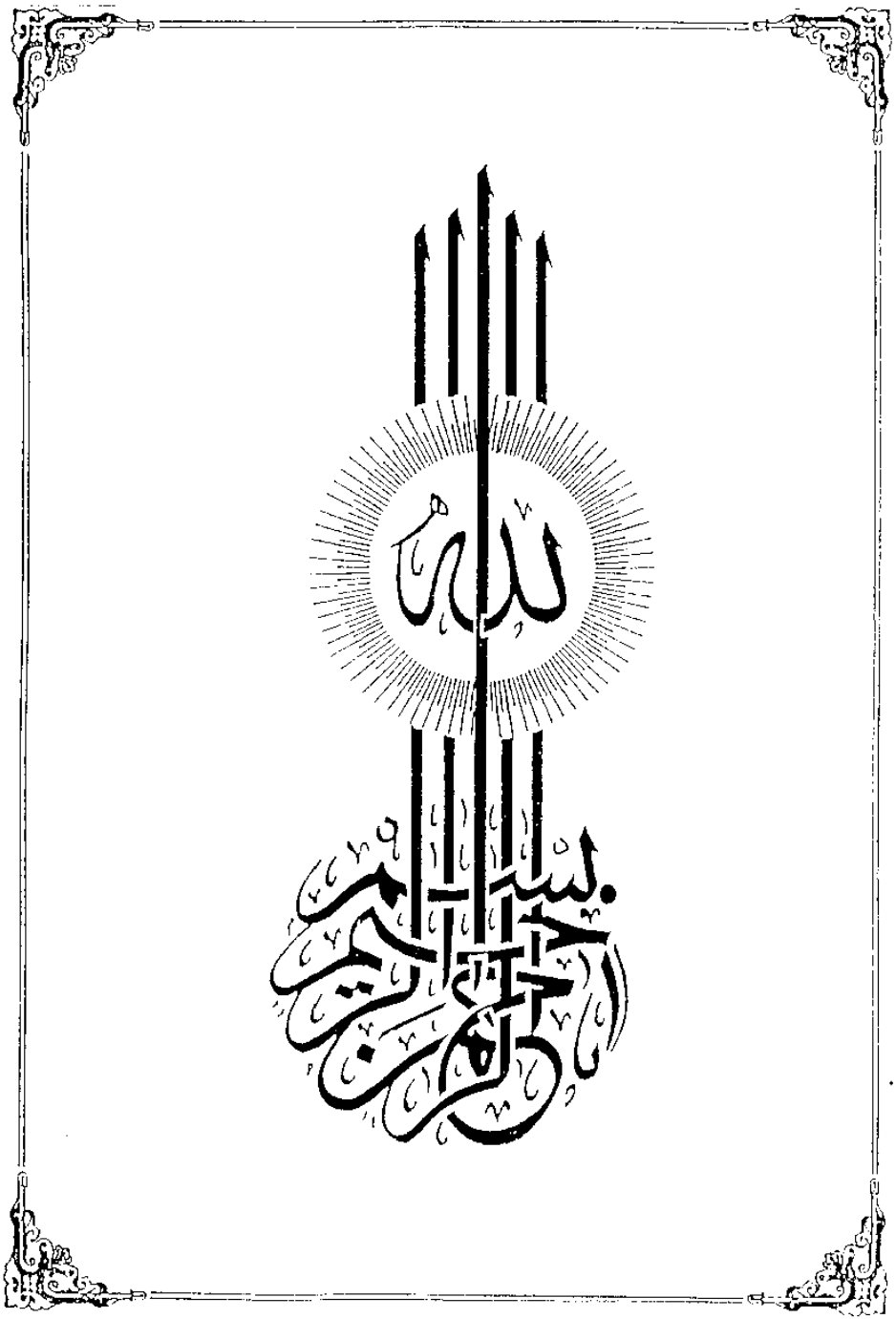

SYNTHESIS AND REACTIONS WITH

SOME NEW PHTHALAZINONE DERIVATIVES

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N O T E

Beside the work carried out in this thesis, the candidate has attended post-graduate course 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.

(7) Macromolecular chemistry.

She had successfully passed an examination in these topics.

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C O N T E N T S

STATMENT AND OBJECTIVES OF THE WORK

The 1(2H)-phthalazinones have become of increasing importance in the recent years due to their use as remedies for artroisosclerosis and thrombosis, and have also been found useful as developable light sensitive materials. This prompted us to synthesise some new phthalazinones via interaction of benzalphthalide and o-aroylbenzoic acid with hydrazine, and also in the hope of obtaining some pharmaceutical action.

In view of the reactivity of the methyl group position 2- in 3,1-benzoxazin-4-ones and quinazolinones, the author sought to prepare 2-methyl-1(2H)-phthalazinone with the aim of study the reactivity of methyl group in position-2 towards some electrophiles e.g. aromatic aldehydes and acid anhydrides. The results indicated that the methyl group in phthalazinone nucleus is highly reactive, this was obtained from study of the yield and conditions of the reaction.

Recently, it was reported that 6-substituted phenyl-1,2,4-triazolo-[4,3-b] pyridazines have a pharmacological properties. Some of these derivatives also exhibited hypotensive activity when tested in spontaneously hypertensive rats (SHR), on the other hand, some derivatives exhibited anxiolytic activity. The present work also

deals with the reaction of the chlorophthalazine derivative with acylhydrazines in boiling butanol to give 6-aryl-3-methyl-1,2,4-triazolo-[3,4-a] phthalazine, in the hope of obtaining some pharmacological properties.

SUMMARY OF THE ORIGINAL WORK

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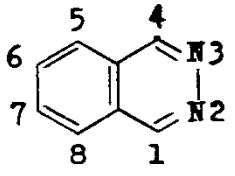
The phthalazinone derivatives IIa-c have been synthesised from the interaction of benzalphthalide or o-aroylbenzoic acids with hydrazine hydrate. The behaviour of these derivatives toward electrophilic reagents e.g. acetic anhydride, dimethylsulphate, ethyl chloroacetate, chloroacetic acid, formaldehyde and amines under Mannich reaction conditions, ethylene chlorohydrine has been investigated. The structure of all products has been supported via the chemical and physical tools. On the other hand, the behaviour of phthalazinone derivatives toward nucleophiles e.g. carbon nucleophiles (aryl and alkyl halides under Grignard reaction conditions) and chlorine nucleophiles ($PCl_5/POCl_3$) has been described with the aim of obtaining some new chlorophthalazine derivatives which used as key starting material for synthesis of a diverse of phthalazine derivatives and other heterocycles i.e. the chloro derivative reacts with hydrazine and gave hydrazinophthalazine, with sodium azide gives tetrazole derivative, with glycine afforded phthalazinyl glycine, with ethoxy carbonylhydrazine gives carbazate derivative, with acetylhydrazine produced triazolophthalazine. The structures of all prepared compounds have been established via physical and chemical tools.

GENERAL PART

CHEMISTRY OF 1(2H)-PHTHALAZINONES

PHTHALAZINE AND ITS DERIVATIVES

Phthalazine is benzo[d]pyridazine. The fundamental ring systems involved in this thesis are named, numbered and oriented as shown in formula I.



(I)

The chemistry of the phthalazines has been reviewed by Vaughan[1].

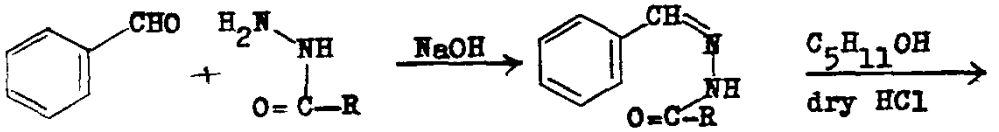
SYNTHESIS OF PHTHALAZINES

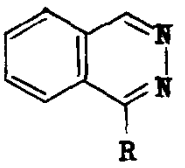
All known synthesis of phthalazines proceed through closure of the pyridazine ring either between the 1 position and the benzene ring (Type I) or between the 1 and 2 (or 3 and 4) positions (Type II).

Type I ring closures :

When an aromatic aldehyde is condensed with a hydrazide of an acid, an acyl hydrazone of the aldehyde is formed. On cyclodehydration of this hydrazone a

1-substituted phthalazine results (II)[2,3].





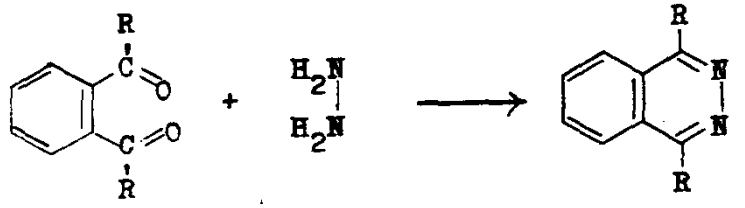
(II)

The yields of phthalazines in general do not exceed 50 %. The reaction has been successful with veratric and p-anisic aldehydes, piperonal, benzaldehyde, and o-methoxy-benzaldehyde. Some doubt exists as to whether meta-substituted benzaldehydes (CH_3O or NO_2) yield phthalazines[2]. Hydrazides of benzoic; phenylacetic, piperonylic, and veratric acids have been used.

Type II Ring Closures:

When an o-diaroylbenzene is condensed with hydrazine, a 1,4-diarylphthalazine (IV) results directly[4-10]. The reaction also proceeds with phthalaldehyde[11], and there seems to be no reason other than the inaccessability of the requisite o-diacyl benzenes to suppose that it will

not proceed when R = alkyl in formula III.

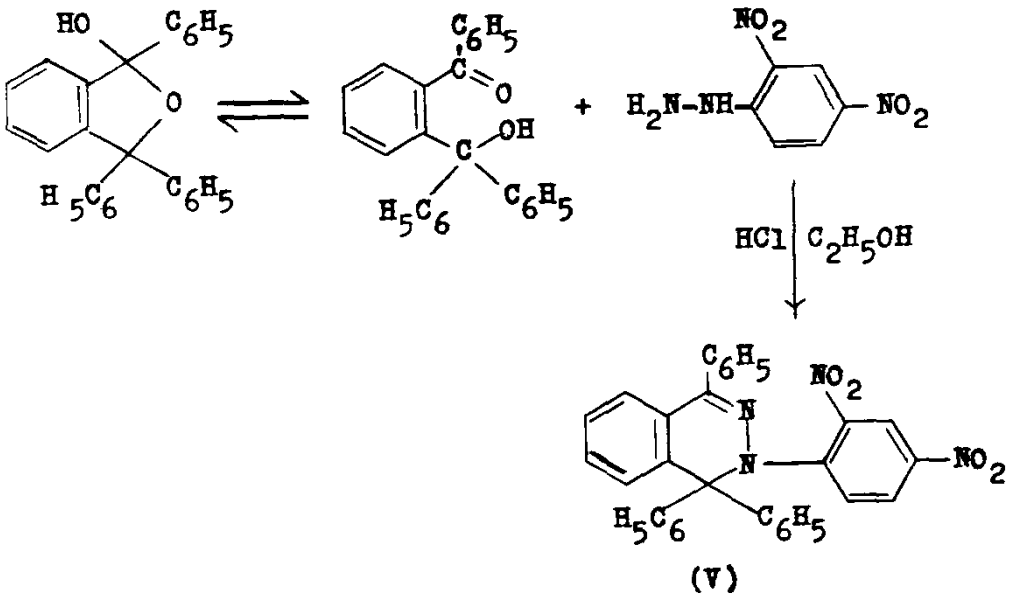


(III) (IV)

R = aryl

Closely related to the above reaction is the condensation of α , α , α`, α`-tetrahalo-o-xylene derivatives with hydrazine which gives phthalazines[11,12].

A 1,2-dihydrophthalazine derivative has been prepared by the following reaction[13].



(V)