SYNOPSIS

CHAPTER I

1. Medicinal chemistry has been a fascinating field of study in the last few decades on account of its successful application in the discovery of new drugs for the treatment of various diseases.

2. The main approaches to the discovery of new drugs centre around the isolation and structure elucidation of the active principles of medicinally useful plants and synthesis of new compounds (a) by chemical manipulation of the molecule of the active principle, or (b) based on the partial structures of the molecule of the active compound. In recent years, however, as a result of the study of metabolism of the known drugs, the synthesis of new compounds has been based more on the concept of structure-activity-relationship derived from the data of pharmacodynamic properties of drugs.

3. The salicylates and the hydroxysalicylates are well-known to be clinically useful as analgetic, antipyretic and antirheumatic drugs. The clinical usefulness of sodium salicylate was first discovered by Buss in 1875 as an antipyretic and in the following year Stricker discovered its value in the treatment of rheumatic fever. After the discovery of clinical efficacy of these compounds, phenyl salicylate and acetylsalicylic acid were soon discovered.

It was, therefore, considered of interest in the present investigation to synthesise a variety of N-substituted anthranilic
acid derivatives (I) for a study of their physiological action, as these are isoelectronic and isosteric analogues of salicylic acid (II).

\[ \text{COOH} \]
\[ \text{NHR} \]
\[ \text{I} \]

\[ \text{COOH} \]
\[ \text{II} \]

CHAPTER II

Chapter II describes the synthesis of substituted N-benzyl-, N-\( \alpha \)-alkylbenzyl-, N-hexahydrobenzyl-, N-\( \alpha \)-methylfurfuryl-, and N-\( \alpha \)-methylthielenylantranilic acids having the following general structure (III).

\[ R \]
\[ \text{COOH} \]
\[ \text{NH-X-Z} \]
\[ \text{III} \]

Where \( R = \text{H}, \text{Cl}, 4-\text{NO}_2, 4-\text{CH}_3, 5-\text{Cl} \) and 5-\( \text{NO}_2 \)

\[ X = \text{-CH}_2-, \text{-CH-}, \text{-CH-}, \text{-CH-}, \text{-CH-} \]
\[ \text{CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{C}_6\text{H}_5 \]

\[ Z = \text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{CH}_3\text{C}_6\text{H}_4, 3-0\text{CH}_3\text{C}_6\text{H}_4, 4-0\text{CH}_3\text{C}_6\text{H}_4, 3,4-\text{Cl}_2\text{C}_6\text{H}_3, 3,4-(0\text{CH}_3)_2\text{C}_6\text{H}_3, 3,4,5-(0\text{CH}_3)_3\text{C}_6\text{H}_2, 2\text{-thienyl, 2-furyl and cyclohexyl.} \]
These compounds were prepared by:

(a) reacting suitably substituted 2-chloro-, or 2-bromobenzoic acids with aralkylamines in the presence of potassium carbonate and catalytic amount of copper oxide (Ullmann reaction).

(b) the reduction of various N-benzylidene anthranilic acids with sodium borohydride.

(c) reacting appropriately substituted benzylchloride with anthranilic acid in the presence of aqueous potassium carbonate.

CHAPTER III

In this chapter has been given the preparation of substituted N-phenylethyl-, and N-γ-phenylpropylantranilic acids represented by the general formula (IV).

\[
\text{IV}
\]

Where \( R = \text{H, 4-Cl, 4-NO}_2, 4-\text{CH}_3, 5-\text{Cl, 5-NO}_2 \)

\( X = -\text{CH}_2-\text{CH}_2-, -\text{CH}-\text{CH}_2-, -\text{CH}_2-\text{CH}_2-, -\text{CH}_2-\text{CH}_3-, -\text{CH}_2-\text{CH}_2-\text{CH}_3-, -\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_3- \)
In chapter IV, the preparation of compounds, where the phenyl ring A of N-aralkylanthranilic acids described in chapters II and III above, is replaced by a pyridyl moiety, is described. The general formula for these compounds being (V).

\[
\text{Ar} = \text{phenyl, substituted phenyl having substituents like} \\
4-\text{Cl}, 4-\text{CH}_3, 4-0\text{CH}_3, 3,4-\text{Cl}_2, 3,4-(0\text{CH}_3)_2, \\
3,4\text{-methylenedioxy, thiethyl, furyl and cyclohexyl.}
\]

These compounds were prepared by heating a mixture of 2-chloronicotinic acid and an aralkylamine at 160-180°.

CHAPTER V

This chapter embodies the synthesis of N-aralkylisatoic anhydrides, pyridyl analogues of isatoic anhydrides and 1-substituted-1H-quinazolin-4-ones of the following general structures (VI) and (VII).
Where $X = -CH_2$, $N$  
$Y = -CH_2$, $-CH_3$, $-CH_2-CH_2-$

$Ar = \text{phenyl, substituted phenyl having substituents like }$  
$4-\text{Cl}, 4-\text{CH}_3, 4-\text{OCH}_3, 3,4-\text{Cl}_2, 3,4-(\text{OCH}_3)_2, \text{furyl and}$  
$cyclohexyl.$

$N$-substituted isatoic anhydride derivatives and their pyrido analogues were prepared by reacting $N$-aralkylantranilic acids and 2-aralkylaminonicotinic acids with ethyl chloroformate.

1-Substituted quinazolin-4-ones were obtained by condensing $N$-aralkylantranilic acids with formamide.

CHAPTER VI

The pharmacological findings of the compounds described in chapters II-V are given in this chapter.

The primary screening of these compounds showed mild to strong analgetic and antipyretic activity. Some of the compounds were further tested for their antiinflammatory and diuretic properties. The following compounds show promising antiinflammatory activity in experimental animals against carrageenin and
formalin induced oedema.

1. N-phenethylanthranilic acid

2. N-(3,4-dimethoxyphenyl)ethylanthranilic acid

3. N-(α-ethylbenzyl)anthranilic acid

4. 2-(α-Ethylbenzyl)aminonicotinic acid

5. 2-Furfurylaminonicotinic acid
One of the compounds belonging to the N-phenethyl series i.e., N-phenethylanthranilic acid is currently undergoing clinical evaluation in humans as an antiinflammatory agent. Preliminary observations indicate that this compound is tolerated, absorbed well and has not so far exhibited any appreciable side effects.

Further evaluation of this compound in comparison with known therapeutically useful antiinflammatory drugs is in progress.