NOVEL METHODS FOR THE SYNTHESIS OF (A) PYRIDAZINE DERIVATIVES AND RELATED N-HETEROCYCLES FROM SUBSTITUTED 1, 4-DIKETONES AND (B) CYCLOPROPANE ACETIC ACID ETHYL ESTERS AND HEXA-3, 5-DIENOIC ACID METHYL ESTERS *VIA* LEAD (IV) ACETATE OXIDATIONS

By

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I, **Mr Rishan Lang Nongkhlaw**, hereby declare that the subject matter of this thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other university or institute. This is being submitted to the North Eastern Hill University for the degree of Doctor of Philosophy in Chemistry.

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Dedicated To

My Beloved Father

(Late) Makrom Pathaw

and Brother

(Late) Tyngshain Lang Nongkhlaw

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PREFACE

The thesis consists of six chapters which are divide into two parts: **Part A** deals with the synthesis of N-heterocycles. N-heterocycles formed the basic skeleton of many biologically important classes of natural products such as antibiotics, vitamins, marine products, animal toxins, and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting systems such as Haemoglobin, Chlorophyll, Vitamin B_{12} etc. Heterocyclic units such as pyridazines, triazines and their analogues are of special interest in pharmacology, due to their important biological activities. The work here highlighted the novelty of synthetic studies of pyridazine derivatives and related N-heterocycles starting from simple starting compounds *via* the 1, 4-dicarbonyl compound in a one pot reaction without isolation of the intermediates.

The first chapter deals with the general introduction of N-heterocycles. In the second chapter the synthesis of 3, 5, 6-triaryl pyridazines from aryl methyl ketones and aromatic 1, 2-diketones is discussed. This method has been generalized by the use of heteroaromatic 1, 2-diketones.

The third chapter deals with the synthesis of trisubstituted 1, 2, 4-triazines starting from amides and 1, 2-diketones. The advantage of our methods is that in all the reported methods the reaction intermediates were isolated before proceeding to the next step.

Part B deals with the synthetic applications of lead tetra acetate. Lead tetra acetate, as a versatile oxidizing agent, has been used for selective and partial oxidation of various reactive groups, depending on the reaction condition and nature

of the substrate. It oxidizes organic molecules and itself gets reduced from lead (IV) to lead (II) either through ionic or radical mechanism.

The fourth chapter gives a general introduction on lead (IV) acetate oxidation. In In the fifth chapter the 1, 2-carbonyl transposition of cyclopropyl methyl ketones to give cyclopropane acetic acid ethyl esters effected by lead (IV) acetate in triethyl ortho formate and a catalytic amount of perchloric acid is discussed.

In continuation of the studies concerning the carbonyl transposition, the synthesis of substituted hexa-3, 5-dienoic acid methyl esters from conjugated dienones using lead (IV) acetate and boron trifluoride etherate-methanol combination is discussed in the last chapter.

Each chapter is framed into Introduction, Results and discussions and Experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The reference of the published work of the present investigation is cited in the respective chapter.

CHAPTER-I

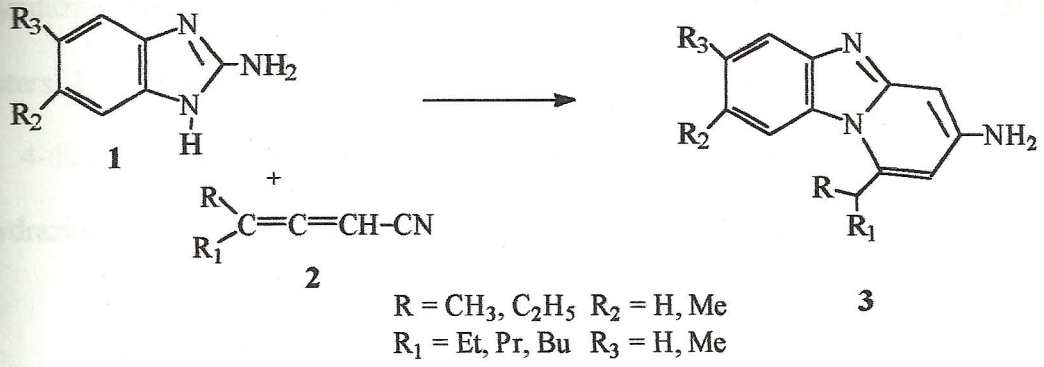
"GENERAL INTRODUCTION ON N-HETEROCYCLES"

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures and for the physiological and industrial significance of heterocyclic compounds.

The importance of N-heterocycles in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. An important approach for the synthesis of these types of compounds involve application of annelation methods, that is construction of cyclic compounds from open chain precursors.

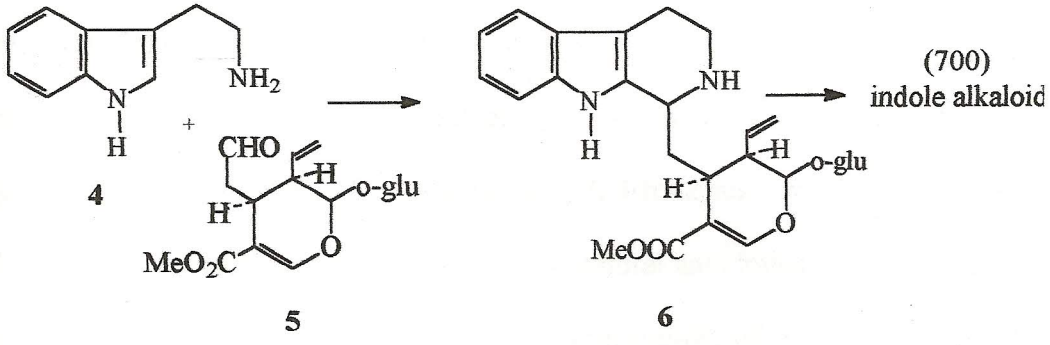
N-heterocycles formed the basic skeleton of many biologically important classes of natural products such as antibiotics, vitamins (vitamin B_{12} ie Cyanocobalamine), marine products, animal toxins, and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting systems such as Hemoglobin, Chlorophyll, Vitamin B_{12} etc. Derivatives of dideoxynucleoside analogs[1, 2] were found to be potent anti-AIDS drugs. Substituted ellipticines were found to have anti-tumour activity.[3] 5-alkyl/aryl-2-(2, 4-dichlorophenyl)-1, 3, 4-oxa/thia-diazol-[3, 2-a]-s-triazine-7-thiones was found to have anti-bacterial activity. The building up of these heterocyclic compounds was found to be from small and simple starting compounds.

The reaction of allenic nitriles **2** with 2-amino benzimidazoles **1** give 2-amino pyrimido [1, 2-a]benzimidazoles **3** (Scheme-1) which are found to possess slight antibiotic and anti-arrythmic properties.[4]



Scheme-1

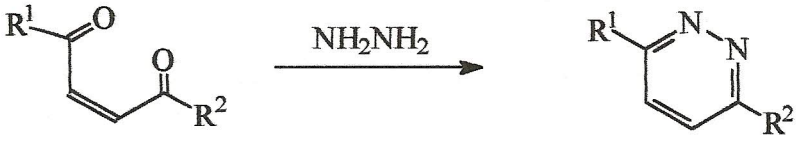
The condensation of tryptamine (or tryptophan) **4** with secologanin **5** gives rise to a nitrogenous glucoside **6** from which a great variety of indole alkaloids (700) are formed in living plants.



Scheme-2

Heterocyclic units such as pyridazines, pyrimidines and triazines and their analogues are of special interest in pharmacology, due to their important biological activities.[5, 6, 7] An important approach for the synthesis of these types of compounds involve cyclisations from open chain precursors. Dicarbonyl compounds were found to be important starting materials for the building up of these N-heterocycles.

Pyridazine derivatives **8** were easily obtained by the treatment of γ-keto acids or esters, 1, 4-diketones **7** etc with hydrazines.[8] (Scheme-3). Saturated and unsaturated 1, 4-diketones have been applied in several pyridazine syntheses. Reactions with hydrazine were usually performed in the presence of mineral acids.



7

R^1 = alkyl, aryl,
R^2 = alkyl, aryl, OH, OR^1

8

Scheme-3

Another important class of heterocycles is the asymmetric triazines which have been widely reported in the literature and in a number of review papers. Interest in the biochemical properties of 1, 2, 4-triazines has remained constantly high because a number of 3, 5-disubstituted 1, 2, 4-triazines represent aza analogues of pyrimidine nucleo bases while a number of natural antibiotics are pyrimido-[5, 4-e]-1, 2, 4-triazines[9]. Common methods of preparation of 1, 2, 4-triazines also involve dicarbonyl compounds as the main component.

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