A Thesis

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STUDIES ON PYRIDAZINES, SYNTHESIS OF NEW COMPOUNDS WITH EXPECTED BIOLOGICAL ACTIVITY

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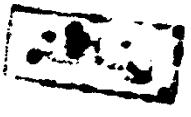

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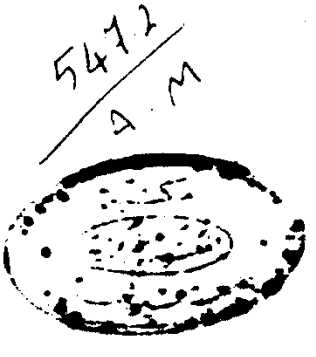

National Research Centre

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STUDIES ON PYRIDAZINES, SYNTHESIS OF NEW COMPOUNDS
WITH EXPECTED BIOLOGICAL ACTIVITY

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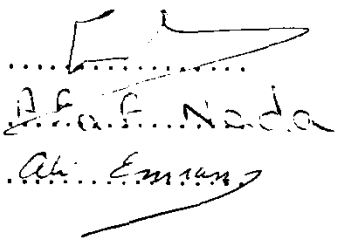

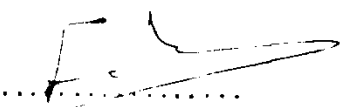

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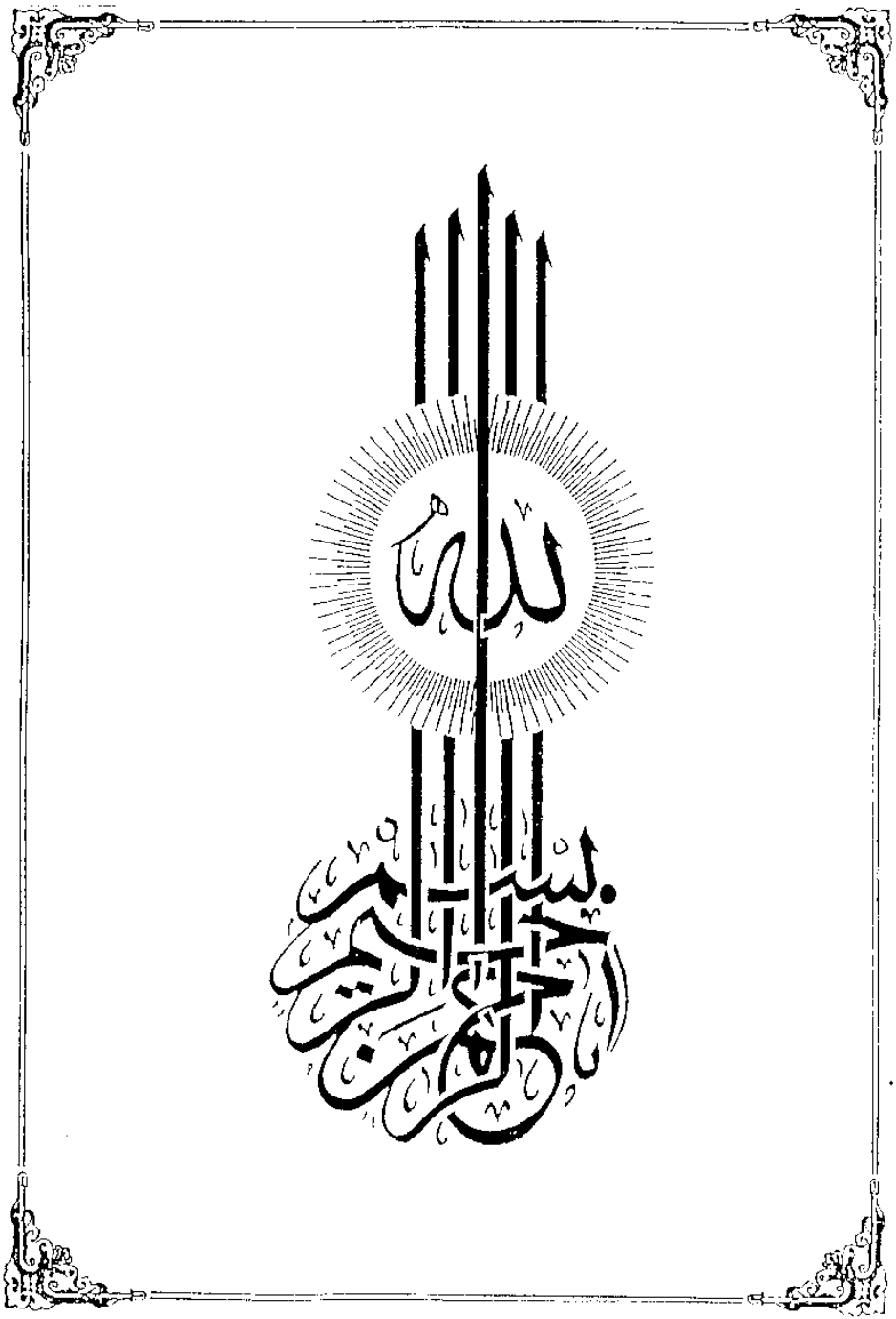

N O T E S

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 mechanisms.
2) Electronic, infrared, n.m.r. and mass spectroscopy of organic molecules.
3) Advanced steroid, heterocyclic and polymer chemistry and organic reactions.

He has successfully passed an examination in these topics.

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SUMMARY

SUMMARY

6-Aryl-3-chloropyridazines (53a-c) were prepared from the reaction of 6-aryl-2,3-dihydropyridazin-3-ones (52a-c) with phosphorus oxychloride.

6-Aryl-2,3-dihydro-4-methyl-pyridazin-3-ones (56a-c) were prepared from the reaction of 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (54a-c) with formaldehyde in alcoholic potassium hydroxide.

6-Aryl-3-chloro-4-methylpyridazines (57a-c) were similarly prepared by the action of phosphorus oxychloride on 6-aryl-2,3-dihydro-4-methyl-pyridazin-3-ones (56a-c), the infrared and ultraviolet spectra of the 3-chloropyridazines obtained were discussed.

3-Chloropyridazines (53a & b) and (57a) reacted with sodium azide in n-butanol to give 6-aryl-tetrazolo [1,5-b] pyridazines (60a & b) and 6-(3,4-dimethylphenyl)-3-methyl-tetrazolo [1,5-b] pyridazine (60c). The same products (60a-c) were prepared from the reaction of 3-chloropyridazines (53a & b) and (57a) with hydrazine hydrate, followed by nitrosation of the unstable hydrazinopyridazines obtained (64a-c) to give the cyclic tetrazoles (60a-c).

When 6-aryl-3-chloropyridazines (53a & b) and 3-chloro-6-(3,4-dimethylphenyl)-4-methylpyridazines (57a) reacted with sodium methoxide, they gave 3-methoxypyridazines (65a-c).

The reactions of 3-chloropyridazines (53a & b) and (57a) with different haloubstituted phenols was performed to give 6-substituted- and 4,5-disubstituted-3-haloaryloxypyridazines (67a-l) and (68a-f).

3-Chloropyridazines (53a & b) and (57a) reacted with p-hydroxy-acetophenone in presence of anhydrous sodium carbonate to give 4'-[[6-(aryl)-3-pyridazinyl] oxy]acetophenones (69a & b) and 4'-[[6-(3,4-dimethylphenyl)-4,5-dimethyl-3-pyridazinyl] oxy]acetophenone (69c).

4'-[[6-(3,4-Dimethylphenyl)-3-pyridazinyl] oxy]acetophenone (69a) reacted with hydrazine to give 4'-[[6-(3,4-dimethylphenyl)-3-pyrida-zinyl] oxy] acetophenone hydrazones (70a & b).

4'-[[6-(3,4-Dimethylphenyl)-3-pyridazinyl] oxy]acetophenone [illegible] prepared by the reaction of 4'-[[6-(2,4-[illegible]] oxy] acetophenone (69b) with hydrazine [illegible]

GENERAL PART

INTRODUCTION

Pyridazine derivatives have recently received attention from the synthetic and theoretical point of view, since many derivatives were found to possess therapeutic potential as plant growth regulating effect[1].

Because of the ease of preparation and reactivity of halopyridazines they have found wide use in pyridazines chemistry. They are useful as intermediates for a wide variety of reactions and are found to show biological activity as herbicides, fungicides, antituberculosis, antitumer and antimicrobial agents[2].

I. Properties of Halopyridazines

A. Reactivity and Reaction Rates.

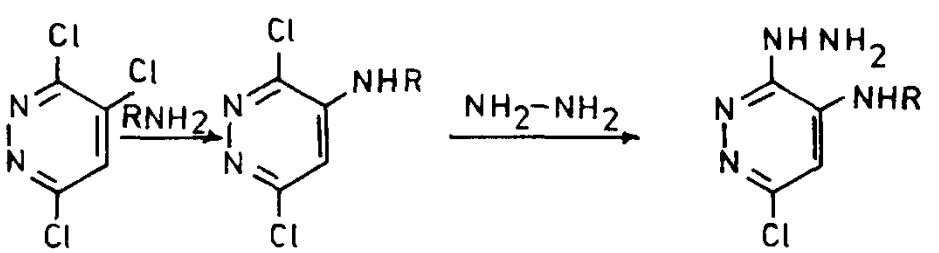
The reactivity of halogens attached to the pyridazine nucleus towards nucleophilic attack is greatly influenced by the type and position of the halogen, the nucleophile, influence of other groups present and reaction conditions.

In comparison with 2-chloropyridine which is quite stable, 3-chloropyridazine decomposes easily even when kept at $0^{o}C$[3]. This instability may be due to self quaternization, since replacement of the chlorine by other groups requires relatively high temperatures.

Since kinetic data are scarce, a comparison of relative reactivities of halogen atoms at different positions in the pyridazine or pyridazinone molecule is difficult. The differences in reactivities which will be referred to are based on synthetic work. It is also reported that chlorine atom at position 4, in a polychlorinated pyridazine, is usually the most reactive for nucleophilic attack because of the lowest electron density.

The reactivity of different chloropyridazines has been studied in view of the position of the chlorine atom in the pyridazine molecule. The study made by Chan and Miller[4] showed that the reactivity of 3- and 4-chloropyridazine is the same towards p-nitrophenoxide ion in methanol. The 4- and 5-chlorine atom in 3,4,5-trichloropyridazine were both replaced when the latter was allowed to react with ammonia[5,6]. On the other hand, in 3,4,6-trichloropyridazine, the 4-position was found to be most active towards many reagents[7].

The 3-chlorine atom was the one attacked when 4-amino-3,6-dichloropyridazine (1) was treated with hydrazine to give 4-amino-6-chloro-3-hydrazinopyridazine (2)[6,8].



(1) (2)

In case of 3,6-dichloropyridazine, monosubstitution was observed and hydrolysis of one chlorine atom usually took place[9].

The reactivity of 3-, 4-, 5- and 6- halopyridazine 1-oxide with alkoxides and amines was studied[10-12]. The rate order of position reactivity was 5 > 3 > 6 > 4.

B. Infrared Spectra

Extensive studies on the infrared spectra of halopyridazines have been reported[13-17]. Salisbury et al[18] reported pyridazine ring bands at 1600-1540, 1325-1295, and 1065-935 cm^{-1} after studying the infrared absorption spectra of a large number of 3-halo-6-alkoxypyridazines. A shift toward lower energy in the CH stretch frequency was observed in changing from chloro to bromo to iodo substituents.

C. Ultraviolet Spectra

Eichenberger et al[19] reported data for many chloropyridazines. Similar studies was done by Levisalles[20] and Magee[21]. Kuraishi[22] measured the u.v. absorption spectra of some 4-substituted (H, CH_3, Cl, CH_2H_5, NH_2, $NHNH_2$) 3,6-dichloropyridazines. Other investigators[13,23-25] have also reported u.v. spectra.

D. Nuclear Magnetic Resonance Spectra

Tori, Ogata and Kano[26] applied nuclear magnetic resonance in the determination of the position of the N-oxide group in pyridazine N-oxides. Several chloropyridazines containing other substituents as well have been investigated. Declerck et al[27] and Tori and Ogata[28] have reported nuclear magnetic resonance studies on chloropyridazines and pyridazines containing other groups (CH_3, OR) in addition to chlorine. Substituted pyridazines have very simple n.m.r. spectra. Tori[28] found very little effect on ring proton shifts from methyl groups or chlorine atoms. Price and co-workers[29], by the use of n.m.r., studied conformational changes in tetrahydro and hexahydropyridazine derivatives. Ogden[30] carried out n.m.r. studies on 1,2-dimethyl-3,4,5,6-tetrafluoropyridazine.

Daniels and Roseman[31] used proton magnetic resonance (p.m.r.) to determine the conformation of 1,2,3,6-tetrahydro-4-chloropyridazine in a study of the stereochemistry of the Diels-Alder reaction of heterodienophiles. Stidham and Farrell[32], by the use of chlorine-35, measured the nuclear quadrapole resonance of 3,6-dichloro- and 3,4,5,6-tetrachloropyridazine.

E. Mass Spectra

The mass spectra of several chloro and substituted chloropyridazines have been recently reported[33]. It was found in the mass spectral decomposition of pyridazines the probable formation of cyclobutadiene-type