CHAPTER I

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The turn of the century has seen the development of many organic medicinal agents, a great majority of which have been produced in the last three decades. Medicinal chemistry has, therefore, become a fascinating field of study as it has been applied successfully in the discovery of new drugs for the treatment of various diseases.

The main approaches to the discovery of new drugs centre around (1) the isolation and structure elucidation of the active principles of medicinally useful plants; (2) the synthesis of organic compounds whose structures are closely related to those of naturally occurring compounds that have been shown to possess useful medicinal properties; and (3) the efforts of pure synthesis in which no effort has been made to pattern after a known naturally occurring compound exhibiting some activity. 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 on pharmacodynamic properties of drugs.

The chemical changes compounds undergo in the body are of considerable interest and are frequently of great practical value in the search for new and improved medicinals. For example, oxyphenbutazone, which is a metabolite of phenylbutazone, resembles the latter in some of its anti-inflammatory properties.
Phenylbutazone

Oxyphenbutazone has proved to be a useful anti-rheumatic drug and is marketed as such under the trade name Tanderil.

As another example, 2,5-dihydroxybenzoic acid (gentisic acid), a metabolite of the salicylates, has been used for the treatment of rheumatic conditions, and at one time it was suggested that the anti-rheumatic action of the salicylates might be due to their transformation to gentisic acid in the body. This is not believed at the present time because only a small percentage of the salicylate is converted to this product, and the anti-rheumatic action of sodium gentisate is about the same as that of the salicylates.

Salicylates and hydroxysalicylates are well-known for their remarkable analgesic, anti-pyretic, anti-inflammatory, anti-rheumatic and uricosuric effects in man. The clinical usefulness of sodium salicylate was first discovered by Buss in 1875 as an anti-pyretic 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 (N-aralkylanthranilic acids) for a study of their physiological action, as these are isoelectronic and isosteric analogues of salicylic acid.

These compounds (wherein R is a benzyl or a phenethyl moiety and both the phenyl nuclei carry substituents) were screened for a general profile of biological activity, such as anti-pyretic, analgesic, anti-inflammatory and diuretic actions. Pharmacological screening data show that many of them possess promising anti-inflammatory and anti-arthritic properties. The pharmacological evaluation of these compounds for anti-inflammatory activity was motivated by the following considerations.

1. Winder et al. tested a number of N-arylanthranilic acids and found that two of them, viz., N-(2,3-xylyl)anthranilic acid (mefenamic acid) and N-(α,α,α-trifluorom-tolyl)anthranilic acid (flufenamic acid) have potent analgesic, anti-pyretic and anti-inflammatory properties.

2. Whitehouse in a recent publication has stated that the uncoupling of oxidative phosphorylation (a biochemical property...
which most of the non-steroidal anti-inflammatory agents possess) by anthranilic acids depends upon each of the following factors: (a) an unsubstituted carboxyl group; (b) an ortho-imino group; and (c) aromatic character. The N-aralkylanthranilic acids synthesized in the present investigation fulfill all the three requirements as given by Whitehouse.

(3) Interest in obtaining a non-steroidal anti-inflammatory agent, as is indicated by the amount of research that has been carried out in this area during the last few years.

Although the remarkable ability of cortisone and related compounds to suppress the inflammatory manifestations of rheumatoid arthritis have been recognised since 1949, the untoward side effects directly related to their hormonal properties limit their use over long period of time. On account of these limitations research on non-steroidal anti-inflammatory drugs did not stop and a variety of new compounds have become available. In fact, the last few years have seen a rapid development in this area. These non-steroid anti-inflammatory drugs represent a wide range of chemical compounds ranging from inorganic compounds, e.g., gold sodium thiosulphate through organometal complexes such as aurothio compounds to purely organic compounds. These latter in turn represent quite a chemical spectrum. The diversity of chemical structure of some of these drugs is illustrated by their structural formulae as given on the next page.
Sodium aurothiomalate

Salicylic acid

Cinchophene

Flufenamic acid

Phenylbutazone

Indomethacin

Chloroquine

Ibufenac
**N-Arylanthranilic acids**

This series includes some of the most potent anti-inflammatory agents made available to the suffering humanity so far. Much information has been forthcoming in literature in the form of publications and patents regarding the preparation of a variety of N-arylanthranilic acids and claiming them as promising anti-inflammatory agents. Two important compounds of the series (known as the fenamate family) are N-(2,3-xylyl)anthranilic acid (mefenamic acid, trade-named Ponstan) and N-(3,5-trifluoro-m-tolyl)-anthranilic acid (flufenamic acid, Arlef). Flufenamic acid seems to be a potent anti-inflammatory which has been claimed to show minimal side effects. However, later work has shown that diarrhea and other gastrointestinal reactions are the unwanted side effects. Although not as potent as flufenamic acid, mefenamic acid has both analgesic and anti-inflammatory properties. A related compound, N-(2,6-dichloro-m-tolyl)anthranilic acid (meclofenamic acid), has recently been reported to be more potent than either mefenamic acid or flufenamic acid.

![Mefenamic acid](Image)

![Flufenamic acid](Image)

![Meclofenamic acid](Image)
Interest in close analogues of fenamates is illustrated by the preparation of 8-trifluoromethyl phenothiazine-1-carboxylic acid, and an anthranilic acid substituted with the anti-malarial quinoline nucleus. This compound, 2,3-dihydroxypropyl N-(7-chloro-4-quinolyl)anthranilate (Glafenin) has been introduced to the European market as an analgetic as 200 mg tablets.

2-Anilinonicotinic acid derivatives which are the pyridine analogues of the fenamates were investigated by at least four laboratories independently to study if the anti-inflammatory activity of mefenamic acid and flufenamic acid was affected appreciably when the phenyl ring carrying the pharmacophore was replaced by a pyridine nucleus.

(1) \( R^1 = H, \quad R^2 = CF_3 \)
(2) \( R^1 = R^2 = CH_3 \)
(3) \( R^1 = CH_3, \quad R^2 = Cl \)
(4) \( R^1 = CH_3, \quad R^2 = NO_2 \)
Niflumic acid (1) is comparable to flufenamic acid in animals and is used in Europe at 1-1.5 g per day.

Juby et al. prepared analogues of a series of known N-phenylanthranilic acid anti-inflammatory agents where the carboxyl group was replaced by a tetrazole moiety, and concluded that the 5-tetrazolyl is an effective substitute for the carboxyl group for the retention of anti-inflammatory activity in the series of N-phenyl anthranilic acid agents studied.

Various other biological properties which N-substituted anthranilic acid derivatives have been shown to exhibit are —

(1) **Tuberculostatic activity**

N-Phenylanthranilic acid and its nuclear substituted derivatives have been shown to possess high *in vitro* activity in veal broth medium against *Mycobacterium tuberculosis* (H 37 strain). The activity is enhanced by the presence of a halogen substituent in the 4- or 5-position and (or) a phenoxy, methoxy, phenyl or phenylamino group in the 4'-position. Diphenylamine-2-carboxylic acids with such substituents completely inhibit
the growth of \( M. \) tuberculosis at concentrations of the order of 0.1 mg%, i.e., 1 p.p.m. The activity is inhibited by the presence of amino or acetamido groups in either nucleus.

At concentrations greater than the minimum bacteriostatic concentration the compounds appeared to be bactericidal. The activity is specific for \( M. \) tuberculosis since the compounds have only slight activity against \( M. \) phlei and no activity against \( B. \) proteus, \( B. \) pyocyaneus, \( S. \) pyogenes and \( S. \) aureus at significant dilutions.

(2) \textit{Diuretic and saluretic activity}

A number of patents\(^{15-17}\) have been taken on \( N \)-substituted-5-sulphamoyl anthranilic acids claiming them as diuretic and saluretic agents. The compounds can be represented by the following formula:

\[
\begin{align*}
\text{H}_2\text{NO}_2\text{S}^- & \quad \text{COOH} \\
\text{NH}^+ & \quad \text{R} \\
\end{align*}
\]

where \( X = \text{Cl or Br} \)

\( R = \text{benzyl, furfuryl, thienyl, cyclohexyl, diethyl, piperidino, allyl, methyl, n-octyl} \)

Another furfuryl based compound, i.e., 4-chloro-\( N \)-\((2\text{-furylmethyl})\)-5-sulphamoyl anthranilic acid, which was originally reported by Kleinfelder\(^{18}\),
has been shown to possess diuretic properties of potential value. It differs chemically from the thiazide diuretics by the replacement of the thiazidine ring by a furfuryl group on the amino nitrogen of anthranilic acid.

Clinically in healthy volunteers it was not superior to hydrochlorothiazide, but in oedematous patients was about twice as diuretic and 1.68 as effective in sodium excretion. The drug is marketed under the name Lasix\(^2\) (Frusemide, Furosemide) and is indicated in all forms of cardiac oedema, oedema of renal origin and of pregnancy, pulmonary and cerebral oedema.

(3) **Fibrinolytic activity**\(^2\)

Gryglewski and Gryglewska tested twenty N-substituted anthranilates and found that only N-arylanthranilates dissolve human plasma clots, most active compounds being N-(4-fluorophenyl)anthranilate, N-(2,3-dimethylphenyl)anthranilate, and N-(3-trifluorophenyl)anthranilate. When the phenyl ring is substituted for condensed rings, acyl or alkyl groups the compounds so obtained do not dissolve the clots.

**Present work**

The foregoing survey shows that although a number of potent analgesic, anti-inflammatory and anti-rheumatic compounds have been patented and marketed, the search for a better drug is still continuing. Again a survey of the literature revealed that few N-benzylanthranilic acids have been prepared so far, and that they have not been evaluated for pharmacological action. It was, therefore, considered worthwhile to synthesise a series of N-benzyl and N-phenethylanthranilic acids and test their biological activity in experi-
mental animals.

Chapter II describes the synthesis of N-benzyl, N-α-alkylbenzyl, N-furfuryl, N-thenyl, and N-hexahydrobenzyl anthranilic acids having substituents such as chloro, nitro, methyl and methoxy in various isomeric positions of the phenyl rings. Compounds thus synthesised are represented by the general structure,

\[
\begin{align*}
R & \quad \text{COOH} \\
& \quad \text{NH} - X - Z
\end{align*}
\]

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

\[
X = -\text{CH}_2-, -\text{CH}-, -\text{CH}-, -\text{CH}-, -\text{CH}-
\]

\[
\text{CH}_3 \quad \text{C}_2\text{H}_5 \quad \text{nC}_3\text{H}_7 \quad \text{C}_6\text{H}_5
\]

and \( Z = \text{phenyl, substituted phenyl, furyl, thieryl, and cyclohexyl groups} \)

Chapter III describes the preparation of N-phenylethyl and N-phenylpropyl anthranilic acid derivatives. Compounds thus synthesised can be represented again by the same general formula

\[
\begin{align*}
R & \quad \text{COOH} \\
& \quad \text{NH} - X - Z
\end{align*}
\]

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

\[
X = -\text{CH}_2-\text{CH}_2-, -\text{CH-CH}_2-, -\text{CH-CH}_2-, -\text{CH}_2-\text{CH}-,
\]

\[
\text{CH}_3 \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5
\]
Chapter IV describes the preparation of 2-aralkylaninononicotinic acids which can be represented by the formula

\[
\text{COOH} \\
\text{NH-X-Ar}
\]

where \( X = \text{-CH}_2, \text{-CH}, \text{-CH}_2, \text{-CH}_2- \)

and \( Ar = \text{phenyl, substituted phenyl, thienyl, furyl and cyclohexyl groups} \)

These compounds were synthesised to see if there was any change in the physiological action, when the phenyl ring of the N-aralkylanthranilic acids was replaced by the pyridine nucleus.

Chapter V gives the preparation of some N-aralkylisatoic anhydrides, N-aralkyl substituted pyridine analogues of isatoic anhydride and N-aralkyl-1H-quinazolin-4-ones, represented by the following general formulae

\[
\text{where } Y = \text{-CH}_2, \text{-CH}, \text{-CH}, \text{-CH}_2- \]

\[
\text{CH}_3 \\
\text{C}_2\text{H}_5
\]
and $\text{Ar} = \text{phenyl, substituted phenyl, furyl, and cyclohexyl groups}$

which were prepared during the course of present work.

Pharmacological evaluation of compounds described in Chapters II, III, IV and V is given in Chapter VI.

A brief survey of literature regarding the methods of preparation of $N$-arylanthranilic acids, $N$-benzylanthranilic acids, 2-anilinonicotinic acids, 1-substituted isatoic anhydrides and 1-substituted-1$H$-quinazolin-4-ones is given at the end of the thesis in Appendix.
References


